AIDS Behav (2014) 18:1186–1197
DOI 10.1007/s10461-014-0743-x

ORIGINAL PAPER

Successful Cognitive Aging and Health-Related Quality of Life in Younger and Older Adults Infected with HIV

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Published online: 18 March 2014

Abstract Neurocognitive impairments commonly occur and adversely impact everyday functioning in older adults infected with HIV, but little is known about successful cognitive aging (SCA) and its health-related quality of life (HRQoL) correlates. Seventy younger (≤40 years) and 107 older (≥50 years) HIV+ adults, as well as age-matched seronegative comparison groups of younger ($N = 48$) and older ($N = 77$) subjects completed a comprehensive battery of neuropsychological, psychiatric, medical, and HRQoL assessments. SCA was operationalized as the absence of both performance-based neurocognitive deficits and self-reported symptoms (SCA-ANDS) as determined by published normative standards. A stair-step decline in SCA-ANDS was observed in accordance with increasing age and HIV serostatus, with the lowest rates of SCA-ANDS found in the older HIV+ group (19 %). In both younger and older HIV+ adults, SCA-ANDS was strongly related to better mental HRQoL. HIV infection has additive adverse effects on SCA, which may play a unique role in mental well-being among HIV-infected persons across the lifespan.

Keywords Successful aging · Well-being · Neuropsychological assessment · AIDS-related dementia

Introduction

There has been a notable shift in the demographics of the HIV epidemic in recent years such that individuals over 50 make up more than one fourth of the US HIV/AIDS population and account for 15 % of new infections [1, 2]. Older HIV+ adults are at heightened risk for poor health outcomes, including immunovirological dysregulation [3], neural injury [4, 5], non-HIV-associated comorbidities (e.g., cardiovascular disease) [6], and mortality [1, 7]. Furthermore, high rates of neurocognitive disorders are also observed among older HIV+ adults [8]. Both age and HIV-infection are risk factors for cognitive decline, mild cognitive impairment, and dementia, with older HIV-infected adults at a three-fold risk for HIV-associated neurocognitive disorders (HAND) as compared to their younger counterparts [9–11]. Among older HIV-infected adults, deficits in episodic memory [11, 12] and executive functions (e.g., cognitive flexibility) are particularly common [13]. These neurocognitive declines, in addition to subjective cognitive symptoms, may be particularly detrimental to the real-world functioning of HIV-infected older adults, potentially interfering with antiretroviral non-adherence [14] and automobile driving capacity [15], perhaps as well as health-related quality of life (HRQoL) [16–18] and emotional well-being [19, 20].

Given the individual and public health impact neurocognitive impairment confers in older HIV-infected adults, there is a growing need to understand factors associated with successful cognitive aging (SCA). Indeed, there is an emergent interest in identifying factors associated with

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SCA [21], which has been defined as minimal (or absence of) objective neurocognitive impairment and subjective cognitive symptoms compared to "average" demographically similar adults. That is, SCA signifies that an individual is free from actual and perceived neurocognitive impairment [21–23]. When describing fears associated with aging, the loss of mental facilities and independence are commonly among older adults' chief concerns [24, 25]. Although there are inconsistencies in SCA studies of non-pathological older adults in terms of the age groups examined, operational definitions, and measures used to classify SCA, prevalence rates have been reported to be as high as 50 % [26]. Furthermore, among healthy older adults, there has been consistency in factors related to SCA, including cognitive reserve (e.g., education, intellectual ability), higher socioeconomic status [27], positive psychosocial factors (e.g., social engagement [28], wisdom [29], resilience [30, 31]), positive physical (e.g., exercise) and mental (e.g., cognitively challenging leisure activities) health behaviors [32, 33], as well as various clinical and biomedical predictors (e.g., genetic factors, such as absence of APOE-ε4, and freedom from psychiatric illness).

To date, however, there have been a limited number of studies specifically examining the prevalence, correlates, and clinical predictors of SCA in HIV. A study from our group showed that SCA is possible among adults aging with HIV, with approximately one-third (32 %) of HIV-infected adults with at least 5 years estimated duration of infection, who were on average 51 years old (standard deviation = 6.6), meeting criteria for SCA as defined by the absence of neurocognitive deficits and symptoms [23]. Speaking to the clinical relevance of SCA in HIV [23], that same study showed that SCA was associated with better mood, fewer declines in activities of daily living, higher levels of adherence to prescribed antiretroviral regimens, and greater confidence in dealing with healthcare providers. We are unaware of any other empirical studies that have specifically focused on SCA in HIV infection.

