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Understanding the relationship between cognitive performance and function in daily life after traumatic brain injury

Lindsay Wilson[1], Lindsay Horton[1], Kevin Kunzmann[2], Barbara J. Sahakian[3], Virginia J Newcombe[4], Emmanuel A. Stamatakis[4], Nicole von Steinbuechel[5], Katrin Cunitz[5], Amra Covic[5], Andrew Maas[6], Dominique van Praag[7], David Menon[4] and the CENTER-TBI participants and investigators*

[1] Division of Psychology, University of Stirling, Stirling, UK
[2] MRC Biostatistics Unit, University of Cambridge, UK
[3] Department of Psychiatry, University of Cambridge, Cambridge, UK
[4] Division of Anaesthesia, University of Cambridge, Addenbrooke's Hospital, Cambridge, UK
[5] Institute of Medical Psychology and Medical Sociology, University Medical Center Goettingen and Georg-August-University, Goettingen
[6] Department of Neurosurgery, Antwerp University Hospital and University of Antwerp, Edegem, Belgium
[7]Department of Psychology, Antwerp University Hospital and University of Antwerp, Edegem, Belgium

* Listed at end of the manuscript

Corresponding author:
Lindsay Wilson
Division of Psychology
University of Stirling
Stirling FK9 4LA
UK

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Abstract

Objective: Cognitive impairment is a key cause of disability after traumatic brain injury (TBI) but relationships with overall functioning in daily life are often modest. The aim is to examine cognition at different levels of function and identify domains associated with disability.

Methods: 1554 patients with mild to severe TBI were assessed at six months post-injury on the Glasgow Outcome Scale - Extended (GOSE), the Short Form-12v2, and a battery of cognitive tests. Outcomes across GOSE categories were compared using ANCOVA adjusting for age, sex, and education.

Results: Overall effect sizes were small to medium, and greatest for tests involving processing speed (η_p^2 0.057 to 0.067) and learning and memory (η_p^2 0.047 to 0.051). Deficits in cognitive performance were particularly evident in patients who were dependent (GOSE 3 or 4) or who were unable to participate in one or more major life activities (GOSE 5). At higher levels of function (GOSE 6 to 8), cognitive performance was surprisingly similar across categories. There were decreases in performance even in patients reporting complete recovery without significant symptoms. Medium to large effect sizes were present for summary measures of cognition (η_p^2 0.111), mental health (η_p^2 0.131) and physical health (η_p^2 0.252).

Conclusions: This large-scale study provides novel insights into cognitive performance at different levels of disability and highlights the importance of processing speed in function in daily life. At upper levels of outcome any influence of cognition on overall function is markedly attenuated and differences in mental health are salient.

Key words: Traumatic brain injury, cognition, functional outcome, prospective observational study

Running head: Cognition and functional outcome after TBI

INTRODUCTION

TBI is a leading cause of disability, creating a huge burden on individuals and society.[1] Over half of patients presenting with mild TBI report limitations in function at 6 months,[2] and disability may persist for many years.[3] Despite a high prevalence, much of this disability is unexplained, representing a barrier to effective treatment.[4] Studies show that cognitive test performance is associated with aspects of function in daily life after TBI, including independence and return to work.[5,6] However, the relationship between cognitive impairment and everyday functioning is incompletely understood.

It is often assumed that cognitive impairment will have a strong influence on overall functional outcome; however, reported associations are typically modest.[6] Chaytor et al[5] found that cognitive test performance accounted for 20% to 30% of outcome variance on the Functional Status Exam, which provides a multi-domain evaluation of function. A systematic review[7] of studies relating cognition to global functional outcome found that multiple dimensions of cognition were associated with the Glasgow Outcome Scale – Extended (GOSE), explaining 31% of the variance in outcome. However, these studies were relatively small, with a median sample size of 135 (range 37-334).[7] As a consequence, there is little information concerning cognitive performance at different levels of functional recovery.

Past work indicates that cognitive impairment is present in individuals who are unable to return to work, and is even greater in those that are dependent. However, the role of cognition in higher levels of functional recovery is unclear. Impaired performance on cognitive tests has been reported in individuals graded as Good Recovery on the GOSE.[8] Possible explanations include unrecognized cognitive impairment identified by objective testing, poorly matched normative data for tests, or use of a coarse global scale.

We address these issues by studying the relationship of the GOSE to cognitive assessment in a cohort of patients who form part of the Collaborative European NeuroTrauma Effectiveness Research (CENTER-TBI) project (www.center-tbi.eu).[9] Over 1500 patients had detailed cognitive assessment at 6 months, providing an opportunity for more fine-grained analyses than hitherto possible. The aim of our study was to better characterize the association between cognitive performance and global functional outcome, and to tackle key questions concerning this relationship.

METHODS

Participants

CENTER-TBI recruited 4509 patients to core data collection from 65 centres.[9] Criteria for inclusion were: a diagnosis of TBI, clinical indication for a CT scan, presentation within 24 hours of injury, and consent obtained.[9] The study enrolled patients from emergency rooms, hospital admissions, and intensive care units. Participants were only excluded if they had a severe pre-existing neurological disorder that would confound outcome assessments. The sample thus included patients with very mild injuries, as well as those at the most severe end of the spectrum. Analyses here were confined to patients aged 16 or older who had been assessed on the GOSE at the six-month time point and had completed one or more computerized cognitive tests (Supplementary figure S1). The last criterion was included to select the main group that had contributed cognitive data.

Procedure

Demographic and clinical data were recorded during the acute stage. A composite baseline Glasgow Coma Scale (GCS) was created using assessment at the time of emergency room (ER) discharge as the preferred measure, and where that was not available, working progressively earlier in time. The first Computed Tomography (CT) scan after injury was used to identify whether imaging abnormalities were present.

All patients were scheduled for follow-up at the six-month time point, which is the focus of the current study. When translations of assessments were not available from the publisher, the material originally in English was translated into local languages using a process of linguistic validation based on guidelines.[10] Patients agreeing to neuropsychological assessment were seen face-to-face. Assessors recorded completion codes for cognitive assessments, which included reasons for non-completion.[11]

Outcome assessments

Cognitive performance

The battery consisted of the Rey Auditory Verbal Learning Test (RAVLT), the Trail Making Task (TMT) part A and B, and 6 subtests from the Cambridge Neuropsychological Test Automated Battery (CANTAB). The CANTAB tasks are language independent, facilitating multinational use. Details of the assessments are provided in Table 1 and in supplementary methods. Cognitive tests covered areas known to be affected by TBI, including memory and learning, processing speed, attention, and aspects of executive functions. Procedures for conducting testing were specified in a study manual, and assessors were given face to face training in testing.

Table 1. Cognitive tests included in the CENTER-TBI battery, the domains that they primarily assess, and the specific measures that were used in analyses.

