The Significance of Emerging Electroencephalographic Patterns in Critically Ill Patients

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Statement of Originality

This is to certify the content of this thesis is my own original work. This thesis has not been submitted for consideration for any other degree or purpose. I certify that the intellectual content of this thesis is the product of my own work and that all the assistance received in preparing this thesis and sources have been acknowledged.

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Authorship Attribution Statement

The chapters presented in this thesis resulted from research undertaken at the Western Sydney (Baludarri) Precinct, The University of Sydney, Sydney, Australia in conjunction with Yale School of Medicine, New Haven, Connecticut, United States of America.
I identified the relevant clinical questions, designed the studies, collected patient data, performed statistical analysis, and prepared and reviewed manuscripts for publication.

The following chapters have been published in peer reviewed journals/ books:

Chapter 1: *Introduction and Literature Review.* I contributed to the literature in the definition and classification of critical care EEG. I am the second author and manuscript generating author of the American Clinical Neurophysiology Society's (ACNS) standardized critical care EEG terminology guideline. I joined Hirsch and Brenner as a co-author of the "Atlas of EEG in Critical Care" and the first author of three book chapters on critical care EEG and rhythmic and periodic patterns.

Chapter 3: *Association of Rhythmic and Periodic Patterns with Seizures and Status Epilepticus.* I designed the study, collated patient data, was involved in data analysis with statistician assistance for predictive modelling, and was the co-first author of the manuscript being involved in preparation and review.

Chapter 4: *Lateralized Rhythmic Delta Activity including unilateral and bilateral asymmetric variants.* I designed the study, collated patient data, performed data analysis, and was responsible for manuscript preparation and review.

Chapter 5: *Burst Suppression with Highly Epileptiform Bursts (HEBs) in the Determination of Subsequent Seizures in patients with Status Epilepticus.* I designed the study, collated patient data, performed data analysis, and was responsible for manuscript preparation and review.

Chapter 6: *Burst Suppression with Identical Bursts (IBs) in the Prognostication in Adult Survivors of Cardiac Arrest.* I designed the study, collated patient data, performed data analysis, and was responsible for manuscript preparation and review.

In addition to the statements above, in cases where I am not the corresponding author of a published item, permission to include the published material has been granted by the corresponding author.

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As primary supervisor for the candidature upon which this thesis is based, I can confirm that the authorship attribution statements above are correct.

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Publications Arising from this Thesis

Book Publications:

Hirsch LJ, Fong MWK (co-author), Brenner RP. Hirsch and Brenner's Atlas of EEG in Critical Care. *Second Edition ed: Wiley Blackwell U.S.A; 2023.*

Chapter Publications:

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Fong MWK, Hirsch LJ. Chapter 10: Rhythmic and Periodic Patterns, Seizures, and Status Epilepticus. *Current Practice of Clinical Electroencephalography. Ebersole JS, Hussain AM, Nordli DR. Wolters Kluwer; 5th edition, 2023*

Fong MWK, Hirsch LJ, Bleck TP. Chapter 117: Electroencephalography in the Intensive Care Unit. *Epilepsy: A Comprehensive Textbook. Engel J, Moshe S. Lippincott Williams & Wilkins USA; 3rd edition 2023*

Guideline Publications:

Hirsch LJ, Fong MWK (guideline review and revision, manuscript preparation and review), Leitinger M, et al. American Clinical Neurophysiology Society's Standardized Critical Care EEG Terminology: 2021 Version. *J Clin Neurophysiol. 2021;38(1):1-29.*

Original Research:

Chapter 3: Snider SB: Fong MWK (co-first authors), Nolan NM, et al. Clinical and Electroencephalographic Predictors of Seizures and Status Epilepticus in 12,450 Critically Ill Adults: A Retrospective Cohort Study. *Crit Care Med. 2023;51(8):1001-1011.*

Chapter 4: Fong MWK, Jadav R, Alzawahmah M, Hussein OM, Gilmore EJ, Hirsch LJ. The Significance of LRDA With Bilateral Involvement Compared with GRDA on EEG in Critically Ill Patients. *J Clin Neurophysiol. 2023;40(5):434-442.*

Chapter 5: Fong MWK, Pu K, Beekman R, et al. Retrospective Visual and Quantitative Assessment of Burst Suppression With and Without Identical Bursts in Patients After Cardiac Arrest. *Neurocrit Care. 2025 Feb 3. doi: 10.1007/s12028-024-02208-7. Epub ahead of print.*

Chapter 6: Fong MWK, Pu K, Jadav R, Khan T, Hirsch LJ, Zaveri HP. Quantitative assessment of burst suppression as a predictor of seizure recurrence in refractory status epilepticus. *Clin Neurophysiol. 2023; 150:98-105.*

Publications Related to Critical Care EEG but Not Included in this Thesis

Original Research:

Sheikh ZB, Dhakar MB, Fong MWK (data collection and analysis, manuscript review), et al. Accuracy of a Rapid-Response EEG's Automated Seizure-Burden Estimator: AccuRASE Study. *Neurology. 2025;104(2): e210234.*

Fong MWK, Stephens E, Brockington A, et al. Status epilepticus in Auckland, New Zealand: Treatment patterns and determinants of outcome in a prospective population-based cohort. *Epilepsia. 2024;65(6):1605-1619.*

Alzawahmah M, Fong MWK (data analysis, manuscript preparation and review), Gilmore EJ, Hirsch LJ. Neuroimaging Correlates of Lateralized Rhythmic Delta Activity, Lateralized Periodic Discharges, and Generalized Rhythmic Delta Activity on EEG in Critically Ill Patients. *J Clin Neurophysiol. 2022;39(3):228-234.*

Abou Khaled KJ, Bou Nasif M, Freiji C, Hirsch LJ, Fong MWK (supervising author). Rapid response EEG with needle electrodes in an intensive care unit with limited resources. *Clin Neurophysiol Pract. 2023; 8:44-48.*

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Journal Articles:

Xiao EY, Wong CH, Kaplan PW, Hirsch LJ, Fong MWK (supervising author). Treating Potentially Ictal Patterns in Critically Ill Populations. Definitions, Misconceptions, and Practical Approaches. *Clin Neurophysiol Pract. 2025 (under review)*

Fong MWK, Hirsch LJ. Twenty years of SIRPIDs: What have we learned? *Neurophysiol Clin. 2024;54(6):103024.*

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Abstract

A large proportion of critically ill patients have altered mental state or coma. In these patients the electroencephalogram (EEG) is the only way of adequately monitoring for seizures and status epilepticus (SE). Historical studies have shown that in critically ill cohorts the vast majority of seizures have no clinical manifestations and would not be detected without continuous EEG monitoring (cEEG). As a result, cEEG has increased exponentially in certain regions around the world. As the amount of cEEG recorded has increased there has been documentation of EEG patterns whereby the clinical relevance of these patterns has only been reported on a preliminary basis.

This thesis aimed to consolidate the associations of rhythmic and periodic patterns (RPPs) with seizures and SE. In addition, it aimed to validate the clinical significance of specific EEG patterns that had either had preliminary reports or no reports at all. The thesis utilized the Critical Care EEG Monitoring Research Consortium (CCEMRC) publicly available database to study the associations of RPPs with seizures and SE. It then identified three specific patterns, bilateral asymmetric lateralized rhythmic delta activity (LRDA-ba), burst suppression with highly epileptiform bursts (HEBs), and burst suppression with identical bursts (IBs) as cohorts to describe or confirm the clinical significance of these patterns.

The CCEMRC database collated the cEEG findings of 12,450 adult patients from three tertiary epilepsy centers in the United States of America. The final analysis of this database provided real world associations of clinical etiologies and RPPs and their modifiers with seizures and SE specifically. The overall rate of seizures in this cohort was 9.8% with 3.5% qualifying as SE. The study found that patients following cardiac arrest, clinical seizures prior to cEEG, brain neoplasms and cEEG findings of Lateralized Periodic Discharges (LPDs), Generalized Periodic Discharges (GPDs), and Brief potentially Ictal Rhythmic Discharges (BIRDs) had particular risks for the development of SE in addition to their previously documented risk of developing seizures.

Large databases are good at determining overall group associations but the contribution of any rare subset of patients/ patterns cannot be determined. The thesis therefore set to assess three specific cohorts within this. A cohort of 258 patients with bilateral asymmetric Lateralized Rhythmic Delta Activity (LRDA-ba) was compared to a 1:1 matched cohort of patients with Generalized Rhythmic Delta Activity (GRDA). This analysis found that LRDA-

ba represented a statistically distinct entity that was comparatively associated with acute focal structural brain injuries and focal EEG features of cortical excitability, including sporadic epileptiform discharges, LPDs, and seizures.

Specific burst suppression patterns have been preliminary reported in single center experiences but not well validated. This thesis confirmed that for patients with refractory status epilepticus (RSE) treated to the point of burst suppression (BS), the success of withdrawal of continuous intravenous antiseizure medication (cIVASM) was not determined by conventional measures of BS, such as duration or amplitude of bursts or interburst intervals, but by how "epileptiform" the bursts were. It also for the first time placed quantitative measures on the epileptiform content of bursts which greatly assists in the generalizability of the findings.

For adult survivors of cardiac arrest identical bursts (IBs) were validated as a very poor prognostic indicator in a North American cohort with a low proportion of early withdrawal of life-sustaining therapy (WLST). In addition, this thesis demonstrated that increasing measures of how "identical" bursts were strengthened these associations.

The thesis overall makes significant headway in our understanding of critical care EEG monitoring. It provides clinicians with robust data to be able to make decisions at the patient level. It consolidated the understanding of RPPs with seizures and extended the understanding of their associations with SE. It provided the first assessment of the clinical significance of LRDA-ba and validated and extended upon initial descriptions of burst suppression with HEBs and IBs. The next stage of critical care EEG research is the progression into well-designed prospective clinical trials and the work completed in this thesis lays the foundations towards achieving this gold standard.

Contents

Abbreviations

ACNS	American Clinical Neurophysiology Society
ASM	Antiseizure medication
ATP	Adenosine triphosphate
AUROC	Area under the receiver operating characteristic
BIRDs	Brief potentially ictal rhythmic discharges
BS	Burst suppression
CCEMRC	Critical Care EEG Monitoring Research Consortium
cEEG	Continuous electroencephalogram monitoring
cIVASM	Continuous intravenous antiseizure medication
CPC	Cerebral performance category
CT	Computed tomography
EDs	Epileptiform discharges
EEG	Electroencephalogram
ESE	Electrographic status epilepticus
ESz	Electrographic seizure
FIRDA	Frontal intermittent rhythmic delta activity
GCS	Glasgow coma scale
GCSE	Generalized convulsive status epilepticus
GPDs	Generalized periodic discharges
GRADE	Grading of recommendations assessment, development, and evaluation
GRDA	Generalized rhythmic delta activity
HEBs	Highly epileptiform bursts

IBs	Identical bursts
IBI	Interburst interval
IPH	Intraparenchymal hemorrhage
IRB	Institutional review board
IV	Intravenous
LPDs	Lateralized periodic discharges
LRDA	Lateralized rhythmic delta activity
LRDA-ba	Bilateral asymmetric lateralized rhythmic delta activity
MRI	Magnetic Resonance Imaging
NCS	Nonconvulsive seizures
NCSE	Nonconvulsive status epilepticus
PDs	Periodic discharges
PLEDs	Periodic lateralized epileptiform discharges
RPPs	Rhythmic and periodic patterns
ROSC	Return of spontaneous circulation
RSE	Refractory status epilepticus
SAH	Subarachnoid hemorrhage
SD	Sporadic epileptiform discharge
SDH	Subdural hematoma
SE	Status epilepticus
SW	“spike-and-wave” “sharp-and-wave”
USA	United States of America
WLST	Withdrawal life-sustaining therapy

Chapter 1: Introduction and Literature Review

Introduction

Continuous monitoring of patients with electroencephalography (EEG) has become an essential component of the care of critically ill patients. In these patients often with altered mental state or coma, the EEG is often the only consistent real time monitor of cerebral activity. It allows the rapid detection of epileptiform patterns and immediate feedback on treatment efficacy. In addition, continuous EEG monitoring (cEEG) has many other utilities including detection of delayed cerebral ischemia, assessment of encephalopathy and coma, and prognostication (especially after cardiac arrest). Continuous EEG monitoring has become widely available, and according to multiple studies it appears to be cost effective, and to improve patient outcomes, including mortality. The greatest difficulty in the care of critically ill patients has been deciphering clinical and EEG heterogeneity. With respect to cEEG itself there are a large range of electrographic patterns, and the terms/ labels provided to these patterns would often vary significantly by clinician or center. This introduction discusses historical perspectives as to the development of cEEG, the currently accepted indications, duration of cEEG required to adequately exclude seizures, classification of findings, and clinical significance of these findings. This forms the background for the development of the clinical questions of this thesis, which focuses on determining the clinical significance of specific EEG patterns in critically ill patients.

Historical Perspectives

At the emergence of critical care EEG approaches were relatively ad hoc. The field emerged from the findings that patients, especially young patients with epilepsy, who then presented with a convulsive seizure followed by altered mental state or coma had a very high rate of purely electrographic seizures (ESz) (with no clinical manifestations) and non-convulsive status epilepticus (NCSE) (Claassen, Mayer, Kowalski, Emerson, & Hirsch, 2004; DeLorenzo et al., 1998). The early stages involved defining the patient populations at particular risk of developing ESz/ electrographic status epilepticus (ESE) (Chin et al., 2006; Claassen et al., 2004; Towne et al., 2000; Wu, Shek, Garcia, Zhao, & Johnston, 2002). Following these determinations the natural question was whether increased detection and

treatment of these seizures improved clinical outcomes. This did seem to hold true with several large North American studies that demonstrated patients who received cEEG had a reduced mortality compared to either those who do not have an EEG, and even those that received a routine (20 min) EEG (Hill et al., 2019; Ney, van der Goes, Nuwer, Nelson, & Eccher, 2013). The caveat to the Hill et al. study was the multivariable analysis did not show improvement in outcome with use of cEEG in those with a primary diagnosis of seizure/status epilepticus, but did show improvement in those with SAH, ICH, and "altered consciousness". Some of the lower mortality in those receiving cEEG may have been related to the cohort being younger (18-39 years 19.4% vs 12.7%, >80years: 10.8% vs 17.8%, $p < 0.001$); however to offset this, patients who received cEEG had worse comorbidity scores (score ≥4: 65.8% vs 56.4%, $p < 0.001$), and were more likely to receive palliative care consultation (12.1% vs 5.3%, $p < 0.001$). In the Hill et al. study, costs were greater in patients receiving cEEG compared to no EEG, but in the Ney et al. group the costs between those receiving cEEG vs. routine EEG were no different (Hill et al., 2019; Ney et al., 2013) . These early studies defined patient populations at particular risk of developing ESz/ ESE and showed that not only did the greater detection of seizures overall lead to better clinical outcomes, but it was relatively cost effective when taken at a population level (Hill et al., 2019; Ney et al., 2013).

Additional evidence to support this was that an increasing burden of recorded seizures were associated with worse functional outcomes across several patient cohorts (De Marchis et al., 2016; Payne et al., 2014). Payne et al. identified that, in a population of critically ill children, if the maximum seizure burden reached 20% per hour (or 12 min of seizure in any given hour), both the probability and magnitude of neurological decline rose sharply, and the odds of neurological decline continued to increase by an odds ratio of 1.13 (confidence interval 1.05-1.21) for every 1% increase in maximum hourly seizure burden (Payne et al., 2014). Similarly, De Marchis et al. showed the detection of any seizure on cEEG in adults with SAH was associated with a greater than threefold increase in the odds of an unfavorable functional outcome at 3 months; furthermore, having greater than 1 hour of seizure on cEEG was an independent predictor of decline (De Marchis et al., 2016). On multivariable analysis, seizure burden was associated with mortality, disability, and lower cognitive scores (De Marchis et al., 2016).

Hence, ESz/ ESE without clinical manifestations is common in critically ill patients. Detection of these seizures, as well as an increase in the burden of these seizures have been

associated with increased harm, in the way of worse functional neurological outcomes and mortality. That cEEG remains the only reliable way to detect and measure these harms, saw a drastic increase in the use of cEEG around the world, although several regions were greater universal adopters of this ethos (Hilkman, van Mook, Mess, & van Kranen-Mastenbroek, 2018; Hill et al., 2019; Park et al., 2016).

As the sheer amount of cEEG recorded began to grow it became evident it had clinical utility outside of seizure detection (discussed in indications). There needed to be some guide as to which patients would value the most from cEEG given that the test has a high requirement for technical training and maintenance (duration of cEEG). Furthermore, clinicians frequently encountered EEG patterns that were not seizures, which required standardized terminology to reliably define and classify these patterns to allow for multicenter research studies in an effort to understand their significance (classification).

Indications for continuous EEG monitoring

The spectrum of patients that could benefit from cEEG has expanded greatly over the past few decades. Non-convulsive seizures are common. Of all patients who have seizures in the ICU, between 75% and 92% will have purely non-convulsive seizures that would not have been detected without cEEG (Claassen et al., 2004; Herman et al., 2015; Limotai et al., 2019). In addition to seizure detection, cEEG is critical in the titration of highly sedating anti-seizure medications (ASMs), tracking the degree of encephalopathy in patients with a poor clinical examination, detecting delayed cerebral ischemia, and assisting with the prognostication of patient outcomes. The most common indications for cEEG were outlined in a "*Consensus Statement on Continuous EEG in Critically Ill Adults and Children 2015"* issued by the American Clinical Neurophysiology Society (ACNS; www.acns.org) (Herman et al., 2015). These have been summarized in table 1. The consensus statement covers common indications for cEEG, but as our understanding of disease processes, and EEG patterns in these conditions, expands so does the utility of cEEG.

Indications for Continuous EEG in Adults and Children (Herman et al., 2015)
Diagnosis of non-convulsive seizures (NCS), non-convulsive status epilepticus (NCSE), and other paroxysmal events
• Persistently abnormal mental status following generalized convulsive status epilepticus (GCSE) or other clinically-evident seizures • Acute supra-tentorial brain injury with altered mental status • Fluctuating mental status or unexplained alteration of mental status without known acute brain injury • Periodic discharges (PDs) on routine or emergent EEG • Requirement for pharmacological paralysis (e.g., therapeutic hypothermia or extracorporeal membrane oxygenation [ECMO]) and risk of seizures • Clinical paroxysmal events suspected to be seizures
Assessment of efficacy of therapy for seizures and status epilepticus
• To monitor the response of seizures and status epilepticus (SE) to treatment • For patients with refractory status epilepticus (RSE; to monitor the efficacy of continuous intravenous antiseizure medications) • Recurrence of altered consciousness in a patient with known prior NCS • Usually for 24 hours after the last NCS to ensure seizures have not reoccurred • Usually for 24 hours continuous intravenous ASMs have been withdrawn to ensure seizures have not reoccurred
Adjunct method to identify delayed cerebral ischemia in high-risk patients (largely those following sub-arachnoid hemorrhage [SAH])
Monitoring of sedation and high-dose suppressive therapy
• Pharmacologically-induced coma • Pharmacologically-induced burst-suppression
Assessment of severity of encephalopathy and prognostication
• Severe traumatic brain injury • Hypoxic-ischemic encephalopathy after cardiac arrest • Severe SAH

Table 1: Indications for continuous EEG (cEEG). The table outlines the most common indications for cEEG in critically ill patients. The table does not list all the indications for cEEG and new uses and indications for cEEG monitoring emerge regularly. Adapted from Herman, S. T., et al. (2015). *Consensus Statement on Continuous EEG in Critically Ill Adults and Children, Part I.* Journal of Clinical Neurophysiology 32(2): 87-95.

Appropriate duration of continuous EEG monitoring

Continuous EEG has great utility, but a limiting factor for many centers has been the resources required to perform high quality, prolonged cEEG recording that is regularly reviewed by expert practitioners. A valid question has been, the extent to which cEEG benefits patients compared to performing a shorter (20 – 60 min) recording. There is little doubt that a greater number of abnormalities, including seizures, are detected with more

prolonged recording (A. F. Struck, Osman, et al., 2017). Limotai et al. performed a meta-analysis including critically ill patients with a mixed cause of admission. In this group, routine EEG detected either non-convulsive seizures (ESz) or non-convulsive *status epilepticus* (ESE) in 6.3% of patients, whereas cEEG detected ESz or ESE in 15.6% of cases (Limotai et al., 2019). Thus, a "routine" EEG will detect seizures in under half of patients who go on to have them documented on more prolonged recording. The rate of ESz on cEEG increased to 23.9% if there was a central nervous system infection, 22.6% in patients post cardiac arrest, and 32.9% following resolution of convulsive SE (Limotai et al., 2019).

Although the ability to perform cEEG has expanded greatly in many centers, this capacity is rarely unlimited. The role of the critical care EEGer often involves the prioritization of one EEG over another. In such instances, it is valuable to understand the patients at particularly high risk of seizures and therefore are at greatest risk of additional seizure related brain injury. Several cohort studies have demonstrated the strongest independent risk factors for the development of seizures on the EEG. These risk factors in order of strength are 1) coma at the beginning of the cEEG, 2) being less than 18 years of age, 3) having a history of epilepsy and 4) convulsive seizures (including subtle motor phenomena) prior to monitoring and during the intercurrent illness (Claassen et al., 2004; Schmitt, 2017). Etiology and the initial findings of the EEG greatly modify this risk. Processes with a particularly high rate of seizures are post-cardiac arrest, acute supratentorial brain injury of any sort, CNS infection and CNS tumors (including extra-axial tumors) (Limotai et al., 2019; Newey, Kinzy, Punia, & Hantus, 2018).

The risk of seizures based on interictal findings can be estimated using risk score calculators, such as 2HELPS2B. 2HELPS2B is a scoring system that gives interictal EEG findings a value (Table 2); having a prior clinical seizure is the only non-EEG feature included in the scale. The sum of these values is then added to provide a risk that a patient will go on to have a recorded seizure (Table 3).

2HELPS2B Scoring System	Points assigned
2Hz epileptiform activity (any GRDA, LRDA, GPDs, LPDs, or BIPDs with a frequency of greater than 2 Hz)	1
Epileptiform discharges (sporadic)	1
LPDs or LRDA or BIPDs	1
Plus features (presence of any plus modifier, rhythmic, fast or sharp)	1

Seizures (any history of seizures, acute or remote)	1
2BIRDs (Brief potentially ictal rhythmic discharges)	2

Table 2: 2HELPS2B Risk Calculator. The 2HELPS2B risk calculator takes findings from the interictal EEG and assigns them a point score. These scores are added together to give a total added score. The rate of seizure within 72h of recording has been characterized for each sum total (Table 3). GRDA (generalized rhythmic delta activity), LRDA (lateralized rhythmic delta activity), GPDs (generalized periodic discharges), LPDs (lateralized periodic discharges), or BIPDs (bilateral independent periodic discharges). Adapted from Struck, A. F., et al. (2017). *Association of an Electroencephalography-Based Risk Score with Seizure Probability in Hospitalized Patients.* JAMA Neurology 74(12): 1419.

2HELPS2B total added score	Risk of seizure within 72 hours
0	5%
1	12%
2	27%
3	50%
4	73%
5	88%
6 or 7	>95%

Table 3: Risk of seizure within 72 h for each 2HELPS2B points score. The left column is the total added score determined from the 2HELPS2B scoring system (table 2). For each sum total the rate of seizure within 72h of recording has been determined (right column). It is intuitive that the greater the number of interictal epileptiform findings, the greater the risk of seizures. This is reflected with the higher the total score, the higher the risk of seizures. Note: the total scores of 6 or 7 are grouped as no patient in the study had a total of 7 points. Adapted from Struck, A. F., et al. (2017). *Association of an Electroencephalography-Based Risk Score with Seizure Probability in Hospitalized Patients.* JAMA Neurology 74(12): 1419. This table was reproduced with permission from the American Medical Association.

The 2HELPS2B score consolidated the risk of seizure over 72 hours based on the initial 60 minutes of recording but also with careful modeling allowed the estimation of the duration of required to adequately exclude those seizures (A. F. Struck, Osman, et al., 2017; Aaron F. Struck et al., 2020). "Adequately exclude" was defined as either the subsequent risk of seizure dropping below 5% or 2% depending on the clinical suspicion (Aaron F. Struck et al., 2020; A. F. Struck, Ustun, et al., 2017).

This modelling is best visualized by Figure 1 that demonstrated the risk of subsequent seizures over time based on the 2HELPS2B score. For practical purposes, the model was further refined and we now have the duration of recording without seizures required for the seizure risk within 72 hours to fall below 5% and 2% respectively (Table 4) (Aaron F. Struck et al., 2020).

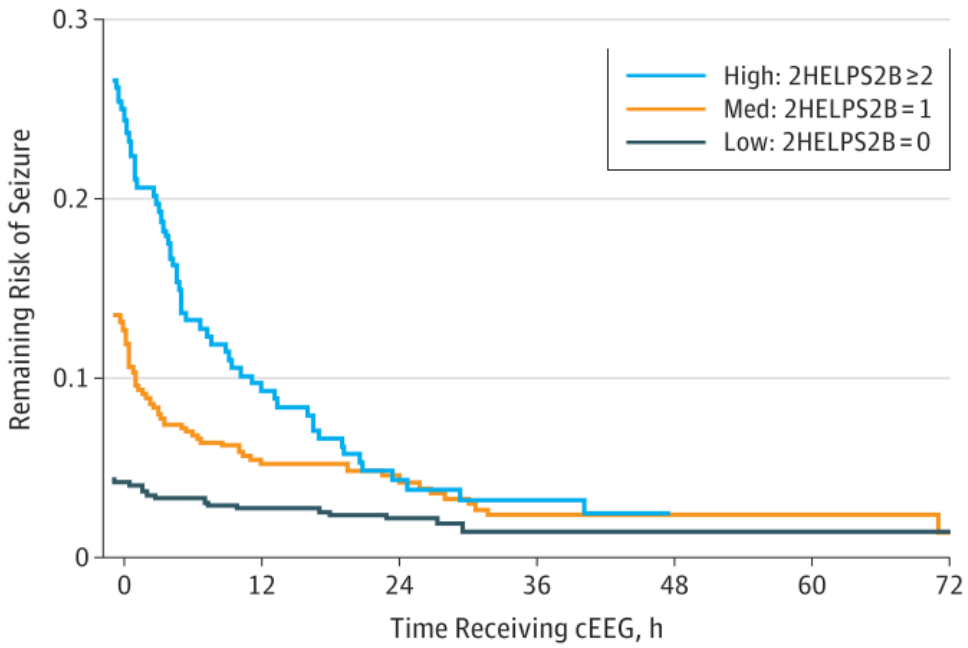

Figure 1: Time-dependent seizure risk: risk stratification with 2HELPS2B score. This figure demonstrates the remaining risk of seizure (Y axis) vs. the time of cEEG monitoring without seizures. For each line it can be seen that the probability of seizures is the highest at the beginning and then as time goes on the longer the recording without any seizures this probability significantly falls. These risks have been provided based on the 2HELPS2B score (legend). Notably when the 2HELPS2B score is low (in particular 0) then the probability of seizures is low and much of this risk exists within the first 60 minutes of recording. For higher 2HELPS2B scores the probability of seizures was high, which takes a longer duration of recording for this probability to subsequently fall below 5% and 2% (Table 4). cEEG: continuous EEG monitoring. Reproduced from Struck A.F. et al., Assessment of the Validity of the 2HELPS2B Score for Inpatient Seizure Risk Prediction. JAMA Neurology. 2020;77(4):500.

2HELPS2B score at 60 min of cEEG	Predicted risk of seizure over 72 hours	Duration of cEEG without seizures required:	
		For seizure risk to fall below 5%	For seizure risk to fall below 2 %
0	3.1%	1 hr.	3.3 hrs.
1	12.0%	12 hrs.	29 hrs.
≥2	>25%	>24 hrs.	>30 hrs.
Excludes cardiac arrest patients			

Table 4: Duration of cEEG without seizures required until the risk of seizure drops below 5% and 2% stratified by the 2HELPS2B score. This has been further simplified; when including the initial EEG findings, coma is no longer an independent predictor. In addition to the duration of prolonged EEG without seizures required for the seizure risk in 72h to fall below 5%, the model also provides the duration required for the risk to fall below 2% (which can be valuable in providing additional reassurance to clinical teams). cEEG: continuous EEG monitoring. Adapted from Struck A.F. et al., *Assessment of the Validity of the 2HELPS2B Score for Inpatient Seizure Risk Prediction.* JAMA Neurology. 2020;77(4):500.

The above modelling was mostly in the context of seizure detection. There are select cohorts in which cEEG (compared to routine EEG) may not change the clinical outcome (Alvarez, Sierra-Marcos, Oddo, & Rossetti, 2013; Eskioglou, Stähli, Rossetti, & Novy, 2017; A. O. Rossetti et al., 2020). In the post cardiac arrest setting, Alvarez et al. reported that in a small patient cohort the utilization of cEEG did not seem to affect outcome when compared to repeated routine EEGs (Alvarez et al., 2013). Eskioglou et al. performed a similar comparison in 29 patients with non-convulsive SE without coma who underwent repeated extended EEG, who had similar outcomes (return to baseline condition, new disability or death) when compared to a historical age-matched group that only received routine EEG (Eskioglou et al., 2017). The limitations to this trial are the small sample size (at risk of type II error) and the exclusion of patients with coma (one of the strongest risk factors for the development of seizure). More recently, Rossetti et al. performed the only prospective, large scale, randomized trial on the clinical utility of cEEG. In this study, 402 adults with "altered consciousness and no recent seizure" were randomized to either cEEG recording (30-48 hours, with no overnight monitoring of the EEG) vs. routine EEG (two 20-30 min recordings over 48 hours [without repetition within the same day]) (A. O. Rossetti et al., 2020). The mortality (primary outcome measure) in these two groups was no different, and there was no obvious difference in functional outcome. Limiting factors of this trial were; 1) the average time from admission to EEG commencement was >2.5 days, however all EEGs were performed within 4 hours of being requested (meaning some of these EEGs may not have

been indicated at the time of admission), 2) the lack of overnight monitoring of the EEG (lead to delayed treatment), and only 21% of patients that underwent cEEG had any change in treatment, meaning a minority had any intervention that could have altered the primary outcome. It should be noted that the Rossetti et al. study specifically excluded patients with recent seizures (up to 36 hours prior to randomization) or status epilepticus (96 hours prior), as it was felt that those patients required cEEG (A. O. Rossetti et al., 2020). It may be that the outcome of patients with a low risk of seizure would not be altered by cEEG (vs. routine). Not performing cEEG in these patients would arguably miss a lower proportion of their overall seizure burden, which would mean very large numbers of patients would have to be compared to assess if modest reductions in this burden could be translated into meaningful clinical measures. The broader utility of cEEG is not in question, but from a resource management perspective, there may be select sub-populations where shorter duration EEG (or longer duration of EEG) may be appropriate. A good example is that when using cEEG to monitor for seizure recurrence in a patient with refractory status epilepticus on highly sedating intravenous (IV) antiseizure medications (ASM) the utilization of the above scores and literature would not apply and clinical discretion becomes paramount in those settings.

Classification of critical care EEG

There has been considerable effort towards standardized terminology for the classification of cEEG. This has been performed as a world-wide expert consensus and culminated in the American Clinical Neurophysiology Society (ACNS) guideline on the standardized terminology in critical care EEG. Prior to the ACNS standardization, there was no widely accepted terminology for the classification of EEG patterns in critically ill patients. Although it is true that some of the language was widely adopted (e.g., Frontal Intermittent Rhythmic Delta Activity [FIRDA]), Periodic Lateralized Epileptiform Discharges [PLEDs], or triphasic waves [TW]) what was understood by these terms differed between practitioners and more importantly differed greatly between centres. In this context, most historical studies on Rhythmic and Periodic Patterns (RPPs) were limited to a single or a few centre(s). In addition to this, the historical terms did not accommodate for newly recognized patterns. It was for these reasons that in the early 2000's a subcommittee of the ACNS set out to "standardize terminology of periodic and rhythmic EEG patterns in the critically ill to aid in future research involving such patterns" (L. J. Hirsch et al., 2005). The initial proposed terminology, intended primarily for research, was published in 2005 (L. J. Hirsch et al., 2005). This was

presented at many meetings on several continents, subjected to multiple rounds of testing of inter-rater reliability, underwent many revisions, and was then published as an ACNS *clinical* guideline in 2012, with the manuscript printed in 2013 (L. J. Hirsch et al., 2013). This guideline allowed for the study of large numbers of patients with these patterns, across multiple practitioners that were based in many centres (mostly in North America, but also around the world). These studies greatly furthered the understanding of the patterns associated with seizures, the patterns that potentially alter prognosis, and the specific characteristics of those patterns that determined these outcomes. Since that initial clinical guideline, the volume of critical care EEG and related research has continued to grow. The result was that even more patterns were being discovered and the clinical significance of these new patterns, and how they interact with the current state of understanding needed to be expanded.

The ACNS therefore provided an exhaustive update to the standardized critical care EEG terminology guideline in 2021 (L. J. Hirsch et al., 2021). Although at first glance the updated standardized terminology can be daunting, it is worth remembering that it was designed to be all inclusive. Many patterns in critically ill patients are relatively rare, seen only once or twice per month in a single centre (even one that performs large volumes of continuous EEG). The goal of the terminology was to provide a widely accepted, standardized definition of these patterns, so that large numbers of these patients could be collated (which often requires collaborative efforts from several centres). Only by this method can an attempt be made to determine the clinical implications of such patterns. This introduction is not designed to replace the published ACNS standardized critical care EEG terminology guideline, 2021 version. It does however importantly discuss the rationale behind many of the changes that were made to terms; introduce emerging patterns/terms that were not present in the original 2012 version; which sets the scene for discussing current understanding of mechanisms and clinical significance of many of the patterns. This classification forms the foundation of this thesis and original research works and all terminology throughout this thesis has been classified in accordance with the ACNS terminology.

The framework for classification of EEG in critically ill patients is based on principles encountered in reviewing any surface EEG. An EEG reader begins by assessing the background EEG, determining the Rhythmic and Periodic Patterns (RPPs), and then identifying seizures or *status epilepticus.* The major difference in the critical care setting is that the prevalence of RPPs and other epileptiform patterns is high; and the distinction

between what is an interictal RPP and what is a seizure can be difficult). An easy-to-follow summary of this approach was set out in the reference chart of the ACNS terminology guideline (Figure 2). If one diligently works through the classification for each record, it soon becomes second nature, and the advantages of classifying critical care EEG become apparent. For example, for a given patient the burden of patterns can be objectively followed over multiple reporting periods, even with different readers, and group inferences for a particular pattern can be made.

The Rhythmic and Periodic Patterns (RPPs) form a reasonable component of the standardized terminology, and the original 2012 version mainly focused on those findings. Rhythmic and periodic patterns refer to any "rhythmic" (repetition of a waveform with relatively uniform morphology and duration and *without* an interval between consecutive waveforms) or "periodic" (repetition of a waveform with relatively uniform morphology and duration *with* a clearly discernible inter-discharge interval between consecutive waveforms and recurrence of the waveform at nearly regular intervals) pattern; RPPS also includes "spike-and-wave"/ "sharp-and-wave" (SW) (L. J. Hirsch et al., 2021). RPPs can be classified in accordance with "main term 1" (localization), and "main term 2" (morphology) descriptors of the ACNS terminology (L. J. Hirsch et al., 2021). Examples of commonly encountered patterns and their descriptions are demonstrated in Figure 3. These main patterns can then be further refined by applying the "major" and "minor" modifiers (Figure 4). The inter-rater agreement was "almost perfect" for main terms 1 and 2, and either "almost perfect" or "substantial" for many of the major and minor modifiers (Gaspard et al., 2014). Given RPPs have been very well defined with excellent inter-rater reliability large multicentre EEG databases were formed to better study these patterns. One example was the freely available database published by the Critical Care EEG Monitoring Research Consortium (CCEMRC), which formed the basis for patient identification for several chapters of this thesis.

