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Cognitive and Physiologic Reserve Independently Relate to Superior Neurocognitive Abilities in Adults Aging With HIV

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Background: To investigate joint contributions of cognitive and physiologic reserve to neurocognitive SuperAging in older persons with HIV (PWH).

Methods: Participants included 396 older PWH (age range: 50–69 years) who completed cross-sectional neuropsychological and neuromedical evaluations. Using published criteria, participants exhibiting global neurocognition within normative expectations of healthy 25-year-olds were classified as SuperAgers (SA; n = 57). Cognitively normal (CN; n = 172) and impaired (n = 167) participants were classified with chronological age-based norms. Cognitive reserve was operationalized with an estimate of premorbid verbal intelligence, and physiologic reserve was operationalized with a cumulative index of 39 general and HIV-specific health variables. Analysis of variance with confirmatory multinomial logistic regression examined linear and quadratic effects of cognitive and physiologic reserve on SA status, adjusting for chronological age, depression, and race/ethnicity.

Results: Univariably, SA exhibited significantly higher cognitive and physiologic reserve compared with CN and cognitively impaired (ds ≥ 0.38, ps < 0.05). Both reserve factors independently predicted SA status in multinomial logistic regression; higher physiologic reserve predicted linear increases in odds of SA, and higher cognitive reserve predicted a quadratic "J-shaped" change in odds of SA compared with CN (ie, odds of SA > CN only above 35th percentile of cognitive reserve).

Conclusions: Each reserve factor uniquely related to SA status, which supports the construct validity of our SA criteria and suggests cognitive and physiologic reserve reflect nonoverlapping pathways of neuroprotection in HIV. Incorporation of proxy markers of reserve in clinical practice may improve characterization of age-related cognitive risk and resilience among older PWH, even among PWH without overt neurocognitive impairment.

Key Words: SuperAging, HIV-associated neurocognitive disorder, cognitive reserve, physiologic reserve, comorbidity burden, cognitive aging

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INTRODUCTION

The longevity of persons with HIV (PWH) taking effective antiretroviral therapy (ART) is now approaching that of the general population. Older PWH, however, are at enhanced risk for premature and accelerated development of geriatric syndromes, including neurocognitive impairment and frailty.[1] With an estimated half of PWH in the United States aged 50 and older,[2] elucidating mechanisms that support healthy neurocognitive aging in older PWH is paramount for addressing their complex neuromedical needs.[3,4]

Recent studies in adults without HIV have identified a subgroup of elders with "youthful" neurocognitive abilities resilient to age-related neurocognitive decline, termed cognitive "SuperAgers" (SA).[5] Compared with cognitively average (but non-Super) peers, SA exhibit less Alzheimer-related neuropathology and greater brain integrity, neuroimmune function, and psychological well-being.[6] We recently characterized a group of older (50 years and older) PWH with global neurocognition akin to that of a healthy 25-year-old,[7] thereby extending the SuperAging literature into chronic illness. Our initial estimates suggest ~17% of older PWH meet SuperAging criteria, and these individuals report better daily functioning and quality of life than their cognitively average counterparts.

Cognitive reserve theory posits that the deleterious effects of neuropathology (eg, neuronal loss due to aging and HIV) on neurocognitive decline can be mitigated by adaptive

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brain processes that preserve neurocognition through efficient neural firing and compensatory recruitment of additional neural networks.[8–10] Although it is difficult to directly measure these neural mechanisms in clinical settings, cognitive reserve is often measured with sociobehavioral proxies that are expected to contribute to neural complexity.[10] Higher single-word reading performance, which indicates higher premorbid verbal intelligence, is a cognitive reserve proxy that mitigates the effect of neuropathology on neurocognition in middle-to-late adulthood[11,12] and predicts better cross-sectional[13–15] and longitudinal neurocognition[16] in older PWH.

Similar to cognitive reserve, physiologic reserve is an indicator of resilience that describes the capacity to withstand biological stress and maintain homeostasis across multiple organ systems.[17] Aging and chronic illness can diminish biological resilience such that health deficits accumulate, and the phenotypic expression of depleted physiologic reserve is often referred to as frailty.[17,18] PWH are particularly susceptible to physiologic damage, as evidenced by higher rates of age-related comorbid conditions than age-matched controls and similar rates to that of an older population.[19,20] However, the rates at which individuals accumulate health deficits vary significantly,[18] and composite indices of health deficits that capture this variability predict neurocognition and longevity.[21–23]

Although cognitive and physiologic reserve putatively facilitate the preservation of neurocognition with advancing age, the convergent validity of proxy markers of cognitive and physiologic reserve with elite neurocognitive aging has not been examined in HIV disease. Thus, this study jointly modeled linear and nonlinear associations of cognitive and physiologic reserve with SA status in a multisite, national cohort of older PWH.

