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Bedside quantitative EEG improves assessment of consciousness in comatose subarachnoid hemorrhage patients

Jan Claassen, MD, PhD¹, Angela Velasquez, MD¹, Emma Meyers, BS¹, Jens Witsch, MD¹, Christina Maria Falo, PhD¹, Soojin Park, MD¹, Sachin Agarwal, MD¹, J. Michael Schmidt, PhD¹, Nicholas D. Schiff, MD², Jacobo D. Sitt, MD, PhD³, Lionel Naccache, MD, PhD³, E. Sander Connolly, MD⁴, and Hans-Peter Frey, PhD¹

¹Department of Neurology, Columbia University, New York, NY, USA

²Department of Neurology & Neuroscience, Weill Cornell Medical College, New York, New York 10021, USA

³Institut du Cerveau et de la Moelle Épineière Research Center, Institut National de la Santé et de la Recherche Médicale, U975 Paris, France

⁴Department of Neurosurgery, Columbia University, New York, NY, USA

Abstract

Objective—Accurate behavioral assessments of consciousness carry tremendous significance in guiding management, but are extremely challenging in acutely brain-injured patients. We evaluated whether EEG and multimodality monitoring parameters may facilitate assessment of consciousness in patients with subarachnoid hemorrhage.

Methods—A retrospective analysis was performed of 83 consecutively treated adults with subarachnoid hemorrhage. All patients were initially comatose and had invasive brain monitoring placed. Behavioral assessments were performed during daily interruption of sedation and categorized into three groups based on their best examination as (1) comatose, (2) arousable (eye opening or attending towards a stimulus), and (3) aware (command following). EEG features included spectral power and complexity measures. Comparisons were made using bootstrapping methods and partial least squares regression.

Results—We identified 389 artifact-free EEG clips following behavioral assessments. Increasing central gamma, posterior alpha, and diffuse theta-delta oscillations differentiated patients that were arousable from those in coma. Command following was characterized by a further increase in central gamma and posterior alpha, as well as an increase in alpha permutation entropy. These EEG features together with basic neurological examinations (e.g., pupillary light reflex)

Address for Correspondence and Reprints: Jan Claassen, MD, PhD, Neurological Institute, Columbia University, 177 Fort Washington Avenue, MHB 8 Center, Room 300, New York, NY 10032, Phone: 212-305-7236; Fax: 212-305-2792 ; jc1439@columbia.edu.

Author Contributions

J.C., A.V., E.M., J.M.S., and H.P.F. contributed to conception and design of the study; J.C., A.V., E.M., J.W., M.C.F., S.P., S.A., J.M.S., E.S.C., and H.P.F. contributed to data acquisition and analysis; J.C., J.W., N.D.S., J.D.S., L.N., E.S.C., and H.P.F. contributed to drafting the manuscript and figures.

Potential Conflicts of Interest

None of the authors have any conflicts of interest pertinent to this publication to report.

contributed heavily to a linear model predicting behavioral state while brain physiology measures (e.g., brain oxygenation), structural injury, and clinical course added less.

Interpretation—EEG measures of behavioral states provide distinctive signatures that complement behavioral assessments of patients with subarachnoid hemorrhage shortly after the injury. Our data support the hypothesis that impaired connectivity of cortex with both central thalamus and basal forebrain underlies decreasing levels of consciousness.

Keywords

consciousness; quantitative EEG; subarachnoid hemorrhage

Introduction

Impaired consciousness is frequent after brain hemorrhages, cardiac arrest, and trauma.¹ Survival from these severe acute brain injuries (ABI) has dramatically improved but poor functional outcomes often associated with prolonged or permanent impairment of consciousness can still occur.^{2, 3} Currently, most patients with ABI that do not survive the ICU die after withdrawal of care following discussions between caregivers and families about the likely patient outcome.^{4–7} As patients and caregivers associate worthwhile survival in large parts with recovery of consciousness,^{8, 9} reliable objective assessments of consciousness in the acute setting are of tremendous practical and ethical significance. These determinations are extremely challenging as behavioral examinations carry a high test-retest and inter-examiner variability, effects of sedatives and analgesics are difficult to separate from brain injury, and altered cerebral metabolic functions need to be considered.¹⁰ Extensive neurological examinations are time consuming and challenging to obtain in a hectic critical care environment even when performed by highly trained physicians. This is in contrast to basic neurological assessments such as pupillary light reflex or best motor response that are reliably obtained by less experienced health care professionals. Reliable measures of consciousness would allow a paradigm shift in the management of patients with ABI providing potential biomarkers for the development of early interventions to improve recovery of consciousness.

