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"Cognitive event related potentials during the sub-acute phase of severe traumatic brain injury and their relationship to outcome"

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Abstract

Predicting outcome in the early phase after severe traumatic brain injury (sTBI) is a major clinical challenge, particularly identifying patients with potential of good cognitive outcome.

The current single center prospective study aimed to explore presence and normalization of electroencephalography (EEG)-based event related potentials (ERPs) in the early phase following sTBI, and their relationship to functional and cognitive outcome 6 months post-injury. Fourteen adult patients with sTBI were recruited from the neurointensive care unit (mean age=38.2 years (SD=14.7); 8 males; mean lowest Glasgow Coma Scale score within first 24 hours=5.4, SD=1.87). EEG-recordings were conducted biweekly at three time-points applying an ERP paradigm encompassing a passive condition involving hearing their own name randomly interspersed between an unfamiliar name, and an active condition with instruction to count their own name. Functional and cognitive outcome 6 months post-injury was measured with Glasgow Outcome Scale-Extended (GOSE) and neuropsychological tests of attention and memory. Ten patients demonstrated a significantly enhanced cognitive P3 in the active counting task compared to passive listening across recordings, and 6 presented with normalization of P3 in the counting task. Moreover, P3-amplitude to the counting task at the third time-point was positively correlated with both functional outcome (GOSE) and cognition (verbal learning, attentional set-shifting and switching) 6 months post-injury. ERP can index cognitive capacities in the early phase following sTBI, and the cognitive P3 component in an active design is associated with functional and cognitive outcome, demonstrating that the cognitive P3 may yield valuable information of residual cognition and provide supplementary prognostic information.

Key words: brain injury, prognosis, cognition, EEG, event-related potentials

Introduction

Substantial long-lasting disability with cognitive deficits,[1-3] impaired overall health,[4,5] and difficulties with community integration and work[6] are common after moderate to severe traumatic brain injury (sTBI). However, the severity of chronic symptoms and the rate of recovery is highly variable. Some patients regain good cognitive capacities and functional independence, while a minority of patients remain in a state of prolonged disorder of consciousness (DoC).[7-9] Early and

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reliable recognition of those who might regain good cognitive outcome is a great challenge, but essential for treatment planning.

Major effort has been put into developing prognostic models based on clinical and laboratory parameters from the acute phase following TBI. Both the IMPACT (International-Mission-For-Prognosis-And-Clinical-Trial) and CRASH (Corticosteroid-Randomisation-After-Significant-Head injury) models are based on large, prospective patient cohorts. Studies of the two prognostic models have demonstrated that high age, low Glasgow Coma Scale (GCS),[10] absent pupillary reactivity, and certain CT characteristics are associated with poor outcome or death.[11-13] However, the psychometric properties of the methods and their limitations in mainly focusing on predicting mortality have been criticized.[14,15] Also, the fact that they do not take newer advancements in critical care management into consideration causes overestimation of the risk of mortality or unfavorable outcome.[16]

Neurophysiological techniques such as somatosensory evoked potentials (SEPs) have shown some promise in aiding prognostication.[17] Specifically, SEPs have demonstrated high specificity in predicting poor outcome in anoxic coma, but presence of SEPs is not necessarily predictive of good recovery.[18,19] Importantly, for TBI-related coma with initial absence of cortical responses, recovery of bilaterally abolished SEP followed by favorable outcome may occur more often than after other etiologies.[18-20] Also, most studies lack serial SEP recordings with potential to demonstrate sub-acute SEP-normalization, they are restricted by coarse outcome measures, and often use follow-up time-points as early as one month post injury.[18,19,21]

ERPs are based on time-locked encephalographic (EEG) activity elicited by external or internal events, providing a neurophysiological correlate of cognitive processing at the millisecond level. ERPs range from early components representing largely sensory and automatic brain processes, i.e. the mismatch negativity component (MMN), to later components mediating increasingly more complex cognitive processes, such as the well-established P3 component, reflecting allocation of attentional and memory resources.[22,23] A P3 response in healthy persons typically peaks between 300 and 600 ms post stimulus, while brain injury is associated with prolonged latencies and attenuated amplitudes.[22,24-26] A meta-analysis concluded that the MMN and the P3 appear to be reliable predictors of awakening from TBI-induced coma,[27] but few ERP-

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studies have explored the relationship to recovery levels. One exception is Lew and colleagues,[28] whom summarize a review of existing literature in stating that despite promise, EEG-based techniques currently have limited clinical application beyond the prediction of negative outcomes in the acute phase. The P3 component elicited in active cognitive tasks has also been widely investigated as a marker of consciousness in patients with DoC.[29-31] The probability of eliciting cortical neurophysiological responses in patients with severe brain injury increases with the use of salient, self-referential stimuli.[32] Thus, including the subject's own name (SON) randomized with unfamiliar name (UN), in an active condition instructing subjects to count the number of SON (denoted as active or effortful ERP tasks), has proven robust and sensitive in healthy subjects as well as patients with DoC.[31,33-35] Compared to patients with non-traumatic disorders, patients with TBI are also more likely to follow commands in active paradigms.[36] There is however scarce knowledge of the prognostic utility of ERPs beyond mere awakening from coma and detection of consciousness.

The main aim of the present study was to investigate residual cognitive capacity using ERPs in the sub-acute phase after very sTBI, and to explore their association to outcome. Presence and normalization of cognitively mediated P3 responses was explored, along with investigation of the relationship between sub-acute P3 and 6 months outcome. It was anticipated that cognitive P3 elicited in an active task could be detected at an individual level in the sub-acute phase. It was furthermore expected that P3 elicited to SON in an active task would be related to better functional and cognitive outcome 6 months post-injury.

