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Impairments in component processes of executive function and episodic memory in alcoholism, HIV infection, and HIV infection with alcoholism comorbidity

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Abstract

Background—Executive functioning and episodic memory impairment occur in HIV infection (HIV) and chronic alcoholism (ALC). Comorbidity of these conditions (HIV+ALC) is prevalent and heightens risk for vulnerability to separate and compounded deficits. Age and disease-related variables can also serve as mediators of cognitive impairment and should be considered, given the extended longevity of HIV-infected individuals in this era of improved pharmacological therapy.

Methods—HIV, ALC, HIV+ALC, and normal controls (NC) were administered traditional and computerized tests of executive function and episodic memory. Test scores were expressed as age- and education-corrected Z-scores; selective tests were averaged to compute Executive Function and Episodic Memory Composite scores. Efficiency scores were calculated for tests with accuracy and response times.

Results—HIV, ALC, and HIV+ALC had lower scores than NC on Executive Function and Episodic Memory Composites, with HIV+ALC even lower than ALC and HIV on the Episodic Memory Composite. Impairments in planning and free recall of visuospatial material were observed in ALC, whereas impairments in psychomotor speed, sequencing, narrative free recall, and pattern recognition were observed in HIV. Lower decision-making efficiency scores than NC occurred in all three clinical groups. In ALC, age and lifetime alcohol consumption were each unique predictors of Executive Function and Episodic Memory Composite scores. In HIV+ALC, age was a unique predictor of Episodic Memory Composite score.

Conclusions—Disease-specific and disease-overlapping patterns of impairment in HIV, ALC, and HIV+ALC have implications regarding brain systems disrupted by each disease and clinical ramifications regarding the complexities and compounded damping of cognitive functioning associated with dual diagnosis that may be exacerbated with aging.

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Keywords

HIV Infection; Alcoholism; Executive Functions; Episodic Memory; Comorbidity

Chronic alcoholism (ALC) is a common co-occurrence in HIV infection (HIV) (Conigliaro et al., 2006; Gongvatana et al., 2014), with the rate of alcoholism in this group being twice as high as that reported in the general population (Justice et al., 2010). Each condition is associated with a specific profile of cognitive impairments, involving component processes of executive functioning [ALC: (Beatty et al., 1993; Bernardin et al., 2014; Nixon and Parsons, 1991; Noel et al., 2001; Oscar-Berman and Marinkovic, 2007); HIV: (Giesbrecht et al., 2014; Heaton et al., 2011; Woods et al., 2009)] and episodic memory [ALC: (Becker et al., 1983; Parsons, 1977; Pitel et al., 2007; Riege et al., 1981; Sullivan et al., 2000); HIV: (Maki et al., 2015; Stout et al., 1995)].

Even in the era of combination and highly-active antiretroviral therapy (CART/HAART) neurocognitive impairment associated with HIV infection occurs (Clifford and Ances, 2013; Heaton et al., 2011; Saylor et al., 2016). Focus on HIV-related cognitive impairment, however, has shifted from motor-related domains to cognitive domains, specifically from slowed motor speed and rate of information processing (Becker et al., 1997) to compromise in executive functions and episodic memory (Heaton et al., 2011; Sacktor and Robertson, 2014). Planning, efficiency, monitoring, and strategic aspects of memory encoding and retrieval are among the executive function component processes most compromised in HIV infection (Cattie et al., 2012; Woods et al., 2013). As antiretroviral treatment has extended longevity of individuals with HIV infection, it is now relevant to determine the influence of other variables that can mediate or moderate cognitive deficits in this population including aging, neurotoxicity from long-term effects of medication, chronic inflammatory processes, medical conditions (e.g., Hepatitis C), comorbid psychiatric conditions (e.g., depression), and substance use disorders (Hardy and Vance, 2009; Sheppard et al., 2015; Woods et al., 2009).

Cognitive deficits associated with chronic alcoholism partially overlap with those associated with HIV infection and involve executive functions and episodic memory processes (Fama et al., 2004; Glenn and Parsons, 1992; Oscar-Berman et al., 2004; Tivis et al., 1995). Working memory, mental flexibility, inhibition, processing speed, concept formation, planning, and problem-solving capacities are among the most vulnerable executive function component processes in chronic alcoholism (Bernardin et al., 2014). Deficits in attentional set shifting and working memory were reported in abstinent alcohol-dependent men, with greatest impairment observed in men who had been abstinent for one year or less (Kopera et al., 2012). Episodic memory compromise associated with chronic long-term alcoholism include impairments in encoding, retrieval, and spatiotemporal context (Pitel et al., 2007). Efficiency scores, reflecting time-accuracy trade-offs for tasks requiring executive functions and episodic memory processes have also been reported in alcoholism (Nixon and Bowlby, 1996; Nixon and Parsons, 1991). Factors that can moderate cognitive deficits in chronic alcoholism, include age, length and pattern of drinking, and comorbid medical or psychiatric conditions.

