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Research Report

Synchronization between the anterior and posterior cortex determines consciousness level in patients with traumatic brain injury (TBI)

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ABSTRACT

Survivors of traumatic brain injury (TBI) often suffer disorders of consciousness as a result of a breakdown in cortical connectivity. However, little is known about the neural discharges and cortical areas working in synchrony to generate consciousness in these patients. In this study, we analyzed cortical connectivity in patients with severe neurocognitive disorder (SND) and in the minimally conscious state (MCS). We found two synchronized networks subserving consciousness; one retrolandic (cognitive network) and the other frontal (executive control network). The synchrony between these networks is severely disrupted in patients in the MCS as compared to those with better levels of consciousness and a preserved state of alertness (SND). The executive control network could facilitate the synchronization and coherence of large populations of distant cortical neurons using high frequency oscillations on a precise temporal scale. Consciousness is altered or disappears after losing synchrony and coherence. We suggest that the synchrony between anterior and retrolandic regions is essential to awareness, and that a functioning frontal lobe is a surrogate marker for preserved consciousness.

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1. Introduction

Patients with severe traumatic brain injury (TBI) who are diagnosed as being in the minimally conscious state (MCS), show a minimal level of behavioral response to their surroundings. If the diagnosis is severe neurocognitive disorder (SND), patients show a preserved state of alertness and better levels of consciousness, although the content may not correspond to reality. The ongoing treatment and clinical management of these patients would benefit from greater knowledge of the emergence of consciousness. An analysis of the different behavioral responses of these two groups would help determine which neurophysiological and/or neurobiological correlates are needed for consciousness to emerge.

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The flow of information within the brain is primarily affected by two mechanisms: the suppression of activity in various regions when important system components are "turned off", and the scrambling of signaling mechanisms which facilitate communication between regions (Alkire et al., 2008). Thus, experiences or stimuli with complex information, which eventually become the content of consciousness, could depend on the adequate flow of information within different neural regions via synchronization and coherence. Historically, beta waves have been associated with mental activity (Berger, 1938). Activity in beta bands (12.5–20 Hz) reflects cortico-cortical information processing through an increased flow of information from the thalamus to the cortex and vice versa. The generation of beta oscillation enhances the range of temporal delays between elements in a neural assembly, allowing synchronization within these assemblies to take place (Kopell et al., 2002). Synchronized nonrandom beta discharges occur within separate brain regions when producing information signals. The physical integration and coordination of this flow of information in a global workspace produces consciousness (Baars, 1989; Gaillard et al., 2009). This process requires the functional integration and encoding of a series of ordered regional links by means of synchronized activity dispersed among many cerebral regions. According to Weiskrantz (1999), the pattern of activity among several regions would be more critical for awareness than that within a particular brain region. The disruption of consciousness is associated with a breakdown in this interregional cortical connectivity.

The content of consciousness is regulated by activation of the frontal parietal network (Dehaene et al., 2006). Research has shown that a disconnected cerebral network causes disorders of consciousness (Laureys et al., 1999; Schiff et al., 2005). Two types of cortical areas, comprised of interacting neurons, are purported to be involved in consciousness (Crick and Koch, 2003). One group is said to project from the posterior cortex, and the other from the anterior cortex. The anterior, or executive, cortex appears to be "looking at" the posterior, or sensory, cortical system. These two groups of neurons continuously interact via long and short cortico-cortical and cortico-thalamo-cortical routes to create consciousness (Crick and Koch, 2003). Leon-Carrion et al. (2006) suggest that the temporal organization of stimuli in the brain requires serial and alternating engagement of frontal and posterior cortices.

A large body of neuropsychological evidence supports the existence of these cortical areas, reinforcing the relevance of frontal lobe and retrolandic areas in the generation of consciousness. Regulation of the content of consciousness has been associated with the flexibility of prefrontal cortical functions, while various aspects of sensory processing have been linked to posterior cortical functions (Fuster, 2008; Lhermitte, 1983; Passingham, 1993). According to John (2005), awareness is reduced when the prefrontal cortex (PFC) is depressed. The specific sequences of neural links engaged in consciousness and awareness may be disturbed in patients with frontal lobe lesions (Luria, 1966; John, 2005; Leon-Carrion et al., 2008).

