



HAL
open science

Skin conductance biofeedback training in adults with drug-resistant temporal lobe epilepsy and stress-triggered seizures: A proof-of-concept study

Jean-Arthur Micoulaud-Franchi, Iliana Kotwas, Laura Lanteaume, Christelle Berthet, Mireille Bastien, Jean Vion-Dury, Aileen Mcgonigal, Fabrice Bartolomei

► To cite this version:

Jean-Arthur Micoulaud-Franchi, Iliana Kotwas, Laura Lanteaume, Christelle Berthet, Mireille Bastien, et al.. Skin conductance biofeedback training in adults with drug-resistant temporal lobe epilepsy and stress-triggered seizures: A proof-of-concept study. *Epilepsy & Behavior*, 2023, 41, pp.244-250. 10.1016/j.yebeh.2014.10.017 . hal-01384073

HAL Id: hal-01384073

<https://hal.science/hal-01384073v1>

Submitted on 10 Mar 2023

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

Skin conductance biofeedback training in adults with drug-resistant temporal lobe epilepsy and stress-triggered seizures: A proof-of-concept study

Jean-Arthur Micoulaud-Franchi ^{a,b,*}, Iliana Kotwas ^{c,1}, Laura Lanteaume ^d, Christelle Berthet ^a,
Mireille Bastien ^c, Jean Vion-Dury ^{a,b}, Aileen McConigal ^{e,f}, Fabrice Bartolomei ^{e,f,g}

^a *Unité de Neurophysiologie (UNPN), Pôle de Psychiatrie "Solaris", Centre Hospitalier Universitaire de Sainte-Marguerite, 270 Bd de Sainte-Marguerite, 13009 Marseille, France*

Laboratoire de Neurosciences Cognitives (LNC), UMR CNRS 7291, Aix-Marseille Université, Marseille, France

^c *Laboratoire Parole et Langage (UMR 7309), Aix-Marseille Université, Marseille, France*

^d *CIC-CPCE – Centre de Pharmacologie Clinique et Evaluations Thérapeutiques, Aix-Marseille Université, Marseille, France*

^e *Unité mixte INSERM Epilepsie et Cognition UMR 751, 27 Bd Jean Moulin, 13385 Marseille Cedex 05, France*

^f *Service de Neurophysiologie Clinique, Centre Hospitalo Universitaire de la Timone, 264, rue Saint-Pierre, 13005 Marseille, France*

^g *Hôpital Henri Gastaut, Etablissement hospitalier spécialisé dans le traitement des epilepsies, 300 Boulevard de Sainte-Marguerite, 13009 Marseille, France*

The present proof-of-concept study investigated the feasibility of skin conductance biofeedback training in reducing seizures in adults with drug-resistant temporal lobe epilepsy (TLE), whose seizures are triggered by stress. Skin conductance biofeedback aims to increase levels of peripheral sympathetic arousal in order to reduce cortical excitability. This might seem somewhat counterintuitive, since such autonomic arousal may also be associated with increased stress and anxiety. Thus, this sought to verify that patients with TLE and stress-triggered seizures are not worsened in terms of stress, anxiety, and negative emotional response to this nonpharmacological treatment. Eleven patients with drug-resistant TLE with seizures triggered by stress were treated with 12 sessions of biofeedback. Patients did not worsen on cognitive evaluation of attentional biases towards negative emotional stimuli ($P > .05$) or on psychometric evaluation with state anxiety inventory ($P = .059$); in addition, a significant improvement was found in the Negative Affect Schedule ($P = .014$) and in the Beck Depression Inventory ($P = .009$). Biofeedback training significantly reduced seizure frequency with a mean reduction of -48.61% ($SD = 27.79$) ($P = .005$). There was a correlation between the mean change in skin conductance activity over the biofeedback treatment and the reduction of seizure frequency ($r(11) = .62$, $P = .042$). Thus, the skin conductance biofeedback used in the present study, which teaches patients to achieve an increased level of peripheral sympathetic arousal, was a well-tolerated nonpharmacological treatment. Further, well-controlled studies are needed to confirm the therapeutic value of this nonpharmacological treatment in reducing seizures in adults with drug-resistant TLE with seizures triggered by stress.

1. Introduction

Antiepileptic drugs (AEDs) are the main treatment in the management of epilepsy. However, more than 30% of patients with epilepsy have inadequate control of seizures despite optimal AED treatment [1]. Thus, throughout the past decade, research into nonpharmacological treatments [2] and, in particular, psychological managements of epilepsy (i.e., cognitive behavioral therapy, relaxation therapy, biofeedback, cognitive rehabilitation, and educational intervention) have gained

greater attention [3–6]. Indeed, it was found that the majority of patients could identify factors that trigger their seizures (i.e., a factor whose presence is associated with an increased probability of seizures over a relatively brief, defined time period) [4,7–9] and that some report the ability to terminate, prevent, or reduce their seizures [4,10]. It is, thus, possible to train patients with drug-resistant epilepsy to identify habitual triggers of their seizures and to develop counter measures using cognitive and behavioral methods that may interrupt seizure onset and neutralize triggering factors [3,4]. Research in this field may enhance the possibility of management of drug-resistant epilepsy, in particular when surgical treatment is contraindicated, which is the case in 30% of focal drug-resistant epilepsy [11], or when patients prefer nonsurgical management options.

