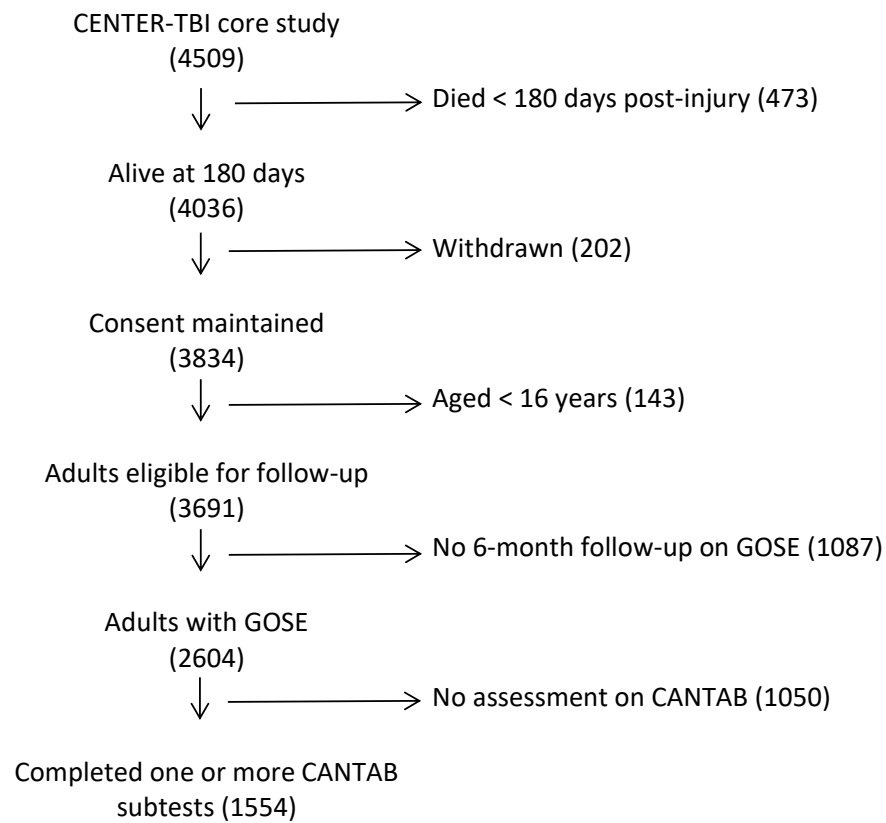


Supplementary material**Methods**

Figure S1. CONSORT diagram for analysis sample



COGNITIVE BATTERY

All participants completed a comprehensive battery of tests assessing cold cognition.¹ The neuropsychological tests implemented were designed to measure multiple cognitive domains including cognitive flexibility, planning, inhibition, attention, learning and memory. The assessment used subtests from the Cambridge Neuropsychological Test Automated Battery (CANTAB) (www.cambridgecognition.com)²⁻⁵ and two conventional neuropsychological tests, the Rey Auditory-Verbal Learning Task⁶ and Trail Making Part A and B).⁶ CANTAB assessments have been used in a wide variety of studies across the TBI injury severity range.⁷⁻¹⁷

CANTAB assessments were administered using a Gigabyte S1082 tablet PC and responses were recorded either using the touch sensitive screen of the tablet or an attached V2 press pad. Tests were administered and results extracted using CANTAB Research Suite 6.^{18,19}

CANTAB Paired Associates Learning (PAL):

The CANTAB PAL (Figure 1 A) is an eight-minute test assessing visuospatial learning and memory. Boxes are displayed on the screen and opened in a random order. One or more boxes will contain a pattern. The patterns are subsequently displayed in the middle of the screen and the participant must select the box in which the pattern was previously presented. If the participant makes an error, the boxes are opened in the same order again. This is to remind the participant of the locations of the patterns. The outcome measure is the total number of errors adjusted (errors added for stages not completed). This test is a good indicator of mild cognitive impairment.²⁰ Performance on the PAL test is strongly associated to the hippocampus.²¹ Salmond et al.²² found impaired paired associate learning in patients following traumatic brain injury (TBI) compared to controls. These disruptions were still present 3 years post-injury.⁸ Lauer et al.¹⁵ similarly showed lower performance on the PAL test in TBI patients. Moreover, performance was associated with widespread cortical and sub-cortical tissue loss.

