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Development and Validation of a Cognitive Reserve Index in HIV

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Abstract

Objectives: In the neuroHIV literature, cognitive reserve has most often been operationalized using education, occupation, and IQ. The effects of other cognitively stimulating activities that might be more amenable to interventions have been little studied. The purpose of this study was to develop an index of cognitive reserve in people with HIV, combining multiple indicators of cognitively stimulating lifetime experiences into a single value. **Methods:** The data set was obtained from a Canadian longitudinal study (N = 856). Potential indicators of cognitive reserve captured at the study entry included education, occupation, engagement in six cognitively stimulating activities, number of languages spoken, and social resources. Cognitive performance was measured using a computerized test battery. A cognitive reserve index was formulated using logistic regression weights. For the evidence on concurrent and predictive validity of the index, the measures of cognition and self-reported everyday functioning were each regressed on the index scores at study entry and at the last follow-up [mean duration: 25.9 months (SD 7.2)], respectively. Corresponding regression coefficients and 95% confidence intervals (CIs) were computed. **Results:** Professional sports [odds ratio (OR): 2.9; 95% CI 0.59–14.7], visual and performance arts (any level of engagement), professional/amateur music, complex video gaming and competitive games, and travel outside North America were associated with higher cognitive functioning. The effects of cognitive reserve on the outcomes at the last follow-up visit were closely similar to those at study entry. **Conclusion:** This work contributes evidence toward the relative benefit of engaging in specific cognitively stimulating life experiences in HIV.

Keywords: Cognitive performance, Cognitive reserve, HIV, Cognitively stimulating activities, Measurement, Brain health

INTRODUCTION

Despite effective antiretroviral treatment, as many as 30–50% of individuals with HIV infection experience some degree of cognitive impairment, which may adversely impact the instrumental activities of daily living (Gorman, Foley, Ettenhofer, Hinkin, & van Gorp, 2009; Heaton et al., 2010) including medication adherence (Becker, Thames, Castellon, & Hinkin, 2011; Patton et al., 2012), driving (Foley et al., 2013; Vance, Wadley, Crowe, Raper, & Ball, 2011), employment, and financial management (Vance et al., 2011). It may also influence health-related quality of life (Tozzi et al., 2003; Vance et al., 2016) and contribute to accelerated mortality (Vivithanaporn et al., 2010).

Could people living with HIV somehow protect themselves from cognitive impairment? Cognitive reserve is conceived of as a potential buffer against the impact of brain pathology on cognitive performance. Cognitive reserve, built up through cognitively enriching experiences over the lifespan, is thought to explain, at least in part, the disparity between a given degree of brain pathology and its clinical manifestations (Stern, Arenaza-Urquijo, & Bartrés-Faz, 2018). Although mainly studied in relation to aging and Alzheimer's disease, cognitive reserve has been proposed as relevant in HIV (Milanini et al., 2016). It is hypothesized to mediate the relationship between neuropathology and cognitive performance (Isobel et al., 2018; Kaur, Dendukuri, Fellows, Brouillette, & Mayo, 2019; Richards & Deary, 2005; Stern, 2002) rather than having a strong direct effect on cognition *per se*. In turn, cognitive performance affects outcomes related to functioning in everyday life (Vance et al., 2011).

While in the neuroHIV literature, cognitive reserve has most commonly been operationalized using conventional

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indicators: education, occupation, and IQ (Kaur et al., 2019), there is some evidence in the aging literature that physical, social, and intellectual activities often done as part of leisure and recreation may also contribute to cognitive reserve (Richards & Deary, 2005; Sobral & Paúl, 2013; Sposito, Neri, & Yassuda, 2015; Stern et al., 2018). These are of particular interest as they are more amenable to change in adulthood, offering the potential for intervention.