This is important because SCA might be a determinant of adaptive real-world functioning and well-being among persons living with HIV. The traditional approach to research on the aging HIV-infected brain has been centered on the pathology of neurocognitive impairment, which refers to deficits in two or more cognitive domains [34]. Thus under this system, individuals with impairment in only one cognitive domain (and on multiple other cognitive tests) is considered "neurocognitively normal" [35]. In deficit-focused studies, HAND—and especially executive dysfunction and psychomotor slowing—is uniquely associated with lower physical functioning, emotional well-being, social functioning, and general health perceptions [17]. However, the impact of SCA specifically on HRQoL in HIV is unknown. Recently, the National Institute of Health (NIH) Office of AIDS Research placed a priority of research programs aimed at identifying factors that could improve adaptive functioning and HRQoL in individuals aging with HIV [36]. One prior study of successful (non-cognitive) aging by our group [37] supports the notion that SCA might be an important predictor of HRQoL in HIV; two-thirds of older HIV-infected adults had high self-rated successful aging (i.e., "a holistic, multidimensional assessment of one's overall physical and mental health" p. e417), which did not vary by HIV disease severity. Higher self-rated (non-cognitive) successful aging in the HIV sample was related to better HRQoL (physical and mental health composite scores from the SF-36), lower perceived stress, and increased positive psychological traits, such as resilience, optimism, and personal mastery. Given these encouraging findings for non-cognitive successful aging, it is plausible that SCA specifically may be an important predictor of HRQoL in older HIV-infected adults.

Thus, the aim of the present manuscript was to identify the factors that are associated with the successful end of the neurocognitive continuum in HIV, rather than the presence of impairment. Deficit-focused approaches to cognitive functioning tend to ignore the factors that lead to the absence of cognitive difficulties; indeed, many individuals who are considered neurocognitively "normal" by way of the Frascati criteria for HAND actually demonstrate impairment in one neurocognitive domain (and often on multiple tests across domains). By focusing on the upper end of the neurocognitive spectrum, we can thus gain a clearer picture of the factors that are associated with neuropsychological health in older adults living with HIV. As previously stated, there is a NIH priority research area to better understand how to promote brain health in older adults, including those living with HIV infection [36]. Thus, the current study extends the very limited prior literature on SCA in HIV by investigating: (1) the prevalence of SCA in HIV-infected individuals as defined by an absence of neurocognitive deficits and symptoms (SCA-ANDS) in older adults as compared to younger HIV-infected persons, as well as older and younger seronegative comparison cohorts; (2) the clinical correlates of SCA-ANDS among both younger and older cohorts; and (3) the relationship of SCA-ANDS to mental and physical HRQoL. It was hypothesized that the prevalence of SCA-ANDS would be lower among both younger and older HIV+ participants compared to their age-matched HIV-negative counterparts. Furthermore, we expected that SCA-ANDS would be an independent predictor of HRQoL components in both the younger and older HIV+ cohorts, above and beyond other clinical and demographic factors.

Methods

Participants

Three hundred and two HIV+ and HIV− participants aged 25–40 and 50–69 were recruited into an NIMH-funded study on memory and aging at the University of California, San Diego (UCSD) HIV Neurobehavioral Research Program. Participants were recruited from community organizations, substance use recovery clinics, HIV community organizations, and HIV treatment clinics in San Diego County. HIV serostatus was determined by MedMira Multiplo rapid test or by enzyme-linked immunosorbent assays and confirmatory Western blot test. Acquired immune deficiency (AIDS) status was based on 1993 Centers for Disease Control classification [38]. Inclusion criteria were: age (≤40 years or ≥50 years), resulting in the following subgroups: 48 younger HIV-uninfected (Y−), 70 younger HIV-infected (Y+), 77 older HIV-uninfected (O−), and 107 older HIV-infected (O+). For the HIV-infected groups, study participants were required to have an estimated duration of infection greater than 1 year. Exclusion criteria were: psychotic disorders (e.g., schizophrenia), neurological disease (e.g., head injury with loss of consciousness >30 min, seizure disorder, stroke), major medical conditions that might impact cognition (e.g., advanced liver disease or other organ system failures), estimated verbal IQ scores <70 (as determined by the Wechsler Test of Adult Reading [39]), current substance use disorder, and/or a positive urine toxicology screen for illicit drugs (not including marijuana). A principle goal of the parent R01 study was to identify memory deficits associated with HIV infection in older adults; therefore, our approach to inclusion and exclusion was guided by the Frascati clinical research criteria for HAND [34]. Participants with common comorbidities, such as depression and non-active substance use disorders that are unlikely to impact cognitive functions, were included in the study and these factors were measured with questionnaires and structured diagnostic interviews. The exclusion criteria (e.g., major psychiatric disorders, including psychosis; neurological conditions; current substance use disorder) were based on factors that preclude a diagnosis of HAND according to Frascati criteria [34] because they would not allow us to attribute any observed neuropsychological deficits at least in part to HIV infection. The parent study was approved by the UCSD Human Research Protections Program, and all participants provided written informed consent. None of the participants (both HIV+ and HIV−) in this study had previously participated in the prior study on SCA in HIV from our group [23].

The study samples' clinical characteristics are presented in Table 2. The four groups were comparable on the prevalence of lifetime substance dependence disorders and measures of cognitive reserve, including oral word reading ($ps > 0.05$). The Younger and Older samples were comparable on age by serostatus, whereas the Y+ subjects had lower education than the other three groups ($p < 0.05$). There was a greater proportion of women in the Y− sample than in the Y+ and O+ groups ($p < 0.05$), and the two Older groups contained fewer ethnic minorities than the Younger groups ($p < 0.01$). More participants in the HIV+ groups had diagnoses of affective disorders ($p < 0.01$). As would be expected with regard to HIV disease characteristics, the O+ group had a longer estimated duration of infection, higher prevalence of AIDS, and lower nadir CD4 counts ($ps < 0.01$). The two HIV+ groups did not differ on current CD4 counts, HIV RNA in plasma, or cART status ($ps > 0.05$).

