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Lower Cognitive Reserve Among Individuals with Syndromic HIV-associated Neurocognitive Disorders (HAND)

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Abstract

HIV-seropositive individuals with low cognitive reserve are at high risk for developing HIV-associated neurocognitive disorders (HAND). The present study evaluated the hypothesis that cognitive reserve would also play a unique role in the expression of everyday functioning complications among those with HAND (i.e., syndromic versus subsyndromic impairment). Eighty-six individuals with HIV infection were evaluated; 53 individuals evidenced normal neurocognitive performance, 16 had subsyndromic HAND (i.e., Asymptomatic Neurocognitive Impairment), and 17 were diagnosed with a syndromic HAND based on a comprehensive neurobehavioral evaluation. Cognitive reserve represented a combined score including years of education, estimated verbal IQ, and highest occupational attainment. The groups were comparable (e.g. demographics), and the HAND groups had similar rates of global neurocognitive impairment. The Syndromic HAND group evidenced lower reserve scores relative to both other groups, suggesting that HIV-infected individuals with high cognitive reserve more effectively counteract their neurocognitive impairment to maintain independence in daily living activities.

Keywords

Cognitive reserve; HIV/AIDS; activities of daily living; neuropsychological assessment

INTRODUCTION

The human immunodeficiency virus (HIV) is a neurovirulent infection that invades and dysregulates the central nervous system (CNS) early in the course of the disease. Through direct neurotoxic exposure to viral proteins (i.e., gp120 and Tat) and a cascade of chemokines and cytokines leading to immune activation and neuroinflammation (see [1] for a review), the resulting HIV-associated neuropathology, primarily synaptodendritic injury and neurodegeneration (e.g., [2]), manifests behaviorally as neurocognitive complications in up to half of all infected individuals [3]. HIV-associated neurocognitive disorders (HAND) present with a range of neurocognitive and functional severity, from mild impairment with no impact on everyday functioning to more severe syndromic impairment with marked

functional disability [4]. It is likely that several converging factors account for who develops HAND and at what level of severity, including both viral and host factors (e.g., [1]).

One host factor that has been investigated for its role in the development of HAND is cognitive reserve. The construct of reserve against brain damage has been conceptualized as two separate but not necessarily exclusive types of reserve models, including brain reserve capacity (i.e., a passive model) and cognitive reserve (i.e., an active model) (see [5] for a review). The *brain* reserve capacity model suggests that thresholds for clinical symptoms are fixed; therefore, individuals with high reserve can withstand a greater degree of neuropathology before reaching that threshold, thereby delaying symptom onset. According to the *cognitive* reserve (active) model the brain counteracts the effects of neural burden through enhanced strength of cognitive networks [5], perhaps in combination with more effective strategy use, in individuals with higher levels of cognitive reserve. As such, cognitive reserve is often operationalized as full-scale or verbal IQ, educational attainment, highest level of occupation, or some combination thereof. Applying the cognitive reserve model to HIV infection, the threshold of synaptodendritic injury at which an individual with a high level of cognitive reserve would develop HAND would be higher relative to an individual with lower cognitive reserve, even if those two individuals had similar brain reserve.

Despite considerable interest in the cognitive reserve theory, only a few studies have examined this influential model in HIV infection. An early study by Satz and colleagues [6] showed that neurocognitive impairment was more prevalent among medically asymptomatic HIV-seropositive individuals with low cognitive reserve as compared to those with high reserve. This finding was extended by two subsequent studies demonstrating that individuals with low cognitive reserve had significantly lower cognitive scores relative to those with high reserve across multiple ability areas [7], with the exception of motor functions [8]. Cognitive reserve may also mediate HIV-associated neurocognitive declines over time (i.e., [9]). Although these findings speak to the potential importance of cognitive reserve in the expression of HAND, the existing literature was mostly conducted in the pre-cART era and has several limitations, including failure to use education-corrected neuropsychological test scores and inclusion of only a limited range of cognitive reserve indicators.