A broader view of indicators of cognitive reserve may be relevant, but there are measurement and statistical challenges in quantifying cognitive reserve using multiple indicators (Jones et al., 2011). Combining all the potential indicators, i.e. education, occupation, IQ, and leisure activities, into one quantity, is not straightforward. Different statistical methods have been applied to create total scores including principal component analysis, item response theory, and summation of standardized scores (Leon, Garcia-Garcia, & Roldan-Tapia, 2014; Nucci, Mapelli, & Mondini, 2012; Sobral, Pestana, & Paúl, 2014; Valenzuela & Sachdev, 2007). An alternative method involves application of weights based on the influence that each potential indicator has on a relevant outcome (here, cognitive performance). Impact weights have been used to generate indices of cardiovascular and stroke risk (D'Agostino et al., 2008; Nobel, Mayo, Hanley, Nadeau, & Daskalopoulou, 2014). Likewise, comorbidity indices have been developed based on the impact on mortality and length of hospital stay (Deyo, Cherkin, & Ciol, 1992) and recovery from stroke (Tessier, Finch, Daskalopoulou, & Mayo, 2008). Here, for the first time, we apply this approach to develop an index of cognitive reserve in HIV.

The primary aim of this study was to develop an index of cognitive reserve for people living with HIV based on combining multiple indicators of cognitive stimulating lifetime experiences into a single value. A secondary aim was to estimate the extent to which the Cognitive Reserve Index in HIV (CRI-HIV) was associated with concurrent values of cognitive performance and everyday functioning and predicted future values for these outcomes. The specific hypotheses were that the CRI-HIV scores would be related moderately to cognition and less strongly with the more distal outcomes of everyday functioning concurrently and would predict future values on these outcomes.

METHODS

The data for this study were acquired from the Positive Brain Health Now (+BHN) cohort (N. Mayo, Brouillette, Fellows, & Investigators, 2016). HIV+ men and women diagnosed for at least 1 year, age ≥35, able to communicate adequately in either French or English, and able to give written informed consent were recruited. Excluded were people who had dementia [operationalized as a Memorial Sloan Kettering (MSK) rating stage 3 or more – cognitive component only (Price & Brew, 1988)] or had a non-HIV-related neurological disorder, active CNS opportunistic infection, known psychotic disorder, substance dependence, or abuse within the past 12 months or life expectancy of < 3 years as judged by the treating physician. The cohort composed of 856 HIV-positive participants recruited from five clinics in four Canadian cities: Montreal, Toronto, Hamilton, and Vancouver. The study procedures were in accordance with the ethical standards of the participating institutional research boards.

A computerized battery testing various cognitive domains, that are affected by HIV and are essential for everyday functioning, including executive functions, memory, attention, and processing speed, was administered at study enrollment and every 9 months over 27 months of follow-up (Brouillette et al., 2015; N. E. Mayo et al., 2020). The battery composed of the following tasks: Corsi block task (forward and backward), mini Trail-Making Test B, Eriksen flanker task, phonemic fluency, and recall of a list of 8 words. Using Rasch methodology, all of these tests were combined to create a unidimensional measure of cognitive performance (Brief Cognitive Ability Measure B-CAM©) with linearized units. Extensive work has been done previously for the development of the B-CAM (Brouillette et al., 2015; Koski et al., 2011). It takes under 40 minutes for the administration and scoring of the B-CAM. It was designed specifically to minimize practice effects and avoid conducting analyses test by test which creates problems with multiple comparisons (Brouillette, Fellows, Finch, Thomas, & Mayo, 2019).

We used the B-CAM values at the study entry and at the last follow-up., i.e., the last available B-CAM scores for each participant. This approach was taken to ensure the longest possible follow-up of cognitive performance. Previous work on the CNS HIV Anti-Retroviral Therapy Effect Research (CHARTER) data set has shown that more than 80% of the HIV+ participants without any cognitive intervention remained stable in their cognition over 36 months using the group-based trajectory method (Brouillette et al., 2016).

The B-CAM score was transformed into a binary variable (high/not high) with individuals scoring at or above the 75th percentile (≥ 23) considered to have high cognitive performance. Sociodemographic and clinical variables including years since HIV diagnosis, nadir CD4 cell count, and percentage of participants with nadir CD4 count <200 cells/μL were also obtained from the +BHN data set.

