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Variable patterns of neuropsychological performance in HIV-1 infection

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Abstract

Based upon prior findings with group means, a “prototypical pattern” of neuropsychological results with HIV infection has emerged: impaired executive functioning, motor skills, speed of information processing, and learning, with intact memory retention, most language skills, and visuospatial functioning. We examined neuropsychological results from 553 HIV+ adults to determine the number of patterns seen among individuals with HIV infection. Factor analysis of a relatively comprehensive neuropsychological battery identified 6 component factors: verbal memory (VeM), visual memory (ViM), processing speed (PS), attention/working memory (A/WM), executive function (EF), and motor (M). These factor scores were submitted to hierarchical cluster analysis, to determine the appropriate number of clusters or patterns in the cohort. Final cluster membership was then determined by K-means analysis, based on the Lange, Iverson, Senior, and Chelune (2002) method. A 6-cluster solution was found to be most appropriate. The definitions of the clusters were based upon ipsative scoring of factor scores to indicate relative strengths and weaknesses (independent of overall level of performance): Cluster 1: strong EF; Cluster 2: strong M, weak VeM and EF; Cluster 3: strong PS, weak ViM and EF; Cluster 4: strong VeM, weak M; Cluster 5: strong A/WM; Cluster 6: strong VeM, weak EF. Neuropsychological impairment rates differed across clusters, but all 6 clusters contained substantial numbers of impaired and unimpaired individuals. Cluster membership was not explained by demographic variables or psychiatric or neuromedical confounds. Thus, there does not appear to be a single, prototypical pattern of neuropsychological impairment associated with HIV infection for this battery of representative neuropsychological tests.

In using neuropsychological tests for diagnostic purposes, clinicians typically evaluate a range of abilities and then compare the pattern of results with expectations for various types of brain disorders. Although these decisions are made for individual patients, most of the research concerning patterns of impairment considered prototypical of disorders involves analysis of *group* averages rather than examination of *individual* performance. This invites the possibly unwarranted assumption that patterns of group means on tests apply to most or all of the individuals within the groups.

For example, in general, studies of individuals infected with HIV suggest a prototypical pattern involving poor attention and working memory, speed of information processing, learning, executive functions, and motor skills, but with relatively intact language skills,

visuospatial skills, memory (delayed retention), and sensory-perceptual skills (Heaton et al., 1995; Reger, Welsh, Razani, Martin, & Boone, 2002; Sahakian et al., 1995). This pattern is consistent with neuropathological and neuroimaging evidence of preferential involvement of fronto-striatal brain areas in individuals infected with HIV (Pomara, Crandall, Choi, Johnson, & Lim, 2001; Poutiainen, Haltia, Elovaara, Lähdevirta, & Iivanainen, 1991). However, there is also considerable heterogeneity in patterns of neuropathologic changes associated with HIV infection (Masliah, Ge, Achim, Deteresa, & Wiley, 1996; Wiley, 1994), which could well result in variable patterns of neuropsychological performance. Also, patients with HIV infection not infrequently have histories of comorbid conditions that could account for substantial neuropsychological impairments observed in such cases. Some common examples of such comorbidities are substance use disorders and hepatitis C infection (Cherner et al., 2002a; Letendre et al., 2005; Rippeth et al., 2002; Rippeth et al., 2004) and depression (Goggin et al., 1997; Moore et al., 2001).

In interpreting neuropsychological results of individuals infected with HIV, with and without significant comorbidities, it would be helpful to know whether only one “prototypical” pattern or multiple patterns of neuropsychological impairment are associated with HIV infection, and whether any of these patterns are linked to commonly seen comorbid factors—for example, substance use disorders (abuse or dependence), psychiatric disorders. This would allow the clinician to interpret the etiology of the neuropsychological impairment with more certainty. If multiple patterns exist, it would be important to also know prevalence and any demographic or clinical correlates. The present study uses cluster analytic methods to address these questions within a large sample of individuals infected with HIV.

In an effort to determine the best number of clusters from a large sample ($n=298$) of HIV+ gay or bisexual males from four different sites in the Los Angeles region, van Gorp and colleagues (van Gorp et al., 1993) found three stable profiles determined by a K-means analysis. These profiles were based on four neuropsychological factors (verbal memory, processing speed, visuospatial ability, and verbal ability) and one mood factor determined by principal components analysis. Due to the method of cluster analysis employed by van Gorp and colleagues, the three profiles were influenced not only by pattern but also by overall ability level of the participants, which was confirmed by a discriminant functions analysis. The three profiles included one containing only normally performing subjects and two clusters with subjects demonstrating some poor performances: one with lowered processing speed and verbal memory and the other with weaknesses in verbal and visual abilities. These authors also found significant differences between profile groups with respect to site where the data was collected, as well as the age and education of the participants. However, they found no differences between clusters in HIV-related degree of immunosuppression (CD4 cell counts). Of note, this study was conducted in a time before combination antiretroviral treatment regimens were introduced. These medications have had a dramatic effect on HIV-related mortality and morbidity, and there are indications that they have reduced the incidence of neurocognitive impairment and may even improve cognitive impairment in some infected persons (Letendre et al., 2004). Considering the widespread implementation of combination antiretroviral therapy, as well as changes in demographic and cofactors (e.g., increased substance use disorders) in the HIV infected population of the US (Centers for Disease Control and Prevention, 2001, 2004), the application of these earlier results to current HIV+ populations may be misleading.