Objective assessments of consciousness using quantitative EEG analysis may offer an alternative as suggested by studies of patients with chronic disorders of consciousness^{11–14} and anesthesia induced reversible loss of consciousness.^{15–18} Alterations of thalamocortical and thalamostriatal connectivity resulting in widespread changes of cortical excitation, affecting particularly the anterior forebrain, underlie decreasing levels of consciousness according to the mesocircuit hypothesis.^{19, 20} Predictable spectral EEG changes should be observed with increasing degrees of functional or structural thalamocortical deafferentiation under this model.²⁰ Careful characterization of the EEG spectra allows the placement of behavioral states observed shortly after brain injury into a theoretical mechanistic framework of brain injury potentially guiding individualized interventional approaches of the future.

Shortly after brain injury pathophysiological processes in the brain are in a state of flux due to a mix of effect of an underlying recovery process, secondary worsening of various injury processes (often occurring simultaneously), medication effects and the impact of metabolic

dysregulation. Disorders of consciousness following ABI have received little attention but studies in a small subset of patients have suggested that quantitative EEG measures in coma may track more closely with chronic disorders of consciousness in the unresponsive wakefulness patient than the minimally conscious state.²¹ It is unclear if in this environment objective assessments using EEG are feasible and helpful. In a comprehensive assessment of acute hemorrhagic stroke patients, combining local EEG coherence and resting state functional magnetic resonance imaging dysfunction of frontal networks has been implicated underlying impaired consciousness.²²

Here we identified reproducible, quantitative EEG features and physiological measurements assessed by invasive multimodality monitoring that correlate with routine behavioral assessments of consciousness early after hemorrhagic stroke during daily interruption of sedation.

Methods

Subjects

We studied all poor grade subarachnoid hemorrhage (SAH) patients admitted to the neurological intensive care unit at Columbia University Medical Center between June 2006 and October 2014 who underwent invasive brain monitoring. Inclusion criteria were: (1) nontraumatic, spontaneous SAH, (2) underwent invasive multimodality monitoring, and (3) EEG available for analysis during behavioral assessments. Exclusion criteria were: (1) age <18 years, (2) pregnant, or (3) patients or families did not want to participate in the study. Diagnosis of SAH was established by CT or xanthochromia of the cerebrospinal fluid if the CT was negative. Data were collected as part of a prospective observational cohort study approved by the local institutional review board.

General Management

Management was in accordance with American Heart Association guidelines including strict blood pressure control before securing of aneurysms by open or endovascular means, reversal of anticoagulation, treatment of hydrocephalus, and therapy for delayed cerebral ischemia, as needed.²³

Multimodality monitoring (MMM) was initiated as part of the patients' routine clinical care following our institutional protocol in comatose patients with a Glasgow Coma Scale of less or equal to 8 if patients (1) were unlikely to regain consciousness within the following 48 hours, and (2) had a high probability of surviving for the next 48 hours.²⁴ This decision was made by the attending neurointensivist and head neurosurgeon. According to our protocol invasive multimodality monitoring included measurements of intracranial pressure (ICP; Integra Neurosciences Inc, Plainsborough, NJ), interstitial cerebral microdialysis (CMA-70 microdialysis catheter, analyzed for lactate, pyruvate, and glucose using the CMA-600TM, CMA Inc, Stockholm, Sweden), partial brain tissue oxygenation (PbtO₂, using a flexible polarographic Licox Clark-type probe; LICOXTM, Integra Neurosciences Inc, Kiel, Germany), and regional cerebral blood flow (rCBF, Bowman Perfusion Monitor, Hemedex Inc, Cambridge, MA).

Behavioral Assessment and Outcomes

In all patients, neurological examinations with assessments of consciousness were performed daily during morning rounds (between 8 am and 11 am) with interruption of sedation if tolerated. The decision to abort an assessment or the sedation break was at the discretion of the primary medical team based on clinical judgment. The ability to follow commands was determined by applying a protocolized, hierarchical battery of behavioral assessments. The following neurological findings were recorded: no response to stimulation (“coma”), opening eyes to stimulation and/or eyes attending to stimulation (“arousal”), and following simple or complex commands (“awareness”).

Additionally, hourly basic neurological examinations performed by nursing staff including the pupillary light reflex (present or not for each eye), pupillary size (equal or asymmetric if > 1.5mm difference), and motor response (none, extensor or flexor posturing, withdrawal from or localization painful stimulus) were recorded. We assessed the modified Rankin Scale at discharge and three months following the initial bleed by telephone.^{24, 25}

Multimodal monitoring analysis

MMM data was extracted for up to 3 hours prior to the beginning of each EEG recording. The median value of each measure in this time-range was used for further analysis. We expected that patterns of activity would allow for detection of subgroups of patients using unsupervised learning techniques. Therefore k-means clustering with the numbers of clusters determined by the elbow method was applied to normalized MMM data.

