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Research Paper

Development and validation of the Epilepsy Perceived Stress Inventory for Adults (EPSI-A): A pilot study

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ABSTRACT

Introduction: Stress is one of the most common trigger factors for epileptic seizures and is strongly related to clinical and emotional variables. Despite its influence in the course of the disease, there is an absence of instruments for measuring perceived stress in people with drug-resistant epilepsy. Therefore, this study develops and validates the Epilepsy Perceived Stress Inventory for Adults (EPSI-A), a self-report inventory in Spanish designed to quantify perceived chronic stress in this population.

Method: The sample consisted of 236 patients with drug-resistant epilepsy who underwent a neuropsychological assessment in which anxiety, depression, and quality of life were explored. In addition, from 125 patients in the sample, 9 measures of salivary cortisol were collected during the evaluation.

Results: The EPSI-A consisted of 15 items, with higher scores indicating higher perceived stress. The exploratory factor analysis showed a four-factor solution: *epilepsy concerns* (5 items); *impact on daily performance* (4 items); *social consequences* (3 items); and *epilepsy severity* (3 items). These factors explained 63.3 % of the total variance. Internal consistency reliability measured with McDonald's omega and Cronbach's alpha coefficients was satisfactory, with values $\geq$ 0.78 (except for epilepsy severity with values of 0.59 and 0.58, respectively). Construct validity was demonstrated by its correlation with several psychological scales and clinical variables.

Conclusions: The results showed that the EPSI-A is a reliable and valid tool for assessing perceived chronic stress in people with epilepsy. Its conciseness, rapid administration time, and specificity make it an appropriate instrument for this population.

1. Introduction

Epilepsy is a disease characterized by a predisposition and recurrence of seizures that comprehensively affect the individual [1]. About one-third of this population has drug-resistant epilepsy and, in these cases, antiseizure medications (ASMs) are ineffective for controlling seizures [2]. The repetition of seizures, as well as the lack of perceived control and predictability of their occurrence, suggests that drug-resistant epilepsy can be considered a potentially chronic stress state [3] with seizures as recurrent acute stressors [3,4].

A bidirectional relationship between stress and epilepsy has been proposed [3]. On the one hand, stress has a key role in epileptogenesis [4,5] and is implicated in an increased hyperexcitability of neural circuits that could lead to seizure generation [6,7]. Thus, as expected, perceived stress is considered one of the most common seizure precipitants [8], being positively associated with seizure frequency [9–11]. On the other hand, epilepsy and seizures can influence the activation of the hypothalamic–pituitary–adrenal (HPA) axis, which increases the

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production of cortisol as an outcome of stress response [7,12,13]. A systematic review pointed out that in 45% of the studies explored, people with epilepsy had higher basal cortisol levels than healthy people [3]. Nevertheless, some discrepancies were also found, probably due to methodological aspects, such as the variability and sample size, the different types of specimens used to collect cortisol, or the moment of the day in which cortisol was gathered [3,14].

Despite the relevance of this issue in epilepsy, there is a lack of measures designed to quantify perceived stress in these patients. As far as we know, only Snyder [15] provided a specific test to measure stress intensity, the Revised Epilepsy Stressor Inventory (ESI-R). However, this instrument was validated with only 25 subjects, and, to our knowledge, no factor analysis was performed, leaving the most relevant aspects of the perceived stress of people with epilepsy unclear. This could explain its scarce use in previous literature, as most studies have employed scales designed to assess perceived stress in the general population [11,16,17]. However, perceived stress in patients with epilepsy appears to differ from the general population, as the types of stressors they face can pose a threat to survival, with an increased risk of accidents and sudden death [18,19]. This is in line with the restrictive definition offered by Koolhaas et al. [20], which qualifies that stress should be limited to uncontrollable and unpredictable life-threatening experiences. Given that epilepsy is a chronic disease that impacts quality of life and considering its conceptualization within the framework of chronic stress [3], the development of a questionnaire to quantify the effects of epilepsy-related factors on persistent stress levels in this population is crucial. For these reasons, this study develops the Epilepsy Perceived Stress Inventory for Adults (EPSI-A), a self-report questionnaire designed in Spanish to measure perceived chronic stress in adult patients with drug-resistant epilepsy. The EPSI-A aims to capture the cumulative stress associated with living with epilepsy over the last 6 months, rather than moment-to-moment stress responses to acute stressors. The present study also validates the EPSI-A by examining its relationships with psychological and clinical variables, as well as with objective indicators of the HPA functioning (i.e., cortisol levels).

2. Materials and methods

2.1. Participants and data collection

Participants were recruited from the Refractory Epilepsy Unit of the Hospital Universitario y Politécnico La Fe (Valencia, Spain) between June 2015 and February 2024. The inclusion criteria were: a) patients with a diagnosis of drug-resistant epilepsy; b) a chronological age of at least 18 years; and c) a completed neuropsychological assessment. Excluded were patients who: a) were not fluent in Spanish; b) had a severe intellectual disability, in whom the assessment could not be carried out properly; and c) had a history of severe psychiatric conditions, as they could have scores on negative affect tests and hormone samples that may be unrepresentative of the study population.

2.2. Procedure

This is a cross-sectional study conducted following the Declaration of Helsinki and with the approval of the ethics committee of the hospital. This report followed the STROBE guidelines [21]. All participants provided written informed consent.

