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SuperAging in Adults with HIV Disease: Biopsychosocial Predictors of Neurocognitive Aging Trajectories

A dissertation submitted in partial satisfaction
of the requirements for the degree of Doctor of Philosophy

in

Clinical Psychology

by

Rowan Saloner

Committee in charge:

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2022

The dissertation of Rowan Saloner is approved, and it is acceptable in quality and form for publication on microfilm and electronically.

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2022

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Chapter 2, in full, is a reprint of the material as it appears in the *Journal of the International Neuropsychological Society*, Saloner, R., Campbell, L. M., Serrano, V., Montoya, J. L., Pasipanodya, E., Paolillo, E. W., Franklin, D., Ellis, R. J., Letendre, S. L., Collier, A. C., Clifford, D. B., Gelman, B. B., Marra, C. M., McCutchan, J. A., Morgello, S., Sacktor, N., Jeste, D. V., Grant, I., Heaton, R. K., Moore, D. J., CHARTER & HNRP Groups (2019). The dissertation author was the primary investigator and author of this paper.

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PEER-REVIEWED PUBLICATIONS

1. Sundermann, E. E., **Saloner, R.**, Rubtsova, A., Nguyen, A. L., Letendre, S., Moore, R. C., Cherner, M., Ma, Q., & Marquine, M. J. (2022). The association between benzodiazepine use and greater risk of neurocognitive impairment is moderated by medical burden in people with HIV. *Journal of neurovirology*, 10.1007/s13365-022-01076-1. Advance online publication. https://doi.org/10.1007/s13365-022-01076-1

2. **Saloner, R**., Lobo, J., Paolillo, E.W., Campbell, L.M., Letendre, S. L., Cherner, M., Heaton, R.K., Ellis, R.J., & Moore, D. J. (*in press*). Cognitive and Physiologic Reserve Independently Relate to Superior Neurocognitive Abilities in Adults Aging with HIV. *Journal of acquired immune deficiency syndromes (1999)*, 10.1097/QAI.0000000000002988. Advance online publication. https://doi.org/10.1097/QAI.0000000000002988

3. **Saloner, R.,** Savini, N., Letendre, S. L., Moore, D. J., & Montoya, J. L. (2022). Neopterin Relates to Lifetime Depression in Older Adults With HIV on Suppressive Antiretroviral Therapy. *Journal of acquired immune deficiency syndromes (1999)*, *89*(4), 454–461. https://doi.org/10.1097/QAI.0000000000002883

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Invited Book Chapters
1. Cherner, M., **Saloner, R.,** Sundermann, E., & Moore, D.J. (2022). Infectious Disorders: HIV, Hepatitis C, and COVID-19 Pandemic. *APA Handbook of Neuropsychology*.

ABSTRACT OF THE DISSERTATION

SuperAging in Adults with HIV Disease: Biopsychosocial Predictors of Neurocognitive Aging Trajectories

by

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Doctor of Philosophy in Clinical Psychology

University of California San Diego, 2022
San Diego State University, 2022

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Deficit models that predominate neuroHIV research describe adverse, synergistic effects of HIV and older age on neurocognitive impairment, yet many older persons with HIV (PWH) exhibit unimpaired neurocognition. HIV-seronegative studies have identified a subgroup of elders with youthful neurocognition, termed SuperAgers (SA). SA demonstrate stable neurocognitive trajectories and robust neurobiological integrity, consistent with models of cognitive and physiological reserve (CR and PR). However, the construct validity of SuperAging in HIV, including its prevalence, trajectory, and biopsychosocial correlates, is unknown. This three-paper dissertation: 1) established classification criteria for SuperAging in PWH; 2) examined the joint influence of CR and PR on SuperAging; and 3) characterized longitudinal

trajectories of SuperAging. All three studies used archival data from older PWH (age range: 50-69) enrolled in studies coordinated by the HIV Neurobehavioral Research Program.

Study 1 (N=724, Saloner et al., 2018). Individuals with intact global neurocognition based on normative standards for healthy 25 year-olds were classified as SA (n=124 [17.1%]). SA had similar HIV disease severity but better real-world outcomes (e.g., functional independence) than cognitively normal but non-super (CN) and cognitively impaired (CI) individuals.

Study 2 (N=394, Saloner et al., 2022). CR was operationalized as estimated premorbid verbal intelligence (i.e., WRAT4 Reading subtest) and PR was operationalized with a validated disease burden index composed of 39 health variables. Higher PR predicted linear increases in odds of SA (vs. CN and CI) and higher CR predicted a quadratic 'J-shaped' change in odds of SA compared to CN (i.e., odds of SA>CN only above 35th percentile of CR).

Study 3 (N=184, Saloner et al., 2021). Growth mixture modeling identified a 3-class solution that included Class 1$_{Stable\ Elite}$ (n=31 [16.8%], a latent class defined by stable and elite global neurocognition across a 5-year longitudinal period. Higher CR, PR, and SA status at baseline increased odds of Class 1$_{Stable\ Elite}$ membership.

Findings support SuperAging in HIV as a construct reflecting neurocognitive resilience that converges with markers of robust biopsychosocial health. Replication of methodology in even older PWH (i.e., 70+ years) may improve characterization of cognitive risk and resilience, particularly among PWH without overt neurocognitive impairment.

CHAPTER 1: INTRODUCTION

In the U.S., HIV is no longer considered an acute and rapidly debilitating terminal illness, but rather a chronic medical condition when treated with antiretroviral therapy (ART (Stoff, 2004). The life expectancy of adults taking ART is now similar to that of the general population, with an estimated half of persons with HIV (PWH) in the U.S. aged 50 and older (Centers for Disease Control and Prevention, 2018). Despite the success of ART in prolonging the lifespan of PWH, neurological complications and neurocognitive impairment (NCI) are common among PWH. The presentation of severe HIV-associated dementia has become relatively rare since the advent of ART, yet milder forms of NCI are estimated to affect 30-50% of PWH (Heaton et al., 2010; Heaton et al., 2011; Saloner & Cysique, 2017) and contribute to adverse real-world outcomes, including unemployment (Heaton, Marcotte, et al., 2004), suboptimal medication adherence (Moore, Montoya, Casaletto, & Hampton Atkinson, 2018), and poor health-related quality of life (Degroote, Vogelaers, & Vandijck, 2014).

Neuropathogenesis of Aging with HIV

Soon after HIV seroconversion, an increase in peripheral pro-inflammatory signaling facilitates the transmigration of HIV-infected monocytes and lymphocytes across the blood-brain-barrier and into the central nervous system (CNS; Chaudhuri, Yang, Gendelman, Persidsky, & Kanmogne, 2008). After invading the CNS, HIV is capable of replicating in CNS immune cells that most ART medications fail to penetrate (Hellmuth, Valcour, & Spudich, 2015). These CNS viral reservoirs release neurotoxic proteins and pro-inflammatory factors that disrupt neuroimmunological homeostasis, resulting in neural insults that compromise synaptic functioning (Ellis, Langford, & Masliah, 2007). Neuroimaging and cerebrospinal fluid data indicate elevated levels of neuroinflammatory biomarkers in virally-suppressed PWH, and this

chronic neuroinflammatory state is thought to underlie the persistence of NCI in the era of effective ART (Bandera et al., 2019; Cysique et al., 2018; Masters & Ances, 2014).

Given the growing population of older PWH, neuroHIV research efforts have preferentially focused on the combined neurobiological burdens of aging and HIV. These studies have generated models of accelerated and accentuated aging to explain the early onset and disproportionate rates of geriatric syndromes in PWH (Pathai, Bajillan, Landay, & High, 2014; Sheppard et al., 2017), including NCI (Cohen, Seider, & Navia, 2015), frailty (Guaraldi et al., 2011), and functional dependence (Stoff, Goodkin, Jeste, & Marquine, 2017). Aging with HIV appears to have a heightened neurotoxic effect, as evidenced by accelerated rates of cortical and subcortical atrophy (Cohen et al., 2015; Masters & Ances, 2014; Pfefferbaum et al., 2014), and excessive levels of neuroinflammation (Chang et al., 2004; Cysique et al., 2013). The source of these neurological vulnerabilities is likely multifactorial, as older PWH have higher rates of biological (e.g., metabolic syndrome) and psychosocial (e.g., social isolation) risk factors for neurobehavioral decline (Pasipanodya et al., 2019; Rueda, Law, & Rourke, 2014). As it stands, the healthcare system is poorly equipped to handle the growing number of older PWH with complex medical needs, necessitating a stronger understanding of mechanisms that support positive outcomes in neurocognitive aging (High et al., 2012; Mills, Bärnighausen, & Negin, 2012).

Successful Cognitive Aging with HIV

Despite the neurotoxic hazards associated with aging with HIV, one to two-thirds of older PWH do not meet criteria for NCI (Becker, Lopez, Dew, & Aizenstein, 2004; Malaspina et al., 2011; Valcour et al., 2004) and may follow a normal, as opposed to premature or accelerated, trajectory of neurocognitive aging. To identify targets for enhancing positive outcomes in older

PWH, recent work has examined the clinical correlates of successful cognitive aging. To date, successful cognitive aging paradigms in PWH have conducted comparisons between older adults with NCI and those who are neurocognitively and functionally unimpaired (Malaspina et al., 2011; Moore et al., 2017; Moore et al., 2014). These studies have linked successful cognitive aging to positive psychological factors (e.g., grit), higher cognitive reserve, lower frailty, better ART adherence, and higher quality of life (Malaspina et al., 2011; Moore et al., 2017; Moore et al., 2014; Wallace et al., 2017).

Although clinically informative, the neuropsychological criteria for successful cognitive aging requires only the absence of NCI and does not consider inter-individual differences in global neurocognition (e.g., low average to superior) within the neurocognitively unimpaired group. Even among PWH on ART who have undetectable HIV virus, HIV-related neural injury can precede detectable NCI and progress over time (Cysique et al., 2018; Cysique et al., 2013). Thus, while some unimpaired PWH may be approaching the threshold of neural injury required to elicit neurocognitive deficits, others may follow a more stable neurocognitive trajectory. Differentiating patterns of neurocognition within this unimpaired group, such as separating out average or preclinical neurocognitive aging from superior neurocognitive aging, can enhance understanding of the factors that promote sustained neurocognition compared to factors that ward off NCI but do not prevent 'normal' age-related decline.

Neurocognitive SuperAging

The concept of neurocognitive SuperAging (SA) provides a natural framework for studying neurocognitive resilience. SA theory posits that although aging increases the risk of encountering adverse events that contribute to neuronal damage, aging itself does not necessitate neurocognitive decline (Rogalski et al., 2013). Within the general aging population, SA is

defined as neurocognitive performance (typically episodic memory) equivalent to that of young

or middle-aged adults, suggesting that these individuals avoid age-related decline (Harrison,

Maass, Baker, & Jagust, 2018; Rogalski et al., 2013; Sun et al., 2016). In HIV-seronegative

seniors, SA is associated with greater brain integrity (Cook et al., 2017; Dekhtyar et al., 2017;

Harrison et al., 2018; Lin et al., 2017; Rogalski et al., 2013; Sun et al., 2016; Wang et al., 2017),

less inflammation (Bott et al., 2017) and oxidative stress (Mapstone et al., 2017), reduced

Alzheimer's-related neuropathology (Gefen et al., 2015; Lin et al., 2017; Rogalski et al., 2013),

and greater psychological well-being (Cook Maher et al., 2017). Figure 1.1 displays theoretical

trajectories of neurocognitive aging. The trajectory of SA is relatively flat and always remains

within the range of peak performance. Normal neurocognitive aging follows a trajectory of

decline that gets faster with older age, but remains within the range of unimpaired performance.

Finally, accelerated neurocognitive aging shows a rapid decline that reflects impairment beyond

the expectations of normal aging.
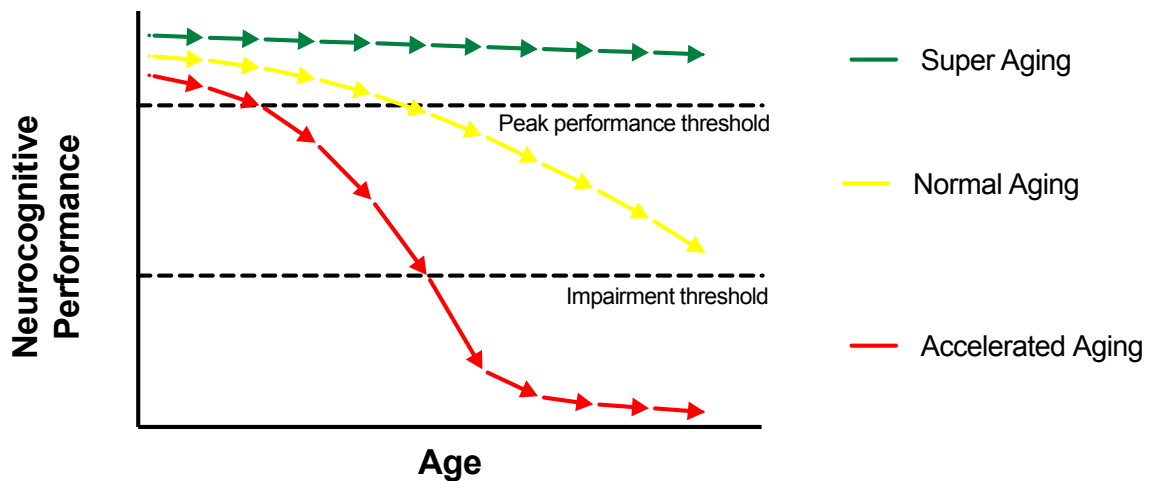
Figure 1.1. Simplified model of neurocognitive aging trajectories.

Cognitive Reserve

Cognitive reserve (CR) is the predominant theory for inter-individual differences in resilience to age- and disease-related neurocognitive decline (Stern, 2009; Vance, McDougall, Wilson, Debiasi, & Cody, 2014). According to this theory, the deleterious effects of neuropathology on neurocognition can be mitigated by adaptive brain processes (Stern et al., 2018). These complex and robust brain processes tolerate injury and maintain neurocognition through efficient neural firing and compensatory recruitment of additional neural networks. Importantly, CR may be malleable through interventions that target neuroplasticity, such as cognitive remediation (Vance, McDougall, et al., 2014). In animals, synapto-dendritic complexity can be enhanced through enrichment of intellectual and physical environments (Beauquis, Roig, De Nicola, & Saravia, 2010; Greenough & Volkmar, 1973; Hoffman et al., 2016; Shih, Yang, & Wang, 2013).

While it is difficult to directly measure these neural mechanisms in clinical settings, CR is often measured with sociobehavioral proxies that are expected to contribute to neural complexity (Stern et al., 2018). Education, estimated premorbid IQ, and occupational attainment are common proxies of CR that predict risk of incident dementia (Stern, 2012) and moderate the effect of Alzheimer's-related neuropathology on neurocognition in middle-to-late adulthood (Bennett et al., 2003; Vuoksimaa et al., 2013). In PWH, higher CR cross-sectionally reduces risk of NCI and daily-functioning impairment (Morgan, Woods, et al., 2012; Pereda et al., 2000; Satz et al., 1993; Stern, Silva, Chaisson, & Evans, 1996), and may be particularly neuroprotective in older PWH who have greater exposure to neurobiological stressors (Foley et al., 2012; Moore et al., 2014; Thames, Foley, et al., 2011). Higher baseline CR in PWH can predict stable (Basso & Bornstein, 2000) or improved (Heaton et al., 2015) neurocognition over time, suggesting a salient role in the preservation of neurocognition.

Physiologic Reserve

Similar to CR, physiologic reserve (PR) is a putative indicator of resilience with relevance to aging and HIV. PR describes the body's capacity to withstand physiological stress and maintain homeostasis across multiple organ systems (Bagshaw & McDermid, 2013). In a healthy state of high PR, robust biological functioning facilitates adaptation to environmental stressors. In the context of aging and chronic illness, biological resilience is diminished and results in the accumulation of health deficits that increase vulnerability to adverse events (Rockwood & Mitnitski, 2011). This phenotypic expression of depleted PR is often referred to as frailty. Frailty, as a surrogate marker of PR, can be operationalized continuously as an index or proportion of acquired age-related comorbidities (Rockwood & Mitnitski, 2011; Searle, Mitnitski, Gahbauer, Gill, & Rockwood, 2008). Frailty indices are practical in secondary analyses because they can be generated using easily accessible information from a patient's clinical record (Franconi et al., 2018). Cumulatively, a frailty index is a more robust predictor of overall morbidity and mortality than any individual deficit (Mitnitski, Mogilner, & Rockwood, 2001).

PWH are particularly susceptible to physiological damage, as evidenced by higher rates of age-related comorbid conditions than age-matched controls and similar rates to that of an older population (Althoff et al., 2014; Guaraldi et al., 2011; Rodriguez-Penney et al., 2013; Thurn & Gustafson, 2017). Members of our group and others have demonstrated that limiting the acquisition of comorbidities improves other clinical outcomes in PWH, as lower frailty index scores are related to greater longevity and better neurocognition, even when accounting for markers of HIV disease severity (Guaraldi et al., 2015; Oppenheim et al., 2018; Wallace et al., 2017). Although aging is correlated with decreases in PR, the rate at which any given individual

accumulates health deficits can vary significantly (Rockwood & Mitnitski, 2011). The positive

correlation between frailty index scores and age flattens after age 50 in PWH (Oppenheim et al.,

2018), suggesting considerable heterogeneity in resiliency to the potent physiological stressors of

aging with HIV. Frailty indices outperform chronological age as a predictor of adverse health

outcomes (e.g., mortality, Alzheimer's disease) and may therefore represent a more precise

measure of biological age with relevance to SA (Mitnitski, Graham, Mogilner, & Rockwood,

2002; Trebbastoni et al., 2017).

Study Objective

  Examining SA in chronic illness is a logical extension of previous SA studies among

healthy older adults and provides a unique opportunity to uncover mechanisms of

neuroprotection. Moreover, CR and PR have not been systematically evaluated with respect to

SA in PWH despite their documented relationships with neurocognitive aging and HIV.

Determining how these factors support the preservation of elite neurocognition in PWH has great

implications for the development of new models and treatments to elevate quality of life in older

PWH, with potential relevance to older adults with other chronic medical conditions. Thus, this

three-paper dissertation project evaluated the construct validity of SA in HIV by establishing

classification criteria for SA in PWH (Study 1) and its relationship to CR and PR (Study 2) and

latent trajectories of peak global neurocognition (Study 3).

