Theoretically derived CVLT subtypes in HIV-1 infection:
Internal and external validation

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Abstract
The present study sought to delineate empirically derived memory subtypes using the California Verbal Learning Test (CVLT; Delis et al., 1987) in a sample of adults with HIV-1 infection (N = 154). Confirmatory factor analysis was used to evaluate eight models of the CVLT structure suggested by Wiegner and Donders (1999). A four-factor model, consisting of Attention Span, Learning Efficiency, Delayed Recall, and Inaccurate Recall appeared to be the best fitting model. Variables with the highest factor loadings from the model were entered in a two-stage cluster analysis. Four reliable CVLT clusters or subtypes were identified: Normal, Atypical, Subsyndromal, and Frontal-striatal. Internal and external validation of subtypes demonstrated that clusters were stable and clinically interpretable. Subtypes were meaningfully related to neuropsychological functioning, and to some extent, depressive symptomatology. Subtypes did not differ significantly with respect to subjective neurocognitive complaints and markers of HIV-1 disease. The present findings highlight the heterogeneity of memory profiles in HIV-1 infection and support a frontal-striatal conceptualization of verbal memory performance. The identification of robust HIV-1 memory subtypes may have important implications for the clinical management of adults infected with HIV-1 infection. (JINS, 2003, 9, 1–16.)

Keywords: HIV, AIDS, Neuropsychological, Memory, CVLT

INTRODUCTION
The California Verbal Learning Test (CVLT; Delis et al., 1987) is a multidimensional measure of verbal learning and memory. The CVLT is regarded as a useful tool for characterizing memory profiles associated with different neuropsychological disturbances, including Alzheimer’s disease (AD), Huntington’s disease (HD), and Korsakoff’s syndrome (e.g., Delis et al., 1991), HIV-1 infection (Becker et al., 1995; Delis et al., 1995; Peavy et al., 1994; White et al., 1997), depression (Massman et al., 1992), and schizophrenia (Paulsen et al., 1995). The scoring system of the CVLT allows quantification of several indices including style of learning (e.g., semantic categorization of related words), consistency of item recall across learning trials, retention of information over short and longer delays, vulnerability to interference, recall errors (e.g., intrusions), and discriminability (ability to detect target words from distracters on recognition testing). In this manner, the CVLT enables inference about the integrity of component memory processes such as learning, encoding, retention/storage, and retrieval (Delis et al., 1991). The purpose of this investigation was to evaluate the construct and criterion validity of the CVLT in a clinical sample of individuals with HIV-1 infection.

While the CVLT has demonstrated utility for characterizing different memory profiles associated with different clinical populations, issues of construct validity hamper interpretation of CVLT profiles. Delis et al. (1987) reported a six-factor structure for the CVLT in a large sample of normal subjects and a five-factor solution in a mixed neurological sample using principal components analysis with
varimak rotation. These findings indicate that there are multiple constructs assessed by the CVLT. However, there are several limitations associated with exploratory factor analytic approaches such as principal components and orthogonal rotation procedures that may significantly hinder the task of identifying underlying latent test factors. Problems associated with these analytic approaches include their inability to account for all sources of variance (e.g., random error variance), the inability to make allowances for the possibility of correlations between factors, and the inability to find a unique or “best” solution among an infinite number of possible solutions (Maruyama, 1997). In this regard, confirmatory factor analysis is a more powerful statistical technique. Specifically, confirmatory factor analysis is a theory-driven method in which a researcher develops factor model(s) beforehand (a priori) and then evaluates which factor models best fit the data (Bryant & Yarnold, 1995). Confirmatory factor analysis addresses the potential shortcomings of other factor analytic procedures, thereby making it a methodologically sound approach for the identification of constructs measured by an instrument.

Investigations of CVLT profiles of individuals with HIV-1 infection have reported that the pattern of verbal memory performance is characteristic of predominant subcortical dysfunction (Becker et al., 1995; Delis et al., 1995; Peavy et al., 1994; White et al., 1997). Specifically, CVLT profiles (impaired learning and recall, intact retention, ability to benefit from recognition testing relative to recall) are thought to be indicative of a retrieval deficit in a subgroup of individuals with HIV-1 infection/AIDS. There is also implication of mild encoding deficits (characteristic of cortical involvement) in more advanced stages of HIV-1 disease (Delis et al., 1995).

While initially described as a “subcortical” dementia, current conceptualization of the neuropsychological disturbance associated with HIV-1 infection is consistent with dysfunction of frontal-subcortical circuitry (Back et al., 1998). Recent converging evidence from neuropsychological and neuroimaging studies implicate abnormalities of prefrontal circuits in HIV-related neurocognitive dysfunction (e.g., Castellon et al., 2000; Chang et al., 2001; Hinkin et al., 2000; Johnson et al., 2001; Martin et al., 2001). Differential involvement of the prefrontal-subcortical circuitry may explain the variability of neuropsychological symptomatology in HIV-1 infection (Back et al., 1998).

The heterogeneity of neuropsychological and neuropathological sequelae in HIV-1 infection raises the possibility of distinct subtypes of HIV-1-related memory impairment. Previous research in HIV-1 infection may be limited due to shortcomings associated with the characterization of memory profiles in terms of a strict “subcortical” versus “cortical” distinction (Becker et al., 1995; Delis et al., 1995; Peavy et al., 1994; White et al., 1997). There is evidence in the literature to support the existence of multiple memory systems linking frontal and subcortical regions (Crosson, 1992; Cummings, 1993a; Lichter & Cummings, 2001). Factors such as depression and severity of HIV-1 disease may also contribute differentially to variability in memory performance. Hence, the delineation of unique memory profiles in individuals with HIV-1 infection remains unclear.

To our knowledge, the present investigation is the first systematic attempt to isolate empirically derived memory subtypes based on the factor structure of the CVLT in a sample of adults with HIV-1 infection. The major objectives of this study are threefold: 1) to determine the underlying latent constructs of memory (CVLT) in a clinical sample of individuals with HIV-1 infection using confirmatory factor analysis, 2) to use the results of this analysis to delineate distinct and reliable clusters (subtypes) of memory performance, and 3) to evaluate the external validity of these memory subtypes using neuropsychological test performance, subjective neurocognitive complaints, mood symptomatology, and markers of HIV-1 disease. This novel subtyping approach to characterizing HIV-1-related memory performance may have significant utility in the overall clinical management of individuals with HIV-1 infection (e.g., improving diagnostic accuracy).

The present study tested eight models of the CVLT latent structure suggested by Wiegner and Donders’ (1999) investigation of individuals with traumatic brain injury (see Table 1). It is possible that individuals with HIV-1 infection exhibit distinct patterns of verbal learning and memory, as found in the traumatic brain injury literature (Curtiss et al., 2001; Deshpande et al., 1996; Millis & Ricker, 1994; Wiegner & Donders, 1999).

