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RELATIONSHIP BETWEEN FATIGUE AND COGNITIVE FUNCTION IN HUMAN IMMUNODEFICIENCY VIRUS PATIENTS

DISSERTATION

Presented in Partial Fulfillment of the Requirements for the Degree Doctor of Philosophy in the Graduate School at The Ohio State University

By

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1998

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ABSTRACT

The objective of this investigation was to determine if fatigue is associated with cognitive impairment in HIV infected individuals. This investigation consisted of two separate studies. The first study employed a large battery of standard neuropsychological tests that have been shown to be sensitive to the subcortical cognitive dysfunction in HIV patients. Fatigue was assessed by a self report questionnaire that inquired about the occurrence and duration of fatigue. Fatigue was associated with cognitive impairment in the symptomatic HIV patients, but not the asymptomatic HIV patients. The adverse effects of fatigue on cognitive function were observed on a wide range of cognitive domains even when controlling for the effects of depression.

The second study involved a separate cohort of HIV patients and aimed to replicate and extend the findings of the first study. The second study employed a more comprehensive neuropsychological test battery which assessed multiple components of attention, in addition to those domains of cognition that were assessed in the first study. Fatigue was measured from the perspective that fatigue is a multidimensional phenomenon including cognitive and physical components.
Similar to the first study, fatigue was associated with cognitive dysfunction across a broad range of cognitive domains in symptomatic HIV patients. The multidimensional assessment of fatigue and depression facilitated the differentiation between self reported fatigue and depression. Peripheral measures of immune status, immune activation, or viral load did not differ based on the presence of fatigue or fatigue severity.

This investigation indicates that fatigue is associated with cognitive dysfunction in symptomatic HIV patients and this effect can not be attributed to depression. The findings imply that for some HIV patients, fatigue may be a sign of the neurological manifestations of symptomatic HIV disease.
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INTRODUCTION

Overview of HIV Infection

Human immunodeficiency virus type 1 (HIV) is the primary cause of acquired immunodeficiency syndrome (AIDS). Human immunodeficiency virus is spread by sexual contact, exposure to infected blood or blood products or through perinatal transmission from mother to child. The HIV envelope protein gp120 binds to the CD4 membrane antigen and, with the aid of coreceptors, infects CD4+ cells (Weiss, 1996). The human CD4+ T lymphocyte and monocyte/macrophage are the major cellular targets for HIV infection (Gupta, 1996).

Macrophages contribute to the pathogenesis of HIV infection by being a reservoir for HIV in infected persons throughout the course of infection; by contributing to CD4 T cell depletion through a fusion process between infected macrophages and uninfected T cells; by contributing to HIV-related dementia by carrying HIV into the central nervous system (CNS) and producing neurotoxic substances; and by functioning abnormally following infection thus adding to the immune system compromise (Crowe, 1995).
T-helper cells orchestrate the body's antigen specific immune response and coordinates cell mediated immune responses. Specific functions of T-Helper cells include, coordinating B-lymphocyte production of antibodies to antigens; producing cytokines which are important in activating and coordinating other immune cells including B-lymphocytes, CD8+ T lymphocytes, and natural killer cells, and inducing CD8+ T lymphocytes to become activated and cytotoxic to viral infected host cells (Abbas et al., 1994). As a consequence of T helper cell depletion, there is increased susceptibility to infections and malignancies that becomes more pronounced as HIV disease progression occurs. Therefore, CD4+ T lymphocyte count is a prognostic indicator of HIV disease progression (Stein et al., 1992).

Flu-like symptoms may be reported upon initial HIV infection. However, some people have no symptoms during the initial period of HIV infection, while others may have neurological complications, including a meningoencephalitis like episode (Harrison & McArthur, 1995; Tindall, et al., 1988). The initial immune response to HIV is strong enough to partially control the virus but the virus is not cleared from the body. This leads to steady state levels of HIV in which there is active HIV replication with an estimated 1 billion new virions being produced daily and at the same time virus is being cleared by the host immune response (Havlir, Douglas & Richman, 1996).

Initially, the immune system remains relatively intact so that a steady level of HIV RNA is found in plasma that represents a
balance between the high virus turnover and immune system clearance of the virus. The clinical latency period is characterized by the gradual decline in CD4+ cells. HIV RNA levels can fluctuate during this period but in general they slowly increase as the steady state begins to favor HIV (Havlir, Douglas & Richman, 1996). This steady state level of HIV is predictive of disease progression with high HIV RNA levels associated with a more rapid progression to AIDS and death occurring earlier (O'Brien, et al., 1996; Mellors, et al., 1996).

The typical course of HIV is for the clinical latency period to last for an average of 8 years (Havlir, Douglas & Richman, 1996). As CD4+ cell counts decline this increases the risk for developing opportunistic infections. Constitutional symptoms such as fatigue, diarrhea, fever, and weight loss may be the first signs of the transition to symptomatic HIV disease. Thrush and herpes zoster are two common conditions seen early in the course of symptomatic HIV disease. These conditions are usually seen as CD4 cell counts fall below 400 and HIV RNA levels increase above 10,000 copies per milliliter of plasma (Pantaleo, Graziosi, & Fauci, 1993).

The latter stages of HIV disease are characterized by CD4 cell counts below 200 and HIV RNA levels of $10^5$ to $10^7$ copies per milliliter. Common opportunistic infections include; *Pneumocystis carinii* pneumonia, mycobacterium infection, and toxoplasma (Turner, et al. 1994). Neurological complications related to opportunistic infections become more frequent as disease progression continues. Cryptococcal meningitis, cerebral
toxoplasmosis, primary CNS lymphoma, cytomegalovirus encephalitis, and progressive multifocal leukoencephalopathy are common neurological manifestations of HIV disease that occur as CD4 cell counts fall below 200. HIV dementia is also most likely to occur during advanced symptomatic HIV disease (Price, 1996; Simpson & Tagliati, 1994).

As the immune system becomes more and more compromised opportunistic infections become more frequent and destructive. In fact, the immune system may have lost the ability to be reconstituted since there is thymus and lymphoid tissue atrophy. In addition, bone marrow progenitor cells may become infected with HIV in the most advanced stages of disease (Fauci, et al., 1996). Eventually the immune system becomes so depleted that it is not able to combat the infections and the person dies.

The reverse transcriptase inhibitor zidovudine (azidothymine; AZT) was approved by the Food and Drug Administration in 1987 for treatment of HIV disease. Treatment with AZT has been shown to decrease mortality rate, reduce the frequency of opportunistic infections, and reduce the decline of CD4 cell counts (Fischl et al., 1987). The recent development of new antiretroviral medications aimed at different steps in the HIV life cycle has dramatically changed the course of HIV disease progression and decline of CD4 cells in HIV patients. For many patients the combination therapy of antiretroviral medications is associated with delayed progression of disease, prolonged survival, and increased quality of life (Brodt et al., 1997; Collier et al., 1996). Therefore the HIV disease
progression overview described above is most likely to remain true
for those patients that do not have access to antiretroviral
medications. For those patients that do have access to the new
antiretroviral medications, disease progression, CD4 cell levels and
viral load will most likely depend on their response to treatment.

The benefits of anti-HIV medications in terms of neurological
and neuropsychological involvement is less clear. Despite the
effectiveness of the antiretroviral drug combinations in reducing
plasma levels of HIV RNA (Brodt et al., 1997), the effectiveness of
these medications on CNS levels of HIV remains in doubt. The blood
brain barrier prevents or reduces the entry of many hydrophilic
drugs, including antiretroviral medications. Improvements in AIDS
dementia complex (ADC) and neuropsychological test performance
have been seen with treatment of AZT (Goodkin et al., 1997; Schmitt
et al., 1988; Sidtis et al., 1993). However, improvements may occur
only at high doses of medication and may be transient (Tozzi et al.,
1993). Other studies have found conflicting results in the ability of
AZT to prevent the development of ADC (Day et al., 1992; Baldeweg
et al., 1995). Improvements in attention and memory performance
have been shown to occur with combination therapy of AZT and
DDI, particularly in those patients with cognitive impairment as
baseline (Brouwers et al., 1997).
Neurological Involvement of HIV

Mechanisms of HIV entry into brain

The deleterious effects of HIV are not limited to peripheral immune destruction. Central nervous system effects of HIV are also seen early in the course of HIV infection and become more pronounced as disease progression occurs. Upon initial infection, HIV disseminates widely throughout the body. Eventually HIV is found in many tissues and fluids of the body including peripheral blood T cells, monocytes/macrophages, bone marrow, lymph nodes, semen, brain, cerebrospinal fluid, spinal cord, and peripheral nerve (Ho et al., 1985; Fauci, et al., 1996; Sei, et al. 1994; Spector et al., 1993).

During the period of clinical latency HIV invades the CNS early in the course of infection (Resnick et al., 1988). Approximately half of early stage patients have HIV present in cultures of cerebrospinal fluid (Glass & Johnson, 1996) and HIV is found via RNA-PCR detection in a majority of HIV positive individuals regardless of disease stage (Chiodi, et al., 1992). Indirect evidence for early HIV infection of the CNS includes increased CSF levels of proteins and white blood cells (Elovaara et al., 1987), and increased CSF beta-2 microglobulin (Brew et al., 1992).

There are a variety of proposed mechanisms for HIV entry into the brain involving several different cell types and/or cell free HIV (Hurwitz et al., 1994; Moses & Nelson, 1994; Nottett and Gendelman, 1995). What is most likely to occur is that peripheral
immune activation and HIV infected macrophages interact to allow HIV to be carried into the brain via HIV infected macrophages. Nottett and Gendelman, (1995) have proposed a model in which peripheral immune stimulation by secondary infections or HIV infection alone will cause increased levels of Interleukin 1(IL-1) and tumor necrosis factor-alpha (TNF-alpha). This increase in cytokine levels cause the increased expression of E-selectin and VCAM-1 on the endothelial cells of the blood brain barrier. HIV infected macrophages are then more likely to bind the adhesion molecules and HIV infected macrophages can more readily pass across the blood brain barrier. In support of this model macrophages and microglia are the most abundantly infected cells within the CNS and are most abundant in the perivascular areas (Bagasra et al. 1996).

Neuropathology in HIV Infection

Navia et al., (1986a,b) were among the first to note pathological changes in HIV infected brain suggesting subcortical dementia.

More recently, autopsy and imaging studies demonstrate a pattern of neuropathological abnormalities which further establish the neuroanatomical basis of subcortical cognitive impairment in HIV. Diffuse myelin pallor and myelin vacuolation of subcortical white matter are common abnormalities. Autopsy studies of patients dying from AIDS have found a regional distribution of virus in the brain in which viral antigen is most often colocalized with
macrophages and microglia to subcortical structures including the basal ganglia, midbrain, and thalamus (Brew et al, 1995; Glass & Johnson, 1996).

Studies employing PCR find HIV RNA and DNA in nearly all brains tested with microglia and macrophages most often being infected with HIV. Astrocytes and microvascular endothelial cells may also be infected with HIV indicating that these cell types may facilitate viral entry into the CNS from the bloodstream (Bagasra et al., 1996; Moses & Nelson, 1994). Neurons and oligodendrocytes are rarely found to be infected with HIV even with the most sensitive molecular techniques. Therefore, the atrophy and neuronal loss is most likely due to indirect mechanisms and to processes facilitated by HIV activated resident microglia and invading macrophages (Dickson et al., 1994).

Activated microglia and macrophages disrupt CNS function by fusing together to form multinucleated giant cells (MNGC) which often colocalize with HIV in the brain. The presence of diffuse myelin pallor (DMP) and MNGC are associated with the occurrence and severity of HIV dementia (Glass et al., 1995). While the presence of MNGC can be detected upon autopsy, MRI often fails to detect the presence of the MNGC.

MRI studies show that there is general cerebral atrophy in the brains of patients with AIDS dementia complex. Signs of brain atrophy include decreases in white and gray matter including the caudate, diencephalon, and temporal limbic area with reductions in caudate being related to decreased cognitive performance (Glass &
A few studies reveal subtle subclinical neuropsychological decrements related to quantitative MRI studies (Hall et al., 1996). However, changes in MRI are not often found in asymptomatic patients (Syndulko et al., 1994) indicating that the cognitive dysfunction in asymptomatic subjects may be a reversible disorder of function best viewed with functional imaging.

In a comparison study (Tran Dinh et al., 1994), SPECT was more sensitive to the early neuroanatomical changes than MRI, with 88% of asymptomatic HIV positive subjects showing hypoperfusion compared to only 14% of asymptomatic HIV patients showing abnormalities on MRI. Positron emission topography studies reveal focal disruptions in the basal ganglia, thalamus, and frontal regions in HIV patients with further abnormalities in the temporal lobes associated with dementia (Rottenberg et al., 1987; van Gorp et al., 1992). It is hypothesized that these functional changes are related to increased NMDA receptor activity, since the highest concentration of the NMDA receptors are found in the basal ganglia, hippocampus, and frontal cortex (A. Martin, 1994). Increased NMDA receptor activity is one of several hypothesized indirect mechanisms by which HIV causes neurotoxicity and cognitive impairment (Lipton, 1991 & 1994).

**Indirect Mechanisms of HIV Neuropathology**

Evidence indicates that direct infection of neurons and cell lysis are not responsible for the neuropathology seen in HIV.
infection (Everall, et al., 1993). In addition, the amount of virus in brain is not correlated with dementia severity further implicating indirect causes of HIV related neuropathology (Glass et al., 1995; Brew, et al., 1995).

**Quinolinic Acid**

The kynurenine pathway metabolite, quinolinic acid (QUIN) is an agonist of the NMDA receptor and excitotoxin. Macrophages and microglia readily convert L-tryptophan into QUIN in response to immune activation (Heyes et al., 1992). Increased QUIN levels are observed in response to many inflammatory and autoimmune disorders. Increased QUIN levels may induce neuronal dysfunction and neuron death and thereby result in neurologic symptoms (Heyes et al., 1992). Increases in cerebrospinal fluid QUIN concentration are seen in the early stages of HIV infection with larger and sustained increases in CSF QUIN observed with disease progression. Quinolinic acid CSF levels are correlated with the occurrence and severity of ADC and neuropsychological impairment over a broad range of cognitive domains including motor dexterity, reaction time, attention, visual spatial ability, verbal fluency, memory, and learning (Heyes et al., 1989; A. Martin et al., 1992, ). Treatment with AZT reduces CSF QUIN concentration which is correlated with higher scores on neuropsychological tests and less ADC severity (Heyes, et al., 1991).

The NMDA receptor has a prominent role in many theories regarding the indirect causes of HIV related neuropathology
(Achim, et al., 1993; Heyes, 1989; Lipton, 1991). The NMDA receptor can bind the excitatory amino acid glutamate, quinolinic acid, and gp 120 (HIV envelope glycoprotein). Upon activation of the NMDA receptor the ion channel opens allowing the influx of calcium. Calcium can bind to calmodulin which leads to the activation of Nitric Oxide (NO) synthase and the production of NO. Free radicals can be produced from NO which then can damage brain cells. If too much calcium enters, proteases and lipases are activated which causes cell detraction and demyelination. The neurotoxic effects of QUIN may account for neuron death. Based on these findings several treatments for HIV related brain dysfunction have been proposed including calcium channel blockers, NMDA receptor antagonists, free radical scavengers and gp120 antibodies (Lipton, 1994).

Cytokines

Cytokines are important in the initiation, propagation, regulation, and suppression of immune and inflammatory responses. Macrophages and microglia produce a number of cytokines and cytotoxic substances and are the predominant cell types infected with HIV in the CNS (Merrill & Chen, 1991). Therefore, they are likely contributors to the indirect mechanisms of HIV neuropathology. Immune activation within the CNS occurs in the absence of complicating neoplasms or infections, with further increases evident when CNS opportunistic infections do occur (Mastroianni et al, 1992; Tyor et al., 1992).
There are several cytokines that are thought to be important in HIV neuropathology. Cytokine levels are correlated with other markers of CNS inflammation and severity of ADC. Substantial evidence exists implicating tumor necrosis factor-alpha (TNF-alpha), interleukin-1 (IL-1), transforming growth factor beta 1 (TGF-beta1), and Interferon-gamma (IFN-G) in the immune response, inflammation, and indirect mechanisms of neuropathology within HIV infected brain (Vitkovic, da Cunha, & Tyor, 1994).

Tumor necrosis factor-alpha is upregulated in AIDS brain and is produced by perivascular and parenchyma macrophages, microglia, endothelial cells, and astrocytes. TNF-alpha localizes primarily with macrophages and microglia in AIDS brain (Benveniste, 1994). The release of TNF-alpha by these cells can cause autocrine and paracrine stimulation that further enhances activation and cytokine production (IL-1, TNF-alpha, IL-6). HIV infection of macrophages and microglia causes increased production of TNF-alpha and in reciprocal fashion TNF-alpha can also increase HIV replication within macrophages and microglia. Tumor necrosis factor-alpha can induce astrogliosis thereby forming glial scars, damages myelin and can destroy oligodendrocytes resulting in the myelin pallor and vacuolation seen in AIDS brain. TNF-alpha can also stimulate NO production which may lead to free radical production and neuronal damage (Vitkovic, Cunha, & Tyor, 1994; Dickson et al., 1994).

There is an elevation of TNF-alpha messenger RNA expression in the brains of patients dying from AIDS with this elevation also
being related to premorbid ADC severity and neuropsychological test performance (Glass et al., 1993). Elevated CSF TNF-alpha has been reported in patients with ADC however, other studies have found no association between CSF TNF-alpha levels and neurological symptoms, and several studies have not been able to detect TNF-alpha in the CSF at all (Wiley et al., 1992).

Interleukin-1 is released by macrophages in the periphery and is important in the activation of the T helper cells upon binding of MHC class II and the T cell receptor. Within the CNS IL-1 is produced by microglia, infiltrating macrophages, astrocytes, and oligodendrocytes (Benveniste, 1994). HIV infection of macrophages and microglia leads to increased production of IL-1. Studies have found IL-1 in CSF to be related to ADC (Benveniste, 1994). The deleterious effects of IL-1 in the CNS are most likely mediated by its ability to amplify the inflammation process since IL-1 can increase the production of IL-6, TNF-alpha, and TGF-Beta by macrophages, microglia and astrocytes (Merrill & Benveniste, 1996). In fact, TGF-B is often localized with IL-1 indicating that TGF-B may suppress some of the inflammatory actions of IL-1. Interleukin-1 stimulates oligodendrocytes, macrophages, microglia and astrocytes to produce TGF-B.

TGF-B is seen in brain of HIV infected people but not usually in controls. TGF-B serves protective and deleterious roles in HIV CNS disease. TGF-beta is chemotactic for macrophages, microglia and astrocytes (Benveniste, 1994). This may cause increased infiltration of HIV infected cells into the brain and also amplify the
inflammation response. As a consequence TGF-B is often localized to areas of pathology which include macrophages, microglia and astrocytes (Wahl et al., 1991). TGF-B has many protective functions related to neuropathology including the ability to down regulate the immune response via inhibiting and decreasing cytokine production by macrophages and microglia. TGF-B also induces oligodendrocytes precursors to differentiate into myelin producing cells. This may offer some protection from the demyelination associated with other proinflammatory cytokines (Vitkovic, da Cunha, & Tyor, 1994).

Interferon-gamma is released from activated macrophages and microglia usually in response to viral infections (Dickson et al., 1994). Interferon gamma activates the indoleamine-2,3-dioxygenase (IDO) enzyme that converts tryptophan to quinolinic acid which is associated with ADC severity and neuropsychological impairment in HIV disease (Heyes et al, 1991). Interferon-gamma also increases the levels of beta-2 microglobulin and neopterin, which are markers of general immune activation, and are also correlated with ADC (Heyes et al., 1992) In addition, interferon gamma can also activate NO synthase in astrocytes which leads to NO synthesis and eventually free radical formation and neurotoxic anions (Dawson et al., 1994).

Examination of brain tissue of HIV positive patients who died before becoming symptomatic show an abundance of microglia and macrophages, increased MHC class II expression, and increased cytokine levels. This immune activation within brain occurs even in the absence of detectable HIV by PCR (An et al, 1996; Sinclair, et al.,
This suggests the state of immune activation seen AIDS is already present in brain of asymptomatic patients and cytokines may be triggering a series of events which will lead to brain damage.

**Beta2-microglobulin**

Beta2-microglobulin is a low molecular weight protein in the immunoglobulin superfamily that is expressed on the surface of most nucleated cells and forms part of the class I major histocompatibility complex molecule. Elevated serum levels of beta2-microglobulin are associated with activation of T lymphocytes and macrophages.

In HIV infected individuals serum beta2-microglobulin levels show strong correlations with soluble TNF receptors, soluble Intracellular adhesion molecule 1, neopterin, quinolinic acid, viral load and are inversely correlated with CD4 cell count; indicating that beta2-microglobulin is a proxy for general HIV related peripheral immune status and activation. (Diez-Ruiz et al., 1993; Henne, et al., 1997; Salazar-Gonzalez et al., 1997; Zangerle, et al., 1994).

