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Past Life Experiences and Neurological Recovery: The Role of Cognitive Reserve in the Rehabilitation of Severe Post-Anoxic Encephalopathy and Traumatic Brain Injury

Arianna Menardi[1], Giannettore Bertagnoni[2], Giuseppe Sartori[3,4], Massimiliano Pastore[5] and Sara Mondini[4,6,*]
[1]Department of Neuroscience, Padova Neuroscience Center, University of Padova, Via Giuseppe Orus, 35131 Padova, PD, Italy
[2]Division of Physical and Rehabilitative Medicine of the San Bortolo Hospital, Viale Ferdinando Rodolfi, 37, 36100 Vicenza, VI, Italy
[3]Department of General Psychology, University of Padova, Via Venezia, 8, 35131 Padova, PD, Italy
[4]Human Inspired Research Centre, University of Padova, Via Luzzatti, 4, 35122 Padova, PD, Italy
[5]Department of Developmental and Social Psychology, University of Padova, Via Venezia, 8, 35131 Padova, PD, Italy
[6]FI.S.P.P.A. Department, University of Padova, Via Venezia 14, 35131 Padova, PD, Italy

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Abstract

Objective: Patients with an equivalent clinical background may show unexpected interindividual differences in their outcome. The cognitive reserve (CR) model has been proposed to account for such discrepancies, but its role after acquired severe injuries is still being debated. We hypothesize that inappropriate investigative methods might have been used when dealing with severe patients, which have very likely reduced the possibility of observing meaningful influences in recovery from severe traumas. **Methods:** To overcome this issue, the potential neuroprotective role of CR was investigated, considering a wider spectrum of clinical symptoms ranging from low-level brain stem functions necessary for life to more complex motor and cognitive skills. In the present study, data from 50 severe patients, 20 suffering from post-anoxic encephalopathy (PAE) and 30 with traumatic brain injury (TBI), were collected and retrospectively analyzed. **Results:** We found that CR, diagnosis, time of hospitalization, and their interaction had an effect on the clinical indexes. When the predictive power of CR was investigated by means of two machine learning classifier algorithms, CR, together with age, emerged as the strongest factor in discriminating between patients who reached or did not reach successful recovery. **Conclusions:** Overall, the present study highlights a possible role of CR in shaping the recovery of severe patients suffering from either PAE or TBI. The practical implications underlying the need to routinely considered CR in the clinical practice are discussed.

Keywords: Cognitive reserve, Brain reserve, Traumatic brain injury, Post-anoxic encephalopathy, Functional recovery, Rehabilitation

INTRODUCTION

The concept of reserve was first introduced to try to explain the absence of a direct relationship between the clinical severity of a patient and his/her clinical manifestations (Katzman et al., 1988; Satz, 1993; Stern, 2002). Indeed, interindividual differences following a neurological insult have long been reported among patients with an otherwise similar clinical background, for example, when a given brain pathology might result in profound levels of impairment in one subject, while leaving another individual relatively unaffected. Evidence was first reported by Katzman et al., (1988) relative to 10 elderly women who suffered from advanced Alzheimer's disease (AD)—which was only revealed by post-mortem investigations—but who were cognitively intact during life. According to Katzman et al., (1988), the greater resilience of those women could be explained by the relatively bigger size of their brain, which enabled them to sustain the pathology better and longer. This theoretical framework has then evolved into the so-called *brain reserve* (BR) and *threshold theory* hypotheses (Katzman et al., 1988; Satz, 1993), according to which brains with greater volumetric properties (e.g., cortical thickness, number of neurons, and synapses) are more robust in the face of a pathology. In this sense, a pathology might remain "silent" or "subthreshold" because of the greater availability of neurological substrates and redundant networks in the brain (Satz, 1993). The BR

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*Correspondence and reprint requests to: Sara Mondini, FI.S.P.P.A. Department, University of Padova, Via Venezia 14, 35121 Padova, PD, Italy. E-mail: sara.mondini@unipd.it

framework has, however, been criticized for being a passive and quantitative-based model, as it relies upon the assumptions that fixed cut-offs exist that determine pathological dysfunctions and that impairments sum up linearly until such cut-offs are reached. On the other hand, active models, such as *cognitive reserve* (CR) theory (Stern, 2009), have been introduced that recognize engagement in a cognitively stimulating and active life as fundamental in determining the "differential susceptibility to functional impairment in the presence of pathology or other neurological insult" (Barulli & Stern, 2013). According to the CR hypothesis, following a major insult the brain is actively involved in compensating. At higher levels of reserve, individuals might benefit from networks capable to operate despite the damage, for example, by recruiting alternative brain areas usually not dedicated to the resolution of the task at hand (Stern, 2002). In this sense, CR can operate through three distinct mechanisms: *reserve, maintenance*, and *compensation* (Cabeza et al., 2018). The first refers to the progressive accumulation of resources as a function of genetic and environmental factors that starts during childhood and continues during the life span (Cabeza et al., 2018). On the other hand, maintenance refers to the "preservation of neural resources, which entails ongoing repair and replenishment of the brain in response to damage" (Cabeza et al., 2018). As pointed out by the author, maintenance and compensation differ in that the former involves the progressive building up of one's own strength beyond the current level, whereas the latter refers to the capacity of returning to the same proficiency as before the damage (Cabeza et al., 2018). Finally, compensation is the capacity to recruit additional neural resource to carry out highly demanding cognitive tasks, and it is therefore directly related to the individual cognitive performance (Cabeza et al., 2018). This suggests that individuals with either high or low levels of reserve do not have different brains (e.g., different number of neurons and synapses), but rather they differ in how efficiently the same resources are implemented (Stern, 2002, 2006). These resources are accumulated as a function of the exposure of the individual to enriched environments, such as high level of education and cognitive demanding working occupations and leisure time activities (Barulli & Stern, 2013; Stern, 2006, 2009). Therefore, according to the BR model, a patient with high reserve might sustain a greater loss of neurons before showing any functional impairment, whereas CR theory hypothesizes that, given the same amount of neurons left, patients with higher reserve will compensate better (Stern, 2002). Overall, BR and CR are not mutually exclusive. Indeed, both volumetric brain properties, such as total intracranial volume (TICV) and intelligence quotient (IQ) have been proved to play a role in determining patients' outcome from acquired injuries (e.g., lower TICV was associated with lower IQ and greater pre- *vs.* post-IQ changes) (Kesler, Adams, Blasey, & Bigler, 2003). As such, the combined contribution of both BR and CR is most likely the best way to explain individual resilience to brain damage. Nevertheless, the interpretation of the mechanisms underlying CR and BR is not always straightforward and different models have provided divergent interpretations of the matter. For instance, approaches that support a role of *moderation* suggest that low-reserve individuals have a decay in performance that occurs at a faster rate compared to the high-reserve counterpart, thus progressively widening their diversity. This is known as the *differential-preservation* hypothesis (Tucker-Drob, Johnson, & Jones, 2009). On the other hand, models that support *stability*, and thus embrace the *preserved-differentiation* hypothesis, believe that high- and low-reserve individuals show similar slopes of decay, but differ in their initial starting point (Tucker-Drob et al., 2009).