The present study aims to explore how synchronized nonrandom neural circuits across cortical regions are integrated to generate consciousness. The study included two groups, patients in the MCS with inconsistent but discernible behavioral evidence of consciousness, and patients with SND, who show a consistent level of consciousness but whose content of consciousness may be altered. We analyzed their behavioral responses in an attempt to determine which neural discharges are meaningful for consciousness, and which cortical areas work together in synchrony to produce consistent evidence of consciousness (Tononi, 2004; Ward, 2011). Our hypothesis is that the emergence of consciousness requires synchronized circuitry to differentially integrate anterior and posterior cortices. Patients with SND should display greater synchrony and connectivity between anterior and posterior regions than patients in the MCS. Anterior brain activation would play a major role in organizing representations of consciousness, while retrolandic activity would act as a cortical stereotype of reflexes associated with its content. Moreover, the loss or reduction of frontal activity may abolish or limit conscious processing.

We used functional connectivity analysis to identify brain connectivity networks in task-free resting state EEG recordings (Beckmann et al., 2005; Greicius et al., 2003). Two methods were applied to ascertain the cause and effect relationships among all electrodes. The first method measured synchronization activity between pairs of electrodes and the second determined the strength and direction of functional connectivity. An analysis of the functional connectivity of these networks at rest may be particularly informative, as it provides a means to evaluate brain region interactions independent of task-induced activation/deactivation in patients with altered states of consciousness (Buckner et al., 2008).

2. Results

2.1. *Coherence*

Overall, SND patients showed a higher number of connections between predefined regions than the MCS group for most threshold values. Fig. 1 shows the differences in average number of connections between the two patient groups. Exhaustive calculations indicated that the best threshold to maximize differences was 0.4.

We calculated the differences in number of functional connections between SND and MCS patients for the 0.4 threshold. SND patients showed a higher number of functional connections in features 6, 9 and 12, which correspond, respectively, to the number of connections between frontal and parietal occipital, frontal and left temporal, and left temporal and parietal occipital regions (see Table 3). Frequency bands made significantly different contributions to the features: delta, theta, alpha, beta and full bandwidth were important in feature 9, whereas alpha, beta, gamma and full bandwidth were important in features 6 and 12 (all corrected $Ps < 0.05$). The same set of features differed significantly for connections at threshold value 0.3. Fig. 1 illustrates which areas showed significant differences in number of connections between groups.

2.2. *Granger causality*

Granger networks using bSMART (pair-wise univariate modeling) resulted non-conclusive due to the high number of connections and lack of a clear connectivity pattern in any frequency band

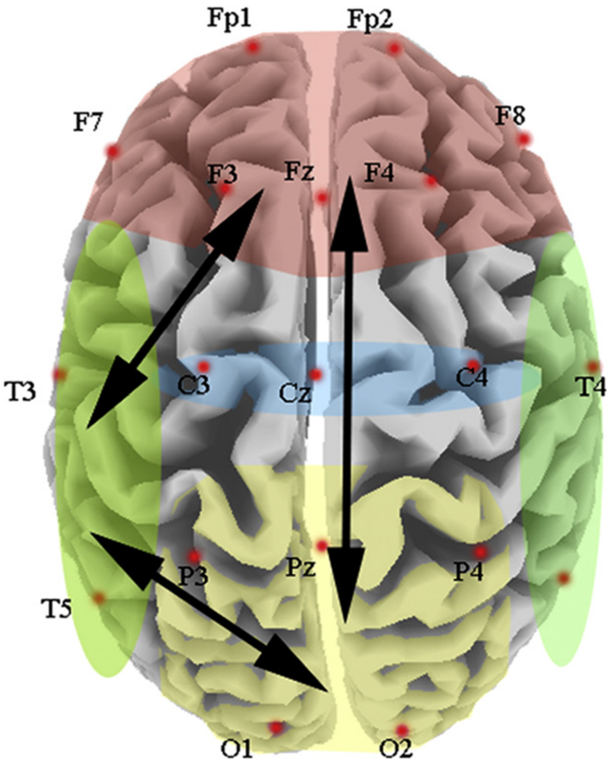

Fig. 1 – Areas with significant differences in number of functional connections between SND and MCS patients using plain coherence analysis.

