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Topological disintegration of resting state functional connectomes in coma

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ABSTRACT

Graph theory has been playing an increasingly important role in understanding the organizational properties of brain networks, subsequently providing new tools for the search of neural correlates of consciousness, particularly in the context of patients recovering from severe brain injury. However, this approach is not without challenges, as it usually relies on arbitrarily fixing a threshold in order to retain the strongest connections proportionally equal across subjects. This method increases the comparability between individuals or groups but it risks the inclusion of false positive and therefore spurious connections, especially in the context of brain disorders.

Resting state data acquired in 25 coma patients and 22 healthy subjects was compared. We obtained a representative fixed density of significant connections by first applying a p value-based threshold on healthy subjects' networks and then choosing a threshold at which all individuals exhibited meaningful connections. The obtained threshold (i.e. 10%) was used to construct graphs in the patient group. The findings showed that coma patients have lower number of significant connections with approximately 50% of them not fulfilling the criteria of the fixed density threshold. The remaining patients with relatively preserved global functional connectivity had sufficient significant connections between regions, but showed signs of major whole-brain network reorganization. These results warrant careful consideration in the construction of functional connectomes in patients with disorders of consciousness and set the scene for future studies investigating potential clinical implications of such an approach.

1. Introduction

Neurobiological theories of consciousness suggest that local and global information processing, enabled through highly connected brain regions (i.e. hubs), might be crucial to generate and maintain conscious experience (Dehaene and Changeux, 2011). Among the behavioral continuum of acquired pathological consciousness perturbations which could be related to brain injury (Giacino et al., 2014), the state of unarousable unresponsiveness named coma is the most severe and acute form of disorder of consciousness (DOC) and therefore constitutes a clinically and fundamental relevant model of study of conscious access (Laureys and Schiff, 2012). Following this lead, recent brain functional connectivity studies in coma patients at rest, have provided promising but divergent accounts about the spatial extent and topography of functional brain changes related to coma (Achard et al., 2012; Amico et al., 2017; Demertzi et al., 2015; Koenig et al., 2014; Malagurski et al., 2017; Norton et al., 2012; Silva et al., 2015; Vanhaudenhuyse et al., 2010).

Graph theory is a robust mathematical framework well-suited to deal with the complexity intrinsically associated to brain functional connectivity data. This approach enables accurate topological analysis of neuroimaging data (De Vico Fallani et al., 2014) and permits the quantification of relevant information processing-derived parameters (Rubinov and Sporns, 2010) across multiple scales, spanning from single brain areas (i.e. nodes) to networks and eventually whole brain analysis. Nevertheless, despite the promise held by these approaches, there have

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only been a few graph theoretical studies in patients with chronic DOC (Achard et al., 2012; Beudel et al., 2014; Chennu et al., 2014, 2017; Crone et al., 2014) and none of them have fully explored the potential contribution of such mathematical methods to specifically address the relationship between coma and the whole brain complex topological disturbances that may underpin this pathological state of acute DOC.

We aimed to characterize during this extreme condition of acquired consciousness abolition (i.e. coma), brain's residual ability to segregate and integrate information at both global and local networks levels. In line with network-level theoretical frameworks of conscious access (Tononi and Koch, 2008; Tononi et al., 2016; Dehaene and Changeux, 2011; Dehaene and Naccache, 2001), we hypothesize that the complete loss of consciousness that is observed during coma is related to the massive breakdown of whole brain functional connectivity. Possibly underpinning coma patient's considerable neurological outcome heterogeneity, we expect to identify among patients a large repertoire of local and global topological disturbances, spanning from well-preserved to almost completely dissolute (i.e. randomized) networks, generating less efficient and costlier functional brain configurations than small-word arrangement (Fornito et al., 2015; Stam, 2014).

2. Methods

2.1. Participants

Patients were included from three critical care units affiliated with the University Teaching Hospital (Toulouse, France) between January 2013 and January 2015. We compared rs-fMRI data of 25 cardiac arrest survivors with severe anoxic-ischemic brain injury, who met the clinical definition of coma (Glasgow Coma Scale score (Teasdale and Jennett, 1974) at the admission to hospital < 8, with motor responses < 6; Mean = 51y; SD = 18y; age range = 18-80y; 12M) to 22 age-matched healthy controls (Mean = 44y; SD = 20y; age range = 22-74y; 10M). Patients were scanned at least 2 days (4±2 days) after complete withdrawal of sedation and under normothermic condition. The delay between primary brain injury (i.e. cardiac arrest) and MRI scan was of 6 days (Mean = 6; SD = 3). Standardized clinical examination was performed on the day of the scanning using the Glasgow Coma Scale and the Full Outline of Unresponsiveness (Wijdicks et al., 2005). This study was approved by the Ethics committee of the University Hospital of Toulouse, France ("Comité Consultatif pour la Protection des Personnes", CHU Toulouse, ID-RCB: 2013-A00009-34). Written informed consent was obtained directly from the healthy volunteers and from the legal surrogate of the patients.