CHAPTER 2: STUDY 1

Neurocognitive SuperAging in older adults living with HIV: demographic, neuromedical and everyday functioning correlates

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ABSTRACT

Objective: Studies of neurocognitively elite older adults, termed *SuperAgers*, have identified clinical predictors and neurobiological indicators of resilience against age-related neurocognitive decline. Despite rising rates of older persons living with HIV (PLWH), SuperAging (SA) in PLWH remains undefined. We aimed to establish neuropsychological criteria for SA in PLWH and examined clinically-relevant correlates of SA.

Methods: 734 PLWH and 123 HIV-uninfected participants between 50 and 64 years of age underwent neuropsychological and neuromedical evaluations. SA was defined as demographically-corrected (i.e., sex, race/ethnicity, education) global neurocognitive performance within normal range for 25-year-olds. Remaining participants were labeled cognitively normal (CN) or impaired (CI) based on actual age. Chi-square and ANOVA tests examined HIV group differences on neurocognitive status and demographics. Within PLWH, neurocognitive status differences were tested on HIV disease characteristics, medical comorbidities, and everyday functioning. Multinomial logistic regression explored independent predictors of neurocognitive status.

Results: Neurocognitive status rates and demographic characteristics differed between PLWH (SA=17%; CN=38%; CI=45%) and HIV-uninfected participants (SA=35%; CN=55%; CI=11%). In PLWH, neurocognitive groups were comparable on demographic and HIV disease characteristics. Younger age, higher verbal IQ, absence of diabetes, fewer depressive symptoms, and lifetime cannabis use disorder increased likelihood of SA. SA reported increased independence in everyday functioning, employment, and health-related quality of life than non-SA.

Conclusion: Despite combined neurological risk of aging and HIV, youthful neurocognitive performance is possible for older PLWH. SA relates to improved real-world functioning and may be better explained by cognitive reserve and maintenance of cardiometabolic and mental health than HIV disease severity. Future research investigating biomarker and lifestyle (e.g., physical activity) correlates of SA may help identify modifiable neuroprotective factors against HIV-related neurobiological aging.

Introduction

Antiretroviral therapy (ART) has facilitated increased life expectancy for people living with HIV (PLWH; Wing, 2016). In 2014, 45% of PLWH in the United States were over the age of 50 (Centers for Disease Control and Prevention, 2018) and this proportion is expected to increase (Smit et al., 2015). HIV-associated neurocognitive disorder (HAND) affects approximately half of PLWH (Heaton et al., 2010; Norman et al., 2011; Saloner & Cysique, 2017), and older PLWH are at three times higher risk for HAND compared to younger PLWH (Valcour et al., 2004). Furthermore, there is evidence to suggest that HIV accelerates and accentuates neurocognitive aging (Pathai et al., 2014; Sheppard et al., 2017). Older PLWH are at increased risk for functional decline (Thames, Kim, et al., 2011; Vance, Fazeli, & Gakumo, 2013), which is not only costly, but also negatively affects quality of life (Morgan, Iudicello, et al., 2012). Identifying factors that promote successful cognitive aging with HIV and developing interventions to sustain or enhance them may avoid or reverse the adverse effects of aging.

While definitions of successful cognitive aging in PLWH differ slightly, all definitions require individuals to be neurocognitively unimpaired and functionally independent (Malaspina et al., 2011; Moore et al., 2017). Successful cognitive aging rates in older PLWH range from 19-32%, and translates into real-world benefits, including greater success in managing medication and medical appointments, less decline in activities of daily living, and better psychological health and health-related quality of life (Malaspina et al., 2011; Moore et al., 2017; Moore et al., 2014). Given that the neuropsychological criteria for successful cognitive aging solely requires the absence of neurocognitive impairment, taking into consideration age, there likely remains considerable heterogeneity in neurocognitive performance (e.g., low average to superior) among the successful cognitive aging group. Thus, distinguishing older PLWH with superior

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neurocognitive abilities from those with average neurocognitive abilities may explain additional variance in everyday functioning outcomes.

Older adults with preserved cognition appear to resist "normal" age-related decline. The term "SuperAger" refers to older adults that perform equivalently to young or middle-aged adults on episodic memory tests (Harrison et al., 2018; Rogalski et al., 2013; Sun et al., 2016). Alternatively, others have researched "SuperNormals" or "Optimal Memory Performers" – older adults who demonstrate above-average episodic memory performance in comparison to average older adults (Dekhtyar et al., 2017; Lin et al., 2017; Mapstone et al., 2017; Wang et al., 2017). Both definitions provide evidence that older adults with superior memory perform better on other cognitive domains, particularly executive functioning (Dekhtyar et al., 2017; Gefen et al., 2015) and processing speed (Dekhtyar et al., 2017; Harrison et al., 2018). Additionally, SuperAgers have larger volumes of the cerebral cortex, hippocampus, and cingulate cortex (Dekhtyar et al., 2017; Harrison et al., 2018; Lin et al., 2017; Rogalski et al., 2013; Sun et al., 2016; Wang et al., 2017) as well as slower rates of cortical atrophy (Cook et al., 2017). Furthermore, SuperAgers display lower levels of biomarkers of neurodegeneration such as oxidative stress (Mapstone et al., 2017), inflammation (Bott et al., 2017), and amyloid (Lin et al., 2017; Rogalski et al., 2013) and tau deposition (Gefen et al., 2015).

Despite not having a gold-standard definition of SuperAging (SA) or preserved cognition, commonalities exist among the definitions. Most studies have classified SuperAgers based on superior memory performance alone and only required either average age-adjusted performance for a few other neuropsychological measures (Harrison et al., 2018; Rogalski et al., 2013). Some have required that they be otherwise neurocognitively normal (Dekhtyar et al., 2017; Lin et al., 2017). Thus, SA studies predominantly focus on superior memory performance rather than

superior global neurocognitive performance. The majority of these studies, which consist of primarily septua- and octogenarians, require SuperAgers to perform equivalent to or better than those in their mid-50's; however, most neurocognitive abilities peak in the mid-20's and then begin to decline (Hartshorne & Germine, 2015; Heaton, Taylor, & Manly, 2003; Salthouse, 2003, 2009). Although SA is typically evaluated in healthy adults who are at least 60 years old, the aging population of PLWH is younger with 50 years old serving as a cut-off for defining a medically advanced age (Blanco et al., 2012). Nevertheless, neurocognitive aging studies have demonstrated substantial inter-individual variability in neurocognition for healthy adult cohorts below the age of 60 (Lachman, Teshale, & Agrigoroaei, 2015; Martin & Zimprich, 2005; Schaie & Willis, 2010). Importantly, this heterogeneity in neurocognition tracks with variation in biopsychosocial factors such that high neurocognitive performance correlates with high cognitive reserve and low comorbidity burden (Anstey, Sargent-Cox, Garde, Cherbuin, & Butterworth, 2014; Ferreira et al., 2017).

While current definitions of SA may be appropriate for studying healthy older adults resistant to the clinical expressions of biological aging and Alzheimer's disease, SA criteria should be tailored for study in older PLWH who are younger and at greater risk for multi-domain neurocognitive decline rather than focal memory deficits. Thus, we aimed to: 1) establish neuropsychological criteria for neurocognitive SA in PLWH; 2) identify clinical predictors of SA in PLWH; 3) assess the everyday functioning correlates of SA status.

Methods

Participants

Participants included 734 PLWH and 123 HIV-uninfected controls aged 50-64 years. 340 PLWH were enrolled in the NIH-funded CNS HIV Anti-Retroviral Therapy Effects Research

(CHARTER) study, consisting of six participating university centers: Johns Hopkins University (Baltimore, MD, n=51); Mt. Sinai School of Medicine (New York, NY, n=92); University of California at San Diego (San Diego, CA, n=32); University of Texas Medical Branch (Galveston, TX, n=73); University of Washington (Seattle, WA, n=38); and Washington University (St. Louis, MO, n=54). The remaining 394 PLWH and 123 HIV-uninfected participants were enrolled in other NIH-funded research studies at the University of California, San Diego's HIV Neurobehavioral Research Program (HNRP). All participant visits for the present study took place between 2002 and 2017. All studies were approved by local Human Subjects Protection Committees and all participants provided written informed consent. All PLWH were required to have ≥5 years of estimated duration of HIV disease to be considered for inclusion. Exclusion criteria were: 1) diagnosis of psychotic or mood disorder with psychotic features, neurological, or medical condition that may impair neurocognitive functioning, such as traumatic brain injury, stroke, epilepsy, or advanced liver disease; 2) low verbal IQ of <70 as estimated by the reading subtest of the Wide Range Achievement Test (WRAT; Wilkinson & Robertson, 2006); or 3) evidence of intoxication by illicit drugs (except marijuana) or Breathalyzer test for alcohol on the day of testing by positive urine toxicology.

Procedures

Neurocognitive Assessment

Participants were classified as SA based on their performance on a comprehensive and standardized battery of neurocognitive tests (Table 2.1), which has been described in detail elsewhere (Carey et al., 2004; Heaton et al., 2010). Briefly, the battery covers seven neurocognitive domains commonly impacted in HIV-infected persons: verbal fluency, executive functioning, processing speed, learning, delayed recall, attention/working memory, and motor

skills (Heaton et al., 2010). Since some participants had been exposed to the test battery at prior research visits, raw scores for each test were converted to practice effect-adjusted scaled scores (Heaton et al., 2001). These demographically-uncorrected scaled scores were converted to T scores (M=50, SD=10) that corrected for the effects of age, education, sex, and race/ethnicity on neurocognition (Heaton, Miller, Taylor, & Grant, 2004; Heaton et al., 2003; Norman et al., 2011).

In order to generate variables that reflect maximum neurocognitive performance at a younger age, a second set of adjusted T scores were computed in which the age of 25, instead of actual age, was entered into the demographic correction formulas along with actual education, sex, and race/ethnicity. These scores, referred to as "peak-age" T scores, consequently compare an individual's neurocognitive performance to normative standards for 25 year-olds of the same education, sex, and race/ethnicity (Heaton, Miller, et al., 2004; Heaton et al., 2003; Norman et al., 2011). Both the actual-age and peak-age T scores for each measure were averaged to compute global and domain-specific T scores within each cognitive ability area. T scores were converted to actual-age and peak-age domain-specific deficit scores (DDS) that give differential weight to impaired, as opposed to normal scores, on a scale ranging from 0 (T $\geq$ 40; normal) to 5 (T < 20; severe impairment). DDS were then averaged to generate an actual-age and peak-age global deficit score (GDS). Consistent with prior studies, the presence of global impairment was defined by GDS $\geq$ 0.5 and domain-specific impairment by DDS > 0.5 (Blackstone et al., 2012; Carey et al., 2004).

SuperAging Criteria

To estimate intact and peak neurocognitive functioning, SA status was operationally defined as: 1) peak-age GDS < 0.5; and 2) actual-age DDS $\leq$ 0.5 for all seven neurocognitive

domains. Participants that did not meet SA criteria were classified as either cognitively normal (CN) or cognitively impaired (CI) using the standard actual-age GDS impairment cut-point of $\geq$ 0.5 (Figure 2.1).

Neuromedical and Laboratory Assessment

All participants underwent a comprehensive neuromedical assessment, including a medical history that included medications, Centers for Disease Control (CDC) staging, and blood draw. HIV infection was diagnosed by enzyme-linked immunosorbent assay with Western blot confirmation. Routine clinical chemistry panels, complete blood counts, rapid plasma reagin, hepatitis C virus antibody, and CD4+ T cells (flow cytometry) were performed at each site's Clinical Laboratory Improvement Amendments (CLIA)–certified, or CLIA equivalent, medical center laboratory. Levels of HIV viral load in plasma were measured using reverse transcriptase-polymerase chain reaction (Amplicor, Roche Diagnostics, Indianapolis, IN, with a lower limit of quantitation 50 copies/ml).

Psychiatric Assessment

678 PLWH had available data from the Composite International Diagnostic Interview (CIDI), a fully-structured, computer-based interview, to determine DSM-IV diagnoses for current and lifetime mood and substance use disorders. (World Health Organization, 1998). Additionally, a subset of PLWH (n=712) completed the Beck Depression Inventory-II (BDI-II; Beck, Steer, & Brown, 1996) to assess current symptoms of depressed mood.

Everyday Functioning and Quality of Life Assessment

Instrumental activities of daily living (IADL) dependence was assessed using a revised version of the Lawton and Brody (1969) self-report measure of everyday functioning (Heaton, Marcotte, et al., 2004; Woods et al., 2008), in which participants rated current abilities compared

to previous abilities across 13 everyday functioning domains. Two outcome variables were generated: 1) A continuous variable of the number of declines in IADL; and 2) a dichotomous variable for IADL dependence, defined as ≥2 declines at least partially attributable to cognitive problems.

The Patient's Assessment of Own Functioning Inventory (PAOFI) is a 33-item self-report measure used to measure perceived cognitive symptoms in everyday life (Chelune, Heaton, & Lehman, 1986). Items endorsed as fairly often or greater are considered clinically significant cognitive symptoms. A continuous variable for total number of clinically significant everyday cognitive symptoms and a dichotomous variable for employment status (i.e., employed/unemployed) were examined as outcome variables.

A subset of PLWH (n=490) completed the Medical Outcome Study 36 Item Short-Form version 1.0 (MOS-SF-36), which assesses health-related quality of life (HRQoL). The reliability and validity of the MOS-SF-36 has been extensively documented in PLWH (Henderson et al., 2010; Wu, Revicki, Jacobson, & Malitz, 1997). For this study, the physical and mental health composite scores were examined as primary outcome variables.

Statistical Analyses

HIV group differences on neurocognitive status and demographics were examined using ANOVAs or Kruskal-Wallis tests for continuous variables and Chi-square statistics for categorical variables. For the PLWH group only, the same statistical tests examined neurocognitive status group differences on demographics, HIV disease severity, medical and psychiatric characteristics, and everyday functioning outcomes. All pair-wise post-hoc comparisons (SA versus CN, SA versus CI, and CN versus CI) were conducted for any variable with at least an omnibus trend-level (i.e., p<0.10) difference across neurocognitive status groups.

To control for multiple comparisons and limit Type I error, Tukey's Honest Significant Difference (HSD) tests were conducted for continuous variables and Bonferroni-corrections were applied to Chi-square tests (MacDonald & Gardner, 2000). Cohen's *d* statistics are presented for estimates of effect size for pair-wise comparisons. All group difference analyses were performed using JMP Pro version 12.0.1 (JMP®, Version *<12.0.1>*, SAS Institute Inc., Cary, NC, 1989-2007).

Next, any variable that displayed at least an omnibus trend-level difference was entered into a multinomial regression to determine the degree to which demographic and clinical characteristics segregate according to neurocognitive status. Race/ethnicity, sex, and education were not included in the model because the criteria for establishing neurocognitive status already adjusted for these factors. Actual age, however, was included in the model since the SA criteria adjusted each participant's performance at peak age (i.e., 25) instead of actual age.

In order to determine the impact of age on global functioning within each neurocognitive status group (PLWH only), we conducted Pearson partial correlations between age and demographically-uncorrected global scaled scores stratified by group, co-varying for education, sex, and race/ethnicity. We calculated standardized Pearson partial r values that serve as effect sizes to enhance comparability and interpretability of the relationship between age and global neurocognitive performance across the neurocognitive status groups. Statistical differences in the magnitude of the Pearson partial correlations were compared using Fisher's r-to-z transformations for independent correlations. Multinomial regression and Pearson's partial correlations were performed using SPSS 24 (SPSS Inc., Chicago, IL).

Results

SuperAging Prevalence

Of the 734 PLWH, 124 (17%) met criteria for SA. Of the remaining 610 non-SA participants, 279 (38%) were CN and 331 (45%) were CI. Figure 2.2 displays differences in actual-age T and peak-age T scores within and across SA and CN PLWH with Cohen's *d* effect size estimates for actual-age T scores. The prevalence of SA and CN were significantly higher, and prevalence of CI was significantly lower, in the HIV-uninfected group (=63.7, *p*<.0001). Of the 123 HIV-uninfected participants, 43 (35%) were SA, 67 (55%) were CN and 13 (11%) were CI.

Demographics

Table 2.2 displays PLWH neurocognitive status group differences in demographic, clinical, and neuromedical variables. Only percent non-Hispanic white differed significantly among demographic factors. Although the CN group exhibited the lowest proportion of non-Hispanic white, no significant pairwise differences were found. SA individuals were on average a year younger than their CN and CI counterparts and this difference approached significance, but this did not result in significant pairwise differences. Although groups did not differ with respect to education, SA displayed significantly higher WRAT scores than CN (*d*=0.43) and CI (*d*=0.61) participants.

Compared to PLWH, the HIV-uninfected comparison group had significantly higher rates of non-Hispanic white participants (81% vs. 58%; *p*<.0001), females (38% vs. 16%; *p*<.0001), mean years of education (14.4 vs. 13.6; *p*<.001), and higher mean WRAT scores (106 vs. 98; *p*<.0001). By design, the HIV-uninfected group did not significantly differ from PLWH in mean age (55.5 vs. 55.1; *p*=.87).

HIV Disease Characteristics

A stair-step pattern of indicators of HIV disease severity was commonly observed such that SA displayed the lowest amount of HIV disease burden followed by CN then CI individuals. Although this stair-step pattern occurred for history of AIDS diagnosis, detectable plasma HIV , current CD4 count, and nadir CD4<200; only omnibus group differences in current CD4<200 were significant. Post-hoc comparisons indicated that the SA group had significantly lower rates of participants with current CD4<200 than the CI group. In the full sample, participants with current CD4<200 were more likely to be off ART (19.6%) compared to those with current CD4≥200 (9.8%; =6.7, p=.01). No noteworthy group differences were found for estimated duration of HIV disease or receipt of ART.

Medical Comorbidities

Examination of medical comorbidities revealed significant group differences for rates of HCV seropositivity and diabetes. Post-hoc comparisons indicated that SA had significantly lower rates of HCV than the CN group and lower rates of diabetes than both the CN and CI groups. No significant group differences were found for other markers of metabolic syndrome (i.e., hypertension, hyperlipidemia, BMI).

Psychiatric and Substance Use Characteristics

Significant group differences were observed for rates of lifetime cannabis use disorder and cocaine use disorder. SA had significantly higher rates of cannabis use disorder than CI individuals and CN individuals displayed higher rates of cocaine use disorder than the CI group (Table 2.3). Although lifetime and current diagnoses of major depressive disorder (MDD) did not differ across groups, SA endorsed significantly fewer depressive symptoms on the BDI-II than both the CN (*d*=-0.35) and CI (*d*=-0.46) groups.

