Decreased electrodermal activity in patients with epilepsy

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Abstract

Objective: Biofeedback therapy using electrodermal activity (EDA) is a new non-invasive therapy for intractable epilepsy. However, the characteristics of EDA in patients with epilepsy are little known; therefore, we assessed the EDA characteristics in patients with epilepsy.

Methods: A cross-sectional observational study was conducted in 22 patients with epilepsy and 24 healthy individuals. We collected information on demographic characteristics, EDA, and state anxiety from both groups, and epilepsy diagnosis, seizure number per month, disease duration, and number of anti-epileptic drugs (AED) from the epilepsy group. A wristband device was used to measure resting EDA from both wrists for 10 minutes under controlled temperature and humidity. We compared the EDA levels between the epilepsy group and the control group and examined correlations between EDA and epilepsy-associated factors in the epilepsy group.

Results: A decreasing trend in EDA was observed during the first 1 minute from the start of the measurement in 22 epilepsy patients (with or without seizures) compared with healthy controls ($P = 0.12$). However, a significant decrease in EDA was found in 18 epilepsy patients with seizures compared with healthy controls (-0.48 versus -0.26; $P = 0.036$). Furthermore, seizure frequency showed a significant inverse correlation with EDA in the epilepsy group ($\rho = -0.50$, $P = 0.016$). However, neither disease duration nor the number of drugs prescribed correlated with EDA in the epilepsy group.

Significance: Marginally decreased EDA was observed in patients with epilepsy, and significantly decreased EDA was found in patients with a higher seizure frequency. The present findings shed light on the appropriateness of EDA-biofeedback therapy in epilepsy.

Keywords: electrodermal activity, biofeedback therapy, seizure numbers, non-invasive, galvanic skin response, intractable epilepsy

Abbreviations

BFT Biofeedback treatment

CNV Contingent negative variation

EDA electrodermal activity

SCP slow cortical potential

Original Research Articles

1. INTRODUCTION

Epilepsy is a chronic disease triggered by excessive electric activity in cerebrocortical neurons that causes repeated epileptic seizures, leading to a sudden loss of consciousness or convulsions. The prevalence is roughly 1% worldwide (1, 2). Drug therapy suppresses seizures in about 70% of patients; the remaining 30% suffer from refractory epilepsy where seizures cannot be suppressed by drugs. Surgical operation could be considered for refractory epilepsy. The seizure suppression rates were high to some extent in resective surgery of the lesional focus (60-75%), resective surgery of the non-lesional focus (32-51%) (3), and vagus nerve stimulation (8.0%) (4). However, these surgical treatments are highly invasive and burdensome on the patient; therefore, there is a great need for non-invasive treatments.

Biofeedback treatment (BFT) aims to assist patients in drawing feedback from biological information including heartbeat, respiration, and brainwaves using various techniques to enable them to adjust these values voluntarily. BFT has been used for a variety of physical and mental disorders, including migraine and attention deficit hyperactivity disorder (5, 6). Electroencephalographic BFT, which has long been used for epilepsy treatment, has certain effects on epilepsy symptoms (7-9). Recently, BFT for epilepsy using electrodermal activity (EDA-BFT), an index of peripheral sympathetic nerve function, has been considered a promising non-invasive treatment (10-13).

EDA, which is the minute electrical activity measured on the skin surface, reflects peripheral synthetic nerve function (14). More specifically, it represents changes in sweat gland activity triggered by postganglionic cholinergic fiber activity in peripheral nerves (14). Because EDA shifts acutely according to emotional changes, it has been used widely to measure emotional responses, such as anxiety and fear, in the neuropsychological field (15, 16). Several studies have demonstrated

that EDA is inversely correlated with cerebral cortex activity in patients with epilepsy (17, 18), and the findings provide a basis for the hypothesis that increasing the level of EDA using BFT would reduce cerebral cortex activity, thus resulting in seizure suppression.

