Delayed Latency of the Event-Related Brain Potential P3A Component in HIV Disease

Progressive Effects With Increasing Cognitive Impairment

George Fein, PhD; Christie A. Biggins, PhD; Shane MacKay, MD

Objective: To examine the degree to which P3A latency was sensitive to the early and progressive effects of human immunodeficiency virus (HIV) disease on frontal cortex function by studying HIV-positive subjects who varied in degree of cognitive impairment.

Design: Event-related brain potential studies of four groups of subjects: cognitively nonimpaired high-risk HIV-negative subjects, cognitively nonimpaired HIV-positive subjects, cognitively mildly to moderately impaired HIV-positive subjects, and cognitively severely impaired HIV-positive subjects.

Setting: Voluntarily participating subjects on an outpatient basis at a medical center facility.

Participants: Seventy-one community-residing gay or bisexual HIV-positive male volunteers were compared with 17 HIV-negative male gay or bisexual subjects used as a control sample. The HIV-positive subjects were stratified with regard to severity of cognitive impairment into the following three subsamples: subjects who were cognitively normal (n=35), subjects with mild to moderate cognitive impairment (n=20), and subjects with severe cognitive impairment (n=16), with the samples closely matched in age. The HIV-positive subsamples were closely matched on percentage of CD4 lymphocytes. Subjects were excluded if they reported a history of drug or alcohol abuse, a major mental disorder, a head injury with loss of consciousness, or brain disease other than HIV related.

Main Outcome Measure: P3A latency.

Results: P3A latency was significantly delayed in HIV-positive subjects compared with HIV-negative control subjects, with a delay of 12 milliseconds in the cognitively normal group (P<.02) and the magnitude of delay increasing with increasing severity of HIV-associated cognitive impairments (P<.001). Delayed P3A was primarily associated with the progression of HIV-associated cognitive impairment, with a secondary and additive association with severity of HIV-associated medical illness.

Conclusion: This finding suggests that delayed P3A latency is sensitive to the early central nervous system effects of HIV and progresses with worsening of the central nervous system effects of HIV.

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SUBJECTS AND METHODS

SUBJECTS

Seventy-one gay or bisexual HIV-positive male subjects (mean age ± SD, 37.7 ± 7.6 years) were compared with 17 HIV-negative male gay or bisexual control subjects (mean age ± SD, 38.3 ± 10.8 years). The HIV-positive subjects were stratified with regard to severity of cognitive impairment as follows: subjects who were cognitively normal (n=35; mean age ± SD, 37.1 ± 8.9 years), subjects with mild to moderate cognitive impairment (n=20; mean age ± SD, 39.5 ± 6.2 years), and subjects with severe cognitive impairment (n=16; mean age ± SD, 36.9 ± 6.2 years), with the groups having been closely matched in age. Seronegativity for HIV in the control subjects was documented by means of polymerase chain reaction testing. Data from all HIV-negative control subjects and from 36 of the HIV-positive subjects have been reported previously, where they were compared with those of male gay or bisexual alcohol-abusing HIV-negative and HIV-positive samples. The HIV-positive non-alcohol-abusing subjects from the prior study were, for the most part (n=27), not cognitively impaired (only seven subjects had mild to moderate cognitive impairment, and two subjects had severe cognitive impairment). The non-alcohol-abusing subjects from that study were recruited from advertisements in the San Francisco (Calif) gay/bisexual newspapers and from flyers posted throughout the gay/bisexual neighborhoods in San Francisco. For the current analysis, samples from the previous study were primarily stratified with regard to severity of cognitive impairment. These additional subjects were recruited by delivery of flyers describing the study to all HIV-positive individuals enrolled in a local AIDS agency program that provides two meals a day to HIV-infected individuals who wish to help provide meals for themselves because mental or physical disabilities make meal preparation difficult.

Subjects were excluded if they reported a history of abuse of alcohol or other drugs, a major mental disorder, a head injury with loss of consciousness, or brain disease not HIV related. If accepted into the study, a potential subject underwent a number of procedures performed by various members of the research team, each of which was used to check again for an exclusionary condition that had not been reported in the phone interview.

