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A Family History of Substance Dependence Obscures the Group Differences in Brain Function Associated with HIV-1 and ART

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Abstract

BACKGROUND—Recently, the NIH called for additional research on the topic of viral and host factors contributing to impaired cognitive and neural function in HIV/AIDS patients and their response to antiretroviral treatment. This investigation responds to that call by examining a host factor, a family history of substance dependence, often overlooked in cognitive and neuroimaging studies of HIV/AIDS.

METHODS—We categorized 146 HIV-1 seropositive patients receiving antiretroviral treatment (ART) and 92 seronegative volunteers by the presence or absence of alcohol, cocaine, or heroin dependence affecting a biological parent. Seropositive patients were further categorized by the estimated ability of their individual ART regimens to penetrate the CNS. The indicator of brain function was a 3–7 Hz oscillatory electroencephalographic response (theta ERO) evoked by target stimuli presented during a simple selective attention task.

RESULTS—The analysis revealed that the presence of a family history of substance dependence obscured the reduction in frontal theta ERO power accompanying the presence of HIV-1 as well as the improvement in frontal theta ERO power accompanying treatment with ART agents estimated to have greater ($n=41$) versus lesser ($n=105$) CNS penetrance. Secondary analyses employing sLORETA source localization techniques revealed that the source of the theta ERO response was similarly reduced by the presence of either HIV-1 or a family history of substance dependence.

CONCLUSIONS—We conclude that a family history of substance dependence complicates and obscures the subtle neurophysiological changes which typically accompany HIV/AIDS and ART. Studies of new therapeutic agents for HIV-1-associated cognitive and neurophysiological impairments must consider this complication and exclude or control it.

Keywords

HIV; Substance Use Disorder; Family History; Event Related Potentials; AIDS; Antiretroviral Treatment

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Conflict of interest

Although the author, Dr. Bauer, serves as an *ad hoc* consultant to Best Practice Project Management, Inc., the present article and study are not related to this agreement or past, present, or planned consulting agreements.

1. INTRODUCTION

Before the discovery of effective antiretroviral treatment (ART), HIV-1 Associated Neurocognitive Disorders (HANDs) were prevalent and severe. Fortunately, in the current ART era, they are far less disabling. An example is the incidence of HIV-1 Associated Dementia, which has declined to a negligible rate in the United States and developed world (Heaton et al., 2011). Unfortunately, other, more moderate HANDs have not demonstrated a similar decline. Their prevalence has remained remarkably high--between 15 and 50 percent (Cysique and Brew, 2011).

This persistence of mild and moderate HANDs in the ART era has generated intense discussion and speculation, as well as several possible explanations (McArthur et al., 2011). One explanation focuses on the brain as a reservoir for HIV-1 and the argument that the doses of ART used for remediating immunosuppression might not be sufficient for challenging HIV-1 across the blood-brain barrier (BBB). A related explanation emphasizes the variable degree to which different ART agents can pass the BBB to reduce brain HIV-1 concentration (Cysique et al., 2011; McArthur et al., 2011). A third explanation posits that brain damage incurred at the disease peak, i.e., marked by the nadir CD4 count (Ellis et al., 2011), simply cannot be reversed, in total, by ART or other therapeutics.

In this article, we discuss a fourth explanation for the impairments in brain function that exist during ART. The explanation focuses on a host factor often overlooked in cognitive and neuroimaging studies of HIV/AIDS patients. The factor is prevalent among these patients for it is connected another host factor, substance dependence, which is also prevalent (Bing et al., 2001; Byrd et al., 2011; Petry, 1999) in the population. More specifically, our interest is in a family history of substance dependence (FHSD) and how it contributes to HIV-associated neurophysiological changes that may underly HANDs. The present study is not a direct examination of HANDs *per se*.

1.1. A FHSD and functional brain impairment in HIV/AIDS

It is well known from family history and twin studies that substance use disorders are familial and heritable (Kendler et al., 2000; Lieb et al., 2002; Nurnberger et al., 2004). For example, as a group, patients with substance use disorders are more likely than the general population to have relatives who are similarly affected. Also, for twin pairs in which one member is substance-dependent, the probability of the co-twin also being substance-dependent is greater if the pair is 100% versus 50% genetically identical. Admittedly, the contribution of these family history and genetic variables to risk will vary with the severity of the substance use disorder: dependence is more familial and heritable than abuse or use. But, the association is generally quite impressive. Approximately 40–60% of the variance in substance dependence can be explained by genetic risk.

