

Brain Network Motif Topography May Predict Emergence from Disorders of Consciousness: A Case Series

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Submitted to: Neuroscience of Consciousness

Date: March 16, 2020

Number of tables: 1

Number of figures: 6

Number of supplemental figures: 10

Abstract word count: 242 words

Manuscript word count: 6 915 words

Keywords: disorders of consciousness, electroencephalography, anesthesia, brain networks, graph theory, network motifs, network hubs

Abstract

Neuroimaging methods have improved the accuracy of diagnosis in patients with disorders of consciousness (DOC), but novel, clinically translatable methods for prognosticating this population are still needed. In this case series, we explored the association between topographic and global brain network properties and prognosis in patients with DOC. We recorded high-density electroencephalograms in three patients with acute or chronic DOC, two of whom also underwent an anesthetic protocol. In these two cases, we compared functional network motifs, network hubs and power topography (i.e. topographic network properties), as well as relative power and graph theoretical measures (i.e. global network properties), at baseline, during exposure to anesthesia and after recovery from anesthesia. We also compared these properties to a group of healthy, conscious controls. At baseline, the topographic distribution of nodes participating in alpha motifs resembled conscious controls in patients who later recovered consciousness and high relative power in the delta band was associated with a negative outcome. Strikingly, the reorganization of network motifs, network hubs and power topography under anesthesia followed by their return to a baseline patterns upon recovery from anesthesia, was associated with recovery of consciousness. Our findings suggest that topographic network properties measured at the single-electrode level might provide more prognostic information than global network properties that are averaged across the brain network. In addition, we propose that the brain network's capacity to reorganize in response to a perturbation is a precursor to the recovery of consciousness in DOC patients.

1 Introduction

Brain injury often leads to loss of consciousness. Individuals who survive but fail to regain behavioural responsiveness to pain or external cues are considered to be in a disorder of consciousness (DOC). Awareness fluctuates greatly in patients with DOC according to their diagnosis: in unresponsive wakefulness syndrome (UWS), individuals exhibit spontaneous eye opening and reflexive behaviours such as eye blinking and swallowing, but are not aware of themselves or their environment (Monti, Laureys, & Owen, 2010), while those in a minimally conscious state (MCS) are inconsistently able to respond to commands and to their environment (Giacino et al., 2002). When diagnoses are made based on clinical consensus, over 40% of patients in MCS are estimated to be misdiagnosed with UWS – a phenomenon that has been attributed to variations in behavioural assessment and interpretation (Peterson, Cruse, Naci, Weijer, & Owen,

2015; Schnakers et al., 2009). Moreover, some patients diagnosed with UWS have demonstrated awareness through willful modulation of their brain activity in a functional magnetic resonance imaging (fMRI) scanner (Monti, Vanhaudenhuyse, et al., 2010; Owen et al., 2006) and during high-density electroencephalography (EEG) recordings (Cruse et al., 2011). Such neuroimaging approaches have revealed that even when the best available behavioral assessment (Coma Recovery Scale – Revised; CRS-R) is used, there is still a misdiagnosis rate of approximately 15% (Kondziella, Friberg, Frokjaer, Fabricius, & Møller, 2016). Both the high misdiagnosis rate of behavioural assessment and the presence of “covert” consciousness in behaviourally unresponsive patients highlight the need for objective assessment tools. However, as the gold standard for the assessment of consciousness is self-report and response to commands, there will always be uncertainty associated with any new diagnostic test for unresponsive individuals (Peterson et al., 2015). An alternative approach is to develop tools for prognostication: since clinical outcomes can be reliably gathered, prognostic tools have the potential to achieve higher reliability and accuracy than diagnostic tools in this population. Such tools can have substantial impact on patient quality of life, influencing treatment and end-of-life decision-making.

Advances in neuroimaging have improved prognostication in this patient population beyond what is possible with clinical measures such as age at injury or etiology alone. Positron-emission tomography (PET) measures of brain glucose metabolism and fMRI measures of functional connectivity in the default mode and attention networks have predicted outcomes with accuracies of up to 88% (Song et al., 2018; Stender et al., 2016). EEG in particular has been extensively explored for prognosis due to its high translational potential. Spectral power ratios (Bagnato et al., 2017; Sitt et al., 2014) and the presence of long-latency event-related potentials (ERPs) have been established as predictors of recovery from DOC (Faugeras et al., 2011; Frédéric Faugeras et al., 2012; Steppacher et al., 2013; Wijnen, Van Boxtel, Eilander, & De Gelder, 2007). More recently, brain network characteristics have been explored for their prognostic value. Network features including low functional connectivity in low frequency bandwidths (Bai, Xia, Wang, He, & Li, 2019; Sitt et al., 2014), and feedback-dominant frontoparietal connectivity and posterior-dominant network hubs (Blain-Moraes et al., 2016) have been associated with favourable outcomes in patients with DOC. Graph theory analysis of EEG has demonstrated that path length, participation coefficient, modularity and clustering of brain networks are potential prognostic markers (Chennu et al., 2017; Stefan et al., 2018). Finally, the complexity of the brain’s EEG response to transcranial magnetic stimulation has been associated with the degree of recovery from DOC (Casarotto et al., 2016). While these EEG studies have

established the enormous potential of this neuroimaging technique for prognosis in this population, to date, none have achieved sufficient prognostic accuracy, specificity and sensitivity to be clinically useful ($\geq 85\%$ for all three metrics), particularly in UWS patients. There is therefore a need to explore novel EEG prognostic measures, or refine existing ones, in this population.

Brain network motifs are recurring connectivity patterns in a network that are present at numbers significantly higher than in random networks (Milo et al., 2002). These subgraphs are thought to be the building blocks of larger networks, with functional motifs representing communication channels between nodes (Sporns & Kötter, 2004). Motifs may reveal granular changes in network composition that are associated with the capacity of a network to sustain consciousness (Kafashan, Ching, & Palanca, 2016; Shin, Mashour, Ku, Kim, & Lee, 2013) and thus may have strong prognostic value for DOC patients. Our group has demonstrated in healthy participants that three-node functional motifs exhibit topographically-distinct patterns associated with states of anesthetic-induced unconsciousness (Duclos et al., 2020). We have also demonstrated the feasibility of using anesthesia to perturb the brain networks of a DOC patient, allowing us to measure changes in the network that herald the recovery of consciousness (Blain-Moraes et al., 2016). Driven by these findings, in this study, we investigate the prognostic potential of three-node functional network motifs in three DOC patients in an acute or chronic state, two of whom were exposed to anesthesia. We hypothesize that patient prognosis is associated with motif topography before, during and after exposure to anesthesia. Furthermore, we compared motif topography to other topographic network properties (network hubs and power topography) and global network properties (graph theoretical network properties and relative power). We predict that the spatial information provided by topographic network properties will be more predictive of patient outcome compared to global brain network characteristics, which are averaged across nodes in the network.

2 Materials and methods

2.1 Participants

A convenience sample of three patients in a DOC following acquired brain injury were recruited from the Montreal Neurological Hospital and the surrounding Montreal area. Participants were included if they were between 18 and 80 years old and were in UWS or MCS, as assessed using the CRS-R by a trained experimenter (CA). They were excluded if they presented with elevated intracranial pressure, hepatic or renal failure and/or hemodynamic instability, were receiving active

vasopressor therapy, were in a medically-induced coma for intracranial hypertension or status epilepticus, had a neurosurgical intervention in the 72 hours prior to the study (due to open-head injury or intracranial pathology), or had a documented allergy to propofol. Participants were also excluded for pregnancy, or if they were deemed medically unsuitable for the study by their attending physician. Next of kin provided written informed consent for all participants. The study was approved by the McGill University Health Center Research Ethics Board (15-996-MP-CUSM).

2.2 Experimental design

We present a series of case studies of three patients in a DOC, who underwent a high-density EEG recording. Details of each case are presented in the results section. Importantly, two patients were in an acute state (< 3 months post-injury), while one was in a chronic state. We expected that the acute patient in MCS would exhibit EEG patterns similar to healthy controls (positive control), whereas the chronic UWS patient would not (negative control). In the acute UWS patient, we tested the hypothesis that topographic network properties – particularly, network motifs – were associated with prognosis.