Another, more recently published attempt to discern the number and stability of HIV-associated cognitive patterns using cluster analysis found four profiles, based on a reduced number of variables from a factor analysis (Lojek & Bornstein, 2005). Cluster 1 was described as having poor psychomotor speed ($n=12$, Grooved Pegboard), Cluster 2 had poor

memory and learning ($n=48$; Selective Reminding Test), Cluster 3 showed various cognitive deficits ($n=17$; all tests), and Cluster 4 was normal on all cognitive measures ($n=98$). Although this work is of considerable interest, the results must be considered preliminary because the cluster analysis was not conducted according to recommended methodologies. First, the sample size ($n=165$) was substantially lower than the minimum of 300 participants recommended by Meehl (1995) for cluster analysis. Although it was acknowledged that this type of taxometric research may be attempted with smaller data set, Meehl also cautioned researchers that “some questions can only be answered with large samples” (p. 274). The Lojek and Bornstein study also did not employ the recommended two-stage methodology for defining the number and composition of clusters (Cheng & Milligan, 1995; Donders, 1996; Lange et al., 2002). In the two-stage method, the initial analysis ascertains the optimal number of clusters, and the second iterative procedure then defines these clusters and allows reallocation of cases that may have been initially incorrectly assigned to another cluster. It also appears that the clustering technique employed in the Lojek and Bornstein study was primarily susceptible to magnitude differences (i.e., overall level of performance) rather than pattern or profile of performance (see Lange et al., 2002). Therefore, although these findings are interesting, the question of whether truly heterogeneous neuropsychological pattern-based profiles are associated with HIV infection remains unanswered.

Using recommended clustering techniques with data from a large group of individuals infected with HIV, the present study aims to identify and test the clinical correlates of neuropsychological profiles that are based on relative neurobehavioral strengths and weaknesses.

METHOD

Participants

The study cohort consisted of 553 individuals infected with HIV who were enrolled in a number of studies at the HIV Neurobehavioral Research Center (HNRC), University of California San Diego, USA. Participants were administered semistructured psychiatric interviews—*Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders—Fourth Edition* (DSM-IV; American Psychiatric Association, 1994) Axis I Disorders (SCID; Spitzer, Williams, Gibbon, & First, 1996) or the Psychiatric Research Interview for Substance and Mental Disorders (PRISM; Hasin et al., 1996) to determine presence or absence of mood and substance use disorders. The Patient's Assessment of Own Functioning Inventory (PAOFI; Chelune, Heaton, & Lehman, 1986), a 41-item questionnaire exploring the frequency with which participants experience cognitive and sensorimotor difficulties in everyday life, was also completed. This information assists in the determination of AIDS-associated diagnoses (e.g., minor cognitive motor disorder or HIV-associated dementia), according to American Academy of Neurology AIDS Task Force (1991) criteria, as modified in 1999 by Grant and Atkinson. All participants in this study were fluent and tested in English.

Potential participants were excluded if they had not completed all of the measures in the neuropsychological test battery, or if they had been diagnosed with psychosis, developmental disorders (e.g., autism, dyslexia, attention deficit hyperactivity disorder), central nervous system opportunistic infections (e.g., cytomegalovirus, progressive multifocal leukoencephalopathy), or neurologic disease not due to HIV-1 infection (e.g., seizure disorder, traumatic brain injury with loss of consciousness ≥ 30 minutes or neurologic sequelae, multiple sclerosis). Participants were not excluded based on current alcohol, methamphetamine or cocaine use disorders, or a diagnosis of current major depression, because these comorbidities are frequently found in the HIV population today, and their exclusion would have resulted in a nonrepresentative sample. However, possible

effects of these comorbidities on cluster membership were explored. Due to the low number of participants who met criteria for current abuse of alcohol, methamphetamine, and/or cocaine, over and above the diagnosis of dependence for these substances, ($n=14$, $n = 7$, and $n = 3$, respectively), abuse and dependence were combined into “use disorders.” Further characteristics of this sample are presented in Table 1.

Neuropsychological measures

Table 2 lists the cognitive-motor measures for this analysis, which we have conceptualized as measuring seven major ability domains (verbal fluency, speed of information processing, attention/working memory, executive functioning, learning, memory, and motor abilities). While this test battery is designed to be brief but quite sensitive to the deficits associated in neuroAIDS (Woods et al., 2006), it does not cover all possible domains that may be of interest (e.g., certain verbal or visuospatial abilities).

All raw scores from these tests were converted to demographically corrected T-scores (mean = 50, $SD=10$) using appropriate norms (Benedict, 1997; Brandt & Benedict, 2001; Heaton, Miller, Taylor, & Grant, 2004b; Kongs, Thompson, Iverson, & Heaton, 2000; Psychological Corporation, 1997; Taylor & Heaton, 2001). The T-scores were then used as the basis for future analyses. Overall cognitive status was measured by the Global Deficit Score (GDS; see Carey et al., 2004, for full explanation). For this purpose, the demographically corrected T-scores are converted to deficit scores ranging from 0 (no impairment) to 5 (severe impairment) for each test. When these deficit scores are averaged, the resultant score is the GDS, which shows good sensitivity and specificity in identifying neurologic disorders (Carey et al., 2004; Heaton et al., 1995; Heaton et al., 2004b).

