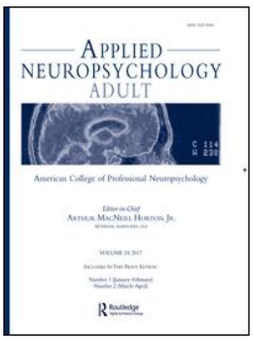

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Cognitive reserve index and functional and cognitive outcomes in severe acquired brain injury: A pilot study

Debora Bertoni[a], Federica Petraglia[b], Benedetta Basagni[a], Giuseppe Pedrazzi[c], Katia De Gaetano[a], Cosimo Costantino[d], and Antonio De Tanti[a]

[a]Centro Cardinal Ferrari, Fontanellato, Italy; [b]Rehabilitation Medicine Service, Rehabilitation Geriatrics Department, NHS-University Hospital of Parma, Parma, Italy; [c]Department of Medicine and Surgery, Unit of Neuroscience Interdepartmental Centre of Robust Statistics (Ro.S.A). University of Parma, Parma, Italy; [d]Department of Medicine and Surgery, University of Parma, Parma, Italy

ABSTRACT

Background: Many variables affect outcome after brain injury. Cognitive reserve (CR) is a subjective factor that reflects a set of personal characteristics and that differentiates individuals. It may influence an individual's capacity to react to brain injury.
Objective: To study the effects of cognitive reserve on functional and cognitive outcome at the end of rehabilitation, in patients with severe acquired brain injury (sABI), by means of the Cognitive Reserve Index questionnaire (CRIq).
Methods: We report a retrospective study of a continuous series of sABI patients on first admission to a rehabilitation center. Disability and cognitive outcomes were recorded.
Results: In the 94 patients enrolled, the assessments after rehabilitation showed a significant gain measured with the disability Rating Scale for patients with a higher CR (CRIq$\geq$ 85). A significant negative correlation was found: between CRIq scores and the interval elapsing before first access to neuropsychological assessment, between CRIq scores, especially level of education, and tests that measure the same domain (attention).
Conclusions: Improvements in overall and cognitive disability emerged, but CR did not seem to substantially influence outcome in this sample of patients. This result may be partly due to the clinical severity of the population studied and the sample's dimension, although quantitatively representative of the population.

KEYWORDS
Cognitive reserve; functional outcome; neurological rehabilitation; severe acquired brain injury

Introduction

The term severe acquired brain injury (sABI) includes a variety of acute brain lesions of traumatic and non-traumatic origin (tumours, anoxia, brain hemorrhage and ischemia, infections and toxic-metabolic encephalopathy), characterized by onset of variably prolonged coma (Glasgow Coma Scale $<=$8) and simultaneous motor, sensory, cognitive and/or behavioral impairment (De Tanti et al., 2015). According to the *International Classification of Functioning Disability and Health* (ICF, OMS WHO, 2001, 2002; Lexell & Brogårdh, 2015), patients with sABI often have a variety of neuromotor and cognitive sequelae that influence their participation in daily activities. However, individuals with organic damage of the same severity often have very different functional outcomes (McHugh et al., 2010; Nichol et al., 2011) and prediction models are difficult to apply in clinical practice (Greicius et al., 2009). To explain differences in outcome, many studies have analyzed a number of possible prognostic factors in patients with sABI. Briefly, these factors can be classified as *objective* and *subjective*, where *objective* means data on the lesions, and *subjective* means personal characteristics. Among objective variables, etiology (Avesani et al., 2018), severity (Harvey, 2015), site and dimension of organic damage (Baker et al., 2019), duration of the state of altered consciousness and sequelae derived from the lesion (Allanson et al., 2017) have been investigated in previous studies. New and emerging genetic and biomarker predictors (Bagnato et al., 2020), as well as high resolution magnetic resonance imaging predictors are being defined (Maas et al., 2005). Among predictive subjective variables, age at onset (Hukkelhoven et al., 2003), psychological characteristics before the event and sociodemographic aspects (Hoofien et al., 2002; Seagly et al., 2018), such as education (Van der Naalt et al., 2017), have been examined in the literature.

The concept of Reserve (R) was introduced in order to clarify what differences determine dissimilar functional outcomes in persons who suffered similar brain damage. R is therefore a set of personal characteristics prior to a cognitive disease, that differentiate individuals and that could influence outcome (Stern, 2002; Mathias & Wheaton, 2015). At a theoretical level, researchers have divided R into *passive* and *active* (Katzman, 1993; Stern, 2002). The model of *passive* reserve states that individuals have a capacity that defines to what extent an insult (due to pathology or age) can be

CONTACT Benedetta Basagni benedetta.basagni@centrocardinalferrari.it Centro Cardinal Ferrari, via IV Novembre 21, Fontanellato, Parma, Italy.

sustained before causing impairment of function. This concept is in line with a quantitative model of passive brain reserve in terms of neurons and synapses, known also as Brain Reserve (Katzman et al., 1988), according to which overall performance is better in individuals with a larger brain mass. This model is sustained by studies showing a lower incidence of dementia in individuals with higher brain mass (Mathias & Wheaton, 2015; Solé-Padullés et al., 2009; Stern, 2002, 2009), identifying this condition as a protective factor against brain disease. In contrast to this view, the *active* reserve model takes a more dynamic and less quantitative perspective, in which R is correlated with the extent to which an individual uses the resources available to him. It is a model in which the brain reacts actively to damage, exploiting previously learned cognitive processes or utilizing compensating approaches (Mathias & Wheaton, 2015). Thus, individuals with a quantitatively lower passive R might use their resources more efficiently than individuals with a larger passive R; this model takes the name of Cognitive Reserve, CR (Barulli & Stern, 2013; Solé-Padullés et al., 2009; Stern, 2002, 2009; Tucker-Drob et al., 2009). Although there is no clear distinction between the effects of Brain Reserve and Cognitive Reserve, Stern suggests that there is a close correlation between number of neurons and good use of brain areas in subjects with higher CR (Stern, 2009).

The role of CR has been studied in various diseases, such as dementia (Roe et al., 2010; Soldan et al., 2018; Stern et al., 2018), multiple sclerosis (Fuchs et al., 2019), Parkinson's disease (Lee et al., 2019), epilepsy (Giovagnoli, 2019), head trauma (Bigler & Stern, 2015) and stroke (Gil-Pagés et al., 2019; Nunnari et al, 2014). With regard to severe acquired brain injury, recent research suggests that cognitive capacities have a greater influence on functional outcomes than the structural variables described above (Medaglia et al., 2015). In sABI patients, the role of CR has been evaluated by means of indirect subjective indicators, such as education level and intelligence quotient prior to the event, and by indirect objective indicators, such as brain size, biomarkers and neuroimaging parameters (Medaglia et al., 2017). In a retrospective study, Schneider et al. (2014) found that the education level of subjects with TBI was correlated with overall long-term functional outcome in terms of disability. In a review, Nunnari et al. (2014) state that stroke patients with a higher level of education showed a better outcome in neurocognitive tests, whereas patients with TBI and a higher intelligence quotient before the event showed a correlation with better post-lesional outcomes. Moreover, the results of a study by Kesler et al. (2003) suggest that larger brain volumes before the event and higher education levels can reduce vulnerability to cognitive deficits following head trauma. Finally, recent studies suggest that CR may influence motor outcome in stroke patients and that it plays a protective role after brain damage (Krch et al., 2019; Padua et al., 2020; Umarova et al., 2019). However, there is little evidence to explain the role of CR in the link between organic damage, clinical sequelae and functional outcome in sABI patients. To our knowledge, there have been no studies that frame CR in terms of psychosocial factors before the event (such as occupation or social activities and hobbies), using a validated tool in sABI patients.

