NAVAL HEALTH RESEARCH CENTER

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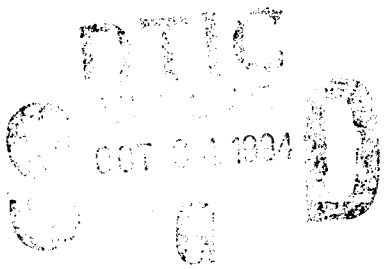

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NAVAL MEDICAL RESEARCH AND DEVELOPMENT COMMAND
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Event-Related Potentials Index Subclinical Neurological Differences in HIV Patients During Rapid Decision-Making*

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Summary

Thirteen asymptomatic HIV-infected and 13 healthy control subjects underwent a battery of behavioral and electrophysiological assessments. The behavioral measures tested IQ, computational skills, visual-spatial memory, and psychomotor ability with normative data for comparison. The electrophysiological measures included event-related potentials (ERPs) in response to auditory, "oddball" targets in either a single or dual channel delivery. The behavioral results indicated that the HIV group performed similarly to the Control group. The ERP results indicated that the HIV group produced similar ERPs indexing target detection in the single oddball delivery. The ERPs recorded from the HIV group in response to the dual oddball task showed atypical morphology and topography relative to those recorded from the Control group. These results suggested that auditory ERPs elicited by rapid, dichotic stimulus presentations were more sensitive to subclinical effects of HIV-related neuropathology than conventional behavioral measures.

Introduction

It is unknown how soon after initial infection with the human immunodeficiency virus (HIV), and in what ways, individuals begin to decline in cognitive processing capabilities. Some experts (1, 2, 3, 4, 5, 6) have reported cognitive impairment in a percentage of HIV-infected (HIV+) asymptomatic subjects on several neuropsychological tasks that required speed of information processing, verbal memory, psychomotor speed, and attention, while others have reported no impairment (7, 8, 9, 10, 11). This disparity suggests that either most HIV+ individuals do not become impaired until they are in a more advanced stage of HIV infection, or that some neuropsychological measures may be insensitive to subtle changes in cognitive function until neuropathology is so extensive that cognition and behavior are more dramatically affected. Another possible explanation for the inconsistencies in the HIV-related neuropsychological literature is that some tests allow the individual to perform at his/her own pace, with no restriction in the time allotted for each question in a test. Time-urgency, or lack thereof, may account for some of the inconsistent results. If forced to make decisions at a pace faster than normal then a patient's performance may be noticeably different from control subjects. For example, for tasks in which sequences of events occur close together in time, the decision to respond to one event could interfere with response production for the previous event, resulting in slower responses and performance degradation (12). HIV-infected individuals might experience an inability to make a series of split-second decisions that may be within the capability of normal, healthy individuals. The purpose of the current study was to examine decision-making in HIV patients under slow and rapid information deliveries. We predicted that by increasing the "cognitive load" using rapid and demanding information delivery tests that asymptomatic HIV+ subjects might have substantial difficulty in responding to them compared to healthy control subjects.

Most performance measures can only record the overt response (e.g., percent correct, misses, false alarms, and reaction time) and not the covert decision-making

process (i.e., sensory-perception, attention, detection, and memory recognition). Psychophysiological measurement of brain function is an alternative method to tap into the decision-making process. This can be accomplished by averaging brain electrical responses timelocked to events of interest, producing records known as event-related potentials (ERPs). These ERPs can index the dynamic neural state of the brain during rapid information presentation by measuring changes in brain activity following specific stimulus events. ERP waveforms consist of a series of distinct positive and negative components that represent voltage fluctuations generated in various populations of neurons synchronously activated during or after experimental events (13). Of primary interest in this study are the largest components generated in the first 400 ms after stimulus onset -- normally called the N100 (a negative peak at about 100 ms), P200 (a positive peak at about 200 ms), and P300 (a positive peak at about 300 ms). The first two of these components are known to change both in amplitude and latency as a function of both the physical characteristics of the stimuli (e.g., signal strength, 14) and the attentional demands of the task (15). The P300 can be produced by occasional target (or "oddball") signals that have been given psychological relevance by asking subjects to respond to them (16).

Some experts have used ERPs to evaluate cognitive function in HIV patients (17, 18, 19, 20, 21, 22, 23, 24, 25, 26). Using versions of a simple, relatively slow (1 tone/sec delivery), undemanding cognitive paradigm (the simple "oddball" task), they have reported longer latency P300 components (approximately 20 - 70 ms) in an AIDS subgroup as compared to control subjects (17 - 26). Among these experts, several research groups have reported delayed P300s (approximately 20 ms) in some asymptomatic patients compared to controls (17, 19, 20, 21). From among the latter studies, one study reported a statistical trend in delayed P300s correlating with longer reaction times to detected target stimuli (21), which might imply that HIV patients needed longer processing and decision time prior to making a response. Nevertheless, when HIV patients were tested to a given number of artifact-free responses, accuracy was high (19, 20, 21, 22, 23, 25). Other studies have reported

that delayed P300s elicited by both types of HIV patients during an oddball test correlated with delayed responding on neuropsychological, psychomotor tests (24, 25), suggesting a diminished responsiveness to any form of time-dependent tests. Overall, these reports indicate that some asymptomatic patients may show slowing in ERPs, but it is not yet clear if this result will translate into slower, less accurate performance with disease progression.

A research paradigm often used in ERP research is the selective attention paradigm, in which two, alternating "oddball" sequences of stimuli are delivered to opposite ears (27, 28, 29). The subject is instructed to focus his/her attention on only one of the sequences and to respond to target signals embedded in the attended input sequence, while ignoring targets embedded in the unattended sequence. Generally, the amplitude of the auditory N100 and P200 components in response to a given stimulus are enhanced when attention is focused on the channel from which that stimulus is delivered. The amplitude enhancements reflect neuronal processes that have been activated by initial feature analysis of incoming sounds in the attended ear (27). The time course of the attention effect in the ERP waveform can be manipulated by changing stimulus speed or complexity ("sensory load"; 27). Large, early attention effects (near 100 ms) are evident when a heavy sensory load is imposed on subjects, either by increasing the rate of stimulation or by decreasing stimulus intensity. Large, later attention effects (near 200 to 300 ms) are evident when sensory load is reduced, either by using slower stimulus presentation rates or by increasing stimulus intensity. To increase the level of difficulty in detecting oddball target signals, the target signals may be made to share several attributes with the nontargets (e.g., by giving them the same duration or pitch as the nontargets but a lower intensity). Under such conditions, the target recognition process becomes slow and demands more attention (27). The more attributes the targets and nontargets share, the higher the level of attentional and cognitive involvement needed to distinguish targets from nontargets.

Näätänen and Picton (15) suggest that subcortical thalamic structures are involved in the attentional enhancement of the N100 component. If the disease process of HIV damages thalamic structures and/or parathalamic structures, then the attentional system could be compromised. There is evidence that HIV infection may damage some subcortical regions during the early stages of the disease. For example, lesions in the region of the splenium of the corpus callosum and fornix have been discovered in asymptomatic HIV+ subjects using newly-improved magnetic resonance imaging (MRI), which were not detected using older MRI systems (30). Therefore, our hypothesis was that if early HIV infection affects subcortical pathways involved in the attention system, then ERPs could index the outcome of subcortical damage in at least two ways: 1) either by reduction of enhancement in the 100 to 200 ms period representing loss of perceptual sensitivity, and/or 2) by a reduction near 300 ms representing loss of cognitive resources required to select appropriate responses.

Methods

Subjects

Thirteen HIV-infected males (Walter Reed stagings I-V; approximate mean duration of infection = 3.6 yrs, SD $\pm$2.8; mean T4 cell/ml^3 = 542, SD $\pm$174; Table 1) and 13 healthy control males participated in this study. All were active-duty military personnel in either the U.S. Navy or U.S. Marine Corps. Extensive medical histories were compiled for all HIV patients, which inlcuded records prior to HIV infection (with the exception of one subject who was already infected on his first Navy screening; Table 1). Members in the control group were confirmed to be free of HIV through blood serology assays known as the enzyme-linked immunoabsorbant assay (ELISA). The two groups did not differ significantly in age or intellect. Intellect was evaluated with a mathematical (Arithematic Reasoning) and a vocabulary (Word Knowledge) subtest of the Armed Services Vocational Assessment Battery (ASVAB). These two

Table 1. Demographic information and test scores.

HIV Subjects												Control Subjects						
								ASVAB ◊							ASVAB ◊			
								Previous		Current					Previous		Current	
Subj	Race*	Age	HIV+	HIV-	T4	Stage†	AZT	AR	WK	AR	WK	Race*	Age	ELISA	AR	WK	AR	WK
1	CA	22	3/93	9/91	360	III	YES	55	50	59	56	CA	35	HIV-	54	57	50	51
2	CA	31	7/91	7/89	580	I	NO	50	56	65	61	CA	30	HIV-	66	58	61	61
3	AA	30	6/93	10/91	320	V	NO	53	54	47	55	CA	30	HIV-	64	49	65	57
4	CA	30	2/88	5/86	700	I	YES	56	57	59	59	CA	31	HIV-	60	50	59	59
5	CA	29	7/88	2/88	550	II	NO	53	54	54	59	CA	29	HIV-	53	60	66	60
6	CA	24	5/92	7/91	650	I	NO	56	58	59	59	CA	30	HIV-	52	53	50	54
7	AA	34	4/87	7/86	690	II	NO	59	58	50	59	CA	33	HIV-	62	58	65	57
8	AA	41	7/93	2/92	210	IV	YES	59	57	53	57	CA	20	HIV-	55	58	66	60
9	AI	30	8/92	9/91	690	I	NO	--	--	58	47	HI	41	HIV-	57	59	53	65
10	HI	32	9/93	9/92	440	II	YES	59	61	59	60	CA	32	HIV-	51	57	50	60
11	CA	21	7/93	4/93	780	I	NO	--	--	66	64	CA	26	HIV-	50	56	47	57
12	CA	25	9/88	12/85	430	I	NO	57	55	59	56	CA	22	HIV-	64	61	66	61
13	CA	33	5/86	?	640	II	YES	49	56	55	60	CA	24	HIV-	64	61	66	61
Means		29.4						55	56	57	58		29.5		57	56	59	59
SD		±5.4						±4	±3	±5	±4		±5.6		±5	±4	±8	±4

* CA = Caucasian, AA = African American, AI = American Indian, and HI = Hispanic.