ACNS Standardized Critical Care EEG Terminology 2021: Reference Chart

A. EEG Background

Symmetry	Background EEG frequency	PDR	Continuity	Reactivity	State Changes	Cyclic Alternating Pattern of Encephalopathy (CAPE)	Voltage	AP Gradient	Breach effect
Symmetric	**Beta**	**Present** Specify frequency	**Continuous:** <1% **periods of suppression** (<10 μV) or **attenuation** (≥10μV but <50% of background voltage)	**Reactive**	**Present with normal stage N2 sleep transients**	**Present**	**High** ≥150 μV	**Present**	**Present**
Mild asymmetry <50% Voltage OR 0.5-1 Hz Frequency	**Alpha**	**Absent**		**Unreactive**	**Present but with abnormal stage N2 sleep transients**	**Absent**	**Normal** ≥20 to <150 μV	**Absent**	**Absent**
Marked asymmetry ≥50% Voltage OR >1 Hz Frequency	**Theta**	**Unclear**	**Nearly continuous:** 1-9% **periods of suppression attenuation**	**SIRPIDs only**	**Present but without stage N2 sleep transients**	**Unknown/unclear**	**Low** 10 to <20 μV	**Reverse**	**Unclear**
	Delta		**Discontinuous:** 10-49% **periods of suppression** or **attenuation**	**Unclear**	**Absent**		**Suppressed** <10 μV		
			Burst-suppression or **Burst-attenuation:** 50-99% **periods of suppression** or **attenuation**	**Unknown**					
			Suppression: >99% **periods of suppression** or **attenuation**						

Localization of Bursts (G/ L/ BI/ UI/ Mf)
Highly Epileptiform Bursts (Present or Absent)
Identical Bursts (Present or Absent)

If Burst-suppression or Burst-attenuation then specify if: ←

B. Sporadic Epileptiform Discharges

Prevalence
Abundant ≥1/10s
Frequent ≥1/min but <1/10s
Occasional ≥1/h but <1/min
Rare <1/h

C. Rhythmic and Periodic Patterns (RPPs)

Main term 1	Main term 2
G *Generalized* *- Optional: Specify frontally, occipitally, or midline predominant; or generalized, not otherwise specified.*	**PD** *Periodic Discharges*
L *Lateralized* *- Optional: Specify unilateral, bilateral asymmetric, or bilateral asynchronous* *- Optional: Specify lobe(s) most involved or hemispheric*	**RDA** *Rhythmic Delta Activity*
BI *Bilateral Independent* *- Optional: Specify symmetric or asymmetric* *- Optional: Specify lobe(s) most involved or hemispheric*	**SW** *Spike and Wave* *OR* *Polyspike and Wave* *OR* *Sharp and Wave*
UI *Unilateral Independent* *- Optional: Specify unilateral, bilateral asymmetric, or bilateral asynchronous for each pattern* *- Optional: Specify lobe(s) most involved*	
Mf *Multifocal* *- Optional: Specify symmetric or asymmetric* *- Optional: Specify lobe(s) most involved or hemispheric*	

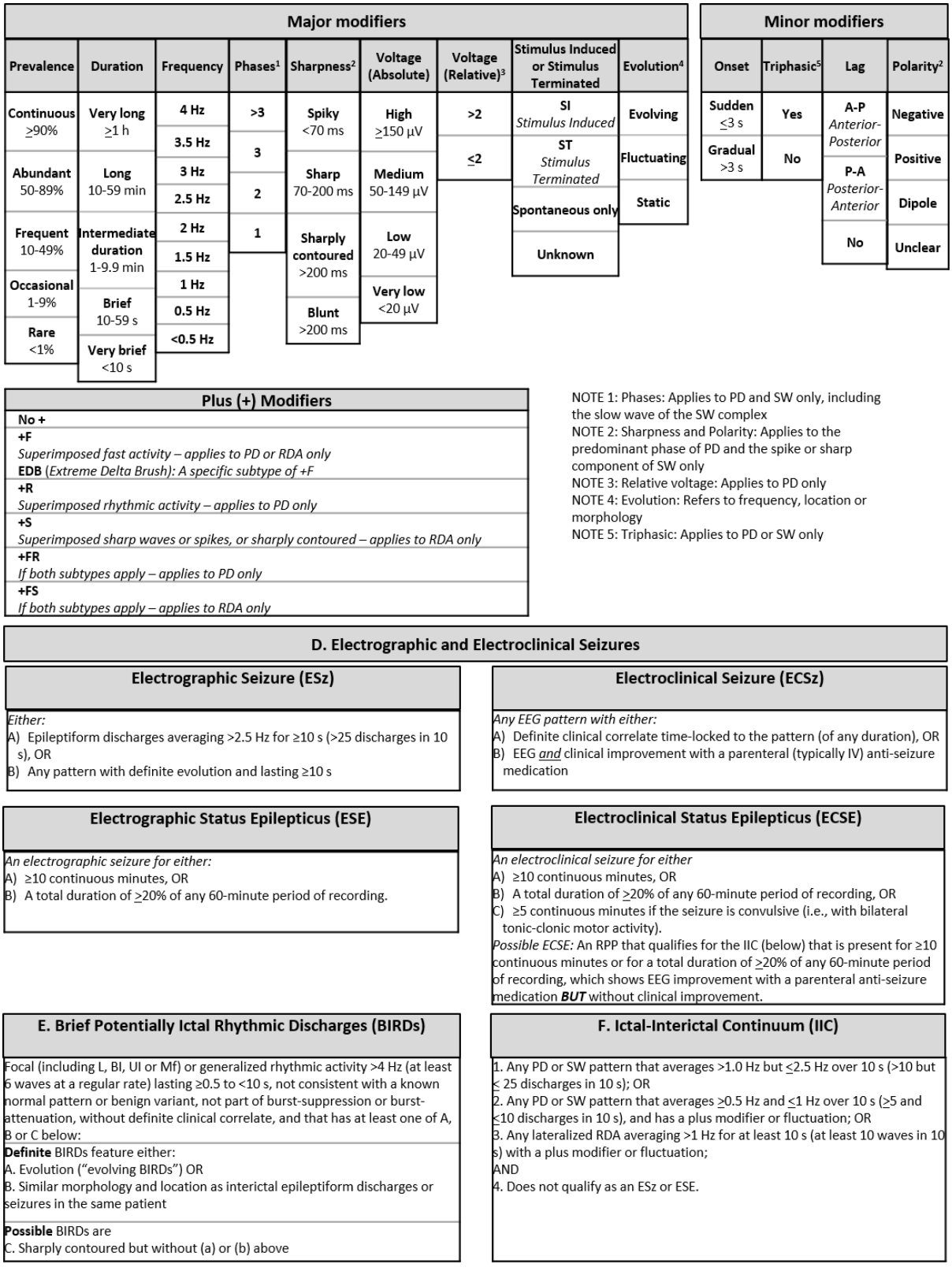

Figure 2: Reference Chart, American Clinical Neurophysiology Society (ACNS) Critical Care EEG Terminology: 2021 version. The ACNS critical care EEG terminology standardized the way the interictal EEG was classified. This allowed large volumes of patients from different centers to be grouped together, and the acute seizure risk defined for each pattern. This reference chart provides an overview of the terms that are included in the consensus paper and the modifiers that allow for

the very accurate classification of a wide variety of findings (both epileptiform and not). Replicated from Hirsch LJ, Fong MWK, Leitinger M, et al. American Clinical Neurophysiology Society's Standardized Critical Care EEG Terminology: 2021 Version. *J Clin Neurophysiol.* 2021;38(1):1-29. Also available at https://www.acns.org/practice/guidelines.

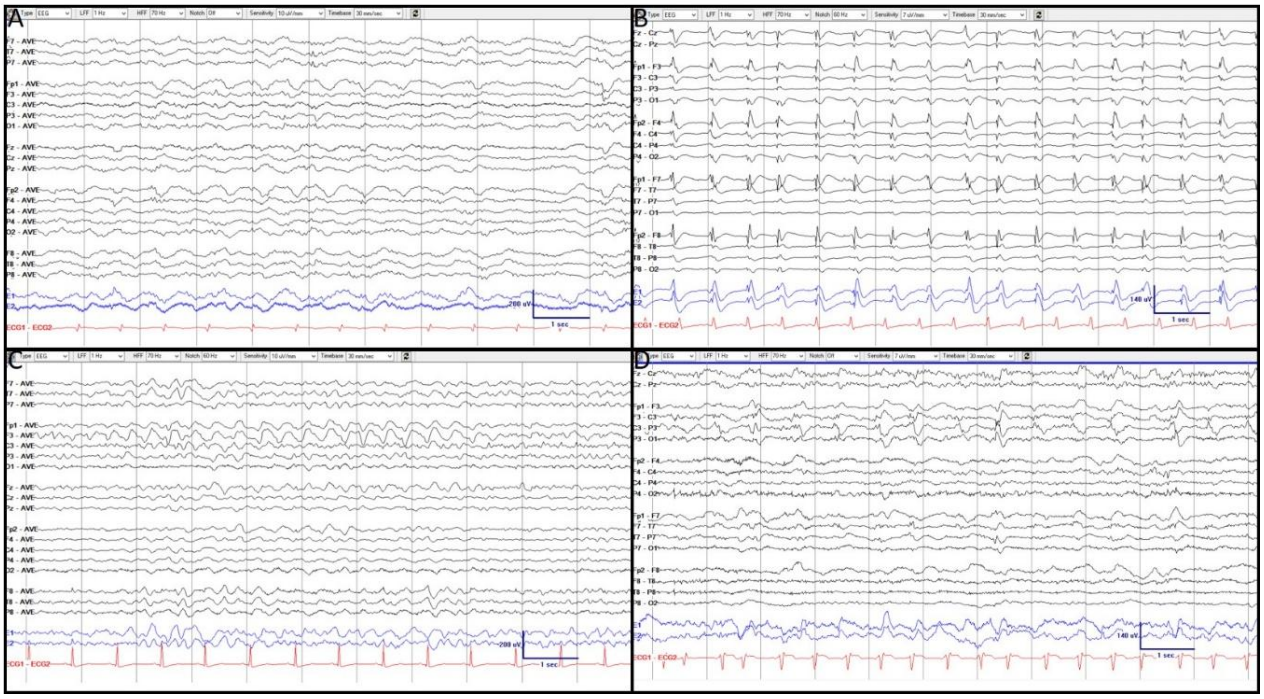

Figure 3: Common rhythmic and periodic patterns. Panel A: Generalized Rhythmic Delta Activity GRDA), from a 64-year-old woman that presented with altered mental state (AMS) in the context of polysubstance abuse and COPD. Referential longitudinal average montage, demonstrating very brief GRDA that is frontally predominant. Panel B: Generalized Periodic Discharges (GPDs), from a 59-year-old male post cardiac arrest. Bipolar longitudinal L/R L/R montage, demonstrating attenuation of background rhythms and GPDs occurring at 1-1.5Hz. Panel C: Lateralized Rhythmic Delta Activity (LRDA), from a 46-year-old male with an acute left sub-dural hematoma (SDH). Referential longitudinal average montage, demonstrating very brief 2Hz LRDA maximal at F3 (the region of the SDH). The patient went on to have electrographic seizures from that region later in the record. Panel D: Lateralized Periodic Discharges (LPDs), from a 57-year-old woman with anti-GAD mediated limbic encephalitis. Bipolar longitudinal L/R L/R montage, demonstrating continuous 1Hz LPDs of the left fronto-central region (maximal at C3). The patient had electrographic seizures from this region and a period of focal non-convulsive status epilepticus (NCSE).

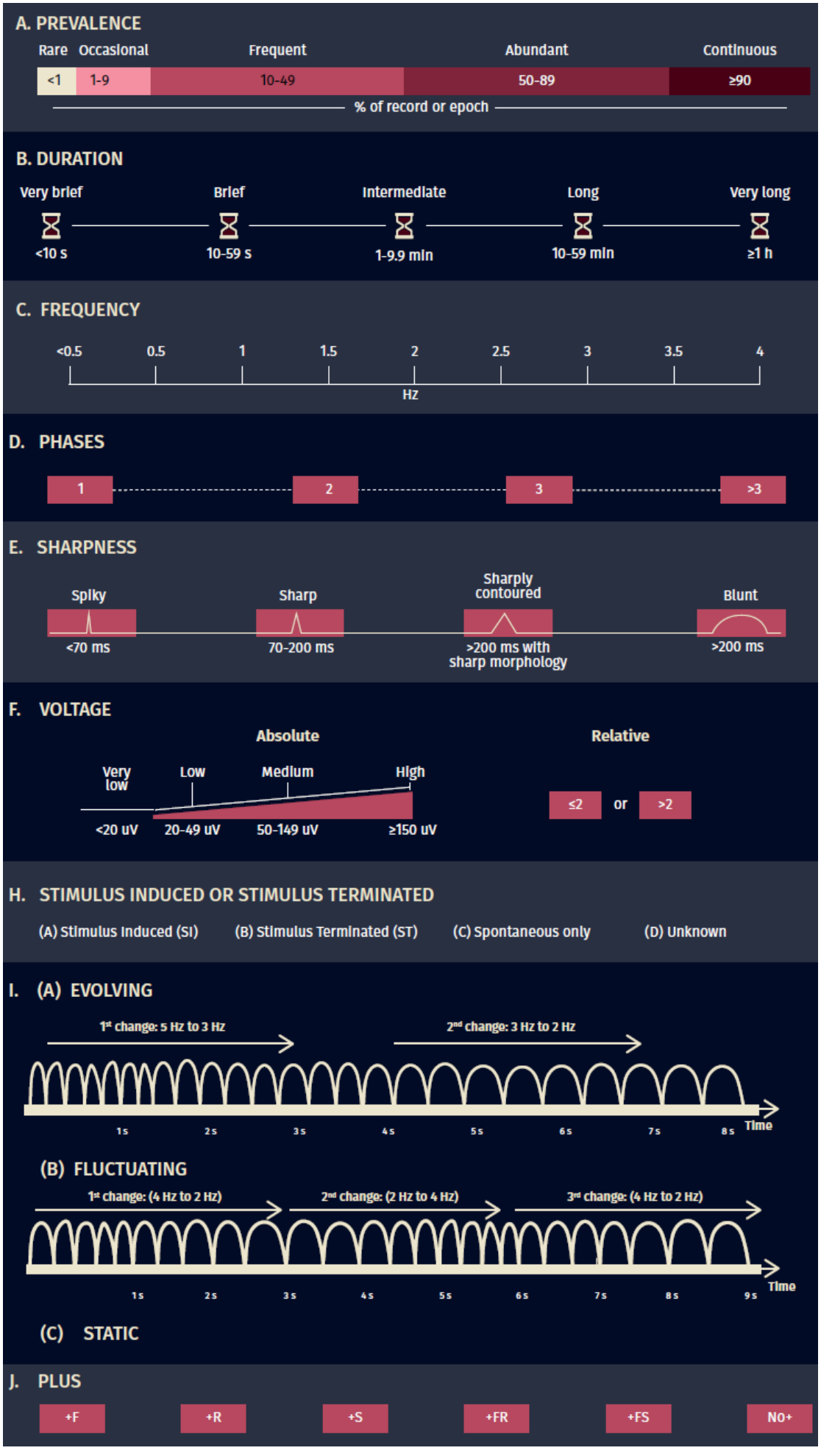
A. PREVALENCE
Rare
Occasional
Frequent
Abundant
Continuous
<1
1-9
10-49
50-89
≥90
% of record or epoch
B. DURATION
Very brief
Brief
Intermediate
Long
Very long
<10 s
10-59 s
1-9.9 min
10-59 min
≥1 h
C. FREQUENCY
<0.5
0.5
1
1.5
2
2.5
3
3.5
4
Hz
D. PHASES
1
2
3
>3
E. SHARPNESS
Spiky
Sharp
Sharply contoured
Blunt
<70 ms
70-200 ms
>200 ms with sharp morphology
>200 ms
F. VOLTAGE
Absolute
Relative
Very low
Low
Medium
High
<20 uV
20-49 uV
50-149 uV
≥150 uV
≤2
or
>2
H. STIMULUS INDUCED OR STIMULUS TERMINATED
(A) Stimulus Induced (SI)
(B) Stimulus Terminated (ST)
(C) Spontaneous only
(D) Unknown
I. (A) EVOLVING
1st change: 5 Hz to 3 Hz
2nd change: 3 Hz to 2 Hz
1s
2s
3s
4s
5s
6s
7s
8s
Time
(B) FLUCTUATING
1st change: (4 Hz to 2 Hz)
2nd change: (2 Hz to 4 Hz)
3rd change: (4 Hz to 2 Hz)
1s
2s
3s
4s
5s
6s
7s
8s
9s
Time
(C) STATIC
J. PLUS
+F
+R
+S
+FR
+FS
NO+

Figure 4: Major modifiers. The infographic depicts the major modifiers of the ACNS terminology. Regarding panel I: "evolution", only evolution/ fluctuation in frequency has been shown. Evolution/ fluctuation can be in frequency, morphology, or location with the details provide in the ACNS terminology. A caveat regarding J: "plus" modifiers. A plus modifier cannot be applied to a term if that characteristic is intrinsic to the pattern (i.e., PDs cannot have "plus sharp", RDA cannot have "plus rhythmic", but they can both have "plus fast"). This graphic demonstrates the "major" modifiers and not the "minor" modifiers. The minor modifiers include: a. "sudden onset" vs. "gradual onset", b. "triphasic morphology", c. "anterior-posterior lag" or "posterior-anterior lag", and d. "polarity". +F *plus* fast, +R *plus* rhythmic, +S *plus* sharp, +FR *plus* fast and rhythmic, +FS *plus* fast and sharp.

A pattern with an unequivocal and strong association with seizures is Brief potentially ictal rhythmic discharges (BIRDs). BIRDs (Figure 5) are defined as focal or generalized rhythmic activity >4 Hz (at least 6 waves at a regular rate) lasting ≥0.5 to <10 s, not consistent with a known normal pattern or benign variant, not part of burst-suppression or burst-attenuation, without definite clinical correlate, and that has at least one of the following features: (L. J. Hirsch et al., 2021)

a. Evolution ("evolving BIRDs", a form of definite BIRDs)

b. Similar morphology and location as interictal epileptiform discharges or seizures in the same patient (definite BIRDs)

c. Sharply contoured but without (a) or (b) (possible BIRDs)

If BIRDs were present during cEEG there was a 75-89% chance that seizures were also present at some stage of the prolonged record; when seizures were adequately treated BIRDs also resolved (Yoo et al., 2021a; Yoo, Rampal, Petroff, Hirsch, & Gaspard, 2014). The internal frequency of BIRDs did not seem to be an independent factor in determining seizure risk; however patients with "evolving BIRDs" had a 100% chance of subsequent seizures (Yoo et al., 2021a).

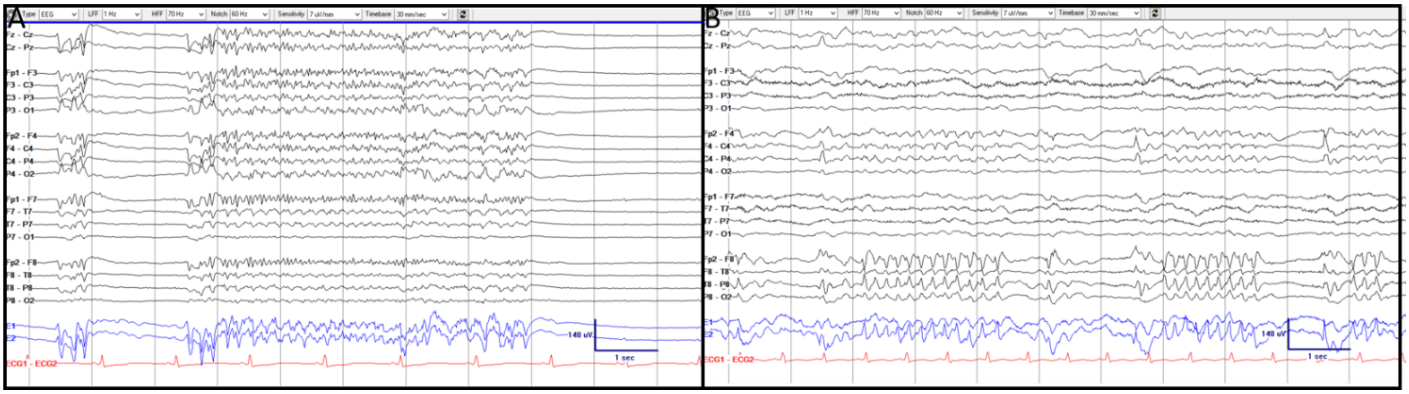

Figure 5: Brief potentially Ictal Rhythmic Discharges (BIRDs). Panel A: BIRDs (Generalized), from a 59-year-old man post cardiac arrest. Bipolar longitudinal L/R L/R montage, demonstrating a suppressed background and then a sudden 5.5 second run of generalized bifrontal predominant 5-6Hz activity with over-riding beta range activity. There is clear evolution within these BIRDs. In the last two seconds of the run of discharges the frequency becomes slower 2.5-3Hz, less rhythmic and the faster rhythms are not as well formed. If the pattern persisted for >10 seconds it would be classified as a seizure. This patient did go on to develop electrographic seizures (with a similar electrographic pattern as the BIRDs but lasting 15-20 seconds) and a period of non-convulsive status epilepticus (NCSE). Panel B: BIRDs (Focal), from a 59-year-old male with traumatic brain injury and seizures. Bipolar longitudinal L/R L/R montage, demonstrating a 2.5 sec, shortly followed by a 1.5 sec, run of rhythmic, sharply contoured 5-6Hz activity in the right temporal region. In prior pages the patient had continuous 1Hz LPDs in that region and shortly after developed focal electrographic seizures.

Clinical significance of continuous EEG findings

EEG background

The classification of background patterns was not a major focus of the terminology in 2012 (published in 2013) (L. J. Hirsch et al., 2013). It has however been increasingly established that several patterns contained within the "background" section hold significant clinical implications, especially regarding prognosis. The most established of these associations are discussed here.

Continuity and Reactivity

“Continuity” and “reactivity” in the correct clinical setting can form a strong prognostic dichotomy. In the example of patents post cardiac arrest, out of all the clinical and electrographic variables studied, “early EEG continuity” and “early EEG reactivity” (“early” being defined as during targeted temperature management [TTM], vs. “late” that was after return to normothermia and off sedation, 48-72 hours into admission), or a “benign” EEG at any stage (“benign” defined as continuous, not suppressed background with reactivity, and without epileptiform discharges) were the only electrographic features that predicted a good outcome (with positive predictive value [PPV] >70% for these measures) (A. O. Rossetti et al., 2017). The only other feature associated with a favourable outcome was a motor response of 3 or more on the GCS (PPV 82.4 ± 73.4-89.4%) (A. O. Rossetti et al., 2017). An unreactive record at any time when not on high dose sedatives was a strong predictor of mortality. If a record was unreactive the false positive rate (FPR) (i.e., the chance that the variable incorrectly predicted death, meaning the chance that they survived) was ≤1.5 % (early unreactive FPR 1.5% [95% confident interval, CI 0.3-4.2%], late unreactive FPR 0.5% [95% CI 0.0-2.7]) (A. O. Rossetti et al., 2017). This was on par with clinical features such as bilaterally abnormal corneal reflexes, bilaterally abnormal pupillary reflexes, early myoclonus; or laboratory measures such as bilaterally absent SSEPs, Neuron Specific Enolase (NSE) ≥75 μg/L, or a “malignant” EEG at any time (“malignant” being defined as suppression or burst-suppression, with or without periodic discharges) (A. O. Rossetti et al., 2017).

The clinical implications of the terms “continuity” and “reactivity” are such that it was recommended that a higher level of certainty be reached before the term “unreactive” is applied to a record (L. J. Hirsch et al., 2021). It was suggested that if an EEG is “unreactive” after one round of stimulation, a second round of standardized noxious stimulation should be performed to confirm the finding and should be applied with the patient in their non-stimulated state. If the EEG was “unreactive” and the patient on sedatives or paralytics at the time they were assessed, it was suggested to include this important caveat in the impression (L. J. Hirsch et al., 2021). It is important to note that if the reactivity is equivocal, even after multiple rounds of standardized stimulation, then it is valuable to use the term “unclear” (again because calling a record “unreactive” will often result in direct inferences of poor prognosis to clinical teams).

Burst-suppression.

Burst-suppression can occur in a wide variety of clinical settings. An EEG that has between 50-99% suppression (i.e., the suppression percent is 50-99%, or the periods of suppression [≥1 second each] comprises 50-99% of the duration of the record) alternating with higher voltage activity classifies as burst-suppression (Figure 6) (L. J. Hirsch et al., 2021). As always, the aetiology of the EEG pattern is of great importance, with medication induced burst-suppression (as can be seen in normal people under anaesthesia) clearly being of vastly different implication compared to post cardiac arrest burst-suppression in the absence of sedative medication.

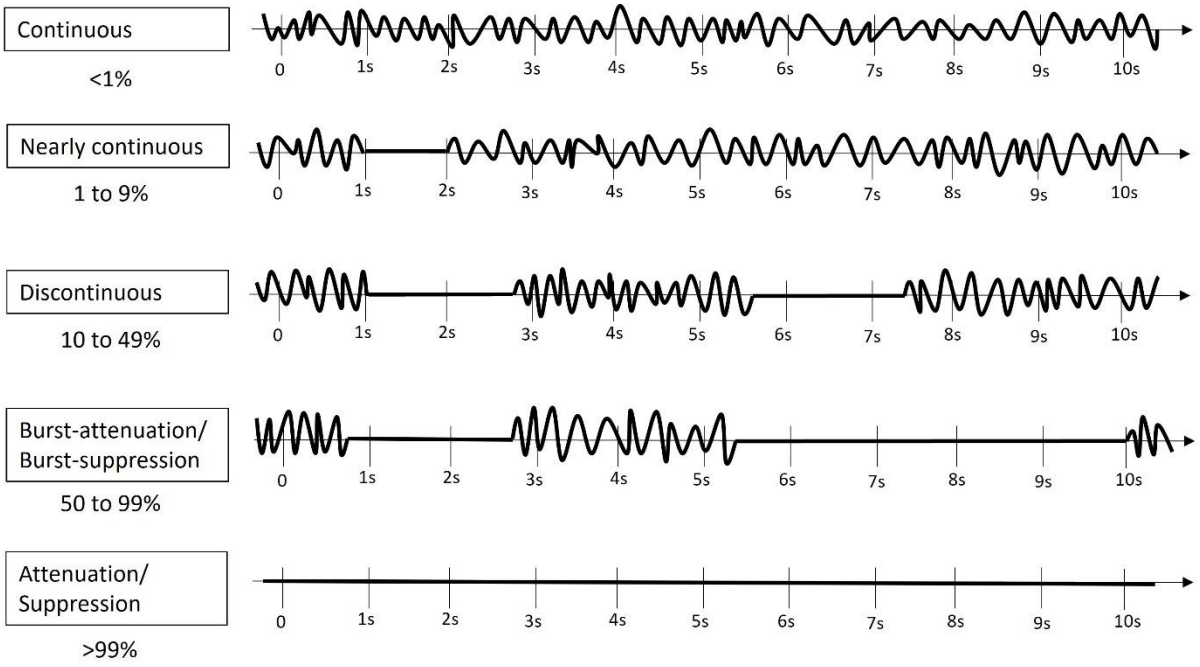

Figure 6: Continuity. The current classification of ”continuity“. The percentages under each title denotes the range of attenuation or suppression percentages for each category. For example, burst-attenuation/ burst-suppression is present if the record is 50-99% attenuated/suppressed. Attenuation refers to any activity that is <50% of higher voltage background activty but still ≥10 µV, and suppression is activity <10 µV. Note how this definition does not comment at all as to the content of the bursts, and therefore burst-suppression can include a wide variety of patterns. In relation to burst-suppression it is suggested that additional descriptive information be documented regarding burst content, as shown in the reference chart. This understanding is required for Chapters 5 and 6 of this thesis, which investigate specific characteristics of burst suppression in two different clinical scenarios. Reproduced from Hirsch LJ, Fong MWK, Leitinger M, et al. *American Clinical Neurophysiology Society's Standardized Critical Care EEG Terminology: 2021 Version.* J Clin Neurophysiol. 2021;38(1):1-29.

Most of our understanding regarding the mechanism and cerebral metabolic implications of burst-suppression originates from the literature surrounding the use of anaesthetic agents or hypothermia. The morphological features of burst-suppression have been replicated with a computational model that inferred bursts result in an ≈25% consumption of baseline adenosine triphosphate (ATP), or the energy storing capacity of a cell (Ching, Purdon, Vijayan, Kopell, & Brown, 2012). This energy depletion was hypothesized to lead to the activation of K_{ATP} channels, which resulted in hyperpolarization and therefore suppression (Ching et al., 2012). In the hyperpolarized state, ATP slowly recovers to a point where a burst is again feasible, and the cycle continues (Ching et al., 2012). The duration of the suppressed/ attenuated period is hypothesized to be governed therefore by the capacity for ATP regeneration, with progressive reductions in this capacity (by ≈30-50% baseline) resulting in more prolonged periods of suppression (and eventually a suppressed record with reductions >50% baseline) (Ching et al., 2012).

In patients undergoing cardiac surgery (i.e., with no cerebral pathology), propofol-induced burst-suppression lead to significant reduction in cerebral blood flow (CBF), cerebral oxygen delivery (DO2), and cerebral metabolic rate (CMRO2) (Newman et al., 1995). This was more recently replicated in a neurosurgical setting, with propofol-induced burst-suppression again reducing CBF, but with inconsistent reductions in CMRO2 (indicating that in those with cerebral pathology, the usual responses may be altered) (Vimala, Arulvelan, & Chandy Vilanilam, 2020). At least at a mechanistic and gross level, burst-suppression seems to hold some relation to depletion of cellular energy stores, combined with an impairment of ATP regeneration (either due to medication-related reductions in cerebral metabolic rate, or induced as a component of the primary neurological diagnosis [e.g., post anoxic burst-suppression]).

This becomes important when considering burst-suppression as a prognostic tool (Chapter 6 of this thesis). As mentioned above, patients with burst-suppression following cardiac arrest had a significantly worse prognosis compared to those with a continuous record, which has been replicated in many studies (Lamartine Monteiro et al., 2016; A. O. Rossetti et al., 2017; Barry J. Ruijter et al., 2019; Erik Westhall et al., 2016). The finding is perhaps expected when assuming the mechanism of burst-suppression; a cerebral insult leading to burst-suppression (i.e., a state with impaired ATP regeneration) would be more severe than a state

where these mechanisms are preserved. As an extension of this, it may be intuitive to consider patients with higher suppression percentages (i.e., leading to 100%, or "suppression") as having worse states of energy regeneration and therefore prognosis. This however has not been well established.

There are two components to burst-suppression: the suppressed component and then the burst. In addition to the suppression percent, the burst content can also provide valuable information. There was an early observation that within patients with burst-suppression, a cohort existed where the content of each burst was "identical" (initially labelled "extreme stereotypy") (Hughes, 1986).

Further work has refined what is considered "identical", which are now defined as present if (Figure 6): (L. J. Hirsch et al., 2021; Hofmeijer, Tjepkema-Cloostermans, & van Putten, 2014)

- The first 0.5 s or longer of each burst is visually similar in all channels in the vast majority (>90%) of bursts, or
- The first 0.5 s or longer of each of **two or more** bursts in a **stereotyped cluster** are visually similar in all channels in the vast majority (>90%) of bursts.

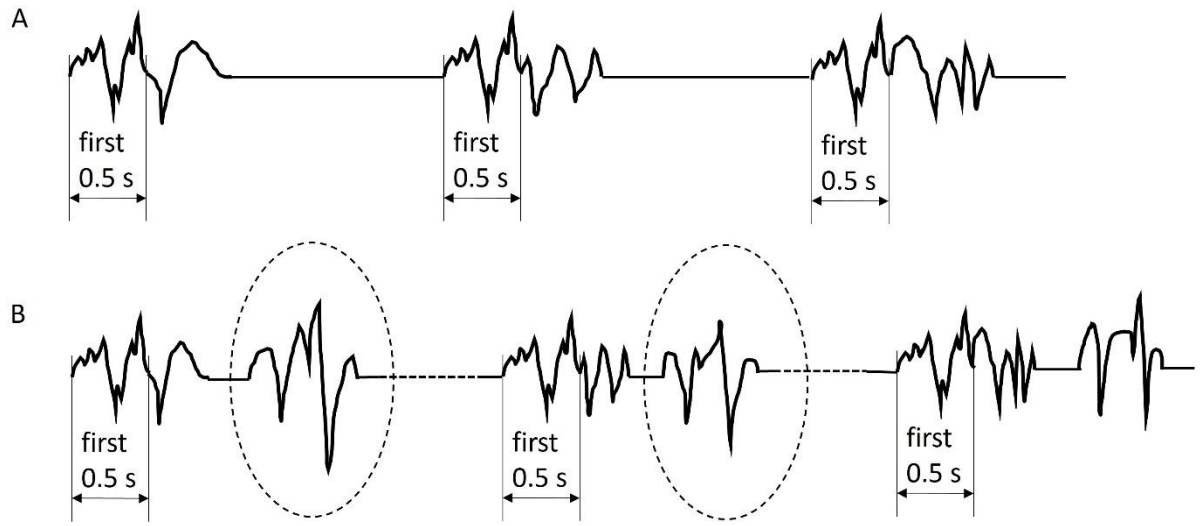

Figure 6: Identical Bursts. Identical bursts are present if either:

- The first 0.5 s or longer of each burst is visually similar in all channels in the vast majority (>90%) of bursts (Panel A), or
- The first 0.5 s or longer of each of **two or more** bursts in a **stereotyped cluster** are visually similar in all channels in the vast majority (>90%) of bursts (Panel B)

Note in the first example, panel A, only the first 0.5 seconds of each burst is visually similar (i.e., following the first ½ second the bursts vary). These would still qualify as identical bursts, and the prognostic utility of the finding has been characterized when only assessing the first ½ second (i.e., even if only the first ½ second is identical this already carries clinical significance). In panel B, the second component of "a stereotyped cluster" of bursts varies (dashed ellipses). Again, however as the first 0.5 seconds of the stereotyped cluster of bursts is visually similar these continue to qualify as identical bursts. Reproduced from Hirsch LJ, Fong MWK, Leitinger M, et al. *American Clinical Neurophysiology Society's Standardized Critical Care EEG Terminology: 2021 Version.* J Clin Neurophysiol. 2021;38(1):1-29.

Under more physiologic conditions the content of bursts is variable. Our understanding of burst generation and synchronization has changed in the past decade, mostly in response to intracranial EEG studies. It was previously thought that burst-suppression was a "generalized" process, with thalamic/subcortical projections giving rise to synchronous activation of broad regions of cortex in both hemispheres (possibly akin to the generation of a generalized epileptiform discharge). It turns out that burst generation is much more complex than this. Although on the surface it may seem as though activity is being generated from everywhere at once, on an intracranial level it has been shown that local cortical regions can act independently (i.e., one region can demonstrate burst suppression at the same time that another region does not, even when scalp EEG does not show burst suppression at all) (Lewis et al., 2013).

For any given burst, the surface morphology is determined by the summation of distinct regions, which are weighted by the regions that are most active (inactive) at that given point in time. With this concept it becomes easy to appreciate why under more physiologic conditions bursts are "variable" (i.e., "not identical"). They are still governed by thalamic/ subcortical mediators but the content and morphology of each burst changes from one burst to the next, as the weighted sum of cortical regions fluctuates from one moment to the next. In fact, if bursts are variable and contain more "normal" frequencies (such as theta) these patients can do well, even in the setting of post cardiac arrest burst-suppression (Sekar, Schiff, Labar, & Forgacs, 2019). The more abnormal state therefore is loss of this fluctuation, resulting in the same weighted set of cortical regions being activated each time. This results in "identical bursts" on surface EEG, an extreme state of "invariance" where the brain is only capable of generating a single pattern over and over again. This concept was proven in the post cardiac arrest setting, at least in one study. Identical bursts were documented in 20 patients (out of 101 comatose patients post cardiac arrest), and all of these patients died (i.e.,

100%, vs. a 36% chance of a poor outcome in those without identical bursts) (Hofmeijer et al., 2014). There are rare cases of patients awakening from post anoxic coma characterized by burst suppression with identical bursts (Coppler et al., 2021). The significance of the finding requires validation on a larger scale, ideally using visual assessment of identical (vs. non-identical) bursts so findings can be better applied to routine patient care.

Another application of burst-suppression has been as a surrogate goal in the treatment of refractory status epilepticus (RSE). This approach has been more recently debated, mainly because centres have developed greater access to continuous EEG. It was the case previously that very few centres could provide long term EEG in critically ill patients, at any time of the day, with review by expert practitioners. This meant that in patients with RSE an EEG could only be achieved for several hours in any given day (and often much shorter than this). Most seizures in the critical care setting are non-convulsive, so given the prior restraints it meant there was no means of monitoring for seizure recurrence, i.e., if seizures were controlled at the time of EEG recording there was low confidence that seizures would not return in several hours. This was why burst-suppression was commonly sought as a surrogate marker of an adequate level of highly sedating anti-seizure medication (ASM). The potential consequence of such an approach however is that for many patients it meant the administration of highly sedating infusions at a level that may have not been necessary for seizure control, and often for 24-48 hours when shorter durations may have sufficed. There have been suggestions that patients who achieve burst-suppression in this setting have greater mortality, although this may be related to burst-suppression reflecting the severity of the underlying condition (i.e., the need for burst-suppression) rather than purely medication effect (L. J. Hirsch, 2015; Hogan et al., 2020; Andrea O. Rossetti et al., 2011; Watson et al., 2008). With greater access to continuous EEG, ASM can be adjusted to a sufficient level to control seizures, and then seizure recurrence can be reliably determined via monitoring; thus, one does not have to guess at what dose to use but can titrate to the minimal dose required to stop seizures (the goal dose in most cases). This approach potentially leads to a reduced administration of highly sedating ASM and therefore fewer consequences of that (i.e., intubation, ventilation, ICU days). Seizure control (i.e., seizure cessation) without achieving burst-suppression or suppression has been associated with good outcomes in patients with refractory status epilepticus (Hocker, Britton, Mandrekar, Wijdicks, & Rabinstein, 2013).

With the above caveats in place, shorter durations of therapeutic coma, especially in younger patients presenting with convulsive status epilepticus, may be safe and effective; in fact,

some studies have found that aggressive early treatment (including short duration of deep induced coma) may be the most effective treatment in refractory cases (P. De Stefano et al., 2021; Muhlhofer et al., 2019). Recently, there has been a focus on determining the characteristics of EEG patterns that assist with predicting seizure recurrence when treating RSE with therapeutic coma. Historically, if burst-suppression was utilized as a surrogate for highly sedative ASM titration, a common approach was that medication was titrated to achieve inter-burst intervals (i.e., typical duration of the suppressed components) of approximately 10 or more seconds. This approach was arbitrary, and other features, such as the total duration of burst-suppression required, were poorly defined. It is now evident that inter-burst interval, burst suppression ratio, and even length of bursts are not good predictors of seizure recurrence when the highly sedating ASM is weaned (Johnson, Martinez, & Ritzl, 2016). It has become apparent that the burst content is important. When bursts contain epileptiform activity or are of high voltage (defined as ≥125 μV for that study) the chance of successfully weaning highly sedative ASM is low (Johnson et al., 2016).

This was furthered with the definition of "highly epileptiform bursts". Highly epileptiform bursts (HEBs) are present if (Figure 7): (L. J. Hirsch et al., 2021; Thompson & Hantus, 2016)

- Two or more epileptiform discharges (spikes or sharp waves) are seen within most (>50%) bursts and occur at an average of 1 Hz or faster within a single burst (frequency is calculated as the inverse of the typical interpeak latency of consecutive epileptiform discharges within a single burst), or
- If a rhythmic, potentially ictal-appearing pattern occurs within most (>50%) bursts.