Test	Domains	Measure
CANTAB Paired Associate Learning (PAL)	Visual learning and memory	Total errors adjusted (i.e. errors for all trials, allowing for trials not completed)
Rey Auditory-Verbal Learning Task (RAVLT)	Verbal learning and memory	Total correct words recalled for the 15-item principal list over 5 trials
Trail Making Test A (TMT A)	Attention and processing speed	Time to draw lines between 25 numbers in sequence (secs)
Trail Making Test B (TMT B)	Attention and processing speed, task switching	Time to draw lines in alternating sequence between 13 numbers and 12 letters (secs)
CANTAB Choice Reaction Time (RTI)	Processing speed	Median decision time for correct responses (msec)
	Motor speed	Median movement time for correct responses (msec)
CANTAB Rapid Visual Processing (RVP)	Sustained attention	A' (A prime): accuracy of target detection calculated from hits and correct rejections
	Sustained attention	Latency of correct responses (msec)
CANTAB Attention Switching Task (AST)	Attention, task switching	Total correct responses
	Attention, task switching	Median latency of correct responses (msec)

CANTAB Spatial Working Memory (SWM)	Strategy and working memory	Between errors: number times a search is incorrectly repeated for the same location.
CANTAB Stockings of Cambridge (SOC)	Planning, problem solving	Trials solved in the minimum possible moves

Global functional outcome and health-related quality of life

Glasgow Outcome Scale – Extended. The GOSE was assessed either as a structured interview[12] or a questionnaire completed by the patient or carer.[13] A composite GOSE was created by scoring both the interview and the questionnaire centrally, and combining the ratings, with the interview as the preferred source (94% of assessments). Outcome categories on the GOSE are: Upper Good Recovery (8), Lower Good Recovery (7), Upper Moderate Disability (6), Lower Moderate Disability (5), Upper Severe Disability (4), and Lower Severe Disability (3). Criteria used to assign the categories are detailed in supplementary methods (Table S1).

Short-Form-12v2 (SF-12v2). The SF-12v2 is a 12-item health-related quality of life assessment completed by the patient.[14] The Physical Component Summary (PCS) provides an overall measure of global functional outcome, while the Mental Component Summary (MCS) assesses outcome related to aspects of mental health. When the SF-12v2 had not been completed, but the Short Form-36v2 was available, we used the 12 corresponding items from the latter to derive summary scores. Outcomes are expressed as T-scores (standardized using the normative sample to a mean of 50 and standard deviation (SD) of 10).

Statistical analyses

A reference group was created by dividing patients who reported complete recovery (GOSE 8) into two groups: GOSE 8a consisted of patients with GCS=15 at recruitment and no abnormality on early CT, while GOSE 8b consisted of remaining patients with Upper Good Recovery. The reference group was GOSE 8a, and our expectation was that individuals in this group would be at the very mildest end of the spectrum of TBI severity, and therefore least likely to have persisting cognitive impairment. These “ultra-mild” patients are matched to the whole group with respect to the experience of the clinical processes associated with TBI. As a check on the reference group, previously published normative data was used to calculate expected mean scores allowing for the age distribution of the patient group. Demographic and clinical characteristics of the GOSE 8a and GOSE 8b subgroups were compared using chi-square for categorical variables and t-testing for age.

Distributions of scores on individual tests were inspected, and a log 10 transform was applied to reduce unequal variance in measures from the following: Trail Making A and B, RTI, PAL, RVP, SWM and AST latency. To provide a common metric for tests, cognitive measures were converted to z-scores using the mean and standard deviation of the reference group (i.e. group GOSE 8a). Scores were coded so that negative values indicated poorer performance than reference. A composite cognition score was calculated by averaging z-scores across tests, when six or more cognitive outcomes were available. Scores that were one or more SDs below the reference were considered to indicate at least borderline cognitive impairment.

GOSE categories were compared using one-way ANCOVA, adjusting for age, sex and level of education. ANCOVA is a linear model, with test score as the dependent variable. Missing values for level of education were imputed using the mice function in R to generate ten datasets.[15] Outcomes were included in the imputation process, but imputed values of outcomes were not used in subsequent analyses. Pooled estimates for adjusted means and 95% confidence intervals (CIs) were

derived from the ANCOVA. CIs are provided to aid interpretation of the graphed results: differences between means are considered to have p<.05 when the CIs overlap less than 50%, and p<.01 when they do not overlap.[16] The CIs do not make any adjustment for multiple comparisons. Pooled F-values for the omnibus comparison from the imputed datasets were obtained using the mi.anova function in R. Controlling for the family-wise error rate (FWER) the significance threshold is (0.05/15) 0.0033. Effect sizes from the ANCOVA are partial eta-squared (η_p^2), with a conventional interpretation 0.01 = small, 0.06 = medium, and 0.14 = large. We conducted 15 pairwise comparisons (12 cognitive tests and 3 composites) of the adjusted means of outcomes for groups GOSE 8a and GOSE 8b, and controlled the results for a 15% false discovery rate using the Benjamini and Hochberg procedure.[17] In contrast to FWER adjustment, this procedure corrects for multiple comparisons where differences on specific individual tests are not critical to the overall conclusion.

Data was collected on an electronic case report form (Quesgen Systems Inc, USA), hosted on the International Neuroinformatics Facility (INCF) platform and extracted via INCF Neurobot (INCF, Sweden). Version 2.1 of the CENTER-TBI database was downloaded on 10th November 2019, and analyses were conducted using SPSS 25.0 and R 3.5.1 (R Foundation for Statistical Computing, Vienna, Austria).

Ethical approval

Ethical approval was obtained for each recruiting site, and consent was obtained in all patients according to national and local procedures. A complete ethics statement can be found at https://www.center-tbi.eu/project/ethical-approval

RESULTS

Assessment of cognitive performance at 6 months was carried out in 1554 patients out of 2604 survivors with a GOSE follow-up. Cognitive test completion rates were influenced by GOSE category (see supplementary Table S2): patients with GOSE 3 had the lowest completion rates (8%-21% across cognitive tests), followed by patients with GOSE 4 (35%-57%), while completion rates for patients with higher GOSE outcomes were substantially greater, and generally around 70% (GOSE 5 59%-74%, GOSE 6 65%-81%, GOSE 7, 62%-79%, and GOSE 8, 53% - 69%). In the GOSE 3 category a common reason given for non-completion was the presence of cognitive or neurological deficits (supplementary Table S2). Over all categories, logistical reasons and patient availability were most commonly cited for non-completion. Since the absolute number of individuals tested in the GOSE 3 category was small (N=31), GOSE 3 and 4 were combined into one category of patients with severe disability (GOSE 3/4, N=115).

Demographic and clinical information concerning the study sample is given in Table 2, and corresponding information for the whole sample and the sample alive and eligible for assessment at 6 months is provided in supplementary Table S3. Compared to the non-study group, the study sample were more likely to have progressed to a higher level of education, and were more likely to be working and partnered before injury. The study group were also less severely injured by GCS and AIS criteria than the non-study group, and had better outcomes on the GOSE. Patients who had completed some cognitive assessment are therefore a selected subgroup of the eligible sample, particularly in relation to injury severity and outcome.

Information concerning the subgroups with Upper Good Recovery (GOSE 8a and GOSE 8b) is given in Table 2. There were significant differences between subgroups on variables reflecting severity of injury (baseline GCS, care pathway, imaging abnormality, and both head and neck and non-head and

neck AIS scores). On demographics, differences for employment history reached significance, but not for age, sex, race, level of education, or marital status.

