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Cognitive Reserve Protects Against Memory Decrements Associated With Neuropathology in Traumatic Brain Injury

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Objective: To evaluate whether cognitive reserve (CR) moderates the relationship between neuropathology and cognitive outcomes after traumatic brain injury (TBI). **Setting:** Outpatient research organization. **Participants:** Patients with complicated mild ($n = 8$), moderate ($n = 9$), and severe ($n = 44$) TBI. **Design:** Prospective, cross-sectional study. **Main Measures:** Cognitive reserve was estimated using a test of word reading (Wechsler Test of Adult Reading). Diffusion tensor imaging (functional anisotropy) was used to quantify neuropathology. Neuropsychological test scores were submitted to principal components analyses to create cognitive composites for memory, attention, executive function, and processing speed domains. **Results:** At lower levels of neuropathology, people with higher CR exhibited better memory than those with lower CR. This benefit diminished as neuropathology increased and disappeared at the highest levels of neuropathology. Cognitive reserve ceased exerting a protective effect at premorbid intelligence levels below average. **Conclusion:** Cognitive reserve may differentially protect some cognitive domains against neuropathology relative to others. A clinical cutoff below which CR is no longer protective, together with a possible neuropathology ceiling effect, may be instructive for prognostication and clinical decision-making in cognitive rehabilitation. **Key words:** *cognitive reserve*, *intelligence*, *neuropathology*, *neuropsychological tests*, *rehabilitation*, *traumatic brain injury*

APPROXIMATELY 2.8 MILLION individuals sustain a brain injury in the United States each year.[1] An estimated 10% of these cases are moderate to severe, with the remainder classified as complicated or uncomplicated mild traumatic brain injury (TBI).[2,3] A total of 3.2 million Americans are living with chronic disabilities related to a TBI,[4] with cognitive impairments as one of the most important factors in disability status.[5]

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Despite the considerable body of research linking injury severity with cognition in TBI, substantial variability in clinical expression of neuropathology remains.[6] The inconsistent relationship between neurological insult and cognitive outcome can be explained, at least in part, by cognitive reserve (CR), which purports that intelligence and intellectual enrichment protect against neuropathology. Higher CR allows a person to withstand greater neuropathology before exhibiting cognitive impairments. At equivalent levels of cognitive performance, neuropathology will be more severe for individuals with higher CR than those with lower CR[7,8] due to the fact that cognitive deficits are only present when pathology is more severe. Considerable evidence supports CR's role in explaining the incomplete relationship between neuropathology and cognition in Alzheimer disease (AD).[8] Cognitive reserve's protective effect has also been established in other neurological populations, including Parkinson's disease,[9] stroke,[10] multiple sclerosis,[11] and TBI.[12]

Despite fewer studies on CR in TBI, initial studies show promising results. At a neuropsychological level, investigators have demonstrated that proxies of CR are

associated with postinjury cognitive status across multiple cognitive domains[13] and associations remain after controlling for injury severity.[14] Associations were present at acute and chronic time points postinjury.[15] One study comparing individuals with TBI with healthy controls across levels of CR found that at lower education levels, individuals with TBI showed impaired cognition relative to healthy controls, whereas at higher education, cognition was equivalent between groups.[12] Further support for CR's buffering effect comes from a study directly comparing premorbid intelligence in a small sample of individuals with severe TBI to postinjury cognition. Individuals with lower premorbid IQ showed significant postinjury cognitive decline not seen in individuals with higher premorbid IQ.[16] Despite evidence supporting CR's buffering effect, investigators to date have been unable to show that CR predicts recovery trajectory or studies have not evaluated whether CR moderates the impact of neuropathology on cognition.[15,17] The current study seeks to first verify cognitive evidence of CR in TBI and extend prior research by investigating CR's moderating effect. We hypothesized an interaction between CR and neuropathology such that individuals with TBI and higher CR will be more resistant to neuropathology-related decrements in cognition than individuals with lower CR.

