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Buffered Cortisol Response to Stress in Patients With Epilepsy and Its Association With Memory and Quality of Life

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Abstract

Background and Objectives

Epilepsy is a chronic stress condition associated with dysregulation in the hypothalamic-pituitary-adrenal axis and cognitive and emotional comorbidities. Therefore, we aimed to examine the acute stress response integrity in adults with epilepsy and its relationship with affectivity, memory, and quality of life (QOL).

Methods

This hybrid single-blind controlled study involved 3 groups: an experimental group (EG) of patients with epilepsy exposed to the Trier Social Stress Test (TSST) during a neuropsychological assessment; a control group of patients with epilepsy who underwent neuropsychological testing without stress exposure; and a healthy group (HG) also exposed to the TSST. Patients were recruited from the Refractory Epilepsy Unit and randomly assigned to the experimental or control group. Six saliva samples were collected from all groups at consistent intervals to measure cortisol levels. Repeated measures analyses of covariance and Spearman correlations were performed.

Results

The sample consisted of 147 participants: 38 patients in the EG (50% women; 38.50 ± 10.92 years), 50 patients in the control group (48% women; 40.82 ± 8.55 years), and 59 individuals in the HG (58% women; 40.82 ± 8.55 years). The EG showed an abolition of the stress response and no differences with those not exposed to the TSST. The HG exhibited the expected cortisol response to stress with a rise in the area under the curve with respect to increase, which contrasts with the decreases observed in both groups of patients ($F_{(2,146)} = 9.15$, $\eta^2 = 0.11$) with and without stress (mean difference [MD] = −107.90, 95% CI −176.75 to −39.05, and MD = −89.19, 95% CI −152.81 to −25.56, respectively). Cortisol production in the EG was related to lower seizure frequency ($\rho = -0.40$, 95% CI −0.66 to −0.08), and better memory retrieval ($\rho = 0.43$, 95% CI 0.15–0.68) and QOL ($\rho = 0.40$, 95% CI 0.10–0.65).

Discussion

Patients with epilepsy may exhibit a buffered cortisol response to acute stress. Preservation of this response is associated with better clinical, cognitive, and QOL outcomes. Despite limitations such as the cross-sectional design and sample specificity, these findings could help clarify the underlying mechanisms of stress-epilepsy interaction.

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Glossary

ANOVA = analysis of variance; **ASM** = antiseizure medication; **AUC_g** = area under the curve to ground; **AUC_i** = area under the curve with respect to increase; **CG-E** = control group of patients with epilepsy; **EG** = experimental group; **HG** = healthy group; **HPA** = hypothalamic-pituitary-adrenal; **MD** = mean difference; **QOL** = quality of life; **TLE** = temporal lobe epilepsy; **TSST** = Trier Social Stress Test.

Introduction

Epilepsy has been proposed as a model of chronic stress in humans.[1] Uncontrollable and unpredictable seizures, mood comorbidities, and side effects of antiseizure medications (ASMs) affect patients' quality of life (QOL) during prolonged periods.[2,3] Glucocorticoids, as the final product of the stress response, increase during periods of interictal epileptiform discharges and after seizures[4,5] and play an important role in seizure onset.[6,7]

In the general population, and in patients with neurologic symptoms, chronic stress has been related to a buffered cortisol awakening response and responsivity to acute stress.[8,9] Moreover, a dampened response to acute stress in healthy people has been proposed as a predictor of future anxiety and depression[10] while chronic stress has been associated with mood disorders.[11] Regarding cognition, acute mild-intensity stress can enhance encoding and memory consolidation in implicit and declarative memory tasks, but not in the case of acute high-intensity stress.[12,13] However, chronic stress can have a pernicious effect on cognition.[14,15]

To our knowledge, only 2 studies have examined the stress response to psychosocial stressors in adults with epilepsy.[16,17] Those studies suggested a greater cortisol reactivity to an acute stressor in patients with epilepsy than in healthy individuals,[16,17] and this response was positively related to seizure frequency in patients with poor seizure control.[16] In adolescents and children, a standardized acute stressor was administered and a buffered cortisol response was found in patients with stress-dependent seizures compared with patients without seizures and healthy controls.[18]

Although these results represent an important step forward, few studies address the interaction between acute stress response and mood and cognition in this chronically stressed population. Potential results could explain mechanisms underlying the stress-epilepsy relationship. Therefore, the aim of this study was to check the integrity of the stress response to the Trier Social Stress Test (TSST),[19] a well-known standardized psychosocial stressor, and determine the possible relationship with affectivity, memory, and QOL. We hypothesize that people with epilepsy will have a greater cortisol reactivity to the TSST than healthy people and that those patients exposed to the stressor will have a higher cortisol production than those who were not. Finally, we hypothesize that preservation of the cortisol response will be related to better mood, memory performance, and QOL.

Methods

Participants

The sample included 3 sex-balanced groups: an experimental group (EG) of patients with epilepsy exposed to psychosocial stress during neuropsychological evaluation; a control group of patients with epilepsy (CG-E) not exposed to psychosocial stress but underwent the same neuropsychological evaluation; and the healthy group (HG), a second control group of healthy individuals who were also exposed to psychosocial stress but did not undergo neuropsychological assessment. All participants completed the assigned protocol.