Among psychological treatments in epilepsy [2], biofeedback presents two advantages. Firstly, by steady feedback, its use can restore

* Corresponding author at: Pôle de Psychiatrie "Solaris", Centre Hospitalier Universitaire de Sainte-Marguerite, 270 Bd de Sainte-Marguerite, 13009 Marseille, France. Tel.: +33 622 364 019.

E-mail address: jarthur.micoulaud@gmail.com (J.-A. Micoulaud-Franchi).

¹ These authors contributed equally to the work.

perceived control in the participants [12], which is known to be a significant variable in the psychological impact of epilepsy [13]. Indeed, pervasive loss of control has been associated with a negative effect on seizure control [14] and with a low quality of life [15]. Secondly, biofeedback is more than a psychological treatment because it enables the participant, by online feedback to a covert physiological activity, to actively learn self-directed strategies to obtain and control a physiological response. Thus, biofeedback can be considered as a psychophysiological treatment that enables targeting, in a noninvasive and drug-free manner, specific physiological activity related to a disorder [16].

A number of biofeedback approaches have been suggested for the management of epilepsy [2,17–19]. Among these approaches, biofeedback using skin conductance presents two advantages. Firstly, skin conductance is an easily recorded physiological activity compared with brain electrical activity. Secondly, skin conductance changes are related to peripheral sympathetic nervous activity changes that can be considered as a relevant physiological target for the nonpharmacological management of epilepsy. An increase in skin conductance (i.e., an increase in the electrical conductance measured in microsiemens) is related to an increase of arousal level [20]. Moreover, it has been shown that an increase in arousal level might be associated with a decrease in cortical excitability, thus with a decrease in the probability of seizures [21]. Biofeedback methods that teach the patient how to increase skin conductance have shown a significant reduction in seizure frequency [22], which was maintained up to 3 years after the termination of biofeedback treatment [23].

However, limitations of biofeedback efficacy studies have been that the type of epilepsy has often not been taken into account and that analysis of efficacy has not been based on a homogenous sample of patients with similar seizure types [17,22]. Temporal lobe epilepsy (TLE) is the most common drug-resistant epilepsy. Moreover, TLE is characterized by abnormal electrical changes starting from one region or several regions of the temporal lobe including the amygdala [24], which is known to be involved in the regulation of arousal and anxiety level and in the response of emotional negative stimuli [25]. Thus, it would be interesting to investigate the efficacy of biofeedback in TLE. More specifically, patients with TLE who could identify stress factors that trigger their seizures have been described [26]. Stress is a complex phenomenon but can be defined in terms of its biological, environmental, and psychological aspects, whereby external demands exceed adaptive capacity [27]. Thirty to fifty percent of patients with TLE are reported to perceive stress as a factor whose presence is associated with an increased probability of seizures [7–9]. These patients disclosed specific attentional biases towards negative emotional stimuli compared with patients without a stress factor trigger for seizures. Moreover, the degree of attentional biases correlated with abnormal metabolism in the amygdala [28].

To the best of our knowledge, no previous studies have investigated nonpharmacological treatment in TLE with stress as a trigger for seizures. Thus, the aim of the present study was to be a proof of concept to demonstrate feasibility of skin conductance biofeedback in TLE with stress-triggered seizures. We aimed to replicate the methodology used in the study of Nagai et al. and to verify that it is well tolerated in this specific type of epilepsy. For that purpose we (i) included patients with TLE with seizures triggered by stress [26], (ii) treated these patients with skin conductance biofeedback using a method similar to that used previously [22], and (iii) evaluated the effect of biofeedback on seizure frequency, on psychometric evaluation of stress and affectivity, and on cognitive evaluation of attentional biases towards negative emotional stimuli. As skin conductance biofeedback increases levels of peripheral sympathetic arousal, which can be associated with stress response, anxiety, and exposure to negative emotional stimuli [29–32], in this proof-of-concept study, we sought to verify that patients with TLE and stress-triggered seizures are not worsened in terms of stress, anxiety, and negative emotional response to this nonpharmacological treatment. We aimed to check the following: i) whether patients with

TLE with stress-triggered seizures, treated with biofeedback, did not worsen on psychometric evaluation of stress and affectivity and on cognitive evaluation of attentional biases towards negative emotional stimuli and ii) whether patients showed reduction in seizure frequency. In cases of a positive result concerning seizure frequency, we expected a correlation between changes in seizure frequency and changes in skin conductance over the period of biofeedback treatment.

2. Methods and materials

2.1. Participants

The study duration was 17 months (January 2013–May 2014). Patients were selected if they presented with both drug-resistant TLE and stress-triggered seizures. Five patients were selected from an existing database established in our center, having already been identified and previously included in the studies by Lanteaume et al. [29]. An additional 6 patients were prospectively recruited over the study period. Thus, 11 patients with TLE with stress-triggered seizures were recruited in the Epilepsy Unit of the Clinical Neurophysiology Department of the Marseille University Hospital (France). According to the previous study of Nagai et al., a sample size of more than 10 would have sufficient power to find an effect. Inclusion criteria were as follows: TLE with stress-triggered seizures, drug-resistant epilepsy, age between 18 and 60 years, duration of epilepsy more than 3 years, frequency of seizures more than 1 per month, stable medication one month before the study and during the study duration, and sufficient cognitive ability to keep a seizure diary. The diagnosis of TLE was documented clinically and confirmed with video-EEG investigations. All patients underwent brain magnetic resonance imaging (MRI) and fluorodeoxyglucose-positron emission tomography (FDG-PET).