METHODS

Participants

Sixty-one adults with complicated mild to severe TBI were enrolled through outpatient TBI clinics, TBI support groups, and the Brain Injury Alliance of New Jersey. We additionally recruited from an institutional review board–approved participant database that contains contact information for individuals interested in research participation. Injury severity was confirmed by medical record review (loss of consciousness, positive computed tomographic findings, or surgical intervention, and caregiver/family report; see Arciniegas[18]). All participants were aged 18 to 65 years, at least 1 year postinjury, with no history of neurological injury other than TBI, substance abuse, or language learning disability. Participants with a history of diagnosed depression, schizophrenia, and bipolar disorder I/II were excluded. All participants were screened for magnetic resonance imaging compatibility and intact language comprehension via the Token Test.[19] Participants signed an informed consent approved by the institutional review board. Participants were divided into high, moderate, and low CR subgroups based on a test of word reading in order to compare maximally disparate groups (see details in the "Materials and Procedures" section). See Table 1 for participant demographics/injury-related characteristics.

Materials and procedures

The research was conducted consistent with ethical guidelines for the conduct of research.

Cognitive reserve

Cognitive reserve was estimated with the Wechsler Test of Adult Reading (WTAR).[20] Word reading is a "hold" approach to estimating premorbid cognitive ability, in other words, one that is resistant to cognitive decline due to neurological impairment and age-related cognitive decline.[21,22] Furthermore, word reading reflects premorbid educational attainment and therefore may be a more powerful measure of CR relative to others (eg, education).[23] Although education and occupation are often used to reflect CR, 34% of our sample sustained their TBI before the age of 25 years, prior to completion of education and career development, rendering these proxies inappropriate.[24] The WTAR is one of the better indicators of estimating more crystalized premorbid abilities.[25] The WTAR standard score was thus used in all analyses.

Cognitive outcomes

Participants were administered a comprehensive neuropsychological battery wherein each cognitive domain

TABLE 1 *Demographic and injury-related characteristics*

Variable	Overall sample ($N = 61$), mean (SD)	Low CR group ($n = 21$), mean (SD)	High CR group ($n = 21$), mean (SD)
Age	41.2 (12.8)	37.5 (19.3)	43.9 (13.6)
Age at injury	33.1 (13.54)	30.5 (11.3)	36.8 (15.4)
Education	14.4 (2.0)	13.0 (0.9)	15.7 (2.1)
Years since injury	8.5 (7.3)	7.4 (6.5)	7.9 (7.5)
Sex	46 M, 15 F	17 M, 4 F	12 M, 9 F
Severity	8 complicated mild, 9 moderate, 44 severe	2 complicated mild, 5 moderate, 14 severe	4 complicated mild, 5 moderate, 12 severe

Abbreviations: CR, cognitive reserve; F, female; M, male.

was assessed with multiple tests. To reduce the number of cognitive variables used in the analyses, the original data were submitted to principal components analysis (PCA) to obtain composite scores. Raw scores associated with each domain were entered into separate PCAs for memory, attention, executive function, and processing speed. Composite indices were created from each factor derived from the PCA from factor loading scores using the regression method. The memory PCA resulted in 2 components, one containing noncontextualized memory tests and the other that contained contextualized memory tests. Noncontextualized memory tests require an individual to impose his or her own organization on the material and thus depend partially on executive processes to facilitate learning, whereas contextualized memory tests provide a logical framework for remembering the information, decreasing executive demands. Attention, executive function, and processing speed PCAs each resulted in a single component. Composite scores were utilized in all subsequent analyses.

