Supplementary Methods

Locked-in Syndrome (LIS) Patients

LIS patients were diagnosed by their injury as seen on MRI scans (two patients had lesions in the medulla while the other two patients had lesions in the pons). They were all able to communicate with eye or limb movements. They also underwent psychological tests to assess and confirm their cognitive function, which was preserved in all patients. Further, LIS patients obtained high scores on the CRS-R assessment.

PET Data Collection and Analysis

Flurodesoxyglucose-PET (FDG-PET) scans were acquired from all subjects using methodology described in (Stender et al., 2014), about 30 minutes after intravenous injection of 150 or 300 MBq of FDG on a Philips Gemini TF PET-CT scanner (Philips Medical Systems). An examiner was present during the whole acquisition to ensure that the patient remained awake and eyes open in a silent and dark room (tactile or auditory stimuli were administered when patients were closing their eyes). Data analysis and interpretation followed what was used in (Stender et al., 2014). Briefly, Statistical Parameter Mapping (SPM8) was used to identify regions with relatively decreased and preserved metabolism in patients as compared to controls. A ‘PET positive’ or ‘PET negative’ diagnosis based on the PET scan was made by visual examination of the results of this analysis result: following previous findings, complete bilateral hypometabolism of the associative frontoparietal cortex with no voxels with preserved metabolism led to a PET negative, whereas incomplete hypometabolism and partial preservation of activity within these areas yielded a diagnosis of PET positive (Laureys et al., 2004; Nakayama et al., 2006; Thibaut et al., 2012).
**EEG Data Pre-processing**

EEG data from 173 channels on the scalp were retained, discarding channels on the neck, forehead and cheeks, as these channels contributed most of the movement-related noise in patients. Data from the selected channels were filtered between 0.5-45Hz, and segmented into 10-second epochs. Time points within each epoch were baseline-corrected relative to the mean voltage over the entire epoch.

Data with excessive eye movement or movement artefact were removed as follows: abnormally noisy channels and epochs were first identified by calculating their normalised variance, and then manually rejected or retained by visual inspection. On average, approximately 11% of channels (mean = 20, S.D. = 17) were rejected and interpolated. Independent Components Analysis (ICA) based on the Infomax ICA algorithm (Bell and Sejnowski, 1995) was then used to identify and remove components that were generated by non-neural noise sources.

Channels previously removed as noisy were interpolated with the cleaned data using spherical spline interpolation. Each channel was re-referenced to the average of all channels. The first 60 clean epochs (i.e., 10 minutes) from each subject were retained for further analysis. This ensured that there was no difference between subject groups in the number of epochs contributing to the estimation of brain connectivity. An average of 11 minutes (S.D. = 1.6 minutes) of EEG data had to be collected to obtain at least 60 clean epochs.

**Brain Connectivity Estimation**

We used the debiased weighted Phase Lag Index (dwPLI) to estimate spectral connectivity between pairs of channels. The dwPLI (and its precursor, the Phase Lag Index) measure of
phase relationships is an estimator of scalp-level connectivity that is more robust and partially invariant to volume conduction in comparison to other estimators (Peraza et al., 2012).

dwPLI between a pair of EEG channel time series is a number between 0 and 1 indexing the extent to which the phases of the oscillations in each channel within a particular band have a consistent phase relationship with respect to each other. Importantly, dwPLI down-weights phase differences near 0° and 180°, as these could arise simply due to volume conduction rather than true interactions between underlying brain sources.

**Brain Network Metrics**

Clustering coefficient is a measure of the local efficiency in the connectivity of individual network nodes, while characteristic path length measures the whole network’s global efficiency. The modularity of a network captures the extent to which the network can be divided up into interconnected sub-networks. Given a particular division of network nodes into modules, the participation coefficient of an individual node measures the diversity of its inter-modular connections. Nodes with high participation coefficients interconnect multiple modules together, and hence can be seen as key connectivity hubs. Both modularity and participation coefficient were calculated from the community structure estimated in the network by the heuristic Louvain algorithm (Blondel et al., 2008). The algorithm was repeatedly run 50 times to account for the inherent randomness in the heuristic, and values of these two metrics obtained after each run were averaged over the repetitions.

Given a thresholded graph and a community structure identified by the Louvain algorithm, the modular span $S$ of a non-degenerate module $M$ (i.e., a module with more than one member), was defined as:
where \( n_M \) is the number of nodes in the module, and \((i, j)\) are a pair of member nodes therein, \(d_{ij}\) is the normalised Euclidean distance between the pair of corresponding electrodes over the scalp, and \(c_{ij} = 1\) if there is an edge between nodes \(i\) and \(j\), and zero otherwise. As \(d_{ij}\) is the normalised distance (i.e., \(d_{ij} = 1\) for the most distant pair of electrodes), modular span is dimensionless. Modular span can be interpreted as the sum of the topographic lengths of all the edges between the nodes comprising a module, scaled by the size of the module. Greater values of modular span indicate that modules identified by graph theory span greater physical distances over the scalp, hence capturing long-distance connectivity. As with modularity and participation coefficient, values of modular span calculated after each repetition of the Louvain heuristic were averaged over the 50 repetitions. We have previously shown that modular span of brain networks in particular is specifically impaired in DoC patients relative to controls (Chennu et al., 2014). Here, we evaluated its comparative efficacy in differentiating groups of DoC patients.