Previous studies demonstrated an approximately 45% decrease in epileptic seizures with the use of EDA-BFT (10, 11), and seizure frequency decreased by more than 50% in 6 out of 10 individuals (12). This rate of 50% responders indicates that the therapeutic effects of EDA-BFT are comparable with those of novel AED (14–60%) (19, 20), vagus nerve stimulation (45%) (21), and ketogenic diet (53%) (22). Although few findings are available regarding the long-term prognosis, one study suggests that the seizure suppression effect can last for more than three years (23). Additionally, EDA-BFT, which has been drawing attention as a stress management intervention in epilepsy, not only reduces epileptic seizures but also improves psychiatric comorbidities, including major depressive disorder and anxiety disorder (24).

The purpose of EDA-BFT is to increase the level of EDA in patients with epilepsy. However, little has known about EDA characteristics in patients with epilepsy underlying BFT. Only one report compared patients with epilepsy with healthy controls was available to the best of our knowledge, which indicated that the EDA in patients with epilepsy might be increased (25). Moreover, it remains unclear how epilepsy-related factors, such as seizure frequency, disease duration, and drug treatment, affect EDA in patients with epilepsy. Clarifications of these issues would allow us to assess the appropriateness of EDA-BFT. Therefore, this study compared EDA characteristics between epilepsy patients and healthy controls and also investigated the relationship between epilepsy-related factors and EDA characteristics in epilepsy patients.

2. METHODS

2.1 Study design

This was a single-center, cross-sectional, non-invasive controlled study conducted at Hokkaido University Hospital, one of the epilepsy centers in Japan.

2.2 Standard protocol approvals, registrations, and patient consents

This study was approved by the institutional review board of Hokkaido University Hospital, and written informed consent was obtained from all participants.

2.3 Study participants

Participants were recruited from outpatients with epilepsy who visited the Department of Psychiatry at Hokkaido University Hospital from January 2016 to March 2018. Age- and sex-matched healthy controls were also recruited.

Patients with more than 18 years of age and diagnosed with epilepsy according to International League Against Epilepsy criteria were included in this study (26). Patients with hyperhidrosis or hypohidrosis, which may directly affect EDA measurements; those with lesions or burns at measurement sites; and those with concomitant mental disorders determined by the Diagnostic and Statistical Manual of Mental Disorders 5 were excluded from this study.

The information on age, sex, and resting EDA was collected at the time of measurement, and anxiety was assessed in both groups using state anxiety scores with the State and Trait Anxiety Inventory (STAI) (27). Additionally, information on the epilepsy syndrome, seizure frequency, number of prescribed AED, and disease duration was obtained from the epilepsy group. We defined “without seizures” as no seizure for more than one year.

2.4 Measurement device and measurement environment

An E4 wristband® (Empatica Inc., Milan, Italy), a wearable wristband device, was used for EDA measurement. The E4 wristband, which adopts an external measurement technique using alternating current, measures EDA with two dry silver-plated electrodes attached to the inner surface of the wrist. The sampling rate is 4 Hz, and the device is capable of measuring 0.01 μS to 100 μS. Data obtained from the E4 wristband are comparable with those obtained from the conventional, orthodox EDA measurement technique in which wet electrodes are placed on the palm (28, 29). Therefore, the E4 wristband has been used broadly in clinical studies (30, 31).

EDA measurement was carried out in a dark, quiet room with the participant sitting on a sofa. The room temperature was set at 23 ℃, the humidity was set at 60%, and brightness and ambient noise were controlled (14). All measurements were conducted by the same investigator (TH) during the same time frame (14:00–15:00).

2.5 Measurement procedure

After entering the room, the participant was asked to sit on a sofa and fill out the STAI, an anxiety assessment scale. Alcohol swab was used to clean the patient's wrists (14), and the patient was then required to wear E4 wristbands on both wrists; noise-canceling headphones (QuietComfort 35 headphones I®, Bose Corporation, Framingham, MA, USA) were used for the purpose of blocking noise. The patient was instructed to not move his/her body while closing eyes, to feel relaxed, and to not fall asleep. EDA measurement was started 1 minute after the instructions and continued for 10 minutes.

2.6 primary and secondary outcomes

The difference in resting EDA between the epilepsy group and the control group was determined as the primary outcome. Correlations between resting EDA and seizure frequency, the number of drugs prescribed, or disease duration were assessed as the secondary outcomes.