The HIV-positive subsamples were closely matched on the percentage of CD4 lymphocytes, a measure of degree of systemic immunosuppression (cognitively normal, 16.0% ± 10.0%; mild to moderately cognitively impaired, 12.6% ± 9.2%; and severely cognitively impaired, 15.7% ± 8.7%). Among the HIV-positive nonimpaired subjects, 18 were classified as CDC clinical category A, 12 as CDC clinical category B, and five subjects as CDC clinical category C. Of the mild to moderately impaired HIV-positive subjects, seven were classified as CDC clinical category A, six as CDC clinical category B, and seven subjects as CDC clinical category C. Of the severely impaired HIV-positive subjects, five were classified as CDC clinical category A, five as CDC clinical category B, and six subjects as CDC clinical category C.

All procedures were approved by the University of California–San Francisco Committee on Human Research, and written consent was obtained from all subjects after the nature of the procedures was fully explained prior to study.

METHODS

Neuropsychologic Assessment

All subjects underwent neuropsychologic testing, during which a wide range of cognitive skills, including attention, concentration, memory, verbal language, problem-solving, visuospatial skills, and fine motor ability were assessed. The battery included the following: Wechsler Adult Intelligence Scale–Revised Digit Symbol and Digit Span,12 Shipley Institute of Living Scale,20 the Visual Functions Scale of the Luria-Nebraska Neuropsychological Battery,14 Rey-Osterreith Complex Figure,15 Trail Making Tests A and B,56 the Logical Memory I and II and the Visual Reproduction I and II subscales of the Wechsler Memory Scale,23 Finger Tapping, Grip Strength, Reaction Time, a 15-item modification of the Fuld Object Memory Evaluation,20 Short Category Test,57 Controlled Oral Word Association,62 Neurobehavioral Cognitive Status Examination,61 and the Hooper Visual Organization Test.62 Each test was scored according to its norms. We generated a global impairment score by first ranking each test score on a scale from 0 to 2, depending on severity of impairment. A subject was scored 1 if his performance was between the fifth and 15th percentile and 2 if his performance was below the fifth percentile. Points earned on all tests were then summed, and a subject was classified as not impaired, if the summed score was 0 to 1; mildly impaired, if the summed score was between 2 and 5; and severely impaired, if the summed score was 6 or greater. All the HIV-negative control subjects were scored as not impaired on the global impairment measure.

In addition to the measurement of clinical impairment, which was used to classify HIV-positive subjects into subsamples, an average percentile score for all neuropsychologic tests was calculated for each subject, as was an average percentile score for the four tests designed to measure prefrontal cortex functioning (Trails B, Controlled Oral Word Association, Digit Symbol, and the Short Categories Test). Table 1 presents the mean (SD) percentile scores for the control sample and for each of the HIV-positive subsamples.

Event-Related Brain Potential Recording

Initially, data were only recorded from an auditory three-condition P3A paradigm, using a 16-channel system (i.e., 14 electroencephalographic [EEG] channels and two eye-movement channels). Subsequently, the system was upgraded to 32 channels (the original 14 channels plus 16 additional EEG channels and the two eye-movement channels) and data were collected for both auditory and visual three-condition P3A paradigms. Forty-six subjects (17 control subjects, seven nonimpaired HIV-positive subjects, nine mild to moderately impaired HIV-positive subjects, and 13 severely impaired HIV-positive subjects) were tested with both auditory and visual protocols. For the auditory P3A, all data were analyzed using the 14-channel montage. Electroencephalographic recordings were made using an electrode cap with trolle cap with trolle cap with trolle cap with
trode cap with tin disk electrodes (Electro-Cap International, Eaton, Ohio), referenced to a tin electrode clipped to the left earlobe. Electrode locations for the auditory paradigm included Fp1, Fz, F4, T3, C3, Cz, C4, T4, P3 on the right, and Fp2, Fz, F3, T4, C4, Cz, T3, P4 on the left. Vertical eye movements were monitored via gold cup electrodes placed above and below the right eye, and horizontal eye movements were monitored via electrodes placed at the lateral canthi. For the visual paradigm, the 14 electrodes mentioned above were supplemented with electrodes at the following locations: F3, F4, P3, P4, Pz, O1, O2, F7, F8, C3, C4, CP3, CP4, O1, and O2. Vertical eye movements were monitored via gold cup electrodes placed above and below the right eye, and horizontal eye movements were monitored via electrodes placed at the lateral canthi. For the visual paradigm, the 14 electrodes mentioned above were supplemented with electrodes at the following locations: F3, F4, P3, P4, Pz, O1, O2, F7, F8, C3, C4, CP3, CP4, O1, and O2. All impedances were below 5000 $\Omega$ and signals were amplified 50,000 times by a data system (Grass Model 12 Neurodata Acquisition System, Quincy, Miss), with analog filters at 0.1 and 100 Hz. Stimulus presentations were controlled, and data were collected by an event-related brain potential (ERP) software system (ERPSYSTEM Software, Neurobehavioral Laboratory Software, San Francisco, Calif) using a laboratory interface card (Analog Devices RTI 800-815/79, Norwood, Mass) on a 20-MHz personal computer (based on Intel 80386, Euchel 386-20, Fremont, Calif). Data were sampled for 800 milliseconds at a 250-Hz within-channel resolution beginning 40 milliseconds prior to stimulus presentation. The lag between samples on successive channels was 12 microseconds, resulting in a 168-microsecond offset between samples on the first and 14th EEG channel. Individual trials were rejected if activity on either eye-movement channel exceeded 575 pV. 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 and Visual Stimuli

