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Apathy in Persons with HIV Infection

A dissertation submitted in partial satisfaction of the requirements for the degree Doctor of Philosophy in

Clinical Psychology

by

Rujvi Kamat

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2014
The Dissertation of Rujvi Kamat is approved, and it is acceptable in quality and form for publication on microfilm and electronically:


Chair

University of California, San Diego

San Diego State University

2014
DEDICATION

For my parents, family and friends. Your constant love, support, and encouragement through the years have been my inspiration and strength.
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**Honors and Awards**

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**BOOK CHAPTER**


**POSTER PRESENTATIONS**


ABSTRACT OF THE DISSERTATION

Apathy in Persons with HIV Infection

by

Rujvi Kamat

Doctor of Philosophy in Clinical Psychology

University of California, San Diego, 2014
San Diego State University, 2014

Professor Thomas Marcotte, Chair

Apathy is a cluster of symptoms that include a reduction in self-initiated, goal-directed behavior, and a lack of motoric, emotional, and cognitive motivation. It has been recognized as a clinical manifestation of HIV infection, but has received limited empirical attention. Previous studies of other neurologic groups indicate that apathy is associated with poor treatment response, deficits in everyday functioning, lower quality of life, and worse global cognitive functioning. HIV-associated brain pathology involves frontostriatal circuits, which are also implicated in the expression
of apathy. Three studies were conducted to examine the neural, psychiatric (e.g.,
depression), and functional correlates of apathy in HIV infection.

In all three studies, self-reported ratings of apathy were obtained using the
Frontal Systems Behavior Scale (FrSBe). In the first investigation, relative to
seronegative comparison subjects, HIV+ persons reported higher levels of apathy.
Independent of major depressive disorder and other disease covariates, apathy ratings
were found to be significantly associated with increased cognitive complaints and
dependence in activities of daily living. Next, in a separate cohort, MRI Diffusion
Tensor Imaging was used to examine the correspondence between these ratings and
white matter abnormalities in the cortical nodes of the thalamocorticostriatal loop that
reportedly subserves apathy. Results indicated that apathy severity was related to
changes in neural integrity in frontomedial regions (i.e., anterior corona radiata, genu
of corpus callosum, and orbitomedial prefrontal cortex). The strength of this
relationship was associated with lower CD4 count, raising the possibility that dynamic
changes in immune functioning may modify CNS pathology and consequent
psychiatric outcomes. Finally, we examined whether depression, a comorbid
psychiatric condition that is distinct from apathy, is related to change in apathy ratings
across two visits in a cohort of 258 HIV+ participants. An inter-visit major depressive
episode was associated with an increase in apathy ratings only in those participants
who were not apathetic at their first visit. Regardless of initial apathy status, a new
episode of major depression resulted in a higher risk of developing or maintaining
clinically elevated apathy. These findings highlight the necessity to assess both
depression and apathy, as they may interact to exacerbate psychiatric burden in HIV-infected cohorts.

The findings of these three studies provide a greater understanding of the etiology of apathy and factors contributing to its expression in HIV+ individuals. Such information may help to identify patients at particular risk for functional impairments and potentially inform psychopharmacologic, behavioral, and HIV-treatment specific interventions that may mitigate apathy. This would be expected to help persons with HIV infection maintain better levels of functioning in their daily lives.
Introduction

HIV infection

HIV infection in the CNS

The human immunodeficiency virus (HIV) not only compromises immune function, but is also highly neurovirulent. HIV crosses the blood brain barrier early in the course of infection (e.g., Davis et al., 1992; Lentz et al., 2009) and accumulates in the basal ganglia (e.g., Haase, 1986). Neurons are not directly infected with HIV, but the virus triggers a cascade of neurotoxic molecular events that alter neuronal functioning (e.g., Gonzalez-Scarano & Martin-Garcia, 2005). HIV-associated neuropathology is commonly seen in HIV-infected individuals at autopsy (Ellis, Langford, & Masliah, 2007; Moore et al., 2006). In the current era of highly active antiretroviral therapy (HAART), HIV-associated metabolic and neuronal integrity abnormalities have been shown to reduce to some extent after treatment onset (Chang et al., 1999; Stankoff et al., 2001).

While rates of parenchymal HIV brain pathology appear to have reduced in the current era of efficacious antiretroviral therapy, there is still evidence for neuronal damage (Everall et al., 2009). Across immunohistochemical and neuroimaging studies there is evidence that HIV-associated neuropathology is not specific to any one brain region. However, frontostriatal circuits involving the basal ganglia as well as frontal cortical white and gray matter appear to be particularly vulnerable (e.g., Aylward et al., 1993; Archibald et al., 2004; Langford, Hurford, Hashimoto, Digicaylioglu, & Masliah, 2005). Severe white matter damage likely stemming from demyelination appears to be
one characteristic feature of the immune reconstitution that occurs in response to HAART (Langford et al., 2002).

Increasingly, in vivo evidence of HIV-associated white matter abnormalities has been provided by diffusion tensor imaging (DTI). This MRI method is more sensitive to early microstructural white matter changes (e.g., Alexander, Lee, Lazar, & Field, 2007; Kleffner et al., 2008) and thus has been used in a number of studies examining the impact of HIV infection on axonal integrity.

DTI can be used to quantify the magnitude and directionality of tissue water mobility (i.e., diffusion) in three dimensions (Basser & Jones, 2002). Myelin sheaths, membranes, and white matter tracts act as barriers to water diffusion and consequently result in greater diffusion along the axis of the barrier and reduced diffusion perpendicular to the axis. This type of restricted diffusion is termed as “anisotropic”. Various DTI indices such as fractional anisotropy (FA) and mean diffusivity (MD) can be calculated. FA is a scalar measure derived from the eigenvalues generated, and has a range of 0 (perfectly isotropic diffusion) and 1 (perfectly anisotropic diffusion). White matter structures are highly anisotropic and have high FA values, and consequently, low FA values indicate decreased white matter integrity due to axonal damage or myelin degeneration. MD is calculated from the diffusion coefficient at each voxel of the magnetic resonance data (Basser & Jones, 2002). Greater MD intensity corresponds to areas with high diffusion, which indicates decreased white matter integrity. However, this variable does not provide a measure of the collinearity of white matter fibers within a voxel. Increasingly, Radial Diffusivity and Axial Diffusivity have been utilized as markers of myelin loss and axonal degeneration.
respectively (Song et al., 2002; 2003). However, a thorough investigation of the underlying neural structural characteristics is recommended prior to interpreting the nature of white matter pathology as indicated by these values (Wheeler-Kingshott & Cercignani, 2009). Together, these DTI indices provide information regarding the integrity of the white matter regions being examined.

Findings from DTI studies using voxel-wise analyses as well as a priori regions of interest placement approaches suggest that relative to seronegatives, HIV+ individuals do not demonstrate frank disconnection in white matter tracts, but evidence decreased integrity in major white matter tracts in the frontal lobes, internal capsule, inferior longitudinal fasciculus, occipital lobes, and optic radiation (e.g., Filippi et al., 2001; Pfefferbaum et al., 2009; Ragin et al., 2005; Thurnher et al., 2005; Wu et al., 2006; Pomara et al., 2001; Gongvatana et al., 2009; Chen et al., 2009; Stebbins et al., 2007).

These structural changes in white matter regions and subcortical gray matter have been found to be associated with HIV disease severity, such as low nadir CD4 levels (e.g., Cohen et al., 2010; Jernigan et al., 2011) and AIDS status (Gongvatana et al., 2009). Interestingly, studies have shown that despite effective antiretroviral treatment, axonal injury is evident in HIV+ individuals and is prominently associated with previous level of immunosuppression (Harrison et al., 2008; Gongvatana et al., 2011). Taken together, the literature emphasizes the importance of remote history of immune suppression on current CNS status in the present era.

In sum, the neuroanatomical studies of the CNS changes accompanying HIV infection reflect diffuse neuropathology, but support specific frontal-subcortical
involvement. The corresponding frontostriatal white matter tracts connect various anatomical regions involved in affect regulation and goal-directed behavior (Cummings 1993; Tekin & Cummings, 2002). Consequently, it is reasonable to expect prominent symptoms of neurobehavioral disturbance (e.g., disinhibition, executive dysfunction, and apathy) to be associated with HIV infection.

Neuropsychiatric and neurobehavioral changes during HIV infection

Psychiatric dysfunction may develop in HIV+ individuals as a direct (e.g., effect of the virus in the CNS) or indirect (e.g., reaction to loss) consequence of the disease. Of these psychiatric disturbances, depression has received the most attention, although other alterations such as apathy and irritability are increasingly being examined in the context of HIV/AIDS.

Major depressive disorder (MDD) is commonly observed in HIV-infected individuals (Ciesla & Roberts, 2001). The prevalence of lifetime MDD in HIV-infected cohorts is reported to be between 40 – 60% (e.g., Atkinson et al., 2009; Cysique et al., 2007), and the incidence of new or recurrent depression is reported to be approximately 10% over an average two-year period (Cysique et al., 2007).

HIV-associated CNS involvement and MDD share common frontostriatal neural circuit pathology (Tekin & Cummings, 2002). However, studies examining the neuropathogenesis of MDD in HIV have reported mixed findings. Stubbe-Drager et al. (2012) reported that HIV+ individuals who endorsed depressive symptoms showed bilateral alterations of the ventral tegmental area, nucleus accumbens, and globus pallidus. Similarly, in a DTI study, altered white matter integrity was noted in the right
anterior cingulate and left thalamus in HIV+ adults with depression (Smith et al., 2008). In contrast, depressive symptoms have not been found to be associated with basal ganglia atrophy (Davison et al., 1997) or nucleus accumbens volume loss (Paul, Brickman, et al., 2005) in HIV+ cohorts. While methodological differences in these studies may account for some inconsistencies, these findings provide some evidence to suggest that depression in HIV is not purely reactive but has a specific biologic basis, likely due to HIV-associated CNS abnormalities.

Despite this, there is consistent evidence that HIV-associated NP impairment is not affected by comorbid depression (e.g., Cysique et al., 2007; Millikin et al., 2003). It is important to note however, that depressed mood is associated with poor functional status in HIV+ patients, suggesting that even though mood disturbance is not a primary source of NP impairment in HIV infection, it should be considered in the assessment of everyday functioning declines and diagnosis of HIV-Associated Neurocognitive Disorders (HAND; Cysique et al., 2007; Thames et al., 2011).

This consideration should be extended to other neuropsychiatric comorbidities (e.g., mania, bipolar disorder, apathy), which commonly occur in HIV and are expected to have similar functional consequences. These syndromes need to be examined closely so as to disentangle the etiology of each factor at the neural systems level and consequently clarify the interplay among these comorbidities. Such information may elucidate the potential differential impact that each symptomatic condition has on clinical and functional outcomes in HIV-infected cohorts. Unfortunately, few studies have addressed this issue. This is particularly true for apathy, which like depression involves the same frontostriatal systems affected by
HIV. In the context of evidence from various neurodegenerative disease groups (e.g., Alzheimer’s disease; discussed below) indicating the significant impact of apathy on functional status and quality of life, the investigation of this syndrome in HIV infection is clearly warranted.

Apathy

Definition

Apathy is conceptualized as a lack of motoric, emotional, and cognitive motivation (Marin et al., 1995). Its symptoms include reduced drive, poor initiation and control of self-directed purposeful directed behavior (e.g., Stuss, van Reekum, & Murphy, 2000; Levy & Dubois, 2006). This syndrome results from damage to specific frontal-subcortical structures and circuits, which are involved in the initiation, monitoring, and regulation of behavior (Cummings, 1993).

Neuropathology of apathy

Apathy is most commonly observed in patients with frontal lobe pathology. For example, it is the hallmark feature of progressive supranuclear palsy (PSP), with 92% of patients exhibiting moderate to severe symptoms (Litvan et al., 1996). Patients with neurodegenerative dementias also evidence high rates of apathy. In Alzheimer’s disease (AD), 59% of patients exhibit symptoms of apathy (Landes, Sperry, & Strauss, 2005), whereas in subcortical dementias the prevalence rates are 17% to 70% for patients with Parkinson’s disease (PD; Aarsland, Marsh, & Schrag, 2009) and 34% –
76% for those with Huntington’s disease (HD; Paulsen et al., 2001; Craufurd et al., 2001).

Apathy has received much attention in the context of neurological disorders. Neuroimaging studies in AD, PD, and amyotrophic lateral sclerosis (ALS) link apathy symptoms with abnormalities in orbitofrontal, medial, and dorsolateral prefrontal regions, supracallosal cingulate, basal ganglia (specifically, putamen and caudate nucleus), posterior cingulate, and inferior frontal gyrus (Apostolova et al., 2007; Bruen et al., 2008; Cummings, 1992; Starkstein et al., 2009; Tsujimoto et al., 2011). These findings are highly consistent with the brain circuits perspective which posits that symptoms of apathy are linked to pathology in neuroanatomical regions within the anterior cingulate circuit (Cummings, 1993).

**Apathy and depression**

While certain aspects of apathy and depression overlap (e.g., anhedonia), these two constructs are considered to be separable on behavioral and neuropathological bases. Depression is defined as a syndrome characterized by a permanent abnormal mood, lasting two weeks or more, and accompanied with a significant, diminished interest or pleasure. Decreased energy, excessive guilt, recurrent thoughts of death, poor concentration, sleep disturbance, and appetite change may also be present. While apathy may be one of the clinical expressions of depression, it is not a clinical criterion of the same (Marin et al., 1994, 1997). These syndromes are separable with regards to psychiatric symptomatology as demonstrated across studies of dementia patients. For example, Levy et al. (1998) compared PSP, AD, HD, PD, and
frontotemporal dementia patients and observed that the presence of depression did not predict the presence of apathy and vice versa. Furthermore, depression is associated with anxiety, agitation, hallucinations, and irritability, while apathy appears to be linked to older age, faster cognitive and functional decline, as well as abnormal motor functioning (Levy et al., 1998; Starkstein et al., 2006). For example, Marin and colleagues (1994) demonstrated that elevated apathy scores in the absence of elevated depression were most frequent in patients with AD and right hemisphere stroke. The authors concluded that the relationship between apathy and depression differs across diagnostic groups and therefore supports the discriminability of the two constructs (Marin et al., 1994). Additionally, they reported that apathy and depression each correlated with a distinct set of behavioral and psychiatric symptoms, further establishing the discriminant validity of these two constructs (see Lubarsky & Juncos, 2008 for review).

A dissociation between these disorders has been demonstrated on a neural systems level as well. Imaging studies across clinical groups (e.g., HIV, dementia, and aging cohorts) show evidence of orbital prefrontal and limbic system dysregulation being associated with depression, whereas apathy is thought to be driven by medial prefrontal, anterior cingulate, and deep subcortical pathology (e.g., Hoare et al., 2010; Lavretsky et al., 2007; Paul, Brickman et al., 2005; Starkstein et al., 2009). Apathy and depression also involve distinct neurotransmitter pathways. This has been demonstrated in part by reports that the use of selective serotonin reuptake inhibitors (SSRIs) results in higher rates of apathy despite an improvement in depressive symptoms (e.g., Garland & Baerg, 2001; Wongpakaran et al., 2007; Dubini, Bosc, &
Polin, 1997). Taken together, these psychiatric, neuroanatomical, and psychopharmacologic studies provide growing evidence regarding the independence of apathy and depression in various clinical populations.

Interestingly, a recent study by Withall and colleagues (2011) examining the longitudinal relationship between apathy and depression in patients with a history of stroke found that these neuropsychiatric syndromes were initially uncorrelated and thus deemed to be independent constructs, but evidenced an increase in comorbid depression and apathy approximately one year post-stroke. The authors suggest that increases in brain pathology (specifically frontal atrophy and deep white matter changes) over time may contribute to the merging of these disorders and consequently result in a greater rate of comorbid depression and apathy (Withall et al., 2011). This raises the possibility of duration of illness (HIV or otherwise) being an important factor in the expression of these neuropsychiatric syndromes.

In sum, the extant body of literature on apathy indicates that although apathy and depression sometimes co-occur, they are dissociable in terms of their psychiatric manifestations and neural substrates. With regards to apathy, neuroanatomical changes in the pallidal-thalamic-frontomesial-limbic loop, involving cortical regions such as the anterior cingulate cortex and orbitofrontal cortex are most commonly reported to be associated with the expression of this syndrome (Engelborghs et al., 2000; also see Casanova et al., 2011 for review). However, the etiology of apathy may be impacted by specific diseases and comorbidities, and as such must be examined in detail for those neurodegenerative disorders where this syndrome has received little attention.
Apathy in the context of HIV infection

Apathy has long been recognized as a clinical manifestation of HIV infection (e.g., Navia, Cho, Petito, & Price, 1986). However, only in the past decade has research emerged on the prevalence, correlates, and neural underpinnings of this important neuropsychiatric symptom in the setting of HIV infection (Rabkin et al., 2000; Castellon, Hinkin, & Myers, 2001; Castellon, Hinkin, Wood, & Yarema, 1998; Paul, Flanigan et al., 2005). Approximately 30 to 50% of HIV-infected persons demonstrate clinically elevated signs of apathy (e.g., Castellon et al., 1998, 2000; Rabkin et al., 2000). The presence and severity of apathy appears to be largely unrelated to HIV disease severity, including CD4 cell counts, HIV RNA viral load in plasma, and AIDS status (e.g., Castellon et al., 1998; Rabkin et al., 2000; Paul, Flanigan et al., 2005), with the possible exception of longer estimated duration of infection (Paul, Flanigan et al., 2005).

To the extent that apathy is reflective of CNS involvement in HIV infection, it should be associated with other markers of CNS compromise. One potential marker of HIV-associated CNS disturbance is cognitive impairment. The cognitive expression of frontostriatal neural injury in HIV includes deficits in executive functions, episodic memory, psychomotor processing speed, and working memory (e.g., Woods et al., 2009). However, the literature has yielded mixed findings regarding the association between apathy and neurocognitive functioning. Rabkin et al. (2000) reported small, non-significant correlations between apathy and measures of episodic memory, executive functions (i.e., set-switching and inhibition), and fine motor ability. Similarly, apathy was found to be a non-significant predictor of neurocognitive
performance as assessed by a six-domain test battery (Robinson-Papp et al. 2008). Other studies have reported modest associations between apathy and cognitive deficits. For example, apathy severity was significantly correlated with worse performance on tests of verbal and non-verbal episodic memory and cognitive set-switching (Paul et al. 2005). Negative correlations between apathy and performance on auditory working memory tasks (Castellon et al. 1998; Bogdanova et al., 2009) as well as conflict resolution and speed of information processing (Castellon et al. 2000) have been reported. It is unknown whether apathy is more strongly associated with a broader range of cognitive abilities such as decision-making and prospective memory, which have a more direct correspondence to the neural pathways involved in apathy.

Clinical consequence of apathy

The current body of literature indicates that while apathy is prevalent in HIV-infection, it is likely separable from neurocognitive functioning and may therefore be worthy of clinical consideration. For example, apathy and loss of motivation may affect performance on many aspects of instrumental activities and interpersonal functions (Cummings & Mega 2003). Approximately 35-50% of individuals with HAND experience significant functional impairments (e.g., Heaton et al., 2004). Neurocognitive deficits, psychiatric symptoms, and medical factors (e.g., HIV disease severity) are notable predictors of functional deficits in this population (see Gorman, Foley, Ettenhofer, Hinkin, & van Gorp, 2009 for review). Yet only three studies have evaluated the potential role of apathy in the expression of everyday functioning difficulties in HIV. With regard to antiretroviral (ARV) medication management,
apathy has been linked to ARV nonadherence (Barclay et al., 2007), greater perceived barriers to adherence, poor interpersonal support, lower intentions to adhere, and lower perceived treatment utility (Rabkin et al., 2000). In both of these medication-focused studies, the strength and independence of the apathy effects were dampened after controlling for other predictors such as health beliefs, depression, and substance use. Higher levels of apathy in HIV+ persons have also been reported to be associated with poorer health-related quality of life, specifically in the emotional role functioning and mental health domains. Although the magnitude of association was somewhat weaker than that noted for depressive symptoms, apathy remained a significant predictor of lower quality of life after controlling for mood (Tate et al., 2003).

While prior data illustrate that apathy may play at least a modest role in certain critical aspects of the daily lives of persons infected with HIV, its potential unique contribution to other important functional outcomes (e.g., vocational performance, automobile driving, and other instrumental and basic activities of daily living) remains to be studied.