Self-reported cognitive difficulties and work productivity were ascertained using the Perceived Deficits Questionnaire (PDQ) (Sullivan, Edgley, & Dehoux, 1990) and Stanford Presenteeism Scale (SPS), (Turpin et al., 2004) both deemed to be indicators of everyday functioning. The PDQ is composed of 20 items and asks participants to report on their cognitive functioning within the previous 4 weeks. The response options range from 0 (never) to 4 (almost always). This measure taps into attention, retrospective memory, prospective memory, and planning and organization. It yields a total score ranging from 0 to 80, with a higher score indicating the presence of more cognitive difficulties. A score of 40 on the PDQ indicates cognitive impairment. The SPS assesses work productivity among employed individuals (n = 443), with higher

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scores indicating better work productivity; it has a total score of 50. The total score is the sum of responses to ten items scored on a 5-point ordinal scale for the frequency in the past 4 weeks the individual experiences work challenges due to HIV. Higher scores indicate better work productivity.

Indicators of cognitive reserve measured in the +BHN data set included education, occupation, social resources, number of languages spoken, and engagement in six other cognitively engaging activities. These six activities are most often identified in the literature as contributing to cognitive reserve (Leon et al., 2014; Nucci et al., 2012; Sobral et al., 2014; Valenzuela & Sachdev, 2007), but have not been studied in HIV (Kaur et al., 2019). Education was categorized into primary, high school, collegiate diploma programs, bachelor's degree, or graduate degrees including medicine and law. Work was classified as professional/executive (CEO, MD, university professor, lawyer, judge, surgeon, chartered accountant, engineer), administrative/highly-skilled (nurse, electrician, plumber, IT specialist, teacher, administrative assistant), or clerical/service position (sales representative, cashier, taxi driver, call center operator, day laborer). The other cognitively engaging experiences included visual arts (such as painting, drawing, photography), music, performance/literary arts, sports, travel, and games. The level of engagement ranged from professional, amateur, personal enjoyment to none in the first four activities. For traveling, the lowest level of engagement was indicated by travel within a province, and the highest level of engagement was indicated by travel to more than two continents outside North America. For games, the level of engagement was classified into four categories: competitive games, complex games (e.g., virtual reality), simple card/board games, or none. Social resources were elicited with the first three items of the Older Americans Resources and Services Social Resources Scale (OARS) (Fillenbaum, 1990). All participants were taking combined antiretroviral therapy. The PDQ, SPS, and OARS items are presented in the supplementary material.

Statistical Analysis

Polychoric correlations were computed for the association between all the indicators of cognitive reserve (as these were ordinal variables). Logistic regression was used to identify the extent to which each indicator was associated with the performance of having a high B-CAM (score ≥ 23). All indicators were categorical, and the reference category was the lowest level for each. Regression parameters, odds ratios (ORs), and 95% confidence intervals (CIs) were estimated for each indicator. The lowest regression coefficient (β) associated with an OR that excluded the null value (1.0) was taken as the cutoff for inclusion of that category in the index. This corresponded to a β of 0.4 and an OR of 1.5. All variables with at least one category with $\beta \geq 0.4$ were included whether or not their associated 95% CI excluded 1.0. This was done to avoid basing relevance on sample size. Nondifferent levels in each categorical indicator were combined and the models were reevaluated. Weights were assigned to the levels of each indicator by multiplying the regression coefficient (β) by 10. A weighted index (CRI-HIV) score was derived by summing the βx10. The odds ratios were not used for this purpose as it is only the regression coefficients that are additive (Harrell, 1996; Mehta, Mehta, Girman, Adhikari, & Johnson, 2016).