2.2. Data acquisition

In all participants, 11 min resting state fMRI was obtained using a 3T magnetic resonance scanner (Intera Achieva; Philips, Best, the Netherlands). Two hundred and fifty multislice T2*- weighted images were retrieved with a gradient echo-planar sequence using axial slice orientation (37 slices; voxel size: 2 x 2 × 3.5 mm; TR = 2600 ms; TE = 30 ms; flip angle = 90°; FOV = 240 mm). In addition, a 3D T1-weighted sequence (170 contiguous slices; TR = 8.1 ms, TE = 3.7 ms, FOV = 220|232|170 mm, flip angle = 8°, resolution = 1mm3 isovoxel) was also acquired in the same session and later used for visual assessment of the structural integrity of regions of interest.

2.3. Data preprocessing and parcellation

Functional data were preprocessed using Statistical Parametric Mapping (version SPM 12; http://www.fil.ion.ucl.ac.uk/spm/). The fMRI images were realigned (motion corrected), slice-time corrected, coregistered to each subject's T1-weighted image and normalized to standard stereotaxic anatomical Montreal Neurological Institute (MNI) space. T1-weighted images were segmented to compute grey matter, white matter and cerebro-spinal fluid images, and normalized to MNI space. The fMRI images were not smoothed in order to minimize the spillage of the signal of the neighboring ROIs. The brain images were parcellated according to a whole-brain functional atlas composed of 268 regions (Finn et al., 2015; Shen et al., 2013). In addition, we regrouped these regions into large-scale resting-state networks, according to the atlas of Power et al. (2011). The full detailed list of brain regions used in our study can be found in Supplementary Information (Appendix A).

2.4. Time series extraction and wavelet decomposition

In each brain parcel, regional mean time series were estimated by averaging, at each time point, the fMRI voxel values weighted by the grey matter probability of these voxels. This weighting limits the contamination of the time-series by white matter signals and cerebrospinal fluids. In addition, non-neuronal sources of noise were estimated using the anatomical component based noise reduction method (CompCor) (Behzadi et al., 2007), which consisted of applying the principal component analysis (PCA) to characterize the time series data from white matter and the CSF voxels (i.e. normalized T1 segmented masks). Five principal components of the signals from the noise voxels were then introduced as covariates in a general linear model (GLM) as an estimate of the physiological noise (Behzadi et al., 2007). Residual head motion was removed by regressing out motion parameters, estimated during realignment, and composite scan-to-scan movement parameters calculated using ART (integrated within the CONN toolbox, Whitfield-Gabrieli and Nieto-Castanon, 2012; http://www.nitrc.org/projects/conn). In addition, we calculated the average scan-to-scan movement (i.e. for the entire MRI session) for each subject and correlated this with network metrics to investigate the impact of motion on brain network analysis (please see Appendix B).

The residual time series were decomposed in four scales using discrete dyadic wavelet transformation (Achard et al., 2006). We used the maximal overlap discrete wavelet transform (MODWT) to each regional mean time series and estimated the pairwise inter-regional correlations at each of the four wavelet scales. Given that the wavelet decomposition is dependent on the repetition time (TR = 2.6s) of the rs-fMRI acquisition protocol, we decomposed all regional mean time series into the following scales: scale 1 (0.1–0.19 Hz); scale 2 (0.05–0.1 Hz); scale 3 (0.02–0.05 Hz); and scale 4 (0.01–0.02 Hz). We decided to primarily focus on scale 2, because previous studies indicated that this frequency band contains relevant information for rs-fMRI and is most sensitive to differences between aberrant and healthy brain functioning (Váša et al., 2018). Still, some analysis has been repeated for scale 3 (see Supplementary Information – Appendix B).

2.5. Graph computation

2.5.1. Threshold selection

Lower levels of overall functional connectivity have been associated with higher degree of randomness in the individual proportionally thresholded (i.e. connection density) brain graphs. Edges with low functional strength have a higher probability of being spurious and often lead to differences in clustering and global efficiency not necessarily reflecting real changes in network organization but artificially induced differences due to low overall functional connectivity (van den Heuvel et al., 2017).

In order to eliminate the possible group differences in functional connectivity strength, we first thresholded each subject's matrix at an FDR-adjusted significance level of $p < .05$, and termed the surviving edges as significant connections (Benjamini & Yekuteli, 2001).