Most of the evidence in favor of CR guaranteeing an appropriate level of cognitive functioning despite the underlying degree of severity (and consequently delaying the time of a clinical diagnosis) has been collected with respect to neurodegenerative pathologies, especially AD (Bennett et al., 2003; Roe et al., 2008; Snowdon, 2003; Stern, 2006). On the other hand, very few studies have been conducted investigating the role of CR in acquired injuries to explore the relationship between reserve and post-acute indexes of recovery, such as neuropsychological tests or clinical scales (Fortune, Walsh, & Richards, 2016; Jeon et al., 2008; Schneider et al., 2014). In line with the assumptions of CR theory, studies on traumatic brain injury (TBI) patients have generally reported a positive relationship between premorbid demographic factors and patients' clinical outcome (Bittner & Crowe, 2009; Kesler et al., 2003), at least in mild to moderate patients (Jeon et al., 2008). Less clear results have been obtained with severe TBI patients, for which functional outcome scores seem to be better explained by the severity of the injury rather than individuals' demographic factors, that is, their level of CR (Jeon et al., 2008). Such findings may suggest that higher CR has limited power in favorably shaping patients' outcome when the underlying damage is too pervasive and diffused. It can also suggest that cognitive outcome scores generally assessed by means of neuropsychological batteries might have the downside of not being able to capture small improvements in severe patients, thus resulting in a floor effect.

In the present study, we aimed to address some of those limitations, specifically looking at the role of CR in severe patients suffering from either post-anoxic encephalopathy (PAE) or TBI. PAE patients are characterized by diffuse cortical and subcortical damage resulting from the prolonged lack of oxygen following cardiac arrest, strangulation, carbon monoxide intoxication, or drowning. The most vulnerable regions include the cerebellum, basal ganglia, thalamus, hippocampus, and the third layer of the cerebral cortex (Auer & Benveniste, 1997), leading to a more or less constant finding of impaired memory and motor skills. Prolonged periods of coma characterize the most severe patients, resulting in spatial, visual, and executive deficits too (Lim, Alexander, LaFleche, Schnyer, & Verfaellie, 2004). On the other hand, TBI patients are affected by damage resulting from the head striking an object, such as an accidental fall or a car crash. In the latter, a coup and countercoup are common, resulting in lesions mainly to the frontal and occipital lobes. Depending on the focality of the damage, patients can present very selective deficits (such as following a penetrating injury) or might display broad cognitive impairment and processual slowing (especially in the occurrence of axonal tiring). No unique patterns of cognitive deficits can be reported, as patients vary greatly depending on the location of the damage. As PAE and TBI differ in their patterns of damage, we were interested in assessing whether CR might also show a differential contribution depending on the pathology, especially considered the high epidemiological impact of both. The potential neuroprotective role of CR was investigated considering a wider spectrum of clinical symptoms, ranging from low-level brain stem functions necessary for life to more complex motor and cognitive skills. To our knowledge, no similar approach has been verified so far in the literature; furthermore, all the research data on the role of CR have focused on patients with dementia (Le Carret et al., 2005; Poletti, Emre, & Bonuccelli, 2011; Scarmeas, Levy, Tang, Manly, & Stern, 2001), multiple sclerosis (Sumowski, Chiaravalloti, & DeLuca, 2009), and TBI or stroke (Bittner & Crowe, 2009; Kesler et al., 2003; Nunnari, Bramanti, & Marino, 2014). However, evidence on patients with PAE is still missing. Furthermore, even among the studied pathologies, very little research has been conducted looking at severe patients, for which we propose an ad-hoc investigative protocol.

METHODS

Ethical Approval

Data collection was approved by the Vicenza Hospital Medical Directorate, and their study and analysis were approved by the Local Ethical Committee of the School of Psychology of the University of Padova, in accordance with the principles of the Declaration of Helsinki.

Participants

Data considered for the study were collected from the medical charts of hospitalized patients for a period of 10 years (2007–2017) in the division of Physical and Rehabilitative Medicine of the San Bortolo Hospital in Vicenza (Italy). The study selected only patients with a main diagnosis of PAE and patients with a main diagnosis of TBI. Inclusion criteria were comprehensive of a Glasgow Coma Scale (GCS) (Teasdale & Jennett, 1974) score <8 and the absence of other preexisting pathologies of the central nervous system. Exclusion criteria were anoxic etiologies different from cardiac arrest (e.g., carbon monoxide intoxications, drowning, or strangulation) as well as a condition of a persistent vegetative state. Etiologies different from cardiac arrest represented only a minority of the overall sample, but were discarded from further analysis in order to keep our sample as homogeneous as possible and avoid unwanted biases. Only severe PAE and TBI patients were considered, as we aimed to study the role of CR in severely affected individuals, considered the paucity of results reported in the literature so far. Overall, 50 patients, 20 with a diagnosis of PAE (12 male, mean age 49 ± 14.6) and 30 with TBI (23 male, mean age 47.9 ± 12.24), were considered in the study.

CR Measure

As CR is a hypothetical construct, its estimation has to rely on indirect measures. As such, IQ, education, occupation, and socioeconomic status are among its most commonly recognized proxies (Stern, 2002). However, one major concern regards the fact that they might have a relationship with the individual cognitive performance by means of paths other than CR (Jones et al., 2011). As an example, education is taken to explain interindividual differences in cognitive performance as it might account for differences in CR, but could also be due to other variables (such as childhood IQ and general cognitive skills), which in turn might have played a role in determining academic success (Jones et al., 2011). For this reason, estimates of CR need to be multimodal, reducing the ambiguity associated with each single proxy and helping avoid biases from non-CR influences, while also assuring a more complete picture of CR (Jones et al., 2011). For these reasons, in the present study measures of CR were obtained through the Cognitive Reserve Index questionnaire (CRIq), which is a semi-structured interview (Nucci, Mapelli, & Mondini, 2012). The CRIq gives a composite measure of CR, calculated from the cumulative experiences of the individual in all the main proxies of CR: education (CRI-*Education*), occupational status (CRI-*WorkingActivity*), and the engagement in cognitively stimulating leisure time activities (CRI-*LeisureTime*). Typical items of the CRIq include "Years of education," "Occupation (e.g., Low-skilled manual work, Professional occupation, Highly responsible or Intellectual occupation)," "Weekly frequency of reading newspapers and magazines," or "Monthly frequency of voluntary work." Only the CRI total score calculated from the average of its three subcomponents was considered. A comprehensive and detailed overview of the questionnaire structure can be found in the original article by Nucci et al., (2012). CRIq is freely available at http://www.cognitivereserveindex.org. In our study, it was administered either directly or by phone to the patient or to a family member, depending on the patient's cognitive integrity. The patient was interviewed only if he/she was considered able to carry out a complex conversation and accurately remember his/her life prior to the injury. The CRIq was administered at the time of data collection, thus at different times post-injury for each participant. Nevertheless, all interviewees were asked to answer the questionnaire by referring to their lives prior to the injury, in order to have an estimate of CR unbiased by any experience that might have occurred since the event.

