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Identifying Disruptions in Intrinsic Brain Dynamics due to Severe Brain Injury

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Abstract

Recent studies suggest that disruptions in resting state functional connectivity - a measure of stationary statistical association between brain regions - can be used as an objective marker of brain injury. However, fewer characterizations have examined the disruption of intrinsic brain dynamics after brain injury. Here, we examine this issue using electroencephalographic (EEG) data from brain-injured patients, together with a control analysis wherein we quantify the effect of the injury on the ability of intrinsic event responses to traverse their respective state spaces. More specifically, the lability of intrinsically evoked brain activity was assessed by collapsing three sigma event responses in all channels of the obtained EEG signals into a low-dimensional space. The directional derivative of these responses was then used to assay the extent to which brain activity reaches low-variance subspaces. Our findings suggest that intrinsic dynamics extracted from resting state EEG signals can differentiate various levels of consciousness in severe cases of coma. More specifically the cost of moving from one state to another in the state-space trajectories of the underlying dynamics becomes lower as the level of consciousness of patients deteriorates.

I. Introduction

An extensive brain injury generally leads to a disorder of consciousness (DOC) that inhibits the level of consciousness [1]. The severity of disorders of consciousness varies from comatose patients who exhibit a complete absence of wakefulness [2] to vegetative state (VS) where the patients seem awake but unresponsive to external stimuli [3], and to minimally conscious state (MCS) where the patients are characterized by partial responsiveness to environment [4]. Distinguishing different levels of consciousness (detecting conscious behavior) is necessary for effective diagnosis and prognosis of disorder of consciousness [5]. However, the assessment of consciousness in brain-injured patients is

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difficult and has become a major challenge of modern medicine. This is especially true for patients who do not respond to external stimuli and therefore make traditional bedside behavioral examinations imprecise [6].

Hence, identifying neuroimaging and electrophysiology-based biomarkers that can distinguish different levels of consciousness without relying on behavioral examinations is an active area of research and various measures of consciousness based on such modalities have been proposed in the literature [7]–[9]. However, the majority of these methods depend on event-related potentials (ERPs) [10], where their robustness in differentiating various degrees of consciousness are debated [11]. Moreover, these assays require the administration of external stimuli to assess the level of consciousness. Therefore, even though ERPs show significant potential for providing information about loss of consciousness, there is still a need for more robust discriminating factors [9]. Furthermore, the generated stimulus generally triggers specific sensory modalities that are associated with one particular brain region, which might have been damaged in certain patients. Given this information, developing methods that do not depend on external stimuli is essential for real-world clinical application of neuroimaging-based biomarkers to assess the conscious state of patients with disorders of consciousness. To our best knowledge, the work by Demertzi and his co-authors [12] is the only study that focused on resting state neuroimaging data for assessing consciousness. However, this study is based on intrinsic functional connectivity of the brain extracted from Functional magnetic resonance imaging (fMRI) scans, which limits its real-world application (i.e., bedside implementation).

In this study, we focus on identifying neural signatures of consciousness in severe coma patients using electroencephalographic (EEG) signals, and how subtle changes of consciousness can be detected using a simple, interpretable measure. To this end, we focus on quantifying the extent to which the brain makes low variance transitions. More specifically, we look at resting state EEG signals from a dynamical systems point of view and assess the reachability [13] of intrinsically evoked brain activity. We hypothesize that reaching low variance regions of the state space gets progressively harder as the level of consciousness deteriorates. To test this hypothesis and evaluate the proposed method we consider the correlates of the proposed measure with different levels of Glasgow Coma Scale (GCS), which is a standardized neurological scale for assessing the conscious state of a person and ranges from three for deep coma/death to fifteen for a fully awake person [14]. Our results indicate that there is, in fact, a correlation between the lability of intrinsically evoked brain activity and the GCS.