Statistical analysis

With the inclusion of more dependent variables, cluster analysis becomes increasingly vulnerable to producing questionably reliable clusters whose origins are tenuous (Everitt, 1974). To address these concerns regarding the consequences of a possibly excessive number of dependent variables in the cluster analysis, the T-scores from all the tests were subjected to an exploratory factor analysis: principal components utilizing oblimin rotation. The purpose of factor analysis was to reduce the size and complexity of the database by producing a smaller number of representative and stable measures.

Factor scores were calculated based on mean T-scores of the main test loadings on each factor for each participant. Then a mean score across the six factors was computed to represent the overall level of functioning on the neuropsychological battery. This overall summary score was then subtracted from the score of each of the individual factors to create a deviation score, reflecting the degree to which the factor was a relative strength or weakness for each participant. These six deviation scores were then used as the dependent variables in the cluster analysis conducted using MATLAB 6.5.1 (The Mathworks, Inc., 2004). Deviation scores minimize the effects of overall level of performance on the cluster analysis and instead emphasize the pattern of the profiles. This ipsative scoring method was selected since the pattern of the profile was our main interest.

The cluster analysis was completed in two parts. Firstly, a hierarchical cluster analysis was completed using Pearson correlation as the similarity metric and the squared Euclidean distance as the distance metric. Hierarchical analysis is the best method for determination of cluster number, but it does not allow the reallocation of cases to more cohesive clusters once they are attributed to an initial cluster. Pearson correlation was chosen as the similarity metric as it is the least susceptible to any magnitude effects (Lange et al., 2002). Following the hierarchical analysis, a K-means analysis method was then utilized to establish the final

cluster solution, with careful attention paid to the cluster centroid means, silhouette plots, and iteration statistics.

Determination of the number of clusters was completed by the assessment of the inverse scree plot and the dendrogram from the hierarchical cluster analysis. The inverse scree plot assists in the determination of the number of clusters in a similar manner to the scree plot in factor analysis, such that the number of likely clusters is indicated by a change in slope in the inverse scree plot. The dendrogram indicates the likely number of clusters as being a natural “break” in the graph. The K-means procedure allows the reallocation of cases to clusters throughout the analysis, thereby allowing clusters to be formed that are more cohesive and made up of more similar cases. This should ensure a more stable and consistent solution (Lange et al., 2002). Finally, the resulting cluster groupings were examined for possible differences in demographic composition, measures of HIV disease severity, psychiatric diagnoses, and coinfection with hepatitis C virus, as well as overall level of neuropsychological functioning and prevalence of neuropsychological impairment. This was completed with a series of analyses of variance (ANOVAs) and chi-squares, adjusted for multiple comparisons, to assess each group of characteristics separately, followed by post hoc tests to clarify the sources of significant differences across clusters.

RESULTS

Factor analysis

An exploratory principal components analysis with oblimin rotation was performed on the T-scores for the entire sample. After screening data for multivariate outliers, the initial factor solution, comprising four factors, accounted for 59.5% of the variance. However, as all of the speed, attentional, and motor tests fell onto one factor (Trail Making Test–Part A, Trail Making Test–Part B, Symbol Search, Digit Symbol, Letter–Number Sequencing, Paced Auditory Serial Addition Test–50, Controlled Oral Word Association Test–FAS, and Grooved Pegboard Dominant and Nondominant Hand trials), a more differentiated solution was sought that may also account for a higher overall percentage of variance in the neuropsychological data. The final factor solution of six factors accounted for 69.5% of the variance. The eigenvalues, percentage of variance, cumulative percentage of variance, and factor loadings of the six factors based on the rotated pattern matrix are presented in Table 3. This six-factor solution was chosen as it made sense from a theoretical perspective and explains a high percentage of variance in neuropsychological test performance. Items with absolute factor loadings of less than .40 have been suppressed in the table to better illustrate the factor structure. The six-factor solution accounted for an additional 10% of the variance in neuropsychological test performance (beyond the initial fourfactor solution with all factors having eigenvalues of >1). The final six-factor solution also provides coverage of more of the ability domains recommended for neuropsychological assessment of HIV effects (Butters et al., 1990) and is more consistent with prior theoretical assignments of tests to domains (Lezak, 2004) and prior factor analytic work with large samples of normals (Tulsky et al., 2003).