It was predicted that models including constructs of attention and learning efficiency (Models 4, 7, and 8) would be viable models for HIV-1 infection. These models have both theoretical and clinical relevance to HIV-1 infection. Attention and concentration disturbances are predominant neuropsychological sequelae of HIV-1 infection (Heaton et al, 1995; Hinkin et al., 1998). The Learning Efficiency factor also represents a theoretically meaningful construct in HIV-1 infection. An ineffective learning style, reflected by poor use of semantic clustering, an elevated recency effect (passive recall of items at the end of the list), and inconsistent recall of list items, has been reported with individuals with HIV-1 infection (Delis et al., 1995; Peavy et al., 1994). Moreover, organizational strategies that facilitate learning have been linked to prefrontal cortex (Savage et al., 2001; Stuss et al., 1994), a region that is vulnerable to the effects of HIV-1. Thus, how well an individual is able to learn may depend on the functional integrity of prefrontal brain systems. Cluster analytic methods are designed to group data that are relatively homogeneous. In neuropsychology, cluster analytic techniques are mainly used for the purposes of subtype generation (e.g., learning disabilities) (Morris et al., 1981). Using cluster analysis, it was anticipated that individuals with HIV-1 infection would display quantitatively and qualitatively different CVLT profiles (i.e., level and/or pattern of preserved and impaired memory components). At least two clusters or subtypes were expected to exhibit differences in overall level of performance (i.e., average and below average) on the basis of clinical and theoretical
rationale. Prior research suggests that HIV-1-associated neuropsychological impairment may be classified into three subgroups (“subsyndromic,” “minor neurocognitive disorder,” and “HIV-associated dementia”) (see Grant et al., 1999). More specific hypotheses regarding CVLT subtypes could not be made until reliable subtypes were discerned from the clustering procedures. In accordance with Wiegner and Donders (1999), only those CVLT variables with the highest factor loadings (i.e., factors from the best fitting model) were used in the cluster analysis. This method ensures that variable redundancy is reduced, and more importantly, that variables are selected based on theoretical considerations (Morris & Fletcher, 1988).

METHOD

Research Participants

The sample of subjects for this study was obtained through archival records from the HIV-1 Neuropsychology Laboratory at St. Michael’s Hospital (Wellesley Central Site) in Toronto. Data used in the present study were collected between March 1996 and August 2000. The sample consisted of 154 adults (146 males, 8 females) with HIV-1 infection who were recruited from three sources (HIV primary care medical and infectious disease clinics, psychiatric service, and research pool) in order to increase generalizability. Participants were excluded if they had a history of neurological illness (e.g., seizure disorder), head injury with loss of consciousness for more than 30 minutes, CNS opportunistic infection, significant developmental disability, or significant substance abuse/dependence in the two months prior to the study. Although exact data regarding ethnicity and sexual orientation were not available for all participants, approximately 90% were known to be Caucasian and either gay or bisexual.

Participants had a mean age of 41.36 (SD = 8.11) years and had an average 14.64 (SD = 2.62) years of education. The mean Beck Depression Inventory (BDI) score for the sample was 18.20 (SD = 10.41) (Beck & Steer, 1993), indicating mild to moderate depressive symptomatology. The mean modified BDI score (sum of first 13 items) for the sample was 10.65 (SD = 7.34), with 44% scoring in the “moderate” depression range according to the clinical cutoff (i.e., scores of 10 or less are classified as “not depressed” and scores greater than 10 are indicative of “moderate” depression) (Beck & Steer, 1993). Eighty-four percent of the sample was receiving antiretroviral treatment at the time of assessment (i.e., 61% of the sample was on HAART, 23% of the sample was taking some combination of antiretroviral medication, and 16% were not taking any antiretroviral medications). Thirty-nine percent of individuals in this sample were prescribed antidepressants. Table 2 displays the demographic characteristics of the sample.

The Centers for Disease Control (CDC93) revised classification system for HIV-1 infection (CDC, 1992) was used to categorize individuals on the basis of clinical conditions associated with infection and degree of immunosuppression (CD4 T-cell count). Of the total sample, 16 were asymptomatic (CDC-A), 41 were mildly symptomatic (CDC-B), and 97 had AIDS-defining illnesses or CD4 lymphocyte counts less than 200 (CDC-C) according to the CDC93 criteria. Participants in each of the three CDC93 clinical categories were similar in age, education, depressive symptoms, and total neurocognitive complaints (all p values > .05). As expected, the CDC-C group had significantly lower CD4 lymphocyte counts than either the CDC-A or CDC-B groups [F(2, 151) = 19.71, p < .0001].
Table 2. Demographic characteristics of sample (N = 154)

<table>
<thead>
<tr>
<th>Demographic</th>
<th>Mean (Standard Deviation)</th>
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<tbody>
<tr>
<td>Age (years)</td>
<td>41.36 (8.11)</td>
</tr>
<tr>
<td>Education (years)</td>
<td>14.64 (2.62)</td>
</tr>
<tr>
<td>BDI Total Scorea</td>
<td>18.20 (10.41)</td>
</tr>
<tr>
<td>Modified BDIc</td>
<td>10.65 (7.34)</td>
</tr>
<tr>
<td>Recent CD4 Countb</td>
<td>343.73 (227.30)</td>
</tr>
<tr>
<td>Recent Viral Loadc</td>
<td>50</td>
</tr>
<tr>
<td>% AIDS (CDC-93)</td>
<td>63</td>
</tr>
<tr>
<td>% on HAART</td>
<td>61</td>
</tr>
<tr>
<td>% on antidepressants</td>
<td>39</td>
</tr>
</tbody>
</table>

Note. BDI = Beck Depression Inventory; Modified BDI = items 1–13 (cognitive and affective items only); HAART = highly active antiretroviral therapy.

Several a priori criteria were used to select CVLT variables for inclusion in the confirmatory factor analysis. First, only variables with standard z-scores (based on age and gender) were included to enable direct comparison of performance on CVLT indices. Second, variables that were interdependent (i.e., the absolute score on one variable directly affects the absolute score on another variable) were excluded from the analysis. For example, given the interdependency between the semantic and serial clustering variables, the former was selected over the latter because this variable was thought to reflect an efficient or active learning style. Lastly, variables associated with inherent scoring and interpretation difficulties were omitted. For example, the learning slope variable (a quantification of the average number of new words acquired per trial of List A) is problematic since performance on trial 1 may be influenced by various psychological states (e.g., anxiety). Such reactions may interfere with participants’ ability to recall list items presented for the first time (Delis et al., 2000). The perseveration variable may also lend itself to scoring difficulties since patients’ tendency to repeat list words during recall trials may be misjudged as perseverative responses. Altogether, these criteria resulted in a total of 14 CVLT variables. The variables used in the present investigation are the same variables previously used by Wiegner and Donders (1999). Table 1 depicts these variables according to each of the eight hypothesized factor models.

<table>
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<th>Measures</th>
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| Neuropsychological tests were selected based on recommended guidelines from the National Institute of Mental Health Workshop on Neuropsychological Assessment Approaches of AIDS-related Cognitive Changes (Butters et al., 1990). This battery included the following tests: (1) WAIS–R Information, Digit Span, Picture Completions, and Digit Symbol subtests (Wechsler, 1981); (2) Boston Naming Test (Kaplan et al., 1983); (3) Letter and Category Verbal Fluency (Spreen & Strauss, 1991); (4) Trail Making Test, Parts A and B (Reitan & Wolfson, 1993); (5) Symbol Digit Modalities Test (Salthouse et al., 1991; Smith, 1973); (6) Grooved Pegboard Test (Klöve, 1963); (7) California Verbal Learning Test (Delis et al., 1987); (8) Wisconsin Card Sorting Test (Heaton et al., 1993); and (9) Beck Depression Inventory (Beck & Steer, 1993).

