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Electrophysiological correlates of thalamocortical function in acute severe traumatic brain injury

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Abstract

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Tools assaying the neural networks that modulate consciousness may facilitate tracking of recovery after acute severe brain injury. The ABCD framework classifies resting-state EEG into categories reflecting levels of thalamocortical network function that correlate with outcome in post-cardiac arrest coma. In this longitudinal cohort study, we applied the ABCD framework to 20 patients with acute severe traumatic brain injury requiring intensive care (12 of whom were also studied at ≥6-months post-injury) and 16 healthy controls. We tested four hypotheses: 1) EEG ABCD classifications are spatially heterogeneous and temporally variable; 2) ABCD classifications improve longitudinally, commensurate with the degree of behavioral recovery; 3) ABCD classifications correlate with behavioral level of consciousness; and 4) the Coma Recovery Scale-Revised arousal facilitation protocol yields improved ABCD classifications. Channel-level EEG power spectra were classified based on spectral peaks within pre-defined frequency bands: 'A' = no peaks above delta (<4 Hz) range (complete thalamocortical disruption); 'B' = theta (4–8 Hz) peak (severe thalamocortical disruption); 'C' = theta and beta (13–24 Hz) peaks (moderate thalamocortical disruption); or 'D' = alpha (8–13 Hz) and beta peaks (normal thalamocortical function). Acutely, 95% of patients demonstrated 'D' signals in at least one channel but exhibited within-session temporal variability and spatial heterogeneity in the proportion of different channel-level ABCD classifications. By contrast, healthy participants and patients at follow-up consistently demonstrated signals corresponding to intact thalamocortical network function. Patients demonstrated longitudinal improvement in ABCD classifications ($p < .05$) and ABCD classification distinguished patients with and without command-following in the subacute-to-chronic phase of recovery ($p < .01$). In patients studied acutely, ABCD classifications improved after the Coma Recovery Scale-Revised arousal facilitation protocol ($p < .05$) but did not correspond with behavioral level of consciousness. These findings support the use of the ABCD framework to characterize channel-level EEG dynamics and track fluctuations in functional thalamocortical network integrity in spatial detail.

Keywords

EEG; Traumatic brain injury; Consciousness; Intensive care unit

1. Introduction

Clinical evaluation of level of consciousness in patients with acute severe brain injury is limited by a lack of reliable biomarkers. The 'mesocircuit' model proposes that the central thalamus and its projections to the cerebral cortex are critical to supporting the recovery of consciousness (Schiff, 2010, 2016). Disruptions in this thalamocortical network have been implicated in disorders of consciousness (DoCs) following severe brain injury (Coulborn, Taylor, Naci, Owen, & Fernández-Espejo, 2021; Fischer et al., 2016; Fridman, Beattie, Broft, Laureys, & Schiff, 2014; Lutkenhoff et al., 2015). Tools that assay thalamocortical network integrity may therefore allow for more precise tracking of neurological recovery than is possible with behavioral assessments alone.

The mesocircuit model provides a framework for classifying power spectra of clinical, resting-state EEG into four categories ('A,' 'B,' 'C,' 'D'). These categories correspond to widely separated levels of functional thalamocortical network integrity (Schiff, 2016),

and application of this 'ABCD framework' has been shown to correlate with outcome in both post-cardiac arrest coma and subarachnoid hemorrhage (Forgacs et al., 2017, 2021). The ABCD categories and their functional correlates in the mesocircuit model are as follows. The 'A' category (no spectral peak above the delta [<4 Hz] range) corresponds to a completely disconnected thalamocortical network that can be likened to the 'cortical slab preparation,' wherein neocortical neurons are markedly hyperpolarized and exclusively produce low frequency oscillations (Timofeev, Grenier, Bazhenov, Sejnowski, & Steriade, 2000). The 'B' category (spectral peak in the theta [4–8 Hz] range) corresponds to a severely disconnected system wherein cortical neurons are comparatively more depolarized resulting in theta frequency bursting (Silva, Amitai, & Connors, 1991). The 'C' category (spectral peaks in the theta and beta [13–24 Hz] ranges) corresponds to a moderately disconnected system wherein thalamic neuron bursting produces coexisting theta and beta frequency oscillations in connected cortex (Llinás, Ribary, Jeanmonod, Kronberg, & Mitra, 1999; Llinás, Urbano, Leznik, Ramírez, & van Marle, 2005). Finally, the 'D' category (spectral peaks in the alpha [8–13 Hz] and beta ranges) corresponds to a fully intact thalamocortical network wherein a sufficiently structurally and functionally interconnected thalamus and cortex allows for production of alpha and beta frequency oscillations (Schomer & Lopes da Silva, 2017).

Because the ABCD framework provides a means for inferring thalamocortical functional integrity from EEG dynamics, it has potential to aid clinicians in the assessment of acute severe brain injury. The intensive care unit (ICU) setting poses a number of challenges to patient assessment including sedation, medical comorbidities, a high rate of misdiagnosis with behavioral exams, and the potential presence of cognitive motor dissociation (CMD) (Edlow, Claassen, Schiff, & Greer, 2021; Schiff, 2015; Schnakers et al., 2009). Therefore, resting-state measures that can be gleaned from recordings collected during routine clinical care with widely available equipment, such as EEG, may serve as useful complements to advanced task- and stimulus-based assessments (e.g., EEG and functional MRI [fMRI] command-following and passive language paradigms) (Bardin et al., 2011; Braiman et al., 2018; Chatelle et al., 2020; Claassen et al., 2019; Coleman et al., 2007; Cruse et al., 2011; Curley, Forgacs, Voss, Conte, & Schiff, 2018; Edlow et al., 2017; Goldfine et al., 2013; Goldfine, Victor, Conte, Bardin, & Schiff, 2011; Iotzov et al., 2017; Monti et al., 2010; Owen et al., 2006; Sokoliuk et al., 2021) as well as allow for higher sampling frequencies and dynamic tracking in a population that experiences unpredictable arousal fluctuations (Casali et al., 2013; Curley et al., 2018; Gibson et al., 2014; Piarulli et al., 2016; Schiff et al., 2007; Wannez, Heine, Thonnard, Gosseries, & Laureys, 2017; Williams et al., 2013).

However, prior to its implementation in the clinical setting, the generalizability of and optimal method of applying the ABCD framework need to be understood. To date, this approach has only been studied in post-cardiac arrest coma (Forgacs et al., 2017), subarachnoid hemorrhage (Forgacs et al., 2021), and a heterogeneous sample of patients with acute non-hypoxic-ischemic brain injury (Alkhachroum et al., 2020). Moreover, its utility in analyzing EEG topography has not been explored in prior studies wherein each participant was assigned to a single ABCD category based on visual inspection of either all EEG channels simultaneously (Forgacs et al., 2017, 2021) or a single channel (Alkhachroum et al., 2020). While these approaches may be suitable for patients with uniform injury

burden across the cerebrum (such as in hypoxic-ischemic injury), patients with traumatic brain injury (TBI) present with heterogeneous, multifocal disruptions of the thalamocortical network caused by axonal shearing injury (Sharp, Scott, & Leech, 2014). As a result, portions of the thalamocortical network are often preserved, even in patients with severe injuries who present in coma (Edlow et al., 2013).

In the present study, we applied the ABCD framework to investigate channel-level EEG signal dynamics in a sample of patients with acute severe TBI to determine the topographic distribution of ABCD classifications across patients. We studied the within-session temporal stability of ABCD classifications during a single, 2-h data collection session. In a subset of patients, we investigated the longitudinal evolution of EEG signals at ≥6-months post-injury to elucidate how ABCD classifications change with recovery. We tested four hypotheses: 1) given the well-established spatial heterogeneity of thalamocortical disconnection and susceptibility to state fluctuations in severe TBI, patients exhibit spatial heterogeneity and within-session temporal variability in channel-level ABCD classifications; 2) ABCD classifications improve longitudinally after severe TBI, commensurate with the degree of behavioral recovery; 3) ABCD classifications correlate with behavioral level of consciousness in the acute and subacute-to-chronic phases of recovery; and 4) administration of the Coma Recovery Scale-Revised (CRS-R) arousal facilitation protocol, which is a commonly used clinical maneuver to promote arousal in patients with DoC (Giacino, Kalmar, & Whyte, 2004), yields improved EEG dynamics along the ABCD scale. Our aim was to investigate the characteristics of EEG signals in the context of the ABCD framework so as to inform future clinical implementation of this approach for patients with severe TBI.

2. Materials and methods

We report how we determined our sample size, all data exclusions (if any), all inclusion/exclusion criteria, whether inclusion/exclusion criteria were established prior to data analysis, all manipulations, and all measures in the study.

