Cognitive-motor dissociation and time to functional recovery in patients with acute brain injury in the USA: a prospective observational cohort study

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Summary

Background **Recovery trajectories of clinically unresponsive patients with acute brain injury are largely uncertain. Brain activation in the absence of a behavioural response to spoken motor commands can be detected by EEG, also known as cognitive-motor dissociation. We aimed to explore the role of cognitive-motor dissociation in predicting time to recovery in patients with acute brain injury.**

Methods **In this observational cohort study, we prospectively studied two independent cohorts of clinically unresponsive patients (aged ≥18 years) with acute brain injury. Machine learning was applied to EEG recordings to diagnose cognitive-motor dissociation by detecting brain activation in response to verbal commands. Survival statistics and shift analyses were applied to the data to identify an association between cognitive-motor dissociation and time to and magnitude of recovery. The prediction accuracy of the model that was built using the derivation cohort was assessed using the validation cohort. Functional outcomes of all patients were assessed with the Glasgow Outcome Scale–Extended (GOS-E) at hospital discharge and at 3, 6, and 12 months after injury. Patients who underwent withdrawal of life-sustaining therapies were censored, and death was treated as a competing risk.**

Findings **Between July 1, 2014, and Sept 30, 2021, we screened 598 patients with acute brain injury and included 193 (32%) patients, of whom 100 were in the derivation cohort and 93 were in the validation cohort. At 12 months, 28 (15%) of 193 unresponsive patients had a GOS-E score of 4 or above. Cognitive-motor dissociation was seen in 27 (14%) patients and was an independent predictor of shorter time to good recovery (hazard ratio 5·6 [95% CI 2·5–12·5]), as was underlying traumatic brain injury or subdural haematoma (4·4 [1·4–14·0]), a Glasgow Coma Scale score on admission of greater than or equal to 8 (2·2 [1·0–4·7]), and younger age (1·0 [1·0–1·1]). Among patients discharged home or to a rehabilitation setting, those diagnosed with cognitive-motor dissociation consistently had higher scores on GOS-E indicating better functional recovery compared with those without cognitive-motor dissociation, which was seen as early as 3 months after the injury (odds ratio 4·5 [95% CI 2·0–33·6]).**

Interpretation **Recovery trajectories of clinically unresponsive patients diagnosed with cognitive-motor dissociation early after brain injury are distinctly different from those without cognitive-motor dissociation. A diagnosis of cognitive-motor dissociation could inform the counselling of families of clinically unresponsive patients, and it could help clinicians to identify patients who will benefit from rehabilitation.**

Funding **US National Institutes of Health.**

Introduction

For patients with acute brain injury and disorders of consciousness (ie, clinically unresponsive), prediction of outcome can be imprecise.[1] Furthermore, for the families of these patients, providing guidance about care decisions can be challenging and might result in inadequate support to promote patient recovery, including inefficient allocation of rehabilitation resources. Access to and criteria that qualify patients for rehabilitation vary widely between health-care systems,[2,3] with many systems requiring that patients must participate in rehabilitation services for a minimum amount of time. However, recovery from an acute brain injury might occur months or even years after the injury occurred, with early recovery typically seen in patients with traumatic brain injury.[4] Late recovery and functional independence are possible for patients with an acute brain injury, including those who are initially clinically unresponsive from brain injuries other than traumatic brain injury,[3,5,6] and the potential for rehabilitation interventions to improve outcomes of patients with brain injury cannot be overstated.[6,7] The imprecision of predicting recovery of consciousness and long-term outcomes has been identified as a major gap in knowledge.[8,9]

Patients with inconsistent behavioural evidence of consciousness, such as intermittent interactions with the

Research in context

Evidence before this study

We searched PubMed for articles published until April 1, 2022, using the following search terms: "brain injury" AND ("acute" OR "early") AND ("coma" OR "disorder of consciousness" OR "unconscious" OR "vegetative state" OR "unresponsive wakefulness syndrome") AND ("cognitive motor dissociation" OR "covert consciousness" OR "brain activation") AND ("recovery" OR "prognosis" OR "prognostication"). We did not restrict the search by language or publication date, and the search identified 30 articles. 12 were on chronic disorders of consciousness, 11 were reviews or editorials, two were unrelated to the topic, one focused on how the diagnosis of cognitive-motor dissociation would be perceived by health-care proxies and caregivers, and four were prospective studies that diagnosed cognitive-motor dissociation using MRI or EEG in patients early after brain injury. These four studies showed that cognitive-motor dissociation could be detected early after brain injury in an intensive care unit (ICU) setting in approximately 15% of patients, and three of the four studies found an association with a behavioural outcome, command-following, or functional recovery. In one study, patients diagnosed with cognitive-motor dissociation during the ICU stay were more likely to be able to take care of themselves for at least 8 h in a day, at 1 year after the injury.

Added value of this study

Our study is—to the best of our knowledge—the first to prospectively investigate the role of cognitive-motor dissociation or covert consciousness in predicting time to functional recovery in clinically unresponsive patients with acute brain injury. This study showed that the diagnosis of cognitive-motor dissociation in an ICU setting independently predicted earlier time to recovery. Other predictors included better neurological status on admission (assessed as Glasgow Coma Scale score ≥8) and traumatic brain injury as the mechanism of injury. Among patients discharged home or to a rehabilitation setting, cognitive-motor dissociation diagnosed in an ICU setting was associated with improved functional outcomes (ie, higher scores on the Glasgow Outcome Scale–Extended), seen as early as 3 months after the injury. Even though patients with cognitive-motor dissociation who were discharged to a higher-level care setting without access to rehabilitation service, such as skilled nursing facilities, had a marginally better functional status at hospital discharge than did those without cognitive-motor dissociation, no outcome differences were seen at any of the follow-up timepoints.

