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I, Brandon Foreman M.D., hereby submit this original work as part of the requirements for the degree of Master of Science in Clinical and Translational Research.

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Seizures and Cognitive Outcome after Traumatic Brain Injury

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Seizures and Cognitive Outcome after Traumatic Brain Injury

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by

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Abstract

Objective: Seizures and abnormal periodic or rhythmic patterns are observed on continuous electroencephalography (cEEG) in up to half of patients hospitalized with moderate-to-severe traumatic brain injury (TBI). We aimed to determine the impact of seizures and abnormal periodic or rhythmic patterns on cognitive outcome 3 months following moderate-to-severe TBI.

Design: Post-hoc analysis of a multicenter randomized, controlled phase 2 clinical trial conducted from 2010-2016 across 20 US Level I trauma centers. Patients with non-penetrating TBI and post-resuscitation Glasgow Coma Scale (GCS) 4–12 were included. Bedside cEEG was initiated per protocol upon admission to intensive care and the burden of ictal-interictal continuum (IIC) patterns including seizures was quantified. A summary global cognition score at 3 months following injury was used as the primary outcome.

Measures and Main Results: 142 patients (age mean+/-SD 32+/-13 years; 131 [92%] male) survived with a mean global cognition score of 81+/-15; nearly one-third were considered to have poor functional outcome. 89/142 (63%) patients underwent cEEG, of whom 13/89 (15%) had severe IIC patterns. The quantitative burden of IIC patterns correlated inversely with the global cognition score (r=-0.57; p=0.04). In multiple variable analysis, the burden of IIC patterns was independently associated with the global cognition score after controlling for demographics, pre-morbid estimated intelligence, injury severity, sedatives and antiseizure drugs.

Conclusions: The burden of seizures and abnormal periodic or rhythmic patterns was independently associated with worse cognition at 3 months following TBI. Their impact on longer-term cognitive endpoints and the potential benefits of seizure detection and treatment in this population warrant prospective study.

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Introduction

Traumatic brain injury (TBI) is endemic and affects nearly 3 million each year in the US alone; nearly one in ten are hospitalized(1). After brain trauma, the incidence of seizures ranges between 2.6% and 33%(2, 3) and the majority are only detected during monitoring with continuous electroencephalography (cEEG). In patients undergoing cEEG, abnormal periodic or rhythmic patterns that lie along an ictal-interictal continuum (IIC) may be observed in nearly half(3, 4). The presence of seizures and periodic discharges after brain injury has been associated with injury severity(3), increases in intracranial pressure(5), metabolic crisis(6), and hippocampal atrophy(7). Brain Trauma Foundation guidelines suggest preventing early seizures in the setting of the most severe TBI(8) and experts recommend monitoring and treating seizures in this population(9).

In a recent post-hoc analysis of a prospective randomized controlled trial, seizures were uncommon despite protocolized cEEG monitoring starting within 8 hours of injury. Those with severe IIC patterns, including seizures, showed no difference in the level of functional recovery 3 months after injury compared to those without severe IIC patterns(3). Given the pathophysiological effects of seizures(6, 10), one plausible explanation is that seizures create neuronal injury that impacts *higher* cognitive functions than those captured by functional outcome assessments such as the Glasgow Outcome Scale-Extended (GOSE). It is well-recognized that this may occur in patients with epilepsy(11), but little data exists on the effects of *acute* seizures on cognitive outcome after brain injury. Therefore, we investigated whether the burden of seizures and periodic or rhythmic discharges impacts cognitive recovery at 3 months following moderate-to-severe TBI.

Methods:

We performed a follow-up post-hoc analysis of INTREPID[2566] as previously described(3). INTREPID[2566] was a multicenter randomized, controlled phase 2 clinical trial of patients with moderate-to-severe TBI conducted from April 2010 to January 2016 across 20 US centers. INTREPID[2566] was conducted to evaluate the safety and efficacy of glycyl-L-2-methylprolyl-L-glutamic acid (trofinetide; NNZ-2566), a novel analog of the tripeptide glycine-proline-glutamate (GPE), a naturally-occurring protein within the brain that results from the enzymatic cleavage of insulin-like growth factor-1. Patients were centrally randomized 2:1 to study drug or placebo; those randomized to receive study drug were assigned one of three weight-based dosing tiers. Allocation was masked to participants, clinical care providers, and outcome assessors. Eligible patients were 18-70 years of age with non-penetrating TBI, post-resuscitation GCS 4–12, post-resuscitation hemodynamic stability, and able to be randomized within 8 hours of injury. Exclusion criteria were spinal cord injury, significant bodily co-injuries, prior brain injury requiring hospitalization, severe comorbidities, weight >150kg, fluid resuscitation >6L prior to randomization, and those at-risk for QT prolongation. INTREPID[2566] demonstrated no significant differences in either adverse events or its primary endpoint, the GOSE at 3 months.

Standard Protocol Approvals, Registrations, and Patient Consents

INTREPID[2566] (Clinicaltrials.gov: NCT00805818) was conducted in accordance with Good Clinical Practice and was approved for exemption from informed consent (EFIC) by the Institutional Review Board at each participating institution. Legally-authorized representatives provided written informed consent in all cases in which they were available prior to initiation of study procedures; patients could be randomized under EFIC until written informed consent could be obtained.

Data Collection

Clinical features were collected including demographics, TBI-specific parameters (i.e., injury description, Injury Severity Score (ISS), Marshall CT classification within the first 24 hours), neurological examination findings (i.e., post-resuscitation Glasgow Coma Scale (GCS), pupillary reactivity), and the use of sedative agents and anti-seizure drugs (ASDs). Variables included in The International Mission for Prognosis and Analysis of Clinical Trials in TBI (IMPACT) core model were specifically recorded and a sum score was calculated(12). Functional outcome was documented using GOSE(13) and dichotomized as unfavorable or poor (GOSE 1-4) vs favorable or good (GOSE 5-8).

EEG & Seizure Burden

The trial protocol included bedside cEEG initiated upon admission to the intensive care unit and continued at least through the 72-hr maintenance drug infusion. Thirteen scalp electrodes were positioned based on the International 10–20 System: Fp1, F7, C3, T3, T5, O1, Cz, Fp2, F8, C4, T4, T6, and O2. EEG was prospectively interpreted by a Core EEG Laboratory consisting of a group of 5 board-certified EEG readers blinded to treatment allocation at the University of Cincinnati (MP). Post-hoc, raw cEEG was independently reviewed and quantified by study authors (HL, BF, MAM) trained in the ACNS Standardized Critical Care EEG Terminology(14) as described previously(3). Seizures and abnormal periodic or rhythmic patterns were classified based on their potential association with seizure activity or neuronal injury; together these classifications were termed the ictal-interictal continuum (IIC). Electrographic seizures (ESz) were defined as any spikes, sharp waves, or sharp-and-slow wave complexes with a frequency >2.5 Hz lasting for 10s, or any rhythmic or periodic discharges (i.e. IIC patterns) with clear evolution in frequency, morphology, or location. The primary exposure for this study focused on patterns classified as *severe IIC*, defined as ≥1.5 Hz lateralized rhythmic delta activity (LRDA) or generalized periodic discharges (GPD), and any lateralized periodic discharges (LPD) or ESz. We calculated the IIC *burden* based on IIC

prevalence and frequency (e.g., if 1.5-Hz periodic discharges were detected for 50% of an 8-hr record, then 25% of the next 24-hr, the IIC duration would be 4-hr + 6-hr = 10-hr, and the IIC burden would be 1.5-Hz × 10-hr = 15 Hz-hours) and adjusted for recording duration.

