STRESSORS IN EPILEPSY: IMPACT ON COGNITION, QUALITY OF LIFE, AND SOCIAL FUNCTION

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THESIS OUTLINE

Epilepsy is a neurological disorder that affects almost 1% of the general population. It is characterized by the predisposition and recurrence of epileptic seizures, with neurobiological, cognitive, psychological, and social consequences. Furthermore, epilepsy is associated with an increased risk of comorbidities, which can affect the prognosis of the disease and impact other areas of the individual, such as social life, in which patients with epilepsy face challenges. All these factors interact with each other, directly or indirectly affecting quality of life. Therefore, the correct management and treatment of epilepsy should include aspects beyond seizure control, promoting early detection of those patients especially vulnerable to its consequences.

Stress is defined as the process triggered by a stimulus perceived as harmful to homeostasis, which elicits a response to restore equilibrium. Thus, stress can be conceptualized within the Stimulus-Organism-Response model. The maintenance or recurrence of stressors can lead to a situation of chronic stress, which has been identified as a factor related to pathological processes.

Due to their unpredictability, uncontrollability, and the threat they pose to health, epileptic seizures have been considered acute stressors. Therefore, seizure repeatability leads to the conceptualization of epilepsy within a chronic stress model. The close relationship between stress and epilepsy supports this framework, such as the role of stress as a seizure trigger, the higher levels of perceived stress, or the dysregulation of the hypothalamic-pituitary-adrenal axis in this population. This approach in epilepsy could help to achieve more appropriate disease management as well as a more comprehensive perspective. Therefore, this Thesis, which is divided into eleven chapters, aims to explore the stress process in epilepsy.

The first chapter is a general introduction organized in two sections. The first one describes the impact of epilepsy on the individual, focusing on two of the most common comorbidities (i.e., mood disorders and cognitive impairment) and the impact of epilepsy on the social area and quality of life. The second section conceptualizes epilepsy within a chronic stress model, describing the stress process and the relationship between stress and epilepsy.

Due to the scarcity of studies addressing epilepsy within this theoretical framework, and considering the importance of subjective appraisal in the stress process, the second chapter contains a systematic review of perceived stress and epilepsy. This study aims to offer a more

homogeneous view of its impact and facilitate understanding its particularities in this population.

The third chapter describes the theoretical model that follows the present Thesis, detailing the proposed aims and the enunciated hypotheses.

The fourth chapter attempts to determine the impact of a social stressor. This chapter includes Study 1, which aims to explore the effect of academic and/or employment insertion on cognitive performance, perceived social support, negative affectivity, and quality of life, as well as the relationship between these variables.

The fifth and sixth chapters are focused on exploring individual modulator factors of stress in epilepsy. The fifth chapter comprises Study 2, which examines the effect of a new antiseizure medication on cognitive performance, negative affectivity, and quality of life after three and six months of adjunctive treatment. The sixth chapter contains Study 3, aimed at identifying stress profiles in epilepsy, and studying the differences in cognitive performance and quality of life according to these phenotypes.

The seventh chapter addresses the cortisol response to acute psychosocial laboratory stressor exposure. In this chapter, Study 4 explores the differences in the cortisol response to the Trier Social Stress Test between patients with epilepsy and healthy people. In addition, it compares cortisol levels between patients with epilepsy who were subjected to the stressor and patients with epilepsy who were not. Finally, it examines the relationship between cortisol response and memory functioning, mood, and quality of life.

These chapters emphasize the importance of the consideration of stress in epilepsy. Nevertheless, there is a need for appropriate instruments to assess perceived stress in drug-resistant epilepsy. Therefore, the eighth chapter, through Study 5, discusses the development and validation of a new scale to measure perceived stress in this population.

The ninth chapter provides a general discussion of the results obtained. Moreover, the clinical implications, limitations and future directions are provided.

The tenth chapter summarizes the main conclusions of the present Thesis.

Finally, the eleventh chapter provides a comprehensive summary of this Thesis in Spanish, encompassing the objectives through to the conclusions reached.

ABBREVIATIONS

ANT = Animal Naming Test

ASM = antiseizure medication

AUC = area under curve

AUC_g = area under the curve with respect to ground

AUC_i = area under the curve with respect to the increase (baseline)

BDI-II = Beck Depression Inventory-II

BNT = Boston Naming Test

BS = breakthrough seizures

C = cortisol

CBD = cannabidiol

CBZ = carbamazepine

CG = control group

CG-H = control group of healthy individuals

CG-E = control group of patients

CLZ = clonazepam

CNB = cenobamate

CV = calidad de vida

CVLT = California Verbal Learning Test

DASS-21 = Depression, Anxiety and Stress Scales

DDD = defined daily dose

DRE = drug-resistant epilepsy

EAP = Expanded Access Program

EEG = electroencephalography

EFA = exploratory factor analysis

EG = experimental group

EPSI-A = Epilepsy Perceived Stress Inventory for Adults

EOR = Estímulo-Organismo-Respuesta

ESI-R = Revised Epilepsy Stressor Inventory

ETLE = extratemporal lobe epilepsy

FAES = fármacos antiepilépticos

FCD = focal cortical dysplasia

FDG = fluorodeoxyglucose

FAS = focal aware seizure

FBTCS = focal to bilateral tonic-clonic seizure

FIAS = focal impaired awareness seizure

FLE = frontal lobe epilepsy

FS = functional seizures

GAD-7 = Generalized Anxiety Disorder Assessment

GC-E = grupo control de pacientes con epilepsia

GC-S = grupo control de individuos sanos

GE = grupo experimental

HADS = Hospital Anxiety Depression Scale

HCs = healthy controls

HHA = hipotálamo-hipofiso-adrenal

HPA = hypothalamus-pituitary-adrenal

HS = hippocampal sclerosis

ILAE = International League Against Epilepsy

ILE = insular epilepsy

LEV = levetiracetam

LH = left-hemisphere

LTG = lamotrigine

LTLE = left temporal lobe epilepsy

J-SACL = Japanese-Stress arousal Check List

K = Kessler Psychological Distress Scale

KMO = Kaiser-Meyer-Olkin

MOS = Medical Outcomes Study Social Support Survey

MRI = magnetic resonance imaging

n.s.d. = no significant differences

n.e. = not specified

n.s.r. = no significant relationship

PANAS = Positive and Negative Affect Schedule

PB = phenobarbital

PCE = posterior cortex epilepsy

PET = positron emission tomography

PHQ = Patient Health Questionnaire

PM = percent mediation

PMD = primidone

PS = perceived stress

PSS = Perceived Stress Scale

PWE = people with epilepsy

OLE = occipital lobe epilepsy

QOL = quality of life

QOLIE-31 = Quality of Life in Epilepsy Inventory

RCI = reliable change index

RMET = Reading the Mind in the Eyes Test

ROCF = Rey-Osterrieth Complex Figure test

SEEG = stereotactic implantation of depth electrodes

SOR = Stimulus-Organism-Response

SPECT = single photon emission computed tomography

STAI = State-Trait Anxiety Inventory

STAI-S = state anxiety scale of the STAI

STAI-T = trait anxiety scale of the STAI

STROBE = Strengthening the Reporting of Observational Studies in Epidemiology

SUD = substance abuse disorder

TAVEC = Test de Aprendizaje Verbal España-Complutense

TLE = temporal lobe epilepsy

TMT = Trail Making Test

TSST = Trier Social Stress Test

VPA = valproic acid

WCE = well-controlled epilepsy

WCST = Wisconsin Card Sorting Test

WHO = World Health Organization

WMS-III = Wechsler Memory Scale-Third Edition

WWE = women with epilepsy

CHAPTER 1

General introduction

1. Individual impact of epilepsy

Epilepsy is a neurological disorder characterized by a lasting predisposition and recurrence of spontaneous seizures, that comprehensively impacts the individual (Fisher et al., 2017). It affects approximately 70 million people worldwide (Thijs et al., 2019), and is one of the most prevalent brain diseases. In Spain, according to the Spanish Society of Neurology (2019), around 400,000 people have epilepsy, with 62.6 new diagnoses per 100,000 inhabitants per year (García-Martín & Serrano Castro, 2018).

Epilepsy diagnosis requires the fulfillment of at least one of the following conditions: a) at least two unprovoked seizures occurring more than 24 hours apart; b) one unprovoked seizure and a probability of further seizures similar to the general recurrence risk after two unprovoked seizures (i.e., at least 60% occurring over the next 10 years); and c) the diagnosis of an epilepsy syndrome (Fisher et al., 2014). Epileptic seizures are described as the "transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain" (Fisher et al., 2005) and can be classified into three categories, depending on their onset (i.e., focal, generalized, and unknown). Focal onset seizures are those that are limited to one hemisphere; generalized onset seizures rapidly activate bilaterally distributed networks; and unknown onset seizures are those that cannot be classified in the above categories due to insufficient evidence (Fisher et al., 2017). Moreover, within these categories, seizures can be subclassified according to the presence or absence of motor symptoms, and focal seizures can also be subcategorized depending on the impairment of consciousness (Fisher et al., 2017).

First-choice epilepsy treatment includes the use of antiseizure medications (ASMs) to control the occurrence and frequency of seizures. Although this treatment is effective for most patients (Kwan et al., 2011), in about one-third of this population ASMs are not successful in controlling seizures, suffering what is known as drug-resistant epilepsy (Sultana et al., 2021). Drug-resistant epilepsy has been defined as the "failure of adequate trials of two tolerated, appropriately chosen and used antiepileptic drug schedules (whether as monotherapies or in combination) to achieve sustained seizure freedom" (Kwan et al., 2010). In some of these patients, surgery can be considered an alternative treatment, with proven efficacy in seizure remission (Helmstaedter, 2013).

People with drug-resistant epilepsy suffer the global burden of epilepsy (Jacoby & Baker, 2008). These patients experience more severe clinical conditions, probably due to the poor

control of seizures (López-González et al., 2015). Thus, people with drug-resistant epilepsy have an increased risk of mortality (Tomson et al., 2005), worse cognitive performance (Monteagudo-Gimeno et al., 2020), a wider range of comorbidities (Scheffer et al., 2017), and a greater likelihood of experiencing adverse effects from ASMs (Jacoby & Baker, 2008) than people with well-controlled epilepsy. Furthermore, these patients seem to have a vulnerable profile to the psychological effects of epilepsy, showing higher levels of depression and anxiety (Gilliam et al., 2004; Micoulaud-Franchi et al., 2016). Finally, drug-resistant epilepsy has been related to poor social function, with more work-related difficulties (Majkowska-Zwolińska et al., 2012), lower social support (Amir et al., 1999), higher perceived stigma (Deleo et al., 2020) and lower quality of life (QOL) (Akdemir et al., 2016).

As can be seen, epilepsy affects different areas of the individual, as stated in its latest conceptualization, which follows a holistic health perspective. The International League Against Epilepsy (ILAE) recognizes in the definition of this disorder the associated neurobiological, cognitive, psychological, and social consequences (Fisher et al., 2014). This comprehensive effect on the lives of people with epilepsy may be due, at least in part, to aspects such as the recurrence of seizures, emotional and social disturbances, and comorbid disorders, which are especially common in epilepsy (Aydemir et al., 2004; López-González et al., 2015) and whose interest has increased in recent years.

1.1. Comorbidities in epilepsy and their underlying mechanisms

Comorbidities in epilepsy can affect its prognosis (Keezer et al., 2016) and impact on QOL (Cano-López et al., 2018, 2023; Pauli et al., 2017). In 2017, the ILAE emphasized the importance of their consideration for proper management of epilepsy (Scheffer et al., 2017), contemplating them within the last classification of epilepsies. Comorbidities are more frequent in patients with severe epilepsy conditions. Specifically, a higher prevalence of comorbidities has been found in older patients with focal and structural epilepsy and with higher seizure frequency (Giussani et al., 2021). Moreover, its prevalence seems to vary according to the system involved, with the most common systems affected by comorbidities being developmental (21.3%), psychiatric (16.7%), cardiovascular (15.7%), endocrine (10.3%), cerebrovascular (7.6%), and neurological (4.9%) (Giussani et al., 2021).

1.1.1. Mood comorbidities

Mood comorbidities have been widely studied in this population due to the higher rates (Josephson et al., 2017), especially in patients with temporal lobe epilepsy (TLE) and focal onset (de Araújo Filho et al., 2011; de Oliveira et al., 2010). About 30% of people with epilepsy have mood comorbidities (Mula et al., 2021), and the most common are depressive and anxiety disorders, with prevalences of 35.0% and 25.6%, respectively (Lu et al., 2021). These comorbidities can affect the prognosis of the disease, showing a positive relationship to clinical variables, such as seizure frequency (Dehn et al., 2017), the side effects of ASMs (Kanner et al., 2012; Josephson et al., 2017), and the epilepsy duration (Scott et al., 2020; Yang et al., 2020).

Among mood disorders, major depressive disorder emerges as the most prevalent in people with epilepsy (Lu et al., 2021). This relationship appears bidirectional, since people with depression have twice the risk of developing epilepsy (Hesdorffer et al., 2012). Several theories try to explain the underlying mechanisms, which are not mutually exclusive. From a psychological viewpoint, depression in epilepsy could be conceptualized within the diathesis-stress model (Hoppe & Elger, 2011), in which the burden of epilepsy and the feeling of uncontrollability and hopelessness can place these patients in a vulnerable situation, depending on the individual's psychological and coping capacities. In other words, if the demands exceed the individual's coping faculties, the probability of developing a depressive mood will be higher.

From an electrophysiological perspective, depressive symptoms could be related to the ictal discharges. First, depressive symptoms could appear before seizures. Privitera et al. (2014) found that having a history of depression in the past and increased depressive symptomatology were associated with stress-precipitated seizures. Second, depressive mood could also occur between seizures. Kanner et al. (2004) found that 38 patients out of the 100 showed interictal symptomatology, 34 of whom experienced depressive symptoms. Accordingly, Mula et al. (2010) showed that 21.8% of the patients had interictal dysphoric disorder and that, between them, 54.8% of the cases were related to seizures. Third, postictal depression (i.e., depressive symptoms occurring within five days after a seizure) has been found in a high percentage of patients. In this line, Kanner et al. (2010) showed that 43% of patients experienced depressive symptoms after seizures, and this symptomatology could last from hours to days (Hoppe & Elger, 2011).

Finally, depressive symptoms could be a side effect of ASMs (Angus-Leppan et al., 2023; Mula et al., 2024). About 17% of patients show mood or behavioral side effects associated with the pharmacological treatment, and depressive symptoms are the second most common, after irritability (Chen et al., 2017; Weintraub et al., 2007). More specifically, levetiracetam (Chen et al., 2017), zonisamide (Cavanna & Seri, 2013; Chen et al., 2017), and perampanel (Lee et al., 2020) have been related to depressive symptoms, while lamotrigine seems to promote mood stabilization (Besag et al., 2021; Chen et al., 2017). This fact underlines the importance of matching the pharmacological treatment to the psychological characteristics of the patients, especially in those with a family and/or personal psychiatric history (Mula, 2017).

While the mechanisms underlying depression in epilepsy have been extensively studied, that statement does not apply to anxiety. Anxiety was described by Kanner (2011) as the "forgotten psychiatric comorbidity" despite its high prevalence and impact on the lives of people with epilepsy. According to Hingray et al. (2019), this could be due to the increased heterogeneity of anxiety disorders (Josephson et al., 2017) and the higher sensitivity of clinicians to detect and treat mood disorders (Jansen et al., 2019). Nevertheless, some mechanisms that underlie depression in epilepsy could also explain anxiety. Indeed, the relationship between anxiety and epilepsy is likewise bidirectional, since there is also an increased risk of anxiety prior to the epilepsy onset (Munger Clary, 2014), showing a higher incidence even up to three years before the diagnosis (Hesdorffer et al., 2012).

Furthermore, anxiety could also be conceptualized within a framework of epilepsy as a chronic stress model (Cano-López & González-Bono, 2019), in which patients with ineffective tools to cope with the stressors (e.g., seizures) might be more likely to suffer from anxiety symptoms. Moreover, anxiety has been described as a self-perceived seizure trigger (Lanteaume et al., 2009; Sperling et al., 2008). In this line, Lanteaume et al. (2009) found that TLE patients who identified emotional stimuli as precipitators of seizures presented an attentional preference for threatening inputs compared to those neutral, supporting the hypothesis that attentional biases towards these types of stimuli might underlie the increased vulnerability to anxious symptomatology.

Considering the neuroanatomical viewpoint, anxiety may respond to the activation of a neural network, in which the limbic system plays an important role. In this regard, Biraben et al. (2001) studied four cases of patients with drug-resistant epilepsy who underwent

stereotactic implantation of depth electrodes (SEEGs), showing that anxiety symptoms appeared when the discharge activated the orbitofrontal, prefrontal, anterior cingulate, and temporal limbic cortices. However, some studies have focused on the relevance of the amygdala. This area has a key role in processing emotional stimuli and in the fear/stress response. The amygdala nucleus has certain cell types and pathways that are important for natural defensive behaviors, like those related to anxiety (Fadok et al., 2018). Furthermore, the amygdala is implied in the manifestation of anxious symptomatology and epileptic discharges in TLE (Beyenburg et al., 2005), especially in those with hippocampal sclerosis (HS) (Hudson et al., 1993; Miller et al., 2016). This implication appears to have a lateralizing pattern, in which the direct electrical stimulation of the right amygdala triggers anxiety symptoms, and the stimulation of the left side can induce pleasant emotions (Lanteaume et al., 2007).

From a pathophysiological view, anxiety could be related to electroencephalography (EEG) changes in the preictal stages (Petitmengin et al., 2006), predicting seizure occurrence (Haut et al., 2012). Nevertheless, preictal anxiety is the most difficult to differentiate (Kimiskidis & Valeta, 2012), as these patients have higher baseline levels of anxiety than the general population and the symptomatology can occur days or hours before the seizures (de Toffol et al., 2018). Ictal anxiety, on the other hand, is a more common phenomenon that can be manifest in about 15% of patients with partial seizures as an aura (Kimiskidis & Valeta, 2012), especially in those with TLE (Vazquez & Devinsky, 2003). This event is characterized as an intense fear or panic attack, although depersonalization, déjà vu, hallucinations, and other symptoms can also be experienced (Beyenburg et al., 2005). The manifestation of interictal anxiety differs slightly, and is represented as anxiety disorders or other related, such as generalized anxiety disorder, panic disorder, and posttraumatic stress disorder (Vazquez & Devinsky, 2003). However, as with preictal anxiety, it is difficult to differentiate whether these symptoms are due to the effect of abnormal electrical discharges. Finally, postictal anxiety has been found to be the most prevalent postictal symptom, manifesting in 45 out of 100 patients (Kanner et al., 2004). Postictal anxiety usually lasts about 24 hours and is normally expressed as concern, intense fear, panic, or agoraphobia (Kimiskidis & Valeta, 2012). Nonetheless, it is noteworthy that postictal anxiety tends to occur together with depressive symptomatology, suggesting that they could be considered as a single cluster of symptoms that may be due solely to the postictal period, the result of the severity of postictal symptoms, or even both (Kanner et al., 2010).

As well as depressive symptomatology, anxiety in epilepsy can be influenced by the effect of ASMs. In this regard, Ketter et al. (1999) found that drugs that potentiate GABAergic transmission (i.e., valproic acid, phenobarbital, benzodiazepines, primidone, gabapentin, tiagabine, and vigabatrin) can reduce anxiety symptomatology, whereas drugs that attenuate glutamatergic synaptic excitation (i.e., felbamate and lamotrigine) may have anxiogenic effects. Nevertheless, more recent research offers more accurate results. More detailed, levetiracetam, topiramate, lamotrigine, and felbamate seem to cause anxiogenic effects, whereas barbiturates, benzodiazepines, gabapentin, and pregabalin may mitigate anxiety symptoms (Kanner, 2016; Perucca & Mula, 2013). Despite this, it should be noted that these effects may not solely result from the individual impact of each drug, but could also be influenced by the interaction of different ASMs (Perucca & Mula, 2013), especially in this population, where a high percentage of patients receives polytherapy.

The similarities between depression and anxiety in their underlying mechanisms and their impact on the lives of people with epilepsy suggest that their joint study could constitute a more comprehensive approach, providing a more complete understanding of epilepsy and its consequences. Furthermore, by considering epilepsy as a model of chronic stress, investigating depression and anxiety together (hereafter referred to as "negative affectivity") may provide stronger evidence and avoid the loss of information that could occur when addressing them separately. Therefore, the term negative affectivity will be used in this Thesis to refer to the intensified emotional response (i.e., depression and anxiety) to epileptic seizures, as well as to limitations in autonomy and daily life activities (Kotwas et al., 2017). This concept has already been coined in previous epilepsy literature (e.g., Cano-López et al., 2018; Kwon & Park, 2014; Lozano-García et al., 2021).

1.1.2. Cognitive impairment

Cognitive impairment is a very common comorbidity in epilepsy, affecting between 70% and 80% of patients (Helmstaedter & Witt, 2017; Ives-Deliperi & Butler, 2021). This impairment responds to a set of interrelated multifactorial interactions, where demographic, clinical, morphological, and treatment variables influence the patient's cognitive performance (Helmstaedter & Witt, 2017), with memory, attention, executive functions, and language being particularly responsive (Wang et al., 2019).

Previous literature has delineated a neuropsychological profile influenced by demographic variables, in which an older age, unemployment, limited reserve capacity, and low social support are related to poor cognitive performance (Brodie et al., 2009; Dikmen & Morgan, 1980; Helmstaedter, 1999; Hohmann et al., 2021; Qin et al., 2022). Regarding clinical variables, epileptiform activity has been proven to be related to memory decline, impaired attention, language difficulties, and behavioral disorders (Stafstrom & Carmant, 2015). Fortunately, these effects on cognition can be reversible and limited in time (Helmstaedter & Witt, 2017), although recurrent epileptic discharges can have a more severe and permanent impact (Landi et al., 2019; Novak et al., 2022). Other factors related to poor cognitive performance include an early epilepsy onset, long epilepsy duration, and high seizure frequency, among others (Lenck-Santini & Scott, 2015).

