Assessment

Validation of a dynamic measure of current cognitive reserve in a longitudinally assessed sample of healthy older adults: The Tasmanian Healthy Brain Project

Journal:	*Assessment*
Manuscript ID	ASMNT-16-0171.R2
Manuscript Type:	Original Manuscript
Keywords:	cognitive reserve, validity, confirmatory factor analysis, older adults, healthy, education

ABSTRACT

Cognitive reserve (CR) is a theoretical construct describing the underlying cognitive capacity of an individual that confers differential levels of resistance to, and recovery from, brain injuries of various types. To date, estimates of an individual's level of CR have been based on single proxy measures that are retrospective and static in nature. To develop a measure of dynamic change in CR across a lifetime, we previously identified a latent factor, derived from an exploratory factor analysis of a large sample of healthy older adults, as current CR (cCR; Ward, Summers, Saunders, & Vickers, 2015). In the present study we examined the longitudinal results of a sample of 272 older adults enrolled in the Tasmanian Healthy Brain Project (Summers et al., 2013). Using results from 12 month and 24 month re-assessments we examined the longitudinal validity of the cCR factor using confirmatory factor analyses. The results of these analyses indicate that the cCR factor structure is longitudinally stable. These results, in conjunction with recent results from our group demonstrating dynamic increases in cCR over time in older adults undertaking further education (Lenehan et al., 2016), lend weight to this cCR measure being a valid estimate of dynamic change in CR over time.

KEYWORDS: Cognitive Reserve, validity, confirmatory factor analysis, older adults, healthy, education

INTRODUCTION

The concept of reserve emerged from attempts to explain intra- and inter-individual differences in recovery from neurological insult and brain injury (Stern, 2002, 2009). Theoretically, reserve encompasses two related and overlapping constructs: brain reserve and cognitive reserve. Brain reserve refers to passive biologic neural processes enabling the brain to compensate for or resist neural injury. Cognitive reserve (CR) refers to the active cognitive strategies and networks available to the individual to actively compensate for cognitive deficits resulting from neural injury (Stern, 2009). Therefore, inter-individual differences in severity of deficits following identical injuries reflect inter-individual differences in CR and in brain reserve. The construct of reserve has sound ecological validity in describing the wealth of evidence of inter-individual differences in cognitive function as well as recovery following brain injury. However, little progress has been made in developing reliable and valid longitudinal measures of reserve suitable for assessing change in CR over time.

To date, research examining both brain and CR has relied on the use of proxy measures to estimate underlying reserve and the relationship between proxy estimates of reserve and changes in function. Measures of brain reserve include imaging-derived estimates of brain volume and synaptic density, as well as measures of head circumference (Mortimer, Snowdon, & Markesbery, 2003; Stern, 2009). For CR, proxy measures include years of education, occupational attainment, literacy, estimates of intellectual capacity, or estimates of prior engagement in mental activity (Manly, Schupf, Tang, & Stern, 2005; Manly, Touradji, Tang, & Stern, 2003; Richards & Sacker, 2003; Sharp & Gatz, 2011; Stern, 2009; Stern, Alexander, et al., 1995; Stern, Tang, Denaro, & Mayeux, 1995; Wilson, Barnes, & Bennett, 2003). The assumed validity of such proxy measures is contingent on a linear relationship between the proxy measure and the construct of reserve. However, the proxy measures in use do not display a stable linear relationship. For example while education is correlated with

other measures of function (e.g., vocabulary, intelligence), a sizeable proportion of the variance in these functions (i.e., intelligence) is not explained by prior education as factors specific to education (such as quality, access, and engagement) as well as factors extrinsic to education (such as genetic factors, cultural, and sociodemographic factors) create additional variance (Lezak, Howieson, Bigler, & Tranel, 2012). Further, the proxy measures used to estimate reserve are predominantly retrospective measures (e.g., prior education) and can therefore only provide a static estimate of reserve. If reserve reflects the overall cognitive capacity of an individual arising from the sum of experiences of a person throughout their lifetime, then the construct of reserve is inherently dynamic with ongoing experience leading to changes in this capacity. A valid measure of reserve must therefore also be dynamic and capable of modification over time and with experience. As such, proxy measures of reserve that are static and retrospective in nature are unlikely to provide a valid estimate of the current cognitive reserve capacity of the individual.