Auditory stimuli consisted of 1000- and 2000-Hz tones and excerpts from a sound effects tape. Tone stimuli were generated by a 4-MHz generator (Function Generator model 182A, WaveTek, San Diego, Calif), passed through an attenuator (Hewlett-Packard 350D Attenuator, Hewlett-Packard, Palo Alto, Calif), amplified by a stereo receiver/amplifier (Pioneer SX-2300, Tokyo, Japan), and delivered to the subject over headphones (Realistic NOVA 20, Tandy Corp, Houston, Tex). Stimulation was binaural with the same monaural signal delivered to each ear of the headphones. Each subject's threshold for detecting the stimulus was established using a method of limits procedure, after which stimuli were presented at 55 dB above threshold. Each trial consisted of a 52-millisecond presentation of a tone or a 52-millisecond excerpt from the sound effects tape. The interstimulus interval varied randomly between 1.9 and 2.0 seconds. Seventy percent of the trials were 1000-Hz "standard" tones, 15% were 2000-Hz "target" tones, and the remaining 15% were the "novel nontarget" excerpts from the sound effects tape. Visual stimuli consisted of two vertical lines (standards), two horizontal lines (targets), and random line fragments (rare nontargets), with stimuli in all three classes having identical average intensities. Stimuli were presented to the subject on a low-resolution frequency emission computer monitor set 75 cm from the subject. All stimuli were presented in the center of the upper half of the monitor screen and subtended at an angle of 1.88° horizontally and 2° vertically. Each trial consisted of a 796-millisecond presentation of one of the stimuli. Seventy percent of the trials were standards, 15% were targets, and 15% were novel nontargets.

Experimental Session Procedure

During the session, the subjects were relaxed, awake, and seated upright in a room that was acoustically isolated. They were instructed to sit quietly, listen to or watch the stimuli (depending on the paradigm), try to keep their eyes still, and to respond as quickly as possible only to the target stimuli by lifting their right index finger off a response pad.

Waveform Analysis

All waveform analyses were performed blindly, with respect to the subject's HIV and cognitive impairment status. Average waveforms for each subject were calculated from the single-trial data after elimination of trials with eye-movement artifacts. To diminish the effects of eye movements that were below the rejection criterion, the data were subjected to a frequency-domain eye-movement correction procedure. Component latencies and amplitudes were then determined by examination of topographic maps in combination with plots of global field power. Global field power is a reference-free measurement of mean potential difference between electrodes. Since 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. We present a complete description of this method and the rationale for its use in our article on auditory P3A component latency in patients with HIV disease with and without concomitant alcohol abuse. Briefly, for the standard condition, a topographic map of the data was constructed for each time point between 76 and 264-millisecond poststimulus for measurement of N100 and P200 components for the auditory paradigm and for each time point between 76 and 456 milliseconds poststimulus for measurement of N100, N165, and P230 components for the visual paradigm. For the target and novel nontarget conditions, topographic maps were created for each time point between 76 and 456 milliseconds poststimulus for measurement of the N200, P3A, and P3B components (for the auditory paradigm) and for each time point between 76 and 530 milliseconds poststimulus for measurement of the P3A and P3B components (for the visual paradigm), in addition to the components mentioned above. A component was identified by looking for the conjunction of its characteristic topographic distribution, ie, for N100, a centrally occurring negativity around 100 milliseconds, 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 topographic maps. Figure 1 presents the topographic maps and global field power plot for the P3A and P3B interval for a typical subject. If, as sometimes happened, especially with P3A, the map identification of the component did not correspond to a peak in the global field power, the component latency was determined from the maps and the component amplitude was determined from the global field power at that latency.
Because HIV is primarily recovered from macrophages, microglia, and multinucleated giant cells rather than from neurons or oligodendrocytes, the indirect effects of HIV infection have been hypothesized as causes of HAD.

