Subjective cognitive complaints in HIV infection: Utility in predicting neuropsychological deficits.

Sherri L. Carter
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Subjective Cognitive Complaints in HIV Infection:
Utility in Predicting Neuropsychological Deficits

by

Sherri L. Carter

M.A., University of Windsor. 1996

A Dissertation
Submitted to the Faculty of Graduate Studies and Research
through the Department of Psychology
in Partial Fulfilment of the
Requirements for the Degree
of Doctor of Philosophy at the
University of Windsor

Windsor, Ontario, Canada

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Abstract

The main objective of this retrospective study was to clarify the nature of the relationship between subjective cognitive complaints and actual neuropsychological skills in HIV-infected individuals. The sample consisted of 156 HIV-positive adults (148 men; 8 women), of whom 18 were asymptomatic (CDC-A), 61 were mildly symptomatic (CDC-B), and 76 had AIDS-defining illnesses or CD4 counts less than 200 (CDC-C). Neuropsychological functioning was assessed by clinical ratings based on neuropsychological test performance. In Part One of the study, the interrelationships among variables affecting cognitive complaints were examined using a structural equation model. Cognitive complaints independently predicted poorer neuropsychological performance, despite the influence of depressed mood and systemic illness on cognitive complaints. In Part Two, the utility of specific cognitive complaints in predicting HIV-associated neuropsychological impairment was evaluated. Cognitive complaints were most strongly associated with psychomotor skills. Spatial complaints, lexical complaints, and some memory complaints significantly predicted neuropsychological impairment. In Part Three of the study, a decision tree analysis was used to develop a screening protocol for HIV-related impairment. The Symbol Digit Modalities Test was the best predictor of global neuropsychological impairment in HIV infection. When neuropsychological performance was not included in the decision tree, increased total cognitive complaints predicted neuropsychological impairment. Overall, however, cognitive complaints did not demonstrate a strong relationship with neuropsychological impairment. The implications for the predictive value of cognitive complaints and the identification of individuals at risk for HIV-associated neuropsychological impairment are discussed.
Dedication

This work is dedicated to my parents, Ken and Carol Carter,
who taught me to believe in myself.
Acknowledgements

The work reported herein could not have been completed without the aid of many individuals. I would like to acknowledge the invaluable contributions of Dr. Sean Rourke. His generous donation of data, time, and effort made this dissertation possible, and my research skills have been greatly enhanced by his feedback and suggestions. I owe a debt of gratitude to Dr. Doug Shore for his guidance and continued encouragement over the years; he has helped me keep perspective throughout this long and sometimes daunting process. I would like to thank my committee members, Drs. B. P. Rourke, M. L. Drake and external examiner Dr. B. Axelrod for their thoughtful and instructive feedback on this project. I would like to extend my appreciation to Plenum Press for their permission to include the PAOF questionnaire in my dissertation. I would also like to acknowledge the secretarial support of Barb Zakoor, who is always willing and able to help graduate students in crisis.

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Chapter I

Introduction

As a recently discovered medical disease, infection with the human immunodeficiency virus (HIV) has been the focus of considerable attention in the past two decades and is a relatively new area of neuropsychological research. In addition to health risks, HIV infection poses a threat to neuropsychological functioning in infected individuals. Early studies described HIV-associated dementia, or HAD, in more advanced stages of the illness (Navia, Jordan, & Price, 1986; Navia & Price, 1987), but milder neuropsychological deficits in earlier stages of the infection have only recently been recognized (Grant, Marcotte, Heaton, & the HNRC group, 1999; Heaton et al., 1995). Due to advances in medical treatment, the expected lifespan of HIV-positive individuals has been extended in recent years. Consequently, these individuals are more likely to experience the impact of neuropsychological deficits on everyday activities, including social and occupational functioning.

As a result, a thorough neuropsychological evaluation is a valuable tool in ascertaining the extent and pattern of cognitive deficits in HIV-positive individuals. Neuropsychological assessment is particularly important in the early detection of neuropsychological deficits associated with HIV infection (Butters et al., 1990). However, neuropsychological impairment in the initial stages of HIV infection is mild and variable (Heaton et al., 1995; Hinkin, Castellon, Van Gorp, & Satz, 1998). Standard neuropsychological tests may not be sensitive enough to detect the subtle
neuropsychological deficits present in the early stages of the disease (Sahakian et al., 1995).

Self-reported cognitive symptoms are a potentially important source of additional information in evaluating neuropsychological skills. Increased knowledge regarding the clinical significance of cognitive complaints in HIV infection will augment the ability of clinicians to identify early neuropsychological impairment in those individuals at risk, particularly when combined with a complete neuropsychological assessment. It is especially important to identify neuropsychological deficits in HIV-positive individuals early because the potential for effective rehabilitation may be greater than in more cognitively compromised individuals.

The subjective experience of patients is not often considered in neuropsychological research. The neuropsychological literature on HIV infection, however, reflects a commendable attempt to access this potentially valuable fund of knowledge. Self-reported cognitive symptoms communicate an individual’s perception of their neuropsychological deficits and the impact of these deficits on everyday activities (Gordon, Haddad, Brown, Hibbard, & Sliwinski, 2000). In addition to the clinical benefit provided by a better understanding of cognitive symptoms, this improved knowledge will assist in validating the subjective experience of neuropsychological deficits in order to reassure and normalize the situation for individuals.

Other studies have investigated the relationship between cognitive complaints and neuropsychological skills in populations including dementia, multiple sclerosis, head injury, chronic fatigue syndrome and Lyme disease, as well as in Gulf War veterans, hemodialysis patients, and the elderly. Some of these studies have found an association between cognitive
complaints and poorer neuropsychological performance (Gass & Apple, 1997; Jonker, Launer, Hooijer, & Lindeboom, 1996; Schofield et al., 1997; Sunderland, Harris, & Baddeley, 1983; Zelinski, Gilewski, & Anthony-Bergstone, 1990). In addition to neuropsychological performance, studies have connected cognitive complaints to affective disturbances such as anxiety or depression (Bassett & Folstein, 1993; Binder, Storzbach, Anger, Campbell, & Rohlman, 1999; Brickman, Yount, Blaney, Rothberg, et al., 1996; Derouesne et al., 1989; Elkins, Pollina, Scheffer, & Krupp, 1999; Gass & Apple, 1997; Grut et al., 1993; Jorm et al., 1994; Levy-Cushman & Abeles, 1998; O'Connor, Pollitt, Roth, Brook, & Reiss, 1990; Schofield et al., 1997; Wearden & Appleby, 1996). Finally, cognitive complaints have also been associated with poor physical health in a few studies (Bassett & Folstein, 1993; Levy-Cushman & Abeles, 1998).

The present set of studies investigated the relationship between subjective cognitive complaints and actual neuropsychological skills in HIV infection. The goals of the investigation were threefold: 1) to examine the relationship between cognitive complaints and neuropsychological skills while accounting for the possible influences of mood and systemic medical illness on cognitive complaints, 2) to determine the utility of specific cognitive complaints in predicting HIV-associated neuropsychological impairment and 3) to improve the ability to identify HIV-positive individuals at risk for neuropsychological impairment based on subjective cognitive complaints and screening measures of neuropsychological functioning.

The remainder of this thesis is organized as follows. Chapter I reviews the relevant literature, discussing the epidemiology, medical effects, neuropsychological and
psychological consequences of HIV infection, and the accuracy of self-reported cognitive symptoms in this population. This review presents a general survey of neuropsychological findings for individuals with HIV and Acquired Immune Deficiency Syndrome (AIDS) and focuses on neuropsychological functioning in the earlier, rather than more advanced stages, of HIV infection. The review is not intended to be comprehensive, but it aims to provide an overview of the area as groundwork for the present set of studies. Further, Chapter I presents the objectives and hypotheses of this set of studies. Chapter II discusses the method used to address the goals and hypotheses. Chapter III presents the results, and Chapter IV discusses their implications for theoretical and clinical work.

Epidemiology

In 1978, AIDS was first recognized in the United States; by 1984, the associated virus had been isolated and characterized (Cummings & Benson, 1992). The prevalence of AIDS has increased steadily since that time. According to the World Health Organization (WHO), approximately 1.1 million people in the United States were seropositive for the virus in 1995 (Adams, Victor, & Ropper, 1997). Recent statistics published by Health Canada indicate that as of June 1999, there were 55 AIDS cases for every 100,000 people in Canada and as of August 1998, 258 cases per 100,000 in the United States (Health Canada, 1999). At the end of 1999, an estimated 49,800 individuals were HIV-positive in Canada (Centre for Infectious Disease Prevention and Control, 2000). The estimated incidence of HIV infection in Canada was 4,190 new cases in 1999 (Centre for Infectious Disease Prevention and Control, 2000).

The annual incidence of AIDS varies considerably, according to the population in
question, the criteria used to determine cases (Hinkin et al., 1998) and geographic location (Adams et al., 1997). For example, the incidence of AIDS is substantially higher in some African regions than in North America. In mid-1995, the WHO estimated that 11 million adults in sub-Saharan Africa were infected with HIV, and more than 3.2 million children and adults had contracted AIDS (Adams et al., 1997). The rapid spread of HIV and AIDS represents a major medical concern and AIDS-related programs incur significant health care costs (Cummings & Benson, 1992).

HIV infection is an acquired disease. In Canada, the primary populations to contract HIV are homosexual and bisexual men (38% of new cases in 1999) and intravenous drug users (34% of new cases in 1999) (Centre for Infectious Disease Prevention and Control, 2000). Transmission through heterosexual contact has increased over the past several years, and accounted for 21% of new cases in 1999 (Centre for Infectious Disease Prevention and Control, 2000). Individuals with hemophilia and others who receive infected blood or blood products currently have a low risk of contracting the virus (Centre for Infectious Disease Prevention and Control, 2000). AIDS may also be transmitted from mothers to infants in utero, during delivery, or through breast feeding (Cotran, Kumar, & Collins, 1999).

**Diagnosis and Classification**

Antibodies to HIV develop following exposure to the virus and this process is termed seroconversion. HIV diagnostic screening tests are used to detect the presence of HIV-antibodies. These screening tests are based on an enzyme-linked immunoassay (ELISA or EIA) (Cotran et al., 1999). A more specific technique is the Western blot test, which
identifies antibodies to specific viral proteins, and is recommended to confirm a positive screening test (Adams et al., 1997).

The most recent classification system for HIV infection was established by the Centers for Disease Control and Prevention (1992) and it is based on both level of immunosuppression (i.e., CD4 T-cell count per microliter of blood) and clinical conditions associated with the disease. Individuals are classified into one of three main categories (A, B, and C) that successively increase in disease severity. Category A applies to individuals who are either asymptomatic or minimally symptomatic (e.g., persistent generalized lymphadenopathy). Category B describes mildly symptomatic individuals who have mild physical symptoms or “minor” opportunistic infections such as oral candidiasis. Category C applies to individuals with AIDS-defining illnesses, such as Kaposi’s sarcoma or *Pneumocystis carinii* pneumonia. Each of the three main categories is further subdivided into three additional subdivisions based on degree of immunosuppression. The three subdivisions are as follows: CD4 counts of $\geq 500$ cells/mm$^3$ (Classification groups A1, B1, C1), CD4 counts of 200-499/mm$^3$ (Classification groups A2, B2, C2), and CD4 counts $< 200$/mm$^3$ (Classification groups A3, B3, C3). Thus, this revised classification system accommodates individuals whose clinical disease stage is not consistent with their level of immunosuppression (e.g., CD4 count $> 500$/mm$^3$ combined with an AIDS-defining illness).

**Medical and Neurological Effects of HIV/AIDS**

Infection with the HIV retrovirus causes an extreme reduction in cell-mediated immunity (Adams et al., 1997; Cotran et al., 1999). Effects of immunosuppression include
lymphopenia, reversal of the T-helper/T-suppressor cell ratio (i.e., CD4/CD8 lymphocytes), and reduced immunological response to antigens and mitogens (Adams et al., 1997; Cotran et al., 1999). Consequently, individuals with HIV are susceptible to a variety of opportunistic infections and neoplasms, which may affect all organ systems, including the central nervous system (CNS) (Cummings & Benson, 1992). The AIDS virus may also directly affect the CNS (Adams et al., 1997; Tyler, 1990).

The clinical presentation of HIV-positive individuals and course of their symptoms can vary substantially (Price et al., 1988). Many individuals infected with HIV are clinically asymptomatic despite being seropositive. Others demonstrate a wide range of systemic illnesses, including diarrhea, malaise, weight loss, chronic fevers, and night sweats (the AIDS-related complex), and/or widespread lymphadenopathy (Adams et al., 1997; Cotran et al., 1999; Reitan & Wolfson, 1992). Full-blown clinically significant AIDS reflects the direct effects of the AIDS virus on multiple organ systems, as well as the effects of parasitic, fungal, viral, and bacterial infections, and different types of neoplasms (Adams et al., 1997; Tyler, 1990).

Neurological abnormalities are clinically evident in 40-60% of AIDS patients, and effects on the nervous system are present in 90% of cases at autopsy (Cotran et al., 1999). AIDS is often accompanied by various peripheral neuropathies, myopathies, and/or myelopathies, including acute and chronic inflammatory demyelinating polyneuropathies and predominantly sensory polyneuropathy (Adams et al., 1997; American Academy of Neurology AIDS Task Force, 1991). HIV is believed to be directly responsible for HIV-associated dementia (HAD), aseptic meningitis, and peripheral neuropathy (Cotran et al.,

The most common opportunistic illnesses to infect the immunocompromised AIDS patient are toxoplasmosis, cytomegalic inclusion disease, cryptococcosis, herpes simplex and herpes zoster, as well as unusual types of tuberculosis (Adams et al., 1997). *Pneumocystis carinii* pneumonia is often associated with AIDS, as well as several types of cancer, including Kaposi’s sarcoma, non-Hodgkin lymphoma and cervical cancer in women (Adams et al., 1997; Cotran et al., 1999). The most common fungal infection in AIDS is candidiasis (Cotran et al., 1999).

The most recent statistics from Health Canada indicate that the median time from HIV infection to a diagnosis of AIDS is over 10 years (Centre for Infectious Disease Prevention and Control, 2000). Although this interval has been prolonged over the past two decades through pharmacological developments, it is widely held that virtually all seropositive individuals will eventually develop AIDS (Adams et al., 1997). In North America, once AIDS becomes clinically evident, 50% of infected individuals die within one year, and the majority of patients die within 3 years (Adams et al., 1997). Opportunistic infections are responsible for approximately 80% of deaths in AIDS cases (Cotran et al., 1999). Recent advances in antiretroviral drug therapy have shown promise in slowing the progression of the disease (Kalichman, Ramachandran, & Ostrow, 1998); treatment will be discussed in more detail in a later section of this paper.

**Pathology**

At autopsy, structural anomalies are present in 70 to 90% of the brains of AIDS-
infected individuals (Cummings & Benson, 1992). Computed tomography (CT) and magnetic resonance imaging (MRI) scans reveal ventricular dilatation and atrophy (Adams et al., 1997; Aylward et al., 1993; Navia & Price, 1987; Tyler, 1990) that increases with disease severity (Stout et al., 1998). Spotty changes and hyperintensity in white matter and subcortical grey matter are also evident on MRI, possibly reflecting necrosis or demyelination (Adams et al., 1997; Grant & Heaton, 1990; Navia & Price, 1987). White matter changes may also be due to alterations in the blood-brain barrier (Power et al., 1993). Myelin pallor is often present, particularly in the centrum semiovale, although the significance of this finding is unclear (Grant, 1990; Navia & Price, 1987). Decreased white matter volume and progressive reductions in the caudate nucleus are present on volumetric MRI (Aylward et al., 1995; Jernigan et al., 1993; Stout et al., 1998).

While most pathology findings are subcortical, there is also evidence of some cortical neuron loss in AIDS (Gray et al., 1991; Ketzler, Weis, Haug, & Budka, 1990). Functional MRI reveals increased cerebral blood volume primarily in the deep gray matter, but also in the cortex (Tracey et al., 1998). Positron emission tomography (PET) scans show hypermetabolism of the basal ganglia and thalamus in the early phases of HAD and both cortical and subcortical gray matter hypometabolism in later stages (Rottenberg et al., 1987). In addition to decreased white matter volume, individuals with HAD also exhibit reduced basal ganglia and posterior cortical volumes on MRI (Aylward et al., 1995; Aylward et al., 1993).

In 2/3 of individuals with AIDS, electroencephalograms (EEG) are abnormal (Cummings & Benson, 1992). Biochemical abnormalities may also be present (Chang, Ernst,
Leonido-Yee, Walot, & Singer, 1999). Cerebrospinal fluid (CSF) levels of HIV RNA (i.e., viral load) increase as the infection progresses (Gisslen, Hagberg, Fuchs, Norkrans, & Svennerholm, 1998) and are correlated with neurological signs (Di Stefano et al., 1998; Robertson et al., 1998). Plasma HIV RNA levels predict the presence of HAD (Childs et al., 1999), and CSF RNA levels are correlated with dementia severity, even after adjusting for CD4 count (McArthur et al., 1997).

The pathology of HIV and AIDS infection is characterized by perivascular and parenchymal collections of multinucleated giant cells, macrophages, and lymphocytes, which are primarily found in the centrum semiovale and subcortical gray matter (Grant & Heaton, 1990; Navia & Price, 1987). Focal rarefaction of the white matter and vacuolar myelopathy may be present (Navia & Price, 1987; Price et al., 1988; Tyler, 1990). Pathological evidence of cytomegalovirus is also present in some cases (Cummings & Benson, 1992).

Typically, HIV does not affect neurons directly (Cotran et al., 1999; Cummings & Benson, 1992; Tyler, 1990). Macrophages are the most frequently infected type of cell, and the virus also affects glia, mononuclear cells, and endothelial cells (Cummings & Benson, 1992; Grant & Heaton, 1990). Various theories have been put forth to explain the mechanism of cerebral injury in HIV (Grant & Heaton, 1990). While it is possible that HIV simply infects the brain directly (Cummings & Benson, 1992; Navia & Price, 1987), other hypotheses include neuronal damage due to a "bystander" effect (Grant & Heaton, 1990) and a "Trojan horse" hypothesis, which suggests that macrophages are responsible for the transfer of HIV to the CNS (Cotran et al., 1999; Cummings & Benson, 1992; Swindells, Zheng, & Gendelman, 1999).
**HIV-Associated Dementia (HAD)**

As the disease advances, leading to increased immunosuppression, AIDS-defining illnesses, and more severe opportunistic infections, cognitive functioning is also more likely to be affected. In the late stages of HIV infection, HAD or the AIDS dementia complex, is often present (Navia & Price, 1987). Other terms previously used to describe HAD include AIDS or HIV encephalopathy or encephalitis (Adams et al., 1997; Cummings & Benson, 1992; Navia & Price, 1987). Although HAD may present as the earliest manifestation of HIV infection, it usually emerges in the later stages of AIDS with other AIDS-defining illnesses (Navia & Price, 1987), and it is sufficient for a diagnosis of AIDS (American Academy of Neurology AIDS Task Force, 1991). Prevalence estimates for HAD have ranged widely from 15% to 60% of late-stage cases (Grant et al., 1999). HAD carries a poor prognosis and cases of dementia often result in death within 6 months of onset (McArthur et al., 1993).

HAD has been described as a progressive subcortical dementia (Cummings & Benson, 1992), although the course can be slow or rapid (Adams et al., 1997). The dementia involves neuropsychological impairment accompanied by motor deficits and/or behavioural changes (Navia et al., 1986). Cognitive features include memory loss, decreased attention and concentration, difficulty maintaining train of thought, and cognitive slowing (Adams et al., 1997; Cummings & Benson, 1992; Navia et al., 1986; Navia & Price, 1987). As HAD progresses, individuals may become disoriented or confused and demonstrate language difficulties (e.g., naming problems) (Grant, 1990), problems with visuospatial skills, calculation, and abstraction, in addition to worsening attention and memory impairment (Cummings & Benson, 1992; Grant, 1990; Heaton et al., 1996).
HAD is frequently associated with motor deficits, such as incoordination, ataxia, tremor, and impaired eye movements (Adams et al., 1997; Navia et al., 1986; Tyler, 1990). The disease may result in a positive Babinski’s sign, grasp and suck reflexes, and heightened tendon reflexes in the later stages of HAD (Adams et al., 1997; Navia et al., 1986). Eventually, progressive deterioration may lead to lower limb weakness, paraplegia, bladder and/or bowel incontinence, mutism, and severe psychomotor retardation (Adams et al., 1997; Cummings & Benson, 1992; Grant & Heaton, 1990; Navia et al., 1986; Navia & Price, 1987). HAD is frequently associated with a myelopathy (i.e., vacuolar degeneration), although this condition is not exclusive to HAD (Adams et al., 1997; Navia & Price, 1987). Additional neurological signs such as peripheral neuropathy may be present in later stages of AIDS, but they are not typically associated with HAD severity (Grant, 1990).

Grant, Heaton, and Marcotte (1997) outline the following criteria for diagnosing HAD in the HNRC (HIV Neurobehavioral Research Center) program, a large-scale study of HIV-infected individuals. Marked neuropsychological impairment must be present in at least two cognitive domains, whether determined by history, mental status examination, or formal neuropsychological assessment. Neuropsychological impairment must interfere significantly with daily functioning, such as work, home life, and social activities. Finally, neuropsychological impairment must be present for at least one month, the individual does not meet criteria for delirium, and there is no evidence of another pre-existing etiology.

Overall, the neuropsychological performance of individuals with HAD is similar to that of individuals with subcortical dementia processes (e.g., Parkinson’s disease, Huntington’s disease), as opposed to the neuropsychological profile associated with cortical
dementias, such as Alzheimer's disease (Van Gorp, Mitrushina, Cummings, Satz, & Modesitt, 1989; White et al., 1997). For example, individuals with HAD do not demonstrate the rapid forgetting associated with cortical dementias, and they benefit from recognition formats, as opposed to free recall, on memory tests such as the California Verbal Learning Test (CVLT) (White et al., 1997).

Psychometric intelligence scores are diminished in HAD, including Full Scale IQ, Verbal IQ, and Performance IQ scores (Van Gorp et al., 1989). Attention, verbal and nonverbal learning and memory, cognitive flexibility, and psychomotor speed are typically impaired (Grant & Heaton, 1990; The Dana Consortium on therapy for HIV dementia and related cognitive disorders, 1996; Van Gorp et al., 1989; White et al., 1997). Although performance on simple reaction time tests is often comparable to controls, individuals with HAD demonstrate significantly poorer performance than controls on choice reaction time tasks (Perdices & Cooper, 1989).

Behavioural changes associated with HAD include apathy, lethargy, decreased spontaneity, and social withdrawal; hallucinations and/or delusions, agitation, and psychosis occur less frequently (Cummings & Benson, 1992; Navia et al., 1986; Navia & Price, 1987). Individuals with mild HAD exhibit significantly more symptoms of depression, apathy, and extrapyramidal signs than individuals with HIV-associated minor cognitive/motor disorder (see following section) and individuals without neuropsychological impairment (The Dana Consortium on therapy for HIV dementia and related cognitive disorders, 1996). Irritability, emotional lability, and more rarely, violent behaviour, may occur in later stages of HAD (Grant & Heaton, 1990; Navia et al., 1986).
McArthur et al. (1993) examined risk factors for the development of HAD in the MACS (Multicenter AIDS Cohort Study), a large longitudinal study of homosexual and bisexual men. HAD was fairly common in their sample, and individuals were more likely to develop HAD in the later stages of HIV infection. Risk factors for more rapid development of HAD included anemia (i.e., lower levels of hemoglobin), a lower body mass index, older age, and more systemic medical symptoms prior to developing AIDS. Anemia prior to AIDS was the most significant predictor of the development of dementia. The Dana Consortium on therapy for HIV dementia and related cognitive disorders (1996) also reported that individuals with HAD showed significantly lower levels of hemoglobin and hemocrit than individuals with HIV-associated minor cognitive/motor disorder and HIV-positive individuals without neuropsychological impairment. Measures of immune status, such as CD4 lymphocyte count, were not predictive of HAD in the MACS study (McArthur et al., 1993).

**HIV-Associated Minor Cognitive/Motor Disorder**

A working group of an AIDS task force sponsored by the American Academy of Neurology, and comprised of neurologists, neuropsychologists, psychiatrists, and sociologists, proposed a new diagnosis of HIV-associated minor cognitive/motor disorder (MCMD) in 1991. A diagnosis of MCMD requires less severe cognitive and motor impairment than a diagnosis of HAD. Unlike HAD, MCMD is not sufficient for a diagnosis of AIDS (American Academy of Neurology AIDS Task Force, 1991). Diagnosis of MCMD requires at least two of the following symptoms, which have been present for a minimum of
one month: 1) impaired attention or concentration, 2) mental slowing, 3) impaired memory, 4) slowed movements, 5) incoordination, and 6) personality change, irritability, or emotional lability (American Academy of Neurology AIDS Task Force, 1991). In order to receive a diagnosis of MCMD, cognitive and/or motor symptoms should be verified by neurological examination and/or neuropsychological assessment. Furthermore, symptoms must cause at least mild impairment in work or activities of daily living.

Grant et al. (1997) outline the following criteria for determining HIV-associated mild neurocognitive disorder. Neuropsychological performance must be impaired (i.e., at least one standard deviation below the mean for age and education appropriate normative data) in at least two domains, provided that the assessment covers 1) verbal/language skills, 2) attention/speeded processing, 3) abstraction/executive functioning, 4) memory (learning and retention), 5) complex perceptual-motor performance, and 6) motor skills. In agreement with the AAN criteria, impairment must mildly interfere with day-to-day functioning, as evidenced by self-report or observation by others. The AAN time frame of one month is followed, etiologies other than HIV infection should be ruled out, and the individual must not meet criteria for delirium or dementia.

Of note, Grant et al. (1997)'s diagnostic criteria for MCMD are in part dependent on patient self-report of the significance of cognitive problems in their everyday life. Using such criteria illustrates the importance of determining the accuracy of cognitive complaints and whether there is a direct relationship between subjective complaints and neuropsychological impairment in HIV infection. According to this definition of MCMD, cognitive complaints have direct implications both with respect to diagnosis and access to appropriate healthcare
services.

**HIV-Related Neuropsychological Deficits**

While HAD is the most dramatic example of HIV-associated neuropsychological impairment, research has also documented milder neuropsychological dysfunction in HIV-positive individuals. 30-55% of individuals with HIV suffer from neuropsychological deficits, of varying severity, at some point in the illness (Heaton et al., 1995). HIV-associated neuropsychological dysfunction has been reported in the domains of attention and concentration, speed of information processing, learning novel verbal and nonverbal information, verbal fluency, psychomotor speed and abstraction (Grant, 1990; Grant et al., 1999; Heaton et al., 1995). Moreover, the pattern of neuropsychological deficits in HIV infection does not appear to vary significantly across samples from different global geographic regions (Maj et al., 1994), supporting its relative stability despite sometimes substantial individual variation.

In general, HIV-associated neuropsychological impairment is more likely to occur as the disease progresses to more advanced stages (Bornstein et al., 1991; Grant et al., 1987; Heaton et al., 1995; Lunn et al., 1991; Stern et al., 1995). For example, Bornstein, Nasrallah, Para, Whitacre, Rosenberger et al. (1993) showed that greater proportions of HIV-positive individuals demonstrate neuropsychological impairment as disease severity increases from asymptomatic to mildly symptomatic (ARC) to full-blown AIDS. This study also reported that asymptomatic individuals, mildly symptomatic individuals (ARC), and individuals with AIDS demonstrated poorer performance than controls on various neuropsychological
measures. Individuals with AIDS performed in the mildly to moderately impaired range on these measures. In contrast, the performance of asymptomatic individuals often remained within normal limits, with the exception of performance on measures of verbal memory, reaction time, and manual dexterity (i.e., Grooved Pegboard Test).

There is little doubt that neuropsychological impairment occurs in the late, symptomatic stages of AIDS. Most individuals with late HIV infection demonstrate neuropsychological impairment in learning, memory, speeded information processing, and abstraction (Grant & Heaton, 1990). In contrast, the possible presence of neuropsychological deficits in asymptomatic HIV-positive individuals was originally a controversial issue. Initial studies yielded relatively inconsistent findings in this subgroup. Although some studies suggested that asymptomatic individuals exhibit mild neuropsychological impairment in a number of neuropsychological domains (e.g., Bornstein, Nasrallah, Para, Whitacre, Rosenberger et al., 1993; Grant et al., 1987; Lunn et al., 1991), others failed to find evidence of neuropsychological impairment in asymptomatic individuals (e.g., Franzblau et al., 1991; Gibbs, Andrewes, Szmukler, Mulhall, & Bowden, 1990; Miller et al., 1990; Poutiainen et al., 1993).

