Neuropsychological Functioning in a National Cohort of Severe Traumatic Brain Injury: Demographic and Acute Injury Related Predictors

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Conflicts of Interest:

We certify that no party having a direct interest in the results of the research supporting this article has or will confer a benefit on the authors or on any organization with which we are associated.

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Abstract

Objectives: To determine the rates of cognitive impairment 1 year after severe traumatic brain injury (TBI) and to examine the influence of demographic, injury severity, rehabilitation and sub-acute functional outcomes on cognitive outcomes 1 year after severe TBI. **Setting:** National multicenter cohort study over 2 years. **Participants:** Patients (N=105) aged ≥16 years with Glasgow Coma Scale (GCS) 3-8 and Galveston Orientation and Amnesia Test >75. **Main Measures**: Neuropsychological tests representing cognitive domains of *Executive Functions*, *Processing Speed*, and *Memory*. Injury severity included Rotterdam CT score, GCS, and post-traumatic amnesia (PTA), together with length of rehabilitation and Glasgow Outcome Scale-Extended (GOSE). **Results:** Totally, 67% of patients with severe TBI had cognitive impairment. *Executive Functions*, *Processing Speed*, and *Memory* were impaired in 41%, 58%, and 57% of patients, respectively. Using multiple regression, *Processing Speed* was significantly related to PTA, GOSE, and length of inpatient rehabilitation (R^2=.30); *Memory* was significantly related to GOSE (R^2=.15); and *Executive functions* to PTA (R^2=.10). Rotterdam CT and GCS scores were not associated with cognitive functioning at one year post-injury. **Conclusion:** Findings highlight cognitive consequences of severe TBI with nearly two-thirds of patients showing cognitive impairments in at least one of three cognitive domains. Regarding injury severity predictors, only PTA was related to cognitive functioning.

Key words: Traumatic Brain Injury, Outcome Prediction, Cognitive impairment, Executive functions, Memory.

Text

Severe traumatic brain injury (TBI) is generally a complicated trauma that is associated with multiple medical, functional, and cognitive consequences. The outcome is fatal in 20-35% of cases[1-3] and 52% of survivors present with some level of disability at 1 year post-injury.[4] In a recent population-based study in Norway, the incidence of severe TBI was estimated to be 5.2/100,000 in 2009 and 4.1/100,000 in 2010.[5] The majority of survivors with severe TBI suffer wide-spread brain damage[6-8] and neuropsychological assessments indicate long-lasting cognitive deficits,[6,9-15] ranging from 48%-73% at three months post-injury[16,17] to 31-63% at 1 year post-injury, in particular on measures of memory and executive functions.[13]

There are several studies that have examined which factors may influence cognitive impairment after TBI. Consistently, older individuals seem to fare more poorly than younger individuals in all stages of recovery from acute care,[18] during the first years after TBI,[19,20] and between 5 to 22 years after injury.[21] Lower education has been modestly associated with poorer cognitive outcome,[18,19,22] and with slower rate of recovery[22] in the TBI literature. In studies using path analysis, premorbid factors, particularly being employed before injury, had positive influence on cognitive status at 1 year after TBI.[23,24] Lower cognitive scores at admission to inpatient rehabilitation have been associated with prolonged stay of rehabilitation.[25] Moreover, extensive cognitive deficits have been associated with severity of the initial injury, such as the Glasgow Coma Scale (GCS)[23,26] and duration of post-traumatic amnesia (PTA).[11,20,23,26-28] The GCS score and duration of PTA are documented as predictors of neuropsychological functioning at 2 to 6 weeks after TBI,[27] at 6 months,[24] at 1 year,[23,29] and 10 years after injury.[11] Moreover, a meta-analysis has indicated that PTA is a valuable predictor of intellectual impairment.[28]

The structural basis of reduced cognitive functioning is evaluated in neuroimaging studies using computed tomography (CT) and magnetic resonance imaging (MRI). Memory and

intellectual impairments correlated with smaller brain size volume[22] and number of brain abnormalities,[30] and poorer test performances on visuospatial processing and verbal reasoning 1-year after injury were related to traumatic subarachnoid haemorrhage.[29] In the last decade, large databases have been used to build prognostic models for in-hospital mortality and functional outcomes after moderate-to-severe TBI. A revised CT classification system was identified as an important early predictors.[7,31,32] However, the impact of the CT classification system on neuropsychological tests after severe TBI,[19] and on long-term functional disability 1 and 2 years after mild-to-severe TBI[33] could not clearly be demonstrated. Taking into account that the CT brain scan remains the modality of choice for the initial assessment in the detection of fractures and acute hematomas, more studies are needed for prognostic purposes. Currently, there are no nationwide studies describing the relationship between important acute variables and cognitive functioning after severe TBI 1 year post-injury. The present national study from four Trauma Referral Centers is the first to investigate cognitive functioning in a population-based cohort of patients with severe TBI. The aims were to (1) determine the rates of cognitive impairment in executive functions, processing speed, and memory after severe TBI and (2) to examine the influence of demographic, injury severity, rehabilitation and sub-acute functional outcomes on cognitive outcomes 1 year after severe TBI. In accordance with previous literature, predictors included: age, education, PTA, GCS, CT classification scores, length of inpatient rehabilitation stay and functional status.

METHODS

This study was approved by the regional Committee for Medical Research Ethics, South-East Norway.