Proposed mechanisms of HIV-associated CNS damage include toxic effects from the release of virus-coded products or cell-coded cytokines by infected cells, from immune responses to HIV, and from the generation of neurotoxins o wing to cell-to-cell interactions between infected monocytes and astrocytes. On autopsy, abnormalities are found predominantly in the white matter and subcortical areas, with relative sparing of the cortex; however, in a recent series of postmortem studies, losses in prefrontal and frontal cortical neurons have been found. Frontal cortex functional abnormalities have also been demonstrated in studies using single photon emission computed tomography and positron emission tomography. The abnormalities depicted on single photon emission tomographic scan are not only evident in neurologically symptomatic HIV-positive patients but also in asymptomatic HIV-positive subjects. It is not known whether these frontal results reflect the direct effects of HIV on the frontal cortex or frontal changes secondary to HIV effects on subcortical structures or on frontostriatal or frontothalamic white matter, which may result in reduced frontal afferent input.

Functional CNS manifestations of HIV infection in medically symptomatic patients are seen in a number of areas. Psychomotor slowing is the most consistent finding, manifested as a decrement in performance on timed motor tasks involving a cognitive component, such as the Trails B Test, the Digit-Symbol subtest of the Wechsler Adult Intelligence Scale-Revised, and certain reaction time tests. Slowness on purely motor tasks (eg, finger tapping and grooved pegboard) has also been found consistently as has impairment in verbal memory and frontal lobe functions such as abstract reasoning, concept formation, and cognitive flexibility (eg, the Categories test and the Similarities subtest of the Wechsler Adult Intelligence Scale-Revised). Medically asymptomatic patients exhibit a more subtle pattern of deficits, with decrements primarily in memory and manual dexterity areas, although mild decrements on measures of attention, concentration, information processing speed, mental flexibility, and perseveration have also been demonstrated.

A number of reports have suggested that increased latency of certain evoked potential measures may be a sensitive early indicator of the CNS effects of HIV infection. However, the sensitivity of evoked potential measures to HIV CNS effects is not uniformly reported.

We recently examined auditory P3A component latency in patients with HIV disease with and without concomitant alcohol abuse. We chose the P3A component because of the evidence suggesting that it reflects a kind of frontal cortex-orienting response that occurs when novel nontarget stimuli are presented in the midst of a target detection paradigm. The paradigm that we used was originally developed for visual stimuli by Courchesne and colleagues; we used an auditory modality variant of this paradigm. The P3A response to novel nontarget stimuli in this type of paradigm has been shown to be sensitive to frontal cortex damage, although the precise location of the P3A generator is currently unknown. In the studies by Knight and Yamaguchi and Knight, patients with circumscribed lesions of the dorsolateral frontal cortex demonstrated a reduction in P3A amplitude, with relative sparing of P3B. This was true for P3A generated in three different modalities (auditory, visual, and somatosensory). In contrast, patients with lesions of the temporoparietal junction showed near abolition of both P3A and P3B. It was postulated that the integrative functions of the temporoparietal junction are necessary for P3 generation, although this site could not be the sole generator of the P3. The differential effect of frontal lesions on P3A and P3B argues for a distinctive frontal cortex contribution to P3A generation only and at least partially different generator locations for P3A and P3B.

We found that latency of the P3A component was delayed with either HIV disease or alcohol abuse and that concomitant active alcohol abuse worsened the effect of HIV disease on P3A latency. Post hoc analyses suggested that, in nonalcoholic individuals, the HIV-related increase in P3A latency was evident primarily in clinical category C patients, as classified by the Centers for Disease Control and Prevention (CDC) (Atlanta, Ga) criteria, while in alcoholic individuals, increased P3A latency was also evident in CDC clinical category A and category B patients.

Table 1. Percentile Scores of All Neuropsychologic Tests and of the Four Tests Designed to Measure Prefrontal Cortex Functioning for Each Sample

<table>
<thead>
<tr>
<th>Test</th>
<th>HIV-Negative Sample, Control</th>
<th>Nonimpaired</th>
<th>Mildly Impaired</th>
<th>Severely Impaired</th>
</tr>
</thead>
<tbody>
<tr>
<td>Auditory</td>
<td>67.82 (10.47)</td>
<td>65.78 (6.26)</td>
<td>68.27 (10.30)</td>
<td></td>
</tr>
<tr>
<td>Prefrontal</td>
<td>68.82 (10.47)</td>
<td>65.78 (10.30)</td>
<td>68.27 (10.30)</td>
<td></td>
</tr>
<tr>
<td>Visual</td>
<td>68.82 (10.47)</td>
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<td></td>
</tr>
</tbody>
</table>

*NP indicates neuropsychologic; HIV, human immunodeficiency virus. Data are mean (SD).
information processing and preservation have also suggested that increased measures may be associated with the effects of HIV infection. Evoked potential measures uniformly reported.