Cognitive Outcome Measures

Follow up occurred in-person at 3 months following injury and a neuropsychological battery was performed by trained study personnel blinded to study drug allocation per study protocol. To estimate premorbid intelligence, The North American Adult Reading Test (NAART)(15) was used which asks patients to read a list of phonetically irregular words. The ability to correctly pronounce even unfamiliar words correlates significantly with verbal and full-scale intelligence independent of age, education, and socioeconomic factors and is thought to be insensitive to the effects of brain injuries,(16, 17) although reading performance tasks may underestimate premorbid intelligence after severe TBI(18). Our primary outcome measure consisted of the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS)(19, 20), which is a brief test of five major cognitive domains using abbreviated versions of standard tests such as list learning and story memory (immediate recall), figure copy and line orientation (visuospatial ability), picture naming and semantic fluency (language), digit span and coding (attention), and list recall and story recall (delayed memory). The sum of each of the subscores forms the total or **global cognition score**, which ranges from 40-160 and has a population age-adjusted mean+/-standard deviation of 100+/-15.

In addition to our primary outcome, we considered each RBANS domain-specific subscore individually. In order to test executive function specifically, we used the Trail Making Test (TMT) Parts A & B which asks the subject to connect sequences of numbers or letters and measures the time and number of errors made during each part.

Statistical Analysis

Clinical variables were summarized using means (+/- standard deviation [SD]) or medians (interquartile range [IQR]) for continuous variables as appropriate and proportions for categorical variables. Patients were dichotomized into poor vs good cognitive outcome based on the median 3-month global cognition score. Those with poor outcome had global cognition scores that fell below the median for the cohort and those with good outcome had global cognition scores at or above the median. Univariate comparison of cognitive outcome between groups (good vs poor) utilized the t-test for normally distributed continuous variables, Wilcoxon rank-sum test for non-normally distributed continuous variables, and Chi-square ($\chi 2$) test for categorical variables. The distribution of continuous variables were visually inspected when appropriate; however, continuous variables were assumed to be non-normally distributed except in the case of standardized cognitive test scores and age. The burden of severe IIC patterns was log-transformed to approximate a normal distribution prior to analysis. All tests were two-tailed and significance was considered for p-values < 0.05.

A general linear model was constructed using backward selection with a pre-specified significance level to stay in the model of $p < 0.05$; the treatment variable (study drug vs placebo) was included in each model. To avoid overfitting, the significance-level based model selection process terminates when addition of a variable to the model increases the predicted residual sum of squares. The variance inflation factor was used to verify variables exhibited no collinearity using a threshold of 10. In an exploratory analysis, we conducted the same analyses with each of the RBANS domain-specific subscores and the TMT. Coefficients from each model were then standardized by subtracting the mean and dividing by twice the corresponding standard deviations so that the resulting coefficients between continuous and untransformed binary predictors were directly comparable(21). The standardized regression coefficients were then plotted on the same forest plot for each outcome variable for both the full and reduced

model. All analyses were conducted using SAS version 9.4 (SAS Institute, Cary, NC) and the plots were generated using R software(22) version 3.6.1.

Data Availability Statement

Data for this study was made available by Neuren Pharmaceuticals Limited through a data use agreement. Neuren Pharmaceuticals Limited retains sole ownership of individual participant data.

Results

A total of 261 patients with moderate-to-severe TBI were eligible for enrollment in the INTREPID[2566] study; 10 were excluded prior to study drug administration. At 3 months following injury, 142/251 (57%) patients survived and were able to perform cognitive testing; 63/251 (25%) survived to assessment could not complete cognitive testing, 24 (10%) died, and 15 (6%) were lost to follow-up (Figure 1). Patients who were able to complete cognitive testing were younger (32+/-13 years vs 38+/-15 years; p<0.01) and more likely male (131/142 [92%] vs 90/109 [83%]; p=0.03) with better admission GCS (median 7 [IQR 6-9] vs median 7 [IQR 6-8]; p<0.01), lower ISS (median 22 [IQR 13-30] vs median 26 [IQR 18-34]; p=0.03) and lower IMPACT sum scores (median 2 [IQR 0-4] vs median 3 [IQR 2-6]; p<0.01). On CT, patients able to perform cognitive testing had less traumatic interventricular hemorrhage (IVH; 31/142 [22%] vs 40/109 [37%]; p<0.01). Of patients able to perform cognitive testing, 43/140 (31%) had poor 3-month functional outcome; two patients did not have available functional outcome assessment (Table 1).

Univariate Associations with Cognitive Outcome

The mean global cognition score across the cohort was 80.5+/-15.3 (Top of Figure 2). There were no significant group differences between mean global cognition scores and GOSE (Bottom of Figure 2; p=0.42). The mean time to complete the TMT A & B were 46.7+/-38.0 seconds and 113.4+/-78.1 seconds, respectively. Table 2 summarizes the results of cognitive testing. Cognitive outcome was dichotomized as good vs poor based on a median global cognition score of 80 (IQR 73-92). Statistically significant univariate associations with cognitive outcome included ethnicity and estimated pre-morbid intelligence with trends toward associations with age, admission GCS, and Marshall CT classification (Table 3). A total of 89/142 (63%) patients underwent EEG monitoring starting a mean of 13.6+/-10.4 hours following injury. The presence

of severe IIC patterns was not significantly more common in those with poor cognitive outcome (9/44 [20.5%]) compared to those with good cognitive outcome (4/45 [8.9%]; p=0.21). However, there was a trend toward a greater IIC burden in those with poor outcome (0.73+/-2.4 Hz-hr vs 0.03+/-0.13 Hz-hr in those with good outcome; p=0.06). In the 13/89 (15%) who had severe IIC patterns, the log of the IIC burden was inversely correlated with the global cognition score (r=-0.57; p=0.04; Figure 3).