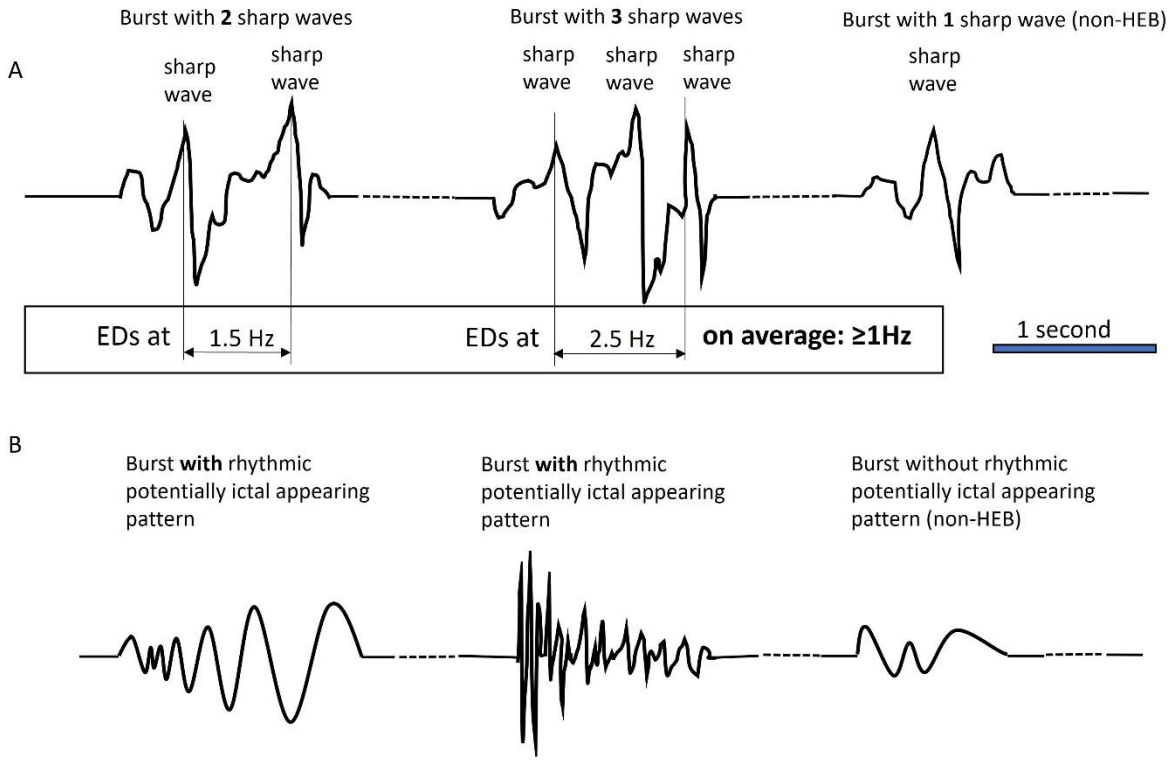

Figure 7: Highly Epileptiform Bursts. Highly epileptiform bursts are present if either:

- Two or more epileptiform discharges (spikes or sharp waves) are seen within most (>50%) bursts and occur at an average of 1 Hz or faster within a single burst (Panel A) or
- If a rhythmic, potentially ictal-appearing pattern occurs within most (>50%) bursts (Panel B).

Note that in panel A the first two bursts have epileptiform discharges a rate of ≥1 Hz (1.5 Hz in the first, and 2.5 Hz in the second). The third burst has an epileptiform discharge, however it does not have ”two or more” discharges and is therefore not “highly epileptiform”, which can also be referred to as non-highly-epileptiform bursts (non-HEBs). The same would apply for bursts that contained two or more epileptiform discharges at a rate of <1Hz, these would also not be HEBs. Panel B has two patterns that look like the beginning of seizures and are therefore HEBs. The third burst in this panel is not “potentially ictal appearing” and is therefore a non-HEB. Reproduced from Hirsch LJ, Fong MWK, Leitinger M, et al. *American Clinical Neurophysiology Society's Standardized Critical Care EEG Terminology: 2021 Version.* J Clin Neurophysiol. 2021;38(1):1-29.

The absence of HEBs have been confirmed to be a good predictor of successful ASM wean (i.e., if HEBs were not present then the chance of successfully weaning ASM was high). In one study, when aesthetic medication was weaned in 17 patients with HEBs, 11 had seizure recurrence in the subsequent 24 hours, but none of the 16 patients without HEBs had seizures in the subsequent 24 hours (Thompson & Hantus, 2016). It is therefore proposed that burst content be used to guide weaning of ASM. For example, if a patient with refractory SE achieves burst-suppression and the bursts are HEBs, the probability of successfully weaning ASM at that point is not favourable, irrespective of the inter-burst interval. At that point,

measures could be taken to improve that probability (i.e., optimize reversible causes of seizures, additional anti-seizure medications, additional time at current level of sedation). If the burst-suppression evolves to non-HEB burst-suppression, at that point the probability of successfully weaning sedative infusions is high. That approach is not always possible, but it is a valuable discussion that it seems burst content, rather than the historical inter-burst interval, is a better surrogate measure of treatment success and/or readiness for weaning. Utilizing HEBs as a predictive marker to guide highly sedative IV ASM weaning in RSE is the topic of Chapter 5 of this thesis.

Rhythmic and Periodic Patterns

The preliminary analysis of the CCEMRC database in 2017 improved our understanding of the association of RPPs to seizures. A schematic of this interaction has been replicated from Rodriguez-Ruiz et al. (Figure 8). For the most part RPPs are significantly associated with ESz/ ESE or may in themselves be the electrographic pattern of electroclinical SE/ NCSE. This section goes through the commonly encountered RPPs and summarizes the current understanding of the neurophysiologic basis to each pattern, which sets the basis to understanding their associations with seizures.

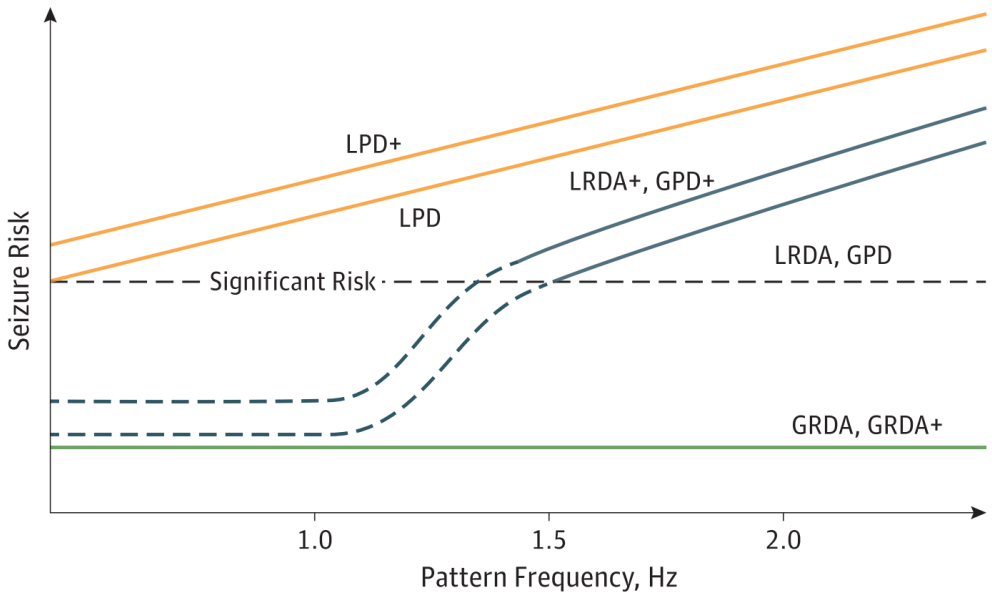

Figure 8: Model of Rhythmic and Periodic Pattern's (RPPs) and Seizure Risk. The figure is a schematic of risk of seizure for each pattern at a given frequency. Note the figure is conceptual and not to scale. The odds ratio (odds of having a seizure vs. not having a seizure) at <1.5Hz was Generalized Rhythmic Delta Activity 1.34 (0.91-1.93), Generalized Periodic Discharges 1.35 (0.94-1.91), Lateralized Rhythmic Delta Activity 1.56 (0.87-2.66) and Lateralized Periodic Discharges 7.55 (6.03-9.46). These odds ratios increase as the frequency increases, apart from GRDA. Odds ratio for ≥2 Hz for GRDA 1.31 (0.78-2.12), GPDs 3.30 (1.79-5.87), LRDA 3.98 (2.41-6.50) and LPDs 16.40 (8.97-30.64). As depicted by the model, any plus modifier (+) increased these risks even further. There is a similar finding for prevalence of the pattern, where an increase in the odds ratio for seizure is seen as the pattern increases from rare/occasional, to frequent, to abundant/continuous. Replicated from Rodriguez Ruiz, A et al. *Association of Periodic and Rhythmic Electroencephalographic Patterns with Seizures in Critically Ill Patients*. JAMA Neurology 2017 74(2): 181.

Generalized Rhythmic Delta Activity

Although the historical descriptor of Frontal Intermittent Rhythmic Delta Activity (FIRDA) is at times used interchangeably with GRDA the two are not synonymous. The majority of patterns classified as FIRDA would also meet criteria for GRDA, with the exception of FIRDA with fewer than 6 cycles that does not qualify as GRDA (not that there has been any pathophysiologic evidence to support this somewhat arbitrary distinction). Conversely, there are many patterns that qualify as GRDA that would not be included as FIRDA. This is because GRDA can be "frontally predominant", "occipitally predominant", "midline predominant", or "generalized, not otherwise specified", as is the case with any "generalized" pattern, and can be continuous rather than intermittent. Under this classification only intermittent "frontally predominant GRDA" would equate to FIRDA, whereas the others would not.

Despite this distinction, the clinical implications for patients with GRDA have been largely consistent with those described in patients with FIRDA. When compared to focal RPPs (i.e., LRDA and LPDs), patients with GRDA were more likely to have a toxic-metabolic encephalopathy, the administration of highly sedating anti-seizure medication (ASM), and a normal MRI brain (although a high proportion still had acute focal abnormalities) (Alzawahmah, Fong, Gilmore, & Hirsch, 2022). It (mostly speaking of FIRDA) was initially thought to occur as a consequence of deep midline lesions, hydrocephalus, or posterior fossa tumours; however both forward and backward solutions have not supported this (i.e., patients who had deep midline lesions did not have a greater proportion of FIRDA, and patients with GRDA do not have a disproportionate number of deep midline or posterior fossa lesions, or

hydrocephalus, even when the imaging was independently scored (Accolla, Kaplan, Maeder-Ingvar, Jukopila, & Rossetti, 2011; Alzawahmah et al., 2022; Fariello, Orrison, Blanco, & Reyes, 1982; Schaul, Gloor, & Gotman, 1981; Watemberg et al., 2002). The current mechanism that determines GRDA (vs. generalized irregular/polymorphic slowing) is not well established but felt to represent a particular type of diffuse cortical dysfunction that is modulated by thalamocortical efferents. In a large, 3-center study, GRDA (even when sharply contoured, or associated with spikes/sharp waves [i.e., GRDA+S]) was not associated with seizures (Rodriguez Ruiz et al., 2017).

Lateralized Rhythmic Delta Activity (LRDA)

Historically speaking, the finding of lateralized (including focal or regional) RDA on surface EEG has been highly associated with focal epilepsy. This statement originates from the literature surrounding Temporal Intermittent Rhythmic Delta Activity (TIRDA). TIRDA (when recorded on routine interictal outpatient EEG) was highly associated with focal temporal epileptiform discharges and had a very high positive predictive value for a patient also having "complex partial seizures" (now termed focal seizures with impaired awareness [FIA]) (Normand, Wszolek, & Klass, 1995; Reiher, Beaudry, & Leduc, 1989). In the critical care setting TIRDA is classified as LRDA (maximal in the temporal region). However, there are many patterns that qualify as LRDA that are not TIRDA (e.g., as for all lateralized patterns, LRDA can also be "frontal", "parietal", "occipital", or "hemispheric"); furthermore, LRDA can be continuous rather than intermittent (L. J. Hirsch et al., 2021).

Patients with LRDA have a similarly high rate of acute focal abnormalities on MRI brain when compared to patients with LPDs (Alzawahmah et al., 2022). LRDA was seen as the projection of periodic epileptiform discharges or even electrographic seizures when recording from underlying intracranial EEG (P. De Stefano, Vulliemoz, Seeck, & Megevand, 2020; P. Vespa et al., 2016; Witsch et al., 2017). It is therefore not surprising that LRDA (in any location) has a high association with focal (polymorphic/irregular) slowing, focal epileptiform discharges, lateralized periodic discharges (LPDs), and subsequent focal ESz on scalp EEG (originating from the same region as the LRDA) (Alzawahmah et al., 2022; Gaspard, Manganas, Rampal, Petroff, & Hirsch, 2013; Husari, Johnson, & Ritzl, 2021; Rodriguez Ruiz et al., 2017). In one study the rate of acute seizures (mostly electrographic) was no different in patients with LRDA (63%) compared to those with LPDs (57%), and was even higher in patients with both patterns (82%) (Gaspard et al., 2013; Husari et al., 2021).

Lateralized Periodic Discharges (LPDs)

Lateralized Periodic Discharges are associated with acute focal (mostly cortical) brain abnormalities, are highly associated with ESzs/ESE, and subsequent epilepsy (Alzawahmah et al., 2022; Kalamangalam, Diehl, & Burgess, 2007; Punia, Bena, Krishnan, Newey, & Hantus, 2018; Rodriguez Ruiz et al., 2017; Snodgrass, Tsuburaya, & Ajmone-Marsan, 1989). The major difference between LPDs and the prior term PLEDs is that LPDs clarified that "discharges" do not have to be "epileptiform" to be included (i.e., they can be sharply contoured/ blunt). As with LRDA, not all patterns within LPDs have the same seizure associations. "Sharply contoured/spiky" LPDs (that were defined between 50-200 milliseconds duration, which would be termed "spiky" or "sharp" under the ACNS terminology) had a high association with seizures (57.7%) and status epilepticus (26.8%) (Newey, Sahota, & Hantus, 2017). However, patients with "blunt delta" LPDs had a lesser association; out of 29 patients with blunt LPDs 8 (27.6%) had seizures and only 1 (3.4%) developed status epilepticus (Newey et al., 2017). When taken as a whole, LPDs have an ≈ 50-80% association with acute seizures (depending on modifiers and co-existent patterns) (Gaspard et al., 2013; Newey et al., 2017; Rodriguez Ruiz et al., 2017). "Sharply contoured" (by ACNS criteria) and "blunt" LPDs still have a fairly strong association with seizures, even if less than that associated with "spiky" or "sharp" LPDs. This provides justification of the term LPDs. The term "PLEDs" technically excluded many patterns of clinical significance due to the "E" for epileptiform.

For the most part LPDs have been considered inter-ictal; however, this concept has been challenged and there are clearly times when they are ictal, i.e., causing clinical symptoms or additional neuronal injury. It has long been documented that LPDs have a strong relationship with focal ESE and ESz (Snodgrass et al., 1989). If a patient presented with focal ESE there was a reasonable chance that the EEG would demonstrate LPDs when the status was treated, and LPDs were often seen in between frequent focal ESz (Snodgrass et al., 1989). A concept was formed that LPDs (especially with certain characteristics, e.g., spiky, or with associated fast activity [LPDs + F]) could represent an extension of what is currently defined as ESz/ESE. LPDs can be both "symptomatic", such as when there is a muscle jerk with each discharge, qualifying as ESE if persistent; or potentially "injurious". Even LPDs that do not meet criteria for ESz/ESE have been associated with "metabolic crisis", potentially leading to additional neuronal injury and loss (P. Vespa et al., 2016; Witsch et al., 2017). There are many patients with LPDs alone (i.e., without definite ESz/ESE) where a trial of ASM may be warranted. Many symptoms/ signs have been associated with LPDs that have resolved when

the LPDs were treated (e.g., aphasia, amnesia, hemianopsia, hemiparesis, gaze deviation) (Ericson, Gerard, Macken, & Schuele, 2011; Hughes, 2010). The determination of who needs to be treated may be based on the characteristics of the pattern but likely needs to incorporate clinical and neuroimaging features. The difficult part will be in further defining which of these is causing symptoms and which imparts the greatest risk of neuronal injury, and therefore which are potentially worth treating more aggressively (Gelisse, Crespel, Genton, Jallon, & Kaplan, 2021).

Generalized Periodic Discharges (GPDs)

GPDs (previously termed Generalized Periodic Epileptiform Discharges [GPEDs]), with the E removed for similar reasons as with PLEDs, discussed above) have been described in a wide variety of clinical settings, such as, post cardiac arrest, following status epilepticus, as a part of toxic-metabolic encephalopathy, in advanced dementia (including Creutzfeldt Jacob disease), or medication related (Foreman et al., 2012; Husain, Mebust, & Radtke, 1999; Van Putten & Hofmeijer, 2015).

There remains debate as to the clinical associations, implications for seizures, and prognostic value of patients with GPDs of different types (various frequencies and morphologies). As is true for all RPPs, the prevalence of GPDs depends highly on the duration of EEG recorded, the patient's state, and the clinical context in which that EEG is being recorded. GPDs are found on ≈4-12% of all cEEG records (≥6 hours) performed on critically ill patients (Foreman et al., 2012; Rodriguez Ruiz et al., 2017). The most common presenting illnesses documented in patients with GPDs are acute brain injuries (44%) (including ischemic and haemorrhagic strokes and TBI), acute systemic illness (38%) (including toxic-metabolic, with a high proportion of sepsis), cardiac arrest (14.5%), and epilepsy (3.5%) (Foreman et al., 2012). However, these proportions do not differ greatly when compared to presentations of patients without GPDs undergoing cEEG (Foreman et al., 2012). Historically, the denominator has been hard to define (i.e., GPDs are common in the setting of toxic-metabolic encephalopathy, however what proportion of all patients with toxic-metabolic encephalopathy get GPDs has been harder to quantify [mainly because it is usually only a select subset of patients with toxic-metabolic encephalopathy that get an EEG]). For this reason, it is also not entirely apparent that GPDs are necessarily more common in patients with toxic-metabolic encephalopathy vs not.

Despite GPDs being encountered almost daily in a critical care EEG, determining the pathophysiologic mechanism underlying the pattern has been difficult. However, it is

valuable to discuss the presumed pathophysiology, and contrasting this with other patterns, as it helps interpret the literature regarding GPDs across a variety of clinical settings. Before discussing the presumed mechanism for GPDs, it is worth contrasting the pattern with burst-suppression (discussed earlier in this chapter). Burst-suppression is hypothesized to be due to a dysfunctional state where the burst (even if relatively physiologic theta activity) leads to consumption of remaining energy capacity, which causes suppression until energy restoration machinery can overcome this (and another burst can be generated). The mechanism underlying burst-suppression does not seem to feasibly apply to GPDs: 1. The inter-discharge EEG (or "background") for GPDs can be relatively normal or can be suppressed/attenuated (i.e., suggesting diffuse and significant hyperpolarization is not always present); and 2. the inter-discharge intervals in GPDs are too short to be explained by cellular metabolism overcoming ATP depletion. This comparison has been made to highlight a conceptual difference. GPDs require synchronous activation of large volumes of the cortex in both hemispheres followed by a mechanism that quickly inhibits this, allowing for a "discharge" to be generated without progressing into a seizure. The mechanism most favoured at this stage is a loss of "feed-forward inhibition" (Van Putten & Hofmeijer, 2015). Feed-forward inhibition is a protective mechanism designed to prevent excess cortical activation. Under normal conditions an excitatory efferent (e.g., a thalamocortical projection) also leads to subsequent inhibition of its target following a short delay, mediated via an interneuron (Paz & Huguenard, 2015). The protective capacity is intuitive; any action potential will be subsequently regulated by an interneuron, ensuring it is not capable of firing tonically.
The effect of disrupting feed-forward inhibition can be evidenced in a mouse model by selectively introducing loss of function mutations to cortical interneurons (in particular fast-spiking basket cells containing the calcium binding protein parvalbumin), which leads to generalized spike-wave seizures (Rossignol, Kruglikov, Van Den Maagdenberg, Rudy, & Fishell, 2013). The reason that this is valuable is because a model of impaired feed-forward inhibition can be used to replicate GPDs (Van Putten & Hofmeijer, 2015). A thalamocortical projection with diffuse arborization may activate large volumes of the cortex, and without timely interneuron inhibition, a generalized discharge. If inhibition is present but delayed the cortex is eventually brought back under control (i.e., the EEG returns to its background state) from which a subsequent discharge can be triggered. If inhibition is lost altogether then a seizure may be generated, as has been observed in the mouse model and recent computational model of GPDs (Ligtenstein et al., 2021; Rossignol et al., 2013). Source analysis and directed connectivity analysis in a cohort of patients with post-anoxic GPDs suggested broad

activation of limbic and other structures (in particular medial-orbitofrontal, thalamus, amygdala, hippocampus, cingulate), that was driven by thalamic and hippocampal projections (Pia De Stefano, Carboni, Pugin, Seeck, & Vulliémoz, 2020). The finding provides a neuroanatomic substrate to the theory of impaired feed-forward inhibition as a mechanism in GPD production.

One of the better studied clinical scenarios where GPDs are often seen is following cardiac arrest. After cardiac arrest, persistent GPDs on a suppressed background carries a very poor prognosis (Backman et al., 2018; Jadeja, Zarnegar, & Legatt, 2017; A. O. Rossetti et al., 2017; Barry J. Ruijter et al., 2019; Erik Westhall et al., 2016). The critical caveat to this statement is that it only applies to GPDs on a suppressed background, and not GPDs on any other background. The early recovery of the background following cardiac arrest (even in the presence of GPDs) has been associated with good outcomes (Barry J. Ruijter, Van Putten, & Hofmeijer, 2015; E. Westhall et al., 2018). This makes inherent sense when considering the presumed pathophysiology. As discussed above, GPDs are theoretically caused by failure of interneuron mediated inhibition. This process alone presumably cannot lead to suppression between discharges (i.e., progressive loss of interneuron inhibition leads to increased cortical excitability and generalized seizures [the opposite of suppression]). Suppression is likely caused by impairment of the cortical generators of the EEG signal. Therefore, the presumed order of dysfunction from mild to severe would be: 1. GPDs on a continuous background, 2. GPDs on a suppressed background, and 3. Suppression (without GPDs, where there is not sufficient functioning cortex to generate discharges). This theory is supported by the finding that in patients with post anoxic GPDs, good outcomes are seen in those that had a continuous background, higher discharge frequency (i.e., the reduced ability to generate discharges suggested greater dysfunction), and lower discharge periodicity (i.e., more variability) (Barry J. Ruijter et al., 2015). Thus, in the end, GPDs themselves do not have much prognostic utility after cardiac arrest; the background is a much more reliable predictor.

The prognostic utility of GPDs outside the post cardiac arrest setting is not as well established. Excluding patients post cardiac arrest, GPDs have been associated with increased mortality on univariate analysis (Foreman et al., 2012). However, when multivariate analysis was performed, GPDs were no longer an independent determinant of mortality (Foreman et al., 2012). Instead, in that study, the independent predictors of mortality were cardiac arrest, coma, NCSE, and sepsis (i.e., mostly clinical factors or NCSE) (Foreman et al., 2012). Similarly, in another cohort of patients with GPDs, mortality was determined by cardiac arrest, dementia, COPD, poor mental state, and chronic focal abnormalities on neuroimaging

(although that study did not include the presence of NCSE, or specific features of the pattern such as typical frequency or burden) (Jadeja et al., 2017). In the post cardiac arrest setting the prognostic value of GPDs needs to mostly consider the background recovery; in any other setting it seems it is just one relatively minor factor that must be incorporated into the severity of additional clinical, neuroimaging, and electrographic findings.

There has been a long-time debate whether GPDs simply represent dysfunction, or whether they are markers of increased cortical excitability (and hence associated with seizures). Practically speaking, both statements are true; they are theoretically caused by a specific type of dysfunction (one that presumably affects interneurons to a greater extent than pyramidal cells), which leads to diffuse increases in cortical excitability (resulting in high voltage synchronous and symmetric discharges), and are highly associated with seizures (based on association studies including 1000s of patients summarized below; and animal and computational models as discussed above) (Foreman et al., 2012; Ligtenstein et al., 2021; Rodriguez Ruiz et al., 2017).

The greatest scepticism has surrounded GPDs of "triphasic morphology". The origins of this stems from early literature on "triphasic waves" that were first described in the context of hepatic encephalopathy; they were soon after broadly associated with "metabolic encephalopathies", as they were described in an increasing number of such conditions, and the patterns between these conditions could not be reliably differentiated from one another (Bickford & Butt, 1955; Fisch & Klass, 1988; Karnaze & Bickford, 1984; Sundaram & Blume, 1987). "Triphasic morphology" is currently included in the ACNS terminology as a minor modifier and defined as either: (L. J. Hirsch et al., 2021)

1. Three phases, negative-positive-negative, with each phase longer than the previous, and the second (positive) phase of highest voltage, OR
2. The same but with the first (negative) phase of sufficiently low voltage to be obscured by background activity, leaving a biphasic waveform, positive-negative in polarity. Note that a biphasic waveform may be categorized as "triphasic" by this definition.

"Triphasic morphology" can be applied to any EEG phenomenon, and hence not entirely synonymous with the historical term "triphasic waves". "Triphasic waves" referred to morphology only and there was no distinction between patterns. For example, by ACNS terminology sporadic epileptiform discharges can have triphasic morphology, and GPDs can have triphasic morphology (both of which would have been previously included as "triphasic waves"), however the association of these patterns (sporadic discharges versus long runs of GPDs with triphasic morphology) with seizures is significantly different (Rodriguez Ruiz et

al., 2017). Although triphasic waves were initially described in patients with metabolic encephalopathy, as the volume (and variety) of patients monitored with cEEG has increased, the specificity of this finding has decreased. GPDs with triphasic morphology have now been documented in a wide range of conditions, including in patients with prior epilepsy and status epilepticus (Hartshorn & Foreman, 2019). In a large cohort of patients with GPDs where the triphasic nature or lack thereof was determined by 11 experts in a blinded fashion (i.e., no access to clinical information), those with triphasic morphology were no more likely to have toxic-metabolic encephalopathy (in fact they were significantly less likely) (Foreman et al., 2016). In the same study, the proportion of patients with GPDs plus triphasic morphology who had definite seizures was identical to the patients that had GPDs without triphasic morphology; in both groups, 25% had seizures (Foreman et al., 2016). This is contrary to traditional teaching that triphasic waves are not related to seizures. Furthermore, source localization of triphasic waves have demonstrated dipole origins (i.e., orbitofrontal, mesial frontal, and hippocampal), not too dissimilar to those described for GPDs when taken as a whole, although source localization for GPDs with triphasic morphology has not been directly compared to those without (Kural, Fabricius, Christensen, Kaplan, & Beniczky, 2021; Zafar, Rahman, Ehrenberg, & Kaplan, 2021).

GPDs (including those with triphasic morphology) are highly associated with seizures (Foreman et al., 2012; Foreman et al., 2016; Husain et al., 1999; Rodriguez Ruiz et al., 2017). From a case-control study with 200 patients with GPDs, 46% of patients with GPDs had a seizure at some point of their admission, compared to 34.0% in the control group (without GPDs) (Foreman et al., 2012). In the GPD group 46.4% of seizures were focal (absolute percentage, 21.3% of all patients with GPDs had a focal seizure), vs. control group where 94.1% of seizures were focal (absolute percentage, 32.0% of all control patients had a focal seizure). For generalized seizures, those with GPDs had an absolute rate of 30.7% (i.e., 30.7% of all patients with GPDs had a generalized seizure), vs. only 2.0% in the control group (Foreman et al., 2012). The point to make is that the presence of GPDs significantly increased the probability of a generalized seizure, whereas the rate of focal seizures between the two groups were relatively similar. This provides evidence toward the hypothesis that GPDs are a result of diffuse increases in cortical excitability and hence a risk for ESz with generalized EEG correlates (whereas the rate of focal ESz seems governed by other factors [such as acute focal brain abnormalities, or lateralized patterns of cortical hyper-excitability]).

Summary and Clinical Questions

Critical care EEG or cEEG has become a fundamental component of managing patients with acute brain injuries, seizures, and/ or altered mental state or coma. The rate of ESz/ ESE in these patients is high and given the vast majority do not have any clinical manifestations these would not be detected at all without cEEG. The use of cEEG has been associated with improved mortality and increasing seizure burden has been attributed to worsened functional neurological outcomes.

These patients express a wide variety of EEG patterns that are seen rarely when the EEG is performed in other settings, such as the Epilepsy Monitoring Unit (EMU) or outpatient ambulatory EEG. As can be garnered by the introduction, classification of these patterns has been mostly based on expert observation and consensus rather than any particular neurophysiological basis. Even taking the most commonly encountered patterns, such as LPDs or GPDs there remains grossly differing opinions and messages from the literature.

The first part of this thesis was to consolidate the understanding of RPPs with ESzs. This thesis then aimed to further understanding of the association of RPPs with SE specifically, and how clinical etiology and major/ plus modifiers adjusts these associations (Chapter 3).

There are components of the terminology that have only been described and never studied or validated. An example was the debate as to whether a particular variant of LRDA, bilateral asymmetric LRDA held the same association with ESz/ ESE compared to unilateral LRDA. At the time of study design there were vastly opposing opinions and the only way to resolve this was with a dedicated cohort study with a matched comparator (Chapter 4). Within burst suppression (BS) the described patterns of Identical Bursts (IBs) and Highly Epileptiform Bursts (HEBs). Identical bursts were described more than 10 years ago in 2024. Despite the finding theoretically being of fairly profound clinical significance in the prognostication of patients following cardiac arrest, it had not been systematically validated in a cohort or patients without early withdrawal of life sustaining therapy (WLST) (Chapter 6) (Hofmeijer et al., 2014). Similarly, despite being of high practical utility and arguably practice changing, the use of HEBs to guide weaning off sedative antiseizure medications in refractory status epilepticus (RSE) had only been reported in a single cohort of 19 patients in 2016 (Chapter 5) (Johnson et al., 2016).

The chapters of this thesis therefore aimed to validate the most uncertain components of the ACNS terminology. The chapters consolidate the understanding of the associations of RPPs

with seizures and SE (Chapter 3), determine the clinical relevance of bilateral asymmetric LRDA (Chapter 4), objectively assess the utility of HEBs in guiding when to wean highly sedative ASM in patients with RSE (Chapter 5), and objectively assess the prognostic value of IBs in adult survivors of cardiac arrest in a healthcare setting without early WLST (Chapter 6).

Chapter 2: Methodology

Study population

Patients were retrospectively selected from the Critical Care EEG Monitoring Research Consortium (CCEMRC) multicenter database. Details of this database have been previously published (Lee et al., 2016). The database was a publicly available database that was developed to serve as a repository for research data to facilitate multicenter studies (https://www.acns.org/research/critical-care-eeg-monitoring-research-consortium-ccemrc/ccemrc-public-database). Over the time the database was active (February 2013 to June 2021) it was a part of routine clinical EEG reporting in three large academic epilepsy centers in the United States of America (Brigham and Women's Hospital [BWH, Boston, MA], Yale New Haven Hospital [YNHH, New Haven, CT], and Emory University Hospital [EUH, Atlanta, GA]). This meant that at each of these centers basic clinical data and the EEG findings from all patients undergoing cEEG were prospectively entered on a daily basis and used to generate the EEG report for that day. Reports were generated daily, so for a given patient the EEG findings for each day of EEG were entered. Patients entered into the database were primarily 18 years and over, were deemed to have an indication for cEEG in keeping with the ACNS guideline on cEEG indications (Herman et al., 2015), and had a minimum of 6 hours of cEEG. Patients undergoing cEEG for a nonacute indication, like epileptic spell capture, were not included in this database.

Chapter 3 presents findings from a multicenter cohort study reporting the findings from all three centers. Over the duration of its active use the CCEMRC multicenter database had 12,592 unique subjects. Excluding 142 subjects less than 18 years old, the study population included 12,450 adult subjects (BWH 3,687 patients, YNHH 4,236, EUH 4,527). All other chapters were single center studies that selected particular cohorts from the YNHH database. All studies were approved under Yale New Haven Hospital Institutional Review Board 2011 "Urgent Inpatient EEG and Multimodality Monitoring Databank" (IRB protocol MOD00040247). The requirement for informed consent was waived. The analysis from the multicenter study was additionally approved by the Brigham and Women's Hospital IRB 2012 "Critical Care EEG Monitoring Research Consortium Database" (IRB protocol 2012P001187).

Clinical characteristics

Basic clinical characteristics were a part of the CCEMRC database. Data entry was prospectively performed by attending neurologists who were either board certified or board eligible in clinical neurophysiology or epilepsy, and clinical neurophysiology/epilepsy fellows who had completed neurology residency. Basic clinical data mostly consisted of demographic information such as age and biological sex and clinical diagnoses.

Where additional clinical measures were required, such as details as to the primary condition or the assessment of a clinical outcome (Chapter 6), review of the electronic health record (EHR) was required often in conjunction with a clinical repository. For example, in Chapter 6 clinical data was extrapolated by cross-referencing the patients identified by the CCEMRC database with a cardiac arrest clinical repository. Details of the repository have been published previously (Kim et al., 2023; Kitlen et al., 2023). In that study, discrepancies between these databases were adjudicated by clinical review of the electronic health record (EHR) to determine the most accurate information. For example, if the CCEMRC database listed a patient as having presented after cardiac arrest and the clinical repository did not, then the EHR was reviewed to verify the truth. Patients that had EHR reviews who did not have sufficient evidence of cardiac arrest were excluded. Patients with missing EEG data were also excluded, i.e., the EEG database confirmed EEG was recorded at that timepoint but was not accessible for technical reasons.

Some clinical variables such as the exact times of continuous IV antiseizure medication (cIVASM) wean in Chapter 5 could not be deemed from any database and these were extrapolated by retrospective EHR review by author MF.

Neuroimaging findings

Chapter 4 required documentation of the neuroimaging findings in order to correlate these with the clinical and EEG findings. For this imaging reports were reviewed, but to further classify the findings and document the location and lateralization of abnormalities each computed tomography (CT) scan was reviewed by a senior author. A system to classify these findings was pre-determined before review of the imaging. These separated the findings into acute vs. chronic (or both), confirmed the clinical diagnosis (such as intraparenchymal hemorrhage) and documented the side and location of the abnormality. The neuroimaging locations were also determined before rating of the scans and split into brain regions, such as

frontal, temporal, parietal, occipital, but also cortical vs. subcortical, and other areas of interest such as involvement of the thalamus or basal ganglia. In patients with multiple CT scans the scan that occurred closest to the respective EEG was selected.

Visual assessment of EEG

There were two timepoints where visual assessment of the EEG was required.

1. Prospective at the time of database entry

The prospective entry of cEEG findings into the database was performed by the same attending neurologists/ neurophysiologists that entered the basic clinical characteristics. Given the centers were large academic epilepsy centers all raters were trained in the ACNS Standardized Critical Care EEG Terminology (L. J. Hirsch et al., 2021; L. J. Hirsch et al., 2013). Details of the training/certification procedure have been previously published (Gaspard et al., 2014; Lee et al., 2016).

2. Retrospective validation at the time of study review

All single center studies required some repeat validation of cEEG findings. All repeat classification was performed by author MF. Author MF is fellowship trained in critical care EEG, certified in the ACNS terminology, and 2nd author of the 2021 ACNS terminology (L. J. Hirsch et al., 2021).

Chapter 4 required patients to have either GRDA or LRDA-ba with no overlap between groups. These findings were confirmed by author MF. This was particularly relevant for patients prospectively identified as having both patterns. For these author MF retrospectively reviewed these EEGs to adjudicate which was more accurate. If the patient had an equal predominance of GRDA and LRDA-ba then the patient was excluded.

Chapters relating to burst suppression (BS, Chapter 5 and 6) both required confirmation that the patients were in BS at specified time points and also repeat visual classification as to the characteristics of BS at these time points. For Chapter 5 this took place pre- and post-wean of cIVASM. For Chapter 6 this took place at pre-determined time points following commencement of cEEG (0-, 12-, 24-, 48-, and 72-hours). EEG findings were rated within a 2-hour period from the specified time (i.e., 1-hour preceding and 1-hour postceding the specified time). For timepoint 0- the first 2 hours were assessed to maintain consistency of

duration of EEG assessed. EEGs were also rated at the conclusion of monitoring in this chapter. Patients that did not have BS at any of the pre-specified timepoints (following retrospective adjudication) were excluded.

EEG findings were then assessed in accordance with the 2021 ACNS standardized critical care EEG terminology (L. J. Hirsch et al., 2021), including continuity, reactivity, suppression percent, highly epileptiform bursts (HEBs), identical bursts (IBs), the presence of electrographic seizures (ESz)/ electrographic status epilepticus (ESE), and the presence of myoclonic status epilepticus (myoclonic SE, a subset of electroclinical SE) (L. J. Hirsch et al., 2021).

Quantitative assessment of EEG

For Chapters 5 and 6 episodes of burst suppression had to manually marked to allow quantitative analysis. All markings were manually performed by author MF; example provided in Figure 1. Fifty consecutive pairs of bursts and interburst intervals (IBI) were manually marked by author MF. Interburst intervals consisted of the lower amplitude segment of an alternating burst suppression pattern. By this definition the IBI could have been suppressed or attenuated and could have included sporadic EDs. The 50 pairs of bursts/IBIs were selected from a relatively artifact free epoch of EEG within the pre-specified time periods. The onset of 51 bursts and 50 IBIs were marked. Given the alternating pattern, the beginning of the IBIs marked the end of the bursts, and vice versa. The 51st burst needed to be marked to determine the end of the 50th IBI, but the 51st burst itself was not analyzed.

