Alcohol Abuse and HIV Infection Have Additive Effects on Frontal Cortex Function as Measured by Auditory Evoked Potential P3A Latency

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Both alcohol and human immunodeficiency virus (HIV) infection have been shown to produce central nervous system (CNS) morbidity in frontal brain regions. The degree to which the CNS morbidity in HIV infection, as it affects frontal cortex function, may be preferentially increased by alcohol abuse was examined using the auditory P3A evoked potential. The P3A indexes an orienting response, maximal over frontal cortex that occurs when novel nontarget stimuli are presented in the midst of a target detection paradigm. Four groups of subjects were compared: HIV+ alcohol abusers, HIV+ light/nondrinkers, HIV+ alcohol abusers, and HIV- light/non-drinkers. The alcohol abuser and light/nondrinker HIV+ groups were matched on percent CD4 lymphocytes, insuring that the results reflected specific CNS effects and were not a result of differences between the groups in the degree of systemic immune suppression. Alcohol abuse and HIV infection had at least additive effects on P3A latency, consistent with alcohol abuse worsening the effect of HIV disease on frontal cortex function. Post-hoc analyses suggested that concomitant alcohol abuse results in the effects of HIV infection on P3A latency becoming manifest earlier in the HIV disease process.

Key Words: P3A, HIV infection, alcohol abuse, auditory EP

Introduction

The late stages of infection by the human immunodeficiency virus (HIV) are associated with a neurological syndrome, HIV Associated Dementia (HAD), characterized by disordered cognition, motor function, and behavior (Working Group 1991; Navia et al 1986b; Price et al 1988; Snider et al 1983). Patients with neurological complications of acquired immunodeficiency syndrome (AIDS) may either have diffuse encephalopathy caused by HIV or other virus infection, or multi-focal deficits attributable to opportunistic organisms (Detmer & Lu 1986). Although about 75% of autopsies on unselected AIDS patients show central nervous system (CNS) pathology (Anders et al 1986), less than 40% of AIDS patients are neurologically symptomatic (Levy et al 1985). Although there can be CNS effects secondary to opportunistic CNS infection, CNS effects in most HIV+ patients are due to the direct effects of CNS HIV infection. On autopsy, abnormalities are found predominantly in white matter and subcortical areas, with relative sparing of the cortex (Navia et al 1986a), however a recent series of postmortem studies has found losses in prefrontal and frontal cortical neurons (Masliah et al 1992a, 1992b;
Wiley et al (1991). Functional abnormalities in frontal regions have also been demonstrated in studies using Single-Photon Emission Computed Tomography (SPECT) and Positron Emission Tomography (PET) (Holman et al 1992; Pascal et al 1991; Tran Dinht al 1990; Woods et al 1991). These functional abnormalities are not only evident in neurologically symptomatic HIV+ patients but also in asymptomatic HIV+ subjects. It is not known if these frontal results reflect direct effects of HIV on frontal cortex or reflect frontal changes secondary to damage to subcortical or fronto-striatal white matter, which result in reduced frontal afferent input.

Functional CNS manifestations of HIV infection in asymptomatic seropositive patients are seen in a number of areas. Psychomotor slowing is the most consistent finding, manifesting as a decrement in performance on timed motor tasks involving a cognitive component, such as the Trails B Test (Joffe et al 1986; Ollo and Pass 1988; Rotenberg et al 1987; Rubinow et al 1988; Saykin et al 1988; Tross et al 1988), the Digit-Symbol subtest of the Wechsler Adult Intelligence Scale-Revised (WAIS-R) (Ollo and Pass 1988), and certain reaction time tests (Martin et al 1992). Slowness on purely motor tasks (e.g., finger tapping and grooved pegboard) has also been found consistently (Rotenberg et al 1987; Tross et al 1988), as have impairments in verbal memory and in frontal-lobe functions such as abstract reasoning, concept formation and cognitive flexibility (e.g., the Categories test [Grant et al 1987; Joffe et al 1986; Rubinow et al 1988] and the Similarities subtest of the WAIS-R [Joffe et al 1986; Silberstein et al 1987; Van Gorp et al 1989]).