2.1. Participants

We enrolled 20 patients who presented with acute traumatic coma to the ICU at an academic medical center between March 2012 and January 2017 (median age: 26.5 years, interquartile range [IQR]: 7.8 years, 14 males), 12 of whom were studied longitudinally at ≥6-months post-injury (median: 215 days; range: 160–1172 days) (Table 1). We attempted to contact all surviving patients or their surrogates for follow-up. Our study cohort included a previously published cohort of 16 patients prospectively enrolled in the ICU (P1-16) (Edlow et al., 2017), as well as a convenience sample of four additional patients that were enrolled at ≥6-month follow-up (P17-20) after being referred to an investigator's NeuroRecovery Clinic (B.L.E.). For the four enrolled at follow-up (Snider et al., 2020), their acute clinical EEG and behavioral data were obtained retrospectively.

Inclusion criteria for the original studies from which this patient cohort was derived (Edlow et al., 2017; Snider et al., 2020) were: 1) age 18–65 years; and 2) head trauma with Glasgow Coma Scale (GCS) score of 3–8 and no eye opening for ≥24 h. Exclusion criteria were: 1)

life expectancy <6 months, as estimated by a treating physician; 2) prior neurodegenerative disease or severe brain injury; 3) body metal precluding MRI; and 4) no fluency in English prior to injury (because the task- and stimulus-based paradigms administered as part of the study protocol were administered in English). Given that this study was a retrospective analysis of all data collected in a previously published study (Edlow et al., 2017) and that previously published data on the ABCD classification framework are insufficient to inform a power calculation, we included all patients with resting-state EEG data available to us. We also enrolled 16 healthy control participants (median age: 27 years, IQR: 21–32.5 years, 12 males). All studies were approved by the Mass General Brigham Institutional Review Board. We obtained written informed consent from healthy control participants and from surrogate decision-makers of patients with DoCs. Patients who recovered consciousness at follow-up provided informed consent for their continued participation in the study.

2.2. Neurobehavioral assessments

To evaluate behavioral level of consciousness, we either administered the CRS-R (P1-16 acutely and all patients at follow-up) (Giacino et al., 2004) (https://www.sralab.org/rehabilitation-measures/coma-recovery-scale-revised) or derived level of consciousness from a clinical bedside neurological exam conducted on the same day as each EEG (P17-20 acutely). We graded the level of consciousness as coma, vegetative state (VS), minimally conscious state with/without language function (MCS+/−) or emerged from the minimally conscious state (EMCS). We used the Confusion Assessment Protocol (CAP) (Sherer, Nakase-Thompson, Yablon, & Gontkovsky, 2005) (https://www.tbims.org/combi/cap/caprat.html) to confirm whether patients who emerged from MCS were in a post-traumatic confusional state (PTCS) or recovered from PTCS (R-PTCS) (Sherer et al., 2020). A single investigator (B.L.E.) conducted all CRS-R and CAP assessments, blinded to the EEG data. Acute clinical neurological exams were conducted by treating physicians.

2.3. EEG data acquisition and preprocessing

We acquired two to five 5-min blocks of resting-state EEG from all participants, depending upon the study protocol each participant was originally enrolled in (discussed further below) and contingent upon logistical factors in the ICU that affected each participant's ability to complete the full protocol. Sedative, anxiolytic, and/or analgesic medications were administered to a subset of patients before and/or during the acute EEG recording at the discretion of the clinical team for patient safety or comfort (Supplementary Table 1). For healthy control participants, patients P1-16 acutely, and all patients studied at follow-up, five rest blocks were intended to be interspersed within a previously published 2-h battery of task- and stimulus-based EEG paradigms (e.g., motor imagery, language, and music) (Edlow et al., 2017). The CRS-R arousal facilitation protocol, which is designed to promote wakefulness via sustained deep pressure stimulation of face, sternocleidomastoid, trapezius, arm, and leg muscles (Giacino et al., 2004), was administered immediately prior to the penultimate rest block in a subset of patients studied acutely (n = 12) and at follow-up (n = 10) that were able to complete the full study protocol. During EEG collection, participants in this subset were instructed to keep their eyes closed (to maintain consistency with participants that could not open their eyes) and were not disturbed by members of the investigational team, with the exception of administration of the CRS-R arousal facilitation

protocol between rest blocks four and five. We did not screen for sleep because we aimed to maintain consistency across participants given the lack of reliable electrophysiologic indicators of sleep in acute brain injury (Foreman, Westwood, Claassen, & Bazil, 2015).

For patients P17-20, we obtained EEG from the acute hospitalization by selecting the earliest 5-min clinical EEG segments (2 blocks at a minimum) with minimal ambient noise and artifact that immediately followed auditory or tactile stimulation (e.g., from routine nursing care) to increase the likelihood of capturing data from periods of maximal patient level of arousal (Chatelle et al., 2020).

We collected EEG with a Natus XLTEK EEG system (San Carlos, CA) with 19 electrodes arranged via a 10–20 system (200, 250 or 256 Hz sampling frequency) (Jasper, 1958). Data were detrended, filtered (third-order Butterworth, zero-phase shift digital filter [1–30 Hz]), cut into 3-s non-overlapping epochs, and re-referenced to the Hjorth Laplacian montage to increase our ability to localize the sources of recorded signals (Hjorth, 1975; Thickbroom, Mastaglia, Carroll, & Davies, 1984). We performed all data processing in MATLAB (The Mathworks, Natick, MA) using a combination of EEGLAB and the Chronux toolbox (Bokil, Andrews, Kulkarni, Mehta, & Mitra, 2010; Delorme & Makeig, 2004).

We visually inspected signals and rejected epochs and, if necessary, entire rest blocks, contaminated by electromyogenic, eye-blink, or electrical interference artifact. A single investigator (W.H.C.) blinded to clinical and behavioral assessment data performed all manual artifact rejection to ensure consistency across blocks (Curley et al., 2018; Forgacs et al., 2014, 2017). Manual artifact rejection resulted in an average of 40.2% of 3-s epochs rejected for healthy controls and 60.9% of 3-s epochs rejected for patients, consistent with previously reported artifact rejection rates for this method (Curley et al., 2018).

2.4. EEG spectral analysis and ABCD classification

We calculated channel-level power spectral densities for each 3-s epoch with the multitaper method using the Chronux toolbox (five tapers, yielding a frequency resolution of 2 Hz and estimates spaced 1/3 Hz apart) and then averaged these spectra within each rest block (Bokil et al., 2010; Percival & Walden, 1993; Thomson, 1982). To assess the effect of the CRS-R arousal facilitation protocol on ABCD classifications for the subset of patients that it was performed on (n = 12 patients acutely, n = 10 patients at follow-up), we computed spectra from the 2 min immediately following the completion of the arousal facilitation protocol (given the transient nature of the protocol's effect on arousal) and compared the corresponding ABCD classifications (assigned as described below) to the ABCD classifications from the spectra calculated from the 5-min rest block immediately preceding the arousal facilitation protocol (block four).

For each rest block, we assigned each channel's EEG recording to a pre-defined ABCD category via visual inspection of its spectrum (Alkhachroum et al., 2020; Forgacs et al., 2017, 2021; Schiff, 2016). The criteria were as follows: an ‘A’-type spectrum either lacked any spectral peaks or contained a delta (<4 Hz) frequency peak; a ‘B’-type spectrum contained only a theta (4–8 Hz) frequency peak; a ‘C’-type spectrum contained both theta and beta (13–24 Hz) frequency peaks; and a ‘D’-type spectrum contained both alpha (8–

13 Hz) and beta frequency peaks. For spectra that met multiple requirements, the most favorable category (D > C > B > A) was assigned. We rejected spectra with evidence of electromyogenic artifact contamination and left those recordings unscored. Spectra that did not fit into any category (e.g., presence of an alpha peak only) were also unscored. To quantify ABCD classifications for each participant, we coded channel-level ABCD classifications (omitting the unscored recordings) as numeric values (A = 1, B = 2, C = 3, D = 4) and then derived an 'ABCD index' by averaging across channels.

To mitigate potential bias in the visual assessment of spectral peaks that might be associated with knowledge of the participant, cohort (healthy control, acute patient, follow-up patient) or channel location, we performed ABCD classification on spectra that were randomly shuffled without any identification of participant, cohort, channel, or block. As previously reported by Forgacs et al. (2017), this method of visual inspection-based classification has a high inter-rater reliability (89% concordance). Thus, ABCD spectral classification was conducted by a single investigator (W.H.C.) who did not have patient contact, was not involved in data collection, and was blinded to all participant identifiers, channel information, and clinical variables. This investigator was also one of the raters in the previous study demonstrating high inter-rater reliability of visual inspection-based classification of ABCD spectra (Forgacs et al., 2017).