Demographic characteristics (i.e., age, sex, educational level, academic/employment insertion, and household members) and clinical data (i.e., epilepsy type, lateralization of seizure onset, age at epilepsy onset, epilepsy duration, magnetic resonance imaging (MRI) findings, number of previous failed ASMs, number of ASMs, seizures per month, and seizure type) were extracted from clinical charts. Epilepsy diagnosis was made by experienced epileptologists and based on available seizure semiology, electroencephalogram data, neuropsychological test results, as well as functional and structural imaging data [22]. Any disagreements were resolved by consensus after a thorough review.

A comprehensive neuropsychological assessment was carried out on all patients following the recommendations of the E-PILEPSY consortium [23]. From this evaluation, which lasted approximately three hours, anxiety, depression, and quality of life (QOL) tests were selected for the present study. Furthermore, nine saliva samples were collected to measure cortisol secretion. To minimize hormonal circadian variations and accurately analyze the cortisol decline in the evening [24,25], the evaluation session was carried out between 3:00 pm and 8:00 pm. During this assessment, saliva samples, labelled from C1 to C9, were collected approximately every 15 min, although this interval could vary depending on the patient's performance. Anxiety, depression, and QOL tests were performed between samples C8 and C9 at the end of the assessment session.

2.3. Instruments

2.3.1. Negative affectivity

The State-Trait Anxiety Inventory (STAI) [26] was used to explore anxiety. The trait anxiety scale (STAI-T) assesses relatively stable aspects of anxiety and consists of 20 items rated on a four-point scale ranging from 0 ('hardly ever') to 3 ('almost always'). Higher scores indicate higher anxiety. Cronbach's alpha of the Spanish adaptation of this inventory is 0.94 [27].

The Beck Depression Inventory-II (BDI-II) [28] was used to assess depression symptomatology, with 21 items rated on a four-point scale. Higher scores indicate higher depression levels. Cronbach's alpha of the Spanish adaptation is 0.89 [29].

2.3.2. QOL

QOL was examined using the Quality of Life in Epilepsy Inventory (QOLIE-31) [30], in its Spanish version [31]. This test includes 31 items distributed in seven scales: seizure worry; overall QOL; emotional well-being; energy; cognitive self-rating; medication effects; and social functioning. Scores for each subscale were obtained by converting the raw precoded numeric values of items to 0–100 scores, with higher scores indicating better QOL in all cases (with seizure worry and medication effects inversely scored). A QOL composite score was computed using a weighted average of the different subscales. Cronbach's alpha of the Spanish adaptation of this inventory was 0.92 [31].

2.4. Salivary cortisol

Saliva samples are a good method to measure stress and are widely used in previous literature, since cortisol levels remain stable at ambient temperature for one day and for one week at 4°C [32]. Salivettes (Sarstedt, Nümbrecht, Germany) were used to collect saliva samples. To guarantee correct use, participants were instructed to keep the cotton swab in their mouths for two minutes. Saliva samples were centrifuged at 3000 rpm for 15 min and obtaining in a clear supernatant with low viscosity that was kept at −80°C. Analyses were carried out in the Laboratory of Social Cognitive Neuroscience, Faculty of Psychology (Universitat de València). Salivary cortisol levels were quantified 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 inter-duplicate variation coefficient of 8%. The intra- and interassay variation coefficients were 1.47% and 7.9%, respectively. Cortisol levels were expressed in nmol/L.

Furthermore, to study the associations between repeated measures in cortisol levels, the area under the curve to ground (AUC_g), as well as increases (AUC_i), were computed [33]. These two formulas provide information on the variation in cortisol levels; the AUC_g indicates the total quantity of cortisol released during the assessment, while the AUC_i is a measure of the changes in cortisol levels during the assessment and is

more related to the sensitivity of the system [33].

2.5. Statistical analysis

Reliability analyses were carried out. Items with item-total correlations lower than 0.2 were eliminated one by one by deleting the item with the weakest correlation [34]. When all items had item-total correlations above 0.2, an exploratory factor analysis (EFA) was performed. Data from the EPSI-A was examined using the Kolmogorov-Smirnov test, with all items showing a non-normal distribution ($p < 0.0001$). Therefore, unweighted least squares were computed using an extraction method as no distributional assumptions are required [35]. Furthermore, theorizing that our factors would be correlated [36], an oblique rotation was used [37]. Barlett's sphericity test and the Kaiser-Meyer-Olkin (KMO) statistic were employed to assess the appropriateness of the data for the EFA. The number of factors was determined using the scree plot and Kaiser's rule, which requires eigenvalues greater than 1 [38]. For factor adequacy, considering the number of participants in the study, pattern coefficients equal to or greater than 0.34 were considered salient [39]. Items with pattern coefficients under this value were removed, and the remaining factors were included in another EFA. This procedure was repeated until all items showed satisfactory values. Cross-loaded items were then identified as items with loadings equal to or greater than 0.32 for more than one factor [40] and with differences between these loadings of less than 0.1 [41]. These items were removed until no cross-loading was detected. Furthermore, internal consistency was estimated for the responses of each factor, as well as for the test, with Cronbach's alpha and McDonald's omega coefficients (since the single use of Cronbach's alpha may underestimate the value of internal consistency in 5-point Likert scales) [42]. Finally, to explore convergent validity, Pearson correlations were performed to examine relationships between the factors identified in the EFA and tests that were considered to be related (i.e., STAI-T, BDI-II, and QOLIE-31), as well as clinical variables (such as seizure frequency, previous failed ASMs, number of ASMs, and age at epilepsy onset) and cortisol (such as samples, AUC_g and AUC_i). Multiple testing correction controlling the False Discovery Rate (FDR) was applied to these correlations [43]. The FDR was set to 0.10, which implies that the proportion of significant associations which are actually false discoveries is limited no $>$ 10%, as in other studies with this population [44].