Table 2. Demographic and clinical characteristics of the study sample, and the two subgroups with GOSE 8 (Upper Good Recovery). GOSE 8a is used as a reference in subsequent analyses, and consists of patients with GCS=15 at recruitment and no abnormality on early CT; GOSE 8b consists of remaining patients with Upper Good Recovery. Tests for significance are for comparison of groups GOSE 8a and GOSE 8b.

	N (%)						
	Study sample (n=1554)		GOSE 8a (n=301)		GOSE 8b (n=302)		P
Age							
Mean (SD)	47.9	(18.8)	47.5	(18.9)	46.8	(21.2)	0.663
Sex							
Female	513	(33)	94	(31)	77	(25)	0.141
Male	1041	(67)	207	(69)	225	(75)	
Race							
Caucasian	1465	(97)	292	(98)	288	(98)	1.00
Other	38	(3)	6	(2)	6	(2)	
Missing	51		3		8		
Highest level of education							
Primary	182	(13)	29	(10)	44	(16)	0.056
Secondary	468	(33)	90	(32)	90	(33)	
Training	300	(21)	59	(21)	38	(14)	
College	461	(33)	106	(37)	99	(37)	
Missing	143		17		31		
Employment Status							
Working (full or part time)	852	(58)	176	(60)	139	(49)	0.032
Not working	117	(8)	15	(5)	19	(7)	
Retired	317	(22)	65	(22)	73	(26)	
Student/ homemaker	180	(12)	36	(12)	54	(19)	
Missing	88		9		17		
Marital status							
Partnered	805	(54)	161	(55)	149	(51)	0.707
Previously partnered	207	(14)	36	(12)	37	(13)	
Single/ other	469	(32)	98	(33)	105	(36)	
Missing	73		6		11		
Care pathway							
Emergency Room	346	(22)	179	(60)	42	(14)	<0.001
Admitted to hospital	588	(38)	109	(36)	153	(51)	
Intensive Care Unit	620	(40)	13	(4)	107	(35)	

Table 2 (continued)

	N (%)						
	Study sample (n=1554)		GOSE 8a (n=301)		GOSE 8b (n=302)		p
ASA Pre-injury Physical Health							
Healthy patient	943	(61)	183	(61)	205	(69)	0.159
Mild systemic disease	469	(30)	93	(31)	73	(24)	
Severe systemic disease	129	(8)	22	(7)	21	(7)	
Missing	13		3		3		
Cause of injury							
Road traffic accident	671	(44)	97	(33)	109	(37)	0.549
Fall	644	(42)	150	(51)	137	(46)	
Violence/assault	87	(6)	21	(7)	26	(9)	
Other	124	(8)	29	(10)	25	(8)	
Missing/ unknown	28		4		5		
GCS score at baseline							
3-8	224	(15)			28	(10)	<0.001
9-12	107	(7)			29	(10)	
13-15	1181	(78)	301	(100)	227	(80)	
Missing	42				18		
CT Imaging abnormality							
Absent	654	(44)	301	(100)	55	(21)	<0.001
Present	843	(56)			213	(79)	
Missing/ uninterpretable	57				34		
Head & neck AIS[1]							
No injury/ Minor injury	284	(18)	131	(44)	27	(9)	<0.001
Moderate injury	231	(15)	99	(33)	39	(13)	
Serious injury	523	(34)	63	(21)	148	(49)	
Severe injury	271	(17)	5	(2)	52	(17)	
Critical injury/ unsurvivable injury	245	(16)	3	(1)	36	(12)	
Major extracranial injury[2]							
Absent	1029	(66)	254	(84)	225	(75)	0.004
Present	525	(34)	47	(16)	77	(26)	
GOSE at six months							
3/4 Severe Disability	115	(7)					
5 Lower Moderate Disability	184	(12)					
6 Upper Moderate Disability	250	(16)					
7 Lower Good Recovery	402	(26)					
8 Upper Good Recovery	603	(39)	301	(100)	300	(100)	

[1]Head & neck AIS = maximum Abbreviated Injury Score for head, neck and cervical regions.
[2]Any non-head & neck AIS ≥ 3 (serious injury)

Raw scores for assessments of the reference group were compared with norms predicted from the healthy population (see supplementary Table S4). For some cognitive tests the reference group scores are almost identical to the predicted scores (Trail Making A and B, RTI Choice reaction time,

SOC problems solved), while for others they are better (RTI movement time, RVP latency, SWM Between Errors) or worse (PAL total errors, RAVLT, RVP A prime). Overall, there are no systematic trends that would indicate cognitive impairment in the reference group. The SF-12v2 summary score means for the reference group were close to norms.

Percentages of scores one SD or more below the reference group mean are given in Table 3. The scores are based on z-scores of transformed variables and have not been adjusted for covariates. The expectation from the normal distribution is that 16% of scores will be one SD or more below the mean. As can be seen, tests for the reference group conform closely to expectation (13% to 20%), while the percentages of clinically significant scores for the most disabled groups (GOSE 3/4 and GOSE 5) are always greater than 16% (20% to 59%).

Table 3. Number (percentage ±95% confidence interval) of standardized test scores 1 SD or more below the mean for the reference group (GOSE 8a). The expected value from the normal distribution is 16%.

	GOSE Category						
	3/4	5	6	7	8b	8a	Total
PAL Total Errors Adjusted	47(44%±9%)	51(28%±6%)	47(19%±5%)	92(23%±4%)	57(19%±4%)	53(18%±4%)	347(23%±2%)
RAVLT Total recall of principal list	61(59%±9%)	58(34%±7%)	54(22%±5%)	108(28%±4%)	73(25%±5%)	48(17%±4%)	402(27%±2%)
Trail Making Part A time (secs)	63(59%±9%)	62(35%±7%)	43(18%±5%)	91(23%±4%)	72(25%±5%)	44(15%±4%)	375(25%±2%)
Trail Making Part B time (secs)	52(53%±10%)	53(31%±7%)	49(20%±5%)	78(20%±4%)	68(23%±5%)	41(14%±4%)	341(23%±2%)
RTI Choice Reaction Time (msec)	49(48%±10%)	58(33%±7%)	34(14%±4%)	78(20%±4%)	49(17%±4%)	43(16%±4%)	311(22%±2%)
RTI Movement Time (msec)	42(41%±9%)	48(27%±7%)	38(16%±5%)	74(19%±4%)	31(11%±4%)	37(14%±4%)	270(19%±2%)
RVP A prime	37(48%±11%)	54(35%±7%)	51(23%±5%)	76(22%±4%)	51(19%±5%)	40(15%±4%)	309(23%±2%)
RVP latency (msec)	33(43%±11%)	44(28%±7%)	40(18%±5%)	63(18%±5%)	49(18%±5%)	36(13%±4%)	265(20%±2%)
AST Total correct	51(51%±10%)	54(31%±7%)	40(17%±5%)	103(27%±4%)	60(21%±5%)	53(19%±5%)	361(25%±2%)
AST latency (msec)	39(39%±9%)	44(25%±6%)	39(17%±5%)	65(17%±4%)	40(14%±4%)	46(16%±4%)	273(19%±2%)
SWM Between errors	35(37%±10%)	35(20%±6%)	36(15%±5%)	75(20%±4%)	55(19%±4%)	32(11%±4%)	268(18%±2%)
SOC Problems solved	29(35%±10%)	33(20%±6%)	44(19%±5%)	81(22%±4%)	64(23%±5%)	57(20%±5%)	308(22%±2%)

The results of omnibus comparisons of outcome categories adjusting for age, sex and level of education are given in Table 4. Estimated means and 95% CIs for each measure are shown in Figure 1, after adjusting for covariates. As can be seen, there are differences in cognitive performance across groups for all measures. Overall effect sizes were small to medium (Table 4), and greatest for tests involving processing speed (RTI Decision Time and Trail Making Test A and B) and learning and memory (PAL and RAVLT), followed by tests of sustained attention (RVP) and attention switching (AST). The smallest effect sizes were observed for two tasks assessing executive functions (SWM and SOC).