◊ Arithmetic (AR) and Word Knowledge (WK) subtests of the Armed Services Vocational Assessment Battery (ASVAB) were used to measure intellect.

† Walter Reed Staging Classification.

tests were chosen instead of more traditional tests like the Weschler Adult Intelligence Test for three reasons: 1) the ASVAB is the military's version of an intelligence test that is used at time of enlistment by recruiters to help direct enlistees into jobs that appear to be within their capabilities; 2) these subtests are highly correlated with success in chosen military careers (31, 32); and 3) most importantly, we could compare ASVAB scores at time of enlistment to our scores in order to determine if any intellectual decline had occurred that might be attributable to the progression of HIV. The two groups scored similarly in our administration of the subtests from the ASVAB (Table 1). These results were confirmed statistically through a series of independent t-tests. In addition, a repeated measures, mixed-model analyses of variance consisting of Group (2) x ASVAB scores (2) with the latter variable being the repeated measure, confirmed that the current ASVAB scores of either group did not differ from those on record.

Hearing thresholds were determined across a variety of frequencies (100 Hz, 500 Hz, 1 kHz, 2 kHz, 3 kHz, 4 kHz, 6 kHz, and 8 kHz). All subjects had relatively good hearing. However, two HIV subjects had slightly elevated hearing threshold levels (25-30 dB HL) for 3-kHz tones, which was a frequency near one used in the study. These two individuals were further tested with the actual auditory tasks used in this study, and through visual verification of recorded button presses, both demonstrated acceptable discrimination of tonal differences in each of the tasks. Oral temperatures were taken to assure all individuals were not suffering from fever. Both groups were within a normal range of body temperature (HIV Mean = 98.2° F, SD $\pm$0.5; Control Mean = 98.3° F, SD $\pm$0.5). Anxiety and depression were also evaluated using the Spielberger State-Trait Anxiety Inventory (33) and the Beck Depression Inventory (34). A series of independent t-tests indicated no significant group differences in the responses to these inventories. Both groups appeared to have normal, low levels of anxiety (HIV Mean State = 34, SD $\pm$11; Control Mean State = 29, SD $\pm$6; HIV Mean Trait = 29, SD $\pm$10; Control Mean Trait = 24, SD $\pm$5) and no

depression (HIV Mean Depression = 5, SD ±5; Control Mean Depression = 4, SD ±5).

Cognitive Performance Measures

Four cognitive performance tests were given to each subject prior to undergoing ERP testing. These tests focused on visual-spatial memory and psychomotor capabilities for comparison with findings reported in the HIV literature (1, 2, 3, 4, 5, 6). These prototypes, part of an overall test battery known as the Enhanced Computer Administered Test (ECAT) battery, are under consideration by the Department of the Navy for inclusion in a computerized version of the ASVAB. Normative data were derived from a substantial database of approximately 25,000 enlistees and were used for comparison. The following subtests from the ECAT were administered:

Integrating details (ID). The ID is a 40 item complex spatial problem solving test. Each item consists of two separate screens. The first screen contains from 2 to 6 regular geometric puzzle pieces that must be mentally brought together to form a completed object, much like a jig-saw puzzle. Having connected all of the puzzle pieces, the individual must remember the final object, then press a response key indicating that he is ready. Once the key is pressed, the puzzle pieces are replaced by a new screen with a single object. The subject must indicate if the object shown is a product of the original puzzle pieces. Percent correct and time spent on task were the dependent measures for this test.

Mental counters (MC). *The MC is a complex 40 item working memory test* that involves spatial information. Each screen contains three horizontal lines, arranged left to right. Each line represents a counter with an initial value of zero. Boxes appear sequentially, one at a time, either above or below one of the three lines. If a box appears above a line, the value for that counter should be incremented by 1. If a box appears below a line, that counter should be decreased by 1. On each trial either 5 or 7 boxes appear. The boxes appear at one of two rates, either every 1.33

seconds or every .75 seconds. The subject's task is to make a series of rapid calculations and to report the final value from a multiple choice list of each of the three counters. Percent correct and time spent on task were also the dependent measures for this test.

One-hand tracking (1TR). The 1TR is a psychomotor test using a response pedestal. Each item begins with a contiguous string of lighted screen pixels forming a "path" on the computer screen. The path goes up/down and/or right/left, parallel with the sides of the screen and makes only 90 degree turns. At one end of the path is a diamond indicating the path's termination point. Starting at the other end is a box that travels forward along the path. The subject moves a joy-stick that controls the movement of a "cross-hair." The subject's task is to keep the cross-hair on the moving box. The trials vary in path length, which is inversely related to the speed at which the box moves (total duration is thus constant). For each trial, the "score" is the average absolute Cartesian pixel distance between the cross-hair and the moving box (a distance reading is taken every 50 ms during a trial). There are 18 trials. The dependent variable for the test is the average of the 18 trial scores.

Two-hand tracking (2TR). The 2TR is another psychomotor test that has exactly the same structure and task constraints as One-Hand Tracking described above. The only difference is that movement of the cross-hair is controlled by two slide potentiometers. One of the slides controls the horizontal (left/right) movement of the cross-hair while the second slide controls the vertical (up/down) motion of the cross hair. One hand must be used for each slide control. The slides are arranged such that the horizontal slide's physical movement is right and left while the vertical slide's physical movement is up and down. Number of items, test scoring, and final test score are the same as above.

ERP Stimuli And Task

Three different tasks were used to evaluate the ability to selectively focus attention and cognitive decision-making capabilities. The tasks ranged from simple to perform to increasingly difficult to perform by varying stimulus delivery rate, and by varying either one (delivered binaurally) versus two (delivered dichotically) channels of stimuli. The 1 tone/sec simple oddball task, delivered binaurally, was used for comparison to findings reported in the literature. The 2 tone/sec dual oddball task, delivered dichotically, was used as practice in preparation for the more rapid 3 tone/sec dual oddball task.

1 tone/sec simple oddball stimuli. A sequence of loud (80 dB SPL), 1000 Hz nontarget tones and soft (65 dB SPL), 1000 Hz target tones were delivered binaurally at a delivery rate of approximately 1 tone per second (i.e., random interstimulus interval [ISI] between 800 to 1200 ms). There were two runs. Each run consisted of 160 (80%) nontargets and 40 (20%) targets. Subjects were instructed to press a button (with their preferred hand) to detected targets. Stimuli were delivered through Neuro Scan 10Ω insert earphones, which air-conducted the sounds through 25 cm plastic tubing into foam eartip (ER3-14C) pieces.

2 tones/sec "practice" dual oddball stimuli. A dual oddball selective attention task paradigm was used similar to one reported by Woldorff & Hillyard (24). Stimuli consisted of a sequence of 1000-Hz tone pips presented to the left ear, interspersed with a sequence of 3150 Hz tone pips presented to the right ear. The tones were of short duration (14 ms), were presented at approximately 2 tones per second (i.e., random ISI 331 ms to 505 ms), and alternated between the two ears. Five percent of the tones in each ear were soft-intensity "targets" (70 dB SPL) as compared to the other 95 percent "nontargets," which were relatively louder (85 dB SPL). The subject's task was to attend to only the designated ear and to press a button in response to targets detected in the designated ear while ignoring sounds in

the other ear. Each run consisted of 313 loud and 17 soft tone pips delivered in each ear in a semirandom order. There were two runs of this set of practice stimuli (attend-left and attend-right) with the attend-left instruction always given first.

Thus, there were two channels of input with two categories of stimuli in each channel: (a) Attended ear - attend targets, attend nontargets; (b) Ignored ear - ignore targets, ignore nontargets. These stimuli were presented simultaneously in both ears.

3 tones/sec "dual" oddball stimuli. A "faster" version of the dual oddball task described above was the main portion of this experiment. The stimuli were identical in every way; however, the delivery rate was approximately 3 tones per second (i.e., ISI 131 - 305 ms). The designated "attended" ear was alternated across 8 runs (i.e., 4 runs per attended ear). The target detection instruction was the same as described above.

ERP Recording Procedure

Subjects were tested individually in a sound attenuated room. Silver chloride electrodes were attached to the scalp at frontal (Fz), central (Cz) and parietal (Pz) scalp sites using the Ten-Twenty International electrode placement system (35), with left ear reference. A ground electrode was placed on the forehead, and two Beckman electrodes, one supraorbital and one at the outer canthus of the left eye, were attached to monitor eye movements. Impedances were checked before testing, and all were below 5 kΩ. The electrodes were connected to a four-channel Grass Model 12 Neurodata Acquisition system using J10 miniamplifiers. The frequency bandwidth used with these anologue amplifiers was set between 0.1 Hz to 100 Hz and amplification of the signals (EEG) set at 20,000 times. The EEG signals were then digitized online at a sampling rate of 256 Hz using the data acquisition portion (Scan) of the commercial digital-to-analogue system and software package known as Neuro Scan (36), digitally filtered (low pass - 32 Hz, slope - 24 dB/octave; high pass - 2.56

Hz, slope - 24 dB/octave), recorded on the hard disk of an ALR-486 personal computer, and stored on optical disks for later off-line analysis.

