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

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ABSTRACT

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

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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