Annals of Physical and Rehabilitation Medicine xxx (2020) xxx–xxx

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Original article

Potential for recovery between 4 and 8 years after a severe traumatic brain injury. Data from the PariS-TBI longitudinal study

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ARTICLE INFO

Article history:
Received 12 November 2019
Accepted 5 July 2020

Keywords:
Traumatic brain injury
Outcome assessment
Mood
Adult
Longitudinal study

ABSTRACT

Background: Severe traumatic brain injury (TBI) is a leading cause of complex and persistent disability. Yet, long-term change in global functioning and determinants of this change remain unclear.
Objectives: This study aimed to assess change in global functioning in the long-term after severe TBI and factors associated with the change.
Methods: This was a prospective observational study of an inception cohort of adults with severe TBI in the Paris area (PariS-TBI). Outcome was assessed at 1, 4 and 8 years post-injury. For the included participants (n = 257), change in global outcome between 4 and 8 years was evaluated with the Glasgow Outcome Scale Extended (GOSE) score, and its association with pre-injury, injury-related and post-injury variables was tested with univariate and multivariable analyses.
Results: More than half of the 73 participants evaluated at both 4 and 8 years showed global improvement (of at least one point) in GOSE score and an improvement in mood, executive function, and subjective complaints. On univariate analysis, none of the pre-injury, injury or post-injury variables were associated with GOSE score change between 4 and 8 years, except for GOSE score at 4 years (rho = −0.24, P = 0.04). On multivariable analysis, probability of increased GOSE score was associated with more years of education (odds ratio 1.18 [95% confidence interval 1.02–1.37], P = 0.03). The change in GOSE score was significantly correlated with change in Hospital Anxiety Depression Scale score between 4 and 8 years (rho = −0.42, $P < 0.001$).
Conclusions: Most participants with severe TBI in the present sample showed a late improvement (4 to 8 years post-injury) in global functioning. Of the socio-demographic and injury-related factors, only more years of education was associated with improvement in global functioning. Decreased anxiety and depression symptoms were associated with improved global functioning. Targeting interventions to enhance resilience may be the most effective in the long-term after severe TBI.

1. Introduction

Traumatic brain injury (TBI) is a leading cause of acquired disability and an important public health concern worldwide. Its consequences can persist for a long time and interfere with daily functioning. The average annual incidence of TBI is 262/100,000 inhabitants in Europe [1]. The prevalence of persistent sequelae

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https://doi.org/10.1016/j.rehab.2020.07.005
1877-0657/

was estimated at 704/100,000 inhabitants in a French national survey [2]. About 10% of TBI case are considered severe, and the risk of persistent impairment increases with TBI severity.

Although the long-term prognosis is of major importance for individuals with TBI, their relatives, and professionals and from a medico-economic perspective, the literature on this issue remains scarce. Most published studies focused on a 6-month or 1-year outcome [3]. In the few previous studies describing change over a longer time, more than 2 years post-TBI, results were controversial [4–6]. Some studies suggested a global long-term stability [7,8], whereas others found a continued improvement, then a delayed decline 10 years after TBI [5,9] or a decline for half of the sample between 5- and 10-year follow-up [6]. A special emphasis was given to psychological and behavioral sequelae, considered the most serious problems in the long-term in previous research [10,11]. Previous publications mostly included people with moderate to severe TBI rather than exclusively severe TBI. Most studies that assessed long-term outcome focused on factors accounting for outcome, rather than those accounting for change over time. Recent studies described trajectories of overall disability at different times and predictors of these trajectories by using individual growth curve analysis [5,6,9].

In this study, we aimed to describe the late changes (between 4 and 8 years) in overall disability after exclusively severe TBI. Few results are available in this particular population. Moreover, little is known about the factors that account for late changes in post-TBI outcomes. A second aim was to assess variables that could account for these late changes. Recovery and outcome after TBI are multidetermined, and previous studies reported the impact of pre-injury, injury and post-injury variables in prognostic studies [5,6]. In the present study, we addressed these issues by assessing long-term changes between 4 and 8 years post-TBI and testing factors that could account for these changes among the pre-injury, injury and post-injury variables. We hypothesized a stability or slight improvement in global functioning between 4 and 8 years and that long-term change would be related to the pre-traumatic state rather than severity factors.

