



The Influence of Seizures and Periodic Discharges on Cognitive Outcome After Brain Trauma

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Introduction

- Seizures have been reported in as many as 18-30% of patients after moderate-to-severe traumatic brain injury (TBI) (1) and abnormal EEG patterns, including periodic or rhythmic discharges, may be even more common (2).
- Seizures and periodic discharges exist along an ictal-interictal continuum (IIC) and have been associated with metabolic crisis after severe TBI (2,3).
- While functional disability may not be impacted by the development of IIC patterns (4) it is possible that cortical injury and therefore cognitive dysfunction result.
- We performed a post-hoc analysis of a prospective, randomized multicenter trial, which included continuous EEG (cEEG) per protocol, to examine the impact of IIC burden on cognitive outcome.

Methods

- We performed a post-hoc analysis of a randomized controlled clinical trial (INTREPD²⁵⁶⁶) for patients aged 18-70 with non-penetrating moderate-to-severe TBI defined as post-resuscitation Glasgow Coma Scale of 4-12.
- The primary outcome of the parent study was the Glasgow Outcome Scale-Extended (GOSE) at 3 months.
- Cognitive outcome was rated by the Repeatable Battery for the Assessment of Neuropsychology Status (RBANS) **global cognition score** (RBANS), which ranges from 40-160 with lower values indicating worse cognitive outcome.
- A linear regression model was constructed using admission clinical predictor variables (age and post-resuscitation motor Glasgow Coma Scale (GCS) score and pupillary exam) (5) and the Injury Severity Score (ISS)

Continuous EEG

- cEEG was initiated within the first 24 hours and continued up to 7 days.
- Review of cEEG was performed retrospectively by fellowship-trained EEGers certified in ICU EEG terminology (HL, MM, BF) (6).
- IIC was defined as ≥ 1.5 Hz lateralized rhythmic delta activity or generalized periodic discharges, and any lateralized periodic discharges or seizures (Figure 1).
- The IIC burden was calculated as follows:
 - Daily Pattern Burden = Prevalence/Day (Hrs)
 - Daily Pattern Burden Index = Pattern Burden (Hrs) * Frequency (Hz)

Table 1: Univariate Analysis

Variable	IIC (n=13)	No IIC (n=76)	p-value
Age	31.2+/-13.6	32.4+/-13.5	0.75
Sex (Male)	12/13 (92.3)	73/76 (96.1)	0.55
Motor GCS	5 (4-5)	5 (4-5)	0.12
Pupillary Reactivity (both)	12/13 (92.3)	67/76 (88.2)	0.66
LPcore	-0.98+/-0.75	-0.84+/-0.71	0.47
Injury Severity Score	26 (16-29)	19 (12-29)	0.32
Poor outcome	4/13 (30.8)	12/76 (15.8)	0.36
Global Cognition Score	71.8+/-15.0	80.8+/-15.7	0.04