Clinical Indexes of Prognosis

Data obtained retrospectively from the medical charts were comprehensive of the recorded presence/absence of two brain

Table 1. Patients' information

	Post-anoxic encephalopathy		Traumatic brain injury	
	$n = 20$		$n = 30$	
	Mean (SD)		Mean (SD)	
Measure of interest	Admission	Discharge	Admission	Discharge
AGE	49 (14.6)		47.9 (12.24)	
CRIq-TOT	102.8 (13.36)		100.4 (14.1)	
LCF	3.5 (1.36)	5.5 (1.34)	3.6 (1.47)	6.3 (2.02)
DRS	19.3 (4.45)	11.9 (5.34)	18.8 (4.76)	8.7 (6.83)
FIM	22.7 (13.8)	65.6 (38.31)	27 (17.28)	81.3 (36.19)
BI	4 (13.63)	39.2 (38.28)	5.3 (12.66)	60 (42.12)
Tracheostomy	Present in 16 patients	Present in 0 patients	Present in 19 patients	Present in 3 patients
Enteral nutrition	Present in 17 patients	Present in 22 patients	Present in 5 patients	Present in 7 patients
GCS	3.8 (1.26)		4.7 (1.74)	
SEPS	Present in 9 patients		Present in 6 patients	
Pupillary reflex	Present in 15 patients		Present in 18 patients	
Corneal reflex	Present in 18 patients		Present in 17 patients	
Seizures	Present in 8 patients		Present in 11 patients	
LOS (days)	149 (53.9)		129.2 (67.79)	

stem reflexes (i.e., pupillary reflex and corneal reflex), the need of tracheostomy and enteral nutrition, the preserved presence of somatosensory evoked potentials (SEPs), and the incidence of seizures in the acute phase. A dichotomous score (1 if present; 0 if absent) was assigned for each of those measures.

Furthermore, CR was also investigated as possibly predictive of the overall length of staying (LOS) in hospital, measured in days, and of the obtained scores at four different clinical scales assessing patients' functionality and independence: the Rancho Los Amigos Levels of Cognitive Functioning (LCF) Scale (Hagen, Malkmus, & Durham, 1972), the Disability Rating Scale (DRS) (Rappaport, Hall, Hopkins, Belleza, & Cope, 1982), the Functional Independence Measure (FIM) (Granger, Hamilton, Keith, Zielezny, & Sherwin, 1986), and the Barthel Index (BI) (Mahoney, 1965). All scales were administered at two different times: the day of the injury/hospitalization and the day of hospital discharge, which was different for each of our subjects, ranging from 1 to 6 months of hospitalization. The aforementioned scales share a similar purpose of assessing recovery from basic physical advances to cognitive improvement, but differ in the extent to which cognitive functions are investigated, that is, in terms of orientation—as per the LCF scale—or social cognition and employability levels—as per the FIM and DRS. Furthermore, clinical scales differ in their range of scoring, with consequent differences in threshold sensitivity and in the ability to detect even minor improvements. To ensure accurate assessment of patients' level of functioning, all the indexes were addressed by expert personnel, including medical doctors, occupational and speech therapists, by means of direct observation and interview with the patient (see Table 1).

Statistical Analysis

Statistical analysis of the collected data was performed by means of the *R program*, version 3.3.2 (R Core Team, 2016). To investigate the possible existing relationship between CRI measures and the collected indexes of clinical severity and prognosis, linear mixed effects models (LMMs) were used, which allow to control for both repeated sampling and variance among subjects. LMM particularly suits our case where some of the data were retrieved at two different times (hospital admission and hospital discharge) across two different clinical populations: PAE and TBI patients. For each measure of interest in our study, several nested mixed effects models with "subjects" as our random effect were compared with the null model and between them, considering the effect of time, of the different diagnosis and of their interaction (time × diagnosis). In other words, LMM allowed us to directly test how much of our variable scores (e.g., outcome scores at the clinical scales) was explained by the individual level of *CR*, or by the additional effect of *CR* and *time*, or by three factors (*CR, time*, and type of *diagnosis*). The model that best explained the variable score was chosen based on the (i) Akaike information criterion (AIC), where lower values are indicative of a more informative model, (ii) their delta (δ AIC), considered from the subtraction of the lowest AIC value from the AIC of each other model, (iii) and the Akaike weights, which are representative of the probability of each model to make the best prediction of the data.

For those variables that were only assessed once (i.e., either at hospital admission or at discharge), the complexity of the nest was significantly reduced, given that only the added contribution of *diagnosis* and not of *time* was assessed.

Machine Learning

Machine learning (ML) models are usually regarded as outperforming more traditional statistical techniques in classification tasks. Various classifiers were developed using a 10-fold cross-validation technique. Cross-validation is primarily used in applied ML to estimate the skill of a ML model on unseen data, that is, to use a limited sample in order to estimate how the model is expected to perform in general when used to make predictions on data not used during the training phase. The steps of the 10-fold-cross-validations are: (1) shuffle the dataset randomly, (2) split the dataset in 10 groups of subjects, (3) take out 1 group for blind testing the model and train on the remaining 9/10 groups, (4) fit the model on the training dataset and test on the holdout dataset, and (5) rotate the holdout dataset and retrain. The final model will be the average of all the 10 models trained using this method.

In the present study, we compared the goodness of two ML algorithms [i.e., logistic model tree (LMT) and random forest (RF)] in classifying patients' outcome—either as successful or as unsuccessful—using WEKA (Waikato Environment for Knowledge Analysis), an open source software developed at the University of Waikato (Witten, Frank, Hall, & Pal, 2016), New Zealand.

The final classification of patients in successful/unsuccessful outcome recovery was determined using a cut-off point of 92 at the FIM scale. Prior large cohort studies have already proved FIM scores around 90 to be indicative of only moderate impairment (Whitlock, 1992; Whitlock & Hamilton, 1995). As in our study it was found to correspond to the median score of our collected measures at T2, this was accepted as a reasonable cut-off value. Consequently, patients with scores on the left side of the curve (<92 FIM score) were considered as not successfully recovered, whereas those with scores on the right side of the curve (>92 FIM score) were considered successfully recovered. Fifty instances corresponding to the number of patients and 13 input variables (e.g., the clinical indexes of prognosis at admission) were used to predict the output variable (i.e., rehabilitation success). The predictive goodness of the ML classifiers was based on a set of performance metrics (see another example of this analysis in Facal et al., 2019): (i) *Kappa* statistic, which represents a measure of goodness of the classification when compared with a random result; (ii) *precision*, which represents the probability that a positive prediction is correct; (iii) *recall*, which represents the proportion of instances belonging to the positive class that are correctly predicted as positive; (iv) *F-measure*, which indicates the weighted average of *precision* and *recall*, and (v) *receiver operating characteristic (ROC)* curve, which is a plot of true-positive rate *versus* false-positive rate.

RESULTS

Model Comparison

For each variable of interest in the study, different models were compared in their goodness of fit according to the AIC, for which lower values are indicative of better fit, and the Akaike weights, which instead estimate the probability of the model to provide accurate data prediction. Table 2 summarizes the main findings for each model, listed in order of best fit.