All factors appeared to be well defined. Factor 1 includes tests of speed of information processing (Trail Making Test–Part A, Trail Making Test–Part B, Symbol Search, and Digit Symbol). The second factor is composed of tests related to verbal episodic memory (Hopkins Verbal Learning Test–Revised and Story Memory Test, learning and delayed recall), while Factor 3 is based upon the test of executive functioning (conceptual and set-shifting abilities; Wisconsin Card Sorting Test–64: Categories Completed and Perseverative Responses). Factor 4 is a visual episodic memory factor (Brief Visuospatial Memory Test–Revised and Figure Memory Test, learning and delayed recall), and Factor 5 relates to motor functioning (Grooved Pegboard; Dominant and Nondominant hand trials). The sixth and

final factor reflects working-memory/attentional abilities (Letter–Number Sequencing, Paced Auditory Serial Addition Test–50, Controlled Oral Word Association Test–FAS). These six factors formed the basis of the deviation scores, which were calculated as described previously.

Hierarchical cluster and K-means analysis of the sample

Following computation of the hierarchical cluster analysis, examination of the inverse scree plot and the dendrogram indicated that although two- to nine-cluster solutions were feasible, a six-cluster solution was most appropriate. The K-means analysis, using random seed points, designated the membership for the six-cluster solution. The silhouette plot derived from this analysis indicated some overlap among clusters. The centroids presented as derived mean factor T-scores indicated the profile for each cluster. The hierarchical and K-means solutions were compared for the purposes of internal validation, finding reasonably good matches between the two solutions.¹ For descriptive purposes, relative strengths and weaknesses are based on mean factor T-scores being more than 5 points above or below the overall mean score across all six factors.

Independence of cluster solutions

The pattern of scores for each of the clusters was investigated for independence. This was done by examining the correlations among mean factor scores between each pair of cluster profiles. Positive correlations indicate similarity while negative correlations are indicative of dissimilarity (opposite patterns of relative strengths and weaknesses) between these pairs of profiles. The only significantly ($p < .05$) correlated profiles were Clusters 1 and 6 and Clusters 2 and 4, both of which were negatively correlated ($r = -.92$ and $r = -.90$, respectively), indicating dissimilarity between these pairs of profiles. Lack of statistically significant, within-group positive correlations between any pair within the six profiles identified by the K-means analysis indicates that the clusters are relatively independent.

Profile characteristics

The six profiles from the K-means analysis are presented graphically in Figures 1 to 3. These graphs indicate the mean factor T-scores of participants classified within each profile-based cluster. Figures 1 and 2 contain the two pairs of profiles (Clusters 1 and 6 and Clusters 2 and 4, respectively), which are negatively correlated and therefore have opposite patterns of strengths and weaknesses, while Figure 3 contains the remaining two profiles (Clusters 3 and 5).

Profile 1 ($n=98$; Figure 1) shows a relative strength in the area executive functioning. Also depicted in Figure 1 is Profile 6 ($n=132$), which is negatively correlated with Profile 1 and shows the opposite pattern: an isolated weakness in executive functioning with a relative strength in verbal memory. Figure 2 displays the other two negatively correlated profiles (Profiles 2 and 4; respective $ns=83$ and 84). Profile 2 consists of relative strength in motor skills but weaknesses in verbal memory and executive function, whereas participants with Profile 4 present with a relative weakness in motor functions and a relative strength in verbal memory. The remaining two profiles (3 and 5; respective $ns=79$ and 77) are displayed in Figure 3. Profile 3 reflects a relative strength in processing speed versus relative weaknesses in visual memory as well as executive function. Profile 5 reflects a relative strength in working memory.

¹Correlation match ($p < .05$): H2=K3, H4=K4, H5=K1, H6=K6; correlation match ($p > .05$): H1=K2, H3=K5.

Examination of profile membership

A series of ANOVAs and chi-square analyses were completed to determine whether any of the six clusters differed with respect to demographics, neuropsychological impairment, depression, substance use disorders, hepatitis C coinfection, or indicators of more advanced HIV disease (Tables 4 and 5). No significant cluster group differences were found on age, education, gender distribution, AIDS status, current or nadir CD4 cell count, percentage with current detectable HIV-1 viral load, hepatitis C seropositivity, overall number of subjective cognitive complaints, or current rates of major depression or substance use disorders. The only significant differences ($p < .003$) among the clusters were in the percentage of Caucasians included in each cluster, estimated premorbid verbal IQ as measured by the Wide Range Achievement Test–Third Edition (WRAT-3) Reading scores and the overall level of neuropsychological performance (mean T-scores) and neuropsychological impairment (GDS). Clusters 2 and 3 had smaller proportions of Caucasians than the other clusters (especially 4 and 5), and Clusters 4 and 5 performed better on the WRAT-3 Reading than did other clusters (especially Cluster 2). Therefore, people in Clusters 4 and 5 probably had better premorbid verbal abilities than others. Along with these differences it was found that participants within Cluster 1 had the highest prevalence of global neuropsychological impairment (GDS ≥ 0.5 , 72.4%) whereas those in Clusters 3, 5, and 6 had the lowest (46.8%, 44.2%, and 41.7%, respectively). All clusters contained participants with and without psychiatric and neuromedical confounds (major depressive disorder, substance use disorders, hepatitis C coinfection). Even when all participants with these comorbidities were excluded, neuropsychological impairment was still seen in all clusters. Finally, in the group without confounds, it was again seen that the highest rates of impairment were in Clusters 1 and 4, and the lowest rates in Clusters 3, 5, and 6.