Measures and Procedure

Successful Cognitive Aging

In order to examine our primary study aim (i.e., differences in rates of SCA by age and HIV status), participants were classified as to the absence of neurocognitive deficits and symptoms (SCA-ANDS) based on both neuropsychological performance and subjective cognitive functioning being within normal limits. To assess neurocognition, a standardized battery of tests measuring motor skills, executive functions, attention, episodic learning, episodic memory, verbal fluency, and information processing speed, was administered. This battery was constructed in accordance with the NIMH recommendations for evaluating neurocognitive domains most commonly impaired with HIV infection [34], and has been described in detail elsewhere [35, 40]. See Table 1 for details about the neuropsychological tests included in the battery.

Raw test scores were adjusted for age, education, gender, and ethnicity, as indicated by published normative standards. Subjective cognitive functioning (i.e., cognitive complaints) was assessed with the 7-item Confusion-Bewilderment subscale of the Profile of Mood States (POMS) [41]. On this self-report measure, participants rate adjectives (e.g., "unable to concentrate") based on their experience of cognitive difficulties during the past week on a scale from 0 = *not at all* to 4 = *extremely*. Normative standards adjusting for age and gender were applied to the POMS [42].

Of note, we used the same approach as previously reported by Malaspina et al. [23]. in which participants were classified as SCA-ANDS if they had both a global clinical neuropsychological rating <4 [40] based on the normed results of the comprehensive neurocognitive test battery and a Confusion/Bewilderment subscale score on

Table 1 Neuropsychological test scores used to establish global clinical neurocognitive rating

Domain	Tests
Retrospective memory	CVLT-II recognition discriminability index
	WMS-III Logical Memory II
Attention and working memory	WAIS-III Digit Span
	CVLT-II trial 1
Executive functions	ToL-DX total move score
	TMT, Part B
Speed of information processing	ToL-DX total time score
	TMT, Part A
Learning	CVLT-II total (total trails 1-5)
	WMS-III Logical Memory I
Verbal fluency	Action Fluency test
Motor	Grooved Pegboard Test (dominant and non-dominant hands)

CVLT-II California Verbal Learning Test-Second Edition, *ToL-DX* Tower of London-Drexel, *TMT* Trail Making Test, *WAIS-III* Wechsler Adult Intelligence Scale-Third Edition, *WMS-III* Wechsler Memory Scales-III

the POMS <1 standard deviation away from the mean of age and gender corrected scores. A global clinical rating less than 4 indicates that no single cognitive domain fell in the impaired range (i.e., T-scores >39). This SCA definition differs from the deficit approach traditionally used in the operationalization of global impairment for diagnoses of HAND, which requires that 2 or more domains are impaired (i.e., ratings ≥5). Overall, 94 out of the 302 participants met criteria for SCA-ANDS, including 44 of the HIV+ participants (24.9 %) and 50 of the HIV− participants (40.0 %).

Cognitive Reserve

To evaluate cognitive reserve, a cognitive reserve composite was created by averaging the z-scores of participants' education, Wechsler Test of Adult Reading (WTAR) [39], and the Hollingshead Highest Occupation variable [43]. A combination of higher education, higher estimated verbal IQ, and higher occupational complexity have been found to comprise what has been termed "cognitive reserve", which is thought to be the ability to optimize normal cognitive performance [44], and may serve as a protective factor from the expression of neuropathology [45, 46].

Psychiatric Assessment

To evaluate lifetime and current affective disorders (i.e., major depressive disorder and generalized anxiety disorder) and substance use disorders, the Composite International Diagnostic Interview was administered (CIDI, v2.1) [47]. Diagnostic criteria for the CIDI are based on the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders [48].

Medical Assessment

All participants completed standardized research neuromedical evaluations. These evaluations included a thorough medical history, assessment of medications, and current symptoms, physical and neurological evaluation, CDC staging, and blood draw. To measure levels of ribonucleic acid (RNA) in plasma and cerebrospinal fluid, reverse transcriptase-polymerase chain reaction was used (RT-PCR; Amplicor, Roche Diagnostics, Indianapolis, IN, USA).

Psychosocial and Functional Characteristics

The Medical Outcome Study 36 Item Short-Form version 1.0 (MOS-SF-36) [49] was used to assess HRQoL, and the reliability and construct validity of the SF-36 has been well established for use in people with HIV infection [16, 50]. The physical and mental health component scores were used as primary outcome variables, while the subscales were used in post hoc analyses.

