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Neuropsychological test profile differences between young and old human immunodeficiency virus–positive individuals

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Human immunodeficiency virus (HIV) dementia remains as an important cause of neurological morbidity among HIV-seropositive (HIV+) individuals. Differences in the neuropsychological profiles between older and younger HIV+ individuals have not been examined extensively. The objective of this study was to examine the neuropsychological test performance between old and young HIV+ individuals (a) with and without cognitive impairment (total cohort) and (b) with dementia. One hundred thirty-three older (age $\geq$ 50 years) HIV+ individuals and 121 younger (age 20 to 39 years) HIV+ individuals were evaluated with a standardized neuropsychological test battery. Differences between age groups in the mean *z* score for each neuropsychological test were determined. The older HIV+ (total) cohort had greater impairment in tests of verbal memory ($P = .006$), visual memory ($P < .002$), verbal fluency ($P = .001$), and psychomotor speed ($P < .001$) compared to the young HIV+ (total) cohort. After adjusting for differences in education, older HIV+ patients with dementia ($n = 31$) had a greater deficit in the Trail Making test Part B ($P = 0.02$) compared to younger HIV+ patients with dementia ($n = 15$). Age was associated with lower performance in tests of memory, executive functioning, and motor performance in older HIV+ individuals with and without cognitive impairment (total cohort), compared to younger HIV+ individuals. Among HIV+ patients with dementia, age may be associated with greater impairment in a test of executive functioning. These differences could be a result of advanced age itself or age-associated comorbidities such as coexisting cerebrovascular or neurodegenerative disease. *Journal of NeuroVirology* (2007) **13,** 203–209.

Keywords: age; dementia; HIV; neuropsychological; test

Introduction

Highly active antiretroviral therapy (HAART) is associated with a decreased mortality rate among human immunodeficiency virus (HIV)-1–seropositive (HIV+) individuals. Consequently, an increasing proportion of HIV+ individuals in the United States are now 50 years of age or older. According to the Centers for Disease Control and Prevention in the United States, 90,513 cases of acquired immunodeficiency syndrome (AIDS) occurred in individuals 50 years of age or higher, representing a cumulative frequency of 11% as of December, 2001 (Valcour *et al,* 2004). In the state of Hawaii, nearly 20% of AIDS cases reported to the Hawaii State Department of Health were 50 years of age or higher in 2001 (Valcour *et al*, 2004).

HIV-1–associated dementia (HIV dementia) continues to be an important cause of morbidity among HIV+ individuals in the era of HAART. Most studies of the relationship between age and HIV-associated cognitive impairment have focused on prevalence

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rates, with an increased prevalence of cognitive impairment among older HIV+ individuals found in several studies (Becker *et al*, 2004; Cherner *et al*, 2004; Hinkin *et al*, 2001; Janssen *et al*, 1992; Wilkie *et al*, 2003). In a recent study from the Hawaii Aging with HIV Cohort, the frequency of dementia among older (50 or more years old) HIV+ individuals (25.2%) was nearly twice the frequency of dementia among younger (20 to 39 years old) HIV+ individuals (13.7%) (Valcour *et al*, 2004). Differences in the profile of neuropsychological test performance between older and younger HIV+ individuals with cognitive impairment have not been examined extensively. One study evaluated the rates of neuropsychological impairment in specific cognitive domains and found higher rates of impairment across most cognitive domains for older HIV+ individuals compared to younger HIV+ individuals (Cherner *et al*, 2004). Another study suggests that older HIV+ individuals are not at an increased risk for HIV-associated cognitive impairment when normal age-related cognitive changes are taken into account (Kissel *et al*, 2005). Increasing age itself among HIV seronegative (HIV−) individuals can be associated with impairment on tests of executive functioning and timed measures (Sanchez Rodriguez and Rodriguez, 2003).

The objective of this study was to examine the profiles of neuropsychological test performance of old and young HIV+ individuals (a) with and without cognitive impairment (total cohort) and (b) with dementia to determine if there were any differences in the pattern of cognitive performance between the old and young groups.