Individuals with both diseases (HIV+ALC) may be at heightened risk for compounded untoward effects in verbal reasoning, working memory, and episodic memory (Fama et al., 2009; Fama et al., 2011; Gongvatana et al., 2014; Green et al., 2004; Rothlind et al., 2005). Even a remote history of alcoholism has been associated with lower levels of cognitive functioning in HIV-infected individuals, particularly in working memory, episodic memory, and visuomotor function (Gongvatana et al., 2014). These compounded deficits may be due to the interaction of dysfunction in separate [e.g., frontocerebellar in ALC (Oscar-Berman and Marinkovic, 2007; Sullivan et al., 2003) and frontostriatal in HIV (Ipser et al., 2015)] and overlapping [e.g., limbic system (ALC: Sullivan et al., 1995 HIV: Ortega et al., 2013)] neural systems. The pattern and extent of executive function and episodic memory deficits in ALC, HIV, and HIV+ALC, however, are heterogeneous both between and within these diseases, and cognitive deficits are not observed in all individuals [ALC: (Arciniegas and Beresford, 2001; Fein and Landman, 2005) ; HIV: (Woods et al., 2009)].

This study examined component processes of executive function and episodic memory in alcoholism, HIV infection, and their comorbidity and relations between these cognitive processes and demographic and disease-related variables. Traditional and computerized tests were chosen based on their sensitivity to assess these cognitive processes in alcoholism and HIV infection. We tested two hypotheses: (1) ALC and HIV would be impaired in component processes of executive functions and episodic memory compared with the controls and that the comorbid group (HIV+ALC) would demonstrate greater compromise than either single diagnosis group. Different component processes of executive function would be compromised in ALC and HIV due to different neural involvement (frontocerebellar compromise in ALC and frontostriatal compromise in HIV), accordingly, decision making, complex attention and set shifting would be more affected in ALC, whereas psychomotor speed, planning, monitoring, and sequencing would be more affected in HIV. Shared limbic region compromise would result in similar component processes of episodic memory being affected in HIV and ALC; (2) Level of executive function and memory compromise in the clinical groups would be associated with select demographic and disease related variables in the clinical groups, specifically, older age (over and above normal aging effects) and higher reported lifetime alcohol consumption would be associated with greater executive function and memory deficits in the alcohol groups, and lower CD4 cell counts would be associated with greater executive function and memory deficits in the HIV infection groups.

Materials and Methods

Participants

Participants included 36 individuals who were HIV seropositive (HIV), 39 individuals who met DSM-IV criteria for alcohol dependence within 3 years prior to baseline study entry and were seronegative for HIV (ALC), 42 individuals who were seropositive for HIV infection and met criteria for alcohol dependence within 3 years prior to baseline study entry (HIV +ALC), and 31 individuals who were neither seropositive for HIV infection nor met criteria for alcohol dependence or abuse (NC). Participants were part of an ongoing longitudinal study on the effects of HIV infection and alcohol on brain structure and function. All

subjects gave written informed consent to participate in this study, which was approved by the Institutional Review Boards of SRI International, Stanford University, and Santa Clara Valley Medical Center.

At the time of testing 20 HIV and 24 HIV+ALC participants met CDC criteria for AIDS (CD4 cell count <200, AIDS-defining event) sometime during the course of their illness. Most of the HIV and HIV+ALC participants (31 HIV and 32 HIV+ALC) were on HAART (highly active antiretroviral therapy). In addition, 12 of the 36 HIV, 7 of the 39 ALC, and 18 of the 39 HIV+ALC subjects tested positive for Hepatitis C in their lifetime.