Concerning morphological variables, different cognitive profiles have been found depending on the location of the epileptic focus, which could be one of the mechanisms underlying neuropsychological deficits in epilepsy. In this regard, approximately 70% of TLE patients show an impairment in declarative memory (Helmstaedter & Kockelmann, 2006). Considering lateralization, a study that compared the effect of epileptic activity on memory showed that left temporal lobe seizures were associated with a worsening in verbal recognition memory, while right TLE was related to a decline in visual recognition memory (Helmstaedter et al., 1994). Nevertheless, other cognitive domains can also be affected in people with TLE, such as language, executive functions, attention, or psychomotor speed (Agah et al., 2017; Elverman et al., 2019; Hermann et al., 2006; Stretton & Thompson, 2012). Regarding frontal lobe epilepsy (FLE), the second most common type of epilepsy, patients often show problems in attention, working memory, planning, cognitive flexibility, response inhibition, psychomotor speed, verbal fluency, and problem-solving (Arrotta et al., 2022; Elger et al., 2004; Wang et al., 2019). Finally, posterior cortex epilepsy (PCE) (i.e., parietal and occipital lobe) has been less explored, probably influenced by the lower prevalence compared to other epilepsy types. PCE patients have shown worse performance in visuoconstruction, language, and executive functions than healthy people (Traianou et al., 2019).

Another clinical factor that could influence cognitive performance is pharmacological treatment, particularly polytherapy (Helmstaedter & Witt, 2020; Witt et al., 2015; Witt & Helmstaedter, 2013). In fact, cognitive side effects are the least tolerated (Witt &

Helmstaedter, 2013), probably due to their impact on daily life activities and their relationship with QOL (Giovagnoli et al., 2014). Attention and executive functions are one of the most sensible domains of the pharmacotherapy effects, although memory and language can also be affected (Witt & Helmstaedter, 2013). Some of the ASMs that have been related to worse cognitive outcomes are benzodiazepines, phenobarbital, topiramate, zonisamide, and bromide, whereas levetiracetam, brivaracetam, lamotrigine, lacosamide, gabapentin, eslicarbazepine, and perampanel are considered safer in terms of cognition (Helmstaedter et al., 2020; Witt & Helmstaedter, 2013).

Although all these factors could be influencing cognitive performance in patients with epilepsy, it seems that neuropsychological deficits are not only the result of the disease and its treatment, since poor performance can also be seen in newly diagnosed patients who have not yet received treatment. In this regard, Witt & Helmstaedter (2012) found that about 75% of 247 patients with this profile showed memory, attention, or executive function deficits. Along the same line, Taylor et al. (2010) showed that people with newly diagnosed epilepsy without treatment performed worse than healthy people on 10 out of 16 cognitive measures. When the results were adjusted by age, sex, or study level, these differences remained significant for memory and psychomotor speed. Furthermore, Pugh et al. (2024) found that newly diagnosed patients showed poorer performance in executive functions, as well as in verbal learning and memory, than healthy people. Thus, it can be suggested that common mechanisms might be underlying both, cognitive impairment and epileptic seizures, given the engagement of shared neural networks.

1.1.3. Relationship between negative affectivity and cognitive performance

Negative affectivity and cognitive performance are closely related (Wang et al., 2019). Nevertheless, the number of studies that have addressed the impact of depression and anxiety together are few and far between, showing heterogeneous results. In this regard, Bingaman et al. (2023) pointed out that depression severity was associated with generalized-impairment phenotype, whereas anxiety had no impact on cognitive performance. Contrarily, Miller et al. (2016) and Cano-López et al. (2019) found that anxiety, but not depressive symptoms, predicted memory performance in patients with epilepsy. Finally, other studies have obtained more conciliatory results, showing that both, depression and anxiety, are negatively related to cognition (Jarčušková et al., 2020; Tang et al., 2013).

Analyzing studies that have addressed the effect of depression on cognitive performance independently, it has been found that patients with epilepsy and comorbid depression are more likely to have cognitive impairment (Arend et al., 2018). Indeed, Rayner et al. (2016a) found that depression in people with epilepsy may be more strongly linked to deficits in cognitive networks than primary depression. Paradiso et al. (2001) showed that TLE patients with depression had lower scores on the intellectual quotient, language function, visual memory, and psychomotor speed than those without depression. Nevertheless, Tracy et al. (2007) found no differences in cognitive performance between patients with and without depression, although the low cut-off used to classify patients could explain, at least in part, this result.

Differentiating by domains, and according to the cognitive functions explored in this Thesis, the severity of depressive symptoms has been related to memory deficits (Rösche et al., 2012), although Helmstaedter et al. (2004) stated that this relationship could be observed only in patients with left lateral TLE. Espinosa et al. (2010) found that depressive symptoms in TLE patients were related to poor executive functions, even compared to patients with only depression (Galioto et al., 2017). Interestingly, Ramirez et al. (2010) found a differential effect of depressive symptoms, showing that, in TLE patients, depression affected tasks related to verbal executive functioning, while in FLE patients depression was related to worse verbal fluency. In addition, depression was found to exacerbate language impairments associated with epileptogenic lesions; specifically, depression was related to worse visual confrontation naming performance in patients with left mesial TLE and to poorer verbal fluency in patients with FLE compared to patients with right mesial TLE (Ramirez et al., 2010). Given the strong neural connectivity between the frontal and mesial temporal lobe, the exacerbation of deficits may be due to an impact of depression on the underlying dysfunctional neural circuit (Ramirez et al., 2010).

Although more limited, other studies have also addressed the effect of anxiety separately. In this regard, a negative relationship between memory performance and anxiety has been found (Brown et al., 2014; Cano-López et al., 2023). However, Ramirez et al. (2010) found contrary results, showing that anxiety was correlated to better performance in visual confrontation naming and semantic fluency in patients with FLE, proposing that moderate levels of anxiety could have a positive effect on cognitive performance, following the inverted-U hypothesis (Ramirez et al., 2010). Interestingly, Brown et al. (2014) observed

that, in a group of patients with low anxiety levels, those with left TLE performed worse in verbal memory than patients with right TLE. Hence, these authors stated that lateralization of verbal memory through neuropsychological measures may not be fully sensitive in patients with high levels of anxiety.

1.2. Social consequences

In addition to the recurrence of seizures, patients with epilepsy deal with challenges in social life. Traditionally, patients with epilepsy have been the subject of social stigma that used to be linked to the absence or bias in the information available to the population. Social stigma is a complete construct to evaluate because it is usually susceptible to social desirability biases. However, it is reflected in certain demographic indicators such as lower employment ratios, study levels, or marriage rates, which are more common among people with epilepsy, as well as poor social support (Kinariwalla & Sen, 2016; Stavem et al., 2000). This setting can compromise the self-esteem and autonomy of people with epilepsy, affecting their QOL (Jacoby & Austin, 2007; Marinas et al., 2011) and being even better predictors of QOL than clinical variables (Tombini et al., 2021).

1.2.1. Employment insertion

Unemployment rates among people with epilepsy are higher than in the general population (de Souza et al., 2018; Viteva, 2013), and it has been related to negative affectivity (Gandy et al., 2015; Wo et al., 2016). The main proposed predictors of unemployment are epilepsy chronicity, the occurrence of seizures during the last year, and polytherapy; the uncontrollability of the seizures being the more powerful predictor (Majkowska-Zwolińska et al., 2012; Marinas et al., 2011).

Different reasons can explain the high percentage of unemployment in people with epilepsy. On the one hand, people with epilepsy deal with objective restrictions (Smeets et al., 2007). For example, employment opportunities are limited due to potential hazards. As a result, these patients often have to deal with risky situations to keep their jobs (Almatrood et al., 2024; Elwes et al., 1991). Furthermore, the restrictions on driving restrict the jobs to which they can gain access. Driving limitations are highly significant, since it is the area

most affected by epilepsy according to the patient's opinion, with Spain being the European country with the highest impact (Strzelczyk et al., 2023).

On the other hand, patients with epilepsy feel stigmatized, both in terms of getting jobs and by their co-workers. In this line, Smeets et al. (2007) stated that stigma could greatly affect having and maintaining employment in epilepsy. Furthermore, this situation appears more serious than other chronic conditions. A survey of patients with epilepsy and patients with heart disease showed that 32% of people with epilepsy claimed to have been dismissed due to the disease, whereas only 6% of patients with heart disease stated having experienced this (de Souza et al., 2018). In addition, 44% of patients with epilepsy reported not getting jobs because of the disease, compared to the 4% in the group of people with heart disease (de Souza et al., 2018).

In this line, Harden et al. (2004) surveyed having a co-worker with epilepsy, multiple sclerosis, or depression, showing that 50% of people would feel comfortable giving first aid to a colleague with multiple sclerosis or depression, but only 30% would feel comfortable giving first aid to a colleague with epilepsy. Furthermore, respondents perceived greater concern about the possibility of unpredictable behavior and greater discomfort in social interactions with peers with epilepsy than in the other diagnoses, including those outside the work environment (Harden et al., 2004). Therefore, Harden et al. (2004) concluded that the level of discomfort in relating to people with epilepsy was more associated with concern for their health than with negative connotations, proposing that epilepsy first aid instruction could decrease stigma.

However, Parfene et al. (2009) found that, even when controlling the reasons most commonly given for discrimination against people with epilepsy in the workplace, the stigma remained, suggesting that there is a social rejection of the disease that goes beyond concern for the patient, highlighting the need for greater workplace education and awareness of epilepsy. This stigmatization has a direct impact on the disease and is associated with a more vulnerable clinical profile, especially in those with tonic-clonic seizures (Rätsepp et al., 2000). Particularly, perceived stigma has been related to poorer seizure control, higher severity of seizures, higher number of epilepsy-related accidents, greater number of comorbidities, worse negative affectivity, and higher number of ASMs and side effects (Baker et al., 2000; Harden et al., 2004; Shi et al., 2017).

The impact of unemployment on epilepsy involves all areas of the individual and is one of the major concerns for these patients. First, it negatively affects the patient's economy, which in some countries may limit access to medical care and appropriate treatment. Even among those who are working, people with epilepsy earn less income than employed healthy people (Jennum et al., 2011). Second, unemployment in people with epilepsy has been related to lower self-esteem (Lee, 2005; Schachter et al., 1993), impacting the person's own identity, perceived dignity, and autonomy (Smeets et al., 2007). Third, employment insertion is associated with social support. In this regard, Wo et al. (2016) studied the differences between people with epilepsy with high and low employability (i.e., the percentage of actual months working over the expected working period), showing that patients in the high employability group had higher social support, lower perceived stigma, higher self-esteem, and higher self-determined motivation than the low employability group. Nevertheless, although some studies have explored the benefits of work in this population, few have addressed the question of whether employment is a source of social support.

1.2.2. Social support

Social support is an essential factor in the study of chronic diseases, as it promotes well-being and improves patient functioning (Sherbourne & Stewart, 1991). Social support can be conceptualized as the perception of being part of a social network, where help could be available from other network members (McDowell, 2023). Therefore, it can come from different sources, such as friends, family, coworkers, or even communities (Liu et al., 2024).

Although it is difficult to establish a patient profile based on social support, Liu et al. (2024) found that patients with late-onset epilepsy differed in sociodemographic variables depending on social support levels. Specifically, patients with high social support tended to be younger, married, live in urban areas, have higher educational level, experience earlier epilepsy onset, and have fewer generalized seizures (Liu et al., 2024). Additionally, they were more likely to have been seizure-free in the past year and to have an unknown etiology compared to those with poor social support (Liu et al., 2024).

Social support has been proven to be a highly significant variable for people with epilepsy, due to its strong relationship with QOL (Jacoby et al., 2009). In addition, it promotes safer behaviors (Siqueira et al., 2011) and is associated with improved health

conditions (Cohen, 2004). In this regard, Lu & Elliott (2012) found that patients with more severe epilepsy were those who had poor social support and not those with poor seizure control. Remarkably, Amir et al. (1999) found that social support mediated the relationship between disease severity and self-efficacy in epilepsy. In addition, people with epilepsy and poor social support have been shown to perceive worse health status, with a higher number of physical comorbidities and experiencing an increased burden of psychiatric comorbidities (Charyton et al., 2009; Liu et al., 2024).

Indeed, the buffering role of social support seems to extend also to these psychiatric comorbidities (Wang et al., 2015). Social support has been considered a protective factor against negative affectivity (Batchelor & Taylor, 2021) and depressive symptoms separately (Lee et al., 2010), even in the long term (Reisinger & DiIorio, 2009). Regarding anxiety, reports addressing its relationship with social support are scarce. Nevertheless, Gülpek et al. (2011) showed that higher levels of social support in terms of friendship were related to lower anxiety levels. Therefore, a greater focus on the interaction between these two variables could help to elucidate questions that remain unresolved.

1.3. Impact on QOL

The World Health Organization (WHO) defines QOL as "a broad ranging concept affected in a complex way by the person's physical health, psychological state, personal beliefs, social relationships and their relationship to salient features of their environment" (WHO, 1995). Thus, it is a multidimensional concept that encompasses the well-being of the individual, which goes beyond the dichotomy of health and disease, and whose interest in the field of epilepsy has been supported by a large body of research.

QOL in epilepsy has been conceptualized within the model of Baker et al. (1993) which comprises physical (e.g., seizure frequency or severity), psychological (e.g., emotional and cognitive), and social (e.g., employment or personal relationships) variables. This theoretical framework is supported by scientific evidence, finding direct relationships between QOL and these variables.

Beginning with physical/clinical variables, lower seizure frequency (Akdemir et al., 2016; Piperidou et al., 2008; Şenol et al., 2007), less severe seizures (Bautista & Tannahill Glen, 2009; Sancho et al., 2010), older age at epilepsy onset (George et al., 2015; Szaflarski

et al., 2006), shorter epilepsy duration (Ayanda & Sulyman, 2020; Piperidou et al., 2008; Szaflarski et al., 2006), lower number of ASMs (George et al., 2015; Thomas et al., 2024; Wang et al., 2022) and less adverse effects of ASMs (George et al., 2015; Perucca et al., 2009) have been related to better QOL. In a systematic review, Taylor et al. (2011) found that seizure frequency was the most common predictor, with fairly consistent results. Nonetheless, physical variables, in general, explained about 20% of the variance in QOL, whereas psychological factors explained up to 35% of the variance (Johnson et al., 2004; Suurmeijer et al., 2001; Taylor et al., 2011).

Among psychological factors, depression, anxiety, and cognitive impairment are considered in the QOL model developed by Baker et al. (1993). Regarding negative affectivity, depression and anxiety have been found to be one of the strongest predictors of QOL, despite the variety of measures used (Taylor et al., 2011). In this line, it has been suggested that depression and anxiety negatively and independently affect QOL (Choi-Kwon et al., 2003; Johnson et al., 2004; Kwan et al., 2009), even to a greater extent than seizure control (Kwan et al., 2009). Yeni et al. (2018) proposed a more complex model, in which knowledge about epilepsy was positively related to the attitude toward the disease, reducing depression and anxiety and, consequently, improving QOL.

The role of depression has been studied more extensively, showing to be a good predictor of poorer QOL (Akdemir et al., 2016; Şenol et al., 2007), independently of the seizure type (Cramer et al., 2003) and other clinical variables (Ehrlich et al., 2019). Tombini et al. (2020) found that depressive symptoms, together with emotion dysregulation, were related to poorer QOL and higher perceived stigma. Loring et al. (2004) studied the relevance of depression, age at epilepsy onset, years of education, verbal memory functioning, personality, and epilepsy-associated concerns, showing that depression was the main predictor of QOL.

Anxiety also has a key role in QOL, independently of depression (Gur-Ozmen et al., 2017). In fact, some studies have pointed to a more potent effect of anxiety (Chen et al., 2018; Choi-Kwon et al., 2003; Fiest et al., 2017). Lima et al. (2021) showed that negative affectivity was more relevant than clinical factors for QOL, and trait anxiety was the most potent predictor in patients with TLE and HS. Interestingly, Cano-López et al. (2018) obtained similar results exploring a different model that encompassed negative affectivity, neurosensory symptoms, and cognitive performance variables, finding that the most

powerful predictor of QOL was negative affectivity, explaining 56% of the variance, and highlighting the relevance of trait anxiety.

Cognitive performance, as already mentioned, has also been related to QOL, although less consistently. Better functioning in language, general intelligence, attention, and executive functions have been associated with better QOL (Giovagnoli et al., 2014; Meneses et al., 2009). Furthermore, Ehrlich et al. (2019) showed that executive functions, but not verbal memory, predicted QOL in TLE patients. Nonetheless, Cano-López et al. (2018) found that long-term verbal memory did significantly predict better QOL.

The mediating effect of some variables on the relationship between cognitive performance and QOL has also been explored. In this regard, Lozano-García et al. (2021) found that cognitive performance, measured with the EpiTrack test, a screening tool to assess attention and executive functions, was related to QOL and that this relationship was mediated by the number of ASMs. Furthermore, Cano-López et al. (2023) found that trait anxiety mediated the relationship between delayed memory and QOL, even controlling for the effect of sociodemographic and clinical variables (i.e., educational level, employment status, age at epilepsy onset, seizure frequency, and number of ASMs).

Finally, social factors (e.g. employment, educational level, or social support) are important in terms of QOL. In this sense, unemployment, low educational level, and poor social support, together with other variables of different nature (i.e., negative affectivity and seizure frequency) have been related to poor QOL (Akdemir et al., 2016; Azuma & Akechi, 2014; Choi-Kwon et al., 2003). Gu et al. (2016) used a more specific model, noting that working patients had higher QOL than unemployed patients, finding particularly significant differences in social function. However, while other studies have found "conflicting" results regarding the role of employment in the QOL (George et al., 2015; Taylor et al., 2011), the impact of social support is more consistent. The relationship between social support and QOL has been addressed in different studies for decades, concluding that social support is a predictor of QOL (Charyton et al., 2009), although depressive symptomatology could mask its role (Whatley et al., 2010). Interestingly, Amir et al. (1999) showed that social support was related to better QOL and that this relationship was mediated by self-efficacy; this is, high social support was associated with an increased sense of control in coping with the disease, which in turn correlated with an increase in QOL.

As can be seen, QOL is a holistic concept encompassing different areas of the individual with epilepsy. Therefore, the correct management and treatment of epilepsy should include aspects beyond seizure control, promoting the early detection of those patients who are particularly vulnerable to the consequences of epilepsy and in whom the QOL is affected, as suggested by Taylor et al. (2011). This highlights the need for further research to determine the key factors that impact QOL, understanding the mechanisms and nature of these relationships.

2. Stress and epilepsy: towards a more comprehensive perspective

The definition of stress has evolved since its first appearance in the scientific literature by Selye (1950), who defined stress as a non-specific response to noxious stimuli. Since then, the interest in and the complexity of the concept has led to a heterogeneity of contributions depending on the focus of the study. In general terms, stress is a process triggered after the presentation of a stimulus that is perceived as noxious to homeostasis, and which elicits a response to reestablish the balance. This stress response involves different systems, entailing emotional, cognitive, behavioral, and physiological reactions (Campbell & Ehlert, 2012).

Following a psychobiological perspective, stress can be conceptualized within the Stimulus-Organism-Response (SOR) model, originally proposed by Woodworth (1918). According to this theoretical framework, the perception of a stimulus and its subsequent processing by the organism as threatening will induce a stress response (Zhang et al., 2021). Therefore, this model helps understand how individuals react to stressors, emphasizing the importance of cognitive processing and the impact of mediators in the stress response.

The stress response can be influenced by different factors, with the duration of the stressor and the individual characteristics being particularly relevant (Radley et al., 2011). The duration of the stressor leads to the differentiation between the concepts of ‘acute stress’ and ‘chronic stress’. While acute stress implies the adaptation of the organism to the demands of the environment, prolonged and repeated exposure to the stressor can result in chronic stress. The chronic nature of stress is closely related to the pathological process, with a harmful impact on different areas of the individual (Koolhaas et al., 2011). From a health perspective, chronic stress has been conceptualized as the process in which environmental

demands exceed the individual's ability to cope, leading to psychological and physiological consequences, and increasing the risk of disease (Cohen et al., 2007; O'Connor et al., 2021). Therefore, the repeated or maintained activation of this response can elicit biological changes in the individual, altering the functioning of the organism and, thus, favoring the development or maintenance of the disease (Cohen et al., 2016). The allostatic load model meets this situation. Following this theoretical framework, the allostatic load is defined as the cost paid by the organism for chronic exposure to physiological responses triggered by the presence of challenges that the individual interprets as stressful (McEwen & Stellar, 1993). These authors suggested tha clarifying the interaction between between behavior and the neural, immune, and endocrine systems is necessary to understand the relationship between chronic stress and disease.

However, the stress process can also be influenced by individual characteristics, such as previous experiences or genetic predisposition (Radley et al., 2011). Lazarus and Folkman (1984), in their transactional theory of stress and coping, proposed that the stress process is shaped by the cognitive appraisal of the stimulus and, if it is perceived as threatening, by the coping strategies employed. This is where the concept of resilience becomes pertinent. Resilience can be defined as the ability to cope successfully with adversity (Hornor, 2017). Within the framework of stress, resilience has been considered as a dynamic process of adaptation to stressor exposure (Denckla et al., 2020), suggesting that it can be a protective factor against stress (Ong et al., 2006). Therefore, resilient skills could help people to cope with stress and have an adaptative response to the stressor, decreasing the likelihood of developing pathological processes.

One of the main mediators of the relationship between stress and health is the hypothalamic-pituitary-adrenal (HPA) axis. The HPA axis is a key system involved in acute and chronic stress responses. This axis is activated in stressful situations, triggering a secretion of the corticotropin-releasing factor from the hypothalamus, which increases the release of corticotropin in the anterior pituitary, promoting cortisol production in the adrenal glands (Charmandari et al., 2005). Cortisol has receptors on many cell types and neural tissues, and can influence different systems with the aim of promoting stress coping (Karin et al., 2020). Thus, cortisol is considered one of the main stress biomarkers (Hellhammer et al., 2009).

In chronic stress conditions, such as some long-term pathologies, a dysregulation of the HPA axis may be observed. In this regard, evidence supports that people with epilepsy show differences in basal cortisol levels compared to healthy people (Cano-López & González-Bono, 2019). Although the results are far from homogeneous, previous literature points out that people with epilepsy exhibit hypercortisolism (Allendorfer et al., 2014; Cano-López et al., 2019; Marek et al., 2010) compared to the general population. In this line, Robertson et al. (1986) found that patients with epilepsy receiving polytherapy failed to suppress cortisol after the dexamethasone test. This suggests that the dysregulation of the HPA axis could be related to a reduced sensitivity to negative feedback and an increased susceptibility to seizures (Cano-López & González-Bono, 2019).