Heaton et al. (1995) published a comprehensive study of the neuropsychological functioning of a group of 500 men at various stages of HIV infection. There were higher rates of neuropsychological impairment in more advanced stages of the infection. Neuropsychological impairment was present in 30.5% of their sample of asymptomatic individuals (CDC-A), 44.2% of mildly symptomatic individuals (CDC-B) and 55.6% of symptomatic individuals (CDC-C).
illness, neuropsychological deficits in asymptomatic individuals were milder and fewer neuropsychological domains were likely to be affected. These findings were consistent regardless of whether group differences were determined by statistical comparison or clinical ratings of neuropsychological profiles (Heaton et al., 1995). Neuropsychological impairment was most likely to occur on measures of attention, speeded information processing, and learning of both verbal and nonverbal material. Heaton et al. (1995) interpreted their results to reflect the early effects of HIV infection on cognitive functions subserved by subcortical or frontostriatal systems. This large-scale, methodologically sound study supports the presence of neuropsychological deficits in asymptomatic HIV-positive individuals.

Further support for neuropsychological impairment in asymptomatic individuals is provided by a review of 57 studies of neuropsychological functioning in asymptomatic individuals conducted by White, Heaton, Monsch, and the HNRC group (1995). This review reported inconsistent findings across studies. While 32% of studies reported significant performance differences between asymptomatic individuals and controls, 47% of studies failed to find significant group differences. However, median impairment rates across studies were 35% for asymptomatic individuals and 12% for seronegative controls, suggesting that neuropsychological impairment is present in some asymptomatic individuals, despite studies that fail to find group differences.

While a topic of debate at first, recent large-scale studies and reviews demonstrate that at least a subset of asymptomatic HIV-infected individuals show evidence of neuropsychological deficits in some domains. When present, neuropsychological deficits in asymptomatic individuals tend to be subtle, variable, and affect few neuropsychological
domains relative to individuals in more advanced stages of the illness (Bornstein, Nasrallah, Para, Whitacre, Rosenberger et al., 1993; Heaton et al., 1995). Findings for specific neuropsychological domains in HIV-infected individuals will be outlined in more detail in the following sections.

**Psychometric Intelligence**

Performance on the nonverbal subtests of the Wechsler Adult Intelligence Scales (WAIS) is often diminished in HIV-infected individuals, particularly in mildly symptomatic (ARC) individuals and those with AIDS (e.g., Bornstein, Nasrallah, Para, Whitacre, Rosenberger et al., 1993; Poutiainen, Iivanainen, Elovaara, Valle, & Lahdevirta, 1988). As in other neurological conditions. Digit Symbol appears to be the nonverbal subtest most sensitive to the effects of HIV infection (Becker et al., 1997; Hinkin et al., 1998). For example, Gibbs, Andrewes, Szmulker, Mulhall, and Bowden (1990) found significantly poorer performance on Digit Symbol for individuals with ARC relative to both asymptomatic individuals and controls. Presumably, performance on nonverbal subtests is adversely affected by the psychomotor slowing that is often present in individuals with HIV (Becker et al., 1997; Hinkin et al., 1998; Sacktor et al., 1996). In general, performance tends to be relatively better on the verbal subtests of the WAIS, such as the Vocabulary and Information subtests (Hinkin et al., 1998). Relative to the other verbal subtests, HIV-positive individuals are more likely to exhibit greater difficulty on the Arithmetic subtest and the digits backward component of the Digit Span subtest (Hinkin et al., 1998; Levin, Berger, Didona, & Duncan, 1992); both of these subtests are thought to tap attention and
concentration.

**Speech and Language**

The mechanics of speech are often affected in HIV-infected individuals, resulting in slowed speech, dysarthria, and/or hypophonia (Hinkin et al., 1998; Navia et al., 1986). In contrast, language is rarely affected; performance on neuropsychological measures of language is typically within normal limits (American Academy of Neurology AIDS Task Force, 1991; Hinkin et al., 1998).

Individuals with HIV sometimes demonstrate depressed performance on measures of verbal fluency, but not consistently. For example, Bornstein, Nasrallah, Para, Whitacre, Rosenberger et al. (1993) reported that individuals with AIDS demonstrated significantly poorer performance than controls and asymptomatic individuals on a verbal fluency task. Other studies have reported poorer verbal fluency performance for asymptomatic HIV-positive individuals relative to controls (Marsh & McCall, 1994; Stern et al., 1995; Stern et al., 1991). However, Sahakian et al. (1995) reported comparable verbal fluency for groups of symptomatic and asymptomatic individuals relative to controls. It is important to acknowledge that verbal fluency tasks may reflect difficulties with problem-solving or information processing speed rather than language.

**Visuospatial and Constructional Skills**

Recent research findings suggest that most individuals with HIV infection perform within normal limits on measures of visuospatial skills (Becker et al., 1997; Hinkin et al.,
1998; Marsh & McCall, 1994). However, they sometimes achieve lower scores on timed visuospatial measures (e.g., WAIS Block Design subtest), likely because performance is adversely affected by slowed psychomotor speed (Hinkin et al., 1998). Furthermore, performance on more complicated or less structured visuospatial and/or constructional tasks may be affected, possibly due to difficulties with planning and problem-solving rather than visuospatial deficits (Hinkin et al., 1998).

**Attention, Concentration, and Working Memory**

Attention and concentration are commonly affected in HIV-infected individuals, and are particularly apparent on more complex tasks. Problems with attention, concentration, and speeded information processing are reflected in diminished performance on tests such as Auditory Consonant Trigrams and the Paced Auditory Serial Attention Test (PASAT) (Bornstein, Nasrallah, Para, Whitacre, Rosenberger et al., 1993; Grant et al., 1987; Hinkin et al., 1998; Marsh & McCall, 1994). Performance on measures of simple attention, such as the digits forward portion of the WAIS Digit Span subtest, is usually within normal limits, even in the early stages of HAD (Hinkin et al., 1998). While there is a general consensus that attention and concentration problems are associated with HIV infection, specific findings have varied across studies.

Stern et al. (1991) and Stern et al. (1995) found significantly poorer performance for asymptomatic HIV-positive individuals relative to controls on the WAIS-R Digit Span subtest, although they questioned the clinical significance of this finding. Bornstein, Nasrallah, Para, Whitacre, Rosenberger et al. (1993) reported significantly poorer
performance on measures of visual attention and speeded information processing [i.e., Visual Attention Span subtest of the Wechsler Memory Scale-Revised (WMS-R); PASAT] for HIV-positive individuals relative to controls.

Stout et al. (1995) investigated performance on tasks tapping different aspects of attention, concentration, and working memory in groups at various stages of HIV infection (i.e., asymptomatic, mildly symptomatic, and symptomatic). Relative to controls, the symptomatic group exhibited poorer performance on WMS-R Digit Span (both forward and backward conditions) and on two indices of a Reading Span Test. In general, performance of the mildly symptomatic and asymptomatic groups fell between the symptomatic and control groups, but did not differ significantly from that of controls. Overall, a larger proportion of HIV-positive individuals was impaired on the two tasks relative to controls. The proportion of impaired individuals on two measures (i.e., Reading Span and Digit Span backward) was higher for more advanced stages of HIV infection. In addition, there were significant, although small, associations between Digit Span scores and clinical ratings of "central neurological dysfunction" from a neurological examination.

Castellon, Hinkin, Wood, and Yarema (1998) reported that individuals with AIDS performed significantly worse on a working memory task (i.e., Calculation Span) than both asymptomatic individuals and controls. Furthermore, working memory performance in this sample was mediated by apathy. The authors proposed that both apathy and working memory deficits result from disruption of the frontal-subcortical circuitry in HIV infection. Law et al. (1994) failed to find significant differences between asymptomatic individuals and controls on working memory tasks.
The results from these studies suggest that, as in other HIV-associated neuropsychological impairments, working memory deficits are more evident in later, symptomatic stages of the infection than in earlier, asymptomatic stages of the disease. It is also important to consider the contribution of other variables to attention and concentration difficulties in HIV infection, such as the effects of medication, psychological distress, and systemic symptoms such as fatigue (Hinkin et al., 1998). This neuropsychological domain is particularly susceptible to the adverse effects of such factors; these confounds may partly account for variation in research findings.

**Learning and Memory**

Problems with learning and memory may be among the earliest neuropsychological effects of HIV, worsening in later phases of the infection (Bornstein, Nasrallah, Para, Whitacre, Rosenberger et al., 1993). Bornstein, Nasrallah, Para, Whitacre, Rosenberger et al. (1993) reported that memory problems were the most frequent neuropsychological finding in their sample of individuals at various stages of HIV infection. Learning of new information, verbal memory, and nonverbal memory performance may all be affected in HIV (Becker et al., 1997; Delis et al., 1995; Hinkin et al., 1998; Levin et al., 1992; Marsh & McCall, 1994; Peavy et al., 1994). Procedural memory may also be affected in a subgroup of individuals with HIV (Hinkin et al., 1998).

Typically, HIV-infected individuals demonstrate a "subcortical" pattern of memory impairment (Becker et al., 1995; Peavy et al., 1994). In other words, they exhibit problems retrieving, rather than storing, information. For example, while they may show difficulty with
free recall tasks, performance improves when they are given cues, multiple-choice options, or other recognition formats (Becker et al., 1995; Hinkin et al., 1998; Peavy et al., 1994).

**Verbal Learning and Memory.**

Miller et al. (1990) reported that symptomatic individuals demonstrated significantly poorer performance on a verbal memory measure, the Rey Auditory Verbal Learning Test (RAVLT), than controls. Maj et al. (1994) also found significantly poorer verbal learning and memory performance for symptomatic individuals relative to controls in 2 out of 5 centers located in various geographic regions. Gibbs et al. (1990) reported that a subset of individuals with ARC exhibited significantly poorer performance on some indices of the RAVLT relative to controls; the performance of asymptomatic individuals did not differ significantly from controls.

Differences in verbal memory performance have also been documented in asymptomatic individuals relative to controls (Bornstein, Nasrallah, Para, Whitacre, Rosenberger et al., 1993; Levin et al., 1992; Lunn et al., 1991). Van Gorp et al. (1994) found significantly poorer RAVLT performance for a group of mixed asymptomatic and symptomatic participants relative to controls. Stern et al. (1991) and Stern et al. (1995) reported that asymptomatic men performed more poorly than controls on a verbal memory measure (i.e., Selective Reminding Test) over a series of assessments spanning a 4 ½ year period.

In order to clarify the pattern of memory deficits in HIV infection, several studies have compared the performance of HIV-positive individuals on verbal learning and memory measures to prototypical performance profiles that differentiate subcortical (e.g.,
Huntington's disease) from cortical (e.g., Alzheimer's disease) pathological processes. Peavy et al. (1994) reported significantly impaired performance for symptomatic individuals relative to controls on various indices of a verbal memory measure (i.e., CVLT), including learning. The symptomatic group was also more likely to use inefficient recall strategies. Asymptomatic individuals performed at a level between the symptomatic group and controls, although their performance did not differ significantly from that of controls. Individual case classification classified more symptomatic and asymptomatic individuals as impaired than controls. Use of discriminant function equations to classify the pattern of verbal memory deficits in HIV infection as normal, cortical, or subcortical indicated that when deficits were present, they were more likely to be classified as subcortical.

In a similar study at another center, Becker et al. (1995) examined CVLT performance in a group of HIV-positive individuals. Relative to controls, memory deficits for infected individuals were more frequently classified as subcortical. There was also a trend for the subcortical pattern of memory performance to occur more frequently in individuals diagnosed with AIDS. Comparison to performance on another memory measure (i.e., WMS-R) indicated that among individuals with subcortical profiles, performance on verbal memory subtests, but not on nonverbal subtests, was poorer relative to controls. It is important to note that the memory performance of a sizable proportion (i.e., 61%) of HIV-positive individuals was classified as "normal", indicating that memory performance varies considerably in HIV infection.

A subcortical pattern of memory impairment has also been investigated in individuals diagnosed with MCMD (Delis et al., 1995). For a MCMD group, approximately half of
scores on the CVLT (e.g., short and long delayed recall) were impaired relative to controls; 67% of the MCMD group was impaired according to normative data. In contrast, individuals without a diagnosis of MCMD were impaired on only one CVLT score relative to controls (i.e., the first learning trial), a score that is often interpreted to reflect attention. Furthermore, performance on some of the CVLT indices was significantly poorer for individuals with MCMD relative to those without MCMD. The general pattern of MCMD performance was consistent with a subcortical profile, with markedly better recognition memory relative to free recall. However, there was also evidence of mild difficulty discriminating target words from distractors on the recognition trial, which is more consistent with a cortical memory problem. An important finding is that more individuals in the MCMD group were at later stages of HIV infection than in the non-MCMD group. The authors concluded that the pattern of memory impairment in MCMD is primarily consistent with a subcortical pathology, but milder problems consistent with a cortical pattern of memory deficits may be present, particularly in later phases of the infection.

**Nonverbal Learning and Memory.**

With respect to nonverbal memory, Sahakian et al. (1995) reported relatively intact performance on two visual memory measures for both symptomatic and asymptomatic individuals. Symptomatic individuals, however, demonstrated mildly impaired performance on a measure of pattern recognition. In contrast, Lunn et al. (1991) reported that individuals with AIDS demonstrated significantly poorer performance on a measure of nonverbal learning and memory relative to controls. Marsh and McCall (1994) found that asymptomatic and mildly symptomatic individuals performed significantly more poorly than controls on
immediate and delayed visual memory measures, although groups did not differ in the percentage of material retained over a delay.

The consistency of findings documenting learning and memory problems in HIV infection across numerous studies with different samples and using various memory measures indicates that these results are relatively robust. These studies show that symptomatic individuals are more susceptible to memory deficits than those in earlier stages of HIV infection, while findings for asymptomatic individuals are more variable. Although asymptomatic individuals may demonstrate decreased learning efficiency and poorer memory performance than controls, test scores often remain within the normal range. It is also important to consider the possible adverse effects of well-documented attention and concentration deficits on memory performance in HIV infection. However, the reliability of these findings indicates that learning and memory problems cannot be solely attributed to impaired attention or concentration in this population.

**Problem-Solving**

According to a review by Hinkin et al. (1998), global problem-solving skill is generally intact in individuals with HIV infection. For example, Gibbs et al. (1990) reported no significant differences in performance on an abbreviated booklet version of the Halstead Category Test between individuals with ARC, asymptomatic individuals, and controls. However, some aspects of planning and organization may be affected. A small subset of individuals with HIV infection may exhibit diminished judgement and disinhibition (Hinkin et al., 1998). When difficulties with problem-solving are present, they often occur in later
stages of the disease (Bornstein, Nasrallah, Para, Whitacre, Rosenberger et al., 1993).

Grant et al. (1987) reported significantly poorer performance on the Halstead Category Test for a small group of individuals with AIDS relative to controls. Stern et al. (1991) and Stern et al. (1995) reported significantly poorer performance in HIV-infected individuals relative to controls on the Odd Man Out Test, a measure purportedly sensitive to executive functioning. Bornstein, Nasrallah, Para, Whitacre, Rosenberger et al. (1993) found that individuals with AIDS performed significantly more poorly than controls and asymptomatic individuals on measures sensitive to concept formation and problem-solving (e.g., Wisconsin Card Sorting Test (WCST)).

Sahakian et al. (1995) reported that symptomatic and asymptomatic individuals performed significantly worse than controls on measures of set-shifting, planning, and problem-solving requiring strategy development. In particular, HIV-positive individuals committed more errors and had difficulty developing efficient strategies to solve the more difficult problems on a measure of spatial working memory. HIV-positive individuals also performed more poorly than controls on the more difficult items of problem-solving tasks (i.e., 2 versions of the Tower of London). The impairment was characterized as “relatively mild”, although deficits became more salient as task difficulty increased. Sahakian et al. (1995) concluded that individuals with HIV exhibit relatively mild impairment in problem-solving skill that is most likely to surface as task difficulty increases.

**Psychomotor and Motor Skills**

A hallmark of HIV infection is decreased psychomotor and motor speed with disease
progression. An early sign of the emergence of HAD is a decline on measures of psychomotor speed (Van Gorp et al., 1989). The performance of HIV-infected individuals on a composite measure of psychomotor speed (i.e., TMT Part A; Digit Symbol) accurately predicts neuropsychological test performance in other neuropsychological domains, including memory, verbal fluency, spatial skills, and problem-solving skills (Becker et al., 1997). These results illustrate the importance of psychomotor skills in HIV infection and their predictive utility in determining the likelihood of neuropsychological impairment in HIV infection.

Mildly symptomatic individuals and individuals with AIDS demonstrate higher rates of impairment on measures of manual dexterity (e.g., Grooved Pegboard Test (GPT)) relative to controls (Bornstein, Nasrallah, Para, Whitacre, Rosenberger et al., 1993). Decreased performance on the Trail Making Test (TMT) and the Digit Symbol subtest of the WAIS tests is also interpreted as evidence of decreased psychomotor speed (Hinkin et al., 1998). Lunn et al. (1991) reported significantly poorer scores on Digit Symbol and the TMT for individuals with AIDS relative to controls. Asymptomatic individuals performed more poorly than controls only on Part B of the TMT (Lunn et al., 1991). Maj et al. (1994) found significantly poorer performance on Digit Symbol, the TMT Part A, and a modified TMT test for symptomatic individuals relative to controls. Miller et al. (1990) reported significantly poorer performance on the GPT, TMT Part B, and the Symbol Digit Modalities Test (SDMT) for symptomatic individuals relative to controls.

In a longitudinal study conducted over a 9-year period at the Baltimore site of the MACS, Sacktor et al. (1996) examined the predictive utility of a decline in psychomotor
speed over a series of neuropsychological assessments. These authors investigated the effects of both a one-time decline in psychomotor speed, and a sustained decline that persisted over at least two assessments in a one-year period. A sustained decline in psychomotor speed (i.e., performance on the TMT and SDMT) was associated with a significantly higher risk of dementia, AIDS, and death, regardless of the severity of neuropsychological impairment. A one-time decline in psychomotor speed was significantly associated with an increased risk of dementia, but not of AIDS or death. Psychomotor speed performance on only two brief measures was more predictive of these criteria than using a larger neuropsychological test battery, suggesting that these two brief tests may be an effective screening tool. Performance on the complete battery was not associated with an increased risk of dementia, AIDS, or death, although this finding does not negate the utility of a larger neuropsychological test battery to ascertain patterns of neuropsychological functioning in HIV infection.

In sum, performance on neuropsychological measures of psychomotor and motor skills demonstrates one of the most robust relationships with disease progression in HIV infection. The value of a decline in psychomotor speed in predicting morbidity and mortality is particularly striking. These findings emphasize the importance of including measures of psychomotor performance in the neuropsychological evaluation of HIV-infected individuals.

**Reaction Time**

Studies that have investigated performance on measures of reaction time have generally found that complex, rather than simple, reaction time is more likely to be affected in HIV infection (Hinkin et al., 1998). If simple reaction time is affected, it is often in the
more advanced, symptomatic stages of the illness (Hinkin et al., 1998). However, as in other neuropsychological domains, findings for asymptomatic individuals are more variable.

Stout et al. (1995) reported poorer performance on the reaction time component of the Sternberg memory scanning task in mildly symptomatic and symptomatic groups relative to controls. Martin et al. (1992) found an increased effect on a reaction time version of the Stroop test for both asymptomatic and symptomatic individuals. Law et al. (1995) reported that for a group of HIV-positive individuals at various disease stages, performance on both simple and choice reaction time tasks was significantly slower than controls. In addition, HIV-positive individuals failed to benefit from longer preparation intervals prior to responses for the simple reaction time task. In an earlier study, Law et al. (1994) reported that asymptomatic individuals exhibited poorer performance on measures of both simple and complex reaction time relative to a control group. Bornstein, Nasrallah, Para, Whitacre, Rosenberger et al. (1993) reported significantly slower performance on some measures of simple and choice reaction time in asymptomatic individuals relative to controls. E. M. Martin et al. (1995) reported that HIV-positive individuals performed significantly more poorly than controls on some aspects of a global-local reaction time task. They interpreted their results to suggest that controlled aspects of attention are more likely to be affected in HIV infection than automatic attentional processing.

Hinkin, Castellon, and Hardy (2000) reported that on simple and choice reaction time measures, the performance of a group of mixed stage HIV-positive individuals was comparable to that of seronegative matched controls. However, when participants were required to perform both reaction time tasks simultaneously (i.e., dual-task performance),
which typically results in a drop in performance (i.e., difference in reaction time from dual
to single task performance), HIV-positive individuals exhibited a significantly larger drop
on both the simple and choice reaction time tests than controls. Individuals with clinical
AIDS tended to show larger differences between dual and single-task performance than those
who had not yet developed AIDS, although this finding did not reach statistical significance.
The authors interpreted their results as evidence of difficulty simultaneously processing
competing stimuli in HIV infection. In addition, performance differences across single and
dual tasks were significantly correlated with poorer performance on the interference trial of
the Stroop task for HIV-positive individuals. The authors interpreted the relationship
between these variables as additional evidence of difficulties with executive functioning in
HIV infection.

Longitudinal Studies

While most of the previously discussed research findings were based on cross-
sectional investigations, several research groups have conducted longitudinal studies of HIV-
positive individuals to monitor the course of neuropsychological deficits over time. Such
studies are of paramount importance because they shed light on the likelihood and nature of
cognitive decline at different stages of HIV infection. This issue is of great interest to
clinicians working with HIV-infected individuals, particularly because of the gradually
increasing life expectancy in this population.

Bornstein, Nasrallah, Para, Whitacre, and Fass (1993) followed asymptomatic
individuals for one year to assess any changes in neuropsychological functioning.
Performance at the one-year assessment became "abnormal" in 29% of HIV-positive individuals, a significantly larger percentage than controls. At baseline, individuals who developed "abnormal" profiles showed significantly poorer performance on measures of verbal learning and memory, speeded information processing, and reaction time. There were no significant differences in age, education, CD4 counts, or depression between individuals who developed neuropsychological dysfunction and those who remained stable. In fact, higher CD4 counts were noted in the group whose neuropsychological performance became "abnormal". The authors concluded that individuals who demonstrate early neuropsychological difficulties on similar tasks are at increased risk of subsequent neuropsychological decline, even if overall performance is not impaired.

Saykin et al. (1991) followed groups of individuals with persistent generalized lymphadenopathy (PGL) and ARC over an 18-month period. Both longitudinally and across neuropsychological domains, the ARC group exhibited poorer performance than the PGL group and controls. There was a trend for individuals with PGL to demonstrate poorer performance relative to controls. Individuals with ARC demonstrated mild problems on measures of attention, verbal and nonverbal memory, verbal fluency, naming, and psychomotor skills relative to controls both at baseline and follow-up. At follow-up, their performance on a measure of abstraction (i.e., Category Test) was also significantly poorer than controls. When additional measures were added at follow-up, the ARC group exhibited problems with a distractibility task and also reported problems with activities of daily living, including attention/planning, memory, language/reading, and motor skills. In general, however, overall neuropsychological performance did not change significantly over time for
the entire sample, with the exception of a “mild decline” on measures of learning and verbal memory for a few individuals.

Stern et al. (1995) reported that both HIV-positive participants and controls demonstrated improved performance on most neuropsychological measures over a series of assessments conducted up to 4 ½ years. These results presumably represented a practice effect. HIV-positive groups, however, showed significantly less improvement over assessments than controls on measures of attention and language. For each assessment, HIV-positive groups performed more poorly on memory measures than controls. However, Stern et al. (1991) commented that differences in neuropsychological performance between HIV-positive individuals and controls were of questionable clinical significance because of the small effect size. Individuals with clinical AIDS demonstrated significantly poorer performance on measures of memory and problem-solving relative to asymptomatic or mildly symptomatic individuals. Individuals with AIDS also showed less improvement over time on measures of memory, verbal fluency, and motor speed.

The MACS conducted a longitudinal investigation of HIV-positive individuals over the course of developing clinically diagnosable AIDS or at least one episode of low CD4 count (i.e., <200) (Selnes et al., 1995). Participants completed at least four neuropsychological assessments, two prior to being diagnosed with AIDS, and two following a diagnosis of AIDS, thus providing a unique longitudinal investigation both before and after time of diagnosis. Prior to the diagnosis of AIDS, two groups of individuals (one with low CD4 counts and one with AIDS-defining illnesses) did not demonstrate neuropsychological decline across assessments. However, individuals with clinically diagnosed HIV-associated
dementia exhibited significant decline on measures of psychomotor speed, but not on other neuropsychological measures. These findings suggest that neuropsychological performance does not necessarily decline prior to developing either clinical conditions associated with AIDS or high levels of immunosuppression, except when dementia is present. Following diagnosis of AIDS, individuals with dementia demonstrated significant performance decline on all tests. Individuals with clinical AIDS demonstrated significant decline solely on a measure of psychomotor speed (GPT). Individuals with low CD4 counts, however, did not exhibit any decline in neuropsychological performance following a diagnosis of AIDS. The authors interpreted these findings to suggest that immunosuppression is not necessarily associated with neuropsychological decline in the absence of AIDS-defining illness.

Overall, longitudinal studies of the progression of cognitive changes over time in HIV infection suggest that neuropsychological deficits are more likely to be present in later, symptomatic stages of the illness. Similarly, neuropsychological decline is more likely to occur in symptomatic individuals than asymptomatic individuals, and a decline in psychomotor speed may be one of the first significant neuropsychological indicators of progressive cognitive deterioration. However, mixed findings from longitudinal studies indicate that neuropsychological outcome in HIV infection is variable. While some HIV-positive individuals show relative stability in their cognitive profile, others experience worsening neuropsychological impairment over the course of the disease.

Summary

In summary, research findings suggest that at least some HIV-infected individuals
experience related neuropsychological impairment. Both cross-sectional and longitudinal studies indicate that the likelihood of neuropsychological impairment rises as the disease progresses in severity (Bornstein et al., 1991; Bornstein. Nasrallah. Para. Whitacre. Rosenberger et al., 1993; Grant et al., 1987; Heaton et al., 1995; Selnes, McArthur. Royal, et al., 1992; Stern et al., 1995). Most individuals in the early, medically asymptomatic stages of HIV infection do not present with neuropsychological impairment. A small proportion, however, may suffer from mild, patchy neuropsychological deficits that are difficult to detect without a thorough assessment tapping all cognitive domains.

Neuropsychological deficits occur most often in the areas of attention and concentration, information processing speed, and learning efficiency for both verbal and nonverbal information (Grant et al., 1999; Heaton et al., 1995). Decreased psychomotor and motor speed is frequently, if not always, present (Bornstein. Nasrallah. Para. Whitacre. Rosenberger et al., 1993; Lunn et al., 1991; Miller et al., 1990; Sacktor et al., 1996; Van Gorp et al., 1989). Other potentially affected areas include memory retrieval (Becker et al., 1995; Delis et al., 1995; Peavy et al., 1994) and complex reaction time (Law et al., 1995; Law et al., 1994; E. M. Martin et al., 1995). While there are common areas of neuropsychological impairment in HIV infection, deficits are often subtle, and profiles are quite variable, particularly in early, asymptomatic stages of the disease. The inherent variability in neuropsychological functioning suggests that subtypes of neuropsychological impairment may exist in HIV infection. Some preliminary research in this area supports this suggestion.

In a unique study of the neuropsychological status of HIV-infected individuals, Van
Gorp, Hinkin et al. (1993) used cluster analysis to identify three different subtypes of neuropsychological functioning associated with HIV infection. Cluster 1 represented essentially normal neuropsychological and affective functioning, and these individuals performed within expectations on neuropsychological measures. Approximately 75% of individuals in this cluster were asymptomatic. Cluster 2 was comprised of individuals who evidenced psychomotor slowing, poorer performance on verbal memory measures (e.g., RAVLT), and endorsed more symptoms of anxiety and depression. 61% of the individuals in this cluster were symptomatic. The pattern of neuropsychological functioning in Cluster 2 is similar to that expected in a subcortical process and is consistent with previous descriptions of neuropsychological dysfunction in HIV infection. Individuals categorized into Cluster 3 did not demonstrate any significant mood problems, but showed impaired performance on neuropsychological measures assessing both verbal and visuospatial skills. Approximately equivalent percentages of Cluster 3 were asymptomatic and symptomatic. These results suggest that at least three types of cognitive profiles may be present in individuals infected with HIV. Van Gorp, Hinkin et al. (1993) provide a method of conceptualizing HIV-related neuropsychological impairment as empirically tested subtypes that should prove useful in differentiating among possible neuropsychological profiles in HIV-infected individuals. Future studies may establish other neuropsychological subtypes in HIV infection that will clarify the associated patterns of neuropsychological deficits and their relationship to disease progression.

Currently, it is unclear whether there is a continuum of neuropsychological decline in HIV infection, such that individuals with mild neuropsychological deficits in early stages
inevitably develop severe neuropsychological impairment or dementia. Some research groups have disputed this point of view, suggesting that HAD and mild neuropsychological deficits in early HIV infection differ both in presentation and course (American Academy of Neurology AIDS Task Force, 1991; Heaton et al., 1995; Selles et al., 1995). Longitudinal studies indicate that although progressive cognitive decline can occur, neuropsychological deficits remain relatively stable for some individuals (Bornstein, Nasrallah, Para, Whitacre, & Fass, 1993; Saykin et al., 1991; Selles et al., 1995; Stern et al., 1995). Failure to find a significant association between CD4 count and classification into one of the neuropsychological subtypes described by Van Gorp, Hinkin et al. (1993) also suggests that these neuropsychological patterns are not simply different stages in the progression of HIV infection. Milder forms of neuropsychological impairment in HIV infection may have a fluctuating, rather than static or progressive, course (Grant et al., 1999). Further research, particularly additional longitudinal studies, are required in order to clarify the exact nature of neuropsychological decline in HIV infection and its relationship to the development of HAD.