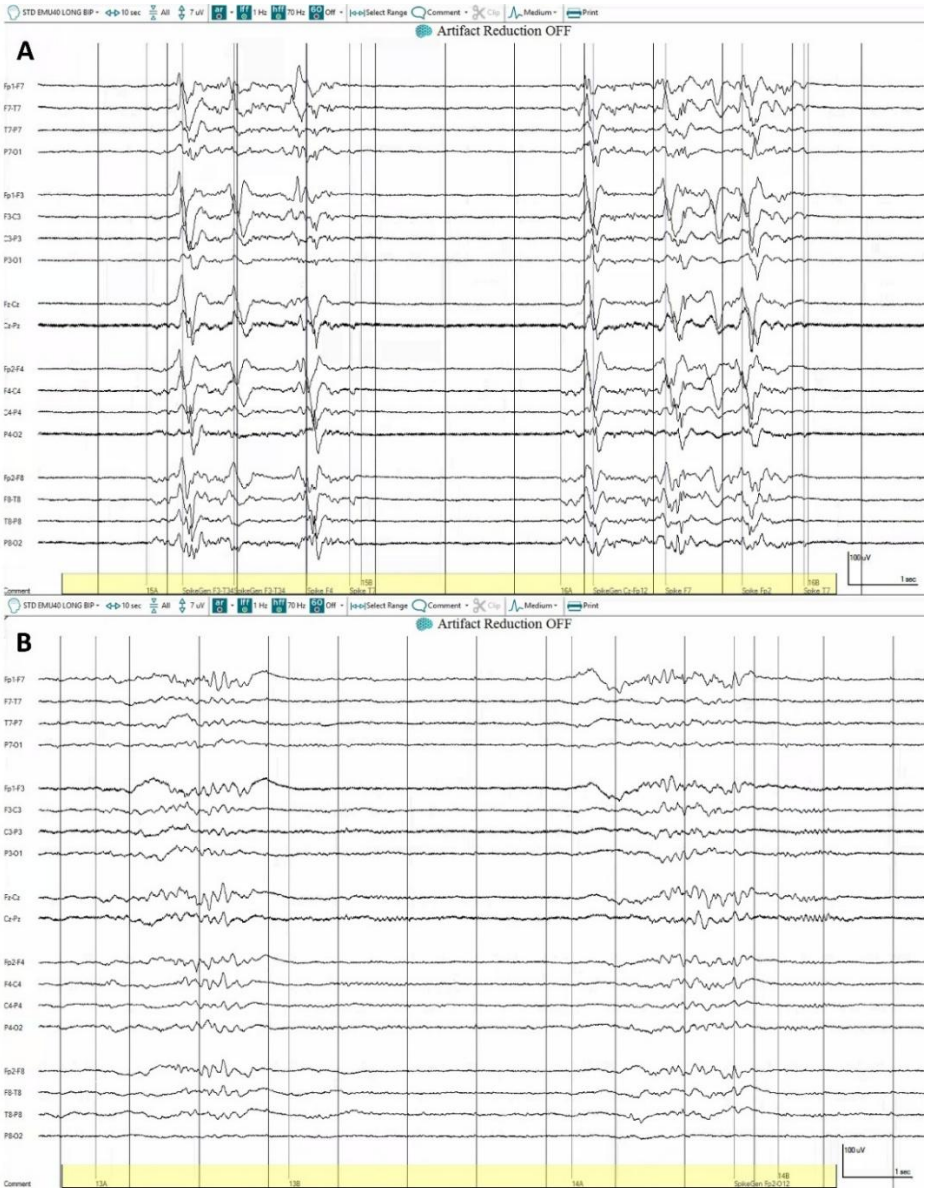

Figure 1: Example of manual marking of highly epileptiform and non-highly epileptiform bursts from Chapter 5. Panel A demonstrates the marking of burst suppression with highly epileptiform bursts (HEBs). Panel B demonstrates a patient where the bursts were not highly epileptiform. Note the manual annotations at the bottom of the EEG page represent the markings. Each contiguous burst and interburst interval was meticulously marked with a number followed by A or B. For example, 1A = beginning of first burst, 1B = end of first burst and beginning of first inter-burst interval (IBI), 2A = end of first IBI and beginning of second burst, 2B = end of second burst and start of second IBI etc. Also note that Panel A has discharges that have been detected by Persyst^{TM} automatic spike detector (as discussed below).

Once the bursts and IBI's were marked the data was exported for quantitative analysis of bursts and IBIs. These analyses were performed with MATLAB (MathWorks, Natick, MA). Standard measures of EEG were determined including mean amplitude, mean duration, total

and band power, Teager energy of bursts and IBIs, and Approximate Entropy (ApEn). Teager energy is a weighted measure of signal energy such that higher frequency signals have a greater contribution than lower frequency signals (Boudraa & Salzenstein, 2018). This emphasis on higher frequencies results in a measure which is akin to the line length measure. ApEn is a measure of the complexity of the time-series (Fan, 2011).

In addition to standard measures, for Chapter 5 included measures of how "epileptiform" bursts and IBIs were. Information on epileptiform discharges (including spikes and sharp waves) for bursts and IBIs was taken from an established commercial quantitative EEG platform (Persyst™ version 13) with standard/ medium sensitivity settings. Quantitative surrogates for "evolution" were used as our measure of "ictal appearing". "Change-in" measures were obtained for each power and Teager energy estimate as a positive 50% from baseline cut off. To achieve this, the activity from the first 3 seconds of a burst was averaged and this was used as a baseline to compare to the activity from the 4th second. A 50% increase in the measure in the 4th second compared to baseline qualified as a marker of evolution. By this definition, only bursts lasting at least 4 seconds could be included in this analysis.

For Chapter 6, how "identical" bursts were was conducted in accordance with Hofmeijer et.al., by the determination of correlation coefficients (Hofmeijer et al., 2014). The correlation coefficient was a measure of how well each of the 50 bursts (or IBIs) correlated with each other. If all 50 bursts were truly identical then the correlation coefficient would be 1; if there was no morphological relationship between any of the 50 bursts, then the correlation coefficient would be 0. Correlation coefficients were calculated based on the first 0.5-, 1-, and 2-seconds of bursts. "Whole burst" correlation coefficients could not be assessed as the duration of bursts between patients was too variable; if a patient had a typical burst duration of 3 seconds this could not be compared to a patient with a typical burst duration of 12 seconds as these patterns were inherently different (i.e., not correlated).

Primary Outcomes

The primary outcomes for Chapters 3 – 5 were electrographic seizures (ESz) or status epilepticus (SE). Chapters 3 and 4 were predominantly database association studies where the outcome of ESz/ SE was determined at the time of prospective database entry. In the database, ESz and/or SE were defined for each cEEG epoch by the reading physician. In general, these followed the modified Young criteria (ESz) (Young, Jordan, & Doig, 1996)

and modified Salzburg criteria (SE) (Leitinger et al., 2015; Trinka et al., 2015). Seizure and SE semiology were categorically classified. Clinical events (including myoclonus) without electroencephalogram correlate were not classified as seizure/SE in any participating center. These initial chapters were descriptive, documenting the association of RPPs (Chapter 3) or specific RPP (Chapter 4) with ESz/ SE.

The primary outcome for Chapter 5 was also ESz but this was directly adjudicated. This was because the primary outcome was the recurrence of ESz by 48 hours following commencement of cIVASM weaning. For this study the cEEG was manually reviewed by author MF for the 48 hours following identified time of cIVASM weaning to determine an accurate time of ESz/ SE recurrence.

The primary clinical outcome of Chapter 6 was survival to hospital discharge, which was determined by the cardiac arrest clinical repository (details provided above).

Statistical analysis and regression modelling

Descriptive and Comparative Statistics

Descriptive statistics were presented as mean and standard deviation for parametric variables, or median and interquartile range for non-parametric variables. For categorical variables the counts in each group were presented with the proportions either of that group or of the entire cohort specified where relevant. Comparisons between groups were achieved with Student's t-test for parametric data, or Pearson's Chi-Square test for non-parametric data. Where the distribution of parametric data differed between the two groups, a two-sample t-test with unequal variances were applied. For non-parametric variables with more than one outcome either Chi Square or Kruskal Wallis 1-way ANOVA was used. These tests determined if there was any significant difference in the distribution of cases across several outcomes between groups. If the distribution of a pattern was statistically significant, individual comparisons could be made with Mann Whitney U test. For simple comparative statistics, significance was determined as p values less than 0.05. For quantitative data, especially in Chapters 5 and 6 where analysis was performed at the burst/ IBI level, a Bonferroni correction was applied to limit the effect of multiple comparisons with significance set at $p < 0.0038$. It has been specified where Bonferroni correction has been applied.

Regression Modeling

There were several studies in this thesis where the relative weight of a significant finding towards outcome was relevant. Take for example, Chapter 5 where univariate analysis identified that there were several variables that on their own had significant association with seizure recurrence by 48 hours. For these a binomial logistic regression model was used to determine the likelihood of a significant independent variable on a binary outcome (e.g., seizure recurrence vs. not seizure recurrence, or survival vs. non-survival).

For analysis of the CCEMRC cohort (Chapter 3), the cohort was randomly split into 90% training (n = 10,745) and 10% testing (n = 1,190) samples. Within the training sample, there was a screening procedure to fit a multivariate adjacent category logit regression model to the ordinal outcome. There was first a univariate screen within the training sample, retaining variables with a p value of less than 0.1 for significance of association with either ESz or SE. Then two separate models were fit. The first was a basic model, including demographic variables, clinical diagnoses, and the presence/absence of each RPP. The second was an expanded model, which included demographics, clinical diagnoses, and major modifiers that met inclusion criteria. The area under the receiver operating characteristic curves (AUROCs) for each model were calculated in the 10% held-out testing sample for outcomes ESz and SE. Confidence was generated using 2,000 bootstrap replicates. The resulting AUROCs were compared using DeLong test. Analyses were performed in either SPSS Statistics Version 29 (IBM, New York, U.S.A) or R Version 4.1.2 (R Foundation for Statistical Computing, Vienna, Austria).

Chapter 3: Association of Rhythmic and Periodic Patterns with Seizures and Status Epilepticus

Plain English summary

This chapter represents the final analysis of the Critical Care EEG Monitoring Research Consortium (CCEMRC) publicly available database of 12,450 adult patients who underwent continuous EEG monitoring (cEEG). The CCEMRC database represents the largest cohort worldwide of prospectively collected findings of patients undergoing cEEG. With this cohort the study documented the associations of clinical etiology and rhythmic and periodic patterns (RPPs) and their modifiers on cEEG with the probability of developing seizures or status epilepticus (SE).

The overall rate of seizures in this study was 9.8% with 3.5% qualifying as status epilepticus (SE). The study found that patients following cardiac arrest, clinical seizures prior to cEEG, brain neoplasms and cEEG findings of Lateralized Periodic Discharges (LPDs), Generalized Periodic Discharges (GPDs), and Brief potentially Ictal Rhythmic Discharges (BIRDs) had particular risks for the development of SE in addition to their previously documented risk of developing seizures. These risks were specifically defined, and it was also assessed how these risks changed with cEEG features such as typical frequency (i.e., number of waveforms per second) or sharpness (i.e., its morphology, or how pointy it was) of the RPP.

The findings greatly consolidated the associations of clinical etiology and RPPs with seizures and documented for the first time with large data the associations of these features with SE specifically. The finding is of great practical utility and allows clinicians to provide very accurate estimates that a given patient with a particular set of clinical and cEEG features will go on to develop seizures or SE over the next 72 hours.

Abstract:

Status epilepticus (SE) is associated with significantly higher morbidity and mortality than isolated seizures. The primary objective was to determine clinical diagnoses and rhythmic and periodic EEG patterns (RPPs) associated with SE and seizures. A retrospective cohort study using data from the Critical Care EEG Monitoring Research Consortium (CCEMRC) database. The CCEMRC cohort prospectively collected and classified the findings from 12,450 adult hospitalized patients undergoing continuous EEG monitoring (cEEG) from three tertiary-care hospitals in the U.S.A between February 2013 to June 2021. The main outcome measures were an ordinal outcome in the first 72 hours of cEEG: no seizures, isolated seizures without SE, or SE (with or without isolated seizures). Composite groups included isolated seizures or SE (AnySz) and no seizure or isolated seizures.

In this cohort (mean age: 60 ± 17 yr), 1,226 patients (9.8%) had AnySz, and 439 patients (3.5%) had SE. In a multivariate model, factors independently associated with SE were cardiac arrest (9.2% with SE; adjusted odds ratio, 8.8 [6.3–12.1]), clinical seizures before cEEG (5.7%; 3.3 [2.5–4.3]), brain neoplasms (3.2%; 1.6 [1.0–2.6]), lateralized periodic discharges (LPDs) (15.4%; 7.3 [5.7–9.4]), brief potentially ictal rhythmic discharges (BIRDs) (22.5%; 3.8 [2.6–5.5]), and generalized periodic discharges (GPDs) (7.2%; 2.4 [1.7–3.3]). All above variables and lateralized rhythmic delta activity (LRDA) were also associated with AnySz. Factors disproportionately increasing odds of SE over isolated seizures were cardiac arrest (7.3 [4.4–12.1]), clinical seizures (1.7 [1.3–2.4]), GPDs (2.3 [1.4–3.5]), and LPDs (1.4 [1.0–1.9]). LRDA had lower odds of SE compared with isolated seizures (0.5 [0.3–0.9]). RPP modifiers did not improve SE prediction beyond RPPs presence/absence ($p = 0.8$).

Using the largest existing cEEG database, we identified specific predictors of SE (cardiac arrest, clinical seizures prior to cEEG, brain neoplasms, LPDs, GPDs, and BIRDs) and seizures (all previous and LRDA). These findings could be used to tailor cEEG monitoring for critically ill patients.

Introduction

Electrographic seizure burden has now been shown to be associated with clinical outcomes in a variety of clinical contexts (De Marchis et al., 2016; Payne et al., 2014; P. M. Vespa et al., 2010; P. M. Vespa et al., 2003; S. F. Zafar et al., 2021). More seizures increase the likelihood of early neurologic decline and long-term disability (Payne et al., 2014; S. F. Zafar et al., 2021). On a population level, the use of continuous electroencephalogram (cEEG) monitoring has been associated with reduced in-hospital mortality (Hill et al., 2019) and delays in starting cEEG are associated with mortality (Sanchez Fernandez et al., 2017). Patients with status epilepticus (SE) have the highest seizure burdens and are at greatest risk of seizure related harm (Fung et al., 2021; Roberg et al., 2022; Shneker & Fountain, 2003; Wagenman et al., 2014).

While some clinical predictors of SE are established (e.g., presentation with seizure or coma) (Bergin et al., 2019; Power, Gramstad, Gilhus, & Engelsen, 2015; Towne et al., 2000), whether there are specific electroencephalographic predictors is uncertain. Identifying patients at high risk for SE could lead to increased cEEG monitoring duration and frequency and potentially prophylactic anti-seizure medication treatment.

Critically ill patients have a high rate of rhythmic and periodic patterns (RPPs) detected with cEEG (Rodriguez Ruiz et al., 2017). Many of these patterns are associated with electroclinical seizures (Rodriguez Ruiz et al., 2017) and have been used to create seizure prediction models (A. F. Struck, Ustun, et al., 2017). It is unknown if these same RPPs are also associated with SE, which is the outcome of greatest clinical importance and poses the greatest risk of harm.

This study investigated the relationship between clinical diagnoses, RPPs, isolated seizures, and SE in the Critical Care EEG Monitoring Research Consortium (CCEMRC) database, the largest existing multicentre cEEG database. The tested hypothesis was that a combination of clinical diagnoses, RPPs and their modifiers could predict isolated seizures and SE via the following three objectives:

Primary: Determine which clinical diagnoses, RPPs, and RPP modifiers were independently associated with SE.

Secondary: Determine which clinical diagnoses, RPPs and their modifiers were independently associated with any seizures (AnySz).

Tertiary: Determine which clinical diagnoses, RPPs and their modifiers had a specific association with SE (i.e. an association that differed significantly from the association with isolated seizures [SzNoSE]).

Methods

Cohort Description

This was a retrospective cohort study of 12,592 subjects from three centers (Brigham and Women's Hospital [Boston, MA], Yale New Haven Hospital [New Haven, CT], and Emory University Hospital [Atlanta, GA]) that used the CCEMRC multicenter database (Lee et al., 2016) daily between February 2013 and June 2021. Detailed descriptions of this cohort (Lee et al., 2016), along with an analysis of the initial 4,772 patients enrolled through 2015 (Rodriguez Ruiz et al., 2017), have been previously reported. Excluding 142 subjects less than 18 years old, our study population included 12,450 adult subjects. For patients with multiple, nonconsecutive cEEG records, only the first record was analyzed. Among 11,740 patients for which hospital location was recorded, 9,496 (81%) were in an intensive care setting during electroencephalogram monitoring. Patients undergoing cEEG for a nonacute indication, like epileptic spell capture, were not included in this database. There was no study-wide protocol for prophylactic antiseizure medication or electroencephalogram monitoring indications, although the latter largely occurred within the American Clinical Neurophysiology (ACNS) guideline on cEEG indications (Herman et al., 2015). This analysis was approved under Brigham and Women's Hospital 2012 Institutional Review Board (IRB) protocol (2012P001187: "Critical Care EEG Monitoring Research Consortium Database") and Yale New Haven Hospital IRB protocol. Need for informed consent was waived. Procedures followed were in accordance with IRB (MOD00040247: "Urgent Inpatient EEG and Multimodality Monitoring Databank") ethical standards for human experimentation and the Helsinki Declaration of 1975.

Data variables:

Data entry was prospectively performed by attending neurologists who were either board certified or board eligible in clinical neurophysiology or epilepsy, and clinical neurophysiology/epilepsy fellows trained and certified to use the American Clinical

Neurophysiology Society (ACNS) Standardized Critical Care EEG Terminology (L. J. Hirsch et al., 2021; L. J. Hirsch et al., 2013). Details of the training/certification procedure have been previously published (Gaspard et al., 2014; Lee et al., 2016). The current manuscript uses the first (2013) version of the terminology (L. J. Hirsch et al., 2013), which was in use in this database until it was locked on (June 1, 2021). The multicenter database includes demographic information (age and sex), clinical diagnoses, and the presence or absence of RPPs including lateralized periodic discharges (LPDs) (including bilateral independent and multifocal periodic discharges), generalized periodic discharges (GPDs), lateralized rhythmic delta activity (LRDA), generalized rhythmic delta activity (GRDA), and brief potentially ictal rhythmic discharges (BIRDs). For each patient, only RPPs from the first 24 hours of cEEG were included. For each RPP (excluding BIRDs) the applicable ACNS modifiers (L. J. Hirsch et al., 2021), including prevalence, frequency, sharpness, "Plus" Modifiers, and relative amplitude, were also assessed.

To limit heterogeneity and selection bias, only modifiers with less than 20% missing data were included as candidate predictors in the subsequent multivariate model. Only prevalence, typical frequency ($\leq$1 Hz, $>$1Hz to $<$2 Hz, $\geq$2 Hz), and superimposed Plus modifiers met this criterion. Patients with missing data from the above modifier groups were also excluded (n = 515, 4%), leaving 11,935 patients for model fitting and testing. We screened predictor variables for collinearity and found no pair with Spearman Rho greater than 0.4.

Primary Outcome

In the database, electroclinical seizures and/or SE were defined for each cEEG epoch by the reading physician. In general, these followed the modified Young criteria (seizures) (Young et al., 1996) and modified Salzburg criteria (SE) (Leitinger et al., 2015; Trinka et al., 2015). Seizure and SE semiology were categorically classified. Clinical events (including myoclonus) without electroencephalogram correlate were not classified as seizure/SE in any participating center. Given our intention to identify factors specifically associated with SE (not just any seizure), we defined an ordinal, mutually exclusive outcome using the first 72 hours of cEEG recording: no seizures (NoSz), SzNoSE, or SE (with or without isolated seizures). We additionally defined two composite groups: AnySz and no SE (NoSE).

Variable Screening and Regression Modeling:

Due to relative outcome rarity, to maximize power, we randomly split the cohort into 90% training (n = 10,745) and 10% testing (n = 1,190) samples, retaining the relative outcome proportions in each sample. Within the 90% training sample, we used a screening procedure to fit a multivariate adjacent category logit regression model to the ordinal outcome (NoSz, SzNoSE, or SE). Adjacent category logit models are similar to logistic regression models but without the proportional odds assumption. Each observation is assigned a (log) probability of each outcome level. For each variable, these models estimate a separate odds ratio (OR) for each pair of the ordinal outcome categories. However, variables with increased odds of SzNoSE versus NoSz, but no increased odds of SE relative to SzNoSE, may still have increased odds of SE when compared with NoSE. We used the same models to also report ORs for composite outcomes (AnySz vs NoSz, SE vs NoSE) for a more straightforward clinical interpretation.

To winnow a large set of candidate predictor variables, we first conducted a univariate screen within the training sample, retaining variables with a p value of less than 0.1 for significance of association with either level of the outcome (SzNoSE or SE). We used reverse, Bayesian Information Criterion (BIC) based variable selection. BIC-based selection is more restrictive (favoring fewer variables in the model) than Akaike Information Criterion-based selection. Two separate models were fit. The first was a basic model, including demographic variables, clinical diagnoses, and the presence/absence of each RPP. The second was an expanded model, which included demographics, clinical diagnoses, and major modifiers that met inclusion criteria. The area under the receiver operating characteristic curves (AUROCs) for each model were calculated in the 10% held-out testing sample for outcomes SE and AnySz. Confidence was generated using 2,000 bootstrap replicates. The resulting AUROCs were compared using DeLong test. Analyses were performed in R Version 4.1.2 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Cohort Characteristics

A total of 12,450 subjects at least 18 years old underwent cEEG at one of three centers between 2013 and 2021. The mean age was 60 years (± 17 yr) and 50% were male (Table 1).

The median duration of continuous recording was 1 day (interquartile range, 1–3 d). One thousand nine hundred forty-three subjects (16%) had monitoring that extended beyond 3 days and was excluded in the analysis of the primary outcome. Over the first 72 hours of cEEG, 1,226 subjects (9.8%) had AnySz, 439 (3.5%) had SE, and 787 (6.3%) had SzNoSE (Table 1). Patients with AnySz or SE had longer cEEG monitoring periods than those without (AnySz: 95% CI, 1.5–2.0 additional days; $p < 0.001$ and SE: 2.2–3.0 additional days; $p < 0.001$). The distribution of demographics, diagnoses, RPPs, seizures, and SE differed by study but with effect size measures (Cramer's Phi or Eta2) that were either negligible or small.

Variables	Full Cohort (N = 12,450)	90% Training Sample (n = 10,745)	10% Testing Sample (n = 1,190)
% Emory	4527 (36)	3958 (37)	429 (35)
% Brigham and Women's Hospital	3687 (30)	2989 (28)	348 (29)
% Yale	4236 (34)	3798 (35)	413 (35)
Age, years, mean (SD)	60 (17)	60 (17)	59 (18)
Male (%)	6271 (50)	5440 (51)	584 (49)
Diagnostic Category			
Clinical seizure/ status (%)	3368 (27)	2900 (27)	356 (30)
Toxic metabolic encephalopathy (%)	2944 (24)	2557 (24)	261 (22)
Intraparenchymal hemorrhage/ subarachnoid hemorrhage (%)	1801 (14)	1564 (15)	160 (13)
Cardiac arrest (%)	988 (8)	848 (8)	100 (8)
Neoplastic (%)	865 (7)	735 (7)	80 (7)
Stroke, ischemic (%)	824 (7)	723 (7)	79 (7)
Traumatic brain injury/ subdural hematoma (%)	764 (6)	643 (6)	75 (6)
Other (%)	562 (5)	499 (5)	53 (4)
Infectious or inflammatory (%)	209 (2)	182 (2)	20 (2)
Alcohol/drug withdrawal (%)	106 (1)	94 (1)	6 (1)
Rhythmic and Periodic Patterns			
Brief potentially ictal rhythmic discharges (%)	266 (2)	222 (2)	23 (2)
Generalized rhythmic delta activity (%)	1298 (10)	964 (9)	119 (10)
Lateralized periodic discharges (%)	1078 (9)	862 (8)	94 (8)
Generalized periodic discharges (%)	954 (8)	679 (6)	75 (6)
Lateralized rhythmic delta activity (%)	596 (5)	460 (4)	53 (4)

Primary outcomes within 72 hours			
Any seizure/SE (%)	1226 (9.8)	1026 (9.5)	115 (9.7)
SzNoSE (%)	787 (6.3)	656 (6.1)	73 (6.1)
SE (%)	439 (3.5)	370 (3.4)	42 (3.5)
Primary outcomes all recording			
Any seizure/SE (%)	1423 (11)	1198 (11)	135 (11)
SzNoSE (%)	902 (7)	775 (7)	87 (7)
SE (%)	521 (4)	443 (4)	48 (4)
Days to first seizure, median (IQR)	0 (0 – 1)	0 (0 – 1)	0 (0 – 1)
Days to SE, median (IQR])	0 (0 – 1)	0 (0 – 1)	0 (0 – 1)

Table 1: Cohort Characteristics. IQR = interquartile range, SE = status epilepticus, SzNoSE = seizure without status epilepticus

Clinical Diagnoses

The proportion of patients with SE ($\chi^2_9 = 252$; $p < 0.001$) and AnySz ($\chi^2_9 = 288$; $p < 0.001$) differed by clinical diagnostic category (Figure. 1A). Patients with cardiac arrest were at highest risk for SE (prevalence of SE: 10% ± 1%, OR vs toxic metabolic encephalopathy: 6.0 [4.3–8.4]; $p < 0.001$) and patients with ischemic stroke were at lowest risk (prevalence: 0.6% ± 0.3%; OR, 0.3 [0.1–0.8]; $p = 0.02$]). None of the 111 patients with drug or alcohol withdrawal had SE. The highest risk for AnySz occurred in patients presenting with clinical seizures within 24 hours of cEEG (prevalence of AnySz: 16% ± 1%, OR vs toxic metabolic encephalopathy: 3.1 [2.6–3.7]; $p < 0.001$) and those with an infectious or inflammatory brain disorder (prevalence: 16% ± 2%; OR, 2.9 [2.0–4.3]; $p < 0.001$). Patients presenting with alcohol or drug withdrawal had the lowest risk of AnySz (2% ± 1%; 0.3 [0.1–1.2]; $p = 0.1$).

Rhythmic and Periodic Patterns

The incidence of SE ($\chi^2_4 = 503$, $p < 0.001$) and AnySz ($\chi^2_4 = 1601$, $p < 0.001$) differed by RPP. Patients with LPDs had the highest prevalence of SE (15 ± 1%) and AnySz (43 ± 1%), regardless of whether they occurred alone or with another pattern (Figure 1B). In patients with LRDA, 4 ± 1% had SE and 24 ± 2% had AnySz; among GPDs: 8 ± 1% SE and 13 ± 1% AnySz: among GRDA alone, 1 ± 1% SE and 5 ± 1% AnySz (Figure 1B). In the absence of other patterns, and compared with those without any RPPs, patients with GRDA trended toward a lower incidence of SE ($\chi^2_1 = 3.6$; $p = 0.06$) and had no difference in the prevalence of AnySz ($\chi^2_1 = 1$; $p = 1$).

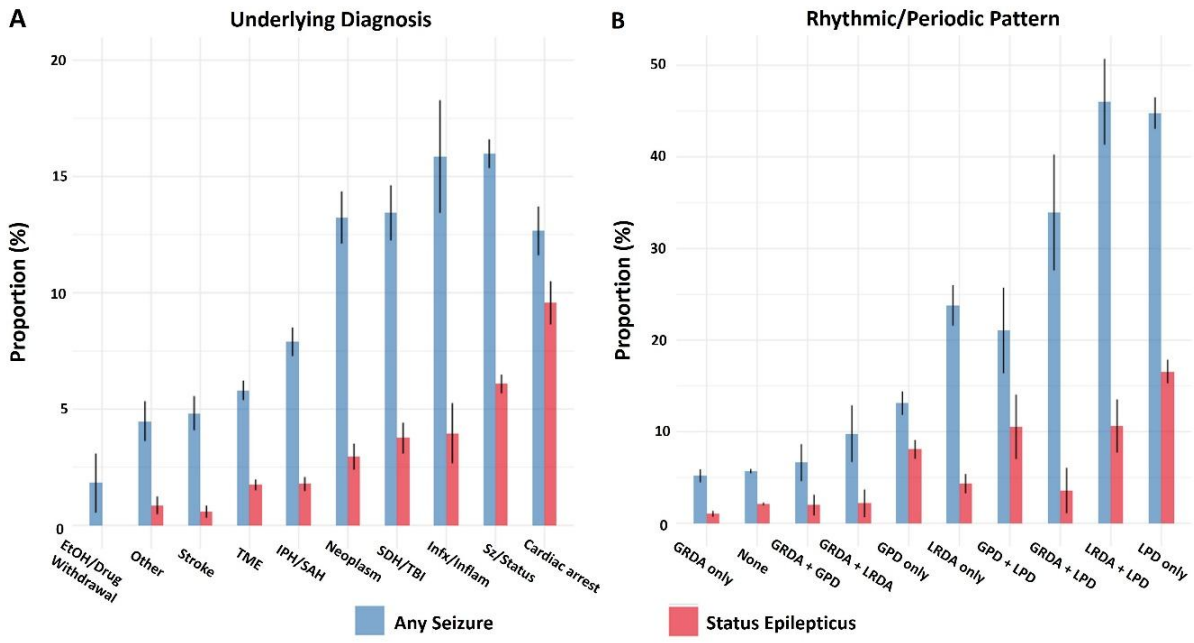

Figure 1. Prevalence of seizures (ESz) and status epilepticus (SE) differs by clinical diagnosis and rhythmic or periodic pattern. Proportion of the overall cohort with any electroclinical Sz (blue bars) or electroclinical status epilepticus (red bars) within the first 72 hr. of electroencephalogram recording. **A**, Stratified by clinical diagnostic category. **B**, Stratified by every combination of rhythmic and periodic patterns encountered in at least 10 patients. Error bars represent standard error. EtOH = ethyl alcohol, GPDs = generalized periodic discharges, GRDA = generalized rhythmic delta activity, IPH = intraparenchymal hemorrhage, LRDA = lateralized rhythmic delta activity, SAH = subarachnoid hemorrhage, SDH = subdural hematoma, TBI = traumatic brain injury, TME = toxic metabolic encephalopathy.

Diagnostic Categories and RPPs: Multivariate Model (excluding modifiers)

Using the training sample (n = 10,745), univariate associations with SE and isolated seizures were determined for demographics, clinical diagnoses and RPPs. Adjusted ORs (aORs) from the final multivariate model are shown in Figure 2A. Factors independently and significantly associated with SE (vs NoSE) were: cardiac arrest (9.2% SE; aOR, 8.8 [95% CI, 6.3–12.1]), clinical seizures prior to cEEG (5.7%; 3.3 [2.5–4.3]), brain neoplasms (3.2%; 1.6 [1.0–2.6]), LPDs (15.4%; 7.3 [5.7–9.4]), BIRDs (22.5%; 3.8 [2.6–5.5]), and GPDs (7.2%; 2.4 [1.7–3.3]) (Figure 2A: left column). All the above variables, as well as LRDA (aOR, 3.3 [2.6–4.2]), were also associated with AnySz (vs NoSz, Fig. 2A: middle column).

Variables with an increased odds of SE relative to isolated seizures (SE vs SzNoSE) included cardiac arrest (aOR, 7.3 [4.4–12.1]), clinical seizures/SE (1.7 [1.3–2.4]), GPDs (2.3 [1.4–

3.5]), and LPDs (1.4 [1.0–1.9]) (Fig. 2A: right column). LRDA was the only RPP with lower odds of SE versus isolated seizures (SE vs SzNoSE: 0.5 [0.3– 0.9]). In a sensitivity analysis including all outcomes (SE: n = 472, SzNoSE: n = 831) occurring within 7 days (rather than 72 hr.) of cEEG recording, the final model was minimally altered. In sensitivity analyses using no missing-modifier exclusions (n = 11,208), or separating bilateral independent periodic discharges combined with multifocal periodic discharges from LPDs, rather than grouping all three together, the final model was unaltered. Of the 96 patients with cardiac arrest and SE, 63 (65%) had myoclonic SE. Excluding these patients and repeating the model selection procedure (n = 10,693) revealed mostly the same associations with SE and isolated seizures. However, the univariate strength of association between cardiac arrest and SE (3% with SE, OR vs SzNoSE: 1.9 [1.1–3.3]), and GPDs with SE (5% with SE, OR vs SzNoSE: 1.9 [1.2– 3.0]) was diminished. The multivariate aOR for SE vs NoSE of cardiac arrest fell from 8.8 to 2.9, and GPDs fell from 2.4 to no longer being selected by the model.

To determine whether associations between RPPs and seizures/SE differed based on the underlying clinical diagnosis, we screened our multivariate model for significant interaction terms between RPP and clinical diagnoses. For LPDs and LRDA, the magnitude of associations did not differ by clinical diagnosis (all $p > 0.05$). The association between GPDs and SE was greater in patients with clinical seizures and cardiac arrest than in patients with brain neoplasms ($p < 0.05$). The discriminative performance of the multivariate model was assessed by testing its performance in the held-out testing sample. The model had an AUROC of 0.81 (95% CI, 0.74–0.88) for predicting SE (vs NoSE, Figure. 2B) and 0.78 (0.74–0.83) for predicting AnySz (vs NoSz, Figure. 2C). Model predictions were well-calibrated; Hosmer and Lemeshow test SE: $p = 0.4$; AnySz: $p = 0.9$).

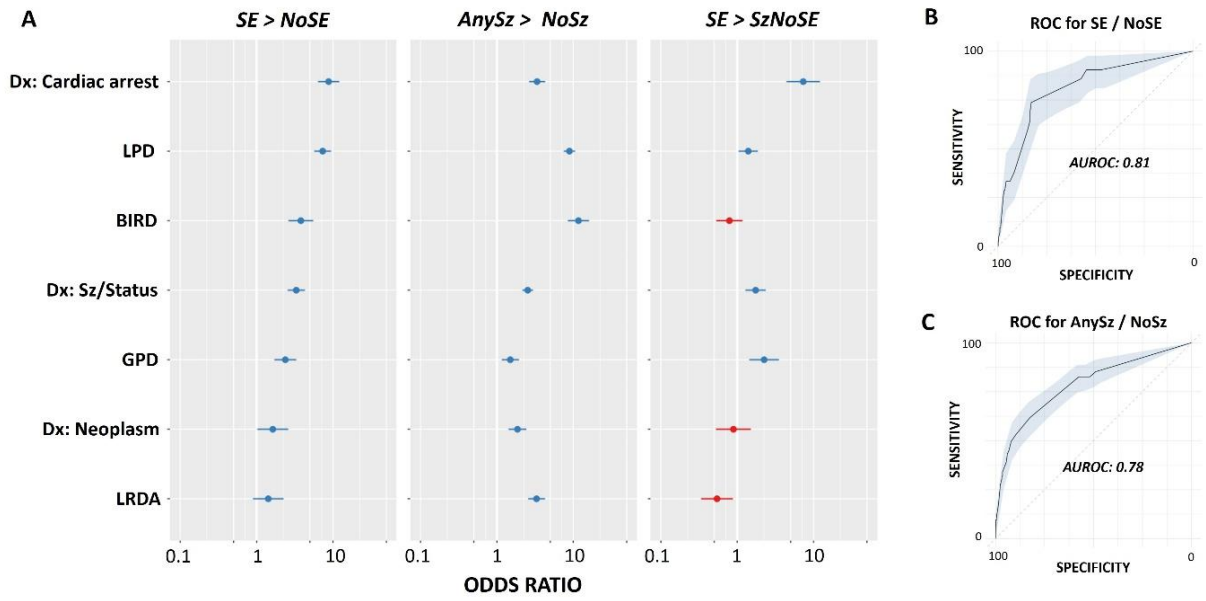

Figure 2. Multivariate seizure (Sz) and status epilepticus (SE) prediction model. Variables selected (demographics, clinical diagnoses, rhythmic and periodic patterns) in the final multivariate adjacent category logit model are shown in a forest plot (**A**). The left column displays odds ratios for SE compared with no SE (NoSE), the middle column displays odds ratios for any Sz (AnySz) compared with no Sz (NoSz), and the right column displays odds ratios for SE as compared with Sz without SE (SzNoSE). **B**, Model's receiver operating characteristic (ROC) curve for discriminating SE from NoSE in the held-out test sample. C, Model's ROC curve for discriminating AnySz from NoSz. The shaded area represents bootstrapped 95% CI. AUROC = area under the ROC curve, BIRDs = brief potentially ictal rhythmic discharges, Dx = diagnosis, GPDs = generalized periodic discharges, LPD = lateralized periodic discharges, LRDA = lateralized rhythmic delta activity.

RPP Modifiers

The distribution of modifiers in patients with GPDs, LPDs, GRDA, and LRDA are shown in Table 2 and the proportion with SE and AnySz are shown in Figure 3. The highest prevalence of SE occurred in patients with spiky (< 70 ms.) GPDs (34 $\pm$ 6%, Figure 3D). The highest prevalence of AnySz occurred in patients with spiky LPDs (64 $\pm$ 4%, Figure 3D). The lowest prevalence of AnySz occurred in patients with GRDA with a low typical frequency ($\leq$ 1 Hz: 7 $\pm$ 1%, Figure 3A).

Variables	Generalized Periodic Discharges (n = 954)	Lateralized Periodic Discharges (n = 1078)	Generalized Rhythmic Delta Activity (n = 1298)	Lateralized Rhythmic Delta Activity (n = 596)
Prevalence				
Rare (%)	70 (7)	72 (7)	139 (11)	85 (14)
Occasional (%)	255 (27)	242 (22)	499 (38)	218 (37)
Frequent (%)	297 (31)	317 (29)	494 (38)	205 (34)
Abundant (%)	226 (24)	274 (25)	117 (9)	58 (10)
Continuous (%)	78 (8)	153 (14)	15 (1)	12 (2)
Missing (%)	28 (3)	20 (2)	34 (3)	18 (3)
Frequency				
$\leq$ 1 Hz (%)	530 (56)	740 (69)	421 (32)	187 (31)
$>$1 Hz to $<$ 2 Hz (%)	148 (16)	169 (16)	470 (36)	205 (34)
$\geq$ 2 Hz (%)	105 (11)	68 (6)	226 (17)	141 (24)
Missing (%)	171 (18)	101 (9)	181 (14)	63 (11)
Plus modifier (%)	199 (21)	371 (34)	170 (13)	147 (25)
Sharpness				
Spiky (< 70 ms.)	65 (7)	126 (12)	--	--
Not Spiky ($\geq$ 70ms)	443 (46)	558 (52)	--	--
Missing	446 (47)	395 (37)	--	--
Relative amplitude				
$>$ 2:1	248 (26)	325 (30)	--	--
$\leq$ 2:1	35 (4)	62 (6)	--	--
Missing	671 (70)	691 (64)	--	--

Table 2: Rhythmic and Periodic Pattern modifying characteristics. Dashes indicate data is not relevant for these categories.