Methods

Study setting

This single center prospective study included adult patients admitted to the intensive care unit at Oslo University Hospital (OUH), a level 1 trauma center for the southeast of Norway, between September 2013 and June 2015. For inclusion, patients needed to be adults aged between 18-65, fluent Norwegian speakers prior to their injury, admitted with sTBI defined according to the International Classification of Diseases, Tenth Revision, criteria (S06.1-S06.9: intracranial brain injury presenting as traumatic cortical edema; focal or diffuse TBI; epidural, subdural, or subarachnoid hemorrhage, and/or other specified or unspecified intracranial injury) within 24 hours of injury, and had GCS score 3-8 during the first 24 hours after injury, representing

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the severe range of TBI.[37] In order to recruit the most severe end of the sTBI population, additional criterions were in need of at least five days of neurointensive care. Patients were excluded if they had severe comorbidities prior to injury such as progressive neurological disorders, severe psychiatric and substance abuse disorders in need of treatment, or lack of Norwegian residency. Patients treated with hemicraniectomy were excluded due to problems with EEG-recordings. Patients were excluded if they had a bilaterally absent brainstem auditory evoked potentials (BAEP) along with absent auditory N1 ERP component, indicating primary sensory processing disorders. Patient lists were screened on a weekly basis. 76 with GCS lower than 9 were considered for study inclusion. Of excluded patients, 2 were excluded due to lack of consent from next of kin, 7 died during the initial phase, 10 had hemicraniectomies, 11 lacked Norwegian residency or were not prior fluent Norwegian speakers, and the rest were not eligible due to high age, severe premorbid psychiatric or substance abuse disorders, or had early transfer to neurointensive care unit (ICU) at a local hospital. The study was conducted in agreement with the Helsinki Declaration and approved by the Regional Committee for Medical Research Ethics in South East Norway (2013/407). Written informed consent was obtained from the next of kin at inclusion, and from those patients capable to provide consent at follow-up.

Procedures and design

Demographic variables (age, gender) and injury-related characteristics were extracted from medical charts. The Injury Severity Score (ISS)[38] and the Abbreviated Injury Scale (AIS head)[39] were used as indicators of injury severity.

EEG-recordings were performed biweekly three times (T1, T2 & T3). Intravenous sedation was ended at least four days before the first EEG-recording. The average time between injury-onset and day of first EEG-recording was 19 days (SD= 5.9), and then the second and third recording were conducted biweekly. Average time between T1 and T2 was 16.4 days and between T2 and T3 15.8 days. The recordings were thus conducted in the transition from acute to sub-acute phase following sTBI.[40,41] GCS was scored at the day of each EEG-recording. Level of consciousness was assessed with the Coma Recovery Scale-Revised (CRS-R)[42,43] on the day of EEG-recording at T1 and T2, and also at T3 for those with DoC at previous EEG-recordings. Vegetative State (VS) and Minimally Conscious State (MCS) were classified according to established criteria.[44,45] The distinction between MCS+ and MCS- was also established, with MCS+ defined as presence of

reproducible response to command (CRS-R auditory subscale score ≥ 3), and MCS- as no reproducible response to command (CRS-R auditory subscale score < 3).[46] Patients were classified with Post-Traumatic Confusional State (PTCS),[47] if emerged from DoC (i.e. showing functional use of objects or functional communication at the CRS-R), but presenting with disorientation and confusion, that is a verbal score of 4 at the GCS. Patients emerged from DoC and a maximum verbal score of 5 at the GCS were classified as fully conscious and oriented. At follow-up, the first author conducted a clinical interview and assessed the patients with the GOSE and a neuropsychological test battery.

ERP acquisition

EEG-data were acquired bedside with a 32-electrode cap (Quik-Cap; Compumedics Neuroscan) with electrode positions according to the 10-20 system, connected to a portable digital NuAmp EEG amplifier (Compumedics Neuroscan). Electro-oculogram was recorded using the electrodes located above and below the left eye and at the outer canthi of the two eyes. The ground electrode was placed near Fz with a nasal reference. EEG signals were recorded (NeuroScan Inc.) in DC with a 500 Hz sampling rate. Impedance was kept below 10 kΩ. Stimuli were presented binaurally with a maximum 90 dB sound pressure level. The procedure lasted approximately 25-30 minutes including breaks.

The auditory ERP paradigm (see figure 1) included two-stimuli conditions with subject`s own name (SON) and an unfamiliar name (UN) in a passive and an active effortful task, with 50 SON randomly interspersed in between 50 UN. The passive condition was presented first (each condition contained four sets of consecutive blocks of 25 stimuli). In the passive condition, the patients were instructed to do nothing but stay awake. In the active condition, they were instructed to count the number of times they heard SON. Instructions were repeated between each block of 25 stimuli. A short break and, if needed, brief auditory or deep pressure stimulation according to CRS-R protocol were applied between conditions in order to ensure optimal arousal levels. All names were digitally recorded from a female, middle-aged native Norwegian speaker (stimulus duration range: approximately 500–600 ms), with stimulus onset asynchrony of 2000 ms. UN was confirmed unfamiliar by a close family member prior to the recording, that is, not the name of a close relative or friend of the subject. This paradigm represents a modified version of the original name-paradigm of Perrin et al.,[34,35] which included a total of 7 different UN. Hence, the current version

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constitutes a simpler design with reduced cognitive load, accustomed to patients with the most severe brain injuries and low cognitive capacity. This modified design has proven robust in both healthy controls and in patients with DoC.[48] In a previous study, 19 of 20 included healthy controls demonstrated an enhanced P3 component when instructed to count SON, compared to only passive listening, while 9 of 20 patients in MCS showed an enhanced P3 response in the active counting task.

