Effect of APOE Proxy Genotype on HIV-Associated Neurocognitive Impairment

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

in
Clinical Psychology

by
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# TABLE OF CONTENTS

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Signature page</td>
<td>iii</td>
</tr>
<tr>
<td>Table of Contents</td>
<td>iv</td>
</tr>
<tr>
<td>List of Figures</td>
<td>v</td>
</tr>
<tr>
<td>List of Tables</td>
<td>vi</td>
</tr>
<tr>
<td>Acknowledgements</td>
<td>vii</td>
</tr>
<tr>
<td>Vita</td>
<td>viii</td>
</tr>
<tr>
<td>Abstract</td>
<td>xiv</td>
</tr>
<tr>
<td>Introduction</td>
<td>1</td>
</tr>
<tr>
<td>Methods</td>
<td>20</td>
</tr>
<tr>
<td>Results</td>
<td>30</td>
</tr>
<tr>
<td>Discussion</td>
<td>35</td>
</tr>
<tr>
<td>Appendix</td>
<td>49</td>
</tr>
<tr>
<td>References</td>
<td>62</td>
</tr>
</tbody>
</table>
LIST OF FIGURES

Figure 1. Relationship between Global Rating and Age by APOE ε4 Carrier Status in Caucasians

.................................................................61
LIST OF TABLES

Table 1. Demographic, Disease, and Psychiatric Characteristics of the Full Sample………51
Table 2. Predictors of Severity of Global Impairment in the Full Sample……………………….53
Table 3. Demographic, Disease, and Psychiatric Characteristics of the Caucasian Group…..54
Table 4. Demographic, Disease, and Psychiatric Characteristics of the Non-Caucasian Group……………………………………………………………………...56
Table 5. APOE ε4 Proxy Carrier Status as Predictor of Global Impairment Stratified by Ethnicity…………………………………………………………………………………...58
Table 6. Prevalence of Global Neurocognitive Impairment by APOE ε4 Proxy Carrier Status in Ethnicity Groups..........................................................................................59
Table 7. Prevalence of Mild Global Impairment by APOE ε4 Proxy Carrier Status in Ethnicity Groups..........................................................................................59
Table 8. Prevalence of Moderate-Severe Global Impairment by APOE ε4 Proxy Carrier Status in Ethnicity Groups..........................................................................................60
Table 9. Predictors of Domain Impairment in Caucasians..................................................61
Table 10. Predictors of Total Cognitive Complaints in Caucasians.....................................62
Table 11. Predictors of IADL Dependence in Caucasians...................................................62
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PROFESSIONAL PRESENTATIONS


Recent evidence suggests that examination of host genetics may contribute to identification of HIV-seropositive individuals at risk for developing neurocognitive impairment. Specifically, HIV-seropositive carriers of a known risk factor for developing Alzheimer’s disease, i.e., the apolipoprotein E (APOE) ε4 allele, reportedly demonstrate a nearly threefold increased risk for HIV-associated dementia (HAD) in some studies. In the present study, the relationship of APOE ε4 carrier status to the spectrum of HIV-associated neurocognitive impairment was examined in a sample of 276 well-characterized HIV-seropositive individuals, stratified by ethnicity. It was hypothesized that APOE ε4 carrier status would be associated with increased risk for all levels of impairment, particularly greater severity of impairment, and the pattern of APOE ε4-related domain impairment was explored.
Overall, the results of the current study suggest that carrying an APOE ε4 proxy allele confers greater risk for moderate-severe HIV-associated neurocognitive impairment in Caucasians based on associations observed using a proxy single nucleotide polymorphism (SNP) in high linkage disequilibrium with APOE. The study failed to demonstrate a hypothesized relationship between APOE ε4 proxy carrier status and milder forms of neurocognitive impairment in HIV, and no APOE ε4 proxy carrier effect was observed for any analyses in the African American group. Results also suggest that Caucasian carriers of the APOE ε4 proxy allele were more likely to demonstrate memory and motor impairment, which are the domains that have been shown to be the most sensitive to HIV infection. As such, these domain-level findings provide additional, albeit tentative, support for the potential role of APOE ε4 in increasing risk for HIV-associated neurocognitive impairment. Implications of these findings are discussed, and limitations to the study are also presented, with particular emphasis on limitations to conclusions regarding associations between APOE genotype and HIV-associated neurocognitive impairment based on the use of a proxy SNP.
INTRODUCTION

HIV invades the central nervous system (CNS) early in the course of infection (Davis et al., 1992), resulting in neuropathology through both direct and indirect mechanisms. Infected monocytes from the blood cross the blood brain barrier and differentiate into perivascular macrophages, which, along with microglia, are thought to be the only cells in the brain productively infected by HIV (Gonzalez-Scarano & Martin-Garcia, 2005). Infected perivascular macrophages and microglia release viral proteins (e.g., gp 120, Tat), cytokines (e.g., TNF-α), and chemokines (e.g., MCP-1), which can then activate uninfected macrophages and microglia (Kaul, Garden, & Lipton, 2001). The expression of viral proteins mediates syncytia, or the process of cell-to-cell fusion that results in multinucleated giant cells, one of the hallmarks of HIV encephalitis (Gonzalez-Scarano & Martin-Garcia, 2005). Although HIV does not infect neurons, there is some evidence that direct contact with viral proteins has a neurotoxic effect (Jones & Power, 2006). Exposure to viral proteins can also cause oxidative stress, which can lead to cellular dysfunction and death (Steiner et al., 2006). An indirect, or “bystander,” effect involves intercellular interactions via soluble factors that can lead to neuronal injury (Jones & Power, 2006; Kaul et al., 2001; Gonzalez-Scarano & Martin-Garcia, 2005). An inflammatory response is promoted due to the expression of cytokines and chemokines by activated macrophages and microglia. Excitotoxicity occurs as the immune activated macrophages and microglia release neurotoxic substances (e.g., glutamate), which initiate a chain of events including neuronal injury, dendritic and synaptic damage, and apoptosis (i.e., programmed cell death). Astrocytes that have been exposed to factors released by activated macrophages and microglia may also have a role in the excitotoxic process, as this exposure induces release of glutamate and impairs reuptake (Kaul et al., 2001). The direct neuronal injury, inflammatory processes, oxidative stress, and excitotoxicity that occur in the context of HIV infection result in widespread neuronal and glial pathology.
Although HIV-related neuropathology is evident throughout the central nervous system, there is a preferential impact on the circuits connecting the basal ganglia and frontal lobes (e.g., Aylward et al., 1993; Langford, Everall, & Masliah, 2005). Dendritic damage, occurring particularly in the frontal cortex and basal ganglia, results in a loss of dendritic complexity that has been shown to be a strong correlate of HIV-associated neurocognitive impairment (Cherner et al., 2002; Ellis et al., 2007; Masliah et al., 1997; Moore et al., 2006). Neuroimaging studies also support the preferential involvement of the frontal lobes and fronto-striato-thalamo-cortical circuits, including evidence of volume loss (e.g., Stout et al., 1998), increased blood oxygenation dependent (BOLD) signal (e.g., Chang et al., 2000) and reduced fractional anisotropy (e.g., Pomara et al., 2001). Moreover, alterations in magnetic resonance (MR) spectroscopic markers of inflammation and neuronal damage have been detected in the frontal lobes (e.g., Chang et al., 2005). A study by Castelo, Sherman, Courtney, Melrose, and Stern (2006) supported the effect of HIV on the fronto-striatal circuits, but also demonstrated that the hippocampal system is affected. In this study using fMRI, an HIV-seropositive group demonstrated reduced activation in portions of the prefrontal cortex and reduced signal change in medial temporal regions in comparison to healthy controls. Furthermore, the HIV group demonstrated recruitment of frontal and posterior parietal areas, suggesting compensatory activation was needed due to disruption of both the fronto-striatal and hippocampal systems (Castelo et al., 2006). In addition, thinning of primary sensory, motor, and premotor cortices was demonstrated, and the level of cortical atrophy in prefrontal and parietal regions was shown to be a powerful predictor of neurocognitive impairment in patients with AIDS (Thompson et al., 2005). Given previous evidence suggesting that dendritic simplification (Mazliah et al., 1997) and synaptic density and volume (Everall et al., 1999), Moore and colleagues (2006) used a combined index of dendritic and synaptic markers examined in brain tissue collected postmortem to investigate the relationship between specific cortical and subcortical brain regions (i.e., hippocampus and basal ganglia, respectively) and antemortem global neurocognitive impairment. Results of this study demonstrated that
neurodegeneration (as measured by the combined index of dendritic and synaptic markers) in both the hippocampus and putamen accounted for unique variance in clinical ratings of the severity of antemortem neurocognitive impairment, emphasizing the importance of considering multiple brain regions in understanding the relationship between HIV-associated neuropathology and neurocognitive impairment (Moore et al., 2006).

**HIV-Associated Neurocognitive and Functional Impairment**

HIV-associated neurocognitive impairment is common, affecting approximately 30% to 50% of infected individuals (Grant et al., 1987; Heaton et al., 1995). Highly active antiretroviral therapy (HAART) has advanced the treatment of HIV-infected individuals through suppression of viral replication (Hammer et al., 1997), improved immunosuppression and medical status, and extended longevity (Detels et al., 1998), as well as reduction in the incidence of HIV-associated neurocognitive impairment, particularly HIV-associated dementia (HAD) (MacArthur, 2004; Robertson et al., 2007; Sacktor et al., 2001). However, as infected individuals are living longer with the disease and the required complex medication regimens, neurocognitive impairment remains quite prevalent. A recent prospective investigation of HIV-seropositive individuals who initiated a HAART regimen through participation in a clinical trial reported that 39% of individuals met criteria for mild cognitive impairment and 26% had mild to moderate impairment, despite at least 20 weeks of antiretroviral treatment (Robertson et al., 2007). Impaired individuals who are symptomatic, meaning that their neurocognitive impairment interferes with everyday functioning (e.g., work, independent living), receive a diagnosis of Minor Neurocognitive Disorder (MND) or HAD, depending on the severity of the cognitive and functional impairment (Antinori et al., 2007).

The neuropsychological profile of HIV infection reflects the preferential frontostrial neuropathology of the disease. The prototypic pattern of neuropsychological deficits includes slowed motor and information processing speed, executive dysfunction, and episodic memory deficits characterized by deficient higher-level encoding and retrieval (e.g., Reger, Welsh, Razani, Martin, & Boone, 2002). More specifically, the characteristic pattern of diminished free
recall contrasted with relatively intact retention and recognition (i.e., limited “forgetting”) has been linked to diminished use of organizational strategies, indicating that the memory profile in HIV infection is consistent with dysfunction of the strategic (i.e., executive) aspects of learning and retrieval (Murji et al., 2003). Support for the role of deficient higher-level encoding and retrieval has been provided by numerous prior studies of episodic memory in HIV (e.g., Carey et al., 2006; Delis et al., 1995; Gongvatana et al., 2007; Peavy et al., 1994; Woods et al., 2006). Recent investigations have reported that prospective memory (ProM), a form of episodic memory involving the ability to successfully retrieve and initiate a previously formed intention (or, “remember to remember;” Kvavilashvili & Ellis, 1996), is also impaired in HIV infection (Carey et al., 2006). Examples of ProM in daily life include medication adherence (e.g., remembering to take medication at 12 hour intervals, or with a meal), remembering to stop at the post office on the way home from work to mail a bill, and remembering to periodically check food cooking on the stove. These examples illustrate the potentially serious impact that impaired ProM could have on an individual’s ability to live independently. Evidence from studies of ProM have shown that HIV seropositive individuals demonstrate mild-to-moderate time-based (Carey et al., 2006; Martin et al., in press) and event-based (Carey et al., 2006) ProM. An analysis of error types has suggested that ProM deficits in HIV infection are due to diminished strategic encoding and retrieval of future intentions, which is consistent with prefrontostriatal circuit disruption (Carey et al., 2006). Interestingly, a study of HIV biomarkers of macrophage activation (i.e., monocyte chemoattractant protein 1 [MCP-1]) and axonal injury (i.e., tau) revealed an association with ProM but not retrospective memory, suggesting the possibility of a distinct neuropathogenic process (Woods et al., 2006).

Importantly, a subset of individuals with HIV-associated neurocognitive impairment also experience functional decline. That is, they will experience difficulty with everyday activities in the “real world” that they were previously able to perform. Complex everyday tasks that are likely to be affected in HIV, including activities such as managing finances and medications, are known as instrumental activities of daily living (IADLs). Approximately one-
half of individuals with HIV-associated neurocognitive impairment demonstrate problems with managing IADLs independently (Heaton et al., 2004). Importantly, a robust relationship between neurocognitive impairment and everyday functioning has been demonstrated in the literature even when controlling for medical status and depression. Heaton and colleagues (2004) reported that the HIV-infected participants performed worse on a comprehensive battery functional measures (which included standardized tasks assessing functional abilities such as grocery shopping, cooking, financial management, and medication management) than healthy comparison participants, and impairments in executive functioning, learning, verbal abilities, and attention/working memory were most predictive of performance on functional measures. Studies of specific functional abilities have indicated that neuropsychological impairment is associated with disruption of vocational functioning (e.g., Heaton et al., 1994; van Gorp et al., 1999; van Gorp et al., 2007), automobile driving (e.g., Marcotte et al., 1999, 2000, 2004), and medication management (e.g., Albert et al., 1999; Hinkin et al., 2002). As HAART treatment advances have improved outcomes such as improved health status, and longer life expectancy yet subtler forms of neurocognitive impairment persist, the functional impact of that impairment could lead to substantial challenges as individuals return to the workforce, manage complex daily medication regimens, and engage in other important daily activities such as driving. In order to maintain an updated and relevant understanding of the cognitive consequences of HIV infection in the HAART era, especially as HIV-seropositive individuals reach advanced ages, continued study is necessary to further elucidate the nature HIV-associated neurocognitive impairment and its impact on the functional demands faced by these individuals in their daily lives. Given that not all infected individuals experience neurocognitive dysfunction, host genetics may have a role in the development of cognitive dysfunction. Early detection of individuals at risk for HIV-associated neurocognitive impairment, perhaps through identification of genetic risk factors, could assist in treatment planning and improved prognosis.
Apolipoprotein E Genotype and Cognition

Apolipoprotein E is a protein involved in lipid transport and metabolism (e.g., cholesterol) in the brain. Polymorphism of the apolipoprotein E (APOE) gene results in three allelic variations (i.e., APOE ε3, APOE ε2, and APOE ε4, in descending order of prevalence) and corresponding protein isoforms. The APOE ε4 allele frequency has been examined in different ethnic groups, and is known to vary with ethnicity. The range in reported APOE ε4 allele frequency for middle-aged and elder Caucasians is 9 – 15% (Blair et al., 2005; Borenstein et al., 2006; Howard et al., 1998; Mayeux et al., 1995). For African Americans, the range of reported frequencies for APOE ε4 allele is 23 – 30% (Blair et al., 2006; Borenstein et al. 2006; Mayeux et al., 1995). In the Mayeux and colleagues study (1995), the allele frequency for the Hispanic sample was similar to the typical rate for Caucasians (i.e., 12%).

Numerous studies have investigated the presence of an APOE ε4 allele as a risk factor for Alzheimer’s disease (AD), and results have indicated that carrying an APOE ε4 allele approximately doubles the lifetime risk of developing AD (e.g., Mayeux et al., 1998). Moreover, a meta-analysis demonstrated a gene dose-response effect in that the risk of developing AD may actually be approximately three- to fourfold for heterozygous APOE ε4 carriers and approximately tenfold for homozygous APOE ε4 carriers (Farrer et al., 1997). Although this report also concluded that carrying an APOE ε4 allele was a significant risk factor regardless of ethnicity, the strength of the relationship varied by ethnic group; the association between being a APOE ε4 carrier and AD was strongest for Japanese individuals (heterozygous carrier OR = 5.6, 95% CI = 3.9-8.0; homozygous carrier OR = 33.1, 95% CI = 13.6-80.5) and Caucasians (heterozygous ε2/ε4 OR = 2.6, 95% CI = 1.6-4.0; heterozygous ε3/ε4 OR = 3.2, 95% CI = 2.8-3.8; homozygous carrier OR = 14.9, 95% CI = 10.8-20.6), but the association was weaker in the Hispanic group and was inconclusive in the African American group due to variability in odds ratios (Farrer et al., 1997). Moreover, several newer studies have demonstrated that APOE ε4-related risk for developing AD was absent or weakly
associated in African Americans (Evans et al., 2003; Sahota et al., 1997; Tang et al., 1998). Despite the different allele frequencies and AD-risk relationships in separate ethnic groups, several published studies reported no interaction of ethnicity and APOE genotype (e.g., Blair et al., 2005; Fillenbaum et al., 2001; Jorm et al., 2004). Age has also been examined as a moderator of the relationship between APOE genotype and AD risk, with some studies indicating that the risk is lower for individuals at advanced ages (Breitner et al., 1999; Farrer et al., 1997; Welsh-Bohmer et al., 2009). However, another study demonstrated APOE ε4-related risk for memory decline may be present in non-demented individuals older than 75 years (e.g., Dik et al., 2000). Along with evidence that APOE ε4 carriers may actually demonstrate better memory performance than non-carriers at younger ages (e.g., Mondadori et al., 2006), these findings suggest that effects of APOE on cognition may vary throughout the lifespan. Evidence for a positive APOE ε4 effect on cognition at younger ages, contrasted with detrimental effects in later life, have led to the suggestion that the APOE ε4 allele is an example of antagonistic pleiotropy (Alexander et al., 2007), which is the theory that natural selection favors genes with positive effects in early life.

Published reports also have suggested that APOE ε4 may influence cognitive functioning prior to diagnosis of AD. Evidence has shown that cognitive changes, particularly in learning and recall, can be detected during a preclinical period preceding onset of AD (e.g., Bondi et al., 1995; Boyle, Buchman, Wilson, Kelly, & Bennet, 2010; Linn et al., 1995), and the APOE ε4 allele has been shown to be a significant predictor for conversion to AD (Bondi et al., 1999). Furthermore, APOE ε4 carriers have shown preclinical memory decline at two-year follow-up in a longitudinal study (Baxter, Caselli, Johnson, Reiman, & Osborne, 2003; Caselli et al., 2007), and increased risk of MCI with more rapid rate of decline (Boyle et al., 2010). The literature is somewhat divided with regard to the role of the APOE ε4 allele as a risk factor in normal aging. Some studies have reported that APOE ε4–related cognitive deficits and decline not observed when non-demented individuals were carefully screened for incipient dementia (e.g., Bunce, Fratiglioni, Small, Winblad, & Backman, 2004; Smith et al., 1998).
These findings support the perspective that cognitive differences demonstrated between APOE genotype groups might simply indicate that a greater number APOE ε4 carriers were in the preclinical stage of dementia, rather than serving as evidence for the influence of the APOE ε4 allele on cognition. Furthermore, a recent study failed to demonstrate an interaction of age and APOE genotype in a cross-sectional study of cognitive functioning in non-demented adults aged 20 to 64 years (Jorm, Mather, Butterworth, Anstey, Christensen, & Eastel, 2007). However, a review of longitudinal studies examining risk factors for cognitive change reported that APOE genotype, in addition to low education, hypertension, and indices of health and cardiovascular disease, was a significant predictor of cognitive change in older adults over an average follow-up period of seven years (Anstey & Christensen, 2000). Notably, APOE ε4 status was shown to be a risk factor for decline in older adults who were designated as “high functioning” at baseline evaluation, thereby reducing the likelihood of inclusion of participants with incipient dementia, and showed significant decline in memory, naming, and constructional praxis performance over a seven-year follow-up period (Bretsky, Guralnik, Launer, Albert, and Seeman, 2003). Participants in the Scottish Mental Survey of 1932 showed no effect of APOE genotype on cognitive test performance (involving verbal and non-verbal reasoning) during initial testing in childhood, but significant differences emerged for a subset of those individuals who were not demented and were retested at age 80, such that the APOE ε4 carriers showed poorer performance relative to non-carriers and evidenced greater decline from initial performance, even after comorbidities (e.g., cardiovascular disease) were statistically considered (Deary et al., 2002).

Inconclusive results have been shown when comparing the association between APOE genotype and risk for cognitive decline between community-based samples of healthy, older Caucasians and African Americans (e.g., Blair et al., 2005). One study reported a significant relationship between the APOE ε4 allele and cognitive decline but demonstrated no interaction of genotype and ethnicity (Fillenbaum et al., 2001), while another reported a
significant association between APOE ε4 and poorer cognitive performance in Caucasians but not in African Americans (Borenstein et al., 2006).

Studies investigating the APOE ε4 effect on specific ability areas in non-demented older adults have revealed that presence of an APOE ε4 allele was associated with poorer performance on tests of global cognitive functioning, episodic memory, and executive functioning (see Small et al., 2004 for a meta-analysis). Cognitive domains that are not typically affected by APOE genotype include attention, visuospatial skills, verbal abilities, and perceptual speed (Small et al., 2004). Episodic memory impairment observed on list- and story-memory tasks have been observed in APOE ε4 carriers relative to non-carriers in nondemented, elderly adults (Deary et al., 2004; Helkala et al., 1995), and middle-aged to older adults (Blair et al., 2005; Flory, Manuck, Ferrell, Ryan, & Muldoon, 2000; Kozauer, Mielke, Chan, Rebok, & Lyketsos, 2007; Levy et al., 2004; Schultz et al., 2009; Wehling, et al., 2007). The APOE ε4 allele has also been associated with specific decline in episodic memory over a follow-up period in nondemented, elderly adults (Helkala et al., 1996, Mayeux et al., 2001; Wilson, Bienias, Berry-Kravis, Evans, & Bennett, 2002). Additional findings suggest that APOE ε4 is associated with poorer performance on tasks requiring intact executive functioning, such as working memory (e.g., Caselli et al., 2001; Greenwood, Lambert, Sunderland, & Parasuraman, 2005; Rosen et al., 2002), category fluency (i.e., total animal names generated and total clusters of names; Rosen et al., 2005), executive aspects of spatial attention (i.e., deficient attentional shifting after a cue; Greenwood et al., 2000) and the effect of attention on visuospatial memory (i.e., cues of varying size displayed prior to presentation of a target stimulus modulated memory for location of the target; Greenwood et al., 2005).

In summary, a review of the literature reveals that carriers of the APOE ε4 allele are at greater risk for neurocognitive impairment as they age relative to non-carriers, and an APOE ε4 effect on impairment has most often observed for the episodic memory and executive functioning domains. In many cases, these effects have been observed years, even decades,
before the typical age of onset for AD. This preponderance of evidence suggests that APOE ε4-related effects may not solely be due to inclusion of individuals in preclinical stages of dementia, and instead could represent an APOE-modulated aging process. A limitation frequently noted in studies examining the effect of APOE genotype on cognition is limited power to detect effects due to relatively small sample sizes. This is particularly the case for the low-frequency homozygous allele pair, and several studies have demonstrated a gene dose-related APOE effect on cognition such that the effect stronger in homozygotes (e.g., Caselli et al., 2007; Corder et al., 1993; Farrer et al., 1997). As such, small numbers of APOE ε4 homozygotes in previous studies may have masked potential effects. In addition to the effects of the APOE ε4 allele, the ε2 allele has consistently been reported as a protective factor (Blacker et al., 2007; Farrer et al., 1997; Wilson et al., 2002). Furthermore, APOE ε4 status has been associated with risk of Vascular dementia (VaD; e.g., Baum et al., 2006; Davidson et al., 2006), and cognitive outcomes following traumatic brain injury (Ariza et al., 2006; Teasdale, Murray, & Nicoll, 2005; Teasdale, Nicoll, Murray, & Fiddes, 1997). Notably, a 10-fold increase in risk of AD following a TBI has been demonstrated for APOE ε4 carriers (Mayeux et al., 1995). Relevant to the current study, APOE ε4 carrier status is believed to have a role in CNS response to chronic infection (Urosevic & Martins, 2008) and has been shown to increase risk for HIV-associated dementia (HAD; Corder et al., 1998, Valcour et al., 2004). Mechanisms by which APOE genotype may affect cognitive performance are discussed in the following section.

**APOE: Mechanisms, Biomarkers, and Neural Substrates**

Apolipoprotein E (apoE) is the protein associated with the APOE gene. Protein isoforms apoE2, apoE3, and apoE4 correspond to the three APOE allelic variations (i.e., APOE ε2, APOE ε3, and APOE ε4). apoE has been linked to longevity and successful versus unsuccessful aging, given the link between apoE4 and risk for heart disease, stroke, and AD (see Smith, 2002 for a review). With regard neuropathology, several apoE-related mechanisms have been proposed. Two pathways by which apoE4 may contribute to brain
pathology that leads to neurocognitive decline have been described in reports by Mahley and Huang (2006) and Mahley, Weisgraber, and Huang (2006), and are summarized as follows. The differing properties of the apoE isoforms are important for understanding why apoE4 is specifically associated with neuropathogenesis. The apoE4 isoform is the least stable, meaning that it denatures more easily (e.g., at the pH level found in lysosomes), leading to a partial unfolding into a reactive intermediate state known as a molten globule. These molten globules are involved in both proposed apoE-related pathways to neuropathology. In one pathway, the structure of apoE4 increases production of amyloid-beta (Aβ), stimulates Aβ deposition, and inhibits Aβ clearance, leading to formation of plaques that have an important role in the pathogenesis of AD. Also, in the presence of Aβ peptide, apoE4 can be taken up by neurons, and the molten globule that form in the context of the low pH of lysosomes enhance the ability of Aβ to cause membrane instability and lysosomal leakage, which can lead to apoptotic cell death. The second pathway involves synthesis of apoE by neurons exposed to a stressor, such as aging, ischemia, oxidative stress, Aβ deposition, hypercholesteremia, or hypertension, which has been hypothesized to occur due to the role of apoE in neuronal maintenance, repair, and protection of synaptodendritic connections. Given its instability, apoE4 is susceptible to proteolytic cleavage, which can lead to cytoskeletal changes due to the formation of truncated fragments that accumulate into neurofibrillary tangles, leading to cell death.

APOE genotype effects have been examined in relation to biological markers and neural systems in older adults without dementia. With regard to biomarkers, a recent study revealed that a sample of middle-aged to young elderly APOE ε4 carriers who performed within normal limits on neuropsychological testing nevertheless showed significantly higher levels of CSF F2- isoprostane, which reflects lipid membrane oxidative damage, and markers of neurofibrillary tau (i.e., total tau and hydrophosphorylated tau) (Mosconi et al., 2008). In the same study, CSF biomarkers were not significantly different between individuals who reported subjective memory complaints and those who did not, but a significant interaction was
revealed such that APOE ε4 carriers who reported subjective memory complaints had higher levels of these biomarkers compared to noncarriers (Mosconi et al, 2008).

Neuroimaging studies have provided evidence that frontotemporal systems are affected by APOE ε4. For example, the following two studies presented evidence of compensatory processes in APOE ε4 carriers during cognitive tasks observed with fMRI, suggesting that APOE ε4 carriers require additional cognitive effort to achieve performance level similar to noncarriers. In neurologically normal middle-aged to elder adults, APOE ε4 carriers showed increased signal intensity during a memory activation task (involving learning and recall) in left hippocampal, prefrontal, and parietal regions, and the degree of activation at baseline correlated with degree of memory decline at two-year follow-up (Bookheimer et al., 2006). Another study of nondemented, older APOE ε4 carriers with normal learning and memory performance showed greater magnitude and extent of BOLD response than noncarriers in multiple brain regions, i.e., bilateral fusiform and medial frontal gyri, left interior and middle frontal, right superior parietal, and right hippocampal cortices (Bondi, Houston, Eyler, & Brown, 2005). In addition, the APOE ε4 group showed lower brain response in the left hippocampus relative to noncarriers, despite equal learning and memory performance between the groups. The authors of the study concluded that because the BOLD response differences observed in the APOE ε4 carriers could not be accounted for by differential memory abilities, differential atrophy, or overall physiologic differences, their findings represent a compensatory process (Bondi et al., 2005). Furthermore, findings of hypometabolism in the parietal cortex of APOE ε4 carriers has been linked to damage in the hippocampal region (Lind et al., 2006). Recently, APOE ε4 was associated with greater hippocampal volumetric declines over time in nondemented older adults, which the authors suggested could indicate that accelerated hippocampal atrophy occurs even in elderly individuals without dementia (Jak et al., 2007). This finding supports previous reports of greater hippocampal volume loss associated with APOE ε4 in healthy, older adults (Cohen, Small, Lalonde, Friz, & Sunderland, 2001; den Heijer et al., 2002). In addition, a recent study
investigated whether APOE genotype influences the relationship between brain function (i.e., cognitive processing speed) and myelin integrity in healthy older adults due to inefficiency of apoE4 in myelin repair (Bartzokis et al., 2007). The results of the study revealed an association between cognitive processing speed and myelin breakdown in frontal lobe white matter and the genu of corpus callosum that was exclusive to APOE ε4 carriers. Interestingly, the authors suggested that due to its role in age-related myelin breakdown, apoE4 influences rate of age-related decline in cognitive processing speed, which, in turn, may underlie consequential memory dysfunction (Bartzokis et al., 2007).

Collectively, these findings demonstrate regional brain differences by APOE genotype, specifically in frontal and temporal regions, in healthy aging adults. Furthermore, genotype-specific findings regarding biomarkers support the purported role of apoE4 in development of brain neuropathology.

**APOE ε4 in HIV Infection**

One of the pathways by which apoE4 is purported to contribute to neuropathology is an inefficient and deleterious response to CNS stressors that can lead to neuronal death, which is related to instability of the apoE ε4 structure (Mahley & Huang, 2006; Mahley, Weisgraber, & Huang, 2006). The inflammatory processes and direct neurotoxic effects related HIV infection represent CNS stressors, and APOE genotype therefore might influence the response of the nervous system to HIV-related injury, resulting in HIV-associated neuropathology for APOE ε4 carriers (Corder et al., 1998; Esiri et al., 1998). The differential structure of apoE isoforms may also influence CNS response to HIV infection given that the amphipathic helical domains of apolipoproteins may act as viral fusion inhibitors, and apoE e4 may be a less efficient fusion inhibitor due to its compact structure, and apoE e4 may less effectively block attachment of HIV to the cell-surface receptors between the cell surface and viral lipid (Dobson et al., 2006). Possibly related to the modulation of viral attachment and fusion to cells, APOE ε4 homozygous genotype has been associated with enhanced entry of HIV into cells and a faster rate of disease progression (Burt et al., 2008). Recent studies have
also reported that increased oxidative stress (i.e., another CNS stressor triggering the maintenance/repair response in neurons) was present after exposure to HIV proteins in APOE ε4 positive human neuronal cultures, and that increased levels of oxidative stress indictors have been observed maximally the frontal lobes of APOE ε4 carriers (see Steiner et al., 2006, for a review). Another pathway by which APOE ε4 may play a role in HIV-associated neuropathogenesis, especially as infected individuals age with the disease, is increased risk of the hallmarks of AD pathology (Brew, Crowe, Landay, Cysique, and Guillemin, 2009). This may represent a change in the presentation of HIV-associated neurocognitive disorders (HAND) in the HAART era in accordance with the hypothesis that individuals with a history of CNS insults such as chronic infectious disease, including HIV, may be at greater risk for developing AD (Brew, et al., 2009; Urosevic & Martins, 2008). Consistent findings have demonstrated that CSF beta amyloid levels are reduced among HIV seropositive individuals with HAND, suggesting plaque accumulation (Brew et al., 2005; Clifford et al., 2009). Furthermore, an increased prevalence of argyrophilic amyloid plaques, has been observed in HIV (Achim et al., 2009; Esiri et al., 1998). However, the Green and colleagues (2005) failed to find an association between cerebral beta amyloid plaque accumulation and HIV neuropathology, suggesting a role for APOE ε4-related mechanisms of HIV neuropathology related to the non-amyloid pathway (i.e., involving ineffective neuronal maintenance and repair) in manifest neurocognitive impairment in this population.

Although the link between APOE genotype and neurocognitive disorders has not been fully established in HIV disease, APOE ε4 has been investigated as a risk factor for developing HAD in six studies, three of which demonstrated an APOE e4-related effect on presence of HAND while three others failed to find an association between APOE ε4 carrier status and HAND. One study that failed to demonstrate an association between APOE genotype and HAD examined a restricted sample of AIDS patients in Oslo during the pre-HAART era, and an unclear operationalization of HAD was used (Dunlop et al., 1997). The findings of the study were based on correlational analyses only, with the assumption that the
detrimental effects of APOE alleles are ordered such that e2 alleles are the least detrimental and ε4 are the most detrimental. No direct examination of prevalence or risk (i.e., odds ratios) was conducted, and there was no evidence that the authors accounted for important cofactors such as age, ethnicity, indices of disease severity (e.g., nadir CD4), or potential psychiatric comorbidities in the study. Another study that failed to demonstrate an APOE ε4 effect on presence of HAD was conducted by Burt and colleagues (2008), in which a faster rate of HIV disease progression was observed for homozygous APOE ε4 carriers, but not heterozygous carriers, which prompted the authors to examine whether APOE ε4 homozygosity was related to a faster progression to HAD. The authors did not observe this effect, and they sought to confirm their findings by conducting a logistic regression predicting presence versus absence of ε4/ε4 genotype by AIDS-defining illnesses, among which HAD was included. An association between HAD and presence of ε4/ε4 genotype was not observed while opportunistic infections (e.g., mycobacterium avium) included as predictors in the same model did demonstrate this association, from which the authors concluded the lack of an APOE ε4 effect in HAD. APOE ε4 carrier rates did not differ between HAD and control groups in another study, but the study sample was comprised of predominantly younger HIV-seropositive individuals, which may have masked the APOE ε4-relationship to HAD (Pemberton, Stone, Price, van Bockxmeer, and Brew, 2008). In contrast, HAD has been reported to be twice as prevalent in APOE ε4 carriers as compared to non-carriers in a study in which the authors attempted to isolate the APOE ε4 effect by demonstrating that the higher rate of HAD among APOE ε4 carriers was not due to confounding factors such as disease characteristics (i.e., the APOE ε4 effect was greater when CD4 count was included in the statistical model), thereby increasing the likelihood that they were detecting an APOE ε4-specific signal (Corder et al., 1998). Moreover, a recent investigation failed to find a relationship between APOE ε4 carrier status and HAD in the total sample of HIV seropositive individuals, but when the sample was stratified into younger and older age groups (less than 40 years of age versus 50 years of age and older), the presence of an APOE ε4 allele was associated with a threefold independent risk for HAD
in the group of older HIV-seropositive individuals (Valcour et al., 2004). The authors also demonstrated that the effect remained even after controlling for factors known to relate to HAD, including age and diabetes mellitus diagnosis. Interestingly, a recent study of HIV seropositive individuals in China concluded that presence of an APOE ε4 allele was associated with risk for neurocognitive impairment by demonstrating that a greater proportion of APOE ε4 carriers were impaired relative to APOE ε4 non-carriers (Spector et al., 2010). The study authors also reported that controlling for indices of HIV disease severity that have been shown to relate to HAND did not account for the APOE ε4 effect.

**Genetic Study Methodology**

Prior studies investigating the association between APOE ε4 carrier status and cognition (e.g., AD and HAD) have utilized a candidate gene approach whereby APOE genotype was directly determined for inclusion in statistical models. Genome-wide association studies (GWAS), which are typically non-hypothesis driven examinations of associations between chromosomal loci and disease (see Hardy & Singleton, 2009) are increasingly common, and APOE variants are not represented (i.e., tagged) on many genome arrays. Investigators with research hypotheses involving APOE genotype may nevertheless be able to make use of data from GWAS given the availability of information regarding relationships among genes such as that provided by the International HapMap Project (International HapMap Association, 2005), which has characterized patterns of human genomic variation, particularly SNPs, by examining frequencies and patterns of association among common SNPs in multiple populations. Understanding these relationships among genes has provided the foundation for GWAS, which examine associations between single nucleotide polymorphisms (SNP), or sites within the genome where variants differ by a single nucleotide base between individuals or between paired chromosomes within an individual, across the genome and disease (Hardy & Singleton, 2009; Hirschorn & Daly, 2005). Given that there are roughly ten million SNP sites, directly typing each site would be costly and time intensive, and the methodology of GWAS studies allows for estimation of untyped SNPs through a process
of imputation from typed SNPs by capitalizing on a “shortcut” that relies on haplotypes, or sets of alleles at multiple sites on the chromosome that tend to be transmitted together, and linkage disequilibrium, which is nonrandom association of alleles at sites on the same chromosome. Two polymorphic sites are in LD when the alleles tend to be inherited together so that the allele of one SNP is predictive of the allele of the other SNP. The HapMap elucidated patterns of LD so that once a selection of SNPs (i.e., tag SNPs) is typed, the likely variants of other SNPs in a region can be estimated (International HapMap Association, 2005). As such, GWAS methods allow for the use of existing genotyping platforms which type only a targeted number of SNPs given that those tag SNPs can serve as proxies for untyped SNPs, and the degree of LD can be represented by an $r^2$ index ranging from 0 to 1 such that 1 represents two alleles are always inherited together (high LD) and 0 indicates a low proportion of observations in which the alleles have occurred together (low LD), or by a $D'$ estimate, which has a similar interpretation. A review by Manolio and colleagues (2008) concluded that a large number of robust genetic associations with common diseases (i.e., associations between chromosomal loci and diseases) have been demonstrated with GWAS methodologies, many of which have been replicated. Notably, a study by Coon and colleagues (2007) provided empirical support for the use of the GWAS approach in examining genetic risk for AD, i.e., APOE was identified as the major susceptibility gene for sporadic AD despite the fact that APOE variants were not actually typed and a tag SNP in high LD with APOE (i.e., rs4420638) was used instead. This evidence provides a precedent for examining APOE ε4 variant-related risk for phenotypic disease expression using a proxy from a GWAS.

**Summary, Aim, and Hypotheses of the Present Study**

Collectively, current published findings suggest that further study of APOE genotype in neuroAIDS is warranted based on the reported effect of APOE ε4 on risk for HAD, and given the proposed mechanisms of APOE ε4 which may modulate the response of the CNS to chronic infections, such as HIV, resulting in neuropathology. That is, HIV infection (e.g., inflammation, oxidative stress) challenges the CNS and may elicit the detrimental effects of
carrying an APOE ε4 allele. Furthermore, multiple CNS stresses have been shown to increase the likelihood of impairment with aging (such as TBI and aging, e.g., Mayeux et al., 1995), which may become a greater concern as members of the HIV population live to advanced age due to treatment improvements. In addition to the demonstrated risk of HAD associated with APOE ε4, one prior study has demonstrated APOE ε4 risk for milder forms of HIV-associated neurocognitive impairment. Conducted in China, this study may have limited generalizability to the U.S. population. Therefore, the aim of the current study is to investigate whether APOE ε4 carrier status affects a full range of cognitive performance in HIV-seropositive individuals, by using a proxy SNP in high LD with APOE.

**Hypothesis 1.** The group of HIV-seropositive individuals who are APOE ε4 allele proxy carriers will demonstrate greater risk for HIV-associated neurocognitive impairment than those who are APOE ε4 non-carriers. Support for this hypothesis will be consistent with past research indicating that there is a greater risk for HAD in APOE ε4 carriers and would extend the finding to milder forms of HIV-associated neurocognitive impairment, for which only one study has demonstrated an effect, providing additional evidence for the role of APOE ε4 in the neuropathogenesis of HIV. The relationship of APOE ε4 proxy carrier status to milder forms of neurocognitive impairment was expected based on prior studies of APOE ε4-related risk for mild impairment in the preclinical aging population and in individuals with MCI.

**Hypothesis 2.** Given that prior studies have demonstrated an association between APOE ε4 carrier status and HAD, it was hypothesized that carrying an APOE ε4 proxy allele would be related to risk for greater severity of impairment. APOE ε4 carrier status was also expected to predict severity of neurocognitive impairment across levels of impairment (i.e., continuous neurocognitive performance criterion). Specifically, it was expected that a higher proportion of APOE ε4 proxy carriers than non-carriers would demonstrate neurocognitive performance within the moderate-severe range, which is a criterion for HAD according to the latest research nosology of HAND (Antinori et al., 2007). Exploratory analyses were conducted to examine the patterns of APOE ε4 proxy-related cognitive domain impairment.
Findings demonstrating that HIV-seropositive APOE ε4 proxy carriers who have been administered a comprehensive neuropsychological battery evidence poorer performance on specific ability domains could bolster prior research with other diseases indicating that selective aspects of cognitive performance (e.g., episodic memory) are particularly affected in carriers of the APOE ε4 allele. No studies to date have examined the APOE ε4 effect on specific cognitive domains in HIV.

**Hypothesis 3.** Presence of an APOE ε4 allele proxy in neuropsychologically impaired HIV-seropositive individuals was expected to be related to a higher risk for disruption in everyday functioning. That is, it was hypothesized that APOE ε4 proxy carriers with impairment would demonstrate more severe impairment (Hypothesis 2) and more cognitive complaints and higher rates of dependence in instrumental activities of daily living (IADL). Potential interactions of APOE ε4 proxy carrier status with current depression may be demonstrated. Regarding everyday functioning in HIV disease, the association between global neurocognitive impairment and IADL dependence may be stronger in the APOE ε4 proxy carrier group relative to non-carriers, which would extend prior findings demonstrating an effect of HIV on IADL dependence.
METHOD

Participants

Participants included 309 individuals with HIV infection who were enrolled in a larger, ongoing study at the HNRC: CNS HIV Antiretroviral Therapy Effects Research (CHARTER). The CHARTER study broadly aims to investigate neurological complications of HIV infection in the era of highly active antiretroviral therapy (HAART) and other emerging antiviral treatments. Funded in September 2002 in response to NIMH RFA 00-AI-0005, the combined effort of six CHARTER sites is coordinated by UCSD, the principal grantee institution, through the involvement of scientific, technical, and administrative cores. As part of the CHARTER study, participants’ HIV-serostatus was confirmed by ELISA and a Western Blot confirmatory test, and all participants in the CHARTER cohort receive comprehensive neuromedical, neurocognitive, psychiatric, functional (i.e., self-reported IADLs), and laboratory examinations. The CHARTER Option Period began in September 2007, allowing for the findings of the initial study period to be refined to focus on emerging areas of interest in neuroAIDS, including host genetics. The CHARTER Host Genetics project includes participants from the Longitudinal Pathogenesis Study cohort (N=652) who were evaluated semi-annually. From the final CHARTER Host Genetics study cohort (N=536 after exclusions based on quality control procedures described below), a set of exclusion criteria were utilized for the present study in order to isolate a subset of individuals with minimized exposure to potential confounding effects of comorbid psychiatric and neurological disorders known to adversely affect cognitive functioning, while allowing for a limited exposure to such confounds so that a representative sample of HIV-seropositive individuals was yielded (i.e., results from a sample with no exposure to these confounds would have limited generalizability). A review of CHARTER cases conducted by a senior neuropsychologist using a standard set of criteria (Antinori et al., 2007) rated each case as “incidental,” “contributing,” or “confounded.” Cases rated as “confounded” had reported histories of major neuromedical comorbid conditions (including active CNS opportunistic infections, seizure disorders, head injury with extended loss of
consciousness, intracranial neoplasms, multiple sclerosis, and cerebrovascular accidents) or selected psychiatric disorders, including psychotic disorders (e.g., schizophrenia), severe substance dependency history with significant overdoses, mental retardation and other serious developmental disorders; these conditions, in various combinations, were considered by the rater to be sufficient to cause any neurocognitive impairment that may be present, which precludes a diagnosis of HAND. Therefore, all “confounded” cases were excluded for the present study. “Contributing” cases were defined as having lesser degree of exposure to comorbid conditions, which were considered likely to contribute to neurocognitive impairment in HIV infection but not account for it entirely, suggesting an independent (and in some cases, potentially additive) role of HIV infection. Given that the relative contributions of HIV and the comorbid factors in these cases could not be estimated more precisely, “contributing” cases also were excluded. Therefore, the remaining cases were those rated “incidental,” for which there was a higher degree of certainty that observed neurocognitive and/or neurological consequences were related to HIV infection given their limited exposure to comorbid factors. Additionally, individuals were excluded from the present study if they were unable to speak English. However, individuals with Major Depressive Disorder (MDD), Dysthymic Disorder, and Generalized Anxiety Disorder (GAD) were included because these are the most commonly comorbid psychiatric disorders in HIV seropositive individuals, and they do not typically have a substantial effect on standardized neuropsychological testing. Participants were also excluded from the present study if they met Diagnostic and Statistical Manual of Mental Disorders – 4th Edition (DSM-IV; American Psychiatric Association, 1994) criteria for any current substance use disorder (i.e., abuse or dependence), which was determined by a semi-structured clinical interview. Given that participants with any current substance use disorder diagnosis were excluded, individuals were not excluded based on positive urine toxicology screening on the day of testing. Furthermore, individuals with a history of past substance dependence were not excluded so that the sample would be more representative of the HIV seropositive population, and because those with a history of severe substance
dependence that would likely impact current functioning would have been among the cases labeled “contributing” that were excluded.

Procedure

Psychiatric interview. Administered to all participants, the Structured Clinical Interview for the DSM-IV (SCID; First, Spitzer, Gibbon, & Williams, 1996) was used to document current and lifetime psychiatric and substance-related disorders. This semi-structured clinical interview provided diagnoses for the purpose of determining eligibility and for characterizing the sample.

Neuropsychological assessment. The neuropsychological battery administered to CHARTER participants met the standard of practice for neuropsychological research in HIV (Butters et al., 1990) by providing a comprehensive yet relatively brief evaluation of the cognitive domains affected by HIV. The approximately 3-hour battery was administered and scored by trained psychometrists following standard procedures in the test manuals. The battery included measures divided into seven domains in the following manner: (1) Verbal Fluency: Controlled Oral Word Association Test (COWAT-FAS; Benton, Hamsher, & Sivan, 1994; Gladsjo et al. 1999) and semantic verbal fluency (animals; Gladsjo et al., 1999); (2) Speed of Information Processing: TMT-A (Army Individual Test Battery, 1994; Heaton et al., 1991), WAIS-III Digit Symbol and Symbol Search (Heaton et al., 2002; The Psychological Corporation, 1997), Stroop Color Naming (Golden, 1978); (3) Attention/Working Memory: Paced Auditory Serial Addition Test (PASAT, Diehr, Heaton, Miller, & Grant, 1998; Gronwall, 1977; Gronwall & Sampson, 1974), Wechsler Adult Intelligence Scale-III (WAIS-III; Heaton, Taylor & Manly, 2002; The Psychological Corporation, 1997) Letter Number Sequencing; (4) Executive Functions: Halstead Category Test (Heaton et al., 1991; Reitan & Wolfson, 1993), Wisconsin Card Sorting Test-64 Card Version (WCST-64; Kongs, Thompson, Iverson, & Heaton, 2000) Perseverative Responses, Trail Making Test Part B (TMT-B; Army Individual Test Battery, 1994; Heaton et al., 1991), Stroop Interference Ratio (Golden, 1978); (5) Learning: Hopkins Verbal Learning Test-Revised (HVLT-R; Benedict, Schretlen, Groninger, &
Brandt, 1998) Total Trial 1-3 Recall, Brief Visuospatial Memory Test-Revised (BVMT-R; Benedict, 1997) Total Trial 1-3 Recall; (6) **Memory**: HVLT-R Delayed Recall (Benedict et al., 1998), BVMT-R Delayed Recall (Benedict, 1997); (7) **Motor**: Grooved Pegboard Dominant and Non-dominant hand (Heaton et al., 1991; KlØve, 1963).

In an effort to minimize the effect of demographic characteristics, such as age, education, sex, and ethnicity, on neuropsychological test performance, raw scores from the measures listed above were converted to demographically-corrected T-scores using the best available normative data. These demographically-corrected T-scores were entered into a computerized algorithm that assigned clinical ratings by following a highly specified set of criteria for evaluating global cognitive status and the separate cognitive domains (Woods et al., 2005; Antinori et al., 2007). The use of clinical ratings of neuropsychological test scores has been recommended for investigation of HIV-associated neurocognitive impairment given the sensitivity of the ratings to detect the mild and “spotty” frontal-subcortical deficits typically observed in seropositive individuals (Butters et al., 1990). The algorithm used in the current study was based on the clinical ratings approached operationalized by Heaton and colleagues (1994), and is consistent with the recently published guidelines for classifying HAND (Antinori et al., 2007). In brief, the algorithm first groups the individual test scores by domains of functioning (described above), and a rating is assigned to each domain on a scale of one (above average rating) to nine (severely impaired rating). A rating of four indicates borderline neuropsychological functioning, and a rating of five is a cut-score denoting mild neuropsychological impairment. Ratings of seven or higher indicate moderate to severe neuropsychological impairment, and are consistent with the diagnosis of HAD. A carefully delineated set of guidelines takes the domain ratings into consideration for derivation of the global rating, with greater weight placed on domain ratings that fall within the impaired range (Woods et al., 2004). Consistent with the most recent nosology of HAND (Antinori et al., 2007), at least two domains must be impaired to meet criteria for a classification of global impairment. Historically, domain and global cognitive functioning have been classified by the
HNRC using and actuarial approach whereby demographically-corrected T-scores are used to calculate an objective summary score that takes into account the number and severity of deficits demonstrated by an individual on the neuropsychological test battery, and weights performances in the impaired range (Heaton et al., 1994, 1995). Although the GDS has shown good sensitivity to mild global neurocognitive impairment (Carey et al., 2004) and a significant association between the GDS and biological makers of HIV-related immunosuppression (i.e., CD4 count and cerebrospinal fluid viral load) has been demonstrated (Gonzalez et al., 2003), there are advantages to the use of the rating algorithm. First, clinical ratings are considered to be a gold standard, and the ratings algorithm was designed to provide a systematic, standardized method for replicating the clinical considerations a qualified rater would take into account when evaluating a battery of demographically-corrected T-scores, which theoretically enhances the sensitivity of the ratings to HIV-associated neuropsychological impairment. Furthermore, the distribution of the GDS is highly skewed, making it potentially inappropriate for use as an outcome in parametric statistical procedures. Nevertheless, to capitalize on the fact that the GDS has been extensively studied and demonstrated to be a sensitive indicator of HIV-associated neurocognitive impairment, only cases for which the GDS and algorithm-based global impairment were in agreement were included (resulting in exclusion of 74 individuals; in one case the algorithm classified an individual as globally “normal” whereas the GDS classified that case as “impaired,” and the remaining 73 cases were classified as “impaired” by the algorithm and “normal” by the GDS). This approach yields the highest degree of confidence in classification of impairment in the sample.

Self-report questionnaires. Participants also completed questionnaires to examine self-reported degree of independence in completing IADLs, number of cognitive complaints, and mood state. In order to assess participants’ self-report of IADL independence, they completed a modified version of the Lawton & Brody (1969) self-report Activities of Daily Living questionnaire. The original questionnaire assesses a range of activities required for living independently, from basic skills (e.g., bathing) to more complex abilities (e.g., managing
finances). In an effort to focus on instrumental activities of daily living, 9 of the original 13 scale items were included in the adaptation for the current study, excluding basic abilities that are more dependent upon physical/motor functioning and may be more related to medical status (i.e., bathing, dressing). Given the possibility confounding factors (e.g., physical limitations, legal issues; Heaton et al., 2004), the childcare and employment items have also been excluded. For the current proposal, level of independence in completing the following subset of everyday tasks will be evaluated with the modified version of the scale: Financial Management, Medication Management, Laundry, Transportation, Grocery Shopping, Housekeeping (cleaning), Cooking, and Telephone Use. Dependence will be defined as rating current level of functioning to be lower than the highest (previous) level of functioning in two or more of these areas of functioning (consistent with Heaton et al., 2004).

Regarding cognitive complaints, participants completed the Patient’s Assessment of Own Functioning (PAOFI; Chelune, Heaton, & Lehman, 1986). For each of the 33 items of the questionnaire, the participant rated the frequency with which he or she experiences difficulty with aspects of specific abilities or activities (i.e., memory, language and communication, use of his/her hands, sensory perception, higher level cognitive and intellectual functions, work, and recreation). Frequency is rated on a likert-type scale ranging from 1 (“almost always”) to 6 (“almost never”), and a rating of 3 (“fairly often”) or lower is considered clinically significant. Those items with a clinically significant frequency rating are summed to create the PAOFI Total Score (range = 0 to 33).

Neuromedical evaluation. The following information was gathered during the neuromedical evaluation: Medical history, current medications and medication history, neurological examination, physical examination, and laboratory evaluations (e.g., blood and cerebrospinal fluid collected for banking and testing).

Genetic characterization. As part of the neuromedical examination for the CHARTER Host Genetics project, participants underwent a blood draw, for which 10-12 mL of plasma and 5 mL of serum are collected, and 4 mL of peripheral mononuclear blood cells
(PBMCs) are stored (providing an adequate quantity for genetic analysis). One of the aims of the CHARTER Host Genetics project was detection of a "genetic signature" among several candidate SNPs, and a genome-wide association study (GWAS) approach was used. For the CHARTER Host Genetics Project, the Affymetrix Genome-Wide Human SNP Array 6.0 was used, which features 1.8 million genetic markers and in excess of 900,000 SNPs (product website: http://www.affymetrix.com/products/arrays/specific/genome_wide_snp6/genome_wide_snp_6.affx). Unbiased selection is used for approximately half of the SNPs on the array, and selection of the remaining SNPs is, in part, based on tag SNPs. APOE variants are not typed by the Affymetrix 6.0 Array, and therefore the estimation of APOE variants was based on LD. Based on the Coon and colleagues (2007) study, SNP rs4420638 found to be in significant linkage disequilibrium with the SNPs that characterize the APOE variants. An extensive quality control (QC) procedure was completed by Cinnamon Bloss, Ph.D., a consultant to the CHARTER Host Genetics project from the Scripps Genomic Institute. This process includes steps such as verifying that genotyped sex matches reported sex in the sample and examination of outliers so that systematic differences within the cohort can be examined (Hardy & Singleton, 2009). Hardy-Weinberg equilibrium, a check for the expected allele frequencies within the cohort, was also examined and confirmed in the present sample. Importantly, SNP rs4420638 had a 100% call rate in identification from the array. The minor allele of this gene has been linked to APOE ε4, and therefore individuals who are homozygous for the minor allele (GG) or heterozygous (AG) are estimated to be APOE ε4 carriers (i.e., APOE ε4 proxy Carriers), whereas those who are homozygous for the major allele (AA) are estimated to be non-carriers (i.e., APOE ε4 proxy Non-carriers).

Data Analyses

The research hypotheses for the current proposal necessitate the use of a cross-sectional, static-group comparison research design (Campbell & Stanley, 1963). Given that presence of the minor allele of the typed SNP has been associated with the APOE ε4 variant, a dichotomous "proxy carrier status" variable was created to group individuals who were
heterozygous (AG) or homozygous for the minor allele (GG) as “APOE ε4 proxy carriers” (i.e., carriers of the SNP that is in high LD with APOE ε4), and those who were homozygous for the major allele were grouped as “APOE ε4 proxy non-carriers.” Notably, this approach only estimated presence or absence of the APOE ε4 variant and did not provide full genotype information; that is, no information regarding APOE e2 could be gleaned from the proxy SNP, and therefore dose-dependent differences in risk for impairment (i.e., greater risk for APOE ε4 homozygous carriers versus heterozygous carries) could not be examined. Given that proxy carrier status was determined after the final sample was identified, the carrier and non-carrier groups may not be matched on important demographic characteristics, and therefore the potential confounding effects of unmatched factors that are known to affect cognition were addressed statistically, including the use of demographically-adjusted normative standards to classify neuropsychological impairment.

An important consideration in GWAS is allele frequency differences between groups with different ancestral backgrounds that may potentially confound the findings of a gene-disease association in a study with a sample comprised of individuals with diverse backgrounds, an effect most commonly evidenced by significant associations observed in Caucasian individuals (i.e., those of European ancestry) but not in individuals of African ancestry (e.g., Hardy & Singleton, 2009; Manolio et al., 2008). Importantly, the effects of population stratification can be corrected statistically through multidimensional scaling (MDS) analysis, a type of multivariate analysis that can reveal hidden population substructure by identifying clusters of data points that can be accounted for in association tests (Zhu & Yu, 2009). For the present study, MDS clusters were derived from the total sample (i.e., the full sample comprise participants with mixed ethnicities) for inclusion in regression analyses in order to correct for population stratification. A genetics consultant to this project, Cinnamon Bloss, Ph.D., derived the MDS clusters using the PLINK whole genome toolset.

The relationship between APOE ε4 proxy carrier and global cognition was evaluated by testing for group differences (i.e., t-test) in mean global rating between APOE ε4 proxy
carriers and non-carriers, and APOE ε4 proxy carrier status was examined as a predictor of
global rating in a multiple linear regression model. Age (a continuous variable) and the
interaction of APOE ε4 proxy carrier status with age were included in the model a priori given
that differential relationships between carrying an APOE ε4 allele and neurocognitive
impairment have been demonstrated in different age groups. Typically, a stronger APOE ε4-
related effect on cognition has been demonstrated with advancing age, including in an HIV-
seropositive sample (Valcour et al., 2004). In the present study, age by APOE ε4 proxy carrier
status interactions were probed by stratifying the sample into two age groups based on a
cutpoint of 50 years of age and greater defining the “older” group, and all individuals under 50
were classified as “younger.” Whenever appropriate, MDS covariates were included to correct
for population stratification, and demographic, disease, and psychiatric factors that were not
equivalent between the groups and/or those that demonstrated a significant association with
the global cognition outcome variable (i.e., significant correlations) were included to control for
their potentially confounding effects. Specifically, the potential cofactors examined included
the following: estimated duration of infection, AIDS diagnosis (yes versus no), nadir CD4, CSF
HIV viral load, plasma HIV viral load, HAART status (HAART versus non-HAART; the non-
HAART group included those who had never taken antiretrovirals, those who had taken them
previously but not at the time of evaluation, and those who took antiretrovirals but not a
HAART regimen), HCV co-infection (positive versus negative), current and lifetime MDD
diagnosis (yes versus no), and lifetime substance dependence diagnoses (yes versus no).

Differences in the prevalence of HIV-associated neurocognitive impairment in the
APOE ε4 proxy carrier and non-carrier groups were evaluated using chi-square analyses or
Fisher’s Exact Tests, depending on the smallest cell size. In these analyses, levels of global
impairment were defined by global ratings cutpoints that were consistent with the most recent
research nosology for HAND (Antinori et al, 2007). Global impairment was defined as a
dichotomous (i.e., impaired versus unimpaired) variable based on a global rating cutpoint of
greater than or equal to five, which includes all levels of impairment. APOE ε4 proxy carrier
versus non-carrier group differences in mild impairment (global ratings = 5 or 6) were evaluated with a Fisher’s Exact test in which those with greater levels of impairment were excluded (i.e., excluding ratings greater than 6), and group differences in moderate-severe impairment (global rating = 7 to 9) were examined with a Fisher’s Exact test in which those with mild impairment were excluded (i.e., excluding those with global ratings of 5 or 6).

Regarding examination of the pattern of cognitive domain impairment as a function of proxy carrier status, logistic regression was employed to evaluate APOE ε4 proxy carrier status as a predictor of presence versus absence of domain impairment for each domain. Selection of predictor variables for specification of domain-level models was similar to analysis of global impairment, except that important co-factors were included in the models on the basis of their association with the domain ratings as opposed to global ratings. A more conservative alpha level of $p = 0.01$ was used to evaluate the pattern of impairment at the domain level, given that comparisons were made for each of the seven domains. However, the threshold for inclusion of co-factors in relevant regression models based on their association with the outcome was held at $p = 0.05$.

Separate regression models were conducted in the group of impaired individuals order to evaluate APOE ε4-proxy related risk for increased cognitive complaints and IADL dependence, and the models included APOE ε4 proxy carrier status, age, current MDD diagnosis, and the interaction between APOE ε4 proxy carrier status and current MDD.
RESULTS

Given that MDS covariates were derived from the current full sample in order to account for the effects of population stratification, the relationship between proxy carrier status and severity of neurocognitive impairment was first evaluated in the full sample. Table 1 shows the demographic, disease, and psychiatric characteristics of the full sample and proxy carrier groups, as well as indices of group differences between the proxy carrier groups ($p$-values, Cohen's $d$ effect sizes). The APOE ε4 proxy carrier groups differed on lifetime opioid dependence diagnosis, but this variable was not significantly associated with the dichotomous global impairment outcome variable (impaired versus normal) or with the continuous global rating (all $p$s > 0.1). Numerous previous reports have observed SNP associations with disease in Caucasians and not in non-Caucasian samples, among which is the association of the APOE ε4 allele with cognitive impairment in AD (e.g., Evans et al., 2003; Tang et al., 1998), and therefore a dichotomous ethnicity group variable defined as Caucasian versus African American was included in the model, as was the interaction of the ethnicity group variable with proxy carrier status in order to determine whether the sample should be stratified by ethnicity group. The overall model accounted for a significant amount of variance in global rating, $F(4, 271) = 3.65, p = 0.007, R^2 = 0.05$ (Table 2). The partial regression coefficient representing the comparison of APOE ε4 proxy carriers to non-carriers was not significant, $b = 0.11, p = 0.2$. The partial regression coefficient reflecting the relationship between age and global rating was statistically significant such that higher age was associated with greater impairment, $b = 0.08, p = 0.01$. Furthermore, although the partial regression coefficient reflecting the relationship between ethnicity group and global rating was not statistically significant, $b = -0.02, p = 0.8$, but the interaction of ethnicity group and ε4 proxy carrier status and global rating was significant, $b = -0.22, p = 0.007$. These findings, supported by the literature, suggest that despite the inclusion of MDS variables derived from the full sample to account for population stratification, the hypotheses of the current study should be evaluated in separate ethnicity groups rather than in a combined sample given that the relationship between APOE ε4 proxy
carrier status and global impairment differs between the groups. Tables 3 and 4 display
demographic, disease, and psychiatric characteristics of the Caucasian and African American
groups, respectively. A post-hoc power analysis revealed that the study was powered to
detect medium effects for all proposed analyses ($\beta > .80, \alpha < .05$) in the separate ethnicity
groups.

In the Caucasian group, the mean global rating was higher (indicating greater severity
of impairment) in the APOE $\varepsilon4$ proxy carrier group ($M = 4.41, SD = 1.45$) relative to the $\varepsilon4$
proxy non-carrier group ($M = 3.78, SD = 1.38$), $t$-ratio = -2.51, $p = 0.01$, Cohen’s $d = 0.45$
(small to medium effect). However, in the African American group there was no difference
between the APOE $\varepsilon4$ proxy carriers ($M = 4.0, SD = 1.04$) relative to the $\varepsilon4$ proxy non-carriers
($M = 4.1, SD = 1.26$), $t$-ratio = 0.87, $p = 0.39$, Cohen’s $d = 0.09$ (small effect). To further
examine the relationship between APOE $\varepsilon4$ proxy carrier status and degree of impairment, a
multiple linear regression model examining predictors of global rating was also conducted in
each ethnicity group. In each group, APOE $\varepsilon4$ proxy carrier status, age, and the interaction of
age and $\varepsilon4$ proxy carrier status were included as predictors. In the Caucasian group, the
model accounted for a significant amount of variance in global rating, $p = 0.01$, $R^2 = 0.08$
(Table 5; Figure 1). The partial regression coefficient representing the comparison of APOE $\varepsilon4$
proxy carriers to non-carriers on global rating was significant such that $\varepsilon4$ proxy carriers were
more impaired than non-carriers, $b = 0.31, p = 0.01$, but the partial regression coefficient
reflecting the association between age and global rating was not statistically significant, $b =
0.001, p = 0.94$. The partial regression coefficient reflecting the relationship the interaction of
age and $\varepsilon4$ proxy carrier status to global rating was significant at a trend-level, $b = -0.03, p =
0.05$. Therefore, simple bivariate regressions with APOE $\varepsilon4$ proxy carrier status as the
predictor and global rating as the criterion were evaluated in age-stratified groups to probe the
trend-level interaction, revealing that carrying an APOE $\varepsilon4$ proxy allele was associated with
greater impairment (i.e., higher global rating) in the younger Caucasian group [$F(1, 32) = 7.8,$
$p = 0.006, R^2 = 0.07, b = 0.42, p = 0.006$], but not in the older Caucasian group [$p > 0.1$]. In
the African American group, the model also accounted for a significant amount of variance in global rating, $p = 0.02$, $R^2 = 0.07$ (Table 5), but the partial regression coefficient relating $\varepsilon4$ proxy carrier status to global rating was not statistically significant, $b = -0.12$, $p = 0.23$. However, the partial regression coefficient reflecting the relationship between age and global rating was statistically significant such that higher age was associated with greater impairment, $b = 0.04$, $p = 0.01$. The partial regression coefficient relating the interaction of age and APOE $\varepsilon4$ proxy carrier status to global rating was not statistically significant, $b = -0.01$, $p = 0.3$.

The prevalence of global impairment did not differ as a function of proxy carrier status in either the Caucasian or African American groups ($ps > 0.05$), as displayed in Table 6. Given that two previous studies that have demonstrated an association between APOE genotype and risk for neurocognitive impairment in HIV infection have used HAD as the cognitive outcome, the present study also investigated whether an APOE $\varepsilon4$ proxy-related effect would be observed for moderate-severe versus mild levels of impairment. The rate of mild global impairment did not differ between the APOE $\varepsilon4$ proxy carrier versus non-carrier groups in either ethnicity group ($ps > 0.05$), as shown in Table 7. However, the prevalence of moderate-severe impairment (i.e., the required level of impairment for a diagnosis of HAD; Antinori et al., 2007) among APOE $\varepsilon4$ proxy carriers was significantly greater than that of $\varepsilon4$ proxy non-carriers in the total Caucasian group ($p = 0.03$), whereas null findings were observed in the opposite direction in the African American group ($p = 0.3$), displayed in Table 8.

Regarding the pattern of impairment, the relationship between carrying an APOE $\varepsilon4$ proxy allele and domain-level impairment was examined for each cognitive domain in the Caucasians only given the null findings observed at the global level in African Americans. An APOE $\varepsilon4$ proxy allele effect was observed only in the memory and motor domains; for all other domains in the Caucasian group, the overall models did not differ significantly from the null (all $ps > 0.01$). Regarding the memory domain, the overall model differed significantly from the null, $p = 0.001$, $R^2 = 0.19$ (see Table 9). A significant effect was observed for APOE $\varepsilon4$ proxy
carrier status as a predictor of memory impairment such that carriers were more likely to have memory impairment than non-carriers \((p = 0.03)\). Notably, carrying an APOE ε4 proxy was associated with a 3.33 \((95\% \text{ CI} = 1.1, 10)\) increase in the likelihood of memory impairment. Age was also significantly associated with memory impairment such that increased age was associated with greater impairment \((p = 0.004)\), but the interaction of age and ε4 proxy carrier status was not significantly associated with memory impairment \((p = 0.7)\). For the motor domain, nadir CD4 < 50 was included in the model as a co-factor \((X^2 = 4.06, p = 0.04; \text{NB.},\) unexpectedly, there was a higher prevalence of motor impairment in the group for which there was no history of a nadir CD4 below 50). The overall model differed significantly from the null, \((p = 0.006, \text{Nagelkerke} \ R^2 = 0.16; \text{see Table 9})\). APOE ε4 proxy carrier status was not significantly associated with motor impairment, \((p = 0.08)\), nor was age associated with motor impairment, \((p = 0.22)\), but the interaction of age and proxy carrier status was significantly associated with motor impairment \((p = 0.02)\). The interaction was probed by examining the effect of APOE ε4 carrier status on prevalence of motor impairment in the age-stratified groups, which revealed no differences for the older Caucasian group (Fisher’s Exact Test \(p = 0.64)\) and a significant APOE ε4 carrier effect in the younger group whereby a significantly higher prevalence of motor impairment was observed in ε4 proxy carriers \((n = 12, 33.3\%)\) compared to non-carriers \((n = 8, 11.4\%)\) using Fisher’s Exact Test, \(p = 0.009, \text{OR} = 3.89 \ (95\% \text{ CI} = 1.41, 10.65)\).

In order to explore the possible explanations for the differential relationship between APOE ε4 proxy carrier status and neurocognitive impairment in the younger versus older Caucasian groups, post-hoc comparisons were conducted for demographic, disease, and psychiatric factors. Regarding education, the older group \((M = 14.74, SD = 2.43)\) had significantly more years of education than the younger group \((M = 13.48, SD = 2.36, t\text{-ratio} = -2.69, p = 0.008)\). Also, a higher proportion of the older group had an AIDS diagnosis \((n = 23, 67.7\%)\) than the younger group \((n = 50, 46.7\%, X^2 = 4.61, p = 0.03)\), and the older group also had a longer duration of infection than the younger group (Wilcoxon Rank Sum Test, \(Z = 2.75, p = 0.006\)).
$p = 0.006$). The younger group had a higher prevalence of lifetime cocaine dependence ($n = 20, 18.7\%$) compared to the older group ($n = 0$; Fisher’s Exact Test, $p = 0.004$), and a higher prevalence of lifetime methamphetamine dependence ($n = 27, 25.2\%$) compared to the older group ($n = 2, 5.9\%$; Fisher’s Exact Test, $p = 0.01$). However, when those participants with a history of lifetime cocaine and/or methamphetamine dependence were excluded ($n = 42$), there remained an effect of APOE ε4 proxy carrier status on motor impairment in the younger group (Fisher’s Exact Test $p = 0.02$) but not the older group (Fisher’s Exact Test $p = 0.63$).

As displayed in Table 10, a model was evaluated in order to identify predictors of cognitive complaints in Caucasians. The overall model was significant ($p < 0.0001$), and a significant association between current MDD and total complaints was observed ($p < 0.0001$), but no interaction between APOE ε4 proxy carrier status and global rating was observed ($p > 0.01$). A model was also examined for determining predictors of IADL dependence, but the overall model was non-significant ($p > 0.05$; see Table 11).
DISCUSSION

Host genetics are believed to have a role in predisposing HIV-seropositive individuals to development of disease-related neurocognitive impairment, and there is evidence to suggest that carrying an APOE ε4 allele is a risk factor for HAD (Corder et al., 1998; Valcour et al., 2004). The current study aimed to examine the broader association between APOE ε4 proxy carrier status and HIV-associated neurocognitive impairment, including milder forms of impairment that are increasingly the most prevalent form of HIV-associated neurocognitive disorder (HAND). Notably, the significantly higher mean global rating in the Caucasian APOE ε4 proxy carrier group relative to the ε4 non-carriers suggests that, on average, the APOE ε4 proxy carriers were rated as more impaired than the ε4 non-carriers. Similarly, in the multivariate regression model, APOE ε4 proxy carrier status was a significant predictor of global rating among Caucasians in the expected direction, whereby carrying an APOE ε4 proxy allele was associated with greater impairment. In contrast, there was not a significant APOE ε4 proxy carrier group difference on mean global rating in the non-Caucasians, nor did ε4 proxy carrier status significantly predict the global rating in this group’s multivariate regression model.

When the prevalence of global impairment (i.e., defined the mild impairment cutpoint and including all levels of impairment) by APOE ε4 proxy carrier status was evaluated separately in the ethnicity groups, no significant differences emerged as a function of ε4 proxy carrier status in either group. That is, overall rates impairment (including milder impairment) were not more prevalent among APOE ε4 proxy carriers relative to non-carriers; thus, when the threshold for impairment was set to include milder forms of impairment there appeared to be no increased risk for impairment among APOE ε4 proxy carriers in either group. To examine the relationship between APOE ε4 proxy carrier status and different levels of impairment severity more directly, rates of mild-to-moderate and moderate-to-severe impairment were separately compared in the APOE ε4 proxy carrier versus ε4 proxy non-carrier groups. There was no difference in the rate of milder impairment as a function of APOE
ε4 proxy carrier status in either group, but when the definition of impairment was restricted to moderate-to-severe impairment (excluding those with milder impairment), APOE ε4 proxy carriers showed a significantly higher prevalence of impairment relative to ε4 non-carriers in the Caucasian group (again, no APOE ε4 proxy carrier effect was observed in the African American group). Importantly, the risk for being classified as moderately-severely impaired was 4.9 times higher among APOE ε4 proxy carriers relative to ε4 proxy non-carriers. These findings are consistent with prior studies that have demonstrated greater risk for HAD among APOE ε4 carriers (Corder et al., 1998; Valcour et al., 2004) because they demonstrate APOE ε4 proxy-related risk for moderate-severe impairment, which is commensurate with the level of impairment required for HAD (Antinori et al., 2007) but does not take into account functional decline. It is notable that an APOE ε4-proxy effect on risk for moderate-severe impairment was detected in the Caucasian group even without consideration of functional status, which raises the possibility that if a higher number of individuals meeting full HAD criteria had been included in the present sample an even stronger APOE ε4 carrier effect may have been observed. However, contrary to the findings demonstrated by Valcour and colleagues, the APOE ε4 proxy effect on risk for moderate-severe impairment was present in the younger but not older HIV-seropositive individuals, which may be partly explained by examination of domain-level findings as described below.

These findings support the conclusion that an association between APOE ε4 proxy carrier status and HIV-associated neurocognitive impairment exists in the Caucasian group but only at the level of moderate-severe neurocognitive impairment, such as that seen in HAD. Several measures were taken to ensure that a potential APOE ε4 proxy carrier status effect, if present, was not obscured, including use of demographically-adjusted normative standards in determining the global ratings by which the outcomes were defined, and consideration of the potential role of factors known to affect cognition, such as age, disease severity, and comorbid psychiatric conditions. By the use of this approach, it is not likely that an existing effect was masked by inadequate consideration of these factors. Nevertheless, it is important to note the
recent demonstration of a significantly higher rate of neurocognitive impairment among APOE ε4 carriers relative to non-carriers in China, given that the threshold for impairment utilized by the study included milder forms of impairment (Spector et al., 2010). It is not likely that differences in HIV treatment account for the findings given that the APOE ε4 effect remained in the Chinese sample following 12 months of antiretroviral treatment. However, there may be other factors that limit the generalizability of these findings to a U.S. sample, such as duration of illness prior to treatment, which may have allowed for greater CNS impact of HIV infection.

Null findings regarding APOE ε4 carrier-related risk for global impairment in African American HIV-seropositive individuals were observed for all levels of HIV-associated neurocognitive impairment, which suggests that a weaker APOE gene-disease relationship may exist in HIV among African Americans relative to Caucasians, similar to that which is observed for AD (Evans et al., 2003; Sahota et al., 1997; Tang et al., 1998). Specifically, a multiple linear regression model examining prediction of global impairment severity in the combined sample of Caucasians and African Americans revealed that despite the inclusion of MDS variables in the models to account for population stratification (i.e., different allele carrier rates based on ancestry that may confound statistical results), the relationship between APOE ε4 carrier status and global impairment rating differed in the Caucasian versus African American groups, as evidenced by a significant proxy carrier status by ethnicity group interaction. Although this finding is inconsistent with some past studies that did not demonstrate a significant APOE ε4 carrier status by ethnicity group interaction (e.g., Blair et al., 2005; Fillenbaum et al., 2001; Jorm et al., 2004), the observed interaction is concordant with previous reports of lower APOE ε4-related risk for AD in African American and Hispanic samples relative to Caucasians (Evans et al., 2003; Tang et al., 1998). Importantly, therefore, the present findings especially highlight the need for investigation of risk factors for HIV-associated neurocognitive impairment at all levels of severity in African Americans. For example, markers of disease severity may be more predictive of neurocognitive impairment in this group (as might be suggested by the relationship between nadir CD4 and global rating in
the African American group, shown in Table 5), which may be related to different genetic profiles, disparities in health care (e.g., access to healthcare, quality of care), or differential response to treatment (e.g., lower efficacy of antiretroviral therapy possibly related to physiological factors or poor adherence).

Although the findings of the present study are limited to demonstration of an APOE ε4 proxy carrier effect on moderate-severe impairment, they are notably inconsistent with the studies that have failed to find an association between APOE genotype and HAD (Burt et al., 2008; Dunlop et al., 1997; Pemberton et al., 2008), and may shed some light on interpretation of their findings. In contrast to these prior studies, age was included in regression analysis a priori (see Pomara et al., 2008; Valcour et al., 2004 for justification), relevant disease, psychiatric, and genetic (i.e., population stratification) cofactors were examined for their potential effect, and a statistical approach for examining APOE ε4 proxy-related risk was used (i.e., investigation of APOE ε4 proxy carrier group differences in impairment prevalence rates and APOE ε4 carrier status as a predictor of impairment). In these prior studies with null findings, age and/or ethnicity were not explicitly modeled into their analyses (i.e., Burt et al., 2008; Dunlop et al., 1997; Pemberton et al., 2008). Additionally, choice of statistical approach may have influenced the findings in these studies, such as inclusion of only correlational analyses without stratification (Dunlop et al., 1997; Pemberton et al., 2008) and examination of APOE ε4-modulated rate of progression to HAD (Burt et al., 2008). Carrier status is not consistently associated with rate of progression to AD either, despite the fact that it is an established risk factor for development of AD (i.e., APOE ε4 carrier status may increase risk for moderate-severe HIV-associated neurocognitive impairment but not hasten progression to impaired status). The results of the present study, combination with prior reports (e.g., Valcour et al., 2004), suggest that the potential effects of ethnicity and age should be methodologically and/or statistically addressed (e.g., evaluation of interactions, stratification of study sample) in order to investigate an association between APOE ε4-carrier status and neurocognitive impairment in HIV.
**APOE ε4-Effect on Pattern of HIV-associated Neurocognitive Impairment**

Investigation of the APOE ε4 proxy carrier effect on specific cognitive domains may enhance the interpretation of findings at the global level of HIV-associated impairment and allow for comparison to domain-specific APOE ε4 effects observed in some uninfected populations (e.g., normal aging), which are typically observed for episodic memory and executive functioning (Small et al., 2004). Increased APOE ε4 proxy-related risk for memory and motor domain impairment was observed in our Caucasian group, but no effect of APOE ε4 proxy carrier status was observed for any other domain. Interestingly, the memory and motor domains have been demonstrated to be the most sensitive to HIV infection as demonstrated in a study by Carey and colleagues (2004b) which showed that measures of memory (i.e., HVLT-R) and motor (i.e., Grooved Pegboard test) functioning demonstrated high degrees of sensitivity and specificity in classifying HIV-associated neurocognitive impairment.

For the memory domain in the Caucasian group, a significant main effect of APOE ε4 proxy carrier status in predicting memory impairment (defined as an impairment cutpoint based on the continuous memory rating) was revealed, and carrying an APOE ε4 proxy allele was shown to be associated with an approximately threefold increase in the likelihood of having memory impairment in HIV. Demonstration of an APOE ε4 proxy carrier effect in the memory domain is consistent with a wealth of literature suggesting the memory is particularly susceptible to impairment among APOE ε4 carriers across diseases (Small et al., 2004). Furthermore, there is evidence to suggest that memory may be affected by APOE ε4 carrier status outside of the context of frank dementia, demonstrated in preclinical and/or MCI samples (e.g., Bondi et al., 1995; Linn et al., 1995), and even in individuals who do not meet criteria for a cognitive disorder diagnosis (Anstey & Christensen, 2000). The present study is the first to present evidence suggesting specific APOE ε4-related memory domain impairment in HIV. Memory domain results in the current study also demonstrated a significant main effect of age whereby higher age was associated with greater impairment, but there was not a significant interaction of these factors. Taken together, the memory domain findings suggest
that APOE ε4 carriers show increased memory impairment relative to ε4 proxy non-carriers across age. That is, although APOE ε4 proxy carriers are more likely to demonstrate memory impairment (as evidenced by the odds ratio of 3.27), there is no evidence to suggest that carrying an APOE ε4 proxy is associated with disproportionately greater risk for memory impairment as HIV-infected individuals age. The lack of an APOE ε4 carrier status interaction with age is notable given that the effect of carrying an APOE ε4 allele on risk for memory impairment and neurocognitive disorders (e.g., MCI, dementia), has typically been demonstrated in individuals of advanced age outside of the context of HIV (i.e., middle-aged or older), and Valcour and colleagues (2004) showed increased risk for HAD among older HIV-seropositive APOE ε4 proxy carriers only.

For the motor domain, the regression model conducted in the Caucasian group demonstrated no significant main effects of either APOE ε4 proxy carrier status or age, but a significant interaction of APOE ε4 proxy carrier status by age was observed. Follow-up examination of group differences in the rate of motor impairment by APOE ε4 proxy carrier status in younger and older groups revealed that a significantly greater proportion of the younger APOE ε4 proxy carriers evidenced motor impairment relative to non-carriers, and motor impairment was demonstrated to be 3.89 times more likely among the younger APOE ε4 proxy carriers relative to ε4 non-carriers. By contrast, in the older group no such ε4 proxy carrier status effect on motor function was seen. The observation of an APOE ε4 proxy carrier effect on motor impairment at younger but not older ages was unexpected given that carrying an APOE ε4 allele has typically been demonstrated to relate to increased risk of neurocognitive disorders in advanced age (i.e., middle-aged and older), and Valcour and colleagues (2004) did not observe an APOE ε4 effect on HAD in the younger age-stratified sample. However, it is noted that the present study is the first to report findings regarding the APOE ε4-effect specifically on motor domain impairment, and therefore an attempt should be made to replicate these results. Post-hoc analyses investigating possible confounding factors
(e.g., higher rates of lifetime methamphetamine and cocaine dependence in the younger HIV-seropositive individuals) failed to account for the findings.

Although not directly examined, consideration of the apparent differential expression of APOE ε4 proxy-related risk for HIV-associated neurocognitive impairment in younger and older individuals may provide insight into the underlying APOE ε4-modulated mechanism of neuropathology in HIV that then manifests as impaired neurocognitive performance. Based on the fact that carrying an APOE ε4 proxy allele does not appear to pose a differential level of risk for presence of memory impairment in older individuals compared to younger (i.e., absence of age by APOE ε4 proxy carrier status interaction), this study does not provide evidence to support the expected increase in APOE ε4-related risk for memory impairment in APOE ε4 carriers relative to non-carriers as they age. Notably, a differential expression of APOE ε4-related risk for motor impairment was observed in the younger and older age groups in which motor performance was most affected in younger APOE ε4 proxy carriers relative to non-carriers in the present study. In combination, these age-related findings could suggest that APOE ε4 carrier status may indeed modulate host response to HIV infection in the CNS through the pathway of ineffective neuronal maintenance and repair in the context of neuroinflammation, oxidative damage, and excitotoxicity resulting from infection rather than through AD-like neuropathology (e.g., amyloid accumulation) which would be expected to exert disproportionate effects on HAND in older age (see Brew et al., 2009). Although speculative, possible explanations for the age by APOE ε4 carrier status interaction observed in the motor domain and at the global level (i.e., prediction of global rating) include increased effects on motor functioning during early/acute infection (i.e., possible APOE ε4-modulated preferential impact of HIV infection on the neural pathway involved in motor functioning during early infection), and possible differential expression of antagonistic pleiotropy. That is, APOE ε4 carrier status is known to have different relationships to disease outcomes across the lifespan; for example, with regard to AD it has been reported that carrying an APOE ε4 allele may be beneficial earlier in life but then presents a risk factor for poor cognitive outcomes.
during a period lasting from middle-age to older adulthood, and in very advanced age it presents no greater risk than any other APOE allele (e.g., Alexander, 2007).

The expression of APOE ε4 carrier status across age has not been directly explored in HIV in a longitudinal study, and the results of the current study suggest that such an investigation may reveal additional insights into the role of APOE ε4 in risk for neurocognitive impairment in HIV. It is possible that APOE ε4 may predispose HIV-seropositive individuals to motor impairment at a younger age, and may not relate to significant risk for motor impairment at older ages, whereas this shift in the age period in which HIV-infected individuals are at risk for motor impairment does not appear to occur in APOE ε4 proxy non-carriers, whose risk for motor impairment increased as age increased. However, the current findings are preliminary and based on the fact that this finding was unexpected and the current study used a cross-sectional study, these results must be replicated before conclusions regarding expression of the APOE ε4-related risk for HIV-associated neurocognitive impairment across time can be made.

The third study hypothesis stated that the relationship between neurocognitive impairment and daily functioning outcomes such as increased cognitive complaints and risk or IADL dependence might differ as a function of APOE ε4 proxy carrier status. In predicting cognitive complaints, only current MDD was significantly associated with the total number of reported complaints such that individuals with current MDD had higher levels of complaints. APOE ε4 proxy carrier status did not modulate the relationship between neurocognitive performance and complaints. Based on the findings of the current study, a relationship between APOE ε4 proxy carrier status and IADL dependence was expected to be observed in the Caucasians given that carrying an APOE ε4 proxy allele was significantly associated with moderate-severe impairment, which may put individuals at increased risk for disruption of daily functioning. However, no interaction between the continuous global rating (representing the full range of neurocognitive performance) and APOE ε4 proxy carrier status was observed in predicting IADL dependence. Given the demonstration of an APOE ε4-associated effect on
moderate-severe neurocognitive impairment among Caucasians, it is surprising that no significant difference in risk for IADL dependence was observed between APOE ε4 carriers and non-carriers. Given the cross-sectional design of the study, is it not known whether carrying an APOE ε4 proxy allele is associated with risk of becoming IADL dependent in the future, which may be plausible given that carrying an APOE ε4 proxy allele was related to higher risk for greater severity of impairment (i.e., moderate-severe impairment) and may influence progression to a level of impairment which disrupts daily functioning. Additional considerations include the fact that IADL performance was assessed using a self-report measure (i.e., modified from Lawton & Brody, 1969), which may contribute to the observed null findings. Notably, there is a demonstrated link between current depression and response style on self-report measures, and it is therefore possible that similar patterns of responding on the self-report IADL questionnaire among those diagnosed with current MDD in both groups masked an existing APOE ε4 effect. Future examination of the APOE ε4 proxy carrier status effect on functional outcomes should be conducted with measures that are less susceptible to current mood, such as collateral report and performance-based laboratory measures of everyday functioning, on which a significant effect of HAND has previously been demonstrated (e.g., Heaton et al., 2004).

**Limitations of the Present Study and Suggestions for Future Directions**

The present study has several limitations. Although the combined sample size is quite large, stratification based on ethnicity resulted in more modest sample sizes for the proposed analyses. The study was powered to detect medium effect sizes, but some of the effects observed were subtle, and if additional small effects were present they may not have been detected due to inadequate power. However, the samples are not notably smaller than those represented in published reports in which an APOE ε4 carrier effect was previously demonstrated in HIV. The most critical limitation in the current study was the use of the APOE ε4 proxy instead of actual APOE variant information to classify ε4 carriers versus non-carriers. The study used a SNP in high LD with APOE, which can indirectly provide information about
APOE genotype given that alleles of the proxy SNP are likely to be inherited with APOE alleles in a predictable pattern, but this approach does not provide direct information about APOE genotype. The use of the proxy may, in part, account for the fact that some hypothesized effects were not observed. However, there is a precedent for demonstrating an association between the APOE ε4 proxy SNP and AD (Coon et al., 2007), which suggests that the findings observed with the APOE ε4 proxy may represent the same pattern as would be observed with the APOE variants, but this cannot be known for certain. Furthermore, the use of the APOE ε4 proxy SNP does not provide important details regarding all APOE genotypes. Therefore only analyses investigating hypothesized effects between ε4 proxy carriers and non-carriers can be evaluated and dose-dependent relationships with outcomes (e.g., ε4/ε4 homozygous effects), which may demonstrate stronger effects, could not be evaluated.

Importantly, the cross-sectional design of the study did not allow for examination of APOE ε4 proxy carrier effects on longitudinal outcomes such as a relationship with neurocognitive decline, rate of progression to HIV-associated neurocognitive impairment, and risk for future IADL decline. Although the present study examined many cofactors in order to account for their potential influence, such as demographic factors (e.g., age), disease characteristics (e.g., HAART treatment status, nadir CD4 count, estimated duration of infection, AIDS diagnosis), and psychiatric factors (e.g., MDD and substance use disorder diagnosis), there are many other variables that may warrant consideration, such as cardiovascular risk factors (e.g., hypertension, diabetes mellitus), markers of cerebrovascular disease, effectiveness of antiretroviral CNS penetration, other genetic risk factors (e.g., monocyte gene expression; Sun et al., 2010), and potential unmeasured gene-environment interactions. Furthermore, the current study did not include biomarker or imaging data, which would allow for more direct examination of the potential APOE ε4-related manifestations of HIV-associated neurocognitive impairment. Regarding generalizability and relevance to the HI-infected population, the current findings as presented suggest that APOE ε4 carrier status
may be a risk factor for HIV-associate neurocognitive impairment in Caucasians only, and little evidence regarding risk factors for non-Caucasians is provided.

Based on the findings and limitations of the present study, several recommendations for future directions are offered. Of primary importance, the study should be replicated with actual APOE variant information in order evaluate the hypotheses of the study and determine APOE ε4-related risk in the present sample of otherwise well-characterized HIV-seropositive individuals. Importantly, availability of APOE variants would allow for examination of APOE ε4 dose-dependent relationships, which may demonstrate a stronger effect on HIV-associated neurocognitive impairment. Another suggestion for future study is examination of APOE ε4 carrier status as a predictor of neurocognitive decline, which has been investigated in terms of APOE ε4-related rate of progression to HAD in a single study with null findings (Burt et al., 2008). Additionally, examination of relationships between APOE ε4-related effects on cognitive outcomes and biomarkers of neuropathology may serve to further elucidate the role of APOE ε4 in the neuropathological processes underlying HIV-associated neurocognitive impairment. Specifically, recent evidence has suggested that an established neuroAIDS marker of macrophage activation (i.e., macrophage chemoattractant protein-1 or MCP-1) predicted global HIV-associated neurocognitive impairment whereas traditional cortical dementia markers (e.g., CSF beta amyloid and tau) did not (Morgan et al., 2010). Combined examination of genetic, neurocognitive, and/or biomarker data within a single study may help to delineate the mechanism of APOE ε4-related risk for impairment in HIV, as well as provide evidence regarding the clinical utility of these biomarkers in identifying HAND and/or those at risk for HAND. Several neuroimaging techniques may be useful in characterizing APOE ε4-modulated neuropathogenesis in HIV that may relate to neurocognitive impairment. For example, examination of white matter integrity with diffusion tensor imaging may be informative given the preferential impact of HIV on subcortical white matter pathways (Gongvatana et al., 2007) and evidence supporting an APOE ε4 effect on myelin breakdown (Barkzokis et al, 2007), and PET studies may help to determine whether APOE ε4-related
neuropathological effects are associated with the decrease in dopaminergic transporter availability in the basal ganglia that has been demonstrated in HIV (Wang et al., 2004), especially given the present motor domain findings. Consideration of other important cofactors such as cardiovascular risk factors, markers of cerebrovascular disease, and effects of ARV regimens (e.g., CNS penetration) may also help to clarify the nature of the relationship between APOE ε4 carrier status and neurocognitive impairment in HIV, given that it is most likely a complex relationship which is influenced by a number of host and environmental factors. The intriguing memory and motor domain findings could provide the basis for examination of hypothesized APOE ε4-related effects on component processes and types of domain functioning. Specifically, it would be interesting to examine whether APOE ε4 carrier status is more related to the prototypical memory profile observed in HIV, which reveals deficient executive control of encoding and retrieval consistent with the preferential impact of HIV on prefrontostriatal circuitry (Woods et al., 2005), versus a pattern that would be more consistent with a cortical profile (e.g., poor recall and recognition performance, suggestive of impaired memory storage) that would be similar to that observed in AD. Such analyses would be particularly interesting in a sample including older HIV-seropositive adults in order to examine the potential influence that APOE ε4 carrier status has on expression of HIV-associated neurocognitive impairment in aging with the virus because increased risk for developing and AD-like process with advancing age in HIV has been proposed but not yet firmly established (e.g., Brew et al., 2009). Furthermore, the effect of carrying an APOE ε4 allele and HIV infection separately demonstrate an effect on prospective memory (e.g., Driscoll et al., 2005 and Carey et al., 2006, respectively), a cognitive construct representing “remembering to remember,” but no studies to date have examined the potential APOE ε4-related effect on prospective memory in an HIV population. Based on the APOE ε4 signal detected in the motor domain, further characterization of differences in motor functioning related to APOE ε4 carrier status may be examined through more thorough characterization of
the components of motor functioning, electrophysiologic, radiologic, and/or metabolic studies (see Berger & Arendt, 2000).

Conclusions and Implications of the Present Study

Host genetics are believed to have a role in predisposing individuals to neurocognitive impairment, and the present study provides evidence that presence of the APOE ε4 allele may be a risk factor for developing moderate-severe HIV-associated neurocognitive impairment in Caucasians, findings which support previous reports of APOE ε4-related increased risk for HAD (Corder et al., 1998; Valcour et al., 2004). Interestingly, there is tentative evidence to suggest that an APOE ε4-related risk for moderate-to-severe impairment exists in younger but perhaps not older HIV-seropositive adults, contrary to prior demonstration of APOE ε4-related risk for HAD in older adults. The hypothesized relationship between APOE ε4 and risk for milder forms of HIV-associated neurocognitive impairment, which are increasingly common in the post-HAART era, was not demonstrated in the present study in Caucasians or non-Caucasians. Furthermore, domain-level analyses in the Caucasian group suggest that carrying an APOE ε4 proxy allele confers risk for memory impairment across the span of adulthood, and may be related to motor impairment in younger HIV-seropositive individuals but not in those middle-aged or older. Notably, the memory and motor domains have been shown to be the most sensitive to the effect of HIV on neuropsychological performance, and therefore demonstration of an APOE ε4 proxy effect in these domains may suggest that presence of APOE ε4 modulates CNS response to HIV infection in Caucasians, possibly related to ineffective repair and maintenance of neurons in response to neuropathological processes of HIV. In terms of daily functioning, individuals with current MDD had higher level of cognitive complaints, but no interaction of APOE ε4 proxy carrier status with global cognitive rating was observed in predicting cognitive complaints or IADL dependence. Importantly, the results of the present study are based on a proxy APOE SNP and may not adequately reflect the actual relationship between APOE genotype and HIV-associated neurocognitive impairment, and replication of the study with the actual APOE variant is
recommended. Identification of individuals at risk for HIV-associated neurocognitive impairment remains an important endeavor given that up to half of all HIV-seropositive individuals develop impairment despite treatment advances, and host genetics have represented a promising avenue for identification of those at risk. With clear demonstration of APOE ε4 as a risk factor for HAND, APOE genotype could be included among a set of clinical information utilized in identifying HAND as in the case of AD. However, the present findings suggest that the clinical utility of APOE genotype may be limited to Caucasians, and identification of risk for the highly prevalent milder forms of HIV-associated neurocognitive impairment may not be enhanced for African Americans by consideration of presence versus absence of APOE ε4. Nevertheless, although the findings of the present study are limited, the detection of a potential APOE ε4 effect in classifying HIV-associated neurocognitive impairment, even with a proxy SNP, suggests that future study of the relationship between APOE genotype and HAND is warranted.
Table 1

Demographic, Disease, and Psychiatric Characteristics of the Full Sample

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total Sample (N = 276)</th>
<th>Proxy Carrier (n = 97)</th>
<th>Proxy Noncarrier (n = 179)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>43 (8.4)</td>
<td>43.4 (8.1)</td>
<td>42.8 (8.6)</td>
<td>0.56</td>
</tr>
<tr>
<td>Age Groups:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 50 y.o.</td>
<td>56 (20.3%)</td>
<td>20 (20.6%)</td>
<td>36 (20.1%)</td>
<td>0.49</td>
</tr>
<tr>
<td>&lt; 50 y.o.</td>
<td>220 (79.7%)</td>
<td>77 (79.4%)</td>
<td>143 (79.9%)</td>
<td></td>
</tr>
<tr>
<td>Education</td>
<td>13.2 (2.5)</td>
<td>13.1 (2.4)</td>
<td>13.2 (2.5)</td>
<td>0.72</td>
</tr>
<tr>
<td>Sex (% Male)</td>
<td>220 (79.7%)</td>
<td>81 (83.5%)</td>
<td>139 (77.7%)</td>
<td>0.24</td>
</tr>
<tr>
<td>Ethnicity:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>141 (51.1%)</td>
<td>46 (47.4%)</td>
<td>95 (53.1%)</td>
<td>0.37</td>
</tr>
<tr>
<td>African American</td>
<td>135 (48.9%)</td>
<td>51 (52.6%)</td>
<td>84 (46.9%)</td>
<td></td>
</tr>
<tr>
<td>WRAT-3 Score</td>
<td>96.3 (13.7)</td>
<td>95.1 (14.3)</td>
<td>96.8 (13.3)</td>
<td>0.29</td>
</tr>
<tr>
<td><strong>Disease Characteristics</strong></td>
<td></td>
<td></td>
<td></td>
<td>0.21</td>
</tr>
<tr>
<td>ARV Status:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HAART</td>
<td>186 (67.4%)</td>
<td>70 (72.2%)</td>
<td>116 (64.8%)</td>
<td></td>
</tr>
<tr>
<td>Non-HAART</td>
<td>90 (32.6%)</td>
<td>27 (27.8%)</td>
<td>63 (35.2%)</td>
<td></td>
</tr>
<tr>
<td>ARV Naïve</td>
<td>43 (15.6%)</td>
<td>14 (14.4%)</td>
<td>29 (16.2%)</td>
<td></td>
</tr>
<tr>
<td>No ARV</td>
<td>36 (13%)</td>
<td>12 (12.4%)</td>
<td>24 (13.4%)</td>
<td></td>
</tr>
<tr>
<td>Non-HAART</td>
<td>11 (4%)</td>
<td>1 (1%)</td>
<td>10 (5.6%)</td>
<td></td>
</tr>
<tr>
<td>AIDS Diagnosis (%AIDS)</td>
<td>158 (57.5%)</td>
<td>57 (58.8%)</td>
<td>101 (56.7%)</td>
<td>0.75</td>
</tr>
<tr>
<td>Nadir CD4 &lt; 50</td>
<td>57 (20.8%)</td>
<td>21 (21.7%)</td>
<td>36 (20.3%)</td>
<td>0.8</td>
</tr>
<tr>
<td>HIV CSF Viral Load (% Detectable)</td>
<td>83 (34.4%)</td>
<td>29 (34.9%)</td>
<td>54 (34.2%)</td>
<td>0.91</td>
</tr>
<tr>
<td>HIV Plasma Viral Load (% Detectable)</td>
<td>154 (56.2%)</td>
<td>52 (54.7%)</td>
<td>102 (57%)</td>
<td>0.72</td>
</tr>
<tr>
<td>HCV Co-infection (% positive)</td>
<td>57 (21%)</td>
<td>26 (27.4%)</td>
<td>31 (17.4%)</td>
<td>0.06</td>
</tr>
</tbody>
</table>
Table 1 continued

Demographic, Disease, and Psychiatric Characteristics of the Full Sample

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total Sample (N = 276)</th>
<th>Proxy Carrier (n = 97)</th>
<th>Proxy Noncarrier (n = 179)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Psychiatric Characteristics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current MDD</td>
<td>34 (12.3%)</td>
<td>7 (7.2%)</td>
<td>27 (15.1%)</td>
<td>0.08</td>
</tr>
<tr>
<td>LT MDD</td>
<td>134 (48.6%)</td>
<td>40 (41.2%)</td>
<td>94 (52.5%)</td>
<td>0.08</td>
</tr>
<tr>
<td>LT Alcohol Dependence</td>
<td>88 (31.9%)</td>
<td>33 (34%)</td>
<td>55 (30.7%)</td>
<td>0.58</td>
</tr>
<tr>
<td>LT Cannabis Dependence</td>
<td>28 (10.1%)</td>
<td>12 (12.4%)</td>
<td>16 (8.9%)</td>
<td>0.4</td>
</tr>
<tr>
<td>LT Cocaine Dependence</td>
<td>87 (31.5%)</td>
<td>34 (35.1%)</td>
<td>53 (29.6%)</td>
<td>0.35</td>
</tr>
<tr>
<td>LT Methamphetamine Dependence</td>
<td>34 (12.3%)</td>
<td>11 (11.3%)</td>
<td>23 (12.8%)</td>
<td>0.71</td>
</tr>
<tr>
<td>LT Hallucinogen Dependence</td>
<td>3 (1.1%)</td>
<td>1 (1.1%)</td>
<td>2 (1.1%)</td>
<td>0.95</td>
</tr>
<tr>
<td>LT Inhalant Dependence</td>
<td>1 (0.4%)</td>
<td>1 (1%)</td>
<td>0 (0%)</td>
<td>0.35</td>
</tr>
<tr>
<td>LT Opioid Dependence</td>
<td>31 (11.2%)</td>
<td>17 (17.5%)</td>
<td>14 (7.8%)</td>
<td>0.03</td>
</tr>
<tr>
<td>LT PCP Dependence</td>
<td>5 (1.8%)</td>
<td>1 (1%)</td>
<td>4 (2.2%)</td>
<td>0.66</td>
</tr>
<tr>
<td>LT Sedative Dependence</td>
<td>6 (2.2%)</td>
<td>3 (3.1%)</td>
<td>3 (1.7%)</td>
<td>0.43</td>
</tr>
<tr>
<td><strong>Daily Functioning Characteristics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IADL Dependent (%)</td>
<td>40 (15.7%)</td>
<td>13 (14.9%)</td>
<td>27 (16.1%)</td>
<td>0.86</td>
</tr>
<tr>
<td>Cognitive Complaints (Mdn, IQR)</td>
<td>2 (0, 6)</td>
<td>2 (0, 7)</td>
<td>3 (1, 6)</td>
<td>0.3</td>
</tr>
</tbody>
</table>

Note. p-values were based on group differences between APOE ε4 proxy carrier groups tests including chi-square, Fisher’s Exact Test, and t-tests; ARV = antiretroviral; HAART = highly active antiretroviral therapy; LT = lifetime; MDD = Major Depressive Disorder; IADL = instrumental activities of daily living; Mdn = median; IQR = interquartile range
Table 2

*Predictors of Severity of Global Impairment in the Full Sample*

<table>
<thead>
<tr>
<th>Predictors</th>
<th>F ratio</th>
<th>p</th>
<th>R²</th>
<th>b</th>
<th>t-ratio</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model $(df = 4, 271)$</td>
<td>3.65</td>
<td>0.007</td>
<td>0.05</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proxy Carrier Status [Carrier]</td>
<td>0.11</td>
<td>1.30</td>
<td>0.2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>0.08</td>
<td>2.48</td>
<td>0.01</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ethnicity Group [AA]</td>
<td>-0.02</td>
<td>-0.26</td>
<td>0.8</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ethnicity [AA]*Proxy Carrier Status [Carrier]</td>
<td>-0.22</td>
<td>-2.7</td>
<td>0.007</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Note. Multidimensional scaling factors for correction of population stratification included in the model
Table 3

Demographic, Disease, and Psychiatric Characteristics of the Caucasian Group

<table>
<thead>
<tr>
<th>Variable</th>
<th>Caucasian Group (n = 141)</th>
<th>Proxy Carrier (n = 46)</th>
<th>Proxy Noncarrier (n = 95)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>43.3 (9.3)</td>
<td>42.7 (8.6)</td>
<td>43.5 (9.7)</td>
<td>0.64</td>
</tr>
<tr>
<td>Age Groups:</td>
<td></td>
<td></td>
<td></td>
<td>0.65</td>
</tr>
<tr>
<td>≥ 50 y.o.</td>
<td>34 (24.1%)</td>
<td>10 (21.7%)</td>
<td>24 (25.3%)</td>
<td></td>
</tr>
<tr>
<td>&lt; 50 y.o.</td>
<td>107 (75.9%)</td>
<td>36 (78.3%)</td>
<td>71 (74.7%)</td>
<td></td>
</tr>
<tr>
<td>Education</td>
<td>13.7 (2.4)</td>
<td>13.7 (2.8)</td>
<td>13.8 (2.3)</td>
<td>0.77</td>
</tr>
<tr>
<td>Sex (% Male)</td>
<td>123 (87.2%)</td>
<td>41 (89.1%)</td>
<td>82 (86.3%)</td>
<td>0.64</td>
</tr>
<tr>
<td>WRAT-3 Score</td>
<td>103.4 (10.3)</td>
<td>103.6 (9.5)</td>
<td>103.3 (10.6)</td>
<td>0.89</td>
</tr>
<tr>
<td><strong>Disease Characteristics</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>ARV Status:</td>
<td></td>
<td></td>
<td></td>
<td>0.63</td>
</tr>
<tr>
<td>HAART</td>
<td>88 (62.4%)</td>
<td>30 (65.2%)</td>
<td>58 (61.2%)</td>
<td></td>
</tr>
<tr>
<td>Non-HAART</td>
<td>53 (37.6%)</td>
<td>16 (34.8%)</td>
<td>37 (39.0%)</td>
<td></td>
</tr>
<tr>
<td>ARV Naïve</td>
<td>25 (47.2%)</td>
<td>8 (50%)</td>
<td>17 (45.9%)</td>
<td></td>
</tr>
<tr>
<td>No ARV</td>
<td>20 (37.7%)</td>
<td>7 (43.8%)</td>
<td>13 (35.1%)</td>
<td></td>
</tr>
<tr>
<td>Non-HAART</td>
<td>8 (15.1%)</td>
<td>1 (6.3%)</td>
<td>7 (18.9%)</td>
<td></td>
</tr>
<tr>
<td>AIDS Diagnosis (%AIDS)</td>
<td>73 (51.8%)</td>
<td>23 (50%)</td>
<td>50 (52.6%)</td>
<td>0.77</td>
</tr>
<tr>
<td>Nadir CD4 &lt; 50</td>
<td>21 (14.9%)</td>
<td>8 (17.4%)</td>
<td>13 (13.7%)</td>
<td>0.56</td>
</tr>
<tr>
<td>HIV CSF Viral Load (% Detectable)</td>
<td>39 (32%)</td>
<td>15 (37.5%)</td>
<td>24 (29.3%)</td>
<td>0.36</td>
</tr>
<tr>
<td>HIV Plasma Viral Load (% Detectable)</td>
<td>75 (53.6%)</td>
<td>23 (51.1%)</td>
<td>52 (54.7%)</td>
<td>0.69</td>
</tr>
<tr>
<td>HCV Co-infection (% positive)</td>
<td>17 (12.1%)</td>
<td>5 (10.9%)</td>
<td>12 (12.8%)</td>
<td>0.74</td>
</tr>
<tr>
<td><strong>Psychiatric Characteristics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current MDD</td>
<td>19 (13.5%)</td>
<td>3 (6.5%)</td>
<td>16 (16.8%)</td>
<td>0.12</td>
</tr>
<tr>
<td>LT MDD</td>
<td>81 (57.4%)</td>
<td>22 (47%)</td>
<td>59 (62.1%)</td>
<td>0.11</td>
</tr>
<tr>
<td>LT Alcohol Dependence</td>
<td>43 (30.5%)</td>
<td>17 (40%)</td>
<td>26 (27.4%)</td>
<td>0.25</td>
</tr>
<tr>
<td>LT Cannabis Dependence</td>
<td>12 (8.5%)</td>
<td>5 (10.9%)</td>
<td>7 (7.4%)</td>
<td>0.53</td>
</tr>
<tr>
<td>LT Cocaine Dependence</td>
<td>20 (14.2%)</td>
<td>7 (15.2%)</td>
<td>13 (13.7%)</td>
<td>0.81</td>
</tr>
<tr>
<td>LT Methamphetamine Dependence</td>
<td>29 (20.6%)</td>
<td>9 (19.6%)</td>
<td>20 (21.1%)</td>
<td>0.84</td>
</tr>
</tbody>
</table>
Table 3 continued

**Demographic, Disease, and Psychiatric Characteristics of the Caucasian Group**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Caucasian Group (n = 141)</th>
<th>Proxy Carrier (n = 46)</th>
<th>Proxy Noncarrier (n = 95)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>LT Hallucinogen Dependence</td>
<td>3 (2.1%)</td>
<td>1 (2.2%)</td>
<td>2 (2.1%)</td>
<td>1.0</td>
</tr>
<tr>
<td>LT Inhalant Dependence</td>
<td>1 (0.7%)</td>
<td>1 (2.2%)</td>
<td>0</td>
<td>0.33</td>
</tr>
<tr>
<td>LT Opioid Dependence</td>
<td>9 (6.4%)</td>
<td>5 (10.9%)</td>
<td>4 (4.2%)</td>
<td>0.15</td>
</tr>
<tr>
<td>LT PCP Dependence</td>
<td>3 (2.1%)</td>
<td>1 (2.2%)</td>
<td>2 (2.1%)</td>
<td>1.0</td>
</tr>
<tr>
<td>LT Sedative Dependence</td>
<td>2 (1.4%)</td>
<td>2 (4.4%)</td>
<td>0</td>
<td>0.1</td>
</tr>
</tbody>
</table>

**Daily Functioning Characteristics**

<table>
<thead>
<tr>
<th></th>
<th>Caucasian Group (n = 141)</th>
<th>Proxy Carrier (n = 46)</th>
<th>Proxy Noncarrier (n = 95)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IADL Dependent (%)</td>
<td>24 (18.6%)</td>
<td>7 (18%)</td>
<td>17 (18.9%)</td>
</tr>
<tr>
<td>Cognitive Complaints (Mdn, IQR)</td>
<td>3 (0, 6)</td>
<td>3 (0, 9)</td>
<td>3 (0, 5)</td>
</tr>
</tbody>
</table>

Note. *p*-values were based on group differences between APOE ε4 proxy carrier groups tests including chi-square, Fisher’s Exact Test, and t-tests; ARV = antiretroviral; HAART = highly active antiretroviral therapy; LT = lifetime; MDD = Major Depressive Disorder; IADL = instrumental activities of daily living; Mdn = median; IQR = interquartile range
Table 4

Demographic, Disease, and Psychiatric Characteristics of the African American Group

<table>
<thead>
<tr>
<th>Variable</th>
<th>Non-Caucasian Group (n=135)</th>
<th>Proxy Carrier (n=51)</th>
<th>Proxy Noncarrier (n=84)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>42.8 (7.4)</td>
<td>44 (7.61)</td>
<td>42 (7.13)</td>
<td>0.12</td>
</tr>
<tr>
<td>Age Groups:</td>
<td></td>
<td></td>
<td></td>
<td>0.42</td>
</tr>
<tr>
<td>≥ 50 y.o.</td>
<td>22 (16.3%)</td>
<td>10 (19.6%)</td>
<td>12 (14.3%)</td>
<td></td>
</tr>
<tr>
<td>&lt; 50 y.o.</td>
<td>113 (83.7%)</td>
<td>41(80.4%)</td>
<td>72 (85.7%)</td>
<td></td>
</tr>
<tr>
<td>Education</td>
<td>12.5 (2.4)</td>
<td>12.5 (1.9)</td>
<td>12.5 (2.6)</td>
<td>0.92</td>
</tr>
<tr>
<td>Sex (% Male)</td>
<td>97 (71.9%)</td>
<td>40 (78.4%)</td>
<td>57 (67.9%)</td>
<td>0.3</td>
</tr>
<tr>
<td><strong>Disease Characteristics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ARV Status:</td>
<td></td>
<td></td>
<td></td>
<td>0.23</td>
</tr>
<tr>
<td>HAART</td>
<td>98 (72.6%)</td>
<td>40 (78.4%)</td>
<td>58 (69.1%)</td>
<td></td>
</tr>
<tr>
<td>Non-HAART</td>
<td>37 (27.4%)</td>
<td>11 (21.6%)</td>
<td>26 (31%)</td>
<td></td>
</tr>
<tr>
<td>ARV Naïve</td>
<td>18 (13.3%)</td>
<td>6 (11.8%)</td>
<td>12 (14.3%)</td>
<td></td>
</tr>
<tr>
<td>No ARV</td>
<td>16 (11.6%)</td>
<td>5 (9.8%)</td>
<td>11 (13.1%)</td>
<td></td>
</tr>
<tr>
<td>Non-HAART</td>
<td>3 (2.2%)</td>
<td>0</td>
<td>3 (3.6%)</td>
<td></td>
</tr>
<tr>
<td>AIDS Diagnosis (%AIDS)</td>
<td>85 (63.4%)</td>
<td>34 (66.7%)</td>
<td>51 (61.5%)</td>
<td>0.54</td>
</tr>
<tr>
<td>Nadir CD4 &lt; 50</td>
<td>36 (27.1%)</td>
<td>13 (25.5%)</td>
<td>23 (28.1%)</td>
<td>0.75</td>
</tr>
<tr>
<td>HIV CSF Viral Load (% Detectable)</td>
<td>44 (37%)</td>
<td>14 (32.6 %)</td>
<td>30 (39.5%)</td>
<td>0.45</td>
</tr>
<tr>
<td>HIV Plasma Viral Load (% Detectable)</td>
<td>79 (59%)</td>
<td>29 (58%)</td>
<td>50 (59.5%)</td>
<td>0.86</td>
</tr>
<tr>
<td>HCV Co-infection (% positive)</td>
<td>40 (30.1%)</td>
<td>21 (42.9%)</td>
<td>19 (22.6%)</td>
<td>0.02</td>
</tr>
<tr>
<td><strong>Psychiatric Characteristics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current MDD</td>
<td>15 (11.1%)</td>
<td>4 (7.8%)</td>
<td>11 (13.1%)</td>
<td>0.34</td>
</tr>
<tr>
<td>LT MDD</td>
<td>45 (33.3%)</td>
<td>18 (31.4%)</td>
<td>29 (34.5%)</td>
<td>0.71</td>
</tr>
<tr>
<td>LT Alcohol Dependence</td>
<td>56 (33.3%)</td>
<td>18 (30.5%)</td>
<td>38 (34.9%)</td>
<td>0.57</td>
</tr>
<tr>
<td>LT Cannabis Dependence</td>
<td>16 (11.9%)</td>
<td>7 (13.7%)</td>
<td>9 (10.7%)</td>
<td>0.6</td>
</tr>
<tr>
<td>LT Cocaine Dependence</td>
<td>67 (49.6%)</td>
<td>27 (52.9%)</td>
<td>40 (47.6%)</td>
<td>0.55</td>
</tr>
</tbody>
</table>
Table 4 continued

Demographic, Disease, and Psychiatric Characteristics of the African American Group

<table>
<thead>
<tr>
<th>Variable</th>
<th>Non-Caucasian Group (n=168)</th>
<th>Proxy Carrier (n=59)</th>
<th>Proxy Noncarrier (n=109)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>LT Methamphetamine Dependence</td>
<td>5 (3.7%)</td>
<td>2 (3.9%)</td>
<td>3 (3.6%)</td>
<td>1.0</td>
</tr>
<tr>
<td>LT Hallucinogen Dependence</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>NA</td>
</tr>
<tr>
<td>LT Inhalant Dependence</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>NA</td>
</tr>
<tr>
<td>LT Opioid Dependence</td>
<td>22 (16.3%)</td>
<td>12 (23.5%)</td>
<td>10 (11.9%)</td>
<td>0.08</td>
</tr>
<tr>
<td>LT PCP Dependence</td>
<td>2 (1.5%)</td>
<td>0</td>
<td>2 (2.4%)</td>
<td>0.52</td>
</tr>
<tr>
<td>LT Sedative Dependence</td>
<td>4 (3%)</td>
<td>1 (2%)</td>
<td>3 (3.6%)</td>
<td>1.0</td>
</tr>
</tbody>
</table>

Daily Functioning Characteristic

<table>
<thead>
<tr>
<th></th>
<th>Non-Caucasian Group (n=168)</th>
<th>Proxy Carrier (n=59)</th>
<th>Proxy Noncarrier (n=109)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>IADL Dependent (%)</td>
<td>16 (12.7%)</td>
<td>6 (12.5%)</td>
<td>10 (12.8%)</td>
<td>1.0</td>
</tr>
<tr>
<td>Cognitive Complaints (Mdn, IQR)</td>
<td>2 (1, 7)</td>
<td>1 (0, 4)</td>
<td>2 (1, 7)</td>
<td>0.05</td>
</tr>
</tbody>
</table>

Note. p-values were based on group differences between APOE ε4 proxy carrier groups tests including chi-square, Fisher’s Exact Test, and t-tests; ARV = antiretroviral; HAART = highly active antiretroviral therapy; LT = lifetime; MDD = Major Depressive Disorder; IADL = instrumental activities of daily living; Mdn = median; IQR = interquartile range
Table 5

*Predictors of Global Impairment Stratified by Ethnicity*

<table>
<thead>
<tr>
<th>Groups / Models</th>
<th>F-ratio</th>
<th>p</th>
<th>R²</th>
<th>b</th>
<th>t-ratio</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Caucasian</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model (df = 3, 137)</td>
<td>3.84</td>
<td>0.01</td>
<td>0.08</td>
<td>0.31</td>
<td>2.50</td>
<td>0.01</td>
</tr>
<tr>
<td>Proxy Carrier Status</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>0.001</td>
<td>0.08</td>
<td>0.94</td>
<td>0.03</td>
<td>-1.98</td>
<td>0.05</td>
</tr>
<tr>
<td>Age*Proxy Carrier Status [Carrier]</td>
<td>-0.03</td>
<td>-1.98</td>
<td>0.05</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>African American</strong></td>
<td>3.34</td>
<td>0.02</td>
<td>0.07</td>
<td>-0.12</td>
<td>-1.20</td>
<td>0.23</td>
</tr>
<tr>
<td>Proxy Carrier Status</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>0.04</td>
<td>2.60</td>
<td>0.01</td>
<td>0.01</td>
<td>-1.06</td>
<td>0.3</td>
</tr>
<tr>
<td>Age*Proxy Carrier Status [Carrier]</td>
<td>-0.01</td>
<td>-1.06</td>
<td>0.3</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Note: Severity of global impairment measured by global rating; MDS covariates included in non-Caucasian model
<table>
<thead>
<tr>
<th>Groups</th>
<th>Global Impairment</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Normal (%)</td>
<td>Impaired (%)</td>
<td>$X^2$</td>
<td>$p$</td>
<td>OR (95% CI)</td>
</tr>
<tr>
<td>Caucasian</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proxy Carrier</td>
<td>31 (67.4%)</td>
<td>15 (32.6%)</td>
<td>2.61</td>
<td>0.11</td>
<td>1.94 (0.87, 4.29)</td>
</tr>
<tr>
<td>Proxy Non-Carrier</td>
<td>76 (80%)</td>
<td>19 (20%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>African American</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proxy Carrier</td>
<td>41 (80.4%)</td>
<td>10 (19.6%)</td>
<td>0.53</td>
<td>0.47</td>
<td>1.37 (0.58, 3.22)*</td>
</tr>
<tr>
<td>Proxy Non-Carrier</td>
<td>63 (75%)</td>
<td>21 (25%)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Note. OR = Odds ratio, which reflects odds of neurocognitive impairment unless marked by an asterisk, in which case OR reflects the odds of normal cognition; CI = confidence interval

<table>
<thead>
<tr>
<th>Groups</th>
<th>Normal (%)</th>
<th>Mild Imp (%)</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Caucasian</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proxy Carrier</td>
<td>31 (77.5%)</td>
<td>9 (22.5%)</td>
<td>0.48</td>
<td></td>
<td>1.38 (0.55, 3.45)</td>
</tr>
<tr>
<td>Proxy Non-Carrier</td>
<td>76 (82.6%)</td>
<td>16 (17.4%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>African American</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proxy Carrier</td>
<td>41 (80.4%)</td>
<td>12 (19.6%)</td>
<td>1.0</td>
<td></td>
<td>1.1 (0.46, 2.63)*</td>
</tr>
<tr>
<td>Proxy Non-Carrier</td>
<td>63 (78.8%)</td>
<td>17 (21.3%)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Note. *$p$*-values based on Fisher’s Exact Test; Imp = impairment; OR = Odds ratio, which reflects odds of neurocognitive impairment unless marked by an asterisk, in which case OR reflects the odds of normal cognition; CI = confidence interval
Table 8

*Prevalence of Moderate-Severe Global Impairment by APOE ε4 Proxy Carrier Status in Ethnicity Groups*

<table>
<thead>
<tr>
<th>Groups</th>
<th>Normal (%)</th>
<th>Mod-Sev Imp (%)</th>
<th>p</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Caucasian</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proxy Carrier</td>
<td>31 (83.8%)</td>
<td>6 (16.2%)</td>
<td>0.03</td>
<td>4.9 (1.15, 20.85)</td>
</tr>
<tr>
<td>Proxy Non-Carrier</td>
<td>76 (96.2%)</td>
<td>3 (3.8%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>African American</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proxy Carrier</td>
<td>41 (100%)</td>
<td>0</td>
<td>0.3</td>
<td>NA</td>
</tr>
<tr>
<td>Proxy Non-Carrier</td>
<td>63 (94%)</td>
<td>4 (6%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Note. *p*-values based on Fisher’s Exact Test; Mod-Sev Imp = moderate-severe impairment; OR = Odds ratio, which reflects odds of neurocognitive impairment unless marked by an asterisk, in which case OR reflects the odds of normal cognition; CI = confidence interval.
Table 9

Predictors of Domain Impairment in Caucasians

<table>
<thead>
<tr>
<th>Model/Variables</th>
<th>Full Model</th>
<th>Parameter Estimates</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>df</td>
<td>$X^2$</td>
</tr>
<tr>
<td>Memory Domain</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model</td>
<td>3</td>
<td>16.82</td>
</tr>
<tr>
<td>Proxy Carrier Status</td>
<td>-1.21</td>
<td>4.87</td>
</tr>
<tr>
<td>Age</td>
<td>-0.11</td>
<td>8.18</td>
</tr>
<tr>
<td>Age*Proxy Carrier Status [Carrier]</td>
<td>0.02</td>
<td>0.15</td>
</tr>
</tbody>
</table>

| Motor Domain    | 4  | 14.3  | 0.006 | 0.16 |    |           |   |            |
| Model           |    |       |       |      |    |           |   |            |
| Proxy Carrier Status | -0.86 | 3.11 | 0.08 | 2.38 (0.91, 6.25) |
| Age             | -0.38 | 1.52 | 0.22 |
| Age*Proxy Carrier Status [Carrier] | 0.12 | 5.18 | 0.02 |
| Nadir < 50 [No] | -1.64 | 2.4  | 0.12 |

Note: For all other domains the overall model was non-significant; OR = odds ratio; CI = confidence interval.
### Table 10

**Predictors of Total Cognitive Complaints in Caucasians**

<table>
<thead>
<tr>
<th>Groups / Models</th>
<th>F ratio</th>
<th>p</th>
<th>R²</th>
<th>b</th>
<th>t-ratio</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caucasian</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model (df = 4, 124)</td>
<td>9.31</td>
<td>&lt;0.0001</td>
<td>0.22</td>
<td>0.81</td>
<td>1.41</td>
<td>0.16</td>
</tr>
<tr>
<td>Proxy Carrier Status</td>
<td>0.81</td>
<td>1.41</td>
<td>0.16</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current MDD [No]</td>
<td>-4.12</td>
<td>-5.24</td>
<td>&lt;0.0001</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Global Rating</td>
<td>0.45</td>
<td>1.15</td>
<td>0.25</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Global Rating*Proxy Carrier Status</td>
<td>-0.35</td>
<td>-0.88</td>
<td>0.38</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Note: Total cognitive complaints were measured by Patients’ Own Assessment of Functioning (POAFI); MDD = Major Depressive Disorder

### Table 11

**Predictors of IADL Dependence in Caucasians**

<table>
<thead>
<tr>
<th>Model/Variables</th>
<th>df</th>
<th>df</th>
<th>p</th>
<th>R²</th>
<th>B</th>
<th>X²</th>
<th>p</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model</td>
<td>5</td>
<td>10.79</td>
<td>0.06</td>
<td>0.13</td>
<td>0</td>
<td>0</td>
<td>1.0</td>
<td>1.0 (0.32, 3.08)</td>
</tr>
<tr>
<td>Proxy Carrier Status</td>
<td>-0.04</td>
<td>2.03</td>
<td>0.15</td>
<td>1.04 (0.99, 1.1)*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>0.96</td>
<td>2.22</td>
<td>0.14</td>
<td>2.6 (0.74, 9.13)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current MDD</td>
<td>-3.89</td>
<td>3.07</td>
<td>0.08</td>
<td>1.47 (0.95, 2.72)*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Global Rating</td>
<td>0.14</td>
<td>0.15</td>
<td>0.7</td>
<td>1.15 (0.56, 2.34)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Global Rating*Proxy Carrier Status</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Note: OR = odds ratio; CI = confidence interval; OR represents odds of IADL dependence unless marked by an asterisk, in which case OR represents odds of IADL independence; IADL = instrumental activities of daily living; MDD = Major Depressive Disorder
Figure 1. Relationship between Global Rating and Age by APOE ε4 Carrier Status in Caucasians (higher global rating indicates greater neurocognitive impairment)
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