The familial and genetic differences that precede and promote substance dependence are relevant to brain function generally, and brain function in HIV/AIDS patients specifically. Across dozens of studies, the offspring or other relatives of substance-dependent patients have been shown to exhibit subtle but statistically significant impairments in brain function in comparison to volunteers without this family history. For example, FHSD+ participants demonstrate reductions in the amplitudes of event related electroencephalographic (EEG) responses, such as the P300 (Iacono et al., 2002; Polich et al., 1994; Singh and Basu, 2009; Singh et al., 2009), during attention and memory tests. They also show impairments in reaction time or accuracy during tests of working memory (Cservenka et al., 2011; Harden and Pihl, 1995), cognitive control (Lovallo et al., 2006), and motor control (Eng et al., 2005; Gillen and Hesselbrock, 1992; Heath et al., 1999). In part, these impairments are related to a co-occurring antisocial or impulsive personality style, which is likely related to an inherited

decrement in brain volume (Gilman et al., 2007) especially involving frontal brain regions (Raine et al., 2000).

In this complicated context, some of the decrements in brain function described in the HIV/AIDS literature could be re-interpreted. Because a significant overlap exists among HIV/AIDS, a personal history of substance dependence, and a FHSD, it seems likely that a FHSD might influence or, in other cases, entirely explain the purported effects of the other variables as well as the presence of an asymptomatic or mild form of HAND. Several publications from our laboratory support this position. For example, in 2008, we reported the results of two studies measuring cognitive control in HIV/AIDS patients. One study (Bauer, 2008a) examined performance and event related EEG responses in patients and seronegative controls while they performed the Stroop color-word interference task. The other study (Bauer, 2008b) examined these measures in the same sample while they performed the Simon task—a task in which participants are asked to inhibit the impulse to respond in the same spatial direction as the stimulus. In both studies, we found that the EEG response of HIV/AIDS patients was impaired in comparison to the response of participants in the seronegative control group. However, the statistical effect of HIV/AIDS was masked by the presence of a FHSD.

In the present article, we report a similar study of seropositive patients and seronegative controls while they perform a simple selective attention task. The study employs a different cohort than we have studied previously. All of the HIV/AIDS patients examined here were receiving antiretroviral treatment. Another major difference from our previous studies is a focus on examining the relative impact of different types of ART. More specifically, we contrasted ART agents estimated to have greater (Zidovudine, Nevirapine, Indinavir, Vicriviroc) versus lesser (all others) central nervous system penetrance (McArthur et al., 2011). Also, we examined an evoked 3–7 Hz oscillatory response (theta ERO power) as the principal dependent measure versus the P300 or slow wave responses studied previously. A previous study (Rangaswamy et al., 2007) demonstrated that total (evoked plus induced power) theta ERO power is reduced among adolescents with a positive family history. Induced power in the theta frequency band has not been found to differentiate family history positive and negative groups (Andrew and Fein, 2010).

2. METHOD

2.1. Recruitment and Screening Procedures

HIV-1 seropositive volunteers were recruited via advertisements posted at outpatient Infectious Disease Clinics in the greater Hartford, CT region. HIV-1 seronegative volunteers were recruited principally through word-of-mouth advertising provided by the seropositive patients. Both groups of volunteers were invited to telephone a member of the research staff for initial eligibility screening. The telephone interview included questions about their demographic characteristics, general medical status, substance use, and psychiatric symptoms. Those volunteers who passed this screen were invited to visit the Health Center on a subsequent day for additional eligibility screening and laboratory evaluations.

On that day, HIV-1 seropositive and seronegative volunteers were asked to complete informed consent and medical release documents and provide a blood sample for confirmation of HIV serostatus. The clinical laboratory evaluation also included a CBC with differential, HIV RNA viral load (if applicable), CD4 lymphocyte count and percent, VDRL, HBV and HCV screens, and toxoplasmosis and cytomegalovirus antibody titers. In addition, toxicological analyses for cocaine, opiates, amphetamine, and marijuana were performed on urine samples (Ontrak™, Varian Inc., Palo Alto, CA) and a breathalyzer was

used to detect recent alcohol use. An Optec 2000 Vision Tester™ was used to confirm normal color vision and acuity (with correction).