Insert figure 1 here

ERP analysis

EEG data were analyzed with custom-made MATLAB (The MathWorks, Inc., Natick, MA, USA) scripts built on the open source EEGLAB environment and the study function in EEGLAB (http://sccn.ucsd.edu/eeglab/).[49] Data were high-pass-filtered above 1 Hz. Artifact correction was performed on epoched data (−500 to 1500 ms) by excluding independent components (ICs) characteristic of non-brain artifact (e.g., eye, muscle, or line noise) identified by inspection of topographies, time courses, and activity spectra. Following artifact removal, data were low-pass-filtered below 20 Hz. Bad channels were interpolated and trials with amplitudes exceeding ±75 μV at electrodes F3, Fz, F4, C3, Cz, C4, P3, Pz, and P4 were rejected. Average activity between −200 and 0 ms was defined as baseline. Due to heterogeneity in latencies of the P3 component, it was inspected visually (by authors S. L. Hauger and M. Løvstad) at an individual level over the three midline electrodes (Fz, Cz, and Pz). Based on this, peak (maximum) amplitudes of the P3 component were extracted between 300 and 800 ms post-stimulus. Comparable P3-data in healthy controls have been published previously.[48]

Outcome measures at six months follow-up

Global functional outcome was measured with the Glasgow Outcome Scale Extended (GOSE),[50] which is a recommended core outcome measure in TBI research,[51] categorizing outcome between 1 and 8. All but one patient were conscious and oriented at follow-up and could go through a neuropsychological assessment including IQ (Wechsler Abbreviated Scale of Intelligence (WASI)),[52] verbal memory and learning (Hopkins Verbal Learning Test-Revised (HVLT-R)),[53] , attentional set-shifting (Letter-Number Switching condition from the Trail Making Test (TMT), Delis-Kaplan Executive Function System (D-KEFS)),[54] inhibition and switching (Color-Word

Interference Test (CWIT 3 and 4 from D-KEFS)),[54] and working memory (Digit Span backwards, from the Wechsler Adult Intelligence Scale-Fourth Edition (WAIS-IV)).[55]

Statistical analysis

Firstly, P3 to SON in the active task was identified by visual inspection at an individual level in each recording. In cases where a P3 to SON was established, P3-amplitude differences in the passive versus the active condition to SON in T1, T2 and T3 were investigated with two-tailed paired t-tests on a trial-by-trial basis in each individual for each sampling point (in the individual P3 time-window to SON) at the midline electrodes, using the EEGLAB study function. Signs of normalization of P3 elicited in the active task, that is, a development towards a clearly identifiable P3 component with increasing amplitudes across the 3 EEG-recordings, was explored by visual inspection, resulting in a group of 6 patients (1, 4, 7, 8, 10, 12) whom displayed normalization, and a group of 8 without detectable normalization. Normalization was then primarily analyzed as amplitude change over time for each condition, comparing peak P3-amplitudes at each midline electrode between T1 and T2, T2 and T3, and T1 and T3 in each group and experimental condition, using paired-samples t-tests. Secondarily, changes in amplitude difference between active and passive conditions were explored in each group, time-point and midline electrode.

The relationship between P3 to SON in the active task and outcome at 6 months was examined with Pearson`s correlations, including the following sub-set of outcome measures; functional outcome (GOSE), verbal learning (HVLT-R, total words learned), working memory (Digit Span backwards), attentional set-shifting (TMT) and inhibition and switching (CWIT 3 and 4). The effect of GCS on these associations was examined in partial correlations where acute GCS was controlled for. Analyses involving neuropsychological variables were conducted on raw scores.

Normality distribution was investigated with the Shapiro-Wilk's test ($p < .05$), and in cases of violation, analyses were repeated with non-parametric tests, with any subsequent changes in results being reported. *P*-values ≤ .05 were considered statistically significant. Effect size is reported with *r* for correlations and Cohen´s d for t-tests, with values of 0.1, 0.3, and 0.5 and 0.2, 0.5, and 0.8, being considered small, medium and large effect sizes, respectively.[56] Statistical analyses were performed using SPSS for Macintosh, version 23 (SPSS Inc, Chicago, IL).

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Results

The initial included sample consisted of 19 patients. Five were excluded due to lack of cooperation, low EEG-quality or medical complications. The remaining 14 patients (mean age =38.2 (SD=14.7); 8 males) completed the experimental procedure, included follow-up. Demographic, injury-related and clinical characteristics are presented in table 1. The patients had very severe injuries with a mean lowest GCS score within the first 24 hours after injury of 5.43 (SD=1.87), all had an AIS-head score of 5 and intracranial pressure (ICP) monitoring. Mean days in ICU was 21 (SD=6.4). Thus, the patient sample was in the most severe range of TBI.

Insert table 1 here

Insert table 2 here

Insert table 3 here

Presence of P3 in the active task

For all patients except one (patient 6), a P3 component to SON in the active task was identified at Pz, Cz and/or Pz in at least one of the three recordings. Ten of the 14 patients had a significant P3-amplitude difference between the active and the passive condition in at least one of the sub-acute EEG-recordings, but only two demonstrated this P3-amplitude difference across all three recordings (patient 7 and 10, see table 2). Patients with significant P3-amplitude differences to SON between the active and passive conditions are presented in Figure 2A. Of the 4 patients (patient 5, 6, 11 and 12) without significant P3 difference at any recording, 2 (patient 6 and 12) were the most severely injured, both being in a VS at the first recording, evolving to MCS during later recordings. Five patients had a significant P3-amplitude difference at T1 and T3 (patient 3, 4, 8, 13 and 14), patient 9 only at T1, patient 2 only at T2, and patient 1 only at T3. Also, of all 23 recordings with no significant P3-amplitude difference (see example figure 2B), 2 were in patients in a VS at T1, 4 recordings were in patients in a MCS-, 2 in patients diagnosed as MCS+, 6 in patients with PTCS, and 9 recordings were in conscious and oriented patients.

