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Reorganization of functional connectivity as a correlate of cognitive recovery in acquired brain injury

Nazareth P. Castellanos,[1] Nuria Paúl,[2] Victoria E. Ordóñez,[1] Olivier Demuynck,[3] Ricardo Bajo,[1] Pablo Campo,[1] Alvaro Bilbao,[4] Tomás Ortiz,[2] Francisco del-Pozo[1] and Fernando Maestú[1,5]

1 Laboratory of Cognitive and Computational Neuroscience, Centre for Biomedical Technology (CTB), Universidad Politécnica de Madrid, Madrid, 28660, Spain
2 Department of Psychiatric and Medical Psychology, Medicine School, Universidad Complutense de Madrid, 28040, Spain
3 Department of Signals, Systems and Radiocomunications, Universidad Politécnica de Madrid, 28040, Spain
4 National Centre for Brain Injury Treatment (CEADAC) Madrid, 28034, Spain
5 Department of Basic Psychology II – Cognitive Process, Universidad Complutense de Madrid, 28223, Spain

Correspondence to: Nazareth P. Castellanos,
Laboratory of Cognitive and Computational Neuroscience,
Centre for Biomedical Technology,
Campus de Montegancedo 28660,
Universidad Politécnica de Madrid,
Spain
E-mail: nazareth@pluri.ucm.es

Cognitive processes require a functional interaction between specialized multiple, local and remote brain regions. Although these interactions can be strongly altered by an acquired brain injury, brain plasticity allows network reorganization to be principally responsible for recovery. The present work evaluates the impact of brain injury on functional connectivity patterns. Networks were calculated from resting-state magnetoencephalographic recordings from 15 brain injured patients and 14 healthy controls by means of wavelet coherence in standard frequency bands. We compared the parameters defining the network, such as number and strength of interactions as well as their topology, in controls and patients for two conditions: following a traumatic brain injury and after a rehabilitation treatment. A loss of delta- and theta-based connectivity and conversely an increase in alpha- and beta-band-based connectivity were found. Furthermore, connectivity parameters approached controls in all frequency bands, especially in slow-wave bands. A correlation between network reorganization and cognitive recovery was found: the reduction of delta-band-based connections and the increment of those based on alpha band correlated with Verbal Fluency scores, as well as Perceptual Organization and Working Memory Indexes, respectively. Additionally, changes in connectivity values based on theta and beta bands correlated with the Patient Competency Rating Scale. The current study provides new evidence of the neurophysiological mechanisms underlying neuronal plasticity processes after brain injury, and suggests that these changes are related with observed changes at the behavioural level.

Keywords: brain injury; functional connectivity; magnetoencephalography; plasticity

Abbreviations: MEG = magnetoencephalograhy; PCRS = Patient Competency Rating Scale; WAIS = Wechsler Adult Intelligence Scale III

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Introduction

Brain plasticity has been described as the brain's ability to evolve, an intrinsic property of the nervous system that persists throughout life and plays an important role in maturity, development and acquisition of new skill processes. Importantly, plasticity becomes fundamental for functional recovery from a brain injury (Nudo, 1996, 2006; Leocani, 2006), being the mechanism underlying the potential capability of the brain to compensate for lesions. Acquired brain injury constitutes one of the leading causes of mortality and disability around the world, leaving motor and cognitive sequels that vary depending on aetiology, extent and severity of damage (Katz *et al*., 2006). In particular, cognitive deficits are the main sources of disability after traumatic brain injury and stroke, so rehabilitation strategies to promote their recovery and reduce their disability are needed (Cicerone *et al.*, 2000, 2005), and must be designed to take full advantage of plasticity (Butz *et al.*, 2009). In order to treat cognitive deficits, neuropsychological rehabilitation has been developed as a systematic, functionally oriented therapeutic intervention, based on the assessment and understanding of a patient's cognitive deficits, emotional or behavioural regulation problems and functional disabilities. Currently, it is possible to find a large amount of literature that supports the benefits of various types of cognitive interventions with traumatic brain injury patients (Cicerone *et al.*, 2000; 2005; Halligan and Wade, 2005; Katz *et al.*, 2006; McCabe *et al.*, 2007; Turner-Stokes, 2008). However, the debate is still open, as it is emphasized by Cicerone (Cicerone *et al.*, 2000) and Rholing's group (Rholing *et al.*, 2009) in their systematic reviews about the topic.

The study of the cerebral mechanisms underlying brain injury and their plastic changes could boost our knowledge about neural recovery. Nowadays, the increased use of neuroimaging techniques is enhancing our understanding of brain damage and neuronal plasticity (Wilson, 2008). Several works show evidence of neuronal reorganization following traumatic brain injury and recovery (for a review see Muñoz-Cespedes *et al*., 2005) but have also noted the heterogeneity of results from activation measures. Researchers have used a variety of tasks and techniques and consequently there is a corresponding diversity of results (Kelly *et al.*, 2006). It is necessary to study this problem from another point of view, probably by means of the changes in the interaction between brain areas, and not just by measurements of local changes in activation patterns.

A possible framework to study brain strategies for brain injury recovery is based on the idea that the brain is a complex network of dynamical systems with abundant interactions between local and more remote brain areas (Varela *et al*., 2001). More than a half century ago Hebb (1949) suggested that neuronal cortical connections can be remodelled by our experience. Since then, plasticity in the cerebral cortex has been studied in depth (Bennett *et al.*, 1964; Rosenzweig *et al.*, 1966; Kolb *et al.*, 1995), for example in learning (Merzenich *et al.*, 1984) and in response to brain lesions (Jenkins and Merzenich, 1987; Florence *et al.*, 1998). A focal brain lesion induces changes in adjacent and other remote, but interconnected, brain regions (Lee and van Donkelaar, 1995; Nudo, 1996; Witte and Stoll, 1997). A mechanism proposed as responsible for functional remodelling in local and distant brain regions could be the rewiring of its anatomical connections by retraining, compensating and/or substituting brain functioning (Wilson, 2008). A new approach is to study the impact of a lesion on the brain by means of the functional interactions ('functional connectivity') that take place between brain regions (Quigley *et al.*, 2001; Stam *et al.*, 2002; Salvador *et al.*, 2005). In the study of such interactions between brain areas the concept of functional connectivity has emerged, referring to the statistical interdependencies between physiological time series recorded in various brain areas simultaneously (Aertsen *et al.*, 1989). Functional connectivity is, probably, an essential tool for the study of brain functioning (Tononi and Edelman, 1998; Singer, 1999; Bressler, 2002; Varela *et al.*, 2001) and its deviation from healthy patterns could be used as an indication of lesion. Electroencephalographic and magnetoencephalographic (MEG) recordings have been shown to be reliable techniques for the study of functional connectivity (Varela *et al.*, 2001; Schnitzler and Gross, 2005, Guggisberg *et al.*, 2008). For example, functional connectivity from such continuous time series have demonstrated alterations in functional connectivity of Alzheimer's disease (Stam *et al.*, 2002), multiple sclerosis (Cover *et al.*, 2004, 2006) and patients with brain injury (Bartolomei *et al.*, 2006*a*; Douw *et al.*, 2008; Nakamura *et al.*, 2009; Cao and Slobounov, 2010).

The present study was developed with the aim of quantifying functional connectivity changes in patients with traumatic brain injury, who underwent resting-state MEG recordings following traumatic brain injury and after a rehabilitation treatment, compared with control subjects. We calculated, by means of the time averaged wavelet coherence, the interaction between the whole-head MEG signals (Figs 1A–C) in the standard frequency bands. To quantify differences with respect to those from healthy controls, we proposed a measure of distance-to-control connectivity patterns that helped us to study how altered these connectivity parameters were following a traumatic brain injury and how, as expected, they were after recovery. In order to link the neurophysiological evaluation of patients with their cognitive ability, we correlated changes in connectivity parameters with changes in neuropsychological test scores. Finally, network architecture in patients in both conditions were checked to see if they were distinguishable or not from control topology by means of a linear discriminant analysis (Fig. 1C), with the aim of evaluating whether reorganization of the network occurs during recovery. The current study would like to provide, for the first time, evidence of the neurophysiological mechanisms underlying the process of neuronal plasticity after brain injury, and test whether those changes in functional connectivity at the neurophysiological level are related with changes observed at the behavioural level.

Materials and methods

Subjects

The dataset was composed of 29 subjects: 15 patients with traumatic brain injury (recruited from a Rehabilitation Centre where they