In the ALC group, 56.4% of participants met lifetime criteria for non-alcohol substance abuse or dependence diagnosis; the median reported sobriety duration from drugs was 115 weeks. In the HIV groups, 44.4% of the HIV-only and 87.2% of the HIV+ALC subjects met lifetime, but not current, criteria for a non-alcohol substance abuse or dependence diagnosis; the median reported sobriety duration from drugs was 724 weeks for the HIV participants and 121 weeks for the HIV+ALC participants. The most common drugs of abuse were cocaine, reported by 41 of 75 (55%) individuals with drug history, followed by cannabis, reported by 39 (52%) individuals with a drug history. Abuse of opiates and stimulants was less frequently reported. Criteria for cannabis abuse were met for 3 participants (1 HIV and 2 HIV+ALC) within the month prior to neuropsychological testing. ALC participants had a mean alcohol dependence remission time of 87 weeks (median 25 weeks, range 0 to 484 weeks), whereas HIV+ALC had a mean alcohol dependence remission time of 211 weeks (median 120 weeks, range 0 to 1207 weeks). Median age of onset of alcohol diagnosis was 20 years old in the ALC group and 21 years old in the HIV+ALC group. Lifetime and current nicotine use differed among the groups ($\chi^2(3)=26.99$, $p<.001$ for both time frames), with 10% of NC, 59% ALC, 36% HIV, and 54% HIV+ALC meeting criteria for lifetime nicotine dependence and 6% NC, 54% ALC, 14% HIV, and 46% HIV+ALC meeting criteria for current nicotine dependence. Thus, a significantly greater number of ALC than HIV ($p=.048$) or NC ($p<.001$) met criteria for nicotine dependence sometime in their life; similarly more HIV and HIV+ALC met lifetime criteria for nicotine dependence than NC (HIV vs. NC: $p=.01$, HIV+ALC vs. NC $p<.001$). These group differences were the same for current nicotine dependence diagnosis, except that a greater number of HIV+ALC met criteria for nicotine dependence compared with HIV, and the difference between HIV and NC was not significant.

The HIV, ALC, and HIV+ALC groups were older than the NC group and had fewer years of formal education and a lower NART-IQ estimate (Table 1). The clinical groups had lower socioeconomic status than the controls as assessed by level of education and occupation level (Hollingshead, 1975). As expected, the ALC and HIV+ALC groups drank significantly more over their lifetime than the HIV and NC groups, and the ALC group had higher lifetime alcohol consumption than the HIV+ALC group. Severity of depressive symptoms was higher for the three clinical groups than the control group. CD4 cell counts were comparable in the HIV and HIV+ALC groups. Total score on the *Dementia Rating Scale – 2* (Mattis, 2004), which assesses overall current general cognitive function, was lower in HIV and HIV+ALC than controls and lower in HIV+ALC than ALC.

Procedure

All participants were screened using the Structured Clinical Interview for DSM-IV (SCID) (First et al., 1998) and structured questionnaires on health status. Upon initial assessment, subjects were excluded if they had fewer than 8 years of education, a significant history of medical (e.g., , epilepsy, stroke, multiple sclerosis, uncontrolled diabetes, or loss of consciousness > 30 minutes), psychiatric (i.e., schizophrenia or bipolar I disorder) or neurological disorder (e.g., neurodegenerative disease) other than the diagnosis directly related to their clinical grouping. Other exclusionary criteria were recent substance dependence other than alcohol in the clinical groups, a serious medical condition or HIV-related opportunistic infection in the HIV and HIV+ALC groups, or any DSM-IV Axis I disorder in the NC group.

All subjects underwent a semi-structured interview (Skinner, 1982; Skinner and Sheu, 1982) to quantify lifetime alcohol consumption. Severity of depressive symptoms was assessed with the Beck Depression Inventory-II (Beck et al., 1996). Blood samples were used to determine HIV status via HIV antibody test, plasma viral load, and CD4 cell count. At the time of recruitment, all HIV positive individuals had CD4>100 cells per mm³ and a Karnofsky score >80, which provides a global measure of general abilities in activities of daily living (Karnofsky, 1949).

Executive functions (working memory, planning, problem solving, decision making) and explicit memory (immediate free recall, recognition) processes were assessed with traditional and computerized test measures. The *Trail Making Test Part B* required subjects to sequence numbers and letters in alternate and ascending order, assessing working memory and planning (Borkowski et al., 1967; Reitan, 1958). The *Logical Memory* subtest of the Wechsler Memory Scale – Revised (Wechsler, 1987) required subjects to recall two short narratives that had just been read to them, assessing immediate verbal memory. The *Rey-Osterrieth Complex Figure* (Osterrieth and Rey, 1944; Rey, 1942) required subjects to draw from memory a complex figure they just copied, assessing immediate visual memory. Each of these test was administered and scored according to standardized instructions.

