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Research Article

Effects of HIV on Neuroelectric Responses: AERP and EDA

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Summary

Aim We aimed to test our hypothesis that electroencephalography (EEG) responses and electrodermal activity (EDA) in response to auditory stimuli in HIV/AIDS patients will differ to those of healthy individuals.
Method Data was collected from 20 AIDS patients receiving anti retroviral treatment for an average duration of five years and 20 healthy individuals matched for age/sex. Participants were presented with auditory stimuli consisting of pure sound tones with 1000 Hz (non-target) and 2000 Hz (target) frequency. Frontal EEG and EDA recordings were taken using a biopotential amplifier system.
Results P1, N1, P2, N2 ($p<0.001$) responses obtained from the frontal region to target stimuli were higher in HIV group; while the P3 response was higher in control group. The latencies of all responses to target stimuli were significantly delayed in HIV group compared to control group. In HIV group, amplitudes of P1, N2 and P3 responses to target stimuli were found to be higher than to non-target stimuli; N1 and P2 responses to non-target stimuli had higher amplitude.
Conclusion The findings of this study demonstrate the effects of HIV on both the peripheral (EDA) and central nervous system (EEG). The differences in neuroelectrical activity found between HIV patients and healthy individuals can be concluded to be due to the direct or indirect effects of the virus and antiretroviral medication on neurons. The method of simultaneous monitoring of auditory ERP and EDA may contribute to the detection of subclinical neural deterioration in HIV patients.

Key words: AERP, EDA, P1, N1, P2, N2, P3, HIV/AIDS

Nöroelektrik Yanıtlara HIV'in Etkisi: AERP ve EDA

Özet

Amaç Bu araştırmada HIV/AIDS hastalarının, işitsel uyaranlara karşı ortaya çıkan elektroensefalografi (EEG) yanıtlarının ve elektrodermal aktivitelerinin (EDA) sağlıklı bireylere göre farklılık göstereceği hipotezimizi test etmeyi amaçladık.
Yöntem Veriler ortalama 5 yıldır anti retroviral tedavi alan 20 AIDS hastasından ve bunlara yaş - cinsiyet olarak eşleştirilmiş 20 sağlıklı bireyden elde edildi. Katılımcılara 1000 Hz

(hedef olmayan) ile 2000 Hz (hedef) frekansına sahip saf ses tonundan oluşan işitsel uyaranlar dinletildi. Taşınabilir biyopotansiyel anfi sistemi ile frontal EEG ve EDA kayıtlaması yapıldı.
Bulgular Frontal bölgede, hedef uyaranlara karşı alınan P1, N1, P2, N2 ($p<0.001$) yanıtlarında HIV grubu daha yüksek iken; P3 yanıtı kontrol grubunda daha yüksekti. Hedef uyaranlara karşı alınan tüm yanıtların latansları HIV grubunda kontrol grubuna göre istatistiksel olarak anlamlı derecede gecikmişti. HIV grubunda hedef uyaranlara karşı elde edilen P1, N2 ve P3 yanıtlarının genlikleri, hedef olmayan uyaranlara göre daha yüksek bulundu. N1 ve P2 yanıtları hedef olmayan uyaran için daha yüksek genlikliydi. Kontrol grubunda hedef uyaranlara karşı elde edilen P1, P2 ve P3 yanıtlarının genlikleri, hedef olmayan uyaranlara göre daha yüksekti. Kontrol grubunda N1 ve N2 yanıtları hedef olmayan uyaran için daha yüksek bulundu.
Sonuç Bu çalışmanın bulguları HIV"in hem periferal hem de merkezi sinir sistemi üzerindeki etkilerini EEG ve EDA verileriyle göstermektedir. HIV ile enfekte hastalar ve kontrol grubu arasında bulunan nöroelektrik aktivite farklılıklarının altında virüsün ve antiretroviral ilaçların nöronlar üzerindeki direk veya dolaylı etkilerinden kaynaklandığı söylenebilir. İşitsel ERP ve eş zamanlı alınan EDA izlenmesi metodunun HIV hastalarında subklinik nöral bozulmaların belirlenmesine katkısı olabilir.

