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CLINICAL MEMORY SUBTYPES IN HIV-1 INFECTION:

A NOVEL APPROACH

by

Shemira Murji

A Dissertation
Submitted to the Faculty of Graduate Studies and Research
through the Department of Psychology
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ABSTRACT

The present study sought to delineate empirically derived memory subtypes using the California Verbal Learning Test (CVLT; Delis, Kramer, Kaplan, & Ober, 1987) in a sample of HIV-1 infected adults ($\underline{N}$ = 154). First, 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. Next, 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. The four memory subtypes differed with respect to both level and pattern of CVLT performance. In particular, learning efficiency and delayed recall variables appeared to be the most influential in differentiating between subtypes. The four memory subtypes were meaningfully related to neuropsychological functioning, and to some extent, depressive symptomology. Subtypes did not differ significantly with respect to subjective neurocognitive complaints and markers of HIV-1 disease. The utility of the "subcortical" versus "cortical" dichotomy previously used to characterize memory profiles of various neurological disorders is discussed. Overall, the present findings highlight the heterogeneity of memory profiles in HIV-1 infection and suggest a different interpretation of CVLT profiles than that provided in the manual.

DEDICATION

"Live to the fullest what lies deep in your heart,
and see how the miracles of life
unfold before you"

For Nina,

who continues to inspire and awe.

ACKNOWLEDGEMENTS

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CHAPTER I. INTRODUCTION AND LITERATURE REVIEW

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INTRODUCTION

Acquired Immunodeficiency Syndrome (AIDS) was first identified in 1981 as a condition of compromised cellular immunity resulting in the development of constitutional symptoms, severe infections, and cancers (Levy, Bredesen, & Rosenblum, 1985; Snider et al., 1983). In 1984, the retrovirus, HIV-Type 1 (HIV-1) was discovered as the primary cause of AIDS (Gallo et al., 1984). HIV-1 produces disease by gradually destroying T cells (specifically T4 or CD4+) which are involved in the body's immune function. This progressive depletion of T4 cells is the hallmark of HIV-1 infection (Grant & Martin, 1994; Nair & Schwartz, 1994). The typical AIDS patient has a CD4+ cell count below 200/mm^3. Such immunodeficiency levels are characterized by the development of severe infections or cancers (e.g., Kaposi's sarcoma) (Grant & Martin, 1994).

AIDS is a disease of the central nervous system as well as the immune system (CNS) (Grant & Heaton, 1990; Kaemingk & Kaszniak, 1989). HIV-1 can invade the brain soon after infection (Grant & Martin, 1994) and can have a profound and widespread effect on the nervous system (Levy & Bredesen, 1988). Neurological disturbances were described since the beginning of the epidemic. As clinical experience grew, it became apparent that neurological complications were common in HIV-infected individuals (McArthur, 1994). While opportunistic infections or tumors can affect the central nervous system, the majority of neurological disorders have been attributed to the effects of HIV itself (Levy et al., 1985; McArthur, Selnes, Glass, Hoover, & Bacellar, 1994; Snider et al., 1983). The most common neurological changes in HIV-1 infected patients include a constellation of cognitive, motor, and behavioural disorders, often referred to as the AIDS

dementia complex and more recently, as HIV-1-associated cognitive/motor complex (McArthur, 1994; Navia, Cho, Petito, & Price, 1986a; Navia, Jordan, & Price, 1986b). Dementia associated with HIV-1 infection is regarded as the most severe neurological manifestation of HIV-1 (Kelly, Grant, Heaton, Marcotte, & the HNRC Group, 1997).

Neuropsychological understanding of HIV-1 infection has greatly increased over the last decade, from early reports of cognitive decline in AIDS (Navia et al., 1986b) to large-scale multicentre investigations of the neurological, neuropsychological, and psychiatric features of HIV disease (e.g., Heaton et al., 1995; Maj et al., 1994; Miller et al., 1990). While the presence of cognitive impairment in the early stages of disease has been subject to much controversy, it is generally agreed that neuropsychological deficits are more common in advanced stages of infection. There is considerable variability in the clinical presentation of HIV-1 infection, with varying degrees of neuropsychological deficits. Abnormalities may range from subtle disturbances in cognitive functions (e.g., information processing speed, memory) to clinically apparent dementia, which is often characterized as a subcortical dementia (Grant & Atkinson, 1990). In general, the literature depicts two types of neurobehavioural disorders: HIV-related dementia and a milder neurocognitive disorder (Grant & Martin, 1994).

The focus of this review involves the neuropsychological features of HIV-1/AIDS in adults, with emphasis on milder forms of neurocognitive disturbances that are associated with HIV-1 infection. Milder neurocognitive disturbances frequently involve neuropsychological services for several reasons. First, they are more common than severe cognitive manifestations or HIV-related dementia. Second, since neurobehavioural abnormalities may be subtle in the early stages of infection, they are detected primarily by

neuropsychological testing (Heaton et al., 1996). Lastly, unlike dementia, which signals rapid decline, milder neurobehavioural dysfunction may last for prolonged periods of time, and can have an adverse effect on quality of life (Kelly et al., 1997).

This review begins with a brief overview of the epidemiological characteristics of HIV-1 infection/AIDS. Next, terminology and diagnostic criteria typically used to describe the physical and neuropsychological aspects of HIV-1 illness are covered. Following this, the natural history and clinical course of HIV-1 infection is described, with an emphasis on the cognitive sequelae of HIV-1/AIDS. While the precise etiology of HIV-related brain impairment is unknown, current theories of the pathogenesis of HIV-1 are based on neurological and neuropathological investigations. Hence, the major findings from these studies are presented.

The remaining sections mainly review the neuropsychological characteristics of HIV-1 infection. Attention will be given to neuropsychological investigations of HIV-1 infected individuals at various stages of infection, particularly early-stage HIV-1 illness. In addition, the clinical significance of neuropsychological impairment will be explored. Neurological and immunological correlates of neuropsychological functioning are also considered. Next, the relationship between depression and neuropsychological functioning will be reviewed since mood disturbances are commonly seen in persons afflicted with the HIV-1 illness. Subjective cognitive complaints and their relationship with neuropsychological and mood factors will also be covered. Since memory disturbance is a frequent complaint of individuals infected with HIV-1, studies assessing metamemory in HIV-1 infection are described in detail. Lastly, classification research involving HIV-related memory functioning is discussed, with emphasis on subgrouping

individuals according to their learning and memory profiles. The heterogeneity in neuropsychological presentation in HIV-1 infection and the clinical utility of delineating qualitatively distinct memory subtypes is highlighted. The delineation of empirically derived memory subtypes in HIV-1 infection is the focus of the current thesis.

Epidemiology

The scope of HIV-1 infection is vast: an estimated 2 million persons worldwide have AIDS (Health Canada, 1999), and more than 12 million are thought to be infected with HIV-1 (Grant & Martin, 1994). In Africa alone, more than 700,000 AIDS cases have been officially reported (Health Canada, 1999). According to the Centers for Disease Control (CDC, 1997), more than one million people the United States are HIV-seropositive (HIV+). Despite encouraging trends showing a decline in the number of AIDS-related deaths (CDC, 1997)[1], HIV-1 infection is one of the leading causes of death in the United States among persons aged 15 to 44 (Ventura, Peters, Martin, & Maurer, 1997). In Canada, present estimates suggest that there are 43,347 HIV+ individuals and more than 16,000 victims of AIDS. As of December 1998, approximately 11,427 Canadians have died from AIDS (Health Canada, 1999). Initially recognized in young homosexual men and intravenous drug users, the spread of HIV-1 by heterosexual contact, blood transfusions, and in utero transmission from mother to infant has contributed to the growing number of cases (McArthur, 1994). The number of women

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[1] In the United States, a decline in the number of deaths due to AIDS was seen in 1996 compared to 1995, suggesting that antiretroviral therapies were having a beneficial effect on disease progression (CDC, 1997).

testing positive for HIV-1 is also increasing, with women currently accounting for nearly 22% of all adult HIV-positive cases (Health Canada, 1999).

With respect to neuroepidemiology, HIV-related neurological disorders are due to the direct or indirect effects of HIV-1 (Levy et al., 1985). An estimated one to two-thirds of AIDS patients will develop clinically obvious signs of neurological disturbance (McArthur et al., 1994). HIV-related dementia, the most severe CNS complication of HIV, is thought to develop in up to 30% of individuals with advanced HIV-1 disease (Heaton et al., 1995; McArthur et al., 1993). Approximately one third of nondemented individuals may present with varying degrees of neuropsychological impairment (Grant & Heaton, 1990). However, the precise incidence and prevalence rates of cognitive impairment in HIV-1 infection remain unknown. In fact, there is significant variability in reports of the degree and frequency of neurocognitive disturbances associated with HIV-1 infection. (This is addressed in the neuropsychology section of the review.)

Nomenclature and Diagnostic Criteria

Inconsistencies in terminology and definitions for HIV-related CNS manifestations have led to considerable confusion, both among health care professionals and the lay public (Hinkin, Castellon, van Gorp, & Satz, 1998). Various diagnostic labels have been used interchangeably. Navia et al. (1986b) first introduced the term "AIDS dementia complex" (ADC) to emphasize the importance of progressive cognitive decline associated with AIDS. The term "complex" underscored the constellation of motor and/or behavioural disturbances that frequently accompany the cognitive deficits in the syndrome. Other labels used synonymously with ADC, have included "HIV encephalopathy", "AIDS encephalopathy", "subacute encephalitis", and "HIV-1-

associated cognitive/motor complex" (Berger, 1988; Brew, 1993; Hinkin et al., 1998). Moreover, adding to the confusion, AIDS dementia complex has also been used in reference to less severe cognitive impairment associated with HIV disease (e.g., Brew, 1993; Price & Brew, 1988). In an attempt to develop consensus nomenclature and criteria for HIV-1 infection, standard diagnostic criteria and classification schemes have been proposed by various organizations. These are described below.

American Academy of Neurology.

The American Academy of Neurology AIDS Task Force (AAN, 1991) developed consensus diagnostic criteria to help objectify the various HIV-1 associated neurologic conditions. Importantly, they separated HIV-1-associated cognitive/motor complex (also commonly referred to as AIDS dementia complex) into two categories on the basis of severity (see Table 1 below). The severe manifestations include: (A) HIV-1-associated dementia complex, which emphasizes cognitive/behavioural dysfunction, and (B) HIV-1-associated myelopathy, in which motor disturbances (e.g., lower-extremity weakness, paraparesis) are predominant.

The label HIV-1-associated minor cognitive/motor disorder is used to depict a mild form of the HIV-1 syndrome. The major difference between the severe and minor forms of this complex is the degree of impairment in activities of daily living or work performance. Individuals with minor cognitive/motor disorder are able to adequately perform most tasks of daily living and exhibit mild difficulties with only the most demanding aspects of work or day-to-day functioning. In contrast, the person with HIV-1-associated dementia complex will show obvious impairment in activities of daily living.

Table 1. Proposed Nomenclature for HIV-1-Associated Central Nervous System Disorders and Terms Currently in Use for the Same Disorders[1]

HIV-1-associated cognitive/motor complex
AIDS dementia complex

I. *Severe manifestations*

    A. HIV-1-associated dementia complex

        Subacute encephalitis

        HIV encephalopathy

        AIDS-related dementia

    B. HIV-1-associated myelopathy

        HIV encephalopathy

II. *Mild manifestations*

        HIV-1-associated minor cognitive/motor disorder

        HIV-1-associated neurocognitive disorder

        HIV-associated neurobehavioral abnormalities

[1] Proposed nomenclature is shown in boldface.

Note. From AAN (1991).

Important from a neuropsychological perspective, the AAN classification scheme is useful for depicting the cognitive manifestations of HIV-1 infection. The diagnoses of HIV-1-associated dementia complex (HIV-1 dementia) and HIV-1-associated minor cognitive/motor disorder are of particular interest to the neuropsychologist. Briefly, HIV-1 dementia is diagnosed when a person demonstrates deficient performance in at least two cognitive domains (e.g., attention, memory, language/speech), and the degree of impairment is severe enough to cause disturbances in work or daily activities. This condition is also characterized by abnormalities in motor function (e.g., gait disturbances, weakness) or behavioural changes (e.g., apathy, emotional lability, impaired judgement). The diagnosis of minor cognitive/motor disorder requires the person to exhibit deficits in at least two cognitive, motor, or behavioural domains (e.g., mental slowing, incoordination, irritability). However, these disturbances do not hinder the individual

from performing the most demanding daily tasks of living. The criteria for HIV-1-associated cognitive/motor complex are listed in Appendix A.

An attempt was made to incorporate the AAN terms in this review. For example, the commonly used term AIDS dementia complex is also referred to as HIV-1-associated cognitive/motor complex. However, in many cases, it was difficult to use standardized terms because information regarding the precise stage of HIV-1 illness was unclear in the reviewed studies. It is important that classification systems and diagnostic criteria are standardized and that researchers adhere to them in order to prevent conflicting and contradictory results. For instance, one important source of the inconsistencies found in the neuropsychological literature is likely due to different researchers using different criteria to define severity of HIV-1 illness as well as HIV-related cognitive disturbances.

Centers for Disease Control (CDC).

In 1987, the CDC published diagnostic criteria for HIV-related encephalopathy (AAN term: HIV-1-associated cognitive/motor complex). In addition, the CDC provided a system for staging of the disease, mainly for surveillance and classification purposes. This staging scheme consisted of four groups: group 1 contained individuals with short-lived medical symptoms (flu-like illness) appearing soon after infection; group II included carriers of HIV-1 that had no medical symptoms (i.e., asymptomatic); group III was also mainly symptom-free, with the exception of progressive generalized lymphadenopathy (enlarged lymph nodes); and group IV was comprised of persons with AIDS or AIDS-related complex, including those with constitutional symptoms (e.g., fever, diarrhea, weight loss) or major opportunistic infections. This system was criticized for ill-defining key terms as well as for its failure to consider level of immunosuppression (i.e., CD4

count) or non-specific symptoms (e.g., fatigue) prior to the onset of AIDS (Hinkin et al., 1998).

The CDC revised its classification system for HIV-1 infection (CDC, 1992) to include both a marker of physical status (asymptomatic, symptomatic, or AIDS-defining illnesses or infections) and degree of immunosuppression on the basis of CD4 T-cell count per microliter of blood (>500 cells/mm^3, 200-499 cells/mm^3, or <200 cells/ mm^3). Therefore, the revised CDC classification scheme categorizes individuals on the basis of clinical conditions associated with infection and CD4 counts. Briefly, category A describes individuals who have no medical symptoms (asymptomatic) or are minimally symptomatic (e.g., persistent generalized lymphadenopathy). Category B includes patients with mild physical symptoms or "minor" opportunistic infections (e.g., oral candidiasis, herpes zoster). Individuals in category C exhibit more serious infections or AIDS-defining illnesses (e.g., *Pneumocystis carinii* pneumonia, Kaposi's sarcoma or lymphoma, wasting syndrome). In general, individuals in higher categories (i.e., C) tend to be more symptomatic compared to those in lower categories (i.e., B or A). Moreover, individuals are likely to develop severe infections or cancers once their T4 cell count drops below 200/mm^3 (Grant & Martin, 1994). However, this new staging system also addresses the observation that medically symptomatic patients can have high CD4 counts and asymptomatic individuals can have low CD4 counts (Hinkin et al., 1998). The CDC 1993 classification system, which is commonly used in the staging of physical status in HIV-1 infection, is shown in Table 2.

Table 2. Centers for Disease Control and Prevention (1993) Revised Classification
System for HIV-1 infection, and Expanded AIDS Surveillance Case Definition for
Adolescents and Adults

CD4+ T-cell categories	Clinical Categories		
	(A) Asymptomatic	(B) Symptomatic	(C) AIDS-defining illnesses/infections
(1) ≥500/L	A1	B1	C1
(2) 200-499/L	A2	B2	C2
(3) <200/L	A3	B3	C3

Note. Clinical categories C1-C3, B3, and A3 constitute the expanded AIDS surveillance
case definition. From CDC (1992).

American Psychiatric Association.

The Diagnostic and Statistical Manual of Mental Disorders (DSM-IV; American

Psychiatric Association, 1994) has also included HIV-1 dementia into its nosology of

psychiatric illnesses. In order to meet the diagnostic criteria for dementia due to HIV-1

disease, patients must exhibit learning/memory impairment in addition to disturbance in

at least one other cognitive domain (e.g., language, motor, executive function). Further,

evidence should indicate that neuropsychological deficits are directly related to HIV-1

infection and must result in marked impairment in day-to-day functioning.

Clinical Features

Clinically, there can be considerable variability in the individual presentation of

HIV-1 infection, with some individuals exhibiting minimal dysfunction for prolonged

periods of time, while others show progressive decline over the course of infection (Price

& Brew, 1988). In general, HIV-1-associated cognitive/motor complex is thought to

progress in a series of stages, from early signs of brain involvement (e.g., mild

forgetfulness) to global dementia, paraplegia, mutism, and incontinence (Hinkin et al.,

1998; Navia et al., 1986a, 1986b). Once a person has been infected, antibodies to HIV-1

are detected several weeks to several months after exposure (i.e., seroconversion) (Grant

& Atkinson, 1990). Soon after infection, some individuals may report flu-like symptoms, headaches, and sensitivity to light (photophobia). After these symptoms diminish, there is a symptom-free period (asymptomatic infection) which ranges from months to years. On average, the asymptomatic phase of the infection may last as long as 10 years before symptoms arise (Hinkin et al., 1998). During this phase there is progressive depletion of CD4 T-cells, which results in lowered cell-mediated immunity. Consequently, persons with HIV-1 infection are increasingly susceptible to developing secondary opportunistic infections, tumors, or other neurological diseases (Grant & Martin, 1994; Kelly et al., 1997). Usually, medical complications emerge when an individual's CD4 count falls to 400 or below (healthy persons tend to have CD4 counts above $1000/mm^3$) (Grant & Atkinson, 1990). In general, the life expectancy of individuals with HIV-1 infection is variable (Grant & Martin, 1994). However, with recent advances in medical treatment, persons with HIV-1 infection are living longer. New medications used in combinations such as highly active antiretroviral therapies (HAART) appear to be effecting in slowing progression of HIV-1 infection (Kalichman, Ramachandran, & Ostrow, 1998).

Currently, the literature on HIV-1 infection describes two types of neurobehavioural disturbances that are differentiated on the basis of severity: HIV-1 dementia and minor cognitive/motor disorder. (This distinction is in accord with the AAN [1991] classification scheme.) The clinical profile of HIV-1 dementia closely resembles that of a subcortical dementia, with prominent cognitive and psychomotor slowing, attention and concentration difficulties, and poor recall of information (Brew, 1993; Heaton et al., 1996). Language, with the exception of slowed speech and hypophonia (diminished volume of speech), is spared until more advanced stages of the illness (AAN,

1991; Heaton et al., 1996). Motor problems associated with HIV-1 dementia include unsteady gait, leg weakness, and tremor. Often, behavioural disturbances such as apathy, irritability, loss of libido, and social withdrawal are present (AAN, 1991; Navia et al., 1986b). An estimated 10 to 30% of individuals with AIDS will eventually develop a dementing illness (Grant & Atkinson, 1990; Maj et al., 1994; McArthur et al., 1993). Typically, HIV-1 dementia develops relatively late in HIV-1 infection, with onset of dementia being uncommon before the development of other AIDS-defining illnesses (McArthur et al., 1993). With an annual incidence of dementia estimated at 7% (McArthur et al., 1993) and a median survival of 6 months (McArthur et al, 1993; Navia et al., 1986a), HIV-1 dementia is undoubtedly one of the most serious CNS complications of HIV-1 infection.

The more common neurobehavioural complication of HIV-1 infection, termed minor cognitive/motor disorder (MCMD) is considerably less severe than HIV dementia. According to American Academy of Neurology (1991) criteria, MCMD is diagnosed when at least two cognitive deficits are present but the impairment does not adversely affect performance of daily tasks. Most prominent cognitive disturbances include poor attention, slowed information processing, and problems with learning new information (Grant & Martin, 1994). There is little agreement regarding the prevalence of MCMD in earlier stages of infection. (The issue of neuropsychological impairment in asymptomatic HIV-1 infection has been subject to considerable debate in the literature. This issue will be discussed in following sections of the review.) Presently, it is unclear whether MCMD and HIV-1 dementia are similar entities at differing points along the same continuum, or whether they reflect separate phenomena altogether (AAN, 1991; Kelly et al., 1997).

Some evidence suggests that patients with milder forms of HIV-1 infection do not necessarily develop more severe cognitive disturbances or dementia (e.g., Mauri, Sinforiani, Muratori, Zerboni, & Bono, 1993; Saykin et al., 1991, Selnes et al., 1992).

Generally, disturbances in cognition tend to increase as the disease progresses into its symptomatic phase. Neuropsychologically, patients tend to show minimal dysfunction in the asymptomatic course of the infection, although a subset of patients demonstrate evidence of cognitive impairment (White, Heaton, Monsch, & the HNRC Group, 1995). With respect to cognitive changes and their impact on activities of daily living, the prototypical clinical course in HIV-1 infection is illustrated in Table 3 below.

Table 3. Stages of Cognitive Impairment in HIV-1-Associated Cognitive/Motor Complex

Stages	Cognitive Sequelae	Activities of Daily Living
Subclinical	loss of concentration, attentional disturbances, mild forgetfulness, self-reported cognitive inefficiency[a]	unimpaired
Mild	forgetfulness, psychomotor slowing, work performance is affected	difficulty with more challenging daily tasks (e.g., finances)
Moderate	memory is impaired	assistance required to perform more demanding household tasks (e.g., cooking), may be unable to work or drive
Severe	global cognitive impairment	complete dependence on others for most, if not all, activities of daily living
End-stage	severe global dementia	bedridden, mute, incontinent

Note. Compiled from Hinkin et al. (1998); Navia et al. (1986b).
[a]Psychiatric difficulties, notably depression, should be considered in early self-reports of cognitive disturbances.

Neurological involvement.

It has been shown that HIV-1 can invade the central nervous system (CNS) early in the course of infection (Navia et al., 1986a). Evidence supporting the early infiltration of the virus into the CNS has come from the detection of HIV-1 in the cerebrospinal fluid (CSF) of patients shortly after infection (McArthur et al., 1989; Sönnerborg, von Stedingk, Hansson, & Strannegård, 1989). In addition, studies have demonstrated that cognitive impairment is the earliest detectable CNS manifestation of HIV-1-associated cognitive/motor complex (Navia & Price, 1987; Saykin et al., 1988; Selnes et al., 1991).

However, despite the virus' early penetration of the CNS, neurological examinations are usually normal in these patients (McAllister et al., 1992; McArthur et al., 1989; Selnes et al., 1991; Stern et al., 1991). Neurological complications tend to develop later in the course of the disease and are more frequently associated with immune deficiency, constitutional symptoms, and systemic opportunistic infections (McArthur et al., 1994). For instance, neurological sequelae, such as extrapyramidal signs and frontal release signs, tend to become increasingly evident with disease progression, particularly among HIV-1 infected individuals with low CD4 cell counts (Marder et al., 1995).

The nervous system appears to be susceptible to both direct and indirect effects of the HIV-1 virus. Neurological disorders can result from the direct involvement of HIV-1 in the brain or indirectly via the consequences of compromised immunity (Berger, 1988). Opportunistic infections, the major cause of neurological disturbance in the latter category, occur more frequently in immunocompromised patients. Generally, CNS opportunistic processes develop once CD4 count has fallen below 200/mm^3 (McArthur, 1994; Price, 1994). The most common opportunistic infections affecting the CNS are

toxoplasmosis, cryptococcal meningitis, cytomegalovirus (CMV) encephalitis, and progressive multifocal leukoencephalopathy (PML) (McArthur, 1994).