II. Materials and Method

A. Data Description

The retrospective EEG data including complete medical records were collected from 54 comatose patients and 20 control subjects (that were not in coma) over the course of three years (2013–2016). The patients underwent EEG recording for routine monitoring purposes in the Neurological and Neurosurgical Intensive Care Unit (NNICU) at Barnes-Jewish Hospital, which is affiliated with Washington University School of Medicine in St. Louis. Each patient underwent one recording session with exceptions of four patients for whom two

recordings were performed. EEG Data was acquired using 19 electrodes positioned according to the standard 10–20 system of electrode placement. The recording was done for at least fifteen minutes for each patient. The original signals were recorded against a common reference electrode and re-referenced to 18 bipolar channels (FP1–F7, F7–T7, T7–P7, P7–O1, Fp1–F3, F3–C3, C3–P3, P3–O1, Fz–Cz, Cz–Pz, Fp2–F4, F4–C4, C4–P4, P4–O2, Fp2–F8, F8–T8, T8–P8, and P8–O2) for analysis. The signals were recorded at either 250 or 500 Hz. Table I provides detailed information of the patients including age, gender, Glasgow coma scale, injury type, and injury location. Trained neurologists administered the clinical ratings and Glasgow coma scale evaluation. In case of the intubated patients, the verbal score was estimated using the process described in [15]. The study was approved by the ethics committee of Washington University in St. Louis and conducted in accordance with the declaration of Helsinki. Informed consent was obtained from controls and each patient's legal representative.

B. Data Preprocessing

Preprocessing steps include downsampling, removing small epochs from start and end of each recording to take into account the EEG setup noise, bandpass filtering the data, standardization, and removing sections of data with large amplitude artifacts, which were all implemented in MATLAB using in-house code. More specifically, the data initially recorded at 500 Hz was downsampled to 250 Hz to make the sampling rate of all the recordings consistent. Next, first and last five seconds of the recordings were discarded to take into account the possible EEG setup noise followed by employing a window-based finite impulse response (FIR) bandpass filter to filter the signals into the 0.5 – 30 Hz frequency range. Finally, EEG signals were standardized to zero mean and unit variance, and the large-amplitude artifacts (in this case samples more than six sigma away from the signal mean) were discarded.

C. Quantifying Intrinsic Dynamics

The overall framework of extracting intrinsic dynamics is shown in Fig. 1 and explained in the following subsections.

1) Identifying Intrinsic Events: After the data has been preprocessed, each channel of recordings from each patient is considered as the source channel, and all the points that are more than three standard deviations away from the signal mean in the selected source channel are identified. These points are marked as intrinsic events, and a window of size $w = 2s$ is centered on each of these identified events. Next, the corresponding windows in the other recorded channels (target channels) of the same recording are identified and averaged to obtain a response signal for each target channel with regards to a specific source channel. Then, for each target channel, the responses from different source channels are averaged to obtain one typical response signal for each target channel. Finally, the obtained typical responses are averaged across different subject groups (i.e., Control, Patients$\in \{GCS = 3, \ldots, GCS = 8\}$).

2) Obtaining Brain State Trajectories: The obtained responses for each target channel within each subject group is collapsed into three dimensions using principal

component analysis (PCA). Principal component analysis is a statistical procedure that applies an orthogonal transformation to uncorrelate possibly correlated variables. PCA decomposes the original data $X \in R^{N \times M}$ into uncorrelated components using transformation matrix W and sorts them according to the variance explained by each component [16]. In this case, our X is the averaged responses in different target channels, N is the number of channels, and M is the length of averaged responses ($w = 2s$). Instead of applying the entire PCA transformation matrix, generally the first k columns of the W matrix (here $k = 3$) that explain a certain percentage of the variance in the signal is used. In this case, PCA acts as dimensionality reduction method and reduces the dimension of the original data while retaining as much variance in the dataset as possible.

