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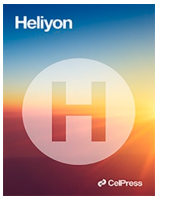

Association between depressive and anxious symptoms with cognitive function and quality of life in drug-resistant epilepsy

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1. Introduction

Epilepsy is one of the most common neurologic conditions in the world, affecting approximately 70 million people worldwide [1]. Despite antiepileptic treatment is effective in most cases of epilepsy, studies estimate that 30–40 % become resistant to treatment with antiepileptic drugs (AED) [2]. Drug-resistant epilepsy (DRE) is defined as failure of adequate trials of two tolerated and appropriately chosen and used AED schedules (whether as monotherapies or in combination) to achieve sustained seizure-freedom [3]. DRE represents the greatest socioeconomic and psychosocial burdens as DRE and its accompanying comorbidities require an overwhelming amount of time, dedication and attention from healthcare providers [4].

Depressive and anxious symptoms and disorders are the most frequent psychiatric comorbidities in epilepsy [5], and they are expected to be more prevalent in DRE [6,7]. Epilepsy is also associated with neurocognitive deficits [8] and to a greater extent in DRE [7,9].

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Both comorbidities contribute to an impaired quality of life (QOL); some authors consider that they contribute even more than epileptic seizures themselves [10]. Among patients with DRE, the presence of psychiatric disorders (PD), especially depression and anxiety, have been proven to negatively affect QOL [10,11]. Cognitive impairment has also been significantly related to QOL in DRE, particularly disturbances in memory, attention and executive function [9,12]. Therefore, identification and assessment of comorbid psychiatric and neuropsychological impairment must be included in the clinical management of patients with DRE.

Regardless of the aforementioned and specifically in DRE, symptoms related to depression or anxiety and cognitive impairment are frequently investigated separately, with limited attention given to examining the relationship between these psychiatric and neuropsychological symptoms in this particular group of patients [13]. These symptoms often coexist and it is thought that they might rely on common pathophysiological mechanisms [14], and some studies in epilepsy (not DRE) have demonstrated a relationship between these psychiatric symptoms and impairment in memory, language, executive functions, visuoperceptual ability or psychomotor speed [15,16]. However, among patients with DRE, only few studies have aimed to relate these two comorbid conditions of epilepsy. As stated in a recent review, the influence of psychiatric symptoms on cognitive function among patients with DRE remains unknown and studies are lacking and heterogeneous [17].

The present study was aimed at assessing the relationship between severity of depressive and anxious symptoms and cognitive function and QOL in adults with DRE. We hypothesized that symptoms of depression and anxiety may be associated with worse cognitive performance and lower QOL in adults with DRE.

2. Materials and methods

Cross-sectional, retrospective study of subjects treated at an Epilepsy Unit at *Hospital Clínic de Barcelona* from January 2007 to December 2017.

2.1. Patients

Adult individuals diagnosed with Drug-Resistant Epilepsy who were admitted to the Epilepsy Unit at *Hospital Clínic de Barcelona* between January 2007 and December 2017 were enrolled in the study. They were undergoing evaluation for potential neurosurgical interventions as a treatment option. All participants met the criteria for DRE as defined by the International League Against Epilepsy (ILAE), which states that drug resistant epilepsy is characterized by the "failure of adequate trials of two tolerated and appropriately chosen and used antiepileptic drug (AED) schedules (whether as monotherapies or in combination) to achieve sustained seizure freedom" [18]. Additionally, individuals with any of the following conditions were excluded: non-Spanish speakers, being diagnosed with mental retardation, primary sensory or motor impairments that could affect test performance and those who had previously undergone neurosurgery.

The study received approval from the Human Research Ethics Committee of *Hospital Clínic de Barcelona*, and all patients provided written consent for participation.

2.2. Assessment

Patient's admission to the Epilepsy Unit lasted one week. During this time, they underwent assessments conducted by specialists in the fields of neurology, psychiatry and neuropsychology. These evaluations included video-encephalography monitoring as well as neuropsychological testing. Details concerning socio-demographic data (gender, age, education level and employment status) as well as epilepsy-related information (age of onset, seizure frequency, duration, focus, AEDs and neuroimaging results) were obtained from the patients' medical records.