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Normalization of P3 across ERP recordings

The 6 patients identified as the "normalization group" (see figure 3A) showed a significantly larger P3-amplitude to SON in the active task at T3 compared to T1 at Cz ($t(5) = -3,75$, $p < .03$, $d = 1.53$), and a borderline significant difference at Pz ($t(5) = -2,47$, $p < .06$, $d = 1.0$). No significant differences were seen neither in the non-normalization group, nor in the passive condition. There was also a significantly larger peak P3-amplitude in the active compared to the passive condition at T3 at Cz ($t(1,5) = -3.52$, $p < .02$, $d = 1.44$), while borderline significantly larger at Pz ($t(5) = -2,47$, $p < .06$, $d = 1.0$), not seen in the non-normalization group (see figure 3A and B).

Insert figure 2 A&B here

Insert figure 3 A&B here

Relationship between P3 in active task and outcome

Of the 14 patients, one achieved a good recovery level (GOSE 7–8), 9 had moderate disability (GOSE 5–6) and 4 had severe disability (GOSE 3–4). All but one patient had emerged from DoC at follow-up. Patient 12 still presented with PTCS, and could not be assessed neuropsychologically. A strong positive correlation was found at T3 between the P3-amplitude to SON in the active task and global outcome (GOSE; $r(12) = .54$, $p < .05$), while no significant relationships were evident at T1 or T2. After controlling for the role of acute GCS, P3 elicited in the active task was still significantly correlated with GOSE at T3: $r(12) = .61$, $p < .05$. There was also a strong positive correlation between P3-amplitude and learning at T3 $r(11) = .60$, $p < .03$, but not at T1 and T2. Also, P3 elicited in the active task at T3 was significantly correlated to better performance on inhibition (CWIT condition 3; $r_s(11) = -.65$, $p < .02$), inhibition and switching (CWIT condition 4; $r(11) = -.56$, $p < .05$), as well as set-shifting (TMT; $r(11) = -.57$, $p < .05$). When controlling for acute GCS, all previous significant associations were still significant, and as with GOSE, some even more strongly associated (learning; $r(11) = .61$, $p < .05$, and set-shifting; $r(11) = -.58$, $p < .05$). No significant associations were found between P3 elicited in the active task and working memory (Digit Span backwards), and GCS alone was not significantly associated with GOSE or any of the neuropsychological tests.

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Discussion

To our awareness, this study is the first to investigate both the presence and normalization of sub-acutely recorded cognitive ERP as well as it`s association to global and cognitive functioning 6 months after very sTBI.

Ten of the 14 patients displayed a significant difference in the P3-amplitude to SON between the active and the passive task, demonstrating that neurophysiological indices of cognitive capacity can be identified even in the early phases after sTBI, and that neurophysiological methods encompassing active experimental conditions can tap into residual cognitive functioning in patients with sTBI, even long before standardized neuropsychological assessment is feasible. This P3-amplitude difference even preceded overt evidence of command-following in 2 non-communicating patients in MCS- (patient 8 and 10). However, a significant difference in P3-amplitude between the active and passive task could not be established in 23/42 recordings across the 3 time-points. Surprisingly, the majority of negative findings was in patients presenting with PTCS or regained orientation. This highlights that cognitive ERPs have low sensitivity, understood in this context as the ability of the neurophysiological assessment to detect effortful cognition in patients behaviorally displaying such capacity. It has previously been shown that the P3 component elicited in active paradigms can be a marker of consciousness in patients with DoC, but a wide variety in sensitivity rates have been found in ERP-studies, ranging from 100% to 14%.[31,57,58] It is, however, difficult to disentangle whether negative ERP-recordings can be explained by underlying patient deficits, or by methodological limitations inherent to the paradigm or recording technique. Patients with sTBI may suffer from severe cognitive impairments, such as deficits in language, attention, memory, executive functioning, cognitive drive, as well as behavioral impairments characterized by reduced motivation and lack of cooperation, all potentially preventing them from responding in active tasks despite having regained consciousness and cognitive resources. Issues related to compliance to task instructions and high levels of movement artifacts can be particularly prominent in the PTCS phase, as severe symptoms of PTCS is associated with poor cooperation.[59]

Six patients showed normalization of P3 to SON in the active task. However, the remaining eight did not display such normalization within the time frame of this study. Studies investigating test-retest reliability of the P3-amplitude in healthy subjects, have shown variable results, ranging from 0.31 to 0.93, although the majority of studies reported moderate-to-strong reliability estimates over periods ranging from weeks to years.[60,61] Conducting bedside EEG-recordings in the early phase after severe brain injury is challenging and involve dealing both with environmental noise from the recording site, technical and movement artifacts, as well as potential underlying cognitive deficits. All these factors may contribute to low signal-to-noise ratios, resulting in negative findings as well as low ERP stability. In the normalization-group, the P3-amplitude was significantly larger in the active task compared to the passive at T3. Wijnen and colleagues[26] investigated ERPs in severely brain-injured patients during recovery from VS to consciousness with a paradigm encompassing regular and irregular tones, including comparison of passive listening to an active condition. They did not find differences in P3-amplitudes between patients who recovered consciousness and those who did not, nor did they see a P3-difference between active and passive tasks within the group that regained consciousness. This emphasizes the importance of including robust experimental paradigms in addition to using salient stimuli in ERP studies of patients with the most severe brain injuries.