Results

Group Differences in the Absence of Neurocognitive Deficits and Symptoms (SCA-ANDS)

A logistic regression predicting SCA-ANDS status from HIV serostatus, age, and their interaction was conducted, controlling for the variables that differed between groups (see Table 2). While there was no interaction between HIV status and age on SCA-ANDS χ^2 (1, $N = 295$) = 1.89, $p = 0.17$, additive effects of HIV status χ^2 (1, $N = 295$) = 6.64, $p = 0.01$ and age group χ^2 (1, $N = 295$) = 9.65, $p < 0.01$ were observed. As shown in Fig. 1, a stairstep decline in SCA-ANDS was evident across the four groups, ranging from 47.9 % in the Y- participants to 18.7 % in the O+ participants. A similar stairstep pattern was observed for both within normal limits neuropsychological performance and an absence of subjective cognitive failures when these factors were considered separately (see Fig. 1).

Clinical Correlates of SCA-ANDS among Younger and Older HIV+

To determine the clinical correlates of SCA-ANDS in the Y+ and O+ groups, a series of independent samples *t*-tests and Chi square tests were conducted on the variables listed in Table 2. Descriptive characteristics of the SCA-ANDS

Table 2 Demographic and clinical characteristics of the participants

	Younger HIV− ($n = 48$)	Older HIV− ($n = 77$)	Younger HIV+ ($n = 70$)	Older HIV+ ($n = 107$)	p	Pairwise comparisons
Demographic characteristics						
Age[a] (years)	31.2 (4.5)	56.2 (4.6)	32.8 (4.6)	56.2 (5.2)	<0.001	Y− = Y+ < O− = O+
Sex (% female)	33.3	28.6	15.7	16.8	0.033	Y− > Y+ , O+
Ethnicity (% Caucasian)	43.8	66.2	40.0	68.2	<0.001	Y− = Y+ < O− = O+
Cognitive reserve composite (z-scores)[b]	−0.01 (0.7)	0.1 (0.9)	−0.21 (0.6)	0.08 (0.8)	<0.06	–
Education[a] (years)	14.2 (2.3)	14.0 (3.0)	12.8 (2.0)	14.2 (2.5)	0.003	Y−, O−, O+ > Y+
WTAR verbal IQ[a]	103.3 (9.2)	102.9 (11.1)	100.9 (10.6)	102.1 (11.1)	0.615	–
HH highest occupation[a]	26.2 (8.4)	29.8 (8.8)	26.4 (8.3)	29.4 (8.3)	0.015	Y− = Y+ < O− = O+
Psychiatric characteristics						
Affective disorder[c,d] (%)	29.2	45.5	72.9	69.2	<0.001	Y− < O+ , Y+ ; Y+> O−; O− < O+
Alcohol dependence[d] (%)	31.3	31.2	44.3	27.1	0.116	–
Non-alcohol dependence[d] (%)	27.1	38.0	50.0	44.9	0.076	–
Medical characteristics						
Hepatitis C (%)	4.2	21.1	5.7	30.8	<0.001	Y− < O−, O+; Y+ < O−, O+
HIV disease characteristics						
Est. duration of HIV[a] (years)	–	–	8.0 (5.6)	17.6 (7.2)	<0.001	Y+ < O+
AIDS (%)	–	–	37.7	67.3	<0.001	Y+ < O+
cART (%)	–	–	90.0	91.6	0.719	–
Nadir CD4[e] (cells/μl)	–	–	250 (147.8, 369.5)	125 (50, 245)	<0.001	Y+ > O+
Current CD4[e] (cells/μl)	–	–	568 (402, 806.5)	507 (381.3, 759.5)	0.672	–
Plasma detectable (%)	–	–	20.0	15.1	0.410	–
Health-related quality of life[a,f]						
Physical component	89.4 (11.4)	75.6 (21.7)	77.2 (19.5)	61.5 (23.4)	<0.001	Y− > Y+ , O−, O+; O+ < Y+, O−
Mental component	78.0 (13.5)	74.2 (18.7)	64.5 (21.8)	60.7 (22.3)	<0.001	Y− = O− > Y+ = O+
Physical functioning	95.0 (15.6)	80.0 (22.3)	86.9 (19.5)	69.8 (24.4)	<0.001	Y− > O−, O+; O+ < Y+ = O+
Physical role limitations	88.5 (26.3)	73.0 (40.5)	65.7 (42.4)	50.0 (42.8)	<0.001	Y− > Y+ , O+; O− > O+
Emotional role limitations	88.8 (30.6)	79.0 (34.9)	63.3 (43.3)	57.9 (43.5)	<0.001	Y− > Y+ , O+; O− > O+
Energy/vitality	65.4 (15.7)	64.7 (20.5)	57.1 (20.4)	48.6 (24.1)	<0.001	O+ < Y+ , Y−, O−
Emotional well-being	78.7 (12.6)	76.2 (16.5)	68.2 (18.0)	68.9 (19.1)	0.001	Y− > Y+ ; O− > Y+, O+
Social functioning	85.7 (18.0)	81.0 (21.0)	72.0 (27.2)	67.5 (27.5)	<0.001	Y− > Y+ , O+; O− > O+
Pain	84.5 (21.5)	69.9 (27.3)	74.6 (22.7)	63.8 (27.2)	<0.001	Y− > O−,O+; Y+ > O+
General health	80.7 (16.0)	70.7 (20.9)	67.8 (20.9)	53.3 (23.9)	<0.001	Y− > Y+ , O+; O+ < Y+ , O−