Anahtar Kelimeler: AERP, EDA, P1, N1, P2, N2, P3, HIV/AIDS

INTRODUCTION

Human Immunodeficiency Virus (HIV) continues to be a global public health problem. Since the beginning of the HIV epidemic, 78 million people have been infected with HIV, 36.7 million of whome are still living with HIV (UNAIDS Fact Sheet 2016 statistics) (1). HIV infection has been observed in our country since 1985. Turkish Public Health Agency reported that the total number of cases was 3 in 1985, but it was 11998 on 31 December 2015 (2).

HIV is a lentivirus which, in time, causes Acquired Immunodeficiency Syndrome (AIDS). AIDS causes progressive failure of the immune system which allows life-threatening opportunistic infections and various cancers to develop. Furthermore, by infecting the brain, HIV disrupts the functions of the Central Nervous System (CNS). Combination of antiretroviral therapy cannot eradicate CNS complications. Although the severity of disease declines with this therapy, HIV related neurocognitive impairments prevail. This is due to the monocytes in the circulation and the glia cells in the brain which act as an HIV reservoir (3). Cortical white and gray matter are found to be declined in HIV patients with low CD4+ (cluster of differentiation 4) T cell levels (4). On the surface of human lymphocytes, specific glycoproteins are available that are involved in the activity and functions of the cell. CD4+ cell surface antigen carrying lymphocytes contribute to immunological reactions. CD4+ lymphocytes are also the primary target of HIV infection. Over the course of the HIV infection the number of CD4+ T cells gradually decline. Other studies have shown that there is a reduction in cortical gray matter thickness and brain volume. It has been shown that there is a positive linear relationship between this reduction and the severity of the cognitive disruption (5,6). Several researches examine the effects of HIV infection on cognitive processes via electroencephalography (EEG) (7-11).

Spontaneous electrical activity of the brain can be monitored with EEG. Brain activity in response to repeated stimuli (sound, light, tactile, etc.) is defined as evoked potential (EP) or event related potential (ERP) (12-14). The phasic neural population activity in response to auditory stimuli form the Auditory Event Related Potential (AERP) responses. ERP

responses occur in up to 600ms depending on the complexity of the auditory stimulus. Those responses which occur after 200ms reflect the brain"s cognitive functions while those that occur before 200ms reflect sensory processes. Especially when a participant is given the task of attending to a target stimulus within a series of stimuli, a positive P3 response is formed at about 300 milliseconds. P3 is the response most associated to cognition in psychophysiological research (15-18). Polich et al, have shown that the amplitude of P300 is smaller and it's latency is greater in patients infected with HIV compared to controls (11). It is suggested that before the prevalence of neurological and cognitive degeneration in patients with AIDS there is an increase in background alpha activity, which is suppressed with antiretroviral treatment and that EEG can be used as a treatment monitoring tool (19).

Besides its destructive effects on the CNS, HIV has neuropathological effects on the peripheral nervous system. In AIDS patients electrodermal activity is shown to be higher in relation to their arousal (20,21). The activity of eccrine sweat glands in the periphery increases as the sympathetic nervous system is activated. This activity can be accessed via suitable systems and the response obtained is called Galvanic Skin Response (GSR) or Electrodermal Activity (EDA). EDA is obtained by measuring the variance in resistance or conductivity between two electrodes placed on the skin. In other words the sympathetic action potentials of peripheral nerves can be monitored by means of EDA (22).

In this study we aimed to test the hypothesis that EEG responses and electrodermal activity elicited in response to auditory stimuli will differ in patients with HIV/AIDS compared to healthy individuals.

MATERIAL AND METHODS

Participants:

Twenty HIV-positive patients (mean age: 44.78±7.36; 2 female, 18 male) who were diagnosed and ongoing anti retroviral treatment in HIV/AIDS outpatient clinic for an average duration of five years participated in the study. Patients with acute/chronic illness and neurological/psychiatric disorders unrelated to HIV were not included in the study.

The control group consisted of individuals (matched with patients for age and sex) who were working in the hospital where the study was conducted. People reporting acute/chronic and neurological/psychiatric diseases were not included in the study.

Procedure:

The research was conducted with the permission of the local ethics committee. The auditory stimuli defined below were applied during electrophysiological assessment to the participants who consented to taking part in the research.

