

Original Investigation

Resting-State Functional Magnetic Resonance Imaging Activity and Connectivity and Cognitive Outcome in Traumatic Brain Injury

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IMPORTANCE The study of brain activity and connectivity at rest provides a unique opportunity for the investigation of the brain substrates of cognitive outcome after traumatic axonal injury. This knowledge may contribute to improve clinical management and rehabilitation programs.

OBJECTIVE To study functional magnetic resonance imaging abnormalities in signal amplitude and brain connectivity at rest and their relationship to cognitive outcome in patients with chronic and severe traumatic axonal injury.

DESIGN Observational study.

SETTING University of Barcelona and Hospital Clinic de Barcelona, Barcelona, and Institut Guttmann-Neurorehabilitation Hospital, Badalona, Spain.

PARTICIPANTS Twenty patients with traumatic brain injury (TBI) were studied, along with 17 matched healthy volunteers.


INTERVENTIONS Resting-state functional magnetic resonance imaging and diffusion tensor imaging data were acquired. After exploring group differences in amplitude of low-frequency fluctuations (ALFF), we studied functional connectivity within the default mode network (DMN) by means of independent component analysis, followed by a dual regression approach and seed-based connectivity analyses. Finally, we performed probabilistic tractography between the frontal and posterior nodes of the DMN.


MAIN OUTCOMES AND MEASURES Signal amplitude and functional connectivity during the resting state, tractography related to DMN, and the association between signal amplitudes and cognitive outcome.

RESULTS Patients had greater ALFF in frontal regions, which was correlated with cognitive performance. Within the DMN, patients showed increased connectivity in the frontal lobes. Seed-based connectivity analyses revealed augmented connectivity within surrounding areas of the frontal and left parietal nodes of the DMN. Fractional anisotropy of the cingulate tract was correlated with increased connectivity of the frontal node of the DMN in patients with TBI.

CONCLUSIONS AND RELEVANCE Increased ALFF is related to better cognitive performance in chronic TBI. The loss of structural connectivity produced by damage to the cingulum tract explained the compensatory increases in functional connectivity within the frontal node of the DMN.

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Cognitive deficits after traumatic brain injury (TBI) are a major cause of daily life disability.¹ Persistent disabling sequelae are caused by the structural brain damage that occurs not only in the early stage but also after a period of apparent recovery.² Traumatic axonal injury is associated with the most severely impaired outcomes after TBI. Neuropathological studies have shown that TBI affects structural brain networks progressively, from focal axon alteration to delayed axonal disconnection.³ Functional magnetic resonance imaging (fMRI) studies suggest that white matter damage alters structural connectivity, which in turn can affect functional connectivity, and both contribute to cognitive dysfunctions in TBI.⁴⁻⁷

Resting-state fMRI studies have recently emerged as a useful tool for investigating brain functional connectivity after severe TBI^{4,8-11} and in subjects with mild TBI examined during the early stages.^{12,13} These studies provide information about brain activity and connectivity in the absence of task performance, a condition that allows researchers to investigate patient populations with broader ranges of injury severity, because no specific cognitive ability is required. Advanced neuroimaging processing tools provide information about brain activity and functional connectivity during resting-state fMRI. Low signal fluctuations that occur during rest have been shown to reflect strong connectivity between functionally related brain regions.^{14,15}

Although different functional connectivity networks can be identified during the resting state,¹⁶ the most widely studied is the default mode network (DMN), which is reported to be affected in a broad range of brain disorders and is commonly related to cognitive processes.¹⁷ The spatial pattern of the DMN includes the ventromedial prefrontal cortex, the posterior cingulate cortex, the lateral parietal cortex, and the precuneus. For the main nodes of the DMN, their functional connectivity is supported by an underlying structure of white matter pathways,¹⁸ with the cingulum as the key tract that interconnects the anterior and posterior core regions of the DMN.¹⁹

In addition to disrupted functional connectivity, studies of white matter integrity using diffusion tensor imaging²⁰⁻²³ have shown that structural connectivity is also greatly affected after TBI. In a previous study,⁵ we found that disrupted structural connectivity after traumatic axonal injury was responsible for altered functional connectivity during working memory performance. In the current research, we used new advances in resting state-related fMRI methods to determine whether the amplitude of spontaneous low-frequency fluctuations in brain activity and DMN connectivity may be sensitive biomarkers for cognitive dysfunction after TBI. To this end, we measured the amplitude of resting-state blood oxygen level-dependent signal fluctuations in the whole brain and the DMN, studying global and network-based functional connectivity, as well as structural connectivity of the main fasciculi within the DMN.