All analyses were performed with IBM SPSS Statistics version 25.0, except McDonald's omega coefficient and its confidence intervals, which were calculated using Rstudio (https://www.r-project.org/, version 4.3.0).

3. Results

3.1. Characteristics of the total sample

The total sample consists of 236 patients (110 men and 126 women; mean age = 40.05, SD = 11.90). The mean epilepsy duration was 22.5 years (SD = 15.02), and the mean seizure frequency was 16.31 seizures per month (SD = 32.76). The mean of previous failed ASMs was 5.81 (SD = 3.40), and patients were taking a mean of 2.89 ASMs (SD = 0.97). No missing values were detected in any variable, except for cortisol, which was collected in 125 patients. The mean of the nine cortisol measures was 3.40 nmol/L (SD = 2.03). Additional sociodemographic and clinical data from the sample are shown in Table 1.

3.2. Conceptual analysis and item selection

Items were initially created by two psychologists holding PhDs in neuroscience (ICL and EGB) based on previous literature (e.g., Cano-López & González-Bono [3]; Koolhaas et al. [20]) and tests that measure related concepts (e.g., Beck et al. [28]; Cramer et al. [30]; Spielberger [26]) to capture the specific dimensions of chronic stress in patients with

Table 1
Sociodemographic and clinical data from the sample (mean ± *SD* or n (%)).

	Mean ± *SD* or n (%)
Age (years)	40.05 ± 11.90
Sex	
Men	110 (46.6 %)
Women	126 (53.4 %)
Educational level	
Primary	52 (22.0 %)
Secondary	55 (23.3 %)
Lower university	84 (35.6 %)
University	45 (19.1 %)
Academic/employment insertion	
Yes	115 (48.7 %)
No	121 (51.3 %)
Household members	
Family	82 (34.7 %)
Partner	128 (54.2 %)
Flatmate	4 (1.7 %)
Living alone	22 (9.3 %)
Epilepsy type	
FLE[a]	43 (18.2 %)
TLE[b]	161 (68.2 %)
TLE[b] plus	14 (5.9 %)
ILE[c]	1 (0.4 %)
Posterior cortex	15 (6.4 %)
Multifocal	2 (0.8 %)
Lateralization of seizure onset	
Left	120 (50.8 %)
Right	103 (43.6 %)
Bilateral	13 (5.5 %)
Age at epilepsy onset (years)	17.55 ± 12.49
Epilepsy duration (years)	22.50 ± 15.02
MRI[d] findings	
HS[e]	73 (30.9 %)
FCD[f]	40 (16.9 %)
Tumour	28 (11.9 %)
Gliosis	5 (2.1 %)
Heterotopia	6 (2.5 %)
Cavernoma	18 (7.6 %)
Atrophy	2 (0.8 %)
Encephalomalacia	3 (1.3 %)
Meningoencephalocele	1 (0.4 %)
Non-specific pathology	60 (25.4 %)
Number of failed ASMs[g]	5.81 ± 3.40
Number of ASMs[g]	2.89 ± 0.97
Seizures per month	16.32 ± 32.76
Seizure type	
FAS[h]	33 (14.0 %)
FIAS[i]	126 (53.4 %)
FBTCS[j]	15 (6.4 %)
FAS[h] + FIAS[i]	13 (5.5 %)
FAS[h] + FBTCS[j]	12 (5.1 %)
FIAS[i] + FBTCS[j]	30 (12.7 %)
FAS[h] + FIAS[i] + FBTCS[j]	7 (3.0 %)
STAI-T[k]	26.25 ± 11.30
BDI-II[l]	13.17 ± 10.39
QOL[m] composite score	52.76 ± 16.07
Mean cortisol levels (nmol/L)	3.40 ± 2.03

Note. [a] FLE: frontal lobe epilepsy; [b] TLE: temporal lobe epilepsy; [c] ILE: insular lobe epilepsy; [d] MRI: magnetic resonance imaging; [e] HS: hippocampal sclerosis; [f] FCD: focal cortical dysplasia; [g] ASM: antiseizure medication [h] FAS: focal aware seizure; [i] FIAS: focal impaired awareness seizure; [j] FBTCS: focal to bilateral tonic-clonic seizure; [k] STAI-T: Trait Anxiety Scale; [l] BDI-II: Beck Depression Inventory-II; [m] QOL: quality of life.

epilepsy. Specifically, we selected items referring to the unpredictability and uncontrollability of stressors (i.e., seizures) [3,20], frequency and severity of the stressors (i.e., seizures) [3], causal attributions related to the disease (i.e., internal and external attributions) – as they have been associated with coping with stress strategies [45], epilepsy concerns (e.g., seizure worry) [30], and epilepsy consequences (e.g., social and cognitive functioning) [30]. Nevertheless, no factors were theorized a priori. It should be noted that one of the objectives during the development of the EPSI-A was to identify patients at higher risk of experiencing stress-related seizures. This objective was directly considered during the item selection process, particularly in the inclusion of items that assessed long-term stress management and coping with the unpredictability of the condition, and the cumulative impact of chronic stressors in daily life, which have been shown to exacerbate seizure frequency [4,46].