The presence of a stress trigger for seizures was assessed with the *impact of seizure precipitant scale* described previously [26]. A face-to-face interview was carried out in which patients were questioned about several clinical triggers. The importance of stress triggers was evaluated on a balanced 10-point Likert scale ranging from 0 (“never”) to 10 (“always”). Patients with TLE had to have a score of more than 5 to be included in the present study.

Exclusion criteria were as follows: reduced capacity to consent, poor antiepileptic drug compliance, mental disorders, severe cognitive impairment, and comorbid chronic medical conditions (other than epilepsy), e.g., severe diabetes, cerebrovascular disease, or chronic obstructive bronchopneumonia. Patients were screened for any current or lifetime history of a DSM-IV axis I disorder based on the Mini-International Neuropsychiatric Interview (MINI) [33].

Gender, age, laterality, age at onset of epilepsy, number and type of AEDs, and number of seizures were collected as data (Table 1).

After receiving a detailed description of the study, participants gave their informed written consent. This study was conducted in accordance with the Declaration of Helsinki and French Good Clinical Practices.

2.2. Procedure

2.2.1. Clinical evaluation

2.2.1.1. Seizure frequency evaluation. Patients were asked to keep a seizure diary for 3 months before (baseline seizure frequencies) and 3 months after the biofeedback treatment. Average seizure frequency (per month) was calculated for each of these periods.

2.2.1.2. Psychometric evaluation of stress and affectivity. Patients completed the State-Trait Anxiety Inventory (SAI) in order to evaluate the state of anxiety [34], the Positive and Negative Affect Schedule (PANAS) in order to evaluate the negative affectivity (NA) and the positive affectivity (PA) [35], and the Beck Depression Inventory (21 items, BDI-21) in order to

Table 1
Patient demographic and clinical characteristics.

	Gender	Age	Laterality of the TLE	Age at onset of epilepsy	Number and type of antiepileptic drugs ^a	Total number of seizures during 3-month period before biofeedback	Total number of seizures during 3-month period after biofeedback	Percentage of seizure frequency changes ^b
P1	Women	47	Left	6	CBZ, PGB	3	2	-33.33
P2	Men	24	Left	19	CBZ, TPM	21	9	-57.14
P3	Women	45	Left	27	LMT, LEV	30	6	-80
P4	Men	35	Left	19	CBZ, VPA	30	16	-46.67
P5	Women	33	Right	7	OXC, TPM, LCM	89	3	-96.63
P6	Women	39	Left	15	LMT, LEV	8	6	-25.00
P7	Women	27	Right	17	CBZ, LCM	15	8	-46.67
P8	Women	33	Right	22	LMT	16	5	-68.75
P9	Women	44	Left	14	-	48	20	-58.33
P10	Women	37	Left	32	LMT, LEV	3	3	0
P11	Women	40	Bilateral	15	CBZ	9	7	-22.22

^a CBZ: carbamazepine, LCM: lacosamide, LEV: levetiracetam, LMT: lamotrigine, OXC: oxcarbazepine, PGB: pregabalin, TPM: topiramate, VPA: valproic acid.

^b Percentage of seizure frequency changes 3 months before and 3 months after the biofeedback treatment, as also shown in Fig. 1.

evaluate depressive mood [36]. These evaluations were completed the week before and the week after the biofeedback treatment.

2.2.1.3. Cognitive evaluation of attentional biases. The cognitive paradigm we used to study attentional biases towards negative emotional stimuli was the probe detection task. This task measures the modulation of spatial attention by negative and neutral stimuli and allows the assessment of attentional vigilance towards negative stimuli and attentional disengagement from negative stimuli. As previously described [26,28], each experimental trial consisted of three successive steps: i) display of a black fixation cross (500 ms), ii) display of a word pair (500 ms): “negative-neutral” or “neutral-neutral”, and iii) a dot display (until the response was given). Participants were asked to give the location of the dot by pressing the corresponding button as quickly and as accurately as possible. In each “negative-neutral” pair, the combination of the location of the words and the location of the dot led to congruent conditions (i.e., dot replaces negative word) and to incongruent conditions (i.e., dot replaces neutral word). For each “neutral-neutral” pair, all conditions were considered as control conditions. Manipulation of congruent, incongruent, and control pairs allows measurements of 3 indices related to attentional biases. The most important is a score of congruency (a positive score indicates a modulated attention by the negative stimuli). A modulated attention by the negative stimuli could be related to two kinds of attentional biases: i) a facilitated effect of negative stimuli presented congruently to the dot (measured by a positive score of vigilance) and ii) a difficulty in disengaging attention from the negative stimuli presented incongruently to the dot (measured by a positive score of disengagement). These scores are calculated by the differences of reaction time between the congruent, the incongruent, and the control conditions as described previously [26,28]. The cognitive evaluation was conducted the week before and the week after the biofeedback treatment.

2.2.2. Skin conductance biofeedback

2.2.2.1. Material. Measurement of skin conductance and implementation of biofeedback sessions were undertaken using a biofeedback system (Biograph, Thought Technology Ltd., Montreal, Quebec, Canada) that had been modified for experimental use in the present study.

