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The relationship between memory and quality of life is mediated by trait anxiety in patients with temporal lobe epilepsy

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Abstract

Purpose Memory deficits are very frequent in patients with drug-resistant epilepsy, but they predict a small proportion of variance of their quality of life (QOL) in previous studies, possibly due to the lack of consideration of mediating factors of this relationship. This study aimed to examine whether trait anxiety mediates the relationship between memory and QOL in this population, controlling the influence of demographic and seizure-related factors.

Methods In this cross-sectional study, 119 adults with drug-resistant temporal lobe epilepsy (TLE) underwent a neuropsychological evaluation, in which memory, anxiety, and QOL were assessed.

Results In the total sample, better delayed memory had an effect on better QOL indirectly through lower trait anxiety ($B = 0.13$, SE = 0.06, $p = 0.04$, $ab_{cs} = 0.13$; $\kappa^2 = 0.18$; $PM_{ind} = 0.76$). Additionally, delayed memory has not a direct association with QOL ($B = 0.04$, SE = 0.09, $p = 0.64$, Cohen's $f^2 = 0.005$; $PM_{dir} = 0.24$), and the total effect of delayed memory on QOL tended to reach statistical significance ($B = 0.17$, SE = 0.10, $p = 0.08$). The proposed mediation model yielded excellent fit (CFI = 1.00, RMSEA = 0.0001, SRMR = 0.009, and χ^2 (1) = 0.50, $p = 0.48$) and explained 38% of the variance of QOL.

Conclusion These findings suggest that trait anxiety is an important factor in understanding the relationship between memory and QOL in patients with TLE, considering the influence of demographic and seizure-related variables, and may have relevant implications for decision-making in this population.

Keywords Memory · Quality of life · Trait anxiety · Drug-resistant epilepsy · Temporal lobe epilepsy

Introduction

Epilepsy is one of the most common neurological diseases, affecting almost 1.0% of the general population [1]. Approximately 30% of patients suffer from drug-resistant epilepsy and continue to have seizures despite optimal treatment with antiseizure medications (ASMs) [2], being temporal lobe epilepsy (TLE) the most frequent type [3]. These patients can be considered exposed to a chronic stress condition [4] involving unpredictable and uncontrollable seizures, side-effects of ASMs, associated disabilities, social discrimination, and most of the burden of the disease, which could compromise their quality of life (QOL) [5].

QOL is a complex construct referred to the patient's perspective regarding his/her global health, including physical, social, and psychological domains [6], and has been proposed as an indicator of the need for surgery in patients with drug-resistant epilepsy [7]. In these patients, QOL has been related to demographic factors such as educational level [8] and employment status [9], and seizure-related factors such as age at epilepsy onset [10, 11], seizure frequency [10, 11], and number of ASMs [12].

Despite the relevance of demographic and seizure-related factors on QOL in patients with drug-resistant epilepsy, it has been suggested that psychological factors contribute more to the variance of QOL than these factors, having a

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more pervasive and lasting impact [7]. Specifically, some studies have found that trait anxiety is the factor most strongly related to QOL in patients with drug-resistant epilepsy [12, 13], being a major predictor for many QOL domains [14]. Nevertheless, memory functioning predicts a small proportion of variance in QOL [13, 15] and there are even studies showing that, despite subjective memory is associated with QOL, objective memory performance is not [10].

Given that memory complaints are very frequent in these patients and are one of their main concerns [16], it is possible that a strong relationship between memory and QOL has not been found due to the lack of consideration of the possible mediating effect of trait anxiety on this relationship, together with their direct relationship. Trait anxiety has been defined as proneness to appraising internal stimuli or external events in such a way that results in anxiety [17]. Individuals with high trait anxiety are likely to show a bias toward appraising ambiguous or uncertain situations as threatening or likely to have an aversive outcome [18]. Stimulus processing is affected by the prior knowledge and experience available in long-term memory, and there are relevant differences between the stimulus as presented and the stimulus as encoded because of the inferential processes developed depending on prior knowledge [19]. It should be noted that both high trait anxiety, memory deficits, and seizures might share overlapping brain circuits (e.g., amygdala, and hippocampus). Thus, the amygdala is involved in the processing of emotional inputs from other limbic structures (e.g., hippocampus and hypothalamus) [20], and these neural circuits are key for memory functioning [21] and represent the site of seizure onset in patients with TLE [20, 22]. Therefore, is not surprising that trait anxiety has been associated with poor memory functioning in patients with TLE [23].