For the evidence of interpretability with respect to the concurrent measures, B-CAM, PDQ, and SPS scores at the study entry were regressed on the weighted index score, controlling for age and sex. For the evidence of interpretability to predict future values, each of the measures (B-CAM, PDQ and SPS) at the last visit was regressed on the weighted index score adjusted for age and sex. Corresponding regression coefficients and 95% CI were presented for each. Effect sizes were estimated for each predictor using t-values (i.e., the ratio of β to its standard error) (Cohen, 1988). All statistical analyses were carried using SAS version 9.4 for Windows (SAS Institute, 100 SAS Campus Dr, Cary, NC, USA).

RESULTS

Table 1 shows the characteristics of the full sample at study entry and at the last follow-up visit. As there was attrition over time, also shown are the values at study entry for those with follow-up in the middle column. At study entry, the mean age of the entry sample was 53.0 years (SD: 8.3), and there were more men (84%) than women (16%). There were 73 participants who did not have any follow-up data. Among those with follow-up, the mean age was very similar (53.4 years; SD: 8.3). This similarity between values for the entry sample and those with follow-up was observed for the other measures. The mean time between the study entry and the last follow-up assessment was 25.9 months ($SD = 7.21$).

Only a few pairwise correlations were greater than 0.4: education and work (polychoric $r = 0.46$); music and performance arts (polychoric $r = 0.42$); visual arts and performance arts (polychoric $r = 0.41$); and all social resource variables (polychoric r ranged from 0.45 to 0.50). The pairwise correlations have been presented in the Supplementary Table 1.

Table 2 shows the methods for creating the scoring algorithm to derive CRI-HIV score based on those variables with at least one category meeting our criterion for inclusion (β: 0.4; OR: 1.5).

Column 1 presents the indicator and column 2 gives the categories within each indicator. Column 3 presents the frequency distribution across indicator-categories. For education, the modal category was college education (34%) and only 11% of the sample had a master's or doctoral degree. Across the other cognitively engaging activities, the most frequent level of engagement was for "personal enjoyment". Higher levels of engagement were rare: visual arts, 26%; performance arts, 12%; games, 14%; sports, 9%; and music, 8%. Travel outside of North America was common (57%). Men had higher values for engagement in visual arts, performance arts and travel, but the study was neither designed nor powered for testing these differences. Only 37 % of the sample

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Table 1. Characteristics of the sample.

Characteristic	Study entry	Study entry with last follow-up*	Last follow-up
Number of participants	856	783	783
Demographic variables			
Age, years (mean, SD)	53.0 (8.2)	53.4 (8.3)	55.4 (8.3)
Men (n, %)	722 (84%)	667 (85%)	667 (85%)
Women (n, %)	134 (16%)	116 (15%)	116 (15%)
HIV-related variables			
Years with HIV (mean, SD)	17 (7.8)		19.14 (8.0)
Nadir CD4 count, cells/μL (mean, SD)	217.05 (169.15)		212.91 (163.4)
Nadir CD4 Count <200 cells/μL (%)	51%		52%
Cognitive and everyday functioning variables			
B-CAM (0–36)	19.5 (4.7)	19.6 (4.6)	20.7 (4.5)
PDQ (0–80)	34.1 (17.8)	33.4 (17.8)	32.5 (17.2)
SPS (0–50; n = 443)	39.7 (6.4)	40.0 (6.4)	39.9 (6.7)

*Characteristics of those with the follow-up data that were included in the analysis.
B-CAM, Brief Cognitive Ability Measure; higher scores are better.
PDQ, Perceived Deficits Questionnaire; ≥40 indicates cognitive impairment.
SPS, Stanford Presenteeism Scale; higher scores are better.

were monolingual but no category of multilingualism met our criterion for inclusion (β: 0.4; OR: 1.5). This was also true for variables relating to social resources.