Study setting

A population-based multicenter cohort study was conducted in Norway during the 2-year period from January 2009 to January 2011. The Norwegian adult population (aged ≥16 years) was 3,824,127 inhabitants in 2009 and 3,876,857 inhabitants in 2010 (source: Statistics Norway 2013). There are four health regions in Norway associated with four Trauma Referral Centers: the University Hospital of North Norway in the northern region, St. Olav's Hospital in the central region, Haukeland University Hospital in the western region, and Oslo University Hospital in the south-eastern region of Norway. All the regional Trauma Referral Centers were invited to participate. The northern and central regions of Norway are considered more rural due to long distances and the western and south-eastern regions as more urban.[5] The patients were enrolled during the acute hospital stay. Each regional coordinator was responsible for data collection and participated in video-conference meetings to diminish variability of procedures across study regions. The Oslo University Hospital was responsible for the database. Injury details and clinical characteristics were based on a systematic review of hospital admission medical charts and other available clinical data from the acute hospital stay. A standardized telephone interview was administered at 3 months post-injury, and an in-person interview and a neuropsychological evaluation were performed at 1 year post-injury. Neuropsychological data were collected by neuropsychologists at the rehabilitation centers in the four health regions.

Adults with severe TBI who were admitted to the neurosurgical departments of the four regional Trauma Referral Centers were included. Inclusion criteria were: (1) Norwegian residents aged ≥16 years with severe TBI as defined by the International Classification of Diseases (ICD-10) diagnosis codes (S06.1-S06.9); (2) GCS 3-8 during the first 24 hours after injury; and (3) admitted to a regional trauma center within 72 hours of injury. Exclusion criteria were diagnoses which interfere with cognitive outcomes: (1) neurological diseases

(n=19) known to affect the central nervous system (progressive diseases, stroke, previous TBI, spinal cord injury, mental retardation, dementia); (2) diagnosis of severe psychiatric diseases (n=11) according to the ICD-10 (psychosis, suicide); (3) diagnosis of severe alcohol and/or intravenous drug abuse disorders (n=16) according to the ICD-10; and (4) being homeless (n=2). Informed consent was obtained for the medical part of the study at 3 months follow-up and a separate consent form was obtained for the neuropsychological part of the study at 1 year follow-up. Eligibility criteria for this neuropsychological study included patients who had a Galveston Orientation and Amnesia Test (GOAT)[34] score >75 at 1 year and speaking the Norwegian language. A GOAT score >75 indicated emergence from PTA. This restricted inclusion to patients who were out of PTA and prevented some patients who were disoriented from being included.

A total of 334 patients met the inclusion criteria, 48 were excluded in the acute phase and 10 patients refused to participate in the medical part of study (see Figure 1). There were 155 eligible patients for the neuropsychological part of the study at 1 year post-injury. Non-participants included eligible patients who were: asked to participate but refused (n=25); unable to attend the in-person follow-up (n=14); included during the acute hospital stay but not reachable at 1 year follow-up because two hospitals were not able to participate in the neuropsychological study (n=11).

[INSERT FIGURE 1 HERE]

Procedures

Demographics (gender, age) and employment and marital status at the time of injury were recorded during hospitalization or by interviews performed at 3 months or 1 year post-injury. Clinical variables were collected from medical records, including the lowest GCS score

during the first 24 hours after injury, ICD-10 diagnoses, and duration of PTA. The inpatient rehabilitation length of stay was recorded for patients receiving rehabilitation. The GOAT was performed routinely in the rehabilitation centers. The duration of PTA was categorized as <7 days, 7-13 days, 14-20 days, 21-27 days or >27 days.[35] Brain CT scans conducted at admission were analyzed according to the revised CT classification system (Rotterdam CT scores).[7] The Rotterdam CT score includes the presence of basal cisterns, midline shift, intracranial hemorrhages and subarachnoid blood, and types of mass lesions. Higher scores (range 1-6 points) indicate worse intracranial pathology.[7] The trauma scores of the Abbreviated Injury Score (AIS)[36] and the Injury Severity Scale (ISS)[37] were used to indicate the severity of head injury and total body injury, respectively.

Participants

A total of 105 patients participated 1 year after their injury (age range=16-85 years). Table 1 presents the characteristics of participants and non-participants. The external causes of injury in the participants were: 49 traffic accidents (47%), 43 falls (41%), 7 violence (7%), and 6 others (5%). There were significant differences between participants (n=105) and non-participants (n=50) regarding age ($t(153)=-2.65$, $P=.009$), education ($\chi^2(1)=4.04$, $P=.044$), employment status before injury ($\chi^2(1)=11.97$, $P=.001$), the Glasgow Outcome Scale-Extended (GOSE)[38] at 3 months ($t(147)=-2.20$, $P=.029$), and inpatient rehabilitation length of stay ($t(128)=2.98$, $P=.003$).

[INSERT TABLE 1 HERE]

Measures

Neuropsychological assessment

The neuropsychological test battery was selected according to our previous studies[8,17,26] and included measures to evaluate executive functions, processing speed, and memory. The following tests were included: (1) the *California Verbal Learning Test-II* (CVLT-II)[39] to evaluate verbal learning (List A Trials 1-5), working memory (List B Words Recalled), and long-term verbal memory (List A Long Delay Free Recall); (2) the *Rey-Osterrieth Complex Figure Test* (ROCF)[40] to measure long-term visual memory; (3) the *Letter-Number Sequencing* (LN) subtest of the Wechsler Adult Intelligence Scale third edition (WAIS-III)[41] to assess working memory; (4) the *Color-Word Interference Test* (CWIT conditions 1-4) subtest of the *Delis-Kaplan Executive Function System* (D-KEFS)[42] to assess selective attention, response inhibition, and cognitive-shifting abilities; (5) the *Trail Making Test* (TMT conditions 1-5) subtest of the D-KEFS to measure visual scanning, processing speed, mental flexibility, and motor speed; and (6) the *Verbal Letter Fluency Test* of the D-KEFS to assess verbal productivity.