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Importantly, the P3-amplitude to SON in the active task at T3 was related to outcome, both in terms of global functioning and with regard to verbal learning, cognitive switching, and attentional set-shifting six months post-injury. Also, the P3 in the active task showed a specific relation to outcome superior to that of the acute GCS scores. A P3 component elicited in an active condition is associated with allocation of attentional and memory resources, and the task instructions require language comprehension.[22,23] To our knowledge, this study is the first to investigate the positive association between cognitive P3 elicited in an active task and global and cognitive outcome following the most severe range of TBI, indicating prognostic utility. A previous study has shown high correlations between amplitudes of the MMN component and recovery from VS to consciousness in patients with DoC after severe brain injuries of mixed ethiologies.[62] Yet, study outcome was limited to recovery of consciousness. Houlden and colleagues[21] found that a normalized SEP obtained within the first week after injury was positively correlated with higher levels of functioning as well as better attentional performance one-year post-injury. However, SEP, even more so than the MMN component, is a highly automatic, bottom-up driven somatosensory evoked potential, but does not imply effortful cognitive processing, as does a P3 component

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elicited in an active task. Importantly, a previous study recorded ERP and SEP within 8 days post sTBI. When comparing SEP and ERP in relation to outcome, ERP was found superior to SEP for prognosticating good functional outcome.[63] The fact that ERP can tap into cognitive capacities sub-acutely, and even more so, that the cognitive P3 component significantly relates to outcome both measured by GOSE, verbal learning, and attentional set-shifting and switching capacity, is highly noteworthy.

All patients included in the current study were in the most severe spectrum of TBI. Still, global functioning at 6 months post-injury showed large variation in outcome, with GOSE scores ranging from 3 to 8. A score of 8 represents “Good Recovery-Upper Level”, encompassing patients with the full functional recovery after the TBI. A score of 3, on the other hand, represents “Severely Disabled-Lower Level”, including patients that are completely dependent on others.[50,64] Total IQ at follow-up varied from 69 to 115 (see table 3). In sum, the outcomes indicated substantial heterogeneity in functional level 6 months post-injury, as has been previously established in studies of outcome following sTBI.[4,65-67] Hence, there is a need for more precise prognostication at an individual level in the early phase even in the most severe category of TBI, as the initial severity of the TBI, as routinely measured by the GCS, does not sufficiently predict patient outcome. Also, there is a need to not only make prognostic estimations regarding unfavorable outcomes or death, but also to early on identify those who have a good chance of positive outcome. This is potentially helpful both in guiding early therapeutic decisions, and to better inform the families.

Study limitations

Several limitations should be considered when interpreting the results of this study. Firstly, it was limited to a small consecutively included patient sample, both due to strict inclusion criteria, as well as low prevalence of the most severe injuries. This limits the statistical analysis that could be performed in the study, and there is a need for precaution with regard to representativeness of the included patients with sTBI. Also, performing repeated ERPs in the sub-acute clinical setting is complicated. For instance in ICU, the EEG-recordings might be interrupted by critical medical events, arousal may be difficult to maintain, or the patient is characterized by motor restlessness, all hazards to EEG quality. The current ERP study results are thus in need of replication in larger studies. The passive-active ERP paradigm included two names, that is, the patients own name and

an unfamiliar name. Linguistic features of the name-stimuli, such as gender or frequencies of syllables, were not controlled for.

Conclusions

In summary, there is a need to identify early signs of cognitive restoration, and to recognize those patients with prospect of good outcome. This study shows that ERPs elicited in an active task requiring mental effort in the early phase after sTBI may yield valuable information of residual cognitive capacities and their association to outcome. Today, there is no prognostic tool with perfect sensitivity for predicting outcome after sTBI. Combining ERP components with other clinical methods may optimize prognosis of functional recovery.

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Author Disclosure Statement

No competing financial interests exist.

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Table 1. Demographic, injury-related and clinical characteristics

Patients	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Demographic														
Age	53	47	50	32	27	20	17	57	42	19	31	30	58	52
Gender	F	M	F	F	M	M	M	M	F	M	M	F	M	F
Injury-related factors														
Cause of injury	Traffic	Fall	Fall	Traffic	Traffic	Traffic	Traffic	Fall	Fall	Fall	Fall	Traffic	Traffic	Traffic
GCS at site of injury	6	3	11	12	6	3	6	7	14	4	9	3	6	8
Lowest GCS within first 24 hours	6	3	8	3	6	3	6	7	8	4	7	3	6	6
AIS_{head} score	5	5	5	5	5	5	5	5	5	5	5	5	5	5
ISS score	43	25	29	34	43	35	50	38	34	26	42	43	25	45
Isolated injury head														

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yes/no		no	yes	no	no	no	no	no	no	no	
	yes no	no	yes	no							
ICP monitoring yes/no		yes	yes	yes	yes	yes	yes	yes	yes	yes	
	yes yes	yes	yes	yes							
Days on respirator		14	16	9	17	17	30	13	24	16	23
	22 28	12	14								
Days sedated		13	4	7	14	12	20	12	10	10	17
	19 14	4	8								
Days before eye opening		11	6	7	13	8	26	11	14	14	
	25 19	15	6	9							
Total days in ICU		20	17	11	21	20	30	18	25	21	20
	33 29	13	15								
Total days in											
rehabilitation		16	92	4	42	127	149	25	71	95	
	158 78	119	111	65							
Data related to EEG-recording											
Days between sedation											
and first EEG-rec.		4	12	5	4	6	10	7	8	4	6
	8 14	8	4								
Time since injury											
and first EEG-rec.		17	16	14	18	18	30	19	18	14	23
	27 28	12	12								

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Clinical status 1st. EEG-recording

Level of consciousness	MCS+	PTCS	PTCS	PTCS	MCS-	VS	PTCS	MCS-	MCS+	
MCS-	PTCS	VS	MCS+	PTCS						
GCS score		12	13	14	14	8	4	14	8	11	6
13	5	10	14								
CRS-R total score		16	22	23	23	12	2	23	10	18	6
23	6	14	23								

Clinical status 2nd. EEG-recording

Level of consciousness	C&O	C&O	C&O	C&O	PTCS	MCS-	C&O	PTCS	C&O	
MCS-	C&O	MCS-	PTCS	C&O						
GCS score		15	15	15	15	14	8	15	14	15	10
15	9	13	15								
CRS-R total score		23	23	23	23	23	12	23	23	23	10
23	8	23	23								

Clinical status 3rd. EEG-recording

Level of consciousness	C&O	C&O	C&O	C&O	PTCS	MCS+	C&O	C&O	C&O	
PTCS	C&O	MCS-	PTCS	C&O						
GCS score		15	15	15	15	14	12	15	15	15	11
15	8	14	15								
CRS-R total score		N.P	N.P	N.P	N.P	N.P	18	N.P	N.P	N.P	20
N.P	9	N.P	N.P								

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Abbreviations: GCS, Glasgow Coma Scale; AIS_{head}, Abbreviated Injury Scale head score; ISS, Injury Severity Score; ICP, intracranial pressure; ICU, Intensive care unit; EEG, electroencephalogram; CRS-R, Coma Recovery Scale-Revised; M, male; F, female; VS, vegetative state; MCS+, minimally conscious state pluss; MCS-, minimally conscious state minus; PTCS, post-traumatic confusional state; C&O, patients that are both conscious and oriented; N.P, not performed.