Moreover, no studies to date have examined whether cognitive reserve might explain vulnerability to syndromic forms of HAND. According to the HAND diagnostic nomenclature (i.e., Frascati criteria; [4]), the multiple levels of HAND are based on severity of neurocognitive impairment and its impact on daily functioning. An important distinction is made between syndromic HAND (Minor Neurocognitive Disorder [MND] and HIV-associated Dementia [HAD]), which involves greater severity of neurocognitive impairment with an impact on everyday functioning ranging from mild interference with day-to-day functions to marked dysfunction in activities of daily living, and subsyndromic (i.e., asymptomatic) neurocognitive impairment (ANI), in which case there is no evidence of disruption of everyday functioning. Precisely why some individuals experience varying degrees of everyday functioning impairment related to HIV-associated cognitive decline (i.e., syndromic HAND), while others demonstrate impaired cognitive performance with no related impact on their daily functional ability (i.e., ANI) is not fully understood, but factors such as demographics, disease severity, and psychiatric comorbidities likely play an important role. Another possibility is that individuals with low cognitive reserve are more likely to experience functional declines in the setting of neurocognitive impairment because of a reduced ability to rely cognitive networks and use compensatory strategies. Therefore, the present study hypothesized that cognitive reserve would differentiate individuals with syndromic HAND, who were expected to have lower cognitive reserve scores, from those with ANI and HIV-seropositive individuals without HAND. To strengthen the significance

of our expected findings, both a rigorous diagnostic nosology was applied (i.e., [4]) and cognitive reserve was operationalized as a multifaceted score including estimated verbal IQ, years of education, and highest occupational level achieved.

METHOD

Participants

The current study sample comprised 86 adults with HIV infection who were participating in an adherence substudy of a National Institute of Mental Health funded grant that recruited participants from local HIV clinics and the greater community of San Diego, CA. This study was approved by the Institutional Review Board of the University of California, San Diego (UCSD). HIV status was determined by enzyme linked immunosorbent assays and confirmed by a Western Blot test. For the present study, individuals were excluded if their verbal IQ scores were below 70 (based on Wechsler Test of Adult Reading; WTAR [10]) or if they reported histories of severe psychiatric (e.g., psychosis), medical (e.g., advanced liver disease), or neurological (e.g., stroke, traumatic brain injury with loss of consciousness > 30 min, seizure disorders) conditions that are known to affect cognition, including substance dependence within six months of the study visit (as determined by the Composite International Diagnostic Interview; CIDI version 2.1; [11]) or positive urine toxicology test for illicit substances on the day of testing. As shown in Table 1, the groups were comparable with regard to lifetime histories of psychiatric conditions (i.e., CIDI diagnoses) that are frequently comorbid in HIV infection, including Major Depressive disorder (MDD), Generalized Anxiety disorder, and substance dependence disorders (with the exception of opioid dependence, which was only present in the Subsyndromic HAND group), as well as current levels of affective distress (i.e., Profile of Mood States Total Mood Disturbance, range of scores = 0 to 200; [12]).

Materials and Procedure

All participants completed a comprehensive neuropsychological battery that evaluated performance across several cognitive domains that are commonly affected in HAND, consistent with the most recent neuroAIDS guidelines [4]. Assessment of Learning and Memory included Total Trials 1-5 and Long Delay Free Recall from the California Verbal Learning Test (2nd ed., CVLT-2; [13]), Logical Memory I and II from the Wechsler Memory Scale (3rd ed., WMS-III; [14]), and the Immediate and Delayed Presence and Accuracy scores from the Rey Complex Figure Test, Boston Qualitative Scoring System (BQSS; [15]). Measures of Executive Functions included total time to complete Part B of the Trail Making Test (TMT; [16]) and Total Move Score from the Tower of London, Drexel version (ToL; [17]). Information processing speed was assessed with measures including TMT Part A (total time; [16]) and ToL Total Execution Time [17]. Measures of Attention and Working Memory included WMS-III Digit Span subtest (total score; [14]) and Self-Ordered Pointing Test total errors (see [18]). To evaluate verbal fluency, several fluency trials were administered, including letter (C; [19]), animal [20], and action [21] fluency tasks. Finally, the dominant and nondominant hand trials of the Grooved Pegboard test [22] were used to assess fine motor speed and coordination. Based on these demographically-adjusted neuropsychological measures, a trained neuropsychologist assigned clinical ratings for each domain, which were then used to determine a global cognitive function rating. Consistent with updated recommendations, a minimum of mild impairment (or greater) in at least two cognitive domains was required for determination of an impaired global score (i.e., global rating score of 5 or greater; see [23] for additional details regarding the ratings procedure).

