Epilepsy & Behavior 92 (2019) 125–134

Contents lists available at ScienceDirect

Epilepsy & Behavior

journal homepage: www.elsevier.com/locate/yebeh

Cortisol and trait anxiety as relevant factors involved in memory performance in people with drug-resistant epilepsy

Irene Cano-López [a,*], Vanesa Hidalgo [a,b], Kevin G. Hampel [c], Mercedes Garcés [c], Alicia Salvador [a], Esperanza González-Bono [a], Vicente Villanueva [c]

[a] IDOCAL/Department of Psychobiology, Psychology Center, University of Valencia, Avda. Blasco Ibañez, 21, 46010, Valencia, Spain
[b] Department of Psychology and Sociology, Area of Psychobiology, Social and Human Sciences Center, University of Zaragoza, Campus Ciudad Escolar, 44003, Teruel, Spain
[c] Multidisciplinary Epilepsy Unit, Neurology Service, Hospital Universitario y Politécnico La Fe, Bulevar sur, s/n Carretera de Malilla, 46026, Valencia, Spain

ARTICLE INFO

Article history:
Received 12 October 2018
Revised 19 December 2018
Accepted 22 December 2018
Available online 15 January 2019

Keywords:
Cortisol
Trait anxiety
Memory
Drug-resistant epilepsy

ABSTRACT

People with drug-resistant epilepsy are exposed to unpredictable and uncontrollable seizures, which can be considered as a chronic stress condition. Additionally, these patients present memory deficits and a high prevalence of depression and anxiety. Cortisol, the main stress hormone, has a modulatory role on memory in healthy individuals and patients with emotional disorders, but its role in memory and emotional processes remains unclear in people with epilepsy. This study analyzes the differences in cortisol levels in people with epilepsy with high and low memory performance, and the relationships among cortisol levels, epilepsy-related factors, memory, anxiety, and depression. Fifty-two adults with drug-resistant epilepsy underwent a neuropsychological evaluation, in which nine saliva samples were collected to analyze the ability of the hypothalamic–pituitary–adrenal axis to descend in accordance with the circadian rhythm. Cortisol area under the curve (AUC) was computed to study the global cortisol changes. Patients with low immediate and delayed memory performance and left-hemisphere focus showed higher cortisol levels. Additionally, patients with low memory scores had higher cortisol AUC, and therefore slower declining levels in the afternoon. Memory performance was negatively related to the cortisol AUC and trait anxiety, being both reliable predictors of memory performance, especially in patients with left-hemisphere focus. These results suggest that memory deficits in people with drug-resistant epilepsy may be influenced by exposure to cortisol derived from chronic stress. Additionally, trait anxiety could contribute to increasing the vulnerability to stress.

1. Introduction

People with drug-resistant epilepsy can be considered as exposed to a chronic stress condition involving unpredictable and uncontrollable seizures. In turn, stressful events could act as predisposing and precipitant factors of seizures. In addition, these patients present memory deficits [1,2], especially those with temporal lobe epilepsy (TLE) and hippocampal sclerosis (HS) [3], and a high prevalence of depression and anxiety [4–6].

In the last decade, research on cognitive and affective processes in relation to stress has received special attention, due to its capability to modify neural excitability, neurogenesis, and migration. In this context, cortisol, considered as the main stress hormone, is the final product of the hypothalamus–pituitary–adrenal (HPA)-axis activation, and has been proposed as an indicator of the neuroendocrine health status [7] for cognitive and emotional processes [8].

The role of cortisol levels in memory has been frequently studied in healthy individuals [9–11], as well as in patients with emotional disorders [12,13]. Although the results point to complex interactions, several studies with healthy elderly people have linked increased basal cortisol levels with impairment in hippocampus-dependent learning and memory processes, suggesting that prolonged exposure to stressors may lead to decreased memory performance [11,14]. Additionally, increased basal cortisol levels have been found in patients with emotional disorders – such as depression – that are also characterized by memory impairments [13], as cortisol levels are related to these memory impairments [12].

Even though stress, memory impairments, and affective alterations are common in epilepsy, few studies have focused on the potential interactions among these aspects in this disease. Thus, the role of cortisol on memory performance, anxiety, and depression remains unclear in this population and the few results are far from consistent. Devinsky et al. [15] found a positive association between cortisol levels and depression. Afifi et al. [16] reported higher cortisol levels in people with epilepsy and depression than in people with epilepsy without depression or healthy controls. To our knowledge, only Busch's study

* Corresponding author.
E-mail address: irene.cano@uv.es (I. Cano-López).

https://doi.org/10.1016/j.yebeh.2018.12.022
1525-5050/

considers all these variables in a sample of persons with epilepsy [17], showing that cortisol levels are negatively related to long-term verbal and visual memory, but positively related to trait anxiety scores (although not to depression or anxiety symptoms).

To establish more on the relationships between cortisol and cognitive and affective processes in people with drug-resistant epilepsy, this study analyzed the differences in afternoon cortisol levels for those with high and low immediate and delayed memory performance, considering the side of seizure focus, the epilepsy type (temporal or extratemporal), the presence of HS, and seizure frequency due to possible influence on memory performance. The above-mentioned studies were carried out in the morning, when circadian rhythms favor greater fluctuations of cortisol that could overlap target effects [18]. To minimize these fluctuations, several cortisol samples were assessed in the afternoon. Moreover, such timing could also help characterize cortisol profiles in people with epilepsy by comparing them with those reported in the CIRCORT database [19]. The CIRCORT database provides normative reference values for the general population and is a useful tool for comparing adrenocortical functioning in epidemiological research and clinical practice. In addition, our study aimed to examine the relationships for cortisol levels with anxiety and depression in people with epilepsy. We hypothesized that patients with low memory performance would have higher cortisol levels than those with high memory performance, especially patients with left-hemisphere (LH) and temporal focus who are at higher risk of an accelerated forgetting of declarative memory [20]. Thus, we hypothesized that cortisol levels would be negatively related to memory performance — but positively related to anxiety and depression scores.

2. Material and methods

2.1. Participants

In this cross-sectional study, patients were recruited from the Refractory Epilepsy Unit, Hospital Universitario y Politécnico La Fe (Valencia, Spain), between April 2015 and October 2017. Our reporting followed the Strengthening the Reporting of Observational Studies in Epidemiology statement guidelines [21].

The inclusion criteria for the study comprised the following: 1) people with a diagnosis of drug-resistant focal epilepsy; 2) candidates for epilepsy surgery; 3) chronological age of at least 18 years; and 4) a neuropsychological assessment performed prior to surgery. Excluded were patients who as follows: 1) were older than 60 years; 2) had severe cognitive impairment that prevented a reliable neuropsychological evaluation; 3) had not completed primary education; 4) suffered an endocrine disease; 5) were not fluent Spanish speakers; and 6) declined to participate in the study. Characteristics of the sample are shown in Table 1.

2.2. Procedure

The procedure was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of the Hospital Universitario y Politécnico La Fe.

Medical history provided demographic characteristics of the patients (sex, age, and educational level) and clinical data (age at epilepsy onset, duration of epilepsy in years, frequency of seizures per month, seizure type, number of antiepileptic drugs (AEDs), type of AEDs, total defined daily dose (DDD) of all AEDs and strong enzyme inducer drugs, such as carbamazepine, phenytoin, phenobarbital, or primidone, that could modulate cortisol levels [22,23]).

Presurgical assessment included diagnosis of the type of epilepsy and the lateralization of the epileptogenic area. Assessment was made by members of a multidisciplinary team and based on a comprehensive evaluation that included: seizure history and semiology; neurologic examination; long-term video-electroencephalography (EEG) monitoring; 3-Tesla magnetic resonance imaging (MRI), psychiatric assessment, and neuropsychological evaluation for all patients. Fluorodeoxyglucose (FDG)-positron emission tomography (PET), single photon emission computed tomography (SPECT), and intracranial EEG recording were performed selectively. Etiology of pathology was established based on MRI findings. If concerns about postsurgical memory outcome were not solved by prior evaluation, a Wada test was performed to help in the decision-making process.

The neuropsychological evaluation session was performed before the surgery. Prior to this session, participants were instructed to abstain from eating, drinking stimulants (such as tea, coffee, or alcohol), brushing their teeth, or smoking during the two-hour period before arriving at the hospital. The neuropsychological evaluation was always carried out between 4:00 pm and 8:00 pm to minimize hormonal circadian variations, and each session lasted approximately 3 h. During each neuropsychological assessment session, nine saliva samples (from C1 to C9) were collected to measure cortisol secretion and analyze accurately the cortisol decline in the late afternoon and evening — the circadian trough [11,24]. Saliva samples were collected with a mean 20-min interval between samples, although this interval could vary depending on the duration of tests. Memory assessment was performed between C4 and C9 samples after habituation to the clinical setting. State anxiety was evaluated at the beginning and at the end of the neuropsychological evaluation, while trait anxiety and depression were evaluated at the end of the assessment session.

2.3. Salivary cortisol

Saliva samples were collected using salivettes (Sarstedt, Nümbrecht, Germany) for cortisol. Participants were instructed to keep the cotton swab in their mouths for 2 min. The samples were centrifuged at 3000 rpm for 15 min, resulting in a clear supernatant with low viscosity that was stored at −80 °C until analyses were performed in the Laboratory of Social Cognitive Neuroscience, Faculty of Psychology (University of Valencia). Salivary cortisol concentrations were determined in duplicate with the salivary cortisol enzyme-immunoassay kit from Salimetrics (Newmarket, UK). Assay sensitivity was <0.007 μg/dL. For each patient, all the samples were analyzed in the same trial. The criterion for measurement replication was fixed as an interduplicate variation coefficient of 8%. The intra- and interassay variation coefficients were 1.47% and 7.9%, respectively. Cortisol levels were expressed in nmol/L.

2.4. Neuropsychological assessment (Table S1)

The Spanish version [25] of the Wechsler Memory Scale-Third Edition (WMS-III) [26] was used to evaluate learning, immediate, and delayed recall, as well as recognition of verbal and visual information. We used the following scales of the WMS-III: Logical Memory I and II (immediate and delayed recall, and delayed recognition for a short story); Verbal Paired Associates I and II (immediate and delayed recall, and delayed recognition for eight-word pairs); Faces I and II (immediate and delayed recognition of faces); and Family Scenes I and II (immediate and delayed recall for family scenes). These scales provide two general memory indices (immediate memory and delayed memory), material-specific memory indices (immediate auditory memory, delayed auditory memory, delayed auditory recognition, immediate visual memory, delayed visual memory), and indices related to auditory processes (single-trial auditory learning, auditory learning slope, auditory retention, and auditory retrieval), expressed in age-adjusted scalar scores. These scores were transformed to age-adjusted percentile scores, which were used in all analyses.