Table 6 presents some of this same information in a different manner, to consider whether the majority of people with the designated demographic or clinical characteristics fall within any specific cluster(s). The *ns* differ, depending upon the subject characteristic being considered (e.g., 343 with AIDS, 293 neuropsychologically impaired, and 133 with no psychiatric or medical confounds). Also one should be cautious about comparing the percentages in the rows of this table, because these are affected by the cluster *ns*, which differ considerably (77 in Cluster 5 to 132 in Cluster 6). Keeping these caveats in mind, it should be noted first that in no case is there a majority of participants with any of these characteristics in a single cluster. Also, some participants with each characteristic have each of the six neuropsychological profiles. Finally, neuropsychologically impaired individuals without confounds (“pure” HIV cases) showed virtually identical distributions of cluster membership to those of the total participant group.

DISCUSSION

This study used a two-stage clustering procedure that identified six independent patterns of neuropsychological performance in a large sample of individuals infected with HIV-1. By employing ipsative scoring of the neuropsychological factors (reflecting deviation from each individual’s own mean score across factors), the effects of profile pattern rather than level of performance became the focus of analysis. When participants were thus assigned to clusters according to their patterns of neuropsychological performance, all six clusters/profiles were well represented: percentages of the total sample in the various clusters ranged from 13.9 in Cluster 5 to 23.9 in Cluster 6.

The six independent clusters each contained substantial numbers of normatively impaired and unimpaired individuals—that is, there was no single pattern of performance that characterized HIV-related neuropsychological impairment. This was true, whether or not

HIV-infected participants with potential neuropsychiatric confounds were excluded (i.e., those with substance use disorder, major depressive disorder, or coinfection with the hepatitis C virus). In fact, the cluster/profile associated with the highest rate of neuropsychological impairment (Cluster 1: relative strength in executive functioning) contained less than a quarter (24.2%) of all neuropsychologically impaired participants, whereas the cluster with the lowest rate of impairment (41.7% in Cluster 6: relative strength in verbal memory, but with a relative weakness in executive functioning, and with a larger total *n*) contained only 29.6% of all neuropsychologically normal participants. These results strongly suggest that there is no single prototypical pattern of neuropsychological impairment associated with HIV infection. In this respect they are consistent with the variable patterns of neuropathology seen in patients who die with AIDS (Ellis, Merdes, Masliah, & Langford, 2005).

In addition, using different methods, we have confirmed the findings of Lojek and Bornstein (2005) regarding multiple patterns of neuropsychological performance and impairment in HIV infection. The specific nature of these patterns did differ somewhat between our study and theirs, most likely due to differences in the test batteries, statistical methods, and our use of ipsative scoring of the neuropsychological factors in order to deemphasize overall level of performance on identified clusters. Nevertheless, both studies identified clusters characterized by particularly poor motor skills (our Cluster 4 and their Cluster 1) and another in which multiple abilities were impaired (our Cluster 1 and their Cluster 3).

To enhance the external validity of this study, we did not exclude individuals infected with HIV who also had comorbid conditions (confounds) that are commonly seen within the general population of HIV-infected adults. These include substance use disorders, major depression, and coinfections with hepatitis C virus. It should be noted, however, that each of these confounds was well represented among all six clusters and, therefore, did not account for cluster membership. In addition, 312 participants had none of these confounds. These more “pure” cases of HIV infection, both neuropsychologically impaired and unimpaired, also were well represented in all six clusters, and in similar proportions to what were seen in the total subject group (Tables 4, 5, and 6). Although common psychiatric and neuromedical comorbidities undoubtedly do contribute to neuropsychological impairment in some HIV-infected individuals, the present results suggest that the multiple patterns of neuropsychological impairment associated with HIV infection in our study cannot be explained by these confounds.

In general, the neuropsychological cluster membership appears to be relatively independent of demographics, premorbid IQ estimates, HIV disease characteristics and treatment status, and the comorbidities just discussed. The only exceptions to this were that Cluster 2 profile (relatively high motor, but relatively low verbal memory and executive skills) had a higher percentage of non-Caucasian participants and lower premorbid IQ estimates than those in the cluster with the opposite pattern (Cluster 4: relatively low motor but higher verbal memory) and Cluster 5 (low motor, executive, and episodic memory skills, high working memory). These differences could reflect a lower quality of educational backgrounds in ethnic minority participants (Manly, Byrd, Touradji, & Stern, 2004). Despite their differences in estimated premorbid intelligence, however, participants in these three clusters had roughly equivalent rates of neuropsychological impairment (53.0% for Cluster 2, 53.4% for combined Clusters 4 and 5). Thus, it seems unlikely that these background characteristics significantly biased our evidence of current, HIV-associated neuropsychological impairments in these groups.