Column 4 presents the βs for each of the categories of the included indicator variables and column 5 gives corresponding ORs. The categories with dark gray highlighting fulfilled the criteria for inclusion, those with light gray highlighting did not and were combined as shown in column 6. For example, for work, as service/clerical and highly skilled or administrative jobs did not differ, they were combined and served as the referent category for the professional/executive level. For visual arts, each category was unique. For all other activities, only one category was retained. The ORs and corresponding 95% CI intervals for the category-indicators, which contributed to the index, are presented in columns 7 and 8, respectively. Column 9 shows the weights assigned to these specific category indicators. Professional sports received the highest points (15), whereas bachelor's degree, master's, and doctorate level education received the second highest points (8). Personal level of enjoyment was awarded points only for visual and performance arts.

The maximum possible score of the index is 68. In this sample, the highest achieved score was 37. The mean score was 13.4 (SD: 7).

Table 3 shows adjusted regression parameters and 95% CI for the validation measures: B-CAM (cognitive performance), PDQ (self-reported cognitive deficits), and SPS (work productivity) at the study entry and at the last visit. As expected, the CRI-HIV showed an association with B-CAM at the study entry. People who differed on CRI-HIV by one unit differed on the B-CAM by 0.19 (β) units; people who differed by 1SD on CRI-HIV differed by 0.19*4.7 units, where 4.7 is the SD on the B-CAM at the study entry. The effect size (t-statistic) for this association was highest (β/SE = 8.0). The CRI-HIV also showed associations with the other concurrent measures: PDQ (β = −0.39; 95% CI: −0.58 to −0.19; t-value = −4.0) and SPS (β = 0.09; 95% CI: 0.008 to 0.8; t-value = 2.2). The effects of CRI-HIV on the last follow-up visit were closely similar to those at the study entry.

There were significant age and sex effects for B-CAM with women and older people scoring lower at the study entry. However, there was no interaction with cognitive reserve and sex indicating that the effect of CRI-HIV on B-CAM did not depend on sex (although power was low for this comparison). For age, the interaction was significant (β = −0.005; 95% CI: −0.008 to −0.001; t = −2.21) indicating that effects of CRI-HIV on B-CAM depended on age with the effects attenuating with older age. For PDQ there was a similar age effect (older age reported more deficits), but no interaction with CRI-HIV scores (β = 0.006; 95% CI: −0.015 to 0.027; t = −0.57). For SPS, there was neither an age nor sex effect.

DISCUSSION

In this study, various contributors of cognitive reserve were combined into an index of cognitive reserve (CRI-HIV) based on their impact on a measure of cognitive performance in older people living with HIV. The CRI-HIV score behaved as hypothesized in relation to concurrent measures of cognitive performance and everyday functioning and predicted these outcomes at the last follow-up visit (see Table 3). Cognitive reserve could help maintain the cognitive performance in people with HIV over time.

There is a consensus that leisure or recreational activities are important in building cognitive reserve, in addition to education and occupation in the non-HIV literature (Cheng, 2016; Helzner, Scarmeas, Cosentino, Portet, & Stern, 2007; Sobral & Paúl, 2013; Stern, 2002; Wang

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Table 2. Frequency distribution of cognitive reserve indicators and outcomes of the key steps involved in the development of Cognitive Reserve Index in HIV (CRI-HIV)

