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Yuri Rassovsky^{abc}, Yifat Levi^a, Eugenia Agranov^{de}, Michal Sela-Kaufman^f, Anna Sverdlik^{de} & Eli Vakil^{ab}

^a Department of Psychology, Bar-Ilan University, Ramat-Gan, Israel

^b Leslie and Susan Gonda (Goldschmied) Multidisciplinary Brain Research Center, Bar-Ilan University, Ramat-Gan, Israel

^c Department of Psychiatry and Biobehavioral Sciences, University of California, Los Angeles (UCLA), Los Angeles, CA, USA

^d The Chaim Sheba Medical Center at Tel Hashomer, Ramat-Gan, Israel

^e Faculty of Medicine, Tel-Aviv University, Tel-Aviv, Israel

^f Department of Behavioral Sciences, the Academic College of Tel-Aviv-Yaffo, Israel
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Predicting long-term outcome following traumatic brain injury (TBI)

Yuri Rassovsky^{1,2,3}, Yifat Levi¹, Eugenia Agranov^{4,5}, Michal Sela-Kaufman⁶, Anna Sverdlik^{4,5}, and Eli Vakil^{1,2}

¹Department of Psychology, Bar-Ilan University, Ramat-Gan, Israel

²Leslie and Susan Gonda (Goldschmied) Multidisciplinary Brain Research Center, Bar-Ilan University, Ramat-Gan, Israel

³Department of Psychiatry and Biobehavioral Sciences, University of California, Los Angeles (UCLA), Los Angeles, CA, USA

⁴The Chaim Sheba Medical Center at Tel Hashomer, Ramat-Gan, Israel

⁵Faculty of Medicine, Tel-Aviv University, Tel-Aviv, Israel

⁶Department of Behavioral Sciences, the Academic College of Tel-Aviv-Yaffo, Israel

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Objective: Traumatic brain injury (TBI) is the most common cause of brain damage, resulting in long-term disability. The ever increasing life expectancies among TBI patients necessitate a critical examination of the factors that influence long-term outcome. Our objective was to evaluate the contribution of premorbid factors (which were identified in our previous work) and acute injury indices to long-term functioning following TBI. **Method:** Eighty-nine participants with moderate-to-severe TBI were evaluated at an average of 14.2 years postinjury (range: 1–53 years) with neuropsychological battery, medical examination, clinical interviews, and questionnaires. **Results:** TBI severity predicted cognitive, social, and daily functioning outcomes. After controlling for injury severity, preinjury intellectual functioning predicted cognitive status, as well as occupational, social, emotional, and daily functioning. Preinjury leisure activity also predicted cognitive, emotional, and daily functioning, whereas socioeconomic status failed to predict any of these variables. **Conclusion:** Findings offer further support for the cognitive reserve construct in explaining significant variance in TBI outcome, over and above the variance explained by injury severity.

Keywords: Injury severity; Traumatic brain injury; Head injury; Cognitive reserve; Rehabilitation; Functional outcome.

Traumatic brain injury (TBI) is the most common cause of brain damage (Kurtzke, 1984), resulting in long-term mental and physical disability. Falls are the most common cause of TBI in infants, young children, and the elderly, whereas motor vehicle accidents are the leading cause in the other age groups (Williamson, Scott, & Adams, 1996). The

National Center for Health Statistics (2010) estimate that TBI requiring a physician visit occurs with an incidence of 1.74 million per year in the United States (Ma, Chan, & Carruthers, 2014). Although medical and biotechnological developments have reduced TBI mortality rates, many patients continue to experience long-term disability

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The authors wish it to be known that, in their opinion, the first two authors should be regarded as joint first authors.

Address correspondence to: Yuri Rassovsky, Department of Psychology, Bar-Ilan University, Ramat-Gan 52900, Israel (E-mail: yurir@biu.ac.il).

(Zaloshnja, Miller, Langlois, & Zelasie, 2008) that is characterized by physical, cognitive, emotional, and behavioral difficulties (Bazarian, Cernak, Noble-Haesslein, Potolicchio, & Temkin, 2009; Langlois, Rutland-Brown, & Wald, 2006). In accordance with the diffuse nature of the injury, these deficiencies are not homogeneous. Impairments most frequently reported include concentration and attention, information processing, executive functions, and memory skills (Ponsford et al., 2014; Tate et al., 2014; Velikonja et al., 2014). Difficulties in generalization, inappropriate behavior, stimulus-bound behavior, and recurrent loss of control and unrestrained anger have been reported in the behavioral domain (Simpson, Sabaz, Daher, Gordon, & Strettles, 2014). In addition, various emotional problems have been observed, from flattened affect to extreme emotional reactions (Bryant et al., 2010; Grauwmeijer, Heijenbrok-Kal, & Ribbers, 2014; Sela-Kaufman, Rassovsky, Agranov, Levi, & Vakil, 2013). As a result of these factors, patients often experience substantial difficulties in psychosocial and occupational adjustment (Saltychev, Eskola, Tenovuo, & Laimi, 2013; Williams, Rapport, Millis, & Hanks, 2014).

