## Hubs of brain functional networks are radically reorganized in comatose patients

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Human brain networks have topological properties in common with many other complex systems, prompting the following question: what aspects of brain network organization are critical for distinctive functional properties of the brain, such as consciousness? To address this question, we used graph theoretical methods to explore brain network topology in resting state functional MRI data acquired from 17 patients with severely impaired consciousness and 20 healthy volunteers. We found that many global network properties were conserved in comatose patients. Specifically, there was no significant abnormality of global efficiency, clustering, small-worldness, modularity, or degree distribution in the patient group. However, in every patient, we found evidence for a radical reorganization of high degree or highly efficient "hub" nodes. Cortical regions that were hubs of healthy brain networks had typically become nonhubs of comatose brain networks and vice versa. These results indicate that global topological properties of complex brain networks may be homeostatically conserved under extremely different clinical conditions and that consciousness likely depends on the anatomical location of hub nodes in human brain networks.

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brain network organization really matter in terms of supporting special aspects of human brain function such as consciousness?

Neuroimaging methods, such as PET and task-related functional MRI (fMRI), have previously been used to demonstrate different patterns of functional connectivity depending on level of consciousness in comatose patients admitted to critical care departments following cardio-respiratory arrest or traumatic brain injury (6-9). A global disconnection syndrome between higher-order association cortices and primary cortical areas was observed in vegetative state patients, whereas the preservation of large-scale cortical networks associated with language and visual processing was noted in minimally conscious patients (8, 9). Furthermore, the thalamocortical connectivity was found to be restored in a few patients who recovered consciousness after being in a chronic vegetative state (10). Connectivity of the medial parietal cortex (precuneus) has been proposed as a biomarker that best differentiates between healthy volunteers and patients with consciousness disorders (7). The precuneus is a component of the default mode network (DMN), which is hypothetically related to self-consciousness (11). DMN connectivity has been investigated in noncommunicative brain-damaged patients (12-14), and a relationship was found between the amount of connectivity in the DMN and the degree of clinical impairment of consciousness (14). However, to date, there has been no analysis of global or nodal metrics of brain network topology in patients with impaired consciousness.

We measured functional brain graphs in 17 patients with severely impaired consciousness and 20 healthy volunteers matched approximately for sex and age with the patient group. At the time of scanning, the comatose patients did not require assisted ventilation, but they were deeply unconscious as a result of a range of major acute medical events (Table S1). We estimated functional connectivity between each pair of 417 brain regions in each fMRI dataset using wavelet analysis to focus on correlated time series activity in the low-frequency interval 0.02–0.04 Hz. From these individual association matrices, we constructed binary adjacency matrices or graphs over a range of connection densities. We first explored the global properties of these connectivity matrices and

rain networks have traditionally been analyzed in anatomical Brain networks have traditionally over analyzed considering the topological aspects of brain networks. Topological metrics characterize the relationships between elements of a system regardless of their physical location. From neuroimaging data, it has been possible to model large-scale human brain networks as "brain graphs" of regional cortical and subcortical nodes (each in the order of cubic centimeter volume), with edges or lines drawn between nodes to represent their functional or anatomical connectivity (1, 2). Topological analysis of human brain graphs has found that they are generally small-world, modular, and comprise a number of highly connected hub nodes (3). "Hubness" can be measured in many ways; for example, nodes may be defined as hubs because they have an unusually high degree, or centrality, or importance for intermodular connectivity (4). Many other complex systems, including high-performance computer chips (5) and transportation and social networks, have similar topological attributes; these complex graphical properties also seem to be qualitatively well conserved in nervous systems across scales of space and time and in different species (3). Thus, it is plausible that many aspects of brain network organization are not specific to the human brain and are therefore not, presumably, critical to the distinctive functions of the human brain, such as normal consciousness. To frame the point as a question: if brains are part of a large class of information processing systems that share certain complex topological features in common, what can we continue to say is special about the human brain? Or which specific aspects of

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brain graphs and then investigated differences between comatose patients and healthy volunteers at the level of individual nodes.