Dry nickel-plated electrodes were placed on the palmar surface of the participant's index and middle finger of the left hand. A computer-generated graphic was presented visually on a computer monitor. Two simultaneous feedbacks were presented to the patient. The first feedback was presented to the patients in the form of a graphical thermometer, inspired by previous MRI feedback studies [37], which displayed a green bar that increased when skin conductance activity increased and a red bar that decreased when skin conductance activity decreased. For the feedback, the bar was continually updated with new skin conductance information. The second feedback was presented

to the patients in the form of a female facial continuum from sad to happy. The facial images were created from a set of black and white photographs [38]. The two prototype endpoint photographs (100% sad and 100% happy) were morphed to create a linear continuum of nine facial images. Each intermediate image was transformed by a 10% increment according to a morphing technique described previously [38]. The feedback facial display moved towards the happy face when skin conductance activity increased and towards the sad face when skin conductance activity decreased. For the feedback, the facial display was continually updated at intervals of 1.5 s. We chose this kind of feedback because we posited that emotional feedback would be more adapted to patients with TLE and stress-triggered seizures than a neutral feedback used by Nagai et al. [22]. The aim of the teaching was that patients learn to increase their arousal level while associating this with positive emotion.

2.2.2.2. Biofeedback session. Patients attended a total of 12 sessions (1 session/week) in a quiet room kept as constant as possible at 23 °C to avoid variation of skin conductance in relation to ambient temperature [20,39]. Each session lasted 1 h. During the first session, information about biofeedback was given. Patients were instructed that the use of arousal and alertness cognitive activity combined with the feedback could enable them to control the thermometer bar and the face. However, no specific strategies were provided. Before beginning the following session, a short face-to-face interview was carried out in which patients were questioned about evolution since the last session in terms of seizure frequency, intensity of stress triggers, perceived self-control, motivation, and learning of self-strategies to obtain and control the skin conductance.

A baseline block was conducted during 2 min before the biofeedback. Patients were instructed to relax in order to bring skin conductance back to the baseline level. It, thus, enabled calibration of the baseline and the range of the thermometer. During baseline blocks, a landscape screen was presented to the patients without any feedback. Each training session lasted 30 min, during which the patients received biofeedback and were instructed to enhance skin conductance activity. At the end of each biofeedback session, patients were actively asked to report any discomfort during the feedback, in particular concerning feelings of stress. The training also explicitly emphasized the goal of transfer of the skills learned during the session into everyday life. The patient was encouraged to train at home as if he or she were sitting in front of the monitor at home, and a downscaled picture of the feedback computer screen was given as a memory aid handout to the patients. Moreover, patients were also encouraged to practice self-regulation skills in seizure-prone situations.

2.3. Statistical analyses

Descriptive statistics of the obtained data included frequencies and percentages of categorical variables together with means and standard

deviations of continuous variables. Data analyses were performed using SPSS software (Version 18 for Mac, PASW Statistics). For all the tests, the accepted significance level was 5%.

2.3.1. Comparison statistics

Clinical evaluations (seizure frequency, SAI, PA, NA, BDI-21, score of congruency, vigilance, and disengagement) were compared before and after the 12 sessions of the biofeedback treatment using the Wilcoxon signed-rank test.

2.3.2. Relation between skin conductance changes and seizure frequency changes

For each patient, change in seizure frequencies was calculated as the percentage of variation compared with baseline seizure frequencies.

Change in skin conductance during a session was calculated by subtracting the mean skin conductance level for the first 2 min and for the last 2 min and by calculating the percentage of variation compared with the first 2 min. Percentage change in skin conductance was averaged for each patient over the 12 biofeedback sessions.

The progress in the training over the course of the 12 biofeedback sessions was calculated by subtracting the average percentage change in the first 3 sessions and the last 3 sessions and by calculating the percentage of variation compared with the first 3 sessions according to the methodology used in the study of Nagai et al. [22]. The percentage change in the first 3 sessions and that in the last 3 sessions were compared using the Wilcoxon signed-rank test.

Spearman's rank correlation was used to analyze the relationship between change in seizure frequency and change in skin conductance over the biofeedback treatment and progress in the training during the 12 biofeedback sessions.

2.3.3. Relation between psychometric changes and seizure frequency changes

For each patient, changes in psychometric evaluation (SAI, PA, NA, and BDI-21) were calculated as the percentage of variation compared with baseline. Spearman's rank correlation was used to analyze the relationship between change in psychometric evaluation and change in seizure frequency.

3. Results

3.1. Sample characteristics

The mean age was 36.72 years (SD = 7.28, range: [24–47] years old); 9 women and 2 men. The mean age at onset of epilepsy was 17.54 (SD = 7.69). One patient was on no medication by choice. All of the other patients were treated by AEDs. The mean *impact of seizure*

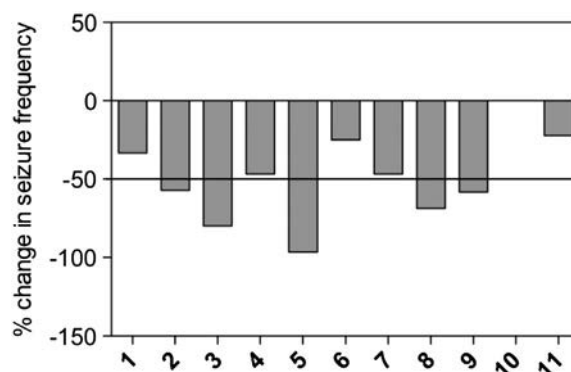


Fig. 1. Percentage of seizure frequency changes 3 months before and 3 months after the biofeedback treatment. In x axis, result for each patient.

precipitant scale was 6.91 (SD = 1.45), indicating a high prevalence of stress-triggered seizures [26]. None of the patients included was taking antidepressant medication.

3.2. Seizure frequency, psychometrics, and cognitive changes

Clinical evaluations are detailed in Table 2. There was a significant difference before and after the biofeedback treatment concerning the seizure frequency with a mean reduction of -48.61% (SD = 27.79), with 5 (45%) patients having more than 50% seizure reduction. Table 1 and Fig. 1 show individual patient's percentage seizure frequency change after the biofeedback treatment.