As recommended by the latest algorithm for classifying HAND [4], the present study not only utilized self-report of everyday functional decline for determining HAND diagnosis,

but also objective, performance-based evidence of functional impairment (see [24]). Regarding self-reported daily functioning problems, a modified version of the Activities of Daily Living Scale [25] was used to characterize each individual's level of dependence in performing a variety of everyday activities, ranging from complete independence to requiring varying degrees of assistance from others. Individuals were classified as "dependent" if they reported decline from their "best" level of functioning in at least two domains (see [26]). Specifically, medication nonadherence (i.e., defined as < 90% of doses taken correctly by the participant as measured by the Medication Event Monitoring System; Aprax Corporation, Union City, CA) and unemployment status were considered in order to classify cases as Syndromic HAND. In each case, self-report of functional impairment was not sufficient if the individual had current depression (see [4]), and a syndromic diagnosis was made only if an objective indicator of functional impairment was present. Furthermore, each case was reviewed so that unemployment status only contributed to Syndromic HAND diagnosis when it was clearly not due to a factor other than HIV disease (e.g., back injury). Using these rigorous criteria, 53 (61.6%) individuals did not have HAND (HIV+/No HAND; i.e., global neurocognitive performance was within normal limits), whereas 16 (18.6%) met criteria for Subsyndromic HAND (i.e., Asymptomatic Neurocognitive Disorder [ANI], which is defined as global neurocognitive impairment without evidence of major functional disability) and 17 (19.8%) met criteria for Syndromic HAND (MND or HAD; i.e., global neurocognitive impairment ranging from mild-to-moderate to severe with at least moderate functional disability) based on multidisciplinary case conference diagnosis utilizing results of a comprehensive neuropsychological, psychiatric, and neuromedical assessment (see [27]) in accordance with the Frascati criteria [4]. Table I displays the demographic, HIV disease, and psychiatric characteristics of the study groups, which were comparable with regard to demographic and psychiatric factors ($p > .10$). The sample had relatively well-controlled HIV disease characteristics overall (e.g., 97.7% on antiretroviral therapy), and the groups were well balanced on these factors ($p > .10$). Importantly, the Syndromic and Subsyndromic HAND groups did not differ with regard to global neurocognitive rating scores ($p = .98$), for which higher scores represent greater impairment (for additional description see [23]).

The primary criterion of interest in the present study was cognitive reserve, which was calculated as an average of three sample-based z-scores: 1) years of education; 2) estimated verbal IQ as measured by the WTAR; and 3) Hollingshead score for highest occupation level. The z-scores for each measure are presented by group in Table I. In brief, the Hollingshead [28] system was used to code each individual's highest level of employment along a continuum ranging from 1, which is the highest level of employment (e.g., professional positions requiring specialized graduate training, such as a physician, or involving upper level administration, such as a president of a large company) to 7, which is the least specialized level of employment (e.g., positions involving non-specialized manual labor). The Hollingshead z-scores were adjusted to ensure consistency with the other indices in that higher scores reflect higher levels of cognitive reserve.