Table 4. Summary of ANCOVA for the overall difference across GOSE categories adjusted for age, sex, and education level. Statistics are based on pooling after multiple imputation of education level.

Measure	N	F	(df1, df2)	P	η_p^2
PAL Total errors adjusted	1525	16.41	(5,1053801)	<0.0001	0.052
RAVLT total	1489	14.74	(5, 186787)	<0.0001	0.048
Trail Making Part A	1510	21.44	(5, 402889)	<0.0001	0.067
Trail Making Part B	1473	20.71	(5, 41897)	<0.0001	0.067
RTI Decision time	1443	17.28	(5, 371581)	<0.0001	0.057
RTI Movement time	1443	11.94	(5, 907334)	<0.0001	0.040
RVP A prime	1350	9.79	(5, 147074)	<0.0001	0.035
RVP latency	1350	11.77	(5, 163509)	<0.0001	0.042
AST Total correct	1467	9,12	(5, 46026)	<0.0001	0.031
AST latency	1467	12.06	(5, 884657)	<0.0001	0.040
SWM Between errors	1464	6.49	(5, 397235)	<0.0001	0.022
SOC problems solved	1421	3.62	(5, 182029)	0.0026	0.013

Notes: η_p^2 = partial eta-squared

Figure 1 indicates generally monotonic associations between cognitive test performance and order of outcome categories. Lower cognitive performance was particularly evident in patients who were dependent (GOSE 3 or 4) or who were unable to participate in one or more major life activities (GOSE 5). As can be seen from Figure 1, these two groups consistently have poorest performance. On many measures (PAL, RAVLT, TMT A and B, RVP latency, RTI and AST), there are clear differences between GOSE 5 and GOSE 6 (i.e. the CIs do not overlap). In contrast, performance for the groups with GOSE 6, 7, and 8 was surprisingly similar across categories (i.e. many of the CIs overlap by 50% or more).

Figure 1 about here

Overall effect sizes from ANCOVA for the three summary measures were medium to large: 0.11 for cognition (F=36.98, df 5, 36425, p<.0.0001), 0.25 for the physical health summary (F=100.74, df 5, 110351, p<0.0001), and 0.13 for the mental health summary (F=45.22, df 5, 2680243, p<0.0001). Figure 2 displays z-score differences from group GOSE 8a.

Figure 2 about here

Inspection of Table 3 and Figure 1 suggests small but systematic deficits in cognitive performance in GOSE group 8b compared to 8a. The following pairwise comparisons between these groups met the Benjamini and Hochberg criteria (raw p values in brackets): Trail Making Part A (p=0.007), cognition composite (p=0.013), RAVLT (p=0.027), AST correct (p=0.042), RTI Reaction Time (p=0.050), RVP latency (p=0.067), Trail Making Part B (p=0.077), and SWM Between errors (p=0.079). There are thus

systematic differences in cognitive performance between Groups 8a and 8b. In contrast the groups had similar the physical and mental health summary scores (p=0.417 and 0.956, respectively).

DISCUSSION

Cognitive impairment is believed to be a key driver of disability, but important gaps remain in our understanding of this relationship. The current study provides two key pieces of information about this relationship: (1) it identifies cognitive domains most strongly related to function in daily life, and (2) it establishes where cognitive deficits most impact on difference between levels of function.

Prior to discussing the main findings, it is appropriate to consider the issue of missing data.[18] Much past work on cognition in TBI has used test completion as an inclusion criterion (either explicitly or implicitly), and thus provides little information on completion rates. In clinical trials that have included cognitive outcomes as an endpoint, completion by around half of patients recruited has been reported.[19,20] We found that completion of cognitive assessments was strongly related to outcome on the GOSE, a result that echoes a report by Clifton and colleagues.[21] In their group of 110 cases included in the Traumatic Coma Data Bank there was 6 month cognitive assessment in 60% of patients with Good Recovery while only 6% of patients with Severe Disability were tested. Explanations include cognitive impairment that prevents testing and logistical factors relating to availability of patients who are dependent.[19] Particular caution is therefore needed concerning interpretation of findings for the severely disabled category (as indicated in Figure 2). The comparison of completers and non-completers suggests other factors, such as level of education, play a role in follow-up but the differences here appear relatively minor.

Cognitive domain and function in daily life

The results provide novel insight into cognitive test performance at different levels of disability, and highlight the particular importance of processing speed in function in daily life. TMT part A and RTI Decision Time are both measures of processing speed and were among tests showing the greatest differences between outcome categories. TMT part B adds task switching demands, but this did not appear to make the task more sensitive. We conclude that processing speed has the strongest overall relationship with functional outcome in current analyses. In addition to processing speed, learning and memory and aspects of attention were related to functional outcome, while two measures of executive function showed the smallest differences across categories of outcome. This cognitive profile replicates that reported by Salmond et al [22] and may reflect cholinergic dysfunction. Impairment of processing speed and on tasks such as SOC implicates other neurochemical systems, including dopaminergic pathways.[23]

Our findings are concordant with previous evidence that processing speed particularly influences functional outcome at 12 months post-injury.[24] Furthermore, Ponsford and colleagues[25] found that slow processing speed was the area of cognition most strongly related to the GOSE 10 years after TBI, implying that this deficit has a long-term impact.[26]

It is thought that slowing disrupts timing and synchrony of mental operations and has a general impact on cognitive function.[23] Processing speed after TBI is thus a prime target for pharmaceutical interventions,[23,27] and the current study supports the potential value of cognitive enhancers for improving function in daily life. The critical impact of processing speed in this context may be explained by the widely distributed neuroanatomical network which underpins it, and hence makes it vulnerable to diffuse pathologies.[28-30]

Cognition and level of functional recovery

The study allowed cognitive performance across levels of disability to be examined in greater detail than previously. The most disabled groups showed clearest evidence of poor cognitive performance. In addition, as already noted, many severely disabled patients did not complete testing, consistent with profound cognitive impairment in this group. There were also clear decreases in performance in patients with GOSE 5. Individuals in this category are unable to participate in one or more major areas of activity, such as work or social and leisure activities. Cognitive assessment in these cases can identify particular barriers to functional recovery, and areas that can be targeted by rehabilitation.[31]

A surprising finding is that cognitive performance is similar across higher levels of functional recovery (GOSE 6 to 8b), explaining why the amount of variance in functional outcome accounted for by cognition can be modest.[5,7] In these groups, decreases in performance are small, and any evidence of impairment limited to a minority. It appears to have been assumed in the past that the relationship between the GOSE and cognition is essentially linear. It has been suggested, for example, that cognitive testing could help to improve the granularity of upper categories of functional outcome.[32] However, our findings argue against such a conception of the relationship.

