RESEARCH ARTICLE

Neurophysiology State Dynamics Underlying Acute Neurologic Recovery After Cardiac Arrest

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Abstract

Background and Objectives

Epileptiform activity and burst suppression are neurophysiology signatures reflective of severe brain injury after cardiac arrest. We aimed to delineate the evolution of coma neurophysiology feature ensembles associated with recovery from coma after cardiac arrest.

Methods

Adults in acute coma after cardiac arrest were included in a retrospective database involving 7 hospitals. The combination of 3 quantitative EEG features (burst suppression ratio [BSup], spike frequency [SpF], and Shannon entropy [En]) was used to define 5 distinct neurophysiology states: epileptiform high entropy (EHE: SpF ≥4 per minute and En ≥5); epileptiform low entropy (ELE: SpF ≥4 per minute and <5 En); nonepileptiform high entropy (NEHE: SpF <4 per minute and ≥5 En); nonepileptiform low entropy (NELE: SpF <4 per minute and <5 En), and burst suppression (BSup ≥50% and SpF <4 per minute). State transitions were measured at consecutive 6-hour blocks between 6 and 84 hours after return of spontaneous circulation. Good neurologic outcome was defined as best cerebral performance category 1–2 at 3–6 months.

Results

One thousand thirty-eight individuals were included (50,224 hours of EEG), and 373 (36%) had good outcome. Individuals with EHE state had a 29% rate of good outcome, while those with ELE had 11%. Transitions out of an EHE or BSup state to an NEHE state were associated with good outcome (45% and 20%, respectively). No individuals with ELE state lasting >15 hours had good recovery.

Discussion

Transition to high entropy states is associated with an increased likelihood of good outcome despite preceding epileptiform or burst suppression states. High entropy may reflect mechanisms of resilience to hypoxic-ischemic brain injury.

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Glossary

BSup = burst suppression ratio; **CPC** = cerebral performance category; **EHE** = epileptiform high entropy; **ELE** = epileptiform low entropy; **En** = Shannon entropy; **NEHE** = nonepileptiform high entropy; **NELE** = nonepileptiform low entropy; **QEEG** = quantitative EEG; **ROSC** = return of spontaneous circulation; **SpF** = spike frequency; **TTM** = targeted temperature management.

Introduction

Coma is a common clinical presentation after acute brain injury from cardiac arrest, trauma, and subtypes of stroke.[1,2] Recovery from coma is often protracted and difficult to diagnose at the bedside, making early patient selection to therapeutic interventions and prognostication challenging to clinicians and caregivers.[3,4] Cardiac arrest is one of the few medical conditions in which continuous brain monitoring with EEG is routinely started within a few hours from coma onset.[5,6] This feature of current clinical practice affords the unique opportunity to observe the longitudinal evolution of the neurophysiology of coma recovery before neurologic improvement is perceptible to clinicians, creating new avenues for studying coma neuroscience at a scale and resolution not possible for other acute coma etiologies.[5,7-9]

Coma neurophysiology research using EEG for chronic disorders of consciousness and general anesthesia has provided critical insights about the evolution of neural processes involved in conscious awareness.[10,11] Entropy, band power, coherence, and regional connectivity are EEG features proposed as surrogate markers of consciousness emergence in these clinical contexts.[11-14] Translation of knowledge about coma neurophysiology dynamics from chronic to acute coma recovery has been limited nonetheless.[15-18] Differently from chronic disorders of consciousness, brain rhythms change rapidly during the first few days after injury, and seizures, epileptiform activity, or burst suppression are present in more than half of comatose cardiac arrest patients.[5,8,9,18] These patterns are associated with poor neurologic outcomes, but some patients may recover despite injury causing this type of physiology.[6,19,20] To advance the current management of acute brain injury and identify patients with potential for coma recovery despite unfavorable EEG patterns, we must understand the wide range of concurrent neurophysiologic processes contributing to acute coma soon after brain injury and their temporal changes.

In this large multicenter international study, we aimed to define the longitudinal evolution of 4 EEG signal domains using quantitative EEG (QEEG) during acute coma recovery from cardiac arrest: epileptiform activity (QEEG: spike frequency), background continuity (burst suppression ratio and regularity), background complexity and variability (entropy), and frequency (spectral power in delta, theta, alpha, and beta frequency bands). We hypothesized that the timing and type of transitions between neurophysiology states characterized by these QEEG features are associated with the likelihood and degree of neurologic recovery from acute coma after cardiac arrest and that these neurophysiology patterns are consistent across cohorts from different hospitals.

Methods

Participants

Seven large (>750 beds each) university-affiliated hospitals participated in this study (4 from the United States, 2 from the Netherlands, and 1 from Belgium). Adult (older than 18 years) comatose patients diagnosed with hypoxic-ischemic brain injury after out-of-hospital or in-hospital cardiac arrest who had a Glasgow coma score of 3–8 after return of spontaneous circulation (ROSC) were included. Individuals who had a cerebral hemorrhage as the cause of arrest or those not undergoing targeted temperature management (TTM) were excluded. The TTM goal temperature used across centers was 32–34°C or 36°C. Data from the 2 hospitals from the Netherlands were analyzed as a single institution because both hospitals and investigators are affiliated with the same University. Investigators abstracting outcomes and other clinical information were blinded to QEEG analysis. Additional information about TTM and EEG monitoring is available in supplemental content (eMethods, links.lww.com/WNL/C967).

Neurologic Prognostication and Outcome Assessment

All participating hospitals have protocols for multimodal neurologic prognostication that follow international guideline recommendations.[21,22] Formal neurologic prognostication is deferred until the normothermia phase and confounding from sedatives can be minimized. Neurologic functional outcome was determined using cerebral performance categories (CPCs). For the descriptive analysis evaluating the evolution of QEEG trends, we stratified patient as "good" coma recovery (CPC score of 1 or 2, i.e., independence for activities of daily living), "partial" coma recovery (CPC of 3–4, i.e., moderate to severe neurologic disability), and death (CPC of 5).[23] For all remaining analyses, we used the standard binarization of CPC scores CPC 1–2 vs CPC 3–5, and we will refer to this classification in this study as "good neurologic outcome" and "poor neurologic outcome," respectively. The primary outcome was defined as the best CPC score achieved by 3 and 6 months after initial cardiac arrest.[9] Long-term outcome was obtained prospectively at 6 months for all cardiac arrest individuals surviving hospital discharge through an in-person or telephone interview for hospital 5. For the remaining hospitals, individuals with a CPC of 1 or 2 or CPC of 5 at discharge were considered to have achieved a good or poor best neurologic outcome, respectively; therefore, further chart

review was not performed. Individuals with CPC 3 or 4 at discharge had an additional retrospective chart review to determine whether their CPC scores changed in the following 3–6 months.