Concerning the psychometric and cognitive changes, there were significant differences before and after the biofeedback treatment for the NA, with a mean reduction of -20.21% (SD = 19.23), and the BDI, with a mean reduction of -37.65% (SD = 36.99). There was a trend for the SAI, with a mean reduction of -9.71% (SD = 19.54). Note that all the Z scores of the Wilcoxon signed-rank test were negative.

None of the patients reported any stress discomfort, nor did any seizure occur during the biofeedback session. None of the patients dropped out of the study, suggesting that the treatment was well tolerated and good observance of the sessions.

3.3. Relation between skin conductance changes and seizure frequency changes

The mean change in skin conductance activity over the biofeedback treatment was 30.15% (SD = 14.92). A significant correlation was found

Table 2

Change in seizure frequency per month, psychometric evaluation of stress and affectivity, and cognitive evaluation of attentional biases the week before and the week after the biofeedback treatment (12 sessions).

	Pretreatment		Posttreatment		Z	P value ^a
	Mean	SD	Mean	SD		
Seizure frequency (per month)	6.17	6.31	1.93	1.39	-2.8	.005
Psychometric evaluation of stress and affectivity						
State anxiety inventory	48.91	12.17	43.09	11.97	-1.88	.059
Positive affect schedule	28.30	5.77	33.09	8.90	-1.28	.201
Negative Affect Schedule	26.40	11.69	21.73	7.55	-2.45	.014
Beck Depression Inventory	17.82	11.92	9.82	6.89	-2.60	.009
Cognitive evaluation of attentional biases						
Score of congruency ^b	2.39	13.86	.69	22.46	-.44	.657
Score of vigilance ^c	1.82	14.42	-5.40	19.59	-.71	.477
Score of disengagement ^d	.58	19.93	6.09	21.69	-.18	.859

^a Wilcoxon signed-rank test.

^b A positive score indicates a modulated attention by the negative stimuli.

^c A positive score indicates a facilitated effect of negative stimuli presented congruently to the dot.

^d A positive score indicates a difficulty in disengaging attention from the negative stimuli presented incongruently to the dot.

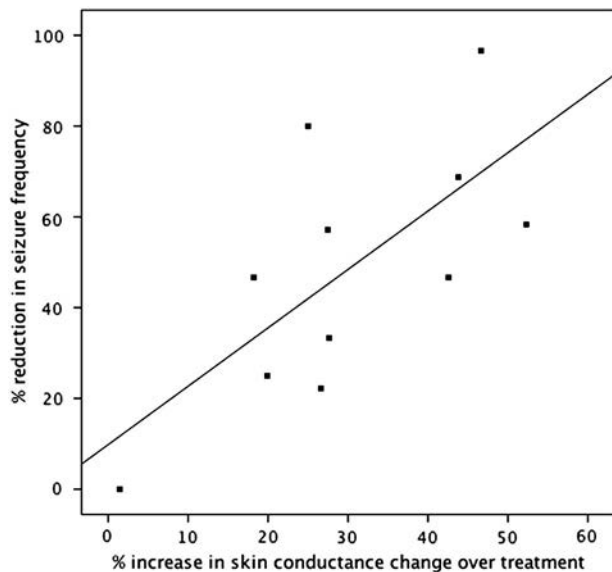


Fig. 2. Relation between seizure frequency changes 3 months before and 3 months after the biofeedback treatment and skin conductance change over the 12 sessions.

between seizure frequency change and skin conductance activity change over the biofeedback treatment ($r(11) = .62, P = .042$) (Fig. 2).

The progress in the training through the course of the 12 biofeedback sessions showed a trend towards significance: the mean change in the first 3 sessions was 45.72% ($SD = 30.85$), and the mean change in the last 3 sessions was 55.44% ($SD = 33.35, P = .091$). The progress in training was 13.61% ($SD = 61.44$). No significant correlation was found between progress in training and seizure frequency change ($r(11) = -.24, P = .47$).

3.4. Relation between psychometric changes and seizure frequency changes

There was no significant correlation between seizure frequency change and SAI change ($r(11) = -.19, P = .57$), PA change ($r(11) = -.11, P = .76$), NA change ($r(11) = -.024, P = .95$), or BDI change ($r(11) = .17, P = .62$).

4. Discussion

While there is interest in the use of nonpharmacological treatments in epilepsy [2], there is currently a lack of robust data to support the use of psychological therapies [4–6]. To the best of our knowledge, this is the first study to investigate psychological management in drug-resistant TLE with stress-triggered seizures. Patients treated with biofeedback did not worsen on subjective psychometric evaluation of stress and affectivity or on objective cognitive evaluation of attentional biases towards negative emotional stimuli. In fact, significant improvement was found for negative affect and depressed mood symptoms, with a nonsignificant trend to improvement for the anxiety state. Moreover, the face-to-face interview carried out in each biofeedback session revealed no stress discomfort and a high level of motivation of each patient. No patient dropout occurred as in the biofeedback group of Nagai et al. [22]. Thus, despite the fact that increases in skin conductance could be related to increases in stress level, this effect was not shown in our study. These results indicate that the skin conductance biofeedback used in the present study, which teaches an increased level of peripheral sympathetic arousal, was a well-tolerated nonpharmacological treatment. Two explanations can be emphasized in line with the biofeedback protocol specifically designed in the present study. The first is the use of an emotional facial continuum as feedback that allowed patients to associate an increase of arousal with positive emotion. The second is the use of a graphical thermometer that allowed a continuous feedback. Indeed,