In addition to this theoretical grounding, the development of the EPSI-A was informed by qualitative data. Testimonials from people with epilepsy collected in semi-structured interviews and mutual-aid groups were considered. These sessions provided critical insights into the subjective experiences of stress among these individuals, allowing for the inclusion of items that reflected real-world stressors and challenges specific to this population. The interviews were carried out by neuropsychologists specializing in epilepsy, ensuring that the data gathered was both relevant and sensitive to the condition being studied.

To further refine the item pool, a panel of experts with backgrounds in psychology and neuroscience and extensive research experience in stress and epilepsy reviewed the items to ensure they adequately covered the key domains of stress in epilepsy, such as seizure concerns, perceived epilepsy severity, unpredictability and controllability of seizures, and social, cognitive, and emotional consequences. The expert review process also ensured that items were clear and comprehensible to patients.

As a result, 28 items were designed in Spanish for the instrument, with a 5-point Likert-type scale (1 = completely disagree; 2 = disagree; 3 = neither agree nor disagree; 4 = agree; 5 = completely agree). Higher scores indicate higher perceived stress. The initial EPSI-A version in Spanish is shown in Appendix 1. For the non-validated English version, please see Appendix 2.

3.3. Reliability and validity of the EPSI-A

The initial version of this inventory contained 28 items (Appendix 1). After conducting reliability analyses, items 8, 7, 9, 6, 14, 16, 15 and 13 were removed in that order, as the item-total correlations were lower than 0.2. Item-total correlation for each item and Cronbach's alpha of the test after removing that item are shown in Table 2.

An EFA was then performed. Barlett's sphericity test was significant ($p < 0.0001$) and the KMO index was acceptable (KMO = 0.85), indicating that the EFA was appropriate. After exploring factor adequacy, items with pattern coefficients lower than 0.34 were removed. In the first step, item 20 was deleted (pattern coefficient = 0.31). Therefore, the EFA was repeated with this new version and item 12 was subsequently removed when it was shown to have a pattern coefficient of −0.32. The third EFA showed that item 17 had a pattern coefficient of 0.31, and so it was eliminated as well. Finally, the fourth EFA showed pattern coefficients of at least 0.34 for all items – and no cross-loaded items were detected.

Table 2
Item-total correlation and Cronbach's alpha of each version.

Items removed	Item-total correlation	Cronbach's alpha
Initial version		0.831
Item 8	0.053	0.838
Item 7	0.065	0.844
Item 9	0.077	0.851
Item 6	0.156	0.854
Item 14	0.158	0.857
Item 16	0.174	0.858
Item 15	0.158	0.860
Item 13	0.172	0.865

Nevertheless, item 18 was studied further, as it had the lowest item communality, with a value of 0.19 (the remaining items ranged from 0.33 to 0.78). This fact was corroborated by its structure coefficient, which showed the lowest result (structure coefficient = 0.38) while the other items had values of between 0.50 and 0.88. Furthermore, due to removal of items in the reliability analyses, this item theoretically did not fit with the rest of the questionnaire. Finally, it was found that its deletion would not affect Cronbach's alpha value (which would remain stable). For these reasons, and considering that its removal could provide more benefits than its retention, item 18 was deleted.

Due to this decision, another EFA was performed to check possible changes in the structure of the questionnaire. Barlett's sphericity test was significant ($p < 0.0001$) and the KMO index was 0.83. Four factors with eigenvalues greater than 1.0 were detected, and pattern coefficients ranged between 0.39 and 0.91. Item 23 was identified as cross-loaded as it had high saturations in factors 2 and 3 (0.40 for both), and so following Costello & Osborne [40] and Çokluk et al. [41] the item was deleted and the EFA was repeated. This last EFA also showed four factors, while no cross-loaded items were determined. Thus, a 15-item definitive version was obtained (please, see Appendix 3 for the Spanish version, and Appendix 4 non-validated English Appendix 4).

The first factor was composed of 5 items: item 1: 'I am worried about having another seizure'; item 2: 'I am afraid of having another seizure in the next month'; item 3: 'I am worried about harming myself during a seizure'; item 4: 'I am worried about the discomfort or social problems that having a seizure may cause me'; and item 5: 'I find having a seizure upsetting'. These items relate to the fear and anticipation of possible future events related to epilepsy. Therefore, this factor was called *Epilepsy concerns*.

Factor 2 was composed of 4 items: item 11: 'My seizures interfere with my daily activities'; item 22: 'I have problems at work because of my epilepsy'; item 27: 'I have had difficulties in activities of daily living (driving, cooking, etc.) because of epilepsy'; and item 28: 'I have had difficulties in some leisure activities that I enjoy because of epilepsy'. This factor relates to the impact that epilepsy has on day-to-day life, so it was labelled *Impact on daily performance*.

