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A Family History of Psychopathology Modifies the Decrement in Cognitive Control Among Patients with HIV/AIDS

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Abstract

The present study was designed to evaluate the effect of HIV/AIDS on cognitive control and to determine if the effect is modified by familial risk for either alcohol or mood disorders. Sixty HIV-1 seropositive and 75 seronegative volunteers were assigned to 4 subgroups defined by the crossing of a diagnosis of alcohol dependence in the biological father with diagnoses of either major depressive disorder or bipolar disorder in the biological mother. Cognitive control was evaluated during a task in which subjects were asked, on occasion, to inhibit the impulse to respond in the same physical direction as the stimulus and instead respond in the opposite direction. Event related brain potentials and measures of task performance were recorded.

The task evoked a negative shift in a late slow potential (SP) as well as an increment in reaction time when cognitive control was challenged. An important finding was an interaction between trial type, HIV/AIDS, and family history: HIV/AIDS and family history each attenuated the negative shift in the SP to such a degree that no further attenuation could be accomplished by the other. The effects of familial risk for alcohol versus mood disorders were equivalent.

In conclusion, the absence of change in a late slow potential following a challenge to cognitive control may represent a marker of familial risk for both externalizing and internalizing disorders. The effects of familial risk on this slow potential are sufficiently robust as to attenuate the effects of HIV/AIDS on the probable generators of the response: the anterior cingulate and prefrontal cortex.

Keywords

HIV; Family History; Event Related Potentials; Mood Disorder; Alcoholism; Internalizing Disorders; Externalizing Disorders; P300; AIDS

1. Introduction

The present study evaluated the ability of HIV-1 seropositive patients to exercise cognitive control during a laboratory task. Admittedly, problems with cognitive control are not specific to this population (Bolla et al., 2004; Chen, Wong, Chen, & Au, 2001; Dao-Castellana et al., 1998; Domes et al., 2006; Flannery et al., 2007; Hanes, Andrewes, Smith, & Pantelis, 1996; Hiatt, Schmitt, & Newman, 2004; Kerns et al., 2005; Kim et al., 2006; LeGris & van Reekum, 2006; Perlstein, Larson, Dotson, & Kelly, 2006; Soeda et al., 2005; Tedstone & Coyle, 2004; Weiss et al., 2007; Yucel et al., 2007). Yet, they may be a prevalent feature. Acting impulsively

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and failing to exercise good judgment when contemplating high risk behaviors, including intravenous drug use and unprotected sex, now accounts for the majority of new cases of HIV-1 infection.

Numerous reports have presented evidence suggesting impaired cognitive control among patients infected with HIV-1 (Castellon, Hinkin, & Myers, 2000; Chang et al., 2002; Geier et al., 1993; Hinkin, Castellon, Hardy, Granholm, & Siegle, 1999; Llorente et al., 1998; Martin et al., 2004; Martin et al., 1998; Martin et al., 1992a). HIV/AIDS patients exhibit a pattern of deficits wherein frontal and striatal brain regions appear disproportionately affected (Castello, Sherman, Courtney, Melrose, & Stern, 2006; Cloak, Chang, & Ernst, 2004; Weed & Steward, 2005; Wiley et al., 1998). These impairments are particularly (Claypoole et al., 1993; Egan, Brett, & Goodwin, 1992; Martin et al., 1993; Reger, Welsh, Razani, Martin, & Boone, 2002), but not exclusively (Arendt, Hefter, Nelles, Hilperath, & Strohmeyer, 1993; Baldewicz et al., 2004; Forton et al., 2005; Goodwin, Pretsell, Chiswick, Egan, & Brett, 1996; Martin, Sorensen, Edelstein, & Robertson, 1992b; Paul, Cohen, & Stern, 2002; Stern, Silva, Chaisson, & Evans, Bauer 1996), evident in the advanced stages of disease, and can remain significant despite antiretroviral treatment (Bauer & Shanley, 2006; Chao, Lindgren, Flenniken, & Weiner, 2004).