The Tasmanian Healthy Brain Project (THBP) is a novel longitudinal study examining the potential for further education to alter the trajectory of age-related cognitive decline in healthy older adults. Participants in the THBP have undertaken annual comprehensive neuropsychological and cognitive assessment across multiple measures of current cognitive capacity (Summers et al., 2013). In addition, commonly used proxy measures of cognitive reserve have been utilised (Summers et al., 2013). We used exploratory factor-analyses to develop a composite measure of prior cognitive reserve (pCR) and current cognitive reserve (cCR) (Ward et al., 2015). Using the results of the baseline assessment of 467 healthy older adults enrolled in the THBP, a series of static measures of function (prior education, prior intelligence, mid-life occupation, and mental activity in young adulthood and middle adulthood) combined on a single factor. This factor, referred to as pCR and explained 77.1% of the variance in the data set (Ward et al., 2015). The second factor, referred to as cCR was

derived from three dynamic measures of function (current intellectual capacity, spelling ability, arithmetic ability) explained 59.87% of the variance in the dataset (Ward et al., 2015).

The aim of the present study was to explore the longitudinal validity of the cCR factor derived by Ward et al. (2015) in a subset of the THBP participants assessed annually over the first 3 years of the THBP. We hypothesised that the latent structure of cCR derived by exploratory factor analysis of baseline data would be validated using confirmatory factor analysis of 12 month and 24 month annual re-assessment data in a subsample of the THBP cohort.

METHOD

Commencing in 2011, the Tasmanian Healthy Brain Project (THBP) progressively recruited 566 healthy older adults aged 50 years and older until recruitment ceased in 2014. The current cohort has completed between 2-6 years of annual re-assessments. To date, of the 566 participants who entered the study and completed baseline assessment, 107 have withdrawn representing a retention rate of 81% over 6 years. The majority of withdrawing participants (97%) report withdrawing due to factors unrelated to the study: 24% due to geographic relocation away from the study site; 16% unable to recontact the participants (presumed relocation); 16% due to serious medical illness or terminal health condition; 14% being too busy to continue in the study; 2% deceased; and, 25% provide no reason for withdrawal. Only 3% of the withdrawals relate to the study itself, such as not enjoying the assessment process.

Participants

Of the 459 participants currently enrolled in the THBP, we selected those participants who had completed 3 years of annual assessment and excluded any cases with missing data at any of these assessment points. Participants were drawn from two groups in the THBP: an intervention group (n = 358, 78%) who undertook a minimum of 12 months further education at university level following commencing in the THBP study; and, a control group (n = 101, 22%) who did not undertake any further university education. A total of 187 of the 459 enrolled participants were missing data at Year 2 and/or Year 3 assessment points, reflecting the rolling recruitment into the THBP. Examination of the missing data pattern revealed that data was missing at random. The resultant sample comprised 272 participants, with 207 (76.1%) from the intervention group and 65 (23.9%) from the control group, which is consistent with the group distribution of the THBP cohort. The cCR factor model was developed with a sample of 467 THBP participants examining performance on baseline assessment (Ward et al., 2015). The present study utilises a subsample of 272 participants from the THBP, all of whom were included in the original sample for developing the cCR factor model (Ward et al., 2015). Examination of key demographic variables indicates that the sub-sample of 272 selected for this study are consistent with the sample for the original cCR factor model (see Table 1).

[INSERT TABLE 1 HERE]

Materials

Participants enrolled in the THBP complete a comprehensive test battery assessing neuropsychological, cognitive, psychological, social, and medical factors. The protocol for the THBP is described in detail elsewhere (Summers et al., 2013).