A structured psychiatric interview, viz., the CDIS-IV (American Psychiatric Association, 1994; Robins, 2002), was then administered to detect DSM-IV Axis I and II disorders. Other background characteristics were assessed using the Addiction Severity Index (ASI; McLellan et al., 1980), Michigan Alcoholism Screening Test (MAST; Selzer, 1971), Drug Abuse Screening Test (DAST-10; Skinner, 1982), and Beck Depression Inventory Version II (BDI-II; Beck, 1996). The Kaufman Brief Intelligence Test (KBIT; Kaufman, 1990) was administered to derive an estimate of IQ.

Exclusion criteria included pregnancy, seizures, mental retardation, neurosurgery, and a history of head injury with loss of consciousness for greater than 10 minutes. In addition, volunteers were required to have no acute illness, an IQ score greater than 70, and no major neurological or medical (i.e., hypertension, chronic obstructive pulmonary disease, Type 1 diabetes, cirrhosis, hepatic encephalopathy, ocular disorders, etc.) disorders unrelated to HIV-1. Positive urine toxicology or breathalyzer tests were also exclusions. However, current use of methadone was not. Volunteers were likewise excluded if they met the DSM-IV criterion for a diagnosis of schizophrenia or bipolar disorder. Major Depressive Disorder was not an exclusion.

At the end of the screening phase, 146 seropositive and 92 seronegative participants were eligible. They were assigned to one of two family history subgroups by the presence (FHSD+) versus absence (FHSD-) of a report during the interview that either biological parent met DSM criteria for a diagnosis of alcohol, cocaine, heroin, or amphetamine dependence. The Family History Assessment Module (Rice et al., 1995) was used. We would have preferred to conduct direct interviews with the parents to verify these parental diagnoses, but the majority of our ~40-year-old participants were unable or unwilling to involve their parents in the study.

2.2. EEG Data Collection and Processing

Tin EEG electrodes were applied to 31 scalp sites positioned by an electrode cap (ElectroCap International, Eaton, Ohio). A reference electrode was taped over the bridge of the nose. The ground electrode was applied to the middle of the forehead. Interelectrode impedance was maintained below 5 Kilohms. After the electrodes were applied, the participant was escorted into a sound-shielded chamber and seated in a comfortable chair facing a 14-inch computer monitor. The monitor was used for the presentation of visual stimuli. A response panel with two response keys was also placed in front of the participant.

The participant performed several cognitive tasks in the laboratory. The data reported in this article were obtained during a simple “oddball” task that required attention to, and a button press indicating detection of, a rarely occurring event. The task involved the presentation of a Bernoulli series of two visual stimuli, the letter “X” ($p=0.2$) and the letter “T” ($p=0.8$), presented for 50 msec each at a rate of one stimulus every 1.2–1.8 sec. Three hundred stimuli were presented in total. The participant was instructed to press a key whenever the “X” was presented. He/she was instructed to ignore the other stimulus.

While the participant performed the task, the electroencephalogram was simultaneously recorded from 31 electrodes placed across the scalp. Eyeblinks and eye movements were also recorded, using a pair of electrodes placed diagonally above and below the left eye. The EEG and eye movement channels were appropriately amplified (EEG gain=20K, EOG gain=2K) and filtered (bandpass=0.01–30 Hz). Along with markers indicating stimulus and response onsets, these data were routed to an A/D converter, and sampled at a rate of 200 Hz

for 100 msec preceding and 1000 msec following the onset of each target stimulus. Epochs surrounding correctly identified targets were retained for analysis.

During off-line computations, the 1100 msec epochs were sorted by electrode and processed through a digital bandpass filter (0.5–30Hz, 24 db/octave roll-off). A linear regression algorithm implemented in Scan version 4.3 software (Compumedics/Neuroscan, Inc) mathematically removed eye movement and eye blink artifacts from each epoch. The corrected epochs were then aligned by the average voltage of the pre-stimulus period and screened to eliminate epochs with a voltage deviation <-50 or $>+50$ microvolts. The minimum threshold for retaining data from a participant was at least 12 acceptable epochs.