Accordingly, in the “Apathy – Functional outcomes” study (see Chapter 1) we examined the associations between apathy and self-reported declines in instrumental activities of daily living and neurocognitive complaints in HIV+ persons. Apathy was found to be a significant, independent predictor of self-reported functional complaints (Kamat et al., 2012). The findings suggest that the clinical detection of apathy may help identify HIV-infected individuals at particular risk for functional impairments who may require additional support to maintain independence. Furthermore, in light of the functional implications of apathy in HIV+ persons, a closer examination of this
syndrome in the context of neuropathological substrates and psychiatric comorbidities is warranted.

**Neuroimaging studies of apathy in HIV**

HIV-associated CNS injury in frontostriatal circuits (e.g., anterior cingulate, orbitofrontal cortex, basal ganglia) is posited to underlie the expression of apathy in this population (van Reekum, Stuss, & Ostrander, 2005). To date, only two neuroimaging studies have addressed this question. In one study of 12 asymptomatic HIV+ individuals, Paul and colleagues (2005) reported a significant correlation between apathy and reduced volume in the nucleus accumbens, a central structure of the anterior cingulate circuit, which is involved in the initiation and regulation of behavior and emotional response. Volume of the caudate nucleus, which plays a critical role in the dorsolateral and orbitofrontal circuits, was not associated with apathy ratings (Paul et al., 2005). While the inclusion of disease duration did not impact the significance of apathy as a predictor of structural abnormality, it is unknown whether markers of disease severity such as nadir CD4 level and AIDS status would also impact the correspondence between HIV-associated neuropathology and apathy. Given the cross-sectional nature of their study, the inclusion of participants with a history of substance use disorder as well as head injury, and the absence of neuroimaging data for the seronegative comparison group, the association between apathy and volumetric changes in the nucleus accumbens cannot be conclusively attributed to HIV infection (Paul et al., 2005).
Hoare et al. (2010) examined the neural correlates of apathy in a South African HIV clade C cohort using a DTI approach. They classified HIV+ individuals into apathetic (n=13) and non-apathetic (n=13) groups. A group of healthy controls (n=10) was also included in this study. The authors conducted voxel-wise comparisons of FA values across the three groups and found that in relation to healthy controls, the HIV+ non-apathetic individuals had lower FA values in the frontal white matter tracts (i.e., corticospinal tract, the body of the corpus callosum, the anterior thalamic radiation, the superior corona radiata, and the genu of the corpus callosum). Within the HIV+ group, those who were apathetic demonstrated significantly lower FA values in the genu of the corpus callosum, the superior corona radiata, and the anterior thalamic radiation. Thus, HIV-associated abnormalities were predominantly seen in medial-frontal white matter tracts, and furthermore, alterations in a subset of these regions were associated with apathy. Of note, while the voxel-wise or “whole brain white matter” analyses employed in this study provide an atheoretical method that may uncover unexpected relationships between white matter alterations and function, they have the drawback of being highly dependent on the thresholds used to determine statistical significance between voxels (i.e., $\alpha=0.05$ in the case of Hoare et al. 2010), thereby increasing the likelihood of identifying spurious differences (i.e., Type I error; Mori, Wakana, Van Zijl, & Nagae-Poetscher, 2005).

Despite different imaging methodology, these two studies support the role of frontal and subcortical neural alterations underlying the expression of apathy in HIV infection. The nucleus accumbens is a gray matter structure in the limbic system and is thought to play a role in emotion processing (e.g., Goto & Grace, 2008). Its
projections go to the ventral palladium and subsequently to the dorsal thalamus and prefrontal cortex regions. It receives inputs from the amygdala, prefrontal association cortices, and the ventral tegmental area. Given its functional importance in emotional processing and goal-directed behavior, volume loss in this region would be expected to result in an apathetic syndrome as noted by Paul et al. (2005). The frontal white matter tracts implicated in the expression of apathy in the South African cohort of HIV-infected individuals connect regions such as the nucleus accumbens and the prefrontal cortex. For example, the corona radiata, one of the regions that showed a negative association between FA and apathy in the South African study, plays an important role in the interhemispheric relay and integration of input from various cortical and subcortical structures such as the basal ganglia. Abnormalities in the corpus callosum are reported to be associated with longer response latency and slowed initiation of action, consistent with the nature of the symptoms seen in apathy.

These early studies of the neural correlates of apathy in HIV infection have served to initiate this area of research and provide preliminary support for certain regions known to be a part of the brain circuits underlying the apathy syndrome. However, a comprehensive approach, in which the important nodes of the circuit are considered together to determine their relative contribution to the production of apathy symptomatology in HIV is still pending. Additionally, the nature of the relationship between apathy and white matter changes in the context of variables such as disease duration, AIDS status, and nadir CD4 count needs to be established. These factors might indicate the extent of disease burden and impact the severity of HIV-associated CNS disturbance, consequently modifying the severity of neurobehavioral
Finally, the utility of apathy as a behavioral marker of frontostriatal pathology depends its unique association with abnormalities in specific anatomical structures. For example, as theorized by Cummings (1993), frontal systems behavior disturbances, i.e., disinhibition, executive dysfunction, and apathy are associated with pathology in the oribolateral prefrontal cortex, dorsolateral prefrontal cortex, and anterior cingulate circuits respectively. To date, there have been no studies in HIV infection that have investigated whether the severity of apathy, but not other behavioral disturbance, is specific to damage in certain regions in the thalamocorticostriatal loop.

Study 2 (Chapter 3, Apathy – Neuroimaging) aimed to augment this nascent literature by examining correlations between apathy and DTI indices in specific regions of interest (ROIs) that were selected based on their theorized involvement in both HIV infection as well as the apathy syndrome. Focusing on the gray matter areas implicated in the expression of apathy, the white matter tracts underlying the orbital medial prefrontal cortex were examined, as well as the genu of the corpus callosum and the superior and anterior corona radiata. Our findings support the unique relationship between apathy severity and white matter injury in specific frontomedial regions, and provide preliminary evidence of the impact of immune suppression (i.e., low CD4 count) on this association. These findings contribute to a better understanding of apathy, an important neuropsychiatric syndrome. They also have implications for the potential optimization of patient care, given the demonstrated responsiveness of white matter change to antiretroviral treatment (Gongvanata et al., 2011).
Correlates of longitudinal progression of apathy in HIV infection

While neuroimaging studies are integral in examining the etiology of apathy in HIV, research is needed to characterize the longitudinal progression of this syndrome. Accumulating evidence from studies of non-HIV cohorts suggests that the progression of apathy is associated with greater rates of neurocognitive impairment and functional difficulties at follow-up (Starkstein et al., 2006; Mayo et al., 2009). There also appears to be a synergy between apathy and depression, such that incident apathy is associated with an increase in depressive symptomatology (e.g., Starkstein et al., 2006). Given the demonstrated impact of apathy on important functional outcomes in individuals with HIV, the examination of the correlates of longitudinal change in apathy is warranted. In this context, it is important to disentangle this syndrome from other co-occurring conditions such as depression, and examine whether the occurrence of a depressive episode impacts the manifestation and severity of apathy.

Apathy and major depressive disorder are both common in HIV infection and are thought to be secondary to HIV-associated damage to frontostriatal circuits. The secondary nature of both syndromes has typically been studied by examining their respective association with HIV-associated cognitive impairment. Another approach to address this issue is to investigate their relationship with each other, as this would also serve to improve the understanding of the mechanisms of these neuropsychiatric consequences of HIV infection.

Cross-sectional studies that have examined the association between apathy and depression report mixed findings. These two syndromes are significantly associated
with one another in HIV-infected cohorts, with at least two studies reporting
moderately strong, positive correlations between self-reported apathy and depression
scores (Castellon et al., 1998; Rabkin et al., 2000). Nevertheless, there is ample
evidence of the separability of these related constructs. Excluding items common to
both apathy and depression from the Hamilton Rating for Depression and Beck
Depression Inventory resulted in an attenuation of their associations (Rabkin et al.,
2000). This suggests that while apathy and depression are co-morbid in HIV infection,
there may not be a one-to-one correspondence between the two constructs. Also, three
studies reported that apathy ratings of HIV+ individuals do not co-vary with depressed
mood (Paul, Brickman et al., 2005; Paul, Flanigan et al., 2005; Tate et al., 2003),
while another study found that elevated levels of apathy are present in non-depressed
HIV-infected persons as compared to seronegatives (Hoare et al., 2010).

While these findings together elucidate to some degree the mechanisms of
apathy and depression in HIV infection, limitations of these studies must be addressed.
The divergent findings in the literature may be attributed to methodological
differences across studies. Apathy and depression have generally been measured using
self-report, with little overlap across studies in the instruments used. Consequently, the
definitions of clinically elevated apathy and depression have differed in the literature.

Within HIV+ cohorts, the extant literature has only focused on current
depression status (i.e., current mood rather than a standard diagnosis of a major
depressive episode; MDE) and its relationship with apathy. The association between
apathy and major depressive disorder (MDD) is of diagnostic and clinical utility. The
current knowledgebase provides a limited understanding of the mechanisms through
which apathy and depression may interact in HIV to result in a greater
neuropsychiatric burden. It could be the case that despite the demonstrated separability
of MDD and apathy in HIV-infected cohorts, incident (i.e., new or recurrent) MDE in
HIV+ individuals is associated with apathy in at least a proportion of cases.

To address this gap in the literature, we investigated the change in apathy
across two visits in a cohort of HIV+ individuals (See Chapter 4, Longitudinal change
in Apathy). The neuropsychiatric and medical correlates of progression in apathy were
examined, with an emphasis on depression. Specifically, we explored whether the
development of a depressive episode between visits was associated with change in
apathy in a cohort of HIV+ individuals. It was observed that a new episode of MDD
exacerbated apathy symptomatology in participants, however, the magnitude of this
effect depended on whether individuals had clinically elevated levels of apathy at their
first visit. These findings provide preliminary evidence for the interaction between
these two common psychiatric syndromes, and suggest that close monitoring and
intervention of depressive symptomatology may reduce the psychiatric burden of
HIV-infected persons by minimizing the development of apathy.
Chapter 1

Abstract

Apathy is a relatively common clinical feature of HIV-Associated Neurocognitive Disorders, but little is known about its implications for everyday functioning outcomes. In the present study, we examined the associations between apathy and self-reported instrumental activities of daily living (IADL) and neurocognitive complaints in 75 participants with HIV infection and 52 demographically comparable seronegative comparison subjects. All volunteers completed the apathy subscale of the Frontal Systems Behavioral Scale as part of a comprehensive neuromedical, psychiatric, and neurocognitive research evaluation. As compared to the seronegative comparison participants, the HIV+ group reported significantly higher current levels of apathy, but not did not differ in self-report of prior (i.e., pre-seroconversion) apathy. Higher current apathy self-ratings were associated with greater severity of IADL declines and more numerous cognitive complaints in the HIV+ sample, even after adjusting for potential psychiatric (e.g., depression), medical (e.g., hepatitis C co-infection), and neurocognitive predictors. Cognitive complaints, but not IADLs, were also uniquely associated with ratings of executive dysfunction and disinhibition. All told, these findings suggest that apathy may make a unique contribution to important everyday functioning outcomes among persons living with HIV infection. The clinical detection of apathy may help identify HIV-infected individuals at particular risk for functional impairments who may require additional support to maintain independence.
Implications of Apathy for Everyday Functioning Outcomes in Persons Living with HIV Infection

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Abstract

Apathy is a relatively common clinical feature of HIV-Associated Neurocognitive Disorders, but little is known about its implications for everyday functioning outcomes. In the present study, we examined the associations between apathy and self-reported instrumental activities of daily living (IADL) and neurocognitive complaints in 75 participants with HIV infection and 52 demographically comparable seronegative comparison subjects. All volunteers completed the apathy subscale of the Frontal Systems Behavioral Scale as part of a comprehensive neuromedical, psychiatric, and neurocognitive research evaluation. When compared with the seronegative comparison participants, the HIV+ group reported significantly higher current levels of apathy, but did not differ in self-report of prior (i.e., pre-seroconversion) apathy. Higher current apathy self-ratings were associated with greater severity of IADL declines and more numerous cognitive complaints in the HIV+ sample, even after adjusting for potential psychiatric (e.g., depression), medical (e.g., hepatitis C co-infection), and neurocognitive predictors. Cognitive complaints, but not IADLs, were also uniquely associated with ratings of executive dysfunction and disinhibition. All told, these findings suggest that apathy may make a unique contribution to important everyday functioning outcomes among persons living with HIV infection. The clinical detection of apathy may help identify HIV-infected individuals at particular risk for functional impairments who may require additional support to maintain independence.

Keywords: HIV/AIDS; Activities of daily living; Apathy; Everyday functioning

Introduction

HIV infection is commonly accompanied by a wide range of neuropsychiatric complications, including depression (e.g., Atkinson et al., 1988; Ciesla & Roberts, 2001), mania (e.g., Lyketsos, Hanson, Fishman, & Rosenblatt, 1993), and anxiety (Elliott, 1998). Although apathy has long been recognized as a clinical manifestation of HIV-Associated Neurocognitive Disorders (HAND; e.g., Navia, Cho, Petito, & Price, 1986), only in the past decade research has emerged on the prevalence, correlates, and neural underpinnings of this important neuropsychiatric symptom in the setting of HIV infection (Castellon, Hinkin, Wood, & Yarema, 1998; Castellon, Hinkin, & Myers, 2001; Paul, Flanagan et al., 2005; Rabkin et al., 2000). Apathy refers to a cluster of symptoms that include a reduction in self-initiated, goal-directed behavior, and a lack of motoric, emotional, and cognitive motivation (Marin, 1997). Approximately 30–50% HIV-infected persons demonstrate...
clinically elevated signs of apathy (e.g., Castellon et al., 1998, 2000; Rabkin et al., 2000). The presence and severity of apathy appears to be largely unrelated to HIV disease severity, including CD4 cell counts, HIV RNA viral load in plasma, and AIDS status (e.g., Castellon et al., 1998; Paul, Flanigan et al., 2005; Rabkin et al., 2000), with the possible exception of longer estimated duration of infection (Paul, Flanigan et al., 2005).

Apathy and depression, often characterized by symptoms such as dysphoria and anhedonia, commonly co-occur in HIV infection, which may be expected given the overlap in their clinical presentation (e.g., diminished interest and loss of motivation). In fact, apathy and depression are significantly associated with one another in HIV-infected cohorts, with at least two studies reporting moderately strong, positive correlations between self-reported apathy and depression scores (Castellon et al., 1998; Rabkin et al., 2000). Nevertheless, there is ample evidence of the separability of these related constructs. Excluding items common to both apathy and depression from the Hamilton Rating for Depression and Beck Depression Inventory resulted in an attenuation of their associations (Rabkin et al., 2000). This suggests that while apathy and depression are co-morbid in HIV infection, there may not be a one-to-one correspondence between the two constructs. Three studies also reported that apathy ratings of HIV+ individuals do not co-vary with depressed mood (Paul, Brickman et al., 2005; Paul, Flanigan et al., 2005; Tate et al., 2003), while another study found that elevated levels of apathy may be present in nondepressed HIV-infected persons when compared with seronegatives (Hoare et al., 2010). This is consistent with the dissociation between these two neuropsychiatric syndromes demonstrated by research in Parkinson’s disease (PD) and Alzheimer’s disease (AD). Findings in these patient populations suggest that these mood disturbances may occur alone or concurrently and may have independent neurophysiological bases (Ott, Noto, & Fogel, 1996; Starkstein et al., 1992). Imaging studies across clinical groups (including HIV-infected persons) show evidence of left prefrontal and limbic system dysregulation being associated with depression, whereas apathy is thought to be driven by medial prefrontal and deep subcortical pathology (Hoare et al., 2010; Paul, Brickman et al., 2005; Starkstein et al., 1992).

Although HIV-associated neural injury is not specific to any one brain region, HAND is reliably associated with damage to frontostriatal circuits, including the anterior cingulate circuit (Jernigan et al., 2011). Lesions to these circuits, which include the ventral striatum and are thought to be involved in emotion regulation and initiation of behavior, are known to produce prominent symptoms of apathy (Cummings, 1993; Tekin & Cummings, 2002). To date, two neuroimaging studies have examined the correspondence between apathy and HIV-associated neural injury. Paul, Brickman et al., (2005) reported a significant association between apathy and lower nucleus accumbens volumes, which was independent of HIV disease severity and depression ratings. Similarly, in a study using diffusion tensor imaging, lower fractional anisotropy in the medial frontal brain regions (e.g., corpus callosum and corona radiata) was observed in the aphasetic HIV+ individuals (Hoare et al., 2010). Together, these data provide direct evidence that HIV-associated abnormalities within frontostriatal circuits are uniquely associated with higher levels of apathy.

Given the overlapping neural circuits involved in apathy and HIV-associated neuropathology and the above-described evidence for their shared variance, one might predict that higher levels of apathy would correspond to greater risk of HIV-associated neurocognitive deficits. However, the literature has yielded mixed findings in that regard. Small, nonsignificant correlations between apathy and a wide range of cognitive abilities were reported in two previous studies (Rabkin et al., 2000; Robinson-Papp et al., 2008). Other studies suggest modest associations between apathy and deficits in episodic memory, cognitive set-switching (Paul, Flanigan et al., 2005), conflict resolution, working memory, and speed of information processing (Castellon et al., 1998, 2000). Thus, the current body of literature indicates that apathy is prevalent in HIV infection and is associated with HIV-related neural injury, but it is likely separable from depression and neurocognitive functioning and may therefore be worthy of clinical consideration.

For example, apathy and loss of motivation may affect the performance on many aspects of instrumental activities and interpersonal functions (Cummings & Mega, 2003). Approximately 35–50% of individuals with HAND experience significant functional impairments (e.g., Heaton et al., 2004). Neurocognitive deficits, psychiatric symptoms, and medical factors (e.g., HIV disease severity) are notable predictors of functional deficits in this population (see Gorman, Foley, Ettenhofer, Hinkin, & van Gorp, 2009 for review). Yet only three studies have evaluated the potential role of apathy in the expression of everyday functioning difficulties in HIV. With regard to antiretroviral (ARV) medication management, apathy has been linked to greater perceived barriers to adherence, lower intentions to adhere, and lower perceived treatment utility (Rabkin et al., 2000). Using Medication Event Monitoring System caps, Barclay, Hinkin and Castellon (2007) reported that higher levels of apathy were associated with ARV nonadherence in younger, but not older HIV+ individuals. In both of these medication-focused studies, the strength and independence of the apathy effects were dampened after controlling for other predictors such as health beliefs, depression, and substance use. Higher levels of apathy in HIV+ persons have also been reported to be associated with poorer health-related quality of life, specifically in the emotional role functioning and mental health domains. Although the magnitude of association was somewhat weaker than that noted for depressive symptoms, apathy remained a significant predictor of lower quality of life after controlling for mood (Tate et al., 2003).
While prior data illustrate that apathy may play at least a modest role in certain critical aspects of the daily lives of persons infected with HIV, its potential unique contribution to other important functional outcomes (e.g., vocational performance, automobile driving, and other instrumental and basic activities of daily living) remains to be studied. In the present study, we therefore aimed to determine the association between apathy and self-reported declines in instrumental activities of daily living and neurocognitive complaints in HIV+ persons. It was specifically hypothesized that elevated levels of current apathy would uniquely predict decline in instrumental activities of daily living and severity of neurocognitive complaints, independent of other known variables associated with these functional outcomes (e.g., depression, neurocognitive deficits).