Recent reports have suggested that increased latency of certain evoked potential measures may be a sensitive early indicator of the CNS effects of HIV infection (Arendt et al 1990; Goodin et al 1990; Goodwin et al 1990; Messenheimer et al 1990; Ollo et al 1991); however, the sensitivity of evoked potential measures to HIV CNS effects is not uniformly reported (McAllister et al 1990).

The evidence for significant toxicity of chronic alcohol consumption on the central nervous system derives from neuropsychological findings, neuroimaging studies, and neuropathological examinations. In chronic alcoholics, neuropsychological impairments have been noted in abstraction-ability and concept formation on a variety of tests (Donovan et al 1976; Grant and Reed 1985; Jones and Parsons 1972; Ron et al 1980). Perceptual motor deficits have also been described (Grant and Reed 1985). Further, many chronic alcoholics show perceptual impairments on tasks that lack a motor component (Brandt et al 1983; Robertson et al 1985), and demonstrate both anterograde and retrograde memory deficits (Brandt et al 1983; Butters & Brandt 1985; Robertson et al 1985). On brain computed tomography (CT) studies, chronic alcoholics show evidence of cerebellar atrophy, dilation of the cerebral ventricle and increased sulcal width, particularly in the frontal and frontal-parietal-temporal areas (Jernigan et al 1986; Wilkinson 1985). Sulcal widening has been found fairly consistently in alcoholics of all ages, whereas ventricular dilatation is found more frequently in older alcoholics (Pfefferbaum et al 1988). Cerebral blood flow and glucose metabolism studies have found: (1) a significant negative correlation between hemispheric gray matter blood flow and total alcohol consumption, and (2) decreased glucose utilization in the medio-frontal area in chronic alcoholics (Rogers et al 1983; Samson et al 1986), and (3) an increased incidence of focal perfusion defects in alcoholics compared to controls (Melgaard et al 1990). Neuropathological examinations, in addition to confirming the neuroradiological findings of enlarged sulci, dilated ventricles, and cerebellar degeneration, have revealed patchy loss of neurons, axons, and dendrites, as well as hemorrhagic lesions in the periaqueductal and periventricular gray matter, thalamus, and mammillary bodies (Courville 1955; Victor et al 1971). Cortical neuronal counts demonstrate loss of neurons from the superior frontal cortex (Harper et al 1987). There is no loss of neurons from motor, anterior cingulate, or middle temporal gyri (Krill and Harper 1989), although there is a shrinkage of the mean area of neuronal cell bodies in the superior frontal, cingulate and motor areas. Neuropsychological studies also suggest that the frontal lobes are more susceptible to the deleterious effects of alcohol on brain function than are other cortical regions (Walsh 1983; Waugh et al 1989; reviewed in Fein et al 1990). Animal studies (reviewed in Walker et al 1981) and human studies (reviewed in Harper and Kri1 1990) strongly suggest that chronic ethanol treatment leads to learning deficits, loss of dendritic spines, reduction in dendritic branching, and cell death in vulnerable areas of the brain, and that these are toxic effects of ethanol rather than secondary nutritional effects. A general model proposed by Harper and Kril (1990) is that alcohol-related cortical brain damage falls into two different classes. There is loss of dendritic arbor and shrinkage of neuronal body size. These changes are potentially reversible and occur in many brain regions. In contrast, there is actual neuron death, which is irreversible and has been demonstrated to date primarily in frontal cortex.

Alcohol abuse may lead to increased systemic immune dysfunction in HIV+ individuals via immune suppressive effects (Bagasra et al 1987; Glassman et al 1985; Watson et al 1985), with associated increased morbidity. The research reported here used evoked potential measures to examine the degree to which the CNS morbidity of HIV is preferentially increased by alcohol abuse (i.e., beyond that expected on the basis of alcohol’s systemic immunosuppression). To accomplish this goal, we controlled for the degree of systemic immune dysfunction by studying HIV+ samples of...
active alcohol abusers and light/nondrinkers that were com-
parably stratified with regard to percentage of CD4 lympho-
cytes, a marker of systemic immunosuppression. The effect of
alcohol abuse in HIV+ samples was compared to the effect
of alcohol in the absence of HIV infection.