Table 2. Level of consciousness and presence of significant P3-difference in active compared to passive ERP task post-acutely at each time point

Patients	1	2	3	4	5	6	7	8	9	10	11	12	13	14
T1	MCS+/n.s.	PTCS/n.s	PTCS/*	PTCS/***		MCS-/n.s		VS/n.s	PTCS/*	MCS-/*		MCS+/**		MCS-/*
	PTCS/n.s	VS/n.s		MCS+/*		PTCS/**								
T2	C&O/n.s.	C&O/*	C&O/n.s	C&O/n.s	PTCS/n.s	MCS-/n.s		C&O/*	PTCS/n.s	C&O/n.s		MCS-/*	C&O/n.s	
	MCS-/n.s		PTCS/n.s	C&O/n.s										
T3	C&O/*	C&O/n.s	C&O/*	C&O/***		PTCS/n.s	MCS+/n.s	C&O/*	C&O/*	C&O/n.s		PTCS/***		
	C&O/n.s	MCS-/n.s		PTCS/**	C&O/*									

Abbreviations: VS, vegetative state; MCS+, minimally conscious state plus; MCS-, minimally conscious state minus; PTCS, post-traumatic confusional state; C&O, patients that are conscious and oriented.

n.s. = no significant P3-difference

* = significant P3-difference present at p<.01

** = significant P3-difference present at p<.02

*** = significant P3-difference present at p<.05

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Table 3. Functional and cognitive outcome 6 months post injury

Patients			1	2	3	4	5	6	7	8	9
10	11	12	13	14							
GOSE score		6	5	5	6	4	3	8	6	5	3
6	3	5	6								
Total IQ		108	100	93	112	69	98	100	113	89	85
100	N.P	115	111								
Verbal learning											
(Hopkins, trials 1-3;											
raw score/T-score)		32/60	28/50	21/33	31/57	6/≤20	21/30	31/57	20/32	20/30	
15/≤20	24/40	N.P	11/≤20	20/32							
Digit Span backwards											
(maximum digits*/											
cumulative percent)		5/53,2	5/53,2	5/53,2	5/53,2	3/98,7	4/86,4	5/66,2	4/98,6	5/56,5	
3/100	5/52,4	N.P	3/100	5/53,2							
TMT condition 4											
(raw score/											
scaled score)		91/10	155/3	67/12	40/13	221/1	156/1	66/10	84/11	60/12	
110/5	179/1	N.P	146/6	80/11							
CWIT condition 3											
(raw score/											
scaled score)		45/13	42/13	41/14	42/13	126/1	69/5	57/9	66/9	44/13	
123/1	75/4	N.P	108/1	75/7							
CWIT condition 4											

(raw score/

scaled score) 46/14 51/12 52/13 39/14 160/1 136/1 73/7 98/6 52/12 88/4 75/6 N.P 82/8 62/11

Abbreviations: GOSE, Glasgow Outcome Scale Extended; IQ, Intelligence Quotient; CWIT, Color-Word Interference Test; N.P, not performed.

*maximum number of digits reported.

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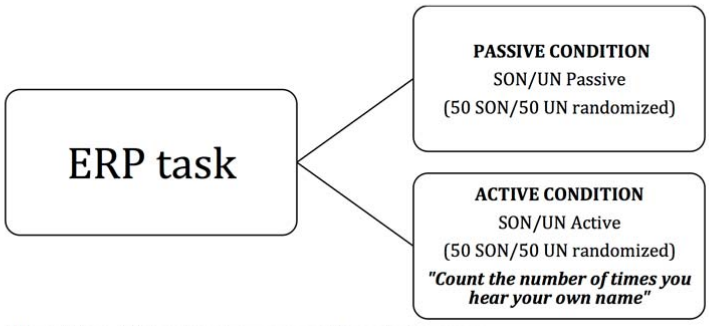
Figure Legends

Figure 1. Experimental task design.



Abbreviations: SON: subject´s own name; UN: unfamiliar name.