However, to our knowledge, previous studies have focused on relationships between memory functioning and trait anxiety [23], memory functioning and QOL [10, 13, 15], and trait anxiety and QOL [12–14], but not how these may be related beyond a bivariate approach. The consideration of the possible mediating role of trait anxiety in the relationship between memory functioning and QOL in patients with drug-resistant TLE in a global model that also includes the direct relationship between these variables could contribute to a better understanding of the pathways through which memory is associated with QOL. This issue is especially relevant because QOL is increasingly being used as a key parameter for personalized treatment approaches and decision-making in this population [24]. Based on the above, this study aims to examine whether trait anxiety mediates the relationship between memory and QOL in this population, controlling the influence of demographic and seizure-related factors. With this aim, we will test a model, hypothesizing that patients who have poor memory functioning may experience higher anxiety, which would be associated with poor QOL. Furthermore, we will compare this model with another one that does not consider the effect of mediation, hypothesizing that memory functioning, without the consideration of trait anxiety as a mediating variable, may have no significant relationship with QOL, predicting a small proportion of its variance. We will focus on memory functioning because TLE is the more frequent epilepsy type associated with memory deficits [25], so these deficits affect 70% of patients with TLE [26] and, consequently, they may be a major contributor to the burden of the disease [27].

Method

Participants

Participants were recruited from the Refractory Epilepsy Unit, Hospital Universitario y Politécnico La Fe (Valencia, Spain), a center belonging to European Reference Network for Epilepsy (EpiCARE), between April 2015 and December 2021. The inclusion criteria of this study comprised: a) patients with a diagnosis of drug-resistant TLE; b) patients with focal aware seizures, focal impaired awareness seizures, and/or focal to bilateral tonic–clonic seizures; c) candidates for epilepsy surgery; d) with a chronological age of at least 18 years; and e) who had completed a neuropsychological assessment before surgery. Excluded were patients who: a) had uncompleted primary education; b) in whom the assessment could not be carried out with a minimum of reliability due to their high level of cognitive impairment (e.g., patients with dementia of any etiology); c) suffered severe psychiatric conditions; and d) were not fluent Spanish speakers.

Procedure

This is a cross-sectional study, whose reporting followed the Strengthening the Reporting of Observational Studies in Epidemiology statement guidelines (STROBE) [28]. The procedure was conducted according to the Declaration of Helsinki and approved by the Ethics Committee of the Hospital Universitario y Politécnico La Fe. Informed consent was obtained from all participants.

Presurgical evaluation was made by a multidisciplinary team, including seizure history and semiology; neurologic evaluation; 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. This assessment established the diagnosis of the epilepsy type and the lateralization of the

epileptogenic area. Demographic characteristics (i.e., age, sex, educational level, marital status, and social insertion as active employment or education), and clinical data (i.e., age at epilepsy onset, epilepsy duration, seizure frequency per month, seizure type, and number of ASMs) were registered.

The neuropsychological evaluation was performed before the surgery and included the following cognitive domains: attention, executive function, memory, language, and motor function, following the recommendations of the International League Against Epilepsy (ILAE) [29]. In these patients (i.e., TLE patients) the evaluation of attention and executive functions was more focused on monitoring possible problems in these domains than on evaluating them per se, the main objective being the assessment of memory to predict the possible post-surgical memory changes. From this assessment, memory, anxiety, and QOL tests were selected for the present study. No missing data were detected for any variable.

Measures

Memory. It was examined using the Wechsler Memory Scale-Third Edition (WMS-III) [30], in its Spanish version [31]. This battery was selected against other available tools since the WMS is one of the most widely used batteries in neuropsychological presurgical assessment for surgery candidates in epilepsy surgery centers across Europe [29], its results correlate with hippocampal volumes in patients with TLE [32], and allows verbal and visual memory to be tested together (using the same battery). The following subtests were employed: Logical Memory I and II (immediate and delayed verbal recall of short stories), Verbal Paired Associates I and II (immediate and delayed verbal recall of 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 subtests provide material-specific memory indices (immediate auditory memory, delayed auditory memory, delayed auditory recognition, immediate visual memory, delayed visual memory), as well as two general memory indices (immediate memory and delayed memory). The delayed memory index was calculated with the following subtests according to manual instructions: Logical Memory II, Verbal Paired Associates II, Faces II, and Family Scenes II [31]. In this study, we selected the delayed memory index for data analyses since it has shown greater reliability than subtests scores and other indices [31]. Furthermore, the availability of a single index that summarizes de delayed recall of verbal and visual information allows us to reduce the number of predictors in path analysis to maintain an acceptable statistical power [33]. This index was expressed in an age-adjusted percentile score.