QEEG Artifact Detection and Feature Extraction

All EEG data available up to 84 hours from ROSC were used. We performed EEG preprocessing and artifact detection before feature acquisition. Preprocessing: all EEG signals were resampled to 100 Hz and band filtered at 0.5–30 Hz. EEG channels were rereferenced to a bipolar montage. Nine QEEG features were calculated: delta, theta, alpha, and beta power, alpha-delta power ratio, regularity, burst suppression ratio (BSup), spike frequency (SpF), and Shannon entropy (En).[9] A continuous EEG was defined as BSup ≤10%. The mean automated SpF was determined based on the number of epileptiform discharges detected in consecutive 5-minute epoch using an automated spike detection algorithm (SpikeNet).[24] The mean QEEG feature values were averaged to provide a single hourly value for each QEEG feature.

Neurophysiology States Definition

In clinical practice, neurologists interpret EEG recordings longitudinally using distinct categories such as "continuous" vs "burst suppression" or "epileptiform" vs "nonepileptiform" or "high vs low variability."[8,9,25] To emulate the heuristics of qualitative EEG review and to evaluate how these canonical EEG patterns evolve over time, we selected 3 QEEG features to characterize QEEG trajectories after cardiac arrest: spike frequency (corresponding to sporadic epileptiform discharges to generalized periodic discharges to seizures), BSup (corresponding to background continuity), and En (corresponding to background complexity and variability). High entropy EEG signals usually correspond to continuous and variable background in contrast with suppressed or more static patterns seen with severe brain injury or deep anesthesia.[26]

First, we selected a threshold for each QEEG feature to determine categories with "low" or "high" feature values. Burst suppression has a well-defined quantitative threshold; we used 50% suppression as the threshold for BSup.[25] For SpF and En thresholds, we used the median feature value across the entire 84 hours of recording for all individuals. Second, we categorized each hour of EEG for an individual as having a "high" or "low" value for these 3 QEEG features. Hence, there were 8 possible high or low QEEG feature combinations. To enhance interpretability of these feature combinations, we grouped them as epileptiform predominant states when high spike frequency was identified independent of other features and burst suppression state when BSup was above 50% and epileptiform activity was low. States without epileptiform activity or burst suppression were subdivided as high or low background complexity based on En levels. Epileptiform states were also further subdivided based on En levels. Therefore, the 8 possible feature combinations were summarized into 5 neurophysiology states: epileptiform with high entropy (EHE: SpF ≥4 per minute, En ≥5, and high or low BSup); epileptiform with low entropy (ELE: SpF ≥4 per minute, En <5, and high or low BSup); burst suppression (BSup ≥50% and low SpF [<4 per minute] with high or low entropy); nonepileptiform low entropy (NELE: En <5 with low SpF and BSup <50%), and nonepileptiform high entropy (NEHE: En ≥5 with low SpF and low BSup).

Neurophysiology State Transitions and State Burden

A coma state transition was defined as a change from 1 coma state to 1 of the other 4 states between consecutive 6-hour blocks. Neurophysiology states were determined hourly based on the presence or absence of a neurophysiology state, and the burden is a sum of the prevalence of each individual state across the entire EEG recording. The association between the probability of a good neurologic outcome and the time spent in a given state (the "state burden") was evaluated for each state. For example, for the EHE state, if there were 10 patients who spent at least 15 hours in the EHE state, and 2 of them had good outcome, the good outcome probability at 15 hours of EHE burden would be 20%. Probability analysis for each number of hours of state burden included only individuals who were in a state for at least that duration. The goal of this analysis was to evaluate whether patients staying in a state for a longer period (i.e., cumulative state burden) have a different likelihood of recovery than those staying for a shorter time and vice versa.

Statistical Analysis

Univariate analysis for good neurologic outcome (CPC 1–2) vs poor neurologic outcome (CPC 3–5) groups used independent *t* test for continuous variables with normal distribution and Pearson χ^2 tests for categorical variables. Statistical significance was set to an alpha level of 0.05. Statistical analysis used MATLAB (version 17a; MathWorks, Natick, MA). No adjustment based on hospital of origin was performed.

To further interpret the relationship between QEEG feature values and neurologic outcomes, for each patient and QEEG feature, we calculated the mean feature value over the entire period of EEG monitoring. We then normalized all features to have zero mean and unit variance and created a histogram with 10 bins. Good neurologic outcome probability associated with a particular mean value was defined as the proportion of individuals with good neurologic outcome whose mean values were within a given bin.

To visualize the relationship of QEEG feature ensembles at the individual level and corresponding neurophysiology states and neurologic outcomes, we used an embedding algorithm (t-distributed stochastic neighbor embedding) for nonlinear dimensionality reduction.[27]

Standard Protocol Approvals, Registrations, and Patient Consents

Data collection and analysis were performed under independent Institutional Review Board approvals at participating hospitals (IRB #20013P001024 Partners Healthcare [Massachusetts General Hospital and Brigham and Women's Hospital], Beth Israel Deaconess Medical Center, Yale New Haven Hospital,

Rinjstate Hospital, and Medisch Spectrum). A data sharing agreement was made among participating hospitals. This was a retrospective analysis of data obtained as part of the usual care, and the requirement for informed consent was waived.

Data Availability

Deidentified participant data that support the findings of this study are available from the corresponding author E. Amorim on reasonable request after permission from each participating centers is granted. Study protocol and statistical analysis will be made available during publication for additional statistical analyses from qualified investigators.

Results

One thousand thirty-eight individuals were included in the study (50,224 hours of EEG data). Fifty-one individuals were excluded because of incomplete baseline demographic information. Good coma recovery (CPC 1–2) was achieved by 373 participants; 48 had partial coma recovery (CPC 3–4), and 617 died (CPC 5) (Table 1 and eTable 1, links.lww.com/WNL/C968). Individuals in the good outcome group were younger (mean age 57 vs 63 years, $p < 0.001$) and more commonly had an initial shockable rhythm (71% vs 32%, $p < 0.001$) than those with poor neurologic outcomes (CPC 3–5). Eighty (7.7%) individuals were managed with TTM 36°C.

Coma Neurophysiology Trends

In Figure 1A, trends for SpF, BSup, and En were always discriminative between outcome groups starting at 11 hours. A monotonic relationship characterized these 3 QEEG features across outcome groups, with individuals in the partial coma recovery group having intermediate feature values between the good coma recovery group and those who died (Figure 1). The mean SpF per minute for individuals with good coma recovery peaked at 48 hours (3 spikes per minute), while individuals with partial coma recovery or death had a rapid increase from 12 to 48 hours (1.5–5.6 and 2–7 spikes per minute, respectively, $p < 0.05$, Figure 1A). The mean BSup in the good coma recovery group was 25% at 12 hours, decreasing to 4% by 48 hours; for the partial coma recovery and death groups, the mean BSup was 42% and 55% at 12 hours, decreasing to 14% and 22% by 48 hours ($p < 0.05$, Figure 1B). A continuous background was present at 12 hours in 58% of individuals with good coma recovery vs 64% and 28% for partial coma recovery and death groups, respectively. At 48 hours, a continuous background was present in 92% individuals in the good coma recovery group, 85% in the partial coma recovery group, and 66% in the death group. Entropy was always higher in those with good coma recovery, but all outcome groups had comparable improvement in entropy from 12 to 48 hours (16% absolute increase for all, Figure 1C). We observed that probability of good outcome decreased with higher spike frequency or higher burst suppression ratio. The inverse happened with entropy levels, as a higher entropy was associated with a higher probability of good neurologic outcome. (Figure 2).