Unfortunately, the interpretation of studies of cognitive control in HIV/AIDS patients is not straightforward. Though the disease may directly affect the processes involved in resolving stimulus-response conflict, it may indirectly impair control by delaying the recognition of conflict. For example, HIV/AIDS patients exhibit slowing on simple tasks measuring information processing speed as well as impaired stimulus processing as evidenced by abnormal event related potentials (ERP) (Bauer & Shanley, 2006; Bungener, Le Houezec, Pierson, & Jouvent, 1996; Chao et al., 2004; Evers, Husstedt, Luttmann, Bauer, & Grotemeyer, 1996; Goodwin et al., 1996; Husstedt et al., 2002; Kellinghaus et al., 2006; Polich & Basho, 2002; Polich, Ilan, Poceta, Mitler, & Darko, 2000; Tartar et al., 2004). In addition, the most compromised of patients (Koss, Ober, Delis, & Friedland, 1984) may adopt a bias wherein responses are deliberately and indiscriminantly delayed (Laming, 1979; Rabbitt, 1966) in an attempt to simplify the task (Band, Ridderinkhof, & van der Molen, 2003; Kohnert, Bates, & Hernandez, 1999; Koss et al., 1984). All three alternatives are possible accounts for the different levels of performance of HIV-1 seropositive and seronegative groups (Castellon et al., 2000; Chang et al., 2002; Geier et al., 1993; Hinkin et al., 1999; Llorente et al., 1998; Martin et al., 2004; Martin et al., 1998; Martin et al., 1992a) on, for example, the Stroop test (Alvarez & Emory, 2006; Demakis, 2004; Derrfuss, Brass, Neumann, & von Cramon, 2005; MacLeod, 1991). These accounts do not provide a complete explanation. But, they may explain a portion of the variance.

Apart from this discussion regarding neurocognitive factors contributing to impairment is a more important discussion of patient characteristics that may amplify impairment. One example is a family history (FH) of either a mood or substance use disorder. Mood disorders are over-represented in the HIV-1 seropositive population (Bing et al., 2001; Penzak, Reddy, & Grimsley, 2000; Rosenberger et al., 1993) and in the family members of patients with mood disorders (Giles, Biggs, Rush, & Roffwarg, 1988; Weissman et al., 2005). Similar findings have been reported for substance use disorders (Bing et al., 2001; Lieb et al., 2002; Nurnberger et al., 2004; Petry, 1999). Thus, as a group, HIV/AIDS patients are more likely than seronegative volunteers to possess a modestly different familial and genetic background which, in part, contributes to their elevated risk for mood and substance use disorders and cognitive dysfunction. A greater understanding of the role of family history could prove important for identifying the subset of seropositive patients who will continue to exhibit cognitive impairments in the current era of improved antiretroviral treatment and thereby face greater

challenges to their personal safety, workplace performance, or quality of life (Lopez, Wess, Sanchez, Dew, & Becker, 1998; Osowiecki et al., 2000).

A question arising from this proposed analysis of family history is whether its different forms have different effects. More specifically, one can ask whether a FH of an externalizing disorder (e.g., alcoholism; FHA) and a FH of an internalizing disorder (e.g., major depressive or bipolar disorder; FHM) differentially affect brain function, as measured, for example, by event related brain potentials (Nieuwenhuis, Aston-Jones, & Cohen, 2005; Polich & Criado, 2006). Some authors have argued that a family history of alcoholism (Iacono, Carlson, Malone, & McGue, 2002; Iacono, Malone, & McGue, 2003; Patrick et al., 2006) and other externalizing disorders is a more critical determinant of ERP amplitude decrements than is a FH of depression and other internalizing disorders. One older meta-analysis of studies (Polich, Pollock, & Bloom, 1994) published prior to 1994 is often cited in support of the association with familial alcoholism. Yet, a number of more recent studies have not replicated it (Bauer, Hesselbrock, O'Connor, & Roberts, 1994; Bauer, 1997; Bauer & Hesselbrock, 1999a, 1999b; Fein & Chang, 2006; Houston, Bauer, & Hesselbrock, 2004; Preuss et al., 1999; Viana-Wackermann, Furtado, Esser, Schmidt, & Laucht, 2006). Debate has therefore continued with some investigators arguing that a high familial density should be required in the definition of a positive FH to reduce the number of phenocopies. However, one outcome of this requirement is an increased prevalence of other psychiatric disorders, including internalizing disorders, in the family (Nurnberger et al., 2004). The overlap of a FHA with other disorders in the family may mediate, amplify, or add to, its effects on ERPs and thereby call into question the specificity of the ERP decrement.