Methods

Study Participants

Twenty patients with chronic and diffuse TBI were recruited from the Head Injury Unit of the Guttman Institute-Neurorehabilitation Hospital. The criteria followed for sample selection

Table 1. Demographic and Clinical Characteristics of Patients and Control Subjects

Characteristic	Patients With TBI (n = 20)	Control Subjects (n = 17)
Age, mean (SD), y ^a	27.50 (5.28)	26.29 (4.95)
Educational level, mean (SD), y ^b	15.20 (2.96)	14.64 (2.85)
Sex, No. ^c		
Male	11	10
Female	9	7
GCS score, mean (SD)	5 (1.74)	...
Time since injury, mean (SD), y	4.10 (1.18)	...
Microbleeds (TAI)		...
Frontal lobes	17	
Temporal lobes	12	
Corpus callosum	14	
Basal ganglia	10	
Parietal lobes	9	
Cerebellum	6	
Thalamus	5	
Midbrain	5	
Contusions (<10-mL volume)		...
Frontal lobes	4	
Temporal lobes	2	

Abbreviations: GCS, Glasgow Coma Scale; MRI, magnetic resonance imaging; TAI, traumatic axonal injury; TBI, traumatic brain injury.

^a $t = 0.71$; $P = .48$.

^b $t = 0.57$; $P = .57$.

^c $t = 2.29$; $P = .82$.

have been described elsewhere.⁵ This study is part of a project on long-term impairment of connectivity in diffuse TBI, and some results already have been published.^{5,24} Patients' demographic and clinical characteristics are summarized in **Table 1**. Patients underwent magnetic resonance imaging (MRI) a mean (SD) of 4.1 (1.2) years after injury, and all showed microbleeds as a sign of diffuse disease in the T2* and fluid-attenuated inversion recovery sequences. Table 1 provides detailed clinical and neuroradiological characteristics for each patient in the study. The cause of TBI was motor vehicle crashes in all cases.

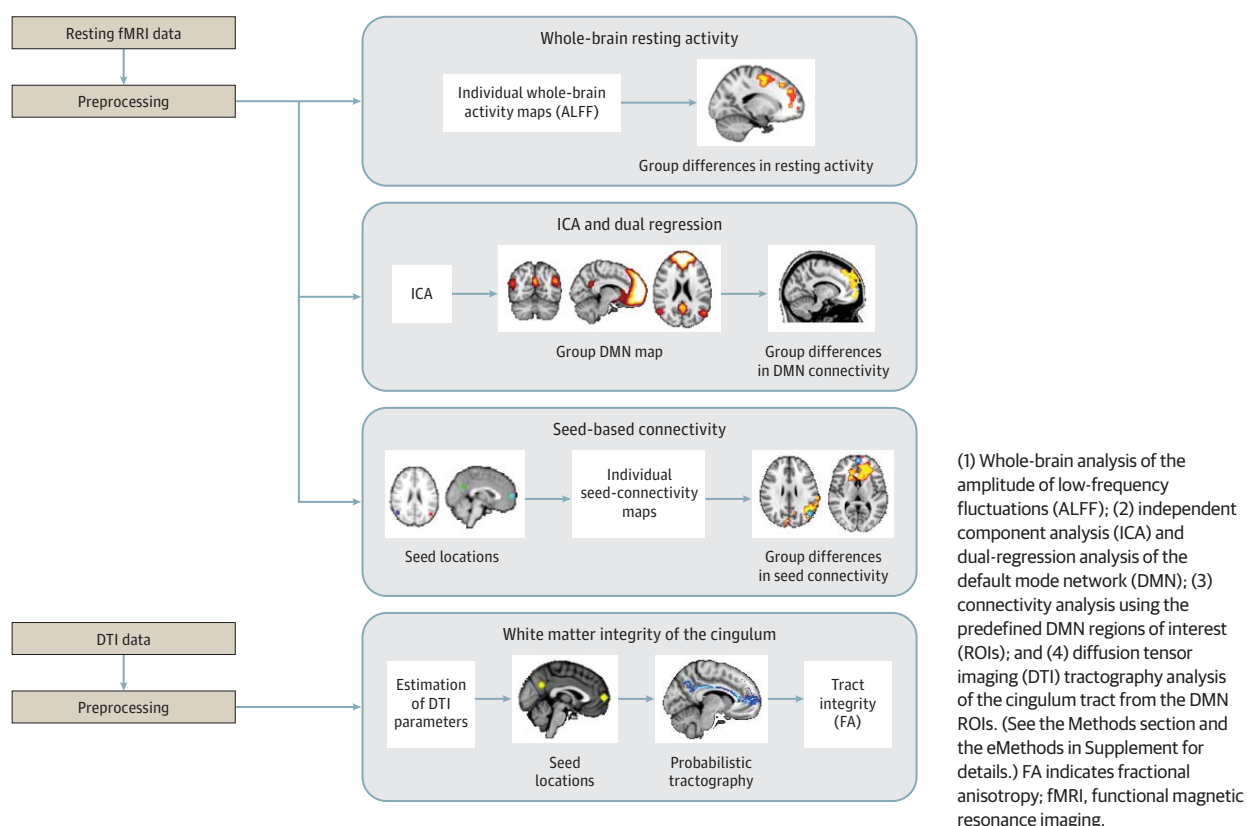
The control group comprised 17 healthy volunteers matched by age, sex, and educational level. None had a history of neurological or psychiatric diseases. Their demographic characteristics are provided in Table 1.