CANTAB Reaction Time (RTI):

The RTI (Figure 1 B) is a five-minute test measuring reaction time, both motor and decision time. The test is divided into several stages of increasing complexity. In the simple touch stage, participants are required to touch the screen when a yellow dot appears in the centre of the screen. In the simple release stage the participant must hold down the press pad button until the yellow dot on the screen appears. In the five-choice touch stage, the yellow dot may appear in one of five locations. In the simple release and touch stage, the participant must hold down the press pad button until the yellow dot appears and touch the screen where the dot appears. Finally, in the five-choice release and touch stage participants are required to hold down the press pad button until the yellow dot appears and then touch the screen in one of the five location that the dot appears. In each stage participants are trained to a criterion (5 out of 6). If the participant fails to reach the criterion, the test is terminated. Salmond et al.²² reported increased reaction time on the CANTAB simple reaction time task in patients following TBI compared to the controls.

CANTAB Rapid Visual Information Processing (RVP):

The RVP (Figure 1 C) measures sustained attention by presenting a rapid stream of digits and requiring participants to detect target sequences. A white box is displayed in the centre of the screen in which digits 2-9 are rapidly presented at 100 digits per minute. Participants are required to

detect target sequences (e.g. 2-4-7, 3-5-7 or 4-6-8) and respond to this target sequence as quickly as possible. Outcome measures include A' , a signal detection theory measure of target sensitivity, and mean response latency. Coull et al.²³ demonstrated that a frontal-parietal network, specifically involving the bilateral inferior frontal gyrus, was involved during test performance. Salmond et al.²² demonstrated a clear disruption in sustained attention on the CANTAB RVP task in individuals with TBI compared to controls.

CANTAB Attention Switching Task (AST):

The AST (Figure 1 D) is an eight-minute test of attentional switching. Participants are presented with an arrow, pointing left or right, on the right- or left-hand side of the screen. In each trial a cue is presented whether the participant must respond to the direction of the arrow, or the side of the screen on which the arrow appears. For some trials, the side of the screen and the direction of the arrow are incongruent (a right-facing arrow on the left side of the screen).

CANTAB Spatial Working Memory (SWM):

The CANTAB SWM (Figure 1 E) is a nine-minute test assessing spatial working memory. Test performance requires the retention and manipulation of visuospatial information. Coloured boxes are shown on screen and participants must select a box with a token. The token is stored on the edge of the screen and will not appear in the same location for the rest of the trial. The colour and position of the boxes used are changed from trial to trial to discourage the use of stereotyped search strategies. Mehta et al.²⁴ suggested a frontal-parietal network associated with SWM performance, moreover, this network and performance were enhanced by methylphenidate. Salmond et al.²² demonstrated that accuracy on the SWM was intact in TBI patients, compared to controls, however, there was an increased reaction time in TBI patients. Furthermore, the deficits were observable several years following the injury.⁸

CANTAB Stockings of Cambridge (SOC):

The SOC (Figure 1 F) is a test of visuospatial planning and working memory based on a modified version of the Tower of London. Participants are shown example configurations of three coloured balls. There are two displays and participants are asked to match the example configuration by moving one ball at a time. The problems increase in the number of moves required to match the example configuration, starting at one move progressing to four moves. If the participant makes twice the number of necessary moves, the trial is terminated. If three trials in a row are terminated, the whole test is terminated. Vaghi et al.²⁵ found an association with resting-state functional connectivity between the dorsolateral prefrontal cortex and the putamen during planning performance of the One-Touch version of the SOC. Shum et al.²⁶ found increased errors on the Tower of London Task in individuals following TBI compared to controls, suggesting impairments in planning.

Rey Auditory-Verbal Learning Test (RAVLT)

This is a test of verbal memory that assesses the ability to learn a list of 15 words.⁶ Recall is assessed after each presentation of the list, after the recall of an interference list, and again following a 20-minute delay.