Factor 3 consisted of 3 items: item 24: 'I experience difficulties in my personal relationships due to epilepsy'; item 25: 'I have problems in my family life because of epilepsy'; and item 26: 'I have lost friendships because of epilepsy'. This factor refers to how epilepsy interferes with interpersonal relationships, so it was named *Social consequences*.

Finally, the fourth factor was composed of 3 items: item 10: 'During seizures, I lose consciousness'; item 19: 'My seizures have put my life in danger'; and item 21: 'I have memory problems after having a seizure'. These items relate to the physical and cognitive consequences of seizures, asking about what events occur during or after seizures, and exploring factors directly related to the intensity of seizures. Therefore, this factor was called *Epilepsy severity*.

The four factors explained 63.30% of the total variance. Specifically, *epilepsy concerns* accounted for 32.77% of the variance; *impact on daily performance* accounted for 13.68%; *social consequences* accounted for 10.16%; and *epilepsy severity* accounted for 6.69% of the variance.

Regarding internal consistency, both McDonald's omega and Cronbach's alpha had similar values. McDonald's omega was 0.85 (95% CI: 0.81–0.88) for the total inventory; 0.84 (95% CI: 0.79–0.87) for *epilepsy concerns*; 0.80 (95% CI:0.74–0.84) for *impact on daily performance*; 0.80 (95% CI: 0.72–0.84) for *social consequences*; and 0.58 (95% CI: 0.47–0.67) for *epilepsy severity*. Cronbach's alpha was 0.85 (95% CI: 0.82–0.88) for the total inventory; 0.84 (95% CI: 0.80–0.87) for *epilepsy concerns*; 0.80 (95% CI: 0.75–0.84) for *impact on daily performance*; 0.78 (95% CI: 0.73–0.83) for *social consequences*; and 0.58 (95% CI: 0.48–0.67) for *epilepsy severity*. Item loadings for each factor, reliability

estimations, and explained variance for each factor are shown in Table 3.

3.4. Descriptive statistics of the final EPSI-A version

The mean value of the 15 items was 2.50, with a mean standard deviation of 0.78. No missing data were detected. The skew and kurtosis indices show that the item distributions were displaced to the left (skewness = −0.60) and distribution was platykurtic (kurtosis = −0.48). The items with the highest mean and so seeming to generate most stress were: item 5 ('It is annoying for me to have a seizure'); item 27 ('I have had difficulties in activities of daily life (driving, cooking, etc.) because of my epilepsy'); and item 21 ('I have memory problems after suffering a seizure'). Item descriptive statistics from this final version are shown in Table 4.

3.5. Construct validity

Epilepsy concerns factor was positively related to the STAI-T score ($r(236) = 0.162$, $p = 0.013$) and the BDI-II score ($r(236) = 0.220$, $p = 0.001$) and negatively related to the QOL composite score ($r(236) = -0.356$, $p < 0.001$). Furthermore, a positive association was found between this factor and the current number of ASMs ($r(236) = 0.183$, $p = 0.005$). All correlations passed FDR multiple testing correction. No other relationships were found for this factor.

Impact on daily performance was positively related to the STAI-T score ($r(236) = 0.316$, $p < 0.001$) and the BDI-II score ($r(236) = 0.371$, $p < 0.001$), being negatively associated with the QOL composite score ($r(236) = -0.538$, $p < 0.001$). Regarding clinical variables, this factor was positively related to the number of previous failed ASMs ($r(236) = 0.233$, $p < 0.001$) and the current number of ASMs ($r(236) = 0.277$, $p < 0.001$), and negatively associated with the age at epilepsy onset ($r(236) = -0.182$, $p = 0.005$). These correlations passed FDR multiple testing correction.

Social consequences was positively associated with the STAI-T score ($r(236) = 0.314$, $p < 0.001$) and the BDI-II score ($r(236) = 0.365$, $p < 0.001$), and negatively related to QOL composite score ($r(236) = -0.408$, $p < 0.001$). Concerning clinical variables, this factor was positively related to the number of seizures per month ($r(236) = 0.135$, $p = 0.038$), the number of previous failed ASMs ($r(236) = 0.186$, p = 0.004), and the current number of ASMs ($r(236) = 0.273$, $p < 0.001$), showing a negative relationship with age at epilepsy onset ($r(236) = -0.181$, $p = 0.005$). All correlations passed FDR multiple testing correction.

Epilepsy severity was positively related to the STAI-T score ($r(236) = 0.232$, $p < 0.001$) and the BDI-II score ($r(236) = 0.289$, $p < 0.001$), showing a negative relationship with QOL composite score ($r(236) = -0.418$, $p < 0.001$). All correlations passed FDR multiple testing correction. No relationships for this factor with clinical variables were found.

Regarding the total score, the EPSI-A was positively correlated to the STAI-T score ($r(236) = 0.318$, $p < 0.001$) and the BDI-II score ($r(236) = 0.398$, $p < 0.001$), and negatively associated with QOL composite score ($r(236) = -0.552$, $p < 0.001$). In addition, the total score was associated with a higher number of previous failed ASMs ($r(236) = 0.187$, $p = 0.004$), higher current number of ASMs ($r(236) = 0.279$, $p < 0.001$), and younger age at epilepsy onset ($r(236) = -0.170$, $p = 0.009$). All correlations passed FDR multiple testing correction.