(see Fig. 2). Nevertheless, SND patients typically showed more connections than MCS patients using this approach, especially in delta, alpha, and beta bands (Fig. 2).

Multivariate modeling using the Seth and DANCI approaches showed a clearer connectivity pattern. At $P<0.01$, significant differences were found in beta band for feature numbers 1 (inside frontal region), 10 (from left temporal to frontal), 14 (from central to frontal), 18 (from right temporal to frontal), and 22 (from parietal occipital to frontal) (Table 4). Using a less strict value of $P<0.05$, feature number 13 (from left temporal to parietal occipital) became significant in theta band (see Fig. 3).

3. Discussion

This is the first study to explore functional connectivity during resting state in SND patients and patients in the MCS using two different analytical methods. Of the two groups, we found stronger coherence during resting state in patients with SND. Our results suggest that preserved consciousness would require the simultaneous participation of anterior and posterior neural cortical structures responsible for executive functioning and cognitive representations, respectively. Patients in the MCS showed frontal cortex disconnection from other cortical regions, whereas patients with SND showed a high number of functional connections between the following regions: frontal and parietal occipital, frontal and left temporal, and left temporal and parietal occipital. Significant differences were found in delta, theta, alpha, and beta bands as well as in the full bandwidth. Multivariate modeling to detect the directions of these connections showed connections from all areas to the frontal region. These connections reached significance for the beta band (including connections inside the frontal region), whereas left temporal to parietal occipital connections were significant only for the theta band.

Our data reveal significant differences in full bandwidth coherence (delta, theta, alpha and beta) between SND and MCS groups. SND patients, with better-preserved consciousness, have a higher number of connections and display higher connectivity between retrolandic and anterior regions. Granger causality analysis indicates a clear connectivity pattern in beta ($P<0.01$) and theta bands ($P<0.05$). Our results illustrate the existence of a large scale network surviving in patients in the MCS (Schiff et al., 2005), and in SND patients (Giacino and Schiff, 2009), although the latter display a higher level of synchronization.

Our results point out that consciousness uses synchronized neural codes to extract, represent and store information. Consciousness would need the combined efforts of distant neural assemblies, at nonrandom levels of synchronization and coherence, to create an experience. It also requires a coherence executive system (frontal cortex) that permits the binding of temporally dispersed representations of multimodal stimuli into an integrated percept of personal experience. The activation of high frequency bands facilitates long distance synchronization within the brain. Synchronized beta oscillations provide a mechanism for binding distributed somatosensory and motor areas of the cortex into a functioning network (Brovelli et al., 2004). This rhythm maintains cell assemblies with higher level processing involved in long range coordination. On the other hand, frontal and hippocampal theta activity have a role in the formation of associations between hippocampal episodic memories and specific motor plans in the frontal cortex (Lisman, 2005; Singer and Grey, 1995). The correct functioning of the prefrontal cortex is linked to its involvement in processing temporally complex events (Wilson et al., 2010). Real cortical connection matrices, when implemented as dynamic systems, give rise to highly complex functional connectivity, due to the existence of functionally coupled subsets of areas (Sporns et al., 2002).

According to our results, two functional neural circuits would exist, both with intrinsic connectivity subserving consciousness: a “cognitive network” reflecting retrolandic neural activity, and an “executive control network” revealing anterior cortex activity.

Table 1 – Diagnosis criteria for minimally conscious state (MCS).

Criteria for MCS
Intermittent ability to interact normally with others
Scarce or inconsistent behavioral response to visual, acoustic, tactile or verbal stimuli
Scarce or inconsistent verbal comprehension or expression
Intermittent state of alertness compatible with sleep/wake cycle
Maintenance of autonomic functions alone or with medical or nursing care
Inconsistent eye-tracking of objects and people
Scarce or inconsistent response to familiar emotional stimuli

Table 2 – Diagnosis criteria for severe neurocognitive disorder (SND).