Recent candidate gene studies also suggest that ERP decrements are not specific to a FH of alcoholism or externalizing disorders. Polymorphisms of the CHRM2 gene have been associated in several independent studies with both alcohol dependence and major depressive disorder (Luo et al., 2005; Wang et al., 2004). Furthermore, these same polymorphisms have been shown to alter the low frequency components of the ERP which define the P300 (Jones et al., 2006; Jones et al., 2004) as well as overlapping slow potentials (SP). Thus, the popular interpretation (Iacono et al., 2002; Iacono et al., 2003; Patrick et al., 2006) of a decrease in the amplitude of a late slow potential, such as the P300, as a marker of familial risk for externalizing disorders appears incomplete. One additional contribution of the present study was to confront the question of specificity by contrasting the effects of familial risk for externalizing (alcohol dependence) and internalizing (major depressive or bipolar disorder) disorders in the same subjects.

The task employed for revealing differences in the ERP and behavioral correlates of cognitive control associated with HIV/AIDS and family history was a version of the Simon task (Bauer, 2002; Simon, 1969; Simon, Small, Ziglar, & Craft, 1970). In this version, subjects are briefly presented with a right or left-pointing arrow on a computer monitor. An additional word, 'same' or 'opposite', appears on the same monitor screen directing the subject to select a left or right response key that is spatially consistent with, or opposite to, the direction of the arrow. Previous investigations of the Simon task have demonstrated that the SP (Bauer, 2002; Valle-Inclan, 1996a, 1996b; Zhou, Zhang, Tan, & Han, 2004), like behavioral performance, is diminished or delayed when the direction of the prepotent response, cued by the arrow's direction, and the direction indicated by the instruction are in conflict.

2. Method

2.1 Recruitment and Screening Procedures

Sixty HIV-1 seropositive subjects were recruited via advertisements posted within outpatient Infectious Disease Clinics in the greater Hartford, CT region. Interested individuals were

invited to telephone a member of the research staff for eligibility screening. The telephone interview included questions about demographic characteristics, general medical status, substance use, and psychiatric symptoms. Individuals who passed the initial telephone screen were invited to visit the Health Center on a subsequent day, during which an IRB-approved consent form and a medical records release were signed. Additional eligibility screening and laboratory evaluations were performed on that day.

The most common method for recruiting the 75 members of the HIV-1 seronegative group was word-of-mouth advertising provided by the seropositive participants. HIV-1 seronegative volunteers were invited to telephone the research assistant for initial screening and were brought to the Health Center for further screening. They were subject to the same protocol as the HIV/AIDS patients.

After completing the informed consent and medical release documents, all subjects were asked to provide a blood sample for laboratory confirmation of HIV serostatus. The clinical laboratory evaluation also included CBC with differential, HIV RNA viral load, CD4 lymphocyte count and percent, VDRL, HBV screen, HCV, toxoplasmosis and cytomegalovirus antibody titers, renal and liver function, serum protein, albumin, and G-6-PD. 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. In addition, 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, 1994; Robins, 2002), used for detecting DSM-IV Axis I and II disorders, was then administered by a research assistant formally trained in its administration and with 11 years of relevant experience. Subjects also completed questionnaires or brief interviews assessing medical history, medication use, parental psychopathology, demographics, psychiatric symptoms, alcohol and drug use, and cognitive status. The assessments included the Addiction Severity Index (ASI; (McLellan, Luborsky, Woody, & O'Brien, 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)]. In addition, the Kaufman Brief Intelligence Test [KBIT; (Kaufman, 1990)] was administered to derive an estimate of VIQ.

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, participants 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 or recent (past year) dependence upon alcohol, cocaine, or opiates were also exclusions. However, current use of methadone was not. Subjects 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.