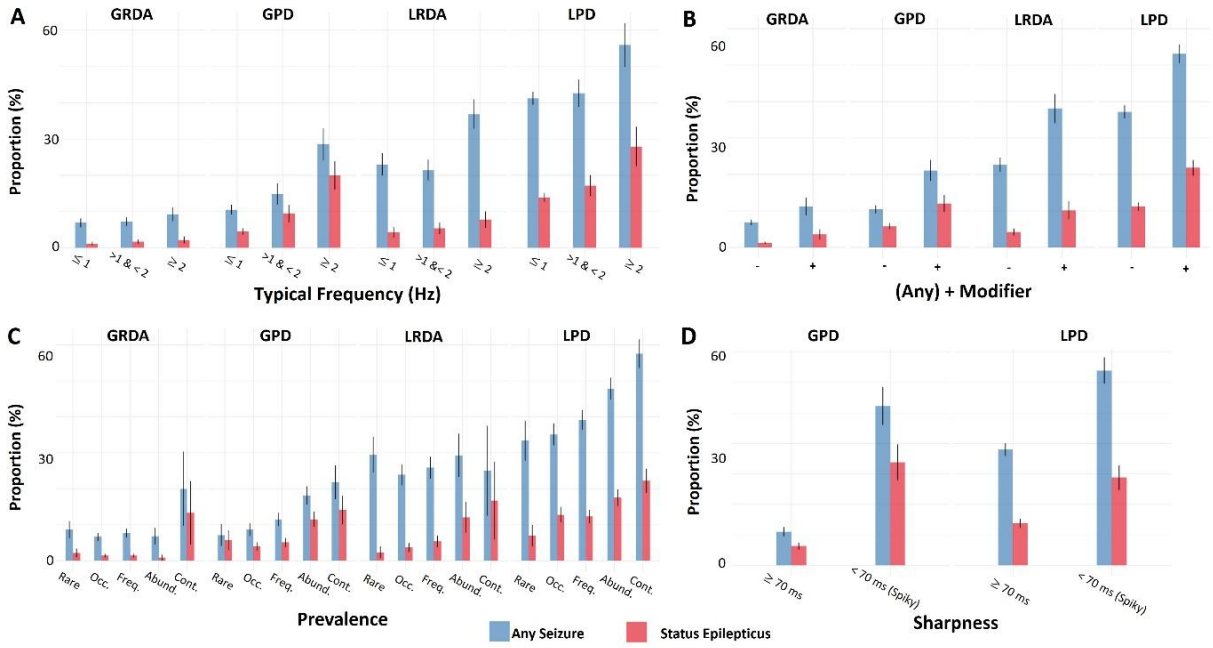

Figure 3. Prevalence of seizures and status epilepticus differ by rhythmic and periodic pattern (RPP) modifiers. Proportion of the overall cohort with any electroclinical seizure (blue bars) or electroclinical status epilepticus (red bars) within the first 72 hr. of electroencephalogram recording. **A**, Stratified by RPP typical frequency, by the presence of a plus modifier (**B**), by prevalence (**C**), and by periodic discharge sharpness (**D**). Error bars represent standard error. + modifier = any plus modifier, prevalence categories, rare less than 1% of the record/epoch, occasional 1–9%, frequent 10–49%, abundant 50–89%, continuous greater than or equal to 90%, GPDs = generalized periodic discharges, GRDA = generalized rhythmic delta activity, LPDs = lateralized periodic discharges, LRDA = lateralized rhythmic delta activity.

Diagnostic Categories and RPPs: Multivariate Model (including modifiers)

The univariate screen was repeated and model fitting with RPPs subdivided by major modifiers was performed. Sharpness was excluded due to missing data.

In the final RPP modifier model, higher typical frequency determined much of the SE risk for periodic discharges (GPDs ≥ 2 Hz: aOR, 7.9 [95% CI, 4.3–13.8] and LPDs ≥ 2 Hz: 10.3 [5.1–20.0]. LPDs with a Plus modifier were also associated, though to a lesser extent than typical frequency, with SE (2.1 [1.4–3.1]). While not associated with SE, higher typical frequency of LRDA (i.e., ≥ 2 Hz) increased the odds of AnySz (4.3 [2.7–6.6]). Among all the RPP modifiers, only GPDs with typical frequency greater than or equal to 2 Hz were specifically associated with SE (SE vs SzNoSE: 3.3 [1.4–7.7]). In a sensitivity analysis using different typical frequency groupings (≤ 1 Hz, > 1 Hz to ≤ 2 Hz, > 2 Hz), the final model was

minimally altered. This model had an AUROC of 0.81 (0.74–0.88) for predicting SE versus NoSE; and 0.78 (0.73– 0.82) for predicting AnySz versus NoSz in the held-out testing sample. The performance of this model (including modifiers) was not different from the first model (no modifiers) for SE (95% CI for AUROC difference, –0.03 to 0.02; p = 0.8) or AnySz (95% CI, –0.02 to 0.01; p = 0.3).

Discussion

In this analysis of the largest existing prospectively collected multicenter cEEG database, we report novel insights about the relationship of clinical diagnoses and RPPs with seizures and SE. We identified factors associated with SE: cardiac arrest, clinical seizures prior to cEEG, brain neoplasms, LPDs, BIRDs, and GPDs. While all these factors and LRDA were also associated with AnySz, cardiac arrest, clinical seizures prior to cEEG, GPDs, and LPDs showed a stronger association with SE than isolated seizures. LRDA was the only RPP where the association with SE was significantly less than its association with isolated seizures. SE could be accurately predicted using a combination of only three clinical features (cardiac arrest, clinical Sz/SE in the prior 24 hr., and brain neoplasm) together with the presence or absence of highly epileptiform patterns (BIRDS, GPDs, LPDs, and LRDA), with a discriminative capacity equivalent to that of previously published seizure prediction models (A. F. Struck, Ustun, et al., 2017). The typical frequency of an RPP held the greatest independent association with SE but did not significantly improve predictive performance.

Cardiac arrest showed the strongest clinical association with SE. When myoclonic SE was excluded from this group, the association was diminished but still present. Stroke has a previously reported association with SE (Fountain, 2000; Mayer et al., 2002). In our sample, which included more than 2,600 patients with ischemic stroke and brain hemorrhage, these diagnoses carried a lower risk of SE (vs all other diagnoses).

Among the RPPs, LPDs and BIRDs carried the strongest association with SE, although only LPDs had an increased relative risk of SE compared with isolated seizures. LRDA was the only RPP with a significantly lower odds of SE as compared with isolated seizures. LRDA can be the surface electroencephalogram representation of poorly propagated periodic discharges and/or seizures when recording with intracranial electroencephalogram (Waziri et

al., 2009). Deeper ictal abnormalities may not sustain, as well as cortically superficial seizures. In conflict with previous data (Gaspard et al., 2013), patients with LRDA had a lower prevalence of AnySz and SE than patients with LPDs. This discrepancy may be due to some readers including regional polymorphic slowing, a lower risk pattern (Gaspard et al., 2013), under this term.

While GPDs were significantly and specifically associated with SE, this association was largely driven by patients with cardiac arrest and myoclonic SE. Myoclonic SE after cardiac arrest, particularly those patients with burst suppression and nonevolving EEG spikes, may have a distinct pathophysiology from other types of SE, and an unclear benefit from treatment (Elmer et al., 2016; Freund & Kaplan, 2017; Rittenberger, Popescu, Brenner, Guyette, & Callaway, 2012). This study did not have the granularity necessary to stratify patients in accordance with these described electroclinical phenotypes (Elmer et al., 2016), but future work may greatly assist in identifying prognostically relevant and/or treatment responsive subgroups.

Consistent with previous reports (Rodriguez Ruiz et al., 2017), GRDA was not a risk factor for seizures or SE. Patients with continuous GRDA and/or GRDA-plus may have an increased risk of seizures, but the numbers were too small to be conclusive.

Increased typical frequency, prevalence, and presence of a Plus modifier have previously been associated with greater seizure risk (Rodriguez Ruiz et al., 2017). Few studies have assessed how other modifiers adjust seizure risk. Only one other study demonstrated that spiky LPDs had a greater association with seizures than sharply contoured discharges (Newey et al., 2017), and no study has provided the relative weighting of major modifiers. In our study, spiky (< 70 ms.) GPDs had the greatest univariate association with SE, but the significant proportion of missing data precluded analysis in the complete multivariate context. Future studies that provide the relative contributions of each modifier (including modifiers excluded from the current study due to incomplete data) on seizure/SE risk would have great clinical utility. Finally, we demonstrated for the first time that apart from GPDs, associations between RPPs and seizures/ SE do not differ by clinical diagnosis. While the absolute prevalence of each outcome differs substantially depending on the underlying diagnosis, the relative risk conferred by each RPP was unchanged.

This SE prediction model is similar to established seizure prediction models (A. F. Struck, Ustun, et al., 2017). Future studies could compare this SE-specific model to established

seizure prediction scores in independent datasets. The ultimate goal is to use cEEG to identify patients at risk of SE and secondary neuronal injury from clinical diagnoses and RPPs early in their admission.

Though the incidence of any seizure in patients with GPDs in this study (13%) was less than previously reported values (25-33%)(Foreman et al., 2012), GPDs were significantly and specifically associated with SE. This association may reflect patients with abundant GPDs that increase in typical frequency (and therefore qualify as seizures themselves), though the mechanism behind this tendency is uncertain. Consistent with previous reports(Rodriguez Ruiz et al., 2017), patients with GRDA had a risk of seizures and SE equivalent to patients without RPPs. It is possible that the subgroup of patients with continuous GRDA and/or GRDA-plus have an increased risk of seizures, but the numbers in these groups were too small to be conclusive.

This work includes several limitations that are common to retrospective studies. First, we cannot rule out the possibility that unmeasured confounders, including differences in medical treatments, concomitant medical disorders, and metabolic disturbances, contributed to the observed associations. Second, given that we analyzed only information that was entered into a standardized database rather than the electroencephalogram waveforms themselves, we could not ensure that RPPs invariably preceded the measured outcomes. Third, though reading physicians followed standardized criteria for the characterization of RPPs, seizures and SE, between-site variability in practice may have reduced our power to measure true underlying associations. Fourth, clinical practice around cEEG and seizure prophylactic therapy may have varied between sites, adding additional heterogeneity. Fifth, while this is the largest study of its kind, due to missing data, it is likely that we were underpowered to study some of the individual RPP modifiers. Sixth, no information regarding race and ethnicity was collected in this database, preventing demographic comparisons to other cohorts, as well as race stratified or comparative analyses. Finally, criteria for electroclinical seizures and SE, not present in 2013, were introduced to the Standardized ACNS Critical Care EEG terminology in 2021 (L. J. Hirsch et al., 2021) after database lock. Certain patients may have been reclassified as SE according to the new criteria

Conclusions

In critically ill patients undergoing cEEG, cardiac arrest, clinical seizures, brain neoplasms, BIRDS, and periodic discharges were independently associated with SE. LRDA was not associated with SE but was associated with isolated seizures. Of RPP modifying characteristics, typical frequency showed the dominant association with SE but did not add significant predictive value. Understanding why RPPs show differential associations with isolated seizures and SE will require further investigations into the underlying brain physiology they represent.

Chapter 4: Lateralized Rhythmic Delta Activity including bilateral asymmetric variants

Plain English summary

Large prospectively collected datasets are excellent at determining the group associations of particular clinical diagnoses or cEEG findings with seizures or SE. When analyzed as a large cohort the effects of subsets within a group get diluted by the effect of the group overall. The best way to determine the effect of a particular pattern within a group is a case control study design. There is a particular pattern of rhythmic delta activity (RDA) on cEEG that shares similarities between lateralized and generalized patterns. This pattern has been classified as bilateral asymmetric lateralized rhythmic delta activity (LRDA-ba), which appears in both hemispheres but clearly and consistently favors one hemisphere. It has been debated whether this truly represents LRDA and carries the same association with acute focal structural brain injury and seizures, or whether it is GRDA that is being adjusted by one side being dysfunctional with no association with seizures.

This chapter represented a case control study of 258 patients with LRDA-ba and matched 1:1 to a cohort of GRDA with similar cEEG characteristics (apart from the main pattern). This was the first study that assessed LRDA-ba directly.

The study found LRDA-ba occurred significantly more on the side of an acute structural brain injury documented on CT, when compared to the matched cohort of patients with GRDA. Patients with LRDA-ba were more likely to have other markers of focal cortical excitability (spontaneous focal epileptiform discharges, and lateralized periodic discharges [LPDs]) and seizures. The association of seizures was present when taking patients with LRDA-ba alone with no other cEEG markers of focal cortical excitability, but the effect was not sufficient to achieve significance, although it was close.

This is the first study that has specifically assessed bilateral asymmetric patterns on cEEG and justified these to be classified and treated as a unique electrographic entity with clearly different features and associations compared to GRDA.

Abstract

Lateralized Rhythmic Delta Activity (LRDA) is highly associated with seizures but Generalized Rhythmic Delta Activity (GRDA; symmetric and synchronous by definition) has no known seizure association. A subset of LRDA includes patterns that are *"bilateral asymmetric"* (LRDA-ba), falling between purely unilateral LRDA and GRDA. The significance of this finding has not been previously addressed. This study was a retrospective cohort of clinical, EEG and imaging findings in all patients with > 6 hours of continuous EEG and LRDA-ba between 2014-2019. They were compared to a control group of patients with GRDA, matched 1:1 for prevalence, duration, and frequency of the predominant rhythmic pattern.

Two-hundred-fifty-eight patients with LRDA-ba and 258 matched controls with GRDA were identified. Statistically significant findings included that patients with LRDA-ba were more likely to have presented with an ischemic stroke (LRDA-ba 12.4% vs GRDA 3.9%) or subdural hemorrhage (8.9% vs 4.3%); those with GRDA were more likely to have a metabolic encephalopathy (GRDA 10.5% vs LRDA-ba 3.5%), or "altered mental state" without clear etiology (12.5% vs. 4.3%). Patients with LRDA-ba were significantly more likely to have a background EEG asymmetry (LRDA-ba 62.0% vs GRDA 25.6%) or focal (arrhythmic) slowing (40.3% vs. 15.5%), and acute (65.5% vs 46.1%) or focal (49.6% vs 28.3%) abnormalities on CT scan. Patients with LRDA-ba were more likely to have focal sporadic epileptiform discharges (SDs) (95.4% vs 37.9%), Lateralized Periodic Discharges (LPDs) (32.2% vs 5.0%), and focal electrographic seizures (ESz) (33.3% vs. 11.2%); however, patients with LRDA-ba alone (i.e., without SDs or PDs) showed only a trend towards increased seizures (17.3%) compared to a matched group of patients with GRDA alone (9.9%, p=0.08).

Patients with LRDA-ba had a higher proportion of acute focal abnormalities compared to a matched group of patients with GRDA. LRDA-ba was associated with additional evidence of focal cortical excitability on EEG (SDs and LPDs) and seizures, but with only a trend towards increased seizures when other signs of focal excitability were absent.

Introduction

In 2012 the American Clinical Neurophysiology Society (ACNS) published standardized critical care EEG terminology, which has been revised in 2021 (L. J. Hirsch et al., 2021; L. J. Hirsch et al., 2013). In this nomenclature, Rhythmic Delta Activity (RDA) was mostly separated into "Generalized" (GRDA) and "Lateralized" (LRDA) patterns, although Bilateral Independent (BI) and Multifocal (Mf) patterns also exist (L. J. Hirsch et al., 2021; L. J. Hirsch et al., 2013). Since then, LRDA has been established as a pattern of hyper-excitability with a strong association with seizures, whereas GRDA has not (Gaspard et al., 2013; Husari et al., 2021; Rodriguez Ruiz et al., 2017). A pattern that is often debated is the "bilateral asymmetric" LRDA pattern. These patterns are "seen bilaterally but clearly and consistently higher amplitude in one hemisphere" (L. J. Hirsch et al., 2021; L. J. Hirsch et al., 2013). These patterns are currently included under the "Lateralized" main term. The debate has been that at times LRDA-bilateral asymmetric (LRDA-ba) resembles GRDA but with attenuation of the pattern in the dysfunctional hemisphere (Figure 1). If these patterns would be higher amplitude on the healthier hemisphere they would not be expected to be associated with seizures and merely a marker of dysfunction.

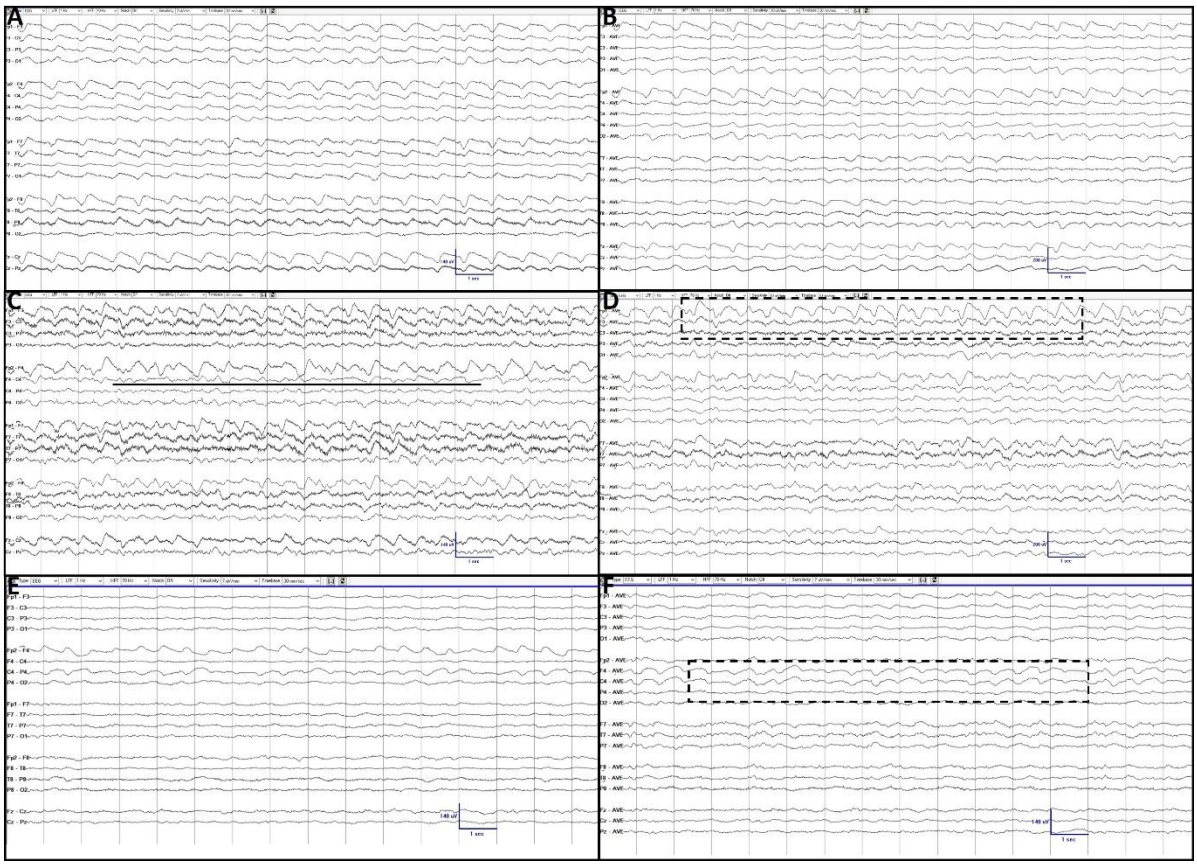

Figure 1: Rhythmic Delta Activity. The figure demonstrates Generalized Rhythmic Delta Activity (GRDA) (**Panel A**, Bipolar Longitudinal **and B**, Referential montage), Lateralized Rhythmic Delta Activity (LRDA), bilateral asymmetric (**Panel C and D**), and Lateralized Rhythmic Delta Activity, unilateral (**Panel E and F**). Panel C demonstrates RDA that is maximal in the left frontal region (Fp1) but is also present in the right frontal region (Fp2) (underlined). On the referential montage (Panel D) it becomes more apparent that the RDA is clearly and consistently of greater amplitude on the left (dashed box). It is lateralized but present in both hemispheres, therefore classified as LRDA-ba. Panel E and F contrast this with LRDA, unilateral. The RDA is maximal in the right frontal region (F4/C4) (dashed box) but not present on the left at all. NOTE in this set of examples, the LRDA-ba (especially in Panel C), more closely resembles GRDA (Panel A), than LRDA, unilateral (Panel E).

In prior studies of Rhythmic and Periodic Patterns (RPPs) that included large numbers of patients, LRDA has always been studied as a whole, with LRDA-ba making up a small proportion of these cases (Rodriguez Ruiz et al., 2017). It is questioned whether LRDA-ba more resembles GRDA, and whether its inclusion in "Lateralized" falsely reduces the rate of associated seizure in this group. The current study therefore specifically selects patients with LRDA-ba and compares them directly with a matched group of patients with GRDA. The null hypothesis being that those with LRDA-ba would not differ in etiology, other clinical features, associated seizures or imaging findings compared to those with GRDA.

Methods

Patients

Patients were selected from retrospective reviews of all cases in a critical care EEG database (Yale Comprehensive Epilepsy Center) between December 2014 and December 2019. During this time period, the Yale Comprehensive Epilepsy Center used the Critical Care EEG Monitoring Research Consortium's (CCEMRC) publicly available database https://www.acns.org/research/critical-care-eeg-monitoring-research-consortium-ccemrc/ccemrc-public-database). All patients were screened and included if they were older than 18 years of age, had greater than 6 hours of continuous EEG monitoring and had the finding of LRDA-ba (as the predominant pattern, the pattern with the greatest overall burden) at some point during their EEG recording. Patients were then matched in a 1:1 ratio with patients who had GRDA taken from the same database. Since an increase in the prevalence (burden), duration, or typical frequency (i.e., cycles per second, or Hertz) of patterns have been associated with an increase in seizure rate (Rodriguez Ruiz et al., 2017), patients with

GRDA were blindly matched for these EEG characteristics i.e., without any knowledge of the clinical or other electrographic features. Only those 3 electrographic features were matched, and only for the predominant pattern, i.e., if the patient had several patterns only the prevalance, duration and typical frequency of the predominant patten was matched. In the case that an identically matched patient (i.e., with exactly same prevalance, duration, and typical frequency) could not be found the patient that had the "best" match was selected. The "best" match meant two of the modifiers were identical, but the third differed only by 1 prevelance/ duration category, or 0.5 Hz typical frequency. Other major modifiers (such as *plus* modifiers) also determine seizure risk. These modifiers were not additionally matched as that many modifiers would have made it difficult to achieve accurate matching of LRDA-ba and GRDA groups. Patients could not be included in both the GRDA and LRDA-ba groups. The EEG findings of all patients were confirmed by author MF. This was particularly relevant for patients in the database having both patterns coded prospectively. Author MF reviewed the studies retrospectively (without any knowledge of the clinical features) and determined the predominant pattern. If the patient had an equal predominance of GRDA and LRDA-ba then the patient was excluded. The matched modifiers did change across recording sessions for any given patient. At the time of matching, all database entries for a given patient were available for review. Patients were only allowed to be included using the set of modifiers that were deemed "typical" for that given patient (i.e., if a patient had 3 records with a continuous, very long, 1.5-Hz RPPs, and 1 record with frequent, brief, 1-Hz RPPs that patient could only be selected as having the former "typical" set of modifiers).

Clinical data were collected from electronic chart reviews and additional EEG characteristics from retrospective review of critical care EEG database information, which was entered prospectively as part of clinical care. The CT imaging findings of each patient were also gathered. Imaging reports were reviewed, but to further classify the findings and document the location and lateralization of abnormalities each CT scan was reviewed by either author MF or RJ. The EEG was often performed within 48 hours of the presenting CT scan; however, patients did often have several CT scans during admission. In those cases, all CT scans during the acute admission were reviewed and if an abnormality was found on any of those scans the findings were recorded. Lateralized findings, such as focal slowing on EEG, focal seizures, or acute brain abnormalities were also recorded as either concordant (same side), or discordant (opposite side) to the hemisphere in which LRDA-ba was maximal.

Statistical Analysis

Quantitative variables were presented as the mean and standard deviation. Qualitative variables were presented as number of cases (n) and frequencies (%). Given two independent groups (LRDA-ba vs. GRDA), the statistical significance between two parametric variables was determined with a Student t-test, whereas the statistical significance between two non-parametric variables utilized a Mann Whitney U test. For non-parametric variables with more than one outcome either Chi Square or Kruskal Wallis 1-way ANOVA was used. These tests determined if there was any significant difference in the distribution of cases across several outcomes between groups (LRDA-ba vs. GRDA). Examples that utilized such methods were assessing if there was any difference in distribution of "prevalence" or "duration" between patterns. If the distribution of a pattern was statistically significant, individual comparisons could be made with Mann Whitney U test. The statistically significant value for these comparisons was $p<0.05$.

Results

Accuracy of Matching

Patients were matched for the "burden" of a pattern, meaning relatively similar prevalence, duration (of a typical instance of the pattern) and typical frequency (Table 1). The two groups (LRDA-ba and GRDA) were well matched. Using Kruskal Wallis 1-way ANOVA; there was no difference in the distribution of *"prevalence"* ($p=0.98$) or *"duration"* ($p=0.92$) between patients with LRDA-ba or GRDA. Using Student t-test, there was no difference in the *"typical frequency"* of patterns between patients with LRDA-ba and GRDA ($p=0.51$).

Variables	Lateralized Rhythmic Delta Activity – bilateral asymmetric n=258	Generalized Rhythmic Delta Activity n=258
Prevalence		
Continuous (≥90%)	7	4
Abundant (50-89%)	32	37
Frequent (10-49%)	113	110
Occasional (1-9%)	89	91
Rare (<1%)	17	16
Duration		
Very Long (≥1 hour)	10	9
Long (5-59 min)	24	26
Intermediate (1-4.9 min)	27	30
Brief (10-59 s)	94	89
Very brief (<10 s)	103	104
Typical Frequency (Hz)	1.40 ± 0.45 SD	1.37 ± 0.44 SD

Table 1: Accuracy of Matching. Summarizing the distribution of prevalence and duration between patients with LRDA-ba and GRDA. For prevalence and duration values represent n, number of patients. Typical frequency of the pattern in both groups is also shown. Here the values are mean frequency in Hz ± standard deviation (SD).

Patient Demographics

Between December 2014 and December 2019 there were 4953 patients entered into the database, of these 258 (5.2%) had LRDA-ba and 941 (19.0%) had GRDA. Patients with LRDA-ba were older than patients with GRDA (Mean age ± Standard Deviation, LRDA-ba 61.0 ± 17.3 years vs. GRDA 55.5 ± 16.9 years, p=0.01) (Table 2). Patients with LRDA-ba were more likely to have a clinical diagnosis associated with a focal process, such as an ischemic stroke (LRDA-ba 12.4% vs GRDA 3.9%, p=0.01), or subdural hemorrhage (SDH) (8.9% vs 4.3%, p=0.03). Patients with GRDA were more likely to have diagnoses with more diffuse or nonspecific processes including "altered mental state (not otherwise specified)", which is a diagnosis that is only entered when there is no clearly apparent cause of altered mental state (LRDA-ba 4.3% vs. GRDA 12.5%, p=0.01), or a toxic-metabolic encephalopathy (LRDA-ba 3.5% vs. GRDA 10.5%, p=0.01). Patients with LRDA-ba were more likely to have documented focal neurological deficits (LRDA-ba 53.9% vs. GRDA 33.7%, p=0.01), were more likely to have been administered an anti-seizure medication (ASM) (LRDA-ba 83.3% vs. GRDA 64.7%, p=0.01), were exposed to a greater number of

ASMs (Mean ± Standard Deviation, LRDA-ba 1.35 ± 0.07 vs. GRDA 1.05 ± 0.07, p=0.01), and were more likely to have died during their admission (LRDA-ba 24.8% vs. GRDA 15.5%, p=0.01).

Variables	Lateralized Rhythmic Delta Activity – bilateral asymmetric n=258	Generalized Rhythmic Delta Activity n=258	P value
Age	61.0 ± 17.3 years	55.5 ± 16.9 years	0.01*
Sex			0.597
Female	135 (52.3)	129 (50.0)	
Male	123 (47.7)	129 (50.0)	
Primary Diagnosis			
Seizure	33 (12.8)	40 (15.6)	0.38
Status epilepticus	12 (4.7)	9 (3.5)	0.50
Stroke (ischemic)	32 (12.4)	10 (3.9)	0.01*
Sub-dural hemorrhage (SDH)	23 (8.9)	11 (4.3)	0.03*
Subarachnoid hemorrhage (SAH)	43 (16.7)	29 (11.3)	0.08
Intracerebral hemorrhage (ICH)	30 (11.6)	21 (8.2)	0.18
Intraventricular hemorrhage (IVH)	2 (0.8)	2 (0.8)	
Sinovenous thrombosis	1 (0.4)	0 (0)	
Traumatic brain injury	12 (4.7)	17 (6.6)	0.33
Altered mental state (not otherwise specified)	11 (4.3)	32 (12.5)	0.01*
Metabolic encephalopathy	9 (3.5)	27 (10.5)	0.01*
Hypoxic-ischemic encephalopathy (HIE)	14 (5.4)	24 (9.3)	0.09
CNS infection	9 (3.5)	13 (5.1)	0.38
CNS inflammation	4 (1.6)	2 (0.8)	0.41
CNS neoplasm	13 (5.0)	8 (3.1)	0.27
Non-alcohol drug intoxication/withdrawal	0 (0)	4 (1.6)	
Hydrocephalus	3 (1.2)	0 (0)	
Other	6 (2.3)	7 (2.7)	0.80
Clinical Seizure Prior to admission or EEG recording			0.79

Yes	85 (32.9)	78 (30.2)	
No	152 (58.9)	157 (60.9)	
Unknown	21 (8.1)	23 (8.9)	
Mental state (at commencement of EEG)			0.68
Comatose	53 (20.5)	57 (22.1)	
Obtunded	78 (30.2)	80 (31.0)	
Lethargic	62 (24.0)	72 (27.9)	
Asleep	1 (0.4)	2 (0.8)	
Drowsy	25 (9.7)	20 (7.8)	
Awake	36 (14.0)	25 (9.7)	
Unknown	3 (1.2)	2 (0.8)	
Intubated	143 (55.4)	161 (62.4)	0.11
Focal Neurological Deficits			0.01*
Yes	139 (53.9)	87 (33.7)	
No	97 (37.6)	144 (55.8)	
Unknown	22 (8.5)	27 (10.5)	
Highly sedating medications*	76 (29.5)	107 (41.5)	0.01*
Number of patients on any Anti-Seizure Medication (ASMs)	215 (83.3)	167 (64.7)	0.01*
Number of Anti-Seizure Medications (ASMs)	1.35 ± 0.07	1.05 ± 0.07	0.01*
Discharge Destination			
Home	47 (18.2)	70 (27.1)	0.02*
Rehabilitation	109 (42.2)	103 (39.9)	0.59
Long term facility	23 (8.9)	16 (6.2)	0.24
Other hospital	5 (1.9)	15 (5.8)	0.02*
Hospice	10 (3.9)	14 (5.4)	0.40
Deceased	64 (24.8)	40 (15.5)	0.01*

Table 2: Clinical Characteristics. Summarizing the clinical characteristics for patients with LRDA-ba vs. those with GRDA. Most variables were non-parametric and have been shown as number of cases (n), followed by percentage of cases in parentheses (%). If there was no significant difference between LRDA-ba and GRDA the p value for the groups has been shown in the final column. If the distribution of outcomes was different between groups, then individual comparisons were made, and those p values are shown in the final column. For parametric variables with two independent groups (e.g., age, or number of ASMs) the values have been shown as mean ± standard deviation. In these cases, the p value derived from the comparison utilizing Student t-tests have been shown in the final column. *Highly sedating medications were defined as any benzodiazepine infusion, propofol, ketamine, etc.

EEG Characteristics

In this study, the "prevalence", "duration", and "typical frequency" were matched between patients with LRDA-ba and those with GRDA (Table 1). Patients with LRDA-ba had distinctly different EEG characteristics compared to those with GRDA. Patients with LRDA-ba had significantly more features to suggest focal dysfunction. The background was more likely to be asymmetric (LRDA-ba 62.0% vs. GRDA 25.6%, p=0.01), they were more likely to have focal slowing (40.3% vs. 15.5%, p=0.01), and were more likely to have a breach effect (20.5% vs. 8.5%, p=0.01) (Table 3). Patients with LRDA-ba were more likely to have Sporadic Epileptiform Discharges (SDs) (LRDA-ba 50.4% vs. GRDA 33.7%. p=0.01), a Plus Sharp modifier (45.0% vs. 32.9%, p=0.01), occur in the same record as Lateralized Periodic Discharges (LPDs) (32.2% vs. 5.0%, p=0.01), and electrographic seizures (ESz) at any point of their recording (34.9% vs. 17.4%, p=0.01). The differences in the rates of epileptiform patterns between groups were due to significant differences in focal findings. Patients with LRDA-ba had the same rate of Generalized Periodic Discharges (GPDs) or generalized ESz's as those with GRDA. For SDs, patients with GRDA had a significantly greater proportion of generalized discharges compared with the LRDA-ba cohort (LRDA-ba 2.3% vs. GRDA 20.9%, p=0.01).

For patients that had LPDs in addition to LRDA-ba the seizure rates were higher than those with LRDA-ba without LPDs (LRDA-ba ***AND*** LPDs 51.8% [n=43/83] vs. LRDA-ba without LPDs 26.9% [n=47/175], p=0.01). Patients with LRDA-ba alone (n=104), (i.e., without any other epileptiform finding including SDs or PDs) had a lower rate of seizures 17.3% (n=18/104) vs. LRDA-ba with any epileptiform finding (46.8% [n=72/154]; p=0.01). In patients with GRDA alone (n=162), the confirmed seizure rate was 9.9% (n=16/162), vs. GRDA with any epileptiform finding (30.2% [n=29/96], (p=0.01). Patients with LRDA-ba alone (i.e., no other epileptiform findings) demonstrated a trend towards greater seizures than those with GRDA alone (LRDA-ba 17.3% vs. GRDA 9.9%, p=0.08). LRDA-ba was maximal in the frontal region in 116 patients (45.0%), temporal 76 (29.5%); parietal 9 (3.5%) and occipital 4 (1.6%). The remainder of the patients had hemispheric involvement, n=53 (20.5%). There was no significant difference in the probability of seizures depending on the region that LRDA-ba was maximal, i.e., if it were frontal vs temporal maximal etc., p=0.25.

Variables	Lateralized Rhythmic Delta Activity – bilateral asymmetric n=258	Generalized Rhythmic Delta Activity n=258	P value
Posterior Dominant Rhythm (PDR) present	95 (36.8)	101 (39.1)	0.59
Continuity			0.24
Continuous	169 (65.5)	175 (67.8)	
Nearly continuous	49 (19.0)	51 (19.8)	
Discontinuous	22 (8.5)	21 (8.1)	
Burst suppression/ Burst attenuation	8 (3.1)	9 (3.5)	
Overall suppression/ attenuation	10 (3.9)	2 (0.8)	
Background Symmetry			0.01*
Symmetric	98 (38.0)	192 (74.4)	
Asymmetric	160 (62.0)	66 (25.6)	
Focal slowing or attenuation	104 (40.3)	40 (15.5)	0.01*
Breach	53 (20.5)	22 (8.5)	0.01*
Sporadic Epileptiform Discharges (SDs)	130 (50.4)	87 (33.7)	0.01*
Focal	124 (48.1)	33 (12.8)	0.01*
Generalized or Multifocal	6 (2.3)	54 (20.9)	0.01*
Evolution			0.64
Evolving	8 (3.1)	6 (2.3)	
Fluctuating	58 (22.5)	53 (20.5)	
Static	191 (74.0)	199 (77.1)	
Plus Sharp	116 (45.0)	85 (32.9)	0.01*
Co-occurrence of Generalized Periodic Discharges (GPDs)	30 (11.6)	28 (10.9)	0.78
Co-occurrence of Lateralized Periodic Discharges (LPDs)	83 (32.2)	13 (5.0)	0.01*
Electrographic Seizure (ESz)	90 (34.9)	45 (17.4)	0.01*
Focal	86 (33.3)	29 (11.2)	0.01*
Generalized	19 (7.4)	16 (6.2)	0.60

Table 3: Electrographic Characteristics. Summarizing the electrographic characteristics of patients with LRDA-ba vs. GRDA. Shown as number of cases (n) and proportion of cases in parentheses (%). For variables with a dichotomous outcome the p value from the Chi square analysis has been shown in the final column. For variables with more than two outcomes, i.e., “continuity”, the p value from the Kruskal Wallis 1-way ANOVA has been shown in the final column.

Computed Tomography Imaging Findings

Patients with LRDA-ba were more likely to have an abnormal CT scan compared to those with GRDA (LRDA-ba 81.4% vs. GRDA 56.6%, p=0.01) (Table 4). These abnormalities were more likely to be acute (a new finding upon presentation to hospital) in patients with LRDA-ba (65.5% vs. 46.1%, p=0.01), but there was no significant difference in the proportion of chronic abnormalities between groups. Imaging abnormalities were more likely to be discrete in patients with LRDA-ba (including *"focal, 1-2 locations within the same hemisphere"* [LRDA-ba 49.6% vs. GRDA 28.3%, p=0.01] and *"bilateral, 2 locations but with 1 in each hemisphere"* [LRDA-ba 21.7% vs. GRDA 10.1%, p=0.01]), whereas patients with GRDA were more likely to have "diffuse" (no particular brain region clearly affected the most) or "multifocal" (at least 3 locations with at least 1 in each hemisphere) abnormalities (LRDA-ba 9.7% vs. GRDA 19.0%, p=0.01). A number of focal pathologies were significantly greater in patients with LRDA-ba including Intracerebral Hemorrhage (ICH) (LRDA-ba 18.6% vs. GRDA 10.5%, p=0.01), Subdural Hemorrhage (SDH) (14.3% vs. 5.8%, p=0.01) and ischemic stroke (25.6% vs. 14.0%, p=0.01). Patients with LRDA-ba were more likely to have a skull defect (LRDA-ba 27.9% vs. 14.7%, p=0.01), and a greater proportion of involvement of frontal (LRDA-ba 62.0% vs. GRDA 36.4%, p=0.01) and temporal (LRDA-ba 45.7% vs. GRDA 27.5%, p=0.01) regions. Patients with GRDA were more likely to have had imaging abnormalities involving the occipital (LRDA-ba 8.9% vs. GRDA 18.6%, p=0.01) and infra-tentorial (LRDA-ba 6.6% vs. GRDA 13.6%, p=0.01) regions. There was no difference between groups with regard to involvement of the insula, basal ganglia, thalamus or "deep midline" structures.