Then, we calculated the ratio of the number of these significant connections to the total number of possible edges in a given graph. The resulting connection densities were used to select a fixed density threshold that contained only significant edges for all subjects, including controls and coma patients (Achard et al., 2006; De Vico Fallani et al.,

2014).

Importantly, to keep the graph fully connected, we extracted the minimum spanning tree (MST) for each subject, based on the correlation matrix with absolute weights. The remaining values of the correlation matrices were then added at the selected fixed connection density threshold to the MST skeleton resulting in an undirected binary adjacency matrix for all subject in the two groups.

The code used to calculate the significance of edges is integrated in an R-based package entitled brainwaver, available at https://cran.r-project.org/web/packages/brainwaver/.

It is worth noting that we calculated the significance of connections using absolute values of negative and positive correlation coefficients, which do seem to play a different role in disorder of consciousness (Di Perri et al., 2016; Malagurski et al., 2017). However, our additional analysis indicated that there were significantly more positive links which were also higher in strength in comparison to negative links in both groups (see Appendix B). Thus, our final thresholded matrices (at 10%) included only the (binarized) connections that were based on positive correlation coefficients, for both controls and patients.

2.5.2. Network metrics

The network analysis was done in R (v.3.3.2; The R Project for Statistical Computing; http://www.R-project.org/) using the brainwaver (v.1.6) and iGraph (v.1.1.2) package freely downloadable at http://cran.r-project.org.

Following global metrics were calculated: clustering and global efficiency. The clustering (global average local efficiency – see description below) is a topological measure of segregated information transfer. The global efficiency (GE) is a metric for efficiency of integrative information transfer across the network. This measure is inversely related to the characteristic path length (average shortest path between nodes) but is adapted to fragmented that is disconnected graphs.

To explore the local/nodal network metrics we employed the degree and the local efficiency. Each of these measures describe different aspects of topological node centrality permitting the identification of nodes that have the highest influence on network-wide processes. The degree represents the number of links connected to the node, assuming that nodes with many connections have a higher influence on the network in comparison to low-degree nodes. The local efficiency measures the integration capacity between immediate neighbors of a given node. This metric also reflects the network resilience by indicating how efficiently neighbors of a given node communicate when this node is disrupted.

2.5.3. Network reorganization mechanism

To detect network reorganization in comatose patients we have also computed the *hub disruption index* (HDI) for nodal measures (Achard et al., 2012). To calculate HDI for a given metric, for example the degree, we subtract the healthy group mean degree from the degree of the corresponding node in an individual subject, and plot this individual difference against the healthy group mean. The slope of a straight line fitted to a given plot is referred to as hub disruption index. A negative HDI close to −1, indicates a severe network reorganization, meaning that nodes with highest degree (i.e. hubness) in controls show greatest reduction in patients, whereas the nodes with lowest nodal degree in controls show the greatest increase in patients.

2.6. Statistical analysis

Global and nodal statistics (and functional connectivity) were compared between groups with the aid of the permutation test (10000 iterations) using the package perm (v.1.0–0.0) implemented in R (v.3.3.2; The R Project for Statistical Computing; http://www.R-project.org/). For each nodal metric, the significance level of p-values was adjusted to 0.05/N ($p = .00018$), where N represent the number of nodes included in the analysis. The results were visualized with the BrainNet Viewer (Xia et al., 2013).

3. Results

3.1. Randomness

The results showed that the number of significant connections in the graphs of coma patients were significantly lower in comparison to those of healthy controls, exhibiting a lower connection density of significant connections at an FDR-adjusted significance level of $p < .05$ (Appendix B - Table 1). The median connection density of these thresholded graphs in patients was 14% (range 0–56%), meaning that the maximum connection density that graphs could be built to, while ensuring that all subject's connectomes contain only significant edges was much lower in comparison to the control group. These results were reproducible across several levels of parcellation of the functional atlas used in the principal analysis (Finn et al., 2015; Shen et al., 2013), as shown in the Supplementary Information (Appendix B - Table 1).

The final fixed threshold for exclusion of patients was set to 10% significant connections density, the lowest value found in healthy control subjects. Therefore, to allow meaningful interpretation of patients' global and local network topology that is not related to low functional connectivity, but to node related topological changes, we decided to calculate the graph measures excluding patients ($N = 12$) that did not have at least 10% of significant connections, leaving a total of 13 patients for further analysis. The patients that were included in further analysis are referred to as the "effective" patient subgroup, while the excluded patients were referred to as the "non-effective" patient subgroup (see Fig. 1). This nomenclature was chosen as effectiveness refers to the fact that the effective patient subgroup satisfied the significant connections density criteria so as to be able to construct the connectivity graphs.