The aim of the present study was to assess the correlation between CR, measured by means of the Cognitive Reserve Index questionnaire, CRIq (Nucci et al., 2012), and its subindices and functional results recorded in sABI patients admitted to a center specialized in intensive rehabilitation after acute events. Since it is useful and often essential know the main factors affecting functional recovery of patients with acquired brain injury in order to design personalized rehabilitation, another aim of this study is to evaluate the relation between CR and cognitive outcome in a population of patients undergoing neuropsychological rehabilitation.

Materials and methods

Study design

This is a retrospective study of a continuous series of sABI patients on first admission to our rehabilitation center.

Inclusion criteria

First admission to a rehabilitation center after an acute neurological event that caused altered state of consciousness with a Glasgow Coma Scale (GCS) score $\leq$8 (Teasdale & Jennett, 1974) for more than 24 h, no neurological or psychiatric history before the event, total independence in all basic activities of daily living (bADL) before the event, native speakers of Italian, age between 18 and 70 years on admission.

Exclusion criteria

Absence of caregiver to answer the CRIq, interruption of stay in the center due to transfer to another unit for more than 20 days.

Objectives

Primary endpoints: identification of a correlation between CR (CRIq score) and functional outcomes after sABI.

Secondary endpoints: evaluation of any correlation between Cognitive Reserve Index (measured by CRIq) and cognitive outcome (measured by specific neuropsychological tests) of sABI patients undergoing cognitive rehabilitation.

Study protocol

The study protocol includes collecting the following data:

- demographic data and medical history;
- main event data: data on the acute event, etiology, coma (GCS at onset), primary brain damage;
- clinical data on admission with evaluation of: secondary damage, structures, functions (support for basic vital functions, motor impairment), cognitive impairment,

state of consciousness (Level of Cognitive Functioning scale, **LCF**, Lexell & Brogårdh, 2015; Sherer et al., 2002), activity and participation (Disability Rating Scale, **DRS**, Rappaport et al., 1982 and modified Barthel Index, **mBI**, Shah et al., 1989; Mahoney & Barthel, 1965);
- neuropsychological assessment: specific tests are used to investigate the principal cognitive domains (attention, learning and memory, executive functions) in patients with a sufficient LCF (see below).

Brief description of the tests used:

- Visual Search (Della Sala et al., 1992) is a visual scanning test that evaluates the capacity for focused attention and exploration speed;
- Trail Making Test (TMT) (Giovagnoli et al. 1996) is a test of visual attention and task switching, including visual motor coordination, execution speed and cognitive flexibility;
- Digit span forward and backward (Monaco et al., 2013) is a measure of short-term verbal memory. The backward version includes evaluation of working memory;
- Corsi span forward and backward (Monaco et al., 2013) is a test to evaluate short-term spatial memory. The backward version includes evaluation of working memory;
- Corsi supraspan (Capitani et al., 1991) examines visual spatial learning of new information;
- Rey auditory verbal learning test (Carlesimo et al., 1996) evaluates verbal learning capacity and spontaneous long-term recall;
- Cognitive Estimation Test (Della Sala et al., 2003) evaluates capacity for cognitive estimation based on logical reasoning, research and critical comparison of previously acquired general knowledge;
- Raven's Matrices test (Caffarra et al., 2003) evaluates logical and operative reasoning ability.

All scores were normalized for age, sex and education level according to the authors' guidelines.

- *CRIq data* (Nucci et al., 2012) regarding the patient's state before the event, obtained by administering the Cognitive Reserve Index questionnaire (CRIq) to the caregiver. CRIq is a semi-structured interview addressed to a family member who knows detailed patient history. It is a standardized assessment that quantifies cognitive reserve through information regarding the individual's entire adult life. It consists of three parts: CRI-Education (CRI-E: level of education; the raw score is the sum of years of schooling and years of extra-scholastic training), CRI-WorkingActivity (CRI-WA: years worked at distinct levels of occupation based on the cognitive input required and level of responsibility; the raw score is the number of years worked in proportion to the cognitive commitment that each occupation requires), and CRI-LeisureTime (CRI-LT: all activities normally done during a person's free time; the raw score is the sum of the years passed in leisure-time activities in proportion to the frequency of the activities). Each sub-index and the total CRIq score are correlated with age and expressed on scale where the mean is 100 and the SD is 15. The questionnaire has been part of the center's usual assessment protocol starting from January 1, 2016 and is administered to a family member in the first two weeks from the admission.

Procedure

- All patients admitted to our center between January 1, 2016 and December 31, 2017, who met the inclusion/exclusion criteria, were enrolled in the study. The evaluation and treatment procedure followed in our rehabilitation center envisages recording the descriptive data listed in the above assessment protocol on admission (T1). On the basis of initial LCF score (T1), patients were divided into two groups (Figure 1):

- Group 1 with LCF $\geq$ 6 (G1): patients in this group underwent formal neuropsychological (NPS) assessment in our neuropsychology unit on admission (T1). They then underwent a personalized cognitive rehabilitation program. Before discharge (T2), a follow-up NPS test was performed, administering the LCF, DRS and mBI scales.
- Group 2 with LCF <6 (G2): patients in the second group only did the basic LCF, DRS and mBI tests on admission and at discharge (T1 and T2), since cognitive impairment did not allow access to formal NPS assessment.

The LCF scale periodically administrated, was used to submit patients, who at any time during admission reached a score of 6, to a formal NPS assessment.

Statistical analysis

All statistical analysis was performed with the SPSS v.23 (IBM Corp.) statistical package and/or with the R version 3.6.2 open source statistical system and the many additional CRAN packages (Comprehensive R Archive Network; cran.r-project.org). Continuous quantitative variables were described by their trends, dispersion and form. We calculated arithmetic mean, 5% trimmed mean, median, mode, variance, standard deviation, standard error, quartiles, interquartile interval, slope, kurtosis, minimum and maximum. Where pertinent, 95% confidence intervals were also recorded. Categorical data was reported in frequency tables and expressed as absolute, relative and cumulative frequencies and percentages. Bivariate correlations between continuous and ordinal variables were tested by the Pearson *r* and Spearman rho coefficients of correlation.

Linear regression was used to study the relation between result predictors and variables. Differences in repeated measures (T1, T2) of quantitative data between groups were tested