2. Material and methods

2.1. Participants

We conducted an observational study focusing on long-term functional evolution in a French multicentric inception cohort of individuals with severe TBI, the PariS-TBI study. Consecutive individuals aged ≥ 15 with Glasgow Coma Scale (GCS) score ≤ 8 before hospital admission in the absence of other causes of coma were recruited by mobile emergency services in the Paris area from 2005 to 2007. A total of 504 individuals with TBI were included in the cohort; 247 (49%) died during the acute phase. For the 504 individuals with TBI, most were men (76%), and the mean (SD) age was 42 (20) years. The leading causes of TBI were road traffic accident (53%) and accidental and non-accidental falls (23% and 13%, respectively). GCS scores for brain injury severity were as follows: score 3 or 4, 207 (41%) individuals; score 5 or 6, 148 (29%), and score 7 to 8, 139 (28%).

3. Assessments

3.1. PariS-TBI study design

Pre-injury socio-demographic data were collected during the acute stage, as were severity-related factors. Disability was assessed with the Glasgow Outcome Scale (GOS) [12] at intensive care unit (ICU) discharge. Participants were evaluated at 1, 4 and 8 years post-injury. Assessment consisted of a telephone interview at 1-year follow-up and a face-to-face interview at 4 and 8 years. All assessments were conducted by trained neuropsychologists, and data were collected from participants and/or their relatives when possible. Of the 257 survivors at the end of the acute phase, 134 were evaluated at 1 year (118 lost to follow-up and 5 deceased), 147 at 4 years (98 lost to follow-up and 7 deceased), and 86 at 8 years (128 lost to follow-up, 22 refused to participate, 7 deceased). The actual sample size was not calculated and directly reflected the initial sample minus dead participants, those lost to follow-up, and those who refused to participate.

Global functioning was assessed with the GOS Extended (GOSE) scale, a maximum score of 8 corresponding to full recovery and 1 to death [13]. The Dysexecutive Questionnaire (DEX) [14] was completed by the participant and/or relatives to assess executive dysfunctions in daily life. The DEX questionnaire consists of 20 items exploring emotional, motivational, behavioral, and cognitive domains on a scale from 0 to 4, with a maximum score of 80; higher scores indicate more severe disorders. Mood disorders were measured with the Hospital Anxiety and Depression Scale (HADS), a self-reporting questionnaire with 2 subscores for anxiety and depression, both ranging from 0 to 21; higher scores (maximum = 42) correspond to more severe anxiety and depression symptoms [15]. Subjective physical, cognitive and behavioral complaints were assessed with the Brain Injury Complaint Questionnaire (BICoQ) [16], a complaint questionnaire designed to assess a wide range of difficulties commonly reported by participants with acquired brain injury. It contains closed questions (yes/no) about cognitive processes (language, memory, attention, and executive functions), fatigue, mood, sleep, somatic disorders and behavior (irritability/apathy). GOSE, DEX, HADS, and BICoQ questionnaires were completed at 4 and 8 years post-injury.

The longitudinal outcome of the PariS-TBI cohort at different follow-up times were previously reported [17–27].

4. Statistical analyses

Pre-injury socio-demographic factors, injury-related factors, and post-injury factors are reported with mean (SD) and range for continuous variables. Median and interquartile range were used to describe numerical variables in small samples. Categorical variables are described with number (%). In case of missing data, percentages are based on the number of participants who answered. To study the biases linked to lost to follow-up, evaluated participants were compared to non-evaluated participants by Student *t*-test for quantitative data and Chi^2 test for categorical variables (α error 5%). Post-hoc analyses for the Chi^2 test involved adjusted standardized residuals.

The change in GOSE score between 4 and 8 years was calculated (8-year GOSE score minus 4-year GOSE score, a positive score indicating improvement and a negative score deterioration) and further treated as an ordinal variable. To assess variables associated with GOSE score change between 4 and 8 years, we used univariate analyses with Spearman's rank correlation coefficient for continuous and ordinal variables, with Mann–Whitney test for dichotomous independent variables and Kruskal–Wallis test for nominal independent variables. A multivariable ordinal model was computed with change in GOSE score as the dependent variable and variables that predicted functional outcome after TBI in previous studies as independent variables [6]. We felt that it would be unwarranted to include a covariate that resulted in excluding $> 10\%$ of the sample. Only pre-injury and injury-related variables were included in the model to respect proportional-odds assumption and avoid missing data. The correlation of HADS and BICOQ score changes between 4 and

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8 years was assessed with Pearson's r. Missing data were not imputed. $P < 0.05$ was considered statistically significant. All analysis involved using R v3.5 [28].