## Results

**Global Connectivity and Network Topology.** There were no significant differences between groups on any global measure of functional connectivity or network topology. The global mean wavelet correlation, a band-passed (0.02–0.04 Hz) measure of the strength of functional connectivity between brain regions on average over all pairs of regions in the brain, was about 0.3 in both groups (Fig. 14). The functional networks in both groups also had similar global efficiency and clustering (Fig. 1; Fig. S1). Both healthy volunteers and comatose patients demonstrated the characteristically "small world" property of high clustering combined with high global efficiency of random networks with the



**Fig. 1.** Global functional connectivity and topological properties of brain networks in healthy volunteers (white) and comatose patients (gray). (A) Mean wavelet correlation, a measure of functional connectivity on average over all pairs of regions in the brain. (B) Global efficiency, a topological measure of integrative information transfer inversely related to characteristic path length. (C) Clustering, a topological measure of segregated information transfer. (D) Maximum modularity, a global measure of the near-decomposability of the network into a community structure of sparsely interconnected modules. (E) Degree distribution, the probability distribution of the degree of a node in the network (patients in red and healthy volunteers in black). Corresponding results for other global metrics (betweenness centrality, participation coefficient, degree distribution parameters), other wavelet scales, spatial parcellation scales, and graph connection densities are in Figs. S1 and S6–S9.

same number of nodes, connection density and degree distribution; Fig. 1 B and C). Networks were also modular in both groups, and there was no significant difference in global modularity between groups (Fig. 1D). There were also no differences between groups in global averages of betweenness centrality or the participation coefficient (Fig. S1). Finally, the probability distribution of nodal degree (the number of edges connecting each node to the rest of the network) was best fit by an exponentially truncated power law in each individual dataset, and there were no significant differences between groups in the degree distribution parameters ( $\alpha$ , the power law exponent;  $\beta$ , the exponential cutoff) (Fig. 1E; Fig. S1). In short, despite the marked difference in clinical state between patients and comparison subjects, their brain networks had conserved global properties of small-worldness, modularity, and fat-tailed degree distributions signifying the existence of high-degree hub nodes.

Nodal Connectivity and Network Topology. Many measures of connectivity and network topology can also be estimated from each individual node in the network, thus allowing a finer-grained analysis of changes in brain function associated with clinically impaired consciousness. The strength of functional connectivity, efficiency, clustering, degree, betweenness centrality, and participation coefficient were all estimated for each node on average over all subjects in each group. As shown in Fig. 2, there were significant differences between groups in these measures at several locations in the cortex. In some regions, such as occipital cortex and precuneus, the patients had significantly decreased efficiency, clustering, and degree, whereas these measures were significantly increased in patients in other regions such as lateral parietal and prefrontal cortex. This pattern of abnormally increased or decreased nodal properties could be summarized by plotting, for a given metric, the mean value at each node in the healthy volunteer group versus the difference between patient and volunteer groups at each node (Fig. 2A). We defined a new measure, denoted  $\kappa$ , as the gradient of a straight line fitted to these data. This coefficient can be called a hub disruption index, as it measures the way the network's nodes are radically reorganized in comparison with healthy volunteers, with increased hubness of some regions and decreased hubness of others (see SI Text for details on estimation of the hub disruption index). For each metric considered, this analysis demonstrated a significant negative hub disruption index,  $\kappa \sim -1$ ; in other words, the nodes that had the highest hubness scores in healthy volunteers showed the greatest reduction in patients, whereas the nodes that had the lowest hubness scores in healthy volunteers showed the greatest increase in patients. Importantly, this was true for all of the tested brain connectivity and network metrics, including the unthresholded wavelet correlation measures of functional connectivity and the topological measures on thresholded binary graphs (degree, global efficiency, clustering, betweenness centrality, and participation coefficient). For example, this disruption of nodal topology is clearly represented by the analysis of degree: some of the highest-degree nodes in the healthy volunteer network showed the greatest reduction of degree in patients, whereas some of the lowest-degree nodes in the volunteer network showed the greatest increase of degree in the patients (Fig. 2). Comatose patients, on average, had abnormally reduced hubness of nodes in the occipital cortex and abnormally increased hubness of nodes in the prefrontal and lateral parietal cortex. This between-group difference in mean network topology was observed in the context of differences between individual patients in the anatomical locations of topologically disrupted network nodes (Fig. S2). Moreover, we found that this disrupted hub profile was not only evident in the comparison between group mean networks but was also consistently demonstrated in each individual patient's network. To show this, we estimated the hub disruption index for each individual patient (and each of the connectivity and topological