For the other features not included in the neurophysiology states classification, regularity was higher in the good coma recovery group initially, but by 46 hours, it became comparable across groups (Figure 1D). Improvement in power was observed across all outcome groups during the first 48 hours without differences between outcome groups (Figure 1, F–I); however alpha-delta ratio decreased in individuals with a good coma recovery after 48 hours (Figure 1E). A summary of the longitudinal background frequency evolution is shown using spectrograms (Figure 1, J–L).

Heterogeneity in Coma Neurophysiology Trends Among Hospitals

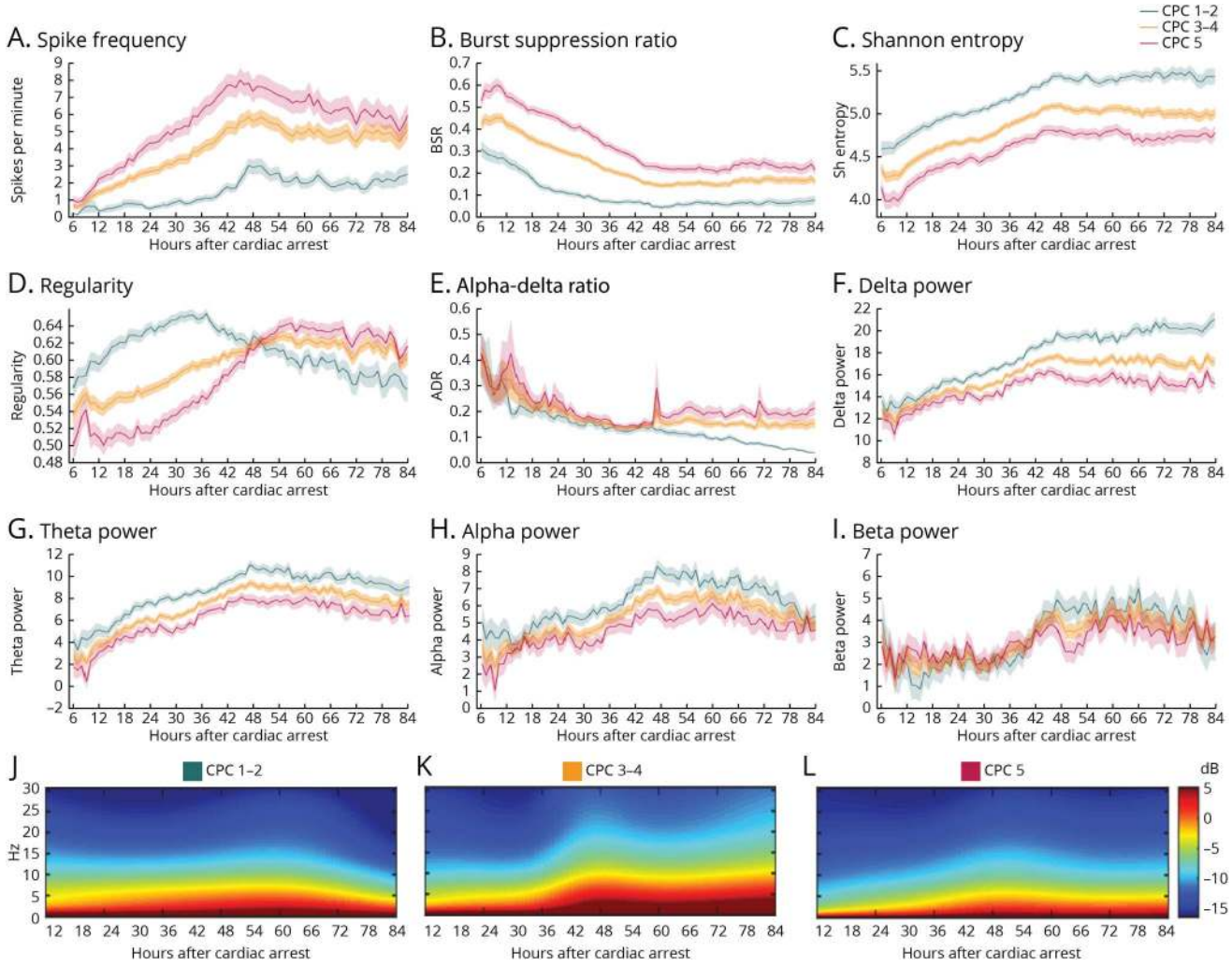
There was heterogeneity in QEEG trends evolution for good and poor neurologic outcome groups between medical centers, especially after 48 hours (Figure 3 and eFigure 1, links.lww.com/WNL/C966). Spike frequency was higher for the poor neurologic outcome group in most hospitals; however, there was considerable heterogeneity in the degree of this difference between outcome groups. For example, hospitals 4 and 6 and hospitals 3 and 5 had comparable SpF trends after 48 hours, but the SpF trajectories of these hospitals were distinct from each other (Figure 3A). Burst suppression ratio tended to improve for both outcome groups in most centers; however, no significant improvement in BSup was observed for the good neurologic outcome group in hospital 2 or for

Table 1 Demographics and EEG Monitoring Information

	CPC 1–2	CPC 3–4	CPC 5
No. of participants	373	48	617
Age, y, mean (SD, IQR)	57 (15, 18–90)	62 (16, 23–85)	62 (16, 16–101)
Sex, female (%)	28	40	32
Shockable rhythm (%)	71	42	31
EEG start time from ROSC, h, mean (SD, IQR)	16 (14, 6–20)	17 (11, 9–22)	19 (17, 8–22)
EEG duration, h, mean (SD, IQR)	55 (36, 35–67)	82 (56, 40–113)	55 (40, 25–71)

Abbreviations: CPC = cerebral performance category; IQR = interquartile range; ROSC = return of spontaneous circulation.