Criteria for SND
Ability to interact with others
Consistent behavioral response to visual, acoustic, tactile or verbal stimuli
Preserved state of alertness and sleep/wake cycle
Notable decline from prior level of functioning
Difficulty with work, study or family life
Severe deterioration of memory structures and/or processes
Severe deterioration of other neurocognitive functions: attention, language, motor abilities, recognition, imagery, and/or executive functioning
Anatomical or functional neuroimaging should demonstrate brain abnormalities
Behavioral and cognitive disturbances will not meet the criteria for delirium, or amnesic disorder
Behavioral–cognitive impairment is visible from the acute phase

These networks produce signal fluctuations during resting state and are typically coactivated when a person is conscious (SND patients), and partially deactivated when consciousness is altered (patients in the MCS). The executive control network reflects strong temporal coherence and long distance synchronization between anterior and posterior regions of the brain. This synchronization is subserved by the beta band within the frontal cortex and connections between specific brain regions: left temporal to frontal, central to frontal, right temporal to frontal and parietal occipital to frontal. Thus, all cortical areas must send information to the frontal lobe to be integrated. In patients in the MCS, frontal cortices do not appear to function without information from the posterior cortex.

Our findings support the existence of an executive control network equipped to identify salience (operations requiring attention to pertinent stimuli, i.e., behavioral choices, shifting conditions, background demands, and others) and respond to novel situations (Seeley et al., 2007). This executive network may be where sustained attention and working memory reside. Our findings are also in accordance with the global workspace model, which states that “once a representation is consciously accessed, a broad distributed network, involving in particular prefrontal cortex, ignites and broadcasts its content”; long distance connectivity between cortical areas appears to be bidirectional, with a dominant direction of causality from posterior to anterior cortex (Gaillard et al., 2009). These dynamic cortical connections give rise to highly complex functional connectivity due to the existence of functionally coupled subsets of areas including nonlinear, or modulatory, interactions between areas (Sporns et al., 2002).

Awareness and action require a series of properly ordered successive links. When the frontal lobe is disturbed, the correct neural sequence is altered, and even well-established actions disintegrate into a series of isolated fragments that may produce residual cortical activity. Representations of firmly established actions may remain in the retrolandic cortex, which stores stereotyped reflexes formed by experience. These representations are accessible to consciousness through simultaneous activation of the frontal lobe and retrolandic areas. The most important condition for awareness is the ability to maintain these representations in memory, which occurs when neural circuits reverberate as they expand from retrolandic regions towards the PFC (Gaillard et al., 2009). Awareness also requires working memory, an executive cognitive function mediated by the PFC (Fuster, 2008; Goldman-Rakic, 1995; Luria, 1966). Hence, when the synchronization between frontal cortex and retrolandic areas is disturbed or dysfunctional, awareness is altered as well.

Our results further suggest that connections to and from frontal cortices are essential for the precuneus (parietal cortex) to properly display all of its behavioral properties. However, some argue that there are “insufficient grounds for affording the resting state a privileged status in accounts of human behavior”, including individuals with severe disorders of consciousness (coma, vegetative state, or minimally conscious state) (Cavanna, 2007).

4. Conclusion

Numerous studies on consciousness have shown that a connection exists between the prefrontal zone and other cerebral regions (Gaillard et al., 2009; Lau and Passingham, 2006; Leon-Carrion et al., 2006). However, this is the first study to provide evidence that awareness level depends on the synchronization between retrolandic and frontal cortical areas in MCS and SND patients. This synchronization is severely disrupted in patients in the MCS as compared to patients with SND, who show better levels of consciousness and a preserved state of alertness. According to our results, two synchronized coherence networks subserve consciousness, a retrolandic or cognitive network, and a frontal or executive control network. The executive control network facilitates the synchronization and coherence of large populations of distant cortical neurons using high frequency oscillations (beta) on a precise temporal scale. Consciousness is altered or disappears after losing synchrony and coherence, a disruption of the neural networks which mediate awareness. We suggest that the synchrony between anterior and

Table 3 – Name and number of feature which results from the possible electrode combinations for coherence analysis.