TBI often leads to cognitive impairments whose severity and duration vary from person to person (Kesler, Adams, Blasey, & Bigler, 2003; Vakil, 2005). In an attempt to explain these individual differences, many researchers have focused on injury-related variables, such as injury severity. However, as Kesler et al. (2003) noted, these studies have been inconsistent and do not offer a satisfactory explanation of many of the neurocognitive outcomes. Whereas some studies have found that injury severity indices predicted functional outcome (e.g., Asikainen, Kaste, & Sarna, 1998; Felmingham, Baguley, & Crooks, 2001; Kelly et al., 1997; Spettell et al., 1991; Tate & Broe, 1999; Temkin, Corrigan, Dikmen, & Machamer, 2009), other studies have failed to detect such relationships (Ip, Dornan, & Schentag, 1995; Kesler et al., 2003; Sherer, Bergloff, High, & Nick, 1999). This could be due to a host of potential variables that mediate the relationship between injury severity and outcome. For example, Novack, Bush, Meythaler, and Canupp (2001) reported that the relationship between injury severity and functional outcome was mediated by premorbid variables and by cognitive deficits in the subacute stage of the injury. Similarly, Rassovsky et al. (2006a, 2006b), using structural equation modeling, found that neurocognitive difficulties consistently mediated the relationship between injury severity and functional outcome at 12 months postinjury.

One of the theories that may explain the variance in clinical symptomatology following TBI is the reserve hypothesis (Satz, 1993; Stern, 2002), which suggests that the relationship between brain pathology and its clinical expression is partly mediated by premorbid factors. As Tucker (2005) noted, at the time of the injury, a complex array of factors converge to contribute to recovery or to the lasting neurobehavioral and cognitive effects of the injury. Since TBI is an acquired injury, a brain's "health" and overall functional integrity at the time of injury should be key factors in the ultimate effects of the injury (Bigler, 2006). Accordingly, various reserve indices (e.g., IQ, education, occupation, head circumference, and participation in leisure activities) have been associated with slower cognitive decline in normal aging, as well as reduced risk of dementia (e.g., Dik, Deeg, Visser, & Jonker, 2003; Manly, Schupf, Tang, & Stern, 2005; Mortimer, Snowden, & Markesbery, 2003; Qiu, Backman, Winblad, Aguero-Torres, & Fratiglioni, 2001; Scarmeas, Levy, Tang, Manly, & Stern, 2001; Wilson, Barnes, & Bennett, 2003). In TBI studies, preinjury characteristics that were reported as predictors of increased cognitive deficits following TBI included psychiatric or neurological problems (MacMillan, Hart, Martelli, & Zasler, 2002; Novack et al., 2001; Ropacki & Elias, 2003; Sherer et al., 1999), learning disability (Farmer et al., 2002), marital difficulties (Kreutzer et al., 2003), lower socioeconomic and occupational status (Gollahar et al., 1998; Hoofien, Vakil, Gilboa, Donovan, & Barak, 2002; Sherer et al., 2002), lower education (Gollahar et al., 1998; Novack et al., 2001; Schneider et al., 2014; Sherer et al., 2002), and lower intracranial volume (Kesler et al., 2003). Therefore, it seems that a comprehensive examination of injury outcome must take into account both preinjury and acute severity measures.

In order to enable effective prognosis of injury outcome, it is necessary to address TBI as a multifactorial structure that combines different variables throughout life. In a recent paper, we reported the findings of a systematic validation of the reserve construct through factor analyses (Levi, Rassovsky, Agranov, Sela-Kaufman, & Vakil, 2013). In that study, we found a content-based, three-factor structure, which consists of premorbid intellectual functioning, leisure activity, and socioeconomic status. The aim of the present study was to examine the prognostic value of these factors in predicting real-world long-term outcome. Specifically, we examined the predictive power of injury severity and preinjury variables on long-term outcome. This was conducted by linking preinjury measures, acute injury status, and long-term

postinjury assessments of current cognitive, occupational, functional, social, and mental status, in a cross-sectional research design of individuals who sustained moderate-to-severe TBI. First, the predictive power of injury severity variables on long-term outcome was evaluated. Next, the relative contribution of each of the three preinjury factors to predicting outcome was examined, while controlling for injury severity. This was done to determine whether the preinjury measures have additive prognostic value beyond that of injury severity.