For the analysis, HIV-1 seropositive and seronegative subjects were assigned to one of two subgroups defined by the presence (FHM+) versus absence (FHM-) of a report during the interview that the biological mother met DSM criteria for a diagnosis of either major depressive disorder or bipolar disorder. The groups were further divided by the presence (FHA+) or absence (FHA-) of a report that the biological father met DSM-IV diagnostic criteria for alcohol dependence. The Family History Assessment Module (Rice et al., 1995) was used. It would have been preferable to conduct direct interviews with parents to verify the diagnoses. But, the majority of these ≈ 40-year-old subjects were unable or unwilling to involve their parents in the study.

2.2 Data Collection

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 electrode application was complete, the subject was escorted into a sound-shielded chamber and seated in a comfortable chair. The chair faced a 14-inch computer monitor used for the presentation of visual stimuli. Two response keys were located at opposite ends of a response panel which the subject held in his/her lap.

The subject performed a version of the Simon Task wherein the computer was programmed to present a total of 80 discrete trials. The intertrial interval was fixed at 2 s. The task duration was 200 s. A small fixation spot was present in the center of the computer monitor throughout the task.

On each trial, the computer simultaneously displayed either a right- or left-pointing arrow as well as a single word, viz., 'SAME' or 'OPPOSITE', for 500 ms. The subject was instructed to press the response key whose spatial location corresponded to the direction indicated by the arrow when the word 'SAME' was displayed (i.e., no spatial conflict between stimulus and response). He/she was instructed to press the response key on the opposite side when the word 'OPPOSITE' was displayed (spatial conflict). The trial types were equiprobable and intermixed. The subject was allowed to practice the task for five to ten trials to verify his/her comprehension of the instructions. Accuracy in responding was emphasized over speed.

The electroencephalogram was recorded throughout the task. For the detection of eyeblink and eye movement artifacts, a pair of electrodes was placed diagonally above and below the left eye. The 31 channels of the EEG and 1 channel of eye movement (EOG) activity were appropriately amplified (EEG gain=20K, EOG gain=2K) and filtered (bandpass=0.01–12 Hz) using a SA Instrumentation Company amplification system. Along with markers indicating stimulus and response onsets, the EEG and EOG channels were routed to an A/D converter, and sampled at a rate of 200 Hz for 50 msec preceding and 1200 msec following the onset of each stimulus. During off-line computations, single trial data were sorted by electrode and trial type. Before averaging, trials containing an eye movement deviation greater than 50 μ V were deleted. Trials with A/D converter overflow and incorrect responses were also deleted.

Time-point averaged waveforms were then created from a minimum of 15 (mean=23.3, sd=4.7) accepted trials of each category. The amplitude of the SP was estimated by the average area under the curve between 700 and 1100 ms following stimulus onset. This area measure was chosen over a peak amplitude measure because a distinct peak was not consistently present in the records of all subjects under both trial conditions. The interval of 700–1100 msec was chosen because it is a time period previously shown (Bauer, 2002) to differentiate ERPs between no-conflict and conflict trials.

Behavioral performance indices were also recorded during the task and summarized offline. Average reaction time and the percentage of trials with correct responses were sorted by trial types and 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. Significant interaction effects revealed by ANOVA were further evaluated with Tukey post hoc tests.

The analyses of reaction time and performance accuracy were conducted with simple repeated measures ANOVA models with 3 grouping factors (HIV/AIDS, FHA, FHM) and one repeated measures factor (Trial Type). Similar analyses were conducted on SP area. We considered various options for summarizing SP area prior to the ANOVA. One of the considered options was to employ data from all 31 electrode sites and calculate an average measure of SP area across correlated electrode sites, e.g., within anterior and posterior scalp regions. However, an alternative option was chosen. The latter choice was guided by an examination of the scalp topography (Figure 1) of the SP difference between no-conflict and conflict trials, i.e., the Simon effect. Because the voltage difference was focused near the Fz electrode, analyses of the effects of the grouping and repeated measures factors only employed data from this electrode site. Including data from additional electrode sites in the analysis would have added noise to the measurement of the SP.