The next step in the processing of the data was not to create a time-point average of the EEG responses to the target event, as is typically done. Instead, we used a data reduction method that is less affected by latency jitter across trials—an artifact that is under-appreciated in EEG studies of patients with HIV/AIDS or dementia. The method involved the calculation of power (in μV^2) in the theta frequency band within single trials. These single trial event related theta oscillations (theta ERO) were derived at a center frequency of 5 ± 2 Hz, and computed in 5 msec steps from +50 to +850 msec post-stimulus onset. A separate routine summed power across at least 12 artifact-free sweeps and then calculated the average over epochs. The summary measure of theta ERO power was the area under the curve between +200 to +550 msec post-stimulus onset at 6 representative electrode sites: F3, F4, C3, C4, P3, and P4. Theta ERO power was also measured at all other electrode sites for a separate secondary analysis of group differences in theta ERO topography.

Behavioral performance indices were also recorded during the task and summarized offline. Average correct reaction time and the proportion of trials with correct responses were preserved for analysis.

2.3. Data Analysis

The 8 groups of subjects were initially compared on background characteristics. Pearson's Chi-Square Test evaluated group equivalence on categorical variables. A three-factor ANOVA served the same purpose for continuous variables.

The next step in analysis plan was an examination of the statistical effects of HIV-1 on theta ERO power and how these effects might be qualified by the presence versus absence of FHSD as well as sex. The analysis design was therefore a 2 (HIV) by 2 (FHSD) by 2 (Sex) factorial. A multivariate ANOVA was performed as an omnibus test of statistical significance across the 6 electrode sites. Two performance measures, percent correct and reaction time, were also included in the MANOVA.

Univariate ANOVAs were then performed for these 8 dependent measures if and only if the omnibus test of the corresponding main or interaction effect in the MANOVA was significant ($p < 0.05$). In all of these analyses, four covariates were entered. These covariates were employed because previous research, and our own analysis (Table 1), demonstrated that they can confound theta ERO power or related measures, e.g., P300 amplitude. The covariates were: (1) age; (2) BDI-II score; (3) a principal components analysis factor score reflecting the common variance across three indicators of substance dependence severity, i.e., MAST and DAST scores as well as lifetime number of treatments for substance use problems; and (4) a PCA factor score reflecting the common variance across three indicators of recency of substance use, i.e., the number of days since last use of alcohol, cocaine, or heroin. We employed factor scores as covariates in place of the individual measures because these scores would more broadly capture the construct of interest and be more reliable than an individual measure.

The third major step in the analysis used sLORETA to derive the cortical current source density distribution of the generators of theta ERO power across three groups of particular interest: the FHSD-/HIV- control group and the groups characterized by the presence of either FHSD or HIV but not both. sLORETA CSD distributions were computed from a boundary element method anatomical model using the Brainstorm software package (Tadel et al., 2011).

The fourth analysis step focused on a question about the relative benefit of ART agents hypothesized to have greater versus lesser CNS penetrance and their statistical effects on theta ERO power and task performance. The analysis was modeled after the 2x2x2 MANOVA described above. However, it only included HIV+ participants who were grouped by FHSD (+/-) and ART CNS penetrance [very good CNS penetrance (Zidovudine, Nevirapine, Indinavir, Vicriviroc) versus all others; see Figure 9 in (McArthur et al., 2011)].

3. RESULTS

3.1. Background Characteristics

The participants included in the analyses can be broadly characterized as men and women of various racial/ethnic origins (73.5% Black or Hispanic), 40.4 years of age, and educated for an average of 12 years. Many had a lifetime history of cocaine (51.8%), opiate (37.3%), and/or alcohol (35%) dependence. Approximately fourteen percent were taking methadone daily. Thirty percent met DSM-IV criteria for a lifetime diagnosis of recurrent Major Depressive Disorder.

The HIV-1 seropositive participants were remarkably healthy (Table 2): log10 viral loads were low, 1.03 copies/mL, and current CD4+ T-lymphocyte counts were 590 cells/ μ L. The average lifetime nadir CD4 count is not known or knowable because many patients had unreliable access to health care and/or incomplete records.