2.2.1. Psychiatric assessment

A psychiatrist conducted assessments for the presence of Axis-I disorders following the Structured Clinical Interview for DSM-IV (*SCID-IV)* [19]*, which were categorized into the following disorder groups: mood, anxiety, psychotic and others*.

To assess depressive and anxious symptoms, the Spanish version of the Hospital Anxiety and Depression Scale (HADS) [20] *was employed. It was created to assess anxious and depressive symptoms in non-psychiatric populations over the previous week, with the primary goal of facilitating the* identification of emotional disorders [21]. It is considered an effective screening tool for individuals with epilepsy [22]. It is comprised of 14 multiple-choice items divided into two subscales: anxiety and depression. Items are rated using a 4-point Likert scale with scores ranging from 0 to 3. The final score extends from 0 to 21. In order to minimize the number of false-positive results, a cutoff point was used of 11 for each of the subscales, which indicates probable presence of a clinically relevant depressive or anxiety disorder [20].

Anxious and depressive symptoms were additionally evaluated using the Spanish version of the Symptom Checklist-90-R questionnaire (SCL-90R) [23]. *It evaluates symptoms during the week prior to the evaluation, and consists* of 90 items which are rated from 0 to 4 and categorized into nine symptom scales. In accordance with the aim of our study, we focused on two dimensions: depression and anxiety.

2.2.2. Neuropsychological assessment

Neuropsychological evaluation was performed using the Wechsler Adult Intelligence Scale 3rd Edition (WAIS III) [24] and the Wechsler Memory Scale (WMS III) [25]. The following subtests from WAIS III were used: vocabulary (V), similarities (S), block design (BD), digit symbol-coding (DSC) and digit span (DS). The following subtests form WMS III were used: immediate visual memory (IVM),

delayed visual memory (DVM), immediate logical memory (ILM), and delayed logical memory (DLM). Trail Making Test A and B (TMTA and TMTB), Rey auditory-verbal learning test (RAVLT) and Boston Naming Test (BNT) were also used. Test scores were transformed into normalized *Z* scores based on age, sex and education.

2.2.3. Quality of life assessment

The assessment of QOL was conducted using the Spanish version of the Quality of Life in Epilepsy Inventory-31 (*QOLIE-31), a tool designed to evaluate* patients' subjective perceptions of their QOL across several facets associated to epilepsy [26,27]. This inventory encompasses seven multiple item subscales that evaluate different aspects: overall quality of life (OQL), seizure worry (SW), emotional well-being (EWB), energy/fatigue (EF), cognition (COG), social functioning (SF), and medication effects (ME). Each includes an item that measures the level of subjective distress to that specific subscale. Scores range from 1 to 100, with lower scores indicating worse quality of life. An overall total score (QOLIET) is obtained by using a weighted average of scores from the multi-item subscales.

2.3. Data analysis

The sample was classified into groups based on the presence or absence of a clinically relevant symptom. Anxious and depressive symptoms were studied in separate analyses, according to the established cutoff point of 11 for both scales. A group comparison was performed between subjects with presence or absence of a clinically relevant specific symptom (anxious or depressive) for twelve cognitive variables (V, S, BD, DSC, DS, IVM, DVM, ILM, DLM, TMTA, TMTB, RAVLT, BNT) and eight QOLIE-31 variables (OQL, SW, EWB, EF, COG, SF, ME and QOLIET). The relationship between the scores on the anxiety and depression SCL-90R dimensions and all

Table 1
Sociodemographic and neurological characteristics.