2.5. Statistical analyses

All statistical analyses were conducted with Prism 9.0 (GraphPad Software, San Diego, CA) and P-values < .05 were considered statistically significant. To test whether the ABCD index and percentages of individual ABCD classifications changed between acute ICU hospitalization and follow-up, we used Wilcoxon matched-pairs signed rank tests (two-tailed). We calculated Mann–Whitney statistics (two-tailed) to investigate the difference in ABCD indices from patients with and without command-following.

To assess the within-session temporal stability of ABCD classifications, we calculated block-level ABCD indices for each participant. For each participant with five rest blocks recorded during a continuous 2-h window (n = 13 healthy controls, n = 10 acute and follow-up patients), we calculated the root mean square deviation (RMSD) of the ABCD index across rest blocks as a measure of inter-block variability. We used a Wilcoxon matched-pairs signed rank test (two-tailed) to assess the difference in acute versus follow-up patient RMSDs and Mann–Whitney statistics (two-tailed) to assess the difference in control versus acute patient and control versus follow-up patient RMSDs.

To test the hypothesis that the CRS-R arousal facilitation protocol increases the ABCD index in acute (n = 12) and follow-up (n = 10) patients, we used Wilcoxon matched-pairs signed rank tests (one-tailed) to compare the ABCD index from the rest block preceding the CRS-R arousal facilitation protocol to the ABCD index from the 2 min immediately following the completion of the arousal facilitation protocol.

2.6. Data availability

Given study protocol data sharing restrictions and that participants did not consent to public data archiving, the data that support the findings of this study are not publicly archived.

However, these materials are available upon request from the corresponding author and approval of a formal data sharing agreement by the relevant Institutional Review Board(s). No portion of the study procedures or analyses was pre-registered prior to the research being conducted.

3. Results

3.1. Patient demographics

The patient cohort studied acutely consisted of 20 individuals with the following behavioral diagnoses at time of acute EEG collection: coma ($n = 6$), VS ($n = 1$), MCS− ($n = 2$), MCS+ ($n = 4$), PTCS ($n = 7$) (Table 1). One patient studied acutely (P2) was diagnosed as MCS− with a relatively low CRS-R total score (4) – the only behavior warranting a diagnosis of MCS− was localization to noxious stimuli (Table 1). All patients assessed with clinical neurological exam rather than CRS-R (P17-20) were in coma at the time of acute EEG. In these patients, the diagnosis of coma was based on the absence of eye opening (spontaneously, in response to verbal stimulation, or in response to noxious stimulation), the lack of purposeful movements, and the lack of eye gaze fixation or tracking when clinicians manually opened the patients' eyelids. Median time from injury to acute EEG was 9 days (range: 2–28 days). Patients P1-16 were enrolled consecutively as part of a previously published study (399 consecutive patients screened for eligibility, 28 patients met all eligibility criteria, 16 patients were enrolled) (Edlow et al., 2017), while patients P17-20 represent a convenience sample enrolled at follow-up. Sedative, analgesic, and anxiolytic medications administered before and/or during EEG are reported in Supplementary Table 1. In total, six patients received continuous infusions of sedatives and 11 patients received intravenous boluses of enteral analgesics or anxiolytics before and/or during the acute EEG. One patient (P12) died in the ICU after withholding life-sustaining therapy. Twelve patients were studied at ≥6-month follow-up (median: 215 days; range: 160–1172 days) and had the following behavioral diagnoses: VS ($n = 1$), MCS− ($n = 2$), MCS+ ($n = 1$), R-PTCS ($n = 8$). Eight patients did not complete follow-up for one of the following reasons: they were deceased, they were unable to participate because of logistical and/or ongoing medical issues, or they (or their surrogate) declined to participate further.

3.2. ABCD-classified EEG signal characteristics

Overall, EEG data from all participants were successfully classified into ABCD categories. We classified 86.9% and 75.3% of channel-level spectra from controls and patients into ABCD categories, respectively. Spectra that were not classified either contained spectral peak patterns not consistent with any of the ABCD categories (11.9% for controls, 20.2% for patients) or were rejected because of artifacts (1.2% for controls, 4.5% for patients). Of classifiable channels, healthy participants demonstrated 'D' signals in an average of 93.7% of channels, and 75.0% (12/16) of healthy participants demonstrated 'D' signals in all channels. The majority (95.0%) of patients demonstrated 'D' signals in one or more channels acutely, but there was marked inter-patient heterogeneity in both the proportion and location of different ABCD classifications (Fig. 1). Patients studied acutely demonstrated 'D' signals in a mean 37.4% of classified channels (range: 0–93.9%, standard deviation (SD): 31.6%), 'C' signals in 28.0% (range: 0–90.5%, SD: 23.0%), 'B' signals in 22.6%

(range: 0–80.0%, SD: 26.6%), and 'A' signals in 12.0% (range: 0–57.5%, SD: 15.9%). Visual inspection of channel-level ABCD classifications revealed homogeneity throughout the brain in a subset of patients (e.g., P2), while others demonstrated coexistence of multiple disparate ABCD classifications (e.g., P20). By contrast, healthy controls generally had 'D' signals in most or all channels (Fig. 1).

3.3. Within-session temporal stability of ABCD classifications

We utilized the ABCD framework to assess within-session fluctuations of EEG dynamics (Fig. 2) by examining how classifications changed within a recording session among participants who had five discrete rest blocks recorded within a 2-h window ($n = 13$ healthy controls, $n = 10$ acute and follow-up patients). In the acute recordings, there was significantly higher inter-block variability relative to healthy controls (difference of medians: .3, 95% confidence interval [CI]: .07–.4, $P = .005$). There was no significant difference in inter-block variability in acute recordings relative to follow-up recordings (difference of medians: .1, 95% CI: −.4–.2, $P = .2$) or in follow-up recordings relative to healthy control recordings (difference of medians: .09, 95% CI: 0–.2, $P = .5$). Thirty-five percent (7/20) of acute patients demonstrated an inter-block ABCD index range ≥1 (corresponding to the interval between ABCD categories), while the same was true for only 6.3% (1/16) of controls and 8.3% (1/12) of follow-up patients (Fig. 2B-C). Additionally, all controls demonstrated 'D'-type signals in all channels during the first rest block (block one) and the last rest block (block five), which immediately followed administration of the CRS-R arousal facilitation protocol (Fig. 2B).

3.4. Longitudinal changes in ABCD dynamics

In Fig. 3A, we show the ABCD index calculated across all channels and rest blocks for each patient studied acutely and at follow-up (an interval of at least 6 months). ABCD indices significantly increased between the acute ICU hospitalization and follow-up among the 12 patients studied longitudinally (median change: .6, 95% CI: .3–1.0, $P = .006$). All patients with available follow-up demonstrated behavioral improvement and only one patient demonstrated a decreased ABCD index at follow-up. We also assessed the change in the percentage of different ABCD categories for each patient (Fig. 3B) and found that, on a group level, the proportion of 'D' signals increased between the acute ICU hospitalization and follow-up (median change: 36.7%, 95% CI: 4.2–72.5%, $P = .02$), while the proportion of 'A' signals decreased (median change: −5.3%, 95% CI: −16.9–0%, $P = .008$). As the increase in the fraction of 'D' signals was greater than the decrease in the fraction of 'A' signals, the proportion of 'B' and 'C' signals also decreased, but these differences were not statistically significant. Fig. 3C shows subject-level topographic plots averaged across all rest blocks in the acute ICU setting and at follow-up with patients stratified by behavioral diagnosis at follow-up, corroborating the increase in 'D' classifications at follow-up versus the acute recording shown in Fig. 3B. Fig. 3C also shows that 'D' classifications were more common in patients with higher behavioral levels of consciousness, which we investigate below.

3.5. Association of ABCD classifications with command-following and behavioral diagnosis

Eleven of 20 acute patients and nine of 12 follow-up patients demonstrated behavioral command-following at the time of EEG (Fig. 4A). Given the presence of rapid state fluctuations among patients studied acutely (Fig. 2), we assessed whether patients' 'best ABCD index,' defined as the highest ABCD index across all recorded rest blocks, was associated with behavioral level of consciousness at the same timepoint (Fig. 4A). There was no difference in the best ABCD index for acute patients with behavioral command-following as compared to those without (difference of medians: .09, 95% CI: −.9–.4, $P = .4$). By contrast, follow-up patients with behavioral command-following demonstrated significantly higher best ABCD indices as compared to those without (difference of medians: 1.0, 95% CI: .9–1.7, $P = .005$). Of note, we observed that all follow-up patients diagnosed as MCS+ or R-PTCS ($n = 9$) demonstrated best ABCD indices ≥3.8 while all follow-up patients diagnosed as VS or MCS− ($n = 3$) demonstrated best ABCD indices ≥3.1 (Fig. 4B).