Neuropathology of HIV-1 Infection/AIDS

The vast majority of persons dying of AIDS will show neuropathological abnormalities on postmortem examination (Navia et al., 1986a; Vago, Trabattoni, Lechi, Cristina, & Budka, 1990). Cerebral atrophy with sulcal widening and ventricular dilation is the most common anatomical change in persons with AIDS (Navia et al., 1986a; Poutiainen et al., 1993; Price, 1994; Vago et al., 1990). Pathology of subcortical structures and white matter has also been documented in the brains of AIDS patients. In their second landmark study, Navia and colleagues (1986a) performed autopsies on 70 AIDS patients (the majority of whom were demented). Microscopic anomalies were predominant in the white matter and subcortical gray regions, with relative sparing of the cortex. White matter changes were observed, including ill-defined pallor (most common finding), multifocal rarefaction, and vacuolation. Multinucleated giant cells, macrophages, lymphocytes, and reactive astrocytosis were found in the basal ganglia and pons in a subgroup of patients with dementia. Navia et al. (1986a) concluded that the pathological substrate of the AIDS dementia complex (AAN term: HIV-1-associated cognitive/motor complex) and the progressive cognitive decline seen with the disease resembled other subcortical dementias, thus providing validity for the concept of subcortical dementia in HIV disease. (The "subcortical" versus "cortical" distinction in HIV-1 infection is addressed in latter sections of the review.)

Neuroimaging investigations have provided valuable information regarding anatomical and functional changes associated with HIV-1 infection/AIDS. Both

computerized tomography (CT) and magnetic resonance imaging (MRI) investigations have revealed diffuse cerebral atrophy, widened cortical sulci, and enlarged ventricles in patients with HIV-1 infection/AIDS (Elovaara et al., 1990; Grant et al., 1987; Navia et al., 1986a; Raininko et al., 1992). White matter abnormalities are more readily demonstrated on MRI than CT, appearing as ill-defined areas of increased signal intensity, particularly in the periventricular white matter, on T2-weighted images (Berger, 1988; Elovaara et al., 1990; Hesselink, Jernigan, & Heindel, 1994). Unlike other neurological illnesses, such as multiple sclerosis, frank demyelination of the white matter does not appear to be a neuropathological hallmark of HIV-associated dementia complex (Power et al., 1993).

Generally, the severity of brain atrophy and white matter changes tend to be more pronounced at late stages of HIV-1 infection (Elovaara et al., 1990; Raininko et al., 1992). Imaging studies of brain changes in early HIV-1 infection seem to be inconclusive (see McAllister et al., 1992; McArthur et al., 1989; Raininko et al., 1992). For instance, MRI abnormalities have been found with equal frequency in infected individuals and healthy controls (McArthur et al., 1989), suggesting that radiological findings are not due solely to HIV-1 infection. Moreover, some HIV-1 infected patients show normal CT and MRI scans even late into the disease (Hinkin et al., 1998). Given the lack of correspondence between structural neuroimaging and clinical findings, it has been suggested that the main utility of these measures is in detecting secondary opportunistic infection (e.g., lymphomas) (Hinkin et al., 1998; McArthur et al., 1994) and in ruling out other possible causes of CNS disturbance (Berger, 1988).

Functional neuroimaging techniques such as positron emission tomography (PET) and single-photon emission computerized tomography (SPECT) provide an index of how the brain functions. Studies utilizing SPECT have largely found reduced blood flow in both early and late stages of AIDS (cited in Hinkin et al., 1995). PET studies have demonstrated that the basal ganglia, thalamus, and temporal areas of the brain are affected in AIDS (van Gorp et al., 1992) with relative hypermetabolism of thalamus and basal ganglia in nondemented AIDS subjects (Hinkin et al., 1995; van Gorp et al., 1992). In overt dementia, there is diminished metabolism (hypometabolism) of the temporal lobes, the area actively involved in memory. Evidence exists in support of the hypothesis that HIV-1 initially exerts its influence on subcortical structures (e.g., basal ganglia) and then affects the cortex as the disease worsens (Hinkin et al., 1995).

CSF analyses have yielded important insights into the pathogenesis of AIDS. CSF abnormalities, including elevated white blood cell and protein levels, are found with high frequency in HIV-seropositive subjects, including those in the early, asymptomatic stages of infection (Collier et al., 1992; McArthur et al., 1989; Poutiainen et al., 1993). The presence of HIV-1 in the CSF, however, does not necessarily indicate the presence of HIV-1 in the brain (Price, 1994) and the clinical significance of this finding requires further study. CSF markers indicative of cellular immune activation (beta-2-microglobulin [$\beta_2 M$]), neopterin acid) and viral load (HIV RNA), have been implicated in the etiology of neuronal dysfunction in HIV-1 infection (Ellis et al., 1997b; McArthur et al., 1992, 1997; Sönnerborg et al., 1989). In addition, neurotoxic effects of cytokines (i.e.,

tumor necrosis factor [TNF-α]), quinolinic acid[2], and glycoprotein 120 (gp120)[3] have also been linked to neuronal injury and neuronal loss (Price, 1994). Specifically, it has been postulated that infected macrophages secrete toxic products, thereby causing neuronal dysfunction in an indirect manner (Grant & Heaton, 1990, Navia et al., 1986a; see Price, 1994 for a comprehensive review of the pathogenesis of HIV-1-associated cognitive/motor complex).

Despite the advancement in diagnostic and laboratory methods, the neuropathogenesis of HIV-1-associated cognitive/motor complex remains obscure. Several methodological limitations and observations appear to challenge current understanding of the pathological role of HIV-1 in the CNS. For instance, the propensity for HIV-1 to exclusively infect macrophages (and related microglia), with the absence of productive infection in neurons, astrocytes, or oligodendroglia has been puzzling with respect to the cause of neuronal dysfunction (Price, 1994). Moreover, clinicopathological correlations are poor. The precise relationship between HIV-1 infection, brain dysfunction, and clinical findings is vague (McArthur et al., 1994; Price, 1994). Further, despite the presence of neuropathological and CSF abnormalities in the majority of HIV-1 infected individuals, not all develop progressive dementia. Conversely, clinically demented persons may exhibit insignificant neuropathological changes (see McArthur, 1994).

There are no neurological signs that are pathognomonic for HIV-1-associated cognitive/motor complex (AAN, 1991). As Grant and Heaton (1990) suggest, it is

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[2] Quinolinic acid is a neurotoxin acting at N-methyl-D-aspartate (NMDA) receptors (Price, 1994).

[3] Gp 120 is a viral envelope protein that can bind firmly with CD4 cells (Greene, 1993).

perhaps best to seek convergent lines of evidence, utilizing measures that are reliable, sensitive, and specific to CNS disease, to elucidate the natural course of HIV-1 infection. One such approach for inferring the presence of brain dysfunction is neuropsychological testing.

Neuropsychology of HIV-1 Infection

Neuropsychological services provide a valuable resource for the diagnosis and treatment of HIV-1 infected individuals. Specifically, neuropsychological assessment has been used to identify and describe cognitive, affective, and psychomotor changes at various stages of HIV-1 infection (Saykin et al., 1991). Neuropsychological efforts are largely directed to early stages of illness since subtle/subclinical cognitive impairment during the long asymptomatic phase of HIV-1 illness is the most common form of HIV-associated morbidity (Kelly et al., 1997).

Several key issues/questions have been examined with respect to the neuropsychological features of HIV-1 infection. The issue of whether HIV-1 infected individuals without AIDS exhibit neuropsychological impairment has received a great deal of attention in the literature. Large-scale and longitudinal studies have examined the nature and extent of cognitive deficit at various stages of infection. There has also been growing curiosity regarding the predictive utility of early neuropsychological deficits. Do cognitive disturbances associated with asymptomatic illness, or more commonly, symptomatic infection, eventually progress to dementia? The real life significance of neuropsychological dysfunction (e.g., employment) is of great importance despite having received relatively scarce attention in the literature. Relationships between neuropsychological functioning and immunological, medical, and neurological aspects of

HIV-1 infection have been considered in an attempt to clarify the pathological substrates of HIV-1 disease. The influence of depression on cognition remains an important topic of investigation. In addition, investigators have explored the utility of subjective cognitive complaints for assessing HIV-related brain impairments. In particular, more recent research involving the relationship between actual and self-perceived memory dysfunction has increased understanding of metamemory in HIV-1 infection. Lastly, investigators have attempted to identify qualitatively distinct learning and memory profiles in HIV-1 infection. The classification of HIV-1 infected individuals into empirically derived memory subtypes and the clinical utility of this subgrouping approach is considered in the present investigation.

Asymptomatic HIV-1 infection.

While there is a general consensus that neurobehavioural impairment is a fairly common concomitant of advanced HIV-1 illness, the issue of neuropsychological dysfunction in the early stages of HIV-1 infection has been subject to considerable controversy. In fact, findings in the literature vary widely. Some studies support the notion of cognitive impairment during the asymptomatic stages of HIV-1 infection. For example, Grant et al. (1987) found a 44% impairment rate in asymptomatic HIV+ subjects (compared to 9% in the control group) on summary measures of neuropsychological impairment. Bornstein et al. (1993b) reported a twofold increase in the prevalence of cognitive impairment in asymptomatic patients compared to controls. In a well-controlled study of 20 asymptomatic (CDC 1987 groups I and II) HIV+ homosexual men, Perry, Belsky-Barr, Barr, and Jacobsberg (1989) also found evidence of mild impairment in a subset of infected men. Stern and associates (1991) observed slight

but significant differences between asymptomatics and controls on tests of attention, memory, executive function, and abstract reasoning. Lunn et al. (1991) found significant differences between asymptomatic and seronegative control subjects on measures of verbal memory and psychomotor speed. Bornstein and his group (1992) corroborated these results with a larger study of 131 HIV+ asymptomatic and 74 HIV-negative (HIV-) men using an extensive neuropsychological battery.

In contrast, several investigations have failed to document significant cognitive impairment in HIV-infected asymptomatic subjects (e.g., Franzblau et al., 1991; Gibbs, Andrews, Szmukler, & Mulhall, 1990; Goethe et al., 1989; Janssen et al., 1989; McAllister et al., 1992; Poutiainen et al., 1993). For example, Janssen et al. (1989) did not find significant differences between asymptomatic and symptomatic seropositive subjects using both a screening and comprehensive neuropsychological test battery. Poutiainen et al. (1993) did not find that cognitive performance differentiated patients at early infection from that of controls. Their conclusion was that "cognitive deficits of subjects at early infection are slight and clinically insignificant" (p. 92). Several reports from the Multicenter AIDS Cohort Study (MACS) have also indicated no differences between medically asymptomatic HIV+ and HIV- individuals (McArthur et al., 1989; Miller et al., 1990; Selnes et al., 1990). Others suggest that confounding factors such as head injury, substance abuse, developmental difficulties, and previous psychiatric illness account for the cognitive deficits seen in asymptomatic stages of HIV-1 infection (see Claypoole et al., 1993; Wilkins et al., 1990).

The controversy regarding neuropsychological impairment in asymptomatic HIV-1 infection seems to stem, at least in part, from a number of methodological issues. These

include the following: (a) limited statistical power due to small group sizes (e.g., Poutiainen, Iivanainen, Elovaara, Valle, & Lähdevirta, 1988); (b) lack of standardized diagnostic criteria for defining subject groups; (c) inconsistencies in the use of neuropsychological tests; (d) differences in the sensitivity of tests; (e) use of population norms to gauge impairment[4] (e.g., Collier et al., 1992); (f) different methods used to define neuropsychological impairment (i.e., clinical ratings, cutoffs of 1, 1.5, or 2 standard deviation [SD] below control group means); (g) failure of selection criteria or data analyses to control for potential confounds such as psychological distress (e.g., anxiety and depression), substance abuse, and preexisting neurological conditions (e.g., McAllister et al., 1992), and lastly; (h) the absence of self-reported data (i.e., subjects' own evaluations of their cognitive abilities).

Skoraszewski, Ball, and Mikulka (1991) conducted a meta-analysis of previous studies in order to integrate the disparate results. They noted mild to moderate deficits in visual-motor, auditory, and abstraction functions, with relative sparing of verbal abilities for asymptomatic subjects relative to controls. Consistent with these findings, literature reviews of previous HIV-1-related neuropsychological research have generally concluded that HIV-1 infected individuals without AIDS display only mild deficits in various neuropsychological domains (see Kaemingk & Kaszniak, 1989; Perry, 1990).

In a more thorough consideration of the ongoing debate, White et al. (1995) reviewed 57 neuropsychological studies of asymptomatic HIV-1 infection (published between 1987 and 1994). Several factors were considered closely in their summary of the

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[4] The reliance on test norms to establish impairment levels, in place of a well-matched HIV seronegative control group, is deemed an inferior approach since HIV subject groups are generally not comparable to the population at large (Bornstein, 1994; Ingraham, Bridge, Janssen, Stover, & Mirsky, 1990).

literature including sample size, test battery type, test battery size, mode of infection (e.g., sexual contact, intravenous drug use), and method of data analysis. White et al. found that 32% of studies reported significant differences in performance between HIV-positive asymptomatic and seronegative control groups, whereas 47% of the studies did not report significant group differences. Perhaps more telling is the difference in reported rates of neuropsychological impairment in the asymptomatic (35%) and control (12%) groups. The authors also found that among several variables, only mode of infection and test battery size seemed to influence study outcomes. With respect to the latter, the results of the review suggested that larger, more comprehensive test batteries, are more likely to capture neuropsychological deficits in asymptomatic subjects compared to small test batteries. Based on the results, the authors concluded that there is clear evidence of a "modest" increase in the risk for neuropsychological impairment in medically asymptomatic HIV-1 infected individuals and that decrement in performance is more readily detected if a relatively comprehensive neuropsychological test battery is employed.

Collectively, there appears to be emerging consensus that a subgroup of HIV+ patients without AIDS will experience mild to modest neuropsychological impairment. These data indicate that HIV-1 infection can produce subtle cognitive abnormalities early in the course of infection. Given that impairment may be subtle and variable, measures that are both specific and sensitive to cognitive changes in asymptomatic stages of infection are warranted. Tests of attention, speed of information processing, and memory are recommended by the National Institute of Mental Health (NIMH) for their reported

sensitivity to cognitive changes associated with early HIV-1 infection (Butters et al., 1990).

Neuropsychological functioning at various stages of HIV-1 infection.

Numerous questions remain unsolved with respect to the nature and prevalence of neuropsychological deficits at different disease stages of HIV-1 infection. Several investigations have examined cognitive function at various phases of HIV-1 infection, from early asymptomatic stages to the development of the full AIDS syndrome[5]. Despite discrepancies regarding cognitive impairment in the early stages of the illness, there appears to be general agreement as to which cognitive functions are susceptible to the effects of HIV-1 infection. Briefly, these include sustained attention/concentration (Krikorian, Wrobel, Meinecke, Liang, & Kay, 1990; Maj et al., 1994; E. M. Martin et al., 1992a), divided attention (E. M. Martin et al., 1995; Sorensen, E. M. Martin, & Robertson, 1994), verbal and nonverbal memory (Bornstein et al., 1993b; Poutiainen et al., 1993; Stern et al., 1991, 1995), learning/encoding of new information (Heaton et al., 1995; Miller et al., 1990), verbal fluency (Saykin et al., 1988), psychomotor speed (Bornstein et al., 1993b; Miller et al., 1990; Skoraszewski et al., 1991; Tross et al., 1988), speed of information processing (Grant et al., 1987; Heaton et al., 1995; Miller & Wilkie, 1994), and selected executive or frontal system functions (Heaton et al., 1995; Krikorian et al., 1990). In contrast, visual-spatial abilities (Saykin et al., 1988; Stern et al., 1991)

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[5] For reviews on the neuropsychological features of HIV-1 infection, refer to Grant and Martin (1994), Hinkin et al. (1998), and Kelly et al. (1997).

and expressive and receptive components of language are usually preserved until more advanced stages of the disease (Hinkin et al., 1998)[6].

There appears to be a general trend towards increased neuropsychological deficiency as HIV-1 infected persons progress to more medically symptomatic stages of infection (e.g., Bornstein et al., 1993b; Grant et al., 1992; Heaton et al., 1995; Skoraszewski et al., 1991; Tross et al., 1988). This notion of progressive neuropsychological impairment with advanced stage of infection has received much support from both cross-sectional and longitudinal investigations. Large-scale studies, in particular, have provided important insights into the neuropsychological abnormalities associated with HIV-1 infection. These include the Multicenter AIDS Cohort Study (MACS) (Miller et al., 1990), the WHO Neuropsychiatric AIDS Study (Maj et al., 1994), and the HIV Neurobehavioral Research Center (HNRC) 500 study (Heaton et al., 1995). A review of salient studies follows.

A well-conducted study of neuropsychological performance at all stages of HIV-1 infection by Bornstein and colleagues (Bornstein et al., 1993b) will be described in some detail in order to familiarize the reader with the general methodological and conceptual issues involved in HIV-1 research. The study sample consisted of 233 HIV-1 infected homosexual/bisexual men who met CDC 1993 criteria (asymptomatic [$\underline{n}$ = 133], mildly symptomatic [$\underline{n}$ = 61], AIDS [$\underline{n}$ = 39]), and 77 HIV-negative control subjects. Subjects were excluded if they had a history of intravenous drug use, head injury (loss of consciousness exceeding one hour), or any other neurological diseases. Enzyme-linked

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[6] See Hinkin et al. (1998) for a concise review of neuropsychological domains affected and spared in HIV-1 infection.

immunosorbant assay (ELISA) and Western blot were performed to confirm HIV status. Absolute CD4 cell counts were calculated from white blood cell count and lymphocyte percentages.

The neuropsychological test battery consisted of traditional measures for assessing a broad range of cognitive abilities (e.g., general intellectual abilities, memory, attention and concentration, executive function, language, and psychomotor functioning). In addition, reaction time tasks (i.e., simple reaction time, choice reaction time, Go/No Go task) were used due to their purported sensitivity to early HIV-related cognitive impairment. To define impairment on each test, Bornstein et al. used a criterion of 1 SD or more below the mean of the control group. Moreover, they rated subjects' overall performance as impaired if six or more (of a total of 15) tests were rated as impaired. This relatively relaxed criterion for impairment was developed in order to detect subtle disturbances in cognition. Greater prevalence of neuropsychological impairment was observed in subjects with more advanced disease. Prevalence of overall cognitive impairment was increased twofold for asymptomatic subjects and fourfold in symptomatic subjects relative to controls. The same results were obtained using a more stringent criterion of impairment (1.5 SD below control group mean). Measures of verbal memory, psychomotor speed, and reaction time were indicators of early neuropsychological dysfunction whereas frontal lobe deficits (e.g., cognitive flexibility) were characteristic of later stages of disease progression. Memory impairment was common across all stages of infection. This study clearly demonstrates that neuropsychological abnormalities tend to become more prevalent with advanced stages of HIV-1 infection. Also, the pattern of deficits seems to differ according to disease stage.

The Multicenter AIDS Cohort Study (MACS) was designed as an epidemiological study of the natural history of HIV-1 infection. A total of 4,954 homosexual/bisexual men were recruited from four U.S. cities (Baltimore, Chicago, Los Angeles, and Pittsburgh) and were assessed every six months since 1984. Assessments included medical examinations, immunological testing, and structured interviews. Subsamples of the full MACS cohort (769 HIV-, 727 asymptomatic HIV+, 84 symptomatic HIV+ subjects) were enrolled in the neuropsychological study. Miller et al. (1990) did not find any statistically significant differences between asymptomatic HIV+ and HIV- groups, suggesting low prevalence of neuropsychological abnormalities among asymptomatic HIV-1 infected homosexual men. In contrast, symptomatic HIV+ subjects were impaired on measures of psychomotor speed and dexterity (Grooved Pegboard, Symbol Digit Modalities Test, Trail Making Test) and verbal learning and memory (Rey Auditory Verbal Learning Test). Miller and associates speculated that HIV-related cognitive disturbances tend to occur as the disease progresses into its symptomatic stage, with the onset of constitutional symptoms or AIDS-defining illnesses. It is important to note that the MACS protocol utilized a screening battery of six neuropsychological tests. While the authors attest to the sensitivity of these measures, it is likely that this battery was not sufficiently comprehensive to detect subtle cognitive impairments among asymptomatic HIV-1 individuals.

The WHO Neuropsychiatric AIDS Study (Maj et al., 1994) also had, as one of its primary goals, the investigation of neuropsychological abnormalities in asymptomatic and symptomatic HIV-seropositive individuals. However, unlike many investigations that used mostly white, well-educated, male homosexual men in Westernized countries, the

WHO Study was conducted on a cross-cultural sample from five different geographic areas predominantly affected by the HIV-1 epidemic (i.e., Zaire, Kenya, Thailand, Germany, and Brazil). Not surprisingly, the prevalence of neuropsychological deficits was significantly higher among symptomatic HIV+ subjects relative to controls in all five countries. Most frequently affected cognitive domains included sustained and selective attention, fine motor control, verbal memory, and cognitive flexibility. Neuropsychological disturbances correlated with difficulties in daily living activities in all geographic contexts. Asymptomatic HIV+ subjects performed significantly worse than controls on neuropsychological tests in only two centres (Zaire, Kenya). Interestingly, low-education was correlated with overall neuropsychological impairment for asymptomatic HIV+ men in the two African sites. The authors postulated that an inadequate education may reduce "cerebral reserve" (redundancy of cerebral networks), thereby affecting neuropsychological functioning. Daily living activities of asymptomatic subjects were not adversely affected in any centre.

The HIV Neurobehavioral Research Center (HNRC) study led by Heaton et al. (1995) is a well-conducted, multidisciplinary investigation of neuropsychological functioning of 500 HIV+ and HIV- individuals. Using CDC 1993 criteria, four subject groups were formed: HIV- controls (n = 111), CDC-A (n = 249) subjects were asymptomatic or had generalized lymphadenopathy, CDC-B (n = 86) subjects were mildly symptomatic (e.g., minor opportunistic infections, constitutional symptoms, and/or peripheral neuropathies), and CDC-C (n = 54) subjects had a history of AIDS-defining illnesses such as *Pneumocystis carinii* pneumonia or Kaposi's sarcoma. Prevalence of neuropsychological impairment at different stages of HIV-1 infection seemed to reflect

the expected increase with each progressive stage of infection (i.e., 30.5%, 44.2%, and 55.6% for CDC A, B, and C groups, respectively). CDC-C subjects displayed deficits on the majority of neuropsychological tests, most consistently on measures of abstraction and motor abilities. Medically asymptomatic subjects (CDC-A) displayed mild impairments in areas of attention, speed of information processing, and learning efficiency. Confidence in these findings is strengthened as they are based on a large sample using a comprehensive battery that assesses all major neuropsychological domains suggested by the NIMH Workshop (Butters et al., 1990). Moreover, the impairment rate of the asymptomatic group (30.5%) closely resembles that reported by White et al. (1995) in their review of neuropsychological studies of medically asymptomatic subjects (35%). However, Heaton et al. highlight that despite increased neuropsychological dysfunction in asymptomatics compared to non-infected controls, a large majority (approximately 65 to 70%) of HIV+ asymptomatic individuals did not display deficits in neuropsychological functioning.