Adjusted Associations with Cognitive Outcome

In a multiple variable regression model, the burden of severe IIC patterns was independently associated with the global cognition score after controlling for age, gender, ISS, post-resuscitation GCS and pupillary reactivity, radiologic findings, the use of antiseizure drugs (ASDs), the use of γ-aminobutyric acid (GABA)-acting sedative agents, and background EEG characteristics. Estimated pre-morbid intelligence, race, ethnicity, and the Marshall CT Class II (cisterns present) relative to normal CT were also independently associated with the global cognition score (see Table 4 & Figure 4). An order of magnitude change in the raw burden of severe IIC (Hz-hr) is predicted to lead to a decline in global cognition score of 0.73 points.

Similar models were constructed for each RBANS domain-specific subscore. In summary, the IIC burden was independently associated with immediate and delayed memory subscores and time to complete both TMT A & B (Figure 5).

Antiseizure Drugs

In the cohort of patients with cognitive testing, 21/142 (15%) received no ASDs, whereas 53 (37%) received levetiracetam (LEV) and 68 (48%) received phenytoin or fosphenytoin (PHT). Of those who received ASDs, 9/121 (7%) received more than one ASD; eight of these were on PHT plus one to three additional agents and one was on both LEV and valproic acid. In

univariate analysis, patients who received LEV had higher IMPACT sum scores (median 2 [IQR 2-6] vs median 2 [IQR 0-3] in those without ASD or receiving PHT; p=0.02), more IVH (18/53 [34%] vs 2/21 [10%] in those without ASD and 11/68 [16%] in those receiving PHT; p=0.02), and more subarachnoid hemorrhage (SAH; 40/53 [76%] vs 8/21 [38%] in those without ASD and 39/68 [57%] in those receiving PHT; p=0.01). Of the 89 who underwent EEG monitoring, IIC patterns were observed only in those receiving ASDs; however, there were no differences between those on LEV vs PHT in the proportion of patients with severe IIC patterns (6/33 (18%) vs 7/43 (16%); p=0.26) or burden of IIC patterns (0.41+/-1.71 Hz-hr vs 0.46+/-2.01 Hz-hr; p=0.70). There were similarly no differences in the proportion with poor functional outcome (2/21 [15%] vs 11/53 [33%] and 13/68 [30%], respectively; p=0.13) or global cognition score (83.9+/-16.5 vs 81.8+/-17.0 and 78.4+/-13.4, respectively; p=0.27) (Figure 6).

Discussion

In patients with moderate-to-severe TBI, the burden of IIC patterns, including electrographic seizures and abnormal periodic or rhythmic discharges, was associated with worse cognitive outcome at 3 months in this post-hoc analysis of a randomized, controlled trial. Cognition – encompassing domains such memory, attention, processing speed, and executive functioning - is commonly impaired after TBI. In our cohort of 142 TBI survivors, the median global cognition score was nearly 1.5 standard deviations from the normative mean (Top of Figure 2). We controlled for known confounders, including estimated pre-morbid intelligence and injury severity, and found that the burden of IIC inversely correlated with global cognition score and was independently associated with worse cognitive performance, particularly in memory, attention, and executive functioning. We found no relationship between the use of ASDs and either functional or cognitive outcome.

This study provides important evidence linking neuronal injury to clinically-important patient outcomes. Prior research has clearly established the impact of seizures on cortical physiology after primary brain injury. In a study of patients with SAH, electrographic seizures were found to exert similar physiologic effects as generalized tonic-clonic seizures[10]. Subsequent work has linked seizures with metabolic crisis(6) and increasingly frequent periodic discharges have been shown to increase oxygen extraction, decreasing the pool of dissolved tissue oxygen, or PbtO2(23). These findings help to explain the observation that seizures following TBI may be associated with hippocampal atrophy(7); however, no study has definitely linked seizures following TBI with mortality or functional outcome.

There are two potential reasons for this lack of association with morbidity and mortality. First, the traumatic brain injury itself may contribute to functional disability far more than the subsequent development of seizures. We previously found that seizures and periodic

discharges were more common in those with more severe injury, explaining perhaps why seizures had no independent impact on functional outcome(3). In this study, we found that global cognitive scores in survivors able to undergo cognitive testing was not statistically different across a range of functional recovery from low severe disability to upper good recovery. This supports the notion that cognition is a function of distributed neuronal networks and may not be uniformly affected by moderate-to-severe injuries(24–26). Seizures on the other hand may disrupt neuronal networks in a way that impacts cognition specifically(27). The burden of seizure activity, a quantification of seizure activity over time, in patients with epilepsy has been linked with cognitive dysfunction resulting in the term *epileptic encephalopathy* to describe "…cognitive and behavioral impairments *above and beyond* what might be expected from the underlying pathology alone."(11, 28). Here, we controlled for both injury severity and pre-morbid cognitive ability and found that lower global cognition scores were independently associated with the burden of acute seizures or abnormal periodic or rhythmic patterns. This mirrors a recent study of 402 patients with diffuse SAH(29) in which a similar proportion (50/402 [12%]) had electrographic seizures. The time spent with acute seizures was linearly associated with cognitive scores assessed via telephone interview even after controlling for level of education and ethnicity. Whether and how acute seizures, or the subsequent development of epilepsy, modify cognitive recovery deserves further study.

Second, seizures may affect tissue that does not contribute to gross functional disability yet still may impact domain-specific cognitive function. In a recent cohort of 90 patients with moderate-to-severe TBI enrolled in a longitudinal study of post-traumatic epilepsy, nearly 27% developed seizures within the first week of the study, of whom three-quarters had temporal contusion or hemorrhage(30). Prior work has shown that temporal contusions are associated with dysfunction in attention and processing efficiency along with temporal atrophy 6-months following injury(31). In a highly selected cohort of patients with TBI, frontal lesions correlated

with executive dysfunction while temporal lesions correlated with memory dysfunction(32). MRI studies of patients with seizures and status epilepticus have shown that focal seizures from any location result in diffusion restriction within the temporal lobe in more than two-thirds of cases(33–35). This might explain in part why seizures after brain trauma have been associated with hippocampal atrophy independent of the presence of contusion(7). Our study was unable to examine specific lesion location, but the cohort consisted of 102/142 (72%) Marshall CT Grade I-IV (without mass lesion) and nearly half had normal CT or no compressive lesions present. Therefore, this study suggests that focal seizures may contribute to memory, attention, and executive dysfunction even after controlling for age and estimated pre-morbid cognition.

Current guidelines recommend the use of PHT to prevent early seizures (level of evidence IIa(8)). In patients with TBI, randomized controlled trial data suggests that there are no differences in one-year cognitive outcome between those who receive PHT vs placebo(36). However, after diffuse SAH, the use of PHT has been linked with worse cognitive outcome(37). More recently, LEV has become the predominant ASD used in neurocritical care(38). Data from patients with focal intracerebral hemorrhage has suggested that patient-reported cognitive function after recovery might be adversely affected by LEV(39). We found that the rates of seizures or periodic discharges in patients with TBI were similar between those receiving LEV vs PHT at a rate similar to prior studies(40, 41). Further, we found no differences in functional or domain-specific cognitive outcomes related to the use of either ASD compared to those in our cohort who did not receive ASDs.