Patients were recruited from the Refractory Epilepsy Unit, Hospital Universitario y Politécnico La Fe, between May 2015 and February 2020, and were randomly assigned to the experimental or the control group. The inclusion criteria comprised the following: (1) drug-resistant epilepsy with a hypothesis of temporal lobe epilepsy (TLE) before the assessment; (2) candidates for epilepsy surgery; (3) age 18 years or older; and (4) a neuropsychological assessment performed before surgery. Excluded were patients (1) older than 65 years, (2) with severe cognitive impairment or psychiatric conditions, (3) with an endocrine disease, and (4) who were not fluent in Spanish. Participants of the HG were recruited using local advertisements distributed through posters and social media. Assessed participants were encouraged to inform others (maintaining confidentiality regarding the characteristics of the study) following a snowball sampling approach. The inclusion criteria comprised an age between 18 and 65 years. Participants with drug prescriptions (including neurologic and psychiatric drugs); severe cognitive impairment; or endocrinologic, neurologic, or psychiatric conditions (including mood disorders) were excluded.

Standard Protocol Approvals, Registrations, and Participant Consents

This was a hybrid single-blinded controlled study that combined a randomized EG with 2 control groups (1 randomized and 1 nonrandomized). Its reporting followed the Transparent Reporting of Evaluations with Nonrandomized Designs statement.[20] The protocol followed the Declaration of Helsinki and was approved by the hospital's ethics committee (number 2017/0144). All participants provided informed consent.

Procedure

Before the assessment session, participants were instructed to abstain from eating, consuming stimulants, drinking alcohol, smoking, or brushing their teeth 2 hours before the session. After checking these conditions and obtaining informed consent, demographic characteristics were recorded.

A multidisciplinary team gathered presurgical data, including seizure history; neurologic and psychiatric evaluations; long-term video-EEG monitoring; 3T MRI; and selectively performed fluorodeoxyglucose-PET, SPECT, and intracranial EEG. This assessment determined the epilepsy type, including localization and lateralization of the epileptogenic area. Demographic characteristics and clinical data were registered. Given the possible effect of ASMs on cortisol levels,[21] the defined daily dose of all ASMs was calculated following the World Health Organization Collaborating Centre for Drug Statistics Methodology ATC index.[22]

The assessment session was conducted at the Hospital Universitario y Politécnico La Fe between 4.00 PM and 8.00 PM to minimize the hormonal circadian rhythms. This session differed for the 3 groups. For the EG, a TSST protocol was administered after habituation to the clinical setting during the neuropsychological assessment, specifically after the attention, executive function, and naming exploration and before the memory assessment. The protocol included the collection of 6 saliva samples for cortisol determination: before the stressor (baseline); immediately after the stressor; and 30, 45, 60, and 75 minutes after the stress onset. Memory assessment was performed more than 1 hour after the end of the stressor to avoid a possible effect of acute stress. For the CG-E, only the neuropsychological evaluation was conducted to control clinical variables related to epilepsy itself and the evaluation effect. Six saliva samples were collected to measure cortisol secretion during evaluation and accurately analyze the cortisol decline in the late afternoon and evening—the circadian trough.[23,24] Saliva samples were collected at 15-minute intervals while endeavoring to use the same timing between samples as in the EG. In both groups of patients, baseline cortisol levels were measured approximately 90 minutes after the start of the session, ensuring a stress recovery of cortisol levels. Finally, for the HG, a demographic interview was conducted and, after a habituation period, the TSST was administered to control stress response, with similar timing between saliva samples as for the EG. No participants received incentives. Figure 1 demonstrates the protocol used in each group.

The neuropsychological exploration was designed following the E-PILEPSY consortium recommendations.[25] For this study, memory, state and trait anxiety, state mood, depression, and QOL tests were selected. No missing data were detected for any variable. State anxiety and mood were evaluated at the beginning and end of the neuropsychological assessment while trait anxiety, depression, and QOL were explored at the end.

Psychosocial Stress

Participants of the EG and HG were challenged with the TSST.[19] The TSST mainly consists of a 5-minute preparation task, a 5-minute speech task, and a 5-minute mental arithmetic task in front of an audience. The audience comprised 2 reviewers (a man and a woman) who were dressed in smocks. During the 15 minutes of the TSST, a video recording was simulated to enhance the evaluative threat. This protocol has been shown to induce significant activation of the hypothalamic-pituitary-adrenal (HPA) axis, with 2–3-fold increases of free cortisol in healthy men.[19,26]

Salivary Cortisol

Salivary cortisol was collected using Salivettes (Sarstedt, Germany). Samples were centrifuged at 3,000 rpm for 15 minutes, and the clear supernatant was stored at −80°C until analysis at the Laboratory of Social Cognitive Neuroscience (Universitat de València). Cortisol was analyzed in duplicate using an enzyme immunoassay kit (Salimetrics, London, United Kingdom; sensitivity <0.007 μg/dL). All samples from each participant were analyzed in the same trial. Results were accepted if interduplicate variation was ≤8%. Intra-assay and interassay variation coefficients were 1.47% and 7.9%, respectively. Concentrations were reported in nanomoles per liter.

Neuropsychological Assessment

Memory

The Wechsler Memory Scale–Third Edition,[27] in its Spanish version,[28] was used to assess verbal and visual memory. The indices obtained were immediate and delayed auditory memory, delayed auditory recognition, immediate and delayed visual memory, immediate and delayed memory, single-attempt learning, learning slope, retention, and retrieval. These indices were expressed in age-adjusted scalar scores. The test-retest reliability was 0.87.[28]