Factors Mediating Neuropsychological Dysfunction

One possible reason for variation in findings to date is the potential for individual differences on factors that mediate neuropsychological skills in HIV infection. Possible mediating variables include systemic medical illness, pain, demographic variables such as gender and age, as well as current or past substance abuse (e.g., intravenous drug use), a history of head injury or sexually transmitted diseases (STD), and iatrogenic effects from
treatment with antiretroviral drugs. Another major factor that may conceivably affect neuropsychological performance in HIV infection is depression. This topic will be covered in some detail in a later section of this paper.

Systemic medical illness is one variable that may mediate neuropsychological performance in HIV infection. More advanced stages of systemic illness can adversely affect performance on neuropsychological tests (Van Gorp, Lamb, & Schmitt, 1993). In addition, complaints of increased fatigue and insomnia in HIV infection have been significantly associated with poorer performance on measures of motor speed and dexterity; this relationship was independent of depression (Perkins et al., 1995). Thus, “nonspecific illness factors” may contribute to documented neuropsychological dysfunction in HIV infection (Van Gorp, Lamb et al., 1993). Consequently, self-reported cognitive problems may also be related to systemic medical symptoms, such as fatigue.

Pain is another illness factor that appears to mediate neuropsychological functioning in HIV infection. D. Moore et al. (2000) found that 42% of their HIV-positive sample reported pain at the time of neuropsychological testing. Individuals who reported pain were more likely to be neuropsychologically impaired in the “perceptual-motor” and “learning” domains. However, report of pain was not related to impairment ratings for global neuropsychological functioning or six other neuropsychological domains. Notably, individuals who reported that pain interfered with “the ability to concentrate or think” were more likely to be classified as impaired in global neuropsychological functioning, and in 5 of the 8 neuropsychological domains assessed (i.e., abstraction, attention, learning, motor, and sensory skills). These results suggest that pain may subtly affect neuropsychological
functioning in HIV infection, particularly for individuals who report that pain interferes with thinking. It is noteworthy that medication use, peripheral neuropathy, and depression did not account for the findings in this study.

Demographic variables such as gender and age may also influence neuropsychological performance in HIV infection. For example, Stern et al. (1996) reported that while overall neuropsychological functioning did not differ substantially between male and female drug users, memory performance was significantly related to CD4 count in men, but not in women. There are few studies of neuropsychological functioning in HIV-positive women, primarily because of lower prevalence rates (White et al., 1995). Although neuropsychological studies of HIV infection have included more women over the past decade, they are not representative of the number of infected women in the population (Fox-Tierney, Ickovics, Cerreta, & Ethier, 1999). Furthermore, the number of HIV-positive women included in neuropsychological studies is typically insufficient to conduct analyses of potential sex differences (Fox-Tierney et al., 1999). However, recent studies of HIV-positive women suggest that women also demonstrate reduced psychomotor speed (Durvasula, Miller, Myers, & Wyatt, 2001) and that neuropsychological deficits adversely affect quality of life (Osowiecki et al., 2000). While the paucity of research in this area does not permit any firm conclusions, neuropsychological functioning in HIV infection may be affected differently in men versus women.

Although gender may mediate neuropsychological functioning in HIV infection, age does not appear to be associated with greater risk of HIV-related neuropsychological impairment, after accounting for the effects of normal aging (Van Gorp et al., 1994).
Intravenous drug use is relatively common in HIV-positive individuals (Centre for Infectious Disease Prevention and Control, 2000). As shown in other populations, prolonged substance use adversely affects neuropsychological functioning (Lezak, 1995). Claypoole et al. (1993) identified recent drug use (i.e., during the 6 months prior to testing) as an important risk factor for decreased neuropsychological performance in HIV-positive individuals relative to controls. Selnes, McArthur, Royal, et al. (1992) reported no significant differences in the neuropsychological performance of HIV-positive IV drug users relative to HIV-negative drug users. Results remained stable at 6 or 12 month follow-ups. However, both asymptomatic HIV drug users and controls evidenced comparable impairment in neuropsychological performance. In a longitudinal study, Stern et al. (1996) reported neuropsychological deficits in HIV-positive IV drug users, such as memory problems. Neuropsychological performance at baseline was significantly poorer in IV drug users than in non-drug users. However, these authors suggested that the longitudinal effects of HIV infection did not differ between IV drug users and individuals without a history of drug use. Research results on the neuropsychological effects of IV drug use in HIV are variable, and this issue requires further investigation. A history of chronic substance use, however, is an important possible confound to consider when evaluating neuropsychological research in HIV infection.

A history of head injury has been linked to decreased neuropsychological performance in HIV infection (Claypoole et al., 1993; Marder et al., 1992). Marder et al. (1992) reported an interaction between head injury and HIV disease stage in IV drug users on measures of memory, language, and visuospatial skills. For individuals with a history of
head injury including a loss of consciousness, neuropsychological performance on these measures was poorer in more advanced stages of HIV infection. Individuals with risk factors of a history of head injury and recent drug use exhibit the poorest performance on neuropsychological measures relative to individuals with either one or the other risk factor (Claypoole et al., 1993).

Neuropsychological dysfunction in HIV infection appears to be significantly associated with a history of other sexually transmitted diseases. Wallace et al. (1997) reported that a history of syphilis or gonorrhea was significantly correlated with lower scores on neuropsychological measures. Although a history of syphilis was predicted to be more strongly associated with neuropsychological impairment because of its known CNS effects, a history of gonorrhea was actually more strongly associated with poorer neuropsychological performance. The authors were unable to explain this finding completely. They suggested that other unidentified STDs or multiple strains of HIV infection may have accounted for poorer neuropsychological performance in the individuals with a history of gonorrhea.

Another factor possibly mediating neuropsychological performance is the iatrogenic effects resulting from treatment with multiple pharmaceutical agents. This treatment may affect neuropsychological functioning in HIV infection and this topic is discussed in more detail in a later section of this paper.

**Methodological Issues**

Several important methodological considerations need to be addressed in any review of neuropsychological functioning in HIV infection. The variation of research findings in the
study of HIV-associated neuropsychological impairment is likely due in part to some of these factors. These issues generally fall into three broad categories. The first category pertains to the basic construction of the study, including variables such as sample selection and the use of control groups. The second category relates to the method used to determine neuropsychological deficits, including test selection, interpretation of test results, and the criteria used for defining neuropsychological impairment. Finally, the third category relates to the medical issues involved in HIV infection.

Methodological issues common to most neuropsychological research may affect outcome in studies of HIV-infected individuals. Differences in sample composition and methods of participant selection exist; exclusion criteria may vary considerably across studies. As previously mentioned, risk factors such as a history of head injury and/or IV drug use may differentially impact neuropsychological performance and must be considered in participant selection (Van Gorp, Lamb et al., 1993). Wilkins et al. (1990) reported that neuropsychological deficits in HIV infection were significantly related to confounding factors such as pre-existing neurological or psychiatric illness. The use of control groups and their appropriateness may also lead to differences in studies (Heaton, Kirson, Velin, Grant, & the HNRC group, 1994). Sample size, premorbid intellectual level, and the prevalence of mood disturbances are some other factors that vary across studies (Van Gorp, Lamb et al., 1993).

Van Gorp et al. (1995) investigated the effect of selection site in the recruitment of HIV-positive individuals for neuropsychological research. They compared neuropsychological test performance in samples from 3 different sites: 1) patients recruited
from a community volunteer group (LA-MACS), referred because they had performed poorly on a brief neuropsychological screening protocol, 2) a consecutive series of patients from an immunodeficiency clinic at a Veteran Affairs (VA) Medical Center, and 3) patients from a private medical group (POMG), who were referred for neuropsychological assessment because of suspected cognitive problems or psychological issues. Asymptomatic and symptomatic groups of individuals were compared separately in the study.

The results indicated that individuals from the VA sample were the most impaired on neuropsychological testing. This finding is particularly interesting because the VA sample was consecutively recruited and individuals were not referred because of suspected cognitive problems. Individuals from the other two groups (i.e., LA-MACS, POMG) performed better than individuals from the VA group, although they were specifically referred for neuropsychological testing. The LA-MACS sample was least impaired, and the performance of individuals from the POMG measured in between the two other groups. Van Gorp et al. (1995) suggested that differences across these three samples may have reflected variables other than HIV-associated impairment, such as “socioeconomic status, nutrition, early development, and lifestyle” (p. 209). As a result, reported differences in neuropsychological performance across groups were likely pre-existing.

These results demonstrate that sample selection may play an important role in neuropsychological research findings in HIV infection. The results of this study suggest that selection site and method of selection affects the outcome of neuropsychological research in HIV infection. Consequently, it is important to examine neuropsychological performance across different samples in order to obtain an accurate evaluation of neuropsychological
impairment in HIV infection.

The specific neuropsychological measures used in studies may also account for a great deal of variation because of differences in test characteristics such as sensitivity (Van Gorp, Lamb et al., 1993). For example, the MACS study (McArthur et al., 1989) used only a brief screening battery to assess neuropsychological functioning. According to Grant and Heaton (1990), the low rate of neuropsychological impairment reported in this study logically resulted from the relative insensitivity of the assessment measures used. The impact of variation in neuropsychological test selection is more likely to be evident in studies of the mild, subtle neuropsychological impairment that may be present in the asymptomatic stages of HIV infection (Grant & Heaton, 1990). Similarly, the interpretation of neuropsychological test results may vary widely across studies, including the criteria used to differentiate neuropsychological impairment from normal performance (Grant & Heaton, 1990; Van Gorp, Lamb et al., 1993) and use of different normative data (Heaton, Kirson et al., 1994; Van Gorp, Lamb et al., 1993).

Different stages of systemic medical illness in individuals with HIV infection may influence study findings. For example, outpatients are typically more medically stable than inpatients, who have more critical medical symptoms. Therefore, any differences reported in the comparison of such samples may not be due solely to HIV infection (Van Gorp, Lamb et al., 1993). This problem is more likely to occur in the investigation of symptomatic individuals, and Van Gorp, Lamb et al. (1993) suggest that a chronic illness control group might be appropriate in such situations.

Another issue raised by Grant and Heaton (1990) is that most studies are unable to
pinpoint the exact date of seroconversion for participants. Therefore, members of a sample may be at different stages in the course of HIV infection. Individuals who have been asymptomatic but seropositive for a longer time may be more likely to develop neuropsychological deficits than those in earlier stages (Grant & Heaton, 1990), and the relative proportions of such individuals may vary across samples and sites. Knowledge of serostatus may also affect study findings, particularly in terms of anxiety (Van Gorp, Lamb et al., 1993). Furthermore, HIV-positive individuals may also suffer from a number of unidentified co-infections, such as sexually transmitted diseases (e.g., syphilis, gonorrhea, herpes) or hepatitis B, that could adversely influence neuropsychological functioning (Grant & Heaton, 1990). Lack of consensus regarding diagnosis (i.e., “vague criteria”) may also pose problems in comparisons across studies (Van Gorp, Lamb et al., 1993).

In their review of 57 studies, White et al. (1995) investigated possible contributing factors to discrepant findings across studies of asymptomatic HIV-positive individuals. They concluded that a larger neuropsychological test battery was more likely to detect impairment in asymptomatic individuals than a smaller battery. Mode of HIV infection was also associated with study outcome. Individuals who had contracted HIV through blood or blood product transfusion did not demonstrate neuropsychological impairment in any of the studies reviewed. However, only three studies investigated neuropsychological functioning in this group of HIV-positive individuals. Results for individuals who contracted HIV through sexual contact were mixed. While results from studies of intravenous drug users were also mixed, there was a trend toward finding impairment in this group. Other factors, such as size of the sample, a clinical versus more experimental (e.g., computerized) test battery, and the
method of examining group differences (i.e., comparison of group means versus prevalence rates) did not appear to influence study outcome (White et al., 1995). The results of this review indicate that while some important factors are not significantly associated with study outcome, other variables, such as size of the battery used and mode of HIV infection, may play a role in whether neuropsychological impairment is reported in investigations. It is critical to keep these methodological differences in mind when evaluating neuropsychological research findings for individuals with HIV infection.

**Relationship of Neuropsychological Deficits to Disease Markers**

Numerous studies have demonstrated a link between neuropsychological deficits and brain pathology in HIV infection (Grant et al., 1987; Masliah et al., 1997; Perdices & Cooper, 1989), such as atrophy, higher subcortical fluid volumes (Heaton et al., 1995), and increased cerebral blood volume in deep gray matter on functional MRI (Tracey et al., 1998). After partialling out the contribution of disease severity, clinically significant neurological signs are also associated with poorer neuropsychological functioning in HIV (Stern et al., 1995; Stern et al., 1991).

Masliah et al. (1997) investigated the relationship of neuropsychological skills to both dendritic complexity (pre- and post-synaptic) and viral load in a sample of 20 AIDS patients. Poorer neuropsychological functioning was significantly associated with dendritic loss in the midfrontal cortex. Neuropsychological performance, however, was not significantly associated with dendritic density in the globus pallidus or putamen. Dendritic loss in the midfrontal area was predictive of poorer scores in specific neuropsychological domains,
described by the authors as learning, perceptual-motor skills, abstraction, and verbal skills. Dendritic loss did not significantly predict performance on measures of attention, memory, motor skills, or sensory functioning. The extent of dendritic loss was more variable in individuals with milder neuropsychological impairment. Individuals diagnosed with HAD or MCMD were more likely to have higher viral load ratings, although viral load was not significantly correlated with global neuropsychological functioning. It is noteworthy that traditional pathological findings used to establish the presence of HIV disease (e.g., multinucleated giant cells, microglial nodules) were not significantly associated with neuropsychological skills (Masliah et al., 1997).

Studies of the relationship between immune functioning and neuropsychological impairment have yielded inconsistent results. Some studies have shown a relationship between neuropsychological performance and immune status in HIV infection (e.g., Becker et al., 1997; Bornstein et al., 1991; Stern et al., 1991). Other studies have failed to find a significant association between neuropsychological functioning and measures of immune function, such as CD4 count (e.g., Miller et al., 1990; Stout et al., 1995; Van Gorp, Hinkin et al., 1993).

Ellis et al. (1997) reported that neuropsychological impairment was significantly associated with CSF viral load (i.e., higher levels of HIV RNA in the CSF) for individuals with CD4 counts less than 200. There was no significant relationship between neuropsychological impairment and viral load for individuals in earlier stages of HIV infection.

Stern et al. (1991) found that a global rating of neuropsychological performance was
inversely correlated with the CD4/CD8 ratio in HIV-positive men. A lower ratio was significantly correlated with greater neuropsychological dysfunction, although the correlation was small. HIV-positive men with a CD4 count less than 200 showed less improvement or a decline over time across a series of assessments on measures of attention, memory, language, and problem-solving relative to HIV-positive men with less immunosuppression (Stern et al., 1995). Stern et al. (1995) interpreted their findings to suggest that HIV-associated neuropsychological sequelae worsen in more advanced stages of the illness.

Bornstein et al. (1991) reported that poorer performance on tests of memory and reaction time was significantly related to a more rapid decline in the percentage of CD4 per total lymphocytes. Furthermore, these findings were not related to illness severity or CD4 level at the time of the neuropsychological assessment.

Becker et al. (1997) reported that CD4 count significantly predicted performance on a composite measure of psychomotor speed in HIV-positive individuals. De Ronchi, Lazzari, Rucci, Cangialosi and Volterra (1996) reported significant correlations between CD4 count and performance on the Vocabulary, Digit Span, Digit Symbol, and Block Design subtests of the WAIS in symptomatic, but not asymptomatic, individuals.

Gibbs et al. (1990) reported small but significant correlations between CD4 count and performance on WAIS-R Digit Symbol and the RAVLT. These correlations, however, were primarily related to a relationship between CD4 count and neuropsychological performance in individuals with ARC but not asymptomatic or seronegative individuals. The authors concluded that while the likelihood of neuropsychological dysfunction increases as immunosuppression worsens, there is not an “absolute association” between decreased
immune function and neuropsychological problems.

Bornstein, Nasrallah, Para, Whitacre and Fass (1993) did not find a significant relationship between CD4 count and neuropsychological dysfunction in asymptomatic individuals. As mentioned previously, Van Gorp, Hinkin et al. (1993) failed to find a significant relationship between CD4 count and classification into one of three neuropsychological subtypes. Miller et al. (1990) divided asymptomatic individuals into low and high CD4 count groups (less than or greater than 500), and failed to find any differences between these two groups on neuropsychological measures. Maj et al. (1994) reported few significant correlations between CD4 count and neuropsychological performance, and CD4 count did not significantly predict global neuropsychological functioning.

Measures of immune status, such as CD4 count, were not predictive of HAD in the MACS study (McArthur et al., 1993). However, in one branch of the MACS study, CD4 count was weakly correlated with a decline in neuropsychological performance on two measures (i.e., TMT and SDMT) across assessments (Dal Pan et al., 1998). Various measures of viral load were not significantly associated with neuropsychological performance (Dal Pan et al., 1998).

Heaton et al. (1995) failed to find sizable associations between neuropsychological test performance, immune functioning (e.g., CD4 count), and systemic symptoms. Systemic symptoms and neuropsychological performance were not significantly associated in asymptomatic individuals. Nevertheless, neuropsychological skills were associated with some immunological variables. For example, individuals with an abnormally high CSF beta-2-microglobulin (B2M) value demonstrated a significantly greater rate of neuropsychological
impairment.

Basso and Bornstein (2000) investigated the relationships between immune status (i.e., CD4 count), disease severity, and neuropsychological skills. Individuals with AIDS-defining illnesses generally performed more poorly on learning and memory tests relative to those who were asymptomatic, symptomatic, and a group with CD4 count less than 200. The group with AIDS-defining illnesses was more likely to obtain “impaired” scores than the other groups. In contrast, neuropsychological performance of the group with CD4 count less than 200 was comparable to controls, although the group with AIDS-defining illnesses had equally low CD4 counts. Consequently, the authors suggested that neuropsychological deficits are more likely when immunosuppression is accompanied by disease severity. As previously mentioned, Selnes et al. (1995) also suggested that immunosuppression may not result in neuropsychological decline in the absence of an AIDS-defining illness.

These findings demonstrate that some measures of immune status, but not all, are related to neuropsychological impairment in HIV infection. Inconsistent results in previous studies suggest that commonly used measures of immune function, such as CD4 count, may not be good indicators of a relationship between neuropsychological deficits and immune status. One possibility is that the immunological measures used to date may not be sensitive enough to detect relationships between immune function and neuropsychological impairment (Dal Pan et al., 1998). Advances in medical technology are resulting in increasingly sophisticated methods of assessing immune function in HIV-infected individuals and more advanced techniques may clarify earlier results. Another possibility is that the relationship between neuropsychological impairment and immune status is more complex than originally
presumed. For example, the interaction between disease severity and immunosuppression may be an important determining factor of neuropsychological impairment in HIV infection. As suggested by Basso and Bornstein (2000), both conditions may be required in order to produce neuropsychological deficits in HIV. These possibilities have not yet been fully explored, and the relationship between immunosuppression and neuropsychological impairment is clearly an area which requires further investigation.

**Impact of HIV-Associated Neuropsychological Problems on Everyday Functioning**

Neuropsychological impairment has practical consequences for individuals with HIV infection. Several studies have demonstrated a relationship between neuropsychological impairment, faster cognitive decline, and an increased risk of death (Albert et al., 1995; Mayeux et al., 1993; Stern et al., 1995). Even if individuals are medically asymptomatic with few physical problems, HIV-associated neuropsychological deficits may cause difficulty performing tasks at work or in everyday activities (Maj et al., 1994). Recent treatment success in prolonging the life of HIV-positive individuals essentially characterizes HIV as a chronic rather than an acute disease (Albert et al., 1995). The investigation of functional outcome in neuropsychologically impaired individuals is of utmost importance because infected individuals are living longer, and consequently are more likely to return to work, volunteer work, or engage in other social activities.

The Dana Consortium on therapy for HIV dementia and related cognitive disorders (1996) reported that HAD and MCMD were both predictive of poor physical functioning as assessed by self-report for daily activities, even after controlling for other potential
confounds (e.g., age, CD-4 level, hemoglobin level, medication, depression). Neurological and/or behavioural problems were most frequently coupled with both neuropsychological impairment and significant functional limitations (The Dana Consortium on therapy for HIV dementia and related cognitive disorders, 1996).

Bornstein, Nasrallah, Para, Whitacre, Rosenberger et al. (1993) found significant associations between summary neuropsychological impairment ratings and ratings on the Sickness Impact Profile, a measure of the impact of illness on daily activities. Correlations were highest for scales relating to work, sleep and rest, alertness, and recreation, even after adjustment for the possible influence of other variables (i.e., age, education, depression, and weekly alcohol consumption).

Heaton, Velin et al. (1994) demonstrated that HIV-positive individuals with neuropsychological impairment were approximately three times more likely to be unemployed. Individuals who continued to work were more likely to report difficulty with job performance. In a later study, Heaton et al. (1996) reported that neuropsychological impairment in HIV was associated with higher rates of unemployment, more subjective complaints of performance problems at work, and reduced performance on work samples on a standardized measure.

Albert et al. (1995) investigated whether neuropsychological impairment was a risk factor for “work disability” status over a 4 ½ year period. Work disability was operationally defined as a change in working hours from greater than or equal to 20 hours per week to less than 20 hours for at least a 2 year period. HIV-positive individuals demonstrated a significantly higher risk of work disability relative to controls. In particular, individuals who
were asymptomatic at baseline were approximately three times more likely to meet criteria for work disability relative to controls. This finding was accounted for by a subset of individuals with impaired neuropsychological performance at follow-up, and poorer baseline performance relative to those who did not develop work disability. Asymptomatic individuals who performed within normal limits on neuropsychological tests did not show an increased risk of work disability. Neuropsychological dysfunction continued to predict work disability after controlling for neurological and immunological factors.

A few studies have investigated the relationship between HIV-associated neuropsychological impairment and the ability to safely operate a motor vehicle. HIV-positive individuals classified as neuropsychologically impaired performed more poorly on a driving simulator both relative to unimpaired individuals and controls (Marcotte et al., 2000; Marcotte et al., 1999). Marcotte et al. (2000) found that impaired individuals were also less likely to have driven over the past year, and more likely to have been charged with a moving violation. There was a trend for impaired individuals to have had more accidents over the past year. The authors concluded that HIV-positive individuals with mild neuropsychological difficulties may be at greater risk while driving. More recent findings have confirmed the results of driving simulator studies; neuropsychologically impaired individuals are more likely to exhibit unsafe driving performance during on-the-road evaluations (Marcotte et al., 2001). The consequences of HIV-associated neuropsychological impairment for safe driving is an area that calls for additional inquiry and is an issue of great practical relevance for infected individuals.
Psychological Issues Associated with HIV Infection

While depressed mood is common in HIV infection, with up to 80% prevalence in some studies, clinically diagnosable major depressive episodes are much less prevalent (10-15%) (Hinkin et al., 1998). Recent studies suggest that the incidence of clinically significant anxiety and depression is only slightly higher in individuals with ARC or AIDS relative to asymptomatic individuals (Grant, 1990). In fact, Bornstein, Pace et al. (1993) reported no significant differences in scores on the Hamilton Depression Rating Scale (HDRS) among asymptomatic individuals, mildly symptomatic (i.e., ARC) individuals, and individuals with AIDS relative to controls, although individuals with AIDS obtained higher scores, indicating more depressive symptoms.

Rates of depression, anxiety, and other psychiatric symptoms tend to be highest during HIV testing, while waiting for HIV test results, and immediately after receiving a positive diagnosis (Grant, 1990; Hinkin et al., 1998). Follow-up research suggests that the initial emotional distress associated with a positive test result subsides over the first 6 months following diagnosis (Grant, 1990). Interestingly, the rate of anxiety and depression in HIV-negative individuals at risk for infection is similar to prevalence rates (10-20%) for those who are HIV-positive and do not have ARC or AIDS (Grant, 1990).

Depressed mood in HIV infection can be viewed as a reaction to a chronic, fatal illness (Hinkin et al., 1998), and the social repercussions associated with contracting HIV infection may also contribute to low mood. Depressed mood may be triggered at critical stages of the illness (Grant & Atkinson, 1990). Current views hold that mood alterations in HIV infection are often related to pre-existing psychiatric history (Grant, 1990). Subcortical
brain damage may also lead to depressed mood or altered affect (Hinkin et al., 1998).

In a sample of HIV-positive men, Hays, Turner, and Coates (1992) found that medical symptoms significantly predicted depression, both currently, and at re-assessment one year later. Depressed mood was more likely to occur when medical symptoms were active, demonstrating the interactive relationship between mood and physical illness in HIV infection. Individuals who reported greater satisfaction with their social support, whether characterized as informational, practical, or emotional support, were less likely to experience depression. In particular, high satisfaction with informational support was related to less depression as medical symptoms worsened, suggesting that support needs may vary at different points in the progression of HIV infection. However, one caveat is that satisfaction with social support does not necessarily reflect actual levels of support.

This study has direct implications for health care professionals working with HIV-infected individuals who are in a position to provide informational support to patients. Improved understanding of the relationship between cognitive complaints and neuropsychological impairment will allow health care professionals to provide better informational support to HIV-infected individuals, which is possibly important in improving low mood.

Low mood has the potential to adversely affect neuropsychological test performance in depressed HIV-positive individuals. There is substantial literature documenting the adverse effects of major depression on neuropsychological functioning, particularly on attention/concentration, memory, and speed (Cassens, Wolfe, & Zola, 1990; Lezak, 1995). In many studies of HIV infection, however, group findings do not demonstrate significantly
poorer performance on neuropsychological measures for depressed individuals relative to those who are not depressed (Hinkin et al., 1998; Mapou et al., 1993; Stout et al., 1995; Van Gorp et al., 1991). Nevertheless, it is important to keep in mind that negative group findings may not always apply to individual cases. As in the investigation of neuropsychological functioning in HIV infection, there is some variation in results across studies.

Stern et al. (1991) reported that summary measures of neuropsychological test results were significantly correlated with scores on two measures of depression and anxiety (HDRS; Hamilton Anxiety Scale) in HIV-positive men. Depressive symptoms were related to poorer performance on measures of verbal memory and psychomotor speed in a longitudinal study of HIV-infected individuals (Selnes et al., 1995). Harker et al. (1995), however, did not find a significant relationship between depression and performance on measures of psychomotor speed, memory, or problem-solving.

Bornstein, Pace et al. (1993) investigated the impact of depressed mood on neuropsychological test performance in asymptomatic individuals. Depression was assessed by three different methods: 1) the Structured Clinical Interview for the DSM-III-R (SCID), 2) scores on the Beck Depression Inventory (BDI), and 3) scores on the HRSD. Overall, depressed mood did not greatly affect neuropsychological test performance. Performance on only one measure (i.e., TMT, Part B) was poorer in depressed individuals across all three methods used to define depression. There were some other minor differences across the three methods used to classify depression (e.g., significantly slower GPT speed with the non-dominant hand in the group classified as depressed by the HDRS). Furthermore, HIV-positive individuals who were not depressed also demonstrated significantly poorer
performance than controls on some tasks, such as verbal memory and manual dexterity measures. These authors concluded that depressed mood does not account for neuropsychological dysfunction in asymptomatic individuals, regardless of whether depression is assessed by diagnostic interviews or self-report questionnaires.

Goggin et al. (1997) reported no significant differences in the prevalence of global neuropsychological impairment between depressed and non-depressed HIV-positive men. Depressed individuals, however, demonstrated significantly poorer performance on measures of verbal and nonverbal memory. Despite this difference, memory scores for most depressed individuals were not in the impaired range. Furthermore, there was no significant relationship between neuropsychological dysfunction and the severity of depression.

Kalechstein, Hinkin, Van Gorp, and Castellon (1998) analyzed the influence of depressed mood on neuropsychological functioning for two types of depressive symptoms: affective/cognitive symptoms (i.e., first 14 BDI items) and somatic symptoms (i.e., last 7 BDI items). Total BDI scores may mask relationships between neuropsychological functioning and depressive symptoms because somatic items on the BDI, such as weight loss and fatigue, may be confounded with the physical symptoms of HIV infection. Poor performance on a measure of procedural memory (i.e., Pursuit Rotor Task) predicted greater endorsement of affective/cognitive symptoms on the BDI. Total BDI scores and somatic symptoms, however, were not associated with performance on this task. On the other hand, BDI scores were not significantly associated with verbal memory (i.e., CVLT) performance. Decreased immune function (i.e., lower CD4 counts) was significantly associated with greater endorsement of both total depressive symptoms and somatic symptoms of depression.
Castellon et al. (1998) reported that higher scores on the affective/cognitive items of the BDI, but not on the somatic items, were significantly associated with slowed and less accurate performance on a choice reaction time test. Apathy (as assessed by the apathy subscale of the Neuropsychiatric Inventory) was significantly associated with poorer performance on a task of working memory (i.e., C-SPAN), although depressive symptoms were not. Both apathy and depression were more prevalent in AIDS and pre-AIDS patients relative to controls, although BDI scores for several of the controls also suggested moderate depression. As mentioned previously, Castellon et al. (1998) suggested that both apathy and working memory deficits result from disruption of the frontal-subcortical circuitry in HIV infection.