The computerized measures administered were subtests of a larger test battery - the Cambridge Neuropsychological Test Automated Battery (CANTAB) – which assesses accuracy and response time parameters for various component processes of executive functions and episodic memory (Morris et al., 1987; Sahakian and Owen, 1992). Seven subtests of the CANTAB were examined: (1) *Motor (MOT)* subtest screens for difficulties in vision, movement, and comprehension. Subjects are instructed to touch the flashing cross when it appears on the screen to ensure that they could understand directions and navigate the touch screen; (2) *Intra-Extra Dimensional Set Shift (IED)* The IED subtest assesses rule acquisition and rule reversal. Rule criteria changes after 6 consecutive correct responses. Individuals with frontostriatal dysfunction have been shown to be impaired on this type of cognitive task (Heaton, 1981). For this subtest, number of extra-dimensional errors is a dependent measure; (3) *Stockings of Cambridge (SOC)* The SOC subtest assesses planning and working memory. Subjects match target displays of increasing difficulty by moving 3 balls (1 each of yellow, red, blue) one at a time across three pegs. Number of problems solved in minimal moves is a dependent measure; (4) *Cambridge Gambling Task (CGT)* The

CGT subtest assesses decision making and risk taking. Subjects place bets on whether the target is behind a blue or yellow square. Ratio odds are clearly displayed across the ten blocks (e.g., if 7 blocks are blue and 3 blocks are yellow the best prediction based on odds would be to bet on blue), thus, no learning across trials is required. Accuracy score reflects the quality of decision making, based on whether the subject chose to bet on the color that afforded the best odds of winning. Response time was the average deliberation time to choose a monetary bet value; (5) *Spatial Working Memory (SWM)* The SWM subtest assesses ability to attend to and mentally manipulate spatial information. Subjects find a blue token that is hidden behind one of the boxes in an array. Returning to the same box more than once in a trial or choosing a box that has already been associated with a blue token are defined as errors. The number of between trial errors is a dependent measure; (6) *Spatial Recognition Memory (SRM)* The SRM subtest assesses ability to attend and maintain spatial information over a short interval. A white square is shown sequentially in 5 different locations. The subject is then shown two white blocks on the screen and has to pick the white block that is in one of the previously displayed locations. Number correct and mean response latency times on correct items are dependent measures; (7) *Pattern Recognition Memory (PRM)* The PRM assesses visual pattern recognition. Subjects are instructed to remember the patterns presented in a box on the screen. Immediately after presentation subjects are given a 2-choice forced recognition test and asked to select the pattern just seen. Number correct and mean response latency times on correct items are dependent measures. Examples of IED, SOC, and CGT subtests are in supplemental materials.

Statistical Analyses

Conceptually-derived composite scores were calculated to reflect executive function and episodic memory processes (Table 2). Age- and education-corrected Z scores for individual test parameters were calculated based on the normal control group [mean and standard deviation for NC group: $Z=0\pm1$], allowing direct comparisons. Where higher raw scores indicated worse performance, scores were multiplied by -1 , so that in all cases lower Z scores indicated worse performance. Efficiency ratio scores (accuracy/response time) were calculated for tests that had both accuracy and response time scores (i.e., CGT, SRM, PRM).

Between group differences were assessed with ANOVAs. To help protect against Type I error, a Bonferroni correction was used for two-group analyses when investigation of omnibus group differences was significant. Nonparametric analyses (Mann-Whitney U test) assessed within group differences (e.g., whether individuals with Hepatitis C or AIDS showed a greater degree of cognitive impairment than those without Hepatitis C or AIDS). Pearson product moment correlations tested relations between select demographic and disease-related variables and composite (Bonferroni correction for 2 family wise comparisons $p<.025$) and individual test scores (Bonferroni correction for multiple comparisons set at $p<.017$).

Results

Between Group Analyses

Groups did not differ on the CANTAB motor screening subtest assessing sensorimotor accuracy and computer-related task demands (MOT: $F(3,141)=1.55$, $p=.20$).

Executive Function Composite Score—Group differences were observed on the Executive Function Composite score [$F(3,141)=9.27$, $p<.0001$] (Figure 1). Further analyses indicated that all 3 clinical groups scored lower than NC (HIV+ALC vs. NC $p=.0001$; HIV vs. NC $p=.0001$; ALC vs. NC $p=.0004$).

Examination of individual test scores within the Executive Function Composite score indicated significant group differences on - Trails B [$F(3,137)=4.63$, $p=.004$], Cambridge Gambling Test [$F(3,141)=5.38$, $p=.002$], Stockings of Cambridge [$F(3,141)=5.23$, $p=.002$], Intra-Extra Dimensional Set Shift Test [$F(3,141)=5.58$, $p=.001$], and a trend was noted on Spatial Working Memory [$F(3,141)=2.30$, $p=.08$] (Figure 2). Raw scores for these tests for all groups are in Table 3. Two group comparisons are presented in Table 4.