The P3A component latency with and without cognitive impairment of the P3A component begins at its onset when novel nontarget stimuli in the midst of a target demand is evident. In the studies by Courchesne and colleagues, the different modalities evoked potential measures were sensitive to frontal cortex function, with relative sparing in the three different modalities (auditory, visual, somatosensory). In contrast, the topographic maps for P3A and P3B. It was clear that the onset of the temporal generator of the P3A component was different from that of the P3B component. P3A latency should be even more markedly delayed in HIV-positive patients with moderate or severe cognitive impairment. We also expanded on our initial investigation by using both auditory and visual P3A paradigms.

The patients in our HIV/alcohol study were, for the most part, cognitively normal, evidencing relatively little impairment secondary to either HIV disease and/or alcohol abuse. The purpose of the study reported herein was to extend the prior investigation to examine non-alcohol-abusing patients with significant cognitive impairment secondary to HIV disease. If P3A latency was indeed sensitive to the early effects of HIV disease on frontal cortex function, P3A latency should be even more markedly delayed in HIV-positive patients with moderate or severe cognitive impairment. We also expanded our analysis of P3A latency to the novel non-target stimuli in both auditory and visual paradigms as an ERP measure of frontal cortex function. Subsequent to the analysis of P3A latency, we examined other ERP-component amplitudes and latencies and the performance measures in a post hoc manner. For both the a priori and post hoc analyses, differences among the groups were first tested using one-way analyses of variance. If significance at P<.05 was obtained, one-tailed t tests comparing each HIV subsample with the control sample were conducted (including adjustment of degrees of freedom for unequal variances, where appropriate), and a single degree of freedom linear trend was also tested for, in which samples were weighted by their average neuropsychologic test percentile score. This trend analysis tested for a difference between the control sample and HIV-positive subsamples such that the difference would be smallest for the nonimpaired HIV-positive subsample and progressively larger for the mild to moderately and severely impaired HIV-positive subsamples. Similar trend analyses were performed using average prefrontal test performance.
Table 2. Latencies of the Auditory and Visual P3A in the Novel Nontarget Condition for Each Sample

<table>
<thead>
<tr>
<th></th>
<th>HIV-Negative Sample, Control</th>
<th>HIV-Positive Sample*</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Nonimpaired</td>
<td>Mildly Impaired</td>
<td>Severely Impaired</td>
</tr>
<tr>
<td>P3A Latency</td>
<td>305.25 (21.85)</td>
<td>317.53 (18.94)</td>
<td>335.40 (26.41)</td>
</tr>
<tr>
<td></td>
<td>370.78 (29.85)</td>
<td>370.86 (30.58)</td>
<td>404.89 (45.33)</td>
</tr>
<tr>
<td></td>
<td>344.31 (38.31)§</td>
<td>416.31 (46.37)†</td>
<td></td>
</tr>
</tbody>
</table>

*HIV indicates human immunodeficiency virus. Data are mean (SD).
†Different from control subjects, P < .05.
‡Different from control subjects, P < .001.
§Different from control subjects, P < .01.

There were no differences among the samples on the percentage of trials lost to eye movements in any of the three conditions. Because of a computer error, data on the novel nontarget condition were lost in one nonimpaired HIV-positive subject and in one severely impaired HIV-positive subject. The P3A component was identified in all other subjects, except for two severely impaired HIV-positive subjects for whom no P3A or P3B could be identified. In the novel nontarget condition, HIV infection resulted in an average delay in P3A latency of 22.8 milliseconds compared with that in the control sample (t18=3.1, P<.003). This delay was 12.3 milliseconds in the nonimpaired HIV-positive subsample (t18=2.04, P=.02), 30.2 milliseconds in the mild to moderately impaired HIV-positive subsample (t18=3.67, P<.001), and 39.1 milliseconds in the severely impaired HIV-positive subsample (t18=3.27, P=.002). Of the 67 patients with identified P3A latencies, 12 (18%) had P3A latencies greater than 2 SDs above the control mean (two [5.5%] of 34 patients in the nonimpaired HIV-positive subsample, six [30.0%] of 20 patients in the mild to moderately impaired HIV-positive subsample, and four [30.8%] of 13 patients in the severely impaired HIV-positive subsample). No control subject had a P3A latency above this cutoff.

