Focal electroencephalographic changes index post-traumatic confusion and outcome

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Abstract

While the duration and severity of post-traumatic confusional state (PTCS) following traumatic brain injury have well-established implications for long-term outcomes, little is known about the underlying pathophysiology and their role in functional outcomes. Here we analysed the delta-to-alpha frequency band power ratios (DAR) from localized scalp areas derived from standard resting electroencephalographic (EEG) data recorded during eyes closed state in 49 patients diagnosed with post-traumatic confusional state. Higher global, occipital, parietal and temporal DARs were significantly associated with Confusion Assessment Protocol (CAP) severity symptoms observed on the same day, after controlling for injury severity. Also, occipital DARs were positively associated with both the CAP disorientation score 2, and the symptom fluctuation score 4, after controlling for injury severity (n=35). Posterior DARs were also significantly associated with Functional Independence Measure-cognitive subscale average score at 1 (n=45), 2 (n=42), and 5 (n=34) year(s) post-injury. The associations at 1 (temporal left) and 2 (parietal left) years survive after controlling for an injury severity index. Our finding that posterior DAR is a marker of post-traumatic confusional state and functional recovery post-injury likely reflects functional de-afferentation of the posterior medial complex in PTCS. Altered function of the posterior medial complex is proposed as a unifying physiological mechanism underlying both acute and chronic confusional states. We discuss the

relationship of these findings to electrophysiologic markers associated with disorders of consciousness.

Keywords: Post-traumatic confusional state, EEG, Delta Alpha Ratio, Delirium, Cognitive Outcomes

Introduction

In patients recovering from moderate to severe TBI, a period of impaired consciousness known as the post-traumatic confusional state (PTCS)[1] typically arises; the duration and severity of PTCS have well-established implications for long-term outcomes[2,3]. Recent models of the pathophysiologic mechanisms underlying disorders of consciousness have been advanced and tested[4–7], but their role in the continuing recovery process, specifically to the level of PTCS, has not been characterized. Characterizing the mechanisms underlying PTCS is important for facilitating development of prognostic biomarkers and informing future therapies.

Although impaired attention is a cardinal feature[1], PTCS also presents with protean symptoms such as disorientation and amnesia, fluctuation of presentation, restlessness, nighttime sleep disturbance, daytime decreased arousal, and psychotic-type symptoms[2,8]. This collection of symptoms and their prognostic significance have been quantified using the Confusion Assessment Protocol (CAP)[2]. Whereas the duration[3] and severity[2] of PTCS symptoms have well-established implications for long-term outcomes, little is known about the underlying pathophysiology specific to the associated symptoms. To the best of our knowledge, no prior study has examined electrophysiologic correlates of PTCS symptoms and their impact on functional outcomes.

EEG is a sensitive and reliable indicator of cerebral function and has long been used to characterize clinical changes following TBI[9,10]. While EEG has been

used in the acute phase of recovery[11] to detect seizures[12] and prognosticate survival[13,14], little is known about the physiology underlying the specific and quantifiable symptoms of acute confusion. EEG has also been utilized to characterize medical delirium and to provide an objective measure of its severity[15,16]. The overlap of delirium and PTCS symptoms further suggests the potential value of EEG as an electrophysiologic marker of PTCS.

The purpose of this study was to determine if changes in spectral power of EEG are associated with the severity and symptoms of PTCS[2], and to evaluate the utility of EEG spectral markers for predicting long-term outcome after TBI. The participants for this retrospective study were selected from a larger sample with well-characterized injury and outcome measures.

Methods

Study Population:

The study population was comprised from TBI Model Systems participants admitted to the brain injury unit of a freestanding rehabilitation hospital from 1999 through 2008. The participants met the criteria for the National Institute on Disability and Rehabilitation Research TBI Model Systems program which include: 1) medically documented TBI, 2) treatment at an affiliated Level I trauma center within 24 hours of injury,3) receipt of inpatient rehabilitation within the Model System, 4) admission to inpatient rehabilitation within 72 hours of discharge from acute care, 5) age of at least 16 years at the time of injury and 6) provision of informed consent[2]. Because behavioral data came from a sub-study examining acute confusion phenomenology and the EEG records were the primary focus of this current study, the exclusion criteria focused on EEG quality (artifacts) and type (resting eyes closed). To ensure that the subject had emerged from minimally conscious state (MCS), we only included subjects who had a documented CAP 14 days or less prior to the EEG recording. Further, due to the rapidly fluctuating and transitory nature of confusional symptoms, we assessed the relationship of EEG to CAP symptoms only for participants who had both studies completed on the same day. For the assessment of EEG to long-term outcome, we included participants who had a CAP assessment within 14 days prior to the EEG record. The study received approval by the local institutional review board. As noted in the inclusion criteria, written informed consent was obtained.

Behavioral Measures:

Confusion Assessment Protocol (CAP)[2]*:* The CAP provides a structured and repeatable method for measuring seven key symptoms of post-traumatic confusion: (1) cognitive impairment, (2) disorientation, (3) agitation, (4) symptom fluctuation, (5) nighttime sleep disturbance, (6) decreased daytime arousal and (7) psychotic symptoms. Symptoms are rated dichotomously (i.e., absent or present). Items are summed to obtain a total CAP score ranging from 0 to 7 with higher scores indicating greater confusion severity. The CAP is well-validated with construct and criterion validity[3] .CAP classification (i.e. confused/not-confused) was consistent with *DSM-IV*-based delirium diagnosis with 84% overall accuracy[2,17].

Functional Independence Measure (FIM) [18]*:* The FIM total score (range: 18-126) is comprised of the Cognition and Motor subscales. For each of the items described below, a score of 1 reflects complete dependence or inability and a score of 7 reflects complete independence and normal ability.

Cognition Subscale (range: 5-35): The cognition subscale is composed of 5 items designed to measure functional status in cognition (language comprehension, language expression, social interaction, problem solving, memory).

Motor Subscale (range: 13-91): The motor subscale is composed of 13 items designed to measure functional motor status (eating, Grooming, Bathing, Dressing - upper body, Dressing-lower body, toileting, bladder management, bowel management, transfers - bed/chair/wheelchair, transfers – toilet, transfers -

bath/shower, walk/wheelchair, stairs).