Variables	Lateralized Rhythmic Delta Activity – bilateral asymmetric n=258	Generalized Rhythmic Delta Activity n=258	P value
CT Abnormality			0.01*
Normal	48 (18.6)	104 (40.3)	
Abnormal	210 (81.4)	146 (56.6)	
Not performed	0 (0)	8 (3.1)	
Acuity of CT Abnormality			
Acute	169 (65.5)	119 (46.1)	0.01*
Chronic	66 (25.6)	60 (23.3)	0.54

Both Acute and Chronic	25 (9.7)	30 (11.6)	0.48
Focality of CT Abnormality			
Focal	128 (49.6)	73 (28.3)	0.01*
Bilateral	56 (21.7)	26 (10.1)	0.01*
Diffuse or Multifocal	25 (9.7)	49 (19.0)	0.01*
CT Diagnosis			
Intracerebral Hemorrhage (ICH)	48 (18.6)	27 (10.5)	0.01*
Subarachnoid Hemorrhage (SAH)	58 (22.5)	31 (12.0)	0.01*
Sub-dural Hemorrhage (SDH)	37 (14.3)	15 (5.8)	0.01*
Stroke (Ischemic)	66 (25.6)	36 (14.0)	0.01*
Traumatic Brain Injury (TBI)	7 (2.7)	24 (9.3)	0.01*
Central Nervous System (CNS) Neoplasm (including leptomeningeal involvement)	20 (7.8)	18 (7.0)	0.74
Skull Defect	72 (27.9)	38 (14.7)	0.01*
Brain Regions Involved			
Frontal	160 (62.0)	94 (36.4)	0.01*
Temporal	118 (45.7)	71 (27.5)	0.01*
Parietal	69 (26.7)	81 (31.4)	0.25
Occipital	23 (8.9)	48 (18.6)	0.01*
Insula	15 (5.8)	23 (8.9)	0.18
Basal Ganglia	26 (10.1)	24 (9.3)	0.77
Thalamus	8 (3.1)	11 (4.3)	0.48
Deep Midline	5 (1.9)	9 (3.5)	0.28
Infra-tentorial	17 (6.6)	35 (13.6)	0.01*
Hydrocephalus	40 (15.5)	29 (11.2)	0.16

Table 4: CT Imaging Findings. Summarizing the CT imaging findings between patients with LRDA-ba and GRDA. All values are given in number of patients (n) and proportion of group affected (%). The p value of individual independent comparisons has been shown in the final column.

Electroencephalogram and CT findings specific to LRDA-ba

Regional or hemispheric dysfunction (slowing or attenuation) on the same side as LRDA-ba (concordant) occurred in 55.0% of cases, compared with only 7.0% of patients demonstrating dysfunction on the opposite side to the LRDA-ba (discordant) (Table 5). Concordant focal slowing was found in 33.3% of cases vs. 7.0% with discordant slowing; and a breach effect was concordant with LRDA-ba in 16.7% of cases vs. 3.9% discordant with LRDA-ba. Evidence of hyper-excitability was also largely concordant, with focal SDs occurring on the same side as LRDA-ba 42.2% of the time vs. only 7.8% having SDs on the opposite side; and ESz occurring on the same side as LRDA-ba in 29.5% of cases vs only 3.9% of cases with seizures occurring from the other hemisphere. The p values for all of the above comparisons were <0.01. There was no difference in the rates of concordant/discordant seizures when LRDA-ba was divided into brain regions (i.e., frontal [concordance rate 87.5%], temporal [85.2%], parietal [80.0%], occipital [100%, but only 2 patients in this subgroup], or hemispheric [95.0%], p=0.78), i.e., there was an equal chance of seizures being discordant if LRDA-ba was maximal in the frontal vs temporal region.

Acute brain abnormalities on CT scan (irrespective of region involved) occurred on the same side as LRDA-ba in 64.3% of cases vs. 14.7% of patients having the majority of abnormality in the opposite hemisphere, p<0.01. The rates of concordant/discordant acute brain abnormality were no different if LRDA-ba was separated into the region that it was maximal, p=0.10; i.e., an acute brain abnormality was just as likely to be in the opposite hemisphere to LRDA-ba if the pattern was maximal in the frontal vs. temporal region (see Table 5).

Variables	Concordant	Discordant
EEG evidence of regional or hemispheric dysfunction	142 (55.0)	18 (7.0)
EEG evidence of focal slowing or attenuation	86 (33.3)	18 (7.0)
EEG evidence of a breach effect	43 (16.7)	10 (3.9)
Focal Sporadic Epileptiform Discharges (SDs) on EEG	109 (42.2)	20 (7.8)
Electrographic Seizures (ESz) on EEG	76 (29.5)	10 (3.9)
CT evidence of an acute brain abnormality (region not specific)	166 (64.3)	38 (14.7)
CT evidence of a skull defect	58 (22.5)	16 (6.2)
Seizure concordance by LRDA-ba region	Concordant w Seizure	Discordant w Seizure
Frontal	28 (87.5)	4 (12.5)

Temporal	23 (85.2)	4 (14.8)
Parietal	4 (80.0)	1 (20.0)
Occipital	2	0
Hemispheric	19 (95.0)	1 (5.0)
Acute CT Abnormality concordance by LRDA-ba region	Concordant w Acute CT Abnormality	Discordant w Acute CT Abnormality
Frontal	77 (66.4)	23 (19.8)
Temporal	52 (68.4)	7 (9.2)
Parietal	4 (44.4)	2 (22.2)
Occipital	2 (50.0)	1 (25.0)
Hemispheric	31 (58.5)	5 (9.4)

Table 5: EEG and CT findings specific to LRDA-ba. Summarizes the number of patients that have additional findings on the same side as the LRDA-ba (concordant) vs. on the opposite side as the LRDA-ba (discordant). Values are given in number of patients (n) and proportion of patients with LRDA-ba as a whole that have the concordant or discordant finding (%). The p values for all comparisons between concordant vs. discordant were $p<0.01$. There was no difference in the rates of seizure concordance when divided into brain regions ($p=0.78$), and there was no difference in the rates of CT abnormality concordance when divided into brain regions ($p=0.10$).

Discussion

Lateralized Rhythmic Delta Activity, bilateral asymmetric (LRDA-ba) represents a pattern with associations that are distinct to those attributed to GRDA. The pattern was associated with a significantly greater proportion of acute focal findings (clinical, electrographic and imaging). It was also associated with focal epileptiform findings such as focal SDs, LPDs, and focal ESz, but showed only a trend towards an independent association with seizures. Clinically, patients with LRDA-ba were (not surprisingly) more likely to have presented with focal pathologies such as an ischemic stroke (LRDA-ba 12.4% vs GRDA 3.9%), or SDH (8.9% vs 4.3%), whereas patients with GRDA were more likely to have diagnoses with more diffuse processes ("altered mental state, NOS" [LRDA-ba 4.3% vs. GRDA 12.5%], or metabolic encephalopathy [3.5% vs. 10.5%]), and more likely to receive highly sedating medication (29.5% vs. 41.5%). Patients with LRDA-ba were also more likely to have documented focal neurological deficits (53.9% vs. 33.7%), the limitation here being that the presence or absence of a focal deficit was taken from the EEG database and was not confirmed from the clinical record (although the finding remains consistent with there being a greater number of focal abnormalities on imaging in patients with LRDA-ba).

Electrographically, patients with LRDA-ba were (again, not surprisingly) more likely to have evidence of a background asymmetry (LRDA-ba 62.0% vs. GRDA 25.6%), or focal slowing

(40.3% vs. 15.5%). They were also more likely to have additional evidence of focal hyper-excitability, such as focal SDs (LRDA-ba 48.1% vs. GRDA 12.8%) comorbid LPDs (32.2% vs. 5.0%), and focal ESz (33.3% vs. 11.2%). When taken as a whole, these findings remain consistent with the current understanding of patients with LRDA, being associated with acute focal abnormalities (Alzawahmah et al., 2022).

What was surprising was that when patients with LRDA-ba alone (with no other epileptiform findings or patterns) were taken as a sub-group (about 40% of the total group), the rate of recorded seizure (17.3%) was substantially lower than similar patients with any additional epileptiform finding or pattern (46.8%), and this rate was not significantly different (though it showed a trend, p=0.08) from a matched group of patients with GRDA (9.9%). There are important caveats to this preliminary finding. Any subgroup analysis significantly reduces statistical power and therefore the confidence of a finding. The number of patients was automatically less than half, which could introduce confounders, for example patients without additional epileptiform patterns may have a lower typical frequency, or lower burden patterns compared to those with additional findings. The more appropriate statistical method to interrogate this would be to take a large number of patients with LRDA-ba and perform multivariate logistic regression (as was done in the Rodriguez-Ruiz et al. study that included more than 5000 patients) (Rodriguez Ruiz et al., 2017), obviously the limitation here is that LRDA-ba was not that common, so access to such a large population was not possible. Still the finding is important for clinicians, mainly because LRDA as a whole has been repeatedly demonstrated to have a strong independent association with seizures (Gaspard et al., 2013). The current finding may suggest that when LRDA-ba is documented by itself (i.e., without any additional epileptiform findings), the risk of seizures is lower. It is important to note that the methods used in the current manuscript are more stringent that some prior studies of LRDA, i.e., LRDA-ba without any other epileptiform findings have been analyzed separately to see if that pattern alone is specifically associated with seizures. In the Gaspard et al. study of the 26 patients with LRDA, 5 had coincident sporadic sharp waves (that did not qualify as a pattern of LRDA+S). These patients were included in the overall analysis. That study did mention that if a patient had both LRDA and LPDs the rate of seizure was 84%, compared to 47% with LRDA without LPDs, but few studies have specifically assessed the rate of seizure in patients with LRDA alone by means of excluding all those with co-incident epileptiform patterns (including LPDs and sporadic EDs).

A hypothesis going into this study was that LRDA-ba may represent GRDA that was poorly formed on the side of dysfunction. Our results show several points against this. If this were the case one would expect the patterns that most represented GRDA (being frontally predominant or hemispheric LRDA-ba) to have a lower rate of seizures compared to LRDA-ba maximal in the temporal region, which was not the case. In addition, one would expect that LRDA-ba (especially frontal or hemispheric) would more often be of greater voltage in the hemisphere opposite to the side of dysfunction (being the side of slowing or attenuation), which also was not the case. In fact, LRDA-ba was usually maximal in the dysfunctional hemisphere (i.e., concordant in 55.0% of total group, or 88.8% of patients with hemispheric dysfunction), regardless of its regional predominance. An additional hypothesis has been that LRDA-ba may be more prominent in one hemisphere due to breach effect. Although again this may be the case in some patients, 79.5% of patients with LRDA-ba did not have a documented breach rhythm so this was not sufficient to explain the findings in the majority. In addition, skull defects primarily affect faster frequencies, with minimal effect on delta activity.

Patients with LRDA-ba were more likely to have had an acute (LRDA-ba 65.5% vs. GRDA 46.1%) and focal (49.6% vs. 28.3%) abnormality on their head CT scans, which remains consistent with prior imaging studies of LRDA.(Alzawahmah et al., 2022) These abnormalities for the most part occurred on the same side that the LRDA-ba was maximal (concordant 64.3% of all patients [or 81.3% of patients with an acute focal abnormality] vs. discordant 14.7% [or 18.6% of patients with an acute focal abnormality]). The imaging findings supported the clinical presentation, with a greater proportion of patients with LRDA-ba having focal processes (such as ICH, SDH and ischemic stroke). It is valuable to note that when based on CT review diagnoses such as ICH were significantly more likely in patients with LRDA-ba (as opposed to using primary diagnosis [derived from the database] where it was not). The finding reflects the value of independent review of imaging, which provides a more accurate depiction of the prevalence of intracranial findings. These processes often involved frontal (LRDA-ba 62.0% vs. GRDA 36.4%) or temporal (LRDA-ba 45.7% vs. GRDA 27.5%) regions, which seemed to approximate the distribution that LRDA-ba appeared maximally on EEG, however these two features were not specifically correlated for each patient. In addition, the lobe where the acute lesion was, did not affect the whether the electrographic pattern was concordant/discordant, which again argues against “bifrontal LRDA-ba” being a subset of GRDA that is attenuated due to a lesion in the frontal lobe.

The findings from this study seem to establish LRDA-ba as a unique pattern, justifying its inclusion in the ACNS ICU EEG terminology as a specific sub-term (L. J. Hirsch et al., 2021; L. J. Hirsch et al., 2013). The study confirms findings from previous studies of LRDA, establishing LRDA-ba as a pattern that is associated with acute focal abnormalities (clinical, electrographic and imaging) (Alzawahmah et al., 2022). A critical finding however was that although LRDA-ba was associated with additional patterns of hyper-excitability (focal SDs and LPDs), when taken by itself demonstrated a non-significant trend toward a greater proportion of recorded seizures (when compared to a matched group of patients with GRDA). This suggests that although it does not mimic GRDA, not all lateralized patterns are equally associated with seizures. This point is easy to conceptualize, mainly because not all LPDs have an equal rate of seizure (Rodriguez Ruiz et al., 2017). The rate of seizures in a patient with occasional brief 0.5-Hz LPDs is not the same as a patient with abundant long 2-Hz LPDs with associated fast activity (LPDs + F). In this example there are multiple components of the pattern that make it more or less epileptic. It seems therefore plausible that LRDA-ba (with more diffusely projected patterns over both hemispheres compared to unilateral LRDA) is yet another determinant factor in the increasingly complex algorithm that determines a patient's seizure risk.

There were several limitations to the study. The study did not include a second comparison group, most notably a matched group of patients with unilateral LRDA. Several studies have already documented the associations of LRDA when taken as a whole, which have also established the pattern to be highly associated with seizures (Alzawahmah et al., 2022; Gaspard et al., 2013; Rodriguez Ruiz et al., 2017). The main goal of the study was to determine if LRDA-ba was merely a subset of GRDA, holding similar implications (i.e., would be better classified as a generalized pattern). In this regard the study has fulfilled its purpose, and clearly documents the pattern has distinct associations with focal (lateralized) pathology, providing justification of its inclusion as such. A comparison to unilateral LRDA would have been of greater importance if LRDA-ba was clearly independently associated with seizures, because then the question would have been asked if this association is to the same extent as in patients with unilateral LRDA, but this was not the case (though a trend towards greater seizures did exist).

A greater number of patients with GRDA were administered highly sedating medications (41.5% vs 29.5%). This could have resulted in a greater number of patients without an acute structural abnormality being included in this group, however it does not detract from the main

finding that those with LRDA-ba (at some stage of their record) had a high proportion of focal findings. The study did not provide direct adjudication for all EEGs. One may argue that some patients were included in the incorrect group. Although this may be true it is argued that this represents the minority, and didn't seem to greatly affect the result of this study. The inter-rater reliability for the main terms has been shown to be "almost perfect", in particular the inter-rater agreement for Main term 1 (differentiating generalized from lateralized patterns) was 91.3% (Gaspard et al., 2014). It could be argued that in practice a greater number of LRDA-ba is included as GRDA than vice versa; this would bias a greater number of focal abnormalities into the GRDA group, which clearly was not the case. It is also true that although the study reviewers were blinded, the clinicians entering information into the database as a part of patient care were not. There is the possibility that this biased a greater number of focal findings in patients with LRDA-ba than GRDA, but again it is argued this represents the minority of cases (especially because the majority of LRDA-ba was concordant). Finally, variables without a well-established association with seizures (e.g., number of patterns) were not additionally included.

Conclusion

The complexity of Rhythmic and Periodic Patterns continues to grow, and there is a possibility that how diffuse (or discrete) a pattern is has some bearing on its epileptic potential, akin to how the frequency, prevalence, and presence or absence of fast activity ("plus F" modifier) modulates the risk of seizure at the other end of the spectrum. The finding adds another layer of nuance to an already challenging proposition.

Chapter 5: Burst Suppression with Highly Epileptiform Bursts (HEBs) in the Determination of Subsequent Seizures in patients with Status Epilepticus

Plain English summary

Burst suppression patterns are another cEEG pattern that were not well assessed by the CCEMRC cohort. This was because burst suppression is relatively uncommon, and the clinical significance varies drastically depending on the clinical context that it occurs. This meant that the relevance of burst suppression (BS) as a group could not be assessed by the large cohort. In order to assess the relevance of Highly Epileptiform Bursts (HEBs), a particular pattern within BS, a cohort study was developed.

The proposed utility of HEBs has been in the context of guiding when to wean continuous intravenous antiseizure medication (cIVASM) in patients with refractory status epilepticus (RSE). This study identified patients with RSE who had been treated to the EEG target of BS. The EEG at the time of weaning cIVASM was then assessed by both visual and quantitative analysis. This study focused on determining BS features that predicted successful or unsuccessful (i.e., seizures returned) withdrawal of cIVASM.

This study represented the largest cohort of HEBs in the context of RSE and the only to quantitatively assess the EEG features. The study found that it was not conventional measures of BS, such as duration or amplitude of bursts or interburst intervals, that determined whether seizures would return; but instead, how “epileptiform” the bursts were.

This study arguably changes clinical practice as to how BS is used in the management of RSE. Care can be tailored to an individual patient, whereby how “epileptiform” the bursts are can be used as a surrogate to guide when withdrawal of cIVASM would be successful.

Abstract

To determine whether quantitative EEG analysis of burst suppression can predict seizure recurrence in patients with refractory status epilepticus (RSE) being treated with anesthetic doses of continuous IV antiseizure medications (cIVASM). Quantitative assessment of burst suppression (including epileptiform discharges [EDs] and evolution) in 31 occasions (from 27 patients), and correlation with seizure recurrence up to 48 hours post sedative wean.

Occasions resulting in seizure recurrence (vs. no seizure recurrence) had lower burst (8.4 vs. 10.6 μV) and interburst interval (IBI) (4.2 vs. 4.8 μV) average amplitude, duration (bursts 2.8 vs. 3.6 s: IBIs 3.6 vs. 4.4 s); and burst total power (0.4 vs. 0.7 μV^2). Bursts (0.86 vs. 0.60) and IBIs (0.28 vs. 0.07) with EDs, higher number of EDs within bursts (mean 2.1 vs. 1.4) and IBIs (0.6 vs. 0.2), and positive evolution measures all predicted seizure recurrence, although EDs had the greatest adjusted odds ratio on multivariate analysis.

For patients in burst suppression, successful wean of cIVASM was not determined by classical burst suppression measures, but instead how "epileptiform" bursts and IBIs were, as determined by EDs in both bursts and IBIs and surrogates for evolution within bursts. If confirmed, these objective measures could be used during clinical care to help determine when to wean cIVASM in patients with RSE.

Introduction

Burst suppression on an electroencephalogram (EEG) has historically been a treatment target (a surrogate for seizure control) in the titration of anesthetic doses of continuous IV antiseizure medication (cIVASM) for patients with refractory status epilepticus (RSE) (A. O. Rossetti, Logroscino, & Bromfield, 2005; Shorvon, 2001). Despite the practice standing for half a century, there remains little robust evidence to guide clinicians as to the features of the EEG pattern that determines adequate seizure control, and more importantly, the features that would signify that weaning sedative medications would be successful (i.e., RSE would not recur). Historically, arbitrary targets were chosen, such as burst suppression where the interburst intervals (IBIs) were at least 10-30 seconds in duration, or maintaining burst suppression for 12-48 hours (Shorvon, 2001). The issue with such an approach is that cIVASM, typically involving high-dose IV anesthetics such as pentobarbital, midazolam or propofol is not benign and several studies have suggested increased harm and mortality with more prolonged therapeutic coma in this context (A. O. Rossetti et al., 2005; Watson et al., 2008). A major problem with the historical approach has been that the amount and duration of sedative administered is often center specific, based on local practices, and not patient specific. This likely exposes many patients to unnecessary total cumulative doses of sedation and in turn the associated harm (Schmutzhard & Pfausler, 2011) .

Recognizing this, there has been a shift towards using the EEG features of burst suppression at a given time to stratify patients into having a high or low risk of seizure recurrence should cIVASM be weaned (Johnson et al., 2016; Thompson & Hantus, 2016). By this method, if burst suppression is required in the treatment of RSE, etiology can be corrected and non-sedating anti-seizure medication (ASM) can be optimized, then the EEG can guide the appropriate time for weaning cIVASM for a given individual, thereby minimizing the total sedative exposure and limiting harm. One EEG feature suggestive of seizure recurrence is the presence of highly epileptiform bursts (HEBs) (Thompson & Hantus, 2016). The American Clinical Neurophysiology Society (ACNS) defined the term by consensus in 2011 with a minor revision in 2021. As of 2021 HEBs are defined as: “Present if two or more epileptiform discharges (spikes or sharp waves) are seen within most (>50%) of bursts and occur at an average of 1 Hz or faster within a single burst; Also present if a rhythmic, potentially ictal-appearing pattern occurs within most (>50%) bursts” (L. J. Hirsch et al., 2021; L. J. Hirsch et al., 2013; Thompson & Hantus, 2016). This work aims to determine the relative weighting of the two defining criteria for HEBs--epileptiform discharges (EDs) and

evolution (defined further in methods)--and how these factor in to all other EEG characteristics of burst suppression (e.g., amplitude, duration, spectral content, etc.) in determining seizure recurrence, using objective quantitative methods (Johnson et al., 2016; Thompson & Hantus, 2016).

Methods

Patients

Patients were selected from retrospective reviews of all cases in a critical care EEG database (Yale New Haven Hospital [YNHH]) between December 2014 and December 2020. During this time, YNHH used the Critical Care EEG Monitoring Research Consortium's (CCEMRC) publicly available database https://www.acns.org/research/critical-care-eeg-monitoring-research-consortium-ccemrc/ccemrc-public-database). Patients were screened if they were older than 18 years of age, had greater than 6 hours of continuous EEG monitoring (cEEG) and had burst suppression on their EEG present at any time during the admission.

Patients were then excluded if cardiac arrest or hypoxic ischemic encephalopathy were the indications for the EEG, or if the EEG was not burst suppressed at the time of identified wean of cIVASM (e.g., discontinuous, nearly continuous, continuous, or suppressed), using ACNS criteria (L. J. Hirsch et al., 2021). A flowchart with inclusion and exclusion criteria and the steps of the analysis are shown in Figure 1. This analysis was approved under the YNHH Institutional Review Board (IRB) 2011 "Urgent Inpatient EEG and Multimodality Monitoring Databank" (IRB protocol MOD00040247). The requirement for informed consent was waived.

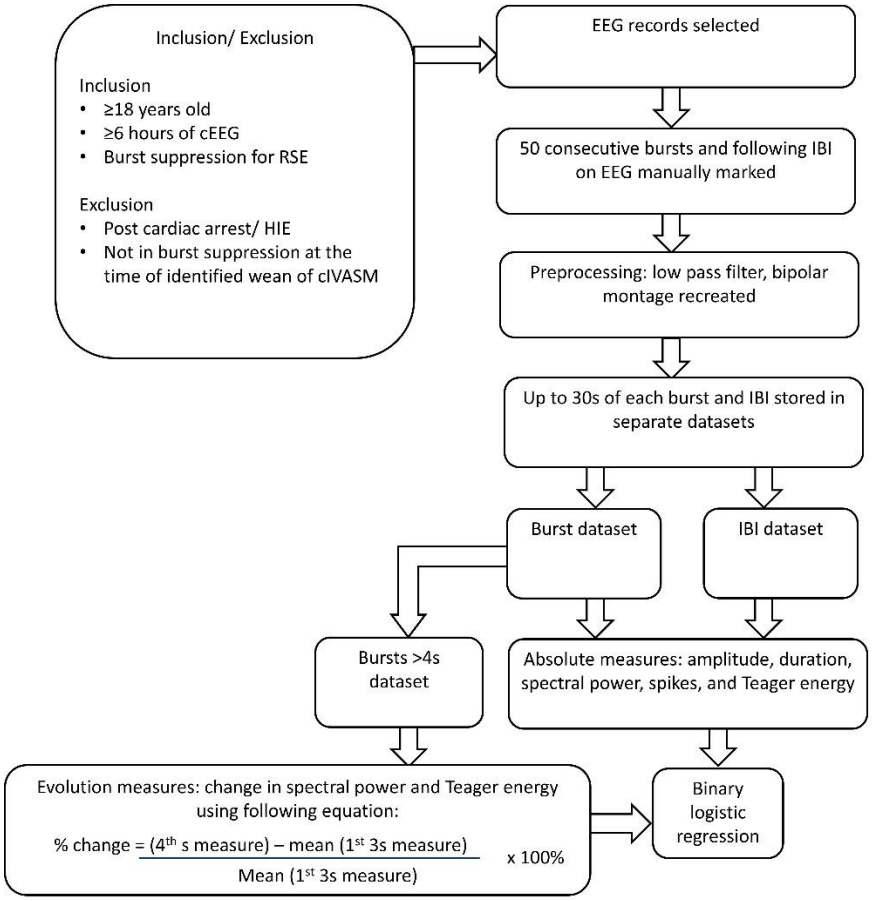

Figure 1: A flowchart illustrating the inclusion and exclusion criteria and the steps of the analysis. Outline of the screening and analysis process including screening, pre-processing, analysis (for absolute measures and those included in evolution measures), leading to binary logistic regression. cEEG: continuous EEG monitoring. RSE: Refractory Status Epilepticus. HIE: hypoxic ischemic encephalopathy. cIVASM: continuous intravenous antiseizure medication. IBI: Interburst interval.

Selection of Bursts/ Suppressions for Analysis

Electronic chart review, combined with EEG annotation review, identified occasions where a trial of weaning cIVASM occurred (including infusions of midazolam/ lorazepam, propofol, ketamine, and pentobarbital). Over the course of a patient's admission more than one occasion of weaning cIVASM may have occurred, but for subsequent trials to be included they had to be separated by at least 48 hours from the original trial. As per above, for subsequent trials to be included they also had to qualify as burst suppression at the time of the subsequent wean.

For quantitative analysis, 50 consecutive pairs of bursts and interburst intervals (IBI) were manually marked by author MF who is fellowship trained in critical care EEG, certified in the

ACNS terminology, and co-author of the 2021 ACNS terminology (L. J. Hirsch et al., 2021). Interburst intervals consisted of the lower amplitude segment of an alternating burst suppression pattern. By this definition the IBI could have been suppressed or attenuated and could have included sporadic EDs. The 50 pairs of bursts/IBIs were selected from a relatively artifact free epoch of EEG within 1 hour preceding the time of identified cIVASM wean. The onset of 51 bursts and 50 IBIs were marked. Given the alternating pattern, the beginning of the IBIs marked the end of the bursts, and vice versa. The 51st burst needed to be marked to determine the end of the 50th IBI, but the 51st burst itself was not analyzed. Examples of marking of bursts and IBIs have been provided in Figure 2.

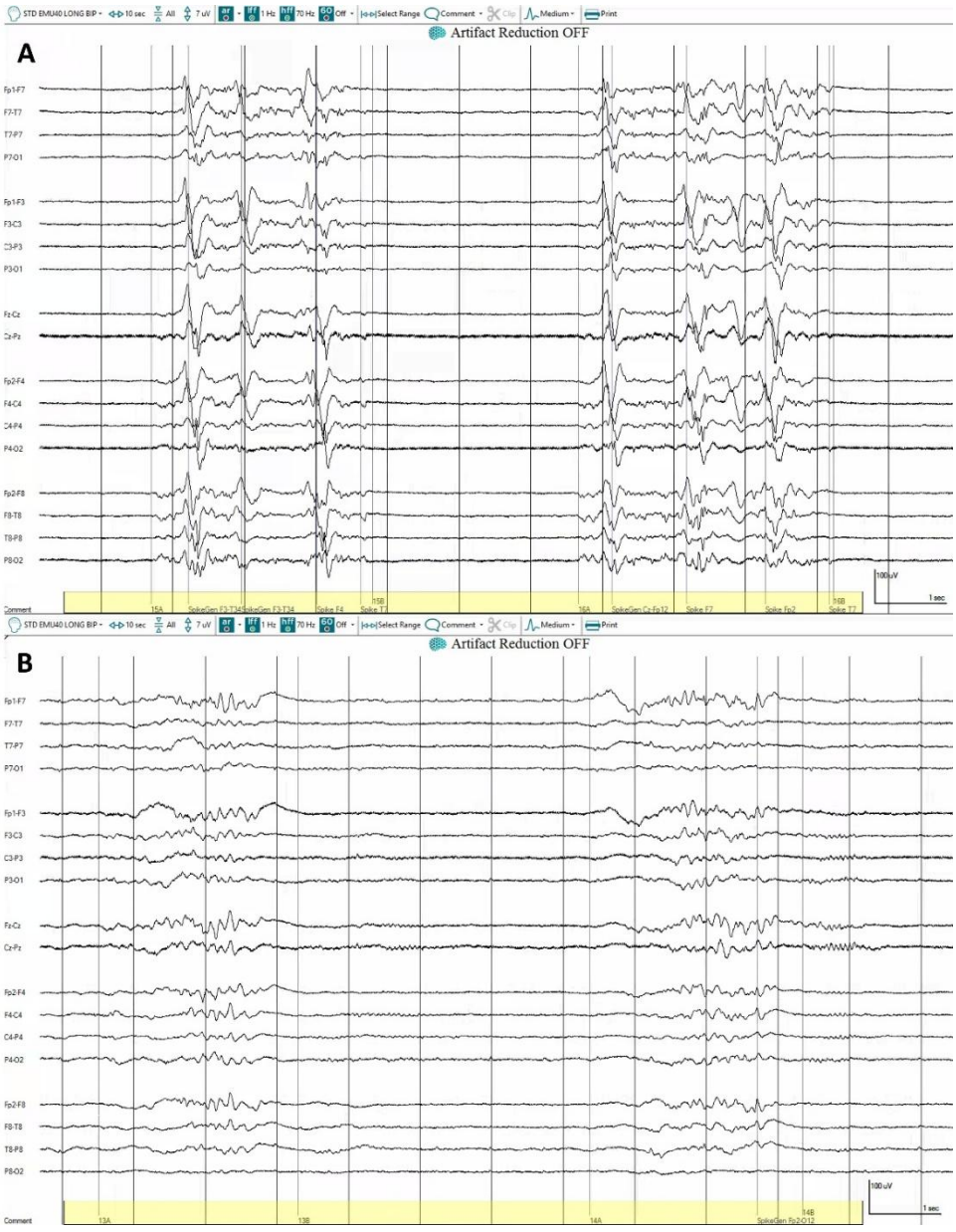

Figure 2: Example of marking of highly epileptiform and non-highly epileptiform bursts. Panel A demonstrates the marking of burst suppression with highly epileptiform bursts (HEBs). The

automated spike detections can be seen in the bottom comment of the panel (highlighted box). Within each manually marked burst there are consistently 3-4 epileptiform discharges (EDs) occurring at ≥1 Hz. Panel B demonstrates a patient where the bursts were not highly epileptiform. The automated spike detector suggests there is an occasional ED, but these are not consistent across bursts (in this example there are none detected in the first burst shown and 1 detected in the second burst). The occasion in panel A resulted in generalized electrographic status epilepticus following continuous IV antiseizure medication wean, whereas panel B resulted in a successful wean (i.e., did not result in seizure recurrence).

Primary Outcome

Electrographic seizure recurrences by 48 hours following commencement of weaning cIVASM. Forty-eight hours post wean (vs. 12 or 24 hours) was chosen to provide the most accurate reflection of seizure recurrence. Common clinical practice has been to wean and cease sedation over 24 hours and then discontinue the EEG at that point if seizures have not returned (Note, our center routinely continues cEEG for 24 hours post wean). If taking seizure recurrence at 24 hours as the primary outcome, a proportion of patients would have just ceased cIVASM and most would not have had an adequate duration of cEEG following sedative medication cessation to accurately reflect the true rate of seizure recurrence.

Quantitative Analysis

The quantitative analysis of bursts and IBIs for occasions associated with seizure recurrence vs. occasions that were not (i.e., occasions that were successful) was performed with MATLAB (MathWorks, Natick, MA). Standard measures of EEG were determined including mean amplitude, mean duration, total and band power, and Teager energy of bursts and IBIs. Teager energy is a weighted measure of signal energy such that higher frequency signals have a greater contribution than lower frequency signals. This emphasis on higher frequencies results in a measure which is akin to the line length measure. For consistency, a maximum duration of 30 seconds was set for each EEG segment, either bursts or IBIs. Note: this threshold was set as by definition activity lasting greater than 30 seconds can no longer count as a “burst” and prolonged IBIs (>30 sec) are almost universally suppressed with no background (the first 30 seconds of which were still included in analysis).

In order to include additional measures of how “epileptiform” bursts were, information on EDs (including spikes and sharp waves) for bursts and IBIs was taken from an established

commercial quantitative EEG platform (Persyst™ version 13) with standard/ medium sensitivity settings. Quantitative surrogates for "evolution" were used as our measure of "ictal appearing". "Change-in" measures were obtained for each power and Teager energy estimate as a positive 50% from baseline cut off. To achieve this, the activity from the first 3 seconds of a burst was averaged and this was used as a baseline to compare to the activity from the 4th second. A 50% increase in the measure in the 4th second compared to baseline qualified as a marker of evolution. By this definition, only bursts lasting at least 4 seconds could be included in this analysis.

Statistical Analysis

Quantitative measures for bursts and IBIs have been shown for occasions that resulted in seizure recurrence vs. those that did not. Measures have been shown with means and 95% confidence intervals (CI). Comparisons between groups (seizure recurrence vs. no seizure recurrence) were achieved with Student's t-test for parametric data, or Pearson's Chi-Square test for non-parametric data. Clinically and statistically relevant variables were then added to a binary logistic regression model to determine the relative contribution of each variable to a distinction between seizure recurrence and no seizure recurrence. The result was statistically significant if p values were less than 0.05.

Results

Inclusion/ exclusion

In the study period 4226 patients were entered into the YNHH critical care EEG database. Of these, 312 patients had burst suppression at any time of their admission, and 220 occurred in the post cardiac arrest/ hypoxic-ischemic encephalopathy (HIE) setting, leaving 92 that were screened (Figure 1). Out of these 92, 45 had RSE (i.e., the other 47 had burst suppression occurring in another context, e.g., diffuse cerebral dysfunction), and 27 were ultimately included (i.e., they had burst suppression present at the time of identified weaning of cIVASM, compared to 18 that were not in burst suppression at the time of weaning [discontinuous, nearly continuous, etc.]). In these 27 patients that qualified for our inclusion, only 2 met the fairly strict criteria to allow more than 1 occasion per admission (1 patient

with 2 occasions and 1 patient with New Onset Refractory Status Epilepticus [NORSE] with 4 occasions). This resulted in 31 unique occasions where a patient was in burst suppression at the time of identified trial of cIVASM wean; 15 occasions resulted in seizure recurrence by 48 hours and 16 did not. Of the 15 occasions with seizure recurrence, the electrographic seizure was generalized in 6 and focal in 9. Two of the 15 occasions (13%) resulted in electroclinical (in addition to electrographic) seizures, with fixed gaze deviation and facial hemiclonus in one patient and the other with rhythmic non-clonic head movement.

Quantitative analysis of bursts/suppressions

The occasions associated with seizure recurrence had lower mean burst amplitude (seizure 8.4 ± 0.2 μV [standard deviation] vs. no seizure 10.6 ± 0.4 μV) and mean IBI amplitude (4.2 vs. 4.8 μV), Table 1 and Figure 3. Occasions resulting in seizures had shorter burst (2.8 vs. 3.6 sec) and IBI (3.6 vs. 4.4 sec) duration; and lower burst total power (0.4 vs. 0.7 μV^2), burst delta power (0.2 vs. 0.5 μV^2), burst theta power (0.1 vs. 0.2 μV^2), and burst alpha power (0.03 vs. 0.04 μV^2). The IBI power was low across all spectral power estimates for those with seizure recurrence and those without, but the Teager energy for suppressed components was greater in those with seizure recurrence (0.66 vs 0.39). In occasions resulting in seizure recurrence, bursts were more likely to contain EDs (0.86 vs. 0.60), as were the IBIs (0.28 vs. 0.07), with the average number of EDs per burst greater in those with seizure recurrence (2.1 vs. 1.4), a finding that was held true for IBIs as well (0.6 vs. 0.2).

Variable	No seizure recurrence	Seizure recurrence	p-value
Burst amplitude (μV)	10.6 ± 0.4	8.4 ± 0.2	< 0.01
IBI amplitude (μV)	4.8 ± 0.2	4.2 ± 0.1	< 0.01
Burst duration (s)	3.6 ± 0.1	2.8 ± 0.1	< 0.01
IBI duration (s)	4.4 ± 0.2	3.6 ± 0.2	< 0.01
Burst total power (μV^2)	0.7 ± 0.1	0.4 ± 0.04	< 0.01
Burst delta power (μV^2)	0.5 ± 0.1	0.2 ± 0.02	< 0.01
Burst theta power (μV^2)	0.2 ±0.02	0.1 ± 0.02	0.02
Burst alpha power (μV^2)	0.04 ± 0.01	0.03 ± 0.01	0.02
Burst beta power (μV^2)	0.02 ±0.01	0.02 ± 0.01	0.97
Burst gamma power (μV^2)	0.004 ± 0.001	0.004 ± 0.0004	0.67
Burst Teager energy	2.5 ± 0.20	2.3 ± 0.2	0.15
IBI total power (μV^2)	0.04 ± 0.01	0.04 ± 0.01	0.51
IBI delta power (μV^2)	0.03 ±0.01	0.02 ± 0.01	0.02
IBI theta power (μV^2)	0.004 ± 0.001	0.005 ± 0.001	0.03
IBI alpha power (μV^2)	0.002 ± 0.001	0.003 ± 0.001	< 0.01
IBI beta power (μV^2)	0.002 ± 0.001	0.003 ± 0.001	< 0.01
IBI gamma power (μV^2)	0.001 ± 0.001	0.001 ± 0.001	0.01
IBI Teager energy	0.39 ± 0.03	0.66 ± 0.08	< 0.01
Bursts with EDs	0.60 ± 0.03	0.86 ± 0.03	< 0.01
IBI with EDs	0.07 ± 0.02	0.28 ± 0.03	< 0.01
Number of EDs within bursts	1.4 ± 0.1	2.1 ± 0.1	< 0.01
Number of EDs within IBIs	0.2 ± 0.1	0.6 ± 0.1	< 0.01

Table 1: Signal characteristics for occasions without seizure recurrence vs. those that resulted in seizure recurrence. Characteristics of bursts and IBIs have been presented as mean ± 95% confidence interval (95%CI). IBI: interburst interval, EDs: epileptiform discharges.