To validate the model of cCR developed using baseline data from the THBP dataset (Ward et al., 2015), we selected the three measures that contributed to the latent factor of cCR: WAIS-III-SF1 FSIQ, WRAT-4-PMV Spelling LES; and WRAT-4-PMV Math Computation LES (Ward et al., 2015). The WAIS-III-SF1 FSIQ is a full scale intelligence quotient score derived from performance across four subtests of the Wechsler Adult Intelligence Scale, 3rd edition (WAIS-III short-form; Donnell, Pliskin, Holdnack, Axelrod, & Randolph, 2007). The WAIS-III-SF1 extrapolates an estimate of the full scale WAIS-III intelligence quotient from performance on four subtest (picture completion, digit symbol coding, similarities, and arithmetic) (Donnell et al., 2007).

The WRAT-4-PMV assesses academic performance factors of word reading, sentence completion, spelling, and maths computation in adults with higher secondary school education (Roid & Ledbetter, 2006). Performance on the WRAT-4-PMV subtests increase with level of education, including at University/College level (Roid & Ledbetter, 2006), indicating that the WRAT-4 is sensitive to performance enhancement following education. Consistent with the model of cCR developed by Ward et al. (2015), the subtests for Spelling and Maths Computation were used.

Procedure

Participants were administered the selected measures by trained assessors as part of the larger THBP protocol (Summers et al., 2013). The full protocol examines multiple cognitive domains (memory, language, spatial, executive function) as well as non-cognitive domains (psychological, social, quality of life). The full assessment protocol takes an average of 4 hours to complete and is undertaken in a standard quiet assessment room. Participants are

encouraged to take regular rest breaks as needed during the course of the assessment to reduce symptoms of fatigue.

Data analysis

Confirmatory factor analyses were performed using IBM SPSS AMOS v 22. Two separate confirmatory factor analyses (CFA) were conducted using maximum likelihood estimation to examine the validity of the exploratory factor analytic derived model of cCR at baseline assessment (Ward et al., 2015; Figure 1). The first CFA examined 12 month re-assessment data from the selected sample of 272 THBP participants (Phase 1) by fixing the parameter estimates to the factor loadings between each observed variable and the latent cCR factor as described by Ward et al. (2015; Figure 1). An second CFA was then performed examining the 24 month re-assessment data (Phase 2) in the same cohort of 272 THBP participants, with the parameter estimates also being fixed to be the observed factor loadings between each observed variable and the latent cCR factor as described by Ward et al. (2015; Figure 1). The validity of the cCR factor over time was assessed by the model fit between the CFA derived models at each time point with parameter estimates fixed to the factor loadings identified in the original exploratory factor analysis by Ward et al. (2015).

[INSERT FIGURE 1 HERE]

Goodness-of-fit measures based on the chi-square statistic (i.e. likelihood ratio chi-square statistic) were used to evaluate the model fit. As the chi-square statistic is sensitive to sample size (Byrne, 2010), additional measures of fit were used to assess the model. Seven additional

measures of goodness-of-fit were selected (Byrne, 2010): root mean squared error of approximation (RMSEA); comparative fit index (CFI); Tucker-Lewis index (TLI); closeness of fit (PCLOSE); Akaike's Information Criterion (AIC); Expected Cross-Validation Index (ECVI); and, Hoelter's Critical N (Hoelter). A good model fit is observed if chi-square is non-significant; RMSEA values are .05 or less; CFI is equal or greater than .95; TLI values are equal or greater than .95 for large samples; PCLOSE returning a $p > .50$; AIC and ECVI values are smaller for the predicted model than either the independence or saturated models; and a Hoelter value of greater than 200 at the .05 and .01 levels (Byrne, 2010).

RESULTS

Confirmatory factor analysis of the cCR factor structure at phase 1 assessment was performed with the parameter estimates between the cCR factor and the observed variables of WAIS-III-SFI FSIQ, WRAT spelling, and WRAT math computation being fixed to the regression coefficients identified by the exploratory factor analysis of baseline data by Ward et al. (2015). Examination of the standardized model estimates of the factor structure revealed a model (Figure 2) similar to the model by Ward et al. (2015; see Figure 1).