Results

Demographics

The demographics for the young and old HIV+ individuals for the total cohort and the dementia patients only are summarized in Table 1. The median age in the young and old HIV+ cohorts were 35 and 55 years respectively. The old HIV+ cohort overall had a greater proportion of men, a higher education, a greater portion who were Caucasian, and were more likely to be men who have sex with men, compared to the young HIV+ cohort who had a greater proportion of Asian Pacific Islanders and a greater proportion of HIV cases acquired through heterosexual transmission. The old HIV+ cohort also had a lower mean log plasma HIV RNA level, a longer duration of HIV infection, a longer duration since their CD4 nadir, an increased frequency of hypertension, and more extrapyramidal signs as measured by the Unified Parkinson's Disease Rating Scale (UPDRS) total score.

Neuropsychological test performance in the young and old HIV+ cohorts

Neuropsychological test performance in each of the three cognitive domains is summarized in Figure 1 for the entire young and old HIV+ cohorts. In the memory domain, compared to the young HIV+ cohort, old HIV+ individuals performed worse (greater impairment) in the tests of verbal memory (z score mean [SD]): Rey Auditory Verbal Learning Test [RAVLT] trial 5, old = −0.6 [1.2] versus young = −0.2 [1.2], $P = .006$; RAVLT recognition memory, old = −1.2 [2.0] versus young = −0.7 [1.3], $P = .02$; RAVLT delayed recall, old = −0.5 [1.1] versus young = −0.2 [1.1], $P = .02$) and visual memory (z score mean [SD]: Rey Complex Figure [RCF], old = −0.7 [1.0] versus young = −0.2 [1.1], $P = .002$). In the executive functioning domain, compared to the young HIV+ cohort, old HIV+ individuals had greater impairment in the Verbal Fluency (FAS) (z score mean [SD]: old = 0.0 [1.3] versus young = 0.4 [1.9], $P = .001$). In tests of motor speed, compared to the young HIV+ group, old HIV+ individuals had greater impairment in the Digit Symbol test (z score mean [SD]: old = 0.0 [1.0] versus young = 0.5 [1.0], $P < .001$, although neither group had impaired performance, i.e., a negative z score).

Neuropsychological test performance in the young and old HIV+ individuals with dementia

Older HIV+ individuals with dementia ($n = 31$) had higher education (mean [SD] 14.7 [2.1] years) compared to younger HIV+ individuals with dementia ($n = 15$), (13.2 [0.9] years) ($P = .008$). After adjusting for differences in education, in the executive functioning domain, compared to the young HIV+ individuals with dementia, old HIV+ individuals with dementia had greater impairment in the Trail Making test Part B (z score mean [SD]: old = −2.3 [2.2] versus young = −1.6 [1.9]) ($P = .02$). Without adjusting for differences in education, in the executive functioning domain, there was a consistent trend towards worse performance among the old HIV+ individuals with dementia compared to the young HIV+ individuals with dementia in the Trail Making test Part B (z score mean [SD]: old = −2.0 [1.5] versus young = −1.4 [1.5]) and the Verbal Fluency (FAS) test (z score mean [SD]: old = −0.7 [1.2] versus young = −0.4 [0.8]). After adjusting for differences in education in the memory and motor speed domains, there were no differences in any of the tests between the two groups.

Discussion

Increased age is a strong risk factor for neurodegenerative diseases causing dementia such as Alzheimer's disease (Janssen *et al*, 1991) and Parkinson's disease (Hotelling 1947). Multiple studies (Becker *et al*, 2004; Cherner *et al*, 2004; Hinkin *et al*, 2001; Kissel *et al*, 2005; Wilkie *et al*, 2003) have also demonstrated that advanced age is associated with an increased frequency of cognitive impairment in HIV infection. However, differences in the neuropsychological test