Auditory Stimuli:

The participants were presented auditory stimuli consisting of 1000 Hz and 2000 Hz frequency pure sound tones of 500 ms duration (sinusoidal waves with 30 ms rise and fall). The stimuli were applied by means of an earphone (Sony MDR-027, Japan) connected to a computer. The 1000 Hz and 2000 Hz stimuli were respectively defined as non-target, and target. These stimuli were introduced to the participant before the electrophysiological recordings. A total of 120 auditory stimuli were applied, 25% of which were target and 75% non-target. The target stimuli were pseudo-randomly distributed within the series of stimuli.

Electrophysiological Recordings: All electrophysiological recordings were conducted by means of a portative biopotential amplifier system (Nexus 10, MindMedia, Holland) and a computer which enabled wireless communication with this system (Dell Inspiron N5110, People's Republic of China).

The participant's electrical brain activity was recorded bilaterally from the frontal region (F3-F4) via EEG sensors employing the International 10-20 electrode placement system. The area of skin on which electrodes were to be placed was wiped with cotton moistened with medical alcohol. EEG paste was applied under the electrodes which were placed on the area. Reference electrodes applied with EEG paste were placed on each earlobe. The ground electrode was designated as FCz. Electrode impedances were kept to be lower than 5kΩ. EEG was recorded at 1024Hz/sec sampling rate with 0.05-48Hz band pass filter.

An electrode each was placed on the second knuckle of the fore and middle finger of the non dominant hand and a harmless very weak current was applied to record EDA. As the conductivity between two electrodes was measured, responses obtained were simultaneously recorded with EEG signals on the computer.

EEG Analysis:

Offline EEG was epoched between -100ms for prestimulus and +600ms for poststimulus and filtered at 1-30Hz (Zero phase shift, 12dB/oct). Artifacted epoches were rejected. Equal number of target and non-target epoches were randomly selected and averaged. The corresponding AERP component measurement was carried out from the most prominent positive and negative peaks consecutively starting at 40ms. Averaged epoches, obtained from twenty individuals, were used to determine AERP latencies for each group. In control: 40-80ms (P1), 80-120ms (N1), 130-150ms (P2), 150-220ms (N2) and 230-320ms (P3) time intervals were used. HIV group had delayed responses. Therefore, 40-100ms (P1), 100-160ms (N1), 160-210ms (P2), 210-300ms (N2) and 300-380ms (P3) time intervals were used.

Statistics:

SPSS 15.00 (Leadtools, USA) program was used for the statistical analysis of data. Normality of the distribution of data was tested with the Kolmogorov Smirnov Test. Paired and independent samples t-tests were applied to data with normal distribution and paired and independent samples Mann Whitney U tests were applied to data that did not have a normal distribution. Findings with a p value less than 0.05 were accepted to be statistically significant.

RESULTS

EDA, as indicators of sympathetic action potentials of the peripheral nerves, were measured to be 2.50μSiemens (±1.84) in individuals with HIV, and 1.80μSiemens (±1.06) in controls (mean±SD). No statistically significant difference was found between the HIV and control group.

AERP (P1, N1, P2, N2 ve P3) amplitudes were examined in the HIV (H) and Control (C) groups.

In the frontal region, P1 (H: 2,35±1,56μV; C:2,01±1,52μV), N1 (H:-2,26 ±1,35μV; C:-1,54±1,84μV), P2 (H:2,43±1,28μV; C:2,17±1,52μV), N2 (H:-3,32±1,43μV; C:-1,68±0,95μV) responses obtained for target stimuli were higher in the HIV group while P3 (H:2,39±0,88μV; C:2,72±1,13μV) responses were higher in the control group. Among these findings a statistically significant difference between the HIV and control group was observed only for the N2 response ($p<0.001$) (Figure 1).

AERP latencies (response times) were examined in the HIV and Control groups.

All latencies of responses obtained for target stimuli in the frontal region were significantly longer in the HIV group compared to the control group. P1 (H:87.23±26.76ms; C:61.42±12.30ms; $p<0.01$), N1 (H:142.13±47.70ms; C:99,28±22.64ms; $p<0.01$), P2 (H:193±63.90ms; C:141.40±19.48ms; $p<0.01$), N2 (H:253.43±84.66ms; C:195.90±21.30ms; $p<0.05$), P3

(H:354.13±67.45ms; C:279.39±15.50ms; p<0.01) (Figure 2).