Two of the three patients were also exposed to anesthesia, as per the anesthetic protocol detailed in (Blain-Moraes et al., 2016). Briefly, high-density EEG was measured at baseline, during exposure to anesthesia, and after recovery from anesthesia. We followed the guidelines of the Canadian Anesthesiologists' Society in all regards, including pre-anesthetic assessment, fasting, and monitoring. An Alaris PK Carefusion pump (Carefusion, Switzerland) was used to administer propofol in a target-controlled infusion mode using the Marsh kinetic set (Marsh, White, Morton, & Kenny, 1991). The parameters to drive the pump were based on the age and weight of the patients. The effect site concentration was of 2 $\mu\text{g/mL}$ and was held constant for the duration of the anesthetic exposure (40 min). The patients maintained adequate spontaneous respiration throughout. The beginning of the recovery period was defined as the moment the effect site concentration reached 0.5 $\mu\text{g/mL}$.

Global and topographic network properties in DOC patients were compared against nine healthy controls undergoing anesthetic-induced unconsciousness, induced by propofol and maintained for 3 hours using isoflurane (Duclos et al., 2020; Maier et al., 2017). Similarly to DOC patients, high-density EEG was recorded during baseline, anesthesia exposure and recovery.

2.3 Electroencephalographic data acquisition and preprocessing

EEG signals were collected from the scalp using a 128-channel electrode net (Electrical Geodesics, Inc., Eugene, OR, USA) referenced to Cz. Data were sampled at 1 kHz, and electrode impedances were kept below 50 k Ω . Pre-processing was performed in EEGLAB (Delorme & Makeig, 2004). The data were bandpass filtered from 0.1 to 50 Hz, and non-scalp channels were discarded, leaving 99 channels for subsequent analyses. Noisy channels were also removed, and the data were re-referenced to an average reference. When present, eye blinks were removed using ICA. Five-minute segments of EEG were extracted during three analysis epochs – baseline, anesthesia and recovery – while patients were presented with auditory stimuli to induce ERPs. (The results of ERP analysis are not presented in this publication.) Upon visual inspection by a trained experimenter (DN), noisy segments within each epoch were removed.

2.4 Network construction

Functional networks were constructed using custom MATLAB scripts (version R2018b). Data were first filtered into the delta (1-4 Hz), theta (4-8 Hz) or alpha (8-13 Hz) band using a Butterworth filter. Functional connectivity and directed functional connectivity were calculated across 10-second windows and averaged within each analysis epoch and frequency band to generate representative connectivity matrices for baseline, anesthesia and recovery periods. Functional connectivity was calculated using weighted phase lag index (wPLI), and directed functional connectivity using directed phase lag index (dPLI) – measures robust against the effects of volume conduction (Stam & van Straaten, 2012; Vinck, Oostenveld, van Wingerden, Battaglia, & Pennartz, 2011).

The wPLI between two channels was computed as:

$$wPLI_{ij} = \frac{|E\{\Im(C_{ij})\}|}{E\{|\Im(C_{ij})|\}} = \frac{|E\{|\Im(C_{ij})| \text{sgn}(\Im(C_{ij}))\}|}{E\{|\Im(C_{ij})|\}}$$

where $\Im(C_{ij})$ is the imaginary part of the cross-spectrum C_{ij} between signals i and j , and sgn is the signum function. When one signal leads the other, the wPLI is close to 1, with a value of 1 indicating perfect phase locking between signals. When there is no phase relationship between the signals, the wPLI is equal to 0.

A Hilbert transform yielded the instantaneous phase time series for each channel, and the phase difference $\Delta\phi_{ij}$ between all pairs of signals i and j was calculated. dPLI was defined as:

$$dPLI_{ij} = \frac{1}{N} \sum_{t=1}^N H(\Delta\phi_{ij})$$

where N is the length of the analysis segment and t is a given time point. H is the Heaviside step function, such that when i leads j , the dPLI is between 0.5 and 1; when j leads i , the dPLI is between 0 and 0.5; and, when there is no phase relationship between the signals, the dPLI is equal to 0.5. As the matrices were symmetrical, they were transformed into phase-lead matrices. dPLI values below 0.5 (i.e. phase-lag) were set to zero and the remainder (i.e. phase-lead) were normalized between 0 and 1.

The effects of spurious phase relationships in both the wPLI and dPLI connectivity matrices were controlled through a surrogate analysis, where signal i remained fixed while the phase time-series of signal j was scrambled, abolishing the phase relationship between the signals while maintaining their other (e.g. spectral) properties. wPLI and dPLI values were compared against a distribution of the means of 20 surrogate analyses and were retained if they were significantly different ($p < 0.05$ level). Non-significant connections were set to 0 (wPLI) or 0.5 (dPLI).

2.5 Global network properties

We defined global network properties as network measures which were averaged across all nodes in the network, resulting in a single value for each network. The global network properties examined in this study were relative power, and a set of graph theoretical network properties.

2.5.1 Relative power analysis

Spectral power in the delta, theta, alpha and broadband (1-13 Hz) frequency bands was computed over 10-second windows using a multi-taper power spectral density estimate (number of tapers = 3, time-bandwidth product = 2, spectrum window size = 3 seconds) from the Chronux package (Partha Mitra, 2007; Partha Mitra et al.). Power was averaged across time windows and all electrodes. Relative spectral power was equal to the ratio between the average delta, theta or alpha power and the average broadband power.

2.5.2 Graph theoretical network properties

In each network, four graph theoretical properties were computed using the Brain Connectivity Toolbox (BCT) (Rubinov & Sporns, 2010): 1) Global efficiency - the inverse of the average path length ($\frac{1}{L_w}$), where L_w is the average shortest path length between all pairs of nodes in the network (Latora & Marchiori, 2001). A high global efficiency reflects a more integrated network, where nodes across the network are connected using short paths. 2) Clustering coefficient (C_w) - the ratio between the number of connections between a node's neighbors, and the number of possible connections these neighbors could make, averaged across all nodes (Watts & Strogatz, 1998). A high clustering coefficient indicates a more segregated network with high local efficiency, where nodes tend to cluster together. 3) Modularity - the sum of the strength of connections within a module, where modules are computed using Louvain's algorithm (Rubinov & Sporns, 2010). High modularity indicates a more segregated network, with strong within-module connections and weak between-module connections (Newman, 2006). 4) Binary small-worldness - the ratio between the clustering coefficient and the average path length ($\frac{C_w}{L_w}$). This measure reflects both the segregation and integration required in an efficient network (Watts & Strogatz, 1998).

Prior to computing these properties, networks constructed using wPLI (see section 2.4) were binarized by thresholding them at the top $n\%$ of connectivity values. To determine the optimal threshold n for each participant, custom MATLAB scripts were used to explore thresholds ranging from 1 to 90%. Specifically, for each participant's baseline network, n was decreased from 90% in steps of 1% until at least one node became disconnected from the rest of the graph. Disconnection was assessed using path length; when disconnected, nodes had an infinite path length. The smallest n that did not result in node disconnection was selected for each participant (n 's ranged from 13 to 59 for healthy controls and from 33 to 48 for DOC patients). This procedure resulted in networks which had a minimal number of connections but no isolated nodes (H. Kim et al., 2018), corresponding to what we would expect in a human brain network with no isolated brain regions and an economical number of connections. When connectivity values fell above the selected optimal threshold, connections were set to 1, while all others were set to 0.

Network properties for baseline, anesthesia and recovery epochs were calculated by averaging the properties across 10-second windows within each epoch. To account for spurious measurements, 10 random binary networks where the degree distribution of connections was fixed, but the connections

were randomized, were-computed. Connections were randomly rewired 10 times while preserving node degree (Maslov & Sneppen, 2002). Global efficiency and clustering coefficient were normalized by taking the ratio between the properties of the original network and the properties of the average random network.

2.6 Topographic network properties

We defined topographic network properties as measures that were computed at the single-node level and visualized on a topographic head map. Topographic maps were plotted using EEGLAB's *topoplot* function (Delorme & Makeig, 2004).

2.6.1 Power analysis

As described previously, spectral power in the delta, theta and alpha frequency bands was computed using the multi-taper method (see section 2.5.1). Power topography was mapped as the power at each node relative to all the other nodes in its network. Specifically, the z-score for each node was calculated using the mean and standard deviation of power across all nodes in the network.

2.6.2 Hub analysis

From the binarized wPLI networks (see section 2.5.2), the degree of each node in each network was calculated to assess the location of high-degree network hubs, using the BCT. The topographic distribution of hubs was mapped as the degree of each node relative to all the other nodes in its network. Specifically, the z-score for each node was calculated using the mean and standard deviation of the degrees of all nodes in the network. For clarity, hub topographic maps were visualized using wPLI matrices binarized at the top 5% of connections.