For our repeated measures model, a strong effect of time was observed for most of our variables, whereas the least effect was found when CRI alone was considered as a predictor. In predicting variation at the LCF and DRS, the most fitting model was the one accounting for both time and CRI (Figure 1, panels a and b). On the other hand, variation in achieving successful decannulation or in becoming tracheostomy free was not observed to have any meaningful interaction with patients' CRI, but rather to occur as a mere function of time (Figure 1, panels e and f). When the diagnosis was added to the predictions, it provided a pejorative contribution, leading to a concomitant increase in the AIC values and a reduction in the overall weight of the model.

The only exception was observed for the BI and FIM scales, where the ability of the model to predict the scores is strongly determined by the cumulative effects of CRI, time, and diagnosis (Figure 1, panels c and d).

On the other hand, a different pattern was observed for our single measurements, that is, those variables of interest that were assessed either at the time of hospital admission or at the time of hospital discharge. The type of diagnosis was observed to entail a strong impact in determining GCS scores and the preserved presence of corneal reflex (Figure 2, panels a and b), whereas it added no additional strength to the predictive power of CRI when tested in regard of patients' likelihood to show preserved pupillary reflex (Figure 2, panel c). Finally, CRI alone was observed to be a better estimator of shorter periods of hospitalization, of lower incidence of seizures in the acute phase, and of preserved presence of SEPs (Figure 2, panels d, e and f).

Classification Algorithms: LMT and RF

We developed two differing ML classifiers (i.e., LMT and RF) in classifying patients' outcome—either as successful or as unsuccessful—in order to predict the patients' outcome. The first model, LMT, consists of decision tree with logistic regression functions at its leafs (Landwehr, Hall, & Frank, 2003, 2005). The second model, known as RF (Breiman, 2001), provides a final classification of the data from the most voted response from a collection of random trees. LMT and RF can deal with binary variables, in the presence of both numeric and nominal attributes and missing values (Landwehr et al., 2005). Ten-fold cross-validation was applied to reduce both variability and overfitting. In this method, 9/10 of the data are used for training and 1/10 for testing. Validation results are then averaged over 10 rounds.

As shown in Table 3, LMT holds the strongest capacity to correctly discriminate between patients with successful or unsuccessful recovery, reaching an accuracy of the 80% and a Kappa statistic (KHAT) of 0.60, which is indicative

Table 2. Model comparison

Measure of interest	Model	Formula	AIC	δAIC	Weight
		Repeated measures (hospital admission, hospital discharge)			
LCF	M2	CRI + time	358.11	0.00	0.44
	M4	CRI + time × diagnosis	358.96	0.85	0.29
	M3	CRI + time + diagnosis	359.09	0.98	0.27
	M1	CRI	421.85	63.74	6.36E-09
DRS	M2	CRI + time	580.16	0.00	0.39
	M3	CRI + time + diagnosis	580.64	0.48	0.31
	M4	CRI + time × diagnosis	580.68	0.52	0.30
	M1	CRI	642.85	62.69	9.53E-09
FIM	M3	CRI + time + diagnosis	878.10	0.00	0.43
	M4	CRI + time × diagnosis	878.70	0.60	0.32
	M2	CRI + time	879.15	1.05	0.25
	M1	CRI	935.18	57.08	1.73E-07
BI	M4	CRI + time × diagnosis	947.54	0.00	0.57
	M3	CRI + time + diagnosis	948.88	1.34	0.29
	M2	CRI + time	950.30	2.76	0.14
	M1	CRI	998.32	50.78	5.33E-06
Tracheostomy	M2	CRI + time	62.78	0.00	0.65
	M3	CRI + time × diagnosis	64.76	1.98	0.24
	M4	CRI + time + diagnosis	66.50	3.72	0.10
	M1	CRI	137.66	74.88	3.60E-11
Enteral nutrition	M2	CRI + time	77.64	0.00	0.72
	M3	CRI + time + diagnosis	79.62	1.98	0.27
	M4	CRI + time × diagnosis	85.89	8.25	0.16
	M1	CRI	141.00	63.36	1.26E-08
		Single measures (hospital admission or hospital discharge)			
GCS	M2	CRI + diagnosis	175.98	0.00	0.66
	M1	CRI	177.28	1.30	0.34
SEPS	M1	CRI	12.03	0.00	0.60
	M2	CRI + diagnosis	12.88	0.85	0.39
Pupillary reflex	M1	CRI	55.94	0.00	0.50
	M2	CRI + diagnosis	55.94	0.00	0.50
Corneal reflex	M2	CRI + diagnosis	43.75	0.00	0.80
	M1	CRI	46.59	2.84	0.19
Seizures	M1	CRI	67.45	0.00	0.71
	M2	CRI + diagnosis	69.27	1.82	0.29
LOS	M1	CRI	514.42	0.00	0.55
	M2	CRI + diagnosis	514.85	0.43	0.44

of the agreement between the predicted and the observable categorizations of the dataset while correcting for agreements that occur by chance. At the time of data analysis, five patients were missing FIM T2 scores, and therefore their outcome measures could not be entered in the model. Nevertheless, the number of incorrectly classified instances remained low (9 out of 45). The goodness of the model is further demonstrated by the area under the ROC curve, proving a good sensitivity of the model for all the possible values of specificity (Hajian-Tilaki, 2013).

On the other hand, RF algorithm was found to be slightly less efficient in discriminating between patients' outcome. Despite the observed decrease in accuracy (71.1% compared to 80% in LMT), the model entails the major advantage of enabling the computation of attribute importance based on the average impurity decrease, such as that CR was observed to contribute the most—together with age—in decreasing model's entropy, thus in better discriminating between patients' successful and unsuccessful outcome. The complete list of predictors in order of importance is reported in Table 4.

The Role of CR in the Recovery from Severe TBI and PAE

The role of CR in severe TBI injuries has been rarely addressed in the literature; and to our knowledge, no research has so far been conducted on PAE patients. In our study, patients with higher CR, irrespective of diagnosis, were more likely to show preserved pupillary reflex and SEPs immediately after the injury (Table 2; Figure 2, panels c and f).