WTAR Wechsler Test of Adult Reading, *HH* Hollingshead, *POMS* Profile of Mood States

[a] Standard deviations in parentheses

[b] Cognitive Reserve Composite includes education, WTAR, and HH highest occupation

[c] Includes Major Depression and Generalized Anxiety

[d] Denotes a lifetime diagnosis

[e] Data represent medians with interquartile ranges in parentheses

[f] All HRQoL variables from the MOS-SF-36

and non-SCA-ANDS Y+ and O+ groups are presented in Table 3. With regard to demographics, the Y+ SCA-ANDS group had higher cognitive reserve (d = 0.88, $p < 0.01$) and had more Caucasian participants (OR = 3.2, $p < 0.05$) as compared to the Y+ non-SCA-ANDS group. In terms of clinical characteristics, a shorter duration of HIV infection (d = 0.86) and lower prevalence of lifetime alcohol dependence (OR = 3.57) was observed in the Y+

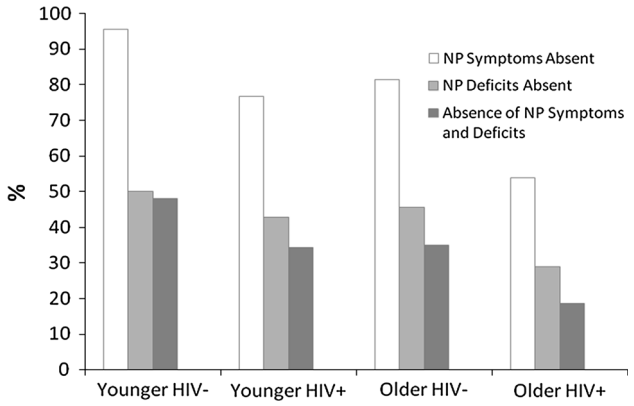

Fig. 1 SCA-ANDS by age and HIV status. *NP* neuropsychological. NP symptoms = T < 60 on POMS confusion/bewilderment scale; NP deficits = global clinical neurocognitive rating <4, meaning no individual cognitive domains fall in impaired range; NP symptoms and deficits = SCA-ANDS. *Y−* younger HIV−, Y+ younger HIV+, *O−* older HIV−, *O+* = older HIV+. Significant differences pairwise: Y−/O−, NP Symptoms (young less symptoms); Y−/O+, all 3 comparisons; Y−/Y+, NP Symptoms; Y+/O−, no differences; Y+/O+, NP Symptoms; NP Symptoms and Deficits. O−/O+: all 3 comparisons

SCA-ANDS group compared to their non-SCA-ANDS counterparts (*p*s < 0.05). In the O+ cohort, SCA-ANDS was associated with higher cognitive reserve ($p < 0.05$, d = 0.42), but no other significant group differences based on SCA-ANDS status were observed on any of the variables in Table 2 (*p*s > 0.10).

SCA-ANDS and HRQoL in HIV

Lastly, we were interested in determining whether SCA-ANDS was uniquely associated with better HRQoL within the Y+ and O+ groups separately. Specifically, we conducted multivariable linear regression models in which HRQoL was assessed with the MOS-SF-36 Physical and Mental Health Components. Those variables in Table 3 that were significantly related to SCA-ANDS status were entered as covariates in the regression models for the Y+ and O+ groups, respectively. To confirm that our choice of covariates in each model did not impact the results, we reran the Y+ multivariate model using the covariates we used in the O+ model, and vice versa, which did not alter the statistical significance or strength of the relationships between SCA-ANDS and HRQoL outcomes in either group as detailed below. Note that, although there were no differences between SCA-ANDS and non-SCA-ANDS participants in the prevalence of affective disorders (major depression or generalized anxiety), these psychiatric comorbidities can have a strong impact on both mental and physical HRQoL in HIV [51] and were thus included in the models. In the Y+ group, SCA-ANDS status (the primary predictor of interest) along with the covariates of cognitive reserve composite, race/ethnicity, estimated duration of HIV infection, history of alcohol dependence, and affective disorder diagnosis were entered into in the model. Both overall models were significant (Physical Health: adjusted $R^2 = 0.18$, $p < 0.01$; Mental Health: adjusted $R^2 = 0.21$, $p < 0.01$). SCA-ANDS was a strong, independent predictor of Mental Health ($\beta = 0.41$, $t(60) = 3.06$, $p < 0.01$) but not Physical Health ($\beta = 0.21$, $t(60) = 1.56$, $p = 0.12$). In the O+ group, SCA-ANDS was again entered as the independent variable of interest, with cognitive reserve composite, AIDS status, and affective disorder diagnosis entered as covariates. Again, both of the overall models were significant (Physical Health: adjusted $R^2 = 0.12$, $p < 0.01$; Mental Health: adjusted $R^2 = 0.31$, $p < 0.001$). Similar to the Y+ group, SCA-ANDS was a strong predictor of Mental Health ($\beta = 0.29$, $t(95) = 3.31$, $p < 0.01$) but not Physical Health ($\beta = 0.18$, $t(96) = 1.86$, $p = 0.07$).

