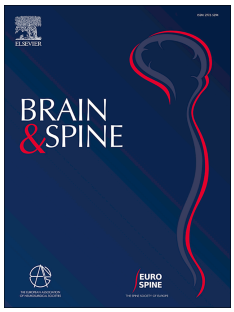

Neurocognitive correlates of probable posttraumatic stress disorder following traumatic brain injury

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Neurocognitive correlates of probable posttraumatic stress disorder following traumatic brain injury

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Abstract

Introduction: Neurocognitive problems associated with posttraumatic stress disorder (PTSD) can interact with impairment resulting from traumatic brain injury (TBI).

Research Question: We aimed to identify neurocognitive problems associated with probable PTSD following TBI in a civilian sample.

Material and methods: The study is part of the CENTER-TBI project (Collaborative European Neurotrauma Effectiveness Research) that aims to better characterize TBI. For this cross-sectional study, we included patients of all severities aged over 15, and a Glasgow Outcome Score Extended (GOSE) above 3. Participants were assessed at six months post-injury on the PTSD Checklist-5 (PCL-5), the Trail Making Test (TMT), the Rey Auditory Verbal Learning Test (RAVLT) and the Cambridge Neuropsychological Test Automated Battery (CANTAB). Primary analysis was a complete case analysis. Regression analyses were performed to investigate the association between the PCL-5 and cognition.

Results: Of the 1,134 participants included in the complete case analysis, 13.5% screened positive for PTSD. Probable PTSD was significantly associated with higher TMT-(B-A) (OR=1.35, 95% CI: 1.14–1.60, p<.001) and lower RAVLT-delayed recall scores (OR=0.74, 95% CI: 0.61-0.91, p=.004) after controlling for age, sex, psychiatric history, baseline Glasgow Coma Scale and education.

Discussion and Conclusion: Poorer performance on cognitive tests assessing task switching and, to a lesser extent, delayed verbal recall is associated with probable PTSD in civilians who have suffered TBI.

Keywords**:** cognition, head injury, neuropsychology, posttraumatic stress disorder, stress

1. Introduction

Each year, more than 50 million people worldwide suffer a traumatic brain injury (TBI) [1] often resulting in a wide range of cognitive, emotional and physical problems in survivors [2]. Typical deficits include impaired memory, attention and executive functioning, slowed information processing, behavioural difficulties and psychological distress [3-6]. Individual consequences are the result of many factors including the severity of the TBI, its location, and injury-specific recovery mechanisms [7]. In addition to psychological and cognitive symptoms as a consequence of TBI, PTSD may be a contributing factor, and is also associated to cognitive impairment. TBI is an established risk factor for posttraumatic stress disorder (PTSD): PTSD is diagnosed in 14% of TBI cases in the civilian setting within the first year after injury and in 7% after one year [8,9]. According to the Diagnostic and Statistical Manual of Mental Disorders–fifth edition (DSM-5), PTSD is a trauma-stressor-related disorder that can develop following exposure to a traumatic event [10]. For a PTSD diagnosis, patients need to manifest symptoms in four clusters: intrusion, avoidance, negative alterations in cognitions and mood, and alterations in arousal and reactivity. However, particularly in the cognitive, mood and arousal domains, the symptoms of PTSD show overlap with those characteristic of TBI [11].

People diagnosed with PTSD may suffer from long-term cognitive deficits [12]. A meta-analysis identified associations between PTSD and neurocognitive impairment in verbal learning, speed of information processing, attention/working memory and verbal memory with medium effect sizes [13]. Individuals with PTSD appear to have difficulty in remembering specific details and contextual information but show enhanced memory functioning for threat-related information. A key issue, here, is that they may have difficulty in disengaging attention from negative stimuli [12]. In their review, Qureshi et al. (2011) suggest that after trauma, attentional impairment can account for the observed memory problems [14]. Moreover,

neurocognitive deficits in individuals with PTSD can be the consequence of the PTSD, but a pretrauma cognitive vulnerability can also be a risk factor for developing PTSD [13].

Symptoms typical of PTSD may coincide with or be related to neurocognitive deficits resulting from the TBI as the latter may not only cause neurocognitive impairment [15] but also constitutes a risk factor for the development of PTSD [4]. Despite the overlap in the neurocognitive symptoms observed in PTSD and TBI, differences have been reported. As noted above, the cognitive impairment following mTBI generally resolves within three months after incurring the injury, whilst the cognitive problems associated with PTSD do not [16,17]. Various studies mainly focusing on mTBI reported greater attentional distraction and less proficient verbal memory, executive functioning (task switching) and verbal fluency in persons with PTSD compared to those with mTBI [18,19]. A study of veterans showed a clear association between less severe PTSD symptoms and more proficient visual memory, irrespective of TBI [20]. However, most studies of PTSD following TBI either had relatively small cohorts or assessed veterans retrospectively [18-20]. As the nature of trauma sustained in conflict settings is generally not comparable to that incurred in civilian events, a particular need exists for more prospective research on PTSD in civilian TBI populations [21].

The present study aims to delineate neurocognitive correlates of probable PTSD following mild, moderate and severe non-combat-related TBI. As the only cognitive function that was consistently found to be associated with PTSD/TBI in previous studies, we hypothesised that verbal memory performance would be associated with probable PTSD after civilian TBI [18,19]. We further explored associations between cognitive functioning and the symptom burden for each of the four PTSD clusters (intrusion, avoidance, cognition and mood, and arousal). In general, we expect that strong cognitive functioning is associated with low PTSD symptoms for each of the clusters [13]. Based on neurocognitive theories and previous work,

we expect associations between intrusion symptoms and attention [22], avoidance symptoms and verbal learning and memory [23] and/or intrusion symptoms and working memory [24].

2. Method

2.1 Study Design and Participants

The data for the present study was collected within the context of the European CENTER-TBI Core study (Collaborative European Neurotrauma Effectiveness Research: www.center-tbi.eu), a prospective, observational trial that aims to better characterise TBI and identify the most effective clinical TBI management interventions (clinicaltrials.gov NCT02210221), [25]. Between December 2014 and December 2017, 4,509 children and adults with a TBI were recruited from 65 hospitals across 19 countries. To be eligible, candidates had to have a clinical diagnosis of TBI defined by the treating physician, an indication for a CT-scan and needed to have been seen in an affiliated study centre within 24 hours of the injury. For the current study, we selected participants aged over 15 years. To exclude individuals unlikely to be able to complete the cognitive assessment, we only included candidates with a 6-month post-TBI score above 3 on the Glasgow Outcome Score Extended (GOSE) [26]. Excluded were candidates with a severe pre-existing neurological disorder that would confound test outcomes.