The Spanish version [27] of the State–Trait Anxiety Inventory (STAI) Scale [28] is composed by two scales: The state scale (STAI-S) evaluates the current state of anxiety, while the trait anxiety scale (STAI-T) evaluates relatively stable aspects of anxiety. Each subscale has 20 items rated on a four-point scale. Cronbach's alpha of the Spanish adaptation is 0.94 [27].

Table 1
Characteristics of groups based on side of seizure focus, epilepsy type, and memory competence (mean ± SD or n (%)) and differences between groups.

Characteristics	Side of seizure focus			Epilepsy type			Immediate memory competence			Delayed memory competence		
	LH (n = 27)	RH (n = 25)	*p*	TLE (n = 38)	ETLE (n = 14)	*p*	High (n = 28)	Low (n = 24)	*p*	High (n = 28)	Low (n = 24)	*p*
Age	37.33 ± 10.26	40.76 ± 10.13	.23	39.45 ± 10.99	37.71 ± 8.11	.59	41.21 ± 10.19	36.38 ± 9.89	.09	38.93 ± 9.33	39.04 ± 11.43	.97
Sex			.28			.26			.18			.18
Female	17 (63.0%)	12 (48.0%)		23 (60.5%)	6 (42.9%)		18 (64.3%)	11 (45.8%)		18 (64.3%)	11 (45.8%)	
Male	10 (37.0%)	13 (52.0%)		15 (39.5%)	8 (57.1%)		10 (35.7%)	13 (54.2%)		10 (35.7%)	13 (54.2%)	
Educational level			.16			.17			.31			.12
Primary	2 (7.4%)	3 (12.0%)		4 (10.5%)	1 (7.1%)		1 (3.6%)	4 (16.7%)		0 (0.0%)	5 (20.8%)	
Secondary	6 (22.2%)	9 (36.0%)		8 (21.1%)	7 (50.0%)		7 (25.0%)	8 (33.3%)		6 (21.4%)	9 (37.5%)	
Lower-university	10 (37.0%)	11 (44.0%)		16 (42.1%)	5 (35.7%)		13 (46.4%)	8 (33.3%)		13 (46.4%)	8 (33.3%)	
University	9 (33.3%)	2 (8.0%)		10 (26.3%)	1 (7.1%)		7 (25.0%)	4 (16.7%)		9 (32.1%)	2 (8.3%)	
Epilepsy type			.87			-			.77			.36
TLE[1]	20 (74.1%)	18 (72.0%)		38 (100.0%)	0 (0.0%)		20 (71.4%)	18 (75.0%)		19 (67.9%)	19 (79.2%)	
ETLE[2]	7 (25.9%)	7 (28.0%)		0 (0.0%)	14 (100.0%)		8 (28.6%)	6 (25.0%)		9 (32.1%)	5 (20.8%)	
Side of seizure focus			-			.87			.39			.39
LH[3]	27 (100.0%)	0 (0.0%)		20 (52.6%)	7 (50.0%)		13 (46.4%)	14 (58.3%)		13 (46.4%)	14 (58.3%)	
RH[4]	0 (0.0%)	25 (100.0%)		18 (47.4%)	7 (50.0%)		15 (53.6%)	10 (41.7%)		15 (53.6%)	10 (41.7%)	
Age at epilepsy onset	15.74 ± 11.76	15.84 ± 11.98	.98	17.58 ± 12.09	10.93 ± 9.52	.07	17.07 ± 12.60	14.29 ± 10.74	.40	16.11 ± 11.90	15.42 ± 11.82	.84
Epilepsy duration	21.59 ± 15.64	24.92 ± 14.19	.43	21.87 ± 15.57	26.79 ± 12.75	.30	24.14 ± 15.40	22.08 ± 14.56	.62	22.82 ± 15.14	23.63 ± 14.94	.85
Etiology of pathology												
HS[5]	8 (29.6%)	4 (16.0%)	.25	12 (31.6%)	0 (0.0%)	.02	4 (14.3%)	8 (33.3%)	.10	4 (14.3%)	8 (33.3%)	.10
FCD[6]	7 (25.9%)	4 (16.0%)	.39	5 (13.2%)	6 (42.9%)	.20	6 (21.4%)	5 (20.8%)	.96	5 (17.9%)	6 (25.0%)	.53
Tumor	2 (7.4%)	2 (8.0%)	.60	3 (7.9%)	1 (7.1%)	.80	2 (7.1%)	2 (8.3%)	.65	3 (10.7%)	1 (4.2%)	.65
Cavernoma	2 (7.4%)	1 (4.0%)	.61	2 (5.3%)	1 (7.1%)	.80	3 (10.7%)	0 (0.0%)	.10	3 (10.7%)	0 (0.0%)	.10
Glioma	3 (11.1%)	1 (4.0%)	.96	3 (7.9%)	1 (7.1%)	.93	1 (3.6%)	3 (12.5%)	.23	2 (7.1%)	2 (8.3%)	.87
Gliosis	1 (3.7%)	1 (4.0%)	.96	2 (5.3%)	0 (0.0%)	.38	1 (3.6%)	1 (4.2%)	.91	1 (3.6%)	1 (4.2%)	.91
Heterotopia	0 (0.0%)	1 (4.0%)	.33	1 (2.6%)	0 (0.0%)	.54	0 (0.0%)	1 (4.2%)	.28	1 (3.6%)	0 (0.0%)	.35
General atrophy	0 (0.0%)	1 (4.0%)	.33	1 (2.6%)	0 (0.0%)	.54	1 (3.6%)	0 (0.0%)	.35	0 (0.0%)	1 (4.2%)	.28
Hippocampal atrophy	1 (3.7%)	0 (0.0%)	.33	1 (2.6%)	0 (0.0%)	.54	1 (3.6%)	0 (0.0%)	.35	1 (3.6%)	0 (0.0%)	.35
Nonspecific	3 (11.1%)	7 (28.0%)	.13	6 (15.8%)	4 (28.6%)	.30	6 (21.4%)	4 (16.7%)	.66	6 (21.4%)	4 (16.7%)	.66
Nonassessable	0 (0.0%)	3 (12.0%)	.08	2 (5.3%)	1 (7.1%)	.80	2 (7.1%)	1 (4.2%)	.65	2 (7.1%)	1 (4.2%)	.65
Number of AEDs[7]	2.48 ± 0.85	3.40 ± 1.12	.01	2.66 ± 0.91	3.64 ± 1.22	.01	2.89 ± 1.23	2.96 ± 0.91	.83	2.86 ± 1.18	3.00 ± 0.98	.64
Type of AEDs[7]												
Levetiracetam	12 (44.4%)	14 (56.0%)	.41	15 (39.5%)	11 (78.6%)	.01	18 (64.3%)	8 (33.3%)	.03	17 (60.7%)	9 (37.5%)	.10
Lacosamide	12 (44.4%)	14 (56.0%)	.41	16 (42.1%)	10 (71.4%)	.06	15 (53.6%)	11 (45.8%)	.58	17 (60.7%)	9 (37.5%)	.10
Carbamazepine	7 (25.9%)	10 (40.0%)	.28	11 (28.9%)	6 (42.9%)	.34	11 (39.3%)	6 (25.0%)	.27	10 (35.7%)	7 (29.2%)	.62
Eslicarbazepine acetate	8 (29.6%)	6 (24.0%)	.65	11 (28.9%)	3 (21.4%)	.59	7 (25.0%)	7 (29.2%)	.74	7 (25.0%)	7 (29.2%)	.74
Valproic acid	5 (18.5%)	5 (20.0%)	.89	6 (15.8%)	4 (28.6%)	.30	4 (14.3%)	6 (25.0%)	.33	4 (14.3%)	6 (25.0%)	.33
Lamotrigine	4 (14.8%)	8 (32.0%)	.14	8 (21.1%)	4 (28.6%)	.57	9 (32.1%)	3 (12.5%)	.09	6 (21.4%)	6 (25.0%)	.76
Perampanel	4 (14.8%)	6 (24.0%)	.40	7 (18.4%)	3 (21.4%)	.81	3 (10.7%)	7 (29.2%)	.09	5 (17.9%)	5 (20.8%)	.79
Clobazam	5 (18.5%)	3 (12.0%)	.51	5 (13.2%)	3 (21.4%)	.46	3 (10.7%)	5 (20.8%)	.31	3 (10.7%)	5 (20.8%)	.31
Zonisamide	3 (11.1%)	2 (8.0%)	.70	5 (13.2%)	0 (0.0%)	.15	1 (3.6%)	4 (16.7%)	.11	1 (3.6%)	4 (16.7%)	.11
Clonazepam	1 (3.7%)	4 (16.0%)	.13	4 (10.5%)	1 (7.1%)	.71	3 (10.7%)	2 (8.3%)	.77	2 (7.1%)	3 (12.5%)	.51
Oxcarbazepine	2 (7.4%)	2 (8.0%)	.94	3 (7.9%)	1 (7.1%)	.93	0 (0.0%)	4 (16.7%)	.03	1 (3.6%)	3 (12.5%)	.23
Phenobarbital	1 (3.7%)	2 (8.0%)	.51	3 (7.9%)	0 (0.0%)	.28	1 (3.6%)	2 (8.3%)	.46	2 (7.1%)	1 (4.2%)	.65
Topiramate	1 (3.7%)	1 (4.0%)	.96	0 (0.0%)	2 (14.3%)	.12	0 (0.0%)	2 (8.3%)	.12	0 (0.0%)	2 (8.3%)	.12
Phenytoin	1 (3.7%)	1 (4.0%)	.96	2 (5.3%)	0 (0.0%)	.38	0 (0.0%)	2 (8.3%)	.12	1 (3.6%)	1 (4.2%)	.91
Lorazepam	1 (3.7%)	1 (4.0%)	.94	1 (2.6%)	1 (7.1%)	.45	1 (3.6%)	1 (4.2%)	.91	1 (3.6%)	1 (4.2%)	.91
Diazepam	1 (3.7%)	1 (4.0%)	.94	2 (5.3%)	0 (0.0%)	.38	0 (0.0%)	2 (8.3%)	.12	0 (0.0%)	2 (8.3%)	.12
Pregabalin	0 (0.0%)	2 (8.0%)	.13	2 (5.3%)	0 (0.0%)	.38	2 (7.1%)	0 (0.0%)	.18	1 (3.6%)	1 (4.2%)	.91
Alprazolam	0 (0.0%)	1 (4.0%)	.33	0 (0.0%)	1 (7.1%)	.10	1 (3.6%)	1 (4.2%)	.35	1 (3.6%)	1 (4.2%)	.35
Total DDD[8]	2.71 ± 1.16	3.45 ± 1.35	.04	2.75 ± 1.17	3.91 ± 1.27	.01	2.87 ± 1.37	3.29 ± 1.19	.24	2.84 ± 1.30	3.32 ± 1.27	.19
Seizures per month	26.88 ± 60.27	21.71 ± 38.24	.72	13.67 ± 26.53	53.50 ± 82.10	.10	28.62 ± 64.25	19.47 ± 27.47	.52	29.50 ± 64.13	18.44 ± 27.40	.44
Seizure type												
SPS[9]	3 (11.1%)	1 (4.0%)	.34	3 (7.9%)	1 (7.1%)	.93	3 (10.7%)	1 (4.2%)	.38	4 (14.3%)	0 (0.0%)	.06
CPS[10]	8 (29.6%)	13 (52.0%)	.11	16 (42.1%)	5 (35.7%)	.68	13 (46.4%)	8 (33.3%)	.34	13 (46.4%)	8 (33.3%)	.34
SPS[9] + CPS[10]	6 (22.2%)	6 (24.0%)	.88	8 (21.1%)	4 (28.6%)	.57	5 (17.9%)	7 (29.2%)	.34	5 (17.9%)	7 (29.2%)	.34
CPS[10] + GCTS[11]	8 (29.6%)	3 (12.0%)	.12	8 (21.1%)	3 (21.4%)	.98	5 (17.9%)	6 (25.0%)	.53	5 (17.9%)	6 (25.0%)	.53
SPS[9] + CPS[10] + GCTS[11]	2 (7.4%)	2 (8.0%)	.94	3 (7.9%)	1 (7.1%)	.93	2 (7.1%)	2 (8.3%)	.87	1 (3.6%)	3 (12.5%)	.23