The groups differed on a few characteristics. For example, the HIV+ groups were slightly older ($F=4.8$, $p=0.02$), spent less time in school ($F=4.7$, $p=0.02$), and reported more depression symptoms on the BDI-II ($F=14.1$, $p<0.001$) than their HIV- counterparts. Also, the HIV+ groups exhibited a lower CD4 count ($F=145$, $p<0.001$) and higher levels of a global marker of inflammation, plasma TNF-alpha level ($F=9.1$, $p=0.003$).

In comparison to the FHSD- groups, the FHSD+ groups showed the predicted elevations in the number of alcohol and drug problems on the MAST ($F=16.4$, $p<0.001$) and DAST ($F=5.7$, $p=0.02$), as well as in the substance dependence severity factor score ($F=18.0$, $p<0.001$). The FHSD+ groups likewise reported more depression symptoms on the BDI-II ($F=4.5$, $p=0.03$). The group that was positive for both HIV and FHSD reported fewer depression symptoms than would be expected from the summated effects of HIV and FHSD (HIV $\times$ FHSD: $F=6.8$, $p=0.009$).

No other main effects or interactions were statistically significant.

3.2. Theta ERO Power and Task Performance

Comparisons of theta ERO power across groups revealed several interesting results. The average values across groups are reported in Table 3. Group averaged theta ERO waveforms are shown in Figure 1.

It is evident in Figure 1, and confirmed by the analysis results, that HIV and FHSD are associated with a reduction in theta ERO power. However, this reduction is only significant

at frontal electrode sites. In addition, the reduction is not detectable as a main effect. Rather, it is submerged within the HIV×FHSD interaction (F3: $F=4.03$, $p=0.04$; F4: $F=4.57$, $p=0.03$). Simple effects tests revealed that theta ERO power was lower among HIV+ patients versus HIV− controls but only among those participants who were also FHSD−. Similarly, theta ERO power was lower among FHSD+ versus FHSD− participants but only among those who were HIV−. In other words, the reduction in theta ERO associated with either of these factors was blunted by the presence of the other. The co-occurrence of HIV and FHSD was associated with no greater reduction than was seen for either factor individually. Task performance was not significantly affected by HIV, FHSD, sex, or their interactions.

Figure 2 shows that cortical current source density distribution of theta ERO power in three of the aforementioned groups. The data in these figures present more information than was used in the MANOVA. Here, all EEG electrodes were used in the computations. The figures clearly show that the cortical distribution of the theta ERO reduction in the FHSD+/HIV− and FHSD−/HIV+ groups is similar. In these two groups, frontal cortical systems appear to be similarly affected.

Another major analysis was performed in HIV+ patients only. It tested the statistical effects of type of antiretroviral treatment classified by its relative ability, very good ($n=41$) versus good-to-poor ($n=105$), to penetrate the CNS. The results depicted in Figure 3 show that the more penetrant ART agents do indeed increase theta ERO power. But, again, the effect is qualified by an interaction (FHSD×penetrance) with FHSD and is limited to the frontal electrode sites (F3: $F=5.8$, $p=0.01$; F4: $F=4.7$, $p=0.03$). Although not statistically significant, there was a trend in the data suggesting that these more penetrant agents also improved two indicators of task performance, proportion correct [$0.93 (.01SE) \rightarrow 0.97 (.01)$; $F=3.5$, $p=0.06$] and reaction time [$0.45 (.01) \text{ sec} \rightarrow 0.42 (.01) \text{ sec}$; $F=2.7$, $p=0.10$], regardless of FHSD status.

These statements about the effects of penetrant ART agents warrant an important qualification. Additional analyses showed that the improvement in theta ERO power, and the marginal improvement in task performance, in the FHSD− groups were not solely related to CNS penetrance. Patients receiving these agents also exhibited signs of better health: a higher CD4 count ($F=4.6$, $p=0.03$) and a marginally lower log10 viral load. However, when these peripheral disease severity markers were entered as covariates, the improvement in theta ERO power (Figures 3 and 4) and marginal improvement in task performance related to CNS penetrance remained significant.