The auditory stimuli were generated by the stimulus delivery portion (Stim) of Neuro Scan. The Stim program ran on a separate personal computer (Everex-386 PC), which was linked to the data-acquisition computer. An 8-bit signal was sent simultaneously during stimulus delivery from the stimulus-generation computer to the data-acquisition computer to "mark" digitized EEG for later off-line analyses into averaged ERPs to the various stimulus conditions. Button presses from the subject during target detections also marked the EEG for later off-line analyses.

Results

Cognitive Performance Data Analyses

Performance on ECAT tests. A series of independent t-tests were conducted on the performance measures. Percent correct and time spent on task were the dependent measures for the MC and ID tests, and estimated fraction of inches was the dependent measure in the 1TR and 2TR tasks. Table 2 details the performance on these tasks. None of the t-tests showed any significant group differences. Both groups performed well in the MC and ID visuospatial memory tests, and they spent a similar amount of time in completing each portion of these tests. Both groups also performed similarly in the 1TR and 2TR psychomotor tasks.

Population percentile rankings were assigned to each subject's performance for comparison with the normative database. Independent t-tests indicated that the two groups did not differ in their percentile ranking in any of these four tests (Table 2). The mean percentile rankings indicated that both groups were near the middle of the normal distribution in performance of the MC and ID tests, but considerably below

Table 2. Descriptive statistics from the Enhanced Computerized Assessment Test (ECAT)*

Group		Accuracy		Tracking Ability (in)	
		MC	ID	1TR	2TR
HIV	Mean	79%	83%	0.33	1.11
	SD	±12	±10	±0.18	±0.39
Control	Mean	82%	80%	0.27	0.86
	SD	±12	±14	±0.12	±0.39

		Normative Comparison Percentile Ranking			
		Accuracy		Tracking Ability	
		MC	ID	1TR	2TR
HIV	Mean	62%-ile	68%-ile	33%-ile	24%-ile
	SD	±26	±27	±26	±26
Control	Mean	66%-ile	58%-ile	42%-ile	34%-ile
	SD	±27	±32	±31	±24

		Time-on-task (sec)	
		MC	ID
HIV	Mean	995	1179
	SD	±169	±384
Control	Mean	985	1353
	SD	±146	±443

MC = Mental Counters; ID = Integrating Details; 1 or 2 TR = 1- or 2-Handed Tracking

* Independent t-tests not significant for the between-group comparisons.

average on the 1TR and 2TR tasks. The latter finding may reflect the fact that (a) there are age-related declines on the 1TR and 2TR psychomotor tasks (37), and (b) the normative sample was an average 10 years-of-age younger than the current experimental sample.

Performance on ERP oddball tests. A series of independent t-tests were conducted on the performance measures from each of the oddball tests. Percent correct, reaction time, misses, and false alarms were the dependent measures. Table 3 details the performance on these tasks. None of the t-tests showed any significant group differences.

Subjects were later asked to rate the level of difficulty of the simple and dual oddball tasks on a continuum ranging from "very easy" to "very hard." Their answers were quantified by measuring the distance from the midpoint in the continuum to their mark on the scale. Both the positive (very easy) and negative (very hard) extremes of each continuum were 66 mm from the midpoint (0). A series of independent t-tests conducted on these measures showed no significant group differences. For the Simple Oddball task, both groups perceived it as an easy test, rated themselves putting forth effort, and performing well on this test. For the Dual Oddball task, both groups perceived it as a difficult test, rated themselves putting forth a great deal of effort, and not performing as well on this test.

Finally, subjects were asked if they felt tired during testing. A minority (HIV 25%, Control 23%) of both groups were tired during the simple oddball tests and the majority (HIV 83%, Control 78%) of both groups were tired at some point during the dual oddball tests. However, χ^2 analyses indicated no significant group differences in these percentages.

Table 3. Performance on Oddball Tests.*

		Percentage Correct Target Detections (Hits)		
Group		PRACTICE	DUAL	SIMPLE
HIV	Mean	43%	42%	92%
	SD	±24	±18	±9
Control	Mean	51%	53%	94%
	SD	±18	±17	±9

		Reaction Time (ms) in Target Detections (Hits)		
Group		PRACTICE	DUAL	SIMPLE
HIV	Mean	506	469	445
	SD	±52	±39	±61
Control	Mean	500	459	412
	SD	±39	±38	±59

		False Alarms		
Group		PRACTICE	DUAL	SIMPLE
HIV	Mean	2	4	2
	SD	±2	±4	±3
Control	Mean	3	7	2
	SD	±2	±9	±4

		Misses		
Group		PRACTICE	DUAL	SIMPLE
HIV	Mean	114	158	7
	SD	±47	±48	±8
Control	Mean	97	128	5
	SD	±35	±46	±8

PRACTICE = Practice Dual Oddball; DUAL = Dual Oddball; SIMPLE = Simple Oddball

* Independant t-tests not significant for the between-group comparisons.

ERP Data Analyses

Digitized EEG were analyzed into single-trial epochs to the various stimulus conditions. An epoch consisted of a 200-ms prestimulus baseline followed by an 800-ms poststimulus period. The epochs were each normalized relative to their baseline by subtracting the mean amplitude of the 200-ms prestimulus baseline period from the poststimulus period. Then they were subjected to an artifact rejection process that excluded epochs containing eye artifact greater than $\pm$50 μV. The remaining artifact-free, normalized epochs were then averaged together according to stimulus type to yield an average ERP for each condition. For the 1 tone/sec simple oddball task, an averaged ERP to nontarget stimuli consisted of approximately 320 single trials (160 x 2 runs) and a target ERP consisted of approximately 80 single trials (40 x 2 runs). For the 2 tones/sec practice oddball task, an averaged ERP to the nontarget stimuli consisted of approximately 1,252 single trials (313 trials x 2 runs x 2 ears attended to) and a target ERP consisted of approximately 68 single trials (17 trials x 2 runs x 2 ears attended to). For the 3 tones/sec dual oddball task, an averaged ERP to the nontarget stimuli consisted of approximately 5,008 single trials (313 trials x 8 runs x 2 ears attended to) and a target ERP consisted of approximately 272 single trials (17 trials x 8 runs x 2 ears attended to).

Responses to nontarget and target stimuli were analyzed separately. By convention, the "attention effect" consisted of the difference between responses to nontarget stimuli while attended (Attend condition) and responses to the same stimuli when attention was directed to the opposite channel of input (Ignore condition). Figure 1 displays the attention effect in the grand average ERPs to nontarget stimuli.

The "target effect" consisted of a P300 component in response to detected target stimuli. Figure 2 and Figure 3 display the target effect in the grand average ERPs for the HIV and Control groups, respectively. Single-trial epochs to only detected targets (i.e., "hits") were averaged together to examine the target effect.

GRAND AVERAGE ERPs TO NONTARGETS DEMONSTRATING "ATTENTION EFFECT"

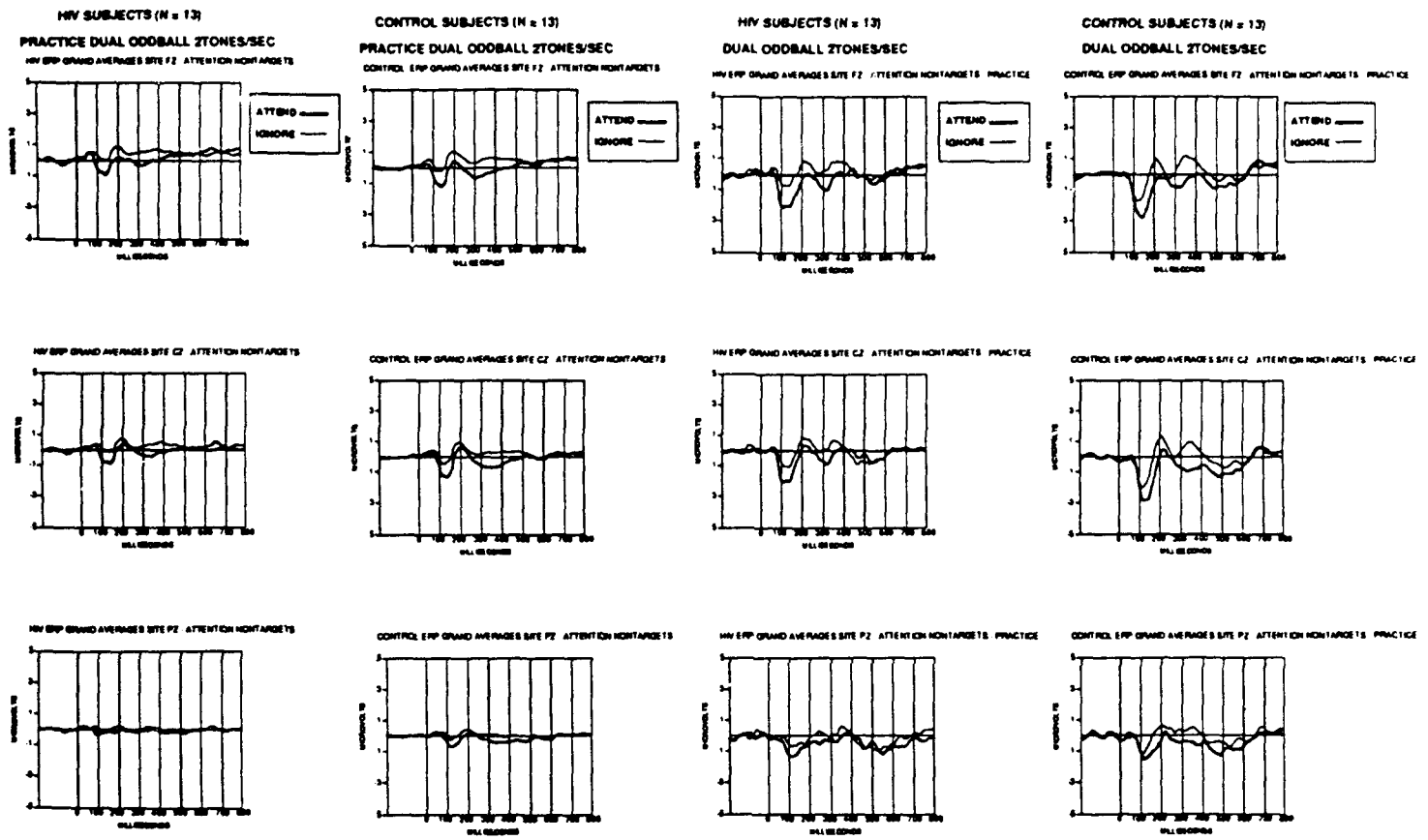

Figure 1. Grand average ERPs for both HIV and Control groups recorded from midline scalp sites Fz, Cz, and Pz in response to Practice and Dual oddball nontarget stimuli. The area separating the attend from the ignore traces in the ERPs represents the affect of attention.