The linear trend, which weighted each group by its average neuropsychologic test percentile score, was highly significant (F1,79=20.26, P<.001). We note that there was no correlation between average neuropsychologic test percentile score and P3A latency in the control sample (r=.06, P=.85). Figure 2 presents the auditory P3A latencies in the novel nontarget condition for the HIV-negative control sample and for each of the HIV-positive subsamples. The pattern of differences in P3A latency in the novel nontarget condition was also present in the target condition, although with reduced magnitude.

There was also an increase in P200 latency, only in the rare nontarget condition, evidenced primarily in the severely impaired HIV-positive subsample (22.8 milliseconds later than in the control sample; t18=3.09, P=.002). The P3A latency differences among the subject samples were not dependent on the P200 latency differences, and remained after partialling out P200 latency effects. After adjustment for P200 latency, the linear trend analysis still revealed a progressive P3A delay, with severity of cognitive impairment (F1,79=9.25, P=.003). There was also an HIV-associated increase in N200 latency, but that was caused by the P200 latency effect (it disappeared after partialling out the P200 latency effects). The P3A latency difference remained after partialling out both P200 and N200 latency effects. There were no significant effects for P3B latency or amplitude, with P3B latency in the target condition being 5 milliseconds faster in severely impaired HIV-positive subjects than in control subjects (P not significant).

Although the samples were matched on CD4 percentage, P3A latency was significantly negatively correlated with CD4 percentage (r=-.33, P=.008), such that patients with a lower CD4 percentage had longer P3A latencies. Within sample, a decreased CD4 percent was also associated with a greater CDC clinical category index of medical disease severity. We examined the relative strength of association between P3A latency, severity of cognitive impairment, and severity of the CDC clinical category index of medical disease using a two-way analysis of covariance, with the cognitive impairment group and CDC clinical category as the class variables and CD4 percentage as a covariate. After partialling out CD4 percentage and severity of medical disease, P3A latency was still significantly longer, with increasing cognitive impairment (F1,30=9.51, P=.003). After partialling out CD4 percentage and severity of cognitive impairment, P3A latency was still significantly longer, with increasing severity of medical disease (F1,30=4.19, P=.05). The interaction between group and CDC clinical category was not significant.

Figure 2. The auditory P3A in the novel nontarget condition for the HIV-negative control sample; bar, sample or sample mean; SD, standard deviation; SE, standard error; P<.01, P<.001.

There were no differences among the HIV-positive subsamples on the percentage of trials lost to eye movements in any of the three conditions. The P3A component was identified in the visual data for all subjects. We note that the visual paradigm sample sizes were smaller than those for the auditory paradigm and should be taken as preliminary. In the novel nontarget condition, compared with controls, HIV infection resulted in an average delay in P3A latency, while the by its average net revealed a stronger visual data, however only in the m subjects, with impaired HIV-posit (24%) had P3A | control mean (or impaired HIV-vc patients in the positive subsam the severely impar trol subject had a presents the vist condition for es in P3A late also present in t ed magnitude.

There were among the sample or P230 compa condition, there we references in P3B: for sample ampli a significant limi mplitude with inc (P=.04). In the n statistically sign samples, but th differences (F3,42 indicating incre tive impairment.
P3A latem a not include CD analysis of va
The P3A latencies in the visual modality were significantly longer in the mildly to severely impaired HIV-positive subsample, with no delay evident for the seven nonimpaired HIV-positive subjects. Of the 29 patients, seven (24%) had P3A latencies greater than 2 SDs above the control mean (one [14.3%] of seven patients in the nonimpaired HIV-positive subsample, two [22.2%] of nine patients in the mild to moderately impaired HIV-positive subsample, and four [30.8%] of 13 patients in the severely impaired HIV-positive subsample). Figure 3 presents the visual P3A latencies in the rare nontarget condition for each of the subject groups. The differences in P3A latency in the rare nontarget condition were also present in the target condition, although with reduced magnitude.