Imaging

All available CT and MRI scans obtained during the ICU stay were coded by an experienced neurologist blinded to the clinical course. We specifically quantified injury in the following regions:²⁶ tegmentum, thalamus, diencephalon, frontal lobe, temporal lobe, and diffuse injury of both hemispheres. Injury was quantified based on visual inspection of available images into none, unilateral, bilateral (affecting 1/3 or less of the territory), and bilateral extensive (affecting more than 1/3). Diffuse injury was categorized as mild (one third or less in either hemisphere) or as extensive (more than one third in both hemispheres).

Electrophysiological data collection

Per clinical protocol all patients that undergo invasive brain monitoring were also monitored with scalp EEG for the duration of invasive monitoring.²⁴ Electrode placement followed the International 10–20 System with 21 electrodes applied with minor adjustments for drains and scalp wounds. EEG was recorded using a digital video EEG bedside monitoring system (XLTEK, Oakville, ON, Canada; low-pass filter=70Hz, high-pass=0.1Hz, sampling rate=200Hz).²⁵ Electrodes were routinely checked in order to keep impedances below 10kΩ and to ensure high signal quality. Based on visual screening, artifact free, EEG clips 30 minutes or longer were selected as close as possible following behavioral assessments (maximum allowed interval between the end of the clinical exam and the start of the EEG clip was 240 minutes).

EEG preparation

All EEG analyses were carried out in Matlab (Mathworks, Natick, MA) using the Fieldtrip²⁷ and the Chronux toolbox,²⁸ as well as custom scripts. The first step of data analysis consisted of detecting bad EEG channels based on the statistics of neighboring channels and subsequent distance weighted linear interpolation.^{29, 30} Then EEG clips were split into non-overlapping epochs of 6 second duration and offsets were removed, which were designated as trials. All trials were either converted to Hjorth Laplacian montage by subtracting the distance weighted average of up to four nearest neighbors from each channel³¹ or to average reference, depending on the type of EEG measure. For each of the resulting trials, we detected artifacts based on eye movements, muscle activity, as well as amplitude threshold violations (110 μ V), and removed trials containing any of these.

EEG measures

Based on the existing literature on assessment of consciousness in the chronic state as well as mechanisms of anesthesia we selected five measures of interest:

First, power spectral density (PSD) for frequencies from 1 to 50Hz was calculated for each trial using multitaper methods as implemented in the function *mtspectrumc* of the Chronux toolbox. Given the trial length of 6s, 5 tapers were used to obtain a 1Hz frequency resolution. In line with previous studies, data were analyzed in four different the frequency bands delta (2–4 Hz), theta (4–7 Hz), and alpha (8–13 Hz) and gamma (30–50 Hz). The median across all trials for a given patient and day were used for display and statistical analyses.

Second, we calculated Permutation Entropy (PE)³⁰ a measure of complexity of time-series data, for each EEG channel. In short, PE first transforms a time series into a sequence of discrete symbols of a given length before estimating entropy of the resulting distribution of sequences. In line with previous studies¹⁴ we chose a sequence length of 3 symbols. For these first two measures, Hjorth Laplacian montage was used, while for all following measures data were referenced to the average of all channels.

Third, coherence between all potential pairs of EEG channels was determined using weighted pairwise phase consistency (WPPC).²⁹ While other measures of synchronization exhibit dependence on number of trials, WPPC does not suffer from this bias. As with other measures of coherence the values range from 0 to 1 (completely coherent). To determine WPPC, we calculated spectral power and phase of each trial using multitaper transformation with discrete prolate spheroidal sequences for frequencies from 1 to 30 Hz and 1Hz smoothing. On the resulting data we calculated the WPPC using the function *ft_connectivityanalysis* implemented in the Fieldtrip toolbox.

Fourth, we calculated weighted symbolic mutual information (wSMI) which is an information-theoretic measure of coupling between EEG channels.³² Similar to PE one first transforms the EEG signals into sequences of symbols. Then mutual information of the probability distribution of two channels is calculated, weighted by binary weights (0 for channels with identical or exactly inverted sequences, since they could represent the same source or the opposite end of a dipole, respectively). In order to display wSMI for a given

channel, the mean of wSMI between this channel and all others was calculated. In a separate analysis we removed the weighting from the wSMI to test for long range connectivity.