Fig. 2. Hub disruption of functional networks in comatose patients. (A) The mean degree of each node in the healthy volunteer group (healthy) (x axis) is plotted versus the difference between groups in mean degree of each node  $\langle coma \rangle - \langle healthy \rangle$  (y axis). Normal hub nodes have a high mean degree in the healthy group and an abnormal reduction of degree in the comatose group, e.g., precuneus or fusiform gyrus, whereas nodes that are normally nonhubs have a low degree in healthy volunteers and an abnormal increase of degree in patients, e.g., angular gyrus. The slope of the (red) line fitted to the data is the hub disruption index,  $\kappa_D \sim -0.8$ ; using the same color scale as in B, the color of the points denotes the difference between groups in mean degree of each node. (B) Cortical surface representation of the difference in mean degree between patient and volunteer groups; red denotes increased degree. on average, in patients compared with healthy volunteers; blue denotes abnormally decreased degree in comatose patients. (C) Cortical surface representation of nodes that demonstrated significant between-group difference in nodal degree; permutation test, two-tailed P < 0.003; red denotes significantly increased degree and blue denotes significantly decreased degree in the patients on average. Corresponding results for other measures of hubness (functional connectivity, global efficiency, clustering, betweenness centrality, and participation coefficient) are shown in Figs. S3 and S6; for further detail on the estimation of the hub disruption index, see Fig. S4.

metrics). As shown in Fig. 3, all patients demonstrated disruption of nodal properties compared with the volunteer group mean, summarized by a negative hub disruption index,  $\kappa < 0$ . When the same analysis was applied to each individual in the healthy volunteer group, the gradient of the fitted lines was typically close to zero,  $\kappa \sim 0$ . There were therefore highly significant between-group differences in this measure of hub profile disruption (Fig. 3). The *P* values obtained from *t* tests for between-group differences in  $\kappa$ were less than  $10^{-5}$  for all connectivity and topological metrics (Fig. S3). There was also a statistically significant between-group difference by a permutation test of  $\kappa_D$  (P < 0.001; Fig. S4).

**Global Modularity and Community Structure.** Modularity is a global measure of how well a network can be decomposed into a set of sparsely interconnected (but densely intraconnected) modules. Although this global measure was unchanged in coma patients (Fig. 1*D*), we hypothesized that the community structure could still be perturbed in coma, in terms of the identity of the nodes making up the different modules. To test this, we used normalized mutual information (NMI) to quantify the pairwise similarity between the modular partitions or community structures obtained for different subjects (15, 16). The mean NMI between a pair of two healthy networks was significantly higher than the NMI

between a pair of two patients or between a pair of one patient and one volunteer. This indicates that community structure was more variable in the patient group than in the healthy group and more similar between different individuals in the healthy volunteer group than between healthy and comatose individuals (between-group permutation test of NMI, P < 0.00001). In short, at a nodal level, the community structure of brain functional networks is reorganized in coma even though the maximum value of global modularity is not different on average between the comatose and healthy groups. This is also illustrated (Fig. 4) by comparing the modular decomposition of a network constructed by averaging the correlation matrix over all healthy volunteers with the modular decomposition of a single representative volunteer. The apparent similarity of community structure between the healthy individual and the healthy group mean contrasts with the evident differences in the anatomical localization of modules found in a representative coma patient.