In acute recordings, we observed a range of best ABCD indices for patients with behavioral diagnoses of coma, MCS+, and PTCS (Fig. 4B). Two of the three longitudinally studied patients with acute best ABCD indices >3 but without behavioral evidence of command-following ultimately recovered to R-PTCS at follow-up (P2, P3) while the remaining patient was diagnosed as MCS− at follow-up (P20) and demonstrated a decrease in the best ABCD index over time. One of the three longitudinally studied patients with an acute best ABCD index <3 recovered to MCS+ at follow-up (P18) while the others were diagnosed as VS (P19) and MCS− (P17) at follow-up.

3.6. Effect of CRS-R arousal facilitation protocol on ABCD classification

To test the hypothesis that the CRS-R arousal facilitation protocol yields an improvement in EEG signal dynamics, we compared the ABCD index in the 5-min rest block preceding the arousal facilitation protocol to the ABCD index in the 2 min immediately following (Fig. 5). Patients studied acutely demonstrated significantly higher ABCD indices following the CRS-R arousal facilitation protocol ($n = 12$, median of differences: .1, 95% CI: −.05–.6, $P = .03$), while follow-up patients demonstrated no change ($n = 10$, median of differences: 0,95% CI: −.08–0, $P = .4$). Of note, the lack of a change in the follow-up recordings may be due to a ceiling effect, as six of 10 patients had ABCD indices >3.9 both prior to and after the CRS-R arousal facilitation protocol.

4. Discussion

In this longitudinal study of patients with acute severe TBI, we analyzed EEG dynamics at the level of individual channels. Our analysis is based on the mesocircuit model for DoCs (Schiff, 2010), which proposes that different levels of functional thalamocortical network integrity correspond to specific EEG dynamics (Forgacs et al., 2017; Schiff, 2016). Because these distinct dynamical patterns are manifest by characteristic peaks in the power spectrum, EEG signals can be visually classified as 'A,' 'B,' 'C,' or 'D,' corresponding to the range of thalamocortical network functioning from absent to normal. We found that while all patients with acute severe TBI, as expected, had EEG signal characteristics indicating dysfunction

of the thalamocortical network, the majority also demonstrated channel-level EEG signals consistent with at least partial thalamocortical network preservation. Moreover, there was marked heterogeneity in both the proportion and location (based on qualitative visual inspection) of ABCD classifications across patients. Acutely injured patients demonstrated significantly more within-session temporal variability in EEG signals in comparison to healthy control participants. Furthermore, over a third of acute patients demonstrated a within-session ABCD index fluctuation ≥1 (the interval between ABCD categories) within a single 2-h window, highlighting the need to perform multiple assessments of thalamocortical network function in patients with acute severe brain injuries. As a group, patients studied at ≥6-month follow-up demonstrated significant improvement along the ABCD scale in comparison to the acute phase of injury, driven by an increase in 'D'-type signals and a decrease in 'A'-type signals. At follow-up, patients with the ability to follow commands also demonstrated higher ABCD indices as compared to those without. Importantly, we found that the CRS-R arousal facilitation protocol yielded improved EEG signal dynamics in the context of the ABCD framework, providing electrophysiological evidence for the utility of this widely used behavioral examination technique. Collectively, these findings support the use of the ABCD framework to characterize channel-level EEG dynamics and thereby track fluctuations in thalamocortical network function in the ICU and other settings.

4.1. State fluctuations in acute severe TBI

We found that in acute recordings, there was significantly more within-session temporal variability in ABCD states relative to healthy control recordings (Fig. 2). Furthermore, over a third of acute patients demonstrated a within-session change in the ABCD index ≥1, indicating a global shift from one state of thalamocortical functioning to another within a single 2-h window. This observation bolsters the notion that patients with severe brain injuries exhibit marked fluctuations in state within short time periods and therefore require repeated assessment to yield accurate diagnoses (Casali et al., 2013; Demertzi et al., 2019; Giacino et al., 2018; Gibson et al., 2014; Kondziella et al., 2020; Piarulli et al., 2016; Schnakers et al., 2009; Wannez et al., 2017). We note that patients at follow-up demonstrated a trend towards increased variability relative to patients studied acutely, and healthy controls demonstrated a trend toward increased variability relative to patients at follow-up. However, these comparisons were not statistically significant.

Given the ease of deriving ABCD classifications from clinical EEG without requiring investigators at the bedside, ABCD classification may provide clinicians with the ability to sample patients' thalamocortical network functioning at a frequency not attainable with other tools. Furthermore, state fluctuations may influence a patient's ability to demonstrate a positive response on task-based assessments (Curley et al., 2018). Thus, a real-time application of ABCD classification may allow for identification of periods of elevated arousal to guide the timing of task-based measures so as to maximize the chance of detecting positive responses in covertly conscious patients. With replication, it may also be used as a validity indicator for standardized behavioral assessments, such as the CRS-R (Giacino et al., 2004). Further investigation into the concordance of simultaneously obtained ABCD and CRS-R scores may also elucidate how ABCD score fluctuations track with behavioral output in real-time.

ABCD-based timing of behavioral assessment and task-based fMRI and EEG may be particularly relevant for patients in the acute phase of injury as within-session ABCD indices remained relatively stable among patients at follow-up. Most control participants and patients at follow-up demonstrated ‘D’-type dynamics across the majority of EEG channels and blocks, which suggests that individuals with globally preserved thalamocortical network integrity may be less prone to state fluctuations than those with disrupted networks. As such, the within-session temporal variability we detected in acute patients may be a consequence of a more vulnerable thalamocortical network incapable of sustaining a consistently high level of functioning. Alternatively, this result may have been influenced by concomitant medical causes of altered consciousness (e.g., renal or hepatic dysfunction) or sedation. The majority (8/12) of follow-up patients showed recovery from PTCS. Thus, with only four patients who did not recover, we lacked statistical power to determine whether patients with chronic DoCs experience similar within-session temporal variability to that observed in patients with acute DoCs.

Unexpectedly, some healthy control participants demonstrated inter-block fluctuations between ‘C’- and ‘D’-type dynamics. Of note, we instructed all participants to keep their eyes closed to maintain consistency of EEG recording characteristics with patients incapable of eye-opening. Furthermore, participants were not disturbed by members of the investigational team during the 2-h battery of EEG paradigms with the exception of administration of the CRS-R arousal facilitation protocol between blocks four and five. To maintain consistency across participants, we did not screen or reject any data based on the presence of EEG features suggestive of sleep given the lack of reliable electrophysiologic markers of sleep in acute brain injury (Foreman et al., 2015). It is therefore possible that some control participants became drowsy or fell asleep during a portion of the 2-h battery of EEG paradigms, resulting in EEG spectra with peaks in the theta frequency range and classification into the ‘C’ category. It is notable, however, that without exception, all controls demonstrated ‘D’-type signals across all channels during the first rest block and immediately following administration of the CRS-R arousal facilitation protocol (Fig. 2B). By contrast, patients demonstrated a range of ABCD indices during the same blocks, which further suggests that the state fluctuations observed in healthy participants may be attributable to sleep or drowsiness.

4.2. ABCD classification as a potential biomarker for recovery of consciousness

As a group, longitudinally studied patients demonstrated an improvement in EEG signal dynamics at ≥6-month follow-up as compared to the acute setting. The three follow-up patients who were diagnosed as VS or MCS− had lower ABCD indices and demonstrated predominantly ‘B’- and ‘C’-type dynamics at follow-up. By contrast, the nine patients who recovered behavioral command-following at follow-up (MCS+ or R-PTCS) had significantly higher ABCD indices and predominantly demonstrated ‘D’-type dynamics (Figs. 3C and 4A). This separation in EEG dynamics at the level of MCS+/− underscores the crucial role of language function in recovery from severe brain injury and supports the notion that the pathophysiologic state of MCS− may be closer to VS rather than MCS+ (Giacino et al., 2020). As Naccache (2017) describes, a behavioral diagnosis of MCS may reflect the presence of cortically mediated behavior, rather than evidence of volitional actions.

It follows that an MCS− diagnosis may not necessarily connote consciousness, and the emergence of language (i.e., MCS+) may be necessary to confirm the presence of consciousness. Furthermore, the stark difference in ABCD indices between these two groups suggests that ABCD classification may prove to be a useful biomarker for recovery of consciousness. Specifically, it has potential to aid in early prognostication, provide a metric for monitoring recovery, and help identify individuals who should undergo additional testing with task-based paradigms to search for CMD.

Emerging evidence indicates that individuals with CMD constitute an estimated 15–20% of behaviorally unresponsive patients with a DoC (Claassen et al., 2019; Curley et al., 2018; King et al., 2013; Kondziella, Friberg, Frokjaer, Fabricius, & Møller, 2016; Monti et al., 2010; Stender et al., 2014, 2016). There is an ethical imperative to identify these individuals (Fins, 2015; Fins & Schiff, 2016; Young & Edlow, 2021) and ABCD classification may serve as an inexpensive, safe, and mobile screening measure well-suited to this purpose, especially when used as an adjunct to other similarly convenient resting-state EEG tools (Engemann et al., 2018).