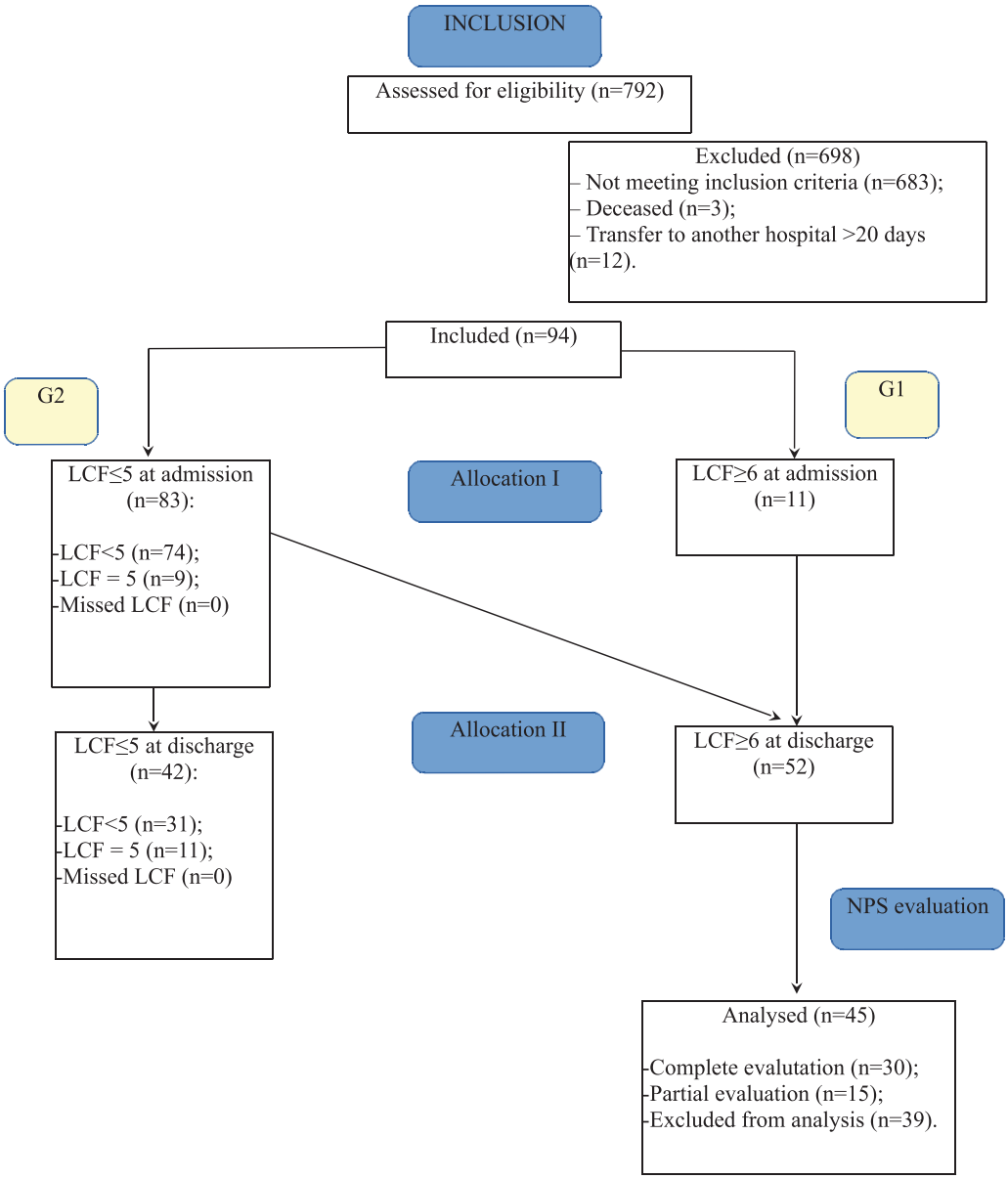

Figure 1. Inclusion Flow Diagram (until December 31, 2017).

by the Wilcoxon rank test, whereas differences between independent groups were investigated by the Mann-Whitney and Kruskal-Wallis tests. Pearson's Pear2 and the Fisher exact test were used to evaluate the association between categorical variables in contingency tables. $p < 0.05$ was taken to indicate a statistically significant difference.

Results

General sample data

We enrolled 94 patients: 69 males, 25 females, mean age 46.24 years (SD = 15.72 years), data shown in Table 1. A majority of patients ($n = 41$) had vascular etiology (ischemia and hemorrhage), followed by TBI ($n = 38$) and anoxic damage ($n = 15$). The prevalence of males was more evident among victims of traumatic brain injury TBI (30 males, 8 females) by 3:1. The mean age of these patients was less than that of patients with other etiologies (36 ± 15 years, mean ± SD). Regarding the severity of disorders of consciousness (DoC) and cognitive level, Table 2 shows LCF values on admission in relation to the origin of injury.

Onset-Admission interval (OAI) and basic scales

Mean OAI, i.e. the interval between the event and admission to rehabilitation, was 77 days (SD = 8.55 days). There was an inverse relation between OAI and change in LCF, i.e. delta LCF (LCF T2-LCF T1) increased with decreasing OAI. The same pattern was observed for mBI and DRS, namely DRS decreased with increasing OAI (Table 3).

Primary endpoint results

Quantification of residual disability. With regard to residual disability measured with the basic scales, 94.7% of patients

Table 1. Characteristics of sABI population at admission (T1) and discharge (T2).

Etiology	Cerebrovascular disease (*n*)	41 (F 13–M 28)
	Traumatic Brain Injury (*n*)	38 (F 8–M 30)
	Anoxic Damage (*n*)	15 (F 4–M 11)
Age	Mean (SD)—years	46.24 (15.72)
LoS	Mean (SD)—days	218.01 (119.36)
OAI	Mean (SD)—days	77 (8.55)
LCF	Mean T1	3.3 (1.45)
	Mean T2	5.14 (1.97)
	T2–T1	1.84 (1.64)
	p-Value	<0.001
mBI	Mean T1 (SD)	4.6 (15.46)
	Mean T2 (SD)	39.7 (40.35)
	T2–T1	34.9 (37.84)
	p-value	<0.001
DRS	Mean T1 (SD)	20.3 (4.76)
	Mean T2 (SD)	13.4 (7.56)
	T2–T1	−7.01 (6.69)
	p-Value	<0.001
CRIq	Mean (SD)	99.80 (14.105)
CRI-E	Mean (SD)	97.18 (13.28)
CRI-WA	Mean (SD)	101.80 (13.63)
CRI-LT	Mean (SD)	100.43 (12.17)

F: Female; M: Male; SD: Standard Deviation; LoS: Length of Stay; OAI: Onset-Admission Interval; CRIq: Cognitive Reserve Index questionnaire; -E: Education; -WA: Working Activity; -LT: Leisure Time.

Table 2. Cognitive functioning at admission (LCF T1) and Etiology.

			Etiology					
			1	2	3	4	5	Total
LCF T1	1	Count	0	1	0	1	0	2
		%	0.0%	50.0%	0.0%	50.0%	0.0%	100.0%
	2	Count	1	11	13	6	0	31
		%	3.2%	35.5%	41.9%	19.4%	0.0%	100.0%
	3	Count	2	16	13	1	0	32
		%	6.3%	50.0%	40.6%	3.1%	0.0%	100.0%
	4	Count	0	1	5	3	0	9
		%	0.0%	11.1%	55.6%	33.3%	0.0%	100.0%
	5	Count	2	2	3	1	1	9
		%	22.2%	22.2%	33.3%	11.1%	11.1%	100.0%
	6	Count	2	2	2	2	0	8
		%	25.0%	25.0%	25.0%	25.0%	0.0%	100.0%
	7	Count	1	0	2	0	0	3
		%	33.3%	0.0%	66.7%	0.0%	0.0%	100.0%
Total		Count	8	33	38	14	1	94
		%	8.5%	35.1%	40.4%	14.9%	1.1%	100.0%

Etiology: 1 = ischemic brain damage; 2 = haemorrhagic brain damage; 3 = traumatic brain injury; 4 = anoxic brain damage; 5 = other etiologies.

showed disability on admission with total dependence measured by mBI, whereas only 51% maintained the same level of disability at discharge. DRS showed *extremely severe* mean disability of the population on admission (i.e. mean score 17–21), including cases of vegetative state, whereas at discharge the mean disability category was *severe* (i.e. mean score 12–16).

The whole sample showed a significant improvement in motor performance measured with disability scales (mBI and DRS) between admission and discharge (Table 1).

CRIq scores. Our sample showed a mean CRIq score of 99.80 (SD = 14.105); for mean scores of the sub-indices, see Table 1.

Relation between CR and functional outcome. No statistically significant correlation was found between CR before the event, measured by CRIq, and gain obtained with regard to disability, except for a borderline significant correlation between mBI and CRI-WA gain ($n = 89$) and mBI and CRI-LT gain ($n = 89$) (Table 4).

Table 3. OAI and correlations with CRIq and changes (delta) in disability scores.

