Attention in HIV

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Abstract

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by

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In contrast to the striking benefit of advances in antiretroviral therapy on longevity and health in the HIV+ population, mild cognitive disorders persist (Heaton, Clifford et al., 2010). Additional factors that may be related to cognitive decline and warrant consideration in this population are aging and physical health status. Among cognitive domains affected, attention and processing speed have emerged as particularly vulnerable to the effects of HIV. There are also age effects observed in these domains, and we proposed that reduced physical health can also impact cognition in these areas, comparably to pain. Sensitive measures of attention that vary attentional demands may be sensitive to subtle cognitive changes associated with aging and physical health status in this population. We examined the impact of aging and self-reported physical health status on several attentional measures that vary attentional demands in a sample of HIV+ adults. We hypothesized that worse physical health and older age would uniquely and additively relate to poorer performances during test conditions of greatest demands. Results indicated that both low physical health and older age each affected performance on attention tasks, with unique main effects observed on different tasks. There were additive effects observed on several attention tasks during high load conditions, with differences largely observed at the extremes; i.e., older adults in poor health demonstrated worse performance compared to younger adults in good health. Importantly, one task indicated worst performance in younger adults in poor health. The results of these findings are discussed in terms of clinical implications and the importance of considering these factors when assessing for cognitive decline in the HIV+ population.
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## Contents

**Introduction** ........................................................................................................................................................... 1  
- Structure and neural mechanisms of HIV in the brain ......................................................................................... 3  
- Physical Health ....................................................................................................................................................... 6  
- Aging ....................................................................................................................................................................... 10  
- Attention ............................................................................................................................................................. 11  
  - Foreperiod Effect ............................................................................................................................................... 16  
  - Covert Orienting ............................................................................................................................................... 17  
  - Attentional Blink ................................................................................................................................................. 18  
**Aims and Hypotheses** ........................................................................................................................................ 21  
**Methods** ............................................................................................................................................................... 25  
- Sample ................................................................................................................................................................. 25  
- Substance Use ..................................................................................................................................................... 26  
- Procedure ............................................................................................................................................................ 27  
- Measures .............................................................................................................................................................. 28  
  - Foreperiod Effect: Simple Reaction Time Task ............................................................................................... 28  
  - Covert Orienting Task ....................................................................................................................................... 29  
  - Attentional Blink Task ....................................................................................................................................... 29  
  - Neuropsychological Measures ......................................................................................................................... 32  
**Analyses** ............................................................................................................................................................... 34  
**Results** ................................................................................................................................................................. 38  
- Preliminary Analyses of Demographic Differences in Dependent Measures ......................................................... 38  
  - Neuropsychological Measures .......................................................................................................................... 38  
  - Simple Reaction Time (SRT) ............................................................................................................................... 38  
  - Covert Orienting .................................................................................................................................................. 39  
  - Attentional Blink ............................................................................................................................................... 39  
- Main Analyses ....................................................................................................................................................... 41  
  - Aim 1 ................................................................................................................................................................. 41  
  - Aim 2 ................................................................................................................................................................. 42  
  - Aim 3 ................................................................................................................................................................. 44  
**Discussion** ............................................................................................................................................................ 48  
**References** ............................................................................................................................................................ 77
List of Tables

Table 1A. Demographics of Sample by Age Group ................................................................. 65
Table 1B. Demographics of Sample by Self-Reported Physical Health Status ........................ 65
Table 2. Results of ANCOVA’s comparing Age Group and Self-Reported Physical Health Status Group on neuropsychological tests ................................................................. 69
List of Figures

Figure 1. Schematic of the SRT Task ................................................................. 66
Figure 2. Schematic of the Covert Orienting Task ........................................... 67
Figure 3. Schematic of the Attentional Blink Task: .......................................... 68
Figure 4. Graph of Validity X Self-Reported Physical Health Status Interaction on Covert Orienting Task 70
Figure 5. Graph of SOA X Age Group interaction on Attentional Blink Task ..................... 71
Figure 6. Graphs of ISI X Age Group X Physical Health Status interaction on the Simple Reaction Time task ........................................................................................................ 72
Figure 7. Graphs of SOA X Age Group X Self-Reported Physical Health Status interaction ........... 73
Figure 8. Graph of SRT results after 350ms ISI for each Age Group X Self-Reported Physical Health Group .............................................................................................................. 74
Figure 9. Graph of Covert Orienting Task results after Invalid Cue for each Age Group X Self-Reported Physical Health Group ......................................................................................... 75
Figure 10. Graph of attentional blink results at 266ms SOA for each Age Group X Self-Reported Physical Health Group .............................................................................................................. 76
Introduction

Clinicians and researchers have long been aware of the detrimental impact of Human Immunodeficiency Virus (HIV) on cognition. The first case of HIV was reported to the Centers for Disease Control and Prevention (CDC) in 1981 (Centers for Disease Control and Prevention, 2001). Shortly thereafter, reports surfaced that HIV infects the brain and affects neurological function (Levy, Shimabukuro, Hollander, Mills, & Kaminsky, 1985; Snider et al., 1983). Early clinical reports described dementia, peripheral and cranial neuropathy, and post mortem reports showed moderate atrophy (Snider, et al., 1983). Recognizing the need to characterize this syndrome, AIDS dementia complex was first outlined in 1986 by Navia et al. (Navia, Jordan, & Price, 1986), who described early manifestations of cognitive impairment in the areas of attention and memory, motor function, and behavior (e.g. apathy, withdrawal), whereas late stages included frank dementia with global impairment. “Slowing and loss of precision in both mentation and motor control” (p. 587) were identified as the most salient features of early cognitive compromise, and the authors emphasized the importance of neuropsychological assessment (Price et al., 1988). Thereafter, most studies of cognitive function in HIV included tests of processing speed, which were quickly taken up as uniquely sensitive measures of dysfunction related to HIV-associated neurocognitive disorders (HAND; A. Martin, 1994; Sacktor et al., 1996).

The characterization of HAND was adopted and sub-classified either cognitive-motor impairment or dementia (Working Group of the American Academy of Neurology AIDS Task Force, 1991), with attentional and processing speed dysfunction listed as prominent symptoms in both. Most recently, the “Frascati criteria” (named after the Italian town that housed the conference at which these criteria were developed) included the addition of a mild type of HIV-related cognitive disorder (Antinori et al., 2007). The three types of disorders in the Frascati criteria for HAND include: Asymptomatic Neurocognitive Impairment (ANI), Mild Neurocognitive Disorder (MND), and HIV-associated dementia (HAD.) Broadly,
these criteria stipulate that neuropsychological deficits must be present in each disorder, however both MND and HAD criteria require the additional presence of functional decline.

The shift to include characterization of more subtle forms of cognitive impairment in HIV is driven by the need to standardize diagnostic criteria across stages of severity in both clinical and research settings. Identifying mild declines in cognition addresses how clinical change can increase functional vulnerability and provide targets for cognitive rehabilitation intervention (Weber, Blackstone, & Woods, 2013). Standardizing diagnostic criteria also allows for more accurate aggregation of data (Cysique, Waters, & Brew, 2011), and informs treatment guidelines for HAND, which remain non-specific (Cysique, et al., 2011; Panel on Antiretroviral Guidelines for Adults and Adolescents, 2011). Even though HIV-dementia is now less common, HIV-related cognitive dysfunction may be progressive, where early impairment would predict later dementia (Mohamed et al., 2010; Schouten, Cinque, Gisslen, Reiss, & Portegies, 2011). Although it remains unclear whether HIV medications are beneficial in improving or preventing HAND, in theory, early initiation of high active antiretroviral therapy (HAART) may prevent or arrest cognitive decline (Woods, Moore, Weber, & Grant, 2009).

Cognitive and psychomotor slowing in HIV has long-been recognized as a hallmark cognitive symptom in HIV+ adults with dementia (Navia, Jordan, et al., 1986), and over time, slowing continues to be identified as a prominent and consistent neuropsychological symptom in early stages of decline (Hardy & Hinkin, 2002a, 2002b), important for the diagnosis of HAND. However, the phenomenon of slowing has not been fully explored in HIV. The measures of processing speed used in most studies often only capture psychomotor speed, and rarely examine cognitive processing speed or the impact of changes in attentional demands on processing speed. Such investigation could offer an important clinical contribution for several reasons. First, full characterization of cognitive decline in HIV is evolving, as the demographics of this population are shifting. With the advent of HAART, individuals with HIV are living longer, healthier lives,
and issues of aging and physical health status become other possible contributing factors to changes in cognitive processing speed decline and slowing. The impact of aging and physical health status on cognition in HIV is the focus of the current study. Using sensitive attention and processing speed measures as well as a comprehensive neuropsychological battery, we explored whether there are unique and interactive contributions of aging and physical health status on cognition. As the understanding of HIV’s neurostructural and neurophysiological impact on the brain continues to develop, it becomes important to understand how processing speed and attention are sensitive to subtle changes related to HIV, aging, and physical health status (Hardy & Hinkin, 2002a).

**Structure and neural mechanisms of HIV in the brain**

Basal ganglia structures (Brew, Rosenblum, Cronin, & Price, 1995; A. Martin, 1994; Nath et al., 2000; Navia, Cho, Petito, & Price, 1986; Wiley et al., 1998) and frontal structures (Everall, Luthert, & Lantos, 1991; Masliah et al., 1997) have long been recognized as targets of HIV infection in the brain. Autopsy studies showed highest levels of HIV RNA in basal ganglia structures in both those with and without HIV encephalitis (Wiley, et al., 1998). Masliah et al. (1997) found that synaptodendritic injury in midfrontal regions was related to deficits in learning, abstraction, perceptual-motor (including tasks of processing speed and attention) and verbal abilities in HIV+ individuals of varying cognitive dysfunction. Additionally, almost 40% neuronal loss in frontal regions was reported in HIV+ subjects compared to controls (Everall, et al., 1991).

Imaging studies implicate fronto-striatal damage that may lead to early impairment in attention and processing speed. For instance, evidence of reduced fronto-striatal activity was found in non-demented HIV+ individuals compared to HIV- controls using fMRI (Melrose, Tinaz, Castelo, Courtney, & Stern, 2008), indicating that damage to the fronto-subcortical circuit exists without evidence of clinical dementia. This could be similar to findings that increased gliosis of neurons in fronto-striatal structures correlates with
slowing in HIV-associated dementia (Paul et al., 2007). Tate et al. (2009) traced white matter tracts in individuals with HIV using diffusion tensor imaging (DTI), and showed that reduced integrity of frontal, subcortical, and cerebellar tracts was associated with poorer processing speed, short-term memory, and mental flexibility. Neuronal dendrite markers (MAP2) and markers of synapses (i.e., synaptophysin) in autopsied putamen and hippocampus have been found to explain nearly half of the variance of global impairment in HIV+ subjects and the authors noted that no differences were observed between those on or off of HAART (Moore et al., 2006). Collectively, the evidence implicates damage to fronto-striatal-thalamo-cortical loops (Woods, et al., 2009), particularly white matter. Such damage is consistent with primary neuropsychological symptoms in the domains of attention and processing speed.

HIV viral particles cross the blood-brain barrier carried inside by infected macrophages, known as the “Trojan Horse” mechanism (Ellis, Langford, & Masliah, 2007; Lane et al., 1996). Several lines of evidence point to a confluence of disruptive activity once HIV infects the central nervous system (CNS) leading to the cognitive dysfunction. In general, HIV-associated neuronal injury is hypothesized to come from two sources: viral factors and host factors (Ellis, et al., 2007). Viral factors include cellular damage and neurotoxicity related to the presence of HIV-encoded proteins (Ellis, Calero, & Stockin, 2009). Specifically, exposure to the HIV envelope protein gp120 can be neurotoxic to human CNS tissue in vitro, and is associated with decreased neuronal processes, greater vacuolization, increased production and size of astrocytes, and decreased MAP2 immunoreactivity compared to control tissue (Iskander, Walsh, & Hammond, 2004). Host factors include chronic immunological response to infection in the brain, including inflammation and increased production of cytokines, chemokines and chemokine receptors (Ellis, et al., 2007). The HIV envelope protein gp120 may directly or indirectly activate specific chemokine receptors leading to increased glial activity and ultimately neurotoxicity (Cartier, Hartley, Dubois-Dauphin, & Krause, 2005). Interestingly, van der Meer et al. found overall increased levels of the chemokine receptor
CXCR4 in HIV infected brain tissue versus control tissue, and higher levels of CXCR4 expression were observed in areas vulnerable to HIV-associated cognitive impairment including the basal ganglia, thalamus, and hippocampus (van der Meer, Ulrich, Gonzalez-Scarano, & Lavi, 2000). An intriguing proposal based on evidence from mouse models of HIV-related cognitive impairment suggests that CXCR4 activation can lead to upregulation of nicotinic receptors, which in turn, leads to neuronal dysfunction and ultimately apoptosis (Ballester et al., 2012). In vivo, this upregulation was particularly prominent in the cognitively vulnerable basal ganglia. Tonically active cholinergic interneurons in the basal ganglia are enervated by projections from the thalamus, and activate nicotinic receptors on dopaminergic neuron terminals (Bonsi et al., 2011). Activating this system produces a “pause” in the tonic activity of the cholinergic interneurons following reward-related stimuli, and this cholinergic “pause” may support shifting attention to salient stimuli in the environment (Ding, Guzman, Peterson, Goldberg, & Surmeier, 2010). This mechanism could directly explain why attention is a particularly vulnerable domain. If one end product of HIV-related neuronal dysfunction is increased nicotinic receptors, introducing higher levels of nicotine might compensate for the existing cognitive dysfunction. In fact, better performance on executive function tasks was reported among women smokers compared to non-smokers, but only in women with HIV (Wojna et al., 2007). It is notable that the HIV envelope protein gp120 may play a role in both “viral” and “host” factors, and Ellis et al. acknowledged that since exact mechanisms of injury are still unclear, the distinction between these factors is fluid (2007).

In summary, the suspected mechanisms of neuronal injury in HIV and the neuropathological evidence point to reduced synaptic efficiency, particularly in frontal-subcortical loops. Thus, it is unsurprising that processing speed and attention emerge as among the most vulnerable cognitive faculties in HIV. As I will next describe, additional factors may further contribute to decline in these areas include decline in physical health status and aging processes.
Physical Health

HAART is a treatment regimen composed of multiple antiretroviral medications. The advent of HAART in the mid 1990’s led to striking improvement in the control of the HIV virus in the body and improved immunological function (Hogg, Heath, Yip, & et al., 1998; Ledergerber et al., 1999; Palella et al., 1998), and treated individuals with well-controlled HIV disease can expect relatively normal life expectancies, living into their 70’s (Hogg et al., 2013; Kuehn, 2014). However, the effect of HAART on cognitive decline and CNS infection is less straightforward. Some studies show either a stable or slight decrease in the incidence of HIV-related cognitive disorders, but stable or increased prevalence (Bhaskaran et al., 2008; McArthur, Steiner, Sacktor, & Nath, 2010; Sacktor et al., 2002), and continued high rates of HIV encephalopathy are found at autopsy (Neuenburg et al., 2002). The large multi-center CHARTER study suggest that HIV-associated dementia is much less prevalent, but that less severe cognitive disorders seem to persist (Heaton et al., 2010). This study’s results indicated that the presence of comorbid disorders (e.g. psychiatric disorders, substance abuse, etc.) also elevate the risk of cognitive impairment, possibly from increased health burden.