The HNRC 500 study by Heaton et al. (1995) has also increased understanding of the neurologic and psychiatric correlates of HIV-1 infection. Detailed analysis of the data failed to support the hypothesis that neuropsychological impairment was due to mood disturbances (i.e., depression and anxiety), past or present substance use, or constitutional symptoms (e.g., headache, fever, fatigue). Both treatment with antiretroviral medication (i.e., zidovudine [AZT]) and duration of treatment were unrelated to neuropsychological impairment. In contrast, MRI measures of central atrophy, markers of elevated immune response (i.e., CSF $\beta_2 M$), and abnormal neurological findings were related to neurocognitive disturbance.

In short, Heaton et al. (1995) concluded that neuropsychological impairment is evident in asymptomatic individuals and increases with advancement of the disease. They also noted that the pattern of deficits is consistent with a subcortical profile, with involvement of frontostriatal brain systems. Lastly, they reported that neuropsychological impairment cannot be attributed to mood disturbance, medical symptoms, or recreational drug or alcohol use.

In sum, cross-sectional large cohort studies have consistently shown that neuropsychological impairment accompanies progressive worsening of HIV-1 disease. Of note, psychomotor slowing appears to be the hallmark of HIV-1 neurobehavioural dysfunction. However, the notion of cognitive impairment during the asymptomatic period is not a consistent finding. Both the MACS and the WHO study failed to find cognitive impairment in asymptomatic HIV-1 infected subjects despite their large sample sizes. It is important to highlight that a significant amount of variability in study findings can be attributed to methodological differences across investigations.[7] For instance, both the MACS and WHO study used a relatively small test battery and stringent criteria for impairment (e.g., 2 or more SD below the mean for seronegative controls). Combined, these factors decrease the likelihood of detecting subtle CNS deficits, leading to a finding of low prevalence of neurobehavioural abnormalities in the asymptomatic stage of infection. In contrast, Heaton and associates (1995) and Bornstein et al. (1993b) found evidence of mild cognitive impairment in asymptomatic subjects utilizing fairly

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[7] For a review of methodological problems inherent in neuropsychological HIV research, the reader is referred to Bornstein (1994) and Grant and Heaton (1990).

comprehensive assessment procedures and impairment criteria sensitive to early CNS involvement.

<u>Longitudinal studies.</u>

The issue of cognitive change over the course of infection is of significant interest to clinicians and researchers working with HIV-1 infected individuals. Longitudinal studies of HIV-1 infection have permitted a closer look at the evolution of HIV-1-associated cognitive impairment. Decline in neuropsychological functioning may occur in some persons at all stages of infection, with the highest rates of decline in more advanced phases of the illness (Kelly et al., 1997). Overt cognitive impairment is more likely to develop with CD4 counts below $200/mm^3$. (Heaton et al., 1995; Stern et al., 1995). However, some individuals with milder forms of HIV illness do not become progressively worse, and in some cases, show improvement on neuropsychological tests (Ellis et al., 1997a; Koralnik et al., 1990), possibly due to practice effects (Selnes et al., 1990).

To date, research studies employing longitudinal designs have yielded mixed findings with respect to cognitive decline during the asymptomatic stage of HIV-1 infection. Methodological inconsistencies mentioned earlier in reference to cross-sectional investigations (e.g., sample size, subject selection, stringent criteria, test battery size) are also applicable here.

Selnes et al. (1990) conducted a prospective analysis of a subsample of 238 asymptomatic HIV-1 infected men and 170 uninfected controls from the MACS. Follow-up at 1.5 years revealed no significant differences in neuropsychological performance between seropositive and seronegative subjects, suggesting that progressive cognitive

decline does not occur during the asymptomatic phase. In a 3-year follow-up of 60 asymptomatic HIV-1 infected subjects, Mauri et al. (1993) demonstrated that mild cognitive impairment in early HIV does not necessarily progress to more severe neuropsychological dysfunction. Similarly, Saykin et al. (1991) showed that minor neuropsychological abnormalities at baseline were not predictive of cognitive decline at 18-months in 13 patients with persistent generalized lymphadenopathy. These findings illustrate the neuropsychological stability of asymptomatic individuals.

In contrast, others have suggested that early cognitive decline is predictive of further cognitive deterioration and a more rapid progression to AIDS. For example, Villa et al. (1996) reported that timed psychomotor tests (e.g., Trail Making Test) and memory tasks involving learning, 'active' monitoring, and retrieval of information (i.e., Digit Span backward, Rey Auditory Verbal Learning Test) were the most sensitive to early HIV-related cognitive decline. Bornstein, Nasrallah, Para, Whitacre, and Fass (1993a) compared 69 HIV-1 infected men who remained asymptomatic over a 12-month period with a control group of 52 uninfected men. Compared to controls, a significantly higher proportion of HIV-1 infected men were classified as abnormal on neuropsychological testing at follow-up (13.5% versus 29% respectively). Interestingly, subjects whose status changed to abnormal at follow-up showed significantly worse performance at baseline testing than controls on measures of information processing, verbal learning and memory, and reaction time. These findings are consistent with other reports implicating learning efficiency, reaction time, and information processing as among the earliest cognitive functions to be affected (Bornstein et al., 1992, Heaton et al., 1995; E. M. Martin, Sorensen, Edelstein & Robertson, 1992b).

A few investigators have explored disease progression in symptomatic HIV-1 disease. Addressing the issue of cognitive decline after progression to AIDS, Selnes and colleagues (1995) conducted a large prospective study of 138 HIV-1 infected MACS participants. They found little decline in cognitive performance before the development of AIDS in nondemented subjects. In contrast, after diagnosis of AIDS, notable decline was observed only in the area of psychomotor speed, with little change in other areas of neuropsychological functioning. The authors concluded that, "in the absence of dementia, there is no evidence to suggest a continuum of cognitive decline in individuals with AIDS" (Selnes et al., 1995, p. 274). These results are comparable to another prospective study of patients with AIDS-related complex (ARC) (i.e., CDC 1987 group IV patients) (Dunbar, Perdices, Grunseit, & Cooper, 1992). No significant differences in neuropsychological performance were observed between patients who progressed to AIDS and non-progressors. While neuropsychological changes were not related exclusively with progression from ARC to AIDS, both seropositive groups (i.e., progressors and non-progressors) showed deterioration in attention and motor domains compared to controls. However, results of this study should be interpreted with caution due to the small number of ARC subjects who progressed to AIDS ($\underline{n}$ = 15) and those who did not ($\underline{n}$ = 19).

Stern et al. (1995) prospectively followed a cohort of 168 (113 HIV+ subjects, 55 HIV- controls) homosexual and bisexual men over a 4.5 year period, with semi-annual assessments. HIV+ subjects displayed significant memory disturbances compared to controls at all visits. In addition, relative to the general improvement over repeated testing, the trend towards improvement in attention and language was significantly

reduced in the HIV+ group. Advanced HIV-1 infection (defined by CD4 count below 200 cells/mm^3) was associated with poorer neuropsychological performance in the attention, memory, and executive function domains. A more rapid decline in attention, language, and executive test performance was found in the group of men who died than those who did not die. Neurological abnormalities were significantly correlated with neuropsychological decline. The results of this study confirm initial baseline observations (Stern et al., 1991) indicating that HIV-related neurological and neuropsychological abnormalities are associated with more rapid disease progression and increased risk of mortality (Stern et al., 1995).

In an investigation of HIV-1 dementia, McArthur and colleagues (1993) conducted a prospective evaluation of 492 homosexual men with AIDS (MACS participants), including 64 men who developed dementia. The diagnosis of dementia was based on information from a history, neuropsychological testing, and neurological assessment. The onset of dementia was infrequent prior to another AIDS-defining illness, and generally occurred in the late stages of disease. Overall, 15% of the cohort developed dementia after AIDS. The incidence of dementia among AIDS survivors was 7% per year. Patients diagnosed with dementia had a median survival of 6 months. Risk factors associated with dementia included low body weight, anemia, more constitutional symptoms before AIDS, and older age at AIDS. Baseline immunological status (e.g., CD4+ count) and medication (i.e., AZT) usage, were not predictive of dementia.

In sum, longitudinal investigations of HIV-related cognitive changes corroborate cross-sectional findings suggesting that neuropsychological functioning is adversely affected in later stages of the disease. In addition, disease progression appears to be

related to more rapid change in neuropsychological functioning. In earlier stages, there is considerable variability in presentation, with the majority of infected individuals showing no signs of decline. However, similar to cross-sectional observations, a subset of infected individuals may exhibit neuropsychological impairment that tends to worsen over time.

Clinical Significance of Neuropsychological Impairment

The functional significance of neuropsychological impairment is certainly an important avenue for HIV-1 research. Difficulties with recalling information, maintaining focus, and organization, for example, can have significant implications for everyday tasks. HIV-1 infection has become more of a chronic disease because medical care and drug treatments are permitting patients to live longer. Neuropsychologists can play a vital role in assessing and treating cognitive disturbances, early on in the course of disease before such deficits result in significant morbidity for the individual afflicted with HIV-1 infection.

Morbidity.

Poor neuropsychological performance in the early stages of HIV-1 infection may signal increased risk of vocational difficulties. Albert et al. (1995) compared 123 asymptomatic HIV-1 infected individuals with 84 HIV-seronegative control subjects. They found that asymptomatic individuals were almost three times more likely to encounter work disability, defined by considerable reductions in work time (i.e., working less than 20 hours/week for two consecutive years), than control participants. The authors reported that neuropsychological deficit at baseline was responsible for increased risk of work disability in a subset of asymptomatic HIV-1 infected subjects. Asymptomatic subjects who showed intact neuropsychological performance did not have an elevated risk

of work disability. Covarying for medical status or CD4 count at the time of disability did not reduce the risk associated with cognitive impairment. Better indices of work disability (i.e., sensitive measures of reduced work capacity) would have strengthened the validity of these study findings.

Heaton and colleagues (1994) found considerably higher rates of unemployment in a group of HIV-1 infected men who evidenced neuropsychological impairment compared to unimpaired subjects. Since most of the subjects were in earlier stages of HIV-1 disease (i.e., CDC 1987 groups II/III), unemployment was unlikely due to constitutional symptoms/medical illnesses. Also, emotional status did not differentiate between employed and unemployed subjects. Subjects with mild neuropsychological deficits who remained employed were more likely to have self-perceived difficulties at work (e.g., decreased competence) than neuropsychologically unimpaired subjects. According to the authors, these findings suggest that cognitive disturbances typically seen in HIV-1 infection are "clinically significant" as they interfere with everyday functioning.

A later study by Heaton and his group (Heaton et al., 1996) confirmed these findings. They reported that neuropsychologically impaired subjects had higher rates of unemployment, complaints of job-related difficulties, and reduced work potential (as demonstrated by performance on standardized work samples) compared to neuropsychologically normal controls. While the use of objective measures to assess subjects' job functioning is a clear improvement from their previous study, Heaton et al.'s (1996) findings are considered to be preliminary given the small group sizes.

The above-mentioned studies investigating the relationship between employment and neuropsychological impairment used a predominantly asymptomatic cohort. Van

Gorp and colleagues (van Gorp, Baerwald, Ferrando, McElhiney, & Rabkin, 1999) corroborated these earlier findings with a group of symptomatic (mainly AIDS) participants. After controlling for the effects of age, CD4 count, and physical limitations, unemployed participants evidenced poorer performance on neuropsychological tests than those individuals who were employed. These authors reported that neurocognitive impairment, specifically learning efficiency and executive functioning (set-shifting, cognitive flexibility, response inhibition), were important predictors of employment. Clearly, more investigations of the clinical significance – the impact of neuropsychological disturbance on everyday activities and quality of life – are warranted.

<u>Mortality.</u>

Other investigations have focused on mortality risks associated with neurocognitive impairment. It is well established that survival rates for individuals with HIV-1 dementia are markedly lower compared to nondemented HIV-1 infected individuals (McArthur et al., 1993). The severe immunodeficiency that occurs during late stages of HIV-1 infection is a strong predictor of mortality, often preceded by various phenomena associated with a compromised immune system, such as opportunistic infections (Mayeux et al., 1993). Less is known concerning the prognostic significance of milder neurocognitive disturbances.

Mayeux et al. (1993) found increased risk of death among asymptomatic and symptomatic HIV-1 infected men with neuropsychological impairment. Approximately two-thirds of the 18 men who died had abnormal neuropsychological performance at baseline, compared to about one third of men who survived. This increased risk of death remained after adjusting for important variables such as CD4 lymphocyte count,

hemoglobin concentrations, and age. Using a large cohort of HIV-seropositive individuals ($\underline{n}$ = 414), Ellis et al. (1997a) also demonstrated that neurocognitive impairment is a significant risk factor for death, corroborating Mayeux et al.'s findings. Specifically, subjects meeting the criteria for HIV-1-associated minor cognitive/motor disorder (MCMD) were more than twice as likely to die compared with neuropsychologically unimpaired subjects. In addition, cognitive impairment was also predictive of death among subjects with advanced HIV-1 disease (i.e., those with AIDS-defining illnesses, low CD4 counts).

Sacktor and colleagues (1996) examined the prognostic utility of tests of psychomotor speed (Trail Making Test, Symbol Digit Modalities Test) in relation to dementia, AIDS, and death. Two hundred and ninety-one HIV-1 infected homosexual men (from the MACS) were followed for nine years with semi-annual assessments. The results were striking: HIV+ individuals with sustained psychomotor slowing (i.e., within a one year period) had a significantly increased risk for dementia, AIDS, and death (five, 2.4, and two times, respectively) compared to HIV+ subjects without a decline in psychomotor performance. A strength of this study was that subjects served as their own controls, with an individual's performance being compared to his previous test scores and not to population norms. This study highlights the importance of a screening measure of psychomotor speed in early HIV-1 infection, particularly when larger neuropsychological batteries are not feasible.

The above findings attest to the clinical relevance and predictive utility of neurocognitive disturbances in HIV-1 infection. Of importance, risk of morbidity and mortality appears to be elevated among HIV-1 infected individuals who display mild

cognitive impairment in early stages of disease. The identification of neuropsychological deficits, such as psychomotor slowing, as risk factors does not necessarily imply causation. However, neuropsychological disturbances may signal increased vulnerability to HIV-1 disease. It has been hypothesized that cognitive impairment in some individuals is indicative of greater host susceptibility, greater virulence of the HIV-1 strain, or both (Ellis et al., 1997a).

Correlates of Neuropsychological Functioning

To further clarify the issue of neuropsychological functioning in HIV-1 infection, neurological, immunological, and medical variables have been considered. Empirical investigations of the relationship between neuropsychological functioning and neurological abnormalities have yielded inconsistent findings. Many researchers have observed relatively normal neurological and neuropsychological findings in HIV-1 infected patients with no or minor symptoms (e.g., Collier et al., 1992; Franzblau et al., 1991; Grant et al., 1992; Janssen et al., 1989; McAllister et al., 1992; McArthur et al., 1989; Stern et al., 1991). In addition, clinical (neuropsychological) correlates of radiological abnormalities appear to be lacking in the asymptomatic HIV-1 population (e.g., Collier et al., 1992; Janssen et al., 1988; McAllister et al., 1992).

In contrast, evidence supporting neurological involvement of HIV-1 in asymptomatic or minimally symptomatic infection has included findings of subtle impairment on neuropsychological tests (e.g., Bornstein et al., 1992; Perry et al., 1989; Saykin et al., 1988), electrophysiological abnormalities (Koralnik et al., 1990; Ollo, Johnson, & Grafman, 1991), increased response latencies on reaction time measures (Bornstein et al., 1992, 1993b; Law et al., 1995; E. M. Martin et al., 1992a, 1992b), and

subjective complaints of cognitive difficulties (Beason-Hazen, Nasrallah, & Bornstein, 1994; Mapou et al., 1993).

More consistent is the finding that neurological and neuropsychological changes are more readily detected as the illness progresses to advanced stages (e.g., AIDS), with the presence of systemic complications and declining immunologic status (Grant et al., 1992; Heaton et al., 1995; Janssen et al., 1989). In addition, with progression of the disease, structural changes (e.g., increased atrophy) in the brain have been associated with neuropsychological deficits (Elovaara et al., 1990; Hall et al., 1996), including memory problems (Poutiainen et al., 1993) and slowed information processing speed (Levin et al., 1990). Also, PET studies have demonstrated a link between brain functioning (increased metabolism of the basal ganglia) and neuropsychological findings (motor and psychomotor disturbances) (Hinkin et al., 1995; van Gorp et al., 1992). Functional and anatomical correlates of neuropsychological test performance lend support to the notion that cognitive deficits correspond to underlying brain changes and do not reflect the effects of nonspecific factors (e.g., anxiety, stress, etc.) (Grant et al., 1992).

Immunologic variables such as CD4 lymphocytes or CSF constituents (i.e., white blood cell count, protein level, HIV antibody, immunoglobulin G [IgG] levels) have been examined as indicators of disease. In general, immunologic parameters (i.e., absolute CD4 cell counts) do not seem to correlate with level of neuropsychological dysfunction (Collier et al., 1992; Elovaara et al., 1992; Franzblau et al., 1991; Janssen et al., 1988, 1989; Maj et al., 1994; Miller et al., 1990; Saykin et al., 1988; Villa et al., 1996). Some researchers, however, have reported significant but low correlations between neuropsychological and immunological functioning (Bornstein et al., 1991; Dunbar et al.,

1992; Stern et al., 1991). For example, rate of CD4 lymphocyte decline has been linked to poor performance on neuropsychological tasks, particularly memory and complex reaction time measures (Bornstein et al., 1991). In addition, higher CSF viral load is associated with increased risk of neuropsychological impairment, but only in individuals who are significantly immunocompromised (CD4 count less than 200) (Ellis et al., 1997b). It is likely that studies employing subjects in early stages of infection will fail to detect relationships between immunologic or virologic indicators of disease due to a restricted range in the level of immunosuppression (Bornstein et al., 1991). Moreover, it has been suggested that neuropsychological functioning is independent of immunological status in the early stages of infection and that the relationship becomes more apparent with progressive immunodeficiency in advanced illness (Dunbar et al., 1992).

The effects of physical symptoms on neuropsychological functioning have received relatively little attention. However, it is conceivable that clinical symptoms such as fatigue, fever, weight loss, or diarrhea may interfere with test performance. Of note, fatigue is one of the most common complaints of HIV-1 infected individuals (Heaton et al., 1995). The few studies examining this issue have reported that constitutional symptoms do not significantly influence neuropsychological test scores (Collier et al., 1992; Heaton et al., 1995; Selnes et al., 1995). However, mild constitutional symptoms (weight loss, fatigue, night sweats) have been documented in patients who demonstrated abnormal neuropsychological test performance compared to those who performed in the normal range (Janssen et al., 1988). Also, in the large-scale HNRC 500 study, the association between fatigue and neuropsychological impairment approached significance (Heaton et al., 1995). Therefore, the question of whether physical discomfort has a

notable impact on neuropsychological performance is unresolved and awaits further research.

The beneficial effects of antiretroviral therapy (e.g., zidovudine, dideoxyinosine, dideoxycytidine, stavudine) on neuropsychological functioning has not been well documented (Bornstein et al., 1992; Heaton et al., 1995; Schmitt et al., 1988; Selnes et al., 1995). There is suggestion that antiretroviral medication has a neuroprotective effect against HIV-related neurocognitive disorders (Ellis et al., 1997b). However, while antiretroviral medications may temporarily slow disease progression, the long-term efficacy of such agents may be negligible (Grant & Atkinson, 1990). (The reader is referred to Schmitt, Dickson, and Brouwers [1994] for a review of neuropsychological outcomes of antiretroviral therapy, particularly AZT.)

With respect to newer antiretroviral therapies, preliminary evidence appears to be promising. In particular, the data suggest that HAART may be effective in improving neuropsychological function in HIV-1 infected individuals (Ferrando et al., 1998; Tozzi et al., 1999). Combination antiretroviral therapy has also been associated with improvements in psychomotor speed performance in HIV-1 infected men (Sacktor et al., 1999). (For a review of recent antiretroviral treatments [e.g., combination therapy] for HIV-1 infection/AIDS, see Weller [1999].)

Depression

Depression is a common complaint of HIV-1 infected individuals. Approximately 10 to 20% of infected individuals in the asymptomatic phase of HIV-1 illness will experience an episode of depression or anxiety, or both (Grant & Atkinson, 1990). Psychological distress tends to lessen over time following knowledge of seroconversion

(Bix et al., 1995; Fell et al., 1993). However, adjustment reactions, adjustment disorders, and depression, may be seen with the emergence of HIV-related medical complications or during the key transitory stages of illness (e.g., discovery of seropositive status, diagnosis of AIDS) (Fell et al., 1993; Grant & Atkinson, 1990).[8] Studies using standardized diagnostic assessments have not found high rates of current psychiatric disorders such as depression and anxiety in HIV-1 infected individuals. In contrast, lifetime prevalence of major depression and substance use disorders are found to be higher than in the general population (Summers et al., 1995; Williams, Rabkin, Remien, Gorman, & Ehrhardt, 1991). In particular, two major risk groups, homosexual men and intravenous drug users have a higher prevalence of psychological difficulties (e.g., depression, personality disturbances) than low risk groups (e.g., heterosexuals). Therefore, investigations of psychological sequelae of HIV-1 infection should account for elevated base rates in persons at risk for HIV-1 infection (Grant & Atkinson, 1990), before ascribing changes in mental well-being directly to HIV-1.

Another cautionary point regarding depression and HIV-1 infection is that both major depressive disorder and organic mood disorder may be seen in patients with HIV-1 infection (Bialer et al., 1991). That is, depressive symptoms may result from a reaction to a life-threatening illness or from direct effects of the virus (Fell et al., 1993). Support for the latter has come from evidence of frontal-subcortical involvement in depression (Cummings, 1993b). Thus, controlling statistically for depression may be inappropriate since depression may be directly related to HIV-1 infection of the CNS (Worth et al.,

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[8] For reviews on HIV-associated psychological and psychiatric complications, see Bialer, Wallack, and Snyder (1991), Miller and Riccio (1990), and Tross and Hirsch (1988).

1993). Moreover, differentiating between psychological reactions to HIV-1 infection and mood disturbance due to organic factors will have important implications for treatment.

It is well established that depressed mood can result in cognitive disturbances such as poor concentration, slowness of thought, memory problems, and decision-making difficulties (Cassens, Wolfe, & Zola, 1990). Since depression is a common complaint of HIV-1 infected individuals, it is reasonable to question the relationship between depression and neuropsychological status. Many studies have generally concluded that depression does not result in a significant increase in neuropsychological dysfunction (Bornstein et al., 1993c; Claypoole et al., 1998; Collier et al., 1992; Harker et al., 1995; Hinkin et al., 1992; Janssen et al., 1988; Kovner et al., 1989; Lunn et al., 1991; McAllister et al., 1992; Poutiainen et al., 1993). While these studies have been criticized for flaws in their methodology (e.g., brief test batteries, small sample size, lack of control groups), well-controlled studies have also failed to find significant associations between depression and neuropsychological disturbances (Bix et al., 1995; Goggin et al., 1997; Grant et al., 1993; Heaton et al., 1995). Further, assessment of depression, whether via self-report such as the Beck Depression Inventory (BDI; Beck & Steer, 1993; Beck, Ward, Mendelson, Mock, & Erbaugh, 1961) or structured diagnostic interview, tend to yield the same results (Bornstein et al., 1993c; Goggin et al., 1997; Pace, Rosenberger, Nasrallah, & Bornstein, 1993). Also, with the exception of transition points in the course of infection, depression does not seem to vary as a function of illness severity (e.g., Bix et al., 1995; Bornstein et al., 1993c; Hinkin et al., 1992). Together, these results imply that neuropsychological impairment and depression have independent associations to HIV-1 illness.