Multinomial Regression Predicting Neurocognitive Status

A multinomial logistic regression was performed with the three neurocognitive groups in PLWH as the dependent variable. Predictors were all outcome variables from Tables 2.2 and 2.3 with a trend-level omnibus effect (excluding race/ethnicity, i.e., age, WRAT, current CD4<200, HCV, diabetes, cannabis use disorder, and BDI-II). Based on available data, the sample size for this model included 113 SA, 259 CN, and 287 CI participants. Overall, the model was significant ((14,659)=83.73; p<0.001; Nagelkerke pseudo-=0.137). Likelihood ratio tests indicated that older age, lower WRAT scores, diagnosis of diabetes, and higher BDI-II scores all increased the likelihood of classification as either CN or CI compared to SA (Table 2.4). Furthermore, a lifetime diagnosis of cannabis use disorder decreased the likelihood of classification as CI compared to SA.

To focus on a clinically relevant subgroup, we reran the multinomial logistic regression among participants with undetectable levels of HIV plasma RNA. Of the 535 participants with an undetectable viral load, 97 (18%) were SA, 208 (39%) were CN, and 230 (43%) were CI. Age, WRAT, BDI-II, and diagnosis of lifetime cannabis use disorder remained significant predictors of neurocognitive status in this virally suppressed subgroup. Although diabetes increased likelihood of CN (OR=1.74, p=0.13) or CI (OR=1.63, p=0.19) compared to SA, these associations were no longer statistically significant.

Age and Global Performance Relationship by Neurocognitive Status

To examine the relationship between age and global neurocognitive performance within each neurocognitive status group in PLWH, we performed Pearson's partial correlations between age and demographically-uncorrected global scaled scores, co-varying for education, sex, and race/ethnicity. Age negatively correlated with lower global scaled scores within the CN (partial r=-.24; p<.001) and CI (partial r=-.15; p<.001) groups. However, age did not significantly relate

to global scaled scores among the SA group (partial r=-.11; p=.24). Despite this lack of significance, comparison of Fisher's r-to-z transformed correlations indicated that the effect size of age on global scaled scores in SA did not significantly differ from the effect sizes of age on global scaled scores in CN (z=1.23; p=.22) and CI (z=.38; p=.70). Similarly, the magnitude of the relationship between age and global scaled scores did not differ between CN and CI (z=-1.15; p=.25).

Everyday Functioning and Health-Related Quality of Life Correlates of Neurocognitive Status

A stair-step pattern was observed for most outcomes from the PAOFI, IADL, and MOS-SF-36 measures, with SA individuals endorsing the most favorable everyday functioning and HRQoL outcomes followed by CN then CI participants. SA individuals endorsed significantly fewer cognitive symptoms on the PAOFI than CN (d=-0.34, p<.001) and CI participants (d=-0.64, p<.0001) and fewer declines in IADLs than either CN (d=-0.42, p<.01) or CI participants (d=-0.70, p<.0001). The CN group also reported significantly fewer cognitive symptoms (d=-0.30, p<.05) and IADL declines (d=-0.33, p<.001) than the CI group. Figure 2.3 displays similar group differences on rates of unemployment and IADL dependence as well as the MOS-SF-36 physical and mental HRQoL composite scores.

Discussion

The emerging concept of neurocognitive SA has produced invaluable insights into age-related neurocognitive phenotypes and has undermined the widely-held assumption that age-related neurocognitive deterioration is inevitable. However, the prospect of maintaining intact neurocognitive capacities throughout the lifespan is highly daunting for PLWH. In our study sample with 17% meeting criteria for SA, we demonstrate that youthful neurocognitive performance is possible for older PLWH. Our findings suggest that SA status is independently

related to diverse factors that reflect current physical and mental health as well as premorbid neurocognitive functioning. Furthermore, SA status is associated with better everyday functioning, supporting the ecological validity of distinguishing SA from CN and CI individuals.

Given the marked difference in average age between our cohort of older PLWH and previous SA cohorts of healthy elders, our SA criteria and study results cannot be directly linked to the extant SA literature. However, there are several strengths of our peak-age approach to defining neurocognitive SA in the context of HIV infection. First, we do not focus on one specific domain of neurocognitive functioning. Instead, our SA criteria are defined by absence of peak-age impairment in global neurocognitive functioning and absence of actual-age impairment in all domains assessed. PLWH are a heterogeneous group whose neurocognition may be impacted by HIV and demographic and clinical confounds, contributing to a neurocognitive profile that is not defined by deficits in any one neurocognitive domain. Thus, we demonstrate merit in defining SA by global performance to match what is known about neurocognitive functioning among PLWH. An important feature of our global estimates of neurocognitive functioning is that they are adjusted for practice effects, as some study participants had prior exposure to the neurocognitive testing battery. Practice, or learning, effects complicate assessment of SA because seemingly elite neurocognition can be an artifact of prior testing experience. By correcting for normal test-retest fluctuations, we reduce the likelihood of overestimating neurocognitive ability and enhance the stringency of our SA criteria. We compared neurocognitive functioning of our sample to normative standards for age 25 when neurocognitive functioning is maximal (Salthouse, 2009). The concept of SA (Rogalski et al., 2013) posits that within an individual's adult life, aging does not necessitate neurocognitive decline. Rather, aging increases the likelihood of encountering adverse events that contribute to

neuronal damage and decline in neurocognition. Defining SA in this way may facilitate understanding of the kinds of events or experiences that either support, or damage, neurocognitive functioning.

SA had lower rates of unemployment and IADL dependence than the other neurocognitive status groups and higher self-reported physical and mental HRQoL. Thus, our method for defining SA appears to be concurrently valid with measures of everyday functioning and HRQoL. Importantly, CN and SA groups differ in real-world outcomes, indicating heterogeneity among neurocognitively unimpaired individuals. Unlike prior investigations of SA, our definition of SA did not require self-reported IADL independence as a criterion. Despite performance-based data indicating SA, a small proportion of the SA group endorsed IADL dependence. Among our SA group, self-reported declines in IADL may represent actual decline, such that SA individuals may have started at higher levels of functioning and experienced a decline that is not necessarily at an impaired level. To this point, our measure of IADL dependence may be overly sensitive in detecting decline and not specific in detecting whether this decline represents a shift from within normal functioning to impairment status. Given that most other studies rely on absence of IADL dependence or decline when defining SA, these studies may be potentially misidentifying SA individuals who perform at peak-age levels on neurocognitive tests. Thus, future investigations need to consider the appropriate use of performance-based versus self-reported deficits when classifying individuals as SA versus CN.

Consistent with prior research, the WRAT reading subtest, an estimate of premorbid verbal IQ that is relatively resistant to HIV-associated neurocognitive decline (Casaletto et al., 2014), was higher in SA and predicted SA status. Moore et al. (2014) demonstrated a positive correlation between a composite measure of cognitive reserve, including verbal IQ, and

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successful cognitive aging in older PLWH. The theory of cognitive reserve postulates that effects of neural insults, such as age and comorbidities, are buffered by robust brain networks (Stern, 2002). Although operational definitions and methods of quantifying cognitive reserve may vary across studies (Moore et al., 2014; Nucci, Mapelli, & Mondini, 2012; Reed et al., 2010; Selzam et al., 2017), cognitive reserve is considered to reflect a combination of genetically-driven intellectual capacity and cognitively stimulating life experiences that promote resilience against age-related neurocognitive decline (Daffner, 2010; Stern, 2012). Although SA displayed higher premorbid functioning on the WRAT, neurocognitive status groups did not differ on years of education. Thus, neuroprotective benefits measured by higher WRAT performance may be better explained by factors other than education, such as genetically-driven neurocognitive resilience. More granular methods of quantifying both the genetic (e.g., polygenic risk scores) and environmental (e.g., educational quality, socioeconomic factors) loadings of cognitive reserve are needed to thoroughly address questions regarding premorbid functioning and age-related neuroprotection.

Among HIV-uninfected individuals, diabetes is also strongly associated with neurocognitive impairment and is considered to be a predisposing factor for later development of vascular dementia and Alzheimer's disease (Cheng, Huang, Deng, & Wang, 2012; Taguchi, 2009). Insulin resistance and diabetes are associated with MRI structural abnormalities and functional alterations of the blood brain barrier, resulting in processes that facilitate the pathogenesis and progression of neurocognitive impairment (Archibald et al., 2014; Mogi & Horiuchi, 2011; Prasad, Sajja, Naik, & Cucullo, 2014). We found a stair-step effect for the influence of diabetes on neurocognitive status such that CI individuals were characterized by the highest rates of diabetes, followed by CN, and then SA participants; associations between

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diabetes and neurocognitive status remained in multivariable analyses. Other studies have found similar increases in risk for HAND among HIV-infected persons with self-reported diabetes or elevated fasting insulin levels (McCutchan et al., 2012; Valcour et al., 2006; Valcour et al., 2005; Vance, Fazeli, et al., 2014). Thus, for SA participants, their relatively low incidence of diabetes likely contributed to better neurocognitive functioning. However, the effect of diabetes was not significant when restricting our multinomial regression analysis to virally suppressed participants, underscoring the importance of other contributing factors to SA status.

SA had lower BDI-II scores than both CN and CI univariately and in the multinomial logistic regression. In contrast, rates of current and lifetime MDD diagnoses did not significantly differ by neurocognitive status group, indicating that among older PLWH, current subclinical depressive symptoms are associated with neurocognitive functioning more closely than active or remote clinical depression. This relationship may reflect known neurological consequences of depression, including neuroinflammation and associated neuronal damage, apoptosis, and reduced neurogenesis (Kubera, Obuchowicz, Goehler, Brzeszcz, & Maes, 2011; Maes et al., 2009). Behavioral mechanisms may also underlie the relationship between depression and neurocognition, as depressive symptoms (even those that are subclinical) negatively impact engagement in activities known to promote neurocognitive health, including exercise, healthy nutrition, and social activity (Jeste, Depp, & Vahia, 2010; Moore, Hussain, et al., 2018; Vahia et al., 2010).

SA displayed greater rates of lifetime cannabis use disorder in comparison to CI, and this pattern also remained significant in the multinomial logistic regression. This result is supported by evidence suggesting neuroprotective effects of cannabis use through activation of cannabinoid receptors (i.e., CB_1 and CB_2) in the central nervous system (Sanchez & Garcia-Merino, 2012).

Specifically, CB_1 agonists reduce excitotoxity in post-synaptic neurons (Marsicano et al., 2003) while CB_2 agonists promote anti-inflammatory and immunomodulatory actions (Rom & Persidsky, 2013). Nevertheless, the relationship between cannabis use and brain integrity among PLWH and HIV-uninfected adults remains a controversial matter. While chronic cannabis use has been associated with neurometabolic abnormalities, reduced gray matter volumes, and memory deficits in cohorts comprised of PLWH and seronegative controls (Battistella et al., 2014; Chang, Cloak, Yakupov, & Ernst, 2006; Cristiani, Pukay-Martin, & Bornstein, 2004; Thames et al., 2017), emerging evidence suggests that active cannabis use may limit HIV viral replication and attenuate HIV-related immunosuppression, inflammation, and cerebral glutamate depletion (Chang et al., 2006; Rizzo et al., 2018; Thames, Mahmood, Burggren, Karimian, & Kuhn, 2016). These neuroprotective properties of the cannabinoid system are not referenced in the context of a cannabis use disorder, which may reflect problematic use or heavy exposure that could exceed therapeutic levels. Moreover, prior studies examining elite neurocognition in healthy elders have excluded participants with substance use histories that could influence neurocognition. Thus, our cannabis-related findings cannot be compared to prior SA studies and the relationship between cannabis use disorder and neuroprotection in HIV remains poorly characterized. Future research is needed to explore therapeutic levels of cannabis use and identify potential benefits of cannabinoid receptor activation on neurocognition among PLWH.

Despite stair-step patterns for HIV disease characteristics in SA individuals compared to CN and CI participants, only the proportion of participants with current CD4 counts below 200 was statistically significantly different among the neurocognitive status groups. Specifically, the SA group had a lower proportion with current CD4 counts below 200 than the CI group. However, this difference was not statistically significant when controlling for other clinical and

demographic variables (e.g., age, WRAT, and depressive symptoms). Unexpectedly, the SA and CN groups had low nadir CD4 counts comparable to the CI group, possibly reflecting underlying resilience to the "legacy" effects of advanced immunosuppression. In a comparison of predictors of HAND before and during the era of ART, only low nadir CD4 was found to increase risk of neurocognitive impairment in both treatment eras (Heaton et al., 2011). However, when examining factors associated with decline to symptomatic HAND, current CD4 also predicted decline to symptomatic status (Grant et al., 2014). SA with current CD4 counts below 200 were more likely to be off ART. Furthermore, the higher proportion of participants with CD4 counts below 200 in the CI group may result from poorer ART adherence that is a consequence of their cognitive impairment. Given that the majority of participants were likely to begin ART after having advanced HIV, it is unclear whether similar relationships between HIV disease severity and neurocognitive status exist for modern era patients who typically start treatment at earlier stages.

The observation that SA prevalence was twice as high in HIV-uninfected comparison participants as compared to PLWH provides important context to our findings. This difference, in addition to the higher prevalence of CN and lower prevalence of CI in HIV-uninfected controls, aligns with the known independent neurotoxic effects of HIV and potential synergistic effects of aging with HIV. Compared to their seronegative counterparts, older PLWH must withstand a greater amount of exposure to neural insults in order to sustain an elite level of neurocognitive performance. It is important to note that the HIV-uninfected group was demographically distinct from the PLWH group, as indicated by a higher prevalence of non-Hispanic Whites, more years of education, and better WRAT Reading scores. Thus, the

estimated two-fold difference in SA prevalence may be partially confounded by potential socio-demographic advantages of the HIV-uninfected group.

Several limitations to the present study warrant discussion. Our peak-age corrected neurocognitive scores, based on a normative sample of 25 year-olds, serve as proxy measures for neurocognitive resilience and do not directly capture the true within-subject change in neurocognitive performance since age 25. Because our data is cross-sectional, we cannot rule out the possibility that members of the SA group have experienced considerable lifetime neurocognitive decline and that their SA status is an artifact of superior baseline neurocognitive capacity. Although our analysis demonstrating that older age was associated with lower global scaled scores in CN and CI groups, but not the SA group, preliminarily supports the validity of our SA criteria, the magnitude of these age effects were small and did not significantly differ across groups. In addition to other factors importantly contributing to variance in global neurocognitive performance, these small effect sizes are likely influenced by the narrow age range of our sample.

Our results highlight clinically informative predictors and benefits of neurocognitive resilience; yet, the racial/ethnic composition of our sample was predominantly non-Hispanic white men and may limit the generalizability of our findings to more socio-demographically diverse populations. Furthermore, our cohort of older PLWH is relatively young compared to the healthy adult cohorts studied in the extant SA literature of persons not living with HIV, but the age range is indicative of some of the oldest PLWH with a sufficient sample size to be studied. Although the inclusion of an age-matched HIV-uninfected comparison group provided an informative anchor point for SA prevalence in healthy adults, this comparison group was not comparable to the PLWH group on other important demographic factors. Consequently,

important questions remain regarding the extent to which our definition of SA in PLWH reflects resilience to the effects of HIV and aging into late adulthood, which may only be adequately addressed with data from ideal comparison groups. As the proportion of PLWH older than 65 years of age increases, longitudinal cohort studies of PLWH will be better equipped to address critical questions related to the prevalence, stability, and impact of SA in PLWH compared to healthy seniors. Although we focused on evaluating the relationships between SA status and clinical correlates commonly assessed in PLWH, the absence of biomarker data indicative of central nervous system integrity (e.g., neuroimaging, cerebrospinal fluid assays) prevents us from determining the neurobiological correlates of SA status. Additionally, an assessment of modifiable behaviors (e.g., physical activity, neurocognitive activity, positive psychological outlook) that may mediate the relationships between SA status and psychosocial, medical, and everyday functioning correlates could help to prioritize research in clinical interventions to increase the fraction of SA in PLWH (Vance & Burrage, 2006).

Taken together, our results demonstrate that a substantial fraction of older, HIV-infected patients maintain their maximal neurocognitive abilities that confer real-world benefits even compared to patients with normal age-related cognitive decline. Although HIV disease negatively impacts the prevalence of SA, our findings highlight the clinical value in identifying neurocognitive resilience within PLWH and focus on the potential for positive outcomes despite aging with HIV. Examination of the stability of SA status through longitudinal analysis, exploration of biological and genetic markers of neuronal integrity, and assessment of modifiable lifestyle factors should enhance studies of future interventions to improve neurocognitive aging in older PLWH.

Acknowledgments

Table 2.1. Neurocognitive tests administered by domain

Domain	Test
Verbal Fluency	**Category Fluency**[a]
	Letter Fluency[a]
Attention/Working Memory	**Paced Auditory Serial Addition Task**[a]
	WAIS–III Letter-Number Sequencing[bc]
	WMS-III Spatial Span[bc]
Processing Speed	**WAIS–III Digit Symbol**[a]
	WAIS–III Symbol Search[a]
	Trail Making Test A[a]
	Stroop Color & Word Test Color Score[bd]
Executive Functioning	**Wisconsin Card Sorting Test-64 Perseverative Errors**[a]
	Trail Making Test B[a]
	Stroop Color & Word Test Interference Score[bd]
	Halstead Category Test[b]
Learning	**Hopkins Verbal Learning Test–Revised Total Learning**[a]
	Brief Visuospatial Memory Test–Revised Total Learning[a]
	Heaton Story Memory Test Learning[be]
	Heaton Figure Memory Test Learning[be]
Delayed Recall	**Hopkins Verbal Learning Test–Revised) Delayed Recall**[a]
	Brief Visuospatial Memory Test–Revised Delayed Recall[a]
	Heaton Story Memory Test Delayed Recall[be]
	Heaton Figure Memory Test Delayed Recall[be]
Motor skills	**Grooved Pegboard Test- Dominant Hand**[a]
	Grooved Pegboard Test- Non-dominant Hand[a]

[a]Core test administered across all studies with less than 5% missing data in the present sample.
[b]Supplemental test administered in select studies.
[c]Each study participant completed WAIS-III Letter-Number Sequencing (n=525) and/or WMS-III Spatial Span (n=224).
[d]n=308.
[e]Hopkins Verbal Learning Test-Revised and Brief Visuospatial Memory Test-Revised data were not used for learning and delayed recall domain scores for participants who also completed Heaton Story Memory Test and Heaton Figure Memory Test (n=138) data.
Bolded items have the greatest influence on global neurocognitive performance scores.