Increased levels of serum beta2-microglobulin is the most common peripheral immune status measure that correlates with cognitive dysfunction and has been used to identify a subgroup of HIV asymptomatic patients with neuropsychological impairment (Boccellari et al., 1993 & 1994). In subjects without dementia a strong correlation exists between elevated CSF beta2-microglobulin and serum beta2-microglobulin. However, in HIV patients with
dementia CSF beta2-microglobulin is elevated independently of serum levels, indicating that CSF beta2-microglobulin may be produced in the brain of ADC patients (McArthur et al., 1992). Elevated levels of CSF beta2-microglobulin are correlated with ADC severity and neuropsychological test impairment. Similar to CSF QUIN concentrations, CSF beta2-microglobulin levels decrease with AZT treatment which is accompanied by improved neuropsychological performance and decreased ADC severity (Brew et al., 1992).

Peripheral Immune Activation in HIV Infection

Elevations in peripheral levels of beta2-microglobulin, TNF-alpha, IL-1 and other immune activation markers are common findings in HIV infected individuals particularly in the symptomatic stages of disease (Rimaniol, et al., 1996). Dunne et al., (1996) divided subjects into four groups, controls(1), asymptomatic(2), symptomatic without current opportunistic infections(3) and symptomatic with current opportunistic infections(4) and several markers of immune activation were measured. Beta2-microglobulin, was increased in all patient groups compared to controls. Within the patients groups beta2-microglobulin was significantly higher in the latter stage patients with current infections compared to those with no infections. Similarly, markers of monocyte activation (serum neopterin and Fc gamma receptor III) were significantly increased in group 4 patients. This suggests that
like CNS immune activation, there is peripheral immune activation due to HIV infection and opportunistic infections can cause further increases in peripheral immune activation. Furthermore, longitudinal study shows that systemic illness results in a subset of patients developing subtle neurological signs (Lopez et al., 1996).

There is increasing evidence that peripheral infections cause alterations in circulating transmitters and humoral factors which can directly or indirectly alter neurotransmitter levels and/or neuronal activity within the CNS (Hickie & Lloyd, 1995). In animals the peripheral increases of cytokines are capable of producing changes in neural activity that lead to a constellation of symptoms that are collectively known as sickness behavior (Segall & Crnic, 1990). Sickness behavior can take the form of reduced social interest, decreased food intake, behavioral fatigue and can be accompanied by fever, shivering, and difficulty on cognitive tasks. Peripheral administration of IL-1 beta and TNF-alpha produce changes in hippocampal function and deficits in learning and memory tasks (Gibertini, 1997). Intraperitoneal injections of lipopolysaccharide, which induces a proinflammatory response, have long lasting changes in electrophysiological activity of locus coeruleus neurons mediated via IL-1. The locus coeruleus is important in attention, vigilance, arousal and other cognitive functions (Robbins and Everitt, 1995).

In a murine model of immunologically mediated fatigue, peripheral as well as central increases of TNF-alpha and IL-1 beta occurred in response to C. parvum antigen challenge and were
thought to be responsible for producing behavioral fatigue (Sheng et al., 1996). In humans, similar results have been found when cytokines are administered as part of cancer therapy. Also, patients that suffer from infectious diseases that produce a potent peripheral immune response commonly report fatigue (Hickie & Lloyd, 1995). Interferons are responsible for many of the symptoms and neuropsychological impairment associated with viral illness. Administration of interferons to healthy controls and cancer patients produce dose related effects including fatigue, myalgia, headaches, and anorexia. Neurocognitive complications include increased reaction time, motor slowing, memory difficulties, mental slowing and EEG slowing (Mannering et al., 1986; Smith et al., 1988). Meyers et al., (1994) found acute neurotoxic effects due to the administration of IL-2 and TNF-alpha in renal cell carcinoma treatment. A pattern of cognitive deficits including diminished verbal memory, motor incoordination, attention impairment and executive dysfunction was consistent with mild frontal-subcortical dementia. A SPECT scan revealed diminished frontal perfusion that was bilateral but more pronounced on the right side. MRI was negative for any abnormalities. One month after cessation of treatment, neuropsychological test scores improved to normal and the SPECT showed resolution of the hypoperfusion.

These findings raise the possibility that infectious processes in the periphery produce changes within the CNS which can produce illness related behavior including fatigue along with the simultaneous occurrence of cognitive impairment. HIV infected
individuals suffer from a variety of infections that can cause transient increases in peripheral immune activation and increased cytokine levels. Furthermore, HIV infection by itself is associated with increased immune activation. Therefore, the steady state level of immune activation which exists in the periphery and CNS may be responsible for producing cognitive impairment and the constitutional symptoms of HIV.

**Fatigue**

**Defining Fatigue**

In many pathological conditions fatigue is a common complaint (Kroenke et al., 1988; Nelson et al., 1987). Despite the common occurrence of fatigue the concept of fatigue is not clearly understood. In fact the term "fatigue" is problematic for researchers because fatigue can have many different meanings depending on the system of study and the level of analysis. As early as 1921, researchers questioned whether fatigue could be measured (Muscio, 1921). In more recent studies the definition of fatigue often depends on the context in which fatigue is being investigated.

There are a wide variety of definitions for fatigue which highlights the multidimensional nature of fatigue. Kellum (1985) envisioned four types of fatigue. First, normal fatigue occurs after prolonged physical exertion, inadequate rest, as a consequence of stress, or due to an unstimulating daily routine. Second, pathophysiological fatigue is part of the sequela which accompanies
viral infections, chronic infection, endocrine or metabolic disorders, and malignancies. Third, situational fatigue occurs in the face of extreme stress, crisis or problems with a close personal relationship. Finally, psychological fatigue is associated with anxiety and depression.

In physiological studies (Marsden, et al., 1983) fatigue refers to when a motor unit can no longer fire. This type of fatigue is a neuromuscular event and occurs when the threshold for firing can no longer be met after repeated firing. This so called physiological fatigue may be relieved in only a few moments once the threshold for firing can be met and a muscle contraction can occur once again.

At the behavioral level fatigue is the decline in performance that occurs in any prolonged or repeated task (Kennedy, 1988). Behavioral fatigue can be due to repeated muscle contraction and is quantifiable by the number of hand grip pulls over a period of time or the slower pace of a runner as a marathon progresses.

In terms of mental performance, fatigue can be thought of as a decline in attention and increased susceptibility to distraction (Kennedy, 1988). Mental fatigue occurs when accuracy decreases as the number of trials increases or task duration lengthens (Cohen, 1993). An increase in response variability so that performance becomes inconsistent is a sign of mental fatigue. The cause of mental fatigue remains illusive although neuropathological abnormalities as well as changes in neurochemistry and brain function are possible explanations for mental fatigue (Goldstein, 1996).
Even when the behavioral and mental aspects of fatigue are quantifiable the ability to quantify self reported fatigue remains difficult. Numerous attempts have been made to quantify the subjective experience of fatigue which is different from the objective aspects of physiological, mental and behavioral fatigue (Barofsky and Legro 1991; Varricchio, 1985). Subjective fatigue is the perception of a diminished ability to persist on a mental or behavioral task regardless of the person's actual performance. Subjective fatigue can also be a sense of tiredness or lethargy that accompanies many chronic disorders such as multiple sclerosis and HIV disease (Packer, Sauriol, & Brouwer, 1994; Whalen et al., 1994).

Fatigue in HIV Disease

In acute HIV infection fatigue is a common symptom being reported by individuals who become infected with HIV (Fox et al., 1987; Quinn, 1997; Tindall et al., 1988). In chronic HIV infection fatigue is a frequent and troubling constitutional symptom. Estimates of the prevalence of fatigue range from 9 to 80 percent with these estimates varying depending on HIV disease stage and how fatigue is defined (Darko et al., 1992; Heaton et al., 1995; Hoover et al., 1993; Whalen et al., 1994). Darko et al., (1992) reported that fatigue is often or always a problem for 57% of symptomatic HIV patients. In contrast, persistent fatigue occurs in less than 10% of asymptomatic individuals (Hoover et al., 1993). Fatigue has been shown to increase in prevalence with HIV disease progression (Heaton et al., 1995). For some HIV patients fatigue
interferes with the ability to work and is responsible for unemployment. Fatigue can also negatively impact patient well being and quality of life (Darko et al., 1992). Despite the high prevalence of fatigue and the impact on patients lives little is known about the cause of HIV-related fatigue.

Fatigue in HIV infected individuals has a variety of proposed causes which may overlap with other symptoms of HIV infection. Fatigue due to peripheral mechanisms of disease including inefficient respiration, anemia, muscle abnormalities, endocrine changes, and medication side effects have been studied with the source of fatigue remaining unresolved for a majority of the patients (Abbott, et al., 1995; Cupler et al., 1996; R. Miller et al., 1991; Sinwell, et al., 1995). Relatively few studies of HIV-related fatigue have explored the neuropathological, neuroimmunological, and cognitive correlates of fatigue. Several studies have focused on the psychological correlates of fatigue but the results of these studies are often difficult to interpret because of the interrelationship between the subjective symptoms of fatigue and depression.

**Fatigue and Depression**

Symptoms of fatigue are included in the operational criteria for dysthymia and major depression, in the Diagnostic and Statistical Manual-IV (American Psychiatric Association, 1994). Fatigue is also included in the Beck Depression Inventory (Beck et al., 1961) and the Hamilton Rating Scale for Depression (Hamilton,
1960). The Profile of Mood States (McNair, et al., 1981) found by factor analysis that fatigue is a separate factor from depression, implying that in normal subjects depression and fatigue are independent. However, the practicality of such a separation comes into question when the Profile of Mood States manual lists a strong correlation of .60 between the fatigue and depression factors. It is not surprising then that in many diseases fatigue is related to depression, especially in the context of patient self report. However, several studies have begun to disentangle depression from fatigue.

Some studies involving MS patients find no correlation between fatigue and depression. In studies where depression is initially related to fatigue, further analysis reveals that fatigue severity is related to the medical symptoms of depression like tiredness and exhaustion, and not the emotional symptoms of depression such as lack of self esteem, suicidal ideations, or feelings of hopelessness (Krupp & Pollina, 1996; Moller et al., 1994; Roelcke et al., 1997).

Similar results are found in chronic fatigue syndrome. Several factors differentiate CFS patients from individuals diagnosed with depression. CFS patients compared to depressed patients are more likely to having severe debilitating fatigue, acute onset of illness, post-exertional malaise, alcohol intolerance, nausea and flu-like symptoms. Furthermore, those CFS patients with a sudden flu-like onset of disease compared to those CFS patients with a gradual onset are more likely to have disabling cognitive abnormalities and suffer less depression (Jason et al., 1997).
Depression is common in HIV infected individuals with estimates ranging from 0 to 78% depending upon several factors including gender, drug and alcohol use, socioeconomic status, study site, diagnostic criteria, and stage of disease (Stober et al., 1997). The measurement of depression in people infected with HIV is complicated by the fact that many symptoms of HIV disease (including fatigue, sleep disturbance, weight loss, cognitive problems, and the inability to work) are also symptoms of depression. This can lead to an over estimation of depression in medically ill HIV patients.

Several studies have investigated the association between depression and fatigue in HIV disease. A study (Perkins et al., 1995) of asymptomatic HIV patients found that fatigue was related to depression and not related to CD4 cell counts or neuropsychological test performance. Increases in fatigue over a six month period were associated with increases in non-HIV-related symptoms of major depression and in severity of dysphoric mood. Fatigue was also related to depression in a different study involving symptomatic patients (Kalichman et al., 1995). However, further investigation showed that the somatic symptoms of depression were related to HIV-related symptoms including fatigue and inversely related to CD4 cell count. The affective symptoms of depression were related to number of months since being tested HIV positive, anxiety, and hypochondrias. The authors concluded that depression scores should be interpreted differently depending on HIV stage, and those patients who have HIV-related symptoms including
fatigue, should be tested for depression using instruments which do not probe for somatic symptoms. One of the objectives of this study is to determine if fatigue can be differentiated from depression in HIV patients.

Depression negatively influences neuropsychological test performance in normal individuals across many domains of cognitive function. Depression has been associated with impairment in the abilities of attention, abstraction, verbal fluency, verbal memory, visuospatial skills, visual memory, and motor skills (Cassens et al., 1990). Therefore it will be important to establish that any effect of fatigue on cognitive function is independent of depression. Several studies within the HIV population have shown that depression can not account for the cognitive dysfunction in HIV infection (Bornstein et al., 1993b; Grant et al., 1993; Heaton et al., 1995; Hinkin et al., 1992; Mapou et al., 1993).

Fatigue and Cognitive Impairment

Human immunodeficiency virus disease shares many similarities to other neuroimmunological disorders in which fatigue and subcortical cognitive impairment are common symptoms. Several lines of evidence indicate that HIV related fatigue may be caused by central and/or peripheral immune activation. Furthermore, neuropathology of brain regions associated with fatigue in other neurological diseases is seen in HIV and may be
responsible for the simultaneous occurrence of cognitive impairment and fatigue in HIV disease.

**Multiple Sclerosis**

Multiple sclerosis (MS) is a demyelinating disease of the central nervous system in which the loss of the myelin sheath occurs with preservation of the underlying axon (Merrill, 1992). Multiple sclerosis is thought to be an autoimmune disease in which blood born inflammatory cells invade the CNS and destroy myelin. Similar to HIV neuropathology increased cytokine expression is a marker for chronic immune activation within the MS CNS (Wiley et al., 1992b). Evidence of an active immune response within the CNS includes increased expression of MHC class II on infiltrating macrophages, resident microglia, and astrocytes and the accumulation of activated CD4+ and CD8+ T cells (Pender & McCombe, 1995).

The symptoms of MS are often related to the site of lesion and include, dysarthria, nystagmus, tremor, ataxia, loss of bladder control, fatigue and cognitive dysfunction (Pender & McCombe, 1995). The term subcortical dementia characterizes the cognitive deterioration seen in MS patients which is similar to the cognitive impairment seen HIV disease (Lundervold et al., 1994). Multiple sclerosis patients are most likely to show impairment on measures of memory, attention, psychomotor ability, problem solving and exhibit slowed information processing speed (Rao, 1986).
Between 76 and 92 percent of MS patients report fatigue with fatigue being the most severe and disabling symptom for some patients (Freal et al., 1984; Krupp et al., 1988; Schwartz et al., 1996). Similar to HIV research fatigue in MS is most often not associated with peripheral mechanisms (Latash, et al., 1996; Sandroni et al., 1992). Subjective fatigue reported by MS patients is associated with decreased performance in the abilities of selective and sustained attention with greater response variability being seen on tasks requiring sustained attention (Cohen & Fischer, 1988, Cohen, 1993). However, other researchers have found that fatigue reported by MS patients is unrelated to cognitive dysfunction or depression (Geisler et al., 1996). These studies indicate that complaints of mental fatigue are associated with cognitive impairment, but physical fatigue may not be related to cognitive impairment.

Magnetic resonance imaging has shown that fatigue in MS is related to hyperintense areas in the brainstem and midbrain, but unrelated to depression (Moller et al., 1994). Positron emission topography reveals that self reported fatigue severity is correlated with decreased cerebral glucose metabolism in the frontal cortex (particularly on the right side of the prefrontal cortex), basal ganglia and frontal-subcortical white matter. Increasing fatigue severity is also associated with increased regional cerebral glucose metabolism in the anterior cingulate gyrus (Roelcke et al., 1997).

The possibility of a common mechanism for the neurological dysfunction seen in MS and HIV infection has been explored with many similarities and common approaches to treatment being
suggested (Wiley et al., 1992b). One therapeutic strategy for HIV related cognitive impairment and dementia involves down regulating intracellular calcium by antagonizing NMDA receptor activity. In this context it is of interest that amantadine (a NMDA receptor antagonist and dopamine agonist), has been shown to be effective in treating fatigue in MS patients (Cohen & Fisher, 1989; Kemp & Gora, 1993). Furthermore, increased cerebrospinal fluid levels of quinolinic acid (a NMDA receptor agonist) have been correlated with slowing of reaction time (A. Martin et al., 1992) and associated with AIDS dementia (Heyes et al., 1989). Also, AZT related decreases in quinolinic acid are associated with improved cognitive function (A. Martin et al., 1993).

Post-Polio Fatigue Syndrome

Post-polio syndrome is defined as the development of new weakness, fatigue, and pain which is unrelated to any known cause, that usually begins 25-30 years after an acute attack of paralytic poliomyelitis (Dalakas, 1995). The symptom of fatigue is common in post-polio- myelitis syndrome (PPS), occurring in up to 89 percent of patients and may be one of the most disabling symptoms. Post-polio myelitis syndrome related fatigue is attributable to a wide variety of etiologies with PPS patients complaining of both a central fatigue as well as a peripheral fatigue. Complaints of muscle weakness and decreased muscle endurance suggest peripheral fatigue. Proposed causes of peripheral fatigue include neuromuscular junction transmission defects. A large majority of
post polio survivors reporting fatigue also report difficulties with attention, maintaining concentration, thinking clearly and word finding. Research into this "central fatigue" has produced a model of mental fatigue which contends that damage to periventricular and deep white matter, the reticular activating system and subcortical areas (putamen, caudate, locus coerulesus and substantia nigra) may be responsible for producing fatigue and attention difficulties (Bruno et al., 1995).

The model first arose from research involving a small sample of carefully chosen polio survivors in which subjects were excluded for many comorbidities that could cause fatigue or attention dysfunction (e.g. anemia, depression, cardiac disease). Those subjects reporting severe fatigue showed clinically significant deficits on tests of attention and information processing speed while those subjects reporting none or mild fatigue showed no such deficits. Impairment was not seen on tests of higher cognitive function in either fatigue group (Bruno et al., 1993).

Anatomical evidence for this model was found in a magnetic resonance study (Bruno et al., 1994) in which areas of hyperintense signal in the reticular formation, putamen, and deep white matter were found in approximately half of those participants reporting severe or moderate fatigue while no areas of hyperintense signal were found in those polio survivors reporting none or mild fatigue. In another study of fatigued post polio patients, the number of subcortical lesions on MRI were related to attention impairment (Bruno et al., 1996).
Bromocripitpine has been found to lessen the self reported fatigue in post polio survivors along with improving attention and concentration difficulties (Bruno et al., 1996). These beneficial effects were thought to be due to bromocriptine's ability to stimulate dopamine receptors within the basal ganglia and the brain's activating system.

**Chronic Fatigue Syndrome**

Common complaints of chronic fatigue syndrome (CFS) patients include fatigue, concentration difficulties, memory problems, myalgias and sleep disturbances. The Centers for Disease Control criteria for a diagnosis of chronic fatigue syndrome is severe, unexplained, persistent or relapsing fatigue that has persisted for six months, plus four of the following eight symptoms: 1) impairment of short-term memory or concentration, 2) sore throat, 3) tender lymph nodes, 4) muscle pain, 5) multiple joint aches without swelling or redness, 6) headaches of a new type, pattern, or severity, 7) unrefreshing sleep, 8) post-exertional malaise lasting more than 24 hours (Fukada et al., 1994). A diagnosis of CFS is made only after an extensive medical work up rules out other causes of fatigue.

Several studies focusing upon the subjective reports of CFS patients have concluded that CFS is indistinguishable from depression. The self reported symptoms of depression overlap with the symptoms of fatigue and may account for these findings. Other studies focusing on the biological changes in CFS have found
endocrine, immunological, EEG, and brain imaging abnormalities that
distinguishes CFS patients from depressed individuals and healthy
controls (Goldstein, 1996; Jorge & Goodnick, 1997). The cause of CFS
is unknown, but several studies indicate that persistent immune
activation in response to viral infection may be responsible for CFS
(Barker et al., 1994; Klimas et al., 1990; Suhadolnik et al., 1997).

Goldstein, (1993) initially hypothesized most symptoms of
chronic fatigue syndrome have a limbic component. This hypothesis
has been updated based upon PET and SPECT imaging studies
suggesting that the symptoms of CFS are caused by dysfunction in
frontal-thalamic-striatal-limbic circuits. According to Goldstein
(1996) the final common pathway of CFS is inappropriate gating of
sensory information so that external and internal information is
processed improperly. This dysfunction in sensory gating can then
lead to the symptoms of fatigue, myalgia and cognitive dysfunction.
Neuropsychological studies of CFS patients have found impairment
in information processing speed and other signs of cognitive
dysfunction that are not related to depression, but is similar to
deficits seen in multiple sclerosis (Krupp et al., 1994; Michiels et
al., 1996; Ray et al., 1993).

Subcortical dementia in HIV

Dementia is characterized by an acquired and persistent
impairment of intellectual abilities involving several domains of
cognitive function (Cummings, 1986). There are primarily two types or patterns of dementia that have been characterized. Cortical dementia is associated with loss in the abilities of language, declarative memory, perception, calculation, and manifested by aphasia, amnesia, agnosia, acalculia, and apraxia. The pattern of cognitive deficits in Alzheimer's disease is the most extensively studied example of cortical dementia (Lezak, 1995).