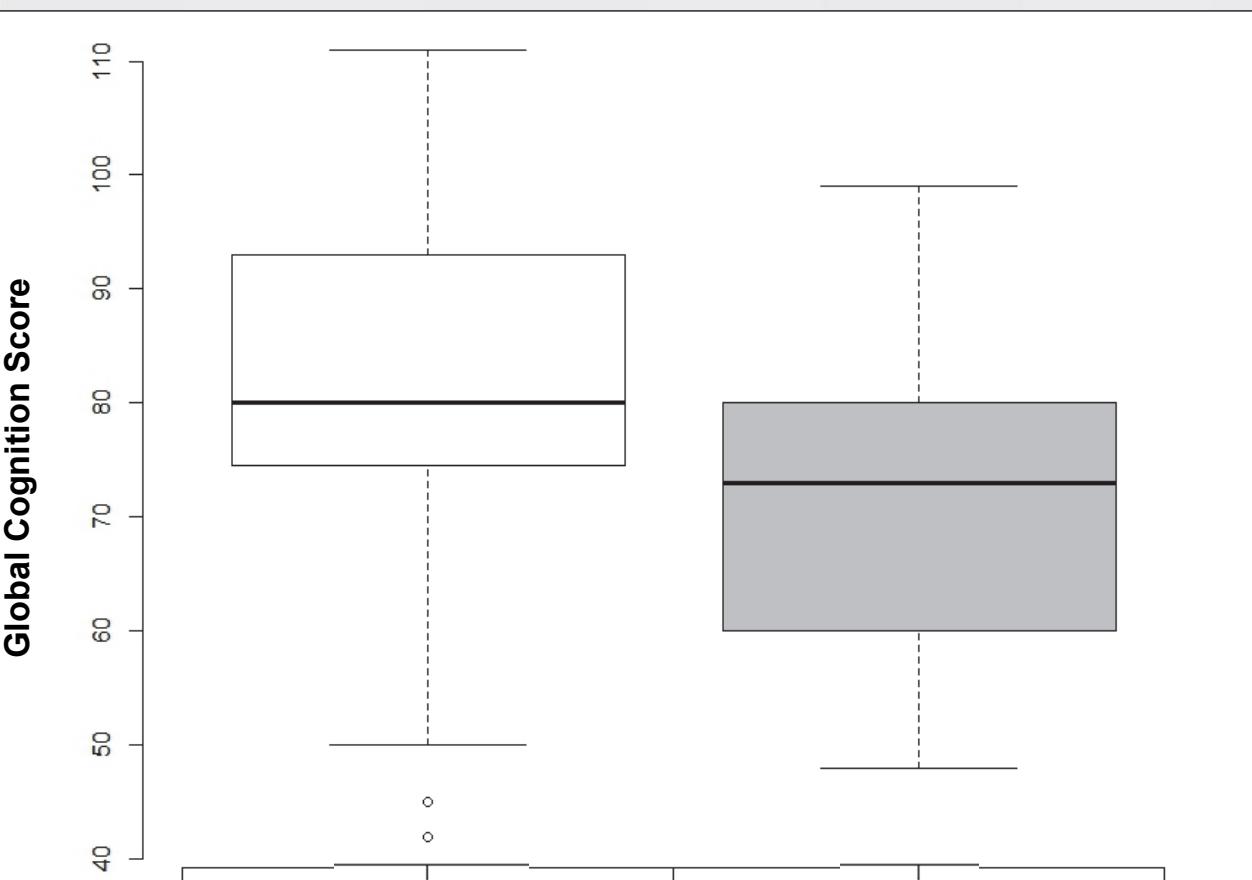


Figure 2: Box plot of global cognition score between those with IIC patterns and those without IIC patterns

Results

- N=152 patients with moderate-to-severe TBI were enrolled and underwent cEEG recording. 133/152 (87.5%) survived and 89/152 (58.6%) were able to undergo 3-month cognitive testing.
- The mean age was 32.2 ($SD \pm 13.4$) years and 85 (96%) were men. The median (interquartile range) admission GCS was 7 (7-9) and admission ISS was 20 (12-29). **Table 1** shows differences in characteristics of those with and without IIC.
- A total of 13/89 (14.6%) had IIC patterns with a median 0.85 Hz-Hr (0.16-2.26) IIC Burden Index; 3/89 had unequivocal seizures.
- At 3 months, the median GOSE was 6 (4-8) and the median RBANS score was 80 (73-92). Those with IIC patterns had lower median RBANS ($p=0.04$; **Figure 2**). The log-transformed IIC Burden Index correlated with the RBANS ($r=-0.57$, $p=0.04$; **Figure 3**).
- A linear regression showed a trend toward an association between log-transformed IIC burden and the RBANS after controlling for core predictor variables and injury severity (OR 0.01 95%CI 0.00-0.92, $p=0.08$; model $R^2 = 28.1\%$)