In a partial sample of 125 patients, the EPSI-A scores were negatively correlated with cortisol, except for the *epilepsy concern* factor. The *impact on daily performance* factor was associated with the C7 measure of cortisol ($r(125) = -0.199$, $p = 0.026$); *social consequences* was related to the C1 to C4 samples of cortisol ($r(125) = -0.176$, $p = 0.049$; $r(125) = -0.197$, $p = 0.028$; $r(125) = -0.177$, $p = 0.048$; and $r(125) = -0.177$, $p = 0.049$, respectively); and *epilepsy severity* was related to the C7, C8, and C9 samples of cortisol ($r(125) = -0.228$, $p = 0.010$; $r(125) = -0.212$, $p = 0.018$; and $r(125) = -0.185$, $p = 0.039$, respectively) and also to the AUC_g ($r(125) = -0.180$, $p = 0.045$). Finally, the total score of the EPSI-A was correlated to cortisol levels in the C2 sample ($r(125) = -0.181$, $p = 0.044$). None of these correlations passed FDR multiple testing correction.

Table 3
Factor loadings of the pattern matrix using the unweighted least squares extraction method and oblique rotation, reliability estimations, and explained variance (%).

	Factor 1	Factor 2	Factor 3	Factor 4
EPSI-A 1	0.91*	−0.14	0.00	−0.01
EPSI-A 2	0.86*	−0.11	0.02	0.03
EPSI-A 3	0.60*	0.08	−0.05	0.17
EPSI-A 4	0.60*	0.16	0.05	−0.13
EPSI-A 5	0.60*	0.13	−0.08	−0.10
EPSI-A 10	−0.05	−0.05	−0.02	0.67*
EPSI-A 11	0.15	0.51*	−0.02	0.07
EPSI-A 19	0.13	0.14	0.12	0.38*
EPSI-A 21	−0.08	0.23	0.00	0.44*
EPSI-A 22	0.14	0.60*	0.14	−0.06
EPSI-A 24	−0.02	−0.05	0.88*	0.00
EPSI-A 25	−0.01	−0.02	0.83*	−0.02
EPSI-A 26	−0.03	0.07	0.54*	0.03
EPSI-A 27	−0.05	0.67*	−0.09	0.08
EPSI-A 28	−0.08	0.94*	0.02	−0.06
McDonald's omega	0.84	0.80	0.80	0.59
Cronbach's alpha	0.84	0.80	0.78	0.58
Explained variance	32.77 %	13.68 %	10.16 %	6.69 %

Note. Factor 1: *epilepsy concerns*; Factor 2: *impact on daily performance*; Factor 3: *social consequences*; Factor 4: *epilepsy severity*; *: Predominant load, and, therefore, the item has been included in that factor.

Table 4
Item descriptive statistics of the final EPSI-A version.

Item	M	SD	Min	Max	Skew (SD)	Kurtosis (SD)	$r_{item\text{-}total}$
EPSI-A 1	2.90	1.31	0	4	−1.00 (0.16)	−0.17 (0.32)	0.49
EPSI-A 2	2.74	1.38	0	4	−0.77 (0.16)	−0.71 (0.32)	0.52
EPSI-A 3	2.67	1.44	0	4	−0.75 (0.16)	−0.84 (0.32)	0.54
EPSI-A 4	2.85	1.32	0	4	−1.01 (0.16)	−0.15 (0.32)	0.50
EPSI-A 5	3.28	1.03	0	4	−1.61 (0.16)	2.22 (0.32)	0.41
EPSI-A 10	2.68	1.54	0	4	−0.75 (0.16)	−0.96 (0.32)	0.29
EPSI-A 11	2.54	1.41	0	4	−0.63 (0.16)	−0.88 (0.32)	0.53
EPSI-A 19	2.55	1.45	0	4	−0.60 (0.16)	−1.00 (0.32)	0.51
EPSI-A 21	2.97	1.29	0	4	−1.18 (0.16)	0.25 (0.32)	0.38
EPSI-A 22	2.74	1.43	0	4	−0.90 (0.16)	−0.57 (0.32)	0.61
EPSI-A 24	1.19	1.44	0	4	0.81 (0.16)	−0.79 (0.32)	0.49
EPSI-A 25	1.27	1.50	0	4	0.73 (0.16)	−1.01 (0.32)	0.47
EPSI-A 26	1.14	1.53	0	4	0.87 (0.16)	−0.90 (0.32)	0.39
EPSI-A 27	3.14	1.26	0	4	−1.48 (0.16)	1.13 (0.32)	0.46
EPSI-A 28	2.89	1.38	0	4	−1.13 (0.16)	0.00 (0.32)	0.61

Note. EPSI-A: Epilepsy Perceived Stress Inventory for Adults; $r_{item\text{-}total}$ = item-total corrected correlation.