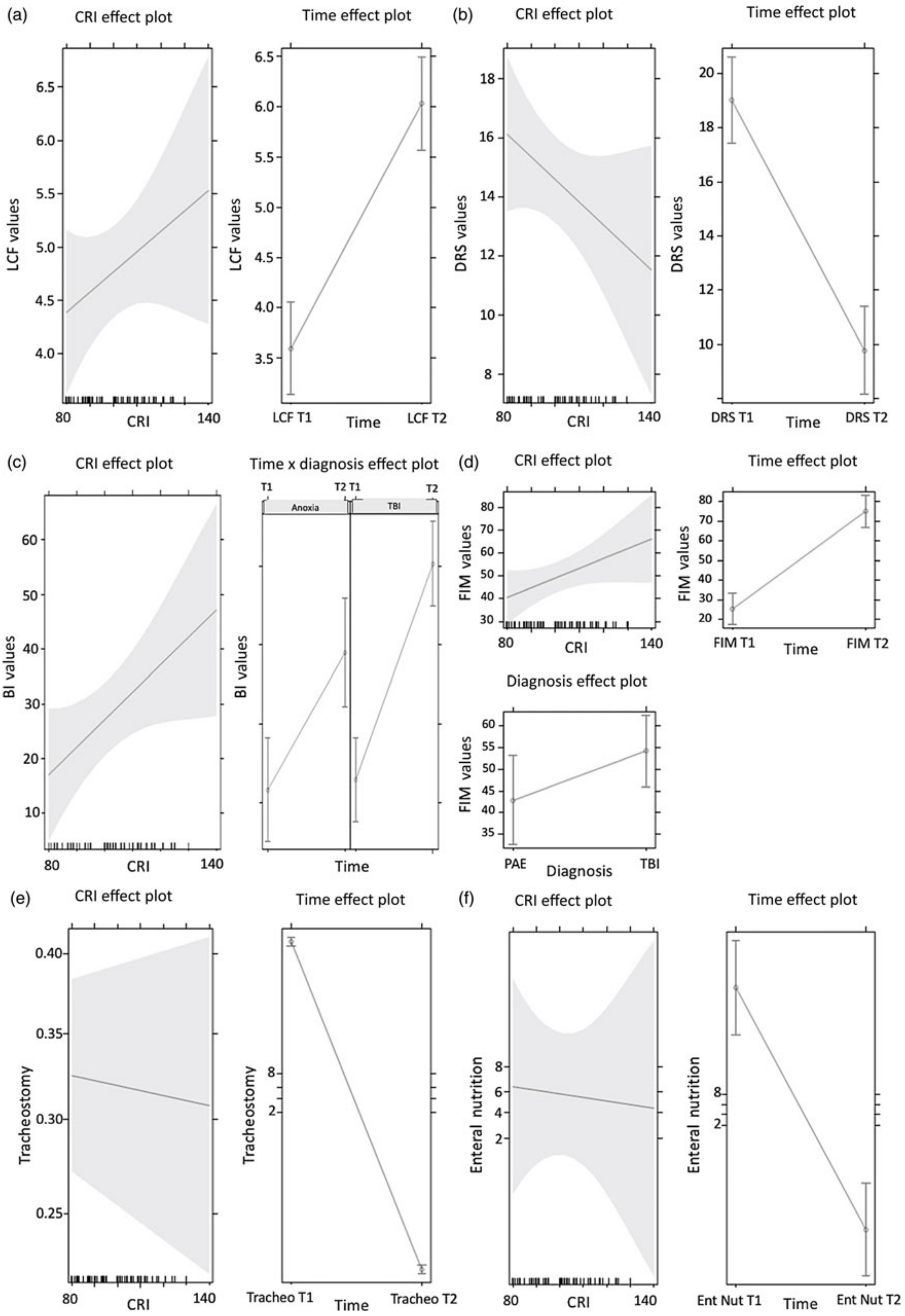

Fig. 1. Graphic representation of the relationship between CRI and our variables of interest. Variations at the clinical scales are shown in panels (**a**), (**b**), (**c**), and (**d**). The relationship with tracheostomy and enteral nutrition is shown in panels (**e**) and (**f**).

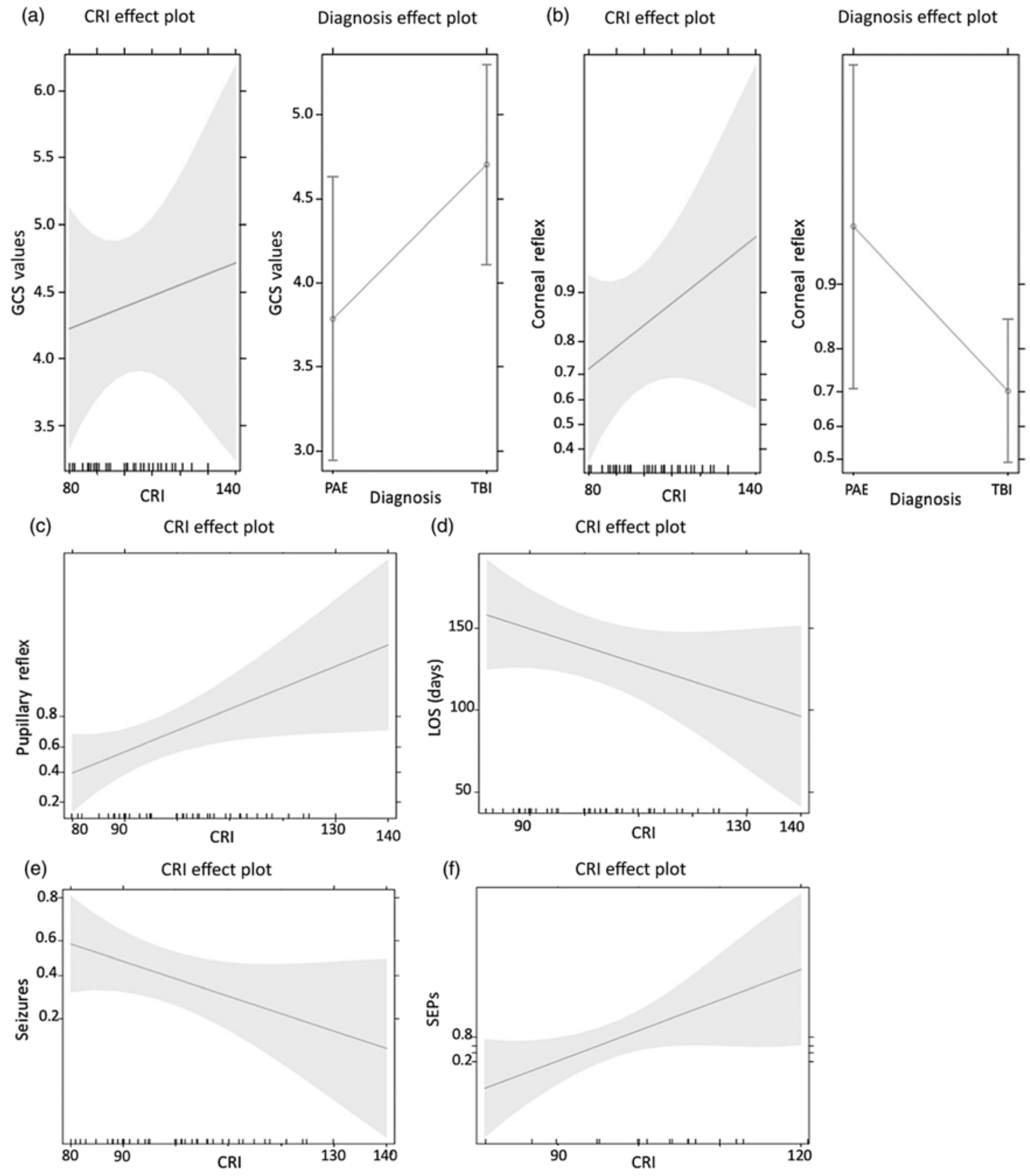

Fig. 2. Graphical representation of the investigated relationship between CRI and our variables of interest. Relationships with the Glasgow Coma Scale (**a**), corneal reflex (**b**), pupillary reflex (**c**), length of hospitalization (**d**), seizures (**e**), and presence of SEPs (**f**) are shown.