Episodic Memory Composite Score—Group differences were also observed on the Episodic Memory Composite score [$F(3,141)=11.31$, $p<.0001$] (Figure 1). Again, all 3 clinical groups scored lower than NC (HIV+ALC vs. NC $p<.0001$; HIV vs. NC $p=.001$; ALC vs. NC $p=.006$). Additionally, the HIV+ALC group scored lower than the ALC group ($p=.002$) and HIV group ($p=.013$).

At the individual test level, group differences were observed on all memory measures – WMS-R Logical Memory Recall [$F(3,136)=3.76$, $p=.012$], Rey-Osterrieth Complex Figure Recall [$F(3,140)=4.76$, $p=.003$], Spatial Recognition Memory [$F(3,141)=13.23$, $p=.0001$], and Pattern Recognition Memory [$F(3,141)=4.18$, $p=.007$]. Raw scores for these tests by group are in Table 3, and two group comparisons are presented in Table 4.

Efficiency Scores—Efficiency ratios (accuracy/response time) were calculated for tests that had response time scores that directly related to accuracy scores. Response time measures (msec) for these tests are in Table 5. Efficiency ratios were corrected for age and education based on the controls. Group differences were observed for all efficiency ratios (CGT: $F(3,141)=4.56$, $p=.004$; SRM: $F(3,141)=3.39$, $p=.02$; PRM: $F(3,141)=4.10$, $p=.008$) (Figure 3).

Two group comparison analyses (Bonferroni correction $p<.017$) indicated that the HIV +ALC group scored lower than the NC on all 3 efficiency ratios (CGT: $p=.0004$; SRM: $p=.008$; PRM: $p=.0006$). In addition, the HIV-only and ALC-only groups had lower efficiency ratios than NC on CGT (HIV vs. NC: $p=.011$; ALC vs. NC: $p=.016$), and the HIV+ALC group had a lower SRM efficiency ratio than the ALC-only ($p=.011$) group and a modestly lower SRM ratio than the HIV-only ($p=.018$) group.

Within-Group Analyses

Relations between Disease-Related Variables and Composite Scores—Higher lifetime alcohol consumption was correlated with lower Executive Function ($r=-.38$, $p=.018$) and Episodic Memory Composite scores ($r=-.38$, $p=.020$), even after an outlier (ALC participant who drank 4436 kg, with the next highest consumption reported by an ALC participant at 3007 kg) was excluded from analysis. At the individual test level, lifetime alcohol consumption was correlated with a higher number of errors on Spatial Working Memory ($r=.40$, $p=.014$) and lower Logical Memory immediate recall scores ($r=-.44$, $p=.008$).

In the HIV group, neither CD4 cell count nor viral load was significantly correlated with Executive Function or Episodic Memory Composite scores. No relationship between age of alcohol onset, lifetime alcohol consumption, CD4 cell count, or viral load and cognitive scores were significant in the HIV+ALC group.

Hepatitis C and AIDS and Composite Scores—Individuals with Hepatitis C in the 3 clinical groups were modestly older [$t(112)=1.78$, $p=.08$] and had fewer years of education [$t(112)=3.11$, $p=.002$] than those without Hepatitis C. Hepatitis C was not associated with lower scores on Executive Function or Episodic Memory Composite scores in any of the clinical groups. In the HIV and HIV+ALC groups, individuals with and without AIDS were comparable in age and education and did not differ on Executive Function or Episodic Memory Composite scores.

Relations between Age and Age- and Education-corrected Cognitive Scores in ALC, HIV, and HIV+ALC—In the ALC group, age was correlated with Executive Function ($r=-.39$, $p=.015$) and Episodic Memory Composite scores ($r=-.47$, $p=.003$) (Figure 5). At the individual test level, older age was correlated with poorer scores on Spatial Working Memory ($r=.45$, $p=.004$), Cambridge Gambling Test ($r=-.41$, $p=.009$), Logical Memory ($r=-.45$, $p=.006$), Spatial Recognition Memory ($r=-.37$, $p=.02$), and Pattern Recognition Memory ($r=-.41$, $p=.01$). Older age was also correlated with lower efficiency scores for Pattern Recognition Memory ($r=-.37$, $p=.02$) in ALC.

In the HIV+ALC group, older age was correlated with Episodic Memory Composite scores ($r=-.39$, $p=.014$) (Figure 5). At the individual test level, this relation was observed for immediate recall scores on Logical Memory ($r=-.55$, $p=.0005$) and the Rey-Osterrieth Complex Figure ($r=.37$, $p=.02$). Age was also correlated with the efficiency score for the Cambridge Gambling Test ($r=-.45$, $p=.004$).