Table 1 Baseline demographics

	Young HIV+ group (total)	Old HIV+ group (total)	*P* value	Young HIV dementia group	Old HIV dementia group	*P* Value
Sample size, *n*	121	133		15	31	
Age, mean ± SD	35.2 ± 4.8	55.2 ± 5.0		36.5 ± 3.9	54.5 ± 4.0	
Gender: *n* (%) male	92 (76)	122 (92)	<.001	13 (87)	28 (90)	.709
Education: n (%)			<0.001			0.009
High school or less	77 (64)	46 (35)		12 (80)	10 (32)	
Some college	40 (33)	67 (51)		3 (20)	19 (60)	
College or greater	4 (3)	19 (14)		0 (0)	2 (7)	
Ethnicity: *n* (%)			<0.001			0.767
Caucasian	52 (43)	93 (70)		7 (47)	18 (58)	
Asian Pacific Islander	44 (36)	30 (23)		5 (33)	8 (26)	
Hispanic	9 (9)	4 (4)		1 (8)	1 (4)	
Other	25 (21)	10 (7)		3 (20)	5 (16)	
Risk category: *n* (%)			0.002			0.683
MSM only	69 (57)	99 (75)		7 (58)	17 (63)	
IVDU only	2 (2)	3 (2)		0 (0)	1 (4)	
Heterosexual only	33 (27)	12 (9)		2 (17)	2 (7)	
More than one	17 (14)	19 (14)		3 (25)	7 (26)	
Antiretroviral therapy: *n* (%)						
HAART	64 (67)	82 (80)	.053	7 (58)	21 (78)	.213
NNRTI-based regimen	66 (76)	82 (80)	.535	8 (67)	22 (81)	.311
PI-based regimen	42 (48)	54 (52)	.569	6 (50)	15 (56)	.748
CD4 count, mean ± SD	426 ± 230	480 ± 266	0.088	328 ± 335	393 ± 270	0.483
Nadir CD4 count, mean ± SD	249 ± 219	200 ± 166	0.051	152 ± 140	155 ± 144	0.947
Duration of HIV infection (years), mean ± SD	7.5 ± 5.6	11.9 ± 5.3	<0.001	9.9 ± 4.5	10.7 ± 5.5	0.614
Years since CD4 nadir, mean ± SD	6.0 ± 3.2	8.3 ± 3.2	<0.001	6.7 ± 3.4	7.8 ± 2.4	0.220
Detectable plasma HIV RNA: *n* (%)	71 (59)	66 (50)	0.148	12 (80)	13 (42)	0.015
Log plasma HIV RNA, mean ± SD	3.2 ± 1.5	2.7 ± 1.3	0.008	4.0 ± 1.6	2.8 ± 1.4	0.013
On antiretroviral therapy: *n* (%)	90 (74)	110 (83)	0.080	12 (80)	25 (81)	0.956
Current substance dependence: *n* (%)	14 (12)	10 (8)	0.261	2 (13)	0 (0)	0.038
Current substance abuse: *n* (%)	27 (22)	11 (8)	0.002	3 (20)	1 (3)	0.058
Lifetime substance abuse: *n* (%)	69 (57)	66 (50)	0.238	10 (67)	14 (45)	0.171
BDI score, mean ± SD	9.3 ± 7.3	8.6 ± 7.3	0.466	14.1 ± 7.8	11.7 ± 9.1	0.404
History of stroke: *n* (%)	1 (1)	3 (1.)	0.361	0 (0)	2 (6)	0.315
History of TIA: *n* (%)	0 (0)	2 (1)	0.176	0 (0)	1 (3)	0.482
Current hypercholesterolemia: *n* (%)	27 (23)	46 (35)	0.031	3 (20)	10 (33)	0.352
Current hypertension: *n* (%)	9 (7)	29 (22)	0.001	0 (0)	9 (29)	0.020
Family history of psychiatric illness: *n* (%)	29 (25)	23 (18)	0.177	3 (20)	6 (20)	0.709
UPDRS, total score, mean ± SD	2.1 (2.6)	4.4 (5.0)	<0.001	4.1 (4.2)	8.5 (7.3)	0.043

MSM = men who have sex with men; IVDU = IV drug use; HAART= highly active antiretroviral therapy; NNRTI=non-nucleotide reverse transcriptase inhibitor ; PI= protease inhibitor; BDI = Beck Depression Inventory.

profile between young and old HIV+ individuals with cognitive impairment have not been examined in detail.