The comparison of group GOSE 8b with the reference group shows that some cognitive impairment is present even in patients reporting complete recovery. The influence of cognitive impairment on function may be attenuated by active compensation.[33] For example, the person with cognitive slowing may adapt by taking greater time and effort to complete tasks, show increased compensatory recruitment (e.g. of the prefrontal cortex) in processing speed tasks,[34] and report more fatigue,[35] in keeping with greater effort. Subtle changes in cognition are thus still likely to be consequential, and could, for example, be a source of stress in demanding work settings. In the long-term cognitive decline will reduce reserve, and may make the individual vulnerable to the effects of degenerative illness in later years.[36] Formal cognitive assessment is valuable to establish whether impairment is present, even in individuals who have apparently recovered well.

Diffuse white matter changes are a key neuropathological substrate for both cognitive deficits and poor daily life outcomes.[37] Newcombe and colleagues [38] found that diffusion tensor imaging (DTI) abnormalities were related to the GOSE, and report findings qualitatively very similar to the trajectory shown for cognitive impairment in Figure 2. We therefore hypothesize that cognitive impairment is a major mediator of the relationship between diffuse white matter damage and poor functional outcome after TBI.

Comparison of cognitive, physical, and mental health outcomes

In contrast to the cognitive outcomes, there are clear differences in mental and physical health-related outcomes at the upper levels of recovery. Comparison with the SF-12v2 physical health summary argues against the idea that the relative coarseness of the GOSE explains absence of cognitive differences at upper levels of recovery: participants with GOSE 8a and GOSE 8b are close to the healthy norm, and thus unlikely to include a substantial subgroup with functional limitations. Furthermore, there are clear differences in SF-12v2 mental and physical health outcomes across GOSE categories 6 to 8b, and no overlap that would explain the similarity in cognitive performance between these groups.

Overall, the findings indicate contrasting relationships of cognition and mental health with functional outcome after TBI. Cognitive impairment appears to be a key influence on disability at lower levels of outcome. On the other hand, differences in aspects of mental health are prominent at upper levels of recovery,[8] and seem likely to play a role in whether the person achieves a complete

recovery. Although relationships between function in daily life and mental health will be bi-directional, understanding mental health problems provides a clear focus for treatment which may also improve functional outcome.

The physical health component of the SF-12v2 tracks outcome across GOSE categories, confirming a close relationship between these assessments of global functional outcome.[39] It is also likely that aspects of physical health, such as continuing effects of extracranial injury, are drivers of overall functional outcomes, particularly in individuals with mild injuries.[40]

These findings are important in the context of developing multidimensional outcome measures which characterise outcome beyond the GOSE.[41] Our data indicate that assessments of cognitive performance and psychological health are likely to have distinct contributions across different parts of the outcome spectrum. The findings thus strongly support separate evaluation of cognition, mental health, and function in daily life after TBI as multidimensional descriptors of outcome.

Limitations and future directions

The reference group was at the very mildest end of the spectrum but may nonetheless have included individuals with impaired cognitive performance, and this would result in underestimation of the extent of impairment. Use of additional markers of brain injury, such as post-traumatic amnesia, MR imaging, or biomarkers could help to define a reference group. The use of an internal comparison group provides a strong control for factors associated with TBI, including variables not explicitly measured such as accident trauma and aspects of TBI care. While acknowledging that it is a conservative approach, the comparison provides even greater confidence in the differences found.

As already discussed, a further limitation of the study concerns missing outcomes. Since this inevitably includes some individuals with the greatest cognitive impairment, the effect will be to lead to underestimation of cognitive impairment in the most disabled categories of outcome.

To our knowledge, this is the first study of cognition in TBI large enough to describe in detail performance at different levels of functional outcome. Unexpectedly, we found little difference in cognitive performance at upper levels of outcome. This raises two key issues for future research. The first concerns the drivers of outcome and whether emotional and mental health factors play a key role at the upper end of functional recovery.[42] The second relates to the nature and significance of cognitive impairment in these patients. The instruments we used address cognition without the contextual stresses of everyday life. Further, they do not account for increased cognitive fatigability reported by many patients, and provide only limited measures of the effortfullness of these tasks,[43] which have identifiable neuroanatomic correlates.[44] Tests of “hot cognition”[45] and measures of effortfullness and fatigue may bring additional value to assessments, and identify potential targets for therapy.

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***The CENTER-TBI participants and investigators:**