As noted above, we used ipsative scoring of the neuropsychological factors to define clusters on the basis of pattern (not overall level) of neuropsychological performance. This

permits meaningful comparisons among the pattern-based clusters with respect to overall level of neuropsychological functioning and impairment rates. Inspection of Tables 4 and 5 indicates that Cluster 1 participants (showing relatively good executive functioning but relatively poor scores in the other neuropsychological factors) had the lowest overall mean neuropsychological T-scores and highest mean global deficit scores, compared to the other cluster/profile groups; participants in Cluster 1 were unremarkable in terms of demographics, disease or treatment characteristics, or potential confounds. Although this group had slightly higher rates of current major depressive disorder (33.8%), and coinfection with hepatitis C (36.8%) than other groups, these group differences were not statistically significant. Also, almost two thirds of the participants in Cluster 1 did *not* meet criteria for major depressive disorder, so it is unlikely that depression is significantly influencing the neuropsychological status of Cluster 1 participants. This is consistent with findings of several studies that have demonstrated relative independence of major depression and neuropsychological impairment in HIV-infected populations (Cysique et al., 2007; Goggin et al., 1997; Millikin, Rourke, Hallman, & Power, 2003; Richardson et al., 1999). Recent findings have indicated an additive effect on neurocognitive function when HIV infection is associated with comorbid hepatitis C infection (Cherner et al., 2005; Letendre et al., 2005). The fact that Cluster 1 contains the highest percentage of hepatitis C virus coinfecting people may have contributed to the especially high rate of neuropsychological impairment in this cluster. On the other hand, since less than half of the neuropsychologically impaired persons in Cluster 1 were positive for hepatitis C virus ($n=17$, 42.5%), this pattern of neuropsychological impairment frequently is seen with HIV monoinfection as well.

In this study, we have demonstrated several specific neuropsychological pattern-based profiles in HIV-infected adults. Nevertheless, our findings are inconclusive regarding the sources and clinical relevance (if any) of these patterns. The patterns do not appear to be due to demographics, premorbid verbal intelligence, psychiatric confounds, or coinfection with hepatitis C. Also, participants with the six neuropsychological patterns were comparable with respect to history of AIDS and nadir CD4 cell counts, as well as current CD4 cell counts and HIV viral load. Most participants in all six clusters were currently being treated with highly active antiretroviral therapy (HAART). Future longitudinal research should determine whether patterns of neuropsychological performance are stable and whether they predict differences in neuropsychological change (e.g., worsening) over time and other clinically relevant outcomes, either independently or in concert with level of performance indicators (e.g., the Global Deficit Score). Outcomes of interest include unemployment (Benedict, Mezhr, Walsh, & Hewitt, 2000; Heaton et al., 2004a; Rabkin, McElhiney, Ferrando, Van Gorp, & Lin, 2004), difficulties on performance-based instrumental activities of daily living (Benedict et al., 2000; Heaton et al., 2004a), adherence to prescribed medication regimens (Hinkin et al., 2002; Levine et al., 2005), complaints of cognitive problems in everyday functioning (Heaton et al., 2004a), and early mortality (Ellis et al., 2005; Mayeux et al., 1993). Also of interest is whether the neuropsychological profiles identified here, especially when seen with HIV-infected people who also have impaired overall levels of neuropsychological functioning, will be associated with differential patterns of brain abnormalities on neuroimaging (Ragin et al., 2005; Tucker et al., 2004) and postmortem neuropathology studies (Cherner et al., 2002b; Ellis et al., 2005).

One limitation of this study is that the neuropsychological test battery was selected specifically for its sensitivity to HIV-related central nervous system (CNS) disturbances and as a consequence only provided coverage of abilities that prior HIV research has identified as being vulnerable to these conditions. It is quite possible that the inclusion of other tests with less general sensitivity to HIV-related disorders (e.g., tests of receptive and expressive dysphasia, spatial cognition, sensory-perceptual functions) would have resulted in more pattern-based clusters and/or somewhat different clusters than those identified here.

We used the best neuropsychological test norms available, all of which were demographically corrected using very large standardization groups with gender balance, and good representation of the age and education ranges of the current study's participants. A total of 13 of the 19 variables also had correction of Caucasian versus African American ethnicity, of which 83% of the current sample was composed. The remaining variables do not currently have ethnicity corrections available, so this may have affected the pattern of test results and cluster assignment of some participants. However, if we consider only Caucasians, obviating the need for demographic corrections, there continue to be substantial numbers of participants with all six cluster profiles. Also, the proportions of this Caucasian subsample within the various clusters are similar to those reported for the total sample in Table 6 (respective percentages for Clusters 1 through 6: 20, 11, 11, 18, 16, and 24).

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Figure 1.
Profile 1 and Profile 6 ($r = -.92, p < .05$).

Figure 2.
Profile 2 and Profile 4 ($r=-.90, p < .05$).

Figure 3.
Profile 3 and Profile 5 ($r=.39$, $p > .05$).