Identification of cognitive impairment

In this study, individuals with GOAT $\leq$ 75 (n=13) and those in a vegetative state (n=5) were included in the sample of patients studied with cognitive impairment. For all participants (n=105), a neuropsychological subtest score was considered to be in the impaired range if it was 1.5 SD below the mean (7^{th} percentile). This criterion is consistent with those previously used to define impairment in the neuropsychological literature[43] and related studies of TBI.[17,44] Furthermore, individuals were classified with impairment within cognitive domains using the sum of the number of impaired subtest scores below 1.5 SD divided by the total number of subtests within each cognitive domain. Cognitive impairment in this study was considered identified when the proportion of impaired subtest scores was greater than one-

third. This proportion was chosen to exceed the rate for cognitive impairment in the general population using similar number of neuropsychological tests.[43,45] For example, when the average correlation between tests is *r*=0.50 in a battery of six tests, 18.64% of the population are expected to exhibit one or more abnormally low scores (<5th percentile). [45]

Functional outcome measure

The Glasgow Outcome Scale-Extended (GOSE) was used to assess sub-acute functional outcome at 3 months post-injury.[38] The GOSE is based on a structured interview and scores represent the following: 1=dead, 2=vegetative state, 3=lower severe disability, 4=upper severe disability, 5=lower moderate disability, 6=upper moderate disability, 7=lower good recovery, and 8=upper good recovery.

Data Analysis

Neuropsychological scores were calculated by transforming raw scores into standardized T scores (mean=50, SD=10) using age- and gender-corrected published normative data. Complete neuropsychological data were collected from 93 of 105 individuals. The number of participants having missing data for any of the neuropsychological variables ranged from 1 (CVLT-II, Verbal Fluency) to 8 (D-KEFS CWIT). Cognitive deficits (e.g. aphasia, visual neglect, executive dysfunction) prevented most of these cases from completing the test. Therefore, cases that were unable to complete the test due to cognitive deficits were assigned an "impaired" score (T-score=20) and rates of impairment presented in this study also reflect these cases. The imputed values were used in all of the statistical analyses in the study. This also increased the sample size (n=105) in compliance with the recommendation that the sample should be higher than 100 in factor analysis and the subjects-to-variables ratio should be 5 or greater.[47]

The chi-square test (χ^2) was used to evaluate ordinal data and *t* tests were used to compare interval data. Due to the number of analyses conducted for the *t* tests analysis, the level of statistical significance was adjusted to Bonferroni using the formula *P*=.05/15=.003. To group the 15 neuropsychological subtests into specific cognitive domains, an exploratory factor analysis was performed using principal component analysis. Given that some of the neuropsychological measures and subtests of the D-KEFS might be correlated, loadings were obtained from the promax rotated solution (oblique) which allows inter-correlations between rotated factors. Following the results of the exploratory factor analysis, both univariate and multivariate predictors of cognitive domains (i.e., the three factor scores from the factor analysis) were examined by regression analyses. The acute injury-related predictors were chosen based on those that predicted cognitive outcome in the literature i.e., GCS score (lowest score in first 24 hours), PTA (5 categories: <7 days, 7-13 days, 14-20 days, 21-27 days or >27 days), and Rotterdam CT scores. Age (in years) and education (4 categories: 0-9 years, 10-12 years, 13-16 years or >16 years) were entered first in hierarchical multiple regression analysis, followed by the acute injury-related predictors, and finally the GOSE and length of inpatient rehabilitation stay (in days). A maximum number of seven independent variables were entered using N>50+8*k* (where k is the number of predictors).[48] The regression analysis had a sufficient power of 0.95 (sample size=105, predictors=7, a medium effect size f^2=0.15) using G*Power3.[49] Finally, a Receiver Operating Characteristic (ROC) curve analysis was performed to determine what PTA categorization best predicts dichotomous cognitive functioning at 1-year (impaired versus not impaired). Statistical analyses were performed using PASW 18.0.

RESULTS

Cognitive Outcomes

Exploratory factor analysis of 15 neuropsychological subtests was conducted, using principal component analysis with the promax rotation (correlated factors) solution. Factors were determined to be significant based upon eigenvalues greater than 1.0 and a scree plot. The exploratory factor analysis extracted three factors, explaining 70.8% of the total variance of the 15 subtests, with one significant cross loading between factors (see Table 2). The three factors were interpreted and labelled as: (1) *Executive Functions,* with high loadings from the CWIT, LN, and Verbal Fluency; (2) *Processing Speed,* with high loadings from the TMT; and (3) *Memory*, with high loadings from the CVLT-II and ROCF. The Kaiser-Mayer-Olkin measure of sampling adequacy was 0.89, and the Bartlett's test of sphericity was significant indicating that correlations between tests were sufficiently large ($\chi^2(105)=1067.8$, $P<.001$).