METHOD

Participants

The study included 89 individuals (80 males) with moderate-to-severe TBI from the Day Treatment Rehabilitation unit and the outpatient clinics of the Rehabilitation Hospital at the Chaim Sheba Medical Center, Ramat-Gan, Israel ($n = 62$) and from the Rehabilitation Center for Veterans after TBI, Jaffa, Israel ($n = 27$). This was the same sample as that described in Levi et al. (2013). The characterization of TBI severity was based on three measures: Glasgow Coma Scale (GCS), loss of consciousness (LOC), and posttraumatic amnesia (PTA). Moderate TBI was defined as GCS 9–12, LOC 20 minutes–36 hours, and PTA 1–7 days; severe TBI was defined as GCS 3–8, LOC more than 36 hours, and PTA more than 7 days (Williamson et al., 1996). For the participants recruited, mean GCS was in the severe range at 5.71 ($SD = 3.01$, range = 3–13). The mean age at the time of the injury was 26.06 ($SD = 8.2$; range = 18–58), and mean age at the time of assessment was 40.3 ($SD = 13.55$, range = 19–73). Mean education level was 13.2 years ($SD = 2.31$, range = 6–20). We only included participants who were at least 18 years old at the time of injury to avoid potential confounds related to neural plasticity in children. Additionally, we included only participants that were at least a year after injury, to ensure certain stability in their neuropsychological condition. All participants gave written informed consent after receiving a full explanation of the procedures according to approvals by the Institutional Review Boards.

Measures

As part of an extensive long-term outcome study conducted by this group, various preinjury, acute, and postinjury data were collected. These included indices of preinjury status, measures of injury severity, and assessments of long-term postinjury

functioning. Data were collected through medical examinations, questionnaires, clinical interviews, and neuropsychological evaluations. Several sessions were conducted with each patient (3 to 5 sessions, in accordance with his or her ability), each lasting approximately three hours, and took place in the rehabilitation center. Data were supplemented with information collected from the patient's medical file.

Preinjury indices

As noted earlier, these measures were based on our previous work and are described in detail elsewhere (Levi et al., 2013). Structural equation modeling (SEM) was used to examine the hypothesized underlying structure of the cognitive reserve (CR) construct. A one-factor model with 10 indicators that represented premorbid intelligence, premorbid socioeconomic status (SES), and leisure activity as a single reserve construct was compared to a three-factor model that represented premorbid intelligence, SES, and leisure activity as three separate constructs. Difference between the chi-square coefficients was used to compare the relative fit of the models. These analyses identified the following three factors:

- (1) Premorbid intelligence factor included Information, Vocabulary, and Matrix Reasoning subtests from the Hebrew version of the Wechsler Adult Intelligence Scale III (WAIS-III; Wechsler, 1997). These subtests are considered to be relatively resistant to a brain insult (e.g., Green et al., 2008; Lezak, Howieson, & Loring, 2004).
- (2) Premorbid SES factor included premorbid parents' occupation, self-reported SES, salary, and sibling number.
- (3) Premorbid leisure activity factor included premorbid cognitive leisure activity, physical leisure activity, and social leisure activity.

In the current study, for every participant, three weighted factor scores (*intelligence factor* weighted score, *SES factor* weighted score, and *leisure activity factor* weighted score) were calculated using regression analyses. As sibling number was negatively correlated with SES, its scale was inverted, so that higher scores correspond to fewer siblings.

Injury severity indices

Glasgow Coma Scale (GCS). The GCS (Teasdale & Jennett, 1974) is a clinical-rated

instrument used to quantify level of consciousness following TBI. It is composed of three parameters (eye opening, verbal response, and motor response) and ranges from 3 to 15.

Length of coma (loss of consciousness (LOC)). Length of coma, measured in days, was assessed based on medical files.

Posttraumatic amnesia (PTA). PTA duration was evaluated by the rehabilitation physician, based on the participants' medical records. In order to overcome problems of reliability resulting from inaccurate medical history, this measure was classified with a 7-point ordinal scale (1 = no PTA, 2 = less than an hour, 3 = 1–24 hours, 4 = 1–7 days, 5 = 8–28 days, 6 = 29–60 days, 7 = more than 60 days).

Number of disabilities related to brain injury at the time of the injury. This index is based on the index of Hoofien et al. (2002). Based on the participant's medical file and a clinical interview, the rehabilitation physician answered a "Yes–No" questionnaire of 10 possible brain-injury related disabilities (i.e., right/left hemiplegia and hemiparesis, ataxia, aphasia, apraxia, agnosia, epilepsy, neglect, visual impairments, and hearing impairments). Each marked disability was assigned one point. The average score was 2.93 ($SD = 1.63$), with 5.68% of the participants having no disabilities, 58% with one to three disabilities, and 36% with four disabilities or more.