4. Discussion

The EPSI-A is a self-report instrument developed in Spanish to assess chronic perceived stress in people with epilepsy. It consists of 15 items organized into four factors: *epilepsy concerns*; *impact on daily performance*; *social consequences*; and *epilepsy severity*. Our results provide evidence of the reliability of the instrument and its validity is supported by correlations found with other psychological tests (i.e., STAI-T, BDI-II, and QOLIE-31). From an overall view, higher scores on the EPSI-A were related to increased anxious and depressive symptoms, poorer QOL, and greater epilepsy refractoriness, all together being coherent with a high-risk profile of patients. Our findings show that the EPSI-A is a valid instrument for this purpose, which can be administered in approximately 5 min.

Temkin and Davis [47] expressed the need for a method to identify patients at risk of having stress-related seizures. Therefore, the main challenge of this study was to develop an instrument that would measure stress while remaining sensitive to the particularities of epilepsy. We consider that the EPSI-A and its four factors encompass the main aspects of the current definition of epilepsy, including items related to clinical aspects directly associated with the disease, but also to the impact on daily lives and considering the overall consequences for individuals [1].

This study has demonstrated good reliability coefficients for the whole instrument and for three of the four factors (McDonald's omega and Cronbach's alpha $\geq$ 0.78). Nevertheless, the *epilepsy severity* factor showed lower values, with a McDonald's omega of 0.59 and a Cronbach's alpha of 0.58. Cronbach's alpha coefficient of 0.60 is considered acceptable [48], especially for initial developments of instruments [49,50]. Hence, although the reliability coefficient of this factor is quite close, it has not reached an acceptable value, and this is probably influenced by consisting of only three items. It is noteworthy that a forced three-factor-solution EFA was performed, but the results reported a considerable impoverishment of the psychometric properties of the test. Therefore, given that construct validity provided interesting results for this scale and that it theoretically fitted, this factor was maintained in line with other instruments which have been shown to be useful in the literature despite having adjusted reliability indices in some subscales [31,51,52].

The factors obtained can be classified as clinical factors (i.e., *epilepsy concerns* and *epilepsy severity*) and factors related to functionality in daily life activities (i.e., *impact on daily performance* and *social consequences*). All factors were correlated to all the psychological tests used and most of the clinical variables. Indeed, epilepsy-related variables have been associated on several occasions with measures frequently used to evaluate perceived stress. A higher number of ASMs was associated with higher anxiety [53], higher depressive symptoms [54], and poorer QOL [55–58]. Furthermore, an early epilepsy onset has been related to poorer QOL, with this relationship being explained, at least in part, by mood and other comorbidities [59].

Regarding perceived clinical factors of the EPSI-A, *epilepsy concerns* factor refers to the anticipatory fear and worry about potential future events associated with epilepsy, such as having another seizure or the social discomfort it might cause. In contrast, *epilepsy severity* factor addresses the actual physical and cognitive consequences that occur during or after seizures, such as losing consciousness or experiencing memory problems, which are directly linked to the intensity and impact of the seizures themselves. *Epilepsy concerns* factor was associated with the current number of ASMs. However, *epilepsy severity* was not related to variables associated with epilepsy characteristics and its treatment. This suggests that the stress associated with the severity of the disease could be more influenced by the perception of the disease than by the pathophysiology itself. Therefore, psychological variables involved in coping strategies (such as resilience) may be crucial. Resilience has been proposed as a protective factor for mood changes in patients with epilepsy [60], with resilient patients showing a higher QOL [61,62]. Thus, resilience may mitigate the adverse effects of stress.

Both factors related to functionality in activities of daily life were associated with the number of previous ASMs, the number of current ASMs, and the age at epilepsy onset, which could be considered as indicators of epilepsy refractoriness. These variables have been related to a greater impact on activities of daily life and interpersonal relationships. Baker et al. [63] found that the percentage of patients stating that epilepsy and its treatment impacted their social life increased with seizure frequency. Furthermore, epilepsy severity is negatively associated with social support [64], which is positively related to perceived epilepsy control [65]. Epilepsy refractoriness variables can then be associated with social factors which, in turn, can be correlated with emotional variables, such as unemployment or a driving ban, which have been proven to impact anxiety and QOL [54,66,67]. Therefore, future studies should explore whether patients who work or drive differ in perceived stress from those who cannot.

To complete the stress-related variables, it was considered appropriate to associate the results of the inventory with salivary cortisol, which is considered one of the most important biomarkers of stress [68]. As previous literature suggests [69,70] and compared to data provided by the CIRCORT database [71], patients with epilepsy in our sample showed higher cortisol levels than the general population at the same time of the day. Nevertheless, other reports have shown contradictory findings about the relationship between epilepsy and cortisol, some studies reporting lower cortisol levels in people with epilepsy [72–74] or even no differences [75,76]. This heterogeneity in the results could be due to clinical factors that can interact with the hormone levels, such as the presence of interictal epileptiform discharges [77], the type and dose of ASMs [78,79] or the type and lateralization of epilepsy [3,80].