The examiner reads the words aloud with a one second interval between each of the 15 words. Immediately after the words are read, the participant recalls as many as possible, each recorded by

the examiner. Correct responses are defined as stimulus words recalled correctly by the participant. Plural forms of stimulus words are counted as correct (e.g. drums for drum). Raw data is entered as the count of the number of words correctly recalled (0-15) for each trial. The procedure is repeated five times, and the RAVLT recall score is the total number of words correctly recalled over the five trials.

Trail Making Test Part A and Part B (TMT A and TMT B)

The Trail Making Test Part A involves visual search and psychomotor speed while Part B adds a task switching demand.⁶ TMT, particularly part A, is regarded as a measure of processing speed and Part B includes executive functions.²⁷ Part A requires the individual to draw lines to connect in sequence 25 encircled numbers distributed on a page. Part B is similar except the person must alternate between numbers and letters and is therefore more difficult and takes longer to complete. The time for completion in seconds is recorded separately for Parts A and B. The maximum score for Part A is 100 seconds with 101 seconds indicating the test was discontinued. The maximum score for Part B is 300 seconds with 301 seconds indicating the test was discontinued.

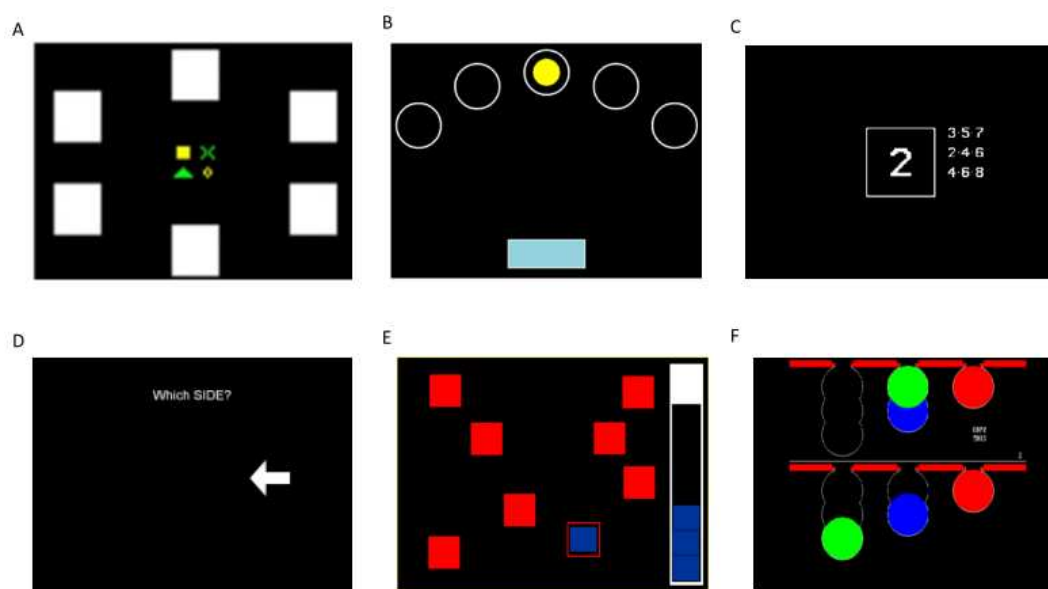


Figure S2 Composite image of the CANTAB tests. A) CANTAB PAL; B) CANTAB RTI; C) CANTAB RVP; D) CANTAB AST; E) CANTAB SWM; F) CANTAB SOC.

GLOBAL FUNCTIONAL OUTCOME**Glasgow Outcome Scale-Extended (GOSE)**Table S1: Summary of the functional levels of the Glasgow Outcome Scale (GOS)²⁸ and Glasgow Outcome Scale – Extended (GOSE).²⁹