Our results suggest that among HIV+ individuals with and without cognitive impairment (total cohort), older HIV+ individuals were associated with lower performance in multiple neurocognitive domains including tests of both verbal memory (RAVLT trial 5 and RAVLT recognition memory) and visual memory (RCF delayed recall), executive functioning (verbal fluency), and motor speed (Digit Symbol) compared to younger HIV+ individuals. In contrast, among HIV+ individuals with dementia, older HIV+ individuals were associated with greater impairment specifically in a test of executive functioning (Trail Making test Part B). The small number of young HIV+ individuals with dementia ($n=15$) may have prevented significant differences in several other tests from being detected.

The relationship between normal aging (in an HIV−population) and cognitive function is an area of considerable controversy. Some studies suggest that normal aging can be associated with cognitive changes in memory, executive functioning and working memory, and psychomotor speed performance (Grigsby *et al*, 2002; Park *et al*, 2003). Indeed, the neuropsychological test profile in a sample of HIV−, healthy older individuals (mean age = 70) can be similar to the neuropsychological test profile in a young group of individuals with AIDS (mean age = 36) (Hinkin *et al*, 1990). Cognitive decline in older individuals can also be interpreted not as a function of the aging process itself, but instead, as a result of comorbid events that occur with aging.

In contrast, the neuropsychological test profile of Alzheimer's disease is different from the profile seen in individuals with early HIV dementia. Individuals with HIV dementia show increased problems with

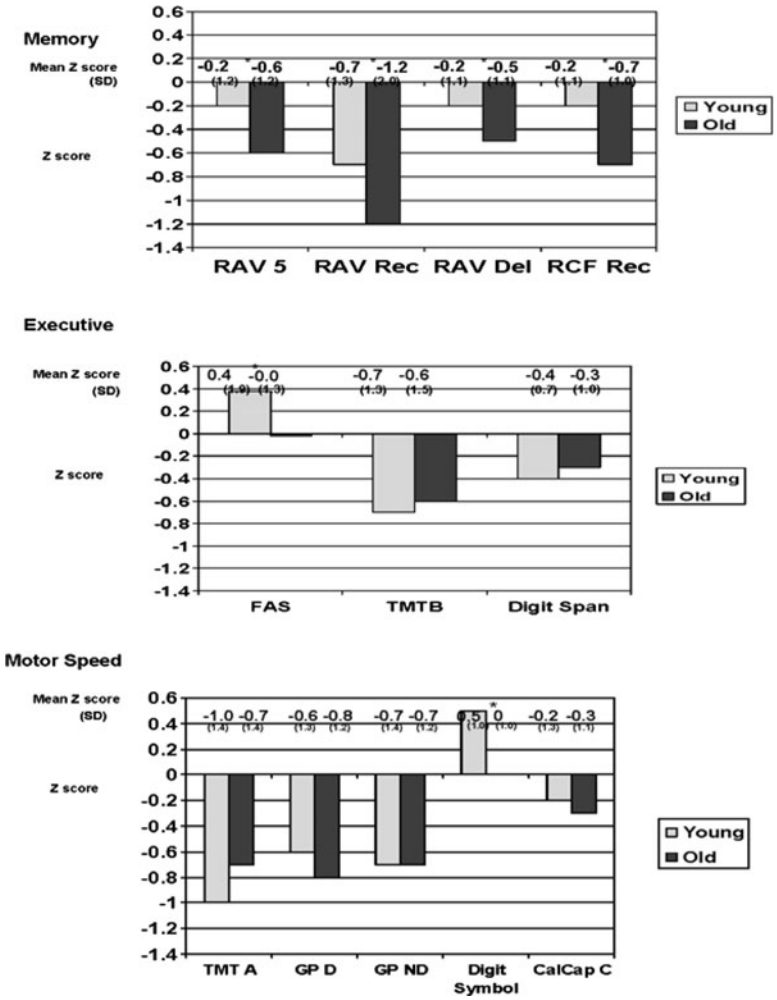

Figure 1 Neuropsychological test performance in young and old HIV+ cohorts. $^{*}P < .05$.