		OAI	CRI-q	Δ_LCF	Δ_DRS	Δ_mBI
OAI	Pearson *r*	1	0.246*	−0.359**	0.391**	−0.356**
	p-Value		0.019	<.001	<.001	<.001
	N	94	91	94	91	92

**Correlation significant at 0.01 level (2-tailed).
*Correlation significant at 0.05 level (2-tailed).
OAI: Onset-Admission Interval; Δ: Delta score.

In order to verify an effect on clinical improvement of patients with high cognitive reserve, the sample was divided into patients above and below a CRI cutoff of 84 (total CRIq > 84, $n = 81$), the mean score of CRIq, also chosen by the authors of the test (Nucci et al., 2012).

Thus stratified, the sample was studied in relation to the trend of the basic scales. The sample was also divided dichotomously according to disability measured by DRS (DRS >16: extremely severe disability and DRS ≤16: severe disability) as shown in Table 5.

At discharge, there was a significant gain in DRS score for patients with CRIq ≥85 before the event (35/40 who improved in terms of disability showed high CR scores). For patients with CR <85 it was not possible to define a statistical significance due to small sample size ($n = 10$). With stratification by DRS, a significant gain was evident in the vascular etiology and TBI group, whereas the gain was not significant in the anoxic damage group (Table 5).

When disability was measured and stratified according to mBI, no relation with CRIq scores ≥85 seemed to emerge.

On assessment of LCF, we had a total of ten subjects with CRIq <85 and LCF <6 at T1, and six subjects with LCF <6 at T2, sample numbers too small to look for correlations.

OAI and correlations with CRIq and cognitive outcomes. A significant correlation was found between OAI and CRIq ($p = 0.019$). Regarding the relation between OAI and NPS testing, an inverse proportional relationship was found between OAI and part B of the Trail making test (TMT-B): the earlier rehabilitation starts, the greater the gain in part B of TMT ($n = 13$, $p = 0.013$). 9 of these 13 subjects (23.7% of the total sample) had TBI, three had cerebrovascular damage (7.31%) and one had a neoplastic lesion (category "other").

Secondary endpoint results

General considerations on cognitive rehabilitation

45 patients underwent cognitive rehabilitation (Figure 1): mean length of stay was 218 days (SD = 119.36 days) and mean duration of treatment was 109.7 days (SD = 63 days). It was not possible to detect any association between total CRIq scores and recovery time (length of stay). A significant negative correlation was found between CRIq scores and time to achieve criteria for access to neuropsychological

Table 4. Correlations between CRIq subindex and disability scale delta scores.

	CRI-q	CRI-E	CRI-WA	CRI-LT	Delta_LCF	Delta_DRS	Delta_mBI
CRI-q							
Pearson *r*	1	.764**	.817**	.774**	−.016	.105	−.147
p-Value		<.001	<.001	<.001	.883	.329	.170
N	91	81	81	81	91	89	89
CRI-E							
Pearson *r*	.764**	1	.525**	.459**	.012	.139	−.131
p-Value	<.001		<.001	<.001	.910	.195	.221
N	81	91	91	91	91	89	89
CRI-WA							
Pearson *r*	.817**	.525**	1	.476**	−.031	.014	−.049
p-Value	<.001	<.001		<.001	.767	.898	.647
N	81	91	91	91	91	89	89
CRI-LT							
Pearson *r*	.774**	.459**	.476**	1	−.023	.117	.211*
p-Value	<.001	<.001	<.001		.828	.277	.047
N	81	91	91	91	91	89	89

**Correlation significant at 0.01 level (2-tailed).
*Correlation significant at 0.05 level (2-tailed).
CRI-E: CRI Education; CRI-WA: CRI Working Activity; CRI-LT: CRI Leisure Time.

Table 5. CRIq distribution with DRS stratification in T1 and T2 and etiology.

			DRS T2			
CRIq			<=16	>16	Total	McNemar test *p*-Value
<85	DRS T1	>16	5	5	10	
	Total	Count	5	5	10	
	DRS T1	≤16	15	0	15	
= >85		>16	35	30	65	
	Total	Count	50	30	80	<0.001
Total	DRS T1	≤16	15	0	15	
		>16	40	35	75	
	Total	Count	55	35	90	<0.001
Cerebrovascular disease	DRST1_01	≤16	7	0	7	
		>16	18	15	33	
	Total	Count	25	15	40	<0.001[a]
Traumatic Brain Injury	DRST1_01	≤16	6	0	6	
		>16	21	11	32	
	Total	Count	27	11	38	<0.001[a]
Anoxic Damage	DRST1_01	<= 16	3	0	3	
		>16	2	9	11	
	Total	Count	5	9	14	0.500[a]

[a]Binomial distribution used.

Table 6. Correlation between CRIq scores and time to first neuropsychological evaluation.

		CRI-q	LOS	val T1
CRI-q	Pearson *r*	1	−.019	−.296*
	p-Value		.860	.043
	N	91	91	47
LOS (length of stay)	Pearson *r*	−.019	1	.668**
	p-Value	.860		<.001
	N	91	94	50
val T1	Pearson *r*	−.296*	.668**	1
	p-Value	.043	<.001	
	N	47	50	50

LOS: length of stay; val T1: interval between admission and access to first NPS assessment.

assessment (measured as the interval between admission to the rehabilitation center and the first NPS assessment), as shown in Table 6.

Effect of level of education

Regarding education level as a significant factor of cognitive reserve (Nucci, 2012), 35% of our sample completed 13 years of schooling, 12.8% 8 years and 10.6% 11 years. Only 7% completed more than 18 years of education. No relation was found between the number of years of schooling completed and the change in LCF (T2–T1) or the change in mBI. 83% of the sample did not frequent any additional courses beyond schooling (as assessed by CRI-School), 6.4% did one course (lasting at least 6 months) and 4.5% did more than one course lasting more than 6 months.

We considered the variable "years of education completed" (of CRIq Education) because it was more complete than the other components of the sub-scale (years frequented and courses). This component was compared with changes in the scores of NPS tests to identify a possible effect of education on score gains. A significant gain was only evident between years completed and TMT-A, however the sample was small ($n = 8$) (Table 7). This correlation persisted even ignoring the initial value of TMT-A at T1.

In the neuropsychological assessments, some tests showed a significant improvement in performance after cognitive rehabilitation (from T1 to T2), as shown in Table 8. Regarding the correlation between CRIq or its sub-indices and cognitive performance measured by NPS tests, significant differences were found between CRIq and TMT-A and CRI-WA and TMT-A (Pearson 0.009), but sample size was

Table 7. Correlations between CRIq index and changes in neuropsychological test *z*-scores.