The following tests comprised the *noncontextualized memory composite*: California Verbal Learning Test, 2nd Edition (CVLT-II) Trials 1-5; CVLT-II Short Delay Free Recall; CVLT-II Long Delay Free Recall; Wechsler Memory Scale, Fourth Edition (WMS-IV) Designs 1 and 2; Brief Visuospatial Memory Test Revised (BVMT-R) Trials 1-3; and BVMT-R Delayed Recall.[26–28] The *contextualized memory composite* comprised the WMS-IV Logical Memory I and II.[28] The *attention composite* included Wechsler Adult Intelligence Scale, Fourth Edition (WAIS-IV); Digit Span Forward; and the Brief Test of Attention Total Score.[29,30] The *executive function composite* included Stroop Color-Word, Color Trails Test 2, and phonemic (FAS) and semantic verbal fluency.[31–33] Finally, the *processing speed composite* comprised the oral version of Symbol Digit Modalities Test, WAIS-IV Symbol Search, Color Trails Test 1, Letter and Pattern Comparison, and Stroop Color Naming and Word Reading.[30–32,34,35]

Neuroimaging procedures

Neuroimaging data collection began on a 3-tesla (T) Siemens Allegra scanner (25 participants) and was completed on a 3-T Siemens Skyra scanner (36 participants). For this reason, scanner was included as a covariate in all analyses including imaging metrics. A high-resolution magnetization prepared rapid gradient echo (MPRAGE) image was acquired (Allegra: TE = 4.38 milliseconds, TR = 2000 milliseconds, FOV = 220 mm, flip angle = 8°, slice thickness = 1 mm, NEX = 1, matrix = 256 × 256, in-plane resolution = 0.859 × 0.859 mm; Skyra: TE = 3.5 milliseconds, TR = 2500 milliseconds, FOV = 256 mm, flip angle = 8°, slice thickness = 1 mm, NEX = 1, matrix = 256 × 256, in-plane resolution = 1 × 1 mm). Diffusion tensor imaging (DTI) was acquired using a 12-direction sequence (Allegra: *b*-value = 1000, TE = 88 milliseconds, TR = 7300 milliseconds, flip angle = 90°, FOV = 210 mm, matrix = 96 × 96, slice thickness = 2.5 mm, 26 slices; Skyra: *b*-value = 1000, TE = 88 milliseconds, TR = 3800 milliseconds, flip angle = 90°, FOV = 210 mm, matrix = 128 × 128, slice thickness = 4 mm, 28 slices).

Given its sensitivity to microscopic white matter changes, DTI was used to quantify neuropathology. White matter integrity was assessed by fractional anisotropy (FA). Within-subject FA values were calculated using Tract-Based Spatial Statistics in FSL (http://www.fmrib.ox.ac.uk/fsl). Diffusion images were fitted with a tensor model to create an FA image for each participant. Each FA image was brain extracted, corrected for head motion and eddy currents, and transformed into standard space. The ICBM-DTI-81 atlas was then applied to extract FA values for selected structures. A single FA component score was calculated using PCA with promax rotation. The FA component score, which represented whole brain white matter integrity, was utilized in the regressions.

Statistical analyses

All statistical analyses were performed using SPSS version 24.0.[36] To evaluate the neuropsychological relationship between CR and cognition, participants were separated into tertiles based on the sample distribution's WTAR standard scores, with an approximately equal number of participants in each group. The first tertile (low CR) comprised scores under 97, and the third tertile (high CR) comprised scores 111 and above. To maximize differences, high and low CR groups were compared on test performance across the 5 cognitive composites. Given significant variance heterogeneity for the 2 memory composites, Welch analyses of variance (ANOVAs) were conducted for these dependent variables.[37,38] All other variables met normality assumptions and thus traditional ANOVAs were conducted.

To evaluate whether CR moderates the relationship between neuropathology and cognition, regression-based moderation analyses were conducted for each of the cognitive outcomes using the Hayes PROCESS macro for SPSS.[39] Model 1 in this macro refers to simple moderation. Predictors that built the interaction term (CR and FA) were mean centered. The PROCESS macro automatically calculates the moderation effect and the proportion of the variance explained by the moderating effect of CR (R^2 increase due to the interaction). Because harmonization was not conducted at the time of data collection, we controlled for interscanner variability by including scanner as a

covariate in each of the moderation models. For any moderation analysis in which the interaction term was statistically significant, the model was graphed in order to confirm whether the slopes from the interaction were in the hypothesized direction. To identify points along the continuum of the moderator *where* the effect of the predictor transitions from being statistically significant to nonsignificant, conditional effects were tested using the Johnson-Neyman output from the PROCESS approach.