Subjective neurocognitive complaints were assessed by the Patient’s Assessment of Own Functioning (PAOF) Inventory (Chelune et al., 1986). The PAOF is a 33-item self-report instrument “designed to elicit patients’ self-perceptions regarding the adequacy of their functioning in various everyday tasks or activities” (Chelune et al., 1986, p. 96). The items are grouped into four ability areas according to face validity: memory (10 items), language and communication (9 items), sensory-perceptual and motor skills (5 items), and higher-level cognitive and intellectual functions (9 items).

Procedure

Recruitment and testing of participants used in this study was approved by the St. Michael’s Hospital Research Ethics Board. Administration of a background interview, questionnaires, and neuropsychological testing generally took between 3 to 4 hours with a 30 to 45 minute break in the middle.

The CVLT was administered by a trained psychometrist as part of the neuropsychological test battery. The CVLT is a list learning task that involves the oral presentation of 16 “shopping” items (List A). Examinees are asked to recall list items in any order. The list is presented five times with list items presented in the same order each time. List items are comprised of words from common categories (i.e., fruits, spices, clothing, tools). Words from the same category are not presented consecutively in order to assess the examinee’s learning strategy (i.e., serial order or semantic clustering). Following presentation of the fifth learning trial, an interference list (List B) is presented for one trial. After recall of List B items, the examinee is asked to recall List A items, using both a free- and cued-recall format (short-delay trials). A delay of 20 minutes (filled with nonverbal testing) is introduced. Next, free- and cued-recall of List A is conducted (long-delay trials), followed by recognition testing (yes/no format) which requires the detection of 16 target items (List A) from a list that also includes 28 distractors. CVLT scoring software (Fridlund & Delis, 1987) was used to score test protocols. Raw scores were converted to age- and gender-corrected z-scores and T-scores using this software.

Part I: Confirmatory factor analysis

Confirmatory factor analysis, a basic class of structural equation modeling, was conducted in order to test hypothesized...
relations between measured variables and unobservable constructs (latent variables or factors) (Francis, 1988). Using AMOS 4.0 (Arbuckle & Wothke, 1999), maximum-likelihood structural equations were derived from the covariance matrix of 14 CVLT variables. In order to assess model fit and parsimony of the eight theoretical factor models, fit indices, parameter estimates, and residuals were examined. With regard to model fit indices, several measures were used according to previously established criteria (Bentler, 1989; Browne & Cudeck, 1993; Bryant & Yarnold, 1995; Hatcher, 1994; Kelloway, 1998; Kline, 1998). Specifically, $\chi^2$/df less than 2, GFI, NNFI, and CFI values exceeding .90, RMSEA values less than .08, and PNFI values greater than .60 were associated with better fitting models. In addition, the model with the lowest AIC was preferred for comparing non-hierarchical models (i.e., models 1 to 4).

Part II: Cluster analysis

CVLT variables with the highest factor loadings (from the best fitting model identified by confirmatory factor analyses) were selected for cluster analysis. CVLT indices were subjected to a two-stage clustering process entailing Ward’s (1963) minimum variance method as the first-stage agglomerative clustering method with squared Euclidean distance as the similarity measure, followed by k-means iterative partitioning. This two-stage clustering method has been shown to have good success in previous studies using cluster analysis (Donders, 1996; Wiegner & Donders, 1999).

Since cluster analysis will always generate groups of subjects (even in random data sets), the validity of clusters or subtypes is a critical aspect of the clustering procedure (Feuerst & Rouge, 1995). Internal validity (reliability) is essential for evaluating the stability of a clustering solution (Morris et al., 1981). The stability of cluster solutions was gauged by the degree to which solutions were replicated across different clustering techniques.

External validity is a measure of the clinical meaningfulness, prognostic utility, or generalizability of clusters across different samples (DeLuca et al., 1991). To evaluate the external validity of the cluster solution, memory subtypes were compared on measures of neuropsychological functioning (attention, psychomotor speed, language, verbal fluency, and conceptual skills and problem solving), subjective neurocognitive complaints (PAOF), depressive symptoms (BDI), and markers of HIV-1 disease severity (i.e., CD4 count, viral load, CDC stage). Analyses using a modified version of the BDI (i.e., excluding somatic items) were also conducted in order to ensure that somatic or vegetative items were not confounding the results.

Analysis of variance (ANOVA) was conducted on continuous variables whereas chi-square statistics were performed on discrete variables. With respect to the PAOF analyses, individual ratings across each ability area (i.e., memory, language, sensory-motor, higher-level cognitive/intellectual) were summed and divided by number of items in each major area to yield a mean rating for each complaint area. Also, in order to balance the relative risks of Type 1 and Type 2 errors, and in order to focus on findings with likely practical implications, it was decided a priori that only those findings/differences that were associated with a univariate effect size greater than .05 would be interpreted.

RESULTS

Part I: Confirmatory Factor Analysis

Maximum-likelihood structural equations were computed for each of the eight latent factor models. Inspection of factor solutions and parameter estimates indicated significant problems with models 5 to 8. Specifically, factor solutions for these models were not admissible due to significant estimation problems (i.e., zero or negative eigenvalues, near-zero error variances, factor intercorrelations approaching 1.00). All four models yielded factor intercorrelations of .99 (between short- and long-delayed recall factors) suggesting that separating the delayed recall factor (i.e., short vs. long delay or free vs. cued recall) results in unstable and unreliable factor solutions.

Since only models 1 to 4 were considered reliable with respect to their factor solutions, the remainder of the analyses focused exclusively on these models. Table 3 lists the fit indices for the competing models. Model 1 failed to meet criteria for adequate model fit (i.e., $\chi^2$/df > 2, GFI, NNFI, CFI < .90, RMSEA > .08). Of the remaining three models (models 2 to 4), Model 4 seemed to “fit” best relative to the other models. Specifically, Model 4 had the highest GFI, NNFI, and CFI values (≥ .90), an RMSEA value less than .08, and only a negligible loss in parsimony over models 2

<table>
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<th>Table 3. Fit indices for CVLT latent variable models</th>
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<td>Model</td>
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<td>4</td>
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Note. GFI = goodness-of-fit index; NNFI = nonnormed fit index (also known as Tucker-Lewis index); CFI = comparative fit index; RMSEA = root mean squared error of approximation; PNFI = parsimonious normed fit index; AIC = Akaike’s information criterion; ECVI = expected value cross-validation index.
and 3 (PNFI of .71 vs .73). Also, Model 4 had lower values of $\chi^2$/df, AIC, and ECVI than any other model. Lastly, residuals from Model 4 were symmetrically distributed, further supporting the four-factor solution of the CVLT.

On the basis of these findings as well as theoretical rationale supporting separate Attention Span and Learning Efficiency factors, Model 4 was deemed the best fitting model of the underlying factor structure of the CVLT in this sample of individuals with HIV-1 infection. The standardized regression weights (factor loadings) and factor intercorrelations for Model 4 are displayed in Figure 1.