Figure 1 Longitudinal Neurophysiology Trends Postcardiac Arrest Stratified by Neurologic Outcome (CPC 1–2, CPC 3–4, and CPC 5)



(A–I) Hourly quantitative EEG features trends for 6–84 hours postcardiac arrest. (J–L) Average compressed spectral array displays summarized by outcome. ADR = alpha-delta ratio; BSR = burst suppression ratio; CPC = cerebral performance category; Sh entropy = Shannon entropy.

the poor neurologic outcome group in hospital 6 (eFigure 1A, links.lww.com/WNL/C966). Most centers had higher En in the good neurologic outcome group, except hospital 4 (eFigure 1B). Pairwise comparison of relative mean absolute difference of features among centers is summarized in Figure 3, B and C and highlight the variability in feature values between hospitals. We report only good vs poor neurologic outcome results because the number of individuals with CPC 3–4 per hospital was small.

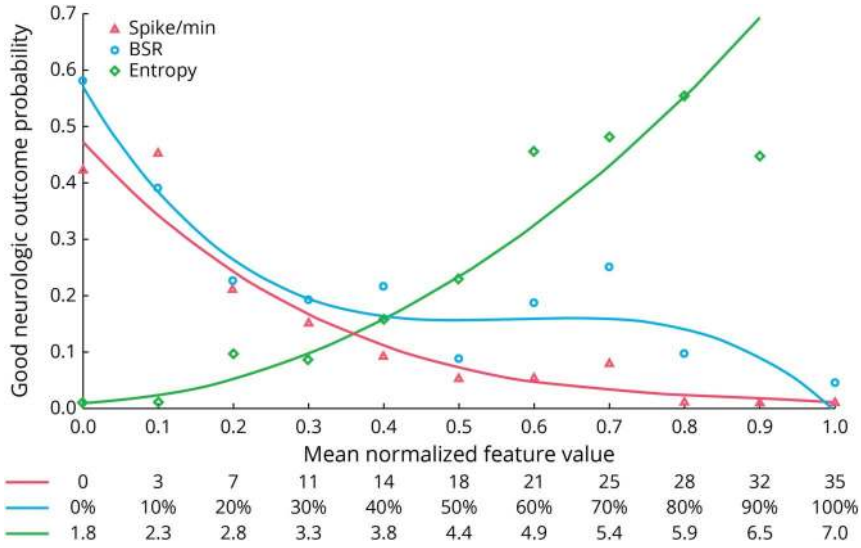
Neurophysiology State Dynamics

State Transition Dynamics and State Burden

Individuals with a high entropy state with low spike and low BSup feature combination for at least 6 hours had a 52% probability of good neurologic outcome compared with 29% for the high spike frequency, high entropy, and low burst suppression ratio combination and 11% for the 3 subgroups with high spike frequency without high entropy or in association with high burst suppression (Figure 4, A and B). Representative raw EEG snapshots for each QEEG feature combination group are shown in Figure 4C. Examples of raw EEG, spectrogram, and neurophysiology state evolution over time for each individual are shown in Figure 5.

Individual-level (hourly) and group-level (every 6 hours) neurophysiology state transition dynamics and coma state burden averaged by outcome group are shown in Figure 6, A and C. The probability of having a coma state transition between 6-hour blocks was comparable between good (25%) and poor (20%) neurologic outcome groups; however, the type and timing of these transitions were different. Of importance, stationarity in neurophysiology states was dominant for most individuals, and a substantial number of individuals in both outcome groups were already on a nonepileptiform high or low entropy state early after ROSC (Figure 6C). However, there

Figure 2 Probability of Good Neurologic Outcome (CPC 1-2) Based on Range of Quantitative EEG Feature Values (Mean Spike Frequency per Minute, Burst Suppression Ratio, and Entropy)



The mean normalized feature value for each bin (x-axis) represents the average mean feature value for each of the 3 features. The probability of good neurological outcome (CPC 1-2) is the proportion of subjects with CPC 1-2 among all cases within each bin. BSR = burst suppression ratio; Sh Entropy = Shannon entropy; CPC = cerebral performance category.

was a much higher burden of burst suppression and ELE states in the poor neurologic outcome group in contrast to the higher burden of the NEHE state in the good neurologic outcome group (Figure 6B).

Group-level dynamics for the good neurologic outcome group showed a rapid decrease in burst suppression state prevalence over the first 48 hours and a gradual increase in EHE state after 24–48 hours (Figure 6C). Emergence of epileptiform activity from an NEHE state was observed primarily after the first 48 hours for the good neurologic outcome group.

Epileptiform States (6-Hour Blocks)

Longitudinal transition to an epileptiform state (EHE or ELE) increased in both outcome groups (Figure 6C). The proportion of individuals with good neurologic outcome having a predominant epileptiform state for at least 6 hours within the first 24 hours was 5%, increasing to 18% and 29% at 24–48 hours and 48–84 hours, respectively.

Burst Suppression State (6-Hour Blocks)

BSup state incidence decreased over time for both groups, specifically going from 26% at 6–24 hours to 7% at 48–84 hours for the good neurologic outcome group (Figure 6C). The probability of good neurologic outcome associated with transitions from BSup to an NEHE or NELE was 49% and 15% at 6–24 hours and 48–84 hours.

High or Low Entropy States (6-Hour Blocks)

The proportion of individuals with good neurologic outcome having a predominant NEHE or NELE state for at least 6 hours within the first 24 hours was 92%, increasing to 95% at 24–48 hours (Figure 6C).

Good Neurologic Outcome Probability at Current Coma State

The probability of good neurologic outcome decreased for individuals with the BSup state over time, but increased for the EHE group (Figure 6D). Note that in Figure 6D, each line represents the proportion of patients within that state who go on to have a good outcome. For example, at hour 50, the pink line (NEHE state) is at approximately 24%. This means that, among patients in the NEHE state at hour 50, approximately 24% go on to have a good outcome.