Outcome measures

Intellectual functioning. Cognitive abilities were assessed with the Hebrew version of the Wechsler Adult Intelligence Scale III (WAIS–III; Wechsler, 1997). Since all 14 WAIS–III subtests were administered for only 59 of the participants, the Ward 7-subtest short form of the WAIS–III (Ward, 1990; which was administered to all participants) was used. The correlations found for Full Scale IQ (FIQ) of the 7-subtest form and the original FIQ was .98 ($n = 59$), indicating that this is a good index of FIQ.

Neuropsychological assessment. An extensive neuropsychological battery was administered, consisting of standardized tests found to be sensitive to cognitive sequelae of TBI (e.g., Clifton, Hayes, Levin, Michel, & Choi, 1992; Levin, Graftman, & Eisenberg, 1987). Due to the large number of tests administered, in the present analyses only core

measures were included. Verbal learning and memory was assessed with the Hebrew version of the Rey Auditory Verbal Learning Test (RAVLT; Rey, 1964; Vakil & Blachstein, 1993) and indexed with total number of words recalled correctly across the five trials. Visual learning and memory was assessed with the Rey–Osterrieth Complex Figure Test–Delayed Recall (ROCF delay; Rey, 1964) and indexed with the number of details recalled correctly (out of 36). Executive functions were assessed with the Wisconsin Card Sorting Test (WCST; Heaton, Chelune, Talley, Kay, & Curtiss, 1993) and indexed with total errors across the test; and also with the Hebrew version of the Semantic Fluency and Phonemic Fluency tests (Kave, 2005), indexed with semantic and phonemic sum scores. All scores were transformed into z scores using age-specific standard tables.

Vocational status. Vocational status was assessed using an index of occupation level, constructed for this study. This index is partially based on Roe's (1956) categories, modified to include two additional categories to fit the study's population. The index is scored on a 5-level scale as following: 0–unemployed, 1–working in sheltered employment or as a volunteer, 2–unskilled occupation, 3–skilled occupation, 4–professional occupation.

Social functioning. Social functioning was assessed using a Social Activity Questionnaire, which was constructed for this study and assesses the frequency of social interactions with relatives (parents, children, spouses, siblings, and other close family), friends, and acquaintances. This questionnaire consists of seven questions and is scored on the following scale: 1–never, 2–once a year, 3–once every three weeks to a month, 4–once a week to two weeks, 5–every day. The score was calculated by summing the answers and dividing the result by the maximum score the participant could achieve, not including irrelevant questions (e.g., a question regarding brothers and sisters for an only child).

Daily functioning. Based on the research of Hoofien et al. (2002), daily functioning was assessed by the Home Activities subscale of the extended activities of daily living (ADL) questionnaire (*ADL-home*; Melamed, Ring, & Najenson, 1985). This questionnaire includes 11 questions (e.g., Do you cook by yourself?) scored on a scale of 1 (not at all) to 5 (very frequent). In addition, the Independence in Mobility subscale of the same questionnaire (*ADL-mobility*) was also used,

consisting of nine questions (e.g., Do you manage climbing up the stairs?). Each participant answered these questionnaires twice: once regarding his functioning prior to injury and the second regarding current functioning. The delta between pre- and postinjury functioning was calculated for both subscales, with higher delta indicating more functional reduction due to injury.

Mental status. Mental status was assessed using the Brief Symptom Inventory (BSI; Derogatis, 1975; Derogatis & Melistratos, 1983), the brief form of the Symptom Checklist-90-R (Derogatis, Rickels, & Rock, 1976). The BSI is a self-report symptom inventory designed to assess the psychological symptom status of individuals (Derogatis & Melistratos, 1983). The instrument comprises 53 items selected to reflect nine primary symptom dimensions. In the current study, we used two core global indices of distress associated with the BSI: the General Severity Index (GSI) and the Positive Symptom Distress Index (PSDI).

Data analysis

A preliminary analysis of Pearson bivariate correlations (two-tailed) among the study variables was conducted in order to examine zero-order correlations and identify potential covariates. Since the variable “years since injury” was correlated with the key variables, it was entered as a covariate in subsequent analyses.

The predictive power of injury severity variables was examined using multiple regressions with the 12 dependent variables reflecting long-term

functioning. The underlying structure of injury severity was also examined, using principal component analysis (PCA) with varimax rotation. This was conducted in order to estimate common factors, as well as to reduce the number of variables used in subsequent analyses. Eigenvalues were set to 1, and minimum loading of a single variable on a factor was 0.30. The predictive power of preinjury indices, beyond that of injury severity, was then examined. We performed a series of multiple regressions, in which three preinjury factors (weighted scores) were regressed on the dependent variables, while controlling for injury severity.