Similarly, individuals with high CR showed proportionally shorter periods of hospitalization—which in our subjects ranged between 1 and 6 months—and a simultaneous reduced risk of having seizures while hospitalized (Table 2; Figure 2 panels d and e). CR was found to be associated with lower scores at the GCS, even though the type of diagnosis also had a significant effect: PAE patients tended to have lower GCS scores compared to TBI (Table 2; Figure 2 panel a). Nevertheless, all patients had a clinical severity between 3 and 8 GCS and further analysis revealed no significant difference between our samples ($M_{PAE} = 3.8$, $SD_{PAE} = 1.26$; $M_{TBI} = 4.7$, $SD_{TBI} = 1.75$; $t(43) = -1.77$, $p = 0.083$). A combined effect of both CR and diagnosis was also observed in the likelihood of showing preserved corneal reflex: higher probability was observed in individuals with higher CR and mostly in PAE rather than TBI patients (Table 2; Figure 2 panel b). On the other hand, CR did not play any meaningful role in other low-level life functions, such as respiration, swallowing, and chewing assessed by the need of tracheostomy and enteral nutrition (Table 2; Figure 1 panels e and f). Indeed, patients showed improvement only as a function of time, regardless of their level of CR. Moving toward higher level of functioning, higher CR in our patients was partly associated with higher

Table 3. Machine learning

Logistic model tree			
Total no. of instances		45	
Correctly classified		36 (80%)	
Incorrectly classified		9 (20%)	
Kappa statistic (KHAT)		0.600	
Mean absolute error		0.289	
	Successful recovery	Unsuccessful recovery	Weighted average
Precision	0.818	0.783	0.801
Recall	0.783	0.818	0.800
F-measure	0.800	0.800	0.800
ROC area	0.820	0.803	0.811
Random forest			
Total no. of instances		45	
Correctly classified		32 (71.1%)	
Incorrectly classified		13 (28.9%)	
Kappa statistic (KHAT)		0.422	
Mean absolute error		0.391	
	Successful recovery	Unsuccessful recovery	Weighted average
Precision	0.727	0.696	0.712
Recall	0.696	0.727	0.711
F-measure	0.711	0.711	0.711
ROC area	0.755	0.678	0.717

Table 4. Attribute importance based on average impurity decrease

List of attributes	Average decrease of entropy
Age	0.46
CRI	0.46
Diagnosis	0.40
Seizures	0.40
DRS at T1	0.39
Pupillary reflex	0.38
FIM at T1	0.36
GCS	0.35
LCF at T1	0.33
Enteral nutrition	0.29
Tracheostomy	0.28
Corneal reflex	0.23
BI at T1	0.23
SEPs	0.09

scores at the LCF, BI, and FIM scales and with lower scores at the DRS (Table 2; Figure 1 panels a, b, c, and d). As expected, the time factor had the most significant contribution to the model, explaining the clinical improvement between hospital admission and discharge. Few differences between PAE and TBI patients were observed at the BI and FIM scale, where TBI showed a greater improvement. Finally, the overall role of CR in the recovery from severe TBI and PAE was best captured by two ML algorithms. These classifiers correctly discriminated patients who eventually reached successful or unsuccessful outcome with a 71.2% and 80% of accuracy. Age and CR were the strongest predictors (Table 4), both equally ensuring up to a 46% reduction of model entropy.

DISCUSSION

The present study aimed to investigate the role of CR in the recovery from two acquired injuries: PAE and TBI. Few relevant works on TBI patients have already confirmed the role of CR in modulating post-injury cognitive deficits, as observed from the administration of neuropsychological batteries (Kesler et al., 2003; Ropacki & Elias, 2003; Sumowski, Chiaravalloti, Krch, Paxton, & DeLuca, 2013). However, this approach has the major disadvantage of not being always suitable for severe patients (Green et al., 2008; Jeon et al., 2008), for whom less clear results have been reported. Furthermore, to our knowledge, no prior study has been conducted assessing the role of CR in anoxic patients, despite their epidemiological relevance.

To try and fill this gap, we proposed a new methodological approach focusing on the association between measures of CR and early clinical indexes of severity and prognosis, as well as on four of the most well-known clinical scales assessing patient's autonomy and independence. A major advantage of the present study is the possibility to establish a continuum in the evaluation of the patient from the more basic vegetative brain stem functions (eye movements in response to light/touch, respiration, swallowing, etc.) to higher levels of performance—including motor and basic cognitive abilities—up to when a complete independence in everyday activities could be eventually reached. As CR is a hypothetical construct, particular care should be paid when assessing its measurement (Jones et al., 2011). Education represents its most widely recognized proxy, due to the numerous findings that highly educated individuals can sustain a pathology better and for longer (Stern, 2002). Nevertheless, the use of a single stand-in measure of CR can result in a less accurate measurement of reserve and in a greater risk of bias due to CR-unrelated factors (Jones et al., 2011). For this reason, composite estimates of CR should be preferred. In the present study, CR was computed from the administration of an ad-hoc questionnaire—the CRI questionnaire (Nucci et al., 2012)—considering individuals' education, working occupation, and overall involvement in cognitive stimulating leisure time activities.

We found that CR might have a modulatory role in enhancing the likelihood of the individual to present greater robustness in the face of damage. This can occur as a function of both greater *reserve* accumulation (leading to greater resilience to the damage) and better *maintenance* capacity (i.e., faster recovery scenario that leads to a faster return to baseline performance levels) (Cabeza et al., 2018). This was expressed as a function of a positive association between our estimates of reserve and the preserved presence of SEPs and of pupillary reflex. Furthermore, higher reserve seemed to be accompanied by a decreased incidence of seizures across our two groups of patients. On the other hand, corneal reflex and GCS scores—assessing clinical severity in the acute phase—showed modulation as a function of both CR and type of diagnosis in that PAE patients had lower GCS scores compared to TBI (i.e., greater severity), while they tended to show greater likelihood of displaying preserved corneal reflex. Apart from the GCS, other clinical scales were administered to our patients at the time of hospital admission and re-administered at the end of the rehabilitative program, thus closely monitoring for recovery in terms of functionality and independence. The relationship between CR and those scales is, however, hard to interpret. Specifically, CR seemed to show a positive association with the measures obtained at the LCF, FIM, and BI scales, and a negative relationship with the DRS scale, for which lower scores are indicative of milder severity. Nevertheless, from the statistical point of view, CR alone cannot be considered the strongest single predictor of the obtained scores. Rather, most of the observed variation appeared imputable to the time factor, suggesting general amelioration as a function of recovery only partly shaped by patients' reserve. Nevertheless, despite not being *statistically* significant, graphic depictions of the relationship between CR and the clinical scales might present *clinically* relevant patterns of recovery. The LCF scale is representative of the main eight stages of recovery, ranging from the unconscious phase that characterizes the initial stage up to when appropriate cognitive functioning is restored, in terms of orientation, awareness, appropriate behavior, and recovery from post-traumatic amnesia, but with no focus on more complex cognitive functions (Van Baalen et al., 2003). On the other hand, the DRS covers a spectrum ranging from coma to reintegration of the individual in the community (Hall, Bushnik, Lakisic-Kazazic, Wright, & Cantagallo, 2001). The association between CR and both LCF and DRS scales could, for example, suggest that CR might exert a longitudinal effect, starting from motor and low-level functioning up to the recovery of finer cognitive and social skills. These data are partly supported by the reported association between CRI and early indexes of prognosis (i.e., brain stem reflexes, seizures, and evoked potentials), and partly by its association with the remaining two clinical scales, BI and FIM. These scales differ from the former two because they cover a greater range of scores, ranging from 0 to 100 for the BI and from 18 to 126 for the FIM, compared to the 8 LCF levels used to assess improvement or the up-to-29 score used in the DRS. The major advantage of a broader scoring within the BI and FIM scales is lowering the sensitivity threshold, which allows the monitoring of even small improvements over time. Similarly to the DRS, the FIM scale also assesses high cognitive functions such as communication and social cognition (Granger et al., 1986), providing a comprehensive picture of recovery up to its final stages. Overall, the greater sensitivity to changes of the scores of the last two scales may explain their being influenced by type of diagnosis and not only by time and CR. In particular, PAE patients had lower FIM measures compared to the TBI group, but comparable scores at the BI. Considering that only the FIM scale examines cognitive functioning, the worst performance of PAE patients may reflect the extent of the damage itself—with the lack of oxygenation affecting the entire neocortex—compared with TBI damage, which is more likely to expand in depth rather than on the surface. Consequently, cognitive impairments following anoxic damage may span over multiple cognitive domains, ultimately resulting in greater impairment of the individuals' activities of daily living. On the other hand, no meaningful interaction could be observed between CR and low-level functions necessary for life, such as swallowing, chewing, and ultimately respiration, which in our study were assessed by the need of the patients to be tracheostomized or to be fed by enteral nutrition. As for the association with the length of hospitalization, patients with higher measures of reserve show a trend for shorter periods of hospitalization, compared to their counterpart with lower CR.