## Discussion

We used noninvasive (fMRI) neuroimaging to measure brain functional connectivity and network properties in 17 patients in a comatose state as a result of an acute brain injury. A key theoretical and clinical question of interest was the nature of any topological abnormality in the brain network organization of the patients that might relate to their state of severely impaired consciousness and therefore perhaps shed light on which aspects of normal brain network organization might be critical for consciousness.

The first main finding was the absence of any evident difference between the groups of comatose patients and healthy volunteers on any global measure of functional connectivity or network topology. In terms of global efficiency, clustering, modularity, betweenness centrality, participation coefficient, and degree distribution parameters, there were no significant differences between the two groups. These results demonstrate that global



**Fig. 3.** Individual comatose patients consistently demonstrate hub disruption of functional brain networks. (*A* and *C*) The hub disruption indices  $\kappa_D$  and  $\kappa_S$  were estimated for each patient as the gradient of a straight (red) line fitted to the scatterplots of the individual differences in nodal degree (D) or functional connectivity (S) vs. the healthy group mean nodal degree or connectivity. The black horizontal line shows the equivalent function estimated for the individual differences of each healthy volunteer vs. the healthy group mean (error bars = SD). (*B* and *D*) Boxplots of the individually estimated hub disruption indices for the healthy volunteer group (white) and the comatose patient group (gray). For both  $\kappa_D$  and  $\kappa_S$ , the healthy group mean is approximately zero, whereas for the patient group, it is closer to -1. The between-group differences in  $\kappa$  are significant by *t* test ( $P < 10^{-5}$ ) and by permutation test (P < 0.001; Fig. S4). Corresponding results for other hubness measures are shown in Fig. S3.



**Fig. 4.** The community structure of functional networks is abnormally variable between comatose patients. (*Right*) Each matrix element represents the similarity between the community structure (modular decomposition) for a pair of participants, as measured by normalised mutual information (NMI). The first 20 rows/columns represent healthy volunteers, whereas the next 17 rows/columns correspond to the comatose patients; *insets* show group means (and SEMs) for NMI. The NMI values on the diagonal were set to zero (instead of their natural value of 1) for clarity of visualization. (*Left*) Cortical surface representations of the community structure of the healthy volunteer group on average (*Top*), a single representative healthy volunteer (*Middle*), and a single representative comatose patient, with median modularity in the patient group (*Bottom*). It is evident that the normal affiliation of specific cortical regions to topological modules (color coded on the cortical surface) is extensively disrupted in the comatose patient.

fMRI connectivity and network properties are unlikely to be useful biomarkers of clinical status in patients following acute brain injury. To put it another way, global functional network properties are homeostatically conserved under the very different clinical conditions of a patient in deep coma following a major brain injury versus a healthy volunteer.

In a sense, this is not surprising. The complex topological properties of human brain networks, such as small-worldness, modularity, and fat-tailed degree distribution, are known to be qualitatively similar to those of many other biological, social, and computational networks (3, 17, 18). At the level of global network description, the brain has a number of organizational features in common with other, substantively diverse but topologically isomorphic, complex systems. Therefore, it is not unexpected that brain networks should conserve at least qualitatively similar topological properties under different clinical conditions. Indeed there are prior data demonstrating conservation of fundamental network properties-such as small-worldness and modularityacross a wide range of clinical disorders causing cognitive impairment, including Alzheimer's disease and schizophrenia. Nevertheless, it is notable that in most network studies of clinical disorders, there have been some quantitative differences between patient and control groups in the value of global network parameters. For example, patients with Alzheimer's disease have abnormally reduced global efficiency (19), whereas patients with schizophrenia have abnormally reduced clustering (20). In contrast, the comatose patients in this study were not quantitatively distinguishable from the normal comparison group on any global measure of network organization.