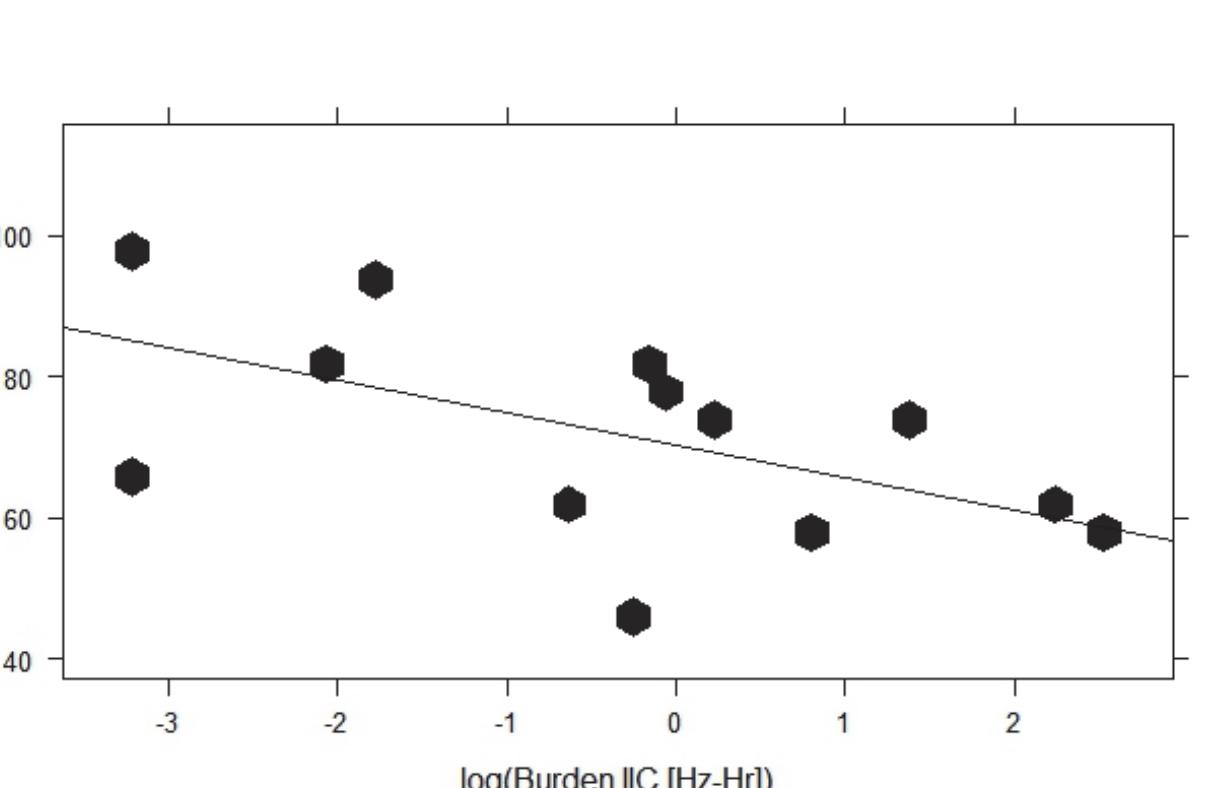
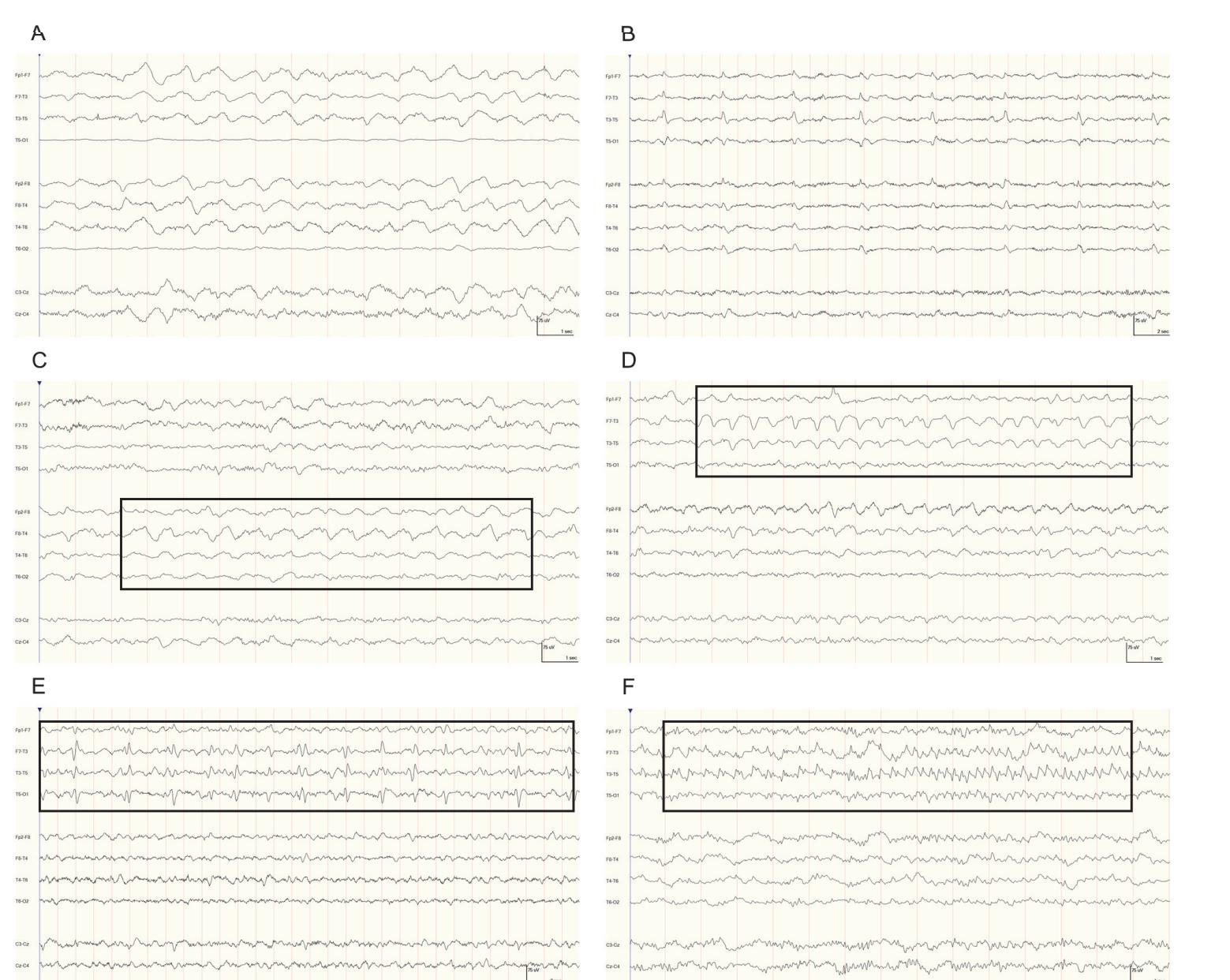