As a result of the increasing effectiveness and wide-spread administration of HAART, individuals with HIV are living longer and the clinical focus has become managing disease and symptoms, and maintaining health. Cognitive disorders (i.e. HAND) however, continue to be troubling clinical and public health issues particularly because they can interfere with an individual’s ability comply with complex medication regimens (Woods, et al., 2009), and adherence is necessary. Studies show maximum efficacy of HAART on viral suppression at 95% adherence (Maggiolo et al., 2007) and low adherence may lead to the development of drug resistance (Bangsberg et al., 2000), although resistance may differ by drug class (Bangsberg, Moss, & Deeks, 2004). Cognitive impairment has been shown to impact medication adherence, particularly declines in attention and learning (B. W. Becker, Thames, Woo, Castellon, &
Hinkin, 2011; Patton et al., 2012). Hinkin et al. (2002) have also found that individuals with cognitive impairment who have more complex medication regimens may be at particular risk for non-adherence. Therefore, identification of cognitive impairment and resulting treatment considerations are critical factors in overall disease management and health maintenance.

Another effect of HAART is dramatically improved health status in this population. Five-year longitudinal data collected from 1,000 HIV+ patients of the French longitudinal study ANRS CO8 demonstrated initial improvement of health related quality of life after initiation of HAART followed by relatively stable maintenance (Protopopescu et al., 2007). Moreover, long-term well-controlled HIV disease can protect against HIV-related cognitive decline. Cole and colleagues (2007) investigated performance on select attention and processing speed measures across three groups over 5 years: 1) HAART-treated HIV+ asymptomatic group with undetectable viral load; 2) an untreated HIV+ group without history of AIDS (i.e. CD4 count below 200 cells/µL) for at least 15 years; 3) an HIV+ group without history of AIDS at both the first and final time points not included in the other groups and 4) an HIV- control group. They reported relatively well-maintained disease markers over the five-year course of the study (i.e. the average nadir CD4 count did not decrease below 400 cell/µL in any group). Overall, they found that performance on attention and processing speed measures did not decline over time across HIV+ groups relative to the HIV- control group, suggesting that preserved cognition can occur in these HIV+ groups with historically well-controlled disease, either with HAART or naturally. The HIV+ samples were relatively young, with a mean ages of 43 (±6.4 in the HAART group, and ±5.3 in the non-HAART group) and the authors posited that well-controlled HIV disease early after infection and maintaining viral suppression over time (aided by antiretroviral medication or naturally occurring) may prevent HIV-related cognitive decline. Conversely, the authors also suggested that presence of cognitive
decline in apparently healthy HIV+ individuals might indicate worsening health. This is consistent with earlier reports of precipitant cognitive decline after the development of AIDS (Selnes et al., 1995).

A salient issue these (Cole et al., 2007) findings raise is the impact of physical health on cognitive function in HIV. Tozzi et al. (2003) reported worse self-reported physical health in a group of cognitively impaired HIV+ adults compared to an unimpaired HIV+ group, and self-reported physical health was related to worse performance on cognitive measures across groups. Most of the sample was being treated with HAART, and the percent on HAART did not differ between impaired and unimpaired groups.

Physical health in HIV has been associated with HIV-related biological indices such as CD4 count and viral load, but the relationship between these biomarkers and cognitive function is not clearly established (Bossi et al., 1998; Stankoff et al., 1999; Vitiello et al., 2007). Additionally, results from an HIV-related dementia incidence study suggested that HAART might reduce the predictive value of viral load on incident dementia (Sevigny et al., 2004). Malaspina et al. (2011) reported no differences on HIV biomarkers of disease severity between cognitively healthy older HIV+ adults performing 1 standard deviation below normal limits on a neuropsychological battery or mood scale. The authors postulated that other biomarkers might be more informative in studies of cognitive decline in HIV.

Our current study explores the possibility that a measure of self-reported health status could provide such valuable information. That is, self-perception of physical status taps into a dimension of health unassessed by laboratory measures and provides valuable information about the well-being of the individual. Such information may capture a more global gauge of physical health, arising from the milieu of factors contributing and related to physical health and not a singular, targeted measure of disease. In support of this, observational studies have found that worse self-reported physical health scores are associated with mortality (DeSalvo, Bloser, Reynolds, He, & Muntner, 2006; Idler & Benyamini, 1997). The strength of this approach is that self-report benefits from the individual’s history of physical self-awareness and captures
current health status relative to their personal context (i.e. their own health history, age group, etc.; Jylhä, 2009). It can be argued that comparing current status against a whole history of subjective self-awareness leads self-reported status to be a more meaningful measure of change in health status.

An analogy to the use of self-perception measures of physical status and attention comes from research in pain. It is widely recognized in the literature that pain “interrupts attention and behavior and urges one to act” (C. Eccleston & Crombez, 1999). Attentional complaints are common in patients with chronic pain (McCracken & Iverson, 2001), and individuals with chronic pain have been shown to have deficits specifically on attentionally demanding tasks (C. Eccleston, 1994; see Moriarty, McGuire, & Finn, 2011). Eccleston and colleagues have hypothesized that pain competes for limited available attentional resources, and thus the disruption due to pain is more prominent during more demanding tasks (C. Eccleston & Crombez, 1999). For example, results from studies examining the effects of acute heat have show that it can disrupt performance on divided attention tasks (Moore, Keogh, & Eccleston, 2012). Psychomotor slowing as measured by reaction time tasks has been another common finding in patients with chronic pain (Hart, Martelli, & Zasler, 2000; Moriarty, et al., 2011; Oosterman, Derksen, van Wijck, Kessels, & Veldhuijzen, 2012). Worse performance on cognitive measures has also been documented in older adults with chronic pain (compared to older adults without chronic pain) and attention and processing speed performance was found to be related to pain intensity ratings (Weiner, Rudy, Morrow, Slaboda, & Lieber, 2006). Although not directly addressed, this also raises the question of whether such relationships are more pronounced in older adults.

The effects of pain on attention may be similar to the relationship between decline in physical health status and attention, where each draws on attentional resources. In HIV, this may manifest as reduced or even impaired attentional function, contributing to the persistent cognitive disorders observed in individuals with objectively controlled disease indices. We propose that self-reported physical health
status may provide valuable information about the role of health in cognitive function. The Medical Outcomes Study HIV Health Survey (MOS-HIV; Wu, Revicki, Jacobsen, & Malitz, 1997) is a self-report questionnaire that assesses health-related quality of life and well-being, and provides indices of overall self-perceived physical and mental health.

Aging

The relationship between aging processes and decline in aspects of attention are well-documented (Salthouse, 1996; Verhaeghen & Cerella, 2008). The age-related decline in processing speed (Salthouse, 2000; Salthouse, Kausler, & Saults, 1990) is found in divided attention or switching (J. T. Becker, Butters, Hermann, & D’Angelo, 1983; McDowd & Craik, 1988), and in selective attention, including inhibiting distracters (Gazzaley & D’Esposito, 2007). Underlying mechanisms for attentional decline in aging are, in part, attributed to reduced white matter integrity (Guttmann et al., 1998), mimicking primary factors related to cognitive decline in HIV (Tate, et al., 2009).

As individuals are living longer on HAART, the synergistic impact of aging and HIV processes is a major concern. The Centers for Disease Control and Prevention estimate that over half of those with HIV will be over 50 years old by 2015 (Centers for Disease Control, 2010) and that demographic is at greater risk for developing cognitive disorders compared to HIV− older adults (J. T. Becker, Lopez, Dew, & Aizenstein, 2004). As attention and processing speed are processes vulnerable in both HIV and aging, these may be most informative domains to detect the presence of early, mild deficits in older HIV+ adults (Hardy & Vance, 2009).

Reports of cognitive function in older HIV+ individuals portray a complex picture, however. One study reported significantly worse performance in older HIV+ adults (median-split, 37 years and older) across neuropsychological domains with particularly low performance on psychomotor processing speed tasks (Hardy et al., 1999). It was also noted that while a history of AIDS impacted performance in both
groups, the most impaired performance on processing speed tasks was found in older adults with AIDS, indicating particular vulnerability.

Comparison of young and old HIV+ groups with and without dementia showed that older participants were overall more impaired than younger ones on memory, attention and motor speed, and verbal fluency, than the younger group, and the older dementia group was worse on an executive attention task (Trail-Making Test B) than the younger dementia group (Sacktor et al., 2007). A recent study of older and younger HIV+ adults with HAND indicated that performance on measures of memory (e.g., visual delayed recall) best discriminated age groups (Tan et al., 2013). It warrants consideration that the impact of HIV on cognition maybe be relatively smaller in older adults with already low scores, which could reduce the likelihood of observing an interaction in observational studies. Some studies have failed to find an interaction between older age and HIV on neuropsychological tests (Valcour, Paul, Neuhaus, & Shikuma, 2011; van Gorp et al., 1994; Wilkie et al., 2003), however Valcour et al. (2011) suggested that HIV disease severity may play a role in any age-HIV interactions. Additionally, Morgan et al. (2011) found greater intraindividual variability in older adults compared to younger HIV+ or HIV- adults, which may limit the power of group comparisons in studies. And lastly, the impact of physical health decline may differentially influence cognitive functioning. While the impact of medical illness on cognition is a primary concern in cognitive assessment of all older adults (Potter & Attix, 2006), its impact remains a significant concern in HIV. Attention and processing speed are widely targeted for investigating any interactive effects of aging and HIV as this research develops (Hardy & Vance, 2009).

Attention

Attention is not a unidimensional construct (Cohen, 1993). A variety of measures have been described in neuropsychological literature as broadly capturing “attentional” function, and this is also the case with studies of HIV. Measures that tap different aspects of attention may provide unique and sensitive
means of assessing the impact of aging and physical health in this population, as well as providing insights into specific mechanisms that might be vulnerable. Such investigation is maximally informative when the attentional constructs pursued are carefully defined and measured.

Processing speed in HIV is a particular focus of most neuropsychological assessments, and simple reaction time tasks have consistently shown slowing to be present in HIV-related cognitive impairment (Carey et al., 2004; Hardy & Hinkin, 2002b; Heaton et al., 1995; Karlsen, Reinvang, & Froland, 1992; Woods, et al., 2009). Peripheral neuropathy is a common manifestation of HIV-related neurological changes (Evans et al., 2011) and may interact with neuropsychological performance, particularly on tasks that measure simple reaction time (Hall, Snyder, Messenheimer, & et al., 1991). As such, it can be a challenge to disentangle whether slowing on simple reaction time tasks is due to peripheral neurological disorders such as neuropathy, or primary cortical/subcortical dysfunction (Hardy & Hinkin, 2002a), but is nonetheless important to pursue. Studies using reaction time tasks that can discriminate attentional components should be more informative of cognitive processing speed. Studies of simple reaction time detection in HIV have been reviewed by Hardy and Hinkin (2002a) and the following discussion focuses on more complex reaction time studies.

Perdices and Cooper (1989) hypothesized that reaction time tests may be a sensitive measure of cognitive decline in HIV. While they found a significant linear increase between reaction time and HIV disease stage on a choice reaction time task, a simple reaction time task did not differ between groups (Perdices & Cooper, 1989). Similarly, Dunlop and colleagues investigated performance on different reaction time tests in HIV+ adult men with mild/moderate disease progression versus more severe disease progression, and controls (Dunlop, Bjorklund, Abdelnoor, & Myrvang, 1992). They also found that a “complex reaction time” test, involving judgment and choice, was most sensitive to functional differences between groups. Comparing choice versus simple detection tasks revealed that the additional attentional
demands compound slowing, as longer reaction times were found in an HIV+ sample compared to seronegative controls (Hardy & Hinkin, 2002b). Comparisons across disease severity staging indicate that attention and information processing speed are particularly sensitive in distinguishing symptomatic HIV from AIDS (Cysique, Maruff, & Brew, 2006; Reger, Welsh, Razani, Martin, & Boone, 2002).

In order to distinguish psychomotor processing speed from cognitive processing speed, Llorente and colleagues (1998) investigated performance in asymptomatic HIV+, symptomatic HIV+, and HIV- control groups on various processing speed tasks. These include: 1) psychomotor speed tasks (i.e. Trail Making Test, Grooved Pegboard, and Symbol Digit Modalities); 2) computerized psychomotor speed choice reaction time and sequential reaction time tasks; 3) cognitive processing speed tasks that subtracted psychomotor performance from a complex reaction time task, and; 4) a cognitive processing speed task requiring inhibition of over learned responses (i.e. the Stroop Interference Task accounting for reading speed.) Performance on all tasks was worse in the HIV+ symptomatic group than the HIV+ asymptomatic group or HIV- control group. The asymptomatic HIV+ group was worse than the HIV- group only on the Grooved Pegboard, which the authors suggested might be related to the particular sensitivity of that measure to HIV-related neurological damage or the effects of peripheral neuropathy. Nonetheless, these results support that HIV-related slowing manifests in both psychomotor and cognitive processing speed tasks.

Attention is often assessed in other ways as well. Heaton et al. (1995) investigated neuropsychological performance using an extensive battery in HIV+ groups varying by disease stage according to CDC criteria, and found attention - including untimed tasks, vigilance tasks, and working memory tasks, to be the most sensitive tasks to cognitive decline across all groups, followed by learning and verbal performance. Stern and colleagues (2001) followed 146 HIV+ adults biyearly for 2.5 years with clinical and neuropsychological evaluations. Of the forty five participants who developed dementia (pre-
HAART era), their poorer performance on attention and processing speed tasks (i.e. Digit Symbol and Grooved Pegboard) was already detected at baseline, providing support that attention and processing speed performance had predictive properties of future conversion to dementia. A meta-analysis of 41 studies (Reger, et al., 2002) compared performance of HIV participants across asymptomatic, symptomatic, and AIDS groups to seronegative controls. The greatest effect sizes were reported for the cognitive domains of motor speed, speed of information processing (including simple and choice reaction time tasks, sustained attention, working memory, and psychomotor speed), executive function, and language. Another meta-analysis comparing HIV+ groups at varying stages of disease severity without HAART treatment (Cysique, et al., 2006) found the highest mean effect sizes in the HIV+ symptomatic group to be the cognitive domains of motor coordination and complex attention (including measures of sustained attention, working memory, and executive function).

Cortical activity observed in EEG studies indicated that asymptomatic HIV+ adults compared to HIV- controls exhibited less efficient attentional processing during an auditory attention task involving detection and decision-making (Linnville & Elliott, 1997). Other EEG evidence also showed dysfunctional attentional processes. One study (Fein, Biggins, & Mackay, 1995) reported that the P3A latency (a component hypothesized to be related to frontal attentional processes) was delayed and was related to the progression of cognitive impairment in HIV.

Cohen described that most attempts to measure attentional function often rely in part on processing speed (2009). As slowed information processing speed undercuts attentional capacity and efficiency, it is therefore difficult to test attentional functions independent of processing speed (Cohen, 2009). Cohen did describe some executive attentional capacities such as inhibition, initiation, and executive control that, when tested in untimed conditions (1993), may indicate attentional abilities unmediated by processing speed. Thus, to improve characterization of HIV-related cognitive decline,
meaningful measures of multiple attentional faculties are needed to characterize mild impairment in HIV. Assessing different components of attention using multiple types of measures are critical and measures should include attentional abilities that can be dissociated from processing speed.