The study was approved by the research ethics committees of the Guttman Institute-Neurorehabilitation Hospital and the University of Barcelona. All participants gave written informed consent.

Image Acquisition

Data were acquired with a Siemens Magnetom Trio Tim syngo 3-T system at the Centre de Diagnostic per la Imatge of the Hospital Clinic, Barcelona. A high-resolution T1-weighted structural image was obtained for each subject with an MPRAGE (magnetization-prepared rapid acquisition gradient-echo) 3-dimensional protocol (repetition time [TR], 2300 milliseconds; echo time [TE], 3 milliseconds; inversion time, 900 milliseconds;

Figure 1. Image processing and analysis methods



field of view [FOV], 244 mm; and 1-mm isotropic voxel) and a 5-minute fMRI resting-state, single-shot, gradient-echo, echo-planar imaging sequence (TR, 2000 milliseconds; TE, 16 milliseconds; flip angle, 90°; FOV, 220 mm; and voxel size, $1.7 \times 1.7 \times 3.0$ mm). Diffusion-weighted images were sensitized in 30 non-collinear directions with a b value of 1000 s/mm^2 in an echo-planar imaging sequence (TR, 9300 milliseconds; TE, 94 milliseconds; section thickness, 2.0 mm; voxel size, $2.0 \times 2.0 \times 2.0$ mm; FOV, 240 mm; and no gap). For the lesion description, the neuroradiologist (N.B.) considered T1-weighted, fluid-attenuated inversion recovery (TR, 9000 milliseconds; TE, 85 milliseconds; section thickness, 3.0 mm; voxel size, $1.3 \times 0.9 \times 3.0$ mm; and FOV, 240 mm), and T2* gradient-echo sequence (TR, 518 milliseconds; TE, 20 milliseconds; section thickness, 3.0 mm; voxel size, $0.9 \times 0.8 \times 3.0$ mm; and FOV, 240 mm) sequences. All the images were visually inspected to ensure that they did not contain MRI artifacts or excessive movement before analysis.

Neuropsychological Assessment

A trained neuropsychologist masked to the clinical data administered tests to assess the main cognitive functions impaired after TBI. The assessment included the following: letter-number sequencing; digit span test (forward and backward measures); the Trail Making Test (parts A and B); the Rey Auditory Verbal Learning Test; the Rey-Osterrieth complex figure; reading, color naming, and reading word-color conditions from the Stroop test; and measures of verbal semantic and phonemic fluency.²⁵ Fac-

tor analysis was used to obtain a single measure that was representative of overall cognitive outcome, based on tests in which patients were significantly impaired compared with controls (eMethods and eTable in Supplement).

MRI: Image Processing and Analysis

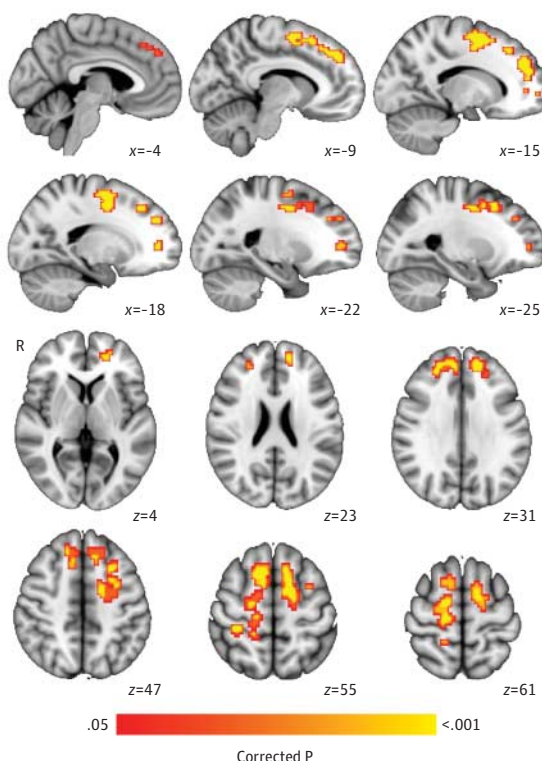
Amplitude Measures of Resting-State Data

The amplitude of low-frequency fluctuations (ALFF) was measured using a method based on the fast Fourier transform of the resting-state time series for each voxel.²⁶ After individual ALFF maps were obtained, they were registered to the Montreal Neurological Institute (MNI) standard space by means of linear registration (FLIRT [FMRIB's Linear Image Registration Tool] from FSL [http://fmrib.ox.ac.uk/fsl]).²⁷ Voxel-wise group comparisons were performed on these maps by using permutation-based comparisons with general linear modeling. Differences were considered significant at $P < .05$ (family-wise error corrected; see the eMethods in Supplement and Figure 1 for a full description of the procedures used).