It is worth noting that this first step of global network analysis, appears to have a potential value for neuroprognostication in this challenging clinical setting, as five out of six patients who did not have any significant connections at any level of parcellation (i.e. non-effective subgroup) did not recover consciousness at 3 months post coma (Appendix B – Table 2).

Further, we compared the overall functional connectivity strength (without threshold) between all patients and controls, and between patients who had satisfied the criteria of edge significance and healthy subjects. There were no significant differences in the overall (average) functional connectivity (FC) between the effective patient subgroup and controls ($p = .081$) (Fig. 1.).

Finally, we examined whether there was a significant association between the overall FC and graph metrics across the final groups of subjects. We found a significant relationship between the FC strength and clustering ($r = -0.59$, $p = .0002$), and global efficiency ($r = -0.38$, $p = .02$) in the group of all subjects – controls and the effective patient subgroup (van den Heuvel et al., 2017). Given that there were no significant differences in the average FC strength between the two subgroups, this association should not significantly influence the group comparison results. See supplementary information (Appendix B – Fig. 1) for the same analysis for scale 3 (0.02–0.05 Hz).

3.2. Disruption of hub rank order

This hub disruption index summarizes the pattern of network reorganization, in subtracting the healthy group mean value from the value of the corresponding node in coma patients, and plotting this individual difference against the healthy group mean. The slope of a straight line fitted to a given plot is referred to as hub disruption index (Achard et al., 2012). A negative HDI close to −1, indicates a severe network reorganization, meaning that nodes with highest nodal efficiency (i.e. hubness) in controls show greatest reduction in patients, whereas the nodes with lowest nodal efficiency in controls show the greatest increase in

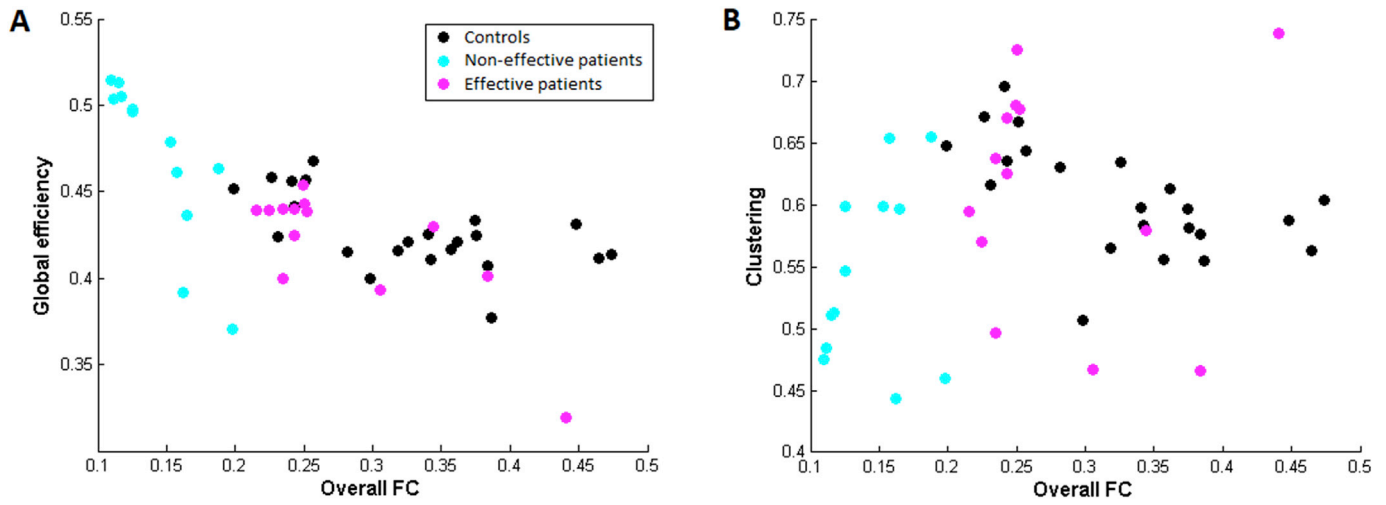

Fig. 1. Functional connectivity (Pearson's r) over all pairs of nodes (without a threshold) plotted against the global metrics – global efficiency (A) and clustering (B) (at wavelet scale 2). Patients with the significant connections density lower than 10% are marked using the cyan colour. These patients have a lower average functional connectivity in comparison to the other subgroup of patients and controls. There are no significant differences in the overall (average) functional connectivity between the effective patient subgroup (in purple) and the control group ($p = .081$).