With the exception of False positives, factor loadings for all variables were greater than .40, indicating a modest to strong relationship between variables and their respective hypothetical factors. Composite reliabilities for factors 1 to 4 were .59, .42, .93, and .60, respectively. Values greater than .60 are desirable (Hatcher, 1994). Factor intercorrelations were generally high (except for Inaccurate Recall), with amount of shared variance between factors ranging from 35% to 81%. These results suggest that while factors are separate, they should not be considered as completely independent of each other. In contrast, the Inaccurate Recall factor appears to represent a construct that is quite distinct from the other three factors (shared variance of only 4% to 15%).

Part II: Cluster Analysis

Variables with the highest factor loadings from Model 4 were selected for inclusion in a two-stage clustering process (see Figure 1). The four variables were List A trial 1, List A trial 5, Long-delay cued recall, and Cued recall intrusions. These are the same CVLT variables found to have the highest loadings on their respective factors in Wiegner and Donders’ (1999) study. All variables were standardized to $z$-scores, with higher scores indicating better performance.

Since many clustering methods are sensitive to the presence of outliers (Everitt, 1980), data from eleven participants (identified as having extreme values on CVLT variables) were deleted. This resulted in a sample size of 143 for the cluster analyses. Analysis of the dendogram (tree diagram) and the clustering (fusion) coefficients suggested between four and six clusters. Specifically, large “gaps” (indicating large within-cluster variance when combining the previous two clusters) in the fusion coefficients were used to decide the number of clusters (Morris et al., 1981). Replication of the four-, five-, and six-cluster solutions using different clustering methods (see below) demonstrated good replicability (stability) of the four-cluster solution. In addition, examination of the cluster profile means suggested that a four-cluster solution was clinically interpretable, further providing support for the four-cluster solution. Starting seed values from the initial (four-cluster) Ward’s analysis were then used in a $k$-means iterative partitioning method. This procedure yielded four final clusters that were comparable to the initial Ward clusters with respect to level and pattern of performance.

Replicability (reliability) and clinical interpretability are essential for assessing the adequacy of a specific cluster solution (Everitt, 1980; Fuerst & Rourke, 1995). Reliability of the four-cluster solution was assessed with two different agglomerative clustering methods, complete linkage (Sorensen, 1948) and average linkage (Sokal & Michener, 1958). Both of these procedures demonstrated 87% agreement with Ward’s method in terms of classifying individuals into the same clusters. The CVLT profiles of the four clusters were also considered to be interpretable from a clinical standpoint. Figure 2 presents the cluster profiles.

Inspection of Figure 2 shows that clusters differed in terms of level and pattern of performance. Overall, clusters differed most on List A5 and LDCR variables. In contrast, there was little variation between clusters with respect to inaccurate recall (CINT). Clusters 1 and 2 exhibited somewhat similar patterns of performance with the exception of LDCR scores, indicating that Cluster 2 evidenced lowered delayed cued recall in comparison to Cluster 1. Clusters 2 and 3 displayed distinct patterns of performance. Specifically, these clusters were most discrepant on List A5, with Cluster 3 exhibiting markedly lower $z$-scores than Cluster 2. These results suggest that Cluster 3 evidenced problems with learning efficiency while Cluster 2 demonstrated intact learning ability. In contrast, there was little difference between Clusters 2 and 3 on LDCR, suggesting that recall after a brief delay was similar for both clusters. Lastly, within the context of similar CINT performance, Clusters 3 and 4 appeared to differ mainly with respect to profile level. In particular, performance on List A5 and LDCR variables clearly differentiated these two cluster subgroups.

Table 4 displays the $z$-scores for the four cluster variables as well as other CVLT variables. The latter are provided for descriptive purposes. Statistical tests comparing cluster performance across selected CVLT indices are inappropriate since these variables were not independent of variables used in the clustering process (Morris et al., 1981).

Clusters did not evidence rapid forgetting as reflected by minimal or no differences between short-delay and long-delay free recall $z$-scores. A recognition format did not appear to significantly improve performance relative to recall for any of the clusters. Cluster 4’s better performance on discriminability (a measure of recognition accuracy) compared to long-delay free recall was due only to the fact that they made very few false positive errors. None of the clusters demonstrated a susceptibility to proactive (List A1 vs. List B) or retroactive (List A5 vs. short-delay free recall) interference, with $z$-scores typically within one half of a standard deviation of each other. Informal comparisons of learning variables (i.e., semantic clustering and recall consistency) demonstrated that Clusters 1 and 2 obtained scores within normal limits whereas Cluster 4’s scores were greater than one standard deviation from the normative mean.
Fig. 1. Path diagram for Model 4 with standardized regression coefficients. Ellipses represent latent variables or factors. Rectangles are used to depict observed variables (in this case, CVLT variables). Arrows indicate associations that are either directional (straight arrows) or nondirectional (curved arrows). Note: Error associated with observed variables are omitted from the diagram to preserve simplicity of the structural model.
In terms of demonstrating intact neuropsychological function, however, it was anticipated that participants in the Atypical subtype would differ from Normals with respect to number of subjective mood and cognitive complaints. Cluster 3 (“Subsyndromal” subtype) was hypothesized to exhibit a “mild subcortical” or subsyndromal presentation. In other words, subtle and “spotty” neuropsychological impairment was predicted in this group of individuals (e.g., psychomotor slowing). Lastly, a “subcortical plus frontal” presentation was predicted for Cluster 4 (“Frontal-striatal” subtype) consisting of a pattern of lowered overall neuropsychological test performance, including disturbances in fronto-executive skills.

**Demographic data**

As seen in Table 5, there were no statistically significant differences between clusters in terms of age \( [F(3,139) = 0.82] \) and WAIS-R Information T-scores. However, statistically significant differences in years of education were demonstrated between clusters \( [F(3,139) = 5.31, p = .002] \), with an effect size of .10. Post hoc analyses indicated that the Normal subtype (Cluster 1) had a higher level of education than the Subsyndromal and Frontal-striatal subtypes (Cluster 3 and Cluster 4, respectively). The Atypical subtype (Cluster 2) also had more years of education than the Frontal-striatal subgroup (Cluster 4).

The clusters did not exhibit statistically significant differences on self-reported depressive symptomatology (BDI) \( (p > .10) \). Analyses using modified BDI scores were also conducted in order to ensure that somatic or vegetative items were not confounding the results. Using the clinical cut-off for the modified BDI (scores greater than 10 suggestive of “moderate” depression) (Beck & Steer, 1993), the Frontal-striatal subtype (Cluster 4) had a larger proportion of individuals that were considered to be moderately depressed \( [\chi^2(3) = 10.11, p < .05] \). The relationship between cluster membership and markers of HIV-1 disease (i.e., CD4 lymphocyte counts, CDC93 categories [asymptomatic, mildly symptomatic, AIDS], and viral load) was not significant (Table 5).

**Neuropsychological data**

The validity of the four-cluster solution was also evaluated with neuropsychological measures. One-way ANCOVAs (education as a covariate) were used to compare the four clusters on measures (raw scores) of attention, psychomotor speed, language, verbal fluency, and problem solving and conceptual abilities (Table 6).