For any cognitive variables wherein moderation was significant, ANOVAs were conducted to explore whether findings were present when considering injury severity. We divided the sample into 2 TBI subgroups: complicated mild/moderate and severe TBI. The same low CR and high CR groups as in the neuropsychological analyses were used.

RESULTS

The distribution of the WTAR reflected the normal IQ distribution ($M = 103.1$, SD = 14.4) and was unrelated to time since injury ($r = 0.06$, $P = .68$) or neuropathology (as measured by FA; $r = 0.14$, $P = .32$), supporting word reading as independent of injury-related variables and an appropriate measure for CR.

Comparison of low and high CR on cognitive outcomes

See Table 2 for group means, standard deviations, and confidence intervals. Of the demographic and injury-related characteristics, the high and low CR groups differed only on education. Given that education is an alternative CR proxy, a significant difference between high and low CR groups is expected; thus, education was not covaried in these analyses. The high CR group performed significantly better than the low CR group in contextualized memory ($F_{1,27.577} = 12.09$, $P = .002$, $\omega^2 = 0.24$) and executive function ($F_{1,35} = 4.53$, $P = .04$, $\eta_p^2 = 0.12$). Although the high CR group scored higher than the low CR group on noncontextualized memory and attention, these differences were not statistically significant (noncontextualized memory: $F_{1,29.599} = 1.54$, $P = .23$, $\omega^2 = 0.01$; attention: $F_{1,40} = 2.63$, $P = .11$, $\eta_p^2 = 0.06$). Performance between groups was equivocal on processing speed ($F_{1,36} = 0.03$, $P = .86$, $\eta_p^2 = 0.00$).

Evaluating if CR moderates neuropathology's effect on cognitive outcomes: Neuropathology results

Age was unrelated to WTAR standard score ($r = 0.18$, $P = .17$), noncontextualized memory ($r = -0.09$, $P = .51$), contextualized memory ($r = 0.08$, $P = .60$), attention ($r = -0.01$, $P = .92$), executive function ($r = -0.11$, $P = .43$), or processing speed ($r = -0.21$, $P = .13$); thus, age was not controlled for in regression analyses.

Full regression results are summarized in Table 3. There were significant interactions between WTAR and FA in noncontextualized and contextualized memory regression models. These findings indicate that CR moderated the relationship between neuropathology and cognition in both memory domains. Interactions were not significant for attention, executive function, or processing speed.

Visualizing how and where CR moderates neuropathology's effect on memory

The significant interactions for noncontextualized and contextualized memory are illustrated in Figure 1. In both interactions, at higher FA (lower levels of neuropathology), individuals with higher CR have better

TABLE 2 *Means, standard deviations, and confidence intervals at low and high cognitive reserve across cognitive composite domains*

	Low cognitive reserve				High cognitive reserve				
			95% CI for mean				95% CI for mean		
	N	Mean (SD)	Lower bound	Upper bound	*N*	Mean (SD)	Lower bound	Upper bound	*P*
Noncontextualized memory	20	−0.28 (0.64)	−0.58	0.02	20	0.09 (1.16)	−0.45	0.63	.225
Contextualized memory	15	−0.45 (0.48)	−0.72	−0.19	20	0.50 (1.09)	−0.01	1.01	.002
Attention	21	−0.41 (0.90)	−0.82	−0.00	21	0.09 (1.10)	−0.41	0.60	.113
Executive function	18	−0.38 (0.93)	−0.85	0.08	19	0.36 (1.17)	−0.21	0.92	.040
Processing speed	20	−0.16 (0.95)	−0.61	0.28	18	−0.22 (1.04)	−0.74	0.29	.855

Abbreviation: CI, confidence interval.