		Deltaz_IR_Rey	Deltaz_DR_Rey	Deltaz_VisualSearch	Deltaz_Raven's_Mat	Deltaz_Corsi_supraspan	Deltaz__CET	Deltaz_ds_forw	Deltaz_ds_back	Deltaz_TMT_A	Deltaz_TMT_B	Deltaz_TMT_BA
CRI-q	Pearson r	−0.31	−0.185	−0.27	−0.142	−0.517	0.156	0.168	−0.267	.632**	−0.075	−0.28
	p-Value	0.115	0.356	0.224	0.549	0.085	0.437	0.383	0.169	0.009	0.807	0.355
	N	27	27	22	20	12	27	29	28	16	13	13
Education (years passed)	Pearson r	−0.91	0.063	−0.102	0.071	−0.227	−0.147	0.211	−0.244	−.786**	−. 393	−0.082
	p-Value	0.644	0.751	0.634	0.76	0.478	0.464	0.263	0.201	<.001	0.184	0.79
	N	28	28	24	21	12	27	30	29	16	13	13
CRI-WA	Pearson r	−0.136	−0.337	−0.17	−0.183	−0.388	0.121	0.126	−0.271	.666**	−0.117	−0.287
	p-Value	0.499	0.86	0.449	0.44	0.213	0.546	0.515	0.163	0.005	0.704	0.342
	N	27	27	22	20	12	27	29	28	16	13	13
CRI-LT	Pearson r	−0.308	−0.94	−0.247	−0.196	−0.254	0.114	0.194	0.16	0.262	0.115	0.136
	p-Value	0.118	0.642	0.268	0.407	0.426	0.572	0.313	0.935	0.326	0.709	0.658
	N	27	27	22	20	12	27	29	28	16	13	13

**Correlation is significant at the 0.01 level (2-tailed).
*Correlation is significant at the 0.05 level (2-tailed).

much reduced ($n = 16$) with respect to the initial sample. On the other hand, there was no correlation between delta TMT-A and delta mBI or mBI at T2. Table 7 shows the correlations between sub-indices of CRIq and the change in *z*-scores for each test, for a cutoff of 84 (total CRIq >84), the mean score of CRIq (range 85–114), also chosen by the authors of the test (Nucci, 2012).

36 patients with high cognitive reserve (CRIq tot > 84) did not have access to formal NPS assessment (complete protocol) because their LCF was below 6. Twelve of these patients died, and three of the other 24 started with a DRS of 22 ± 0.8 (mean ± SD) (vegetative state) at T1. Subjects with high cognitive reserve (CRIq tot > 84) who had access to formal NPS assessment (LCF > 5) began with a DRS of 18 ± 1.3 (mean ± SD) (extremely severe disability) at T1.

It was not possible to analyze the inverse hypothesis in our population, namely whether those with CRIq tot < 85 achieved a significant gain, because they numbered ten, only two of whom did the NSP tests.

Discussion

The prevalence of males in the population of the present study is in line with the literature (Apolone et al., 2007; Avesani et al., 2013), whereas the frequency of traumatic brain lesions in men is higher than that reported in the literature (Bruns & Hauser, 2003). The mean age of these patients is in line with the data of the GISCAR study (Zampolini et al., 2012). Regarding the severity of disorders of consciousness and cognitive damage, most patients (67%, see Table 2) had a LCF of 2 or 3 on admission (vegetative state or minimally conscious state, respectively), conditions mostly due to bleeding or trauma. Regarding functional outcome, 51% of patients maintained the same level of disability at discharge, and these results are consistent with those of other multicentre studies (e.g. Chiavaroli et al., 2016, Avesani et al., 2018). Nevertheless, the basic scales generally showed a significant improvement between admission and discharge (T1 and T2), at least in part due to rehabilitation. Moreover, the indirect relation between access to intensive rehabilitation and gain as measured by the basic scales (Tables 3 and Table 9) suggests that despite initial severity (Table 2), the shorter the interval between the event and admission to rehabilitation, the greater the improvement in basic functioning (for all the clinical scales used). However, it seems that pre-event cognitive reserve, measured by CRIq (Nucci et al., 2012), does not influence this outcome. Only the DRS (Rappaport et al., 1982) indicated that most patients who improved in terms of disability had high CR scores, but it was not possible to demonstrate a role of CR due to the small statistical sample, and this significance was not confirmed by mBI (Mahoney & Barthel, 1965). These incongruences could be due to the use of different basic scales (DRS and mBI) and/or to severity on admission to intensive rehabilitation, which could have a greater effect on cognitive than on functional outcomes. Stratification of the sample by disability categories, both for DRS and mBI, showed an extremely high percentage of patients (83.3% for

Table 8. Improvements after cognitive rehabilitation (T2-T1).

				95%—CI				
	n	Mean	SD	Inf.	Sup.	*t*	*df*	*p*-Value
IR-15 Rey T1 P Z—IR-15Rey T2 Z	28	−0.29	0.80	−0.60	0.02	−1.93	27	0.064
DR-15 Rey T1 Z—DR-15Rey T2 Z	28	−0.69	0.69	−0.96	−0.42	−5.31	27	<.001
VisualSearchT1 Z -VisualSearch T2 Z	24	−0.23	1.17	−0.72	0.27	−0.95	23	0.351
Raven's Matrices T1 Z—Raven's Matrices T2 Z	21	−1.14	0.97	−1.58	−0.70	−5.38	20	<.001
Corsi supraspan T1 Z—Corsi supraspan T2 Z	12	−0.47	1.28	−1.29	0.34	−1.28	11	0.227
CET T1 Z—CET T2 Z	27	0.48	1.89	−0.27	1.23	1.32	26	0.198
Digit Span For. T1 Z—Digit Span For. T2 Z	30	−0.24	0.64	−0.48	0.00	−2.08	29	0.047
Digit Span Back. T1 Z—Digit Span Back. T2 Z	29	−0.53	0.88	−0.87	−0.20	−3.26	28	0.003
TMT part A T1 Z—TMT part A T2 Z	16	0.89	2.02	−0.19	1.96	1.76	15	0.098
TMT part B T1 Z—TMT part B T2 Z	13	0.70	0.85	0.18	1.21	2.96	12	0.012
TMT B-A T1 Z—TMT B-A T2 Z	13	0.72	0.97	0.13	1.31	2.66	12	0.021

95%-CI: 95% Confidence Interval; SD: Standard deviation; df: degree of freedom.
**Correlation significant at 0.01 level (2-tailed).
*Correlation significant at 0.05 level (2-tailed).

DRS) with extremely severe disability on admission. In line with Formisano et al. (2017), this suggests that better recovery and more positive outcomes may not be due to early rehabilitation, but that the sooner a patient can be transferred from the acute ward to intensive rehabilitation is itself a prognostic index that indicates better or worse clinical instability and neurological severity. It is therefore possible that the protective effects of CR on functional and cognitive outcome could be observed in a sample of patients with less severe disabilities. With regard to the sub-indices of the CRIq, there were weak correlations between gain in mBI and CRI-LT and between mBI and CRI-WA. These results seem in line with the recent literature on stroke (Padua et al., 2020).

Regarding cognitive outcome, recovery time does not appear to be influenced by CR scores prior to the event, although a significant correlation was found between CR and access to neuropsychological assessment (those with a higher cognitive reserve can be assessed sooner). Regarding cognitive outcome, in our sample it was not possible to define a clear correlation between pre-lesional CR and cognitive outcomes after sABI, despite the improvements in performance profile evident after NPS rehabilitation. Access to NPS assessment only seems to affect TMT-B and this raises the question of the incongruent results obtained with the other tests of attention that require almost the same basic capacities (e.g. visual search). We only found a significant effect of education level (years of schooling completed) for TMT-A and not for the other tests of attention. We also found a positive correlation between CRIq scores, especially CRI-Education, and those of tests that measure the same domain (attention). This could be due to the fact that attention exercised in the real world depends on a lifetime of experiences (CR). However, in both cases, sample size was reduced and the gain obtained by these subjects did not prove to depend on the degree of overall disability.

Although sample size was sufficient for correlations between CRIq, its sub-indices and basic scales, the number of subjects who had access to formal NPS assessment was much smaller ($n = 45$), depending on LCF score. This result is affected by the clinical severity of the patient population.

Limits of the study are that the results obtained are influenced by the clinical severity of the patient series and an insufficient statistical sample. It would be useful to consider patients with moderate to mild acquired brain lesions in order to check a possible relation between CR and cognitive outcome and the role of CR on outcomes in general. It would also be worthwhile including more patients in future studies so as to have a sufficient sample with access to NPS assessment. It could be interesting to compare equal-sized samples of patients with brain injury of different severity (severe versus moderate-mild).