RESULTS

Injury severity variables as predictors of long-term functioning

The predictive power of injury severity on long-term functioning following TBI was examined by correlating each of the four injury severity variables with the dependent variables (see Table 1) and by regressing these variables on the dependent variables (see Table 2). As can be seen (Table 1), GCS, PTA, and LOC were correlated with almost all cognitive variables. In addition, GCS was correlated with occupation level, and PTA and LOC were correlated with social activity and ADL-mobility. Number of disabilities was correlated only with ADL-mobility. Stepwise regressions were then conducted by first entering the covariate (years since injury) and subsequently the injury severity variables. Of the predictors of injury severity, after controlling for years since injury (see

TABLE 1
Bivariate correlations of injury severity variables with dependent variables

Domains	Variables	GCS	PTA	LOC	Number of disabilities
Cognitive functioning	FIQ	.286**	-.416**	-.352**	-.199
	RAVLT	.224*	-.301**	-.229*	-.125
	ROCF delay	.259*	-.207	-.240*	-.101
	WCST	.338**	-.286**	-.286**	-.128
	Semantic fluency	.276**	-.358**	-.321**	-.135
	Phonemic fluency	.126	-.243**	-.131	-.106
Vocational status	Occupation level	.230*	-.167	-.105	-.143
Social functioning	Social activity	.184	-.351**	-.303**	-.145
Daily functioning	ADL-home	.158	-.019	.119	.013
	ADL-mobility	-.104	.215*	.293**	.219*
Mental status	GSI	.109	-.107	-.112	.018
	PSDI	.151	-.073	-.005	-.020

Notes. GCS = Glasgow Coma Scale; PTA = posttraumatic amnesia; LOC = loss of consciousness; FIQ = Full IQ; RAVLT = Rey Auditory Verbal Learning Test (total learning); ROCF delay = Rey-Osterrieth Complex Figure Test-Delay; WCST = Wisconsin Card Sorting Test (total errors); ADL = activities of daily living; GSI = General Severity Index; PSDI = Positive Symptom Distress Index.

* $p < .05$. ** $p < .01$.

TABLE 2
Regression analyses of injury severity variables predicting long-term functioning following TBI

Regression steps	Domains													
	Cognitive functioning						Vocational status		Social functioning		Mental status		Daily functioning	
	FIQ	RAVLT	WCST	Semantic fluency	Phonemic fluency	ROCF delay	Occupation level	Social activity	PSDI	GSI	ADL-home	ADL-mobility		
Step 1: Covariates	$\Delta R^2 = .074^*$	$\Delta R^2 = .042$	$\Delta R^2 = .034$	$\Delta R^2 = .038$	$\Delta R^2 = .102^{**}$	$\Delta R^2 = .030$	$\Delta R^2 = .050^*$	$\Delta R^2 = .123^{**}$	$\Delta R^2 = .005$	$\Delta R^2 = .007$	$\Delta R^2 = .013$	$\Delta R^2 = .016$		
Years since injury	$-.273^*$	$-.204$	$-.184$	$-.196$	$-.319^{**}$	$-.174$	$-.223^*$	$-.351^{**}$	$-.071$	$-.086$	$-.115$	$.127$		
Step 2: Injury severity	$\Delta R^2 = .121^{**}$	$\Delta R^2 = .062^*$	$\Delta R^2 = .094^{**}$	$\Delta R^2 = .097^{**}$		$\Delta R^2 = .051^*$		$\Delta R^2 = .064^*$				$\Delta R^2 = .075^{**}$		
Years since injury	$-.156$	$-.121$	$-.117$	$-.092$		$-.125$		$-.267^*$				$.077$		
PTA	$-.367^{**}$	$-.263^*$	$-.075$	$-.328^{**}$	$-.158$	$-.031$	$-.104$	$-.267^*$	$-.054$	$-.084$	$.018$	$.049$		
GCS	$-.035$	$.046$	$.313^{**}$	$.071$	$.063$	$.232^*$	$.192$	$-.054$	$.140$	$.094$	$.138$	$.009$		
LOC	$-.163$	$-.080$	$-.180$	$-.160$	$-.079$	$-.154$	$-.067$	$-.144$	$.007$	$-.099$	$.142$	$.279^{**}$		
Number of disabilities	$-.063$	$-.021$	$.029$	$-.019$	$-.034$	$.024$	$-.096$	$-.044$	$-.004$	$.040$	$.041$	$.146$		

Notes. Standardized regression (beta) coefficients for the study's independent variables and R^2 for each step are presented. TBI = traumatic brain injury; GCS = Glasgow Coma Scale; PTA = posttraumatic amnesia; LOC = loss of consciousness; FIQ = Full IQ; RAVLT = Rey Auditory Verbal Learning Test (total learning); WCST = Wisconsin Card Sorting Test total learning); ROCF delay = Rey-Osterrieth Complex Figure Test-Delay; PSDI = Positive Symptom Distress Index; GSI = General Severity Index; ADL = activities of daily living.