Cluster performance on a measure of fine-motor speed and dexterity (Grooved Pegboard Test) was significantly different for both dominant \( [F(3,138) = 3.77, p < .05] \) and nondominant \( [F(3,137) = 4.01, p < .01] \) hands, with an effect size of .08 for each hand. The Normal subtype (Cluster 1) exhibited significantly faster speeds than all other clusters for the dominant and nondominant hand trials. In the language domain, significant differences were found on category fluency \( [F(3,138) = 6.89, p < .001] \), with an
effect size of .13. On this task, the Frontal-striatal subtype (Cluster 4) exhibited performance inferior to that of all other clusters.

Lastly, on selected indices of the Wisconsin Card Sorting Test, statistically significant differences were found between clusters with respect to the number of categories achieved \( [F(3,131) = 2.75, p < .05] \), the percentage of perseverative responses \( [F(3,131) = 4.36, p < .01] \), and the total number of errors \( [F(3,131) = 3.39, p < .05] \). Effect sizes were .06, .09, and .07, respectively. In comparison to the Normal subgroup (Cluster 1), the Frontal-striatal subtype (Cluster 4) achieved significantly fewer categories. The Frontal-striatal subtype also exhibited a higher percentage of perseverative responses compared to participants in the Normal and Atypical subtypes. Both the Subsyndromal and Frontal-striatal subtypes (Cluster 3 and Cluster 4, re-

<table>
<thead>
<tr>
<th>Cluster variable</th>
<th>Cluster 1 ( (n = 36) )</th>
<th>Cluster 2 ( (n = 42) )</th>
<th>Cluster 3 ( (n = 46) )</th>
<th>Cluster 4 ( (n = 19) )</th>
</tr>
</thead>
<tbody>
<tr>
<td>CVLT variable</td>
<td>M ( (SD) )</td>
<td>M ( (SD) )</td>
<td>M ( (SD) )</td>
<td>M ( (SD) )</td>
</tr>
<tr>
<td>List A trial 1 (^a)</td>
<td>-0.06 ( (1.01) )</td>
<td>-0.64 ( (0.73) )</td>
<td>-0.70 ( (0.84) )</td>
<td>-1.42 ( (0.69) )</td>
</tr>
<tr>
<td>List A trial 5 (^a)</td>
<td>1.17 ( (0.65) )</td>
<td>-0.05 ( (0.44) )</td>
<td>-1.61 ( (0.68) )</td>
<td>-3.32 ( (0.89) )</td>
</tr>
<tr>
<td>List B</td>
<td>0.31 ( (1.24) )</td>
<td>-0.21 ( (1.34) )</td>
<td>-0.09 ( (1.24) )</td>
<td>-1.16 ( (0.83) )</td>
</tr>
<tr>
<td>Short-delay free recall</td>
<td>0.72 ( (0.94) )</td>
<td>-0.48 ( (0.99) )</td>
<td>-1.24 ( (0.74) )</td>
<td>-2.68 ( (0.82) )</td>
</tr>
<tr>
<td>Short-delay cued recall</td>
<td>0.83 ( (0.56) )</td>
<td>-0.40 ( (0.89) )</td>
<td>-1.26 ( (0.83) )</td>
<td>-2.63 ( (1.26) )</td>
</tr>
<tr>
<td>Long-delay free recall</td>
<td>0.78 ( (0.72) )</td>
<td>-0.38 ( (0.62) )</td>
<td>-1.07 ( (0.71) )</td>
<td>-2.68 ( (0.89) )</td>
</tr>
<tr>
<td>Long-delay cued recall (^a)</td>
<td>1.03 ( (0.65) )</td>
<td>-0.64 ( (0.85) )</td>
<td>-1.17 ( (0.82) )</td>
<td>-3.00 ( (0.88) )</td>
</tr>
<tr>
<td>Semantic clustering</td>
<td>0.72 ( (1.21) )</td>
<td>0.00 ( (1.08) )</td>
<td>-0.80 ( (0.91) )</td>
<td>-1.11 ( (0.74) )</td>
</tr>
<tr>
<td>Recency</td>
<td>-0.39 ( (0.60) )</td>
<td>-0.14 ( (0.84) )</td>
<td>0.30 ( (0.99) )</td>
<td>0.58 ( (1.35) )</td>
</tr>
<tr>
<td>Recall consistency</td>
<td>0.22 ( (0.68) )</td>
<td>-0.38 ( (0.79) )</td>
<td>-0.80 ( (1.07) )</td>
<td>-1.26 ( (1.10) )</td>
</tr>
<tr>
<td>Intrusions—free recall</td>
<td>-0.47 ( (0.70) )</td>
<td>-0.02 ( (0.81) )</td>
<td>-0.41 ( (0.54) )</td>
<td>-0.16 ( (1.01) )</td>
</tr>
<tr>
<td>Intrusions—cued recall (^a)</td>
<td>-0.86 ( (0.35) )</td>
<td>-0.10 ( (0.76) )</td>
<td>-0.50 ( (0.66) )</td>
<td>-0.16 ( (0.83) )</td>
</tr>
<tr>
<td>Recognition hits</td>
<td>0.36 ( (0.72) )</td>
<td>-0.67 ( (1.26) )</td>
<td>-0.87 ( (1.36) )</td>
<td>-2.68 ( (1.77) )</td>
</tr>
<tr>
<td>Recognition false positives</td>
<td>0.03 ( (0.17) )</td>
<td>0.21 ( (0.52) )</td>
<td>0.15 ( (0.52) )</td>
<td>0.21 ( (0.42) )</td>
</tr>
<tr>
<td>Discriminability</td>
<td>0.19 ( (0.48) )</td>
<td>-0.26 ( (0.59) )</td>
<td>-0.35 ( (0.77) )</td>
<td>-1.11 ( (0.81) )</td>
</tr>
<tr>
<td>List A, trials 1–5 (^b)</td>
<td>57.11 ( (8.08) )</td>
<td>47.05 ( (7.02) )</td>
<td>37.37 ( (7.85) )</td>
<td>23.57 ( (5.27) )</td>
</tr>
</tbody>
</table>

*Note. CVLT = California Verbal Learning Test.

\(^a\) Variable selected for cluster analysis.

\(^b\) T-score.
spectively) displayed a greater number of total errors than participants in the Normal subtype. These results highlight the Frontal-striatal subgroup’s difficulties with problem solving and executive skills.

Subjective cognitive complaints (PAOF data)

Comparison of clusters on the Patient’s Assessment of Own Functioning, a measure of subjective neurocognitive complaints, did not yield significant differences. In general, there was a trend toward increasing number of memory complaints across cluster subtypes, with the Normal cluster reporting the fewest complaints and the Frontal-striatal cluster endorsing the most difficulties (p = .07). (See Table 5 for the total number of PAOF complaints.)

DISCUSSION

The main goals of this study were three-fold: 1) to determine the underlying latent structure of the CVLT in a sample of adults with HIV-1 infection, 2) to identify whether there are distinct and reliable memory subtypes within this sample, and 3) to externally validate these subtypes using other neuropsychological measures, self-reported cognitive and depressive complaints, and markers of HIV-1 disease. The results indicated that constructs of Attention Span, Learning Efficiency, Delayed Recall, and Inaccurate Recall seem to be representative of the underlying latent memory structure in individuals with HIV-1 infection. Based on the latent factor structure of the CVLT, four empirically derived memory subtypes were delineated. These subtypes differed with respect to pattern and level of CVLT performance and were meaningfully related to neuropsychological functioning, and to some extent, mood variables. Overall, these findings highlight the heterogeneity of memory profiles in HIV-1 infection.