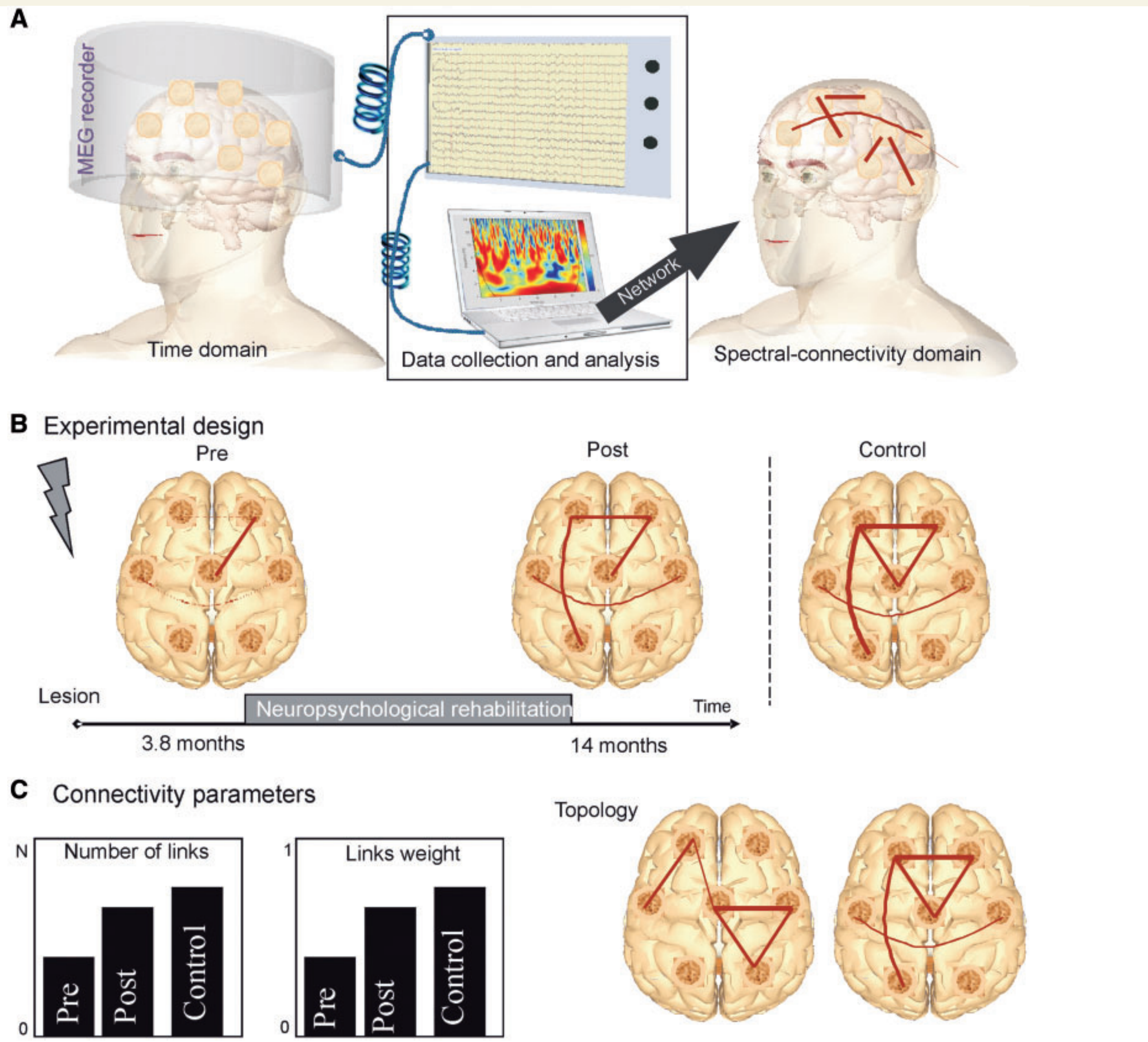


Figure 1 (**A**) Transformation from time domain (148 MEG time series are recorded) to Connectivity domain (a posterior connectivity analysis was performed in order to infer the functional connectivity between each pair of signals). (**B**) Illustration of experimental protocol and hypothesis: functional connectivity patterns from patients with traumatic brain injury were calculated a few months after injury (pre-rehabilitation condition). After a neuropsychological rehabilitation (post-rehabilitation) the connectivity pattern of the same group of patients was calculated. These pre- and post-rehabilitation networks were compared with those from the group of healthy controls. (**C**) Parameters defining a network: the number of links (3, 4 and 5 for pre-rehabilitation, post-rehabilitation and control networks in **B**, respectively) and the weight of these links (coded in the networks from **B** as the thick coupling lines). The proposed measure, distance-to-control connectivity pattern, $D^{\mathrm{control}}_{\mathrm{pre,post}}$ aims to quantify differences by means of both connectivity parameters (number and weight). We hypothesize that connectivity parameters of post-rehabilitation networks are closer than pre-rehabilitation networks to those parameters of control networks (illustrative bar diagrams), i.e. $D^{\mathrm{control}}_{\mathrm{post}} < D^{\mathrm{control}}_{\mathrm{pre}}$. Differences between patient and control group networks could also be due to differences in the topology (architecture) of the network. We show two examples of topologies where the connectivity parameters such as number of links (5 in this case) and weight (all lines have the same thickness) are equivalent but their architectures are very different. Linear discriminant analysis aims to capture differences in the sense of topology.

underwent a neurorehabilitation) and 14 healthy controls. Patients had suffered severe traumatic brain injury, according to the period of post-traumatic amnesia (Lishman, 1968). All patients showed severe cognitive impairments in several domains such as attention, memory and executive function. Mean age of the patients was 32.13 years (18, 51), and the mean level of education was 13.7 years (8, 18). Mean time since injury at the beginning of the study was 3.8 months (2, 6), and the neurorehabilitation program lasted for an averaged period of 9.4 months (7, 12). Values in brackets refer to range. Table 1 summarizes the demographic and clinical profile of the patients. Experimental and healthy control groups were matched for age (31.93), educational level (15.57) and gender. Exclusion criteria for the selection of all participants included previous medical history of psychiatric disease and extended psychoactive drug consumption.

Patients had MEG recordings and neuropsychological assessments (done close to the day of MEG recording) before and after the neuropsychological rehabilitation program (hereafter called 'pre-' and 'post-' rehabilitation). In this study control subjects

Table 1 Demographic and clinical profile of patients included in the study

Patient no.	Sex	Age	Years of education	Aetiology	Location of lesion
1	M	26	17	Traumatic brain injury	RF, DAI, THAL,
2	M	30	11	Traumatic brain injury	LF, LT
3	M	25	16	Traumatic brain injury	BF, BT, LC, DAI,
4	M	18	11	Traumatic brain injury	DAI, BT, BF
5	M	33	8	Traumatic brain injury	RC, DAI
6	M	19	12	Traumatic brain injury	RF, RT, RO
7	F	51	9	Traumatic brain injury	LF, DAI, RT
8	M	41	15	Traumatic brain injury	R HEMIPH, LF
9	M	22	17	Traumatic brain injury	BF, LT, DAI
10	M	44	14	Traumatic brain injury	BF, DAI
11	M	21	14	Traumatic brain injury	BF, RC, T, DAI
12	M	48	18	Traumatic brain injury	LC, RF, R BG
13	M	28	10	Traumatic brain injury	DAI, FR, R BG
14	M	48	17	Traumatic brain injury	BF, LC, LT, L THAL
15	F	28	17	Traumatic brain injury	BF, RC, RT, DAI

M = male; F = female; R = right; L = left; B = bilateral, F = frontal; T = temporal; C = central; O = occipital; DAI = diffuse axonal injury; THAL = thalamus; BG = basal ganglia.

were measured once, assuming that brain networks do not change in their structure in less than one year, as demonstrated previously in young (Damoiseaux *et al.*, 2006) and elderly subjects (Beason-Held *et al.*, 2009).

All participants or legal representatives gave their written informed consent to participate in the study. The study was approved by the Local Ethics Committee.

Neuropsychological rehabilitation program and neuropsychological assessment

All study patients completed a neurorehabilitation program that was adapted to each individual's requirements. This program was conducted in individual sessions attempting to offer an intensive neuropsychological-based rehabilitation, provided in 1 h sessions for 3–4 days a week. In some cases, cognitive intervention was coupled with other types of neurorehabilitation therapies according to the patient's profile (physiotherapy, speech therapy or occupational therapy). Depending on the severity and deficit features of each case, strategies of restitution, substitution and/or compensation were applied as well as training in daily living activities, external aids or the application of behavioural therapy. Patients and controls underwent a neuropsychological assessment, in order to establish their cognitive status in multiple cognitive functions (attention, memory, language, executive functions and visuospatial abilities) as well as their functioning in daily life. All subjects completed the Wechsler Adult Intelligence Scale III (WAIS-III; Wechsler, 1997), the Wechsler Memory Scale Revised (Wechsler, 1987), the Brief Test of Attention (Schretlen, 1997), the Trail Making Test (Reitan, 1992), the Stroop Colour Word Test (Golden, 1978), the Wisconsin Card Sorting Test (Heaton,1991), the Verbal Fluency Test (Gladsojo *et al.*, 1999), the Tower of Hanoi (Édouard, 1983), the Zoo Map Test (from the Behavioral Assessment of the Dysexecutive Syndrome; Wilson *et al.*, 1996) and the Patient Competency Rating Scale (PCRS; Prigatano *et al.*, 1991). This last scale is formed from 30 items related to different daily living activities (basic and instrumental activities as well as social skills and cognitive and emotional issues) and the patient's level of competency on a five-point Likert scale.

Magnetoencephalographic recordings

Magnetic fields were recorded using a 148-channel whole-head magnetometer (4D-MAGNES® 2500 WH, 4-D Neuroimaging) confined in a magnetically shielded room. Raw data were collected using a sampling rate of 169.45 Hz and band-pass filtered between 0.1 and 50 Hz. MEG data were submitted to an interactive environmental noise reduction procedure. Fields were measured during a no task eyes-open condition. Time-segments containing eye movement or blinks (as indicated by peak-to-peak amplitudes in the electro-oculogram channels in excess of 50 μV) or other myogenic or mechanical artefacts were rejected and time windows not containing artefacts were visually selected by experienced investigators, up to a segment length of 12 s. Digitized MEG data were imported into MATLAB Version 7.4 (Mathworks, Natick, MA, USA) for analysis with custom-written scripts.

Analysis

Wavelet coherence

Wavelet transform can be used as an alternative to Fourier transform for the performance of time-spectral analysis when dealing with non-stationary time series (Mallat, 1998). By using wavelet transform, we can perform a time-frequency analysis of rhythmic components in a MEG signal, and hence estimate the wavelet coherence for a pair of signals, a normalized measure of association between two time series (Torrence and Compo, 1998; Grinsted *et al.*, 2004). The global wavelet coherence, C^G_{xy}, can be obtained by time averaging local (time-dependent) coherence

$$C^G_{xy}(p) = \frac{1}{T}\int_0^T C_{xy}(p,z)dz$$

where $C_{xy}(p,z)$ is the wavelet coherence between signals $x(t)$ and $y(t)$ at the p scale and z time-localization, T is the length of the signal (Percival, 1995) with time-predominant connectivity values. To evaluate the significance level we use a surrogate data test (Theiler *et al.*, 1992; Schreiber and Schmitz, 2000, Korzeniewska *et al.*, 2003) with Monte Carlo simulation to establish a 95% confidence interval and avoid spurious couplings. Global wavelet coherence, C^G_{xy}, was then averaged in the following frequency bands: δ (1–4) Hz, θ (4–8) Hz, α (8–13) Hz and β (13–30) Hz for all combinations of the 148 signals. Further spatial averaging in whole head was done: in frontal, central, right and left temporal and occipital regions to obtain local connections within a brain area, and long-distance connections between two different brain regions (frontal and central; frontal and right temporal; frontal and left temporal; frontal and occipital; central and right temporal; central and left temporal; central and occipital; right temporal and left temporal; occipital and right temporal; occipital and left temporal).