Nonetheless, it is noteworthy that other studies have found contradictory results. In samples composed of women, lower cortisol levels have been found among those with epilepsy than in healthy people (Hill et al., 2011; Tuveri et al., 2008). Furthermore, a lack of differences in cortisol levels was observed between people with epilepsy, people with functional seizures, and healthy people (Bakvis et al., 2009). An explanation of this heterogeneity in the results could be found in the effect of clinical variables on hormonal levels, such as the type and dose of ASMs (Johannessen & Landmark, 2010) or the presence of seizures (Galimberti et al., 2005; Zhang & Liu, 2008).

Concerning cortisol response to stress in patients of epilepsy, certain consensus exists about the capability of a wide variety of seizures to produce cortisol increases (Cano-López & González-Bono, 2019). However, only two studies have examined the cortisol response to acute psychosocial stressors in patients with left temporal lobe epilepsy (LTLE) and healthy controls (Allendorfer et al., 2014; Goodman et al., 2019). The authors stated that patients with epilepsy showed greater cortisol reactivity (Allendorfer et al., 2014; Goodman et al., 2019), which was positively related to seizure frequency in patients with poor seizure control (Allendorfer et al., 2014).

Cortisol levels have been also related to cognition impairment in the general population (Almela et al., 2011; Hidalgo et al., 2015). However, despite the increased vulnerability of patients with epilepsy to cognitive deficits, studies addressing the relationship between cortisol levels and cognitive performance in this population are scarce. In this regard, Busch et al. (2012) found that TLE patients with higher cortisol levels had worse memory performance. In the same line, Cano-López et al. (2019) found different results in cortisol

levels depending on the lateralization of the epileptic focus and the memory performance. In particular, they showed that patients with left-hemisphere focus and poor delayed memory performance had higher cortisol levels. Furthermore, patients with poorer memory scores had higher cortisol area under the curve (AUC), independently of the side of the seizure focus, and both the cortisol AUC and trait anxiety were predictors of memory performance (Cano-López et al., 2019). All these results suggest that cortisol plays an important role in epilepsy. However, However, the question of whether there is a differential impact in the response to acute or chronic stressors in this population remains unknown.

2.1. Epilepsy within a chronic stress framework

Seizures have been considered acute stressors in drug-resistant epilepsy, due to their repeatability, and the difficulty of controlling and predicting them (van Campen et al., 2014). Furthermore, seizures can pose a threat to health, with a higher risk of mortality than the general population (Sander & Bell, 2004). Considering this, and understanding the global impact of epilepsy on the individual, epilepsy has been proposed as a chronic stress model in humans (Cano-López & González-Bono, 2019). This conceptualization fits with the model of Koolhaas et al. (2011), who argued that the concept of stress should be limited to those stimuli that are unpredictable, uncontrollable, and a threat to survival.

The close relationship between stress and epilepsy supports the conceptualization of epilepsy within a stress framework. This link appears to be bidirectional, as stress may increase the risk of seizures, but epilepsy itself may also raise stress levels, due to the chronic condition of the disease and the recurrence of seizures (Novakova et al., 2013; Ponnusamy et al., 2012).

The role of stress as a precipitating factor of seizures has been extensively studied. Stress may influence epileptogenesis by activating inflammatory responses in the brain and negatively impacting neurogenesis in the hippocampus (Friedman et al., 2011). This appears to be enhanced when stress is experienced at an early age (Koe et al., 2009), affecting the regulation of the HPA axis and brain morphology and functionality (van Campen et al., 2014), and may persist in adulthood, increasing the vulnerability of the individual to several diseases, including epilepsy (Koe et al., 2009; Lupien et al., 2009). Interestingly, stress, which is the most common seizure precipitant informed by patients (McKee & Privitera,

2017), is more frequently reported as a trigger for seizures in patients who experienced a traumatic situation in childhood (Lee et al., 2015). Therefore, stress can affect the recurrence of seizures, probably through different mechanisms (Friedman et al., 2011). In this regard, stress increases the release of corticotropin-releasing hormone, which contributes to neuronal hyperexcitability and modulates glutamatergic transmission in animal models (Liu et al., 2004). In addition, glucocorticoids increase glutamate release, affecting calcium currents and, consequently, impacting neuronal activity (Chameau et al., 2007).

Additionally, supporting the idea that epilepsy could increase stress levels, these patients report higher perceived stress compared to healthy people (Gargiulo et al., 2022; Lacey et al., 2009), and seizure control has been considered a predictor of perceived stress (Moon et al., 2016). Furthermore, people with epilepsy appear to have a dysregulation of the HPA axis (Wulsin et al., 2016), and seizures seem to activate the response of this axis (Maguire & Salpekar, 2013). This situation has been also observed in people with chronic stress, as well as in other disorders, such as depression (Pearson-Murphy, 1991; Zhu et al., 2014). Finally, mood disorders are common among people with epilepsy, and chronic stress has been linked to their development (Bale, 2006). Thus, although it may seem speculative, the increased stress in people with epilepsy may be related to the increased risk of having mood disorders (Mazarati et al., 2008).

Despite the importance of stress in this population, few studies have defined the main stressors in epilepsy. Snyder (1990) presented a ranking of the primary sources of stress in epilepsy, with the need to take daily medication, the unpredictability of seizures, and the increased memory loss, in that order, being the most powerful stressors rated by patients. However, this study was conducted based on a closed list of twenty-two situations, so other stressors that could be important, such as unemployment, may not have been explored. Temkin & Davis (1984) tried to associate the daily stressful events that occurred to the patients and the occurrence of seizures. In this regard, they found that attendance at work or school was the only event related to seizures. Haut et al. (2003) identified the life events that were related to seizures following patients' reports, showing that family tension was the most common stressor, followed by the death of a loved person. Interestingly, Gélisse et al. (2015) explored the stressful events that could be related to epilepsy onset. They found that 54% of patients reported the loss of a closed person as a trigger of epilepsy, followed by 32% who reported having ended a relationship with someone close, and 14% who were victims of

violence (Gélisse et al., 2015). Taking all this into consideration, the main stressors in epilepsy appear to be related to treatment, employment, and social support.

In conclusion, these results highlight the particularity of the stress process in epilepsy, from the stimuli considered as stressors to the stress response itself. Stress has been recognized as one of the most important factors to consider in chronic diseases. However, despite this, only a few reports have approached epilepsy from a stress framework. Addressing the main difficulties of these patients and the global impact on the individual from this point of view could help to understand the determinants of their QOL comprehensively and achieve better disease management. Therefore, the proper approach to the study of the impact of stress on epilepsy must incorporate a social, emotional, cognitive, and clinical perspective. Nevertheless, some barriers to overcome emerge, such as the heterogeneity of the concept of stress, the need for standardized tests for measuring stress in this population, and the understanding of the implications of perceived stress in patients with epilepsy. These issues, along with others, will be addressed in Chapter 2 through a systematic review.

CHAPTER 2

Perceived stress in epilepsy: a systematic review [1]

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1. Introduction

Epilepsy is a neurological disorder characterized by a predisposition to suffer epileptic seizures with neurobiological, cognitive, psychological, and social consequences (Fisher et al., 2014, 2017). Continued exposure to unpredictable seizures (Novakova et al., 2013), together with their comorbidities, treatments, and their impact on the daily life of the individual (Beghi, 2016) are major components of the burden of epilepsy, and have led to the conceptualization of epilepsy within a framework of chronic stress in humans (Cano-López & González-Bono, 2019).

The interaction between stress and epilepsy is complex and encompasses different systems of the organism. The temporal lobe, which is the most common epileptogenic area, is involved in emotional and cognitive comorbidities of epilepsy (Metternich et al., 2014). It contains critical neural structures in the stress response, such as the hippocampus and the amygdala, which have a high concentration of glucocorticoid receptors (Maguire & Salpekar, 2013). Moreover, a dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis has been found in patients with epilepsy, affecting the hormonal response to stress (Allendorfer et al., 2014; Goodman et al., 2019) and cognitive functioning (Cano-López et al., 2019).

Limited studies have addressed the relationship between epilepsy and perceived stress. However, stress can increase seizure frequency and occurrence (Frucht et al., 2000; McKee & Privitera, 2017; Sperling et al., 2008), as well as the risk of developing epilepsy (van Campen et al., 2014). Furthermore, seizures have been considered acute stressors (Cano-López & González-Bono, 2019; van Campen et al., 2014), but there may be variability in the perception of this and other stressors associated with epilepsy. In fact, in the stress processes, the triggering of the stress response primarily depends on the individual's subjective appraisal of the stimulus and the perception of available resources to cope with it (Lazarus & Folkman, 1984). Therefore, the subjective experience in the face of a potential stressor is a key factor in the stress process. Factors related to the specific attributes of the stressor (i.e., intensity, duration, and recurrence), personal characteristics (e.g., resilience), and the environment (i.e., available resources) can either mitigate or amplify the impact of stress, thereby regulating its pathological effects.

This rationale has favored the measurement of perceived stress in epilepsy and the analysis of the factors that could modulate it. However, although some reviews provided information about stress as a seizure precipitant factor (McKee & Privitera, 2017; Novakova et al., 2013), especially considering the neurobiological perspective (Jhaveri et al., 2023), to the best of our

knowledge, no systematic reviews have investigated the role of perceived stress, considering only specific self-report measures, in the global impact of epilepsy. For this, the present review aims to explore the knowledge about the relationship between perceived stress and epilepsy, in order to clarify its particularities and its potential effects on the prognosis and consequences of the disease.

2. Materials and methods

2.1. Data sources and searches

This review was conducted and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA; Page et al., 2021) and it was registered in PROSPERO.

The search was performed in the following databases: Web of Science, Scopus, PubMed/MEDLINE, and Embase on April 4, 2024. The following terms were used for a Boolean search: (epilep* OR seizure* OR convulsion*) AND ("perceived stress" OR "psychological stress" OR "psychologic stress"). These keywords were examined in the title, keywords, and abstract. A reverse review was performed by analyzing the references of the studies to detect articles not included in the databases. The search was restricted to peer-reviewed journal papers. Nevertheless, it was not limited by date or age, to avoid the exclusion of papers that could be useful.

2.2. Eligibility

The inclusion criteria were: a) original and empirical articles published in peer-reviewed journals; b) adults with a diagnosis of epilepsy; c) in case of mixed samples (i.e., with other diagnoses), data from patients with epilepsy separated from other groups of patients included in the study; d) studies focused on perceived or psychological stress in people with epilepsy; and e) English or Spanish language. The exclusion criteria were: a) studies with mixed data on people with epilepsy and other groups of patients; b) exclusively including patients with functional seizures; c) single-case studies, reviews, meta-analyses, editorials, or conference abstracts; d) studies with samples composed by children or adolescents. Studies were not excluded based on the presence of other premorbid/comorbid conditions or the etiology of epilepsy.

2.3. Study selection

Duplicate references were removed using Endnote X9 and Rayyan software (Ouzzani et al., 2016). Two authors (JCL and ICL) independently reviewed the titles and abstracts to determine their possible agreement with the inclusion criteria. There were discrepancies with four abstracts, which were resolved through critical discussion among the three authors (JCL, EGB, and ICL) until 100% agreement was achieved. Then, the researchers individually assessed the full text of the selected articles to confirm if they met the inclusion criteria. Those studies that did not meet the inclusion criteria were excluded, with the reasons for exclusion documented in Fig. 1.

2.4. Data extraction

Data from the included studies were extracted and displayed in Table 1. The extracted data included: (1) reference; (2) sample size; (3) sex; (4) mean age; (5) epilepsy type or semiology; (6) treatment; (7) perceived stress measures; (8) results about perceived stress in epilepsy.

2.5. Data synthesis

Data extracted from the included articles were divided into four categories: (1) conceptualization of stress; (2) effects of stressful life events on the perceived stress of patients with epilepsy; (3) perceived stress as a seizure trigger; (4) differences in perceived stress among people with epilepsy and healthy controls; (5) differences in perceived stress among people with epilepsy compared to other clinical populations and comorbidities; and (6) demographic and clinical factors associated with perceived stress.

2.6. Methodological quality assessment

The methodological quality of the studies was assessed by two reviewers (ICL and JCA), and discrepancies were consulted and discussed between the three authors (JCA, EGB, and ICL).

The Critical Appraisal Checklist for Analytical Cross-Sectional Studies (JBI; Moola et al., 2020) was used to evaluate the quality and the extent of bias of the studies included in this systematic review. This tool is composed of eight questions that address the following points:

(a) clarity of the inclusion criteria; (b) presence of a detailed description of the sample and setting; (c) validity and reliability of the measures; (d) use of objective and standardized measures; (e) identification of unclear factors; (f) strategies to manage unclear factors; (g) validity and reliability of measuring results; and (h) use of appropriate statistical analyses (Moola et al., 2020).

3. Results

3.1. Study selection

The initial search yielded a total of 455 articles, of which 214 were identified as duplicates. Therefore, 241 articles remained after eliminating them. One hundred ninety-nine articles were excluded after reviewing the title, abstract, and keywords. Of the 42 articles that were reviewed in full, 11 were excluded for three different reasons: studies with mixed data (n=5); studies with no perceived stress data (n=5), and studies with a sample without epilepsy diagnosis (n=1). Therefore, thirty-one articles were initially included in the review. However, three articles were found through reverse search. Thus, thirty-four articles were included in the review. Included studies have been marked with the symbol (*) in the references section. Figure 1 shows the flow diagram of the identification and selection of studies. Table 1 includes a summary of the selected studies.

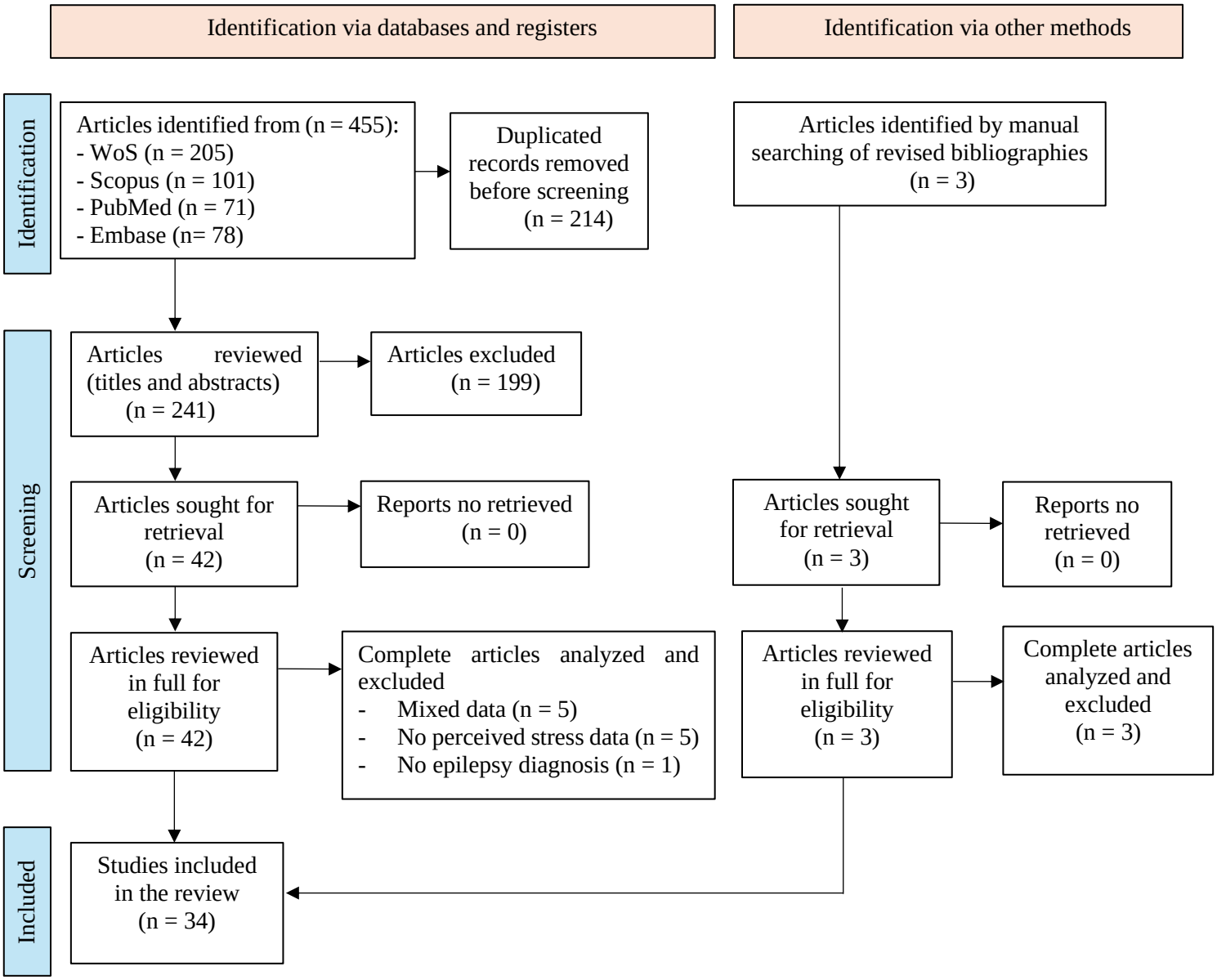

Figure 1. Flow diagram of the identification and selection of studies.

Table 1. Summary of the results of the studies selected exploring perceived stress in people with epilepsy.

Reference	Sample size (N)	Sex (% women; % men)	Mean age ± SD	Epilepsy type; semiology	Seizure frequency	Treatment	Perceived stress measures	Results about PS
Aishwarya et al. (2023)	40 WCE 40 DRE	WCE: 52.5%♀, 47.5% ♂ DRE: 60% ♀, 40% ♂	WCE: 33.7 ± 8.3 DRE: 33.4 ± 9.0	n.s.	3-4 seizures/month	WC: 50% monotherapy (VPA/PHT), 50% polytherapy (VPA+CBZ) DRE: 100% polytherapy (VPA, PHT, CLZ, CBZ, and LEV)	PSS-10, PHQ-9 and GAD-7	DRE > WCE
Al-Kattan et al. (2015)	55 BS 32 WCE	BS: 43.6% ♀, 56.4%♂ WCE: 54.3% ♀, 45.7%♂	BS: 32.6 ± 12.2 WCE: 30.9± 12.6	Generalized epilepsy Seizures: BS: 38.2% focal, 61.8% generalized WCE: 22.9% focal, 77.1% generalized	BS: 70.9% <1 seizure, 27.3% 1-2 seizures, 1.8% >2 seizures in the last year WCE: 8.6% <1 seizure, 51.4% 1-2 seizures, 40% >2 seizures in the last year	BS: 54.5% one ASM, 36.4% two ASMs, 9.1% three ASMs WCE: 82.9% one ASM, 17.1% two ASMs	Questionnaire with 8 precipitating factors (among them, psychological stress)	PS was the 3rd most frequent seizure trigger (reported by 34.5% of patients)
Alkhotani et al. (2020)	156 PWE	62% ♀, 38% ♂	< 20 years 14.7%, 20-40 years 66.7%; 40-60 years 15.4%, > 60 years 3.2%	Seizures: 32.7% focal, 37.8% generalized, 29.5% FBTCS	48.0% less than one seizure, 5.8% one seizure, 25.6% two seizures, 20.5% more than two seizures	47.4% one ASM, 26.3% two ASMs, 26.3% more than two	An electronic self-administered questionnaire	Increase in PS during the pandemic: - Reported by 54% of patients - Related to increase in seizure frequency
Allendorfer et al. (2014)	23 LTLE 23 HCs	LTLE: 74% ♀, 26% ♂ HCs: 77% ♀, 23% ♂	LTLE: 40 ± 11 HCs: 38 ± 10	LTLE	LTLE: 3.2 ± 5.9 seizures in the last 3 months	LTLE: 1.9 ± 0.8 ASMs	PSS-10	LTLE = HCs n.s.r. between seizure occurrence and PSS-10 scores n.s.d. in PS between LTLE patients with and without seizures

Reference	Sample size (N)	Sex (% women; % men)	Mean age ± SD	Epilepsy type; semiology	Seizure frequency	Treatment	Perceived stress measures	Results about PS
Baniya et al. (2021)	352 PWE: 145 with depression 207 without depression	39.2% ♀, 60.8%♂ With depression: 53.1%, ♀,46.9%♂ Without depression: 29.5%♀, 70.5% ♂	35 ± 11 18-30 years 30.7%, 31-45 years 56.3%, ≥ 45 years 13.1% With depression: 18-30 years 25.5%, 31-45 years 59.3%, ≥ 45 years 15.2% Without depression: 18-30 years 34.3%, 31-45 years 54.1%, ≥ 45 years 11.6%	Seizures: 23.6% focal, 21.9% absence, 10.3% myoclonic, 44.3% tonic-clonic With depression: 22.8% focal, 21.4% absence, 9.0% myoclonic, 46.9% tonic-clonic Without depression: 24.2% focal, 22.2% absence, 11.1% myoclonic, 42.5% tonic-clonic	6.0% less than one seizure, 17.9% two-four seizures, 41.8% five-eight seizures, 34.4% more than eight seizures in the last year With depression: 4.8% < one seizure, 11.0% two-four seizures, 42.8% five-eight seizures, 41.4% > eight in the last year Without depression: 6.8% < than one seizure, 22.7% two-four seizures, 41.1% five-eight seizures, 29.5% > eight in the last year	30.4% monotherapy, 69.6% polytherapy. 81.53% VPA, 22.4% CBZ, 13.0% LEV, 32.4% PHT, 12.8% PB With depression: 21.4% monotherapy, 78.6% polytherapy. 78.6% VPA, 27.6% CBZ, 11.7% LEV, 34.5% PHT, 16.6% PB Without depression: 36.7% monotherapy, 63.3% polytherapy. 83.6% VPA, 18.8% CBZ, 14.0% LEV, 30.9% PHT, 10.1% PB	PSS-14. Cut-off value for the presence of stress was ≥ 20	Higher percentage of PWE with elevated PS in those with depression
Bifftu et al. (2015)	405 PWE	37% ♀, 63% ♂	28.8 ± 9.7	n.s.	20.7% no seizures, 71.8% one-eleven seizures, 7.4% ≥ 12 seizures per year	76.3% monotherapy 23.7% polytherapy	PSS. Cut-off value for the presence of stress was ≥ 20	PWE with high PS had more than 6 times odds of depression than those with lower PS