2.6.3 Motif analysis

While motifs can theoretically be calculated for any number of nodes in a network, the exponentially increasing computational cost – and reduction in clinical translatability – associated with higher numbers of nodes were motivators to focus this analysis on three-node motifs. Of the 13 possible three-node motifs, only five (ID = 1, 2, 3, 5, 7) can be constructed based on the unidirectional connectivity between nodes as calculated by dPLI (Figure 1).

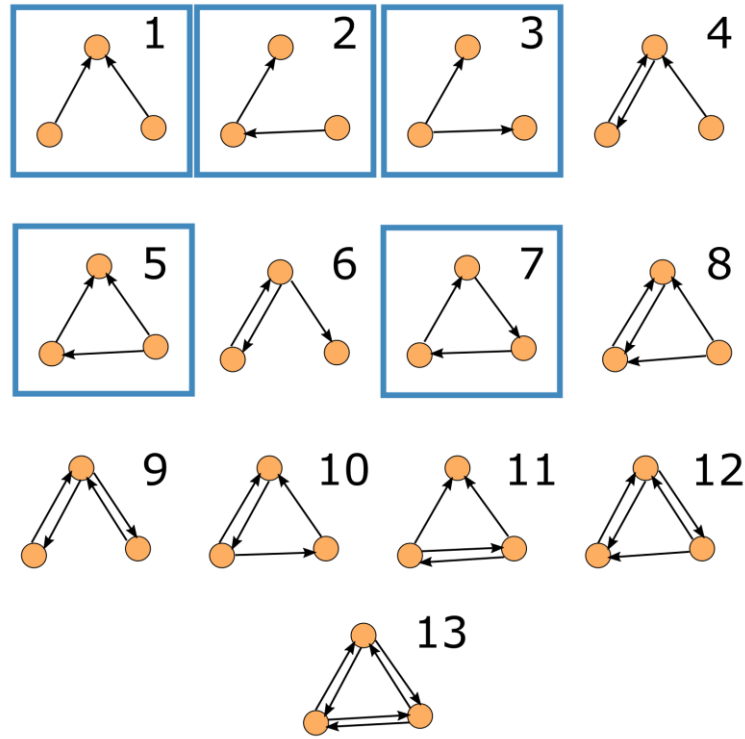


Figure 1. Three-node unidirectional network motifs explored during motif analysis. Only unidirectional motifs can be computed using the directed phase-lag index (dPLI) and are surrounded by boxes. Circles indicate nodes in the network and arrows represent functional relationships between nodes.

Motifs were computed on the dPLI networks (see section 2.4) using custom MATLAB scripts and the BCT. The motif topography for each analysis epoch was calculated based on motif frequency – the number of times a given node in the network participated in a given motif with any other node in the network. Spurious connectivity was accounted for by comparing the sum of motif frequencies across all nodes in each network against 100 surrogate networks using a z-score. Surrogate networks were generated by randomly shuffling connections while preserving the degree and weight distributions of each node in the network. When the sum of motif frequencies was non-significant ($p > 0.05$), the frequency for all nodes in that network was set to zero.

The topographic distribution of each motif was mapped as the motif frequency at each node relative all the other nodes in its network. Specifically, the z-score for each node was calculated using the mean and standard deviation of the motif frequencies across all nodes in the network.

2.7 Comparison of electroencephalographic measures across states of anesthesia exposure and against conscious controls

2.7.1 Comparison across states of anesthesia exposure

Within each subject, topographic network properties across baseline, anesthesia and recovery were compared using cosine similarity (s):

$$s = \frac{b_1 \cdot b_2}{\|b_1\| \|b_2\|}$$

where b_1 and b_2 are the z-scores corresponding to motif frequency, node degree or power for states 1 and 2. Cosine similarity ranges between -1 and 1, with 1 indicating identical and -1 indicating completely opposite topographic distributions. A value of 0 indicates orthogonality or decorrelation.

2.7.2 Comparison against conscious controls

For topographic properties, cosine similarity was used to compare motif, hub and power topographies between DOC patients and each healthy control. The median cosine similarity value was used as a representative quantitative measure of the comparison between each patient and the group of controls.

For global properties, DOC patients' properties were plotted relative to the distribution of properties for the control population. This allowed us to estimate whether DOC patients were outliers (greater or less than the median ± 1.57 times the interquartile range), and whether changes in global network properties across baseline, anesthesia and recovery were similar between patients and controls.

3 Results

The ability of topographic and global network properties to distinguish between consciousness and anesthetic-induced unconsciousness was first validated in the healthy control dataset. Then, for each DOC patient, a case report, followed by the results of each analysis is presented. A summary of patients' demographic and clinical data is shown in Table 1. For clarity, results for the alpha band are presented in the main body of the paper, while results for the theta and delta bands are presented in the Supplemental Material.

3.1 Validation of analysis techniques in conscious controls

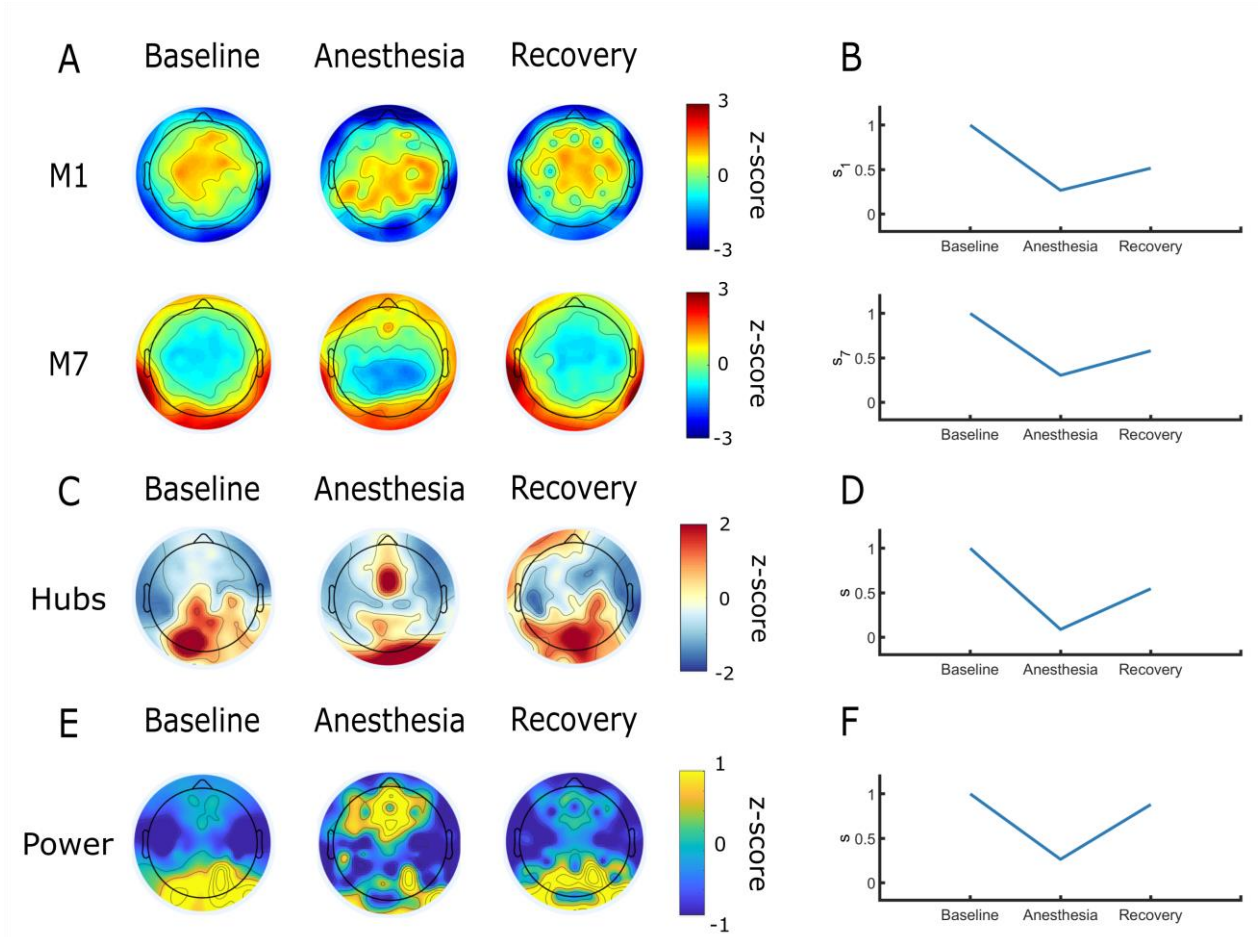


Figure 2. Topographic network properties in the alpha band distinguish between consciousness and anesthetic-induced unconsciousness in healthy controls; adapted from Duclos *et al.* (2020). In a cohort of 9 healthy controls, the average topographies of alpha motif frequency, node degree and power undergo anterior-posterior shifts across stages of anesthetic-induced unconsciousness. Topographic maps represent z-scores comparing motif frequency (A), node degree (C) and power (E) of each electrode to the distribution across all electrodes. Cosine similarity to baseline quantitatively reflects these shifts (B, D and F, respectively). *M1 = motif 1*, *M7 = motif 7*.