2.2 Procedure

Demographic variables, pre-TBI history and TBI-related data were collected at the time of recruitment. Six months post-injury, candidates completed all self-report questionnaires and cognitive assessments under the supervision of a trained research nurse or neuropsychologist, who were instructed to record test validity issues using test completion codes [27], and results flagged as invalid were removed. When a visit to the research centre was not possible or candidates declined to take the neuropsychological tests, the self-report questionnaires were

sent by post. All efforts were made to obtain responses. The data collected was entered into an electronic case report form, de-identified and stored in a secure database.

2.3 Ethical Approval

The CENTER-TBI study (EC grant 602150) has been conducted in accordance with all relevant EU laws if directly applicable or of direct effect, and all relevant laws of the country where the recruiting sites are located, including but not limited to, the relevant privacy and data protection laws and regulations (the "Privacy Law"), the relevant laws and regulations on the use of human materials, and all relevant guidance relating to clinical studies from time to time in force including, but not limited to, the ICH Harmonised Tripartite Guideline for Good Clinical Practice (CPMP/ICH/135/95) ("ICH GCP") and the World Medical Association Declaration of Helsinki entitled "Ethical Principles for Medical Research Involving Human Subjects". Informed consent was obtained from all patients recruited in the Core Dataset of CENTER-TBI and documented in the electronic case report form. Ethical approval was obtained for each recruiting site. The list of sites, Ethics Committees, approval numbers and approval dates can be found on the following website: https://www.center-tbi.eu/project/ethical-approval.

2.4 Measures

Posttraumatic Stress Disorder Checklist for DSM-5 (PCL-5).

The PCL-5 is a self-report measure to screen for PTSD, determine PTSD symptom severity, monitor symptom change after treatment or make a provisional diagnosis of PTSD. Although a formal diagnosis requires a more thorough evaluation [28], the checklist includes 20 items reflecting the DSM-5 diagnostic criteria for PTSD. Patients are asked to indicate how much they have been bothered by each problem over the past month on a 5-point Likert scale ranging from 0 to 4. The sum score can range from 0 to 80, with higher scores indicating more pronounced symptoms. We used the four DSM-5 symptom cluster scores to arrive at a probable PTSD diagnosis to ensure that all PTSD symptoms and not just symptoms of depression

(cognition and mood) or arousal (arousal cluster) were present. Items with a score of 2 or higher are considered clinically relevant. For a probable diagnosis of PTSD, this needs to apply to at least one item in the intrusion and one item in the avoidance clusters, two or more negative alterations in cognition and mood, and two or more arousal symptoms. The symptom cluster method is a well-established measure with sensitivity scores up from 0.39 to 1.00 and specificity scores from 0.79 to 0.97 [29,30].

Other outcome instruments

Overall functional outcome was assessed by the Glasgow Outcome Scale-Extended (GOS-E) [26]. The GOSE has 8 categories: death, vegetative state, severe disability (lower and upper), moderate disability (lower and upper), and good recovery (lower and upper). A GOSE of less than 8 indicates that recovery is incomplete.

Symptoms of anxiety and depression were measured with respectively the Generalised Anxiety Disorder-7 (GAD-7) [31] and the Patient Health Questionnaire-9 (PHQ-9) [32]. The GAD-7 consists of 7 symptoms of anxiety that are rated on a four-point scale. Higher scores indicate more emotional distress. The clinical cut-off is a score of 8 or more. The PHQ-9 includes 9 symptoms of depression that are rated on a four-point scale. Higher scores indicate greater emotional distress. The clinical cut-off is a score of 10 or more.

Postconcussion symptoms were assessed with the Rivermead Post-concussion symptom Questionnaire (RPQ) [33]. The RPQ consists of 16 symptoms typically reported after concussion that are rated on a five-point scale. Higher scores indicate more severe symptoms. Scores equal to or greater than 16 were considered indicative of significant post-concussion symptoms [34].

Cognitive Assessment Battery.

The test battery comprised the Trail Making Test (TMT) [35,36], the Rey Auditory Verbal Learning Test (RAVLT) [37-39], and the Cambridge Neuropsychological Test Automated

Battery (CANTAB) [40-42]. The TMT is a two-part test that assesses information processing, attentional functioning and task switching/cognitive flexibility and the RAVLT assesses verbal learning and memory. The CANTAB is a computerised neuropsychological battery examining a range of domains including attention, memory and executive functioning. Using mainly nonverbal stimuli, the test is language- and culture-independent. We included the following subtests: the reaction time task (RTI), the attention switching task (AST), the spatial working memory task (SWM), the paired associate learning task (PAL), the rapid visual information processing task (RVP) and the stockings of Cambridge task (SOC). Appendix A provides an overview of the cognitive outcomes, which neuropsychological functions they reflect and short descriptions of the tests.

2.5 Statistical Analysis

We used SPSS version 27 for our analyses [43]. The CENTER-TBI data (version 2.1) was accessed using the bespoke data management tool Neurobot (https://neurobot.incf.org/).

To identify the neurocognitive test outcomes most strongly related to PTSD following TBI, we used multiple logistic regression, with the probable PTSD diagnosis as the binary dependent variable. Age, sex, educational level, history of psychiatric disorders and baseline Glasgow coma Scale (GCS) score [44] were entered as demographic and TBI-related covariates. Multiple imputation with chained equations was used to address missing data for these covariates, assuming the data was missing at random (educational level: n=92, GCS: n=30 and psychiatric history: n=8). Covariates were selected from the following tests; TMT-A, TMT-(B-A), RAVLT-immediate recall, RAVLT-interference recall, RAVLT-delayed recall, CANTAB RTI, AST, PAL, SOC, SWM and RVP. For comparability across tests, outcomes were converted to z-scores based on the sample descriptive statistics. We explored interaction effects of TBI severity and cognitive test scores on the PCL-5 diagnosis of PTSD. The primary analysis was a complete case analysis for the outcome of interest. As a sensitivity analysis, we

repeated our main analysis with the PCL-5 total score as the dependent variable in a linear regression.

Linear regression models were used to study the association between cognitive test outcomes and the four PCL-5 clusters (symptoms indicative of intrusion and/or avoidance, negative alterations in cognition and mood, and alterations in arousal).

For all linear and logistic models, model selection was based on covariate significance ($p < 0.2$) and adjusted R^2. The selection procedure only included the cognitive variables after controlling for demographic and injury-related variables. Multicollinearity was checked by means of the variance inflation factor (VIF). Models with an issue of multicollinearity were not considered (VIF > 4), [45]. In general, the RAVLT outcome variables were highly correlated and could not be entered simultaneously. Significance was set at $p < 0.01$.