Data Collection Procedures:

Research assistants collected information from hospital and emergency medical service records and from interviews with participants and their family members. The data collected include demographic characteristics, injury severity (Emergency Department Glasgow Coma Scale, Time to Follow Commands (TFC), duration of post-traumatic amnesia and length of stay. TFC was defined as the interval from injury to the occurrence of 2 consecutive days of command following. Emergence from post-traumatic amnesia was assessed prospectively by repeated administration of the Galveston Orientation Amnesia Test (GOAT)[19], 24- 72 hours apart until 2 consecutive scores were achieved at or above the threshold for clearing post-traumatic amnesia [20,21]. Upon admission and serially during hospitalization, a neuropsychologist rated each participant on the CAP using semi-structured neurobehavioral examinations, medical record review and staff consultation[2]. Rehabilitation clinicians or research assistants rated functional independence at the time of rehabilitation discharge, and via patient or caregiver interview (generally by telephone) at 1, 2, and 5 years post-injury. Raw EEG data were retrieved from medical records. These records were reviewed for study inclusion as described above. The demographics of the subjects (excluded and included) are shown in Table 1. Clinicians obtaining CAP data were masked to EEG findings.

Electroencephalography (EEG) data:

EEG data were recorded from 19 scalp electrodes placed individually according to the International 10-20 system using the Nicolet vEEG device (www.natus.com) with the 10-20 system standardized protocol. The signals were sampled at 250 samples per second and filtered from DC to 100Hz. A respiratory therapist, trained in clinical EEG, monitored subjects and noted behavior during administration of standardized recording protocol (30 minute duration). At the time of the EEG study, recordings were reviewed for clinical purposes by a consulting staff epileptologist.

EEG data processing: The EEG records were visually reviewed per study inclusion/exclusion criteria as described below. The EEG analysis required at least 2 minutes of eyes closed resting state. Spectral analysis of EEG was performed with in-house software written in Matlab (The Mathworks, Natick, MA). For each subject, the eyes closed period was first segmented into 3-second epochs. Epochs with significant artifacts from line noise, eye blink, or muscle activity were removed after visual inspection. If multiple eyes closed periods were available within the same recording, they were combined after ascertaining similar spectral content. EEG signals were next converted to the Hjorth Laplacian montage to improve source localization[22]. The power spectral density for each channel was then calculated separately for each epoch using Thomson's multitaper method[23,24], as implemented by mtspectrumc in the Chronux Matlab toolbox (Mitra and Bokil 2007; chronux.org). Using 1 multitaper, a frequency

resolution of 0.66 Hz was obtained. See Supplementary Figure 1 for EEG tracings and Figure 2 for spectra from three subjects.

Deriving delta and alpha ratios (DAR):

To derive the DAR, the average difference of log spectral power within the frequencies of 1-4 Hz (delta) and 8-12 Hz (alpha) was obtained for each scalp channel (Figure 3). We chose a set alpha band to allow for standardization across the subjects. The averages of specific channels were then grouped as follows, Global: F3, Fz, F4, C3, Cz, C4, P3, Pz, P4, O1, Oz, O2; Global Left: F3, C3, P3, O1; Global Right: F4, C4, P4, O2; occipital = O1, Oz, O2; occipital Left: O1; occipital Right: O2; parietal: P3, Pz, P4; parietal Left: P3; parietal Right: P4; temporal: T3, T4, T5, T6; temporal Left: T3, T5; temporal Right: T4, T6; Frontal = F3, Fz, F4; Frontal Left: F3; and Frontal Right: F4. We focused on the delta-alpha band power ratio to facilitate comparisons with existing literature[15,26,27].

Statistical analysis:

Simple regression model

A simple regression analysis was performed to assess the relationship between DAR and CAP severity for datasets where EEG and CAP were obtained on the same day (n=35). The DAR values for global, occipital, parietal and frontal (all, left, right) were analyzed separately.

Multivariable linear regression model

Candidate predictors for the multivariable model were age, acute length of stay, TFC, and interval in days from injury to EEG recording. Variables showing univariable significant association with CAP severity ($p \leq 0.05$) were included in the multivariable model. Only TFC met this criterion and was entered as a co-variate in a multivariable model.

Logistic regression model

Logistic regression analyses were used to determine the relationships between DAR values and each of the 7 CAP subscores for participants where EEG and CAP were obtained on the same day (n=35). The presence of each CAP symptom was noted with a binary scale (1=yes, 2=no). Both simple and multivariable models with TFC as a covariate were examined.

Similarly, the association between DARs and FIM Cognitive scores at 1 (n=45), 2 (n=42), and 5 (n=34) years post-injury was assessed for datasets where CAP data were available within 14 days or less before the EEG. To create a dichotomous outcome, the average cognitive FIM score was derived for each patient and those with a 6 or above were coded as independent = 1 and the others as not independent = 0.

Non-parametric analyses

To compare the results of the regression analyses, bootstrapping and permutation of differences between all possible pairs was conducted. For the linear regression, differences between each of the β values (down the column

and across the rows of Table 2) were assessed for significance by a) bootstrapping (1000 times) to obtain confidence limits and b) permutation (1000 times) to obtain a p-value (Supplementary Table 1). For the logistic regression, the log differences of the odds ratio were likewise compared (Supplementary Tables 2-5).

Receiver operating characteristic (ROC) analysis

ROC analysis was used to determine the area under the curve (AUC) using DAR to classify patients into a) Post-traumatic Amnesia (PTA resolution as determined by GOAT[19] before/on date of EEG (n=35) and b) Post-traumatic confusional state (grouped as confused if showing either 4 or more symptoms or 3 or more symptoms providing 1 is disorientation) on date of EEG (n=35). Threshold values on DAR variables that optimally discriminated patients on each classification were identified using Youden's j statistic ($J = \max_c \{Se(c) + Sp(c) - 1\}$). Sensitivity and specificity were calculated at the optimal thresholds selected for each DAR variable of interest.

All p-values are two-sided and statistical significance was evaluated at alpha = 0.05. Statistical analysis was performed using SAS Version 9.4 (SAS Institute Inc., Cary, NC) and/or Matlab (Mathworks, Inc., Natick, MA).