In sum, most studies have not demonstrated a strong relationship between depressed mood and lowered neuropsychological test performance in HIV infection. However, affective and cognitive symptoms of depression, as opposed to somatic symptoms, show some evidence of a relationship with neuropsychological deficits in HIV-infected individuals. Therefore, it is important to consider the potential influence of depressed mood on neuropsychological performance in HIV infection, particularly in individual case analysis.

Furthermore, systemic medical illness in HIV appears to interact with depressed mood. Mood disturbance in HIV infection appears to be significantly associated with increased medical symptoms (Hays et al., 1992; Perkins et al., 1995) and poorer perceived health status (Fawzy, Namir, Wolcott, Mitsuyasu, & Gottlieb, 1989). Depressed HIV-positive individuals also report more fatigue relative to individuals who are not depressed (Goggin et al., 1997). Physical symptoms reported by depressed HIV-positive individuals may stem
from somatic manifestations of depression, the effects of constitutional illness, or both. In turn, both mood and systemic medical illness may interact with neuropsychological functioning, and potentially subjective cognitive complaints, in HIV infection.

Treatment

Since the advent of pharmacological treatment for HIV infection, there have been rapid advances and changes in treatment options. The primary goal of treatment is to reduce viral activity (Cummings & Benson, 1992). Common medications include reverse transcriptase inhibitors, such as Azidothymidine (AZT) and 3-TC, and the more recent protease inhibitors, such as indinavir (Adams et al., 1997). Most individuals are on combination therapy or “drug cocktails”, a regimen of several different antiretroviral drugs. Highly active antiretroviral therapy, or HAART, is an aggressive form of treatment involving a combination of three antiretroviral medications. HAART is the most frequent treatment approach used in HIV infection and is recommended by the International AIDS Society (Carpenter et al., 1997). Studies to date have demonstrated the positive benefits of HAART on both morbidity and mortality in HIV infection, including improved immune functioning and reduced viral load (Hammer et al., 1996; Hammer et al., 1997; Kalichman et al., 1998; Palella et al., 1998).

In 90% of individuals receiving combination treatment, the virus may become undetectable for at least a one year period (Adams et al., 1997). While clinical improvement is often noted for up to several months with AZT use, initial treatment success is usually reversed and the infection continues to progress (Cummings & Benson, 1992).
Unfortunately, AZT treatment runs the risk of multiple adverse side effects (Cummings & Benson, 1992). Therefore, AZT treatment regimens must be monitored carefully. Other pharmacological treatments are specifically directed at the target symptom or processes, such as infections, metabolic imbalances, and depression.

It is unclear whether pharmacological treatment improves neuropsychological functioning; results of studies are mixed (Grant & Heaton, 1990). Studies that have not specifically investigated treatment outcome generally do not report significant treatment effects on neuropsychological performance (e.g., Selnes et al., 1995; Stout et al., 1995). However, other studies have demonstrated cognitive improvements associated with antiretroviral treatment. Schmitt et al. (1988) reported improvements in neuropsychological performance for individuals receiving AZT compared to a placebo group. The AZT group, however, demonstrated a significant drop in distress caused by physical, emotional, and cognitive symptoms, which may have contributed to improved neuropsychological functioning. Other research groups have also reported improved neuropsychological test performance in individuals receiving AZT (Riccio, Burgess, Hawkins, Wilson, & Thompson, 1990; Tozzi et al., 1993). De Ronchi et al. (1996) found better neuropsychological performance in individuals treated with AZT or ddI (2', 3'-Dideoxyinosine) relative to those who did not receive antiretroviral drug treatment.

More recent studies investigating the effects of HAART on neuropsychological functioning also suggest associated cognitive benefits. Ferrando et al. (1998) reported significantly better performance on measures of learning, memory, and psychomotor speed for individuals receiving HAART relative to those without HAART. Tozzi et al. (1999)
reported reductions in the prevalence of neuropsychological impairment in individuals receiving HAART. Improvement in psychomotor speed for individuals on HAART has been well documented (Sacktor et al., 1999; Sacktor et al., 2000). Cohen et al. (2001) also reported improvements in verbal fluency, psychomotor skills, and executive functioning in women taking HAART for 18 months or longer. It is important to be aware of these findings because of their implications for neuropsychological performance and interpretation, but this literature will not be reviewed completely in this paper as it is not central to the purpose of this investigation.

**Subjective Cognitive Complaints in HIV Infection**

Traditional neuropsychological measures may not be sensitive enough to detect subtle neuropsychological deficits in HIV infection, particularly in asymptomatic stages (Sahakian et al., 1995). Self-reported cognitive symptoms may be an additional important source of information regarding early neuropsychological changes in the disease. Early in the course of HIV infection, subjective complaints may include decreased attention and concentration, forgetfulness, difficulty completing more than one task simultaneously, and slowed thinking, which may be coupled with fatigue at times (Gibbs et al., 1990; Grant, 1990; Hinkin et al., 1998; Maj et al., 1994). Such complaints are more frequently reported in symptomatic individuals relative to asymptomatic individuals and HIV-negative controls (Gibbs et al., 1990; Maj et al., 1994; Saykin et al., 1991).

Despite complaints of neuropsychological difficulties, many HIV-positive individuals continue to perform within normal limits on neuropsychological measures (Hinkin et al.,
1998). Subjective cognitive complaints in HIV infection may be influenced by many factors: they may accurately reflect neuropsychological dysfunction, depressed mood, or systemic medical illness, including an individual's perception of medical or neurological symptoms (Hinkin et al., 1998; Lopez, Wess, Sanchez, Dew, & Becker, 1998). It is particularly difficult to distinguish among potential causes of cognitive symptoms in early stages of the disease (Grant, 1990).

Studies in other populations have linked cognitive complaints to three factors: neuropsychological performance, affective disturbances, and overall physical health. Cognitive complaints have been associated with poorer neuropsychological performance (Jonker et al., 1996; Schofield et al., 1997; Sunderland et al., 1983; Zelinski et al., 1990), affective disturbances such as anxiety or depression (Bassett & Folstein, 1993; Derouesne et al., 1989; Grut et al., 1993; Jorm et al., 1994; Levy-Cushman & Abeles, 1998; O'Connor et al., 1990; Schofield et al., 1997), and poorer physical health (Bassett & Folstein, 1993; Levy-Cushman & Abeles, 1998). Depressed individuals may report more neuropsychological problems, and yet underestimate their performance on neuropsychological measures (Grut et al., 1993). Furthermore, self-reported health status is significantly predictive of performance on some neuropsychological measures, including verbal memory tasks (Hultsch, Hammer, & Small, 1993).

With respect to the accuracy of subjective cognitive complaints in HIV infection, research findings have been mixed. Some research groups have reported good agreement between perceived neuropsychological functioning and performance on standardized neuropsychological tests (e.g., Mapou et al., 1993; Poutiainen & Elovaara, 1996; Rourke,
Halman, & Bassel, 1999a). Other studies have demonstrated poor concordance between cognitive complaints and actual test performance; cognitive complaints were instead significantly related to psychiatric symptoms (e.g., Van Gorp et al., 1991; Wilkins et al., 1991). Mixed findings may reflect both methodological differences across studies and failure to consider the interrelationships among multiple factors affecting cognitive complaints, such as neuropsychological deficits, mood, and systemic medical illness (Beason-Hazen, Nasrallah, & Bornstein, 1994; Lopez et al., 1998).

Wilkins et al. (1991) investigated the relationship between subjective cognitive complaints and neuropsychological performance at various stages of HIV infection. 49% of their sample reported neuropsychological problems. Cognitive complaints were generally not related to actual test performance, but they were significantly related to psychiatric symptoms, such as depression and anxiety. The only neuropsychological measure that was significantly correlated with cognitive complaints was performance on the Digit Symbol subtest of the WAIS. In contrast, motor symptoms (16% of sample) were significantly correlated with poorer performance on most gross and fine motor tests. Unlike cognitive complaints, motor complaints were not significantly associated with psychiatric symptoms. However, only four items were used to assess cognitive complaints in this study, and a high percentage of the sample met criteria for a psychiatric diagnosis. For example, 82% of the individuals who voiced cognitive complaints met DSM-III criteria for a psychiatric illness, most often major depression.

Similarly, Van Gorp et al. (1991) found that asymptomatic individuals who endorsed more cognitive complaints also reported more symptoms of depression. Although relatively
small, there was a significant relationship between scores on a measure of cognitive complaints (i.e., CFQ) and scores on a measure of depression (i.e., Center for Epidemiologic Studies-Depression scale). Self-reported cognitive problems were not related to neuropsychological test performance. In addition, CFQ scores did not differ significantly between asymptomatic individuals and controls, indicating that HIV-positive individuals did not endorse more cognitive complaints. It is noteworthy, however, that this sample was drawn from the MACS investigation, which has also failed to find significant neuropsychological impairment relative to other studies.

L. H. Moore et al. (1997) also failed to find a significant relationship between neuropsychological performance and subjective cognitive complaints in a group of symptomatic individuals. However, cognitive complaints were significantly associated with scores on self-report mood inventories (i.e., BDI, HDRS, Hamilton Anxiety Scale).

Claypoole et al. (1998) reported that memory complaints were strongly associated with severity of depression in HIV-positive individuals diagnosed with a major mood disorder. Neuropsychological performance was not significantly associated with complaints of memory or attention problems in their sample. Furthermore, treatment with antidepressants resulted in fewer cognitive complaints. This study clearly illustrates the relationship between depressed mood and cognitive complaints, although it does not rule out a possible association between cognitive complaints and neuropsychological skills in non-depressed HIV-positive individuals.

Stern et al. (1991) found that HIV-positive individuals reported cognitive complaints more often than HIV-negative controls in a structured interview. Individuals with HIV more
frequently reported memory problems, as well as lower mood and increased social withdrawal. For HIV-positive individuals, but not for controls, cognitive complaints were significantly related to both overall neuropsychological test performance, and to performance in neuropsychological domains that corresponded with complaints.

Maj et al. (1994) found that for symptomatic, but not asymptomatic, individuals, endorsement of at least one cognitive complaint was significantly related to overall neuropsychological impairment in 2 out of 5 centers. Endorsement of cognitive complaints was also related to symptoms of depression in both asymptomatic and symptomatic individuals in some centers (Maj et al., 1994).

Mapou et al. (1993) investigated the relationship between cognitive complaints, as ascertained by a semi-structured interview, and performance on various neuropsychological measures in HIV-positive individuals. Participants who reported cognitive problems were more likely than individuals who denied cognitive problems to obtain test scores below the cutoff (operationally defined as 1.5 SD below the mean of the control group performance). Participants with cognitive complaints were more likely to demonstrate poorer performance on measures of memory, reaction time, and motor skills, even if cognitive complaints were in other domains. In other words, neuropsychological deficits in memory, response speed, and motor functioning may underlie complaints in other cognitive domains in HIV infection. The relationship between neuropsychological test performance and subjective complaints for the total group of participants was similar in subgroups of asymptomatic and symptomatic individuals.

Mapou et al. (1993) also investigated the relationship of mood to both cognitive
complaints and neuropsychological test performance. Individuals who reported cognitive problems were more likely to score below cutoffs on the BDI and State-Trait Anxiety Inventory (STAI) indicative of depression and/or anxiety. However, neuropsychological test performance was not significantly related to affective symptoms (with the exception of one item on the STAI). These findings suggest that while neuropsychological performance is not adversely affected by depressive symptoms, both mood and neuropsychological deficits are related to cognitive complaints. The authors suggested that there may be two types of HIV-positive individuals with cognitive complaints: one group whose complaints relate to actual neuropsychological impairment, and a second group whose cognitive complaints primarily reflect low mood or other psychiatric factors. This study illustrates the complex interrelationships among mood, subjective cognitive complaints, and neuropsychological test performance, which have yet to be clearly delineated.

Beason-Hazen et al. (1994) reported that subjective complaints on the Current Symptoms Questionnaire (CSQ) were related to neuropsychological performance, particularly on measures of information processing and reaction time, in asymptomatic individuals. Furthermore, the presence and duration of physical symptoms (e.g., fatigue, headaches, dizziness) were significantly associated with performance on information processing speed (e.g., PASAT) and reaction time tasks. CD4 count did not appear to account for these relationships. These findings highlight the importance of systemic medical illness in potentially mediating the relationship between cognitive complaints and neuropsychological test performance. Although CSQ symptom endorsement was significantly correlated with self-reported depressive symptoms, depression did not account
for the relationship between subjective complaints and neuropsychological performance.

Poutiainen and Elovaara (1996) examined cognitive complaints in both asymptomatic and symptomatic individuals. Cognitive complaints were assessed in an interview. Concentration and memory problems were the most common complaints and were more often reported by symptomatic individuals. There was a significant association between cognitive complaints and poorer performance on verbal memory tests in symptomatic individuals. Motor complaints were also associated with poorer performance on tests of "cognitive speed and flexibility" (i.e., Stroop, Trails B, Mental Rotation) in symptomatic individuals. Depression and other psychiatric disorders did not account for these relationships, although HIV-positive individuals obtained significantly higher BDI scores than controls (scores remained within the average range). In contrast to Mapou et al. (1993), neuropsychological test performance and cognitive complaints were not significantly associated in asymptomatic individuals. The results of this study suggest that the relationship between cognitive complaints and neuropsychological performance may differ for symptomatic and asymptomatic individuals. Systemic medical illness may be one variable that affects the relationship between subjective cognitive complaints and neuropsychological test performance in individuals at different stages of HIV infection.

A different way to approach the investigation of accuracy in subjective cognitive complaints is to examine patterns of response in different subgroups of individuals. Hinkin et al. (1996) split their sample into two groups based on CFQ responses: 1) a group with low CFQ scores, indicating fewer cognitive complaints, and 2) a group with high CFQ scores, indicating relatively more cognitive complaints. Individuals with few cognitive complaints
(i.e., "minimizers") demonstrated significantly poorer performance on memory tests (i.e., CVLT; WMS-R Verbal Memory and General Memory indices). Conversely, individuals who reported memory problems obtained significantly higher scores on memory measures than minimizers. High CFQ scorers also obtained significantly higher scores on 2 out of 3 mood measures (i.e., Hamilton Anxiety and Depression Rating Scales, but not the BDI), indicating that cognitive complaints were associated with self-reported psychiatric symptoms. Participants fell into 3 different groups: 37% reported more cognitive problems than they demonstrated on testing, 26% denied neuropsychological difficulties but exhibited memory deficits, and neuropsychological performance agreed with self-report in 37% of the sample.

These results demonstrate agreement between subjective cognitive complaints and neuropsychological performance in a subgroup of HIV-positive individuals. Furthermore, most of the "minimizers" with memory impairment also met diagnostic criteria for AIDS, which suggests that denial or unawareness of neuropsychological deficits is more likely to occur in more advanced stages of the illness. This study also demonstrates that both mood and awareness play roles in mediating the relationship between complaints and neuropsychological impairment.

Discrepancies between Hinkin et al. (1996)'s findings and results from other studies may be partly due to methodological differences. Many of the study participants met diagnostic criteria for AIDS; participants in most previous studies had not yet developed AIDS. Some studies have used interviews rather than standardized measures to assess cognitive complaints. Perhaps most importantly, Hinkin et al. (1996) used a different grouping technique to investigate the relationship between cognitive symptoms and
neuropsychological functioning. As such, this study is a more complex extension of previous research.

Two recent investigations by Rourke and his colleagues examined the relationship between neuropsychological performance and self-reported cognitive complaints in HIV infection. Rourke et al. (1999a) analyzed cognitive complaints for a sample of HIV-positive individuals at all three CDC stages (A, B, and C). There were no significant differences in cognitive complaints across various stages of disease severity (i.e., asymptomatic, mildly symptomatic, clinical AIDS). Complaints were significantly associated with both depressive symptoms and performance on neuropsychological measures of attention and working memory, learning efficiency, and psychomotor skills. The bulk of variance in cognitive complaints was accounted for by depressive symptoms, with a smaller contribution from psychomotor speed. Consequently, these findings assist in clarifying some of the discrepancies in earlier studies by suggesting that both mood and neuropsychological skills play a role in explaining cognitive complaints in HIV infection.

Rourke, Halman, and Bassel (1999b) further explored the accuracy of subjective cognitive complaints in HIV infection using a subgroup approach. Rourke et al. (1999b) used scores on the Patient’s Assessment of Own Functioning Inventory (PAOF) and a memory measure (i.e., CVLT) to cluster four different subgroups of HIV-positive individuals according to their cognitive symptoms and memory test performance. Based on neuropsychological performance, two subgroups were “accurate” in their perceived neuropsychological functioning, and two subgroups were “inaccurate”. Of the two accurate subgroups, one group correctly denied neuropsychological difficulties and performed within
expectations on neuropsychological tests. The other group reported significant neuropsychological difficulties that matched their impaired performance on neuropsychological measures. Of the inaccurate groups, Rourke et al. (1999b) described one group as "overreporters" and the other as "minimizers" (i.e., "underreporters"). The "overreporters" reported significant cognitive problems but performed within expectations on formal testing. The "minimizers" denied any neuropsychological deficits, but their neuropsychological performance was impaired. The "minimizers" also demonstrated significantly poorer performance on a measure of problem-solving (i.e., WCST) relative to the other three groups. These results were interpreted to suggest that "minimizers" may lack insight into their neuropsychological dysfunction, which is consistent with their relatively poor performance on the WCST.

Lopez et al. (1998) investigated complaints of cognitive and motor slowing in HIV infection using a self-rating slowness scale. Complaints of slowness were significantly associated with neurological symptoms, systemic medical symptoms, and other cognitive symptoms. Smaller associations were found between slowness complaints and poorer performance on several neuropsychological tests, including measures of verbal and nonverbal memory and psychomotor speed. The authors developed a model indicating that complaints of slowness were significantly predicted by neurological complaints, peripheral neurological problems (e.g., neuropathy), and other cognitive symptoms. Other less influential predictors included psychomotor speed performance, depression, severity of HIV infection, and demographic variables such as age and education. The development of a multifactorial model to describe the relationships among self-reported complaints of various types (e.g., physical
and cognitive symptoms), neuropsychological performance, HIV status, mood, and demographic factors contributed to a better understanding of the complex relationship between cognitive complaints and neuropsychological performance. This approach is an excellent method of delineating the interrelationships among salient variables while examining one particular outcome (in this case, complaints of mental and motor slowness).

To date, the results of studies investigating subjective cognitive complaints in HIV infection have varied considerably. Methodological differences across studies have likely contributed to these discrepancies. In addition to the methodological concerns addressed earlier in this paper, problems noted in this area include differences in sample selection, stage of HIV infection, and the method of assessing cognitive complaints (e.g., standardized measures versus interviews) (Beason-Hazen et al., 1994). Moreover, HIV-positi

As a result, the variables that affect cognitive complaints in HIV infection, and the interrelationships among these variables, have not been clearly and completely delineated. At least two main variables may contribute to cognitive complaints: actual neuropsychological deficits and low mood (Rourke et al., 1999a). Another likely contributor to cognitive complaints is systemic medical illness, whether measured as physical symptoms or perceived poorer physical health status (Beason-Hazen et al., 1994; Lopez et al., 1998).

A model is one useful way to describe the interrelationships among the variables that potentially affect cognitive complaints in HIV infection, and the relationship of cognitive complaints to neuropsychological skills. Such a model provides a comprehensive overview
of the nature and strength of the relationships among variables. Interpretation of the model would improve understanding of the significance of cognitive complaints in HIV infection and assist in clarifying some of the discrepancies in the literature. In addition, understanding the relationships among these variables will improve the ability of clinicians to appreciate the many factors that impinge on an individual’s subjective experience of cognitive difficulties while living with HIV.

The accuracy of self-reported neuropsychological problems is particularly important for treatment decisions, which are often based on patient report (Hinkin et al., 1998). Improvements in our ability to predict neuropsychological impairment in HIV infection based on patient self-report would also assist in clarifying the discrepant findings to date, and provide a valuable clinical tool for the identification of individuals at risk for neuropsychological dysfunction. Further, these improvements would allow health care providers to help patients understand the relationship between their subjective experience of neuropsychological deficits and the cognitive sequelae of HIV infection.

Furthermore, cognitive symptoms may play an important role in the early identification of individuals at risk for HIV-associated neuropsychological impairment. While many researchers have investigated the relationship between cognitive complaints and neuropsychological performance in HIV infection, the ability of specific cognitive symptoms to predict neuropsychological deficits has not been examined. Some types of items on self-report questionnaires may possess more discriminative power than others in the prediction of neuropsychological impairment. Identification of items with the greatest predictive accuracy will establish the clinical significance of specific self-reported symptoms.
Moreover, the identification of such items may aid in teasing out the relative contributions of neuropsychological deficits, psychological factors, and systemic illness to subjective cognitive complaints. Consequently, these findings would lead to improved assessment and treatment of individuals with HIV infection. HIV-positive individuals will benefit from validation of their cognitive complaints, regardless of their source, as well as receiving health services in a timely and appropriate fashion.

Assessment of Cognitive Complaints

Cognitive complaints are generally reviewed in the initial assessment interview. Self-report measures are a more standardized fashion of assessing perceived neuropsychological functioning. Self-report questionnaires of cognitive complaints take various forms. Most questionnaires assess the occurrence and frequency of perceived neuropsychological difficulties overall, and sometimes for specific cognitive domains, such as memory, language, and judgement. Two examples of such self-report scales are the Patient’s Assessment of Own Functioning Inventory (PAOF) (Chelune, Heaton, & Lehman, 1986) and the Cognitive Failures Questionnaire (CFQ) (Broadbent, Cooper, FitzGerald, & Parkes, 1982).

Patient’s Assessment of Own Functioning Inventory (PAOF)

One instrument that has been developed to assess cognitive complaints is the PAOF, or Patient’s Assessment of Own Functioning Inventory (Chelune et al., 1986). The PAOF is a self-report questionnaire of symptoms in various neuropsychological domains, “designed
to elicit patients' self-perceptions regarding the adequacy of their functioning in various everyday tasks and activities" (Chelune et al., 1986, p. 96). The questionnaire consists of 47 items, but a shorter 33-item version is typically used because the additional 14 items are narrative. Item selection was based both on the neuropsychological domains regularly assessed in neuropsychological test batteries, as well as common cognitive complaints identified through clinical experience. The items are arranged in eight scales which were “rationally grouped...according to the general nature of the abilities” in question (Chelune et al., 1986, p. 96). These scales include memory (10 items), language and communication (9 items), motor and sensory-perceptual skills (5 items), and higher level cognitive and intellectual functions (9 items) (Chelune et al., 1986). Participants rate the frequency of cognitive symptoms on a Likert-type scale of 6 points ranging from “almost never” to “almost always” (see Appendix A). Scores can be tabulated for each of the four neuropsychological domains separately, and a total score is summed across neuropsychological domains.

Chelune et al. (1986) examined the psychometric properties of the 33-item PAOF in a series of studies. Data were collected from 703 screened participants. Of these participants, 105 were normal controls, 285 were referrals from neurology sources, 186 were referrals from psychiatry sources, and 127 were from other referral sources, such as vocational rehabilitation or legal referrals. Patient groups were significantly more impaired on global neuropsychological measures (e.g., IQ scores; Halstead Impairment Index; Average Impairment Rating), and demonstrated significantly higher levels of emotional distress on the Minnesota Multiphasic Personality Inventory (MMPI) than controls. Patient groups
reported a significantly higher frequency of neuropsychological difficulties than controls on all of the PAOF items except one. These data were used to determine cut-off scores to maximize discriminability between patient and control groups.

Chelune et al. (1986) also examined the structure of the PAOF empirically through factor analysis. Five factors were extracted, which the authors interpreted as 1) a language and communication factor, 2) a cognitive/intellectual factor, 3) a sensory/motor factor, and two memory factors: 4) general memory and orientation and 5) memory for specific information. The authors concluded from these studies that “the items within the PAOF scales...represent meaningful clusters of everyday difficulties with central themes (i.e., memory, language and communication, sensori-motor functioning, and cognitive/intellectual skills)” (Chelune et al., 1986, p. 103). Thus, although the PAOF was developed primarily through rational means and based on clinical experience, the grouping of items into different neuropsychological domains was empirically valid.

In addition, Chelune et al. (1986) investigated potential predictors of self-reported cognitive symptoms on the PAOF. Age and education accounted for a relatively small amount of variance in cognitive complaints (i.e., less than 3%). Contrary to expectations, MMPI scores explained a greater amount of variance in PAOF scores than neuropsychological test performance, with the exception of sensory/motor complaints. Patients who reported more cognitive complaints, regardless of their neuropsychological status, had MMPI profiles that differed markedly from the profiles associated with fewer complaints (Chelune et al., 1986). Individuals with higher PAOF scores were more likely to demonstrate elevations on the D (depression), Hs (somatic concerns), Pt (anxiety and
rumination), and Sc (unusual thinking) scales of the MMPI. In sum, these results indicated that more cognitive complaints were accompanied by increased psychological distress, irrespective of the individual’s actual level of neuropsychological functioning.

These findings suggested that cognitive complaints on the PAOF were related to psychological status, rather than solely to neuropsychological functioning. These results are consistent with some of the previously described studies. However, Chelune et al. (1986) also suggested, in agreement with other studies (e.g., Rourke et al., 1999b) that individuals can be categorized into different subtypes based on their cognitive complaints. Cognitive complaints and neuropsychological test performance may be more strongly associated in some subsets of individuals. These results again emphasize the complex relationships among cognitive complaints, neuropsychological skills, and psychological functioning.

The PAOF is a well-developed, brief questionnaire of self-reported cognitive symptoms. Questionnaire development was based on clinical experience, and this measure has been validated through empirical studies. The PAOF provides one appropriate and satisfactory means of investigating cognitive complaints in individuals with HIV infection.

**Cognitive Failures Questionnaire (CFQ)**

The Cognitive Failures Questionnaire (Broadbent et al., 1982), or CFQ, is a 25-item self-report questionnaire of common cognitive complaints. Respondents rate the frequency of cognitive symptoms on a Likert-type scale of 0-4 points ranging from “never” to “very often”. Total score is the sum of item scores for the entire questionnaire, ranging from 0 to 100. Scores can also be examined for separate areas of neuropsychological
function, such as memory, perception, and motor skills. Items were selected based on personal experience, with the goal of creating situations that many people had experienced in everyday life (Broadbent et al., 1982).

Broadbent et al. (1982) reported that CFQ scores were significantly associated with ratings on an accompanying measure, the CFQ-for-others, completed by spouses of CFQ respondents. CFQ scores have acceptable test-retest reliability and are not unduly related to social desirability (Broadbent et al., 1982). CFQ scores are also correlated with current psychiatric symptoms (Broadbent et al., 1982), vulnerability to stress (Broadbent, Broadbent, & Jones, 1986), BDI scores (Rabbitt & Abson, 1990), and scores on the SCL-90, a measure of physical, psychological, and cognitive symptoms (Scogin & Rohling, 1989).

The CFQ has commonly been used as a measure of everyday failures of attention, memory, and absent-mindedness (Pollina, Greene, Tunick, & Puckett, 1992; Rabbitt & Abson, 1990; Tipper & Baylis, 1987). Higher CFQ scores are related to poorer selective attention (Tipper & Baylis, 1987), slowed performance on tasks of focused attention (Meiran, Israeli, Levi, & Grafi, 1994), and poorer performance on measures of problem-solving, such as the WCST (Kramer, Humphrey, Larish, Logan, & Strayer, 1994).

Pollina et al. (1992) conducted a principal components factor analysis of the CFQ for a large sample of college students. Five factors were extracted, which the authors interpreted as 1) distractibility, 2) misdirected actions, 3) spatial/kinaesthetic memory, 4) interpersonal intelligence, and 5) memory for names. Matthews, Coyle and Craig (1990), however, reported at least two possible factor solutions for the CFQ. One strongly defined structure included a general factor and a specific factor related to people's names. A second less well-
defined solution extracted seven different factors. A more recent study also concludes that multiple factor solutions are interpretable for the CFQ (Larson, Alderton, Neideffer, & Underhill, 1997a, 1997b).

A number of studies investigating the perception of neuropsychological deficits in HIV infection have used the CFQ (e.g., Hinkin et al., 1996; Van Gorp et al., 1991). It would be useful to extend these findings by using the CFQ in additional studies at other centers, particularly because relationships among CFQ scores, neuropsychological performance, and psychiatric status remain unclear. Symptoms on the CFQ reflect everyday cognitive failures, lapses, or slips and therefore differ from the type of complaints on other measures, such as the PAOF. The use of two measures of cognitive symptoms (i.e., the PAOF and CFQ) will permit comparisons of the relationships among neuropsychological skills, mood, and systemic medical illness for different types of cognitive complaints.