Finally, we compared the classification goodness of two ML algorithms—LMT and RF—in discriminating between patients who eventually reached a successful or unsuccessful recovery. Both models reached high predictive power (80% and 71.1%, respectively); RF further enabled us to address which, among all factors, were the ones with the greater weight in driving the classifier. In terms of discriminative power, CR measures were observed to contribute as much as age in predicting patients' outcome, resulting in the top three factors contributing to the decrease of model entropy. The present findings confirm the widely known role of young age in ensuring greater robustness to damage and faster recovery paths. Furthermore, it provides evidence for the contribution of higher CR in favorably determining successful recovery, with a rate equal to the effect of age.

Overall, the present study seems to suggest that CR could play a meaningful role in the rehabilitation of pathologies not usually studied, especially neurodegenerative disorders. Indeed, the formal estimation of CR has recently been promoted as a crucial part of the Comprehensive Geriatric Assessment to allow a more accurate diagnosis and prognosis of dementia (Devita et al., 2019). As more evidence is progressively gathered on the role of CR in sudden-onset pathologies, a rationale for the routinely investigation of CR in these patients should be promoted as well. In particular, knowledge of a patient's CR could be informative on many aspects of his/her life habits prior to the injury, which could be used to build tailored interventions. As an example, high CR individuals are more likely to have enjoyed activities such as regularly reading books and newspapers, as well as playing cognitive stimulating board games (e.g., chess), all of which could be easily implemented in the rehabilitative process to promote greater compliance with the treatment and more ecological interventions overall. On the other hand, lower CR subjects are more likely to find those interventions distressing and unfamiliar, and thus different approaches will be needed. Knowing the personal history of the individual and his/her family guarantees a better doctor–patient relationship and a greater compliance in the interest of the patient.

LIMITATIONS

One of the shortcomings of the present study is the relatively small number of patients and the associated clinical information that could be retrieved from their medical records. However, the need to control for possible confounding factors—to avoid or at least limit the incidence of undue influences and biases—was preferred over the possibility to recruit a greater number of individuals. A further limitation is that neuroimaging data have not been collected which could have provided useful information on the extensiveness of the cortical damage. Future investigations might address how the role of CR in rehabilitation is affected in focal *versus* diffuse injuries.

CONCLUSIONS

In the present study, the role of CR was investigated in the recovery from PAE or TBI. Our findings seem to suggest a possible role of reserve in modulating patients' outcome and rehabilitation success, even from severe acquired pathological conditions. Therefore, we believe that CR should be routinely taken into account in the clinical practice to provide help in personalizing interventional therapies. Detailed estimates of individuals' CR could help know patients better and guide the construction of ad-hoc interventional care.

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CONFLICTS OF INTEREST

The authors have nothing to disclose.

REFERENCES

Auer, R.N. & Benveniste, H. (1997). Hypoxia and related conditions. In D.I. Graham, P.L. Lantos (Eds.), *Greenfield's neuropathology* (6th ed., pp. 263–314). New York: Oxford University Press. https://doi.org/10.1201/b13319

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

Bennett, D.A., Wilson, R.S., Schneider, J.A., Evans, D.A., de Leon, C.F.M., Arnold, S.E., Barnes L.L., & Bienias, J.L. (2003). Education modifies the relation of AD pathology to level of cognitive function in older persons. *Neurology*, *60*(12), 1909–1915. https://doi.org/10.1212/01.WNL.0000069923.64550.9F

Bittner, R.M. & Crowe, S.F. (2009). The relationship between working memory, processing speed, verbal comprehension and FAS performance following traumatic brain injury. *Brain Injury*, *21*(7), 709–719. https://doi.org/10.1080/02699050701468917

Breiman, L. (2001). Random forests. *Machine Learning*, *45*(1), 5–32. https://doi.org/10.1023/A:1010933404324

Cabeza, R., Albert, M., Belleville, S., Craik, F.I.M., Duarte, A., Grady, C.L., Duarte, A., Lindenberger, U, Nyberg, L, Park, D.C., Rugg, M.D., Reuter-Lorenz, P.A., Steffener, J., & Rajah, M.N. (2018). Maintenance, reserve and compensation: The cognitive neuroscience of healthy ageing. *Nature Reviews Neuroscience*, *19*(11), 701–710. https://doi.org/10.1038/s41583-018-0068-2

Devita, M., Mondini, S., Bordignon, A., Sergi, G., Girardi, A., Manzato, E., Mapelli, D., & Coin, A. (2019). The importance of cognitive reserve in comprehensive geriatric assessment for dementia. *Aging Clinical and Experimental Research*, 1–3. https://doi.org/10.1007/s40520-019-01285-5

Facal, D., Valladares-Rodriguez, S., Lojo-Seoane, C., Pereiro, A.X., Anido-Rifon, L., & Juncos-Rabadán, O. (2019). Machine learning approaches to studying the role of cognitive reserve in conversion from mild cognitive impairment to dementia. *International Journal of Geriatric Psychiatry*, *34*(7), 941–949. https://doi.org/10.1002/gps.5090

Fortune, D.G., Walsh, S.R., & Richards, H.L. (2016). Cognitive reserve and preinjury educational attainment: Effects on outcome of community-based rehabilitation for longer-term individuals with acquired brain injury. *International Journal of Rehabilitation Research*, *39*(3), 234–239. https://doi.org/10.1097/MRR.0000000000000175

Granger, C.V., Hamilton, B.B., Keith, R.A., Zielezny, M., & Sherwin, F.S. (1986). Advances in functional assessment for medical rehabilitation. *Topics in Geriatric Rehabilitation*, *1*(3), 59–74.