Results

Study Sample:

During the study period, 178 participants with 253 EEG records met study inclusion and exclusion criteria. CAP data was available for only 160 participants. For participants with multiple EEG records, we used the record for which there was a CAP assessment within 14 days prior to the EEG. If there was more than one CAP assessment in this interval, we used the one most proximal to the EEG record. This resulted in exclusion of 93 EEG records. Additional exclusion criteria included lack of at least 2 minutes of eye closure during EEG (n=55) and presence of suspected sleep (to allow for uniform comparisons across all subjects on the same state) or excessive muscle artifact on EEG (n=23). Further, those without CAP data within 2 weeks prior to EEG (n=33) were excluded, resulting in a total of 111 exclusions. This resulted in a study sample of 49 eligible participants as illustrated in the Figure 1 CONSORT diagram. From these 49 subjects, sub analyses were conducted on those with 1) concurrent CAP and EEG on the same day (n=35) and 2) outcome analyses at 1 (n=45), 2 (n=42), and 5 (n=34) years post-injury including those with CAP data within the 14 days prior to the EEG. Table 1 provides summary demographics and injury severity for those excluded (n=111) and those retained (n=49) for analyses. Comparisons of the sample included (n=49) and sample excluded (n=111) revealed significant differences in certain clinical parameters summarized in Table 1. Individuals excluded from analyses had greater injury severity. As such, the sample excluded also had a longer interval from injury until EEG recording.

DAR and Confusion Severity

For the subset with concurrent EEG and CAP administration, 63% of participants met criteria for confusional state with most evidencing severe confusion (86%). Univariate linear regression models (Table 2) were used to evaluate DAR from localized brain areas as predictors of total CAP score (severity) obtained on the same day. After adjusting for injury severity (TFC), we found significant positive association (i.e. increased DAR associated with increased severity) between total CAP score (confusion severity) and DARs from global (all, left), occipital (all, left, right), parietal (left) and temporal (all, left) regions. Comparisons of the β values show that Global DAR has significantly higher association with total CAP score when compared to occipital and parietal but not temporal.

DAR and Confusion Phenomenology

The association between DAR and the 7 aspects of confusion phenomenology measured by the CAP were modeled using logistic regression (Table 3). After controlling for TFC, DARs from the occipital areas were significantly associated (i.e., increased DAR associated with symptom presence) with CAP subscore 2 (disorientation[28,29]) (all, right), as well as CAP subscore 4 (symptom fluctuation) (all, left, right). Parietal, global and frontal DAR did not have a significant unique relationships with CAP subscores (results not shown). Comparisons of the odds ratio's (Supplementary Table 2), show that those reported for CAP 4 and CAP 6 are significantly different than the others.

DAR and Long-term Outcome

Regression analyses showed that several DARs were significantly associated with cognitive functional outcomes at 1, 2 and 5 years post-injury (Table 4). After controlling for injury severity (TFC), only temporal left (1 year) and parietal left (2 years) passed significance criteria. Comparisons of the odds ratios (Supplementary Tables 3-5), indicated stronger associations in the left regions compared to the right.

Similar analyses were conducted to predict other outcome measures: FIM Motor score, FIM Total score, Disability Rating Scale (DRS) and Glasgow Outcome Scale (GOS). No significant relationship was found between DAR and FIM Motor outcomes at 1, 2 and 5 years. Significant univariate relationships between the FIM Total score and occipital (1 and 2 years) and occipital and parietal left (1, 2 and 5 years) did not survive multivariate regression. No significant relationship was found for DRS. Significant relationships between DAR (global, global left, occipital, occipital left, occipital right and parietal left) and GOS (at only 2 years) was found. The relationship between DAR (occipital, occipital left, and parietal left only) and GOS survived multivariate regression.

DAR and diagnostic utility:

Based on the criteria described in methods, n=17 remained in PTA and PTCS at time of EEG. The continuous variable for overall occipital had the highest AUC among the DAR variables for the PTCS outcome (AUC = 0.66) and the PTA outcome (AUC = 0.77) (see Supplementary Table 6) and best maximized

sensitivity and specificity for both outcomes. For the PTA outcome, parietal left and frontal right showed high sensitivity (>90%) but low specificity (<40%). For the PTA outcome, both frontal right and temporal right had perfect sensitivity at the cost of low specificity.

Discussion

Here we identify EEG correlates of specific symptoms of post-traumatic confusional state and functional outcomes over time. Specifically, we find that increased delta and decreased alpha in the occipital, parietal and temporal brain areas is associated with a significant increase in the severity of confusion, as indicated by the CAP symptom count. Additionally, increased occipital DAR is positively associated with both disorientation and fluctuation of symptoms. Occipital DAR also proved the best discriminator of those who were still in PTA and PTCS with those who had resolved these conditions by GOAT or CAP criteria at the time of EEG. Finally, increased DAR in the posterior regions is significantly associated with cognitive outcomes at 1, 2 and 5 years with the associations at 1 and 2 years surviving after inclusion of injury severity regressor. The evidence of strong relationships between posterior DAR and CAP total score (and two of the CAP subscores), and its enduring association with functional outcomes at 1, 2, and 5 years post-injury, has mechanistic implications.

Our findings of increased delta and reduced alpha activity (increased DAR) in the posterior cortices can reflect either structural and/or functional de-afferentation across cortico-cortical and thalamocortical connections as a result

of TBI. Increased delta activity has been correlated with alterations in deeper brain structures, such as the thalamus or mesencephalic reticular formation[30], damage to cholinergic basal forebrain[31,32] or cholinergic white matter tracts[33], and more global white matter deafferentation[30,34,35]. Similarly, functional down-regulation of neocortical neurons may produce increases in delta, as seen in the intact brain during microsleep intrusion within wakefulness[36] or during general anesthesia[37]. More specific to our results, studies in both animals[38,39] and humans[40–44] have shown the contribution of the parietal, temporal and occipital cortices, along with the thalamus, to posterior alpha rhythm generation. Reduced alpha activity has been generally correlated with gray matter lesions[34] and interpreted as evidence of reduced cortical excitability[45]. The specificity of the posterior cortices in our results can be compared with lesion studies of post-stroke confusion and delirium, which share an overlap of symptoms with PTCS[8], and implicate posterior parietal, temporal, occipital[46,47] and thalamic[48] sites.