	Whole sample (N = 272)	CR depressive symptoms group (N = 33)	Not CR depressive symptoms group (N = 239)	Difference (p_value)	CR anxious symptoms group (N = 71)	Not CR anxious symptoms group (N = 201)	Difference (p_value)
Sociodemographic							
Age (mean, sd)	56.3 (12)	44.2 (12.8)	37.4 (11.7)	0.006	39.6 (12.6)	37.8 (11.8)	0.268
Gender (%)				0.03			0.022
Women	56.3	72.7	46		67.6	52.3	
Men	43.7	27.3	54		32.4	52.2	
Education (%)[a]				0.595			0.753
Primary	42.3	36.4	43.1		43.7	41.8	
Secondary	42.3	48.5	41.4		42.3	42.3	
Tertiary	15.1	15.2	15.1		14.1	15.4	
Occupation (%)				0.009			0.306
Inactive	38.2	51.5	36.4		40.8	37.3	
Housewife/student	16.9	27.3	15.5		21.1	15.4	
Active	44.9	21.2	48.1		38.2	47.3	
Marital status (%)[b]				0.017			0.230
Married	54	63.6	52.7		59.2	52.3	
Divorced/widowed	10.3	18.2	9.2		11.3	9.9	
Single	34.9	18.2	37.2		28.2	37.3	
Neurological Etiology (%) [c]				0.845			0.592
Idiopathic	63.6	54.5	64.9		59.2	65.2	
Secondary	29.4	27.3	29.7		31	28.9	
Type of seizures (%) [d]				0.993			0.716
Focal onset	68.7	66.7	69		73.2	67.2	
Generalized onset	25.7	24.2	25.9		21.1	27.4	
Locus (%) [e]		5	28	0.180	10	23	0.457
Temporal	48.2	24.2	16.7		47.9	48.3	
Extratemporal	22.1	24.2	21.8		25.4	20.9	
Unestablished	17.6	36.4	49.8		12.7	19.4	
Number of seizures per month (%) [b]				0.601			0.107
<1	5.1	6	5		5.6	5	
1-5	40.1	33.3	41		29.6	43.8	
>5	54	60.6	53.1		64.8	50.2	

CR: clinically relevant.
[a] Data missing for 1 participant.
[b] Data missing for 2 participants.
[c] Data missing for 19 participants.
[d] Data missing for 15 participants.
[e] Data missing for 33 participants.

cognitive variables were also analyzed. Analyses were carried out by standard regressions controlling for sex and age as covariates. Statistical significance was determined using Freedman Lane permutation algorithm [28], which is resilient to deviations from normality. To address multiple comparisons, we utilized the Bonferroni correction within each scale and comparison group. Statistically significant results were defined as corrected P values < 0.05. Statistical analyses were conducted using R-4.0.1 software.

3. Results

3.1. Clinical and sociodemographic characteristics

A final number of 272 individuals fulfilled inclusion criteria, 153 being female (56.3 %). Mean age of the total sample was 38.21 years (SD = 12.037) and average age of seizure onset was 17.44 years (SD = 13.748). Sociodemographic and clinical characteristics are summarized in Table 1.

3.2. Psychopathological profile

A total of 112 (41.2 %) patients had received at least one diagnosis according to *SCID-IV*: 61 subjects had been diagnosed with mood disorder, 53 subjects with anxiety disorder, 10 subjects with psychotic disorder and 7 were grouped in other disorders.

The mean HADS scores for the total sample was 12.66 (SD = 7.50) for the total scale, 5.15 (SD = 4.09) for the depression subscale and 7.51 (SD = 4.32) for the anxiety subscale.

Using a cut-off point of 11 for both subscales, the study sample contained 33 (12.13%) subjects with clinically relevant depressive symptoms and 71 (26.10 %) subjects with clinically relevant anxious symptoms.

The mean score for the depression dimension of the SCL-90R was 1.44 (SD = 0.889) and for the anxiety dimension 1.16 (SD = 0.792).

3.3. Neuropsychological profile

Mean results of the different battery of tests range from 40,40 (RAVLT) to 47,20 (S). **Table S1** in Supplementary material provides more information.

3.4. Quality of life

Outcomes from the complete sample regarding the assessment of quality of life using QOLIE-31 are presented in **Table S2** in Supplementary material. The dimensions resulting in the lowest scores were SF (43,00), followed by SW (43,49). However, it is noticeable that all subscales showed low scores.

3.5. Differences in cognition between individuals with clinically relevant psychiatric symptoms and individuals without psychiatric symptoms

No statistically significant differences were found in the cognitive variables between the group with anxious or depressive symptoms and the group without these symptoms. That said, using uncorrected P values we found lower scores in TMTB (p.uncorr = 0.026) variable in the group with anxious symptoms.

Moreover, we did not observe a statistically significant association between the depression and anxiety dimensions of the SCL-90R and cognitive variables.

Table 2
Freddman multiple regression between QOLIE-31 variables and depressive or anxious symptoms assessed by HADS.