We did not detect a similar separation in the ABCD indices of acute patients with and without behavioral command-following. Given that few non-comatose patients studied acutely exhibited lower-level behavioral diagnoses (i.e., VS or MCS−), the majority of variability in acute ABCD dynamics was present in patients with higher-level behavioral diagnoses (i.e., MCS+ or PTCS). Therefore, it is possible that EEG command following did not discriminate between high- and low-level neurological functioning acutely, but rather, between comparatively high-functioning brains. By contrast, patients with/without behavioral command following at follow-up may have been more widely separated in terms of overall neurological functioning, allowing us to resolve a difference in ABCD indices between these two groups.

Interestingly, however, one acute patient (P4) was behaviorally diagnosed as PTCS but demonstrated ‘A’-type dynamics in the majority of EEG channels (mean 56.7%, Figs. 1 and 4B). It is possible that this discrepancy, as well as our inability to resolve a difference in ABCD indices among acute patients with and without command-following, are attributable to the rapid state fluctuations that we observed in the acute cohort (Fig. 2). However, this individual patient also demonstrated ‘D’-type dynamics in a mean of 28% of channels, and the coexistence of widespread cortical injury and partial thalamocortical network preservation has been previously observed in covertly conscious patients (Fernández-Espejo, Rossit, & Owen, 2015; Forgacs, Fridman, Goldfine, & Schiff, 2016). This phenomenon warrants further study, but our findings suggest that only a limited amount of thalamocortical functional connectivity is necessary for the generation of consciousness. Therefore, channel-level analysis of EEG signal dynamics may be preferable to approaches that treat the entire cortex as a single entity (Alkhachroum et al., 2020; Forgacs et al., 2017, 2021), especially in the setting of multifocal cerebral injury.

It is also notable that a wide range of ABCD indices were demonstrated by acutely comatose patients. One of the two coma patients with predominantly ‘D’-type dynamics acutely went on to recover to R-PTCS, while the other recovered to MCS− and demonstrated a worsening

of EEG signal dynamics at follow-up. By contrast, one of the three coma patients with predominantly ‘B’- or ‘C’-type dynamics acutely recovered to R-PTCS, while the other two recovered to MCS− and VS. Our observations suggest a need for larger studies to assess the prognostic relevance of the ABCD framework for the acute severe TBI population. The wide variability among acutely comatose patients also highlights the ethical obligation to further investigate patients who exhibit a dissociation between neurophysiologic measurements and behavior (Fins, 2015; Fins & Schiff, 2016; Scolding, Owen, & Keown, 2021; Thengone, Voss, Fridman, & Schiff, 2016; Young & Edlow, 2021).

4.3. CRS-R arousal facilitation protocol as a causal test of the mesocircuit model

To our knowledge, our observations serve as the first demonstration that the CRS-R arousal facilitation protocol effectively upregulates arousal in patients with DoCs to the point that it is detectable with neurophysiologic measurements (Fig. 5). Administration of the CRS-R arousal facilitation protocol involves sustained, rhythmic application of deep pressure stimulation to the face, sternocleidomastoid, trapezius, arm, and leg muscles (Giacino et al., 2004), which produces a nonspecific afferent input into the anterolateral system (Fig. 6). Canonically, ascending anterolateral neurons innervate the ventral posterolateral and ventromedial nuclei of the thalamus, but these ascending neurons also innervate the lateral wing of the central lateral nucleus of the thalamus (Minciacchi, Granato, Antonini, Sbriccoli, & Macchi, 1991). Increasing evidence identifies the central lateral nucleus as a thalamic hub for the consciousness-supporting thalamocortical network, serving as the link between the anterior forebrain mesocircuit and the frontoparietal network (Laureys & Schiff, 2012; Redinbaugh et al., 2020; Schiff, 2020; Schiff et al., 2007). Given that the ABCD framework is theorized to index the functioning of the thalamocortical network, it follows that administration of the arousal facilitation protocol would yield improved EEG signal dynamics in this context through activation of thalamocortical afferents emanating from the central lateral nucleus.

Furthermore, our analysis serves as a causal test that the mesocircuit model, and its instantiation as the ABCD framework, captures expected changes in functional thalamocortical network integrity. According to the model, increased functional integrity of the thalamocortical network produced by the arousal facilitation protocol results from the direct driving of the central thalamus, which in turn produces increased excitatory tone across the neocortex reflected in measured EEG dynamics (Fig. 6). If thalamocortical connectivity remains intact, the model predicts that dynamics should consistently shift in the direction of ‘D’ on the ABCD scale, whereas if structural injuries to the thalamocortical network are too severe, such changes in both ABCD dynamics and arousal should not occur. Studies applying the ABCD framework to smaller samples of patients have examined other gradations in functional and structural integrity of the thalamocortical network, including a predicted anterior-posterior gradient in ‘B,’ ‘C,’ and ‘D’ patterns linked to variations in drug-induced arousal state (and, in one patient, variations in cerebral resting metabolism) (Williams et al., 2013). The pathological linkage of theta and beta/gamma oscillations in an isolable dynamical component of the resting EEG generated along the edge of cortical lesions has also been established (Drover & Schiff, 2018). Our observation that stimulation of the central thalamus via the CRS-R arousal facilitation protocol yields

improved ABCD signal dynamics provides unique supporting evidence that the model is indexing thalamocortical network function. Nonetheless, further study is needed to more firmly establish pathophysiologic linkages.

4.4. Limitations and future directions

Our method for classifying EEG signals into ABCD categories relied on visual inspection of power spectral estimates. While this method has been demonstrated to have high inter-rater reliability (Forgacs et al., 2017), it is labor-intensive and requires expertise in EEG spectral analysis. Development of an automated method for ABCD classification is a key goal for future studies, as it would allow for efficient analysis of large-scale datasets and EEG assessments by clinicians without spectral analysis experience. Some of the challenges to the development of such a method include: 1) artifact identification in the raw signal; 2) automated rejection of artifact-contaminated spectral estimates; 3) standardization across different EEG collection hardware, montages, environments, and participants; 4) capturing human criteria for distinguishing spectral peaks from the background shape; 5) validating algorithm performance against human raters; and 6) comparison of automated versus human discrepancies with interrater reliability.

The acute EEG and behavioral data for the four patients enrolled at ≥6-months post-injury (P17-20) were collected under different conditions than the 16 prospectively enrolled patients (P1-16), in that they did not have discrete rest blocks interspersed within a larger study protocol in the ICU (Edlow et al., 2017) and behavioral level of consciousness was derived from clinical neurological exams instead of the CRS-R. As a result, there were likely inherent differences in the study environment between these two groups because for the former group, investigators were not present at the bedside to ensure minimization of distractors and to conduct other components of the study protocol (e.g., CRS-R arousal facilitation protocol, etc.). Additionally, lack of CRS-R assessments for some patients in the acute setting may have led to underestimation of level of consciousness.

We were also limited by sample size in this study, as we were only able to study 12 patients longitudinally, all of whom demonstrated behavioral improvement at follow-up. As such, we were not able to investigate the prognostic relevance of ABCD classification as it pertains to the acute severe TBI population. Furthermore, we were unable to investigate ABCD dynamics in patients who exhibit behavioral stability or degradation, rather than improvement, over time. Recovery from severe brain injury is known to be variable in both time course and trajectory, and chronic CMD can emerge late in recovery (Curley et al., 2018; Forgacs et al., 2016; Thengone et al., 2016). Therefore, larger studies with long-term follow-up are needed to assess the prognostic relevance of ABCD classification in TBI and shed light on the optimal application of the approach (i.e., whether cross-channel averaging to calculate an ABCD index is preferable to considering the relative proportions of each ABCD category). This work also raises the question of identifying electrode montages that facilitate more stable estimates of ABCD indices (within blocks) or more reliable measures of ABCD changes during recovery (with corrections for multiple comparisons). Results from a prior study were suggestive of a potential prognostic utility of ABCD classification in a mixed sample of acute non-hypoxic-ischemic patients (7% TBI) (Alkhachroum et

al., 2020), but additional studies investigating the characteristics of ABCD-classified EEG signals in other etiologies of severe brain injury are needed to determine the generalizability of this approach.