Indicator	Level (Category)	n (%)	β ≥0.4	OR	β for Combinations	OR	95% CI	Weight
Education	Primary School	31 (4)	Referent		Referent			0
	High School	204 (27)	0.1082	1.1				
	CEGEP/College	257 (34)	0.5655	1.7	0.4712	1.6	1.0–1.4	5
	Bachelor's degree	175 (23)	0.921	2.5	0.8256	2.2	1.4–3.4	8
	Master's/PhD	80 (11)	0.9178	2.5				
Work	Service/Clerical	274 (37)	Referent		Referent			0
	Highly skilled/Admin	310 (42)	0.2201	1.2				
	Professional/Executive	157 (21)	0.5028	1.6	0.3828	1.5	0.9–2.1	4
Visual arts	None	131 (18)	Referent		Referent			
	Personal enjoyment	405 (55)	0.5224	1.6	0.5224	1.6	1.0–2.7	5
	Amateur	111 (15)	0.6429	1.9	0.6429	1.9	1.0–3.4	6
	Professional	83 (11)	0.5878	1.8	0.5878	1.9	0.9–3.4	6
Music	None	200 (28)	Referent		Referent			0
	Personal enjoyment	471 (65)	0.266	1.3				
	Amateur	43 (6)	0.7723	2.2	0.3856	1.5	0.8–2.6	4
	Professional	15 (2)	−0.0911	0.9				
Sports	None	280 (38)	Referent		Referent			0
	Personal enjoyment	389 (53)	0.2677	1.3				
	Amateur	55 (8)	0.064	1.0				
	Professional	6 (1)	1.2368	1.6	1.0839	2.9	0.5–14.7	11
Travel	Within province	166 (23)	Referent		Referent			0
	Within North America	146 (20)	−0.1356	0.9				
	1 continent other than NA	176 (24)	0.4974	1.6	0.5594	1.7	1.1–.2.6	6
	2 continents other than NA	237 (33)	0.6042	1.8	0.6662	1.9	1.3–2.8	7
Games	None	263(36)	Referent		Referent			0
	Simple card/board games	369 (50)	0.3361	1.4				
	Complex video games	78 (11)	0.7739	2.1	0.2210	1.5	0.9–2.4	2
	Competitive games	22 (3)	0.1295	1.1				
Performance Arts	None	325 (45)	Referent		Referent			0
	Personal enjoyment	309 (43)	0.4191	1.5	0.3852	1.5	1.0–2.0	4
	Amateur	52 (7)	0.0888	1.0				
	Professional	39 (5)	0.4818	1.6				

Column 4 presents the regression coefficients (β) for each of the categories of the included indicators, and column 5 lists the ORs. The categories with dark gray highlighting fulfilled the criteria for inclusion (β: 0.4 or OR: 1.5) in the index, those with light gray highlighting did not and were combined as shown in column 6 (combinations). Columns 7 and 8 show the ORs and corresponding 95% CI, respectively. Column 9 shows the weights (β for combinations x 10) assigned to these specific category indicators that made to the index.
β, regression coefficient; OR, odds ratio; CIs, confidence intervals.

Table 3. Linear regression parameters for cognitive ability and measures of everyday functioning*

Outcome	Study entry			Last follow-up		
	β	95% CI	**t-statistic	β	95% CI	t-statistic
B-CAM	0.19	0.14 to 0.23	8.0	0.13	0.09 to 0.18	5.8
PDQ	−0.39	−0.58 to −0.19	−4.0	−0.40	−0.5 to −0.2	−4.2
SPS	0.09	0.008 to 0.18	2.2	0.15	0.05 to 0.24	3.2

*Adjusted for age and sex.
**Effect size.
B-CAM is Brief Cognitive Ability Measure; higher scores are better, PDQ is Perceived Deficits Questionnaire; higher scores are worse, and SPS is Stanford Presenteeism Scale; higher scores are better; *β, regression coefficient.*

et al., 2012). These activities form the backbone of the principle of neuroplasticity (i.e., the ability of the human brain to adapt according to environmental stimuli or even after experiencing neurological damage) (Bosch et al., 2010; Wolf et al., 2006) in the aging populations. One of the unique features of this study is the demonstration of the relative

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benefit of engaging in specific cognitively stimulating life experiences for those living with HIV. A recent white paper on cognitive reserve highlights the need for such measures to improve upon the current summary approach (Stern et al., 2018). To our knowledge, the present study was the first attempt to tease out the relative contributions of specific life experiences of people with HIV on cognitive performance.

This study showed that cognitively stimulating activities such as visual and performance arts (any level of engagement), professional/amateur music, complex video gaming and competitive games, travel outside North America, and professional sports were associated higher cognitive functioning in people with HIV. Conceptually, cognitive reserve is believed to be a dynamic entity that can be enhanced through engagement in cognitively stimulating activities across the lifespan (Stern et al., 2018). Our work suggests that those who did not have the opportunity to acquire a high level of education could benefit from recreational activities, especially visual arts and performance arts as even when these activities were done for personal enjoyment, they were associated with higher cognitive functioning in this data set.