Subcortical dementia is associated with psychomotor slowing, memory impairment (different from cortical dementia), attention dysfunction, problem solving and concept formation difficulties, visuospatial dysfunction and disturbances of mood and arousal. The subcortical pattern of dementia occurs in disorders with involvement of the basal ganglia, thalamus, and brainstem structures. The cognitive deficits seen in Parkinson's disease illustrates subcortical dementia (Lezak, 1995; Lundervold, et al., 1994).

A variety of terms are used to describe the changes in brain structure and function which accompany HIV infection. Navia et al., (1986a,b) were among the first to note pathological changes in HIV infected brain suggesting subcortical dementia. The term AIDS dementia complex was used by this research group to describe the central nervous system abnormalities seen in AIDS patients. According to the researchers early symptoms of ADC included behavioral (apathy, dysphoric mood), cognitive (confusion, loss of concentration, slowness of thought), and motor (loss of balance, leg weakness) components. Late stage signs of ADC included
psychomotor retardation, ataxia, tremor, hypertonia, incontinence, and severe dementia.

In approximately three percent of HIV patients ADC is the initial AIDS defining illness. AIDS dementia complex is increasingly more prevalent as disease progression occurs with <1%, 5%-10%, and 20-30% of CDC A, CDC B, CDC C staged individuals being diagnosed with ADC (Harrison & McArthur, 1995). There is some variance in these figures depending on criteria used and the subpopulation studied.

Through magnetic resonance imaging and neuropsychological testing, Grant et al. (1987) showed early central nervous system involvement of human immunodeficiency virus and suggested mild cognitive impairment may be seen in otherwise asymptomatic HIV infected people. Since then a subcortical pattern of neuropsychological impairment has been established (Grant et al., 1995; Peavy et al., 1994; Becker et al., 1995).

Studies investigating cognitive impairment in HIV infection have used a variety of criteria to define impairment. Impairment is usually defined in relation to the neuropsychological performance of a control group. Some studies have focused on only a few domains of cognitive function, while other investigations have employed a large number of neuropsychological tests probing for impairment across many domains of cognitive function (Becker et al., 1995; Bornstein et al., 1993a; Dunlop et al., 1992; Heaton et al, 1995; Villa et al., 1996).
Diagnostic criteria have been established in order to more clearly differentiate AIDS dementia from the more subtle cognitive abnormalities seen in HIV positive individuals. This subtle cognitive impairment has been termed mild neurocognitive disorder (MCD) (Atkinson & Grant, 1994) or minor cognitive/motor disorder (Working Group of the American Academy of Neurology AIDS Task Force, 1991). In order to meet diagnostic criteria, patients must show impairment on at least two neuropsychological domains. Impairment is more clearly outlined in the MCD criteria with impairment in cognitive functioning being defined as 1 standard deviation below age and education appropriate norms on standard neuropsychological tests. The neuropsychological assessment must cover at least the following abilities: verbal/language, attention/speed of information processing, abstraction, memory, complex perceptual-motor performance, motor skills.

Similar to ADC studies, neuropsychological investigations have found that mild cognitive impairment also increases along with disease progression. A summary of 57 neuropsychological studies focusing on asymptomatic patients (White, et al., 1995) found median rates of cognitive impairment of 35% and 12% for HIV asymptomatics and seronegative controls, respectively. In a large and comprehensive study, Heaton et al. (1995) examined 389 HIV positive individuals and 111 uninfected controls for the prevalence of neuropsychological deficits across eight different areas of cognitive ability. The overall rate of cognitive impairment across disease stage was also determined. The researchers found
increasing rates of neuropsychological impairment at each successive stage of HIV infection, 17%, 31%, 44%, and 56% for control, CDC93 Group A, CDC93 Group B, and CDC93 Group C, respectively. For those rated impaired, the abilities of attention/speed of information processing were most often affected.

The Heaton et al., (1995) study along with others (Bornstein et al., 1993; Villa et al., 1996) have found that in addition to the increasing prevalence of cognitive impairment the nature of the cognitive deficits follows a progression related to disease stage. For purposes of review, cognitive function will be divided into five domains so that an orderly and easily followed review of the literature can take place. The domains will approximate the recommendations published by Atkinson and Grant (1994). These divisions between cognitive domains are not meant to be absolute since adequate performance on many tasks require proper function in more than one cognitive domain. Furthermore those areas of cognition that remain intact in all but the most demented HIV patients will not be reviewed.

The Heaton et al. (1995) study is probably the most comprehensive description of the nature of cognitive dysfunction that occurs with HIV disease progression. There is also a wealth of knowledge that has accumulated from over a decade of research into the course, severity and nature of cognitive dysfunction in HIV disease. The domains of cognition will be reviewed in the order in which they are listed here: reaction time, motor, learning and memory, executive function/abstraction, and attention. Particular
focus will be given to attention since this is one area of cognitive function that is most likely to be impaired due to fatigue. By understanding the neuroanatomy and conceptual foundations of attention it is hoped that any correlations between attention and fatigue will provide some clues into the pathophysiological mechanisms of HIV related fatigue.

**Reaction Time**

Several studies have shown reaction time differences between early stage HIV patients and controls (Bornstein et al., 1992; Karlsen et al., 1992). Differences are found on simple and choice reaction time measures and on decision time indicating that cognitive processes and not just motor slowing may responsible for the differences (E. Martin et al., 1992b). Some studies have shown progressive slowing in reaction times from asymptomatic HIV subjects to AIDS patients (Kokkevi et al., 1991; Perdices & Cooper, 1989).

Other studies have not revealed any HIV group differences which suggests the parameters within the reaction time paradigms may be important in detecting differences. Dunlop et al., (1992) examined the sensitivity of five different types of reaction time tasks to HIV disease stage. Simple and complex reaction time tasks discriminated HIV positive subjects from controls. In addition, a cognitively complex decision making task and a task designed to evaluate rapid motor movements were the most sensitive to subtle
differences between control subjects and asymptomatic HIV patients and were able to detect changes across disease stage.

HIV positive subjects compared to seronegative controls show more variability in response time. This variability suggests that deficits in arousal, orienting, sustaining attention, and/or motor processes are impaired in HIV positive subjects (E. Martin et al., 1992a, b). Some investigators suggest that fatigue may be partly responsible for the poor reaction time performance because many reaction time tasks take 15 minutes or longer and require sustained attention (Grant & A. Martin, 1994).

Motor

Human immunodeficiency virus disease progression is associated with a higher rate of motor ability impairment. Motor performance decline is one of the earliest signs of mild cognitive impairment. Differences in manual dexterity and psychomotor performance between seronegative controls and HIV positive individuals may be seen when other domains of cognitive function remain intact (Bornstein, et al., 1993a; E. Miller et al., 1990, Villa et al., 1996). Other motor tasks including grip strength and tapping test show differences between symptomatic and asymptomatic HIV patients (Heaton et al., 1995).

Learning and Memory

The Heaton et al. (1995) study demonstrated that learning/memory and attention were the two domains of cognitive...
function most commonly impaired in HIV patients with these abilities being impaired in over half of the HIV positive subjects. Although learning and memory deficits have been reported for asymptomatic and symptomatic HIV-infected patients these deficits have not been consistently observed, particularly in asymptomatic patients where deficits may exist in only a subset of patients (Delis et al., 1995). One explanation for these differences is the fact that learning and memory can be defined and assessed in a variety of ways. Memory is a complex process by which the individual registers, retains, and retrieves information (Gordon, 1997). Several different types of memory exist with different neuroanatomical systems underlying proper memory formation and retrieval.

Memory of declarative information involves recalling facts, events, and knowledge of pictures, faces and places. The hippocampus and related medial temporal structures are important in translating temporary cortical activity into more permanent forms of declarative information which is stored in the cortex. Damage to the medial temporal lobe prevents the formation of new declarative memories. Cortical atrophy that is seen in many neurodegenerative diseases causes the loss of declarative memory and is characteristic of Alzheimer's disease. Consistent with the subcortical neuropathology in HIV, the cortical information stores in HIV patients remain intact. Verbal and nonverbal declarative memory deficits are rarely seen in HIV infection except in severe cases of ADC (Becker et al., 1995; Grant & A. Martin, 1994).
Implicit memory or procedural memory is the term applied to learning and memory that does not require an explicit statement, but which is revealed in the course of performance of a task (Gordon, 1997). Implicit memory is not dependent on the medial temporal lobes, rather it is dependent upon the specific regions of brain involved in the function. For example motor skill learning is an example of implicit memory and damage to the basal ganglia is detrimental to this type procedural memory. (Squire and Zola-Morgan, 1991). Several studies have found differences between HIV patients and controls on motor skill learning tasks congruent with the subcortical nature of HIV neuropathology (A. Martin et al., 1993; Wilkie et al., 1992)

Verbal learning and memory difficulties occur early in the course of HIV infection and may become more prevalent in the later stages of disease (Bornstein et al., 1993a, Villa et al., 1996). Several list learning tests show that the nature of verbal learning deficits are useful in discriminating between Alzheimer's patients and HIV patients. In standardized list learning tasks such as the California Verbal Learning Test, HIV patients show primarily a retrieval deficit (Becker et al., 1995; Delis et al., 1995; Peavy et al., 1994). This deficit is consistent with subcortical cognitive dysfunction. Encoding deficits, which are often associated with cortical dementia, are usually mild or nonexistent in HIV patients (Delis et al., 1995, Becker et al, 1995).

Working memory is conceptualized as a memory system in which a central executive allocates attentional resources for
processing and manipulating information that is held in short term stores (Baddeley, 1992). Working memory tasks require a subject to hold information in the temporary store, allocate attention to process new information while holding the old information in the store, or to shift attention between these two processes. The dorsolateral prefrontal cortex is important in working memory (Goldman-Rakic, 1995) and similar to other domains of cognitive function with a heavy reliance on frontal lobe function, working memory dysfunction in HIV disease is most commonly seen in AIDS patients (Stout et al., 1995).

Executive Functions

Executive function can be conceptualized as having four components: volition, planning, purposive action, and effective performance. All are necessary for appropriate, socially responsible, and effective self-serving adult conduct (Lezak, 1995). Frontal lobe damage is implicated in executive function impairment although subcortical damage can also give rise to executive dysfunction via frontal-striatal circuits. Difficulties with abstraction and concept formation often occur along with executive function problems since both abilities strongly depend upon the functional integrity of the frontal lobes. Verbal fluency abnormalities may be seen along with executive function impairment since both abilities involve the frontal lobes. (Bornstein & Leason, 1985; Lezak, 1995).

Executive function and frontal lobe abilities usually remain free from impairment until the latter stages of HIV infection.
(Bornstein et al. 1993a, Heaton et al., 1995; Villa et al., 1993). This is consistent with autopsy and imaging studies in which frontal lobe abnormalities are most commonly seen in HIV positive individuals diagnosed with AIDS (Price & Perry, 1994). However, executive function deficits can be found in asymptomatic HIV patients particularly on more demanding tasks which explicitly tests for higher level planning abilities (Sahakian et al., 1995).

**Neuroanatomy and Components of Attention**

Attention is not a single phenomenon, but is instead divided into various domains and these domains can be formed upon neuroanatomical, functional, or conceptual bases. Several different models or theories of attention have been developed in order to explain the multidimensional nature of attention.

Attention can be conceptualized as existing on three neuroanatomical levels (Stuss and Benson 1984). These three levels include the reticular activating system which provides the tonic levels of arousal and alertness associated with sustained attention, the diffuse thalamic projections which are associated with the phasic levels of alertness, and the frontal-thalamic gating system which is responsible for selected and directed aspects of attention. Furthermore, connections with the thalamus and frontal cortex allow the basal ganglia to perform a gating function for sensory information therefore making the basal ganglia important in selective attention. The basal ganglia along with the premotor area
of the frontal cortex are also important in the timing and automatic execution of learned motor plans (van Zomeren and Brouwer, 1994).

The prefrontal cortex receives projections from most areas of the brain including the reticular activating system, the limbic system and caudate. The prefrontal cortex is involved in the temporal arrangement of responses with the inhibition of some responses occurring until the appropriate moment (Goldman-Rakic, 1995). Damage to the prefrontal cortex causes poor performance in tasks involving interference, divided attention, and executive function (van Zomeren and Brouwer, 1994). The prefrontal cortex's downward projections can also influence the reticular activating system.

Mesulam (1985) calls the reticular activating system the pacemaker for attentional tone upon which the goal directed aspects of attention operate. Serotonergic projections of the midline raphe, and noradrenergic projections of the locus coeruleus serve as modulators of the attentional matrix. Similar to Mesulam, Posner & Petersen (1990) propose a vigilance network which is important in maintaining an alert state and arises from the rostral norepinephrine projections of the locus coeruleus. Increased alertness acts on the attentional system to enhance the speed of actions taken toward a target. Therefore, sustaining a certain level of attention is important in many timed tasks (e.g. reaction time) requiring rapid response for good performance.

The two most prominent structures of the limbic system in attention theories are the cingulate gyrus and hippocampus. The
The hippocampus is essential for storage of information and therefore distinguishes between old and new stimuli. This allows the hippocampus to determine if a stimulus is considered a novel stimulus. Novel stimuli are more likely to increase arousal and prompt orientation to the novel stimulus (Pribram and McGuinness, 1975).

The cingulate gyrus has a prominent role in the anterior attention system proposed by Posner & Petersen (1990). The anterior network is important in conscious, focused attention and signal detection regardless of the source or sensory modality. In general the anterior cingulate gyrus is involved in the selection of targets from competing inputs. Anterior cingulate activity increases with the number of targets in a set of stimuli and the activity decreases with practice of any single stimulus set. As practice proceeds feelings of effort and continuous attention decreases and details of performance drop out of subjective experience. Increased positron emission topography (PET) activity in the anterior cingulate gyrus is associated with the subjective experience of effortful attention especially on interference tasks (Posner & Petersen, 1990). Mesulam (1990) also features the anterior cingulate gyrus in his network of attention. In this model the anterior cingulate plays a pivotal role in assigning motivational relevance to sensory stimuli according to past experience as well as present needs. Therefore the cingulate gyrus may participate in directing or shifting attention to more important stimuli.
**Attention in HIV**

Most studies of cognitive function in HIV disease include measures of attention. The importance of attention performance in diagnosing subtle cognitive/motor dysfunction in HIV disease was highlighted by a NIMH workshop (Butters et al., 1990). A neuropsychological test battery was recommended with special emphasis given to measuring the divided and sustained components of attention. These areas of attention were emphasized since they were most likely to be compromised in HIV infected subjects. However, most studies (Rubinow et al., 1988; Heaton et al., 1995; Villa et al., 1996) involving neuropsychological testing of attention function usually only find differences between patients in the most advanced stages of disease and HIV negative controls with subtle differences between asymptomatic HIV patients and controls infrequently being found.

The inability to detect mild attention dysfunction with neuropsychological tests in HIV infection, even though experimental paradigms have found differences (E. Martin et al., 1992a,c; Sorensen et al., 1994) has been addressed by White et al., (1995). In this review the most important factor in detecting subtle differences in cognitive function was the length and comprehensiveness of the neuropsychological battery. Longer and more comprehensive batteries were three times more likely to detect subtle impairment compared to shorter batteries. The comprehensive test batteries were also more likely to establish any
relationship between cognitive function and important biological variables and to fully characterize the nature of the impairment.

Attention is a multifaceted function comprised of several components. Most neuropsychological test research studies which probe for attention function in HIV disease do so in the context of measuring cognitive impairment in general. As a consequence, attention is usually assessed as a single domain.

Good performance on many tests associated with other domains of cognition require attention ability to be intact. Studies investigating executive function, reaction time, verbal memory and working memory in HIV patients have suggested that attention dysfunction may be contributing to the poor performance seen in these domains of cognition. Despite this few studies have focused on determining which components of attention are impaired in HIV patients. Furthermore, fatigue induced impairments in cognitive function most often include difficulties with attention (Bruno, Galski, & DeLuca, 1993; Cohen & Fischer, 1988). Therefore a comprehensive assessment of attention function will allow a closer examination of which components of attention are most vulnerable to fatigue.

Fatigue and Cognitive Impairment in HIV Infection

Multiple sclerosis, post polio syndrome, and chronic fatigue syndrome are examples in which fatigue and subcortical cognitive impairment are interrelated symptoms of disease (Krupp & Pollina, 1996). The basal ganglia, reticular formation, prefrontal cortex, and
subcortical white matter appear to be important neuroanatomical correlates of fatigue in these neuroimmunological diseases (Bruno et al., 1994; Goldstein, 1996; Roelcke et al., 1997). Similar to these disorders, HIV disease is characterized by subcortical cognitive impairment, fatigue, and subcortical neuropathology (Glass & Johnson, 1996; Heaton et al., 1995). However, the relationship between fatigue and cognitive performance in HIV patients has received little attention.

Heaton et al. (1995), found that fatigue was the most prevalent constitutional symptom reported among all HIV positive individuals. A trend for fatigue to be associated with neuropsychological impairment was found. However, similar analyses looking at the association between fatigue and neuropsychological impairment within each stage of disease were not presented. Furthermore, the relationship between fatigue and neuropsychological performance across several domains of cognitive function was not investigated. Therefore, a more detailed investigation of the association between fatigue and cognitive performance in HIV infection is needed to determine if fatigue is related to cognitive dysfunction. A better understanding of the correlates of fatigue may provide some clues in determining the mechanism(s) of HIV-related fatigue and give some insight into potential therapies. Therefore, the proposed study will investigate the relationship between fatigue and cognitive dysfunction in HIV disease.
Purpose of the Present Investigation

As reviewed in the introduction, HIV infection is primarily associated with neurological abnormalities within subcortical white matter and subcortical neuroanatomical structures (Bencherif & Rottenberg, 1998; Navia, et al. 1986b). These abnormalities include multinucleated giant cell formation, diffuse myelin pallor, white matter vacuolation, and astrogliosis. The most frequent abnormalities in neuroimaging studies, are found within the basal ganglia, thalamus, midbrain, and frontal regions (Glass & Johnson, 1996). Consistent with these studies, mild subcortical cognitive impairment may be seen in the early stages of HIV, with more profound impairment evident in symptomatic HIV disease (Bornstein et al., 1993a; Heaton et al., 1995). Fatigue is associated with cognitive dysfunction in several diseases including multiple sclerosis, post polio syndrome and chronic fatigue syndrome (Bruno et al., 1993; Cohen & Fisher, 1988; Goldstein, 1996). Neuroimaging studies involving patients with these neuroimmunological diseases have shown fatigue related abnormalities in many of the same subcortical structures that are damaged in HIV disease (Goldstein, 1996; Grafman et al., 1995; Moller et al., 1994; Roelcke et al., 1997). Therefore the current investigation will explore the relationship between subcortical cognitive dysfunction and fatigue in HIV infected individuals.

Depression is common in HIV infected people (Stober et al., 1997) and is also associated with neuropsychological dysfunction in otherwise healthy people (Cassens, 1990). In addition, depression
may be caused by dysfunction within subcortical circuits (Cummings, 1993). Therefore, the present investigation must show that the effects of fatigue on cognitive function in HIV infected individuals are independent of depression.

Fatigue can have behavioral, affective, and cognitive components. Despite this, most studies involving HIV patients, have investigated fatigue as a unitary construct, inquiring about the occurrence of fatigue. This investigation will attempt to quantify the multidimensional nature of fatigue in HIV patients and how the different dimensions of fatigue are related to cognitive dysfunction.

The investigation will be composed of two separate studies. Fatigue will be measured as a yes or no construct in the first study in which only the occurrence and duration of fatigue will be measured. The initial study will employ a large battery of neuropsychology tests which probe for dysfunction across several domains of cognitive function. The investigation of cognitive function in the second study will also cover several domains of cognitive function along with a more detailed investigation of attention. Attention will be studied from the perspective that there are several components of attention. One aim of the second study is to determine if fatigue is associated with decrement in all areas of attention or if there are specific decrements in attention associated with fatigue. The measurement of fatigue in the second study will be extended so that the severity and multidimensional nature of fatigue will be assessed.
CHAPTER 2

STUDY 1

Hypothesis 1: Effects of fatigue on cognitive function

Fatigue is hypothesized to be related to HIV disease neuropathology. Therefore, the effects of fatigue are expected to be seen across several domains of cognitive function consistent with the subcortical neuropathology of HIV. In comparison to symptomatic HIV disease, there is relatively little neuropathology within the asymptomatic patients. In addition, previous research has shown that within the asymptomatic HIV patients fatigue is associated with the affective symptoms of depression (Perkins et al., 1995). Research indicates that depression can not account for the cognitive dysfunction in HIV (Bornstein et al., 1993b). Based upon these findings, it is hypothesized that fatigue will have little or no effect on cognitive function within the asymptomatic HIV patients.

Fatigue in the latter stages of HIV disease may be more likely due to the biological aspects of HIV disease instead of the affective symptoms of depression (Darko et al., 1992; Kalichman et al., 1995; Perkins et al., 1995). In addition, subcortical neuropathology is more prominent in the symptomatic stages of HIV disease (Glass &
Johnson, 1996). Therefore, fatigue in the symptomatic patients is hypothesized to be caused by the underlying neuropathology that is associated with cognitive impairment. It is expected that the symptomatic HIV patients with fatigue will perform worse on tests of cognitive function than those symptomatic HIV patients without fatigue and the asymptomatic HIV patients. The effects of fatigue on cognitive function are expected to be independent of depression.