[INSERT FIGURE 2 HERE]

The Phase 1 cCR model displayed good fit returning a non-significant chi-square. Examination of the additional 7 indicators of goodness-of-fit (Table 2) revealed that the exploratory factor analysis model parameters applied to a confirmatory factor analysis of

phase 1 data displayed good fit to the data, meeting criterion for all fit measures: RMSEA, CFI, TLI, PCLOSE, AIC, ECVI, and Hoelter.

[INSERT TABLE 2 HERE]

A second confirmatory factor analysis of the cCR factor structure at phase 2 assessment using the same parameter estimates between the cCR factor and the observed variables revealed a model (Figure 3) that is also similar to the model by Ward et al. (2015; see Figure 1).

[INSERT FIGURE 3 HERE]

The Phase 2 cCR model displayed a similar pattern of goodness-of-fit (Table 2) as reported for the Phase 1 cCR model across all fit measures: RMSEA, CFI, TLI, PCLOSE, AIC, ECVI, and Hoelter.

DISCUSSION

The present study examined the longitudinal validity of a composite measure of dynamic cognitive reserve, referred to as current cognitive reserve (cCR) in a longitudinally assessed sample of healthy other adults. The results of this study demonstrate that the cCR factor model developed at baseline assessment (Ward et al., 2015) displays a high level of fit to data collected from the same sample at repeat assessment of these variables 12 and 24 months following baseline assessment. The high level of fit detected at analysis indicates that the

factor structure for cCR initially identified by Ward et al. (2015) displays consistency over repeated assessments.

The cCR measure developed was designed to assess CR dynamically over time, enabling increases or decreases in CR to be assessed as the impact of other factors on CR emerge (e.g. degenerative disease, further education, etc.). The present series of confirmatory factor analyses are silent on the capacity of the cCR measure to validly capture dynamic change in CR over time, indicating instead that the proportional relationship between the observed measures (WAIS FSIQ, WRAT spelling, and WRAT math computation) remains stable over repeated assessments.

Recently, we employed the cCR measure in a latent growth curve analysis of the performance of the THBP cohort over the first 4 years of the study (Lenehan et al., 2016). The results of this analysis indicate that when adjusted for pCR, 92.5% of the intervention group (further education) displayed a significant growth in cCR over 4 years compared to 44.3% of the control (no further education) group displaying an increase in cCR (Lenehan et al., 2016). These findings provide evidence that the cCR measure is a valid measure of dynamic changes in reserve following an education intervention in older adults.

A significant barrier to research examining the relationship between sociodemographic factors and risk for diseases of advanced age is the significant time gap between the occurrence of the risk modifying factor (e.g. early education) and the consequential outcome (e.g dementia in late life). As a result, studies identifying a reduced risk for dementia in old age associated with higher levels of educational attainment in early adulthood offer little in terms of potential risk mediation to those beyond early adulthood. There is an emerging body of research suggesting that in order to modulate risk for dementia at a clinically-significant level, interventions that reduce risk must occur in middle adulthood and in the absence of

signs neurodegenerative disease (Ritchie, Ritchie, Yaffe, Skoog, & Scarmeas, 2015). The composite cCR measure developed in the present study offers a method of assessing the efficacy of cognitive interventions delivered in mid and late adulthood, life stages that are temporally proximal to onset of elevated risk for neurodegenerative diseases such as dementia.