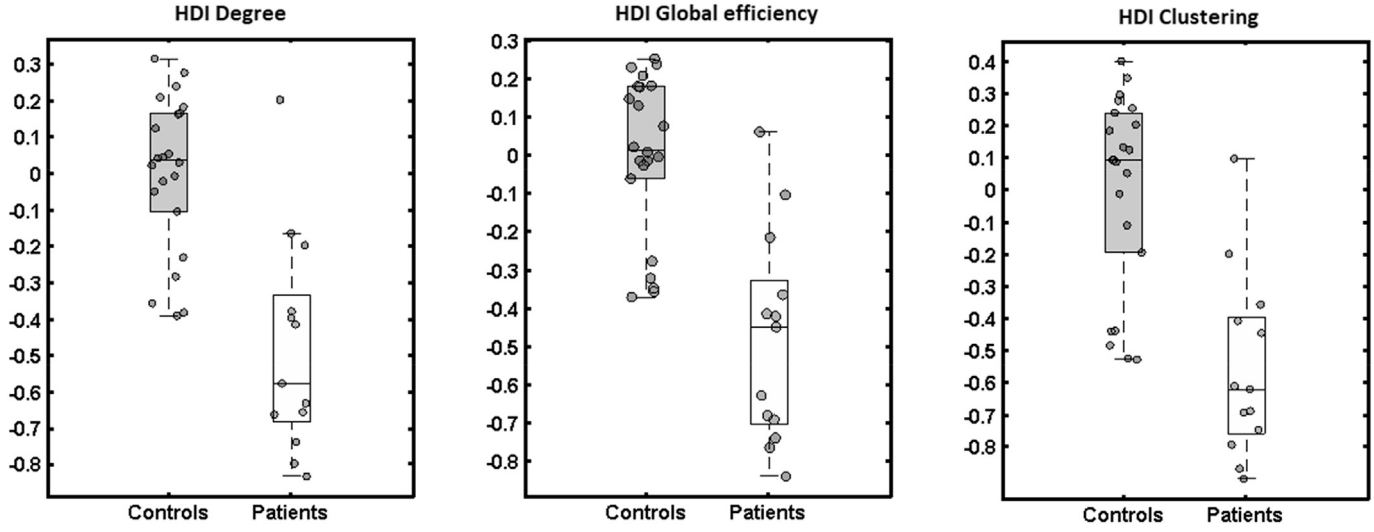

Fig. 2. Hub disruption index (degree, global efficiency and clustering) for each of the subjects in the control and the patient group.

patients. The hub disruption index calculated with the global (nodal) efficiency ($p < .0001$) and local efficiency ($p < .0001$) implied significant brain network reorganization within the effective patient subgroup (Fig. 2). Further, HDI calculated using the degree implied the same significant brain network reorganization within the patient group in comparison to the control group ($p < .0001$; Fig. 2), and we found evidence of a critical reorganization of high degree nodes (i.e. hubs). Namely, cortical regions that were hubs of healthy brain networks seemed to become non-hubs of comatose brain networks and vice versa (Fig. 3). However, there seemed to be significant heterogeneity within the coma patient group (Fig. 2), with some individuals showing severe reorganization at global level, while others having similar values to healthy subjects.

3.3. Network topology

There were no statistically significant differences in clustering (at cost 10% permutation test $p = .88$) and global efficiency (permutation test $p = .57$) between the effective patient subgroup and the control group (Fig. 4). In addition, we ran a general linear model to determine a statistically significant difference between the effective patient subgroup and controls in global metrics after controlling for the global functional connectivity and its interaction with the group variable. The results showed that there was no significant main effect of the group on clustering ($F(1,31) = 0.035$, $p = .85$) and global efficiency ($F(1,31) = 0.84$, $p = .37$) after controlling for the covariates. The interaction between the FC and group was not significant, after the Bonferroni correction, for the clustering ($F(1,31) = 0.035$, $p = .85$) and for the global efficiency ($F(1,31) = 6.26$, $p = 1$).

However, Fig. 5 Shows multiple regions that significantly differ between the patients and the control group at nodal level. Overall, we can see a disruption in brain node centrality in the patient group reflected in a combination of decrease and increase of node degree, suggesting specific regional changes in brain network organization. The decrease of nodal degree was shown in the right crus (I) of the cerebellum (not classified in a network), while the increase of nodal degree encompassed the left angular gyrus (default mode network) and the left fusiform gyrus (not classified in a network).