We used an evoked potential paradigm designed to assess
frontal cortex function, with the hope that such a paradigm
would detect both the effects of alcohol abuse and the early
effects of HIV infection on brain functions. This paradigm,
called the P3A paradigm, was originally developed for vi-
sual stimuli by Courchesne and colleagues (1975) to mea-
sure a kind of frontal cortex orienting response that occurs
when novel nontarget stimuli are presented in the midst of a
target detection paradigm. We used a variant of this para-
digm in the auditory modality, which also reflects a CNS
component of the orienting response and has been shown to
be sensitive to frontal cortex damage (Knight 1984). We

tested the hypothesis that both chronic alcohol abuse and
HIV infection may affect P3A latency or amplitude either
via direct effects on frontal cortex or via effects on subcorti-
cal afferent input to frontal cortex.

Methods

Subjects

Gay/bisexual men were recruited via posting of flyers in the gay
community and advertisements in the gay community
newspapers in San Francisco. Four samples were studied:
31 HIV seropositive (HIV+) alcohol abusers (mean age 36.8
± 8.6 years), 37 HIV+ light/nondrinkers (mean age 37.7 ±
8.4 years), 18 HIV seronegative (HIV−) alcohol abusers
(mean age 40.5 ± 10.0 years), and 16 HIV− light/nondrinkers
(mean age 37.0 ± 9.7 years). The flyers and adver-
tisements asked for HIV+ and HIV− light/nondrinkers and
“men who could hold their liquor.” HIV seronegativity was
documented via Polymerase Chain Reaction (PCR) testing
(one subject who was recruited as HIV− had a positive PCR
and was excluded from the study). Subjects were excluded
if they were currently using or had a history of intravenous
IV drug abuse, or had a history of significant use of other
drugs of abuse, including prescription drugs.

The inclusion criteria for the alcohol abuser groups was a self-re-
port of consumption of greater than 120 drinks/month
currently and for at least 3 years prior to participation in the
study. One drink was defined as 1 oz of hard liquor, 4 oz of
wine or 12 oz of beer. HIV+ and HIV− alcohol abusers
drank an average of 229.5 and 228.6 drinks per month,
respectively, and drank for an average of 12.91 and 12.53
years, respectively. For the light/nondrinking groups, sub-
jects must by self-report have never consumed greater than
50 drinks/month. HIV+ and HIV− light/nondrinkers
consumed an average of 9.2 and 12.1 drinks per month,
respectively.

The alcohol abuser and light/nondrinker HIV+ samples
were closely matched on percentage of CD4 lymphocytes
(alcohol abusers: 17.5% ± 9.6%; light/nondrinkers: 17.4% 
± 9.3%). Among the HIV+ light/nondrinkers, seven had
reached Centers for Disease Control (CDC) stage IV, seven
were in CDC stage III, and the remaining 23 subjects were in
CDC stage II. For the HIV+ alcohol abusers, only 2 had
reached CDC stage IV, 14 were in CDC stage III, and the
remaining 15 subjects were in CDC stage II.

None of the alcohol abusing patients were intoxicated
when they participated in any of the study procedures. All
alcohol-abusing subjects reported refraining from drinking
on the mornings of study appointments, at our request. All
procedures were approved by the University of California at
San Francisco (UCSF) Committee on Human Research and
written consent was obtained from all subjects prior to study.