Table 2.2. Demographic and clinical characteristics by neurocognitive status in people living with HIV

Variable	SA (n=124)	CN (n=279)	CI (n=331)	p	Pair-wise comparisons[a]
Demographics					
Age (years)[b]	54.3 (3.97)	55.2 (3.91)	55.3 (4.08)	.06	
Gender (male)	107 (86.3)	235 (84.2)	276 (83.4)	.75	
Race/ethnicity (non-hispanic white)	79 (63.7)	142 (50.9)	203 (61.3)	.01	
Cognitive Reserve					
Education (years)	13.4 (2.58)	13.4 (2.64)	13.8 (2.69)	.14	
Estimated premorbid verbal IQ (WRAT)	103.5 (11.82)	98.1 (13.32)	96 (12.83)	<.001	SA > CN, CI
HIV Disease Characteristics					
History of AIDS	90 (72.6)	211 (75.6)	259 (78.3)	.43	
Detectable virus[c]	27 (21.8)	71 (25.5)	101 (30.5)	.13	
Current CD4 count	507 [367 – 700]	491 [333 – 691]	488 [275 – 674]	.16	
Current CD4 <200	9 (7.3)	31 (11.1)	52 (15.7)	.03	SA < CI
Nadir CD4 count	112 [18 – 258]	96 [19 – 225]	97 [21 – 209]	.72	
Nadir CD4 <200	79 (63.7)	196 (70.3)	236 (71.3)	.29	
Years of known HIV-infection					
Mean (SD)	18 (6.27)	17.9 (6.6)	17.7 (6.54)	.90	
Min - Max	5.6-31.1	5.4-31.0	5.2-33.7	-	
On ART	107 (86.3)	249 (89.3)	297 (89.7)	.59	
Medical Comorbidities					
Hypertension	48 (38.7)	124 (44.4)	148 (44.7)	.48	
Hyperlipidemia	42 (33.9)	90 (32.3)	108 (32.6)	.95	
BMI	26.5 (5.14)	26.6 (5.03)	26 (5.08)	.31	
Diabetes	12 (9.7)	56 (20.1)	62 (18.7)	.02	SA < CN, CI
HCV	37 (29.8)	119 (42.7)	124 (37.5)	.05	SA < CN

Note. Values are presented as mean (SD), median [IQR], or N (%); WRAT = Wide-Range Achievement reading subtest version 3 or 4; ART = antiretroviral therapy; BMI= body mass index; HCV= hepatitis C virus
[a]Pair-wise comparisons were examined using Tukey's HSD (α = 0.05) for continuous outcomes and Bonferroni-adjustments (α = 0.05/3 = 0.0167) for dichotomous outcomes
[b]Range of study sample restricted to 50-64 years for each neurocognitive status group
[c]Defined as >50 copies/mL

Table 2.3. Neuropsychiatric characteristics by neurocognitive status in people living with HIV

Variable	SA (n=119)	CN (n=264)	CI (n=295)	*p*	Pair-wise comparisons [a]
Lifetime Substance Use Disorders					
Alcohol	72 (60.5)	145 (54.9)	164 (55.6)	.57	
Cannabis	48 (40.3)	91 (34.5)	76 (25.8)	.01	SA > CI
Cocaine	46 (38.7)	114 (43.2)	96 (32.5)	.03	CN > CI
Methamphetamine	31 (26.1)	57 (21.6)	70 (23.7)	.62	
Opioid	15 (12.6)	43 (16.3)	52 (17.6)	.44	
Depression					
Lifetime MDD	66 (55.5)	160 (60.6)	182 (61.7)	.50	
Current MDD (n=651)	12 (10.4)	30 (11.6)	34 (12.2)	.88	
BDI-II (n=714)	8.7 (8.06)	11.9 (10.33)	13.0 (10.36)	<.001	SA < CN, CI

Note. Values are presented as mean (SD) or N (%); MDD= major depressive disorder; BDI-II= Beck Depression Inventory-II total score
[a]Pair-wise comparisons were examined using Tukey's HSD. (α = 0.05) for BDI-II and Bonferroni-adjustment (α = 0.05/3 = 0.0167) for diagnosis variables.

Table 2.4. Multinomial logistic regression predicting neurocognitive status in people living with HIV

Outcome: Classification as CN (reference: SA)				Outcome: Classification as CI (reference: SA)			
Predictor	OR	95% CI	*p*	Predictor	OR	95% CI	*p*
Age	1.10	[1.03, 1.17]	<.001	Age	1.11	[1.05, 1.19]	.001
WRAT	0.96	[0.94, 0.98]	<.001	WRAT	0.95	[0.93, 0.97]	<.001
CD4<200	1.40	[0.60, 3.26]	.63	CD4<200	1.98	[0.86, 4.51]	.11
HCV	1.32	[0.80, 2.18]	.28	HCV	0.97	[0.59, 1.62]	.92
Diabetes	2.23	[1.11, 4.47]	.02	Diabetes	2.14	[1.06, 4.33]	.03
Cannabis	0.74	[0.46, 1.20]	.22	Cannabis	0.46	[0.28, 0.75]	.002
BDI-II	1.04	[1.02, 1.07]	<.001	BDI-II	1.06	[1.03, 1.09]	<.001

Note. OR= Odds Ratio; 95% CI= 95% Confidence Interval; WRAT= Wide-Range Achievement reading subtest version 3 or 4; HCV= hepatitis C virus; Cannabis= lifetime cannabis use disorder; BDI-II= Beck Depression Inventory-II total score.
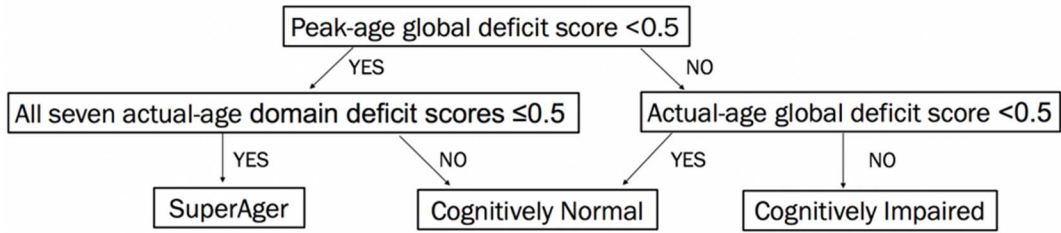
Figure 2.1. Neurocognitive status criteria. SuperAging was operationalized as a peak-age global deficit score within normal limits (i.e., less than 0.5) and normal performance on all seven actual-age deficit scores (i.e., less or equal than 0.5).
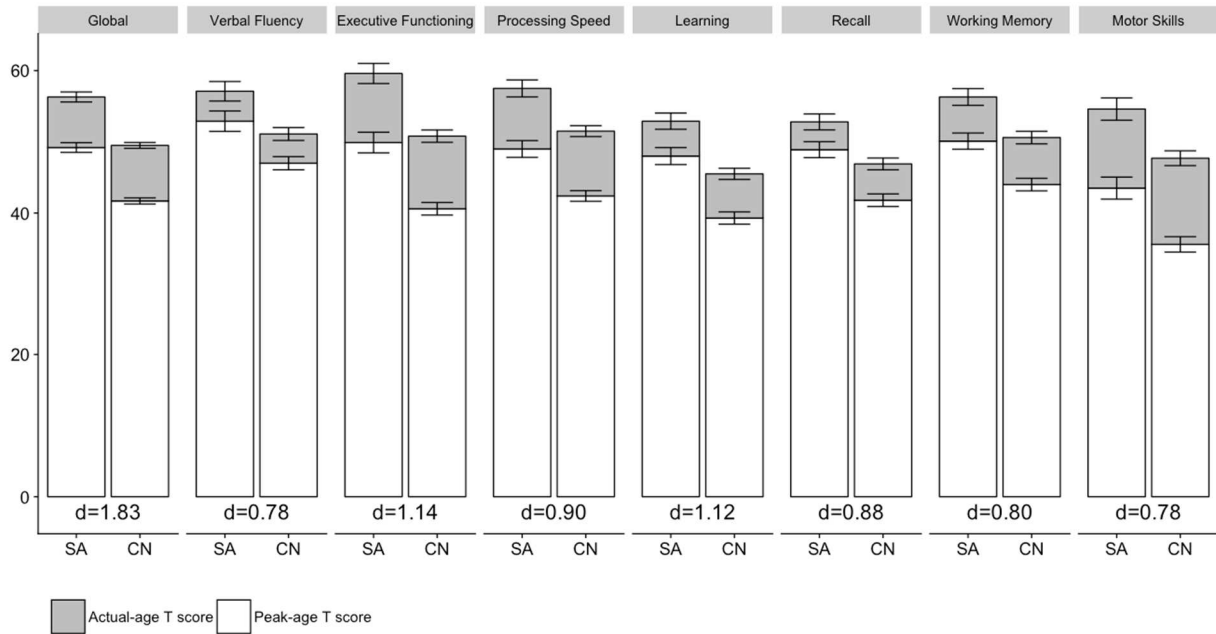
Figure 2.2. SuperAger (SA) versus cognitively normal (CN) differences in neurocognitive performance**.** Cohen's d effect size estimates reflect differences in actual-age T scores.
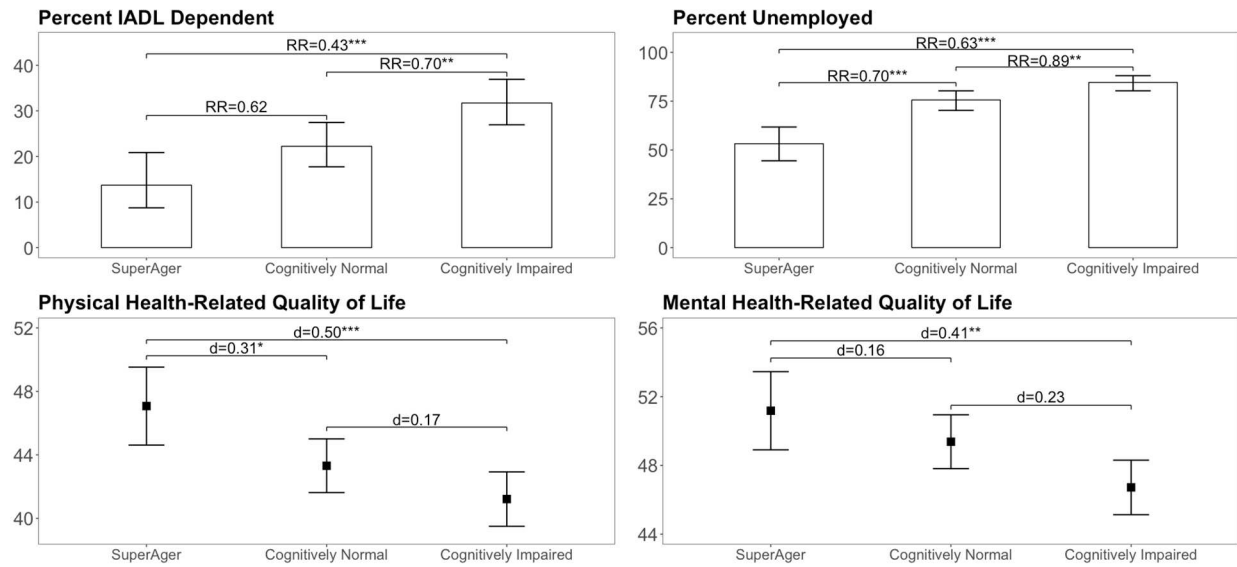
Figure 2.3. Everyday functioning and health-related quality of life by neurocognitive status. Risk ratio (RR) estimates represent the reduction in risk of IADL dependence or unemployment for each pair-wise comparison. Cohen's *d* effect size estimates reflect differences in health-related quality of life for each pair-wise comparison. All *p*-values are significant after Bonferroni-adjustment or Tukey's HSD.

***$p<.001$

**$p<.01$

*$p<.05$

Chapter 2, in full, is a reprint of the material as it appears in the *Journal of the International Neuropsychological Society*, Saloner, R., Campbell, L. M., Serrano, V., Montoya, J. L., Pasipanodya, E., Paolillo, E. W., Franklin, D., Ellis, R. J., Letendre, S. L., Collier, A. C., Clifford, D. B., Gelman, B. B., Marra, C. M., McCutchan, J. A., Morgello, S., Sacktor, N., Jeste, D. V., Grant, I., Heaton, R. K., Moore, D. J., CHARTER & HNRP Groups (2019). The dissertation author was the primary investigator and author of this paper.

CHAPTER 3: STUDY 2

Cognitive and Physiologic Reserve Independently Relate to Superior Neurocognitive Abilities in

Adults Aging with HIV

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ABSTRACT

Background: A subgroup of older persons with HIV (PWH) possess "youthful" neurocognitive abilities characteristic of SuperAging (SA). We examined joint contributions of cognitive reserve (CR) and physiologic reserve (PR), which reflect resilience against neural and systemic stressors, respectively, to SA in older PWH.

Methods: Using published criteria, 396 older PWH (aged 50+ years) were classified as SuperAgers (SA; n=57), cognitively normal (CN; n=172) or cognitively impaired (CI; n=167). Estimated verbal IQ and a validated comorbidity burden index defined CR and PR, respectively.

Results: Neurocognitive groups did not differ by HIV disease severity. Adjusting for age, depression, and race/ethnicity, both reserve factors predicted SA status in multinomial logistic regression. Higher PR predicted linear increases in odds of SA and higher CR predicted a quadratic 'J-shaped' change in odds of SA compared to CN (i.e., odds of SA>CN only above 35th percentile of CR).

Conclusions: Each reserve factor uniquely related to SA status, which supports the construct validity of our SA criteria and suggests CR and PR 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.

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 (Pathai et al., 2014). With an estimated half of PWH in the U.S. aged 50 and older (Centers for Disease Control and Prevention, 2018), elucidating mechanisms that support healthy neurocognitive aging in older PWH is paramount for addressing their complex neuromedical needs (High et al., 2012; Mills et al., 2012).

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; Rogalski et al., 2013). Compared to cognitively average (but non-Super) peers, SA exhibit less Alzheimer's-related neuropathology and greater brain integrity, neuroimmune function, and psychological well-being (de Godoy et al., 2020). We recently characterized a group of older (≥50-years-old) PWH with global neurocognition akin to that of a healthy 25-year-old (Saloner, Campbell, et al., 2019), 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 (e.g., neuronal loss due to aging and HIV) on neurocognitive decline can be mitigated by adaptive brain processes that preserve neurocognition through efficient neural firing and compensatory recruitment of additional neural networks (Stern, 2009; Stern et al., 2018; Vance, McDougall, et al., 2014). While 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 (Stern et al., 2018). 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 (Baker et al., 2017; Stern, 2012) and predicts better cross-sectional (Foley et al., 2012; Moore et al., 2014; Thames, Foley, et al., 2011) and longitudinal neurocognition (Heaton et al., 2015) 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 (Bagshaw & McDermid, 2013). 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 (Bagshaw & McDermid, 2013; Rockwood & Mitnitski, 2011). 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 (Guaraldi et al., 2011; Thurn & Gustafson, 2017). However, the rates at which individuals accumulate health deficits vary significantly (Rockwood & Mitnitski, 2011), and composite indices of health deficits that capture this variability predict neurocognition and longevity (Guaraldi et al., 2015; Oppenheim et al., 2018; Wallace et al., 2017).

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, the present study jointly modelled linear and non-linear associations of cognitive and physiologic reserve with SA status in a multi-site, national cohort of older PWH.

Methods

Participants

      Participants included 396 PWH enrolled in the CNS HIV Antiretroviral Therapy Effects

Research (CHARTER) study (Heaton et al., 2010) from 2003 to 2018. CHARTER is composed

of six 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 (e.g., severe learning disability),

psychiatric (e.g., psychosis), neuromedical (e.g., epilepsy), or substance use (e.g., positive

toxicology screen) histories that confounded the interpretation of neuropsychological test data

and its association with HIV disease, as previously described (Heaton et al., 2010; Saloner,

Heaton, et al., 2019). CHARTER Study procedures were approved by local Institutional Review

Boards (IRBs) 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 (Carey et al., 2004; Heaton et al., 2010). To determine the extent to which test

performance in older PWH deviated from "youthful" performance levels, individual test scores

were first compared in reference to the normative range of performance for HIV-seronegative

25-year olds (Saloner, Campbell, et al., 2019) while still adjusting for the known demographic influences of sex, education, and race/ethnicity on test performance (Heaton, Miller, et al., 2004; Heaton et al., 2003; Norman et al., 2011). Using our published criteria for SuperAging in PWH (Saloner, Campbell, et al., 2019), 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 '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 (Blackstone et al., 2012; Carey et al., 2004).

Cognitive Reserve

Cognitive reserve was measured using standardized scores from the Reading subtest of the Wide Range Achievement Test, version 4 (WRAT4; Wilkinson & Robertson, 2006), a validated proxy for cognitive reserve that is robust to neurocognitive decline in older HIV-seronegative adults and PWH (Baker et al., 2017; Casaletto et al., 2014; Siedlecki et al., 2009). The WRAT4 is considered a more direct estimate of educational attainment or quality than total years of education completed (Stern, 2009), particularly in racially diverse and marginalized older adult populations (Manly, Jacobs, Touradji, Small, & Stern, 2002). For analysis, we compared cognitive reserve measured with the WRAT4 standard scores as well as with race/ethnicity-adjusted WRAT4 scores in order to partial out the influence of racial/ethnic disparities in educational quality that cannot be attributed to premorbid intelligence(Avila et al., 2021; Cohen, White, & Cohen, 2012).

Physiologic Reserve via *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(Bagshaw & McDermid, 2013; Rockwood & Mitnitski, 2011; Searle et al., 2008). For the present study, the cumulative physiologic reserve variable was composed of 39 unique variables encompassing a range of physiologic systems, including routine clinical laboratory measures (e.g., glucose, lipids), medical comorbidities (e.g., hepatitis C co-infection, diabetes), and indicators of HIV-disease severity (see Table 3.1). Each variable was dichotomized as normal or deficient based on prior studies that established the convergent validity of frailty indices as predictors of longevity and neurocognitive impairment in PWH(Guaraldi et al., 2015; Oppenheim et al., 2018). The present 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 employed a cut-point of 0.75 (<0.75 = low; ≥0.75 = high) that has been validated as a predictor of mortality (Rockwood, Andrew, & Mitnitski, 2007). In accordance with standard frailty index guidelines (Searle et al., 2008), we excluded variables that had >5% missing data (i.e., phosphorous, LDL cholesterol, fasting insulin) or had <1% of participants meeting deficit criteria (i.e., sodium, peripheral vascular disease, congestive heart failure).

Psychiatric Evaluation

A psychiatric evaluation ascertained DSM-IV diagnoses of current and lifetime mood and substance use disorders via the structured Composite International Diagnostic Interview (CIDI; World Health Organization, 1998). Current mood symptoms were assessed with the Beck Depression Inventory-II (BDI-II; Beck et al., 1996). Cognitive, affective, and somatic BDI-II subscales were computed based on a prior factor analysis in the CHARTER cohort (Hobkirk et al., 2015).