Note. [1]TLE: temporal lobe epilepsy, [2]ETLE: extratemporal lobe epilepsy, [3]LH: left-hemisphere, [4]RH: right-hemisphere, [5]HS: hippocampal sclerosis, [6]FCD: focal cortical dysplasia, [7]AEDs: antiepileptic drugs; [8]DDD: defined daily dose; [9]SPS: simple partial seizure, [10]CPS: complex partial seizure, [11]GTCS: secondarily generalized seizures.

The Spanish version [29] of the Beck Depression Inventory-II (BDI-II) [30] was used to assess depression by means of 21 items rated on a four-point scale. Cutting scores for different depression levels were as follows: 0–13 for minimum depression; 14–19 for mild depression; 20–28 for moderate depression; and 29–63 for severe depression [30]. As variations in the cutting scores are frequent in research with this instrument and that this could complicate comparison between studies [31], we used the total score as an indicator of depression level, but not the classification of depression levels. Cronbach's alpha of the Spanish adaptation is 0.89 [29].

2.5. Statistical analyses

The Kolmogorov–Smirnov test was carried out to examine data normality. The result showed that the distribution of cortisol raw data was not normal, and a logarithmic transformation was performed for this variable. In addition, of the 468 data for cortisol (nine samples × 52 individuals), 4 data were missing, due to insufficient volume of saliva sample for determinations. It supposes a percentage of less of 1% of missing data. These 4 data were estimated using the full information maximum likelihood (FIML) estimation method, which retains cases

that are missing in survey waves and avoids the biased parameter estimates that can occur with pairwise or listwise deletion, according to Schafer and Graham [32].

Patients were distributed into groups based on memory competence. Age-adjusted percentile scores one standard deviation below the mean (percentile scores lower than 16) were classified as "low competence", while those higher than one standard deviation below the mean (percentile scores higher than 16) were classified as "high competence". This criterion was in accordance with previous studies using WMS-III that suggest that a one standard deviation cutoff yields the most balanced levels of sensitivity and specificity to establish criteria for cognitive impairment [33]. Patients were distributed into two groups based on immediate memory (auditory and visual) competence ($p = .0001$): group 1 with high immediate memory scores (mean = 49.03, SD = 25.73) (13 patients with LH focus and 15 patients with right-hemisphere (RH) focus); and group 2 with low immediate memory scores (mean = 5.52, SD = 4.00) (14 patients with LH focus and 10 patients with RH focus). Patients were also distributed into two groups based on delayed memory (auditory and visual) competence ($p = .0001$): group 1 with high delayed memory scores (13 patients with LH focus and 15 patients with RH focus); and group 2 with low delayed memory scores (14 patients with LH focus and 10 patients with RH focus). All but four of the patients had the same level of memory competence (low or high) in the immediate and delayed indices.

For between-group comparisons based on the side of seizure focus, epilepsy type, and profiles of memory competence, the chi-square test was used to study the differences between frequencies in categorical variables. We employed *t*-tests for independent samples in descriptive variables, as well in trait anxiety, depression, and memory variables. A repeated measures analysis of variance (ANOVA) was carried out for state anxiety. When significant differences in these variables were found, they were included as covariates in further ANOVAs. These analyses were repeated in the subgroup of patients with TLE, including the presence of HS as the between-subject factor, and anxiety, depression, and memory scores as dependent variables.

The area under the curve (AUC) with respect to increase (AUC_i) and the AUC with respect to ground (AUC_g) were used to study the cortisol fluctuations with the trapezoid formula [34]. These two formulas can show different information inherent in the repeated measurements, simplifying the statistical analyses when the number of repeated measurements is high [34]. Thus, the AUC_i is a measure of the dynamic of the cortisol changes over the evaluation, more related to the sensitivity of the system, while the AUC_g is an estimate of the total cortisol secretion over the evaluation [34]. We also computed a cortisol percentile for each patient considering its mean value of cortisol and the normative reference values in the general population at similar hours [19]. Preliminarily, we performed *t*-tests for independent samples to analyze differences in cortisol levels, percentiles and AUCs between patients who were taking strong enzyme inducer drugs and the rest of the sample. Univariate ANOVAs were carried out to analyze differences in cortisol levels, percentiles, and AUCs among patients who were taking one enzyme inducer drug, more than one, and none.

To test the impact of the side of seizure focus, epilepsy type, and memory competence on cortisol levels, we carried out repeated measures ANOVAs with "side of seizure focus", "epilepsy type", and "memory competence" (immediate or delayed) as the between-subject factors; the "moment" (C2 to C9) as the within-subject factor; and initial cortisol levels (C1) and age as covariate variables. Although no registration of seizures close to the neuropsychological assessment was available, their potential impact on cortisol levels was controlled since C1 was used as a covariate, and C2 was measured more than 45 min after the beginning of the evaluation. To facilitate data interpretation, the values of cortisol in the figures and tables represent raw values and not logarithmic-transformed values. The age was covariate since various studies have found age differences in cortisol levels [11, 35]. Univariate ANOVAs were carried out to investigate the impact of the "side of seizure focus", "epilepsy type" and "memory competence" (immediate or delayed) on the cortisol AUC_i and AUC_g, considering age as a covariate variable, and on cortisol percentiles. These ANOVAs were repeated in the subgroup of patients with TLE, including the presence of HS as a between-subject factor. Greenhouse–Geisser adjustments of the degree of freedom were applied where appropriate. When a factor was significant in repeated measures ANOVAs, Bonferroni tests were performed.

Relationships between variables were calculated using Pearson or Spearman correlations where appropriate.

To evaluate the role of the cortisol AUC_i and the trait anxiety as predictors of memory performance, controlling seizure frequency and epilepsy type, hierarchical regressions were carried out in the total sample and in groups with LH and RH focus. Immediate and delayed memory percentile scores were included as dependent variables in the regression analyses. We sequentially entered three separate blocks of independent variables. Block 1 included the seizure frequency and epilepsy type. Block 2 was comprised of cortisol AUC_i. Block 3 included trait anxiety. After the entry of each block, we evaluated the adjusted R^2 change to determine the proportion of variance explained.

All cortisol analyses were repeated excluding two patients who suffered a seizure during neuropsychological evaluation.

Statistical analyses were carried out using SPSS 22.0, and two-tailed tests with p set to .05 were considered as significant.

3. Results

3.1. Preliminary analyses

The sample was composed of 52 adults with drug-resistant epilepsy (mean age = 38.98, SD = 10.25; mean epilepsy duration (years) = 23.19, SD = 14.91). Demographic and clinical characteristics of groups depending on the side of seizure focus, epilepsy type, and memory competence are shown in Table 1. Patients with LH focus significantly consumed fewer AEDs and had a lower total DDD than patients with RH focus. Patients with TLE consumed fewer AEDs, and less frequently levetiracetam, had lower DDD, and more frequently had HS than those with extratemporal epilepsy (ETLE). Patients with high immediate memory consumed more frequently levetiracetam and less frequently oxcarbazepine than those with low immediate memory. These variables were controlled in further analyses. No other differences were found in demographic and clinical variables.

No differences were found in memory indices, anxiety, or depression scores between patients with LH focus and RH focus neither between patients with TLE and ETLE (Table 2). In the group of patients with TLE, those with HS had lower scores in most of the memory indices, including immediate and delayed memory, immediate and delayed auditory memory, immediate visual memory, and single-trial auditory learning ($t(36) = -2.85$, $p = .007$; $t(36) = -2.81$, $p = .008$; $t(36) = -2.23$, $p = .03$; $t(36) = -2.81$, $p = .009$; $t(36) = -2.66$, $p = .012$; and $t(36) = -2.21$, $p = .034$, respectively) in respect to patients without HS. No differences in anxiety or depression scores were found between patients with HS and those without HS. As expected, patients with high memory competence (immediate and delayed) had better memory performance than those with low memory competence. These groups also differed in trait anxiety, patients with high memory competence having lower trait anxiety than those with low memory competence (for immediate memory groups: $p = .05$; for delayed memory groups: $p = .0001$) (Table 2), so this variable was controlled in further analyses.