However, when we examined network organization at a finergrained level of analysis, focusing on key properties of individual cortical nodes such as their degree, we found consistent evidence for a highly significant abnormality in the comatose patients. We

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can summarize this network abnormality as a disruption of hub rank order. Brain regions, such as fusiform gyrus and precuneus, which were high-degree hubs in the normal brain networks, became low-degree nonhubs in the comatose brain networks, whereas regions, such as angular gyrus, which were low-degree nonhubs in the normal group became high-degree hubs in the patient group. This disruption of the order of importance of specific cortical nodes was demonstrated not only for degree but also for nodal connectivity strength, clustering, and efficiency, and it was statistically significant not only at the level of between-group mean comparisons but also at the level of each individual patient compared with the control group mean. There was a parallel finding in terms of modularity: the global measure of modularity was not significantly different between groups, indicating that brain networks could be equally well decomposed into a set of modules in both patients and healthy volunteers, but the anatomical identity of the nodes comprising specific modules was markedly abnormal, and abnormally variable, in the comatose patients.

Consistent with this general principle of hub rank disruption, a previous fMRI study has advocated abnormal reduction in functional connectivity of the precuneus (normally a hub) as a biomarker for brain functional status after acute brain injury (7). We found a significantly reduced degree of the precuneus, a key region in coma patients, whose activity is related to the level of consciousness (14) and whose metabolism was partially restored in the rare patients that recover consciousness after being in a chronic vegetative state (21). However, our finding that the reduced importance of normal hubs is approximately balanced by the increased importance of normal nonhubs is unique in the context of coma studies. We found abnormally increased importance of cortical nodes in four main regions: the orbitofrontal cortex, the inferior parietal lobe extending to the angular gyrus and to the supramarginal gyrus, the temporal poles, and the amygdala. There have been no prior reports of abnormally increased connectivity or degree of individual cortical areas in patients with acute brain injury, but such hub reorganizations have been previously described in Alzheimer's disease (where connectivity between frontal nodes is increased) (19, 22), stroke (23), and schizophrenia (20).

To return to the motivating question, what does this pattern of results tell us about functional brain network organization in relation to normal states of consciousness? It suggests that global topological properties, such as small-worldness and modularity, are not sufficient to describe the brain network organization required for consciousness (13, 24). In addition, the more specific details of how topological features such as network hubs are mapped to particular anatomical areas of cortex are likely to be important in understanding the brain substrates of consciousness more completely. Again, this is arguably not too surprising. The optimal function of an engineered network, such as a computer circuit, is not specified entirely by the global topological statistics of its wiring diagram, but is also dependent on a spatially precise mapping of topological features to the circuit board (5, 25). As we have shown here, the normal anatomical location of network hubs and modules is radically reorganized in comatose patients, implying that a specific topological-to-spatial mapping is critical for functional network organization for conscious processing.

How can we explain the conservation of global network properties, and the anatomical reorganization of local network properties, in relation to the clinical status of the patients participating in this study? The patients were all scanned within a few days of an acute brain injury associated with severe loss of consciousness, due to a number of causes, most often cardiorespiratory arrest. There is evidently some diversity between individual patients in the anatomical locations of affected hubs and nonhubs (see Fig. S2 for representative networks of four individual patients). There was also some heterogeneity in the comatose group in terms of clinical outcome and the immediate cause of coma. However, the power of this dataset to relate individual differences in the cause of coma to differences in network topology and, ultimately, to differences in outcome is limited. For example, level of consciousness was measured using a standardized instrument [Wessex Head Injury Matrix (WHIM) scale] on only one occasion, and most patients were rated in a narrow range at or close to the minimum score (signifying deep coma) on this scale (Table S1). Correlations between WHIM score and network measures, including the hub disruption index, were not statistically significant, but this could reflect lack of dynamic range and serial measures in the clinical profiling of these patients.