State and Trait Mood

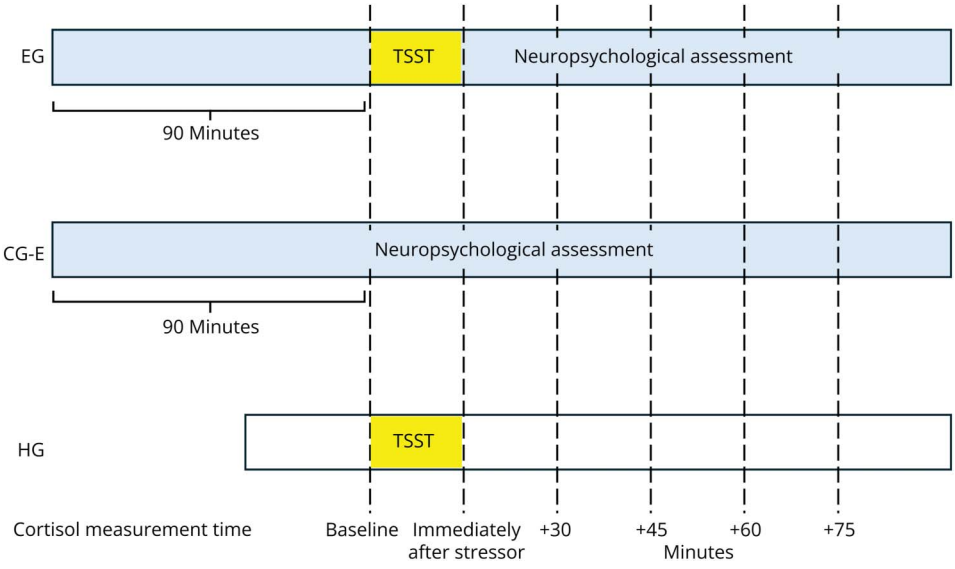
Mood State

The Spanish version[29] of the Positive and Negative Affect Schedule[30] was used for measuring mood state. This self-reported questionnaire consists of a Positive Affect Scale and a Negative Affect Scale, each containing 10 items. A 5-point Likert scale was used, from 1 ("very slightly or not at all") to 5 ("extremely"). The Cronbach α of the Spanish adaptation was 0.92 for the Positive Affect Scale and 0.88 for the Negative Affect Scale.[29]

State Anxiety

This item was assessed using the State-Trait Anxiety Inventory.[31] The State-Trait Anxiety Inventory consists of 20 items rated on a 4-point scale, ranging from 0 ("hardly ever") to 3 ("almost always"). Higher scores indicate higher state anxiety. The Cronbach α of the Spanish adaptation was 0.94.[32]

Figure 1 Protocol Used in Each Group (EG, CG-E, and HG)



CG-E = control group of patients with epilepsy; EG = experimental group; HG = healthy group; TSST = Trier Social Stress Test.

Trait Anxiety

The State-Trait Anxiety Inventory trait anxiety scale[31] evaluates relatively stable aspects of anxiety and consists of 20 items rated on a 4-point scale ranging from 0 ("hardly ever") to 3 ("almost always"). Higher scores indicate higher anxiety. The Cronbach α of the Spanish version was 0.90.[32]

Depression

The Beck Depression Inventory-II[33] was used to assess depression and consists of 21 items rated on a 4-point scale, with higher scores indicating higher depression levels. The Cronbach α of the Spanish adaptation was 0.89.[34]

QOL

The Quality of Life in Epilepsy Inventory,[35] in its Spanish version,[36] was used to assess QOL. It includes 7 scales: seizure worry, overall QOL, emotional well-being, energy, cognitive self-rating, medication effects, and social functioning. Scores for each subscale ranged from 0 to 100, with higher scores indicating better QOL. A QOL composite score was computed using a weighted average of subscales. The Cronbach α of the Spanish adaptation ranged from 0.55 to 0.92.[36]

Statistical Analysis

The sample size was calculated using G*power (version 3.1). Cortisol levels were log-transformed to allow the application of parametric statistics. Greenhouse-Geisser adjustments for the degree of freedom were performed in all the repeated measures analyses. To estimate the magnitude of the cortisol response, the area under the curve to ground (AUC_g) and the area under the curve with respect to increase (AUC_i) were calculated.[37]

To test differences in cortisol levels depending on the group, repeated measures analyses of covariance with "time point" as a within-participant factor (5 levels, immediately after the stressor, and 30, 45, 60, and 75 minutes after the stressor onset) and "group" as a between-participant factor (3 groups) were performed, using baseline cortisol levels as a covariate to control possible between-individual variations in initial cortisol levels.[38] To examine the cortisol-level evolution for each group, paired *t* tests were performed separately. One-way analyses of variance (ANOVAs) were performed to explore differences among groups in AUC_g and AUC_i. These analyses were repeated including sex (in all cases) and side of seizure focus (for comparing epilepsy groups) as between-participant factors.

For demographic and clinical variables, independent *t* tests for quantitative variables and chi-square tests for categorical variables were performed for the comparisons between both groups of patients. Neuropsychological variables were compared between groups of patients using independent *t* tests. Mood and anxiety state scores, examined before and after the evaluation, were contrasted using repeated measures ANOVAs, with "evaluation phase" as a within-participant factor (2 levels) and the "group" as a between-participant factor (2 groups of patients). Changes in mood and anxiety states were calculated as postevaluation minus preevaluation scores. Associations between cortisol response and clinical and neuropsychological variables were performed with Spearman correlations.

Bonferroni tests were used as post hoc analyses. Eta squared (η^2) and power (P) were calculated as indicators of statistical power. Analyses were performed using SPSS 28.0, and 2-tailed tests with *p* set at 0.05 were considered significant. CIs for Spearman correlations were calculated with Jamovi software version 2.3.38.