In the total sample, the mean values of cortisol were compared with the normative reference values for cortisol in the general population [19] — 9.6% of the sample having cortisol levels located in the 50–59th percentile, 7.7% in the 60–69th percentile, 15.4% in the 70–79th, 9.6% in the 80–89th percentile, and 57.7% in the 90–99th percentile. In the

Table 2
Memory (percentile scores), and anxiety and depression (direct scores) in groups based on the side of seizure focus, epilepsy type and memory competence (mean ± SD).

Scores	Side of seizure focus			Epilepsy type			Immediate memory competence			Delayed memory competence		
	LH (n = 27)	RH (n = 25)	p	TLE (n = 38)	ETLE (n = 14)	p	High (n = 28)	Low (n = 24)	p	High (n = 28)	Low (n = 24)	p
WMS-III												
Immediate memory	27.79 ± 29.76	30.20 ± 28.59	.77	30.24 ± 30.33	25.45 ± 25.49	.60	49.03 ± 25.73	5.52 ± 4.00	.0001	47.19 ± 27.94	7.67 ± 7.95	.0001
Immediate auditory memory	30.61 ± 30.13	41.05 ± 32.23	.23	36.27 ± 31.89	33.89 ± 30.71	.81	55.97 ± 28.15	11.89 ± 12.23	.0001	55.82 ± 28.52	12.07 ± 11.90	.0001
Immediate visual memory	31.06 ± 27.09	27.21 ± 25.98	.60	31.84 ± 28.02	22.04 ± 20.47	.18	46.21 ± 24.28	9.37 ± 9.35	.0001	42.55 ± 25.93	13.63 ± 16.81	.0001
Delayed memory	29.18 ± 28.44	33.20 ± 31.81	.50	31.67 ± 31.79	29.59 ± 24.96	.83	48.44 ± 30.27	10.90 ± 10.60	.0001	51.69 ± 26.68	7.10 ± 5.14	.0001
Delayed auditory memory	32.64 ± 30.86	40.72 ± 31.05	.09	39.63 ± 33.95	40.44 ± 27.57	.93	58.91 ± 29.24	17.61 ± 17.93	.0001	60.60 ± 28.26	15.64 ± 14.52	.0001
Delayed visual memory	34.08 ± 29.00	29.67 ± 28.75	.58	33.86 ± 29.91	26.80 ± 25.34	.44	47.40 ± 28.35	13.94 ± 15.86	.0001	49.74 ± 26.86	11.22 ± 11.96	.0001
Delayed auditory recognition	35.00 ± 30.04	40.72 ± 31.05	.50	37.13 ± 31.27	39.42 ± 28.81	.81	48.30 ± 32.39	25.44 ± 22.80	.006	52.85 ± 27.99	20.13 ± 22.88	.0001
Single-trial auditory learning	40.93 ± 27.21	42.08 ± 26.68	.88	39.63 ± 27.05	46.50 ± 26.01	.42	55.75 ± 25.19	24.83 ± 17.26	.0001	56.04 ± 25.05	24.50 ± 16.88	.0001
Auditory learning slope	48.48 ± 33.33	59.36 ± 25.84	.20	51.16 ± 32.00	60.64 ± 24.26	.38	60.46 ± 29.15	45.83 ± 30.03	.08	60.89 ± 27.51	45.33 ± 31.55	.06
Auditory retention	40.78 ± 31.95	52.80 ± 31.30	.18	46.76 ± 33.98	46.00 ± 26.61	.94	55.50 ± 31.51	36.13 ± 29.68	.03	62.82 ± 29.53	27.58 ± 23.15	.0001
Auditory retrieval	46.44 ± 31.28	40.48 ± 33.80	.51	45.50 ± 31.29	38.36 ± 35.70	.32	40.25 ± 33.39	47.46 ± 31.31	.43	46.11 ± 32.67	40.63 ± 32.38	.56
STAI												
Trait anxiety	24.81 ± 11.81	25.64 ± 11.15	.80	25.87 ± 11.83	23.43 ± 10.32	.50	22.36 ± 10.96	28.54 ± 11.20	.05	19.89 ± 10.26	31.42 ± 9.48	.0001
State anxiety pre-	19.96 ± 9.80	22.40 ± 10.41	.43	21.80 ± 10.17	19.50 ± 9.93	.49	22.63 ± 10.95	18.59 ± 8.08	.20	21.28 ± 10.76	20.79 ± 9.28	.88
State anxiety post-	20.13 ± 8.49	19.55 ± 11.86	.85	20.53 ± 10.74	18.43 ± 8.53	.52	21.07 ± 10.94	17.94 ± 8.36	.32	20.24 ± 9.43	19.37 ± 11.04	.78
State anxiety differences	0.17 ± 7.63	−2.85 ± 10.28	.27	−1.27 ± 9.30	−1.07 ± 8.47	.95	−1.56 ± 9.42	−0.65 ± 8.40	.75	−1.04 ± 9.03	−1.42 ± 9.08	.89
BDI-II												
Depression	11.74 ± 7.96	11.40 ± 6.53	.87	11.37 ± 6.74	12.14 ± 8.71	.74	12.11 ± 7.74	10.96 ± 6.73	.58	10.54 ± 7.19	12.79 ± 7.26	.27

51.9% of the sample, cortisol levels were located above the 95th percentile of cortisol levels for the general population. Cortisol levels, percentiles, and AUCs were not related to seizure frequency in the total sample, although a positive association between seizure frequency and cortisol levels was found in patients with both partial and secondarily generalized seizures ($r(15) = 0.54$, $p = .037$, $r(15) = 0.48$, $p = .07$, $r(15) = 0.49$, $p = .06$, $r(15) = 0.53$, $p = .04$, and $r(15) = 0.48$, $p = .07$, for C4, C5, C6, C7 and C8, respectively). Seizure frequency was also marginally related to AUC_g in these patients ($r(15) = 0.47$, $p = .08$). Additionally, cortisol levels, percentiles, and AUCs were not related to the number of AEDs, the total DDD (for all, $p > .06$), nor the total dose of strong enzyme inducer drugs (such as carbamazepine, phenytoin, phenobarbital, or primidone) in the total sample. No differences in cortisol levels, percentiles, or AUCs were found between patients who were taking strong enzyme inducer drugs (n = 19) and the rest of the sample (n = 33) neither among patients who were taking one enzyme inducer drug (n = 12), more than one (n = 7), and none (n = 33).

Considering the side of the seizure focus, cortisol AUC_g was positively related to seizure frequency in the group with RH focus ($r(25) = 0.47$, $p = .018$), but not in the patients with LH focus. No other significant relationships for the side of seizure focus, epilepsy type, or memory competence groups were found between cortisol and descriptive or clinical variables.

3.2. Profiles of memory performance: cortisol, side of seizure focus, and epilepsy type

A significant effect of the "moment * side of seizure focus * immediate memory competence" interaction on cortisol levels was found (Table 3). Specifically, in the group of patients with LH focus, those with low immediate memory scores had higher cortisol levels at C4, C5, C7, and C8 (for all, $p < .05$) (Fig. 1A). In the group of patients with RH focus, there were no differences in cortisol levels that depended on immediate memory scores (Fig. 1B).

The interaction "moment * side of seizure focus * delayed memory competence" on cortisol levels was also significant (Table 3). Specifically, in the group of patients with LH focus, those with low delayed memory scores had higher cortisol levels at C7 ($p = .008$) (Fig. 1C). In the group of patients with RH focus, there were no differences in cortisol levels that depended on delayed memory scores (Fig. 1D).

Additionally, significant effects of "immediate memory competence" and "delayed memory competence" on cortisol AUC_i were found (Table 3). Patients with low immediate and delayed memory scores had higher cortisol AUC_i independently of the side of seizure focus or the epilepsy type (see Fig. 2).

All these effects remained significant even when the two patients who suffered a seizure during the evaluation were excluded, and when variables in which there were significant differences between groups based on the side of seizure focus, epilepsy type, and memory competence (number of AEDs, DDD, consumption of levetiracetam, consumption of oxcarbazepine, and trait anxiety) were covariated.

Patients with LH and RH focus presented similar levels of cortisol and AUCs. Additionally, no significant effects of epilepsy type or HS were found in these variables. No significant effects were found on cortisol percentiles.

3.3. Predictors of memory performance

In the total sample, the cortisol AUC_i was negatively related to immediate and delayed memory ($r(52) = -0.27$, $p = .04$ and $r(52) = -0.22$, $p = .05$, respectively). The cortisol AUC_i was also negatively related to specific memory indices such as immediate and delayed auditory memory ($r(52) = -0.29$, $p = .036$ and $r(52) = -0.30$, $p = .031$, respectively). Cortisol percentiles were negatively associated with auditory retrieval ($r(52) = -0.29$, $p = .036$). Additionally, trait anxiety was negatively related to most of the memory indices, including immediate and delayed memory, immediate and delayed auditory and visual memory, single-trial auditory learning, and auditory learning slope ($r(52) = -0.48$, $p = .0001$; $r(52) = -0.50$, $p = .0001$; $r(52) = -0.40$, $p = .003$; $r(52) = -0.40$, $p = .003$; $r(52) = -0.41$, $p = .002$; $r(52) = -0.48$, $p = .0001$; $r(52) = -0.40$, $p = .004$; and $r(52) = -0.32$, $p = .019$, respectively).

Table 3
Cortisol levels (nmol/L) and cortisol AUCs (arbitrary units) in groups based on side of seizure focus and memory competence (mean ± SD).