3.1.1 Topographic network properties

Motif analysis: Motifs 1, 2 and 7 were present at frequencies statistically higher than in random networks across participants. On average, in the alpha band, motif 1 was centrally dominant during consciousness and shifted posteriorly during unconsciousness, while motif 7 demonstrated the

reverse pattern (i.e. posterior-dominant during consciousness, both posterior- and anterior-dominant during unconsciousness) (Figure 2A). These visual changes were reflected by a decrease in cosine similarity during anesthesia, and an increase post-anesthesia (Figure 2B). Motifs in the theta band exhibited similar patterns (Suppl. Figure 1A), while motifs in the delta band did not clearly reorganize across states (Suppl. Figure 2A). Motif 2 did not reflect changes in states of consciousness, and therefore was not discussed in this paper.

Hub analysis: Network hubs underwent topographic shifts associated with states of consciousness. On average, alpha hubs were posterior-dominant during consciousness, and anterior-dominant during unconsciousness (Figure 2C). Visually observed changes were captured by cosine similarity (Figure 2D). Theta hubs exhibited similar patterns (Suppl. Figure 1B), while delta hubs exhibited the opposite pattern (i.e. anterior-dominant during consciousness, posterior-dominant during unconsciousness) (Suppl. Figure 2B).

Power analysis: Alpha power topography distinguished between states of consciousness. On average, alpha power was concentrated posteriorly during consciousness and shifted anteriorly under anesthesia (Figure 2E). These changes were captured by cosine similarity (Figure 2F). In the theta band, power was concentrated anteriorly at baseline, and was suppressed under anesthesia (Suppl. Figure 1C). There were no anesthetic-induced topographical shifts in power in the delta band (Suppl. Figure 2C).

3.1.2 Global network properties

Graph theoretical network properties: In the alpha band, there was an increase in clustering coefficient, binary-small worldness and modularity during anesthesia, and no change in global efficiency (Figure 6A, blue boxes).

Relative power analysis: During anesthesia, there was a decrease in relative alpha power, as well as an increase in relative theta and delta power (Figure 6B, blue boxes).

Table 1. Demographic and clinical data of patients.

Case	Age	Sex	Etiology	Time post-injury	State	Clinical diagnosis	CRS-R score						
							Auditory	Visual	Motor	Oromotor	Communication	Arousal	Total
1	35	F	Stroke	53 d	Acute	MCS	2	3*	4*	1	0	2	12
2	50	F	Stroke	25 d	Acute	UWS	1	1	1	0	0	0	3
3	24	M	Anoxia	8 y 6 mo	Chronic	UWS	1	0	2	1	0	1	5

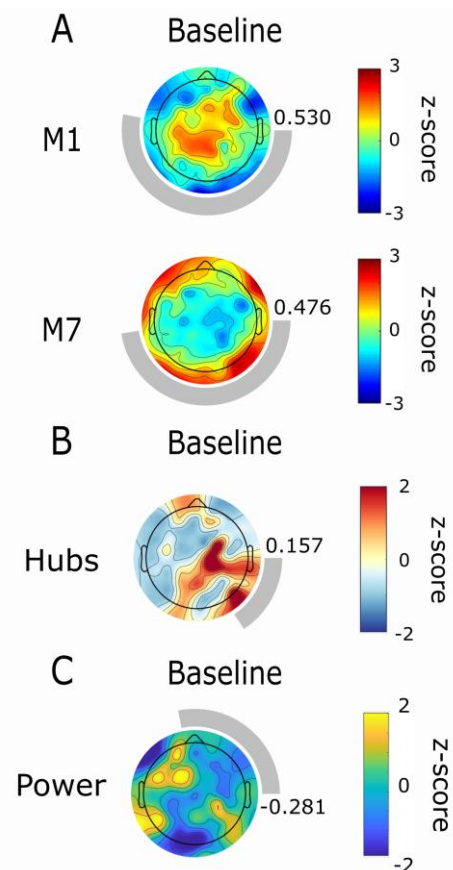
* denotes MCS

3.2 Case 1: Motif patterns in minimally conscious state are similar to healthy controls

3.2.1 Case report

A 35-year-old female presented with a ponto-mesencephalic intracerebral hemorrhage due to a ruptured arteriovenous malformation (AVM). After an initial partial recovery (with complete return of her level of consciousness), she went to a rehabilitation center where, five months later, she experienced a second intraparenchymal hemorrhage in the pons and midbrain, extending to the 4th ventricle, complicated by seizures and hydrocephalus. Once more, she regained consciousness following this second hemorrhage and underwent a surgical resection of her AVM eighteen days after the second ictus. During the operation, she suffered from a hemorrhage in the 4th ventricle and in the pontine surgical cavity. Post-operatively, she developed obstructive hydrocephalus which was treated with extra-ventricular drainage. However, she failed to regain normal consciousness during the weeks that followed. She was recruited to the study 53 days post-operation, when she was in a minimally conscious state (MCS) (CRS-R = 12, Table 1). This patient was excluded from the anesthetic protocol as she was persistently febrile. Two weeks after data collection, she began obeying commands with her right foot and left arm. Upon discharge, 5 months and 23 days after data collection, the patient was behaviourally responsive and communicative (CRS-R = 23).

Figure 3. Alpha network motif topographies resemble those of healthy controls in an individual who emerged from minimally conscious state. Topography of alpha motif frequency, but not of node degree or power, are similar to those of healthy controls at baseline. Topographic maps represent z-scores comparing motif frequency (A), node degree (B) and power (C) of each electrode to the distribution across all electrodes. Rings surrounding the topographic maps represent the median cosine similarity to conscious controls; a more complete ring corresponds to higher similarity, the value of which is also indicated to the right of each topographic map. *M1* = motif 1, *M7* = motif 7.



3.2.2 Topographic network properties

Motif analysis: The participant's alpha motifs had similar topographic patterns to conscious controls (Figure 3A). As they were close to emergence (CRS-R = 12), this was expected and may suggest that their brain network had the capacity to sustain consciousness. Motif 1 was concentrated in central brain regions ($s_1 = 0.530$); motif 7 was spread across peripheral electrodes ($s_7 = 0.476$). Motifs in the theta (Suppl. Figure 3A) and delta bands (Suppl. Figure 4A) were also similar to conscious controls.

Hub analysis: Alpha network hubs were dissimilar to conscious controls ($s = 0.157$) (Figure 3B), as were hubs in the theta (Suppl. Figure 3B) and delta bands (Suppl. Figure 4B).

Power analysis: At baseline, alpha power topography did not resemble the distribution for conscious controls ($s = -0.281$) (Figure 3C). Neither did theta (Suppl. Figure 3C) or delta (Suppl. Figure 4C) power topography.

3.2.3 Global network properties

Graph theoretical network properties: At baseline, in the alpha band, global efficiency was within the range of conscious controls, while clustering coefficient, binary small-worldness and modularity were all elevated relative to conscious controls (Figure 6A, red circles). Graph theoretical properties in the theta (Suppl. Figure 9, red circles) and delta band (Suppl. Figure 10, red circles) were either lower than or within the range of conscious controls.

Relative power analysis: Relative power in the delta band was within the range of conscious controls, while relative theta power was higher and relative alpha power was lower than in conscious controls (Figure 6B, red circles).

3.3 Case 2: Motif, hub and power topographic reorganization in unresponsive wakefulness syndrome is similar to healthy controls and predicts recovery of consciousness

3.3.1 Case report

A 50-year-old woman presented with a high-grade subarachnoid hemorrhage (Fisher grade IV, World Federation of Neurosurgeons (WFNS) grade V, with a right frontotemporal intraparenchymal hematoma) secondary to a ruptured right middle cerebral artery (MCA) aneurysm. She was

behaviorally unresponsive upon admission (GCS = 3). The patient underwent a decompressive craniectomy and clot evacuation as well as the insertion of an extraventricular drain on the day of admission. She did not regain consciousness after this first surgery. Two days later, she underwent a second operation for clipping of her right MCA aneurysm. She did not regain normal consciousness during the four weeks that followed. At the time of data collection, 25 days post-injury, the patient was behaviourally unresponsive and in UWS (CRS-R = 3, Table 1). It is important to note that the right bone flap of the patient was resected prior to data collection. As the electrode net lacked tension on this side of the skull, their brain networks' topographic patterns were skewed. Three months and seven days following data collection, the patient recovered behavioural responsiveness, and was able to spontaneously open her eyes, obey commands and produce slow but oriented speech (GCS = 15).