Statistical Analysis

The cognitive reserve score was normally distributed (Shapiro-Wilk W-test $p > .10$) and therefore a parametric approach was used. A logistic regression was conducted to evaluate whether cognitive reserve, the primary predictor, was associated with HAND group status, including HIV+/No HAND, Subsyndromic HAND, and Syndromic HAND. Although the groups were statistically comparable on the rates of AIDS diagnosis and lifetime MDD, these factors were included *a priori* in the regression model given their known relationship to everyday functioning. The rate of lifetime opioid dependence did differ between the groups, but given that there were no participants in the Syndromic HAND group with this

diagnosis, there was no stable way to include it in our regression models. As such, and considering that it represents a potentially conservative bias, it was not included in the analyses. Follow-up between-group comparisons were planned to further characterize the differences in level of cognitive reserve between the three groups. Finally, a second, more restricted logistic regression analysis was planned to evaluate how well cognitive reserve differentiates Syndromic HAND from Subsyndromic HAND (i.e., HIV+/No HAND excluded), even when factors that are known to contribute to everyday functioning decline (i.e., AIDS, MDD) were included in the model.

Although employment status is a component of the Frascati criteria [4] for a Syndromic HAND diagnosis, there are many potential reasons other than neurocognitive impairment that people with HIV might be unemployed. As such, the analyses were run without inclusion of employment status in the Syndromic HAND criteria and the pattern of results was unchanged.

RESULTS

The logistic regression analysis that was run with the three-level HAND diagnosis group variable (i.e., HIV+/No HAND, Subsyndromic HAND, and Syndromic HAND) was statistically significant ($df = 6$, $X^2 = 18.5$, $p = .009$). Cognitive reserve was the sole significant predictor (Wald $X^2 = 8.76$, $p = .01$; all other $ps > .10$). Figure 1 displays planned group contrasts showing that, consistent with our hypothesis, cognitive reserve scores in the Syndromic group were significantly lower than both the Subsyndromic HAND ($p = .02$, Cohen's $d = 0.75$) and HIV+/No HAND ($p = .002$, Cohen's $d = 0.88$) groups. The former pair-wise comparison was confirmed with a second logistic regression, which showed that cognitive reserve was a significant predictor of Syndromic HAND, even when AIDS and lifetime MDD were included in the model (model: $df = 3$, $X^2 = 12.3$, $p = .006$), as shown in Table II. In contrast, the HIV+/No HAND group was statistically equivalent to the Subsyndromic group ($p = .88$, Cohen's $d = 0.04$).

DISCUSSION

The findings of the current study supported the hypothesis that individuals with Syndromic HAND would evidence lower cognitive reserve relative to those without HAND or with a Subsyndromic diagnosis (i.e. ANI). These results extend prior findings regarding the role of cognitive reserve in HIV-associated neurocognitive impairment, which have shown that - consistent with our data - individuals with lower reserve were more likely to evidence cognitive deficits as compared to individuals with high reserve [6, 7, 8]. Interestingly, the present findings are unique in that they broaden this demonstrated relationship between cognitive reserve and neurocognitive impairment to HAND, wherein the primary distinction between Subsyndromic (i.e., ANI) and Syndromic HAND is based on functional ability. That is, the Subsyndromic and Syndromic HAND groups were comparable with regard to global neurocognitive impairment, and yet the Syndromic HAND group had significantly lower cognitive reserve scores. This finding is striking because it may, in part, explain why some HIV-seropositive individuals evidence impairment on neuropsychological testing, but have no evidence of dysfunction in their everyday activities (i.e., ANI).

The application of the cognitive reserve model to a functional criterion is consistent with the definition of cognitive reserve as proposed by Stern [5], who described cognitive reserve as the capacity to efficiently utilize brain networks, and possibly recruit alternate networks, in order to optimize performance. An important feature of the cognitive reserve model is that the threshold for cognitive impairment is different in each person as a function of that ability. For example, in two HIV-seropositive individuals with similar levels of brain reserve