Cortisol	Side[1]	Immediate memory competence		Delayed memory competence		Total	Statistics
		High	Low	High	Low		
C1	LH[2]	4.86 ± 2.96	2.62 ± 1.88	4.84 ± 2.98	2.63 ± 1.87	3.70 ± 2.67	M[6]: $F(4.3, 42) = 1.76$, $p = .13$, $n^2_p = 0.04$
	RH[3]	4.37 ± 1.94	3.04 ± 2.22	3.90 ± 2.11	3.75 ± 2.24	3.84 ± 2.12	M × S[7]: $F(4.3, 42) = 0.80$, $p = .54$, $n^2_p = 0.02$
	Total	4.60 ± 2.43	2.78 ± 1.99	4.34 ± 2.55	3.10 ± 2.06	3.76 ± 2.40	M × IM[8]: $F(4.3, 42) = 0.53$, $p = .73$, $n^2_p = 0.01$
C2	LH[2]	5.18 ± 4.40	2.94 ± 2.61	5.25 ± 4.32	2.87 ± 2.66	4.01 ± 3.69	M × DM[9]: $F(4.5, 42) = 0.51$, $p = .74$, $n^2_p = 0.01$
	RH[3]	4.17 ± 2.24	3.11 ± 1.97	3.63 ± 2.44	3.92 ± 1.78	3.75 ± 2.16	M × S × IM[10]: $F(4.3, 42) = 3.30$, $p = .01^*$, $n^2_p = 0.07$
	Total	4.64 ± 3.38	3.01 ± 2.32	4.38 ± 3.47	3.31 ± 2.35	3.88 ± 3.03	M × S × DM[11]: $F(4.5, 42) = 3.55$, $p = .006^*$, $n^2_p = 0.08$
C3	LH[2]	4.45 ± 3.46	3.22 ± 3.79	4.52 ± 3.39	3.16 ± 3.82	3.81 ± 3.62	S[12]: $F(1, 42) = 0.09$, $p = .77$, $n^2_p = 0.01$
	RH[3]	4.00 ± 2.10	3.65 ± 2.96	3.71 ± 2.26	4.07 ± 2.77	3.86 ± 2.43	IM[13]: $F(1, 42) = 2.84$, $p = .10$, $n^2_p = 0.06$
	Total	4.21 ± 2.77	3.40 ± 3.40	4.09 ± 2.82	3.54 ± 3.39	3.83 ± 3.07	DM[14]: $F(1, 42) = 1.28$, $p = .26$, $n^2_p = 0.03$
C4	LH[2]	3.46 ± 2.62	3.51 ± 3.72	3.52 ± 2.56	3.45 ± 3.76	3.49 ± 3.18	
	RH[3]	3.87 ± 1.81	2.33 ± 1.66	3.51 ± 2.07	2.86 ± 1.57	3.25 ± 1.88	
	Total	3.68 ± 2.19	3.02 ± 3.04	3.52 ± 2.26	3.21 ± 3.01	3.37 ± 2.61	
C5	LH[2]	3.03 ± 2.17	3.33 ± 3.30	3.10 ± 2.09	3.26 ± 3.35	3.18 ± 2.76	
	RH[3]	3.35 ± 1.32	2.28 ± 1.53	3.06 ± 1.53	2.71 ± 1.44	2.92 ± 1.48	
	Total	3.20 ± 1.74	2.89 ± 2.71	3.08 ± 1.78	3.03 ± 2.69	3.06 ± 2.22	
C6	LH[2]	2.57 ± 1.70	2.59 ± 2.51	2.65 ± 1.64	2.52 ± 2.55	2.58 ± 2.12	
	RH[3]	2.73 ± 1.18	1.92 ± 1.14	2.54 ± 1.31	2.21 ± 1.07	2.41 ± 1.21	
	Total	2.66 ± 1.42	2.31 ± 2.05	2.59 ± 1.45	2.39 ± 2.04	2.50 ± 1.73	
C7	LH[2]	1.97 ± 1.41	2.38 ± 1.83	2.02 ± 1.37	2.33 ± 1.87	2.18 ± 1.62	
	RH[3]	2.11 ± 1.10	1.60 ± 0.94	1.96 ± 1.12	1.83 ± 0.98	1.91 ± 1.05	
	Total	2.04 ± 1.23	2.05 ± 1.55	1.99 ± 1.22	2.12 ± 1.55	2.05 ± 1.37	
C8	LH[2]	1.83 ± 1.00	2.15 ± 1.91	1.86 ± 0.96	2.11 ± 1.94	1.99 ± 1.52	
	RH[3]	1.87 ± 1.17	1.77 ± 1.48	1.74 ± 1.23	1.96 ± 1.40	1.83 ± 1.28	
	Total	1.85 ± 1.07	1.99 ± 1.72	1.80 ± 1.09	2.05 ± 1.70	1.91 ± 1.40	
C9	LH[2]	1.78 ± 1.06	1.78 ± 1.61	1.75 ± 1.09	1.81 ± 1.59	1.78 ± 1.35	
	RH[3]	1.79 ± 1.10	1.71 ± 0.93	1.68 ± 1.08	1.88 ± 0.96	1.76 ± 1.02	
	Total	1.79 ± 1.06	1.75 ± 1.34	1.71 ± 1.06	1.84 ± 1.34	1.77 ± 1.19	
AUC_i[4]	LH[2]	−471.34 ± 469.05	7.88 ± 488.44	−454.54 ± 477.90	−7.72 ± 496.38	−222.86 ± 529.50	S[12]: $F(1,51) = 0.20$, $p = .65$, $n^2_p = 0.01$
	RH[3]	−363.62 ± 287.10	−199.47 ± 292.76	−307.87 ± 272.16	−283.09 ± 340.96	−297.96 ± 294.89	IM[13]: $F(1,51) = 5.25$, $p = .027^*$, $n^2_p = 0.11$
	Total	−413.63 ± 378.83	−78.52 ± 423.42	−375.97 ± 381.40	−122.45 ± 1.34	−258.96 ± 430.45	DM[14]: $F(1,51) = 3.85$, $p = .05^*$, $n^2_p = 0.09$
							S × IM[15]: $F(1,51) = 1.16$, $p = .29$, $n^2_p = 0.03$
							S × DM[16]: $F(1,51) = 2.09$, $p = .16$, $n^2_p = 0.05$
AUC_g[5]	LH[2]	739.95 ± 454.75	657.59 ± 585.74	751.00 ± 442.60	647.33 ± 592.53	697.25 ± 518.41	S[12]: $F(1,51) = 0.01$, $p = .95$, $n^2_p = 0.01$
	RH[3]	725.34 ± 300.99	557.24 ± 342.40	662.73 ± 338.63	651.16 ± 313.90	658.10 ± 322.30	IM[13]: $F(1,51) = 5.58$, $p = .45$, $n^2_p = 0.01$
	Total	732.12 ± 372.74	615.78 ± 492.29	703.71 ± 385.40	648.93 ± 1.34	678.43 ± 431.60	DM[14]: $F(1,51) = 0.10$, $p = .75$, $n^2_p = 0.01$
							S × IM[15]: $F(1,51) = 0.16$, $p = .69$, $n^2_p = 0.01$
							S × DM[16]: $F(1,51) = 0.02$, $p = .88$, $n^2_p = 0.01$

Note. [1]Side: side of seizure focus, [2]LH: left-hemisphere, [3]RH: right-hemisphere, [4]AUC_i: area under the curve with respect to increase, [5]AUC_g: area under the curve with respect to ground, [6]M: moment effect, [7]M × S: moment * side of seizure focus interaction, [8]M × IM: moment * immediate memory competence interaction, [9]M × DM: moment * delayed memory competence interaction, [10]M × S × IM: moment * side of seizure focus * immediate memory competence interaction, [11]M × S × DM: moment * side of seizure focus * delayed memory competence interaction, [12]S: side of seizure focus effect, [13]IM: immediate memory competence effect, [14]DM: delayed memory competence effect, [15]S × IM: side of seizure focus * immediate memory competence interaction, [16]S × DM: side of seizure focus * delayed memory competence interaction, *: significant.

When correlations were examined in groups with LH and RH focus, these patterns of relationships were mainly found in the group with LH focus. In this group, immediate and delayed memory, immediate and delayed auditory memory, immediate visual memory, and auditory retention were negatively associated with the cortisol AUC_i ($r(27) = -0.39$, $p = .045$; $r(27) = -0.37$, $p = .05$; $r(27) = -0.39$, $p = .045$; $r(27) = -0.46$, $p = .016$; $r(27) = -0.41$, $p = .035$; $r(27) = -0.42$, $p = .03$, respectively), while immediate and delayed memory, immediate and delayed auditory and visual memory, single-trial auditory learning, and auditory learning slope were negatively related to trait anxiety ($r(27) = -0.53$, $p = .003$; $r(27) = -0.53$, $p = .005$; $r(27) = -0.47$, $p = .014$; $r(27) = -0.46$, $p = .017$; $r(27) = -0.55$, $p = .003$; $r(27) = -0.51$, $p = .006$; $r(27) = -0.49$, $p = .01$; and $r(27) = -0.42$, $p = .03$, respectively). In patients with RH focus, we only found that trait anxiety was negatively related to immediate and delayed memory, and delayed visual memory ($r(25) = -0.32$, $p = .03$; $r(25) = -0.49$, $p = .013$; $r(25) = -0.43$, $p = .03$, respectively).

No significant associations of cortisol AUCs or percentiles with trait anxiety, state anxiety, and depression were found in the total sample neither in the group of patients with LH focus nor in the group of patients with RH focus (for all, $p > .07$).

Because of the complexity of these relationships, hierarchical regressions were carried out to examine reliable predictors of memory performance in the total sample and in both groups of patients. The results of the hierarchical regressions with memory performance as dependent variables, controlling seizure frequency and epilepsy type, are shown in Table 4.

In the total sample, higher immediate memory scores were predicted by the lower cortisol AUC_i and lower trait anxiety. When groups based on the side of the seizure focus were considered separately, this model remained significant in the group of patients with LH focus, but not in the group of patients with RH focus.

However, higher delayed memory scores were only predicted by the lower trait anxiety in the total sample. This model remained significant in the group of patients with RH focus. In the group of patients with LH focus, both lower trait anxiety and lower cortisol AUC_i predicted higher delayed memory scores.

These regression models remained significant even when the two patients who suffered a seizure during the evaluation were excluded.