Background EEG features such as anterior-posterior organization and sleep reflect network brain functions. The loss of posterior alpha frequencies has been associated both with delirium(42, 43) and with loss of command following, a surrogate for conscious awareness, during anesthesia induction(44) or after brain injury(45). Sleep transients have been associated with outcome after brain injury, including SAH(46) and TBI(47). In our previous study, we

showed that the presence of a posterior dominant rhythm and/or the presence of sleep transients within 24 hours of monitoring added significantly to prognostic models of functional outcome(3). In this study, the presence or absence of anterior-posterior organization within 24 hours of monitoring did not specifically correlate with cognitive dysfunction, but we selected only survivors able to complete cognitive testing. Although three-quarters exhibited no posterior dominant rhythm, this may have reflected transient rather than permanent dysfunction. In fact, only the absence of sleep transients within the first 24 hours had an independent association with cognitive testing, specifically errors on TMT B. Errors on TMT B have been linked to injury to the dorsolateral prefrontal cortex in patients after ischemic stroke(48). This region is typically deactivated during sleep and plays a role in working memory, but it would be speculative to tie our findings to a specific hypothesis in this regard as the number of errors on average across the study cohort was relatively small.

This study is limited by its post-hoc study design. There were no raw images to allow for an analysis of lesion burden and location, which precluded a detailed assessment of neuroanatomic correlates of cognition or EEG. However, we leveraged the prospective review of raw cEEG by a group of highly-trained electroencephalographers and an independent validation and quantification by physicians trained in the critical care EEG terminology standards in order to minimize variability in the interpretation of EEG variables used as our primary predictor. We chose to include only those survivors able to perform cognitive testing in order to make specific inferences about the burden of IIC patterns, but recognize this may limit generalizability in survivors unable to perform these assessments. Further, despite inclusion of EEG in the study protocol, many patients did not undergo monitoring, potentially creating bias in the study cohort.

Studies of post-traumatic cognition are challenging as a substantial proportion of the moderate-to-severe TBI population are unable to complete cognitive tests due to disability. In our study,

almost half of patients initially enrolled did not complete cognitive assessments. These patients were older with more severe injuries. However, we found that global cognition scores in those able to complete cognitive testing were not significant different across a broad range of disability. For the purposes of this study, we excluded those unable to complete cognitive testing from primary analysis, leveraging the population-based normative RBANS index scores to understand the impacts of the IIC burden. Strategies to include *all* survivors in future studies, including those unable to participate in standard neurocognitive testing, might include an ordinal ranking of cognitive *and* non-cognitive outcome scores including death and level of disability. Alternatively, later time points might be used to maximize survivors who eventually regain the ability to perform cognitive tasks. Learning and memory deficits improve substantially in the first 4-6 months(24) and even in those with disorders of consciousness, more than two-thirds regain consciousness within 6-8 weeks and exhibit significant increases in cognition that continue for up to five years(49). Despite this continued long-term recovery, 60% of those with the most severe brain injuries continue to have cognitive deficits(26), with average global cognition scores in one series of patients seven years following severe brain injury of 71+/-13(19).

In conclusion, we found that the presence of seizures and abnormal periodic or rhythmic discharges after brain trauma were independently associated with objective measures of cognitive function after controlling for estimated pre-morbid intelligence and injury severity. Detection and treatment of IIC patterns in the initial post-injury period may be warranted in order to improve cognitive outcome in survivors of moderate-to-severe TBI.