Socioeconomic status is seen as a contributor to cognitive reserve (Jefferson et al., 2011). Our findings showed extensive travel seems to have a cognitively nurturing effect, but it may not be a pragmatic option to boost reserve, given the expense involved. That said, the correlation between travel and other indicators of high socioeconomic status (education and occupation) was only 0.29 (see Supplementary Table 1), considered weak under the assumption that they are part of the same latent construct. It is likely that income may correlate strongly with travel and may also be a gateway to healthier lifestyle and behavior including access to cognitively stimulating activities including participation in reading clubs, art, etc., which could potentially build cognitive reserve (Cadar et al., 2018). Keeping this mind, it might be advisable that lifestyle interventions should target individuals who are socioeconomically disadvantaged as they might be particularly vulnerable to cognitive deficits caused by poor health behaviors and reserve-building activities. Future studies should also explore whether there are any cognitively stimulating activities that might be less influenced by socioeconomic status.

The CRI-HIV was based on a formative measurement model as various indicators (such as education, occupation, and lifestyle pursuits) form the construct of cognitive reserve. The direction of the relationship is from the items to the construct in a formative model. This is in contrast to reflective models where the construct is a feature of the person and is reflected in many different factors, measured and unmeasured (Edwards & Bagozzi, 2000). This index can be applied in research settings to adjust for the effect of multiple indicators such as education, occupation, and other cognitively engaging pursuits in a parsimonious manner. This might be particularly useful in clinical trials, e.g. of cognitive training or rehabilitation programs, as participants may respond to interventions based on their cognitive reserve. The index also avoids the statistical challenges (interpretation, collinearity, reduced power) associated with the common practice of accounting for the effects of each indicator individually (Arbogast & Ray, 2011; Biondi-Zoccai et al., 2011). Moreover, the index may aid clinical interpretation of the scores from neuropsychological tests.

A variety of cognitive reserve indices and questionnaires have been developed among diverse populations (Leon et al., 2014; Nucci et al., 2012; Sobral et al., 2014; Valenzuela & Sachdev, 2007). Overall, these measures vary in the type of cognitively engaging pursuits covered, their number, frequency, and timeframe. The CRI-HIV is to date the only index based on a scoring algorithm which takes impact weights, of each contributing indicator, into consideration to quantify cognitive reserve in HIV.

Employment status may fluctuate during the lifetime of an individual (Vance, Cody, Yoo-Jeong, & Nicholson, 2015). Therefore, participants in this study were asked to choose their level of engagement in a job based on their longest job instead of their current or last job. This study showed a relationship between the CRI-HIV scores and work productivity in HIV. Work productivity has not been extensively studied in HIV. Most studies focus on employment status and its relationship with neurocognitive abilities and everyday functioning among people living with HIV and have suggested that employment may be a way of preserving cognition (Blackstone et al., 2012; Vance et al., 2016). The present study found that higher cognitive reserve was associated with higher work productivity in people with HIV who had a paid job (n = 443).

Social support was not incorporated into the CRI-HIV as the association between B-CAM and the social resources (Arbogast & Ray, 2011) variables available in this study was weak. Concordant with this finding, a 2018 meta-analysis (n = 30,037) also revealed a weak association between social network and measures of cognitive performance ($r = 0.072$) (Isobel et al., 2018) in healthy older adults. Although bilingualism has been proposed to foster cognitive reserve, bi-or- plurilingualism did not contribute to the index in our sample. There are mixed findings from studies examining the relationship between bilingualism and cognitive reserve among people with Alzheimer's disease (Calvo, García, Manoiloff, & Ibáñez, 2015). The disparity across studies could have arisen due to the differences in the paths to plurilingualism (voluntary learning versus necessity), sampling procedures, and outcome measures used to investigate this area (Valian, 2015).