free recall (retrieval) of test items, whereas individuals with Alzheimer's disease have greater difficulty with encoding and storage. Another study compared remote memory in HIV dementia, Huntington's disease, and Alzheimer's disease (Sadek *et al*, 2004). Both the HIV dementia and Huntington's disease groups had a preferential cuing benefit relative to the Alzheimer's group. The differences in these cognitive patterns are similar to the differences between subcortical and cortical dementias described by Benson and Cummings, with HIV dementia and Huntington's disease representing a subcortical dementia and Alzheimer's disease representing a cortical dementia (Sadek *et al*, 2004). In our study, there was no difference in the pattern of recognition memory performance between young and old HIV+ individuals with dementia. This result suggests that the profile in older HIV+ cases with dementia is not typical for the profile seen in Alzheimer's disease. If Alzheimer's disease was the cause of the dementia syndrome in our older HIV+ cases, then the old HIV+ group with dementia may have had worse performance in the RAVLT recognition memory component compared to the young HIV+ group with dementia. Rather, advanced age by itself may specifically be associated with deficits of executive functioning and may account for the differences between the young and old HIV groups with dementia (Royall *et al*, 2003).

Other potential factors besides advanced age could also contribute to additional deficits in the older dementia group. In particular, advanced age is associated with an increased risk for subcortical small vessel ischemic disease. Cerebrovascular disease associated cognitive impairment can also be characterized by deficits in executive functioning and may account for the differences between the two dementia groups (Shenkin *et al*, 2005). This hypothesis is supported by the increased frequency of hypertension in the older groups compared to the younger groups in this study. Advanced age is also associated with a greater risk of metabolic diseases such as diabetes or hypercholesterolemia. In this cohort, diabetes has been found to be a strong risk factor for HIV dementia (Valcour *et al*, 2005).

Other differences in demographics between the two groups could also be a contributing factor. The older HIV+ group had a longer duration of HIV infection compared to the younger HIV+ group. If the syndrome of HIV dementia progresses more rapidly in the specific cognitive domain of executive functioning compared to other cognitive domains, this explanation could also account for the difference between the two groups. The older HIV+ group also had more extrapyramidal signs, which could interfere with tests of executive function or motor speed.

In conclusion, older HIV+ individuals with and without cognitive impairment were associated with lower performance in tests of memory, executive functioning, and motor performance compared to younger HIV+ individuals with and without cognitive impairment, whereas older HIV+ individuals with dementia may have greater decline in executive functioning compared to younger HIV+ individuals with dementia. This difference among older HIV+ individuals with dementia could be a result of advanced age itself or age-associated comorbidities such as subcortical small vessel ischemic disease. Our older HIV+ individuals with dementia were predominantly in their mid 50s. For HIV+ individuals with dementia who are 60 or 70 years of age, a neurodegenerative condition such as Alzheimer's disease could also be playing a role in the dementia syndrome. Further studies with larger sample sizes are necessary to define the etiology of a dementia syndrome specific to each decade of life in older HIV+ individuals with dementia. Longitudinal studies also are necessary to determine if older HIV+ individuals with dementia are at greater risk for progression.

Material and Methods

Cohort recruitment

The Hawaii Aging with HIV Cohort Study is a collaboration between the University of Hawaii and Johns Hopkins University to evaluate older (50 years of age or higher) and younger (20 to 39 years of age) HIV+ individuals. Baseline data from 133 older HIV+ individuals and 121 younger HIV+ individuals were examined for this study. All individuals were living in Hawaii. Major exclusion criteria included the following: (1) major psychiatric disorder including bipolar disorder, schizophrenia, or active major depression; (2) head injury with loss of consciousness greater than 1 hour; (3) central nervous system (CNS) opportunistic infection; (4) learning disability; and (5) neurologic disease such as major stroke, multiple sclerosis, or delirium. English was the primary language for all individuals. Broad community-based recruitment techniques were implemented, including recruitment from AIDS service organizations, advertisement in local newspapers, referrals from community physician clinics, and participation in local HIV/AIDS events. Participants were recruited from all major islands of Hawaii.