Age was not correlated with Executive Function or Memory Composite scores in the HIV group.

Multiple regression analyses examined the relative contribution of age and lifetime alcohol consumption in the ALC and HIV+ALC groups on the Executive Function and Episodic Memory Composite scores. Age ($p=.022$) and lifetime alcohol consumption ($p=.027$) were both unique predictors of the Episodic Memory Composite score in the ALC group, together accounting for approximately 21% of the variance. Age and lifetime alcohol consumption

were modest predictors of the Executive Function Composite scores in this group (age $p=.074$, lifetime alcohol consumption $p=.078$), together accounting for approximately 14% of the score. In the HIV+ALC group, age, but not lifetime alcohol consumption, was a unique predictor of the Episodic Memory Composite (age: $p=.017$, lifetime alcohol consumption: $p=.86$) and Executive Function Composite scores (age: $p=.039$; lifetime alcohol consumption: $p=.74$).

Discussion

Chronic alcoholism and HIV infection were each associated with selective deficits in component processes of executive functions and episodic memory. Executive function impairments in planning occurred in chronic alcoholism, whereas psychomotor speed and sequencing were particularly impaired in HIV infection. Decision making, impulsivity, and set shifting were compromised in both chronic alcoholism and HIV infection. Lower efficiency scores than NC occurred in all three clinical groups on decision making. Impairments in impulsivity, decision making, planning, and set-shifting in chronic alcoholism provides evidence for frontal lobe system dysfunction, particularly involving the prefrontal cortex, highlighted in neural models of addiction (Noel et al., 2013; Koob, 2014). Further, compromised executive function processes in alcoholism are associated with impulsive decision-making, which in turn may play a role in the occurrence of risky behavior, a hallmark symptom of alcoholism (Camchong et al., 2014). For episodic memory processes, visual free recall was particularly compromised in chronic alcoholism, whereas narrative free recall and pattern recognition was impaired in HIV infection. Both free recall and recognition processes were impaired in the comorbid group, which exhibited a compounded deficit in spatial recognition. Lower efficiency scores for recognition memory was also observed in the comorbid group, with longer response times taken to perform the task.

Direct relations between disease-related variables and cognitive performance in chronic alcoholism and HIV infection have often been elusive and have been speculated to be due to demographic, disease history, genetic, and other physiological sources of heterogeneity of these clinical groups. Nonetheless, this study successfully demonstrated relations between reported lifetime alcohol consumption in chronic alcoholism and poorer spatial working memory and narrative recall. Neither Hepatitis C nor occurrence of a lifetime AIDS-defining event, however, was related to performance. We caution that, given the relatively small sample size of these within-group analyses, it is unwise to conclude that these medically-related comorbidities are without untoward cognitive effects as reported elsewhere (e.g., Richardson et al., 2005; Vivithanaporn et al., 2012).

An age effect, over and above age-related differences observed, was noted in the alcoholic group for executive functioning and episodic memory, namely spatial working memory, decision making, verbal episodic recall, and visually-based recognition memory. Even after taking lifetime alcohol consumption into account, age endured as a unique predictor of episodic memory and a modest predictor of executive functioning in chronic alcoholism. In the comorbid group, age was associated only with poor free recall memory. These results are consistent with previous studies demonstrating greater cognitive impairment in older than

younger individuals with alcoholism and HIV with alcoholism (cf., Sullivan et al., 2010, Tan et al., 2013). Thus, as individuals with alcoholism and those comorbid for HIV infection and alcoholism age, more pronounced impairments may be observed in component processes of executive function and episodic memory processes. These speculations require confirmation with longitudinal study.

Limitations of this study include the inability to assess with multivariate approaches the separate and interactive contributions of demographic and disease variables on cognitive performance within clinical groups due to relatively small sample sizes. Larger samples and longitudinal analyses would add to the findings of this cross-sectional study and could provide information on the time line of cognitive decline in these domains. Another limitation that should be noted is that a number of our alcoholic subjects were abstinent for many years, and generalizability to alcohol groups with shorter abstinent durations is cautioned. Finally, due to the cross-sectional nature of this study we also cannot conclude whether these deficits observed in component processes of executive function and episodic memory are long-lasting deficits or, alternatively, preexisting deficits.