2.7 Statistical analysis

Individuals who fell asleep (14), were unable to remain still, or developed epileptic seizures during measurement were excluded from the study. The t-test was used to compare resting EDA between the epilepsy group and the control group. Spearman's rank method was used to examine correlations between resting EDA and seizure frequency, the number of prescribed AED, or disease duration in the epilepsy group. In addition, the t-test, $\chi 2$ test, and Wilcoxon signed-rank test were respectively used to analyze age, sex, and state anxiety in these two groups. EDA data from the left and right wrists were averaged for each participant in the analysis, and a log conversion was then performed to obtain a normal distribution (14, 32, 33). All P-values were two-tailed, and the significance level was set at $P < 0.05$. R statistical software (version 3.3.3) was used for statistical analyses.

2.8 Data availability statement

Anonymized data can be made available to qualified investigators upon request to the corresponding author.

3. RESULTS

Twenty-two patients with epilepsy and twenty-four healthy individuals participated in this study (Table 1). The measurements were carried out without problems, and no participants were excluded from the analysis because of sleeping or epileptic seizures during measurement. The male-to-female

ratio, age, or state anxiety did not significantly differ between the epilepsy group and the control group. Among the 22 participants in the epilepsy group, 21 suffered from focal seizures, and 14 had temporal lobe onset epilepsy. The average disease duration (22.5 years) was relatively long. All participants in the epilepsy group used AED, and the average number of prescribed AED was 2.27. Epileptic seizures were completely suppressed in four participants but were still observed in 18 participants in the epilepsy group. The seizure frequency varied greatly with an average frequency of 8.4 per month and a maximum frequency of 40 per month.

The log-transformed average resting EDA during 10 minutes, the primary outcome, was -0.56 in the epilepsy group and -0.50 in the control group, and no significant differences were observed between these two groups (95% CI, -0.08 to 0.21; P = 0.39). Participants in both groups showed gradually declined EDA during the 10-minute duration, and the greatest difference between the two groups was observed immediately after the start of the measurement (Fig. 1). Thus, the log-transformed average EDA during 1 minute after the start of the measurement was then compared between the epilepsy group and the control group. A trend of decreased EDA was observed in the epilepsy group compared with the control group (-0.42 versus -0.26; 95% CI, -0.04 to 0.36; P = 0.12). Subsequently, 18 individuals in the epilepsy group, in whom epileptic seizures were still observed, were classified as the epilepsy with seizures group, which was further compared with the control group. Notably, a significantly decreased EDA was found in the epilepsy with seizures group compared with the control group (-0.48 versus -0.26; 95% CI, 0.02 to 0.43; P = 0.04).

We further examined the secondary outcomes in the epilepsy group. A significant inverse correlation was observed between the EDA during the first 1 minute from the start of measurement and seizure frequency in the epilepsy group, and the correlation was moderate (P = 0.02; ρ = -0.50) (Fig. 2). In addition, other epilepsy-related factors, including the number of drugs prescribed and the disease

duration, were not correlated with the EDA during the first 1 minute. Furthermore, no correlations were observed between the EDA and state anxiety, age, or sex in all the groups.

4. DISCUSSION

4.1 Main results and their interpretations

This study demonstrated a decrease in EDA in patients with epilepsy and a greater decrease in patients with a higher seizure frequency. During the first 1 minute from the start of measurement, the EDA tended to be lower in the epilepsy group than in the control group and was significantly lower in the epilepsy with seizures group than in the control group.

The EDA slowly decreased during the measurement duration in both the epilepsy and control groups, and the observation could be explained by the physiological mechanism of EDA. EDA increases with enhanced activity of the sympathetic nervous system during emotional stimuli and movements but decreases with relaxation and rest (34). Hence, a series of behaviors, including entering the room, sitting on the sofa, completing the STAI, wearing the E4 wristband and headphones, listening to the instructions, and waiting for a minute until the measurement started, were reflected in the EDA at the start of the measurement (35). However, when the patient remained at rest, sympathetic activity started decreasing, and the EDA started decreasing accordingly.