To quantify the possible restoration of functional connectivity patterns, we defined a measure of distance between connectivity matrices of patients and control groups. This measure combines both parameters defining the connectivity matrices, the number of connections (density of existing links) and their weight. This measure quantifies the percentage of increase (or decrease) with respect to control connectivity parameters. Distance-to-control connectivity pattern is therefore given by:

$$D_{\text{post}}^{\text{control}} = \frac{BC_{\text{control}} - BC_{\text{post}}}{BC_{\text{control}}} + \frac{WC_{\text{control}} - WC_{\text{post}}}{WC_{\text{control}}}$$

A similar equation is defined for $D_{\text{pre}}^{\text{control}}$. This measure was calculated separately for each local and long-distance connection and each frequency band. Small values of $D_{\text{pre,post}}^{\text{control}}$ indicate that patient's connectivity pattern parameters were close to those shown by the control group, and hence restoration of functional connectivity had taken place; whereas large values of $D_{\text{pre,post}}^{\text{control}}$ suppose deviation from control parameters. We hypothesize that the connectivity pattern parameters of post-rehabilitation condition will be closer to the parameters of healthy controls than those exhibited by patients following a brain injury, i.e. $D_{\text{post}}^{\text{control}} < D_{\text{pre}}^{\text{control}}$. The procedure is illustrated in Figs 1B and C.

Linear discriminant analysis

Connectivity pattern parameters (such as number of connections and their weight) could be just one of the causes of differences in functional connectivity between patients' conditions and healthy controls, as quantified above by $D_{\text{pre,post}}^{\text{control}}$. However, there could also be differences related to the network architecture (Fig. 1C). To study how the network topology reorganizes in both patient conditions, we utilized a discriminant technique able to identify subjects as separated groups according to the network topology. For this purpose Fisher-LDA has been proposed as an information reduction technique which preserved the discriminant data for classification, emerging from the question of how labelled information can be utilized for finding informative projections (Ripley, 1996; Jaakkola and Haussler, 1999; Huan and Ramaswamy, 2004; Maindonald and Braun, 2007; Lehmanna *et al.*, 2007). The solution of Fisher-discriminant is the election of a specific direction to project data into one-dimensional space. As a measure of distance between centres of groups the statistic D2 of Mahalanobis was used, calculated from the variance–covariance matrix.

Statistical analysis

In order to increase statistical power and reduce the effect of non-Gaussian distribution, we normalized connectivity values by means of a logarithmic transformation (Gasser *et al.*, 1982; Pivik *et al.*, 1993). A Kruskal–Wallis test was used to compare control, pre- and post-rehabilitation conditions at $P < 0.05$ (see Brookes *et al.*, 2005; Kilner *et al.*, 2009; Campo *et al.*, 2010, for a similar statistical approach). Neuropsychological data were analysed using the statistical program SPSS 15.0, and ANOVA analysis ($P < 0.05$) was used in order to identify differences among the control group and each stage (pre- and post-rehabilitation) of the patient group.

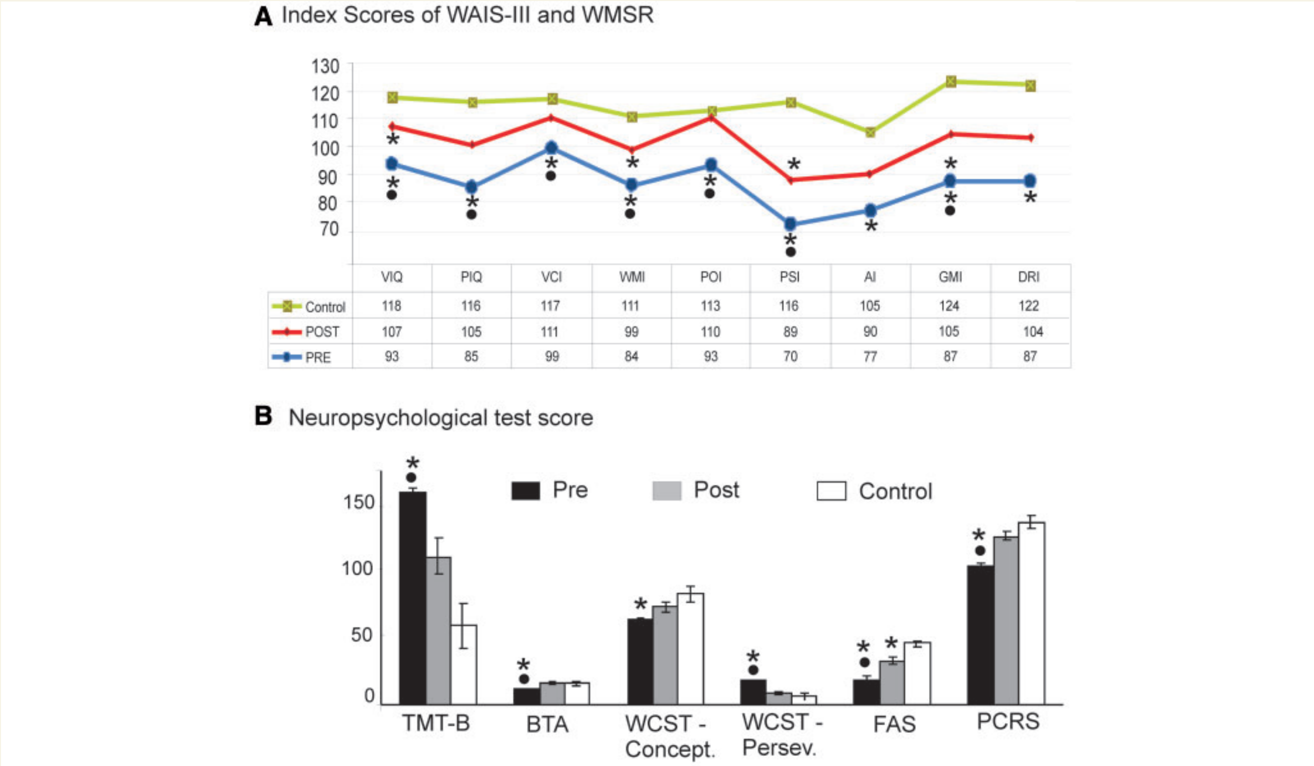
Results

Neuropsychological results

Pre-rehabilitation results in the neuropsychological assessment indicate that patients with traumatic brain injury had scores that were statistically lower compared with both control subjects and patients post-rehabilitation in most of the tests used (asterisks and points in Figs 2A and B). All neuropsychological results at post-rehabilitation followed a trend towards improvement in comparison with pre-execution in the tests analysed (better performance and reaction time reduction). Post-rehabilitation results are statistically similar to those of controls in most of the tests (asterisks in Figs 2A and B). Regarding the cognitive processes implicated in the results obtained, there was a statistical improvement in attentional skills (Trail Making Test and Brief Test of Attention), memory processes (Wechsler Memory Scale Revised, Working Memory Index), executive functions (Wisconsin card sorting test) and PCRS. In addition, some measures of the post-assessment relating to attention, memory and executive functions did not show statistically significant differences with the control group. The recovery effect has been produced in five of six tests exposed (Fig. 2B) and five of nine global indexes (Fig. 2A).

Distance-to-control connectivity pattern

We have proposed a measure of distance-to-control connectivity pattern, which takes into account the two parameters defining the connectivity pattern: number and weight of connections, as defined by $D_{\text{pre,post}}^{\text{control}}$. Figure 3 shows the distance-to-control parameters in patients before, $D_{\text{pre}}^{\text{control}}$ (lower panels), and after rehabilitation, $D_{\text{post}}^{\text{control}}$ (upper panels), for each local and long-distance link, per spectral band. The most remarkable results are found in the delta spectral band, where distance-to-control reaches greater reductions from the pre- to the post-rehabilitation group. The highest $D_{\text{pre}}^{\text{control}}$ are localized in local connections within central (62% higher than control) and right temporal (66%) regions and in long-distance connections as right temporal–central (60%), right temporal–frontal (55%), central-occipital (50%) and frontal-central (57%). Connections where the highest reduction in distance-to-control occurred were: 57% from $D_{\text{pre}}^{\text{control}}$ to $D_{\text{post}}^{\text{control}}$ within right temporal with $D_{\text{post}}^{\text{control}}$ 2.7%, being the lowest value and hence the most close to control values; 68% in occipital where $D_{\text{post}}^{\text{control}}$ converged to 13%; 59% in frontal; 72% in frontal-right temporal leading $D_{\text{post}}^{\text{control}}$ to 8%; 69% in left temporal–occipital where $D_{\text{post}}^{\text{control}}$ reached 11%; 60% in frontal-left temporal; 82% in frontal-occipital; 53% in frontal-central; and 67% in occipital-central. Pre-rehabilitation distance-to-control, $D_{\text{pre}}^{\text{control}}$, in the delta band had a negative sign, i.e. both the number of connections and their weight in pre-rehabilitation patients are higher than in controls, a contrary effect to that which occurred in the other frequency bands, principally in the alpha spectral band. The main difference with the controls in theta-based distance-to-control is localized in connections within frontal (35%) and occipital (64%) that decreases after rehabilitation to 41 and 13%, respectively. The lower $D_{\text{post}}^{\text{control}}$ occurs in frontal-right temporal (7%), frontal-left temporal (3%) and frontal-occipital (10%) connections, with a reduction of 30, 58 and 18% with respect to the pre-rehabilitation group value. In the alpha spectral band, the higher $D_{\text{pre}}^{\text{control}}$ is localized in occipital-right temporal (49%), occipital-left temporal (45%), frontal-left temporal (62%) and right temporal–left temporal (55%) connections. A considerable reduction in distance-to-control is found in right temporal–central (28%), left temporal–central (72%), frontal-central (55%) and right temporal–left temporal (71%) connections. The lower $D_{\text{post}}^{\text{control}}$ values



	VIQ	PIQ	VCI	WMI	POI	PSI	AI	GMI	DRI
Control	118	116	117	111	113	116	105	124	122
POST	107	105	111	99	110	89	90	105	104
PRE	93	85	99	84	93	70	77	87	87

Figure 2 (**A**) Means of the general scores in the WAIS-III and some indexes of the Wechsler Memory Scale–R pre- (blue line) and post-rehabilitation (red line) and in controls (green line). VIQ = verbal IQ; PIQ = performance IQ; VCI = Verbal Comprehension Index; WMI = Working Memory Index; POI = Perceptual Organization Index; PSI = Processing Speed Index. AI = Attention Index; GMI = General Memory Index; DRI = Delayed Recall Index. (**B**) Means and statistical differences of some neuropsychological scores pre- and post-rehabilitation and for the control group. Asterisk indicates a statistically significant difference ($P < 0.05$) with the control group, and black dot indicates a statistically significant difference between pre- and post-rehabilitation stages. TMT-B = Trail Making Test-B (time in seconds); BTA = Brief Test of Attention (total score); WCST-Concept = percentage total score of conceptual level; WCST-Persev = percentage total score of perseverative responses; FAS = Verbal Fluency Test (phonetic verbal fluency total score); PCRS = daily living competency (total score).