4. Discussion

The results of the current study indicate that patients with low immediate and delayed memory performance have higher cortisol levels and AUC_i — and levels, therefore, decline more slowly in the afternoon (independently of the side of seizure focus). Moreover, memory performance is negatively related to AUC_i and trait anxiety in the total sample. Even after controlling for seizure frequency and epilepsy type, lower cortisol AUC_i and lower trait anxiety are reliable predictors of higher immediate memory performance in the group of patients with LH focus,

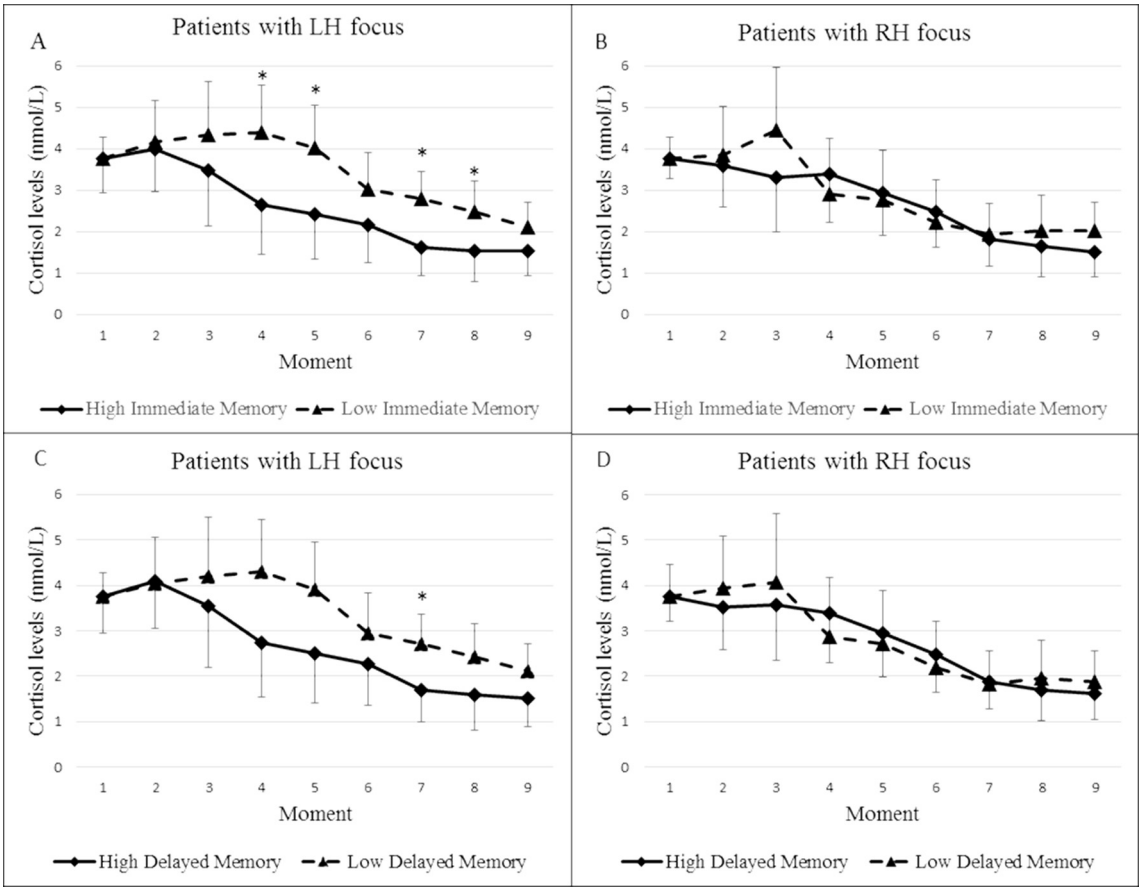

Fig. 1. Cortisol levels in groups based on side of seizure focus and memory competence. (A) Cortisol levels in patients with LH focus depending on immediate memory competence. (B) Cortisol levels in patients with RH focus depending on immediate memory competence. (C) Cortisol levels in patients with LH focus depending on delayed memory competence. (D) Cortisol levels in patients with RH focus depending on delayed memory competence. Note: error bars represent 95% confidence intervals.

although not in the patients with RH focus. Lower trait anxiety significantly predicted delayed memory performance in the total sample and in both groups of patients with LH and RH focus, while cortisol AUC_i was a significant predictor only in the group of patients with LH focus. Furthermore, no significant relationships of cortisol with anxiety and depression have been found in the sample studied.

Most demographic and clinical characteristics did not differ depending on the side of seizure focus or the epilepsy type. However, patients with RH focus had higher number of AED consumption and total DDD than those with LH focus, and patients with ETLE had more AED consumption (more frequently levetiracetam), higher DDD, and lower frequency of HS than those with TLE. It is worth noting that AEDs could modulate cortisol levels, especially strong enzyme inducer drugs [22,23], although the results are not homogeneous [36]. However, in our sample, there were no differences for cortisol levels between patients with LH and RH focus or between patients with TLE and patients with ETLE. In the subgroup of patients with TLE, those with HS had similar cortisol levels than those without HS. Additionally, cortisol levels were not related to the number of AEDs nor the total DDD or type of AED, and no differences in cortisol were found depending on the consumption of strong enzyme inducer drugs.

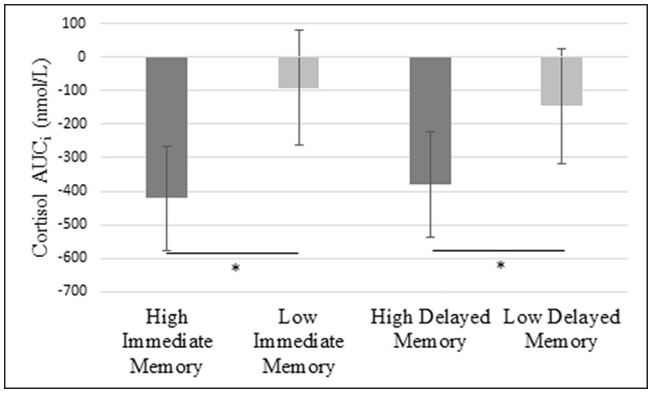

Fig. 2. Cortisol AUC_i in groups with high and low immediate memory and in groups with high and low delayed memory (independently of the side of seizure focus). Note: error bars represent 95% confidence intervals.

No differences in memory indices were found depending on the side of seizure focus or the epilepsy type. The material-specific model establishes that the left temporal lobe sustains verbal memories, while the right temporal lobe sustains nonverbal memories [37]. However, chronic epilepsy could imply an additional indirect impairment of functional compensation in nonepileptic areas, producing progressive cognitive deterioration in people with drug-resistant epilepsy [38]. Patients in the present study have suffered epilepsy for a mean of 23.19 years, and this could explain the scarce differences found in cognitive profile between patients with LH and RH focus or between those with TLE and ETLE. However, in the subgroup of patients with TLE, those with HS were more likely to have lower memory scores than those without HS, according to previous studies [39]. Mesial TLE with HS is a severe focal epilepsy type associated with a high degree of pharmacoresistance [40], more closely associated with cortical function disturbances than other focal epilepsy syndromes [41].

Patients did not differ in anxiety and depression scores depending on the side of seizure focus or the epilepsy type in contrast to previous studies that suggested that LH lesions [42] and temporal focus [42,43] are related to higher susceptibility to anxiety and depression. Surprisingly,

Table 4
Hierarchical regression analyses investigating the effect of the cortisol AUC_i and the trait anxiety on memory performance in the total sample and in patients with LH and RH focus.

	Total sample					
	Std β	Lower limit[1]	Upper limit[1]	Δ R^2	R^2	*F*
Immediate memory						
Block 1				0.01		
Seizure frequency	−0.01	−0.16	0.15			
Epilepsy type	−0.11	−24.27	10.15			
Block 2				0.08*		
Cortisol AUC_i^1	−0.25*	−0.03	0.00			
Block 3				0.22***	0.31	5.25**
Trait anxiety	−0.48***	−1.87	−0.58			
Delayed memory						
Block 1				0.01		
Seizure frequency	0.17	−0.06	0.26			
Epilepsy type	−0.14	−26.80	8.44			
Block 2				0.05		
Cortisol AUC_i^1	−0.17	−0.03	0.01			
Block 3				0.27***	0.32	5.53**
Trait anxiety	−0.54***	−2.07	−0.76			
	Patients with LH focus					
	Std β	Lower limit[1]	Upper limit[1]	Δ R^2	R^2	*F*
Immediate memory						
Block 1				0.04		
Seizure frequency	−0.10	−0.25	0.16			
Epilepsy type	0.01	−24.96	26.63			
Block 2				0.19*		
Cortisol AUC_i^1	−0.42*	−0.04	−0.01			
Block 3				0.22*	0.45	4.54*
Trait anxiety	−0.52*	−2.20	−0.40			
Delayed memory						
Block 1				0.03		
Seizure frequency	0.20	−0.09	0.29			
Epilepsy type	0.03	−22.02	26.39			
Block 2				0.14		
Cortisol AUC_i^1	−0.36*	−0.04	−0.01			
Block 3				0.30*	0.47	4.92*
Trait anxiety	−0.60*	−2.28	−0.59			
	Patients with RH focus					
	Std β	Lower limit[1]	Upper limit[1]	Δ R^2	R^2	*F*
Immediate memory						
Block 1				0.03		
Seizure frequency	0.07	−0.26	0.36			
Epilepsy type	−0.23	−40.58	11.85			
Block 2				0.01		
Cortisol AUC_i^1	0.06	−0.04	0.05			
Block 3				0.20*	0.24	1.57
Trait anxiety	−0.47*	−2.27	−0.12			
Delayed memory						
Block 1				0.01		
Seizure frequency	0.03	−0.30	0.35			
Epilepsy type	−0.30	−48.14	5.87			
Block 2				0.01		
Cortisol AUC_i^1	0.18	−0.02	0.06			
Block 3				0.29*	0.35	2.66*
Trait anxiety	−0.56*	−2.69	−0.48			

Note. [1]AUC_i: area under the curve with respect to increase, *, $p < .05$; **, $p < .001$; ***, $p < .0001$; (t), $p = .06$; [1]95% C.I. = confidence intervals.

in the total sample, anxiety and depression scores were not significantly related to the cortisol AUC or percentiles. Previous studies found a positive association between cortisol and depression scores [15,16], but also no relationship in people with epilepsy [17]. It should be noted that our sample had subclinical levels of depression (mean score of 11.58), and the score of 16 has been identified as the BDI cutoff point indicating levels of depression susceptible to psychological intervention [44]. This could explain the lack of significant associations between cortisol and depression scores in our study. Moreover, trait anxiety scores were not related to cortisol levels in contrast to the study of Busch et al. [17] with a single sample of midnight cortisol. In the present study, trait anxiety was not related to cortisol levels, although it was negatively related to most of the memory indices, according to previous studies with people with epilepsy [45–47].