Independent Component Analysis of Resting-State Data

We entered preprocessed resting fMRI data into an independent component analysis (ICA) using MELODIC²⁸ software from FSL. This enabled us to obtain a set of independent components and identify the common resting-state functional networks.^{14,16,19,29} Before group ICA decomposition, all individual fMRI data sets were linearly registered to the MNI standard space.²⁷ Finally, we selected the independent component map of the DMN. The pro-

Figure 2. Increased amplitude of low-frequency fluctuations during the resting-state in patients with traumatic brain injury



Red-yellow regions represent areas with statistically significant differences between patients and controls (corrected $P < .05$).

cedure for selecting the DMN within the whole set of components was based on the computation of spatial cross-correlation between each independent component and a previously published template corresponding to the DMN.¹⁶

We then used a dual regression approach^{4,30} to investigate between-group differences in the DMN maps. The significance threshold of the voxel-wise differences was set at $P < .05$ (family-wise error corrected) (eMethods in Supplement and Figure 1).

Seed-Based Analysis of the DMN

The peak coordinates of the DMN identified with ICA were used to create 4 spherical regions of interest (ROIs) representing the main nodes of this network: medial prefrontal cortex (MPFC), precuneus/posterior cingulate (PPC), and left and right parietal cortices (eMethods in Supplement and Figure 1).

For each seed (or DMN node), we created whole-brain functional connectivity maps and tested group differences of these maps. All seed-based connectivity analyses were performed using the functional data sets that had been previously pre-processed and registered to the MNI standard space.

Analysis of MRI Diffusion Data

Diffusion MRI images were analyzed with FDT (FMRIB's Diffusion Toolbox) software from FSL. After first extracting individual fractional anisotropy (FA) maps, we then used diffusion tensor imaging data in a probabilistic tracking algorithm to estimate

Table 2. MNI Maximum Coordinates, Cluster Size, and Statistical Significance of the Increased Activity on Resting-State Spatial Maps

Brain Area	Cluster Size (Voxels)	Coordinate			P Value
		x	y	z	
Frontal pole	274	-21	45	36	.02
Frontal pole	192	15	45	33	.02
Gyrus					
Superior frontal	75	15	-6	60	.02
Middle frontal	21	-27	18	45	.03
Paracingulate	14	-18	48	3	.04

Abbreviation: MNI, Montreal Neurological Institute.

white matter pathways connecting the 2 DMN ROIs (ie, MPFC ROI and PPC ROI) extracted from the analysis of the resting-state fMRI data. These ROIs (from fMRI analysis) were originally in MNI standard space. They were then moved to each subject's diffusion space before we performed tractography (using linear registration implemented with FSL software).²⁷ Individual tracts were registered again to MNI to compute the group-average maps. White matter pathways were averaged across controls and patients separately. Finally, the average connectivity map of the 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 (Figure 1).

Cognitive Outcome and Structural and Functional Connectivity Data

Mean signal amplitude (ALFF scores) and connectivity (functional connectivity and structural connectivity) scores were extracted within the areas that resulted significantly from the whole-brain ALFF analysis, the ICA, and the seed-based functional connectivity and tractography analyses. We used Pearson correlations in SPSS software (IBM) (eMethods in Supplement) to study these measures together with the measure of cognitive outcome.

Results

Amplitude of Resting-State Fluctuations

Compared with controls, patients had greater ALFF in several brain areas (corrected $P < .05$), including the frontal pole, superior frontal gyrus, middle frontal gyrus, paracingulate gyrus, and superior parietal lobe (see Figure 2 and Table 2 for MNI coordinates and cluster size). Because the map of increased ALFF in the middle frontal areas showed a large overlap with the frontal node of the DMN, we analyzed the brain connectivity of this network.

Independent Component Analysis

Using ICA with temporal concatenation, we obtained a set of 37 independent components and identified the main resting-state networks (eResults and eFigure 1 in Supplement). Within this set of networks, we selected the DMN for further analysis.