5. Ethical aspects

The research was completed in accordance with the Helsinki Declaration. Individuals with TBI and their families were informed about the purpose of the PariS-TBI observational study upon inclusion in the database. Before the 8-year assessment, participants and their proxies were given written and oral information and gave their oral consent to participate, in accordance with French legislation. The study was approved by the local ethics committee (*Comité de Protection des Personnes*, CPP XI, Poissy-Saint Germain hospital) and by the Consultative Committee for Treatment of Health Research Information (CCTIRS, from the French Ministry of Health). The study was registered at ClinicalTrials.gov in August 2011 (identifier: NCT01437683).

6. Results

Table 1 shows descriptive statistics and univariate analyses comparing initial social-demographic characteristics and core acute-care data for participants who were followed up at both 4 and 8 years (evaluated, $n = 73$) and those who could not be evaluated at these times (128 lost to follow-up, 22 refused to participate, 13 not evaluated at 4 years). Mean (SD) time (months) since the accident was 49.5 (6.2) and 98.1 (8.3) months at 4 and 8 years, respectively. The 2 groups significantly differed in frequency of pre-injury employment and in occupational class. Adjusted standardized residuals were only at least ± 2 for the "white collar" occupational class, which was overrepresented in evaluated participants. Hence, significantly more participants were employed pre-injury in this group. The 2 groups did not differ in other characteristics.

At 8 years, GOSE assessment of overall disability in the 73 evaluated participants was distributed as follows: 14 (19%) had a severe disability, 34 (47%) moderate disability, 25 (34%) good recovery. Between 4 and 8 years, global functioning deteriorated for 9 (12%) participants, remained stable for 26 (36%) and improved for 38 (52%) (Fig. 1). The change in GOSE scores between 4 and 8 years is illustrated in Fig. 2. Participants with improvement in function between 4 and 8 years were mostly those who at 4-year assessment needed partial assistance in activities of daily living (ADL); who at 4-year assessment, although independent in ADL, were not able to resume work/school or previous social activities; or who at 4 years, had minor physical and mental deficits that affected daily life (i.e., GOSE scores 4–6). Univariate analysis of the change in GOSE score between 4 and 8 years is shown in Table 2. None of the pre-injury demographic, severity-related or 1-, 4- or 8-year outcome variables were significantly associated with GOSE score change, except for the 4-year GOSE score (Pearson's rho = −0.24, $P = 0.04$). In a multivariable ordinal model, among the pre-injury and injury severity-related variables, only years of education was associated with GOSE score change (Table 3). More years of education was associated with increased probability of improvement in global functioning between 4 and 8 years post-TBI.

The HADS score was recorded for 61 participants at both 4 and 8 years. Overall, 43% of participants showed an increase in anxiety and depression symptoms; for 10%, symptoms remained stable; and for 47%, symptoms improved. According to the previously defined 8-point cut-off score for anxiety and depression subscales, 43% had anxious disorders and 31% had a probable depression at 4 years. At 8 years, these rates were 33% for both anxiety and depression. The change in GOSE score was significantly correlated with change in HADS score between 4 and 8 years (Spearman's rho = −0.42, $P < 0.001$) (Fig. 3).

Table 1
Univariate analysis of evaluated and non-evaluated patients with traumatic brain injury.