One cleverly designed study (Jasiukaitis & Fein, 1999) used lexical decision-making tasks to assess whether the integrity of attentional networks in HIV and/or processing speed were responsible for impairment. Performance was compared between two HIV+ groups who were categorized as cognitively impaired or unimpaired, and a HIV- control group (Jasiukaitis & Fein, 1999). Using a lexical decision-making task, the researchers captured reaction time to target words after a semantic prime (the word’s antonym) and, using a stimulus categorization task, measured reaction time to target words after a repetition prime. They found that all three groups showed faster reaction times when the target word was primed with repetition, and the HIV+ unimpaired group and HIV- control group demonstrated faster reaction time after a semantic prime. However, the HIV+ impaired group showed no difference in reaction time with or without a semantic prime, suggesting that those participants benefitted from the visuospatial cue (the target word), but did not benefit from a semantic cue (the target word’s antonym.) These findings supported the preservation of posterior visuospatial attentional processes in the context of cognitive impairment in HIV, and implicated impaired attentional function mediated by frontal semantic circuits. Such results also indicated that attentional function not reliant on processing speed is also at risk in HIV.

Taken together, these results indicate that deficits in processing speed and attention occur in early stages of HIV-related cognitive impairment. Additionally, motor and cognitive processing speed are both affected, but processing speed alone is not solely responsible for the observed attentional decline. Rather, other attentional components are at risk as well and should be independently considered in neuropsychological studies of HIV. Finally, novel measures focused on specific, fundamental aspects of
attentional processes may be more sensitive to subtle decline in HIV, aging, and poor physical health status, which can help illuminate the status of attentional function with greater specificity for investigations such as this one.

With these caveats in mind, we selected three visual attention tasks for the current study that tapped different components of neuroattentional circuitry: (1) a Simple Reaction Time Task that captures the foreperiod effect (Bherer & Belleville, 2004; Niemi & Näätänen, 1981); (2) a Covert Orienting Task (Corbetta & Shulman, 1998; Posner, Snyder, & Davidson, 1980) used to address the benefits of spatial orienting; and (3) an Attentional Blink task (Kavcic & Scheid, 2011; Perry & Hodges, 2003) used to address cognitive differences in attention with and without top-down cues. All tasks were also selected because we could manipulate the influence of attentional load. Thus, we were able to explore the impact of aging and self-reported physical health under conditions of heightened attentional load in detection, orienting, and cognitive attention and processing speed measures.

**Foreperiod Effect**

The foreperiod effect is the preparatory period before reacting to a stimulus (Niemi & Näätänen, 1981). Typically, very short interstimulus intervals (ISIs) lead to increased reaction time. One explanation for this phenomenon is that the longer the duration between expected stimuli the more likely the stimuli will occur, thus increasing the readiness to respond (Niemi & Näätänen, 1981). As excellently described by Bherer and Belleville (2004), the longer one is waiting at a red traffic light, the greater the probability of it turning green and thus the more one is prepared to react (i.e., step on the gas) when it does turn green, resulting in short reaction times. Conversely, if the light turns green very quickly after it had turned red, one is less prepared to step on the gas, resulting in longer reaction times.
This foreperiod effect may be vulnerable to aging. Bherer and Belleville’s study (2004) demonstrated that while older adults (>65 years old) were overall slower to react compared to younger adults (20-26 years old), this difference widened significantly at very short preparatory periods. The authors suggested that older adults are less efficient at maintaining preparedness for uncertain events. It is likely that older adults are less able to maintain an optimally attentive state under the demands imposed by variable and short interstimulus intervals.

To our knowledge, there are no prior studies of the foreperiod effect in HIV, and it warrants particular interest in HIV and aging. First, as described above, older adults may experience reduced efficiency for attending to uncertain events, resulting in slowed reaction time. Further, it has been hypothesized that frontal neural circuitry is responsible for “preparatory attention” (Stuss, Shallice, Alexander, & Picton, 1995). As described above, frontal-subcortical processes are particularly vulnerable to HIV-related cognitive decline. Thus, measures of the foreperiod effect may be particularly useful in assessing subtle attentional changes in aging and HIV.

Covert Orienting

Posner’s Covert Orienting paradigm (Posner, et al., 1980), measures the influence of pre-target spatial cues on reaction time. The orienting mechanism is considered covert because cues are presented for durations shorter than a saccade (i.e., 350 msec) and participants are instructed not to move their gaze from a central fixation point throughout the task. According to Posner and colleagues (Posner, Walker, Friedrich, & Rafal, 1984), the steps involved in orienting include disengaging from the current focus of attention, shifting to the new location of the target, and re-engaging attention on the new target. Evidence from Posner’s seminal studies (1980) demonstrated that pre-target predictive cues (i.e., valid cues) facilitate reaction time, whereas pre-target counter-predictive cues (i.e., invalid cues), hinder reaction time. The “cost” in reaction time to the target following an invalid cue is the time needed to disengage, shift, and re-
engage in the new target. Evidence from patients with focal parietal lobe brain injury (Posner, et al., 1984) and neuroimaging studies (Corbetta, Kincade, Ollinger, McAvoy, & Shulman, 2000; Corbetta & Shulman, 1998) indicate that parietal areas are largely responsible for these attentional orienting mechanisms.

There have been prior studies of covert orienting in healthy aging and in HIV+ adults; however, no prior studies have investigated the interaction of aging and HIV on this attentional mechanism. Covert orienting studies in healthy aging have found that older adults and adults with dementia of the Alzheimer’s type demonstrate greater costs from invalid cues compared to younger adults (Faust & Balota, 1997). Of the components of orienting (i.e., disengage, shift, and re-engage) that may decline in aging and lead to such greater costs, slowed ability to disengage is a likely candidate. Parasuraman et al. (1992) demonstrated that patients with mild to moderate Alzheimer’s disease showed greater costs from invalid cues compared to controls, but had comparable benefits from valid cues, suggesting that the ability to quickly disengage was likely compromised.

Covert orienting is also affected in HIV. Symptomatic HIV+ individuals showed smaller effects of valid attentional cueing than asymptomatic HIV+ individuals and healthy controls (E. M. Martin, Sorensen, Robertson, Edelstein, & Chirurgi, 1992), indicating reduced efficiency of the orienting system. But, not all studies have found similar effects. Non-spatial cueing (i.e., increased screen luminance) on another covert orienting task (Maruff et al., 1995) was found to impede reaction times in patients with AIDS Dementia Complex, whereas performance after directive cueing was normal, raising the question of whether directive cueing is vulnerable in HIV. Given the evidence of an independent impact of aging and HIV on mechanisms of orienting attention, we selected a covert orienting paradigm to investigate the possible subtle synergistic effects.

**Attentional Blink**
When stimuli are presented in rapid succession, resources used for processing and identifying the first stimulus can prevent or impair accurate processing of the succeeding stimulus, known as the “attentional blink” (AB) phenomenon (Duncan, Ward, & Shapiro, 1994). A common attentional blink paradigm is the rapid serial visual presentation paradigm, in which two targets (typically letters) are placed among a stream of stimuli (Raymond, Shapiro, & Arnell, 1992). The attentional blink phenomenon is then measured by the accuracy of the second target after varying stimulus onset asynchrony (SOA; i.e., durations between the onset of stimuli).

There is evidence that age affects the duration of the attentional blink. Older adults take longer to accrue resources and are only able to identify the second of two targets when it is after a longer interval (i.e., have a greater dwell period), compared to younger adults who exhibited a shorter dwell period (Georgiou-Karistianis et al., 2007; Lahar, Isaak, & McArthur, 2001). Perry and Hodges (2003) examined attentional blink in subjects with Mild Cognitive Impairment (MCI) using a variation of the classic rapid serial visual presentation paradigm. In brief, their experimental apparatus involved varying the time between targets as opposed to number of distracters. They found that MCI subjects had worse accuracy (i.e., greater attentional blink magnitude) at short intervals compared to healthy older adult controls.

While the exact neuropsychological mechanisms of the attentional blink remain in question, evidence from other disease models are useful. Increased attentional blink duration has been observed in patients with multiple sclerosis (Kavcic & Scheid, 2011), and Huntington’s disease (Georgiou-Karistianis et al., 2012) and disruption of frontal-subcortical and frontal-parietal and white matter tracts have been implicated. Again, as these are also areas vulnerable in HIV, an attentional blink experimental paradigm was selected to examine attentional function in HIV. To our knowledge, no prior studies have investigated the attentional blink in HIV.
An additional component of the attentional blink paradigm used in our study allowed us to investigate the effects of top-down processing. Our experimental procedure, modeled after Perry and Hodges (2003) experiment, allows us to examine the effects of an a priori instruction condition indicating what item to attend to – this was identified as a top-down instruction condition and could provide an advantage for faster, more accurate performance. There is evidence of reduced executive attentional control in aging and specifically decline in top-down processing. Gazzaley and colleagues found that older adults (60-77 y.o.) had greater difficulty suppressing irrelevant stimuli when given a top-down instruction (e.g. trying to remember one type of stimuli) during an rapid serial visual presentation task compared to younger adults (19-30 y/o; Gazzaley, Cooney, Rissman, & D'Esposito, 2005). Subsequent EEG studies from this group showed that top-down mechanisms evident in the pattern of activity observed in a younger sample were not similarly evident in an older sample (Gazzaley et al., 2008). Their data indicated reduced efficiency among the older sample such that activity in primary visual areas (i.e., the occipital cortex) and top-down executive areas (i.e., medial pre-frontal cortex), were uniform regardless of whether there was a top-down condition. However, not all studies have found similar age-related decline in top-down processing. For instance, one guided search study (Madden, Whiting, Cabeza, & Huettel, 2004) did not find any age-related differences in the effects of top-down instruction. In their alternate rapid serial visual presentation task, participants saw both targets and distracters simultaneously, rather than serially. It can be argued that any age-related effect on suppression would not be as apparent in the Madden et al. study (2004) because the viewer could shift attention to other stimuli, including the target, volitionally. In contrast, the studies performed by Gazzaley and colleagues (2005, 2008) involved presentation of irrelevant stimuli at the same frequency and duration as target stimuli. The serial exposure to stimuli involves keeping the top-down instruction set active while processing one stimulus at a time, thus this paradigm uniquely includes a fixed temporal demand that may be vulnerable in older adults. To our knowledge, there have been no studies of top-down processing using reaction time attention tasks in HIV. Considering the
evidence of reduced top-down processing in aging with the indication that changes in frontal suppression mechanisms are responsible, we aimed to examine this phenomenon in HIV and the possible impact of aging and self-reported physical health status.

Several questions remain unanswered in the field of cognitive dysfunction associated with HIV. First, as a large proportion of this population advances into older age, what is the contribution of aging processes on cognition in what we know is an already cognitively vulnerable group? In addition to cognitive vulnerability, this population is also vulnerable to decline in health stemming from combined effects of longer periods of immunocompromise and long-term effects of chronic infection. Given this, are there general health factors that may contribute to or worsen cognitive decline? Further, does aging and physical health interface and result in particular susceptibility to cognitive decline? With these considerations in mind, how can we meaningfully assess cognitive differences to understand if vulnerabilities associated with HIV are specific to difference factors? The present study was designed to contribute to address these questions, by increasing our understanding of cognitive decline in HIV examining the relationship between the important factors of aging and physical health status using select measures hypothesized to be sensitive to these relationships.

**Aims and Hypotheses**

The current review raises several questions about the influence of physical health and aging in HIV. We were interested in whether measures of cognition, and attention in particular, revealed the influence of worse health status or advancing age in persons with HIV. Those cognitive functions with known underlying neural substrates compromised by HIV or by aging would be likely be most susceptible, e.g., the subcortical-striatal or frontal executive system. The effect of poor physical health on specific neural substrates in HIV is less well understood, but given the findings from pain research, it is reasonable to
predict that high-load cognitive tasks that further tax resources of an already stressed neural system are the best candidates to observe such an effect.

This project investigated the impact of self-reported physical health, aging, and their interaction on load-related attention and cognition in adults with HIV. **Aim 1** posits that if poor physical health drains cognitive resources, more demanding cognitive tasks that also stress the same resources would be particularly vulnerable. Given this, **Aim 1** was designed to examine whether poor physical health would compromise function at higher attentional load, using three different attention tasks, each representing different underlying neural mechanisms. Further, **Aim 1** examined the effects of poor physical health on other more complex neuropsychological tests sensitive to high resource demand (e.g., tests of working memory, tests under timed conditions, and mental flexibility.) **Aim 2** examined whether the cognitive skills of slowed processing speed and executive functioning are especially susceptible to demands under limited resources, considering the robust evidence that these systems are compromised in HIV. To investigate attention, we chose three tasks that represented disparate underlying neural mechanisms and could be manipulated under varying load conditions. We thus examined performance of high load conditions in a simple reaction time task using the foreperiod effect (subcortical-frontal system), top-down executive conditions in an attentional blink task (executive system), and effects of invalid cueing in covert orienting (parietal system). We independently examined the if speed was particularly compromised on executive measures. Lastly, **Aim 3** examined whether the combined effects of poor health and advancing age can detrimentally affect cognition in persons with HIV. Again, we examined if more demanding tasks differed from less demanding tasks, suspecting that the combination of poor health and older age with cognitive tasks that tax resources could be particularly detrimental to persons with HIV.

**Aim 1:** To examine the impact of physical health status on attention and other standard cognitive domains in non-demented HIV+ individuals.
Hypothesis 1a: We hypothesized that the HIV+ group with lower self-reported health status will demonstrate worse performance compared to the HIV+ group with better self-reported health status on each of the three attention tasks attention tasks on conditions of high attentional load.

Hypothesis 1b: We hypothesized that the HIV+ group with low health status will demonstrate worse performance compared to the HIV+ group with high health status on neuropsychological measures of working memory, cognitive and psychomotor processing speed, and mental flexibility in timed conditions.

AIM 2: To examine the impact of aging in HIV on cognition by comparing performance on specific attentional measures between younger (<50 y.o.) and older (≥50 y.o.) non-demented individuals with HIV.

Hypothesis 2a: We hypothesized that the HIV+ group of older adults will demonstrate worse performance compared the HIV+ group of younger adults on attention tasks that draw on executive processes under temporal demands, i.e., the foreperiod, the attentional blink, and top-down application of executive control.

Hypothesis 2b: We hypothesized that the HIV+ group of older adults will demonstrate worse performance compared the group of younger HIV+ adults on neuropsychological tests of executive functioning under temporal demand (i.e. set-shifting, verbal fluency).

AIM 3: To examine the synergistic effects of worse physical health status and older age on attention in HIV.

Hypothesis 3a: We hypothesized that there will be an interaction between health status and age, such that those older HIV+ adults with lower self-reported physical health status will perform most poorly on high load attention measures involving executive processes (i.e., the foreperiod, attentional blink, and top-down executive control) than younger HIV+ adults with higher self-reported physical health status.
**Hypothesis 3b:** We hypothesized that there will be a linear additive relationship between lower self-reported physical health, older age on high load attention measures.