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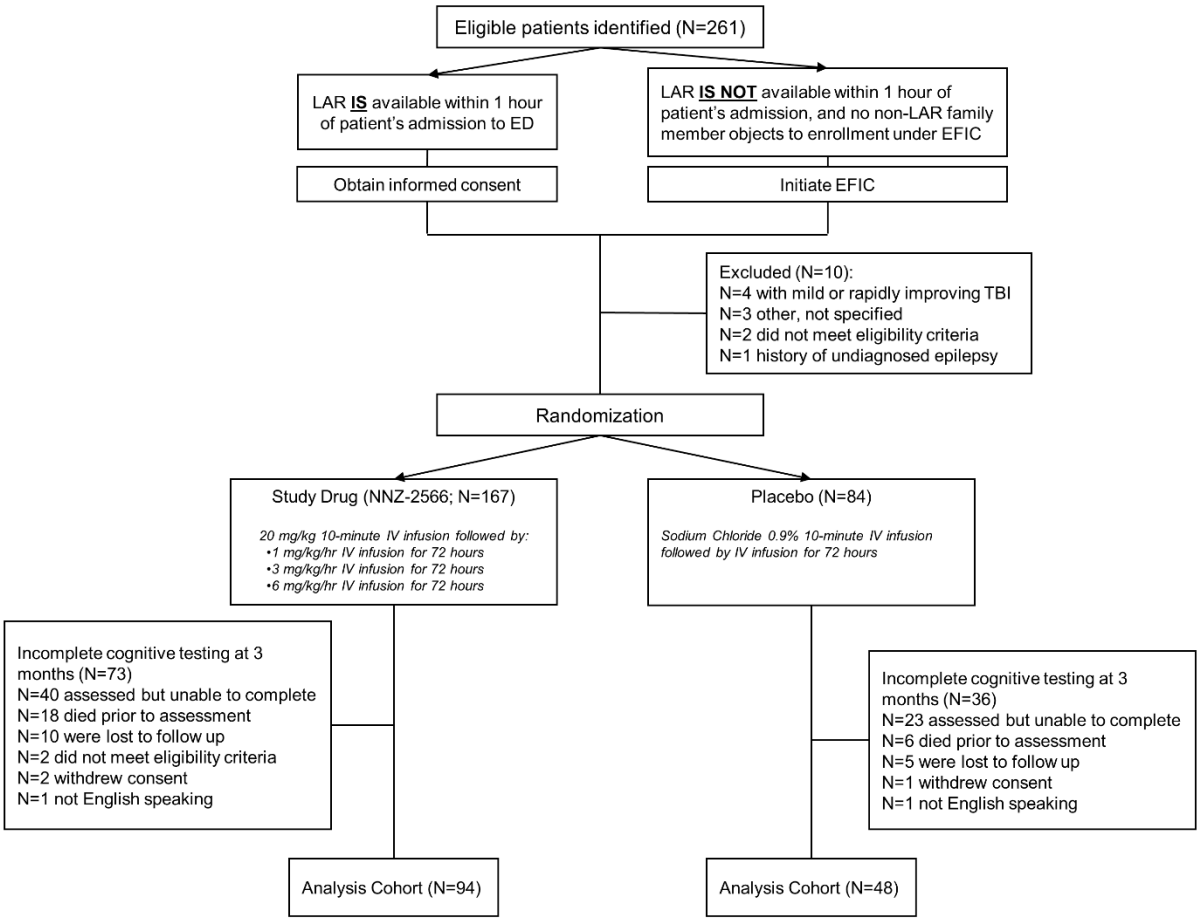
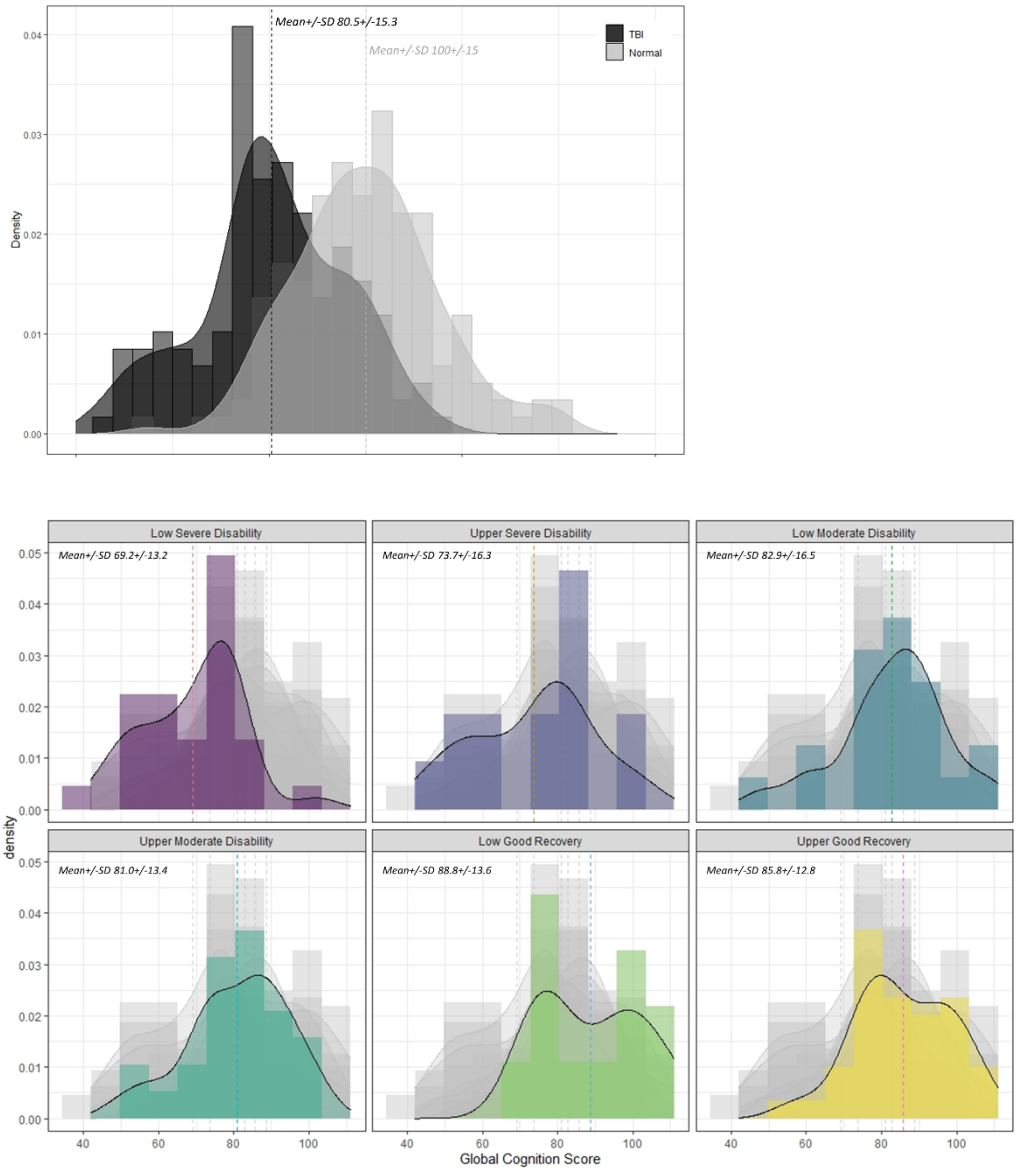
Figure 1: CONSORT diagram



Modified from study protocols (Neu-2566-TBI-001 and Neu-2566-TBI-002)

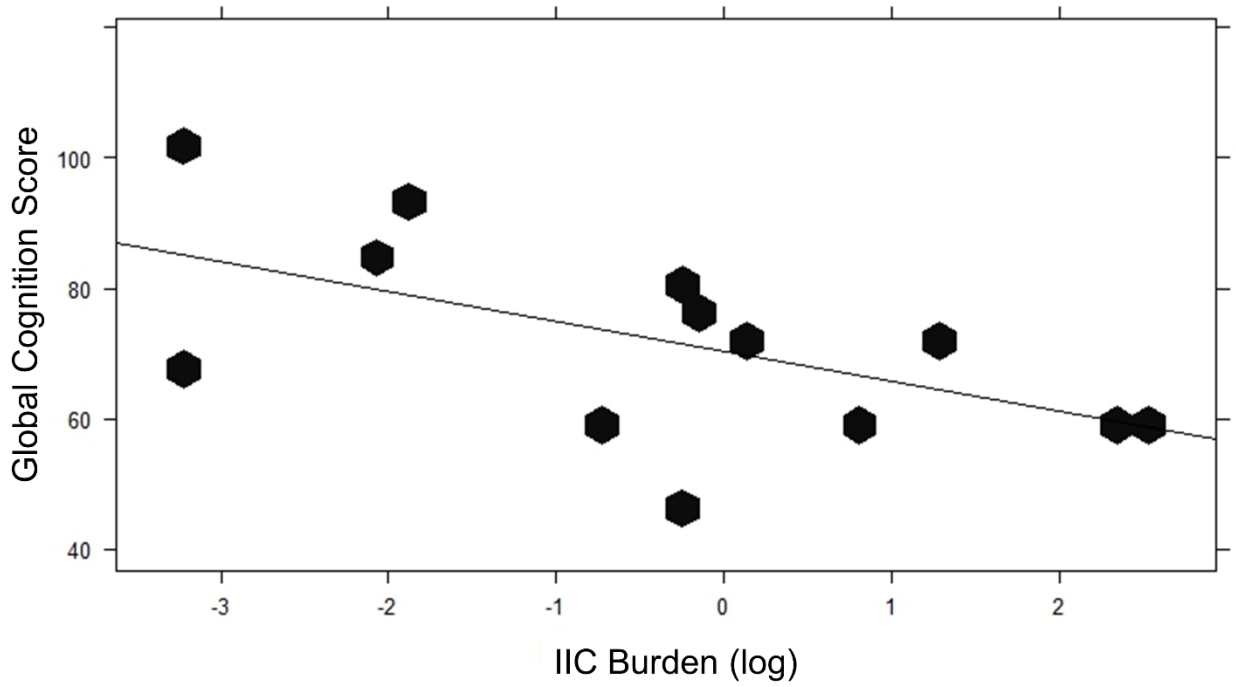
EFIC = exception from informed consent; ED = emergency department; LAR = legally authorized representative