Green, R.E., Colella, B., Christensen, B., Johns, K., Frasca, D., Bayley, M., & Monette, G. (2008). Examining moderators of cognitive recovery trajectories after moderate to severe traumatic brain injury. *Archives of Physical Medicine and Rehabilitation*, *89*(12), S16–S24. https://doi.org/10.1016/j.apmr.2008.09.551

Hagen, C., Malkmus, D., & Durham, P. (1972). *Levels of cognitive functioning*. Downey, CA: Rancho Los Amigos Hospital.

Hajian-Tilaki, K. (2013). Receiver Operating Characteristic (ROC) curve analysis for medical diagnostic test evaluation. *Caspian Journal of Internal Medicine*, *4*(2), 627.

Hall, K.M., Bushnik, T., Lakisic-Kazazic, B., Wright, J., & Cantagallo, A. (2001). Assessing traumatic brain injury outcome measures for long-term follow-up of community-based individuals. *Archives of Physical Medicine and Rehabilitation*, *82*(3), 367–374. https://doi.org/10.1053/apmr.2001.21525

Jeon, I.-C., Kim, O.-L., Kim, M.-S., Kim, S.-H., Chang, C.-H., & Bai, D.-S. (2008). The effect of premorbid demographic factors on the recovery of neurocognitive function in traumatic brain injury patients. *Journal of Korean Neurosurgical Society*, *44*(5), 295. https://doi.org/10.3340/jkns.2008.44.5.295

Jones, R.N., Manly, J., Glymour, M.M., Rentz, D.M., Jefferson, A.L., & Stern, Y. (2011). Conceptual and measurement challenges in research on cognitive reserve. *Journal of the International Neuropsychological Society*, *17*(4), 593–601. https://doi.org/10.1017/S1355617710001748

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

Landwehr, N., Hall, M., & Frank, E. (2003). Logistic model trees. In *Proceedings of 14th European Conference on Machine Learning*. (pp. 241–252). Springer-Verlag.

Landwehr, N., Hall, M., & Frank, E. (2005). Logistic model trees. *Machine Learning*, *59*(1–2), 161–205. https://doi.org/10.1007/s10994-005-0466-3

Le Carret, N., Auriacombe, S., Letenneur, L., Bergua, V., Dartigues, J.-F., & Fabrigoule, C. (2005). Influence of education on the pattern of cognitive deterioration in AD patients: The cognitive reserve hypothesis. *Brain and Cognition*, *57*(2), 120–126. https://doi.org/10.1016/j.bandc.2004.08.031

Lim, C., Alexander, M.P., LaFleche, G., Schnyer, D.M., & Verfaellie, M. (2004). The neurological and cognitive sequelae of cardiac arrest. *Neurology*, *63*(10), 1774–1778. https://doi.org/10.1212/01.WNL.0000144189.83077.8E

Mahoney, R.I. (1965). Functional evaluation: The Barthel Index. *Maryland State Medical Journal*, *14*, 61–65.

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*, *35*(10), 1513–1518. https://doi.org/10.1007/s10072-014-1897-z

Poletti, M., Emre, M., & Bonuccelli, U. (2011). Mild cognitive impairment and cognitive reserve in Parkinson's disease. *Parkinsonism & Related Disorders*, *17*(8), 579–586. https://doi.org/10.1016/j.parkreldis.2011.03.013

R Core Team. (2016). *R: A language and environment for statistical computing*. Retrieved from https://www.R-project.org/

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., D'Angelo, G., Xiong, C., Grant, E.A., & Morris, J.C. (2008). Alzheimer Disease and cognitive reserve: Variation of education effect with carbon 11–labeled Pittsburgh compound B uptake. *Archives of Neurology*, *65*(11), 1467–1471. https://doi.org/10.1001/archneur.65.11.1467

Ropacki, M.T. & Elias, J.W. (2003). Preliminary examination of cognitive reserve theory in closed head injury. *Archives of Clinical Neuropsychology*, *18*(6), 643–654. https://doi.org/10.1093/arclin/18.6.643

Satz, P. (1993). Brain reserve capacity on symptom onset after brain injury: A formulation and review of evidence for threshold theory. *Neuropsychology*, *7*(3), 273–295. https://doi.org/10.1037/0894-4105.7.3.273

Scarmeas, N., Levy, G., Tang, M.-X., Manly, J., & Stern, Y. (2001). Influence of leisure activity on the incidence of Alzheimer's disease. *Neurology*, *57*(12), 2236–2242. https://doi.org/10.1212/WNL.57.12.2236

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

Snowdon, D.A. (2003). Healthy aging and dementia: Findings from the nun study. *Annals of Internal Medicine*, *139*(5_Part_2), 450. https://doi.org/10.7326/0003-4819-139-5_Part_2-200309021-00014

Stern, Y. (2002). What is cognitive reserve? Theory and research application of the reserve concept. *Journal of the International Neuropsychological Society*, *8*(3), 448–460. https://doi.org/10.1017/S1355617702813248

Stern, Y. (2006). Cognitive reserve and Alzheimer Disease. *Alzheimer Disease & Associated Disorders*, *20*, S69–S74.

Stern, Y. (2009). Cognitive reserve. *Neuropsychologia*, *47*(10), 2015–2028. https://doi.org/10.1016/j.neuropsychologia.2009.03.004

Sumowski, J.F., Chiaravalloti, N., & DeLuca, J. (2009). Cognitive reserve protects against cognitive dysfunction in multiple sclerosis. *Journal of Clinical and Experimental Neuropsychology*, *31*(8), 913–926. https://doi.org/10.1080/13803390902740643

Sumowski, J.F., Chiaravalloti, N., Krch, D., Paxton, J., & DeLuca, J. (2013). Education attenuates the negative impact of traumatic brain injury on cognitive status. *Archives of Physical Medicine and Rehabilitation*, *94*(12), 2562–2564. https://doi.org/10.1016/j.apmr.2013.07.023

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

Van Baalen, B., Odding, E., Maas, A.I.R., Ribbers, G.M., Bergen, M.P., & Stam, H.J. (2003). Traumatic brain injury: Classification of initial severity and determination of functional outcome. *Disability and Rehabilitation*, *25*(1), 9–18. https://doi.org/10.1080/dre.25.1.9.18

Whitlock, J.A. (1992). Functional outcome of low-level traumatically brain-injured admitted to an acute rehabilitation programme. *Brain Injury*, *6*(5), 447–459. https://doi.org/10.3109/02699059209008140

Whitlock, J.A. & Hamilton, B.B. (1995). Functional outcome after rehabilitation for severe traumatic brain injury. *Archives of Physical Medicine and Rehabilitation*, *76*(12), 1103–1112. https://doi.org/10.1016/S0003-9993(95)80117-0

Witten, I.H., Frank, E., Hall, M.A., & Pal, C.J. (2016). *Data mining: Practical machine learning tools and techniques*. Cambridge, MA: Morgan Kaufmann.