Part I: Confirmatory Factor Analysis

Findings from the present investigation offer support for separate but overlapping constructs of learning and memory performance in HIV-1 individuals. This study replicates in an HIV-1 infected sample, the four-factor model reported by Wiegner and Donders (1999) in their investigation of memory performance in traumatic brain injury.

Table 6. Cluster validation with neuropsychological measures

<table>
<thead>
<tr>
<th>NP ability area</th>
<th>Normal (Cluster 1) (n = 36)</th>
<th>Atypical (Cluster 2) (n = 42)</th>
<th>Subsyndromal (Cluster 3) (n = 46)</th>
<th>Frontal-striatal (Cluster 4) (n = 19)</th>
<th>ANCOVA Contrasts</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Attention/Psychomotor Speed</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Digit Span Forward</td>
<td>9.17 (2.43)</td>
<td>9.17 (1.99)</td>
<td>8.98 (2.34)</td>
<td>8.21 (2.72)</td>
<td>ns</td>
</tr>
<tr>
<td>Digit Span Backward</td>
<td>8.00 (2.39)</td>
<td>7.79 (2.30)</td>
<td>7.78 (2.41)</td>
<td>7.05 (2.44)</td>
<td>ns</td>
</tr>
<tr>
<td>Digit Symbol</td>
<td>58.17 (12.95)</td>
<td>53.78 (11.95)</td>
<td>52.65 (12.86)</td>
<td>52.00 (10.58)</td>
<td>ns</td>
</tr>
<tr>
<td>SDMT&lt;sup&gt;b&lt;/sup&gt;</td>
<td>53.91 (8.75)</td>
<td>49.33 (9.48)</td>
<td>49.39 (12.14)</td>
<td>46.22 (8.27)</td>
<td>ns</td>
</tr>
<tr>
<td>Trails A&lt;sup&gt;d&lt;/sup&gt;</td>
<td>25.19 (5.86)</td>
<td>26.78 (9.51)</td>
<td>29.09 (13.15)</td>
<td>28.36 (9.36)</td>
<td>ns</td>
</tr>
<tr>
<td>Trails B&lt;sup&gt;d&lt;/sup&gt;</td>
<td>57.94 (21.20)</td>
<td>64.07 (25.38)</td>
<td>74.72 (39.39)</td>
<td>74.95 (36.13)</td>
<td>ns</td>
</tr>
<tr>
<td>GPT—DH</td>
<td>64.89 (9.91)</td>
<td>74.73 (17.88)</td>
<td>75.24 (16.91)</td>
<td>79.78 (18.68)</td>
<td>1 &gt; 2, 3, 4*</td>
</tr>
<tr>
<td>GPT—NDH&lt;sup&gt;d&lt;/sup&gt;</td>
<td>70.39 (12.15)</td>
<td>84.24 (26.57)</td>
<td>80.39 (18.92)</td>
<td>87.50 (22.53)</td>
<td>1 &gt; 2, 3, 4**</td>
</tr>
<tr>
<td><strong>Language &amp; Fluency</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Boston Naming Test</td>
<td>57.36 (3.14)</td>
<td>56.79 (3.00)</td>
<td>55.39 (4.01)</td>
<td>54.32 (3.13)</td>
<td>ns</td>
</tr>
<tr>
<td>FAS Fluency&lt;sup&gt;d&lt;/sup&gt;</td>
<td>43.02 (11.16)</td>
<td>40.67 (12.24)</td>
<td>40.69 (13.83)</td>
<td>39.21 (11.85)</td>
<td>ns</td>
</tr>
<tr>
<td>Category Fluency</td>
<td>52.81 (9.08)</td>
<td>50.57 (9.11)</td>
<td>48.89 (10.38)</td>
<td>38.89 (8.48)</td>
<td>1, 2, 3 &gt; 4***</td>
</tr>
<tr>
<td><strong>Problem Solving</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WCST—Categories&lt;sup&gt;e&lt;/sup&gt;</td>
<td>5.89 (0.47)</td>
<td>5.29 (1.63)</td>
<td>5.23 (1.46)</td>
<td>4.44 (2.28)</td>
<td>1 &gt; 4*</td>
</tr>
<tr>
<td>WCST—PR&lt;sup&gt;e&lt;/sup&gt;</td>
<td>8.63 (2.94)</td>
<td>11.68 (10.13)</td>
<td>13.34 (8.92)</td>
<td>19.50 (14.50)</td>
<td>1, 2 &gt; 4**</td>
</tr>
<tr>
<td>WCST—Total Errors&lt;sup&gt;e&lt;/sup&gt;</td>
<td>15.49 (8.66)</td>
<td>23.15 (19.21)</td>
<td>25.89 (19.45)</td>
<td>34.31 (20.93)</td>
<td>1 &gt; 3, 4*</td>
</tr>
</tbody>
</table>

*Note. NP = Neuropsychological; SDMT = Symbol Digit Modalities Test; GPT = Grooved Pegboard Test; DH = dominant hand; NDH = non-dominant hand; WCST = Wisconsin Card Sorting Test; PR = percent perseverative responses.
*raw scores.
<sup>a</sup>n = 141.
<sup>b</sup>n = 132.
<sup>c</sup>n = 142.
<sup>d</sup>n = 141.
<sup>e</sup>n = 136.
identified constructs of attention and concentration as important components of memory functioning using clinical (Burton et al., 1999; Roth et al., 1990; Woodard, 1993) and standardized samples (Burton et al., 1993; Donders, 1999).

Learning Efficiency was the second construct identified in the four-factor model. This factor was defined by both quantitative (List A trial 5) and qualitative (semantic clustering, recency, recall consistency) indices of learning style. It should be noted, however, that the composite reliability of this factor (.42) is lower than the desired value (.60) (Hatcher, 1994). The pattern of factor loadings on Learning Efficiency (i.e., high positive loadings with List A trial 5 and semantic clustering and a modest negative loading with recency) suggests that learning strategies that are active, efficient, and organized are associated with improved memory performance. The high correlation between the Learning Efficiency and Delayed Recall factors (.90) further bolsters the close association between learning efficiency and memory (i.e., recall) performance. These findings are consistent with recent CVLT literature demonstrating that active and efficient learning strategies are linked to better memory performance (Donders, 1999; Shear et al., 2000).

Variables comprising the Delayed Recall factor (i.e., short-delay free recall, short-delay cued recall, long-delay free recall, long-delay cued recall) all had very high positive loadings. Moreover, these variables were highly correlated with one another. These results suggest that timing of delay (i.e., short or long) and recall format (i.e., free or cued) are less salient when interpreting memory performance of adults with HIV-1 infection. Donders (1999) reported separate Free Delayed Recall and Cued Delayed Recall factors using the CVLT children’s version. However, given that factors were very highly correlated (.95), it is difficult to know if this distinction is due to method variance alone (Donders, 1999).