Feature	Name of feature
f1	Within frontal region
f2	Within left temporal region
f3	Within central region
f4	Within right temporal region
f5	Within parietal–occipital region
f6	Across frontal region and left temporal region
f7	Across frontal region and central region
f8	Across frontal region and right temporal region
f9	Across frontal region and parietal–occipital region
f10	Across regions left temporal region and central region
f11	Across regions left temporal region and right temporal region
f12	Across left temporal region and parietal–occipital region
f13	Across central region and right temporal region
f14	Across central region and parietal–occipital region
f15	Across right temporal region and parietal–occipital region

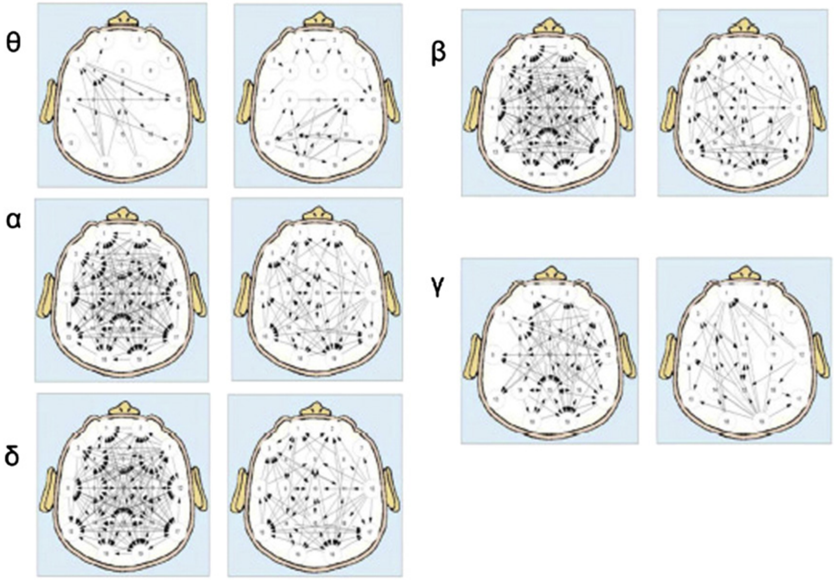

Fig. 2 – Connectivity patterns resulting from bivariate Granger causality analysis for a threshold value of 0.4. SND patients (left templates) showed richer connectivity than MCS patients (right templates), especially in delta, alpha and beta bands.

retrolandic regions is essential to awareness and that a functioning frontal lobe is a surrogate marker for preserved consciousness. Given its potential as a diagnostic marker of consciousness, the level of synchronization between anterior and posterior cortical regions could be useful for monitoring the progress of TBI patients during rehabilitation and aiding the clinical management of patients with disorders of consciousness. Future studies on the synchronization between frontal and retrolandic regions in altered states of consciousness would be necessary to replicate these findings and determine their relationship with conscious perception.

5. Experimental procedures

5.1. *Patients*

We evaluated the resting state network of two carefully matched severe TBI patient groups (16 patients). Seven patients (6 M, 1 F; mean age = 28.43) were classified as being in the minimally conscious state (MCS) (Giacino et al., 2002) (see Table 1). The control group included nine totally conscious TBI patients (6 M, 3 F; mean age = 29.5) with cognitive impairment that severely affects their daily living activities, impeding their return to work, school or a normal family life after TBI, diagnostic criteria for SND (Leon-Carrion, 2002). A number of studies provide evidence of how altered cognitive functions in TBI patients disrupt their everyday life (Goldstein and Levin, 1995; Luukinen et al., 1999; Marshall et al., 1991). As shown in Tables 1 and 2, patients in the MCS showed an inconsistent low level of arousal, minimal integration of content of consciousness, and severely restricted awareness. Patients with SND displayed a consistent level of arousal and are completely aware, but their content of consciousness is disrupted. We compared the resting state networks between patients in the MCS and patients with SND. Behaviorally, SND subjects were able to interact with their environment and respond to its demands, albeit in a dysfunctional manner, whereas patients in the MCS had little to no relationship with their surroundings. Both patient groups provided a natural laboratory for studying the different levels of consciousness. Tables 1 and 2 show the diagnostic criteria for MCS and SND, respectively.