TABLE 3 *Linear regression analyses evaluating cognitive reserve's protective effect across cognitive domains*

	b[a]	SE	*t*	*P*
Noncontextualized memory				
Constant	0.09	0.14	0.65	.518
WTAR	0.02	0.01	2.25	.030
FA	0.52	0.13	4.09	.000
WTAR × FA	0.02	0.01	2.21	.032
Scanner	−0.09	0.29	−0.32	.752
Model $R^2 = 0.35$, MSE = 0.7608		R^2 change due to interaction = 0.03		
$F_{4,44} = 8.71$, $P < .001$		$F_{1,44} = 4.89$, $P = .032$		
Contextualized memory				
Constant	0.17	0.20	0.87	.391
WTAR	0.03	0.01	2.70	.010
FA	0.36	0.12	2.93	.006
WTAR × FA	0.03	0.01	2.86	.007
Scanner	−0.25	0.30	−0.83	.412
Model $R^2 = 0.30$, MSE = 0.8035		R^2 change due to interaction=.11		
$F_{4,38} = 8.63$, $P < .001$		$F_{1,38} = 8.15$, $P = .007$		
Attention				
Constant	0.15	0.16	0.90	.374
WTAR	0.02	0.01	2.37	.022
FA	0.23	0.14	1.59	.118
WTAR × FA	−0.01	0.01	−0.87	.387
Scanner	−0.22	0.31	−0.71	.482
Model $R^2 = 0.17$, MSE = 0.9710		R^2 change due to interaction = 0.01		
$F_{4,47} = 8.08$, $P < .001$		$F_{1,47} = 0.76$, $P = .387$		
Executive function				
Constant	−0.10	0.15	−0.65	.517
WTAR	0.02	0.01	2.14	.038
FA	0.39	0.12	3.16	.003
WTAR × FA	0.01	0.01	0.87	.392
Scanner	0.21	0.26	0.81	.423
Model $R^2 = 0.36$, MSE = 0.6968		R^2 change due to interaction = 0.01		
$F_{4,44} = 4.97$, $P = .002$		$F_{1,44} = 0.75$, $P = .392$		
Processing speed				
Constant	0.05	0.19	0.25	.805
WTAR	0.003	0.01	0.33	.741
FA	0.57	0.15	3.78	.0005
WTAR × FA	0.001	0.01	0.13	.895
Scanner	−0.15	0.27	−0.55	.583
Model $R^2 = 0.29$, MSE = 0.8549		R^2 change due to interaction = 0.0002		
$F_{4,44} = 4.09$, $P = .007$		$F_{1,44} = 0.02$, $P = .895$		

Abbreviations: FA, fractional anisotropy; MSE, means squared error; WTAR, Wechsler Test of Adult Reading.
[a] *b* is an unstandardized coefficient.

memory than those with lower CR. This benefit diminishes as FA decreases (neuropathology increases) and disappears entirely at the highest levels of neuropathology. To statistically test where neuropathology's effect varied with CR and characterize the nature of the significant interactions, we used the Johnson-Neyman technique (see Figure 2). Results indicated that FA exerts a significant effect on noncontextualized memory at WTAR scores of approximately 91 and above (all Ts > 2.02, all Ps ≤ .05), but below this value, FA was not significantly related to memory. Neuropathology exerts a significant effect on contextualized memory at WTAR scores of approximately 103 and above (all Ts > 2.02, all Ps ≤ .05) but was unrelated to memory below this region of significance.