Fifth, phase-amplitude coupling between the phase of low-frequency oscillations (1Hz) and amplitude in higher frequencies was determined.¹⁸ To this end, we calculated spectral power and phase of each trial using wavelet decomposition using a wavelet with five cycles. For this kind of measure, multitaper methods are not feasible, since each of the different tapers is shifted and therefore represents a different part of the oscillatory phase. The phase of the low-frequency oscillation was then binned into 20 bins and the median amplitude of the higher frequency determined for each phase bin.

Statistical analysis

As a first step, we analyzed the topographic differences for the different measures between comatose patients, those who open their eyes, and those who followed commands. Since the experimental design was not balanced we used a bootstrapping procedure to determine statistical differences in each channel.²² In short, 5000 samples of each channel's data were obtained with replacement. A difference between two states was considered significant if the following two conditions were met. (1) We determined the 95% confidence interval for each distribution using bias-corrected estimators. If the upper limit for one condition was lower than the lower limit for the comparison condition the first condition was met. (2) Based on the bootstrapped data we determined mean values as well as variance and degrees of freedom (using the original number of trials). We then determined the t-statistic for distributions with unequal variance. If the p-value was below 0.05 (two-sided test), the second condition was fulfilled. Using these two conditions provides a conservative approach for determining statistical significance.

Since EEG amplitudes might be affected by sedatives, we conservatively excluded all trials that were collected within two elimination half-lives of any of the sedatives that patients were receiving (in brackets elimination half-life in hours; excluded time window: pentobarbital [15 to 50; 100 hrs], midazolam [1.8 to 6.4 up to 12 hours in the critically ill; 24 hrs], fentanyl [4; 8 hrs], dexmedetomidine [2; 4 hrs], propofol [0.5 to 1; 2 hrs]). The statistical approach described in the previous paragraph was extremely strict, minimizing the risk of false positive results. On this reduced dataset the number of trials was too low to reach power sufficient for this test. Instead we examined differences between conditions at single channels using the Kolmogorov-Smirnov test, a robust statistical procedure. The difference between feature values of two conditions was deemed significant if the probability is lower than 0.05.

Linear model

To further probe whether the different states of consciousness are related to different amplitude and distributions of cortical activity, we performed a partial least squares (PLS) regression on the three different levels (0: no response; 1: eye opening/attending; 2: following commands). In short, PLS regression performs a principal component analysis on all feature vectors first and then applies a least-squares regression using those components which explain the most variance. Since the dimensionality of the feature space was as high

(about 530 dimensions, using a selection of measures) as the number of EEG recordings, this approach produced the best results. In order to test performance of this model we performed 500 repetitions using the first four principal components and leave-n (10%) out in order to prevent overfitting and determined averaged explained variance. We added variables capturing the clinical course (herniation, aneurysmal re-bleeding, hydrocephalus, sepsis, meningitis and ventriculitis, vasospasm, cerebral infarction, and clipping/coiling of the aneurysm), doses for the five most commonly used sedatives at time of exam and EEG recording, neurological exam, and imaging findings to our model to explain behavioral states.

Feature selection

In an effort to automatically select those features which best describe the level of consciousness we employed a novel automatic feature selection approach called minimum redundancy maximum relevance.³³ This approach uses statistical parameters such as mutual information and correlation to select features which are dissimilar to each other while at the same time highly related to the variable that we want to classify. It allows us to examine which of the features we selected (EEG, imaging, clinical course, cranial nerve exam and motor examination, and sedation) best describe our outcome variable.

Results

Study cohort

From a series of 98 SAH patients with invasive brain monitoring, 83 were included and 15 did not meet inclusion criteria as behavioral or EEG measures were not available for analysis. Overall baseline characteristics of included and excluded patients were similar (Table 1).

Behavioral assessment of consciousness

We were able to identify 389 artifact free EEG clips following behavioral assessments (median 4/patient, IQR 2–7; Table 2). 67 EEG clips were available following examinations without any response to stimulation (“coma”), 206 for exams showing eye opening or attending (“arousal”), and 116 following exams of patients that were following simple or complex commands (“awareness”).

Imaging

At least one CT scan was available in all patients and 45% (N=37) also underwent at least one MRI scan. Diffuse cortical injury was seen in 8% of patients affecting less one third of the brain or more in half of these cases. Patients were found to have focal structural injury in the tegmentum (unilateral 2%, bilateral 1%), thalamus (7%, 1%), diencephalon (2%, 1%), and frontal lobe (27%, 13%). Bilateral focal injury was mild (affecting one third or less of the territory), except for 4% of those with frontal lobe injury which had extensive injury.

EEG recording

Almost all SAH patients had the full 21 EEG channels available: 96.9% of recording (377 out of 389) had the full recording montage. For 3 recording sessions (0.8%) there were 20 electrodes, for 7 recordings (1.8%) there were 19 electrodes, and for 2 recordings (0.5%) there were 18 electrodes.