Figure 1

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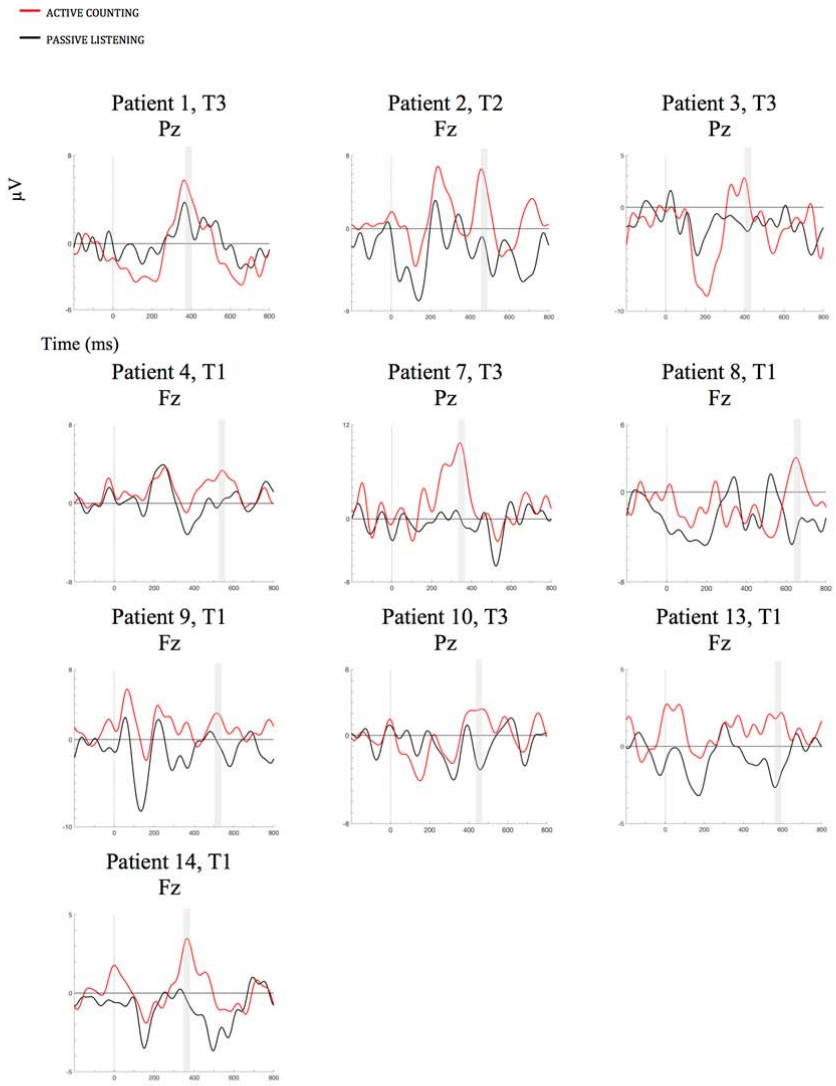
Figure 2. A: Significant P3 in active task in individual patients



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B: Example of patient without significant P3 difference between active and passive task

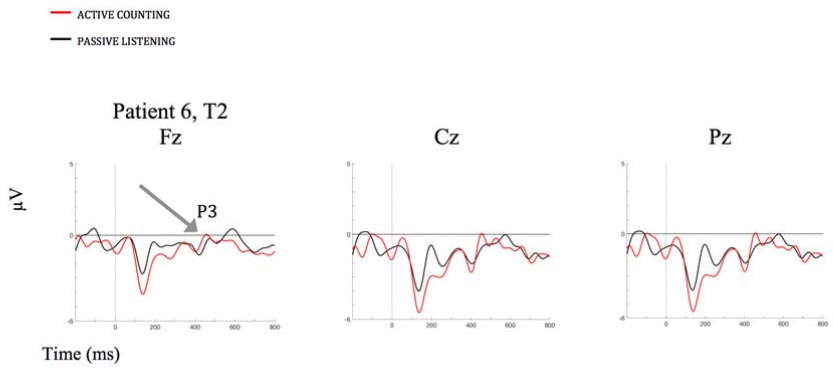

Figure 2. A: Presence of P3 to SON in active task in all 10 individuals presenting with a significant P3-difference between active and passive task, exemplified with one electrode. Recording time-point is indicated above each curve. The averaged ERPs in the active counting (red) versus passive (black) condition (*y*-axis, amplitude in µV; *x*-axis, time in ms) are illustrated. Observed significant differences of P3-amplitude between conditions (values < .05 to .001) are marked with grey line at the P3 curve. B: Example of patient presenting with no significant P3-difference between active and passive task. Recording time-point and electrodes are indicated above the curves.

Figure 2 A&B

Figure 2.A: Presence of P3 to effortful task in all 10 individuals presenting with a significant P3-difference between active and passive task, exemplified with one electrode. Recording time-point is indicated above each curve. The averaged ERPs in the active counting (red) versus passive (black) condition (*y*-axis, amplitude in µV; *x*-axis, time in ms) are illustrated. Observed significant differences of P3-amplitude between conditions (values < .05 to .001) are marked with grey line at the P3 curve. B: Example of patient presenting with no significant P3-difference between active and passive task. Recording time-point and electrodes are indicated above the curves.

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Figure 3A. Grand average ERPs in the patient group (n=6) with normalization of P3