Statistical Analyses

Neurocognitive status differences on demographic, psychiatric, HIV disease, cognitive reserve, and physiologic reserve variables were examined using analysis of variance (ANOVA), 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 to 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 modelled neurocognitive status as a function of linear and quadratic terms for cognitive and physiologic reserve, as well as the interaction of linear terms. In addition to race/ethnicity, variables were screened for inclusion as covariates at a $p<.10$ association with the primary dependent variable of neurocognitive status. The Johnson-Neyman (J-N) technique (Johnson & Neyman, 1936; Preacher, Curran, & Bauer, 2006) 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. Results were considered statistically significant at $p<.05$. All analyses were conducted in R (version 3.5.0.).

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. With regard to 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 3.2. 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=.027). This finding was driven by differences in somatic (p=.042) and affective (p=.024) symptoms, but not cognitive (p=.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 to nadir CD4 counts (median= 124 cells/mm^3) and active ART use (84%). Rates of viral suppression (i.e., undetectable plasma HIV RNA) ranged from 57% (CI) to 63% (SA), comparable to the full CHARTER cohort and data collection period (2003 to 2018).

Cognitive and Physiologic Reserve

Cognitive reserve (i.e., 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=.09, p=.085). Figure 3.1 displays neurocognitive status group differences in cognitive (panel A) and physiogic reserve (panel B). Univariably, SA exhibited higher cognitive reserve scores vs. CI (d=0.41, p=.008) and trended toward higher scores vs. CN (d=0.29, p=.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<.001), the association between neurocognitive status and cognitive reserve strengthened. Specifically, SA exhibited higher cognitive reserve vs. both CI (d=0.64, p<.001) and CN (d=0.39, p=.011), and CN exhibited higher cognitive reserve vs. CI (d=0.25, p=.023). Univariably, SA exhibited higher physiologic reserve vs. both CI and CN (both ds=0.39, ps=.012), whereas physiologic reserve did not differ between CN and CI (d=0.00, p=.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=-.04, p=.469).

Figure 3.2 displays odds ratios comparing SA to CI (panel A) and CN (panel B) for each individual health deficit criterion that comprised the cumulative physiologic reserve index and Table 3.3 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% CI: 0.24 – 0.86], p=0.015) and CN (OR=0.43 [95% CI: 0.23 – 0.80], p=0.008). Compared to CI, SA had lower rates for 77% (30 out 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 – 0.90], p=0.020). Compared to CN, SA had lower rates for 79% (31 out 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 – 0.98], *p*=0.039).

Multinomial Logistic Regression

Multinomial logistic regression modelled 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*<.001) such that a one

standard deviation 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*=.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*<.001; quadratic: beta=0.38, ΔOR=2.14, *p*=.033). Specifically, higher

cognitive reserve related to higher odds of SA vs. CN and this positive slope increased by 114%

for every additional standard deviation increase in cognitive reserve. Using the J-N 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 (i.e., 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*=.029; quadratic: beta=-0.24,

ΔOR=0.62, *p*=.030). Higher cognitive reserve initially related to higher odds of CN vs. CI,

however this slope decreased by 38% for every additional standard deviation 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

(i.e., WRAT4<96.4). Figure 3.3 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 standard deviation increase in physiologic reserve corresponded to a 44-45% increase in odds of SA (vs. CI: beta=0.37, OR=1.45, p=.042; vs. CN: beta=0.36, OR=1.44, p=.043). Physiologic reserve did not significantly relate to odds of CN vs. CI (beta=-0.01, OR=0.99, p=.939).

With respect to covariates, older age (beta=-0.18, OR=0.83, p=.001), higher BDI-II scores (beta=-0.04, OR=0.96, p=.026), and non-Hispanic White race/ethnicity (vs. non-Hispanic Black; beta=-1.54, OR=0.22, p<.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<.001).

Discussion

Neurocognitive SuperAging provides a natural framework for studying resilience against the multi-faceted 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, the present study observed higher estimated premorbid verbal intelligence and less accumulation of health deficits in SA compared to 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.

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-to-medium sized increase in cognitive reserve (i.e., 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 to 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. This quadratic pattern adds important context to prior studies, including our initial documentation of SuperAging with HIV(Saloner, Campbell, et al., 2019), that have assumed a linear relationship between cognitive reserve and neurocognitive impairment. Our findings also converge with the notion that a deficit-based approach to quantifying neurocognitive predictors (e.g., low IQ vs. 'normal' IQ) lacks the precision to detect differences between older adults with 'normal' age-related neurocognition compared to those with superior neurocognition. 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 (e.g., CSF inflammation, 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 two non-mutually 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 Hispanics (Avila et al.,

2021). 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 (Avila et al., 2021; Manly et al., 2002; Manly et al., 1998). Although accounting for reading level improves the predictive utility of neuropsychological tests, structural factors also contribute to racial/ethnic disparities in literacy (Cohen et al., 2012; Manly et al., 2002). Our data is consistent with this, as 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) employed 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 to both CN and CI, who did not differ in physiologic reserve. The psychometrically-advantageous cumulative physiologic reserve index also exhibited greater statistical precision than the majority of the 39 individual health variables comprising the index, which aligns with prior work showing that a cumulative index approach outperforms any individual deficit in predicting mortality (Mitnitski et al., 2001). It is also noteworthy that physiologic reserve predicted SA status above and beyond chronological age given that prior 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 (Rogalski et al., 2013), including frailty index scores in PWH (Oppenheim et al., 2018). Taken together, physiologic reserve may more precisely measure 'biological age' than chronological age and can be computed using routinely-collected clinical record data (Mitnitski et al., 2002; Trebbastoni et al., 2017).

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 to 69 years is younger than most aging study cohorts without HIV disease. Our data accordingly cannot be directly compared to 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 (Blanco et al., 2012). Our data importantly integrates 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.

Our findings support the construct validity of SuperAging in HIV, as the neurocognitively elite SA exhibited higher levels of cognitive and physiologic reserve compared to both CN and CI. Cognitive and physiologic reserve were 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 reflect nonoverlapping pathways of neuroprotection in PWH. Incorporation of proxy markers of reserve in clinical practice may help providers better characterize age-related cognitive risk and resilience among older PWH. 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, even among those without overt neurocognitive deficits.

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Table 3.1. Physiologic reserve index criteria

Variable	Deficit Criteria
Clinical Measurements	
1. Abnormal BMI	>25 or <18kg/m^2
2. Low white blood cell count	<4000 cells/µl
3. Abnormal MCHC	Male: <27.8 or >33.8; Female: <26.9 or >33.3
4. Abnormal BUN	<8 mg/dl or >23 mg/dl
5. Abnormal creatinine	<.6 mg/dl or >1.2 mg/dl
6. Abnormal calcium	<9.2 mg/dl or >10.8 mg/dl
7. Abnormal chloride	<96 mEq/l or >106 mEq/l
8. Abnormal total protein (serum)	<6 mg or >7.8 mg
9. Low albumin (serum)	<3.5 mg
10. Elevated fibrinogen	>3.25
11. Low eGFR	<60
12. Low hemoglobin	Male: <12 µmol/l; Female: <10 µmol/l
13. Elevated AST	>31 U/l
14. Elevated ALT	>31 U/l
15. Abnormal ALP	<38 U/l or >126 U/l
16. Abnormal potassium	<3.5 or >5.3 mEq/l
17. Elevated total bilirubin	>1.1 mg/dl
18. Elevated triglycerides	≥150 mg/dl
19. Elevated total cholesterol	>200 mg/dl
20. Low HDL cholesterol	Male: <40 mg/dl; Female: <50 mg/dl
21. Elevated glucose	>200 mg/dl
22. Weight loss	>10 lbs in past year
23. Low platelets	<150 billion/l
Comorbidities	
24. HCV	Positive
25. Diabetes mellitus	Positive
26. COPD	Positive
27. Malignancy	Positive
28. Myocardial infarction	Positive
29. Renal disease	Positive
30. Hypertension	Positive or >130 mmHg systolic or > 85 mmHg diastolic
31. Hyperlipidemia	Positive
32. Cerebrovascular accident	Positive
33. Sensory neuropathy	Positive
34. Distal neuropathic pain	Positive

Table 3.1. Physiologic reserve index criteria, continued

Variable	Deficit Criteria
35. Smoking (ever)	Positive
HIV Specific	
36. Low current CD4	<500 cells/µl
37. Nadir CD4	<200 cells/µl
38. Detectable plasma HIV RNA	>40 copies/ml
39. Duration of disease	>10 years

Abbreviations: 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.

Table 3.2. Study sample characteristics by neurocognitive status

	CI (n=167)	CN (n=172)	SA (n=57)	*p*
Demographics				
Age (years), 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 (years), 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 years 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

Abbreviations: BDI-II = Beck Depression Inventory-II; WRAT4 = Wide Range Achievement Test Reading subtest, version 4; ART = antiretroviral therapy.

Table 3.3. Proportion of participants meeting criteria for each health deficit comprising the physiologic reserve index by neurocognitive status

Physiologic reserve variable	CI	CN	SA
BMI	109 (65.3%)	98 (59.4%)	30 (54.5%)
White blood cell count	26 (15.6%)	31 (18.0%)	7 (12.5%)
MCHC	107 (64.1%)	108 (63.2%)	31 (55.4%)
BUN	19 (11.4%)	27 (15.7%)	4 (7.0%)
Creatinine	30 (18.1%)	34 (19.8%)	9 (15.8%)
Calcium	47 (28.7%)	55 (32.7%)	20 (35.1%)
Chloride	20 (12.1%)	26 (15.3%)	7 (12.3%)
Total protein (serum)	81 (49.1%)	78 (45.9%)	18 (31.6%)
Albumin (serum)	13 (7.8%)	5 (2.9%)	2 (3.5%)
Fibrinogen	12 (7.2%)	15 (8.7%)	3 (5.4%)
eGFR	15 (9.0%)	21 (12.2%)	5 (8.8%)
Hemoglobin	13 (7.8%)	9 (5.2%)	4 (7.1%)
AST	79 (47.3%)	88 (51.2%)	28 (49.1%)
ALT	88 (52.7%)	94 (54.7%)	33 (57.9%)
ALP	41 (24.7%)	33 (19.4%)	10 (17.5%)
Potassium	8 (4.8%)	15 (8.8%)	1 (1.8%)
Total bilirubin	31 (18.6%)	29 (16.9%)	9 (15.8%)
Triglycerides	88 (54.7%)	92 (54.1%)	29 (50.9%)
Total cholesterol	51 (31.7%)	60 (35.7%)	15 (26.3%)
HDL cholesterol	66 (41.2%)	68 (40.7%)	24 (42.9%)
Glucose	16 (9.6%)	9 (5.2%)	2 (3.5%)
Weight loss	20 (12.0%)	20 (11.8%)	2 (3.6%)
Platelets	19 (11.4%)	22 (12.8%)	5 (8.9%)
HCV	52 (32.7%)	58 (35.2%)	19 (36.5%)
Diabetes mellitus	29 (18.2%)	24 (14.5%)	7 (13.5%)
COPD	14 (8.8%)	18 (10.9%)	4 (7.7%)
Malignancy	5 (3.1%)	6 (3.6%)	5 (9.6%)
Myocardial infarction	7 (4.4%)	9 (5.5%)	1 (1.9%)
Renal disease	3 (1.9%)	3 (1.8%)	0 (0.0%)
Hypertension	94 (58.4%)	101 (59.8%)	25 (48.1%)
Hyperlipidemia	21 (13.2%)	30 (18.2%)	9 (17.3%)
Cerebrovascular accident	10 (6.3%)	6 (3.6%)	0 (0.0%)
Sensory neuropathy	133 (81.1%)	132 (78.1%)	40 (70.2%)
Distal neuropathic pain	64 (39.0%)	71 (42.0%)	15 (26.8%)
Smoking (ever)	131 (78.9%)	138 (80.2%)	42 (73.7%)

Table 3.3. Proportion of participants meeting criteria for each health deficit comprising the

physiologic reserve index by neurocognitive status, continued

Physiologic reserve variable	CI	CN	SA
Current CD4	82 (49.7%)	94 (55.6%)	29 (51.8%)
Nadir CD4	118 (70.7%)	106 (61.6%)	35 (61.4%)
Detectable plasma HIV RNA	121 (72.5%)	120 (69.8%)	40 (70.2%)
Duration of infection	70 (44.0%)	65 (39.9%)	20 (37.0%)

Effect sizes (odds ratios) comparing the prevalence of individual health deficits in SA vs. CI and
CN are presented in Figure 3.2.
Abbreviations: 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.
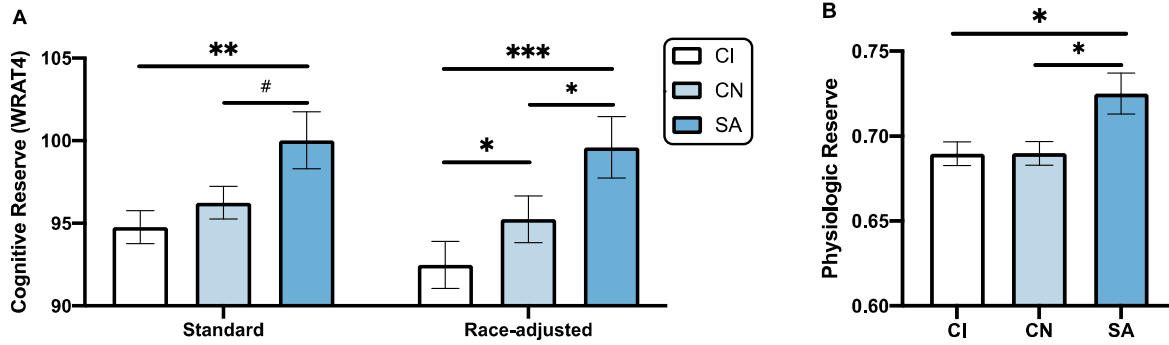
Figure 3.1. SuperAgers exhibit higher cognitive and physiologic reserve compared to non-SuperAgers. Panel A) Raw and race/ethnicity-adjusted cognitive reserve (i.e., WRAT4 reading scores) by neurocognitive status. SuperAgers (SA) univariably exhibit higher cognitive reserve compared to cognitively impaired (CI) and cognitively normal (CN) individuals, and this relationship strengthens after adjusting for the influence of race/ethnicity on WRAT4 reading performance. Panel B) SA exhibit higher levels of physiologic reserve, or fewer health deficits, compared to CI and CN, whereas CI and CN do not differ on physiologic reserve.

$\# = p < .10$

$* = p < .05$

$** = p < .01$

$*** = p < .001$
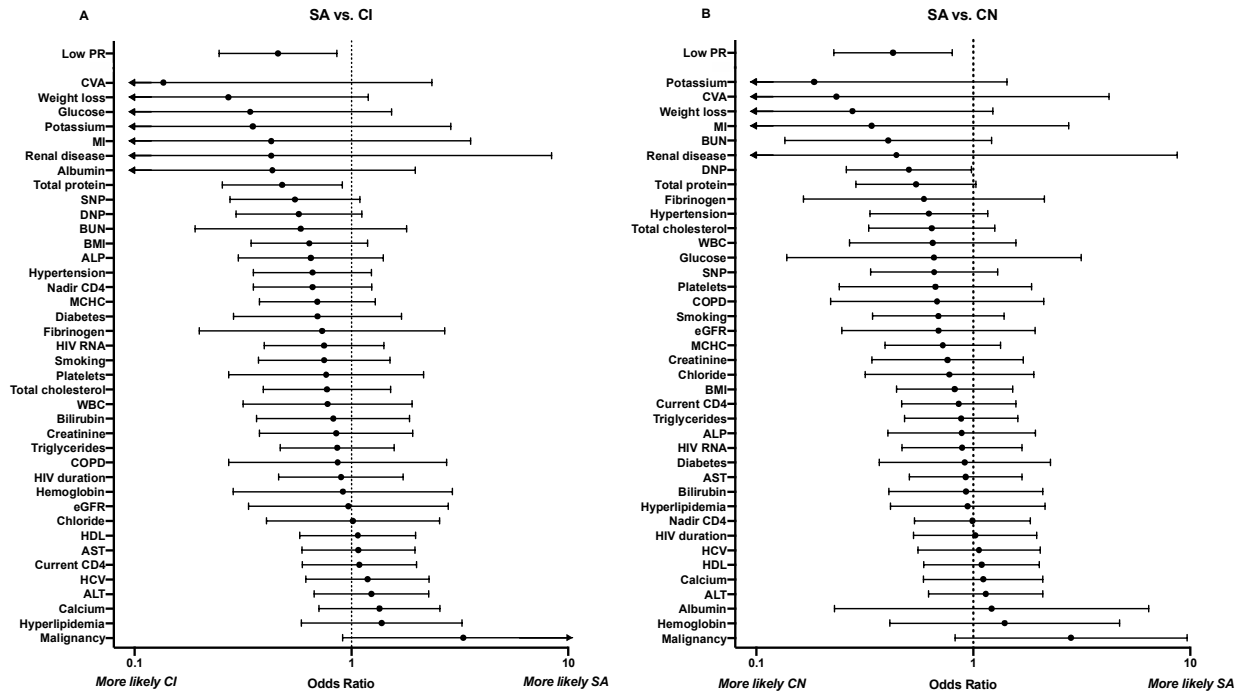
Figure 3.2. Association of physiologic reserve index components and SuperAging. Forest plot displaying the magnitude and precision (95% confidence intervals) of odds ratio effect size estimates reflecting the relationship between SuperAger (SA) status and individual health deficits comprising the cumulative physiologic reserve (PR) index. SA were less likely to meet criteria for the majority of individual index components compared to cognitively impaired (CI; panel A) and cognitively normal (CN; panel B) individuals, however almost all odds ratios reflecting these individual health deficit differences failed to reach statistical significance due to poor precision. Conversely, the odds ratio 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 odds ratio of 1). The prevalence of individual health deficits by neurocognitive status are provided in Table 3.