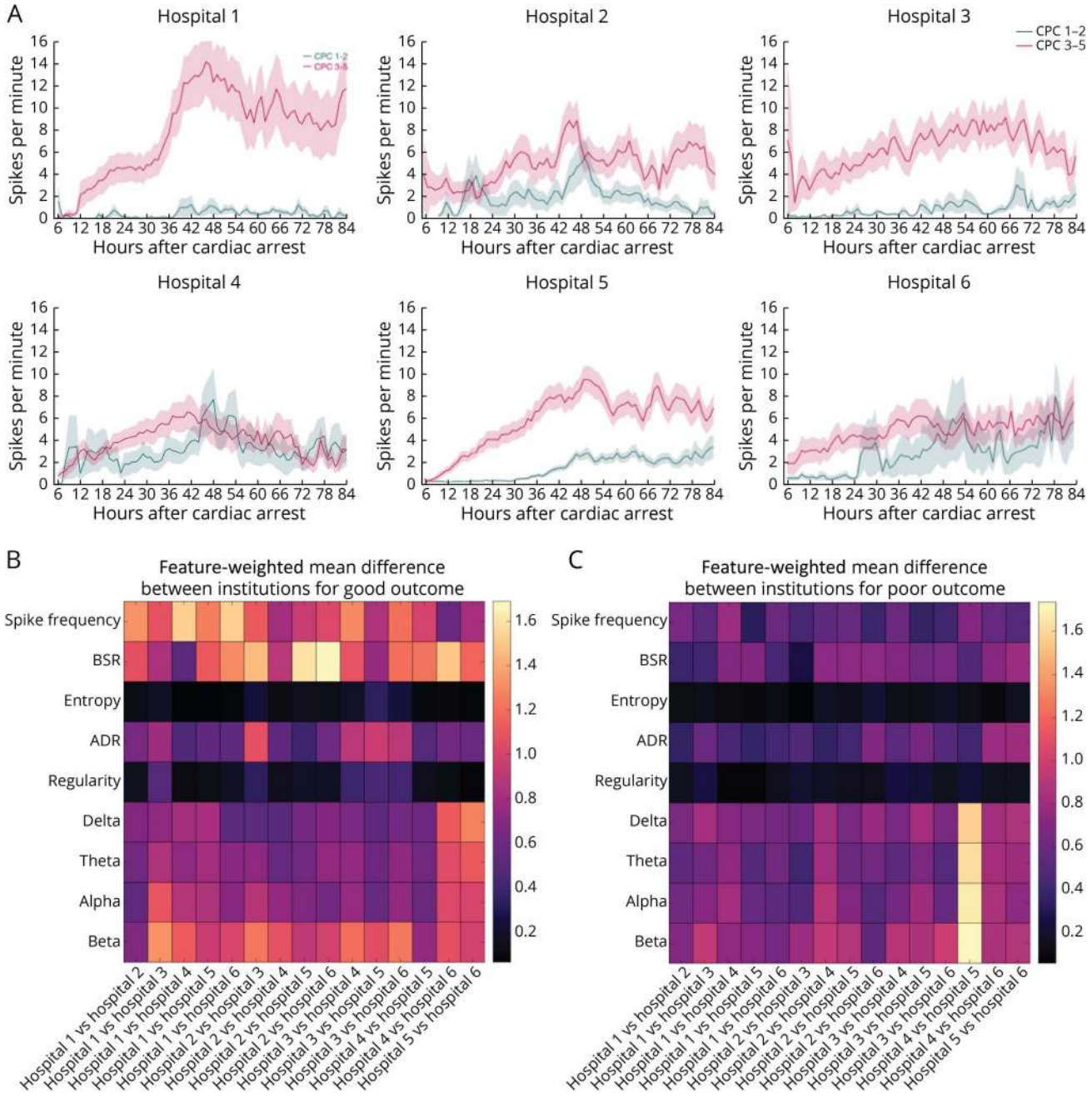
Good Neurologic Outcome Probability Based on Cumulative Coma State Burden

No individuals staying in an ELE state for longer than 15 hours, BSup for 53 hours, or EHE for 57 hours had good neurologic outcome (Figure 6E). Individuals with a longer duration of an NEHE had a higher probability of good outcome, and all individuals who accumulated 70 or more hours in the NEHE state had a good outcome.

Discussion

This retrospective study describes distinct neurophysiology states that underlie the process of acute coma recovery from cardiac arrest. Using interpretable and clinically relevant QEEG features recorded from a large international multicenter cohort, we demonstrate that type and timing of neurophysiology state transitions between epileptiform, burst suppression, and entropy EEG domains carry important information about acute coma recovery potential. Of importance, our results demonstrate that individuals with severe acute brain injury resulting in early epileptiform discharges or burst suppression may recover consciousness

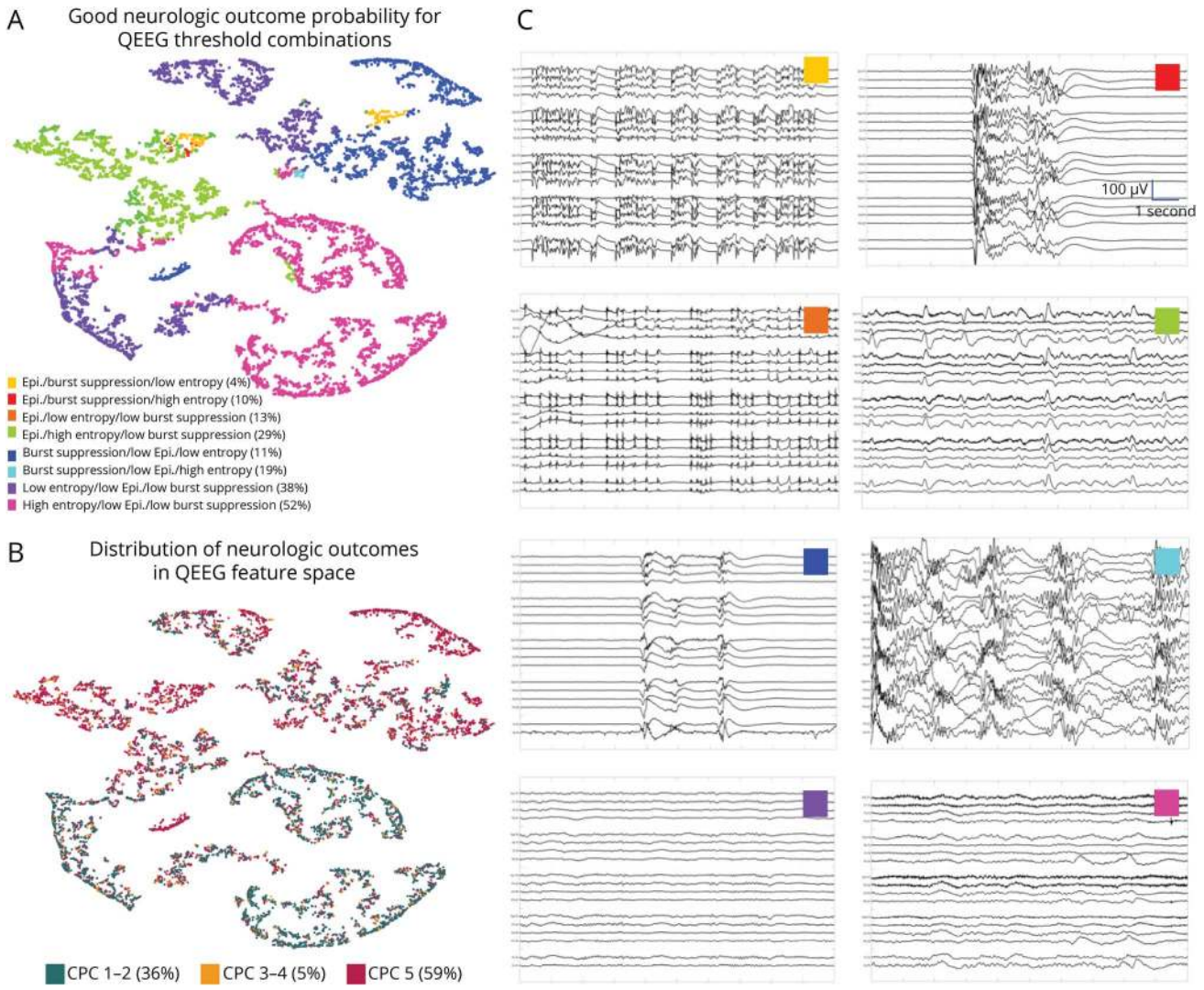
Figure 3 Neurophysiology Trends Postcardiac Arrest Variability per Hospital Stratified by Neurologic Outcome (CPC 1–2 and CPC 3–5)