Implications of all the available evidence

These findings could provide clinicians with information that helps them better explain possible recovery trajectories to families of patients who are clinically unresponsive from an acute brain injury. Cognitive-motor dissociation allows bedside quantification of the residual integrative function of the injured brain and could become the foundation of a biologically meaningful classification of patients, which will be required for the successful design of clinical trials aimed at promoting recovery of consciousness. Moreover, a diagnosis of cognitive-motor dissociation could enable clinicians to identify patients who have a high potential to benefit from rehabilitation interventions, possibly even among individuals who do not meet current criteria to be discharged to a rehabilitation setting.

examiner, have an increased chance of later functional recovery.[4] Unfortunately, bedside behavioural assessments alone are insufficient to accurately predict functional outcome trajectories.[10–12] Detection of brain activation to motor commands using bedside EEG has been associated with 12-month functional outcomes and might increase the accuracy of predictions.[13] This state, called cognitive-motor dissociation or covert consciousness, indicates detection of volitional brain activity by task-based functional MRI or EEG in patients who appear unresponsive on bedside behavioural assessments, without the ability to meaningfully communicate with the examiner.[14] We aimed to study the recovery trajectory over the first year of unconscious patients with acute brain injury with and without cognitive-motor dissociation admitted to a single intensive care unit (ICU).

Methods

Study design and participants

We prospectively screened all patients with acute brain injury who were admitted to the neurological ICU at Columbia University Irving Medical Center, New York Presbyterian Hospital, New York, NY, USA. We included two cohorts; data for the first cohort have been published previously.[13] We enrolled all patients (aged 18 years or older) who were in a coma, vegetative state, or minimally conscious state–minus (defined as unresponsiveness with preserved visual fixation or pursuit, or localisation to noxious stimuli) and who were unable to follow spoken commands, had an acute brain injury of any kind, were connected to or were expected to be connected to continuous EEG monitoring, and spoke English or Spanish as their primary language. We excluded all patients who either were younger than 18 years, had a pre-existing disorder of consciousness or confounding neurological condition (ie, baseline aphasia or advanced dementia) before the onset of their presenting acute brain injury, were deaf before the acute brain injury, had clinically recovered the ability to follow commands before enrolment, did not want to participate or whose family did not want them to participate, had uncontrolled seizures, or had logistical reasons that hindered their enrolment.

As part of our standard practice, and in accordance with guidelines regarding EEG monitoring of patients in the

ICU,[15] all unresponsive patients were either monitored by continuous EEG or were anticipated to be connected to EEG monitoring within 12 h after screening, unless death was imminently expected. Treating physicians, patients, and their families were unaware of the results of the cognitive-motor dissociation testing to avoid biasing their treatment decisions, and these results were also not made available to treating clinicians regarding the withdrawal of life-sustaining therapies.

This study was approved by the Columbia University institutional review board. We obtained written informed consent from patients' surrogates. Patients who recovered consciousness during follow-up were given the opportunity to withdraw from the study. Results are reported according to Strengthening the Reporting of Observational Studies in Epidemiology guidelines.[16]

Procedures

We prospectively collected data on baseline patient demographic and clinical data (including diagnosis on admission and Glasgow Coma Scale [GCS] score), outcomes, and complications that occurred during the hospital stay. Patients' diagnoses on admission were classified into structural brain injury with trauma, structural brain injury without trauma (ie, intracerebral haemorrhage, subarachnoid haemorrhage, or acute ischaemic stroke), or non-structural brain injury (ie, cardiac arrest or meningitis; appendix p 1–2).[17] Some in-hospital variables (eg, length of stay and diagnosis) were collected retrospectively for all patients through an electronic medical record review. For patients who were alive at hospital discharge, we recorded the discharge disposition, which we categorised into home rehabilitation (eg, home with or without services, or acute, subacute, or outpatient rehabilitation) and higher-level support with limited rehabilitation services (eg, skilled nursing facility, long-term acute care in hospital, and hospice care).

See Online for appendix

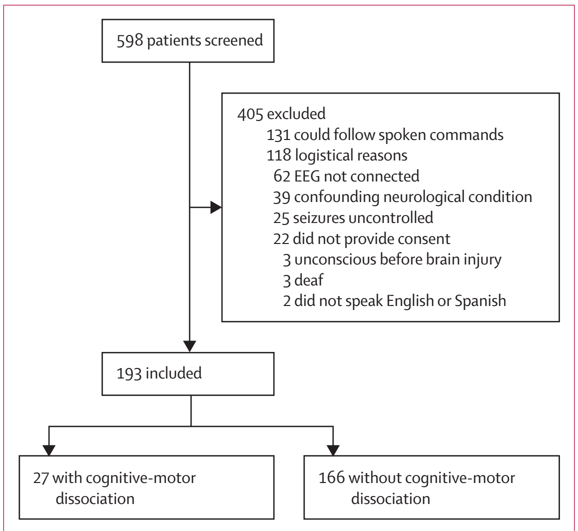

Figure 1: **Study profile**

Daily behavioural testing was done with the Coma Recovery Scale–Revised,[18] which is a six-dimension 23-point scale of hierarchically arranged assessments. This test was used to categorise the patient's behavioural examination at the time of enrolment and daily during the morning rounds. Findings were used to diagnose coma, vegetative state, or minimally conscious state–minus. Additionally, an assessment for the presence of cognitive-motor dissociation was done to identify brain activation to motor commands. Sedation was interrupted or decreased for neurological and cognitive-motor dissociation assessments if doing so was deemed safe by the attending clinician during bedside clinical rounds. Patients who were receiving deep sedation or neuromuscular blockade were not included on that day (appendix p 1).