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, approximately 39.2 years of age, and educated for an average of 12.3 years. Many had histories of illicit drug abuse and/or alcohol abuse; however, DSM-IV-defined dependence on illicit drugs or alcohol during the year prior to the assessment was exclusionary. The HIV-1 seropositive participants were remarkably healthy: viral loads were low and CD4+ T-lymphocyte counts were, in 68.3% of the cases, greater than 200 cells/ μ l. Seventy-percent of the patients were actively participating in antiretroviral treatment. None met the MMSE criterion for a diagnosis of dementia. Table 1 summarizes the demographic, substance use, psychological, and medical characteristics of the subjects as a function of HIV-1 serostatus, FHA, and FHM.

The groups differed on a few characteristics. The differences were expected and often served to validate the independent variables. For example, the HIV+ and HIV- groups differed on CD4 cell count [$F(1,127)=46.2$, $p<.001$]. In addition, the FHA+ and FHA- groups differed on the lifetime number of alcohol and drug problems respectively reported on the MAST [$F(1,127)=10.2$, $p<.002$] and DAST-10 [$F(1,127)=5.2$, $p<.025$]. Also, the FHM+ and FHM- groups differed significantly [$F(1,127)=11.0$, $p<.001$] on the number of depression symptoms reported on the BDI-II. No other group differences in alcohol or drug use, or CD4 cell count were indicated by significant main or interaction effects.

There were no significant differences among the groups in gender or racial composition. Yet, the groups did differ in the number of childhood conduct disorder symptoms. Generally, more symptoms were reported by HIV+ than HIV- subjects [$F(1,127)=4.0$, $p<.05$]. However, no further increment in symptoms was present in HIV+ subjects with a FHA [HIV $\times$ FHA: $F(1,127)=5.9$, $p<.02$] or with a FH of both alcoholism and depression [HIV $\times$ FHA $\times$ FHM: $F(1,127)=4.3$, $p<.04$].

3.1 Task performance

Analyses of reaction time [$F(1,127)=25.2$, $p<.001$] and proportion correct [$F(1,127)=17.7$, $p<.001$] both revealed a significant main effect of repeated measures factor, trial type (Table 2). In general, reaction time was slowed by 46 ms and the hit rate deteriorated by 5.1% when subjects were asked to inhibit the prepotent response. These analyses revealed no significant main effects of the grouping factors.

The only interaction to attain statistical significance was an interactive effect of trial type and FHM on reaction time [$F(1,127)=4.12$, $p<.05$]. An examination of cell means revealed that the

magnitude of the Simon effect among subjects with no FH of mood disorder was +64 ms (mean $\pm$ se: $.78 \pm .02$ vs. $.85 \pm .03$). Among subjects with a FH of mood disorder, this effect was attenuated, +28 ms ($.83 \pm .05$ vs. $.86 \pm .06$), and no longer statistically significant in post hoc tests.

3.3 SP area

The ANOVA of SP area at the Fz electrode revealed a simple main effect of trial type [$F(1,127) = 9.81, p < .003$]. The Slow Potential shifted in a less positive direction (Figure 1) on trials requiring inhibition of the prepotent response (mean $\pm$ se: $+5.05 \pm 1.1 \mu V$ vs. $+4.08 \pm 1.1 \mu V$). This decrement in the slow potential occurred in parallel with the increment in reaction time reported above.

The analysis also revealed a complex series of interactions between trial type and the grouping factors. Specifically, the 3-way interactions of Trial Type $\times$ HIV/AIDS $\times$ FHA [$F(1,127) = 4.31, p < .04$] and Trial Type $\times$ HIV/AIDS $\times$ FHM [$F(1,127) = 4.53, p < .04$] were both statistically significant. In an attempt to interpret these interactions, we conducted Tukey hoc tests evaluating the pairwise difference between SP area on Conflict and No Conflict trials (e.g., Figure 2 and Figure 3) for each combination of the 4 cells formed by the grouping factors, i.e., HIV $\times$ FHM and HIV $\times$ FHA. In the absence of HIV, FHM, and FHA, there was a robust and statistically significant reduction in SP area on Conflict trials. In contrast, the presence of HIV/AIDS was associated with an attenuated and nonsignificant SP response to spatial conflict. The presence of either a FHM or a FHA was also associated with an attenuated SP response. Yet, in the presence of either FHM or FHA, there was no further reduction in SP area associated with HIV/AIDS. The pattern of differences between the trial types associated with a FHM and a FHA was found to be the same.