Trait anxiety. It was assessed using the trait anxiety scale of the State-Trait Anxiety Inventory (STAI) [34], in its Spanish version [35]. It includes 20 items rated on a four-point scale that evaluate the relatively stable aspects of anxiety. A total score was computed, and it was expressed in a percentile score adjusted by age and sex. Cronbach's alpha of this inventory is 0.94 [35].

QOL. It was evaluated using the Quality-of-Life in Epilepsy Inventory (QOLIE-31) [36], in its Spanish version [37]. It is composed of 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 scale were calculated by converting the raw numeric values of items into 0 to 100 scores, with higher scores indicating better QOL in all cases. A QOL composite score was computed by using a weighted average of the different scales and was expressed in a percentile score. Cronbach's alpha of this inventory is 0.92 [37].

Statistical analyses

Preliminarily, differences in memory functioning, anxiety, and QOL depending on categorical demographical and clinical variables were analyzed using univariate ANOVAs. Furthermore, Pearson correlations were computed to examine the relationships of these variables with quantitative demographical and clinical variables. When significant differences or relationships were detected, these demographical and clinical variables were included as covariates in the path analysis. Seizure frequency was also included in the path analysis due to the relevance of this variable to QOL shown in previous studies [10, 11].

To analyze the relationships among memory functioning, anxiety, and QOL, a path analysis was carried out using the lavaan package (version 0.6–5) [38]. The mediation model included delayed memory (percentile score) as the exogenous variable. Trait anxiety and QOL were included as endogenous variables. Anxiety was also set as a predictor of QOL. Educational level, employment status, age at epilepsy onset, seizure frequency, and number of ASMs were included as covariates. To test the significance level of the indirect (mediated) effects, a bootstrapping method (5,000 bootstraps) was employed. Furthermore, a non-mediation model was computed to compare the results with the previous model, including delayed memory as the exogenous variable, QOL as the endogenous variable, and educational level, employment status, age at epilepsy onset, seizure frequency, and number of ASMs as covariates. Excellent model fit was indicated by a comparative fit index (CFI) > 0.95, a root mean square error of approximation (RMSEA) < 0.06, a standardized root mean square residual (SRMR) < 0.08, and a non-significant χ^2 statistic [39]. Cohen's f^2 was computed as a local effect size measure, to quantify the contribution of

each predictor to the exogenous variables, with values near 0.02, 0.15, and 0.35 indicating small, medium, and large effect sizes, respectively [40]. The Completely Standardized Indirect Effect index (ab_{cs}) and the proportion of the maximum possible indirect effect (κ^2) were used to estimate the effect sizes of significant indirect effects [41]. The MBESS package (version 4.1.3) was employed to compute κ^2 [42], and values of 0.01, 0.09, and 0.25 were interpreted as small, medium, and large effect sizes, respectively, according to Cohen [40], as suggested by Preacher and Kelley [41]. The ratio of the indirect to the total effect and the ratio of the direct to the total effect (P_M indices) were also used as relative measures for the indirect and direct effects [41].

Statistical analyses were carried out using Rstudio (https://www.r-project.org/, version 3.5.1, R Core Team, 2016).

Results

Preliminary analyses

The sample was composed of 119 adult patients with drug-resistant TLE (mean age = 39.13, SD = 12.18, range = 18–67 years). Characteristics and cognitive functioning, anxiety, and QOL scores of the patients are shown in Table 1. No missing data were detected.

Trait anxiety and QOL differed depending on employment status (F (2,118) = 8.23, p = 0.005, η^2_p = 0.07; and F (2,118) = 9.19, p = 0.003, η^2_p = 0.07, respectively), participants currently working having lower trait anxiety and better QOL than those not currently working. Delayed memory functioning differed depending on educational level (F (3,118) = 4.89, p = 0.003, η^2_p = 0.11), participants with university studies having better memory functioning than those with primary (p = 0.035) or secondary studies (p = 0.003). Furthermore, better delayed memory functioning was associated with older age at seizure onset (r (119) = 0.29, p = 0.002) and lower number of ASMs (r (119) = −0.29, p = 0.001).

No other significant differences or relationships were found depending on demographical or seizure-related variables (e.g., seizure frequency).