The local efficiency indicates how efficiently neighbors of a given node communicate when this node is disrupted. This decrease in this

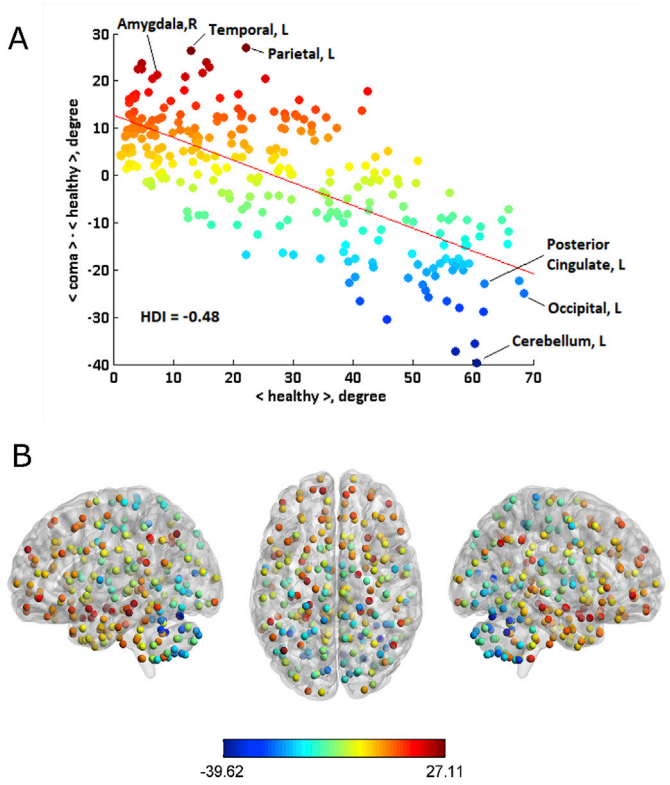

Fig. 3. Hub disruption of functional networks in comatose patients. A) The mean degree of each node in the healthy control group (x axis) is plotted against the difference between the groups in mean degree of each node (y axis). Normal hub nodes with high degree in the healthy group have a reduction in degree in the comatose group (i.e. posterior cingulate cortex, cerebellum), whereas the healthy non-hub nodes have an increase of degree in patients (i.e. amygdala, temporal cortex). The colors correspond to HDI values marked on the Y axis. B) Hub disruption index projected onto a brain surface for an easier interpretation of inter-regional differences.

metric was primarily seen in the right lingual gyrus (visual network).

4. Discussion

Our findings significantly contribute to the growing evidence of the involvement of resting state functional networks in the mechanisms of acquired disorders of consciousness. We observed among comatose patients a large repertoire of topological disturbances, at several levels: (i) whole brain impairments, encompassing gradual disruption in functional connectivity with the most severe changes implying complete randomness (ii) and significant disruption of hubs rank order across local networks metrics, suggesting a critical reorganization of high degree nodes, with cortical regions that were hubs of healthy brain networks becoming non-hubs of comatose brain networks and vice versa.

In agreement with our first hypothesis, systems-level mathematical metrics allows us to identify a massive breakdown of whole brain functional connectivity in coma patients, leading in some cases to a complete randomization of the functional brain networks. It should be stressed that the obtained dichotomization between non-effective and effective whole brain networks, seems to have a potential value for neuroprognostication in this challenging clinical setting, as five out of six patients who did not have any significant connections at any level of parcellation did not recover consciousness after coma. Future and ongoing studies should further investigate in larger and longitudinal patient's cohorts the added value of this promising and straightforward assessment tool of global brain function (Dell'Italia et al., 2018).

Further, the analysis did not show any evidence of significant differences in global network topology between the effective coma patient subgroup and healthy subjects (Achard et al., 2012; Crone et al., 2014). Therefore, patients that had preserved whole-brain functional connectivity, similar to that found in a healthy functioning brain, did not exhibit any disruption in global efficiency and clustering. In fact, our findings are in line with the recently published studies (De Vico Fallani et al., 2014; van den Heuvel et al., 2017; Váša et al., 2018) indicating that edges with low functional connectivity strength are probably spurious and thus artificially induce apparent changes in global topology not necessarily related to an underlying neurobiological mechanism.

Indeed, the conservation of global networks properties has been put in evidence in another graph theory-based study (Achard et al., 2012) with patients with acquired disorders of consciousness, further