EP Recording

Fourteen electroencephalograph (EEG) channels were
recorded using an electrode cap with tin disk electrodes
(Electro-Cap International, Eaton, OH), referenced to a tin
electrode clipped to the left earlobe. Electrode locations
included Fp1, Fp2, F7, Fz, F8, T7, C3, Cz, C4, T8, P7, Pz,
P8, and Oz. Vertical eye movements were monitored via
gold cup electrodes placed above and below the right eye,
and horizontal eye movements were monitored via elec-
rodes placed at the lateral canthi. All impedances were
below 5000 ohms and signals were amplified 50,000 times
times by a Gras Model 12 Neurodata Acquisition System with
analog filters at 0.1 and 100 Hz. Stimulus presentations
were controlled and data were collected by ERPSYSTEM
Software (Neurobehavioral Laboratory Software) using an
Analog Devices RTI 800-815/F laboratory interface card on a
20 MHz Intel 80386-based personal computer. Data were
sampled for 800 msecs at a 250 Hz within channel resolution
beginning 40 m sec prior to stimulus presentation. The lag
between samples on successive channels was 12 μsec, result-
ing in a 168 μsec offset between samples on the first and 14th
EEG channel. Individual trials were rejected if activity on
either eye movement channel exceeded ±75 MV. Data were
collected until there were at least 80 artifact-free single trials
in the standard condition, and 60 artifact-free single trials in
each of the target and novel nontarget conditions.

Auditory Stimulation

Stimuli for this study consisted of 1000 Hz and 2000 Hz
tones, and excerpts from a sound-effects tape. Tone stimuli
were generated by a Wavetek 4 MHz Function Generator
(model 182A), passed through a Hewlett-Packard 350D
Attenuator, amplified by a Pioneer SX-2300 stereo re-
ciever/amplifier and delivered to the subject over Realistic
NOVA’20 headphones (Tandy Corporation, Houston, TX).
The same monaural signal was delivered to each ear of the headphones. After determining the subject's threshold for detecting the stimuli using a method of limits procedure, stimuli were presented at 55 dB SL. Each trial consisted of a 52 msec presentation of a tone or a 52 msec excerpt from the sound-effects tape. The interstimulus interval varied randomly between 1.9 and 2.0 sec. Seventy percent of the trials were 1000 Hz “standard” tones; 15% were 2000 Hz “target” tones; the remaining 15% were the “novel nontarget” excerpts from the sound-effects tape.

Procedure
During the session, the subjects were relaxed, awake, and seated upright in a room that was quiet but not acoustically isolated. They were instructed to sit quietly, listen to the stimuli, and to try to keep their eyes still. Subjects responded only to the target tones by lifting the right index finger off a response pad. They were instructed not to respond to either the standard tones or to the excerpts from the sound effects tape.

Waveform Analysis
ERP data is most commonly analyzed via peak picking on the average waveform at several electrode channels. This method generates separate peak latencies and amplitudes at each electrode location for a component without giving a clear picture of the component topography. For compound components, such as the P300, which includes P3A and P3B components, peak picking can give a misleading indication of either P3A or P3B because examination of waveforms at single channels cannot untangle the contributions of components that overlap in time. An example of the confounding of these two components in the waveforms at Fz and Pz is illustrated in Figure 1A, where peak picking would determine the latency of P3A as 356 msec, and the latency of P3B as 376 msec. The maps clearly indicate contributions from both components at these latencies.

To help solve these problems, we determined component latencies and amplitudes via examination of topographical maps in combination with plots of global field power. Topographical maps give a clearer picture of the changing electrical potential field over the scalp. Global field power is a reference-free measurement of mean potential difference between electrodes (Lehmann and Skrandies 1984). Because peaks in the global field power curve correspond to times of maximal activity on the scalp, they can be used to help determine the latencies of components in the ERP. (The following paragraph describes in detail how we used topographical maps and global field power plots for this purpose.) The use of global field power and topographical maps, which both incorporate information from all electrode sites, improves component identification and helps in the separation of overlapping components, such as the P3A and P3B. Figure 1B illustrates how topographic maps and global field power plots resolve P3A and P3B components for the example in Figure 1A, in which peak picking is problematic. The global field power and topographic maps reveal that P3A is maximal at 336 msec, and P3B is maximal at 404 msec.