Cecilia Åkerlund[1], Krisztina Amrein[2], Nada Andelic[3], Lasse Andreassen[4], Audny Anke[5], Anna Antoni[6], Gérard Audibert[7], Philippe Azouvi[8], Maria Luisa Azzolini[9], Ronald Bartels[10], Pál Barzó[11], Romuald Beauvais[12], Ronny Beer[13], Bo-Michael Bellander[14], Antonio Belli[15], Habib Benali[16], Maurizio Berardino[17], Luigi Beretta[9], Morten Blaabjerg[18], Peter Bragge[19], Alexandra Brazinova[20], Vibeke Brinck[21], Joanne Brooker[22], Camilla Brorsson[23], Andras Buki[24], Monika Bullinger[25], Manuel Cabeleira[26], Alessio Caccioppola[27], Emiliana Calappi [27], Maria Rosa Calvi[9], Peter Cameron[28], Guillermo Carbayo Lozano[29], Marco Carbonara[27], Simona Cavallo[17], Giorgio Chevallard[30], Arturo Chieregato[30], Giuseppe Citerio[31, 32], Iris Ceyisakar[33], Hans Clusmann[34], Mark Coburn[35], Jonathan Coles[36], Jamie D. Cooper[37], Marta Correia[38], Amra Čović [39], Nicola Curry[40], Endre Czeiter[24], Marek Czosnyka[26], Claire Dahyot-Fizelier[41], Paul Dark[42], Helen Dawes[43], Véronique De Keyser[44], Vincent Degos[16], Francesco Della Corte[45], Hugo den Boogert[10], Bart Depreitere[46], Đula Đilvesi [47], Abhishek Dixit[48], Emma Donoghue[22], Jens Dreier[49], Guy-Loup Dulière[50], Ari Ercole[48], Patrick Esser[43], Erzsébet Ezer[51], Martin Fabricius[52], Valery L. Feigin[53], Kelly Foks[54], Shirin Frisvold[55], Alex Furmanov[56], Pablo Gagliardo[57], Damien Galanaud[16], Dashiell Gantner[28], Guoyi Gao[58], Pradeep George[59], Alexandre Ghuysen[60], Lelde Giga[61], Ben Glocker[62], Jagoš Golubovic[47], Pedro A. Gomez [63], Johannes Gratz[64], Benjamin Gravesteijn[33], Francesca Grossi[45], Russell L. Gruen[65], Deepak Gupta[66], Juanita A. Haagsma[33], Iain Haitsma[67], Raimund Helbok[13], Eirik Helseth[68], Lindsay Horton [69], Jilske Huijben[33], Peter J. Hutchinson[70], Bram Jacobs[71], Stefan Jankowski[72], Mike Jarrett[21], Ji-yao Jiang[58], Faye Johnson[73], Kelly Jones[53], Mladen Karan[47], Angelos G. Kolias[70], Erwin Kompanje[74], Daniel Kondziella[52], Evgenios Koraropoulos[48], Lars-Owe Koskinen[75], Noémi Kovács[76], Ana Kowark[35], Alfonso Lagares[63], Linda Lanyon[59], Steven Laureys[77], Fiona Lecky[78, 79], Didier Ledoux[77], Rolf Lefering[80], Valerie Legrand[81], Aurelie Lejeune[82], Leon Levi[83], Roger Lightfoot[84], Hester Lingsma[33], Andrew I.R. Maas[44], Ana M. Castaño-León[63], Marc Maegele[85], Marek Majdan[20], Alex Manara[86], Geoffrey Manley[87], Costanza Martino[88], Hugues Maréchal[50], Julia Mattern[89], Catherine McMahon[90], Béla Melegh[91], David Menon[48], Tomas Menovsky[44], Ana Mikolic[33], Benoit Misset[77], Visakh Muraleedharan[59], Lynnette Murray[28], Ancuta Negru[92], David Nelson[1], Virginia Newcombe[48], Daan Nieboer[33], József Nyirádi[2], Otesile Olubukola[78], Matej Oresic[93], Fabrizio Ortolano[27], Aarno Palotie[94, 95, 96], Paul M. Parizel[97], Jean-François Payen[98], Natascha Perera[12], Vincent Perlbarg[16], Paolo Persona[99], Wilco Peul[100], Anna Piippo-Karjalainen[101], Matti Pirinen[94], Horia Ples[92], Suzanne Polinder[33], Inigo Pomposo[29], Jussi P. Posti [102], Louis Puybasset[103], Andreea Radoi [104], Arminas Ragauskas[105], Rahul Raj[101], Malinka Rambadagalla[106], Jonathan Rhodes[107], Sylvia Richardson[108], Sophie Richter[48], Samuli Ripatti[94], Saulius Rocka[105], Cecilie Roe[109], Olav Roise[110,111], Jonathan Rosand[112], Jeffrey V. Rosenfeld[113], Christina Rosenlund[114], Guy Rosenthal[56], Rolf Rossaint[35], Sandra Rossi[99], Daniel Rueckert[62], Martin Rusnák[115], Juan Sahuquillo[104], Oliver Sakowitz[89, 116], Renan Sanchez-Porras[116], Janos Sandor[117], Nadine Schäfer[80], Silke Schmidt[118], Herbert Schoechl[119], Guus Schoonman[120], Rico Frederik Schou[121], Elisabeth Schwendenwein[6], Charlie Sewalt[33], Toril Skandsen[122, 123], Peter Smielewski[26], Abayomi Sorinola[124], Emmanuel A. Stamatakis[48], Simon Stanworth[40], Robert Stevens[125], William Stewart[126], Ewout W. Steyerberg[33, 127], Nino Stocchetti[128], Nina Sundström[129], Anneliese Synnot[22, 130], Riikka Takala[131], Viktória Tamás[124], Tomas Tamosuitis[132],

Mark Steven Taylor[20], Braden Te Ao[53], Olli Tenovuo[102], Alice Theadom[53], Matt Thomas[86], Dick Tibboel[133], Marjolein Timmers[74], Christos Tolias[134], Tony Trapani[28], Cristina Maria Tudora[92], Peter Vajkoczy [135], Shirley Vallance[28], Egils Valeinis[61], Zoltán Vámos[51], Mathieu van der Jagt[136], Gregory Van der Steen[44], Joukje van der Naalt[71], Jeroen T.J.M. van Dijck [100], Thomas A. van Essen[100], Wim Van Hecke[137], Caroline van Heugten[138], Dominique Van Praag[139], Thijs Vande Vyvere[137], Roel P. J. van Wijk[100], Alessia Vargiolu[32], Emmanuel Vega[82], Kimberley Velt[33], Jan Verheyden[137], Paul M. Vespa[140], Anne Vik[122, 141], Rimantas Vilcinis[132], Victor Volovici[67], Nicole von Steinbüchel[39], Daphne Voormolen[33], Petar Vulekovic[47], Kevin K.W. Wang[142], Eveline Wiegers[33], Guy Williams[48], Lindsay Wilson[69], Stefan Winzeck[48], Stefan Wolf[143], Zhihui Yang[142], Peter Ylén[144], Alexander Younsi[89], Frederick A. Zeiler[48,145], Veronika Zelinkova[20], Agate Ziverte[61] , Tommaso Zoerle[27]

[1] Department of Physiology and Pharmacology, Section of Perioperative Medicine and Intensive Care, Karolinska Institutet, Stockholm, Sweden
[2] János Szentágothai Research Centre, University of Pécs, Pécs, Hungary
[3] Division of Surgery and Clinical Neuroscience, Department of Physical Medicine and Rehabilitation, Oslo University Hospital and University of Oslo, Oslo, Norway
[4] Department of Neurosurgery, University Hospital Northern Norway, Tromso, Norway
[5] Department of Physical Medicine and Rehabilitation, University Hospital Northern Norway, Tromso, Norway
[6] Trauma Surgery, Medical University Vienna, Vienna, Austria
[7] Department of Anesthesiology & Intensive Care, University Hospital Nancy, Nancy, France
[8] Raymond Poincare hospital, Assistance Publique – Hopitaux de Paris, Paris, France
[9] Department of Anesthesiology & Intensive Care, S Raffaele University Hospital, Milan, Italy
[10] Department of Neurosurgery, Radboud University Medical Center, Nijmegen, The Netherlands
[11] Department of Neurosurgery, University of Szeged, Szeged, Hungary
[12] International Projects Management, ARTTIC, Munchen, Germany
[13] Department of Neurology, Neurological Intensive Care Unit, Medical University of Innsbruck, Innsbruck, Austria
[14] Department of Neurosurgery & Anesthesia & intensive care medicine, Karolinska University Hospital, Stockholm, Sweden
[15] NIHR Surgical Reconstruction and Microbiology Research Centre, Birmingham, UK
[16] Anesthesie-Réanimation, Assistance Publique – Hopitaux de Paris, Paris, France
[17] Department of Anesthesia & ICU, AOU Città della Salute e della Scienza di Torino - Orthopedic and Trauma Center, Torino, Italy
[18] Department of Neurology, Odense University Hospital, Odense, Denmark
[19] BehaviourWorks Australia, Monash Sustainability Institute, Monash University, Victoria, Australia
[20] Department of Public Health, Faculty of Health Sciences and Social Work, Trnava University, Trnava, Slovakia
[21] Quesgen Systems Inc., Burlingame, California, USA
[22] Australian & New Zealand Intensive Care Research Centre, Department of Epidemiology and Preventive Medicine, School of Public Health and Preventive Medicine, Monash University, Melbourne, Australia
[23] Department of Surgery and Perioperative Science, Umeå University, Umeå, Sweden