Figure 2: Distribution of global cognition scores



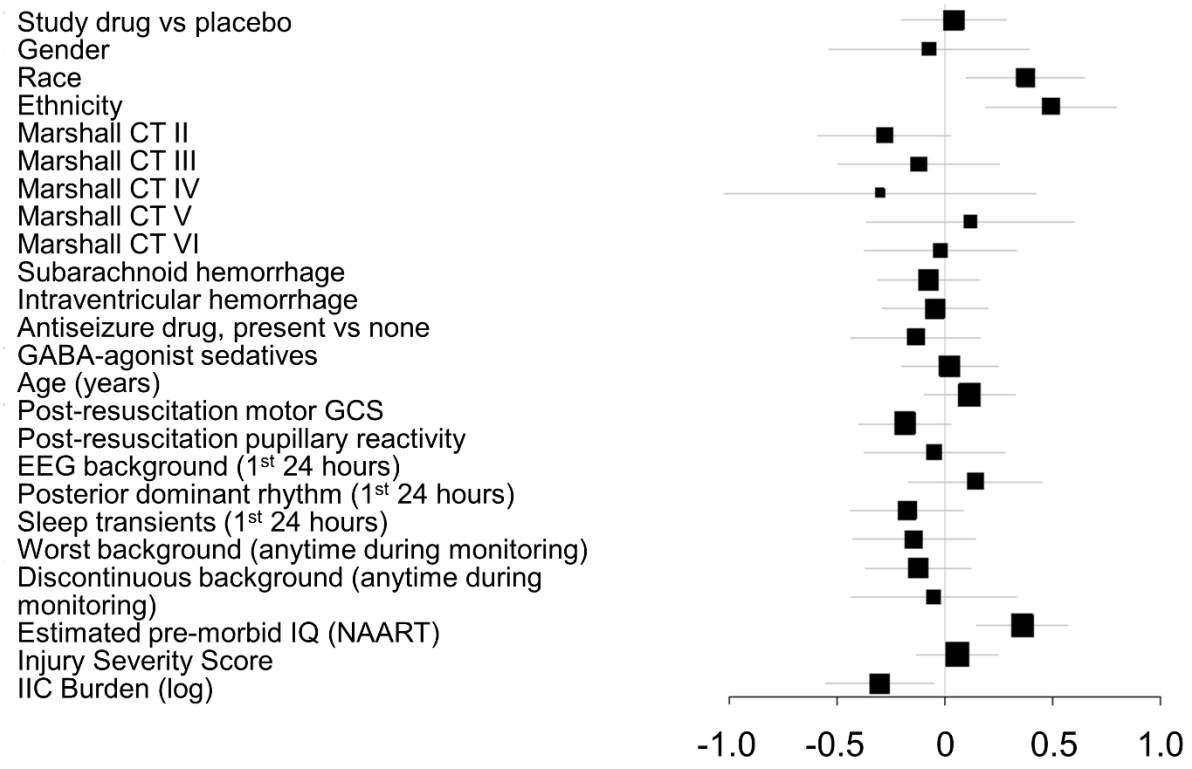
Top) A density plot of the distribution of the global cognition scores across patients with TBI in this study (black) compared with a normal distribution centered around the population age-adjusted mean of the global cognition score (light gray). Vertical dashed lines represent the mean for each distribution. Botom) A facet wrapped density plot of the distribution of global cognition scores stratified by GOSE at 3 months. Vertical dashed lines represent the mean for each GOSE score and the mean +/- standard deviation (SD) is listed for each score. There were no group differences between GOSE scores and the mean global cognition score (Kruskal-Wallis χ^2=53.5; p=0.42).

Figure 3: Relationship between the burden of ictal-interictal continuum patterns and global cognition scores



A scatterplot of the relationship between the global cognition score (y-axis) and the log-transformed burden of severe ictal-interictal continuum (IIC) patterns (x-axis) across the 13 patients with IIC patterns. There was a significant inverse correlation (Pearson *r*= -0.57; p=0.04).

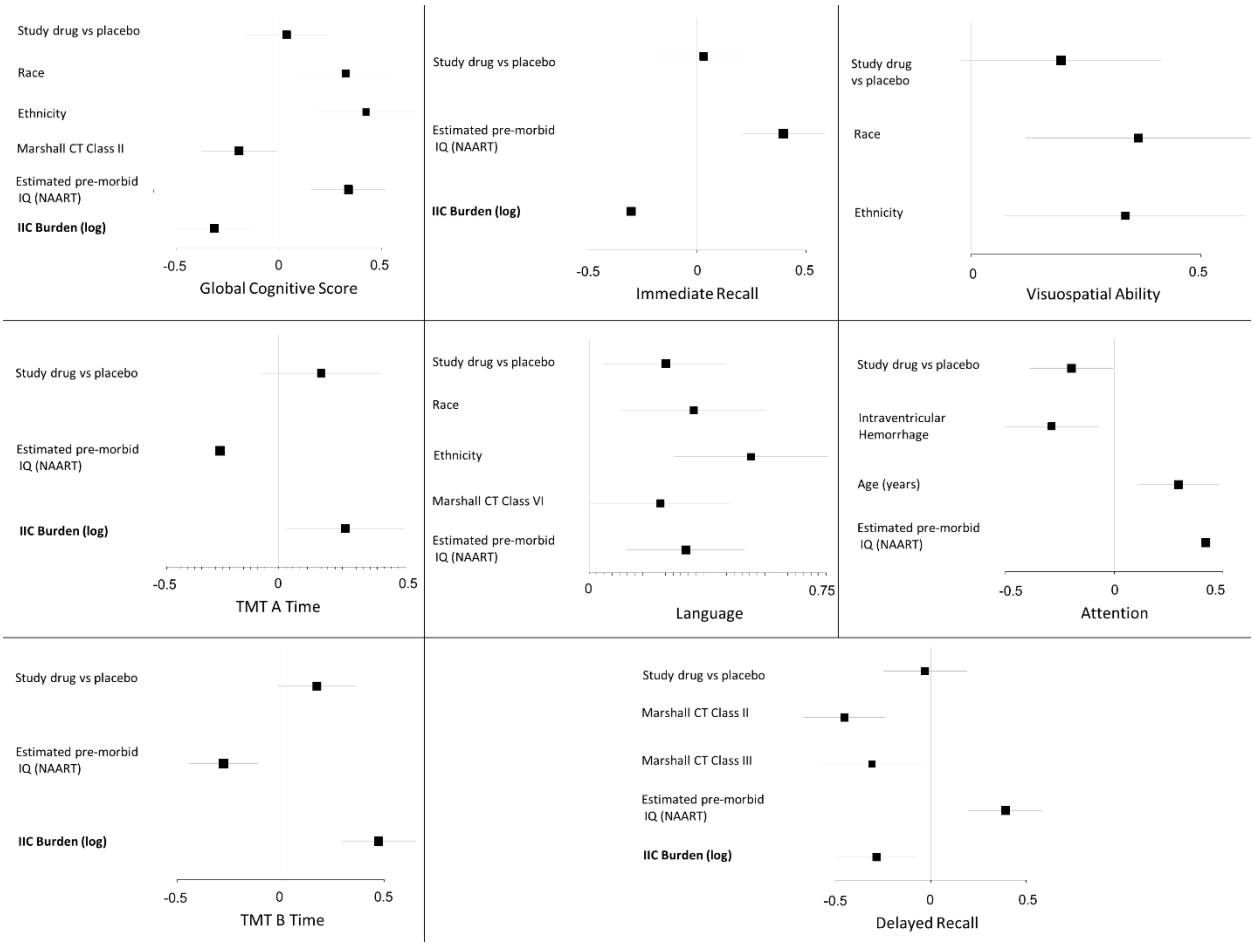
Figure 4: Forest plot of multiple variable regression coefficients