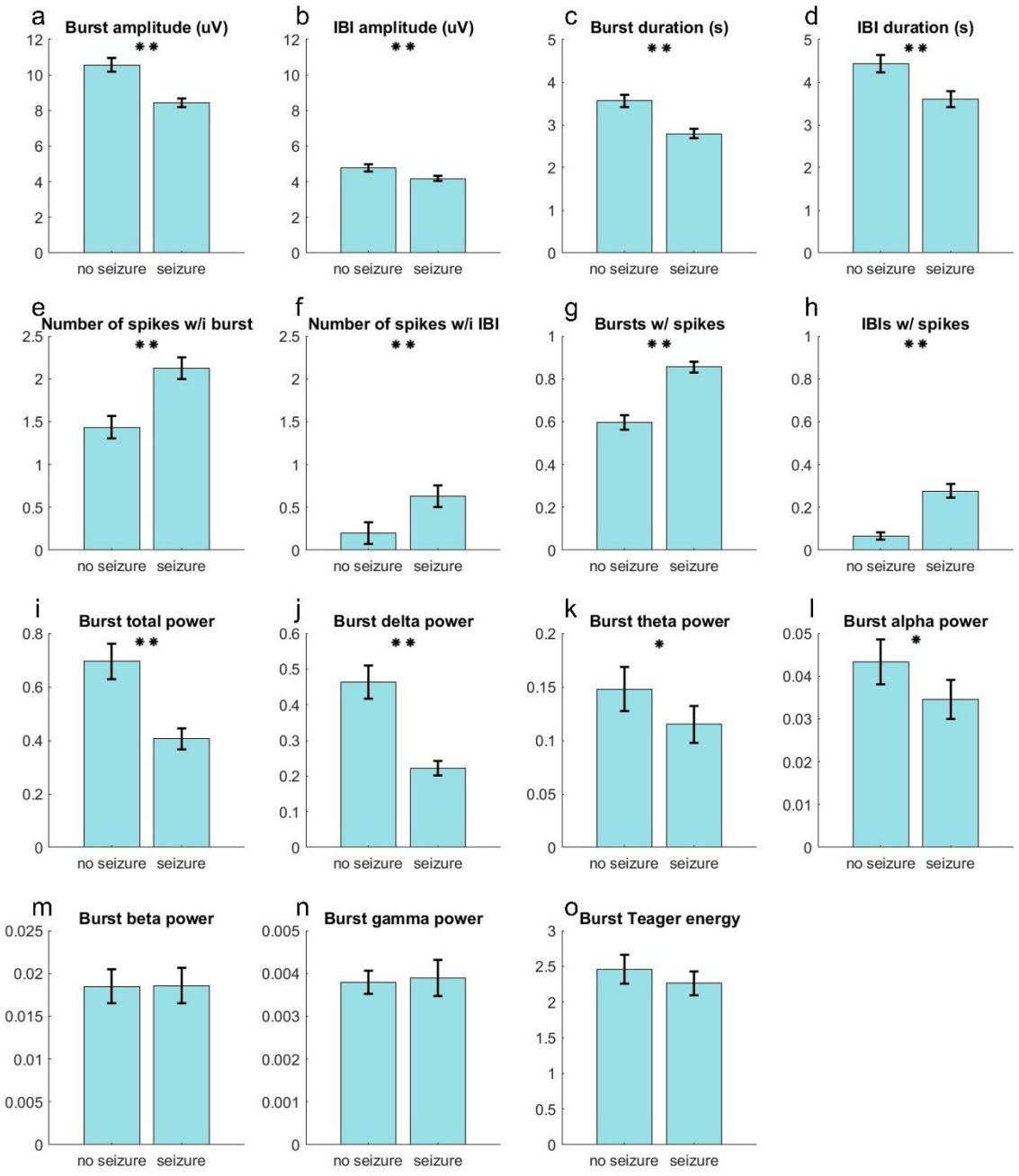

Figure 3: Burst and Interburst Interval (IBI) signal segment characteristics for occasions without seizure recurrence vs. those that resulted in seizure recurrence. The results from Table 1 are plotted as bar graphs to highlight the differences between the two groups. Error margins for each bar represent the 95% confidence interval. One asterisk for p values <0.05, two asterisks for p values <0.01.

Cumulative seizure recurrence probability was plotted against number of EDs in bursts and IBIs, Figure 4. Considering bursts, and to a lesser extent IBIs, as the number of EDs increased so did the probability of seizure recurrence. This effect was most pronounced for a small number of EDs. For bursts, 2 EDs already gave a seizure probability >50% with little additional increase after 5-6 EDs.

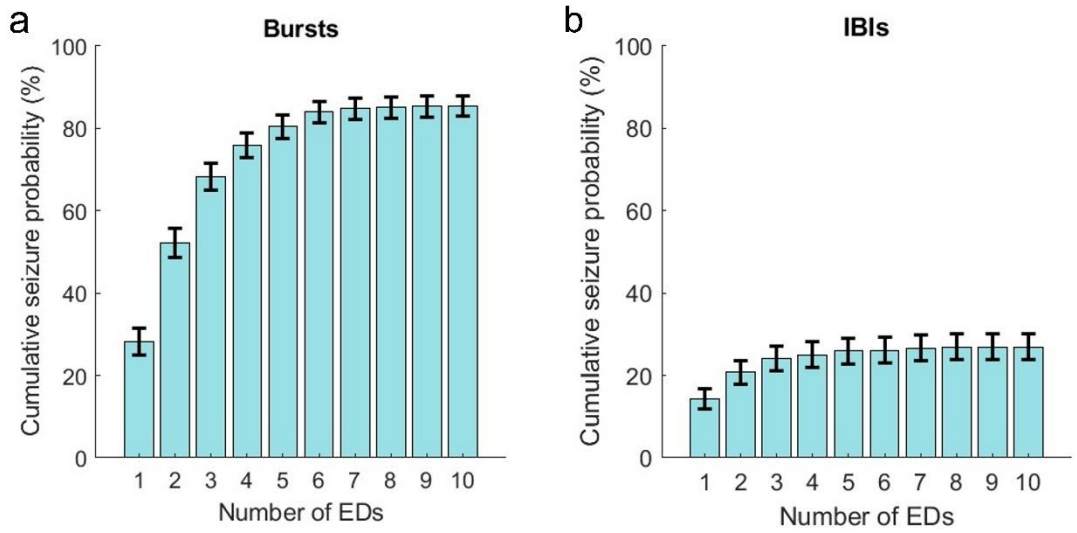

Figure 4: The cumulative probability for seizure recurrence as a function of the number of epileptiform discharges (EDs) in (a) bursts and (b) interburst intervals (IBI). The error margins for each bar represent the 95% confidence interval. A considerable increase in seizure recurrence probability was seen with the first few EDs observed during bursts.

Signal evolution / change-in measures clearly differed between groups by visual inspection of the trends, which was especially true for bursts (Figure 5). Given evolution measures required at least 4 seconds by definition, 274 bursts (out of 1550) were analyzed (106 associated with seizure recurrence and 168 without). For these cases, occasions with seizure recurrence had a greater positive change in total power (seizure 108.4 ± 45.8% vs. no seizure -22.7 ± 5.0%), delta power (129.7 vs. -21.2%); and alpha (81.5 vs. -19.9%), beta (88.4 vs. -16.4%), and gamma (4.6 vs. -17.6%) power (Table 2). Occasions with recurrent seizures were also associated with bursts with greater positive change in Teager energy (27.1 vs. -22.2%, not shown in figure).

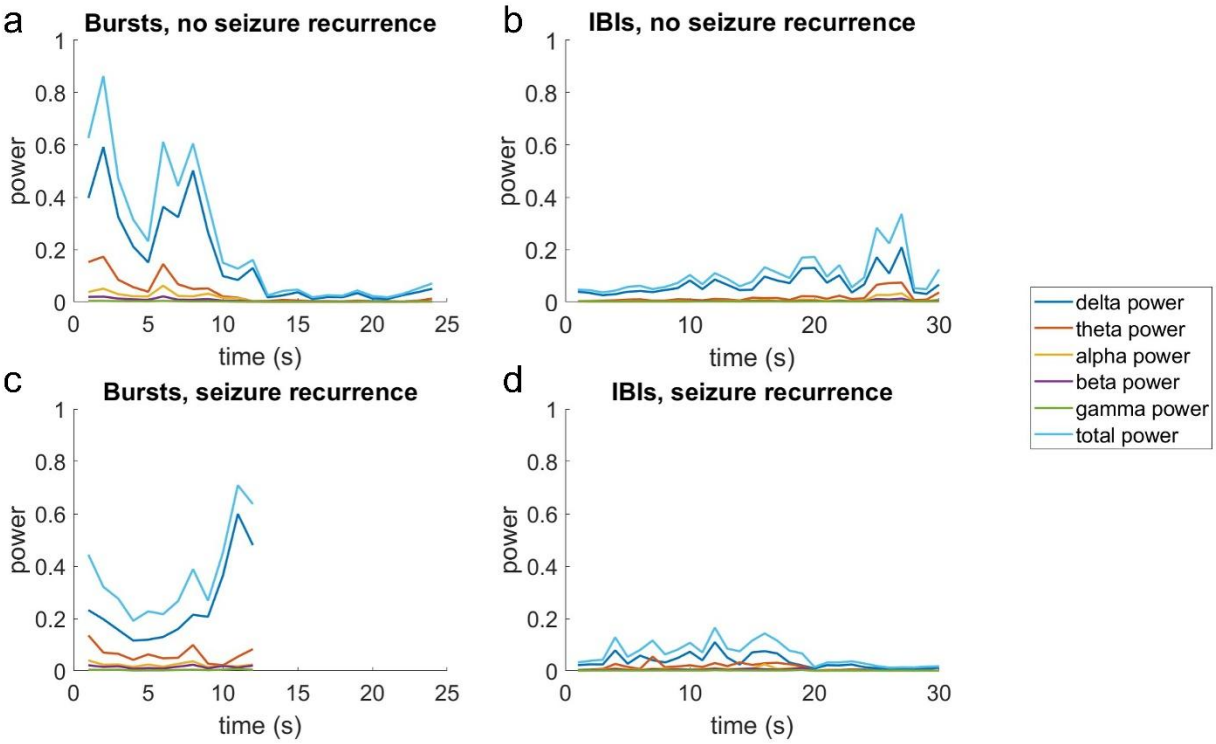

Figure 5: The signal band power measures associated with seizure recurrence or not over the duration of bursts and interburst intervals (IBIs).

Variable	No seizure recurrence	Seizure recurrence	p-value
Change in total power (%)	-22.7 ± 9.1	108.4 ± 83.5	< 0.01
Change in delta power (%)	-21.2 ± 10.0	129.7 ± 94.3	< 0.01
Change in theta power (%)	-16.8 ± 15.3	192.6 ± 193.2	0.07
Change in alpha power (%)	-19.9 ± 9.8	81.5 ± 67.5	0.01
Change in beta power (%)	-16.4 ± 9.3	88.4 ± 71.2	0.01
Change in gamma power (%)	-17.6 ± 5.9	4.6 ± 14.8	0.02
Change in Teager energy (%)	-22.2 ± 5.7	27.1 ± 25.9	< 0.01

Table 2: Signal measures changing over the bursts, for patients without seizure recurrence vs. those with. Bursts associated with seizure recurrence had significant positive changes (i.e., band power increased by shown percentage over the course of the burst), compared with bursts without seizure recurrence that all reduced over the burst. Values represent mean ± 95% confidence interval.

Binary logistic regression

Upon assessment, although many variables were statistically significant, the most clinically significant measures were presence or absence of EDs, number of EDs, and evolution measures. These were subsequently placed into a binary logistic regression model with the binary outcome being seizure recurrence vs. not (Table 3). This model demonstrated that the presence of EDs within bursts (adjusted odds ratio [aOR] 8.55 [95% CI 7.82 – 9.27]) followed by EDs within IBIs (4.08 [3.59 – 4.58]) were the greatest determinants for seizure recurrence. The number of EDs within bursts or IBIs was not significant in this model. The likelihood of seizure recurrence was greater if there was evolution in theta power (2.72 [2.39 – 3.05]) and beta power (3.04 [2.68 – 3.39]). Evolution in alpha power did reach statistical significance (p=0.02), but with an aOR of 0.29 (-0.19 – 0.78) was of limited clinical significance.

Variable	No seizure recurrence	Seizure recurrence	Adjusted odds ratio	p-value
Bursts with EDs	0.60	0.86	8.55 (7.82 – 9.27)	<0.01
IBIs with EDs	0.07	0.28	4.08 (3.59 – 4.58)	<0.01
Number of EDs within bursts	1.43	2.13	0.99 (0.99 – 0.99)	0.90
Number of EDs within IBIs	0.20	0.63	0.94 (0.94 – 0.95)	0.64
>50% evolution in total power	0.13	0.25	2.84 (2.17 – 3.51)	0.24
>50% evolution in delta power	0.14	0.25	0.93 (0.88 – 0.97)	0.92
>50% evolution in theta power	0.13	0.27	2.72 (2.39 – 3.05)	0.03
>50% evolution in alpha power	0.15	0.20	0.29 (-0.19 – 0.78)	0.02
>50% evolution in beta power	0.11	0.28	3.04 (2.68 – 3.39)	0.01
>50% evolution in gamma power	0.07	0.10	0.37 (-0.07 – 0.81)	0.11
>50% evolution in Teager energy	0.05	0.14	1.49 (1.31 – 1.67)	0.53

Table 3: Binary logistic regression model for occasions without seizure recurrence vs. those where seizures recurred. Variables with only 2 outcomes (i.e., dichotomous variables) such as the presence or absence of epileptiform discharges (EDs) or the presence or absence of >50 % evolution have been shown as a proportion of that group. Number of EDs have been presented as the mean. Adjusted odds ratios (95% confidence intervals [95%CI]) and p values for each variable are then shown in the respective columns. IBIs: interburst intervals.

Discussion

This study confirmed that for patients in burst suppression for management of RSE, a successful wean of cIVASM was mostly determined by how "epileptiform" bursts and IBIs appear (e.g., complexity of suppressions measured with Teager energy, bursts or IBIs with EDs, and burst evolution measures) as opposed to more classical burst suppression measures (e.g., amplitude, duration, spectral content).

The two most relevant prior works to this study were Johnson et al. and Thompson & Hantus both in 2016. Johnson et al. analyzed bursts from 19 patients and determined that a successful wean could be predicted if bursts had a maximum amplitude <125 μV (i.e., patients that failed weaning had a higher maximum burst amplitude) (Johnson et al., 2016). Our study did not report on maximum burst amplitude, but occasions resulting in seizure recurrence definitely did not have higher mean burst amplitude, and statistically it was significantly lower in those with seizure recurrence. Importantly, in the Johnson et al. study, IBI duration (including a dichotomous variable of ≥10 sec vs. <10 sec), burst suppression ratios, length of bursts, relative alpha power, alpha/delta ratio, high component (alpha + beta) power, high component to total power ratio, and measures of spectral edge did not differentiate between the groups (Johnson et al., 2016). The current study largely supports/ reproduces this aspect. It is true that the current study demonstrated many statistically significant differences between the two groups when assessing the classical burst suppression measures, but this is likely due to the vastly increased power generated by the study design performing analysis on a burst level (as opposed to subject level). In our study, burst and IBI amplitude and duration, and burst power (across all spectra) were actually lower in patients with seizure recurrence. One possible explanation for this is that seizure control was more difficult to achieve in these patients and therefore they administered a greater cumulative dose of sedative medication, resulting in lower EEG amplitude and power. Cumulatively the studies (Johnson et al. and current) make a strong argument that classical burst suppression measures (amplitude, duration, spectral content) are poor differentiators of seizure recurrence.

Instead, it seems that seizure recurrence can be determined by how "epileptiform" bursts are and intuitively how epileptiform IBIs are (although the current work is the first to place an objective measure on the latter). Seizure recurrence was significantly greater if bursts or IBIs had EDs and an increasing cumulative probability with a greater number of EDs. Seizure recurrence was also associated with increases over time within bursts in total, delta, beta, and gamma power as well as Teager energy (surrogates for "evolution" or "ictal appearing").

Johnson et al. and Thompson & Hantus both include measures of epileptiform bursts, however both studies used subjective assessment (i.e., consensus between two raters) to determine the bursts that were epileptiform and those that were not (Johnson et al., 2016; Thompson & Hantus, 2016). The major limitation for both studies is therefore generalizability (i.e., how translatable the findings are to other centers) and subjectivity, which is inherent to all studies using clinical raters. This is highlighted by Johnson et al. where the rating of presence or absence of "epileptiform features" (not further defined in that study) had a kappa value for interrater reliability (IRA) of 0.87 ("almost perfect"), but a determination of the percentage of bursts with epileptiform activity had considerably lower agreement (κ=0.52, "moderate") (Johnson et al., 2016). Thompson & Hantus used the 2012 ACNS definition of HEBs to report on 24 patients where again the presence of HEBs was associated with a greater rate of seizure recurrence; perhaps more importantly, there was no occasion where HEBs were absent and seizures returned within 24 hours of weaning of anesthesia (Thompson & Hantus, 2016). The finding remains important, but the limitation was that Thompson & Hantus did not make comment as to the IRA of HEBs between the two raters involved (in fact, to our knowledge no study has determined the IRA for HEBs) (Thompson & Hantus, 2016). The current study overcomes this by using purely objective quantitative measures. The only subjective component was the manual selection of the beginning and end of bursts, which is rarely ambiguous given the majority of the time this is about determining activity vs. no activity. By this method the findings here are universally generalizable.

The current study, based on objective measures, provides clinical validation to the current ACNS definition of HEBs, which until now has been mostly based on expert consensus. The current study confirms that 2 EDs within a burst were sufficient to result in a cumulative seizure recurrence probability >50% and objective surrogates of evolution were similarly associated with seizure recurrence. This is the first time each criterion of the HEBs definition has been independently assessed. Johnson et al. did not provide specific detail as to "epileptiform", and Thompson et al. utilized HEBs as a whole without specifying if patients qualified as having HEBs because of the presence of EDs or because they were "ictal appearing".

The multivariate analysis demonstrated that much of the risk of seizure recurrence was determined by the presence of EDs within bursts (aOR 8.55 [95% CI 7.82 – 9.27]) or IBIs (4.08 [3.59 – 4.58]). Although univariate analysis confirmed that the average number of EDs

within bursts (2.1 vs. 1.4) and IBIs (0.6 vs. 0.2) was significantly different between groups, and an increasing number of EDs clearly lead to higher cumulative seizure recurrence probability (Figure 3), the significance for number of EDs was lost with multivariate analysis. It is probable that this was lost within the model as the vast majority of this effect was present in the occurrence of only the first 3 EDs and there was no limit on the number of EDs on quantitative assessment. For example, it was true that the seizure probability for a burst with 10 EDs was not that much greater than one with 3 EDs, and this was likely not accommodated for in the model. Evolution in theta (2.72 [2.39 – 3.05]) and beta (3.04 [2.68 – 3.39]) provided significant contributions to greater risk of seizure recurrence, with a non-significant trend for evolution in total power (2.84 [2.17 – 3.51]).

The findings are of considerable clinical significance. It has often been thought that an evolving pattern holds greater clinical significance compared to the presence of EDs (even when occurring in a very brief run). Take for example a pattern similar to HEBs that occur outside of a repeating sequence, such as brief potentially ictal rhythmic discharges (BIRDs). In one study, "evolving BIRDs" universally resulted in seizures occurring in the same EEG session in 30 patients, compared to non-evolving BIRDs where seizures only occurred in 50% of patients (32 out of 64) (Yoo et al., 2021b). The current study suggests that this may not be true for bursts within burst suppression. In RSE, the presence of EDs within bursts or IBIs may already indicate sufficient cortical excitability that seizures are likely to recur if sedation is then weaned.

An important limitation with the current study was that the surrogate quantitative markers for evolution were not validated. In clinical practice, a standard but fairly rudimentary measure of seizure onset (for example when programming responsive neurostimulation) is an increase in the line length by 50%. In our study, we used Teager energy, a measure of signal energy, which is akin to the line length measure. The field of seizure detection is vast in its own right and there is currently no universally agreed upon set of measures for optimal seizure detection (let alone any set of detectors optimized for ictal rhythms in the critical care setting). It was therefore decided to apply the same 50% increase threshold to individual band power to at least determine a change in measures. An argument could have been made for utilizing the commercially available seizure probability calculator and seizure detector to determine if a pattern was "ictal appearing". The critical flaw with that was of course such algorithms have been optimized for detecting seizures. Although evolution measures are a part of this, electrographic seizures by definition are still required to be at least 10 seconds

duration (L. J. Hirsch et al., 2021). In the study design phase, the seizure probability calculator lacked the temporal resolution to be able to output meaningful data on a burst level. Even within our analysis, bursts had to be at least 4 seconds to be included in the assessment for evolution, and our analysis could not differentiate between evolution over 4 seconds vs. evolution over 9 seconds for example. Future work on optimizing detectors for "ictal appearing" rhythms that do not qualify as electrographic seizures, especially in the critical care setting, could lead to further adjustment of the odds ratios determined in our study.

Conclusion

For patients in RSE where use of cIVASMs has led to burst suppression, successful wean of cIVASM was not determined by classical burst suppression measures (amplitude, duration, spectral content of bursts and IBIs), but instead how "epileptiform" bursts and IBIs were (presence of EDs and positive evolution of bursts).

Chapter 6: Burst Suppression with Identical Bursts (IBs) in the Prognostication of Adult Survivors of Cardiac Arrest

Plain English summary

The second burst suppression (BS) pattern of interest has been identical bursts (IB). In this case all the bursts look "identical" or the same. Conceptually when bursts all look the same it is indicative of the same set of neurons being repeatedly activated. It is suggested to be a cEEG marker of severe cerebral dysfunction, mainly because there is no variability where there is so much dysfunction that only a small pool of neurons is capable of working/ firing each time. The significance of IBs has been most relevant to adult survivors of cardiac arrest as a prognostic tool. It has been suggested by two European cohorts that documentation of IBs in this cohort is universally fatal. This had not been validated in a North American cohort where practices differ surrounding early withdrawal of life-sustaining therapy (WLST).

This cohort identified 80 adult survivors of cardiac arrest who had IBs, representing the largest cohort of its kind and only one of 3 studies to quantitatively assess the findings. This study confirmed that if an adult survivor of cardiac arrest were to have IBs on their EEG at any time, none of the patients had a "good neurological outcome". In addition, this study demonstrated for the first time that as the bursts became more identical there were greater associations with mortality.

This study provides visual and quantitative validation to the original descriptions of IBs in adult survivors of cardiac arrest. The prognostication of such patients always includes clinical, hemodynamic, laboratory, imaging, and neurophysiologic variables to decide on WLST, however IBs on EEG provide a powerful tool in this discussion.

Abstract

The objective was to assess the prognostic significance of identical bursts (IBs) in cardiac arrest survivors with burst suppression (BS) on continuous electroencephalogram (cEEG) monitoring. The hypothesis was that BS with IBs are associated with poor neurological outcomes and mortality.

Methods: This was a retrospective analysis of cardiac arrest survivors admitted to a United States academic medical center between 2013 and 2021 who had an EEG background of burst suppression. EEG and clinical features were extracted from our institutional IRB approved repositories. EEG features were qualitatively and quantitatively rated at 0-, 12-, 24-, 48-, and 72-hours following initiation of monitoring. Qualitative visual assessment occurred blinded to all clinical features including outcomes and in accordance with the current American Clinical Neurophysiology Society (ACNS) definition. Quantitative assessment involved manual marking of 50 consecutive pairs of bursts and interburst intervals (IBIs) for analysis. Similarity of bursts/IBIs were assessed with correlation coefficients.

The primary clinical outcome was survival to hospital discharge. Comparisons were performed between groups, and a multivariate model was generated for significant variables.

Results: Of 593 cardiac arrest patients, 203 (34.2 %) had BS. Thirty-one (15.3%) patients with BS survived. IB were detected in 80 patients (39.4% of BS). No patient with qualitatively identified IBs had a good neurological outcome (76 deceased, 4 state of unresponsive wakefulness). Whereas 11/123 (8.9%) with BS without IB had Cerebral Performance Category 1 – 2. Quantitative analysis of 268 instances of BS demonstrated that mortality was associated with longer bursts, longer IBI, and higher burst correlation coefficients (i.e., bursts that were more similar to each other) only when allowing analysis of the first 2 seconds of bursts. Binary logistic regression showed that only independent EEG predictor of mortality was burst correlation coefficient measured over 2 seconds, adjusted OR of 4.82 (95% CI 1.21 – 8.42), p = 0.009.

Conclusions: Using a single-center US cohort, IBs within 72 hours post cardiac arrest were strongly associated with poor outcomes. Quantitative analysis revealed that including the first 2 seconds of the bursts was superior to limiting the analysis to 0.5-1 seconds.

Introduction:

The determination of neurological prognosis following cardiac arrest and adjudication of withdrawal of life sustaining therapy (WLST) represents a complex patient centric discussion that includes clinical, laboratory, neurophysiologic, and imaging features (Rajajee et al., 2023). Regarding the EEG, a prospective cohort identified that an early continuous background and EEG reactivity were associated with favorable neurological outcomes (Barry J. Ruijter et al., 2019). However when assessed with Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology, suppressed or burst suppression background, with or without periodic discharges, on EEG performed > 72 hours from return of spontaneous circulation (ROSC) was only a moderately reliable predictor (low level of evidence) (Rajajee et al., 2023).

The aim of EEG studies in cardiac arrest survivors have been to identify features that determine good or bad outcomes with a high level of accuracy. In 2013, Hofmeijer et.al., described a distinct pattern within burst-suppression that was universally associated with a poor prognosis (Hofmeijer et al., 2014). They described "identical bursts" (IBs) as bursts where the first 500 msec were identical (i.e., appeared visually similar) irrespective of the amplitude or subsequent duration of bursts or inter-burst intervals (Hofmeijer et al., 2014). In their cohort, none of the 20 patients with IBs survived (i.e., 100% mortality) (Hofmeijer et al., 2014). Similarly, Barbella et.al. identified 53 patients with IBs, none of whom survived, however the presence of IBs in a multimodal model did not improve predictive value of poor outcome when compared to the same model with standard clinical and EEG features (Barbella, Novy, Marques-Vidal, Oddo, & Rossetti, 2020). How similar bursts are have been associated with MRI changes of acute brain injury (Shivdat et al., 2024).

In clinical practice, it is rare to have a test with a 100% positive predictive value (in this case 100% determination of mortality). Since Hofmeijer's description there have been several case reports of 1-2 patients with IBs after cardiac arrest who have survived with good outcomes (Coppler et al., 2021). The two main aims of this study were to: 1. Provide clinical validation of IB in a U.S. healthcare setting; and 2. Assess and refine the current definition of IBs formalized by the 2021 American Clinical Neurophysiology Society's (ACNS) standardized critical care EEG terminology. The main component of this was what duration of bursts, first 0.5, 1 or 2 secs, had to be identical to best determine survival (L. J. Hirsch et al., 2021). The null hypotheses for this study were that 1. IB had no association with survival, and 2. This association would not differ if longer components of the bursts were included in analysis. The

clinical impact being that if validated and reproducible in different healthcare settings, IB may be a more specific EEG marker of poor outcomes.

Methods:

Patients

Patients were selected from retrospective reviews of all cases in a critical care EEG database (Yale New Haven Hospital [YNHH]) between February 2013 and June 2021. Over this period YNHH used the Critical Care EEG Monitoring Research Consortium's (CCEMRC) database that was freely available at the time. Patients were included if they were older than 18 years of age, presented after cardiac arrest, had greater than 6 hours of cEEG, and had BS on their EEG identified during the admission. Clinical data was extrapolated by cross-referencing these patients with a cardiac arrest clinical repository. Details of the repository have been published previously (Kim et al., 2023; Kitlen et al., 2023). Discrepancies between these databases were adjudicated by clinical review of the electronic health record (EHR) to determine the most accurate information. For example, if the CCEMRC database listed a patient as having presented after cardiac arrest and the clinical repository did not, then the EHR was reviewed to verify the truth. Patients that had EHR reviews who did not have sufficient evidence of cardiac arrest were excluded. Patients with missing EEG data were also excluded, i.e., the EEG database confirmed EEG was recorded at that timepoint but was not accessible for technical reasons. This analysis was approved under the YNHH Institutional Review Board (IRB) 2011 "Urgent Inpatient EEG and Multimodality Monitoring Databank" (IRB protocol MOD00040247). The requirement for informed consent was waived.

Selection of Bursts/ Suppressions for Analysis

Patients were identified as having BS at some point of their admission from the critical care EEG database. However, whether a patient was in BS or not at the prespecified timepoints was determined independently by author MF with no prior knowledge of the EEG report for that day. All EEGs were visually rated by author MF who was also blinded to all clinical features including outcomes. Author MF is fellowship trained in critical care EEG, certified in the ACNS terminology, and 2nd author of the 2021 ACNS terminology (L. J. Hirsch et al.,

2021). The clinical features, including patient age, sex, type of cardiac arrest, duration to return of spontaneous circulation (ROSC), and outcomes were held within the clinical repository and this information was only accessed after EEG assessment was finalized. The EEGs were assessed at timepoints 0-, 12-, 24-, 48-, and 72-hours following initiation of cEEG. EEG findings were rated within a 2-hour period from the specified time (i.e., 1-hour preceding and 1-hour postceding the specified time). For timepoint 0- the first 2 hours were assessed to maintain consistency of duration of EEG assessed. EEGs were also rated at the conclusion of monitoring, determined as the last hour of EEG performed for a given admission (e.g., if a total of 27 hours of cEEG was performed, 21 hours on day 1 and 6 hours on day 5, then the findings of the final hour of recording on day 5 were documented).

EEGs were assessed in accordance with the 2021 ACNS standardized critical care EEG terminology (L. J. Hirsch et al., 2021), including continuity, reactivity, suppression percent, IBs, highly epileptiform bursts (HEBs), the presence of electrographic seizures (ESz)/ electrographic status epilepticus (ESE), and the presence of myoclonic status epilepticus (myoclonic SE, a subset of electroclinical SE) (L. J. Hirsch et al., 2021). As per the ACNS terminology, IBs were defined as: "Present if the first 0.5 seconds or longer of each burst or of each stereotyped cluster of 2 or more bursts appears visually similar in all channels in most (>90%) bursts" (L. J. Hirsch et al., 2021).

For quantitative analysis, 50 consecutive pairs of bursts and interburst intervals (IBIs) were manually marked by author MF. IBIs consisted of the lower amplitude segment of an alternating burst suppression pattern. By this definition IBIs could have been suppressed or attenuated and could have included sporadic epileptiform discharges (EDs). The 50 pairs of bursts/IBIs were selected from a relatively artifact free epoch of EEG within the EEG rating periods above. The onset of 51 bursts and 50 IBIs were marked. Given the alternating pattern, the beginning of the IBIs marked the end of the bursts, and vice versa. The 51st burst needed to be marked to determine the end of the 50th IBI, but the 51st burst itself was not analyzed.

Primary Clinical Outcome: Survival to discharge.

Secondary Clinical Outcome: Good neurological outcome, defined by Cerebral Performance Category [CPC] 1 – 2) at hospital discharge. CPC at hospital discharge correlates well with long-term prognosis (Hsu et al., 2014; Phelps, Dumas, Maynard, Silver, & Rea, 2013). The CPC scores were determined by a single reviewer (RB, a neurointensivist) via retrospective

chart review of physical, occupational, and speech therapy notes at the time of hospital discharge (Kim et al., 2023).

Quantitative Analysis

The quantitative analysis of bursts and IBIs was compared between patients who survived to hospital discharge vs. those that did not (i.e., non-survivors). Analyses were performed with MATLAB (MathWorks, Natick, MA). Standard measures of EEG were determined for bursts and IBIs, including mean amplitude, mean duration, total and band power, Teager energy and Approximate Entropy (ApEn). Teager energy is a weighted measure of signal energy such that higher frequency signals have a greater contribution than lower frequency signals (Boudraa & Salzenstein, 2018). ApEn is a measure of the complexity of the time-series (Fan, 2011). For consistency, a maximum duration of 30 seconds was set for bursts and 60 seconds for IBIs. Note: these thresholds were set as by definition activity lasting greater than 30 seconds can no longer be characterized as a "burst"(L. J. Hirsch et al., 2021); and prolonged IBIs (>60 sec) are almost universally devoid of cerebral activity (i.e. suppressed). As such, inclusion of segments beyond 60 seconds of suppression were not likely to alter the findings. How "identical" bursts were was conducted in accordance with Hofmeijer et.al., by the determination of correlation coefficients (Hofmeijer et al., 2014). The correlation coefficient was a measure of how well each of the 50 bursts (or IBIs) correlated with each other. If all 50 bursts were truly identical then the correlation coefficient would be 1; if there was no morphological relationship between any of the 50 bursts, then the correlation coefficient would be 0. Correlation coefficients were calculated based on the first 0.5-, 1-, and 2-seconds of bursts. "Whole burst" correlation coefficients could not be assessed as the duration of bursts between patients was too variable; if a patient had a typical burst duration of 3 seconds this could not be compared to a patient with a typical burst duration of 12 seconds as these patterns were inherently different (i.e., not correlated).

Statistical Analysis

Descriptive statistics were presented as mean and standard deviation for parametric variables, or median and interquartile range for non-parametric variables. For categorical variables the counts in each group were presented with the proportions either of that group or of the entire

cohort specified where relevant. Comparisons between groups (survival vs. non-survival) were achieved with Student's t-test for parametric data, or Pearson's Chi-Square test for non-parametric data. Where the distribution of parametric data differed between the two groups, a two-sample t-test with unequal variances was applied. Clinical, qualitative (visually assessed) EEG measures, and quantitative EEG measures for bursts and IBIs were shown for survivors and non-survivors. For simple comparative statistics, significance was determined as p values less than 0.05. For quantitative data a Bonferroni correction was applied to limit the effect of multiple comparisons with significance set at $p < 0.0038$. It has been specified where Bonferroni correction has been applied. To determine the quantitative variable that inferred the greatest weight towards outcome, a binomial logistic regression model was used where outcome was survival or non-survival.

Results

Inclusion/ exclusion

In the study period, 4226 patients were entered into the YNHH critical care EEG database, of which 593 patient presented following cardiac arrest and 218 had BS and were included. Cross referencing the cardiac arrest clinical repository, 15 patients were excluded for either lack of reliable evidence of cardiac arrest (n=5) or missing EEG data (n=10) at any of the specified time points. This resulted in 203 (34.2% of all cardiac arrest patients) unique cases for inclusion.

Clinical Characteristics.

For all patients, the mean age was 58.4 years (standard deviation ± 17.3). There were 127 males (62.6%) and 76 females (37.4%). The cohort was predominantly White with 117 (57.6%) patients, Black/ African American 53 (26.1%), or Other, including Hispanic and Asian 33 (16.3%). Out of hospital cardiac arrest occurred in 157 (77.3%) cases, while 46 suffered in hospital cardiac arrest (22.7%). The initial non-perfusing rhythms were most commonly non-shockable (n = 156, 77%). Myoclonic SE occurred in 99 (48.8%) patients. At hospital discharge, there were 31 (15.3%) survivors, of whom 11 (35.5% of survivors or

5.4% of total cohort) had good neurological outcomes. WLST occurred in 151 (74.4%) of patients at a mean of 9.28 (± 15.67) days from cardiac arrest.

EEG Characteristics

Patients had a median of 65.0 (interquartile range [IQR] 46.8 – 88.0) hours of cEEG. cEEG commenced mean 11.3 ± standard deviation 6.9 hours following presentation (Table 1). The initial EEG (0-hours) was continuous for 7 (3.4 %) patients, nearly continuous for 7 (3.4%), discontinuous for 13 (6.4%), burst-suppressed for 103 (50.7%), suppressed for 58 (28.6%), or had no background (ESz only) in 15 (7.4%). EEG reactivity was most reliably tested within the first 2-hours of monitoring and was reactive in 14 (6.9%), unreactive in 164 (80.8%), SIRPIDs-only in 5 (2.5%), unclear in 10 (4.9%), or unknown/ untested in 10 (4.9%). There were 268 instances of BS for analysis (0-hours 103 cases, 12-hours 89, 24-hours 55, 48-hours 15, and 72-hours 6). HEBs occurred in 92 (45.3%) patients at any given timepoint. An ESz occurred in 116 (57.1%) patients with 64 that qualified as ESE (55.2% of all seizures or 31.5% of the entire cohort). Taking all patients that had a seizure, 63 occurred within the first hour of EEG (54.3%). For the remaining 53 patients, the median time from initiation of cEEG to ESz was 5.0 (IQR 1.0 – 16.0) hours. Qualitative assessment of BS identified IBs in 80 (39.4%) patients during at least one of the pre-determined time points. Burst suppression with IBs were present at 0-hours in 57 (28.1%) patients, 12- hours in 38 (18.7%), 24-hours in 21 (10.3%), 48-hours in 4 (2.0%), and at 72-hours in 0. The final hour of EEG for the admission demonstrated suppression in 91 (44.8%), continuous-discontinuous WITH epileptiform findings in 35 (17.2%), continuous-discontinuous WITHOUT epileptiform findings in 31 (15.3%), generalized periodic discharges (GPDs) on a suppressed background in 22 (10.8%), ESE in 13 (6.4%), BS WITHOUT IBs in 7 (3.4%), or BS WITH IBs in 4 (2.0%).