[24] Department of Neurosurgery, Medical School, University of Pécs, Hungary and Neurotrauma Research Group, János Szentágothai Research Centre, University of Pécs, Hungary
[25] Department of Medical Psychology, Universitätsklinikum Hamburg-Eppendorf, Hamburg, Germany
[26] Brain Physics Lab, Division of Neurosurgery, Dept of Clinical Neurosciences, University of Cambridge, Addenbrooke's Hospital, Cambridge, UK
[27] Neuro ICU, Fondazione IRCCS Cà Granda Ospedale Maggiore Policlinico, Milan, Italy
[28] ANZIC Research Centre, Monash University, Department of Epidemiology and Preventive Medicine, Melbourne, Victoria, Australia
[29] Department of Neurosurgery, Hospital of Cruces, Bilbao, Spain
[30] NeuroIntensive Care, Niguarda Hospital, Milan, Italy
[31] School of Medicine and Surgery, Università Milano Bicocca, Milano, Italy
[32] NeuroIntensive Care, ASST di Monza, Monza, Italy
[33] Department of Public Health, Erasmus Medical Center-University Medical Center, Rotterdam, The Netherlands
[34]Department of Neurosurgery, Medical Faculty RWTH Aachen University, Aachen, Germany
[35] Department of Anaesthesiology, University Hospital of Aachen, Aachen, Germany
[36] Department of Anesthesia & Neurointensive Care, Cambridge University Hospital NHS Foundation Trust, Cambridge, UK
[37] School of Public Health & PM, Monash University and The Alfred Hospital, Melbourne, Victoria, Australia
[38] Radiology/MRI department, MRC Cognition and Brain Sciences Unit, Cambridge, UK
[39] Institute of Medical Psychology and Medical Sociology, Universitätsmedizin Göttingen, Göttingen, Germany
[40] Oxford University Hospitals NHS Trust, Oxford, UK
[41] Intensive Care Unit, CHU Poitiers, Potiers, France
[42] University of Manchester NIHR Biomedical Research Centre, Critical Care Directorate, Salford Royal Hospital NHS Foundation Trust, Salford, UK
[43] Movement Science Group, Faculty of Health and Life Sciences, Oxford Brookes University, Oxford, UK
[44] Department of Neurosurgery, Antwerp University Hospital and University of Antwerp, Edegem, Belgium
[45] Department of Anesthesia & Intensive Care, Maggiore Della Carità Hospital, Novara, Italy
[46] Department of Neurosurgery, University Hospitals Leuven, Leuven, Belgium
[47] Department of Neurosurgery, Clinical centre of Vojvodina, Faculty of Medicine, University of Novi Sad, Novi Sad, Serbia
[48] Division of Anaesthesia, University of Cambridge, Addenbrooke's Hospital, Cambridge, UK
[49] Center for Stroke Research Berlin, Charité – Universitätsmedizin Berlin, corporate member of Freie Universität Berlin, Humboldt-Universität zu Berlin, and Berlin Institute of Health, Berlin, Germany
[50] Intensive Care Unit, CHR Citadelle, Liège, Belgium
[51] Department of Anaesthesiology and Intensive Therapy, University of Pécs, Pécs, Hungary
[52] Departments of Neurology, Clinical Neurophysiology and Neuroanesthesiology, Region Hovedstaden Rigshospitalet, Copenhagen, Denmark
[53] National Institute for Stroke and Applied Neurosciences, Faculty of Health and Environmental Studies, Auckland University of Technology, Auckland, New Zealand

[54] Department of Neurology, Erasmus MC, Rotterdam, the Netherlands
[55] Department of Anesthesiology and Intensive care, University Hospital Northern Norway, Tromso, Norway
[56] Department of Neurosurgery, Hadassah-hebrew University Medical center, Jerusalem, Israel
[57] Fundación Instituto Valenciano de Neurorrehabilitación (FIVAN), Valencia, Spain
[58] Department of Neurosurgery, Shanghai Renji hospital, Shanghai Jiaotong University/school of medicine, Shanghai, China
[59] Karolinska Institutet, INCF International Neuroinformatics Coordinating Facility, Stockholm, Sweden
[60] Emergency Department, CHU, Liège, Belgium
[61] Neurosurgery clinic, Pauls Stradins Clinical University Hospital, Riga, Latvia
[62] Department of Computing, Imperial College London, London, UK
[63] Department of Neurosurgery, Hospital Universitario 12 de Octubre, Madrid, Spain
[64] Department of Anesthesia, Critical Care and Pain Medicine, Medical University of Vienna, Austria
[65] College of Health and Medicine, Australian National University, Canberra, Australia
[66] Department of Neurosurgery, Neurosciences Centre & JPN Apex trauma centre, All India Institute of Medical Sciences, New Delhi-110029, India
[67] Department of Neurosurgery, Erasmus MC, Rotterdam, the Netherlands
[68] Department of Neurosurgery, Oslo University Hospital, Oslo, Norway
[69] Division of Psychology, University of Stirling, Stirling, UK
[70] Division of Neurosurgery, Department of Clinical Neurosciences, Addenbrooke's Hospital & University of Cambridge, Cambridge, UK
[71] Department of Neurology, University of Groningen, University Medical Center Groningen, Groningen, Netherlands
[72] Neurointensive Care , Sheffield Teaching Hospitals NHS Foundation Trust, Sheffield, UK
[73] Salford Royal Hospital NHS Foundation Trust Acute Research Delivery Team, Salford, UK
[74] Department of Intensive Care and Department of Ethics and Philosophy of Medicine, Erasmus Medical Center, Rotterdam, The Netherlands
[75] Department of Clinical Neuroscience, Neurosurgery, Umeå University, Umeå, Sweden
[76] Hungarian Brain Research Program - Grant No. KTIA_13_NAP-A-II/8, University of Pécs, Pécs, Hungary
[77] Cyclotron Research Center , University of Liège, Liège, Belgium
[78] Centre for Urgent and Emergency Care Research (CURE), Health Services Research Section, School of Health and Related Research (ScHARR), University of Sheffield, Sheffield, UK
[79] Emergency Department, Salford Royal Hospital, Salford UK
[80] Institute of Research in Operative Medicine (IFOM), Witten/Herdecke University, Cologne, Germany
[81] VP Global Project Management CNS, ICON, Paris, France
[82] Department of Anesthesiology-Intensive Care, Lille University Hospital, Lille, France
[83] Department of Neurosurgery, Rambam Medical Center, Haifa, Israel
[84] Department of Anesthesiology & Intensive Care, University Hospitals Southhampton NHS Trust, Southhampton, UK
[85] Cologne-Merheim Medical Center (CMMC), Department of Traumatology, Orthopedic Surgery and Sportmedicine, Witten/Herdecke University, Cologne, Germany