GOS 5-point scale	GOSE 8-point scale	Domain	Criteria
<i>Dead</i>	<i>(1) Dead</i>		
<i>Vegetative State</i>	<i>(2) Vegetative State</i>		
<i>Severe Disability (SD)</i> Conscious but dependent	<i>(3) Lower SD</i>	Function in home	Unable to look after themselves for 8 hours
	<i>(4) Upper SD</i>	Function in home Function outside the home	Unable to look after themselves for 24 hours OR Unable to shop OR Unable to travel
<i>Moderate Disability (MD)</i> Independent but with limitations in one or more major roles	<i>(5) Lower MD</i>	Work/ study Social & leisure activities Family & friendships	Unable to work/ study OR Unable to participate OR Constant problems
	<i>(6) Upper MD</i>	Work/ study Social & leisure activities Family & friendships	Reduced work/ study capacity OR Participate much less OR Frequent problems
<i>Good Recovery (GR)</i> Return to normal life	<i>(7) Lower GR</i>	Social & leisure activities Family & friendships Symptoms	Participate a bit less OR Occasional problems OR Some symptoms affecting daily life
	<i>(8) Upper GR</i>		No problems reported

Injury severity

Glasgow Coma Scale (GCS)³⁰ The GCS was collected at the following time points as part of the study protocol: pre-hospital, arrival at referral centre emergency department (ED) (where a secondary transfer took place), arrival at study hospital, and at ED discharge ('post-stabilisation'). A composite GCS was created using ED discharge as the preferred time point, and working progressively earlier in time if this was not available.³¹

Computed Tomography (CT) imaging. Abnormalities on the first CT scan after injury were recorded centrally using categories from the common data elements for TBI imaging.³² Intracranial abnormality excluded skull fractures.

Results

Table S2. Completion of 6 month cognitive assessments in 2604 patients followed-up on the GOSE, and reasons recorded for non-completion. Figures are percentages of patients in the GOSE category.

		Cognitive/ neurological deficits	Non-neurological/ physical reasons	Lack of effort/ uncooperative	Language	Illness/ fatigue	Logistical reasons/ other reasons	Examiner error	Patient not available	Unexplained	Test completed
Lower SD/ VS n=228	PAL	15%	1%	0%	0%	1%	22%	0%	13%	35%	12%
	RAVLT	20%	1%	0%	1%	1%	1%	0%	18%	36%	21%
	TMT	22%	1%	0%	0%	0%	2%	0%	22%	31%	21%
	RTI	13%	1%	0%	0%	1%	22%	0%	12%	39%	12%
	RVP	15%	1%	0%	0%	1%	22%	0%	13%	36%	10%
	AST	16%	2%	0%	0%	1%	22%	0%	13%	34%	11%
	SWM	16%	1%	0%	0%	1%	22%	0%	13%	35%	11%
	SOC	16%	1%	0%	0%	2%	22%	0%	13%	37%	8%
Upper SD n=181	PAL	3%	1%	1%	0%	2%	19%	0%	10%	20%	44%
	RAVLT	2%	1%	3%	0%	2%	2%	1%	12%	21%	57%
	TMT	4%	2%	2%	0%	3%	2%	0%	13%	18%	55%
	RTI	3%	1%	1%	0%	1%	20%	0%	10%	23%	42%
	RVP	8%	2%	2%	0%	3%	20%	0%	10%	25%	30%
	AST	4%	2%	1%	0%	2%	20%	0%	10%	19%	42%
	SWM	6%	1%	1%	0%	2%	19%	0%	10%	24%	38%
	SOC	5%	1%	2%	0%	2%	19%	0%	10%	26%	35%
Lower MD n=264	PAL	1%	0%	1%	0%	0%	8%	0%	9%	11%	70%
	RAVLT	3%	0%	1%	2%	1%	2%	0%	8%	11%	73%
	TMT	2%	0%	0%	2%	1%	2%	0%	9%	9%	74%
	RTI	1%	0%	1%	0%	0%	9%	0%	8%	14%	67%
	RVP	5%	0%	2%	0%	2%	9%	0%	9%	14%	59%
	AST	2%	0%	1%	0%	0%	9%	0%	9%	13%	67%
	SWM	2%	0%	1%	0%	2%	9%	0%	9%	13%	65%
	SOC	2%	0%	2%	0%	1%	9%	0%	9%	12%	64%
Upper MD n=350	PAL	0%	1%	0%	0%	0%	13%	0%	3%	13%	71%
	RAVLT	1%	0%	1%	0%	1%	1%	1%	5%	11%	79%
	TMT	0%	0%	1%	0%	0%	1%	0%	6%	10%	81%
	RTI	0%	1%	0%	0%	0%	13%	0%	3%	15%	68%
	RVP	1%	1%	1%	0%	1%	15%	0%	3%	13%	65%
	AST	0%	1%	1%	1%	0%	14%	0%	3%	13%	67%
	SWM	0%	1%	1%	0%	1%	13%	0%	3%	13%	69%
	SOC	1%	1%	1%	0%	1%	14%	0%	3%	13%	67%
Lower GR n=559	PAL	1%	1%	1%	0%	0%	11%	0%	5%	11%	71%
	RAVLT	1%	0%	1%	0%	0%	1%	1%	8%	9%	79%
	TMT	2%	1%	1%	0%	0%	1%	0%	9%	7%	78%
	RTI	0%	0%	1%	0%	0%	11%	1%	5%	14%	68%