3. Results

Of the 4,509 participants in the CENTER-TBI study, 2,863 met the inclusion criteria for the present study. Of these, 1,134 (39.6%) completed the PCL-5 and all cognitive tests, and were included in the complete case analysis (Figure 1) [46]. Most had suffered mild TBI (77.1%), with 7.2% and 13.1% having sustained moderate and severe TBI, respectively, 2.6% had a missing GCS.

[Figure 1 near here]

A total of 153 participants screened positive for PTSD (13.5%) on the PCL-5. Table 1 summarises the descriptive statistics of the study cohort differentiated for probable PTSD. The occurrence of PTSD differentiated for initial severity as defined by the GCS is presented in Appendix B, Figure 1. Probable PTSD occurred more frequently in patients with moderate TBI (17.1%) compared to those with mild (13.2%) or severe TBI (13.5%). Overall, the participants

with suspected PTSD were younger, had lower levels of education, more frequently reported a history of psychiatric disorders and had more often been injured in road traffic accidents or by violence. Six months post-TBI, two thirds of the study cohort had a GOSE score of 7 or 8, with 14.5% and 4.5%, respectively screening positive for PTSD. The participants with GOSE scores of 4, 5 and 6, were more likely to have PTSD (28.6%, 28.1% and 21.7%, respectively) (see Appendix B, Figure 2).

[Table 1 near here]

Compared to the participants with TBI only, participants with probable PTSD scored significantly worse on the TMT-A, TMT-(B-A), RAVLT immediate recall, interference recall, and delayed recall, and the SWM, RVP and RTI subtests from the CANTAB. The cognitive outcome scores (raw and z-scores) for participants with and without probable PTSD are shown in Appendix C.

3.1 Neuropsychological correlates of probable PTSD following TBI

The regression model associating probable PTSD with the results of cognitive tests is shown in Table 2 (Nagelkerke R^2=.081). After selection, only TMT-(B-A) and RAVLT-delayed recall were included in the final model in addition to the following fixed covariates: age, sex, educational level, psychiatric history and GCS. Adding other (sub)test scores did not improve the model. None of the interaction effects of GCS and subtest scores were significant. Higher TMT-(B-A) scores and lower RAVLT-delayed recall scores were significantly associated with the PCL-5-based diagnosis of PTSD, as were the fixed covariates age and psychiatric history. Associations with sex, educational level and GCS were not significant in the multivariable analysis.

[Table 2 near here]

Sensitivity analysis with the PCL-5 total score as the dependent variable is shown in Table 3 (Nagelkerke R^2=.058). Similar to our main results in table 2, higher TMT-(B-A) scores and lower RAVLT-delayed recall scores were significantly related to PTSD symptoms. In addition to age and psychiatric history, sex and GCS were also significantly related to PTSD symptoms. The association for educational level was not significant.

[Table 3 near here]

3.2 Neuropsychological correlates of PTSD clusters following TBI

Table 4 lists the results of the linear regression models predicting symptoms of intrusion, avoidance, negative alterations in cognition and mood, and alterations in arousal. The outcomes on the TMT-(B-A), the CANTAB RTI and the CANTAB SWM were significantly associated with the intrusion cluster, while only the TMT-(B-A) scores also showed significant associations with the avoidance cluster. Both the TMT-(B-A) and the RTI were related to both the cognition and mood cluster and the arousal cluster. Correlations between clusters are given in Appendix D.

[Table 4 near here]

3.3 Sensitivity analysis with imputed data

Of the 2,863 participants that met inclusion criteria, 1,994 (69.6%) had completed the full PCL-5. The response rate for the cognitive measures ranged from 46.5 to 61.8% (Figure 1). Appendix E shows the characteristics for the participants in our main analysis with complete sets of cognitive scores (n=1,134) and those with missing scores (n=1,729). Sensitivity analysis of all 2,863 study participants were performed with multiple imputation for missing data on demographics, TBI-related features, PCL-5 and cognitive test outcomes. The results show a similar pattern to those of the complete case analysis, with the TMT-(B-A) again being significantly associated with probable PTSD, however the association between the RAVLT-

delayed recall was no longer significant (Appendix F Table 1). Similar to the main analysis, the CANTAB-RTI is significantly associated to the intrusion, cognition and mood, and arousal symptoms. For the imputed data, TMT-(B-A) is only significantly related to intrusion symptoms, and the associations between TMT-(B-A) and avoidance, cognition and mood, and arousal, and the association between intrusive symptoms and SWM could not be confirmed (Appendix F Table 2).

4. Discussion

Exploring the neurocognitive correlates of probable PTSD following civilian TBI, we found task switching performance and, to a lesser extent, delayed verbal recall to be associated with probable PTSD after controlling for age, sex, educational level, history of psychiatric disorders and TBI severity. For each of the PTSD clusters, the severity of PTSD symptoms was associated with poorer task switching/ cognitive flexibility and lower processing speed. To our knowledge, we are the first to study PTSD in a large cohort of individuals having sustained TBI in the civilian setting while considering head trauma of all severities. The percentage of probable PTSD we obtained, i.e. 13.5%, is consistent with the overall prevalence rate reported in a recent meta-analysis of civilian TBI (15.6%, 95% CI:12.9-18.4), [9]. Rates were higher in patients with upper severe or moderate disability (24.0%) compared to those with a GOSE of 7 (14.5 %) or 8 (4.5 %).

4.1 Neuropsychological correlates of probable PTSD after TBI

We included the TMT-(B-A) as a measure of task switching/ cognitive flexibility and the RAVLT-delayed recall as component of long-term verbal memory since previous studies have shown the importance of executive functioning and verbal memory in differentiating between patients with co-occurring mild TBI and PTSD and patients with mild TBI only [18,19]. Pineau and colleagues (2014) found more pronounced attentional distraction in patients with PTSD than they did in those with mTBI only [18], with additional problems in long-term verbal memory in patients with both TBI and PTSD. A longitudinal study in a military population reported similar results, with impairments in verbal memory coinciding with increasing PTSD severity. Follow-up results showed an additional association between reduced proficiency in visual learning and memory, and PTSD severity [20]. Another study of veterans observed significant differences in executive functioning (cognitive flexibility), verbal fluency and verbal memory between individuals with mTBI and PTSD and those with PTSD without mTBI,

compared to veterans with mTBI only and a control group without either condition [19]. Extending previous findings to civilians and all TBI severities, the outcomes we obtained with the RAVLT-delayed recall confirm that this component of long-term verbal memory is associated with probable PTSD following TBI irrespective of the severity of the head trauma. The second correlate, cognitive flexibility as assessed with the TMT-(B-A), was even more strongly associated with probable PTSD/TBI compared to TBI only, which is also consistent with previous literature. However, cognitive functioning appears not to be specific for PTSD/mTBI as it was also observed in PTSD-only groups in previous studies [18,19]. In addition, we found lower age and history of psychiatric illness to be significantly related to probable PTSD after TBI. A pre-injury history of mental illness may thus point to a vulnerability for PTSD, which is a risk factor that clinicians need to take into account when treating patients having suffered a TBI.