3) Quantifying the Brain State Trajectories: In order to quantify the lability of the obtained three-dimensional state trajectories for different groups of subjects, a simple method is used where first a polynomial surface ($f(x)$) is fitted to the trajectories of each subject group, and then the directional derivative for each projected point on the fitted surface ($D_u f(x_t)$) is calculated in the direction of the last point in the time domain ($u = x_T - x_t$). Hence, for each point at time t, we have:

$$D_u f(x_t) = lim_{h \to 0} \frac{f(x_i + hu) - f(x_t)}{h} \quad (1)$$

The positive value here indicates moving towards PC3, which we consider to be the component that is harder to reach. The rationale behind this is that since $\lambda_3 < \lambda_2 < \lambda_1$, moving towards PC3 requires more energy and hence is considered to be more difficult than moving towards PC1 or PC2.

III. Results

Fig. 2 shows the obtained state space trajectories and the fitted surface plots for each subject group. According to the figure, the state space trajectories differ between subject groups. In order to quantify these differences, the directional derivative for each point on the associated surface plot was calculated in the direction of the final point in the time domain. A multiple comparison test based on Kruskal-Wallis method was used to determine the statistical significance of the calculated directional derivative values between different patient groups. According to the results shown in Fig. 3, the directional derivative values between each consequent patient groups (such as $GCS = 5, 6$) was significantly different, except for patient groups $GCS = 7, 8$. Apart from these two groups, the directional derivative was not significantly different between the patient group $GCS = 4$ and patient groups of $GCS \in \{6,7,8\}$ which could be associated with the large variance of partial derivative values in $GCS = 4$ patient group. Finally, the direction of the slope (in this case the sign of the average partial derivatives) also changed from positive to negative for $GCS < 7$.

IV. Conclusion

This study complements current efforts in addressing one of the main challenges of neurology: identifying neuroimaging-based biomarkers for assessing different levels of

consciousness in brain-injured patients. To this end, we investigated the plausibility of using a new notion of intrinsic brain dynamics to distinguish different levels of consciousness in severe coma cases. To the authors' best knowledge this is the first demonstration of the discriminative power of intrinsic brain dynamics extracted from resting state EEG recordings in distinguishing different levels of consciousness in severe cases of coma. We showed that the difficulty of transition from one state to another (in this case the directional derivative) decreases as the level of consciousness deteriorates.

Despite the encouraging results, several limitations should be considered when interpreting the results of this study. First and foremost, the Glasgow coma scale used here is far from perfect for assessing the conscious state of coma patients [17]. It has limited capability in capturing the clinically relevant features and suffers from inter-rater inconsistency. Several alternatives to GCS such as Full Outline of UnResponsiveness (FOUR) score [18] has been proposed in the literature that will be considered in our prospective study. Along the same lines, here we have used the total Glasgow coma scale, whereas the GCS compromise of three different subscores that could provide additional information about the patient's condition. For example, patients one and three in our study have the same total GSC value whereas their individual scores on verbal and motor responses are different. Such heterogeneous patient population may necessitate more sophisticated methods to take into account the inter-subject variations of neuronal dynamics in order to make the method suitable for subject level analysis. Furthermore, we did not have any control over the possible confounds introduced by administrated medications such as sedatives, antiepileptic drugs, and muscle relaxants in this retrospective dataset. Such medications at different doses could influence the recorded EEG signals, which were not accounted in this study. Notwithstanding such limitations, we provided a simple measure that can distinguish different levels of consciousness in severe coma patients without requiring any cooperation from the patient (in this case response to external stimuli). We will endeavor three possible paths in our future work namely extending the proposed method to subject level analysis, using intrinsic brain dynamics to localize the brain injury and explore the possible correlations of intrinsic brain dynamics with the recovery of consciousness in comatose patients (prognosis).