We hypothesize that the association of acute delirium and lesions within parietal, temporal and occipital cortices, and our findings of an association of DAR in these same regions to severity of confusion and long-term functional outcomes, may originate in the known role of the posterior-medial complex in recovery after severe brain injury[49]. Prior studies have shown that the metabolic level of posterior medical complex activity indexes levels of recovery after coma, ranging from vegetative state to normal cognition[4]. In addition, both the structural integrity of the posterior medial complex[5,6] and its functional relationship with the thalamus[7] have been shown to correlate with functional levels in patients with

disorders of consciouness[5].

The posterior medial complex has the highest resting metabolic rate in the healthy adult brain[50], and represents a key node in the default mode network[51], that has been proposed to reflect the baseline state of the human brain. Functional imaging studies have linked posterior medial complex to internally directed cognition, recall of autobiographical memory, and attention regulation[52]. The structural and functional disconnection of the posterior medial complex has been correlated with impaired attention after TBI[31]. Structural lesions within the posterior medial complex, specifically the posterior cingulate region, are associated with retrosplenial amnesia, a symptom complex dominated by loss of episodic memory formation and memory retrieval deficits that can impair orientation and lead to marked amnesia[54]. Recently, functional and structural disconnection between the posterior cingulate cortex and hippocampus in the medial temporal lobe was shown to correlate with episodic memory impairment and processing speed in patients with post-traumatic amnesia[55], a similar population to those in our study. That study also reported on disconnections within the posterior DMN in TBI subjects. More specific to our results, of a stronger relationship between left DAR and cognitive outcomes (Supplementary Tables 3-5), are their findings of functional connectivity losses that are localized to the left hippocampus[55]. Thus, the reported association of increased parieto-occipito-temporal DAR with disorientation measures (including amnesia[2]) and the fluctuation of confusion symptoms may reflect primary dysfunction of neuronal

populations following chronic de-afferentation of the posterior medial complex. Taken together, our results extend and build on the proposed role of the posterior medial complex in the recovery process, from coma to resolution of the confusional state, following TBI.

Comparison with prior literature:

To the best of our knowledge, this is the first study examining the link between quantitative behavioral assessments and electrophysiological activity in PTCS. Increased delta activity and decreased posterior alpha rhythm (visual assessment) have been previously reported in the acute period of recovery after TBI[9], in patients following concussions[56], and have been found to differentiate between mild TBI subjects and controls during eyes closed rest[57]. Importantly, an increase in global DAR was reportedly the best predictor of functional outcome after acute neurorehabilitation of TBI patients[26], but confusional symptoms were not assessed in this investigation. Global DAR measures have also been shown to be predictive of outcome after multifocal ischemic injury following subarachnoid hemorrhage[27].

Our findings also demonstrate strong overlap between EEG changes in PTCS and those reported in medical delirium[8]. In the context of medical delirium, the relationship of occipital DAR to symptoms has been quantified in elderly subjects[58], showing that increases in delta percentage correlate with longer duration of delirium and hospitalization, and an overall increase in slow-wave power and decrease in alpha power correlate with worsening delirium. Taken

together with our present results, these occipital DAR findings in medical delirium suggest a unifying mechanism of dysfunction within posterior medial complex underlying confusional symptoms. In the context of medical deliria arising within a fully connected, structurally uninjured brain, the selective disturbance of posterior medial complex is likely due to the high metabolic demand of these neurons remaining unmet in the setting of limited availability of metabolic substrates caused by acute illness (infection, inflammation, altered cellular function, among others).

Study Strengths and Limitations:

Due to the rapidly fluctuating nature of PTCS and the specific symptomology (e.g., agitation), obtaining EEG in this population is challenging. Further limitations of this study include retrospective analyses of a prospectively collected dataset. When originally recorded, maintenance of a resting state (e.g., eyes closed) for a period of time sufficient for quantitative analyses was not required. Additionally, since the EEGs were obtained for clinical purposes (e.g., seizure detection), CAP was not always administered on the same day. As such, only a subset of patients from the larger dataset met inclusion criteria for analyses (see Figure 1, Table 1 and methods). The included and excluded samples were different on certain clinical parameters. Limited number of events in the logistic regression resulted in wide confidence intervals and borderline significance.

Because of the small sample size, we did not conduct an exhaustive analysis of the dominant rhythm (alpha). Across the cohort, there is variability within the alpha band with absence, reduction and shifting of the peak (see Figure 2). A larger sample size would allow for a more in-depth exploration of these patterns.

Although EEGs were routinely read by a clinical epileptologist for clinical purposes, due to the retrospective nature of this study and inclusion of the subset of EEGs from a much larger database, it was not possible within the scope of this study to collate our results with those of the clinical EEG readings.

Strengths of this study include prospective evaluation of a large sample. These secondary analyses are the first to relate spectral parameters of the EEG against standardized measures of behavioral and rehabilitation outcome. These findings further extend the current literature by examining longitudinal outcomes after TBI up to 5 years post-injury. Despite the wide confidence intervals for some variables, large effect estimates support the presence of real association.

Future work:

The emerging association of dysfunction in the parieto-occipito-temporal regions with clinical symptoms of PTCS and long-term outcome after TBI invite future work exploring their close mechanistic link in terms of symptoms of fluctuation and orientation. Similarly, further studies of the link between physiological substrate underlying EEG changes, neurochemical assays, and the tiered resolution of symptoms[1] during the post-traumatic confusional period will

improve understanding of pathophysiology and direct efforts at developing interventions.

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Disclosure

The views, opinions, and/or findings contained in this article are those of the authors and should not be construed as an official Department of Defense position or any other federal agency, policy or decision unless so designated by other official documentation. The authors declare no conflicts of interest. No competing financial interests exist.