**Methods**

**Subjects**

This first study utilized data which was collected for a longitudinal investigation of the neurobehavioral effects of HIV. Subjects were recruited into the study from October 1989 to July 1993. The subjects were HIV negative controls and HIV positive Caucasian homosexual or bisexual men that were recruited from several sources including the AIDS Clinical Trials Unit at The Ohio State University, HIV-related community agencies, and advertisements in local newspapers and other publications whose primary readership were homosexual and bisexual individuals. Participants knew of their HIV status prior to beginning the study which was determined by the participants personal physician or by the AIDS Clinical Trials Unit. All subjects were given written descriptions of the study and all signed informed consent agreements. The evaluation included an extensive neuropsychological assessment, psychosocial assessment and medical records review. Subjects were paid $100 for their
participation in the study which took approximately eight hours to complete.

Participants were excluded from the analyses based on the following characteristics: unconsciousness greater than 1 hour, history of neurological disease, inpatient psychiatric treatment, history of a learning disability, Full Scale IQ less than 80, or intravenous drug use. Furthermore, those patients with neurological opportunistic infection were excluded from the study to ensure that the effects of HIV on the brain were being studied without the complication of neoplasms or infection within the central nervous system.

Seventy-six seronegative controls qualified for the study. The HIV positive subjects were classified as asymptomatic (Stage A), symptomatic (Stage B), or AIDS (Stage C) based on the 1993 Centers for Disease Control (CDC93) revised classification system for HIV infection (Centers for Disease Control, 1992). Over half (80) of the 155 HIV positive subjects met criteria for asymptomatic classification. The 29 subjects classified as Stage B and the 46 subjects classified as Stage C were combined to form a single group of 75 subjects who were termed symptomatic. This was done in order to provide sufficiently large groups for data analysis since these subjects were further stratified based upon the presence of fatigue. Four groups were formed: asymptomatic without fatigue, asymptomatic with fatigue, symptomatic without fatigue, and symptomatic with fatigue.
Immune Status Measurement

For participants who were recruited from the AIDS Clinical Trials Unit, CD4 cell counts were obtained from the AIDS Clinical Trials Unit. Blood samples were collected in ethylenedinitrilo tetraacetic acid tubes and transported to the AIDS clinical trials laboratory. For determination of CD4 cell counts, whole blood samples were stained with two-color monoclonal reagents (Coulter, Hialeh, Florida, USA) followed by lysis of red blood cells and fixation using the Q-prep Immunology workstation (Coulter). Immediately thereafter, processed samples were analyzed by dual color analysis on a flow cytometer (Epics XL, Coulter). The laboratory in which the cell counts were performed is quality controlled by the AIDS Clinical Trials Group quality control program. For participants recruited outside the AIDS Clinical Trials Unit immune status data were collected from the participant's physicians or supplied by the participants.

Neuropsychological Assessment

The tests within the neuropsychological battery are commonly used measures which cover numerous domains of cognitive function and are consistent with probing for subcortical impairment in HIV infection (Bornstein et al., 1993a; Heaton et al., 1995). The domains of cognitive function assessed are consistent with the recommendations of the NIMH workshop on neuropsychological assessment in HIV infection (Butters et al., 1990) and similar to other neuropsychological test batteries probing for cognitive
impairment in HIV infected individuals across a wide range of abilities (Atkinson & Grant, 1994; Working Group of the American Academy of Neurology AIDS Task Force, 1991). The domains of cognitive function and the neuropsychological tests within each domain are listed in Table 1.

The assignment of the tests to a particular domain is done with the realization that there is overlap between many of these tests in terms of the abilities that they assess. Therefore, assignment to a particular domain of cognitive function is not meant to represent an absolute determination, but rather refers to the degree of sensitivity of that test for a particular function. Each of the tests within the battery will be reviewed in the order in which they are presented in Table 1.
Attention:
1. Trail Making Test A (seconds)
2. Trail Making Test B (seconds)

Executive Function:
1. Wisconsin Card Sorting Test
   a. Categories
   b. Cards
   c. Perseverative errors

Information Processing Speed:
1. PASAT
   a. 2.4 number correct
   b. 2.0 number correct
   c. 1.6 number correct
   d. 1.2 number correct

Verbal Memory:
1. Selective Reminding Test
   a. Trials needed to repeat all 12 words
   b. Total number recalled across all trials
   c. Consistent long term retrieval
   d. 30-minute delayed recall number remembered

Verbal Fluency:
1. Letter Fluency
2. Semantic Fluency

Motor Ability:
1. Grooved Peg Board
   a. Dominant(seconds)
   b. Nondominant(seconds)

Reaction Time:
1. Simple Dominant(milliseconds)
2. Simple Nondominant(milliseconds)
3. Choice (milliseconds)

Table 1. Cognitive domains of the neuropsychological test battery for Study 1.
Description of the Neuropsychology Tests

Attention

Trail Making Test:

Trail Making Test (Reitan, 1958) is a paper and pencil test comprised of two parts (A and B). For part A the subject is required to draw lines connecting randomly distributed numbered circles in ascending order 1 to 25. Part B, there are numbers (1-13) alternating with letters (A-L) and the task is to draw lines from a number to a letter to a number (1-A-2-B-3-C etc.) in ascending order. Separate scores for the time required to complete the task are recorded for parts A and B.

The Trail Making Test requires attention, alertness, and visuomotor tracking. Part A is considered to be more dependent upon on motor performance. Part B requires more complex mental processing since part B requires mental flexibility in order to shift between number and letters. The Trail Making Test is sensitive for motor slowing deficits and also frontal lobe damage as subjects are required to plan and inhibit responses as they alternate between numbers and letters (Lezak, 1995). Performance on the Trail Making Test is impaired in HIV patients particularly in those patients diagnosed with AIDS (Heaton et al., 1995). Both Trails A and B are sensitive to the effects of fatigue in other neuroimmunological disorders (Ray et al., 1993; Michiels et al., 1996).
Executive Function

Wisconsin Card Sorting Test:

During the Wisconsin Card Sorting Test (Heaton et al., 1993) the subject holds a deck of 64 cards each imprinted with a unique combination of symbols that can vary in color, form, and number of symbols. The subject is to match the cards one at a time to 4 key cards that are placed in front of the subject. Matching is done by following a rule (match cards according to the color of the symbols) that is learned by the responses of "right" or "wrong" given by the tester. After 10 successful matches the feature to which the cards is matched is changed (match cards according to form of the symbol) without the subject's knowledge. The subject must again learn the new rule based upon the right and wrong responses of the tester. This continues until there are 10 consecutive matches for 6 different rules or categories. The number of categories completed, number of cards used, number of errors, and the type of errors are recorded.

The Wisconsin Card Sorting Test measures executive function and has been shown to be sensitive to frontal lobe damage particularly lesions affecting the dorsolateral prefrontal cortex (DLPFC) (Milner, 1963). Patients with damage to the DLPFC obtain fewer categories than patients with lesions in other cortical areas. This is thought to be associated with difficulty in forming abstract concepts. They also have more perseverative errors as they continue to respond by placing the stimulus cards based on a previously learned conceptual rule, even when examiner feedback
suggests that they should shift to a new alternative (Lezak, 1995). This inability to shift to another set of conceptual information is thought to represent attention dysfunction (Mirsky et al., 1991). An increased number of perseverative errors on the Wisconsin Card Sorting Test appears in the latter stages of HIV infection, and is most often seen in patients diagnosed with AIDS (Bornstein et al., 1993a). There is little information regarding the sensitivity of the Wisconsin Card Sorting Test to the effects of fatigue.

**Information Processing Speed**

**Paced Auditory Serial Addition Test:**

Paced Auditory Serial Addition Test (PASAT) is a serial addition task used to assess the rate of information processing. The PASAT is also conceptualized as measuring sustained and divided attention since the participant must respond verbally after adding the two numbers presented, inhibit encoding of their own response while attending to the next number in the series, and do so at a predetermined pace (Spreen & Strauss, 1998).

The PASAT is a useful test in detecting closed head injury due to acceleration/deceleration forces, such as that following motor vehicle accidents. In this case the slowed information processing is thought to be due to white matter damage and subcortical damage (Roman et al., 1991). PASAT performance decreases in advanced HIV disease, group differences between asymptomatic patients and controls are not often seen indicating that information processing speed remains intact until more advanced disease stage (Bornstein
et al., 1993a). PASAT performance is sensitive to the effects of fatigue in MS patients and CFS patients (Deluca et al., 1997).

**Verbal Memory**

Selective Reminding Test:

The Selective Reminding Test (SRT) (Buschke, 1973) involves reading the participant a list of words and then having them recall as many words as possible. Each subsequent learning trial involves the selective presentation of only those items that were not recalled on the immediately preceding trial. By measuring recall of items which are not presented on a given trial, this test distinguishes between long term storage and short term storage.

The SRT is associated with learning and memory deficits associated with mild head injury (Lezak, 1995). Previous research employing the SRT has found that verbal memory deficits occur early in the course of HIV infection and may become more prevalent as disease progression occurs (Bornstein et al., 1993a). A study involving MS patients, CFS patients and controls subjects was unable to show any group differences on SRT performance (Krupp et al., 1994). However, another study comparing CFS patients to controls was able to demonstrate group differences on several measures of the SRT (Michiels et al., 1996).

**Verbal Fluency**

The Letter Fluency task requires the participant to say, within one minute, all the words that they can think of that begin with the
letter "A". This is repeated for the letters "F" and "S" and the total number of words is recorded. A similar regimen is used in the Semantic Fluency task except that participants are required to name as many items that belong to a given semantic category (e.g. "animals", "fruits", etc.). Following brain injury, many patients experience changes in the speed and ease of verbal production. Impaired verbal fluency is often seen in cortical aphasic disorders but can also be seen in a variety of other disorders. PET imaging studies have shown that both frontal and temporal regions participate in a system that produces verbal fluency. However, impaired verbal fluency is most often associated with frontal lobe damage particularly on the left side (Lezak, 1995). Impairment in verbal fluency is not seen usually seen in HIV patients except in those AIDS patients with extensive cognitive impairment. Several studies have found that verbal fluency remains intact across the stages of HIV disease (Bornstein et al., 1993a; Heaton et al., 1995). Verbal fluency performance is not decreased in MS patients with fatigue (Krupp et al., 1994).

Motor Ability

Grooved Pegboard:

The Grooved Pegboard (Klove, 1963) consists of a small board containing a 5 by 5 set of slotted holes. Participants are instructed to place 25 small metal pegs into the 25 holes. All pegs are alike and have a ridge along one side which corresponds to a randomly positioned slot in each hole. Participants must rotate each peg to
match each hole. The task is performed with the dominant hand and then the nondominant hand. The total time for each hand is recorded.

The Grooved Pegboard is one the most sensitive tests for detecting mild cognitive impairment in HIV infection. Differences in Grooved Pegboard performance are seen between controls and HIV positive patients. In addition, this test is able to demonstrate differences in motor ability between HIV disease stage groups (Bornstein et al., 1993a; Heaton et al., 1995).

Reaction Time

The participant is told to press a lever as soon a target stimulus (red light) is presented. A warning stimulus 1 to 3 seconds prior to the onset of the red light is given in order to prepare and orient the participant. Simple reaction time is the amount of time between onset of the target stimulus and the lever press. Simple reaction time for both the preferred and nonpreferred hands was tested.

Choice reaction time was tested for only the preferred hand. Choice reaction time involves the participant being instructed to respond to one target stimulus (e.g., red light) and not to respond to other stimuli (e.g., blue or green lights). A warning stimulus is given preceding the presentation of the target stimulus.

As summarized in the introduction reaction time is commonly impaired in HIV patients. The simple and choice reaction time paradigms employed in this study are consistent with
recommendations set forth to detect cognitive dysfunction in HIV disease (Butters et al., 1990). Multiple sclerosis patients perform less well than controls on both simple and choice reaction time tasks. However, those MS patients complaining of fatigue do not perform any worse than those MS patients not complaining of fatigue (Jennekens-Schinkel et al., 1988). Other studies involving CFS patients indicate that both simple and choice reaction time may be slowed due to fatigue (Marshall et al., 1996).

Fatigue measurement

Along with the administration of the neuropsychological test battery a self report questionnaire was given to assess the degree to which subjects experienced many symptoms commonly found in HIV infection. This questionnaire included an item regarding the presence and duration of fatigue. The item ranks fatigue duration from 0 (never) to 6 (more than one year). The item did not incorporate a measure of symptom severity. Scores of 1 to 6 were collapsed to form a single group with fatigue; with scores of 0 representing the no fatigue group.

Depression measurement

The Beck Depression Inventory (BDI) (Beck et al., 1961) was completed along with the neuropsychological test battery. The Beck Depression Inventory is a 21 item scale in which each item is concerned with a particular symptom of depression. Each item contains four statements that are graded in terms of the severity of
the symptom of depression under consideration. The scores range from 0 representing the absence of that symptom to 3 for the most severe rating of that symptom. The Beck Depression Inventory total score is the sum of all statements endorsed by the patient. The BDI contains items that reflect both the somatic and affective components of depression. Items 1 through 13 can be totaled to provide a measure of affective depression severity, while items 14 through 21 reflect the somatic symptoms of depression. Item 13 reflects difficulty in decision making and therefore could be confounded with neuropsychological dysfunction of HIV disease. Therefore, item 13 was included as part of the somatic symptoms subscale of the BDI.

In one study that used a total Beck Depression Inventory score of 15 as a cutoff for depression, 55% of an HIV positive sample was classified as depressed. When only the affective subscale was examined only 34% of the HIV positive sample was classified as depressed (Kalichman et al., 1995). An item by item analysis of the BDI indicated that HIV patients are more likely to endorse the somatic symptoms of depression compared to controls. In contrast, the HIV positive patients were not more likely to endorse the affective symptoms of depression than controls (Harker et al., 1995). Symptomatic HIV patients have higher mean scores of somatic depression compared to asymptomatic HIV patients or seronegative controls but no HIV group differences are seen on the affective component of the BDI (Poutiainen, 1995).
Procedure

The neuropsychological battery, depression scale and fatigue measure were administered by trained research assistants using standardized procedures. These measures were part of a larger research protocol that took nearly eight hours to complete. All statistical analyses were completed using the SPSS 7.0 statistical software package.

Results

Demographics

The asymptomatic and symptomatic subjects were divided into fatigue and no fatigue groups based on self-reported fatigue. Fatigue was reported in 57.5% and 68.9% of the asymptomatic and symptomatic HIV positive groups, respectively, [\(X^2 (1, N=155)=2.9, p=.088\)].

For those subjects suffering fatigue the duration of fatigue for the asymptomatic and symptomatic groups was similar with 63.1% of the asymptomatic subjects and 69.8% of symptomatic subjects indicating that they had experienced fatigue for 6 months or longer [\(X^2 (5, N=99)=5.63, p=.344\)]. The percentage of patients classified as AIDS was approximately the same between the symptomatic patients with fatigue (54.5%) and without fatigue (64.1%), [\(X^2 (1, N=75)=.61, p=.44\)].

The demographic variables and immune status measures were subjected to 2 X 2 Multivariate Analysis of Variance (MANOVA)
having two levels of Stage (asymptomatic or symptomatic) and two levels of Fatigue (no or yes). Table 2 describes the demographic characteristics and immune status of the HIV positive groups with and without fatigue. There was a trend for a significant Stage by Fatigue interaction for the Beck Depression Inventory somatic subscale \( F(1, 151) = 2.97, p = .087 \), such that those symptomatic patients with fatigue had higher somatic depression scores compared to the other three groups. As seen in Table 2 there were no other significant Stage by Fatigue Interactions \( p > .05 \).

There was a significant main effect for CD4 \( F(1, 151) = 93.6, p < .001 \) and CD4 percent \( F(1, 151) = 66.2, p < .001 \) indicating that the asymptomatic patients had higher CD4 and CD4 percent than the symptomatic patients. There were no Stage main effects for age, education, or depression. There were no significant main effects for Fatigue in terms of age, education, or immune status. A significant main effect for Fatigue was found for somatic depression \( F(1, 151) = 12.9.4, p < .001 \), affective depression \( F(1, 151) = 40.5, p < .001 \), and total BDI \( F(1, 151) = 24.6, p < .001 \) such that those HIV patients with fatigue had higher depression.
<table>
<thead>
<tr>
<th></th>
<th>Asymptomatic F-</th>
<th>Asymptomatic F+</th>
<th>Symptomatic F-</th>
<th>Symptomatic F+</th>
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<tbody>
<tr>
<td></td>
<td>(n=34)</td>
<td>(n=46)</td>
<td>(n=22)</td>
<td>(n=53)</td>
</tr>
<tr>
<td>Age(yr.)</td>
<td>32.7</td>
<td>33.2</td>
<td>33.0</td>
<td>35.1</td>
</tr>
<tr>
<td></td>
<td>(6.8)</td>
<td>(7.3)</td>
<td>(8.7)</td>
<td>(6.7)</td>
</tr>
<tr>
<td>Edu.(yr.)</td>
<td>13.8</td>
<td>13.7</td>
<td>14.3</td>
<td>14.3</td>
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<tr>
<td></td>
<td>(2.6)</td>
<td>(2.2)</td>
<td>(2.1)</td>
<td>(2.5)</td>
</tr>
<tr>
<td>BDI Aff.</td>
<td>5.1</td>
<td>8.2</td>
<td>3.6</td>
<td>7.0</td>
</tr>
<tr>
<td></td>
<td>(4.0)</td>
<td>(6.2)</td>
<td>(5.2)</td>
<td>(5.4)</td>
</tr>
<tr>
<td>BDI Som.</td>
<td>2.6</td>
<td>4.6</td>
<td>2.2</td>
<td>5.7</td>
</tr>
<tr>
<td></td>
<td>(2.0)</td>
<td>(2.8)</td>
<td>(2.5)</td>
<td>(2.7)</td>
</tr>
<tr>
<td>BDI Total</td>
<td>7.7</td>
<td>12.9</td>
<td>5.8</td>
<td>12.8</td>
</tr>
<tr>
<td></td>
<td>(5.1)</td>
<td>(8.4)</td>
<td>(7.3)</td>
<td>(7.1)</td>
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<tr>
<td>CD4#</td>
<td>562</td>
<td>532</td>
<td>286</td>
<td>196</td>
</tr>
<tr>
<td></td>
<td>(201)</td>
<td>(250)</td>
<td>(300)</td>
<td>(161)</td>
</tr>
<tr>
<td>CD4%</td>
<td>29.5</td>
<td>27.2</td>
<td>13.4</td>
<td>15.1</td>
</tr>
<tr>
<td></td>
<td>(7.1)</td>
<td>(8.4)</td>
<td>(10.2)</td>
<td>(8.9)</td>
</tr>
</tbody>
</table>

BDI aff.=Beck Depression inventory affective subscale; BDI Som.=Beck Depression inventory affective subscale; CD4# = CD4 cell count (cells/mm³); CD4% = CD4 cell as a percentage of total lymphocytes

Table 2. Demographic characteristics and immune status for the asymptomatic and symptomatic patients with and without fatigue.
Depression and Cognitive Function

Prior to investigating the effects of fatigue on cognitive function, correlational analyses were performed between the depression scores and the cognitive domain. The affective and somatic subscales of the BDI were analyzed separately so that the nature of any relationship between depression and cognitive function could be determined. As seen in Table 3, there were no significant relationships between depression and cognitive function in the asymptomatic patients.

<table>
<thead>
<tr>
<th>Variable</th>
<th>BDI:Total</th>
<th>BDI:Somatic</th>
<th>BDI:Affective</th>
</tr>
</thead>
<tbody>
<tr>
<td>Attention</td>
<td>-.152</td>
<td>-.129</td>
<td>-.160</td>
</tr>
<tr>
<td>Executive</td>
<td>-.189</td>
<td>-.153</td>
<td>-.185</td>
</tr>
<tr>
<td>Speed</td>
<td>-.161</td>
<td>-.099</td>
<td>-.173</td>
</tr>
<tr>
<td>Verbal Memory</td>
<td>-.036</td>
<td>-.017</td>
<td>-.057</td>
</tr>
<tr>
<td>Verbal Fluency</td>
<td>-.065</td>
<td>-.038</td>
<td>-.071</td>
</tr>
<tr>
<td>Motor</td>
<td>.070</td>
<td>.061</td>
<td>.067</td>
</tr>
<tr>
<td>Reaction time</td>
<td>.015</td>
<td>-.064</td>
<td>.051</td>
</tr>
<tr>
<td><strong>BDI = Beck Depression Inventory; n=80</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 3. Correlations between cognitive domain scores and depression for the asymptomatic patients (r values).

However, Table 4 shows there were significant relationships between total BDI levels and reaction time and speed of information...
processing performance but these relationships appear to be due to the somatic symptoms of depression. Significant negative relationships between the somatic symptoms of depression and the cognitive domains of verbal memory, speed of information processing and reaction time were observed. Negative relationships between affective depression and cognitive function were observed but they did not reach statistical significance.