For the cognitive-motor dissociation assessment, motor commands including "keep opening and closing your right hand" and "stop opening and closing your right hand" were presented to patients via single-use headphones throughout the EEG recording (three blocks with eight consecutive trials each for the left and right hand). Digital bedside EEG was recorded using a standard 21-electrode montage.[15] As a control, we used the same protocol on healthy volunteers using motor commands presented in English (n=10) and in Spanish (n=5). Full details of the motor command protocol have been reported previously.[13]

We calculated spectral power in predefined frequency ranges for each electrode of all EEG recordings.[19–21] To make the cognitive-motor dissociation diagnosis, in brief, we trained a machine-learning algorithm (support vector machine [SVM] with a linear kernel) using these power calculations to identify whether the EEG responses that followed the "keep moving" commands systematically differed from the "stop moving" commands. Impaired thalamocortical connectivity has been implicated in cognitive motor dissociation,[22] but underlying mechanisms of this brain activation are to a large extent uncertain. However, machine-learning algorithms are able to detect reproducible motor command specific brain activation. The SVM performance for each EEG recording was estimated as the area under the receiver operating characteristic curve (AUC), with significance of the AUC assessed by a one-tailed permutation test (after random shuffling with 500 training and evaluation repetitions, significance set at 0·5), and accounting for multiple recordings in a patient (Benjamini-Hochberg false-discovery rate method). Full details of the cognitive-motor dissociation classification method and EEG acquisition and processing are reported elsewhere.[13]

The primary outcome investigated in the study was functional recovery, defined as a Glasgow Outcome Scale–Extended (GOS-E) score of greater than or equal to 4 (indicates the ability to be left alone up to 8 h without assistance). Secondary outcomes included shifts in GOS-E scores across all levels. Scores on the GOS-E range from 1 to 8, with higher scores indicating a better outcome.[23,24] Data for functional outcomes were obtained in a structured telephone interview at discharge and at 3, 6, and 12 months after injury by an interviewer trained in the collection of outcomes assessments. If the patient was unable to communicate, functional status was obtained through a close relative or caregiver. Neither the interviewee nor the interviewer who did the outcome assessments were aware of the results of the EEG assessment used to assess the patient's clinical state of consciousness.

Statistical analysis

To identify independent predictors of time to functional recovery (defined as a GOS-E score ≥4), we used a sub-distribution hazard model. Patients who had withdrawal of life-sustaining therapies or were lost to follow-up were censored,[25] and death was treated as a competing risk. The model was stratified by cohort (ie, first and second).[26] Additionally, restricted mean survival times were used to compare the differences of the expected time to recovery over the complete follow-up period of 12 months between patients with cognitive-motor dissociation and those without cognitive-motor dissociation.[27] Other predictors of recovery were adjusted for as covariates.

To identify models with the highest accuracy to predict time to recovery, we built several regression models combining predictors identified in the sub-distribution hazard model using data from the first cohort. We then assessed the accuracy of these models for prediction of functional recovery at hospital discharge and at 3, 6, and 12 months after the injury in the second cohort.[28]

To assess the significance of a shift across all levels of functional outcomes, a modified shift test was applied to the distribution of GOS-E scales comparing patients with cognitive-motor dissociation to those without cognitive-motor dissociation who were alive at hospital discharge, accounting for possibly tied observations.[29] To better interpret the shift effect, a common odds ratio (OR) across all cut points of GOS-E was estimated by a proportional-odds logistic regression model, which indicates the relative effect on the GOS-E increase for patients with cognitive-motor dissociation.[30]

To investigate an association between discharge disposition (higher-level care *vs* home rehabilitation) and recovery among patients alive at discharge, the significance of cognitive-motor dissociation was tested by multivariate Mann-Whitney estimators,[31] correcting separately for other predictors of recovery among patients discharged to higher-level care or home rehabilitation. Additionally, a cumulative ordinal regression analysis was done to predict GOS-E measurements across all follow-up timepoints, analysing discharge disposition and cognitive-motor dissociation.[32]

Categorical variables are presented as n (%), and continuous variables presented as mean (SD) or median (IQR), as appropriate. Associations between

	First cohort (n=100)	Second cohort (n=93)	Combined cohort (n=193)
Demographics			
Age, years	60 (17)	65 (16)	63 (17)
Sex			
Male	56 (56%)	49 (53%)	105 (54%)
Female	44 (44%)	44 (47%)	88 (46%)
Primary language			
English	79 (79%)	65 (70%)	144 (75%)
Spanish	21 (21%)	28 (30%)	49 (25%)
Clinical characteristics			
Duration of mechanical ventilation, days	19 (10–30)	17 (9–28)	18 (9–29)
Tracheostomy	52 (52%)	46 (49%)	98 (51%)
Hospital complications			
Renal failure	10 (10%)	12 (13%)	23 (12%)
Cardiac arrest	19 (19%)	6 (6%)	25 (13%)
Sepsis	48 (48%)	27 (29%)	75 (39%)
Cause of brain injury			
Intracerebral haemorrhage	25 (25%)	38 (41%)	63 (33%)
Cardiac arrest	31 (31%)	9 (10%)	40 (21%)
Subarachnoid haemorrhage	15 (15%)	13 (14%)	28 (15%)
Traumatic brain injury or subdural haematoma	16 (16%)	9 (10%)	25 (13%)
Acute ischaemic stroke	3 (3%)	14 (15%)	17 (9%)
Other*	10 (10%)	10 (11%)	20 (10%)
Disorders of consciousness category (best)			
Coma	44 (44%)	36 (39%)	80 (41%)
Vegetative state	25 (25%)	23 (25%)	48 (25%)
Minimally conscious state–minus	31 (31%)	34 (37%)	65 (33%)
Behavioural assessments			
Admission Glasgow Coma Scale score	6 (3–8)	6 (3–8)	6 (3–8)
Coma Recovery Scale-revised score, median	3 (0–5)	2 (0–5)	2 (0–5)
Coma Recovery Scale-revised score, worst	1 (0–3)	1 (0–3)	1 (0–3)
Coma Recovery Scale-revised score, best	3 (1–7)	3 (1–9)	3 (1–8)
EEG recordings			
Number of EEG recordings per patient	1 (1–2)	2 (1–3)	2 (1– 3)
Time from onset of acute brain injury to first EEG recording >0 days	65 (67%)	67 (72%)	132 (69%)
Cognitive-motor dissociation diagnosis	16 (16%)	11 (12%)	27 (14%)
Glasgow Outcome Scale–Extended score ≥4			
At hospital discharge	2 (2%)	2 (2%)	4 (2%)
3 months after injury	7 (7%)	5 (5%)	12 (6%)
6 months after injury	12 (12%)	9 (10%)	21 (11%)
12 months after injury	19 (19%)	9 (10%)	28 (15%)
Status at hospital discharge			
Dead	37 (37%)	34 (37%)	71 (37%)
Higher-level care	40 (40%)	44 (47%)	84 (44%
Home rehabilitation	23 (23%)	15 (16%)	38 (20%)

Data are n (%), mean (SD), or median (IQR). *Status epilepticus (n=6), toxic metabolic (n=3), encephalitis (N=4), sepsis (n=2), and thrombotic thrombocytopenic purpura, neurosarcoidosis, brain tumour, chimeric antigen receptor T cell toxicity, and uraemia (each n=1).