EEG features

Averaged spectral power maps were generated for each of these behavioral states (Figure 1). Increasing levels of consciousness were associated with an overall increase in power across all frequency bands as indicated by the posterior power spectral density plots (Figure 1, bottom row). Between coma and arousal increasing posterior theta and diffuse delta were observed (Figure 1, top two rows). Progressively increasing central gamma and posterior alpha were seen between exams consistent with coma, arousal, and awareness (Figure 1, rows 3–4). Complexity measures: Theta and alpha frequency PE was significantly higher in aware patients, particularly in the parieto-occipital regions for alpha frequencies (Figure 2, top two rows). Information sharing measures: Minor differences in wSMI were seen between the different behavioral states. Findings were unchanged when removing the weighting from the wSMI (Figure 2, third row). WPPC in alpha frequencies increased from coma (Figure 2, bottom row), but only patients with awareness had a significant increase in central channels compared to coma. Frontal phase-amplitude coupling between low frequency phase (1Hz) and alpha amplitude exhibits a distinct pattern particularly in patients that had intact arousal or awareness but not those in coma (Figure 3). The difference between the amplitude at phases pi and zero was significant only for those patients that were following commands ($p=0.05$) or able to open their eyes ($p<0.01$), but not for comatose patients ($p=0.15$).

Excluding all trials collected within two elimination half-lives of any of the sedatives that patients were receiving resulted in 129 remaining trials and did not fundamentally change results. 76% of the channels that were significant in the main analysis were also significant in the reduced data set. The biggest differences in significant channels were found for alpha and gamma power, when comparing arousable and aware conditions. But comparisons involving coma conditions were mostly identical.

Multimodality monitoring

There were no differences in ICP, CPP, pbtO₂, rCBF, cerebral lactate, cerebral pyruvate, cerebral lactate-pyruvate ratio, cerebral glucose, and ETCO₂ between comatose patients and those who follow commands (Figure 4). Using k-means clustering with 6 clusters we did find subgroups of comatose patients whose combination of ICP and EtCO₂ values discriminated them from each other. However, phenotyping did not reveal any significant differences for clinical and outcome measures.

Linear model

When analyzing all EEG features together the constructed linear model was able to explain about 28% of the variance (Figure 5). The selected features include spectral power, WPPC, and PE. Adding neurological assessments and imaging variables increased explained

variance to almost 41%, while adding sedation didn't improve the model by much. On a limited dataset that included patients with all MMM parameters available (84 observations) the explained variance increased marginally by 6% when adding MMM measures to EEG measures alone.

Feature selection

Automatic feature selection identified the following 50 variables that best model the behavioral state of patients: EEG Amplitude (alpha) in frontal channels (n=4), EEG Amplitude (delta) parietal (n=2), EEG Amplitude (gamma) central (n=5), EEG Amplitude (theta) fronto-temporal (n=4), EEG Coherence (alpha) fronto-central (n=6), EEG Coherence (delta) central (n=4), EEG PE (theta) centro-parietal (theta; n=6), extent of structural injury in the pons, thalamus, diencephalon, and frontal areas as well as diffuse structural injury, neurological examination (pupillary light response, pupillary asymmetry, best motor exam), clinical course variables (cerebral infarction, ventriculitis, sepsis, aneurysmal rebleeding, treatment mode of the aneurysm), and sedation (midazolam, propofol, and dexmedetomidine). In contrast to the linear model, the MRMR method selects structural injury and sedation variables as independent features for estimating level of consciousness.

Using the 50 features obtained using automatic feature selection the linear model also explains 41% of the variance. It therefore appears that the PLS model with all features is close to optimal.

Discussion

Our findings suggest that EEG, independent of sedation and structural injury as visualized on imaging studies obtained as part of routine clinical care, complements the clinical assessment of unconscious patients shortly after brain injury. Despite the enormous challenges of conducting electrophysiological studies and assessment of consciousness in the ABI setting we were able to identify a lawfulness of EEG patterns tracking with degrees of impaired consciousness that build and expand on insights gained from completely different clinical settings. Furthermore, these findings, as interpreted below, integrate acute impairment of consciousness from hemorrhagic stroke into the conceptual context of the anterior forebrain mesocircuit model, a unifying mechanistic theory for impaired consciousness.