Reference	Sample size (N)	Sex (% women; % men)	Mean age ± SD	Epilepsy type; semiology	Seizure frequency	Treatment	Perceived stress measures	Results about PS
DiIorio et al. (2011)	148 PWE 70 EG 78 CG	73.6% ♀, 26.4%♂ EG: 68.6% ♀, 31.4%♂ CG: 78.2% ♀, 21.8%♂	40.9 ± 13.3 EG: 41.9 ± 12.9 CG: 40.0 ± 13.6	Seizures: 13.6% FAS, 27.2% FIAS, 3.4% FBTCS, 6.8% absence, 36.7% tonic-clonic, 8.2% other primary generalized, 4.1% unclassified EG: 11.6% FAS, 31.9% FIAS, 2.9% FBTCS, 5.8% absence, 36.2% tonic-clonic, 10.1% other primary generalized, 1.4% unclassified CG: 15.4% FAS, 23.1% FIAS, 3.8% FBTCS, 7.7% absence, 37.2% tonic-clonic, 6.4% other primary generalized, 6.4% unclassified	9.99 ± 29.28 seizures per month EG: 10.8 ± 32.9 seizures per month CG: 9.3 ± 25.9 seizures per month	At least 1 ASMs in the past 3 months WebEase	PSS-4 and ESI-R	The WebEase program was effective to encourage self-management, but no for the other outcomes, as PS
Engidaw et al. (2020)	402 PWE	37.1% ♀, 62.9%♂	18-24 years 40.3%, 25-34 years 30.1%, 35-44 years 20.3%, ≥ 45 years 9.2%	n.s.	19.9% seizure-free, 71.6% one-eleven seizures per year, 8.5% ≥ twelve per year	76.4% monotherapy, 23.6 % polytherapy. 94.5% PB, 1.5% PHT, 2.2% CBZ, 1.7% VPA	PSS. Cut-off value for the presence of stress was ≥ 20	PWE with high PS had more than 3 times odds of depression than those with lower PS. More patients had high PS among those with depression

Reference	Sample size (N)	Sex (% women; % men)	Mean age ± SD	Epilepsy type; semiology	Seizure frequency	Treatment	Perceived stress measures	Results about PS
Farnia et al. (2021)	79 PWE + SUD 41 PWE	4.1% ♀, 95.8% ♂ PWE+SUD: 1.3% ♀, 98.7% ♂ PWE: 9.8% ♀, 90.2% ♂	10-22 years 20.8%, 23-43 years 43.3%, 44-66 years 35.8% 32.8 ± 11.42 years PWE+SUD: 10-22 years 22.8%, 23-43 years 41.8%, 44-66 years 35.4% PWE : 10-22 years 17.1%, 23-43 years 46.3%, 44-66 years 36.6%	n.s.	n.s.	86.6% ASMs, 3.3% psychiatric treatment, both 10.0%	DASS-21	Prevalence of negative affectivity and stress symptoms in PWE+SUD was 6.02 units higher than in PWE
Frances et al. (1999)	30 FS 30 PWE 30 HCs	FS: 66.7% ♀, 33.3%♂ PWE: 66.7% ♀, 33.3%♂ HCs: 66.7% ♀, 33.3%♂	FS: 36.9 ± 13.7 PWE: 36.2 ± 12.9 HCs: 37.3 ± 13.8	n.s.	n.s.	n.s.	PSS-14	FS = PWE FS > HCs

Reference	Sample size (N)	Sex (% women; % men)	Mean age ± SD	Epilepsy type; semiology	Seizure frequency	Treatment	Perceived stress measures	Results about PS
Gammoh et al. (2024)	280 PWE 102 not taking LEV 178 taking LEV	50.7% ♀, 49.3 ♂ No LEV: 42.2% ♀, 57.8%♂ LEV: 55.6% ♀, 44.4%♂	≥ 25 years 60.4%, < 25 years 39.6% No LEV ≥ 25 years 33.3%, < 25 years 66.7% LEV ≥ 25 years 43.3%, < 25 years 56.7%	Seizures: No LEV 50% absences and other types 50% generalized tonic-clonic LEV 51.7% absences and other types 48.3% generalized tonic-clonic	n.s.	63.6% were taking LEV as monotherapy or adjuvant	PSS-14	n.s.r. between LEV users and PS. 75% of the total sample reported PS
Gargiulo et al. (2022)	60 DRE 28 FS 31 HCs	DRE: 61% ♀, 39% ♂ FS: 85% ♀, 15% ♂ HCs: 58% ♀, 42% ♂	DRE: 30.9 ± 9.1 FS: 31.9 ± 13.6 HCs: 41.4 ± 14.2	n.s.	n.s.	n.s.	PSS-14	DRE > HCs. DRE = FS. PS is positively related to depressive symptoms.
Goodman et al. (2019)	36 LTLE 36 HCs	LTLE: 77.8% ♀, 22.2%♂ HCs: 75% ♀, 25% ♂	LTLE: 40.0 ± 12.1 HCs: 38.6 ± 11	LTLE	8.3 ± 16.1 seizures in the last three months	n.s.	PSS-4 and PSS-10	LTLE = HCs PS increased with seizure frequency. n.s.r between cortisol reactivity and PS in LTLE

Reference	Sample size (N)	Sex (% women; % men)	Mean age ± SD	Epilepsy type; semiology	Seizure frequency	Treatment	Perceived stress measures	Results about PS
Haut et al. (2007)	71 PWE	63% ♀, 47% ♂	41.1	45% TLE, 8% FLE, 14%, ETLE, 33% nonlocalizable	n.s.	3% no ASMs, 45% one ASM, 42% two ASMs, 7% three ASMs, 3% four ASMs	"How much stress do you feel today? From 0 to 10"	An increase in PS associated with an increase in the likelihood of having seizures the next day. Higher PS associated with seizure self-prediction
Haut et al. (2012)	19 PWE	85% ♀, 15% ♂	35	73.7% TLE, 5.3% FLE, 10.5% ETLE, 10.5% nonlocalizable.	3.5 seizures per month	n.s.	"How much stress did you feel today? From 0 to 10" PSS-4	n.s.r. between PS and seizure occurrence
Kim et al. (2019)	66 PWE 737 with other neurological disorders	PWE: 56.1% ♀, 43.9%♂	PWE: 44 ± 17	n.s.	n.s.	n.s.	PSS-10. Cut-off value for moderate-severe stress was ≥ 14	Highest levels of PS, depression, and anxiety in PWE or with cognitive decline
Koh et al. (2021)	461 PWE	50.1% ♀, 49.9%♂	39.2 ± 15.9	Seizures: 54.0% focal, 41.9% generalized, 4.1% unclassified	37.5% no seizures one year before COVID-19, 36% less than one, 26.5% one or more seizures a month	31.2% one ASM, 27.5% two ASMs, 41.2% three or more ASMs	Online questionnaire asking about different possible causes of seizure worsening (among them, stress)	Stress was the second cause most reported (by 24% of patients) Seizure worsening was more common in those who reported that stress was the main cause
Lacey et al. (2009)	652 PWE	53% ♀, 47% ♂	52 (range 18-102 years)	n.s.	n.s.	At least 1 ASM	K-10	The rate of PS is greater in PWE than in the general population. 24% reported high stress, while 8.2% had very high stress

Reference	Sample size (N)	Sex (% women; % men)	Mean age ± SD	Epilepsy type; semiology	Seizure frequency	Treatment	Perceived stress measures	Results about PS
Lee et al. (2010)	150 PWE	42% ♀, 58% ♂	34.7 (range 18–59 years)	40.7% focal with structural etiology, 32.7% focal with unknown etiology, 16.7% generalized with genetic etiology, 10% unclassified	24.7% remission, 12.6% less than one seizure per year, 44% one-eleven seizures per year, 18.7% more than one seizure per month	57.3% monotherapy	Daily Hassles Scale	PS accounted for 38.8% of the variance in depressive symptoms
Lee et al. (2022)	316 PWE	45.9% ♀, 54.1%♂	38.6 ± 14.0	87% focal, 8.9% generalized, 4.1% unclassified Seizures: 2.8% absence, focal 66.1%, 31.1% FBTCS	27.5% seizure-free, 44.9% one-eleven seizures per year, 27.5% one or more per month	62.3% polytherapy	PSS-10	PS was the strongest predictor of depressive symptoms, followed by stigma and social and epilepsy-related factors
Martínez-Fernández et al. (2020)	21 PWE 56 episodic migraine 18 chronic migraine	PWE: 57.1% ♀, 42.9%♂ Episodic migraine: 94.6% ♀, 5.4% ♂ Chronic migraine: 94.4% ♀, 5.6% ♂	PWE: 41.5 ± 14.0 Episodic migraine: 38.4 ± 11.9 Chronic migraine: 46.1 ± 10.4	Seizures: 14.3% FAS, 28.6% FIAS, 57.1% FBTCS	Median = 5 in one year (interquartile range = 54)	n.s.	PSS-10	PWE > People with chronic or episodic migraine
McCann et al. (2021)	65 PWE	49% ♀, 51% ♂	30.4 ± 11.4	DRE	n.s.	CBD	Four 5-point Likert items assessing confidence in controlling life and handling personal problems, and feelings about things going well or difficulties becoming overwhelming	Higher PS was associated with poorer social support and social participation

Reference	Sample size (N)	Sex (% women; % men)	Mean age ± SD	Epilepsy type; semiology	Seizure frequency	Treatment	Perceived stress measures	Results about PS
Michaelis et al. (2024)	14 PWE	78.57% ♀, 21.43% ♂	44.5 (range 23–64 years)	79% focal, 21% FBTCS	n.s.	7.1% no ASMs, 14.3% one ASM, 64.3% two ASMs, 14.3% three ASMs	Semistructured resource-oriented interview (e.g. "today I was emotionally stressed")	Epileptic seizures in some PWE can be preceded by medium-term changes in PS and coping ability
Micoulaud-Franchi et al. (2014)	11 TLE with stress-triggered seizures	81.8% ♀, 18.2%♂	36.7 ± 7.3	TLE with stress-triggered seizures	24.72 ± 24.09 seizures in the last 3 months	1.73 ± 0.75 ASMs Biofeedback	Impact of seizure precipitant scale	No patient reported stress discomfort during biofeedback treatment
Moon et al. (2016)	260 PWE 200 HCs	PWE: 37.3% ♀, 62.7%♂ HCs: 38% ♀, 62% ♂	PWE: 40.0 ± 12.5 HCs: 40.2 ± 12.1	49.2% TLE, 29.6% ETLE, 19.6% generalized, 1.5% unclassified	n.s.	PWE DDD 1.3 ± 0.9 46.5% monotherapy	PSS-10	DRE > HCs HCs < WCE Depression, sleep disturbances, anxiety, and seizure control (in that order) were predictors of PS
Nakamura et al. (2023)	159 PWE	46.9% ♀, 53.1%♂	37.3 ± 14.7	23.5% TLE, 14.0% FLE, 4.0% OLE, 4.0% juvenile myoclonic epilepsy Seizures: 69.8% focal, 20.0% generalized, 10.6% unclassified	64.8% sporadic, 20.7% monthly, 7.8% weekly, 6.7% daily	3.9% no ASMs, 42.5% one ASM, 37.4% two ASMs, 13.4% three ASMs, 2.2% four ASMs, 0.6% five ASMs	J-SACL	PS and arousal were negatively related

Reference	Sample size (N)	Sex (% women; % men)	Mean age ± SD	Epilepsy type; semiology	Seizure frequency	Treatment	Perceived stress measures	Results about PS
Neshige et al. (2021)	196 PWE	44.4% ♀, 55.6%♂	37.8 ± 16.2	50.5% focal (27.1% TLE and 18.4% FLE), 34.2% generalized, 15.3% unclassified Seizures: 26.5% FAS, 35.2% FIAS, 11.2% myoclonus, 31.6% FBTCS, 36.9% bilateral tonic-clonic, 15.3% FS	13.2% weekly or more, 36.2% monthly, 50.5% yearly or less	1.9 ± 1.3 ASMs	K-6	Higher PS before the COVID-19 was associated with seizure increase during the pandemic. 63% of patients with a worsening in seizure frequency had an increase in PS
Novakova et al. (2017)	22 PWE 23 FS	PWE: 59.1% ♀, 40.9%♂ FS: 34.8% ♀, 65.2%♂	PWE: 39.0 ± 16.1 FS: 43.7 ± 12.0	63.6% focal, 4.6% generalized, 31.8% unclassified	PWE: 15.2 ± 24.2 FS: 18.1 ± 37.3	PWE: 4.5% no ASMs, 22.7% monotherapy, 72.7% polytherapy. 31.8% Anti-anxiety/Anti-depressants/Beta-blockers, 36.4% other medication FS: 43.5% no ASMs, 39.1% monotherapy, 17.4% polytherapy. 47.8% Anti-anxiety/Anti-depressants/Beta-blockers, 65.2% other medication	PSS-4 Smith Stress Symptoms Inventory	PWE = FS n.s.r. between physiological responses (cortisol levels and heart rate variability) and PS

Reference	Sample size (N)	Sex (% women; % men)	Mean age ± SD	Epilepsy type; semiology	Seizure frequency	Treatment	Perceived stress measures	Results about PS
Rosengard et al. (2021)	177 PWE	67.8% ♀, 32.2%♂	47 years (interquartile range = 21; range 21-79 years)	79.7% focal, 10.7% generalized, 9.6% unclassified	1 seizure per month in 2019, 0.61 seizures per month in January and February 2020	0-5 ASMs Median = 1 ASM	Questionnaire with four sections: seizure control at baseline, seizure control during COVID-19, seizure precipitants, and stress and access to care during COVID-19.	Stress as a seizure trigger and an increase in PS during the pandemic were more frequent in those with poorer seizure control. 81% of patients with seizure worsening during the pandemic had an increase in PS
Saengsuwan et al. (2015)	203 PWE	47.8% ♀, 52.2%♂	36.5 ± 13.0	n.s.	n.s.	At least 1 ASM	Survey (questionnaire + semistructured interview)	76.4% of PWE had medium or high levels of PS. 50.2% of PWE reported epilepsy as the most common reason for their stress
Spatt et al. (1998)	149 PWE	42.4% ♀, 57.6%♂	35.9 ± 12.9	n.s.	19% without seizures during the last year 57% with more than one seizure during the last month.	n.s.	Questionnaire about six possible precipitants of seizures (i.e., sleep deprivation, alcohol, physical exercise, psychological stress, menses, and change of weather).	The most seizure precipitant reported by patients was PS
Temkin & Davis (1984)	12 PWE	42% ♀, 58% ♂	33 ± 10	Seizures: 91.7% focal, 8.3% FBTCS	70.67 during the 3 months of the study	ASMs	Diary of seizures and stressful events with the question. Visual analog scale: "How stressful was today?"	Positive association between PS and seizure frequency and occurrence

Reference	Sample size (N)	Sex (% women; % men)	Mean age ± SD	Epilepsy type; semiology	Seizure frequency	Treatment	Perceived stress measures	Results about PS
Thapar et al. (2009)	452 PWE	53% ♀, 47% ♂	51	Seizures: 25.9% FIAS, 50.7% FBTCS, 30.3% only FBTCS	49.6% seizure-free for one year, 25% at least one seizure/year but less than one seizure/month, 25.4% one or more seizures/month	Most prescribed ASMs: 29.7% VPA, 29.3% PHT, 28.8% CBZ	PSS-4	Depression, anxiety, and PS predicted independently the variation in seizure recency over time
Toprani et al., (2022)	241 pregnant WWE 74 healthy pregnant women 84 WWE	100% female	Pregnant WWE: 31.1 (18–46 years) Healthy pregnant women: 30.2 (18-40 years) WWE: 30.0 (16–44 years)	Pregnant WWE: 59.8% focal, 32% generalized, 8.3% unclassified/multiple WWE: 59.5% focal, 29.8% generalized, 10.7% unclassified/multiple	n.s.	Pregnant WWE: 79.2% monotherapy (33.5% LTG, 28.7% LEV, 17.0% other), 20.8% polytherapy (8.3% LTG+LEV, 12.6% other) WWE: 79.8% monotherapy (29.8% LTG, 33.3% LEV, 16.7% other), 29.2% polytherapy (7.1% LTG+LEV, 13.1% other)	PSS-14	Healthy pregnant women had lower levels of PS than pregnant WWE. n.s.d. between pregnant WWE and non-pregnant WWE

Abbreviations. ASMs=antiseizure medication; BDI=Beck Depression Inventory; BS=breakthrough seizures; CBD=cannabidiol, CBZ=carbamazepine; CG=control group; CLZ=clonazepam; DASS=Depression, Anxiety and Stress Scale; DDD=daily defined dose; DRE=drug-resistant epilepsy; EG=experimental group; ESI-R=Revised Epilepsy Stressor Inventory; ETLE=extratemporal lobe epilepsy; FAS=focal aware seizures; FIAS=focal impaired awareness seizures; FBTCS=focal to bilateral tonic-clonic seizures; FLE=frontal lobe epilepsy; FS=functional seizures; GAD=Generalized Anxiety Disorder; HADS=Hospital Anxiety Depression Scale; HCs= healthy controls; J-SACL=Japanese-Stress Arousal Check List; K=Kessler Psychological Distress Scale; LEV=levetiracetam; LH=left-hemisphere; LTG=lamotrigine; LTLE=left temporal lobe epilepsy; ne=not specified; OLE=occipital lobe epilepsy; PANAS= Positive and Negative Affect Schedule; PB=phenobarbital; PHQ=Patient Health Questionnaire; PHT=phenytoin; PMD=primidone; PS = perceived stress; PSS=Perceived Stress Scale; PWE=people with epilepsy; n.s.=not specified; n.s.d.=no significant differences; n.s.r.=no significant relationship; STAI=State-Trait Anxiety Inventory; SUD=substance abuse disorder; TLE=temporal lobe epilepsy; VPA=valproic acid; WCE = well-controlled epilepsy; WWE = women with epilepsy.

3.2. Evaluation of the quality of the studies

Regarding the evaluation of the quality of the studies included in the systematic review (Table 2), the percentage of compliance with the JBI criteria ranged from 50 to 100%, depending on the study.

All the studies examined met the following criteria: (a) they measured the exposure in a valid and reliable way; and (b) they used objective and standard criteria for measurement of the condition. Thirty-one of the 34 studies (91%) described the study subjects and the setting in detail. Thirty studies (88%) identified confounding factors. Twenty-eight studies (82%) defined clearly criteria for inclusion in the sample and used appropriate statistical analyses. Twenty-four studies (71%) measured outcomes in a valid and reliable way (i.e., used validated instruments to measure perceived stress). Finally, 20 studies (59%) stated strategies to deal with confounding factors.

3.3. Conceptualization of stress

Nine of the 34 articles (27%) provided a definition of stress (Al-Kattan et al., 2015; Frances et al., 1999; Lee et al., 2022; McCann et al., 2021; Michaelis et al., 2024; Micoulaud-Franchi et al., 2016; Moon et al., 2016; Nakamura et al., 2023; Novakova et al., 2017). Most of the studies that included a conceptualization of stress (n = 8; 89% of this section) defined stress as the process in which the environmental demands exceed the adaptative capacity and the coping resources (Al-Kattan et al., 2015; Frances et al., 1999; Lee et al., 2022; McCann et al., 2021; Michaelis et al., 2024; Micoulaud-Franchi et al., 2016; Moon et al., 2016; Nakamura et al., 2023). Four out of these nine studies (44% of this section) emphasized the implications of different systems. Frances et al. (1999) explained that psychological stress is the result of the interaction between psychological and environmental processes. Micoulaud-Franchi et al. (2016) stated that stress can be explained following a psychological, environmental, or biological perspective. Nakamura et al. (2023) stated that stress is a complex process that impacts homeostasis, activating physiological and psychological reactions. Novakova et al. (2017) highlight that stress is a phenomenon that encompasses the interaction of different systems, in particular autonomic, endocrine, immune, cognitive, affective, and behavioral processes. Finally, two studies (representing 22% of this section) remarked that stress occurs when a situation is perceived as unpredictable and uncontrollable (Frances et al., 1999; Lee et al., 2022).

Table 2. Risk of bias of included studies.

Authors	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	% of compliance
Aishwarya et al. (2023)	Y	Y	Y	Y	Y	Y	Y	Y	100.0%
Al-Kattan et al. (2015)	U	Y	Y	Y	Y	N	N	N	50.0%
Alkhotani et al. (2020)	N	Y	Y	Y	Y	U	N	U	50.0%
Allendorfer et al. (2014)	Y	Y	Y	Y	Y	Y	Y	Y	100.0%
Baniya et al. (2021)	Y	Y	Y	Y	Y	Y	Y	Y	100.0%
Bifftu et al. (2015)	Y	Y	Y	Y	Y	Y	Y	Y	100.0%
DiIorio et al. (2011)	U	Y	Y	Y	N	N	Y	Y	62.5%
Engidaw et al. (2020)	Y	Y	Y	Y	Y	Y	Y	Y	100.0%
Farnia et al. (2021)	Y	Y	Y	Y	Y	Y	Y	U	87.5%
Frances et al. (1999)	Y	Y	Y	Y	Y	N	Y	Y	87.5%
Gammoh et al. (2024)	Y	Y	Y	Y	Y	Y	Y	Y	100.0%
Gargiulo et al. (2022)	Y	Y	Y	Y	Y	Y	Y	Y	100.0%
Goodman et al. (2019)	Y	Y	Y	Y	Y	Y	Y	Y	100.0%
Haut et al. (2007)	Y	Y	Y	Y	Y	Y	U	Y	87.5%
Haut et al. (2012)	U	Y	Y	Y	Y	Y	Y	Y	87.5%
Kim et al. (2019)	U	Y	Y	Y	Y	N	Y	U	62.5%
Koh et al. (2021)	Y	Y	Y	Y	Y	Y	U	Y	87.5%
Lacey et al. (2009)	Y	U	Y	Y	Y	N	Y	Y	75.0%
Lee et al. (2010)	Y	Y	Y	Y	Y	Y	Y	Y	100.0%
Lee et al. (2022)	Y	Y	Y	Y	Y	Y	Y	Y	100.0%
Martínez-Fernández et al. (2020)	Y	Y	Y	Y	Y	N	Y	Y	87.5%
McCann et al. (2021)	Y	Y	Y	Y	Y	N	N	U	62.5%
Michaelis et al. (2024)	Y	Y	Y	Y	N	N	Y	Y	75.0%
Micoulaud-Franchi et al. (2014)	Y	Y	Y	Y	N	N	U	Y	62.5%
Moon et al. (2016)	Y	Y	Y	Y	Y	Y	Y	Y	100.0%
Nakamura et al. (2023)	Y	Y	Y	Y	N	N	Y	Y	75.0%
Neshige et al. (2021)	Y	Y	Y	Y	Y	Y	Y	Y	100.0%
Novakova et al. (2017)	Y	Y	Y	Y	Y	N	Y	Y	87.5%
Rosengard et al. (2021)	Y	Y	Y	Y	Y	N	U	Y	75.0%
Saengsuwan et al. (2015)	Y	Y	Y	Y	Y	N	U	U	62.5%
Spatt et al. (1998)	N	N	Y	Y	Y	Y	U	Y	62.5%
Temkin & Davis (1984)	Y	U	Y	Y	Y	Y	U	Y	75.0%
Thapar et al. (2009)	Y	Y	Y	Y	Y	Y	Y	Y	100.0%
Toprani et al. (2022)	Y	Y	Y	Y	Y	Y	Y	Y	100.0%

Note. N: no; U: unclear; Y: yes; Q1: Were the criteria for inclusion in the sample clearly defined?; Q2: Were the study subjects and the setting described in detail?; Q3: Was the exposure measured in a valid and reliable way?; Q4: Were objective, standard criteria used for measurement of the condition?; Q5: Were confounding factors identified?; Q6: Were strategies to deal with confounding factors stated?; Q7: Were the outcomes measured in a valid and reliable way?; Q8: Was appropriate statistical analysis used?