(A) Mean spike frequency per minute. (B) Weighted mean difference for QEEG features per hospital pairs for the good neurologic outcome group (CPC 1–2). (C) Weighted mean difference for QEEG features per hospital pairs for poor neurologic outcome group (CPC 3–5). CPC = cerebral performance category; QEEG = quantitative EEG.

and achieve functional independence depending on neurophysiology state evolution toward higher entropy. The external validity and generalizability of these early QEEG metrics is corroborated by comparable prediction performance across participating centers in the first 48 hours after cardiac arrest in prior studies from our group using this cohort.[28,29] These findings advance prior work on QEEG dynamics as suitable biomarkers of resilience to hypoxic-ischemic brain injury by capturing the longitudinal evolution of QEEG feature ensembles in well-defined endophenotypes (i.e., neurophysiology states) instead of individual feature trends.[9,30,31] The proposed framework indicates that neurophysiology states' dynamics have both time-dependent and dose-dependent relationships with the degree of long-term functional coma recovery, supporting the development of QEEG biomarkers. This work has

Figure 4 QEEG Features Clustering and Neurologic Function

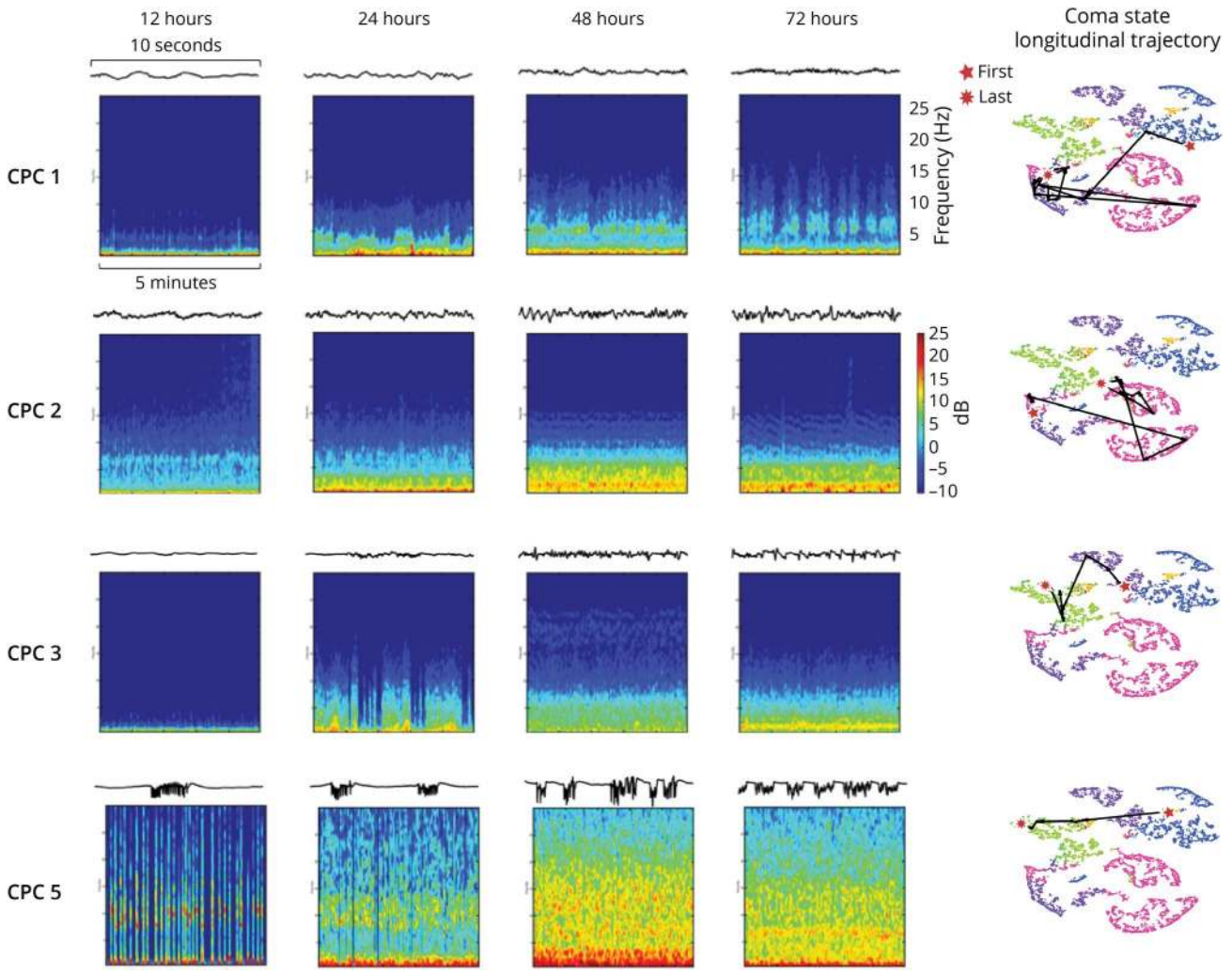


In this visualization, each point represents a vector with all 9 QEEG feature combinations for each 6 hours epoch for an individual participant. The distance between points is determined based on the Euclidean distance between each of these feature vectors. The t-SNE map points is color coded based on the thresholded values for the 3 QEEG features used for neurophysiology state determination (i.e., SpF, BSup, and En); therefore, there are 8 labels for the corresponding 8 possible QEEG feature combinations. (A) t-SNE labeled based on spike frequency, burst suppression ratio, and entropy levels. (B) t-SNE labeled by neurologic function level (CPC 1–2, CPC 3–4, and CPC 5). (C) Examples of raw EEG patterns corresponding to QEEG patterns combinations shown in Figure 4A. BSup = burst suppression ratio; CPC = cerebral performance category; En = Shannon entropy; QEEG = quantitative EEG; SpF = spike frequency; t-SNE = t-distributed stochastic neighbor embedding.

implications to research investigating the underpinnings of coma recovery across brain injury etiologies and may support future investigation about patient selection in clinical trials, monitoring of treatment response to interventions, and coma prognostication.