	QOLIE-31	$R^2_{adjusted}$	β	SE β	95 % CI	$p_{corrected}$
Depressive symptoms	swt	0.08	−0.77	0.15	−1.06, −0.48	<0.0001
	oqlt	0.16	−0.97	0.14	−1.24, −0.7	<0.0001
	ewt	0.28	−1.3	0.14	−1.57, −1.02	<0.0001
	eft	0.26	−1.06	0.12	−1.3, −0.82	<0.0001
	cogt	0.19	−1.19	0.15	−1.48, −0.9	<0.0001
	sft	0.1	−0.77	0.14	−1.04, −0.5	<0.0001
	qoliet	0.31	−1.4	0.13	−1.65, −1.15	<0.0001
Anxious symptoms	swt	0.12	−0.88	0.14	−1.15, −0.6	<0.0001
	oqlt	0.1	−0.71	0.14	−0.98, −0.44	<0.0001
	ewt	0.26	−1.17	0.13	−1.42, −0.92	<0.0001
	eft	0.15	−0.74	0.12	−0.98, −0.5	<0.0001
	cogt	0.13	−0.9	0.15	−1.19, −0.61	<0.0001
	met	0.06	−0.53	0.14	−0.8, −0.26	<0.001
	sft	0.05	−0.54	0.13	−0.81, −0.27	<0.01
	qoliet	0.23	−1.1	0.13	−1.35, −0.85	<0.0001

The association between cognitive variables and clinical diagnosis of mood or anxiety disorder according to SCID-IV was assessed separately. No significant association was found.

3.6. Differences in quality of life between individuals with clinically relevant psychiatric symptoms and individuals without psychiatric symptoms

When analysing the association between QOL and the presence of anxious or depressive symptoms, we observed lower scores in all QOLIE-31 items with the exception of ME (SW, OQL, EWB, EF, COG, ME, SF, QOLIET) were significantly lower in individuals with depressive symptoms. All QOLIE-31 items were found to be statistically lower in subjects with anxious symptoms (see Table 2 and Figs. 1 and 2 and **Table S3** in Supplementary material).

4. Discussion

To the best of our knowledge, the current study is the first to examine the relationship of severity of anxiety and depressive symptoms measured with HADS and SCL-90R and cognitive performance in DRE. Our results suggest that a relationship between anxious and depressive symptoms in DRE measured with HADS and cognition does not exist. These results are consistent with our outcome regarding the SCL-90R dimensions of anxiety and depression and cognition, where no association was found. QOL in DRE and its relationship with anxiety and depressive symptoms were also evaluated. Low scores were found for all items of QOLIE-31 indicating poor levels of QOL and an association between these scores and anxious and depressive symptoms measured with HADS.

Previous studies have demonstrated an association between depressive and anxious symptoms and DRE and how they contribute to impaired QOL [10,29]. Moreover, patients with DRE suffer from higher seizure frequency, having implications in cognitive function [30] which also negatively affects QOL [31]. However, scarce studies have assessed an association between these symptoms and cognition in the specific group of DRE and research has yielded mixed results. An article published by Rayner et al. [32] compared mood disturbance and autobiographical memory in patients with resistant Frontal Lobe Epilepsy with healthy controls. Their