3.4. Effects of stressful life events on the perceived stress of patients with epilepsy

Six studies (18% of the total sample) explored the effects of stressful live events on perceived stress (Alkhotani et al., 2020; McCann et al., 2021; Neshige et al., 2021; Rosengard et al., 2021; Saengsuwan et al., 2015; Temkin & Davis, 1984).

Of them, three studies (50% of this section) addressed changes in perceived stress levels during the pandemic (Alkhotani et al., 2020; Neshige et al., 2021; Rosengard et al., 2021). Alkhotani et al. (2020) found an increase in perceived stress in 54% of patients during this period. Among these three studies, two articles explored the variations in perceived stress depending on the change in seizure frequency during the pandemic (Neshige et al., 2021; Rosengard et al., 2021). Among patients who experienced a worsening in seizure frequency, 63-81% reported a rise in perceived stress. Conversely, among those who remained stable or improved in seizure frequency, 23-50% reported a rise in perceived stress (Neshige et al., 2021; Rosengard et al., 2021).

The remaining three studies of this section (50% of them) explored different stressful life events in epilepsy (McCann et al., 2021; Saengsuwan et al., 2015; Temkin & Davis, 1984). Temkin & Davis (1984) stated that, due to the variability of the stressful events reported, it was not possible to classify them. However, they found that the only stressor event that was significantly associated with the occurrence of seizures was attendance at work or school. McCann et al. (2021) showed that patients with epilepsy experienced at least one stressful event in the last year. The most frequent events reported were financial difficulties (25%), food scarcity (5%), and difficulties in accessing antiseizure medications (2%) (McCann et al., 2021). Saengsuwan et al. (2015) found that 50% of the patients reported that epilepsy was the main cause of stress, followed by problems related to employment (40%) and economy (34%).

3.5. Perceived stress as a seizure trigger

Thirteen studies (38% of the total sample) explored the role of perceived stress as a seizure precipitant (Al-Kattan et al., 2015; Alkhotani et al., 2020; Allendorfer et al., 2014; Goodman et al., 2019; Haut et al., 2007, 2012; Koh et al., 2021; Michaelis et al., 2024; Neshige et al., 2021; Rosengard et al., 2021; Spatt et al., 1998; Temkin & Davis, 1984; Thapar et al., 2009).

Among them, eleven (85% of this section) found that perceived stress could be considered a seizure precipitant (Al-Kattan et al., 2015; Alkhotani et al., 2020; Goodman et al., 2019; Haut et al., 2007; Koh et al., 2021; Michaelis et al., 2024; Neshige et al., 2021; Rosengard et al., 2021; Spatt et al., 1998; Temkin & Davis, 1984; Thapar et al., 2009), while two (15% of the studies in this section) did not find a significant relationship (Allendorfer et al., 2014; Haut et al., 2012).

Of those studies that found a positive correlation, four explored the relationship between seizure frequency and perceived stress in the context of COVID-19 (31% of the studies in this section) (Alkhotani et al., 2020; Koh et al., 2021; Neshige et al., 2021; Rosengard et al., 2021). Alkhotani et al. (2020) found that an increase in perceived stress was correlated to a rise in seizure frequency, together with sleep changes. Koh et al. (2021) showed that an increase in seizures was more frequently reported in those patients who identified stress as the cause of the worsening. In addition, they found that 24% of the sample attributed this worsening to stress, second only to inadequate sleep (29.3%) (Koh et al., 2021). Neshige et al. (2021) identified that high levels of perceived pre-pandemic stress were associated with seizure worsening during the pandemic. Finally, Rosengard et al. (2021) observed that those patients who had a worsening in seizure frequency during the pandemic were more likely to report stress as a seizure precipitant and an increase in perceived stress during the pandemic.

The remaining seven studies (54% of the studies in this section) stating that perceived stress was a seizure trigger explored this relationship globally (i.e., without focusing on COVID-19) (Al-Kattan et al., 2015; Goodman et al., 2019; Haut et al., 2007; Michaelis et al., 2024; Spatt et al., 1998; Temkin & Davis, 1984; Thapar et al., 2009). Al-Kattan et al. (2015) found that psychological stress was the third most frequently reported precipitating factor by patients. In the same line, Goodman et al. (2019) showed that 75% of the patients in their sample identified stress as a seizure trigger. Spatt et al. (1998) found that sleep deprivation and stress were the most common seizure precipitant reported. Although from a qualitative perspective, stress was more frequently informed as a seizure trigger in males and those with higher seizure frequency,

auras, and living in rural areas (Spatt et al., 1998). Thapar et al. (2009) observed that stress was a significant predictor of changes in seizure recency. However, when stress, depression, and anxiety were considered simultaneously as predictors of seizure recency, only depression was a reliable predictor. The other three studies used diaries in which perceived stress levels, the presence of stressful events, and seizure frequency were recorded. Michaelis et al. (2024), in their prospective study using electronic diaries, showed that half of the sample experienced an increase in stressful life events before seizures. However, in 14% of patients in this sample, seizures were preceded by a reduction of the presence of stressors. Similarly, Temkin & Davis (1984), reported that 58% of the sample presented a rise in stress levels and stressful events together with the presence of seizures. Interestingly, this percentage increased to 100% when only patients with recurrent seizures (i.e., more than 60 seizures in the last three months) were considered. Haut et al. (2007) found that the lack of sleep, and higher perceived stress and anxiety levels, were related to higher seizure frequency. Furthermore, this study provided concrete data, specifying that each unit increase in perceived stress corresponded to a 1.12-fold increase in the probability of experiencing a seizure the following day (Haut et al., 2007).

Regarding the two studies that did not find a significant effect of perceived stress on seizure occurrence (accounting for 15% of this section), although Allendorfer et al. (2014) found a lack of correlation between perceived stress and seizure frequency, a significant relationship was found between physiological acute stress and seizure occurrence. Haut et al. (2012) found that neither stress levels measured from 0 to 10 through electronic diaries nor scores on the Perceived Stress Scale (Cohen et al, 1983) were related to seizure frequency.

3.6. Differences in perceived stress among people with epilepsy and healthy controls

Seven studies of the 34 reviewed articles (21%) included a healthy control group (Allendorfer et al., 2014; Frances et al., 1999; Gargiulo et al., 2022; Goodman et al., 2019; Lacey et al., 2009; Moon et al., 2016; Toprani et al., 2022). Four of them (57%) showed higher perceived stress levels in patients with epilepsy than in healthy people (Gargiulo et al., 2022; Lacey et al., 2009; Moon et al., 2016; Toprani et al., 2022), while three (43%) showed that patients with epilepsy and healthy controls did not differ in perceived stress (Allendorfer et al., 2014; Frances et al., 1999; Goodman et al., 2019).

Concerning studies that found differences in levels of perceived stress between people with epilepsy and healthy controls, it should be noted that two of them focused specifically on

patients with drug-resistant epilepsy (DRE) (Gargiulo et al., 2022; Moon et al., 2016). Specifically, Moon et al. (2016) found that patients with DRE had higher perceived stress than healthy controls, whereas patients with well-controlled epilepsy showed lower levels of perceived stress than healthy controls. Regarding the rest of the studies that found significant differences, Toprani et al. (2022) explored the differences in stress levels between pregnant women with epilepsy and healthy pregnant women. They found that pregnant women with epilepsy had higher levels of perceived stress than healthy pregnant women (Toprani et al., 2022). Finally, although Lacey et al. (2009) did not use a healthy control group, they compared the rate of high psychological stress in patients with epilepsy with the general population, showing that the rate was almost twice as high in epilepsy (24% versus 13% in the general population).

Regarding studies that showed no differences in perceived stress between patients with epilepsy and healthy people, it should be underlined that Allendorfer et al. (2014) stated that the perceived stress levels of both, patients with left temporal lobe epilepsy (LTLE) and healthy controls, were higher than in the general population in their study, which could have affected the results.

3.7. Differences in perceived stress among people with epilepsy compared to other clinical populations and comorbidities

Twelve out of the 34 reviewed studies (35%) provided a comparison of perceived stress levels between people with epilepsy and other clinical populations and comorbidities (Aishwarya et al., 2023; Allendorfer et al., 2014; Baniya & Verma, 2022; Bifftu et al., 2015; Engidaw et al., 2020; Farnia et al., 2021; Frances et al., 1999; Gargiulo et al., 2022; Kim et al., 2019; Martínez-Fernández et al., 2010; Moon et al., 2016; Novakova et al., 2017).

Four studies (33% of this section) assessed the differences between patients with epilepsy with and without other comorbidities (Baniya & Verma, 2022; Bifftu et al., 2015; Engidaw et al., 2020; Farnia et al., 2021). Three of them studied the differences in patients with and without comorbid depression (Baniya & Verma, 2022; Bifftu et al., 2015; Engidaw et al., 2020). In this regard, Baniya & Verma (2022) showed that perceived stress was almost doubled in those with depression than those without; however, perceived stress did not predict depression. Bifftu et al. (2015) found that patients with high perceived stress had six times the odds of depression as compared to those patients with low perceived stress. Similarly, Engidaw et al. (2020) found

that participants with high perceived stress had more than three times the rate of depression as compared to those patients who had low perceived stress. Furthermore, there was a higher percentage of patients with high perceived stress among those with comorbid depression (Engidaw et al., 2020). The remaining article studied the differences between patients with epilepsy and comorbid substance use disorder and patients with only epilepsy, showing that stress levels were six units higher in those with comorbid substance use disorder compared to those without (Farnia et al., 2021).

Three studies (25% of this section) explored the differences in perceived stress between patients with epilepsy and patients with functional seizures, showing a lack of significant differences (Frances et al., 1999; Gargiulo et al., 2022; Novakova et al., 2017).

Another three studies (25% of this section) provided information about stress levels in patients with DRE and well-controlled epilepsy (Aishwarya et al., 2023; Allendorfer et al., 2014; Moon et al., 2016). Aishwarya et al. (2023) found that perceived stress was higher in people with DRE than in well-controlled epilepsy. Allendorfer et al. (2014) did not find differences between LTLE patients with and without seizures during the last three months. Although Moon et al. (2016) did not statistically analyze the data between patients with DRE and well-controlled epilepsy, perceived stress scores were higher in patients with DRE (mean score = 21.9) than in well-controlled epilepsy (mean score = 14.6). Interestingly, these authors explored the data of a poorly controlled group (i.e., patients with an intermediate degree of seizure control that did not meet the criteria for DRE or well-controlled epilepsy), and this group showed intermediate perceived stress values (mean score = 17.7) (Moon et al., 2016).

Two studies (comprising 17% of this section) examined the differences between epilepsy and other neurological disorders (Kim et al., 2019; Martínez-Fernández et al., 2010). Kim et al. (2019) explored differences in psychiatric symptoms and perceived stress between patients classified into the following groups: cerebrovascular disease, cord and peripheral neuropathy, headache and pain, dizziness, cognitive decline, movement disorder, miscellaneous, and epilepsy. The epilepsy group was the one that reported more frequently higher stress levels (79%), after the group with cognitive decline (81%). Martínez-Fernández et al. (2020) examined the differences between patients with epilepsy, patients with episodic migraine, and patients with chronic migraine, and showed that patients with epilepsy had higher stress levels than the other groups.

3.8. Demographic and clinical factors associated with perceived stress

Nineteen of the 34 reviewed studies (56%) explored the relationships between perceived stress and other variables (Alkhotani et al., 2020; Baniya & Verma, 2022; Bifftu et al., 2015; DiIorio et al., 2011; Engidaw et al., 2020; Gammoh et al., 2024; Gargiulo et al., 2022; Goodman et al., 2019; Haut et al., 2007; Lacey et al., 2009; Lee et al., 2010, 2022; Martínez-Fernández et al., 2010; McCann et al., 2021; Micoulaud-Franchi et al., 2016; Moon et al., 2016; Nakamura et al., 2023; Novakova et al., 2017; Thapar et al., 2009).

Five of them (representing 26% of this section) explored the association of perceived stress with demographic and clinical variables (Alkhotani et al., 2020; Haut et al., 2007; Lacey et al., 2009; Moon et al., 2016; Novakova et al., 2017). Alkhotani et al. (2020) examined risk factors associated with a rise in perceived stress during the pandemic. In this regard, students, patients with less than 5 years of suffering epilepsy, patients with psychiatric disease, and, consequently, those who were taking antipsychotic drugs, had a higher likelihood of suffering an increase in perceived stress levels. Lacey et al. (2009) found higher perceived stress levels in women, younger patients, and those who used medical services more frequently. However, no relationships between perceived stress and socioeconomic status were found (Lacey et al., 2009). Moon et al. (2016) provided specific information, revealing that being a woman, unmarried, having a low educational level, being unemployed, having low income, and lacking a driver's license were associated with higher perceived stress. Additionally, clinical variables were examined, finding that higher perceived stress scores were linked to partial seizures, TLE, poor seizure control, polytherapy, high ASM load, and sleep problems (Moon et al., 2016). Finally, Novakova et al. (2017) showed that perceived stress levels were similar regardless of the time of day and seizure recency, and Haut et al. (2007) found that perceived stress is positively associated with a higher likelihood of seizure self-prediction.

Remarkably, one of the most studied clinical variables was depression, which was examined by eight reports (constituting 42% of this section) (Baniya & Verma, 2022; Bifftu et al., 2015; Engidaw et al., 2020; Gargiulo et al., 2022; Lee et al., 2010, 2022; Moon et al., 2016; Thapar et al., 2009). There is consistency in the results that point to a positive relationship between perceived stress and depression (Gargiulo et al., 2022; Thapar et al., 2009), with depression having a mediator role in the relationship between stress and change in seizure recency (Thapar et al., 2009). Furthermore, patients with epilepsy and comorbid depression have more often higher stress (Baniya & Verma, 2022; Bifftu et al., 2015; Engidaw et al., 2020). Lee et al. (2010,

2022) explored in both studies the role of perceived stress as a predictor of depression, showing that perceived stress was the strongest predictor, accounting for 38.8% of the variance depression score (Lee et al., 2010), and 42.4% or 23.5% in Lee et al. (2022) (depending if it was entered as the first or last factor in the model, respectively). Conversely, Moon et al. (2016) examined the predictors of perceived stress, identifying depression as the main predictor, followed by sleep problems, anxiety, and seizure control (in that order).

Three studies (accounting for 16% of this section) assessed the relationship between perceived stress and other psychological variables (Martínez-Fernández et al., 2010; McCann et al., 2021; Moon et al., 2016). In this regard, Martínez-Fernández et al. (2010) and Moon et al. (2016) found a positive association between stigma and perceived stress. Additionally, McCann et al. (2021) showed that higher perceived stress was related to poor social support, lower income, and higher global mood disturbance.

Another three studies examined the effects of different treatments on perceived stress (DiIorio et al., 2011; Gammoh et al., 2024; Micoulaud-Franchi et al., 2016). One of them concerned a self-management program aimed at helping people take medication, manage stress, and improve sleep quality (DiIorio et al., 2011). However, no differences were found between patients who received the treatment and the control group in terms of perceived stress. Another study explored the effects of biofeedback treatment in a sample of patients with stress-triggered seizures, stating that no patient reported stress during its implementation (Micoulaud-Franchi et al., 2016). Interestingly, a significant reduction in seizure frequency was observed after 12 sessions (Micoulaud-Franchi et al., 2016). Finally, Gammoh et al. (2024) explored the differences in perceived stress, among other variables, between patients treated with levetiracetam and patients not taking levetiracetam. In this line, no relationship between levetiracetam users and perceived stress was found, although 75% of the total sample reported high perceived stress (Gammoh et al., 2024).

Finally, three studies (making up 16% of this section) assessed the relationship between perceived stress and other stress indicators (Goodman et al., 2019; Nakamura et al., 2023; Novakova et al., 2017). Goodman et al. (2019) and Novakova et al. (2017) found no relationships between perceived stress and cortisol measures. Novakova et al., (2017) also found lack of a relationship between perceived stress and heart rate variability. Additionally, Nakamura et al. (2023) showed that higher perceived stress was related to lower arousal, measured with the Japanese-Stress arousal Check List (J-SACL; Cox & Mackay, 1985).

4. Discussion

This review collects data on perceived stress in adults with epilepsy. Thirty-four studies were selected, most of them addressing issues such as the role of perceived stress as a precipitating factor of seizures, differences in perceived stress between people with epilepsy and other populations, and, finally, demographic and clinical factors associated with perceived stress in epilepsy. Half of the studies used the Perceived Stress Scale (Cohen et al., 1983) for measuring perceived stress, while 32% employed interviews and visual analog scales, and 17% utilized other standardized scales. In broad terms, the identified literature was relatively current; 74% of the studies were published in the last decade, while approximately half of the total sample (53%) was published in the past five years.

The first issue addressed was the stress conceptualization in epilepsy. In general, reviewed studies agree that stress is a process in which the demands of the environment exceed the organism's ability to cope, as 89% of the studies that defined stress followed this perspective. Almost half of the studies in this section pointed out that stress is a process involving different systems, all of them agreeing on the relevance of the psychological component in this process. Remarkably, only two studies defined stress as those situations perceived as unpredictable and uncontrollable (Frances et al., 1999; Lee et al., 2022), although this framework seems to fit the characteristics of seizures. However, we suggest that stressors in epilepsy may go beyond seizures and that other consequences, such as comorbidities or social impact, also contribute to the stress burden (Cano-López & González-Bono, 2019). Therefore, we can consider that epilepsy, within a theoretical framework of stress, should be recognized as a condition in which seizures, as well as the consequences in other areas, are perceived as challenging or threatening, and the individual's strategies are noticed as ineffective in coping with them.

The present review addressed the effect of stressful life events (i.e., stressors) on perceived stress. One of the most discussed topics was the effect of the pandemic, probably motivated by the novelty of the situation. This was explored by half of the studies in this section, which found that the pandemic situation increased stress levels in epilepsy (Alkhotani et al., 2020), and these levels were related to a worsening of seizure frequency (Neshige et al., 2021; Rosengard et al., 2021). Remarkably, in the remaining half of the reports, a common stressor was identified in people with epilepsy: problems directly or indirectly related to work (McCann et al., 2021; Saengsuwan et al., 2015; Temkin & Davis, 1984). Unemployment rates are higher in people with epilepsy than in the general population (de Souza et al., 2018; Willems et al., 2023).

Furthermore, unemployment is accompanied by added difficulties, such as risks of accidents, perceived stigma, and financial difficulties (Almatrood et al., 2024; de Souza et al., 2018; Jennum et al., 2011). This stressor has been proven to double the risk of seizures (Temkin & Davis, 1984), highlighting the need to make the work environment more friendly and adapted for this population. Moreover, Saengsuwan et al. (2015) stated that the main stress source was epilepsy itself, reported by 50% of the patients. This is in line with the consideration of epilepsy as a chronic stress model (Cano-López & González-Bono, 2019).

One of the main topics of the studies reviewed was the role of perceived stress as a seizure trigger. In this regard, there is a consensus in the literature, with 85% of the articles that addressed this topic concluding that perceived stress is related to seizure occurrence. These studies could be classified into two categories; a) studies that explored the correlation between perceived stress levels and change in seizure frequency in the context of COVID-19; and b) studies that examined this relationship globally (i.e., without focusing on COVID-19). The consistency in the results, despite the methodological differences, enhances the robustness of the data and suggests that stress is, objectively and subjectively, a precipitating factor for seizures. Although the mechanisms underlying this relationship remain unknown, in animal models, exogenous peripherally or intracerebroventricularly administration of corticotropin-releasing hormone and corticosterone (i.e., stress hormones) increased seizure activity (Joëls, 2009). Furthermore, in chronic stress, an increase in neurodegeneration and epileptic activity has been observed, being a poor prognostic factor for epilepsy (Joëls, 2009). Previous studies that did not measure perceived stress have suggested that stress may be not only implicated in the onset of seizures in people with epilepsy, but also in the risk of developing the disorder (Christensen et al., 2007; Gélisse et al., 2015; Jones et al., 2013). Christensen et al. (2007) found that the experience of severe stress (i.e., loss of a child under 18 years of age) increased the risk of developing epilepsy, especially in women. Similarly, Gélisse et al. (2015) found that the stressors most frequently associated with the onset of epilepsy were the loss of a loved person (54%), the breakup of a trusting relationship (32%), and being a victim of violence (14%). Although more research is needed, it has been found in animal models that amygdala activation and elevated glucocorticoid secretion due to repeated stress exposure increase the vulnerability to developing epilepsy (Jones et al., 2013).

Among those studies assessing the differences between stress levels in people with epilepsy and healthy controls, 57% concluded that patients with epilepsy had higher levels (Frances et

al., 1999; Gargiulo et al., 2022; Lacey et al., 2009; Moon et al., 2016; Toprani et al., 2022). Accordingly, patients with epilepsy also have shown a specific profile through physiological measures, such as high cortisol levels or alterations in heart rate variability (Cano-López et al., 2019; Goodman et al., 2019; Myers et al., 2018). However, some studies have found a lack of relationship between physiological and psychological measures (Goodman et al., 2019; Novakova et al., 2017). Forty-three percent of studies included in this section found that patients with epilepsy and healthy controls did not differ in perceived stress levels (Allendorfer et al., 2014; Frances et al., 1999; Goodman et al., 2019). Interestingly, Allendorfer et al. (2014) and Goodman et al. (2019) studies used samples composed of LTLE patients. Traditionally, emotional processing has been considered more lateralized on the right hemisphere. Damage to this hemisphere has been associated with difficulties in emotion management and stress response (Palomero-Gallagher & Amunts, 2022). In this line, Lozano-García et al. (2021) found a deficient response to acute stress in patients with right-hemisphere epilepsy on the sympathetic system compared to those with left epilepsy. Therefore, we consider that Allendorfer et al. (2014) and Goodman et al. (2019) results could be biased by the inclusion of only patients with the left-hemisphere epileptogenic area, and that the preservation of the right hemisphere in epilepsy may help to buffer the stress impact.