TABLE 1

Characteristics of the sample

	N	Mean	SD	Range
Age (in years)		40.68	8.52	18–69
Education (in years)		12.92	2.63	6–20
Global Deficit Score		0.69	0.64	0.00–3.93
WRAT-3: Reading SS	543	97.31	13.25	47–120
	N	Median	IQR	Range
PAOFI: Total Score	500	5	1:12	0–31
CD4 Current	550	296	128:535	0.0–2056.0
CD4 Nadir		143	24:300	0.0–2100.0
Plasma VL	550 ^a	4.43	3.62:5.06	1.74–7.20
	N	%		
Gender/ethnicity				
Male	483	87.34		
Caucasian	332	60.04		
African–American	129	23.33		
Hispanic	65	11.75		
Asian	13	2.35		
Other	14	2.53		
Other characteristics				
HAART	364	67.16		
AIDS	343	62.36		
Detectable Plasma VL	304	57.14		
Impaired Global Deficit Score	293	52.98		
Hepatitis C antibody positive ^b	86	28.38		
Major depression ^{c,d}	110	23.06		
Any current substance use disorders ^{c,e}	82	17.00		
Alcohol use disorders ^{c,f}	34	7.07		
Methamphetamine use disorders ^{c,g}	42	8.71		
Cocaine use disorders ^{c,h}	23	4.79		

Note. N = 553 unless otherwise specified. WRAT-3 = Wide Range Achievement Test–Third Edition. SS = Standard Score. IQR = Interquartile Range. PAOFI = Patient's Assessment of Own Functioning Inventory. HAART = highly active antiretroviral therapy. VL = viral load.

^alog 10: N = 304 detectable.

^bn = 303.

^cCurrent; data available.

^dn = 477.

^en = 480.

$$f_n = 482.$$

$$g_n = 481.$$

$$h_n = 480.$$

TABLE 2

T-score means for neuropsychological tests

Tests	M	SD
Letter Fluency (FAS)	47.01	10.72
WAIS-III Digit Symbol	46.31	10.44
WAIS-III Symbol Search	47.65	10.24
Trail Making Test–A	46.86	11.92
Paced Auditory Serial Addition Test: 50	43.93	12.15
WAIS-III Letter–Number Sequencing	47.35	9.60
Story Learning	44.17	11.15
Story Delayed Recall	49.47	14.33
HVLT-R: Learning	41.79	11.13
HVLT-R: Delayed Recall	42.58	11.94
Figure Learning	40.88	10.09
Figure Delayed Recall	45.41	9.56
BVMT-R Learning	44.13	9.81
BVMT-R Delayed Recall	42.62	11.83
WCST Categories Completed	41.13	7.70
WCST Perseverative Errors	44.87	11.73
Trail Making Test–B	44.90	12.13
Grooved Pegboard (Dominant Hand)	43.48	11.93
Grooved Pegboard (Nondominant Hand)	43.26	11.67
Overall mean T-score	44.48	6.48

Note. $N = 553$. WAIS-III = Wechsler Adult Intelligence Scale–Third Edition; BVMT-R = Brief Visuospatial Memory Test–Revised; HVLT-R = Hopkins Verbal Learning Test–Revised; WCST = Wisconsin Card Sorting Test.

TABLE 3

Rotated factor structure of the test battery

Subtest	Factor					
	1	2	3	4	5	6
Hopkins Learn.		0.784				
Hopkins Del. Recall		0.864				
Story Learn.		0.515				
Story Del. Recall		0.510				
BVMT Learn.				-0.835		
BVMT Del. Recall				-0.788		
Figure Learn.				-0.668		
Figure Del. Recall				-0.609		
WCST Cat. Comp.			0.912			
WCST Persev. Resp.			0.900			
Pegboard Dom					0.877	
Pegboard Nondom					0.854	
TMT-A	0.760					
TMT-B	0.633					
Digit Symbol	0.705					
Symbol Search	0.608					
FAS						0.539
PASAT 50						0.430
Letter-Number						0.562
Eigenvalues	6.76	1.92	1.39	1.23	0.97	0.92
% Variance	35.60	10.11	7.30	6.48	5.13	4.84
Cum. % Variance	35.60	45.71	53.00	59.49	64.62	69.46

Note. $N = 553$; BVMT = Brief Visuospatial Memory Test; Learn. = Learning; Dom = Dominant Hand; Nondom = Nondominant Hand; TMT = Trail Making Test; WCST-Cat. Comp. = Wisconsin Card Sorting Test-Categories Completed; WCST Persev. Resp. = Wisconsin Card Sorting Test-Perseverative Responses; Cum = cumulative.

TABLE 4
Demographic and clinical characteristics of the six neuropsychological cluster groups