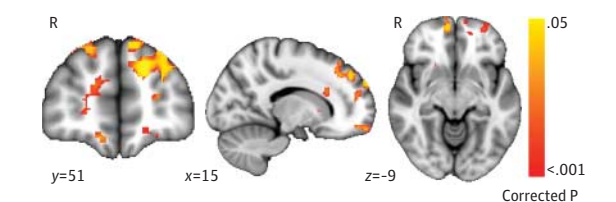
DMN Connectivity

Group Comparisons of the ICA-Based DMN

Using the dual regression approach, patients with TBI had greater functional connectivity than controls within the DMN

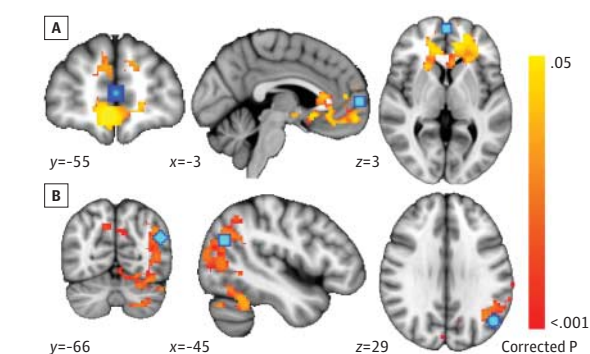
in certain areas of the frontal lobe (Figure 3). These regions included the frontal pole, the anterior cingulate and paracingulate gyrus, the superior frontal gyrus, and a small part of the precentral gyrus.

Figure 3. Increased connectivity within the default mode network in patients with traumatic brain injury to controls



Red-yellow regions represent areas where the connectivity differed significantly between patients and controls (corrected $P < .05$).

Figure 4. Areas showing increased functional connectivity in traumatic brain injury and locations of the seeds



Areas showing increased functional connectivity in traumatic brain injury (red and yellow) and locations of the seeds (blue). A, Increased connectivity with the medial prefrontal cortex region of interest used as a seed. B, Increased connectivity with the left parietal cortex region of interest used as a seed. Significant at $P < .05$ (family-wise error corrected).

Seed-Based Connectivity Analysis

Using the ICA-based spatial map of the DMN, we created 4 spherical ROIs with which to compute seed-based connectivity maps in the MPFC, PPC, and left and right parietal cortex ROIs (see eResults and eFigure 2 in Supplement for exact ROI locations).

With the MPFC ROI as a seed, we found increased functional connectivity of this region with other areas of the MPFC in patients compared with controls (corrected $P < .05$) (Figure 4). Moreover, with the left parietal cortex ROI, we also found a set of brain areas with increased functional connectivity in patients with TBI (corrected $P < .05$) (Figure 4). These areas were located in the left lateral occipital cortex, angular gyrus, supramarginal gyrus, temporo-occipital areas, middle and inferior temporal gyrus, occipital fusiform and lingual gyri, and precuneus. We found no differences in functional connectivity when using the remaining nodes as seeds.

Structural Connectivity Measured With Diffusion Tensor Imaging

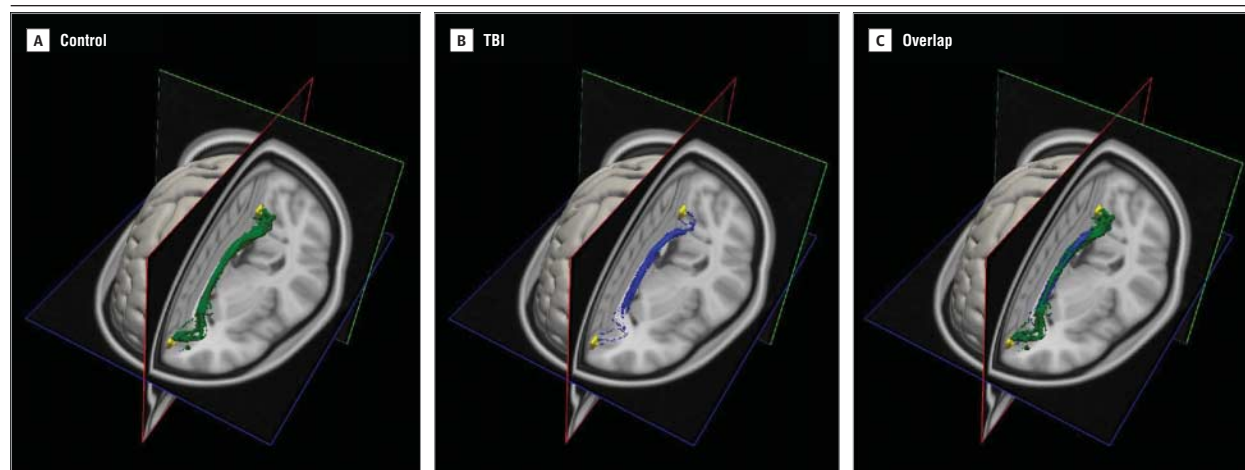
The MPFC and the PPC ROIs were used to reconstruct the white matter pathway connecting the 2 regions. The probabilistic tractography map of each subject was used to create separate average maps for patients and controls. These maps indicate the probability of each voxel being part of a white matter pathway connecting the 2 regions. The main tracts identified were the left and right bundles of the cingulum. Visual inspection of the average maps for each group showed that the size of the cingulum was reduced in patients.