Twelve studies of the total sample studied the differences in perceived stress between patients with epilepsy and other clinical populations and comorbidities. Some of these studies addressed the impact of comorbidities (33%), especially depression. In this regard, a higher prevalence of depression was found among those patients with high perceived stress (Baniya & Verma, 2022; Bifftu et al., 2015; Engidaw et al., 2020). These results agree with the conception of depression in epilepsy within the diathesis-stress model (Hoppe & Elger, 2011), in which hopelessness, uncontrollability of epilepsy, and its consequences place these patients in a vulnerable situation. Moreover, patients with depression have shown a dysregulation of the HPA axis, with higher cortisol levels than the general population (Bertollo et al., 2020; Cano-López et al., 2019; Carroll et al., 2012), suggesting that they are subjected to a situation of chronic stress. Another comorbidity studied was substance use disorder, finding that stress symptoms were more frequent in those with comorbid substance use disorder than in those without (Farnia et al., 2021). Substance use disorder can be conceived as an added stress for the population with epilepsy, which can interact with social life and even with the treatment and prognosis of epilepsy (Jones et al., 2023). In addition, patients with substance use disorder appear to implement maladaptive and ineffective coping strategies to deal with the stressor

(Adan et al., 2017; Marquez-Arrico et al., 2015), which complicates stress management, exacerbating its impact.

Some studies were also focused on patients with functional seizures, showing no differences in stress levels with patients with epilepsy (Frances et al., 1999; Gargiulo et al., 2022; Novakova et al., 2017). While epileptic and functional seizures respond to different etiologies, their consequences for stress perception are quite similar. Both conditions share many of the epilepsy stressors (such as the unpredictability of seizures or social and occupational impact), as well as the high prevalence of psychiatric comorbidities (Diprose et al., 2016). Therefore, it is not surprising that people with functional seizures also have higher perceived stress levels (Testa et al., 2012). Remarkably, other studies of this review did observe higher levels of stress among those patients with DRE compared to those with well-controlled epilepsy (i.e., no seizures during the past year) (Aishwarya et al., 2023; Moon et al., 2016). This suggests that appropriate disease management may be crucial in regulating the emotional impact on the individual. It is noteworthy that, although Allendorfer et al., (2014) did not find significant results, a tendency for higher scores in the group with seizures was observed ($p = 0.055$). The temporal criterion for classifying patients as seizure-free or active epilepsy was less restrictive (i.e., three months), which could affect the sensitivity of the results. Finally, two studies explored the differences in perceived stress levels between patients with epilepsy and other neurological disorders. Kim et al. (2019) performed a comprehensive comparison, including eight different neurological disorders. In this regard, it was found that patients with epilepsy were the second most frequent group to report stress (79% of patients), behind only those with cognitive impairment (which is, interestingly, a frequent comorbidity of epilepsy). Likewise, Martínez-Fernández et al. (2020) showed that patients with epilepsy showed higher levels of stress than those with episodic and chronic migraine. Based on these results, it appears that epilepsy carries with it certain particularities that make it more vulnerable to stress than other neurological conditions, including those with symptom-free periods, such as migraine.

Finally, this review collected data on demographic and clinical factors that have been associated with higher levels of stress in epilepsy. Among the demographic variables that can be considered as risk factors for increased stress, these can be summarized as female sex, young age, low educational levels, unemployment, and poor social support (Alkhotani et al., 2020; Lacey et al., 2009; Moon et al., 2016). As for the clinical variables associated with higher stress levels, the following are included: less than five years of suffering from the disease, patients

with TLE, psychiatric comorbidities, poor seizure control, and receiving polytherapy (Alkhotani et al., 2020; Moon et al., 2016). However, the factor that stands out the most is depression (Lee et al., 2010, 2022; Moon et al., 2016), emphasizing the close relationship between these two conditions. This could be due to common underlying mechanisms, taking into account that HPA alterations have been found in both, epilepsy and depression. However, other structural and functional alterations in the amygdala and hippocampus are involved in the individual's appraisal of stimuli and situations, creating maladaptive schemas (Tafet & Nemeroff, 2016). In turn, this could lead to a chronic stress response and increased vulnerability to depression, whose situation could be exacerbated in patients with epilepsy due to structural and functional damage intrinsic to the pathology.

Three studies addressed the effect of three different treatments (i.e., WebEase program, biofeedback, and levetiracetam) on perceived stress levels, showing no significant impact (DiIorio et al., 2011; Gammoh et al., 2024; Micoulaud-Franchi et al., 2016). However, it should be noted that only the study by DiIorio et al. (2011) specifically targeted stress reduction. Following previous literature, intervention programs designed for stress management have demonstrated efficacy in reducing stress in mixed samples of patients with epilepsy and functional seizures, such as Novakova's self-help program (Novakova et al., 2019). Additionally, the implementation of this kind of treatment (mindfulness, yoga, or cognitive-behavioral therapies, among others) can have potential effects on epilepsy, improving seizure frequency and comorbidities (Kotwas et al., 2017). Therefore, future studies should assess the need for the implementation of treatments aimed at stress reduction in epilepsy, due to the potential clinical benefits that can be derived from them.

In conclusion, the studies considered in this review indicate that, in general, patients with epilepsy show higher levels of perceived stress than healthy controls, but also than other clinical populations, with those with DRE being especially vulnerable. However, these patients do not differ from patients with functional seizures. In addition, the role of perceived stress as a seizure precipitating factor is emphasized, identifying the stressful events most commonly reported by this population. Finally, demographic and clinical risk factors are pointed out, highlighting the relationship between stress and depression, as well as the need for intervention approaches aimed at reducing stress. Therefore, these studies highlight the need for the conceptualization of epilepsy within a chronic stress framework, which could help for more appropriate clinical management of this population.

CHAPTER 3

Aims and hypotheses

1. Aims and hypotheses

As discussed in previous chapters, epilepsy has been considered a chronic stress model in humans (Cano-López & González-Bono, 2019). The stress in epilepsy appears to have specific characteristics, due to the particularities of the disease and its comprehensive impact on the individual (Fisher et al., 2017). The present Thesis includes five studies aimed at exploring the stress process in epilepsy following the SOR model (see Figure 1). Among stressors, the social impact of epilepsy will be approached (Study 1), and clinical variables such as seizure frequency and epilepsy duration will be analyzed from a cross-sectional view in the studies as intensity and chronicity measures of the epilepsy-related stressors. Regarding organism processing, modulator factors of the individual on cognition, negative affectivity, and QOL will be assessed to explore inter-individual variability (Studies 2 and 3). Additionally, cortisol response to acute stress in persons with epilepsy will be examined, exploring the association between cortisol response and cognitive functioning, negative affectivity, and QOL (Study 4). In this setting, due to the need for specific tools to evaluate perceived stress in drug-resistant epilepsy — probably because of the novelty of this framework in epilepsy — this Thesis aims to develop a perceived stress questionnaire specific for patients with this neurological condition.

Following the SOR model, seizures can be considered stressors in drug-resistant epilepsy, due to their unpredictability, uncontrollability, and for posing a threat to survival (van Campen et al., 2014). Furthermore, studies based on self-report questionnaires have shown that social factors, such as unemployment, are one of the main sources of stress for these patients (Saengsuwan et al., 2015; Temkin & Davis, 1984). However, to our knowledge, no studies have assessed objective indicators of social insertion and its impact on subjective social support and other cognitive and mood variables relevant to QOL in the same sample of patients with epilepsy. This lack of comprehensive research highlights the need for an adequate approach to stress in epilepsy, considering stimuli of different nature, and contemplating the overall impact on the individual.

General aim 1. To examine the association of a potential social stressor commonly reported by patients with epilepsy (i.e., unemployment) with cognitive performance, social support, negative affectivity, and QOL. Furthermore, clinical variables such as seizure frequency will be considered.

- **Specific aim 1.1.** To determine whether patients with academic/employment insertion differ in executive functioning, social support, negative affectivity, and QOL from those without insertion.

- **Specific aim 1.2**. To study the direct association between academic/employment insertion and QOL, as well as its indirect relationship through executive functioning, social support, and negative affectivity.

Despite the lack of studies exploring the overall impact of insertion in people with epilepsy, previous literature that has studied isolated relationships with certain variables allows us to develop the following hypotheses:

Hypothesis 1. Patients with academic/employment insertion will show better executive functioning than those without insertion, due to the strong impact on cognitive reserve (Vance et al., 2016).

Hypothesis 2. Academic/employment insertion will act as a source of social support, as a protective factor against negative affectivity (Wo et al., 2016), and as an enhancer of QOL (Azuma & Akechi, 2014).

Hypothesis 3. In addition to its direct effect on QOL, academic and/or employment insertion will have an indirect effect on QOL through cognitive performance, social support, and negative affectivity.

The aim 1 will be addressed in Study 1.

Regarding the individual modulator factors, in their transactional theory of stress and coping, Lazarus and Folkman (1984) highlighted the importance of cognitive appraisal. In epilepsy, ASMs can be considered one of the main modulators, since they have physiological effects that can influence the evaluation of the stimulus and, as a consequence, the stress response. In addition, personal characteristics may also act as vulnerability or protective factors for the impact of stress in people with epilepsy (Ong et al., 2006; Radley et al., 2011).

General aim 2. To identify personal and clinical factors that influence how the stressor is appraised by the organism. To this purpose, the effect of clinical and emotional modulator factors (pharmacological treatment and negative affectivity) will be studied, assessing their

impact on cognitive function and psychological variables in patients with drug-resistant epilepsy.

- **Specific aim 2.1.** To analyze the effect of the introduction of a new generation ASM, cenobamate, in pharmacological treatment on cognition (i.e., attention, executive functions, naming, and memory), negative affectivity, and QOL, after a period of gradual dose increase (i.e., after 3 months) and after achieving a stable dose (i.e., after 6 months), controlling for the impact of age and the consumption of other ASMs and antidepressants.

Only one study has addressed the effect of cenobamate on attention and executive functions (Schuetz et al., 2022). Therefore, given the pioneering nature of this work, no hypotheses can be established about the effect of cenobamate treatment on the rest of the studied variables.

Hypothesis 4. Attention and executive function performance will remain stable after the treatment with cenobamate, as reported by Schuetz et al. (2022).

- **Specific aim 2.2.** To identify vulnerability or protection profiles to the impact of stress in epilepsy, considering indicators of stress intensity (i.e., anxious and depressive symptomatology) and chronicity of the stressor (i.e., epilepsy duration), and to examine differences in cognitive performance (i.e., attention, executive functions, memory, and language) and QOL depending on these profiles.

To our knowledge, no specific stress profiles in epilepsy have been established before. Nevertheless, previous literature that has addressed the effect of resilience on negative affectivity in this population and studies that have examined the impact of negative affectivity on cognition and QOL allow us to establish the following hypotheses:

Hypothesis 5. Risk and protective profiles of the impact of stress will be identified. In particular, we hypothesize the existence of two phenotypes: one characterized by longer epilepsy duration but moderate levels of negative affectivity, suggesting an adaptation to the disease; and another group with longer epilepsy duration and higher levels of anxiety and depression (Ring et al., 2016).

Hypothesis 6. The group of patients with moderate levels of negative affectivity will show better cognitive performance and QOL than those with high negative affectivity (Taylor et al., 2011; Wang et al., 2019).

The aim 2 will be treated in Studies 2 and 3.

Concerning the stress response in terms of cortisol levels, it has been suggested that patients with epilepsy may have a dysregulation of the HPA axis (Cano-López & González-Bono, 2019). However, studies exploring the cortisol response to an acute psychosocial stressor in patients with epilepsy are scarce.

General aim 3. To study the acute stress response in terms of cortisol levels in patients with drug-resistant epilepsy, examining the association between the magnitude of this response and memory, negative affectivity, and QOL.

- **Specific aim 3.1.** To analyze whether the cortisol stress response to a laboratory psychosocial acute stressor differs between patients with epilepsy and healthy people. To control epilepsy-related factors, a second control group of patients with epilepsy who were not exposed to the stressor will be included.

- **Specific aim 3.2.** To examine the possible relationship between the magnitude of the cortisol response with memory performance, negative affectivity, and QOL.

As far as we know, only two studies have addressed the differences in cortisol response to an acute psychosocial stressor between adults with epilepsy and healthy controls (Allendorfer et al., 2014; Goodman et al., 2019). Nevertheless, some questions remained unanswered, such as the cortisol response to the Trier Social Stress Test (TSST) in this population, its relationship with cognitive and emotional variables, and the possible differences in cortisol levels between patients exposed to the stressor and control patients. Therefore, no assumptions can be made in this regard. However, considering the studies of Allendorfer et al., (2014) and Goodman et al., (2019) in patients with epilepsy, and along with those addressing the dynamic of cortisol response to acute stressors in the general population (Dickerson & Kemeny, 2004), it is hypothesized:

Hypothesis 7. A greater cortisol reactivity to a psychosocial acute stressor will be found in patients with epilepsy than in healthy people, attending to the interpretation of the results of previous studies (Allendorfer et al., 2014; Goodman et al., 2019).

Hypothesis 8. People with epilepsy who underwent a laboratory acute stressor will have a higher cortisol production than those who were not exposed, attending the findings in the general population (Dickerson & Kemeny, 2004).

The aim 3 will be treated in Study 4.

Finally, despite the importance of stress on the impact and prognosis of epilepsy, as far as we know there is only one validated instrument to measure perceived stress intensity in this population, the Revised Epilepsy Stressor Inventory (ESI-R; Snyder, 1993). However, this instrument was validated for the general epilepsy population with only 25 participants, and, to our knowledge, no factor analysis was performed. Consequently, the main factors influencing perceived stress in epilepsy remain unclear, possibly contributing to its limited use in previous research. Therefore, there is a need to develop a tool capable of measuring perceived stress in drug-resistant epilepsy, attending to general situations rather than specific events, and encompassing factors such as seizure severity. This could help to study the particularities of stress in drug-resistant epilepsy and the conceptualization of epilepsy within a stress framework.

General aim 4. To develop a specific tool to assess perceived stress in adults with drug-resistant epilepsy, analyzing its psychometric properties and exploring the relationship of perceived stress with clinical, psychological, and hormonal variables.

- **Specific aim 4.1.** To examine the reliability of a new self-report scale designed to measure perceived stress in adult patients with epilepsy, to explore the organization of the items in the different factors, and to evaluate the convergent validity of the test by studying its relationship with clinical (i.e., seizure frequency, previous failed ASMs, number of ASMs, and age at epilepsy onset), psychological (i.e., anxiety, depression, and QOL), and hormonal (i.e., cortisol levels) variables.

The criteria used for the item design (i.e., previous literature and patient testimonials) and the results of studies that have explored the relationship between perceived stress (measured by questionnaires developed for the general population) and negative affectivity and QOL (Endermann et al., 2013; Lee et al., 2022; Nakamura et al., 2023), lead us to hypothesize about the results of the validation. Furthermore, considering epilepsy within a framework of chronic stress model, and given the hypercortisolism found in these patients in the previous literature, we hypothesized:

Hypothesis 9. The instrument developed will be valid for measuring perceived stress in this population, and it will be associated with other related psychological instruments (i.e., Beck Depression Inventory-II (BDI-II), State-Trait Anxiety Scale (STAI), Quality of Life in Epilepsy Inventory (QOLIE-31)).

Hypothesis 10. Higher scores on the perceived stress scale will be associated with greater severity of the patient's clinical conditions, as well as higher cortisol levels (Allendorfer et al., 2014; Cano-López et al., 2019; Marek et al., 2010).

The aim 4 will be addressed in Study 5.

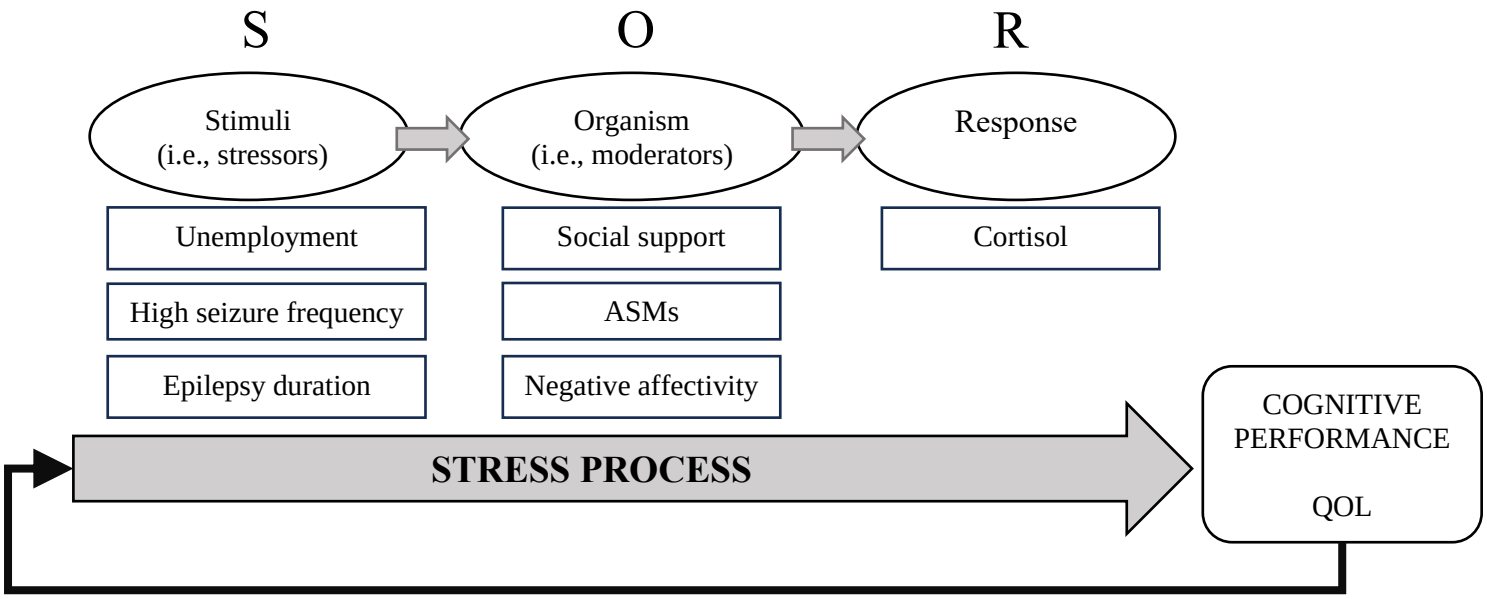

Figure 1. Proposal of the present Thesis of intervening factors in the stress process in epilepsy following the SOR model.

CHAPTER 4

Study 1

Academic and employment insertion as a factor related to quality of life in patients with drug-resistant temporal lobe epilepsy[1]

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[1] Published in: Judit Catalán-Aguilar, Alejandro Lozano-García, Esperanza González-Bono, Vicente Villanueva, Kevin G. Hampel and Irene Cano-López. (2022). Academic and employment insertion as a factor related to quality of life in patients with drug-resistant temporal lobe epilepsy. *Revista de neurologia*, *74*(7), 219-227.

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1. Introduction

Academic or employment insertion has been related to better executive functioning (Lázaro, 2011) and lower anxiety and depression in healthy samples (Fryers et al., 2005). These activities are frequently restricted in epilepsy patients (Majkowska-Zwolińska et al., 2012; Marinas et al., 2011), chronic stress conditions (Cano-López et al., 2019; Cano-López & González-Bono, 2019) (e.g., high seizure frequency (Holland et al., 2009) or social discrimination (Asadi-Pooya et al., 2020) being relevant factors. Temporal lobe epilepsy (TLE) is the most common type of drug-resistant epilepsy and is frequently associated with emotional and cognitive deficits (Cano-López et al., 2019). Although employment insertion or educational level have been related to better executive functioning (Fraser et al., 1986) and reduced anxiety and depression (Mensah et al., 2007; Peterson et al., 2014) in mixed samples of epilepsy patients, there are no studies in TLE patients.

TLE patients suffer a high prevalence of depression and anxiety (Peterson et al., 2014), and cognitive impairments (Vingerhoets, 2006). The high frequency of memory deficits in these patients (Thompson et al., 2016) has led to focus on this domain to the detriment of others such as executive functions (Stretton & Thompson, 2012), which are also compromised (Agah et al., 2017) and are relevant in settings of conflict solving, planning, organizing, and decision making (Tirapu et al., 2018) such as academic and employment contexts (Stuss & Alexander, 2000). It should be noted that academic or employment insertion may be a potential source of social support in TLE patients. Social support promotes well-being (Sherbourne & Stewart, 1991) and has been related to a better quality of life (QOL) in TLE patients (Cano-López et al., 2018), low anxiety and depression (Cano-López et al., 2018; Canuet et al., 2009), and better executive functioning (Ehrlich et al., 2019).

In terms of QOL, the results of previous studies about their potential relationship with insertion are intriguing. On the one hand, higher education level has been related to better QOL in patients with drug-resistant epilepsy (Loring et al., 2004), and employment insertion is a reliable predictor of QOL in a mixed sample of epilepsy patients (Azuma & Akechi, 2014). On the other hand, a lack of association between academic insertion and QOL has been found in patients with different epilepsy types (Azuma & Akechi, 2014). Demographic or social-emotional variables could explain, at least in part, the heterogeneity of the results.

2. Aim

This study aims to analyze differences in QOL, anxiety, depression, social support, and executive functions depending on academic/employment insertion in patients with TLE. We hypothesize that patients with insertion will have better QOL, lower anxiety and depression, and higher social support and executive functioning than those without insertion. Additionally, we aim to investigate the relationships among these variables.

3. Patients and methods

3.1. Patients

This is a cross-sectional study. Patients were recruited from the Refractory Epilepsy Unit, Hospital Universitario y Politécnico La Fe. The study was conducted following the Declaration of Helsinki and approved by the ethics committee of the hospital. Informed consent was obtained from participants. Our reporting followed the STROBE guidelines (von Elm et al., 2007). The inclusion criteria comprised: a) drug-resistant TLE; b) candidates for epilepsy surgery; c) chronological age of at least 18 years; d) and a neuropsychological assessment performed before surgery. Excluded were patients: a) older than 65 years; b) with severe cognitive impairment; and c) with severe psychiatric conditions.