Table 1: **Demographic and clinical characteristics at baseline and follow-up of study cohorts**

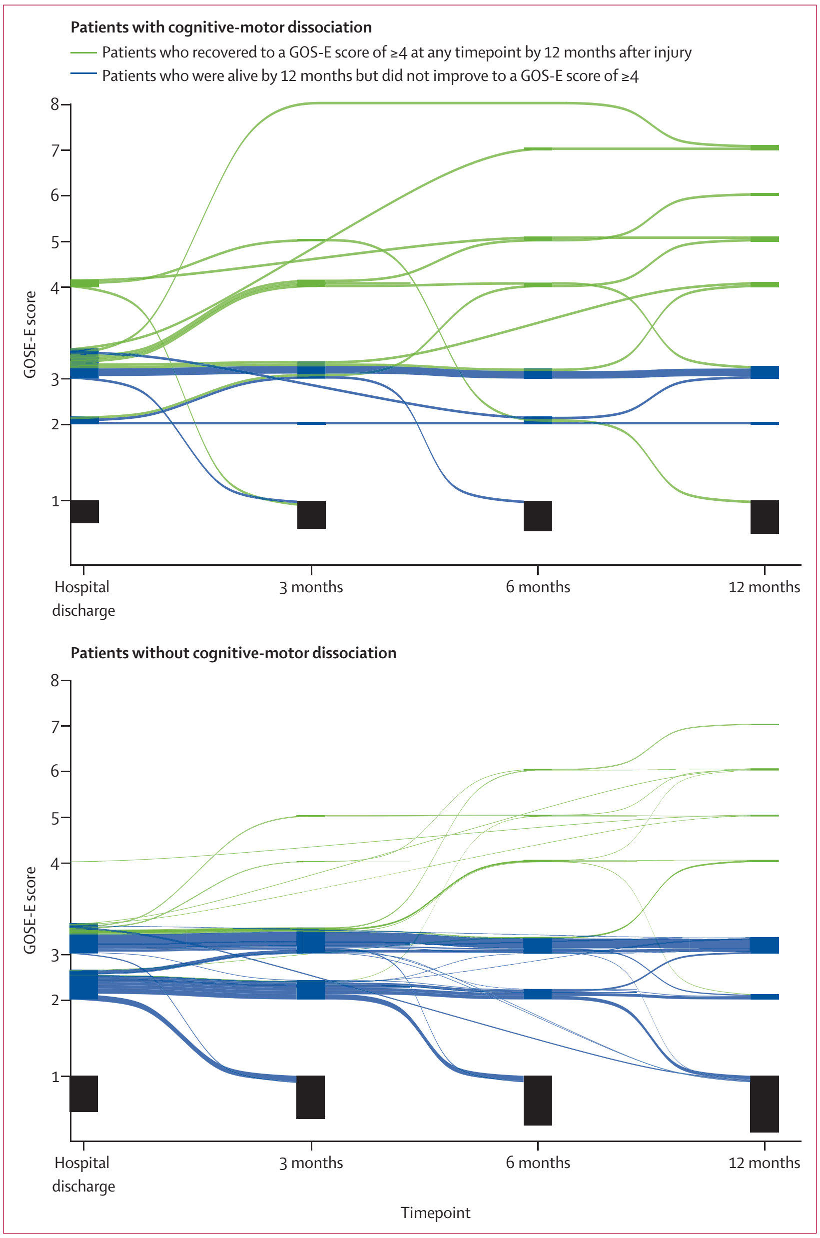

Figure 2: **Recovery trajectories over 12 months following acute brain injury**
Alluvial plots representing individual GOS-E development across follow-up timepoints in 193 patients with acute brain injury (27 patients with cognitive-motor dissociation and 166 without cognitive-motor dissociation). Black boxes represent patients who died, blue those alive without recovery, and green those who recovered. The size of the box represents the percent of patients with a particular GOS-E score at each timepoint among patients with and without cognitive-motor dissociation. GOS-E=Glasgow Outcome Scale–Extended.

variables and outcomes were assessed with a Wilcox rank-sum test for quantitative variables or χ^2 test for qualitative variables. All statistical tests were two-tailed. Variables with a p value less than 0·10 in univariate analysis were considered for multivariate backward stepwise models. We also tested for two-way interactions and the interaction of each variable with time in our final models. We used R (version 4.0.3) for all statistical analyses.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Between July 1, 2014, and Sept 30, 2021, 598 patients with acute brain injury were screened for the study. 193 (32%) patients were enrolled (figure 1), of whom 100 (52%) were in the first (model derivation) cohort and 93 (48%) were in the second (validation) cohort. Patients who were included in the study had similar characteristics to those who were excluded, with regards to age, sex, and admission GCS score (appendix p 3). Patients included in the study were more frequently admitted for intracerebral haemorrhage (63 [33%] of 193 *vs* 66 [16%] of 405), cardiac arrest (40 [21%] *vs* 72 [18%]), traumatic brain injury (25 [13%] *vs* 45 [11%]), and subarachnoid haemorrhage (28 [15%] vs 20 [5%]), compared with those who had been excluded. Excluded patients more commonly had other diagnoses (20 [10%] *vs* 161 [40%]). The mean age of patients included in the study was 63 (SD 17) years. 105 (54%) patients were men and 88 (46%) were women (table 1). The primary language of patients was English for 144 (75%) and Spanish for 49 (25%). Compared with the 100 patients in the first cohort, among the 93 patients enrolled to the second cohort, intracerebral haemorrhage was more frequent and cardiac arrest or traumatic brain injury causing unconsciousness was less frequent (table 1; appendix p 4).