	Not evaluated	Missing data	Evaluated	Missing data	*P*-value[a]
Patients' characteristics	*n* = 163		*n* = 73		
Sex		0 (0%)		0 (0%)	0.92
Female	31 (19%)		15 (20.5%)		
Male	132 (81%)		58 (79.5%)		
Age at injury (years)	33.5 (15.8) [15.2–82.7]	2 (1.2%)	34.1 (13.4) [15.4–74.8]	0 (0%)	0.80
Years of education	11.2 (2.8) [5–20]	64 (39.3%)	12.1 (3.1) [6–19]	2 (2.7%)	0.04
Occupational class		32 (19.6%)		4 (5.5%)	0.02
Blue collar	54 (41.2%)		31 (44.9%)		
White collar	11 (8.4%)		16 (23.2%)		
Retired	12 (9.2%)		3 (4.3%)		
Student	33 (25.2%)		14 (20.3%)		
Unemployed	21 (16%)		5 (7.2%)		
Employment pre-injury		32 (19.6%)		4 (5.5%)	0.02
Yes	65 (49.6%)		47 (68.1%)		
No	66 (50.4%)		22 (31.9%)		
Living alone before TBI		4 (2.5%)		0 (0%)	0.53
No	121 (76.1%)		52 (71.2%)		
Yes	38 (23.9%)		21 (28.8%)		
Alcohol addiction before TBI		10 (6.1%)		5 (6.8%)	0.11
No	128 (83.7%)		63 (92.6%)		
Yes	25 (16.3%)		5 (7.4%)		
Initial GCS					
3–4	39 (25%)	7 (4.3%)	19 (26.4%)	1 (1.4%)	0.90
5–6	57 (36.5%)		24 (33.3%)		
7–8	60 (38.5%)		29 (40.3%)		
Duration of coma (days)	8.8 (7.6) [0–50]	22 (13.5%)	9.7 (6.4) [0–24]	11 (15.1%)	0.37
Time to follow command (days)	11.8 (11.7) [0–81]	28 (17.2%)	12.6 (11) [0–56]	14 (19.2%)	0.62
Length of stay in ICU (days)	25.1 (21.2) [2–134]	1 (0.6%)	28.3 (21.7) [3–119]	0 (0%)	0.30
GOS at ICU discharge	3.8 (0.9) [2–5]	23 (14.1%)	3.8 (0.8) [3–5]	9 (12.3%)	0.82
1-year GOSE	5.2 (1.4) [2–8]	84 (51.5%)	4.8 (1.3) [3–7]	25 (34.2%)	0.14

GCS: Glasgow Coma Scale; ICU: intensive care unit; GOS: Glasgow Outcome Scale; GOSE: GOS Extended. Data are mean (SD) [range] unless indicated.
[a] Chi^2 or Student *t*-test.

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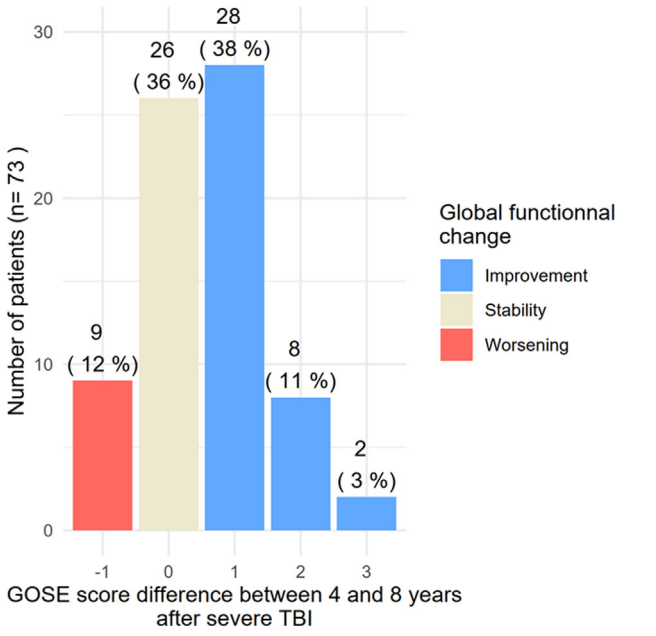

Fig. 1. Difference in Glasgow Outcome Scale Extended scores between 8 and 4 years after traumatic brain injury (TBI) (8-year minus 4-year score).

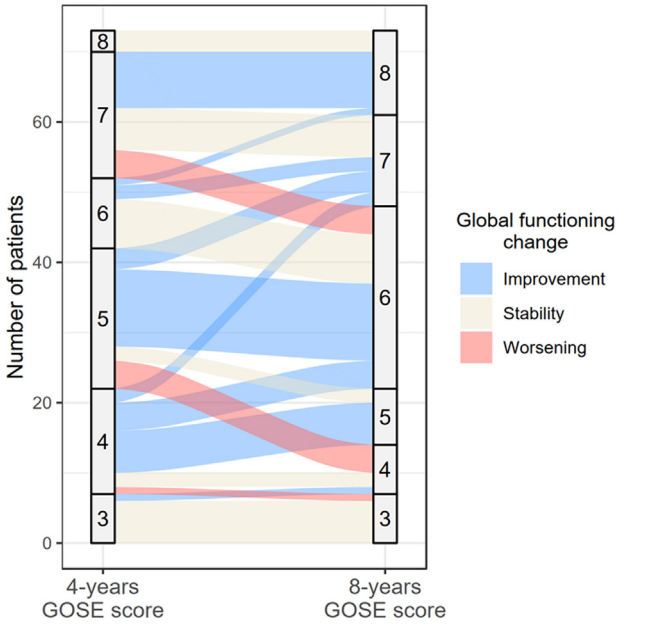

Fig. 2. Changes in GOSE levels between 4 and 8 years after TBI. GOSE, Glasgow Outcome Scale Extended. White: decrease in GOSE score; light grey: stable score; dark grey: increase in GOSE score.