METHODS

Participants

Participants included 396 PWH enrolled in the CNS HIV Antiretroviral Therapy Effects Research (CHARTER) study[24] from 2003 to 2018. CHARTER is composed of 6 participating academic medical centers: Johns Hopkins University (Baltimore, n = 58); Icahn School of Medicine at Mount Sinai (New York, NY, n = 90); University of California at San Diego (San Diego, CA, n = 60); University of Texas Medical Branch (Galveston, TX, n = 83); University of Washington (Seattle, WA, n = 42); and Washington University (St. Louis, MO, n = 63). Inclusionary criteria were aged 50 years or older and completion of a cross-sectional blood draw, neuromedical examination, and neurobehavioral evaluation composed of neuropsychological testing and self-report questionnaires. Participants were excluded from analysis on the basis of severe or complex developmental (eg, severe learning disability), psychiatric (eg, psychosis), neuromedical (eg, epilepsy), or substance use (eg, positive toxicology screen) histories that confounded the interpretation of neuropsychological test data and its association with HIV disease, as previously described.[24,25] CHARTER study procedures were approved by local Institutional Review Boards, and all participants provided written informed consent.

Neuropsychological Evaluation and SuperAging Classification

Neuropsychological testing assessed domains most often affected in HIV: verbal fluency, executive functioning, processing speed, learning, delayed recall, attention/working memory, and motor skills.[24,26] To determine the extent to which test performance in older PWH deviated from "youthful" performance levels, individual test scores were first compared in reference with the normative range of performance for HIV-seronegative 25-year-olds[7] while still adjusting for the known demographic influences of sex, education, and race/ethnicity on test performance.[27–29] Using our published criteria for SuperAging in PWH,[7] participants were classified as SA if their global neurocognition, reflecting average level of performance across the entire test battery, was within normative expectations for the healthy 25-year-old sample. In addition to global "youthful" neurocognition, SA status also required the absence of chronological age-corrected impairment for any individual domains. Individuals not classified as SA were subsequently classified as cognitively normal (CN) or impaired (CI) based on the standard, chronological age-corrected deficit score procedure for classifying global neurocognitive impairment in HIV.[26,30]

Cognitive Reserve

Cognitive reserve was measured using standardized scores from the Reading subtest of the Wide Range Achievement Test, version 4 (WRAT4),[31] a validated proxy for cognitive reserve that is robust to neurocognitive decline in older HIV-seronegative adults and PWH.[12,32,33] The WRAT4 is considered a more direct estimate of educational attainment or quality than total years of education completed,[8] particularly in racially diverse and marginalized older adult populations.[34] For analysis, we compared cognitive reserve measured with the WRAT4 standard scores and with race/ethnicity-adjusted WRAT4 scores to partial out the influence of racial/ethnic disparities in educational quality that cannot be attributed to premorbid intelligence.[35,36]

Physiologic Reserve Through Neuromedical Evaluation

Neuromedical examination assessed for clinical deficits relevant to HIV and geriatric health and physiologic reserve was quantified based on validated methods for constructing a frailty index.[17,18,37] For this study, the cumulative physiologic reserve variable was composed of 39 unique variables encompassing a range of physiologic systems, including routine clinical laboratory measures (eg, glucose and lipids), medical comorbidities (eg, hepatitis C coinfection and diabetes), and indicators of HIV disease severity (see Table 1). Each variable was dichotomized as normal or deficient based on previous studies that established the convergent

TABLE 1. Physiologic Reserve Index Criteria

Variable	Deficit Criteria
Clinical measurements	
Abnormal BMI	>25 or <18 kg/m^2
Low white blood cell count	<4000 cells/μL
Abnormal MCHC	Male: <27.8 or >33.8; female: <26.9 or >33.3
Abnormal BUN	<8 mg/dL or >23 mg/dL
Abnormal creatinine	<0.6 mg/dL or >1.2 mg/dL
Abnormal calcium	<9.2 mg/dL or >10.8 mg/dL
Abnormal chloride	<96 mEq/L or >106 mEq/L
Abnormal total protein (serum)	<6 mg or >7.8 mg
Low albumin (serum)	<3.5 mg
Elevated fibrinogen	>3.25
Low eGFR	<60
Low hemoglobin	Male: <12 μmol/L; female: <10 μmol/L
Elevated AST	>31 U/L
Elevated ALT	>31 U/L
Abnormal ALP	<38 U/L or >126 U/L
Abnormal potassium	<3.5 or >5.3 mEq/L
Elevated total bilirubin	>1.1 mg/dL
Elevated triglycerides	≥150 mg/dL
Elevated total cholesterol	>200 mg/dL
Low HDL cholesterol	Male: <40 mg/dL; female: <50 mg/dL
Elevated glucose	>200 mg/dL
Weight loss	>10 lbs in past year
Low platelets	<150 billion/L
Comorbidities	
HCV	Positive
Diabetes mellitus	Positive
COPD	Positive
Malignancy	Positive
Myocardial infarction	Positive
Renal disease	Positive
Hypertension	Positive or >130 mm Hg systolic or > 85 mm Hg diastolic
Hyperlipidemia	Positive
Cerebrovascular accident	Positive
Sensory neuropathy	Positive
Distal neuropathic pain	Positive
Smoking (ever)	Positive
HIV-specific	
Low current CD4	<500 cells/μL
Nadir CD4	<200 cells/μL
Detectable plasma HIV RNA	>40 copies/mL
Duration of disease	>10 yrs

