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Author(s)	Horinouchi, Toru; Sakurai, Kotaro; Munekata, Nagisa; Kurita, Tsugiko; Takeda, Youji; Kusumi, Ichiro
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1 **Decreased electrodermal activity in patients with epilepsy**

2 **Toru Horinouchi^{1*}, Kotaro Sakurai¹, Nagisa Munekata², Tsugiko Kurita¹, Youji Takeda¹,**
3 **Naoki Hashimoto¹, Ichiro Kusumi¹**

4 ¹Department of Psychiatry, Hokkaido University Graduate School of Medicine, Sapporo, Japan

5 ² Faculty of Computer Science and Engineering, Kyoto Sangyo University, Kyoto, Japan

6

7 1: [Postal address] 060-8638 west 5, north 14, north district, Sapporo city, Hokkaido, Japan

8 [Phone number] +81 01 706 5160

9 [Fax number] +81 01 706 5161

10

11 2: [Postal address] 603-8555 kamikamo honzan, kitaku, Kyoto city, Kyoto, Japan

12 [Phone number] +81 75 705 1913

13 [Fax number] +81 75 705 1438

14 *** Correspondence**

15 Toru Horinouchi

16 Department of Psychiatry and Neurology, Hokkaido University Graduate School of Medicine

17 060-8638 west 5, north 14, north district, Sapporo city, Hokkaido, Japan

18 Phone number: +81 01 706 5160

19 Fax number: +81 01 706 5161

20 Email address: tetsukawa1234@gmail.com

21 **Email Addresses**

22 Kotaro Sakurai: kootaroo@ab.auone-net.jp

23 Nagisa Munekata: nagisa.munekata@gmail.com

24 Tsugiko Kurita: tsugiko@med.hokudai.ac.jp

25 Youji Takeda: ytakeda02@gmail.com

26 Naoki Hashimoto: hashimona@gmail.com

27 Ichiro Kusumi: ikusumi@med.hokudai.ac.jp

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30

31 **Abstract**

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

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

42 **Results:** A decreasing trend in EDA was observed during the first 1 minute from the start of the
43 measurement in 22 epilepsy patients (with or without seizures) compared with healthy controls ($P =$
44 0.12). However, a significant decrease in EDA was found in 18 epilepsy patients with seizures
45 compared with healthy controls (-0.48 versus -0.26 ; $P = 0.036$). Furthermore, seizure frequency
46 showed a significant inverse correlation with EDA in the epilepsy group ($\rho = -0.50$, $P = 0.016$).
47 However, neither disease duration nor the number of drugs prescribed correlated with EDA in the
48 epilepsy group.

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

52

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

55

56 **Abbreviations**

57 **BFT** Biofeedback treatment

58 **CNV** Contingent negative variation

59 **EDA** electrodermal activity

60 **SCP** slow cortical potential

61

62

63 Original Research Articles

64 1. INTRODUCTION

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

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

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

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

89 Previous studies demonstrated an approximately 45% decrease in epileptic seizures with the use of
90 EDA-BFT (10, 11), and seizure frequency decreased by more than 50% in 6 out of 10 individuals
91 (12). This rate of 50% responders indicates that the therapeutic effects of EDA-BFT are comparable
92 with those of novel AED (14–60%) (19, 20), vagus nerve stimulation (45%) (21), and ketogenic diet
93 (53%) (22). Although few findings are available regarding the long-term prognosis, one study
94 suggests that the seizure suppression effect can last for more than three years (23). Additionally,
95 EDA-BFT, which has been drawing attention as a stress management intervention in epilepsy, not
96 only reduces epileptic seizures but also improves psychiatric comorbidities, including major
97 depressive disorder and anxiety disorder (24).

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

107

108 2. METHODS

109 2.1 Study design

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

112 2.2 Standard protocol approvals, registrations, and patient consents

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

115 2.3 Study participants

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

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

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

129 2.4 Measurement device and measurement environment

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

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

141 2.5 Measurement procedure

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

149 2.6 primary and secondary outcomes

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

153 2.7 Statistical analysis

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

163 2.8 Data availability statement

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

166

167 3. RESULTS

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

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171 ratio, age, or state anxiety did not significantly differ between the epilepsy group and the control
172 group. Among the 22 participants in the epilepsy group, 21 suffered from focal seizures, and 14 had
173 temporal lobe onset epilepsy. The average disease duration (22.5 years) was relatively long. All
174 participants in the epilepsy group used AED, and the average number of prescribed AED was 2.27.
175 Epileptic seizures were completely suppressed in four participants but were still observed in 18
176 participants in the epilepsy group. The seizure frequency varied greatly with an average frequency of
177 8.4 per month and a maximum frequency of 40 per month.

178 The log-transformed average resting EDA during 10 minutes, the primary outcome, was -0.56 in the
179 epilepsy group and -0.50 in the control group, and no significant differences were observed between
180 these two groups (95% CI, -0.08 to 0.21; $P = 0.39$). Participants in both groups showed gradually
181 declined EDA during the 10-minute duration, and the greatest difference between the two groups was
182 observed immediately after the start of the measurement (Fig. 1). Thus, the log-transformed average
183 EDA during 1 minute after the start of the measurement was then compared between the epilepsy
184 group and the control group. A trend of decreased EDA was observed in the epilepsy group
185 compared with the control group (-0.42 versus -0.26; 95% CI, -0.04 to 0.36; $P = 0.12$). Subsequently,
186 18 individuals in the epilepsy group, in whom epileptic seizures were still observed, were classified
187 as the epilepsy with seizures group, which was further compared with the control group. Notably, a
188 significantly decreased EDA was found in the epilepsy with seizures group compared with the
189 control group (-0.48 versus -0.26; 95% CI, 0.02 to 0.43; $P = 0.04$).

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

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

196

197 **4. DISCUSSION**

198 4.1 Main results and their interpretations

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

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

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

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

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

240

241 4.2 Autonomic nervous system

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

249 4.3 Confounders

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

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

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

263 4.4 Appropriateness of EDA-BFT in epilepsy

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

278 4.5 limitations of this study

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

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

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

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

297

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307

308 **CONFLICTS OF INTEREST**

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

310

311 **AUTHOR CONTRIBUTIONS**

312 T Horinouchi contributed to the design and conceptualization of the study and drafted the manuscript.

313 K Sakurai, N Munekata, and I Kusumi interpreted the data and revised the manuscript. T Kurita N

314 Hashimoto and Y Takeda revised the manuscript.

315

316 **ETHICAL PUBLICATION STATEMENT**

317 We confirm that we have read the Journal's position on issues involved in ethical publication and

318 affirm that this study is consistent with those guidelines.

319

320 **DATA AVAILABILITY STATEMENT**

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

322

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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

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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

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

436

437 **FIGURE LEGENDS**

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

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

444

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

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

448

449