Salivary cortisol levels were different depending on memory performance. Patients with low and high memory competence had similar demographic and clinical characteristics (except for the consumption of levetiracetam and oxcarbazepine that was more frequent in patients with high immediate memory). These groups differed in trait anxiety, patients with high memory competence having lower trait anxiety than those with low memory competence. Even after controlling for variables in which groups differed, patients with LH focus with low immediate and delayed memory performance showed higher rest cortisol levels, according to the results of Busch et al. [17]. Cortisol levels follow a 24-h circadian rhythm, in which cortisol concentrations present a morning circadian peak, and slowly declining levels in the late afternoon, evening, and night — the circadian trough [11,24]. Cortisol levels exhibited by over half of the sample of the present study during the afternoon were above the 95th percentile of normative reference levels for the general population at similar hours, according to the CIRCORT database [19]. It is not likely to attribute the hypercortisolism of the sample to recent seizures, since, although recent seizures can alter cortisol levels [48], the cortisol peak in most cases appears within 30 min of the onset of stress in healthy people [49], and this period of potential responsiveness was covariated.

High cortisol levels in the afternoon could be interpreted as an inability of the HPA axis to inhibit itself and could be maladaptive in cognitive terms in these patients. This possible explanation is supported by the fact that people with epilepsy have high rates of nonsuppression after the dexamethasone test [50]. In patients with RH focus, no differences in cortisol levels depending on memory performance were found. As far as we know, no studies have analyzed the potential role of the side of seizure focus in the relationship between cortisol and memory performance. However, patients with LH focus are at higher risk of an accelerated forgetting of declarative memory [20] and, although this reasoning remains speculative, this could be influenced by basal cortisol levels. Additionally, the lack of significant effects in patients with RH focus may be influenced by the lower sensitivity of the visual memory measures to the RH integrity (in respect to the verbal memory measures' sensitivity to the LH integrity), being frequently mediated by the verbalization of the information to be learned [51,52].

With regard to the epilepsy type and the HS, we found no effects of these factors in the relationship between cortisol and memory performance. The relative smaller size of the group with ETLE may have affected our ability to detect significant effects, so our findings should be interpreted with caution. To the best of our knowledge, the only study analyzing relationships between cortisol and memory in people with epilepsy only includes patients with TLE [17], limiting the establishment of conclusions about the impact of the epilepsy type. According to our findings, in Busch's study [17], patients with hippocampal atrophy performed worse in verbal memory tasks, independently of midnight cortisol.

Additionally, patients with low immediate and delayed memory scores had higher cortisol AUC_i, independently of the side of seizure focus and the epilepsy type. The AUC_i may be indicative of the ability of the HPA axis to descend in accordance with the daily circadian rhythm [34], and so patients with low memory scores had slower declining levels in the afternoon. Cortisol AUC_i is negatively related to scores in most memory indices. Accordingly, cortisol percentiles are negatively related to memory performance, but only to auditory retrieval. This lower sensitivity of the percentiles with respect to the AUC_i on memory performance could be due to the ceiling effect produced by the accumulation of the sample in the upper cortisol

percentiles. Despite these differences in the sensitivity of the measures employed, our findings are in line to previous studies that analyzed the associations between elevated cortisol and poor cognitive functions in healthy participants and predominantly found deficits in hippocampal-dependent cognitive domains [53,54]. This relationship is coherent with the considerations of the hippocampus as a region involved in episodic and declarative memory [55], rich in glucocorticoid receptors [56], and especially vulnerable to repeated stress [57].

People with drug-resistant epilepsy deal with repetitive, uncontrollable, and unpredictable seizures together with the usual stressors in daily life, and these stressors could imply a price in terms of health. McEwen [57] proposed the term "allostatic load" to refer to the price a person pays for being forced to adapt to daily life stressors. The allostatic load hypothesis links repeated exposure to environmental stressors with disease through wear of the neuroendocrine systems [57]. In the present study, higher seizure frequency has been related to higher cortisol levels, one of the final products of the stress response in patients with both partial and secondarily generalized seizures and in the group of patients with LH focus. This result suggests that certain characteristics of the patients could help to detect individuals with a high risk of presenting stress-related unbalanced states of health.

Controlling seizure frequency and epilepsy type, higher immediate memory performance was predicted by lower cortisol AUC_i and lower trait anxiety in the total sample. This result is mainly due to the patients with LH focus; since this group replicates the pattern of predictors, not found in the patients with RH focus. Regarding delayed memory performance, lower trait anxiety was a reliable predictor in the total sample and in both groups of patients with LH and RH focus, while cortisol AUC_i was a significant predictor only in the group of patients with LH focus. Considering our results, the exposure to psychosocial stressors may facilitate cognitive impairment via elevated cortisol levels [54], especially in patients with LH focus, who more frequently have memory deficits. Additionally, cognitive impairment could affect the family, social, and work environment, and have a global impact on the life of the individual, favoring in turn, higher cortisol levels and anxiety. It is worth noting the role of trait anxiety in cognitive impairments, considering that its scores are not clinical anxiety as evaluated in the present study. The results suggest, firstly, that cognitive and affective aspects are related and must be considered jointly from an integrative view of clinical evaluation; and, secondly, that trait anxiety could be a useful tool to early detect potential comorbidities in epilepsy.

Some limitations of our study should be considered. Firstly, although all the patients presented drug-resistant epilepsy, the group is heterogeneous in terms of the exact localization of the epileptic focus. Secondly, greater sample sizes could provide more information about groups, thereby ensuring statistical power. Thirdly, although we found no relationships between the AEDs (number, type, or total defined daily dose) and cortisol levels, patients were treated with AEDs polytherapy, and the AEDs combination was individualized for each patient. Finally, it should be noted that anxiety and depression scores are not clinical measures (since we considered anxiety as a trait, and depression was only measured once), and so this does not enable establishing a diagnostic criterion [31].

5. Conclusions

In summary, the data suggest a relationship indicating that exposure to elevated levels of cortisol in people with drug-resistant epilepsy who have an LH focus is related to worse memory performance. Additionally, patients with poor memory performance have higher cortisol AUC_i and, consequently, slower declining cortisol levels in the afternoon than those with high memory performance. Considering that cortisol AUC may capture dysregulation in the HPA axis, it is possible that memory deficits in people with drug-resistant epilepsy may be influenced by exposure to chronic stress in this population. Despite the lack of a relationship between cortisol levels and anxiety and depression scores, poor memory performance is related to high trait anxiety that could contribute to individual differences in vulnerability to stress [58]. Further research is needed to clarify to which extent afternoon cortisol, with fewer fluctuations than morning cortisol, could be proposed as an indicator of high risk for memory deficits in people with epilepsy.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.yebeh.2018.12.022.

Declarations of interest

None.

Acknowledgments

This work was supported by the Spanish Ministry of Economy and Competitiveness and the European Regional Development Fund (MINECO/FEDER) [grant number PSI2015-66600-P, 2015]; the Generalitat Valenciana (Valencian Government) [grant number PROMETEOII/2015/020, 2015]; and the FPU Program of the Spanish Ministry of Science, Innovation and Universities [grant number FPU14/00471, 2014]. The authors are grateful to John Rawlins for the revision of English style and grammar.

References

[1] Helmstaedter C. Neuropsychological aspects of epilepsy surgery. Epilepsy Behav 2004;5:45–55. https://doi.org/10.1016/j.yebeh.2003.11.006.
[2] Vingerhoets G. Cognitive effects of seizures. Seizure 2006;15:221–6. https://doi.org/10.1016/j.seizure.2006.02.012.
[3] Helmstaedter C, Elger CE. Chronic temporal lobe epilepsy: a neurodevelopmental or progressively dementing disease? Brain 2009;132:2822–30. https://doi.org/10.1093/brain/awp182.
[4] Kwon OY, Park SP. Depression and anxiety in people with epilepsy. J Clin Neurosci 2014;10:175–88. https://doi.org/10.3988/jcn.2014.10.3.175.
[5] Mensah SA, Beavis JM, Thapar AK, Kerr MP. A community study of the presence of anxiety disorder in people with epilepsy. Epilepsy Behav 2007;11:118–24. https://doi.org/10.1016/j.yebeh.2007.04.012.
[6] Park SP. Depression and anxiety in people with epilepsy: why should we identify? J Epileptology 2016;24:57–62. https://doi.org/10.1515/joepi-2016-0005.
[7] Hellhammer J, Fries E, Schweisthal OW, Schlotz W, Stone AA, Hagemann D. Several daily measurements are necessary to reliably assess the cortisol rise after awakening: state and trait components. Psychoneuroendocrinology 2007;32:80–6. https://doi.org/10.1016/j.psyneuen.2006.10.005.
[8] Adam EK, Kumari M. Assessing salivary cortisol in large-scale, epidemiological research. Psychoneuroendocrinology 2009;34:1423–36. https://doi.org/10.1016/j.psyneuen.2009.06.011.
[9] Almela M, Hidalgo V, Villada C, Espín L, Gómez-Amor J, Salvador A. The impact of cortisol reactivity on memory: gender differences in middle-aged persons. Stress 2011;14:117–27. https://doi.org/10.3109/10253890.2010.514671.
[10] Hidalgo V, Pulopulos MM, Puig-Perez S, Espin L, Gomez-Amor J, Salvador A. Acute stress affects free recall and recognition of pictures differently depending on age and sex. Behav Brain Res 2015;292:393–402.
[11] Lupien SJ, Fiocco A, Wan N, Maheu F, Lord C, Schramek T, et al. Stress hormones and human memory function across the lifespan. Psychoneuroendocrinology 2005;30:225–42. https://doi.org/10.1016/j.psyneuen.2004.08.003.
[12] Campbell S, Marriott M, Nahmias C, MacQueen GM. Lower hippocampal volume in patients suffering from depression: a meta-analysis. Am J Psychiatry 2004;161:598–607. https://doi.org/10.1176/appi.ajp.161.4.598.
[13] Wingenfeld K, Wolf OT. HPA axis alterations in mental disorders: impact on memory and its relevance for therapeutic interventions. CNS Neurosci Ther 2011;17:714–22. https://doi.org/10.1111/j.1755-5949.2010.00207.x.
[14] Lupien SJ, McEwen BS, Gunnar MR, Heim C. Effects of stress throughout the lifespan on the brain, behaviour and cognition. Nat Rev Neurosci 2009;10:434. https://doi.org/10.1038/nrn2639.
[15] Devinsky O, Emoto S, Porter RJ, Theodore WH, Nadi NS. Cerebrospinal fluid biochemical correlates of behavior in partial epilepsy. J Epilepsy 1991;4:81–5. https://doi.org/10.1016/S0896-6974(05)80065-9.
[16] Afifi S, Fadel W, Morad H, Eldod A, Gad E, Arfken CL, et al. Neuroendocrinal study of depression in male epileptic patients. J Neuropsychiatry Clin Neurosci 2011;23:163–7. https://doi.org/10.1176/appi.neuropsych.23.2.163.
[17] Busch RM, Frazier T, Chapin JS, Hamrahian AH, Diehl B, Alexopoulos A, et al. Role of cortisol in mood and memory in patients with intractable temporal lobe epilepsy. Neurology 2012;78:1064–8. https://doi.org/10.1212/WNL.0b013e31824e8efb.
[18] Gadea M, Gómez C, González-Bono E, Espert R, Salvador A. Increased cortisol and decreased right ear advantage (REA) in dichotic listening following a negative mood induction. Psychoneuroendocrinology 2005;30:129–38. https://doi.org/10.1016/j.psyneuen.2004.06.005.