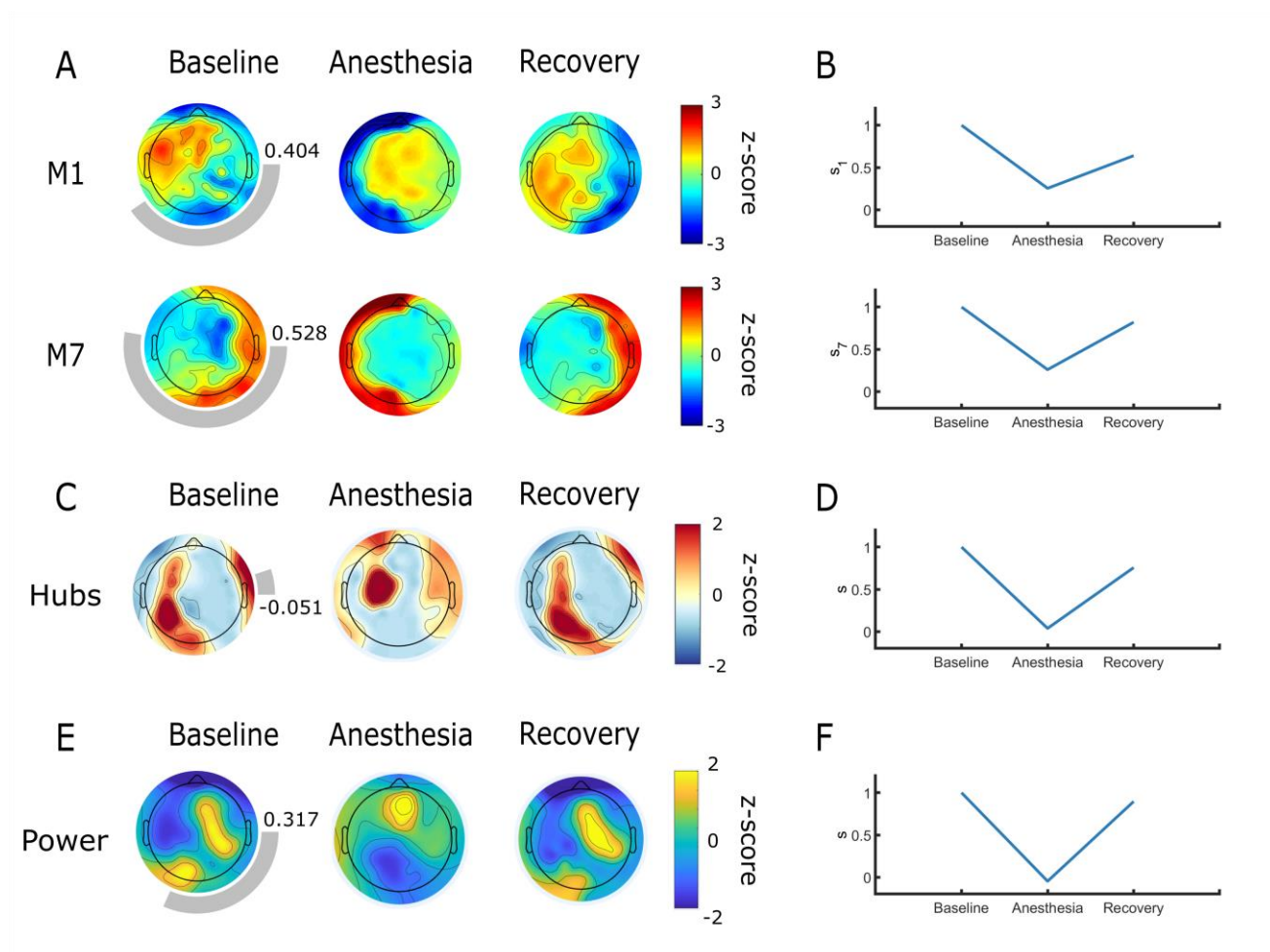


Figure 4. Alpha network motif, hub and power topographic reorganization under anesthesia in a patient who emerged from unresponsive wakefulness syndrome. Topography of alpha motif frequency, but not of node degree or power, are similar to those of healthy controls at baseline. Motif, node degree and power distributions undergo topographic reorganization under anesthesia,

similar to healthy controls. Topographic maps represent z-scores comparing motif frequency (A), node degree (C) and power (E) of each electrode to the distribution across all electrodes. Rings surrounding the topographic maps represent the median cosine similarity to conscious controls; a more complete ring corresponds to higher similarity, the value of which is also indicated to the right of each topographic map. Cosine similarity to the participant's own baseline quantitatively reflects these shifts (B, D and F, respectively). $M1 = \text{motif 1}$, $M7 = \text{motif 7}$.

3.3.2 Topographic network properties

Motif analysis: At baseline, this participant's alpha motif topography was similar to conscious controls, although skewed ($s_1 = 0.404$, $s_7 = 0.528$) (Figure 4A). Strikingly, nodes participating in motifs 1 and 7 reorganized during exposure to anesthesia (Figure 4A-B). While the topographic distribution of motifs in the anesthetized state only has a weak similarity to anesthetic-induced unconsciousness in healthy controls (i.e. not posteriorly- or anteriorly-dominant) the patient's brain network adaptively reconfigured in response to propofol and the topographic patterns returned to their baseline state upon cessation of the anesthetic, perhaps suggesting that the patient was either conscious or had the capacity for consciousness at the time of data collection. In the theta band, motif topographies are dissimilar to conscious controls at baseline but undergo similar topographic reorganization during anesthesia (Suppl. Figure 5A). Motifs in the delta band are similar to conscious controls but did not undergo clear reorganization during anesthesia (Suppl. Figure 6A).

Hub analysis: Alpha network hubs were dissimilar to conscious controls at baseline ($s = -0.051$) (Figure 4C) but reorganized under anesthesia in a similar manner as healthy individuals (i.e. posterior-to-anterior shift) (Figure 4C-D). This may once again be suggestive of consciousness or the capacity of the brain network to sustain consciousness. Theta (Suppl. Figure 5B) and delta hubs (Suppl. Figure 6B) also underwent topographic reorganization under anesthesia.

Power analysis: At baseline, alpha power topography did not resemble the distribution for conscious controls ($s = 0.317$) (Figure 4E) but reorganized under anesthesia (posterior-to-anterior) (Figure 4E-F). Neither theta (Suppl. Figure 5C) or delta (Suppl. Figure 6C) power topography shifted under anesthesia.

3.3.3 Global network properties

Graph theoretical network properties: In the alpha band, all global network properties were similar to conscious controls (Figure 6A, orange circles). While these properties changed across baseline,

anesthesia and recovery, they did not shift in an expected pattern. This was also the case in the theta (Suppl. Figure 9, orange circles) and the delta bands (Suppl. Figure 10, orange circles).

Relative power analysis: Relative power in the delta band was within the range of conscious controls, while relative theta power was higher and relative alpha power was lower than in conscious controls (Figure 6B, orange circles).

3.4 Case 3: Motif, hub and power topographies in persistent unresponsive wakefulness syndrome are dissimilar to healthy controls

3.4.1 Case report

A 24-year-old male suffered from an anoxic brain injury eight years prior to this study, following cardiac arrest caused by *commotio cordis* resulting from a blow to the precordial region, leaving the patient without vital signs for approximately 30 minutes. He did not recover normal consciousness following this injury. At the time of data collection, the patient was diagnosed with UWS (CRS-R = 5, Table 1). At the time of publication, this patient remains in UWS.