* $p < .05$. ** $p < .01$.

Table 2), PTA predicted FIQ, RAVLT, semantic fluency, and social activity; GCS predicted WCST and ROCF delay; and LOC predicted ADL-mobility. Finally, number of disabilities failed to predict any of the dependent variables.

The underlying structure of injury severity

The underlying structure of injury severity was examined in order to estimate common factors. To this end, exploratory factor analysis was conducted on injury severity variables, using PCA with varimax rotation. Four variables were entered: PTA, GCS, LOC, and number of disabilities. The results showed that the optimal solution includes one factor that explained 55.1% of the total variance. Table 3 displays the loadings of variables on each factor.

In order to restrict the number of variables in subsequent analyses, for every participant a weighted score of the four injury severity variables—*injury severity factor* weighted score—was calculated using regression analyses. As GCS was negatively correlated with other injury severity

indices, its scale was inversed, such that higher score would reflect greater injury severity.

Preinjury factors as predictors of long-term functioning, after controlling for injury severity

Finally, we thought to examine which of the pre-injury indices have the highest predictive power of long-term functioning following TBI. To this end, first, Pearson bivariate correlations (two-tailed) between the three factors and the dependent variables were conducted (see Table 4). Secondly, we also examined the additive contribution of preinjury factors to long-term functioning following TBI, beyond the predictive power of injury severity variables. To this end, several hierarchical multiple regression analyses were conducted, with a different dependent variable in each analysis. We did not include FIQ in the regression analyses due to its high correlation with the intelligence factor weighted score. All analyses were conducted in two steps. In the first step, two covariates (years since injury and injury severity factor weighted score) were entered in “enter” mode. In the second step, the three factors were entered in “stepwise” mode. Table 5 displays all the significant models produced by the analyses.

As can be seen in Tables 4 and 5, intelligence factor appears to be the most powerful predictor, having significant correlations with almost all dependent variables in each life domain (except for ADL-home and GSI). Its power is evident in the regression analyses (see Table 5), as it was found to be the first (and mostly only) predictor of almost all dependent variables (except for ADL-

TABLE 3
Loadings of variables into injury severity factor following PCA

Component	1
PTA	0.848
GCS	0.822
LOC	0.641
Number of disabilities	0.632

Note. PCA = principal component analysis; PTA = posttraumatic amnesia; GCS = Glasgow Coma Scale; LOC = loss of consciousness.

TABLE 4
Bivariate correlations of preinjury factors with dependent variables

Domains	Variables	Intelligence factor	Leisure activity factor	SES factor
Cognitive functioning	FIQ	.897**	-.013	.157
	RAVLT	.587**	-.104	.142
	ROCF delay	.480**	-.093	.074
	WCST	.473**	-.158	.010
	Semantic fluency	.586**	-.026	.004
	Phonemic fluency	.423**	.080	.192
Vocational status	Occupation level	.410**	-.089	.230**
Social functioning	Social activity	.449**	-.027	.021
Daily functioning	ADL-home	-.098	.371**	.175
	ADL-mobility	-.312**	.162	.111
Mental status	PSDI	-.274**	.244*	-.143
	GSI	-.160	.103	-.168

Notes. Intelligence, SES, and leisure activity factors are weighted scores of their respective variables. FIQ = Full IQ; RAVLT = Rey Auditory Verbal Learning Test (total learning); ROCF delay = Rey–Osterrieth Complex Figure Test–Delay; WCST = Wisconsin Card Sorting Test (total errors); PSDI = Positive Symptom Distress Index; GSI = General Severity Index; ADL = activities of daily living; SES = socioeconomic status.

* $p < .05$. ** $p < .01$.

TABLE 5
Regression analyses of preinjury factors predicting long-term functioning following TBI, after controlling for injury severity