The existence of a delayed memory factor (separate from immediate recall) has also been reported by other investigators using different memory tests (Roth et al., 1990; Wiegner & Donders, 1999; Woodard, 1993). However, one recent study did not find support for a separate delayed recall construct using the Wechsler Memory Scale–Third Edition (Millis et al., 1999). This latter study used a normal standardization sample whereas the former investigations were conducted on clinical samples. Therefore, it has been postulated that separate immediate and delayed memory constructs tend to emerge in neurologically compromised individuals (Millis et al., 1999).

The fourth factor, Inaccurate Recall (defined by free recall intrusions, cued recall intrusions, and false positives) had negative associations with the Attention Span, Learning Efficiency, and Delayed Recall factors. This pattern of associations suggests that inaccurate responses were related to poorer attention, learning efficiency, and retention. However, factor intercorrelations (i.e., between Inaccurate Recall and the other three factors) were generally low, indicating that recall errors did not strongly influence performance on other indices of the CVLT. Overall, participants in this study generally made few errors on the CVLT. Therefore, the ability to discriminate relevant from irrelevant information appears to be generally preserved in this sample of adults with HIV-1 infection. In contrast, the tendency to make response errors (i.e., intrusions, false positives) on the CVLT seems more characteristic of other neurological conditions such as traumatic brain injury (Wiegner & Donders, 1999) and Alzheimer’s disease (Delis et al., 1991).

Part II: Cluster Analysis

The two-stage clustering procedure yielded a four-cluster solution that was deemed stable and reliable based on replicability of the solution across different clustering techniques and in terms of clinical meaningfulness and interpretability. On the clustering variables (i.e., List A trial 1, List A trial 5, and Long-delay cued recall), the Normal subtype displayed the highest scores (reflecting intact verbal learning and memory performance), whereas the Frontal-striatal subtype exhibited the poorest performance (indicative of deficient verbal learning and memory). The Atypical and Subsyndromal clusters were differentiated mainly with respect to performance on List A trial 5, with only the latter evidencing deficient learning on trial 5 items. The Atypical cluster’s advantage over the Subsyndromal cluster, however, appeared only short-lived, as both clusters exhibited similar performance after a brief time delay (with distracters in between).

Overall, List A trial 5 and Long-delay cued recall variables seemed to best discriminate between subtypes, suggesting that a combination of learning efficiency and delayed recall appear to be important indices of memory performance in HIV-1 infection. These results corroborate earlier reports of ineffective learning (i.e., poor use of semantic strategies, elevated recency effect, and inconsistent recall) and impaired recall of CVLT items in a subset of individuals with HIV-1 infection (Delis et al., 1995; Peavy et al., 1994).

Informal comparisons of the memory subtypes on other CVLT variables revealed several findings compatible with a “subcortical” memory profile (i.e., intact retention, few intrusions, minimal susceptibility to interference). These findings appear consistent with a retrieval-based verbal memory profile associated with predominant subcortical brain dysfunction (Becker et al., 1995; Delis et al., 1991, 1995; Peavy et al., 1994). In contrast, learning and memory characteristics involving forgetting, recall errors, and vulnerability to interference are more common in diseases primarily affecting cortical brain regions (e.g., Alzheimer’s disease) (Delis et al., 1991; Massman et al., 1992).

Among the four memory subtypes, only the Frontal-striatal subtype evidenced compromised discriminability (ability to discriminate target words from distracter items). This finding is suggestive of an encoding problem (Delis et al., 1987, 1991, 1995). Altogether, these results, corroborating Delis et al.’s (1995) findings, suggest that disturbances in both encoding and retrieval processes are evident.
in a subset of adults with HIV-1 infection (i.e., Frontal-striatal subtype). Moreover, the findings from Delis et al. (1995) and the present study support a frontal-striatal (frontal-subcortical) conceptualization of verbal learning and memory performance in HIV-1 infection.

External Validation of Subtypes

Subtypes were compared on a variety of measures not used in the clustering procedure in order to determine their clinical utility and/or generalizability. Overall, the empirically derived subtypes were deemed valid with respect to their neuropsychological profiles and to some extent, subjective mood (i.e., depressive symptomatology). Subtypes were not differentiated in terms of subjective neuropsychological complaints or surrogate markers of HIV-1 disease (i.e., CD4 count or plasma viral load).

Neuropsychological performance

As expected, the Normal subtype (Cluster 1) displayed intact neuropsychological performance in all ability areas. This subtype’s scores were superior compared to other subtypes on measures of psychomotor speed and dexterity, category fluency, and non-verbal problem solving. Individuals in the Atypical subtype (Cluster 2) performed similarly to the Normal subtype on all neuropsychological variables except psychomotor speed. This finding is interesting as it coincides with the well-supported notion that psychomotor slowing is an early neuropsychological indicator of HIV-1 disease (e.g., Bornstein et al., 1993; Sacktor et al., 1996). The Subsyndromal subtype evidenced difficulties in psychomotor speed and some elements of problem solving (i.e., number of errors). This “spotty” performance appears to reflect an overall efficiency problem in this subtype. Lastly, the Frontal-striatal subtype (Cluster 4) exhibited a pattern of lowered neuropsychological performance in all ability areas. These findings attest to the heterogeneity of cognitive functioning in HIV-1 infection and argue against the notion of a unitary neuropsychological profile.

The identification of robust memory subtypes with associated neuropsychological sequelae may have important implications for the clinical management of individuals with HIV-1 infection. For instance, examination of learning efficiency (scores on List A trial 5, semantic clustering, and recall consistency) may provide an indication of how effectively an individual will be able to acquire and organize new information or adapt to novel situations. Evaluation of delayed recall (scores on short-delay free recall, short-delay cued recall, long-delay free recall, long-delay cued recall, and recognition hits) may indicate whether the individual is able to successfully recall information over time in the face of distractions. Moreover, performance on these CVLT variables in conjunction with neuropsychological indices of psychomotor speed may provide clues about preclinical cognitive inefficiencies. In addition, the delineation of distinct and reliable HIV-1 memory subtypes may lead to improved diagnostic accuracy of HIV-1-associated cognitive motor complex (AAN, 1991). Prospective studies are needed to determine the nature and course of memory (neuropsychological) disturbance with progression of HIV-1 disease.

Depressive symptomatology

Statistically significant differences were observed on the modified version of the depression inventory (i.e., excluding somatic/vegetative items). According to standard clinical cut-offs, only the Frontal-striatal subtype had a larger proportion of mean scores considered to reflect “moderate” depressive symptomatology. The finding of elevated mood complaints in the Frontal-striatal subtype appears to fit well with a subcortical dysfunction theory of HIV-1 infection. Specifically, disruptions of pathways linking frontal and striatal (i.e., basal ganglia) structures have been implicated in the pathogenesis of depressive symptoms (Cummings, 1993b). Therefore, while reactive depression cannot be ruled out, these findings are compatible with the organic etiology of mood disturbance in this subset of individuals with HIV-1 infection.

Subjective neurocognitive complaints

Not surprisingly, clinical memory subtypes were not distinguished solely on the basis of subjective complaints. This suggests that self-reported difficulties of cognitive inefficiency should not be interpreted in isolation (Beason-Hazen et al., 1994; Hinkin et al., 1996; Mapou et al., 1993; Rourke et al., 1999a, 1999b). Gauging the individual’s level of accuracy (e.g., based on subjective/objective discrepancy) may be a more fruitful approach than relying exclusively on subjective complaints (Rourke et al., 1999a, 1999b).