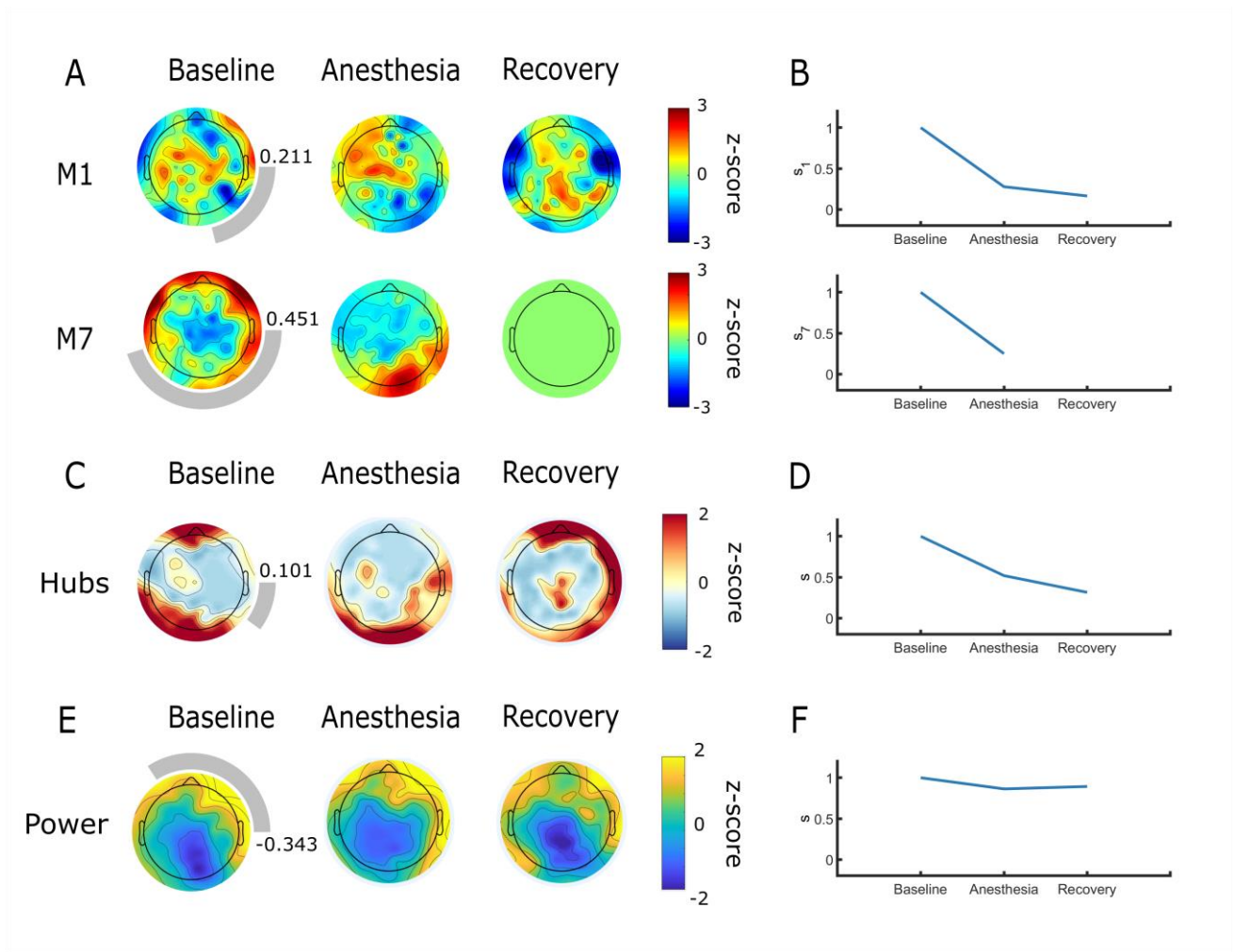


Figure 5. Alpha network motif, hub and power topographies are spatially incoherent in an individual with persistent unresponsive wakefulness syndrome. Topography of alpha motif frequency, node degree and power are dissimilar to healthy controls at baseline. Under anesthesia, distributions either did not reorganize, or did not follow the pattern expected based on observations in healthy controls. Topographic maps represent z-scores comparing motif frequency (A), node degree (C) and power (E) of each electrode to the distribution across all electrodes. Rings surrounding the topographic maps represent the median cosine similarity to conscious controls; a more complete ring corresponds to higher similarity, the value of which is also indicated to the right of each topographic map. Cosine similarity to the participant's own baseline quantitatively reflects the failure of topographic patterns to reorganize in a clear pattern (B, D and F, respectively). *M1 = motif 1, M7 = motif 7.*

3.4.2 Topographic network properties

Motif analysis: At baseline, motif topographies were dissimilar to conscious controls ($s_1 = 0.211$, $s_7 = 0.451$). Motif 1 was spatially dispersed, while motif 7 exhibited the opposite polarity of

topographic distribution that we would expect based on observations in healthy controls (i.e. motif 7 was anteriorly instead of posteriorly dominant) (Figure 5A). This was expected as the participant was in a chronic UWS state and might suggest that the inability of the brain network to sustain consciousness is reflected by its motif characteristics. The topographic organization of motifs 1 or 7 shifted in response to anesthesia but failed to return to baseline state post-anesthesia (Figure 5A-B). Contrary to what we would expect in a healthy individual, high-frequency nodes seemed to become more polarized towards anterior brain regions for motif 1, and posterior brain regions for motif 7. At recovery, node participation in motif 1 regained a disorganized pattern, while motif 7 became insignificant. There were no clear patterns in motif topography or reorganization in the theta (Suppl. Figure 7A) and delta bands (Suppl. Figure 8A); motifs at these frequencies were often non-significant.

Hub analysis: Alpha network hubs did not resemble conscious controls at baseline ($s = 0.101$) (Figure 5C) or return to baseline state post-anesthesia (Figure 5C-D). This may further emphasize that the inability of the brain network to sustain consciousness is associated with topographic network properties. There were no clear patterns in hub topography or reorganization in the theta band (Suppl. Figure 7B), although hubs did undergo anesthetic-induced topographic reorganization in the delta band (Suppl. Figure 8B).

Power analysis: At baseline, alpha power topography did not resemble the distribution for conscious controls ($s = -0.343$) (Figure 4E) and did not reorganize under anesthesia (Figure 4E-F). Neither theta (Suppl. Figure 7C) or delta (Suppl. Figure 8C) power topography shifted under anesthesia.

3.4.3 Global network properties

Graph theoretical network properties: At baseline, in the alpha band, global efficiency was within the range of conscious controls, while clustering coefficient, binary small-worldness and modularity were all elevated relative to conscious controls (Figure 6A, blue diamonds). While these properties changed across baseline, anesthesia and recovery, they did not shift in an expected pattern. This was also the case in the theta (Suppl. Figure 9, blue diamonds) and the delta bands (Suppl. Figure 10, blue diamonds).

Relative power analysis: Relative power in the theta band was within the range of conscious controls, while relative delta power was higher and relative alpha power was lower than in conscious controls

(Figure 6B, blue diamonds). Importantly, this patient, who did not recover consciousness, was the only one with elevated delta power relative to conscious controls.