4.2 Neuropsychological correlates of PTSD clusters following TBI

Examining the four PTSD symptom clusters (intrusion, avoidance, cognition and mood, and arousal) we found associations for processing speed and cognitive flexibility, in which higher levels of intrusion correlated with reduced processing speed and cognitive flexibility. Re-experiencing symptoms (e.g. recurring nightmares of the trauma or reliving the trauma) may be an expression of difficulties with directing attentional focus away from trauma-related cues [22]. Our complete case analysis revealed an additional association between visual working memory and the intrusion cluster. This finding is consistent with the idea that memory encoding and consolidation issues play a role in intrusive symptoms [24]. However, the sensitivity analysis with imputed data did not confirm the relationship between the CANTAB SWM task and intrusion. Reduced processing speed was highly associated with intrusive, cognition and mood, and arousal symptoms, but not to probable PTSD, a finding which was confirmed by the sensitivity analysis with imputed data. The finding that processing speed relates to PTSD

symptoms [20,47], but not to probable PTSD [18,19], is in line with previous studies. We also found that the cognitive correlates for the PTSD-specific (intrusion, avoidance) and non-specific symptoms (cognition and mood, arousal) are the same (TMT-B-A and RTI), with the strongest relation between speed and non-specific PTSD symptoms. That the same cognitive variables (TMT-B-A and CANTAB-RTI) were associated with the symptom burden in each of the four clusters, may be attributed to the fact that the PTSD cluster scores are highly correlated.

4.3 Limitations

As this is a cross-sectional study, we cannot draw any conclusions about causality. Moreover, although the 20-item PCL-5 self-report questionnaire can be used to screen for PTSD, it is insufficient for a formal diagnosis. However, to include all PTSD symptoms and not just symptoms of depression (cognition and mood cluster) or arousal (arousal cluster), we used the symptom cluster method to ensure that symptoms were present relating to all four DSM-5 cluster criteria, i.e. intrusion, avoidance, cognition and mood, and arousal [10].

Since model selection may increase the risk of type-I errors, we used the more stringent significance level of $p < 0.01$. Although the correlates we identified were significant, both for the complete case analysis and the sensitivity analysis of the imputed dataset of the full cohort, we recognise that the Nagelkerke R^2 was low, indicating that discriminatory performance was limited. The associations between cognitive functions and probable PTSD/PTSD symptoms are significant but effect sizes are small.

Limited information on premorbid functioning precluded us from controlling for potential pretrauma cognitive deficits or for cognitive abilities that may have buffered the effects of traumatic stress (e.g. cognitive control, emotion regulation, adaptive re-appraisal of trauma-related cognitions). In people dealing with PTSD following TBI, we need to be aware of possible response bias due to a lack of effort [48]. Although we did not include a formal

performance validity test, the examiners did record apparent low effort and test scores labelled as such were removed from the database. Additionally, rather than entire cognitive profiles, we compared cognitive functions separately while the development of PTSD will depend on the sum of protecting and obstructive cognitive functions. Further, we acknowledge that cognitive tests do not measure single, isolated functions. Cognitive concepts overlap, where an adequate attentional focus, for instance, is a condition for cognitive flexibility. We further recognize that patients screening positive for probable PTSD also had more postconcussion symptoms and symptoms of anxiety and depression. There is overlap between PTSD and postconcussion symptoms (e.g. sleep disturbance, poor memory, irritability), as well with symptoms of depression and anxiety, making accurate attribution complex. We decided not to enter these symptom scales into our regression models to prevent overcontrolling for these symptoms as they are part of the PTSD diagnosis (cluster mood/cognition and arousal). Instead, we performed PTSD cluster analysis which gave more insight in the PTSD-specific symptoms (intrusion, avoidance) and the non-specific symptoms (mood/cognition and arousal) and their relation with cognitive test scores. Finally, we did not control for cognitive-behavioural or psychopharmacological treatments in our analyses.

4.4 Conclusion and future directions

Our study showed that approximately one out of seven adults with TBI screens positive for probable PTSD six months after sustaining the head injury. Performance on tests of cognitive flexibility and, to a lesser extent, delayed verbal recall, are associated with probable PTSD following TBI, regardless of the severity of the injury.

Future research should investigate the impact of cognitive functioning after TBI on the natural course of PTSD symptoms, explore which cognitive strengths or weaknesses influence its course, and investigate the effects of PTSD treatment on attention, cognitive flexibility and verbal memory.

Irrespective of the need for future research, our findings have implications for clinical practice: All clinicians treating patients after TBI should be aware of the relatively high occurrence of PTSD after TBI. Structured follow-up of patients, especially after mild TBI, is often deficient and needs to be improved [49,50]. Our data suggest that all patients who do not attain full good recovery (GOSE = 8) should be screened for PTSD. The PCL-5, which has now been linguistically validated in many languages [51], provides a simple and efficient screening tool. Patients screening positive for probable PTSD should be referred for psychiatric or neuropsychological evaluation for diagnostic confirmation, cognitive evaluation and treatment.

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Disclosure of interest

The authors report no conflict of interest.

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Appendices

Appendix A. Cognitive Covariates

Test	Cognitive domain	Variable
Trail Making Test (TMT)		
TMT A	Attention and processing speed	TMT A: Connect numbers sequentially as fast as possible
TMT B-A	Task switching / Cognitive flexibility	TMT B: Connect numbers and letters alternately as fast as possible (TMT B minus A was calculated for analysis)
Rey Auditory Verbal Learning Test (RAVLT)		Repeat as many words as possible of a list of 15 unrelated words read by the assessor
RAVLT Immediate recall	Verbal short-term memory	Sum of the first 5 trials
RAVLT Interference recall	Interference	Trial 6 after an interference list
RAVLT Delayed recall	Verbal long-term memory	Trial 7 after 20 minutes
Cambridge Neuropsychological Test Automated Battery (CANTAB)		
CANTAB SWM: Spatial working memory	Spatial working memory	Find hidden tokens in displayed boxes. Outcome is the number of times a box is selected in which a token was already presented
CANTAB PAL: Paired associate learning	Visual learning and memory	Number of errors, adjusted for the estimated number of errors they would have made on any problems, attempts and unfinished items
CANTAB RVP: Rapid visual information processing task	Sustained attention and concentration	Detect specific sequences by pushing a button
CANTAB SOC: Stockings of Cambridge task	Spatial planning and problem solving	Number of occasions upon which the participant successfully completed a test problem in the minimum possible number of moves
CANTAB RTI : Choice Reaction Time	Processing speed	Median duration between the onset of the stimulus and the time at which button is released
CANTAB AST: Attention Switching Task	Attention, task switching	Difference between the median latency of responses between assessments in the block in which the rule was switched vs those in the block in which the rule remained constant. Close to zero indicates less variation in latencies across non-switch and switch trials.