Comparison of low and high CR across injury severity

Given the absence of CR's protective effect of memory at higher levels of neuropathology, ANOVAs explored whether this finding was also present when considering injury severity. Although the 2 (injury severity) × 2 (CR) ANOVA interactions were not statistically

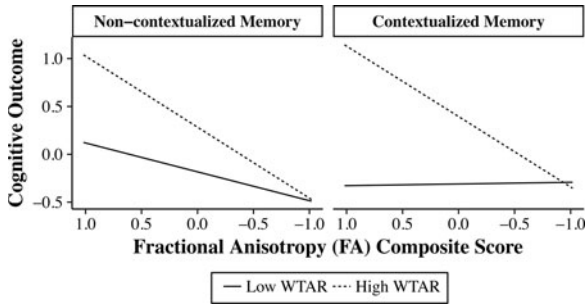

Figure 1. Simple slopes were calculated at 1 SD above and below the mean WTAR standard score to visualize significant interactions from regression models. Fractional anisotropy composite scores on the *X*-axis scale were reversed in order to reflect increasing levels of neuropathology and facilitate interpretation. In both interactions, at lower neuropathology, people with higher CR have better memory than those with lower CR. This benefit diminishes as neuropathology increases and disappears entirely at the greatest levels of neuropathology. WTAR indicates Wechsler Test of Adult Reading; CR, cognitive reserve.

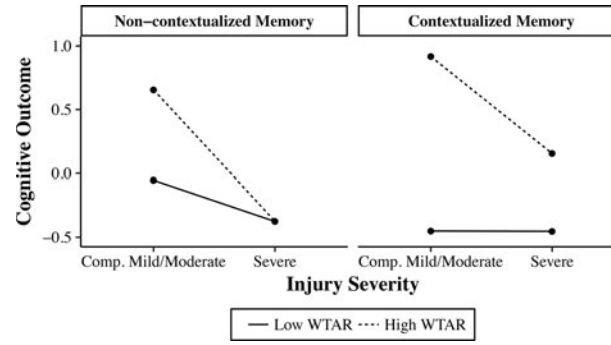

Figure 3. Interactions between injury severity and CR were plotted for those cognitive domains where the neuropathology findings were significant. Although injury severity interactions were not significant, the pattern of a protective effect at less severe injury but not at more severe injury parallels that seen in the neuropathology analyses (see Figure 1). CR indicates cognitive reserve; WTAR, Wechsler Test of Adult Reading.

significant for noncontextualized memory ($F_{1,36} = 1.47$, $P = .23$, $\eta_p^2 = 0.04$) and contextualized memory ($F_{1,31} = 1.56$, $P = .22$, $\eta_p^2 = 0.05$), graphs (see Figure 3) were strikingly similar to those from the moderation analysis, with small to moderate effect sizes.

DISCUSSION

Cognitive reserve theory in TBI has focused primarily on examining the theory's potential at the cognitive level.[13] Neuropsychological findings from the current study demonstrated that higher CR had a protective effect on the influence of TBI on cognitive performance compared with lower CR. That is, relative to persons with low CR, those with high CR had significantly better executive functioning and memory for contextualized information. Significant differences were not evident with respect to attention skills, memory for noncontextualized information, or processing speed. Although the TBI literature generally shows that proxies of CR are associated with postinjury cognition, the presence of significant findings varies by cognitive domain. Most studies show that individuals with high CR have significantly better memory than those with low CR, irrespective of contextualized/noncontextualized content.[14,17] This is in contrast to our sample, where CR's advantage for memory depended upon the presence or absence of context. With respect to executive function and processing speed, studies have shown that whether CR is protective may be contingent upon the stage and severity of injury. That is, in samples where the full severity spectrum was represented (ie, mild through severe) and injury date was more remote, individuals with high CR performed significantly better than those with low CR.[40,41] In studies that evaluated individuals more acutely and/or severely injured, this pattern was generally absent.[42]

