Supplementary Information for

Acute EEG spectra characteristics predict thalamic atrophy after severe TBI

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Detailed Methods

Patient Population

Our convenience sample included 13 severe TBI patients (21-77 years old; see eTable 1). Inclusion criteria were: (1) admission to the UCLA Ronald Reagan Medical Center Neurointensive Care Unit (NICU) with a TBI diagnosis, (2) an initial Glasgow Coma Scale (GCS)[1] score ≤ 8 or 9-14 with computerized tomography (CT) brain scans demonstrating intracranial bleeding, (3) ≥18 years old. Patients were excluded if the admission neurological examination demonstrated brain death or if the patient's GCS improved to above 14 within 8 h of admission. Other exclusion criteria included epileptic seizures, pre-existing neurological disorder, overwhelming concurrent hepatic, metabolic encephalopathy, or burst-suppressing sedation. We note that there is no overlap between the present cohort and those analyzed in our previous MR-based work.[2,3] Patients' responsiveness level was assessed hourly using the GCS; outcome was assessed, at 6 months, using the Glasgow Outcome Scale – Extended (henceforth, GOS-E_{6m}).[4]

This study was approved by the University of California at Los Angeles Institutional Review Board. As per approved procedures, informed consent was obtained from the patient's legal representative.

EEG recording and analysis

Data acquisition. EEG data acquisition has been described in detail previously.[5,6] In brief, ICU Continuous 24-hour EEG monitoring was acquired beginning within 12 hours of injury and continued for up to two weeks post-injury. The International 10-20 System was used

to configure a montage that incorporated 10 electrodes/channels (F3, F4, C3, C4, P3, P4, T3, T4, O3 and O4) of CZ-referenced activity[5].

Data analysis. EEG data were analyzed using the GUI (graphic user interface) of EEGLAB (version 13.2.2b). In order to avoid periods of sleep or lower vigilance, for each patient we selected, within 24 hours of the MRI, the 1 hour of data corresponding to the best GCS. Indeed, it has previously been shown that there is a significant relationship between relative EEG power spectra in different frequencies and GCS, with faster frequencies (i.e., alpha, beta) correlating positively, and slower frequencies (i.e., delta, theta) correlating negatively[7], as well as a relationship between the rate and magnitude of change in EEG power spectra and the rate and magnitude of change in clinical measures of depth of coma over time[8]. Preprocessing included down sampling of the data to 128 Hz, band-pass filtered between 1 and 40 Hz (FIR filter; default setting), automatic artifact rejection (threshold at 100 μV) and Independent Component Analyses (runica ICA; default setting [i.e., with jader decomposition algorithm]) to identify and exclude ocular and motor artifacts related components (the number of components were not pre-specified), and a final visual inspection of the EEG data in order to manually remove any residual artifacts. If after artefact rejection the remaining duration of the EEG data was inferior to 30 minutes, the recording was not considered for further analyses.

For the spectral analysis, the continuous signal of each recording was segmented into 1s epochs. Each epoch was fast Fourier transformed (FFT) with a Hanning-tapered window. Subsequently, all epochs were averaged, and both mean and variance of the power spectral density in different frequency bands were exported for statistical analysis. Frequency bands were chosen at target electrode sites based on previous literature pinpointing sites of maximal amplitude for each band[9–11]: alpha (8-13 Hz) at the occipital (O) electrodes, theta (4-7 Hz) at the

frontal (F) electrodes, and delta (1-3 Hz) at the frontal (F) and central (C) electrodes. The averaged power spectral density extracted for each site (F, C, O) was expressed in absolute power (μV^2).

MRI acquisition and analyses

Data acquisition. In parallel to the EEG recording, each patient underwent a conventional structural MRI T1-weighted 3-dimensional magnetic-preparation rapid gradient echo scan (MPRAGE[12]) within 2 weeks post-injury and at 6 months. Due to the constraints imposed by the NICU context, patient MR data were acquired across multiple Siemens Magnetom devices (Sonata, Allegra, Tim Trio) available at the UCLA Ronald Reagan University Medical Center with comparable, but varying, parameters (TR: 1,900–1,970ms; TE: 3.52–4.40ms; FA: 9–15º). (See Limitations section for further discussion.) Prior to analysis, all data were resampled to the lowest common acquisition resolution (1 mm^3).

MRI Vertex Analysis. To assess local brain change over time we employed a technique referred to as shape analysis [13,14]. This technique allows estimating local tissue displacement – conventionally interpreted as atrophy or growth (though, see the limitations section for discussion of the interpretation of this technique) – across a number of subcortical regions of interest (ROIs). As in our previous work,[3] local tissue displacement was estimated after separating brain from non-brain tissue (using optiBET[15]) and segmenting subcortical ROIs (i.e., thalamus, caudate, putamen, globus pallidus, hippocampus, and brainstem), for each patient, time-point, and hemisphere separately (using FSL FIRST[13]). In addition, the percent brain volume change (PBVC) over time was calculated for each patient (using FSL SIENA[16]). For the purposes of estimating PBVC calculation, each patient's two brain-extracted images ware first

aligned (with FSL FLIRT[17,18]) and resampled into a space halfway between the acute and the follow-up time-points. (All other aspects of the MR analysis, except for group analysis, were performed in each image's native space.) PBVC was included, as a covariate, in all analyses in order for the tissue displacement calculation to reflect localized subcortical shape changes over time independent of overall brain volume changes. (We note that while we did not make use of any additional option beyond the obligatory arguments required by each software mentioned above, we have modified the code of both FIRST and SIENA to make use optiBET for brain extraction, as opposed to standard BET, since we have previously shown that the optiBET pipeline performs more accurate segmentation of brain and non-brain tissue[15].)