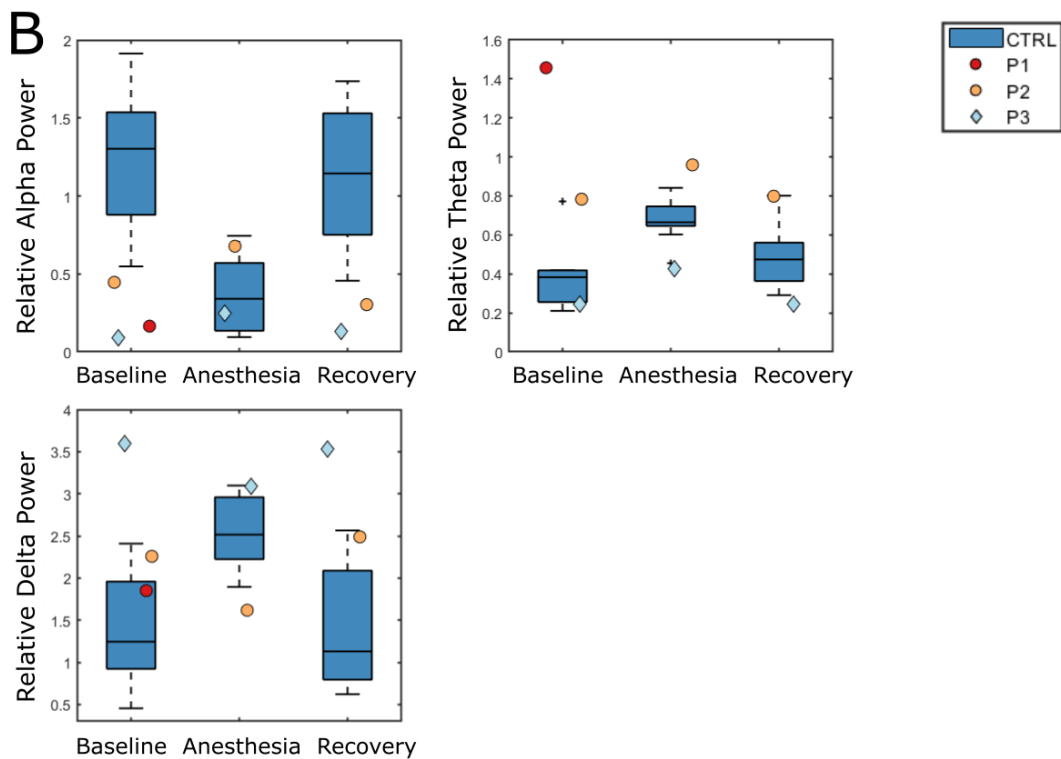
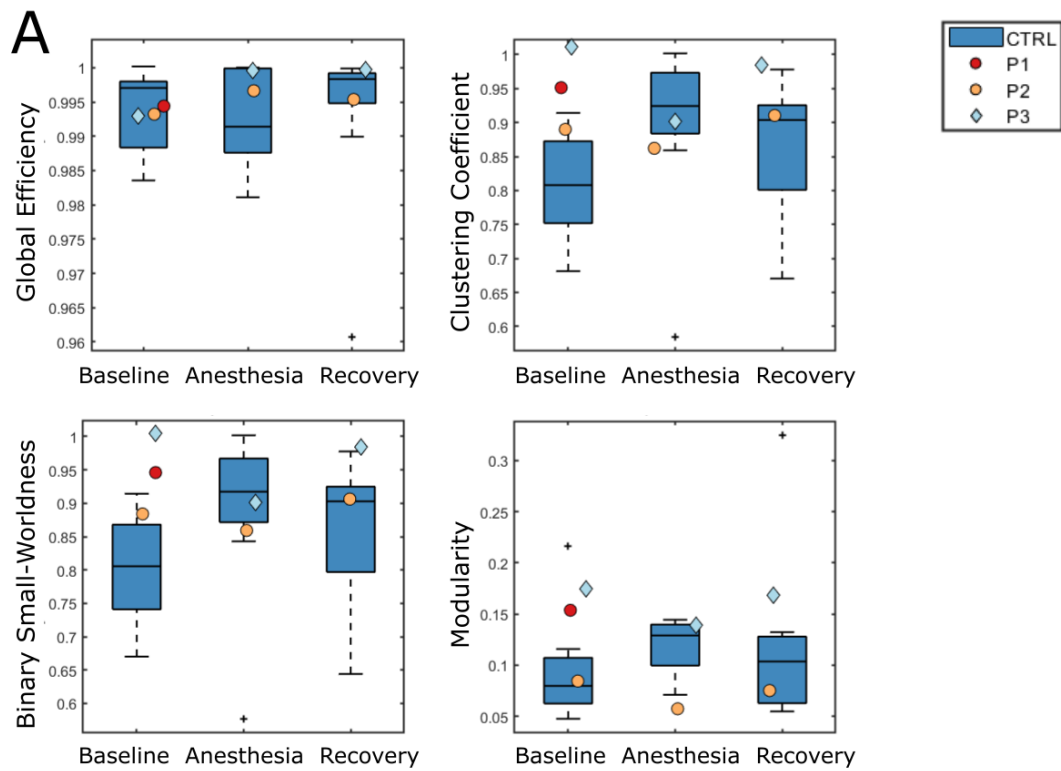


Figure 6. Comparison of alpha global network properties between conscious controls and individuals with disorders of consciousness. Graph theoretical network properties were not associated with prognosis (A), but relative power in the delta band (B) was elevated relative to conscious controls in the patient who did not recover consciousness. Boxes represent the interquartile range of the values for conscious controls, with the median indicated by a horizontal line. The whiskers extend to the minimal and maximal values which are not outliers, while outliers, defined as values greater than the median ± 1.57 times the interquartile range, are represented by crosses. Values for disorders of consciousness patients who recovered behavioural responsiveness are represented by circles, while the values for the patient who remained in unresponsive wakefulness syndrome is represented by a diamond. *CTRL = conscious controls, P = patient.*

4 Discussion

In this study, we provide preliminary evidence through a series of three DOC cases, that network motifs may be associated with prognosis in this patient population. Further, we compared network motifs to other established topographic and global network properties. In the cases presented here, topographic network properties appear to have more prognostic value than global network properties, bringing to light issues that may arise during whole-brain averaging of brain network properties in brain-injured populations. Our findings suggest that network motifs are a promising addition to the existing repertoire of prognostic EEG measures and demonstrate that the perturbation of resting state brain networks using anesthesia can further inform prognosis.

4.1 Brain network motifs show promise as a novel prognostic measure in disorders of consciousness

In the three presented cases, the topographic distribution of three-node functional motifs resembles conscious controls at baseline in patients who later emerged from their DOC. In these cases, nodes participating in motif 1 were concentrated over central brain regions, while those participating in motif 7 were localized over lateral brain regions. Importantly, in a patient who later recovered consciousness, motif topography reconfigured under anesthesia and returned to baseline topography post-anesthesia. This was not the case in the patient in persistent UWS who underwent the same anesthetic protocol.

This is the first study to explore network motifs as prognostic markers in DOC patients. Previously, the emergence and suppression of motifs across states of anesthetic-induced unconsciousness have been observed using EEG (Shin et al., 2013) and fMRI (Kafashan et al., 2016) in healthy individuals.

We build upon this emerging field of study through our use of high-density EEG, which provides greater spatial resolution, and by applying this method in a novel clinical context.

While the neural mechanisms underlying motif topography remain unclear, the specific configuration of motifs 1 and 7 informs hypotheses regarding their role in the brain. Motif 1, which consists of two nodes which converge on an apical node, has been associated with balancing between-module integration and segregation (Sporns & Kötter, 2004). In particular, the apical node is thought to integrate information as part of the “rich club”, a core network of highly-connected hubs (Gollo, Zalesky, Hutchison, van den Heuvel, & Breakspear, 2015). Motif 7 forms a closed loop and has been implicated in fast, within-module integration, particularly in peripheral sensory brain regions (Gollo et al., 2015). Interestingly, nodes participating in motif 7 in both controls and DOC patients are located over peripheral brain regions, and their topography is complimentary to that of motif 1, supporting this theory. In the context of persistent UWS, we observed a disruption of nodes participating in motifs 1 and 7. This may be driven by a breakdown in between- and within-module integration, which has been associated with reduced consciousness (Dehaene & Changeux, 2011; Tononi, 2004). In UWS, reduced thalamocortical integration, mediated by cortical, thalamic or fiber damage, is believed to underly negative behavioural outcomes (Rosanova et al., 2012) and global network integration is thought to shift in favor of local, segregated information processing (Rizkallah et al., 2019).

Our results demonstrate that motif reorganization is not associated with anterior-posterior shifts in alpha power across states of consciousness. The anteriorization of alpha power has traditionally been considered a marker of anesthetic-induced unconsciousness (John et al., 2001; Tinker, Sharbrough, & Michenfelder, 1977). While this phenomenon can be observed in Case 2, the reorganization of network motifs in this participant do not exhibit patterns of change that are associated with the topographic shift in alpha power. Case 3 provides further evidence of the dissociation between alpha power and motifs, as alpha power remains anterior across all three states, while the motif topography reorganizes. Our results also demonstrate that motif reorganization is not associated with shifts in the global network hub location. Previous studies have shown that posterior hub locations are associated with states of consciousness, and anterior hub locations with states of unconsciousness (Blain-Moraes et al., 2016; Lee, Mashour, Noh, Kim, & Lee, 2013). In both Cases 2 and 3, the shift in the topographic distribution of network node degree are not paralleled by the topographic shift in motif 1 or 7. While these results do not provide an explanation of the motif’s underlying neural mechanism,

they demonstrate the added value of this granular network analysis above and beyond these more traditional markers of levels of consciousness. Motif topography in Cases 1 and 2 was more similar to conscious controls at baseline than alpha and hub topography, further suggesting the added value of motif analysis.