ALP, alkaline phosphatase; ALT, alanine transaminase; AST, aspartate transaminase; BMI, body mass index; BUN, blood urea nitrogen; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; HCV, hepatitis C virus; HDL, high-density lipoprotein; MCHC, mean corpuscular hemoglobin concentration.

validity of frailty indices as predictors of longevity and neurocognitive impairment in PWH.[21,23] This study reverse coded each health variable (normal = "1"; deficit = "0") such that higher scores reflected higher levels of physiologic reserve, consistent with the conceptual model of physiologic reserve as a neuroprotective factor. Physiologic reserve scores were constructed by dividing the total sum of normal health variables by the total number of available variables, with a possible range of 0 (all 39 deficits) to 1 (no deficits). For analyses that required dichotomizing index scores into "low" or "high" physiologic reserve, we used a cut point of 0.75 (<0.75 = low; ≥0.75 = high) that has been validated as a predictor of mortality.[38] In accordance with standard frailty index guidelines,[37] we excluded variables that had >5% missing data (ie, phosphorous, LDL cholesterol, and fasting insulin) or had <1% of participants meeting deficit criteria (ie, sodium, peripheral vascular disease, and congestive heart failure).

Psychiatric Evaluation

A psychiatric evaluation ascertained DSM-IV diagnoses of current and lifetime mood and substance use disorders through the structured Composite International Diagnostic Interview.[39] Current mood symptoms were assessed with the Beck Depression Inventory-II (BDI-II).[40] Cognitive, affective, and somatic BDI-II subscales were computed based on a prior factor analysis in the CHARTER cohort.[41]

Statistical Analyses

Neurocognitive status differences on demographic, psychiatric, HIV disease, cognitive reserve, and physiologic reserve variables were examined using analysis of variance, Wilcoxon/Kruskal–Wallis tests, and χ^2 statistics as appropriate. To further characterize the association between neurocognitive status and physiologic reserve, odds ratio (OR) estimates compared SA with CN and CI on the prevalence of each individual health deficit in the physiologic reserve index. To confirm univariable associations and determine independent and combined effects of cognitive and physiologic reserve on neurocognitive status, multinomial logistic regression modeled neurocognitive status as a function of linear and quadratic terms for cognitive and physiologic reserve, as well as the interaction of linear terms. Variables were screened for inclusion as covariates at a $P < 0.10$ association with the primary dependent variable of neurocognitive status. The Johnson-Neyman technique[42,43] probed significant quadratic or interaction effects by identifying the specific range of the moderator at which the effect of the predictor on neurocognitive status reached statistical significance. The results were considered statistically significant at $P < 0.05$. All analyses were conducted in R (version 3.5.0).

DATA AVAILABILITY STATEMENT

Anonymized, deidentified derived data values will be shared on request from any qualified investigator. Data requests should be submitted at https://nntc.org/content/requests.

RESULTS

Study Sample Characteristics

The overall study sample was 81% male with a mean age of 53.5 years (range: 50–69) and mean education of 13.3 years. Regarding race/ethnicity, the overall sample was 50% non-Hispanic White, 39% non-Hispanic Black, 9% Hispanic, and 2% other. Demographic, psychiatric, and HIV disease characteristics by neurocognitive status are presented in Table 2. SA (n = 57), CN (n = 172), and CI (n = 167) groups were comparable with respect to sex, race/ethnicity, and years of education. The SA group was significantly younger than the CN and CI groups, although this only translated to an average difference of 1.6 and 2 years, respectively. Groups did not differ on prevalence of Major Depressive Disorder (both lifetime and last 30 days) or any substance use disorder (lifetime). An omnibus group difference in BDI-II scores approached significance, with SA exhibiting lower median BDI-II scores vs. CI (7 vs. 12, $P = 0.027$). This finding was driven by differences in somatic ($P = 0.042$) and affective ($P = 0.024$) symptoms, but not cognitive ($P = 0.358$) symptoms of depression. HIV disease characteristics did not significantly differ across groups. On average, participants reported a duration of 14.1 years with HIV disease. The full sample displayed evidence of ART-induced immune reconstitution, as indicated by higher current CD4 counts (median = 485 cells/mm^3) compared with nadir CD4 counts (median = 124 cells/mm^3) and active ART use (84%). Rates of viral suppression (ie, undetectable plasma HIV RNA) ranged from 57% (CI) to 63% (SA), comparable with the full CHARTER cohort and data collection period (2003–2018).