All waveform analyses were performed blind with respect to subject’s alcohol and HIV status. For the standard condition, a topographical map of the data was constructed for each time point between 76 and 264 msec poststimulus, for measurement of N100 and P200 only. For the target and novel nontarget conditions, topographical maps were created for each time point between 76 and 456 msec poststimulus, for measurement of N100, P200, N200, P3A, and P3B components. A component was identified by looking for the conjunction of its characteristic topographical distribution, for example, for N100, a centrally occurring negativity around 100 msec, and a corresponding peak in global field power. Component latencies and amplitudes were then determined from the peak in the global field power plots that corresponded to the occurrence of the component maximum in the topographical maps. If, as sometimes happened, the P3A was clearly separated from P3B in the topographical maps, but it only appeared as a slight bump in the ascending part of the P3B global field power peak, the component latency was determined from the maps and the component amplitude was determined from the global field power at that latency. Figure 2 presents the data from such a subject. We note that not all components could be identified for all subjects (especially for the rare nontarget condition).

For comparison purposes, we also determined component latencies and amplitudes for P3A and P3B in the conventional manner. P3A was measured by choosing the largest peak between 260 and 520 msec in the subject’s averaged referenced average waveform at Fz. P3B was measured in a similar manner at Pz.

Component latencies and amplitudes thus measured were subjected to analyses of variance (ANOVAs). As noted in the introduction, our a priori research aim was to examine P3A amplitude and latency to the novel nontarget stimuli as an ERP measure of frontal cortex function. Subsequent to analysis of P3A, we examined the other waveform measures in a post hoc manner. No control for multiple comparisons was incorporated for these analyses, and their results should be taken as suggestive only.

Results
Table 1 presents the amplitude and latency of each component separately by condition (standard, target, novel nontarget), and by subject group.

A Priori Analyses

TOPOGRAPHIC ANALYSIS OF P3A LATENCY AND AMPLITUDE. The P3A component was identified in all but three HIV+ light/non-drinkers, one HIV+ alcohol abuser,
Figure 1. (A) Single channel analysis of one subject's P3A and P3B. These two components overlap in the average waveforms, resulting in misleading component latencies. (B) Topographical analysis. Novel nontarget condition. The use of topographical maps and the global field power plot leads to more accurate component identification.
Figure 2. The topographical maps and global field power plot for the P3A and P3B interval for another subject. Novel nontarget condition. The P3A is clearly separated from the P3B in the topographical maps, but it only appears as a slight bump in the ascending part of the P3B global field power peak.
and two HIV− alcohol abusers. HIV infection and active chronic alcohol abuse each resulted in a lengthening of the P3A latency in the novel nontarget condition, with these two effects being additive. The presence of drinking resulted in a 17 msec increase in P3A latency ($F_{1,95} = 8.38, p = 0.005$), whereas the presence of HIV seropositivity resulted in a 10 msec increase in P3A latency ($F_{1,95} = 3.99, p = 0.05$). Given the nonsignificant interaction between HIV status and drinking status ($F_{1,95} = 0.82, p = 0.37$), the presence of both HIV infection and chronic alcohol abuse had an additive effect, resulting in about a 26.5 msec increase in P3A latency in HIV+ alcohol abusers compared to HIV− light nondrinkers. Figure 3 presents the P3A latencies for each of the subject groups. This pattern of differences in mean P3A latency among the subject groups remained unchanged after partialling out P200 latency differences between the groups (see analysis of P200 below). The effect of alcohol abuse on P3A latency remained significant after controlling for P200 latency ($F_{1,95} = 6.31, p = 0.014$), whereas the significance level dropped just below the 0.05 criterion for the presence of HIV infection ($F_{1,95} = 3.20, p = 0.077$). Figure 4 presents the P3A latencies for the four groups after adjustment for the association between P3A and P200 latencies, illustrating the similarity of the covariate analysis results in comparison to the direct P3A analysis displayed in Figure 3. This analysis provides suggestive evidence that the effects of chronic alcohol abuse and HIV infection on P3A latency are independent of their effects on the processes involved in the generation of the P200 component.