Statistical analyses

The main body of this report describes three analyses. First, we assessed the predictive value of acute bedside neurophysiological variables (i.e., EEG spectra variables) on long-term clinical outcome measures (i.e., GOS-E_{6m}) [henceforth, EEG analysis]. Second, we assessed the secondary damage taking place over the first six-months post-injury, as measured with MRI shape change, and its relation to long-term outcome (i.e., GOS-E_{6m}) and acute bedside neurophysiological measurements (i.e., EEG spectra variables) [henceforth, MRI shape analysis]. Third, we employed a graphical causal approach[19–21] to jointly model the relationships tying covariates (e.g., demographic variables, days post-injury of the MRI assessment, days between MRI and EEG recording, among others; see below for details), acute bedside neurophysiological measurements (i.e., EEG spectra variables), acute-to-chronic brain shape change (i.e., MRI shape change), and long-term clinical outcome (i.e., GOS-E_{6m}) [henceforth, graphical causal model].

EEG analysis. Because of significant correlations, prior to analysis, EEG spectra variables (i.e., average and variance of delta, theta and alpha frequencies) were submitted to a principal component analysis (PCA). The procedure, implemented in SAS using a varimax rotation, returned three components with eigenvalue greater than 1, cumulatively explaining 80% of the variance. The first component (henceforth, alpha power component) was mainly loaded upon by positively by alpha power average and negatively by alpha power variance. The second EEG component (henceforth, delta power average component) was positively loaded upon by the average delta power. Finally, the third EEG component was positively loaded upon by delta power variance. The only variables not to load substantially on any of the three components (i.e., at the conventional .7 threshold as implemented in SAS) were theta power average and variance. The GOS-E_{6m} was then regressed on the three EEG components.

MRI shape analysis. The vertex analysis meshes obtained as described above were entered, as the dependent variable, in three analyses. First, we compared chronic to acute meshes to establish the overall pattern of brain atrophy over time. Following, we regressed brain atrophy over time on clinical outcome (i.e., GOS-E_{6m}) and on EEG spectra components. The latter analysis, in particular, was aimed at assessing whether acute spectra variables are informative of the brain damage that will unfold over the following six months post injury.[2] Significance was assessed with a criterion of $p<0.05$ corrected for multiple comparisons using a non-parametric permutation approach as implemented in FSL-randomize (using the 2-dimensional TFCE option [-T2], the de-meaning option [-D], and setting it to run 5,000 permutations [-n 5,000] as opposed to the standard 500).[22,23] In all 3 analyses covariates were included to parcel out the effect of demographic (gender, age at injury), experimental (days post-injury of MRI; days between acute and 6-months follow-up MRI data acquisition; days between acute MRI and acute EEG data

acquisition), and other (sedation level, PBVC) variables. Because of the significant correlation between these variables, they were also entered into a PCA (implemented as the previous one). The data reduction returned three components with eigenvalue greater than 1, collectively explaining 83% of the total variance. COVAR component 1 (henceforth, "age/sex" component) was loaded upon positively by both demographic factors (i.e., age at injury and gender). COVAR component 2 (henceforth, "experimental variables" component) was loaded upon positively by the time post-injury of the acute MRI data acquisition and days between acute MRI and acute EEG acquisition, and was loaded upon negatively by PBVC. COVAR component 3 (henceforth, "sedation" component) was loaded upon positively by patient sedation level only. We note that the level of sedation was assessed, on the basis of the medications each patient was receiving, on a 3-point scale (deep, mild, no sedation) following the published guidelines of the American College of Critical Care Medicine/Society of Critical Care Medicine (ACCM/SCCM)[24].

Graphical causal modeling. Finally, we employed a graphical causal model approach,[19] implemented in the TETRAD IV platform,[20,21] to jointly model the interactions among background variables (e.g., demographics, sedation), acute EEG spectra characteristics, acute-to-chronic MRI shape atrophy, and their ability to predict clinical outcome. For this analysis, the MRI data was reduced from several hundred values (one per voxel) to a smaller number which could be included in the graphical model. Given our previous results demonstrating atrophy in thalamic nuclei in both (sub)acute[2] and chronic[3] populations after severe brain injury, as well as neuropathological studies demonstrating preferential atrophy and cell death in this region in patients who died in a chronic disorder of consciousness,[25,26] we focused on the bilateral thalamus and segmented each in 7 subareas, on the basis of the Harvard-Oxford thalamic connectivity atlas.[27,28] The average shape change within each subregion was then entered into a

PCA (implemented identically to the previous ones). The analysis returned two components with eigenvalue greater than 1, explaining 93% of the total variance. The first MRI component was loaded upon (positively) by thalamic areas connecting to frontal and parietal cortices (namely, posterior parietal, somatosensory, primary motor, premotor, and prefrontal cortices, bilaterally), while the second MRI component was loaded upon (positively) by thalamic areas connecting to temporal and occipital cortices.