Regression steps	Domains									
	Cognitive functioning				Vocational status		Social functioning		Mental status	
	RAVLT	WCST	Semantic fluency	Phonemic fluency	ROCF delay	Occupation level	Social activity	PSDI	GSI	Daily functioning
Step 1: Covariates	$\Delta R^2 = .076$	$\Delta R^2 = .121^{**}$	$\Delta R^2 = .130^{**}$	$\Delta R^2 = .111^*$	$\Delta R^2 = .070$	$\Delta R^2 = .054$	$\Delta R^2 = .120^{**}$	$\Delta R^2 = .030$	$\Delta R^2 = .023$	$\Delta R^2 = .014$
Years since injury	-.093	-.002	0.024	-.0284*	0.013	-.105	-.0154	-.112	-.038	-.0107
Injury severity	-.227	-.347**	-.369**	-.098	-.0269*	-.171	-.258*	-.099	-.133	-.022
factor										0.261*
Step 2: Preinjury	$\Delta R^2 = .046^*$	$\Delta R^2 = .133^{**}$	$\Delta R^2 = .270^{**}$	$\Delta R^2 = .160^{**}$	$\Delta R^2 = .129^{**}$	$\Delta R^2 = .124^{**}$	$\Delta R^2 = .065^*$	$\Delta R^2 = .060^*$	$\Delta R^2 = .072^*$	$\Delta R^2 = .141^{**}$
Years since injury	-.146	-.032	-.019	-.317**	-.016	-.135	-.175	-.076	-.016	-.098
Injury severity	-.007	-.204	-.165	0.059	-.128	-.033	-.158	-.228	-.238	-.011
factor										0.146
Intelligence	0.616**	0.389**	0.554**	0.426**	0.383**	0.375**	0.271*	-.372**	-.286*	-.187
factor										0.312*
SES factor	0.069	-.037	-.097	0.031	-.059	0.167	-.202	-.105	-.053	0.096
Leisure activity	-.217*	-.224	-.180	0.044	-.190	-.168	-.104	0.245*	0.139	0.375**
factor										0.179

Notes. Standardized regression (beta) coefficients for the study's independent variables and R^2 for each step are presented. Injury severity, intelligence, SES, and leisure activity factors are weighted scores of their respective variables. TBI = traumatic brain injury; RAVLT = Rey Auditory Verbal Learning Test (total learning); WCST = Wisconsin Card Sorting Test (total learning); ROCF delay = Rey-Osterrieth Complex Figure Test-Delay; PSDI = Positive Symptom Distress Index; GSI = General Severity Index; ADL = activities of daily living; SES = socioeconomic status.

* $p < .05$. ** $p < .01$.

home), after controlling for the effects of injury severity and years since injury. The second predictor was the leisure activity factor, with significant correlations with ADL-home and PSDI. It was also the only predictor of ADL-home and the second predictor of RAVLT and PSDI, after controlling for the aforementioned covariates. Finally, SES factor was correlated only with occupation level and failed to predict any of the dependent variables.

DISCUSSION

In a recent work, we have empirically identified three factors, indexing preinjury functioning, that may constitute essential components of the reserve construct (Levi et al., 2013). The present study was an effort to evaluate the predictive power of these factors on long-term outcome following TBI, over and above the contribution of injury severity. We found that TBI severity predicted long-term cognitive, social, and daily functioning outcome. Among the three preinjury factors (after controlling for injury severity), we found that preinjury intellectual functioning (measured according to “hold” principle) predicted long-term cognitive, occupational, emotional, and social outcome, as well as daily functioning. In addition, preinjury leisure activity predicted cognitive, emotional, and daily functioning.

Despite the accumulating body of research on the reserve hypothesis, definitions of the reserve structure have been inconsistent, and its construct validity has not been systematically evaluated (Satz, Cole, Hardy, & Rassovsky, 2011). Many studies have intuitively addressed this concept by implicitly assuming that reserve constructs have convergent validity. As a result, most of the research on reserve indicators has not been systematic or uniform. Our recent finding of three distinct factors suggests that the construct of reserve is not uniform, with each component having its own unique properties (Levi et al., 2013). The present work enabled us to determine which of these components best predicted long-term outcome. Providing further support for the multifactorial nature of the reserve construct, we found that the three factors were differentially associated with post-TBI functioning. Whereas intellectual functioning predicted all the measured outcomes, leisure activities predicted only a few, and none were predicted by SES.

Findings are consistent with the positive association that has often been reported in the literature between injury severity and impairment in

functional outcome (e.g., Asikainen et al., 1998; Dikmen, Machamer, Winn, & Temkin, 1995; Felmingham et al., 2001; Jennett, Snoek, Bond, & Brooks, 1981; Levin et al., 1990; Tate & Broe, 1999). Our findings also showed that injury severity variables were highly associated with one another, thereby likely representing the same structure and content domain.

Our results offer new evidence for a contribution of preinjury reserve factors to post-TBI functioning that goes beyond that of injury severity. We found that premorbid intellectual functioning was the most significant predictor of post-TBI outcome. It is possible that premorbid intellectual functions reflect the neural redundancy in information processing systems, which facilitate compensatory processes following TBI (Grafman, Lalonde, Litvan, & Fedio, 1989; Salazar, Schwab, & Grafman, 1995), thereby explaining the key role for this construct in postinjury outcome.