<table>
<thead>
<tr>
<th>Variable</th>
<th>BDI:Total</th>
<th>BDI:Somatic</th>
<th>BDI:Affective</th>
</tr>
</thead>
<tbody>
<tr>
<td>Attention</td>
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<td>-.211</td>
<td>-.093</td>
</tr>
<tr>
<td>Executive</td>
<td>-.164</td>
<td>-.157</td>
<td>-.141</td>
</tr>
<tr>
<td>Speed</td>
<td>-.236*</td>
<td>-.287*</td>
<td>-.171</td>
</tr>
<tr>
<td>Verbal Memory</td>
<td>-.217</td>
<td>-.322**</td>
<td>-.125</td>
</tr>
<tr>
<td>Verbal Fluency</td>
<td>-.157</td>
<td>-.220</td>
<td>-.098</td>
</tr>
<tr>
<td>Motor</td>
<td>-.201</td>
<td>-.194</td>
<td>-.174</td>
</tr>
<tr>
<td>Reaction Time</td>
<td>-.265*</td>
<td>-.261*</td>
<td>-.225</td>
</tr>
</tbody>
</table>

BDI = Beck Depression Inventory; n=75 *= p <.05 ; **= p <.01

Table 4. Correlations between cognitive domain scores and depression for the symptomatic patients (r values).

Fatigue and Cognitive Function

The neuropsychological battery listed in Table 1 yields a large number of individual raw test scores. As described above, the tests have been grouped into domains of cognitive function. The raw test scores were transformed to T scores (mean = 50, SD = 10) based
upon the mean performance of the HIV negative control group. These T scores were then averaged to derive a mean T score for each domain of cognitive function. Prior to the T score transformation it was determined that the control group did not differ from the HIV patients groups in terms of age or education. Furthermore, preliminary investigation found that there was no difference in cognitive function between those control subjects with and without fatigue. Therefore, in order to simplify data analysis, the entire control group was used for T score transformation. The T scores were used in subsequent statistical analyses in order to investigate the effects of fatigue on cognitive function in HIV infection.

To examine the effects of fatigue on cognitive function in HIV infection a 2 (Stage) X 2 (Fatigue) MANCOVA was conducted on the cognitive domain mean T scores controlling for total BDI. Analysis of the simple main effects were conducted to determine the group differences when any significant Stage by Fatigue interactions were found. In this case the criteria for significance was set at a more conservative level of p < .0167 in order to ensure that the overall probability of making a Type 1 error remained at .05.

A significant Stage by Fatigue multivariate interaction was observed [F (7, 144) = 3.01, p = .006]. Univariate analyses revealed a significant Stage by Fatigue interaction for several cognitive domains (Table 5). These domains were attention, executive function, speed of information processing, motor ability, reaction time and there was also a trend for an interaction for the verbal
memory domain. There was no significant interaction for verbal fluency. The interactions are represented in Figures 1 through 7 and the results of analysis of the simple main effects are presented in Table 5.

Figure 1 shows that the symptomatic subjects with fatigue had significantly lower Mean T scores for attention compared to the asymptomatic without fatigue group \[t(85) = 3.57, p < .001\], asymptomatic with fatigue group \[t(97) = 2.78, p < .01\] and symptomatic without fatigue group \[t(73) = 4.15, p < .001\]. A similar pattern of performance among the groups was seen for executive function (Figure 2) where the symptomatic subjects with fatigue had significantly lower mean T scores compared to the symptomatic patients without fatigue \[t(73) = 2.65, p < .01\] and asymptomatic patients with fatigue \[t(97) = 2.68, p < .01\]. There was also a trend for the symptomatic patients with fatigue to perform worse than the asymptomatic patients without fatigue on executive function \[t(85) = 1.92, p = .058\].

Figure 3 illustrates speed of information processing was significantly lower in the symptomatic with fatigue group compared to the asymptomatic without fatigue group \[t(85) = 2.84, p < .01\], asymptomatic with fatigue group \[t(97) = 3.55, p = .001\] and symptomatic without fatigue group \[t(73) = 3.04, p < .01\]. Figure 4 demonstrates that while the Stage by Fatigue interaction approached significance there was only one significant comparison, in which the symptomatic with fatigue group performed worse on the verbal memory domain compared to the symptomatic subjects.
without fatigue \([t (73)= 3.04, p = .015]\). In addition, the comparison between the symptomatic patients with fatigue and the asymptomatic patient without fatigue \([t (97)= 2.19, p= .031]\) approached significance.

Figure 5 shows that motor ability was significantly worse in symptomatic subjects with fatigue compared to the symptomatic subjects without fatigue \([t (73)= 2.48, p = .016]\). In addition, the comparison between the symptomatic patients with fatigue and the asymptomatic patient with fatigue \([t (97)= 2.21, p= .029]\) approached significance. Figure 6 demonstrates that the symptomatic subjects with fatigue performed worse in terms of reaction time performance than the symptomatic patients without fatigue \([t (73)= 4.22, p < .001]\). However, contrary to expectations the symptomatic patients without fatigue had significantly higher mean reaction time mean T scores than the asymptomatic patients with \([t (66)= 2.95, p < .01]\) and without fatigue \([t (54)= 3.32, p < .01]\).
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* p values represent the level of significance for the Stage by Fatigue Interactions
  a= symF+ < asymF-, asymF+, symF-
  b= symF+ < asymF+, symF-
  c= symF+ < symF-
  d= symF- > asymF-, asymF+, symF+

Table 5. Cognitive Domain Scores for the four subject groups

71
Figure 1. Attention as a function of Stage and Fatigue

Figure 2. Executive Function as a function of Stage and Fatigue
Figure 3. Speed of information processing as a function of Stage and Fatigue

Figure 4. Verbal Memory as a function of Stage and Fatigue
Figure 5. Motor Ability as a function of Stage and Fatigue

Figure 6. Reaction Time as a function of Stage and Fatigue
There was no significant main effect for Stage \[F(7,144)=1.37, p=.219\]. There was a trend for a significant main effect for Fatigue \[F(7,144)=2.13, p=.057\], with univariate analyses revealing a significant main effect for the domains of attention \[F(1,150)=10.4, p<.01\] and reaction time \[F(1,150)=6.6, p<.01\].

Neuropathology and cognitive dysfunction can occur in only a subgroup of patients which may account for the group mean differences. Therefore, the prevalence of cognitive impairment within the fatigue and no fatigue groups was assessed. By determining the prevalence of impairment across domains of
cognitive function it may be possible to determine which areas of neuropsychological function are most susceptible to fatigue.

<table>
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<td>.859</td>
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Table 6. Prevalence of cognitive impairment for the asymptomatic patients with and without fatigue (Percent impaired, criterion for impairment = 1 s.d. below control group mean).

The criteria for impairment were based upon the recommendations for the diagnosis of mild neurocognitive disorder (MCD) (Atkinson & Grant, 1994). Similar to the MCD criteria, impairment on any cognitive domain was defined as 1 standard deviation below the mean of the seronegative control group. In order to meet criteria for being diagnosed with overall cognitive
impairment patients had to demonstrate impairment on at least two neuropsychological domains. Chi Square analyses were performed to determine if there were differences in the prevalence of cognitive impairment on the basis of fatigue.

Table 6 shows that as expected there was no association between cognitive impairment and fatigue in the asymptomatic patients. This was true for the overall rating of cognitive impairment and the seven separate domains of cognitive function. In contrast, Table 7 shows that for the symptomatic patients, fatigue was associated with a higher rate of impairment in terms of overall cognitive function and in most of the individual cognitive domains. There were few patients without fatigue that were impaired in both the asymptomatic and symptomatic groups.

Those symptomatic patients with fatigue (64.2%) were over three times as likely to be impaired compared to symptomatic subjects without fatigue (18.2%) \( (X^2 = 13.1, p < .001) \). Furthermore, the symptomatic patients with fatigue showed significantly higher rates of impairment for five out of the seven cognitive domains in comparison to the symptomatic patients without fatigue. For most of the cognitive domains approximately one-quarter or more of the symptomatic subjects with fatigue met criteria for impairment. The
highest rate of impairment was found on the attention domain
where nearly 45 percent of those symptomatic subjects with fatigue
were rated as impaired. This represented over a threefold increase
in impairment compared to those symptomatic patients without
fatigue. In comparison with the asymptomatic subjects, the rates of
impairment for the symptomatic patients without fatigue were
about the same, suggesting that those symptomatic patients without
fatigue are spared from the cognitive impairment due to latter stage
HIV disease.

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<td>10.7</td>
<td>.001</td>
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Table 7. Prevalence of cognitive impairment for the symptomatic
patients with and without fatigue (Percent impaired, criterion for
impairment = 1 s.d. below control group mean).
Duration of Fatigue and Cognitive Function

It is possible that those patients who have suffered fatigue for longer periods of time may not be able to escape the fatigue through adjustments in lifestyle or coping mechanisms. One explanation in this case, may be that the fatigue is due to the biological or neurological consequences of HIV and possibly be related to cognitive dysfunction. Nonparametric analyses were performed in order to determine if there was any relationship between fatigue duration and cognitive function. The analyses revealed that fatigue duration was not related to cognitive performance for the asymptomatic [$X^2 (5, N= 46), p> .05$] or symptomatic [$X^2 (5, N=53), p> .05$] patients on any of the seven domains of cognitive function.

Discussion

Fatigue is a common symptom in both asymptomatic and symptomatic HIV patients. The prevalence of fatigue within the asymptomatic patients is similar to that seen in outpatients from a family practice clinic, in which 58 percent of the patients reported fatigue. Similar to the current study, the family practice patients were only asked about the occurrence of fatigue (Lees-Haley, 1993). The prevalence of fatigue in the symptomatic HIV patients is similar to the prevalence of fatigue seen in MS patients, with over three quarters of MS patients suffering from fatigue (Krupp et al., 1988).
The prevalence of fatigue in this HIV sample is similar to other studies investigating fatigue in HIV disease. Most studies find that about two-thirds of symptomatic patients report fatigue (Heaton et al. 1995; Whalen et al. 1994). In comparison to the current study, there have been previous reports of less fatigue within asymptomatic HIV patients (Hoover et al., 1993; Darko et al., 1992). For example, when asked "is fatigue a problem for you", 89 percent of asymptomatic patients replied "never or sometimes" while only 11 percent replied "often or always". For the symptomatic patients, 57 percent reported that fatigue was "often or always" a problem (Darko et al., 1992). In another study, nine percent of asymptomatic patients reported fatigue that was defined as persistent and lasting for two or more weeks, compared to only 6 percent of controls. (Hoover et al., 1993).

These studies indicate that the method in which fatigue is assessed is important in determining the prevalence of fatigue. The questionnaire used in this study did not give a definition for fatigue or qualify the criteria for being fatigued in terms of severity, persistence or impact on daily functioning. This may explain the difference in prevalence rates between this study and other studies reporting the prevalence of fatigue in HIV patients.

**Depression**

As expected, depression was higher in those patients reporting fatigue for both the asymptomatic and symptomatic patients.
This study also found a trend for the somatic symptoms of depression to be higher in the symptomatic patients with fatigue than the other three groups. This finding is consistent with previous research in which the somatic symptoms of depression had a stronger relationship with fatigue, than did the affective symptoms of depression, especially within those patients in the latter stages of HIV disease (Perkins et al., 1995). This suggests that higher scores on the somatic subscale of the BDI may be triggered by the course of HIV disease.

Consistent with previous research (Harker et al., 1995; Poutiainen, 1995), the current study found that depression was not related to cognitive function within the asymptomatic HIV patients. For the symptomatic patients, there was no significant relationship between the affective symptoms of depression and cognitive function. This suggests that psychological depression is unrelated to cognitive performance in symptomatic HIV disease. However, there were weak inverse relationships between somatic depression and several cognitive domains. This finding is consistent with another research study in which no significant correlations were obtained between neuropsychological tests and the affective component of the BDI. Although a few neuropsychological tests had modest correlations with the total BDI and the somatic subscale (Harker et al., 1995). The BDI somatic subscale includes items related to appetite, fatigue, work performance, and decision making ability. These symptoms have all been hypothesized to be the result of HIV's effects on the brain (Grant & Martin, 1994; Merrill & Chen,
Therefore, the significant relationships between depression and cognitive function should be viewed with some caution. Furthermore, this suggests that some caution is warranted in using depression scores as a covariate when investigating cognitive function in HIV disease. By covarying total depression, including the somatic component, investigators may be removing an important portion of the effect that they want to measure. An alternative approach would be to just covary for the affective symptoms of depression. Post hoc analyses were performed to determine if covarying for only the affective symptoms of depression would appreciably change the significant effects of fatigue on cognitive function. The analyses revealed that there was no major difference in the findings expect that the probability for making a type 1 error was decreased for most of the cognitive domains. This suggests that the somatic symptoms of depression accounted for a small portion of the effect of fatigue on cognitive function.

Fatigue and Cognitive Function

As hypothesized fatigue is associated with cognitive impairment in the symptomatic HIV patients but not the asymptomatic HIV patients. This indicates that self reported fatigue within the symptomatic patients may be a sign of brain pathology that is manifested by poorer neuropsychological test performance. Cognitive impairment within the symptomatic subjects without fatigue was similar to the rate of impairment in the asymptomatic groups, suggesting that for those subjects with advanced HIV...
disease the absence of fatigue may be an indicator of no further neurological involvement.

The results indicate that group mean comparisons and use of impairment ratings are similar in sensitivity in detecting the negative effects of fatigue on cognitive function. Both group mean comparisons and impairment rating analyses show that fatigue in symptomatic HIV patients is associated with cognitive impairment across a broad range of subcortical cognitive domains. Fatigue was associated with cognitive impairment in nearly two-thirds of the symptomatic HIV patients. The results suggest that fatigue is not related to any one subcortical cognitive domain. Instead, the results suggest that the likelihood of finding an association between fatigue and cognitive function for a particular domain of cognitive function is to some extent based upon the prevalence of impairment in HIV disease. For example, attention impairment is one of the most common cognitive deficits in HIV disease (Heaton et al., 1995) and this study found that attention impairment is the most prevalent cognitive abnormality associated with fatigue. This is consistent with research in other neuroimmunological diseases in which attention dysfunction is the most common cognitive abnormality associated with fatigue (Bruno et al., 1993; Cohen, 1993; Krupp et al., 1994).

In contrast to the deleterious effects of fatigue in the symptomatic HIV patients, there was no cognitive impairment associated with fatigue in the asymptomatic HIV patients. There are several possible explanations for the different effects of fatigue on
cognitive between the asymptomatic and symptomatic groups. The progression of neuropathology that is seen along with advancing HIV disease may explain the difference in the effects of fatigue on cognitive function in HIV patients. If fatigue is caused by neuropathology within the asymptomatic and symptomatic patients, then the neuropathology within the asymptomatic patients may not be sufficient to cause cognitive impairment but severe enough to produce fatigue. It may be that the neuropsychological test battery in the current study was not difficult enough to detect the subtle cognitive impairment due to fatigue. Studies employing experimental as well as standard neuropsychological tests have found that cognitive impairment can be demonstrated on the more demanding experimental tasks even when there is no impairment evident on standard neuropsychological tests (Martin et al., 1992a, c).

Neuroimaging more frequently detects brain abnormalities in asymptomatic patients in comparison to standard neuropsychological testing (Tran Dinh et al., 1990). It would be interesting to know if fatigue in asymptomatic HIV patients is associated with neuroimaging abnormalities. If such an association was found, and fatigue was not associated with cognitive impairment, this would suggest that fatigue in the asymptomatic stages of HIV is associated with brain abnormalities that standard neuropsychological testing is not able to detect. This would indicate that there is a continuum with regard to the association between fatigue and neurological abnormalities. Fatigue in asymptomatic
HIV infection may be associated with neurological abnormalities that only the most sensitive techniques can detect, while an association between fatigue and neurological abnormalities may be more easily detected in the advanced stages of HIV disease.

Differences in fatigue severity may also explain the different findings between the asymptomatic and symptomatic groups. The nonspecific nature of the fatigue questionnaire used in the current study may have selected patients with minimal fatigue as well as patients with more severe fatigue. Research into post polio syndrome (Bruno et al., 1995) indicates that severe fatigue is associated with cognitive impairment while minimal or mild fatigue has no effect on cognitive function. Furthermore, PET abnormalities in MS patients are associated with higher Fatigue Severity Scale scores (Roelcke, et al., 1997). A similar situation may exist in the current study whereby the asymptomatic patients have relatively mild fatigue in comparison to the more severe fatigue experienced by the symptomatic patients.

Several studies have shown that there is a better association between self reported mental fatigue and actual cognitive performance than there is with general or physical fatigue (Bruno et al., 1994; Cohen & Fischer, 1988; Greisler, 1996; Schwartz et al., 1996). It is possible that the nature of the fatigue reported by the asymptomatic and symptomatic groups differ. The results suggest that the asymptomatic patient may suffer from fatigue that is related to general well being. While the fatigue reported by the
symptomatic group may include a cognitive component in addition to general fatigue.

Contrary to expectations, the symptomatic without fatigue group did significantly better than the other three groups on reaction time. It was expected that the symptomatic without fatigue group would do worse, not better, than the two asymptomatic groups. This result in the context of the other significant findings, reinforces the idea that those symptomatic subjects that do not report fatigue are spared from cognitive dysfunction and therefore may perform better than the other HIV positive patients. Although, this unexpected finding may be partially explained by disease stage group differences (see below).

Unexpectedly, there were few main effects for disease stage. Several previous studies have shown poorer performance in HIV positive patients diagnosed with AIDS compared to asymptomatic patients. Relatively few studies show differences between group B patients and group A patients (Heaton et al., 1995; Bornstein et al., 1993a). Groups B and C patients were combined to form a single symptomatic group, this may have prevented the cognitive deterioration between asymptomatic patients and AIDS patients from being detected in this study. Post hoc analyses comparing groups A, B, and C were done in order to investigate this possibility. The analyses revealed significant differences between groups A and C on the attention, verbal memory, and speed of information processing domains of cognitive function. Group B performed better than groups A and C on reaction time. This may explain the
unexpected finding of the symptomatic without fatigue group performing better than both asymptomatic groups. The post hoc analyses suggest that the unexpected result may be due to disease stage differences and not due to fatigue.

**Fatigue and Immune Status**

Immune status was not different between those groups with and without fatigue. This result is similar to a study involving asymptomatic HIV patients that found no relationship between fatigue and immune status (Perkins et al., 1995). However, other studies that have shown that fatigue is associated with lower immune status (Darko et al., 1992; Walker et al., 1997). Several differences exist between the current study and these previous studies. First, the relationship between fatigue and immune status was investigated across all stages of HIV disease in these other studies. Therefore, the relationship between fatigue and declining immune status may be the result of fatigue increasing with disease progression while immune status declines with disease progression. In contrast, this study investigated the association of fatigue and immune status within the asymptomatic and symptomatic HIV patients separately. Second, the previous studies assessed the severity and persistence of fatigue, while this study only measured the presence of fatigue.
Summary

In summary, this study indicates that fatigue negatively influences cognitive in symptomatic HIV infection and this effect cannot be attributed to depression. The adverse effects of fatigue are observed in a broad range of cognitive domains. These findings are consistent with previous research involving post-polio syndrome, multiple sclerosis, and chronic fatigue syndrome in which fatigue was associated with a pattern of cognitive deficits suggesting subcortical dysfunction. Further study regarding fatigue severity and the multidimensional nature of fatigue may provide further insight into the relationship between fatigue and cognitive function.
CHAPTER 3

STUDY 2

This second study is meant to be a replication and extension of the first study, in which fatigue was associated with cognitive dysfunction. This study will employ a more comprehensive battery of neuropsychological tests which probes for multiple components of attention, in addition to those domains of cognition that were assessed in the first study. Self reported fatigue will be measured from the perspective that fatigue is a multidimensional phenomenon including cognitive and physical components. It will also be determined if fatigue severity within those patients reporting fatigue is related to cognitive dysfunction. The overlap and differentiation between fatigue and depression will also be investigated.

Hypotheses

Hypothesis 1: Effects of Fatigue on Cognitive Function

Based upon the results of the first study it is expected that those symptomatic subjects with fatigue will perform worse on several domains of cognitive function compared to the symptomatic
patients without fatigue. Similar to study 1, the detrimental effects of fatigue are expected to span across several domains of subcortical cognitive function.

This study will divide attention into four different components in order to determine if fatigue is associated with impairment in all components of attention. Fatigue is hypothesized to be related to HIV neuropathology. Therefore, the negative effects of fatigue on attention are expected in those domains in which the underlying neuroanatomy is known to be damaged in HIV disease. Mirsky's (Mirsly et al. 1991) model of attention contends that the basal ganglia and subcortical frontal lobe circuits are important for the focus-execute and shift domains of attention. Neuroimaging studies in HIV disease have shown morphological and functional deficits in these two neuroanatomical regions (Rottenberg et al., 1987; van Gorp et al., 1992). Therefore, fatigue is expected to be associated with lower performance in the focus-execute and shift/executive function domains of attention.