capacity (e.g., similar number of synaptodendritic connections pre-infection), the cognitive reserve model could account for the fact that an individual with higher cognitive reserve could withstand more HIV-associated neuropathology before reaching a threshold at which cognitive impairment appears, relative to someone with lower reserve (e.g., [6]) for whom that threshold would be lower [5]. By extension, the cognitive reserve model might also explain, in part, why the functional impairment cutoff is also relative rather than fixed, such that the same capacity that allows for optimizing performance on cognitive tasks would also make it possible for an individual with higher cognitive reserve to tolerate mild-to-moderate cognitive impairment better than an individual with lower reserve, thus raising the symptomatic threshold for manifestation of functional decline (e.g., unemployment and medication non-adherence). Regarding the present results, the Subsyndromic group has higher cognitive reserve, and therefore they may be able to engage strategies and activate cognitive networks to perform everyday tasks without disruption from neurocognitive impairment. In contrast, perhaps the lower cognitive reserve observed in the Syndromic HAND group helps to explain why these individuals were not able to continue functioning successfully at a comparable level of global neurocognitive impairment.

Although to our knowledge no previous studies have directly examined the role of cognitive reserve in HIV-associated functional impairment using both objective and self-report measures, there is an indirect suggestion of this relationship in the literature. Specifically, a study by Waldrop-Valverde and colleagues [29] revealed that HIV-seropositive individuals with a combination of low literacy and cognitive impairment were nine times more likely to be nonadherent to their medication regimen as compared to individuals without this combination. Although these findings were not interpreted in the context of the cognitive reserve model, reading ability can provide an estimate of verbal IQ, which is a common index of cognitive reserve and/or is frequently a component of a composite cognitive reserve score. Therefore, these findings may indirectly suggest a similar extension of the cognitive reserve effect to a functional outcome, specifically medication adherence. Furthermore, better efficiency of brain network utilization as a possible mechanism of cognitive reserve could, in conjunction with enhanced strategy use, account for the ability of cognitively impaired HIV-seropositive individuals to maintain functional independence despite their cognitive status [5]. This interpretation is consistent with fMRI findings of greater activation (i.e., lateral prefrontal cortex, independent of task difficulty) among HIV-seropositive individuals with normal neurocognitive profiles, suggesting that increased activation may represent a greater draw on reserve for maintaining normal performance [30]. Future studies may also reveal greater activation among individuals with Subsyndromic relative to those with Syndromic HAND, which would similarly provide evidence that they efficiently activate brain networks in order to maintain successful cognitive performance and perhaps effective functioning in daily activities.

Limitations to the current study should be noted. Although the limited sample size of our study represented type II error, a cognitive reserve signal was nevertheless detected. However, this finding should be replicated in a larger sample. Furthermore, if larger numbers were available in each of the diagnostic groups, future work could investigate whether the findings extend to the diagnostic categories within the Syndromic HAND group (i.e., lower levels of cognitive reserve among individuals with HAD relative to MND). Additionally, employment status is a complex factor, and there are numerous reasons why HIV+ individuals would be unemployed, some of which may not directly relate to HIV or may not accurately reflect their ability to work (e.g., desire to maintain disability benefits). Therefore, future studies may wish to carefully characterize the reasons for unemployment when including employment status as a criterion for Syndromic HAND diagnosis per Frascati guidelines [4]. The cross-sectional nature of the present study represents a limitation in that it does not describe the relationship of cognitive reserve to functional decline over

time. That is, cognitive reserve hypothetically delays the onset of clinical symptoms (i.e., dysfunction in activities of daily living), and perhaps prevents it entirely in some individuals. Therefore, a longitudinal design would help to elucidate the effect of cognitive reserve on delaying functional decline, and could also investigate the contribution of other factors to that relationship, such as demographic (e.g., age) and disease severity (e.g., AIDS) factors. As such, cognitive reserve may have clinical utility in terms of identifying individuals at risk for decline in their everyday functioning ability, and could therefore be provided services, such as cognitive remediation to learn compensatory strategies, in order to reduce the impact on their daily lives.