In conclusion, this study revealed untoward cognitive effects of chronic alcoholism, HIV infection, and HIV infection with alcoholism on component processes of executive functioning and episodic memory. Compounded impairment in spatial episodic recognition in the comorbid group may reflect effects on neural systems targeted by each disease. These untoward cognitive effects were observed in both alcohol groups (ALC and HIV+ALC) despite including individuals with long sobriety durations. Further, older age and greater lifetime alcohol consumption were associated with impaired cognitive performance, and each was predictive of episodic memory performance in chronic alcoholism. These disease-specific and disease-overlapping patterns of impairment in alcoholism, HIV infection, and HIV infection with alcoholism have implications regarding brain systems disrupted by these diseases and clinical ramifications regarding the complexities and compounded damping of cognitive functioning associated with dual diagnosis.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Bar graphs depicting age- and education-corrected Z scores for the Executive Function and Episodic Memory Composites for all groups.

Figure 2.

Bar graphs depicting age- and education-corrected Z scores for individual test scores that went into the Executive Function and Episodic Memory Composite scores for all groups. SWM=Spatial Working Memory; TRAILS B=Trail Making Part B; CGT=Cambridge Gambling Test; SOC=Stockings of Cambridge; IED=Intra-Extra Dimensional Set Shift; LMI=Logical Memory I; REYO=Rey-Osterrieth Complex Figure; SRM=Spatial Recognition Memory; PRM=Pattern Recognition Memory

Figure 3.
Bar graphs depicting Efficiency Scores (Accuracy/Response Time ratios) for the Cambridge Gambling, Spatial Recognition, and Pattern Recognition subtests of the CANTAB.

Figure 4.

Scatterplots depicting significant relationships between lifetime alcohol consumption and Executive Function Composite scores in the ALC group.

Figure 5. Scatterplots depicting significant relationships between age and Executive Function Composite scores in the ALC and HIV+ALC group and Memory Composite score in the ALC group.

Table 1

Demographic characteristics of subjects (mean, standard deviation, range)

Group	Age (yrs)	Education (yrs)	SES [*]	NART IQ [†]	Lifetime Alcohol Consumption (kg)	Beck Depression Inventory-II	CD4 count	Dementia Rating Scale
HIV-infection (HIV n=36)	49.5 (8.8) 25 to 64	13.4 (2.8) 9 to 19	40.2 (14.9) 11 to 58	105.1 (9.2) 90 to 123	69.5 (64.1) 1 to 289	11.1 (9.7) 0 to 32	576.5 (270.0) 88 to 1372	136.5 (5.2) 121 to 144
Alcoholism (ALC n=39)	48.4 (9.7) 26 to 66	13.5 (2.3) 10 to 21	41.5 (12.9) 18 to 65	106.7 (9.5) 90 to 124	1257.1 (918.6) 227 to 4438	7.7 (5.7) 0 to 22	NA	138.5 (4.6) 127 to 144
HIV-infection with Alcoholism (HIV+ALC n=39)	50.1 (6.8) 31 to 64	13.0 (2.2) 8 to 18	43.8 (11.5) 11 to 62	105.6 (8.3) 91 to 125	843.2 (607.6) 22 to 2504	11.0 (9.0) 0 to 36	551.5 (325.5) 61 to 1179	135.8 (4.5) 127 to 143
Control (NC n=31)	44.1 (9.8) 25 to 62	15.1 (1.9) 11 to 18	30.7 (11.3) 11 to 58	112.5 (9.3) 92 to 126	23.9 (35.1) 0 to 163	3.0 (5.3) 0 to 12	NA	139.9 (2.6) 135 to 144
Follow-up t-tests	HIV,ALC:HIV+ALC>NC p=031	HIV,ALC; HIV+ALC<NC p=002	HIV,ALC; HIV+ALC>NC p=0003	p=006b*/>HIV,ALC; HIV+ALC<NC	ALC,HIV+ALC>HIV, NC ALC>HIV+ALC p=0001	HIV,ALC; HIV+ALC>NC p<0001	ns	HIV,HIV+ALC<NC HIV+ALC<ALC p=0007

NA - Not applicable

^{*} SES - Socioeconomic Status based on education and occupation

[†] NART - National Adult Reading Test - estimated IQ

Table 2**Executive Function and Episodic Memory Composite Scores**

Executive Function Composite

Spatial Working Memory (CANTAB) – Number of between trial errors
Trails B – Time to completion
Cambridge Gambling Test (CANTAB) – Quality of decision making on ascending trials
Stockings of Cambridge (CANTAB) – Number of problems solved in minimal moves
Intra-Extra Dimensional Set Shift (CANTAB) – Number of extradimensional errors