Forest plot of the general linear regression coefficients for the predictors of the global cognition score. Coefficients were standardized by subtracting the mean and dividing by twice the corresponding standard deviations in order to directly compare coefficients between continuous and binary predictors. Controlling for age, gender, estimated pre-morbid intelligence, injury severity, radiographic variables, medications, and EEG background characteristics, the ictal-interictal (IIC) burden was independently associated with the global cognition score.

GABA = γ-aminobutyric acid; GCS = Glasgow Coma Scale; IIC = ictal-interictal continuum; NAART = North American Adult Reading Test

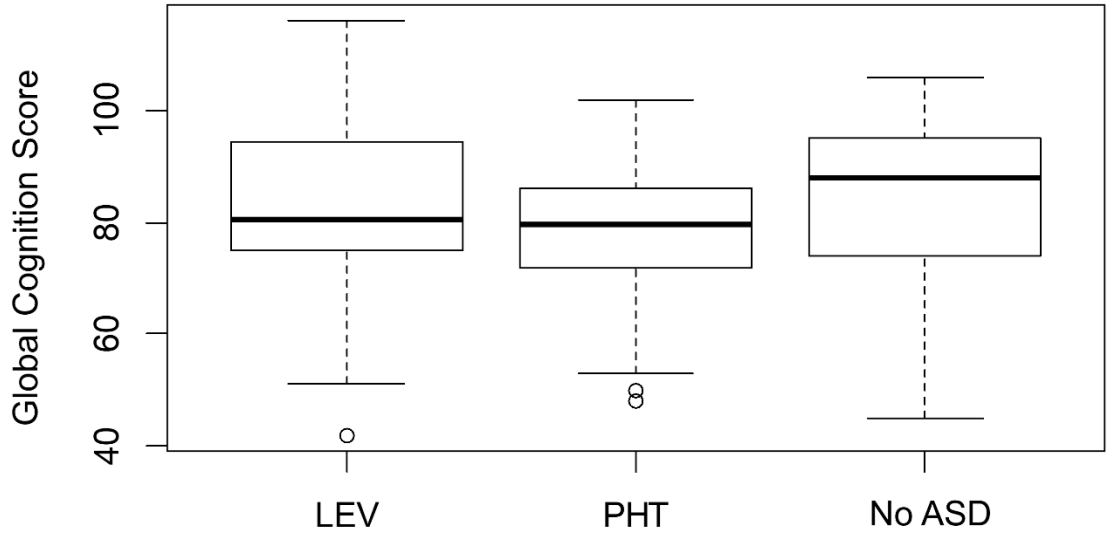
Figure 5: Reduced models for each cognitive subscore



Composite of forest plots for models created for each cognitive subscore. Only variables that remained within the model at a $p<0.05$ were included in each forest plot.

IIC = ictal-interictal continuum; NAART = North American Adult Reading Test; TMT = Trail Making Test

Figure 6: Boxplot of antiseizure drugs and global cognition score



Boxplot of the global cognition score (y-axis) across patients receiving each antiseizure drug. There were no significant differences between each group and global cognition scores.

ASD = antiseizure drug; LEV = levetiracetam; PHT = phenytoin and/or fosphenytoin

Table 1: Characteristics of the enrolled cohort

Variable	Total Cohort; n=251	Global Cognitive Score (RBANS) at 3 Months; n=142	No Global Cognitive Score (RBANS) at 3 months; n=109	P
Age, mean+/-SD	34.3+/-14.4	31.6+/-13.0	37.8+/-15.4	<0.01
Gender (male), n(%)	221 (88.1)	131 (92.3)	90 (82.6)	0.03
Total Glasgow Coma Scale Score, median (IQR)	7 (6-9)	7 (6-9)	7 (6-8)	0.01
Pupils (≥1 unreactive)*, n(%)	28 (11.3)	15 (10.6)	13 (12.3)	0.83
Injury severity score, median (IQR)	24 (16-33)	22 (13-30)	26 (18-34)	0.02
IMPACT sum score, median (IQR)	3 (1-6)	2 (0-4)	3 (2-6)	<0.01
Marshall CT Class, n(%)				0.14
I (normal CT)	28 (11.2)	20 (14.1)	8 (7.3)	
II (cisterns present, shift<5mm)	86 (34.3)	48 (33.8)	38 (34.9)	
III (cisterns compressed, shift <5mm)	44 (17.5)	23 (16.2)	21 (19.3)	
IV (shift>5mm)	28 (11.2)	11 (7.8)	17 (15.6)	
V (evacuated mass)	19 (7.6)	10 (7.0)	9 (8.3)	
VI (non-evacuated mass)	45 (17.9)	30 (21.1)	15 (13.8)	
Presence of traumatic SAH, n(%)	160 (64.0)	87 (61.3)	73 (67.6)	0.37
Presence of traumatic IVH, n(%)	71 (28.3)	31 (21.8)	40 (36.7)	0.02
Study drug (vs. placebo), n(%)	167 (66.5)	94 (66.2)	73 (67.0)	1.00
Antiseizure drug administration, n(%)	206 (82.1)	121 (85.2)	85 (78.0)	0.19
Sedation with GABA-acting agents, n(%)	154 (61.4)	78 (54.9)	76 (69.7)	0.02
Poor Outcome (GOSE 1-4), n(%)**	114/220 (51.8)	43/140 (30.7)	71/80 (88.8)	<0.01

CT = Computed Tomography; GOSE = Glasgow Outcome Scale-Extended; EEG = Electroencephalography; GABA = γ-aminobutyric acid; IIC = Ictal-Interictal Continuum; IMPACT = International Mission for Prognosis and Analysis of Clinical Trials in TBI; IQR = Interquartile Range; IVH = Intraventricular Hemorrhage; SAH = Subarachnoid Hemorrhage; SD = Standard Deviation

*Only a single patient with bilaterally unresponsive pupils was enrolled in the group without cognitive outcome at 3 months.
**Functional outcomes at 3 months were available for 220/251 (87.6%) of patients.