Few studies employing electrophysiological measures to explore consciousness were conducted following ABI^{21, 22} while most studied the anesthesia model of induced states of unconsciousness or chronic disorders of consciousness. Insights gained from these studies do not necessarily apply to ABI as specific anesthesia effects and reorganization seen in chronic disorders of consciousness need to be accounted for. In addition, in anesthesia and chronic disorders of consciousness studies generally do not indicate whether or not patients were able to open their eyes. Most patients with chronic disorders of consciousness even without any awareness are able to open their eyes, a cardinal feature of the UWS.³⁴ Patients under anesthesia on the other hand typically are not able to open their eyes. When placing our observations into the context of these prior studies we will therefore predominantly draw

from the anesthesia literature for our data in the comatose state and from the chronic disorders of consciousness when referring to the arousal without awareness findings.

Coma

Comparing patients that are comatose to those that are not we found a broad decrease of power across all frequency bands (see Figure 1 for power spectral density plots bottom row and spatial plots above). The diffuse decrease in higher frequency oscillations (gamma, alpha) mirrors induced unconsciousness from anesthesia.¹⁸ However, instead of the previously described narrowing of thalamo-frontal oscillations to the alpha range described in propofol-induced unconsciousness^{18, 35} we see frontally dominant oscillations in a broader frequency range, including slow frequencies. The observed EEG changes implicate a more extensive disruption of the anterior forebrain mesocircuit^{19, 20} producing more cellular dysfunction across frontal cortex; a major contribution from the complex projections from both central thalamic neurons and neurons within the basal forebrain are likely producing different frequency effects depending on the complete loss of output from different populations or shift of some central thalamic neurons into burst mode.³⁶

Complexity of the EEG signal is expected to decrease with lower levels of conscious processing.^{37, 14, 36} A number of measures capturing information complexity of the EEG signal have been proposed as candidates to track with consciousness. We did not find striking differences in theta permutation entropy except for a right parietal decrease (Figure 2, top row) of comatose compared to those with intact arousal which supports the only prior study conducted in the ABI setting.²¹ These authors reported that time-frequency balanced spectral entropy of comatose TBI patients was comparable to that recorded for patients with UWS.

Information sharing measures such as coherence and weighted mutual information offer the ability to explore functional connectivity between brain regions and have proven useful to distinguish impaired consciousness from anesthesia.¹⁷ In contrast to these studies, in the current data we did not find any statistical differences in information sharing methods for comatose patients when compared to arousable patients without awareness.

Analysis of phase-amplitude coupling between low frequency phase and higher frequency amplitude in our study supports earlier conclusions drawn from anesthesia data.¹⁸ We observed a similar decrease in phase-amplitude modulations in comatose patients when compared to arousable patients with or without awareness similar to these prior reports.¹⁸ Mechanistically it is postulated that alterations of thalamo-cortical as well as intracortical connectivity¹⁸ underlie this phenomenon, which in consideration of the location of these effects within frontal cortical regions integrates well with the prior findings and further support the interpretation of these findings under the mesocircuit hypothesis.²⁰

Arousal

Comatose patients with ABI may undergo a reorganization of the intrinsic ascending arousal system, which is behaviorally linked to the gradual emergence of sleep wake cycles and eye opening within days or weeks after the insult.²⁶ Following ABI this may be a transitory state on the trajectory to recovery of awareness or a more permanent condition, labeled as UWS.

Arousable patients that do not have awareness were found to have an increase in central and occipital alpha and theta oscillations in our study, as well as an increase in posterior slower frequencies (theta and delta). Only the higher centro-occipital oscillations as well as occipital alpha coherence differentiated arousable patients without from those with intact awareness. Spectral power maps of patients in UWS¹⁴ are comparable to our patients with arousal but no awareness.

Importantly, the eye movement associated with eye opening creates a major EEG artifact and EEG measures differ in topography as well as power levels for patients in an eyes-closed compared to an eyes-open condition,³⁸ both of which need to be accounted for. We conservatively removed all trials with any suggestion of eye movement from the analysis but noise due to this cannot completely be excluded. Therefore, the observed EEG changes may be a result of a common change in brain physiology reflected in EEG changes as well as allowing eye opening but alternatively may also be due to a downstream effect from the eyes-opening compared to the eyes-closed condition.