[86] Intensive Care Unit, Southmead Hospital, Bristol, Bristol, UK
[87] Department of Neurological Surgery, University of California, San Francisco, California, USA
[88] Department of Anesthesia & Intensive Care,M. Bufalini Hospital, Cesena, Italy
[89] Department of Neurosurgery, University Hospital Heidelberg, Heidelberg, Germany
[90] Department of Neurosurgery, The Walton centre NHS Foundation Trust, Liverpool, UK
[91] Department of Medical Genetics, University of Pécs, Pécs, Hungary
[92] Department of Neurosurgery, Emergency County Hospital Timisoara , Timisoara, Romania
[93] School of Medical Sciences, Örebro University, Örebro, Sweden
[94] Institute for Molecular Medicine Finland, University of Helsinki, Helsinki, Finland
[95] Analytic and Translational Genetics Unit, Department of Medicine; Psychiatric & Neurodevelopmental Genetics Unit, Department of Psychiatry; Department of Neurology, Massachusetts General Hospital, Boston, MA, USA
[96] Program in Medical and Population Genetics; The Stanley Center for Psychiatric Research, The Broad Institute of MIT and Harvard, Cambridge, MA, USA
[97] Department of Radiology, University of Antwerp, Edegem, Belgium
[98] Department of Anesthesiology & Intensive Care, University Hospital of Grenoble, Grenoble, France
[99] Department of Anesthesia & Intensive Care, Azienda Ospedaliera Università di Padova, Padova, Italy
[100] Dept. of Neurosurgery, Leiden University Medical Center, Leiden, The Netherlands and Dept. of Neurosurgery, Medical Center Haaglanden, The Hague, The Netherlands
[101] Department of Neurosurgery, Helsinki University Central Hospital
[102] Division of Clinical Neurosciences, Department of Neurosurgery and Turku Brain Injury Centre, Turku University Hospital and University of Turku, Turku, Finland
[103] Department of Anesthesiology and Critical Care, Pitié -Salpêtrière Teaching Hospital, Assistance Publique, Hôpitaux de Paris and University Pierre et Marie Curie, Paris, France
[104] Neurotraumatology and Neurosurgery Research Unit (UNINN), Vall d'Hebron Research Institute, Barcelona, Spain
[105] Department of Neurosurgery, Kaunas University of technology and Vilnius University, Vilnius, Lithuania
[106] Department of Neurosurgery, Rezekne Hospital, Latvia
[107] Department of Anaesthesia, Critical Care & Pain Medicine NHS Lothian & University of Edinburg, Edinburgh, UK
[108] Director, MRC Biostatistics Unit, Cambridge Institute of Public Health, Cambridge, UK
[109] Department of Physical Medicine and Rehabilitation, Oslo University Hospital/University of Oslo, Oslo, Norway
[110] Division of Orthopedics, Oslo University Hospital, Oslo, Norway
[111] Institue of Clinical Medicine, Faculty of Medicine, University of Oslo, Oslo, Norway
[112] Broad Institute, Cambridge MA Harvard Medical School, Boston MA, Massachusetts General Hospital, Boston MA, USA
[113] National Trauma Research Institute, The Alfred Hospital, Monash University, Melbourne, Victoria, Australia
[114] Department of Neurosurgery, Odense University Hospital, Odense, Denmark
[115] International Neurotrauma Research Organisation, Vienna, Austria
[116] Klinik für Neurochirurgie, Klinikum Ludwigsburg, Ludwigsburg, Germany

[117] Division of Biostatistics and Epidemiology, Department of Preventive Medicine, University of Debrecen, Debrecen, Hungary
[118] Department Health and Prevention, University Greifswald, Greifswald, Germany
[119] Department of Anaesthesiology and Intensive Care, AUVA Trauma Hospital, Salzburg, Austria
[120] Department of Neurology, Elisabeth-TweeSteden Ziekenhuis, Tilburg, the Netherlands
[121] Department of Neuroanesthesia and Neurointensive Care, Odense University Hospital, Odense, Denmark
[122] Department of Neuromedicine and Movement Science, Norwegian University of Science and Technology, NTNU, Trondheim, Norway
[123] Department of Physical Medicine and Rehabilitation, St.Olavs Hospital, Trondheim University Hospital, Trondheim, Norway
[124] Department of Neurosurgery, University of Pécs, Pécs, Hungary
[125] Division of Neuroscience Critical Care, John Hopkins University School of Medicine, Baltimore, USA
[126] Department of Neuropathology, Queen Elizabeth University Hospital and University of Glasgow, Glasgow, UK
[127] Dept. of Department of Biomedical Data Sciences, Leiden University Medical Center, Leiden, The Netherlands
[128] Department of Pathophysiology and Transplantation, Milan University, and Neuroscience ICU, Fondazione IRCCS Cà Granda Ospedale Maggiore Policlinico, Milano, Italy
[129] Department of Radiation Sciences, Biomedical Engineering, Umeå University, Umeå, Sweden
[130] Cochrane Consumers and Communication Review Group, Centre for Health Communication and Participation, School of Psychology and Public Health, La Trobe University, Melbourne, Australia
[131] Perioperative Services, Intensive Care Medicine and Pain Management, Turku University Hospital and University of Turku, Turku, Finland
[132] Department of Neurosurgery, Kaunas University of Health Sciences, Kaunas, Lithuania
[133] Intensive Care and Department of Pediatric Surgery, Erasmus Medical Center, Sophia Children's Hospital, Rotterdam, The Netherlands
[134] Department of Neurosurgery, Kings college London, London, UK
[135] Neurologie, Neurochirurgie und Psychiatrie, Charité – Universitätsmedizin Berlin, Berlin, Germany
[136] Department of Intensive Care Adults, Erasmus MC– University Medical Center Rotterdam, Rotterdam, the Netherlands
[137] icoMetrix NV, Leuven, Belgium
[138] Movement Science Group, Faculty of Health and Life Sciences, Oxford Brookes University, Oxford, UK
[139] Psychology Department, Antwerp University Hospital, Edegem, Belgium
[140] Director of Neurocritical Care, University of California, Los Angeles, USA
[141] Department of Neurosurgery, St.Olavs Hospital, Trondheim University Hospital, Trondheim, Norway
[142] Department of Emergency Medicine, University of Florida, Gainesville, Florida, USA
[143] Department of Neurosurgery, Charité – Universitätsmedizin Berlin, corporate member of Freie Universität Berlin, Humboldt-Universität zu Berlin, and Berlin Institute of Health, Berlin, Germany

[144] VTT Technical Research Centre, Tampere, Finland
[145] Section of Neurosurgery, Department of Surgery, Rady Faculty of Health Sciences, University of Manitoba, Winnipeg, MB, Canada

Figure legends

Figure 1. GOSE outcome categories and cognitive performance. Means and 95% CIs of z-scores. Abbreviations: Dec = decision time, Mov = movement time, Lat = latency, Cor= correct.

Figure 2. Contrasting relationships with functional status. Data are differences (z-scores) from reference (dashed line) graphed as means and 95% confidence intervals. The SF-12v2 Physical Component Summary (Physical) and the GOSE are in good agreement, as indicated by the near straight line relationship. The cognition composite (Cognition) strongly separates lower levels of outcome, but not upper; although some cognitive impairment is present even among patients reporting complete recovery. The SF-12v2 Mental Component Summary (Mental) does not distinguish between the lowest categories, but strongly differentiates more favourable outcomes. The shaded area covers data points where test completion rates were relatively low and additional caution is required concerning interpretation.