Figure 3: Hexbin scatterplot of global cognition score and the log-transform of the IIC burden index

Conclusions

- IIC patterns, including seizures, are commonly seen after moderate-to-severe TBI.
- The presence of IIC was associated with lower global cognition scores in survivors of moderate-to-severe TBI able to perform cognitive testing at 3-months.
- In those with IIC, the log-transformed pattern burden index was correlated with global cognition scores with a trend toward an independent association even after controlling for commonly-used clinical outcome predictors and injury severity.
- The low incidence of seizures and the relatively small cohort of survivors with IIC patterns limit the power of this analysis and further work is needed to clarify the impact of seizures and periodic or rhythmic discharges on cognition after TBI.

Figure 1: Definition and Examples of EEG Classification



Ictal-Interictal Pattern Classification

I Normal	None
II Mild	GRDA
III Moderate	Slower frequency (<1.5 Hz) LRDA or GPDs
IV Severe	Faster frequency (≥ 1.5 Hz) LRDA or GPDs, LPDs or ESz

Representative continuous electroencephalogram (cEEG) epochs demonstrating ictal-interictal continuum (IIC) classification. High-frequency filter=70 Hz, notch filter=60 Hz, and time constant=0.12 s. (A) IIC II Mild: generalized rhythmic delta activity (GRDA) that is frontally predominant with a frequency of approximately 1-Hz. (B) III Moderate: slow-frequency (0.25-Hz) generalized periodic discharges (GPDs). (C) III Moderate: lateralized rhythmic delta activity (LRDA) with a frequency of approximately 1-Hz (box), most prominent in the right temporal region. (D) IV Severe: LRDA between 1.5 to 2-Hz (box), predominantly in the left temporal region. (E) IV Severe: irregular (in morphology and repetition rate) 0.5-Hz lateralized periodic discharges (LPDs) in the left hemisphere. (F) IV Severe: electrographic seizure (ESz) that evolves in morphology and frequency from 2-Hz to 5-Hz rhythmic discharges in the left temporal region.

References

- Herman ST, Abend NS, Bleck TP, et al. Consensus statement on continuous EEG in critically ill adults and children, part I: indications. *J Clin Neurophysiol*. 2015;32(2):87-95. doi:10.1097/WNP.0000000000000166
- Vespa P, Tubi M, Claassen J, et al. Metabolic crisis occurs with seizures and periodic discharges after brain trauma. *Ann Neurol*. 2016;79(4):579-590. doi:10.1002/ana.24606
- Vespa PM, Miller C, McArthur D, et al. Nonconvulsive electrographic seizures after traumatic brain injury result in a delayed, prolonged increase in intracranial pressure and metabolic crisis. *Crit Care Med*. 2007;35(12):2830-2836.
- Vespa PM, Nuwer MR, Nenov V, et al. Increased incidence and impact of nonconvulsive and convulsive seizures after traumatic brain injury as detected by continuous electroencephalographic monitoring. *J Neurosurg*. 1999;91(5):750-760. doi:10.3171/jns.1999.91.5.0750
- Steyerberg EW, Mushkudiani N, Perel P, et al. Predicting outcome after traumatic brain injury: development and international validation of prognostic scores based on admission characteristics. *PLoS Med*. 2008;5(8):e165; discussion e165. doi:10.1371/journal.pmed.0050165
- Hirsch LJ, LaRoche SM, Gaspard N, et al. American Clinical Neurophysiology Society's Standardized Critical Care EEG Terminology: 2012 version. *J Clin Neurophysiol*. 2013;30(1):1-27. doi:10.1097/WNP.0b013e3182784729