The amplitudes of responses obtained from HIV and Control groups to target (T) and non-target (NT) stimuli were compared.

In the HIV group;

As shown in Figure 3A the amplitudes of P1, N2 and P3 responses to target stimuli were found to be higher than to non-target stimuli. The amplitudes of N1 and P2 responses were higher for the non-target stimuli compared to the target stimuli. The measured amplitude values are presented in Figure 3A. Paired comparisons revealed no statistically significant differences between amplitudes of responses obtained (to target-nontarget stimuli) in the HIV group (Figure 3A).

In the Control group;

As shown in Figure 3B the amplitudes of P1, P2 and P3 responses to target stimuli were found to be higher than to non-target stimuli. The amplitude of N1 and N2 responses were found to be higher for non-target stimuli. The measured amplitude values are presented in Figure 3B. Paired comparisons in the control group revealed a statistically significant difference between amplitudes of responses obtained (to target-non-target stimuli) for only the P3 response (T:2.31±0.71μV; NT:0.86±0.77μV; p<0.001) (Figure 3B).

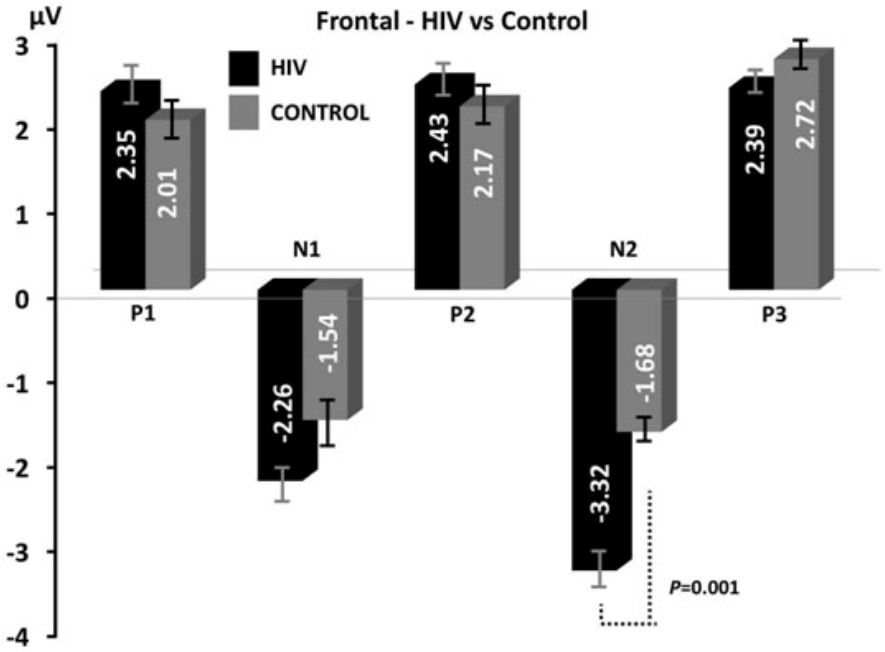

Figure 1: *AERP responses to target stimuli obtained from the frontal region are presented for the control (grey) and HIV (black) groups on the amplitude-time graph. Average amplitude values are displayed on the columns. The bars and dotted lines above the columns respectively depict the amount of standard deviation and the level of statistical significance between the two values.*