Between 4 and 8 years, the change in DEX score (DEX self-completed by participants) was available for 44 participants. The score decreased (improved) for 64% of the sample, remained stable for 2% and increased (worsened) for 34%. We found no significant correlation between changes in DEX and GOSE scores between 4 and 8 years (Spearman's rho = −0.08, $P = 0.59$). Overall, 37 (46%) participants showed a decrease in relative DEX score, 5% stable scores, and 49% an increase. We found no significant correlation between change in relative DEX score and GOSE score between 4 and 8 years (Spearman's rho = −0.04, $P = 0.8$).

A total of 60 participants completed both 4- and 8-year BICoQ assessments. BICoQ score decreased (fewer complaints) for 48% of participants, remained stable for 12% and increased for 40%. We found no significant correlation between change in GOSE and BICoQ scores between 4 and 8 years (Spearman's rho = −0.18, $P = 0.17$) but rather a significant correlation between change in BICoQ and HADS scores (Pearson's r = 0.51, $P < 0.001$).

Table 2
Univariate analysis of the 4- to 8-year change in Glasgow Outcome Scale Extended score with follow-up variables.

	Spearman's rho, Mann–Whitney W or Kruskal–Wallis rank sum test, Chi^2	*P*-value
Age ($n = 73$)	−0.09[a]	0.47
Sex ($n = 73$)	515[b]	0.25
Years of education ($n = 71$)	0.20[a]	0.09
Occupational class pre-injury ($n = 69$)	3.99[c]	0.41
Employed pre-injury ($n = 69$)	570.5[b]	0.47
Living alone pre-injury ($n = 73$)	529.5[b]	0.84
Alcohol abuse ($n = 68$)	142.5[b]	0.72
GCS score ($n = 72$)	529.5[a]	0.83
Duration of coma ($n = 62$)	−0.15[a]	0.26
Time to follow command ($n = 59$)	−0.16[a]	0.23
Length of stay in ICU ($n = 73$)	0.01[a]	0.92
GOS score at ICU discharge ($n = 64$)	< 0.01[a]	0.99
GOSE score at 1 year ($n = 48$)	0.05[a]	0.75
GOSE score at 4 years ($n = 73$)	−0.24[a]	0.04
HADS anxiety score at 4 years ($n = 64$)	0.19[a]	0.13
HADS depression score at 4 years ($n = 64$)	0.15[a]	0.24
HADS total score at 4 years ($n = 64$)	0.19[a]	0.13
DEX score at 4 years (self-report) ($n = 48$)	0.11[a]	0.45
DEX score at 4 years (proxy-report) ($n = 66$)	0.10[a]	0.43
HADS anxiety score at 8 years ($n = 66$)	−0.11[a]	0.39
HADS depression score at 8 years ($n = 66$)	< 0.01[a]	0.97
HADS total score at 8 years ($n = 66$)	−0.05[a]	0.68
DEX score at 8 years (self-report) ($n = 66$)	0.05[a]	0.67
DEX score at 8 years (proxy-report) ($n = 41$)	0.03[a]	0.84

TBI: traumatic brain injury; GCS: Glasgow Coma Scale; GOS: Glasgow Outcome Scale; ICU: intensive care unit; GOSE: Glasgow Outcome Scale Extended; HADS: Hospital Anxiety Depression Scale; DEX: Dysexecutive Questionnaire.
[a] Spearman's rho.
[b] Mann–Whitney test.
[c] Kruskal–Wallis rank sum test.

Table 3
Multivariable regression analysis of factors involved in the 4- to 8-year change in GOSE score ($n = 70$).

	OR	95% CI	*P*-value
Age (years)	0.98	0.94–1.01	0.18
Sex (ref. male)	0.40	0.13–1.18	0.10
Years of education	1.18	1.02–1.37	0.03
GCS score	0.92	0.72–1.16	0.48
Length of stay in ICU (days)	1.01	0.99–1.03	0.34

OR: odds ratio of a higher score at 8 than 4 years from the trauma per 1-unit increase in numerical variables or compared to the reference category of categorial variables; 95% CI: 95% confidence interval; GCS: Glasgow Coma Scale; ref.: reference; ICU: intensive care unit.