Nevertheless, the relationship between neuropsychological performance and depression is not straightforward. A minority of studies have observed decrements in cognitive performance in depressed HIV-1 infected individuals (Kalechstein, Hinkin, van Gorp, Castellon, & Satz, 1998; Selnes et al., 1991, 1995; Stern et al., 1991). Neuropsychological functions reported to be susceptible to elevated levels of depression include psychomotor speed and verbal memory (Hinkin et al., 1992; Selnes et al., 1995), visuomotor sequencing ability (Bornstein et al., 1993b), procedural memory (Kalechstein et al., 1998), and global neuropsychological performance (Stern et al., 1991). It is possible that disruption of frontostriatal systems, which connect the prefrontal cortex and the basal ganglia, may manifest in mood disturbances and psychomotor abnormalities (Cummings, 1993a, 1993b).

The multifactorial nature of depression is another complicating factor in the relationship between depression and neuropsychological impairment. A potential flaw of self-report measures of depression is the inclusion of items assessing both affective and somatic aspects of depression. Endorsement of the latter may result in ambiguity, as such items are not only reflective of depressive symptomatology but can also coincide with the physical symptoms of HIV-1 illness (e.g., fatigue, sleep difficulties, weight loss). There is evidence to suggest that elevated BDI scores in symptomatic individuals are due to higher scores on the somatic, but not the cognitive-affective component of the instrument (Harker et al., 1995). Therefore, separation of the BDI items into affective-cognitive (first 13) and somatic (last 8) items may add further clarity with respect to the relationship between depression and neuropsychological functioning.

Neurocognitive Complaints

Subjective cognitive complaints are a common reason for referral for neuropsychological assessment (e.g., Rourke, Halman, & Bassel, 1999a). Many individuals (up to 52%) with HIV-1 infection report difficulties with cognitive functions, particularly disturbances with memory, concentration, and slowed thought processes (Maj et al., 1994; Mehta et al., 1996; Wilkins et al., 1991). However, the significance and predictive value of these neurocognitive complaints remains unclear. Neuropsychological services, while proving useful in the clinical management of HIV-1 infection, are not always provided due to diminishing health care resources. As a result, clinical decisions regarding the extent of HIV-related brain impairments as well as treatment considerations are frequently based solely on patients' self-reported neurocognitive complaints (Hinkin et al., 1998; Rourke et al., 1999a). However, the assumption that self-reports are valid and reliable indicators of HIV-related brain functioning is not warranted. Accuracy or self-appraisal of cognitive functioning is currently a debatable topic in HIV-1 research.

In a study of 77 HIV-positive subjects (40 asymptomatic, 29 ARC, and 8 AIDS), Wilkins et al. (1991) reported that while cognitive and motor complaints were common, these complaints were associated with psychiatric symptoms (as assessed by DSM-III criteria) but not with neuropsychological variables. However, in a small proportion of subjects (16%), motor complaints were related to actual motor dysfunction. Similarly, van Gorp and colleagues (van Gorp et al., 1991) failed to find a significant relationship between actual and self-perceived neuropsychological deficits in a large sample of asymptomatic HIV+ (n = 233) and HIV-negative (n = 256) individuals. Instead, they reported that cognitive complaints, as assessed by the Cognitive Failures Questionnaire

(CFQ; Broadbent, Cooper, FitzGerald, & Parkes, 1982) were positively correlated with level of depression. It is plausible that the neuropsychological screening battery (five tests) employed in this study lacked sufficient sensitivity to detect subtle changes in cognition.

However, Moore et al. (1997) utilized a comprehensive neuropsychological test battery (16 tests) but also failed to find a significant relationship between subjective complaints and cognitive functioning in a cohort of 92 symptomatic HIV-1 infected homosexual/bisexual men. Varying the criterion for neuropsychological impairment (i.e., subtle or significant impairment) did not alter the outcome of the study. That is, even subjects with more substantial cognitive impairment did not endorse more difficulties on a self-report questionnaire assessing cognitive and affective complaints relative to subjects who performed within normal limits. In addition, the study revealed a positive association between self-reported difficulties and depressive symptoms (as assessed by the BDI and Hamilton Depression Rating Scale). These results are consistent with previous studies of predominantly asymptomatic subjects (van Gorp et al., 1991; Wilkins et al., 1991), and suggest that subjective complaints seem more predictive of depression than actual neuropsychological impairment.

Contrary to these studies, several groups of investigators have shown that subjective complaints are significantly associated with neuropsychological test performance. For example, Stern et al. (1991) compared 124 HIV-positive men (at varying stages of disease) with 84 HIV-negative control subjects. They observed that cognitive complaints (assessed by a structured interview format) were not only more frequent in HIV-1 infected men but that these complaints correlated with objective test

performance. However, these investigators did not explore the influence of depression on self-reported cognitive problems.

Beason-Hazen et al. (1994) investigated the relationship between subjective complaints and neuropsychological performance in 133 asymptomatic HIV+ and 80 HIV-negative homosexual/bisexual men. Subjects were administered the Current Symptoms Questionnaire (CSQ) to assess perceived symptoms in physical, emotional, and cognitive domains. Utilizing an extensive neuropsychological battery as well as measures of reaction time, they found that measures of information processing speed and reaction time were strongly correlated with subjective general physical symptoms. Further, while complaints were also related to depression, the relationship between subjective complaints and neuropsychological performance could not be accounted for by depression or CD4 level. The authors suggested that physical complaints early in the course of infection may predict the subsequent development of neuropsychological abnormalities.

Mapou et al. (1993) used a semi-structured interview to evaluate cognitive, motor, and affective complaints in a group of 79 (mostly asymptomatic) HIV+ and 27 HIV-individuals. Self-reported complaints (regardless of domain) were highly correlated with impairments in reaction time, psychomotor function, and memory. These findings show that subjects who complain of difficulties are more likely to have actual difficulties than those who do not complain. Moreover, disease stage did not influence the results. According to the authors, self-reported difficulties may reflect subcortical motor and cognitive difficulties most commonly seen in HIV-1 disease, rather than impairments in specific neuropsychological domain (e.g., language, visuospatial). In addition, complaints

were also related to symptoms of depression (BDI) and anxiety. However, mood disturbances were independent of neuropsychological performance. Based on these results, Mapou and associates suggested that subjective complaints may reflect either neuropsychological impairment (i.e., subcortical involvement) or mood disturbance.

Rourke and colleagues (1999a) replicated the findings of Beason-Hazen et al. (1994) and Mapou et al. (1993) with 100 HIV-1 infected adults at various stages of infection (12 asymptomatic, 41 mildly symptomatic, and 47 with AIDS). In order to assess subjective neurocognitive complaints, they employed the Patient's Assessment of Own Functioning (PAOF) Inventory (Chelune, Heaton, & Lehman, 1986). The PAOF is a 33-item self-report instrument that assesses the individual's self-perceptions regarding memory, language, sensory-perceptual, and higher level cognitive and intellectual abilities. The results indicated that subjective complaints were related to both depressive symptoms (BDI) and neuropsychological measures of attention and working memory, psychomotor efficiency, and verbal learning. Of note, however, regression analyses indicated that depression symptoms accounted for the majority of variance in neurocognitive complaints (i.e., ranging from 75% to 88%) while psychomotor efficiency (WAIS-R Digit Symbol) accounted for only 12 to 25 % of the total variance in subjective complaints. Clinical implication of these findings is that patients complaining of difficulties with memory or other cognitive functions should be assessed for both mood disturbance/increased depressive symptomatology as well as neuropsychological functioning (specifically in the areas of psychomotor speed, attention, and working memory).

Poutiainen and Elovaara (1996) found a strong association between select neuropsychological functions (i.e., verbal memory, cognitive speed and flexibility) and subjective complaints (i.e., cognitive, motor) in symptomatic ($\underline{n}$ = 27), but not asymptomatic ($\underline{n}$ = 58) HIV-1 infected subjects. These associations were not due to psychiatric status or elevated depression scores (BDI). The authors concluded that subjective complaints may reflect actual cognitive impairment in symptomatic infection, whereas other explanations are likely for asymptomatic individuals. This finding is contrary to other studies reporting an association between subjective complaints and cognitive performance in asymptomatic subjects (e.g., Beason-Hazen et al., 1994). One main source of this discrepancy is that the latter used more sensitive indices (i.e., reaction time, information processing) of subtle cognitive disturbances that are frequently associated with early-stage HIV-1 infection.

Methodological differences have been cited as an explanation for the divergent findings. For example, subject characteristics as well as methods used to assess subjective complaints (e.g., structured/semi-structured interviews) and depression (e.g., BDI, Hamilton Rating Scale for Depression), have varied considerably. More importantly, the majority of investigations have assumed a linear relationship between subjective complaints and neuropsychological test performance. Therefore, one probable explanation for the discrepant findings in the literature is that researchers have failed to consider the existence of subgroups of HIV-1 infected patients who vary in the accuracy of self-reported cognitive difficulties. In this approach, two broad subgroups are defined: persons who are "accurate" (i.e., neurocognitive complaints correspond well with objective neuropsychological data) and those who are "inaccurate" (i.e., poor

concordance between subjective complaints and neuropsychological performance) in their self-appraisals (Rourke, Halman, & Bassel, 1999b).

More recently, a few investigators have focused on a subgroup approach to examine actual versus self-reported memory difficulties in HIV-1 infection (Hinkin et al., 1996; Rourke et al., 1999b). In a study of 46 HIV-seropositive men (12 asymptomatic, 34 with AIDS), Hinkin and his group (1996) investigated memory, mood, and metacognition in HIV-1 infection. On a group level, they did not find that memory complaints (memory items from Cognitive Failures Questionnaire) were related to objective memory measures (i.e., California Verbal Learning Test, Wechsler Memory Scale-Revised). However, looking at objective versus subjective memory dysfunction on an individual basis, they identified three subgroups of HIV-1 infected subjects: 1) those that "over-reported" their memory complaints (37% of subjects), 2) those that "under-reported" or "minimized" their memory problems (26% of subjects), and 3) subjects who were "accurate" in their self-appraisal with respect to performance on memory testing (37%). Consistent with findings in the literature, the "over-reporters" endorsed significantly more symptoms of mood disturbance than subjects with fewer cognitive complaints. Interestingly, the "minimizers" had more advanced illness (i.e., 75% had AIDS), which led Hinkin and his colleagues to hypothesize that advanced HIV-1 infection may be related to decreased awareness of memory disturbances. Moreover, these investigators further speculated that disruptions in the frontal-subcortical pathways (e.g., basal ganglia) may impair memory functioning as well as awareness of cognitive functioning or metacognition.

Rourke and colleagues (1999b) also investigated memory-metamemory dissociations in a group of 91 HIV-1 infected adults (12 asymptomatic, 37 mildly

symptomatic, and 42 with AIDS). Based on each participant's performance on the CVLT (T score) and the PAOF (10-item memory scale), four subgroups were formed: two "inaccurate" subgroups (similar to Hinkin et al.'s "over-reporters" and "minimizers") and two concordant memory-metamemory subgroups ("accurate-impaired", "accurate-normal").

Rourke et al. (1999b) further examined the neuropsychological profiles and depressive symptoms of these four subgroups. The "accurate-normal" group (n = 29) had few memory complaints, endorsed few depressive symptoms, and showed intact performance on neuropsychological tests. The "accurate-impaired" group (n = 20) had significant memory complaints, "moderate" depressive symptomatology, and had a neuropsychological profile consistent with subcortical dysfunction (i.e., deficits in verbal learning and memory, verbal fluency, and psychomotor speed). The "over-reporters" (n = 26), like the "accurate-impaired" group, also had significant memory complaints and "moderate" depressive symptomatology. However, they exhibited relatively normal performance on neuropsychological measures. In contrast, the "minimizers" (n = 16) had fewer memory complaints and lower depressive symptoms, but their pattern of performance on neuropsychological tests suggested a selective disruption in frontal-subcortical brain systems (e.g., performance on measures of executive-type skills was significantly worse than the other three groups). The authors concluded that frontal-executive dysfunction and mood disturbance seem to be key contributors to metamemory inaccuracy.

In light of the above findings, there appear to be "distinct subgroups of HIV-1 infected individuals who vary in the 'accuracy' of the self-appraisal of their

neurocognitive status" (Rourke et al, 1999b, p. 765). Further exploration of the nature and clinical characteristics of HIV-1 memory subgroups could prove beneficial, particularly in determining their predictive utility (i.e., risk for morbidity and mortality). Given that learning and/or memory deficiency is a common problem in HIV-1 infection and that complaints of memory disturbances are frequent among HIV-1 infected individuals, the areas of metamemory or metacognition are avenues worthy for future research.

Memory Subtypes in HIV-1 infection

A number of investigators have attempted to classify HIV-1 infected individuals according to their learning and memory profiles (described below). This research mainly stems from the cognitive neuropsychological arena that has demonstrated qualitatively distinct patterns of memory deficits associated with different neurological and psychiatric disorders. In particular, performance on memory tests is shown to differentiate subcortical from cortical dementias. For example, patients with Huntington's disease (HD), a prototypical subcortical dementia, and Alzheimer's disease (AD), a prototypical cortical dementia, exhibit different patterns of performance on memory tasks. Although both HD and AD patients demonstrate poor recall, HD patients seem to show improvement on recognition, while AD patients are equally impaired on recall and recognition. Therefore, it has been postulated that HD patients suffer from a retrieval deficit since they are able to successfully store and retain new verbal information. In contrast, AD patients exhibit a predominant encoding and storage impairment, as evidenced by their difficulty in consolidating new information, rapid forgetting of stored information, a tendency to make more intrusion errors, and increased sensitivity to proactive interference (Butters, Granholm, Salmon, Grant, & Wolfe, 1987).

The California Verbal Learning Test (CVLT; Delis, Kramer, Kaplan, & Ober, 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, Huntington's disease, and Korsakoff's syndrome (e.g., Delis, Massman, Butters, & Salmon, 1991), HIV-1 infection (Becker et al., 1995; Delis et al., 1995; Peavy et al., 1994; White et al., 1997), depression (Massman, Delis, Butters, Dupont, & Gillin, 1992), and schizophrenia (Paulsen et al., 1995). The CVLT far surpasses traditional memory measures of recall or recognition. 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 (intrusions, perseverations), 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).

Of note, several investigators have used the CVLT to successfully discriminate between cortical (e.g., AD) and subcortical dementias (e.g., HD) (Becker et al., 1995; Delis et al., 1995; Massman et al., 1992; Peavy et al., 1994) by employing discriminant function equations derived by Massman and colleagues (1992). Massman et al. (1992) used three CVLT variables to differentiate between healthy controls, HD, and AD patients. The first variable was total recall over five learning trials (total trials 1-5), which has been found to discriminate between AD and HD from control subjects. The second variable was the number of intrusions on short- and long-delay cued trials (cued

recall intrusions). Since AD patients tend to exhibit a high number of intrusion errors under conditions of categorical cueing, this measure successfully differentiates AD patients from HD patients and controls. The third variable was the difference between recognition and free recall (discriminability minus trial 5). Since recognition testing occurs after a delay, this difference score provides a measure of retention of list items over time. In addition, this score provides a measure of the added benefit to retrieval provided by a recognition format. This variable, in particular, has considerable utility in discriminating AD patients (who display severe retention deficits and are not aided by a recognition format) and HD patients (who demonstrated intact retention and significant improvement on recognition testing relative to free recall). Table 4 compares CVLT variables (component memory processes) in subcortical and cortical dementias.

Table 4. CVLT Profiles Associated with Subcortical and Cortical Dementias

CVLT variables	Cortical	Subcortical
Recall	Impaired	Impaired
Learning rate	Flat	Flat
Learning style	Ineffective	Ineffective
Recall consistency	Inconsistent	Inconsistent
Retention	Poor	Adequate
Intrusion errors	High	Low
Discriminability	Poor	Good

Note. Compiled from Delis et al. (1991); Massman et al. (1992).

Investigations of CVLT profiles of HIV-1 infected individuals have mainly demonstrated that the pattern of verbal memory performance of HIV-1 patients is consistent with predominant subcortical dysfunction (i.e., profiles most similar to HD patients and least similar to that of AD patients). For example, Peavy et al. (1994) administered the CVLT to 31 symptomatic, 94 asymptomatic, and 40 HIV- control subjects. They found that relative to HIV- controls, symptomatic HIV+ subjects

performed poorly on measures of acquisition and retention, and were unlikely to employ semantic clustering strategies. Using the discriminant function equations derived by Massman et al. (1992), Peavy and colleagues classified symptomatic subjects as HD-like (32%), AD-like (3%), and normal (65%). The majority of asymptomatic subjects were classified as normal (83%), with a minority classified as HD-like (16%) and only 1% as AD-like. These findings lend support to the subcortical dysfunction hypothesis of HIV-1 infection as clinical memory profiles of a subset of HIV-1 infected individuals resemble those of HD, a characteristic subcortical dementia. These results also extend previous findings illustrating that a majority of asymptomatic individuals do not experience cognitive impairment and that the severity of cognitive dysfunction is more apparent in later stages of the illness (e.g., Heaton et al., 1995).

Becker et al. (1995) replicated the subcortical/cortical distinction demonstrated by Peavy et al. (1994) in a group of 31 HIV-seropositive community-based participants. Using discriminant function analysis (Massman et al. 1992), this group of authors classified 36% and 3% of HIV-1 infected subjects as "subcortical" and "cortical", respectively. The "normal" group was comprised of 61% of infected individuals. In addition, those individuals with a "subcortical" pattern of memory impairment showed poorer neuropsychological performance (i.e., verbal memory, visualspatial sequencing ability) than individuals classified as "normal". According to the authors, the findings from this study increase the "generalizability of the quantitative and qualitative features of the memory deficit associated with HIV-1 infection and AIDS" (p. 140). However, the authors fail to mention the severity of illness/stage of disease of HIV+ participants, thereby making interpretation of these findings less discernible.

Delis and associates (1995) also found a "subcortical" memory profile among HIV-1 infected patients, specifically those diagnosed with MCMD. Relative to HIV-negative controls and HIV-positive patients without MCMD, HIV-positive MCMD patients performed significantly poorer on several CVLT measures including immediate and delayed recall, use of semantic clustering strategies, and recency effect (suggesting a passive learning style in which the last words on the list are recalled). This pattern of CVLT performance is consistent with a "subcortical" memory profile. However, MCMD patients were also mildly impaired in discriminating targets from distracters on the recognition task. This discriminability problem is more characteristic of an encoding deficit. A pronounced retrieval impairment as well as a mild encoding deficit is suggestive of predominant subcortical involvement and some cortical involvement. This latter finding is consonant with neuropsychological and neuropathological studies demonstrating increased cortical involvement with advanced stages of the disease (Heaton et al., 1995; Maj et al., 1994; Miller et al., 1990; Wiley et al., 1991). These findings question the validity of a strict "subcortical" versus "cortical" distinction in characterizing learning and memory disturbances associated with HIV-1 infection, particularly in more advanced stages of the disease.

White et al. (1997) examined the pattern of memory performance in HIV-1-associated dementia (n = 9), HIV-seropositive (n = 15), and HIV-seronegative (n = 15) participants. Both HIV-1 dementia and HIV+ subjects displayed a constellation of deficits suggestive of subcortical brain dysfunction (i.e., poor learning and recall without forgetting). Despite elevated levels of depression in the HIV-1 dementia group, depression did not seem to affect patterns of memory performance of demented

individuals. Using discriminant function equations (Massman et al., 1992), two-thirds of HIV-1 dementia participants were classified as HD-like (subcortical) compared to only 20% of HIV+ participants. Based on the findings of Delis et al. (1995), a "cortical" profile (in addition to subcortical involvement) would have been expected with advanced illness. While only two out of nine dementia patients were classified as having an AD-like memory profile, this result should be interpreted with caution due to the small sample sizes.

Summary and Critique

Neuropsychological and neuropathological findings in HIV-1 infection are generally consistent with the notion of subcortical dysfunction (e.g., Bornstein et al., 1993; Heaton et al., 1995; A. Martin, Heyes, Salazar, Law, & Williams, 1993; Miller et al., 1990; Navia et al., 1986a; van Gorp et al., 1992). Investigations of patterns of learning and memory performance have also yielded evidence for predominant subcortical involvement in HIV-1 infection (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 suggestive of a retrieval deficit in a subgroup of individuals with HIV-1 infection/AIDS. There is also the implication of mild encoding deficits (characteristic of cortical involvement) in more advanced stages of HIV-1 illness (Delis et al., 1995). In addition, impaired performance on CVLT indices of learning efficiency (i.e., semantic clustering, elevated recency effect) is suggestive of frontal involvement (Stuss et al., 1994). Therefore, since learning and memory profiles of HIV-1 infected individuals are not homogeneous, a "subcortical" or "cortical" characterization may be over simplistic.

As Delis et al. (1995) caution, the "subcortical" versus "cortical" dichotomy, while heuristically appealing, should not be regarded strictly as an anatomical distinction. This caveat is not restricted solely to the HIV-1 population. Investigations of various neurological conditions have also demonstrated limitations of the "subcortical" and "cortical" profile distinction. In particular, patients with a predominant subcortical dementia may also exhibit cortical involvement and vice versa. For instance, a subgroup of patients with Parkinson's disease, a so-called subcortical dementia, evidence memory profiles consistent with cortical dementia (Filoteo et al., 1997). Furthermore, the strict association of a retrieval deficit with subcortical dysfunction warrants caution. For example, while schizophrenic patients manifest a "subcortical" profile reflected by a prominent retrieval deficit, mild encoding difficulties are also apparent, suggesting temporal lobe involvement (Paulsen et al., 1995). Also, there is evidence suggesting that geriatric chronic schizophrenic patients have profiles similar to cortical dementia patients (Putnam & Harvey, 1999). Implications of this finding are that patterns of learning and memory impairment are influenced by factors such as age and severity/chronicity of an illness. Thus, the "subcortical"/"cortical" distinction made in reference to geriatric illnesses (e.g., dementias) may not be applicable to young to middle-aged populations such as HIV-1 infection.

Therefore, in light of these findings, it appears that the notion of mutually exclusive subcortical and cortical categories is inadequate for describing the memory (cognitive) changes associated with HIV-1 infection. Rather, it would appear likely that there are qualitatively distinct subtypes of memory profiles that do not adhere strictly to either "subcortical" or "cortical" categories. While some HIV+ patients may exhibit

predominant subcortical involvement, it is also plausible that some patients may have involvement in both subcortical and cortical brain regions (possibly via anatomically and functionally segregated circuit systems such as those connecting the prefrontal regions of the brain with subcortical structures). Moreover, other factors such as depression and severity of disease may play a vital role in memory performance of some HIV-1 infected individuals.

The HIV-1 literature clearly depicts heterogeneity of both neuropsychological and neuropathological symptomatology, thereby making the search for a single neuropsychological profile seem misguided. In the same manner, it is certainly conceivable that there are distinct subgroups of HIV-1-related memory impairment. Research demonstrating that component memory processes are differentially affected in HIV-1 infection/AIDS lends strong support for the existence of separate memory subtypes. Moreover, memory profiles during earlier stages of HIV-1 illness may differ from those at more advanced phases of the disease. Given the subcortical to cortical progression observed in HIV-1, it is likely that the evolution of memory impairment will also reflect increasing cortical involvement over the course of the disease. Understanding how memory patterns parallel disease progression has obvious clinical implications (e.g., diagnostic accuracy, treatment considerations).