[19] Miller R, Stalder T, Jarczok M, Almeida DM, Badrick E, Bartels M, et al. The CIRCORT database: reference ranges and seasonal changes in diurnal salivary cortisol derived from a meta-dataset comprised of 15 field studies. Psychoneuroendocrinology 2016; 73:16–23. https://doi.org/10.1016/j.psyneuen.2016.07.201.
[20] Jokeit H, Daamen M, Zang H, Janszky J, Ebner A. Seizures accelerate forgetting in patients with left-sided temporal lobe epilepsy. Neurology 2001;57:125–6. https://doi.org/10.1212/WNL.57.1.125.
[21] Von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP, et al. The strengthening the reporting of observational studies in epidemiology (STROBE) statement: guidelines for reporting observational studies. PLoS Med 2007;4:e296. https://doi.org/10.1371/journal.pmed.0040296.
[22] Johannessen SI, Landmark CJ. Antiepileptic drug interactions—principles and clinical implications. Curr Neuropharmacol 2010;8:254–67. https://doi.org/10.2174/157015910792246254.
[23] Putignano P, Kaltsas GA, Satta MA, Grossman AB. The effects of anti-convulsant drugs on adrenal function. Horm Metab Res 1998;30:389–97. https://doi.org/10.1055/s-2007-978903.
[24] Kirschbaum C, Hellhammer DH. Salivary cortisol in psychobiological research: an overview. Neuropsychobiology 1989;22:150–69. https://doi.org/10.1159/000118611.
[25] Pereña J, Seisdedos N, Corral S, Arribas D, Santamaria P, Sueiro M. The Wechsler memory scale. . 3rd ed.Madrid: TEA Ediciones; 2004.
[26] Wechsler D. Wechsler memory scale. . 3rd ed.San Antonio: The Psychological Corporation; 1997.
[27] Guillén-Riquelmeé A, Buela-Casal G. Actualización psicométrica y funcionamiento diferencial de los items en el State Trait Anxiety Inventory (STAI) [Psychometric revision and differential item functioning in the State Trait Anxiety Inventory (STAI)]. Psicothema 2011;23:510–5.
[28] Spielberger CD. State-trait anxiety inventory: a comprehensive bibliography. Palo Alto: Consulting Psychologists Press; 1989.
[29] Sanz J, García-Vera MP. The Beck Depression Inventory-second edition (BDI-II): factor congruence and generalizability of its indexes of internal consistency. In: Řehulka E, editor. School and health 21. General issues in health educationBrno: MSD; 2009. p. 331–42.
[30] Beck AT, Steer RA, Brown GK. Manual for the Beck Depression Inventory-II. San Antonio: Psychological Corporation; 1996.
[31] Kendall PC, Hollon SD, Beck AT, Hammen CL, Ingram RE. Issues and recommendations regarding use of the Beck depression inventory. Cognit Ther Res 1987;11: 289–99. https://doi.org/10.1007/BF01186280.
[32] Schafer JL, Graham JW. Missing data: our view of the state of the art. Psychol Methods 2002;7:147–77. https://doi.org/10.1037/1082-989X.7.2.147.
[33] Taylor MJ, Heaton RK. Sensitivity and specificity of WAIS–III/WMS–III demographically corrected factor scores in neuropsychological assessment. J Int Neuropsychol Soc 2001;7:867–74.
[34] Pruessner JC, Kirschbaum C, Meinlschmid G, Hellhammer DH. Two formulas for computation of the area under the curve represent measures of total hormone concentration versus time-dependent change. Psychoneuroendocrinology 2003; 28:916–31. https://doi.org/10.1016/S0306-4530(02)00108-7.
[35] Pulopulos MM, Hidalgo V, Puig-Pérez S, Salvador A. Psychophysiological response to social stressors: relevance of sex and age. Psicothema 2018;30:171–6. https://doi.org/10.7334/psicothema2017.200.
[36] Galimberti CA, Magri F, Copello F, Arbasino C, Cravello L, Casu M, et al. Seizure frequency and cortisol and dehydroepiandrosterone sulfate (DHEAS) levels in women with epilepsy receiving antiepileptic drug treatment. Epilepsia 2005;46: 517–23. https://doi.org/10.1111/j.0013-9580.2005.59704.x.
[37] Willment KC, Golby A. Hemispheric lateralization interrupted: material-specific memory deficits in temporal lobe epilepsy. Front Hum Neurosci 2013;7(546). https://doi.org/10.3389/fnhum.2013.00546.
[38] Elger CE, Helmstaedter C, Kurthen M. Chronic epilepsy and cognition. Lancet Neurol 2004;3:663–72. https://doi.org/10.1016/S1474-4422(04)00906-8.
[39] Miller LA, Muñoz DG, Finmore M. Hippocampal sclerosis and human memory. Arch Neurol 1993;50:391–4. https://doi.org/10.1001/archneur.1993.00540040051014.
[40] Wieser HG, ILAE Commission on Neurosurgery of Epilepsy. Mesial temporal lobe epilepsy with hippocampal sclerosis. Epilepsia 2004;45:695–714. https://doi.org/10.1111/j.0013-9580.2004.09004.x.
[41] Weber B, Wellmer J, Reuber M, Mormann F, Weis S, Urbach H, et al. Left hippocampal pathology is associated with atypical language lateralization in patients with focal epilepsy. Brain 2006;129:346–51. https://doi.org/10.1093/brain/awh694.
[42] Altshuler LL, Devinsky O, Post RM, Theodore W. Depression, anxiety, and temporal lobe epilepsy: laterality of focus and symptoms. J Neurol 1990;47:284–8. https://doi.org/10.1001/archneur.1990.00530030050016.
[43] Piazzini A, Canevini MP, Maggiori G, Canger R. Depression and anxiety in patients with epilepsy. Epilepsy Behav 2001;2:481–9. https://doi.org/10.1006/ebeh.2001.0247.
[44] Rohling ML, Green P, Allen LM, Iverson GL. Depressive symptoms and neurocognitive test scores in patients passing symptom validity tests. Arch Clin Neuropsychol 2002; 17:205–22. https://doi.org/10.1093/arclin/17.3.205.
[45] Helmstaedter C, Sonntag-Dillender M, Hoppe C, Elger CE. Depressed mood and memory impairment in temporal lobe epilepsy as a function of focus lateralization and localization. Epilepsy Behav 2004;5:696–701. https://doi.org/10.1016/j.yebeh.2004.06.008.
[46] Miller LA, Galioto R, Tremont G, Davis J, Bryant K, Roth J, et al. Cognitive impairment in older adults with epilepsy: characterization and risk factor analysis. Epilepsy Behav 2016;56:113–7. https://doi.org/10.1016/j.yebeh.2016.01.011.
[47] Paradiso S, Hermann BP, Blumer D, Davies K, Robinson RG. Impact of depressed mood on neuropsychological status in temporal lobe epilepsy. J Neurol Neurosurg Psychiatry 2001;70:180–5. https://doi.org/10.1136/jnnp.70.2.180.
[48] Bazil CW, Short D, Crispin D, Zheng W. Patients with intractable epilepsy have low melatonin, which increases following seizures. Neurology 2000;55:1746–8. https://doi.org/10.1212/WNL.55.11.1746.
[49] Kirschbaum C, Pirke KM, Hellhammer DH. The 'Trier social stress test'—a tool for investigating psychobiological stress responses in a laboratory setting. Neuropsychobiology 1993;28:76–81. https://doi.org/10.1159/000119004.
[50] Robertson MM, Coppen A, Trimble MR. The dexamethasone suppression test in medicated epileptic patients. Biol Psychiatry 1986;21:225–8. https://doi.org/10.1016/0006-3223(86)90152-6.
[51] Helmstaedter C, Pohl C, Elger CE. Relations between verbal and nonverbal memory performance: evidence of confounding effects particularly in patients with right temporal lobe epilepsy. Cortex 1995;31:345–55. https://doi.org/10.1016/S0010-9452(13)80367-X.
[52] Vaz SA. Nonverbal memory functioning following right anterior temporal lobectomy: a meta-analytic review. Seizure 2004;13:446–52. https://doi.org/10.1016/j.seizure.2003.12.004.
[53] Fonda SJ, Bertrand R, O'Donnell A, Longcope C, McKinlay JB. Age, hormones, and cognitive functioning among middle-aged and elderly men: cross-sectional evidence from the Massachusetts male aging study. J Gerontol A Biol Sci Med Sci 2005;60: 385–90. https://doi.org/10.1093/gerona/60.3.385.
[54] Lee BK, Glass TA, McAtee MJ, Wand GS, Bandeen-Roche K, Bolla KI, et al. Associations of salivary cortisol with cognitive function in the Baltimore memory study. Arch Gen Psychiatry 2007;64:810–8. https://doi.org/10.1001/archpsyc.64.7.810.
[55] Eichenbaum H, Otto T, Cohen NJ. The hippocampus—what does it do? Behav Neural Biol 1992;57:2–36. https://doi.org/10.1016/0163-1047(92)90724-I.
[56] McEwen BS, Sapolsky RM. Stress and cognitive function. Curr Opin Neurobiol 1995; 5:205–16. https://doi.org/10.1016/0959-4388(95)80028-X.
[57] McEwen BS. Protective and damaging effects of stress mediators. N Engl J Med 1998; 338:171–9. https://doi.org/10.1056/NEJM199801153380307.
[58] Weger M, Sandi C. High anxiety trait: a vulnerable phenotype for stress-induced depression. Neurosci Biobehav Rev 2018;87:27–37. https://doi.org/10.1016/j.neubiorev.2018.01.012.