The significant decrease in EDA was observed only in the first 1 minute from the start of measurement in the epilepsy with seizures group compared with the control group. We speculate that the series of behaviors before measurement could affect EDA; the patients with seizures were less affected, while healthy controls were more affected. The greater decrease in EDA in the first 1 minute in epilepsy patients might be a consequence of reduced function due to repeated abnormal

electrical activity in the central nervous system, which is responsible for generating EDA. The limbic-hypothalamic system is known to constitute areas of the central nervous system responsible for generating EDA (14). It has been demonstrated that stimulation of the amygdala (36) and enhanced cognitive activity mediated by increased activity in the ventromedial prefrontal cortex induce EDA (37). A decrease in EDA was previously demonstrated in patients with epilepsy who underwent temporal lobectomy including that of the amygdala (38), indicating that defects in the central nervous system induce a functional decrease. Moreover, individuals with a higher seizure frequency tend to display a greater decrease in cognitive function (39, 40), and repeated abnormal electrical activity damages the central nervous system function. Because 14 patients, accounting for the largest portion in the epilepsy group in our study, had temporal lobe onset seizures, the greater seizure frequency might be associated with the more severely impaired limbic system, thereby leading to a decreased EDA.

A previous study by Drake et al. found transiently higher amplitude sympathetic skin responses (a type of EDA) evoked by auditory or tactile stimuli in patients with epilepsy than in normal controls (25), and the findings are inconsistent with our results that showed low EDA in epilepsy. Notably, their study examined EDA changes in seconds just after the stimuli, while our study observed those in minutes . Therefore, the different findings in these two studies cannot be compared directly. Additionally, Drake et al. observed longer latency of sympathetic skin response after stimulation in epilepsy patients than in normal controls, indicating that epilepsy patients have lower sympathetic activity. Moreover, Lanteaume et al. demonstrated that epilepsy patients which have seizures evoked by emotional stimuli were more vigilant toward threatening stimuli than those which do not have seizures evoked by emotional stimuli. (41). To the best of our knowledge, no study has observed EDA changes in both seconds and minutes after the stimuli, and no study has combined EDA and emotional stimuli either; such studies might help understand the role of EDA in epilepsy.

4.2 Autonomic nervous system

Many previous studies have investigated the role of the cardiac autonomic nervous system (ANS) in sudden unexpected death in epilepsy. Ponnusamy et al. found that epilepsy patients showed increased cardiac sympathetic activity and decreased parasympathetic activity during epileptic seizures (42), and interictal discharges altered RR interval (43). However, a meta-analysis indicates that AED have no significant effects on cardiac sympathetic or parasympathetic function (44), suggesting that AED might not affect EDA. In fact, to our knowledge, no studies have demonstrated that AED could affect EDA.

4.3 Confounders

Confounders affecting the resting EDA might not have significant effects on our study findings. The impact of drugs is an important factor to be considered. In this present study, the number of AED did not affect EDA. Other drugs such as those with a central noradrenaline inhibitory effect or an anticholinergic effect are known to reduce the levels of EDA (34, 45). However, because no participants in our study were taking those drugs, the impact of drugs was considered unrelated to our study findings.

In addition, EDA is lower in older individuals than in younger individuals (14, 34) as well as in males than in females (14, 34). However, these factors did not affect EDA in our study. Moreover, EDA is known to increase in the dominant arm (14, 34). In this study, because EDA was measured simultaneously from both wrists and the average was used for analysis, the arm dominance did not affect our results. Further, African-Americans have been shown to have higher EDA than Caucasians

(14); however, because all participants in this study were Japanese, racial differences are not needed to be considered.

4.4 Appropriateness of EDA-BFT in epilepsy

EDA-BFT is considered an appropriate treatment. The principle behind the inhibitory effect of EDA-BFT on epileptic seizures lies in the decreased excitability of the cerebral cortex due to increased EDA. Accumulating studies have used the direct current component called the slow cortical potential (SCP) as an index for excitation of the cerebral cortex. SCPs originate in the depolarization of cortical pyramidal cells, which is caused by the input from the thalamus, and reflect excitation in a broad range of cortical regions (46). Contingent negative variation (CNV), a type of SCPs, has been found to be inversely correlated with EDA (17, 18). In fact, a decline in seizure frequency resulting from EDA-BFT has been shown to be correlated with decreased shifts in CNV (17). Therefore, EDA-BFT lowers excitation in the cortex by regulating the thalamocortical projection system. Our study demonstrated a mild decrease in EDA in patients with epilepsy and a greater decrease in EDA in patients with a higher seizure frequency. From this point, it is surmised that EDA-BFT, which can increase EDA, would recover the decreased EDA closer to the normal level in epilepsy patients. Thus, EDA-BFT, which lowers excitation of the cerebral cortex by increasing EDA, is a reasonable treatment option.