There were no statistically significant differences among the samples in latency or amplitude for P100, N165, or P230 components in any condition. In the target condition, there were no statistically significant latency differences in P3B among the samples, but there was a trend for sample amplitude differences (F1,42=2.20, P=.10), with a significant linear trend indicating decreasing P3B amplitude with increasing cognitive impairment (F1,42=4.64, P=.04). In the novel nontarget condition, there were no statistically significant amplitude differences among the samples, but there was a slight trend for sample latency differences (F1,42=1.86, P=.15), with a significant linear trend indicating increasing P3B latency with increasing cognitive impairment (F1,42=4.61, P=.04).

P3A latency in the visual modality was not correlated with CD4 percent (r=.02, P=.91). Therefore, we did not include CD4 percentage as a covariate in a two-way analysis of variance, including the cognitive impairment group and the CDC clinical category as the class variables. In the visual modality, as in the auditory modality, there were independent associations of cognitive impairment and clinical disease severity with delayed P3A latency (F1,42=4.18, P=.05; and F1,42=7.23, P=.01, respectively). There was no significant interaction between cognitive impairment and clinical disease severity.

**Task Performance**

Table 3 presents the reaction times (RTs) and percentage of misses and false responses for each sample for both the auditory and visual paradigms. The within-sample SDs for RTs were much larger than were the corresponding SDs of P3A latency, as presented in Table 2. Although the RT was slowest in the severely impaired HIV-positive subsample, there were no statistically significant sample differences in RTs, even when the linear trend analysis was used (F1,42=3.10, P=.08; and F1,42=1.86, P=.18, for auditory and visual paradigms, respectively). There were significant differences among the samples in target detection, with the severely impaired HIV-positive subjects exhibiting the poorest performance. Significant linear trends existed in both auditory and visual paradigms for the number of misses (failure to respond to the target tone). Severely impaired HIV-positive subjects also had the highest false response rate, although the sample differences did not reach statistical significance. However, it is unlikely that any of these target detection sample differences affected the ERP waveforms since misses averaged less than 2% for each group and false responses averaged less than 3% for each group.

**Auditory-visual P3a Correlations**

Auditory and visual P3A latencies were highly correlated, both in the novel nontarget condition (r=.68, P<.001) and in the target condition (r=.52, P<.001).
This study provides evidence that latency of the ERP P3A component is delayed in HIV disease and that the magnitude of this delay increases with increasing severity of cognitive impairment. In the auditory modality, where adequate samples of cognitively normal and mildly to moderately cognitively impaired HIV-positive subjects were studied, there was a statistically significant P3A latency delay in the cognitively nonimpaired HIV-positive subjects compared with the high-risk control subjects, with the magnitude of the delay increasing with increasing severity of HIV-associated cognitive impairment. These results involved a priori planned comparisons, and their statistical significance was unaffected by the multiple comparisons made on various other aspects of the ERP waveforms. This finding suggests that delayed P3A latency may be sensitive to relatively early CNS effects of HIV infection. Comparison with the RT data is of interest in this context. Although Martin et al reported increased RT associated with cognitive impairment in HIV disease, we did not replicate those results. The RT measures in our study were much more variable than were the P3A latencies. In comparison to P3A latency, RT was not a sensitive indicator of the CNS effects of HIV infection.

The incidence of an abnormal P3A latency (defined as a latency at least 2 SDs above the control mean) was low in the nonimpaired HIV-positive subjects, and it ranged from 22% to 31% in the mild to moderately and severely impaired HIV-positive subsamples. This suggests that, because of the variability of P3A latency within the normal population, a single P3A latency measure in an individual subject is not a sensitive index of HIV CNS morbidity. However, it is possible that increasing P3A latency over time may be a more sensitive indicator of CNS involvement in HIV-positive individuals than is delayed P3A latency at a single testing. Longitudinal studies comparing P3A latency changes over time in HIV-positive and control samples will be needed to determine the sensitivity of change measures to HIV CNS disease.

Event-related brain potential data are 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 P3, which includes the 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. This is particularly a problem in measuring component latency. To help solve these problems, we determined component latencies and amplitudes by examination of topographic maps in combination with plots of global field power (a reference-free measurement of mean potential difference between electrodes). Topographic maps give a clearer picture of the changing electrical potential field over the scalp. The use of global field power and topographic 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.

The close matching of noncognitively impaired, mildly to moderately cognitively impaired, and severely cognitively impaired HIV-positive subsamples on percent CD4 lymphocytes assured that the effects of systemic immunosuppression and cognitive impairment on P3A latency could be separated. Analyses in both the auditory and visual modalities revealed that delayed P3A latency is primarily associated with the progression of HIV-associated cognitive impairment, with a secondary association with severity of medical illness. In addition, an association of delayed P3A latency with the degree of systemic immunosuppression was evident only in the auditory modality. This was not attributable to a sampling bias where the subset of subjects receiving the visual paradigm just happened not to evidence such an association. The correlation of CD4 percentage and auditory P3A latency in only those subjects who also received the visual paradigm was −.37, very close to the correlation between CD4 percentage and auditory P3A latency of −.33, measured in all the subjects receiving the auditory paradigm.