Relationships among memory functioning, anxiety, and QOL controlling for demographic and seizure-related factors

The proposed mediation model yielded an excellent model fit (CFI = 1.00, RMSEA = 0.0001, 90% CI 0.0001–0.22, SRMR = 0.009, and χ^2 (1) = 0.50, p = 0.48) (Fig. 1 and Table 2). The indirect pathways showed that better delayed memory had an effect on better QOL through lower

Table 1 Patients' characteristics, memory functioning, anxiety, and QOL scores (N = 119)

Characteristics	Mean ± SD or *n* (%)
Age (years)	39.13 ± 12.18
Sex	
Female	63 (52.9%)
Male	56 (47.1%)
Educational level	
Primary	12 (10.1%)
Secondary	35 (29.4%)
Lower university	48 (40.3%)
University	24 (20.2%)
Marital status	
Single	61 (51.3%)
Married	52 (43.7%)
Divorced	6 (5.0%)
Currently studying	
Yes	21 (17.6%)
No	98 (82.4%)
Employment status	
Currently working	51 (42.9%)
Not currently working	68 (57.1%)
Side of seizure focus	
Left hemisphere	62 (52.1%)
Right hemisphere	57 (47.9%)
Age at epilepsy onset (years)	17.95 ± 12.59
Epilepsy duration (years)	21.18 ± 15.31
Seizure frequency (per month)	12.81 ± 24.21
Seizure type	
FAS	4 (3.4%)
FIAS	45 (37.8%)
FBTCS	2 (1.7%)
FAS + FIAS	23 (19.3%)
FAS + FBTCS	1 (0.8%)
FIAS + FBTCS	33 (27.7%)
FAS + FIAS + FBTCS	11 (9.2%)
MRI findings	
Hippocampal sclerosis	46 (38.7%)
Focal cortical dysplasia	6 (5.0%)
Gliosis	5 (4.2%)
Tumor	16 (13.4%)
Heterotopia	4 (3.4%)
Cavernoma	9 (7.6%)
Atrophy	2 (1.7%)
Encephalomalacia	1 (0.8%)
Non-specific pathology	30 (25.2%)
Number of ASMs	2.71 ± 0.81
Delayed memory (percentile score)	29.50 ± 27.95
Trait anxiety (percentile score)	61.65 ± 31.07
QOL (percentile score)	36.91 ± 27.22

ASMs anti-seizure medications; *FAS* Focal aware seizure; *FBTCS* Focal to bilateral tonic–clonic seizures; *FIAS* Focal impaired awareness seizure; *MRI* magnetic resonance imaging

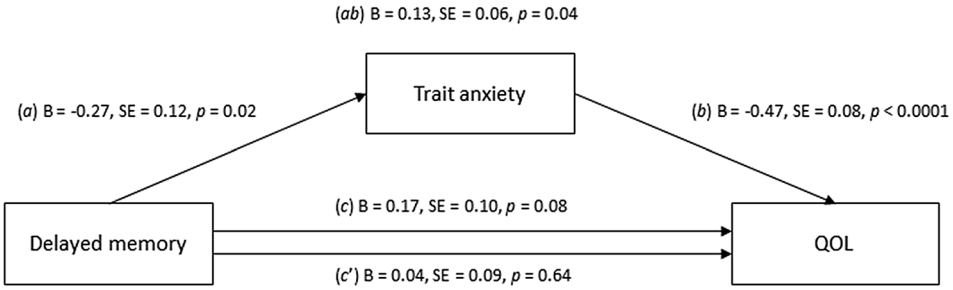

Fig. 1 Model assessing associations among memory functioning, trait anxiety, and QOL, adjusted for educational level, employment status, age at epilepsy onset, presurgical seizures per month, and number of ASMs

Table 2 Parameter estimates from the mediation model

	B	SE	*p*
Anxiety			
Delayed memory	−0.27	0.12	0.02
C_1 (educational level)	−0.96	3.25	0.77
C_2 (employment status)	−11.73	5.89	0.05
C_3 (age at epilepsy onset)	−0.18	0.23	0.44
C_4 (seizure frequency)	0.01	0.13	0.99
C_5 (number of ASMs)	1.58	3.75	0.67
QOL			
Trait anxiety	−0.47	0.08	0.0001
Delayed memory (direct effect)	0.04	0.09	0.64
C_1 (educational level)	−2.26	2.16	0.30
C_2 (employment status)	7.06	4.44	0.11
C_3 (age at epilepsy onset)	−0.30	0.17	0.07
C_4 (seizure frequency)	0.09	0.12	0.45
C_5 (number of ASMs)	−5.75	3.12	0.07
Indirect effect of delayed memory	0.13	0.06	0.04
Total effect of delayed memory (i.e., sum of indirect and direct effects)	0.17	0.10	0.08