4.5 limitations of this study

This study has several limitations. This study was designed to compare resting EDA; however, differences in EDA between the epilepsy and control groups were observed only immediately after the start of measurement, and EDA decreased to the same level in both groups during 10 minutes of rest. Therefore, we used the EDA data obtained during the first 1 minute from the start of measurement to reflect EDA in the waking state in daily lives. Because participants in both groups

followed the same procedure before measurement, the present results are considered to represent the difference in the properties of EDA between the epilepsy and control groups. However, it would be better to measure EDA with stimulation tasks if the differences in EDA in daily lives between these two groups should be assessed.

In addition, the number of participants in this study was small, with 22 individuals in the epilepsy group and 24 individuals in the control group. Therefore, the small sample size might result in no statistically significant differences between the epilepsy group and the control group, although a decreasing trend in EDA was observed in the epilepsy group. Moreover, because the sample size was small, epilepsy symptoms or seizure types were not assessed in these two groups.

In conclusion, this study demonstrated a decrease in EDA in patients with epilepsy and a greater decrease in patients with a higher seizure frequency. EDA-BFT is a technique to increase EDA levels in patients with epilepsy based on BFT. The present findings shed lights on the appropriateness of EDA-BFT in suppressing epileptic seizures.

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CONFLICTS OF INTEREST

All the authors state that there is no direct conflict of interest.

AUTHOR CONTRIBUTIONS

T Horinouchi contributed to the design and conceptualization of the study and drafted the manuscript. K Sakurai, N Munekata, and I Kusumi interpreted the data and revised the manuscript. T Kurita N Hashimoto and Y Takeda revised the manuscript.

ETHICAL PUBLICATION STATEMENT

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this study is consistent with those guidelines.

DATA AVAILABILITY STATEMENT

The datasets generated for this study are available on request to the corresponding author.

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431 **TABLES**

432 **Table 1. Background information of participants in the epilepsy and control groups**

	epilepsy		control	p-value
	with/without seizures	with seizures		
number	22	18	24	N/A
age†	40.3 (20-64)	40.7 (20-64)	40.4 (29-60)	P = 0.68
female‡	15	12	14	P = 0.49
state anxiety§	40.4 (24-66)	40.4 (24-66)	38.1 (20-55)	P = 0.62
diagnosis	FE 21, GE 1	FE 18	N/A	N/A

diagnosis in FE	TLE 14, FLE 5, OLE 1, UK 1	TLE 13, FLE 3, OLE 1, UK 1	N/A	N/A
seizure number (/month)	8.4 (0-40)	10.3 (0.3-40)	N/A	N/A
disease duration (year)	22.5 (9-45)	23.6 (9-45)	N/A	N/A
number of AED	2.27 (1-4)	2.39 (1-4)	N/A	N/A

The number in parentheses of each item indicates the range. †, t-test; ‡, $\chi 2$ test; §, Wilcoxon signed-rank test. FE, focal epilepsy; GE, generalized epilepsy; TLE, temporal lobe epilepsy; FLE, frontal lobe epilepsy; OLE, occipital lobe epilepsy; UK, unknown; AED, anti-epileptic drug.