4. Discussion

The present investigation was designed to answer three questions: (1) Is HIV/AIDS associated with a deficit in cognitive control? (2) Is this deficit modified by family history? And, (3) does the effect of family history vary by type, i.e., a family history of alcohol dependence versus a family history of a mood disorder?

4.1 The Effects of HIV/AIDS on Cognitive Control

The answer to the first question is simple: HIV-1 seropositive subjects did indeed exhibit a deficit in the neurophysiological processing of a challenge to cognitive control. However, this deficit was only apparent in the subset of seropositive subjects free of the complicating effects of a FHA or FHM. When FHA- or FHM- subjects were asked to inhibit the prepotent response elicited by the Simon task, the HIV-1 seronegative subgroup exhibited a significant reduction in SP area whereas the HIV-1 seropositive subgroup exhibited a significantly smaller reduction. The frontal focus (Figure 4 and Figure 5) of the group difference in the magnitude of the Simon effect can be interpreted as reflecting HIV/AIDS-mediated disruption of brain regions, viz., anterior cingulate and prefrontal cortex (Abrahamse & Van der Lubbe, 2007; Barch et al., 2001; Botvinick, Cohen, & Carter, 2004; Carter et al., 2000; di Pellegrino, Ciaramelli, & Ladavas, 2007; Kerns, 2006; Pardo, Pardo, Janer, & Raichle, 1990; Soeda et al., 2005), important for the redirection of processing toward the alternative response. The absence of a corresponding difference between the HIV-/+ groups in the magnitude of the reaction time increment may indicate that the disruption is too subtle to affect behavior. Alternatively, it may indicate that the HIV-1-seropositive patients were capable of recruiting compensatory neural mechanisms, not reflected in our measurements of the SP, to accomplish the task. A different approach to SP measurement, involving a denser electrode array (e.g., ≥ 64 channels) and current source analysis, could be used to evaluate the latter hypothesis. Source analysis from

a dense electrode array could also be informative in deciding whether the SP is a late-occurring P300 (Valle-Inclan, 1996a,1996b) or is more similar to the N2 (Lavric, Pizzagalli, & Forstmeier, 2004;Wendt, Heldmann, Munte, & Kluwe, 2007).

The effect of HIV/AIDS on SP area was modest and likely muted by the good health of the HIV-1 seropositive group. Only one-third (31.7%) of the patients were immunosuppressed or afflicted with an AIDS-defining illness. The percentage of patients meeting DSM-IV criteria for dementia was 0%. A skeptical reader may interpret the health status of the seropositive group as a recruitment bias which underestimates the “true” effects of HIV/AIDS. Yet, it is arguable whether a bias truly exists, because the characteristics of our sample do not markedly deviate from those of the larger population of patients currently living with HIV/AIDS. Since the introduction of highly active antiretroviral therapy, the rate of HIV-1 associated dementia in the developed world has declined 40–50% (Brew & Gonzalez-Scarano, 2007; Gisslen & Hagberg, 2001; McArthur, 2004) and now affects only a small, i.e., < 10%, fraction of patients with advanced disease. Dementia has been replaced, predominantly, by a cognitive and motor impairment similar in severity (Baldewicz et al., 2004; Reger et al., 2002) to the level typically seen in studies of a personal or familial history of mood disorder or alcohol dependence.