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Figure 1. CONSORT flow diagram of study design

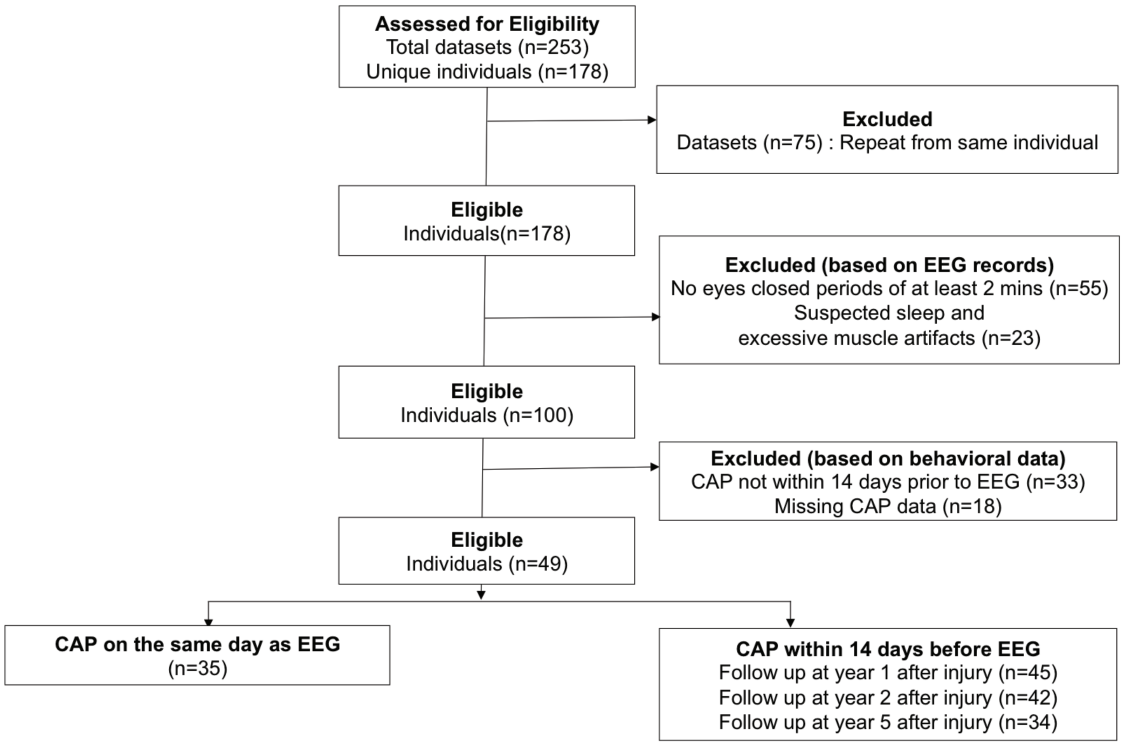


Figure 1

Figure 2. Three example individual spectra of the central channels

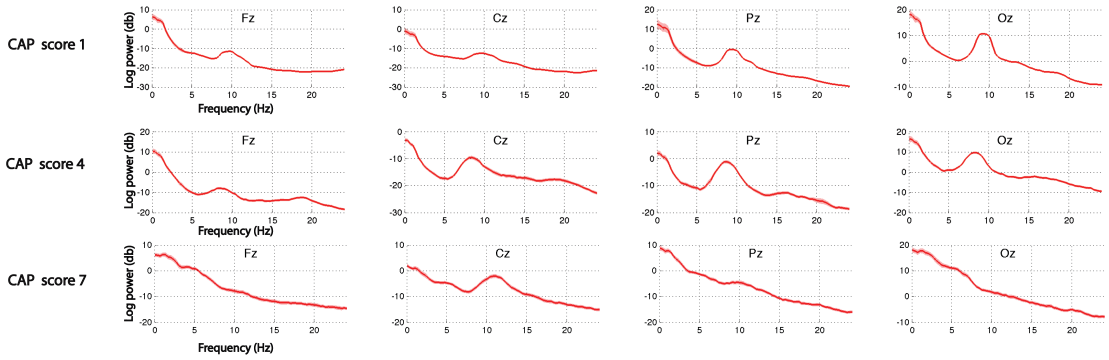
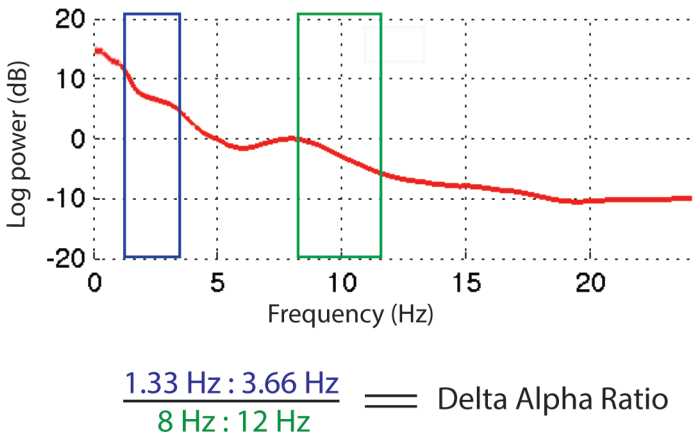


Figure 2

Figure 3. Delta Alpha Ratio



$$\frac{\text{1.33 Hz : 3.66 Hz}}{\text{8 Hz : 12 Hz}} = \text{Delta Alpha Ratio}$$

Figure 3

Table 1: Subject demographics: From the 253 original datasets (178 subjects), repeat records from same subject were excluded (n=75). A further 18 were excluded for not having CAP data. Then, 111 datasets were excluded for: no eyes closed periods (n=55), suspected sleep or excessive muscle artifacts (n=23) and those without a CAP administration within 14 days prior (n=33). # = sample difference.

Table 2: Linear regression results for patients with EEG and CAP on the same day (n=35). Uni: Univariate regression; Multi – multivariate regression corrected for time to follow command **p<0.01; *p<0.05; β: Point Estimate; CI: Confidence Interval

Table 3: Logistic regression results for CAP subscores (n=35) and Occipital channels only. CAP subscores: (1) cognitive impairment, (2) disorientation, (3) agitation, (4) symptom fluctuation, (5) nighttime sleep disturbance, (6) decreased daytime arousal and (7) psychotic symptoms. Uni: Univariate regression; Multi – multivariate regression corrected for time to Follow Command.*p<0.05; OR: Odds ratio; CI: Confidence Interval

Table 4: Logistic regression results for patients with EEG and Cognitive subscale (Functional Independence Measure) at 1 (n=45), 2 (n=42) and 5 years (n=34). Uni: Univariate regression; Multi – multivariate regression corrected for time to follow command. *p<0.05; OR: Odds ratio; CI: Confidence Interval