Beyond redemonstrating the high incidence of cortical hyperexcitability (i.e., epileptiform activity) after acute hypoxic-ischemic brain injury and its association with poor neurologic outcomes, we add to the body of literature in acute coma neurophysiology by demonstrating that epileptiform activity in association with high entropy may distinguish patients with a higher likelihood for good coma recovery.[9,20,32-35] Up to 29% of individuals with epileptiform activity associated with high entropy recovered, although that association was dependent on the timing and type of epileptiform state transition. A high epileptiform and high entropy state was mainly associated with recovery in the postrewarming phase. This type of epileptiform state may represent de novo epileptiform activity, possibly reflecting synaptic imbalance associated with the rewarming period in patients with cortical injury not severe enough to suppress oscillatory brain activity.[36,37] On visual EEG review, the epileptiform and high entropy state usually translates to seizures, generalized periodic discharges, or epileptiform activity that are associated with a continuous background. Epileptiform patterns are indicative of substantial cortical injury, but continuity and spectral activity may represent relative preservation of functional and structural corticothalamic and corti-cortical networks necessary for consciousness recovery.[12,13,38-41] By contrast, early onset of epileptiform activity with or without high entropy was

Figure 5 Coma Neurophysiology State Trajectory

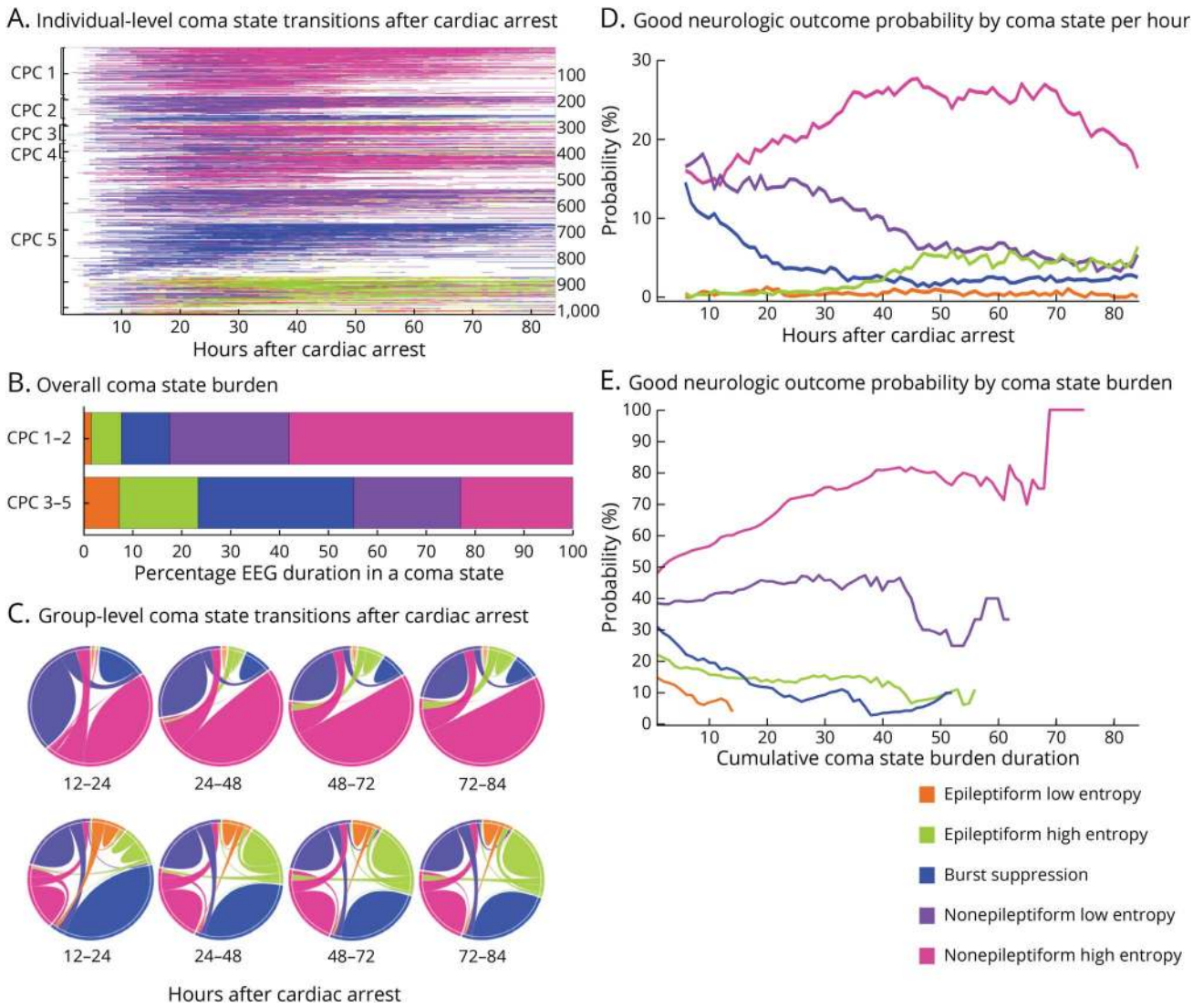


Representative examples demonstrating the evolution of raw EEG and compressed spectral density array in the first 72 hours postcardiac arrest and their corresponding neurophysiology state trajectory in the t-SNE map (5-point star indicated first state and 8-point star last state; arrows show trajectory). CPC 1: Patient with coma recovery with evolution from a suppressed and low amplitude background to delta-theta activity—initial state was burst suppression state evolving to alternation between nonepileptiform low and high entropy states. CPC 2: Patient with coma recovery with evolution from a delta background to theta-alpha activity with a brief period of superimposed epileptiform discharges—initial state was nonepileptiform low entropy, evolving to an epileptiform high entropy state briefly, and followed by primarily a low entropy nonepileptiform state. CPC 3: Patient with moderate neurologic disability with EEG evolving from suppressed to a burst suppressed background followed by alpha activity and periodic discharges superimposed on a continuous background—initial state at the high entropy state cluster located in between the burst suppression and epileptiform clusters evolving to an epileptiform state. CPC 5: Deceased patient with burst suppression with highly epileptiform bursts—initial state was burst suppression evolving to epileptiform low entropy. BSup = burst suppression ratio; CPC = cerebral performance category; En = Shannon entropy; QEEG = quantitative EEG; SpF = spike frequency; t-SNE = t-distributed stochastic neighbor embedding.

generally associated with poor neurologic outcome in a dose-dependent and time-dependent fashion, with no survival being observed in cases in a high epileptiform and low entropy state for more than 15 hours. A high epileptiform and low entropy state often represents generalized periodic discharges superimposed on a suppressed background on visual review, which may reflect selective synaptic failure, thalamocortical disruption severe enough to limit neural oscillatory activity, or augmentation of excitatory neurotransmission and synchronization of epileptiform activity.[37,42] Characterizing different subtypes of epileptiform states and their association with outcomes may be relevant for enrichment of future clinical trials with patients likely to benefit from antiseizure therapy for secondary brain injury prevention.[43]