As shown in eFigure 2, all components (3 COVAR, 3 EEG, and 2 MRI) were entered in a temporally informed graphical causal framework whereby background variables (i.e., COVAR components) were modeled as influencing directly both EEG and MRI components, and EEG components were modeled as influencing outcome (GOS-E_{6m}) both directly and through acute-to-chronic MRI shape changes.

Limitations

Interpretation of these data should be mindful of a number of factors. First, data were aggregated across different Siemens MR systems (including a Magnetom Sonata [1.5T], Magnetom TimTrio [3T], and Magnetom Allegra [3T]). Nonetheless, previous large multi-centric studies have shown that variance in MR system has little impact on results in the context of conventional MPRAGE sequences.[3,29] This issue was specifically addressed in a large cohort study of 137 subjects by the Alzheimer's disease neuroimaging initiative (ADNI)[30]. The report concluded that T1-weighted MPRAGE sequences, such as the one we acquired, were the best suited for aggregating data across different systems (including different field strength [i.e., 1.5T, 3T] and different vendors) due to a number of factors including the favorable white-matter to gray-matter SNR, which is crucial for the segmentations that are at the basis of our analysis.

Second, while our interpretation of (inwards) shape change over time as atrophy is conventional, it is an indirect measure based on displacement of tissue boundaries.[13] Nonetheless, there is converging evidence from other techniques suggesting that shape change is indeed sensitive to tissue atrophy, as assessed in post-mortem studies, in both Alzheimer's[13,31,32] and Huntington's[33–35] disease, as well as in severe brain injury[3,36,37] patients. The exact degree to which other mechanisms (e.g., compression, shift) also play into the results of shape analyses, remains to be fully specified.

Third, in our data theta frequencies did not emerge as an independent component, rather, being loaded upon (weakly) by all three EEG components. Whether this is due to our relatively small sample or reflects a small predictive value of theta oscillations in this context remains to be determined.

Fourth, in the present work we make use of the GCS and GOS-E_{6m} to characterize the level of consciousness and responsiveness of patients at the acute and follow-up time-points, respectively. While both these measures are standard in the ICU context, they are very coarse and do not provides a nuanced characterization of patients. Other scales, such as the Coma Recovery Scale–Revised[38], although longer to administer, might have been preferable in order to get a more detailed clinical characterization of the patient's level of consciousness, particularly in light of its correlation with EEG spectral features at rest[39–41].

Fifth, only 1 hour of EEG data, corresponding to the best GCS, was used in our analyses to ensure we analyzed cerebral activity associated to the highest responsiveness level (and avoid sleep). Indeed, as discussed above, there is a known relationship between the depth (and rate and magnitude of change) of coma, as clinically measured with the GCS, and the EEG power spectrum (and its rate and magnitude of change)[7,42]. Nonetheless, future research should compare

our results to existing approaches based on longer EEG samples, such as the PAV,[43] which has been shown to be a sensitive predictor of six-month recovery and is known to be related to acute thalamic lesions.[6]

Finally, it should also be pointed out that we cannot, in the present work, disentangle higher-order interactions between non-strictly TBI effects (e.g., pain, stress) and exclusively TBI effects. For example, it is possible that patients with worse GCS and worse outcomes also suffered more form these non-directly TBI factors which might, in turn, affect the EEG recordings. Nonetheless, both the individual EEG results (i.e., the relationship between EEG power spectra and outcome) and MRI results (i.e., the atrophy over time) are consistent with previous findings in the EEG[8,40,44] and MRI[2] literatures, thus moderating this potential concern.

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eFigure Legends

eFigure 1. MRI shape analysis results: (a) regions undergoing significant atrophy over the first six months post injury. (b) regions in which the degree of atrophy over time is significantly (negatively) associated with the six-month clinical outcome measure (i.e., GOS-E_{6m}).

eFigure 2. Graphical causal model specification. Depiction of the causal model assessed (for image clarity, each arrow stands for a set of arrows uniting, with the shown directionality, each of the variables at the beginning of the arrow to each of the variables at the end of the arrow). No arrow was placed between COVAR components and outcome since the relationship was found to be not significant (see text). (Abbreviations: COVAR comp, covariate components; exp vars, experimental variables component; sed, sedation component; A → C, acute to chronic change; frnt-par, fronto-parietal component; tmp-occ, temporo-occipital component; α pow, alpha power component; δ avg, delta power average component; δ var, delta power variance component).

eFigure 3. Scatterplot of the components derived from the 3 PCA analyses. (Abbreviations are the same as in eFigure 2.)