[INSERT TABLE 2 HERE]

Descriptive statistics of the neuropsychological tests are presented in Table 3. The means of the T-scores for the total sample varied from 38.1 to 48.2 and the frequency of cognitive impairment across the subtests varied from 13% (TMT; Condition 5) to 41% (CVLT-II List B).

ROC curve analyses showed that PTA categories had a moderate predictive power for cognitive outcomes (area under the ROC curve (AUC)=.70 for *Executive Functions*, AUC=.72 for *Processing Speed*, and AUC=.62 for *Memory*). The category that maximized the sensitivity for cognitive outcome was "PTA>4 weeks" for all the three cognitive domains. Sensitivity and specificity, respectively, was found to be the following: *Executive Functions* (75%, 34%), *Processing Speed* (70%, 31%), and *Memory* (62%, 37%).

Based on the dichotomous ratings of PTA lasting <4 weeks versus PTA >4 weeks, T-scores obtained on the neuropsychological tests were compared between PTA groups using *t* tests with Bonferroni correction (α=.05/15). As shown in Table 3, the group with PTA lasting >4 weeks had significantly lower scores on 10 of the 15 subtests (*P*s=.001-.003) compared to the group with PTA lasting <4 weeks. There were no significant differences between the PTA groups in years of education (*P*=.641). The length of stay in inpatient rehabilitation was significantly longer in the PTA >4 weeks group (mean days=63.1) compared to the PTA <4 weeks group (mean days=32.7) ($t(128)=2.98$, $P=.003$).

[INSERT TABLE 3 HERE]

Cognitive impairment

Bivariate correlations and percent of patients with impairment in each cognitive domain are reported in Table 4. Pearson's correlation coefficients between the three cognitive domains were as follows: *Executive functions* and *Speed of Processing*, $r=.53$; *Executive functions* and *Memory*, $r=.44$; *Speed of Processing* and *Memory*, $r=.49$ (*P*s<.001). As presented in Table 4, individuals being untestable with neuropsychological tests were included in the sample of patients with cognitive impairment. Cognitive impairment was found in 67% of patients (82 of 123); 36% of patients exhibited impairment in one cognitive domain, 33% of patients exhibited impairment in two domains, and 28% of patients exhibited impairment in all three domains.

[INSERT TABLE 4 HERE]

Regression analyses

Tables 5, 6 and 7 present the results of the regression models for *Executive functions*, *Processing Speed*, and *Memory*, respectively. The first column in each table presents the unique variance (R^2) for each variable in predicting cognitive outcomes. In univariate analyses, a shorter period of PTA, better sub-acute functional outcome (GOSE), and shorter length of rehabilitation stay were associated with better outcomes in all three cognitive domains. In general, there were no significant univariate relationships between cognitive outcomes and education and age, except that education provided unique variance to *Processing Speed*. In the multivariate regression analyses, only two regression models were statistically significant: *Speed of Processing* $F(7, 95)=5.45$, $P<.001$ (see Table 6), and *Memory* $F(7, 95)=2.26$, $P=.037$ (see Table 7). The regression models predicted 3-25% of the variance in cognitive functioning as shown by the R^2 *Adjusted* values (.03-.25) for the 3rd step in each of the final models. In Table 5, shorter duration of PTA, after adjusting for age and education, was found to be a significant predictor of better *Executive Functions* scores (i.e., β weights −.23, $P<.05$, at the 2nd step). In Table 6, PTA accounted for 8.4% of the variance in *Speed of Processing* (i.e., β weights −.29 at the 2nd step). Furthermore, better sub-acute functional outcome (GOSE) and shorter length of inpatient rehabilitation predicted better *Speed of Processing* scores, accounting for an additional 16% of the variance ($R^2 \Delta$ =.16 at the 3rd step). In Table 7, better sub-acute functional outcome (GOSE) was the only significant predictor of better *Memory* scores (β weights .33 at the 3rd step). The Durbin-Watson tests for serial correlation of residuals in the three models were found to be from 1.75 to 2.26, indicating a weak correlation and that residuals were independent. Correlation coefficients between predictors ranged from $r=.01$ (PTA and education) to $r=-.61$ (GOSE and Rehabilitation length of stay). Spearman's correlation coefficient of the association between PTA and GCS scores was $r=-.28$, $P<0.01$, and between PTA and Rotterdam CT scores $r=.29$, $P<0.01$.

[INSERT TABLE 5, TABLE 6 and TABLE 7 HERE]

DISCUSSION

This population-based study presents a novel opportunity to generate knowledge regarding cognitive outcomes after severe TBI. At 1 year post-injury, 41% of patients exhibited impaired *Executive Functions*, 58% exhibited impaired *Processing Speed*, and 57% exhibited impaired *Memory*. Good recovery of cognitive deficits occurred in 33% of patients who demonstrated no impairment in any cognitive domain, whereas 28% of patients continued to experience difficulties across all cognitive domains. Similar rates of cognitive impairments were found in this study compared to another study,[13] the latter reported that 52-63% of patients with severe TBI had some degree of impairment on tests of verbal memory and 38-55% on tests of executive functions 1 year post-injury.