**Hypothesis 3c:** We hypothesized that the group of older HIV+ adults with lower self-reported physical health status will perform most poorly on neuropsychological measures of cognitive and psychomotor processing speed reliant on executive processes.

**Exploratory analyses:** While attention and processing speed consistently emerge as vulnerable in HIV, there is no consensus regarding a distinct neuropsychological profile associated with HIV infection. Thus, we sought to examine the effects of self-reported physical health status and age on neuropsychological tests that measure other cognitive domains, including learning and memory, naming, and visuospatial functioning.
Methods

Sample

Forty-two participants were recruited from the Center for HIV Educational Studies and Training (CHEST) of Hunter College of the City University of New York, located in lower Manhattan. This study was approved by the Institutional Review Boards of the Graduate Center, Hunter College, and Queens College of the City University of New York; all participants completed the informed consent process. The sample was divided into young (N=17) and old (N=25) groups, see Table 1A for demographic information. Using a cut-point of 50 years and older for the old group is consistent with conventional grouping in the HIV literature and CDC standards (Centers for Disease Control and Prevention, 2008). Broadly, there were no demographic differences found between groups (aside from age as designed) and groups were largely comparable on estimated IQ, cognitive screening scores, and most HIV disease variables; however, the old group had been diagnosed with HIV for longer than the young group.

Participants were also grouped into high health (N=21) and low health (N=21) based on a median split of the MOS-HIV Physical Health summary score (median = 50.30) see table 1B for demographic information. No group differences were observed on any demographic variables, cognitive screening scores, or HIV disease related variable (aside from MOS-HIV Physical Health Summary score as designed.) There was not a significant difference in health status by age; $\chi^2=2.47, p=.21$. Further, MOS-HIV Physical Health summary scores were comparable between age-groups within each Self-Reported Physical Health Status group (i.e., young-low health was not significantly different from old-Low Health, and young-high health was not significantly different from old-High Health.)

Inclusion criteria included a diagnosis of HIV (verified by medical records, an M11Q form, prescription bottle, or membership card in the Gay Men’s Health Crisis), normal or corrected to normal vision, and cognitive function within normal limits as measured by the Mini-Mental State Examination.
(MMSE; Folstein, Folstein, & McHugh, 1975), with a score of 26 or greater. Exclusion criteria included self-reported history of other neurological disorders including: mild cognitive impairment, dementia, Parkinson’s or Huntington’s diseases, significant cerebrovascular disease, epilepsy, traumatic brain injury with loss of consciousness greater than 20 minutes, attention-deficit/hyperactivity disorder; history of schizophrenia or bipolar disorder; or current use of medication that influences motor or cognitive function such as Benadryl (diphenhydramine), Ativan (lorazepam), Xanax (alprazolam), Restoril (temazepam), Lunesta (eszopiclone), Ambien (zolpidem), and Valium (diazepam). Participants with history of a mood disorder were excluded if the participant reported that it was not well controlled or resolved at the time of enrollment.

Education, gender, and estimated verbal IQ were compared across experimental groups using ANOVA for continuous variables and Chi Square or Fisher’s Exact Test for dichotomous variables, to ensure appropriate comparison on dependent measures (see Table 1).

Substance Use

Prior or current history of substance use is of particular concern in the HIV+ population. In order to better characterize our sample, we examined the frequency of lifetime history of substance use between the groups of interest. We found that the young group had significantly more members with a history of stimulant abuse or dependence (n=5, 29%) compared to the old group (n=0, 0%), $\chi^2 = 8.35, p = .01$. We also found that the old group had significantly more members with a history of opiate abuse or dependence(n=9, 36%) compared to the young group (n=0, 0%), $\chi^2 = 8.35, p = .01$. Between health status groups the only significant difference observed was that there were more individuals in the high health group with a history of stimulant use (n=5, 24%) compared to the low health group (n=0, 0%), $\chi^2 = 8.35, p = .01$; it is noted that these are the same five individuals with a history of stimulant use in the young group.
Although we observed these differences, we did not correct for history of substance abuse/dependence in our analyses for two reasons. First, from a statistical standpoint, with a larger sample size one might be able to repeat analyses after removing the participants with a history of substance abuse/dependence, to determine if any results are impacted. Unfortunately, the number of individuals with a history of stimulant or opiate use in this sample, while relatively small, is a substantial proportion of the groups of interest. Removing these individuals would substantially reduce power. On the other hand, the numbers of individuals with a history of either stimulant or opiate abuse/dependence are too small to compare against those without a history of either substance abuse/dependence. Second, from a scientific perspective, there is precedent to support the inclusion of individuals with substance use history in analysis without correcting for dichotomized use history variables. It has been suggested that proper examination of the impact of substance use requires specific and detailed measurement of various related factors (e.g., nature, type, pattern, duration, etc.; Durvasula & Hinkin, 2006). Few studies are able to accurately capture such comprehensive details due to methodological limitations and such data were not available in our sample. Further, others have recently suggested that in the absence of very specific parameters regarding the nature of the substance use, analyses that include only a binary variable may be minimally informative (Tan, et al., 2013). Thus, substance abuse/dependence was not statistically or methodologically controlled for in this study, but we nonetheless interpreted results being mindful of groups’ substance abuse/dependence histories.

Procedure

Participants were administered a screening questionnaire to assess the above inclusion exclusion criteria, followed by the two cognitive screens (MMSE and DRS). Self-reported demographic information and year of HIV diagnosis was collected. Participants were then administered the battery of
neuropsychological tests and computerized attention tasks. Participants underwent substance abuse interviews and completed the Medical Outcomes Study-HIV Health Survey (MOS-HIV; Wu et al., 1991).

The computerized attention tasks were administered in a well-lit room on a flat screen monitor connected to a mount and an Ergodex® key pad with one key positioned in the center of the pad. After participants were seated within comfortable range of the key pad, the monitors were adjusted to be 50 centimeters from the participant’s face and vertically and horizontally centered at each participant’s line of vision. Participants were instructed not to deviate from that position throughout the experiment, and their placement was continually monitored.

Measures
Foreperiod Effect: Simple Reaction Time Task (SRT). See Figure 1. The SRT assesses reaction time (RT) to detection of a stimulus, measured in milliseconds (ms). The participant is asked to respond with a button press to a stimulus (i.e., an asterisk) presented centrally at varying interstimulus intervals (ISIs). Ten trials at each of five possible ISIs (350, 500, 650, 850, and 1100, ms) were presented randomly, totaling 60 trials. The ISIs were chosen based on previous studies of the foreperiod effect (Niemi & Näätänen, 1981; Vallesi, Shallice, & Walsh, 2007).

RT data management proceeded as follows. First, RT on the first trial for each participant was removed because there was no preceding trial and thus no measure of the foreperiod effect. Z-scores were calculated for RT’s within the performance of each participant, and outliers, operationalized as z-scores greater +3.00 or less than -3.00, were removed from the dataset. Anticipatory trials (RT less than 100 ms), erroneous double clicks, or missed responses were identified and removed from the dataset. All anticipatory and outlier trials were summed, and they totaled <3% of data points for any one participant across the entire sample. Once these trials were removed, median RT was calculated for each participant at
each ISI, which was used as the dependent variable for the analyses. **In the SRT task**, RT under high load was defined as RT after the shortest ISI (350 ms).

**Covert Orienting Task.** See Figure 2. The Covert Orienting paradigm (Posner, 1980) assesses RT to respond to a target (‘X’) preceded by spatially-presented orienting Valid or Invalid cues in the right or left visual field or a Neutral cue condition with cues presented to both visual fields simultaneously. Participants were instructed to fixate on a red cross at the center of the screen for the duration of the experiment. The cue-target interval was set at 250 ms, which is less than a 350 ms estimate of a saccade and prevents overt eye movements to the target. Additional catch trials (trials at different speeds to prevent predictable presentation rates) were included at cue-target intervals of 850 msec. Slower RT’s on invalid cue conditions reflects time to disengage from cue to target, while faster RT’s on the valid condition indicate the benefit of pre-cued orienting. In this task, participants were asked to press a button on the Ergodex immediately upon detecting the stimuli. Five blocks of 34 trials were presented in random order, totaling 170 trials. Within each block of 34 trials, six were catch trials, four were Invalid trials, four were Neutral trials, and the remaining 20 were Valid trials.

Prior to aggregating the data, catch trials were removed from the dataset. RT data were aggregated across trial blocks by cue type (e.g. Valid, Invalid, and Neutral) for each participant, and median RT to cue type was used in the analyses. Due to experimenter error, three participants did not complete all five blocks and thus data for 15 participants in the young group and 24 participants in the old group were included in the Covert Orienting Task analyses. **In the Covert Orienting task**, RT under high load was defined as RT after an Invalid cue.

**Attentional Blink Task.** See Figure 3. The current experimental procedure was modeled after previously published methods of measuring attentional blink used in Alzheimer’s disease (Perry & Hodges, 2003), which allows for a simpler presentation of stimuli rather than the more typical lag presentation. In
this simpler modification, participants are asked to fixate on a red cross at the center of the screen
surrounded by four white boxes to the left, right, top and bottom. Two stimuli of different categories (e.g.
a letter and a number) are presented rapidly in either the left or the right white box. The participant is
asked to verbally report both stimuli, which are then recorded by the examiner. The time interval between
the two stimuli presentations was operationalized as the SOA. Monitor refresh rates were standardized
across participants to be set at 75 Hertz, which produces a refresh rate of 13.3 ms per frame and multiples
of this rate were used in the stimulus design. Five different SOA intervals between stimuli were used: 133,
266, 399, 532, and 665 ms, and were randomized. There was also a 0 ms (or simultaneous exposure)
condition (not included in analyses as described below.) There were four trials of 0 ms SOA and eight trials
of each other SOA, totaling 44 trials. Presentation of the first item could be on the right or left and was
counterbalanced at each SOA and randomized throughout the trials.

Prior to administration of the trials, stimulus calibration was performed for each participant. This
included a single trial in which stimulus exposure times were systematically varied to determine the
duration of stimulus exposure at which 85% detection accuracy was achieved. Of note, there were no
group differences observed on the duration of stimulus exposure for either Age groups or Self-Reported
Physical Health Status groups. That stimulus duration was then recorded and entered into the computer
program that specified stimulus exposure duration for all subsequent trials of the experiment for that
participant. Participants completed 10 practice trials and 44 experimental trials.

Again, two stimuli of different categories (a letter and a number) were presented during each trial.

A) Report Both: In the Report Both instruction condition, participants were asked to report both
the number and the letter stimuli after each trial. In this condition, we are able to
capture the attentional blink because we can document that the first stimulus was accurately perceived.

B) Report One: In the Report One instruction condition, participants were asked to report only one of the stimuli categories (i.e. report the letter or report the number.) All participants underwent both instruction conditions and administration of the first instruction condition was counterbalanced across participants.

Comparison of these conditions allows us to capture the effects of the top-down instruction (i.e., report only one stimuli category.)

This experiment yielded two measures: accuracy of reporting the stimulus presented first and accuracy of reporting the stimulus presented second. Only trials in which the first stimulus was accurately reported were included in analyses of the Report Both condition (in order to capture the AB phenomenon.) For the purpose of these analyses, accuracy at the 0 ms SOA, simultaneous exposure, was excluded because it provides no measure of the blink phenomenon. Therefore, measures of accuracy of the first-reported stimulus and the second-reported stimulus at each of five SOAs were used in analyses. On the attentional blink task, performance under high load was defined as accuracy of the second stimulus after the two shortest SOAs (i.e., 133, and 266 ms) if the first stimulus was correct.

Physical Health. We included a self-report measure of self-reported physical health, the Medical Outcomes Study-HIV Health Survey (MOS-HIV; Wu, et al., 1997), which was developed to assess health-related quality of life, specifically in the HIV population. Responses to questionnaire items were aggregated according to published procedures to produce 11 subscale scores including: (1) General Health Perceptions (2) Physical Functioning, (3) Role Functioning, (4) Pain, (5) Social Functioning, (6) Mental Health, (7) Energy/Fatigue, (8) Health Distress, (9) Cognitive Functioning, (10) Quality of Life, and (11) Health
Transition. A Physical Health Summary Score (MOS-PH) and Mental Health Summary Score (MOS-MH), are derived from aggregating the above subscales at different weights. This study examined only the MOS-PH. The subscales with the highest weights in the MOS-PH calculation were Physical Functioning and Pain, whereas Quality of Life and Cognitive Function were the lowest weights assigned among the subscales. See Appendix for a list of the individual subscale weightings for the MOS-PH and MOS-MH. Higher scores on these measures indicate better health. Participants were grouped using the median-split method into a high health group and low health group (median = 50.30).

Neuropsychological Measures. A battery of standardized neuropsychological measures that included measures of attention and executive control, as well as other measures relevant to the HIV population was administered:

- Verbal intelligence was estimated by the North American Adult Reading Test (Blair & Spreen, 1989).

- Psychomotor speed:
  - Trail Making Test of the Delis-Kaplan Executive Function System (D-KEFS; Delis, Kaplan, & Kramer, 2001): there are 5 different conditions of this test. Condition 1 is a simple measure of visual search; Conditions 2 & 3 are measures of visual search and sequencing using, respectively, letters and numbers; Condition 4 is a selective attention task, alternating search of number versus letter, capturing mental flexibility; and Condition 5 consists of tracing a dotted line and is a measure psychomotor speed. Each condition yields a raw score (measured in seconds) for total time to complete the trail.
  - Grooved Pegboard Test (Klove, 1963): this is a commonly used test in HIV (Carey, et al., 2004), which measures psychomotor speed and manual dexterity. The raw score of total time (in seconds) to place all pegs in a pegboard was used in this study.
• Cognitive Processing speed:
  o Measures of verbal fluency have been previously associated with cognitive processing speed (Boone, Pontón, Gorsuch, González, & Miller, 1998). The current study used FAS phonemic fluency (Benton, Hamsher, Varney, & Spreen, 1983) and Category fluency (animals, fruits, and vegetables; Strauss, Sherman, & Spreen, 2006b). The total raw score (e.g. number of words generated within 60 seconds) on each task was used for analyses.

• Working Memory:
  o Number-Letter Sequencing from the Wechsler Adult Intelligence Test 3rd edition (WAIS III; Wechsler, 1981) is a working memory task that involves mentally sorting lists of letters and numbers; the raw score of total correct trials (out of 21) was used in analyses.

• Memory:
  o The Hopkins Verbal Learning Test-Revised (HVLT-R; Brandt & Benedict, 2001) is a list-learning test that creates scores for total recall (out of 30) across three learning trials of 10 words, delayed recall or number of words recalled after a 20-minute delay (out of 10), and delayed recognition (out of 20). Raw scores of each measure were used in analyses.

• Language:
  o The Boston Naming Test (BNT; Kaplan, Goodglass, & Weintraub, 1983) is a 60-item confrontation naming test; total correct raw score (out of 60) was used in analyses.

• Visuospatial function:
  o Visual Form Discrimination (Benton, Sivan, Hamsher, Varney, & Spreen, 1994) is a visuospatial forced-choice matching task. Participants match a geometric target design to one of four choices, which include the identical design and three similar designs. The total raw score (out of 32) was used in analyses.
We did not convert raw scores to z-scores derived from normative samples since we were interested in examining raw performance between age and self-reported physical health groups, and our aim was not to characterize or identify objective cognitive impairment in these samples. This approach is consistent with other work examining neuropsychological functioning in aging and HIV (Valcour, et al., 2011).