Study Objectives

The primary objective of this set of studies was to clarify the nature of the relationship between the subjective report of cognitive problems and actual neuropsychological skills in individuals with HIV infection. The first goal of this study was to improve understanding of the relationship between subjective cognitive complaints and neuropsychological performance, while accounting for the potential influences of mood and systemic medical illness on cognitive complaints. A second goal of the investigation was to identify self-reported cognitive complaints that are significant predictors of neuropsychological impairment in HIV-positive individuals as opposed to complaints that
are unrelated to neuropsychological deficits. A third goal of the study was to develop a
decision-making model to identify individuals who are at risk for HIV-associated
neuropsychological impairment based on their subjective cognitive complaints, as well as
self-reported symptoms of depression, systemic illness, and neuropsychological performance
on brief screening measures.

This investigation was designed to improve current knowledge of the clinical
significance and predictive utility of cognitive symptoms in HIV infection. Information
regarding the significance of cognitive complaints in HIV infection will be particularly useful
in referring individuals who merit a complete neuropsychological evaluation. A better
understanding of the relationship between cognitive complaints and HIV-associated
neuropsychological impairment will assist care givers when making decisions for individual
cases, providing health care that is both more timely and more cost-effective. In addition, this
knowledge will help health care professionals provide patients with additional informational
support regarding their subjective experience of neuropsychological deficits in everyday
activities. In turn, this information will highlight ways to better treatment and quality of life
for HIV-infected individuals.

**Self-reported cognitive symptoms**

Two self-report questionnaires, the PAOF and the CFQ, were used to assess subjective
cognitive complaints. These questionnaires tap different types of cognitive symptoms, and
both were used to identify complaints that predict neuropsychological impairment.
PAOF.

Self-reported symptoms on the PAOF represent common cognitive complaints derived from clinical experience, as well as the neuropsychological domains typically assessed in a clinical neuropsychological evaluation. Clinically based cognitive symptoms are often reviewed in the evaluation of individuals with suspected neuropsychological dysfunction. These symptoms are a fundamental starting point in the examination of the relationship between subjective cognitive complaints and neuropsychological skills in HIV infection.

CFQ.

 Symptoms on the CFQ reflect everyday cognitive failures, lapses, or slips. Unlike the PAOF, the CFQ was developed from the experimental cognitive literature and such cognitive symptoms are not necessarily associated with a clinical presentation. The examination of everyday cognitive failures is particularly meaningful in the HIV population because of the mild and spotty nature of associated neuropsychological dysfunction.

Each of the two questionnaires contributed different information about the predictive value of cognitive symptoms, from various neuropsychological domains, in the identification of HIV-associated neuropsychological impairment. In addition, using two questionnaires increased the pool of cognitive symptoms available for the development of a screening protocol. Both the PAOF and CFQ were used to determine cognitive symptoms that are most predictive of neuropsychological risk in HIV infection.
Confounding factors

Although face validity suggests that subjective cognitive complaints reflect neuropsychological impairment, in fact, other factors are also associated with cognitive symptoms (e.g., Van Gorp et al., 1991; Wilkins et al., 1991). Therefore, it was important to investigate other potential contributors to self-reported cognitive complaints.

Mood.

Subjective cognitive complaints may be influenced by low mood. Furthermore, the relationship between cognitive complaints and mood may be masked by somatic symptoms of depression, which are confounded by the physical effects of HIV infection. Therefore, it is important to consider cognitive/affective symptoms of depression independently when investigating their relationship to cognitive complaints.

Systemic Illness.

Individuals with advanced medical illness may report increased cognitive complaints due to non-specific systemic symptoms, such as fatigue and shortness of breath. To date, the effects of physical symptoms on cognitive complaints have received little attention, although they may play an important role in perceived cognitive functioning.

Subjective cognitive complaints in HIV-positive individuals may reflect neuropsychological impairment, low mood, systemic medical symptoms, or some combination of these factors. The present set of studies attempted to identify cognitive complaints that predict neuropsychological impairment in HIV infection, and yet minimize the confounds of low mood and medical status. Distinguishing among these three potential causes of cognitive complaints will aid in accurate diagnosis and treatment, and promote
appropriate and timely referrals, whether for neuropsychological assessment, or for psychological or psychiatric assessment and/or treatment.

**Predicting neuropsychological impairment**

Self-reported cognitive complaints were used to predict performance on a battery of neuropsychological tests. Because neuropsychological performance was used as the "gold standard", the identification of predictive cognitive complaints was not expected to replace the neuropsychological assessment, but to aid in the decision-making process for diagnosis and treatment. Cognitive symptoms from the two questionnaires were evaluated for their ability to predict HIV-associated neuropsychological impairment. Subjective cognitive complaints, mood, systemic physical illness, and performance on neuropsychological screening measures were used to develop a decision tree for determining those HIV-positive individuals at increased risk for neuropsychological impairment.

**Developing a decision-making model**

*Sensitivity and specificity.*

Two concepts that require consideration during the development of a decision-making model are sensitivity and specificity. Sensitivity refers to the ability of a diagnostic test to identify a target disorder when that disorder is actually present (Fletcher, Fletcher, & Wagner, 1996; Norman & Streiner, 1998; Sackett, Haynes, & Tugwell, 1991). In contrast, specificity refers to the ability of the test to correctly identify the absence of the target disorder, or to identify the true negative cases (i.e., individuals without the disorder who
obtain a negative test result) (Fletcher et al., 1996; Norman & Streiner, 1998; Sackett et al., 1991).

Increased sensitivity is critical to maximize the number of hits, or true positive cases, identified with a decision tree (i.e., identification of individuals with cognitive complaints and actual neuropsychological impairment). The advantage to maximizing the sensitivity is that “...if a sign, symptom, or other diagnostic test has a sufficiently high sensitivity, a negative [test] result rules out the target disorder” (Sackett et al., 1991). Therefore, the likelihood of identifying individuals with HIV-associated neuropsychological impairment increases accordingly. Sensitivity is a particularly important issue for asymptomatic HIV-positive individuals, where the subtle and spotty nature of neuropsychological deficits may cause them to be missed by tests with poor sensitivity.

Positive Predictive Value.

This study attempted to identify the positive predictive value of cognitive complaints in predicting neuropsychological impairment. The positive predictive value refers to the probability an individual has the disorder given positive test results (Fletcher et al., 1996; Sackett et al., 1991). While sensitivity and specificity are properties of a particular test, the positive predictive value indicates the clinical significance of positive or negative results on a particular measure for a specific sample (Fletcher et al., 1996; Sackett et al., 1991). Predictive cognitive complaints should have predictive power that is greater than chance (i.e., 50%) in the identification of individuals at risk for neuropsychological impairment.

Sensitivity, specificity, and positive predictive value were important considerations in the development of a decision-making model (i.e., tree). However, using sensitivity as a
criterion results in a greater number of false positives, or the identification of individuals with cognitive complaints but normal neuropsychological performance. A reduction in false positive errors increases the chances of committing a second type of misclassification error; false negative errors occur when individuals with neuropsychological impairment deny cognitive complaints. The decision-making model incorporated a higher tolerance for false positives than false negatives, because of the serious ramifications of missing individuals at risk for HIV-associated neuropsychological impairment.

**Description of Studies**

In order to address the previously described goals of this investigation, a set of three related studies was conducted. Objectives for each of the three separate components to this investigation are described below.

**Part One: Modelling the Relationships Among Cognitive Complaints.**

**Neuropsychological Skills, Mood, and Physical Symptoms**

**Objective.**

The primary goal of Part One was to examine the interrelationships among the key constructs underlying cognitive complaints in HIV infection. The specific aim was to determine whether in fact a relationship existed between cognitive complaints and neuropsychological skills when potential confounding factors were taken into account. This was accomplished by building a model of the relationship between neuropsychological performance and cognitive complaints, which also accounted for the contributions of
systemic medical symptoms and depressive symptoms to cognitive complaints. A hypothetical model is presented in Figure 1.

Part Two: The Value of Cognitive Complaints in Predicting Neuropsychological Skills

Objective.

The aim of Part Two was to quantify the predictive value of specific cognitive complaints in predicting neuropsychological impairment in HIV infection. Individual questionnaire items from two measures of self-reported cognitive complaints (i.e., PAOF and CFQ) were used to predict the outcome of neuropsychological testing.

Part Three: The Contribution of Cognitive Complaints to A Screening Protocol for Neuropsychological Impairment

Objective.

The goal of Part Three was to develop a decision tree to identify HIV-positive individuals at risk for neuropsychological impairment. Findings from the literature to date, as well as results from Parts One and Two, were used to decide on relevant variables to include in the decision tree. Self-reported cognitive complaints, performance on brief neuropsychological measures, symptoms of depression, and systemic medical symptoms were used in the decision tree to identify individuals at risk for neuropsychological impairment.
Figure 1. Hypothetical model of interrelationships among cognitive complaints, neuropsychological performance, mood, and systemic medical illness.
Hypotheses

Based on clinical experience and the research findings to date, the following hypotheses were put forth:

1) Rourke et al. (1999a) demonstrated that depressive symptoms (i.e., BDI scores) were significant predictors of both total cognitive complaints and complaints across the four domains of the PAOF. Depressed mood accounted for the majority of variance in cognitive complaints on the PAOF. Several other studies have noted a significant relationship between cognitive complaints and low mood (e.g., Hinkin et al., 1996; Mapou et al., 1993; Van Gorp et al., 1991; Wilkins et al., 1991).

Therefore, it was predicted that cognitive complaints would be significantly related to depressive symptoms.

2) Somatic symptoms have been significantly associated with neuropsychological test performance in HIV infection (Beason-Hazen et al., 1994; Lopez et al., 1998; D. Moore et al., 2000) and these symptoms appear to interact with depressive symptoms in HIV (Fawzy et al., 1989; Goggin et al., 1997; Hays et al., 1992).

Therefore, it was predicted that cognitive complaints would be significantly related to self-reported symptoms of systemic illness.

3) Although results have been mixed, some studies have shown a relationship between subjective cognitive complaints and performance on neuropsychological measures (Beason-
Hazen et al., 1994; Mapou et al., 1993; Poutiainen & Elovaara, 1996; Rourke et al., 1999a, 1999b; Stern et al., 1991).

*Therefore, it was hypothesized that cognitive complaints would be significantly related to neuropsychological test performance. It was suggested that this relationship would likely be influenced by mood and systemic medical illness.*

4) Rourke et al. (1999a) demonstrated that cognitive complaints (although not necessarily in the psychomotor domain) are significantly correlated with performance on measures of psychomotor skills. Furthermore, performance on complex psychomotor speed was a significant predictor of cognitive complaints both across and within four neuropsychological domains on the PAOF. This study suggested that decreased psychomotor functioning may underlie cognitive complaints in other neuropsychological domains, such as memory (i.e., retention).

In addition, Mapou et al. (1993) showed that deficient performance on motor tests was significantly related to an increased likelihood of cognitive complaints, regardless of the specific domain of those complaints. Poutiainen and Elovaara (1996) also reported that symptomatic individuals with motor complaints demonstrated poorer performance on measures of “cognitive speed and flexibility” (i.e., TMT Part B, Stroop interference trial, mental rotation, verbal fluency). Wilkins et al. (1991) indicated that Digit Symbol was the only neuropsychological measure with which cognitive complaints were significantly correlated.

*Therefore, complaints of problems with psychomotor and sensory-perceptual*
functioning were expected to predict neuropsychological impairment.

5) Rourke et al. (1999a) found that subjective cognitive complaints, regardless of the specific domain, were significantly correlated with performance on measures of attention and working memory. In addition, performance on measures of working memory was a small, but significant, predictor of cognitive complaints in the domain of language and communication. Furthermore, the literature indicates that complex attention and/or working memory problems are common neuropsychological difficulties associated with HIV, which also suggests that such complaints may be related to overall neuropsychological status.

Therefore, it was predicted that complaints of problems with attention and working memory would be significantly related to neuropsychological impairment.

6) The relationship between subjective memory complaints and performance on verbal memory measures varies in different subgroups of HIV-positive individuals and appears to be mediated by problem-solving skill and mood for some subgroups (Rourke et al., 1999b). Although previous research has revealed some relationships between cognitive complaints and performance on memory tasks (e.g., Mapou et al., 1993; Rourke et al., 1999a), Rourke et al. (1999a) reported that performance on a verbal memory measure was not significantly predictive of subjective cognitive complaints.

Therefore, it was hypothesized that cognitive complaints of memory (i.e., retention) problems would not predict neuropsychological impairment.
7) Cognitive complaints of language problems were not expected to significantly predict neuropsychological impairment.

8) Cognitive complaints of problems with conceptual skills or executive functioning were not expected to significantly predict neuropsychological impairment.

9) Cognitive complaints of problems with spatial skills were not expected to significantly predict neuropsychological impairment.
Chapter II

Method

Participants

Participants in the study were a series of HIV-positive individuals referred for neuropsychological assessment at St. Michael’s Hospital - Wellesley Center Site, located in Toronto, Ontario. Participants were originally recruited from various sources, including a research pool, primary-care HIV medical clinics, and psychiatric services. Earlier studies indicated that participants recruited from these three sources did not differ significantly in age, education, CD4 lymphocyte count, CDC staging, or subjective memory complaints on the Patient’s Assessment of Own Functioning Inventory (PAOF) (Rourke et al., 1999b).

Participants were selected from a data base according to the following inclusion criteria: no history of CNS opportunistic infection, neurological condition (e.g., seizure disorder), head injury with loss of consciousness exceeding 30 minutes, significant past substance abuse or dependence, or significant developmental problems (e.g., diagnosed learning disability). All participants had completed a 3 to 4 hour neuropsychological assessment, and several behavioural questionnaires, including a self-report measure of depressive symptomatology (i.e., Beck Depression Inventory) and a self-report measure of subjective cognitive complaints.

The total sample consisted of 157 HIV-positive adults (149 men; 8 women). One individual was excluded from the analyses because he had not completed a measure of subjective cognitive complaints (i.e., PAOF or CFQ). All 156 remaining individuals had
completed the PAOF, and a subset of these individuals (n=94) had also completed the Cognitive Failures Questionnaire (CFQ). One hundred and thirty-five participants had completed the 12-item questionnaire of systemic symptoms.

Participants from all three clinical stages of disease severity (as defined by the 1993 CDC revised classification system for HIV infection) were included in the sample. Eighteen were asymptomatic (CDC-A), 61 were mildly symptomatic (CDC-B), and 76 had AIDS-defining illnesses or CD4 counts less than 200 (CDC-C). Mean CD4 count for the sample is presented in Table 1. Eighty-three percent of the sample was receiving antiretroviral treatment at the time of assessment, and 39% of the sample was taking antidepressant medication.

Demographic characteristics of the sample, including age, education, and estimated Verbal IQ scores are summarized in Table 1. Mean scores on measures of mood, physical symptoms, and subjective cognitive complaints are also displayed in Table 1. The mean age was 41.25 (SD=8.33), with a mean of 14.56 (SD=2.67) years of education. Mean estimated Verbal IQ (based on the ANART) was in the high average range at 117.49 (SD=6.45). Mean scaled scores on the Information (M=11.67; SD=2.36) and Picture Completion (M=10.49; SD=2.25) subtests of the WAIS-R were in the average range. Mean BDI score was 18.10 (SD=10.49), indicating that the group had mild to moderate depressive symptomatology.
Table 1

Mean Values for Demographic Characteristics, Mood, Physical Symptoms, and Cognitive Complaints (n=156)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean (Standard Deviation)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>41.25 (8.33)</td>
</tr>
<tr>
<td>Education (years)</td>
<td>14.56 (2.67)</td>
</tr>
<tr>
<td>ANART (estimated Verbal IQ)(^a)</td>
<td>117.49 (6.45)</td>
</tr>
<tr>
<td>WAIS-R Information Scaled Score(^b)</td>
<td>11.67 (2.36)</td>
</tr>
<tr>
<td>WAIS-R Picture Completion Scaled Score(^a)</td>
<td>10.49 (2.25)</td>
</tr>
<tr>
<td>Beck Depression Inventory Total Score</td>
<td>18.10 (10.49)</td>
</tr>
<tr>
<td>HIV 12-Item Medical Symptom Total Score(^c)</td>
<td>2.50 (1.94)</td>
</tr>
<tr>
<td>PAOF Total Score</td>
<td>50.78 (26.94)</td>
</tr>
<tr>
<td>CFQ Total Score(^d)</td>
<td>51.88 (16.65)</td>
</tr>
<tr>
<td>Recent CD4 Lymphocyte Count(^a)</td>
<td>342.44 (228.08)</td>
</tr>
</tbody>
</table>

Note. ANART=North American Reading Test; PAOF=Patient’s Assessment of Own Functioning Inventory; CFQ=Cognitive Failures Questionnaire

\(^a\)n=153
\(^b\)n=150
\(^c\)n=135
\(^d\)n=94

Procedure

Participants completed a detailed developmental and neuromedical background interview, self-report questionnaires, and the neuropsychological test battery in approximately 3 to 4 hours, often with a short break midway through. Recruitment and testing of the participants in the data base was approved by the hospital Research Ethics Board.
Neuropsychological measures were selected according to guidelines developed by the National Institute of Mental Health Workshop on Neuropsychological Assessment Approaches of AIDS-related Cognitive Changes (Butters et al., 1990). Neuropsychological test data included scores on the ANART (Spreen & Strauss, 1991); WAIS-R Digit Span and Digit Symbol subtests (Wechsler, 1981); Trail Making Test - Parts A and B (Reitan & Wolfson, 1993); Boston Naming Test (Kaplan, Goodglass, & Weintraub, 1983); letter (FAS) and category verbal fluency (Spreen & Strauss, 1991); Finger Tapping and Grooved Pegboard Test (Reitan & Wolfson, 1993); California Verbal Learning Test (Delis, Kramer, Kaplan, & Ober, 1987); and Wisconsin Card Sorting Test (Heaton, Chelune, Talley, Kay, & Curtiss, 1993). Scores on the PAOF and CFQ were used to assess subjective cognitive complaints (see earlier descriptions of measures, and Appendix A for the PAOF questionnaire). A self-report measure of 12 HIV medical symptoms (adapted from Whalen, Antani, Carey, & Landefeld, 1994) was administered to assess perceived systemic illness and complications; symptoms assessed included fatigue, oral thrush, night sweats, diarrhea, fever, headaches, weight loss, rash, cough, sore throat, skin abnormalities and shortness of breath. Scores on the Beck Depression Inventory (Beck & Steer, 1993) were used as an index of mood symptoms.

Clinical ratings of neuropsychological test performance were computed for each of the HIV participants by a licensed psychologist specializing in clinical neuropsychology (St. Michael’s Hospital). The method for determining these ratings is outlined by Heaton, Grant, Anthony, and Lehman (1981), and their specific utility in the study of HIV infection is described in Heaton, Kirson et al. (1994) and Heaton et al. (1995). Neuropsychological
clinical ratings were based on a 9-point scale for six major skill areas: attention, learning efficiency, memory (i.e., retention), verbal skills, conceptual skills, and psychomotor and motor skills (see Table 2). An additional global rating is used to describe overall neuropsychological functioning. Global ratings of 5 or greater are indicative of clinically significant neuropsychological impairment.

Table 2

<table>
<thead>
<tr>
<th>Interpretation</th>
<th>Rating</th>
<th>Neuropsychological Performance</th>
</tr>
</thead>
<tbody>
<tr>
<td>&quot;Intact&quot;</td>
<td>1</td>
<td>Above Average</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>Average</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>Below Average</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>Borderline or Atypical</td>
</tr>
<tr>
<td>&quot;Impaired&quot;</td>
<td>5</td>
<td>Mild Impairment</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>Mild to Moderate Impairment</td>
</tr>
<tr>
<td></td>
<td>7</td>
<td>Moderate Impairment</td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>Moderate to Severe Impairment</td>
</tr>
<tr>
<td></td>
<td>9</td>
<td>Severe Impairment</td>
</tr>
</tbody>
</table>

The global clinical neuropsychological rating is a single summary measure that captures the overall pattern of performance on a neuropsychological test battery and characterizes an individual as neuropsychologically "impaired" or "intact". The clinical experience and judgement needed to interpret the overall meaning and complexity of a neuropsychological profile are required to determine global clinical ratings. Global
neuropsychological clinical ratings are superior to assessing neuropsychological function based on only a single test score because they capture the essential features of clinical presentation and neuropsychological test performance, including the presence or absence of pathognomonic signs (Heaton et al., 1981). These ratings have been used to interpret neuropsychological performance in various populations, including multiple sclerosis (Heaton et al., 1985), chronic obstructive pulmonary disease (Grant et al., 1982), and substance abusers (Grant et al., 1978, 1979; Grant, Mohns, Miller, & Reitan, 1976).

Neuropsychological clinical ratings are particularly valuable in HIV infection because of the variability associated with neuropsychological problems in early HIV. Statistical comparisons of group means may mask neuropsychological dysfunction in HIV infection because of the variability and subtlety of neuropsychological problems. Neuropsychological clinical ratings are recommended by the NIMH workshop to document neuropsychological dysfunction in HIV, because they provide a more thorough evaluation of cognition in HIV infection (Butters et al., 1990). In sum, these findings suggest that neuropsychological clinical ratings are an excellent method of examining the relationship between cognitive complaints and neuropsychological status.

Inter-rater reliability of the ratings in this sample was assessed by randomly selecting a subset of 40 cases to be rated by a second party. A neuropsychology graduate student (University of Windsor) completed the second set of neuropsychological clinical ratings, and ratings were compared across the two raters. The reliability of these clinical ratings was important because they were used as measures of neuropsychological functioning in all of the subsequent analyses. Good inter-rater reliability of clinical ratings has been demonstrated
in earlier studies (Heaton et al., 1981), including ratings for HIV-infected individuals (Heaton, Kirson et al., 1994), but it was equally important to ascertain the inter-rater reliability of ratings for the present sample.

Inter-rater reliability was examined in two ways. Because two of three sets of analyses dichotomized clinical ratings into the categories of neuropsychologically impaired (ratings 5-9) versus unimpaired (ratings 1-4), inter-rater reliability was evaluated for these dichotomous groupings. Percentage agreement between raters and Cohen’s kappas were calculated for global neuropsychological ratings and ratings in each of the six neuropsychological domains. Kendall’s tau correlation coefficients were also calculated to evaluate inter-rater agreement for the 9-point rating scale. Table 3 lists these values of agreement between the two raters for clinical rating scores in each domain.

Table 3

<table>
<thead>
<tr>
<th>Neuropsychological Domain</th>
<th>Impaired versus Unimpaired % Agreement</th>
<th>Kappa</th>
<th>Rating Scores 1-9 Kendall’s tau</th>
</tr>
</thead>
<tbody>
<tr>
<td>Global</td>
<td>88</td>
<td>.75</td>
<td>0.81</td>
</tr>
<tr>
<td>Attention</td>
<td>80</td>
<td>.41</td>
<td>0.74</td>
</tr>
<tr>
<td>Learning</td>
<td>100</td>
<td>1.00</td>
<td>0.72</td>
</tr>
<tr>
<td>Memory</td>
<td>93</td>
<td>.54</td>
<td>0.70</td>
</tr>
<tr>
<td>Verbal</td>
<td>93</td>
<td>.73</td>
<td>0.69</td>
</tr>
<tr>
<td>Conceptual</td>
<td>100</td>
<td>1.00</td>
<td>0.69</td>
</tr>
<tr>
<td>Psychomotor/Motor</td>
<td>95</td>
<td>.90</td>
<td>0.77</td>
</tr>
</tbody>
</table>
Cohen’s kappa values indicate moderate to high agreement between the two raters for the dichotomous categories of impaired versus unimpaired. Perfect agreement was obtained for ratings in the domains of learning and conceptual skills. Agreement for psychomotor and motor skills ratings was also high. Kappa values for ratings of attention and memory were considerably lower, although they still represent moderate levels of agreement according to criteria specified by Landis and Koch (1977). Furthermore, although memory ratings had a low kappa value, raters disagreed on only 3 of 40 cases for this neuropsychological domain.

Kendall’s tau correlation coefficients indicated moderate to high agreement between the two raters on the 9-point clinical rating system. The highest association was for ratings of global neuropsychological functioning, which was as expected. The second highest value was for ratings of psychomotor and motor performance; the interpretation of these neuropsychological measures may be less likely to vary across raters. The lowest ratings were in the domains of verbal and conceptual skills. However, inter-rater agreement did not vary substantially across the six specific neuropsychological domains.

Statistical Analyses

Part One: Modelling the Relationships Among Cognitive Complaints, Neuropsychological Skills, Mood, and Physical Symptoms

In order to address Hypotheses 1-3, a theoretical model of the relationships among cognitive complaints, neuropsychological skills, mood, and physical symptoms of HIV was developed using structural equation modeling (SEM). SEM is particularly suited to this type
of analysis, because it simultaneously accounts for multiple relationships among variables, and tests hypothesized directional relationships (Grimm & Yarnold, 2000; Kline, 1998). Overall, SEM is a more powerful statistical technique than multiple regression or path analysis, with more flexible assumptions (Garson, 2000). Unlike more traditional statistical approaches, SEM also accounts for measurement error (i.e., that measures used are not pure reflections of the construct of interest) (Hoyle & Panter, 1995; Kline, 1998). This issue is particularly important in neuropsychology, where multiple sources of error may occur because of the sheer number of tests and questionnaires used.

SEM models are usually presented in path diagrams, with ovals representing unobserved variables, or latent constructs, and rectangles representing observed variables, or indicators of a construct. Arrows between variables indicate the hypothesized direction of relationships. Single-headed arrows represent causal, unidirectional relationships; double-headed arrows represent bidirectional relationships among variables presumed to correlate with one another. Paths (i.e., arrows) can be specified to examine the direct effect of variables on one another, as well as the indirect effects of variables that may exert influence through a mediator variable. The total effect of one variable on another is the sum of all the direct and indirect effects specified in the model. Path coefficients are the effect sizes of specified relationships among variables and are typically displayed above the arrow representing a relationship.

In SEM, the hypothesized model proposed by the researcher is evaluated for its "goodness of fit" with the actual observations in the sample data. Several methods are used to assess the fit of the model. The most common approach is to examine fit indices (Grimm
& Yarnold, 2000; Hoyle & Panter, 1995). A standard measure of overall model fit is $\chi^2$, a test of the difference between the model proposed by the researcher (implied) and that derived from the data (observed). Nonsignificant values of $\chi^2$ indicate better model fit. Relative chi-square, or $\chi^2/df$, is an index of model fit that reduces the sensitivity of the $\chi^2$ statistic to sample size. A value of less than 3 is recommended as an indication of acceptable model fit, with lower values indicating better model fit (Kline, 1998).

Other indices of overall model fit include the Goodness of Fit Index (GFI), the Normed Fit Index (NFI), the Comparative Fit Index (CFI), and the Incremental Fit Index (IFI). The Adjusted Goodness of Fit Index (AGFI) and the Tucker-Lewis Index (TLI) adjust for model complexity, because more complex models by their nature tend to fit the data better. Theoretically, values of these fit indices may range from 0 to 1. with higher values indicating better model fit. Values of .9 or greater are recommended as indications of better model fit (Garson, 2000; Grimm & Yarnold, 2000; Kline, 1998).

Parsimonious models are generally considered better models because they are not rewarded for model complexity (i.e., adding paths to the model) (Garson, 2000). Parsimonious models are those with relatively few parameters compared to the number of variables and the number of relationships among variables that are specified in the model. The root mean square error of approximation (RMSEA) is a fit index that penalizes models with less parsimony. A RMSEA value of less than or equal to .05 reflects good model fit (Kline, 1998). There is also a significance test associated with RMSEA. A nonsignificant test corresponds with lower values of RMSEA and indicates better model fit (Garson, 2000). Standard fit indices also have associated indices that penalize for lack of parsimony. PGFI,
PNFI, and PCFI are all examples of these.

Examining covariance residuals is another method of evaluating model fit. Residuals are the differences in covariances between the implied (i.e., hypothesized) and observed model. Lower values of residuals indicate better model fit because the differences between the proposed model and the model derived from the data are small (Kline, 1998). The Root Mean Squared Residual (RMR) is the square root of the average squared covariance residuals. Lower values of RMR indicate better model fit (Garson, 2000).

The Akaike Information Criterion (AIC) is a fit index that adjusts for model complexity and is used to evaluate competing models that are not nested. Models with lower AIC values better fit the data (Garson, 2000). The Expected Cross-Validation Index (ECVI) is an index of model fit based on information theory that is also sometimes used to compare competing models; lower values on this index are preferable.

Part Two: The Value of Cognitive Complaints in Predicting Neuropsychological Skills

The second set of statistics addressed Hypotheses 4-8 regarding the relationship between subjective cognitive complaints and neuropsychological skills. In order to determine the direction and strength of the relationship between individual items on the self-report questionnaires and neuropsychological status, Pearson-r product-moment correlation coefficients between PAOF items, CFQ items, global neuropsychological clinical ratings, and neuropsychological ratings for each neuropsychological domain were calculated.

For both the PAOF and CFQ, the number of items was also reduced through principal component factor analysis. Items that load onto the same factor likely tap similar cognitive
symptoms. Items with the highest loading on each factor were selected as predictors to enter into logistic regression equations. Based on the results of the PCA factor analyses, a reduced number of questionnaire items were entered into logistic regression equations to determine their ability to predict neuropsychological skills in each of the six neuropsychological domains of interest.