The three regression models presented in the current study were weak, in terms of the R^2 *Adjusted* values (.03-.25), thus indicating that other factors accounted for the remaining variation of cognitive domains. Sub-acute functional outcome assessed at 3 months (GOSE) was associated with subsequent 1-year neuropsychological outcomes of *Memory* and *Processing Speed*, consistent with previously reported studies.[10,16,17,26] In addition, longer length of inpatient rehabilitation stay was significantly related to worse *Processing Speed*. The results are in accordance with findings of a previous study where poorer cognitive scores at rehabilitation admission were among the factors that influenced upon extended rehabilitation length of stay.[25] Another finding of the present study is that the GCS score was not a significant predictor of cognitive outcomes 1 year after severe TBI. The influence of injury severity on cognitive functioning may diminish over time; reflected in previously reported TBI studies.[16,24] In future studies, the sensitivity of injury-related indices to cognitive

deficits could be examined and compared across different time points at 3 months, 6 months, 1 and 2 years post-injury. Notably, acute injury-related variables may serve as better predictors to cognitive outcomes in moderate-to-severe TBI samples documented in other studies,[23,24,31,50] than in selected samples with acute GCS and 1-year GOAT scores used in this study.

In this national study, PTA duration was a stronger predictor than the GCS score and Rotterdam CT score. The ROC curve analyses performed in this study suggest that the presence of PTA beyond 4 weeks post-injury may distinguish between patients with a good or poor cognitive outcomes, in accordance with other findings.[35,51] Individuals with PTA >4 weeks tended to perform considerably poorer on 10 of the 15 neuropsychological tests administered than those with PTA lasting <4 weeks.

Studies using CT findings suggest that the associations of CT classifications and outcomes are mixed.[19,29,31] The present study indicates that the relationship between acute Rotterdam CT scores and cognitive outcomes 1 year post-injury is limited. Despite the impact upon *Processing Speed* in univariate analysis, Rotterdam CT scores did not significantly influence cognitive outcomes in multivariate analyses. This might be due to small variance in CT scores, since all participants had severe TBI. Furthermore, an acute CT brain scan seems to underestimate the severity of cerebral injuries and has low sensitivity in visualizing more severe injuries such as diffuse axonal injury (DAI), and is thus limited to give data for long-term interpretation.[52] Our findings are in line with a study of 46 patients with severe TBI,[19] CT classification had limited predictive value for cognitive functions assessed 1-6 years after injury. The study concluded that age and education were most strongly associated with long-term cognitive disability and that individuals with higher education may have had increased cognitive abilities or made better use of compensatory strategies.[19] A recent study revealed that the Rotterdam CT score did not predict long-term functional disability at 1 or 2 years

after mild-to-severe TBI.[33] Another study found that the Rotterdam CT score was only related to functional outcome following severe TBI.[53] The predictive ability of the Rotterdam CT score on functional outcome was also evidenced in a larger study of 2269 patients with moderate-to-severe TBI.[31] Injuries to frontal and temporal areas of the brain may have a greater impact on executive functions than revealed by CT scans. However, the inclusion of MRI in revealing the extent of such injuries soon after TBI could improve predictive models of cognitive outcomes.[22,30,53]

Assessment of cognitive functions is an important part in rehabilitation after brain injuries and has valuable implications for treatment and prognosis. Severe TBI affects a large range of memory aspects and executive functions that are complex and often difficult to measure.[15,54,55] However, there is considerable variability across individuals with severe TBI, and some achieve a good cognitive outcome, as documented in this national study and also in other studies.[10,13,15,54] Perhaps the most important implication for rehabilitation concerned the relationship of PTA, sub-acute functional outcome, and length of inpatient rehabilitation to predict cognitive functions. This might guide clinicians at the time of rehabilitation admittance to provide prognostic implications for long-term cognitive deficits.

Strengths and caveats

A major strength of the present study is the population-based prospective design and availability of extensive data to characterize the acute injury. Although the sample size is relatively small compared to other multicenter samples in the USA[33] and Europe,[31] it is demographically similar regarding age,[31,33] gender,[31,33] and education.[33]

Some limitations should be noted. This national study used a restricted inclusion criteria consisting of individuals who had GCS 3-8 during the first 24 hours after injury and GOAT score >75 at 1 year post-injury. Another limitation of the study was an exclusion of patients

with substance use disorders (n=16) that supposedly have poorer outcomes than the included sample, due to diverse psychological and cognitive problems. Excluding these individuals, therefore, may have led to an underestimate of the true impairment after severe TBI. On the other hand, by excluding 19 patients with neurological diseases (e.g., stroke, previous TBI, dementia) associated with neurocognitive deficits that could interfere with outcomes, the present study was probably more designed to identify impairments arising from severe TBI. However, there is no universal agreement on the definition of cognitive impairment.[46] Impairment may depend upon the person's premorbid level of cognitive functioning and using a universal cut-off score in this study to define impairment is not without limitations. It is possible that some individuals always performed 1.5 SD below the mean before the injury and would thus be incorrectly identified as having cognitive impairment secondary to severe TBI (i.e., false positives).[46]

Further, participants in this study were younger, better educated and more often employed at the time of injury than non-participants, which may have led to a selection bias. However, our findings may not be the ultimate estimate of the relationship between acute injury predictors and cognitive outcomes due to small sample size and restricted range. One limitation is that the design of the study prevents tracking the sensitivity of the demographic and injury-related variables across time. It is also acknowledged that the three cognitive domains in this study may lack specificity as their selection into the regression models was derived from factor analysis based on 15 tests. Therefore, cognitive domains were not theory-driven and the clinical and real-world applicability of these may be questioned. One methodological weakness was that PTA duration was determined on clinical registration in medical records.