TABLE 2. Study Sample Characteristics by Neurocognitive Status

	CI (n = 167)	CN (n = 172)	SA (n = 57)	*P*
Demographics				
Age (yrs), mean (SD)	53.6 (3.6)	54.0 (4.3)	52.0 (3.2)	0.004
Sex (male), n (%)	130 (77.8%)	143 (83.1%)	48 (84.2%)	0.374
Education (yrs), mean (SD)	13.7 (2.6)	13.2 (2.6)	13.0 (2.9)	0.108
Race/ethnicity				0.131
Non-Hispanic White, n (%)	92 (55.1%)	75 (47.1%)	25 (43.9%)	
Black, n (%)	53 (31.8%)	81 (43.6%)	28 (49.1%)	
Hispanic, n (%)	20 (12.0%)	13 (7.6%)	3 (5.3%)	
Other, n (%)	2 (1.2%)	3 (1.7%)	1 (1.8%)	
Psychiatric				
Lifetime major depressive disorder, n (%)	83 (50.6%)	103 (60.2%)	27 (47.4%)	0.108
Current major depressive disorder, n (%)	24 (14.7%)	26 (15.3%)	5 (8.8%)	0.415
BDI-II, median [IQR]	12 [5, 22]	9 [4, 20]	7.5 [4, 14]	0.085
Cognitive, median [IQR]	2.5 [0, 8]	2 [0, 7]	2 [0, 4]	0.358
Affective, median [IQR]	2 [0, 4]	1 [0, 4]	1 [0, 2.5]	0.024
Somatic, median [IQR]	7 [3, 10]	6 [3, 9]	4 [2, 7.5]	0.042
Lifetime substance use disorder, n (%)	108 (65.9%)	124 (72.5%)	44 (77.2%)	0.194
HIV disease characteristics				
AIDS diagnosis, n (%)	120 (71.9%)	119 (69.6%)	36 (63.2%)	0.476
Estimated yr of disease, median [IQR]	15 [10, 19]	13 [9, 19]	15 [8, 18]	0.618
Nadir CD4 count, median [IQR]	106 [29, 210]	157 [34, 275]	150 [21, 240]	0.333
Current CD4 count, median [IQR]	505 [353, 723]	464 [331, 645]	494 [298, 749]	0.313
On ART, n (%)	140 (83.8%)	143 (84.1%)	47 (82.5%)	0.956
Undetectable plasma virus, n (%)	91 (57.2%)	101 (62.0%)	34 (63.0%)	0.617
Reserve Factors				
Cognitive reserve (WRAT4), mean (SD)	94.8 (13.7)	96.2 (12.1)	100.0 (12.9)	0.029
Physiologic reserve, mean (SD)	0.69 (0.01)	0.69 (0.01)	0.73 (0.01)	0.027

Cognitive and Physiologic Reserve

Cognitive reserve (ie, WRAT4 reading standard scores) ranged from 70 to 131 (mean = 96, SD = 13.0) and physiologic reserve ranged from 0.39 to 0.90 (mean = 0.69, SD = 0.092). Cognitive and physiologic reserve exhibited a small, positive correlation that did not reach statistical significance ($r = 0.09$, $P = 0.085$). Figure 1 displays neurocognitive status group differences in cognitive (panel A) and physiologic reserve (panel B). Univariably, SA exhibited higher cognitive reserve scores vs. CI ($d = 0.41$, $P = 0.008$) and trended toward higher scores vs. CN ($d = 0.29$, $P = 0.056$). Conversely, cognitive reserve did not significantly differ between CN and CI ($d = 0.11$, $P = 0.293$). After adjusting for race/ethnicity, which univariably accounted for 24% of variance in WRAT4 standard scores ($P < 0.001$), the association between neurocognitive status and cognitive reserve strengthened. Specifically, SA exhibited higher cognitive reserve vs. both CI ($d = 0.64$, $P < 0.001$) and CN ($d = 0.39$, $P = 0.011$), and CN exhibited higher cognitive reserve vs. CI ($d = 0.25$, $P = 0.023$). Univariably, SA exhibited higher physiologic reserve vs. both CI and CN (both $ds = 0.39$, $ps = 0.012$), whereas physiologic reserve did not differ between CN and CI ($d = 0.00$, $P = 0.983$). This relationship between neurocognitive status and physiologic reserve was not altered after statistical adjustment for age, which did not correlate with physiologic reserve in the overall sample ($r = -0.04$, $P = 0.469$).