there are differences between the presentation of discrete and continuous stimuli on skin conductance [40]. Discrete stimuli induce phasic increase in skin conductance. The most useful measure is the skin conductance response (SCR) following stimulus onset [40]. The increase of this phasic arousal is known to be related to stress stimuli such as shock [31], fear stimuli [30], or negative emotional stimuli [29,32]. Continuous stimuli modulate increases or decreases in skin conductance. The most useful measure is the skin conductance level (SCL), which was the measure performed in our biofeedback protocol [40]. Skin conductance level can be considered to reflect the tonic arousal level. The increase of tonic arousal level is known to be related to tasks requiring an effortful allocation of attentional resources [41]. The skin conductance biofeedback protocol in the present study has been developed to reinforce essentially SCL, as in the previous study of Nagai et al. [22]. Thus, the strategies learned during the treatment to obtain a control of the physiological response are thought to be more related to attentional cognitive strategies than to emotional strategies. This explanation is supported by the following: i) patients' reporting in the present study that they tried to focus their attention on something in their environment or in their mind, ii) a study showing that cognitive strategies were more likely used in response to seizure-prone situations than behavioral and emotional strategies [10], and iii) the relation between SCL and slow cortical potentials (SCP) [21]. Indeed, an increase in SCL is associated with a reduction of SCP that caused decreased cortical excitability [21]. Thus, SCP neurofeedback has been used in drug-resistant epilepsy, according to the same argument as skin conductance biofeedback, and has shown efficacy [42]. The modulation of SCP has been associated with attentional cognitive modulation [21,43,44]. Moreover, Nagai et al. [21] found that skin conductance biofeedback and SCP neurofeedback were probably more mediated by the attentional regulation of the sensory input to the cortex via the thalamus than the regulation of brain structures involved in emotions and stress (such as amygdala and limbic temporal regions) [45]. These anatomofunctional explanations remain speculative and need further investigation. However, it could explain the efficacy, without side effects, of skin conductance biofeedback that increased the arousal level in patients with TLE shown in the present study despite stress vulnerability.

Concerning the efficacy of the treatment, given the lack of well-controlled conditions and a randomized group, the present result can only be considered as preliminary. However, we replicated the results of Nagai et al. [22]. Firstly, we found a very close mean percentage change in seizure frequency in our sample (-48.61%) to that observed in Nagai et al.'s biofeedback sample (-49.26%) and a similar rate of response (45% versus 60%). Secondly, we found a correlation between changes in seizure frequency and changes in skin conductance over the biofeedback treatment that suggests a causal relationship between the efficacy of skin conductance biofeedback activity and a reduction in seizure frequency.

Some limitations in the current study have to be considered. Firstly, using the methodology of Nagai et al. [22], we found only a trend in the improvement in the degree to which the patients changed their skin conductance level in the first 3 sessions compared with the last 3 sessions. Thus, the progress in training of biofeedback over the 12 sessions was smaller in our study (13.61%) than in the study of Nagai et al. (51.98%). Moreover, in contrast to Nagai et al., we did not find a significant correlation between this progress and reduction in seizure frequency. However, we found that those patients who had the greatest increase in skin conductance during the first 3 sessions maintained their performance across the session, and that they benefited the most from the treatment. One explanation could be that the main difference in our study was to perform the biofeedback session only once per week, contrary to 3 per week in Nagai et al. [22], which could modify the training to increase the skin conductance level. Secondly, biofeedback could be efficacious apart from specific effects because of learned self-regulation of a physiological activity. The information given to the patients about the neurophysiological background of epilepsy, the proposition to treat them with a psychophysiological and

a electrophysiological method, as well as the therapeutic relationship established once a week during 12 weeks all likely contributed to the positive effects of the training, since positive expectations and the experience of self-efficacy are important nonspecific variables in biofeedback [46] and the clinical course of epilepsy [14,15]. Moreover, the improvements in anxiety, negative affect, and depressed mood symptoms in our study could be an intermediate variable to explain the effect of biofeedback in seizure frequency. Indeed, it was found that anxiety [47] and depression [48] are important components to manage with psychological interventions in order to improve seizure frequency. However, the lack of any relationship in our study between seizure reduction and reduced anxiety and depression scores is not in favor of this hypothesis. Thirdly, 81% of the patients were women. This marked female predominance is in contrast to the study by Nagai et al. that included around 50% women. This predominance of female subjects could potentially influence the results because of the known effect of the menstrual cycle on resting skin conductance. This parameter could be controlled in further studies. Lastly, the use of paper-based seizure diaries to assess seizure frequency could be inaccurate [49,50]. The act of self-reporting seizures may itself influence the observation by making the subject attend more vigilantly to seizures after biofeedback treatment. However, seizure diaries currently remain a widely accepted means of estimating seizure frequency in the context of trials to validate antiseizure drugs or devices. Since some studies have documented patient preference and increased compliance for electronic versus paper diaries [51], future biofeedback studies could use electronic diaries. Moreover, the advantages of electronic diaries include the possibility of linkage to a biosensor [51], which would enable recording of the physiological parameters targeted during biofeedback sessions in ecological, "real life" conditions [52].