A potential limitation inherent in the cCR measures developed is the reliance on measures of intelligence and academic performance. The construct of CR refers to active cognitive strategies and networks utilised by an individual to compensate for cognitive deficits following neural injury (Stern, 2009). Our operationalisation of CR using intellectual and academic proxy markers accords with previous attempts to operationalise CR using proxies such as educational attainment, occupational attainment, intelligence, literacy, or engagement in mental activity (Manly et al., 2005; Manly et al., 2003; Richards & Sacker, 2003; Sharp & Gatz, 2011; Stern, 2009; Stern, Alexander, et al., 1995; Stern, Tang, et al., 1995; Wilson et al., 2003). Such proxy markers of CR, including the cCR measure developed here, reflect stable and enduring estimates of overall level of cognitive ability. Development of a measure of CR capable of assessing dynamic change in CR over time is essential to intervention studies aiming to increase CR to protect an individual against decline in crystallised and fluid cognitive functions. Previously, we operationalised CR into two partitions: prior CR (pCR) reflecting a static estimate of CR derived from measures of accumulated lifetime experiences (education, prior intellectual capacity, occupational attainment, and prior mental activity); and current CR (cCR) reflecting a dynamic estimate of CR at any given time-point capable of change over time with ongoing lifetime experiences (Ward et al., 2015). An individual's level of CR at any given time is represented as the combination of pCR and cCR, with an individual's CR level influencing cognitive abilities across all cognitive domains (e.g., memory, learning, language, reasoning, etc.). The cCR measure was developed specifically

for use with the Tasmanian Healthy Brain Project, in order to assess changes in CR due to an education intervention and how these changes impact on aging-related changes across a range of cognitive domains (Summers et al., 2013). As such, it was necessary to exclude measures of active cognitive function (e.g. working memory, episodic memory, executive function, etc) as well as proxy measures of CR (i.e., education level) that form the intervention, from the cCR measure. It is important to recognise that the operational construct of CR employed here excludes a range of cognitive functions that may be considered to be components of CR (e.g. memory, executive functions etc.). Theoretically, as the construct of CR as described by Stern (2009) encompasses all active cognitive strategies and networks, it could be considered to reflect the sum of cognitive function and activity of the individual. For the purposes of intervention based research designed to assess the relationship between modifying an individual's level of CR and changes in discrete cognitive functions, a measure of CR encompassing the totality of cognitive capacity including discrete cognitive functions cannot be utilised. Hence, we have described a measure of CR that is differentiated from measures of discrete cognitive functions to enable examination of the potential effect of interventions designed to alter level of CR within an individual.

We have developed a factor model of CR that assesses dynamic changes in reserve over time. The measure of CR developed combines three proxy measures of intelligence and academic performance. While we do not suggest that these three proxy measures of CR when combined represent the breadth of CR as a construct, we believe that the cCR composite score has higher levels of validity than single proxy measures used in isolation.

ACKNOWLEDGEMENTS

This project is funded by National Health and Medical Research Council (NHRMC) Project grants (1003645 & 1108794), as well as the JO and JR Wicking Trust (Equity Trustees). MS reports personal fees from Eli Lily (Australia) Pty Ltd and grants from Novotech Pty Ltd, outside the submitted work. All other authors report nothing to disclose.

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Figure 1: Exploratory Factor Analysis derived latent factor structure for current Cognitive Reserve at baseline assessment (from Ward et al.. 2015)

Figure 2: Confirmatory Factor Analysis of current Cognitive Reserve at Phase 1 (12 month) re-assessment (standardised estimates shown)

Figure 3: Confirmatory Factor Analysis of current Cognitive Reserve at Phase 2 (24 month) re-assessment (standardised estimates shown)

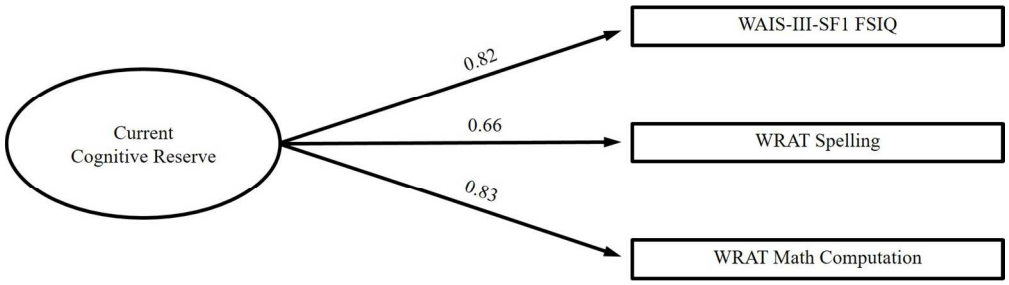

Figure 1: Exploratory Factor Analysis derived latent factor structure for current Cognitive Reserve at baseline assessment (from Ward et al., 2015)