Our findings support previous reports showing that early EEG data obtained within the first 48 hours after cardiac arrest is informative about neurologic prognosis despite hypothermia and sedative use.[8,9,19,44-46] We showed that all outcome groups had improvement in background continuity, frequency, and frequency power in the first 48 hours after cardiac arrest; however, individuals with good coma recovery tend to have earlier and larger improvements in background features than those with poor outcomes. The speed and degree of

Figure 6 Neurophysiology States Longitudinal Evolution Postcardiac Arrest



(A) Swimmer plot with individual-level hourly neurophysiology state transitions ranked by CPC score (brackets separate individuals from best to worse score [CPC 1–5]). (B) Burden of neurophysiology states for good (CPC 1–2) and poor (CPC 3–5) neurologic outcome groups. For the good neurologic outcome group, the predominant states were NEHE (58% burden) and NELE (24%), with 10% of recording time in BSup and 8% in EHE or ELE states. In the poor neurologic outcome group, the predominant state was burst suppression (32%), followed by EHE or ELE (23%) and NELE (23%) or NELE (22%) states. (C) Chord diagram summarizing group-level c neurophysiology state transitions divided into 4 epochs ranging from 12 to 84 hours for good (CPC 1–2) and poor (CPC 3–5) outcome groups (6-hour block transitions). The outer circle in each diagram is equivalent to a donut chart, and their colors represent the final state, and the length of each donut component is the proportion of individuals ending on that state. The width of the chords projecting between states indicate the transition proportion between these 2 states; the chord color is set to the state with the largest net gain between initial and final states. Arches without chord projections between states represent neurophysiology state stationarity within that epoch. (D) Hourly good neurologic outcome probability by neurophysiology state. (E) Good neurologic outcome probability based on cumulative neurophysiology state burden. BSup = burst suppression ratio; CPC = cerebral performance category; EHE = epileptiform high entropy; ELE = epileptiform and low entropy; NEHE = nonepileptiform high entropy; NELE = nonepileptiform low entropy.

recovery of these QEEG features may reflect the degree of resilience of corticothalamic networks to hypoxic-ischemic brain injury and patient's potential for coma recovery.[47] These data support previous reports that up to 1 in 6 cases with early burst suppression may have good outcome.[19,21,31,34] We further confirmed the relevance of early dynamics of neurophysiology states by demonstration that deep learning and machine learning models incorporating early longitudinal EEG data from the first 48 hours after ROSC have superior performance to time-insensitive models.[28,29] A limitation of these prior studies that should be addressed in future analyses that aim to leverage these findings to create improved prognostic models is incorporation of repeated measures model design. In real-world clinical practice, the patient's likelihood for recovery is frequently reassessed as new data become available, but it also takes into consideration previous assessments of recovery likelihood. Important prognostic information may be lost without early continuous EEG monitoring because the value of EEG information may decrease for certain EEG patterns after 24 hours.[8,9,18]

A major strength of this study is the use of data from 7 large hospitals from the United States and Europe. We showed that there is substantial variability in some QEEG trends across participating centers. Specifically, spike frequency and burst suppression trends varied in the good neurologic outcome group (Figure 2D). This finding highlights the importance of pursuing external validation when using QEEG findings in outcome prediction models with data from several institutions and how combining heterogeneous datasets may better capture the variability of EEG trajectories after cardiac arrest and its relationship with outcomes, an important feature for replicable and generalizable algorithms.

This study has notable limitations. Our final model included EEG data exclusively, and we were unable to compare this approach directly with standard multimodal prognostication. We aimed to develop a relatively simple automated EEG classification method, but we acknowledge that incorporation of other neurologic prognostication metrics such as serial neurologic examinations, EEG reactivity, identical burst classification, neuroimaging, serum biomarkers, and sedative information would likely improve the already good performance of the proposed EEG-only method. Specifically, sedatives can affect EEG recordings, and it is plausible that the states and state trends identified could be partially confounded by sedative modulation such as suppression of background activity or epileptiform discharges. High-resolution sedation information was not available for this cohort to enable evaluation of sedative effects on EEG. Clinicians were not blinded to the original EEG data used in our analysis nor other neurologic prognostication results during clinical care; therefore, these tests results might have affected decision about withdrawal of life-sustaining therapies and self-fulfilling prophesy. Heterogeneity of EEG features and clinical practice between hospitals could affect group-level estimates based on EEG data and reduce generalization of the results in other cohorts. While this study does not involve predictive modeling, this observation is substantiated in a previous study by the variability in model performance seen with a leave-one-hospital out analysis involving this cohort, which highlights the need for robust models and local validation within the intended use cohort.[28,29] This study focuses on the description of QEEG trends and comparisons between outcome groups, which could be prone to type I errors. Our other studies using multivariable analysis using QEEG features partially address this limitation and highlight the importance of these QEEG features when creating models for outcome prediction.[9,29] This study was retrospective; therefore, duration of EEG varied between patients, and EEG termination cannot be assumed to be at random. Prospective studies with fixed EEG monitoring times and delay in neuroprognostication for withdrawal of life-sustaining therapies would be necessary to address this potential source of bias. Of importance, in prior work on creating outcome prediction models using EEG, most of the improvement in performance happens in the first 48 hours postcardiac arrest. Therefore, the impact of missing EEG data on the differences in patterns between outcome groups in this study are likely small because EEG discontinuation most of the time happens after this time point for our cohort.[28,29] Outcome prediction models for cardiac arrest prognostication should evaluate the impact and confounding from withdrawal of life-sustaining therapies and the time of death in relation to the time prognostic tests are performed. Our analysis about state burden are limited by variability in EEG initiation and termination between patients, including bias from withdrawal of life-sustaining therapies. Not all centers could perform prospective long-term outcome collection, which could have contributed to biases. However, the use of best CPC at discharge has been supported in other studies in cardiac arrest, demonstrating that discharge scores are similar to scores from long-term assessments.[48,49] The fact that less than 2% of cases in our study required retrospective chart review for outcome determination indicates that the impact of missing prospective long-term outcomes for all individuals is likely low.

The neurophysiology underlying acute coma recovery is dynamic, and the early trajectory of neurophysiology states reflects the likelihood of functional recovery from coma after cardiac arrest. Resilience to hypoxic-ischemic brain injury is reflected by the type and pace of improvement of EEG background continuity, epileptiform activity, and entropy trends in the first 48 hours after cardiac arrest, and the level of background entropy may help differentiate patients with epileptiform activity who have potential for recovery from those with irreversible brain injury.[29] Neurophysiology-informed biomarkers of acute coma recovery hold promise to advance knowledge about coma neurophysiology and enrich interventional clinical trials focused on accelerating neurologic recovery from coma after acute brain injury and preventing self-fulfilling prophesy from premature withdrawal of life-sustaining therapies.

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