Regarding the relationship between cortisol levels and the different EPSI-A factors, none of the associations was significant after FDR multiple testing correction. This lack of significant relationships could be due to the nature of the measurements: while the EPSI-A assesses chronic stress, cortisol levels obtained from individual samples in response to neuropsychological testing reflect situational stress. Thus, despite their conceptual relationship, the two constructs lack a temporal alignment. Future studies aiming to explore the correlation between EPSI-A scores and cortisol levels should use samples that reflect long-term cortisol exposure, such as hair samples. Furthermore, it should also be noted that several studies have found a dissociation between cortisol levels and perceived stress [81–83]. This could be because stress is a complex response that manifests at different levels, producing physiological, cognitive, emotional, and behavioral changes. EPSI-A scores represent the cognitive component of stress, while cortisol levels are physiological measures. Therefore, although both measures provide information about the stress response, the intensity of the response and the time after the stressor at which it occurs may vary between the different levels (i.e., cognitive and physiological) in the same individual. Thus, there may be a more cognitive than physiological response and vice versa, or similar responses at different times. Moreover, the influence of other factors cannot be discarded, such as gender, duration of epilepsy, or the hemisphere mainly affected, since they could be involved in individual differences in stress perception.

One fact that should be mentioned, given the increased recognition by the International League Against Epilepsy (ILAE) [22] and the great impact on daily life, is epilepsy comorbidities, which can be also implicated in the stress processes in these patients. In this respect, Moon et al. [16] showed that the major predictors of perceived stress in epilepsy were depression, sleep problems, anxiety, and seizure control, being depression and anxiety among the most frequent comorbidities in epilepsy [84,85]. Although the EPSI-A does not consider sleep problems, its construct validity has shown a significant relationship with the remaining predictors. This fact is of particular interest since it supports the idea that EPSI-A is a specific instrument for stress in epilepsy.

Despite the data, this study is not exempt from limitations. First, test–retest reliability was not obtained, and future studies should explore this. However, the internal consistency showed good values

which enabled the validation of the instrument. Second, the sample consisted of patients with drug-resistant focal epilepsy, including diverse types of epilepsy. Thus, its generalization to patients with controlled and generalized epilepsy should be investigated in future studies, and the possible impact of other factors, such as gender, epilepsy duration, or lateralization, ought to be explored. Third, although the questionnaire measures chronic stress and participants were instructed to complete it according to how they had felt over the past six months, its administration after a long neuropsychological evaluation may affect the results. In this line, although the interruptions to collect saliva samples could be perceived as stressful, it was incorporated into patient rest periods to mitigate fatigue. Accordingly, we suggest that this method did not elevate acute stress levels during the evaluation. In fact, cortisol levels decreased progressively, consistent with the expected circadian rhythm. Nevertheless, future studies should explore the relationship between EPSI-A scores and clinical or emotional variables in shorter evaluations or administrating the EPSI-A at the beginning of the evaluations, to assess the consistency of these findings. Fourth, correlations between cortisol and the EPSI-A were performed with a smaller sample size than the one used to execute the EFA. This, together with the use of absolute measures of cortisol without considering the deviation from the general population, could bias the results. Therefore, having a larger sample and a control group may help us understand the nature of this relationship. Additionally, cortisol was measured using saliva samples, which provide situational information. In contrast, collecting hair samples, which reflect cortisol levels over the past few months, could yield results more aligned with EPSI-A scores. Fifth, no standardized scores were provided and so this should be the next step. Finally, since this study aimed to develop and validate the EPSI-A, other questions remained unanswered. Therefore, upcoming studies should address the ability of the EPSI-A to discriminate between patients who are more vulnerable to the impact of epilepsy.

As far as we know, the EPSI-A is the first tool that has proven useful in measuring perceived chronic stress in people with drug-resistant epilepsy. Given the results of this study, it is confirmed that this test has strengths. The first is easy implementation. Between 60% and 70% of people with chronic epilepsy show cognitive impairment [86], so inventories that imply low cognitive load are more appropriate. Secondly, the brevity of the test. Its speed of application (i.e., about 5 min) enables its use in various contexts (e.g., consultations and waiting rooms) and provides benefits in terms of efficiency, supporting the routine monitoring of stress in people with epilepsy. Thirdly, the subjectivity of the answers. As mentioned previously, it seems that the impact of stress is more linked to the perception of the situation than to its objective magnitude. Therefore, we consider that the self-reporting nature of the questionnaire could provide greater reliability when exploring the consequences of stress in this population. Fourthly, our findings support that higher scores on the EPSI-A are associated with increased anxiety and depression, poorer QOL, and greater epilepsy refractoriness, all of which align with what would be expected in patients with high-risk profiles. Consequently, we suggest that the EPSI-A could provide valuable information from this population and facilitate the detection of patients with risk profiles and, therefore, improve clinical practice.

CRediT authorship contribution statement

Judit Catalán-Aguilar: Writing – original draft, Validation, Methodology, Investigation, Formal analysis, Data curation. **Irene Cano-López:** Writing – review & editing, Supervision, Methodology, Investigation, Formal analysis, Conceptualization. **Paula Tormos-Pons:** Investigation, Data curation. **Alejandro Lozano-García:** Investigation, Data curation. **Kevin G. Hampel:** Writing – review & editing, Supervision, Investigation, Data curation. **Vanesa Hidalgo:** Writing – review & editing, Supervision, Investigation, Data curation. **Alicia Salvador:** Writing – review & editing, Supervision, Resources. **Vicente Villanueva:** Writing – review & editing, Supervision, Resources, Investigation, Funding acquisition, Data curation. **Esperanza González-Bono:** Writing – review & editing, Supervision, Resources, Investigation, Funding acquisition, Data curation, Conceptualization.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.yebeh.2024.110142.

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