Abbreviations: 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
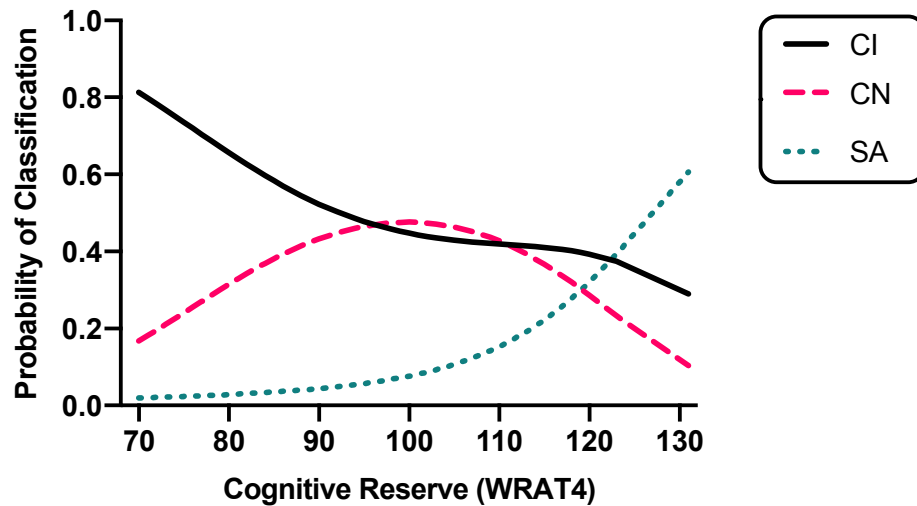
Figure 3.3. Quadratic associations between cognitive reserve and neurocognitive status. Cognitive reserve exhibited independent linear and quadratic effects on neurocognitive status in multinomial logistic regression analyses, accounting for age, depressive symptoms, race/ethnicity, and physiologic reserve. Higher cognitive reserve linearly increased odds of classification as SuperAger (SA) compared to cognitively impaired (CI; dotted line vs. solid line) across the full range of cognitive reserve. Higher cognitive reserve best discriminated SA from cognitively normal (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).

Chapter 3, in full, is a reprint of the material as it appears in *Journal of Acquired Immunodeficiency Syndromes*, Saloner, R., Lobo, J., Paolillo, E.W., Campbell, L.M., Letendre, S. L., Cherner, M., Heaton, R.K., Ellis, R.J., & Moore, D. J. (2022). The dissertation author was the primary investigator and author of this paper.

CHAPTER 4: STUDY 3

Identification of Youthful Neurocognitive Trajectories in Adults Aging with HIV: A Latent Growth Mixture Model

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ABSTRACT

Despite the neurocognitive risks of aging with HIV, initial cross-sectional data suggest a subpopulation of older people with HIV (PWH) possess youthful neurocognition (NC) characteristic of SuperAgers (SA). Here we characterize longitudinal NC trajectories of older PWH and their convergent validity with baseline SA status, per established SuperAging criteria in PWH, and baseline biopsychosocial factors. Growth mixture modeling (GMM) identified longitudinal NC classes in 184 older (age≥50-years) PWH with 1-5 years of follow-up. Classes were defined using 'peak-age' global T-scores, which compare performance to a normative sample of 25-year-olds. 3-classes were identified: Class 1$_{Stable\ Elite}$ (n=31 [16.8%], high baseline peak-age T-scores with flat trajectory); Class 2$_{Quadratic\ Average}$ (n=100 [54.3%], intermediate baseline peak-age T-scores with u-shaped trajectory); Class 3$_{Quadratic\ Low}$ (n=53 [28.8%], low baseline peak-age T-scores with u-shaped trajectory). Baseline predictors of Class 1$_{Stable\ Elite}$ included SA status, younger age, higher cognitive and physiologic reserve, and fewer subjective cognitive difficulties. This GMM analysis supports the construct validity of SuperAging in older PWH through identification of a subgroup with longitudinally-stable, youthful neurocognition and robust biopsychosocial health.

Introduction

In the U.S. and other developed countries, HIV is no longer considered a rapidly debilitating terminal illness, but rather a chronic medical condition when treated with modern antiretroviral therapy (ART; Stoff, 2004). Despite increased longevity in the ART-era, geriatric syndromes such as neurocognitive impairment (NCI) and frailty manifest at younger ages and may accumulate at faster rates in persons with HIV (PWH) compared to HIV-seronegative adults (Greene et al., 2015; Guaraldi et al., 2011). NeuroHIV investigators have accordingly developed models of premature and accelerated aging to characterize the excess risk for age-related central nervous system (CNS) complications in older PWH (Aung et al., 2021; Pathai et al., 2014; Sheppard et al., 2017; Sheppard et al., 2015). Aging with HIV appears to exert a heightened neurotoxic effect, as evidenced by accelerated rates of cortical and subcortical brain atrophy (Cohen et al., 2015; Petersen et al., 2021; Pfefferbaum et al., 2018) and excessive levels of neuroinflammation (Chang et al., 2004; Cysique et al., 2013). The source of these neurological vulnerabilities is likely multifactorial, as older PWH have higher rates of biological and psychosocial risk factors for neurobehavioral decline (Pasipanodya et al., 2019; Rueda et al., 2014).

Age is commonly identified as a risk factor for HIV-associated NCI at the cross-sectional level, however one to two-thirds of older PWH do not meet criteria for NCI and synergistic effects of age and HIV on NCI are not consistently detected (Cysique, Maruff, Bain, Wright, & Brew, 2011; Valcour, Paul, Neuhaus, & Shikuma, 2011; Valcour, 2013). Although a substantial proportion of older PWH do not exhibit overt neurocognitive deficits, neuroHIV studies generally do not consider a full range of inter-individual differences in neurocognition (e.g., low average to superior) within this neurocognitively unimpaired group. Aging is associated with

increased heterogeneity across most health-related outcomes (Nelson & Dannefer, 1992; Rogalski et al., 2013) and the range of unimpaired neurocognitive performance is widened with age-based neuropsychological test score corrections. Differentiating patterns of neurocognition within unimpaired individuals, such as separating out typical neurocognitive aging from superior neurocognitive aging, can enhance understanding of the factors that promote sustained neurocognition compared to factors that ward off NCI but do not prevent "normal" age-related decline.

Neurocognitive aging studies in elders without HIV have recognized the heterogeneous nature of neurocognitive aging and some data suggest that several subpopulations may exist within the broader group of older adults with unimpaired neurocognition. Specifically, there is growing evidence that a subgroup of elders without HIV possess youthful neurocognitive abilities (Rogalski et al., 2013). These individuals, termed cognitive *SuperAgers* (SA), may be resilient to expected age-related neurocognitive decline and they display more robust neurological and psychological functioning compared to the subgroup of cognitively average, but non-super, peers (de Godoy et al., 2020). Despite the neurocognitive hazards of aging with HIV, prior work has also identified a subgroup of older (≥50-years) PWH who exhibit comparable cross-sectional neurocognitive performance to that of a healthy 25-year-old (estimated ~17% of older PWH; Saloner, Campbell, et al., 2019). Compared to their cognitively average and cognitively impaired counterparts with HIV, these SA with HIV exhibit better functioning on key biopsychosocial indicators, including less comorbidity burden and self-reported cognitive and depressive symptoms, as well as higher levels of cognitive reserve.

The initial investigation of SA in PWH highlights the ecological relevance of differentiating SA from cognitively average older PWH, yet these cross-sectional data do not

address whether SA with HIV maintain stable neurocognition over time. Characterizing longitudinal trajectories of neurocognitive functioning is essential for unmasking a subgroup of older PWH with superior/peak neurocognitive abilities that are stable across time. Thus, the present study applied latent growth mixture modeling (GMM) to characterize trajectories of youthful neurocognitive aging in a multi-site, national cohort of older PWH. GMM is a person-centered approach that facilitates the identification of latent longitudinal classes, which account for unobserved intercept and slope heterogeneity in the entire sample, and predictors can be specified in GMM to explain inter-class differences in neurocognitive change (Muthén & Kaplan, 2004; Nagin, 2005). Within this GMM framework, we examined the degree to which baseline SuperAging classifications and baseline indicators of biopsychosocial health at baseline (e.g., cognitive reserve, physiologic reserve, depression) converged with longitudinal classes of neurocognitive aging in PWH. We hypothesized that longitudinal neurocognitive patterns would be heterogeneous and latent classes would reflect theoretical trajectories of neurocognitive aging, including a neurocognitively elite and stable subgroup. We also hypothesized that individuals classified as SA at baseline would have the highest odds of membership in longitudinal class(es) defined by elite and stable neurocognition. Similarly, better baseline biopsychosocial functioning to have higher odds of membership in better longitudinal class(es).

Methods

Participants

Participants included 184 older PWH enrolled in the CNS HIV Antiretroviral Therapy Effects Research (CHARTER) study (Heaton et al., 2010) from 2003 to 2017. As a multi-site study, CHARTER participants were drawn from six participating university centers: Johns Hopkins University (Baltimore, MD, n = 34); Mt. Sinai School of Medicine (New York, NY, n =

42); University of California at San Diego (San Diego, CA, n = 18); University of Texas Medical Branch (Galveston, TX, n = 40); University of Washington (Seattle, WA, n = 25); and Washington University (St. Louis, MO, n = 25). To be included in the present longitudinal analysis, participants must have been aged 50 years or older at their baseline visit and must have completed at least 2 additional CHARTER study visits, which occurred in 6-month follow-up intervals (1200 total visits; median = 6 visits; range = 3-10 visits). Of the 1200 observations, 1103 (92%) reflect novel observations that were not included in our prior analysis of SA in HIV(Rogalski et al., 2013). All participants completed a blood draw and comprehensive neuromedical, neurobehavioral, and neuropsychiatric examinations at each study visit. All CHARTER study procedures were approved by local Institutional Review Boards (IRBs) and all participants provided written informed consent. CHARTER participants with baseline conditions that "confounded" the interpretation of neuropsychological test data and its association with HIV disease were excluded from analysis(Heaton et al., 2010; Saloner, Heaton, et al., 2019). Confounding conditions included history of severe learning disability, diagnosis of a psychotic (e.g., schizophrenia) or mood disorder with psychotic features, and major neurological conditions (e.g., epilepsy). Visits were also excluded if participants had a positive urine toxicology screen for substance use (except marijuana) or Breathalyzer test for alcohol on the day of testing.

Neuropsychological Evaluation

At each timepoint, participants completed a standardized battery of neurocognitive tests in domains most affected in HIV: verbal fluency, executive functioning, processing speed, learning, delayed recall, attention/working memory, and motor skills(Carey et al., 2004; Heaton et al., 2010). Individual raw test scores were first corrected for practice effects associated with

repeat testing (Cysique, Franklin, et al., 2011). Scores were then converted to demographically-adjusted T-scores in which the age of 25, when most fluid neurocognitive capacities peak (Gauvrit, Zenil, Soler-Toscano, Delahaye, & Brugger, 2017; Salthouse, 2003, 2009), was substituted for chronological age in demographic correction formulas (Saloner, Campbell, et al., 2019). These "peak-age" T-scores consequently compare an individual's neurocognitive performance to normative standards for 25-year-olds of the same education, sex, and race/ethnicity. For example, an individual with a peak-age T-score of 40 would have performance 1 standard deviation below the mean of 25-year-olds matched on education, sex, and race/ethnicity. Global peak-age T-scores, which reflect the average peak-age T-score across the entire test battery, were used as indicator variables in GMM. Global peak-age T-scores were selected to estimate longitudinal neurocognitive change (as opposed to traditional chronological age-corrected global T-scores and demographically-uncorrected global scaled scores) because: 1) chronological age-based adjustments can mask the influence of age on neurocognitive change over time; 2) peak-age T-scores have the added benefit of comparing an individual's level of performance to youthful expectations while still adjusting for other salient demographic factors.

In addition to estimating longitudinal neurocognitive change, we employed our criteria for SuperAging in PWH (Saloner, Campbell, et al., 2019) to classify participants into three neurocognitive groups at baseline: SuperAgers (SA), cognitively normal (CN) for their actual age, or cognitively impaired (CI). Participants were classified as SA at baseline if their peak-age global performance was within normative expectations (i.e., ≥-1SD from the mean of the 25-year-old normative sample) and they did not exhibit any isolated impairments for individual domains based on traditional, chronological age-based norms. Individuals who were not classified as SA at baseline were either classified as CN or CI based on the traditional,

chronological age-based deficit score approach for classifying global neurocognitive impairment in HIV(Blackstone et al., 2012; Carey et al., 2004).

Cognitive Reserve and Self-reported Cognitive Symptoms

Cognitive reserve was measured using standardized scores from the Reading subtest of the Wide Range Achievement Test, version 4 (WRAT4; Wilkinson & Robertson, 2006), a validated estimate of premorbid verbal intelligence robust to neurocognitive decline and a standard proxy for cognitive reserve in older HIV-seronegative adults and PWH (Baker et al., 2017; Casaletto et al., 2014; Siedlecki et al., 2009). Self-reported cognitive symptoms were assessed with the Patient's Assessment of Own Functioning Inventory (PAOFI), a 33-item self-report measure used to measure perceived cognitive symptoms in everyday life (Chelune et al., 1986). Items endorsed as fairly often or greater are considered clinically-significant cognitive symptoms. The continuous PAOFI total score is the number of self-reported, clinically-significant cognitive symptoms in everyday life.

Physiologic Reserve via *Neuromedical Evaluation*

The comprehensive neuromedical examination assessed for clinical deficits relevant to HIV and geriatric health. Based on established methods for constructing a frailty index (Bagshaw & McDermid, 2013; Rockwood & Mitnitski, 2011; Searle et al., 2008), a cumulative physiologic reserve variable was composed of 39 unique health variables encompassing a range of physiologic systems, including routine clinical laboratory measures (e.g., glucose, lipids), medical comorbidities (e.g., hepatitis C co-infection, diabetes), and indicators of HIV-disease severity. Each health variable was dichotomized as normal or deficient (normal = "1"; deficit = "0") based on criteria from previous HIV studies (Guaraldi et al., 2015; Oppenheim et al., 2018) and physiologic reserve index 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). Thus, higher scores are reflective of higher levels of physiologic reserve.

Psychiatric Evaluation

The structured Composite International Diagnostic Interview (CIDI; World Health Organization, 1998) was administered to ascertain DSM-IV diagnoses of current and lifetime mood and substance use disorders. Mood symptoms in the past two weeks were assessed with the Beck Depression Inventory-II (BDI-II; Beck et al., 1996).

Statistical Analysis

As an extension of latent growth curve modeling and latent class analysis, GMM identifies subgroups of individuals that share a common longitudinal pattern. GMM can estimate continuous linear and non-linear latent trajectories of change while simultaneously inferring categorical subgroup (i.e., latent class) membership based on unobserved heterogeneity in trajectories (Muthén & Kaplan, 2004; Nagin, 2005). The present study employed GMM to model latent growth classes of global peak-age T-scores measured at the 10 study timepoints, occurring in 6-month intervals. Longitudinal neurocognitive patterns were defined by a latent intercept, representing global peak-age T-scores at baseline, and latent slope parameters reflecting an underlying neurocognitive growth process.

GMM analyses were conducted in *Mplus* Version 8.6 (Muthén & Muthén, 2017). To first determine the best base model for change, unconditional (without covariate specification) latent growth models tested an intercept only, linear, quadratic, cubic, or latent basis model. After identification of the best base model, we iteratively compared 1- to 4-class unconditional GMMs to determine the optimal number of latent classes. For each solution, the best log-likelihood was replicated in order to avoid convergence at a local maximum. The best-fitting solution was

determined based on a combination of: 1) statistical fit indices, specifically Akaike information criterion (AIC), sample size-adjusted Bayesian information Criterion (ssBIC), Lo-Mendell-Rubin likelihood ratio test (LMRT), and entropy; 2) adequate class size, with recommendations of at least 25 individuals per class and each class representing at least 5% of the total sample (Wickrama, Lee, O'Neal, & Lorenz, 2016); 3) theoretical interpretability of classes; and 4) model parsimony.

After the optimal number of classes was identified, classes were substantively interpreted based on examination of latent intercept and slope parameters. Wald χ^2-tests examined the concordance of baseline neurocognitive classifications (i.e., SA, CN, and CI) with latent longitudinal class membership in order to examine the convergent validity of SA criteria with longitudinal neurocognitive patterns and further characterize latent class interpretation. Last, a "3-step" approach modeled class membership as a function of baseline demographic and clinical covariates in multinomial logistic regression. Class membership was assigned prior to inclusion of covariates in order to prevent covariates from altering the structure of latent classes and influencing final class membership (Asparouhov & Muthén, 2014; Vermunt, 2017). Factors that were univariably associated with latent classification at $p < .10$ were included as covariates. Covariates that failed to discriminate latent classification at $p < .10$ in the multinomial logistic analysis were removed and models were re-estimated. Missing data patterns were analyzed and variables significantly associated with missing data were also included as auxiliary variables(Enders, 2010). For all models, full-information maximum likelihood estimation was used to account for missing data (Bauer, 2007; Muthén & Muthén, 2017).

Results

Participant Characteristics

The full sample of 184 PWH was 82% male with a mean baseline age of 52.9 years (age range: 50-68) and mean education of 13.1 years. With regard to race/ethnicity, the overall sample was 46% non-Hispanic Black, 43% non-Hispanic White, 9% Hispanic, and 2% other. Baseline neurocognitive status classification rates were comparable to our larger cross-sectional study of SuperAging, with 19% of participants classified as SA (n=35), 47% classified as CN (n=87), and 34% classified as CI (n=62). With regard to ART use, 82% of participants were actively on ART medication, 11% reported past use of ART, and 7% were ART-naïve. Current CD4 counts (median=475 cells/mm^3) were on average substantially higher than nadir CD4 counts (median=108.5 cells/mm^3). The 57% rate of viral suppression (i.e., undetectable plasma HIV RNA) at baseline was comparable to the overall CHARTER cohort and reflective of the broad period of data collection (2003 to 2017). Additional descriptive statistics for the full sample are presented in Table 4.1.

Missing Data

For the 9 follow-up visits, the percent of participants with available neurocognitive data ranged from 39% to 77%. The lowest covariance coverage for each pair of indicator variables was 0.315, which was above the minimum threshold of 0.10 for model convergence and indicative of acceptable levels of missing data. To determine missing data patterns, the total number of missing timepoints per participant was calculated and associations between number of missing timepoints and study variables were conducted. A higher number of missing timepoints was associated with less education (spearman's rho = -.17, p = .034) and a later baseline study date (spearman's rho = .32, p < .001). Years of education and baseline study date were accordingly specified as auxiliary covariates in GMM with full information maximum likelihood to help reduce potential parameter estimate biases caused by missing data.

Optimal Latent Trajectory Class Solution

Goodness-of-fit indices supported a quadratic growth model with intercept and slope

parameter variances constrained equal across classes as the best base model for change. Table

4.2 presents the AIC, ssBIC, LMRT, entropy, and class sizes for 1- to 4-class solutions for the

quadratic growth model. The AIC and ssBIC metrics were near equivalent within each solution

and progressively decreased with higher class solutions, although the magnitude of these changes

became smaller with higher class solution comparisons. All models exhibited strong class

separation based on entropy. Entropy was lower in the 2-class solution compared to the 3- and 4-

class solutions, whereas entropy values were comparable between the 3- and 4-class solutions.