Analyses

**Preliminary Analyses:** Prior to testing hypotheses, we examined whether performance on dependent variables differed by gender or education. Our study included 31 males (74%) and 11 females (26%). Consistent with previous research on HIV+ patients (Satz et al., 1993), we dichotomized education into those with a High School education or less (≤H.S.; n=18, 43%), and those with more than a High School Education (>H.S.; n = 24, 57%). Gender and Education were submitted as single independent variables to ANOVA's to examine possible differences between groups across neuropsychological measures and experimental attention measures. We also checked the experimental manipulation of our computerized attention tasks by examining the main effects of each experimental condition in analysis of variance.

**Main Analyses:** Hypotheses were tested by first dividing sample into two age groups: young (30-49 years old) and old (50-75 years old); and two Self-Reported Physical Health Status groups: high health and Low Health, based on median split of the MOS-HIV Physical Health Summary Score.

**Hypotheses 1a, 2a, and 3a:** Data from each of the three computerized attention tasks were submitted one mixed-model repeated measures ANCOVA, with Years with HIV as a covariate. To test Hypotheses 1a, the independent variable of Self-Reported Physical Health (two levels: High and Low) was included; to test Hypothesis 2a, the independent variable of Age group (two levels: Young, Old) was
included; to test hypothesis 3a, the interaction between Self-Reported Physical Health and Age group was examined.

For the SRT task, we conducted a 2x2x5 mixed-model repeated measures ANCOVA with the independent and covariate variables above and a within-group variable of Inter-Stimulus Interval (ISI; 5 levels: 350, 500, 650, 800, and 1100 ms), with median reaction time as the dependent variable. For the Covert Orienting Task, we conducted a 2x2x3 mixed-model repeated measures ANCOVA with independent and covariate variables defined above, and the within group variable was the orienting Cue Type (three levels: Valid, Invalid, and Neutral) with median reaction time as the dependent variable.

For the attentional blink task during the report both stimuli condition, we first conducted a 2x2x5 mixed-model repeated measures ANCOVA with the independent and covariate variables defined above and a within-group variable of SOA (5 levels: 133, 266, 399, 532, 665 ms) using percent accuracy of the second stimulus if the first stimulus was correct as the dependent variable. Second (Hypotheses 2a and 3a), we conducted a 2x2x2x5 mixed-model repeated measures ANCOVA with independent and covariate variables defined above and the two within group variables were SOA (5 levels: 133, 266, 399, 532, 665 ms) using percent accuracy of the second stimulus, and Instruction Condition (2 levels: Report One (i.e., Top-Down), Report Both). In these latter analyses, the dependent variable is percent accuracy of the second stimulus, regardless if the first stimulus is correct during the report both condition as there is not an equivalent variable with which to compare on the report one condition (i.e., only one stimulus was reported.)

**Hypothesis 1b:** To test Hypothesis 1b, neuropsychological test scores were examined using univariate ANCOVA with Self-Reported Physical Health (two levels: High and Low) as an independent variable, and Age group (two levels: Young, Old) as another independent variable, and the covariate Years with HIV. The dependent variables were: WAIS-III Letter Number Sequencing (total score); Pegboard
Hypothesis 2b: To test Hypothesis 2b, neuropsychological test scores were examined using univariate ANCOVA with Age group (two levels: Young, Old) as an independent variable, and Self-Reported Physical Health (two levels: High and Low) as another independent variable, and the covariate with Years with HIV. The dependent variables were: D-KEFS Trail Making Tests, Condition 4 (total time in seconds); and Phonemic and Category fluencies (raw total words generated).

Hypothesis 3b: In order to test the linear additive relationship between age and self-reported physical health status on experimental conditions with highest attentional load, we conducted (1) linear contrast analyses, and (2) linear regressions. (1) Linear contrast coefficients were applied to a derived independent variable with four levels as follows: old – low health (-3); old – high health (-1); young – low health (1); young – high health (3). Four contrast analyses were conducted and the dependent variable was performance at each of the four predefined conditions of high attentional load on computerized attention tasks. Planned pair-wise comparisons were conducted on significant contrasts using Fisher’s Least Standard Difference (LSD) procedure. (2) Three hierarchical linear regression analyses were also performed with the pre-defined high load conditions on computerized attention tasks as the dependent variable and three continuous independent predictor variables entered in the following order: Years with HIV, Age, MOS-HIV Physical Health Summary Score.

Hypothesis 3c: To test the interaction between age and self-reported physical health, neuropsychological test scores were examined using univariate ANCOVA with 2 independent variables, Age group (2 levels: Young, Old), and Self-Reported Physical Health (2 levels: High and Low), and the
covariate with Years with HIV, on the following dependent variables: D-KEFS Trail Making Tests,
Condition 4 (total time in seconds); and Phonemic and Category fluencies (raw total words generated).

**Exploratory analyses:** We conducted exploratory analyses with a 2x2 univariate ANCOVA with independent variables of Age group (2 levels: Young, Old), and Self-Reported Physical Health (2 levels: High and Low), and a covariate of Years with HIV on is HVLT Total Trials (raw total score), HVLT Delayed Recall (raw total score), Boston Naming Test (raw total score), and the Visual For Discrimination Test (raw total score.)

When carrying out mixed-model analyses, if it was the case that the Sphericity assumption was not met, the Huyn-Feldt correction was used. When carrying out contrast analyses, if Levene’s test of homogeneity of variances was significant, we reported contrast tests that did not assume equal variances. All post-hoc comparisons were performed using Fisher’s Least Standard Difference (LSD) procedure. Two-tailed tests were used, and all analyses used the \( p < .05 \) level of significance and were carried out using SPSS 19.0 and SPSS 20 software.
Results

Preliminary Analyses of Demographic Differences in Dependent Measures

Neuropsychological Measures. Regarding gender, ANOVA revealed no significant differences between performance of men and women on neuropsychological measures except one: men performed higher on the Boston Naming Test (M = 51.62, SD = 6.78) compared to women (M = 45.09, SD = 6.62), \( F(1,40) = 7.60, p = .01 \). Regarding education, two significant differences were observed in ANOVA among all neuropsychological tests: those with more than a H.S. education were faster on a psychomotor task involving set-shifting (DKEFS Trails Condition 4), \( F(1,40) = 4.56, p = .04 \), and achieved more items on the Letter-Number Sequencing working memory task, \( F(1,40) = 4.77, p = .04 \). Thus, we did not correct for gender or education as we found few differences between men and women consistent with other studies (Faiíde Garrido, Lameiras Fernández, Foltz, Rodríguez Castro, & Carrera Fernández, 2013), and few differences between those with a high school education or less and those with more than a high school education across measures.

Simple Reaction Time (SRT). Results of ANOVA showed that women (M = 395.60, Standard Error (SE) = 24.21) had slower reaction times on this task than men (M = 333.69, SE = 14.42), \( F(1,40) = 4.77, p = .04 \). There was no interaction between gender and interstimulus interval (ISI), \( F(3.58,143.21) = 1.46, p = .22 \), which indicates that the pattern of performance between men and women over ISI conditions was similar. This allowed us to continue to examine the interactive effects of manipulating ISI to capture the foreperiod effect without controlling for gender. There were no differences on SRT by education, \( F(1,40) = .425, p = .52 \), nor was there an interaction between education and ISI, \( F(3.36,151.663) = 1.57, p = .19 \).
**Covert Orienting.** There was no main effect of gender found on ANOVA, $F(1,37) = .34, p = .56$, nor a nor an interaction between gender and cue type, $F(1.53, 56.42) = .94, p = .38$, indicating that men and women performed comparably on this measure. There was no main effect of education, $F(1,37) = .03, p = .87$, nor an interaction between education and cue type, $F(1.54, 56.92) = .10, p = .97$. Thus, we did not control for gender or education in analysis of this measure.

**Attentional Blink.** In the first condition of the attentional blink task (i.e., report both stimuli), there was no main effect of gender $F(1,40) = 2.63, p = .11$, nor an interaction between gender and Stimulus Onset Asynchrony (SOA), $F(3.20, 128) = .48, p = .71$. In the second condition examining the effects of a top-down instruction, there was also no main effect of gender, $F(1,40) = 1.26, p = .27$, nor an interaction between gender, instruction, and SOA $F(3.57, 143) = 1.42, p = .24$. No main effect of Education found in the first condition, $F(1,40) = .003, p = .96$, nor an interaction between education and SOA, $F(3.25, 130.9) = .65, p = .59$. In the second condition, there was also no main effect of Education, $F(1,40) = .001, p = .97$, nor an interaction between education and SOA, $F(3.59, 143) = 1.35, p = .26$. Thus, we did not control for gender or education in analysis of this measure.

**Preliminary Analysis to Check Computerized Tasks’ Manipulations**

We examined attention using three computerized tasks that measure different aspects of attention. We first examined the main effects of each task’s experimental manipulation in the main analyses’ repeated-measures mixed model ANCOVA to confirm that the measures elicited the attentional constructs as designed. This then allowed us to examine interactions with our variables of interest (i.e. self-reported physical health and age.) On the SRT, a main effect of interstimulus interval, $F(3.34, 123.42) = 6.04, p < .001, \eta_p^2 = .14$, indicated that the experimental manipulation (i.e. varying interstimulus intervals) did indeed capture the foreperiod effect, and mean reaction time at the shortest interval (i.e., 350 ms,
was longer than reaction time at longer intervals (i.e., 500 ms, $M=361.56$, $SD=103.94$; 650 ms, $M=325.92$, $SD=83.99$; 1100 ms, $M=326.26$, $SD=96.03$.)

Our second attention task was the Covert Orienting task which captures reaction times after different types of pre-target cues: Valid (same location), Invalid (different location), and Neutral (both locations.) We did find a trend for a main effect of Validity on reaction time, $F(1,74,59.20)=2.68, p=.08$, $\eta_p^2 = .07$, and post-hoc analysis showed that reaction time after the Valid cue ($M=409.96$, $SD=87.26$) was faster than reaction time after a Neutral cue ($M=436.90$, $SD=93.89$) or an Invalid ($M=460.38$, $SD=117.11$; $p's<.05$), as expected in a Covert Orienting paradigm.

The next attention task captured the attentional blink during two instruction conditions: report both stimuli, and report one stimulus. First, we examined accuracy only in during the first instruction condition (i.e., report both stimuli.) We examined percent accuracy of the second stimulus if the first stimulus was reported correctly. Results showed a main effect of SOA, $F(33.55,131.43)=4.48, p<.01$, $\eta_p^2 = .11$, and a significant linear contrast $F(1,38)=11.99, p<.01$. Post-hoc analysis indicated that accuracy was worst at shorter SOAs (i.e., 133 ms; 59%) compared to longer SOAs (i.e., 399 ms, 83%; 532 ms, 92%; 665 ms, 94%; $p's < .05$), demonstrating the attentional blink phenomenon, and allowing us to further examine any interactions.

To examine the effects of a top-down instruction (i.e. report one stimulus), we compared accuracy of the second stimulus presented under both instruction conditions. Data were similarly analyzed with a repeated-measures mixed model ANCOVA. We again found a main effect of SOA, $F(3.30,122.05)=5.59, p=.01$, $\eta_p^2 = .13$ with a significant linear contrast, $F(1,37)=5.59, p<.01$, demonstrating the attentional blink phenomenon. However, we did not find a main effect of the instruction condition, $F(1,135.93)=.09, p=.75$, which indicates that our top-down manipulation, i.e., testing accuracy of the second stimulus with
and without the benefit of a top-down instruction, did not achieve the expected effect of better performance with the aid of a top-down instruction. Therefore, further analysis examining any interaction with the top-down instruction condition was not supported.

Main Analyses

**Aim 1.** To examine the impact of physical health status on attention and other standard cognitive domains in non-demented HIV+ individuals.

**Hypothesis 1a.** To test hypothesis 1a, we examined main effects of Self-Reported Physical Health group on performance at high load conditions. On the SRT, results of the mixed-model repeated measures ANCOVA showed a main effect of Self-Reported Physical Health Status, $F(1,37) = 6.91, p = .01, \eta^2_p = .16$, indicating that reaction time in the low health group was longer ($M=387.45, SE=17.03$) than reaction times among the high health group ($M=312.35, SE=17.03$). However, we did not find any interaction between self-reported physical health status and interstimulus interval, $F(3.26, 123.86) = .76, p=.53$, indicating that the main effect of health status on performance was comparable across conditions of attentional load. On the Covert Orienting task, the mixed-model repeated measures ANCOVA showed a trend for a main effect of self-reported physical health status on the Covert Orienting task, $F(1,34)=3.67, p=.06$, indicating that the low health group had longer reaction times ($M=471.28, SE=20.98$) than the high health group ($M=398.34, SE=21.54$). There was a two-way interaction between Validity and Self-Reported Physical Health Status, $F(1.74,59.20)=4.71, p=.02, \eta^2_p = .12$; with a significant linear contrast, $F(1,34) = 5.04, p=.03, \eta^2_p = .13$. As demonstrated in Figure 4, the low health group took longer to respond after Invalid cues ($M=506.84, SD=134.58$) than after Neutral ($M=468.95, SD=108.65$) or Valid ($M=441.40, SD=98.39$) cues. In contrast, reaction time among those in the high health group was not similarly affected by the presentation of an Invalid cue, and was comparable to their reaction time after a Neutral cue.
On the attentional blink task in the first instruction condition (i.e., report both stimuli), results of a mixed-model repeated measures ANCOVA did not show a significant main effect of self-reported physical health status $F(1,37)=1.93$, $p=.17$, nor a significant interaction with SOA, $F(3.55,131.43)=.92$, $p=.45$. Thus, accuracy between self-reported physical health groups did not differ at conditions of high load (i.e. conditions of varying stimulus onset intervals.)

**Hypothesis 1b.** With regards to neuropsychological measures, results showed that those with low self-reported physical health had slower performances on a psychomotor speed measure involving visual search and sequencing (DKEFS Condition 3), and another involving mental flexibility (DKEFS Condition 4.) We also found that those in low self-reported physical health generated fewer words during a cognitive processing speed task, semantic fluency. See Table 2 for means and standard deviations for each test, and the outcome of each group comparison.

In sum, performance on some measures of attention at conditions of high cognitive load varied by physical health status, but not all. Specifically, among the three attention tasks, those in worse health showed poorer performance at the high load condition only on the Covert Orienting task. Those in worse self-reported physical health had worse performance on neuropsychological measures of psychomotor and cognitive processing speed and mental flexibility under timed conditions.

**Aim 2.** To examine the impact of aging in HIV on cognition by comparing performance on specific attentional measures between younger (<50 y.o.) and older ($\geq$50 y.o.) non-demented individuals with HIV.