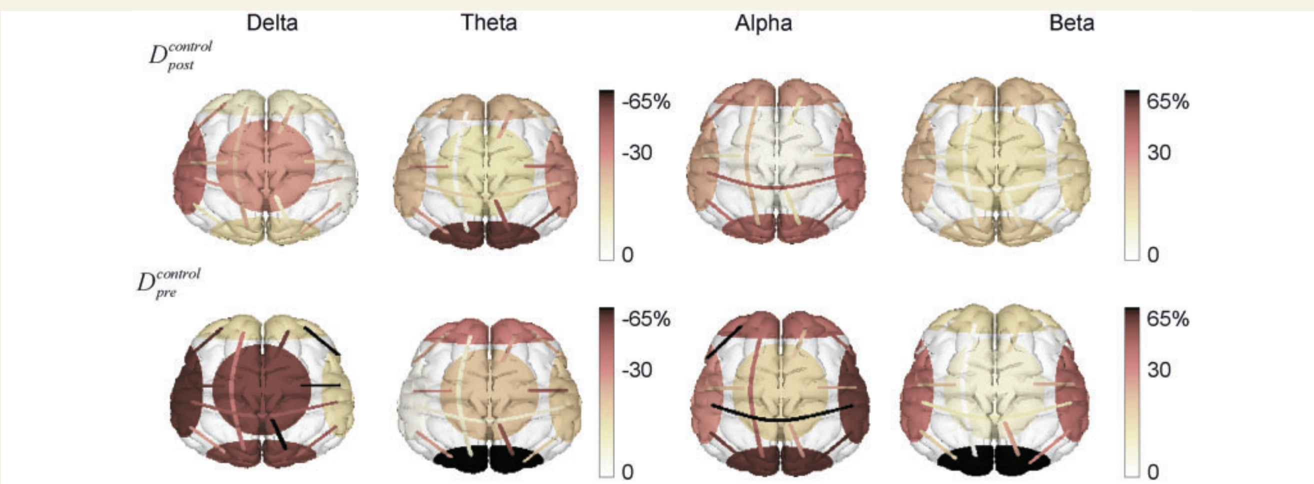


Figure 3 Distance-to-control connectivity patterns from patients pre- (lower panels) and post-rehabilitation (upper panels) per frequency band, $D_{\mathrm{pre}}^{\mathrm{control}}$ and $D_{\mathrm{post}}^{\mathrm{control}}$, respectively. This measure quantifies the percentage of increase (or decrease) with respect to control connectivity parameters. Colour intensity corresponds to the distance-to-control values. Small values of $D_{\mathrm{pre,post}}^{\mathrm{control}}$ indicate that a patient's connectivity pattern parameters are close to those showed by the control group, whereas large values of $D_{\mathrm{pre,post}}^{\mathrm{control}}$ suppose deviation from control parameters.

are localized in connections within central area (8%), frontal-central (7.5%), right temporal–central (6.8%), left temporal–central (7.6%) and occipital-central (8.2%). In the beta spectral band the highest $D_{\text{pre}}^{\text{control}}$ value occurs in connections within frontal (57%), occipital (51%) and frontal-left temporal (54%) areas. The highest reduction occurs in right temporal–central (68%) and frontal (48%) connections. Couplings reaching the lower $D_{\text{post}}^{\text{control}}$ are connections within central (3.6%), frontal-central (3.4%), right temporal–central (14%), left temporal–central (13%) and occipital-central (3.5%) areas.

Distance-to-control connectivity pattern has two contributions: weight and number of connections; changes in these features induce the reductions of $D_{\text{post}}^{\text{control}}$ previously described. The degree of contribution of each parameter over such distance reduction could reflect the mechanism of recovery after traumatic brain injury. To study and quantify this phenomenon, we calculated the percentage of contribution of number or weight of connections over $D_{\text{pre}}^{\text{control}}$and $D_{\text{post}}^{\text{control}}$ as well as the changes of each parameter from pre- to post-rehabilitation. We defined as responsible the mechanism of recovery (to that parameter with a statistically greater reduction from pre- to post-rehabilitation) having a non-dominant contribution degree to $D_{\text{post}}^{\text{control}}$. Figure 4C shows the percentage of contribution of the number of connections over the $D_{\text{pre}}^{\text{control}}$in all frequency bands and areas. Both number and weight parameters contribute equally (around 50% each one) to $D_{\text{pre}}^{\text{control}}$, i.e. the number and weight of connections increase or decrease simultaneously after traumatic brain injury in the majority of the brain area connections and in different frequency bands. Only in the beta frequency band can we observe a predominance of the number of connections for frontal-central, right temporal–central and left temporal–central areas coupling. However, in post-rehabilitation, one of these connectivity parameter components has a greater contribution to recovery (distance-to-control reduction) than the other one. Local connections in delta-based connectivity inside the frontal area experienced a reduction of distance-to-control from pre-rehabilitation values of 59%, leading $D_{\text{post}}^{\text{control}}$= 10%, where only 9% is caused by differences in the number of couplings with respect to control values. This parameter has been reduced by 82% from pre-rehabilitation values, concluding that the reduction in the

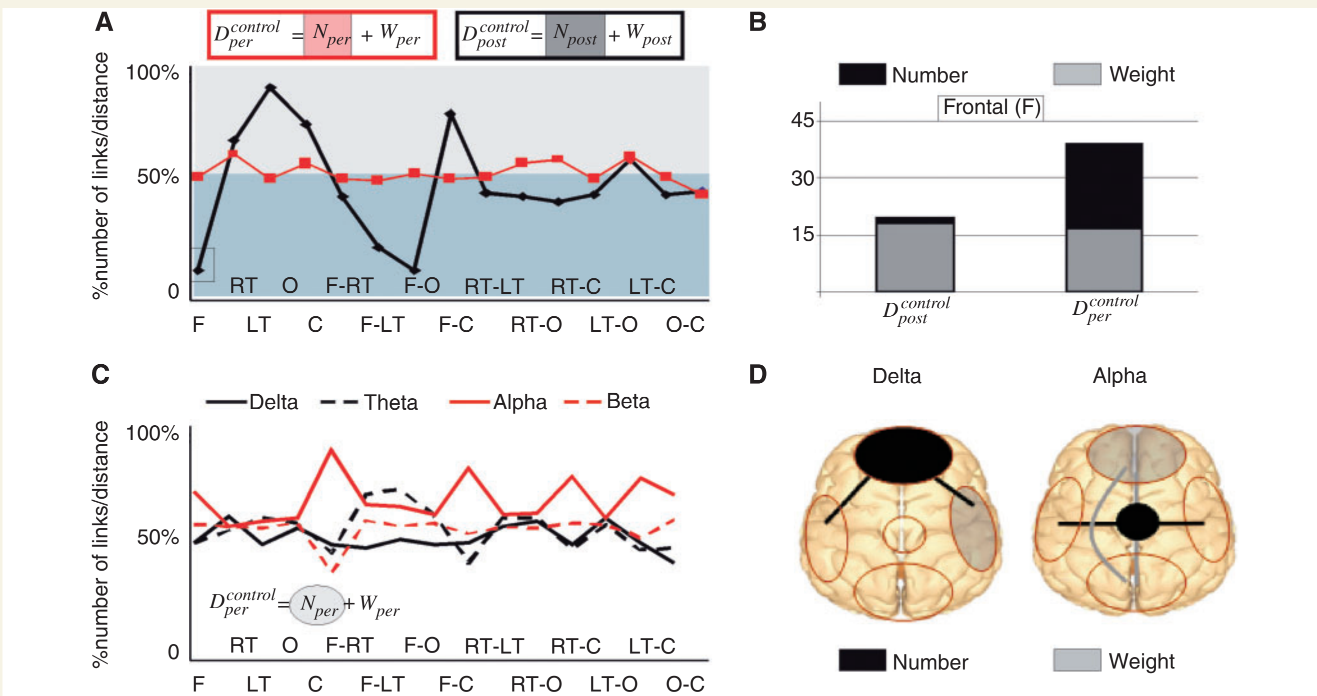


Figure 4 Since distance-to-control depends on both number and weight of coupling, we can study which connectivity parameter is responsible for distance reduction. The responsible mechanism for recovery is defined as the parameter which has a greater reduction of its statistical values from pre- to post-rehabilitation, with a non-dominant contribution degree in $D_{\text{post}}^{\text{control}}$. (**A**) Percentage of contribution of the number of connections over $D_{\text{pre}}^{\text{control}}$ (red line) and $D_{\text{post}}^{\text{control}}$ (black line) for the delta spectral band. Both parameters equally contribute (~50%) to $D_{\text{pre}}^{\text{control}}$. However, a non-equivalent behaviour is found in $D_{\text{post}}^{\text{control}}$, i.e. depending on the connections in brain areas, one of the parameters contribute more than the other over $D_{\text{post}}^{\text{control}}$. (**B**) For illustrative purposes, we show the detailed case of distance-to-control reduction in local connection for the frontal area. Number and weight equally contribute to $D_{\text{pre}}^{\text{control}}$, while post-rehabilitation connectivity parameters change in a different way from ones pre-rehabilitation. Whereas the weight of coupling remains practically invariant, the number of connections reduces by 93%. We can conclude, in this case, that the reduction in the number of links within the frontal area is the responsible mechanism of recovery. (**C**) Percentage of contribution of the number of connections over $D_{\text{pre}}^{\text{control}}$ for all frequency bands and brain regions. For most brain areas both number and weight of connections increase (or decrease) simultaneously after traumatic brain injury. (**D**) Mechanism responsible for reduction in $D_{\text{post}}^{\text{control}}$ in the delta and alpha spectral bands. C = central; F = frontal; LT = left temporal; O = occipital; RT = right temporal.