The LMRT value was significant for the 2-class solution compared to the 1-class solution,

suggesting improved model fit based on log-likelihood in the 2-class solution, but was not

significant for the 3- (vs. 2) and 4-class (vs. 3) solutions. Although the two smallest-sized classes

in the 4-class solution were each greater than 5% of the total sample, the class sizes were smaller

than the recommended minimum class size of 25 and were underpowered for conditional

analyses. Given the class size limitations of the 4-class solution and the AIC, ssBIC, and entropy

indicators favoring the 3-class solution over the 2-class solution, the 3-class solution was

selected as the best fitting model.

Figure 4.1A presents a spaghetti plot of individual longitudinal neurocognitive patterns

and Figure 4.1B presents the estimated timepoint means by class membership. The three

longitudinal classes identified for global peak-age T-score were: 1) Class 1*Stable Elite* (16.8% of the

sample), whose members exhibited stable, high levels of global peak-age T-scores (intercept

[SE] = 49.62 [0.61], $p < .001$; linear [SE] = 0.04 [0.26], $p = .894$; quadratic [SE] = 0.04 [0.04], p

= .361) that generally fell within the range of normative expectations for 25-year-olds (i.e., peak-

age T ≥ 40); 2) Class $2_{Quadratic\ Average}$ (54.3% of the sample), whose members on average exhibited a quadratic, shallow "u-shaped" trajectory (intercept [SE] = 41.91 [0.70], $p < .001$; linear [SE] = -0.45 [0.17], $p = .007$; quadratic [SE] = 0.07 [0.02], $p < .001$) with most individual trajectories fluctuating within the 30 to 50 range of peak-age T-scores; and 3) Class $3_{Quadratic\ Low}$ (28.8%), whose members also on average exhibited a quadratic "u-shaped" trajectory (intercept [SE] = 34.22 [0.93], $p < .001$; linear [SE] = -1.04 [0.29], $p < .001$; quadratic [SE] = 0.12 [0.03], $p < .001$) with most individual trajectories fluctuating within the 20 to 40 range of peak-age T-scores.

SA Criteria and Latent Group Membership

Baseline neurocognitive classifications (i.e., SA, CN, and CI) were validated against the latent longitudinal classes with Wald χ^2-tests. Overall, baseline neurocognitive status significantly segregated by longitudinal class ($\chi^2 = 100.26$, $p < .0001$). Each baseline status comprised at least 63% of a respective longitudinal class. Class $1_{Stable\ Elite}$ was composed of 65% SA (n=20) and 35% CN (n=11); Class $2_{Quadratic\ Average}$ was composed of 63% CN (n=63), 22% CI (n=22), and 15% SA (n=15); and Class $3_{Quadratic\ Low}$ was composed of 75% CI (n=40) and 25% CN (n=13). Since global performance at the baseline timepoint was used in neurocognitive status classifications and as the intercept indicator in the GMM, a secondary GMM model removed baseline performance as an indicator variable. This allowed us to examine the relationship of baseline neurocognitive status to longitudinal classes that were defined solely on data from follow-up timepoints. The 3-class solution based only on follow-up data exhibited comparable class separation (entropy = .891) and class sizes (Class $1_{Stable\ Elite}$ = 27 [15%], Class $2_{Quadratic\ Average}$ = 102 [55%], Class $3_{Quadratic\ Low}$ = 55 [30%]) to the 3-class solution that included baseline performance. Only 8 total participants shifted class membership, with 4 (3 SA, 1 CN) shifting

from Class 1$_{Stable\ Elite}$ to Class 2$_{Quadratic\ Average}$, 3 (2 CN, 1 CI) shifting from Class 2$_{Quadratic\ Average}$ to Class 3$_{Quadratic\ Low}$, and 1 (1 CI) shifting from Class 3$_{Quadratic\ Low}$ to Class 2$_{Quadratic\ Average}$. Baseline neurocognitive status again strongly segregated by longitudinal class ($\chi^2 = 89.67$, $p < .0001$), with each baseline classification comprising at least 60% of a respective longitudinal class.

Baseline Predictors of Trajectory Class Membership

Table 4.3 presents univariable longitudinal class differences on baseline characteristics. The following variables were univariably associated with longitudinal class membership at an omnibus $p < .10$ and were therefore considered as covariates in multinomial regression: age, cognitive reserve [WRAT4], physiologic reserve, depressive symptoms [BDI-II], and subjective cognitive symptoms [PAOFI]. Given our primary focus on peak neurocognition, Class 1$_{Stable\ Elite}$ was used as the reference group for the multinomial logistic regression predicting longitudinal class membership (Table 4.4). Sex, race/ethnicity, and BDI-II scores did not relate to longitudinal class membership at $p < .10$ in the multivariable analysis and were accordingly removed from the model. A one standard deviation-unit higher cognitive reserve, estimated with the WRAT4 Reading subtest (1 standard deviation = 15.4), related to a 77% decrease in odds of membership in Class 2$_{Quadratic\ Average}$ and 88% decrease in odds of membership in Class 3$_{Quadratic\ Low}$. Each additional self-reported cognitive symptom (PAOFI) at baseline also related to a 7% increase in odds of membership in Class 2$_{Quadratic\ Average}$ and 14% increase in odds of membership in Class 3$_{Quadratic\ Low}$. A year older baseline age related to a 20% increase in odds of membership in Class 3$_{Quadratic\ Low}$ (trend-level significance) and a one standard deviation-unit increase in baseline physiologic reserve (1 standard deviation = 0.10) related to a 52% decrease in odds of membership in Class 3$_{Quadratic\ Low}$. Age and physiologic reserve did not relate to odds of membership in Class 2$_{Quadratic\ Average}$.

Discussion

The present study employed GMM to identify homogenous subgroups of longitudinal peak-age neurocognition in a cohort of older PWH with up to 5 years of follow-up. Consistent with our expectation that longitudinal classes would be heterogeneous, the GMM models successfully converged upon a 3-class solution that exhibited strong separation between latent classes. Importantly, GMM identified a latent subgroup of older PWH that sustained youthful levels of global neurocognitive performance across the study period (Class $1_{Stable\ Elite}$). The the other two latent classes on average exhibited quadratic, although relatively modest in magnitude, slopes with intermediate (Class $2_{Quadratic\ Average}$) and low (Class $2_{Quadratic\ Low}$) levels of peak global performance across the study. Baseline SA status was predictive of higher odds of membership in Class $1_{Stable\ Elite}$, even when baseline performance was excluded from the GMM. Furthermore, baseline biopsychosocial indicators of resilience (i.e., cognitive reserve, physiologic reserve, better subjective functioning) also combined to predict higher odds of membership in Class $1_{Stable\ Elite}$. Our findings generally support SuperAging in PWH as a valid construct reflecting age-related neurocognitive resilience, however the young age range of the study sample relative to most HIV-seronegative aging cohorts and the lack of systematic decline among the lower performing longitudinal classes necessitate further validation of these findings in older-aged cohorts of PWH.

The 16.8% prevalence of Class $1_{Stable\ Elite}$ is similar to the 17.1% prevalence of SA identified in our prior cross-sectional evaluation (Saloner, Campbell, et al., 2019). Baseline neurocognitive status was predictive of longitudinal class membership, however meeting SA criteria at baseline did not guarantee membership in Class $1_{Stable\ Elite}$. The lack of full concordance between baseline neurocognitive status and longitudinal class membership is to be expected, as

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some individuals should shift across classifications due to natural intra-individual variability. However, the pattern of longitudinal data in Class 1$_{Stable\ Elite}$ does not broadly support a regression to the mean phenomenon, whereby those who started out with the highest baselines would have exhibited the steepest declines toward the mean. Rather, most individuals in Class 1$_{Stable\ Elite}$ were classified as SA at baseline and continued to exhibit youthful performance in the up to 5 years of follow-up data. Our processing of neurocognitive data also importantly included established test corrections for practice effects (Cysique, Franklin, et al., 2011), which can mask neurocognitive decline when left unaccounted for.

The intra-individual fluctuations and overall quadratic patterns of change within Class 2$_{Quadratic\ Average}$ and Class 3$_{Quadratic\ Low}$, which were statistically significant but subtle in magnitude, are more consistent with the fluctuating neurocognitive trajectories noted in prior neuroHIV studies rather than a progressive cognitive disorder (e.g., pre-Alzheimer's disease; Rubin, Sundermann, & Moore, 2019; Saloner & Cysique, 2017). Although these latent classes did not demonstrate systematic neurocognitive declines, the quadratic growth patterns observed in these groups may reflect cognitive instability and possibly confer risk for future decline (Naveed et al., 2021). These quadratic trajectories may also be more consistent with a regression to the mean phenomenon, whereby early declines in performance are followed by subsequent improvements toward baseline status, which in the present study reflected average or low levels of performance that were concordant with the CN and CI classifications, respectively. Survivor bias, an issue inherent to neuroHIV and aging research (Cysique, Casaletto, & Heaton, 2019; Hunt, 2014), may also partially explain this pattern under the assumption that individuals in Class 2$_{Quadratic\ Average}$ and Class 3$_{Quadratic\ Low}$ who experienced early neurocognitive declines dropped out of the study

due to worsening disease. To help mitigate this possibility, we included auxiliary predictors of missing data, which did not significantly differ by latent trajectory groups.

Importantly, it is possible that individuals in each latent class did experience systematic neurocognitive declines as would be expected with advancing age; however, this GMM classified participants based on both slope *and* intercept (i.e., the absolute values of their baseline peak-age T scores). This likely limited the ability to detect groups solely based on trajectories regardless of baseline/absolute level of cognitive functioning. Similarly, the overall sample size of individuals with declining growth trajectories and the growth parameters of these trajectories were not sufficiently large and/or distinct to be identified as a homogenous latent subgroup by GMM. With an increase in sample size, we would also anticipate an increase in the likelihood of identifying such a "declining" subgroup. Nevertheless, the current GMM approach is clinically important to understand the trajectories of PWH at these different overall levels of cognitive functioning, particularly those with superior performance. Future research in this area may consider using neurocognitive scores that reflect only the change in neurocognitive score over time compared to one's own baseline.

The majority of longitudinal neurocognitive studies in PWH with chronic disease have focused on identifying individuals who exhibit poor/declining trajectories, but have not been designed for detection of an elite longitudinal subgroup. Cysique and colleagues noted in a recent review that these studies focused on decline significantly vary in length and operationalization of neurocognitive change (Cysique et al., 2019), yet the most consistent observation is that the majority of PWH exhibit a stable/non-progressive neurocognitive trajectory while a smaller subgroup may experience a subtle yet systematic decline (Cysique et al., 2019; Heaton et al., 2015). Only a handful of studies have explicitly focused on

neurocognitive change within older groups of PWH (i.e., aged 50 or older), with support for amplified risk of neurocognitive decline compared to younger PWH and older HIV-seronegative adults (Aung et al., 2021; Lam et al., 2021).

Even fewer studies from the broader longitudinal neuroHIV corpus have employed data-driven statistical methods with intercept and slope-based subgroup identification (Brouillette et al., 2016; Chan et al., 2021; Molsberry et al., 2015). Using a mixed membership trajectory model, Molsberry and colleagues characterized trajectories of a trichotomous neurocognitive classification (i.e., normal, mild impairment, severe impairment) in the Multicenter AIDS Cohort Study and identified a 3-class solution, composed of a "normal aging" (60% of the sample; low probability of mild impairment until age 60), "premature aging" (21% of the sample; mild impairment onset between age 45-50), and "unhealthy" (19% of the sample; mild impairment in 20s and 30s) subgroups (Molsberry et al., 2015). The use of a trichotomous classification is congruent with many neuroHIV studies (e.g., normal, mild HAND, severe HAND), however it does not consider variability within the "normal" range and does not utilize neuropsychological test scores that reflect youthful, rather than chronological age-based, neurocognitive abilities. In a group-based trajectory analysis of CHARTER data across the full cohort (including younger aged participants), Brouillette and colleagues modeled separate trajectories of raw test scores for each of the 15 neuropsychological tests in the CHARTER battery (Brouillette et al., 2016). Roughly 16% of individuals identified as "decliners" on at least one test. However, the number of optimal class solutions ranged from 6 to 12 depending on the test and class sizes were frequently lower than the recommended 5% sample size (some as small as n=3), thereby limiting the interpretability of trajectory groups. While informative, it was also noted that these data-driven studies had suboptimal considerations for practice effects (Cysique et al., 2019).

Individuals in Class $1_{Stable\ Elite}$ were slightly but significantly younger than individuals in Class $2_{Quadratic\ Average}$ and Class $3_{Quadratic\ Low}$ in univariable analysis, however these relationships were reduced to non-significance in the multinomial logistic regression. The age of 50 has been identified as a clinically-significant cut-off for increased medical risk among PWH (Blanco et al., 2012), with a recent longitudinal analysis of 1,248 PWH in the National NeuroAIDS Tissue Consortium indicating that baseline global T-scores were strongly predictive of mortality among PWH in their mid-50s but not among younger PWH (Naveed et al., 2021). Nevertheless, the lack of robust age-related effects on longitudinal class membership may also be related to the age range of our older CHARTER cohort, which is still relatively young compared to most HIV-seronegative aging studies. Comorbidity burden may also be a better indicator of biological age in older PWH than chronological age(Stoff et al., 2017), particularly given that the positive correlation between age and physiologic reserve is attenuated among older PWH(Oppenheim et al., 2018). This may explain why the association between younger age and Class $1_{Stable\ Elite}$ was substantially weakened in the multinomial regression model that included the composite physiologic reserve index, which was not correlated with chronological age (data not shown) and was a more robust predictor of Class $1_{Stable\ Elite}$ (relative to Class $3_{Quadratic\ Low}$). Similar to our prior study of SA(Saloner, Campbell, et al., 2019), historical HIV disease factors including AIDS diagnosis, nadir CD4, estimated years of HIV disease, and ART treatment history did not significantly differ by trajectory group, suggesting that non-HIV comorbidities may be driving the current association between physiologic reserve and longitudinal neurocognition.

Higher levels of cognitive reserve, as indexed by the WRAT4 Reading subtest, were strongly associated with higher odds of membership in Class $1_{Stable\ Elite}$ relative to Class $2_{Quadratic\ Average}$ and Class $3_{Quadratic\ Low}$. We observed a similar relationship in our cross-sectional study of

SA (Saloner, Campbell, et al., 2019) and this is consistent with the wide body of literature indicating a protective effect of estimated premorbid intelligence in neurocognitive aging, both in PWH and healthy older adults (Baker et al., 2017; Basso & Bornstein, 2000; Stern, 2009). Years of education was positively correlated with the WRAT4 at r=.51, indicating roughly 25% shared variance, yet years of education did not univariably differ by trajectory group. Although years of education is also thought to contribute to cognitive reserve, measures of premorbid IQ are considered stronger estimates of educational quality than total years of education completed (Stern, 2009), particularly in racially diverse and marginalized older adult populations(Manly et al., 2002). Thus, the theoretically-consistent relationship of the WRAT4 with longitudinal class membership lends further support for the inclusion of premorbid intelligence estimates above and beyond years of education in the analysis and interpretation of neuropsychological test performance.

The construct validity of Class 1$_{Stable\ Elite}$ is also supported by its relationship with fewer self-reported cognitive symptoms at baseline. This finding coupled with our previous observation of lower total PAOFI scores in SA compared to CN and CI (Saloner, Campbell, et al., 2019) suggests that self-reported cognitive symptoms in this population of older PWH may not only discriminate neurocognitively unimpaired PWH from those with NCI, but may also be sensitive to subclinical differences in neurocognition within the unimpaired range of performance. Self-reported cognitive symptoms are also strongly correlated with depressive symptoms, including in our sample (data not shown), yet BDI-II scores were only lower in Class 1$_{Stable\ Elite}$ relative to Class 3$_{Quadratic\ Low}$ in univariable but not multivariable analysis. We previously reported cross-sectional associations between SA and fewer depressive symptoms that persisted in multivariable

analysis (Saloner, Campbell, et al., 2019), however PAOFI total scores were not examined in the same multivariable model.

The present study is not without limitations. Although utilizing preexisting CHARTER data allows us to efficiently address questions pertaining to neurocognitive resilience in older PWH, we are limited by pre-defined CHARTER study parameters. Specifically, CHARTER did not enroll HIV-seronegative comparison participants, which precludes us from examining how neurocognitive trajectories differ by HIV serostatus. Furthermore, CHARTER did not collect data regarding certain modifiable lifestyle behaviors (e.g., diet, exercise; Fazeli et al., 2015; Rubin et al., 2021) and positive psychological factors (e.g., grit, optimism; Moore et al., 2017; Moore, Hussain, et al., 2018) that could potentially inform future interventions targeting biopsychosocial resilience factors (e.g., physiologic reserve, mood) in PWH. Similarly, limited data was available regarding social determinants of health (e.g., early life adversity, housing and food security, neighborhood characteristic) that help explain racial/ethnic disparities in neuropsychological test performance. The CHARTER test battery normative procedures include race/ethnicity as a proxy for these social determinants of brain health factors, and although this aids in adjusting for premorbid influences that are independent of HIV-related CNS dysfunction, it is less desirable than directly adjusting for the social factors that are driving racial/ethnic differences in test performance. The baseline age range (50 – 68 years) and 5-year longitudinal timeframe, which is comparable to other longitudinal aging studies in PWH, reflects a period of enhanced vulnerability to HIV-related neurocognitive difficulties but may not capture enough individuals who have reached an age-related threshold for progressive neurocognitive decline. There are alternate methods of assessing longitudinal neurocognitive change that have been utilized in other studies among PWH, such as regression-based summary change scores,

repeated-measures ANOVA, and linear mixed-effects models. While these techniques have merit, GMM is more flexible as it relates to complex non-linear trajectory modeling, robustness to violations of normality, and simultaneous estimation of latent continuous (i.e., growth factors) and latent categorical (i.e., trajectory classes) variables (Curran, Obeidat, & Losardo, 2010). Latent profile analysis or cluster analysis of change scores, both within CHARTER and other cohorts, have identified domain-specific patterns of neurocognitive change across two timepoints in PWH (Dastgheyb et al., 2019; Rubin, Saylor, et al., 2019). Although characterization of domain-based trajectories was beyond the scope of the present study, some neurocognitive domains are more vulnerable to aging than others (e.g., crystallized vs. fluid skills) and future work should utilize GMM to identify dissociable domain-specific trajectory patterns.