Brain activation to motor commands was seen in all 15 healthy volunteers tested in English or in Spanish. 27 (14%) of 193 patients (16 [16%] of 100 from the first cohort and 11 [12%] of 93 from the second cohort) were diagnosed with cognitive-motor dissociation on at least one bedside EEG recording, and they were first diagnosed a median of 5 days after ICU admission (IQR 3–10). Comparing patients with and without cognitive-motor dissociation, the median time between onset of brain injury and the first cognitive-motor dissociation assessment did not differ (1 day [0–3] *vs* 1 day [0–4]), nor did the total number of EEG recordings (two [1–4] *vs* one [1–3]). Compared with patients without cognitive-motor dissociation, those with cognitive-motor dissociation did not differ with respect to age, sex, race, primary language, and underlying cause of acute brain injury (appendix pp 7–9).

Mean duration of mechanical ventilation was 17 (IQR 9–28) days, and 98 (51%) of 193 patients underwent tracheostomy before hospital discharge. Hospital complications were renal failure requiring dialysis in 23 (12%) patients, cardiac arrest in 25 (13%), and sepsis in 75 (39%). Overall median hospital length of stay was 27 days (14–41) and 56 (29%) patients had withdrawal of life-sustaining therapies. At hospital discharge, 71 (37%) patients were dead, seven (4%) went to a hospice, 38 (19%) to a long-term acute care hospital, 39 (20%) to a skilled nursing facility, seven (4%) to subacute rehabilitation,

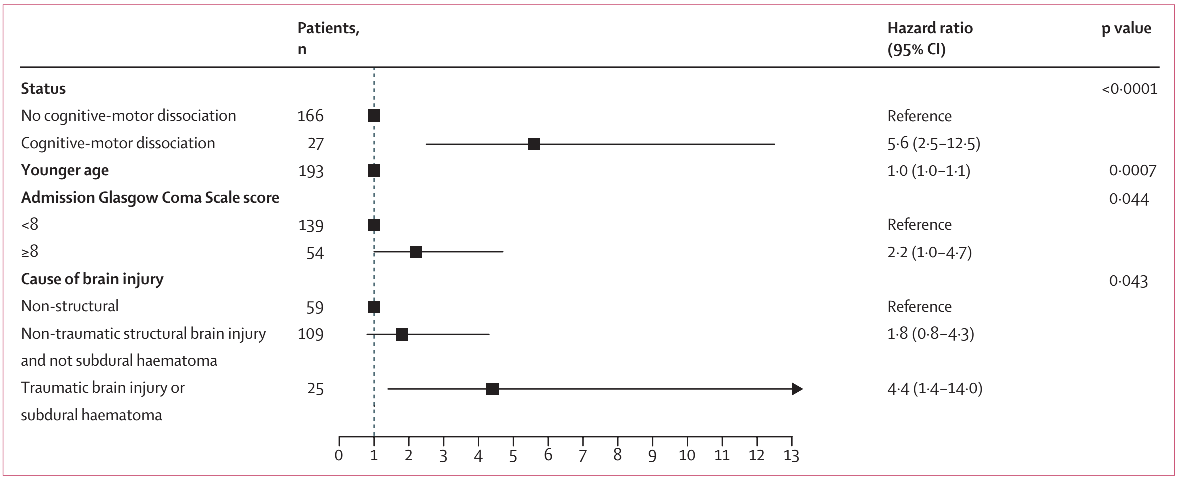

Figure 3: **Predictors of time to functional recovery**

Independent predictors of time to good functional recovery (defined as a GOS-E score of 4 or above) based on a Cox proportional hazards regression model in the overall population. We included variables associated with recovery from the univariate analysis in the multivariable models. GOS-E=Glasgow Outcome Scale–Extended.

27 (14%) to outpatient rehabilitation, and four (2%) went home with or without services.

Of the 193 patients included in the study and followed up to 12 months, 12 (6%) patients at 3 months, 21 (11%) patients at 6 months, and 28 (15%) patients at 12 months had recovered to a best GOS-E score of 4 or above. 27 patients with and 166 patients without cognitive-motor dissociation continued to show increasing rates of functional recovery across all three follow-up timepoints (figure 2; appendix pp 14–15). By 3 months after the injury, seven (26%) of 27 patients with cognitive-motor dissociation had recovered to a GOS-E score of 4 or better compared with five (3%) of 166 patients without cognitive-motor dissociation (OR 11·3 [95% CI 3·3–41·4; p=0·0001). At 6 months, nine (33%) of 27 patients with cognitive-motor dissociation had recovered to a GOS-E score of 4 or better compared with 12 (7%) of 166 patients without cognitive-motor dissociation (6·4 [2·3–17·4; p=0·0002). At 12 months, 11 (41%) of 27 patients with cognitive-motor dissociation and 17 (10%) of 166 patients without cognitive-motor dissociation had a GOS-E score of 4 or better (6·0 [2·4–15·1; p=0·0001). Seven (64%) of the 11 patients with cognitive-motor dissociation who recovered by 12 months had recovered by 3 months, whereas 12 (71%) of the 17 patients without cognitive-motor dissociation who recovered had made their recovery at 6 months or later. The 12-month restricted mean survival time to recovery was 8·0 months for patients with cognitive-motor dissociation and 11·0 months for patients without cognitive-motor dissociation. On average, patients with cognitive-motor dissociation had a 3·0 month (0·8–5·1) shorter recovery compared with patients without cognitive-motor dissociation (p=0·0061).