Table 4 shows the results of the multivariable regressions predicting the subdomains of mental health from SCA-ANDS (and the aforementioned covariates) in the Y+ and O+ groups. In both age groups, SCA-ANDS was associated with better emotional well-being and social functioning (*p*s < 0.05). In the Y+ group, SCA was also associated with fewer emotional role limitations ($p < 0.05$), but not fatigue or general health (*p*s < 0.10), whereas in the O+ group, SCA was associated with less fatigue and better general health (*p*s < 0.05), but not emotional role limitations ($p > 0.10$).

Discussion

Neurocognitive disorders commonly occur among older HIV-infected adults and adversely impact their everyday functioning, but the prevalence, clinical correlates, and well-being benefits of SCA in persons infected with HIV are not well understood. This study demonstrated adverse additive effects of older age and HIV on SCA in well-characterized samples of younger and older adults with and without HIV infection. Specifically, SCA as defined by an absence of neurocognitive deficits and symptoms (SCA-ANDS) followed a stairstep pattern of decreasing prevalence in association with increasing risk factors; i.e., SCA-ANDS was observed in about half the Y- adults, as compared to one-third of the Y+ and the O− adults, versus less than one-fifth of the O+ adults. The additive effects of age and serostatus were independent of important clinical-demographic co-factors, including education, gender, race/ethnicity, affective disorders, and HCV co-infection. Moreover, the study groups were comparable on other important risk factors, such as alcohol and substance use disorders, suggesting that the lower prevalence of SCA-ANDS is likely to be attributable to aging with HIV

Table 3 Demographic and successful cognitive aging, psychiatric and disease characteristics of the HIV+ groups

	Younger SCA ($n = 24$)	Younger comparison ($n = 46$)	Older SCA ($n = 20$)	Older comparison ($n = 87$)
SCA characteristics				
Global clinical neurocognitive rating[a]	3 (2,3)	4 (4,5)	2 (2,3)	4 (4, 6)
POMS confusion/bewilderment[a]	−0.51 (−1.06, 0.32)	0.59 (−0.51, 1.56)	−0.16 (−0.74, 0.38)	1.07 (0.10, 2.31)
Demographics				
Age[b] (years)	32.4 (4.7)	33.0 (4.6)	56.3 (5.5)	56.2 (5.2)
Sex (% female)	8.3	19.6	30.0	13.8
Ethnicity (% caucasian)	58.3	30.4	75.0	66.7
Cognitive reserve composite (z-scores)[b,c]	0.1 (0.6)	−0.4 (0.6)	0.4 (0.6)	0.05 (0.8)
Education[b] (years)	13.6 (2.2)	12.4 (1.7)	14.6 (2.2)	14.1 (2.6)
WTAR verbal IQ[b]	106.6 (8.7)	98.0 (10.4)	107.1 (8.8)	100.9 (11.3)
HH highest occupation[b]	28.5 (9.0)	25.2 (7.8)	32.8 (4.1)	28.7 (8.8)
Psychiatric				
Affective disorder[d,e] (%)	66.7	76.1	60.0	71.3
Alcohol dependence[e] (%)	25.0	54.3	25.0	27.6
Other dependence[e] (%)	50.0	50.0	40.0	46.0
HIV disease characteristics				
Est. duration[b] (years)	5.0 (3.2)	9.6 (6.0)	19.8 (3.5)	17.1 (7.7)
AIDS (%)	29.2	41.3	65.0	67.8
cART (%)	83.3	93.5	85.0	93.1
Nadir CD4[a] (cells/μl)	322.5 (162.5, 410.0)	239.5 (139.8, 354.8)	183.5 (59.8, 287.5)	120.0 (50.0, 240.0)
Current CD4[a] (cells/μl)	559.0 (332, 915)	613.5 (408.0, 769.5)	742.5 (896.0)	492.5 (381.3, 724.0)
Plasma detectable (%)	36.4	11.6	10.0	16.3

Global clinical neurocognitive rating ranges from 1 to 9, with higher scores reflecting greater impairment and scores greater than or equal to 5 reflecting clinical impairment

SCA successful cognitive aging, *HH* hollingshead, *POMS* profile of mood states

[a] Data represent medians with interquartile ranges in parentheses

[b] Standard deviations in parentheses

[c] Cognitive Reserve Composite includes education, WTAR, and HH Highest Occupation scores

[d] Includes Major Depression and Generalized Anxiety

[e] Denotes a lifetime diagnosis

infection. The prevalence of SCA in our O+ adults (19 %) was slightly lower, but in the same general range, as that reported by Malaspina et al. [23] (32 %) in a marginally younger sample. These findings extend that previous work by anchoring the prevalence of SCA in a new sample of older HIV-infected subjects as measured by SCA-ANDS to that of younger persons living with HIV and older and younger seronegative individuals. Indeed, older HIV-infected adults were nearly half as likely to be free of neurocognitive deficits and symptoms as their younger HIV-infected and older seronegative counterparts.