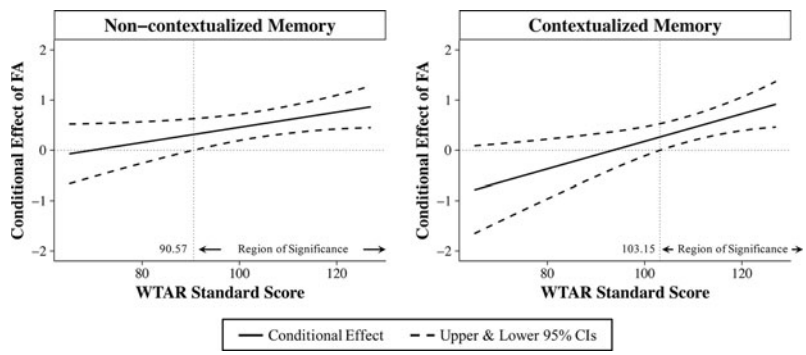

Figure 2. Using the Johnson-Neyman procedure, we calculated the conditional effect of FA across the continuous measure of the WTAR. The conditional effect represents the slope of the relationship between FA and cognition at each possible value of the WTAR. For noncontextualized memory, there was a significant positive association with FA at WTAR scores of 90.57 and above. For contextualized memory, there was a significant positive relationship with FA at WTAR scores at 103.15 and above. FA indicates fractional anisotropy; WTAR, Wechsler Test of Adult Reading.

As CR was developed to better understand cognitive function in the context of brain pathology, we examined whether individuals with higher CR better coped with TBI neuropathology. In the current study, CR was found to moderate the relationship between neuropathology and both contextualized and noncontextualized memory. Specifically, CR protected against neuropathology's impact on memory at higher levels of CR; however, at lower levels of CR, no protection was afforded. When considering injury severity, a very similar pattern was seen. Specifically, at complicated mild/moderate injury, people with higher CR possessed better memory than those with lower CR, whereas no difference between CR groups was seen in memory capacity at severe injury. Consistent patterns between 2 distinct proxies of injury classification and CR lend support for CR theory in TBI, although the limited sample size of the complicated mild/moderate group tempers this interpretation. Nonetheless, larger effect sizes noted in the neuropathology analyses indicate that neuroimaging metrics may be more sensitive in capturing the relationship between extent of injury and outcome.

Having established that CR mitigated the deleterious effects of neuropathology on memory but not at all levels of neuropathology, we sought to characterize the regions wherein CR's benefit was realized. The point at which CR transitioned from attenuating neuropathology's impact occurred at the low end of average intellectual functioning for noncontextualized memory and in the middle of the average range for contextualized memory. In other words, at premorbid intelligence levels below average, neuropathology's effects on cognition are unshielded. In addition, CR's ability to protect memory weakened as neuropathology increased. That is, at the highest levels of neuropathology, CR is essentially depleted and individuals with high CR present as equally impaired as those with low CR. This pattern, shown in Figure 1, replicates the pattern seen in AD at advanced neuropathology.[43] In fact, the graphical representation of AD pathology (adaptation in Figure 4) could easily reflect that of TBI or other neurological populations. Cognitive reserve will withstand increased levels of neuropathology until it reaches a threshold. Once neuropathology breaches this threshold, CR can no longer contain the detrimental impact on cognition and cognitive function will precipitously decline to the point where CR provides no benefit.

Using Figure 4 as a reference, in our sample, we are capturing the upper end of the neuropathology continuum where both the low and high CR groups have passed the clinical threshold (see Figure 4, lighter shading). Although there are no other studies within TBI to compare these findings, one can look to other patient populations to observe when lesser degrees of neuropathology are captured, such as in the darker shaded area of Figure 4. For example, Sumowski and colleagues[44] found that individuals with multiple sclerosis and high CR remained stable across levels of neuropathology relative to those with low CR, who showed decreasing cognitive function as neuropathology increased. Importantly, studies comprising an excess of individuals at significant degrees of neuropathology may conclude that CR offers no protection whereas, in reality, there may be a ceiling effect of neuropathology. This is particularly poignant for researchers investigating CR in TBI, where it is not uncommon to focus on samples comprised exclusively of individuals with moderate to severe injury. This may be what is occurring in the neuropsychological studies discussed earlier, namely, CR cognitive findings tended to be nonsignificant when samples contained more acutely and severely injured persons. Additional evidence for this premise comes from Leary and colleagues,[40] who found that significantly better cognitive functioning in the high versus low CR groups in a mild to severe sample disappeared when they performed the same analyses on only the subset of individuals with severe injury.