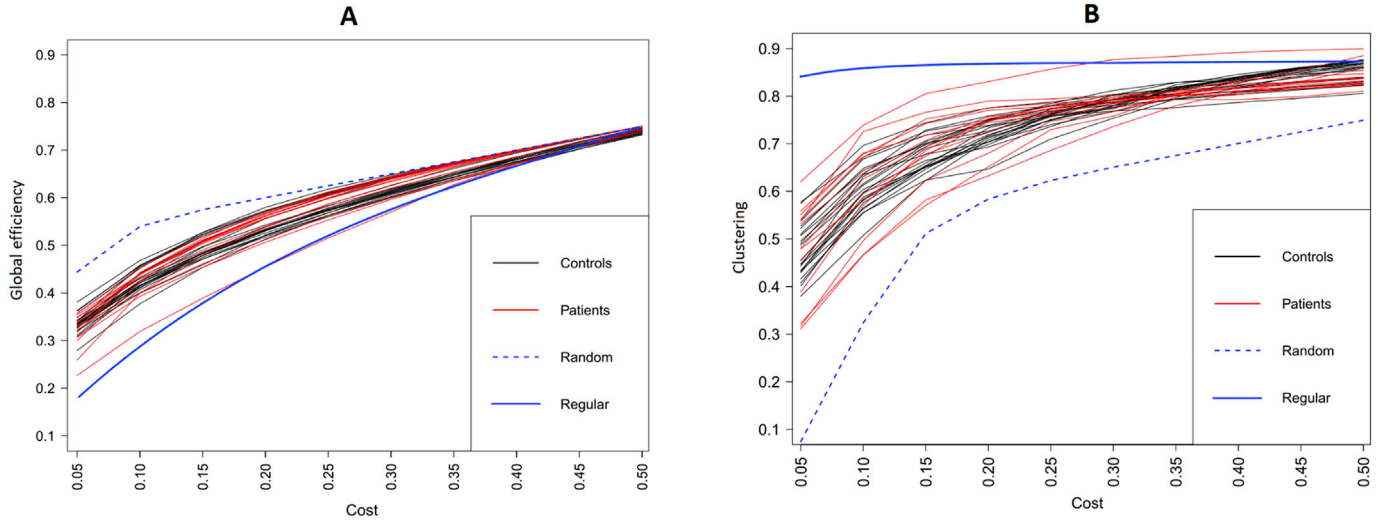

Fig. 4. Global topology in controls and effective patients. A) Global efficiency (GE) in controls and patients in comparison to regular and random networks, at multiple connection density thresholds (5–50%, increment 5%). B) Clustering (average local efficiency) in controls and patients in comparison to regular and random networks, at multiple connection density thresholds (5–50%, increment 5%). There were no group differences in global efficiency ($p = .57$) or clustering ($p = .88$) at the 10% connection density threshold.

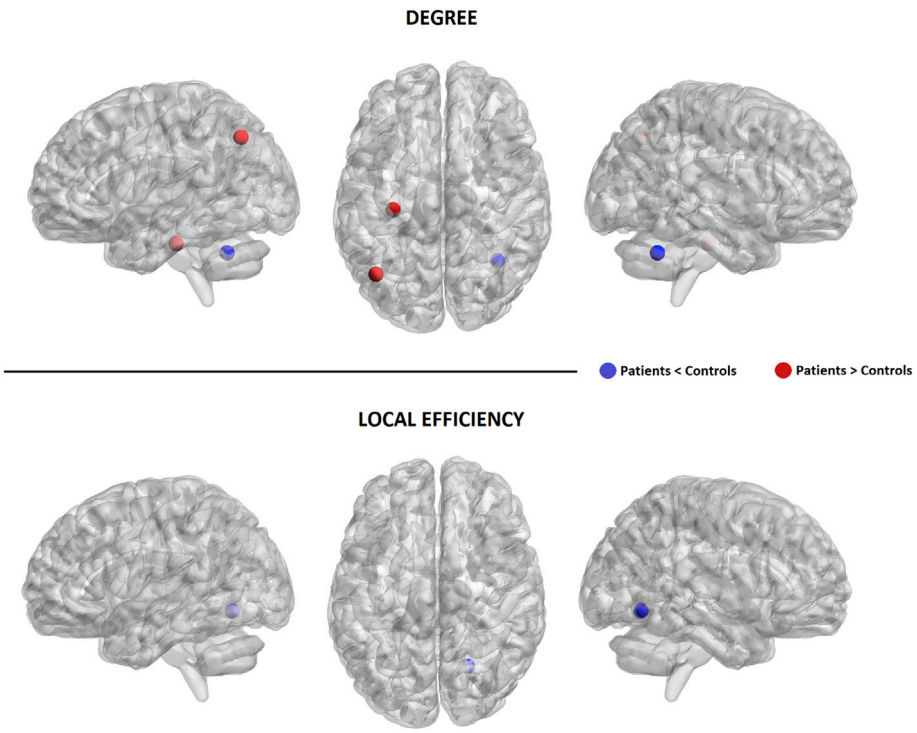

Fig. 5. Brain representation of nodes that demonstrated significant between-group difference in nodal degree and local efficiency. P > C – significantly higher in patients; P < C –significantly lower in patients. The p values are corrected using the Bonferroni correction (p = .00018).

suggesting that fundamental networks characteristics may be homeostatically preserved under clinical conditions such as severe brain-injury and coma. It must be stressed, that these results were found across multiple resolutions of brain parcellations and are probably unrelated to the brain node definition, which has been shown to significantly impact the analysis of brain network topology. Our results not only reproduce the results obtained in the study of Achard et al. (2012), but highlight the robustness of these findings under different acquisition scheme and in an another group of patients from a different hospital. In this study, the acquisition duration was nearly twice as shorter as the one used in Achard et al. (2012), and the patients in the current cohort were more severe and were scanned earlier than in the previous study (Achard et al., 2012), exclusively during the acute phase that follows the primary brain injury (i.e. coma). Without taking into account accurate statistical properties of low functional connectivity, the results would have been misleading because of the lack of signal in the data.