Episodic Memory Composite

Logical Memory (WMS-R) – Number of details recalled on immediate memory trial
Rey-Osterrieth Complex Figure – Number of details recalled on immediate memory trial
Spatial Recognition (CANTAB) – Number Correct
Pattern Recognition (CANTAB) – Number Correct

Table 3

Raw Test Scores for Variables Included in the Executive Function and Episodic Memory Composite Scores
(mean, standard deviation, range)

	HIV	ALC	HIV+ALC	NC
Executive Function Composite				
Spatial Working Memory (Between trial errors)	32.03 (19.44) 0 to 89	31.28 (18.94) 1 to 75	41.56 (20.51) 4 to 77	23.13 (21.94) 0 to 70
Trails B (Time to complete in seconds)	103.06 (70.66) 30 to 371	87.89 (56.10) 31 to 292	100.38 (44.19) 47 to 240	59.39 (17.62) 29 to 105
Cambridge Gambling Test (Quality of Decision Making)	0.78 (0.18) .38 to 1	0.77 (0.19) .46 to 1	0.75 (0.20) .38 to 1	0.91 (0.14) .41 to 1
Stockings of Cambridge (Number of problems completed in minimal moves)	7.97 (2.27) 5 to 12	7.38 (2.17) 3 to 12	6.74 (2.12) 4 to 11	9.00 (1.59) 4 to 12
Intra - Extra Dimensional Set Shift (Number of extradimensional errors)	15.28 (9.59) 1 to 28	14.72 (10.94) 1 to 33	14.72 (10.70) 0 to 30	8.77 (9.62) 0 to 33
Episodic Memory Composite				
Logical Memory (Number of details correct on Immediate Recall)	21.72 7.43 10 to 36	22.86 7.87 11 to 37	21.11 8.02 3 to 34	27.97 7.66 11 to 42
Rey-Osterrieth Complex Figure (Number of details correct on Immediate Recall)	14.01 (7.12) 2.5 to 30.5	12.31 (5.74) 0 to 29	10.10 (5.81) 0.5 to 30.5	17.53 (5.84) 8 to 32
Spatial Recognition (Number Correct)	16.11 (2.49) 10 to 20	16.64 (2.40) 10 to 19	13.92 (3.09) 1 to 18	17.32 (1.83) 14 to 20
Pattern Recognition (Number Correct)	20.42 (2.93) 12 to 24	20.87 (2.82) 13 to 24	20.03 (3.09) 11 to 24	22.42 (1.57) 18 to 24

Table 4

Significant two-group comparisons

Executive Function Composite		p value
Trails B	HIV vs. NC	0.001
	HIV+ALC vs. NC	0.002
Cambridge Gambling Test	ALC vs. NC	0.0025
	HIV vs. NC	0.0024
	HIV+ALC vs. NC	0.0003
Stockings of Cambridge	ALC vs. NC	0.0092
	HIV+ALC vs. NC	0.0003
	HIV+ALC vs. HIV	0.0135
Intra - Extra Dimensional Set Shift	ALC vs. NC	0.0017
	HIV vs. NC	0.0006
	HIV+ALC vs. NC	0.0006
Episodic Memory Composite		
Logical Memory	HIV vs. NC	0.0047
	HIV+ALC vs. NC	0.0032
Rey-Osterrieth Complex Figure	ALC vs. NC	0.0169
	HIV+ALC vs. NC	0.0005
Spatial Recognition	HIV+ALC vs. NC	0.0001
	HIV+ALC vs. ALC	0.0001
	HIV+ALC vs. HIV	0.0003
Pattern Recognition	HIV vs. NC	0.0061
	HIV+ALC vs. NC	0.001

Bonferroni Correction ($p < .017$)

Table 5

Raw Test Scores for Response Times used for efficiency ratios (mean, standard deviation, range)

	HIV	ALC	HIV+ALC	NC
Cambridge Gambling Test (Deliberation Time, ms)	3193.0 (1133.7) 1236 to 6677	3204.2 (1234.6) 1198 to 7976	3693.4 (1804.0) 1220 to 11004	2732.7 (1224.2) 1310 to 6722
Spatial Recognition Memory (Mean Latency Time, ms)	2226.8 (612.3) 1009 to 3946	2267.8 (731.1) 1325 to 3946	2407.4 (720.3) 1162 to 4902	2071.5 (418.9) 1302 to 3084
Pattern Recognition Memory (Mean Latency Time, ms)	1964.5 (466.6) 898 to 3165	2008.2 (498.0) 1295 to 3244	2198.6 (723.8) 1975 to 4447	1869.9 (376.8) 1190 to 2887