ASMs anti-seizure medications; *C* = covariate

trait anxiety ($B = 0.13$, SE = 0.06, $p = 0.04$, $ab_{cs} = 0.13$; $\kappa^2 = 0.18$; $PM_{ind} = 0.76$). Specifically, better delayed memory was associated with lower trait anxiety ($B = -0.27$, SE = 0.12, $p = 0.02$, Cohen's $f^2 = 0.05$), and lower trait anxiety was associated with better QOL ($B = -0.47$, SE = 0.08, $p < 0.0001$, Cohen's $f^2 = 0.39$). However, delayed memory has not a direct association with QOL ($B = 0.04$, SE = 0.09, $p = 0.64$, Cohen's $f^2 = 0.005$; $PM_{dir} = 0.24$), and the total effect of delayed memory on QOL tended to reach statistical significance ($B = 0.17$, SE = 0.10, $p = 0.08$). The model explained 14% of the variance of trait anxiety and 38% of the variance of QOL.

The non-mediation model yielded an excellent model fit (CFI = 1.00, RMSEA = 0.0001, 90% CI 0.0001–0.22, SRMR = 0.01, and χ^2 (1) = 0.50, $p = 0.48$) (Table 3). However, delayed memory was not significantly associated with

Table 3 Parameter estimates from the non-mediation model

	QOL		
	B	SE	*p*
Delayed memory	0.17	0.10	0.10
C_1 (educational level)	−1.81	2.66	0.50
C_2 (employment status)	12.52	5.12	0.01
C_3 (age at epilepsy onset)	−0.22	0.21	0.31
C_4 (seizure frequency)	0.09	0.14	0.51
C_5 (number of ASMs)	−6.48	3.61	0.07

ASMs anti-seizure medications; *C* covariate

QOL ($B = 0.17$, SE = 0.10, $p = 0.10$, Cohen's $f^2 = 0.03$). The model explained 14% of the variance of QOL.

Discussion

The current study proposes a model that shows that trait anxiety is a relevant factor mediating the relationship between poor memory and poor QOL, controlling the influence of demographic and seizure-related factors. These main findings are discussed below.

Trait anxiety scores were above the mean with respect to the normative test data (percentile score of 61.65), whereas QOL scores were below the mean (percentile score of 36.91). Patients currently working had lower trait anxiety and better QOL than those not currently working, according to Catalán-Aguilar et al. [9]. It should be noted that trait anxiety is rooted in personality traits [43], being one of the main facets of the personality factor neuroticism [44]. Spector and O'Connell [45] suggested that personality might relate to employment, affecting job settings into which people are selected, and behavior that in turn affects the employment environment. Specifically, neuroticism has been related to a low tendency to assertive job-seeking behaviors in the general population [46]. Consequently, it may be possible that individuals with high trait anxiety are likely to appear nervous and do less well than those with low trait anxiety, especially in complex jobs [47], and this may explain our results. Furthermore, delayed memory

scores were below the mean with respect to the normative test data (percentile score of 29.50), and, in line with previous works, memory functioning differed depending on educational level [48], age at seizure onset [49], and number of ASMs [50]. Early age of epilepsy onset could compromise cognitive development and favor greater vulnerability to the effects of seizures and ASMs treatment [49, 51]. Together, these results indicate that employment status, educational level, age at seizure onset, and number of ASMs are important factors in understanding the interindividual differences in the variables of interest (specifically, in anxiety and QOL in the case of employment status, and in memory in the case of the rest of variables), so they were included as covariates in the path analysis. It should be noted that, although seizure frequency was not associated with memory, anxiety, or QOL in our study, this variable was also included in the path analysis to control its possible influence, due to its relevance to QOL in previous studies with this population [10, 11]. It has been proposed that a higher seizure frequency could imply an increase in expected brain damage and the likelihood of developing memory deficits and, consequently, a poor QOL [52], but there are methodological difficulties in revealing this logical assumption, including the difficulty in controlling for the influence of age-associated cognitive impairment and the subjectivity of self-reports of seizure frequency [52]. These methodological difficulties may explain, at least in part, the inconsistency among the results of some studies examining this issue.