Presence of cognitive-motor dissociation, age, cause of traumatic brain injury or subdural haematoma, and admission GCS score were associated with time to functional recovery and functional improvement (appendix pp 9–11). Independent predictors of earlier time to recovery were diagnosis of cognitive-motor dissociation (hazard ratio [HR] 5·6 [95% CI 2·5–12·5]), traumatic brain injury or subdural haematoma as the underlying brain injury (HR 4·4 [1·4–14·0]), admission GCS score of at least 8 (HR 2·2 [1·0–4·7]), and younger age (HR 1·0 [1·0–1·1]; figure 3). Among 122 patients alive at hospital discharge, on follow-up the main shift (the greatest improvement) to good outcomes (an increase in GOS-E points) in patients with cognitive-motor dissociation compared with in those without cognitive-motor dissociation occurred at 3 months (OR 5·9 [1·8–20·7]), 6 months (OR 2·6 [0·9–7·4]), and 12 months (OR 3·0 [1·1–8·1]; table 2; appendix pp 16–17). At 3 months and at 12 months after the injury, the distribution of shifts in GOS-E points integrated across all cut points of the scale was 1 point higher for patients with cognitive-motor dissociation compared with those without cognitive-motor dissociation (table 2). However, at hospital discharge we found no difference, and at 6 months there was a non-significant shift towards improved outcomes in patients with cognitive-motor dissociation. Accuracy of the prediction models was assessed using the AUC from risk regression models in the presence of competing risks (appendix pp 12, 18). By comparing models with cognitive-motor dissociation alone, addition of demographic (eg, age) and clinical factors (eg, admission GCS and brain injury cause), and all measures combined, the AUC increased from 71·4 to 77·2 (p=0·020; increase of 5·8 [95% CI 0·9–10·6]) at 12 months when cognitive-motor dissociation was added to a final model that included demographic and clinical factors.

At hospital discharge, 122 (63%) of 193 patients were alive, of whom 38 (31%) were discharged to home or rehabilitation and 84 (69%) to a higher-level care setting. Patients discharged to home or rehabilitation

	Odds ratio* (95% CI)	p value	Distribution shift, GOS-E points	Missing data†	
				Cognitive-motor dissociation (n=27)	No cognitive-motor dissociation (n=166)
Hospital discharge	7·2 (2·2–29·3)	0·0010	0	0 (0%)	0 (0%)
3 months	5·9 (1·8–20·7)	0·0046	1·0	3 (11%)	10 (6%)
6 months	2·6 (0·9–7·4)	0·065	1·0	2 (7%)	24 (15%)
12 months	3·0 (1·1–8·1)	0·028	1·0	1 (4%)	20 (12%)

Data are n (%), unless otherwise indicated. GOS-E=Glasgow Outcome Scale–Extended. *Odds of a favourable shift in GOS-E scores in in patients with cognitive-motor dissociation versus those without. †Includes patients for whom data were not available at that specific timepoint.

Table 2: **Shift in GOS-E scores between patients with cognitive-motor dissociation and those without cognitive-motor dissociation at different follow-up timepoints**

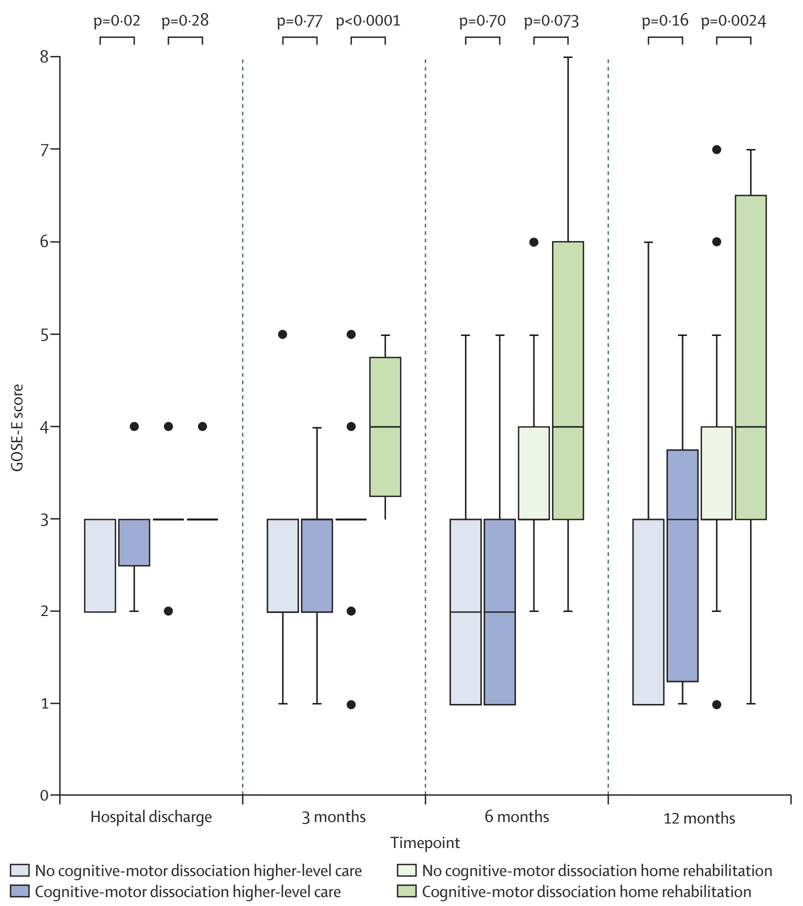

Figure 4: **Functional outcomes stratified by cognitive-motor dissociation diagnosis and discharge disposition**
The tops of the boxes indicate the third quartile, horizontal lines near the middle of the boxes indicate the median, and the bottom of the boxes indicate the first quartile. Whiskers extend from Q1 and Q3 to endpoints that are defined as the most extreme datapoints within Q1 – 1·5 × IQR and Q3 + 1·5 × IQR, respectively. Outliers outside the whiskers are represented by individual marks. GOS-E=Glasgow Outcome Scale–Extended.

had a higher chance of good 12-month functional outcomes compared with those who were discharged to a higher-level care setting (OR 5·4 for GOS-E of ≥4 [95% CI 2·2–13·6]; p=0·0003). Cognitive-motor dissociation status did not predict discharge disposition (1·5 [0·5–4·2]; p=0·44). At the time of hospital discharge, GOS-E scores were higher among patients with cognitive-motor dissociation compared with those without cognitive-motor dissociation who were discharged to a higher-level care setting (2·0 [1·1–4·1]; p=0·020). We found no difference in GOS-E score at hospital discharge between patients with cognitive-motor dissociation and those without cognitive-motor dissociation who were discharged home or to a rehabilitation setting (1·2 [0·8–1·7]; figure 4).