Variables	Survivors (n = 31, 15.3%)	Non-survivors (n = 172, 84.7%)	P value
Clinical Characteristics			
Age (years ± SD)	48.26 (± 17.61)	60.21 (± 16.60)	<0.001*
Ethnicity			0.025*
- White	12 (10.3)	105 (89.7)	
- Black/ African American	14 (26.4)	39 (73.6)	
- Other	5 (15.3)	28 (84.8)	

Cardiac Arrest			0.357
- Out of Hospital	22 (14.0)	135 (86.0)	
- In Hospital	9 (19.6)	37 (80.4)	
Initial ECG Rhythm			0.009*
- PEA	15 (15.3)	83 (84.7)	
- Asystole	2 (4.1)	47 (95.9)	
- VF	7 (21.9)	25 (78.1)	
- VT	5 (50.0)	5 (50.0)	
Myoclonic SE	11 (11.1)	88 (88.9)	0.108
WLST	4 (2.6)	147 (97.4)	<0.001*
Time to WLST, mean days (± SD)	33 (± 25.8)	8.64 (± 14.9)	0.002*
EEG Characteristics			
Duration of cEEG (mean ± SD)	103.2 ± 89.5	76.1 ± 58.3	0.032*
Initial Continuity			< 0.001*
- Continuous	4 (57.1)	3 (42.9)	
- Nearly continuous	1 (14.3)	6 (85.7)	
- Discontinuous	6 (46.2)	7 (53.8)	
- Burst-suppression	6 (5.8)	97 (94.2)	
- Suppression	8 (13.8)	50 (86.2)	
- No Background (EEG seizure only)	6 (40.0)	9 (60.0)	
Initial Reactivity			<0.001*
- Reactive	5 (35.7)	9 (64.3)	
- Unreactive	18 (11.0)	146 (89.0)	
- SIRPIDs-only	3 (60.0)	2 (40.0)	
- Unclear	4 (40.0)	6 (60.0)	
- Unknown	1 (10.0)	9 (90.0)	
HEBs	8 (8.7)	84 (91.3)	0.018*
ESz	14 (12.1)	102 (91.4)	0.143
ESE	12 (18.8)	52 (81.3)	0.350
IBs (at any time point)	4 (5.0)	76 (95.0)	0.001*
EEG at end of recording			<0.001*
- Continuous-Discontinuous WITH epileptiform findings	9 (25.7)	26 (74.3)	
- Continuous-Discontinuous WITHOUT epileptiform findings	12 (38.7)	19 (61.3)	
- Suppression with GPDs	1 (4.5)	21 (95.5)	
- Suppression	2 (2.2)	89 (97.8)	
- ESE	4 (30.8)	9 (69.2)	
- Burst-suppression WITH IBs	1 (25.0)	3 (75.0)	
- Burst-suppression WITHOUT IBs	2 (28.6)	5 (71.4)	

Table 1: Clinical and EEG Characteristics for Survivors and Non-survivors. Numbers of patients in each group have been provided with proportions in parentheses. Proportions represent percentages for a given row, e.g., out of all patients who had an out of hospital cardiac arrest

(n=157), 22 survived giving a proportion of 22/157 = 14.0% compared to 135 (135/157 = 86.0%) of patients that did not (non-survivors). Continuous variables such as age and duration of EEG are shown as mean ± standard deviation. Note: although 11 patients with myoclonic SE survived to discharge only one had a CPC of 2 with the other 10 having CPC of either 4 or 5 and discharged to hospice care. SD standard deviation, PEA pulseless electrical activity, VF ventricular fibrillation, VT ventricular tachycardia, WLST withdrawal of list sustaining therapy. SE status epilepticus. HEBs highly epileptiform bursts. ESz electrographic seizure. ESE electrographic status epilepticus. IBs identical bursts. *statistically significant $p < 0.05$.

Survivors vs. Non-survivors

The clinical and EEG characteristics (qualitative assessment) of survivors vs. non-survivors are shown in Table 1. Non-survivors were significantly older than survivors, mean 60.21 ± 16.60 years vs. 48.26 ± 17.61. Nonshockable rhythms were associated with increased mortality (nonshockable 11.5% survived vs. shockable 27.7%, p=0.007). Patients who survived had on average longer durations of cEEG (survivors mean 103.2 ± 89.5 hours vs. non-survivors 76.1 ± 58.3 hours, p = 0.032). Those that survived to discharge were more likely to have had an initial continuous (survivors 4/31 = 12.9% vs. non-survivors 3/172 = 1.7%) and reactive EEG (5/31 = 16.1% vs. 9/172 = 5.2%). Of the 103 patients that had BS at commencement of cEEG 97 (94.2%) died, similarly if the initial EEG was suppressed 50 out of 58 (86.2%) did not survive to discharge.

There was no significant difference in the proportion with ESz (survivors 14/31 = 45.2% vs. non-survivors 102/172 = 59.3%, p = 0.143) or ESE (12/31 = 38.7% vs. 52/172 = 30.2%, p = 0.350) between survivors and non-survivors. Similarly, there was no difference in the proportions of those with myoclonic SE (11/31 = 35.5% vs. 88/172 = 51.2%, p = 0.108); although for those that survived only one had a CPC of 2 with the other 10 a CPC of either 4 or 5. Patients with IBs at any time point were less likely to survive (4/80 survived = 5.0%) as compared to those without IBs (27/123 = 22.0%, p=0.001). Of the 4 patients with IBs who survived until hospital discharge, IBs occurred at 0-hours in 1, 12-hours in 3, and 24-hours in 1 (1 patient had IBs at both 0- and 12-hours). None of these four patients had a good neurological outcome. All were discharged to hospice care, and all had a CPC score of 4 (i.e., state of unresponsive wakefulness). In patients without IBs, a good neurological outcome was seen in 11 out of 123 patients (8.9%), p=0.006.

For the final hour of EEG for the admission, if the EEG had become suppressed 89 out of 91 (97.8%) patients died, or if suppressed with GPDs 21 out of 22 (95.5%) died. Conversely if the final hour of EEG had improved to continuous-discontinuous with or without epileptiform discharges 21 out of 66 (31.8%) patients survived. Even if the final hour of EEG demonstrated persistent ESE 4 out of 13 (30.8%) of these patients survived.

Quantitative analysis of bursts/suppressions

When comparing burst-suppression between survivors and non-survivors using quantitative measures, survivors had significantly shorter burst duration with survivors' mean 4.10 sec (95% CI 3.29 – 4.92) vs. non-survivors' mean 5.85 sec (5.28 – 6.41), $p = 0.001$ (Table 2, Figure 1). The correlation coefficient was higher (i.e., more identical) in non-survivors, however after Bonferroni correction for multiple comparisons this only reached significance when burst analysis allowed the first 2 seconds of each burst to be considered, 2-sec correlation coefficient for non-survivors 0.659 (0.640 – 0.678) vs. 0.541 (0.474 – 0.607), $p = 0.0032$. The correlation coefficients between the two groups did not meet the adjusted cut off for significance if only the first 0.5 sec or 1 sec of each burst was assessed (Table 2, Figure 2). The distribution of correlation coefficients when allowing the first 0.5-sec, 1-sec, or 2-sec of each burst has been shown in Figure 2. The differences in correlation coefficients between the two groups were apparent at all time points i.e., initial EEG, 12-, 24-, 48-, and 72-hours, however there was not sufficient power at any specific timepoint to determine significance. The correlation coefficients for each time point have been shown for survivals and non-survivors when allowing the first 2 seconds to be analyzed (Figure 3).

There was no significant difference between the two groups when it came to burst amplitude, any power spectra (delta – gamma), Teager energy, or ApEn; although several of these measures demonstrated non-significant trends between groups (Table 2). For IBIs, the only significant feature between the two groups was duration with non-survivors having longer IBI durations (i.e., were more suppressed) mean 33.30 sec (26.88 – 39.73) compared to survivors 16.16 (9.09 – 23.23) sec, $p < 0.001$. All the other measures were not significantly different between groups (Table 2).

Variables	Survivors n=31	Non-survivors n=172	P value
Quantitative analysis of Bursts			
Amplitude (µV)	12.36 (8.58 – 16.14)	18.50 (17.10 – 19.90)	0.007*
Duration (sec)	4.10 (3.29 – 4.92)	5.85 (5.28 – 6.42)	0.001**
Delta power	0.714 (0.118 – 1.310)	1.794 (1.356 – 2.233)	0.007*
Theta power	0.237 (0.062 – 0.412)	0.329 (0.250 – 0.408)	0.356
Alpha power	0.125 (0.018 – 0.232)	0.134 (0.106 – 0.162)	0.878
Beta power	0.085 0.017 – 0.153)	0.145 (0.099 – 0.192)	0.158
Teager Energy	23.60 (5.95 – 41.23)	39.66 (26.94 – 52.37)	0.156
0.5 sec correlation coefficient	0.548 (0.491 – 0.605)	0.630 (0.611 – 0.650)	0.014*
1.0 sec correlation coefficient	0.580 (0.513 – 0.646)	0.668 (0.649 – 0.688)	0.021*
2.0 sec correlation coefficient	0.541 (0.474 – 0.607)	0.659 (0.640 – 0.678)	0.003**
Quantitative analysis of IBIs			
Amplitude (µV)	7.47 (4.63 – 10.31)	7.06 (6.37 – 7.74)	0.786
Duration (sec)	16.16 (9.09 – 23.23)	33.30 (26.88 – 39.73)	0.001**
Delta power	0.076 (0.020 – 0.132)	0.547 (0.101 – 0.993)	0.041*
Theta power	0.006 (0.000 – 0.013)	0.020 (0.007 – 0.033)	0.058
Alpha power	0.010 (-0.001 – 0.021)	0.013 (0.006 – 0.020)	0.630
Beta power	0.033 (-0.008 – 0.074)	0.036 (0.018 – 0.054)	0.900
Teager Energy	20.14 (-4.61 – 44.88)	19.65 (11.71 – 27.58)	0.971
0.5 sec correlation coefficient	0.609 (0.535 – 0.683)	0.652 (0.634 – 0.671)	0.282
1.0 sec correlation coefficient	0.579 (0.510 – 0.649)	0.636 (0.618 – 0.655)	0.135
2.0 sec correlation coefficient	0.546 (0.480 – 0.611)	0.615 (0.597 – 0.634)	0.059

Table 2: Quantitative analysis of bursts and interburst intervals (IBIs). The mean ± 95% confidence intervals have been presented for the analysis of bursts and IBIs. These have been separated into patients that survived until discharge vs. those that did not (i.e., non-survivors). The p values for comparisons between the two groups are included in the right column, following Bonferroni correction p values of < 0.0038 were deemed significant**, trends where the p value was <0.05 but >0.0038 have also been highlighted with an *. IBI interburst interval.

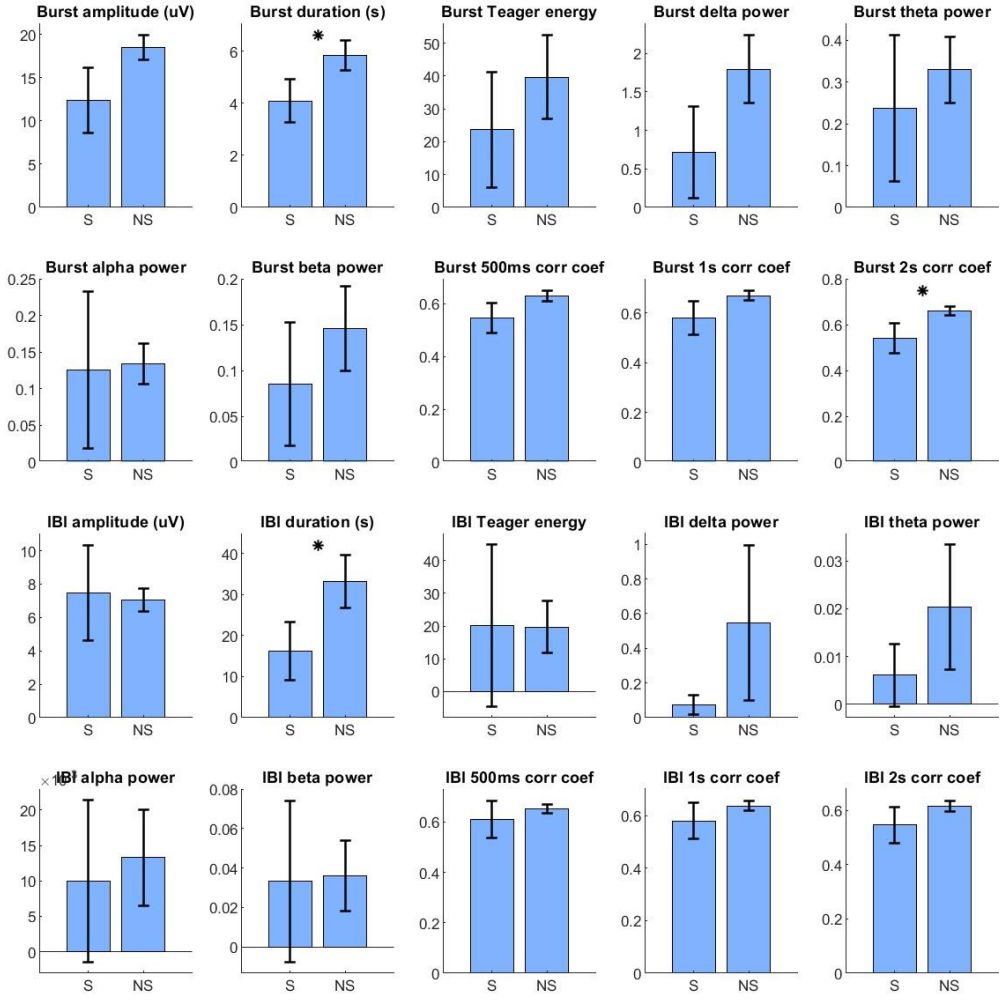

Figure 1: Quantitative analysis of bursts and interburst intervals (IBIs). The results from Table 2 are presented in graphical form. Note although several measures seem to separate survivors and non-survivors the only statistically significant differences are in burst duration, burst correlation coefficient if including the first 2 seconds of bursts and IBI duration, significant differences marked with an asterisk*. Corr coef = correlation coefficient, IBI interburst interval.

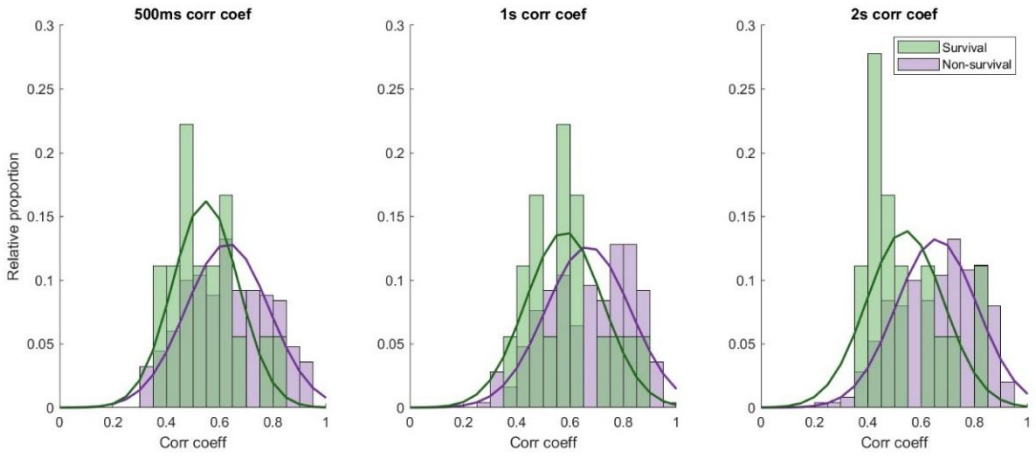

Figure 2: Distribution of burst correlation coefficients for survivors vs. non-survivors. The distribution of burst correlation coefficients (corr coef) has been presented for survivors and non-survivors. The three histograms represent the results if the first 500 msec (i.e., 0.5 sec) of bursts (left histogram), 1 sec (middle), and 2 sec (right) were allowed in the analysis. By this depiction it is easier to appreciate that the separation in distribution between the two groups occurs best if the first 2 seconds of bursts were allowed in the analysis versus if analysis was only performed on the first 500 msec (and ignored the remainder of the bursts).

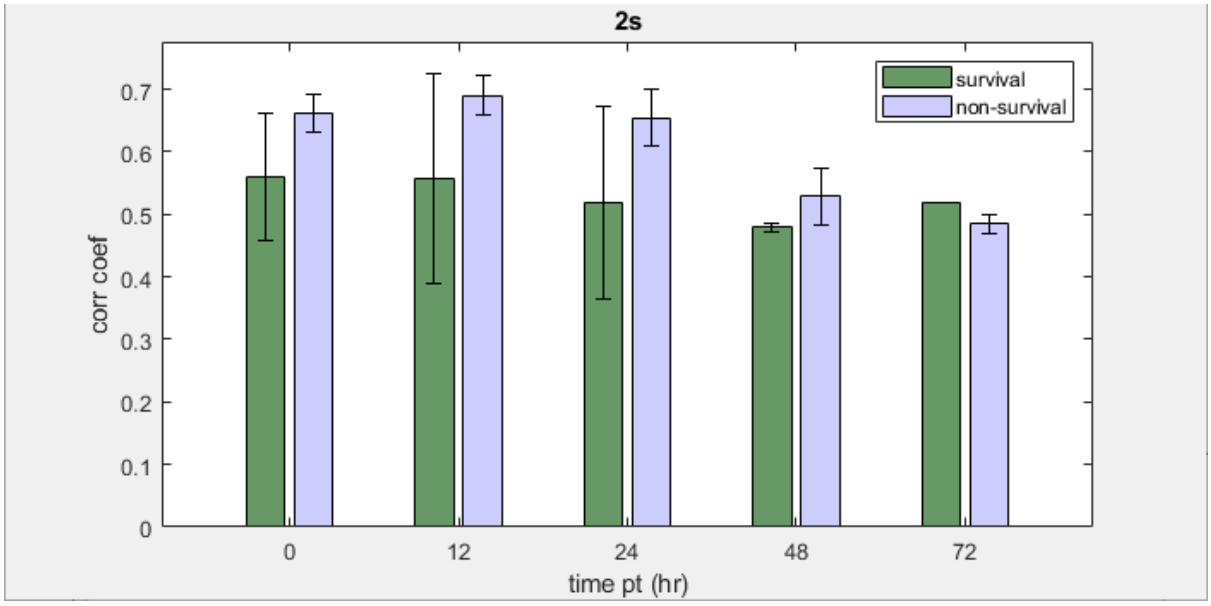

Figure 3: Correlation coefficient provided for survivors and non-survivors at each time point when analyzing bursts using 2 seconds. When each time point was taken individually there were no significant differences between the groups.

Binary logistic regression

The significant EEG features determined by quantitative analysis (i.e., burst duration, burst correlation coefficient utilizing the first 2 seconds of the bursts, and IBI duration) were entered into a binary logistic regression to compare features between survivors or non-survivors. Only burst correlation coefficient using 2 sec remained a significant determinant of prognosis, adjusted odds ratio (aOR) 4.82 (95% CI 1.21 – 8.42) p = 0.009. Burst duration had an aOR of 0.12 (-0.07 – 0.31) p = 0.218, and IBI duration an aOR of 0.01 (-0.01 – 0.03) p = 0.420.

Discussion

We report the first US cohort assessing the prognostic significance of IB and found that the presence of IB prior to 72 hours was highly associated with poor outcome. In addition to qualitatively assessing IB, we report on quantitative features of IB that may be associated with poor prognosis and could be candidate biomarkers for future study. The current study confirmed the findings of the two prior studies that took place in The Netherlands and Switzerland (Barbella et al., 2020; Hofmeijer et al., 2014). Of the 80 patients who were visually assessed as having IBs at any of the pre-determined time points using the ACNS qualitative definition, none had a good neurological outcome; 76/80 died (with the usual major caveat that WLST was common) and the remaining 4/80 all had a CPC of 4 (state of unresponsive wakefulness) at the time of discharge. When comparing quantitative EEG measures between survivors and non-survivors, only burst duration, IBI duration, and burst correlation coefficients significantly differed. When burst correlation coefficients were assessed based only on the first 0.5 second (as currently defined) (L. J. Hirsch et al., 2021), first 1 second, or first 2 seconds of bursts, the greatest separation between survivors and non-survivors occurred when the first 2 seconds of bursts was used and only the correlation coefficient when using the first 2 seconds reached pre-determined statistical significance (survivors 0.659 vs. non-survivors 0.541). A binary logistic regression for the significant quantitative variables revealed most of the effect was in the 2-second burst correlation coefficient (aOR 4.82, p = 0.009) rather than in burst duration (aOR 0.118, p = 0.218) or IBI duration (aOR 0.009, p = 0.420).

This is so far the largest cohort of patients with IBs after cardiac arrest (80 patients), with Barbella et al. 53 patients and the initial Hofmeijer et al. description 20 patients (Barbella et al., 2020; Hofmeijer et al., 2014). All three studies were done completely independently, with no single author of any paper represented in the other two, as well as publications separated by a decade, and with the addition of the current cohort now occurring in heterogenous healthcare settings (USA, 2 x Europe) including phenotypically different patient populations. Although the cohorts have not been directly compared, it is incredibly striking how consistent they were in their determination of IBs and the clinical implications of the finding. Hofmeijer et al. reported the IBs at 24-hours in 20/101 (20%) patients with post cardiac arrest burst suppression (Hofmeijer et al., 2014); while Barbella et al. reported IBs in 53/147 patients (36%) across two protocolized time points of 5-36 hours and 36-72 hours from cardiac arrest with a median time to IBs of 20 hours (range 4.5 – 43) (Barbella et al., 2020). Our study had 80/203 (39.4%) patients with IBs at one or more of the pre-determined time points; importantly 21/203 (10.3%) of patients had IBs at 24-hours from initiation of monitoring. Our results are consistent with previously published cohorts, suggesting that IBs occur most commonly within the first 24 hours with the prevalence decreasing over time.

Clinical neuroprognostication is never based on a single test and requires the integration of complex clinical, laboratory, radiographic, and neurophysiologic findings (Rajajee et al., 2023; Sandroni, D'Arrigo, & Nolan, 2018). It is important to mention that when recently assessed by GRADE methodology suppressed or burst suppression background, with or without periodic discharges, on EEG performed $>$ 72 hours from ROSC was only a moderately reliable predictor (low level of evidence) (Rajajee et al., 2023). When entering IBs into a multivariable model with clinical and other EEG features, Barbella et.al. found that it did not improve the performance or predictability of the model (Barbella et al., 2020). In saying that when taking the 3 cohorts together 0/153 patients with IBs achieved good neurological outcome (defined as CPC 1 – 2); in fact 149/153 patients died with the remaining four in our cohort having a CPC of 4 (state of unresponsive wakefulness) at time of discharge (Barbella et al., 2020; Hofmeijer et al., 2014). The major perceived limitations of the prior two cohorts were: 1. They may not have had sufficient cEEG to provide an accurate reflection of the patient's brain states over the duration of their admission, and 2. The self-fulfilling prophecy of patients with post-cardiac arrest burst suppression having lifesaving therapy withdrawn prematurely. It is argued that the current study overcomes both limitations, at least partly. All patients in the current study had a minimum of 6 hours of

cEEG and the median duration of cEEG was 65.0 hours (IQR 46.8 – 88.0). In addition, it seemed IBs occurred early (≤ 24 hours) and the outcome did not seem to matter at what timepoint IBs were detected (i.e., IBs at any time were associated with a bad outcome). To expand upon this, prior studies were criticized that if they had supported patients longer, the EEG may have improved, and the outcomes may have been more favorable. One of the most useful findings in our study was documentation of the EEG at the conclusion of monitoring. A very small proportion of patients were still in burst suppression (11/203 patients or 5.4%) at the conclusion of the EEG, indicating that the vast majority had been sufficiently supported that at least their EEG/neurological outcome had been determined (positively or negatively). The majority 113/203 (55.7%) of patients were supported until their EEG was either suppressed (91 [44.8%]) or suppressed with GPDs (22 [10.8%]), providing reasonable evidence that in this cohort extending periods of life-sustaining therapy may not have adjusted outcomes. This was also supported by the average time that WLST occurred was 9.28 days.

A major limitation was that over the study duration the EEG including the finding of burst suppression with IBs was a part of routine clinical care, including factoring into the adjudication for WLST. Given that this study was retrospective it was not possible to ascertain how much weight was placed on these findings in decision-making at the time. A larger prospective cohort with minimal early WLST and clear documentation of the factors that contributed to WLST decisions will be required to know if this is of true prognostic significance.

Some of the prior limitations to clinical utility may be explained by the definition. The original Hofmeijer definition was “Bursts were considered identical, if the first 500 ms. were identical, *irrespective of amplitude or subsequent duration* of bursts or inter-burst intervals” (Hofmeijer et al., 2014). From a conceptual perspective each burst within BS is the surface representation of summated cortical rhythms at that given moment, a process that normally shifts between brain regions resulting in burst variability (Lewis et al., 2013). IBs therefore are presumed as a state of extreme invariance where the same exact population of cortical neurons are being activated during each burst (with other brain regions being too dysfunctional to contribute). As a concept, one would then presume that bursts with the highest correlation coefficients or bursts where the entire duration of the bursts were identical represent a neuronal pool with the least variability and result in the worst outcomes. This concept was adopted into the ACNS terminology where IBs were defined as “Present if the

first 0.5 seconds *or longer* of each burst or of each stereotyped cluster of 2 or more bursts appears visually similar in all channels in most (> 90%) bursts" (L. J. Hirsch et al., 2021). From a conceptual EEG perspective, the only time burst correlation coefficient was statistically significant was when up to 2 seconds of each burst was allowed into analysis (not significant with only the first 0.5 or 1 second). This does provide validation to the subtle but important change to the ACNS definition whereby greater proportions of the burst can contribute to whether a burst is identical or not. In saying that, the current study provides clinical validation that visual assessment of post-anoxic burst suppression using the first 0.5 seconds was already sufficient to identify this cohort of patients who experienced poor outcomes with a high level of specificity.

There were several minor limitations that are mostly important for consideration of future studies. The time points have been set from the commencement of cEEG rather than time of cardiac arrest. This was required to accommodate the study design as the assessment of the EEG was done completely blinded to all clinical factors (including time of cardiac arrest). This is a minor limitation mostly because in our center cEEG forms a routine part of the post cardiac arrest protocol and the mean delay to cEEG was less than 12-hours following presentation in this cohort. The amount of sedation administered at the time of cEEG, or the total amount of sedation administered over the course of admissions was not determined. The study did not allow for 6- or 12-month follow-up to reassess neurological outcomes, however the high rate of mortality in the IB group limited the relevance of this. The study selected only cardiac arrest patients that had cEEG. Over the course of this study cEEG became part of standardized care, however in the earlier years' patient recruitment was not consecutive. If future studies are planned, having standardized care pathways to limit heterogeneity will greatly increase the likelihood of an accurate and generalizable result.

A quantitative measure of how identical "whole bursts" was not possible given the significant variation in burst duration, although visual analysis certainly incorporated whole bursts given the ACNS definition. It would be interesting to repeat this visual, qualitative assessment of IBs with the more rigid definition if present only if the first 2 seconds of bursts (or the entire bursts if <2 secs) are visually similar, although as discussed above, even using the current definition that only requires the first 0.5 seconds to be identical, no one had a good neurological outcome.

The statistical model did not account fully for collinearity; however binary logistic regression did highlight burst correlation coefficient over 2 seconds as the only statistically significant determinant of survival when considering burst duration and IBI duration. A more accurate determination of odds ratios could be generated by a machine learning algorithm taking all clinical and EEG features. The limitation of the current study was that this would have led to a heavily skewed result given clinical features and visual EEG analysis were performed on a patient level versus quantitative EEG analysis that was performed at a burst/ IBI level and therefore generated an exponentially greater number of data points. A "cut-off" of the appropriate correlation coefficient to use to label bursts as "identical" was not reassessed. Hofmeijer et al. proposed 0.75 (Hofmeijer et al., 2014), our study seems to show adequate separation of survivors vs. non-survivors at 0.7 (provided analysis was performed on the first 2 seconds of bursts, Figure 2).

Conclusion

Our study provides clinical validation in a US healthcare setting that IBs occurring at any time of post cardiac arrest burst suppression were associated with mortality and poor neurological outcomes. This provided some validation of the ACNS definition whereby the first 0.5 seconds or longer of bursts should be considered in the visual determination of identical bursts. Whether the finding is truly of prognostic significance will more than likely require larger prospective cohorts with minimal early WLST.

Chapter 7: Discussion and Conclusions

This thesis contributed to the understanding of the clinical significance of EEG patterns in critically ill patients. The background efforts completed at the literature review stage helped to set worldwide reference material on the topic, including co-authoring the Atlas of EEG in critical care and the ACNS guideline on standardized critical care EEG terminology (Lawrence J. Hirsch, Fong, & Brenner, 2023; L. J. Hirsch et al., 2021). Multicenter collaborative efforts collated the critical care EEG findings from 12,450 patients, which allowed work in this thesis to determine the accurate associations of rhythmic and periodic patterns (RPPs) with seizures and status epilepticus (SE) including how these probabilities were adjusted by modifiers (Snider et al., 2023). Large datasets do not have the ability to determine the relevance of rare EEG patterns given that any small effect gets diluted by the large cohort. As such the clinical significance of specific EEG patterns was then assessed with a series of well-designed cohort studies.

These cohort studies demonstrated that bilateral asymmetric LRDA was a clinically unique entity when compared to generalized rhythmic patterns and were associated with acute focal structural abnormalities with a trend to greater seizures (Fong, Jadav, et al., 2023). In the context of refractory status epilepticus (RSE) treated to the point of burst suppression, highly-epileptiform bursts (HEBs) were the main EEG determinant of seizure recurrence following weaning of continuous intravenous antiseizure medication (cIVASM) (Fong, Pu, et al., 2023). In adult survivors of cardiac arrest, it was confirmed that burst suppression with identical bursts (IBs) at any time point were associated with greater mortality and poor neurological outcomes, and this effect was more pronounced as the degree to which bursts were identical increased (Fong et al., 2025).

Overall, these findings provide a great step forward in the understanding of these patterns and each has practical clinical relevance to the management of critically ill patients at the individual level. The findings of the critical care EEG monitoring research consortium (CCEMRC) database allow clinicians to classify an RPP and its modifiers and then come up with an accurate and validated probability that a given patient would have a seizure over the next 72 hours (Rodriguez Ruiz et al., 2017; Snider et al., 2023; Aaron F. Struck et al., 2020). This furthered prior assessments and provides clinicians with the best information possible to make decisions regarding the escalation of antiseizure medications (ASM) at the bedside.

A pattern within this, bilateral asymmetric LRDA (LRDA-ba) has now been demonstrated and validated to occur greatest on the side of acute structural brain injury and not as a consequence of the adjustment of GRDA (Fong, Jadav, et al., 2023). The pattern by itself had a modest increase association with electrographic seizures (ESz). Although it may be considered as being less associated with ESz compared to unilateral LRDA it is worth noting that when taken as a large cohort the ESz rate in patients with LRDA overall was 24%, which was not too dissimilar to the 17.3% for patients with LRDA-ba alone (with no other EEG finding of hyperexcitability) (Fong, Jadav, et al., 2023; Snider et al., 2023). Noting that the ESz rate in the control matched group of patients with GRDA alone was 9.9% it was likely that patients with LRDA-ba alone did have increases in ESz although the study was likely underpowered to find statistical significance. The study demonstrated the findings from 258 matched patients representing the largest cohort of patients with LRDA-ba described. Despite this, the sample was comparatively small compared to the CCEMRC cohort and the small effect size meant that this number was not sufficient to reach significance, although it was very close, $p = 0.08$ (Fong, Jadav, et al., 2023).

The use of burst suppression (BS) on EEG in the management of RSE has been historically very arbitrary. The classical teachings have been to BS patients for 12 – 48 hours aiming for interburst intervals (IBIs) between 10 and 30 seconds before weaning cIVASM. This approach has been very practitioner specific or center specific and there has not been much objective evidence to help guide BS targets for a given patient. Highly epileptiform bursts (HEBs) were documented as one method that may predict the success/ failure of cIVASM weaning in this context (Thompson & Hantus, 2016). That study was of 24 patients, and the classification of BS was based on visual rating by two independent reviewers (Thompson & Hantus, 2016). This meant that despite the term's adoption to the ACNS terminology it had not been validated outside that single center experience based purely on visual inspection of the EEG, which limited the confidence in its generalizability. The current work solved both of these issues, now including an additional 31 occasions of cIVASM weaning from 27 patients from an independent center and using readily available quantitative metrics such as a commercially available spike detector and a measure of evolution in order to objectively assess the relevance of HEBs (Fong, Pu, et al., 2023). This work quantitatively validated that the major EEG factor that determined seizure recurrence was the epileptiform content of bursts (i.e., HEBs) rather than any of the classical BS measures such as burst/ IBI amplitude or duration (Fong, Pu, et al., 2023). On a practical patient level this provides conceptual

validation to the individualization of BS in the management of RSE. In this context patients are not treated to an arbitrary threshold, such as 24 hours of BS or maintaining the IBI at 10 seconds. Instead, treatment is individualized whereby for a given patient the reversible factors are adjusted and ASM titrated to the point where burst content is sufficiently non-highly epileptiform. At this point where therapy has been titrated to the absence of HEBs the probability of successful cIVASM wean is greatly improved.

The other BS pattern that was incorporated into the ACNS terminology but not particularly well validated was identical bursts (IBs). The original cohort of 20 patients and only subsequent cohort of 53 patients with the finding both occurred in European cohorts where the practices surrounding early withdrawal of life sustaining therapy (WLST) arguably differ from those in North American cohorts (Barbella et al., 2020; Hofmeijer et al., 2014). The pattern was proposed to represent a state of extreme invariance where in the setting of adult survivors after cardiac arrest the pattern signified severe brain injury whereby a small proportion of neurons would be repeatedly activated (given the remainder were injured and dysfunctional). The current study on IBs was the largest cohort so far (80 patients), occurring in a major North American tertiary hospital (Fong et al., 2025). The strengths of the current study were that neurological outcomes were very carefully documented, and the rate of early WLST was low with EEG confirmation that the patient had either improved or reached a point that was not survivable (i.e., EEG suppression) (Fong et al., 2025). This study not only confirmed that patients with IBs following cardiac arrest had a universally poor neurological outcome but also the extent to which bursts were identical strengthened this association, i.e., the more identical bursts were the stronger the association with mortality (Fong et al., 2025). It remains important to recognize that prognostication following cardiac arrest represents a complex assessment of clinical, hemodynamic, laboratory, imaging, and neurophysiologic findings. However, the presence of IBs is now validated as a powerful tool with reasonable predictive value in several healthcare environments.

The findings of this thesis consolidate the classification of EEG in critically ill patients and greatly contributed to standardization with efforts such as the revision of the Atlas of EEG in Critical Care. The thesis then sets out to consolidate the terms within the guidelines, by reporting the association of RPPs and their modifiers with seizures and SE and validating the clinical relevance of specific terms bilateral asymmetric LRDA, HEBs, and IBs. The thesis overall greatly consolidates the relevance of these terms which in turn sets the stage to their application to clinical practice around the world.

Future directions

The work within this thesis represents the limitation of what can be determined by retrospective cohort studies, even if some of those cohorts constitute 12,450 patients. The next steps have already begun, which are the utilization of machine learning and artificial intelligence (AI) in the large-scale interpretation of critical care EEG; and the development of well-designed prospective clinical trials that assess the significance of a given EEG pattern for a given clinical entity.

One of the largest limitations with work performed within this thesis was that each chapter was incredibly time consuming and therefore not practically applicable across a wide range of clinical care settings. The CCEMRC cohort represents 1000's of hours of clinical staff entering data, the LRDA-ba work required manual visual validation of each pattern included, and the BS chapters required both repeat visual assessment of all patients at all pre-determined time points but also manual marking of the EEG so that quantitative analysis could be performed. One of the reasons the original HEBs or IBs cohorts had not been validated was arguably because it was not practical for a clinician to be able to do this, and certainly not practical on an ongoing clinically applicable basis. AI will largely solve these issues with efforts such as SPaRCNet forging the way to automated detection and classification of patterns (Jing et al., 2023). In the future AI will be able to reliably classify critical care EEG patterns and determine the relevant features of those patterns based on 100's of thousands of cEEGs. This will then be able to provide real time probability of seizure for a given patient and may even be able to predict seizure in select clinical scenarios.

The ultimate question that is posed often is to what extent treatment of EEG patterns including seizures alter clinical outcomes. As discussed in the literature review there are many studies that have demonstrated especially high seizure burdens to be associated with worse functional neurological outcomes (De Marchis et al., 2016; Payne et al., 2014). The difficulty in designing prospective critical care EEG trials has been heterogeneity. For example, aggressive treatment of seizures in young people may be beneficial but the same approach may be harmful to older individuals. Or treating brief electrographic seizures may be beneficial in patients with epilepsy but not in adult survivors following cardiac arrest. Therefore, any trial suggesting treating a pattern overall will be conceptually flawed or would require such large numbers to eventually overcome clinical heterogeneity. The field has recognized this dilemma and shifting towards treatment trials of specific patterns within well-defined clinical entities. For example, the TELSTAR trial demonstrated that treating

predominantly generalized periodic discharges (GPDs) in adult survivors of cardiac arrest did not improve outcome in terms of mortality at 3 months (B. J. Ruijter et al., 2022). It is important to highlight that this does not mean that the treatment of GPDs across all clinical contexts is futile, just in that well defined clinical context. It may be that the treatment of GPDs in patients with septic encephalopathy shortens intensive care or hospital stay and improves functional neurological outcomes, but this will not be determined without as well designed prospective clinical trial.

Conclusion

Critical care EEG has grown exponentially over the past few decades, and this thesis has greatly furthered the field by providing accurate associations of RPPs and their modifiers with seizures and SE. It has also provided validation to previously described EEG patterns, which sets the conceptual basis for their use in clinical practice. The future will be determined by increasing use of AI tools and well-designed prospective clinical trials to determine the significance of EEG patterns across a variety of clinical contexts.

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