In conclusion, both subjective and objective evaluations of stress and affectivity showed that skin conductance biofeedback is a well-tolerated nonpharmacological treatment in patients with drug-resistant TLE and seizures triggered by stress. Moreover, this treatment could be effective and, thus, could potentially be used in the nonpharmacological management of this type of epilepsy. Thus, although methodological limitations necessitate cautious interpretation of results, the present study encourages further well-controlled studies in this field of nonpharmacological treatment for epilepsy.

Fundings

This study was supported by the Fondation Française pour la Recherche contre l'Épilepsie (FFRE) ("Appels à projets 2012").

Conflict of interest statement

The authors report no conflicts of interest.

References

- [1] Kwan P, Brodie MJ. Early identification of refractory epilepsy. *N Engl J Med* 2000; 342:314–9.
- [2] Sheth RD, Stafstrom CE, Hsu D. Nonpharmacological treatment options for epilepsy. *Semin Pediatr Neurol* 2005;12:106–13.
- [3] Schmid-Schonbein C. Improvement of seizure control by psychological methods in patients with intractable epilepsies. *Seizure* 1998;7:261–70.
- [4] Boylan LS. Peri-ictal behavioral and cognitive changes. *Epilepsy Behav* 2002;3: 16–26.
- [5] Engelberts NH, Klein M, Kasteleijn-Nolst Trenite DG, Heimans JJ, van der Ploeg HM. The effectiveness of psychological interventions for patients with relatively well-controlled epilepsy. *Epilepsy Behav* 2002;3:420–6.
- [6] Ramaratnam S, Baker GA, Goldstein LH. Psychological treatments for epilepsy. *Cochrane Database Syst Rev* 2008;CD002029.
- [7] Spector S, Cull C, Goldstein LH. Seizure precipitants and perceived self-control of seizures in adults with poorly-controlled epilepsy. *Epilepsy Res* 2000;38:207–16.
- [8] Spatt J, Langbauer G, Mamoli B. Subjective perception of seizure precipitants: results of a questionnaire study. *Seizure* 1998;7:391–5.
- [9] Sperling MR, Schilling CA, Glosser D, Tracy JI, Asadi-Pooya AA. Self-perception of seizure precipitants and their relation to anxiety level, depression, and health locus of control in epilepsy. *Seizure* 2008;17:302–7.
- [10] Hether SD, Bruno E, Johnson CT, Galupo MP. Spontaneous strategies for psychological control of seizures. *Epilepsy Behav* 2013;27:140–3.
- [11] Engel Jr J. Surgery for seizures. *N Engl J Med* 1996;334:647–52.
- [12] Epstein LH, Blanchard EB. Biofeedback, self-control, and self-management. *Biofeedback Self Regul* 1977;2:201–11.
- [13] Spector S, Cull C, Goldstein LH. High and low perceived self-control of epileptic seizures. *Epilepsia* 2001;42:556–64.
- [14] Velissaris SL, Wilson SJ, Saling MM, Newton MR, Berkovic SF. The psychological impact of a newly diagnosed seizure: losing and restoring perceived control. *Epilepsy Behav* 2007;10:223–33.
- [15] Jacoby A, Ring A, Whitehead M, Marson A, Baker GA. Exploring loss and replacement of loss for understanding the impacts of epilepsy onset: a qualitative investigation. *Epilepsy Behav* 2014;33:59–68.
- [16] Yucha C, Montgomery D. Evidence-based practice in biofeedback and neurofeedback. *Association for Applied Psychophysiology and Biofeedback*; 2008.
- [17] Micoulaud-Franchi JA, Lanteaume L, Pallanca O, Vion-Dury J, Bartolomei F. Biofeedback and drug-resistant epilepsy: back to an earlier treatment? *Rev Neurol (Paris)* 2014;170:187–96.
- [18] Nagai Y. Biofeedback and epilepsy. *Curr Neurol Neurosci Rep* 2011;11:443–50.
- [19] Rockstroh B, Elbert T, Birbaumer N, Wolf P, Ducting-Roth A, Reker M, et al. Cortical self-regulation in patients with epilepsies. *Epilepsy Res* 1993;14:63–72.
- [20] Grapperon J, Pignol AC, Vion-Dury J. The measurement of electrodermal activity. *Encéphale* 2012;38:149–55.
- [21] Nagai Y, Critchley HD, Rothwell JC, Duncan JS, Trimble MR. Changes in cortical potential associated with modulation of peripheral sympathetic activity in patients with epilepsy. *Psychosom Med* 2009;71:84–92.
- [22] Nagai Y, Goldstein LH, Fenwick PB, Trimble MR. Clinical efficacy of galvanic skin response biofeedback training in reducing seizures in adult epilepsy: a preliminary randomized controlled study. *Epilepsy Behav* 2004;5:216–23.
- [23] Nagai Y, Trimble MR. Long-term effects of electrodermal biofeedback training on seizure control in patients with drug-resistant epilepsy: two case reports. *Epilepsy Res* 2014;108:149–52.
- [24] Bartolomei F, Wendling F, Bellanger JJ, Regis J, Chauvel P. Neural networks involving the medial temporal structures in temporal lobe epilepsy. *Clin Neurophysiol* 2001; 112:1746–60.
- [25] Morris JS, Buchel C, Dolan RJ. Parallel neural responses in amygdala subregions and sensory cortex during implicit fear conditioning. *Neuroimage* 2001;13:1044–52.
- [26] Lanteaume L, Bartolomei F, Bastien-Toniazzo M. How do cognition, emotion, and epileptogenesis meet? A study of emotional cognitive bias in temporal lobe epilepsy. *Epilepsy Behav* 2009;15:218–24.
- [27] Novakova B, Harris PR, Ponnusamy A, Reuber M. The role of stress as a trigger for epileptic seizures: a narrative review of evidence from human and animal studies. *Epilepsia* 2013;54:1866–76.
- [28] Lanteaume L, Guedj E, Bastien-Toniazzo M, Magalhães A, Mundler O, Bartolomei F. Cognitive and metabolic correlates of emotional vulnerability in patients with temporal lobe epilepsy. *J Neurol Neurosurg Psychiatry* 2012;83:522–8.
- [29] Lang PJ, Greenwald MK, Bradley MM, Hamm AO. Looking at pictures: affective, facial, visceral, and behavioral reactions. *Psychophysiology* 1993;30:261–73.
- [30] Öhman A. Orienting and attention: preferred preattentive processing of potentially phobic stimuli. In: Campbell H, Richardson R, editors. *Attention and information processing in infants and adults*. Hillsdale, NJ: Lawrence Erlbaum; 1992.
- [31] Dawson ME, Biferno MA. Concurrent measurement of awareness and electrodermal classical conditioning. *J Exp Psychol* 1973;101:55–62.
- [32] Gross JJ. Antecedent- and response-focused emotion regulation: divergent consequences for experience, expression, and physiology. *J Pers Soc Psychol* 1998;74: 224–37.
- [33] Sheehan DV, Lecrubier Y, Sheehan KH, Amorim P, Janavs J, Weiller E, et al. The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. *J Clin Psychiatry* 1998;59(Suppl. 20):22–33 [quiz 34–57].
- [34] Spielberger CD, Vagg PR. Psychometric properties of the STAI: a reply to Ramanaiah, Franzen, and Schill. *J Pers Assess* 1984;48:95–7.
- [35] Watson D, Clark LA, Tellegen A. Development and validation of brief measures of positive and negative affect: the PANAS scales. *J Pers Soc Psychol* 1988;54:1063–70.
- [36] Beck AT, Ward CH, Mendelson M, Mock J, Erbaugh J. An inventory for measuring depression. *Arch Gen Psychiatry* 1961;4:561–71.
- [37] Micoulaud-Franchi JA, Fakra E, Cermolacce M, Vion-Dury J. Towards a new approach of neurophysiology in clinical psychiatry: functional magnetic resonance imaging neurofeedback applied to emotional dysfunctions. *Neurophysiol Clin* 2012;42: 79–94.
- [38] Pollak SD, Kistler DJ. Early experience is associated with the development of categorical representations for facial expressions of emotion. *Proc Natl Acad Sci U S A* 2002; 99:9072–6.
- [39] Boucsein W. *Electrodermal activity*. New York: Plenum Press; 1992.
- [40] Dawson M, Schell A, Filion D. The electrodermal system. In: Cacioppo J, Tassinari L, Berntson G, editors. *Handbook of psychophysiology*. Cambridge: Cambridge University Press; 2007.
- [41] Jennings J. Bodily changes during attending. In: Coles M, Donchin E, Porges S, editors. *Psychophysiology: systems, processes, and applications*. New York: Guilford Press; 1986.
- [42] Kotchoubey B, Strehl U, Uhlmann C, Holzapfel S, König M, Froscher W, et al. Modification of slow cortical potentials in patients with refractory epilepsy: a controlled outcome study. *Epilepsia* 2001;42:406–16.