The study found nothing to clarify the disparity of significance between CR and cognitive tests requiring the same basic capacities (e.g. Visual Search and Trail making). It will therefore be necessary to repeat the analysis using a greater number of tests of attention that rely on the same visual and visual-motor abilities so as to confirm or refute the evidence.

Errors in the use of a single tool (CRIq) may be a reason why a significant role of CR was not distinguished. It would therefore be useful to use different measures of CR independently and simultaneously (e.g. education, CRIq and CoRe-T, Colombo et al., 2018), to minimize this risk.

Conclusions

Clinical practice shows high inter-individual variability of outcome in sABI patients that might be explained by analysis of many objective and subjective factors. Among the latter, the influence of cognitive reserve as a major protective element has been studied in the literature regarding various pathologies. The present study set out to evaluate the concept of active reserve, which implies strategic use of resources according to the previous learning history of sABI patients.

The study sample proved representative of the sABI population and improvements in overall disability and cognition emerged probably as a result of rehabilitation. High CR scores before the event did not seem to substantially influence outcomes. This probably has to do with sample size and the extreme clinical severity of the study population, and leads us to suppose that above a certain level of severity and functional impairment, pre-lesional variables lose their capacity to co-determine recovery possibilities,

Table 9. OAI and correlations with changes (delta) in neuropsychological scores.

	OAI	Δz_IR_Rey	Δz_DRRey	Δz_ Visual Search	Δz_Raven's_Mat	Δz_Corsi_supraspan	Δz_CET	Δz_ds_forw	Δz_ds_back	Δz_TMT_A	Δz_TMT_B	Δz_TMT_BA
OAI												
Pearson r	1	−.101	.025	−.024	−.004	.234	.114	−.242	−.022	−.219	−.666*	−.472
p-Value		.609	.898	.912	.988	.464	.571	.197	.910	.415	.013	.103
N	94	28	28	24	21	12	27	30	29	16	13	13

*Correlation significant at 0.05 level (2-tailed).
OAI: onset-admission interval; Δ: Delta score; Δ_IR_ Rey: delta scores Immediate Recall 15 Rey-Words; Δ_DR_ Rey: delta scores Delayed Recall 15 Rey-Words; Δ_Visual Search: delta scores Visual Search; Δ_Raven's Mat: delta scores Raven's Matrices; Δ_Corsi supraspan: delta scores Corsi supraspan; Δ_CET: delta scores Cognitive Estimation Test; Δ_ ds for: delta scores Digit Span Forward; Δ_ds back: delta scores Digit Span Backward; Δ _TMT_A: delta scores Trail making test part A; Δ_ TMT_B: delta scores TMT part B; Δ_TMT_AB: delta scores TMT part B-A.

whether by improvement in disorders of consciousness or by cognitive-behavioral evolution.

Further prospective and multicentric studies that enable a larger study sample, so as to stratify by different levels of clinical severity, could make it possible to define the role of cognitive reserve in functional and cognitive outcome for sABI patients.

Disclosure statement

No potential conflict of interest was reported by the author(s).

References

Allanson, F., Pestell, C., Gignac, G. E., Yeo, Y. X., & Weinborn, M. (2017). Neuropsychological predictors of outcome following traumatic brain injury in adults: A meta-analysis. *Neuropsychology Review*, *27*(3), 187–201. https://doi.org/10.1007/s11065-017-9353-5

Apolone, G., Boldrini, P., Avesani, R., De Tanti, A., Fogar, P., Gambini, M. G., & Taricco, M. (2007). Conferenza nazionale di consenso bisogni riabilitativi ed assistenziali delle persone con disabilità da grave cerebro-lesione acquisita (GCA) e delle loro famiglie, nella fase post-ospedaliera [2 national consensus conference on rehabilitation and assistance needs of disabled people with severe acquired brain injuries (ABI) and of their families after hospitalization. *Giornale Italiano di Medicina Riabilitativa-MR*, *21*, 29–51.

Avesani, R., Roncari, L., Khansefid, M., Formisano, R., Boldrini, P., Zampolini, M., Ferro, S., De Tanti, A., & Dambruoso, F. (2013). The Italian National Registry of severe acquired brain injury: Epidemiological, clinical and functional data of 1469 patients. European Journal of Physical and Rehabilitation Medicine, *49*(5), 611–618.

Avesani, R., Dambruoso, F., PSyD, M. S., Formisano, R., Antonio De Tanti, M. D., Ferro, S., & Rossato, E. (2018). Epidemiological and clinical characteristics of 492 patients in a vegetative state in 29 Italian rehabilitation units. What about outcome? *Functional Neurology*, *33*(2), 97–103.

Bagnato, S., Andriolo, M., Boccagni, C., Lucca, L. F., De Tanti, A., Pistarini, C., Barone, T., & Galardi, G. (2020). Reduced neuron-specific enolase levels in chronic severe traumatic brain injury. *Journal of Neurotrauma*, *37*(2), 423–427. https://doi.org/10.1089/neu.2019.6449

Baker, E. W., Kinder, H. A., Hutcheson, J. M., Duberstein, K. J. J., Platt, S. R., Howerth, E. W., & West, F. D. (2019). Controlled cortical impact severity results in graded cellular, tissue, and functional responses in a piglet traumatic brain injury model. *Journal of Neurotrauma*, *36*(1), 61–73. https://doi.org/10.1089/neu.2017.5551

Barulli, D., & Stern, Y. (2013). Efficiency, capacity, compensation, maintenance, plasticity: Emerging concepts in cognitive reserve. *Trends in Cognitive Sciences*, *17*(10), 502–509. https://doi.org/10.1016/j.tics.2013.08.012

Bigler, E. D., & Stern, Y. (2015). Traumatic brain injury and reserve. In *Handbook of clinical neurology* (Vol. 128, pp. 691–710). Elsevier.

Bruns, J., Jr,., & Hauser, W. A. (2003). The epidemiology of traumatic brain injury: A review. *Epilepsia*, *44*(s10), 2–10. https://doi.org/10.1046/j.1528-1157.44.s10.3.x

Caffarra, P., Vezzadini, G., Zonato, F., Copelli, S., & Venneri, A. (2003). A normative study of a shorter version of Raven's progressive matrices 1938. *Neurological Sciences: Official Journal of the Italian Neurological Society and of the Italian Society of Clinical Neurophysiology*, *24*(5), 336–339. https://doi.org/10.1007/s10072-003-0185-0

Capitani, E., Laiacona, M., & Ciceri, E. (1991). Sex differences in spatial memory: A reanalysis of block tapping long-term memory according to the short-term memory level. *The Italian Journal of Neurological Sciences*, *12*(4), 461–466.

Carlesimo, G. A., Caltagirone, C., Gainotti, G. U. I. D., Fadda, L., Gallassi, R., Lorusso, S., & Parnetti, L. (1996). The mental deterioration battery: Normative data, diagnostic reliability and qualitative analyses of cognitive impairment. *European Neurology*, *36*(6), 378–384. https://doi.org/10.1159/000117297

Chiavaroli, F., Derraik, J. G., Zani, G., Lavezzi, S., Chiavaroli, V., Sherwin, E., & Basaglia, N. (2016). Epidemiology and clinical outcomes in a multicentre regional cohort of patients with severe acquired brain injury. *Disability and Rehabilitation*, *38*(20), 2038–2046. https://doi.org/10.3109/09638288.2015.1111439

Colombo, B., Antonietti, A., & Daneau, B. (2018). The relationships between cognitive reserve and creativity. A study on American aging population. *Frontiers in Psychology*, *9*, 764. https://doi.org/10.3389/fpsyg.2018.00764

De Tanti, A., Zampolini, M., Pregno, S., & CC3 Group (2015). Recommendations for clinical practice and research in severe brain injury in intensive rehabilitation: The Italian Consensus Conference. *European Journal of Physical and Rehabilitation Medicine*, *51*(1), 89–103.