The encode domain of attention is associated with the functional integrity of the temporal lobes (Mirsky et al., 1991). Abnormalities are observed less frequently in the temporal lobes compared to the basal ganglia and subcortical white matter (Bencherif, & Rottenberg, 1998). The encode domain of attention is expected to be lower in those symptomatic HIV patients with fatigue relative to those symptomatic HIV patients without fatigue. However, the group mean differences may not be as large, compared to the differences seen in the two previously mentioned
attention domains. The brainstem reticular activating system is involved in the ability to sustain attention (Mirsky et al., 1991). There are relatively few abnormalities within the brainstem of HIV infected patients without dementia (Rottenberg et al., 1987; van Gorp et al., 1992) Therefore, the deleterious effects of fatigue are not expected in the sustain domain of attention.

Hypothesis 2: Relationship between fatigue severity and cognitive function

The results from study 1 and other research has shown that the occurrence of fatigue is associated with cognitive impairment. However, a relationship between fatigue severity and cognitive dysfunction is less consistently found (Bruno et al., 1994; Cohen & Fisher, 1988; Greisler, 1996; Schwartz et al., 1996). These studies suggest that fatigue is a multidimensional phenomenon and that the manner in which fatigue severity is assessed is important in determining if a relationship between fatigue and cognitive impairment will be found. Based upon these results it is hypothesized that complaints of cognitive fatigue, but not physical fatigue or general fatigue, will be related to cognitive dysfunction.

Hypothesis 3: Relationship between fatigue and depression

Several studies involving MS patients (Krupp et al., 1989; Moller et al., 1994; Roelcke et al., 1997), CFS patients (Jorge & Goodnick, 1997) and HIV patients (Kalichman et al., 1995) have found that fatigue can be differentiated from depression. In some
cases fatigue is related to depression, but closer analysis reveals that most often fatigue is only related to those symptoms of depression that are associated with disease and not the affective symptoms of depression. This indicates that fatigue and depression may have multiple components. A significant relationship between fatigue and total BDI is expected. However, this relationship is hypothesized to be due to the medical symptoms of advanced HIV disease in the symptomatic HIV patients. Therefore, only the somatic symptoms of depression are expected to be correlated with those aspects of fatigue reflecting physical or cognitive impairment. The affective symptoms of depression are expected to be correlated with those aspects of fatigue related to mood.

**Hypothesis 4: Relationship between fatigue and medical variables**

Fatigue is not related to CD4 cell counts in asymptomatic patients (Perkins et al., 1995) and similar results were found in study 1. Studies of CFS patients have shown that fatigue severity is related to immune activation but not the absolute number of immune cells (Barker et al., 1994). Based upon this research it is expected that fatigue will not be related to immune status, but will be associated with immune activation. Peripheral immune activation may be produced fatigue by acting on neural circuits known to be involved in arousal and attention (Hickie & Lloyd, 1995). Peripheral levels of beta2-microglobulin levels are associated with increased immune system activation and have been correlated with cognitive dysfunction (Boccellari et al., 1993 &
Furthermore, elevated cerebrospinal fluid beta2-microglobulin levels are correlated with serum beta2-microglobulin in HIV patients without dementia (McArthur et al., 1992). This suggests that peripheral beta2-microglobulin may be an indirect marker for the immune activation within the brain. Therefore, it is hypothesized that beta-2 microglobulin will be associated with fatigue.

Peripheral levels of viral load show moderate correlations with CSF HIV RNA levels. However, only CSF viral load is associated with cognitive impairment (Ellis et al., 1997; Lafeuillade et al., 1996; McArthur et al., 1997). Patients report "feeling" better as viral load decreases in response to anti-HIV medication treatment. This may occur because decreased peripheral HIV RNA levels are associated with fewer opportunistic infections and decreased levels of immune activation (Brodt et al., 1997; Collier et al., 1996). Therefore, it is hypothesized that those aspects of fatigue that are related to general well being will be correlated with peripheral viral load, while the mental component of fatigue will not be related to peripheral viral load.

**Methods**

**Subjects**

The second study was meant to be a replication and extension of the first study. Therefore, every effort was made to ensure that the subject characteristics for this study were as close as possible to the original sample. The participants were recruited from many of
the same sources used in the first study. Similar to the first study the primary resource for subject recruitment was the AIDS Clinical Trials Unit at the Ohio State University. Subjects were recruited into the study from June 1996 to March 1998. Participants knew of their HIV status prior to beginning the study.

All subjects were given written descriptions of the study and all signed informed consent agreements. The second study utilized the same exclusion criteria as the first study. The evaluation included an extensive neuropsychological assessment, psychosocial assessment and medical records review. Subjects were paid $75 for their participation in the study which took approximately eight hours to complete.

This study also employed the 1993 Centers for Disease Control revised classification system (Centers for Disease Control, 1992) for staging individuals infected with HIV. Twenty-one seronegative controls that were at risk for becoming infected with HIV were enrolled in the study. Sixty-four HIV positive individuals classified as stage B (n=17) or C (n=47) volunteered for the study. Stages B and C were combined to form a single symptomatic group that were subdivided on the basis of fatigue so that two groups were formed, symptomatic without fatigue and symptomatic with fatigue. Despite our best recruiting efforts for nearly two years, only 17 asymptomatic HIV patients volunteered for the study. As a consequence there are insufficient number of participants in the asymptomatic group to allow a full Disease Stage by Fatigue MANOVA to be conducted. Therefore, most of the analyses will
focus on the symptomatic HIV patients, other more limited analyses, involving the asymptomatic group will also be performed to the extent possible.

Medical Variables

Participants had blood drawn at the Clinical Research Center at the Ohio State University Medical Center. All specimens were labeled and transported with anonymous subject identification numbers. Medical variables included CD4/CD3, CD8/CD3 (absolute and percent of total lymphocytes), CD4/CD8 ratio, beta2-microglobulin, and viral load. Immunophenotyping was performed via flow cytometer in the Ohio State University Medical Center Cytometry Laboratory. Beta2-microglobulin was assessed via the IMx system, which is based on Microparticle Enzyme Immunoassay technology (Abbott Laboratories). Plasma HIV RNA levels were measured by reverse-transcriptase polymerase chain reaction (Roche Diagnostics) via Lab Corp. of America. The serostatus of the control subjects was tested by enzyme immunoassay and confirmed by Western blot analysis. The parent investigation did not have funding for viral load data for a majority of the data collection period. In some cases viral load information was obtained from the patient's physician. In this case the viral load information was only used if there wasn't in any change in antiretroviral medication regimen within three months of the viral load test. This was done because HIV RNA levels can change rapidly in response to treatment.
Neuropsychological Assessment

In order to assess the broad range of attentional components via neuropsychological testing the Laboratory of Psychology and Psychopathology-National Institute of Mental Health (LPP-NIMH) Attention Battery was selected (Mirsky, 1989; Mirsky et al., 1991; Mirsky et al., 1995). The LPP-NIMH Attention Battery is composed of eight tests (Digit Symbol Substitution, Stroop Color-Word Interference Test, Talland Letter Cancellation Test, Trail Making Test parts A and B, Wisconsin Card Sorting Test, Continuous Performance Test, and the Digit Span and Arithmetic subtests of the WAIS-R) measuring four different elements or domains of attention: Focus-Execute, Executive Function/Shift, Sustain, and Encode.

This particular attention battery was chosen for this study because the neuropsychological tests within the battery are widely available, extensively used, and have been shown to be sensitive to attention (Lezak, 1995). Mirsky's model incorporates findings from human and nonhuman primate research models of attention. Therefore, it incorporates research findings from clinical neuropsychological models of attention (Cohen, 1993) and empirical models of attention involving human and animal studies (Goldman-Rakic, 1995; Mesulam, 1990; Posner and Peterson, 1990) without being restricted to a particular disorder.

Based upon clinical and experimental studies, anatomical substrates for these 4 elements of attention are described (Mirsky et al., 1991). By having elements or components of attention associated with neuroanatomical regions it may be possible to infer
the functional integrity of the structures based on neuropsychological test scores. This will allow a first approximation of the underlying neuroanatomy associated with attention impairment in HIV disease.

The neuropsychological tests for this study will be reviewed in a similar manner to study 1. The domains of cognitive function and the neuropsychological tests within each domain are listed in Table 8 and will be described below. Those tests which were already described in study 1 will not be described again, instead the reader is referred to the methods section of study 1.
Attention:
1. Focus-Execute: Selecting target information and responding
   a. Stroop Interference Test (number of words)
   b. Letter Cancellation (seconds)
   c. Trail Making Tests A & B (seconds)
   d. Digit Symbol Substitution (WAIS-R scaled score)
2. Sustain: Ability to maintain focus and alertness overtime
   a. Continuous Performance Test
      i. Mean reaction time (seconds)
      ii. Number of comission errors
      iii. Response variability
3. Encode: Mental manipulation of information
   a. Arithmetic Test (WAIS-R scaled score)
   b. Digit Span (WAIS-R scaled score)
4. Executive Function/Shift: Ability to change attention focus
   a. Wisconsin Card Sorting Test
      i. Categories
      ii. Cards
      iii. Total number of errors

Information Processing Speed:
1. PASAT
   a. 2.4 number correct
   b. 2.0 number correct
   c. 1.6 number correct
   d. 1.2 number correct

Verbal Memory:
1. California Verbal Learning Test
   a. Immediate free recall List A trials 1-5
   b. Short delay free recall
   c. Long delay free recall
   d. Maximum recall List A trials 1-5

Motor Ability:
1. Grooved Peg Board
   a. Dominant (seconds)
   b. Nondominant (seconds)

Verbal Fluency:
1. Verbal Fluency (number of words)
2. Semantic Fluency (number of words)

Reaction Time:
1. Simple Dominant (milliseconds)
2. Simple Nondominant (milliseconds)
3. Choice (milliseconds)

Table 8. Cognitive domains of the neuropsychological test battery for study 2.
Focus-Execute domain of attention

According to Mirsky et al., (1991) the focus-execute domain of attention is the ability to select target information from an array for enhanced processing. This would include being able to efficiently scan stimulus material for a target and make a response quickly. The corpus striatum because of its role in modulating motor responses plays an important role in the focus-execute element of attention. The striatum is important in response selection and the appropriate timing of responses. This is particularly important in the Trail Making Test, Letter Cancellation Test, and Digit Symbol Substitution Test because patients must scan for the appropriate target and then make a motor response upon detection of the target. The striatum is connected with the parietal lobe and the ability to attend to the stimulus material is thought to resemble the ability which is lost in neglect patients.

The Stroop Color Word Interference Test, Letter Cancellation, Trail Making Test (Parts A and B), and the Digit Symbol Substitution Test are all used to probe for dysfunction within this domain of attention. These test have been used extensively in research involving MS patients and CFS patients and performance decline is related to fatigue (Krupp et al., 1994; Ray et al., 1993; Michiels et al., 1996). In regard to HIV patients, these test are common elements of neuropsychological test batteries probing for subcortical cognitive function and are sensitive to the cognitive decline associated with disease progression (Butters et al., 1990).
Stroop Interference Test:

The Stroop Interference Test (Lezak, 1995) requires the subject to first, read a list of color names, second, to name the color of the ink, third to name the color of the ink for words that spell conflicting color names (e.g., the word green printed in red ink). Each task is more difficult and therefore less words are read during the given amount of time. The number of words correctly read in the three conditions (color, word, color-word) are recorded. Among the three conditions the color-word condition is the most sensitive to attention dysfunction. Good performance requires the participant to suppress the automatic response of reading the color words and instead name the ink color the word is printed in. This requires the inhibition of the automatic response and conscious effort to attend to the color feature of the word. Errors are not counted, although they result in a slower performance since the examiner instructs the participant to repeat the item when an error is made.

Letter Cancellation:

Letter Cancellation (Diller et al., 1974) requires the subject to scan a sheet of paper in order to detect particular letters among an array of letters. The number of correct cancellations in a given amount of time is recorded. The basic version consists of six 52-character rows in which target characters are randomly interspersed approximately 18 times in each row. The participants are instructed to cancel out all of the C's and E's. The time to complete the task is recorded as well as the number of errors.
Digit Symbol Modality Test:

Digit Symbol Modality Test (Lezak, 1995) requires the subject to write symbols beneath digits in accordance with a code that is presented on the test sheet. The Digit Symbol Modality Test requires rapid processing of symbolic information and the transcription of numbers that are paired with the symbols. This test requires multiple attentional resources including visual tracking and visuospatial processing of the symbols.

Encode domain of attention

The temporal lobes contain neural systems that are involved in auditory processing, language, encoding information, memory consolidation, and emotional-motivational processing (Cohen, 1993). The auditory processing functions of the temporal lobes contributes to the proper timing and sequencing of verbal information. These functions are important when a person is called upon to repeat back digits or to make mental calculations in response to auditory information. The Arithmetic and Digit Span tests of the Wechsler Adult Intelligence Scale Revised (1981) require the registration, recall, and mental manipulation of verbal numeric information and are thought to represent the functional integrity of the temporal lobes (Mirsky, 1991). However, these two tests require working memory which is associated with frontal lobe function, suggesting that this domain of attention may not be solely dependent upon the temporal lobes (Lezak, 1995).
Arithmetic Test:

The Arithmetic WAIS-R subtest (Wechsler, 1981) requires the subject to make mental math calculations based on simple story problems read by the examiner. Poor performance on the Arithmetic Test can be the result of attention deficits and dysfunction in processing verbal information. The Arithmetic test is often thought to probe for working memory performance since participants need to hold the information long enough to perform the requisite mental operations to come up with the correct response (Lezak, 1995). The number of correct responses are converted to a scaled score based on age and education.

Digit Span:

The Digit Span Forward WAIS-R (Wechsler, 1981) subtest requires the subject to repeat progressively longer strings of single digits in the order read to the subject. The Digit Span Forward test can be performed with minimal attentional effort if the number of digits to be repeated doesn't exceed the span of short term memory (Lezak, 1995). When the number of digits is not too long the Digit Span Forward test only requires automatic language processing and therefore reasonable performance is possible in patients with severe brain damage. The Digit Span Backward WAIS-R subtest is a more sensitive measure of brain damage and attentional dysfunction than Digit Span Forward. Digit Span Backward requires a mental manipulation so that the numbers can be repeated in reverse order. Raw scores are converted to scaled scores based on age and education and are combined to form a single digit span
score. Poor performance on the Digit Span test occurs in the latter stages of symptomatic HIV disease (Stout et al., 1995).

**Sustain domain of attention**

The sustain element of attention represents the ability to maintain focus and alertness over time. The reticular formation is critical for the maintenance of sustained attention (Mirsky et al., 1991). The ability to sustain attention deteriorates over time in MS patients reporting fatigue (Cohen, 1993). The Continuous Performance Test has not been employed in research studies assessing attention in HIV disease, however, HIV patients do show impairment on other tasks requiring sustained attention (Butters et al., 1990).

**Continuous Performance Test:**

The Conner's Continuous Performance Test (1994) is a vigilance or attention test that is used in research and clinical settings. In clinical settings the CPT is commonly used in the diagnosis of attention deficit disorder. The CPT is administered in research applications in order to assess the participants ability to maintain attention.

Subjects are asked to watch a computer screen as a random series of letters are presented on the screen. Participants are required to press the space bar when any letter except "X" appears. A hit is defined as the number of targets (letters other than "X") the person responded to correctly. A comission is the number of times
the person responded to a nontarget ("X"). The hit reaction time is the mean response time in milliseconds for all target responses over the length of the test which lasts approximately 14 minutes.

One measure of the ability to sustain attention is the variability of responses over time. The standard deviation of the mean reaction time is a common proxy for variability of response time. The CPT calculates the standard deviation for each trial so that it can be determined if the variability increases or decreases as the participant progresses through the 14 minute task. If there is a negative slope (decreasing variability with time) then this indicates that the participant is maintaining their attention and their performance is improving as the task progresses. In contrast, if the slope is positive this indicates that the participants are showing fatigue and response variability is increasing with time (Cohen, 1993).

**Executive Function/Shift domain of attention**

The shift element of attention represents the ability to change attention focus in a flexible and adaptive manner. This would include being able to attend to one stimulus feature of an object and then attend to another aspect (Mirsky et al., 1991). The reader is referred to Study 1 were a detailed description of the Wisconsin Card Sorting Test and executive function takes place.
Verbal Memory:

The California Verbal Learning Test (CVLT) (Delis et al, 1987) is a verbal list learning task in which a shopping list of 16 words (list A) is presented for five immediate-recall trials. The list comprises four items from each of four categories. Following the five learning trials a second interference list (list B) is presented for one trial. Free and cued recall for items for list A is assessed after the presentation of list B (short delay). After a 20 minute interval of nonverbal testing free recall, cued recall, and recognition of list A is assessed (long delay).

Scoring of the CVLT allows the assessment of several different aspects of learning and memory. For example the California Verbal Learning Test (CVLT) can successfully discriminate between control subjects, patients with Alzheimer's, and patients with Huntington's disease. Furthermore, several studies using the CVLT have shown that HIV patients exhibit a subcortical learning and memory profile (Becker et al., 1995; Delis et al., 1995; Peavy et al., 1994) . HIV patients perform poorly on the long delay free recall trial but perform relatively well on the recognition trial indicating a retrieval deficit similar to that seen in Huntington's disease. Chronic fatigue syndrome patients also show a pattern of memory deficits on the CVLT that suggests subcortical cognitive dysfunction (DeLuca et al., 1994).
Measurement of Fatigue

The fatigue questionnaire used in the first study was again employed to determine if the HIV positive participants were experiencing fatigue. Fatigue severity was assessed by two self-report measures; the Fatigue Severity Scale and the Piper Fatigue Scale.

Fatigue Severity Scale:

The Fatigue Severity Scale (FSS) has been used extensively in multiple sclerosis fatigue research and assesses the impact that fatigue has on a patient's lifestyle related to physical function (Krupp et al., 1989; Moller et al., 1994; Packard et al., 1994). The FSS instructs participants to read 9 statements related to how fatigue impacts their lives and choose a number between 1 and 7 indicating how strongly they agree with the statement: 1 indicates strongly disagree and 7 indicates strongly agree. The average of the responses on the nine-item Likert scale is taken to represent how severely fatigue interferes with a person's life.

The Fatigue Severity Scale (FSS) was originally designed to measure fatigue in MS and systemic lupus erythematosus patients (SLEP) (Krupp et al., 1989). The FSS has high reliability, internal consistency, differentiates patients from controls and clinical improvement of fatigue is associated with decreases in the FSS. The FSS is weakly correlated with symptoms of depression as measured by the Center for Epidemiologic Studies Depression Scale in MS patients, SLEP patients and controls (Krupp et al., 1989). The FSS is
correlated with the BDI in MS patients however, item analysis indicates that the somatic symptoms of the BDI are responsible for the positive correlation with the FSS (Roelcke et al., 1997). Another study in which MS patients were divided into depressed and nondepressed groups found no difference between the two groups on the FSS (Moller et al., 1994). This same study showed scores on the FSS were related to hyperintense MRI abnormalities in the brainstem and midbrain.

Piper Fatigue Scale:

The Piper Fatigue Scale (PFS) (Piper et al. 1989) was designed to measure the subjective experience of fatigue in cancer patients. The PFS has been revised (Piper 1990, Libbus et al., 1995) and in its current form contains numerically scaled ("0" to "10") items along a horizontal visual analogue scale which can be used to measure several different dimensions of fatigue. Five dimensions of fatigue will be assessed for the purposes of this study. The fatigue severity dimension, measures the distress and the degree of disruption in the activities of daily living resulting from fatigue. The affective dimension assesses the emotional meaning attributed to fatigue. The mood dimension measures the symptoms or feelings of depression related to fatigue. The sensory dimension, measures the bodily sensations associated with fatigue, such as feeling weak. The cognitive dimension measures the mental aspects of self reported fatigue such as an inability to concentrate, remember or think.
clearly. There have been few studies that have looked at the relationship between PFS scores and cognitive function.

**Measurement of Depression**

The Beck Depression Inventory was employed in this study just as it was in the first study. The BDI will allow the somatic and affective dimensions of depression to be investigated.

**Procedure**

The neuropsychological battery, depression scale and fatigue measure were administered by trained research assistants using standardized procedures. These measures were part of a larger research protocol that took nearly eight hours to complete. All statistical analyses were completed using the SPSS 7.0 statistical software package.