Markers of HIV-1 disease

A significant relationship between markers of HIV-1 disease (i.e., CD4 count, CDC stage, and viral load) and memory subtypes was not found in the present study. Previous investigations have also failed to find significant associations between markers of immune functioning and neuropsychological performance (e.g., Basso & Bornstein, 2000a; Miller et al., 1990; van Gorp et al., 1993; Villa et al., 1996). This is an important finding as it suggests that global indexes of disease status may not be specific enough with regard to actual behavioral manifestations, in this case, memory performance.

Another possible explanation is that recent combination drug therapies (antiretrovirals and protease inhibitors) may be masking the relationship between systemic HIV-1 markers and HIV-1-associated cognitive impairments (Rourke et al., 1999a). For example, in this study, a higher percentage of individuals in the Normal subgroup were taking highly active antiretroviral therapy (HAART) compared to those in the Frontal-striatal subgroup (74% vs. 47%). While...
initial evidence supports the beneficial effects of HAART on neuropsychological functioning (Ferrando et al., 1998), further clarification regarding the relationship between memory impairment and medical status is needed in order to determine whether this information may be of some benefit for clinical management of adults with HIV-1 infection.

Demographic data

An unexpected finding was that individuals in the Frontal-striatal subgroup had significantly lower education than the other subtypes. This finding is consonant with the “cerebral reserve” theory which postulates that insufficient educational stimulation may decrease redundancy in cerebral networks (Maj et al., 1994), thereby diminishing the capacity of the brain to “bounce back” from a neurological insult. Individuals with reduced cerebral reserve (e.g., education, premorbid intelligence) may be more susceptible to the effects of HIV-1 infection on the brain (see Basso & Bornstein, 2000b; Maj et al., 1994; Satz et al., 1993; Stern et al., 1996).

Summary

The present investigation provides greater understanding of CVLT constructs in a clinical sample than that presented in the manual (Delis et al., 1987). Specifically, the current findings suggest that interpretation of memory performance in adults with HIV-1 infection should take into consideration performance across four factorial dimensions of the CVLT, namely Attention Span, Learning Efficiency, Delayed Recall, and Inaccurate Recall. Of note, interpretation of CVLT profiles in terms of independent memory components (i.e., encoding, storage, retrieval, and recognition) may not be valid since constructs (all except Inaccurate Recall) were highly correlated. This implies that active organizational strategies can enhance learning effectiveness and subsequently delayed recall of information. Moreover, the ability to utilize effective learning strategies, to retain information over time, and the ability to retrieve information all have important implications for progress in rehabilitation as well as for tasks of daily living.

In particular, CVLT memory profiles may aid clinicians to determine the rehabilitative needs of individuals. For instance, individuals exhibiting the Atypical and Subsyndromal patterns may benefit from pragmatic compensatory strategies (e.g., day planner, palm pilot). Given the neurocognitive difficulties with learning, memory, speed, and problem solving, individuals in the Frontal-striatal group may need to be monitored with respect to their daily activities, particularly with more demanding tasks such as medication management skills, as well as tasks requiring multiple components and effortful processing. Depending on the severity of neurocognitive disturbances, there may be a need for increased structure in daily routines and in the individual’s environment. It is also important that clinicians consider patient complaints (cognitive and mood) when implementing rehabilitative efforts, since increased complaints have been noted among individuals with minor cognitive motor disorder (MCMD) (Marcotte et al., 2001). Lastly, early delineation of learning and memory profiles may have important advantages for the individual with HIV-1 infection, including appropriate referrals (i.e., assessment, counseling, medication), compensatory lifestyle changes, and identification of at-risk individuals who may have difficulties carrying out daily tasks.

Of theoretical relevance, the present findings (i.e., memory subtypes and associated neuropsychological impairment) suggest involvement of both frontal and subcortical brain systems. In particular, the Frontal-striatal subtype’s neuropsychological profile including psychomotor slowing, reduced verbal fluency, decreased cognitive flexibility, poor problem solving, deficient organizational strategies for learning, and impaired retrieval of information is consistent with disruption of the dorsolateral prefrontal circuit (Cummings, 1993a; Lichter & Cummings, 2001). In addition, scores indicative of “moderate” depression in the Frontal-striatal subtype is also consistent with involvement of frontal-striatal circuitry, specifically the dorsolateral prefrontal and orbitofrontal circuits (Liotti & Mayberg, 2001; Mayberg, 1994).

Overall, the pattern of neuropsychological and mood symptomatology of the Frontal-striatal subtype is suggestive of disruption of multiple systems connecting frontal and subcortical regions of the brain. In particular, the findings indicate involvement of segregated circuits processing motor, cognitive, and emotional information (i.e., motor, dorsolateral prefrontal, and orbitofrontal circuits). Individuals in the Atypical and Subsyndromal subtypes (Cluster 2 and Cluster 3, respectively) exhibited diminished psychomotor speed but did not evidence symptoms of clinical depression, suggesting a more circumscribed deficit within the frontal-striatal circuitry (possibly affecting a single system such as the motor or dorsolateral prefrontal circuit). Lastly, the profile associated with the Normal subtype (Cluster 1) subtype suggests relatively preserved functioning of frontal-striatal circuits. Longitudinal studies are needed to determine which memory subtype(s) are likely to evidence decline in cognitive functioning and/or increase in depressive symptomatology. Based on the results of this investigation, a progressive weakening of the frontal-striatal system is predicted with increasing disease burden and associated neuropsychological impairment and mood disturbance. Neuroimaging and/or neuroanatomical studies would permit further clarification of the nature and extent of involvement of frontal-striatal circuitry.

The present investigation is not devoid of methodological limitations. In this regard, the issue of sample size deserves some comment. There is no exact rule regarding an adequate sample size for structural equation modeling. However, it is strongly recommended that the minimum number of cases should be 100 to 150 in order to decrease the likelihood of model estimation problems (Kline, 1998). Although our sample size of 154 appeared to meet these minimum requirements, replication with larger and more diverse samples is desirable to validate our findings.
While this study clarifies the nature and extent of memory disturbances in HIV-1 infection, the generalizability of our findings is limited to Caucasian, well-educated gay men who are medically stable, free of co-morbid neurological complications (e.g., CNS opportunistic infections, significant head trauma, seizure disorder), and who are not actively engaging in illicit drug or alcohol use. Further studies are needed to determine whether our findings generalize to other groups with HIV-1 infection including women, ethnic groups, and different at-risk populations (e.g., injection drug use, blood transfusions) and to individuals with HIV-1 infection with premorbid or confounding characteristics (e.g., neurological complications, substance abuse, psychiatric illnesses).

Future research should explore the robustness of these four memory subtypes over time and across different memory instruments. In addition, other hypothesized factor models should be evaluated in terms of their applicability to HIV-1 infection. Lastly, the predictive utility of memory subtypes via functional outcome measures (e.g., employment, disability, quality of life) will be an important avenue for future neuropsychological research. Of note, the morbidity and mortality risks associated with different memory profiles may prove to have relevance for this population of young to middle aged individuals.

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Theoretically derived CVLT subtypes