Table 1 Characteristics of Both Groups of Patients

	EG (n = 38)	CG-E (n = 50)	*p* Value
Sex (women)	19 (50.0)	24 (48.0)	0.61
Educational level			0.84
Primary	16 (42.1)	20 (40.0)	
Secondary	10 (26.3)	16 (32.0)	
Higher education	12 (31.6)	14 (28.0)	
Academic/employment insertion (yes)	24 (63.2)	22 (44.0)	0.08
Marital status			0.49
Single	19 (50.0)	21 (42.0)	
Married	18 (47.4)	25 (50.0)	
Divorced	1 (2.6)	4 (8.0)	
Epilepsy duration (y)	21.55 ± 13.96	23.38 ± 16.32	0.58
Age at epilepsy onset (y)	16.95 ± 12.01	15.99 ± 11.68	0.71
Epilepsy type			0.17
FLE	3 (7.9)	9 (18.0)	
TLE	35 (92.1)	41 (82.0)	
Lateralization of seizure onset			0.76
Left	17 (44.7)	24 (48.0)	
Right	21 (56.3)	26 (52.0)	
Seizures per month	13.39 ± 36.67	17.27 ± 31.72	0.60
Seizure type			0.46
FAS	0 (0.0)	2 (4.0)	
FIAS	14 (36.8)	21 (42.0)	
FBTCS	1 (2.6)	0 (0.0)	
FAS + FIAS	6 (15.8)	10 (20.0)	
FIAS + FBTCS	15 (39.5)	13 (26.0)	
FAS + FIAS + FBTCS	2 (5.3)	4 (8.0)	
Total DDD	3.43 ± 1.42	3.14 ± 1.25	0.32
No. of ASMs	2.76 ± 0.94	2.80 ± 0.86	0.85
No. of failed ASMs	6.71 ± 3.28	6.7 ± 3.68	0.98
MRI findings			0.36
Hippocampal sclerosis	20 (52.6)	16 (32.0)	
Focal cortical dysplasia	3 (12.0)	9 (18.0)	
Tumor	3 (7.9)	9 (18.0)	
Heterotopia	1 (2.6)	1 (2.0)	
Cavernoma	3 (7.9)	4 (8.0)	
Nonspecific pathology	8 (21.1)	11 (22.0)	

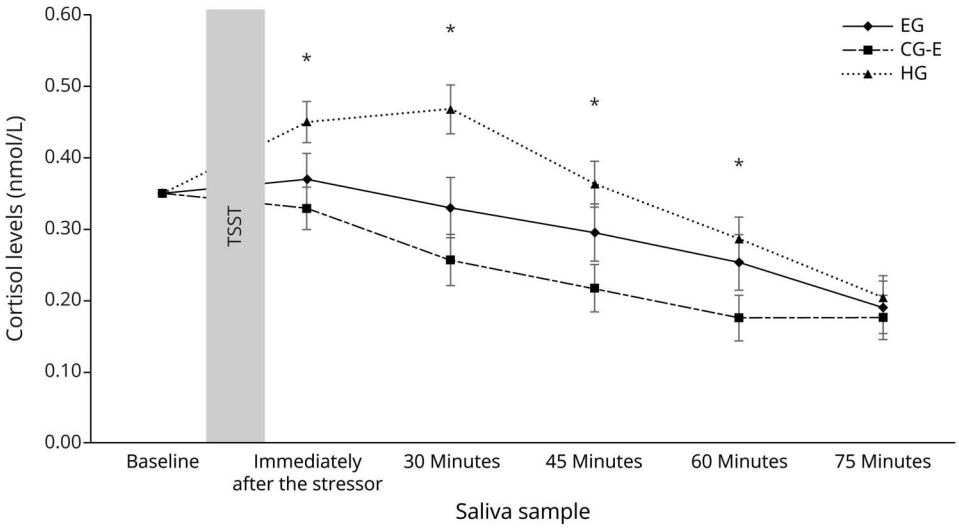
Abbreviations: ASM = antiseizure medication; CG-E = control group of patients with epilepsy; DDD = defined daily dose; EG = experimental group; FAS = focal aware seizure; FBTCS = focal to bilateral tonic-clonic seizure; FIAS = focal impaired awareness seizure; FLE = frontal lobe epilepsy; TLE = temporal lobe epilepsy. Data are given as mean ± SD or n (%).

Table 2 Differences Between the EG and the CG-E in Memory, Mood and Anxiety States Before and After the Neuropsychological Assessment, Trait Anxiety, Depression, and QOL

	EG (n = 38)	CG-E (n = 50)	*p* Value
WMS-III (scalar scores)			
Immediate auditory memory	14.76 ± 5.73	15.32 ± 4.99	0.77
Delayed auditory memory	15.95 ± 6.04	16.46 ± 5.72	0.69
Delayed auditory recognition	8.68 ± 3.28	8.0 ± 3.52	0.36
Immediate visual memory	15.97 ± 5.68	15.58 ± 6.55	0.63
Delayed visual memory	14.42 ± 5.45	16.18 ± 5.33	0.13
Immediate memory	30.37 ± 10.18	30.92 ± 10.0	0.80
Delayed memory	39.63 ± 14.66	40.54 ± 12.75	0.76
Single-attempt learning	18.0 ± 4.56	17.08 ± 5.14	0.39
Learning slope	20.74 ± 5.36	21.16 ± 5.03	0.71
Retention	17.50 ± 5.68	18.60 ± 5.47	0.36
Retrieval	0.94 ± 2.96	−0.13 ± 1.72	0.03[a]
PANAS			
Positive mood before assessment	33.87 ± 8.31	32.84 ± 6.26	0.51
Positive mood after assessment	31.39 ± 9.84	31.30 ± 6.74	0.96
Negative mood before assessment	20.87 ± 7.16	20.0 ± 6.43	0.55
Negative mood after assessment	18.21 ± 8.11	17.26 ± 7.58	0.57
STAI			
State anxiety before assessment	20.92 ± 9.13	20.95 ± 10.18	0.99
State anxiety after assessment	18.66 ± 10.41	19.79 ± 11.09	0.65
Trait anxiety	26.05 ± 10.26	25.96 ± 11.48	0.97
Trait anxiety (PC)	65.31 ± 28.54	64.84 ± 32.45	0.71
BDI-II	11.45 ± 10.17	12.28 ± 9.36	0.69
QOLIE-31			
Seizure worry	47.32 ± 24.19	51.13 ± 28.38	0.49
Overall QOL	63.87 ± 13.93	64.23 ± 15.83	0.91
Emotional well-being	63.47 ± 19.55	62.06 ± 16.39	0.71
Energy	60.68 ± 16.27	58.56 ± 18.64	0.58
Cognition self-rating	49.42 ± 24.64	48.22 ± 21.66	0.81
Medication effects	45.37 ± 32.12	43.36 ± 27.17	0.75
Social functioning	49.29 ± 24.98	47.80 ± 23.62	0.78
QOL composite score	54.29 ± 16.06	54.39 ± 14.12	0.98