Appendix B. Probable PTSD Diagnosis Differentiated for GCS and GOSE Rating

Figure 1. Probable PTSD diagnosis differentiated for GCS rating

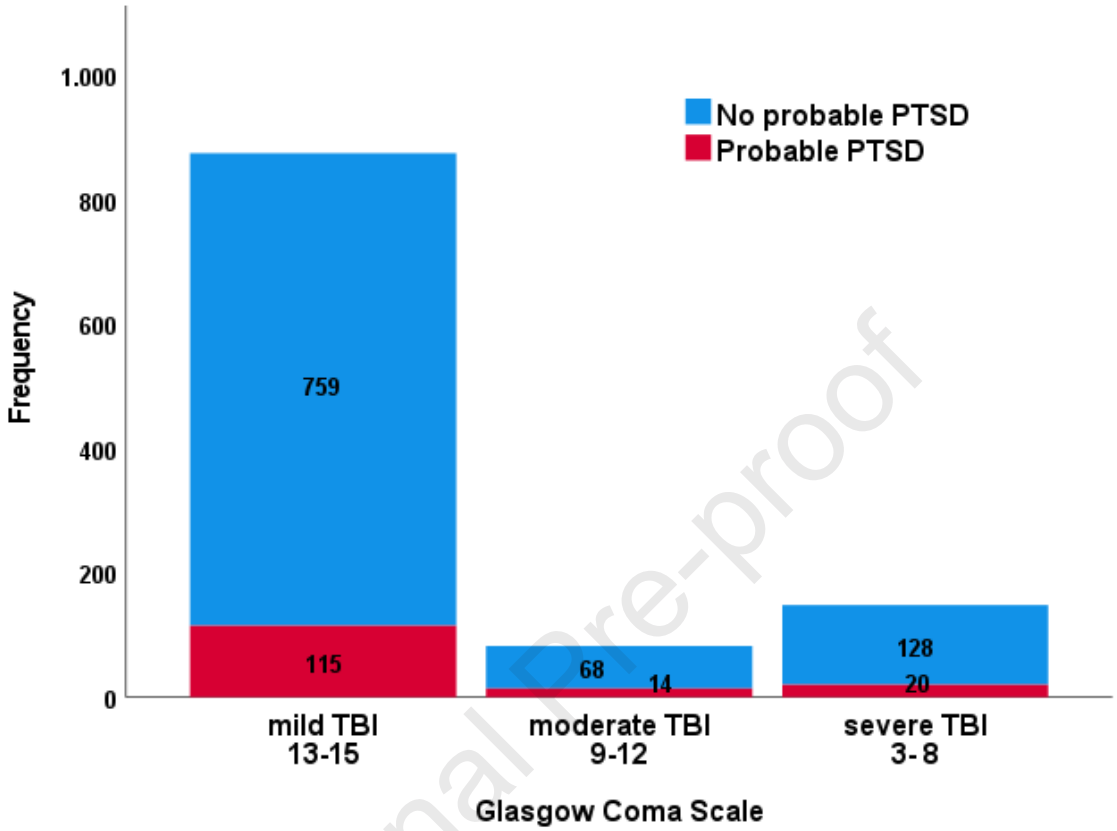
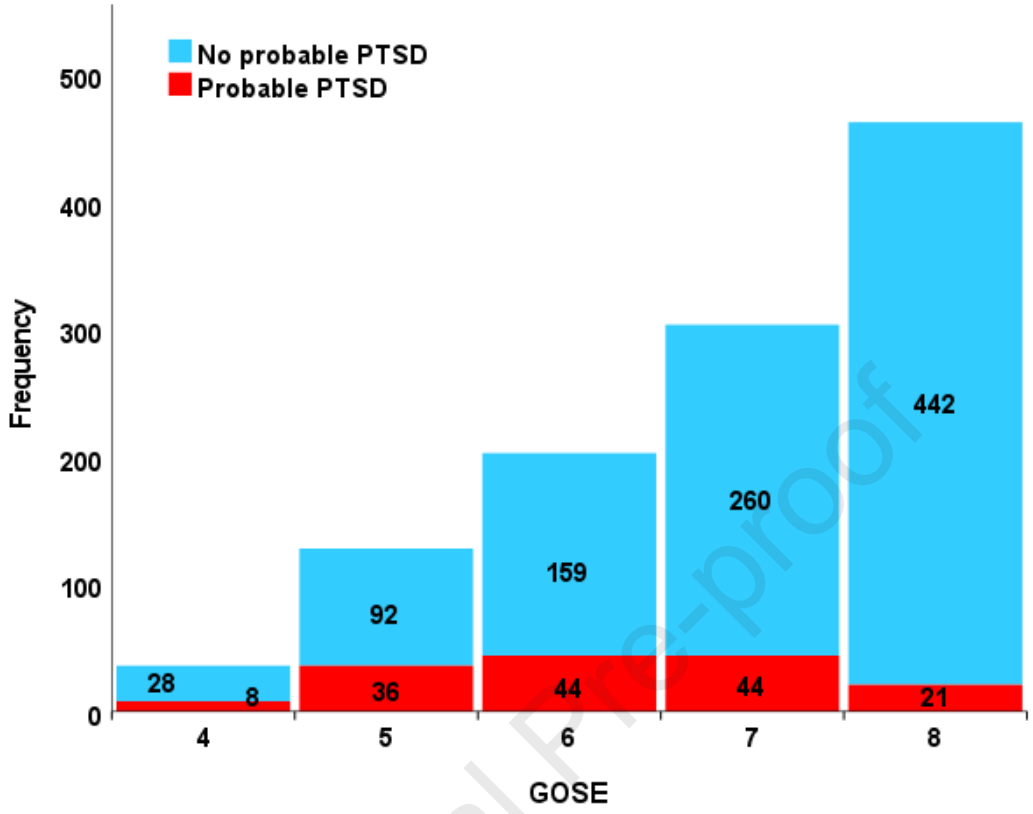


Figure 2. Probable PTSD diagnosis differentiated for GOSE rating



Note: GOSE 4: Upper Severe Disability – needs full assistance in activities of daily living, GOSE 5: Lower Moderate Disability – independent, but cannot resume work/school or all previous social activities, GOSE 6: Upper Moderate Disability – Some disability exists, but can partly resume work or previous activities, GOSE 7: Lower Good Recovery – Minor physical or mental deficits that affects daily life, GOSE 8: Upper Good Recovery – Full recovery or minor symptoms that do not affect daily life