Della Sala, S., Laiacona, M., Spinnler, H., & Ubezio, C. (1992). A cancellation test: its reliability in assessing attentional deficits in Alzheimer's disease. *Psychological Medicine*, *22*(4), 885–901. https://doi.org/10.1017/S0033291700038460

Della Sala, S., MacPherson, S. E., Phillips, L. H., Sacco, L., & Spinnler, H. (2003). How many camels are there in Italy? Cognitive estimates standardised on the Italian population. *Neurological Sciences: Official Journal of the Italian Neurological Society and of the Italian Society of Clinical Neurophysiology*, *24*(1), 10–15. https://doi.org/10.1007/s100720300015

Formisano, R., Azicnuda, E., Sefid, M. K., Zampolini, M., Scarponi, F., & Avesani, R. (2017). Early rehabilitation: benefits in patients with severe acquired brain injury. *Neurological Sciences: Official Journal of the Italian Neurological Society and of the Italian Society of Clinical Neurophysiology*, *38*(1), 181–184. https://doi.org/10.1007/s10072-016-2724-5

Fuchs, T. A., Benedict, R. H. B., Bartnik, A., Choudhery, S., Li, X., Mallory, M., Oship, D., Yasin, F., Ashton, K., Jakimovski, D., Bergsland, N., Ramasamy, D. P., Weinstock-Guttman, B., Zivadinov, R., & Dwyer, M. G. (2019). Preserved network functional connectivity underlies cognitive reserve in multiple sclerosis. *Human Brain Mapping*, *40*(18), 5231–5241. https://doi.org/10.1002/hbm.24768

Gil-Pagés, M., Sánchez-Carrión, R., Tormos, J. M., Ensenat-Cantallops, A., & García-Molina, A. (2019). A positive relationship between cognitive reserve and cognitive function after stroke: Dynamic proxies correlate better than static proxies. *Journal of the International Neuropsychological Society: JINS*, *25*(9), 910–921. https://doi.org/10.1017/S1355617719000638

Giovagnoli, A. R. (2019). Epilepsy and aging. In L. D. Ravdin & H. L. Katzen (Eds.), *Handbook on the neuropsychology of aging and dementia* (pp. 401–425). Springer.

Giovagnoli, A. R., Del Pesce, M., Mascheroni, S., Simoncelli, M., Laiacona, M., & Capitani, E. (1996). Trail making test: Normative values from 287 normal adult controls. *Italian Journal of Neurological Sciences*, *17*(4), 305–309. https://doi.org/10.1007/BF01997792

Greicius, M. D., Supekar, K., Menon, V., & Dougherty, R. F. (2009). Resting-state functional connectivity reflects structural connectivity in the default mode network. *Cerebral Cortex*, *19*(1), 72–78. https://doi.org/10.1093/cercor/bhn059

Harvey, R. L. (2015). Predictors of functional outcome following stroke. *Physical Medicine and Rehabilitation Clinics of North America*, *26*(4), 583–598. https://doi.org/10.1016/j.pmr.2015.07.002

Hoofien, D., Vakil, E., Gilboa, A., Donovick, P. J., & Barak, O. H. R. (2002). Comparison of the predictive power of socio-economic variables, severity of injury and age on long-term outcome of traumatic brain injury: Sample-specific variables versus factors as predictors. *Brain Injury*, *16*(1), 9–27. https://doi.org/10.1080/02699050110088227

Hukkelhoven, C. W. P. M., Steyerberg, E. W., Rampen, A. J. J., Farace, E., Habbema, J. D. F., Marshall, L. F., Murray, G. D., & Maas, A. I. R. (2003). Patient age and outcome following severe traumatic brain injury: An analysis of 5600 patients. *Journal of Neurosurgery*, *99*(4), 666–673. https://doi.org/10.3171/jns.2003.99.4.0666

Katzman, R. (1993). Education and the prevalence of dementia and Alzheimer's disease. *Neurology*, *43*(1), 13–20. https://doi.org/10.1212/wnl.43.1_part_1.13

Katzman, R., Terry, R., DeTeresa, R., Brown, T., Davies, P., Fuld, P., Renbing, X., & Peck, A. (1988). Clinical, pathological, and neurochemical changes in dementia: A subgroup with preserved mental status and numerous neocortical plaques. *Annals of neurology*, *23*(2), 138–144. https://doi.org/10.1002/ana.410230206

Kesler, S. R., Adams, H. F., Blasey, C. M., & Bigler, E. D. (2003). Premorbid intellectual functioning, education, and brain size in traumatic brain injury: An investigation of the cognitive reserve hypothesis. *Applied Neuropsychology*, *10*(3), 153–162. https://doi.org/10.1207/S15324826AN1003_04

Krch, D., Frank, L. E., Chiaravalloti, N. D., Vakil, E., & DeLuca, J. (2019). Cognitive reserve protects against memory decrements associated with neuropathology in traumatic brain injury. *The Journal of Head Trauma Rehabilitation*, *34*(5), E57–E65. https://doi.org/10.1097/HTR.0000000000000472

Lee, P. -C., Artaud, F., Cormier-Dequaire, F., Rascol, O., Durif, F., Derkinderen, P., Marques, A. -R., Bourdain, F., Brandel, J. -P., Pico, F., Lacomblez, L., Bonnet, C., Brefel-Courbon, C., Ory-Magne, F., Grabli, D., Klebe, S., Mangone, G., You, H., Mesnage, V., … Elbaz, A., for the DIGPD Study Group (2019). Examining the reserve hypothesis in Parkinson's disease: A Longitudinal Study. *Movement Disorders*, *34*(11), 1663–1671. https://doi.org/10.1002/mds.27854

Lexell, J., & Brogårdh, C. (2015). The use of ICF in the neurorehabilitation process. *NeuroRehabilitation*, *36*(1), 5–9. https://doi.org/10.3233/NRE-141184

Maas, A. I., Hukkelhoven, C. W., Marshall, L. F., & Steyerberg, E. W. (2005). Prediction of Outcome in Traumatic Brain Injury with Computed Tomographic Characteristics: A Comparison between the Computed Tomographic Classification and Combinations of Computed Tomographic Predictors. *Neurosurgery*, *57*(6), 1173–1182.

Mahoney, F. I., & Barthel, D. W. (1965). Functional evaluation: The Barthel index. *Maryland State Medical Journal*, *14*, 61–65.