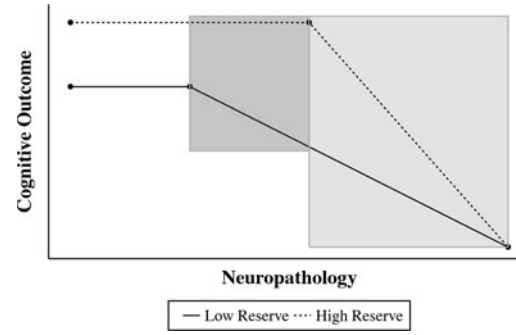

Figure 4. Representation of how cognition remains stable until a clinical threshold of neuropathology is met. The clinical threshold is met at lower levels of neuropathology for those with low CR relative to those with high CR. Adapted from Stern.[43] CR indicates cognitive reserve.

Cognitive reserve is a construct that can only be inferred by a proxy. Premorbid intellectual function is perhaps the proxy most commonly used to reflect CR owing to its resistance to decline after injury or disease and research showing that it better predicts cognitive outcomes than do other proxies.[14] However, CR is a multidimensional construct and other proxies, such as leisure activities and socioeconomic status, have been shown to be uniquely protective.[7,24] Thus, research conducted with premorbid intelligence as a unitary proxy will not fully capture the complexity and nuances of CR. Therefore, the results of the current study are incomplete in their assessment of the CR construct. Inclusion of varied proxies in future research may help clarify whether other cognitive domains are independently protected from the effects of pathology in TBI.

In general, how well any CR proxy is truly predictive of outcomes is unclear. Proxies are based on postinjury inferences about preinjury ability, so they are theoretical by nature. The proxy used in the current study, reading ability, is a measure of crystallized premorbid functioning. Although crystallized measures are utilized because of their resistance to decline after brain compromise,[45] the verbal nature of these measures may make them intrinsically less accurate in ascertaining whether postinjury nonverbal, cognitive functions are protected by CR. Indeed, research shows that crystallized intelligence may not best capture intellectual potential.[46] Rather, fluid intelligence measures may actually best represent CR for some individuals. Our utilization of a verbally based crystallized measure of premorbid intellect may be one of the reasons that we did not find CR to be protective of attention or processing speed.

In addition to the complexity of CR, there is no single biomarker for neuropathology in TBI. We defined neuropathology in the present study using FA in order to detect both impaired networks associated with the presence of lesions and subtle and diffuse white matter changes not captured in atrophy measures. However, even with advanced neuroimaging techniques, such as DTI, the degree of specificity remains at the macro level relative to the detail that can be detected using body fluid markers.[47] These burgeoning approaches to characterizing TBI neuropathology at the histological level may advance our understanding of CR in TBI. Future studies may aim to address this complexity by systematically evaluating various CR proxies and their protective effect across a variety of pathology metrics and cognitive domains. Given the memory-related findings, a logical step may be to narrow the focus of pathology metrics to the medial temporal lobe and limbic areas.

CONCLUSION

In summary, this was the first study to offer evidence that CR attenuates the negative effect of TBI-related neuropathological changes on cognitive outcomes in TBI survivors. These findings may be considered preliminary, particularly as limitations such as lack of scanner harmonization may have impacted the interpretability of imaging findings. Nonetheless, the results of this study extend TBI research to date and provide direction for future research. Cognitive reserve's attenuation effects were limited to memory, introducing the possibility that CR may better differentially protect some cognitive domains against neuropathology relative to others. This finding is consistent with other literature.[48] Consistency of an attenuating effect on memory across neurological populations may lend credence to CR's differential effect.[49] If memory functions are selectively protected after injury, they might also be more malleable to rehabilitation. This is important clinically, given the growing evidence base for efficacious memory rehabilitation treatments in TBI.[50] The finding of a clinical cutoff below which CR is no longer protective, together with a possible neuropathology ceiling effect, may be helpful for prognostication and decisions regarding allocation of clinical resources.

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