Higher cognitive reserve was the lone significant correlate of SCA in the O+ group. A similar association was observed in the Y+ cohort, suggesting that the association between cognitive reserve (i.e., a composite of educational attainment, verbal IQ, and highest occupation) and the absence of neurocognitive deficits and symptoms may be observed earlier in the developmental process of aging with HIV infection. These findings are commensurate with cognitive reserve theory, which posits that the ability to optimize normal neurocognitive performance vis-a-vis neural injury may be related to higher premorbid functioning, including intellectual ability, as well as educational and occupational attainment [44]. In the setting of HIV disease, higher cognitive reserve has been associated with lower rates of neurocognitive impairment [52], stability of neurocognitive functions over time [53], and dependence in everyday functioning [46], perhaps especially among older HIV-infected adults [15]. Cognitive reserve also has been shown to play a role specific to SCA among healthy older adults [54]. Interestingly, the study by Malaspina et al. [23] revealed only a small, non-significant association between SCA and cognitive reserve using the same methods in a smaller and slightly younger

Table 4 Posthoc regression analyses of subcomponents of the SF-36 mental health component

Variable	Younger HIV+					Older HIV+				
	Overall model			SCA-ANDS		Overall model			SCA-ANDS	
	F-value	df	*p* value	Beta (β)	*p*-value	F-value	df	*p*-value	Beta (β)	*p*-value
SF-36 emotional role limitations	4.54	60	<0.01	0.38	<0.01	3.61	100	<0.01	0.10	0.31
SF-36 energy/fatigue	1.34	60	0.25	0.21	0.16	9.77	97	<0.001	0.26	<0.01
SF-36 emotional well-being	2.30	60	0.05	0.36	0.01	9.21	95	<0.001	0.28	<0.01
SF-36 social functioning	3.56	60	<0.01	0.47	<0.01	8.60	100	<0.001	0.27	<0.01
SF-36 general health	1.63	60	0.16	0.12	0.44	4.40	100	<0.01	0.22	0.02

SCA-ANDS neuropsychological symptoms and deficits

cohort. Whether the inconsistency across these two studies is a function of the instability of reserve as a predictor of SCA in older HIV-infected adults and/or modest differences between the study cohorts in age and verbal IQ (or other factors) remains to be determined; however, findings from the present study showing a positive association between cognitive reserve and SCA-ANDS are more in-line with theory and the cART-era HIV literature referenced above.

Consistent with the findings of Malaspina et al. [23], we were surprised to discover that HIV disease treatment and severity variables were not strongly associated with SCA-ANDS. Of particular surprise was the lack of association between SCA-ANDS and nadir CD4 count, higher levels of which have previously shown to be neuroprotective in the context of HAND in cross-sectional studies [55]. The absence of HIV disease-related associations with SCA-ANDS may suggest that non-HIV-associated health factors, such as cardiovascular disease [56] and metabolic syndrome [57], might be of relevance to SCA, as these factors which have been found to be negatively related to cognitive performance in both HIV seropositive and seronegative adults [58, 59]. The lack of relation between SCA-ANDS and nadir CD4 count may also be explained by the fact that our HIV+ groups were relatively healthy as indicated by the high nadir CD4 counts. Nevertheless, the nadir CD4 counts in this study were comparable to other studies that have shown associations between nadir CD4 counts and neuropsychological functioning [55]. Of course, the cross-sectional nature of this study precludes us from drawing any firm conclusions regarding the long-term role of HIV-related health factors in the incidence or worsening of neurocognitive problems among older adults infected with HIV. Moreover, HIV disease variables may re-emerge as important factors in SCA as these individuals age into their sixth and seventh decades of life. Finally, it is also possible that more sensitive biomarkers of HIV-associated neural injury (e.g., MCP-1 [60]) and/or neuroprotection (e.g., fibroblast growth factor-1 [61]) may play a role in SCA.

By way of contrast to the largely null clinical findings in the O+ cohort, SCA-ANDS was associated with a shorter estimated duration of HIV infection and lower prevalence of lifetime alcohol dependence in the Y+ group. With regard to the former, it may be that duration of infection is more directly related to poorer health outcomes in younger versus older adults, perhaps because such relationships in older adults are complicated by survival bias in the pre-cART era. Indeed, age was strongly correlated with estimated duration of infection in the Y+, but not the O+ participants in this study. With regard to the possible role of alcohol use disorders in SCA-ANDS among younger HIV-infected persons, prior research shows generally additive effects of HIV infection and alcohol use on neurocognitive impairment [62], with particular disruption of frontostriatal systems and associated cognitive control processes [63]. In acute and early HIV infection, problematic alcohol use has been related to greater neuropsychiatric symptoms [64]. The role of responsible alcohol consumption in SCA among older HIV+ adults remains to be determined, as prior studies in healthy adults have shown that moderate alcohol consumption is characteristic of successful cognitive agers [54, 65]. Nevertheless, the neurocognitive deficits that are linked to heavy alcohol use in the setting of HIV infection may contribute to poorer HRQoL [66, 67]. Furthermore, it is possible that, consistent with a wealth of literature in seronegative individuals, the impact of alcohol use on SCA in HIV-infected adults may not emerge until this age cohort reaches their mid-60s [68].