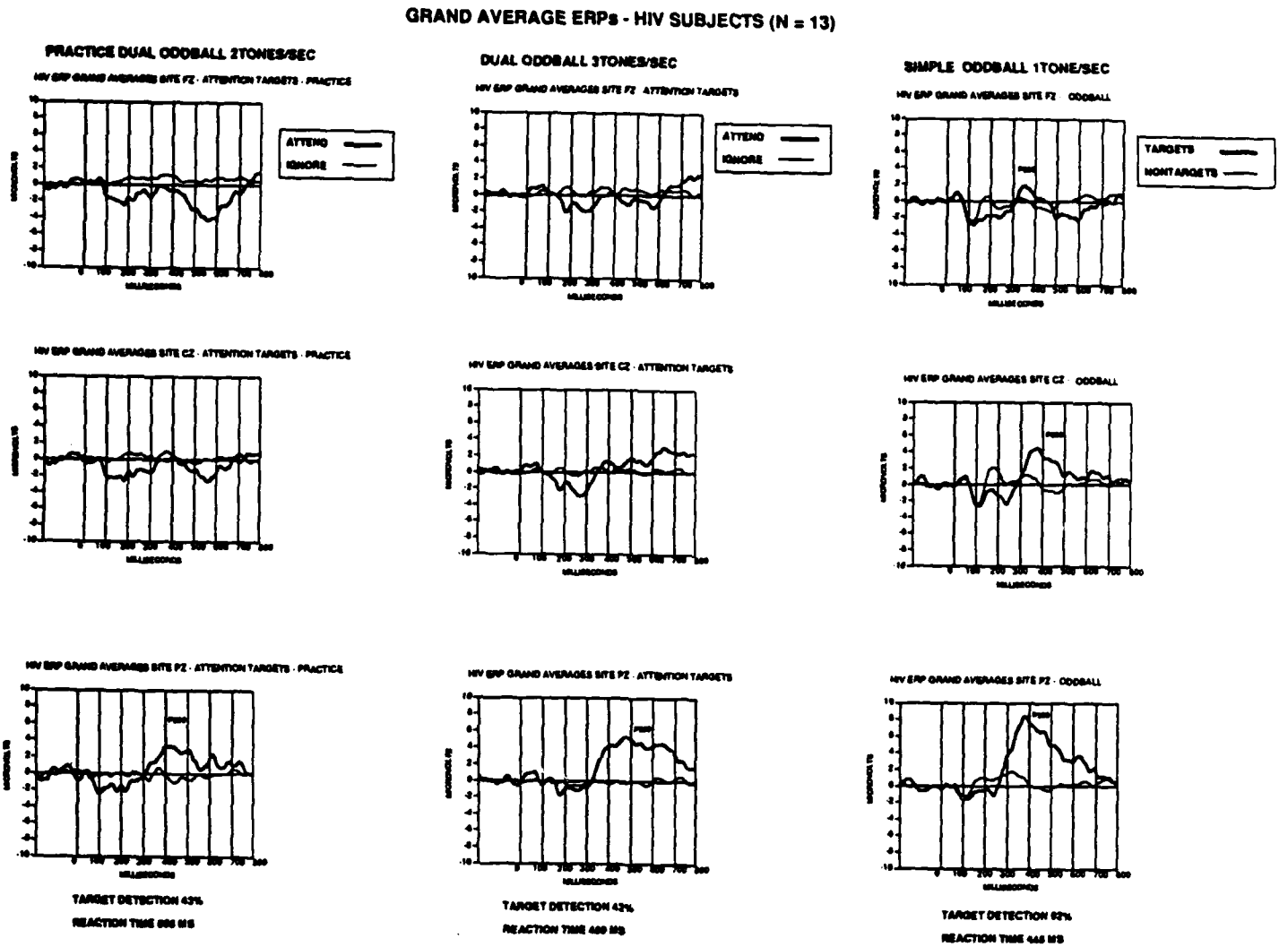

Figure 2. Grand mean ERPs from the HIV group recorded from Fz, Cz, and Pz scalp sites in response to Practice, Dual, and Simple oddball target stimuli. Note that the P300 component is essentially absent from sites Fz and Cz in both the Practice and Dual oddball conditions. In addition, a fronto-central, late (600 - 800 ms), positive component can be seen in the Dual oddball condition.

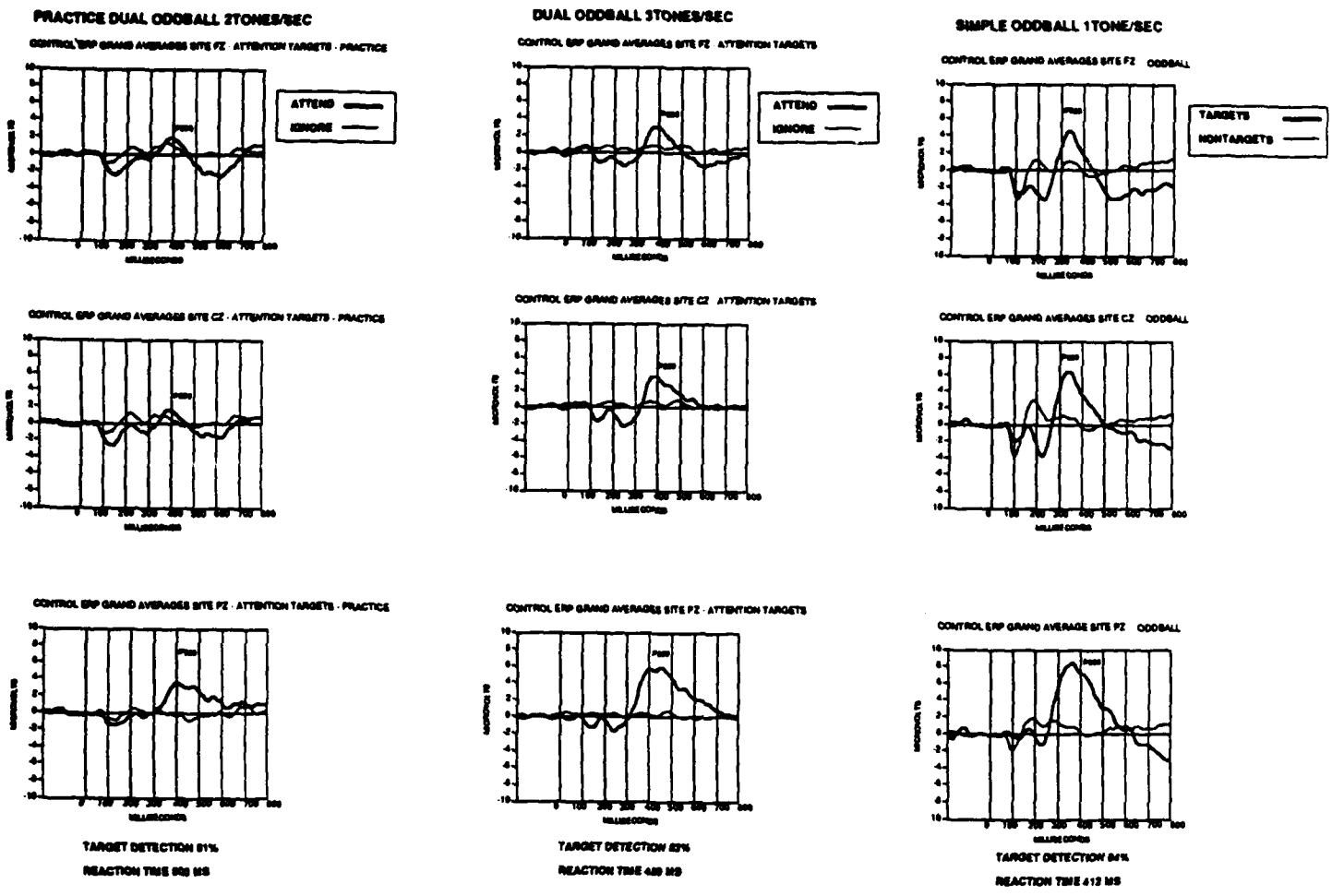

Figure 3. Grand mean ERPs from the Control group recorded from Fz, Cz, and Pz scalp sites in response to Practice, Dual, and Simple oddball target stimuli. The P300 components show the typical topography and morphology, and unlike the HIV group, no late frontal, positive component is present.

Only group differences in attention and target effects are reported below in detail. Effects of electrode Site and/or Attention (Figures 1 - 3) were included in Tables 5 through 8 to help validate the experimental paradigms used in this study. Attention effects demonstrated that subjects followed attention-related instructions, and electrode Site results confirmed predictions of ERP scalp distributions based on previous research. Scheffé "critical difference between means" procedure for planned pairwise comparisons confirmed the direction of all interactions listed in the tables. The Scheffé procedure was used for these multiple sets of analyses to avoid cumulative type I error ($\alpha_{FW} < .05$) during multiple comparisons in an analysis (38).