Table 4 – Name and number of feature resulting from possible electrode combinations and graph theory for Granger causality analysis.

Feature	From	To
f1	Frontal	Frontal
f2	Left temporal	Left temporal
f3	Central	Central
f4	Right temporal	Right temporal
f5	Parieto-occipital	Parieto-occipital
f6	Frontal	Left temporal
f7	Frontal	Central
f8	Frontal	Right temporal
f9	Frontal	Parieto-occipital
f10	Left temporal	Frontal
f11	Left temporal	Central
f12	Left temporal	Right temporal
f13	Left temporal	Parieto-occipital
f14	Central	Frontal
f15	Central	Left temporal
f16	Central	Right temporal
f17	Central	Parieto-occipital
f18	Right temporal	Frontal
f19	Right temporal	Left temporal
f20	Right temporal	Central
f21	Right temporal	Parieto-occipital
f22	Parieto-occipital	Frontal
f23	Parieto-occipital	Left temporal
f24	Parieto-occipital	Central
f25	Parieto-occipital	Right temporal

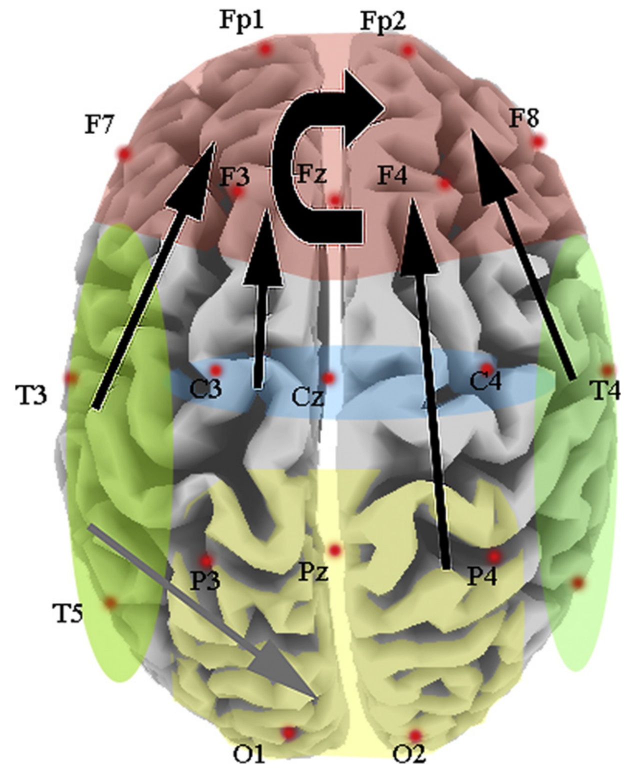

Fig. 3 – Areas with significant differences between patient groups at $P<0.01$ (black arrows) and $P<0.05$ (gray arrow) using multivariate Granger causality analysis. Only overlapping features resulting from Seth and DANCI approaches are represented. Connections from all areas to frontal region resulted significant in beta band. Connections from left temporal region to parietal occipital region resulted significant in theta band.

Patients were consecutively recruited from the Center for Brain Injury Rehabilitation (C.RE.CER.), Seville, Spain, and screened prior to beginning rehabilitation. Exclusion criteria included a pre-trauma history of major psychiatric disorders, drug dependency, epilepsy and other neurological disorders. Inclusion criteria required patients to be in the post-acute phase (>6 months post-injury). The research protocol was in accordance with the Declaration of Helsinki guidelines (http://www.wma.net/e/policy/b3.htm). Written informed consent was obtained from each patient's legal guardian.