Figure 2 displays ORs comparing SA with CI (panel A) and CN (panel B) for each individual health deficit criterion that comprised the cumulative physiologic reserve index, and Table S1, Supplemental Digital Content, http://links.lww.com/QAI/B839, provides the prevalence of each health deficit by neurocognitive status. Consistent with the continuous physiologic reserve score analyses, SA were less than half as likely to be classified as low physiologic reserve (<0.75) vs. CI {OR = 0.46 [95% confidence interval (CI): 0.24 to 0.86], $P = 0.015$} and CN [OR = 0.43 (95% CI: 0.23 to 0.80),

$P = 0.008$]. Compared with CI, SA had lower rates for 77% (30 of 39; OR range: 0.14–3.28) of the individual health deficits examined; however, abnormal total protein was the only factor to reach statistical significance [OR = 0.48 (95% CI: 0.25 to 0.90), $P = 0.020$]. Compared with CN, SA had lower rates for 79% (31 of 39; OR range: 0.18–2.82) of the individual health deficits examined. Distal neuropathic pain was the only factor to reach statistical significance [OR = 0.50 (95% CI: 0.26 to 0.98), $P = 0.039$].

Multinomial Logistic Regression

Multinomial logistic regression modeled linear, quadratic, and interactive effects of cognitive and physiologic reserve on neurocognitive status, controlling for age, race/ethnicity, and BDI-II. The interaction between cognitive and physiologic reserve on neurocognitive status was not significant ($P = 0.981$), and interactions were removed from the model. Cognitive reserve was linearly associated with odds of SA vs. CI (beta = 0.93, OR = 2.53, $P < 0.001$) such that a one SD increase in cognitive reserve corresponded to a 153% increase in odds of SA vs. CI. This effect was not moderated by a quadratic association ($P = 0.797$) and was uniform across the distribution of cognitive reserve. Cognitive reserve exhibited significant linear and quadratic associations with odds of SA vs. CN [linear (conditional on mean cognitive reserve): beta = 0.84, OR = 2.32, $P < 0.001$; quadratic: beta = 0.38, ΔOR = 2.14, $P = 0.033$]. Specifically, higher cognitive reserve related to higher odds of SA vs. CN, and this positive slope increased by 114% for every additional SD increase in cognitive reserve. Using the Johnson-Neyman technique to determine the region of significance, higher cognitive reserve significantly related to higher odds of SA vs. CN only above the 35th percentile of its distribution (ie, WRAT4 > 91.9). Cognitive reserve also exhibited significant linear and quadratic associations with odds of CN vs. CI [linear (conditional on mean cognitive reserve): beta = 0.30, OR = 1.35, P = 0.029; quadratic: beta=−0.24, ΔOR = 0.62, $P = 0.030$]. Higher cognitive reserve initially related to higher odds of CN vs. CI; however, this slope decreased by 38% for every additional SD increase in cognitive reserve. Region of significance analyses indicated that higher cognitive reserve significantly related to higher odds of CN vs. CI only below the 52nd percentile of its distribution (ie, WRAT4 < 96.4). Figure 3 illustrates these quadratic effects by plotting changes in probability of classification in each neurocognitive group across the distribution of cognitive reserve.

Quadratic effects of physiologic reserve ($P = 0.554$) failed to reach statistical significance and were removed from the model. Consistent with univariable analyses, physiologic reserve was linearly associated with neurocognitive status such that a one SD increase in physiologic reserve corresponded to a 44%–45% increase in odds of SA (vs. CI: beta = 0.37, OR = 1.45, $P = 0.042$; vs. CN: beta = 0.36, OR = 1.44, $P = 0.043$). Physiologic reserve did not significantly relate to odds of CN vs. CI (beta =−0.01, OR = 0.99, $P = 0.939$).

Regarding covariates, older age (beta=−0.18, OR = 0.83, $P = 0.001$), higher BDI-II scores (beta = −0.04, OR = 0.96, $P = 0.026$), and non-Hispanic White race/ethnicity (vs. non-Hispanic Black; beta = −1.54, OR = 0.22, $P < 0.001$) related to lower odds of SA vs. CI. Older age also related to lower odds of SA vs. CN (beta = −0.21, OR = 0.81, $P < 0.001$).

DISCUSSION

Neurocognitive SuperAging provides a natural framework for studying resilience against the multifaceted stressors of aging with HIV and allows for examination of mechanisms of neuroprotection or risk across the full spectrum of neurocognitive performance. In a geographically and psychosocially diverse cohort of older PWH, this study observed higher estimated premorbid verbal intelligence and less accumulation of health deficits in SA compared with both CI and CN, indicative of higher cognitive and physiologic reserve. Importantly, cognitive and physiologic reserve exhibited complimentary associations with SA status in multivariable analysis and were statistically robust to other biopsychosocial covariates, specifically chronological age, depressive symptoms, and race/ethnicity.