Our cohort also included a relatively low proportion of patients with an acute, behavioral diagnosis of VS (5%). Recent studies investigating patients with acute DoCs enrolled widely varying proportions of patients with behavioral VS diagnoses (range: 11–41%) (Claassen et al., 2019; Enciso-Olivera et al., 2021; Kondziella et al., 2017; Othman et al., 2021; Seel et al., 2013). The timing of post-injury behavioral assessments in such studies is also often variable. However, even in this context, the proportion of VS patients in our acute cohort was comparatively low and we propose a few possible explanations for this. First, our sample size was relatively small, and the timing of acute behavioral assessment varied across participants, raising the possibility that our sample was not fully representative of the larger acute DoC patient population. Patients studied further out post-injury may have had an increased chance of recovering to a higher level of consciousness before assessment. We also note that four of six patients diagnosed to be in coma acutely underwent behavioral assessment with clinical neurological examination rather than the more comprehensive CRS-R, which, as noted above, may have led to an underestimation of level of consciousness for some of these participants. Importantly, the standard neurological examination does not involve the use of a mirror to assess for gaze tracking – an examination technique in the CRS-R behavioral evaluation that has been shown to detect gaze tracking with higher sensitivity than standard examination techniques, such as asking the patient to track the examiner's finger (Vanhaudenhuyse, Schnakers, Brédart, & Laureys, 2008).

We acknowledge that the median age of our patient cohort was also relatively young. Rates of TBI-related emergency department visits in the United States are highest among individuals in three age groups: 0–4, 15–24, and 75+ years, with motor vehicle/traffic accidents being the most common mechanism among for the 15–24-year group (Faul, Xu, Wald, & Coronado, 2010). As the median age of our patient cohort was closest to the 15–24-year group, with the most common mechanism being motor vehicle or traffic accidents, studies on patients of different age groups with different injury mechanisms may yield different findings.

To minimize bias and maintain methodologic consistency across participants, we did not screen or reject EEG data on the basis of sleep features. We also did not investigate the potential effect of sedatives on our results because of the many different medications administered that do not have well-established equivalencies and because standardized sedation rating scales may not apply to patients with severe TBI (Roberts et al., 2011; Sessler et al., 2002). As such, it is possible that some results may have been influenced by sleep or, for patients studied acutely, sedation. However, ABCD classification is not designed to be used in isolation, especially in the acute setting. As with any method for evaluating patients with severe brain injuries, it would potentially be used as part of a multimodal assessment of brain function that takes into account tests of metabolic and hemodynamic function, in conjunction with behavioral, neuroimaging, and other EEG-based measures (Comanducci et al., 2020; Giacino et al., 2018; Kondziella et al., 2020).

5. Conclusions

Based on the mesocircuit model for DoCs, resting-state EEG power spectra maybe classified into categories (‘A,’ ‘B,’ ‘C,’ ‘D’) corresponding to graded levels of thalamocortical network function. Application of this approach to a cohort of patients with acute severe TBI allowed for identification of improvement in thalamocortical network function among patients followed up at ≤6-months post-injury as well as improved network functioning among patients who recovered behavioral command-following. Furthermore, ABCD classification captured rapid state fluctuations among acutely injured patients as well as neurophysiologic evidence for the effectiveness of the CRS-R arousal facilitation protocol. If validated in future studies, ABCD classification of EEG may emerge as a useful complement to task- and stimulus-based techniques already endorsed for use in the clinical setting for diagnosis and prognosis of patients with DoCs (Giacino et al., 2018; Kondziella et al., 2020).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

CAP	Confusional Assessment Protocol
CI	confidence interval
CMD	cognitive motor dissociation
CRS-R	Coma Recovery Scale – Revised
dB	decibels
DoC	disorder of consciousness
EMCS	emerged from minimally conscious state
fMRI	functional MRI
GCS	Glasgow Coma Scale
Hz	Hertz

ICU	intensive care unit
IQR	interquartile range
MCS+/−	minimally conscious state with/without language
PTCS	post-traumatic confusional state
RMSD	root mean square deviation
R-PTCS	recovered from PTCS
SD	standard deviation
TBI	traumatic brain injury
VS	vegetative state

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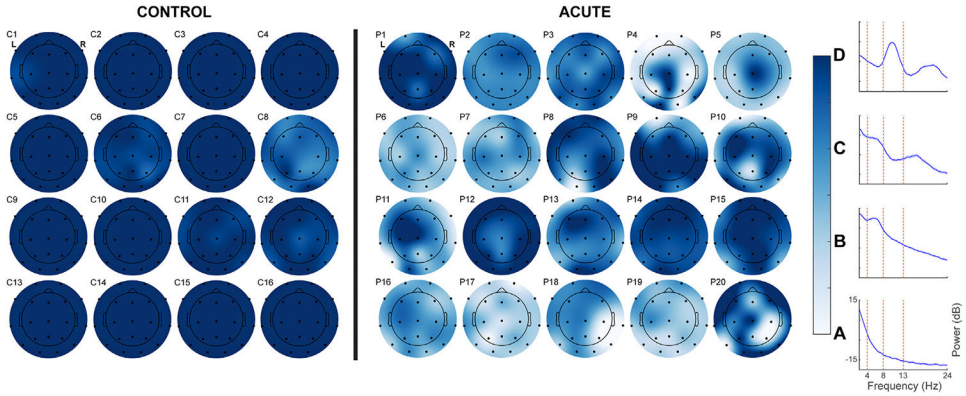

Fig. 1 –.

Heterogeneity of ABCD-classified EEG signals in patients with acute severe TBI. Channel-level averages of ABCD classifications across all rest blocks for all healthy controls (n = 16) and patients studied acutely (n = 20). Heatmaps indicate classification (D = 4, A = 1), according to electrode location on the scalp (represented by black dots). Missing electrodes for some participants represent channels that were omitted on the basis of artifact or inability to be classified into an ABCD category. Representative spectra for each of the ABCD categories are shown to the right of the color bar. dB = decibels, Hz = Hertz.

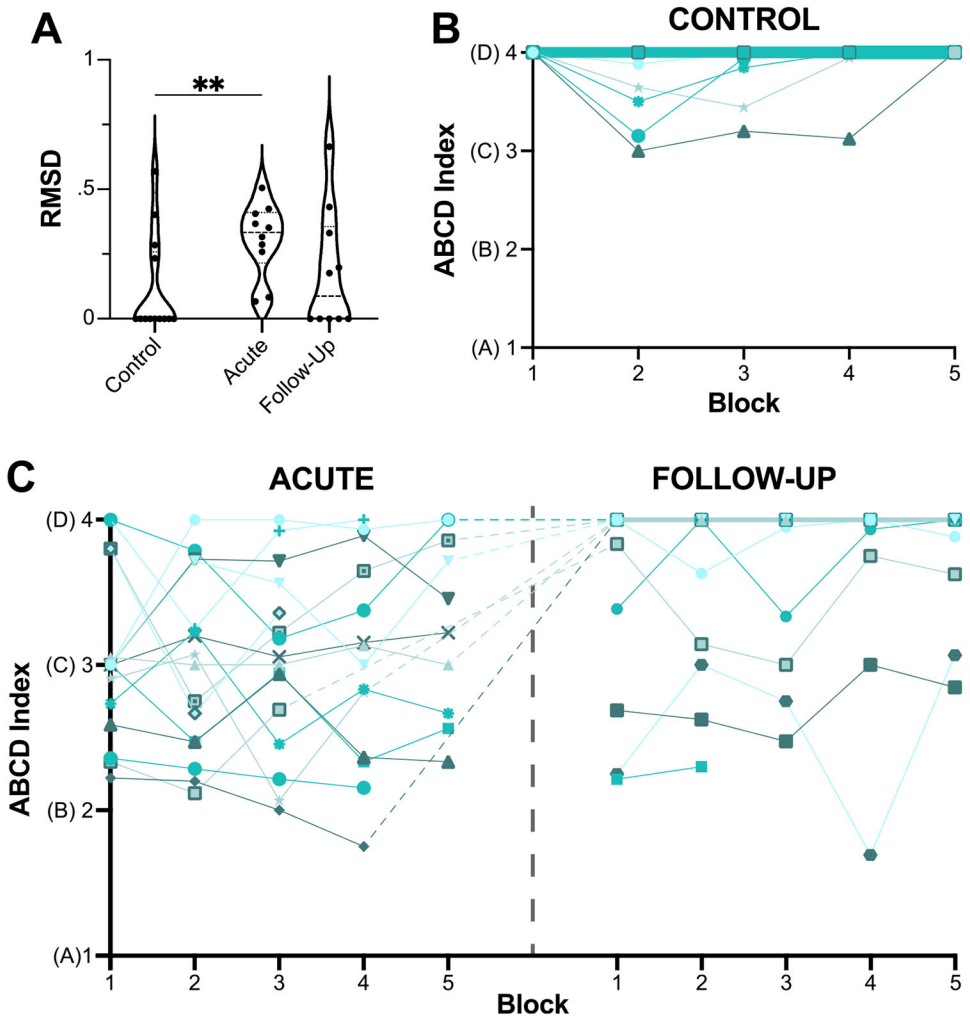

Fig. 2 –.