**Results**

The presentation of the results for this study will be divided into 2 sections. Section 1 will have an extensive analysis of the association between fatigue and cognitive function in the symptomatic HIV patients. Section 2 will include a limited analysis of fatigue and cognitive function in the asymptomatic HIV patients.
Section 1: Symptomatic HIV patients

Demographics

Sixty-four stage B and C subjects met criteria for the study, and were divided into fatigue and no fatigue groups based upon the self report item regarding the occurrence and duration of fatigue. This item appears to be a reliable method in determining the occurrence and duration of self reported fatigue in HIV patients. Fatigue was reported in 70.3 percent of the symptomatic patients which is similar to the 68.9 percent that was reported by the symptomatic patients in study 1. Also, similar to the first study, 73.3 percent of those symptomatic patients with fatigue indicated that they have been experiencing fatigue for 6 months or longer. The percentage of patients classified as AIDS was approximately the same between the symptomatic patients with fatigue (75.5%) and without fatigue (68.4%), \[X^2 (1, n=64) = .349, p=.56\]. There was no difference between the two symptomatic patient groups in terms of antiretroviral medication use; 66.7% and 68.4% of the patients with and without were taking antiretroviral medications, respectively \[X^2 (1 n=64)= .019, p=>.05\].

To determine if there were any group differences Analysis of Variance was performed, and Tukey's post hoc procedure was used to make multiple comparisons. Table 9 shows the demographic characteristics for the control subjects and the two symptomatic patient groups. There were no group differences for age or education. Those symptomatic HIV patients with fatigue had
significantly higher levels of fatigue and depression compared to the symptomatic patients without fatigue and the control group. There were no differences between the control group and the symptomatic patients without fatigue in terms of depression or fatigue. Consistent with the immunopathology of HIV disease (Gupta, 1996), the control group was significantly different from the two HIV positive groups in terms of CD4, CD8, and beta2-microglobulin. There were no differences in immune status, immune activation, or peripheral HIV RNA levels between the symptomatic HIV patients with fatigue and those symptomatic HIV patients without fatigue.
<table>
<thead>
<tr>
<th></th>
<th>Control (n=21)</th>
<th>No Fatigue (n=19)</th>
<th>Fatigue (n=45)</th>
<th>F(2,82)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr.)</td>
<td>33.8(7.03)</td>
<td>34.6(8.2)</td>
<td>37.2(7.1)</td>
<td>1.8</td>
<td>.170</td>
</tr>
<tr>
<td>Education (yr.)</td>
<td>14.4(2.9)</td>
<td>14.3(3.2)</td>
<td>13.8(3.2)</td>
<td>.3</td>
<td>.729</td>
</tr>
<tr>
<td>BDI:Affective</td>
<td>4.1(3.6)</td>
<td>3.2(2.5)</td>
<td>8.6(6.2)</td>
<td>10.0</td>
<td>.00a</td>
</tr>
<tr>
<td>BDI:Somatic</td>
<td>3.5(3.4)</td>
<td>3.1(3.1)</td>
<td>6.5(3.4)</td>
<td>9.8</td>
<td>.00a</td>
</tr>
<tr>
<td>BDI:Total</td>
<td>7.7(6.55)</td>
<td>6.3(4.8)</td>
<td>14.9(8.6)</td>
<td>11.9</td>
<td>.00a</td>
</tr>
<tr>
<td>FSS Mean</td>
<td>3.3(1.2)</td>
<td>3.3(1.6)</td>
<td>5.0(1.3)</td>
<td>16.5</td>
<td>.00a</td>
</tr>
<tr>
<td>PFS Total</td>
<td>16.2(11.3)</td>
<td>13.4(9.6)</td>
<td>25.4(7.2)</td>
<td>15.2</td>
<td>.00a</td>
</tr>
<tr>
<td>CD4#</td>
<td>982(384)</td>
<td>265(200)</td>
<td>349(235)</td>
<td>42.7</td>
<td>.00b</td>
</tr>
<tr>
<td>CD4%</td>
<td>41.4(6.7)</td>
<td>17.1(11.3)</td>
<td>19.3(10.4)</td>
<td>46.6</td>
<td>.00b</td>
</tr>
<tr>
<td>CD8#</td>
<td>723(304)</td>
<td>867(518)</td>
<td>971(561)</td>
<td>1.78</td>
<td>.176</td>
</tr>
<tr>
<td>CD8%</td>
<td>30.6(7.6)</td>
<td>54.5(13.6)</td>
<td>55.3(14.2)</td>
<td>29.3</td>
<td>.00b</td>
</tr>
<tr>
<td>4/8 ratio</td>
<td>1.47(.56)</td>
<td>.36(.30)</td>
<td>.42(.39)</td>
<td>50.6</td>
<td>.00b</td>
</tr>
<tr>
<td>B2-M</td>
<td>1.43(.40)</td>
<td>2.75(1.28)</td>
<td>2.52(.942)</td>
<td>12.7</td>
<td>.00b</td>
</tr>
<tr>
<td>Viral Load</td>
<td>3.93(1.11)</td>
<td>3.97(.91)</td>
<td>.01</td>
<td>.926</td>
<td></td>
</tr>
</tbody>
</table>

a = Fatigue group differs from No Fatigue and Control groups.
b = Control group differs from Fatigue and No Fatigue groups.
B2-M = B2-microglobulin; BDI = Beck Depression Inventory; PFS = Piper Fatigue Scale; FSS = Fatigue Severity Scale

Table 9. Demographic characteristics for the control group and symptomatic HIV patients with and without fatigue.
Fatigue and Cognitive Function

Prior to investigating the effects of fatigue on cognitive function, correlational analyses were performed between the depression scores and the cognitive domain T scores. As seen in Table 10, there were very weak negative relationships between depression and cognitive function, none of these relationships were statistically significant.

<table>
<thead>
<tr>
<th>Variable</th>
<th>BDI:Total</th>
<th>BDI:Somatic</th>
<th>BDI:Affective</th>
</tr>
</thead>
<tbody>
<tr>
<td>Focus</td>
<td>-.143</td>
<td>-.183</td>
<td>-.138</td>
</tr>
<tr>
<td>Sustain</td>
<td>-.079</td>
<td>-.160</td>
<td>-.069</td>
</tr>
<tr>
<td>Encode</td>
<td>-.150</td>
<td>-.119</td>
<td>-.179</td>
</tr>
<tr>
<td>Executive/Shift</td>
<td>-.106</td>
<td>-.209</td>
<td>-.043</td>
</tr>
<tr>
<td>Speed</td>
<td>.050</td>
<td>-.016</td>
<td>.051</td>
</tr>
<tr>
<td>Verbal Memory</td>
<td>-.219</td>
<td>-.097</td>
<td>-.230</td>
</tr>
<tr>
<td>Verbal Fluency</td>
<td>-.091</td>
<td>-.121</td>
<td>-.034</td>
</tr>
<tr>
<td>Motor</td>
<td>-.057</td>
<td>-.253</td>
<td>-.139</td>
</tr>
<tr>
<td>Reaction Time</td>
<td>.008</td>
<td>-.118</td>
<td>.049</td>
</tr>
</tbody>
</table>

BDI = Beck Depression Inventory

Table 10. Correlation between cognitive domain scores and depression for the symptomatic patients (r values).

The neuropsychological battery listed in Table 8 yields a large number of individual raw test scores. Similar to the first study the
tests have been grouped into domains of cognitive function. The raw
test scores were transformed to T scores (mean = 50, SD =10) based
upon the mean performance of the HIV negative control group.
These T scores were then averaged to derive a mean T score for
each domain of cognitive function. Prior to the T score
transformation it was determined that the control group did not
differ from the two patient groups in terms of age or education
(Table 9). Furthermore, consistent with the first study preliminary
investigation found that there was no difference in cognitive
function between those control subjects with and without fatigue.
Mean cognitive domain T scores for the fatigue and no fatigue
groups within the HIV positive patients were compared using
MANCOVA with depression serving as a covariate. A type 1 error
rate of .05 was used in all analyses to identify group differences
considered to be significant.

There was a significant overall main effect for Fatigue on
cognitive function [F(9, 53= 2.3, p=.029)]. Similar to the first study
the detrimental effects of fatigue are seen across a broad range of
cognitive domains thought to reflect subcortical cognitive function.
These results replicate the findings of the first study in which those
symptomatic patients without fatigue remain free from cognitive
dysfunction with most T scores near 50. As reported in Table 11
univariate analyses revealed that the symptomatic patients with
fatigue had significantly lower mean domain T scores for almost all
of the domains of cognitive function that were assessed. There was
a marginally significant effect for the encode domain of attention.
<table>
<thead>
<tr>
<th></th>
<th>No Fatigue (n=19)</th>
<th>Fatigue (n=45)</th>
<th>F(1,61)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Focus-Execute</td>
<td>51.0(9.4)</td>
<td>41.7(10.6)</td>
<td>9.5</td>
<td>.003</td>
</tr>
<tr>
<td>Sustain</td>
<td>50.0(7.2)</td>
<td>47.5(6.0)</td>
<td>1.4</td>
<td>.235</td>
</tr>
<tr>
<td>Encode</td>
<td>52.6(8.8)</td>
<td>47.2(9.7)</td>
<td>1.6</td>
<td>.079</td>
</tr>
<tr>
<td>Executive/Shift</td>
<td>50.3(7.4)</td>
<td>43.6(8.20)</td>
<td>8.2</td>
<td>.006</td>
</tr>
<tr>
<td>Speed</td>
<td>51.7(9.1)</td>
<td>45.0(9.7)</td>
<td>3.4</td>
<td>.002</td>
</tr>
<tr>
<td>Verbal Memory</td>
<td>50.2(8.1)</td>
<td>43.0(8.2)</td>
<td>6.9</td>
<td>.011</td>
</tr>
<tr>
<td>Verbal Fluency</td>
<td>51.6(11.2)</td>
<td>46.4(9.3)</td>
<td>6.9</td>
<td>.012</td>
</tr>
<tr>
<td>Motor</td>
<td>52.4(9.0)</td>
<td>43.9(10.6)</td>
<td>7.8</td>
<td>.007</td>
</tr>
<tr>
<td>Reaction Time</td>
<td>48.4(8.9)</td>
<td>43.6(9.3)</td>
<td>4.9</td>
<td>.031</td>
</tr>
</tbody>
</table>

Table 11. Mean Cognitive Domain T Scores for the symptomatic HIV patients with and without fatigue.
There were no significant differences between the two groups for the ability to sustain attention. Similar to the first study, no relationship between fatigue duration and cognitive function was found ($p > .05$).

**Fatigue Severity and Cognitive Function**

The analyses above found that those HIV patients reporting fatigue performed worse on several domains of cognitive function compared to the HIV patients not reporting fatigue. However, it was not determined if fatigue severity within those patients reporting fatigue is related to cognitive dysfunction. In order to further characterize the effects of fatigue on cognitive function, the relationships between the multiple dimensions of fatigue and the multiple dimensions of cognitive function were investigated. Partial correlation analyses controlling for depression were performed between the PFS, FSS and the cognitive domain mean $T$ scores within those patients reporting fatigue.

Table 12 shows there were significant negative correlations between the cognitive dimension of the PFS and the speed of information processing domain ($r = -.343, p < .01$), focus domain ($r = -.445, p < .01$), encode ($r = -.400, p < .01$), and verbal fluency domain ($r = -.300 p < .05$). There were no other significant correlations between the other dimensions of fatigue and cognitive function.
Table 12. Partial correlations between fatigue and cognitive domain scores controlling for depression in the symptomatic HIV patients with fatigue (r values).

Fatigue and Depression

Fatigue and depression are not unitary constructs, but instead have several different dimensions. Correlations were performed between the different dimensions of fatigue and the depression scores in order to investigate the relationship between fatigue and depression. As reported in Table 13, there was a positive correlation between the BDI total score and the PFS total score. However, further analysis revealed that not all of the components of depression and fatigue are related. The BDI affective subscale was related to the severity and mood dimensions of the PFS, but showed no significant correlations with the affective, sensory, or cognitive dimensions.
dimensions of the PFS. The somatic subscale of the BDI was significantly correlated with all of the PFS dimensions, the only exception was the affective dimension of the PFS.

There was also a significant relationship between the BDI total score and the Fatigue Severity Scale (r=.317, p<.05). However, further analyses revealed that this relationship was mostly due to the strong relationship (r=.456, P<.01) with the somatic subscale of the BDI, with no significant relationship between the BDI affective subscale and the FSS being found (r=.214, p > .05).

<table>
<thead>
<tr>
<th>Variable</th>
<th>BDI:Total</th>
<th>BDI:Somatic</th>
<th>BDI:Affective</th>
</tr>
</thead>
<tbody>
<tr>
<td>PFS-Total</td>
<td>.498**</td>
<td>.525**</td>
<td>.408**</td>
</tr>
<tr>
<td>PFS-Severity</td>
<td>.449**</td>
<td>.500**</td>
<td>.382**</td>
</tr>
<tr>
<td>PFS-Mood</td>
<td>.605**</td>
<td>.330*</td>
<td>.602**</td>
</tr>
<tr>
<td>PFS-Affective</td>
<td>.145</td>
<td>.210</td>
<td>.038</td>
</tr>
<tr>
<td>PFS-Sensory</td>
<td>.200</td>
<td>.332*</td>
<td>.101</td>
</tr>
<tr>
<td>PFS-Cognitive</td>
<td>.348*</td>
<td>.424**</td>
<td>.275</td>
</tr>
<tr>
<td>FSS</td>
<td>.317*</td>
<td>.456**</td>
<td>.214</td>
</tr>
</tbody>
</table>

PFS = Piper Fatigue Scale; BDI = Beck Depression Inventory  
FSS = Fatigue Severity; * = p < .05; ** = p < .01

Table 13. The relationship between fatigue and depression in the symptomatic HIV patients (r values).
Fatigue and Medical Variables

Immune status and viral load did not differ between the symptomatic HIV patients with and without fatigue (Table 9). In order to determine if fatigue severity was related to peripheral immune status, immune activation or viral load, correlation analyses were performed between the fatigue dimensions and the medical variables within those symptomatic HIV patients reporting fatigue. Table 14 shows that peripheral immune status was not related to any dimension of fatigue severity. Furthermore, immune activation, as measured by beta2-microglobulin was not related to any dimension of fatigue severity. No significant relationships between fatigue and viral load were found.

<table>
<thead>
<tr>
<th>Variable</th>
<th>PFS: Severity</th>
<th>PFS: Mood</th>
<th>PFS: Affective</th>
<th>PFS: Sensory</th>
<th>PFS: Cognitive</th>
<th>FSS</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD4 #</td>
<td>-.003</td>
<td>.212</td>
<td>-.008</td>
<td>.164</td>
<td>.214</td>
<td>-.090</td>
</tr>
<tr>
<td>CD4 %</td>
<td>.076</td>
<td>.153</td>
<td>.017</td>
<td>.123</td>
<td>.036</td>
<td>-.031</td>
</tr>
<tr>
<td>CD8 #</td>
<td>-.119</td>
<td>.115</td>
<td>-.087</td>
<td>.102</td>
<td>.246</td>
<td>.040</td>
</tr>
<tr>
<td>CD8 %</td>
<td>.069</td>
<td>.013</td>
<td>.019</td>
<td>.106</td>
<td>.050</td>
<td>.241</td>
</tr>
<tr>
<td>CD4/CD8 ratio</td>
<td>-.128</td>
<td>.215</td>
<td>.136</td>
<td>.112</td>
<td>.021</td>
<td>-.007</td>
</tr>
<tr>
<td>Beta2-M</td>
<td>-.064</td>
<td>-.125</td>
<td>-.020</td>
<td>.131</td>
<td>-.035</td>
<td>-.112</td>
</tr>
<tr>
<td>Viral Load (log10)</td>
<td>.204</td>
<td>.161</td>
<td>.082</td>
<td>.308</td>
<td>-.099</td>
<td>.064</td>
</tr>
</tbody>
</table>

PFS = Piper Fatigue Scale; FSS = Fatigue Severity; (n=45 except for viral load correlation where n=22)

Table 14. The relationship between fatigue and the medical variables for the symptomatic HIV patients with fatigue (r values).
Section 2: Asymptomatic HIV patients

Approximately 41 percent or 7 of the 17 asymptomatic subjects in this study reported fatigue. The demographic, immune status and cognitive domain scores are presented in Table 15. T-tests were performed between the two groups in order to determine if there were any group differences. These analyses are considered to be preliminary given the small sample sizes. As seen in Table 15 there were no group differences for age or education. Similar to the first study those asymptomatic patients with fatigue had much higher levels of depression. There was no difference in immune status between the asymptomatic patients with and without fatigue. Immune activation, as measured by beta2-microglobulin, was not different between the asymptomatic patients with and without fatigue. Those asymptomatic patients reporting fatigue had significantly higher ratings of fatigue severity on both the FSS and the PFS. These ratings of fatigue severity are similar to the severity ratings in the symptomatic HIV patients (Table 9). Cognitive performance did not differ on the basis of fatigue in the asymptomatic patients. In fact, for most domains of cognitive function the asymptomatic patients showed little impairment with T scores near 50.
<table>
<thead>
<tr>
<th></th>
<th>No Fatigue (n=7)</th>
<th>Fatigue (n=10)</th>
<th>t(1.15)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr.)</td>
<td>35.1 (8.1)</td>
<td>33.4 (7.2)</td>
<td>.2</td>
<td>.669</td>
</tr>
<tr>
<td>Education (yr.)</td>
<td>13.3 (2.8)</td>
<td>13.6 (3.2)</td>
<td>.0</td>
<td>.856</td>
</tr>
<tr>
<td>BDI: Affective</td>
<td>2.2 (2.9)</td>
<td>10.3 (4.9)</td>
<td>18.6</td>
<td>.001</td>
</tr>
<tr>
<td>BDI: Somatic</td>
<td>1.8 (1.7)</td>
<td>4.6 (1.9)</td>
<td>10.0</td>
<td>.006</td>
</tr>
<tr>
<td>BDI: Total</td>
<td>4.0 (4.2)</td>
<td>14.9 (5.9)</td>
<td>19.7</td>
<td>.000</td>
</tr>
<tr>
<td>FSS Mean</td>
<td>3.0 (.9)</td>
<td>4.9 (1.5)</td>
<td>9.8</td>
<td>.007</td>
</tr>
<tr>
<td>PFS Total</td>
<td>12.5 (7.2)</td>
<td>24.3 (6.4)</td>
<td>12.0</td>
<td>.003</td>
</tr>
<tr>
<td>CD4</td>
<td>552 (97)</td>
<td>497 (270)</td>
<td>.63</td>
<td>.867</td>
</tr>
<tr>
<td>CD4%</td>
<td>26.0 (5.8)</td>
<td>26.7 (11.3)</td>
<td>.03</td>
<td>.438</td>
</tr>
<tr>
<td>CD8#</td>
<td>1239 (672)</td>
<td>767 (216)</td>
<td>1.78</td>
<td>.100</td>
</tr>
<tr>
<td>CD8%</td>
<td>51.5 (12.5)</td>
<td>44.3 (11.1)</td>
<td>1.22</td>
<td>.239</td>
</tr>
<tr>
<td>4/8 ratio</td>
<td>56.0 (25.9)</td>
<td>69.9 (53.7)</td>
<td>.71</td>
<td>.484</td>
</tr>
<tr>
<td>B2-M</td>
<td>2.0 (.441)</td>
<td>2.3 (.474)</td>
<td>1.8</td>
<td>.195</td>
</tr>
<tr>
<td>Focus-Execute</td>
<td>49.6 (10.4)</td>
<td>49.0 (11.3)</td>
<td>.02</td>
<td>.898</td>
</tr>
<tr>
<td>Sustain</td>
<td>51.5 (6.1)</td>
<td>51.9 (4.0)</td>
<td>.03</td>
<td>.865</td>
</tr>
<tr>
<td>Encode</td>
<td>47.1 (9.9)</td>
<td>47.6 (10.0)</td>
<td>.01</td>
<td>.917</td>
</tr>
<tr>
<td>Executive/Shift</td>
<td>46.6 (11.0)</td>
<td>49.4 (10.1)</td>
<td>.3</td>
<td>.594</td>
</tr>
<tr>
<td>Speed</td>
<td>48.2 (12.6)</td>
<td>47.8 (10.3)</td>
<td>.00</td>
<td>.942</td>
</tr>
<tr>
<td>Verbal Memory</td>
<td>49.4 (7.6)</td>
<td>46.0 (11.5)</td>
<td>.5</td>
<td>.473</td>
</tr>
<tr>
<td>Verbal Fluency</td>
<td>47.0 (11.7)</td>
<td>43.5 (9.8)</td>
<td>.4</td>
<td>.528</td>
</tr>
<tr>
<td>Motor</td>
<td>49.6 (6.1)</td>
<td>47.7 (11.7)</td>
<td>.2</td>
<td>.656</td>
</tr>
<tr>
<td>Reaction Time</td>
<td>46.3 (6.5)</td>
<td>48.4 (9.2)</td>
<td>.3</td>
<td>.592</td>
</tr>
</tbody>
</table>

Table 15. Demographic characteristics, immune status and cognitive domain scores for the asymptomatic HIV patients with and without fatigue.
Discussion

Similar to the first study, this study found that fatigue is common in HIV patients. Even though the participants within these two samples were enrolled during different time periods, the prevalence of fatigue was approximately the same in both studies. This suggests that the fatigue questionnaire is a reliable method in determining the prevalence of fatigue in HIV patients.