Abbreviations: BDI-II = Beck Depression Inventory-II; CG-E = control group of patients with epilepsy; EG = experimental group; PANAS = Positive and Negative Affect Schedule; QOL = quality of life; QOLIE-31 = Quality of Life in Epilepsy Inventory; STAI = State-Trait Anxiety Inventory; WMS-III = Wechsler Memory Scale-III.
Data are given as mean ± SD.
[a] $p < 0.05$.

Figure 2 Cortisol Levels (in Logarithmic Data) After Exposure to a Psychosocial Stressor in the 3 Groups With Baseline Levels as a Covariate

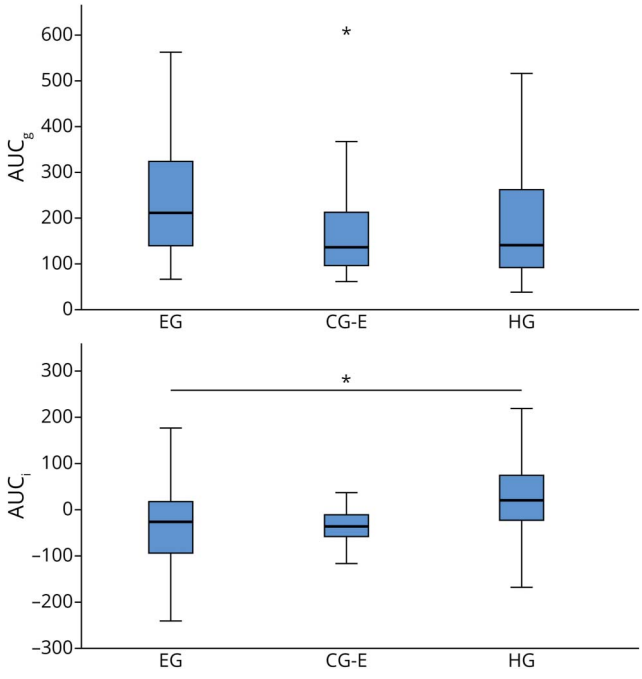


*p < 0.05; error bars represent 95% CIs. Note: time points included before the stressor, immediately after the stressor, and 30, 45, 60, and 75 minutes after the stressor onset. CG-E = control group of patients with epilepsy; EG = experimental group; HG = healthy group; TSST = Trier Social Stress Test.

Data Availability

Data not provided in the article may be shared (anonymized) at the request of any qualified investigator for purposes of replicating procedures.

Figure 3 AUC_g and AUC_i for the 3 Groups of Participants



*p < 0.05; error bars represent 95% CIs. AUC_g = area under the curve to ground; AUC_i = area under the curve with respect to increase; CG-E = control group of patients with epilepsy; EG = experimental group; HG = healthy group.

Results

Preliminary Analyses

The sample comprised 147 participants distributed into 3 sex-balanced groups: the EG (patients exposed to psychosocial stress; n = 38, 50% women), the CG-E (patients not exposed to psychosocial stress; n = 50, 48% women), and the HG (healthy individuals exposed to psychosocial stress; n = 59, 58% women).

No significant differences were found in gender distribution or age between groups. The mean age and SD were 38.50 ± 10.92 years for the EG, 39.38 ± 12.38 years for the CG-E, and 40.82 ± 8.55 years for the HG. No significant differences were found in demographic or clinical variables between both groups of patients (Table 1), nor memory, mood and anxiety state, trait anxiety, depression, or QOL variables, except for memory retrieval, with higher scores in the EG than in the CG-E (t[86] = 2.26, mean difference [MD] = 1.09, 95% CI 0.13–2.05, p < 0.03). For mood state, a significant effect of "evaluation phase" was found for positive mood ($F_{(1,86)}$ = 8.25, p < 0.01, η^2 = 0.09, P = 0.81) and negative mood ($F_{(1,86)}$ = 16.42, p < 0.0001, η^2 = 0.16, P = 0.98), with both cases showing decreases after the evaluation to baseline scores in the total sample. Between-participant differences in these variables across both patient groups are listed in Table 2.