number of links in the frontal region is the responsible phenomenon of distance-to-control reduction (example illustrated in Fig. 4A and B). Additionally, local connections in temporal lobes approached control values with reductions of distance-to-control of 68, 56 and 65% for right temporal, frontal-right temporal and frontal-left temporal, respectively. $D_{post}^{control}$ in right temporal local connections is caused mainly by the number of connections with a 70% contribution of this parameter over $D_{post}^{control}$, whereas the number of connections with the frontal regions is the one that causes a $D_{post}^{control}$ of 65 and 82%, respectively. The responsible mechanism of recovery for right temporal is the reduction in the coupling weight, as opposed to left and right temporal and frontal interactions for which the number of links is responsible. In the alpha spectral band, the number of links reduce the distance-to-control of local connections inside central (this parameter reduces 45%) and right temporal–occipital and left temporal–occipital areas, with reductions of 59 and 47%, respectively. Weight is the responsible mechanism for local connections inside frontal (55% of reduction from pre- to post-rehabilitation values), while occipital-frontal and occipital-central connections decrease to 48 and 66%, respectively. Figure 4B summarizes the results for the delta and alpha bands. No statistically significant responsible mechanism was found in the theta frequency band. In the beta spectral interval, we found a reduction of the weight of local connections in the central area (not shown).

Statistical test *P*-values for number and weight couplings are shown in Table 2.

Correlation between connectivity parameters and neuropsychological test score changes

Further *post hoc* analyses were performed to explore whether changes in the neuropsychological test scores of patients were related to changes in functional connectivity for all frequency bands. The correlations were computed for changes between pre- to post-rehabilitation connectivity parameters and the neuropsychological results of each group. Subsequently, Pearson's correlation coefficients were calculated and *t*-tests were performed ($P < 0.001$). For the delta band, significant negative correlations were found between the Verbal Fluency Test and weight connectivity changes between brain areas (Fig. 5A): frontal-right temporal ($R = -0.69$), central-left temporal ($R = -0.72$), central-right temporal ($R = -0.72$), occipital-right temporal ($R = -0.71$), frontal-occipital ($R = -0.71$), right temporal ($R = -0.75$). Thus the higher the reduction on delta band-based connectivity, the higher the improvement at post-rehabilitation. Alternatively, in the theta band, significant negative correlations were found between PCRS score and the number of neural connections (Fig. 5B): frontal-central ($R = -0.81$), frontal-central in correlation with weight changes ($R = -0.7$), central-left temporal ($R = -0.76$), central-right temporal ($R = -0.76$), occipital-central ($R = -0.70$), occipital-central in correlation with weight changes ($R = -0.7$) and central ($R = -0.68$). For the alpha band, significant positive correlations were found between the Perceptual Organization Index and the connectivity parameters in some brain areas (Fig. 6A): frontal-central number of connections ($R = 0.65$), central-left temporal number of connections ($R = 0.81$), central-right temporal number of connections ($R = 0.68$) and central connection weight ($R = 0.71$). The alpha band also showed significant positive correlations between the Working Memory Index (WAIS-III) and the number of connections in specific brain areas (Fig. 6B): frontal-left temporal ($R = 0.82$), frontal-right temporal ($R = 0.7$), frontal-occipital ($R = 0.84$), frontal-central ($R = 0.72$), frontal ($R = 0.77$) and central ($R = 0.7$). Finally, regarding the beta band, significant positive correlations were found between the PCRS score and brain area connectivity parameters (Fig. 7): frontal-central connection weight ($R = 0.74$), central-left temporal connection weight ($R = 0.79$), central-left temporal number of connections ($R = 0.74$), central-right temporal connection weight ($R = 0.74$), occipital-central connection weight ($R = 0.77$), occipital-central number of connections ($R = 0.77$) and central connection weight ($R = 0.72$).

Topology discrimination

The architecture of the functional connectivity network may be a discriminant population characteristic. To capture the differences in connectivity pattern topology we use linear discriminant analysis as a dimension reduction technique able to classify each person as belonging to an identified group. Values of Fisher are checked to see if they are significantly different, in order to be able to enumerate those connecting areas where pre-rehabilitation Fisher values are distinguishable from post-rehabilitation and control Fisher values, but post-rehabilitation Fisher values are indistinguishable from control Fisher values (grey line in Fig. 8). However, we also mark those areas where the recovery phenomenon is not complete; pre-rehabilitation Fisher values are distinguishable from post-rehabilitation and control Fisher values, but post-rehabilitation Fisher values are not indistinguishable from control Fisher values yet (black line in Fig. 8). Long connections experience more improvement in the delta frequency band. The wiring reorganization after treatment makes the topology of post-rehabilitation patients' networks more similar to the control networks topology when compared with the pre-rehabilitation patients' topology within the following areas: right temporal–left temporal, right temporal–central, frontal-central, frontal-occipital and right temporal–occipital. In the theta spectral band the sub-networks reaching a complete restoration and then becoming indistinguishable are those involving the frontal-right temporal, frontal-occipital, frontal-central, left temporal–central and central areas. In the alpha frequency band the links between frontal-left temporal, frontal-occipital and right temporal–central areas reach indistinguishable separating values, and the network topology within the central area experiences an incomplete phenomenon. In the beta spectral band, reorganization leads to restoring topologies in local networks within frontal and occipital areas, as well as frontal-occipital, frontal-right temporal and frontal-left temporal areas, whereas reorganization in the right temporal area has an incomplete recovery.

Table 2 ***P*-values from Kruskal–Wallis statistical test, comparing Control and Pre-, Control and Post-; and Post- and Pre-connectivity parameters (number and weight of connections) per frequency band and areas coupled**

Area	Parameter	Delta (1–4) Hz			Theta (4–8) Hz			Alpha (8–12) Hz			Beta (12–30) Hz		
		Control-Pre	Control-Post	Post-Pre	Control-Pre	Control-Post	Post–Pre	Control-Pre	Control-Post	Post–Pre	Control-Pre	Control-Post	Post–Pre
F	Number	**0.001**	0.45	**0.03**	0.47	0.83	0.69	0.23	0.5	**0.02**	0.096	0.6	0.12
	Weight	**0.024**	0.37	**0.004**	**0.003**	0.76	**0.002**	0.13	0.56	**0.007**	0.27	0.47	0.12
RT	Number	**0.011**	0.58	**0.045**	0.16	0.43	0.53	**0.023**	0.51	**0.005**	0.21	0.35	0.46
	Weight	**0.026**	0.09	0.071	**0.003**	0.36	**0.001**	0.12	0.46	0.13	**0.031**	0.11	0.1
LT	Number	0.27	0.81	0.16	0.17	0.66	**0.0005**	**0.013**	0.33	**0.022**	0.068	0.13	0.25
	Weight	0.24	0.45	0.21	0.12	0.43	0.35	**0.012**	0.41	**0.009**	0.17	0.32	0.52
O	Number	0.057	0.45	**0.008**	0.21	0.71	0.39	0.07	0.25	0.27	0.06	0.28	0.2
	Weight	0.058	0.13	0.08	**0.005**	0.32	0.28	**0.014**	0.68	**0.005**	**0.023**	0.28	0.15
C	Number	**0.025**	0.17	**0.04**	0.27	0.35	0.17	0.24	0.64	0.33	0.25	0.61	**0.04**
	Weight	**0.022**	0.61	0.09	0.21	0.68	0.16	0.28	0.79	0.27	0.44	0.35	0.12
F-RT	Number	**0.024**	0.25	0.43	0.55	0.17	0.23	0.1	0.61	0.15	0.22	0.47	0.57
	Weight	**0.031**	0.79	**0.018**	0.81	0.91	0.78	**0.019**	0.4	0.055	0.27	0.59	0.52
F-LT	Number	**0.032**	0.69	0.08	0.36	0.24	0.4	0.11	0.68	0.11	**0.004**	0.38	0.31
	Weight	0.076	0.59	**0.042**	0.35	0.32	0.43	0.08	0.75	0.12	**0.01**	0.29	**0.03**
F-O	Number	**0.045**	0.67	0.053	0.36	0.07	**0.015**	**0.047**	0.41	0.26	0.07	0.36	0.44
	Weight	0.110	0.71	0.089	0.86	0.6	0.55	0.051	0.57	0.06	**0.004**	0.16	**0.03**
F-C	Number	**0.0006**	0.68	**0.019**	0.38	0.18	0.89	0.12	0.32	0.31	0.68	0.44	0.74
	Weight	**0.0005**	0.82	**0.0057**	0.25	0.16	0.89	0.25	0.64	0.41	0.33	0.79	0.64
RT-LT	Number	0.06	0.71	0.009	0.10	0.29	0.08	**0.041**	0.31	0.12	0.11	0.19	**0.005**
	Weight	0.07	0.81	**0.025**	0.53	0.53	0.65	**0.034**	0.29	0.1	0.12	0.09	0.55
RT-O	Number	**0.045**	0.6	**0.027**	0.22	0.37	0.32	**0.047**	0.2	**0.02**	**0.01**	0.58	0.1
	Weight	0.065	0.85	**0.011**	0.51	0.19	0.22	0.051	0.16	0.53	0.12	0.28	0.46
RT-C	Number	**0.011**	0.47	**0.043**	0.08	0.47	0.25	0.11	0.57	0.14	0.52	0.57	0.22
	Weight	**0.0006**	0.49	**0.011**	0.06	0.5	0.18	0.16	0.51	0.19	0.35	0.85	0.71
LT-O	Number	0.064	0.75	**0.016**	**0.001**	0.35	**0.002**	**0.017**	0.29	**0.041**	0.04	0.17	**0.04**
	Weight	0.07	0.61	**0.001**	0.23	0.33	0.52	**0.03**	0.25	0.11	0.08	0.21	0.05
LT-C	Number	**0.008**	0.62	**0.029**	**0.05**	0.25	0.12	0.15	0.54	0.27	0.35	0.29	0.32
	Weight	**0.008**	0.42	0.051	0.21	0.71	**0.02**	0.23	0.54	0.43	0.08	0.66	0.56
O-C	Number	**0.01**	0.68	**0.043**	0.25	0.25	0.09	0.12	0.51	0.27	0.55	0.77	0.66
	Weight	**0.01**	0.18	**0.011**	0.19	0.44	0.23	0.21	0.57	0.31	0.61	0.64	0.71

C = central; F = frontal; LT = left temporal; O = occipital; RT = right temporal; Pre = pre-rehabilitation; Post = post-rehabilitation.
Statistical differences ($P < 0.05$) are in boldface.