Mathias, J. L., & Wheaton, P. (2015). Contribution of brain or biological reserve and cognitive or neural reserve to outcome after TBI: A meta-analysis (prior to 2015). *Neuroscience and Biobehavioral Reviews*, *55*, 573–593. https://doi.org/10.1016/j.neubiorev.2015.06.001

McHugh, G. S., Butcher, I., Steyerberg, E. W., Marmarou, A., Lu, J., Lingsma, H. F., Weir, J., Maas, A. I. R., & Murray, G. D. (2010). A simulation study evaluating approaches to the analysis of ordinal outcome data in randomized controlled trials in traumatic brain injury: Results from the IMPACT Project. *Clinical Trials (London, England)*, *7*(1), 44–57. https://doi.org/10.1177/1740774509356580

Medaglia, J. D., Lynall, M. E., & Bassett, D. S. (2015). Cognitive network neuroscience. *Journal of Cognitive Neuroscience*, *27*(8), 1471–1491. https://doi.org/10.1162/jocn_a_00810

Medaglia, J. D., Pasqualetti, F., Hamilton, R. H., Thompson-Schill, S. L., & Bassett, D. S. (2017). Brain and cognitive reserve: Translation via network control theory. *Neuroscience and biobehavioral reviews*, *75*, 53–64. https://doi.org/10.1016/j.neubiorev.2017.01.016

Monaco, M., Costa, A., Caltagirone, C., & Carlesimo, G. A. (2013). Forward and backward span for verbal and visuo-spatial data: Standardization and normative data from an Italian adult population. *Neurological Sciences: Official Journal of the Italian Neurological Society and of the Italian Society of Clinical Neurophysiology*, *34*(5), 749–754. https://doi.org/10.1007/s10072-012-1130-x

Nichol, A. D., Higgins, A. M., Gabbe, B. J., Murray, L. J., Cooper, D. J., & Cameron, P. A. (2011). Measuring functional and quality of life outcomes following major head injury: Common scales and checklists. *Injury*, *42*(3), 281–287. https://doi.org/10.1016/j.injury.2010.11.047

Nucci, M., Mapelli, D., & Mondini, S. (2012). Cognitive Reserve Index questionnaire (CRIq): A new instrument for measuring cognitive

reserve. *Aging Clinical and Experimental Research*, *24*(3), 218–226. https://doi.org/10.3275/7800

Nunnari, D., Bramanti, P., & Marino, S. (2014). Cognitive reserve in stroke and traumatic brain injury patients. *Neurological Sciences: Official Journal of the Italian Neurological Society and of the Italian Society of Clinical Neurophysiology*, *35*(10), 1513–1518. https://doi.org/10.1007/s10072-014-1897-z

Padua, L., Imbimbo, I., Aprile, I., Loreti, C., Germanotta, M., Coraci, D., Piccinini, G., Pazzaglia, C., Santilli, C., Cruciani, A., & Carrozza, M. C., FDG Robotic Rehabilitation Group† (2020). Cognitive reserve as a useful variable to address robotic or conventional upper limb rehabilitation treatment after stroke: A multicentre study of the Fondazione Don Carlo Gnocchi. *European Journal of Neurology*, *27*(2), 392–398. https://doi.org/10.1111/ene.14090

Rappaport, M., Hall, K. M., Hopkins, K., Belleza, T., & Cope, D. N. (1982). Disability rating scale for severe head trauma: Coma to community. *Archives of Physical Medicine and Rehabilitation*, *63*(3), 118–123.

Roe, C. M., Mintun, M. A., Ghoshal, N., Williams, M. M., Grant, E. A., Marcus, D. S., & Morris, J. C. (2010). Alzheimer disease identification using amyloid imaging and reserve variables: Proof of concept. *Neurology*, *75*(1), 42–48. https://doi.org/10.1212/WNL.0b013e3181e620f4

Schneider, E. B., Sur, S., Raymont, V., Duckworth, J., Kowalski, R. G., Efron, D. T., Hui, X., Selvarajah, S., Hambridge, H. L., & Stevens, R. D. (2014). Functional recovery after moderate/severe traumatic brain injury: A role for cognitive reserve? *Neurology*, *82*(18), 1636–1642. https://doi.org/10.1212/WNL.0000000000000379

Seagly, K. S., O'Neil, R. L., & Hanks, R. A. (2018). Pre-injury psychosocial and demographic predictors of long-term functional outcomes post-TBI. *Brain Injury*, *32*(1), 78–83. https://doi.org/10.1080/02699052.2017.1374467

Shah, S., Vanclay, F., & Cooper, B. (1989). Improving the sensitivity of the Barthel Index for stroke rehabilitation. *Journal of Clinical Epidemiology*, *42*(8), 703–709.

Sherer, M., Sander, A. M., Nick, T. G., High, W. M., Jr, Malec, J. F., & Rosenthal, M. (2002). Early cognitive status and productivity outcome after traumatic brain injury: Findings from the TBI model systems. *Archives of Physical Medicine and Rehabilitation*, *83*(2), 183–192. https://doi.org/10.1053/apmr.2002.28802

Soldan, A., Pettigrew, C., & Albert, M. (2018). Evaluating cognitive reserve through the prism of preclinical Alzheimer disease. *The Psychiatric Clinics of North America*, *41*(1), 65–77. https://doi.org/10.1016/j.psc.2017.10.006

Solé-Padullés, C., Bartrés-Faz, D., Junqué, C., Vendrell, P., Rami, L., Clemente, I. C., Bosch, B., Villar, A., Bargalló, N., Jurado, M. A., Barrios, M., & Molinuevo, J. L. (2009). Brain structure and function related to cognitive reserve variables in normal aging, mild cognitive impairment and Alzheimer's disease. *Neurobiology of Aging*, *30*(7), 1114–1124. https://doi.org/10.1016/j.neurobiolaging.2007.10.008

Stern, Y. (2002). What is cognitive reserve? Theory and research application of the reserve concept. *Journal of the International Neuropsychological Society: JINS*, *8*(3), 448–460.

Stern, Y. (2009). Cognitive reserve. *Neuropsychologia*, *47*(10), 2015–2028. https://doi.org/10.1017/S1355617702813248

Stern, Y., Arenaza-Urquijo, E. M., Bartrés-Faz, D., Belleville, S., Cantilon, M., Chetelat, G., Ewers, M., Franzmeier, N., Kempermann, G., Kremen, W. S., Okonkwo, O., Scarmeas, N., Soldan, A., Udeh-Momoh, C., Valenzuela, M., Vemuri, P., Vuoksimaa, E., Arenaza Urquiljo, E. M., Bartrés-Faz, D., … Vuoksimaa, E. (2018). Whitepaper: Defining and investigating cognitive reserve, brain reserve, and brain maintenance. *Alzheimer's & Dementia*. https://doi.org/10.1016/j.jalz.2018.07.219

Teasdale, G., & Jennett, B. (1974). Assessment of coma and impaired consciousness. A practical scale. *The Lancet*, *304*(7872), 81–84. https://doi.org/10.1016/S0140-6736(74)91639-0

Tucker-Drob, E. M., Johnson, K. E., & Jones, R. N. (2009). The cognitive reserve hypothesis: A longitudinal examination of age-associated declines in reasoning and processing speed. *Developmental Psychology*, *45*(2), 431–446. https://doi.org/10.1037/a0014012

Umarova, R. M., Sperber, C., Kaller, C. P., Schmidt, C. S. M., Urbach, H., Klöppel, S., Weiller, C., & Karnath, H.-O. (2019). Cognitive reserve impacts on disability and cognitive deficits in acute stroke. *Journal of Neurology*, *266*(10), 2495–2410. https://doi.org/10.1007/s00415-019-09442-6

van der Naalt, J., Timmerman, M. E., de Koning, M. E., van der Horn, H. J., Scheenen, M. E., Jacobs, B., Hageman, G., Yilmaz, T., Roks, G., & Spikman, J. M. (2017). Early predictors of outcome after mild traumatic brain injury (UPFRONT): An observational cohort study. *The Lancet. Neurology*, *16*(7), 532–540. https://doi.org/10.1016/S1474-4422(17)30117-5

WHO (2001). *ICF Classificazione Internazionale del funzionamento della disabilità e della salute*. World Health Organization; Edizioni Centro Studi Erickson.

WHO (2002). *ICF Classificazione Internazionale del funzionamento della disabilità e della salute*. Edizioni Centro Studi Erickson.

Zampolini, M., Zaccaria, B., Tolli, V., Frustaci, A., Franceschini, M., & Giscar, G. (2012). Rehabilitation of traumatic brain injury in Italy: A multi-centre study. *Brain Injury*, *26*(1), 27–35. https://doi.org/10.3109/02699052.2011.635358