**Methods**

**Participants**

Study participants included 75 HIV+ individuals recruited from HIV treatment centers and community organizations and 52 seronegative comparison subjects who were recruited from community advertisements and word-of-mouth (e.g., friends and family of the seropositive participants). These data were derived retrospectively from a NIDA-funded program project that also recruited individuals who met criteria for methamphetamine dependence within the past year. Given the known influence of chronic methamphetamine use on frontal systems (see Scott et al., 2007 for review), including apathy (Cattie et al., in press) these individuals were excluded from this current study. Individuals with histories of neurological diseases (e.g., seizure disorders, closed head injuries with loss of consciousness greater than 30 min, central nervous systems neoplasms, opportunistic infections) or severe psychiatric illnesses (e.g., schizophrenia) that might affect cognitive functioning were also excluded from

<table>
<thead>
<tr>
<th>Table 1. Sample demographic and clinical characteristics</th>
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<tr>
<td><strong>HBV− (n = 52)</strong></td>
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<tr>
<td>Demographic variables</td>
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<td>Age, years</td>
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<tr>
<td>Education, years</td>
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<tr>
<td>Sex (%men)</td>
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<tr>
<td>Ethnicity (% Caucasian)**</td>
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<tr>
<td>Psychiatric characteristics</td>
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<tr>
<td>Lifetime (current and past) Major depressive disorder (%)*</td>
</tr>
<tr>
<td>ADHD diagnosis (%)*</td>
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<tr>
<td>Apathy (before), T-score</td>
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<tr>
<td>Apathy (after), T-score***</td>
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<td>Disinhibition (before), T-score*</td>
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<td>Disinhibition (after), T-score**</td>
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<td>Executive dysfunction (before), T-score**</td>
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<td>Executive dysfunction (after), T-score***</td>
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<tr>
<td>Correlation between pre-/post-apathy ratings***</td>
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<td>Correlation between pre-/post-disinhibition ratings***</td>
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<tr>
<td>Correlation between pre-/post-executive dysfunction ratings***</td>
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<tr>
<td>Substance use history</td>
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<tr>
<td>Lifetime substance use disorder*</td>
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<tr>
<td>Proportion NP impaired (%)*</td>
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<tr>
<td>IADL complaints, total***</td>
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<tr>
<td>HIV disease characteristics</td>
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<tr>
<td>HIV RNA log10 (median, IQR)</td>
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<tr>
<td>Plasma viral load (% undetectable)</td>
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<tr>
<td>Nadir CD4 count (median, IQR)</td>
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<td>Current CD4 (median, IQR)</td>
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<tr>
<td>Proportion on HAART (%)</td>
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<tr>
<td>Proportion with AIDS (%)</td>
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<tr>
<td>Proportion with HCV (%)</td>
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</table>

*p < .05.

**p < .01.

***p < .001.
the study. The HIV status was determined by enzyme-linked immunosorbent assays and was confirmed by a western blot test. The demographic, clinical, neurocognitive, and psychiatric characteristics of the study sample are displayed in Table 1. Participants were well matched on demographic variables ($p > .10$), with the exception that the HIV+ group had a larger proportion of Caucasians ($p < .01$). The seronegative group had lower rates of Major Depressive Disorder, Attention-Deficit/ Hyperactivity Disorder (ADHD), and neuropsychological impairment ($p < .05$).

Procedure

Participants completed the 14-item apathy subscale of the self-report version of the Frontal Systems Behavioral Scale (FrSBe; Grace & Malloy, 2001). Ratings are on a Likert-type scale that ranges from 1 (“almost never”) to 5 (“almost always”) for each question. Higher ratings indicate more abnormal behavior (e.g., neglecting personal hygiene, leaving things unfinished). Following the manual guidelines, the raw scores are converted into demographically (i.e., age, education, and gender) adjusted T scores. A T-score cut point of 65 or higher is recommended to capture greater degrees of symptomatology and clinical significance. The scale allows for retrospective ratings prior to the injury or illness (before) and for ratings following the injury or illness (after), creating a baseline measure with which to compare subsequent ratings (Grace & Malloy, 2001). Participants were asked to provide retrospective ratings prior to the diagnosis of HIV infection (before) and current ratings (i.e., after seroconversion). Seronegative participants were asked to rate their behavior before age 20 and at present. The FrSBe T-scores (before and after) for the disinhibition and executive dysfunction subscales scores were also used in the analyses. In the HIV+ group, the pre-and post-self-ratings for each subscale were strongly correlated, but not collinear by traditional definitions (see Table 1).

All participants completed a version of the Lawton and Brody (1969) Activities of Daily Living scale, which was modified to enable the detection of temporal changes in ADL dependence at a cross-sectional visit by requiring subjects to rate their “current” and “best” prior level of functioning on numerous daily tasks (e.g., grocery shopping, managing finances, housekeeping; see Heaton et al., 2004). Consistent with prior research (e.g., Woods et al., 2008), the primary dependent variable of interest was the total number of declines reported in current versus past functioning on all of the IADL items (possible range = 0 (no decline) – 13 (increased dependence in all activities)).

Participants also completed the Patient’s Assessment of Own Functioning Inventory (PAOFI; Chelune, Heaton, & Lehman, 1986), which is a 41-item questionnaire in which they reported the frequency of difficulties with memory, language and communication, use of hands, sensory-perception, higher level cognitive and intellectual functions, work and recreation. The total number of cognitive complaints (possible range of 0–33) was used as the dependent variable.

Trained interviewers administered the Composite International Diagnostic Interview (CIDI) to the participants. The CIDI is a computer-assisted interview that provides a cross-cultural assessment of alcohol, drug, and mental disorders using DSM–IV criteria (Wittchen et al., 1991). The CIDI was used to obtain diagnoses of current and lifetime major depressive disorder and of psychoactive substance abuse and dependence disorders.

Participants were administered a standardized neuropsychological battery that included tests of executive functions, learning, memory, speed of information processing, verbal fluency, motor skills, and working memory (see Table 2 for tests in each domain). Raw scores were converted to demographically adjusted T-scores (e.g., Heaton et al., 2004), which were converted to

<table>
<thead>
<tr>
<th>Domain</th>
<th>Tests</th>
<th>Average domain T-score</th>
<th>Cohen’s $d$</th>
<th>$p$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>HIV− ($n = 52$)</td>
<td>HIV+ ($n = 75$)</td>
<td></td>
</tr>
<tr>
<td>Executive functions</td>
<td>Category Test, WCST-64, TMT Part B, Stroop Color and Word Test</td>
<td>50.70 (8.07)</td>
<td>46.30 (11.44)</td>
<td>0.45</td>
</tr>
<tr>
<td>Verbal fluency</td>
<td>FAS Letter Fluency, Category Fluency-Animals</td>
<td>50.29 (7.94)</td>
<td>48.56 (8.61)</td>
<td>0.21</td>
</tr>
<tr>
<td>Attention/working memory</td>
<td>WAIS–III Letter–Number Sequencing, Paced Auditory Serial Addition Task</td>
<td>49.95 (8.63)</td>
<td>48.15 (10.06)</td>
<td>0.19</td>
</tr>
<tr>
<td>Motor skills</td>
<td>Grooved Pegboard Test</td>
<td>48.61 (9.00)</td>
<td>46.25 (10.53)</td>
<td>0.04</td>
</tr>
<tr>
<td>Speed of information processing</td>
<td>WAIS–III Digit Symbol and Symbol Search, TMT Part A</td>
<td>52.69 (9.21)</td>
<td>49.83 (9.06)</td>
<td>0.31</td>
</tr>
<tr>
<td>Learning</td>
<td>HVLT-R Total, BVMT–R Total</td>
<td>47.32 (8.29)</td>
<td>46.16 (7.94)</td>
<td>0.14</td>
</tr>
<tr>
<td>Recall</td>
<td>HVLT–R Delay Recall, BVMT–R Delay Recall</td>
<td>46.48 (8.41)</td>
<td>45.97 (8.85)</td>
<td>0.06</td>
</tr>
</tbody>
</table>

Notes: WCST-64 = Wisconsin Card Sorting Test-64; WAIS-III = Wechsler Adult Intelligence Scale–III; TMT = Trail Making Test; HVLT-R = Hopkins Verbal Learning Test–Revised; BVMT-R = Brief Visual Spatial Memory Test–Revised.
deficit scores (range = 0 [T > 39] to 5 [T < 20]), which were then averaged to generate the Global Deficit Score (GDS; Carey et al., 2004). A GDS of ≥0.5 is the standard cutpoint indicative of global neurocognitive impairment. T-scores for the seven domains assessed in both study groups are presented in Table 2.

Data Analysis

A repeated-measures ANOVA was used to test for an interaction between HIV serostatus (between-subjects) and pre- and post-HIV infection apathy ratings (within-subjects). The prevalence of clinically elevated apathy in the HIV+ and seronegative groups was also examined with a chi-square test. Linear multiple regression analyses were then conducted to determine whether any of the demographic (i.e., ethnicity), psychiatric (i.e., ADHD and lifetime (i.e., current and prior) history of MDD diagnosis), cognitive, and substance use (i.e., lifetime history of any substance use disorder) factors on which the HIV seropositives and seronegatives differed confounded the HIV effect on the current apathy ratings. Next, within the HIV+ group, a repeated-measures approach was used to examine the association between functional complaints and pre- and post- apathy ratings. This approach allowed us to determine whether the association between post-ratings and functional outcomes was statistically larger than that with the pre-ratings (i.e., by virtue of the interaction term and planned follow-up correlations). The alternative analysis in which IADL and PAOFI complaints would serve as the criterion variables and pre-/post-apathy as the predictors would have addressed the contribution of post-apathy ratings in predicting functional outcomes above and beyond that of pre-ratings, which was not our primary question of interest. Moreover, the latter approach would be plagued by increased risk of Type II error due to the strong intercorrelations between pre- and post-ratings, which are better handled by grouping them in a within-subjects fashion. Finally, follow-up multivariable analyses (e.g., Katz, 2006; Peters, 2008) were conducted in which each functional outcome was predicted uniquely by current apathy ratings when considered alongside possible confounding variables (i.e., global neurocognitive impairment, lifetime MDD diagnosis, lifetime history of any substance use disorder, AIDS status, current CD4 count, and HCV serostatus). Results were unchanged when the current MDD was included in the models instead of lifetime MDD. Similar multivariable models using current ratings of disinhibition and executive dysfunction were also analyzed to address the issue of the specificity of the association between apathy and functional outcomes.

Results

HIV Serostatus and Apathy

Repeated-measures ANOVA was conducted with HIV serostatus as the between-subject variable and “before” and “after” apathy ratings as the within-subject variable. There was a main effect of HIV status, F(1, 124) = 9.71, p < .01, with greater levels of apathy reported by HIV+ participants. There was also a main effect of pre- and post-apathy ratings, F(1, 124) = 9.33, p < .01, such that apathy levels increased over time. These effects were tempered by an HIV serostatus by time interaction, F(1, 124) = 13.83, p < .001. Planned post-hoc analyses showed that HIV+ individuals did not differ significantly from their seronegative counterparts for apathy ratings “before,” t(124) = 1.31, p > .1, d = 0.20. Significant group differences were noted on the apathy “after” ratings, t(125) = 4.28, p < .0001, d = 0.76 with HIV+ participants reporting higher levels of apathy (see Table 1).

Multivariable regression with HIV serostatus and confounders (i.e., ADHD diagnosis, lifetime history of any substance use disorder, lifetime diagnosis of MDD, global cognitive impairment, and ethnicity) showed that HIV infection (β = 0.31, t(117) = 3.80, p < .001) and lifetime diagnosis of MDD (β = 0.41, t(117) = 5.02, p < .001) were uniquely associated with higher ratings of current apathy. The full model accounted for a significant amount of variance in the criterion, adjusted R² = .23, p < .0001.

Using the standard FrSBe cutpoint of T ≥ 65, 42% of the HIV+ individuals were classified as apathetic at the current time-point, whereas 19% of the seronegative group fell in this range (χ² = 7.74, p = .005). Odds ratio revealed that after adjusting for depression and other covariates (i.e., ADHD diagnosis, lifetime history of substance use disorder, global cognitive impairment, and ethnicity), HIV+ individuals were approximately three times more likely to endorse clinically elevated levels of current apathy when compared with seronegative subjects (odds ratio = 3.1, 95% confidence interval = 1.35, 7.12).

Apathy and IADLs

Next, in the HIV+ group, to capture the association between current IADL complaints and the change in pre- and post-ratings of apathy, we conducted a repeated-measures model with pre- and post-apathy ratings as the within-subject variable
and total number of IADL complaints as the predictor. This analytic approach provided a rigorous method to determine the relative strength of associations between ADLs and apathy. A trend-level main effect of IADL complaints was detected ($F(1, 73) = 3.5, p = .07$), along with a significant main effect of pre- and post-apathy ratings, $F(1, 73) = 6.21, p = .01$. An interaction was observed, $F(1, 73) = 6.0, p = .02$, such that the number of IADL complaints were significantly correlated with apathy “after” ratings ($r = .30, p < .01$), but not apathy “before” ratings ($r = .07, p > .1$). A follow-up multiple regression analysis was conducted with IADL complaints as the criterion and apathy rating as a predictor, which allowed us to determine whether post/current apathy was uniquely associated with ADL when considered alongside possible confounding variables (i.e., global neurocognitive impairment, lifetime MDD diagnosis, lifetime history of any substance use disorder, AIDS status, current CD4 count, and HCV serostatus). As shown in Table 3, the model was significant (adjusted $R^2 = .15$, $F(7, 63) = 2.70, p = .02$) and revealed that current apathy rating ($\beta = 0.27, p = .04$) and lifetime MDD diagnosis ($\beta = 0.27, p = .03$) were the only significant, independent predictors of IADL complaints (all other $p > .10$).

As shown in Table 4, the highest rates of dependence were reported in the domains of housekeeping, social activities, and comprehension of verbal and written material. A majority of individuals also reported a decline in the work status. We also examined whether apathy was associated with declines in individual domains of everyday functioning. Nominal regression analyses were conducted with the dependence status for each domain on the IADL questionnaire as the dependent variable, and apathy as well as psychiatric (i.e., lifetime MDD and substance use disorder diagnoses), cognitive, and disease characteristics (e.g., AIDS status, current CD4 count, and HCV serostatus) entered as predictors. Three significant models were obtained

<p>| Table 3. Clinical predictors of decline in activities of daily living in the HIV+ sample (n = 75) |
|---------------------------|---------------------------|---------------------------|---------------------------|---------------------------|</p>
<table>
<thead>
<tr>
<th>Variable</th>
<th>Model</th>
<th>$\beta$ 95% CI Parameter ($\beta$)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adjusted $R^2$</td>
<td>0.15</td>
<td></td>
<td>0.016</td>
</tr>
<tr>
<td>$F$</td>
<td>2.70</td>
<td></td>
<td>0.04</td>
</tr>
<tr>
<td>Apathy T-score</td>
<td>0.03</td>
<td>0.003, 0.053</td>
<td>0.27</td>
</tr>
<tr>
<td>LT-MDD</td>
<td>-0.56</td>
<td>-1.06, -0.06</td>
<td>-0.27</td>
</tr>
<tr>
<td>LT-SUD</td>
<td>0.11</td>
<td>-0.47, 0.69</td>
<td>0.05</td>
</tr>
<tr>
<td>Global cognitive impairment</td>
<td>0.18</td>
<td>-0.30, 0.65</td>
<td>0.09</td>
</tr>
<tr>
<td>AIDS status</td>
<td>-0.43</td>
<td>-0.95, 0.08</td>
<td>-0.02</td>
</tr>
<tr>
<td>Current CD4 count</td>
<td>3.51e$^{-1}$</td>
<td>-0.002, 0.002</td>
<td>0.004</td>
</tr>
<tr>
<td>HCV status</td>
<td>-0.36</td>
<td>-0.93, 0.21</td>
<td>-0.16</td>
</tr>
</tbody>
</table>

Notes: LT-MDD = Lifetime Major Depressive Disorder diagnosis; LT-SUD = Lifetime Substance Use Disorder diagnosis; HCV = Hepatitis-C virus.

| Table 4. Frequency of self-reported declines from “best” to “now” in activities of daily living and number of complaints in domains of cognitive functioning in 75 individuals with HIV infection |
|---------------------------------------------------------------|-------------------|
| Activities of Daily Living                                   | % declined       |
| Work                                                         | 63                |
| Housekeeping (cleaning)                                      | 23                |
| Social Activities                                            | 18                |
| Comprehension of reading/TV materials                        | 18                |
| Home repairs                                                 | 15                |
| Grocery shopping                                            | 12                |
| Laundry                                                      | 12                |
| Cooking                                                      | 11                |
| Shopping                                                     | 9                 |
| Financial management                                         | 8                 |
| Telephone use                                                | 5                 |
| Bathing                                                      | 5                 |
| Medication management                                       | 4                 |
| Transportation                                              | 3                 |
| Dressing                                                     | 1                 |
| Cognitive Complaints                                        | Median [IQR]      |
| Memory                                                       | 1 [0, 4]          |
| Language                                                     | 1 [0, 3]          |
| Motor                                                        | 0 [0, 0]          |
| Sensory                                                      | 0 [0, 0]          |
| General cognition                                            | 0 [0, 1]          |
and apathy was a significant independent predictor of dependence in social activities ($\chi^2 = 7.24, p = .007$), shopping ($\chi^2 = 0.09, p = .91$), and comprehension of written/verbal material ($\chi^2 = 7.24, p = .007$).

### Apathy and Cognitive Complaints

Similar analyses were conducted to examine the relationship between apathy ratings and total cognitive complaints on the PAOFI. A repeated-measures model was conducted with pre- and post-apathy ratings as the within-subject variable and total number of PAOFI complaints as the predictor. A significant main effect of PAOFI complaints was detected ($F(1, 67) = 18.16, p < .001$), but there was no main effect for pre- and post-apathy ratings, $F(1, 67) = 2.15, p > .1$. A significant interaction was observed, $F(1, 67) = 13.45, p < .001$; apathy “before” ratings were significantly associated with cognitive complaints ($r = .57, p < .0001$), and the magnitude of this correlation was twice that for pre-infection apathy and current cognitive complaints.

A multivariable regression analysis was conducted with the total number of PAOFI complaints as the criterion and current apathy level as well as the confounding variables (i.e., global neurocognitive impairment, lifetime MDD diagnosis, lifetime history of any substance use disorder, AIDS status, current CD4 count, and HCV serostatus) entered as predictors. As shown in Table 5, the overall model was significant, adjusted $R^2 = .40, F(7, 57) = 7.09, p < .0001$. Current apathy rating ($b = 0.55, p < .001$) and global neurocognitive impairment ($b = 0.24, p = .02$) were the only significant predictors of total cognitive complaints, while the HCV status ($b = 0.20, p < .07$) was associated at the trend level.

**Table 5. Predictors of cognitive complaints in the HIV+ sample**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Model</th>
<th>$\beta$</th>
<th>95% CI Parameter ($\beta$)</th>
<th>$p$-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adjusted $R^2$</td>
<td>0.40</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$F$</td>
<td>7.09</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Apathy T-score</td>
<td>0.13</td>
<td>0.08, 0.18</td>
<td>0.54</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>LT-MDD</td>
<td>−0.63</td>
<td>−1.6, 0.38</td>
<td>−0.13</td>
<td>.22</td>
</tr>
<tr>
<td>LT-SUD</td>
<td>0.15</td>
<td>−1.02, 1.32</td>
<td>0.03</td>
<td>.80</td>
</tr>
<tr>
<td>Global cognitive impairment</td>
<td>1.17</td>
<td>0.17, 2.17</td>
<td>0.24</td>
<td>.03</td>
</tr>
<tr>
<td>AIDS status</td>
<td>−0.22</td>
<td>−1.30, 0.84</td>
<td>−0.04</td>
<td>.67</td>
</tr>
<tr>
<td>Current CD4 count</td>
<td>0.001</td>
<td>−0.003, 0.005</td>
<td>0.07</td>
<td>.52</td>
</tr>
<tr>
<td>HCV status</td>
<td>1.08</td>
<td>−0.11, 2.27</td>
<td>0.20</td>
<td>.07</td>
</tr>
</tbody>
</table>

Notes: LT-MDD = Lifetime Major Depressive Disorder diagnosis; LT-SUD = Lifetime Substance Use Disorder diagnosis; HCV = Hepatitis-C virus.

**Table 6. Models examining disinhibition and executive dysfunction as predictors of cognitive complaints in the HIV+ sample**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Model</th>
<th>$\beta$</th>
<th>95% CI Parameter ($\beta$)</th>
<th>$p$-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adjusted $R^2$</td>
<td>0.22</td>
<td></td>
<td></td>
<td>&lt;.01</td>
</tr>
<tr>
<td>$F$</td>
<td>3.69</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disinhibition T-score</td>
<td>0.14</td>
<td>0.03, 0.24</td>
<td>0.34</td>
<td>.01</td>
</tr>
<tr>
<td>LT-MDD</td>
<td>−0.58</td>
<td>−1.80, 0.63</td>
<td>−0.12</td>
<td>.34</td>
</tr>
<tr>
<td>LT-SUD</td>
<td>0.18</td>
<td>−1.15, 1.52</td>
<td>0.03</td>
<td>.78</td>
</tr>
<tr>
<td>Global cognitive impairment</td>
<td>1.51</td>
<td>0.37, 2.64</td>
<td>0.31</td>
<td>.01</td>
</tr>
<tr>
<td>AIDS status</td>
<td>0.40</td>
<td>−0.76, 1.57</td>
<td>0.08</td>
<td>.49</td>
</tr>
<tr>
<td>Current CD4 count</td>
<td>2.01e−6</td>
<td>−0.004, 0.005</td>
<td>0.01</td>
<td>.93</td>
</tr>
<tr>
<td>HCV status</td>
<td>0.55</td>
<td>−0.81, 1.91</td>
<td>0.10</td>
<td>.41</td>
</tr>
</tbody>
</table>

Notes: LT-MDD = Lifetime Major Depressive Disorder diagnosis; LT-SUD = Lifetime Substance Use Disorder diagnosis; HCV = Hepatitis-C virus.
Finally, multivariable models were analyzed examining the association of apathy and individual domains (i.e., memory, cognition, sensory, motor, and language; see Table 4) on the PAOFI after adjusting for covariates (i.e., lifetime MDD and substance use disorder diagnoses, AIDS status, HCV status, and current CD4). Significant models were only obtained for the domains of memory ($R^2 = 0.36$, $F(7, 62) = 6.69$, $p < .0001$) and general cognitive complaints ($R^2 = 0.27$, $F(7, 62) = 4.51$, $p = .001$). Apathy was an independent, significant predictor of difficulties in memory ($b = 0.41$, $p < .001$) and cognition ($b = 0.45$, $p < .001$) such that higher ratings of apathy were associated with greater complaints in both domains.

Post-hoc Multivariable Analyses Examining the Association of FrSBe Subscales of Disinhibition and Executive Dysfunction and Functional Outcomes

To test the specificity of the effect of apathy on functional outcomes, we examined the association of disinhibition and executive dysfunction, two neurobehavioral sequelae of HIV infection that are also measured by the FrSBe, with cognitive and IADL complaints. Post-hoc multivariable analyses were conducted with the current ratings of disinhibition and executive dysfunction being considered alongside other possible predictors (i.e., global neurocognitive impairment, lifetime MDD diagnosis, lifetime history of any substance use disorder, AIDS status, current CD4 count, and HCV serostatus) of the two functional outcomes of interest. Current ratings of disinhibition ($b = 0.34$, $p = .01$) as well as executive dysfunction ($b = 0.63$, $p < .0001$) were independent predictors of cognitive complaints (see Table 6). However, as noted in Table 7, neither rating was associated with IADL complaints.

Discussion

The prevalence and clinical correlates of apathy in HIV infection have received increased attention in the past decade. Commensurate with prior research (e.g., Castellon et al., 1998; Hoare et al., 2010), findings from this investigation revealed a significant elevation in self-reported apathy ratings among persons living with HIV infection when compared with seronegative subjects. In fact, HIV infection was associated with a significantly higher prevalence of apathy, with 42% of the HIV+ individuals in our sample reporting clinically significant levels of apathy (vs. 19% in the seronegatives). This prevalence estimate is consistent with the 30–50% rates previously reported in HIV+ persons (e.g., Castellon et al., 1998, 2000; Rabkin et al., 2000). Extending the literature, we observed that self-reported symptoms of apathy prior to HIV infection were comparable to those endorsed by seronegatives, but rose significantly in the period after seroconversion. Importantly, the association between HIV serostatus and current apathy was independent of various confounding factors such as lifetime history of any substance use disorder, psychiatric comorbidities, cognitive impairment, and ethnicity. The elevation in apathy post-HIV infection coupled with the higher prevalence of apathy in the HIV+ group appears to be consistent with the underlying

<table>
<thead>
<tr>
<th>Variable</th>
<th>Model</th>
<th>$B$</th>
<th>$95%$ CI</th>
<th>Parameter ($\beta$)</th>
<th>$p$-value</th>
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<td>Disinhibition</td>
<td></td>
<td>0.12</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$R^2$</td>
<td></td>
<td>0.36</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Disinhibition T-score</td>
<td></td>
<td>0.03</td>
<td>-0.009, 0.079</td>
<td>0.21</td>
<td>.11</td>
</tr>
<tr>
<td>LT-MDD</td>
<td>-0.51</td>
<td>-1.05, 0.03</td>
<td>-24</td>
<td>.07</td>
<td></td>
</tr>
<tr>
<td>LT-SUD</td>
<td>0.10</td>
<td>-0.49, 0.69</td>
<td>0.04</td>
<td>.73</td>
<td></td>
</tr>
<tr>
<td>Global cognitive impairment</td>
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<td>-0.22, 0.71</td>
<td>0.12</td>
<td>.29</td>
<td></td>
</tr>
<tr>
<td>AIDS status</td>
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<td>-0.79, 0.19</td>
<td>-0.14</td>
<td>.24</td>
<td></td>
</tr>
<tr>
<td>Current CD4 count</td>
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<td>-0.002, 0.002</td>
<td>-0.04</td>
<td>.75</td>
<td></td>
</tr>
<tr>
<td>HCV status</td>
<td>-0.45</td>
<td>-1.03, 0.13</td>
<td>-0.19</td>
<td>.12</td>
<td></td>
</tr>
<tr>
<td>Executive dysfunction</td>
<td>0.13</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$R^2$</td>
<td></td>
<td>0.02</td>
<td></td>
<td></td>
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<tr>
<td>Executive dysfunction T-score</td>
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<td>0.03</td>
<td>-0.002, 0.059</td>
<td>0.26</td>
<td>.06</td>
</tr>
<tr>
<td>LT-MDD</td>
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<td>-1.02, 0.04</td>
<td>-24</td>
<td>.07</td>
<td></td>
</tr>
<tr>
<td>LT-SUD</td>
<td>0.07</td>
<td>-0.51, 0.66</td>
<td>0.03</td>
<td>.81</td>
<td></td>
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<tr>
<td>Global cognitive impairment</td>
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<td>.52</td>
<td></td>
</tr>
<tr>
<td>AIDS status</td>
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<td>-0.92, 0.11</td>
<td>-0.19</td>
<td>.12</td>
<td></td>
</tr>
<tr>
<td>Current CD4 count</td>
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<td>-0.002, 0.001</td>
<td>-0.03</td>
<td>.06</td>
<td></td>
</tr>
<tr>
<td>HCV status</td>
<td>-0.45</td>
<td>-1.01, 0.14</td>
<td>-0.19</td>
<td>.06</td>
<td></td>
</tr>
</tbody>
</table>

Notes: LT-MDD = Lifetime Major Depressive Disorder diagnosis; LT-SUD = Lifetime Substance Use Disorder diagnosis; HCV = Hepatitis-C virus.
This high prevalence of apathy in HIV+ persons warrants attention to this neuropsychiatric symptom for its role in functional outcomes. Consistent with our expectations, an interaction between the number of IADL complaints and apathy ratings prior to and following HIV infection was observed. A strong association was noted for IADL complaints and current apathy levels, such that individuals with higher ratings of apathy reported more IADL difficulties. These findings are consistent with the previous functional outcome studies (i.e., Barclay et al., 2007; Rabkin et al., 2000; Tate et al., 2003), but extend them by showing strong and independent associations between apathy and everyday functions (e.g., social activities, shopping, and comprehension of written/verbal material). Such findings are also commensurate with research in other clinical populations (e.g., AD and HCV) that suggests that apathy plays an important role in functional difficulties (Freels et al., 1992; Posada et al., 2010).

Self-reported cognitive complaints provide another lens on daily functioning that might be relevant to apathy. This is particularly true in an HIV+ population, as cognitive complaints are commonly endorsed (e.g., Carter, Rourke, Murji, Shore, & Rourke, 2003) and are correlated with higher levels of functional impairments in tasks such as financial management, medication management, cooking, and employment (e.g., Heaton et al., 2004). In this study, using the total number of cognitive complaints endorsed on the PAOFI, a similar association with apathy as that seen for IADL complaints was noted. HIV+ individuals who endorsed higher ratings of apathy were more likely to report having noticed declines in various cognitive domains relevant to their everyday functioning, especially memory. This is consistent with a study of individuals with mild cognitive impairment (MCI) that demonstrated a positive relationship between subjective cognitive complaints and apathy (Robert et al., 2006). This association may reflect the overlap between cognitive complaints and the cognitive aspects of apathy, such as a lack of goal-directed thought content, diminished motivation with regards to executive functions, and decreased verbal fluency.

Fatigue, a strong predictor of cognitive complaints (Woods et al., 2007), may accompany apathy and this may also contribute to the observed association.

Its independence from confounding factors is critical to the clinical and scientific value of apathy as a predictor of functional outcomes. HIV infection is associated with highly prevalent comorbidities that are strong predictors of everyday functioning. These include higher rates of lifetime substance use disorders (Bing et al., 2001), major depressive disorder (Atkinson et al., 1988, 2008; Bing et al., 2001), global neurocognitive impairment (Heaton et al., 1995; Hinkin et al., 2002; Martin et al., 2001), and comorbid HCV infection (e.g., Goulet, Fultz, McGinnis, & Justice, 2005). Functional impairment in HIV disease is also impacted by CD4 cell counts (e.g., Blalock, McDaniel & Farber, 2002) and AIDS status (e.g., Basso & Bornstein, 2000; Heaton et al., 1995). Although there were strong univariate effects of neurocognitive impairment and MDD on ADL complaints, apathy accounted for unique variance beyond these critical factors. In fact, the predictive value of neurocognitive impairment for IADLs (but not cognitive complaints) was diminished by the inclusion of apathy in the model. These findings suggest that relative to other predictors, apathy captures unique aspects of functional impairments and may therefore warrant clinical consideration.

The association between apathy and functional outcomes is consistent with the relationship noted between apathy and lower health-related quality of life. Two studies reported that elevated levels of apathy have a significant, negative impact on quality-of-life ratings (Rabkin et al., 2000; Tate et al., 2003), and this relationship was independent of depressed mood (Tate et al., 2003). Taken together, these findings are consistent with the Wilson and Cleary (1995) model of health-related quality of life, which posits that psychological symptoms may result in functional impairment, thereby impacting an individual’s quality of life. Interestingly, a different pattern of association has been reported in AD and HCV (e.g., Gongvatana, Woods, Taylor, Vigil, & Grant, 2007) and tempers the strength of conclusions that may be drawn based on significant frontal-striatal pathophysiology (e.g., involvement of the ventral striatum and anterior cingulate) common to HIV infection and apathy (Paul, Brickman et al., 2005).
interactions we found for functional outcomes and the pre- and post-HIV infection apathy ratings in a cross-sectional study. The nature of the retrospective ratings raises the concern that a participant’s post self-ratings may be primed by the pre-rating, as illustrated by significant correlations between the two scales (see Table 1). Arguing against this interpretation, however, is the finding that post-ratings and not pre-ratings were related to the outcomes of interest. Functional outcomes were also obtained using self-report instruments. Laboratory-based measures of daily functioning (e.g., Direct Assessment of Functional Status; Lowenstein & Bates, 1992) may have provided greater sensitivity to functional declines when compared with those obtained through self-report (Blackstone et al., 2012). Relatedly, that self-reported neurobehavioral symptoms (e.g., current apathy ratings) are predictive of self-reported functional difficulties deserves some consideration. As demonstrated by the post-hoc analyses, current self-reported ratings of apathy, but not disinhibition and executive dysfunction, were independently associated with IADL deficits. However, all three FrSBe subscales were significant predictors of cognitive complaints, which suggests variable specificity of apathy as a predictor of self-rated functional impairments. It is possible that the maintenance of ADL independence, a generally more severe expression of functional decline than the subjective experience of cognitive declines, is more sensitive to the behavioral aspects of apathy.

Another limitation relates to the sample’s demographic (i.e., a well-educated, predominately male and Caucasian cohort) and well-managed HIV disease characteristics (e.g., only 10% were immunosuppressed), which may restrict the extrapolation of our findings to more diverse and symptomatic HIV+ groups. The cross-sectional study design is another limitation, as it does not allow us to determine how well apathy predicts functional decline at a later time-point, a question that bears considerable clinical relevance for this population. The quasi-experimental, retrospective study design also did not permit the examination of whether the apathy-associated reduced behavioral repertoire led to the declines in functional abilities or, alternatively, increasing functional difficulties prompted the individuals to behaviorally withdraw to minimize the experience of failures.

In the context of prior studies, these findings suggest that apathy symptoms are more prevalent in HIV+ individuals compared with seronegatives, are more prominent following HIV infection, and adversely impact everyday functioning. Domainwise analyses demonstrated that apathy was independently associated with declines in daily activities such as social activities, shopping, and comprehension of verbal and written information, as well as with an increase in memory and general cognitive complaints. This suggests that specific functional activities may be more sensitive to higher levels of apathy. That elevated levels of apathy on the FrSBe appear to be associated with increased cognitive and functional difficulties in HIV+ individuals has implications for clinicians attempting to ascertain an individual’s ability to function and live independently. Given that apathy is associated with a number of adverse outcomes, including functional impairment, preliminary studies across non-HIV patient groups have investigated pharmacological interventions, which suggest promising but methodologically limited evidence for the possible efficacy of dopaminergic agents and amphetamines in the treatment of apathy (van Reekum, Stuss, & Ostrander, 2005). Preliminary studies examining behavioral interventions for apathy in patients with dementia suggest that mentally stimulating activities and interactive social settings may be effective (see Roth, Flashman, & McAllister, 2007 for review). Further investigation of pharmacological and behavioral interventions for HIV-infected cohorts is warranted as such therapies may have a positive impact on functional outcomes and quality of life. Future studies examining apathy in HIV would benefit from a prospective study design, multimodal assessments of daily functioning and apathy symptoms, as well as an exploration of other HIV disease markers of CNS involvement to tease apart the specific behavioral changes associated with apathy and how they manifest in everyday functioning declines.

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Conflict of Interest

None declared.

Appendix

The San Diego HIV Neurobehavioral Research Center [HNRC] group is affiliated with the University of California, San Diego, the Naval Hospital, San Diego, and the Veterans Affairs San Diego Healthcare System, and includes: Director: Igor Grant, M.D.; Co-Directors: J. Hampton Atkinson, M.D., Ronald J. Ellis, M.D., Ph.D., and J. Allen McCutchan, M.D.;

References


Chapter 1, in full, is a reprint of the material as it appears in Archives of Clinical Neuropsychology 2012. Kamat, Rujvi; Woods, Steven Paul; Marcotte, Thomas D; Ellis, Ronald J.; & Grant, Igor, Oxford University Press, 2012. The dissertation author was the primary investigator and author of this paper.
Apathy is associated with white matter abnormalities in anterior, medial regions in persons with HIV

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Abstract

Apathy is a relatively common psychiatric syndrome in HIV infection, but little is known about its neural correlates. In the present study, we examined the associations between apathy and diffusion tensor imaging (DTI) indices in key frontal white matter regions in the thalamocorticostriatal circuit that has been implicated in the expression of apathy. Nineteen participants with HIV infection and 19 demographically comparable seronegative comparison subjects completed the Apathy subscale of the Frontal Systems Behavioral Scale as a part of a comprehensive neuropsychiatric research evaluation. When compared to the seronegative participants, the HIV+ group had significantly more frontal white matter abnormalities. Within HIV+ persons, higher ratings of apathy were associated with greater white matter alterations (i.e., lower fractional anisotropy) in the anterior corona radiata, genu, and orbital medial prefrontal cortex. The associations between white matter alterations and apathy were independent of depression and were stronger among participants with relatively lower current CD4 counts. All told, these findings indicate that apathy is independently associated with white matter abnormalities in anterior, medial regions in persons infected with HIV, particularly in the setting of lower current immune functioning, which may have implications for the initiation of antiretroviral therapy.

Keywords: Diffusion tensor imaging, apathy, HIV/AIDS
Psychiatric dysfunction may develop in HIV seropositive (HIV+) individuals as a direct (e.g., effect of the virus in the CNS) or indirect (e.g., reaction to loss) consequence of the disease. Of these psychiatric disturbances, depression has received the most attention, although other alterations such as apathy have long been recognized as clinical manifestations of HIV-Associated Neurocognitive Disorders (HAND; e.g., Navia et al., 1986). It is only in the past decade that research has emerged on the prevalence, correlates, and neural underpinnings of apathy in the setting of HIV infection (Rabkin et al., 2000; Castellon, Hinkin, & Myers, 2001; Castellon, Hinkin, Wood, & Yarema, 1998; Paul, Flanigan et al., 2005). There is increasing evidence that apathy is associated with negative outcomes in HIV+ persons, including functional impairment and decreased quality of life (Barclay et al., 2007; Kamat et al., 2012; Tate et al., 2003), thus emphasizing the importance of investigating this psychiatric syndrome in the context of HIV infection.

Apathy is conceptualized as a lack of motoric, emotional, and cognitive motivation (Marin et al., 1995). Its symptoms include reduced drive, poor initiation and control of self-directed purposeful behavior (e.g., Stuss, van Reekum, & Murphy, 2000; Levy & Dubois, 2006). This syndrome results from damage to specific frontal-subcortical structures and circuits, which are involved in the initiation, monitoring, and regulation of behavior (Cummings, 1993). While certain aspects of apathy and depression overlap (e.g., anhedonia) across clinical groups (including HIV infection), these two constructs are considered to be separable on behavioral (e.g., Levy et al., 1998; Starkstein et al., 2006) and neuropathological (e.g., Hoare et al., Lavretsky et al., 2007; Paul et al., 2005) bases.
Despite currently available efficacious antiretroviral therapy, there is continued evidence that HIV neuropathology remains common and is not specific to any one brain region (e.g., Everall et al., 2009; Jernigan et al., 2011). Findings from magnetic resonance imaging (MRI), structural imaging, and increasingly, diffusion tensor imaging (DTI) studies suggest that relative to HIV seronegative individuals, HIV+ persons evidence decreased integrity in major white matter tracts in the frontal lobes, internal capsule, inferior longitudinal fasciculus, occipital lobes, and optic radiation (e.g., Filippi et al., 2001; Pfefferbaum et al., 2007; Ragin et al., 2005; Thurnher et al., 2005; Wu et al., 2006; Pomara et al., 2001; Gongvatana et al., 2009; Chen et al., 2009; Stebbins et al., 2007). Frontostriatal circuits involving the basal ganglia as well as frontal cortical white and gray matter appear to be particularly vulnerable (e.g., Aylward et al., 1993; Archibald et al., 2004; Langford, Hurford, Hashimoto, Digicaylioglu, & Masliah, 2005). These circuits, including the anterior cingulate circuit, connect various anatomical regions involved in affect regulation and goal-directed behavior (Cummings 1993; Tekin & Cummings, 2002). Consequently, injury to these circuits is known to produce symptoms of apathy (Cummings 1993; Tekin & Cummings, 2002).

To date, there have been only two neuroimaging studies that have examined the CNS correlates of apathy in HIV-infected individuals. In one structural MRI study of 12 asymptomatic HIV+ individuals, Paul and colleagues (2005) reported a significant correlation, independent of depression and disease duration, between apathy and reduced volume in the nucleus accumbens, a central structure of the anterior cingulate circuit, which is involved in the initiation and regulation of behavior.
and emotional response. Volume of the caudate nucleus, which plays a critical role in the dorsolateral and orbitofrontal circuits, was not significantly associated with apathy ratings (Paul et al., 2005). Using a voxel-wise DTI approach, Hoare et al. (2010) demonstrated that relative to HIV+ participants without apathy, HIV+, apathetic individuals had significantly lower fraction anisotropy values (an indicator of loss of axonal organization) in the genu of the corpus callosum, the superior corona radiata, and the anterior thalamic radiation. The anatomical regions implicated in these two studies of apathy in HIV-infected persons are consistent with those found to be involved in the expression of this syndrome in various other disease groups including Alzheimer’s disease (AD; Choi, Lim, Monteiro, & Reisberg, 2005), Parkinson’s Disease (PD; Reijinders et al., 2010), and amyotropic lateral sclerosis (ALS; Tsujimoto et al., 2011).

The Cummings (1993) neuroanatomical model of frontal systems dysfunction can guide investigations of the brain circuits involved in the expression of apathy in HIV (e.g., Levy & Dubois 2006; Stuss, van Reekum, & Murphy, 2000). The preliminary studies of the neural correlates of apathy in HIV have taken a more targeted approach, which has been instrumental in initiating this area of research (Paul, Brickman et al., 2005; Hoare et al., 2010). In addition, the specificity of these findings with respect to other neuropsychiatric symptoms in HIV is unknown. To complement these findings while taking a “brain circuits” approach, we investigated the white matter adjacent to the cortical structures posited by the Cummings neuroanatomical model of the apathy syndrome. Accordingly, the orbital, medial
frontal components of the subcortical-thalamic-anterior cingulate loop were examined together as opposed to being investigated separately.

The present study thus aimed to identify whether the presence and magnitude of HIV-associated white matter pathology in the tracts underlying the frontomedial cortex is associated with apathy severity by examining correlations between apathy and DTI indices in specific regions of interest (ROI). Based on the theoretically and empirically supported gray matter areas linked to the expression of apathy, the white matter tracts underlying the medial prefrontal cortex were examined, as were the genu of the corpus callosum, as well as the superior and anterior corona radiata.

We specifically hypothesized that higher levels of self-reported apathy will be uniquely associated with lower white matter integrity in the a priori regions selected. Strongest associations were expected in the white matter underlying the orbital medial prefrontal cortex, as theorized across the apathy literature (e.g., Stuss et al., 2000; Levy & Dubois et al., 2006). In addition, we examined the degree to which the relationship between white matter abnormalities and apathy is independent of depression. We also examined the effect of disease severity (i.e., duration of infection, AIDS status, viral load, and nadir as well as current CD4 levels) on the correspondence between apathy and changes in white matter integrity. We also hypothesized that HIV-associated white matter changes in the selected regions would not correspond with other frontal systems disturbances such as executive dysfunction and disinhibition, which are thought to be driven by pathology in the dorsolateral and orbitofrontal prefrontal cortices respectively (see Cummings 1993 for review).
Methods

Participants

Participants included 19 HIV+ individuals recruited from HIV treatment centers and community organizations and 19 seronegative comparison subjects who were recruited from community advertisements and word-of-mouth (e.g., friends and family of the seropositive participants). These 38 participants were enrolled at the University of California San Diego (UCSD) Translational Methamphetamine AIDS Research Center (TMARC). Individuals with histories of current substance dependence or abuse, neurological diseases (e.g., seizure disorders, closed head injuries with loss of consciousness greater than 30 minutes, central nervous systems neoplasms, opportunistic infections) or severe psychiatric illnesses (e.g., schizophrenia) that might affect cognitive functioning were also excluded from the study. Additionally, to be eligible, participants must not have any metal or devices in their body that contraindicate MRI. Given its association with neural injury and apathy, comorbid Hepatitis C Virus infection was also used as a criterion for exclusion in the current study. HIV status was determined by the Med Mira Rapid HIV antibody test. In the HIV+ participants, D4+ T cell counts were measured by flow cystometry at a Clinical Laboratory Improvement Amendments- certified medical center laboratory. HIV RNA levels were measured in plasma and CSF by reverse transcriptase PCR (Roche Amplicor, v. 1.5, lower limit of quantitation 50copies/mL). CD4 nadir was obtained by self-report, with confirmation by documented prior measurements in a subset of individuals. Date of nadir was also obtained by self-report. The study was approved by the institutional review board and informed consent was obtained from
each participant prior to enrollment. The demographic, clinical, neurocognitive, and psychiatric characteristics of the study sample are presented in Table 8. Participants were well matched on all demographic variables \((p > .10)\). The seronegative group had lower rates of lifetime Major Depressive Disorder \((p < .05)\).

**Neuropsychiatric Assessments**

Subjects were administered the 46-item self-report version of the Frontal Systems Behavior Scale (FrSBe; Grace & Malloy, 2001) that elicited the frequency of occurrence of a series of behaviors associated with frontal brain systems. The measure yields scores for three subscales: Apathy, Disinhibition, and Executive Dysfunction. Participants provided ratings on a Likert-type scale that ranges from 1 ("almost never") to 5 ("almost always") for each question, with higher ratings indicating more abnormal behavior (e.g., neglecting personal hygiene, leaving things unfinished). Based on the manual guidelines, raw scores were converted to demographically (i.e., age, education, and gender) adjusted T-scores, scaled so higher scores signify greater pathology. A T-score cut point of 65 is recommended to identify patients with more severe symptoms and greater clinical significance.

Trained interviewers administered the Composite International Diagnostic Interview (CIDI) to the participants. This measure is a computer-assisted interview and provides an assessment of alcohol, drug, and mental disorders using DSM-IV criteria (Wittchen et al., 1991), and was used to obtained diagnoses of current and lifetime major depressive disorder (MDD) and psychoactive substance abuse and dependence disorders.

**Diffusion Tensor MRI Acquisition**
MRI data were acquired using a 1.5T General Electric magnet. An axially acquired whole brain 2D spin echo, echoplanar imaging protocol was applied (Number of shots = 1, number of echoes = 1, TR=9.7s, TE=minimum, FOV=24 cm, matrix=96 x 96, 46 interleaved slices, no spaces, thickness = 2.5 mm, b = 0, 1000 s/mm², 51 gradient directions, with field maps). The B₀ distortions were corrected using field maps. The single diffusion-off image was co-registered to each subject’s T1 high-resolution image using localized Pearson correlation with AFNI’s align_epi_anat routine (Saad et al., 2009). The DTI series was co-registered to the diffusion-off image. Corrections for eddy currents were made using FSL’s eddy_correct routine. Diffusion eigenvectors and eigenvalues were derived from FSL’s dtifit routine. FA, Mean Diffusivity (MD), Axial Diffusivity (AD), and Radial Diffusivity (RD) values were calculated from the eigenvalues derived from the dtifit routine.

White matter Regions of Interest (ROI) were selected within the thalamo-cortico-striatal loop associated with depression according to Cumming’s model, as well as regions previously related to apathy in other HIV studies (Cummings, 1993; Hoare et al., 2010; Paul et al., 2005). An ROI approach is an alternative to the voxel-wise method and helps protect against the Type I error problems by the a priori selection of regions based on their theorized involvement in both HIV infection as well as the apathy syndrome. The ROIs included bilateral regions in the orbital-medial prefrontal cortex (OMPFC) as well as the anterior and superior corona radiata (ACR, SCR). An ROI was also placed in the genu of the corpus callosum. Two raters, blind to one another, defined these ROIs using the Oishi et al (2011) atlas. The degree of
between-rater similarity in the ROIs was assessed using Dice indices (Donner & Zou, 2002), which were as follows: ACR = .88, SCR = .85, OMPFC = .82, Genu = .85. The intersection maps of the two raters were used to derive the final Talairached ROIs. Each rater drew the ROIs on an MNI averaged 152 brain warped into Talairach space. These masks were further processed to produce masks in each subject’s native space. First, gray-white matter segmentation was performed on the T1 anatomical brains. Each individual’s anatomical brain was Talairached, and using this information, the Talairached MNI masks were reverse-warped into native space for each subject. Finally, the intersection of the masks with the white matter tissue segmentation was formed.

**Statistical Analyses**

Group differences between HIV+ and seronegative participants on demographic, neuropsychiatric, and imaging variables were examined using Wilcoxon Rank Sum test or $\chi^2$ tests. The significance threshold was set to $p = .05$ for all analyses.

First, we calculated the correlation between apathy and DTI indices separately for the HIV+ (n=19) and seronegative comparison (n=19) groups in all the ROIs. This permitted us to examine whether the pattern of the association between apathy and white matter changes differed across the two groups. Next, in each group, to determine whether the correspondence between white matter change and apathy was influenced by a history of major depressive disorder, we conducted a multivariate multiple regression analysis (Stata MVREG procedure; StataCorp, 2011). Here, apathy was entered as the predictor of FA values for those ROIs where a moderate or large
(Cohen’s $d > .5$) HIV effect was detected. Depression history was included as a covariate. Multivariate multiple regression differs from ordinary multiple regression in that several outcome variables (in this case, FA values for each ROI) are jointly regressed on the same predictor (here, apathy ratings). This procedure allows for the estimation of between-equation covariances, and thus the coefficients across the equations predicting each ROI can be tested with the Wald test (e.g., Hanssen et al., 2002). Specifically, this method allowed us to directly test the null hypothesis that the coefficient of apathy as a predictor of the FA values in the OMPFC did not differ from the coefficient of apathy as a predictor of FA values in another ROI (e.g., the ACR). Similar multivariate multiple regression models using MD, AD, and RD in the ROIs with robust HIV effects were conducted in the HIV+ group. Multivariate multiple regression was also performed to detect whether HIV disease characteristics moderated the association between apathy and FA values in the ROIs.

Finally, we examined the specificity of the white matter changes in the selected regions to apathy relative to other frontal systems disturbances. To do so, the correlations between FA values in the seven ROIs and the three FrSBe scales (i.e., apathy, disinhibition, and executive dysfunction) in the sample of HIV+ participants were examined. We also tested whether HIV+ persons with or without MDD differed in the extent of white matter alterations in the ROIs.

**Results**

**Demographic and Clinical Findings**
The demographic, clinical, neurocognitive, and psychiatric characteristics of the study sample are presented in Table 8. Participants were generally well matched on all demographic variables (p > .10). The HIV seropositive group had higher rates of lifetime MDD (p < .05). Individuals with HIV infection reported significantly higher levels of apathy relative to the seronegative comparison participants (t(1,37) = 4.13, p < .001, d = 1.3). Using the FrSBe cut point of T ≥ 65 (Grace & Malloy, 2001), none of the HIV- participants reported clinically elevated levels of apathy. In contrast, 8 of the 19 (42%) HIV+ persons were apathetic.

**Neuroimaging Findings**

**HIV infection and frontal white matter abnormalities.** Group differences in white matter abnormality in the ROIs were examined. As shown in Table 9, moderate to large effect sizes (d’s = .54 – 1.28) were noted such that the HIV+ group had lower FA values in bilateral ACR, genu, and the left OMPFC. Small, non-significant differences in FA were noted in right OMPFC and bilateral SCR (d’s = 0.0 - .25). The pattern of the HIV serostatus differences was generally consistent when considering mean, axial, and radial diffusivity, although the effect sizes were somewhat weaker (see Table 9).

Next, within the HIV+ group (n=19), the association between FA values in the seven ROIs and HIV disease variables (e.g., current CD4 count, AIDS status, nadir CD4 count, and duration of illness) was examined. In general, individuals with AIDS (n=12) had lower FA values in the frontal white matter regions selected. Using the Wilcoxon Rank Sum test, significant differences based on AIDS status were noted in the genu ($\chi^2=4.83$, p=.03), the left OMPFC ($\chi^2=5.21$, p=.02) and right OMPFC
Correlational analyses using Pearson’s r demonstrated moderate to strong significant associations between current CD4 count and frontal white matter changes. Specifically, higher CD4 counts were moderately correlated with FA values in the left ACR, genu, left OMPFC, and left SCR (r’s = .50 - .61). Similar associations were noted for nadir CD4 count and FA values in the genu and bilateral OMPFC (r’s = .50 - .59). Estimated duration of HIV infection was not significantly associated with white matter changes in any of the seven regions.

**Apathy and frontal white matter abnormalities.** We examined the correlations between apathy and FA values in the seven ROIs in the two HIV serostatus groups. Within the HIV+ cohort, strong, negative correlations were observed between apathy severity and FA values in the left (r=-0.60, p<.01) and right (r=-0.44, p=.05) ACR, genu (r=-0.53, p=.02), left OMPFC (r=-0.43, p=.06), left (r=-0.45, p=.05) and right (r=-0.41, p=.08) SCR. FA values in the right OMPFC were not associated with apathy in the HIV+ group (p>.2). There were no significant associations between white matter abnormality and apathy ratings observed in the seronegative comparison group (all p’s >.20).

**Multivariate multiple regression**

Bilateral ACR, genu, and left OMPFC ROIs were included as outcome variables in the multivariate multiple regression model examining the unique relationship between apathy and FA values in the HIV+ group. Lifetime diagnosis of major depressive disorder was entered as a covariate. Overall, the multivariate multiple regression model approached significance (F(4, 14) = 3.04, p=.05). To determine whether apathy significantly contributed to the variance explained in the
multivariate multiple regression model, we tested the null hypothesis that all
coefficients related to apathy in the design matrix were zero when depression was
dropped from the model. This null hypothesis was rejected (F(4, 16) = 3.41, p = .03)
indicating a significant association between apathy and FA for the four regions
together. Next, we tested the significance of depression by forcing its coefficients to
be zero while apathy was dropped from the model. The null hypothesis was not
rejected (F(4,16) = .87, p = .50). Together, these findings support the overall unique,
importance of apathy as a predictor in the multivariate multiple regression model. In
general, higher apathy was associated with lower FA values in the four, pre-
determined ROIs. However, as demonstrated by the Wald tests, the magnitude of this
association differed across the regions. The standardized parameter estimates are
presented in Table 10. Specifically, relative to the left OMPFC, the relationship
between apathy and FA values was significantly stronger in the left ACR (F(1,16) =
9.11, p = .01) and the genu (F(1,16) = 5.47, p = .03). The coefficient for apathy as a
predictor of FA values in the left OMPFC did not differ from that in the right ACR.
Compared to the right ACR, the coefficient of apathy was larger for the model
predicting the FA values in the genu (F(1,16) = 4.3, p = .05) as well as the left ACR
(F(1,16) = 4.3, p = .05). The coefficients for the genu and the left ACR were not
significantly different (F(1,16) = 2.62, p = .12).

When the multivariate multiple regression model using the same regions (i.e.,
bilateral ACR, genu, and left OMPFC) was examined in the HIV- group, neither the
overall model nor the individual regressions were significant (all p’s > .3).
Similar multivariate multiple regression models in the HIV+ group were conducted using MD, AD, and RD values in those regions where a robust HIV effect was detected as the outcome variables. The regions included in each model are indicated in Table 9. As before, apathy and depression history were entered as the predictors. Apathy rating was not a significant predictor in the overall model predicting MD values, which was significant \( F(4, 14) = 3.08, p=.05 \). An examination of the individual models revealed that apathy was a significant, independent predictor of MD values in the genu \( (\beta=.54, p=.03) \) only (see Table 10). The multivariate multiple regression model predicting RD values was significant \( F(3, 15) = 4.25, p=.02 \), and apathy showed a trend towards being an independent predictor of RD values \( F(3, 14) = 3.09, p =.06 \). In the individual models, apathy ratings were uniquely associated with RD values in the genu only \( (\beta=.57, p=.02) \). The analyses with AD values as outcome variables demonstrated that neither the MANOVA nor the individual models were significant (all \( p’s >.1 \)). Across the MD, RD and AD models, depression history did not explain a significant amount of variance in the DTI indices. Table 10 presents a summary of results for the individual ROI models in which apathy was a significant predictor of white matter changes.

**Impact of HIV disease characteristics on the relationship between apathy and frontal white matter abnormalities**

To characterize the nature of the relationship between apathy and white matter changes in the context of current immunovirologic status, a multivariate multiple regression analysis with FA values in bilateral ACR, genu, and left OMPFC predicted by apathy was conducted in the HIV+ individuals (n=19) with current CD4 count.
added as a covariate. The interaction between apathy and CD4 count was also entered in the analysis. The model was significant ($F(3, 14) = 4.37, p=.02$). A significant main effect for apathy was observed ($F(1, 14) = 8.6, p=.02$), as well as the interaction between apathy and CD4 count ($F(1, 14) = 5.8, p=.03$). An examination of the individual models indicated that the interaction of apathy and CD4 count was a significant predictor of white matter abnormality (i.e., lower FA) in the left ACR, genu, and the left OMPFC. However, Wald tests demonstrated that the coefficients for this interaction term did not differ across the regions ($p$’s >.1). Similar analyses were performed using MD values in the genu, bilateral OMPFC, and left SCR. The overall model was not significant ($p$.1).

Follow up post-hoc analyses were conducted to examine the relationship between apathy and FA values in the context of current CD4 count. HIV+ participants were split into two groups using the median value of the CD4 count, and consisted of nine participants each. Those with a CD4 count of less than 340, i.e., suggestive of poor immune function, were in the “low CD4” group, while the remaining participants were in the “high CD4” group. We observed strong, significant correlations between apathy and FA in the left ACR, genu, and left OMPFC only in the low CD4 group ($r$’s = -.68 - -.75), such that higher ratings of apathy were associated with greater white matter abnormalities. All the correlations between the variables of interest in the high CD4 group, i.e., those who had relatively intact immune functioning, were non-significant and relatively weaker than the low CD4 group ($r$’s <.5). Figure 1 illustrates the pattern observed in the left OMPFC.
Specificity of the white matter regions to apathy. First we examined whether executive dysfunction and disinhibition, two frontal systems disturbances, were correlated with white matter abnormalities in the regions selected in the HIV+ participants. As demonstrated in Table 11, compared to executive dysfunction and disinhibition, apathy ratings were more strongly associated with white matter changes in the seven ROIs. FA values in the left SCR showed comparable, fairly high associations with ratings of executive dysfunction ($r = -0.49, p = 0.03$) and apathy ($r = -0.42, p = 0.07$). Ratings of disinhibition were consistently unrelated to white matter abnormalities in the ROIs ($p's > 0.3$). Similarly, lifetime (i.e., past and current) diagnosis of MDD was also observed to be unrelated to white matter changes in the selected regions ($p's > 0.4$).

Discussion

The present investigation of the correspondence between HIV-associated white matter microstructure and the expression of apathy was guided by the Cummings (1993) model of brain circuitry implicated in the development of this neuropsychiatric syndrome. The results of our study support our hypothesis that apathy, but not other neuropsychiatric symptoms, is related to HIV-associated alterations in specific areas of frontomedial white matter.

Commensurate with prior research (e.g., Castellon et al., 1998; Kamat et al., 2012), HIV-seropositive participants reported higher ratings of apathy relative to seronegative comparison subjects. DTI as implemented in this study, appears to be sensitive to HIV-related microstructural white matter disturbance in the frontal regions.
selected, as the HIV+ persons showed more abnormalities relative to seronegative comparison participants. The most robust FA changes were observed in the bilateral ACR, genu, and left OMPFC. There may also be HIV-associated injury to the bilateral SCR and the right OMPFC as suggested by the group differences seen in MD, AD, and RD in these regions. The white matter pathology noted in HIV+ participants appears to be driven by immunovirological factors, most notably CD4 counts. Previous reports have linked these HIV disease markers to structural and white matter abnormalities (e.g., Cohen et al., 2010; Gongvatana et al., 2009; Fillipi et al., 2001; Jernigan et al., 2011).

One previous study that examined the white matter correlates of apathy, utilized a South African cohort of HIV- clade C participants (Hoare et al., 2010). Their whole-brain analyses revealed an association between frontal, medial white matter regions and apathy severity. Consistent with these findings, we observed that apathy ratings were strongly associated with overall HIV-associated frontal white matter changes in the selected regions, independent of any history of comorbid major depressive disorder. These findings alone do not fully explain the neuroanatomical correlates of apathy in HIV infection. Thus, we compared the magnitude of the association between apathy and FA changes to examine whether certain regions are more closely involved in the expression of apathy. Based on the orbitomedial cortical nodes of thalamocorticostriatal circuit involved in the apathy syndrome (e.g., Cummings, 1993; Stuss et al., 2000; Levy & Dubois, 2006), we expected apathy to be most strongly related to white matter abnormality in the OMPFC. Although the OMPFC did demonstrate a strong, significant association with apathy, it was not as
strong as that noted in the ACR and genu. It is possible that the white matter directly underlying the cortical structures that regulate goal-directed behavior may not be as central to the apathy syndrome or may not be as susceptible to HIV-associated CNS pathology. Alternatively, differences in neuroarchitecture might explain the varying strength of correlations between apathy and white matter changes across the three regions. Future studies using more sophisticated methodology such as tract based spatial statistics (TBSS) may clarify the present findings. Given the major white matter tracts that are contained in these two relatively superior and medial structures, the present findings, although not consistent with our hypothesis, are not surprising. For example, the ACR contains white matter tracts that connect the anterior cingulate circuit to the striatum and other regions involved in behavior regulation (McCandliss, 2011), while fibers from the orbitofrontal cortex extend within the genu and connect to other cortical regions (Schmahmann & Pandya, 2009). The strong link between diffusion abnormalities (i.e., MD, AD, RD) in the genu and apathy further substantiate the apparent relevance of this region in the regulation of goal-directed behavior. In contrast, within the HIV- group, there were no significant associations between apathy ratings and white matter integrity. This suggests that it is only in HIV+ individuals that CNS pathology exists and corresponds to apathy symptomatology. From a brain circuits perspective, our findings in the HIV+ group regarding the link between apathy and the white matter tracts serving the major cortical nodes of the thalamocorticostriatal loop involved in goal-directed behavior complement those of Paul, Brickman et al. (2005) who, in their sample of HIV+ participants, first identified
the relationship between apathy and volume loss in the nucleus accumbens, an important anatomical structure within this loop.

At present, little is known about the impact of HIV disease characteristics on relationship between neural damage and apathy severity. Current CD4 count is a marker of current immune functioning (e.g., Sousa et al., 2002), and is a commonly used clinical marker of HIV disease or treatment response. Accordingly, we examined whether current CD4 count moderated the correspondence between apathy and frontal white matter abnormalities. It was observed that those individuals with current CD4 counts less than 340 demonstrated a robust correlation between apathy and white matter abnormalities. This association was absent in the HIV+ persons with better immune functioning (i.e., those with CD4 counts of 340 and higher). Low CD4 count, a marker of current immunological function, has previously been shown to be associated with atrophy in frontostriatal regions (Chiang et al., 2007). These neuropathological findings are complemented by our result regarding the moderating effect of CD4 count on the association between apathy and white matter damage. Our preliminary findings have interesting implications for the management of HIV disease as well as neuropsychiatric and neuropathological consequences of HIV infection. Other important factors such as antiretroviral regimen history and medication adherence warrant consideration, as they may impact current CD4 count thereby modifying the magnitude of HIV-associated CNS damage. This potential mechanism raises the possibility of mitigating the neuropsychiatric burden in HIV+ patients via improved antiretroviral treatment.
Extending the literature, we observed that disinhibition, a behavioral syndrome associated with frontal systems disturbance, was not related to white matter abnormality in the selected regions. The same was true for symptoms of executive dysfunction, with the exception of the significant association noted between these ratings and white matter changes in the SCR. These findings are not surprising from a brain circuitry perspective. As described by Cummings (1993) and Alexander et al., (1986), there are five parallel circuits that link subcortical structures to the frontal lobes. The dorsolateral prefrontal, lateral orbital frontal, and anterior cingulate circuits regulate cognition and neuropsychiatric function. Injury to these circuits produce symptoms of executive dysfunction, disinhibition, and apathy. The utility of apathy as a behavioral marker of HIV-associated CNS damage to frontal systems is bolstered by the unique correspondence between the selected regions and the severity of apathy symptoms vis-à-vis ratings of disinhibition and executive dysfunction. As such, these findings supporting the relationship between apathy and the anterior, medial structures targeted in this study are highly consistent with the Cummings brain circuitry model used to explain specific neuropsychiatric disorders. Future studies in HIV-infected cohorts specifically examining the neural correlates of disinhibition and executive dysfunction are needed, given the potential relevance of these behavioral syndromes to everyday functioning outcomes.

MDD status was also not related to white matter changes in the ROIs. Imaging studies across clinical groups (e.g., HIV, dementia, and aging cohorts) show evidence of orbital prefrontal gray matter changes and limbic system dysregulation being associated with depression, whereas apathy is thought to be driven by medial
prefrontal, anterior cingulate, and deep subcortical pathology (e.g., Hoare et al., 2010; Lavretsky et al., 2007; Paul, Brickman et al., 2005; Starkstein et al., 2009). Our findings are commensurate with these reports, and provide further support for the neuroanatomical distinction between the psychiatric constructs of apathy and depression.

Neuropathological studies in HIV have demonstrated that HIV-related toxicity induces myelin and axonal damage, ultimately resulting in neuronal apoptosis and dendritic simplification (Ozdener, 2005; Archibald et al., 2004). In the present study, we observed a correspondence between apathy ratings and HIV-associated alterations in both FA and MD. These DTI indices may reflect the myelin content, extent of axonal damage, and gliosis (Schmierer et al., 2006). Thus, it appears that apathy may be associated with these neuropathological processes. However, this correspondence should be interpreted with caution. Increasingly, RD and AD have been utilized as markers of myelin loss and axonal degeneration respectively (Song et al., 2002; 2003). Although our data suggest a stronger link between apathy and abnormal RD but not AD in the genu, potentially indicating a demyelination process, these findings are not conclusive. A thorough investigation of the underlying neural structural characteristics is recommended (Wheeler-Kingshott & Cercignani, 2009). As such, the exact pathological processes resulting in the observed microstructural frontomedial white matter abnormalities and consequent dysregulation of goal-directed behavior in HIV-infected participants remain to be investigated.

As with all cross-sectional clinical investigations, this study has limitations. Future longitudinal studies should examine the trajectory of white matter alterations in
the context of fluctuations in neuropsychiatric disturbance. Our sample size is small and power issues did not permit thorough examination of all possible covariates (e.g., ART status) that might be influence the correspondence between apathy and HIV-associated white matter alterations. Our preliminary findings would benefit from replication in future studies. Also, we utilized a self-report measure (i.e., FrSBe) of apathy as opposed to a clinical interview such as the Neuropsychiatric Inventory (Cummings et al., 1994). The accuracy of self-reported ratings may be affected by depression, bias, and/or mild anosagnosia and this limitation tempers the strength of our conclusions.

Collectively, our findings suggest that relative to comparison subjects, HIV-infected persons demonstrate white matter alterations in frontal, medial regions. Furthermore, apathy symptoms, but not other psychiatric disturbances (i.e., disinhibition and depression) are related to HIV-associated white matter abnormalities in the frontal medial regions. Apathy ratings most strongly correlated with changes in FA. The correspondence between apathy and CNS disturbance appears to be driven by poor immune functioning (i.e., low CD4 count). This raises the possibility that closer monitoring and treatment of HIV disease may alter the burden of CNS pathology and consequently minimize the expression of apathy. Given that apathy is associated with a number of adverse functional outcomes in HIV infected cohorts (e.g., Tate et al., 2003; Barclay et al., 2007; Kamat et al., 2012), it would be useful to investigate whether different types of antiretroviral treatment regimens have a dynamic impact on neural repair and the manifestation of apathy. Overall, these findings support the
assessment of apathy in HIV-infected individuals seen in clinical settings as it may serve as a proxy of the neuropathologic burden in these patients.

Chapter 2, in full, is currently being prepared for submission for publication.

Kamat, Rujvi; Brown, Gregory G.; Bolden, Khalima; Marcotte, Thomas D.; Letendre, Scott L.; Ellis, Ronald J.; Woods, Steven Paul; Grant, Igor; Heaton, Robert K.

Apathy is associated with white matter abnormalities in anterior, medial regions in persons with HIV. The dissertation author was the primary investigator and author of this paper.
Table 8: Demographic and clinical findings in the sample of HIV- and HIV+ participants

<table>
<thead>
<tr>
<th>Demographic variables</th>
<th>HIV-</th>
<th>HIV+</th>
<th>Cohen’s $d$</th>
<th>$p$-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>38.3 (11.3)</td>
<td>42.9 (11.4)</td>
<td>-.41</td>
<td>.21</td>
</tr>
<tr>
<td>Gender (%male)</td>
<td>90</td>
<td>84.2</td>
<td>-</td>
<td>.60</td>
</tr>
<tr>
<td>Education (years)</td>
<td>14.2 (2.3)</td>
<td>13.8 (2.3)</td>
<td>.23</td>
<td>.63</td>
</tr>
<tr>
<td>Ethnicity (%Caucasian)</td>
<td>65</td>
<td>58</td>
<td>-</td>
<td>.70</td>
</tr>
<tr>
<td>Neuropsychiatric variables</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Apathy T-score</td>
<td>40.1 (7.1)</td>
<td>60.2 (20.4)</td>
<td>-1.32</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Clinical elevation in apathy (T-score &gt;65)</td>
<td>0</td>
<td>42.1</td>
<td>-</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Proportion with Lifetime MDD (%)</td>
<td>20</td>
<td>63.2</td>
<td>-</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Proportion NP impaired (%)</td>
<td>20</td>
<td>42.1</td>
<td>-</td>
<td>.15</td>
</tr>
<tr>
<td>HIV disease variables</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration of illness (months)</td>
<td>-</td>
<td>70.4 (7.7, 70.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proportion with AIDS (%)</td>
<td>-</td>
<td>63.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current CD4 count (median, IQR)</td>
<td>-</td>
<td>340 (215, 500)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nadir CD4 (median, IQR)</td>
<td>-</td>
<td>175 (40, 250)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proportion on CART (%)</td>
<td>-</td>
<td>75</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Log$_{10}$ Plasma Viral Load for those on CART</td>
<td>-</td>
<td>1.6 (1.6, 1.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Plasma viral load (% undetectable of those on CART)</td>
<td>-</td>
<td>80</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Note: CART = combination Antiretroviral Therapy*
<table>
<thead>
<tr>
<th></th>
<th>HIV- (n=19)</th>
<th>HIV+ (n=19)</th>
<th>Cohen’s d</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
</tr>
<tr>
<td><strong>Fractional anisotropy</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACR-L</td>
<td>0.37</td>
<td>0.03</td>
<td>0.34</td>
</tr>
<tr>
<td>ACR-R</td>
<td>0.36</td>
<td>0.03</td>
<td>0.34</td>
</tr>
<tr>
<td>Genu</td>
<td>0.47</td>
<td>0.09</td>
<td>0.38</td>
</tr>
<tr>
<td>OMPFC-L</td>
<td>0.3</td>
<td>0.03</td>
<td>0.27</td>
</tr>
<tr>
<td>OMPFC-R</td>
<td>0.29</td>
<td>0.04</td>
<td>0.28</td>
</tr>
<tr>
<td>SCR-L</td>
<td>0.4</td>
<td>0.03</td>
<td>0.4</td>
</tr>
<tr>
<td>SCR-R</td>
<td>0.39</td>
<td>0.03</td>
<td>0.39</td>
</tr>
<tr>
<td><strong>Mean Diffusivity</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACR-L</td>
<td>0.83</td>
<td>0.05</td>
<td>0.86</td>
</tr>
<tr>
<td>ACR-R</td>
<td>0.85</td>
<td>0.07</td>
<td>0.9</td>
</tr>
<tr>
<td>Genu</td>
<td>1.02</td>
<td>0.28</td>
<td>1.2</td>
</tr>
<tr>
<td>OMPFC-L</td>
<td>0.81</td>
<td>0.07</td>
<td>0.86</td>
</tr>
<tr>
<td>OMPFC-R</td>
<td>0.83</td>
<td>0.08</td>
<td>0.88</td>
</tr>
<tr>
<td>SCR-L</td>
<td>0.73</td>
<td>0.04</td>
<td>0.75</td>
</tr>
<tr>
<td>SCR-R</td>
<td>0.73</td>
<td>0.05</td>
<td>0.79</td>
</tr>
<tr>
<td><strong>Axial Diffusivity</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACR-L</td>
<td>1.16</td>
<td>0.05</td>
<td>1.19</td>
</tr>
<tr>
<td>ACR-R</td>
<td>1.2</td>
<td>0.07</td>
<td>1.24</td>
</tr>
<tr>
<td>Genu</td>
<td>1.56</td>
<td>0.25</td>
<td>1.7</td>
</tr>
<tr>
<td>OMPFC-L</td>
<td>1.07</td>
<td>0.07</td>
<td>1.1</td>
</tr>
<tr>
<td>OMPFC-R</td>
<td>1.1</td>
<td>0.07</td>
<td>1.14</td>
</tr>
<tr>
<td>SCR-L</td>
<td>1.06</td>
<td>0.04</td>
<td>1.09</td>
</tr>
<tr>
<td>SCR-R</td>
<td>1.04</td>
<td>0.06</td>
<td>1.12</td>
</tr>
<tr>
<td><strong>Radial Diffusivity</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACR-L</td>
<td>0.66</td>
<td>0.06</td>
<td>0.69</td>
</tr>
<tr>
<td>ACR-R</td>
<td>0.67</td>
<td>0.07</td>
<td>0.73</td>
</tr>
<tr>
<td>Genu</td>
<td>0.75</td>
<td>0.3</td>
<td>0.97</td>
</tr>
<tr>
<td>OMPFC-L</td>
<td>0.67</td>
<td>0.08</td>
<td>0.73</td>
</tr>
<tr>
<td>OMPFC-R</td>
<td>0.69</td>
<td>0.09</td>
<td>0.75</td>
</tr>
<tr>
<td>SCR-L</td>
<td>0.56</td>
<td>0.04</td>
<td>0.57</td>
</tr>
<tr>
<td>SCR-R</td>
<td>0.56</td>
<td>0.05</td>
<td>0.63</td>
</tr>
</tbody>
</table>

Note: *ROIs that were included as outcome variables in the multivariate multiple regression model for each DTI index with apathy entered as a predictor and depression status as a covariate.

ACR = anterior corona radiata
OMPFC = orbital medial prefrontal cortex
SCR = superior corona radiata
<table>
<thead>
<tr>
<th>DTI index</th>
<th>Region</th>
<th>Coefficient (β)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>FA</td>
<td>Left ACR</td>
<td>-.59</td>
<td>&lt;.01</td>
</tr>
<tr>
<td></td>
<td>Right ACR</td>
<td>-.46</td>
<td>.02</td>
</tr>
<tr>
<td></td>
<td>Genu</td>
<td>-.53</td>
<td>&lt;.01</td>
</tr>
<tr>
<td></td>
<td>Left OMPFC</td>
<td>-.40</td>
<td>.03</td>
</tr>
<tr>
<td>MD</td>
<td>Genu</td>
<td>.54</td>
<td>.03</td>
</tr>
<tr>
<td></td>
<td>Left OMPFC</td>
<td>.08</td>
<td>.76</td>
</tr>
<tr>
<td></td>
<td>Right OMPFC</td>
<td>.33</td>
<td>.19</td>
</tr>
<tr>
<td></td>
<td>Left SCR</td>
<td>.30</td>
<td>.18</td>
</tr>
<tr>
<td>RD</td>
<td>Genu</td>
<td>.57</td>
<td>.02</td>
</tr>
<tr>
<td></td>
<td>Left OMPFC</td>
<td>.11</td>
<td>.67</td>
</tr>
<tr>
<td></td>
<td>Right OMPFC</td>
<td>.35</td>
<td>.16</td>
</tr>
<tr>
<td>AD</td>
<td>Genu</td>
<td>.40</td>
<td>.11</td>
</tr>
<tr>
<td></td>
<td>Left SCR</td>
<td>.01</td>
<td>.95</td>
</tr>
<tr>
<td></td>
<td>Right SCR</td>
<td>.38</td>
<td>.13</td>
</tr>
</tbody>
</table>

Note: Full model included apathy as the predictor with lifetime (past and current) major depressive disorder diagnosis as the covariate.
FA = Fractional anisotropy
MD = Mean diffusivity
RD = Radial diffusivity
AD = Axial diffusivity
ACR = anterior corona radiata
OMPFC = orbital medial prefrontal cortex
SCR = superior corona radiata
Table 11: Pearson’s correlation between the three FrSBe scales and FA values in the HIV+ participants (n=19)

<table>
<thead>
<tr>
<th></th>
<th>Apathy</th>
<th>Disinhibition</th>
<th>Executive dysfunction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left ACR</td>
<td>-.51*</td>
<td>-.1</td>
<td>-.31</td>
</tr>
<tr>
<td>Right ACR</td>
<td>-.48*</td>
<td>-.05</td>
<td>-.27</td>
</tr>
<tr>
<td>Genu</td>
<td>-.57*</td>
<td>-.06</td>
<td>-.17</td>
</tr>
<tr>
<td>Left OMPFC</td>
<td>-.45*</td>
<td>-.23</td>
<td>-.18</td>
</tr>
<tr>
<td>Right OMPFC</td>
<td>-.28</td>
<td>-.07</td>
<td>.05</td>
</tr>
<tr>
<td>Left SCR</td>
<td>-.42</td>
<td>-.25</td>
<td>-.49*</td>
</tr>
<tr>
<td>Right SCR</td>
<td>-.39</td>
<td>-.12</td>
<td>-.40</td>
</tr>
</tbody>
</table>

*Note: *p < .05

ACR = anterior corona radiata
OMPFC = orbital medial prefrontal cortex
SCR = superior corona radiata
Figure 1: Scatterplot demonstrating the different patterns of association between apathy ratings and Fractional Anisotropy values in the left OMPFC across the “High” and “Low” CD4 groups.
Chapter 3

Incident Major Depressive Disorder increases the severity and risk of apathy episode in HIV infection

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Abstract

Apathy and depression are inter-related yet separable and prevalent neuropsychiatric disturbances in persons infected with HIV. In the present study of 258 HIV+ persons, we investigated the role of an incident depressive episode in changes in apathy. Participants completed the apathy subscale of the Frontal Systems Behavior Scale during a detailed neuropsychiatric and neuromedical evaluation at visit 1 and again at approximately 14 month follow-up. The Composite International Diagnostic Interview was used to obtain diagnoses of inter-visit major depressive disorder. At their follow-up visit, participants were classified into four groups depending on their visit 1 elevation in apathy and inter-visit major depressive episode (MDE) status. Of the 157 participants without clinically elevated apathy at visit 1, those who developed an inter-visit MDE (n=23) had greater apathy severity and incidence at follow-up than those without MDE. Apathetic participants at baseline with an inter-visit MDE (n=40) were at risk for continued, clinically elevated apathy at follow-up, although severity of symptoms did not increase. These findings suggest that HIV+ individuals, who do not at yet present with elevated apathy, may be at greater risk of elevated psychiatric distress should they experience a new/recurrent depressive episode. Thus, in the context of previous findings, it appears that although apathy and depression are separable constructs, they interact such that depression is a risk factor for an apathy episode.

Keywords. HIV/AIDS; Neuropsychiatry; motivation; longitudinal study
A longitudinal study of the impact of depression on the severity and incidence of apathy in HIV infection

In the past decade, research has identified the apathy syndrome as a distinct and clinically significant neuropsychiatric disturbance, which, alongside depressive disorders, impacts functional status across many patient populations (e.g., Freels et al., 1992; Posada et al., 2010), including HIV-infected cohorts (e.g., Barclay et al., 2007; Tate et al., 2003). Apathy refers to a cluster of symptoms representing a lack of motoric, emotional, and cognitive motivation (e.g., reduced drive, poor initiation and control of self-directed purposeful behavior; Marin et al., 1991; Stuss, van Reekum, & Murphy, 2000; Levy & Dubois, 2006). Approximately 30 – 50% of HIV+ individuals present with clinically elevated signs of apathy (Castellon et al., 1998, 2000; Rabkin et al., 2000; Kamat et al., 2012). In HIV-infected persons, apathy symptomatology is associated with poor performance on many instrumental activities of daily living, such as medication adherence and quality of life (e.g., Barclay et al., 2007, Tate et al., 2003; Kamat et al., 2012).

Growing evidence from cross-sectional studies suggests that apathy may arise via direct involvement of the central nervous system in HIV; specifically, from HIV-related injury to frontostriatal circuits including the nucleus accumbens (Paul, Brickman, et al., 2005) and frontal white matter tracts (e.g., corona radiata and corpus callosum; Hoare et al., 2010). However, the presence and severity of apathy does not simply reflect HIV disease severity. Although apathy symptomatology has been associated with duration of infection (Paul, Flanigan, et al., 2005), it appears to be
largely unrelated to most standard clinical indices of disease progression, including CD4 cell counts, HIV RNA viral load in plasma, and AIDS status (Castellon et al., 1998; Paul, Flanigan, et al., 2005; Rabkin et al., 2000). In addition, despite common neurobiological substrates, apathy does not appear to correspond strongly with HIV-associated neurocognitive deficits (Rabkin et al., 2000; Robinson-Papp et al., 2008), although other studies suggest that apathy may be modestly related to deficits in specific aspects of executive functions (Castellon et al., 1998; Paul, Flanigan et al., 2005) and episodic memory (Paul, Flanigan et al., 2005). Thus, the current body of literature suggests that apathy is a discrete neuropsychiatric sequelae of HIV infection.

Apathy and depression, often characterized by symptoms of dysphoria and anhedonia, commonly co-occur in HIV infection (e.g., Castellon et al., 2000), but cross-sectional results regarding their association are mixed. At least two studies reported moderately strong, positive correlations between self-reported apathy and depression scores (Castellon et al., 1998; Rabkin et al., 2000), but there is ample evidence of the separability of these related constructs. For example, one study found that elevated levels of apathy are present in non-depressed HIV-infected persons as compared to seronegatives (Hoare et al., 2010). Also, three studies reported that apathy ratings of HIV+ individuals do not co-vary with depressed mood (Paul, Brickman et al., 2005; Paul, Flanigan et al., 2005; Tate et al., 2003), while another study showed that apathy was predictive of functional impairment independent of depression (Kamat et al., 2012). These finding are consistent with the neurophysiological dissociation between the two syndromes demonstrated by
empirical studies in Parkinson’s disease (PD) and Alzheimer’s disease (AD; e.g., Ott, Noto, Fogel, 1996; Starkstein et al., 1992).

Longitudinal studies may provide a clearer lens on the separability of apathy and depression. For example, in a study of participants with AD, Starkstein and colleagues (2006) found that a depressive episode was neither necessary nor sufficient to produce apathy over time, although apathy as baseline was predictive of a longitudinal increase in depressive symptomatology. In the stroke literature, a longitudinal increase in neuropathology is thought to result in greater comorbidity in apathy and depression over time (Withall et al., 2011), raising the possibility of an additive effect through which the neural mechanisms underlying each syndrome may contribute to the longitudinal exacerbation in neuropsychiatric distress. These longitudinal studies provide early evidence regarding the behavioral and neurologic interplay between apathy and depression, such that, while separable, apathy may serve as a risk factor for the exacerbation of major depressive disorder, and vice versa. Within HIV+ cohorts, the extant literature has focused solely on the cross-sectional relationship between apathy and current mood symptoms. In the present study we investigated the separability of depression and apathy using a longitudinal cohort. Specifically, we examined the role of a new depressive episode in the incidence and persistence of apathy. It was hypothesized that the progression of apathy would be most pronounced in participants who were apathetic at their first visit and went on to develop an MDE. The occurrence of MDE was expected to have a lesser, but still notable, impact on participants without clinically elevated apathy at baseline.
Methods

Participants

Study participants included 258 HIV+ individuals recruited from HIV clinics and community organizations, each of whom underwent detailed neuropsychiatric evaluations at two visits, which were a mean of 14.1 (3.3) months apart (range 10 to 24 months) (see Table 1). These data were derived retrospectively from the HIV Neurobehavioral Research Center, an NIMH-funded study of the prevalence, features, course, etiology, and pathogenesis of HIV involvement of the CNS. Individuals with histories of neurological diseases (e.g., seizure disorders, closed head injuries with loss of consciousness greater than 30 minutes, central nervous systems neoplasms, opportunistic infections) or severe psychiatric illnesses (e.g., schizophrenia) that might affect cognitive functioning were excluded from the study, as were participants who met criteria for current methamphetamine dependence (i.e., within the past 30 days) at either visit 1 or visit 2. Participants were only included in this study if they had completed apathy and psychiatric assessments at both visits. HIV status was determined by enzyme-linked immunosorbent assays and confirmed by a western blot test.

Procedure

Apathy Assessment. The 14-item apathy subscale of the self-report version of the Frontal Systems Behavior Scale (FrSBe; Grace & Malloy, 2001) was administered to obtain current ratings of apathy symptomatology. Ratings are on a Likert-type scale that ranges from 1 (“almost never”) to 5 (“almost always”) for each question.
Following the manual guidelines, the raw scores were converted into demographically (i.e., age, education, and gender) adjusted T-scores. The standard FrSBe cut-point of $T \geq 65$ (Grace & Malloy, 2001) was used to classify participants as ‘apathetic’ at each visit. In addition to this categorical classification as 'apathetic' or 'not apathetic', the difference in apathy T-scores at visit 1 and 2 was calculated to provide a continuous index of change in self-reported apathy symptomatology.

**Psychiatric Assessment.** DSM-IV diagnoses of current, inter-visit (i.e., prior to/concurrent with visit 2), and past major depressive disorder and psychoactive substance abuse and dependence were determined via the Composite International Diagnostic Interview (CIDI). The CIDI is a computer-assisted interview that provides a cross-cultural assessment of alcohol, drug, and mental disorders using DSM-IV criteria (Wittchen et al., 1991).

To obtain ratings of current mood symptoms, participants completed the Beck Depression Inventory-II (Beck, Steer, & Brown, 1996). The BDI-II is a 21-item instrument assessing mood symptoms. Each item has four graded statements ordered to show increasing symptomatology. Based on previous studies (e.g., Marin et al., 1994; Castellon et al., 2006; Rabkin et al., 2000; Kamat et al., 2012), severity of depressive symptoms was obtained from an adjusted BDI-II score that excluded three apathy-associated items (i.e., #4: loss of pleasure; #12: loss of interest; and #13: ability to make decisions). Excluding these related items (Cronbach’s $\alpha = .75$) allowed us to minimize the influence of apathy in our assessment of change in mood symptoms.

**Apathy Group Classification.** In order to assess the impact of an incident MDE while taking into consideration pre-MDE apathy status, participants were
classified into one of four groups based on their visit 1 apathy elevation and diagnosis of inter-visit (i.e., prior to/concurrent with visit 2) major depressive episode (MDE): Non-apathetic and without an inter-visit MDE (A-D-; n=134); non-apathetic, with an inter-visit MDE (A-D+; n=21; 48% with current MDD at visit 2); apathetic and without an inter-visit MDE (A+D-; n=71); apathetic, with an inter-visit MDE (A+D+; n=32; 34% with current MDD at visit 2).

The groups did not differ in their duration of illness, plasma viral load, proportion of individuals on ART, and proportion of participants with comorbid HCV (Table 12). The A+D+ group had a lower visit 1 CD4 count relative to the A+D- and A-D- groups (p’s = .01). Change in CD4 count across the two visits did not differ among the four groups (p=.5). Lower nadir CD4 count was also noted for the A+D+ group, relative to the A+D- and A-D+ groups (p’s <.02).

As seen in Table 13, the rate of lifetime MDD at visit 1 was highest in the A+D+ group with the A-D+ and A+D- having intermediate rates of MDD, and the lowest rates being in the A-D- group. Fewer participants in the A-D- group were prescribed antidepressant medication at their first visit compared to the other three groups, although the group differences did not reach statistical significance. The four groups were comparable in terms of lifetime substance use disorders. Overall, the groups differed in the rates of neurocognitive impairment at the trend level (p=.06), driven by lower rates of impairment in A-D- than A+D- group (p < .05).

**Cognitive Assessment.** All participants were administered a standardized neuropsychological battery that included tests of executive functions, learning, memory (delayed recall), speed of information processing, verbal fluency, motor
skills, and working memory (See Marcotte et al., 2004 for a list of tests within each cognitive domain). Raw scores were converted to demographically-adjusted, practice-corrected T-scores (e.g., Heaton et al., 2004; Cysique et al., 2007), which were converted to deficit scores (range = 0 [T > 39] to 5 [T < 20]), and then averaged to generate the Global Deficit Score (GDS; Carey et al., 2004). A GDS of ≥ .05 is the standard cut-point indicative of global neurocognitive impairment.

**Data Analysis.** In order to accommodate departures from normality in individual variable distributions, nonparametric statistical tests were employed, including the Wilcoxon signed-rank test for between-group comparisons and Spearman’s ρ for correlations. Cohen’s d statistic and odds ratio calculations were used to measure the effect sizes of group comparisons. Variables that significantly differed between the groups were included in a least squares regression analysis to examine the relative influence of an incident MDD episode on change in apathy symptomatology at varying levels of apathy elevations. Visit 1 variables (i.e., lifetime diagnosis of MDD, age, neuropsychological impairment (GDS impaired vs. unimpaired), and current CD4 count were included as covariates. A critical alpha level of .05 was set for all analyses.

**Results**

**Demographic and clinical findings**

Of the 258 participants, apathy was diagnosed at visit 1 in 103 individuals (40%). The prevalence rate of apathy over the interval for the entire sample was 51%. Thirty (26.8%) of the visit 1 apathetic individuals presented without a history of
depression at the same visit. Likewise, 73 (50%) of the non-apathetic participants were
diagnosed with a lifetime history of MDD at visit 1. In our sample of HIV+
individuals, 64 participants (25%) developed an inter-visit episode of major depressive
disorder. As demonstrated in Table 12, the four groups were comparable in gender,
ethnicity, age, and education. The four groups were comparable in terms of the follow-
up interval and proportion of participants with lifetime substance use disorders. Group
differences in neuropsychiatric characteristics are displayed in Table 13. Of note,
groups were comparable in the level and longitudinal change in cognitive impairment,
history of antidepressant use, and rate of substance use disorders.

Regression analysis

In order to examine the unique influence of an interim MDE on apathy change
score, we conducted a regression analysis predicting the apathy change score in the
context of visit 1 variables that significantly differed among the four apathy-MDE
groups. Regression variables included apathy-MDE groups, lifetime diagnosis of
MDD, neuropsychological status (impaired vs. unimpaired), and visit 1 CD4 count.
The overall model accounted for a significant amount of variance ($R^2=.14$, \(p<.0001\)),
and revealed that there was a significant effect of apathy-MDE status on apathy
change after controlling for covariates, \(F(3, 239) = 6.5, p < .0001\). Planned contrasts
revealed that apathy decreased in both the apathetic groups (A+D-, A+D+) compared
to the A-D- group (\(p<.0001\), \(p=.04\) respectively). Non-apathetic individuals with an
inter-visit MDE (A-D+) reported worsened apathy compared to those without an MDE
(A-D-) (\(p=.04\)). Of the covariates entered, none were significantly associated with
change in apathy scores (\(p’s >.10\)).
Is inter-visit MDE associated with clinical change in apathy?

We examined whether the group differences noted in univariate and multivariate analyses reflected a change in the risk of clinically elevated apathy. As seen in Figure 2, across apathy groups, an inter-visit MDE resulted in a higher risk for incidence and persistence of clinically elevated apathy over time. The risk of developing elevated apathy at visit 2 was highest in the non-apatheitic individuals who had an inter-visit MDE (OR = 5.9, 95% CI = 2.17, 15.7). The incidence of apathy in participants with an inter-visit MDE was 48%, substantially higher than those who did not develop an inter-visit MDE (13%). In the visit 1 apathetic group, the odds of staying apathetic at the second visit were 1.7 (95% CI = .68, 4.41). The prevalence (i.e., total number of participants who were apathetic at visit 1 and/or 2) of apathy in those who did not develop an inter-visit MDE (n=194) was 29%, while it was 63% in those who had an MDE episode following their first visit.

Longitudinal change in affective distress

To examine the role of other affective symptoms in apathy changes over time, we examined group differences in mood change across the two visits. Apathy-adjusted BDI-II scores (i.e., with apathy items removed) were used in these analyses. The differential effect of incident MDE on the non-apatheitic vs. apathetic participants was not observed for mood symptoms. Regardless of apathy status, the participants with an inter-visit MDE had significantly higher mood ratings than those without an MDE (p<.0001). Both apathetic and non-apatheitic groups reported a comparable increase in adjusted BDI-II scores following an inter-visit MDE. The two groups that did not experience a depressive episode demonstrated a decline in mood symptoms over time,
and were comparable to each other in terms of the magnitude of the change. The relative pattern of change across the visits for these two measures is shown in Figure 2.

**Discussion**

While investigations in the past decade have developed a knowledge base about the cross-sectional prevalence, clinical and functional correlates of apathy in HIV infection, there has been no longitudinal study of apathy in this cohort until the current investigation. Consistent with prior reports (e.g., Atkinson et al., 2008; Castellon et al., 1998; Cysique et al., 2007; Hoare et al., 2010; Kamat et al., 2012) we observed a high prevalence of psychiatric distress, with 40% of our HIV+ participants reporting clinically significant levels of apathy and 25% of individuals developing an inter-visit episode of major depressive disorder. Apathy appears to be a persistent neuropsychiatric feature of HIV infection, as indicated by its high prevalence over the study interval. Extending the current literature in HIV infection, we observed a dissociation between apathy and clinically diagnosed depression. Of the participants who were apathetic at their first visit, almost 30% did not have a past or current history of MDD. Similarly, 47% of participants without clinically elevated apathy had a history of lifetime depression at the first visit. This dissociation held up longitudinally as well. An episode of depression was neither necessary (13% of participants who did not develop an MDE were apathetic at visit 2) nor sufficient (52% of individuals with an inter-visit MDE were not apathetic at follow-up) to produce clinically elevated apathy. These findings demonstrate that although apathy
and depression are comorbid, there is not a one-to-one correspondence between these two psychiatric constructs in HIV infection.

To our knowledge, this is the first study to examine the longitudinal change in apathy in relation to depression in a large cohort of HIV-infected adults. The high prevalence of both apathy and incident depression in this population highlights the need to examine the factors that influence change in psychiatric distress. As hypothesized, we observed that an inter-visit depressive episode exacerbated apathy ratings. The effect of an inter-visit MDE differed across apathy status at visit 1. In those participants who were initially non-apathetic, the development of an MDE was associated with a significant increase in apathy severity over the two visits. In contrast, apathetic participants who experienced an MDE between visits did not demonstrate worsened apathy ratings—in fact contrary to expectations, a drop in T-scores was observed, suggesting that apathy symptomatology decreased despite an inter-visit MDE. However, the decline in T-scores over time did not differ across the two apathetic groups (i.e., A+D- and A+D+), which were noted to be at ceiling for the apathy scores at visit 1. After adjusting for visit 1 variables such as lifetime depression status, CD4 count, and neuropsychiatric impairment, the same pattern of MDE effect was observed such that a new MDE was associated with a worsening in apathy in non-apathetic HIV+ individuals. Future studies are needed to replicate this finding and speak to the relative contribution of other factors (e.g., length of MDE) to the impact of a new episode of depression on the exacerbation of apathy. Also worthy of consideration, is the duration of clinically elevated apathy. It is possible that patients with prolonged apathy may develop some coping skills over time, which reduce their
apathetic symptoms, thereby explaining the reduction in apathy ratings observed here. A closer examination of this neuropsychiatric syndrome and accompanying behavioral changes would be needed to test this theory.

To further explore whether the development of a depressive episode was associated with clinically significant apathy elevations, we examined the risk of being apathetic at follow-up in the four groups. Consistent with the univariate and multivariate results, development of an MDE in the initially non-apathetic participants considerably increased the risk for clinically elevated apathy at the second visit. Although the previous analyses suggested that the apathy ratings for the apathetic group declined despite an MDE, these secondary analyses demonstrated that they did not experience a clinically significant resolution of their apathy. In fact, following an MDE, the risk of staying apathetic over time was almost two-fold in the visit 1 apathetic group. All told, these results suggest that development of a depressive episode modifies the severity and risk of incident apathy, and also contributes to the increased prevalence of this syndrome in HIV+ persons.

Next, to explore the mechanistic underpinnings of change in psychiatric distress, we examined changes in mood symptomatology in the context of apathy and depressive episodes. This was particularly of interest in the visit 1 apathetic group, as these participants demonstrated a decline in apathy ratings over the interval. Accordingly, we sought to examine whether other symptoms, specifically mood, were increasing despite the decrease in apathy scores. It was observed that in the A+D+ group, non-apathy mood symptoms were elevated and persistent. Contrasting with the reduction in apathy ratings reported in this group, the mood symptoms increased over
time. Non-apathetic participants who developed an MDE also reported increased mood symptoms. Those individuals (apathetic or otherwise) who did not develop an MDE reported a decline in mood symptoms over time. These findings raise the possibility that HIV+ persons who have a greater psychiatric burden may experience some alleviation in their symptoms provided they do not suffer an increase in psychopathology. Exacerbation in mood ratings is expected to correspond to a new depressive episode; however, the divergence noted in the pattern of change for apathy and BDI-II scores is notable for its implications for future studies to tease apart the mechanisms of psychiatric distress in HIV infection. From the neuroanatomical perspective, it remains to be seen if the contrasting patterns of mood and apathy changes reflect divergent neural mechanisms of each and the varying susceptibility of the respective pathways to HIV-associated CNS pathology. Neuroimaging techniques may shed light on these theories.

Consistent with findings reported previously in the literature (e.g., Castellon et al., 1998; Paul, Flanigan et al., 2005; Rabkin et al., 2000; Cysique et al., 2007), HIV disease characteristics (e.g., AIDS status, HIV RNA viral load) were largely unrelated to apathy at the first visit as well as development of a depressive episode. In contrast to the association noted by Paul, Flanigan et al. (2005), we did not observe a correspondence between apathy and duration of illness. In general, our participants had been infected with HIV for considerably longer than the individuals in the Paul, Flanigan et al (2005) study (i.e., an average of 156 months vs. 95.5 months). Future studies should examine whether length of infection is more strongly correlated with apathy early in the course of the disease rather than during later stages. In the visit 1
apathetic group, lower nadir and current CD4 count were associated with the
development of an inter-visit MDE. In addition, those participants who were not
apathetic at their first visit were healthier in terms of HIV disease than the A+D+
group. Together, these findings suggest that neuromedical mechanisms might underlie
or contribute to psychiatric dysfunction in HIV infection and warrant closer
examination in future studies.

This study is not without limitations. First, a self-report measure of apathy
(i.e., FrSBe) was used as opposed to a clinical interview (e.g., Neuropsychiatric
Inventory, Cumming et al., 1994). Compared to clinical assessment, the accuracy of
self-report measures may be affected by bias, depression, and/or mild anosognosia.
Second, ceiling and floor effects in the FrSBe ratings of the apathetic and non-
apathetic individuals respectively may also impact the magnitude of change in apathy
detected across the two visits. Third, the sample consisted of well-educated,
predominantly male and Caucasian individuals with relatively well-managed HIV
characteristics (e.g., only 25% were immosuppressed). This may limit the
extrapolation of our findings to more diverse and symptomatic HIV+ groups. Finally,
the duration of follow up was not homogeneous, ranging from 10 to 24 months.
However, the interval duration was similar for all the subgroups analyzed.

In the context of prior studies, these findings suggest that HIV+ individuals
who are not currently apathetic might be at a greater risk of developing clinically
significant levels of apathy if they experience a depressive episode. In persons who are
apathetic, a new depressive episode may serve to maintain their psychiatric distress.
Current and nadir CD4 count were associated with the development of depression. Our
findings suggest that although global neurocognitive deficit and apathy may be comorbid in HIV infection, they are discrete syndromes, as there does not appear to be a one-to-one overlap between the two. We were also able to demonstrate a divergence between apathy and depression on a neurocognitive basis, lending support to the theory that these are two separable neuropsychiatric constructs in HIV infection. Preliminary data from the present study raise the question of whether mood and apathy symptomatology have divergent neural correlates in HIV given that the directionality of change over time differed in these two ratings. Apathy is associated with a number of adverse functional outcomes, and consequently it is important to identify factors that may exacerbate apathy symptomatology. The present findings support efforts for the early detection of depression in HIV+ individuals so as to limit the impact this syndrome has on the development and maintenance of apathy. This may be accomplished by conducting routine assessments of depressive symptomatology and providing psychotropic or behavioral intervention at the earliest opportunity to minimize the risk of developing a depressive episode. Better management of known risk factors of depression, such as decreased social support, stressful life events, substance use, and medication non-adherence may also help avert onset of depression and subsequent apathy symptomatology. Assessing apathy symptoms in clinical settings also appears to be warranted in order to track a patient’s psychiatric burden. Preliminary studies examining behavioral interventions for apathy in patients with dementia suggest that mentally stimulating activities and interactive social settings may be effective (reviewed in Roth, Flashman, & McAllister, 2007). These interventions may have the added benefit of reducing depressive symptoms as well.
Further investigation of pharmacological and behavioral interventions for HIV-infected persons is warranted as such therapies may have a positive impact on functional outcomes and quality of life. The present findings also provide preliminary support for the closer assessment of psychiatric symptomatology in HIV+ persons who present with low CD4 counts. Future studies examining apathy in HIV would benefit from a closer exploration of this disease marker and the possible neuromedical mechanisms that may underlie the development of HIV-associated apathy.

Chapter 3, in full, is currently being prepared for submission for publication.

Kamat, Rujvi; Cattie, Jordan E.; Marcotte, Thomas D.; Woods, Steven Paul; Franklin, Donald R., Corkran, Stephanie, H.; Ellis, Ronald J.; Grant, Igor. A longitudinal study of the impact of depression on the severity and incidence of apathy in HIV infection. The dissertation author was the primary investigator and author of this paper.
Table 12: Demographic and clinical findings for the sample of HIV+ persons (n=258)

<table>
<thead>
<tr>
<th></th>
<th>Non-Apathetic</th>
<th>Apathetic</th>
<th>Group comparisons</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Without inter-visit MDE</td>
<td>With inter-visit MDE</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(a)</td>
<td>(b)</td>
<td></td>
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<tr>
<td></td>
<td>Without inter-visit MDE</td>
<td>With inter-visit MDE</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(c)</td>
<td>(d)</td>
<td></td>
</tr>
<tr>
<td><strong>Demographic variables</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>46.4 (10.3)</td>
<td>45.3 (11.7)</td>
<td>49.3 (9.8)</td>
</tr>
<tr>
<td>Gender (%male)</td>
<td>20.2</td>
<td>28.6</td>
<td>15.5</td>
</tr>
<tr>
<td>Education (years)</td>
<td>13.4 (2.9)</td>
<td>13.0 (13.4)</td>
<td>12.6 (3.4)</td>
</tr>
<tr>
<td>Ethnicity (%Caucasian)</td>
<td>56.7</td>
<td>57.1</td>
<td>60.6</td>
</tr>
<tr>
<td><strong>HIV disease variables</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration of illness (years)</td>
<td>13.4 (6.7)</td>
<td>13.0 (7.1)</td>
<td>13.1 (6.5)</td>
</tr>
<tr>
<td>Proportion with AIDS (%)</td>
<td>63.6</td>
<td>55.0</td>
<td>63.8</td>
</tr>
<tr>
<td>Current CD4 count (median, IQR)</td>
<td>530.5 (308, 770.3)</td>
<td>543.5 (387.3, 762.8)</td>
<td>505 (344.3, 778.3)</td>
</tr>
<tr>
<td>Nadir CD4 count (median, IQR)</td>
<td>150 (32, 232.5)</td>
<td>184 (104.8, 282.3)</td>
<td>162 (36, 262.5)</td>
</tr>
<tr>
<td>Log10 Plasma Viral Load</td>
<td>1.7 (1.7, 1.7)</td>
<td>1.7 (1.7, 2.1)</td>
<td>1.7 (1.7, 1.9)</td>
</tr>
<tr>
<td>Plasma viral load (% undetectable)</td>
<td>76.4</td>
<td>72.2</td>
<td>75.4</td>
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<tr>
<td>ART prescribed (% Yes)</td>
<td>88.3</td>
<td>79.0</td>
<td>90.0</td>
</tr>
<tr>
<td>Proportion with HCV (%)</td>
<td>12.6</td>
<td>8.3</td>
<td>10.5</td>
</tr>
<tr>
<td>Interval between visits (months)</td>
<td>14.0 (0.3)</td>
<td>14.6 (0.7)</td>
<td>13.9 (0.4)</td>
</tr>
</tbody>
</table>

**Note.** Values represent Mean (standard deviation) unless otherwise noted
+ Results from Wilcoxon Rank Sums, Chi-Square, or Fisher’s Exact tests
++ Indicates significant group differences from pairwise comparisons (p<.05, unless otherwise noted)
+++ p<.01
Table 13: Neuropsychiatric findings for the sample of HIV+ persons (n=258)

<table>
<thead>
<tr>
<th></th>
<th>Non-Apathetic</th>
<th>Apathetic</th>
<th>Group comparisons</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Without inter-visit MDE</td>
<td>With inter-visit MDE</td>
<td>Without inter-visit MDE</td>
</tr>
<tr>
<td>Change in apathy T-score</td>
<td>.85 (14.2)</td>
<td>11.6 (21.4)</td>
<td>-.77 (12.8)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proportion with current MDD at visit 1 (%)</td>
<td>1.5</td>
<td>15.8</td>
<td>15.9</td>
</tr>
<tr>
<td>Proportion with Lifetime (past and current) MDD at visit 1 (%)</td>
<td>45.5</td>
<td>57.1</td>
<td>64.8</td>
</tr>
<tr>
<td>Proportion on antidepressant medication at visit 1 (%)</td>
<td>27.6</td>
<td>42.9</td>
<td>40.9</td>
</tr>
<tr>
<td>Change in apathy-adjusted BDI-II score</td>
<td>-1.1 (5.1)</td>
<td>5.9 (7.8)</td>
<td>-3.3 (6.1)</td>
</tr>
<tr>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proportion NP impaired (%)</td>
<td>25.4</td>
<td>28.6</td>
<td>43.7</td>
</tr>
<tr>
<td>Practice corrected change in GDS</td>
<td>0.0</td>
<td>-.24</td>
<td>-.04</td>
</tr>
<tr>
<td>Proportion with current substance use disorders at visit 1 (%)</td>
<td>47.7</td>
<td>47.4</td>
<td>50.7</td>
</tr>
</tbody>
</table>

Note. Values represent Mean (standard deviation) unless otherwise noted
+ Results from Wilcoxon Rank Sums, Chi-Square, or Fisher’s Exact tests
++ Indicates significant group differences from pairwise comparisons (p<.05, unless otherwise noted)
+++ p<.01
Figure 2: Inter-visit MDE increases risk of clinically elevated apathy at follow up.

*Note:* * indicates significant difference in proportion across groups
Figure 3: Pattern of change across two visits in Apathy ratings and apathy-adjusted BDI-II ratings. Standard errors are represented in the figure by the error bars on each column.
Discussion

While apathy has long been recognized as a clinical feature of HIV-infection, only recently has it received increasing empirical attention. To this end, the above three studies present new data regarding the functional, neural, and psychiatric correlates of apathy in HIV infected individuals. Adding to the literature, we observed a strong relationship between apathy and important functional outcomes such as instrumental activities of daily living and cognitive complaints. The results also provide evidence in support of the link between the neuroanatomical nodes within the brain circuits theorized to underlie the apathy syndrome. It appears that poor immune functioning may impact the magnitude of this relationship. Extending the literature, we examined the longitudinal course of apathy in HIV infection and observed that a new or recurrent major depressive episode exacerbated apathy symptomatology. Pre-existing apathy elevation impacted this negative effect of depression.

Prevalence of apathy in HIV infection

Across all three studies, approximately 40% of our HIV-infected participants were classified as apathetic. In contrast, 19% of the seronegative comparison subjects were apathetic in the first study. Although our large cohort of HIV+ individuals differs in demographic (i.e., greater proportion of males), substance use (i.e., no history of recent dependence or abuse), and disease characteristics (i.e., longer duration of infection) from previous studies, our prevalence estimates are consistent with the 30 – 50% rates reported across the literature (e.g., Castellon et al., 1998, 2000; Rabkin et al., 2000). Extending the literature, we observed that self-reported symptoms of apathy prior to HIV infection were comparable with those endorsed by seronegatives, with
apathy ratings rising significantly following seroconversion. Notably, the association between current apathy and HIV status was independent of confounding factors such as lifetime history of any substance use disorder, psychiatric comorbidities, cognitive impairment, and ethnicity. The elevation in apathy following HIV infection together with the higher prevalence of apathy in HIV+ participants appears to be consistent with the underlying frontostriatal pathophysiology common to HIV infection and apathy (see Study 2).

**Impact of apathy on activities of daily living**

Consistent with our hypotheses, we observed an interaction between the number of functional complaints and apathy ratings prior to and following HIV infection (Study 1). Individuals with higher ratings of apathy reported more difficulties in their daily activities as well as more cognitive complaints. Importantly, this association was independent of other factors such as AIDS status, lifetime history of major depressive disorder, substance use, and HCV status. These results are consistent with the previous functional outcome studies (i.e., Barclay et al., 2007; Rabkin et al., 2000; Tate et al., 2003), but extend them by showing strong and independent associations between apathy and everyday functions (e.g., social activities, shopping, and comprehension of verbal/written material). These findings are also commensurate with research in clinical populations such as Alzheimer’s disease and Hepatitis C Virus infection, which suggests that apathy plays an important role in functional difficulties (Freels et al., 1992; Posada et al., 2010). Apathy ratings were demonstrated to correlate positively with subjective cognitive complaints in a cohort of individuals with mild cognitive impairment (Robert et al., 2006). The overlap
between cognitive complaints and the cognitive aspects of apathy (e.g., lack of goal-directed thought content, decreased verbal fluency, and diminished motivation with regards to executive functions) may underlie the association noted between these two psychiatric and functional constructs. Fatigue is commonly reported by HIV+ individuals and may impact ability to execute activities of daily living. As such, its relationship with apathy and functional impairment should also be addressed in future investigations.

The observed correspondence between apathy and functional outcomes is commensurate with the association reported between apathy and lower health-related quality for life. Two studies found that independent of depressed mood, high levels of apathy have a negative impact of quality of life ratings (Rabkin et al., 2000; Tate et al., 2003). In contrast, Barclay and colleagues (2007) reported that apathy was not an independent predictor of adherence behaviors and intentions after accounting for perceptions of self and medication utility. It is unclear whether these discrepancies are accounted for by the sample characteristics or methodological differences in the assessment of depression (i.e., self-report in Rabkin et al. (2000) and Barclay et al. (2007) vs. structured clinical interviews in the present study) and functional outcomes. However, taken together, the findings for quality of life variables, activities of daily living and cognitive complaints, as well as medication adherence behaviors suggest that apathy may affect specific aspects of everyday functioning.

**White matter correlates of apathy**

Commensurate with previous reports of HIV-associated decreases in white matter tracts in the frontal lobes (e.g., Filippi et al., 2001; Pfefferbaum et al., 2009),
we observed greater microstructural frontal white matter abnormalities in the HIV+ participants relative to the seronegative comparison subjects. Alterations in white matter integrity were noted in all the selected regions, although the HIV effect was most robust in the bilateral ACR, genu, and left OMPFC. These regions connect important nodes within the brain circuit involved in the expression of apathy (Levy & Dubois, 2006; McCandliss, 2011; Schmahmann & Pandya, 2009).

In the present sample of HIV-seropositive and seronegative participants, the HIV+ persons endorsed higher levels of apathy. Apathy ratings were significantly associated with white matter abnormalities in the frontal, medial white matter regions in the HIV+ cohort, but not the HIV- participants. When adjusting for history of depression, apathy was found to be a significant predictor of FA changes in the regions. Given the orbitomedial cortical nodes of the thalamocortical loop involved in apathy (Cummings, 1993; Stuss et al., 2000), we expected the OMPFC white matter region to be most strongly associated with apathy ratings. The independent association between apathy and white matter alteration was strongest in the ACR and genu, relative to the OMPFC. This may reflect the greater involvement of the former regions in the generation of apathy. For example, the ACR contains white matter tracts that connect the anterior cingulate circuit to the striatum and other regions involved in behavior regulation (McCandliss, 2011), while fibers from the orbitofrontal cortex extend within the genu and connect to other cortical regions (Schmahmann & Pandya, 2009). The neuroarchitecture of these tracts may also impact the DTI values obtained. Future studies using more sophisticated methodology such as tract based spatial statistics (TBSS) may clarify the present findings.
As demonstrated in the first study (Kamat et al., 2012) apathy ratings increase after seroconversion. In the context of these DTI findings, it is reasonable to conclude that HIV-associated injury to the frontomedial white matter structures may play a role in the production of apathy in this population. From a brain circuits perspective, our results complement the structural MRI findings of Paul, Brickman et al. (2005) that apathy was associated with reduced volume in the subcortical structures involved in the thalamocorticostriatal loops that underlie neurobehavioral disturbance. The present findings are also highly consistent with the relationship between apathy and frontal white matter changes reported in a cohort of HIV clade-C participants in South Africa (Hoare et al., 2010). In all, there is increasing evidence supporting specific neural involvement in the production of apathy symptomatology in HIV infected individuals.

We examined whether current CD4 count, a marker of current immune functioning (e.g., Sousa et al., 2002), moderated the correspondence between apathy and HIV-associated white matter pathology. In participants with low CD4 counts (i.e., under 340), a robust correlation was observed between apathy and FA values. This relationship was absent in those who had better levels of immune functioning (i.e., had a CD4 count of 340 or higher). Prior studies have not examined the sensitivity of the association between apathy and CNS pathology to HIV disease markers. Low CD4 count, which indicates active HIV replication and increased the risk of CNS damage over time, has previously been shown to be associated with atrophy in frontostriatal regions (Chiang et al., 2007). These neuropathological findings are complemented by our result regarding the moderating effect of CD4 count on the association between apathy and white matter damage. Additional factors such as antiretroviral regimen
type and history may be impacting the interaction observed. Particularly of interest is the possibility of improving neuropsychiatric symptoms once immune functioning is improved and CNS pathology is reduced by better medication adherence or modified treatment regimen. Longitudinal studies tracking neuropsychiatric symptoms, neuromedical characteristics, and CNS pathology would be useful in teasing apart the underlying mechanisms.

The utility of apathy as a distinct behavioral marker of HIV-associated white matter abnormalities is bolstered by its unique correspondence to selected frontomedia regions vis-à-vis ratings of disinhibition as well as depression status. The regions of interest were chosen based on their involvement in the circuit underlying apathy. Disinhibition is a behavioral disturbance linked to injury in the orbitolateral prefrontal cortex circuit (Cummings, 1993; Alexander et al., 1986). Similarly, depression is linked to orbital prefrontal gray matter changes and limbic system dysregulation. That these two neurobehavioral syndromes were not correlated with white matter abnormalities in regions hypothesized to be central to the manifestation of apathy provides preliminary support for the neuroanatomical specificity of the apathy syndrome in HIV infection.

**Major depression as a risk factor for increase in apathy symptomatology**

Despite the growing knowledge base regarding the cross-sectional prevalence, clinical and functional correlates of apathy in HIV infection, there has been no longitudinal study of apathy in this cohort until the current investigation. The impact of depression on the progression of apathy has also not received any empirical attention prior to this study. Although depression and apathy appear to have distinct
neural substrates in HIV (see Study 2), they both are prevalent in this population and have significant functional consequences. Thus, the potential inter-relationship between these two constructs is worthy of examination.

Consistent with prior reports (e.g., Atkinson et al., 2008; Castellon et al., 1998; Cysique et al., 2007; Hoare et al., 2010; Kamat et al., 2012) we observed a high prevalence of psychiatric distress, with 40% of our HIV+ participants reporting clinically significant levels of apathy and 25% of individuals developing an inter-visit episode of major depressive disorder. Apathy appears to be a persistent neuropsychiatric feature of HIV infection in some individuals as indicated by its high prevalence (51%) over the study interval. Extending the current literature in HIV infection, we observed a dissociation between apathy and clinically diagnosed depression. Of the participants who were apathetic at their first visit, almost 30% did not have a past or current history of MDD. Similarly, 47% of participants without clinically elevated apathy had a history of lifetime depression at the first visit. This dissociation held up longitudinally as well. An episode of depression was neither necessary (13% of participants who did not develop an MDE were apathetic at visit 2) nor sufficient (52% of individuals with an inter-visit MDE were not apathetic at follow-up) to produce clinically elevated apathy. These findings demonstrate that although apathy and depression are comorbid, there is not a one-to-one correspondence between these two psychiatric constructs in HIV infection.

An inter-visit depressive episode was associated with exacerbated apathy ratings at the second visit in a subset of participants; i.e., those who were not apathetic at their initial visit. Members of this group were at a greater risk of developing
clinically elevated apathy symptomatology after a depressive episode. Apathetic participants demonstrated a decrease in apathy T-scores following an inter-visit depressive episode. However, this did not represent a clinically significant resolution of apathy in this subgroup, as their risk of maintaining clinically elevated apathy status following a new depressive episode was still two-fold compared to individuals without an MDE. All told, these results suggest that development of a depressive episode modifies the severity and risk of incident apathy, and also contributes to the persistence of this syndrome in HIV+ persons. Future investigations of this relationship should examine the relative contribution of factors such as duration of depressive episodes.

To explore the mechanisms of change in psychiatric distress over time, the change in non-apathy mood symptoms was also examined. In the apathetic group, the occurrence of a depressive episode was related to the maintenance of elevated mood symptoms, although this subgroup had demonstrated a decline in apathy T-scores. In those participants who did not develop an episode of depression, mood symptoms decreased over time. In all, it appears that HIV+ persons who have a greater psychiatric burden may experience some alleviation in their symptoms provided they do not suffer an increase in psychopathology. From the neuroanatomical perspective, it remains to be seen if the contrasting patterns of mood and apathy changes reflect divergent neural mechanisms of each and the varying susceptibility of the respective pathways to HIV-associated CNS pathology. Neuroimaging techniques may shed light on these theories.
The high prevalence of both apathy and incident depression in this population highlights the need to examine the factors that influence change in psychiatric distress.

Notably, nadir and current CD4 count were observed to be associated with the development of a depressive episode in those participants who were classified as apathetic at their first visit. Non-apathetic individuals generally had better immune functioning (i.e., had higher nadir and current CD4 counts) relative to subjects in the A+D+ group. These findings hint to the contribution of neuromedical mechanisms in HIV-associated psychiatric dysfunction, an issue that warrants examination in future investigations.

Prior studies have reported a correspondence between apathy and specific cognitive tasks such as episodic memory, cognitive set-switching, conflict resolution, and working memory (Paul, Flanigan et al., 2005; Castellon et al., 1998, 2000; cf Rabkin et al., 2000; Robinson-Papp et al., 2008). In line with these findings, we observed that global cognitive impairment was linked to apathy severity. This may be explained by overlapping neural substrates (e.g., frontostriatal structures and circuits) that are common to both apathy and cognitive deficits. However, this question is best addressed by neuroimaging studies that examine the involvement of these anatomical structures in both these neurobehavioral constructs. An alternative approach would be to examine the relationship between apathy and performance on tests of executive function that more closely map onto the frontostriatal cortical regions. Interestingly, depression was not associated with global cognitive deficit. This finding is highly consistent with previous results. Together, these results provide additional support for the discriminability of apathy and depression.
Limitations

As discussed in the previous three chapters, the studies presented are not without their limitations. The major limitations are summarized here. First, apathy ratings were obtained via a self-report questionnaire (i.e., FrSBe) as opposed to a clinical interview (e.g., Neuropsychiatric Inventory; Cummings et al., 1994). This may be problematic in the context of episodic memory deficits commonly observed in HIV+ persons (e.g., Gongvatana, Woods, Taylor, Vigil, & Grant, 2007) and tempers the strength of conclusions that may be drawn based on significant interactions we found for apathy ratings and functional outcomes, white matter abnormalities, and depression status in HIV+ individuals. Another limitation relates to the samples’ demographic (i.e., a well-educated, predominately male and Caucasian cohort) and generally well-managed HIV disease characteristics, which may restrict the extrapolation of our findings to more diverse and symptomatic HIV+ groups. A relatively small sample was available in the study of the neural correlates of apathy. The restricted power did not permit a thorough examination of all possible covariates that might be related to HIV-associated white matter alterations. Finally, ceiling and floor effects on the apathy measure in the apathetic and non-apathetic individuals respectively may impact the magnitude of change in apathy detected across the two visits. Nonetheless, the three studies present novel perspectives in the study of apathy in HIV infection. However, these results would benefit from a closer focus on the biopsychosocial mechanisms, such as the effects of antidepressants on apathy relative to depression as well as the role of social support in alleviating deficits in goal-directed behavior. Additionally, multimodal assessment methods of psychiatric
distress should also be explored to determine the relative utility of tools such as the FrSBe or Neuropsychiatric Inventory (Cummings et al., 1994) in HIV-infected cohorts.

**Clinical relevance and Implications**

The findings from these three studies emphasize the relevance of apathy in HIV-infected cohorts. The impact of apathy on functional impairments has implications for reduced quality of life. This is consistent with the Wilson and Cleary (1995) model of health-related quality of life, which posits that psychological symptoms may result in functional impairment, thereby impacting an individual’s quality of life. Thus, the assessment of apathy in clinical contexts may help to identify HIV+ persons who are at risk for functional impairment. These individuals may benefit from assistance with their functional tasks to avoid further disability and reduction in quality of life.

The observed link between frontomedial white matter pathology and apathy ratings lends support to the theorized neural underpinnings of this psychiatric syndrome. As such, in clinical settings, apathy may be utilized as a behavioral marker of HIV-associated CNS damage. Our preliminary finding that this association was impacted by an individual’s CD4 count suggests that a subgroup of HIV-infected individuals may be at greater risk for neuropathology and subsequent neuropsychiatric disturbance. Whether antiretroviral regimens with greater CNS penetration have a dynamic impact on neural repair and the manifestation of apathy should be investigated as it bears significant clinical benefit.
Our finding that a depressive episode modifies the severity and incidence of apathy supports the routine assessment of depressive symptomatology as well as apathy in treatment settings. Early psychotropic or psychotherapeutic interventions to minimize the risk of developing a depressive episode may be warranted as this may reduce the likelihood of increasing apathy symptoms and the resultant negative functional outcomes.

**Conclusion**

The present set of studies examined the construct of apathy in HIV through multiple lenses. Complementing our finding that apathy ratings were higher following seroconversion in HIV+ persons, we observed microstructural white matter abnormalities in specific neuroanatomical regions that were unique to apathy severity. Although separable from apathy, the occurrence of a depressive episode was noted to be a risk factor for apathy severity and incidence. This finding, in conjunction with the observed association of apathy and functional impairment, highlights the necessity of early and efficient assessment and management of psychiatric distress in HIV+ patients. As such, interventions to alleviate CNS pathology, comorbid depression, and apathy in these patients deserve empirical and clinical attention.
References


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