4.2 Topographic network properties may be more strongly associated with recovery from disorders of consciousness than global network properties

Global network properties, which are averaged across nodes in the network, were not strongly associated with prognosis. At baseline and across states of anesthesia none of the graph theoretical network properties in any of the frequency bands consistently predicted recovery of behavioural responsiveness. This is in contrast to studies demonstrating that clustering and path length in the alpha band (Stefan et al., 2018), as well as clustering and modularity in the delta band (Chennu et al., 2017) predicted outcomes in large cohorts of DOC patients. In terms of relative power, the patient who did not recover exhibited elevated relative power in the delta band as compared to conscious controls. This is in line with several studies that have associated high delta power with negative outcomes (Bagnato et al., 2017; Golkowski et al., 2017; Sitt et al., 2014; Stefan et al., 2018). On the other hand, topographic network properties were consistently associated with behavioural outcomes. In patients who eventually recovered consciousness, we observed that nodes participating in functional motifs, high-degree nodes and nodes with high alpha power were organized in distinct patterns that reconfigured under anesthesia and returned to their baseline state post-anesthesia. We replicated the finding that alpha network hub and power location shifts under anesthesia, predicting behavioural outcome in patients who will eventually recover consciousness (Blain-Moraes et al., 2016).

Interestingly, unlike global network properties, the information provided by topographic network properties had prognostic value despite the heterogeneity of types of brain injury in our sample. While global network properties provide an overall representation of network functioning, our results suggest that valuable information may be lost during spatial averaging of network properties. Motifs capture region-specific changes in brain functioning, and thus have the potential to be more attuned to granular network changes that affect the capacity for consciousness. This is especially promising in DOC patients, where the heterogeneity of pathological brain networks across individuals calls for analysis techniques that are sensitive to changes in the building blocks of a network.

4.3 The capacity of brain networks to reorganize post-perturbation may predict the recovery of consciousness

Topographic network properties provided additional prognostic information when measured in the context of anesthesia. We observed anterior-posterior shifts in network motif participation and hubs that were predictive of a patient's recovery from UWS. In the case of network hubs, perturbing the brain using anesthesia was particularly informative, as, on its own, similarity of hub topographies to controls at baseline was not predictive of patient outcome. Although this lack of prognostic ability at baseline may have been a result of the cortical lesions distorting DOC patients' brain network organization, this observation nevertheless highlights the prognostic value of applying a perturbation to patients' brain networks.

One of the greatest challenges in DOC diagnosis and prognosis is the absence of a gold standard by which to validate novel assessment tools (Athena Demertzi, Sitt, Sarasso, & Pinxten, 2017). In the absence of self-reported levels of consciousness, DOC patients are often compared to healthy controls. As we have demonstrated in this case series, baseline comparison to controls is not always sufficient for detecting patients who will recover consciousness (as was the case for network hubs and power topography in the cases presented here). The perturbation of DOC brain networks using anesthesia allows for the within-subject comparison of patients to their own baseline. In this way, we control for the heterogeneity of etiology and chronicity of brain injury, which influences between-group comparisons.

The concept of perturbing the brain with an external stimulus and measuring its capacity to adapt to that perturbation in the context of DOC is not new. In particular, transcranial magnetic stimulation has been investigated as one such perturbation. The speed and spatial distribution (Rosanova et al., 2012), as well as the complexity of the brain's response to this type of stimulation (Casali et al., 2013; Casarotto et al., 2016) have shown promise as diagnostic and prognostic markers, achieving prognostic accuracy of up to 81%. Further, right before recovery of consciousness in healthy controls undergoing anesthetic-induced unconsciousness, brain networks meet the conditions required for rapid reconfiguration and synchronization (M. Kim et al., 2016). In a similar vein, higher levels of consciousness have been associated with a higher probability of transitioning between patterns of connectivity measured using fMRI, whereas the brain networks of UWS patients showing no signs of covert consciousness tend to remain in a static pattern (A. Demertzi et al., 2019). These findings are strongly supported by our study, as evidenced by the brain network of a patient who remained in

UWS, which did not respond in an ordered way to anesthetic perturbation at the level of network hubs and alpha motifs. Here, we add to the growing body of evidence suggesting that the brain's ability to reorganize following a perturbation and to transition between states are precursors to emergence from disordered states of consciousness.

4.4 Topographic network analysis strikes a balance between the predictive power of neuroimaging and the need for clinical translatability

We found that clinical measures do not always predict recovery of behavioural responsiveness. It has been established that DOC patients who are older at the time of injury, who experience an anoxic brain injury, who are further from the date of injury, and who are diagnosed as UWS or have low CRS-R scores are less likely to recover consciousness (Chennu et al., 2017; Song et al., 2018). Consistent with these findings, in the cases presented here, the individual in UWS who did not recover was the only case of anoxic brain injury and the most chronic DOC patient at over 8 years post-injury. Clinically, this patient was therefore the most unlikely to recover consciousness and it is worth noting that topographic network properties reaffirmed this. Our study provides further evidence that measures usually obtained in the clinic are important but insufficient to establish a definite prognosis and could be supplemented with neuroimaging assessments.

While, as previously discussed, PET and fMRI imaging achieve high prognostic accuracy, these techniques are not always amenable to clinical implementation. Both neuroimaging methods pose a financial barrier, are unsafe or distorted in the presence of metallic implants, and are highly susceptible to movement artifacts, which may result from the involuntary movements of DOC patients. Studies on DOC prognosis based on motor imagery in fMRI have labelled up to 17% of data as unusable due to excessive motion artifacts (Cruse et al., 2011; Monti, Vanhaudenhuyse, et al., 2010). Patients are often sedated using propofol to reduce movement during MRI but, as we and others have shown, anesthesia is known to impact functional connectivity (Athena Demertzi et al., 2017; Kirsch et al., 2017). With this study, we demonstrate once more that EEG – through its cost efficiency, portability and limited contraindications – is an attractive middle-ground between strictly clinical assessment and PET or fMRI imaging.

4.5 Limitations and future directions

In this study, we presented a series of three exploratory DOC cases to demonstrate the feasibility and prognostic potential of motif analysis in this population, as well as the potential advantages of

topographic versus global network analysis and within-subject comparisons. Our findings are preliminary and will need to be validated in a larger cohort of patients with diverse behavioural and demographic profiles, types of brain injury and chronicity of injury. For instance, the third patient presented was the most clinically unlikely to recover due to the chronicity and mechanism of their brain injury. Our results confirm the poor prognosis, demonstrating the validity of motif analysis in this case, but do not add any additional information beyond the what can be discerned from the clinical profile. In addition, results were influenced by a missing bone flap in one patient; similarly, differences in brain lesions in our patient population may have skewed topographic maps. Future studies might employ source-localized EEG to evaluate functional connectivity between specific brain regions, mapped onto the individual brain anatomy of patients, in order to infer the neural mechanisms underlying the observed topographic reorganization and to account for heterogeneity of brain lesions. Furthermore, connectivity measures other than dPLI, such as symbolic transfer entropy (Staniek & Lehnertz, 2008), could be used to measure bi-directional motifs, which were excluded from our analyses. Finally, limitations in our experimental design must be considered. DOC patients were subjected to a brief anesthetic protocol (45 min) using propofol, while healthy controls underwent propofol induction, followed by 3 hours of isoflurane maintenance. Nevertheless, despite differences in the duration and type of anesthesia, patterns of topographic reorganization in motifs, hubs and power are similar between groups.

5 Conclusion

In a series of three exploratory DOC cases, we found that topographic, but not global, brain network properties measured using high-density EEG were associated with prognosis. We showed that functional network motifs, network hubs and alpha power topography – and their topographical reorganization during anesthesia – may be associated with DOC patient outcomes. We propose that topographic network properties measured at the nodal level might be used to complement clinical and whole-brain global measures for the prognostication of DOC patients. In addition, our findings demonstrate that the brain's capacity to adapt to a perturbation like anesthesia may be predictive of recovery from DOC.

6 Conflict of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

7 Author Contributions

SBM and GP designed the study. CD, AR, CA and DN collected the data. GP, MB and JL administered the anesthetic protocol and monitored participants. YM and DN analyzed the data. CD, YM, DN and SBM interpreted the data and wrote the manuscript. All authors edited the manuscript and approved the final version.

8 Funding

This study was funded by the Canadian Institutes of Health Research (FRN 152562, CD; Fredrick Banting and Charles Best Canada Graduate Scholarship – Masters, DN); the Fonds de Recherche du Québec – Nature et technologies (YM); the Fonds de Recherche du Québec – Santé (DN); and the Natural Science and Engineering Research Council of Canada (Discovery Grant RGPIN-2016-03817; SBM).

9 Acknowledgments

We would like to thank participants and their caregivers for their involvement in this study.

Data Availability Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

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