- [43] Mayer K, Wyckoff SN, Strehl U. One size fits all? Slow cortical potentials neurofeedback: a review. *J Atten Disord* 2012;17:393–409.
- [44] Elbert T, Rockstroh B, Lutzenberger W, Birbaumer N. Biofeedback of slow cortical potentials. *Electroencephalogr Clin Neurophysiol* 1980;48:293–301.
- [45] Nagai Y, Critchley HD, Featherstone E, Fenwick PB, Trimble MR, Dolan RJ. Brain activity relating to the contingent negative variation: an fMRI investigation. *Neuroimage* 2004; 21:1232–41.
- [46] Gevensleben H, Rothenberger A, Moll GH, Heinrich H. Neurofeedback in children with ADHD: validation and challenges. *Expert Rev Neurother* 2012;12:447–60.
- [47] Beyenburg S, Mitchell AJ, Schmidt D, Elger CE, Reuber M. Anxiety in patients with epilepsy: systematic review and suggestions for clinical management. *Epilepsy Behav* 2005;7:161–71.
- [48] Crail-Melendez D, Herrera-Melo A, Martinez-Juarez IE, Ramirez-Bermudez J. Cognitive-behavioral therapy for depression in patients with temporal lobe epilepsy: a pilot study. *Epilepsy Behav* 2012;23:52–6.
- [49] Elger CE, Mormann F. Seizure prediction and documentation – two important problems. *Lancet Neurol* 2013;12:531–2.
- [50] Cook MJ, O'Brien TJ, Berkovic SF, Murphy M, Morokoff A, Fabinyi G, et al. Prediction of seizure likelihood with a long-term, implanted seizure advisory system in patients with drug-resistant epilepsy: a first-in-man study. *Lancet Neurol* 2013;12: 563–71.
- [51] Fisher RS, Blum DE, DiVentura B, Vannest J, Hixson JD, Moss R, et al. Seizure diaries for clinical research and practice: limitations and future prospects. *Epilepsy Behav* 2012;24:304–10.
- [52] Poh M, Swenson N, Picard R. A wearable sensor for unobtrusive, long-term assessment of electrodermal activity. *IEEE Trans Biomed Eng* 2010;57:1243–52.