Appendix C. Cognitive outcomes for probable or no PTSD

	Raw Scores				**Z-scores**		
	Probable PTSD (n=153)		**No probable PTSD (**n=981)		**Probable PTSD (**n=153)	**No probable PTSD (**n=981)	
	Mean (SD)	Min-Max	Mean (SD)	Min-Max	Mean (SD)	Mean (SD)	p-value
TMT-A	38.45 (18.70)	13-101	34.65 (16.93)	8-101	.19 (1.09)	-.03 (.98)	.011
TMT-(B-A)	62.17 (46.86)	12-248	49.34 (36.95)	-68-241	-.29 (1.21)	-.04 (.96)	.001
RAVLT Immediate	42.78 (11.33)	12-66	45.33 (11.31)	13-72	-.20 (1.01)	.03 (.99)	.009
RAVLT Interference	8.75 (3.47)	1-15	9.40 (3.37)	0-15	-.17 (1.02)	.03 (.99)	.027
RAVLT Delayed	8.38 (3.70)	1-15	9.18 (3.55)	0-15	-.19 (1.03)	.03 (.99)	.010
CANTAB SWM	30.90 (21.89)	0-118	27.15 (20.21)	0-88	.16 (1.07)	-.02 (.99)	.035
CANTAB PAL	25.31 (30.26)	0-134	22.98 (29.18)	0-156	.07 (1.03)	-.01 (1.00)	.36
CANTAB RVP	.88 (.06)	.66-1.00	.89 (.06)	.35-1.00	-.20 (1.00)	.03 (1.00)	.008
CANTAB SOC	8.01 (2.04)	3-12	8.25 (2.00)	2-12	-.10 (1.02)	.02 (1.00)	.18
CANTAB RTI	407.47 (146.59)	228.5- 1162.5	376.03 (92.57)	218.0-1168.0	.27 (1.44)	-.04 (.91)	.011
CANTAB AST	165.21 (166.48)	-99.5-633.5	164.02 (172.88)	-270.0-890.0	.01 (.97)	-.01 (1.01)	.94

Participants with complete outcome data (i.e. PCL-5 and all cognitive tests). Independent samples t-tests were conducted to compare outcomes for patients with and without probable PTSD.

Appendix D. Pearson correlations between symptom clusters

	Intrusion	Avoidance	Cognition/mood	Arousal
Intrusion		.74	.66	.69
Avoidance			.62	.60
Cognition/mood				.75
Arousal				

Significance level of each of the correlations: $p < .001$

Appendix E. Comparison of Patients Characteristics – for Patients with Outcome Data and with Missing Outcome Data (n=2863)

	Patients with outcome data (complete cases) n=1134	Patients with missing outcome data (added for sensitivity analysis) n=1729	p-value	Missing (%)
Age in years, Median (IQR)	47 [29-60]	51 [31-66]	*<.001*	0
Male, n (%)	775 (68.3)	1109 (64.1)	*.020*	0
Highest educational level, n (%)			*<.001*	12.4
Primary school or less	122 (11.7)	213 (14.5)		
Secondary school / High school	329 (31.6)	549 (37.5)		
Post-high school training	216 (20.7)	316 (21.6)		
College / University	375 (36.0)	387 (26.4)		
GCS, n (%)			0.78	2.9
Mild TBI	874 (79.2)	1309 (78.1)		
Moderate TBI	82 (7.4)	126 (7.5)		
Severe TBI	148 (13.4)	240 (14.3)		
Care pathway, n (%)			0.62	0
Emergency Room	269 (23.7)	398 (23.0)		
Admitted to hospital	426 (37.6)	681 (39.4)		
Intensive Care Unit	439 (38.7)	650 (37.6)		
History of psychiatric disorders, n (%)	124 (11.0)	240 (14.2)	*.013*	1.6

Patients with complete outcome data (incl. PCL-5 and all cognitive tests). Mann-Whitney Test for age and Pearson's Chi² test for other variables were conducted.

Appendix F. Sensitivity analysis of imputed data (n=2863)

Table 1. Logistic regression: covariates associated with probable PTSD 6 months post-TBI - sensitivity analysis of imputed data (full cohort).

Covariate	**B (SE(B))**	**Odds ratio (95% CI)**	**p-value[b]**	**VIF (range)[c]**
Age	-.026 (.004)	.97 (.96-.99)	*<.001*	1.30
Sex (male)	.26 (.16)	1.29 (.96-1.94)	.13	1.07-1.08
Educational level[a]				1.16-1.19
Primary school or less	.32 (.43)	1.38 (.85-2.41)	.48	
Secondary school / high school	.29 (.26)	1.33 (.83-1.99)	.29	
Post-high school training	.26 (.30)	1.30 (.71-2.32)	.41	
Psychiatric history[d]	.71 (.29)	2.03 (1.52-2.93)	.041	1.01
GCS	.038 (.021)	1.04 (.99-1.07)	.083	1.09
TMT-(B-A)	.25 (.065)	1.28 (1.13-1.50)	*<.001*	1.22-1.25
RAVLT Delayed recall	-.22 (.085)	.80 (.65-.99)	.013	1.36-1.41

Note: [a] Reference category: College / University, [b] Significance level $p < .01$, [c] VIF = variance inflation factor (range) of the original and 5 imputed datasets, [d] Information about the psychiatric history and type of psychiatric disorder(s) was obtained by interview from the patient and/or carer upon admission. Nagelkerke $R^2=.074$.

Table 2. Linear regression models: cognitive tests associated with the four PTSD symptom clusters – sensitivity analysis of imputed data

Covariates	**Intrusion cluster**		**Avoidance cluster**		**Cognition/Mood cluster**		**Arousal cluster**		
	B(SE)	**p-value[b]**	**B(SE)**	**p-value[b]**	**B(SE)**	**p-value[b]**	**B(SE)**	**p-value[b]**	**VIF (range)[c]**
Age	-.026 (.005)	*<.001*	-.014 (.002)	*<.001*	-.050 (.007)	*<.001*	-.033 (.005)	*<.001*	1.17-1.22
Sex (Male)	.17 (.15)	.26	.068 (.083)	.42	.12 (.24)	.62	.42 (.21)	.043	1.03-1.04
Educational level[a]									1.12-1.13
Primary school or less	.55 (.29)	.063	.15 (.13)	.27	.17 (.38)	.66	.47 (.34)	.17	
Secondary school / high school	.47 (.18)	*.008*	.16 (.090)	.071	.13 (.30)	.68	.15 (.23)	.53	
Post-high school training	.39 (.20)	.053	.17 (.10)	.11	.38 (.33)	.25	.76 (.28)	*.009*	
Psychiatric history[d]	1.36 (.32)	*.001*	.52 (.17)	.013	2.16 (.51)	*.002*	1.80 (.30)	*<.001*	1.01-1.02
GCS	.038 (.025)	.13	.022 (.011)	.052	-.091 (.039)	.032	.015 (.031)	.64	1.08-1.10
TMT-(B-A)	.33 (.088)	*<.001*	.13 (.054)	.028	.23 (.16)	.15	.32 (.14)	.045	1.30-1.35
CANTAB RTI	.34 (.10)	*.005*	.13 (.053)	.035	.61 (.11)	*<.001*	.50 (.10)	*<.001*	1.16-1.21
Nagelkerke R^2	.064		.051		.070		.061		