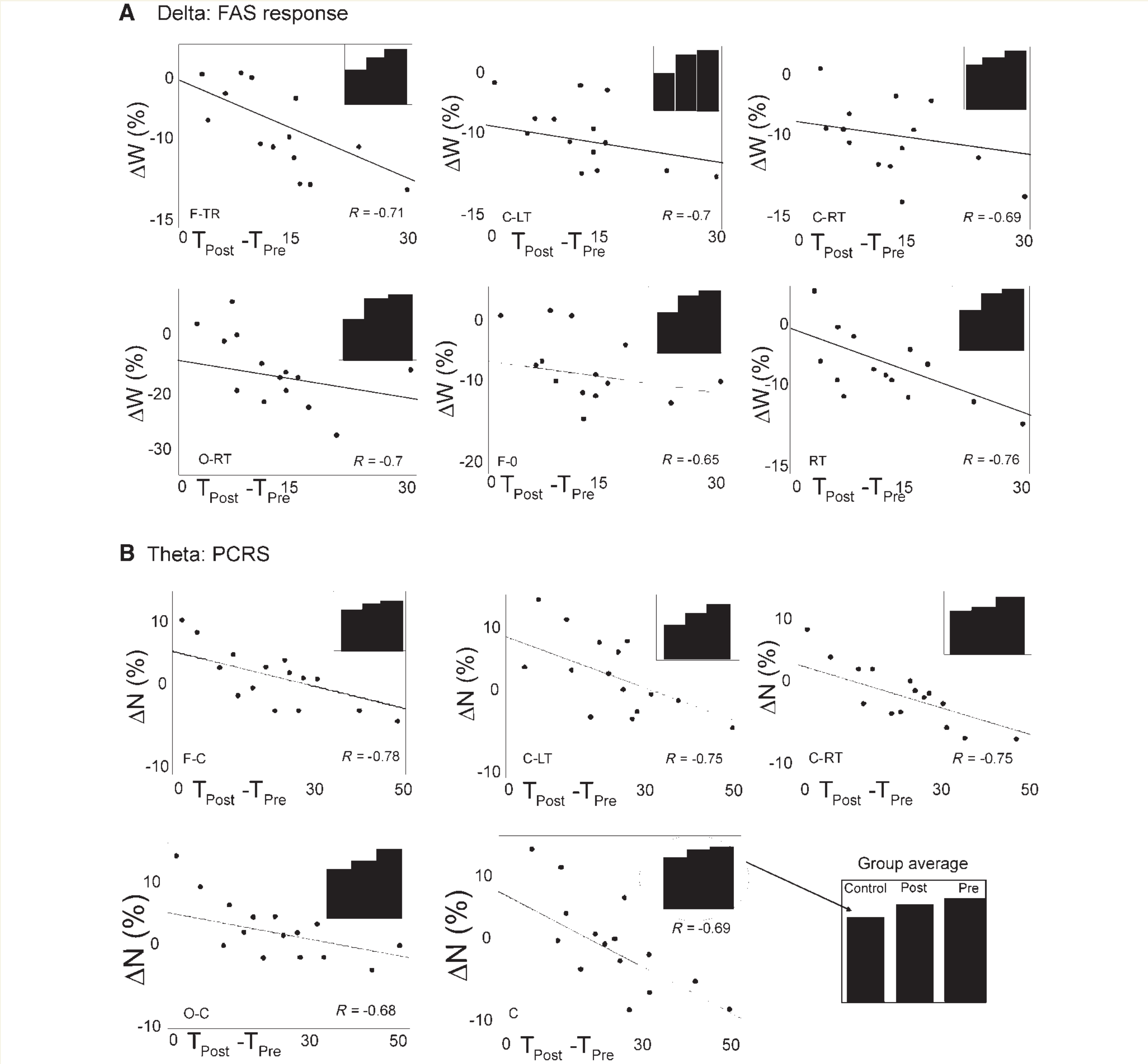


Figure 5 Correlations between changes in connectivity parameters ($\Delta N = N_{Post} - N_{Pre}$ and $\Delta W = W_{Post} - W_{Pre}$) and changes in neuropsychological test scores($T_{Post} - T_{Pre}$). (**A**) Changes in the weight of coupling in the delta spectral band-based connectivity correlates with changes in Verbal Fluency Test (FAS) score. (**B**) Changes in the number of links in the theta spectral band-based connectivity pattern correlate with changes in PCRS test scores. Bar diagrams show the average of the corresponding connectivity parameters (weight and number for delta and theta bands, respectively) of the control group and patients post- and pre-rehabilitation. In slow spectral bands (delta and theta) an increase of the number and weight of couplings is noticed in pre-rehabilitation connectivity pattern, whereas post-rehabilitation connectivity parameters are similar to controls. This progressive decrease in connectivity parameter values from pre-rehabilitation to control reference agree with the negative correlation found. C = central; F = frontal; LT = left temporal; O = occipital; RT = right temporal.

Discussion

In this study we were able to add to our knowledge about the neurophysiological mechanisms underlying brain plasticity that enable restoration of function after damage. Thus, by recording biomagnetic activity from patients following a traumatic brain injury (pre-rehabilitation) and after (post-) rehabilitation, as well as activity from age-matched control subjects, it was possible to describe changes in functional connectivity at the neurophysiological level related to changes observed at the behavioural level. Connectivity profiles for the control and post-rehabilitation groups' connectivity patterns were more similar in the four frequency bands when compared with the pre-rehabilitation patterns. Specifically, comparison between pre- and post-rehabilitation

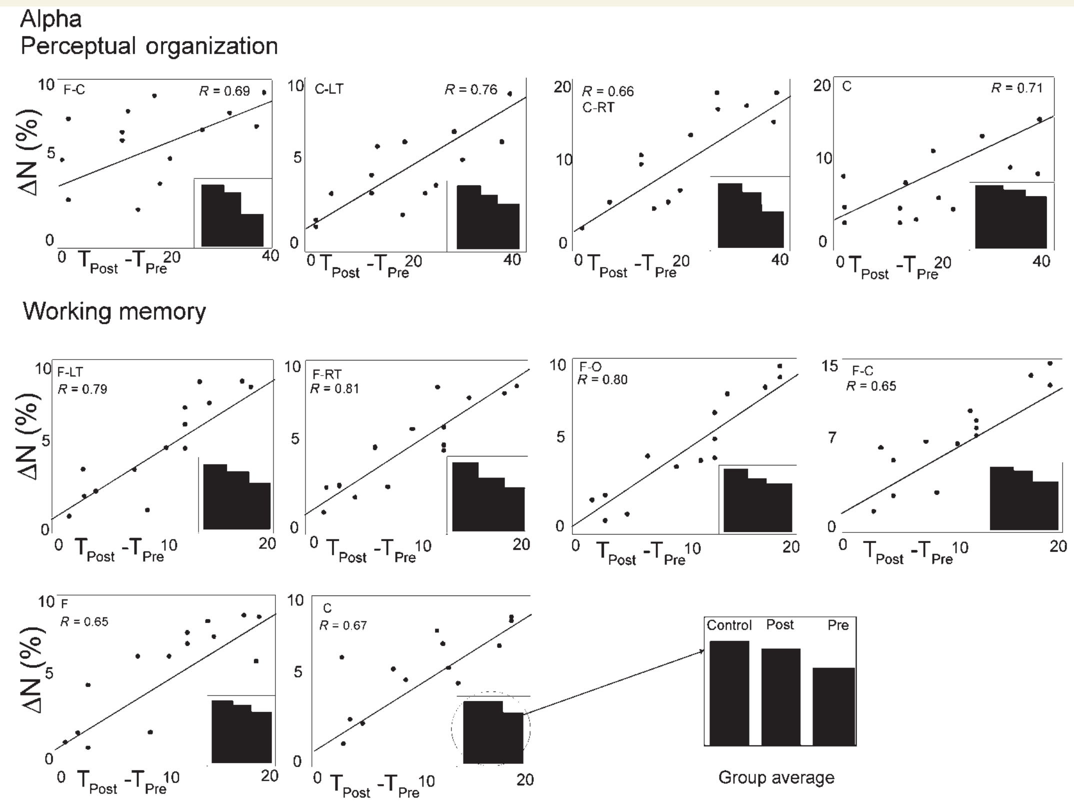


Figure 6 Correlations between changes in the number of links ($\Delta N = N_{Post} - N_{Pre}$) and changes in neuropsychological test scores ($T_{Post} - T_{Pre}$). Changes in the number of links in the alpha spectral band-based connectivity patterns correlate with changes in the Perceptual Organization Index (POI, upper panels) and the Working Memory Index (WMI, lower panels) of the WAIS-III. Bar diagrams show that in the alpha spectral band a decrease in the number of couplings is noticed in the pre-rehabilitation connectivity pattern, whereas the post-rehabilitation connectivity parameters approach controls. This progressive increase in the number of links from pre-rehabilitation to control reference agrees with the positive correlation found. C = central; F = frontal; LT = left temporal; O = occipital; RT = right temporal.

stages revealed a loss of local and long-distance slow band-based connectivity and an increase in higher spectral band-based connections. The reduction of delta-band-based connections and the increment of those based in the alpha band correlates with Verbal Fluency Test scores, as well as with the Perceptual Organization and Working Memory Indexes of the WAIS-III, respectively. Additionally, changes on connectivity values based on theta and beta bands correlate with the PCRS, which reflects a general improvement in a patient's ability to carry out everyday activities. Finally, network architectures in patients were checked to see if they were distinguishable from control topology by means of a linear discriminant analysis, and showed a greater similarity with respect to control topology in post-rehabilitation patients than those pre-rehabilitation. To our knowledge, the current study is the first to provide some evidence about the capability of non-invasive connectivity measures to study the functionality and recovery of brain tissue in patients with traumatic brain injury compared with healthy subjects, showing that changes in functional connectivity at the neurophysiological level are related to changes observed at the behavioural level.