Unfortunately, the importance of subtyping in HIV-1 infection is not reflected in the literature. Previous research findings with HIV-1 infected participants are limited due to shortcomings associated with the characterization of memory profiles in terms of a rigid "subcortical"/"cortical" distinction. Hence, the depiction of unique profiles of memory components in HIV-1 infection remains unclear. Obviously, a more refined

approach to classification is needed. One such approach involves multivariate classification of HIV-1 infected individuals according to their clinical memory profiles. Clustering techniques are particularly well suited for defining subtypes of cognitive performance (e.g., Fletcher & Satz, 1985).

Clinical relevance.

The derivation of memory subtypes using cluster analyses may have considerable clinical utility. For instance, many clinical decisions are often related to subjective complaints of cognitive inefficiency. The source of these complaints, however, may be vague. Deficits in memory functioning may be the basis for many reported difficulties in day-to-day activities (e.g., keeping track of information, forgetfulness, losing train of thought, absent-mindedness). Alternatively, mood disturbances may also largely contribute to subjective complaints of cognitive decline. A better understanding of the major determinants of clinical complaints may have a significant impact on treatment considerations. For example, an individual with a memory profile consistent with subcortical involvement may present with different complaints than an individual with a normal memory profile or one with predominant mood symptomatology. Each of these individuals, in turn, may require different interventions. Therefore, clarification of the precise relationship between memory subtypes (or clusters) and subjective neurocognitive complaints may enhance the overall clinical management of HIV-1 patients.

In addition, discerning the typical neuropsychological profiles associated with empirically derived clusters of memory performance may further theoretical understanding of the cognitive sequelae of HIV-1 infection. Clinically, the depiction of reliable HIV-1 memory subgroups may improve diagnostic accuracy, prognostic utility,

and treatment decisions. Of importance, the real-life significance associated with clinical memory subtypes may prove to be a fruitful endeavor and worthy area of future research with the HIV-1 population. For instance, one's ability to effectively encode, store, and retrieve information will significantly influence their ability to engage in vocational and daily tasks of living.

Factor structure of the CVLT.

The delineation of empirically derived subtypes of memory impairment is heavily dependent on the measure(s) used to assess memory performance. 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. Does the CVLT measure what it is purported to measure? Therefore, it is important to determine the exact constructs or factors that are measured by the CVLT.

Delis et al. (1987) reported a six-factor structure for the CVLT in a large standardization sample of normal subjects and a five-factor solution in a mixed neurological sample using principal components analysis with varimax rotation. These findings suggest 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 latent factors of a test. Problems associated with these analytic approaches include their inability to account for all sources of variance (e.g., random error variance), and the inability to make allowances for the possibility of correlations between factors and interdependencies among variables (see Wiegner & Donders, 1999). In this regard, a more powerful statistical technique is confirmatory factor analysis.

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 that are measured by an instrument.

<u>Purpose</u>

Despite clinical and experimental findings demonstrating qualitatively distinct memory profiles associated with different neurological and psychiatric disorders, there have been no studies examining the existence of subtypes of HIV-1 related memory disturbance. 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 HIV-1 infected participants. The major objectives of this study are threefold: 1) to determine the underlying latent constructs of memory (CVLT) in a clinical sample of HIV-1 infected individuals using confirmatory factor analysis, 2) to use the results of this analysis to delineate distinct and reliable clusters of memory performance, and 3) to evaluate the external validity of these memory subtypes using subjective neurocognitive complaints, mood symptomatology, neuropsychological test performance, and markers of HIV-1 disease. This novel subtyping approach to characterizing HIV-related memory performance may have significant utility in the overall clinical management of HIV-1 infected individuals.

The impetus for classifying individuals according to their memory profiles also comes from reports indicating that complaints of memory loss are a cardinal feature of

HIV-1 infection/AIDS. To some extent, this study will build on the work of Rourke et al. (1999b) involving memory-metamemory subgroup classification of HIV-1 infected individuals. Rourke and colleagues (1999b) used an index of learning efficiency to characterize subgroups of HIV-1 infected individuals that vary in their self-appraisals of memory functioning. The present investigation attempted to define memory subtypes on the basis of latent constructs of memory (e.g., attention, learning efficiency, recall/retrieval). A major goal of the current study was to delineate the relationship between memory profiles and self-appraisal of cognitive abilities. It is anticipated that a better understanding of HIV-related memory subtypes may shed light on the nature of cognitive (memory) complaints.

In accord with previous research findings, several models of memory were evaluated in an attempt to determine the best fitting factorial model. Based on these findings, key variables were included in a cluster analysis to determine distinct and reliable CVLT performance profiles. Lastly, cluster validity was evaluated using subjective complaints, neuropsychological performance, and markers of HIV-1 illness severity.

Hypotheses

Part I: Confirmatory factor analysis.

The present study tested eight models of the CVLT latent structure suggested by Wiegner and Donders (1999). The following models were evaluated: Model 1 - General Memory; Model 2 - Accurate Recall and Inaccurate Recall; Model 3 - Immediate Recall, Delayed Recall, and Inaccurate Recall; Model 4 - Attention Span, Learning Efficiency, Delayed Recall, and Inaccurate Recall; Model 5 - Immediate Recall, Short Delayed

Recall, Long Delayed Recall, Inaccurate Recall; Model 6 - Immediate Recall, Free Delayed Recall, Cued Delayed Recall, Inaccurate Recall; Model 7 - Attention Span, Learning Efficiency, Short Delayed Recall, Long Delayed Recall, Inaccurate Recall; and Model 8 - Attention Span, Learning Efficiency, Free Delayed Recall, Cued Delayed Recall, Inaccurate Recall.

The main hypotheses with regard to confirmatory factor analysis were as follows:

(1) It was predicted that models representing 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 theoretical 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 HIV+ individuals (Delis et al., 1995; Peavy et al., 1994). In addition, frontal system dysfunction may interfere with efficient learning. Higher-order organizational deficits have been associated with impaired list learning in patients with damage to the frontal lobes (Stuss et al., 1994) as well as in older normal participants (Stuss, Craik, Sayer, Franchi, & Alexander, 1996).

(2) Given its conceptual clarity, it was hypothesized that Model 8 would be the best fitting factor model in the confirmatory factor analysis. Of note, Model 8 suggests the presence of separate Free Delayed Recall and Cued Delayed Recall factors. HIV+ patients show poor free recall of verbal information but tend to benefit from cues

(Hinkin et al., 1998). The assistance to retrieval by cueing (e.g., recognition) is indicative of a retrieval deficit, the predominant feature of memory dysfunction in HIV-1 infection (Delis et al., 1991, 1995). Model 7 hypothesizes separate Short Delayed Recall and Long Delayed Recall. Performance on short and long delayed trials provides an index of forgetting which is not a characteristic problem seen in HIV-1 infection (Delis et al., 1995; White et al., 1997) or in other "subcortical" conditions (e.g., Delis et al., 1991; Massman et al., 1992). Model 4 (consisting of Attention Span, Learning Efficiency, Delayed Recall, and Inaccurate Recall) represents the memory structure in traumatic brain injury (TBI) (Wiegner & Donders, 1999), and may not be sufficient for HIV-1 infection. In TBI, the separation of delayed recall variables into short versus long, or free versus cued, does not appear to enhance model fit (e.g., Roth, Conboy, Reeder, & Boll, 1990; Wiegner & Donders, 1999; Woodard, 1993).

Part II: Cluster analysis.

Using cluster analysis, it was anticipated that HIV-1 infected individuals would display qualitatively different CVLT profiles (i.e., level and/or pattern of preserved and impaired memory components). Between three and six clusters were expected on the basis of clinical and theoretical rationale. However, the precise number of clusters would be dependent on the results from the confirmatory factor analyses. In accordance with Wiegner and Donders (1999), only those CVLT variables with the highest factor loadings (i.e., factors from best fitting model) will be used in the cluster analysis. This method ensures that variable redundancy is diminished, and importantly, that variables are selected based on theoretical considerations (Morris & Fletcher, 1988). It was predicted

that the cluster solution would include at least the following major CVLT subtypes: unimpaired ("normal"), mildly impaired ("subcortical"), and generally impaired ("subcortical plus frontal"). More specific hypotheses regarding CVLT subtypes could not be made until reliable subtypes were discerned from the clustering procedures.

METHOD

Participants

The sample of subjects for this study was obtained through archival records at the HIV-1 Neuropsychology Laboratory and HIV Psychiatry Program in St. Michael's Hospital (Wellesley Central Site) in Toronto. The sample consisted of 157 HIV-1 infected adults who, in order to increase generalizability, were recruited from three sources (HIV primary care medical and infectious disease clinics, psychiatric service, and research pool). 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 substance abuse/dependence in the two months prior to the study.

Participants had a mean age of 41.3 ($\underline{SD}$ = 8.4) years and had an average 14.6 ($\underline{SD}$ = 2.7) years of education. Mean WAIS-R Information and Picture Completion $\underline{T}$ scores were 50.5 ($\underline{SD}$ = 9.0) and 50.7 ($\underline{SD}$ = 8.1), respectively. The mean Beck Depression Inventory score for the sample was 18.1 ($\underline{SD}$ = 10.5), indicating that participants had mild to moderate depressive symptomatology. Seventy-five percent of the sample was taking some combination of antiretroviral medication. Thirty-nine percent of individuals in this sample were prescribed antidepressants.

Of the total sample, 18 were asymptomatic (A1 and A2), 61 were mildly symptomatic (B1 and B2), and 77 had AIDS-defining illnesses or CD4 lymphocyte counts less than 200 (A3, B3, and C1-C3) according to the Center for Disease Control (CDC93) revised classification system for HIV-1 infection (CDC, 1992). 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 [$F(2,151) = 20.53$, $p < .0001$].

Measures

Neuropsychological tests were selected based on recommended guidelines from the NIMH 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 Completion, and Digit Symbol subtests (Wechsler, 1981); (2) Boston Naming Test (Kaplan, Goodglass, & Weintraub, 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 (Selnes et al., 1993; Smith, 1973); (6) Grooved Pegboard Test (Reitan & Wolfson, 1993); (7) California Verbal Learning Test (Delis, Kramer, Kaplan, & Ober, 1987); (8) Wisconsin Card Sorting Test (Heaton, Chelune, Talley, Kay, & Curtiss, 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). For each item, participants are required to rate the frequency with which they experience a particular

kind of difficulty on a 6-point scale (0 = almost never; 1 = very infrequently; 2 = once in a while; 3 = fairly often; 4 = very often; and 5 = almost always). (The PAOF is reproduced, with permission, in Appendix B).

Procedure

Recruitment and testing of participants used in this study was approved by the St. Michael's Hospital Review 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. Technical properties of the CVLT presented in the manual show it to be a reliable and valid instrument. Estimates of internal consistency range from .70 to .92. Test-retest correlations indicate that CVLT scores are generally stable over a one-year period. In addition, criterion-related validity (using the Wechsler Memory Scale) and discriminant validity (using different clinical groups) for the CVLT has also been demonstrated (Delis et al., 1987).

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., serially or semantically). 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 (usually 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 distracters. CVLT scoring software (Fridlund & Delis, 1987) was used to score test protocols. Raw scores were converted to demographically-corrected T-scores and z-scores for almost all variables. Description of CVLT indices is presented in Table 5.

Table 5. Description of CVLT Variables

Measures	Description
Recall	
List A - Trial 1	total number words recalled on trial 1
List A - Trial 5	total number words recalled on trial 5
List A - Trials 1-5	total number words recalled on trials 1-5
List B	number of List B words recalled after one immediate recall trial
Short-delay	
Free-recall	number of List A words recalled immediately following List B trial
Cued-recall	number of List A words recalled when category cues are provided
Short-delay savings	percentage of List A trial 5 words that are recalled on the short-delay free-recall trial
Long-delay	
Free-recall	number of List A words recalled after a 20-min delay
Cued-recall	number of List A words recalled when category cues are provided
Long-delay savings	percentage of short-delay free-recall words that are recalled on long-delay free-recall trial
Free-recall intrusions	total number of nontarget words reported on all free-recall trials of List A and List B
Cued-recall intrusions	total number of nontarget words reported on the two cued-recall trials of List A
Recognition	
Discriminability	ability to discriminate targets (hits) from distracters (false positives) on recognition testing
False positives	Number of distracter items identified as hits (List A words)
Response bias	tendency for primarily "yes" or primarily "no" responses on recognition testing

Learning Style	
Semantic clustering	ability to organize target words according to semantic category (i.e., fruits, spices, clothing, tools)
Serial clustering	degree to which target words are recalled in the same order as they are presented
Recall consistency	percentage of List A words recalled on one of the learning trials (trials 1-4) that are also recalled on the very next trial (trials 2-5)
Primacy recall	percentage of total List A words (trials 1-5) that are recalled from the primacy region (first four words)
Recency recall	percentage of total List A words (trials 1-5) that are recalled from the recency region (last four words)

Note. CVLT = California Verbal Learning Test.

Statistical Analyses

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). 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 instance, the use of a serial learning style directly influences the extent to which a participant will utilize a semantic learning strategy. Similarly, recall from the recency region of the word list affects recall from the primacy and middle regions. The recency recall variable, an indicator of passive/less efficient learning, was chosen (over the other two region variables) to complement the more active and efficient learning style gauged by the

semantic clustering variable. Recognition discriminability was also excluded due to its direct relationship with recognition hits and false positive variables.

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 can be influenced by various psychological states (e.g., anxiety, depression). Such reactions may interfere with participants' ability to recall list items presented for the first time (Delis, Kramer, Kaplan, & Ober, 2000). The perseveration variable also lends itself to scoring difficulties since patients' tendency to repeat list words during recall trials may be misjudged as perseverative responses (J. Donders, personal communication, October 2000). Altogether, these criteria resulted in a total of 14 CVLT variables. Table 6 depicts these variables according to each hypothesized factor model described earlier.

Table 6. Eight Hypothesized Latent CVLT Variable Models

CVLT indices	1	2	3	4	5	6	7	8
List A trial 1	G	AR	I	A	I	I	A	A
List A trial 5	G	AR	I	LE	I	I	LE	LE
List B	G	AR	I	A	I	I	A	A
Short-delay free recall	G	AR	D	D	SD	FR	SD	FR
Short-delay cued recall	G	AR	D	D	SD	CR	SD	CR
Long-delay free recall	G	AR	D	D	LD	FR	LD	FR
Long-delay cued recall	G	AR	D	D	LD	CR	LD	CR
Semantic clustering	G	AR	I	LE	I	I	LE	LE
Recency	G	AR	I	LE	I	I	LE	LE
Recall consistency	G	AR	I	LE	I	I	LE	LE
Intrusions – free recall	G	IR	IR	IR	IR	IR	IR	IR
Intrusions – cued recall	G	IR	IR	IR	IR	IR	IR	IR
Recognition hits	G	AR	D	D	LD	CR	LD	CR
Recognition false positives	G	IR	IR	IR	IR	IR	IR	IR

Note. CVLT = California Verbal Learning Test; G = General Memory; AR = Accurate Recall; IR = Inaccurate Recall; I = Immediate Recall; D = Delayed Recall; A = Attention Span; LE = Learning Efficiency; SD = Short Delayed Recall; LD = Long Delayed Recall; FR = Free Delayed Recall; CR = Cued Delayed Recall.

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 since a single index cannot adequately determine model fit (Hoyle & Panter, 1995). These are described next.

Briefly, the chi-square (χ^2) test provides an indication of the discrepancy between the observed correlation (covariance) matrix and the correlation matrix generated by the model. A statistically significant χ^2 implies a significant difference between the observed data and the data that can be explained by the model. Therefore, with confirmatory factor analysis, a nonsignificant χ^2 is desired in order to confirm the null hypothesis of 'no difference' (Bryant & Yarnold, 1995). However, given its sensitivity to sample size, a significant chi-square statistic is plausible even though differences between the model (implied) and data (observed) are minimal (Kline, 1998). The chi-square statistic, is therefore generally interpreted alongside other fit indices. The ratio of chi-square to degrees of freedom (χ^2/df) is often used for comparing models of differing complexity. Model fit improves as the ratio decreases and approaches zero (Bryant & Yarnold, 1995). Similar to the χ^2 test, the goodness-of-fit index (GFI) is also an index of absolute fit. The GFI ranges from 0 to 1.0 and represents the relative amount of variance accounted for by a model. Higher values reflect a better fit, with recommendations of values greater than .90 (Kelloway, 1998).

Incremental fit indices reflect how much better a model fits the data compared to a baseline or null model, which assumes no relationship among variables (Bryant & Yarnold, 1995; Millis, Malina, Bowers, & Ricker, 1999). The incremental fit indices include the Tucker-Lewis index or nonnormed fit index (NNFI), the comparative fit index (CFI), and the adjusted-goodness-of-fit index (AGFI). In general, higher values ($\geq$ .90) are representative of better model fit. The current recommended cutoff for CFI is .95 (Hu & Bentler, 1999). Low values of the expected cross-validation index (ECVI) are associated with better fitting models. The root mean square error of approximation (RMSEA) is a measure of the average fitted residuals (difference between actual correlations among variables and the correlations predicted by a given model). An RMSEA value of zero represents an accurate fit of the model with the data, therefore values closer to zero indicate good model fit (Bryant & Yarnold, 1995; Millis et al., 1999). The parsimonious normed fit index (PNFI) and the Akaike's Information Criterion (AIC) are used to evaluate model parsimony. PNFI values greater than .60 are desired. When comparing models that are not nested (or hierarchical), the model with the lowest AIC is preferred (Kline, 1998).

In addition to the above-mentioned fit criteria, parameter estimates were examined for Heywood cases (negative error variances), factor loadings greater than 1.0, and factor intercorrelations approaching 1.0. Such estimation problems may signal a poorly specified model and question the validity of the factor solution (Hoyle & Panter, 1995). Lastly, residuals were inspected as another indication of model fit. In particular, if there is good "fit" between model and data, standardized residual covariances tend to be normally distributed (Arbuckle & Wothke, 1999).

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. Using SPSS (version 10.0) Hierarchical Cluster and K-Means Cluster procedures, CVLT indices were subjected to a two-stage clustering processing entailing hierarchical agglomerative method, using squared Euclidean distance as the similarity measure, followed by k-means iterative partitioning. Ward's (1963) minimum variance method, a common and relatively well understood procedure, was used as the first-stage agglomerative clustering method. Squared Euclidean distance was selected as the method of profile similarity due to its sensitivity to both elevation and pattern (Aldenderfer & Blashfield, 1984; Morris, Blashfield, & Satz, 1981). Seed values or centroids generated by Ward's method were then used in the k-means iterative procedure. The k-means cluster technique is one in which subjects are successively partitioned into clusters with the most similar centroids until a stable solution is found (Morris et al., 1981). An advantage of the iterative partitioning technique is its method for relocating misclassified subjects to a more suitable cluster (DeLuca, Adams, & Rourke, 1991), thereby decreasing within-cluster variance and maximizing between-cluster variance (Morris et al., 1981).

Since cluster analysis will always generate groups of subjects (even in random data sets), the validity of clusters or subtypes is a critical component in the clustering procedure (Fuerst & Rourke, 1995). Internal validity (reliability) is essential for evaluating the stability of a clustering solution (Morris et al., 1981). The stability of the cluster solution 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 external validity of the cluster solution, memory subtypes were compared on subjective neurocognitive complaints (PAOF), depressive symptoms (BDI), measures of neuropsychological functioning (attention, psychomotor speed, language, verbal fluency, and conceptual skills and problem solving), and markers of HIV illness 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. In addition, discriminant function analyses were performed using PAOF scale scores (memory, language, sensory-motor, higher-level cognitive/intellectual) as predictors and cluster membership as the grouping variable.

RESULTS

Part I: Confirmatory Factor Analysis

The 14 CVLT variables were screened to assess multivariate normality, a common assumption underlying structural equation modeling (Hoyle, 1995). Outliers, in particular, can have striking effects on model fit indices as well as lead to unstable or improper factor solutions (West, Finch, & Curran, 1995). Three multivariate outliers were detected: two via Mahalanobis distance with $p < .001$, and one case with extreme z scores on more than two CVLT variables. All three outliers were removed from the data set, resulting in a sample size of 154.

Maximum-likelihood structural equations were computed for each of the eight latent factor models using the AMOS 4.0 software package (Arbuckle & Wothke, 1999). (The sample CVLT covariance matrix is displayed in Appendix C.) While interval data are assumed in structural equation modeling, standard CVLT scores were used in the confirmatory factor analyses to allow comparability of scores. The weight least squares method (WLS), the method of choice for ordinal variables, was not used in the present study mainly due to the very large sample size requirements (e.g., 2000 cases) of this method. In addition, empirical studies have suggested that WLS and maximum likelihood estimation methods result in comparable fit statistics with little or no differences in interpretation (Garson, 2000).

In order to assess the adequacy of a factor solution, parameter estimates, model fit indices, and residuals were examined. Inspection of factor solutions and parameter estimates indicated significant problems with models 5 to 8. Specifically, factor solutions for models 6 and 8 were "not admissible" due to "not positive definite" covariance

matrices (zero or negative eigenvalues). Models 5 and 7 yielded factor intercorrelations close to 1.0 (between short- and long-delayed recall) and thus were deemed unacceptable. These findings suggested that separating the delayed recall factor (i.e., short versus long delay or free versus 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. In order to evaluate model fit and acceptability, several a priori criteria were established including GFI, NNFI, and CFI values exceeding 0.9 (with CFI values $\geq$ .95), higher values of AGFI, RMSEA values less than .08, PNFI values greater than .60, and low values of ECVI. For comparing non-hierarchical models (i.e., models 1 to 4), the model with the lowest AIC was preferred. Table 7 lists the fit indices for the competing models. Model 1 failed to meet all the criteria for adequate model fit (i.e., GFI, NNFI, CFI < 0.9, 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 and NNFI values ($\geq$ 0.9), a CFI value of .95, an RMSEA values less than .08, and only a negligible loss in parsimony over models 2 and 3 (PNFI of .71 versus .73). Also, model 4 had lower values of χ^2/df, AIC, and ECVI than any other model.

Table 7. Fit Indices for CVLT Latent Variable Models

Model	χ^2	df	χ^2/df	GFI	NNFI	CFI	AGFI	RMSEA	PNFI	AIC	ECVI
1	223.6	77	2.9	.82	.87	.89	.76	.11	.71	279.6	1.83
2	172.4	76	2.3	.86	.91	.93	.81	.09	.73	230.4	1.51
3	146.1	74	2.0	.88	.93	.94	.83	.08	.73	208.1	1.36
4	130.5	71	1.8	.90	.94	.95	.84	.07	.71	198.5	1.30

Note. GFI = goodness-of-fit index; NNFI = nonnormed fit index (also known as Tucker-Lewis index); CFI = comparative fit index; AGFI = adjusted-goodness-of-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.

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 HIV-1 infected individuals.