The average map for the control group was used as a mask to extract mean FA values within the cingulum for each subject. These values were significantly decreased in patients with TBI compared with controls (mean, 0.36 for patients vs 0.42 for controls; $t = 5.9$; $P < .001$) (Figure 5).

Amplitude of Fluctuations and Cognitive Outcome

In patients, the amplitude of resting-state fluctuations was positively correlated with cognitive performance ($r = 0.48$; $P = .03$);

Figure 5. Results of tractography analysis shown as spatial maps of probabilistic tracking



Yellow represents the 2 regions of interest (medial prefrontal cortex and precuneus/posterior cingulate) used as seeds for the fiber-tracking algorithm. Average probabilistic connectivity maps are shown, with the standard

anatomical Montreal Neurological Institute template, for controls (in green) and patients with traumatic brain injury (TBI) (in blue).

the greater the activation, the better the cognitive outcome. There was no significant correlation between these measures in controls ($r = 0.35$; $P = .16$).

Within the patient group, functional connectivity scores for the frontal ROI were negatively correlated with the FA values of the cingulum tract ($r = -0.45$; $P = .04$).

Discussion

The purpose of this study was to provide further insight into the ALFF and their connectivity in the resting state and the possible relationship of these findings with cognitive outcome after traumatic axonal injury. Our main finding was that higher ALFF at rest is associated with better cognitive outcome in patients with diffuse TBI. More specifically, these patients also had increased resting-state functional connectivity in regions surrounding the frontal node of the DMN. Moreover, the increased frontal connectivity could be explained by damage to the cingulum, the key tract connecting the anterior and posterior brain areas of the DMN. These findings suggest that the loss of structural connectivity is compensated for by an increase in the functional connectivity of local circuits.

Few studies to date have considered the ALFF at rest and its implications in terms of cognitive dysfunction. This measure has been found to be decreased in patients with mild cognitive impairment and Alzheimer disease.³¹ In neurodegenerative diseases, these decreases in amplitude probably reflect a loss of neurons that consecutively provokes connectivity deficits and disorganization or breakdown of brain networks. In our study, when comparing whole-brain ALFF in the resting state between groups, the TBI group showed increased amplitudes that were predominantly focused within frontal lobe regions. Moreover, the measures of higher amplitudes in these areas predicted a better general cognitive outcome, suggesting that functional and efficient brain reorganization occurred to compensate for acute brain damage and improve cognitive performance. This finding, together with changes in structural connectivity, may constitute an objective measure of long-term cognitive outcome after TBI.

The specific analyses of the DMN in the resting state also showed increased connectivity in the frontal node of this network in patients with TBI compared with controls. Furthermore, connectivity from each core of DMN nodes to the whole brain revealed a widespread pattern of locally increased functional connectivity surrounding the medial frontal and left parietal nodes of the DMN. Increased functional connectivity has been found in other diseases involving white matter damage, such as multiple sclerosis; subjects with relapsing-remitting multiple sclerosis have compensatory increased connectivity in the posterior cingulate DMN node,³² and in patients with early-stage disease, distinct networks exhibit increases in functional connectivity despite large reductions in white matter integrity.³³

Previous studies investigating the DMN during the resting state in TBI have found alterations that reflect both decreases¹¹ and increases in functional connectivity.¹² The increases have been interpreted as compensatory or adaptive mechanisms because they were often positively correlated with cognitive outcome.^{8,34} Another possible interpretation is that this increased

connectivity, measured in voxels surrounding the DMN nodes, reflects a diffusion of the DMN nodes during recovery from TBI. This latter interpretation also may be supported by the fact that the white matter injury found in the cingulum in TBI precludes the functional inhibition of areas surrounding these nodes. We suggest that the increases found in frontal areas may reflect compensation because the amplitude of the fluctuations in these regions correlated with performance, but the increase in the spread of connectivity around the PPC may reflect a loss of directionality in the connectivity caused by the injury. On the other hand, Mayer et al⁸ described a pattern of decreased long-distance functional connectivity between the nodes of the DMN (ie, between anterior and posterior nodes).