Table 1

*N= 101; **N= 76; ***N= 39; ****N= 36; *****N= 56; @ = median; ^ = percentage;

	Sample excluded (n=111) Mean (SD)	**Sample included (n=49) Mean (SD)**
Age at injury (years)	31.43 (16.4)	34.14 (15.5)
Male (number/^)	69/62%	36/73%
Education (years)	10.33 (4.2)	10.25 (4.7)
Time to Follow Commands (days)	14.46 (22.4)*	10.25 (4.7)
Glasgow Coma Scale Score at ER Admission^		
Mild	16.2	12.2
Moderate	13.5	12.2
Severe	22.5	18.4
Intubated	6.3	8.2
Sedated	41.4	48.9
Acute Care Length of Stay (days)	26.6 (20.6)	22.0 (16.0)
Rehab Length of Stay (days)	28.9 (22.9)	18.6 (8.6)
Post-traumatic amnesia duration (days)	22.3 (18.5)**	22.8 (19.3)***
Time of EEG (days) @	65.5*****	23

Table 2:

	All		Left		Right	
	Uni β (CI)	**Multi β (CI)**	**Uni β (CI)**	**Multi β (CI)**	**Uni β (CI)**	**Multi β (CI)**
Global	3.01** (0.78 5.24)	2.38* (0.46 4.31)	3.05** (0.99 5.11)	2.43** (0.65 4.22)	2.17* (0.06 4.29)	1.68 (-0.13 3.49)
Occipital	2.37** (0.95 3.79)	1.86** (0.61 3.11)	2.18** (0.80 3.57)	1.65* (0.41 2.89)	2.21** (0.81 3.61)	1.81** (0.61 3.01)
Parietal	1.82* (0.08 3.57)	1.36 (-0.15 2.87)	2.05* (0.36 3.74)	1.62* (0.17 3.07)	1.47 (-0.05 2.98)	1.06 (-0.25 2.37)
Temporal	2.53* (0.55 4.52)	2.05* (0.35 3.74)	2.61** (0.81 4.41)	2.07* (0.49 3.62)	1.72 (-0.19 3.62)	1.45 (-0.15 3.05)
Frontal	2.72 (-0.18 5.62)	2.07 (-0.41 4.55)	2.38 (-0.24 4.99)	1.99 (-0.22 4.19)	1.70 (-0.94 4.35)	0.99 (-1.29 3.27)

Table 3:

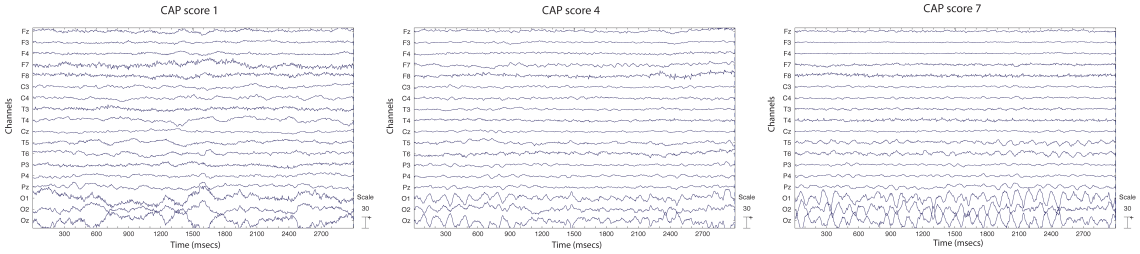
	All		Left		Right	
	Uni OR (CI)	**Multi OR (CI)**	**Uni OR (CI)**	**Multi OR (CI)**	**Uni OR (CI)**	**Multi OR (CI)**
CAP 1	4.06 (0.85 19.35)	3.60 (0.73 17.86)	3.51 (0.78 15.83)	3.03 (0.65 14.24)	4.13 (0.89 19.15)	3.89 (0.81 18.79)
CAP 2	8.47* (1.35 53.19)	7.43* (1.06 51.82)	6.24* (1.18 32.88)	5.30 (0.90 31.19)	8.55* (1.28 57.17)	8.14* (1.11 59.779)
CAP 3	4.19 (0.81 21.59)	3.36 (0.58 19.54)	3.15 (0.70 14.11)	2.38 (0.46 12.22)	4.78 (0.86 26.52)	4.38 (0.71 27.10)
CAP 4	9.96* (1.45 68.22)	9.78* (1.34 71.46)	7.42* (1.17 47.11)	6.86* (1.04 45.12)	10.01* (1.53 65.62)	10.80** (1.49 78.39)
CAP 5	4.25 (0.88 20.54)	3.59 (0.71 17.70)	4.56 (0.97 21.33)	3.85 (0.80 18.54)	3.28 (0.72 14.86)	2.88 (0.63 13.22)
CAP 6	16.53 (0.67 496.08)	6.95 (0.20 246.88)	14.86 (0.87 254.05)	8.53 (0.24 304.10)	8.54 (0.46 158.16)	4.46 (0.17 114.07)
CAP 7	7.16* (1.12 45.66)	5.87 (0.82 42.22)	5.77* (1.06 31.30)	4.67 (0.75 29.26)	5.62 (0.91 34.60)	4.95 (0.73 33.41)

Table 4:

		All		Left		Right	
	Year	Uni OR (CI)	Multi OR (CI)	Uni OR (CI)	Multi OR (CI)	Uni OR (CI)	Multi OR (CI)
Global	1	0.16 (0.02 1.27)	0.25 (0.02 2.89)	0.07* (0.01 0.64)	0.08 (0.01 1.09)	0.43 (0.07 2.56)	0.72 (0.09 5.75)
	2	0.06* (0.00 0.87)	0.12 (0.01 1.85)	0.04* (0.00 0.60)	0.08 (0.01 1.25)	0.17 (0.02 1.58)	0.28 (0.03 2.86)
	5	0.04 (0.00 1.73)	0.09 (0.00 3.38)	0.01* (0.00 0.74)	0.03 (0.00 1.92)	0.18 (0.01 3.43)	0.26 (0.02 4.72)
Occipital	1	0.33 (0.08 1.41)	0.58 (0.11 3.00)	0.30 (0.08 1.24)	0.46 (0.09 2.36)	0.47 (0.13 1.70)	0.69 (0.16 2.98)
	2	0.10* (0.01 0.77)	0.15 (0.02 1.31)	0.10* (0.02 0.73)	0.16 (0.02 1.15)	0.13* (0.02 0.90)	0.18 (0.03 1.34)
	5	0.07 (0.00 1.44)	0.12 (0.01 2.39)	0.06 (0.00 1.11)	0.10 (0.02 1.79)	0.15 (0.01 1.86)	0.23 (0.02 2.59)
Parietal	1	0.38 (0.09 1.62)	0.57 (0.10 3.13)	0.19* (0.04 0.93)	0.22 (0.03 1.48)	0.65 (0.19 2.19)	1.00 (0.24 4.19)
	2	0.15 (0.02 1.00)	0.22 (0.03 1.53)	0.07* (0.01 0.54)	0.10* (0.01 0.83)	0.32 (0.07 1.43)	0.42 (0.09 2.07)
	5	0.28 (0.03 3.08)	0.66 (0.04 12.64)	0.07 (0.01 1.09)	0.11 (0.01 1.55)	0.55 (0.08 3.78)	0.68 (0.10 4.80)
Temporal	1	0.15 (0.02 1.09)	0.21 (0.02 1.97)	0.07* (0.01 0.56)	0.08* (0.01 0.92)	0.46 (0.09 2.27)	0.64 (0.10 3.89)
	2	0.10 (0.01 1.08)	0.18 (0.02 1.97)	0.09* (0.01 0.83)	0.15 (0.02 1.48)	0.23 (0.03 1.68)	0.34 (0.04 2.65)
	5	0.10 (0.00 2.77)	0.17 (0.01 3.69)	0.07 (0.01 1.43)	0.10 (0.01 2.02)	0.37 (0.03 5.42)	0.45 (0.03 6.10)

	1	0.17 (0.02 1.93)	0.19 (0.01 3.37)	0.07* (0.01 0.82)	0.05 (0.00 0.96)	0.67 (0.08 5.59)	1.2 (0.09 1
Frontal	2	0.13 (0.01 2.61)	0.26 (0.01 5.17)	0.11 (0.01 1.86)	0.19 (0.01 3.23)	0.52 (0.04 6.58)	0.9 (0.05 1
	5	0.05 (0.00 3.00)	0.12 (0.00 5.39)	0.02 (0.00 1.20)	0.04 (0.00 3.03)	0.29 (0.01 6.78)	0.3 (0.02 9

Supplementary Figure 1. EEG traces of three individual datasets (see Figure 2 for corresponding spectra).



Supplementary Figure 1

Supplementary Table 1: Comparisons of the β values from Table 2: Only significant differences are shown – red (down the column) and blue (across the row). Dashed line - p<0.05; Solid line - p<0.01.

	All		Left		Right	
	Uni β (CI)	**Multi β (CI)**	**Uni β (CI)**	**Multi β (CI)**	**Uni β (CI)**	**Multi β (CI)**
Global	3.01** (0.78 5.24)	2.38* (0.46 4.31)	3.05** (0.99 5.11)	2.43** (0.65 4.22)	2.17* (0.06 4.29)	1.68 (-0.13 3.49)
Occipital	2.37** (0.95 3.79)	1.86** (0.61 3.11)	2.18** (0.80 3.57)	1.65* (0.41 2.89)	2.21** (0.81 3.61)	1.81** (0.61 3.01)
Parietal	1.82* (0.08 3.57)	1.36 (-0.15 2.87)	2.05* (0.36 3.74)	1.62* (0.17 3.07)	1.47 (-0.05 2.98)	1.06 (-0.25 2.37)
Temporal	2.53* (0.55 4.52)	2.05* (0.35 3.74)	2.61** (0.81 4.41)	2.07* (0.49 3.62)	1.72 (-0.19 3.62)	1.45 (-0.15 3.05)
Frontal	2.72 (-0.18 5.62)	2.07 (-0.41 4.55)	2.38 (-0.24 4.99)	1.99 (-0.22 4.19)	1.70 (-0.94 4.35)	0.99 (-1.29 3.27)

Supplementary Table 2: Comparisons of the OR values from Table 3: Only significant differences are shown – red (down the column) and blue (across the row). Dashed line - p<0.05; Solid line - p<0.01.

	All		Left		Right	
	Uni OR (CI)	**Multi OR (CI)**	**Uni OR (CI)**	**Multi OR (CI)**	**Uni OR (CI)**	**Multi OR (CI)**
CAP 1	4.06 (0.85 19.35)	3.60 (0.73 17.86)	3.51 (0.78 15.83)	3.03 (0.65 14.24)	4.13 (0.89 19.15)	3.89 (0.81 18.79)
CAP 2	8.47* (1.35 53.19)	7.43* (1.06 51.82)	6.24* (1.18 32.88)	5.30 (0.90 31.19)	8.55* (1.28 57.17)	8.14* (1.11 59.779)
CAP 3	4.19 (0.81 21.59)	3.36 (0.58 19.54)	3.15 (0.70 14.11)	2.38 (0.46 12.22)	4.78 (0.86 26.52)	4.38 (0.71 27.10)
CAP 4	9.96* (1.45 68.22)	9.78* (1.34 71.46)	7.42* (1.17 47.11)	6.86* (1.04 45.12)	10.01* (1.53 65.62)	10.80** (1.49 78.39)
CAP 5	4.25 (0.88 20.54)	3.59 (0.71 17.70)	4.56 (0.97 21.33)	3.85 (0.80 18.54)	3.28 (0.72 14.86)	2.88 (0.63 13.22)
CAP 6	16.53 (0.67 496.08)	6.95 (0.20 246.88)	14.86 (0.87 254.05)	8.53 (0.24 304.10)	8.54 (0.46 158.16)	4.46 (0.17 114.07)
CAP 7	7.16* (1.12 45.66)	5.87 (0.82 42.22)	5.77* (1.06 31.30)	4.67 (0.75 29.26)	5.62 (0.91 34.60)	4.95 (0.73 33.41)

Supplementary Table 3: Comparisons of the OR values from Table 4 (Year 1 only): Only significant differences are shown – red (down the column) and blue (across the row). Dashed line - p<0.05; Solid line - p<0.01.