Note: [a] Reference category: College / University, [b] Significance level p < .01, [c] VIF = variance inflation factor (range) of the original and 5 imputed datasets, [d] Information about the psychiatric history and type of psychiatric disorder(s) was obtained by interview from the patient and/or carer upon admission

Appendix G. The CENTER-TBI Investigators and Participants

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Tables

Table 1. Participant characteristics

	Probable PTSD[a]	No probable PTSD	p-value
Demographic characteristics at baseline[b]	N=153	N=981	
Age in years, Median [IQR][c]	43 [28-55]	49 [30-61]	*.009*
Male, n (%)	102 (66.7)	673 (68.6)	.63
Highest educational level, n (%)			*.019*
Primary school or less	22 (15.6)	100 (11.1)	
Secondary school / High school	56 (39.7)	273 (30.3)	
Post-high school training	25 (17.7)	191 (21.2)	
College / University	38 (27.0)	337 (37.4)	
Missing	12	80	
Marital status, n (%)			.17
Never been married	49 (32.7)	304 (32.5)	
Married / Living together / common law	75 (50.0)	519 (55.4)	
Divorced / Separated / Widowed / Other	26 (17.3)	113 (12.1)	
Missing	3	45	
TBI-related characteristics at baseline[b]			
Glasgow Coma Scale, n (%)			.61
Mild TBI	115 (77.2)	759 (79.5)	
Moderate TBI	14 (9.4)	68 (7.1)	
Severe TBI	20 (13.4)	128 (13.4)	
Missing	4	26	
Cause of injury, n (%)			*.003*
Road traffic incident	74 (49.3)	435 (45.1)	
Incidental fall	45 (30.0)	397 (41.1)	
Violence / Assault / Act of mass violence	14 (9.3)	34 (3.5)	
Suicide attempt	3 (2.0)	9 (0.9)	
Other	14 (9.3)	90 (9.3)	
Missing	3	16	
Care pathway, n (%)			.058
Emergency Room	25 (16.3)	244 (24.9)	
Admitted to hospital	60 (39.2)	366 (37.3)	
Intensive care unit	68 (44.4)	371 (37.8)	
Psychiatric history[b,d]			
Psychiatric disorders, n (%)			*.001*
Yes	29 (19.1)	95 (9.8)	
No		879 (90.2)	

Missing	123 (80.9)	7	
	1		
Type of psychiatric disorder, n (%)			
Anxiety	7 (4.6)	27 (2.8)	.65
Depression	17 (11.1)	51 (5.2)	.64
Substance abuse	3 (2.0)	11 (1.1)	.85
Sleep disorder	3 (2.0)	15 (1.5)	.47
Schizophrenia	2 (1.3)	2 (0.2)	.20
Other	7 (4.6)	14 (1.4)	.24
Characteristics 6 months post-TBI[e]			
RPQ total score, Median [IQR]	23.0 [14.0-34.5]	4.0 [0-13.0]	*<.001*
PHQ-9 total score, Median [IQR]	10.5 [6.0-16.8]	2.0 [1.0-5.0]	*<.001*
GAD-7 total score Median [IQR]	8.0 [5.0-14.0]	1.0 [0-4.0]	*<.001*
Medication, n (%)			*.001*
Yes	43 (30.9)	168 (18.7)	
No	96 (69.1)	732 (81.3)	
Missing	14	81	
Type of medication, n (%)			
Psychostimulants	0 (0.0)	3 (0.3)	.38
Antidepressants	13 (8.5)	40 (4.1)	.39
Antipsychotic agents	3 (2.0)	9 (0.9)	.68
Anxiolytics	9 (5.9)	17 (1.7)	.054

Note: [a] Diagnosis based on the PCL-5 self-report questionnaire; [b] At study entry/TBI evaluation upon admission, [c] The Mann-Whitney Test was conducted for age and Pearson's Chi² tests for the other variables; [d] Information about the psychiatric history and type of psychiatric disorder(s) was obtained by interview from the patient and/or carer upon admission; [e] The Rivermead Postconcussion Questionnaire (RPQ, sum scores from 0 to 64 with higher scores reflecting more severe postconcussive symptoms), the Patient Health Questionnaire-9 (PHQ-9, sum scores from 0 to 27 with higher scores reflecting more severe depressive symptoms) and the Generalised Anxiety Disorder-7 (GAD-7, sum scores from 0 to 21 with higher scores reflecting higher levels of anxiety symptoms).

Table 2. Logistic regression: covariates associated with probable PTSD - primary analysis.

Covariate	**B (SE(B))**	**Odds ratio (95% CI)**	**p-value[b]**	**VIF (ranges)[c]**
Age	-.026 (.006)	.97 (.91-.99)	*<.001*	1.30
Sex (male)	.30 (.20)	1.34 (.91-1.98)	.14	1.07-1.08
Educational level[a]				1.16-1.19
Primary school or less	.13 (.31)	1.13 (.62-2.08)	.69	
Secondary school / high school	.23 (.24)	1.25 (.78-2.00)	.34	
Post-high school training	-.012 (.27)	.99 (.58-1.69)	.97	
Psychiatric history[d]	.79 (.24)	2.20 (1.37-3.53)	*.001*	1.01
GCS	.030 (.026)	1.03 (.98-1.09)	.25	1.09
TMT-(B-A)	.30 (.085)	1.35 (1.14-1.60)	*<.001*	1.22-1.25
RAVLT-delayed recall	-.30 (.10)	.74 (.61-.91)	*.004*	1.36-1.41

Note: [a] Reference category: college / university, [b] Significance level $p < .01$, [c] VIF = variance inflation factor (range) of the original and 5 imputed datasets, [d] Information about the psychiatric history and type of psychiatric disorder(s) was obtained by interview from the patient and/or carer upon admission

Table 3. Continuous analysis (linear regression) of covariates associated with PTSD symptoms – sensitivity analysis.