It is notable that all of the patients experienced an acute crisis of extreme cerebral hypoxia or hypoglycemia, and it is known from prior studies that functional network hubs tend to be metabolically more expensive, e.g., having greater rates of glucose metabolism, than nonhubs (26). Thus, the consistent finding across patients that the connectivity of hub nodes was abnormally reduced may reflect the putatively greater vulnerability of hub nodes to metabolic or oxidative stress. After acute brain injury, prior work suggests that two main recuperative phenomena occur (27, 28). The first process is initiated soon after injury and relies on the GABAergic disinhibition of secondary pathways between undamaged brain regions that were not used during normal functioning of the brain (27, 29). The second process occurs later after the injury, and it relies on the growth of new axons (10). It is known from prior modeling studies (30) that functional connectivity measured over longer periods of time more closely approximates the underlying anatomical connectivity or wiring of the system. Given the relatively long period of the resting-state fMRI measurements in this study (20 min), it might be argued that the functional network changes reflected underlying changes of anatomical connectivity. However, we repeated the fMRI analysis using only the first half of each time

series and replicated the key findings of conserved global properties and disrupted hub profiles even when the duration of the fMRI measurements was much reduced (Fig. S5). For this reason, and also because the time interval between onset of coma and the timing of the fMRI scan was short relative to the time interval required for axonal growth (Table S1), we infer that the emergence of new hubs in anatomical regions that were not so topologically important before the injury represents an immediate, perhaps interneuronally mediated, response to brain injury. How this nodal disruption is constrained by homeostasis of global network parameters remains an open question for further investigation.

The study raises a number of other methodological issues. The number of patients is not large, and it is possible that the lack of significant between-group differences in global network properties is a type 2 error reflecting inadequate statistical power. However, we note that the sample size was adequate to detect highly significant differences in nodal network properties in the patients compared as a group and individually with the group of healthy volunteers. There has been recent interest in the confounding effects of small amounts (<0.1 mm) of head movement on measures of functional connectivity in developmental and clinical fMRI studies (31). However, we excluded data not satisfying prior criteria for unacceptable head movement; we applied standard procedures for movement correction by realignment and regression; and post hoc, we demonstrated that there were no significant differences between groups in estimated movement parameters, and there were no significant correlations between small, highfrequency residual movements (framewise displacements) and first-order differences in the movement-corrected fMRI time series (31). We therefore consider it unlikely that the observed differences are attributable to differences in head movement. More generally, there could be other differences between the groups, such as their tendency to maintain eyes closed during scanning, that might affect the pattern of results without being attributable to altered level of consciousness. Reasonable choices of fMRI preprocessing options and network parameters can have major impact on the results of functional connectivity and network analysis. We therefore explored extensively the impact of various other methodological factors on the pattern of results: the key findings were consistent for all connectivity and topological metrics considered and remained robust to reasonable variation of wavelet (frequency) scale, spatial parcellation scale (number of network nodes), and connection density (number of network edges) (see SI *Text* and Figs. S6–S9 for details).

## **Materials and Methods**

Subjects. Twenty-five patients in a coma were scanned (age range, 21-82 y; 9 men). Data on eight patients were subsequently excluded because of unacceptable degrees of head movement (see SI Text for details). The coma severity for each patient was clinically assessed using the 62 items of the WHIM scale: scores range from 0, meaning deep coma, to 62, meaning full recovery (32). The patients were scanned a few days after major acute brain injury, when sedative drug withdrawal allowed for spontaneous ventilation. Therefore, all of the patients were spontaneously ventilating and could be safely scanned at the time of fMRI. The causes of coma were different between patients: 12 had cardiac and respiratory arrest due to various causes; 2 had a gaseous cerebrovascular embolism; 2 had hypoglycemia; and 1 had extracranial artery dissection. Six months after the onset of coma, 3 patients had totally recovered, 9 patients had died, and 5 patients remained in a persistent vegetative state (Table S1). The normal control group comprised 20 healthy volunteers matched for sex (11 men) and approximately for age (range, 25–51 v) to the group of patients. This study was approved by the local Research Ethics Committee of the Faculty of Health Sciences of Strasbourg on October 24, 2008 (CPP 08/53) and by the relevant healthcare authorities. Written informed consent was obtained directly from the healthy volunteers and from the next of kin for each of the patients.