**Part Three: The Contribution of Cognitive Complaints to A Screening Protocol for Neuropsychological Impairment**

The third set of statistics addressed all of the hypotheses regarding the predictive value of cognitive complaints, symptoms of depression, and systemic medical symptoms in predicting neuropsychological impairment. Decision tree analyses were used to assess the contributions of cognitive complaints, mood, and physical symptoms to the classification of individuals with global neuropsychological impairment. Several neuropsychological measures were also selected to include in the decision tree, based on both practical considerations (e.g., length of testing) and proven utility in the identification of HIV-associated impairment.

Classification trees determine the optimal set of specified predictors for predicting membership in classes of a categorical dependent variable (Breiman, Friedman, Olshen, & Stone, 1984). Classification trees are a more flexible way to address classification problems than traditional analyses, such as discriminant function analyses. One advantage is that they easily accommodate a mix of different types of predictor variables (e.g., nominal, ordinal, continuous) (Statsoft, 2000). The hierarchical nature of classification tree analyses permits
inspection of predictor variables' effects one at a time, rather than simultaneously (Breiman et al., 1984). Most importantly, the simplicity of a classification tree structure allows for an ease of interpretation that lends itself well to clinical decision-making (Grant et al., 1993; Statsoft, 2000).

A classification tree analysis produces a classification matrix that shows the number of cases accurately and inaccurately classified by the tree. A better set of predictors will result in lower misclassification rates (Breiman et al., 1984). The goal is to generate the tree with the minimum associated costs, which are typically defined as the proportion of misclassified cases (Statsoft, 2000). Once the classification tree has been generated, the sample data is re-analyzed by the tree. The resubstitution estimate is the proportion of cases misclassified by the tree, and it is used as one method of evaluating the accuracy of a classification tree (Breiman et al., 1984).

Prior probabilities are often used to determine a priori the likelihood that a case will fall into one of the classes. Prior probabilities are most frequently used because existing base rates are not accurately represented in the data set of a particular sample (Statsoft, 2000). Misclassification costs can also be established beforehand. For example, cases with a higher associated misclassification cost may be specified a priori to incorporate this information into the decision tree.

The Classification and Regression Trees (CART) method was used for the current analyses. Because it is an exhaustive search, CART is effective in determining the splits that will result in the best classification (Statsoft, 2000). Furthermore, CART was selected because this method provided the most flexibility by including both prior probabilities and
misclassification costs. CART attempts to make each node of the tree purer (i.e., contain more of the same type of case) (Statsoft, 2000). The Gini measure of node impurity was used as the goodness of fit measure as recommended by Breiman et al. (1984). When the node of a tree is pure (i.e., only one type of case), the Gini measure will equal zero (Breiman et al., 1984). CART algorithms determine the splits on predictor variables that produce the lowest values on the Gini measure, and therefore, the best goodness of fit.

The V-fold cross-validation method is recommended when examining the generalizability of decision trees produced by small samples (Breiman et al., 1984). From the given data set (i.e., learning sample), V-fold cross-validation forms a specified number of random subsamples that are equal in size. The decision tree is then computed the specified number of times, always leaving out one subsample to cross-validate the tree. The cross-validation values are averaged across the analyses to determine the final cross-validation costs.
Chapter III

Results

Prior to statistical analyses, variables were screened for accuracy of data entry, missing values, and fit between their distributions and the assumptions of multivariate statistical procedures. Version 10.0 of the SPSS statistical software package was used for all analyses. Although several univariate and multivariate outliers were detected, they were retained for all analyses because they were considered part of the patient population in question. However, because of the sensitivity of structural equation modelling to the influence of outliers, these analyses were also conducted with outliers excluded from the data. The results of SEM analyses with outliers removed did not differ substantially from those with outliers included.

Part One: Modelling the Relationships Among Cognitive Complaints.

Neuropsychological Skills, Mood and Physical Symptoms

The first set of statistics addressed Hypotheses #1-3 predicting that cognitive complaints would be significantly related to symptoms of depression, systemic medical symptoms, and neuropsychological test performance. A model of the relationships among cognitive complaints, neuropsychological skills, mood, and physical symptoms of HIV infection was developed using SEM. Maximum likelihood estimation was used in the AMOS (Analysis of Moment Structures) module, version 4.0 (Arbuckle & Wothke, 1995) of the SPSS statistical package to complete the analyses. Although using polychoric correlation matrices with the weighted least squares (WLS) method is usually preferred for ordinal
variables, this approach was not used in the present study because of the very large sample size requirements (e.g., 2000 cases). Furthermore, maximum likelihood estimation and WLS methods appear to generate comparable values for fit indices and result in few interpretative differences (Garson, 2000).

A partial hybrid model was constructed, with both unobserved (i.e., latent) and observed (i.e., measured) variables. Cognitive complaints and neuropsychological skills were represented as underlying constructs that were measured by multiple observed variables (i.e., indicators). Summary scores for the four neuropsychological domains of the PAOF (i.e., memory, language and communication, motor/sensory-perceptual, and higher-level cognitive and intellectual functions) were used as indicators of the construct “cognitive complaints”. Clinical neuropsychological rating scores for each of the neuropsychological domains assessed by the neuropsychological test battery (i.e., attention, learning, memory, verbal, conceptual skills, psychomotor and motor skills) were used as indicators of the construct “neuropsychological skills”. Mood and systemic symptoms of HIV infection were specified as observed variables in the model. Mood was measured by scores on the cognitive/affective items of the BDI (i.e., the first 13 items) and HIV-related physical symptoms were measured by scores on the 12-symptom inventory. Mood and physical symptoms were specified as exogenous variables predicting cognitive complaints. The latent variable “neuropsychological skills” was specified as an endogenous variable predicted by cognitive complaints, mood, and physical symptoms.

Only cases with data on each of the variables specified in the model were included in the SEM analysis (n=129). The resulting model, with accompanying path coefficients (i.e.,
regression weights), squared multiple correlations, correlations among variables, and correlations among error terms is presented in Figure 2.

Standardized direct effects, indirect effects, and total effects are displayed in Table 4. For example, reading across the first row of the table shows that BDI scores had a direct effect (and total effect) of .30 on the construct of cognitive complaints, while physical symptoms had a direct (and total) effect of .32 on cognitive complaints. Effects with no listed values were equal to zero by default, because these relationships were not specified in the model. Kline (1998) suggests that standardized path coefficients with values greater than .50 represent a "large" effect, those with values of .30 a "medium" effect, and values less than .10 a "small" effect.

Factor loadings on the construct of cognitive complaints ranged from .61 to .88. Factor loadings on the construct of neuropsychological skills ranged from .50 to .70. Loadings in these ranges indicated that the constructs were relatively well defined. The construct of cognitive complaints was significantly predictive of neuropsychological skills; the path coefficient of .44 indicated a moderate-sized effect ($p < .01$). Cognitive complaints, however, accounted for only 15% of the variance in neuropsychological skills. While both mood ($\beta = .30$, $p < .01$) and physical symptoms ($\beta = .32$, $p < .001$) had moderate effects on cognitive complaints, neither variable significantly predicted neuropsychological skills. Although mood and physical symptoms had small indirect effects on neuropsychological skills through cognitive complaints, total effects on neuropsychological skills were negligible. Not surprisingly, mood and physical symptoms were significantly correlated ($r = .43$, $p < .001$).
Figure 2. Model of relationships among cognitive complaints, neuropsychological (NP) skills, mood, and physical symptoms of HIV infection. Ovals represent unobserved variables; rectangles represent observed variables. Values embedded in unidirectional arrows are standardized regression weights. Values embedded in bidirectional arrows are correlations. Values within variable ovals or rectangles are squared multiple correlations. Note that error terms have not been depicted for simplification.
Table 4

Standardized Direct Effects, Indirect Effects, and Total Effects of Model Variables

<table>
<thead>
<tr>
<th>Dependent Variable</th>
<th>Type of Effect</th>
<th>Predictor Variable</th>
<th>Cognitive Complaints</th>
<th>NP Skills Scores</th>
<th>BDI</th>
<th>12-Item Physical Symptom Scores</th>
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<td>Type of Effect</td>
<td>Predictor Variable</td>
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<td>NP Skills Scores</td>
<td>BDI</td>
<td>12-Item Physical Symptom Scores</td>
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<td><strong>0.67</strong></td>
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<td>Psychomotor and Motor</td>
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<tr>
<td></td>
<td>Total:</td>
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<td><strong>0.31</strong></td>
<td><strong>0.70</strong></td>
<td>-0.005</td>
<td>0.07</td>
</tr>
</tbody>
</table>

Note. Effects equal to or greater than .30 are in bold type. NP=Neuropsychological; BDI=Beck Depression Inventory; PAOF=Patient's Assessment of Own Functioning Inventory; SP=Sensory-Perceptual
Table 5

Fit Indices for SEM model

<table>
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<tr>
<th>Statistic</th>
<th>Value</th>
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<tr>
<td>$\chi^2$</td>
<td>52.38 ($p = 0.31$)</td>
</tr>
<tr>
<td>$\chi^2$/df</td>
<td>1.09</td>
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<tr>
<td>GFI</td>
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</tr>
<tr>
<td>AGFI</td>
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</tr>
<tr>
<td>PGFI</td>
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<tr>
<td>TLI</td>
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</tr>
<tr>
<td>RMR</td>
<td>0.89</td>
</tr>
<tr>
<td>RMSEA</td>
<td>0.03 ($p = 0.81$)</td>
</tr>
<tr>
<td>ECVI</td>
<td>0.88</td>
</tr>
<tr>
<td>AIC</td>
<td>112.38</td>
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</table>

**Note:** GFI = Goodness of Fit Index; AGFI = Adjusted Goodness of Fit Index; PGFI = Parsimony Goodness of Fit Index; TLI = Tucker-Lewis Index; RMR = Root Mean Square Residuals; RMSEA = Root Mean Square Error of Approximation; ECVI = Expected Cross-Validation Index; AIC = Akaike Information Criterion

Measurement error terms for neuropsychological clinical ratings of learning and memory were significantly correlated ($r = .25$, $p < .05$), likely because ratings for these neuropsychological domains are partially derived from the same measures (i.e., CVLT; Figure Learning and Memory). Measurement error terms for neuropsychological clinical ratings of attention and psychomotor speed were also significantly correlated ($r = .32$, $p < .05$).

The fit indices generated by AMOS were examined to assess model fit (see Table 5). Most fit indices were well within expected guidelines. The $\chi^2$ value was not significant ($\chi^2 = 52.38$, $p = .31$), indicating acceptable fit between the hypothesized (implied) model and the observed data. $\chi^2$/df was quite low and well below the recommended value of 3. With the exception of parsimony fit indices, standard fit indices were above .85, with most above .90. The Tucker-Lewis Index, which is less likely to be affected by sample size, was .99. RMSEA
was below .05, and a test of its significance was not significant, indicating an acceptable fit between model specification and the observed data (.03, p = .81).

The feasibility of a model incorporating feedback loops (i.e., non-recursive model) was considered. However, non-recursive models are more problematic, often requiring additional statistical assumptions, as well as specialized statistical techniques (Kline, 1998). For example, it is more difficult to achieve model identification in non-recursive models, a requirement that produces a unique solution for each model parameter (Kline, 1998). These issues, combined with the relatively small sample size for an SEM study, resulted in the decision to use a simpler model that did not specify any feedback loops (i.e., recursive model).

Several alternative models were generated. A simpler model including only cognitive complaints and neuropsychological skills was compared to models including the additional contributions of either mood or physical symptoms. In each case, the size of path coefficients did not change substantially, indicating good model stability. Removing the contributions (i.e., paths) of mood and/or physical symptoms to neuropsychological skills did not significantly alter the model, confirming the minimal contribution of these variables in predicting neuropsychological skills. Fit indices for the simplest model indicated better model fit than the other models tested, likely because it was a more parsimonious model (i.e., fewer parameters). The modest size of the relationships among the variables examined may also have limited the improvement gained by specifying additional variables in the model. Fit indices for the model including mood but not physical symptoms indicated less acceptable fit than those for the model including physical symptoms but not mood, which fit
the data almost as well as the simplest model. Selection of the final model was based on fit indices, residuals, and theoretical soundness. Although the simplest model (i.e., with only cognitive complaints and neuropsychological skills) better fit the data than the model presented, the more complex model was selected to illustrate the minimal impact of mood and physical symptoms on neuropsychological skills in HIV infection.

The possibility of developing multiple models to examine the contributions of cognitive complaints to neuropsychological performance in each cognitive domain was also considered. However, a trial model based on solely one neuropsychological domain did not fit the data adequately (i.e., unacceptable fit indices) and therefore, conclusions drawn from such a model would likely be meaningless.

**Part Two: The Value of Cognitive Complaints in Predicting Neuropsychological Skills**

The second set of results addressed Hypotheses #4-8 predicting that cognitive complaints would be related to neuropsychological performance in the domains of psychomotor and sensory-perceptual skills, attention, and working memory, but not in the domains of memory (i.e., retention), language, spatial skills, or conceptual skills.

**Correlations**

Pearson-r product-moment correlation coefficients were calculated to assess the degree of association among neuropsychological clinical ratings, scores on measures of mood (i.e., BDI cognitive/affective symptoms), HIV-related physical symptoms (i.e., 12-symptom questionnaire), total cognitive complaints, and individual cognitive complaints (i.e., items
on the PAOF and CFQ).

**PAOF.**

The correlation matrix for PAOF items is displayed in Table 6. PAOF total scores were significantly associated with higher BDI scores ($r=.48, p<.001$) and increased physical symptoms of HIV infection ($r=.43, p<.001$), as were summary scores for the four subjective cognitive domains of the PAOF (i.e., memory, language and communication, motor/sensory-perceptual, and higher-level cognitive and intellectual functions). PAOF total ($r=.26, p<.001$) and domain summary scores were also significantly related to global neuropsychological ratings, with increased complaints associated with higher (i.e., worse) global neuropsychological test ratings.

PAOF total and domain scores were significantly correlated with neuropsychological ratings of attention ($r=.25, p<.01$), learning ($r=.16, p<.05$), and psychomotor and motor skills ($r=.33, p<.001$), but not with ratings based on tests of memory, verbal skills, and conceptual skills. The only exceptions to this pattern were that motor/sensory-perceptual complaints were not significantly associated with neuropsychological ratings of learning and higher-order cognitive complaints were significantly correlated with ratings of verbal skills. Total PAOF scores and domain summary scores were most highly correlated with neuropsychological clinical ratings based on psychomotor and motor skills. However, cognitive complaints were more highly correlated with depressive symptoms and systemic symptoms of HIV infection than with clinical ratings based on neuropsychological test performance.
Table 6

Pearson-r Correlation Coefficients for Individual PAOF Items

<table>
<thead>
<tr>
<th>PAOF Item</th>
<th>BDI</th>
<th>HIV Symptoms</th>
<th>Global Rating</th>
<th>Attention Rating</th>
<th>Learning Rating</th>
<th>Memory Rating</th>
<th>Verbal Rating</th>
<th>Conceptual Rating</th>
<th>Psychomotor Rating</th>
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</thead>
<tbody>
<tr>
<td>Total</td>
<td>0.48***</td>
<td>0.43***</td>
<td>0.26***</td>
<td>0.25**</td>
<td>0.16*</td>
<td>0.12</td>
<td>0.14</td>
<td>0.08</td>
<td>0.33***</td>
</tr>
<tr>
<td>Memory</td>
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<td>0.41***</td>
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<td>0.23**</td>
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<td>0.11</td>
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<td>0.33***</td>
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<td>0.15</td>
<td>0.15</td>
<td>0.29***</td>
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<td>Motor/SP</td>
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<td>0.30***</td>
<td>0.18*</td>
<td>0.16*</td>
<td>0.08</td>
<td>0.09</td>
<td>0.03</td>
<td>0.09</td>
<td>0.25**</td>
</tr>
<tr>
<td>Higher Cognitive</td>
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<td>0.25**</td>
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<td>0.08</td>
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Items:
1. 0.32*** 0.28*** 0.22** 0.17* 0.15 0.11 0.08 0.03 0.30***
2. 0.23** 0.13 0.24** 0.13 0.18* 0.18* 0.12 0.06 0.27***
3. 0.26*** 0.29*** 0.31*** 0.29*** 0.19* 0.11 0.12 0.11 0.36***
4. 0.31*** 0.28*** 0.24** 0.21** 0.24** 0.04 0.11 0.03 0.20**
5. 0.29*** 0.27** 0.15 0.14 0.12 0.06 0.04 0.004 0.15
6. 0.28*** 0.36*** 0.18* 0.23** 0.03 -0.00 0.16* -0.02 0.28***
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<tr>
<th>PAOF Item</th>
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<th>Global Rating</th>
<th>Attention Rating</th>
<th>Learning Rating</th>
<th>Memory Rating</th>
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<td>0.36***</td>
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<td>0.16*</td>
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</table>

Note. *p < .05; ** p ≤ .01; *** p ≤ .001; PAOF=Patient's Assessment of Own Functioning Inventory; BDI=Beck Depression Inventory (Items 1-13); SP=Sensory-Perceptual
With the exception of three items, all individual PAOF items were significantly associated with BDI scores and increased physical symptoms of HIV infection. Approximately two-thirds of the individual PAOF items were significantly associated with higher (i.e., worse) global neuropsychological ratings. PAOF items that were significantly correlated with clinical neuropsychological ratings are presented in Table 7 for each area of subjective complaints on the PAOF. Only six of the PAOF items failed to show a significant relationship with clinical ratings in the psychomotor and motor domain. Approximately 2/3 of PAOF items showed significant relationships with ratings based on attention measures. Nine items were significantly associated with ratings based on measures of learning. Few PAOF items demonstrated significant associations with ratings in the memory, verbal, and conceptual skill domains.

Table 7

PAOF Items Significantly Correlated with Neuropsychological Clinical Ratings

<table>
<thead>
<tr>
<th>NP Rating Domain</th>
<th>Significant Items for Each PAOF Domain</th>
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<tr>
<td>Memory</td>
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<td>Conceptual</td>
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<tr>
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</tr>
<tr>
<td>Global</td>
<td>1,2,3,4,6,7,8,9</td>
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</table>

Note. NP= Neuropsychological; PAOF=Patient’s Assessment of Own Functioning Inventory; SP=Sensory-Perceptual
CFQ.

The correlation matrix for CFQ total scores and individual items is displayed in Table 8. While CFQ total scores and memory subscale scores were highly correlated with BDI scores ($r = .50$ and $r = .42$, $p < .001$) and greater HIV-related physical symptom endorsement ($r = .56$ and $r = .46$, $p < .001$), they were not significantly related to global neuropsychological clinical ratings. In addition, total CFQ scores were not significantly correlated with neuropsychological clinical ratings for any of the six neuropsychological domains, except for ratings in the psychomotor and motor domain ($r = .27$, $p < .01$).

Findings for individual CFQ items mirrored those for total scores. With the exception of one item, all CFQ items were significantly associated with higher BDI scores and increased physical symptoms of HIV infection. Only item 9 (i.e., “Do you fail to hear people speaking to you when you are doing something else?”) was significantly associated with higher (i.e., worse) global neuropsychological clinical ratings ($r = .21$, $p < .05$). With respect to specific neuropsychological domains, approximately half of the CFQ items were significantly correlated with clinical ratings in the psychomotor and motor domain (i.e., items 1, 4, 5, 6, 9, 11, 12, 13, 14, 17, 22, 23, and 25). The remaining neuropsychological domains demonstrated few relationships with individual CFQ items. Four items (4, 5, 9, and 13) were significantly associated with ratings based on measures of attention. Two CFQ items (8, 24) were significantly correlated with memory ratings. Individual CFQ items failed to demonstrate significant relationships with neuropsychological clinical ratings in the domains of learning, verbal skills, and conceptual skills.
Table 8

Pearson-r Correlation Coefficients for Individual CFQ Items

<table>
<thead>
<tr>
<th>CFQ Item</th>
<th>BDI</th>
<th>HIV Symptoms</th>
<th>Global Rating</th>
<th>Attention Rating</th>
<th>Learning Rating</th>
<th>Memory Rating</th>
<th>Verbal Rating</th>
<th>Conceptual Rating</th>
<th>Psychomotor Rating</th>
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</thead>
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<tr>
<td>Total</td>
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<td>-0.08</td>
<td>-0.03</td>
<td>0.27**</td>
</tr>
<tr>
<td>Memory</td>
<td>0.42***</td>
<td>0.46***</td>
<td>0.13</td>
<td>0.11</td>
<td>0.03</td>
<td>-0.06</td>
<td>-0.03</td>
<td>-0.03</td>
<td>0.28**</td>
</tr>
</tbody>
</table>

Items:

1. 0.37*** 0.30** 0.06 0.11 -0.02 -0.07 -0.08 -0.01 0.20
2. 0.42*** 0.42*** 0.07 0.03 0.01 -0.06 -0.12 0.04 0.12
3. 0.30** 0.31** 0.06 0.11 0.08 -0.05 -0.06 -0.06 0.10
4. 0.29** 0.26* 0.13 0.25** -0.12 -0.10 -0.02 0.04 0.34***
5. 0.24* 0.41*** 0.12 0.23* -0.06 0.02 -0.01 0.11 0.28**
6. 0.22* 0.26* 0.16 0.14 -0.02 0.06 0.07 0.12 0.29**
7. 0.41*** 0.22* 0.01 0.12 0.07 -0.09 -0.08 -0.16 0.08
8. 0.46*** 0.39*** -0.02 -0.04 -0.02 -0.22* -0.02 -0.003 0.01
9. 0.20* 0.31** 0.21* 0.22* 0.17 -0.02 -0.01 0.06 0.28**
10. 0.46*** 0.33** 0.03 0.03 0.07 -0.13 -0.14 -0.03 0.03
<table>
<thead>
<tr>
<th>CFQ Item</th>
<th>BDI Symptoms</th>
<th>HIV Symptoms</th>
<th>Global Rating</th>
<th>Attention Rating</th>
<th>Learning Rating</th>
<th>Memory Rating</th>
<th>Verbal Rating</th>
<th>Conceptual Rating</th>
<th>Psychomotor Rating</th>
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<td>11.</td>
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<td>-0.09</td>
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<tr>
<td>12.</td>
<td>0.23*</td>
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Note. * p < .05; ** p ≤ .01; *** p ≤ .001; CFQ=Cognitive Failures Questionnaire; BDI=Beck Depression Inventory (Items 1-13)
PCA Factor Analyses

Principal components factor analyses with varimax rotation were then performed to reduce the number of items on the PAOF and CFQ to be used in subsequent analyses.

PAOF

Factor loadings for PAOF items are presented in Table 9. Six factors were extracted that cumulatively accounted for 65% of the variance. The first factor was interpreted as a factor of problem-solving skills (e.g., #31: “Do you have more difficulty now than you used to in solving problems that come up around the house, at your job, etc.?”). Two factors were extracted that related to memory items: one factor was interpreted to reflect long-term memory or retention of material (e.g., #5: “How often do you forget people whom you knew/met a year or more ago?”), and the second factor was interpreted as a working memory factor (e.g., #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?”). The fourth factor represented a greater mix of cognitive complaints, including items pertaining to language, writing, and vision (e.g., #18: “When you write things, how often do you have difficulty forming the letters correctly?”). This factor was interpreted to reflect primarily lexical complaints. The fifth factor related to sensory-perceptual complaints (e.g., #22: “How often do you have difficulty feeling things with your right hand?”). The sixth and final factor appeared to reflect complaints of difficulty with spatial skills (e.g., #28: “How often do you have difficulty finding your way about?”).
Table 9

Factor Loadings for PAOF Items (n=156)

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<tr>
<th>PAOF Item</th>
<th>Factor 1 (PS)</th>
<th>Factor 2 (Retention)</th>
<th>Factor 3 (WM)</th>
<th>Factor 4 (Lexical)</th>
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<td>(WM)</td>
<td>(Lex.)</td>
<td>(SP)</td>
<td>(Spatial)</td>
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<td>.07</td>
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%Exp. Var. 15.77 12.42 10.39 9.42 8.98 8.44

**Note.** Factor loadings equal to or greater than .40 are displayed in bold type. PAOF=Patient’s Assessment of Own Functioning Inventory; PS=Problem-Solving; WM=Working Memory; SP=Sensory-Perceptual; % Exp. Var.=Percentage of Explained Variance

**CFQ.**

Factor loadings for the CFQ are displayed in Table 10. Six factors were extracted with eigenvalues greater than 1.0. The six factors accounted for 68% of the total variance. The first factor was interpreted to reflect working memory complaints (e.g., #2: “Do you find you forget why you went from one part of the house to the other?”; #23 “Do you find you forget what you came to the shops to buy?”). The second factor appeared to relate to focused attention (e.g., #7: “Do you fail to listen to people’s names when you are meeting them?”;
Table 10

Factor Loadings for CFQ Items (n=88)

<table>
<thead>
<tr>
<th>CFQ Item</th>
<th>Factor 1 (WM)</th>
<th>Factor 2 (Attention)</th>
<th>Factor 3 (Spatial)</th>
<th>Factor 4 (Initiation)</th>
<th>Factor 5 (Monitoring)</th>
<th>Factor 6 (Item 3)</th>
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<tr>
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<td>.79</td>
<td>.10</td>
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<tr>
<td>6.</td>
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<td>.53</td>
<td>.10</td>
<td>.19</td>
<td>.00</td>
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<td>.03</td>
<td>.15</td>
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<td>8.</td>
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<tr>
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<td>.19</td>
<td>.19</td>
<td>.68</td>
<td>.00</td>
<td>-.11</td>
</tr>
<tr>
<td>12.</td>
<td>.16</td>
<td>.18</td>
<td>.55</td>
<td>.35</td>
<td>.03</td>
<td>.25</td>
</tr>
<tr>
<td>13.</td>
<td>.60</td>
<td>.31</td>
<td>.31</td>
<td>.23</td>
<td>-.09</td>
<td>.16</td>
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<td>.49</td>
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<td>.17</td>
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<td>.05</td>
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<td>-.03</td>
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<td>.41</td>
</tr>
<tr>
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<td>.69</td>
<td>.09</td>
<td>.18</td>
<td>.27</td>
<td>-.00</td>
<td>.18</td>
</tr>
<tr>
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<td>.22</td>
<td>.21</td>
<td>.10</td>
<td>.80</td>
<td>.16</td>
<td>.05</td>
</tr>
<tr>
<td>20.</td>
<td>.31</td>
<td>.69</td>
<td>.03</td>
<td>.25</td>
<td>-.04</td>
<td>.13</td>
</tr>
<tr>
<td>21.</td>
<td>.66</td>
<td>.35</td>
<td>.06</td>
<td>.24</td>
<td>.12</td>
<td>-.00</td>
</tr>
<tr>
<td>22.</td>
<td>.62</td>
<td>.47</td>
<td>.17</td>
<td>.33</td>
<td>-.00</td>
<td>.09</td>
</tr>
<tr>
<td>CFQ Item</td>
<td>Factor 1 (WM)</td>
<td>Factor 2 (Attention)</td>
<td>Factor 3 (Spatial)</td>
<td>Factor 4 (Initiation)</td>
<td>Factor 5 (Monitoring)</td>
<td>Factor 6 (Item 3)</td>
</tr>
<tr>
<td>----------</td>
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<td>----------------------</td>
<td>------------------</td>
</tr>
<tr>
<td>23.</td>
<td><strong>.75</strong></td>
<td>.18</td>
<td>.20</td>
<td>.25</td>
<td>-.08</td>
<td>.07</td>
</tr>
<tr>
<td>24.</td>
<td><strong>.47</strong></td>
<td>.12</td>
<td><strong>.53</strong></td>
<td>.28</td>
<td>.20</td>
<td>-.28</td>
</tr>
<tr>
<td>25.</td>
<td>.17</td>
<td><strong>.66</strong></td>
<td><strong>.45</strong></td>
<td>.15</td>
<td>-.19</td>
<td>-.03</td>
</tr>
<tr>
<td>%Exp. Var.</td>
<td><strong>20.20</strong></td>
<td>12.11</td>
<td>11.84</td>
<td>10.78</td>
<td>6.87</td>
<td>6.00</td>
</tr>
</tbody>
</table>

Note. Factor loadings equal to or greater than .40 are displayed in bold type. CFQ = Cognitive Failures Questionnaire; WM = Working Memory; % Exp. Var. = Percentage of Explained Variance

#15: “Do you have trouble making up your mind?”). The third factor related to spatial problems (e.g., #5: “Do you bump into people?”; #4: “Do you find you confuse right and left when giving directions?”). The fourth factor was interpreted to reflect failure to follow through or problems with initiation (e.g., #19: “Do you daydream when you ought to be listening to something?”; #11: “Do you leave important letters unanswered for days?”). The fifth factor was interpreted as indicative of problems with self-monitoring in social situations (e.g., #10: “Do you lose your temper and regret it?”; “Do you say something and realize afterwards that it might be taken as insulting”?). Finally, the sixth factor had a high loading for only one item (i.e., #3: “Do you fail to notice signposts on the road?”).

**Logistic Regressions**

Logistic regression analyses were used to examine the utility of individual PAOF and CFQ items in predicting neuropsychological skills.
PAOF.