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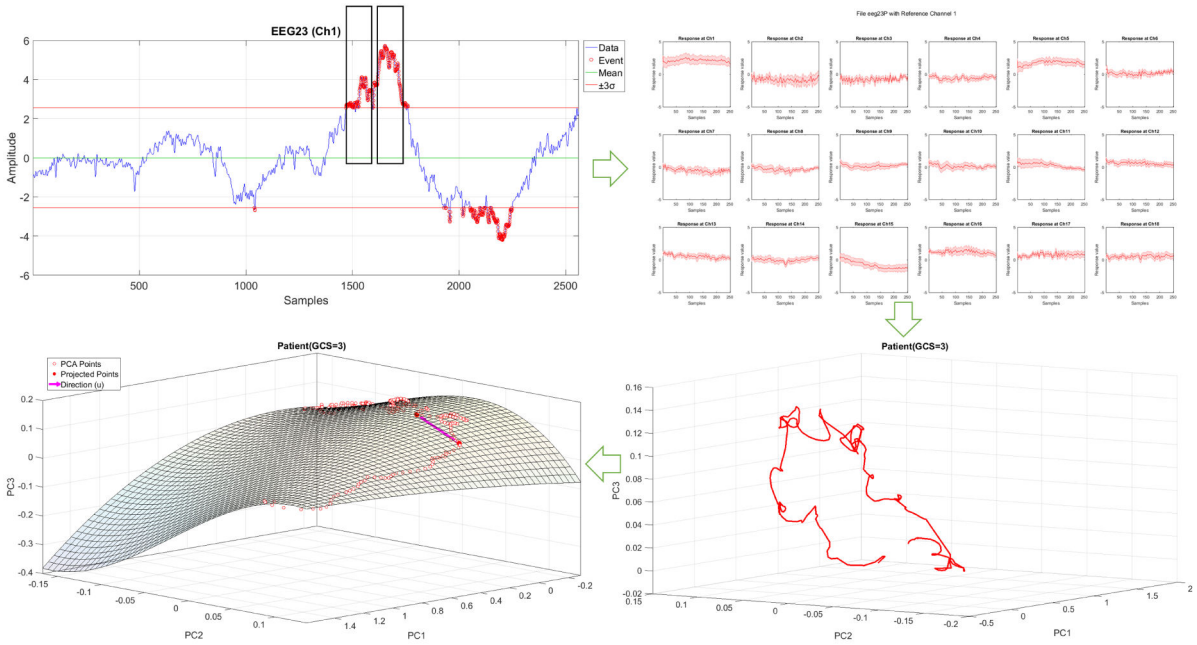

Fig. 1:

The intrinsic dynamics framework includes three main steps of identifying intrinsic events, obtaining brain state trajectories, and quantifying the brain state trajectories. To extract the intrinsic events, for each channel selected as a source channel, the data points that are more than three standard deviations away from the signal mean in the positive direction ($+3\sigma$) are identified. Next, a window of size w (in this case two seconds) is centered on the identified events and the corresponding windows in rest of the channels (target channels) is identified. For each target channel, all the marked windows are averaged to obtain a single response signal for that channel based on the selected source channel, and then the response signals to different source channels are averaged to get a typical response signal for each target channel. Finally, the resulted response signals are averaged for each subject group (in this case different GCS values and the control subjects) and collapsed into three dimensions using the principal component analysis. To quantify this three-dimensional data, a surface ($f(x)$) is fitted to the obtained trajectories and the directional derivative ($D_u f(x_t)$) of each point (x_t) in the direction of final point in the time domain ($u = x_T - x_t$) is calculated.