Conclusions

Patients with severe TBI represent a clinical challenge and can exhibit the range from minor cognitive problems to severe cognitive deficits consistent with the vegetative/minimally conscious state. Our findings demonstrate the heterogeneity of outcomes after TBI, with notably high proportion of individuals (67%) showing residual cognitive impairments, and 33% of individuals who do not expose cognitive impairment 1 year post-injury. Since none of the acute injury predictors accounted for a large proportion of variance in cognitive outcomes, the reasons for this heterogeneity remain poorly understood.

The identification of cognitive impairment found in this study may assist in further planning and designing rehabilitation programs for individuals who have marked cognitive deficits and who might benefit from long-term interventions to address these deficits. Some may need work-related support beyond the first year after injury while others may need long-term rehabilitation for dealing with interpersonal, behavioural and social difficulties. Taking into consideration predictors of cognitive functions after severe TBI has important implication for treatment and prognosis in rehabilitation. The predictive value of GOSE found in this study underlines the importance of assessing functional outcomes in the sub-acute phase and to adapt rehabilitation programs to the needs of the individual, including those with prolonged duration of PTA. The findings of this study may also support the recommendation to conduct comprehensive neuropsychological evaluations 6-12 months after injury, once spontaneous recovery has slowed down. Objective test data can be used to characterize an individual's cognitive strengths and weaknesses and establish an appropriate rehabilitation plan. Future challenges will be to improve the characterization/classification of TBI in the acute phase and to identify factors explaining long-term cognitive outcomes after severe TBI.

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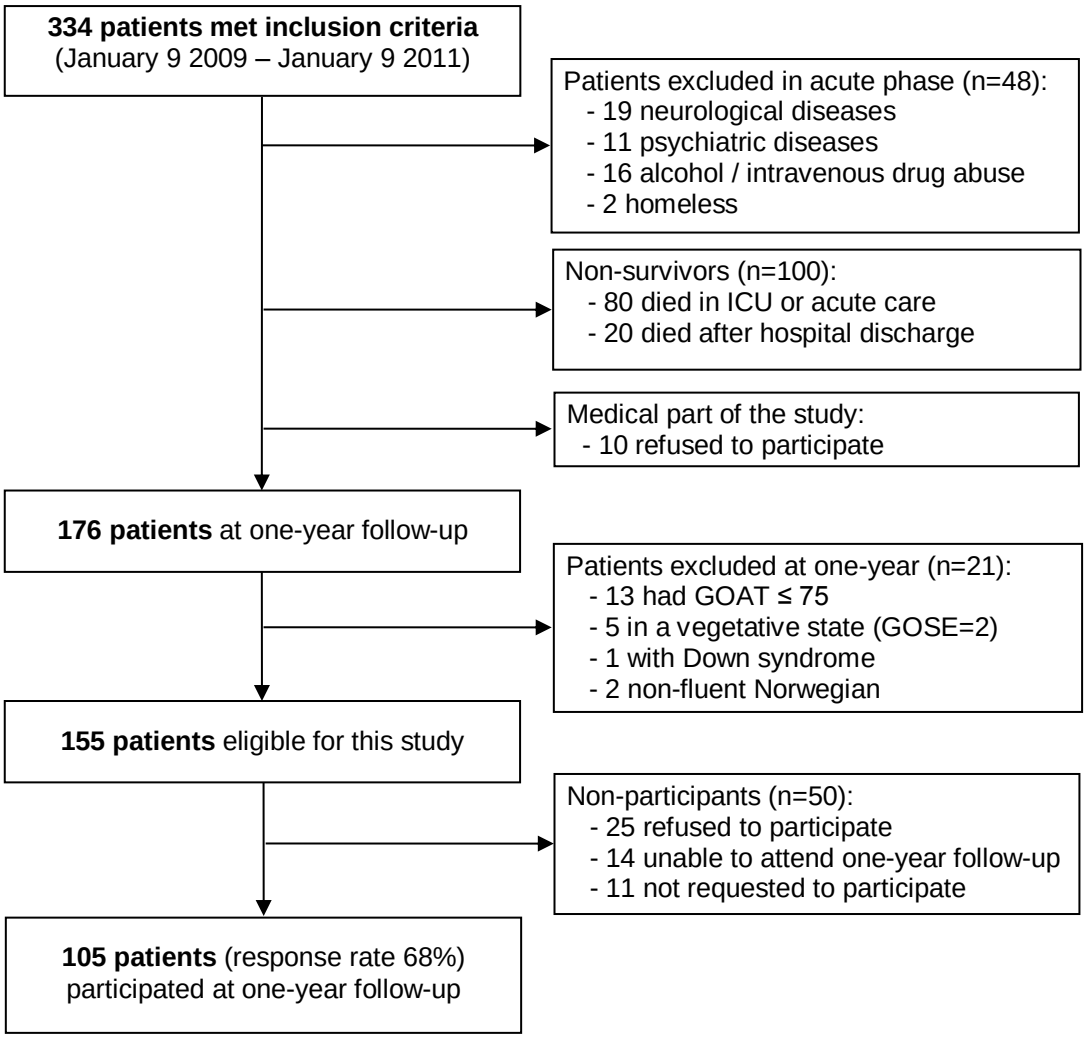

Figure 1.

Flow chart of patient inclusion, follow-up and exclusion criteria.