	RVP	3%	1%	2%	0%	1%	11%	0%	5%	14%	62%
	AST	1%	1%	1%	0%	1%	11%	0%	5%	11%	69%
	SWM	1%	0%	2%	0%	1%	10%	0%	5%	12%	68%
	SOC	2%	1%	2%	0%	2%	10%	0%	5%	13%	65%
Upper GR	PAL	1%	0%	1%	0%	0%	15%	0%	8%	18%	58%
n=1022	RAVLT	0%	0%	1%	0%	0%	2%	0%	10%	18%	68%
	TMT	0%	0%	1%	0%	0%	1%	0%	11%	16%	69%
	RTI	0%	0%	1%	0%	0%	15%	0%	6%	23%	53%
	RVP	2%	0%	2%	0%	0%	15%	0%	8%	19%	53%
	AST	1%	0%	1%	0%	0%	15%	0%	8%	19%	56%
	SWM	1%	0%	1%	0%	0%	15%	0%	8%	18%	57%
	SOC	1%	0%	1%	0%	0%	15%	0%	8%	19%	56%

Table S3. Demographic and clinical characteristics of the full CENTER-TBI patient sample (N=4509), patients alive and eligible for follow-up at six months (N=3691), and the subgroup that was not in the study sample (N=2137). Significance tests are for the difference between the study and non-study groups. The study group (N=1554) is described in Table 2 in the main text.

	N (%)		N (%)		N (%)		p
	Entire sample (n=4509)		Eligible sample (n=3691)		Non-study group (2137)		
Age							
Mean (SD)	49.0	(21.3)	48.4	(19.7)	48.8	(20.3)	0.168
Sex							
Female	1486	(33)	1204	(33)	691	(32)	0.691
Male	3023	(67)	2487	(67)	1446	(68)	
Race							
Caucasian	4158	(97)	3419	(97)	1954	(96)	0.064
Other	138	(3)	113	(3)	75	(4)	
Missing	213		159		108		
Highest level of education							
Primary	641	(18)	459	(15)	277	(16)	<0.001
Secondary	1261	(35)	1108	(36)	640	(38)	
Training	696	(20)	646	(21)	346	(21)	
College	968	(27)	888	(29)	427	(25)	
Missing	943		590		447		
Employment Status							
Working (full or part time)	1946	(49)	1804	(54)	952	(50)	<0.001
Not working	362	(9)	317	(9)	200	(11)	
Retired	1112	(28)	828	(25)	511	(27)	
Student/ homemaker	560	(14)	409	(12)	229	(12)	
Missing	529		333		245		
Marital status							
Partnered	2070	(51)	1751	(52)	946	(49)	0.012
Previously partnered	621	(15)	520	(15)	313	(16)	
Single/ other	1384	(34)	1126	(33)	657	(34)	
Missing	434		294		221		
Care pathway							
Emergency Room	848	(19)	774	(21)	428	(20)	0.003
Admitted to hospital	1523	(34)	1324	(36)	736	(34)	
Intensive Care Unit	2138	(47)	1593	(43)	973	(46)	
ASA Pre-injury Physical Health							
Healthy patient	2501	(57)	2126	(59)	1183	(57)	0.057
Mild systemic disease	1410	(32)	1156	(32)	687	(33)	
Severe systemic disease	462	(11)	325	(9)	196	(10)	
Missing	136		84		71		

Table S3 (continued).