7. Discussion

At 8 years after a severe TBI, about a third of our sample showed good recovery according to the GOSE. Global outcome seemed to agree with previous results for individuals with severe TBI at 10-year follow-up among a cohort with mild to severe TBI from a rehabilitation center [4]. However, when comparing 4- and 8-year outcomes, more than half of our participants showed global improvement (of at least one point) on the GOSE and also improvement in mood (HADS), executive function (DEX) and subjective complaints (BICoQ). The change in GOSE score from 4 to 8 years was inversely correlated with the 4-year GOSE score and the 4- to 8-year HADS change score. Surprisingly, the GOSE change

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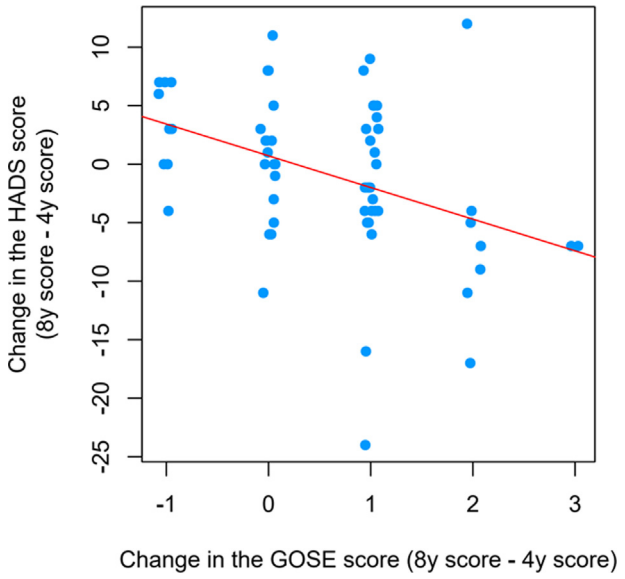

Fig. 3. Correlation between change in GOSE score and change in HADS score between 4 and 8 years after severe traumatic brain injury (TBI) ($n = 61$). GOSE, Glasgow Outcome Scale Extended; HADS, Hospital Anxiety and Depression Scale.

score was not significantly correlated with the DEX or BICoQ change scores. On multivariable analysis, a more years of education was the only pre-injury or TBI severity-related variable associated with increased GOSE score between 4 and 8 years after severe TBI.

The GOSE score was decreased in only 12% ($n = 9$) of participants. Although commonly used in TBI outcome research, the GOSE scale has rarely been used, or with different statistical approaches, in previous longitudinal studies examining functional outcome over 5 years after TBI, so comparing previous research with the present results is difficult. For a group of individuals with moderate to severe TBI, the GOSE score initially increased and peaked approximately at 10 years, then decreased [5]. Similarly, functional outcome evaluated with Barthel Index and Functional Independence Measure improved between acute-care discharge and 3-year evaluation in a prospective cohort of individuals with moderate to severe TBI from acute trauma centres [29]. In contrast, the GOSE score remained stable across 1, 2, and 5 years post-TBI in a cohort of individuals with moderate to severe TBI [30]. In this study, age < 30 years and being employed at the time of injury was associated with improved GOSE score. In contrast, among unemployed participants, older individuals showed stable and decreased GOSE scores. In the same cohort, with a supplementary 10-year follow-up, GOSE score decreased between 5- and 10-year follow-up in 37% of the sample; 56% showed no change [6]. In a study reporting very extended follow-up, mobility, self-care, employability, relationships and living skills domains were stable between 6 and 23 years after a severe TBI in a consecutive series of rehabilitation patients [31]. In individuals with mild to severe TBI, functional outcome was stable across a broad range of areas at 2, 5, and 10 years post-injury [4]. Variability of the change over time in overall disability between studies is surprising and difficult to explain. One hypothesis explaining the overall decrease in disability in our sample is the organization of the French health care system, which provides long-term outpatient rehabilitation and community reentry support [24].