PAOF items with the highest factor loadings from each of the six constructs were entered into a series of logistic regression analyses as predictors of neuropsychological skills. The results of the factor analysis were compared to the factor analysis results reported during the development of the PAOF (Chelune, 1986). When discrepancies existed, both the highest loading PAOF items from the present factor analysis and Chelune’s (1986) were used as independent variables in the logistic regression analyses.

Selected PAOF Items from PCA Factor Analyses
5, 9, 18, 22, 28, 31

Selected PAOF Items from Chelune (1986)
2, 10, 15

Because the SEM model indicated that scores on measures of mood and systemic symptoms of HIV did not significantly influence the relationship between cognitive complaints and neuropsychological skills, these variables were not used as covariates in the logistic regressions.

The dependent variables in the logistic regressions were neuropsychological clinical ratings for each of the neuropsychological domains, including global neuropsychological functioning. The clinical ratings were dichotomized into two groups characterized as neuropsychologically impaired (ratings of 5 or more) or unimpaired (ratings of 4 or less). Significant results of the logistic regression analyses for the PAOF items are presented in Table 11.

Global neuropsychological impairment was significantly predicted by the overall logistic regression equation ($\chi^2=19.29, p<.05$). PAOF items 2 (“How often do you forget
Table 11

**PAOF Item Prediction of Neuropsychological Clinical Ratings**

<table>
<thead>
<tr>
<th>PAOF Item</th>
<th>Neuropsychological Clinical Rating Domain</th>
<th></th>
<th></th>
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<tr>
<td></td>
<td>Global</td>
<td>Psychomotor and Motor Skills</td>
<td>Conceptual Skills</td>
</tr>
<tr>
<td>2.*</td>
<td>B = 0.38</td>
<td>B = 0.32</td>
<td>B = 0.26</td>
</tr>
<tr>
<td></td>
<td>(p = 0.02)</td>
<td>(p = 0.06)</td>
<td>(ns)</td>
</tr>
<tr>
<td>5.</td>
<td>B = -0.05</td>
<td>B = 0.02</td>
<td>B = -0.11</td>
</tr>
<tr>
<td></td>
<td>(ns)</td>
<td>(ns)</td>
<td>(ns)</td>
</tr>
<tr>
<td>9.</td>
<td>B = 0.11</td>
<td>B = 0.23</td>
<td>B = 0.32</td>
</tr>
<tr>
<td></td>
<td>(ns)</td>
<td>(ns)</td>
<td>(ns)</td>
</tr>
<tr>
<td>10.*</td>
<td>B = -0.20</td>
<td>B = -0.03</td>
<td>B = -0.70</td>
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<tr>
<td></td>
<td>(ns)</td>
<td>(ns)</td>
<td>(p = 0.01)</td>
</tr>
<tr>
<td>15.*</td>
<td>B = 0.05</td>
<td>B = -0.06</td>
<td>B = 0.39</td>
</tr>
<tr>
<td></td>
<td>(ns)</td>
<td>(ns)</td>
<td>(p = 0.06)</td>
</tr>
<tr>
<td>18.</td>
<td>B = 0.19</td>
<td>B = 0.35</td>
<td>B = 0.49</td>
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<tr>
<td></td>
<td>(ns)</td>
<td>(p = 0.03)</td>
<td>(p = 0.01)</td>
</tr>
<tr>
<td>22.</td>
<td>B = -0.42</td>
<td>B = -0.42</td>
<td>B = 0.06</td>
</tr>
<tr>
<td></td>
<td>(ns)</td>
<td>(ns)</td>
<td>(ns)</td>
</tr>
<tr>
<td>28.</td>
<td>B = 0.50</td>
<td>B = 0.55</td>
<td>B = 0.09</td>
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<tr>
<td></td>
<td>(p = 0.02)</td>
<td>(p = 0.02)</td>
<td>(ns)</td>
</tr>
<tr>
<td>31.</td>
<td>B = -0.11</td>
<td>B = -0.22</td>
<td>B = -0.22</td>
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<tr>
<td></td>
<td>(ns)</td>
<td>(ns)</td>
<td>(ns)</td>
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</table>

*Note.* Marked items (*) were selected from highest loading PAOF items on the factors described by Chelune et al. (1986). PAOF=Patient’s Assessment of Own Functioning Inventory.
events which have occurred in the last day or two?”) and 28 (“How often do you have difficulty finding your way about?”) were significant predictors. Psychomotor and motor skills were also significantly predicted by PAOF items ($\chi^2=28.73, p < .01$), specifically items 18 (“When you write things, how often do you have difficulty forming the letters correctly?”) and 28, with a trend for item 2. PAOF items also significantly predicted ratings of conceptual skills ($\chi^2=21.04, p < .05$). Specifically, conceptual skill ratings were predicted by PAOF items 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.?”), 18, and a trend for item 15 (“When you speak, are your words indistinct or improperly pronounced?”).

The selected individual PAOF items representative of the six constructs were not significantly predictive of clinical ratings in the remaining neuropsychological domains (i.e., verbal skills, attention, learning, and memory). In summary, out of six different subjective complaint factors extracted from the PAOF, only items from two factors predicted global neuropsychological impairment. Furthermore, PAOF complaints predicted only impaired psychomotor skills and impaired conceptual skills out of six specific neuropsychological domains.

Contrary to expectations, the cognitive complaint representing the spatial factor on the PAOF was predictive of both global neuropsychological impairment and impaired psychomotor and motor skills. The cognitive complaint representing the lexical factor on the PAOF was also predictive of impaired psychomotor and motor skills, as well as impaired conceptual skills. These findings were unexpected and contradicted the hypotheses that spatial complaints and language complaints would not be related to neuropsychological
impairment.

Although complaints representing the memory (retention) and working memory PAOF factors for the present sample did not predict neuropsychological impairment, complaints on these factors from Chelune et al. (1986)’s study were significantly related to neuropsychological impairment. The PAOF item with the highest loading on the memory (retention) factor from Chelune et al. (1986)’s study significantly predicted global neuropsychological impairment. The PAOF item with the highest loading on the working memory factor from Chelune et al. (1986)’s study significantly predicted impaired conceptual skills. These findings only partially supported the hypotheses that working memory complaints, but not memory (i.e., retention) complaints, would be significantly predictive of neuropsychological impairment.

Contrary to the stated hypothesis, complaints of problems with psychomotor and sensory-perceptual functioning did not predict neuropsychological impairment either overall or for any of the six cognitive domains. However, in agreement with predictions, complaints of problems with conceptual skills or executive functioning were not significantly related to neuropsychological impairment, either globally or across individual cognitive domains.

CFQ.

CFQ items with the highest factor loadings on each of the six factors were used as independent variables in logistic regression analyses with dichotomized clinical ratings for each neuropsychological domain (i.e., impaired versus unimpaired) as the dependent variable. CFQ items representative of six different factors demonstrated no significant
relationships with neuropsychological impairment either globally or across six neuropsychological domains (i.e., verbal, attention, learning, memory, psychomotor and motor, and conceptual skills). Although the complaint representing the PAOF spatial factor predicted global neuropsychological impairment, the spatial complaint from the CFQ did not predict impairment.

**Part Three: The Contribution of Cognitive Complaints to A Screening Protocol for Neuropsychological Impairment**

The third set of analyses addressed all the hypotheses predicting relationships between cognitive complaints and neuropsychological test performance, which predicted significant relationships for complaints of problems with psychomotor and sensory-perceptual functioning and attention/working memory. The SPSS module Answer Tree, version 2.0.1 was used to develop a decision tree to assess the utility of cognitive complaints, mood, physical symptoms, and neuropsychological test performance in classifying individuals with global neuropsychological impairment.

Two decision trees were generated with different values specified for prior probability of global neuropsychological impairment. Based on the literature to date (Heaton et al., 1995; White et al., 1995), prior probabilities were set at 40% as a conservative estimate of the rate of global neuropsychological impairment in HIV-infected individuals. A second tree was generated with a prior probability of global impairment set at a more liberal estimate of 50%. In addition to comparing the predictive value of decision trees with differing expected probabilities of impairment, the two trees were compared to determine the stability of
significant predictors of neuropsychological impairment. Furthermore, cases where a neuropsychologically impaired individual was misclassified as intact were assigned twice the cost of other misclassified cases (i.e., misclassifying a neuropsychologically intact individual as impaired) in the analyses because a greater cost is associated with these cases.

V-fold cross-validation was used with 10-fold specified. The "1 standard error rule" was used to select the final tree. This rule recommends selecting the least complex tree with similar cross-validation values to the tree with best cross-validation (Breiman et al., 1984; Statsoft, 2000).

The dependent variable was global neuropsychological clinical ratings, dichotomized as "impaired" (scores 5-9) or "unimpaired" (scores 1-4). Predictors included BDI scores (total, cognitive/affective symptoms, and somatic symptoms) as a measure of mood and scores on the 12-item physical symptom inventory as a measure of HIV-related systemic illness. Neuropsychological measures selected as predictors included TMT Parts A and B, SDMT, WAIS-R Digit Symbol and Digit Span subtests, and verbal fluency (FAS, Category Fluency). The demographic variables of age and education, as well as medical variables of low CD4 count and CDC stage were also included in the analysis as predictors. Total PAOF scores and scores for each of the four neuropsychological domains (i.e., memory, language and communication, motor/sensory-perceptual, and higher level cognitive and intellectual functions) were also included as predictors in the analysis. Individual PAOF items with the highest factor loadings, as well as those additional items that demonstrated significant relationships with neuropsychological clinical ratings in the logistic regression analyses were also included as predictors. Because previous analyses showed little relationship between the
CFQ and neuropsychological clinical ratings, most CFQ items were not included in the decision tree analysis. Only item 9 of the CFQ was included as a predictor because of its significant correlation with global neuropsychological impairment ratings.

The first decision tree (Tree 1) with a prior probability of neuropsychological impairment set at 40% is displayed in Figure 3. Examination of potential surrogates indicated that it was unlikely that significant variables had been masked. The two-level tree had four endpoints or “terminal nodes”. The first split was on the SDMT (Improvement = 0.1588), with 77% of individuals with scores less than or equal to 47 classified as globally neuropsychologically impaired. Additional improvement was achieved by the second split on the SDMT (Improvement = 0.0136), which classified 87% of individuals with scores less than or equal to 44 as globally impaired. The right branch of the tree further classified a few individuals as impaired if their scaled score on the WAIS-R Digit Span subtest was less than or equal to 6 (Improvement = 0.0304). The tree included only neuropsychological measures, and failed to find significant classification value for measures of mood, physical symptoms, demographics, and medical status. Contrary to expectations, cognitive complaints did not contribute significantly to the prediction of neuropsychological impairment.

The associated classification matrix, resubstitution value and cross-validation value are presented in Table 12. The classification tree accurately classified 82% of individuals as neuropsychologically impaired or unimpaired. Sensitivity and specificity of the tree were 82%. The cross-validation value reached only 69%.

The second decision tree (Tree 2) with a set prior probability of 50% global neuropsychological impairment is displayed in Figure 4, and Table 13 presents the associated
classification matrix. Classification accuracy of the tree did not differ substantially from the first tree. Sensitivity of Tree 2 was higher than Tree 1 (93%), but Tree 1 showed significantly greater specificity than Tree 2 (60%). Therefore, the best balance between specificity and sensitivity was achieved by the decision tree with a prior probability of 40% rather than 50%, suggesting that the former (Tree 1) is a more desirable alternative for clinical use in this sample.

Tree 2 was the same size as Tree 1 with the same first split on the SDMT (Improvement = 0.1321), with 77% of individuals with scores less than or equal to 47 classified as globally neuropsychologically impaired. Smaller contributions to the decision tree varied depending on the set value of prior probability of neuropsychological impairment. With a 40% probability of impairment, performance on a measure of basic attention (WAIS-R Digit Span subtest) made a small contribution to predicting global neuropsychological impairment. With a 50% probability of impairment, however, performance on a verbal fluency measure (FAS) contributed to predicting global neuropsychological impairment. With respect to cognitive complaints, the most interesting difference in these decision trees was that one memory complaint from the PAOF (Item #2: “How often do you forget events which have occurred in the last day or two?”) made a small but significant contribution to classifying neuropsychological impairment when a higher probability of impairment was assumed.

In order to examine the predictive utility of cognitive complaints in the absence of neuropsychological test data, decision trees were also generated with neuropsychological measures removed as predictors. For reasons outlined above, two decision trees were
examined specifying either a conservative (i.e., 40%) or a more liberal (i.e., 50%) prior probability of global neuropsychological impairment.

The two decision trees (Trees 3 and 4) are presented in Figures 5 and 6, and associated classification matrices are listed in Tables 14 and 15, respectively. Both trees were quite similar, with three levels and four terminal nodes. The first split on both trees was the total PAOF score (Improvement = 0.0598 and 0.0462, respectively), with 77% of individuals with scores greater than 70 classified as globally impaired. Subsequent smaller splits were on the same variables for each tree, but the order of the splits differed. For Tree 3, the second split (Improvement = 0.0224) was on Item 2 of the PAOF, which classified 40% of individuals endorsing this item as globally impaired. For Tree 4, the second split classified a few more individuals as unimpaired (Improvement = 0.0228) with a PAOF total score between 65 and 70. The second and third splits were reversed in order for Trees 3 and 4. In agreement with Trees 1 and 2, measures of mood, physical symptoms, demographics, and medical status were not significant predictors of global neuropsychological impairment.

The classification accuracy and cross-validation values for Trees 3 and 4 were lower than for the decision trees including neuropsychological measures as predictors (Trees 1 and 2). Although sensitivity of Trees 3 and 4 was excellent (91%), specificity was quite poor (44%) compared to Tree 1. Classification matrices for Trees 3 and 4 indicated that the same number of cases were accurately classified into categories of neuropsychological impairment. However, Tree 4 resulted in slightly better classification accuracy (75% versus 71%) and cross-validation (60% versus 52%) values.
Figure 3. Tree 1: Classification tree with 40% prior probability of global neuropsychological impairment.
Figure 4. Tree 2: Classification tree with 50% prior probability of global neuropsychological impairment
Figure 5. Tree 3: Classification tree with 40% prior probability of global neuropsychological impairment and without neuropsychological measures as predictors
Figure 6. Tree 4: Classification tree with 50% prior probability of global neuropsychological impairment and without neuropsychological measures as predictors.
Table 12

**Classification Matrix for Tree 1: Includes Neuropsychological Measures and 40% Prior Probability of Impairment**

<table>
<thead>
<tr>
<th>Predicted Category</th>
<th>Actual Category</th>
<th></th>
<th></th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Unimpaired</td>
<td>Impaired</td>
<td>Total</td>
</tr>
<tr>
<td>Unimpaired</td>
<td>73 (47%)</td>
<td>12 (8%)</td>
<td>85</td>
</tr>
<tr>
<td>Impaired</td>
<td>16 (10%)</td>
<td>55 (35%)</td>
<td>71</td>
</tr>
<tr>
<td>Total</td>
<td>89</td>
<td>67</td>
<td>156</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Resubstitution</th>
<th>Cross-Validation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk Estimate</td>
<td>0.18</td>
<td>0.31</td>
</tr>
<tr>
<td>Standard Error of Risk Estimate</td>
<td>0.03</td>
<td>0.04</td>
</tr>
</tbody>
</table>

Table 13

**Classification Matrix for Tree 2: Includes Neuropsychological Measures and 50% Prior Probability of Impairment**

<table>
<thead>
<tr>
<th>Predicted Category</th>
<th>Actual Category</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Unimpaired</td>
<td>Impaired</td>
<td>Total</td>
</tr>
<tr>
<td>Unimpaired</td>
<td>53 (34%)</td>
<td>5 (3%)</td>
<td>58</td>
</tr>
<tr>
<td>Impaired</td>
<td>36 (23%)</td>
<td>62 (40%)</td>
<td>98</td>
</tr>
<tr>
<td>Total</td>
<td>89</td>
<td>67</td>
<td>156</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th></th>
<th>Resubstitution</th>
<th>Cross-Validation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk Estimate</td>
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<td>0.31</td>
</tr>
<tr>
<td>Standard Error of Risk Estimate</td>
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<td>0.04</td>
</tr>
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</table>
Table 14

**Classification Matrix for Tree 3: Without Neuropsychological Measures and 40% Prior Probability of Impairment**

<table>
<thead>
<tr>
<th>Predicted Category</th>
<th>Actual Category</th>
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<th>Impaired</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unimpaired</td>
<td>Unimpaired</td>
<td>39 (25%)</td>
<td>6 (4%)</td>
<td>45</td>
</tr>
<tr>
<td></td>
<td>Impaired</td>
<td>50 (32%)</td>
<td>61 (39%)</td>
<td>111</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>89</td>
<td>67</td>
<td>156</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>Risk Estimate</td>
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<td>0.48</td>
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<tr>
<td>Standard Error of Risk Estimate</td>
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<td>0.04</td>
</tr>
</tbody>
</table>

Table 15

**Classification Matrix for Tree 4: Without Neuropsychological Measures and 50% Prior Probability of Impairment**

<table>
<thead>
<tr>
<th>Predicted Category</th>
<th>Actual Category</th>
<th>Unimpaired</th>
<th>Impaired</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unimpaired</td>
<td>Unimpaired</td>
<td>39 (25%)</td>
<td>6 (4%)</td>
<td>45</td>
</tr>
<tr>
<td></td>
<td>Impaired</td>
<td>50 (32%)</td>
<td>61 (39%)</td>
<td>111</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>89</td>
<td>67</td>
<td>156</td>
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<table>
<thead>
<tr>
<th></th>
<th>Resubstitution</th>
<th>Cross-Validation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk Estimate</td>
<td>0.25</td>
<td>0.40</td>
</tr>
<tr>
<td>Standard Error of Risk Estimate</td>
<td>0.03</td>
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Chapter IV
Discussion

The main objective of this set of studies was to clarify the nature of the relationship between subjective cognitive complaints and actual neuropsychological skills in HIV-infected individuals. This relationship was investigated in three different ways: 1) a structural equation model (SEM) was developed outlining the relationships among cognitive complaints, neuropsychological skills, mood and systemic medical illness in HIV infection, 2) the utility of specific cognitive complaints in predicting HIV-associated neuropsychological impairment was evaluated, and 3) a decision tree was generated to identify HIV-positive individuals at risk for neuropsychological impairment using subjective cognitive complaints and screening measures of neuropsychological functioning.

This investigation is an in-depth study that examined the relationship between cognitive complaints and neuropsychological skills in HIV infection, using sophisticated statistical methodology to extend and refine the understanding of this relationship. As such, this study provides a unique contribution to knowledge of how subjective cognitive complaints relate to objective neuropsychological performance. Overall, this investigation suggests that increased cognitive complaints are associated with poorer neuropsychological performance in HIV infection, independently of the influence of depressed mood or systemic medical illness on cognitive complaints. In the absence of neuropsychological test results, increased cognitive complaints overall appear to indicate an increased likelihood of neuropsychological impairment. Furthermore, cognitive complaints are most strongly associated with impairment in specific neuropsychological domains, including psychomotor
and motor skills. Complaints of spatial and lexical problems may represent unusual, potentially "pathognomonic" symptoms in HIV infection that predict neuropsychological impairment. Complaints of frequently forgetting events may also suggest a greater likelihood of neuropsychological impairment.

On the other hand, although these results demonstrated a moderate-sized relationship between cognitive complaints and neuropsychological performance in HIV infection, cognitive complaints accounted for only a small proportion of the variance in neuropsychological skills. In addition, performance on measures of psychomotor speed was a superior predictor of global neuropsychological impairment than subjective cognitive complaints. Moreover, few specific types of cognitive complaints predicted neuropsychological impairment in specific areas of functioning. Rather, the relationship between cognitive complaints and global neuropsychological impairment may be more evident in considering the total number of complaints or symptoms endorsed.

This investigation also highlighted the importance of reduced psychomotor skills in HIV infection, particularly their utility in predicting global neuropsychological impairment. Cognitive complaints were most strongly and consistently associated with psychomotor skills in the present sample. These findings concur with previous research that has demonstrated a strong relationship between psychomotor skills and cognitive complaints in HIV infection (Mapou et al., 1993; Poutiainen & Elovaara, 1996; Rourke et al., 1999a; Wilkins et al., 1991). However, it is important to note that the neuropsychological measures used to assess psychomotor skills in this study (e.g., TMT, SDMT, Digit Symbol) likely tap additional cognitive skills, such as attention, working memory, and speed of information processing.
Consequently, the relationship between cognitive complaints and psychomotor speed reported in this study may also reflect the contributions of these other cognitive skills.

**The Overall Relationship Between Cognitive Complaints and Neuropsychological Skills**

The first goal of this investigation was to determine whether in fact a relationship existed between cognitive complaints and neuropsychological skills when potential confounding factors were taken into account. This is the first study to examine the interrelationships among cognitive complaints, neuropsychological skills in various domains, mood, and systemic medical symptoms in a comprehensive way.

**Implications of the Structural Equation Model**

Relative to previous studies, the use of SEM to build a model allowed a more flexible and powerful method of simultaneously examining the relationship among cognitive complaints and neuropsychological skills, while accounting for possible effects of mood and systemic illness. Another advantage of this statistical approach was that unlike other studies of cognitive complaints, the SEM model accounted for measurement error in the instruments used to assess both cognitive complaints and neuropsychological skills. Consequently, SEM enabled this study to outline the relationships among these variables more precisely than in previous investigations. SEM permitted an advance in knowledge of the complicated interrelationships among factors impinging on cognitive complaints. As such, this statistical approach may also benefit future studies of cognitive complaints, particularly those investigating the influence of additional variables that were not examined in this study.
The principal finding from the model was that cognitive complaints predicted neuropsychological skills in HIV infection, independently of the effects of depressed mood and physical symptoms on cognitive complaints. Although mood and physical symptoms contributed to cognitive complaints, the model illustrated a relationship between cognitive complaints and neuropsychological skills that was not solely due to the effects of mood and physical symptoms. The finding that cognitive complaints are independently related to neuropsychological performance in HIV infection is consistent with several previous investigations (Beason-Hazen et al., 1994; Mapou et al., 1993; Poutiainen & Elovaara, 1996; Rourke et al., 1999a; Stern et al., 1991), as well as studies of memory complaints in the elderly (Jonker, Geerlings, & Schmand, 2000; Jonker et al., 1996; Schofield et al., 1997; Sunderland et al., 1983; Zelinski et al., 1990) and in other populations, such as individuals with rheumatoid arthritis (Hertzog, Park, Morrell, & Martin, 2000). The results of the model supported the predictions that cognitive complaints would be significantly related to neuropsychological test performance, self-reported symptoms of depression, and systemic medical symptoms.

Contrary to expectations, the influence of depressed mood and systemic illness on cognitive complaints yielded only a small indirect effect on neuropsychological performance. In other words, although depression and systemic medical illness contributed to increased cognitive complaints, they did not account for the relationship between increased cognitive complaints and poorer performance on neuropsychological measures. Clinically, these findings suggest that cognitive complaints in individuals who are depressed and/or report systemic medical symptoms may still reflect neuropsychological impairment. These findings
are consistent with other studies demonstrating that increased cognitive complaints in HIV infection are associated with increased symptoms of depression and systemic illness (Claypoole et al., 1998; Lopez et al., 1998; L. H. Moore et al., 1997; Van Gorp et al., 1991; Wilkins et al., 1991), and similar findings in the elderly (Bassett & Folstein, 1993; Derouesne et al., 1989; Grut et al., 1993; Hultsch et al., 1993; Jorm et al., 1994; Levy-Cushman & Abeles, 1998; O'Connor et al., 1990; Schofield et al., 1997). These results, however, suggest that cognitive complaints also accurately reflect neuropsychological dysfunction.

The methodology used in this study to examine the interrelationships among pertinent variables served to clarify discrepancies in the literature. Previous studies have typically related cognitive complaints in HIV infection to either neuropsychological impairment or depression. The present study illustrates that the relationship of depressive symptoms and cognitive complaints is largely separable from that of neuropsychological skills and cognitive complaints. The structural equation model suggests that cognitive complaints may be related to either 1) neuropsychological impairment, 2) depressed mood, or 3) systemic medical illness. Consequently, the seemingly contradictory conclusions of previous investigations relating cognitive complaints to either neuropsychological impairment or depression may both be accurate. These findings suggest that any of one of these three factors may lead to increased cognitive complaints in HIV infection. It is also likely that different combinations of these variables (e.g., in individuals who are both depressed and neuropsychologically impaired) are reflected in the number and type of reported cognitive complaints. It remains to be seen whether the combined effect of these variables on cognitive complaints is directly
additive or varies in systematic patterns for clinically distinguishable groups of patients.

The hypothesis that mood would indirectly affect the relationship between cognitive complaints and neuropsychological performance was based on studies suggesting that cognitive complaints were more strongly related to depressive symptoms than neuropsychological performance (D. Moore et al., 2001; Rourke et al., 1999a). The results indicated that depression plays an important role in contributing to cognitive complaints, but neuropsychological skills also demonstrated a moderate-sized relationship with cognitive complaints. Furthermore, in agreement with the literature, depressed mood was not useful in predicting neuropsychological performance. Most previous studies have shown little relationship between depression and neuropsychological impairment in HIV infection (Bornstein, Pace et al., 1993; Goggin et al., 1997; Kalechstein et al., 1998), although depression may affect neuropsychological performance in other populations (Lezak, 1995). The present study used a more sophisticated statistical approach to confirm the insignificant relationship between depression and neuropsychological functioning in HIV infection.

This study is one of few investigations to examine the impact of systemic medical symptoms on cognitive complaints in HIV infection. In accordance with previous findings (Lopez et al., 1998), the results indicated that increased physical symptoms, in addition to depression, can contribute to increased cognitive complaints. Systemic symptoms do not appear to adversely influence neuropsychological performance, even though HIV-positive individuals often report physical symptoms, such as fatigue, during neuropsychological evaluation. This finding is relevant because it demonstrates the validity of neuropsychological assessment results for individuals with HIV infection, despite the
presence of physical symptoms that, on the surface, might appear to adversely affect test performance. Furthermore, this finding is consistent with the large-scale HNRC study, which reported minimal association between HIV-related symptoms and neuropsychological performance, particularly for asymptomatic individuals (Heaton et al., 1995). However, these preliminary findings do not contradict the possible adverse effect of fatigue and other systemic medical symptoms on cognitive functioning in everyday activities not assessed during a neuropsychological evaluation.

**Implications from the Decision Tree**

This is also the first study to examine the contribution of subjective cognitive complaints to a decision tree used to classify HIV-positive individuals as neuropsychologically impaired or unimpaired. The results suggest that total cognitive complaints predict global neuropsychological impairment when neuropsychological test scores are not available. These results confirm the findings from the SEM model indicating that cognitive complaints are significantly related to neuropsychological impairment. However, cognitive complaints did not predict neuropsychological impairment as well as performance on standardized neuropsychological measures, especially measures of psychomotor speed. Clinically, these findings suggest that cognitive complaints voiced by HIV-infected individuals may signal neuropsychological dysfunction, although psychomotor speed performance is a better predictor of global neuropsychological impairment.

The decision tree methodology was a novel means of investigating the predictive value of cognitive complaints and proved to be an excellent approach to identifying the best
predictor of neuropsychological impairment in the present sample. The value of the decision tree methodology recommends its utility in future studies of cognitive complaints. For example, decision trees may be used to determine the worth of cognitive complaints in predicting 1) neuropsychological impairment in specific domains, 2) membership in clinically derived subgroups of HIV-positive individuals (e.g., depressed and neuropsychologically impaired; minimizers), and 3) impairment in other neuropsychological populations where the clinical significance of cognitive complaints has been controversial (e.g., dementia).

The Value of Specific Cognitive Complaints in Predicting Neuropsychological Skills

The second main question addressed by this study was whether specific types of cognitive complaints predicted neuropsychological impairment. Furthermore, the study attempted to determine whether cognitive complaints predicted impairment in specific neuropsychological domains. Knowledge of the predictive utility of specific cognitive complaints would have great clinical value. Any relationship between cognitive complaints and neuropsychological skills may have been masked in previous studies by examining only total complaints instead of specific cognitive complaints. Few other studies have investigated specific types of cognitive complaints in HIV infection. The present study provides one of the most detailed examinations to date of relationships among specific types of cognitive complaints and neuropsychological performance in different cognitive domains.

Hypotheses predicting the relationships between specific types of cognitive complaints and neuropsychological performance were not well supported. In general,
specific cognitive complaints did not demonstrate strong relationships with neuropsychological impairment. Few specific cognitive complaints from two different measures of subjective cognitive functioning (i.e., Patient’s Assessment of Own Functioning Inventory (PAOF) and Cognitive Failures Questionnaire (CFQ)) predicted neuropsychological impairment, either globally or for individual neuropsychological domains. In fact, specific cognitive complaints were more highly correlated with symptoms of depression and systemic illness than neuropsychological impairment.

**Factor Analyses of Cognitive Complaint Questionnaires**

Cognitive complaints loaded onto six factors for each of the two measures of subjective symptoms (i.e., PAOF and CFQ). Items on the PAOF loaded onto factors representing complaints of difficulty with problem-solving, memory (retention), working memory, lexical skills, sensory-perceptual functioning, and spatial skills. These results corresponded with factors extracted in the original psychometric studies of the PAOF (Chelune et al., 1986), although there was an additional factor reflecting complaints of spatial problems in the present study. These findings indicate that PAOF items can be grouped together such that similar items likely reflect the same type of cognitive complaint. In general, the items under the PAOF domain headings corresponded to the empirically derived factors. However, an exception was that PAOF items under the heading of “memory” were separable into items reflecting problems with retention and those reflecting working memory problems.