Awareness

The presence of command following even if only simple commands are followed in the ICU setting represents definitive recovery of the content processing aspect of consciousness at the lowest level. In our cohort all patients initially did not and then some did start to follow commands. The EEG signature with increasing centro-occipital alpha power resembles that seen in both chronic disorders of consciousness¹⁴ and after emergence from anesthesia.^{17, 39} In anesthesia-induced impairment of consciousness, a classic posterior to anterior shift of alpha frequencies is seen.^{17, 39} Dynamic causal modeling suggests that changes in corticothalamic interactions underlie the increase of frequencies seen with propofol-induced loss of consciousness.¹⁵

Increases in gamma frequencies particularly in fronto-parieto-occipital regions relates to cognitive performance.^{40–42} Additionally, gamma power is lower in UWS patients with chronic disorders of consciousness¹⁴ and during loss of consciousness from general anesthesia.⁴³ Interestingly, some recent data of propofol-induced frontal gamma activity associated with loss of consciousness that persists after behavioral emergence from anesthesia challenges this notion.¹⁸ This discordance of the anesthesia data may relate to a medication effect in the anesthesia model causing high frequency oscillations including in the gamma range and a potential limitation of these models to study impairment of consciousness. This interpretation is further supported by data taken from patients with chronic disorders of consciousness, which demonstrate a similar progressive increase in gamma power when transitioning from vegetative, to minimally conscious, and finally conscious states.¹⁴ The observed power spectra with dominant alpha and theta frequencies for patients with intact awareness in the present study suggest that the central thalamus is in a normal tonic or at least burst firing mode.^{26, 44}

Complexity measures such as permutation entropy in higher frequencies (alpha) appear to be especially powerful in distinguishing patients who follow commands from those that do not,¹⁴ which we were able to support.

Information sharing measures (coherence and weighted mutual information) explore functional connectivity.^{14, 45} In anesthesia models coherence decreases frontally and increases occipitally with increasing levels of consciousness,¹⁸ the former was also observed in our study comparing comatose to patients with intact awareness. We also saw improved long-range connectivity as reflected by higher occipital coherence with a frontal electrode seed (Fz) when comparing arousable patients with to those without awareness (data not shown). Decreased local theta range coherence was seen previously in comatose patients following hemorrhagic stroke patients with intact awareness and supported impairment of the right frontal executive network identified by resting state functional magnetic resonance imaging analysis.²² The results for the weighted symbolic mutual information further support this interpretation, even though the differences in wSMI between different states of consciousness failed to reach significance. As for patients with chronic disorders of consciousness we found biggest differences in wSMI between different clinical states over the centro-posterior cortex, which likely represents projections from important brain network hubs such as posterior cingulate or precuneus.³² Overall likely recovery of cortico-cortical projections in the fully conscious state underlie the changes in these connectivity measures.

Prediction of the current behavioral state

Combining the most distinctive electrophysiological features we were able to predict about 41% of the variance even when accounting for sedatives. This is remarkable considering the large number of confounders, and EEG when combined with some very basic unambiguous neurological exam findings, will likely allow the future construction of an objective assessment tool to quantify consciousness based on these measures that will not require expert interpretation.

Applying a non-biased feature selection approach electrophysiological features together with cranial nerve and motor examination, clinical complications, imaging, and sedation variables were identified that best explained the variance of different behavioral states.

Limitations

A number of limitations are worth mentioning including the crudeness of our behavioral assessments of consciousness but these represent most commonly practiced behavioral measures of consciousness in the ICU setting. Future studies may apply a standardized ICU version of the Coma Recovery Scale-Revised as the behavioral assessment which is currently in development.⁴⁶ Another limitation is the unbalanced nature of our data. Not all patients had (usable) EEG clips for each level of consciousness and some patients never reach command following or even opening eyes. Therefore the different levels of consciousness were not completely balanced and were analyzed using bootstrapping procedures. Connectivity measures may have underestimated differences between behavioral states due to the limited number of electrodes. This electrode setup, however, represents the most widely used clinical standard and allows generalizability of our findings. Confounders such as structural injury, medications, and artifacts were carefully accounted for but may still add to the heterogeneity of the study subjects. We were unable to identify a relationship between MMM parameters and level of consciousness. Most certainly, impaired

consciousness would be expected in prolonged hypoxia of the brain including the frontal lobes the brain region that MMM probes are typically placed. In the current clinical context MMM measurements are used as targets for interventions to optimize perfusion and prevent strokes. The goal is to minimize prolonged episodes of brain tissue hypoxia, which may in part explain the lack of association with level of consciousness. The clinical course following ABI is not static and therefore forces of recovery and secondary brain injury may be encountered in an individual patient at the same time. A few secondary complications such as delayed cerebral ischemia from vasospasm are specific to SAH and these may result in secondary loss of consciousness from a focal injury. Differences between types of acute brain injury such as SAH, traumatic brain injury, and cardiac arrest need to be taken into account when generalizations about ABI are attempted. The impact of structural injury may have been underestimated as only half of the subjects underwent MRI assessments, the coding scheme is somewhat arbitrary, and dedicated sequences to quantify structural injury such as diffusion tensor imaging were not available. Several imaging^{47–50} and EEG^{31, 51–53} studies have shown that consciousness may be present in patients with chronic disorders of consciousness when detection by behavioral examinations are unable to detect this.