No differences existed between the two groups in the time elapsed since brain injury ($P=0.22$). Patients in the MCS scored an average of 2.43 (moderate coma; SD=0.59) on the Coma/Near Coma Scale (Rappaport, 2005), while all SND patients scored 0 (no coma). In the Level of Cognitive Functioning Scales (AKA Rancho Los Amigos Scale) (Hagen et al., 1972), four MCS patients scored 2 and three scored between 2 and 3, implying the presence of at least a generalized response. SND patients scored an average of 5.47 (SD=1.27), implying a consistent (but sometimes inappropriate) response to a command. Finally, in a functional assessment using the FIM™+FAM measure (Hall, 1997; Keith et al., 1987), all MCS patients scored 1 (total assistance in daily life activities), whereas SND patients scored an average of 2.33 (SD=0.81), implying some, albeit minimal, independence in these activities.

5.2. EEG recordings

We obtained resting state EEG data from patients in a three-minute recording session, using a 19-electrode montage in accordance with the International 10–20 electrode placement system (linked ears reference; bandwidth between 0.1 and 128 Hz; sampling frequency of 256 Hz). The electrode positions included seven frontal (Fp1, Fp2, F7, F3, Fz, F4, F8), three central (C3, Cz, C4), four temporal (T3, T4, T5, T6), three parietal (P3, Pz, P4), and two occipital locations (O1, O2). Patients were awake during the recordings. To maintain vigilance, a technician clinically monitored each subject, inspecting EEG traces online, and verbally alerting the subject if behavioral and/or EEG signs of drowsiness—an increase in "tonic" theta rhythms, K complexes, or sleep spindles—appeared during the procedure.

Recordings were carried out in a softly lit, soundproof room, with room temperature set at 23 °C. All recordings were performed between 11:00 am and 2:00 pm. Before each recording, patients were seated in a wheelchair and asked to relax.

5.3. EEG data pre-processing

A bandpass filter between 0.5 Hz and 40 Hz was applied off-line to remove the DC component and high frequency noise. Since continuous artifacts (e.g., muscle artifact due to spasticity) were present in some patients' EEGs, we applied an independent component analysis approach (EEGLAB) (Delorme and Makeig, 2004), which has proven useful in minimizing the impact of these artifacts (Iriarte et al., 2003). EEG data comprised consecutive 2 s epochs. Only artifact-free epochs were considered for analysis. Within each recording, we used split-half and test–retest reliability to examine the edited EEG segments, and only records with >90% reliability entered the subsequent analyses. The mean artifact-free epoch length was 66.96 s (range: 38.10–124.68 s) for the MCS group and 60.11 s (range: 40.33–133.05 s) for the SND group. This small duration difference was not significant ($P=0.73$).

To address potential issues of stationarity and high correlations in the data, we further pre-processed signals in each bandwidth. We removed the spatial and temporal mean across epochs and channels, and then divided by the standard deviation to obtain the zero mean and unit variance signals for each channel (Cui et al., 2008). We also determined the number of necessary data samples in each frequency band that satisfy the Nyquist theorem. This data underwent bandpass filtering and down-sampling to reduce temporal correlations. Finally, we tested the differentiation procedure for covariance stationarity proposed by Box and Jenkins (Box et al., 2008), but it did not provide noticeable differences in our results and was excluded from the final analysis.

5.4. Coherence

Given a set of EEG signals X1, X2,…,XN recorded from N electrodes, coherence (Bendat and Piersol, 2010) operates in the frequency domain, measuring synchronization activity between pairs of channels as a function of frequency.

However, it does not provide information on cause and effect relationships in a network of interacting brain areas. Coherence values were calculated separately for different frequency bands, namely delta (0–4 Hz), theta (4–8 Hz), alpha (8–13 Hz), beta (13–30 Hz) and gamma (30–40 Hz), as well as for the complete signal (0–128 Hz). To reduce the total number of statistical comparisons, and thus the likelihood of type I error when comparing the two patient groups, we lumped the 19 electrodes into 5 groups corresponding roughly to five gross anatomical brain regions, namely frontal (FP1, FP2, F7, F3, FZ, F4, F8), left temporal (T3, T5), central (C3, CZ, C4), right temporal (T4, T6), and parietal occipital (P3, PZ, P4, O1, O2) areas. Subsequently, we considered interactions within and between these five brain regions, and obtained 15 undirected measures of cortical coupling, 10 between regions, and five within regions (Table 3).