3.2. Procedure

Demographic and clinical data were collected. Presurgical assessment included the diagnosis of the epilepsy type and the lateralization of the epileptogenic area based on seizure history and semiology, neurologic assessment, video-electroencephalography (EEG) monitoring, 3-Tesla magnetic resonance imaging (MRI), psychiatric assessment, and neuropsychological evaluation. Fluorodeoxyglucose (FDG)-positron emission tomography (PET), single-photon emission computed tomography (SPECT), and intracranial EEG recording were performed selectively. Neuropsychological evaluation was carried out 3 months before surgery.

3.3. Neuropsychological assessment

The Quality of Life in Epilepsy Inventory (QOLIE-31; Cramer et al., 1998) is composed of 31 items divided into seven subscales: emotional well-being, social functioning, energy,

cognitive self-rating, seizure worry, medication effects, and overall QOL. Scores for each subscale ranged from 0 to 100, with higher scores indicating better QOL. A QOL composite score was computed by using a weighted average of subscales. Cronbach's alpha ranges from 0.55 to 0.92 (Torres et al., 1999).

The trait anxiety scale of the State-Trait Anxiety Inventory (STAI-T; Spielberger, 1989) includes 20 items rated on a four-point scale, with higher scores indicating higher trait anxiety levels. Cronbach's alpha is 0.94 (Guillén-Riquelme & Buela-Casal, 2011).

The Depression Beck Inventory-II (BDI-II; Beck et al., 1996) is composed of 21 items rated on a four-point scale, higher scores indicating higher depression levels. Cronbach's alpha is 0.89 (Sanz & García-Vera, 2009).

The Medical Outcomes Study Social Support Survey (MOS; Sherbourne & Stewart, 1991) includes 20 items rated on a five-point scale divided into four subscales: emotional, instrumental and affectionate support, and positive social interaction. Global social support was obtained by the sum of the four subscales. Cronbach's alpha ranges from 0.91 to 0.97 (Sherbourne & Stewart, 1991)..

The Wisconsin Card Sorting Test (WCST; Heaton et al., 1993) was used to evaluate cognitive flexibility, abstract conceptualization, and responsiveness to feedback. Higher scores indicated worse performance in the following indices: number of trials, percentage of errors, perseverative responses and errors, nonperseverative errors, trials to complete the first category, and failure to maintain set. Additionally, higher scores showed better performance in the following indices: correct responses, percentage of conceptual level responses, categories completed, and learning to learn.

3.4. Statistical analyses

The Kolmogorov-Smirnov test was performed to examine data normality. t-tests for independent samples and chi-square tests were performed for between-group comparisons on patients' characteristics.

Univariate ANOVAs were performed to investigate differences in QOL, anxiety, depression, and executive functions depending on insertion, considering age as a covariate. Bonferroni tests were performed as post hoc analyses. Pearson correlations were performed to examine relationships among variables. Finally, we tested a mediation model using PROCESS

(v3.4.) macro, in which academic/employment insertion was included as an independent variable, global social support, trait anxiety, and percent of conceptual level responses as the mediator variables, and QOL as the dependent variable, adjusting for age. A bias-corrected 95% bootstrap-confidence interval CI (5,000 iterations) was used. To estimate the effect sizes of indirect effects, we used the percent mediation (PM) index, which indicates the proportion of the indirect effect compared to the total effect (Preacher & Kelley, 2011). Statistical analyses were carried out using SPSS 25.0, and two-tailed tests with *p* set at 0.05 were considered significant.

4. Results

4.1. Sample characteristics

The sample is composed of 59 adults with drug-resistant TLE (mean age = 39.49, SD = 12.39). Participants were classified into two groups: with academic/employment insertion (n = 25), 19 patients working and eight studying, and without insertion (n = 34) (Table 1).

Table 1. Characteristics of groups based on academic/employment insertion (mean ± SD or *n* (%)).

	With insertion (n = 25)	Without insertion (n = 34)	Total (n = 59)	*p*
Age (years)	33.68 ± 11.37	43.76 ± 11.46	39.49 ± 12.39	0.001
Sex				0.99
Male	11 (18.6%)	15 (25.4%)	26 (44.1%)	
Female	14 (23.7%)	19 (32.2%)	33 (55.9%)	
Handedness				0.34
Right	20 (33.9%)	30 (50.8%)	50 (84.7%)	
Left	5 (8.5%)	3 (5.1%)	8 (13.6%)	
Mixed	0 (0%)	1 (1.7%)	1 (1.7%)	
Educational level				0.09
Primary education	1 (1.7%)	3 (5.1%)	4 (6.8%)	
Secondary education	6 (10.2%)	18 (30.5%)	24 (40.7%)	
Lower-university education	10 (16.9%)	7 (11.9%)	17 (28.8%)	
University education	8 (13.6%)	6 (10.2%)	14 (23.8%)	

Table 1. Continued.

	With insertion (n = 25)	Without insertion (n = 34)	Total (n = 59)	*p*
Marital status				0.21
Single	15 (25.4%)	13 (22.0%)	28 (47.5%)	
Married	9 (15.3%)	17 (28.8%)	26 (44.1%)	
Divorced/separated	1 (1.7%)	4 (6.8%)	5 (8.5%)	
Household members				0.15
Parents	11 (18.6%)	7 (11.9%)	18 (30.5%)	
Partner	12 (20.3%)	24 (40.7%)	36 (61.0%)	
Living alone	2 (3.4%)	3 (5.1%)	5 (8.5%)	
Side of the seizure focus				0.65
Left	14 (23.7%)	17 (28.8%)	31 (52.5%)	
Right	11 (18.6%)	17 (28.8%)	28 (47.5%)	
Age at epilepsy onset (years)	15.72 ± 11.01	15.73 ± 12.34	15.72 ± 11.70	0.99
Etiology of pathology				0.81
HS[a]	7 (11.9%)	14 (23.7%)	21 (35.6%)	
FCD[b]	3 (5.1%)	2 (3.4%)	5 (8.5%)	
Meningeom	0 (0.0%)	1 (1.7%)	1 (1.7%)	
Gliosis	1 (1.7%)	1 (1.7%)	2 (3.4%)	
Tumor	5 (8.5%)	4 (6.8%)	9 (15.3%)	
Heteroterapia	1 (1.7%)	2 (3.4%)	3 (5.1%)	
Carvernoma	1 (1.7%)	3 (5.1%)	4 (6.8%)	
Encephalomacy	1 (1.7%)	0 (0%)	1 (1.7%)	
Hippocampal atrophy	0 (0%)	1 (1.7%)	1 (1.7%)	
Nonassessable	1 (1.7%)	2 (3.4%)	3 (5.1%)	
Nonespecific	5 (8.5%)	4 (6.8%)	9 (15.3%)	
Number of ASMs	2.64 ± 0.76	2.76 ± 0.99	2.71 ± 0.89	0.60
Seizures per month	18.68 ± 34.88	14.06 ± 28	16.02 ± 30.90	0.58
Seizure type				0.29
FAS[c]	1 (1.8%)	2 (3.5%)	3 (5.1%)	
FIAS[d]	14 (24.6%)	12 (21.1%)	26 (45.6%)	
FBTCS[e]	0 (0%)	1 (1.8%)	1 (1.8%)	
FAS[c]+FIAS[d]	5 (8.8%)	5 (8.8%)	10 (17.5%)	
FIAS[d]+FBTCS[e]	4 (7.0%)	9 (15.8%)	13 (22.8%)	
FAS[c]+FIAS[d]+FBTCS[e]	0 (0%)	4 (7.0%)	4 (7.0%)	

Note. [a] HS: hippocampal sclerosis; [b] FCD: focal cortical dysplasia; [c] FAS: focal aware seizure; [d] FIAS: focal impaired awareness seizure; [e] FBTCS = focal to bilateral tonic-clonic seizures.

Academically/occupationally active patients were younger than those inactive ($p < 0.001$). No other differences were found in participants' characteristics, even considering only patients with university studies.

4.2. Differences in QOL, anxiety, depression, social support, and executive functions depending on academic/employment insertion (Table 2)

Significant differences were found on QOL composite score ($F_{(1,58)}$ = 5.84, p = 0.019, n^2_p = 0.09), social functioning ($F_{(1,58)}$ = 7.58, p = 0.008, n^2_p = 0.12) and cognitive self-rating ($F_{(1,58)}$ = 6.90, p = 0.011, n^2_p = 0.11) depending on academic/employment insertion, patients with insertion having higher scores than those without insertion (for all, p < 0.02; Figure 1). No significant differences were found in other QOL subscales (Figure 1).

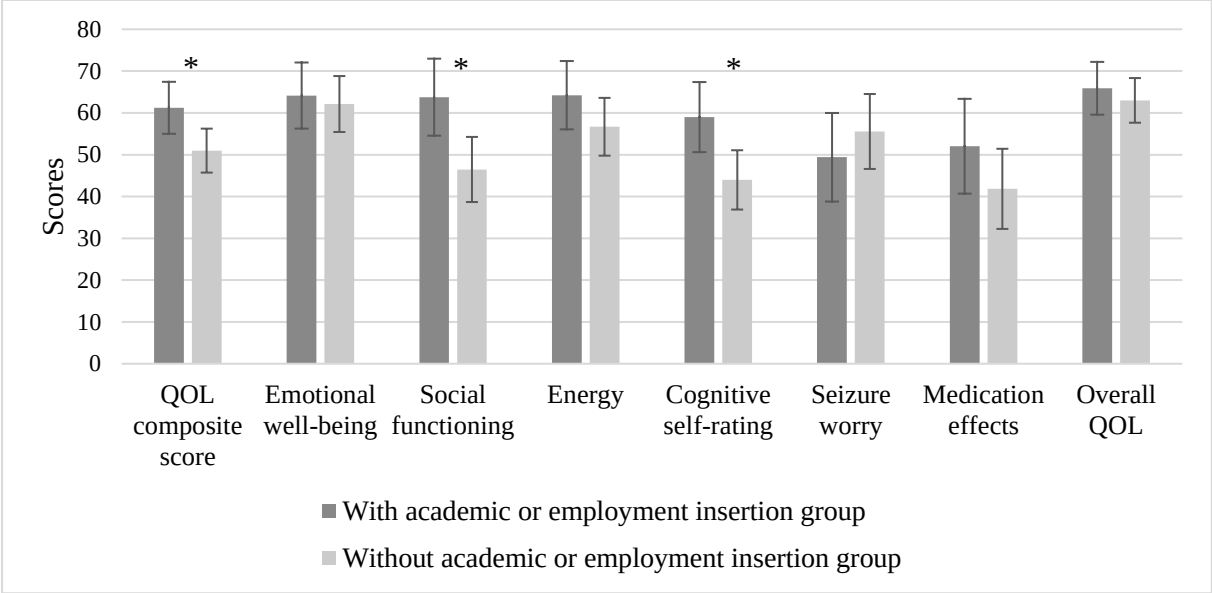

Figure 1. Differences in QOL depending on academic/employment insertion.
Note. *: p < 0.05; Error bars represent 95% confidence intervals.

Patients with academic/employment insertion had significantly lower anxiety than those without insertion ($F_{(1,58)}$ = 4.03, p = 0.04, n^2_p = 0.07), with no differences in depression.

Significant differences were found depending on academic/employment insertion in global social support ($F_{(1,58)}$ = 4.03, p = 0.049, n^2_p = 0.07), emotional support and positive social interaction ($F_{(1,58)}$ = 6.47, p = 0.014, n^2_p = 0.10; $F_{(1,58)}$ = 5.00, p = 0.029, n^2_p = 0.08), patients with insertion having higher scores (for all, p < 0.049).

No significant differences in WCST scores were found, although patients with academic/employment insertion tended to have lower percentage of errors ($F_{(1,58)}$ = 3.33, p = 0.07, n^2_p = 0.06) and higher percent conceptual level responses ($F_{(1,58)}$ = 3.33, p = 0.07, n^2_p = 0.06).

When we examined differences depending on employment insertion separately, differences in these QOL, anxiety, social support variables remained significant between patients who were working concerning those not working. Additionally, patients who were working had a significantly lower percentage of errors ($F_{(1,58)} = 4.47$, $p = 0.039$, $n^2_p = 0.07$) and higher percent conceptual level responses ($F_{(1,58)} = 4.10$, $p = 0.048$, $n^2_p = 0.07$). Given the limited patients that were studying (n = 8), we cannot analyze the effect of academic insertion separately.

Table 2. QOL, anxiety, depression, social support, and executive function scores (mean ± SD) depending on academic/employment insertion

	Total (n=59)	With insertion (n=25)	Without insertion (n=34)	*p*
QOL				
Emotional well-being	62.98 ± 18.39	63.96 ± 19.78	62.26 ± 17.58	0.71
Social functioning	53.80 ± 23.30	64.36 ± 23.39	46.03 ± 20.25	0.01
Energy	59.88 ± 19.43	64.60 ± 18.02	56.41 ± 19.96	0.18
Cognitive self-rating	50.34 ± 21.10	59.60 ± 18.03	43.53 ± 20.82	0.01
Seizure worry	52.94 ± 24.87	49.00 ± 25.16	55.84 ± 24.62	0.40
Medication effects	46.15 ± 26.80	51.88 ± 28.20	41.94 ± 25.32	0.19
Overall QOL	64.22 ± 14.89	66.60 ± 12.78	62.47 ± 16.23	0.51
QOL composite score	55.32 ± 15.52	61.76 ± 12.04	50.58 ± 16.24	0.02
STAI-T	26.49 ± 13.91	21.8 ± 9.51	29.94 ± 15.65	0.05
BDI	11.92 ± 8.88	9.64 ± 8.14	13.59 ± 9.14	0.28
MOS				
Global social support	75.90 ± 19.27	82.16 ± 14.03	71.29 ± 21.40	0 .05
Emotional social support	31.73 ± 9.09	35.28 ± 4.92	29.12 ± 10.54	0.01
Instrumental social support	16.81 ± 4.03	18.28 ± 2.48	15.74 ± 4.61	0.06
Positive social interactions	15.86 ± 4.27	17.36 ± 2.91	14.76 ± 4.79	0.03
Affective support	12.76 ± 2.79	13.24 ± 1.94	12.39 ± 1.94	0.22
WCST				
Number of trials	102.47± 24.65	98.48 ± 26.23	105.41 ± 23.39	0.31
% Errors	29.68 ± 16.45	24.44 ± 12.21	33.53 ± 18.20	0.07
% Perseverative responses	21.25 ± 19.53	16.08 ± 14.16	25.06 ± 22.12	0.24
% Perseverative errors	18.25 ± 15.03	14.48 ± 11.14	21.03 ± 16.97	0.24
% Nonperseverative errors	10.71 ± 7.46	9.52 ± 5.49	11.58 ± 8.6	0.19
Trials to complete first category	18.34 ± 26.03	12.40 ± 4.35	22.71 ± 33.62	0.43
Failures to maintain set	0.59 ± 2.05	0.96 ± 1.34	0.32 ± 2.43	0.33
Correct responses	70.54 ± 13.84	73.56 ± 12.06	68.32 ± 14.80	0.22
% conceptual level responses	60.59 ± 22.50	67.96 ± 14.81	55.16 ± 25.67	0.07
Categories completed	5.05 ± 1.98	5.48 ± 1.16	4.74 ± 2.38	0.26
Learn to learn	-3.74 ± 8.30	-2.49 ± 8.00	-4.78 ± 8.53	0.24

Note. BDI-II: Depression Beck Inventory-II; MOS: Medical Outcomes Study Social Support Survey; STAI-T: trait anxiety scale of the State-Trait Anxiety Inventory; WCST: Wisconsin Card Sorting Test.

4.3. Relationships among variables

QOL composite score was negatively related to anxiety ($p < 0.0001$), and positively to global social support, emotional support, positive social interaction, and percent of conceptual level responses (for all, $p < 0.03$). Cognitive self-rating was negatively related to anxiety and positively related to positive social interaction (for all, $p < 0.04$). Social functioning was negatively associated with anxiety ($p = 0.04$). Additionally, anxiety was negatively related to global social support, emotional support, and positive social interaction subscales, and percent of conceptual level responses (for all, $p < 0.005$). No other significant associations were found.

Mediation analyses adjusted for age showed significant indirect effects of academic/employment insertion on QOL composite score via global social support and anxiety (*path* $a_1d_{21}b_2$: $B = -3.25$, SE = 1.94, 95% CI = -7.85, -0.28; $P_{M\,ind} = 1.34$) (Figure 2). Specifically, academic/employment insertion was related to global social support (*path* a_1: $B = -10.90$, $SE = 5.43$, $t = -2.01$, $p = 0.049$), global social support was associated with anxiety (*path* d_{21}: $B = -0.35$, $SE = 0.08$, $t = -4.12$, $p < 0.0001$), and anxiety was related to QOL composite score (*path* b_2: $B = -0.85$, $SE = 0.11$, $t = -7.52$, $p < 0.00001$). A significant total effect of academic/employment insertion on QOL was found (*path* c_1: $B = -2.42$, $SE = 4.24$, $t = -2.42$, $p = 0.019$), but not a significant direct effect (*path c'*: $B = -4.46$, $SE = 3.04$, $t = -1.47$, $p = 0.15$). No significant mediational effects of percent of conceptual level responses were found.

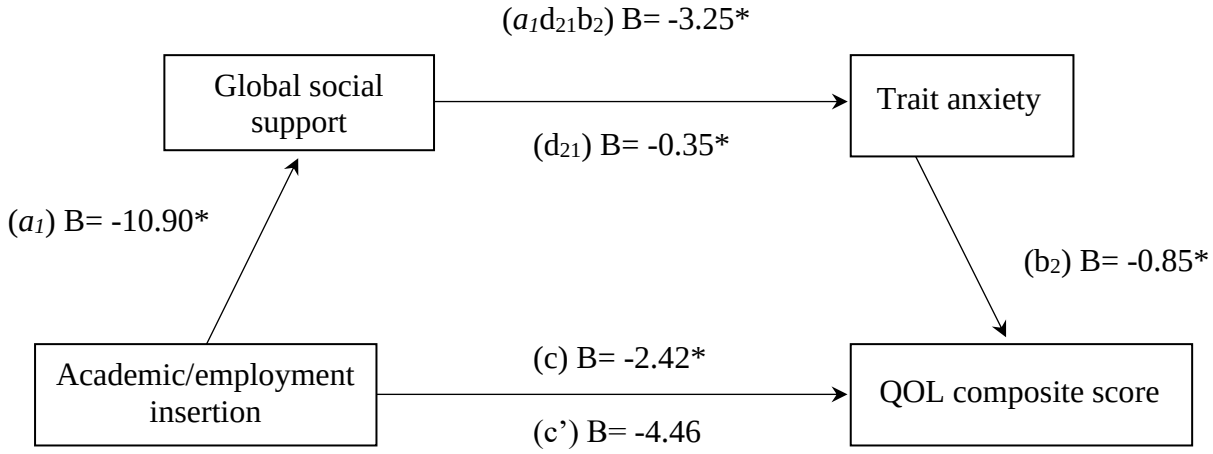

Figure 2. Model assessing the mediation effect of global social support and trait anxiety in the association between academic/employment insertion and QOL composite score adjusted for age. The variance of QOL composite score explained by this model is 13%; $R^2 = 0.13$, $p = 0.01$. * $p < 0.05$.

5. Discussion

Our findings indicate that patients with TLE with academic/employment insertion have significantly better QOL, lower anxiety, and higher social support than those without insertion, this insertion being indirectly associated with QOL through its relationship with social support and anxiety.

Patients with insertion were younger than the other group, but did not differ in other characteristics (e.g., seizure frequency). Even considering only patients with university studies, no significant differences were found in the frequency of seizures depending on insertion. Patients with drug-resistant epilepsy have difficulties dealing with the academic and employment worlds (Majkowska-Zwolińska et al., 2012), and our results indicate that age is an important factor to understand interindividual differences in insertion.

Although differences in seizure type did not reach statistical significance, 14 patients without insertion had secondary generalized seizures, compared to four patients with insertion, whereas the frequency of other seizure types was similar in both groups. Secondary generalized seizures may imply more severe injuries (Asadi-Pooya et al., 2020) and social stigma (Lee et al., 2005; Smeets et al., 2007). Patients with epilepsy perceive that unemployment is more linked to social factors, such as fear of having seizures at work or stigma (Asadi-Pooya et al., 2020), so participants with secondary generalized seizures may be more likely to be unemployed via social stigmatization (Engelberts et al., 2002).

To minimize the impact of age on insertion, we considered the academic and employment insertion together. Patients with academic or employment insertion had better QOL than those without it, even when employment insertion was considered separately (Azuma & Akechi, 2014).

The subscales of QOL showed different sensitivities to insertion. Patients with insertion had higher social functioning and cognitive self-rating than those without insertion but did not differ in the rest of QOL subscales. This highlights the complexity of the construct (Cano-López et al., 2018), being a key aspect in the neuropsychological intervention (Smeets et al., 2007), that could be conditionate for emotional, social, and cognitive areas (Rossiñol et al., 2013; Salado-Medina et al., 2018; Sherbourne & Stewart, 1991), so differences in these areas depending on insertion were evaluated.

Patients with academic/employment insertion had lower anxiety than those inactive, without differences in depression, and these results were maintained when employment insertion was considered separately. As far as we know, no other studies have examined anxiety and depression depending on academic insertion in patients with epilepsy. Regarding employment insertion, our results are partially in line with those of Mensah et al. (2007) and Peterson et al. (2014), which found that it was related to reduced anxiety and depression in a mixed sample of patients with epilepsy. We considered trait anxiety instead of clinical anxiety and our sample had subclinical levels of depression (Rohling et al., 2002), so the use of a clinical depression instrument in this sample may have made it difficult to find differences.

Patients with academic/employment insertion also reported higher social support than those without it, and these results remained significant when employment insertion was considered separately. Social networks, which increase in the work environment, are relevant sources of social support, may imply social acceptance (Baker, 2005), and favour coping with epilepsy (McCagh et al., 2009). The role of social support in epilepsy may be more significant than in other chronic diseases (Demirci et al., 2017).