Mean amplitude measures. Mean amplitude measures computed for several ERP components were analyzed statistically. Table 4 shows the mean amplitude measures and standard deviations for all conditions. The N100 (75 - 175 ms) measurements were input into several ANOVAs using a Group (2) x electrode Sites (3) x Attention (2) repeated measures, mixed-factor design with the latter two variables being the repeated measure. The P300 (300 - 600 ms) and Late Activity (LA; 601 - 800 ms) measurements were input into several ANOVAs using a Group (2) x electrode Sites (3) repeated measures, mixed-factor design with the latter variable being the repeated measure. Table 5 lists the significant main effects and interactions of each ANOVA described in the following results.

Mean Amplitude Results for Practice Dual Oddball ERPs. The ANOVA of the N100 measures of the Practice Dual Oddball nontarget data revealed main effects for electrode Sites and Attention, and an electrode Sites x Attention interaction. The ANOVAs of the P300 and LA measures of the Practice Dual Oddball target data revealed only main effects for electrode Sites.

These results represent the "attention effect" to attended nontarget stimuli and the "target effect" to attended target stimuli in the Practice Dual Oddball condition. The results indicated that the attention effect was similar for both groups (see Figure

Table 4. Mean Amplitudes (μV) and Standard Deviations (SD)

Component	Electrode Site					
	Fz		Cz		Pz	
	Mean	SD	Mean	SD	Mean	SD
Practice Dual Oddball						
N100 (75-175 ms)						
Attend	-1.81	1.38	-1.77	1.44	-1.05	1.08
Ignore	-0.73	0.95	-0.90	0.97	-0.51	0.79
P300 (300-600 ms)						
HIV	-1.81	1.23	-1.02	1.63	1.54	1.54
Control	-0.20	2.06	-0.24	2.60	1.84	1.77
LA* (601-800 ms)						
HIV	-0.96	1.70	-0.16	1.87	1.10	1.44
Control	-0.47	2.41	-0.15	2.66	1.00	3.00
Dual Oddball						
N100 (75-175 ms)						
Attend	-0.56	0.44	-0.65	0.43	-0.30	0.25
Ignore	0.21	0.27	0.35	0.27	0.03	0.21
P300 (300-600 ms)						
HIV	-0.78	2.21	-0.31	1.53	2.22	1.99
Control	0.97	2.30	1.25	2.32	2.90	1.50
LA* (601-800 ms)						
HIV	0.58	4.43	2.07	3.75	3.65	1.77
Control	-0.80	2.66	0.38	2.35	1.18	2.05
Simple Oddball						
N100 (75-175 ms)						
Attend	-2.15	1.71	-1.33	1.55	-0.57	1.23
Ignore	-1.39	1.24	-0.81	1.03	-0.42	0.83
P300 (300-600 ms)						
HIV	-0.29	2.22	2.35	3.11	5.61	2.90
Control	0.02	3.70	2.33	4.19	5.60	2.98
LA* (601-800 ms)						
HIV	-0.33	2.49	0.88	2.71	1.97	4.17
Control	-2.20	1.60	-1.87	2.04	-1.27	2.31

* LA = Late Activity Component

Table 5 Mean Amplitude ANOVA Results

	Result	F-Statistic
N100 (75 - 175 ms)		
Practice Dual Oddball Non-Targets	Sites	$F(2,48) = 13.94$, $p < .0001$
	Attention	$F(1,24) = 16.88$, $p < .0001$
	Sites X Attention	$F(2,48) = 16.52$, $p < .0001$
Dual Oddball Non-Targets	Sites	$F(2,48) = 16.85$, $p < .0001$
	Attention	$F(1,24) = 58.77$, $p < .0001$
	Sites X Attention	$F(2,48) = 30.58$, $p < .0001$
Simple Oddball	Sites	$F(2,48) = 22.39$, $p < .0001$
	Attention	$F(1,24) = 4.98$, $p < .05$
	Sites X Attention	$F(2,48) = 4.65$, $p < .025$
P300 (300 - 600 ms)		
Practice Dual Oddball Targets	Sites	$F(2,48) = 55.22$, $p < .0001$
Dual Oddball Targets	Group	$F(1,24) = 4.34$, $p < .05$
	Sites	$F(2,48) = 22.39$, $p < .0001$
Simple Oddball	Sites	$F(2,48) = 76.28$, $p < .0001$
Late Activity (601 - 800 ms)		
Practice Dual Oddball Targets	Sites	$F(2,48) = 12.85$, $p < .0001$
Dual Oddball Targets	Sites	$F(2,48) = 19.23$, $p < .0001$
Simple Oddball	Group	$F(1,24) = 10.13$, $p < .005$
	Sites	$F(2,48) = 4.11$, $p < .025$

1). The P300 and LA results indicated that the elicitation and resolution of the P300 was similar for both groups (cf., Figures 2 & 3).

Mean Amplitude Results for Dual Oddball ERPs. The ANOVA of the N100 measures of the Dual Oddball nontarget data revealed main effects for electrode Sites and Attention, and an electrode Sites x Attention interaction. This interaction is analogous to that found in the Practice Dual Oddball data. The ANOVA of the P300 measures of the Dual Oddball target data revealed a main effect of Group indicating significantly greater P300s generated by the Control group ($\underline{M}$ = 1.71 μV) compared to the HIV group ($\underline{M}$ = 0.38 μV). The ANOVA of the LA measures of the target data revealed only main effects for electrode Sites. There were no other significant effects or interactions in these analyses.

The N100 results represent the attention effect to attended nontarget stimuli in the Dual Oddball condition, much like that described in the practice condition. Furthermore, the Attention effect was similar for both groups (Figure 1) in this condition. The P300 results revealed that the Control group elicited greater P300s to target stimuli compared to the HIV group in the Dual Oddball condition. This result differed from the practice condition, in which P300s were elicited (note Table 4), but there were no significant group differences.

Mean Amplitude Results for Simple Oddball ERPs. The ANOVA of the N100 measures of the Simple Oddball data (i.e., attended nontargets vs. attended targets) revealed main effects for electrode Site and for Attention, and an electrode Sites x Attention interaction. The ANOVA of the P300 measures of the Simple Oddball target data revealed only a main effect for electrode Sites. The ANOVA of the LA measures of the target data revealed main effects for Group and for electrode Sites. The main effect for Group indicated greater positive amplitudes for the HIV group ($\underline{M}$ = 0.88 μV) compared to the Control group ($\underline{M}$ = -1.78 μV).

The N100 results represent augmentation of the N100 components to attended targets compared to attended nontargets in the Simple Oddball condition with no group differences in the N100. P300s were elicited to target stimuli (note Table 4), but there were no significant group differences in the size of the P300s (cf., Figures 2 & 3). The LA results indicated a group difference in the resolution of P300; that is, the P300s generated by the Control group resolved below baseline early (approximately at 500 ms), resulting in negative mean amplitude values for LA, and the P300s produced by the HIV group resolved to baseline later (approximately at 800 ms), resulting in positive mean amplitude values for LA (cf., Figures 2 & 3).

Principal Component Analysis (PCA). PCA was used to separate the ERPs into their underlying subcomponents, a depth of analysis not possible with mean amplitude measures. PCA separated overlapping components within the ERPs through a series of factor analyses into a few meaningful components that parsimoniously described the experimental variance. Then, each factor (and the variance accounted for by that factor through weighted factor scores) was subsequently placed into an analysis of variance to determine if the factor varied systematically with the experimental treatments. This procedure has been used extensively (39, 40, 41, 42).

The PCA procedure was as follows. A matrix of 204 data points, representing amplitude values from 0 - 800 ms poststimulus, by 156 ERPs [i.e., group (2) x subjects (13) x electrode sites (3) x attention (2)], representing data gathered from all subjects under one of the three experimental conditions (Practice Oddball, Dual Oddball, or Simple Oddall), was input to the BMDP4M factor analysis procedure from the biomedical statistical program package BMDP93 (43). The data matrix of digitized amplitude values was transformed into a covariance matrix, and PCA was then applied to this matrix. From this matrix, a centroid of 204 grand means, which was the common element to ERPs from all conditions, was calculated across all subjects, conditions, and electrode sites. Five factors, which accounted for nearly all the

variability in the covariance matrix, were then extracted with the factor analysis procedure. Factor 1 represented the greatest accounting of variability and the subsequent Factors 2 through 5 decreasing amounts of the remaining variance. Each factor consisted of 204 factor loadings; that is, one for each data point in an ERP. The factor loadings identified locations in the ERP where there was a pattern of high covariation among time points (44). The factors then underwent an orthogonal rotation using the normalized varimax criterion (Kaiser, 1958; cited in 43), which maximized the independence of the variability accounted by each factor while improving their distinctiveness in representing specific temporal locations along the ERPs (44). Figures 4 and 5 illustrate the PCA analyses conducted on the nontarget and target data, respectively, for each of the three experimental conditions. The peaks in each factor represent the temporal location of the greatest covariance in the ERPs in either a positive or negative direction. In addition, a set of 156 weighted factor scores, one for each ERP, was derived for each rotated factor. The weighted factor scores determined the degree to which a factor influenced each individual ERP (44). The 156 factor scores for each factor were subsequently analyzed as the dependent measure in a series of five separate, independent ANOVAs using BMDP8V. The design of the ANOVAs consisted of a repeated measures, mixed-factor design of Group (2) x electrode Sites (3) x Attention (2) conditions with the repeated measures being the latter two variables. Tables 6 through 8 lists the significant main effects and interactions of each ANOVA described below. There were significant main effects for electrode Sites in all the analyses (Tables 6, 7, & 8) representing various topographic differences in amplitude, but they are not mentioned any further in the following results.

PCA-ANOVA Results for Practice Dual Oddball ERPs to Nontargets. The ANOVAs of the Practice Dual Oddball nontarget data (Table 6) identified three electrode Sites x Attention interactions in the analyses of Factors 2, 3, and 5.