4. DISCUSSION

The present investigation was designed to answer a question about the likely role of a family history of substance dependence in complicating our ability to detect neurophysiological impairments associated with HIV/AIDS as well as the remediation of these impairments with ART. The findings provide an answer. While performing a simple and brief selective attention task, HIV/AIDS patients showed a diminished theta ERO response in comparison to a seronegative control group if and only if the patients had no immediate family history of substance dependence. The same complication was apparent in detecting the neurophysiological benefit from ART agents hypothesized to be more versus less CNS penetrant: the benefit was not detectable among patients with a FHSD.

4.1. Are these findings significant?

This investigation did not demonstrate a robust effect of either HIV or FHSD on behavior. Thus, we cannot conclude at this time that the present results are clinically or behaviorally

significant. Yet, the study did examine an EEG feature related to behavior. In secondary analyses, we found significant correlations between theta ERO power at the F3 electrode, for example, and proportion correct ($r = 0.25$, $p < 0.001$) as well as reaction time ($r = -0.23$, $p < 0.001$). In other words, the theta ERO decrement might not be silent or trivial. It may warn of an occult impairment which could become behaviorally significant under other circumstances. In a future study, it would be interesting to challenge HIV-1 seropositive patients with a selective attention task of a longer duration and possibly reveal a more profound behavioral impairment than was shown presently.

A different discussion about significance derives from our demonstration of significant changes in theta ERO power related to HIV-1 and ART. The fact that both variables affected this measure, albeit in the FHSD– groups only, argues strongly for the future use of theta ERO power as practical tool or biomarker for evaluating the neurophysiological aspects of HIV-1 and its treatment. Indeed, theta ERO power offers advantages in economy, convenience, reliability, and capacity (i.e., number of patients and design factors that can be examined) which cannot be matched by functional magnetic resonance imaging (Bennett and Miller, 2010) or other functional neuroimaging methods.

A third discussion about significance pertains to the present failure of HIV-1 seropositive patients with a FHSD to show different responses when treated with more versus less CNS-penetrant ART agents (Figure 3). Of course, one should be very cautious about accepting this null hypothesis of no difference until it is replicated repeatedly. Yet, the apparent lack of an ART effect in this group may imply that HIV+ patients with a FHSD may be members of a neurophysiologically distinct population, which requires a different treatment regimen for their neurophysiological impairments. The second implication of the null finding is that a FHSD should either be a design or exclusion factor in all clinical trials assessing new treatments for cognitive and neurophysiological impairments in HIV/AIDS. Indeed, one wonders if the negligible neurocognitive improvements after ART reported in other studies (Al-Khindi et al., 2011) would have become significant if the studies were limited to patients without the complication of a FHSD.

4.2. Confounds and Caveats

A critical reader may ask if group differences in ART medication adherence might confound our results and limit our ability to interpret them. Unfortunately, we did not monitor ART adherence. Yet, we can marshal two arguments against its role. The arguments could be stated as follows.

First, we know from other studies that a personal history of substance dependence and, by inference, a FHSD are associated with decreased adherence with antiretroviral treatment (Grierson et al., 2011; Nahvi et al., 2012). Therefore, one would predict that a FHSD would be associated with signs, such as a lower CD4 cell count and a higher viral load, indicating a more severe disease state. A more severe state would likely also be reflected in greater neurocognitive impairment in these HIV+/FHSD+ patients. Fortunately, in our sample, we do not see evidence of greater disease severity among patients with a FHSD: their CD4 counts and viral loads were not significantly different from those of patients without a FHSD.

The second argument against medication adherence as a confound focuses on the FHSD+/FHSD– group difference in the response to ART. Here, one need only recognize that we are comparing ART agents with a lesser versus greater ability to penetrate the CNS. There is no logical reason, apart from willingness to tolerate side effects, why patients with a FHSD would be more adherent to one type of antiretroviral treatment versus another and thereby

show a different neurophysiological response. However, a future study should confront the medication adherence issue more directly and test its role.