Human immunodeficiency virus infection has been shown, later in the disease process, to result in loss of neurons, shrinkage of neurons, and loss of dendritic arborization in the frontal cortex. Early in HIV disease, the subcortical white matter axonal degeneration may be an important HIV effect in the data representation between reported frontal cognitive function and the association of specific deficits on the neuropsychological measure of HIV disease. Moreover, the P3 response to novel stimuli may be an additional indication of the stimulopathic measures that are monitored in HIV disease.

Analysis of P3B responses suggests that HIV disease affects the auditory and visual modalities in a manner similar to that reported for the P3A component. Preliminary results support this hypothesis and are consistent with evidence for the involvement of subcortical or frontal structures in HIV disease. Such a model of involvement of subcortical or frontal structures in HIV disease is also supported by studies showing that the lesions in such patients may be that actually result in reduced cortical function, while the remaining cortex is preserved. Thus, human immunodeficiency virus infection is considered primarily pathologic and white matter axonal degeneration may be an important HIV effect in the data representation between reported frontal cognitive function and the association of specific deficits on the neuropsychological measure of HIV disease.
case, the subcortical gray matter is affected and much of the earliest involvement of the white matter in HIV disease involves frontostriatal and frontothalamic connections; both of these may result in relatively early effects on frontal cortex functions. In this regard, executive and integrative functions, which are thought to be subserved by the frontal cortex, are among those affected most early in CNS involvement in HIV disease. We believe that delayed P3A latency may be an indicator of such early effects on frontal cortex function and, as such, may prove to be an important marker of the presence and progression of HIV effects on frontal cortex function. However, in the data reported here, there was insufficient differentiation between the subjects' performance on purported frontal cortex tests vs performance on the entire neuropsychologic battery to support a direct assessment of the association between the P3A effects and specific deficits on the frontal cortex neuropsychologic tests. Moreover, the P3A component is elicited primarily by novel stimuli that are not task relevant and appears to represent an automatic orienting or switching of attention to the stimulus change. Thus, it is not a direct physiologic measure of exactly the same type of function as measured by frontal cortex neuropsychologic tests.

Analysis of the topography of visual and auditory P3B responses suggests that they have different generators, although focusing on the P3B, found modality-dependent topographic differences over frontal as well as parietal sites, suggestive of different generators for the P3A component, depending on modality. Preliminary results from topographic analyses of our data support this hypothesis. The high correlation between visual and auditory P3A latencies in this study, together with evidence for different generators of the auditory and visual P3A components, would suggest that it is the input to the P3A generators that is delayed in HIV disease. Such a model of the effect would be consistent with involvement of subcortical gray matter or damage to frontostriatal or frontothalamic white matter tracts. This model is also supported by the results of Knight and colleagues, who studied patients with frontal lobe lesions. In such patients, they found a reduced P3A amplitude, with no effect on P3A latency. A working model may be that actual damage to the frontal cortex would result in reduced P3A amplitude (or an effect on P3A habituation), while effects on the input to the P3A generators would be reflected in delayed P3A latency, as observed in the current study.

Human immunodeficiency virus–associated dementia is considered a subcortical dementia, involving primarily pathologic changes in subcortical gray matter and white matter tracts. We hypothesize that the delay of P3A latency is more sensitive to this process than is delay of P3B latency, because P3A involves affected frontostriatal and/or frontothalamic input to the frontal cortex. This hypothesis can now be directly tested by means of proton magnetic resonance spectroscopic imaging 1.1,14 to measure subcortical neuronal loss and white matter axonal degeneration in HIV disease and to determine whether the progression of such disease is associated with an increasing delay of P3A latency.

In conclusion, delayed P3A latency is a sensitive index of the CNS effects of HIV disease and reflects the progression of such disease. It is a strong candidate in vivo for use in studies monitoring CNS disease progression and therapeutic response to treatments targeted at the CNS manifestations of HIV disease.

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Reprint requests to Developmental Neuropsychology Laboratory (116R), San Francisco Veterans Affairs Medical Center, 4150 Clement St, San Francisco, CA 94121 (Dr Fein).

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