Interaction between and within regions was computed in terms of the number of connections involved. We calculated the average number of connections for each band and for the entire signal. For example, to compute the interaction between regions A and B in the alpha band, we included all alpha band connections originating from any channel belonging to region A and terminating in any channel belonging to region B. In the end, each subject was described in terms of the above 15 measures computed separately for each frequency band, and for the full bandwidth signal. This was done by summing the number of connections in a particular band for one patient group and dividing by the number of subjects in that group. To designate a connection, we chose a threshold that would differentiate the most between the patient groups in each frequency. For this purpose, we computed the difference in the average number of connections for thresholds ranging from 0.1 to 0.9, in increments of 0.1.

5.5. *Granger causality*

To study causal relationships among EEG connections, we utilized the Granger causality method by means of two different calculations. To implement this method, we used the bSMART (Cui et al., 2008) and Seth's Granger causality (SGC) calculations (Seth, 2005; Seth and Edelman, 2007), implemented in Matlab (The Mathworks, Natick, MA). Causal relationships among all brain areas can be assessed by analyzing all EEG channels X1, X2,.., XN simultaneously. The principle of the Granger Causality (GC) is based on modeling the EEG data as a system of autoregressive time series and on the model's ability to predict future values of each signal Xk using a limited number of past values of itself and of all other signals. Prediction of signal Xk involves an error term ek. If the variance of the prediction error ek is reduced by including Xj in the prediction of Xk, it is said that Xj Granger causes Xk. The significance of this hypothesis is tested via an F-test, while the strength of the connection is estimated by the logarithm of the F-statistic (Seth, 2005; Seth and Edelman, 2007). GC analysis of N data channels yields an N-by-N connectivity matrix describing the entire brain network. As a multivariate analysis, GC can detect both global and local network effects.

In our analysis, we used a variant of the Seth Granger causality algorithm (Seth, 2005; Seth and Edelman, 2007) developed by our group, called Dynamic Autoregressive Neuromagnetic Causal Imaging (DANCI) (Frye et al., 2007a, 2007b). It differs from Seth's method in the calculation of the F statistic, and its implementation provides faster convergence, smaller residual error, and better accuracy (Frye et al., 2007a, 2007b; Pollonini et al., 2010). Granger causality was calculated in the same frequency bands as in coherence, making use of the same electrode groupings, and labeling potential features based on the graph theory (Rubinov and Sporns, 2010). In this case, however, the connections were directed. Thus, there were 20 between- and five within-region measures of cortical coupling. For within-region connections, we only included different electrode pairs, given that self-connections were not allowed.

5.6. *Statistical analysis*

The coherence function for each subject provides a value between 0 and 1, for all possible combinations of channel pairs. In our analysis, we included only connections that exceeded a predefined threshold, which was selected to provide maximum separation between the two patient groups. Separation was defined in terms of the average number of connections in each group and frequency band. The optimum threshold was obtained by an exhaustive search for coherence values between 0.1 and 0.9, in steps of 0.05. In addition, we used t-tests to rank the features that produced the maximum separation between the two groups.

Similarly, the Granger causality algorithm for each subject provides a complete connectivity matrix whose elements contain the statistical significance (P values) of all possible connections between all channel pairs. In our analysis, the optimal model for the regression analysis was obtained using Akaike and Bayesian Criteria (Frye et al., 2007a, 2007b). The three approaches for Granger causality analysis provided f-statistics on the model residuals which indicated statistically significant connections. Two α levels of 0.01 and 0.05, further reduced by Bonferroni correction, were selected for the current study. We further limited the number of important connections using a stricter method, based on the graph theory (de Vico Fallani et al., 2010), which adds another level to the threshold. This method determines the topology of the connectivity network based on a fixed number of connections, providing an optimum balance between local and global connectivity. We used a probability threshold of $P=0.01$ to binarize each subject's matrix, i.e., all connections that passed this threshold were set to 1, whereas those that did not were set to 0, regardless of connection strength. After constructing a network for each subject and counting only significant connections, the two groups were compared using a t-test statistic. These results identified functional connections that differed significantly between the two patient groups.

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