One of the more clinically compelling findings from this study was the strong, unique association observed between SCA-ANDS and mental HRQoL. Specifically, the presence of SCA-ANDS corresponded to better emotional well-being and social functioning in both the Y+ and O+ groups. There is a known buffering effect of social support on depressive symptoms [69–72], a relationship which some have identified as being stronger in those with physical disabilities [73]. Our findings indicate the possibility that SCA may have a buffering effect on mental health and social functioning,

although the direction of causality cannot be determined with these cross-sectional data. Future studies should examine the possible mediating role of social cognition, which is worsened by age [74] and HIV infection [75]. Unique to the O+ adults, SCA-ANDS was linked to better energy and general health, which may reflect the vulnerability of older HIV+ adults to declines in these aspects of mental HRQoL and importance of SCA in protecting against such declines. On the contrary, SCA-ANDS was related to emotional role limitations in the Y+, but not O+, cohort. This association may be due to the younger adults' relatively shorter duration of infection, and less experience and ability to cope with disease-related affective disorder. Interestingly, a negative relationship between neuropsychological functioning and coping among HIV-infected men has been identified, in that individuals with neurocognitive deficits reported using higher levels of confrontational coping [76]. Confrontational coping, in turn, has been associated with poorer psychosocial functioning among HIV− adults [77].

SCA-ANDS was not associated with physical well-being, highlighting the specificity of SCA-ANDS to aspects of HRQoL. This finding is somewhat inconsistent with the literature on successful aging in seronegatives. For example, one study found that better self-perceived physical functioning, mental functioning and cognitive performance were related to higher successful aging in a multivariate model of healthy community-dwelling older adults [78]. However, the literature on the relationship between SCA and physical health functioning in medical populations is likely disease specific, and comparisons to the relationship between physical disabilities and cognitive functioning in other diseases would be premature at this time. Our findings may be partially influenced by the distribution of self-reported physical health scores. In the Y+ group, physical health scores were negatively skewed, with a majority of scores falling in the high range of physical functioning, which may explain the lack of association between SCA and physical functioning, whereas in the O+ group the scores where normally distributed. Additionally, physical health problems are more prevalent among older adults in general, and especially older adults with HIV. These results indicate the possibility of a relationship between certain components of personal physical health perceptions and cognitive health in old age, despite the fact that the SF-36 physical component score was not related to SCA-ANDS. Thus, perhaps those O+ adults who are experiencing SCA may be more likely to positively perceive their physical health status due to the underlying mechanisms of positive psychological traits such as optimism or resilience.

There are several limitations to this study, especially the use of an observational cross-sectional design that precludes causal inferences based on the observed associations. Future studies would benefit from longitudinal and/or more targeted experimental approaches to aid in specifying causal relationships within the trajectories of SCA. Additionally, only a generic physical and mental health assessment of HRQoL was used (cf. HIV-specific measures) and other factors associated with HRQoL were not assessed. These include positive psychological traits (e.g., optimism, resilience), psychosocial functioning, health behaviors (e.g., exercise, smoking), cognitive leisure activities, and an overall outcome measure of successful aging that is not specific to cognition. Several multidimensional models of successful aging have been proposed both among older adults and older adults with HIV [31, 79, 80], and a comprehensive assessment of HRQoL which includes all these factors would provide a broader picture of the complex interplay between SCA and overall functioning.

Despite these limitations, conceptualizing HIV+ adults in terms of SCA offers several targets for interventions and possibly preventative care for individuals who are not aging successfully [22]. Vance and Burrage [81] proposed a conceptual cognitive reserve model of aging with HIV, in which they identified both positive and negative mediators of preventing loss and/or decline of cognitive abilities. High SES, good nutrition, physical activity, social stimulation, and cognitive remediation were included as positive mediators in the conceptual model. Many of these represent modifiable lifestyle factors that may be targeted in interventions tailored at the individual level to each person's unique needs [82]. Promoting factors associated with SCA and a general awareness in the older HIV population about the existence of SCA may make this positive outcome attainable to a greater percentage of older adults with HIV-infection, which in turn may have a positive impact on quality of life and well-being. Interventions aimed at promoting cognitive reserve throughout the lifespan are believed to influence cognitive aging trajectories and promote SCA [22, 83, 84]. For example, cognitive activity [85] and environmental complexity [86] in late life have been found to contribute to cognitive flexibility in old age. However, one review did find that early life (i.e., adolescents) is a time when cognitive reserve is most amenable to change [87]. Given that greater educational attainment and verbal intellectual functioning were related to SCA among the Y+ adults, targeting these factors at a younger age may have implications for not only promoting SCA in younger adults, but also may potentially have positive effects across the lifespan.

Acknowledgments This research was supported by National Institutes of Health (NIH) Grants R01-MH073419 and P30-MH062512. Dr. R.C. Moore is supported by T32 MH019934. Dr. Fazeli is supported by R25-MH081482, R01-MH099987, and ID10-SD-057 from California HIV/AIDS Research Program (CHRP). The views expressed in this article are those of the authors and do not reflect the official policy or position of the Department of the Navy, Department of Defense, or United States Government.

Appendix

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