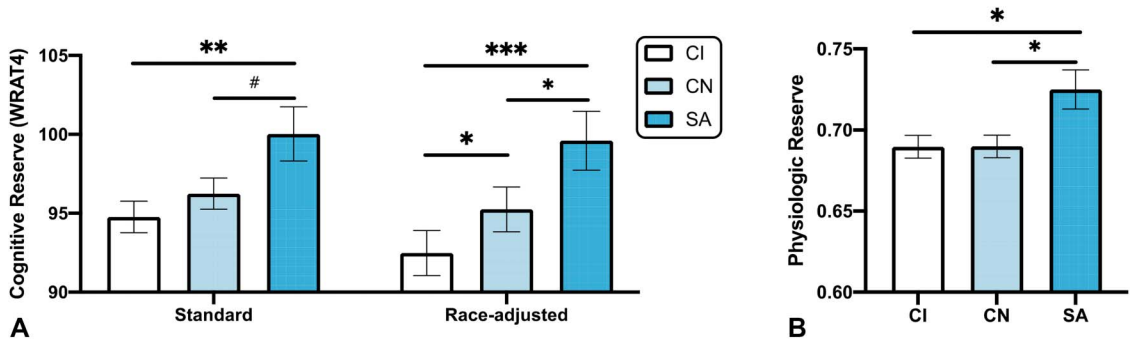

FIGURE 1. SA exhibit higher cognitive and physiologic reserve compared with non-SA. A, Raw and race/ethnicity-adjusted cognitive reserve (ie, WRAT4 reading scores) by neurocognitive status. SA univariably exhibit higher cognitive reserve compared with CI and CN individuals, and this relationship strengthens after adjusting for the influence of race/ethnicity on WRAT4 reading performance. B, SA exhibit higher levels of physiologic reserve, or fewer health deficits, compared with CI and CN, whereas CI and CN do not differ on physiologic reserve. # = $P < 0.10$; * = $P < 0.05$; ** = $P < 0.01$; *** = $P < 0.001$. full color online