Despite the demonstrated importance of premorbid intelligence as a predictor of TBI outcome, some caution is necessary in interpreting this finding. Among the various predictors employed in this study, premorbid intelligence is the only factor based entirely on measures of current performance, whereas all other factors have been based on clinical interviews, medical records, and questionnaires. Therefore, it is possible that the superiority of the intelligence factor over the other preinjury factors may partly be due to its reliance on current cognitive functioning. Unfortunately, “hold” and “best performance” are currently the only methods available for estimating preinjury intelligence, and, as has been previously demonstrated, the shared variance between postinjury estimated intelligence and actual premorbid intelligence is far from perfect (e.g., Hoofien et al., 2002). Thus, given the less than perfect validity of premorbid intelligence estimations, one ought not to rely exclusively on these indices, despite their predictive superiority.

After controlling for injury severity, leisure activities also predicted several indices of cognitive, emotional, and daily functioning. Previous studies of the importance of leisure activities in bolstering reserve focused on normal and pathological aging. These studies report that participation in intellectual, physical, or social leisure activities was associated with slower cognitive decline in old age (Dik et al., 2003; Larsen et al., 2007; Scarmeas & Stern, 2003; Wilson et al., 2003) and with lower risk of dementia (Fratiglioni, Paillard-Borg, & Winblad, 2004; Scarmeas et al., 2001; Scarmeas & Stern, 2003; Valenzuela, 2008). Similarly, studies on adult animal models have demonstrated that

exposure to an enriched environment influences the rate of neurogenesis and may prevent or reduce cognitive deficits (Kempermann, Kuhn, & Gage, 1997; Pham, Soderstrom, Winblad, & Mohammed, 1999; Pham, Winblad, Granholm, & Mohammed, 2002; van Pragg, Kempermann, & Gage, 2000). It has been hypothesized that engagement in leisure activities may enhance CR by producing more efficient cognitive networks (Scarmeas & Stern, 2003; Stern, 2002).

Unlike some earlier studies that suggested a relationship between SES and post-TBI outcome (Gollahar et al., 1998; Hoofien et al., 2002; Ip et al., 1995; Sherer et al., 1999), our findings failed to demonstrate this relationship. Notably, there were additional reports similar to ours. For example, Rutter, Chadwick, and Shaffer (1983) found that social class or SES was of little importance in predicting cognitive outcome following head injury in children. Grafman et al. (1989) noted that although a patient's SES and similar variables are clues to his or her overall premorbid cognitive function, these parameters do not offer the precision required (e.g., actual test performance scores) to estimate such functioning accurately. It should also be noted that because most of the participants in our study were injured at a relatively young age, premorbid SES was examined via sociodemographic indicators of families of origin (preinjury salary, number of siblings, and parents' income and occupation). Therefore, these variables do not necessarily express the patient's true occupation potential, which might be a better proxy of reserve.

The CR hypothesis suggests a useful framework for studying the long-term effects of TBI and for identifying premorbid variables as potential buffers against the detrimental effects of brain pathology (Stern, 2002). Our findings offer further support for the CR construct in predicting unique variance in TBI outcome. Given that the average postinjury life expectancy for people who have suffered TBI is approximately 50 years (Chamberlain, 1995), evaluation of mediating variables with potential influence on long-term outcome have both epidemiological and clinical importance. The combination of pathology severity indices and premorbid variables (i.e., the ability to cope with brain pathology) with clinical symptoms can provide a more complete picture of the patient's condition and thereby aid in prognosis and design of appropriate rehabilitative interventions. The present findings suggest an important role for premorbid IQ in predicting outcome, with little value added by SES data. The "use it or lose it" phrase (Salthouse, 2006) also seems relevant in this context, as engagement in leisure activities may serve

as another buffer against the detrimental effects of TBI.

Of course, the constructs examined in the present study are far from being exhaustive. For example, Sandry, DeLuca, and Chiaravalloti (2014) have recently reported that working memory capacity mediated the relationship between CR and long-term memory impairment in adults with moderate-to-severe TBI. Similarly, Karver et al. (2014) found that CR moderated the responsiveness to a problem-solving intervention in adolescents with mild-to-severe TBI. These and similar studies underscore the complexity and multifactorial nature of the relationship between CR and outcome in TBI. Finally, given the limitations of neuropsychological measures in indexing CR, as shown in the present study, it is necessary to examine more objective criteria (e.g., by collecting blood biomarkers and neuroimaging data) as long-term outcome predictors in TBI. Such major efforts are underway, and, given the potentially greater precision of these techniques, they may prove fruitful in predicting outcome not only in the moderate-to-severe TBI range but also in the more elusive mild-to-moderate TBI range.

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