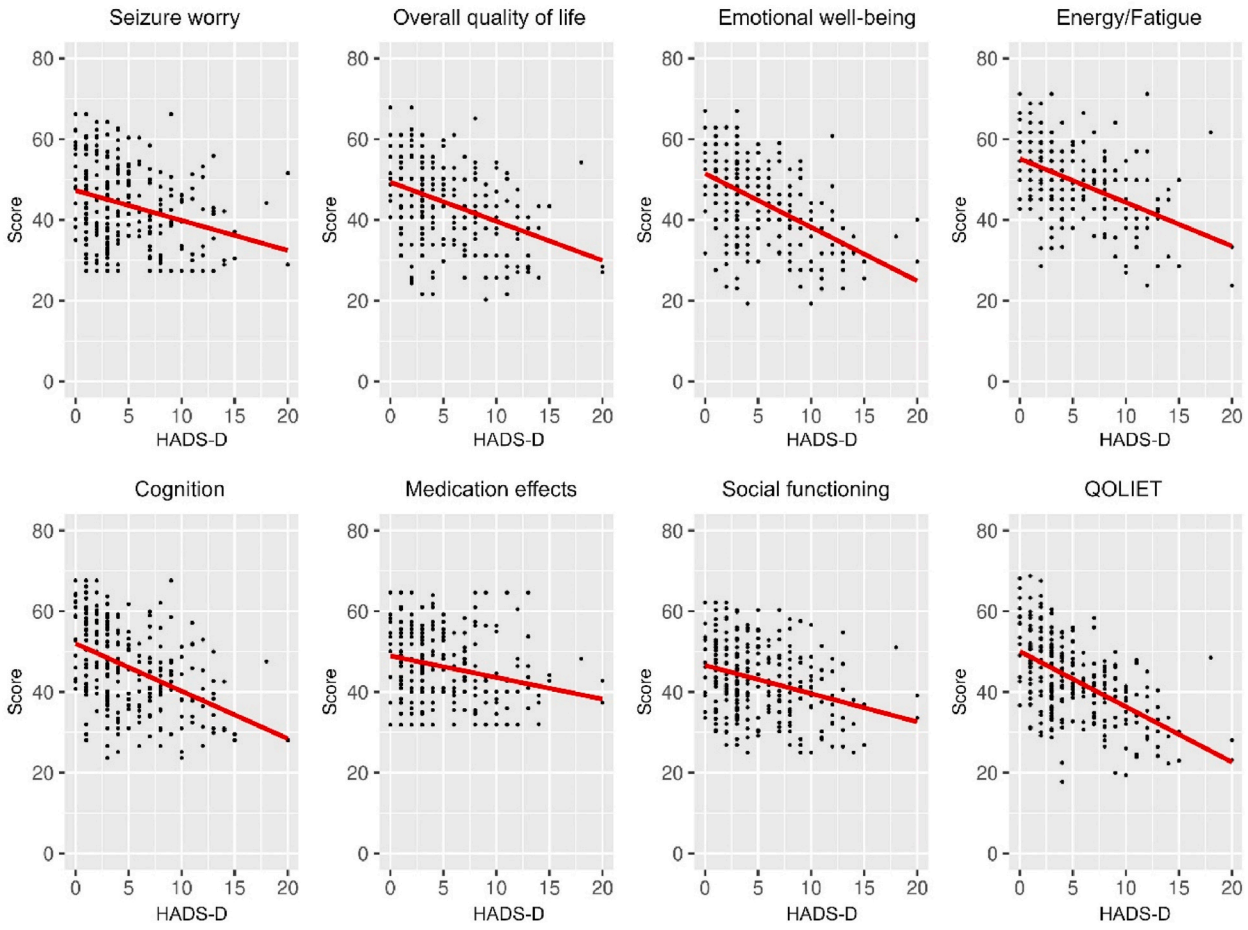

Fig. 1. Association between quality of life measured by QOLIE-31 and presence of depressive symptoms assessed by HADS.