The standardized regression weights (factor loadings) and factor intercorrelations for model 4 are displayed in Figure 1 below.
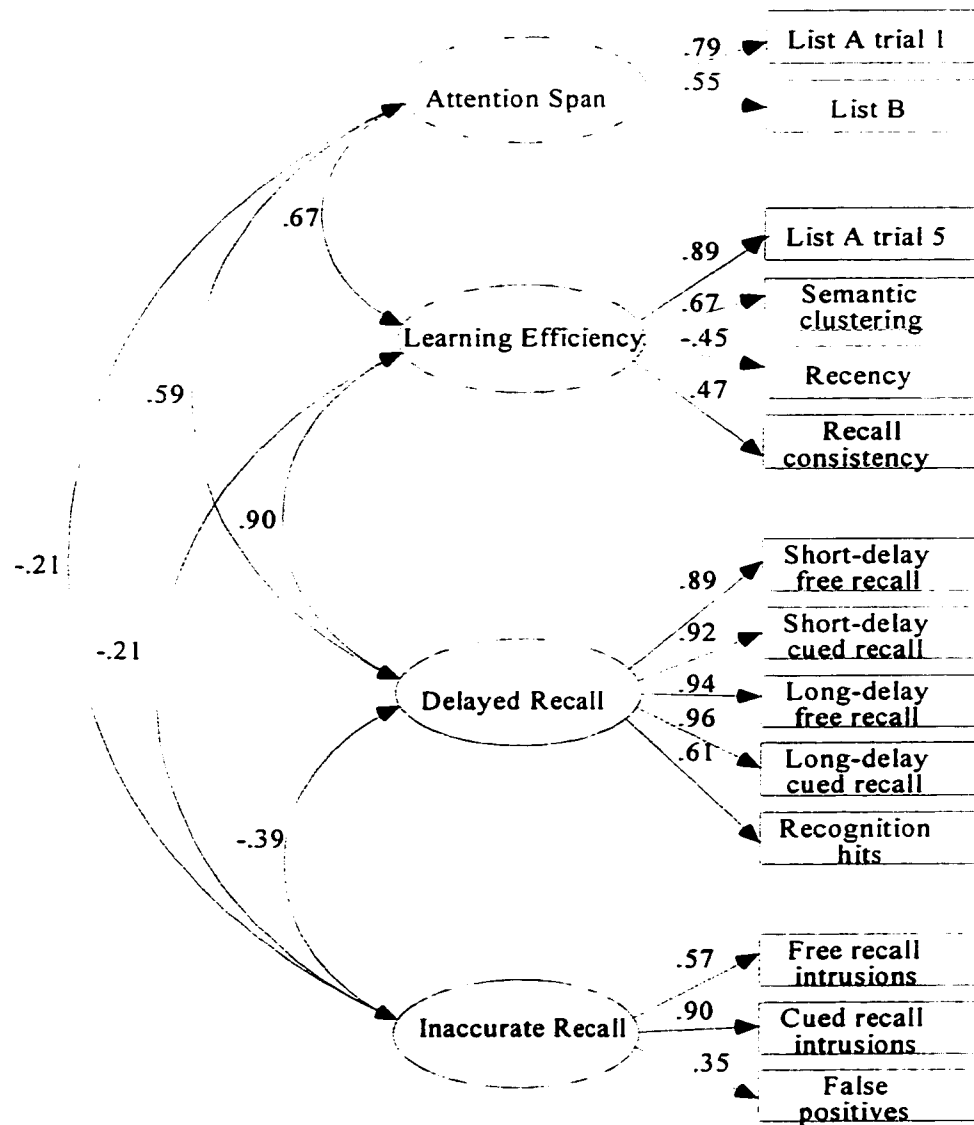
Figure 1. Path diagram for model 4 with standardized regression coefficients. Ellipses represent latent variables or factors. Rectangles are used to depict observed variables (in this case, CVLT variables). Arrows indicate associations that are either directional (straight arrows) or nondirectional (curved arrows). Note: Error associated with observed variables are omitted from the diagram to preserve simplicity of the structural model.

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. 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.

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. All variables were standardized z scores, with higher scores indicating better performance.

Cluster solution.

Since many clustering methods are sensitive to the presence of outliers (Everitt, 1980), eleven outliers (identified as having extreme values on CVLT variables) were deleted. This resulted in a sample size of 143. The first stage of cluster analysis used Ward's (1963) method of agglomeration with squared Euclidian distance as the similarity measure. Analysis of the dendogram (tree diagram) and the clustering (fusion) coefficients suggested between four and six clusters. 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.

Internal validity.

Replicability (reliability) and clinical interpretability are essential for assessing the adequacy of a specific cluster solution (Everitt, 1980; Fuerst & Rourke, 1995). The degree of replicability of a cluster solution provides a check for the internal validity of a solution (Aldenderfer & Blashfield, 1984). 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 these procedures demonstrated 87% agreement with Ward's method in terms of classifying individuals into the same clusters. Table 8 illustrates that, with the exception of Cluster 3, very few individuals were misclassified by the two clustering techniques using Ward's method as the standard of comparison. Overall, these results suggest good replicability of the four-cluster solution.

Table 8. Number of Cluster Misclassifications in Comparison to Ward's Method

Clustering Method	Cluster 1 ($n = 36$)	Cluster 2 ($n = 42$)	Cluster 3 ($n = 46$)	Cluster 4 ($n = 19$)
Complete Linkage	1	2	15	0
Average Linkage	1	2	16	0

The CVLT profiles of the four clusters were also considered to be interpretable from a clinical standpoint. Figure 2 presents the cluster profiles.
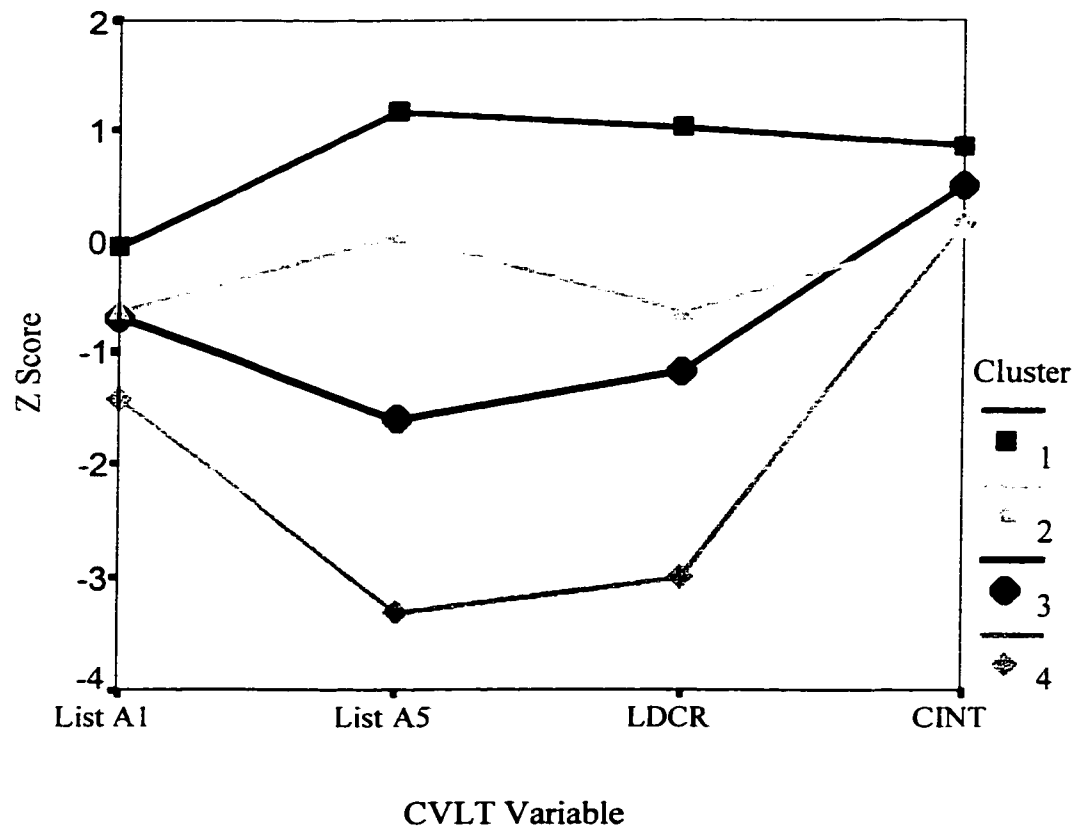
Figure 2. CVLT profiles of four cluster subtypes. List A1 = List A trial 1, List A5 = List A trial 5, LDCR = long-delay cued recall, CINT = cued recall intrusions.

Inspection of Figure 2 shows that clusters differed in terms of level and pattern of performance. 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. While both clusters exhibited similar scores on List A1 (attention span), Cluster 3 had markedly lower z scores on List A5 than Cluster 2. These results suggest that Cluster 3 evidenced problems with learning efficiency while Cluster 2 demonstrated intact learning ability. Lastly, Cluster 3 and 4 appeared to differ solely with respect to profile level. Overall, performance on the List A5 variable seemed to contribute most to

cluster membership, followed by the LDCR variable. The List A variable tended to differentiate only Clusters 1 and 4. Cluster membership did not appear to be influenced by the CINT variable.

Cluster description.

Table 9 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).

Table 9. Cluster Performance (Mean z Scores) on CVLT Variables

CVLT Indices	Cluster 1 (n = 36)		Cluster 2 (n = 42)		Cluster 3 (n = 46)		Cluster 4 (n = 19)	
	M	(SD)	M	(SD)	M	(SD)	M	(SD)
List A trial 1[a]	-0.06	(1.0)	-0.64	(0.73)	-0.70	(0.84)	-1.42	(0.69)
List A trial 5[a]	1.17	(0.65)	-0.05	(0.44)	-1.61	(0.68)	-3.32	(0.89)
List B	0.31	(1.24)	-0.21	(1.34)	-0.09	(1.24)	-1.16	(0.83)
Short-delay free recall	0.72	(0.94)	-0.48	(0.99)	-1.24	(0.74)	-2.68	(0.82)
Short-delay cued recall	0.83	(0.56)	-0.40	(0.89)	-1.26	(0.83)	-2.63	(1.26)
Long-delay free recall	0.78	(0.72)	-0.38	(0.62)	-1.07	(0.71)	-2.68	(0.89)
Long-delay cued recall[a]	1.03	(0.65)	-0.64	(0.85)	-1.17	(0.82)	-3.00	(0.88)
Semantic clustering	0.72	(1.21)	0.00	(1.08)	-0.80	(0.91)	-1.11	(0.74)
Recency	-0.39	(0.60)	-0.14	(0.84)	0.30	(0.99)	0.58	(1.35)
Recall consistency	0.22	(0.68)	-0.38	(0.79)	-0.80	(1.07)	-1.26	(1.10)
Intrusions – free recall	-0.47	(0.70)	-0.02	(0.81)	-0.41	(0.54)	-0.16	(1.01)
Intrusions – cued recall[a]	-0.86	(0.35)	-0.10	(0.76)	-0.50	(0.66)	-0.16	(0.83)
Recognition hits	0.36	(0.72)	-0.67	(1.26)	-0.87	(1.36)	-2.68	(1.77)
Recognition false positives	0.03	(0.17)	0.21	(0.52)	0.15	(0.52)	0.21	(0.42)
Discriminability	0.19	(0.48)	-0.26	(0.59)	-0.35	(0.77)	-1.11	(0.81)
List A, trials 1-5[b]	57.1	(8.1)	47.0	(7.0)	37.4	(7.8)	23.6	(5.3)

Note. CVLT = California Verbal Learning Test.
[a] Variable selected for cluster analysis.
[b] T score.

Cluster 1 displayed scores within normal to high average limits on selected CVLT variables. Cluster 2 performed within one standard deviation of the mean on all CVLT

measures, with scores just below the normative mean. Cluster 3 obtained scores suggestive of mild impairment (i.e., generally around one standard deviation below the mean). Cluster 4 demonstrated the poorest performance on all selected CVLT variables. In particular, Cluster 4 performed three standard deviations below average on the List A5 (learning efficiency) and long-delay cued recall variables (LDCR), reflecting overall deficient learning and memory.

There was not much variation between clusters with respect to inaccurate recall (i.e., number of intrusions, false positives). Also, 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 appeared to significantly improve performance relative to recall only for Cluster 4. Specifically, Cluster 4 evidenced better performance on discriminability compared to long-delay free recall. The former variable, a measure of recognition accuracy, is regarded as a good indicator of recognition memory on the CVLT (Delis et al., 1987). None of the clusters demonstrated a susceptibility to proactive (List A1 versus List B) or retroactive (List A5 versus short-delay free recall) interference, with z scores typically within one half of a standard deviation. Informal comparisons of learning variables (i.e., semantic clustering and recall consistency) were made to ascertain the learning style of each cluster subtype. Clusters 1 and 2 exhibited intact learning efficiency while Cluster 4's scores reflected an ineffective style of learning. Interestingly, Cluster 3's performance on learning indices approached mild impairment levels (z score = -0.80), further supporting the profile distinction between Clusters 2 and 3.

External validity.

External validation of this cluster solution was conducted using a variety of measures not used in the initial clustering procedure, including neuropsychological tests, questionnaires assessing mood and subjective cognitive complaints, and markers of HIV disease. The following a priori predictions were made with respect to the four clusters:

(1) Cluster 1 ("Normal" subtype) would be comprised of individuals who perform within normal limits on neuropsychological testing. In addition, it was hypothesized that the majority of individuals would endorse fewer self-reported cognitive and mood disturbances relative to the other clusters. With respect to disease severity, it was hypothesized that individuals in this subgroup would have the highest CD4 count, the highest percentage of non-detectable plasma viral load, and the fewest percentage of subjects with AIDS-defining illnesses.

(2) Cluster 2 ("Atypical" subtype) was expected to be similar to Cluster 1 in terms of demonstrating intact neuropsychological functioning. In comparison to Cluster 1 individuals, it was predicted that Cluster 2 subjects would report a higher number of depressive and cognitive complaints. This latter group may be comparable to Rourke et al.'s (1999b) "over-reporters" (i.e., individuals who exaggerate or show a tendency to over-report problems relative to their objective test performance). Markers of disease severity were expected to resemble those of Cluster 1 individuals (i.e., highest CD4 count, highest percentage of non-detectable plasma viral load, and fewest percentage of subjects with AIDS-defining illnesses).

(3) Cluster 3 ("Subsyndromal" subtype) was hypothesized to exhibit a "mild subcortical" or subsyndromal presentation. Subtle and "spotty" neuropsychological impairment

was predicted in this group of individuals (e.g., psychomotor slowing). It was also hypothesized that this subtype would be comprised of individuals with subjective complaints (particularly in the area of memory) and mild to moderate depressive symptomatology. Indices of disease severity were expected to be fall somewhere in between Cluster 1 and Cluster 4 (i.e., lower CD4 count than Clusters 1 and 2, non-detectable plasma viral load, and higher percentage of symptomatic than asymptomatic subjects).

(4) A "subcortical plus frontal" presentation was predicted in this cluster subtype. It was anticipated that Cluster 4 ("Frontal-striatal" subtype) would show a pattern of lowered overall neuropsychological test performance, including disturbances in frontal-executive skills. The latter prediction was based on findings from neuropsychological investigations of patients with frontal lobe dysfunction. Specifically, higher-order organizational deficits have been associated with impaired list learning (including recall and recognition deficits) in persons with damaged frontal lobes (e.g., Stuss et al., 1994). Organizational disturbances are implied by Cluster 4's poor scores on indices of learning (List A5), recall (short- and long-delay), recall consistency, and use of semantic clustering strategies.

In addition, based on the hypothesis that disruption of frontal-subcortical brain systems may contribute to both impaired memory and disturbed awareness of memory deficits (or metamemory) (Hinkin et al., 1996; Rourke et al., 1999b), it was predicted that the "Frontal-striatal" subtype would exhibit the fewest neurocognitive complaints despite impaired neuropsychological performance (similar to the "minimizers" subgroup of Hinkin et al. [1996] and Rourke et al. [1999b]). Individuals in this cluster

grouping were expected to have more advanced HIV-1 illness as indicated by the lowest CD4 count, the highest percentage of detectable plasma viral load, and the largest percentage of subjects with AIDS-defining conditions.

(a) Demographic data.

As seen in Table 10, there were no statistically significant differences between clusters in terms of age [$F(3,139)$ = 0.82] and WAIS-R Information T scores. However, the clusters demonstrated statistically significant differences in years of education [$F(3,139)$ = 5.31, p = .002], with an effect size of 0.10. Post hoc analyses indicated that the "Normal" subtype (Cluster 1) had a higher level of education than the "Subsyndromal" and "Frontal-striatal" subtypes (Clusters 3 and 4, respectively). The "Atypical" subtype (Cluster 2) also had more years of education than the "Subsyndromal" 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. Clusters also did not differ significantly on the modified version of the BDI. However, while clusters were not statistically different on the BDI, there appeared to be clinically significant differences between clusters, according to standard clinical cut-offs (Beck & Steer, 1993). Clusters 1, 2, and 3 exhibited 'mild' to 'moderate' depression, while Cluster 4 evidenced 'moderate' depression. Using the clinical cut-off for the modified BDI (scores greater than 10 suggestive of 'moderate' depression) (Beck & Steer, 1993), "Normal" and "Subsyndromal" clusters (1 and 3, respectively) were classified as 'not depressed' whereas the "Atypical" and "Frontal-striatal" subtypes

(Clusters 2 and 4, respectively) were considered to be moderately depressed (see Table 10). These latter findings provide only partial support for the hypotheses, namely that "Atypical" participants would tend to "over-report" symptoms while "Frontal-striatal" individuals would "minimize" complaints.

Contrary to predictions, 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 10).

Table 10. Demographic Characteristics of Clusters

	Cluster 1 (n = 36)		Cluster 2 (n = 42)		Cluster 3 (n = 46)		Cluster 4 (n = 19)		Post hoc Results
	M	(SD)	**M**	(SD)	**M**	(SD)	**M**	(SD)	(p<.05)
Age (years)	41.3	(7.2)	41.6	(8.3)	42.5	(9.0)	38.9	(8.5)	ns
Education (years)	15.7	(2.3)	15.1	(2.5)	14.0	(2.7)	13.2	(2.6)	1>3, 4; 2>4
Information[a]	52.3	(9.5)	48.9	(8.3)	51.9	(8.6)	47.4	(8.4)	ns
BDI[b]	17.3	(9.5)	18.2	(11.1)	16.6	(9.8)	23.4	(10.7)	ns
Modified BDI[b]	9.9	(6.6)	10.9	(7.4)	9.6	(7.1)	14.3	(8.3)	ns
PAOF Total	44.4	(23.4)	51.3	(29.9)	50.0	(26.4)	59.1	(24.9)	ns
Recent CD4 Count[c]	356	(264)	354	(221)	325	(221)	325	(183)	ns
Recent Viral Load[de]	44		45		46		37		ns
% AIDS (CDC-93)[e]	56		46		48		63		ns
% on HAART[e]	74		61		68		47		ns

Note. BDI = Beck Depression Inventory; Modified BDI = items 1-13 (cognitive and affective items only); PAOF = Patient's Assessment of Own Functioning; HAART = highly active antiretroviral therapy.
[a] WAIS-R T score (n = 138).
[b] n = 142.
[c] n = 141.
[d] percent detectable plasma viral load (n = 119).
[e] chi-square analysis.

(b) 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 statistically significant differences. In general, there was a trend towards an increasing number of memory

complaints across cluster subtypes, with "Normal" (Cluster 1) subjects reporting the fewest complaints and "Frontal-striatal" (Cluster 4) subjects endorsing the most difficulties (p = .07). (See Table 10 for the total number of PAOF complaints and Figure 3 for mean level of subjective complaints across cluster subtypes.)
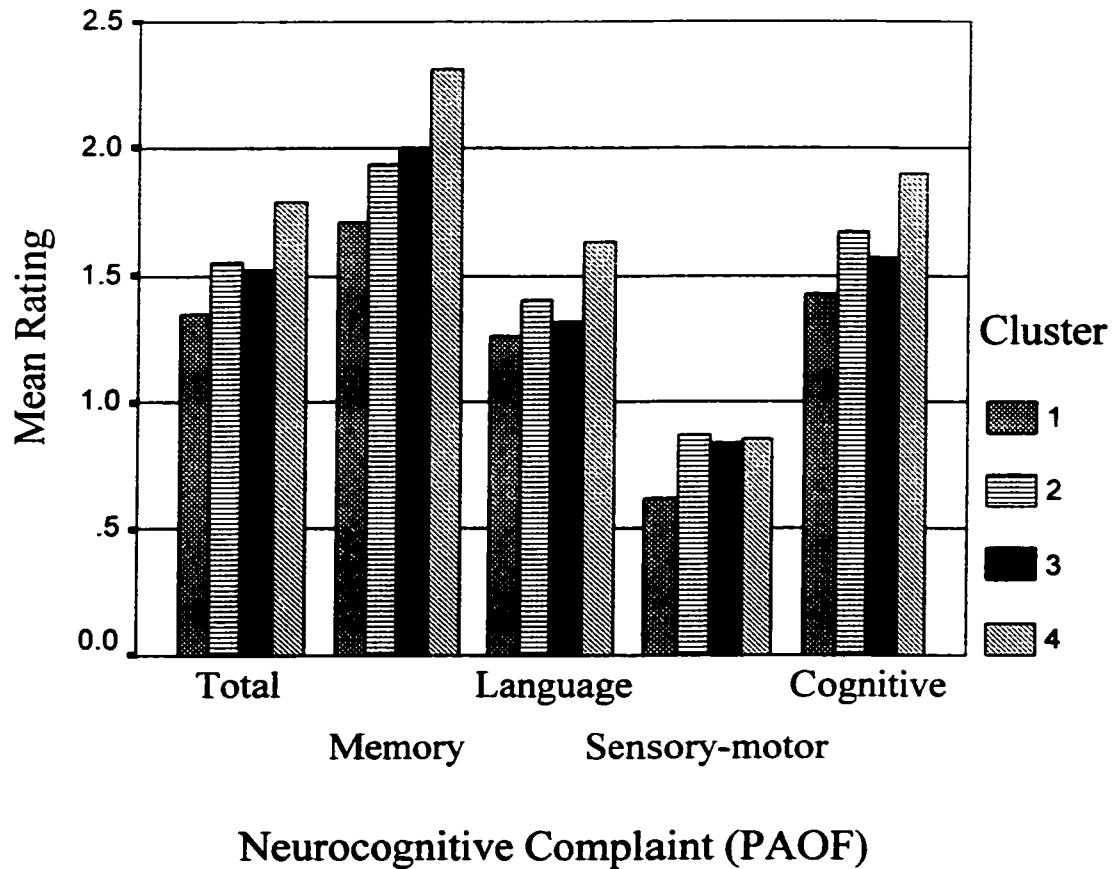
Figure 3. Subjective neurocognitive complaints of four cluster subtypes. PAOF = Patient's Assessment of Own Functioning.

A discriminant function analysis was performed with PAOF summary scores (memory, language, motor, and cognitive) as predictors and cluster membership as the grouping variable. Number of cluster subjects correctly classified were as follows: 17 (47%) in Cluster 1, 10 (24%) in Cluster 2, 11 (24%) in Cluster 3, and 10 (53%) in Cluster

4. A total of 34% of subjects were correctly classified. Altogether, these findings suggest that the number and type of subjective cognitive complaints do not solely predict cluster membership.