Although not directly examining the DMN, other authors have found alterations in resting-state connectivity in TBI in the form of reduced interhemispheric connectivity of the hippocampus and increased ipsilateral connectivity, and these were associated with better cognitive outcome.⁶ In addition, resting-state fMRI studies involving magnetoencephalographic recordings have also provided evidence of brain plasticity and network reorganization mechanisms, specifically increases or decreases in the extent of certain brain connections.³⁵

To find a possible explanation for the observed pattern of augmented functional connectivity in the anterior and posterior areas of the DMN, we performed tractography of the fibers connecting the core of the anterior and posterior regions of this network. This showed reductions within the fibers corresponding to the cingulum, and the FA of this bundle was correlated with the increased connectivity of the frontal node of the DMN. The cingulum is a long, medial associative bundle that runs within the cingulate gyrus all around the corpus callosum, connecting the medial frontal and parietal lobes.³⁶ This finding suggests that damage to this fascicle leads to functional reorganization consisting of increased local connectivity surrounding the nodes of the network, probably resulting from decreased interconnectivity between the frontal and parietal nodes.

Altogether, our results suggest that increased frontal functional activity at rest, measured as the ALFF, is associated with better global cognitive performance and that the altered structural connectivity between related brain regions can be compensated for by increased functional connectivity. Two recent studies have accurately characterized the changes in the DMN connectivity at different time points. Hillary et al,¹⁰ examining resting-state DMN connectivity in a sample of patients in the acute stage with predominant focal lesions, found increases in the connectivity of this network during the first 6 months after injury. On the other hand, Arenivas et al¹¹ examined DMN functional connectivity in a cohort of patients 6 to 11 months after TBI. Using 3 methodological approaches, they found decreased connectivity in the main nodes of the DMN. Although their sample characteristics were similar to our own (patients with white matter damage without significant contusions), our patients were studied a mean of 4 years after injury. Thus, our findings can be generalized only to patients in the late chronic stage and are not directly comparable to findings in the early chronic or postacute stages. However, whereas Arenivas et al¹¹ showed decreases in the core nodes of the DMN, we found diffuse increases in connectivity in areas surround-

ing DMN nodes. The apparent contradiction can be explained by the fact that Arenivas et al did not analyze the regions where we found increases because they studied connectivity within the nodes of the DMN. We suggest that the increased connectivity in areas surrounding DMN nodes, which we found in the late chronic stage, might represent the brain's attempt to com-

pensate functionally for weaker connectivity within DMN nodes caused by structural damage after traumatic axonal injury. Nevertheless, the decreased connectivity of the DMN in this study did not predict the clinical or cognitive deficits. Future longitudinal studies with several follow-up points could clarify the dynamics of cerebral reorganization after TBI.