**Brain Network Visualisation**

We developed a method to visualise brain networks in 3D, drawing upon related approaches (King et al., 2013) and previous work (Chennu et al., 2016), to depict the pattern of sensor-level connectivity overlaid with topological information from graph-theoretic analysis. We used this method to plot both group-averaged (e.g., Fig. 1A) and individual brain networks (Fig. 3). Given with a 173x173 symmetric connectivity matrix of dwPLI values between 0 and 1, we used the steps below to plot each visualisation:
1. The connectivity matrix was proportionally thresholded to retain only the top 30% of dwPLI values. Values below this threshold were set to zero. This was done to highlight the strongest connections with visual clarity.

2. The weighted degree of each electrode was calculated by taking the sum of all the above-threshold dwPLI values between that electrode and all other electrodes.

3. These degree values were then plotted as a heat map over a 3D scalp, using EEGLAB’s headplot function. Hence red regions over the scalp indicate electrodes with high dwPLI connectivity with other nodes.

4. The Louvain modularity algorithm (Blondel et al., 2008) was used to identify a modular decomposition of the thresholded network. This heuristic algorithm identified ‘modules’ within the connectivity network, which are non-overlapping subsets of electrodes with higher connectivity between each other than with electrodes in other modules.

5. For each non-zero dwPLI connectivity value between a pair of electrodes, arcs were plotted over the scalp such that either end of the arc intersected with the scalp at the location of the electrodes.

6. The height of the arc over the scalp was scaled by the strength of the corresponding dwPLI value, such that a dwPLI value of 0 would produce an arc which was approximately parallel to the surface of the scalp and a maximal value of 1 would generate an arc 50% of the height of the 3D head.

7. Each arc was coloured based on the module to which it belonged. For this, first an arbitrary colour was assigned to each module, ensuring that modules were assigned visually distinctive colours. Then, arcs corresponding to intra-modular connectivity values between electrodes belonging to a particular module were all coloured with the colour of the module. For visual clarity, inter-modular connectivity values between electrodes in two different modules were not plotted.
**Classification Analysis**

Classifiers were built using four-fold cross-validation, with each train/test fold containing constant proportions of each subject group (also known as stratification) to prevent any fold-specific effects. The SVM regularisation (soft margin) parameter C, the RBF kernel scaling parameter K, and the connection density parameter D were chosen using cross-validation combined with an exhaustive grid search method. D ranged between 90-10% of the strongest edges in steps of 2.5% (see above), while C and K were picked from the following set of possible values: $2^5$ to $2^{+5}$, $5^{-3}$ to $5^{+3}$ and $10^{-3}$ to $10^{+3}$.

From the cross-validated classifiers built using the above method, posterior probabilities of class affiliation were estimated using Platt’s method (Platt, 1999). A ROC analysis was run on these posterior probabilities to identify the best decision threshold or criterion, defined by Youden’s Index (Youden, 1950), which optimised the balance between sensitivity and specificity in the classification labels generated by the cross-validated classifier. These predicted class labels were compared with the true labels using the $\chi^2$ test to statistically test the classifier’s performance. We also tested the generalisability of classifiers trained on patient data by evaluating their performance on other patient and healthy controls datasets that were not used (kept in a ‘lock box’) for training and parameter optimisation (Skocik et al., 2016).

**Supplementary Figures**
Supplementary Fig. 1 – Data processing pipeline for EEG brain network analysis.

Cross-spectral density between pairs of channels was estimated using dwPLI. Resulting symmetric connectivity matrices were proportionally thresholded before the estimation of graph-theoretic metrics. As an example, in the alpha connectivity matrix shown (bottom left), the threshold has been set to plot the top 30% of strongest connections. Thresholded connectivity matrices were visualised as 3D connectivity topographs (bottom middle, see Methods for details of visualisation). Graph-theoretic metrics were calculated after binarising the thresholded connectivity matrices.
Supplementary Fig. 2 – Inter-subject correlation of alpha participation coefficient topographies. Panel A plots a matrix of correlations between the topographies of participation coefficients of every pair of subjects. For each subject, panel B plots the mean correlation with other subjects in the same group, which became progressively stronger as the level of behavioural awareness increased.

Supplementary Fig. 3 – Median dwPLI connectivity as a function of electrode configuration. Trend in median dwPLI connectivity vs. behavioural diagnosis, as quantified by the Jonckheere-Terpstra (JT) statistic was relatively robust against a progressive reduction in the number of electrodes included in the analysis from 173 down to 11. Further, median
connectivity within electrodes in frontal and parietal regions with high participation coefficient z-scores in controls (see Fig. 1B, CTRL topograph) produced the strongest trend.

Supplementary Fig. 4 – Relative power and median connectivity in the delta band as a function of level of consciousness. Relative power in the delta band averaged over all channels decreased progressively with increase in the behavioural diagnosis of patients (panel A). Median dwPLI connectivity in the delta band was lower in patients with positive outcomes, separated by etiology (panel B; JT trend statistic = 2.02, p = 0.0217).
**Supplementary Fig. 5 – EEG networks and etiology.** Delta networks were stronger in patients with non-traumatic etiology (panel A). Standard deviation of participation coefficients in the delta band were significantly different between etiologies (panel B). This metric was also best able to discriminate etiologies, as measured by AUC (panel C).

**Supplementary Table 1 – Demographic and diagnostic details of patients included in the study.**

**References**