	N(%)		Eligible sample (n=3691)	Non-study group (n=2137)	P
	Entire sample (n=4509)				
Cause of injury					
Road traffic accident	1682 (38)		1411 (39)	740 (36)	<0.001
Fall	2024 (46)		1617 (45)	973 (47)	
Violence/assault	246 (6)		208 (6)	121 (6)	
Other	436 (10)		361 (10)	237 (11)	
Missing/ unknown	121		94	66	
GCS score at baseline					
3-8	986 (23)		659 (18)	435 (21)	<0.001
9-12	389 (9)		285 (8)	178 (9)	
13-15	2957 (68)		2624 (74)	1442 (70)	
Missing	177		123	82	
CT Imaging abnormality					
Absent	1645 (40)		1462 (43)	810 (42)	<0.001
Present	2443 (60)		1911 (57)	1067 (55)	
Missing/ uninterpretable	421		318	260	
Head & neck AIS¹					
No injury/ Minor injury	712 (16)		655 (18)	371 (17)	<0.001
Moderate injury	577 (13)		521 (14)	290 (14)	
Serious injury	1289 (29)		1128 (31)	605 (28)	
Severe injury	788 (18)		637 (17)	366 (17)	
Critical injury/ unsurvivable injury	1143 (25)		750 (20)	505 (24)	
Major extracranial injury²					
Absent	2935 (65)		2435 (66)	1406 (66)	0.001
Present	1574 (35)		1256 (34)	731 (34)	
GOSE at six months					
1 Dead	473 (15)				<0.001
2 Vegetative state	29 (1)		27 (1)	27 (3)	
3 Lower Severe Disability	207 (6)		201 (8)	170 (16)	
4 Upper Severe Disability	187 (6)		181 (7)	97 (9)	
5 Lower Moderate Disability	275 (9)		264 (10)	80 (8)	
6 Upper Moderate Disability	377 (12)		350 (13)	100 (10)	
7 Lower Good Recovery	584 (18)		559 (22)	157 (15)	
8 Upper Good Recovery	1078 (34)		1022 (39)	419 (40)	
Missing	1299		1087	1087	

¹Head & neck AIS = maximum Abbreviated Injury Score for head, neck and cervical regions.

²Any non-head & neck AIS \geq 3 (serious injury)

Table S4. Raw scores for assessments of the reference group and estimates of general population norms. For cognitive tests the values for the norms have been adjusted to match the age composition of the reference group. Predicted values for the RAVLT and Trail Making A and B were calculated from previous meta-analyses.³³ Mean scores on the CANTAB outcomes by age band were used to create expected overall means for the reference group by weighting according to age composition; normative data was not available for the AST test.¹⁹ T-scores for the SF-12v2 are derived from 1998 norms,³⁴ and are not age-corrected.

	Reference group GOSE 8a					Norm Mean
	N	Mean	SD	95% CIs		
PAL Total Errors Adjusted	294	26.1	34.8	22.1	30.0	17.7
RAVLT Total recall of principal list	286	46.2	11.1	45.0	47.5	50.8
Trail Making Part A time (secs)	292	34.1	19.4	31.9	36.3	32.1
Trail Making Part B time (secs)	290	80.8	47.2	75.4	86.2	78.8
RTI Choice Reaction Time (msec)	262	363	81	353	373	366
RTI Movement Time (msec)	262	418	136	401	434	488
RVP A prime	269	0.90	0.06	0.89	0.91	0.91
RVP latency (msec)	269	407	135	391	423	521
AST Total correct	282	150	11.1	149	152	N/A
AST latency (msec)	282	616	170	597	636	N/A
SWM Between errors	289	25.7	19.8	23.4	27.9	29.7
SOC Problems solved in minimum moves	290	8.3	2.0	8.1	8.6	8.5
SF12v2 Physical Component Summary	295	51.3	7.6	50.5	52.2	50.0
SF12v2 Mental Component Summary	295	52.4	8.5	51.4	53.4	50.0

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