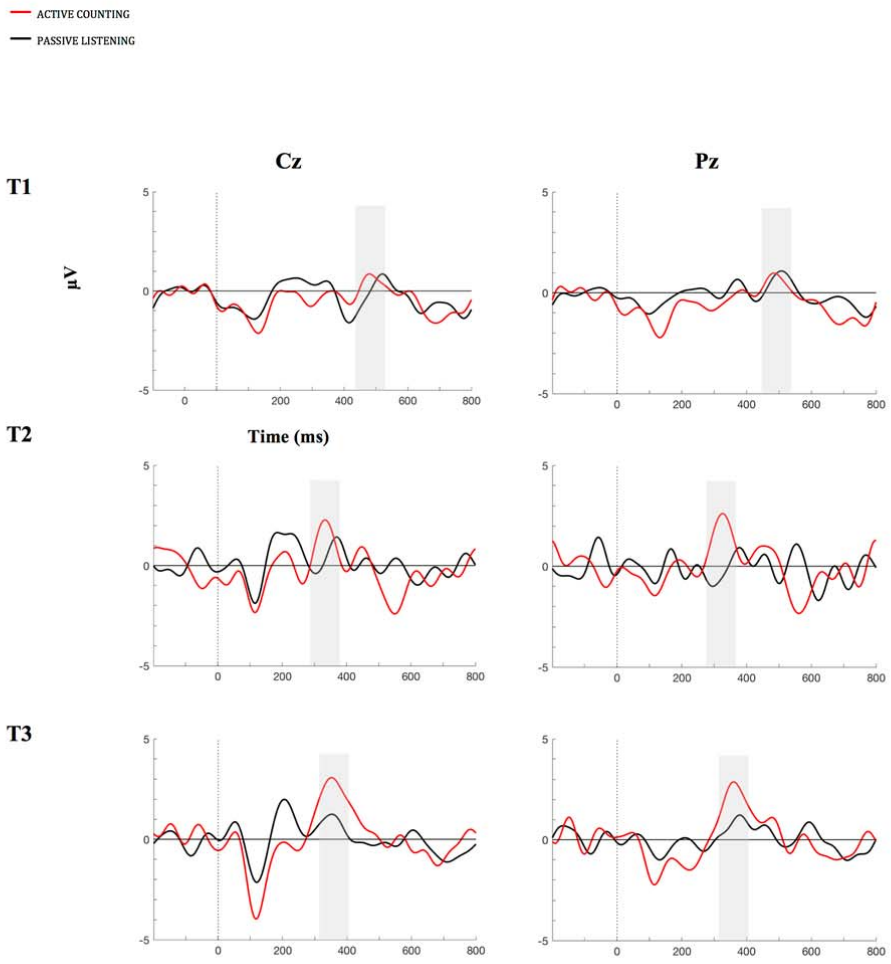

Figure 3A. Grand averaged ERPs in the patient group with normalization of P3 in active task across the three sub-acute recordings, showing significantly larger P3-amplitude to SON in active task at T3 compared to T1 at Cz, while borderline significant at Pz, and a significantly larger peak P3-amplitude in active compared to passive condition at T3 at Cz, also borderline significant at Pz ($p < .05$). The P3 curve elicited in active task is marked with grey line. The active counting condition marked in red and the passive condition marked in black (*y* axis, amplitude in μV; *x* axis, time in ms).

Figure 3A

Figure 3A. Grand averaged ERPs in the patient group with normalization of P3 across the three sub-acute recordings, showing significantly larger effortful P3-amplitude at T3 compared to T1 at Cz, while borderline significant at Pz, and a significantly larger peak P3-amplitude in active compared to passive condition at T3 at Cz, also borderline significant at Pz ($p < .05$). The P3 curve elicited in active task is marked with grey line. The active counting condition marked in red and the passive condition marked in black (y axis, amplitude in μV; x axis, time in ms).

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Figure 3B: Grand average ERPs in the patient group (n=8) without normalization of P3

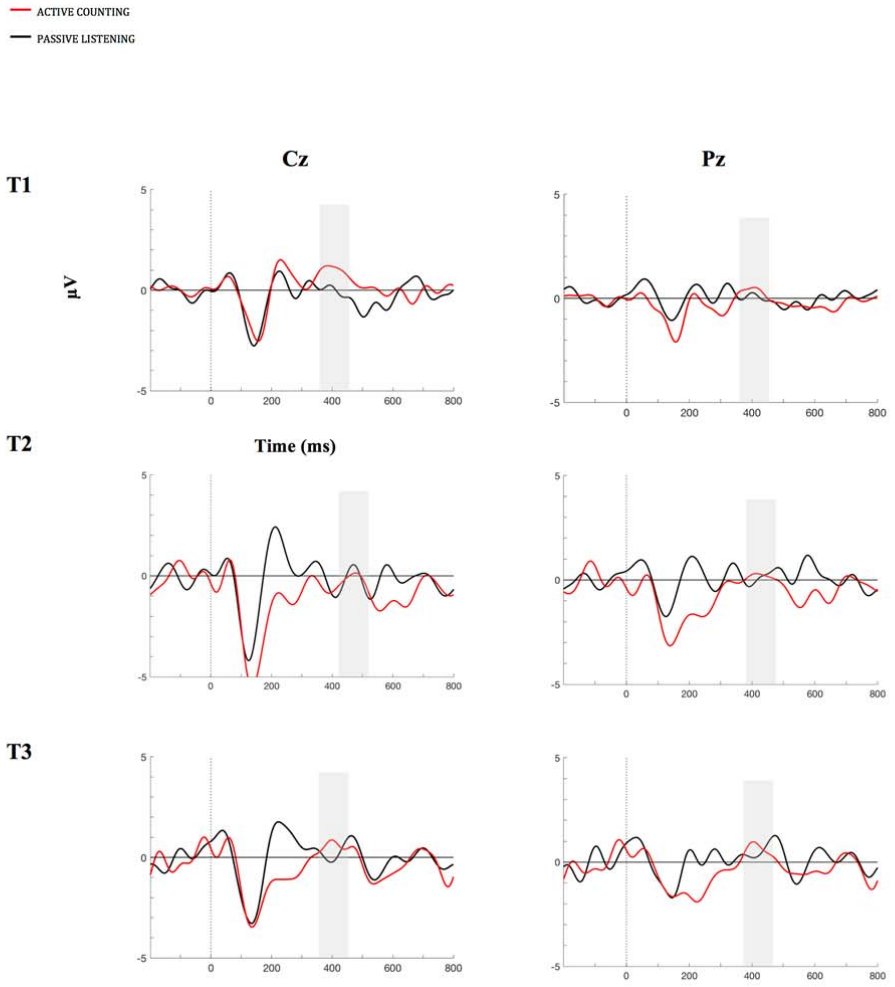

Figure 3B: Grand averaged ERPs in patient group without normalization of P3 in active task across the three time-points sub-acutely. The active counting condition marked in red versus the passive condition marked in black is illustrated (*y* axis, amplitude in μV; *x* axis, time in ms). The P3 curve elicited in active task is marked with grey line.

Figure 3B

Figure 3B: Grand averaged ERPs in patient group without normalization of P3 in active task across the three time-points sub-acutely. The active counting condition marked in red versus the passive condition marked in black is illustrated (*y* axis, amplitude in µV; *x* axis, time in ms). The P3 curve elicited in active task is marked with grey line.

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