Post-hoc analyses comparing subsamples based on CDC stage, although not significant, were suggestive that different patterns of effects were apparent in the alcohol abuser
and lighthondrinker HIV+ samples. Figure 5 presents the P3A latencies separately for the lighth nondrinkers and alcohol abusers, with the HIV+ groups separated into CDC stage II and III combined, and CDC stage IV groups. Among light/nondrinkers, the six patients who had progressed to CDC stage IV had the longest P3A latencies (324 ± 21 msec) compared to CDC stage III patients (306 ± 24 msec), or CDC stage II (i.e., asymptomatic seropositive [ASP] patients: 313 ± 26 msec) or HIV− controls (307.8 ± 21 msec). Among the HIV+ alcohol abusers, the two CDC stage IV patients actually had shorter P3A latencies (320 ± 11 msec) than the 14 CDC stage III (331 ± 23 msec) or the 14 ASP patients (339 ± 19 msec).

There was a trend for P3A amplitude to be reduced in alcohol abusers compared to nondrinkers in both the target ($p = 0.13$), and novel nontarget ($p = 0.08$) conditions.

**CONVENTIONAL (PEAK-PICKING) ANALYSES OF P3A LATENCY AND AMPLITUDE.** The results for P3A from conventional peak picking followed the same pattern as those just described, except that peak picking was not as effective at detecting the latency differences between the alcohol abusers and the lighthondrinkers. HIV infection resulted in a lengthening of the P3A latency in the novel nontarget condition ($F_{1,69} = 4.24, p = 0.04$), whereas there was only a trend for lengthening P3A with alcohol abuse ($F_{1,69} = 2.75, p = 0.10$), with these two effects again being additive (for the interaction between drinking and HIV status: $F_{1,69} = 0.20, p = 0.65$). The presence of drinking resulted in a 11 msec increase in P3A latency, whereas the presence of HIV seropositivity resulted in a 13 msec increase in P3A latency, and the combination of alcohol abuse and seropositivity resulted in a 24.5 msec increase in P3A latency compared to HIV− lighthondrinkers.

Peak picking analyses revealed no significant effects of HIV or drinking status (or their interaction) on P3A amplitude in either the target or novel nontarget conditions.

**Post Hoc Analyses**

**N100.** N100 latency was significantly longer in drinkers compared to nondrinkers in both the standard (100.5 ± 10.0 versus 96.0 ± 7.4 msec; $F_{1,99} = 4.74, p = 0.032$) and novel nontarget conditions (110.1 ± 11.8 versus 104.2 ± 11.0 msec; $F_{1,99} = 3.73, p = 0.058$), but not in the target condition (100.0 ± 10.8 versus 99.2 ± 11.8 msec; $F_{1,99} = 0.02, p = 0.902$). There was a trend toward an increase in N100 latency in HIV+ individuals evident only in the novel nontarget condition (108.3 ± 11.5 versus 104.8 ± 10.9 msec; $F_{1,95} = 2.43, p = 0.12$). There were no suggestions of any HIV status by drinking interactions, nor were there any N100 amplitude effects.

**P200.** P200 latency was lengthened in alcohol abusers in all three conditions. The increase in P200 latency was comparable in the standard and target conditions (13.6 msec, $p = 0.008$; and 14.7 msec, $p = 0.018$, respectively), but was largest in the nontarget condition (20.4 msec, $p = 0.001$). There was no HIV effect on P200 latency in the standard
condition ($p = 0.73$). For the target condition, there was a 13.0 msec increase in P200 latency with HIV infection ($F_{1,99} = 5.77$, $p = 0.018$). For the novel nontarget condition, this HIV effect became a trend, with the latency increase with HIV infection being 7.9 msec ($p = 0.13$). Given the lack of significant HIV status by drinking status interactions ($p > 0.30$ for each condition), these effects resulted in HIV+ alcohol abusers having the longest P200 latencies for the target and novel nontarget conditions, similar to the pattern of effects for P3A latency in the novel nontarget condition. The P200 latency effects were unchanged after N100 latency; however, statistically controlling for P200 latency reduced the effect in the target condition to a trend (9.5 msec difference, $p = 0.07$), whereas more markedly reducing the effect in the novel nontarget condition (5.3 msec difference, $p = 0.37$). There were no significant effects nor trends toward effects on N200 amplitude.