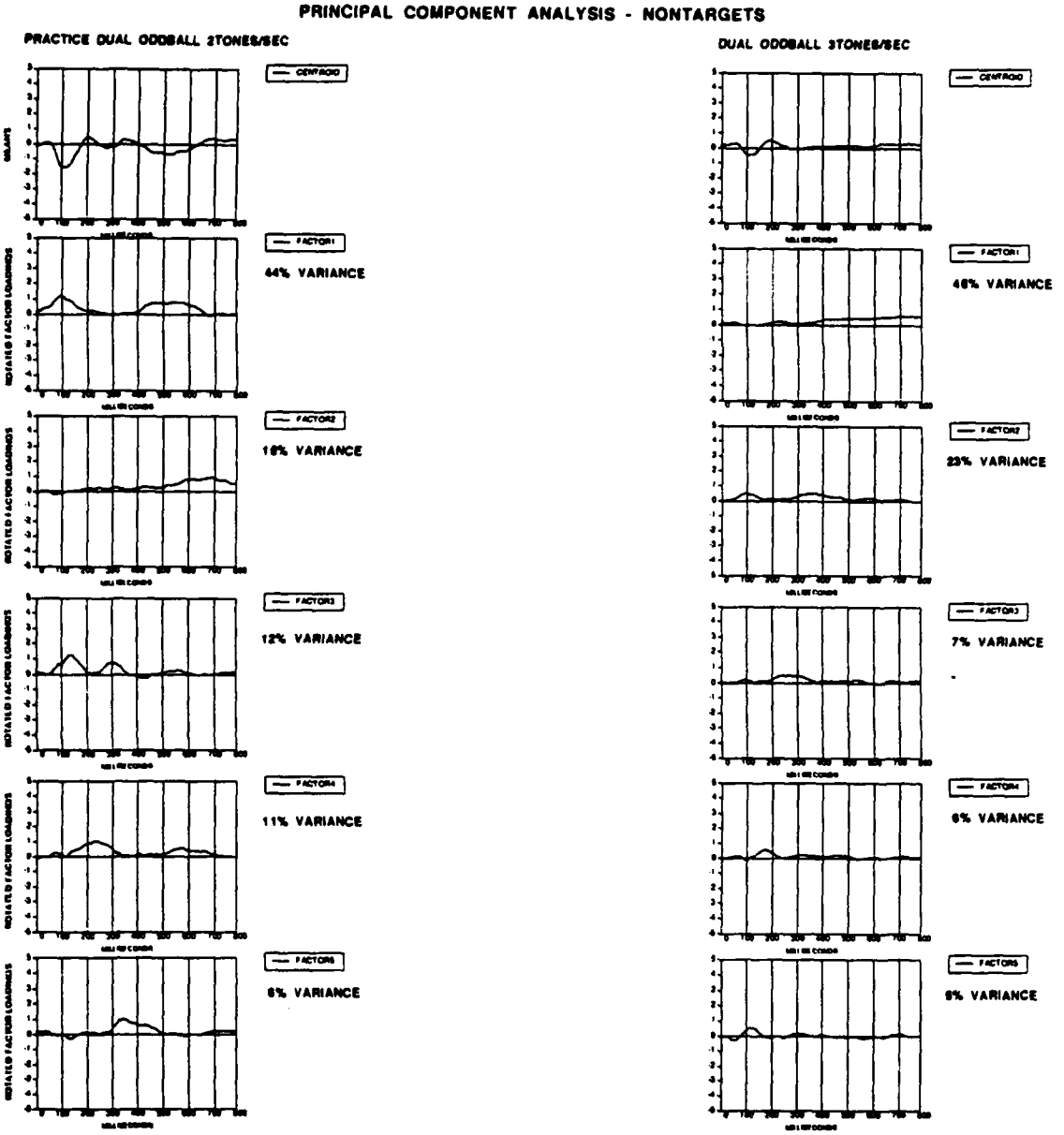

Figure 4. Principal Component Analysis factor scores from Practice and Dual oddball nontarget stimuli. The first trace is the centroid, followed by the factor loadings order from greatest (top) to least (bottom) percentage of variance accounted for by the given factor.

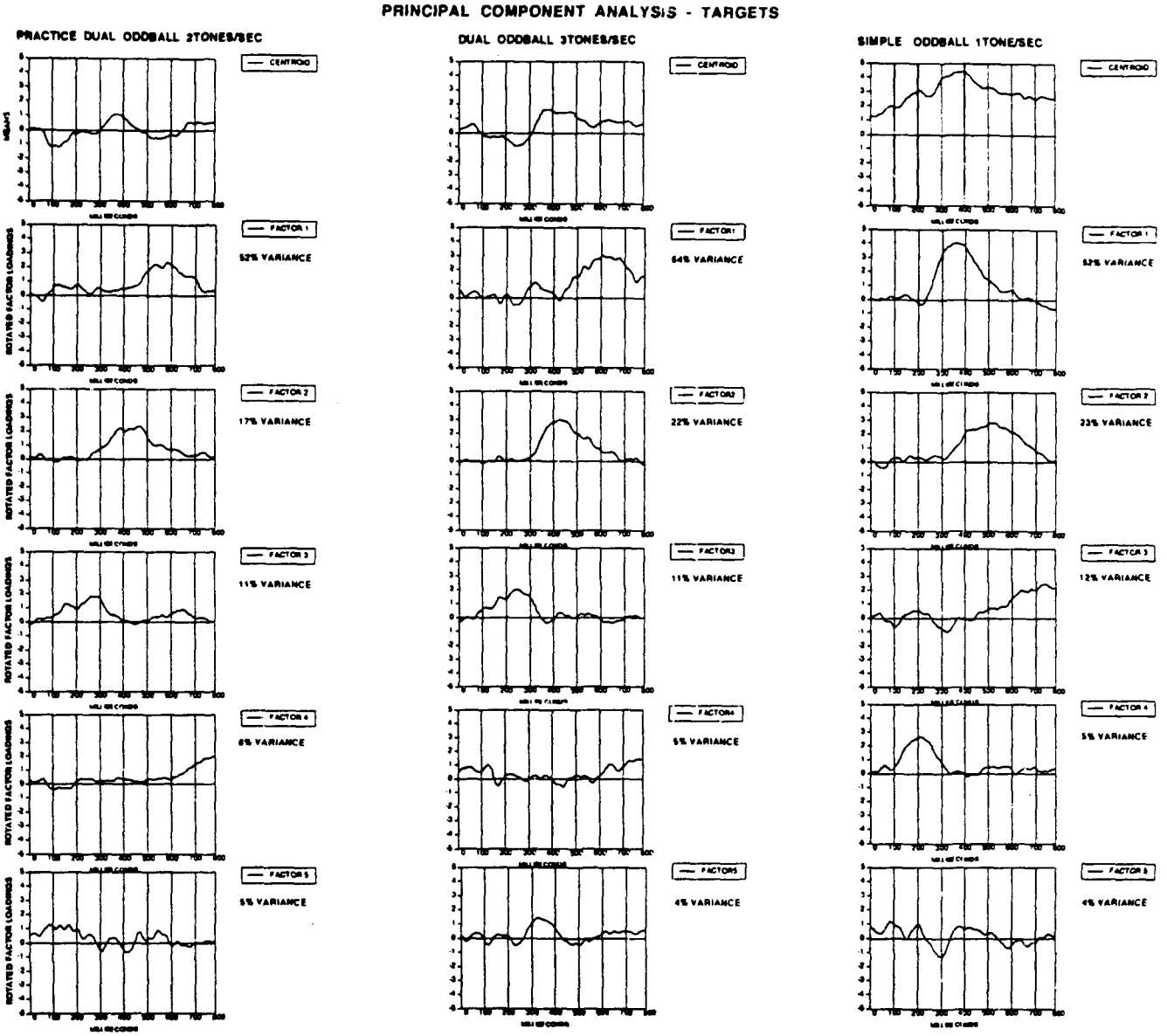

Figure 5. Principal Component Analysis factor scores from Practice and Dual oddball target stimuli. The first trace is the centroid, followed by the factor loadings order from greatest (top) to least (bottom) percentage of variance accounted for by the given factor.

Table 6. PCA - ANOVA Results: ERPs to Practice Dual Oddball Task

Factor	Variance (%)	Result	F-Statistic
		Non-Targets	
1	44	Sites	$F(2,48) = 4.62$, $p < .025$
2	19	Sites	$F(2,48) = 9.34$, $p < .001$
		Sites X Attention	$F(2,48) = 5.70$, $p < .01$
3	12	Sites	$F(2,48) = 33.51$, $p < .00001$
		Attention	$F(1,24) = 18.55$, $p < .001$
		Sites X Attention	$F(2,48) = 15.25$, $p < .00001$
4	11	Sites	$F(2,48) = 19.17$, $p < .00001$
		Attention	$F(1,24) = 5.71$, $p < .05$
5	6	Sites	$F(2,48) = 20.29$, $p < .00001$
		Attention	$F(1,24) = 14.05$, $p < .01$
		Sites X Attention	$F(2,48) = 7.50$, $p < .001$
		Targets	
1	52	Sites	$F(2,48) = 62.59$, $p < .00001$
		Attention	$F(1,24) = 9.08$, $p < .01$
		Sites X Attention	$F(2,48) = 56.42$, $p < .00001$
		Group X Sites X Attention	$F(2,48) = 3.69$, $p < .05$
2	17	Sites	$F(2,48) = 10.86$, $p < .001$
		Attention	$F(1,24) = 5.10$, $p < .05$
		Sites X Attention	$F(2,48) = 46.93$, $p < .00001$
3	11	Sites	$F(2,48) = 4.70$, $p < .025$
		Attention	$F(1,24) = 6.68$, $p < .025$
4	8		n.s.
5	5	Attention	$F(1,24) = 5.20$, $p < .05$