4.2 The moderating effect of FH

Because the neurophysiological impact of HIV/AIDS is now relatively modest in most patients, it is more readily amplified, or moderated, by other variables including personal histories of depression (Baldewicz et al., 2004; Stern et al., 2001) or alcoholism (Green, Saveanu, & Bornstein, 2004; Schulte, Mueller-Oehring, Rosenbloom, Pfefferbaum, & Sullivan, 2005) as well as family histories of these psychiatric disorders. In the present study, we examined the interaction of HIV/AIDS with a FHA and a FHM. Yet, in assigning subjects to subgroups based upon family history, differences between the FH subgroups emerged in their personal histories. As was expected, the FHA+ subgroup reported more alcohol and drug problems than their FHA– peers. Similarly, the FHM+ subgroup reported more depression symptoms than their FHM– peers. Although these differences in personal history serve to validate FH as a risk factor, they also introduce a complication for interpreting the SP findings. To address the issue, we computed correlations between BDI-II, MAST and DAST-10 scores, and SP area and reaction time, within groups. The group-averaged correlations were uniformly not significant (p 's = 0.17 – 0.78). In addition, and importantly, none of participants met DSM-IV criteria for a diagnosis of alcohol or illicit drug dependence during the previous year. Therefore, in interpreting differences associated with family history, or in its interaction with HIV/AIDS, we need not be greatly concerned about personal history as a confound. Of course, if we had not excluded subjects who were in active phase of alcohol/drug dependence, or in a severe and active phase of depression, then the role of these personal history variables would have been more significant.

The analysis of the interaction between FH and HIV/AIDS confirmed the hypothesis: FH reduced the size of the Simon effect on SP area and modified the reduction associated with HIV/AIDS (Figure 3). The interaction of FH and HIV/AIDS suggests that they affect overlapping brain regions. In fact, a wealth of literature implicates both in disrupting various subregions of the frontal brain (Bauer & Hesselbrock, 2002;Castelo et al., 2006;Cloak et al., 2004;Schweinsburg et al., 2004;Viana-Wackermann et al., 2006;Weed & Steward, 2005; Wiley et al., 1998). The underadditive pattern of the interaction further suggests that the disruptive effect of each is so significant as to blunt the disruptive effect of the other. Importantly, the effects of a FHA and a FHM on the SP deficit in HIV/AIDS were found to be equivalent, thereby challenging the notion (Iacono et al., 2002;Iacono et al., 2003;Patrick et al., 2006) that diminished SP amplitude is a specific marker of familial risk for externalizing disorders.

The demonstration of an interaction between HIV/AIDS and FH 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. As noted previously, one candidate worthy of further study is the CHRM2 gene, for it has been implicated in the risk for both alcohol dependence and major depressive disorder (Luo et al., 2005; Wang et al., 2004). In addition, polymorphisms of this gene have been associated low frequency event related oscillations which contribute significantly to the P300 (Jones et al., 2006; Jones et al., 2004) and other slow potentials.

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Figure 1.

The scalp topography of ERPs, averaged across all subjects, recorded during no-conflict (solid line) and conflict (dotted line) trials. Note the frontal scalp focus of the difference between trial conditions.

Figure 2.

Voltage difference at Fz between event-related potential waveforms elicited by Conflict and No Conflict trials as a function of HIV-1 serostatus and familial mood disorder. The difference waveforms as a function of serostatus and familial alcoholism were similar. The epoch width spans -50 to +1200 ms. Stimulus onset time is indicated by the arrow. SP area was calculated over a window of +700 to +1100 ms.

Figure 3.

The magnitude (mean + 1 SEM) of the Simon effect (conflict minus no-conflict) on SP area as a function of HIV-1 serostatus and family history. The interactions of HIV-1 with family histories of mood disorders (FHM) and alcohol dependence (FHA) are respectively shown in the top and bottom panels.

Figure 4.

The scalp topography of the Simon effect (conflict minus no-conflict) on SP area as a function of HIV-1 serostatus and a family history of mood disorders (FHM).

Figure 5.

The scalp topography of the Simon effect (conflict minus no-conflict) on SP area as a function of HIV-1 serostatus and a family history of alcoholism (FHA).

Table 1

Demographic, psychological, and medical characteristics [mean (sd) or percent] of the 8 subject groups. Non-overlapping superscripts designate statistically significant differences ($p < .05$).