Concerning factors associated with long-term outcome, we found the change in the GOSE score between 4 and 8 years negatively correlated with the 4-year GOSE score. Because functional outcome remained stable or improved in most of our participants, this finding reflected that participants with improvement were more disabled at 4 years, that is to say, had a potential range of progression. None of the other tested socio-demographic pre-injury, injury-related, and post-injury variables were correlated with change in global functioning in the long-term in our univariate analysis. More years of education was associated with improved global functioning in our multivariable analysis. In a previous study, 10 years after mild to severe TBI, longer education was associated with better GOSE outcome [32]. This beneficial effect of longer education was found in another major TBI cohort at 5 years [33]. In contrast, in individuals with moderate to severe TBI followed at 1, 2, and 5 years, education duration treated as a dichotomized variable was not associated with GOSE score change, nor at a supplementary 10-year follow-up [6,30]. This difference with our results might be related to the dichotomization of the study duration. We did not find other studies assessing overall disability change by education length after a TBI.

Concerning the age effect, in a large pooled sample study, the odds of a poor outcome at 6 months (i.e., death or unfavorable outcome) linearly increased by 40% to 50% for each 10 years of age. Pretz et al. found age, functional independence measure score at rehabilitation admission, rehabilitation length of stay and race associated with baseline GOSE score as well as rate and extent of both improvement and decline over time [5]. Older age was significantly associated with low initial and high linear decrease of GOSE score over time, with a modest effect. A modest but significant effect of age on GOSE trajectory was reported in a recent 10-year follow-up study [6]. According to previous and our results, older age seems associated with low early functional outcome but does not seem to have an important effect on evolution of global functioning. In previous studies, long-term functional outcome or employability could be predicted with a combination of pre-injury, injury severity-related, and disability-related variables at acute-care or rehabilitation discharge [26,31]. Our results suggest that the pattern of change in functional outcome over the long-term might depend on other factors.

In this regard, the correlation between change in HADS and GOSE scores between 4 and 8 years was an interesting result. Of course, correlation does not imply causation. However, the high rates of anxiety and depression symptoms in our sample should encourage the provision of psychological support in this population, even late after the injury. Psychological resilience has been found a significant predictor of increased participation after mild to severe TBI, and Wardlaw et al. argued for the development of strategies to enhance psychological resilience to limit psychological consequences of TBI and increase participation [34]. Moreover, a specific resilience and adjustment intervention diminished psychological distress in individuals with mild to severe TBI [35]. The significant correlation between changes in BICoQ and HADS scores could be interpreted in two ways. On the one hand, participants may have been less likely to report complaints when their mental health improved and on the other, complaints may have decreased and psychological status improved in parallel with overall functional improvement. However, the lack of significant correlation between changes in GOSE and BICoQ scores did not support this latter hypothesis.

This study has some limitations, the most important being the high attrition rate. This problem is common in long-term follow-up studies, particularly in cohorts of individuals from acute care units. However, our sample was homogenous and the evaluated and non-evaluated groups did not differ in the most common demographic and injury severity-related predictors of long-term outcome. The small sample size also limited the power of the statistical analyses. Finally, the study had a relatively high proportion of missing data regarding DEX scores at both 4- and 8-year assessments, which prevented or limited a comprehensive investigation of the late changes in outcome after severe TBI.

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8. Conclusions

Most individuals with severe TBI in our sample showed a late improvement in functioning (4 to 8 years post-injury), which was an encouraging result. Among demographic and injury severity-related measures, only years of education was significantly correlated with change in overall disability between 4 and 8 years post-TBI. More years of education was associated with improved global functioning. Participants with more severe impairments at 4 years showed improvement between 4 and 8 years. A decrease in anxiety and depression symptoms was associated with improved global functioning. Targeting interventions to enhance resilience may be the most effective in the long-term after severe TBI.

Funding

The first part of this study and the 8-year evaluation were funded by a grant from the French Ministry of Health (Programme hospitalier de recherche clinique 2004 and 2012, AOM04084) and sponsored by AP–HP (Département de la recherche clinique et du développement). The second part of this study (4-year outcome) was funded by a grant from the Institut de recherche en santé publique (IRESP).

Disclosure of interest

The authors declare that they have no competing interest.

Acknowledgements

The authors thank all members of the CRFTC Steering Committee (*Centre Ressource Francilien du Traumatisme Crânien*) for their valuable help.

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Please cite this article in press as: Ruet A, et al. Potential for recovery between 4 and 8 years after a severe traumatic brain injury. Data from the PariS-TBI longitudinal study. Ann Phys Rehabil Med (2020), https://doi.org/10.1016/j.rehab.2020.07.005