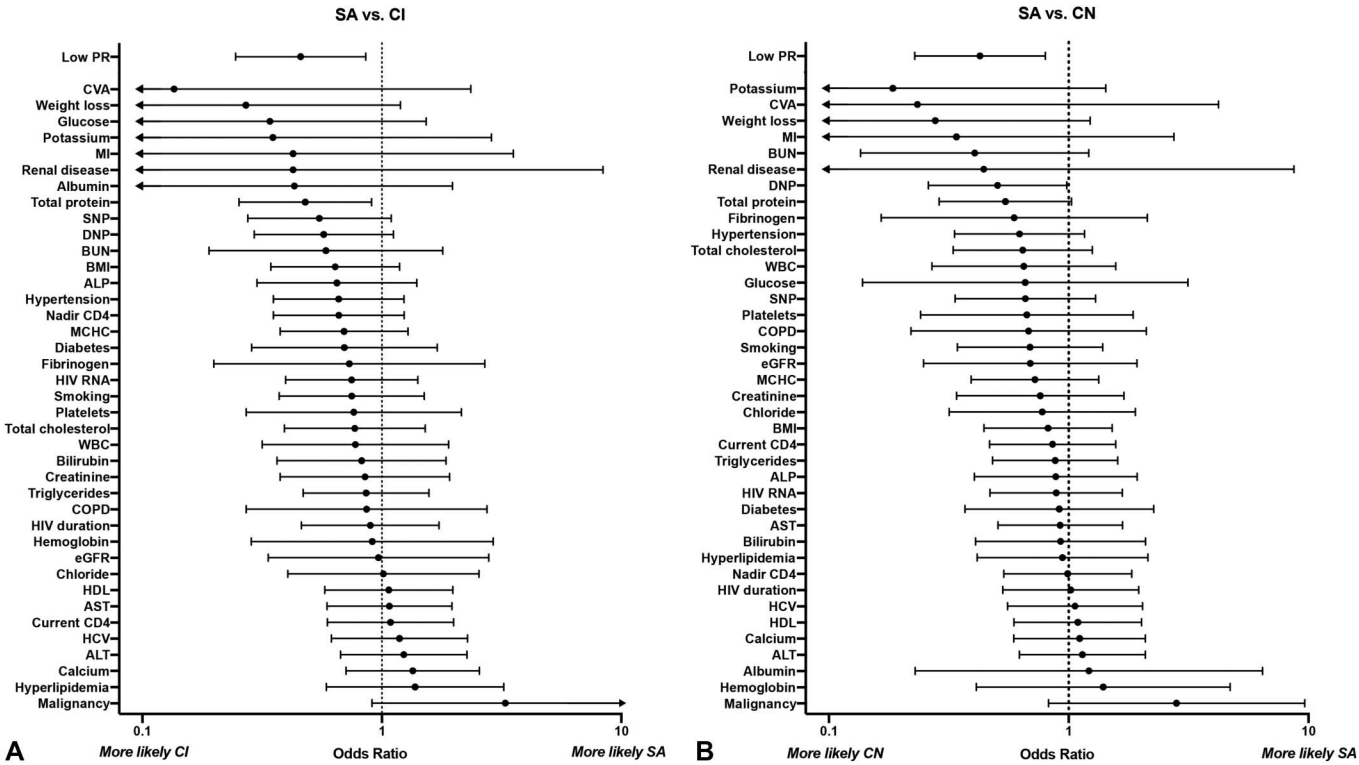

FIGURE 2. Association of physiologic reserve index components and SuperAging. Forest plot displaying the magnitude and precision (95% confidence intervals) of OR effect size estimates reflecting the relationship between SuperAger (SA) status and individual health deficits comprising the cumulative PR index. SA were less likely to meet criteria for most of the individual index components compared with (CI; A) and (CN; B) individuals; however, almost all ORs reflecting these individual health deficit differences failed to reach statistical significance because of poor precision. Conversely, the OR reflecting the relationship between SA and the cumulative PR index (dichotomized as low vs. high PR for purposes of analysis) exhibited sufficient magnitude and precision to reach statistical significance (95% confidence interval does not contain an OR of 1). The prevalence of individual health deficits by neurocognitive status is provided in Table S1, Supplemental Digital Content, http://links.lww.com/QAI/B839. ALP, alkaline phosphatase; ALT, alanine transaminase; AST, aspartate transaminase; BMI, body mass index; BUN, blood urea nitrogen; COPD, chronic obstructive pulmonary disease; CVA, cerebrovascular accident; DNP, distal neuropathic pain; eGFR, estimated glomerular filtration rate; HCV, hepatitis C virus; HDL, high-density lipoprotein; MCHC, mean corpuscular hemoglobin concentration; MI, myocardial infarction; PR, physiologic reserve; SNP, sensory neuropathy; WBC, white blood cell.

Pairwise comparisons that adjusted for racial/ethnic differences in WRAT4 reading scores identified a step-wise pattern whereby each successive level of neurocognitive status corresponded to a small increase and medium-sized increase in cognitive reserve (ie, CI < CN < SA). In multinomial logistic regression, a more complex quadratic relationship between cognitive reserve and neurocognitive status emerged. Specifically, increases in cognitive reserve predicted greater odds of CN compared with CI only for the lower half of the cognitive reserve distribution, whereas increases in cognitive reserve best discriminated SA from CN only for the upper two-thirds of the cognitive reserve distribution. In other words, interindividual differences in cognitive reserve help differentiate SA from CN for a subsample that represents relatively higher levels of cognitive reserve, yet we do not observe the same association in a subsample that represents relatively lower levels of cognitive reserve. This converges with the notion that a deficit-based approach to quantifying neurocognitive predictors (eg, low IQ vs. "normal" IQ) lacks the precision to detect differences between older adults with "normal" age-related neurocognition compared with those with superior neurocognition. Overall, this quadratic pattern adds important context to previous studies, including our initial documentation of SuperAging with HIV,[7] that have assumed a linear relationship between cognitive reserve and neurocognitive impairment. To further clarify the neurobiological mechanisms underpinning these results, future analyses will examine the extent to which cognitive reserve moderates/mediates the relationships of CNS biomarkers (eg, CSF inflammation and white matter integrity) with SuperAging in PWH.

Years of formal education, which is also a common proxy for cognitive reserve, did not differ by neurocognitive status. This may reflect 2 nonmutually exclusive possibilities. First, years of education may be a suboptimal indicator of cognitive reserve in our psychosocially and racially diverse cohort. A recent analysis demonstrated that years of formal education significantly mitigated the deleterious effects of white matter hyperintensities and cortical thinning on cognitive trajectories for older Whites, but not for Blacks or

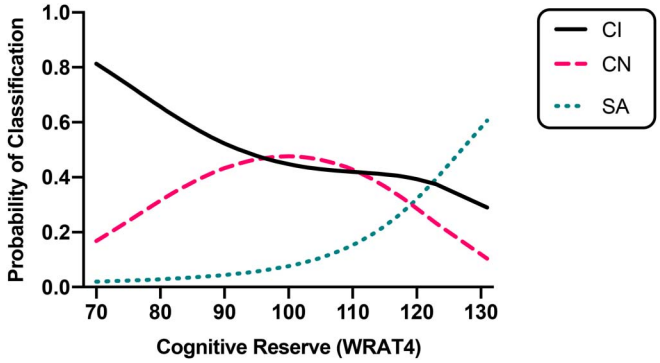

FIGURE 3. Quadratic associations between cognitive reserve and neurocognitive status. Cognitive reserve exhibited independent linear and quadratic effects on neurocognitive status in multinomial logistic regression analyses, accounting for age, depressive symptoms, race/ethnicity, and physiologic reserve. Higher cognitive reserve linearly increased odds of classification as SuperAger (SA) compared with CI (dotted line vs. solid line) across the full range of cognitive reserve. Higher cognitive reserve best discriminated SA from CN (dotted line vs. dashed line) among individuals with scores above the 35th percentile of cognitive reserve (WRAT4 $>$ 91.9). Conversely, higher cognitive reserve best discriminated CN from CI (dashed line vs. solid line) among individuals with scores below the 52nd percentile of cognitive reserve (WRAT4 $<$ 96.4). full color online