	K1 (n=98)			K2 (n=83)			K3 (n=79)			K4 (n=84)			K5 (n=77)			K6 (n=132)		
	M (SD)	Range		M (SD)	Range		M (SD)	Range		M (SD)	Range		M (SD)	Range		M (SD)	Range	
Age	43.3 (9.6)	21–67		39.4 (7.8)	20–64		40.5 (8.5)	22–69		40.1 (8.4)	20–62		42.1 (8.2)	26–63		39.2 (7.9)	20–57	
Education	13.4 (2.5)	7–20		12.4 (2.1)	8–16		12.3 (2.8)	7–18		12.7 (2.6)	7–20		13.7 (2.8)	7–20		13.0 (2.5)	7–20 ^a	
GDS ^a *	1.02 (0.93)	0.00–3.89		0.61 (0.49)	0.00–2.89		0.51 (0.45)	0.00–1.83		0.63 (0.57)	0.00–2.67		0.52 (0.54)	0.00–2.67		0.42 (0.46)	0.00–2.30	
WRAT-3; Read SSb [*]	96.3 (14.2)	47–118		92.2 (14.4)	62–118		96.5 (13.3)	64–120		100.0 (10.8)	62–118		100.5 (12.7)	55–119		98.2 (12.6)	57–119	
Overall mean T-score ^a	40.1 (7.5)	21–58		44.6 (5.5)	27–56		46.6 (6.0)	34–57		44.5 (6.0)	29–56		45.5 (6.5)	28–62		46.6 (6.0)	31–60	
	Med	IQR		Med	IQR		Med	IQR		Med	IQR		Med	IQR		Med	IQR	
PAOFI: Total Score	7	3:17		5	1:12		2	0:11		6	1:13		5	1:14		4	1:10	
Current CD4	266	115: 502		382	136: 536		349	196: 627		236	79: 524		274	119: 274		318	130: 1214	
CD4 nadir	80	16–262		190	23–341		215	44–348		73	16–287		57	20–249		168	52–362	
Plasma viral load ^c	4.33	3.38–4.98		4.3	3.44–4.85		4.47	3.32–5.23		4.42	3.85–5.24		4.76	3.71–5.18		4.33	3.66–5.17	

Note. GDS = Global Deficit Score. WRAT-3 = Wide Range Achievement Test—Third Edition. SS = Standard Score. IQR = Interquartile Range. PAOFI = Patient's Assessment of Own Functioning Inventory.

^a K1 > K2 through K6.

^b K2 < K4 and K5.

^c Detectable. Log10 med.

* $p < .003$ (Bonferroni correction).

TABLE 5
Demographic and clinical characteristics of the six neuropsychological cluster groups by frequencies

	K1 (n=98)	K2 (n=83)	K3 (n=79)	K4 (n=84)	K5 (n=77)	K6 (n=132)
Male	84.7	84.3	84.8	85.7	88.3	93.2
Caucasian ^{a*}	68.4	42.2	46.8	70.2	70.1	60.6
HAART	69.4	63.0	61.8	66.7	71.4	69.0
AIDS	68.4	54.2	53.2	69.0	70.1	58.3
Detectable viral load	57.0	60.8	55.1	56.4	54.1	58.5
Hepatitis C antibody positive ^b	36.8	21.4	31.8	25.0	31.9	23.3
Impaired GDS ^{c*}	72.4	53.0	46.8	61.9	44.2	41.7
Major depressive disorder ^d	33.8	31.6	18.3	20.3	18.5	17.5
Alcohol use disorders ^d	6.5	6.6	8.5	12.2	1.5	6.8
Methamphetamine use disorders ^d	7.8	11.7	5.6	10.8	4.5	10.3
Cocaine use disorders ^d	3.9	3.9	5.6	2.7	6.1	6.0
Any substance use disorders ^d	16.9	18.2	18.3	17.6	12.1	17.9
No psychiatric or medical confounds ^{e,f}	25.8	29.6	37.5	39.5	42.3	45.2
Neuropsychologically impaired (GDS) ^g	52.9	43.8	23.8	57.9	31.8	42.1

Note. Values are frequencies (in percentages). GDS = Global Deficit Score. HAART = highly active antiretroviral therapy.

^a K2 < K4 and K5;

^b $nK1 = 57$, $nK2 = 42$, $nK3 = 44$, $nK4 = 40$, $nK5 = 47$, $nK6 = 73$;

^c K1 < K5 and K6;

^d Current (met DSM-IV criteria within last month prior to testing);

^e Excludes any current substance use disorder, major depressive disorder, or coinfection with hepatitis C virus;

^f $n = 3$;

^g In participants with no psychiatric or medical confounds.

* $p < .003$ (Bonferroni correction).

TABLE 6
Percentage of participants with each designated characteristic, assigned within each neuropsychological cluster

	n	Cluster					
		1	2	3	4	5	6
Non-Caucasian	221	14.0	21.7	19.0	11.3	10.4	23.5
HAART	364	18.1	14.0	12.9	15.4	15.1	24.5
AIDS	343	19.5	13.1	12.2	16.9	15.7	22.4
Hepatitis C antibody positive	86	24.4	10.5	16.3	11.6	17.4	19.8
Impaired GDS	293	24.2	15.0	12.6	17.7	11.6	18.8
Major depressive disorder ^a	110	23.6	21.8	11.8	13.6	10.9	18.2
Alcohol use disorders ^a	34	14.7	14.7	17.6	26.5	2.9	23.5
Methamphetamine use disorders ^a	42	14.3	21.4	9.5	19.0	7.1	28.6
Cocaine use disorders ^a	23	13.0	13.0	17.4	8.7	17.4	30.4
Any substance use disorders ^a	82	15.9	17.1	15.9	15.9	9.8	25.6
No psychiatric or medical confounds ^a	133	10.7	10.1	13.2	18.2	18.9	28.9
Neuropsychologically impaired (GDS) ^b	55	16.4	12.7	9.1	20.0	12.7	29.1

Note. HAART = highly active antiretroviral therapy. GDS = Global Deficit Score.

^aCurrent (met DSM-IV criteria within last month prior to testing);

^bIn participants with no psychiatric or medical confounds.