	N	Yrs Age	Yrs Educ	MAST	DAST-10	BDI-II	CD4 count	LOG ₁₀ Viral Load	% Receiving ART	KBIT composite IQ	% Cauc	% Female	# Conduct Disorder symptoms
HIV -, FHM -, FHA	34	37.9 (6.3)	13.1(2.7)	2.4 (4.2) ^a	1.8(2.5) ^a	8.4 (8.8) ^a	836.8 (258) ^a	--	--	97.6(12)	26.5	44	1.5(1.7) ^a
HIV -, FHM -, FHA	20	40.2 (7.6)	12.3(1.3)	3.3 (5.3) ^b	3.0(3.0) ^b	12.6 (9.7) ^a	958.3 (448) ^a	--	--	90.0(12)	15	45	1.8(1.6) ^a
HIV -, FHM +, FHA	12	37.0 (5.5)	13.6(4.0)	2.3 (1.8) ^a	1.6(2.8) ^a	17.6 (12) ^b	773.6 (294) ^a	--	--	107(15)	8.3	58	1.3(2.3) ^a
HIV -, FHM +, FHA	9	33.6 (8.1)	12.6(2.0)	6.0 (8.7) ^b	3.4(3.3) ^b	18.4 (16) ^b	1089.1 (331) ^a	--	--	92.5(11)	22.2	33	4.7(3.7) ^b
HIV +, FHM -, FHA	21	40.9 (5.0)	11.7(1.9)	2.9 (4.8) ^a	2.9(3.2) ^a	14.1 (11.4) ^a	281.0 (183) ^b	2.3(2.2)	76.2	88.2(14)	19	43	3.2(3.2) ^b
HIV +, FHM -, FHA	14	40.6 (7.2)	11.7(1.9)	6.7 (7.0) ^b	4.3(4.1) ^b	13.2 (9.3) ^a	387.4 (291) ^b	2.9(1.8)	78.5	92.7(11)	42.8	50	3.1(2.4) ^b
HIV +, FHM +, FHA	13	37.2 (5.3)	12.5(1.8)	2.5 (2.0) ^a	2.7(4.1) ^a	27.7 (20.1) ^b	483.2 (329) ^b	3.2(2.1)	61.5	94.5(10)	7.6	38	5.0(3.9) ^b
HIV +, FHM +, FHA	12	40.4 (5.8)	11.5(2.2)	9.9 (6.9) ^b	5.5(3.0) ^b	19.1 (8.5) ^b	444.4 (290) ^b	2.6(2.0)	66.6	96.4(12)	25	42	3.1(2.7) ^b

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Table 2

Task performance and SP area at Fz [mean (se)]

		Reaction Time in sec	Proportion Correct	SP Area at Fz
HIV −, FHM −, FHA −	No Conflict	.70(.04)	.82(.04)	10.1(1.5)
	Conflict	.78(.05)	.77(.05)	7.0(1.5)
HIV −, FHM −, FHA +	No Conflict	.87(.05)	.77(.05)	4.5(1.7)
	Conflict	.93(.05)	.74(.05)	4.9(1.7)
HIV −, FHM +, FHA −	No Conflict	.68(.15)	.57(.15)	3.4(2.2)
	Conflict	.74(.17)	.51(.16)	3.3(2.1)
HIV −, FHM +, FHA +	No Conflict	.92(.09)	.87(.09)	3.9(2.8)
	Conflict	.95(.09)	.83(.09)	2.8(3.0)
HIV +, FHM −, FHA −	No Conflict	.79(.06)	.84(.06)	8.2(1.9)
	Conflict	.84(.06)	.76(.06)	5.6(2.4)
HIV +, FHM −, FHA +	No Conflict	.77(.05)	.79(.05)	3.1(1.8)
	Conflict	.84(.06)	.70(.06)	2.9(2.5)
HIV +, FHM +, FHA −	No Conflict	.95(.13)	.73(.10)	3.9(2.5)
	Conflict	.96(.14)	.74(.12)	3.2(2.7)
HIV +, FHM +, FHA +	No Conflict	.78(.07)	.81(.08)	3.3(2.6)
	Conflict	.80(.08)	.75(.08)	3.0(2.4)