Cortisol Response to Psychosocial Stress

Significant differences were found in cortisol levels before the stressor among groups ($F_{(2,146)}$ = 14.61, p < 0.0001, η^2 = 0.17, P = 1.0), with EG and CG-E showing higher cortisol levels than healthy controls (MD = 0.33, 95% CI 0.18–0.49, p < 0.0001, and MD = 0.20, 95% CI 0.06–0.34, p < 0.002, respectively). Thus, the first cortisol measure was included as

Table 3 Descriptive Statistics of Responders (n = 6) and Nonresponders (n = 32) of the EG

	Responders (n = 6)	Nonresponders (n = 32)	*p* Value
AUC_g	388.43 ± 145.94	218.74 ± 131.81	0.01[a]
AUC_i	165.10 ± 125.10	−120.75 ± 185.32	<0.01[a]
Age	38.17 ± 15.41	38.56 ± 10.20	0.93
Epilepsy duration (y)	12.67 ± 9.99	23.21 ± 14.08	0.09
Age at epilepsy onset (y)	25.5 ± 14.43	15.34 ± 11.11	0.06
Seizures per month	4.61 ± 4.41	15.08 ± 39.90	0.53
No. of ASMs	2.67 ± 1.36	2.78 ± 0.87	0.79
No. of failed ASMs	6.33 ± 3.61	6.78 ± 3.27	0.76
Total DDD	2.85 ± 1.96	3.53 ± 1.31	0.29
WMS-III (scalar scores)			
Immediate auditory memory	20.0 ± 5.58	15.22 ± 5.46	0.06
Delayed auditory memory	20.50 ± 5.89	15.09 ± 5.76	0.04[a]
Delayed auditory recognition	11.50 ± 2.16	8.16 ± 3.20	0.02[a]
Immediate visual memory	15.67 ± 3.88	14.59 ± 6.04	0.68
Delayed visual memory	14.67 ± 5.12	14.38 ± 5.58	0.91
Immediate memory	35.67 ± 8.89	29.38 ± 10.22	0.17
Delayed memory	51.17 ± 19.97	37.47 ± 12.72	0.03[a]
Single-attempt learning	21.83 ± 4.07	17.28 ± 4.33	0.02[a]
Learning slope	22.50 ± 6.68	20.41 ± 5.13	0.39
Retention	20.83 ± 3.92	16.88 ± 5.79	0.12
Retrieval	1.42 ± 2.15	0.69 ± 1.99	0.42
PANAS			
Positive mood change	−0.33 ± 3.88	−2.87 ± 8.11	0.40
Negative mood change	−5.50 ± 2.88	−2.12 ± 7.89	0.31
STAI			
State anxiety change	−2.50 ± 3.33	−2.21 ± 9.51	0.94
Trait anxiety	18.50 ± 10.07	27.47 ± 9.80	0.05[a]
Trait anxiety (PC)	44.0 ± 32.70	69.31 ± 26.37	0.05[a]
BDI-II	7.0 ± 7.48	12.28 ± 10.48	0.25
QOLIE-31			
Seizure worry	56.50 ± 15.37	45.59 ± 25.31	0.32
Overall QOL	73.83 ± 3.76	62.0 ± 14.36	<0.01[a]
Emotional well-being	84.0 ± 9.46	59.63 ± 18.57	<0.01[a]
Energy	68.50 ± 12.62	59.22 ± 16.61	0.20
Cognition self-rating	53.33 ± 21.76	48.69 ± 25.39	0.68
Medication effects	48.33 ± 30.80	44.81 ± 32.80	0.81
Social functioning	48.67 ± 13.98	49.41 ± 26.71	0.95
QOL composite score	61.67 ± 11.03	52.91 ± 16.60	0.23

Abbreviations: ASM = antiseizure medication; AUC_g = area under the curve to ground; AUC_i = area under the curve with respect to increase; BDI-II = Beck Depression Inventory-II; DDD = defined daily dose; PANAS = Positive and Negative Affect Schedule; QOL = quality of life; QOLIE-31 = Quality of Life in Epilepsy Inventory; STAI = State-Trait Anxiety Inventory; WMS-III = Wechsler Memory Scale-III.
Data are given as mean ± SD.
[a] $p < 0.05$.

a covariate to estimate cortisol response while controlling for baseline levels.

Significant effects of the "time point × group" interaction were found on cortisol levels after stress (Figure 2) ($F_{(6.9,492.5)}$ = 5.05, $p < 0.0001$, $\eta^2 = 0.07$, P = 1.0), as well as significant effects of "time point" and "group" main factors ($F_{(3.4,492.5)}$ = 11.30, $p < 0.0001$, $\eta^2 = 0.07$, P = 1.0, and $F_{(1,143)} = 4.43$, $p < 0.01$, $\eta^2 = 0.058$, P = 0.75, respectively). The EG showed a trend toward an abolition of the stress response, with lower cortisol levels than in healthy participants at all time points, especially 30 minutes after the onset of the stressor (MD = −0.14, 95% CI −0.28 to 0.00, $p = 0.05$). Moreover, no significant differences were found between both groups of patients, with and without stress. As expected, significant differences were found between the CG-E and the HG because the latter group was exposed to stress and showed higher cortisol levels than patients immediately after the stressor (MD = 0.12, 95% CI 0.20–0.22, $p = 0.01$) and at 30 (MD = 0.21, 95% CI 0.09–0.33, $p < 0.0001$), 45 (MD = 0.15, 95% CI 0.03–0.26, $p < 0.01$), and 60 (MD = 0.11, 95% CI 0.01–0.22, $p < 0.05$) minutes after the stressor onset. No significant effects of sex or side of seizure focus were found when the analysis included these factors.