Hispanics.[36] Racial/ethnic minority older adults are more likely to have had less quality educational experiences and limited opportunities to pursue advanced education than Whites, and these structural disparities attenuate the specificity of neuropsychological test scores to brain structure and function.[34,36,44] Although accounting for reading level improves the predictive utility of neuropsychological tests, structural factors also contribute to racial/ethnic disparities in literacy.[34,35] Our data are consistent with this because adjusting for racial/ethnic differences in WRAT4 reading scores enhanced the specificity of the WRAT4 to SuperAging. A second explanation for the lack of neurocognitive status differences in years of education may be related to our neuropsychological norms. Specifically, the normative corrections for the effects of years of education on neuropsychological test performance (theoretically unrelated to premorbid ability) used in our neurocognitive status classifications may incidentally capture variance in cognitive reserve and thereby mask the effect of years of formal education in group comparisons.

Physiologic reserve significantly explained variance in neurocognitive group membership such that SA exhibited higher physiologic reserve compared with both CN and CI who did not differ in physiologic reserve. The psychometrically advantageous cumulative physiologic reserve index also exhibited greater statistical precision than most of the 39 individual health variables comprising the index, which aligns with previous work showing that a cumulative index approach outperforms any individual deficit in predicting mortality.[45] It is also noteworthy that physiologic reserve predicted SA status above and beyond chronological age given that previous studies report that markers of physiologic reserve outperform chronological age in predicting mortality and dementia. Our composite index of physiologic reserve was not correlated with age in our sample of PWH aged 50 or older, consistent with the observation that interindividual variability in health-related outcomes increases with advancing age,[5] including frailty index scores in PWH.[23] Taken together, physiologic reserve may more precisely measure "biological age" than chronological age and can be computed using routinely collected clinical record data.[46,47]

Several study limitations merit discussion. Although our cross-sectional analyses shed light on biopsychosocial mechanisms that may differentiate SA from CN and CI, examining longitudinal neurocognitive trajectories of SA with HIV and their convergence with cognitive and physiologic reserve is essential for confirming the stability of our SuperAging criteria and identifying the directionality of its associations with these reserve factors. Toward this end, we are actively collecting and analyzing longitudinal data from the CHARTER cohort. Notably, our study cohort age range of 50–69 years is younger than most aging study cohorts without HIV disease. Our data accordingly cannot be directly compared with the extant SuperAging literature in healthy older adults but rather should be interpreted in the context of the aging with HIV literature, in which 50 is commonly recognized as a medically advanced age.[48] Our data importantly integrate comprehensive neuropsychological phenotypes with clinically accessible markers of biopsychosocial reserve with relevance to aging with HIV, yet our data do not directly measure the underlying neurocircuitry and neuroimmune mechanisms implicated in neurocognitive aging and HIV. Future studies should incorporate neuroimaging and neuroimmune biomarkers to test the degree to which SA with HIV are "resistant" to the manifestation of neuropathology as opposed to "resilient" against the deleterious effects of neuropathology. A similar approach has been taken in studies on older HIV-seronegative cohorts,[49] with recent data showing that SA are more resistant to age-related tau pathology than CN individuals,[50] thereby providing further support for anti-tau interventions for optimization of cognitive health.

Our findings support the construct validity of SuperAging in HIV because the neurocognitively elite SA exhibited higher levels of cognitive and physiologic reserve compared with both CN and CI. Cognitive and physiologic reserve was not significantly correlated, and multivariable analysis identified unique contributions of each reserve factor to the prediction of SA status. This is suggestive of a two-pronged model of reserve whereby cognitive and physiologic reserve reflects nonoverlapping pathways of neuroprotection in PWH. Although research on SA is relatively new and has yet to directly translate to clinical practice, incorporation of proxy markers of reserve in clinical practice may help providers better characterize age-related cognitive risk and resilience among older PWH. From a preventative medicine perspective, individuals without overt neurocognitive deficits could still engage in interventions that promote neurocognitive resilience over normal neurocognitive aging. As these initial characterizations of neurocognitive SuperAging in PWH continue to expand, identifying malleable intervention

targets for increasing cognitive and physiologic reserve may yield clinical benefits for adults aging with HIV across the cognitive spectrum.

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