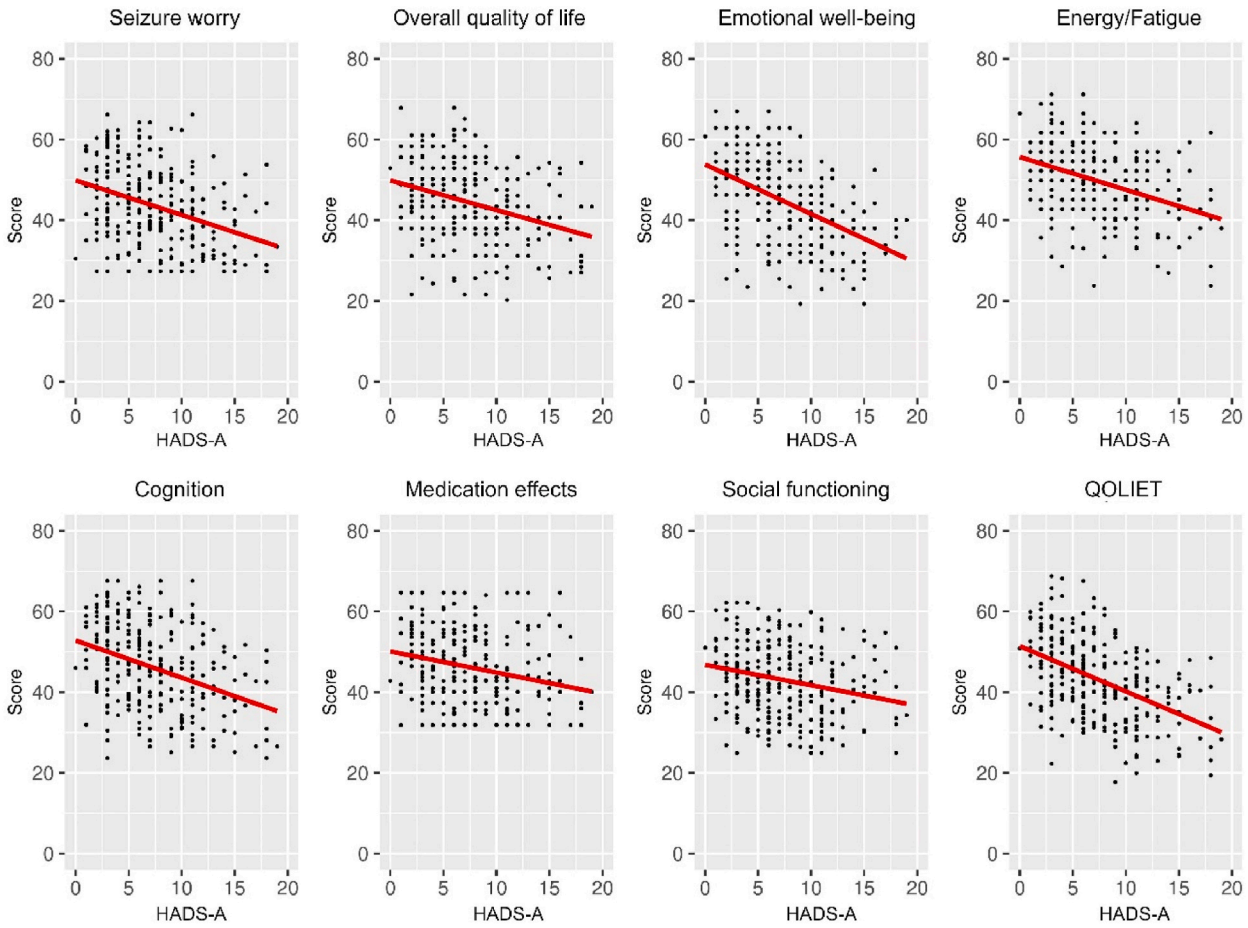

Fig. 2. Association between quality of life measured by QOLIE-31 and presence of anxious symptoms assessed by HADS.

conclusion was that mood disorder was not related to poor autobiographical memory in the subgroup with epilepsy. Furthermore, Tröster et al. [33] studied neuropsychological data from a prior trial [34]. Subjects were assessed at separate times, including before any intervention. No association was found between depression and memory at baseline. However, they mention that this result might be explained by lack of statistical power.

On the other hand, a small number of investigations have aimed to relate anxious or depressive symptoms with cognitive function. Dulay et al. [35] explored the relationship between the extent of depressive symptoms and performance on auditory memory and learning abilities in eighty-four patients diagnosed with DRE and found an impact of depression in memory tasks in subjects with left Temporal Lobe Epilepsy. Tang et al. [7] analyzed the neurocognitive function and psychological profiles of patients with responsive and resistant epilepsy. Despite both groups reported psychological disturbances, a higher number of subjects with DRE presented moderate to severe levels of depression and anxiety. Furthermore, the group with DRE performed worse in almost all the neurocognitive domains. They stated that an association between cognition and psychological measures existed and that this relationship was worthy of further consideration. Nevertheless, it must be mentioned that the instruments for evaluating anxiety and depressive symptoms were different from those used in our research.