		All		Left		Right	
	Year	Uni OR (CI)	Multi OR (CI)	Uni OR (CI)	Multi OR (CI)	Uni OR (CI)	Multi OR (CI)
Global	1	0.16 (0.02 1.27)	0.25 (0.02 2.89)	0.07* (0.01 0.64)	0.08 (0.01 1.09)	0.43 (0.07 2.56)	0.72 (0.09 5.75)
Occipital	1	0.33 (0.08 1.41)	0.58 (0.11 3.00)	0.30 (0.08 1.24)	0.46 (0.09 2.36)	0.47 (0.13 1.70)	0.69 (0.16 2.98
Parietal	1	0.38 (0.09 1.62)	0.57 (0.10 3.13)	0.19* (0.04 0.93)	0.22 (0.03 1.48)	0.65 (0.19 2.19)	1.00 (0.24 4.19)
Temporal	1	0.15 (0.02 1.09)	0.21 (0.02 1.97)	0.07* (0.01 0.56)	0.08* (0.01 0.92)	0.46 (0.09 2.27)	0.64 (0.10 3.89)
Frontal	1	0.17 (0.02 1.93)	0.19 (0.01 3.37)	0.07* (0.01 0.82)	0.05 (0.00 0.96)	0.67 (0.08 5.59)	1.21 (0.09 16.83)

Supplementary Table 4: Comparisons of the OR values from Table 4 (Year 2 only): Only significant differences are shown – red (down the column) and blue (across the row). Dashed line - p<0.05; Solid line - p<0.01.

		All		Left		Right	
	Year	**Uni OR (CI)**	**Multi OR (CI)**	**Uni OR (CI)**	**Multi OR (CI)**	**Uni OR (CI)**	**Multi OR (CI)**
Global	2	0.06* (0.00 0.87)	0.12 (0.01 1.85)	0.04* (0.00 0.60)	0.08 (0.01 1.25)	0.17 (0.02 1.58)	0.28 (0.03 2.86)
Occipital	2	0.10* (0.01 0.77)	0.15 (0.02 1.31)	0.10* (0.02 0.73)	0.16 (0.02 1.15)	0.13* (0.02 0.90)	0.18 (0.03 1.34)
Parietal	2	0.15 (0.02 1.00)	0.22 (0.03 1.53)	0.07* (0.01 0.54)	0.10* (0.01 0.83)	0.32 (0.07 1.43)	0.42 (0.09 2.07)
Temporal	2	0.10 (0.01 1.08)	0.18 (0.02 1.97)	0.09* (0.01 0.83)	0.15 (0.02 1.48)	0.23 (0.03 1.68)	0.34 (0.04 2.65)
Frontal	2	0.13 (0.01 2.61)	0.26 (0.01 5.17)	0.11 (0.01 1.86)	0.19 (0.01 3.23)	0.52 (0.04 6.58)	0.97 (0.05 17.68)

Supplementary Table 5: Comparisons of the OR values from Table 4 (Year 5 only): Only significant differences are shown – red (down the column) and blue (across the row). Dashed line - p<0.05; Solid line - p<0.01.

		All		Left		Right	
	Year	Uni OR (CI)	Multi OR (CI)	Uni OR (CI)	Multi OR (CI)	Uni OR (CI)	Multi OR (CI)
Global	5	0.04 (0.00 1.73)	0.09 (0.00 3.38)	0.01* (0.00 0.74)	0.03 (0.00 1.92)	0.18 (0.01 3.43)	0.26 (0.02 4.72)
Occipital	5	0.07 (0.00 1.44)	0.12 (0.01 2.39)	0.06 (0.00 1.11)	0.10 (0.02 1.79)	0.15 (0.01 1.86)	0.23 (0.02 2.59)
Parietal	5	0.28 (0.03 3.08)	0.66 (0.04 12.64)	0.07 (0.01 1.09)	0.11 (0.01 1.55)	0.55 (0.08 3.78)	0.68 (0.10 4.80)
Temporal	5	0.10 (0.00 2.77)	0.17 (0.01 3.69)	0.07 (0.01 1.43)	0.10 (0.01 2.02)	0.37 (0.03 5.42)	0.45 (0.03 6.10)
Frontal	5	0.05 (0.00 3.00)	0.12 (0.00 5.39)	0.02 (0.00 1.20)	0.04 (0.00 3.03)	0.29 (0.01 6.78)	0.36 (0.02 9.09)

Supplementary Table 6: ROC analysis. Number of subjects remaining in PTA and PTCS at time of EEG = 17.

	Post-traumatic amnesia (n=35)				Post-traumatic confusional state (n=35)			
	Threshold	AUC	Sensitivity	Specificity	Threshold	AUC	Sensitivity	Specificity
Global	0.86	0.68	0.59	0.67	0.86	0.59	0.65	0.72
Global left	0.83	0.69	0.59	0.72	0.82	0.62	0.65	0.72
Global right	0.81	0.65	0.58	0.61	0.81	0.56	0.65	0.67
Occipital	***0.87***	***0.77***	***0.71***	***0.72***	***0.88***	***0.66***	***0.77***	***0.83***
Occipital left	***0.75***	***0.73***	***0.71***	***0.67***	***0.75***	***0.65***	***0.77***	***0.72***
Occipital right	***0.85***	***0.75***	***0.71***	***0.67***	***0.85***	***0.63***	***0.77***	***0.78***
Parietal	0.20	0.64	0.88	0.28	0.74	0.55	0.53	0.78
Parietal left	0.22	0.68	0.94	0.33	0.75	0.60	0.53	0.78
Parietal right	0.10	0.62	0.94	0.28	0.30	0.54	0.77	0.50
Temporal	0.95	0.67	0.41	0.89	0.96	0.57	0.47	1.00
Temporal left	0.82	0.67	0.53	0.78	0.70	0.59	0.77	0.56
Temporal right	1.20	0.60	1.00	0.11	0.87	0.50	0.41	0.83
Frontal	1.20	0.64	0.41	0.94	1.10	0.61	0.47	0.83
Frontal left	1.12	0.61	0.59	0.78	1.10	0.64	0.53	0.72
Frontal right	0.73	0.63	1.00	0.22	0.74	0.56	1.00	0.33