Pre–post comparison at the neuropsychological level

The neuropsychological results reflect improvement, with an approach of patients post-rehabilitation to the healthy control group in terms of most neuropsychological test scores and when compared with patients pre-rehabilitation. The analyses revealed that scores post-rehabilitation differed from those obtained by patients pre-rehabilitation, with higher scores after the cognitive intervention. Additionally, controls and pre-rehabilitation patients showed statistically significant differences in most of the cognitive domains evaluated; while for post-rehabilitation those differences between patients and controls were clearly reduced. Although some punctuations improved significantly in the post-rehabilitation assessment (compared with pre-rehabilitation), some other punctuations continued, showing statistically significant differences with the control group. This trend can represent a cognitive partial improvement related to the fact that patients recovered in a significant way but did not reach full reestablishment of their cognitive processes. Nevertheless this is a valuable result with clinically relevant implications, which serves as an indicator of recovery,

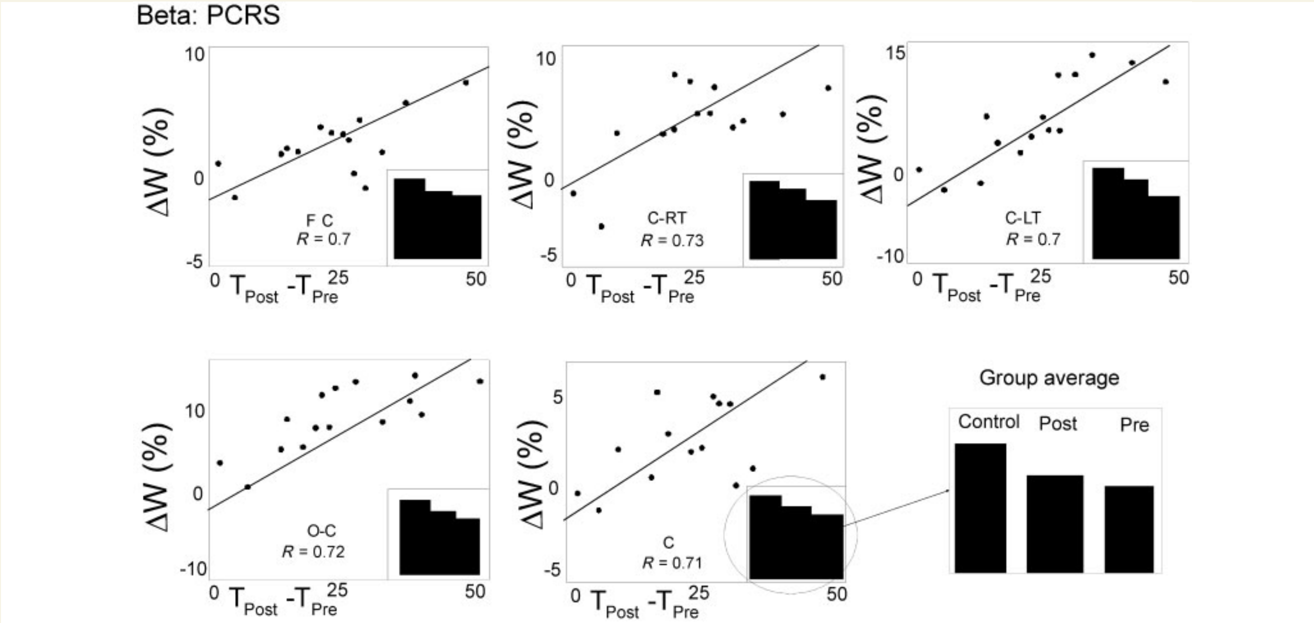


Figure 7 Correlations between changes in connectivity parameters ($\Delta N = N_{\text{Post}} - N_{\text{Pre}}$ and $\Delta W = W_{\text{Post}} - W_{\text{Pre}}$) and changes in PCRS scores ($T_{\text{Post}} - T_{\text{Pre}}$). Bar diagrams show that in the beta spectral band an increase in the number of couplings is noticed for connectivity patterns pre-rehabilitation, whereas such connectivity parameters post-rehabilitation approach the control groups. This progressive increase in the weight of links from pre-rehabilitation to the control reference agrees with the positive correlation found. C = central; F = frontal; LT = left temporal; O = occipital; RT = right temporal.

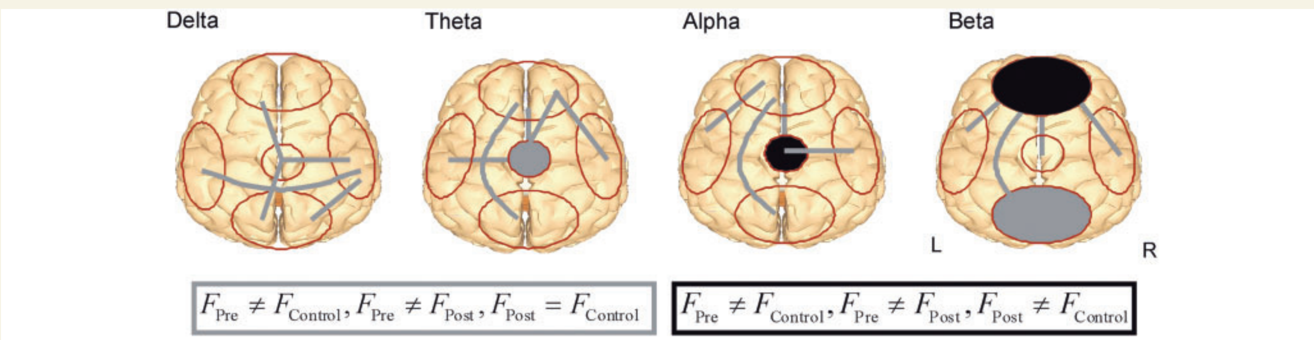


Figure 8 Grey lines connecting brain areas show that we can define a 'recovery phenomenon'; where pre-rehabilitation Fisher values are distinguishable from post-rehabilitation and control values, but post-rehabilitation Fisher values are indistinguishable from control values (i.e. $F_{\text{Pre}} \neq F_{\text{Control}}$, $F_{\text{Pre}} \neq F_{\text{Post}}$, $F_{\text{Post}} = F_{\text{Control}}$). Black lines connecting brain areas show that we can define an 'incomplete recovery phenomenon', where pre-rehabilitation Fisher values are distinguishable from post-rehabilitation and control values, but post-rehabilitation Fisher values are also distinguishable from control values (i.e. $F_{\text{Pre}} \neq F_{\text{Control}}$, $F_{\text{Pre}} \neq F_{\text{Post}}$, $F_{\text{Post}} \neq F_{\text{Control}}$). R = right; L = left.

showing that patients improved in several cognitive domains such as attention, memory and executive functions in agreement with other previous reports (Cicerone *et al.*, 2005; Rholing *et al.*, 2009).

Pre–post comparison at the neurophysiological level

Whether changes in neuropsychological scores are related or not to changes at the physiological level has been a matter of debate. In this work, we tried to describe and compare changes at the physiological level and at the neuropsychological level by means of functional connectivity. Concerning spectral content, a widespread pattern of statistical differences was revealed when comparing pre- and post-rehabilitation connectivity profiles in slow wave bands, as well as with healthy control patterns. Pre-rehabilitation, patients showed higher generalized delta band connectivity values than the control group. Conversely, post-rehabilitation patients and controls did not differ statistically in number or weight of their local or long-distance delta band-based connectivity. Additionally, theta band-based connectivity showed significant changes in the weight of local connections in frontal and right temporal lobes, as well as in bilateral temporoposterior and centroposterior mid-distance connections. The fact that patients and controls do not differ in their patterns of slow band connectivity post-rehabilitation indicates recovery of the connectivity profiles related with this frequency band. The pathological increase of slow wave connectivity is widely documented in literature, for example in tumours and stroke (Bosma *et al.*, 2008, 2009), as well as in traumatic brain injury (Lewine *et al.*, 1999, 2007). Concerning connectivity, Bosma *et al.* (2008, 2009) recently demonstrated that synchronization in the theta band (as measured by synchronization likelihood and phase lag index) is significantly higher in patients with low-grade glioma than in matched healthy controls and in patients with brain tumour (Bartolomei *et al.*, 2006*a, b*; Douw *et al.*, 2008). Thus, from our results, it seems that the increased delta band coherence in patients with traumatic brain injury reflects a generalized physiological malfunctioning that diminishes with cognitive recovery. In fact, the loss of mid- (frontotemporal) and long-distance (frontooccipital) frontal connectivity is correlated negatively with the improvement on Verbal Fluency Test scores. Those patients with traumatic brain injury that showed greater improvement in verbal fluency were those that showed greater loss of delta band-based functional connectivity. A pathological increase of theta band functional connectivity compared with healthy controls has also been reported in other patient groups, such as those with Alzheimer's (Stam *et al.*, 2006) and depressed (Fingelkurts *et al.*, 2007) and autistic adults (Murias *et al.*, 2007). The nature of patients' brain lesions in all of those studies varied greatly, indicating that there seems to be a very robust effect of brain injury on theta band activity. The decrease in theta functional connectivity in patients post-rehabilitation is related to the improvement of cognitive functioning, as it correlates with PCRS scores. These results demonstrate that traumatic brain injury induces changes in functional connectivity that may contribute to explaining the cognitive deficits commonly seen in this pathology (Tucha *et al.*, 2000).