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ABBREVIATIONS

ABI	acute brain injury
APACHE	Acute Physiology and Chronic Health Evaluation
CPP	cerebral perfusion pressure
EEG	electroencephalogram
EtCO₂	end-tidal CO ₂
Hz	Hertz
ICP	intracranial pressure
ICU	intensive care unit
MMM	Multimodality monitoring
pbtO₂	brain tissue oxygenation
PE	Permutation Entropy
PLS	partial least squares
PSD	power spectral density

rCBF	regional cerebral blood flow
SAH	subarachnoid hemorrhage
UWS	unresponsive wakefulness syndrome
WPPC	weighted pairwise phase consistency
wSMI	weighted symbolic mutual information

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Figure 1. Spectral EEG features. Spectral power plots (rows 1–4) and posterior power spectral density (PSD) plots (row 5) stratified by time correlated best behavioral assessment (comatose, eyes opening or attending, following commands). Statistical comparison of grouped effects at each electrode between the different behavioral states (right three columns; grey: $P < 0.05$).

Figure 2. Complexity and coherence measures. Permutation entropy (PE) in the theta (PE theta, top row) and alpha (PE alpha, second row), weighted symbolic mutual information (wSMI theta, third row), and weighted pairwise phase consistency (wPPC alpha, bottom row) stratified by time correlated best behavioral assessment. Both, wSMI and wPPC as connectivity measures are represented using a different color map. Statistical comparison of grouped effects at each electrode between the different behavioral states are displayed (right three columns; grey: $P < 0.05$).

Figure 3.

Phase-amplitude coupling. Frontal phase-amplitude coupling between low frequency phase (1Hz) and alpha amplitude for three behavioral states (red = comatose, blue = eyes opening or attending, black = following commands) are shown with surrounding error bars.

Figure 4. Multimodality monitoring (MMM). Cluster analysis of multimodality monitoring parameters. Each subplot represents one normalized MMM parameter plotted against another one. Colors indicate the behavioral state (red-pink = comatose, light and dark green = eyes opening or attending, light and dark blue = following commands). Within states color differences indicate groups identified by cluster analysis.

Figure 5. Model performance. Median explained variance and standard deviation of the partial least squares model. The performance was determined using 500 repetitions of the model using the first four principal components on 90% of the data and then estimating explained variance using the remaining 10% of data. # indicates that complete data was only available a subset of trials (N=84).

Table 1

Baseline patient characteristics of included and excluded brain hemorrhage patients with multimodality monitoring (MMM).

SAH		
	Study cohort (N=83)	Not in study* (N=15)
Demographics		
Age (yrs)	57 (46, 66)	54 (45, 62)
Female	58 (70%)	8 (53%)
White	24 (29%)	3 (20%)
Admission findings		
Hunt Hess, admission	4.0 (3.75, 5.0)	5 (4.0, 5.0)
Hunt Hess, worst during hospital	5.0 (4.0, 5.0)	5.0 (4.75, 5.0)
Modified Fisher	2.0 (1.0, 3.0)	3.0 (2.25, 3.0)
APACHE II score	22.0 (19.0, 26.0)	20.0 (17.5, 29)
Hospital course		
Aneurysm clipping	56 (68%)	7 (47%)
Delayed Cerebral Ischemia	23 (28%)	5 (33%)
Seizures	25 (30%)	3 (20%)
Outcome 3 months		
Modified Rankin	5.0 (3.0, 6.0)	5.0 (3.25, 6.0)
Dead	24 (32%)	5 (36%)

Data are shown as number (%) or median (IQR).

* includes all patients that fulfilled inclusion criteria but did not undergo MMM, documented behavioral examinations, or EEG available

Table 2

Measurement characteristics (EEG behavioral pairs N=389)

Number of EEG-behavior pairs per patient	4 (2–7)
Time between stopping of sedation and start of behavioral exam [minutes]	68 (25,2838)
Best behavioral assessments	
No response to any stimulus	67 (17.2%)
Eye opening to verbal stimulus	101 (26.0%)
Eye opening spontaneous	73 (18.8%)
Attending to examiner	32 (8.2%)
Following simple commands	105 (27.0%)
Following complex commands	11 (2.8%)
Time to first behavior [days]	
Eye opening or attending	4 (2.2–6.3)
Simple or complex commands	4.7 (2.6–7.8)
EEG	
Time between exam end - start of EEG clip [min]	10 (4–31)
Duration of EEG clip [min]	45 (39, 53)
Medication at time of assessment	
Propofol	161 (41.4%)
Midazolam	20 (5.1%)
Other sedative	277 (71.2%)

Data are shown as number (%) and median (IQR).