Table 7. PCA - ANOVA Results: ERPs to Dual Oddball Task

Factor	Variance (%)	Result	F-Statistic
		Non-Targets	
1	46	Sites	$F(2,48) = 24.99$, $p < .00001$
2	23	Group	$F(1,24) = 8.90$, $p < .001$
		Sites	$F(2,48) = 18.03$, $p < .00001$
		Attention	$F(2,48) = 32.65$, $p < .00001$
		Sites X Attention	$F(2,48) = 32.95$, $p < .00001$
3	7	Sites X Attention	$F(2,48) = 9.93$, $p < .0001$
4	6	Sites	$F(2,48) = 20.96$, $p < .00001$
		Attention	$F(1,24) = 17.70$, $p < .001$
		Sites X Attention	$F(2,48) = 8.71$, $p < .001$
5	5	Sites	$F(2,48) = 20.29$, $p < .00001$
		Sites X Attention	$F(2,48) = 6.38$, $p < .001$
		Targets	
1	54	Sites	$F(2,48) = 25.18$, $p < .00001$
		Sites X Attention	$F(2,48) = 34.22$, $p < .01$
2	22	Group	$F(1,24) = 4.91$, $p < .05$
		Sites	$F(2,48) = 22.49$, $p < .00001$
		Attention	$F(2,48) = 18.78$, $p < .001$
		Sites X Attention	$F(2,48) = 40.95$, $p < .00001$
3	11	Sites	$F(2,48) = 3.75$, $p < .05$
		Attention	$F(2,48) = 18.94$, $p < .001$
		Sites X Attention	$F(2,48) = 40.95$, $p < .001$
4	5	Sites	$F(2,48) = 4.39$, $p < .05$
		Group X Attention	$F(1,24) = 14.00$, $p < .01$
		Sites X Attention	$F(2,48) = 4.37$, $p < .025$
5	4	Sites	$F(2,48) = 21.81$, $p < .00001$
		Group X Attention	$F(1,24) = 5.04$, $p < .05$
		Sites X Attention	$F(2,48) = 6.77$, $p < .01$

Table 8. PCA - ANOVA Results: ERPs to Simple Oddball Task

Factor	Variance (%)	Result	F-Statistic
1	52	Sites	$F(2,48) = 29.89$, $p < .00001$
		Attention	$F(2,48) = 45.71$, $p < .01$
		Sites X Attention	$F(2,48) = 16.70$, $p < .00001$
2	23	Sites	$F(2,48) = 50.53$, $p < .00001$
		Sites X Attention	$F(2,48) = 50.61$, $p < .00001$
3	12	Group	$F(1,24) = 6.33$, $p < .025$
		Group X Attention	$F(1,24) = 11.47$, $p < .01$
4	5	Sites	$F(2,48) = 11.93$, $p < .001$
		Attention	$F(1,24) = 29.80$, $p < .00001$
		Sites X Attention	$F(2,48) = 5.79$, $p < .01$
5	4	Sites	$F(2,48) = 4.88$, $p < .025$
		Sites X Attention	$F(2,48) = 4.21$, $p < .025$

These results represent the augmentation of the N100-P200 components (known as the "attention effect") to attended nontarget stimuli in the Practice Dual Oddball condition. There were no significant group differences in attending to these stimuli. These results, identified by PCA, parallel the mean amplitude results for this condition.

PCA-ANOVA Results for Practice Dual Oddball ERPs to Targets. The ANOVAs of the Practice Dual Oddball target data (Table 6) identified two electrode Sites x Attention interactions in the analyses of Factors 1, and 2, and a Group x electrode Sites x Attention interaction in the analysis of Factor 1. Scheffé planned comparisons of the Group x electrode Sites x Attention interaction at Factor 1 further revealed that the Control group showed significantly more negative amplitudes elicited in the 500 - 700 ms region at sites Fz and Cz to detected targets compared to ignored stimuli (Figure 3). The HIV group showed significantly more negative amplitudes in this region only at site Fz (Figure 2).

The Control group's P300s resolved early and below baseline, especially at sites Fz and Cz. However, the HIV group elicited atypical P300s, especially at site Fz which appeared to be an attenuated P300 component (Figure 2).

PCA-ANOVA Results for Dual Oddball ERPs to Nontargets. The ANOVAs of the Dual Oddball nontarget data (Table 7) identified a main effect for Group in the analysis of Factor 2. Four electrode Sites x Attention interactions appear in the analysis of Factors 2, 3, 4, and 5.

These results represent the attention effect to attended nontarget stimuli in the Dual Oddball condition, much like those reported in the practice condition. The results indicated that the attention effect was similar for both groups; however, as noted by the group effect in Factor 2, the Control group produced larger components overall in both the attend and ignore conditions compared to the HIV group (see Figure 1). The

latter finding, identified by PCA, was not identified by the mean amplitude results for this condition.

PCA-ANOVA Results for Dual Oddball ERPs to Targets. The ANOVAs of the Dual Oddball target data (Table 7) identified five electrode Sites x Attention interactions appear in the analyses of Factors 1 through 5, and two Group x Attention interactions revealed further information from the analyses of Factors 4 and 5. Scheffé planned comparisons of the Group x Attention interaction in Factor 4 revealed that only the HIV group showed significantly more positive amplitudes in the 600- to 800-ms region to attended stimuli compared to ignored stimuli (Figure 2). The Scheffé planned comparisons for the Group x Attention interaction in Factor 5 were not significant, which indicated that some permutation of post hoc comparisons not relevant to the experimental treatments was significant.

These results represent a group difference in the target effect during the Dual oddball condition. The HIV group eliciting a late positivity not found in the Control group (cf. Figures 2 and 3). This late positivity was identified by an independent PCA factor (i.e., Factor 4). These results, provided additional information concerning the underlying components not identified by the mean amplitude analysis for this condition.

PCA-ANOVA Results for Simple Oddball ERPs. The ANOVAs of the Simple Oddball target data compared to the nontarget data (Table 8) identified four electrode Sites x Attention interactions in the analyses of Factors 1, 2, 4, and 5, and a Group x Attention interaction in the analysis of Factor 3. A main effect for Group in Factor 3 indicated that the Control group showed significantly more negative amplitudes in the 500 - 800 ms region compared to the HIV group. Scheffé planned comparisons of the Group x Attention interaction in Factor 3 further revealed that only the Control group showed significantly more negative amplitudes to attended targets compared to attended nontargets (Figure 3).

These results indicated that both groups elicited large P300s to the target tones in the Single Oddball condition (cf., Figures 2 & 3). This pattern occurred at all three electrode sites. Furthermore, a difference between the two groups in the slope of the P300 occurred in the 500 to 800-ms region at all three electrode sites. These PCA results parallel the mean amplitude findings for this condition.

P300 latency. PCA is sensitive to amplitude variability in the ERPs but is not sensitive to variations in latency (44). For each subject, in each condition, the peaks of mean P300 components were identified manually and the post-stimulus peak latency tabulated. To determine if there were HIV-related differences in P300 latency, independent of age influences known to occur (45), a series of one-way analyses of covariance (with Age and P300 Latency as covariants) were conducted. There were no significant differences in these results.

Six months follow-up on three cases. Three HIV+ subjects (Subjects 1, 2, and 6) returned six months later for a followup evaluation. Comparing the dual oddball data from the two visits, Subject 1 produced "normal"-type P300s, Subject 2 produced atypical P300s at site Pz only, and Subject 6 produced abnormal ERPs (see Figure 6). By visit 2, all three subjects showed some late activity. This late activity identified by PCA was significant for the entire HIV group (as previously reported). It was not clear if the late activity in the average ERPs was attributable to latency jitter in the elicitation of single-trial P300s or if there were HIV-induced components that had been generated. Using data from the second visits of subjects 1 and 2, we quantified the number of single trials that contained either a P300, a P300 and late component, or just a late component from all 8 runs delivered. We also compared these data to a representative Control subject. Data from Subject 1 contained 47% single P300s, 17% P300 and late activity, and 4% late activity. Data from Subject 2 contained 54% single P300s, 24% P300 and late activity, and 8% late activity. The Control subject's data by comparison contained 76% single P300s, 5% P300 and late activity, and 4% late activity. These results, though qualitative in nature, suggest that HIV-related