In the case of the CFQ, factors were less well defined. Factors were interpreted to
reflect complaints of problems with working memory, attention, spatial skills, initiation, self-monitoring, and a single complaint of failure to notice signposts on the road. However, the CFQ items that loaded on each factor did not seem to group together as well as the factors extracted from the PAOF. These results are consistent with previous literature on the CFQ that reports variable and less well-defined factor structure, particularly as the number of factors increases (Larson et al., 1997a, 1997b; Matthews et al., 1990; Pollina et al., 1992).

Overall, these results suggest that cognitive complaints measured by the PAOF are more sensitive to neuropsychological impairment in HIV infection than those measured by the CFQ. Unlike the CFQ, PAOF scores were more strongly associated with impairment across neuropsychological domains and demonstrated a well-defined factor structure in the current sample. In addition, several specific PAOF complaints predicted global neuropsychological impairment and impairment in several neuropsychological domains. Furthermore, total PAOF score predicted global neuropsychological impairment in the absence of neuropsychological test results. The utility of the PAOF in predicting neuropsychological impairment relative to the CFQ may reflect its development from common cognitive complaints in populations with known or suspected neuropsychological impairment (Chelune et al., 1986). In contrast, the CFQ may not predict neuropsychological impairment as accurately in HIV infection because it was designed to assess everyday cognitive failures or slips in a normal population (Broadbent et al., 1982). Furthermore, CFQ items did not appear to tap as wide a range of traditional neuropsychological domains as the PAOF; this difference also may have contributed to the lesser utility of the CFQ in predicting HIV-associated neuropsychological impairment.
**Relationship of Cognitive Complaints to Specific Neuropsychological Domains**

Relative to other neuropsychological domains, specific cognitive complaints were most strongly and frequently associated with psychomotor skills in this study. Furthermore, cognitive complaints predicted impairment in only two neuropsychological domains: psychomotor/motor skills and conceptual skills. The strong relationship between cognitive complaints and performance on psychomotor measures is consistent with previous literature on neuropsychological impairment in HIV infection. Decreased psychomotor skills are a hallmark of HIV-associated cognitive impairment (Becker et al., 1997; Hinkin et al., 1998; N. C. Sacktor et al., 1996; Van Gorp et al., 1989). Consequently, it is not surprising that an area of neuropsychological functioning often affected in HIV infection is strongly related to subjective complaints.

Cognitive complaints were most strongly associated with clinical ratings of psychomotor and motor skills, as well as ratings of attention, regardless of the type of cognitive complaint reported. Furthermore, several cognitive complaints predicted impairment in psychomotor/motor skills and conceptual skills. It follows that cognitive complaints show the strongest relationship with these three neuropsychological domains because they are among those most likely to be affected by the fronto-striatal pathology associated with HIV infection (Grant et al., 1999; Heaton et al., 1995; Hinkin et al., 1998; Sahakian et al., 1995). These results are also consistent with those of Mapou et al. (1993), who found that cognitive complaints of various types were more likely to be associated with performance on measures of response speed and motor skills in HIV-infected individuals. However, Mapou et al. (1993) also reported that cognitive complaints were related to
performance on memory measures, a finding that was not replicated in the present study.

**Specific Cognitive Complaints that Predict Neuropsychological Impairment**

Although some specific complaints predicted HIV-associated neuropsychological impairment, these were restricted to a few items. Two types of cognitive symptoms that significantly predicted neuropsychological impairment were spatial and lexical complaints. Report of problems in these areas may represent pathognomonic indicators of neuropsychological impairment in HIV infection. This possibility is suggested because these complaints represent neuropsychological domains which are less likely to be affected in HIV infection (Becker et al., 1997; Heaton et al., 1995; Hinkin et al., 1998; Marsh & McCall, 1994), and yet they were still predictive of neuropsychological impairment. Clinically, individuals who endorse complaints of spatial and lexical problems may have a greater likelihood of neuropsychological impairment. Interestingly, however, although lexical complaints were more likely to reflect neuropsychological impairment in HIV-infected individuals, they did not predict impairment in the corresponding neuropsychological domain. Instead, spatial and lexical complaints are more likely to predict global neuropsychological impairment or impairment in areas more likely to be affected in HIV disease (i.e., psychomotor and conceptual skills). One possible explanation for this finding is that these items on the PAOF are simply more sensitive to HIV-associated neuropsychological impairment than other types of complaints, but in the case of lexical complaints, may not reflect impairment in the domains they appear to assess. Because the neuropsychological battery used in the present sample did not adequately assess spatial skills,
conclusions cannot be drawn from the present study about the relationship between spatial complaints and objective performance on measures of spatial skills. Similarly, future studies may demonstrate a stronger relationship between lexical complaints and measures of language that were not included in the present battery of tests.

Endorsement of specific memory complaints (i.e., forgetting events), including working memory complaints (i.e., forgetting things you are supposed to do), may also suggest neuropsychological impairment in HIV infection, although the clinical significance of these complaints is uncertain. Taken together, these findings suggest that spatial complaints, lexical complaints, and complaints of difficulty remembering events may indicate a greater likelihood of neuropsychological impairment in HIV-infected individuals. Because complaints of problems with sensory-perceptual functioning and problem-solving were generally not predictive of neuropsychological impairment, these types of complaints may not be as sensitive or may be more likely due to other causes, such as depressed mood or systemic medical illness.

It is also important to determine whether these complaints are clinically, as well as statistically, significant. Cognitive complaints that were statistically predictive of neuropsychological impairment may not be meaningful in a clinical context. Conversely, cognitive complaints that did not reach statistical significance in predicting neuropsychological impairment may still be clinically meaningful. In other words, these complaints may still be able to distinguish among clinical groups of individuals when combined with information from history, interview, or clinical presentation. Future studies should investigate these issues by prospectively examining the clinical utility of these
findings in other samples.

In the decision tree, with one exception, total number of complaints was a better predictor of global neuropsychological impairment than specific types of cognitive complaints. These results suggest that the relationship between cognitive complaints and global neuropsychological impairment may be more evident in the total number of symptoms reported rather than specific cognitive complaints. These findings were consistent with the results from regression equations, indicating relatively few significant relationships between neuropsychological impairment and specific types of cognitive complaints. Specific types of complaints may be better predictors of impairment in specific neuropsychological domains than global impairment in a decision tree. Lexical complaints, for example, were better predictors of impaired psychomotor/motor skills and impaired conceptual skills than global neuropsychological impairment in regression equations. The limited number of significant relationships between specific types of cognitive complaints and neuropsychological impairment also suggests that the total number of cognitive complaints is more strongly predictive of neuropsychological impairment than specific types of complaints.

The results of this study regarding specific cognitive complaints were not completely consistent with findings reported recently by Moore et al. (2001). Moore et al. (2001) found that clinical neuropsychological ratings of learning and conceptual skills predicted memory complaints and higher-order cognitive complaints in HIV-infected individuals. The present study confirmed a predictive relationship between cognitive complaints and impaired conceptual skills, although complaints of conceptual problems did not predict neuropsychological impairment. Unlike the results of Moore et al. (2001), cognitive
complaints did not predict impaired learning in the present study.

However, in Moore et al. (2001)’s study, neuropsychological performance was used to predict cognitive complaints, whereas the current study used cognitive complaints to predict neuropsychological impairment (i.e., the reverse). While Moore et al. (2001) were interested in whether neuropsychological impairment contributes to cognitive complaints, the research question of the present study was to determine whether cognitive complaints could be used to draw conclusions about neuropsychological impairment. Furthermore, the method of identifying specific types of cognitive complaints differed across studies. Moore et al. (2001) used subtotal scores for each domain of the PAOF, whereas the current study used empirically derived factors to determine highest-loading PAOF items representative of each neuropsychological domain. These methodological differences may in part explain discrepancies between the two studies. Other possible reasons for variability in findings across studies of cognitive complaints will be considered in the following section.

Additional Variables and Issues Affecting Cognitive Complaints

Previous studies across different types of populations have shown substantial variability in the accuracy of cognitive complaints when compared to neuropsychological performance, calling into question the reliability of cognitive complaints in predicting neuropsychological deficits. There are several possible explanations for the mixed findings in the predictive utility of cognitive complaints across studies. The relationship between cognitive complaints and neuropsychological impairment appears to be complex, and may be mediated by degree of insight into cognitive deficits, level of pre-morbid functioning, and
the extent of neuropsychological decline for an individual. A slight decline in neuropsychological skills may lead to significant cognitive complaints in higher-functioning individuals. Awareness of these deficits may be heightened by demanding work or social environments. Such a decline may not be accompanied by cognitive complaints in individuals with lower pre-morbid functioning. Cognitive complaints may also show stronger relationships with variables other than neuropsychological skills and depressed mood that have not yet been examined. Such variables may mediate the relationship between cognitive complaints and neuropsychological skills, thus contributing to discrepant findings across studies.

(a) Subtypes of Cognitive Complaint Respondents in HIV Infection.

Neuropsychological impairment in HIV infection has been characterized as subtle and highly variable (Heaton et al., 1995), although there are some commonalities in the affected areas of neuropsychological functioning. In fact, statistical comparisons of group means may mask neuropsychological impairment in HIV-infected individuals because of the subtle and “spotty” nature of impairment (Butters et al., 1990). A similar problem may occur in the study of cognitive complaints in HIV infection.

Although the present study explored the possibility of masking effects by examining specific individual, as well as total cognitive complaints, there may be groups of individuals who vary systematically in their report of cognitive complaints. Individuals with limited awareness, for example, would likely endorse fewer cognitive problems. Studies suggest that this may be the case for HIV-infected individuals who minimize memory complaints (Hinkin
et al., 1996; Rourke et al., 1999b). Subtypes of neuropsychological impairment have been described in HIV-infected individuals (Van Gorp, Hinkin et al., 1993) and such groups may endorse cognitive complaints in a different pattern. The SEM model suggested that cognitive complaints may reflect neuropsychological impairment, depressed mood, increased physical symptoms, or combinations of these features. Groups of individuals who fall into different categories on these variables may endorse cognitive complaints in systematic patterns. Cluster analysis or profile analysis of subjective cognitive complaints is one way to examine the possibility of respondent subtypes in future studies.

(b) Type and Course of Disease Process.

Similarly, it is possible that the relationship between cognitive complaints and neuropsychological skills varies across different types of diseases. In particular, cognitive complaints may show less predictive utility in diseases associated with diminished insight (e.g., Alzheimer’s dementia). Such differences may also correspond to particular types of pathological processes. For example, cognitive complaints may more accurately reflect neuropsychological impairment in subcortical processes without dorsolateral frontal involvement, because awareness is less likely to be compromised in such cases. The impact of factors that contribute to cognitive complaints, such as depressed mood and medical illness, may also differ according to the type or stage of disease. For example, because subcortical dementia is more likely to be associated with mood disturbances than cortical dementia (Cummings & Benson, 1992), cognitive complaints of individuals with this type of disorder may more often reflect depressed mood.
The accuracy of cognitive complaints may also vary depending on the course of the illness, although the number of cognitive complaints does not appear to increase with disease progression in HIV (Rourke et al., 1999a). For example, individuals at earlier stages may have greater insight into their cognitive problems, or their subjective report may be less influenced by worsening problems with attention or memory. In addition, there is evidence that the virus affects subcortical structures early in HIV infection and cortical involvement occurs in more advanced stages of the disease (Hinkin et al., 1995), which may differentially affect subjective cognitive complaints at different stages. These are all issues that require additional study.

(c) Personality.

Another variable that may influence cognitive complaints is personality. Individuals who endorse high neuroticism, psychological vulnerability, or other similar attributes on standard personality inventories (e.g., MMPI, NEO) may be more likely to report cognitive complaints. For example, individuals who exhibit “neurotic triad configurations” of the Hypochondriasis (Scale 1), Depression (Scale 2), and Hysteria (Scale 3) scales on the MMPI (Greene, 1991) may be more likely to endorse increased cognitive complaints. Similarly, individuals who are more open may be more likely to report cognitive complaints than individuals who are more private. Previous findings of a strong relationship between depressed mood and cognitive complaints strengthen the suggestion that psychological functioning influences cognitive complaints. Characterological personality traits (i.e., trait rather than state) may play a stronger role than expected in explaining the variance in
cognitive complaints.

(d) Coping Style.

Similarly, cognitive complaints may reflect an individual's coping process to a greater extent than their actual neuropsychological skills. Coping can be defined as "the cognitive and behavioral efforts to manage specific external and/or internal demands appraised as taxing or exceeding the resources of the individual" (Folkman & Lazarus, 1988). Neuropsychological deficits can certainly be viewed as a demand that requires significant resources to manage, and research has demonstrated that memory complaints influence coping behaviours (Verhaeghen, Geraerts, & Marcoen, 2000). Furthermore, personal beliefs regarding the adequacy of, and control over, neuropsychological functioning are often associated with changes in metacognition (Hertzog & Hultsch, 2000).

Individuals with less effective coping strategies may be more easily overwhelmed by neuropsychological deficits and more likely to report cognitive complaints than individuals with effective coping styles. Some types of coping strategies, such as avoidant behaviours or escapism, may result in fewer cognitive complaints even when neuropsychological deficits are present. Even relatively effective coping strategies, such as planful problem-solving (Folkman & Lazarus, 1988), may be counterproductive when the stressor is inherently unchangeable, as in longstanding neuropsychological deficits. At present, the possible impact of coping style on the subjective report of cognitive problems is unclear and future research in this area may assist in clarifying the clinical significance of cognitive complaints.
(e) Measurement Issues.

The reliability of cognitive complaints is directly related to the method used to assess them. The present results suggested that items on the CFQ were of little value in predicting neuropsychological impairment in this sample, while some items of the PAOF were useful. These findings suggest that the use of different instruments may affect whether cognitive complaints are found to be associated with neuropsychological impairment. Particularly with respect to memory, multiple measures of subjective complaints exist. Variation in the self-report questionnaires used to assess cognitive complaints may in part account for discrepant findings across studies.

Similarly, assessing cognitive complaints in interview format may lead to different conclusions about their relationship to neuropsychological impairment than when complaints are assessed by questionnaires (Beason-Hazen et al., 1994). Even within interviews, the type of question asked may influence the response given. When cognitive complaints are assessed via open-ended questions (e.g., “What kinds of problems have you noticed recently?”), individuals may be less likely to spontaneously report cognitive problems than when they are asked specific questions, such as whether they have noticed memory problems in specific situations. In some cases, individuals may be cued by examples given by the interviewer to recall instances in their own experience that are similar, thus causing them to endorse those types of cognitive problems.

Examiner behaviour, such as acceptance, non-verbal cues, and length of time given for responses may also influence responses. Examiner expectancies may be conveyed to patients in subtle cues as to whether they expect individuals to endorse particular types of
cognitive complaints according to the profile expected in specific diseases (Kazdin, 1992).

One reason for potential differences caused by different methods of assessing complaints is the influence of response biases. Individuals may be influenced by particular types of response sets, such as a “yes” bias to endorse most cognitive complaints, or conversely, a “no” bias to minimize cognitive complaints (i.e., “yay-sayers” and “nay-sayers”).

Another reason for possible differences across methods of assessing cognitive complaints is that questions regarding cognitive complaints may need to be more specific in order to demonstrate consistent relationships. A study by Hertzog et al. (2000) examining cognitive complaints in individuals with rheumatoid arthritis supported a behavioural specificity explanation of cognitive complaints. Their findings suggested that cognitive complaints best predict performance when they are assessed using questions regarding specific behaviours in a specific context. Results did not support a domain specificity hypothesis that cognitive complaints tapping a particular neuropsychological domain (e.g., memory) would predict neuropsychological performance within that domain. If the behavioural specificity explanation is accurate, situation-specific cognitive complaints may show stronger predictive relationships with neuropsychological performance. Interestingly, cognitive complaints were not as strongly related to ecologically valid measures (i.e., prospective memory task and medication adherence errors) as they were to neuropsychological tests. Further investigation using more specific situational measures of complaints may clarify their relationship to neuropsychological performance in HIV infection. Measurement issues are particularly important to address as changes in
methodology have recently been hypothesized to alter conclusions about the significance of memory complaints in the elderly (Jonker et al., 2000).

**Development of a Screen for Neuropsychological Impairment in HIV Infection**

The final objective of this study was to develop a decision-making model for use when screening HIV-positive individuals at risk for neuropsychological impairment. A decision tree was used to identify the best predictors of global neuropsychological impairment from cognitive complaints and brief neuropsychological tests suitable for use as screening measures. The results of this study indicated that performance on measures of psychomotor speed is the best predictor of overall neuropsychological impairment. This study recommends the Symbol Digit Modalities Test as a brief and excellent screening measure for HIV-associated neuropsychological impairment.

The Symbol Digit Modalities Test provided the most accurate classification of global neuropsychological impairment in HIV infection. Regardless of whether the prior probability of neuropsychological impairment was set at conservative or liberal values, decreased psychomotor speed was the best predictor in the decision tree. This finding is consistent with the results demonstrating that cognitive complaints were most strongly and consistently associated with clinical ratings of psychomotor performance. The results of the decision tree suggest that slowed psychomotor performance may underlie global neuropsychological impairment in HIV infection. In fact, previous studies have demonstrated that decreased psychomotor speed in HIV infection predicts performance in other neuropsychological domains (Becker et al., 1997) and is associated with a higher risk of dementia, AIDS, and
death (Sacktor et al., 1996). Taken together, these findings reinforce the clinical significance of reduced or impaired psychomotor skills in HIV infection.

Although the most predictive variable (i.e., SDMT) of global neuropsychological impairment did not change with different assumptions of base rates of impairment, other contributing variables may be affected depending on the rate of impairment for the sample in question. Specific neuropsychological measures that contributed to predicting overall neuropsychological impairment (i.e., WAIS-R Digit Span and FAS) varied when liberal or conservative a priori rates of impairment were specified. However, these variables improved classification by only a few cases. The best predictor of neuropsychological impairment did not change with different base rates specified, demonstrating its stability as an excellent predictor of global impairment.

Demographic variables, immunological variables, and performance on other brief neuropsychological measures did not contribute significantly to the classification of global neuropsychological impairment in the present sample. There was a restricted range of age and education level in the sample, which may partly explain the limited predictive value of these variables in classifying global neuropsychological impairment. Furthermore, an earlier study by Van Gorp et al. (1994) demonstrated that age is not associated with a greater risk of HIV-related neuropsychological impairment.

Immunological variables, particularly CD4 count, have been associated inconsistently with neuropsychological impairment in previous research (Basso & Bornstein, 2000; Becker et al., 1997; Bornstein et al., 1991; Ellis et al., 1997; Heaton et al., 1995; Van Gorp, Hinkin et al., 1993). Although the most recent CD4 counts for participants were used in this study,
these values were not all obtained at the time of neuropsychological evaluation. Consequently, neuropsychological impairment in this sample may not directly correspond to poorer immunological functioning as measured by CD4 count. For these reasons, it is not surprising that immunological variables did not significantly predict global neuropsychological impairment in the present sample. Finally, a substantial proportion of this sample was on HAART regimens, which may affect CD4 count and reduce the likelihood of demonstrating a direct relationship between CD4 count and neuropsychological status in HIV-infected individuals.

Finally, the results of the decision tree analysis demonstrated the predictive value of SDMT performance in HIV infection. The SDMT requires writing as many numbers as possible in a 90 second interval that match a series of nine different symbols based on a given key of symbol-number pairs. Knowledge of SDMT performance was more valuable than other brief neuropsychological measures in predicting global neuropsychological impairment in the present sample. There are a number of explanations for the insignificant or lesser contributions of other neuropsychological measures to the decision tree. For example, verbal fluency has been shown to be more weakly and inconsistently related to neuropsychological impairment in HIV infection than measures of psychomotor skills (Bornstein, Nasrallah, Para, Whitacre, Rosenberger et al., 1993; Marsh & McCall, 1994; Sahakian et al., 1995; Stern et al., 1995). It is therefore not surprising that performance on verbal fluency measures did not contribute significantly to the prediction of global neuropsychological impairment in the decision tree with greater specificity.

The WAIS-R Digit Symbol subtest has been shown to be consistently sensitive to
neuropsychological impairment in HIV infection (Becker et al., 1997; Hinkin et al., 1998; Lunn et al., 1991; Maj et al., 1994), and previous studies have also demonstrated the sensitivity of the TMT to HIV-associated neuropsychological impairment in earlier studies (Becker et al., 1997; Lunn et al., 1991; Maj et al., 1994; Miller et al., 1990; Sacktor et al., 1996). In the present study, the SDMT proved more useful in classifying global neuropsychological impairment than either Digit Symbol or the TMT. Because performance on Digit Symbol, the TMT, and the SDMT are strongly correlated, one possibility is that the SDMT accounted for most of the predictive utility provided by the psychomotor speed elements of Digit Symbol and TMT in the decision tree.

TMT Part B is often considered a measure sensitive to conceptual skills or executive functioning because of the mental flexibility required to switch or alternate between numbers and letters (Lezak, 1995). The decision tree demonstrated that this conceptual skill is not as useful in classifying global neuropsychological impairment as "purer" measures of psychomotor speed. Furthermore, the skills required for TMT Part A completion were also not as useful as the SDMT in predicting global neuropsychological impairment. The sequencing element of TMT Part A is likely more automatic and routinized than the skills required by the SDMT. Working memory may also contribute to successful performance on the SDMT because a "key" must be consulted to complete the task and a greater ability to temporarily store the symbols may improve task performance. These differences in task demands may explain why the SDMT was a better classifier than the TMT in the prediction of global neuropsychological impairment, although clearly there is shared variance among these measures. Overall, the increased sensitivity of the SDMT to global neuropsychological
impairment may be related to the more cognitively complex, demanding structure of the task with the additional requirement of fast psychomotor speed.

Another possible reason that SDMT performance was a superior predictor of overall neuropsychological impairment is because it may be a sensitive generalized indicator of global cognitive functioning, or cerebral efficiency, as opposed to a measure solely reflective of psychomotor skills. Successful performance on the SDMT likely taps skills in multiple cognitive domains, including attention, working memory, speed of information processing, and psychomotor skills. As a result, impaired performance on this task may be more likely to reflect global neuropsychological impairment than performance on measures tapping specific cognitive domains (e.g., language). If the SDMT is a good generalized indicator of global cerebral function, this characteristic may explain the consistent findings of a predictive relationship between SDMT performance and neuropsychological outcome in previous studies of HIV-infected individuals (e.g., Sacktor et al., 1996).

Results from the decision tree indicated that when performance on psychomotor measures is available, cognitive complaints do not make significant contributions to classifying HIV-positive individuals as globally impaired or unimpaired. However, when neuropsychological test measures are not included, total cognitive complaints (on the PAOF) is the best predictor of global neuropsychological impairment. Moreover, although cognitive complaints are not as accurate in predicting global neuropsychological impairment as neuropsychological test performance, total number of cognitive complaints provide the next best alternative to neuropsychological performance.

In the absence of information on psychomotor speed performance, a higher number
of cognitive complaints may suggest a greater likelihood of neuropsychological impairment. If possible, using the SDMT would be the single best and least time-consuming method of quickly and accurately identifying HIV-positive individuals who are most likely to be neuropsychologically impaired. Without the resources to administer SDMT (e.g., in a primary care medical clinic), the self-administered PAOF is worth completing, as it will convey some preliminary information on the likelihood of neuropsychological impairment based on the total number of complaints.

Limitations

One caveat to the conclusions drawn from this study is that causality cannot be inferred in the relationship between cognitive complaints and neuropsychological skills in HIV infection. Whereas cognitive complaints predict neuropsychological impairment, the reverse may also hold true. In fact, the relationship may very well be reciprocal, with increases in either cognitive complaints or neuropsychological impairment leading to subsequent increases in the other variable. This possibility was not adequately investigated in this study because feedback loops were purposefully omitted from the SEM model developed.

Another limitation to this study was the lower inter-rater reliability of the neuropsychological clinical rating scores for the domains of attention and memory. Whereas some measures of agreement between raters were high, inter-rater reliability values adjusted for chance were relatively low. Ratings of these domains may have been more affected by different interpretations of test performance across raters, possibly stemming from
differences in experience both with the measures used to determine ratings and the population in question. As such, conclusions of the study specific to the domains of attention and memory must be interpreted more cautiously than findings for other domains. Future studies in this area may clarify this issue by using ratings from more than two raters, reaching a consensus among raters on discrepant cases, matching raters for clinical experience level, or implementing a training protocol for raters. Additional support for the validity of the present findings would also be gained from studies using neuropsychological test scores in addition to clinical ratings.

Limitations to the study conclusions also stem from the characteristics of this sample. The sample used in this study consisted primarily of adult men. Consequently, potential gender differences in the relationship between cognitive complaints and neuropsychological performance were not assessed in this study. In addition, participants were mainly gay Caucasian men with an average of two years post-secondary education. The reported results may differ in samples that are more ethnically diverse, less educated, and include heterosexual individuals. Furthermore, the sample was relatively “clean”, without a significant history of neurological or psychiatric conditions, including IV drug use. As a result, these findings may not apply to HIV-positive individuals with comorbid conditions or significant substance abuse, particularly IV drug use. Whereas screening the sample allowed a purer evaluation of the relationship between cognitive complaints and neuropsychological performance, it restricts the generalizability of these results to a large proportion of HIV-infected individuals.

The conclusions of this study are also limited by the relatively small sample size used
in sophisticated statistical procedures that often require larger samples. Although our sample size met minimum standards for SEM and decision trees, larger samples are typically recommended for such techniques (Grimm & Yarnold, 2000; Kline, 1998).

Finally, it is possible that operationalizing cognitive complaints or neuropsychological impairment in another way may have affected the outcome of this study. For example, the CFQ was not used in the model because fewer individuals completed this measure; however, the CFQ may have contributed additional valuable information regarding the relationship between cognitive complaints and neuropsychological skills in HIV infection. In addition, study outcome may have differed if cognitive complaints were assessed in an interview format rather than completion of self-report questionnaires. Similarly, operationalizing neuropsychological impairment as a cutoff score on a test or series of tests rather than using clinical neuropsychological ratings may also have affected results differently. These issues will need to be addressed in future studies.

Future Directions

Further research is recommended to clarify some of the findings of this investigation. The relationship between specific cognitive complaints and neuropsychological impairment in HIV infection requires further exploration. For example, the predictive utility of spatial and lexical complaints needs to be replicated in other samples. Furthermore, it will be interesting to determine if finer distinctions improve the current understanding of cognitive complaints in HIV infection. For example, cognitive complaints may be more useful in classifying narrowly defined, clinically relevant groups of HIV-positive individuals (e.g.,
depressed and neuropsychologically impaired). As discussed earlier, subtypes of respondents may exist that endorse cognitive complaints in systematic patterns according to neuropsychological deficits, awareness, type of pathological process, and/or stage of illness.

Additional investigations in this area will be needed to address some of the methodological shortcomings of this study. Due to the relatively small sample size in this study, findings require replication with larger samples and with more diverse samples with complicated medical or psychiatric histories, comorbid disorders, and/or IV drug use. The classification tree requires replication in a sample independent of that from which it was derived. Because this study was a retrospective one, prospective investigations of the relationship between cognitive complaints and neuropsychological performance are particularly important to pursue. Cross-validation studies in different samples will assist in confirming or refuting the present results. Additional study in this area will permit increasingly refined hypothesis testing regarding the significance of cognitive complaints in predicting neuropsychological impairment.

It will be interesting to compare these results to studies that use different methods to assess cognitive complaints (e.g., interview format or a different self-report measure). Such investigations will determine the generalizability of the present results in accurately describing the relationship between cognitive complaints and neuropsychological impairment in HIV infection. Additional information on the accuracy of cognitive complaints in HIV infection may be obtained by comparing subjective complaints of HIV-infected individuals to the report of cognitive problems provided by a collateral (e.g., partner, family member).

Finally, other variables that were not examined in this study (e.g., coping style,
personality traits) may mediate the relationship between cognitive complaints and neuropsychological skills and merit further exploration. Studies that account for additional variables, including the severity of neuropsychological impairment and degree of awareness may also elucidate the complex relationship between cognitive complaints and neuropsychological skills both in HIV infection and in other populations.
Appendix A

Patient's Assessment of Own Functioning Inventory (PAOF)¹

Instructions: 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

MEMORY

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

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

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

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

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

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

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

   ( ) almost always
   ( ) very often
   ( ) fairly often

5. How often do you forget people whom you knew/met a year or more ago?
   ( ) 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
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 right 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 left hand?
   ( ) almost always
   ( ) very often
   ( ) fairly often
   ( ) once in a while
   ( ) very infrequently
   ( ) almost never
SENSORY-PERCEPTUAL

22. How often do you have difficulty feeling things with your right hand?

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

23. How often do you have difficulty feeling things with your left hand?

( ) 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
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 how to do things?

- almost always
- very often
- fairly often
- once in a while
- very infrequently
- almost never
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