Given recent research indicating metamemory-memory subgroups (i.e., groups vary in the accuracy of their self-reported memory difficulties) (Hinkin et al., 1996; Rourke et al., 1999b), the accuracy of cognitive complaints of cluster subtypes was evaluated. Specifically, in accordance with Rourke et al. (1999b), the PAOF memory scale (10 items) was used as an index of subjective memory complaints and the CVLT List A trials 1-5 Total T score (CVLT T score) as an objective measure of overall learning efficiency. A discriminant function analysis was performed to evaluate whether subjective memory complaints (PAOF memory score) in conjunction with objective memory performance (CVLT T score) were predictive of cluster membership. The number of cluster subjects correctly classified were as follows: 25 (69%) in Cluster 1, 27 (64%) in Cluster 2, 25 (54%) in Cluster 3, and 17 (90%) in Cluster 4. A total of 66% of subjects were correctly classified. These results suggest that the combination of subjective and objective memory measures tend to be better predictors of cluster membership than subjective complaints alone.

(c) Neuropsychological data.

The validity of the four-cluster solution was also evaluated with neuropsychological measures. One-way ANOVAs and 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 11). On variables of attention and psychomotor speed, significant

differences were obtained on the Symbol Digit Modalities Test [$F_{(3, 128)}$ = 2.62, p < .05], with Cluster 4 performing significantly worse than Cluster 1. Differences in performance on Trails B approached significance [$F_{(3,138)}$ = 2.46, p < .06], with post hoc comparisons revealing Cluster 1's superiority over Cluster 3. These differences, however, were not significant after controlling for the effects of education.

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 non-dominant [$F_{(3,137)}$ = 4.01, p < .01] hands. The "Normal" subtype (Cluster 1) exhibited significantly faster speeds than all other clusters for the dominant and non-dominant hand trials.

In the language domain, significant differences were found on the Boston Naming Test [$F_{(3,138)}$ = 2.61, p < .05] with the "Normal" subgroup (Cluster 1) achieving significantly higher scores than the "Subsyndromal" and "Frontal-striatal" subgroups (Clusters 3 and 4, respectively). The "Atypical" subtype (Cluster 2) was also superior to the "Frontal-striatal" cluster on this task. On category fluency, clusters demonstrated statistically significant differences [$F_{(3,138)}$ = 6.89, p < .001], with the "Frontal-striatal" subtype (Cluster 4) exhibiting 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 in the number of categories achieved [$F_{(3,131)}$ = 2.75, p < .05] and in the total number of errors [$F_{(3,131)}$ = 3.39, p < .05]. In comparison to the "Normal" subgroup (Cluster 1), the "Frontal-striatal" subtype (Cluster 4) achieved a significantly lower number of categories. Also, both the "Subsyndromal" and "Frontal-striatal" subtypes (Clusters 3 and 4, respectively) exhibited a greater number

of total errors than "Normal" participants. These results highlight the "Frontal-striatal"

subgroup's difficulties with problem solving and executive type skills.

Table 11. Cluster Validation with Neuropsychological Measures

NP Ability Area[a]	Normal (Cluster 1) (n = 36)		Atypical (Cluster 2) (n = 42)		Subsyndromal (Cluster 3) (n = 46)		Frontal-striatal (Cluster 4) (n = 19)		ANOVA F value	ANCOVA F value	ANCOVA Contrasts
	M	(SD)	M	(SD)	M	(SD)	M	(SD)			
Attention/ Psychomotor Speed											
Digit Span[b]	11.0	(2.9)	10.9	(2.3)	10.8	(2.6)	9.7	(3.3)	1.04	0.63	ns
Digit Symbol[c]	58.2	(12.9)	53.8	(12.0)	52.7	(12.9)	52.0	(10.6)	1.68	0.33	ns
SDMT[d]	53.9	(8.7)	49.3	(9.5)	49.4	(12.1)	46.2	(8.3)	2.62*	1.88	ns
Trails A[c]	25.2	(5.9)	26.8	(9.5)	29.1	(13.1)	28.4	(9.4)	1.10	1.41	ns
Trails B[c]	57.9	(21.2)	64.1	(25.4)	74.7	(39.4)	74.8	(36.1)	2.46	1.80	ns
GPT – DH	64.9	(9.9)	74.7	(17.9)	75.2	(16.9)	79.8	(18.7)	4.67**	3.77*	1>2, 3, 4
GPT – NDH[c]	70.4	(12.1)	84.2	(26.6)	80.4	(18.9)	87.5	(22.5)	3.98**	4.01**	1>2, 3, 4
Language & Fluency											
Boston Naming Test	57.4	(3.1)	56.8	(3.0)	55.4	(4.0)	54.3	(3.1)	4.60**	2.61*	1>3, 4; 2>4
FAS Fluency[e]	43.0	(11.2)	40.7	(12.2)	39.2	(11.8)	41.1	(12.4)	0.47	0.16	ns
Category Fluency	52.8	(9.1)	50.6	(9.1)	48.9	(10.4)	38.9	(8.5)	9.56***	6.89***	1, 2, 3>4
Problem Solving											
WCST – Categories[f]	5.9	(0.5)	5.3	(1.6)	5.2	(1.5)	4.4	(2.3)	3.73*	2.75*	1>4
WCST – Total Errors[f]	15.5	(8.7)	23.1	(19.2)	25.9	(19.5)	34.3	(20.9)	4.79**	3.39*	1>3, 4

Note. NP = Neuropsychological; SDMT = Symbol Digit Modalities Test; GPT = Grooved Pegboard Test; DH = dominant hand, NDH = non-dominant hand; WCST = Wisconsin Card Sorting Test. * $p < .05$, ** $p < .01$, *** $p < .001$.

[a] raw scores (unless noted).

[b] WAIS-R scaled score.

[c] n = 141.

[d] n = 132.

[e] n = 142.

[f] n = 136.

DISCUSSION

The main goals of this study were three-fold: 1) to determine the underlying latent structure of the CVLT in a sample of HIV-1 infected adults, 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 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 both level and pattern of CVLT performance and were meaningfully related to specific aspects of 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 support the existence of separate but overlapping constructs of learning and memory performance in HIV-1 individuals. This study replicates the four-factor model reported by Wiegner and Donders (1999), who also applied confirmatory factor analytic procedures in their investigation of memory performance in traumatic brain injury. This approach provides a methodologically sound and punctilious analysis of memory performance using the CVLT as compared to the evaluation of memory constructs presented in the manual (Delis et al., 1987). Specifically, the factorial model suggested by Delis and associates (1987) is limited due

to methodological shortcomings associated with principal components analysis (e.g., interdependency issues, orthogonal interpretation of factors).

Four underlying memory constructs were identified using confirmatory factor analysis. The first dimension, which was labelled "Attention Span", consisted of variables that assess immediate auditory attention (List A trial 1, List B). This construct appears to reflect immediate registration or attentional capacity for information presented only once (Donders, 1999). Previous investigations have also identified constructs of attention and concentration as an important component of memory functioning using clinical (Burton, Mittenberg, Gold, & Drabman, 1999; Roth et al., 1990; Woodard, 1993) and standardized samples (Burton, Mittenberg, & Burton, 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. 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 consonant with recent CVLT literature. For instance, Donders (1999) demonstrated that active and efficient learning strategies lead to better retention of information over a delay using the children's version of the CVLT. In addition, organization of list items according to semantic categories is

linked to improved learning and memory performance in healthy young adults (Shear, Wells, & Brock, 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. This issue of multicollinearity (linear dependency of one variable on another) probably explains why models attempting to separate the Delayed Recall factor into short- versus long-delayed recall (models 5 and 7) or free versus cued delayed recall (models 6 and 8), were deemed unstable with respect to their factor solutions. 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 HIV-1 infected adults. 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). Further studies are needed to establish the clinical utility of separate delayed recall factors.

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). It may be that normal

subjects demonstrate little variability in performance on immediate and delayed tasks. In contrast, brain injured individuals are likely to evidence more variable performance, thereby resulting in distinct constructs of memory functioning.

The fourth factor, Inaccurate Recall (defined by free recall intrusions, cued recall intrusions, and false positives variables) had negative associations with the Attention Span, Learning Efficiency, and Delay 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 HIV-1 infected adults. 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

Four-cluster solution.

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 ability. The following descriptors seemed appropriate to characterize the derived CVLT subtypes: Normal (Cluster 1), Atypical (Cluster 2), Subsyndromal (Cluster 3), and Frontal-striatal

(Cluster 4). 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 the latter evidencing deficient learning on trial 5 items. Interestingly, the Subsyndromal and Frontal-striatal subtypes (Clusters 3 and 4, respectively) differed primarily in terms of level of performance.

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 HIV-1 infected individuals (Delis et al., 1995; Peavy et al., 1994).

Subtype performance, particularly on learning efficiency (List A5) and long-delayed cued recall (LDCR) tasks allows speculation in terms of the nature and progression of memory disturbance in HIV-1 disease. That is, cluster profiles suggest that memory components are differentially affected in the course HIV-1 infection (refer to Figure 2, specifically cluster performance on List A5 and LDCR variables). Decline in delayed recall (LDCR) performance may be the earliest appearing symptom of memory dysfunction ($\underline{z}$ score for LDCR is among the lowest in Cluster 2 profile and considerably lower than LDCR performance of Cluster 1). After some decline, delayed recall performance appears to level off or stabilize ($\underline{z}$ scores for LDCR are somewhat similar for

both Clusters 2 and 3). Next, learning efficiency (List A5) appears to decline quickly (z score for List A5 is notably lower in Cluster 3 profile compared to List A5 z score for Cluster 2). Lastly, it appears that both delayed recall and learning efficiency deteriorate (Cluster 4 performance on List A5 and LDCR is markedly impaired and substantially lower than that of Cluster 3), reflecting overall learning and memory impairment.

In brief, it appears that the progression of memory disturbance in HIV-1 infection, from early to later stages of decline, is as follows: delayed recall followed by learning efficiency and then both delayed recall and learning efficiency. Based on this sequence of memory dysfunction, one plausible hypothesis may be that HIV-1 infection affects the automatic aspects of memory (i.e., delayed recall) first, followed by more effortful processing (i.e., learning efficiency). These predictions are tenuous however, given the cross-sectional nature of the data. Longitudinal studies would permit evaluation of these hypotheses.

As mentioned above, List A trial 5 and long-delayed cued recall variables best differentiated among the four clusters. The List A trial 1 (attention span) variable distinguished mostly the Normal and Frontal-Striatal subtypes. With advanced HIV-1 infection, decreased attention may negatively impact encoding of information which in turn may influence other aspects of memory performance (Palav, O'Bryant, Westervelt, & McCaffrey, 2000). In contrast, the List A trial 1 variable did not differentiate between relatively less impaired subtypes (i.e., Atypical and Subsyndromal). One likely reason for this is that immediate attention span seems to be relatively well preserved in HIV-1 infection. Immediate registration on trial 1 of lists A and B may reflect "simple" attentional brain systems as opposed to more complex attentional systems such as divided

attention (e.g., E. M. Martin et al., 1995) and working memory (e.g., Bartok et al., 1997; Stout et al., 1995). Given this inherent limitation in the interpretation of the CVLT attention factor, it is likely that examination of other neuropsychological indices of attention and concentration is necessary in order to obtain a more comprehensive picture of the attentional disturbance in HIV-1 infection.

Finally, cued recall intrusions (CINT) was the least discriminating variable with all four memory subtypes performing within one standard deviation of the mean on this variable. Overall, participants in this study tended to make few recall errors on the CVLT. Therefore, this finding suggests that recall accuracy may be less relevant for characterizing memory profiles in HIV-1 infection than it is for other neurological disorders. Low intrusion errors have been associated with a "subcortical" memory profile, whereas high intrusion rates are more typical of "cortical" conditions such as Alzheimer's disease and alcoholic Korsakoff syndrome (Butters et al., 1987; Butters, Wolfe, Granholm, & Martone, 1986; Delis et al., 1991). Increased intrusion rates have also been associated with dominant or bitemporal lobe lesions (Crosson, Sartor, Jenny III, Nabors, & Moberg, 1993). It is certainly plausible that with increased cortical involvement in HIV-1 infection, the construct representing inaccurate recall may play a more contributory role in the overall memory performance of HIV-1 infected individuals. Future studies are needed to determine whether these four memory constructs are reproducible across more advanced stages of HIV-1 disease.

Cluster description.

Informal comparisons of the memory subtypes on other CVLT indices revealed several findings compatible with a "subcortical" memory profile. As expected, the

clusters demonstrated intact retention of information over a delay (i.e., little forgetting). Subtypes made very few inaccurate responses (i.e., intrusions, false positives) and did not demonstrate vulnerability to the effects of interference. These findings appear compatible 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 susceptibility 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).

A significant feature of a "subcortical" memory profile is improved recognition memory relative to free recall (e.g., Butters et al., 1987). In this investigation, only the Frontal-striatal subtype appeared to benefit from a recognition format compared to free recall. In accordance with the literature (e.g., Delis et al., 1991; Massman et al., 1992), this recall-recognition discrepancy may be suggestive of possible retrieval deficits in this subgroup of individuals. However, this interpretation warrants caution. For example, Wilde, Boake, and Sherer (1995) did not find evidence to support the recall-recognition difference as a marker of retrieval difficulties in patients with closed head injury. While the retrieval deficit hypothesis in HIV-1 infection/AIDS has clinical appeal (given anatomical evidence of disruption in subcortical brain systems), further studies are needed to determine whether the recall-recognition discrepancy is indeed evidence of retrieval failure in HIV-1 infection.

Furthermore, retrieval deficits should not be viewed synonymously with subcortical dysfunction since it is possible that cortical involvement may also produce deficient retrieval (Delis et al., 1995). There has been suggestion that the retrieval

disturbances associated with cortical dementias (i.e., AD) resemble those of subcortical dementias (i.e. HD) (see Brandt, Corwin, & Krafft, 1992). Therefore, given this contradictory evidence, alternate methods of operationalizing the retrieval deficit may be necessary in different clinical populations. Functional brain imaging during cognitive challenges may be helpful in fractionating brain systems important in different aspects of memory functioning.

On the CVLT, the ability to discriminate target list items from distracter items (discriminability) allows inference pertaining to the examinee's encoding ability. In particular, poor discriminability is suggestive of an encoding problem (Delis et al., 1987, 1991, 1995). Among the four memory subtypes, only the Frontal-striatal subtype participants exhibited mildly impaired discriminability. Together, the memory profile of low discriminability and improved recognition relative to free recall suggests both encoding and retrieval disturbances in the Frontal-striatal subtype. These results are consistent with those reported by Delis and colleagues (1995) in their investigation of HIV-1 infected adults with minor cognitive/motor disorder (MCMD). However, interpretation of these findings should take into account the above-mentioned caveat regarding the characterization of retrieval dysfunction. Nonetheless, the findings from Delis et al. (1995) and the current thesis suggest that a strict "subcortical-cortical" dichotomy does not adequately characterize the verbal learning and memory profiles in HIV-1 infection.

External validity.

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). Contrary to expectations, subtypes did not differ in terms of subjective neurocognitive complaints or surrogate markers of HIV-1 disease (i.e., CD4 count or plasma viral load). These results are discussed in more detail below.

(a) Neuropsychological performance

Generally, memory subtype performance on neuropsychological measures was consistent with the study predictions. As expected, the Normal subtype (Cluster 1) displayed intact (i.e., average to above-average) neuropsychological performance in all ability areas. This subtype's scores were superior compared to other subtypes on measures of psychomotor speed and dexterity, confrontational naming, category fluency, and non-verbal problem solving. Atypical subjects (Cluster 2) performed similar to the Normal subtype, with the exception of 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., 1993b; Sacktor et al., 1996). Longitudinal research is necessary to ascertain whether these atypical findings reflect HIV-related neuropsychological complications and whether over time there may be progression of neuropsychological impairment. A mild and "spotty" neuropsychological profile was predicted for the Subsyndromal subtype (Cluster 3). This hypothesis was generally supported. Subsyndromal individuals displayed poorer performance relative to the Normal subtype in the areas of psychomotor speed, confrontational naming, and some elements of problem solving (i.e., number of errors). 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 strongly argue against the notion of a unitary neuropsychological profile.

These findings are somewhat consonant with those of van Gorp et al. (1993). Using a broad sample of HIV-1 infected participants, these authors identified three neuropsychological subtypes: normal/unimpaired subjects (Cluster 1, 39% of total sample), depressed subjects with psychomotor slowing and decreased verbal memory (Cluster 2, 28% of total sample), and subjects with lowered overall neuropsychological performance and normal mood (Cluster 3, 33% of total sample). Interestingly, the pattern of neuropsychological performance depicted by Cluster 2 (psychomotor slowing, reduced verbal memory, depression) is consistent with a "subcortical" profile. Cluster 3's diffuse neuropsychological impairment seems to best resemble the Frontal-striatal subtype in this study. However, the present study failed to find evidence of normal mood in this subtype. In contrast, these participants endorsed the highest level of depressive symptoms than any of the subtypes (discussed next).

(b) Depressive symptomatology

With regards to depressive mood symptomatology, the hypotheses were only partially supported. Statistically significant differences were not found between memory subtypes on self-reported depressive complaints. However, clinically 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 Atypical and Frontal-striatal subtypes had mean scores considered to reflect 'moderate' depressive symptoms.

First, the Atypical subtype's tendency to endorse depressive complaints, despite overall normal neuropsychological performance, is compatible with an "over-reporters" subgroup reported in memory-metamemory investigations (Hinkin et al., 1996; Rourke et al., 1999b). Secondly, in contrast to previous findings (Hinkin et al., 1996; Rourke et al., 1999b), a so-called "minimizer" subgroup was not found in this study. The Frontal-striatal subtype, the most neuropsychologically impaired subgroup in this sample, reported the most (not the least) number of depressive symptoms compared to other subtypes. At the present time, it is difficult to resolve this discrepancy. Certainly subgroup formation was based on different methodological techniques in both studies, with Rourke et al. (1999b) utilizing clinical cut-offs whereas the present thesis employed empirically derived methods (i.e., confirmatory factor and cluster analyses). Moreover, the number and types of variables used for subgroup classification were also different. Clearly, further work is needed to assess the heterogeneity within specific clinical subgroups as well as the essential characteristics that define the limits of each of the clinical memory subtypes or syndromes.

Nevertheless, 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 may provide support for the organic etiology of mood disturbance in this subset of HIV-1 infected individuals.

(c) Subjective neurocognitive complaints

One of the major objectives of this study was to delineate the relationship between memory profiles and subjective neurocognitive complaints. It was anticipated that a better understanding of patterns of memory performance would further clarify the extent or nature of self-reported cognitive (or memory) complaints. However, in contrast to predictions, clinical memory subtypes were not differentiated on the basis of subjective complaints alone. Instead, the combination of subjective and objective measures of memory performance seemed to be more predictive of subtype membership. These results, compatible with previous literature, strongly suggest 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). Again, gauging the individual's level of accuracy (e.g., based on subjective/objective discrepancy) appears to be a more fruitful approach than relying exclusively on subjective complaints (Rourke et al., 1999a, 1999b).

(d) Markers of HIV-1 disease

Another major research question addressed in this study was whether subtypes differed according to severity of HIV-1 disease. The hypothesis that individuals exhibiting memory impairment (i.e., Subsyndromal and Frontal-striatal subtypes) would have more advanced HIV-1 illness was not supported. The failure to find a significant relationship between markers of HIV-1 disease (i.e., CD4 count, CDC stage, and viral load) and memory subtypes was not surprising. Previous investigations have also failed to find significant associations between markers of immune functioning and neuropsychological performance (e.g., Miller et al., 1990; van Gorp et al., 1993; Villa et

al., 1996). However, this is an important finding as it suggests that memory performance may not be directly related to immunological status in HIV-1 infection/AIDS. 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., 1999b). 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.

(e) Demographic data

An unexpected finding was that individuals in the Frontal-striatal group had significantly fewer years of education than the other subtypes. This finding is intriguing in the context of 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. It is conceivable that individuals with reduced cerebral reserve may be more susceptible to the effects of HIV-1 infection on the brain. Previous studies have demonstrated that low education levels (Maj et al., 1994; Satz et al., 1993) and low cognitive reserve (defined by years of education, estimated premorbid intelligence, and occupational attainment) (Stern, Silva, Chaisson, Evans, 1996) are associated with neuropsychological impairment in early-stage HIV-1 disease. Furthermore, recent evidence indicates that estimated premorbid intelligence also has a moderating effect on neuropsychological functioning in more advanced HIV-1 illness (Basso & Bornstein, 2000).

General Implications

The present investigation suggests that interpretation of memory performance in HIV-1 infected adults 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 at a later time, and the ability to retrieve new information all have important implications for progress in rehabilitation as well as for tasks of daily living. Therefore, CVLT memory profiles should provide clinicians with a useful framework to guide assessment and rehabilitation of HIV-1 infected individuals. Ultimately however, the use of other converging sources of information (e.g., interview, behavioural observations, psychometric evaluations, premorbid coping, personality, etc.) will provide a clearer clinical picture.

The current findings also demonstrate that memory profiles (particularly levels of performance) appear to be predictive of neuropsychological status (i.e., psychomotor speed and dexterity, confrontation naming, category fluency, and novel nonverbal problem solving). In particular, learning efficiency and delayed recall seem to be the most important aspects of memory performance with respect to functional (neuropsychological) outcome. In contrast, verbal memory performance in HIV-1 does not seem to be directly predictive of medical status/markers of HIV-1 disease. Moreover,

the present findings emphasize that self-reported cognitive complaints should be interpreted within the context of other data (e.g., neuropsychological status, reports from significant others/heath-care providers familiar with the patient).

The identification of robust memory subtypes with associated neuropsychological sequelae may also have important prognostic implications. Of note, memory profiles may serve as early indicators of HIV-1-associated cognitive decline. Specifically, the determination of core memory subtypes may provide a powerful tool for identifying individuals who may benefit from treatment, thereby slowing disease progression and consequently improving quality of life. In addition, early detection may foster the implementation of compensatory strategies to help individuals circumvent areas of weakness and improve efficiency with activities of daily living. Conversely, individuals with so-called "normal" learning and memory profiles may be reassured of their relatively preserved cognitive status. Although more work is clearly needed in identifying core HIV-1 memory subtypes, the prognostic utility of memory subtypes will be an important avenue of future neuropsychological research.

Of theoretical relevance, these findings argue against a strict "subcortical" versus "cortical" distinction for characterizing memory profiles in HIV-1 infection. The present findings indicate that a subset of HIV-1 infected individuals (i.e., Normal [25%] and Atypical [29%]) exhibit little or no neuropsychological impairment. Another subset (i.e., Subsyndromal [32%]) evidence subtle or "spotty" deficits on neuropsychological tests. Lastly, a minority of individuals (i.e., Frontal-striatal [13%]) demonstrate more diffuse impairment, suggestive of subcortical and cortical (likely frontal) involvement.

Although the "subcortical" or "cortical" classification may have some utility, the heterogeneity of neuropsychological and neuropathological symptomatology in HIV-1 infection (see Grant, Marcotte, Heaton, & the HNRC Group, 1999) suggests that a more detailed analysis of neuroanatomical regions/circuits may be more appropriate. In the present study, memory subtypes and associated neuropsychological impairment suggest involvement of frontal and subcortical regions. Specifically, the data seem to indicate a progressive loss of functional integrity of the frontal-striatal circuitry. Moreover, features of frontal-striatal disruption seemed to be evident in only two of the subtypes (i.e., Subsyndromal and Frontal-striatal), suggesting that frontal-striatal dysfunction may be restricted to a subset of individuals with HIV-1 infection. A brief background in the neuroanatomy of memory and frontal-striatal circuitry is provided to aid understanding of how these data may implicate a selective disruption of frontal-striatal systems.