Patients with cognitive-motor dissociation who were discharged home or to a rehabilitation setting had higher GOS-E scores at 3 months (OR 4·5 [95% CI 2·0–33·6; p=0·0001), 6 months (1·9 [1·0–4·4; p=0·073), and 12 months after the injury (2·6 [1·4–6·2; p=0·0024; figure 4), accounting for other predictors such as age, admission GCS score, and injury type. We found no significant difference between patients with cognitive-motor dissociation and those without cognitive-motor dissociation who were discharged to a higher-level care setting at any of the follow-up timepoints (figure 4). In a multivariate longitudinal ordinal regression model among patients alive at discharge, cognitive-motor dissociation (7·2 [2·0–26·6]; p=0·0028), discharge to home or a rehabilitation setting (5·6 [1·7–17·7]; p<0·0001), and the interaction between time and discharge disposition (1·3 [1·2–1·5]; p<0·0001) independently predicted improvement in GOS-E score over time.

Discussion

In this observational cohort study, 14% of clinically unresponsive patients (ie, without any behavioural signs of command-following) with an acute brain injury showed signs on EEG of command-following within 1 week of injury. Patients with EEG evidence of command-following without accompanying behavioural signs (ie, cognitive-motor dissociation) had higher rates of good functional recovery at all investigated timepoints up to 12 months compared with those without cognitive-motor dissociation, as well as a shorter time to good recovery and a greater improvement in GOS-E score across all levels of functional outcome. A shorter time to good recovery was predicted by the presence of cognitive-motor dissociation, underlying traumatic brain injury, and higher GCS score on admission, with younger age having a minimal effect on time to recovery. Most patients with cognitive-motor dissociation who recovered by 12 months had recovered by 3 months, whereas most patients without cognitive-motor dissociation who recovered by 12 months did so at 6 or 12 months. Patients with cognitive-motor dissociation discharged home or to rehabilitation settings continued to improve at all follow-up timepoints, which was not the case for patients without cognitive-motor dissociation or patients with cognitive-motor dissociation who were not discharged to a home or rehabilitation setting. Detection of cognitive-motor dissociation might allow more accurate prediction of recovery trajectories and could help identify patients who would benefit most from rehabilitation interventions.

We enrolled patients with acute brain injury during the acute phase of hospitalisation, which differs from previous work in cohorts who were studied for recovery of consciousness, for which patients were recruited in the early or subacute rehabilitation setting.[33] We included almost a third of unconscious patients who had been screened for enrolment. Slightly more than a third of the screened cohort did not qualify for the study because they either started following commands clinically before enrolment, had a confounding neurological illness before the acute presentation, had uncontrollable seizures, were deaf, or were unconscious before the injury. The remaining third of screened patients were not included because of logistical reasons, EEG disconnection, or the family did not provide consent. Our results showed that, in healthy volunteers and clinically unresponsive patients with acute brain injury, brain activation was seen in response to commands spoken in both English and Spanish, which also supports the generalisability of our approach to other countries. When we compared characteristics of patients included in the study with those who had been excluded, no differences in demographics or severity of neurological impairment on admission were seen, but patients with brain haemorrhages (intracerebral haemorrhage or subarachnoid haemorrhage), cardiac arrest, and traumatic brain injury were slightly more common in our study, and patients with a mix of other diagnoses were more likely to have been excluded.

Cognitive-motor dissociation was found to predict 12-month functional outcome in the first cohort of 100 patients with acute brain injury.[13] There were slight differences between the first and second cohorts in our study, most importantly in the underlying cause of unconsciousness (in the second cohort, intracerebral haemorrhage was more common and cardiac arrest and traumatic brain injury less common than in the first cohort). These differences probably reflect minor changes in referral patterns possibly related to an ongoing observational cohort study focusing on unconscious intracerebral haemorrhage patients (NCT03990558). Despite minor differences between the two cohorts, cognitive-motor dissociation was predictive of better functional outcomes at all follow-up timepoints, both in the first and second cohorts, which supports the generalisability of our findings.

We have shown previously that brain activation in response to spoken commands can be detected early after brain injury,[13,21] and that the detection of cognitive-motor dissociation in these patients is associated with better recovery at 12 months.[13] Delayed recovery might be seen in unconscious patients in the rehabilitation setting,[6,34] but recovery trajectories of unresponsive patients with acute brain injury in the ICU setting are uncertain,[8] and for families seeking this information, the accurate prediction of recovery is not available.[9] We showed in this study that the recovery trajectories of patients with and without cognitive-motor dissociation are clearly different and, importantly, much earlier and persistently greater degrees of recovery can be expected in patients with cognitive-motor dissociation. Detection of cognitive-motor dissociation could represent a biological endotype, reflecting underlying brain injury mechanisms, which allows precise prediction of recovery and identification of patients who are especially amenable to therapeutic interventions (eg, intense rehabilitation efforts).[9]