The fatigue questionnaire appears to be a valid measure of fatigue as demonstrated by the higher severity scores for those HIV patients reporting fatigue. Those HIV patients classified as having fatigue had mean FSS scores of about 5 which is significantly higher than the FSS scores for those patients without fatigue. Studies measuring fatigue in other neuroimmunological diseases have obtained similar values on the FSS ranging from 4.8 to 5.7 (Geisler et al., 1996; Krupp et al., 1989; Krupp et al. 1994). In addition, the control group and those HIV patients without fatigue had similar mean FSS scores around 3.3. These values are similar to that of other control groups. The PFS scale also demonstrated construct validity with the control and no fatigue groups having similar mean total PFS scores. These two groups had significantly lower PFS total scores compared to those patients classified as fatigued.

Fatigue and Cognitive Function

This study replicated the findings of the first study in which fatigue was associated with cognitive impairment in the symptomatic HIV patients but not the asymptomatic HIV patients.
Similar to the first study the negative effects of fatigue are seen in most domains of cognitive function assessed. However, fatigue does not decrease cognitive performance across all domains of attention. Instead, the negative effects of fatigue are observed in those domains of attention in which the underlying neuroanatomy is known to be damaged in HIV disease. These results suggest that those components of attention not associated with HIV neuropathology are not affected by fatigue, even though fatigue has been shown to decrease performance in these domains in other neuroimmunological patient populations (Cohen, 1993; Bruno et al., 1995). Furthermore, this suggests that the association of fatigue and cognitive dysfunction may be associated with the neuropathology and neuroimaging abnormalities known to exist in HIV disease. This suggests that fatigue and cognitive dysfunction may be related in that both are a manifestation of HIV subcortical neuropathology.

It appears from the results, that Mirsky's model of attention may provide some utility in evaluating fatigue related attention dysfunction within HIV infected individuals. If the current findings are replicated, Mirsky's model may be useful in predicting which domains of attention will be impaired due to fatigue based upon the known neuropathology of the disease being investigated. However, in terms of semantics, Mirsky's model of attention does show some inconsistencies with previous neuropsychology research in general and research involving HIV infected individuals. For example, this study found that there was no effect of fatigue for the sustain
domain of attention. However, previous research has shown that the ability to sustain attention is one domain of attention that is most likely to be impaired in HIV infected individuals (Butters et al., 1990). Furthermore, Mirsky's model of attention includes a neuropsychological test (Wisconsin Card Sorting Test) that is usually not thought of as test of attention (Lezak, 1995). In addition, the assignment of the domains of attention to particular neuroanatomical regions is not consistent with other research in some cases. For example, the encode domain of attention is represented by two neuropsychological tests that are often thought of as representing working memory, which is associated with proper frontal lobe function (Lezak, 1995). This highlights the difficulty in trying to find a model that encompasses the multidimensional nature of attention without defining attention too broadly.

This study found that complaints of cognitive fatigue are related to objective neuropsychological test performance, even when controlling for the effects of depression. These results suggest that complaints of cognitive difficulties can reflect actual deficiencies in cognitive function. A study by Mapou et al., (1993) suggests that the inability to find a significant relationship between cognitive fatigue severity and actual performance on some domains of cognitive function may be a reflection of the type of cognitive fatigue that was assessed by the Piper Fatigue Scale. These researchers found that HIV patients who complained of cognitive difficulties were more likely to have actual neuropsychological
deficits on tests of motor ability, reaction time and other tests of subcortical cognitive function, than those HIV patients who did not complain of difficulties (Mapou et al., 1993). The Mapou et al. (1993), study employed a more detailed examination of cognitive complaints that included motor, language, memory, spatial and sensory components. The current study found no relationship between cognitive fatigue severity and motor ability or reaction time performance. This difference between the two studies may be due to the fact that the three questions relating to cognitive fatigue on the Piper Fatigue Scale are concerned with the perception of being able to concentrate, think clearly, and remember with no mention of motor ability. This implies that cognitive fatigue may have different components much in the same way that the general concept of fatigue can be subdivided into multiple components to reflect it's multi-dimensional nature.

Another explanation, is that there may be a subset of cognitive difficulties that are perceived as fatigue. For example, MS patients who maintained diaries of subjective fatigue, more often described difficulties on neuropsychological tests requiring concentration and attention as fatigue, than difficulties in motor performance (Cohen & Fisher, 1988).

The current study also found that fatigue severity as measured by the FSS, is not related to cognitive function, even though the occurrence of fatigue is associated with decreased cognitive function. This result is consistent with several studies involving MS patients in which fatigue severity, as measured by the
FSS or other general rating scales, is not related to cognitive dysfunction (Geisler et al., 1996; Moller, et al., 1994; Schwartz, et al., 1996). Similarly, complaints of mental fatigue but not physical fatigue are related to cognitive dysfunction in post polio syndrome (Bruno et al., 1994). This suggests that there are different types of self reported fatigue and the ability to find a relationship between fatigue and cognitive performance is dependent upon the measures used.

**Fatigue and Depression**

Similar to the first study, this study found that those patients that report fatigue also have more symptoms of depression. This study also demonstrated that not all aspects of fatigue and depression are related. Overall, there was a significant relationship found between depression and fatigue. The results indicate that the somatic symptoms of depression contribute more to this relationship than do the affective symptoms of depression. There were much stronger relationships between the somatic symptoms of depression and fatigue compared to the affective symptoms of depression for most dimensions of fatigue. In fact, the affective subscale of the BDI was significantly related to only two dimensions of fatigue (severity and mood). The mood dimension asks participants to what degree they are feeling depressed or are having symptoms related to depression. Therefore, a strong relationship between the mood dimension of the PFS and depression would be expected.
The severity dimension of the PFS probes for the degree to which the patient is feeling distress related to their fatigue, as well as the physical limitations associated with fatigue. Patients who report affective symptoms of depression often perceive their lives to be in disorder and stressful. This may explain the relationship between the severity dimension of the PFS and the affective symptoms of depression. The FSS which also probes for fatigue severity asks questions related to only how fatigue affects their physical functioning without any mention of emotional distress. As can be seen in Table 13 the FSS is related to only the somatic symptoms of depression. Therefore, the PFS severity subscale may assess two separate dimensions regarding fatigue severity, one related to subjective distress the other related to impairment of physical functioning. Overall, the results are consistent with previous research in symptomatic HIV patients, in which fatigue was associated with the somatic symptoms of depression, but not the affective symptoms of depression (Kalichman, 1995).

Fatigue and Immune Status

Contrary to the hypothesis there was no significant relationship between fatigue and immune status. This suggests that fatigue may not be due to changes in the peripheral immune system, but instead may be related to central mechanisms. The marker of immune activation employed in this study, B2-microglobulin, is very general and may lack the specificity required to find any association between immune activation and fatigue. In
addition, this study only measured the number of immune cells and did not elucidate the phenotype or functional status of the lymphocytes.

Several cytokines and immune cell activation markers have been associated with fatigue in human studies, as well as animal models of sickness behavior (Hickie & Lloyd, 1995; Segall & Crnic, 1990). Elevated cytokine levels and changes in lymphocyte phenotype are seen in the peripheral blood of HIV patients (Giorgi, 1996). Therefore, the possibility of a relationship between peripheral immune changes and fatigue within this study's sample of HIV infected individuals can not be ruled out.

For example, this study found no relationship between fatigue and CD8+ cell count or CD8+ percent. A similar result was found in CFS patients, however, closer analysis revealed reduced CD11b+ CD8 cells and increased expression of the activation markers CD38 and HLA-DR on CD8+ cells (Barker et al., 1994). Increased expression of CD38 and HLA-DR on CD8+ has also been reported in HIV patients (Giorgi, 1996). This leaves open the possibility that fatigue in HIV is not related to absolute immune cell counts but instead may be related to changes in immune activation.

Fatigue and Viral Load

There was no difference in viral load between those HIV patients with fatigue and without fatigue. Viral load was not correlated with cognitive fatigue, suggesting that peripheral virus levels are not associated with the mental aspect of fatigue. This
result is consistent with previous research looking at the relationship between peripheral viral load and cognitive function (Ellis et al., 1997) and suggests that peripheral HIV RNA levels do not influence brain function. In addition, viral load was not correlated with any other dimension of fatigue severity.

It would be interesting to examine the relationship between fatigue and CSF HIV RNA levels. Mental fatigue is the most likely dimension of fatigue to be related to CSF viral load since it is the most proximate to CSF viral load and CSF viral load is associated with cognitive impairment (Ellis et al., 1997; Lafeuillade et al., 1996). However, the other dimensions of fatigue may be related to central CSF viral load since the perception of malaise and being tired is hypothesized to be generated within the central nervous system (Goldstein, 1996).

Antiretroviral use was not associated with fatigue. This result is difficult to interpret since not everyone on anti-HIV medications has a favorable response to treatment. Therefore, longitudinal study may be the best way to study the effects of antiretroviral therapy on fatigue.

Fatigue and Asymptomatic HIV Infection

Even though the analysis of the asymptomatic patients is limited by the small sample size, several important preliminary findings emerged. Similar to the first study it appears that fatigue is not associated with cognitive impairment within the asymptomatic patients since the cognitive domain scores are roughly the same
between the two groups. Also similar to the first study, there appeared to be no difference in immune status or immune activation between the two asymptomatic groups.

Fatigue severity between the asymptomatic HIV patients with fatigue and the symptomatic patients with fatigue was approximately the same. Therefore, differences in fatigue severity can not explain the different effects of fatigue on cognitive function between the asymptomatic and symptomatic patients. It is possible that the severity across the different dimensions of fatigue changes with advancing HIV disease. Post hoc analyses were done in order to determine if there were any differences in fatigue severity for the five dimensions of fatigue assessed by the PFS. These analyses revealed that there were no differences in terms of fatigue severity between the asymptomatic and symptomatic subjects. This suggests the nature of the fatigue is similar across disease stages.

Some HIV positive individuals may perceive their fatigue as very severe while other individuals may perceive their fatigue as mild even though the fatigue occurs in the context of a similar set of circumstances (HIV disease). This suggests that subjective fatigue severity may partially depend upon personality factors. For example, a study of army recruits (May & Kline, 1988) found that fatigue was reported in almost all the individuals that participated in a three day strenuous battle exercise in which there was no opportunity for sleep. A self-report-fatigue severity questionnaire was able to detect differences between the sleep deprived recruits and a control group that did not participate in the battle exercise.
Along with the fatigue severity questionnaire, the Eysenck Personality Inventory was also administered. Within those individuals participating in the battle exercise, the extroverted recruits were more likely to deny feeling fatigue and reported less severe fatigue. In contrast, those individuals scoring high on the neuroticism scale exaggerated their fatigue. The authors of the study concluded, the fatigue severity questionnaire was able to show differences between the battle exercise group and the control group. However, individual levels of fatigue, within the fatigue group showed some relationship with measures of personality.

**Summary**

This study has replicated the findings of the first study, confirming that fatigue is associated with cognitive impairment in symptomatic HIV disease. The utility of measuring the multiple dimensions of fatigue was demonstrated in this study since only cognitive fatigue severity was related to cognitive impairment. There was no significant relationship found between fatigue and peripheral markers marker of HIV disease. Although, the nonspecific nature of the immune system measures employed in this study leaves open the possibility that fatigue may be associated with peripheral immune activation. In aggregate, this study further supports the notion that fatigue may be a manifestation of the neurological involvement of HIV disease. Techniques that probe for the neurological manifestations of HIV disease (e.g. neuroimaging and markers of central nervous system immune activation) remain
promising methods of study that may further support the hypothesis that fatigue is a component of the neurological manifestations of HIV infection.
CHAPTER 4

General Discussion

This investigation examined the association between fatigue and cognitive function in HIV infected individuals. This question was addressed in two independent samples. The initial study assessed fatigue in a unitary fashion in which only the occurrence and duration of fatigue were assessed. The second study expanded the scope of the investigation by providing a more detailed assessment of fatigue and attention.

Both studies found that symptomatic HIV patients with fatigue performed worse on several domains of cognitive dysfunction, while there was no effect for fatigue in the asymptomatic HIV patients. Fatigue appears to be related to dysfunction in a broad range of cognitive domains, particularly attention. These findings suggest an integral relationship between impaired cognition, fatigue and subcortical neuroanatomical abnormalities. The current investigation did not involve brain imaging or autopsy studies, so any relationship between fatigue and neuroanatomical abnormalities in HIV patients must be inferred from the neuropsychological test scores. However, the results of the current investigation provides indirect evidence for the association fatigue and neuropathology.
Similar to previous research this investigation found very little relationship between depression and neuropsychological test performance. This investigation demonstrates the importance of finding a suitable measure of depression that can assess the psychological distress associated with HIV without inadvertently measuring symptoms of advanced HIV disease. Future study should focus on differentiating fatigue from depression in HIV disease. A more detailed questionnaire probing for the circumstances surrounding the initial occurrence of the fatigue may help in differentiating depression related fatigue and fatigue associated with HIV infection.

Studies involving MS and CFS patients have shown that fatigue can be separated from depression (Jorge & Goodnick, 1997; Moller et al., 1994; Roelcke et al., 1997). For example, those CFS patients that report a gradual onset of fatigue are more likely to be depressed compared to those CFS patients that report a sudden flu-like onset of disease. Furthermore, a sudden onset of fatigue may be associated with immune system abnormalities and cognitive impairment (Jason et al., 1997). Questions related to what exacerbates fatigue in HIV patients may be useful in differentiating fatigue from depression. Fatigue in depressed patients may be alleviated by exercise. However, in MS and CFS exercise is associated with the exacerbation of fatigue in some patients (Krupp et al., 1988; Petersen et al., 1994). The exacerbation of fatigue is thought to be related to increased immune activation associated with exercise.
If other studies find that depression and fatigue are independent in terms of their effects on cognitive function this may have implications for the treatment and diagnosis of fatigue in HIV disease. In many cases depression in HIV is successfully treated as psychiatric disorder (Markowitz, et al., 1994). However, not all HIV patients diagnosed with depression respond to treatment. This may be due to the fact that patients with severe HIV related fatigue have been mistakenly diagnosed with depression. The results from this investigation suggests that this scenario is most likely to occur when a patient has severe somatic complaints but few affective symptoms of depression.

Increased cerebrospinal fluid levels of quinolinic acid (a NMDA receptor agonist) have been correlated with slowing of reaction time (A. Martin et al., 1992) and associated with AIDS dementia (Heyes et al., 1989). Also, AZT related decreases in quinolinic acid are associated with improved cognitive function (A. Martin et al., 1993). Fatigue and cognitive impairment may be interrelated symptoms of the neuropathological effects of quinolinic acid. If such a relationship exists then the cerebrospinal fluid levels of quinolinic acid may be a marker for fatigue. Therefore, lower cerebrospinal fluid levels of quinolinic acid would be expected to be associated with the decreases in fatigue and cognitive impairment.

One potential therapeutic strategy for HIV related cognitive impairment and dementia involves down regulating intracellular calcium by antagonizing NMDA receptor activity. Amantadine, a NMDA receptor antagonist and dopamine agonist has been shown to
be an effective treatment for fatigue in MS patients (Kemp & Gora, 1993; Cohen & Fisher, 1989). In one particular MS study, treatment of fatigue with amantadine resulted in improvement in several dimensions of fatigue including general energy level, concentration/memory function, problem solving ability, and overall well being. However, there were no improvements in self reported depression (Cohen & Fisher, 1989). If HIV related fatigue is related to NMDA receptor mediated neuropathology, amantadine may be a useful therapy for those HIV patients reporting fatigue, particularly those patients reporting cognitive fatigue.

Even though this investigation has demonstrated that the deleterious effects of fatigue on cognitive function can not be explained by depression. There may be other factors associated with fatigue in HIV. However, previous research has found little evidence that fatigue in HIV is due to peripheral mechanisms of disease. For example, lower levels of plasma cortisol have been implicated in chronic fatigue syndrome and cortisol deficiency has been found in late stage HIV patients. However, lower cortisol levels are not related to subjective symptoms of fatigue in HIV (Abbott et al., 1995).

Another proposed hypothesis of self reported fatigue in HIV is the inability to sustain physical activity due to neuromuscular transmission dysfunction. To test this hypothesis, Cupler et al., (1996) studied 43 HIV patients to determine whether elevated acetylcholine receptor antibodies were related to self reported fatigue as measured by the PFS. Three patients had increased ACH
receptor antibodies and were administered pyridostigmine a cholinesterase inhibitor. Two of these patients responded with decreased Piper Fatigue Scale scores during therapy. The Piper Fatigue Scale scores increased after pyridostigmine was stopped. Another study found that fatigue in AIDS patients can not be attributed to altered muscle metabolism or mitochondrial myopathy associated with AZT treatment (R. Miller et al., 1991). These studies suggest that self reported fatigue may be related to neuromuscular junction abnormalities in a small minority of HIV patients. In contrast to these limited findings, the current investigation has demonstrated a much stronger association between fatigue and cognitive impairment, with over half of those patients reporting fatigue being cognitively impaired. The current investigation suggests that neurological mechanisms may account for the fatigue in some of HIV patients, since peripheral mechanisms do not adequately account for fatigue in most HIV patients.

This investigation has shown that fatigue is a multidimensional phenomenon. Cognitive fatigue was associated with decrease cognitive function in several domains of mental performance. However, this investigation failed to find any relationship between complaints of physical fatigue and cognitive performance. It would be interesting to know if the self reported physical fatigue is related to objective measures of behavior in HIV patients. Activity meters have been utilized as an objective measure of behavioral fatigue. This objective measure of behavior has been related to subjective physical fatigue but not depression in CFS
patients and cancer patients (Berger, 1998; Vercoulen et al., 1997). If similar studies were done in HIV patients this may facilitate the differentiation of the mental and physical components of fatigue.

A weakness of the current investigation is that there was little control over the experimental design. Subject recruitment for this investigation was dependent upon the parent studies. In both studies stage B and C patients had to be combined to form a single symptomatic group. This was done because of the high prevalence of fatigue in these groups. Therefore, it was not possible to determine if there is a progression in the association between fatigue and cognitive function across disease stages. Furthermore, the relatively small symptomatic without fatigue group and the small number of asymptomatic subjects, did not provide sufficient power in some statistical analyses. As a consequence, some of the conclusions were tentative.

A definition of fatigue could have been given prior to the patients filling out the questionnaires. This would have qualified the nature of the fatigue and may have helped to ensure that all patients were reporting a similar phenomenon. For example, Whalen et al., (1994) has developed a brief index to measure the symptoms of HIV infection. A definition for each of the symptoms was given. "Fatigue" was defined as "Fatigue, or loss of energy, that keeps you from doing the things you need and like to do." By administering a questionnaire that asked only about the occurrence of fatigue and not qualifying the cause or nature of the fatigue this may have lead to fatigue being reported for any number of reasons.
Several reasons for feeling fatigued in the current study may have been due to factors associated with the study itself. For example, the fatigue questionnaires were filled out at the end of the day, when many patients complained that they were exhausted from the long day of testing. In addition, many patients had to wake up much earlier than usual to participate in the study and therefore lack of sleep may have been a source of fatigue.

The study of fatigue in HIV disease may be most fruitful if done in the context of a within subjects, longitudinal design. This would allow fatigue to be studied in a manner in which many of the between subjects factors that can influence the perception of fatigue to be controlled for. Furthermore, the association between changes in immune status, HIV RNA levels and fatigue over time could be investigated. The measures of fatigue administered in this investigation require about 20 minutes to complete and could be administered as part of an antiretroviral medication trial. Measures of central nervous system immune activation and viral load have been associated with cognitive function (Ellis et al., 1997; Glass & Johnson, 1996; Heyes et al. 1991; Martin et al., 1993). If fatigue is caused by the same neuropathological events that give rise to cognitive impairment, then decreases in the prevalence and severity of fatigue may occur along with decreases in cerebrospinal fluid levels of quinolinic acid, beta2-microglobulin, HIV RNA, or cytokine levels. Neuroimaging abnormalities are associated with fatigue in MS and CFS (Goldstein, 1996; Roelcke, 1997). This investigation has provided preliminary evidence that fatigue is
associated with neurocognitive dysfunction. Therefore, neuroimaging studies may provide more support for the notion that fatigue is associated with neurological abnormalities.

The introduction of new antiretroviral medications aimed at different steps in the HIV life cycle has dramatically changed the course of HIV disease progression. HIV RNA levels may be suppressed so that HIV disease becomes a chronic disorder, that is characterized by occasional increases of viral load that would warrant a change in the anti-retroviral combination. However, the central nervous system may provide a sanctuary for the so that HIV can not be eradicated by current antiretroviral therapy (Goodkin et al., 1997; Schmitt et al., 1988). Assuming that fatigue is associated with central nervous system viral load, fatigue may continue to be a common and troublesome complaint. Past research has indicated that fatigue is among one of the most common, and bothersome symptoms of HIV infection (Darko et al., 1992; Walker et al., 1997). Future study should determine if the prevalence of fatigue decreases in this new era of HIV disease management. If fatigue continues to be a problem, this investigation suggests that research into the neurological correlates of fatigue may provide insights into the cause and potential therapies of HIV related fatigue.
LIST OF REFERENCES


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