Alpha oscillations have been associated with working memory (for review see Palva and Palva, 2007) and attentional functions (Gootjes *et al.*, 2006). Our results show that most of the connections in this band sustained statistically significant changes post-rehabilitation, based on the number of connections. Additionally, local frontal and temporal as well as mid- and long-distance frontocentral and frontooccipital connections changed their weight. Furthermore, when connectivity profiles were compared with the control group, patients with traumatic brain injury showed greater differences at the pre-rehabilitation stage, indicating a lower number and weight of their connections. However, post-rehabilitation patients showed a clear improvement, having a profile closer to that demonstrated by the control group. Alterations in frontoparietal synchrony could be an important factor contributing to working memory and executive function processes, since in normal subjects working memory or direct attentional tasks involve transient synchronization between these two regions (von Stein and Sarnthein, 2000; Halgren *et al.*, 2002). Our data showed a relationship between alpha band-based connections and perceptual and working memory functions. Thus, those patients with greater improvements in the number and weight of their connections also showed increased scores in the Working Memory Index and Perceptual Organization Index of the WAIS-III. All these data could be interpreted under the model of 'global neuronal workspace' (Dehaene *et al.*, 1998). This model emphasizes the importance of the relationship between sensory regions and frontoposterior networks in information processing. Perceptual organization involves both sensory and working memory abilities, increasing the necessity of information integration within the brain. Additionally, Palva and Palva (2007) propose that the alpha band is responsible for the synchronization of working memory networks. Based on this framework, improvements in weight and number of alpha band connections between frontoposterior regions could be a physiological sign of cognitive recovery.

Regarding the beta band, patients showed few changes in the number of mid-distance connections (between right temporal and occipital and central regions) when pre- and post-rehabilitation stages were compared. However, comparison with the control group revealed that the local frontal, right temporal and long-distance frontooccipital, as well as right temporal–occipital, differences that were found at pre-rehabilitation were released after rehabilitation. Again, these changes in the beta band could represent a physiological effect of the rehabilitation process. The correlation found between PCRS score and the decrease-increase in connectivity in the theta and beta frequency bands, respectively, is of great interest. The PCRS reflects a patient's current ability to adapt to daily living activities. PCRS scores improved after the rehabilitation process, because patient and relative ratings became closer. We found that those patients who decreased theta and increased beta band connectivity between anterior (frontal and central) and posterior regions (temporal lobes and occipital region), respectively, were those that showed greater improvements in their PCRS values. Thus, it seems that changes in anteroposterior connectivity improve their ability to adapt to daily living activities.

Although several changes were found in the between-group comparison for post-rehabilitation patients and controls, some of the differences found pre-rehabilitation remained stable across time. While statistical differences were lost for the delta and theta bands, some differences in the alpha and beta bands were not modified after the rehabilitation process. Those differences that remain stable after rehabilitation are local and long-distance alpha and beta connections related with the left temporal lobe (left temporal–right temporal, left temporal–frontal and left temporal–occipital). It is of interest to highlight that those cognitive scores that better correlate with patterns of connectivity were also those related with visuospatial and perceptual functions normally related to the right hemisphere. In fact, while at pre-rehabilitation both verbal and performance IQ were statistically different from the control group, after treatment only verbal IQ still showed differences between patients and controls. This could explain why left temporal lobe connectivity parameters still indicated statistical differences between patients and controls after rehabilitation.

Mathematical and experimental considerations

We are aware that volume conduction effects could be affecting the connectivity pattern because of the influence of common sources. Nearby MEG sensors have a high probability of capturing activity from common sources, and therefore show spurious strong correlation. Several attempts have been proposed to overcome this problem. The first approach is to study functional connectivity in source space. However, to date there is no reliable way to choose the proper model to solve the inverse problem (Hadjipapas *et al.*, 2005; Stam *et al.*, 2009). Another approach is the use of measures of correlation that are not sensitive to volume conduction, such as the phase lag index (Stam *et al.*, 2007) or the imaginary part of the coherency (Nolte *et al.*, 2004). However, we consider that volume conduction effects could not explain the group differences in the connectivity measures that we found. Our results agree with previous studies of brain injury. In this work we show that slow wave-based connectivity increases after a traumatic injury and decreases after recovery (even restoring control values). The pathological increase of slow wave-based connectivity and the increase of higher band-based connectivity have been reported in studies of tumours (Bartolomei *et al.*, 2006*a*, *b*; Bosma *et al.*, 2009). Moreover, in this study the postoperative decrease of theta synchronization, using phase lag index, could be interpreted as a tendency towards a more 'normal' state of the theta band after tumour resection, an idea corroborated by the decrease of seizure frequency. On the other hand, Bosma *et al.* (2008) reported an increase of theta band functional connectivity in patients compared with controls, using synchronization likelihood. This agreement, even using different measures of functional connectivity, is interpreted by these authors as a robustness of the results (Bosma *et al.*, 2008). In a recent work by Stam *et al.* (2009), the authors compare phase lag index results with others obtained with several linear and non-linear measures, displaying a few differences but suggesting: 'Since the phase lag index results are largely in line with the previous studies we can conclude that the influence of volume conduction may have been smaller than has sometimes been suggested'. In order to check whether our results are contaminated by a common source or not, we have calculated the functional connectivity and hence the distance-to-control for pre- and post-rehabilitation and control subjects in delta band using phase lag index. As Supplementary Fig. 1 shows, the distance-to-control (in this case, only coupling strengths are taken into account) is higher pre- than post-rehabilitation. Thus, a recovery (in terms of approach to control) is also observed with phase lag index as well as with wavelet coherence. Therefore, we consider that we can be confident in our results, the pathological increase of delta band-based connectivity and the approach to control values observed in patients post-rehabilitation. Moreover, in this work we have adopted an alternative approach, analysing functional connectivity in sensor space and then grouping the sensor pairs in local and long-distance couplings. We spatially averaged sensors in five regions (frontal, right temporal, left temporal, central and occipital). Wavelet coherence could be influenced by volume conduction; however, it is less likely that such effect can explain group differences in functional connectivity between patients with traumatic brain injury, both pre- and post-rehabilitation, and controls. Furthermore, our results showed changes not only in local but in long-distance connections, which are less likely to be due to volume conduction. Consequently, a general change in these regions must occur to be detected as a group difference. Another technical limitation could be due to the influence of power on the connectivity changes. Our results showed a generalized change in the connectivity pattern in all frequency bands. However, no significant correlation has been found between power and connectivity changes in all frequency bands (Supplementary Fig. 2 and Supplementary Table 1), supporting the idea that the connectivity changes reported in this work are not affected by spectral changes. This absence of correlation could also be an argument to support that a common source does not alter the functional connectivity, since a common source could be expected to alter signal power. On the other hand, because a direct relation between the position of the sensor and the immediate brain region underneath cannot be fully assumed, we should take into account that the labels of brain regions used to describe profiles of connectivity could be subjected to some spatial deviations. However, to limit this effect we have clustered the signals in the sensor space into five sensor groups.

The interpretation of our results could be limited because of the lack of a patient group that did not receive neuropsychological rehabilitation. In order to evaluate a general effect of rehabilitation, patients with traumatic brain injury should be included that do not receive rehabilitation and they should be scanned twice, with a similar interval to those patients that receive treatment. This is necessary to control for spontaneous recovery phenomena. In this case it would be very important to ensure that patients did not receive any kind of rehabilitation (i.e. motor, language, memory) for about 9–14 months, in order to act as a true control group. However, according to the Declaration of Helsinki, a treatment that has already demonstrated benefits for a particular population of patients should not be denied purely for experimental reasons. Taking into account this limitation, the current study provides new evidence for the neurophysiological mechanisms underlying the process of neuronal plasticity after brain injury but does not pretend to be a measure (or test) of effectiveness of rehabilitation. Future studies should evaluate whether: (i) these changes measured during resting state are reproducible during cognitive task performance; (ii) patients with traumatic brain injury and stroke show similar profiles of connectivity recovery or not; (iii) functional connectivity measures are capable of distinguishing between differential neuropsychological and functional outcomes; and (iv) patients at different ages show a differential pattern of functional connectivity recovery. In this study we did not find correlation between connectivity changes and age (Supplementary Fig. 3). This result may be due to a lack of enough variability in age to find a statistical correlation.

Our results support the idea of brain functioning as an integrated complex network, in which focal changes can alter the integrity of the brain as a whole and its functional status. The neurophysiological processes underlying brain damage could be affected by the number of neurons left, but also, and most importantly, by the way they function and the connections they are able to make. These aspects determine functional outcome. Also the rewiring, or evolution, of the topology is a characteristic that might reflect the global structure of the neural systems. In this work we use linear discriminant analysis as a tool that captures the general architecture of the network and is able to discriminate groups according to their topology. However, an approach that catches in more detail the interplay between segregation and integration mechanisms could be graph theory-based analysis (Bullmore and Sporns, 2009; Nakamura *et al.*, 2009, Stam, 2010). Future studies should evaluate whether graph theory analysis could improve the understanding of the mechanisms of neural plasticity induced by the rehabilitation process. Some computational models study the effect of damage and posterior recovery of brain network characteristics after injury (Honey and Sporns, 2008, Rubinov *et al.*, 2009 Alstott *et al.*, 2009; Butz *et al.*, 2009).These models agree that the area producing the largest and most widespread injury-effects on functional interactions are those being highly connected. Alstott and colleagues (2009) demonstrated that the target attack over the frontal lobe induces a severe disruption of the network. In the current study the majority of patients showed impairment over the frontal lobe. Thus the lesion on this brain region influences the difference between controls and patients pre-rehabilitation; and furthermore changes in the pattern of connectivity of the frontal lobe and other regions correlate with working memory score changes in the alpha band. Thus, the improvement of the connectivity in this region correlates with the improvement in cognitive changes.

The literature shows several examples of pathological increase and decrease of functional connectivity, which provide evidence for the idea that a balance in the level of synchronization in healthy controls is required for optimal brain functioning. This study supports several ideas: (i) that reorganization of brain networks affects and even restores healthy functional connectivity patterns in patients with traumatic brain injury; (ii) that the reorganization of a network can be executed by means of different mechanisms, increasing (or decreasing, when needed) the number or weight of its links, and that these mechanisms are responsible for composing a network or organizing its topology; and (iii) we provide evidence that changes in functional connectivity at the neurophysiological level are related to changes observed at the behavioural level. These ideas have implications for the understanding of brain physiology as well as important potential clinical applications.

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Supplementary material

Supplementary material is available at *Brain* online.

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