Covariate	**B**	**SE(B)**	**p-value[b]**	**VIF (ranges)[c]**
Age	-.13	.025	*.003*	1.30
Sex (male)	1.99	.87	*.001*	1.07-1.08
Educational level[a]				1.16-1.19
Primary school or less	1.30	1.41	.022	
Secondary school / high school	2.01	1.02	.060	
Post-high school training	1.08	1.10	.026	
Psychiatric history[d]	6.04	1.25	*.006*	1.01
GCS	.019	.12	*.004*	1.09
TMT-(B-A)	2.08	.43	*.003*	1.22-1.25
RAVLT-delayed recall	-.69	.46	*.002*	1.36-1.41

Note: [a] Reference category: college / university, [b] Significance level $p < .01$, [c] VIF = variance inflation factor (range) of the original and 5 imputed datasets, [d] Information about the psychiatric history and type of psychiatric disorder(s) was obtained by interview from the patient and/or carer upon admission

Table 4. Linear regression models: cognitive tests associated with the four PTSD symptom clusters – primary analysis.

Covariates	**Intrusion cluster**		**Avoidance cluster**			**Cognition/Mood cluster**		**Arousal cluster**		
	B(SE)	**p-value[b]**	**B(SE)**	**p-value[b]**	**VIF (range)[c]**	**B(SE)**	**p-value[b]**	**B(SE)**	**p-value[b]**	**VIF (range)[c]**
Age	-.037 (.007)	<.*001*	-.019 (.003)	<.*001*	1.33-1.34	-.048 (.009)	<.*001*	-.036 (.008)	<.*001*	1.15-1.16
Sex (Male)	.21 (.23)	.36	.10 (.12)	.38	1.05	.42 (.34)	.22	.78 (.29)	.*007*	1.03-1.04
Educational level[a]					1.13-1.15					1.11-1.13
Primary school or less	.77 (.39)	.049	.023 (.19)	.90		-.061 (.55)	.91	.53 (.47)	.26	
Secondary school / high school	.71 (.29)	.016	.22 (.13)	.11		.39 (.40)	.33	.59 (.34)	.084	
Post-high school training	.33 (.30)	.26	.085 (.15)	.57		.19 (.44)	.67	.67 (.38)	.082	
Psychiatric history[d]	1.19 (.34)	.*001*	.53 (.17)	.*002*	1.01	2.39 (.49)	<.*001*	1.88 (.42)	<.*001*	1.01
GCS	.081 (.031)	.010	.026 (.016)	.092	1.09-1.10	-.073 (.045)	.10	.032 (.039)	.41	1.08
TMT-(B-A)	.41 (.12)	.*001*	.21 (.061)	.*001*	1.35-1.36	.46 (.18)	.*009*	.53 (.15)	<.*001*	1.28-1.29
CANTAB RTI	.35 (.12)	.*002*	.15 (.057)	.010	1.19	.67 (.17)	<.*001*	.52 (.14)	<.*001*	1.16-1.17
CANTAB SWM	.38 (.13)	.*003*	.15 (.063)	.020	1.44-1.47					
Nagelkerke R^2	.075		.057			.061		.059		

Note: [a] Reference category: college / university, [b] Significance level p < .01, [c] VIF = variance inflation factor (range) of the original and 5 imputed datasets, [d] Information about the psychiatric history and type of psychiatric disorder(s) was obtained by interview from the patient and/or carer upon admission

Figure

Figure 1

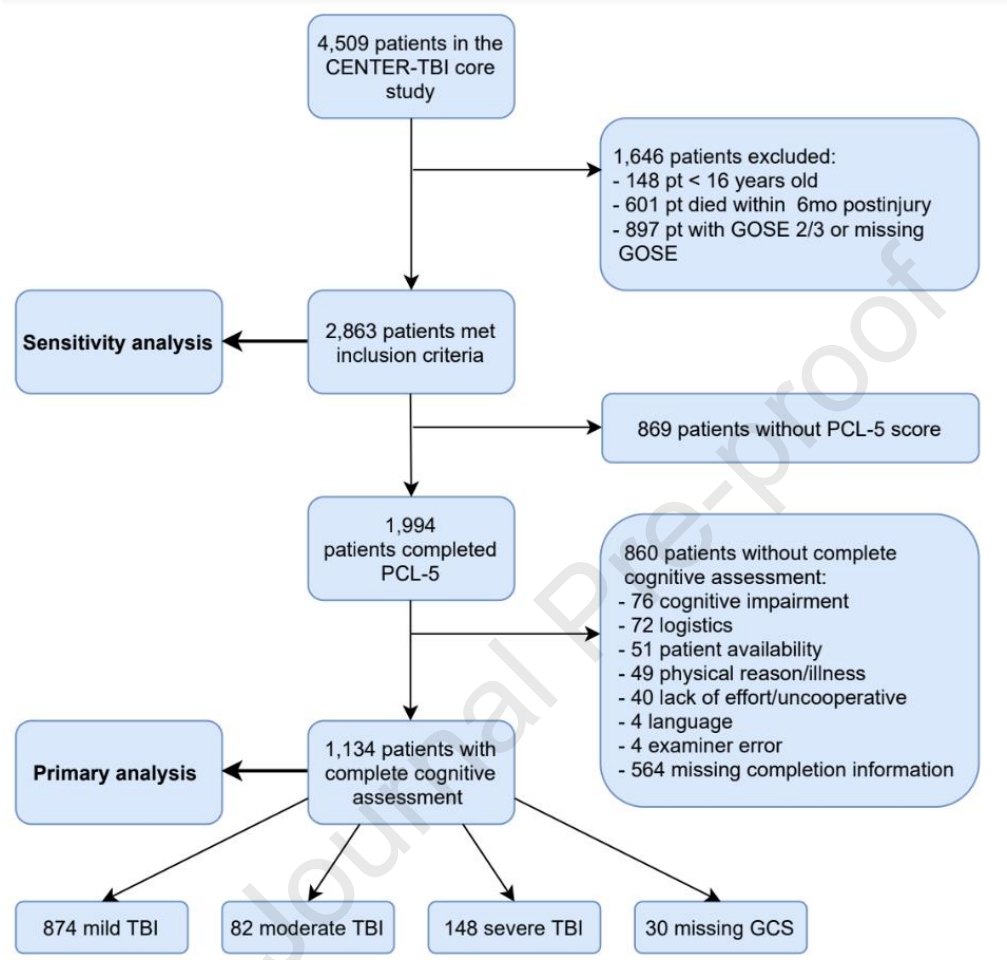

Figure caption

Figure 1. Flowchart of patient inclusion and exclusion

Highlights

- Six months after traumatic brain injury 13.5% of people screen positive for PTSD
- Task switching performance and verbal memory are related to probable PTSD
- PTSD severity is related to processing speed and task switching performance

Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: