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Brain Derived Neurotrophic Factor and Cognitive Status: The Delicate Balance Among People Living with HIV, with and without Alcohol Abuse

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Abstract

Introduction—The advent of combination antiretroviral therapy(cART) has lead to a significant reduction in morbidity and mortality among people living with HIV(PLWH). However, HIV-associated neurocognitive disorders (HAND) still remain a significant problem. One possible mechanism for the persistence of these disorders is through the effect of HIV on brain-derived neurotrophic factor (BDNF). BDNF is influenced by various factors including hazardous alcohol use (HAU), which is prevalent among PLWH. This study attempts to elucidate the relationships between HAU, BDNF and HAND.

Methods—Cross-sectional analyses were conducted on a sample of 199 hazardous alcohol users and 198 non-HAU living with HIV. Members of each group were matched according to sociodemographic characteristics and CD4 count. Research procedures included validated questionnaires, neuropsychological assessments and a blood sample to obtain BDNF and immune measurements.

Results—Hazardous alcohol users showed either significantly lower or significantly higher BDNF levels compared to the Non-hazardous (OR=1.4; 95% CI: 1–2.1, $p = 0.003$). Therefore, for additional analyses, subjects were categorized based on BDNF values in: Group 1 < 4000, Group 2: 4001–7,999 (reference group), and Group 3 for those >8,000 pg/mL. Groups 1 and 3 performed

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CONFLICT OF INTEREST

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significantly worse than those in Group 2 in the domains of processing speed, auditory-verbal and visuospatial learning and memory. Multivariate analyses confirmed that HAU and BDNF are significant contributors of HAND.

Conclusion—Our findings offer novel insights into the relationships between BDNF, and alcohol use among PLWH. Our results also lend support to expanding clinical movement to use BDNF as an intervention target for PLWH, in those with evidence of deficiencies, and highlight the importance of including HAU at the inception of clinical trials.

Keywords

Alcohol drinking; BDNF; hazardous alcohol use; HIV; neurological disorders

INTRODUCTION

A major milestone in the HIV/AIDS epidemic was the development of antiretroviral therapy (ART). Yet, many PLWH still suffer from cognitive impairment, which falls within the spectrum of HIV-associated neurocognitive disorders (HAND)[1]. Neuroimaging studies of HAND suggest that it has been associated with compromised fronto-striatal regions [2]. Furthermore, HAND has been associated with a number of real world consequences including an increased risk of mortality (independent of CD4 counts and viral loads) [3]. Thus, HAND remains a significant threat for the 1.1 million PLWH in the US, and millions more worldwide [4–5]. Of concern, according to the last CHARTER report, is that at least half of PLWH fulfill the criteria for cognitive impairment [1, 4–5]. It appears that adherence to ART regimens has prevented a global AIDS Dementia crisis, with the majority of impairments being more mild or asymptomatic. [1–6]. Though, studies have predicted staggering increases in neurocognitive disorders [6].

While over the past decades we have learned a great deal about the neurotoxic effects of trans-activating regulatory protein Tat, and accessory proteins Nef, Vif, Vpr, Vpu and gp120, the reason why neurocognitive disorders persist amongst ART-treated individuals is still under debate [1–8]. The fact that ART can only partially reverse neurocognitive disorders supports the notion that there are other factors playing key roles. Since PLWH with HAND exhibit decreased synaptic and dendritic density, and cortical and subcortical atrophy, it has been concluded that damages are more in line with alterations in the ability of the brain to undergo changes in neuronal processes and to reorganize an altered synaptic network [9–11]. This function is called synaptic plasticity, and it is influenced by neurotrophic factors, such as the brain-derived neurotrophic factor (BDNF). Though BDNF was characterized only 3 decades ago, it is considered one of the most important neurotrophins, given its essential role in inducing synaptogenesis, sprouting, modulation of dendritic branching, and neuronal survival [9–11]. The influence of BDNF begins prenatally, but continues not only into adulthood, but also to the older years [12]. BDNF is found in nearly every part of the human brain, and plays an especially important role in the hippocampus, which has an essential function in human emotions, learning, and memory [12, 13].

Previous studies suggest that BDNF may play a key role in mood disturbances [14–17]. Depression is considered to some extent, an inherited disorder. The Val/66/Met locus (rs6265) genetic variant of the BDNF gene has been commonly studied in relation to depression. However, not all studies have consistently found a direct relationship between BDNF and mood disturbances [14–18]. Nevertheless, identified BDNF effects of mood disorders, particularly depression is highly relevant, given that rates of clinical depression are significantly higher in PLWH, and are considered an important contributor to morbidity and mortality [19]. Recently, it has been proposed that antidepressant treatment increase neurogenesis, synaptogenesis and the expression of plasticity-related proteins, such as the cyclic adenosine monophosphate response element binding protein (CREB) and BDNF associated improvements in neuronal plasticity [20–21].

Notably, animal studies have suggested that hazardous alcohol use (HAU), which is widespread among PLWH, may lower neuronal plasticity by further decreasing BDNF [22]. Studies on BDNF and HAU in humans are scarce. Findings from existing studies are often inconsistent and many of these studies should be interpreted with caution, due to small sample size. Joe's group reported lowered plasma BDNF in 30-day abstinent alcohol dependent individuals [24]. On the other hand, Umane-Nakano (2008) and Huang and colleagues (2009) found no difference in serum BDNF between alcohol dependent and healthy subjects; yet Huang reported a significant increase in serum BDNF levels after a week of withdrawal [25–26]. However, none of those prior studies were performed in PLWH, and the status information about the relationship between BDNF levels and neurocognitive performance of BDNF is unknown in this population of participants with dual morbidity. Thus, this dearth of data limits the ability to develop new interventions or clinical guidelines and recommendations.

Although BDNF is mainly known for its action in the nervous system, BDNF is also present in the periphery, and can cross the blood–brain barrier [26]. Furthermore, plasma/serum BDNF levels may reflect BDNF levels in the brain [27–29], and peripheral administration of BDNF results in cellular and behavioral adaptations in the brain [30]. The prodomain predecessor of BDNF, proBDNF binds to the pan-neurotrophin receptor p75NTR, instead of TrkB, resulting in very different effects than those elicited by BDNF-TrkB signaling [27–32]. Therefore, a better understanding of the bi-directional relationship between BDNF and HIV is needed, to shed light on how to better address this problem.

Taken together, these findings demonstrate the need for additional studies to: 1) establish if hazardous alcohol use is associated with BDNF disturbances, and thus, at highest risk for neurological disease and 2) assess if those alterations in the BDNF system are associated with neuropsychological disturbances. The Platelets mediating Alcohol and HIV Damage Study (PADS) is a large, single-site multi-ethnic cohort providing a unique opportunity to assess the roles of BDNF and alcohol among PLWH. *A priori*, we hypothesized that among PLWH, HAU will have lower BDNF levels that will lead to have poorer cognitive function when compared to those without HAU and those with normal BDNF levels.

METHODS

Study Population

This paper represents a cross-sectional analysis of baseline data from PADS. The recruitment process started in June 2010 and ended in June 2011 with a total of 400 subjects enrolled in the study. We have also included 50 HIV sero-negative subjects in order to standardize the values for the BDNF assessments. The main focus of this cohort study was to assess the potential effects of alcohol in PLWH and under regular care. Our choice of PLWH in an open-access public health system with standard treatment protocols was purposefully designed to minimize social, medical, and treatment inequalities. Thus participants were questioned regarding alcohol intake in the past six months, using two standardized and validated brief screening questionnaires: the Alcohol Use Disorders Identification Test (AUDIT), and the Alcohol Dependence Scale (ADS) [33–34]. The AUDIT includes three questions on alcohol consumption, three on drinking behaviors and dependence, and four on the consequences or problems related to drinking. The ADS assesses alcohol withdrawal symptoms, impaired control over drinking, awareness of a compulsion to drink, increased tolerance to alcohol, and salience of drink-seeking behavior. Participants were asked to report a serving size using models of 12 ounces of beer, 5 ounces of wine, and 1.5 ounces of liquor. Alcohol consumption scores were computed by averaging cross products of quantity and frequency of beer/wine and hard liquor reported on the AUDIT, and ADS responses. Then, based on the National Institute of Alcohol Abuse and Alcoholism criteria, men who reported >14 drinks/week or >4 drinks in one day, and women who reported >7 drinks/week or >3 drinks in one day were classified as hazardous alcohol use (HAU), while those who reported fewer drinks were categorized as non-HAU [35]. Participants who drank more than five standard drinks in a given day were considered binge drinkers [35]. Alcohol groups were matched demographically and based on CD4 cell counts (above or below 200 cells).

Non-ambulatory patients and those presenting major medical co-morbidities were excluded. Participants were questioned about several medical disorders, and research study staff reviewed medical records to confirm their eligibility. If participants had a history of central nervous system (CNS) opportunistic infection, head injury with or without loss of consciousness, tumor, major psychiatric disease, a developmental disorder, past or current bipolar disorder (as determined *via* medical chart review), severe malnutrition, chronic renal failure, or thyroid, cardiovascular, or immune-based diseases were ineligible. In addition, participants who had cirrhosis, active viral hepatitis, or liver enzymes two standard deviations above normal values were ineligible. To reduce the confounding effects of illicit drug use, the DSM-IV-TR questionnaire was applied, and those participants who were dependent on drugs or injecting illicit psychoactive substances were excluded [36]. The protocol was approved by the Institutional Review Boards at Florida International University and the University of Miami. The study was conducted according to the principles expressed in the Declaration of Helsinki. Those participants who provided written informed consent and signed a medical release form were consecutively enrolled and followed over a period of six months.

Participants' Assessment Protocol

At baseline, we obtained sociodemographic, alcohol use, and medical history information (e.g., HAART details) using computerized structured questionnaires and self-reports; this information was confirmed using available medical records or data was amended when applicable based on medical records. Blood was drawn in fasting subjects, in order to best evaluate immunological, metabolic, and nutritional profiles. At the end, participants completed a neuropsychological assessment to ensuring that participants were sufficiently relaxed and comfortable with the research staff before the assessments were conducted.

Neuropsychological Assessments

An experienced member of the team assessed participants with a neuropsychological battery that complies with national guidelines ("Clinical confirmation of the American Academy of Neurology algorithm for HIV-1-associated cognitive motor disorder) [37]. Eight different neuropsychological tests were completed within the same visit, however, breaks and optimal conditions for testing (e.g., appropriate lighting, silence, and isolation from unnecessary stimuli) were provided. The neurocognitive test battery evaluated the following:

- The Color Trails Test (CTMT, Executive functions.) was used for assessing executive functions, and to minimize the influence of language and cultural bias. Color Trails 1 Form A is a visuoconceptual and visuomotor tracking task involving motor speed and attention [38]. Both, the Color Trails 1 A and B consist of several numbered circles colored in vivid pink or yellow. Form A involves alternatively connecting consecutively numbered while alternating colored circles, which requires the shifting of cognitive sets. The score is the total time taken to correctly complete the test.
- Digital Symbol Substitution contained in the Wechsler Adult Intelligence Scale measures visuo-perceptual and motor processes [39–40].
- Block Design assesses visuospatial/visuoconstructive skills indicative of appropriate functioning of the parietal and frontal lobes. The dependent variable is the total raw score of correctly constructed designs [41].
- The California Verbal Learning Test (CVLT), in which the participant is required to learn a 16-item word list over five trials, and recall and/or recognize them after short and long delays, to assess verbal learning and memory [42].
- The Rey Complex Figure Test (RCFT) was used as a measure of visuospatial functioning, retrieval and recall abilities. The RCFT test outcome included the copying of the complex figure immediately and by retrieval after 30 min [43].
- The Grooved Pegboard Test (GPT). The GPT is a well-established test of manual dexterity and psychomotor efficiency that requires the integration of fine motor dexterity with visual and kinesthetic information. Participants are timed on their speed for placing and for removing the pegs using dominant and non-dominant hands [44].
- The Beck Depression Inventory (BDI) is one of the most widely used instruments to screen and to measure the intensity of depression, and has been translated into

several languages. The BDI contains 21 items that can be answered on a 4-point scale. The total score which ranges from 0–63 is obtained from the sum scores of the 21 items. A total score of 0–9 is considered to be normal, mildly depressed corresponds to score 10–18; a score between 19–28 equals moderate depression, and scores above 29 are considered to be severe depression [45].

Using the corresponding manuals, raw scores were converted into T-scores or z-scores according to the corresponding manual to control for the effects of age, education, gender, and where available ethnicity.

Brain Derived Neurotrophic Factor

Prior studies have demonstrated that plasma levels of BDNF, although different from levels in cerebrospinal fluid (CSF), are correlated with CSF in CNS diseases [29]. Due to this association, circulating levels of BDNF were selected for analyses. To avoid the confounding effects of platelets, depleted plasma was obtained by an additional centrifugation step of the separated plasma at 3500rpm for 10 minutes at 2 – 8° C. Then, BDNF levels were measured according to the manufacturer's instructions (R&D System). Briefly, 50 µl of standard and 20-fold diluted samples were pipetted into wells of a 96-well immunoplates. An enzyme-linked monoclonal antibody specific for BDNF was added to the wells. Following a wash to remove any unbound antibody-enzyme reagent, a substrate solution was added to the wells and color developed in proportion to the amount of BDNF bound in the initial step. The color development was stopped and the intensity of the color was measured. BDNF concentration in plasma was calculated based on a standard curve. The minimum detectable dose of BDNF is typically less than 20 pg/mL. The only limitation is that BDNF ELISA is unable to discriminate between mature BDNF and proBDNF. To establish a reference value for a population of similar background BDNF levels were also measured from 50 samples from HIV negative individuals.

Co-Variates

Since prior studies have postulated some factors which could account for the variability in cognitive performance data in these factors were collected and included: gender [46]; socio-economic status [47], age [48–49], education [50–51], malnutrition (defined with BMI plus albumin levels) [52]; medical history and complications [53]; CD4 percentage and absolute numbers of T CD3+/CD4+, (determined by flow cytometry); HIV viral burden quantified using the Amplicor HIV monitor test (Roche Diagnostic System) and antiretroviral medications used, and prior exposure to HAART were all recorded.

Statistical Analyses

The data were analyzed using SPSS 18.0 for Windows (IBM, Inc., Chicago, IL, USA) and *p* values <0.05 were considered statistically significant. Although this is a prospective cohort study, we used only baseline data for these analyses. The distributions of our primary outcomes of interest were examined with normal probability plots. Descriptive statistics, such as minimum, maximum, median, and mean with SD, were used to summarize the data and to detect outliers and missing values. Log transformations were performed with variables not normally distributed. Percentages and frequencies were used to describe

categorical variables. Viral load results (RNA copies per mL) were log-transformed before analysis.

T-tests and chi squares were used to compare means and proportions respectively between the alcohol (HAU vs non-HAU) and BDNF groups (by tertiles). Differences in demographic, clinical history, and standard scores for cognitive tests were assessed using chisquares for categorical variables, two sample Student's t-test for normally distributed continuous variables, and the Wilcoxon rank sum test for non-parametrically distributed continuous variables. Differences between Groups between baseline and follow-up visit with regard to cognitive function were analyzed using paired-t-test. Correlations between cognitive performance, plasma BDNF levels, HAU and factors that could influence the results were assessed using simple univariate analyses. Finally, any variables that were significant in these analyses, as well as viral load and CD4, were included as independent variables in the multivariate regression analyses, with the cognitive tests as dependent variables.

RESULTS

Sample Characteristics

Demographics data, indices of HIV disease status and general health for HAULWH and non-HAULWH are provided in Table 1. As depicted in this Table 1, alcohol use groups were very similar in these parameters. Overall nutritional status, determined by level of serum albumin, was within the normal range for 99% of the participants (4.3 ± 0.4 g/dL); malnutrition (serum albumin < 3.5 g/dL) was observed in only 1% of the group. The cohort was characterized by normal liver enzymes levels, and CD4 T cell counts near to the 500 counts, suggestive of preserved liver function, and some degree of immune recuperation with therapy.

Participants had open access to antiretroviral medications, and mostly were receiving Truvada: 44%, Atripla: 22%, alone or in combination with Norvir: 32% or Kaletra: 13%. Adherence, as measured by the ACTG questionnaire, was similar between the groups, and was high during the week: 93%, and more limited during weekends: 83%.

Though among non-HAU over half (55%) never or rarely drank, 34% imbibed at least once a week typically more than two drinks per occasion. HAULWH were actively drinking at the time of assessment and imbibed in excess of 7 ± 5 drinks per day. They regularly consumed alcohol in an average of 4 days a week, and the mean total intake was of 31 drinks/week. Since not only the amount consumed, but the type of alcoholic beverage have to be taken into account we pursue further analyses. Data indicated that near two-thirds of the population described themselves as main consumers of wine, yet liquor (48%) and beer 41% was also frequently consumed. In accord with our prior studies, HAU were more likely to be consumers of liquor (OR=3, $p=0.00001$) or beer (OR=3.1, $p=0.0001$). On the other hand, non-HAU were more likely to drink wine (OR=3.5, $p=0.00001$).

Brain Derived Neurotrophic Factor

There was a wide range of BDNF concentration in circulation from 298 to >20,000 (mean 8384 ± 6366 pg/ml). BDNF levels differed by gender, with women exhibiting the highest levels (9958.9 ± 6578 vs 7470 ± 6068 pg/ml, $p=0.001$). As expected, an age effect was evident, PLWH older than 50 years of age have significantly higher levels than their younger counterparts (11207 ± 8790 vs 8369 ± 6529 , $p=0.003$). To determine the extent to which changes in the BDNF levels were due to infection alone, we first tested if BDNF levels differed between people living with and without HIV. Values from PLWH, at least doubled the ones obtained in our HIV negative control population (8583 ± 554 vs HIV-: 3523 ± 2438 pg/ml, $p=0.0001$). Little is known concerning the plausible impact of antiretroviral therapy on BDNF, we compared values between those few that were prescribed and were not taking their antiretrovirals with those receiving treatment. Analyses indicated no significant differences in BDNF levels between the treatment groups (8712 ± 6917 vs 7146 ± 4526 , $p=0.2$).

BDNF and Alcohol Use

To determine if hazardous alcohol use was associated with BDNF alterations, we first examined correlations between plasma BDNF and number of drinks per day, number of days drinking, and total drinks per week in the previous 180 days. The data revealed an inverse relationship between serum BDNF levels and the number of drinks ($r = -0.2$, $p = 0.03$). As depicted in Fig. (1), mean BDNF levels declined as they consumed more drinks per day. While at less than 3 drinks per day no significant differences were observed; beyond this threshold, differences were always statistically significant. However, it needs to be recognized that not all HAU exhibited low BDNF levels, in a subset of these participants (25%) a main effect of groups (HAU vs non-HAU) was observed, with HAU displaying significantly higher risk of having plasma BDNF levels above 8000 pg/ml compared with non-HAU (OR= 1.4; 95% CI 1–2.1, $p=0.003$).

Additional analyses revealed that consumption of beer and liquor was associated with significantly lower BDNF levels, yet results were only statistically significant when analyses were limited to HAU (beer yes = 7961 ± 5366 vs beer no = 11646 ± 7699 pg/ml, $p=0.04$; liquor yes = 5729 ± 5209 vs liquor no = 7780 ± 6300 pg/ml $p=0.05$). No differences in BDNF levels were observed among consumers of wine, yet they tended to have higher rather than lower values (wine yes = 9432 ± 6712 vs 7957 ± 5318 pg/ml, $p=0.1$).

The Triad of BDNF, HAU and Cognitive Performance

A significant positive association between plasma BDNF levels at baseline and several of the cognitive domains was observed. Therefore, for additional analyses, subjects were categorized based on BDNF values in: Group 1 (below the 25th percentile: <4000 pg/mL), Group 2 for those with values between 4001 and 7,999, and Group 3 for those above 8,000 pg/mL. Data for each group is presented in Table 2, participants in Group 1 were twice as likely to be male (95% CI 1.4–3.4, $p=0.003$), more likely to be hazardous drinkers (OR=1.6 95% CI 1–2.4, $p=0.01$), and to have thrombocytopenia (OR=3 95% CI: 1–7.8, $p=0.04$). Plasma BDNF levels of the HAU group were different by ANCOVA with age, BMI, and platelet count as covariates ($F = 25.64$, $p=0.01$).

After splitting the cohort into these three groups, means were calculated for each of the following cognitive tasks. The dementia scores for Group 1 tended to be higher than the mean of Group 2, suggesting a risk for PLWH with lower BDNF levels. Results reached statistical significance among HAU, among them higher dementia scores were associated with difficulties in the memory recall (3.6 ± 0.5 vs 3.1 ± 0.9 , $p=0.01$) and with the construction task (1.17 ± 0.9 vs 0.8 ± 0.9 , $p=0.05$). The null hypothesis links higher dementia scores with lower BDNF among HAU. Additional analyses of the different domains indicated that in addition to the global damage observed in HAULWH, there were some domains that were compromised.

For example, there was evidence of an association between BDNF levels and changes in symbol search speed. As depicted in Table 3, Group 1 average Symbol corrected scores were lower (6.4 ± 2.1 vs 7.7 ± 3.3) than those from Group 2. Compared to Group 2, Group 1 scored poorly on the Color Trail and Block Design tests, which in part assesses executive functioning. Subjects with low BDNF levels also needed more time to finish the two parts of the CTT. They also committed more errors to complete the task.

The average corrected score for the Coding test at baseline was 6.3 ± 2.5 as depicted in Table 3, those in Group 2 outperformed Group 1 in the Coding test, and Group 1 were likely to obtain a 3-point lower score. However, non-significant differences in scores were observed between Group 2 and Group 3.

Differences in performance across the California Verbal learning test trials I–V were used to assess acquisition of auditory verbal material and some of its components were correlated with BDNF levels. Across the entire sample, BDNF was only correlated with total number of words learned in trials I–V ($r^2=0.15$, $p=0.05$). Group 1 performed poorly than Group 2 in list A, across the five trials (total score 35.5 ± 9 versus 38 ± 9.8 , $p=0.01$). Proactive interference results showed dissimilar performances, as Group 1 also tended to have more difficulties with List B (3.6 ± 1.6 versus 4.4 ± 0.5 , $p=0.08$). However, no significant differences in recalls were observed among any of the groups.

Plasma BDNF levels were significantly related to better performance in grooved pegboard dominance ($r=1.3$, $p=0.02$). Mean performance on grooved pegboard non-dominant hand was significantly lower in Group 1. Results of the dominant hand differed between Groups 1 and 2 only among HAU (91.6 ± 26 vs 81.9 ± 24 , $p=0.04$). Only 8% of the subjects dropped a peg during the trials, with similar rates in dominant and non-dominant hand trails. However, the number of dropped pins was significantly higher among HAU with low BDNF (0.5 ± 0.1 vs 0.18 ± 0.07 , $p=0.04$).

BDNF, Alcohol and Depression

Depression Inventory (BDI-II) scores for PLWH were within the mild-elevated range, with mean $\pm$ SD values of 17.6 ± 12 . Of the sample, 17% exceeded the BDI moderate-severe cut-off of 29. Our data showed that participants in Group 1 were more likely to score in the moderate to severe range of the BDI-II (OR=1.7: 95% CI 1–2.99, $p=0.05$). Depression was not associated with neither with socioeconomic status or education, and differences in the rates of depression by gender were not significant.

Since the neurotrophic hypothesis of depression proposes that depression is associated with reduced brain BDNF levels we examined BDNF levels in subjects with and without severe depression (cut-off 19), yet their values were similar (9445 ± 6239 vs 9061 ± 7080 pg/ml, $p=0.17$). Furthermore, we did not identified more significant BDNF decreases or increases with more severe depression (8664 ± 6428 vs 9466 ± 7080 pg/ml, $p=0.3$). Because mood disorders and HAU frequently co-exist, we assessed if BDNF may be more accentuated in HAU with depression. However, HAU with depression did not exhibit significantly different BDNF levels, and results did not change by treatment group (antidepressants yes/no); yet untreated individuals with depression exhibited higher, rather than lower BDNF levels (10986 ± 6969 vs 8278 ± 6051 pg/ml, $p=0.1$).

Multivariate Analyses

We performed one multivariate regression analysis for each of the cognitive subtests (HIV Dementia, Color Trail, Pegboard, and Beck Depression Inventory) including independent variables, sociodemographic (i.e., age, education, gender, and race), HIV factors (viral load, CD4, ART), depression and those variables that were significant in the simple regression analyses. These models are shown in Table 4 and indicates that in this times of widespread use of antiretroviral treatment alcohol use and BDNF alterations are significant predictors of cognitive performance in several parameters. Notably (data not shown) the interaction between alcohol use and BDNF was not significant in any of these models indicating that alcohol and BDNF disarrangements exert and independent effect.

The first regression model examined was the HIV dementia scale and the R^2 was .13, indicating that the model predicted approximately 13% of the variance in the raw scores. The model indicates that BDNF alterations and number of drinks consumed per day are significantly associated with increased risks of dementia. A trend was evident for older age ($p=0.06$).

The second model examined the Pegboard dominant hand and the R^2 was .32, indicating that the model predicted approximately a third of the variance in the scores. The Pegboard variable was predicted by the BDNF levels ($\beta=5.2$, $p=0.021$), and liquor use ($\beta=1.5$, $p=0.009$), underscoring the importance of type of alcoholic beverage analyses. Age was the last variable eliminated from the model.

The performance of Color Trail 2 ($r^2=0.328$) was significantly associated with BDNF levels ($\beta=1.309$, $p=0.045$) and number of days drinking ($\beta=18.34$, $p=0.04$) and thrombocytopenia was the last variable to become non-significant. Notably, these variables were unable to predict CT1. The model predicted 24% of the variance in the scores ($R^2=0.24$).

Finally, depression assessed with the Beck Depression Inventory ($r^2=0.10$) was significantly associated with being receiving antidepressant treatment ($\beta=1.023$, $p=0.0001$) and total number of alcohol drinks per week ($\beta=0.05$, $p=0.02$) but no longer by BDNF.

Please note that together, these analyses suggest that none of the alleged contributing factors, such as sociodemographics (age, gender, race, years of education) current

depression, nutritional status, HIV related variables (CD4, viral load) significantly influenced cognitive performance of these tests. Nevertheless, our models only explained a proportion of the variance indicating that other relevant factors have not been considered.

DISCUSSION

The current project examined the influence of HAU on the current cognitive indicators of HAND, and the potential mechanisms by which it promotes impairments, specifically due to the role of BDNF. Our *in vivo* study indicated that HIV infection significantly impacts BDNF levels, yet our analyses demonstrated significantly high levels of circulating BDNF in PLWH in comparison with our HIV negative control population. Although, it is possible that these elevations reflect increases in BDNF synthesis that accompanies the neuronal remodeling triggered by ART, we did not observe differences in values between ART recipients and those not benefiting from ART. Notably, PLWH with values similar to those of the general population (<4,000 pg/ml) exhibited a more negative profile, they are more likely to be hazardous drinkers, and to have thrombocytopenia. Although the observational nature of our data precludes causal inferences, several facts suggested that this could be the case. First, there is a trend dose response between alcohol intake and BDNF levels. Second, there is a biological plausibility as animal studies have indicated that chronic alcohol can affect BDNF production. Our finding of decreased BDNF levels among HAU (<4,000 pg/ml) is consistent with animal models, in which chronic alcohol exposure leads to reduced BDNF expression in rats [56]. Data thus supported our hypothesis that plasma BDNF levels differed in PLWH with co-occurring HAU compared to PLWH without additional alcohol comorbidities.

While the effect of alcohol consumption assessed as quantities or intensity of alcohol consumption (amounts and time exposure) has been extensively studied, the type of beverage has been overlooked when defining risks. In this regard, our group has been actively looking for those differences between types of alcohol beverages and promoting these types of evaluations that are highly informative. Analyses by type of beverage uncovered, for the first time, a divergent effect on BDNF levels. Liquor and beer consumption was associated with decreases in BDNF while wine use have the opposite trend. The antioxidants and resveratrol contained in wine, but not in the other alcoholic beverages may be responsible for these differential effects, by acting as neuroprotectors against HIV, inflammation and/or alcohol toxic damage. The overall implications of the results of this study are clear, and point to the urgency of addressing alcohol use in PLWH. These outcomes also highlight the need of additional studies aimed at determining what are considered 'normal range' values, which can significantly differ from an 'optimal' level of peripheral BDNF in populations such as PLWH, that may have variations in requirements for BDNF.

To better understand the scope and magnitude of the neurocognitive consequences associated with BDNF changes, we selected a neurocognitive battery that includes tests/ domains reported to be adversely affected by both HIV and HAU. While considerable differences on neuropsychological assessments were evident between HAU and non-HAU, there was also considerable variability within the hazardous alcohol users. Therefore, the

identification of a vulnerable subgroup with impaired neurocognitive functioning was of importance. Although several research groups have demonstrated cognitive impairment in alcohol-dependent patients, to the best of our knowledge none have assessed the influence of BDNF on changes in cognitive function. In this regard, our data uncovered significant differences in BDNF levels that can exacerbate the risks. Analyses of BDNF levels in relationship with cognitive performance suggest a U- or J-shaped where intermediate levels seem to produce a protective effect. Results are also consistent with a paper published last year by Bachis and colleagues using animal models and post-mortem samples indicating that HAND is associated with a significant reduction in mature BDNF, but with increases in proBDNF [55]. The authors postulate that that gp120 shed by the virus can inhibit the appropriate processing of proBDNF into mature BDNF leading to increases in proBDNF and neuronal loss [55]. It needs to be highlighted, that a similar type of response has been observed with corticosteroids. Our finding of decreased cognitive performance among those with low BDNF levels among HAU (<4,000 pg/ml) is probably related to accrued neuro-protective deficits that make neurons more vulnerable to the continuous alcohol-induced damage. It could also be associated with reduced capacity to recover from the neurological damages induced by HIV and/or alcohol. Despite our expectation of observing broader deleterious neuropsychological effects, BDNF deficits impacts some, but not all cognitive domains. HAU with low BDNF were impaired with regard to the performance of color trail, a task assessing executive function. Analyses also revealed deficits in the pegboard, a motor-eye coordination test, as well as in the motor component of the HIV dementia Scale. Low circulating BDNF levels in this at risk group could therefore interfere with cognitive improvement. From the clinical stand point of view, these analyses provide further support to explore pathways to deliver BDNF as an adjuvant for PLWH and to further explore its potential as adjuvant in the management of hazardous alcohol users. While findings can be debated because they are based on circulating BDNF levels and not on CNS direct measurements, it needs to be highlighted that neurons can acquire peripheral BDNF to change neuronal activity and synaptic transmission [30, 57].

Consistent with prior research indicating that BDNF has rapid and short-term effects on synaptic function [21, 58], analyses uncovered that BDNF is required for acquisition of verbal memory as indicated for deficits during trails 1 to 5, yet we did not observe differences in the section on retrieval of information. As far as the acquisition of verbal material, the poor performance in HAU in those with low BDNF is of concern as generally medical instructions are given verbally. Similarly, we found significant differences in the visual memory component of the RCFT test, although the recall scores were similar among groups. These results diverged from those by Holt and others (2009), who showed that in patients with schizophrenia, alterations in BDNF were associated with impaired extinction memory, which, in turn, has been shown in animal models to require increased expression of proBDNF [59].

Similarly to studies among the general medical literature that have observed a relationship between BDNF levels and screening dementia tests, such as the Global Cognitive Score and Mini Mental State Examination score [60], a relationship between BDNF levels and the HIV dementia scoring was evident. These findings are of concern, given the significant association of poor neurological performance with mortality (independent of CD4 counts

and viral loads). The observed disturbances in the BDNF-system highlight the need of additional research as studies in other populations indicated that BDNF affect multiple organ systems, as well as overall mortality.

Although significant efforts are being devoted to increase BDNF levels, nonetheless, it is important to recognize that a sizable proportion of PLWH exhibited high levels of BDNF. The increased BDNF levels in this subsample of individuals could reflect a compensatory overproduction associated with an increased neuronal demand for BDNF because of damage or to protect the CNS stressed by the combination of HIV and the toxic effects of alcohol. These findings may at least partially explain why some alcohol researchers reported lowered plasma BDNF, why some found no difference in BDNF between alcohol users and healthy subjects, and why others reported significant increases [23–25, 61]. Though considering the general belief that increases in BDNF are beneficial, we expected these increases to be associated with well-preserved cognitive functions. Surprisingly, similar to the depleted group, these individuals with elevated BDNF also exhibited impairments in cognitive tests. A possible explanation is that this increase may represent an overproduction of pro-BDNF which is known for causing damage in the CNS. This postulate is supported by prior pre-clinical studies demonstrating that in neurons gp120 promotes a time-dependent intracellular and extracellular accumulation of pro-BDNF, which exerts deleterious effects over the CNS. However, additional studies are needed to confirm this postulate.

In addition, we examined other variables that could possibly affect cognitive performance and/or BDNF levels such as age, gender [62–64], and nutritional status. CD4 and viral load were used as markers of general health. None of these were found to influence or correlate with BDNF levels or with the cognitive tasks included in the battery. Age was not a significant predictor of BDNF or cognitive performance, however, we need to remember that groups were age matched and that these individuals were mostly in the forties; it is possible that cohorts with older individuals may found statistical differences. Depression was measured to evaluate the potential effect of BDNF in mood alterations as well as its potential effect on cognitive performance. However, analyses did not corroborate our hypothesis that a relationship among HAU, depression and BDNF exists. Though initially there was a significant correlation between BDI score and BDNF levels, significant differences in BDNF levels between subgroups that were observed in the multivariate analyses of BDI scores were no longer significant. These results suggest that other neurotransmitters could be mediating this psychological disorder in these individuals with dual comorbidity. While results were unexpected, similar findings have been reported by other groups [65]. We also assessed if there was an additive effect between depression and HAU and found no such relationship. Furthermore, while the beneficial effects of antidepressants have been attributed, at least in part, to restoring BDNF homeostasis in patients with depressive disorders, we could not identify any differences in BDNF levels between subjects with and without antidepressant treatment [66–67]. To reconcile these reports, which are not necessarily contradictory, information is needed regarding pro-BDNF and BDNF genotyping as they can modify these relationships (risks and treatment responses).

There were two principal limitations. First, our study was a cross-sectional analyses, which does not allow us to make causal inferences between BDNF and risks of cognitive impairments. Secondly, we should note that the commercial kit which has been widely use in other studies mostly detect mature BDNF and small proportion of pro-BDNF, but it cannot distinguish between the two sub-fractions, therefore the effect of HAU on pro-BDNF is unknown. Against these limitations, two advantages of the PADS cohort can be highlighted. First, the matched control design reduced the confounding effects of age, education, and stage of the disease, which, along with standardized scores, increased the rigor of control against confounding variables. In addition, our study benefitted from its large sample size and from the inclusion of HAU and non-HAU PLWH from the same population source.

CONCLUSION

HIV associated neurological disorders are a significant clinical problem, and important public health threat, because rates are expected to increase as PLWH are aging. In addition, both the HIV and alcohol epidemics continue - unbeatable and overlapping. Therefore, a better understanding of their interactions is needed to make therapeutic decisions as well as to design new interventions. As the abnormal BDNF system is a key element responsible for both damage and repair, interventions targeting BDNF can be beneficial.