**Hypothesis 2a.** To test hypothesis 1a, we examined main effects of Age group, and interactions between group and experimental manipulation on performance at high load conditions on attention tasks that draw on executive processes under temporal demands. Results of the mixed-model repeated measures
ANCOVA on reaction time during the SRT showed a main effect of Age group, \( F(1, 37) = 4.48, p = .04, \eta^2_p = .11 \), such that the old group was slower (\( M = 391.95, SE = 18.96 \)) than then young group (\( M = 372.76, SE = 15.19 \)). There was no interaction between Age group and interstimulus interval, \( F(3.34, 123.42) = .511, p = .69 \), indicating performance was comparable across attentional load conditions between younger and older adults.

Reaction times on the Covert Orienting task were examined in mixed-model, repeated measures ANCOVA. Older adults did not demonstrate significantly slower reaction times, with no main effect of Age group found, \( F(1, 34) = 2.90, p = .10 \). There was no interaction between Age group and Validity, \( F(1.74, 59.20) = .18, p = .81 \), indicating that the relative impact of different cue types was comparable between younger and older adults.

During the first instruction condition of the attentional blink task (i.e., report both stimuli), percent accuracy of the second stimulus was examined with a mixed-model repeated measures ANCOVA. There was no difference found between age groups, \( F(1, 37) = .01, p = .76 \). However, there was a trend for an SOA x Age group interaction, \( F(3.55, 131.43) = 2.38, p = .06, \eta^2_p = .06 \); indicating that the old group demonstrated a longer attentional blink than the young group. As can be seen in Figure 5, post-hoc analyses showed that at the very shortest SOA (133 ms) accuracy was comparable between the young group (57%) and old group (60%). However, at the next shortest SOA (266 ms), the young group’s performance improves (79%) and is significantly better than the old group’s performance (59%), which largely stays the same. Given that, as described above, there was not a significant effect of the top-down instruction condition, we did not examine any interactions with this variable.

**Hypothesis 2b.** When we examined performance on neuropsychological tests between age groups, results of univariate ANCOVA showed slowed processing speed on some measures in older adults, see
Table 2 means and standard deviations, and the statistic of group comparisons. This effect was found on two psychomotor speed tasks, one a simple tracing task (DKEFS Condition 5) and another task involving manual dexterity (Grooved Pegboard.) It was also found that older adults generated fewer words on a phonemic fluency task (FAS), and had worse performance on a working memory task (WAIS-III Letter-Number Sequencing.) Overall, we found that older adults were slower on one of our reaction time tasks and did demonstrate worse performance on some measures of processing speed and executive control.

**Aim 3.** To examine the synergistic effects of worse physical health status and older age on attention in HIV.

**Hypothesis 3a.** Results of the mix-model repeated measures ANCOVA on reaction time during the SRT task yielded a significant trend for an interaction between aging, self-reported physical health, and interstimulus interval was found, \( F(3.34, 123.86) = 2.43, p = .06, \eta_p^2 = .06 \), with a significant linear contrast, \( F(1,37) = 4.39, p = .04, \eta_p^2 = .11 \). As can been seen in Figure 6, at conditions of highest attentional load (i.e. SOAs 350 and 500 ms) younger adults in lower self-reported physical health were significantly slower (SOA 350: \( M=447.75, SD=108.87 \); SOA 500: \( M=379.17, SD=93.24 \)) than younger adults in higher self-reported physical health (SOA 350: \( M=335.41, SD=67.35 \); SOA 500: \( M=285.27, SD=48.16 \)), whereas there was no difference between self-reported physical health groups among older adults at these conditions. Looking at this interaction another way, age group differences were observed only in the high health group, where older adults were observed to be slower (\( M=428.25, SD=94.86 \)) than younger adults (\( M=335.41, SD=67.35 \)) at the condition of highest load (i.e. SOA 350ms); in the low health group, older and younger adults had comparable reaction times at high load conditions. Results of a mix-model repeated measures ANCOVA on reaction time in the Covert Orienting task did not show an interaction between self-reported physical health, age group, and cue type, \( F(1.74,59.20)=.02, p=.97. \)
In the attentional blink task, results of mixed-model repeated measures ANCOVA on accuracy during the first instruction condition (i.e. report both stimuli) did not indicate and significant interaction between age, self-reported physical health status, and SOA, $F(3.552,131.43) = 1.73, p = .15$.

While we did not examine the effects of a top-down instruction or any interactions with this variable, the mixed-model repeated measures ANCOVA used to analyze these effects did yield a significant interaction between age, self-reported physical health status, and SOA, $F(3.30,135.93)=2.93, p=.03, \eta^2_p = .08$ with a significant quadratic contrast, $F(1,37)=7.61, p<.01, \eta^2_p = .17$. As can be seen in Figure 7, post hoc analysis indicated that the young-low health group had the worst accuracy (i.e., greatest attentional blink magnitude,) at the condition of highest attentional load (i.e., SOA 133 ms; 34%), compared to either the young-high health group (64%), or the old-low health group (64%); the old-low health group performed comparably to the old-high health group.

**Hypothesis 3b.** We also examined linear additive effects of age and self-reported physical health on reaction time at the conditions of highest attentional load using contrast analysis. A significant effect of Age/Self-Reported Physical Health group was found on reaction time on the SRT at the highest load condition (i.e., 350 ms), $F(3,38) = 3.88, p = .02$, with a significant linear contrast, indicating fastest reaction times with younger age and better health ($M=335.41, SD=67.34$), $F(1,38) = 7.90, p = .01$. As can be seen in Figure 8, planned pair-wise comparisons revealed that reaction time of the young – high health group was fastest, and in fact the only group’s performance significantly different from the other three groups (old-Low Health, $M=456.80, SD=104.67$; old-High Health, $M=428.25, SD=94.85$; young-Low Health, $M=447.75, SD=108.87$.) This is also consistent with the results of a linear regression analysis onto reaction time at highest load condition, with Age, MOS-PH Summary Score, and Years with HIV as predictors. A significant final model was found, $F(3,38)=4.04, p=.01$, and there was a trend for the contribution of Self-Reported Physical Health Status ($p=.08$), but age was the only significant contributor
to the model ($p=.02$), with a Standardized Beta of .38. Thus, age emerges as the highest contributing factor to reaction time at the highest load condition on the SRT. To sum, results showed that younger adults in higher self-reported physical health had fastest reaction times compared the other groups, and the relative contributions of age and self-reported physical health status to reaction time during the high load condition on the SRT were not equal, with age emerging as a greater contributing factor.

Contrast analysis of reaction time during the condition of highest attentional load on the Covert Orienting task (i.e., reaction time after an Invalid cue) revealed a significant effect of Age/Self-Reported Physical Health group, $F(3,35) = 3.81, p = .02$. A significant linear contrast was found, indicating faster reaction times with younger age and higher self-reported physical health, $F(1,26.16) = 8.94, p = .01$. As can be seen in Figure 9, planned pair-wise comparisons revealed that reaction time of the young – high health group ($M=377.48, SD=76.11$) was significantly faster than that of the old – low health group ($M=522.81, SD=143.32$); no other significant differences were found. Results of a linear regression onto reaction time during the same high load condition (reaction time after and Invalid cue), with Age, MOS-PH Summary Score, and Years with HIV as predictors, did yield a significant final model, $F(3,35)= 7.42, p=.01$. Both Age ($p=.01$) and Self-Reported Physical Health status ($p=.01$) were significant predictors in the model, and their relative contributions to performance were comparable (Standardized Betas were .40 and -.38, respectively).

We then applied contrast analyses to accuracy during two conditions of high attentional load on the attentional blink task (i.e., SOAs 133ms, and 266ms.) There was no effect of Age/Self-Reported Physical Health group on accuracy after the first high load condition (SOA 133ms), $F(1,38) = .012, p = .91$. There was a significant effect of Age/Self-Reported Physical Health group on accuracy after the second high load condition (266 ms SOA), $F(1,38) = 4.94, p = .03$, and a significant linear contrast, $F(1,38) = 4.94, p = .03$. As can be seen in Figure 10, planned pair-wise comparisons revealed that the only significant
difference between groups was that the old – low health group had significantly worse accuracy (54%) than the young – high health group (80%). Results of regression onto accuracy during the first high load condition of the attentional blink task (accuracy after the shortest SOA (133 ms), with Age, MOS-PH Summary Score, and Years with HIV as predictors did not yield a significant final model, \( F(3,38) = .01, p = .99 \), nor did results of a linear regression onto accuracy during the second high load condition (SOA 266 ms), \( F(3,38) = 1.70, p = .18 \).

**Hypothesis 3c.** There were no significant interactions between self-reported physical health group and age group on measures of cognitive and psychomotor processing speed reliant on executive processes. In sum, there is evidence an additive effect of age and self-reported physical health on high load attention conditions on some tests and mostly observed only when comparing the extremes (i.e., the old-low health group compared to young-high health group.) Results also indicated worst performance among younger adults in low self-reported physical health on one test (attentional blink, second instruction condition), and there were no interactions found on performance on neuropsychological measures.

**Exploratory analyses:** We conducted exploratory analyses examining the effects of self-reported physical health and age, and their interaction, on neuropsychological tests of other standard cognitive domains, including learning and memory, naming, and visuospatial function. We found a main effect of Self-Reported Physical Health status on measures of learning and memory, such that the low health group demonstrated worse performance on HVLT Total Trials and HVLT Delayed Recall, see Table 2 for the means, standard deviations, and statistical outcome. There were neither age group differences nor any interaction between age group and physical health status on any of the exploratory neuropsychological measures.
Discussion

This project examined attention and processing speed in HIV+ adults, focusing on the impact of aging and physical health. We were particularly interested in how aging and self-reported physical health status were related to different aspects of attentional functioning and whether particularly demanding tasks were most sensitive to these effects. Broadly, we hypothesized that worse self-reported physical health status and older age and would impair performance on measures of attention, particularly measures with greater cognitive demands, and that these factors would evidence both independent and interactive additive effects on attention.

Our first aim was to examine the impact of self-reported physical health on performance under high attentional load and in other standard cognitive domains. We found that those with worse self-reported health performed disproportionately slower during the high load condition on one of our three attention measures, namely covert orienting. On this task, those with low self-reported physical health status were adversely affected by invalid cues, showing greater costs to reaction time when invalidly cued during the covert orienting task. As Posner described (1984), the “costs” associated with invalid cueing are explained by the time it takes to disengage from the previously cued foci of attention, shift attention, and re-engage with the target stimuli. While we cannot differentiate any one of these processes, we need to entertain why these functions may be susceptible to the impact of reduced self-reported physical health and result in the observed slower reaction times. Results from our examination of self-reported physical health status on neuropsychological test performance complement these findings. Consistent with our hypothesis, the low health group performed more poorly on a measure of cognitive flexibility and set-shifting (DKEFS Trail Making Test Condition 4). Set-shifting is vulnerable to physical health status and the greater cost of the invalid cueing during covert orienting task reflect reduced ability to efficiently shift attention from the invalid locus in space to the alternate uncued target, leading to longer reaction times. The covert orienting
paradigm is sensitive in adults with other chronic physical illness. Amodio et al. (Amodio et al., 1998) demonstrated slowest reaction times after invalid cueing in patients relative to controls, where cirrhotic patients in worst health (i.e., with the greatest liver damage) also demonstrated slowest reaction times, similar to our findings.

As proposed in this study, cognitive changes associated with pain can provide a model for the relationship between worsening physical health and cognitive decline. The compromised mechanisms of chronic poor health may be comparable to those under investigation in persons with chronic pain. Imaging studies in pain populations have produced interesting findings regarding dysfunctional patterns of activity. fMRI results comparing activity in cortical areas associated with the Default Mode Network (DMN; Marcus E. Raichle et al., 2001) between pain patients and healthy controls before and during an attention task have implicated a “deactivation failure” in those with chronic back pain (Baliki, Geha, Apkarian, & Chialvo, 2008). The authors posit that the brains of patients with chronic pain may never “truly be at rest” and that their cortical activity may reflect an uneven “balance of opposing forces,” borrowing the term from Raichle (2006). Such an imbalance is consistent with the notion that pain drains available attentional resources. Cognition, and specifically attention, was investigated in 17 female adults with temporomandibular disorder (TMD) known to cause chronic pain compared to 17 age-matched controls, and fMRI was used to investigate brain areas activated during attention tasks (Weissman-Fogel et al., 2011). Results showed that individuals with TMD demonstrated slowed reaction times during an attentionally demanding task (involving cognitive interference and the Stroop effect) and showed more prominent deactivation compared to controls in bilateral prefrontal areas and frontal eye fields as well as the right middle temporal gyrus. This finding suggests evidence of a dysfunctional imbalance in brain activity resulting from pain, which by inference, may also be occurring in poor physical health. The impact of such an imbalance may then explain reduced attentional abilities, and particularly reduced abilities during set-shifting, executive control tasks.
that require efficient frontal circuits (Fan, Flombaum, McCandliss, Thomas, & Posner, 2003; Fan, McCandliss, Fossella, Flombaum, & Posner, 2005).

Our second aim addressed the impact of aging in HIV on attention, specifically attention under high load and involving executive control mechanisms. We expected and observed overall slowing in the older group on measures of processing speed, with age-related slowing during both reaction time tasks (i.e., the Simple Reaction Time task and Covert Orienting task) as well as customary neuropsychological measures of psychomotor speed (i.e., DKEFS Trail Making Test Condition 5, Grooved Pegboard.) As expected, while older adults were slower overall compared to younger counterparts on the Covert Orienting task, they were not disproportionately slower under different cued conditions (i.e. Valid vs. Neutral vs. Invalid cueing), indicating that the extent to which cue type impacts reaction time, a mechanism subserved by parietal areas, did not differ between age groups,. We also found evidence of reduced executive control in the older HIV+ adults, with reduced scores on measures of letter fluency (and comparable scores on semantic fluency) indicating that our older sample had greater difficulty summoning frontally mediated executive control strategies to generate words (Baldo, Schwartz, Wilkins, & Dronkers, 2006). These findings of reduced verbal fluency among older compared to younger HIV+ adults are consistent with others’ findings (Sacktor, et al., 2007). We also unexpectedly found age-related differences on a working memory task (i.e., WAIS-III Letter-Number Sequencing), which may also indicate reduced dorsolateral pre-frontal executive processes. Results of DTI imaging in healthy older adults has implicated a negative relationship between cortical white matter integrity overall, and specifically in frontal areas, and performance on a letter fluency task and letter-number sequencing (Deary et al., 2006).

Contrary to expectation, we did not find any main effects of our top-down condition on the attentional blink task. We expected that reduced frontal efficiency in our older HIV+ sample would lead to a differential impact of top-down instruction comparable to the findings of Perry and Hodges (Perry &
Hodges, 2003), who found that those with MCI derived no benefit from applying a top-down instruction, and suspected pre-frontal compromise. It is unclear why there was no main effect of our top-down condition. It may be the case that the top-down effects of this task were too subtle to be detected in a small sample. Findings from other studies in our lab that have also examined the attentional blink using the same task can expand our understanding of these results. Ly (Ly, 2013) investigated the effects of top-down instruction using same computerized attentional blink task among younger (25-59 years old) and older (62-89) healthy adults. She found that the older adults in her sample did benefit from the top-down instruction condition but only under conditions of low load (i.e. longer SOA’s.) It was posited that older adults recruit top-down processes to improve performance but only when limited attentional resources are not otherwise taxed. It is important to note that the sample of “older” adults in this study was a comparatively younger group than Ly’s. Considering these interesting findings and the younger sample used in this study, it is reasonable to consider that the pool of attentional resources may already diminished among adults of any age with HIV and particularly those with low physical health. As such, any relative relief during low load conditions may still only replenish reduced attentional resources that are insufficient to sustain top-down processing, and thus no effect would be detectable. Conversely, conditions that we consider low load in the attentional blink task (i.e. longer SOA’s) still impose a temporal demand, albeit a generous one, and perhaps the necessary resources to sustain top-down processes would be met under conditions of even more lenient temporal demand. Future investigations could examine these possibilities by including other measures of top-down processing using an even broader range of stimulus onset intervals.