ERPs FROM REPEATED VISITS (6-MONTH INTERVAL) BY THREE HIV SUBJECTS

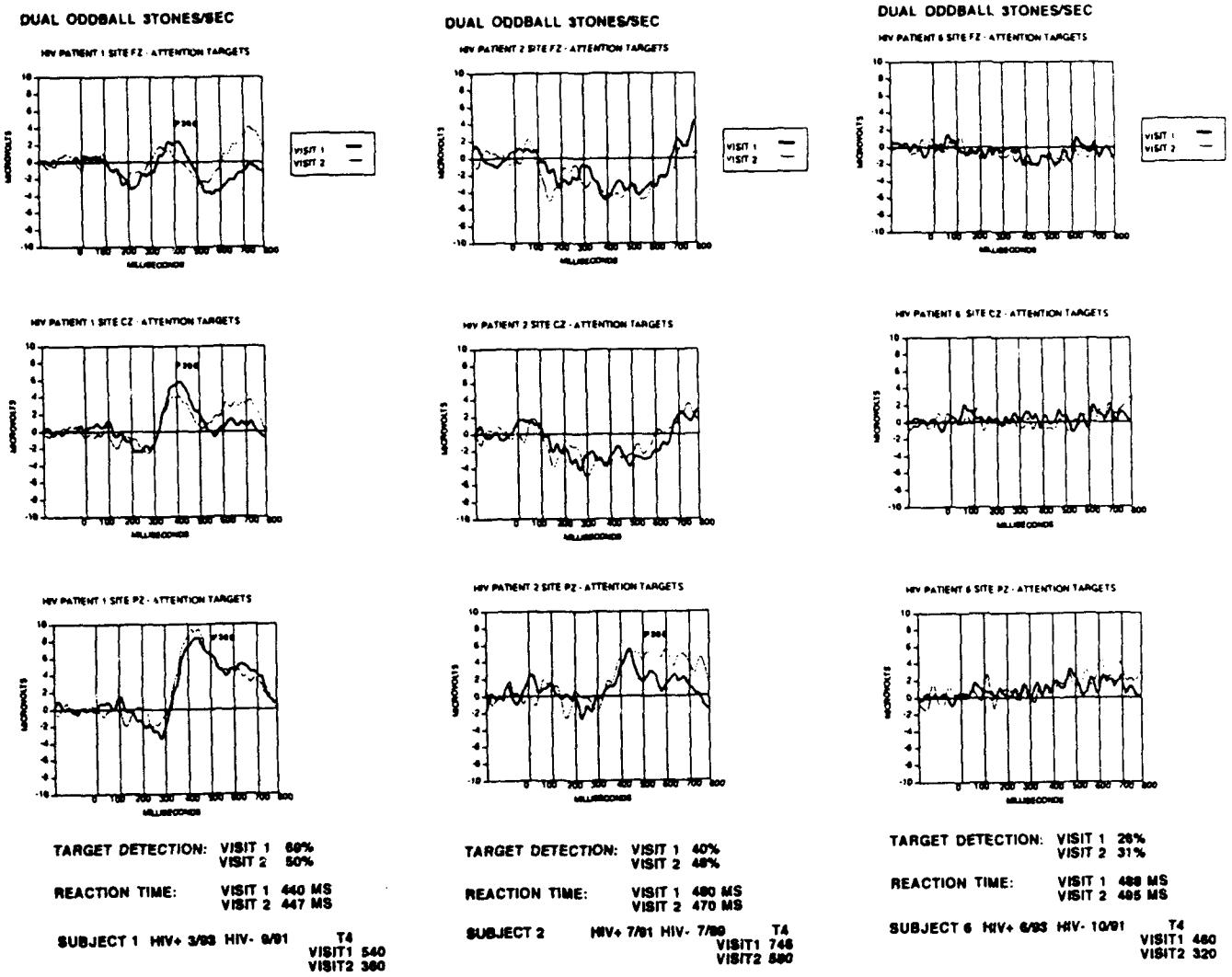

Figure 6. Mean ERPs from repeated visits (6-month interval) from three HIV subjects recorded from Fz, Cz, and Pz scalp sites in response to Dual oddball target stimuli. The ERPs elicited are uniquely different across subjects with ERPs from Subject 1 appearing to be "normal" in P300 morphology, from Subject 2 appearing to be "atypical" in P300 morphology, and from Subject 3 appearing to be "abnormal" by the lack of a P300 morphology. Furthermore, the ERPs are quite similar in morphology between visits for each individual, but with noticeable amplitude difference in the 500 - 800 ms region.

neuropathology may be responsible for the introduction of a previously unkown late component in target ERPs.

Discussion

The purpose of this study was to evaluate the performance of HIV+ asymptomatic subjects using behavioral performance measures that could be compared to normative data and to record performance online during slow and rapid auditory target detection tasks using ERPs. We predicted that the HIV group would perform as well as the Control group on self-paced tests. We expected that the HIV group would not do well and would differ significantly from the Control group when they could not control their pace of performance. The behavioral measures, although delivered fairly rapidly, allowed the individual as much time as needed to make decisions. The ERP measures used slow and fast delivery rates, and forced the subject to take little time in responding in order to be prepared to respond to the next oncoming sequence of input. The slow delivery rates were the 1 tone/sec simple oddball paradigm. The fast delivery rates were the more complex 2 tone/sec and 3 tone/sec dual oddball tasks.

The behavioral performance results indicated that both groups performed well. That is, their ASVAB IQ scores were similar and were stable when compared to IQ assessment at time of enlistment; their ECAT scores were similar and were well within the norm for performance on most of these measures. Thus, on the performance measures alone, our results concur with those reported in the literature that HIV+ asymptomatic patients show little decrement in intellect, computational skills, visual-spatial memory, and psychomotor capabilities in the early stages of the disease (7, 8, 9, 10, 11).

The ERP results indicated that both groups were similar in eliciting an "attention effect" to attended nontarget stimuli. Hillyard and Picton (27) have suggested that the

time course of an attention effect in the ERPs in response to attending a channel of input while ignoring another channel of input is due to additional negative slow wave activity that overlaps the N100 region and extends beyond it, rather than modulating the amplitude of the N100 itself. This additional activity was identified by mean amplitude measures and by PCA in several factors for both dual oddball sequences. In these results, both groups showed a similar frontal-central topographic pattern of augmented N100-P200 responses to the attended nontarget stimuli in the 100 - 200 ms region, compared to the ignored nontarget stimuli (refer to Figure 1). The Control group demonstrated significantly larger ERP responses to nontarget stimuli for the 3 tone/sec dual oddball condition, as identified by PCA. Otherwise, the results suggested that the ability to focus attention selectively to one channel of input was intact in the HIV group.

Furthermore, the target ERP results indicated that both groups elicited P300s to detected targets. The morphology and topographic distribution of P300s were similar between the two groups in the simple oddball deliveries, but were different during fast dual oddball deliveries.

In the simple oddball condition, both groups elicited P300s to detected targets. P300 latencies were similar for both groups. Mean amplitude measures and PCA (Group main effect, Factor 3), however, suggest a group difference in the 600- to 800-ms region which might be attributable to HIV (refer to Figures 2 and 3). Reaction time and number of detected targets were similar. Overall, it appeared that HIV did not affect detecting and responding to targets nor eliciting P300s in the simple oddball condition. Our findings concur with those reported in the literature using this paradigm that there is little difference in the P300s generated by HIV+ asymptomatic subjects in the simple oddball condition (17, 19, 20).

In the two dual oddball sequences, both groups elicited P300s, but there were group differences in the morphology and topography at the P300s. The Control group

produced P300s across all three electrode sites in both the practice and dual oddball conditions. The HIV group produced P300s at only Cz and Pz in both these conditions. Furthermore, the HIV group elicited late activity at Fz and Cz during the dual oddball condition not present in the Control group ERPs. Mean amplitude results indicated that the Control group produced significantly larger P300s in the dual oddball condition. Reaction time and number of detected targets were similar. These findings suggested that while overall performance appeared to be intact, underlying neuronal functioning was altered by HIV, as indicated by ERPs from the 3 tone/sec dual oddball paradigm.

Our results suggest that ERPs may be useful in monitoring HIV-related neuropathology. Individuals infected with HIV on average approximately four years showed underlying neurological differences in attention and cognitive processing. Pashler's (12) "bottleneck" theory of response selection may be a useful description of how HIV might eventually affect attentional and cognitive systems. According to this theory, there exists a maximum rate at which information can be processed and responded to (approximately 300 ms; 12). HIV, over time, may compromise the ability to process and respond to rapid sequences of information. Instead of a normal P300, indicative of an intact response-selection process, HIV+ subjects may produce a smaller P300 and a late component, suggesting a flawed response-selection process. Later, the progression of HIV may produce an uncharacteristic ERP waveform resembling one produced by Subject 6 (refer to Figure 6). To overcome the information processing bottleneck, the stimulus delivery rate would have to be decreased. The slow delivery rate of the simple oddball paradigm may be well within the capabilities of asymptomatic, HIV-infected individuals, while a 3 tones/sec appears to be the threshold rate. This threshold rate may decrease as the disease progresses.

The results from the 3 tone/sec dual oddball task replicate and extend our earlier work (46). In a pilot study testing seven HIV subjects, we used a similar version of the 3 tones/sec dual oddball task. The subjects were asked to maintain a

running mental count of the number of targets detected. This method did not allow the extraction of ERP responses to detected ("hits-only") targets, so all target ERPs (detected or not) were pooled. The results were compared with data gathered by Woldorff (47) on an equal number of healthy subjects using the same paradigm. While the average ERPs from their group showed substantial P300s, the average ERPs produced by our HIV group showed no P300s. Furthermore, the HIV group reported detecting significantly fewer targets (HIV - 48%; Control - 71%). In the present study, we extracted "hits-only" ERP responses, and small (approximately 4-6 μV) P300s with an additional late component emerged, indicating that HIV patients did retain an electrophysiological response to correct detections, but the ERP waveforms were unusual when compared to healthy controls.

In conclusion, it appears from these ERP and behavioral results that HIV+ subjects were able to focus their attention on rapid sequences of stimuli and detect oddball targets as efficiently as Control subjects. However, in time, rapid decisions may be affected in the HIV group due to central nervous system changes. Our results suggest that the auditory dual oddball task is a useful tool in evaluating cognitive processing abilities, and is potentially useful in monitoring HIV-related neuropathology. This task is not a measure of the auditory system, but rather of perception and cognitive processing abilities which are central resources that are associated with all sensory modalities.

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13. ABSTRACT *(Maximum 200 words)*

Thirteen asymptomatic HIV-infected and 13 healthy control subjects underwent a battery of behavioral and electrophysiological assessments. The behavioral measures tested IQ, computational skills, visual-spatial memory, and psychomotor ability with normative data for comparison. The electrophysiological measures included event-related potentials (ERPs) in response to auditory, "oddball" targets in either a single or dual channel delivery. The behavioral results indicated that the HIV group performed similarly to the Control group. The ERP results indicated that the HIV group produced similar ERPs indexing target detection in the single oddball delivery. The ERPs recorded from the HIV group in response to the dual oddball task showed atypical morphology and topography relative to those recorded from the Control group. These results suggested that auditory ERPs elicited by rapid, dichotic stimulus presentations were more sensitive to subclinical effects of HIV-related neuropathology than conventional behavioral measures.

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