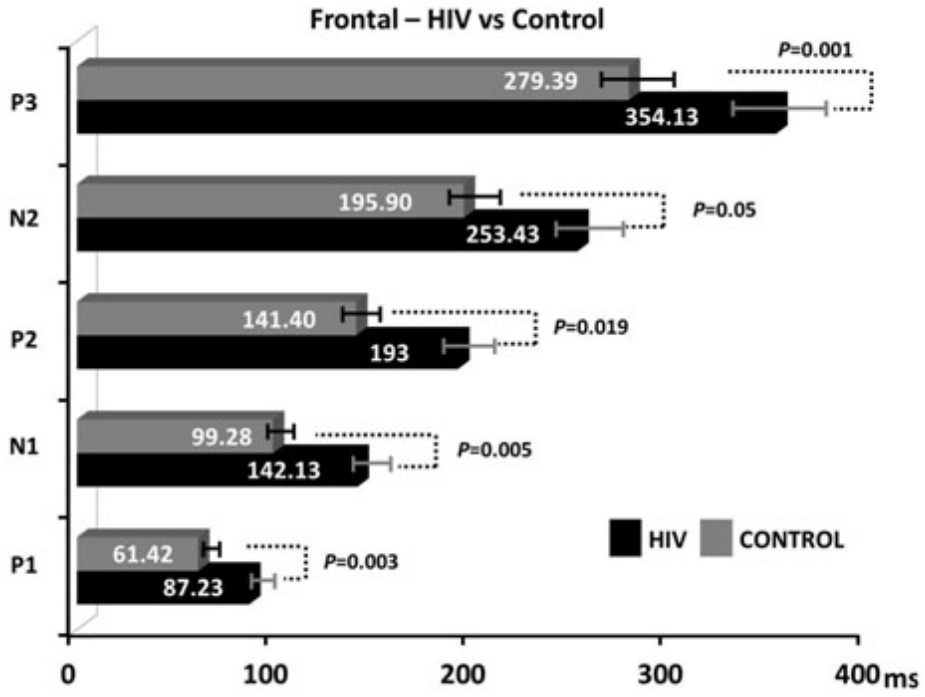

Figure 2: *The AERP responses (P1, N1, P2, N2 and P3) obtained from the frontal region for the target stimuli are displayed on the vertical axis, while response times are displayed on the horizontal axis for the control (grey) and HIV (black) groups on the response-time graph. Average amplitude values are presented on the columns. The bars and dotted lines above the columns respectively depict the amount of standard deviation and the level of statistical significance between the two values.*

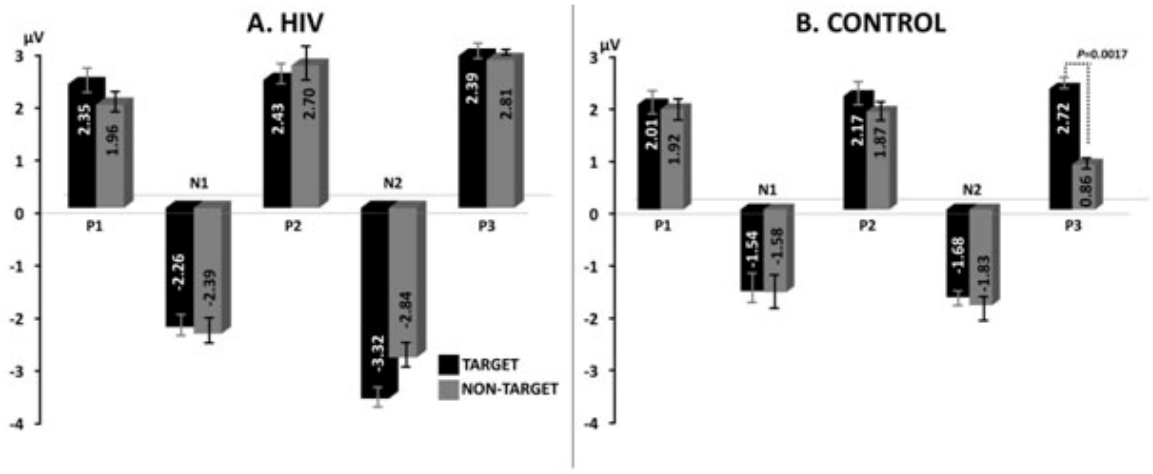

Figure3: *A. Frontal region AERP responses to target (black) and non-target (grey) stimuli in the HIV group; B. Responses of the control group are presented. Average amplitude values are indicated on the columns. The bars and dotted lines above the columns respectively depict the amount of standard deviation and the level of statistical significance between the two values.*