It has been proposed that the pattern of cognitive impairment in HIV may be different for older adults versus younger adults (Brew, Crowe, Landay, Cysique, & Guillemin, 2009). Some studies found few meaningful differences between age groups (Cobb Scott et al., 2011; van Gorp, et al., 1994), while other have found that among those with cognitive impairment, executive tasks (i.e. Trails B) are worse
among older adults (Cobb Scott, et al., 2011; Sacktor, et al., 2007) as well as performance on memory tests (Tan, et al., 2013). It may be the case that there is not a distinct pattern of performance among older HIV+ adults, but that the most salient feature of cognitive decline due to age is greater variability. Greater variability on reaction time tasks has been documented in HIV+ adults (Ettenhofer, Foley, Castellon, & Hinkin, 2010; Levine et al., 2008). Morgan et al. examined intraindividual variability using a measure of dispersion across neuropsychological test performance among younger and older HIV+ adults compared to HIV- adults (Morgan, et al., 2011). They found greater dispersion among older adults, only in the HIV+ group, and that age was the only significantly contributing factor in a model that included nadir CD4, years of disease duration, and Hepatitis C status. While not included in our main analyses, we conducted follow up analyses examining the intraindividual standard deviation of reaction times on the simple reaction time task; indeed, we found a main effect of age group such that they exhibited greater variability across ISI. Future exploratory analyses are planned and will examine intraindividual variability in our sample across tasks.

Our third aim addressed the synergistic effects of self-reported physical health status and aging on attention. We first determined if there were any interactions between age and self-reported physical health status groups during full analyses on attention tasks factoring in all conditions. One interesting significant interaction indicated a particular attentional vulnerability in the young-Low health group. On the attentional blink task, the young-Low health group demonstrated a greater magnitude of attentional blink than any of the other groups. That is, they demonstrated poorest accuracy after the shortest duration between the two stimuli. In contrast, the old group had a longer dwell period compared to the young group. In other words, the younger participants in worse self-reported health were very inaccurate at shortest intervals, whereas the older participants generally took longer garner attentional resources, but were then comparable to younger adults when given enough time.
Not all of our findings indicated such an interaction. While we found no main effect of top-down instruction, we did find a significant interaction between self-reported physical health, age, and stimulus onset interval pointing to a particular vulnerability in the younger adults with worse health. We further inspected which type of instruction condition was driving the significant finding in the young-low health group in supplemental analyses. Accuracy of the second stimulus during the top-down instruction condition (i.e., report one stimulus) was primarily responsible for this finding (there was no such finding examining only accuracy of the second stimulus under the report both condition.) This would suggest that the underlying vulnerable mechanism is one of suppression, that is, the young-low health group had difficulty suppressing or inhibiting the first stimulus in order to efficiently process the second stimulus. This raises an interesting question that echoes our previous findings; perhaps inhibiting or suppressing stimuli and shifting attention to new stimuli is more effortful as a function of an attentional “imbalance” in poor physical health. It is not clear why this effect was observed only in younger adults, whereas older adults were relatively spared on this measure, in contrast to our prediction. One explanation is that the younger adults in our sample had a higher baseline and the impact reduced self-reported physical health status resulted in greater impairment compared to older adults. It may be the case that older adults have plateaued in regards to decline in inhibition and suppression; performance did not greatly vary across conditions in the older group, regardless of self-reported physical health status. Any additional decline related to health status may be minimal and thus not detected in a study with such a small n.

We also examined additive effects of self-reported physical health by applying linear contrast analyses to performance at conditions of greatest attentional demands on, defined a priori, between each of the four derived groups’ (i.e. old-Low Health, old-High Health, young-Low Health, and young-High Health). We found as expected that older adults in worse physical health performed more poorly than young adults with high physical health status. On the simple reaction time task, this effect was driven by
the better performance (i.e., faster reaction time after a 350ms ISI) of the young-high health group compared to the other three groups. However, on the Covert Orienting and Attentional Blink tasks, results were more consistent with a linear model such that the old-Low physical health group performed worst and the young-High physical health group performed best; in both analyses the middle two groups (old-high health and young-low health) were comparable. These findings suggest a somewhat additive relationship between aging and self-reported physical health status in HIV.

Somewhat surprisingly, while we did find main effects of aging and self-reported physical health status on neuropsychological performance, we did not find any interaction effects. The neuropsychological tests used in this study may not be adequately sensitive to subtle interactive effects in this sample; additionally, it also may be the case that we were underpowered to observe such effects.

As more individuals with HIV are expected to live longer healthier lives, health care providers will encounter growing numbers of older adults with HIV. Since health maintenance is now largely achievable due to HAART, there should be a shift in clinical focus to maintaining physical health, quality of life and optimum cognition, and focusing on the possible synergistic effects of aging processes in the context of HIV. Despite such remarkable gains in terms of longevity, cognitive decline and impairment remain problematic, even among those with objectively well maintained disease (Heaton, et al., 2010), a vexing issue for clinicians and researchers. One possible explanation is the effects of chronic CNS inflammation. Some have found that higher levels of a marker of inflammation (plasma sCD14) were associated with worse global impairment, attention and learning scores (Lyons et al., 2011). Additionally, the authors found that inflammatory markers were better predictors of deficits on these scores than CSF or plasma viral load or CD4 counts. Similarly, another study found that plasma sCD14 levels were found to be significantly related to an information processing speed task (Sun et al., 2010), although unrelated to other cognitive tasks.
Neurocognitive performance in our sample is comparable to that reported in other studies of “older” HIV+ adults (Cobb Scott, et al., 2011; Valcour, et al., 2011). It is important to comment that the cutoff of 50 years of age has become the standard in HIV research. The reason is that the life-span of persons with HIV had been shorter, and 50 represented the relatively older subcategory. However, 50 is much lower than the cutoffs used in the traditional aging literature, where age is described as “young old” (~65-75 years), “mid-old” (~75-85 years), and “old-old” (85 years and older). The cognitive decline observed in HIV occurs early (i.e., starting at age 50), yet, the pattern of decline overlaps with that observed in traditional aging, including declines in processing speed, attention, working memory, and executive functions. That younger HIV+ individuals are vulnerable to cognitive decline and are susceptible to conditions often associated with aging has led to the “accelerated aging” hypothesis in HIV (Bhavan, Kampalath, & Overton, 2008; Deeks & Phillips, 2009). In consideration of this hypothesis, we examined performance on select neuropsychological measures in our sample against available normative data. Among our sample, the mean scores of each age group fell broadly within the mean scores of their expected age range on available normative data (i.e., 30-49 and 50-75), on most psychomotor speed tests (i.e., DKEFS; Delis, et al., 2001) and cognitive processing speed tests (i.e., verbal fluency tests (Lucas et al., 1998; Strauss, et al., 2006b) with two exceptions. First, on a psychomotor speed test involving set-shifting (DKEFS Trail Making Test Condition 4), the mean scores of both of our age groups fell in normative range of an older cohort (i.e., our young group’s mean score was comparable to the mean score of individuals 60-69 and our old group’s mean score was comparable to the mean score range of individuals 70-79.) Second, on a psychomotor speed task involving fine motor skills, our old group was found to have a mean score slightly slower compared to the mean of their normative sample (Strauss, Sherman, & Spreen, 2006a). Thus, the results of our neuropsychological battery indicate that our sample fell largely within the expected range on select tests commonly used to examine cognitive decline in HIV, with two exceptions: all individuals in our sample were slower when set-shifting was involved, and older individuals were slower on
a fine motor skills test. Overall, these results are not wholly consistent with the “accelerated aging” hypothesis, as we would expect to find a more consistent profile mapping onto the performance older-aged adults. While we found distinct relationships between slowed processing speed and older age, the observed slowing was not beyond that of healthy individuals of the same age range on most tests. Additionally, our results point to a specific pattern related to poor physical health that is not entirely consistent with a purely aging process. For example, in normal aging reduced letter fluency compared to semantic fluency is commonly observed, whereas we observed that those in worse health had poorer semantic fluency compared to those in better health in our sample, and letter fluency was comparable. Our findings highlight that cognitive decline in HIV is complex, and while the accelerated aging hypothesis presents an intriguing framework, it is not likely adequately representative, as others have also argued.

One powerful argument against the accelerated aging hypothesis is that not all age-related diseases occur in HIV. As pointed out by Dr. Carl Grunfeld in a March 2010 Office of AIDS Research Advisory Council Meeting, there is increased risk for only some types of cancers, cerebrovascular risk increases with age as well as several other risk factors besides HIV, and normal aging is associated with increased weight gain and increased intramuscular adipose tissue, whereas lipodistrophy is common in HIV. While it may be the case that certain conditions occur in both HIV and aging, immunosenescence and chronic inflammation in both aging and HIV can provide one explanation for some of the overlap (Deeks, 2011). There may be common underlying processes that lead to some, but not all, conditions observed in aging as well as HIV, and thus it does not logically follow that HIV is equivalent to accelerated aging. To quote Dr. Grunfeld, “I think it is a disservice to worried, scared patients to tell them that they are aging faster.” (March 2010 Office of AIDS Research Advisory Council Meeting, Bethesda MD).

In contrast to the idea of accelerated aging, our results support the notion of considering both aging and physical health status. One of the strongest clinical implications from our findings is that maintaining
health in HIV has implications for cognitive health as well, regardless of age. Our findings emphasize that reduced physical health can be an important indicator of cognitive impairment, as suggested by others (Cole, et al., 2007), and supports including a measure of self-reported health in clinical and research settings. While the “gold-standard” of health status in HIV are laboratory disease markers, our findings suggest that self-reported measures can provide important information about physical health status. Jylhä (Jylhä, 2009) proposed that self-reported physical health measures provide a means to capture a more holistic picture of the individual’s functioning and contextual status. It is nearly impossible to assess every relevant aspect of health from objective disease and health variables, and thus important information can missed; further, it is entirely plausible that the relative significance of such variables is not uniform across individuals. The strength of self-report is that is draws out information about the individuals relative status in the context of their own self-knowledge and history. Anecdotally, participants of this study have commented that they underwent HIV testing because they had a feeling that something was wrong: “I just felt I wasn’t right; I knew my body.”

One of the strengths of this study was the use of a measure of physical health status that was specific to the target population. The MOS-HIV was developed to specifically focus on health-related quality of life factors relevant to the HIV+ population. For example, pain is a common symptom in HIV and was a targeted symptom in the MOS-HIV (Wu, et al., 1997). The Physical Health and Mental Health Summary T-scores are derived from a normative sample of HIV+ individuals. It is notable that our median was 50.30 suggesting that the central tendency of the scores in our sample is comparable to that of the normative sample, supporting the appropriateness of this measure to dichotomize our sample into to “High” and “Low” health. There are two features of the MOS-HIV to note. The MOS-HIV captures the magnitude and disruptive impact of pain, as well as queries of cognitive functioning including attention, which may represent a potential theoretical confound. The MOS-HIV Physical Health Summary score used to group
participants is an aggregate score calculated from several subscales, including both pain and cognitive functioning, to varying degrees as described above in Methods. Subsequent visual examination of the subscale Z-scores has shown that the low health group had lower scores than the health group across all subscales, including pain and cognitive functioning, resulting in their overall lower aggregate physical health scores, which argues against a specific confound.

In future investigations comparing the relationships between laboratory markers and self-reported health status to cognitive function using measures such as the MOS-HIV, it will be important to determine whether self-reported physical health functioning captures a unique construct relevant to the study of cognition in HIV, as we have proposed. Similarly, future investigations could compare the impact of pain and self-reported physical health status on brain activity during tasks of high demand using fMRI or EEG. If it is the case that changes in cortical activity resulting from chronic pain are similar to changes in cortical activity due to decline in health status, the application of psychotherapeutic techniques used in pain management, such as cognitive interventions, could be beneficial for persons with declining health. Cognitive interventions for pain management often target attention to the painful sensation, and such interventions may be helpful in improving quality of life for those in poor health.

Our study also provides support for the use of varied cognitive measures in assessment of HIV-related cognitive decline. As a primary neuropsychological research focus in HIV has become assessment of milder forms of cognitive impairment, as global measures of cognition or neuropsychological measures developed to identify impairment with limited granularity may be insufficiently sensitive to measuring true cognitive changes in this population. Our results support that sensitive attentional measures that varying degree of cognitive demand can be useful research tools to detect subtle differences between experimental groups in this population. It is important to identify tools that detect such subtle changes in order to identify when supports may be needed to maintain functioning.
Our experimental attentional measures tap different underlying neural circuitries. Given that neuroanatomical systems suspected to be vulnerable in HIV are frontal-subcortical networks, it was expected that our measures of the foreperiod effect and attentional blink would be vulnerable to changes in HIV as each task is susceptible with increasing temporal demand. Indeed, we demonstrated significant findings related to the temporal demands of these tasks in both older age and worse physical health, consistent with reduced integrity of frontal-subcortical systems. However, we unexpectedly found that the Covert Orienting task was sensitive to physical health differences in our sample. Cortical parietal networks are largely responsible for covert orienting mechanisms (Corbetta & Shulman, 1998; Posner, et al., 1984), and thus this was an unexpected finding. One possible explanation may be related to reduced neuronal efficiency secondary to compromised white matter tract integrity. This is particularly vulnerable to the toxic effects of HIV, and DTI imaging has revealed reduced integrity of the corpus callosum (Tate, et al., 2009). The invalid Covert orienting condition requires perceptual and integrative processing of information in both visual hemifields, and reduced interhemispheric efficiency may explain the lowered performance of that experimental condition. This also raises the issue that future investigations could consider not only the integrity of the corpus callosum and interhemispheric communication, but other long white matter tracts and the corresponding tasks that tap functionality of those networks.

The attention tasks in our study do not mimic attentional demands in day-to-day life per se, and we did not include a measure of functioning, preventing us from examining any correlations. Nonetheless, it is important to explore how compromise in these abilities could interfere with daily life. From an evolutionary perspective, we have depended on our vast attentional networks to guide us safely and productively through the world, even without explicit consciousness of these abilities. As penned by William James (James, 1890) in his discussion of attention, “Only those items which I notice shape my mind - without selective interest, experience is an utter chaos. Interest alone gives accent and emphasis, light and
shade, background and foreground - intelligible perspective, in a word.” (page 403.) Attention shapes our understanding of and interaction with the world. We need to trust our capacity to react quickly, even when confronted with tasks before we are prepared to attend to them, as with the foreperiod effect. We rely on our ability to covertly notice and quickly shift attention to dangerous or salient stimuli to react quickly and accordingly, using covert orienting mechanisms. And we depend on our ability to quickly sift through incoming information, identify what is important, and discard the rest, as with the attentional blink. When any of these fundamental systems are compromised, our ability to navigate our environment as desired, in a safe and efficient manner, is put at risk. Although these tasks may not readily correlate with specific aspects of daily life, they are the underlying machinery that allow us to be efficient, productive, and aware of our environment. Relative weaknesses observed in this study caution that important downstream functioning may be vulnerable to decline.