We studied a cohort of unconscious patients with various underlying acute brain injuries, including structural injuries with or without traumatic brain injury, and non-structural mechanisms of injury. We showed that cognitive-motor dissociation—together with widely established predictors of recovery, including a higher GCS score on hospital admission, traumatic brain injury causing the impairment of consciousness, and younger age—predicted time to recovery. The clinical trajectories of patients with various underlying brain injuries might be quite different,[4,6,34] as supported by our multivariate analysis that identified traumatic brain injury or subdural haematoma as a predictor of earlier time to recovery and found that cognitive-motor dissociation was especially predictive for patients with structural non-traumatic brain injury. Up to now, most data for functional recovery trajectories are from patients with traumatic brain injury.[6,34] Studies have shown delayed recovery of consciousness in patients with traumatic brain injury, with 59% of unconscious patients having regained consciousness by 1 year, and 74% by 5 years.[6] In patients with non-traumatic disorders of consciousness, 17% were found to have recovered consciousness by 6 months, and an additional estimated 8% after 6 months.[4,35] Delayed functional recovery has been shown in patients with acute brain injury; however, existing bedside behavioural assessments are unable to accurately predict the trajectory of functional recovery in these patients. We showed that patients with traumatic brain injury as the cause of unconsciousness not only had a greater chance of recovery but also a shorter time to recovery than patients without traumatic brain injury. We also found that younger age remained in the models as an independent predictor of shorter time to recovery, albeit the effect was small for each year of age. Additionally, the diagnosis of cognitive-motor dissociation, particularly in patients with structural brain injury other than traumatic brain injury, might improve the accuracy of outcome predictions.

When applying prediction modelling that is based on population statistics to the bedside, careful counselling of families is warranted. Importantly, difficulties in the assessment of cognitive-motor dissociation are well established, even in healthy volunteers,[14] because conscious patients might decide to not engage with the motor imagery or motor activation paradigm (false-negatives; appendix p 12). Patients with cognitive-motor dissociation also might not recover (false-positives), because functional recovery does not rely on brain recovery alone, and secondary complications during recovery might occur. These considerations are important to address when integrating cognitive-motor dissociation into clinical practice.

Criteria to qualify for rehabilitation services differ between health-care systems globally, but at a minimum, our findings call into question the existing practice in some countries of applying strict participation time cutoffs to identify patients for whom rehabilitation services will be the most successful. We found that patients with cognitive-motor dissociation discharged home or to rehabilitation settings continued to improve at all follow-up timepoints, which was not seen for patients without cognitive-motor dissociation or patients with cognitive-motor dissociation who were not discharged to a home or rehabilitation setting. This finding needs to be interpreted with caution because our observational study design does not allow us to show that patients with cognitive-motor dissociation who did not receive rehabilitation would have benefited from rehabilitation.

Our study has several limitations. First, it was done at a single centre and included fewer than 200 patients, therefore external validity is limited. Large observational studies are warranted to clearly define the reproducibility of detecting cognitive-motor dissociation. However, although the cohort was small, it is by far the largest to date, and we were able to show reproducibility of findings across two independent cohorts at our centre. Routine EEG is sufficient for the diagnosis of cognitive-motor dissociation when combined with time-synchronised motor commands, and the computational algorithm to run the analysis is freely available for download.[13] However, to serve as an early biomarker to predict later recovery, studies will have to clearly define reproducibility across various sites and practice settings. Second, behavioural states are known to fluctuate and, for patients with chronic disorders of consciousness, repeat assessments over several days have been recommended.[36] For patients with acute brain injury in the critical care setting, repeat assessments might not establish a stable baseline as the neurological illness continues to evolve rapidly. Third, extended follow-up for years after the injury might establish a more complete recovery trajectory because increasingly small numbers of patients might still show recovery up to 10 years following brain injury.[34] Fourth, patients in the study might have had post-discharge hospitalisations or illnesses, which could have confounded the measured outcomes. Outcomes in patients who were lost to follow-up are uncertain and secondary worsening is possible. However, our study indicated the potential for cognitive-motor dissociation to show recovery following brain injury. Fifth, outcome measures were limited to crude outcome scales, and future studies should include patient-centred outcomes capturing cognition, mood, and quality of life. Sixth, phenotyping and endotyping—including by analysis of genetics, metabolomics, and standardised MRI protocols—might further support accurate prediction schemes for patients' recovery trajectories.[9] Seventh, we included a heterogenous patient cohort, but including patients with different underlying brain injuries allowed us to show that cognitive-motor dissociation is a behavioural state not restricted to a specific brain injury and predicts shorter time to recovery together with well-established predictors of rapid recovery, such as traumatic brain injury as the cause of the injury, and poor neurological function on hospital admission, supporting the generalisability of our findings. Eighth, decisions about discharge disposition are complex, and unaccounted factors—including socioeconomic elements specific to a particular health-care context—might be the deciding factors. These factors might or might not be easy to change, even with the most precise prediction algorithms. Unmeasured factors that are associated with cognitive-motor dissociation might also drive discharge decisions. It is unclear whether re-triaging patients with cognitive-motor dissociation from higher-level care to a home-rehabilitation setting would result in better outcomes for these patients, because we did not randomly assign patients to rehabilitation type. Lastly, some patients had withdrawal of life-sustaining therapies, which always needs to be considered in natural history studies of acute brain injury. To take this limitation into account, patients who had withdrawal of life-sustaining therapies or who were lost to follow-up were censored, and death was treated as a competing risk.

In conclusion, our study showed that patients with cognitive-motor dissociation recovered earlier after acute brain injury and to a larger degree than did those without cognitive-motor dissociation. Prediction of time to recovery might allow enrichment of interventional trials aimed at supporting recovery of consciousness. Cognitive-motor dissociation could serve as a biomarker of the residual integrative function of the injured brain. Cognitive-motor dissociation is not a static measure but might serve as an indicator of possible recovery, if detected.

Contributors

QS and JC designed the study. JE, QS, and JC wrote the first draft. JE, QS, KD, LG, JCC, AVr, AVe, and JC directly accessed and verified the underlying data. QS, KD, and AB contributed to the statistical analysis. JC was responsible for the decision to submit the manuscript. All authors participated in a critical review and revision of the report and have approved the final draft.

Declaration of interests

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Data sharing

Deidentified data and study protocols used in this publication will be made available to qualified researchers who provide a valid research question. Please direct inquiries to the corresponding author.

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