Neuropsychological, neuroimaging, and neuroanatomical evidence supports the existence of multiple memory systems associated with specific anatomical regions (e.g., Mishkin & Appenzeller, 1987; Squire, 1987; Squire & Zola, 1998; Yancey & Phelps, 2001; Zola-Morgan & Squire, 1993). Two major memory systems are recognized. The medial temporal lobe and hippocampal system are thought to mediate long-term storage of newly learned information. The hippocampus, in particular, appears to be critical in processing memories of episodic or factual information (referred to as declarative memory) (Squire, 1987; Tulving, 1987). Damage to the medial temporal lobe (e.g., hippocampus) or diencephalic structures (e.g., dorsomedial thalamus, mamillary bodies) are associated with an amnestic syndrome (Squire, 1987).

There are also multiple interacting memory systems linking frontal and subcortical regions, specifically between the thalamus, basal ganglia, hypothalamus, and basal forebrain (Crosson, 1992). Frontal-subcortical memory systems appear to be involved in memory activation and search functions (with lesions resulting in impaired retrieval of information with relatively preserved recognition) (Cummings, 1993a). In other words, there seems to be a general deficit in the initiation of systematic retrieval strategies for accessing stored information (Butters et al., 1986). Memory impairment associated with frontal lobe damage is markedly different from that seen in individuals with medial temporal lobe or diencephalic lesions. New learning does not appear to be affected in patients with frontal lobe damage (Shimamura, Janowsky, & Squire, 1991). Both encoding and storage of information are intact presumably because hippocampal-diencephalic circuits are spared. Instead, memory impairment associated with frontal lobe dysfunction is characterized by disturbances in the strategic or organizational aspects of learning and memory which may influence encoding and retrieval of information (Shimamura et al., 1991; Stuss et al., 1994).

Models of frontosubcortical circuitry (cortico-basal ganglia-thalamo-cortical circuits) are thought to involve three functional domains (i.e., motor, prefrontal, and limbic). These structurally and functionally separate circuits are associated with cognitive, behavioural, and emotional functioning (Alexander & Crutcher, 1990). Five major frontal-striatal circuits have been described: motor (originates in supplementary motor area), oculomotor (originates in the frontal eye field), dorsolateral (executive functions), orbitofrontal (inhibitory processes), and anterior cingulate (initiation, motivation, and drive) (Alexander, Crutcher, & De Long, 1990; Lichter & Cummings,

2001). The latter three "non-motor" circuits have origins in the prefrontal cortex and are involved in the processing of cognitive and behavioural/emotional information (Alexander et al., 1990). All five circuits share common structures linking the frontal lobes to the striatum (caudate, putamen), to the globus pallidus and substantia nigra, to the thalamus, and back to the frontal lobe (Lichter & Cummings, 2001).

Results from the present study suggest a progressive deterioration of neurobehavioural functions that are thought to be reliant on the functional integrity of frontal-striatal circuitry. Specifically, the data suggest involvement of motor, dorsolateral prefrontal, and orbitofrontal circuits. Psychomotor slowing was observed in all subtypes (i.e., Atypical, Subsyndromal, and Frontal-striatal) except for the Normal subgroup. This finding suggests that disordered motor function (i.e., motor component of psychomotor task) may be the earliest manifestation of frontal-striatal (specifically motor circuit) dysfunction in HIV-1 infection.

The data, however, are mainly consistent with involvement of the dorsolateral prefrontal circuit. Specifically, neuropsychological deficits associated with disruption of the dorsolateral prefrontal circuit include diminished cognitive flexibility, poor problem solving and difficulty generating hypotheses (as required by the Wisconsin Card Sorting Test), decreased verbal and design fluency, deficient organizational strategies for learning, and impaired retrieval of information. In addition, motor programming abnormalities are associated with dysfunction of dorsolateral prefrontal circuit (Cummings, 1993a; Lichter & Cummings, 2001).

The Frontal-striatal subtype's neuropsychological profile including psychomotor slowing, reduced verbal fluency, decreased cognitive flexibility, and poor problem

solving abilities are consistent with disruption of the dorsolateral prefrontal circuit. In addition, only individuals in the Frontal-striatal subtype (Cluster 4) displayed inefficient learning strategies characterized by poor use of semantic clustering and inconsistent recall of list items. There is evidence suggesting that memory performance is facilitated by strategic aspects of learning (e.g., planning, organization) (Shimamura et al., 1991). Moreover, prefrontal regions, including the dorsolateral prefrontal and orbitofrontal cortices have been implicated in strategic memory processes such as semantic organization of verbal information and the spontaneous generation of effective strategies during free recall (Savage et al., 2001).

Such disturbances in executive functions and memory are thought to involve projections of the dorsolateral prefrontal cortex to basal ganglia and have been observed in other "subcortical" conditions such as Huntington's disease and Parkinson's disease (Cummings, 1993a). Recent evidence suggests that the basal ganglia participates in multiple circuits involved in higher cognitive function (Middleton & Strick, 2000). Given the importance of basal ganglia in HIV-1 disease (e.g., Hinkin et al., 1995; Navia et al., 1986a; van Gorp et al., 1992), findings from the present investigation appear to reflect reduced functioning or integrity of the dorsolateral prefrontal circuit.

Further support implicating involvement of the dorsolateral prefrontal circuit in this sample of individuals with HIV-1 infection is based on the extent of depressive symptomatology. Depression is linked to fronto-striatal structures, namely the frontal lobes and caudate nucleus. Specifically, depression has been described with lesions of the dorsolateral prefrontal cortex and caudate nucleus (Cummings, 1993b). Neuroimaging investigations have also provided strong support for the dorsolateral prefrontal cortex in

negative mood states (e.g., Liotti & Mayberg, 2001). In addition, the orbitofrontal circuit also appears to be involved in depression with studies demonstrating reduced metabolic activity in the orbitofrontal cortex (Mayberg, 1994; Mayberg et al., 1990, 1992). In the present study, the Frontal-striatal subgroup endorsed mood symptomatology suggestive of 'moderate' depression and also reported the most neurocognitive complaints than any other subtype. Together, these findings demonstrate that the functional integrity of dorsolateral prefrontal and orbitofrontal circuits may be compromised in this subgroup of HIV-1 infected individuals.

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 Subsyndromal subtype (Cluster 3) exhibited subtle and "spotty" impairment and 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 dorsolateral prefrontal circuit). Lastly, profiles associated with the Normal (Cluster 1) and Atypical (Cluster 2) subtypes suggest relatively preserved functioning of frontal-striatal circuits. Prospective 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 thesis, 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.

In sum, the existence of anatomical and/or functional brain systems linking frontal and subcortical structures suggests that the "subcortical" versus "cortical" conceptualization of memory performance may be too simplistic. Instead, characterizing subtypes of memory performance on the basis of involvement of separate and dissociable frontal-striatal systems may yield a more accurate depiction. In particular, current models of the functional correlates of frontal-striatal circuits may provide a more useful characterization of memory (neuropsychological) sequelae associated with HIV-1 infection than the "subcortical-cortical" dichotomy used previously. Overall, these findings highlight the importance of assessing the functional integrity of frontal-striatal circuitry in HIV-1 infection.

Limitations

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 and that a sample size of 200 is preferable (Kline, 1998). The sample size of 154 in this study, while meeting minimum requirements, may not have been sufficiently large enough for evaluating the proposed models. Despite this limitation, the present sample was deemed to be "clean" given adherence to strict inclusionary and exclusionary criteria for participant selection. Nonetheless, replication with larger samples is necessary in order to validate findings from the present investigation.

While this study clarifies the nature and extent of memory disturbances in HIV-1 infection, the generalizability of these findings are 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. However, given the broad recruitment of participants, these results are applicable to patients referred from medical and psychiatric clinics as well as those who volunteer in research studies. Further studies are needed to determine whether these findings generalize to other HIV-1 infected groups including women, ethnic groups, and different at-risk populations (e.g., intravenous drug use, blood transfusions) and to HIV-1 infected individuals with premorbid or confounding characteristics (e.g., neurological complications, substance abuse, psychiatric illnesses).

Future Directions

Use of confirmatory factor analytic models to evaluate the latent structure of a memory instrument and was a notable strength of this study. This enabled the selection of clustering variables on the basis of theoretical considerations. Future research should use similar methodologically sound principles to determine the robustness of these four memory subtypes across different memory instruments. In addition, other hypothesized factor models should be evaluated in terms of their applicability to HIV-1 infection. For example, given that participants in the present study made relatively few recall errors (e.g., false positives), future studies should consider using the discriminability variable as part of the Inaccurate Recall factor.

In addition, follow-up studies are important for evaluating the stability of HIV-1 clinical memory subtypes. Another aim of longitudinal investigations should be to

determine whether and how memory disturbance in HIV-1 infection may progress. For example, do Subsyndromal individuals eventually exhibit memory deficits similar to individuals in the Frontal-striatal subtype? Do a subset of Normals or Atypical individuals evidence cognitive deterioration with advancing HIV-1 disease? Would Atypical participants resemble Normals if treated for depression? In addition, neuroimaging studies are needed to increase understanding of anatomical/functional substrates of clinical memory profiles. 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 immense relevance for this population of young to middle aged individuals.

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Appendix A

American Academy of Neurology (AAN) Diagnostic Criteria for HIV-1-Associated Cognitive/Motor Complex

All of the following diagnoses require laboratory evidence for systemic HIV-1 infection (ELISA test confirmed by Western blot, polymerase chain reaction, or culture)

I.   Sufficient for diagnosis of AIDS

HIV-1-associated dementia complex

1. Acquired abnormality in at least *two* of the following cognitive abilities (present for at least 1 month): attention/concentration, speed of processing, abstraction/reasoning, visuospatial skills, memory/learning, and speech/language.

   a)   The decline should be verified by reliable history and mental status examination. In all cases, when possible, history should be obtained from an informant, and examination should be supplemented by neuropsychological testing.

   b)   Cognitive dysfunction causing impairment of work or activities of daily living. This impairment should not be attributable solely to severe systemic illness.

2. At least *one* of the following:
   a)   Acquired abnormality in motor function or performance verified by clinical examination (e.g., slowed rapid movements, abnormal gait, limb incoordination, hyperreflexia, hypertonia, or weakness), neuropsychological tests (e.g., fine motor speed, manual dexterity, perceptual motor skills), or both.

   b)   Decline in motivation or emotional control or change in social behavior. This may be characterized by any of the following: change in personality with apathy, inertia, irritability, emotional lability, or new onset of impaired judgment characterized by socially inappropriate behavior or disinhibition.

3. Absence of clouding of consciousness (delirium) during a period long enough to establish the presence of #1.

4. Evidence of another etiology, including active CNS opportunistic infection or malignancy, psychiatric disorders (e.g., depressive disorder), active alcohol or substance use, or acute or chronic substance withdrawal, must be sought from history, physical and psychiatric examination, and appropriate laboratory and radiologic investigation (e.g., lumbar puncture, neuroimaging). If another potential etiology (e.g., major depressive disorder) is present, it is *not* the cause of the above cognitive, motor, or behavioral symptoms and signs.

II. Not sufficient for diagnosis of AIDS

HIV-1-associated minor cognitive/motor disorder

1. At least two of the following acquired cognitive, motor, or behavioral symptoms (present for at least 1 month) verified by reliable history (when possible, from an informant):
   a) impaired attention or concentration
   b) mental slowing
   c) impaired memory
   d) slowed movements
   e) incoordination
   f) personality change, or irritability or emotional lability

   Acquired cognitive/motor abnormality verified by clinical neurologic examination or neuropsychological testing (e.g., fine motor speed, manual dexterity, perceptual motor skills, attention/concentration, speed of processing, abstraction/reasoning, visuospatial skills, memory/learning, or speech/language).

2. Disturbance from cognitive/motor/behavioral abnormalities (see #1) causes mild impairment of work or activities of daily living (objectively verifiable or by report of a key informant).

3. Does not meet criteria for HIV-1-associated dementia complex or HIV-1-associated myelopathy.

4. No evidence of another etiology, including active CNS opportunistic infection or malignancy, or severe systemic illness determined by appropriate history, physical examination, and laboratory and radiologic investigations (e.g., lumbar puncture, neuroimaging). The above features should not be attributable solely to the effects of active alcohol or substance use, acute or chronic substance withdrawal, adjustment disorder, or other psychiatric disorders.

Note. From AAN (1991).

<u>Appendix B</u>

Patient's Assessment of Own Functioning Interview

ID #: _____   **Date:** _____

<u>Instructions</u>: **Please answer each of the following questions by placing a check next to the response which most accurately describes the way you have been recently**

<u>MEMORY</u>

1. How often do you forget something that has been <u>told</u> to you within the <u>last day or two</u>?

         ( )   almost always
         ( )   very often
         ( )   fairly often
         ( )   once in a while
         ( )   very infrequently
         ( )   almost never

2. How often do you forget <u>events</u> which have occurred in the <u>last day or two</u>?

         ( )   almost always
         ( )   very often
         ( )   fairly often
         ( )   once in a while
         ( )   very infrequently
         ( )   almost never

3. How often do you forget <u>people</u> whom you met in the <u>last day or two</u>?

         ( )   almost always
         ( )   very often
         ( )   fairly often
         ( )   once in a while
         ( )   very infrequently
         ( )   almost never

4. How often do you forget <u>things</u> that you knew a <u>year or more ago</u>?

         ( )   almost always
         ( )   very often
         ( )   fairly often
         ( )   once in a while
         ( )   very infrequently
         ( )   almost never

5. How often do you forget <u>people</u> whom you knew/met <u>a year or more ago</u>?

        ( ) almost always
        ( ) very often
        ( ) fairly often
        ( ) once in a while
        ( ) very infrequently
        ( ) almost never

6. How often do you lose track of time, or do things either earlier or later than they are usually done or are supposed to be done?

        ( ) almost always
        ( ) very often
        ( ) fairly often
        ( ) once in a while
        ( ) very infrequently
        ( ) almost never

7. How often do you fail to finish something you start because you forgot that you were doing it? (Include such things as forgetting to put out cigarettes, turn off stove, etc.)

        ( ) almost always
        ( ) very often
        ( ) fairly often
        ( ) once in a while
        ( ) very infrequently
        ( ) almost never

8. How often do you fail to complete a task that you start because you have forgotten how to do one or more aspects of it?

        ( ) almost always
        ( ) very often
        ( ) fairly often
        ( ) once in a while
        ( ) very infrequently
        ( ) almost never

9. How often do you lose things or have trouble remembering where they are?

        ( ) almost always
        ( ) very often
        ( ) fairly often
        ( ) once in a while
        ( ) very infrequently
        ( ) almost never

10. How often do you forget things that you are supposed to do or have agreed to do (such as putting gas in the car, paying bills, taking care of errands, etc.?)

( ) almost always
( ) very often
( ) fairly often
( ) once in a while
( ) very infrequently
( ) almost never

LANGUAGE AND COMMUNICATION

11. How often do you have difficulties understanding what is said to you?

( ) almost always
( ) very often
( ) fairly often
( ) once in a while
( ) very infrequently
( ) almost never

12. How often do you have difficulties recognizing or identifying printed words?

( ) almost always
( ) very often
( ) fairly often
( ) once in a while
( ) very infrequently
( ) almost never

13. How often do you have difficulty understanding reading material which at one time you could have understood?

( ) almost always
( ) very often
( ) fairly often
( ) once in a while
( ) very infrequently
( ) almost never

14. Is it easier to have people show you things than it is to have them tell you about things?

( ) almost always
( ) very often
( ) fairly often
( ) once in a while
( ) very infrequently
( ) almost never

15. When you speak, are your words indistinct or improperly pronounced?

( ) almost always
( ) very often
( ) fairly often
( ) once in a while
( ) very infrequently
( ) almost never

Note: If this happens, how often do people have difficulty understanding what words you are trying to say?

( ) almost always
( ) very often
( ) fairly often
( ) once in a while
( ) very infrequently
( ) almost never

16. How often do you have difficulty thinking of the names of things?

( ) almost always
( ) very often
( ) fairly often
( ) once in a while
( ) very infrequently
( ) almost never

17. How often do you have difficulty thinking of the words (other than names) for what you want to say?

( ) almost always
( ) very often
( ) fairly often
( ) once in a while
( ) very infrequently
( ) almost never

18. When you write things, how often do you have difficulty forming the letters correctly?

( ) almost always
( ) very often
( ) fairly often
( ) once in a while
( ) very infrequently
( ) almost never

19. Do you have more difficulty spelling, or make more errors in spelling, than you used to?

    ( ) almost always
    ( ) very often
    ( ) fairly often
    ( ) once in a while
    ( ) very infrequently
    ( ) almost never

USE OF HANDS

20. How often do you have difficulty performing tasks with your <u>right</u> hand (including such things as writing, dressing, carrying, lifting, sports, cooking, etc.)?

    ( ) almost always
    ( ) very often
    ( ) fairly often
    ( ) once in a while
    ( ) very infrequently
    ( ) almost never

21. How often do you have difficulty performing tasks with your <u>left</u> hand?

    ( ) almost always
    ( ) very often
    ( ) fairly often
    ( ) once in a while
    ( ) very infrequently
    ( ) almost never

SENSORY-PERCEPTUAL

22. How often do you have difficulty <u>feeling</u> things with your <u>right hand</u>?

    ( ) almost always
    ( ) very often
    ( ) fairly often
    ( ) once in a while
    ( ) very infrequently
    ( ) almost never

23. How often do you have difficulty <u>feeling</u> things with your <u>left hand</u>?

    ( ) almost always
    ( ) very often
    ( ) fairly often
    ( ) once in a while
    ( ) very infrequently
    ( ) almost never

24. Lately do you have more difficulty than you used to in seeing all of what you are looking at, or all of what is in front of you (in other words, are some areas of your vision less clear or less distinct than others)?

( ) almost always
( ) very often
( ) fairly often
( ) once in a while
( ) very infrequently
( ) almost never

Note: If you are having this kind of trouble with your vision, is it more difficult to see things located to your right or to your left?

( ) to the left
( ) to the right
( ) cannot tell whether one side is worse than the other

HIGHER LEVEL COGNITIVE AND INTELLECTUAL FUNCTIONS

25. How often do your thoughts seem confused or illogical?

( ) almost always
( ) very often
( ) fairly often
( ) once in a while
( ) very infrequently
( ) almost never

26. How often do you become distracted from what you are doing or saying by insignificant things which at one time you would have been able to ignore?

( ) almost always
( ) very often
( ) fairly often
( ) once in a while
( ) very infrequently
( ) almost never

27. How often do you become confused about (or make a mistake about) where you are?

( ) almost always
( ) very often
( ) fairly often
( ) once in a while
( ) very infrequently
( ) almost never

28. How often do you have difficulty finding your way about?

    ( ) almost always
    ( ) very often
    ( ) fairly often
    ( ) once in a while
    ( ) very infrequently
    ( ) almost never

29. Do you have more difficulty now than you used to in calculating or working with numbers (including managing finances, paying bills, etc.)?

    ( ) almost always
    ( ) very often
    ( ) fairly often
    ( ) once in a while
    ( ) very infrequently
    ( ) almost never

30. Do you have more difficulty now than you used to in planning or organizing activities (i.e., deciding what to do and how it should be done)?

    ( ) almost always
    ( ) very often
    ( ) fairly often
    ( ) once in a while
    ( ) very infrequently
    ( ) almost never

31. Do you have more difficulty now than you used to in solving problems that come up around the house, at your job, etc.? (In other words, when something new has to be accomplished, or some new difficulty comes up, do you have more trouble figuring out what should be done and how to do it?

    ( ) almost always
    ( ) very often
    ( ) fairly often
    ( ) once in a while
    ( ) very infrequently
    ( ) almost never

32. Do you have more difficulty than you used to in following directions to get somewhere?

    ( ) almost always
    ( ) very often
    ( ) fairly often
    ( ) once in a while
    ( ) very infrequently
    ( ) almost never

33. Do you have more difficulty than you used to in following instructions concerning <u>how to</u> <u>do</u> <u>things</u>?

        ( ) almost always
        ( ) very often
        ( ) fairly often
        ( ) once in a while
        ( ) very infrequently
        ( ) almost never

34. Do you think you are as "bright" now as you were before your accident or present illness?

        ( ) yes
        ( ) no
        ( ) I don't know

Appendix C

Sample CVLT Covariance Matrix

	List A5	LDFR	SDCR	SDFR	FP	CINT	FINT	HITS	LDCR	CONS	REC	SEM	List B	List A1
List A5	2.916	1.806	1.788	1.910	-0.105	-0.233	-0.025	1.292	1.940	0.784	-0.685	1.270	0.692	0.811
LDFR	1.806	1.832	1.646	1.646	-0.147	-0.427	-0.176	1.182	1.903	0.599	-0.498	0.950	0.645	0.642
SDCR	1.788	1.646	2.043	1.730	-0.116	-0.281	-0.149	1.319	1.994	0.651	-0.678	0.956	0.606	0.567
SDFR	1.910	1.646	1.730	2.121	-0.152	-0.360	-0.157	1.173	1.884	0.714	-0.628	0.994	0.626	0.569
FP	-0.105	-0.147	-0.116	-0.152	0.205	0.119	0.052	-0.001	-0.189	-0.017	0.053	-0.063	-0.015	-0.044
CINT	-0.233	-0.427	-0.281	-0.360	0.119	0.684	0.339	-0.214	-0.468	-0.267	0.077	-0.060	-0.163	-0.099
FINT	-0.025	-0.176	-0.149	-0.157	0.052	0.339	0.621	-0.112	-0.225	-0.098	0.114	0.028	-0.097	-0.107
HITS	1.292	1.182	1.319	1.173	-0.001	-0.214	-0.112	2.393	1.410	0.396	-0.578	0.591	0.378	0.410
LDCR	1.940	1.903	1.994	1.884	-0.189	-0.468	-0.225	1.410	2.400	0.676	-0.724	0.972	0.662	0.659
CONS	0.784	0.599	0.651	0.714	-0.017	-0.267	-0.098	0.396	0.676	1.093	-0.128	0.432	0.162	0.159
REC	-0.685	-0.498	-0.678	-0.628	0.053	0.077	0.114	-0.578	-0.724	-0.128	1.079	-0.372	-0.153	-0.196
SEM	1.270	0.950	0.956	0.994	-0.063	-0.060	0.028	0.591	0.972	0.432	-0.372	1.559	0.414	0.603
List B	0.692	0.645	0.606	0.626	-0.015	-0.163	-0.097	0.378	0.662	0.162	-0.153	0.414	1.692	0.577
List A1	0.811	0.642	0.567	0.569	-0.044	-0.099	-0.107	0.410	0.659	0.159	-0.196	0.603	0.577	1.040

Note. CVLT = California Verbal Learning Test; List A5 = List A trial 5; LDCR = Long-delay cued recall; SDCR = Short-delay free recall; FP = False positives; CINT = Cued recall intrusions; FINT = Free recall intrusions; HITS = Recognition hits; LDCR = Long-delay cued recall; CONS = Recall consistency; REC = Recency; SEM = Semantic clustering; List B = List B; List A1 = List A trial 1.

VITA AUCTORIS

Shemira Murji was born in Mwanza, Tanzania on July 25, 1969. She graduated from Crescent Heights High School in Calgary, Alberta in 1987. From there, she went on to the University of Toronto where she obtained a B.Sc. in Neuroscience in 1992. She began her postgraduate studies at the University of Windsor in 1993. She obtained her Master's degree from the University of Windsor in 1995. She is currently a candidate for the Ph.D. degree in Clinical Neuropsychology at the University of Windsor and hopes to graduate in the Spring of 2001.