Some compelling results were revealed by a recent investigation carried out by Cano et al. [36] in which they studied the association between cortisol levels, factors related to epilepsy, anxiety, depression and memory. Regarding anxiety and memory variables, they concluded that low memory performance is correlated with high trait anxiety. However, they used different scales for evaluating anxiety and depression: the Spanish version of the Beck Depression Inventory-II (BDI-II) and the Spanish version of the State-Trait Anxiety Inventory (STAI) Scale. The STAI scale comprises two distinct scales: the state scale (STAI-S), which assesses the current state of anxiety, and the trait anxiety scale (STAI-T), which assesses relatively stable aspects of anxiety. Cano et al. found an association between memory and high trait anxiety, but not with current state of anxiety. This could be in line with the results of our research, as we assessed anxiety but focusing on the symptoms in the last week, and not as a reliable or lasting state. Taking into account these results, it could be suggested that HADS and SCL-90R, despite being useful as a screening instrument for anxiety and depressive symptoms, might not be a convenient tool to detect potential cognitive comorbidities in DRE.

Another point worth noting is the high occurrence of PD in our sample, with 41.2 % of subjects having at least one diagnosis according to SCID-IV, particularly mood and anxiety disorders, in line with previous results [37]. PD are known to be present in

subjects with epilepsy and to a higher extent in DRE [38]. In fact, a bidirectional relationship has been described, as PD are also considered as risk factors for developing DRE [2,4,39].

Finally, our results showed an association between both anxious and depressive symptoms measured with HADS and lower scores in all QOLIE-31 outcomes (except for depressive symptoms and medication effects). This is consistent with preceding research that has demonstrated similar results [11,12] among subjects with DRE. A recently published investigation carried out by Johnstone et al. [40] proposed psychiatric symptoms as the strongest predictors of QOL in patients with DRE. We consider this finding is of crucial significance and should be taken into account in the assessment of patients with DRE, as there is a need for physicians to recognize and treat comorbid psychopathology in an attempt to ameliorate patients' QOL.

Some limitations of the study should be considered. It is subject to bias as an observational retrospective and monocentric study. Due to the pathology's clinical complexity, the study lacks a control group. Also, there is no post-surgery follow-up. Moreover, the sample was drawn from one epilepsy centre. Therefore, results might not be generalized to other patient groups. Despite the fact that HADS is considered an effective screening tool for individuals with epilepsy, as stated before, it assesses *anxiety and depressive symptoms over the prior week, and the use of other methods that assess these symptoms stable in time or as traits could be of interest. Moreover,* the possible effects of AED treatment and its duration were not considered. Finally, in spite of all patients being diagnosed with DRE, the group was heterogeneous in terms of type of epilepsy and epileptogenic zone.

In summary, when assessing patients with DRE, a comprehensive approach should be adopted, in accordance with the evolving notion that epilepsy implies more than seizures. Depressive or anxiety symptoms are often assessed, particularly as a part of preoperative evaluations in DRE, but rarely studied in relation to cognition. Comorbid depression or anxiety alongside cognitive impairment demands specific attention within both diagnostic and therapeutic evaluations, towards a more integrative perspective, especially since part of these impairments are modifiable factors and have a relevant impact in QOL. However, there remains an existing research gap regarding the relationship between anxious and depressive symptoms and cognitive performance in DRE. This complex relationship requires further attention to enhance our comprehension of this condition and to help to shed more light on the actual concept of epilepsy as a part of a spectrum.

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Data availability statement

Data are not publicly available as it contains confidential information.

CRediT authorship contribution statement

E. Monteagudo-Gimeno: Writing – review & editing, Writing – original draft, Visualization, Project administration, Methodology, Investigation, Data curation, Conceptualization. **R. Sánchez-González:** Supervision, Formal analysis, Conceptualization. **J. Raduà-Castaño:** Resources, Formal analysis. **L. Fortea-González:** Resources, Formal analysis. **T. Boget-Llucià:** Investigation, Data curation, Conceptualization. **M. Carreño-Martínez:** Investigation, Data curation, Conceptualization. **A. Donaire-Pedraza:** Investigation, Data curation, Conceptualization. **N. Bargalló-Alabart:** Investigation, Data curation, Conceptualization. **X. Setoain-Perego:** Investigation, Data curation, Conceptualization. **J. Rumià-Arboix:** Investigation, Data curation, Conceptualization. **A. Bulbena-Vilarrasa:** Formal analysis, Data curation. **L. Pintor-Pérez:** Supervision, Formal analysis, Conceptualization.

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.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2023.e20903.

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