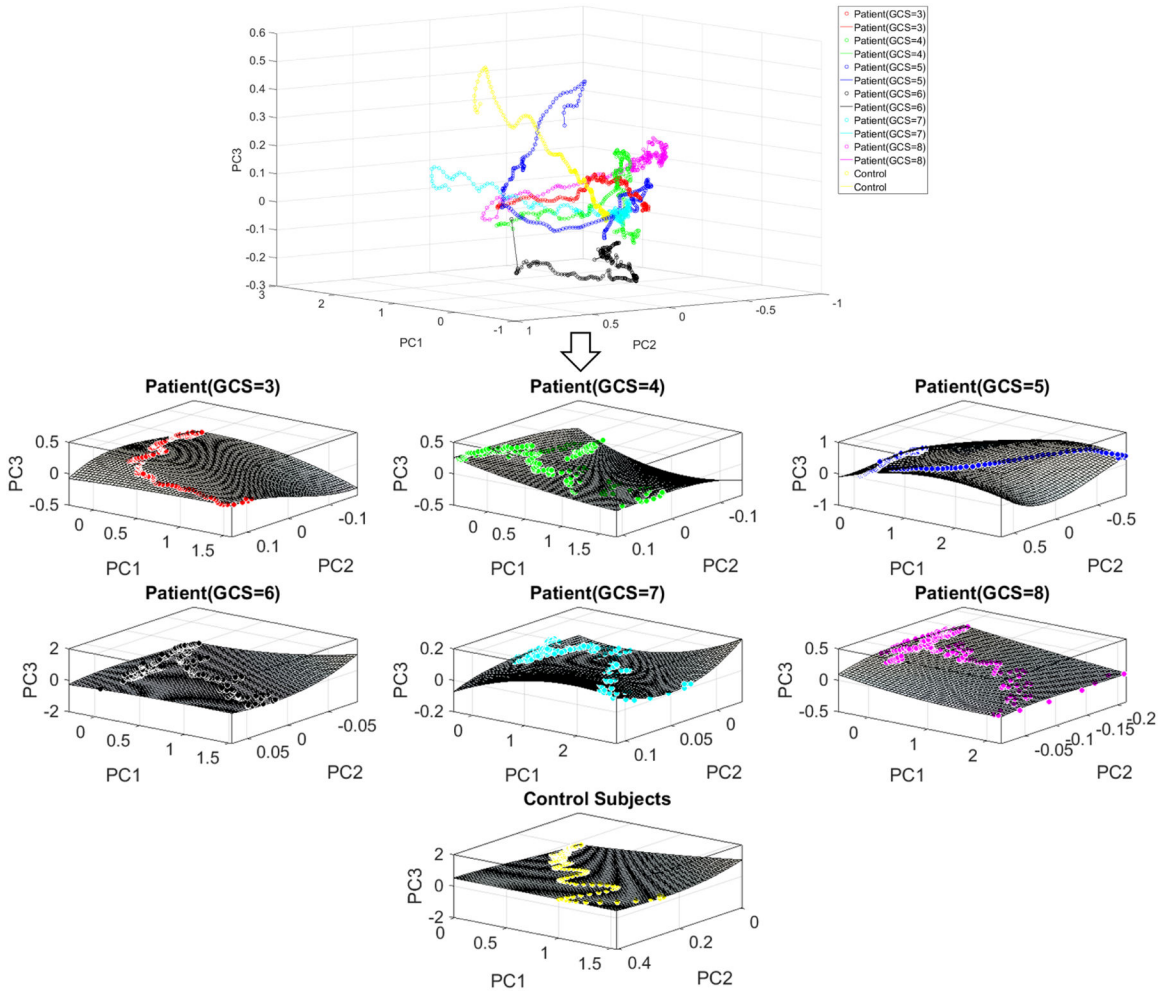

Fig. 2:

Intrinsic activity trajectories and their corresponding surface plots. Each color represents one subject group, and each point represents one time point of the averaged response from all target channels collapsed into three dimensions using PCA.