DISCUSSION

The main finding of our study is that there are differences in terms of EEG and EDA activity between HIV patients and the control group. Our study hypothesized that EDA, which reflects peripheral nervous system activity and EEG findings, exhibiting activity of the central nervous system would vary among HIV patients compared to healthy controls. Despite noteworthy differences observed in EEG data between the patient and control group, an increase was found in EDA values among HIV patients which did not reach the level of statistical significance. Considering that the EDA is a direct and concentrated indicator of sympathetic activity, from this elevation observed in EDA values, we may conclude that the sympathetic system is more active in HIV patients and that there is an increase in their arousal levels. Likewise, in a study in which EDA responses reached higher values in patients with AIDS, EDA values were found to increase as their level of arousal was increased by means of a method named psychovegetative resonance (20). Furthermore in a study in which they measured sympathetic skin response, Kokotis et al showed that HIV neuropathy affected myelinated nerves while antiretroviral treatment affected non-myelinated nerves (21). In light of these findings, it may be said that the effects of the AIDS virus and (since we worked with patients receiving treatment) the neurotoxic effects of antiretroviral medication accounts for the elevation we observed in EDA.

In regard to the EEG findings in our study we see that the P1, N1, P2, N2 responses obtained from the frontal region to target stimuli have a higher amplitude in the HIV group and the P3 component has a larger amplitude in the control group. At the same time, all the ERP components obtained from the HIV group were found to have prolonged latencies. When were firstly examine the P3 response in the HIV group there is a noticeable decrease in its amplitude and an increase in its latency. Furthermore while the P3 target responses are statistically higher than non-target responses in the control group, there is no statistically significant difference in the P3 responses of individuals with HIV to target and non-target stimuli. P3 is an ERP component associated with focused attention and memory update. Latency is accepted to be related to memory, and amplitude to the degree of attention (23-25). In this case, no difference in the P3 component to target and non-target stimuli in HIV patients and its lower amplitude compared to healthy individuals implies that their attention is diminished. Furthermore, prolonged latencies imply retardation and deterioration in the operational processes of neural networks associated to memory. With increased viral loads P3 latency is observed to be prolonged (11). Bauer et al, also showed that P3 latency increased in HIV seropositives (26). There are many studies reporting delta (0.5-3 Hz) and theta (3-7 Hz) activity found to be underlying the P3 ERP component (27-32). Babiloni et al. and Polich et al. have reported increased delta activity in HIV groups compared to controls (7,11). Polich et al. associated increased frontal delta activity in individuals with HIV to their increased level of fatigue and lower arousal compared to controls (11). This conclusion is in line with our opinion that the decreased amplitude of the P3 response in the HIV group, observed in our in our findings, is related to impairment in cognitive processes such as attention and memory. Ernst et al. reported that glutamate level was reduced due to neurotoxicity in parietal gray matter in

individuals with HIV, who were examined by means of magnetic resonance spectroscopy, and that these people had poor performance on cognitive attention tests (33).

When we analyze the other ERP components we find that the amplitude of N2 response obtained to target stimuli in the frontal region is statistically higher in the HIV group. At the same time, the latencies of all ERP components (P1, N1, P2, N2, P3) obtained in the HIV group is prolonged. Firstly, this prolongation of latencies indicates retardation in both sensory and cognitive information processing. This retardation is the EEG reflection of the effect of HIV and antiretroviral medication on the central nervous system. Arendt et al. determined increase in latencies of N2 and P3 in HIV positive patients and suggested this was due to involvement of cortical and subcortical structures (34). On the other hand Bungener et al. note that mood disorders such as depression and anxiety, frequently observed in individuals with HIV, are associated to increase in N2 amplitude and delay in latencies of N1 and N2 (35).

Unlike previous studies in literature the findings of this study demonstrate the effects of HIV on both the peripheral and central nervous system with EEG and EDA data. The neuroelectrical differences found between HIV patients and the control group can be said to be due to the direct or indirect effects of the virus and antiretroviral medication on the neurons. However the identification of these effect mechanisms may be feasible with a prospective longitudinal study employing the same methods planned over a time spanning from the beginning of the disease to a future date. Bungener et al. who used the auditory ERP method similar to our's, reported N1, N2 and P3 responses to be sensitive indicators of HIV disease (35). Another similar study conducted with children with HIV, states that despite the absence of neurological findings EP responses are abnormal (36). In the light of all these studies the method of simultaneous monitoring of auditory ERP and EDA may contribute to the detection of subclinical neural deterioration in HIV patients.

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