Yet, current knowledge is still limited as evident in this paper. To our knowledge, these findings have not been demonstrated in prior work. Our next milestone, is measuring both pro and mature BDNF, to reassess if high levels positively or negatively influence neuropsychological status among people living with HIV with HAU. These analyses may open new pathways to address cognitive impairment among those with dual comorbidities (PLWH +HAU) through tailored and targeted interventions.

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Maria Jose Míguez: The principal investigator: designed research study, analyzed data, wrote the paper.

Luis Espinoza: was the study physician of the study.

John Lewis: Oversee the collection of nutritional and anthropometric data.

Clery Quiros: Help with the recruitment and collection of the data.

Whitehead: Help with the interpretation of neuropsychological assessments.

Asthana Deshratan: Supervised the collection and analyses of laboratory data.

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Fig. (1).
BDNF Levels by Number of drinks Consumed per day.

Table 1

Sociodemographic and clinical characteristics of HIV infected patients by alcohol groups.

Variable	HAU N=198	Non-HAU N=199	P Value
Age	43±6.4	41±6	0.7
Men	67%	60%	0.1
Women	33%	40%	
African American	70%	66%	0.4
Black Caribbean	2%	4%	
Hispanic	22%	23%	
White	6%	4%	
Annual Income: Less than \$10,000	88%	86%	0.7
\$11,000–\$20,000	9%	10%	
\$20,000–\$49,000	2%	2%	
>\$50,000	2%	2%	
Education (years of school)	11.5±2	11.3±2.4	0.1
Albumin mg/dl	4±0.4	4.1±0.5	0.9
AST IU/L	32.5±23	34.1±18	0.6
ALT IU/L	37.1±33	37.8±20	0.8
CD4 cell counts	408±259	455±310	0.1
Viral Load Log	2.7±1.3	2.6±1.3	0.4

Note: Demographic characteristics were expressed as percentages by BMI group. Biological measures were presented as means and standard deviations.

Note: AST =Aspartate transaminase also called glutamic oxaloacetic transaminase (SGOT) and ALT= alanine aminotransferase also called glutamic pyruvic transaminase (SGPT).

Table 2

Sociodemographic and clinical characteristics by BDNF groups.

Variable	Group 1 BDNF <4,000pg/mL N=97	Group 2 4,001–7,999pg/mL N=139	Group 3 BDNF >8,000pg/mL N=161	P Value
Age	43±5.7	42±6.7	43±7	0.7
Men	75%	70%	49% 51%	0.001
Women	25%	30%		
African American	58%	70%	73% 1% 21% 5%	0.2
Black Caribbean	2%	3%		
Hispanic	28%	23%		
White	12%	4%		
Education (years of school)	11.6±2	10.9±3	11.5±2	0.06
Albumin g/dl	4±0.6	4.1±0.5	4.1±0.5	0.9
Platelet Counts	186±66	241.8 ±139	253.5±75	0.001
CD4 cell counts	302±196	391±248	547±322	0.001
Viral Load Log	3.1±1.2	2.8±1.3	2.5±1.2	0.02

Note: Demographic characteristics were expressed as percentages by BDNF group. Biological measures were presented as means and standard deviations.

Table 3

Cognitive performance by BDNF groups.

Variable	Group 1	Group 2	Group 3	P Value
Dementia	6.9±3.2	5.3±3	6.5±2.4	0.04
Coding	5.3±1.4	8.6±1.3	6.5±2.4	0.03
Symbol	6.4±2.1	7.7±3	7.8±2.5	0.02
Color Trail 2	115±49	94±19	113.5±48	0.02
Color Trail Errors	0.7±0.1	0.2±0.2	0.3±0.1	0.05
Beck Depression	21±3	14±8	17±13	0.05

Note: Values represent standardized scores.

Note: For coding and Symbol tests p=values refer only to comparisons between Groups 1 and 2.

Table 4

Results for regression analyses.

HIV Dementia Scale	B	Std. Error	Sig.
Constant	-.316	.173	0.067
Number of Drinks/day	.056	.023	0.015
BDNF group	.182	.090	0.043
Grooved Pegboard Dominant Hand	B	Std. Error	Sig.
Constant	76.474	2.741	.000
Liquor	1.534	.580	.009
BDNF	5.216E-7	.000	.021
Age	.203	.135	.135
Color Trail 2	B	Std. Error	Sig.
Constant	80.849	26.413	.002
BDNF	1.309E	0.000	.045
Number of Days Drinking	18.344	8.814	.038
Thrombocytopenia	-3.499	12.960	.787
California Verbal Learning Test Trails 1–5	B	Std. Error	Sig.
Constant	9861.344	494.451	.000
BDNF	-915.326	291.380	.002
Age	-131.409	25.343	.000
Beck Depression Inventory Total Score	B	Std. Error	Sig.
Constant	26.402	2.253	.000
Antidepressants	-6.421	1.297	.002
Total Drinks	0.54	.024	.000

Note: BDNF refers to Brain Derived Neurotrophic Factor.