A critical reader may also have concerns about the potential role of the participants' personal histories of substance dependence, a history that is likely confounded with the family history. Indeed, in our analyses, we see evidence of this association: participants with a FHSD reported more alcohol and drug use problems in their own lives than participants without a FHSD (Table 2). Further, theta ERO power was negatively correlated with substance dependence severity and positively correlated with duration of abstinence (Table 1). We addressed this confound in the only feasible manner: factor scores estimating each participant's severity of use and recency of use were employed as covariates and thereby discounted from the statistical effects of a FHSD. Because personal and family histories of substance dependence were highly correlated, it was not practical or reasonable to exclude participants with personal histories of substance dependence from the sample. Also, although the total sample size was large, it was not so large as to allow a powerful test of the statistical effects of substance dependence and a FHSD in the same analysis.

4.3. Conclusions

The present demonstration of an interaction between HIV/AIDS and a FHSD raises interesting questions regarding genetic vulnerability to neurocognitive impairment in HIV/AIDS. Admittedly, family history is not an ideal independent variable for testing genetic hypotheses because it captures both genetic and environmental effects. An investigation of candidate genes could be fruitful.

One candidate worthy of further study is the *CHRM2* gene, for it has been implicated in the risk for alcohol dependence and other disorders (Luo et al., 2005; Wang et al., 2004). In addition, polymorphisms of this gene have been associated in a large sample with the same event related theta oscillations studied presently (Jones et al., 2006; 2004). Other worthwhile candidates are *GRM8* (Chen et al., 2009), *DRD4* (Vogel et al., 2006), and *HTR7* (Zlojutro et al., 2011) for they too have been associated with substance dependence, theta ERO power, or an EEG feature, P300, strongly related to theta ERO power. We suspect that an examination of these theta ERO- and substance-dependence-related genes as factors moderating response to NeuroAIDS treatments may be more worthwhile than a study of the genes more typically associated with neurocognitive dysfunction. Indeed, recent studies of these *APOE* (Chang et al., 2011; Joska et al., 2010; Spector et al., 2010) or *COMT* (Levine et al., 2012) gene polymorphisms have not shown that they reliably moderate or amplify the neurocognitive impairments of HIV/AIDS or their response to ART.

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Figure 1.

Group-averaged theta event-related oscillation power from +50 to +850 ms. The vertical line segments bracket the +200 to +550 ms period over which average area under the curve was calculated.

Figure 2.

Cortical projections (overhead view) of sLORETA current source densities in the control (HIV-, FHSD-), HIV+, and FHSD+ groups. Note the similar topographies and amplitudes of the CSD reductions in the HIV+ and FHSD+ groups.

Figure 3. HIV+ patients only. Theta ERO area under the curve [covariate-adjusted Mean (+1 SE)], at F3 and F4 electrodes, as a function of the type [see Figure 9 in (McArthur et al., 2011)] of ART and family history. Note that a positive family history of substance dependence obscures the treatment-related improvements in theta ERO power seen in the FHSD- group (* $p < 0.05$).

Table 1

Correlations of Theta ERO power with three relevant background variables.

	Theta ERO power @ F3	Theta ERO power @ F4	Theta ERO power @ C3	Theta ERO power @ C4	Theta ERO power @ P3	Theta ERO power @ P4
Substance Dependence Severity Factor Score	-0.20 [*]	-0.17 [*]	-0.17 [*]	-0.14 [*]	-0.14 [*]	-0.10
Abstinence Duration Factor Score	0.17 [*]	0.16 [*]	0.17 [*]	0.14 [*]	0.14 [*]	0.09
BDI-II Depression Score	-0.11	-0.09	-0.14 [*]	-0.12	-0.17 [*]	-0.15 [*]

^{*} p<0.05.

Background Characteristics [Mean (SE)]