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Figure 1. Differences in cognitive reserve as a function of HAND diagnosis (error bars represent standard error): Significantly lower reserve observed in the Syndromic HAND group relative to the Subsyndromic and No HAND groups

Table I**Demographic, Psychiatric, and Medical Characteristics of the Study Participants**

Variable	HIV+/No HAND (n = 53)	Subsyndromic HAND (n = 16)	Syndromic HAND (n = 17)	p
Demographic Characteristics				
Age (years)	51.2 (11.7)	51.3 (10.7)	46.9 (13.8)	0.42
Sex (% male)	81.1	93.8	82.3	0.42
Ethnicity (% Caucasian)	67.9	75.0	52.9	0.38
Global Neurocognitive Rating ^a	3.1 (1.0) [*]	5.9 (0.9)	5.9 (0.9)	<.001
Cognitive Reserve Components				
Education (years)	13.8 (2.4)	14.1 (2.9)	12.6 (3.1)	0.20
HH Occupation z-score	0.17 (0.9)	0.09 (0.9)	-0.62 (1.3) [*]	0.02
Estimated verbal IQ ^b	103.5 (11.3)	102.1 (9.4)	95.1 (11.3) [*]	0.03
Psychiatric Characteristics ^c				
Profile of Mood States	50.2 (32.5)	69.4 (37.6)	62.2 (36.7)	0.11
Major Depressive Disorder	50.9	25.0	58.8	0.10
Generalized Anxiety Disorder	13.2	18.8	5.9	0.51
Substance Use Disorders	75.5	68.8	52.9	0.23
Alcohol dependence	54.7	56.3	47.1	0.83
Cannabis dependence	43.4	37.5	23.5	0.32
Opioid dependence	15.1	25.0	0.0	0.04
Any Stimulant dependence	41.4	50.0	23.3	0.25
HIV Disease Characteristics				
HIV Infection Duration (years) ^d	16.6 [6.0, 20.9]	19.1 [7.1, 21.2]	15.8 [5.7, 20.0]	0.55
Current CD4 (cells/ml) ^d	567 [379, 844]	518.5 [423.8, 773.5]	440.5 [281.3, 670.5]	0.47
Nadir CD4 (cells/ml) ^d	200 [87.5, 300]	200 [71.75, 262.5]	148 [45, 196]	0.38
Plasma HIV RNA (log ₁₀) ^d	1.68 [1.6, 1.699]	1.68 [1.6, 1.68]	1.68 [1.6, 1.68]	0.59
CSF HIV RNA (log ₁₀) ^d	1.68 [1.6, 1.699]	1.68 [1.6, 1.69]	1.68 [1.6, 1.68]	0.85
AIDS (%)	50.9	50.0	76.47	0.14
Medication Status (% cART)	96.23	100.00	100.00	0.37
Hepatitis C Co-infection (%)	28.9	37.5	35.3	0.76

Note.

^{*} indicates the group that differed from the other two groups;^a higher rating score indicates greater impairment;^b based on the Wechsler Test of Adult Reading (WTAR);^c lifetime psychiatric diagnoses;^d data are presented as median [IQR]

Significant association between cognitive reserve and HAND status in a 2-group model: Subsyndromic HAND versus Syndromic HAND

Table II

Variable	B	SE	CI	Odds Ratio	Wald X [*]
Cognitive Reserve	1.15	0.55	0.18,2.40	3.17 ^a	4.45 [*]
LT MDD [no diagnosis]	0.86	0.46	0.02, 1.88	5.61 ^b	3.54
AIDS [no diagnosis]	0.88	0.48	0.004, 1.93	5.77 ^c	3.36

Note:

^{*} $p < .05$; LT MDD = Lifetime Major Depressive Disorder; CI = confidence interval;

^a higher reserve is associated with greater likelihood of Subsyndromic versus Syndromic HAND;

^b absence of LT MDD is associated with greater likelihood of Subsyndromic versus Syndromic HAND;

^c absence of AIDS diagnosis is associated with greater likelihood of Subsyndromic versus Syndromic HAND