Examining the evolution of each group (Figure 2), the EG showed decreases in cortisol levels from baseline, which were significant at 45 (MD = −0.13, 95% CI −0.22 to −0.04, $p = 0.01$), 60 (MD = −0.18, 95% CI −0.26 to −0.09, $p = 0.01$), and 75 (MD = −0.24, 95% CI −0.33 to −0.15, $p = 0.01$) minutes after the stressor onset. As is expected according to the circadian rhythm, the CG-E also showed decreases in cortisol levels compared with baseline, which were significant at 30 (MD = −0.11, 95% CI −0.15 to −0.07, $p < 0.0001$), 45 (MD = −0.15, 95% CI −0.21 to −0.10, $p < 0.0001$), 60 (MD = −0.20, 95% CI −0.25 to −0.14, $p < 0.0001$), and 75 (MD = −0.20, 95% CI −0.25 to −0.14, $p < 0.0001$) minutes after the stressor onset. Both patterns of response strongly contrast with that shown by the HG, which exhibited the expected cortisol response: significant increases in cortisol levels immediately after the stressor (MD = 0.13, 95% CI 0.06–0.20, $p < 0.0001$) and 30 minutes after the stressor onset (MD = 0.17, 95% CI 0.08–0.25, $p < 0.0001$), a marginal increase at 45 minutes (MD = 0.08, 95% CI 0.00–0.16, $p = 0.06$), no significant changes at 60 minutes, and significant decreases at 75 minutes after the stressor onset (MD = 0.08, 95% CI −0.15 to >−0.01, $p = 0.05$).

Both stress groups (EG and HG) presented high variability in cortisol levels during the stressor. Considering the absolute criterion of increases of 1.5 nmol/L from baseline as indicative of stress response,[39] only 6 patients of the EG were responders (15.8% of the group size) while 23 participants were responders in the HG (39% of the group size). Only 1 patient (2%) in the CG-E was a responder.

Concerning the magnitude of the response (Figure 3), significant effects were found on AUC_i ($F_{(2,146)}$ = 9.15, $p < 0.0001$, $\eta^2 = 0.11$, P = 0.97), but not on AUC_g. A greater response was found in the AUC_i of the HG during stress, which contrasts with decreases in both groups of patients with and without stress (MD = −107.90, 95% CI −176.75 to −39.05, $p < 0.001$, and MD = −89.19, 95% CI −152.81 to −25.56, $p < 0.003$, respectively).

Cortisol Response and Its Association With Clinical and Neuropsychological Variables in Patients

Baseline cortisol levels were positively associated with epilepsy duration in the total sample of patients (ρ = 0.37, 95% CI 0.23–0.52, $p < 0.001$). Furthermore, the AUC_g in the EG was associated with lower seizure frequency (ρ = −0.40, 95% CI −0.66 to −0.08, $p = 0.02$), and better memory retrieval (ρ = 0.43, 95% CI 0.15–0.68, $p = 0.01$) and overall QOL (ρ = 0.40, 95% CI 0.10–0.65, $p = 0.02$). No significant correlations were found with the AUC_i in this group.

Considering the individual differences, only 6 patients responded to the TSST, whereas 32 patients did not exhibit the typical stress response. Although this distribution leads to viewing the results with caution, responders showed higher AUC_g and AUC_i ($t[36] = 2.85$, MD = 169.68, 95% CI 48.90–290.46, $p < 0.04$, and $t[36] = 3.61$, MD = 285.80, 95% CI 125.04–446.56, $p < 0.001$, respectively) than nonresponders. Responders also showed better performance than nonresponders in delayed auditory memory ($t[36] = 2.10$, MD = 5.41, 95% CI 0.19–10.62, $p < 0.04$), delayed auditory recognition ($t[36] = 2.44$, MD = 3.34, 95% CI 0.56–6.12, $p < 0.02$), delayed memory ($t[36] = 2.21$, MD = 13.70, 95% CI 1.11–26.29, $p < 0.03$), and single-attempt learning ($t[36] = 2.38$, MD = 4.55, 95% CI 0.68–8.43, $p < 0.02$) and close to statistical significance in immediate auditory memory ($t[36] = 1.96$, MD = 4.79, 95% CI −0.16 to 9.72, $p < 0.06$). Finally, responders showed lower trait anxiety than nonresponders ($t[36] = -2.05$, MD = −8.97, 95% CI −17.85 to −0.09, $p < 0.05$) and better overall QOL and emotional well-being ($t[31.60] = 3.99$, MD = 11.83, 95% CI 5.78–17.88, $p < 0.0001$, and $t[36] = 3.12$, MD = 24.38, 95% CI 8.50–40.25, $p < 0.004$, respectively). Descriptive statistics of both groups are given in Table 3.

Discussion

The results of this study suggest the abolition of stress response to the TSST in patients with epilepsy. These patients showed a decreased reactivity to the stressor compared with healthy individuals. In addition, the preservation of the cortisol response was related to lower seizure frequency, better memory retrieval, and better overall QOL in patients exposed to the stressor.

Considering our data, and contrary to our first hypotheses, cortisol levels decreased in patients with epilepsy after a psychosocial stressor, which has demonstrated a powerful stress response in humans.[19] Indeed, similar cortisol levels have

been found in patients with and without exposure to a stressor, both exhibiting the typical cortisol decline of the circadian rhythms in the afternoon. Of interest, the buffered cortisol response of the EG strongly contrasts with the typical response to the TSST found in the healthy controls, especially evident at 30 minutes after the stressor onset and widely documented in previous studies.[40]

To our knowledge, only 3 studies have examined the psychosocial stress response in patients with epilepsy compared with healthy controls.[16-18] In the study by van Campen et al.[18], pediatric patients with stress-dependent seizures exhibited a blunted cortisol response to the TSST compared with patients with non–stress-dependent seizures and healthy participants, probably due to a downregulation of the HPA axis. Regarding the other 2 studies,[16,17] the authors stated that adult patients with epilepsy showed a greater cortisol response to acute stress. However, although patients showed higher levels than healthy controls at all time points, including before the stressor, cortisol levels after the stressor were never higher than before. Therefore, based on the AUC_g and an index of recovery of the cortisol response calculated with the baseline after the stressor, these authors interpreted the results as a higher response in patients than in controls, rather than highlighting the buffering response.[16,17] Thus, the differences between our findings and their conclusions are due to discrepancies in the interpretation rather than the results themselves. Considering this, we conclude that our outcomes are coherent with previous literature,[16-18] with adult patients showing a dampened cortisol response to the stressor.