Table 2

	n	Age (yrs)	Education (yrs)	KBIT Standardized IQ	BDI-II Depression Symptoms	MAST Alcohol Problems	DAST-10 Drug Problems	Substance Dependence Severity Factor Score	Abstinence Duration Factor Score	CD4 Count (cells/ μ L)	Log10 Viral Load (copies/mL)	Plasma TNF-alpha (ng/mL)
Male HIV– FHSD–	14	39.2(1.5)	13.2(6)	89.9(7.1)	6.2(2.2)	2.1(7)	2.2(7)	–0.52(.27)	0.04(.27)	784.7(53.8)		2.0(.3)
Male HIV– FHSD+	28	39.5(1.3)	11.9(.1)	92.1(2.0)	13.1(2.0)	6.4(1.2)	4.0(.5)	0.69(.19)	0.03(.19)	919.4(90.2)		1.9(.1)
Male HIV+ FHSD–	42	43.1(.9)	11.7(.2)	92.1(1.9)	13.7(1.6)	4.6(.9)	3.5(.5)	0.11(.15)	–0.31(.15)	304.8(28.8)	.87(.19)	4.1(.6)
Male HIV+ FHSD+	48	41.3(.8)	12.3(.3)	92.6(2.5)	14.1(1.4)	5.4(.8)	3.3(.4)	0.07(.14)	–0.05(.14)	361.9(37.5)	1.31(.18)	3.9(.4)
Female HIV– FHSD–	20	38.5(1.3)	12.4(1.3)	99.1(3.1)	6.2(1.0)	0.7(.5)	1.3(.4)	–0.69(.22)	0.71(.22)	889.8(68.3)		2.3(.5)
Female HIV– FHSD+	30	39.2(1.2)	12.2(.3)	90.1(2.4)	13.1(2.0)	4.8(1.1)	2.6(.5)	–0.12(.18)	0.04(.18)	1062.7(71.3)		2.0(.3)
Female HIV+ FHSD–	26	39.9(1.2)	11.6(.3)	88.2(2.2)	17.3(2.6)	3.5(.9)	2.1(.5)	–0.27(.19)	0.07(.19)	390.3(49.6)	.89(.25)	2.7(.3)
Female HIV+ FHSD+	30	39.8(1.1)	10.9(.3)	90.7(2.4)	15.5(1.9)	7.1(1.1)	3.4(.6)	0.34(.18)	–0.10(.18)	458.1(72.5)	.91(.19)	3.0(.3)
Significant main or interaction effects		HIV+>HIV–	HIV+<HIV–		HIV+>HIV–FHSD+>FHSD–HIV× FHSD	FHSD+>FHSD–	FHSD+>FHSD–	FHSD+>FHSD–		HIV–>HIV+		HIV+>HIV–

Table 3

Task performance and theta ERO power [covariate-adjusted Mean (SE)] by group

	Reaction Time In sec	Proportion Correct	Theta ERO power @ F3	Theta ERO power @ F4	Theta ERO power @ C3	Theta ERO power @ C4	Theta ERO power @ P3	Theta ERO power @ P4
Male HIV – FHSD–	0.48 (0.02)	0.93 (0.03)	10.1 (2.2)	10.8 (2.1)	11.1 (2.2)	11.2 (2.1)	10.6 (2.3)	10.2 (2.0)
Male HIV – FHSD+	0.45 (0.02)	0.92 (0.02)	9.8 (1.6)	10.3 (1.5)	10.5 (1.6)	10.6 (1.5)	11.1 (1.6)	10.5 (1.5)
Male HIV+ FHSD–	0.44 (0.01)	0.97 (0.02)	8.3 (1.3)	8.2 (1.2)	8.9 (1.3)	8.7 (1.3)	10.0 (1.3)	9.2 (1.2)
Male HIV+ FHSD+	0.45 (0.01)	0.98 (0.02)	11.0 (1.2)	10.6 (1.15)	12.9 (1.2)	11.7 (1.1)	13.7 (1.2)	11.6 (1.1)
Female HIV – FHSD–	0.47 (0.02)	0.95 (0.03)	13.4 (1.9)	13.7 (1.8)	17.4 (1.9)	16.3 (1.8)	18.0 (1.9)	17.3 (1.7)
Female HIV – FHSD+	0.50 (0.01)	0.89 (0.02)	7.8 (1.5)	7.7 (1.4)	9.5 (1.5)	9.4 (1.4)	10.9 (1.5)	10.2 (1.4)
Female HIV+ FHSD–	0.45 (0.02)	0.91 (0.02)	9.2 (1.6)	9.6 (1.5)	12.4 (1.6)	12.9 (1.6)	13.9 (1.7)	13.3 (1.5)
Female HIV+ FHSD+	0.43 (0.02)	0.96 (0.02)	10.0 (1.5)	10.2 (1.4)	11.8 (1.5)	12.0 (1.5)	13.0 (1.5)	12.0 (1.4)
Significant main or interaction effects			HIV × FHSD	HIV × FHSD				