This study contributes our understanding of the interplay between the highly relevant factors of aging and physical health status on cognition in HIV. From a clinical perspective, aging has become a concerning risk factor for cognitive decline in HIV, and our results support that aging is a risk. However, this study additionally raises worsening health as an important factor to monitor not only in and of itself, but also for its potential detrimental impact on cognition, regardless of the age of the individual. In fact, our results indicated that, contrary to expectation, younger adults in worse physical health may be at particular risk. While it is possible that our study used a particularly vulnerable group in younger HIV+ individuals in poor health, the findings raise a new issue or monitoring young HIV+ individuals with significant health problems. Although cognitive decline is the most prominent consideration in older age, there are some considerations for why our younger group in poor health emerged as relatively more vulnerable than our older group. First, our older sample has survived and functioned largely well with HIV for an overall longer period of time than our younger group. As such, our sample may be more robust to the effects of
HIV. We did not collect retrospective physical health status and it may be the case that our older adults in worse health experienced relatively recent changes in health status. Older adults with HIV who have been living with the infection with mild or no cognitive decline and largely preserved physical health for several years may be more resilient to the effects of HIV. This new contribution to the field is the concern that younger adults in worsening health, that is those less robust to the effects of HIV or health changes, warrant additional investigation to determine the need for targeted clinical treatment.

The results of this study can have implications for the efficacy and delivery of preventative and therapeutic interventions, as well as the development of cognitive compensatory strategies. For example, our findings can be helpful to consider when applying manualized interventions that are heavily instructive, such as cognitive behavioral interventions. Across our sample, hippocampal function is largely intact with good retention of information, but that initial acquisition of information may be hindered by poor attention. Specifically, our results suggest that the most efficient method of instruction or intervention will be delivering information focused on one topic at a time over brief periods that allow for plenty of time to process information and repeat if necessary. Overwhelming individuals with too much information or providing insufficient time to process information may result in reduced learning. Those in worse physical health may require more structured/directive interventions. Additionally, older individuals will likely require more time to engage with information than younger adults to learn and retain it and increasing the number of sessions for older adults may be helpful.

Similarly, in order to maintain optimal functioning, our results point to possible compensatory strategies that may be effective in daily life and improve/maintain medication adherence. Poor medication adherence in HIV has been linked to attentional difficulties (B. W. Becker, et al., 2011), regimen complexity (Hinkin, et al., 2002), and older age (Hinkin et al., 2004). Although the current study did not include a measure of adherence, our results suggest that poor attention in worsening health and older age
may lead to functional vulnerabilities including adherence. Regarding cognitive compensatory strategies, retention of learned information was largely intact across our sample, and thus compensatory strategies should be focused on initial acquisition and minimizing distracters. Increasing daily structure and organization in daily life and eliminating multi-tasking are indicated. Our results suggest that HIV+ individuals in worse health may have greater difficulty with set-shifting, and thus may benefit from increased structure, for example medication administration may include prominent alarms/signals indicating that it is not only time to take their medication but that persist until the medication has been administered. For older adults, increasing structure is also likely to be beneficial, although given the evidence of reduced working memory and slowed attentional processes the emphasis may be providing step-by-step instructions and allowing sufficient time to follow these instructions for activities such as medication administration, and keep records of medication times. Longitudinal studies are necessary to answer the question of how aging and physical health status are related to sustained cognitive health. Longitudinal studies are particularly needed to examine the impact of alterations in physical health status, questions highly relevant to informing treatment recommendations. Further, it will be important to understand if cognitive changes associated with fluctuations in physical health (including magnitude of recovery) vary by age. Decline in physical health status appeared to impact different aspects of attention in each age group. Better understanding of the role of physical decline in the context of aging, the parameters of the impact of health decline, and the reversibility of cognitive decline if physical health is restored, can help improve both medical recommendations, and reduce rates of cognitive decline in HIV.

There were several limitations to our study. First, due to study constraints, there was no age-matched seronegative control group with which to make comparisons to the HIV+ group. Thus, we can make no inferences about the effects of aging and physical health status that are unique to HIV. Our sample size was also small, which may have limited our power to detect some effects and weakens support for
generalizability. Our assessment also did not include measures of activities of daily living (ADL), as cognitive decline may affect everyday activities. ADL are relevant discriminators in current HIV literature as indicated by the dissociation of HAND diagnoses based on functioning (Antinori, et al., 2007).

Medication adherence has been targeted in studies (Hinkin, et al., 2002; Woods et al., 2008), and is particularly at risk in aging (Ettenhofer et al., 2009). A more systematic assessment of the relationship between high and low level ADL, attentional function, and physical health is warranted.

While we used a measure of self-reported physical health that has been validated against traditional laboratory HIV disease markers (Wu, et al., 1997), we did not collect any objective markers of disease status in our sample, only self-report. Over 75% of our sample reported that their viral load was undetectable, nonetheless two participants did not know their most recent viral load and it would have been clinically informative to examine the relationship between self-reported health and disease markers on our attention measures. Future studies should aim to collect both self-report health status and objective laboratory disease markers, if feasible.

With regard to demographic information, we did not correct for gender or education as we found few differences between men and women on measures, consistent with others findings (Failde Garrido, et al., 2013), and few differences between those with a high school education or less and those with more than a high school education across measures. Nonetheless, it will be important for future investigations to examine the possible impact of these demographic features. Additionally, while we systematically assessed substance abuse history across street drug class, we did not systematically assess alcohol use. Alcohol abuse history may have an independent impact on cognition and is an important aspect of medical history to capture in studies in this population. Finally, although we screened for untreated depression, we did not include a measure of mood, which may impact performance on neuropsychological performance (Mitchell & Phillips, 2007).
The ongoing pursuit of better understanding the cognitive consequences of the interplay between HIV, aging, and physical health status is important for several reasons. In HIV, cognitive decline related to aging and physical health status may play a key role in the maintenance of optimal functioning and quality of life. Improving our knowledge of which factors result in susceptibility to cognitive decline allow us to identify individuals vulnerable to decline, target vulnerabilities for intervention, and predict outcomes relevant to treatment planning. In addition to improving healthcare for individuals with HIV, the lessons learned from investigations in this population can informative in other disease models. There is increasing awareness that chronic infection and chronic inflammation are important factors to consider in cognitive decline, particularly among older adults. For example, inflammation is a suspected mechanism of neuronal injury in cancer as well as in HIV. The picture of cognitive decline associated with HIV infection becomes clearer all the time, but there remains much work to be done to sustain cognitive health and quality of life in HIV.
Table 1A. Demographics of Sample by Age Group

<table>
<thead>
<tr>
<th>Variable</th>
<th>Young (n = 17)</th>
<th>Old (n = 25)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)*</td>
<td>42.59 (±6.29), 30-49</td>
<td>59.56 (±6.98), 50-75</td>
</tr>
<tr>
<td>% Male</td>
<td>82%</td>
<td>68%</td>
</tr>
<tr>
<td>Education</td>
<td>47%</td>
<td>64%</td>
</tr>
<tr>
<td>% Higher than High School Diploma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Estimated Verbal IQ*</td>
<td>102.47 (±12.47)</td>
<td>100.09 (±9.95)</td>
</tr>
<tr>
<td>MMSE</td>
<td>28.82 (±1.29), 26-30</td>
<td>28.56 (±1.19), 26-30</td>
</tr>
<tr>
<td>DRS</td>
<td>137.41 (±4.84), 130-144</td>
<td>136.80 (±3.92), 128-144</td>
</tr>
<tr>
<td>HIV Disease Duration (in years)*</td>
<td>14.24 (±7.16), 2-24</td>
<td>18.32 (±4.88), 9-25</td>
</tr>
<tr>
<td>% on antiretroviral treatment</td>
<td>94%</td>
<td>92%</td>
</tr>
<tr>
<td>% undetectable viral load</td>
<td>81%</td>
<td>75%</td>
</tr>
<tr>
<td>% history of AIDS Dx</td>
<td>65%</td>
<td>64%</td>
</tr>
<tr>
<td>MOS-HIV Physical Health</td>
<td>52.97 (±8.74), 33.05-63.59</td>
<td>46.73 (±11.30), 24.11-63.92</td>
</tr>
</tbody>
</table>

Note. Information provided in percent (as noted) or means (SD). MMSE = Mini Mental Status Examination (Folstein, Folstein, & McHugh, 1975); DRS = Dementia Rating Scale (Jurica, Leitten, & Mattis, 2001).

*Verbal IQ was estimated with the North American Adult Reading Test (Blair & Spreen, 1989).

*p < .05, Age Group differences.

Table 1B. Demographics of Sample by Self-Reported Physical Health Status

<table>
<thead>
<tr>
<th>Variable</th>
<th>High Health (n = 21)</th>
<th>Low Health (n = 21)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>51.05 (±12.36), 30-75</td>
<td>54.33 (±8.79), 34-66</td>
</tr>
<tr>
<td>% Male</td>
<td>58 %</td>
<td>41%</td>
</tr>
<tr>
<td>Education</td>
<td>68%</td>
<td>48%</td>
</tr>
<tr>
<td>% Higher than High School Diploma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Estimated Verbal IQ*</td>
<td>102.47 (±12.47)</td>
<td>100.09 (±9.95)</td>
</tr>
<tr>
<td>MMSE</td>
<td>28.86 (±1.15), 26-30</td>
<td>28.48 (±1.29), 26-30</td>
</tr>
<tr>
<td>DRS</td>
<td>137.86 (±4.79), 128-144</td>
<td>136.24 (±3.60) 130-143</td>
</tr>
<tr>
<td>HIV Disease Duration (in years)*</td>
<td>16.43 (±7.10), 2-25</td>
<td>16.90 (±5.24), 2-24</td>
</tr>
<tr>
<td>% on antiretroviral treatment</td>
<td>90%</td>
<td>95%</td>
</tr>
<tr>
<td>% undetectable viral load</td>
<td>85%</td>
<td>70%</td>
</tr>
<tr>
<td>% history of AIDS Dx</td>
<td>76%</td>
<td>52%</td>
</tr>
<tr>
<td>MOS-PH mean* (SD), Min-Max</td>
<td>57.87 (4.35), 50.76, 63.92</td>
<td>40.63 (7.69), 24.11-49.86</td>
</tr>
</tbody>
</table>

Note. Information provided in percent (as noted) or means (SD). MMSE = Mini Mental Status Examination (Folstein, Folstein, & McHugh, 1975); DRS = Dementia Rating Scale (Jurica, Leitten, & Mattis, 2001).

*Verbal IQ was estimated with the North American Adult Reading Test (Blair & Spreen, 1989).

*p < .05, Self-Reported Physical Health Status Group differences.
Figure 1. Schematic of the SRT Task

Varied Interstimulus Interval (ISI; msec)
350, 500, 650, 800, 1100
Figure 2. Schematic of the Covert Orienting Task
Figure 3. Schematic of the Attentional Blink Task:
### Table 2. Results of ANCOVA’s comparing Age Group and Self-Reported Physical Health Status Group on neuropsychological tests

<table>
<thead>
<tr>
<th>AGE GROUP</th>
<th>SELF-REPORTED PHYSICAL HEALTH STATUS</th>
<th>D-KEFS – TRAILS</th>
<th>GROOVED PEGBOARD</th>
<th>LETTER FLUENCY</th>
<th>CATEGORY FLUENCY</th>
<th>LETTER NUMBER SEQUENCING</th>
</tr>
</thead>
</table>
| YOUNG (n=17) | OLD (n=23) | MEAN (SD) | STATISTIC | STASTIC | CONDITION 1 21.12 (5.02) 25.65  
ns | 21.90 (6.39) 26.33  
ns | CONDITION 2 35.47 44.35  
n | 35.76 (12.89) 47.47  
n | CONDITION 3 35.88 42.69  
n | 34.09 (11.51) 48.67  
F (1, 37) = 4.47, p = .04 | CONDITION 4 103.88 35.76  
n | 98.33 (12.89) 142.81  
F (1, 37) = 5.287, p = .045 | CONDITION 5 25.47 38.35  
F (1, 37) = 5.51, p = .024 | 27.90 (10.75) 41.38  
ns | GROOVED 78.12 98.13  
F (1, 37) = 5.29, p = .027 | 85.14 (17.55) 102.43  
ns | LETTER FLUENCY SUM (FAS, 3 Min.) 49.76 35.74  
F (1, 37) = 7.93, p = .008 | 50.10 (11.48) 39.76  
F (1, 37) = 9.35, p = .004 | CATEGORY 48.47 43.09  
n | 44.29 (15.76) 38.71  
n | FLUENCY (3 Categories, 3 Min.) 10.00 (2.95) 8.55 (2.70)  
F (1, 37) = 6.44, p = .016 | 9.90 (2.95) 8.21 (2.07)  
ns | LETTER NUMBER SEQUENCING 22.82 (5.93) 20.56  
n | 23.76 (4.96) 19.14  
F (1, 37) = 10.42, p = .003 | HVLT-R TOTAL RECALL 7.12 (3.20) 6.30 (2.72)  
n | 7.71 (2.85) 5.57 (2.48)  
F (1, 37) = 7.04, p = .012 | HVLT-R % 76.23 (26.08) 77.97  
n | 79.16 (20.46) 75.42  
n | RETENTION 51.41 (6.27) 49.52  
F (1, 37) = 10.42, p = .003 | 48.14 (28.77) 51.67 (6.63)  
ns | BNT 28.24 (3.36) 29.04  
n | 28.24 (28.77) 28.71 (2.92)  
ns | VFD 28.24 (3.36) 29.04  
n | 28.24 (28.77) 28.71 (2.92)  
ns |
Figure 4. Graph of Validity X Self-Reported Physical Health Status Interaction on Covert Orienting Task

Vertical bars denote +/- standard errors

Reaction Time (msec)

* p<.05

Cue Type

Valid
Neutral
Invalid

Low Health
High Health
Figure 5. Graph of SOA X Age Group interaction on Attentional Blink Task

Vertical bars denote +/- standard errors

% Accuracy of the 2nd Stimulus

* * p<.05

SOA (msec)
Figure 6. Graphs of ISI X Age Group X Physical Health Status interaction on the Simple Reaction Time task.
Figure 7. Graphs of SOA X Age Group X Self-Reported Physical Health Status interaction

Vertical bars denote +/- standard errors

* p < .05
Figure 8. Graph of SRT results after 350ms ISI for each Age Group X Self-Reported Physical Health Group.
Figure 9. Graph of Covert Orienting Task results after Invalid Cue for each Age Group X Self-Reported Physical Health Group

*p<.05
Figure 10. Graph of attentional blink results at 266ms SOA for each Age Group X Self-Reported Physical Health Group
References


Centers for Disease Control. (2010). September and October National HIV/AIDS Awareness Observances Accent Severity of the Epidemic in Hispanics/Latinos and Gay and Bisexual Men, and Complexity of the Disease in Older Adults e-HAP


82