Taken together, the present study provides a novel contribution to the field of neuroHIV and neurocognitive aging research. Our results indicate that stable and youthful neurocognitive functioning is possible for older PWH, despite the inherent neurocognitive risks associated with aging with a chronic illness. HIV disease factors did not differ across longitudinal classes, whereas perceived cognitive difficulties and markers of cognitive and physiologic reserve were predictive of longitudinal class membership. These results may help elucidate the biopsychosocial mechanisms underlying neurocognitive resilience in the context of chronic HIV disease, which could help promote optimal neurocognitive aging in the rapidly growing population of older PWH.

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Table 4.1. Baseline study sample characteristics

Variable	N = 184
Demographics	
Number of study visits, median [IQR]	6 [4, 9]
Age (years), mean (SD)	52.9 (3.9)
Sex (male), n (%)	151 (82%)
Education (years), mean (SD)	13.1 (2.6)
Race/ethnicity	
Non-Hispanic Black, n (%)	85 (46%)
Non-Hispanic White, n (%)	80 (44%)
Hispanic, n (%)	16 (9%)
Other, n (%)	3 (2%)
Neurocognition	
Neurocognitive status	
SuperAger, n (%)	35 (19%)
Cognitively Normal, n (%)	87 (47%)
Cognitively Impaired, n (%)	62 (34%)
Cognitive reserve (WRAT4), mean (SD)	93.5 (15.4)
PAOFI total score, mean (SD)	2 [0, 8]
Psychiatric	
Lifetime Major Depressive Disorder, n (%)	91 (49%)
Current Major Depressive Disorder, n (%)	23 (12%)
BDI-II, median [IQR]	9 [3, 19]
Lifetime substance use disorder, n (%)	134 (73%)
Medical Characteristics	
AIDS Diagnosis, n (%)	133 (72%)
Estimated years of disease, mean (SD)	13.3 (6.2)
Nadir CD4 count, median [IQR]	109 [19, 247]
Current CD4 count, median [IQR]	475 [341, 693]
ART Status	
Currently on	150 (82%)
Past use only	21 (11%)
ART naïve	12 (7%)
Undetectable plasma virus, n (%)	101 (57%)
Physiologic reserve, mean (SD)	0.70 (0.10)

Abbreviations: BDI-II = Beck Depression Inventory-II; WRAT4 = Wide Range Achievement Test Reading subtest, version 4; PAOFI = Patient's Assessment of Own Functioning Inventory; IADL = instrumental activities of daily living; ART = antiretroviral therapy

Table 4.2. Growth mixture model fit statistics

	1-class	2-classes	3-classes	4-classes
Log Likelihood	-3827.206	-3696.376	-3380.741	-3263.309
AIC	7680.412	7426.752	6803.481	6576.618
BIC	7722.206	7481.406	6870.995	6656.992
Sample size-adjusted BIC	7681.032	7427.563	6804.483	6577.811
Entropy	NA	0.866	0.918	0.923
LMRT	NA	0.0431	0.2444	0.4166
Class Size				
Class 1	184 (100%)	104 (57%)	31 (17%)	14 (8%)
Class 2		80 (43%)	100 (54%)	85 (46%)
Class 3			53 (29%)	66 (36%)
Class 4				19 (10%)

Abbreviations: AIC = Akaike information criterion; BIC = Bayesian information criterion; LMRT = Lo-Mendell-Rubin likelihood ratio test

Table 4.3. Baseline characteristics by latent class membership

Variable	Class 1 *Stable Elite* (n=31)	Class 2 *Quadratic Average* (n=100)	Class 3 *Quadratic Low* (n=53)	Test statistic	p	Pair-wise
Demographics						
Number of study visits, median [IQR]	5 [4, 7]	6 [4, 9]	6 [4, 9]	F=2.83	.062	
Age (years), mean (SD)	51.7 (3.6)	52.6 (3.4)	54.3 (4.7)	F=5.37	.005	2, 3 > 1
Sex (male), n (%)	27 (87%)	80 (80%)	44 (83%)	χ^2=0.89	.640	
Education (years), mean (SD)	12.8 (2.8)	13.0 (2.6)	13.5 (2.6)	F=0.94	.391	
Race/ethnicity				FET	.975	
Non-Hispanic Black, n (%)	14 (45%)	48 (48%)	23 (43%)			
Non-Hispanic White, n (%)	15 (48%)	40 (40%)	25 (47%)			
Hispanic, n (%)	2 (7%)	10 (10%)	4 (8%)			
Other, n (%)	0 (0%)	2 (2%)	1 (2%)			
Neurocognition						
Neurocognitive status				χ^2=100.26	<.001	
SuperAger, n (%)	20 (65%)	15 (15%)	0 (0%)			1 > 2 > 3
Cognitively Normal, n (%)	11 (35%)	63 (63%)	13 (25%)			2 > 1 > 3
Cognitively Impaired, n (%)	0 (0%)	22 (22%)	40 (75%)			3 > 2 > 1
Cognitive reserve (WRAT4), mean (SD)	98.8 (11.8)	94 (14.4)	89.2 (18.1)	F=4.05	.019	1 > 3
PAOFI total score, median [IQR]	1 [0, 6]	2 [0, 7]	2 [0, 12]	F=2.94	.056	3 > 1
Psychiatric						
Lifetime Major Depressive Disorder, n (%)	16 (52%)	49 (49%)	26 (49%)	χ^2=0.97	.966	
Current Major Depressive Disorder, n (%)	3 (10%)	13 (13%)	7 (13%)	χ^2=0.86	.860	
BDI-II, median [IQR]	8 [3, 14]	9 [3, 19]	12 [5, 26]	F=2.55	.081	3 > 1
Lifetime substance use disorder, n (%)	27 (87%)	71 (71%)	36 (68%)	χ^2=4.49	.101	
Medical Characteristics						
AIDS Diagnosis, n (%)	23 (74%)	76 (76%)	34 (64%)	χ^2=2.43	.297	
Estimated years of disease, mean (SD)	14.2 (5.9)	13.1 (6.8)	13.2 (5.2)	F=0.39	.677	
Nadir CD4 count, median [IQR]	87 [19, 230]	103 [14, 246]	138 [35, 253]	χ^2=0.87	.648	
Current CD4 count, median [IQR]	541 [341, 802]	478 [339, 710]	463 [359, 619]	χ^2=1.15	.564	
ART Status				χ^2=6.71	.152	
Currently on	23 (74%)	87 (88%)	40 (75%)			
Past use only	6 (19%)	6 (6%)	9 (17%)			
ART naïve	2 (6%)	6 (6%)	4 (8%)			
Undetectable plasma virus, n (%)	18 (64%)	54 (55%)	29 (57%)	χ^2=0.76	.684	
Physiologic reserve, mean (SD)	0.72 (0.08)	0.71 (0.09)	0.67 (0.11)	F=3.45	.034	1, 2 > 3

Abbreviations: ART = antiretroviral therapy; BDI-II = Beck Depression Inventory-II; FET = Fisher's exact test; IADL = instrumental activities of daily living; PAOFI = Patient's Assessment of Own Functioning Inventory; WRAT4 = Wide Range Achievement Test Reading subtest, version 4

Table 4.4. Multinomial logistic regression predicting latent trajectory group membership

Predictor	Class 2$_{Quadratic\ Average}$			Class 3$_{Quadratic\ Low}$		
	OR	95% CI	p	OR	95% CI	p
Age	1.06	0.88 - 1.26	.540	1.20	0.99 - 1.45	.058
PAOFI	1.07	1.01 - 1.14	.020	1.14	1.06 - 1.22	<.001
Physiologic reserve	0.83	0.49 - 1.39	.470	0.48	0.27 - 0.86	.014
Cognitive reserve	0.33	0.16 - 0.68	.002	0.12	0.06 - 0.28	<.001

Note. Provided estimates are relative to classification in Class 1$_{Stable\ Elite.}$ Estimates for physiologic reserve and cognitive reserve reflect change in odds of class membership per 1 SD-unit increase.
Abbreviations: CI = confidence interval; OR = odds ratio; PAOFI = Patient's Assessment of Own Functioning total score
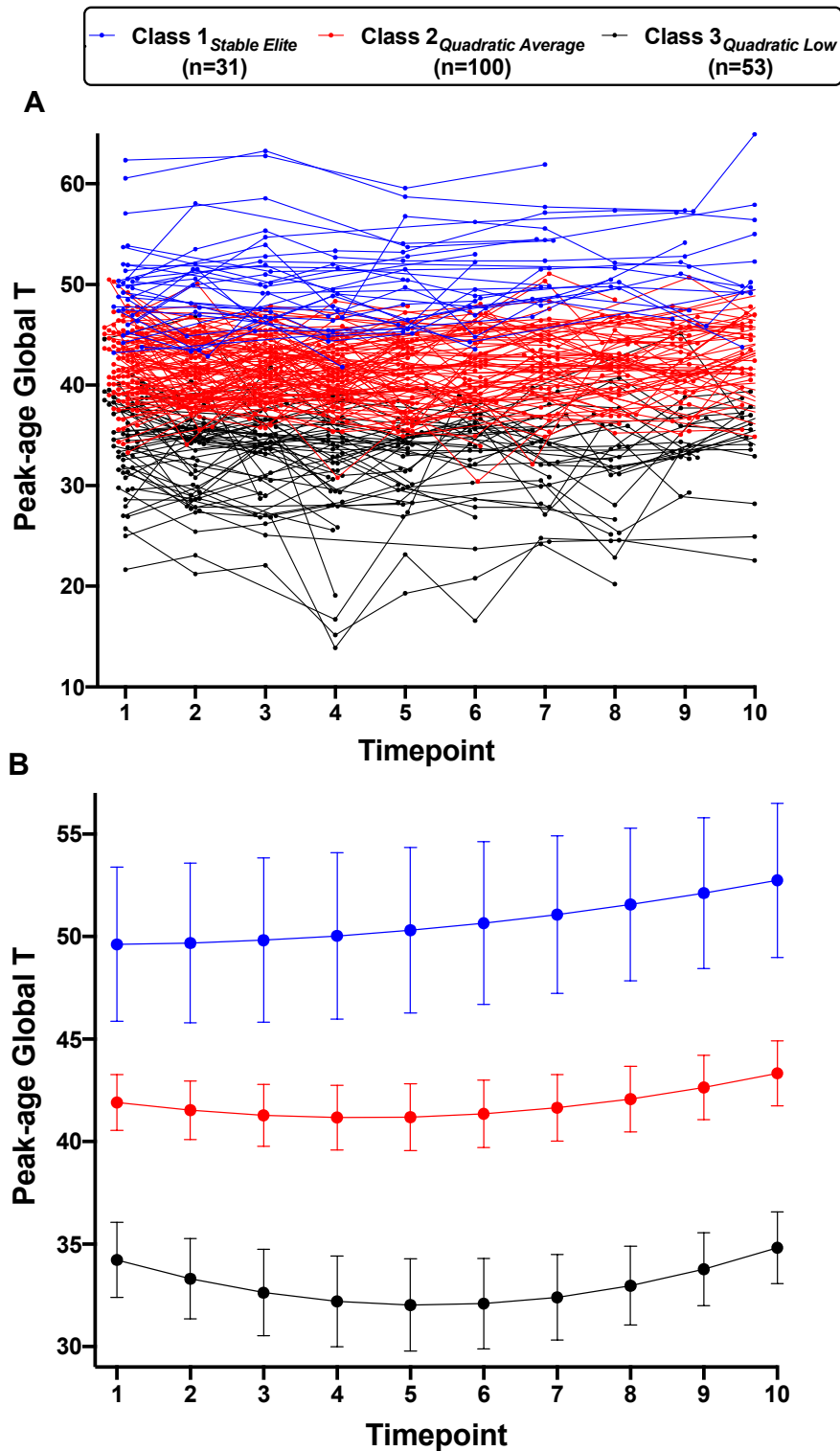
Figure 4.1. Trajectory plots are coded by the three latent trajectory classes: Class 1Stable Elite (blue), Class 2Quadratic Average (red), Class 3Quadratic Low (black). Panel A) Spaghetti plot of individual peak-age global T-scores (y-axis) across the 10 study timepoints (x-axis), which occurred in 6-month intervals. Panel B) Estimated trajectory means by class membership derived from growth mixture modeling. Error bars represent 95% confidence intervals.

Chapter 4, in full, is a reprint of the material as it appears in *AIDS and Behavior*, Saloner, R., Lobo, J., Paolillo, E.W., Campbell, L.M., Letendre, S. L., Cherner, M., Heaton, R.K., Ellis, R.J., Roesch, S.C., & Moore, D. J. (2021). The dissertation author was the primary investigator and author of this paper.

CHAPTER 5: DISCUSSION

Three studies explored the patterns and predictors of youthful neurocognitive performance among older (i.e., 50 years of age or older) PWH. Toward this end, we employed cross-sectional and longitudinal methods to identify elite neurocognitive profiles and determine their relationship with protective biopsychosocial factors, which were operationalized as cognitive and physiologic reserve. In Study 1, we developed neuropsychological criteria for the classification of SA in PWH aged 50 and older. These criteria defined SA as demographically-corrected (i.e., sex, race/ethnicity, education) global neurocognitive performance based on normative standards for a 25 year-old. The results of Study 1 demonstrated that youthful neurocognitive performance occurs in a substantial fraction (~17%) of older PWH. Importantly, the SA group exhibited better real-world outcomes, higher estimated premorbid verbal intelligence (i.e., cognitive reserve), and lower prevalence of diabetes and hepatitis C compared to both CN and CI individuals. Building on the results of Study 1, Study 2 utilized the full extent of available neuromedical data to generate a comprehensive index of physiologic reserve and also modelled non-linear effects of cognitive and physiologic reserve on SA status. These results identified independent contributions of cognitive (quadratic relationship) and physiologic reserve (linear relationship) to neurocognitive status such that odds of SA were highest when both reserve factors were high. Finally, Study 3 expanded on the cross-sectional approaches of Study 1 and Study 2 by characterizing longitudinal trajectories of peak global neurocognition using GMM. Importantly, the GMM analysis identified a latent longitudinal subgroup that exhibited a stable and elite neurocognitive pattern, Class $1_{Stable\ Elite}$. Baseline SA status, cognitive reserve and physiologic reserve were all predictive of membership in Class $1_{Stable\ Elite}$.

Several unifying themes emerged across the three aforementioned studies. Although older PWH are at enhanced risk for NCI, each study demonstrates that elite neurocognitive performance is possible for older PWH. In each study, individuals with elite performance could be differentiated from those with average or impaired performance through examination of biopsychosocial factors, most notably cognitive reserve and physiologic reserve. Collectively, our results suggest that SA in PWH may possess the combination of 1) longstanding advantages, such as higher baseline intelligence as estimated by the WRAT4 reading test; 2) resilience to the adverse effects of acquired HIV disease, exemplified by the comparable profiles of HIV disease severity across neurocognitive groups; and possibly 3) some resistance to the acquisition of age-related comorbidities, as indicated by higher physiologic reserve.

The findings related to cognitive reserve raise a critical question as to whether SA are truly resilient to age-related neurocognitive decline, or whether their elite performance is solely an artifact of starting out at a higher baseline. While the longitudinal approach in Study 3 provides initial support that some SA at baseline show resilience to decline, the overall age range across the study samples (mostly 50s and 60s) is substantially younger than the extant literature on SA in healthy samples. Within the neuroHIV cohorts examined across our studies, younger age showed modest but significant associations with higher odds of SA, suggesting that the likelihood of sustaining elite performance may decrease with older age. Thus, it stands to reason that the subgroup of PWH classified as SA across our three studies may in fact represent two distinct subgroups: 1) true SA who will continue to display elite neurocognition as they age into their 70s and 80s; and 2) 'false positive' SA who met SA criteria in their 50s and 60s, possibly due to high premorbid ability, but are not resistant to age-related neurocognitive decline and will no longer meet SA criteria in their 70s and 80s. Extending study methodology in even older

neuroHIV cohorts will help determine the extent to which elite neurocognition is sustainable in PWH at ages where more prominent declines in neurocognition are observed in the general population.

Future investigations of the contributions of reserve factors to SA in PWH should also consider the multi-factorial nature of both cognitive and physiologic reserve. Although the WRAT4 Reading subtest is a validated proxy of cognitive reserve, both in PWH and the general population, it is a single proxy measure that reflects one formative contributor to the development of cognitive reserve rather than the entire construct (Stern et al., 2018). Moreover, the lack of CNS biomarker data across our three studies precludes us from examining the extent to which the WRAT4 confers resilience against neural injury in the context of our SA cohort. Thus, future study designs should determine how multiple cognitive reserve proxies, such as IQ, occupation, and malleable lifestyle factors (e.g., diet, exercise), independently and in tandem moderate the relationship between CNS integrity and SA. A similar approach could be applied for physiologic reserve, particularly considering that our composite index was composed of 39 distinct health deficits. Decomposing the composite index into clusters of distinct physiologic systems (e.g., metabolic health, HIV disease indicators, vascular factors) may help elucidate which biological pathways most strongly support optimal brain health in PWH. Importantly, there is growing evidence that metrics of 'biological age', including physiologic reserve, may better explain neurocognitive heterogeneity than chronological age among older PWH (Stoff et al., 2017). Our results highlighting independent relationships between physiologic reserve and elite neurocognition further supports this notion, and advocates for the inclusion of metrics of biological age in future neurocognitive aging studies in PWH.

Taken together, these studies present several novel contributions to the neuroHIV and aging field. Biomedical research is rooted in disease models that preferentially study factors linked with adverse, rather than positive, health outcomes. The current dissertation's focus on SA in PWH shifts the lens of neuroHIV research toward the optimal end of the cognitive spectrum. A primary concern among older PWH is not a question of if, but rather when they will experience neurocognitive decline. In this way these three studies challenge current thinking in the scientific community and PWH. The few publications that examine positive outcomes in older PWH have strictly focused on the absence of NCI without consideration for inter-individual differences in neurocognition within unimpaired individuals. The GMM analysis in Study 3 offered an innovative approach to studying inter-individual differences in neurocognitive aging. Given that full neuropsychological evaluations are time-consuming and expensive, particularly in primary HIV treatment settings, clinicians must often rely on heuristics for predicting neurocognitive change. Importantly, proxies of cognitive and physiologic reserve are comprised of routinely collected geriatric assessment data and can be constructed from archival neuroHIV databases, as demonstrated by our analyses. Thus, leveraging preexisting clinical and research data to determine the extent to which indices of reserve predict neurocognitive trajectories in older PWH may guide treatment planning in a manner that requires minimal additional effort from providers.

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