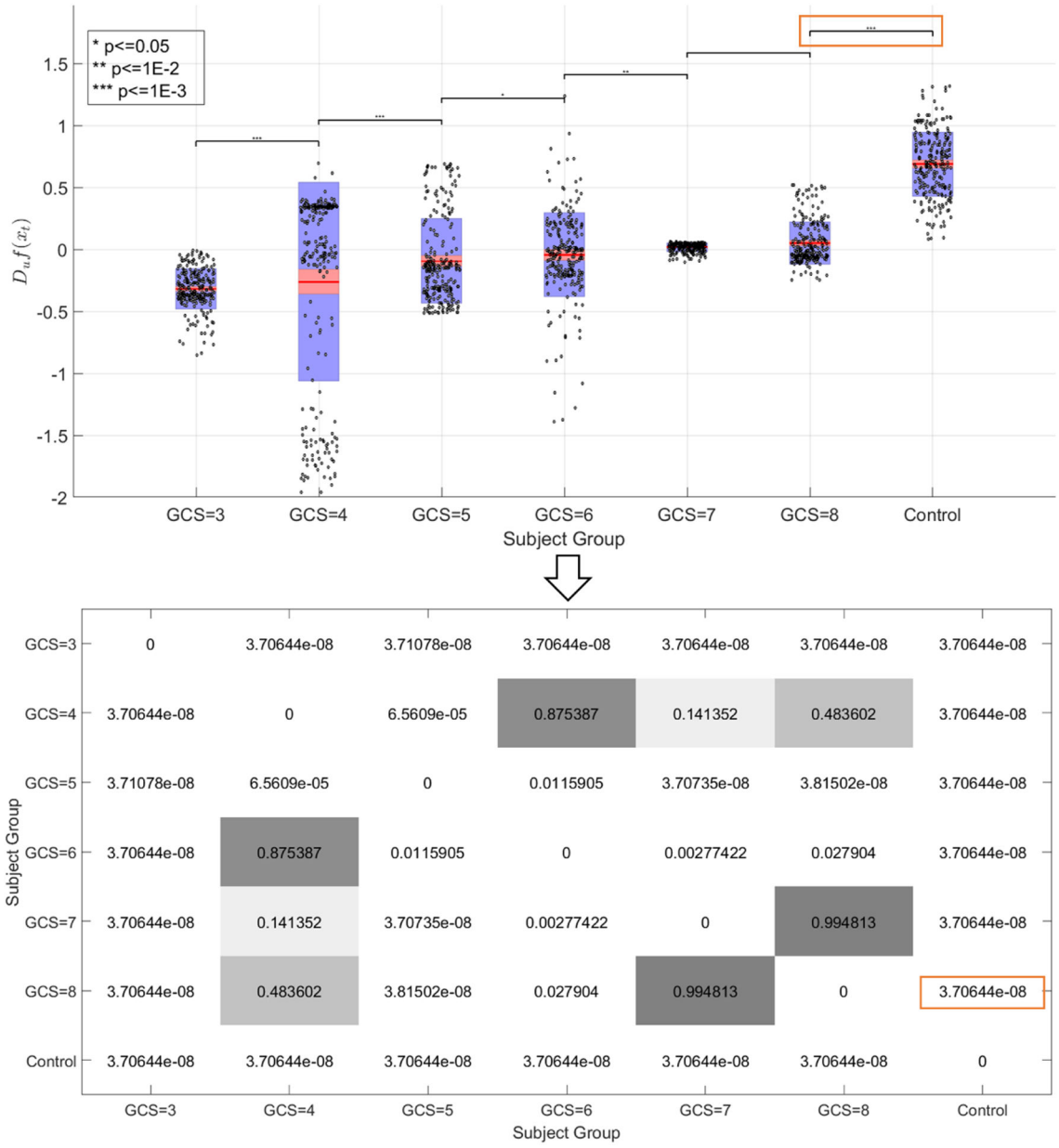

Fig. 3:

Comparison of obtained directional derivatives for various subject groups. Each dot in the top plot represents a directional derivative calculated at time point *t*. The box plots are expressed as mean ± standard deviation, and the significance level for each consequent pair is shown at the top of each box plot. More detailed statistical test results are shown in the bottom figure, where each cell represents the obtained *p*-value between the corresponding subject groups. The white cells represent the significant results ($p < 0.05$).

Table I:

Summary of the study population.

Variable	Distribution
Age	57±19
Gender	Male (32) and Female (22)
Injury Type	Focal (16), Diffuse(23), Mix (15)
Injury Location	Left (11), Right (18), Bilateral (15), Unknown (10)
GCS at time of EEG	Score Three (12), Score Four (8), Score Five (3), Score Six (10), Score Seven (20), Score Eight (5)