Table 1. Demographics and Hospitalization Characteristics of Patients with Severe Traumatic Brain Injury

Patient Characteristics	Non-participants (n=50)	Participants (n=105)	*P*
Pre-injury factors			
Age (years)	45.2 ±21.0	36.9 ±16.7	.009
Male	41 (82)	80 (76)	.414
Married/ cohabitant (yes)	15 (31)	46 (44)	.141
Education > 12 years	9 (21)	40 (39)	.044
Employment pre-injury (yes)	23 (48)	80 (76)	.001
Health region south-east (yes)	31 (62)	66 (63)	.974
Hospitalized admission variables			
Traffic accidents (yes)	17 (35)	49 (47)	.162
Post-traumatic amnesia [a]			
< 7 days	15 (31)	22 (21)	
7-13	4 (8)	14 (13)	
14-20	8 (16)	8 (8)	
21-27 days	9 (18)	12 (11)	
>27 days	13 (27)	49 (47)	.058
Rotterdam CT score (range 1-6)	3.6 ± 0.8	3.5 ± 1.0	.489
GCS lowest score at admission	6.0 ± 2.0	5.9 ± 1.8	.618
AIS_{head}	4.4 ± 0.8	4.2 ± 0.9	.212
ISS	26.1 ± 11.4	27.3 ± 11.4	.550
Length of rehabilitation stay (days) [a]	32.7 ± 33.5	63.1 ± 55.8	.003
Functional outcome			
GOSE at 3 months [a]	5.7 ± 1.5	5.2 ± 1.2	.029

NOTE. Values are mean ±SD or n (%).
Abbreviations: GCS, Glasgow Coma Scale; AIS, Abbreviated Injury Scale; ISS, Injury Severity Scale; GOSE, Glasgow Outcome Scale-Extended.
[a] Missing data: PTA (non-participants=1); Rehabilitation (non-participants=16, participants=9) ; GOSE (non-participants=6).

Table 2. Pattern Matrix from the Exploratory Factor Analysis of Neuropsychological Variables

	Factor		
Variable	1	2	3
D-KEFS CWIT; Condition 1	**.84**	-	-
D-KEFS CWIT; Condition 2	**.94**	-	-
D-KEFS CWIT; Condition 3	**.88**	-	-
D-KEFS CWIT; Condition 4	**.82**	-	-
Verbal Fluency	**.66**	-	-
WAIS-III LN	**.62**	-	-
D-KEFS TMT; Condition 1	-	**.75**	-
D-KEFS TMT; Condition 2	-	**.91**	-
D-KEFS TMT; Condition 3	-	**.69**	-
D-KEFS TMT; Condition 4	-	**.64**	-
D-KEFS TMT; Condition 5	-	**.87**	-
CVLT-II List B words recalled	-	-	**.91**
CVLT-II List A trials 1-5	-	-	**.86**
CVLT-II List A delay free recall	-	-	**.81**
ROCF Long delay recall	-	.52	**.59**
% variance	48.6	11.9	10.3
Eigenvalue	7.3	1.8	1.5
Composite variables	Executive Functions	Speed of Processing	Memory Functions

Note. N=105. Factor loadings <.30 (-) are not shown.
Abbreviations: D-KEFS, Delis-Kaplan Executive Function System; CWIT, Color-Word Interference Test; WAIS-III, Wechsler Adult Intelligence Scale-Third Edition; LN, Letter-Number Sequencing; TMT, Trail Making Test; CVLT-II, California Verbal Learning Test-II; ROCF, Rey-Osterrieth Complex Figure Test.

Table 3. Neuropsychological Profile of Adults with Severe Traumatic Brain Injury 1-year after Injury

Age and gender corrected neuropsychological tests [a]	Total sample (n=105) Mean (SD)	95% Confidence interval	Cognitive impairment [b]	PTA >4 weeks (n=49) Mean (SD)	PTA <4 weeks (n=56) Mean (SD)	*t*-test [c] *P*
Executive Functions						
D-KEFS CWIT; Condition 1	38.1 (12.4)	(35.7-40.5)	33%	34.4 (12.6)	41.4 (11.3)	.003
D-KEFS CWIT; Condition 2	40.3 (12.5)	(37.9-42.7)	32%	37.7 (13.5)	42.6 (11.0)	.040
D-KEFS CWIT; Condition 3	43.1 (14.2)	(40.3-45.8)	29%	39.1 (14.9)	46.5 (12.6)	.007
D-KEFS CWIT; Condition 4	39.9 (14.3)	(37.2-42.7)	36%	35.0 (14.8)	44.2 (12.5)	.001
Verbal Fluency	43.7 (12.9)	(41.2-46.2)	26%	38.8 (12.2)	48.0 (12.0)	.001
WAIS-III LN	43.1 (11.3)	(40.9-45.3)	26%	40.8 (11.4)	45.1 (10.9)	.055
Speed of Processing						
D-KEFS TMT; Condition 1	40.4 (12.4)	(38.0-42.8)	35%	36.6 (11.9)	43.7 (11.9)	.003
D-KEFS TMT; Condition 2	41.4 (12.9)	(38.9-43.9)	32%	36.3 (11.7)	45.9 (12.2)	.001
D-KEFS TMT; Condition 3	40.0 (13.8)	(37.3-42.6)	38%	35.7 (13.4)	43.7 (13.2)	.003
D-KEFS TMT; Condition 4	39.5 (13.8)	(36.8-42.2)	36%	33.6 (12.2)	44.6 (13.2)	.001
D-KEFS TMT; Condition 5	48.2 (10.7)	(46.2-50.3)	13%	46.4 (10.8)	49.8 (10.4)	.109
Memory Functions						
CVLT-II List B words recalled	41.4 (11.3)	(39.2-43.6)	41%	39.5 (11.0)	43.0 (11.5)	.110
CVLT-II List A trials 1-5	41.7 (13.4)	(39.1-44.3)	31%	37.1 (13.3)	45.7 (12.3)	.001
CVLT-II List A delay free recall	40.0 (14.3)	(37.3-42.8)	40%	35.0 (14.4)	44.5 (12.7)	.001
ROCF Long delay recall	42.4 (16.4)	(39.2-45.6)	34%	36.3 (16.1)	47.7 (14.8)	.001