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REFERENCES

- Benedictus MR, Spikman JM, van der Naalt J. Cognitive and behavioral impairment in traumatic brain injury related to outcome and return to work. *Arch Phys Med Rehabil*. 2010;91(9):1436-1441.
- Adams JH, Jennett B, Murray LS, Teasdale GM, Gennarelli TA, Graham DI. Neuropathological findings in disabled survivors of a head injury. *J Neurotrauma*. 2011;28(5):701-709.
- Büki A, Povlishock JT. All roads lead to disconnection? traumatic axonal injury revisited. *Acta Neurochir (Wien)*. 2006;148(2):181-194.
- Sharp DJ, Beckmann CF, Greenwood R, et al. Default mode network functional and structural connectivity after traumatic brain injury. *Brain*. 2011;134(pt 8):2233-2247.
- Palacios EM, Sala-Llloch R, Junque C, et al. White matter integrity related to functional working memory networks in traumatic brain injury. *Neurology*. 2012;78(12):852-860.
- Marquez de la Plata CD, Garcés J, Shokri Kojori E, et al. Deficits in functional connectivity of hippocampal and frontal lobe circuits after traumatic axonal injury. *Arch Neurol*. 2011;68(1):74-84.
- Kasahara M, Menon DK, Salmond CH, et al. Traumatic brain injury alters the functional brain network mediating working memory. *Brain Inj*. 2011;25(12):1170-1187.
- Mayer AR, Mannell MV, Ling J, Gasparovic C, Yeo RA. Functional connectivity in mild traumatic brain injury. *Hum Brain Mapp*. 2011;32(11):1825-1835.
- Bonnelle V, Ham TE, Leech R, et al. Salience network integrity predicts default mode network function after traumatic brain injury. *Proc Natl Acad Sci U S A*. 2012;109(12):4690-4695.
- Hillary FG, Slocumb J, Hills EC, et al. Changes in resting connectivity during recovery from severe traumatic brain injury. *Int J Psychophysiol*. 2011;82(1):115-123.
- Arenivas A, Diaz-Arrastia R, Spence J, et al. Three approaches to investigating functional compromise to the default mode network after traumatic axonal injury [published online July 31, 2012]. *Brain Imaging Behav*. doi:10.1007/s11682-012-9191-2.
- Shumskaya E, Andriessen TM, Norris DG, Vos PE. Abnormal whole-brain functional networks in homogeneous acute mild traumatic brain injury. *Neurology*. 2012;79(2):175-182.
- Slobounov SM, Gay M, Zhang K, et al. Alteration of brain functional network at rest and in response to YMCA physical stress test in concussed athletes: RsfMRI study. *Neuroimage*. 2011;55(4):1716-1727.
- Biswal BB, Mennes M, Zuo XN, et al. Toward discovery science of human brain function. *Proc Natl Acad Sci U S A*. 2010;107(10):4734-4739.
- Fox MD, Raichle ME. Spontaneous fluctuations in brain activity observed with functional magnetic resonance imaging. *Nat Rev Neurosci*. 2007;8(9):700-711.
- Smith SM, Fox PT, Miller KL, et al. Correspondence of the brain's functional architecture during activation and rest. *Proc Natl Acad Sci U S A*. 2009;106(31):13040-13045.
- Buckner RL, Andrews-Hanna JR, Schacter DL. The brain's default network: anatomy, function, and relevance to disease. *Ann N Y Acad Sci*. 2008;1124:1-38.
- Hagmann P, Cammoun L, Gigandet X, et al. Mapping the structural core of human cerebral cortex. *PLoS Biol*. 2008;6(7):e159. doi:10.1371/journal.pbio.0060159.
- van den Heuvel MP, Hulshoff Pol HE. Exploring the brain network: a review on resting-state fMRI functional connectivity. *Eur Neuropsychopharmacol*. 2010;20(8):519-534.
- Kraus MF, Susmaras T, Caughlin BP, Walker CJ, Sweeney JA, Little DM. White matter integrity and cognition in chronic traumatic brain injury: a diffusion tensor imaging study. *Brain*. 2007;130(pt 10):2508-2519.
- Sidaros A, Engberg AW, Sidaros K, et al. Diffusion tensor imaging during recovery from severe traumatic brain injury and relation to clinical outcome: a longitudinal study. *Brain*. 2008;131(pt 2):559-572.
- Kinnunen KM, Greenwood R, Powell JH, et al. White matter damage and cognitive impairment after traumatic brain injury. *Brain*. 2011;134(pt 2):449-463.
- Newcombe V, Chatfield D, Outtrim J, et al. Mapping traumatic axonal injury using diffusion tensor imaging: correlations with functional outcome. *PLoS One*. 2011;6(5):e19214. doi:10.1371/journal.pone.0019214.
- Palacios EM, Sala-Llloch R, Junque C, et al. Long-term declarative memory deficits in diffuse TBI: correlations with cortical thickness, white matter integrity and hippocampal volume. *Cortex*. 2013;49(3):646-657.
- Lezak MD, Howieson DB, Loring DD, et al. *Neuropsychological Assessment*. New York, NY: Oxford University Press; 2004.
- Zang YF, He Y, Zhu CZ, et al. Altered baseline brain activity in children with ADHD revealed by resting-state functional MRI. *Brain Dev*. 2007;29(2):83-91.
- Jenkinson M, Bannister P, Brady M, Smith S. Improved optimization for the robust and accurate linear registration and motion correction of brain images. *Neuroimage*. 2002;17(2):825-841.
- Beckmann CF, Smith SM. Tensorial extensions of independent component analysis for multisubject fMRI analysis. *Neuroimage*. 2005;25(1):294-311.
- Damoiseaux JS, Rombouts SA, Barkhof F, et al. Consistent resting-state networks across healthy subjects. *Proc Natl Acad Sci U S A*. 2006;103(37):13848-13853.
- Filippini N, MacIntosh BJ, Hough MG, et al. Distinct patterns of brain activity in young carriers of the APOE-ε4 allele. *Proc Natl Acad Sci U S A*. 2009;106(17):7209-7214.
- Wang Z, Yan C, Zhao C, et al. Spatial patterns of intrinsic brain activity in mild cognitive impairment and Alzheimer's disease: a resting-state functional MRI study. *Hum Brain Mapp*. 2011;32(10):1720-1740.
- Bonavita S, Gallo A, Sacco R, et al. Distributed changes in default-mode resting-state connectivity in multiple sclerosis. *Mult Scler*. 2011;17(4):411-422.
- Hawellek DJ, Hipp JF, Lewis CM, Corbetta M, Engel AK. Increased functional connectivity indicates the severity of cognitive impairment in multiple sclerosis. *Proc Natl Acad Sci U S A*. 2011;108(47):19066-19071.
- Bonnelle V, Leech R, Kinnunen KM, et al. Default mode network connectivity predicts sustained attention deficits after traumatic brain injury. *J Neurosci*. 2011;31(38):13442-13451.
- Castellanos NP, Paul N, Ordóñez VE, et al. Reorganization of functional connectivity as a correlate of cognitive recovery in acquired brain injury. *Brain*. 2010;133(Pt 8):2365-2381.
- Catani M, Thiebaut de Schotten M. A diffusion tensor imaging tractography atlas for virtual in vivo dissections. *Cortex*. 2008;44(8):1105-1132.