Within-session temporal stability of ABCD classifications. (A) Root mean square deviation (RMSD) of ABCD indices calculated across rest blocks for the subset of participants who had five discrete rest blocks collected within a contiguous 2-h window ($n = 16$ healthy controls, $n = 10$ patients). Patients studied acutely demonstrated significantly higher RMSDs relative to healthy controls (difference of medians: .3, $P = .005$). Within violin plots, dashed lines indicate the median and dotted lines indicate the 25th and 75th percentiles. (B) ABCD indices for each rest block for all healthy controls ($n = 16$). (C) ABCD indices for each rest block for patients studied acutely ($n = 16$) and at ≥6-month follow-up ($n = 12$) with discrete rest blocks recorded at regularly spaced intervals. For B and C, each participant is represented by a line/symbol and, for overlapping lines, line thickness is proportional to the number of participants. $^{**}P < .01$ (Mann–Whitney test).

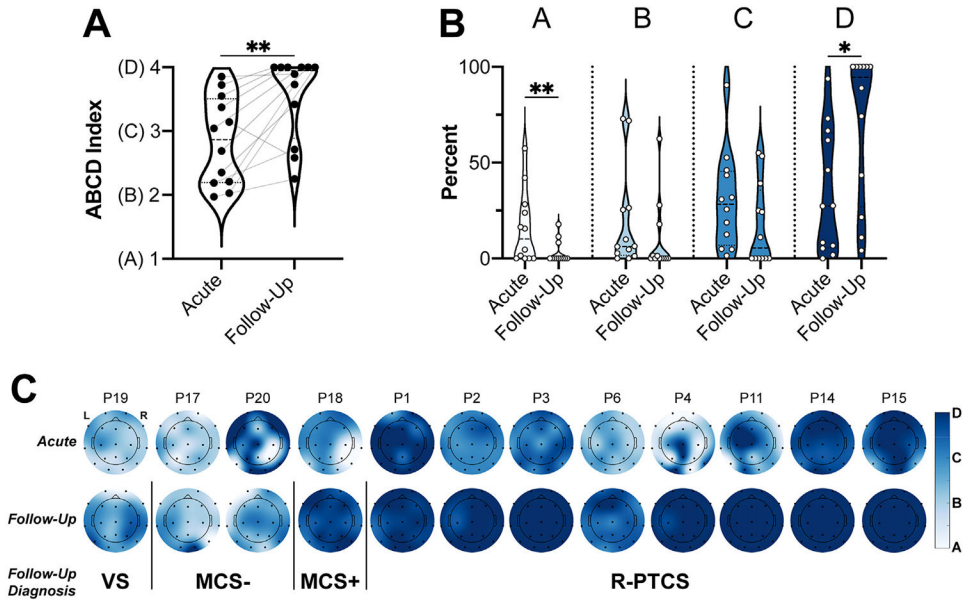

Fig. 3 –.

Longitudinal changes in ABCD dynamics. (A) ABCD index averaged across all channels and rest blocks for each patient studied both acutely in the ICU and at ≥6-month follow-up (n = 12). Patients demonstrated significantly higher ABCD indices at follow-up as compared to the acute setting (median change: .6, P = .006). Lines connect sequential recordings from individual patients. (B) Percent of channels classified into each of the ABCD categories (of the channels that could be classified) for each patient studied both acutely and at follow-up (n = 12). Follow-up patients demonstrated significantly increased proportions of 'D'-type signals (median change: 36.7%, P = .02) and significantly decreased proportions of 'A'-type signals (median change: −5.3%, P = .008). (C) Channel-level averages of ABCD classifications across all rest blocks for patients studied both acutely and at follow-up (n = 12). Patients are ordered according to behavioral diagnosis at ≥6-month follow-up. Heatmaps indicate classification (D = 4, A = 1), according to electrode location on the scalp (represented by black dots). Missing electrodes for some participants represent channels that were omitted on the basis of artifact or inability to be classified into an ABCD category. For A and B, dashed lines within violin plots indicate the median and dotted lines indicate the 25th and 75th percentiles. *P < .05, **P < .01 (Wilcoxon matched-pairs signed rank test).

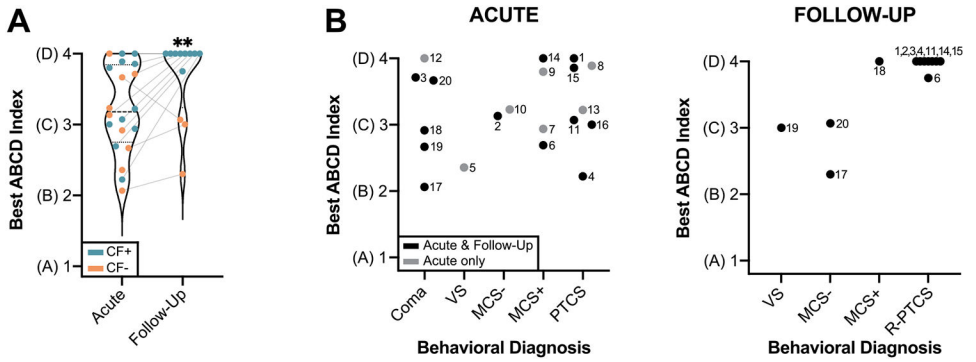

Fig. 4 –.

Comparison of ABCD classification and behavioral diagnosis. (A) Best ABCD index (defined as the highest ABCD index across all rest blocks) for all acute ($n = 20$) and follow-up ($n = 12$) patients with (blue; CF+) and without (orange; CF−) behavioral evidence of command-following. Lines connect sequential recordings from patients studied both acutely and at follow-up ($n = 12$). There was no difference in the best ABCD index for the acute patients with command-following ($n = 11$) as compared to those without ($n = 9$) (difference of medians: .09, 95% CI: −.9–.4, $P = .4$), while follow-up patients with command-following ($n = 9$) demonstrated significantly higher best ABCD indices as compared to follow-up patients without ($n = 3$) (difference of medians: 1.0, 95% CI: .9–1.7, $P = .005$). Within violin plots, dashed lines indicate the median and dotted lines indicate the 25th and 75th percentiles. (B) Best ABCD index for all patients plotted according to behavioral diagnosis. Patients studied longitudinally are plotted in black and patients studied in the acute ICU phase only are plotted in gray. Numbers adjacent to dots represent patient identifiers. $^{**}P < .01$ (Mann–Whitney test).

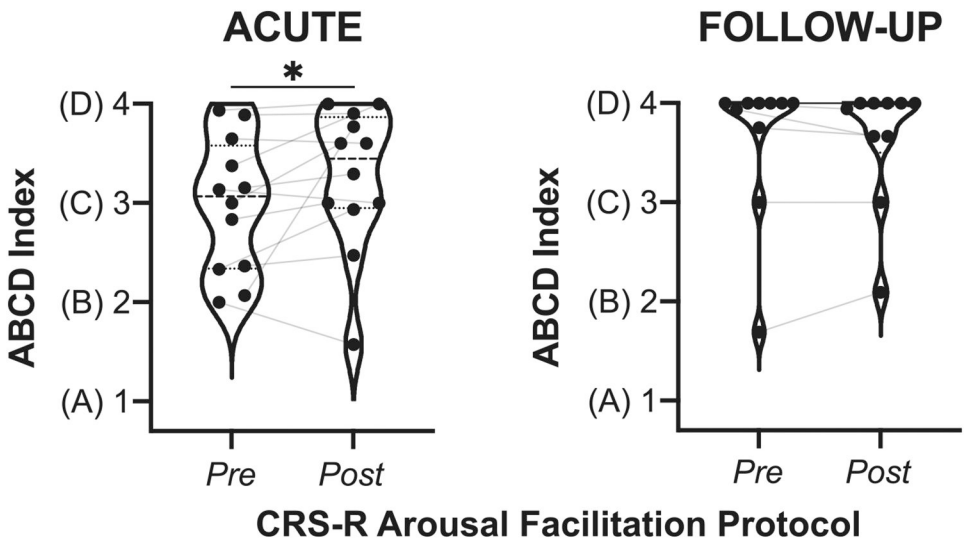

Fig. 5 –.