Table 2: Results of cognitive testing

	Poor cognitive outcome; n=65		Good cognitive outcome; n=77		Pooled difference [mean (95% Confidence Interval of the mean)]
Variable	Value, mean+/-SD	Range	Value, mean+/-SD	Range	
Global Cognition Score	67.5+/-10.1	42-79	91.5+/-9.22	80-116	23.9 (20.7-27.1)**
Index Scores					
Immediate Recall	69.9+/-12.9	40-90	92.1+/-14.1	49-123	23.3 (18.7-27.8)**
Visuospatial Construction	78.8+/-14.5	50-112	96.4+/-17.0	62-131	17.6 (12.3-22.9)**
Language	77.4+/-15.8	40-112	92.3+/-11.6	74-124	14.9 (10.3-19.4)**
Attention	73.9+/-14.2	43-112	94.1+/-14.3	56-125	20.2 (15.4-24.9)**
Delayed Memory	68.0+/-18.9	40-97	94.7+/-11.1	64-122	26.7 (21.6-31.8)**
TMT A Time (s)	61.6+/-49.4	20-300	34.4+/-17.4	11-130	27.1 (15.2-39.1)**
TMT A Errors	0.1+/-0.5	0-3	.02+/-0.5	0-3	0.06 (-0.23-0.11)
TMT B Time (s)	149.5+/-96.2	48-542	84.0+/-40.8	36-253	65.6 (41.5-89.7)**
TMT B Errors	1.3+/-2.0	0-9	0.6+/-1.0	0-5	0.69 (0.18-1.21)*

TMT = Trail Making Test

** $p<0.001$

*$p<0.01$

Table 3: Patient demographics

Variable	All patients with cognitive assessment; n=142	Poor cognitive outcome*; n=65	Good cognitive outcome; n=77	P
Age, mean+/-SD	31.6+/-13.0	29.5+/-11.3	33.4+/-14.0	0.06
Gender (male), n(%)	131 (92.3)	59 (90.8)	72 (93.5)	0.77
Race (white), n(%)	106 (74.7)	44 (57.8)	62 (80.5)	0.12
Ethnicity (Hispanic), n(%)	28 (19.7)	19 (29.2)	9 (11.7)	0.02
NAART (Verbal IQ; n=129/142), mean+/-SD	98.2+/-10.4	93.7+/-10.6	101.6+/-8.9	<0.01
Total Glasgow Coma Scale Score, median (IQR)	7 (6-9)	7 (6-8)	7 (7-9)	0.07
Pupils (≥1 unreactive), n(%)	15 (10.6)	5 (7.7)	10 (13.0)	0.45
Injury severity score, median (IQR)	22 (13-30)	22 (14-32)	21 (12-29)	0.81
IMPACT sum score, median (IQR)	2 (0-4)	2 (0-4)	2 (0-4)	0.95
Marshall CT Class, n(%)				0.09
I (normal CT)	20 (14.1)	5 (7.7)	15 (19.5)	
II (cisterns present, shift<5mm)	48 (33.8)	28 (43.1)	20 (26.0)	
III (cisterns compressed, shift <5mm)	23 (16.2)	12 (18.5)	11 (14.3)	
IV (shift>5mm)	11 (7.7)	3 (4.6)	8 (10.4)	
V (evacuated mass)	10 (7.0)	3 (4.6)	7 (9.1)	
VI (non-evacuated mass)	30 (21.1)	14 (21.5)	16 (20.8)	
Presence of traumatic SAH, n(%)	87 (61.3)	44 (67.7)	43 (55.8)	0.20
Presence of traumatic IVH, n(%)	31 (21.8)	15 (23.1)	16 (20.8)	0.90
Study drug (vs. placebo), n(%)	94 (66.2)	38 (58.5)	56 (72.7)	0.11
Antiseizure drug administration, n(%)	123 (86.6)	58 (89.2)	65 (84.4)	0.55
Sedation with GABA-acting agents, n(%)	78 (54.9)	35 (53.8)	43 (55.8)	0.94
EEG Variables, n(%)	89/142 (62.7)	44/65 (67.7)	45/77 (58.4)	N/A
IIC pattern present, n(%)	13 (14.6)	9 (20.5)	4 (8.9)	0.21
IIC Burden, mean+/-SD	0.37+/-1.7	0.73+/-2.4	0.03+/-0.13	0.06

Background within first 24 hours (delta predominant), n(%)	30 (33.7)	12 (27.3)	18 (40.0)	0.30
Posterior dominant rhythm within first 24 hours (absent), n(%)	67 (75.3)	33 (75.0)	34 (75.6)	1.00
Sleep transients within first 24 hours (absent), n(%)	65 (45.8)	31 (47.7)	34 (44.2)	0.76
Worst background anytime during EEG (delta predominant, discontinuous, or suppressed), n(%)	45 (50.6)	20 (45.5)	25 (55.6)	0.46
Discontinuous background anytime during EEG, n(%)	10 (11.2)	6 (13.6)	4 (8.9)	0.71
Outcome, n(%)	140/142 (98.6)	65/65 (100)	75/77 (97.4%)	N/A
GOS-E, median (IQR)	6 (4-8)	5 (3-7)	6 (5-8)	<0.01

CT = Computed Tomography; EEG = Electroencephalography; GABA = γ-aminobutyric acid; IIC = Ictal-Interictal Continuum; IMPACT = International Mission for Prognosis and Analysis of Clinical Trials in TBI; IQR = Interquartile Range; IVH = Intraventricular Hemorrhage; NAART = North American Adult Reading Test; SAH = Subarachnoid Hemorrhage; SD = Standard Deviation

*Poor cognitive outcome dichotomized based on global cognitive score below the median for the entire cohort.

Table 4: Significant predictors of global cognitive score after adjusting for multiple variables

Variable	Estimate	Standard Error	*t* value	p-value
Intercept	-0.967	0.279	-3.46	<0.001
Study drug (vs placebo)	0.037	0.103	0.36	0.722
Race (white)	0.324	0.115	2.81	0.006
Ethnicity (Hispanic)	0.423	0.120	3.52	0.001
Marshall CT II (cisterns present; shift<5mm)	-0.195	0.093	-2.09	0.040
NAART (Verbal IQ)	0.338	0.092	3.67	<0.001
Log(IIC Burden)	-0.316	0.097	-3.24	0.002

CT = Computed Tomography; IIC = Ictal-Interictal Continuum; NAART = North American Adult Reading Test