N200. N200 latency was increased in alcohol abusers by about 17.7 msec in the target condition ($F_{1,99} = 9.38$, $p = 0.003$), and by about 23.3 msec in the novel nontarget condition ($F_{1,99} = 11.06$, $p = 0.002$). There were no trends or significant effects of HIV infection on N200 latency nor any HIV status by alcohol-use status interactions. The N200 latency effects were unchanged by statistically controlling for N100 latency; however, statistically controlling for P200 latency reduced the effect in the target condition to a trend (9.5 msec difference, $p = 0.07$), whereas more markedly reducing the effect in the novel nontarget condition (5.3 msec difference, $p = 0.37$). There were no significant effects nor trends toward effects on N200 amplitude.

P3B. For P3B latency, there were no main effects for drinking status, HIV status, or their interaction. Within the HIV+ groups, CDC stage-IV patients had the longest P3B latencies ($F_{2,46} = 3.46$, $p = 0.04$; 373 ± 19 msec, $n = 9$ versus 344 ± 28 msec, $n = 21$ in CDC stage III patients and 354 ± 27 msec, $n = 38$ in ASP patients).

For both the target and the novel nontarget conditions, P3B amplitude was reduced in the alcohol abusers (target condition: $F_{1,99} = 5.20$, $p = 0.02$; novel nontarget condition: $F_{1,99} = 6.81$, $p = 0.01$). There was no effect of HIV status on P3B amplitude, nor was there any difference in amplitude as a function of CDC stage within the HIV+ samples (the mean P3B amplitudes were actually largest in the CDC stage IV patients).

Conventional peak picking analyses of P3B were again similar. There were no significant effects on P3B latency for drinking status, HIV status, or their interaction. P3B amplitude was reduced in the alcohol abusers only in the target condition ($F_{1,99} = 5.98$, $p = 0.02$). There was no effect of HIV status on P3B amplitude.

EYE MOVEMENTS: There were no differences among the groups on the percentage of trials lost to eye movements in any of the three conditions. Across all subjects, the average percentage of trials rejected for eye movements for the standard, target, and novel nontarget conditions were 16.2%, 10.8%, and 14.2%, respectively. Grand average
electrooculograms (EOGs) for each group in each condition are shown in Figure 6.

Discussion
Within a three-condition auditory target detection paradigm, the frontal P3A response to the rare nontarget stimulus exhibited increased latency associated with both chronic alcohol abuse and HIV infection. This result reflected the primary a priori planned comparison of this study and its statistical significance was unaffected by the multiple comparisons made on various other aspects of the ERP waveforms. The careful matching of the HIV+ alcohol abuser and light/nondrinking samples on percentage of CD4 lymphocytes assured that differences within the HIV+ cohort consequent to chronic alcohol abuse represent specific CNS effects of the alcohol abuse, rather than epiphenomena secondary to alcohol effects on the systemic immune response. The results reported here are consistent with accumulating evidence that alcohol abuse has deleterious effects on the frontal cortex. Cerebral blood flow studies in alcoholics show a preferential vulnerability of frontal (and partial) cortex to focal blood flow abnormalities (Risberg and Berglund 1987). Neuropathological studies have documented loss of neurons (Harper et al. 1987), shrinkage of neuronal cell body size (Krill and Harper 1989), and a reduction in the dendritic arbor of layer III pyramidal neurons (Harper and Corbett 1990) in superior frontal cortex. Although the location of the P3A generator is currently unknown, the frontal cortex is involved in the response, which is markedly affected by frontal cortex damage (Courchesne et al. 1975; Knight 1984).

We believe that delayed P3A latency holds promise as a potential sensitive and early measure of functional involvement of the frontal cortex in chronic alcohol abuse. We acknowledge the substantial overlap between groups in P3A latency and the limitations of this measure for use in indicating impairments in individual subjects, however.