Effect of CRS-R arousal facilitation protocol on ABCD classification. ABCD index calculated from the rest block immediately preceding (*Pre*) and the 2 min immediately following (*Post*) the CRS-R arousal facilitation protocol in acute ($n = 12$) and follow-up ($n = 10$) recordings. The CRS-R arousal facilitation protocol involves sustained, rhythmic application of deep pressure stimulation to the face, sternocleidomastoid, trapezius, arm, and leg muscles, and is designed to promote arousal in patients with DoCs. In acute recordings, ABCD indices were significantly higher following administration of the CRS-R arousal facilitation protocol (median of differences: .1, 95% CI: −.05–.6, $P = .03$). In follow-up recordings, ABCD indices did not significantly increase following administration of the CRS-R arousal facilitation protocol (median of differences: 0, 95% CI: −.08–0, $P = .4$). Six of 10 follow-up patients had ABCD indices >3.9 both prior to and after the CRS-R arousal facilitation protocol. Within violin plots, dashed lines indicate the median and dotted lines indicate the 25th and 75th percentiles. *$P < .05$ (Wilcoxon matched-pairs signed rank test).

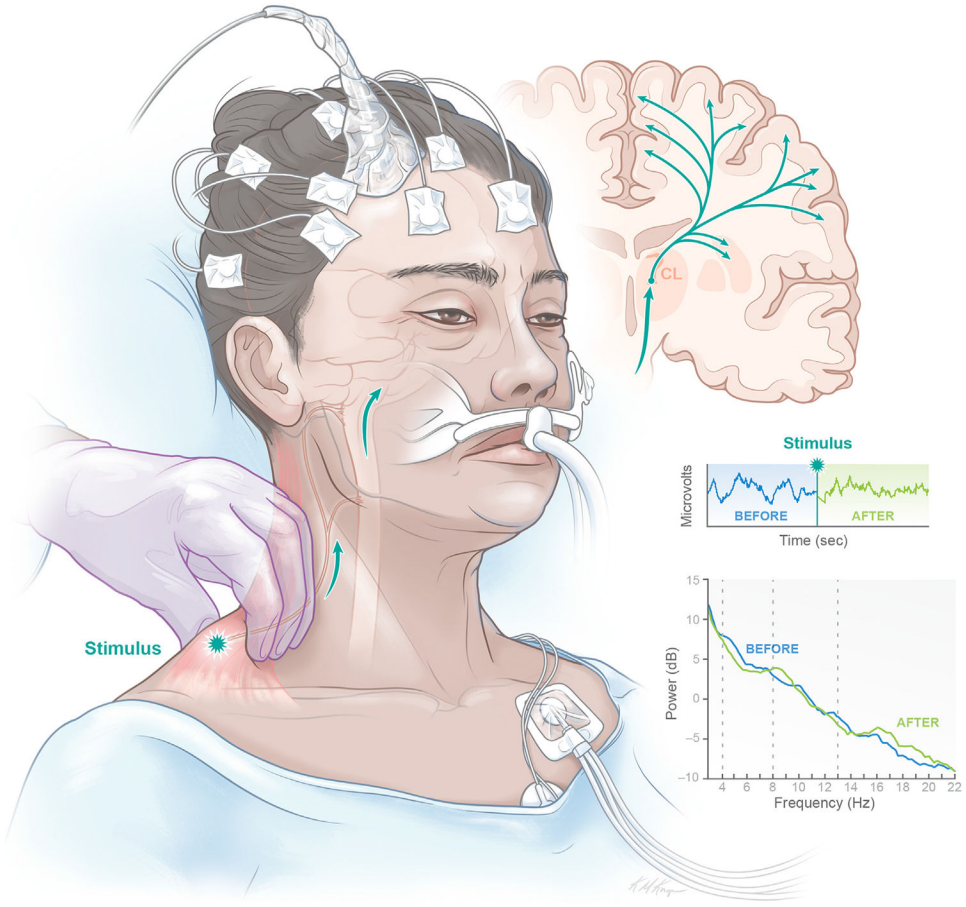

Fig. 6 –.

Schematic of proposed CRS-R arousal facilitation protocol mechanism. Administration of deep pressure muscle stimulation according to the CRS-R arousal facilitation protocol (stimulus) produces a nonspecific afferent input into the anterolateral system (green arrows), which projects to the lateral wing of the central lateral nucleus (orange; CL) in the thalamus. The central lateral nucleus in turn projects to striatum and cortex, thereby increasing excitatory neurotransmission throughout the cortex and shifting electrophysiologic dynamics towards a 'D'-type pattern on the ABCD scale. EEG tracings and power spectra are shown from a representative patient studied acutely (P11). Vertical dotted lines on power spectra indicate separation of delta (<4 Hz), theta (4–8 Hz), alpha (8–13 Hz), and beta (13–24 Hz) frequency ranges. Artwork by Kimberly Main Knoper. dB = decibels, Hz = Hertz.

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Table 1 –

Patient demographics and clinical information.

Patient ID	Age at injury (years)	Sex	TBI mechanism	iGCS range	Acute/ Follow-Up	Day of EEG	LoC at EEG	Total CRS-R at EEG	CRS-R subscale scores at EEG
P1	27	M	MVA	5T	Acute	17	PTCS	23	A4V5M6O3C2Ar3
					Follow-Up	206	R-PTCS	23	A4V5M6O3C2Ar3
P2	21	M	Ped versus car	4–8T	Acute	2	MCS−	4	A0V0M3O1C0Ar0
					Follow-Up	174	R-PTCS	23	A4V5M6O3C2Ar3
P3	19	F	MVA	5T	Acute	4	Coma	1	A0V0M1O0C0Ar0
					Follow-Up	371	R-PTCS	23	A4V5M6O3C2Ar3
P4	19	M	Fall	3–7T	Acute	10	PTCS	22	A4V5M6O3C2Ar2
					Follow-Up	576	R-PTCS	23	A4V5M6O3C2Ar3
P5	34	M	Fall	5T	Acute	16	VS	3	A0V0M0O2C0Ar1
P6	28	F	MVA	3	Acute	10	MCS+	11	A3V2M3O1C0Ar2
					Follow-Up	656	R-PTCS	23	A4V5M6O3C2Ar3
P7	45	M	MVA	5T	Acute	14	MCS+	18	A3V5M5O3C1Ar1
P8	33	M	Fall	5–7T	Acute	8	PTCS	20	A4V5M5O2C2Ar2
P9	32	M	Ped versus car	5–7T	Acute	13	MCS+	15	A3V3M5O1C1Ar2
P10	24	M	Assault	3–7T	Acute	13	MCS−	10	A1V1M5O1C0Ar2
P11	22	F	Ped versus car	6T	Acute	14	PTCS	22	A4V5M6O3C1Ar3
					Follow-Up	187	R-PTCS	23	A4V5M6O3C2Ar3
P12	27	F	Fall	3	Acute	8	Coma	1	A0V0M1O0C0Ar0
P13	18	M	Fall	3–7	Acute	6	PTCS	21	A4V5M6O3C2Ar1
P14	29	M	Ped versus car	4–7	Acute	8	MCS+	7	A3V0M3O0C0Ar1
					Follow-Up	235	R-PTCS	23	A4V5M6O3C2Ar3
P15	33	M	Fall	3–4	Acute	4	PTCS	14	A4V2M6O0C0Ar2
					Follow-Up	191	R-PTCS	23	A4V5M6O3C2Ar3
P16	26	M	Fall	4	Acute	28	PTCS	18	A3V4M6O2C1Ar2
P17	23	F	Ped versus car	3–5T	Acute	4	Coma[a]	N/A	N/A
					Follow-Up	224	MCS−	9	A1V3M2O1C0Ar2
P18	25	M	MVA	3–6T	Acute	5	Coma[a]	N/A	N/A

Patient ID	Age at injury (years)	Sex	TBI mechanism	iGCS range	Acute/ Follow-Up	Day of EEG	LoC at EEG	Total CRS-R at EEG	CRS-R subscale scores at EEG
					Follow-Up	182	MCS+	15	A4V3M3O2C1Ar2
P19	22	F	Ped versus car	3	Acute	4	Coma[a]	N/A	N/A
					Follow-Up	160	VS	5	A2V0M1O1C0Ar1
P20	28	M	MVA	3–5T	Acute	14	Coma[a]	N/A	N/A
					Follow-Up	1172	MCS−	5	A0V0M3O1C0Ar1

Initial Glasgow Coma Scale (iGCS) range is defined as the highest and lowest post-resuscitation GCS score assessed by a qualified clinician and not confounded by sedation or paralytics prior to ICU admission. Level of consciousness (LoC) was assessed with either the Coma Recovery Scale – Revised (CRS-R) (P1-16, all patients at follow-up) or neurological examination (P17-20 acutely) as coma, vegetative state (VS), minimally conscious state with/without language (MCS+/−), post-traumatic confusional state (PTCS), or recovered from post-traumatic confusional state (R-PTCS). CRS-R subscales are as follows: Auditory Function (A), Visual Function (V), Motor Function (M), Oromotor Function (O), Communication (C), and Arousal (Ar).

F = female; M = male; MVA = motor vehicle accident; N/A = not applicable; Ped = pedestrian; TBI = traumatic brain injury.

[a]LoC derived from clinical neurological examination rather than CRS-R.