**fMRI Data Acquisition, Preprocessing, and Data Analysis.** fMRI data were recorded while subjects lay quietly at rest in the scanner for 20 min. Gradient echo echoplanar imaging data sensitive to blood oxygenation level-dependent (BOLD) contrast were acquired using a 1.5-T MR scanner (Avanto; Siemens, Erlangen, Germany) with the following parameters: relaxation time = 3 s, echo time = 50 ms, isotropic voxel size =  $4 \times 4 \times 4$  mm<sup>3</sup>, 405 images, and 32 axial slices covering the entire cortex. The resting-state fMRI data were preprocessed using SPM8 software (www.fil.ion.ucl.ac.uk/spm). For each subject, the data were corrected for head motion and then coregistered with each subject's T1-weighted structural MRI. Time series data were not spatially smoothed and were not corrected for the global mean time series by regression (33). The data were quality controlled for head movement and other possible artifacts: eight images were excluded at this stage for poor quality (see SI Text for details). The structural MRI was segmented into gray matter, white matter, and nonbrain components and then normalized to the Colin27 template image (34) using the nonlinear registration method DARTEL (diffeomorphic anatomical registration using exponentiated Lie algebra) (35). This registration provides a deformation field image that was then used to map the fMRI datasets to a customized parcellation image based on the automated anatomical labeling (AAL) template image (36) but further subdivided into 417 anatomically smaller regions (nodes) with homogeneous sizes (37). Regional mean time series were estimated by averaging the fMRI time series over all voxels in each parcel, weighted by the proportion of gray matter in each voxel of the segmented structural MRIs and corrected for head movement by regression on the time series of estimated head translations and rotations. We estimated the correlations between Daubechie's wavelet coefficients of the 86,736 possible pairs of the N = 417 cortical and subcortical fMRI time series extracted from each individual dataset (1). We focused our analysis on the scale 3 wavelet correlation matrices that represented functional connectivity in the frequency interval 0.02–0.04 Hz. The strength of functional connectivity was estimated for each node as the average of its wavelet correlations with all other nodes in the network. The absolute wavelet correlation matrices were thresholded, over a range of threshold values, to generate binary undirected graphs with connection density (number of edges proportional to the maximum possible number of edges) in the range 2.5-42.5%. The following topological metrics were estimated at

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each node of each individual graph: degree, efficiency, clustering, betweenness centrality, and participation coefficient. The global average of these metrics was estimated over all nodes in each network. The global modularity and the degree distribution were also estimated for each graph (see SI Text and refs. 3 and 38 for more details on these metrics). Global and nodal statistics were compared between groups by t tests or by permutation tests. To control the multiple comparisons by t tests for each nodal metric, we assigned statistical significance to nodes where P < 0.003; at this level of significance, we expect less than one false-positive test per network. To summarize the abnormal profile of nodal connectivity and topological metrics in patients compared with the healthy volunteer group, we defined the hub disruption index,  $\kappa$ . As shown in Fig. 2 and Fig. S4,  $\kappa$  is the gradient of a straight line fitted to a scatterplot of the nodal property of interest, e.g., degree, in an individual participant minus the same nodal property on average over all of the healthy volunteers vs. the mean nodal property in the healthy group. For comatose individuals, this gradient was negative, indicating that nodes with a high degree (or other hub-like properties) in the healthy brain network were less topologically important in the patients, whereas nonhub nodes in the healthy brain networks were more topologically important in the patients (Figs. S3 and S6). Network analysis was implemented in an open source, R-based software library, called brainwaver, which is freely downloadable at http://cran.r-project.org. For visualization, we used Caret v5.61 software (39) to make cortical surface representations of nodal connectivity and topological metrics.

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