Evaluations

Participant evaluations included demographics, medical history, the macroneurologic examination as used in the Adult AIDS Clinical Trials Group including the United Parkinson's Disease Rating Scale to examine for extrapyramidal signs (Gancher, 1997; Schmitt *et al*, 1988), a medication/adherence history, a Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV–based substance abuse/dependence inventory, immunologic and virologic laboratory tests, and neuropsychological testing.

The 80-min neuropsychological test battery assesses multiple cognitive domains affected by HIV-1 and included the following: Choice and Sequential Reaction Time from the California Computerized Assessment Package (CalCap), Rey Auditory Verbal Learning Test (RAVLT), Rey Osterreith Complex Figure (RCF) Copy and Recall, Trail Making tests A and B, WAIS-R Digit Symbol, Grooved Pegboard (dominant and nondominant hands), Verbal Fluency test (FAS), Animal Naming, Boston Naming Test (BNT), the WAIS-R Digit Span (forward and backward), and Timed Gait. Depression symptomatology was assessed using the Beck Depression Inventory (BDI). This neuropsychological test battery was adapted from that used in the NorthEast AIDS Dementia (NEAD) Cohort (The Dana Consortium on Therapy for HIV Dementia and Related Cognitive Disorders, 1996).

Normative neuropsychological data for individuals with a high school or greater education were derived from the Multicenter AIDS Cohort Study (MACS) consisting of 733 HIV seronegative subjects with risk profiles similar to the Hawaii cohort. For individuals with less than a high school education (six younger and three older participants), normative neuropsychological data from the AIDS Link to IV Experience (ALIVE) study ($n=150$) was used (Concha *et al*, 1995). For neuropsychological tests with normative datasets that have few individuals over 54 years of age (e.g., FAS, BNT, RCF), alternative published normative data were used (Heaton *et al*, 1991, 1999; Schmidt 1996; Tombaugh *et al*, 1999; Chiulli *et al*, 1995). All test results were transformed to *z* scores using appropriate age and education-matched normative data sets.

Neuropsychological tests were grouped into three domains: (1) memory, (2) executive functioning, and (3) motor speed. The memory domain included portions of the verbal memory test (RAVLT trial 5, RAVLT recognition memory, and RAVLT delayed recall), and the visual memory test (RCF recall). The executive functioning domain included the Verbal Fluency test (FAS), the Trail Making test Part B, and the Digit Span (forward and backward). The motor speed domain

included the Trail Making test Part A, the Grooved Pegboard test with the dominant and nondominant hands, the Digit Symbol test, and the CalCap choice reaction time.

In order to define HIV dementia, individual cases were discussed in a consensus conference involving two neurologists, two neuropsychologists, and a geriatrician (Valcour *et al*, 2005). HIV dementia cases were defined with the American Academy of Neurology criteria including results from the neurological history and examination, neuropsychological testing, functional assessment, and all clinical data obtained during the study visit (Janssen *et al*, 1991). A diagnosis of HIV dementia required an abnormality in at least two cognitive domains including attention/concentration, speed of information processing, abstraction/reasoning, visuospatial skills, memory/learning or speech/language, and either an abnormality in motor function or decline in motivation/emotional control.

Data management and statistical analyses

Using published normative data, neuropsychological test scores were transformed based on age and education. To address the primary aim of the project, mean differences between older and younger HIV-1 seropositive participants were tested using multivariate analysis of variance (MANOVA). We initially compared differences in test performance between the entire young and old HIV+ cohorts. Then, the differences between only dementia patients in the young and old HIV+ cohorts were compared. Group differences on each cognitive domain were tested globally using the Hotelling's *T*-squared test (Hotelling 1947). If a significant global difference was found, univariate differences were examined using the Student's *t* test.

In addition to comparing the two groups with respect to neuropsychological test scores, key demographic factors were examined between the older and younger HIV-1–seropositive participants using Student's *t* test (for continuous variables) and chi-square test of association (for discrete variables). Because there was a significant difference with respect to number of years of education between the two groups, education was included as a potential confounding variable in the linear regression equation when examining the relationship between age and neuropsychological test performance.

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