It is important to underline that the evidence for the cognitive reserve hypothesis is mostly observational: causal evidence for its potential protective effect on cognition is needed. Clinical trials have shown that interventions, e.g., a 12-week cognitive music training (N = 35) (Biasutti & Mangiacotti, 2018) or a 14-week "productive engagement" in learning digital photography alone or in combination with learning to quilt (N = 259) (Park et al., 2014) rendered benefits to specific cognitive processes (assessed using neuropsychological tests) among older adults. Rigorous randomized controlled trials of the contributors to cognitive

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reserve are needed to strongly recommend interventions that can promote cognitive performance in HIV. While awaiting such evidence, it seems worthwhile to encourage participation in cognitively stimulating activities as these are unlikely to do harm.

Limitations

All longitudinal observational studies have limitations based on the constitution of the cohort and losses to follow-up. We have previously published on the potential for selection bias in this cohort owing to the selective exclusion of those people with HIV who were too busy to enter owing to work responsibilities (Nancy E. Mayo, Brouillette, & Fellows, 2018). This group also reported fewer cognitive difficulties. Thus, our cohort includes people with a greater degree of cognitive challenge. We also did not have follow-up data on 73 participants (~8%), but those included in the analyses were similar to the full cohort (see Table 1).

Our choice of indicators was limited to the ones available in the data set. For example, engagement in learning activities post-formal education was not captured. Also, we did not have data on IQ available to include in the CRI- HIV, although it is traditionally considered in the mix of indicators of cognitive reserve. Cognitive reserve and IQ could be correlated, but they also seem to be distinct concepts. Nucci and colleagues excluded IQ from their index of cognitive reserve and suggested that IQ relates to intellectual performance, whereas cognitive reserve is based on an accumulation of resources acquired through a lifetime of cognitively engaging pursuits (Nucci et al., 2012). Other scales and questionnaires of cognitive reserve in non-HIV populations also do not include IQ (Leon et al., 2014; Sobral et al., 2014; Valenzuela & Sachdev, 2007).

All the indicators of cognitive reserve could have been affected by recall (Sackett, 1979), mood, and social desirability. While it is always possible to conduct reliability tests on data fields in questionnaires, the content queried is part of the person's life course and is likely as reliable as any other personal sociodemographic information collected. We did not verify the veracity of the information provided.

Also, everyday functioning was captured using self-report measures, which can be inaccurate (Blackstone et al., 2012). Proxy reporting of cognitive difficulties was not done nor was work productivity employer confirmed. Such data would involve additional ethics considerations and were beyond the scope of the cohort study.

In this work, the criteria used for inclusion of indicators in the CRI-HIV, i.e., $\beta = 0.4$ and OR = 1.5, were data driven and not based on any precedent or theory. The threshold was chosen to allow every indicator to have the same criterion to enter the index regardless of the degree of statistical significance associated with the regression parameter. The measure of cognitive ability (B-CAM) employed in this study did not have any published cutoff points for discrimination between high and low cognitive performance. Instead, the highest quartile was used to define people who are likely to have a high level of cognitive performance. This approach facilitated the estimation of regression weights and also ensured we had sufficient numbers for stable estimates.

CONCLUSION

This study documented the development of an index of cognitive reserve in older people living with well-controlled HIV infection. The CRI-HIV was associated with cognitive performance and measures of everyday functioning at study entry and also predicted these outcomes at the last follow-up visit. The index developed here might also apply to clinical groups other than people living with HIV; further work would be needed to test its generalizability. The index can serve as an efficient research tool to quantify and account for the effect of cognitive reserve. Lifestyle-modifying intervention strategies should integrate avenues for 'reserve-building' pursuits, especially for those who may not have had the opportunity to acquire extensive education or achieve high occupational complexity. Such reserve-building strategies need to be tested in randomized trials, to provide the causal evidence that remains scarce in work on cognitive reserve.

SUPPLEMENTARY MATERIAL

To view supplementary material for this article, please visit https://doi.org/10.1017/S1355617721000461

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CONFLICTS OF INTEREST

The authors have no conflicts of interest to declare.

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