[a] Scores have a mean of *T*=50 and SD=10.
[b] Participant's cognitive impairment defined as scores 1.5 SD below the mean.
[c] Bonferroni correction: $\alpha = .05/15 = .003$.
Abbreviations: D-KEFS, Delis-Kaplan Executive Function System; CWIT, Color-Word Interference Test; WAIS-III, Wechsler Adult Intelligence Scale-Third Edition; LN, Letter-Number Sequencing; TMT, Trail Making Test; CVLT-II, California Verbal Learning Test-II; ROCF, Rey-Osterrieth Complex Figure Test; WASI, Wechsler Abbreviated Scale of Intelligence.

Table 4. Bivariate correlations and proportions of patients with impairment in each cognitive domain [a]

	Correlations		Cognitive impairment
Cognitive domains	Processing Speed	Memory	Participants and non-testable patients [b] (n=123)
Executive Functions	.53**	.44**	41%
Processing Speed	-	.49**	58%
Memory	.49**	-	57%

[a] Factor scores from the factor analysis.
[b] Non-testable patients with GOAT ≤ 75 (n=13) and in a vegetative state (n=5).
** *P*<.001

Table 5. Predictors of Executive functions at 1 Year in the Multiple Hierarchical Regression Model

		Univariate		Multivariate						
Step	Predictors	R^2	β	B	SE	R^2	R^2 Adjusted	$R^2\,\Delta$	*F*	*P*
1	Age	.00	.01	.01	.01					
	Education	.01	.01	.01	.14	.01	−.02	.00	0.01	.996
2	PTA	.06*	−.23*	−.14	.07					
	GCS	.03	.12	.07	.06					
	Rotterdam CT	.02	−.03	−.03	.11	.09	.04	.09	1.70	.143
3	GOSE	.08**	.11	.09	.11					
	Rehabilitation LOS	.05*	−.07	−.01	.01	.10	.03	.02	1.44	.200

NOTE. Predictors that were entered at each step are reported in the table. No predictors in steps 1 and 2 were significant when entering a new step.
Abbreviations: PTA, Post-Traumatic Amnesia; GCS, Glasgow Coma Scale; CT, Computed Tomography; GOSE, Glasgow Outcome Scale-Extended; LOS, Length of Stay.
* *P*<.05
** *P*<.01

Table 6. Predictors of Processing Speed at 1 Year in the Multiple Hierarchical Regression Model

		Univariate		Multivariate						
Step	Predictors	R^2	β	B	SE	R^2	R^2 Adjusted	$R^2\,\Delta$	*F*	*P*
1	Age	.01	−.11	−.01	.01					
	Education	.04*	.11	.14	.14	.02	.00	.02	0.98	.378
2	PTA	.11***	−.29**	−.18	.06					
	GCS	.01	.01	.01	.06					
	Rotterdam CT	.04*	−.13	−.14	.11	.14	.10	.12	3.03	.014
3	GOSE	.20***	.28*	.23	.10					
	Rehabilitation LOS	.19***	−.26*	−.01	.01	.30	.25	.16	5.45	.001

NOTE. Predictors that were entered at each step are reported in the table. No predictors in steps 1 and 2 were significant when entering a new step.
Abbreviations: PTA, Post-Traumatic Amnesia; GCS, Glasgow Coma Scale; CT, Computed Tomography; GOSE, Glasgow Outcome Scale-Extended; LOS, Length of Stay.
* *P*<.05
** *P*<.01
*** *P*<.001

Table 7. Predictors of Memory at 1 Year in the Multiple Hierarchical Regression Model

		Univariate		Multivariate						
Step	Predictors	R^2	β	B	SE	R^2	R^2 Adjusted	$R^2\,\Delta$	*F*	*P*
1	Age	.00	.09	.01	.01					
	Education	.02	.06	.08	.14	.01	-.01	.01	0.62	.543
2	PTA	.07**	−.19	−.12	.07					
	GCS	.03	.10	.05	.06					
	Rotterdam CT	.01	−.06	−.06	.11	.08	.03	.07	1.55	.182
3	GOSE	.15***	.33**	.28	.11					
	Rehabilitation LOS	.06*	.03	.01	.01	.15	.09	.07	2.26	.037

NOTE. Predictors that were entered at each step are reported in the table. No predictors in steps 1 and 2 were significant when entering a new step.
Abbreviations: PTA, Post-Traumatic Amnesia; GCS, Glasgow Coma Scale; CT, Computed Tomography; GOSE, Glasgow Outcome Scale-Extended; LOS, Length of Stay.
* *P*<.05
** *P*<.01
*** *P*<.001