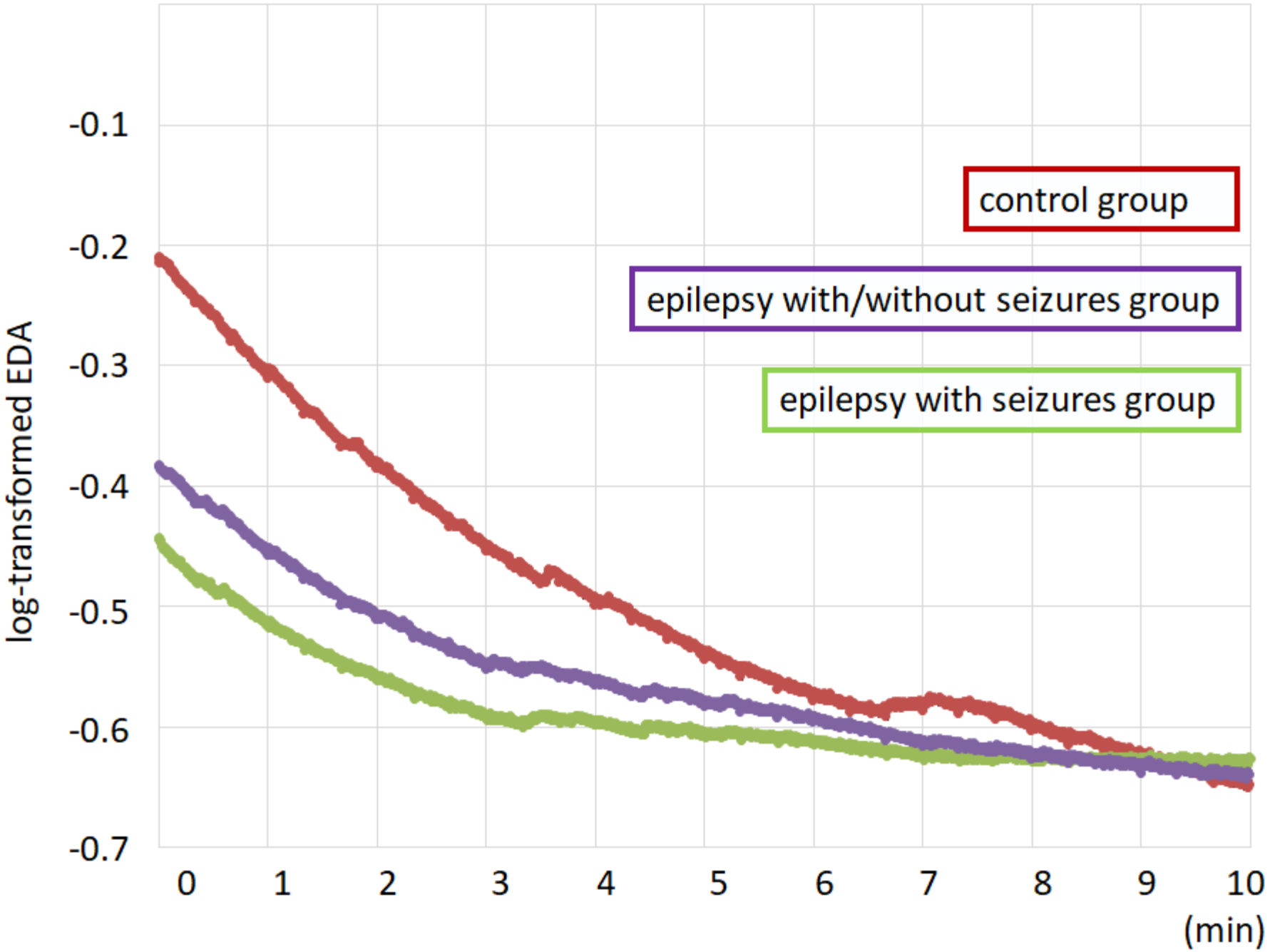
FIGURE LEGENDS

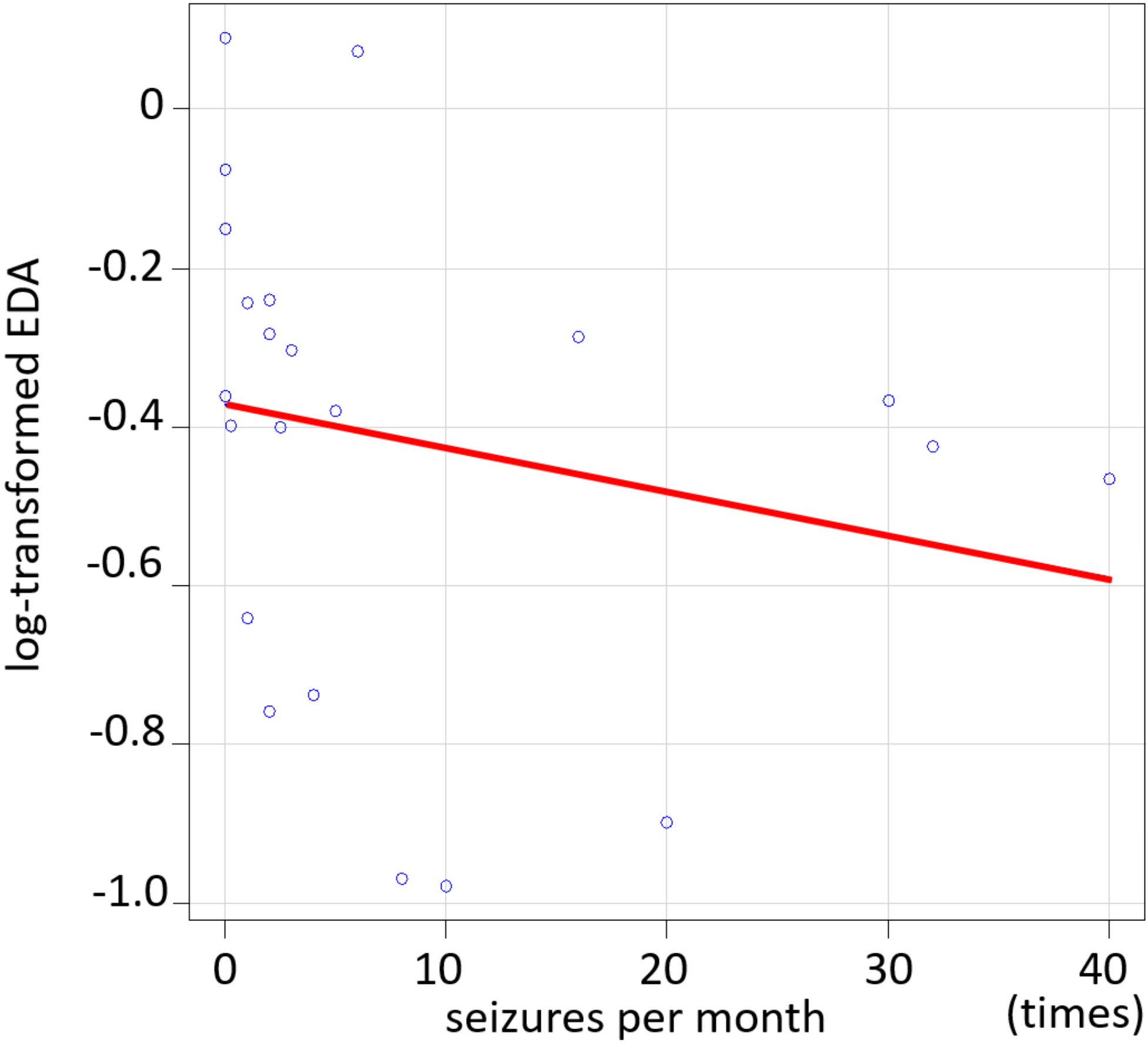
Figure 1. Measurement results for the resting electrodermal activity (EDA) in each group

The graph represents the resting EDA during the test duration in the epilepsy with/without seizures group, the epilepsy with seizures group, and the control group. A decreasing trend in EDA during the first 1 minute from the start of measurement was observed in the epilepsy with/without seizures group (95% CI, -0.04 to 0.36; P = 0.12), and a significant decrease in EDA was found in the epilepsy with seizures group (95% CI, 0.02 to 0.43; P = 0.04).

Figure 2. A scatter plot of seizure frequency and EDA levels in the first 1 minute after the start of measurement in the epilepsy group

The seizure frequency showed a significant inverse correlation with EDA levels ($P = 0.02$; $\rho = -0.50$).


log-transformed EDA
-0.1
-0.2
-0.3
-0.4
-0.5
-0.6
-0.7
0
1
2
3
4
5
6
7
8
9
10
(min)
control group
epilepsy with/without seizures group
epilepsy with seizures group


0
-0.2
-0.4
-0.6
-0.8
-1.0
log-transformed EDA
0
10
20
30
40
seizures per month
(times)