In this study, the sample comprised patients with drug-resistant epilepsy, mainly TLE. TLE damages limbic structures that regulate the HPA axis, and their vulnerability to prolonged activation may create a feedback loop that sustains and intensifies a chronic severe stress state.[41] Supporting this, both groups of patients had higher cortisol levels than in healthy controls, and this was positively associated with epilepsy duration. This hypercortisolism is in line with previous literature[42-44] that characterizes chronic stress regimens and may be related to the loss of glucocorticoid feedback control of the HPA axis.[45] Indeed, the blunted cortisol response to acute stress has also been described in other samples exposed to chronic stress, such as family caregivers or patients with post-traumatic stress disorder.[46-48] Mounting evidence supports that both exaggerated and blunted stress reactivity of the HPA axis are related to altered glucocorticoid signaling.[49] Thus, hypercortisolism might promote a buffered response to acute stress because of a physiologic ceiling or starvation of the stress system.

Despite these results, cortisol levels were highly variable in patients with epilepsy during the stressor. Classification of responders and nonresponders using absolute criteria is commonly accepted in healthy individuals.[40] From a conservative viewpoint, the absolute criterion revealed that only 15.8% of the EG of patients were responders, which contrasts with the 39% of responders in the HG and agrees with the blunted cortisol response in epilepsy.

Regarding the magnitude of the cortisol response, patients did not differ in the AUC_g. However, the AUC_i of the EG showed decreases that were similar to those found in patients without TSST exposure, which differ from the increases shown by the HG. It would be expected that both groups exposed to the stressor would show greater cortisol production (i.e., higher AUC_g). However, patients with epilepsy had higher baseline cortisol levels than healthy controls. This baseline hypercortisolemia in both patient groups may have offset the buffered cortisol response to stress in the EG. These interpretations are supported by the differences observed in AUC_i, which reflects the system's sensitivity to produce dynamic changes over time. Notably, our results show that greater AUC_g (consistent with a typical stress response) is related to a lower seizure frequency in the EG, in agreement with previous literature.[16]

There is a lack of research exploring the interaction between acute stress and cognition in epilepsy. In our study, patients exposed to the stressor performed better in memory retrieval than patients who did not undergo the TSST. Although a possible residual impact of acute stress cannot be denied, the memory assessment was performed over an hour after the end of the stressor. Furthermore, no significant differences were found between cortisol levels close to the memory assessment (i.e., 45, 60, and 75 minutes after the stressor onset). Nevertheless, other results suggest that the stress response in patients with epilepsy could have implications for cognitive performance and perceived QOL. According to our last hypothesis, in the EG, the AUC_g was related to better memory retrieval and overall QOL. In addition, although results must be interpreted with caution, the 6 responders to the TSST of the EG showed better memory performance, higher QOL, and lower trait anxiety than the nonresponders. If these results are replicated, they would suggest that the preservation of the cortisol response to acute stress, from an adaptive view, is associated with other adaptive processes in neurologic patients such as memory, emotional well-being, and QOL.

This study has some limitations. First, this research was based on cross-sectional data, so it was not possible to establish causal relationships. Second, the sample of patients was limited to people with drug-resistant epilepsy, which limits the applicability of the findings to patients with non–drug-resistant epilepsy. Third, the neuropsychological assessment could have acted as a stressor, which may explain the higher baseline cortisol levels in patients than in healthy controls. However, this fact may also reflect the hypercortisolemia[1] and increased chronic stress commonly associated with epilepsy.[50] It is important to note that this factor is unlikely to have differentially affected the patient groups because both groups underwent the same assessment and showed no differences in cortisol levels or AUC_i. In addition, it is noteworthy that the first cortisol sample was collected 90 minutes after the start of

the session, far exceeding the habituation period, so the possible stress response elicited by the assessment would be expected to have dissipated. Fourth, other clinical factors such as epilepsy type or hemisphere lateralization could explain differences in basal cortisol levels. However, most patients had TLE (92%), and the lack of effects of the side of seizure focus leads us to consider that lateralization is not a plausible reason for the discrepancies in the results. Moreover, no mood data were available for healthy controls, so future studies should include this variable to check whether mood changes explain, at least in part, the buffered response of patients compared with healthy controls. Finally, although no differences were found in the ASM load, certain ASMs could interact with cortisol levels. Thus, future studies should consider the possible effects of pharmacologic treatment in more detail.

Despite these limitations, this study has strengths, such as the assessment of cortisol response to stress using several saliva samples in the afternoon to minimize cortisol fluctuations. Furthermore, the inclusion of 2 control groups (i.e., patients with epilepsy who did not undergo the TSST and healthy participants who were exposed to the stressor) offers additional data on a poorly studied procedure in patients with epilepsy. Our findings suggest that patients with epilepsy show an abolition of cortisol response to a psychosocial stressor. Moreover, these results show that stress response is related to memory retrieval and QOL in these patients. These data could contribute to clarifying the underlying mechanisms of the stress-epilepsy interaction and highlight the potential impact of stress management on cognitive function and QOL in patients with epilepsy.

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Author Contributions

J. Catalán-Aguilar: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data. E. González-Bono: drafting/revision of the manuscript for content, including medical writing for content; study concept or design; analysis or interpretation of data. V. Villanueva: drafting/revision of the manuscript for content, including medical writing for content; study concept or design. K.G. Hampel: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. A. Lozano-García: major role in the acquisition of data. V. Hidalgo: drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data. A. Salvador: drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data. P. Tormos-Pons: analysis or interpretation of data. I. Cano-López: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data.

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