The proposed mediation model yielded an excellent fit [39]. As hypothesized, patients with poor memory functioning experienced higher trait anxiety, which was associated with poor QOL. Specifically, QOL decreased by 0.13 standard deviations for every 1*SD* decrease in memory functioning indirectly via higher trait anxiety. The effect size for the mediation effect was medium [40]. Regarding the effect size of the direct relationships included in the mediation model (indicated by Cohen's f^2), the relationship between memory and trait anxiety was small, whereas the association between trait anxiety and QOL had a large effect size [40]. Past research focused on relationships between memory functioning and trait anxiety [23], memory functioning and QOL [10, 13, 15], and trait anxiety and QOL [12–14], but not how these may be related beyond a bivariate approach.

It should be noted that memory deficits were not directly associated with poor QOL in the mediation model, and the total effect (i.e., the sum of indirect and direct effects) tended to reach statistical significance. The non-mediation model showed no significant relationship between memory and QOL, as hypothesized, according to the study by Giovagnoli and Avanzini [10]. Our findings suggest that trait anxiety provides a reason why individuals who had poor memory endorse poorer QOL, allowing us to recommend the inclusion of this variable in the study of memory functioning and its relationship with QOL in this population. It should be noted that, as indicated above, in our study trait anxiety scores from STAI were above the mean with respect to the normative test data, and this instrument has shown an adequate sensibility for anxiety disorders detection in patients with TLE [53]. These disorders are especially frequent in patients with drug-resistant epilepsy, existing a diagnostic gap [54], so detecting certain susceptibilities to clinical disorders could be useful for the prevention of poor QOL in patients with TLE.

This study has strengths such as the large and relative homogeneous sample (i.e., adult patients with drug-resistant TLE), and the fact that, as far as we know, it is the first to evaluate the indirect effects of memory functioning on QOL via trait anxiety in a path model that globally considers these variables and the demographic and seizure-related factors, so it represents an advance over previous studies. Despite these strengths, some limitations should be considered. First, the cross-sectional design of the study does not permit to establish causal relationships, so longitudinal studies are needed to shed more light on the relationships among these variables (e.g., studies in which cognitive rehabilitation can be shown to improve QOL via shifts in trait anxiety). Second, high trait anxiety may imply attentional biases that result in increased threat detection [55]. This study has focused on memory functioning because memory deficits are the most frequent in patients with TLE [26], whereas attention and executive function have not been included in path analysis in order to maintain an acceptable statistical power, by including around one predictor per 10 individuals, as recommended [33]. However, future studies should explore the role of trait anxiety as a mediator factor in the relationship between other cognitive domains (i.e., attention and executive function) and QOL. Finally, QOL instruments provide a comprehensive evaluation of the effects of an illness and its treatment [56], but they are based on the patients' perceptions and may or may not coincide with their functionality and autonomy in daily life. Future studies should consider functionality and autonomy measurements.

Conclusion

This study provides a model that shows that trait anxiety is an important factor in understanding the relationship between memory and QOL in patients with drug-resistant TLE, considering the influence of demographic and seizure-related variables. The model explained a substantial proportion of the variance of QOL (38%) and the mediation had a medium effect size [40]. Given that memory complaints are one of the main concerns of patients with TLE [16], understanding the mechanisms through which memory

deficits are associated with poor QOL may have relevant implications for decision-making in this population. Previous studies suggest that cognitive rehabilitation could be a promising approach for memory improvement in patients with drug-resistant epilepsy [57] and, consequently, could improve their QOL. Considering that trait anxiety mediates the relationship between memory functioning and QOL, our findings suggest that supplementing cognitive rehabilitation with strategies focused on reducing trait anxiety (e.g., through the modification of interpretative biases) [58, 59] may have a beneficial effect on QOL.

Author contributions EG-B and VV: conceptualization. IC-L, AL-G, JC-A, KG.H: methodology. IC-L: statistical analyses. IC-L: writing—original draft preparation. KG.H, EG-B and VV: writing—review and editing. EG-B and VV: funding acquisition. EG-B and VV: resources. EG-B and VV: supervision. All authors read and approved the final manuscript.

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Data availability The data that support the findings of this study are available from the corresponding author upon reasonable request.

Declarations

Conflict of interest The authors have no relevant financial or non-financial interests to disclose.

Ethical approval The procedure was conducted according to the Declaration of Helsinki and approved by the Ethics Committee of the Hospital Universitario y Politécnico La Fe.

Consent to participate Informed consent was obtained from all individual participants included in the study.

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