Although some of the CNS damage due to chronic alcohol abuse is irreversible, there is clinical evidence for varying degrees of recovery of neuropsychological function and
brain volume with continued abstinence. In this regard, animal models of alcohol toxicity have demonstrated reductions of the dendritic arbor of Purkinje cells (Tavares et al 1983) and hippocampal neurons (Davies and Smith 1981) after chronic intoxication, with some recovery in the dendritic arbor of hippocampal pyramidal neurons with sustained abstinence (McMullen et al 1984). It has been suggested (Harper and Corbett 1990) that the re-arborization of neurons that have not yet died may underlie the recovery of neuropsychological function and the partial recovery of brain shrinkage with continued abstinence. P3A latency is a candidate physiological in vivo marker of such recovery, in that recovery may be reflected in a decreasing P3A latency over time in an individual.

If, as our results suggest, alcohol abuse and HIV infection have at least additive effects on one aspect of frontal cortex function, the cumulative effects of the alcohol and HIV insults on the brain may result in more impairment of substrate and less potential for recovery of function with abstinence. We note that all of the alcohol-abusing patients in this study were actively drinking. If less potential for recovery with abstinence occurs in HIV+ alcohol abusers, this would have important educational, outreach, and treatment implications. Earlier and more vigorous interventions in such patients may be warranted. Data on the recovery of function with abstinence in HIV+ alcohol abusers are urgently needed.

All of the points raised above regarding alcohol effects on frontal cortex function apply in a similar manner to the effects of HIV infection. HIV infection results in loss of neurons, shrinkage of neurons, and loss of dendritic arborization in frontal cortex (Wiley et al 1991, 1992). Executive and integrative functions are among those affected most early in CNS involvement in HIV disease. Furthermore, the striatum is affected early and much of the earliest involvement of the white matter in HIV disease involves fronto-striatal connections; both of these may result in effects on frontal cortex functions. We believe that increased P3A latency may prove to be an important measure of the presence and progression of HIV effects on frontal cortex function.

The results of this study provide suggestive evidence that concomitant active alcohol abuse worsens the effect of HIV disease on frontal cortex function. Post-hoc analyses suggested that in nonalcohol abusers, the HIV-related increase in P3A latency was evident primarily in CDC stage IV patients, whereas in alcohol abusers, increased P3A latency was also evident in patients in CDC stages II and III. This is consistent with concomitant alcohol abuse leading to earlier frontal cortex involvement secondary to HIV infection. Given the small sample sizes for the CDC stage by drinking status analyses, we acknowledge that this specific result was only suggestive. Replication of this finding in larger samples is important because of the implications that early intervention in HIV+ alcohol abusers may be warranted.

In this study, P3A effects were limited to P3A latency, with no effects apparent for P3A amplitude. Other investigators have demonstrated that P3A amplitude is affected by arousal and its dysfunction (Clark et al unpublished data; Grillon and Ameli unpublished data), and by noradrenergic neurotransmitter system manipulations (Turetsky and Fein unpublished data).

Our finding of increased auditory P3B latency with HIV infection occurring only in CDC stage IV patients is in agreement with Ollo et al (1991). We note that they reported deficits earlier in the disease process in a visual P300 paradigm. Whether a visual paradigm will also be more sensitive to frontal P3A deficits is an open question. Although Courchesne’s original study of the frontal P3A phenomena used a visual paradigm (Courchesne et al 1975), P3A has not been as robust a phenomenon when recorded in visual compared to auditory experiments.

Finally, we replicated the often reported decrease in P3B amplitude in alcoholic subjects. Decreased P3B amplitude is present in the adolescent children of alcoholics and has been proposed as both a genetic marker for the vulnerability to alcohol abuse and a consequence of alcohol abuse (Begleiter et al 1984; Elmasian et al 1982). We acknowledge the possibility that increased P3A latency may also be a vulnerability marker. In retrospect, it would have been invaluable to have collected family history data in our alcohol-abusing subjects to allow estimates of the potential genetic contribution to alcohol abuse and to the evoked potential findings in our samples.

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