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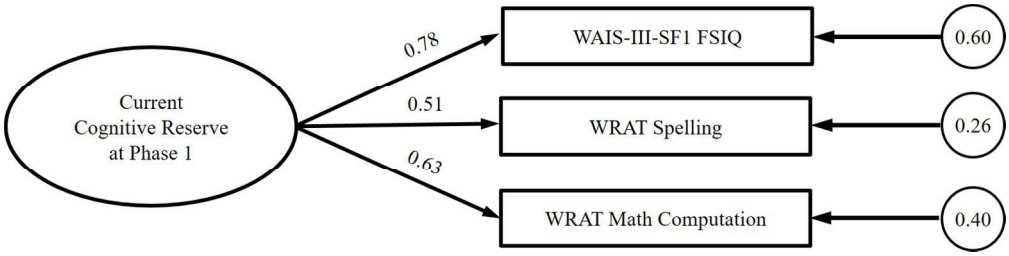

Figure 2: Confirmatory Factor Analysis of current Cognitive Reserve at Phase 1 (12 month) re-assessment (standardised estimates shown)

271x67mm (150 x 150 DPI)

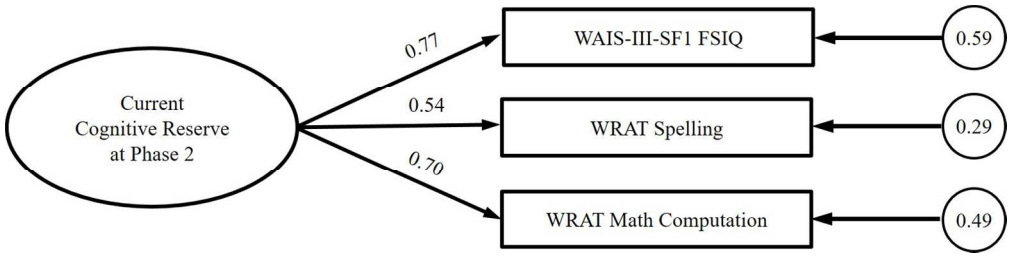

Figure 3: Confirmatory Factor Analysis of current Cognitive Reserve at Phase 2 (24 month) re-assessment (standardised estimates shown)

271x67mm (150 x 150 DPI)

***Table 1*:** Descriptive statistics of the study sample (n = 272) and prior (Ward et al., 2015) study sample (n = 467)

	Current Study M *(SD)*	**Ward et al (2015)** M *(SD)*	***p.*** ***(t-test)***
n	272	467	
%female:%male	68% : 32%	68.3% : 31.7%	(χ^2) .982
Age at baseline (yrs)	61.34 *(6.67)*	60.64 *(6.81)*	.182
Education (total years)	13.85 *(2.58)*	13.84 *(2.75)*	.962
WAIS FSIQ baseline	120.51 *(12.48)*	118.97 *(13.42)*	.122
WRAT-4-PMV Spelling LES baseline	571.05 *(17.95)*	568.78 *(16.04)*	.439
WRAT-4-PMV Math Computation LES baseline	536.60 *(19.49)*	534.99 *(19.97)*	.285

WAIS = Wechsler Adult Intelligence Scale, FSIQ = full scale intelligence quotient; WRAT-4-PMV = Wide Range Achievement Test, 4th edition, Progress Monitoring Version; LES = level equivalent scores

Table 2: Goodness-of-fit statistics for Phase 1 and Phase 2 confirmatory factor analysis models

Goodness of fit		Phase 1 model	Phase 2 model
Chi square *p.*		.583	.436
RMSEA		<.001	<.001
CFI		1.000	1.000
TLI		1.011	1.003
PCLOSE		.751	.637
AIC	Model	15.079	15.661
	Saturated	18.000	18.000
	Independence	141.295	164.411
ECVI	Model	.056	.058
	Saturated	.066	.066
	Independence	.521	.607
Hoelter	.05	1505	978
	.01	2313	1503