Further, a finer-grained exploration of network organization in coma patients highlighted a disruption of the order of importance of specific brain nodes, where brain regions such as the posterior cingulate cortex and the cerebellum which were high-degree nodes in healthy brain networks became low-degree nodes in coma patients, whereas low-degree non-hub regions such as the amygdala and the temporal cortical region became highly connected hub nodes in coma patients. This reorganization was further put in evidence with other nodal properties such as the hub rank disruption of nodal and local efficiency of brain regions.

In fact, previous functional connectivity studies with patients with acquired disorders of consciousness, have suggested significant changes along high-order midline posterior parietal regions, encompassing the posterior cingulate cortex, in this setting (Hannawi et al., 2015; Malagurski et al., 2017; Silva et al., 2015). In fact, these highly important regions have been previously suggested to be involved in self-related processing and potentially critical for consciousness emergence (Boly et al., 2017).

Among these brain regions, we found robust evidence of a loss of connectedness of the cerebellum, indicated by the hub disruption index and supported by the local network topology results. We hypothesize that this circuit-selective significant reduction of cerebellum centrality could be linked to diaschisis phenomena caused by a reduced excitatory drive from the damaged cortex, to which cerebellum is densely connected (Herculano-Houzel, 2012) and could represent in the context of global brain severe injury, a potential relevant biomarker of diffuse cortico-cortical and cortico-thalamic widespread functional disruption. From a cognitive point of view, this cerebellar disconnection seems in line with recent studies which have highlighted the cognitive role of this brain structure in consciousness related processes as attention, working memory and self-reference tasks (Buckner, 2013; Sokolov et al., 2017).

Finally, the network reorganization index pointed to an increase in nodal degree in coma patients in the least central nodes found in the healthy controls, implying potential compensatory brain plastic processes, reflected through reallocation of critical residual neural resources to otherwise not so central nodes (Di Perri et al., 2014; Hillary et al., 2015; Liu et al., 2017).

4.1. Methodological considerations and limitations

We thresholded each subject's graph at an FDR-adjusted significance level of p < .05, and used the resulting connection densities to select a fixed density threshold that contained only significant edges for all subjects, including controls and coma patients. The final threshold was set to 10% of significant connections, according to the minimal value found in the sample of healthy subjects. This approach certainly has the advantage of reducing the effect of potentially spurious connections by highlighting patients with insufficient functional connectivity, however, other significance levels should also be considered, to make sure that these findings are not specific to a single threshold (Váša et al., 2018).

Different brain parcellation methods should be taken into account when defining regions of interest, as the choice of nodes has been shown to significantly impact the topological organization (De Vico Fallani et al., 2014). However, the “randomness”, that is the loss of functional connectivity, found in some of our patients has been identified across multiple levels of parcellation implying potential global-level changes independent of the choice of brain nodes.

Further, since the BOLD signal is hemodynamic in origin, it is worth investigating if alterations in global functional connectivity found in our patients might be, in some cases, a reflection of altered neurovascular coupling and consequent signal loss, as previously highlighted in cerebrovascular and ischemic disorders (Hillman, 2014).

Further research needs to include more patients with accurate long-term longitudinal follow-up, encompassing repeated behavioral and fMRI assessment because topological organization could significantly change over the course of time (Castellanos et al., 2011; Nakamura et al., 2009). Additionally, comatose patients with different etiologies, such as traumatic brain injury, should be also studied aiming to identify potential etiology-related pathology mechanisms.

5. Conclusions

In summary, the probabilistic p value–based thresholding which we applied highlighted significant whole-brain reorganization in coma patients, with the most severe changes implying a global reduction in functional connectivity and consequent randomness. The remaining patients had sufficient significant connections between regions, but showed globally reorganized brain networks put in evidence by a disruption in hub rank order across several local metrics. Apart from a deeper understanding of the neural correlates of consciousness, the obtained dichotomization between the non-effective and effective patient subgroups, has potential clinical implications and might be particularly relevant for outcome prediction and could inspire new therapeutic options.

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Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.neuroimage.2019.03.012.

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