Patients with academic/employment insertion tended to have better executive functioning than those inactive, although these results only reached statistical significance when employment insertion was considered separately. Executive functioning measured with WCST was related to work behavior in other chronically stressed populations (McGurk & Meltzer, 2000). Fraser et al. (1986) found that a cognitive task that requires cognitive flexibility discriminated between patients with different epilepsy types who entered or not into the job market. It is unclear whether employment insertion favors executive function performance, or whether participants with better executive functioning have better employment insertion, so longitudinal studies are needed to clarify cause-effect relationships.

Executive functioning was related to better QOL, but no significant mediational effects were found in the relationship between academic/employment insertion and QOL. However, academic/employment insertion was related to higher social support, which was associated with lower anxiety, and this was related to better QOL. This suggests that networks created through insertion could increase perceived social support, which in turn would reduce anxiety, which would be related to a better QOL. High perceived social support has been related to lower anxiety in mixed patients of epilepsy (de Souza & Salgado, 2006), and lower anxiety has been associated with better QOL (Cano-López et al., 2018). Our results propose a new model that

allows an integral understanding of the patients' QOL in TLE, considering both direct and indirect effects of socio-emotional variables.

Some limitations should be considered. Due to the cross-sectional nature of the data, we cannot conclude causality in the relationships. Additionally, larger sample sizes could provide more information, ensuring statistical power. Moreover, executive function is a complex cognitive domain, so the inference of executive function only from WCST scores should be considered with caution (Miranda et al., 2020). Future studies should expand the neuropsychology assessment battery. Finally, although our anxiety and depression scores could be useful for detecting susceptibilities to clinical disorders (Cano-López et al., 2019), they are not clinical/diagnostic measures (Kendall et al., 1987).

6. Conclusion

This study emphasizes the relevance of academic and employment insertion on QOL, trait anxiety, and social support in TLE patients, and provides a model that points out the key role of increased social support and reduced anxiety associated with insertion to improve QOL. Social support may buffer the negative impact of stressful events and chronic health conditions (Thoits, 1986), while high anxiety could contribute to individual differences in stress vulnerability (Weger & Sandi, 2018). Our findings could contribute to optimal care in TLE patients, favoring the implementation of programs that promote academic/employment reinsertion, considering socio-emotional and cognitive domains.

CHAPTER 5

Study 2

Prospective study of cenobamate on cognition, affectivity and quality of life in focal epilepsy[1]

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1. Introduction

Cenobamate (CNB), a tetrazole alkyl carbamate derivative, is a new antiseizure medication (ASM) with dual antiseizure activity: blocking the persistent component of sodium currents, enhancing and prolonging the inactivation of the transient component of sodium currents, and potentiating GABA A receptors to decrease neuronal excitability (Nakamura et al., 2019; Sharma et al., 2020).

In the USA, CNB is indicated for the treatment of focal seizures in adult patients (Food and Drug Administration, 2019). In Europe, CNB has been approved for the adjunctive treatment of focal-onset seizures, with or without secondary generalization, in adult patients with epilepsy who have not achieved adequate seizure control despite treatment with at least two ASMs (European Medicines Agency, 2021). The efficacy of CNB in seizure control has been established in two randomized, double-blind controlled trials (Chung et al., 2020; Krauss et al., 2020). Long-term effectiveness and tolerability have been confirmed in open-label studies (French et al., 2021; Klein et al., 2022; Sperling et al., 2020). Finally, real-world data information regarding the use of this medication has been reported in a few observational studies (Peña-Ceballos et al., 2023; Villanueva et al., 2023).

In previously mentioned studies, dose-related adverse events have been found. Chung et al., (2020) showed that 76.1% of patients who were treated with 200 mg/day of CNB reported adverse events during the 12-week treatment period. In the same line, Krauss et al., (2020) found that, after 18 weeks of treatment, the percentage of patients reporting adverse effects increased with dose, with 65% of patients taking 100 mg/day, 76% of those taking 200 mg/day and 90% of those taking 400 mg/day. These adverse events were mild to moderate in severity and related to the central nervous system (Lattanzi et al., 2020).

To our knowledge, no studies have comprehensively addressed the effects of CNB on cognitive functioning in people with epilepsy. In animal models, a single administration of 10 and 30 mg/kg intraperitoneally CNB (corresponding to 0.81 and 2.44 mg/day in humans) has been found to have anxiolytic effects in the elevated zero maze and impaired recognition and object location memory (Song et al., 2022). In the same study, mice that received chronic treatment of 5 mg/kg (equivalent to 0.41 mg/kg in humans) after a period of adaption of 10 days showed impaired recognition and spatial learning performance (Song et al., 2022).

Despite these interesting results, only one human study has examined this topic with a cognitive screening tool. The results showed that 72% of patients who took CNB doses that ranged from 50 to 250 mg/day for approximately three months (with a mean of 125 mg/day) had stable scores in the Epitrack screening tool, while 16% of the patients even improved (Schuetz et al., 2022). However, although this test is a sensitive tool for exploring the cognitive effects of ASMs, it is an instrument focused exclusively on attention and executive functions (Lutz & Helmstaedter, 2005). Therefore, other cognitive domains remained unexplored, such as memory or language, equally affected in patients with temporal lobe epilepsy (Thompson & Duncan, 2005).

Finally, as far as we know, there are also no studies that have addressed the effects of CNB on comorbidities often associated with epilepsy, such as negative affectivity (i.e., anxiety and depression) or poor quality of life (QOL), despite their increased recognition by the International League Against Epilepsy (ILAE) in recent years (Scheffer et al., 2017). For these reasons, the present study aims to determine the possible effects of adjunctive CNB treatment with doses ranging from 50 to 250 mg/day on cognition performance, negative affectivity, and QOL in people with drug-resistant epilepsy after three and six months of administration.

2. Methods

2.1. Participants and experimental design

This is a longitudinal and prospective cohort study in which participants were recruited from the Refractory Epilepsy Unit of the Hospital Universitario y Politécnico La Fe between December 2021 and June 2023. This reporting followed STROBE guidelines (von Elm et al., 2007) and the study was conducted following the Declaration of Helsinki and approved by the Ethics Committee of the hospital. All participants provided informed consent.

The inclusion criteria were: a) patients with a diagnosis of drug-resistant epilepsy; b) age of at least 18 years; and c) patients with focal aware seizures, focal impaired awareness seizures, and/or focal to bilateral tonic–clonic seizures. Excluded were patients who: a) were older than 70 years; b) with a recognized and diagnosed severe intellectual disability, in whom the assessment could not be performed with a minimum of reliability; and c) were not fluent in Spanish. Participants who were enrolled before the 15th of September 2022 were part of the Expanded Access Program (EAP), before reimbursement authorization.

Demographic and clinical data were extracted from clinical charts. Epilepsy types were independently classified following the classification of epilepsy from the ILAE by two experienced epileptologists (MG and KH) and based on available seizure semiology, EEG data, neuropsychological test results, as well as functional and structural imaging data (Scheffer et al., 2017). Any disagreements were resolved through consensus after a thorough review.

In the initial sample, thirty-five patients underwent a neuropsychological assessment before starting CNB treatment (baseline, T0). However, three patients discontinued the treatment before the follow-up assessment: two men due to the onset of a rash, and one woman due to dizziness. As a result, the final sample consisted of thirty-two patients who also performed a follow-up assessment after the introduction of adjunctive treatment with CNB (short-term evaluation, T1). This assessment was performed after a tiritation period, with doses ranging from 50 to 200 mg, usually three months after T0 (mean = 96.47 days, SD = 22.12). Moreover, to study possible effects with higher doses and after reaching a stable dose, twenty-two patients of those who undertook the T1 assessment also underwent a long-term assessment (T2), which was usually after six months of T0 (mean = 193.05 days, SD = 33.17). CNB dose ranged from 150 to 250 mg. The same neuropsychological battery was applied to every assessment. To organize the results and provide an overview of the effects of CNB after a period of gradual increase and after reach a stable dose, comparisons between T0 and T1 will be presented in Study 1, and comparisons between T0 and T2 in Study 2.

2.2. Pharmacological treatment

CNB titration was performed according to the SmPC. In all patients, CNB was started at 12.5 mg/day and increased every 2 weeks to 25, 50, 100, 150, and 200 mg/day. The initial target dose was 200 mg/day, but lower and higher maintenance dosages were allowed. To determine the drug load of other ASMs (i.e., without considering CNB dose), the defined daily dose (DDD) was used following the ATC index of the WHO Collaborating Centre for Drug Statistics Methodology (WHO, 2023).

2.3. Seizure frequency

Seizure frequency was assessed during a structured interview in which information provided by both the patient and the relative was collated. Furthermore, patients were advised to keep a seizure diary, which was used in T1 and T2 assessments, to obtain greater accuracy of the data collected.

2.4. Neuropsychological assessment

A comprehensive assessment was designed following the recommendations of the E-PILEPSY consortium (Vogt et al., 2017) that provided data from different domains. It lasted approximately two hours and tests were always administered in the same order. All participants completed the full assessment.

2.4.1. Attention and executive functions

The EpiTrack (Lutz & Helmstaedter, 2005) is a screening tool particularly sensitive to the adverse cognitive effects of ASMs (Lutz & Helmstaedter, 2005). It assesses response inhibition, attention, cognitive tracking, processing speed, verbal fluency, and working memory through six subtests: an interference test, Trail-Making Test A and B, a maze test, word fluency, and digit span backward. Based on the results of the subtest, a total age-adjusted Epitrack score was calculated, ranging from 9 to 49 points, with higher scores indicating better performance.

2.4.2. Naming functions

The Boston Naming Test (BNT; Kaplan et al., 2001) in its 60-item version was used to assess visual confrontation naming. Semantic and phonemic cues were provided to patients in the case of no response or incorrect response. The total score was computed as the number of cards correctly named without phonemic cues, 60 being the maximum score.

2.4.3. Memory

The Spanish version (Pereña et al., 2004) of the Wechsler Memory Scale-Third Edition (WMS-III; Wechsler, 1997) was used to evaluate both immediate and delayed memory (scalar scores ranging from 4 to 76 and from 5 to 95, respectively). To obtain an immediate memory score, the following tests were used: Faces I, Family Scenes I, Logical Memory I and the Verbal Paired Associates I. Regarding the delayed memory index, Faces II and Family Scenes II were used, together with Logical Memory II, Verbal Paired Associates II, and their recognition. These tests provide specific indices of immediate auditory and verbal memory and delayed auditory and verbal memory (for all, scalar scores from 2 to 38); and auditory-related indices as delayed auditory recognition (scalar scores from 1 to19). For all, higher scores indicate better performance.

2.4.4. Trait anxiety

It was assessed using the State-Trait Anxiety Inventory (STAI; Spielberg, 1989). The trait anxiety scale (STAI-T) evaluates relatively stable aspects of anxiety and is composed of 20

items rated on a four-point scale ranging from 0 ("hardly never") to 3 ("almost always"), being 60 the maximum score. Higher scores indicate higher anxiety.

2.4.5. Depression

The Beck Depression Inventory-II (BDI-II; Beck et al., 1996) was used to assess depression with 21 items rated on a four-point scale, with scores ranging from 0 to 63. Higher scores indicate higher depression levels.

2.4.6. QOL

Quality of Life in Epilepsy Inventory (QOLIE-31; Cramer et al., 1998), in its Spanish version (Torres et al., 1999), was used to assess QOL and includes 31 items distributed in seven scales: seizure worry; overall QOL; emotional well-being; energy; cognitive self-rating; medication effects; and social functioning, ranged from 0 to 100. A QOL composite score was computed using a weighted average of subscales (including seizure worry and medication effects, which were scored on an inverse scale), with higher scores indicating better QOL.

2.5. Statistical analyses

Descriptive statistics were computed for demographic and clinical variables. We explored differences depending on the time of the evaluation (i.e., T0, T1, or T2) on clinical variables such as the number of ASMs or DDD using repeated measures ANOVAs. To explore the differences in seizure frequency the Wilcoxon signed rank test for repeated measures was used since this variable was not normally distributed. Furthermore, repeated measures ANOVAs were also performed to check changes in cognitive performance, negative affectivity and QOL. In these analyses, the time of the evaluation was taken as a within-subject factor, using the DDD at T1 as a covariate in Study 1 and the DDD at T2 in Study 2. In both studies, age was included as a covariate, given the use of direct scores in the neuropsychological evaluation, and also the DDD of antidepressants, since their concomitant use can interact with CNB.

To study the relationships between seizure control, negative affectivity, and QOL, Pearson correlations were performed. The percentage of seizure reduction in T1 and the change between T0 and T1 in the BDI-II, the STAI-T, and the QOLIE's total score was used for Study 1, replicating the same analysis with the results of T2 in Study 2.

Moreover, meaningful cognitive changes were assessed using the Reliable Change Index (RCI; Jacobson & Truax, 1991). The RCI identifies reliable changes in cognitive performance

that cannot be explained by typical test-retest variations, such as practice effects or regression to mean (Davies et al., 2005). Due to the lack of a control group, the RCIs were derived from the SD and reliability data for each test (Cano-López et al., 2017; Lozano-García et al., 2021), except for the Epitrack. This test provides RCIs, considering a significant improvement with gains of ≥ 4 points and a significant deterioration in cases of loss of ≥ 3 points (Lutz & Helmstaedter, 2005). Data used to calculate RCIs and the reliable change criterion to exceed the 95th centile of the RCIs is provided in Table 1.

Table 1. Test-retest reliability, SD, and RCI criterion of each test.

	Test-retest reliability	SD	RCI[a] criterion
BNT[b] (Kaplan et al., 2001; Sachs et al., 2012)	0.86	3.47	± 3.60
TMT[c] A	0.90	10.40	± 9.12
TMT[c] B	0.90	28.20	± 24.72
WMS-III[d] (Wechsler, 1997)			
Immediate Memory	0.85	14.50	± 15.57
Delayed Memory	0.87	14.60	± 14.59
Delayed Auditory Recognition	0.62	14.40	± 24.61
Letter-Number Sequencing	0.71	2.60	± 3.88
BDI-II[e] (Spielberg et al., 1982)	0.87	7.76	± 7.76
STAI-T[f] (Beck et al., 2009)	0.89	10.39	± 9.55
QOLIE-31[g] (Cramer et al., 1998)	0.89	16.00	± 14.71

Note. [a]RCI = Reliable Change Index; [b]BNT = Boston Naming Test; [c]TMT = Trail Making Test; [d]WMS-III = Wechsler Memory Scale-III; ; [e]BDI-II = Beck Depression Inventory-II; [f]STAI-T = Trait Anxiety Scale; [g]QOLIE-31 = Quality Of Life Epilepsy Inventory.

Finally, to explore whether seizure freedom predicted cognitive, emotional and QOL changes, a binary logistic regression model was performed. In this model, seizure freedom (Yes/No) at T1 for Study 1 and T2 for Study 2 was considered as a predictor, and dichotomous variables based on the RCI as dependent variables (No change/Improvement VS Worsening).

Statistical analyses were carried out using SPSS 25.0 and two-tailed tests with *p* set to 0.05 considered significant.

3. Results

3.1. Clinical changes after CNB administration at 3 and 6 months

In Study 1, the sample consisted of 32 patients (22 men and 10 women; mean age = 39.63, SD = 14.55) who underwent a neuropsychological assessment at T0 and T1, after three months of CNB administration. CNB doses ranged from 50 to 200 mg/day. Most patients were taking 200 mg/day of CNB (59.4%), followed by 150 mg/day (18.8%) and 100 mg/day (18.8%), and 50 mg/day (3.1%). During these three months, patients were in the titration period.

After three months of CNB administration, a decrease in seizure frequency at T1 was found ($p < 0.001$), from a mean of 29.53 seizures per month at T0 (SD = 65.00) to a mean of 17.97 in T1 (SD = 53.63). More specifically, 71.9% of patients showed a reduction of at least 25% and, among them, 28.1% showed seizure freedom. The remaining 28.1% of patients either experienced a reduction of less than 25% or had no change or increase in their seizure frequency (9.4% for each of them). This improvement was reached even when the number and the DDD of other ASMs, apart from CNB administration, significantly decreased from T0 to T1 ($F_{(1,31)} = 5.74$, $p = 0.023$, $n^2_p = 0.16$, and $F_{(1, 31)} = 15.50$, $p < 0.001$, $n^2_p = 0.33$, respectively). Changes in clinical variables are shown in Table 4.

Among patients of Study 1, 22 of them (16 men and 6 women; mean age = 39.05, SD = 15.14) participated in Study 2 and underwent a follow-up evaluation (T2) six months after T0. CNB doses at T2 ranged from 150-250 mg/day. Most patients (68.2%) were taking 200 mg/day of CNB at T2, followed by 150 mg/day (18.2%) and 250 mg/day (13.6%). All of them were taking a stable dose.

After six months of CNB administration, a decrease in seizure frequency was found ($p = 0.001$), from a mean of 38.32 seizures per month (SD = 77.01) in T0 to 20.73 (SD = 47.49) in T2. Specifically, seizure frequency decreased by at least 25% in 72.7% of patients in Study 2, with 13.6% of these patients showing a 100% reduction. Furthermore, 9.1% of the patients showed no changes in seizure frequency, and 13.6% showed an increase. Patients in T2 also took a lower number of ASMs and DDD than in T0 ($F_{(1,21)} = 8.35$, $p = 0.009$, $n^2_p = 0.29$ and $F_{(1,21)} = 14.78$, $p = 0.001$, $n^2_p = 0.41$).

Sample characteristics of Studies 1 and 2 are shown in Table 2. Furthermore, concomitant ASMs at T0, T1, and T2 are listed in Table 3. Finally, the description of the CNB administration, the changes in DDD of other ASMs, and the evolution in seizure frequency in both studies are shown in Table 4.

Table 2. Characteristics of the sample at T0 in Study 1 and Study 2 (mean ± SD or n (%)).

	Study 1 (n = 32)	*Study 2 (n=22)*
Age (years)	39.63 ± 14.55	39.05 ± 15.14
Sex		
Male	22 (68.8%)	16 (72.7%)
Female	10 (31.3%)	6 (27.3%)
Educational level		
Primary	13 (40.6%)	8 (36.4%)
Secondary	9 (28.1%)	7 (31.8%)
Lower university	3 (9.4%)	3 (13.6%)
University	7 (21.9%)	4 (18.2%)
Academic/employment insertion		
Yes	21 (65.6%)	14 (63.6%)
No	11 (34.4%)	8 (36.4%)
Household members		
Parents	12 (37.5%)	8 (36.4%)
Partner and/or sons	16 (50%)	13 (59.09%)
Living alone	4 (12.5%)	1 (4.6%)
Epilepsy type		
FLE[a]	6 (18.8%)	5 (22.7%)
TLE[b]	20 (62.5%)	11 (50%)
PCE[c]	4 (12.5 %)	4 (18.2%)
Multifocal	2 (6.3%)	2 (9.1%)
Side of the seizure focus		
Left	13 (40.6%)	8 (36.4%)
Right	15 (46.9%)	10 (45.5%)
Bilateral	4 (12.5%)	4 (18.2%)
Age at epilepsy onset (years)	15.12 ± 11.5	13.64 ± 8.74
Epilepsy duration (years)	24.56 ± 16.01	25.41 ± 16.29
MRI[f] findings		
HS[g]	1 (3.1%)	0 (0%)
FCD[h]	8 (25%)	7 (31.8%)
Cavernoma	1 (3.1%)	0 (0%)
Normal	14 (43.8%)	10 (45.5%)
Encephalomalacia	3 (9.4%)	3 (13.6%)
Hypothalamic hamartoma	1 (3.1%)	1 (4.6%)
Non-specific pathology*	4 (12.5%)	1 (4.6%)
Previous brain surgery		
Yes	15 (46.9%)	10 (45.5%)
No	17 (53.1%)	12 (54.5%)
Seizure type		
FAS[i]	4 (12.5%)	2 (9.1%)
FIAS[j]	11 (34.4%)	6 (27.3%)
FBTCS[k]	1 (3.1%)	0 (0%)
FAS[i]+FIAS[j]	4 (12.5%)	3 (13.6%)
FAS[i]+ FBTCS[k]	2 (6.3%)	2 (9.1%)
FIAS[j]+FBTCS[k]	8 (25%)	7 (31.8%)
FAS[i]+FIAS[j]+FBTCS[k]	2 (6.3%)	2 (9.1%)

Note. [a] FLE = frontal lobe epilepsy; [b] TLE = temporal lobe epilepsy; [c] PCE = posterior cortex epilepsy; [d] OLE = occipital lobe epilepsy; [e] ILE = insular lobe epilepsy; [f] MRI = magnetic resonance imaging; [g] HS = hippocampal sclerosis; [h] FCD = focal cortical dysplasia; [i] FAS = focal aware seizure; [j] FIAS= focal impaired awareness seizure; [k] FBTCS = focal to bilateral tonic-clonic seizures; T0 = baseline assessment; * Non-specific pathology, such as white matter changes or atrophy, refers to findings on a cerebral MRI that are not specific to a particular neurological disorder.

Table 3. Concomitant drugs at T0, T1, and T2 in studies 1 and 2 (n (%)).

	Study 1 (n=32)		*Study 2 (n = 22)*	
	T0	T1	T0	T2
Carbamazepine	14 (43.8%)	11 (34.4%)	10 (45.5%)	8 (36.4%)
Valproic acid	5 (15.6%)	6 (18.8%)	5 (22.7%)	5 (22.7%)
Clobazam	7 (21.9%)	7 (21.9%)	5 (22.7%)	5 (22.7%)
Levetiracetam	7 (21.9%)	6 (18.8%)	5 (22.7%)	5 (22.7%)
Lacosamide	14 (43.8%)	12 (37.5%)	10 (45.5%)	9 (40.9%)
Eslicarbazepine	5 (15.6%)	4 (12.5%)	3 (13.6%)	3 (13.6%)
Zonisamide	4 (12.5%)	4 (12.5%)	2 (9.1%)	2 (9.1%)
Topiramate	1 (3.1%)	1 (3.1%)	1 (4.5%)	1 (4.5%)
Lamotrigine	10 (31.3%)	11 (34.4%)	8 (36.4%)	8 (36.4%)
Clonazepam	3 (9.4%)	4 (12.5%)	3 (13.6%)	1 (4.5%)
Perampanel	12 (37.5%)	12 (37.5%)	8 (36.4%)	4 (18.2%)
Brivaracetam	14 (43.8%)	13 (60.6%)	8 (36.4%)	7 (31.8%)
Oxcarbazepine	1 (3.1%)	1 (3.1%)	1 (4.5%)	1 (4.5%)
Diazepam	1 (3.1%)	0 (0%)	1 (4.5%)	0 (0%)
Pregabalin	2 (6.3%)	1 (3.1%)	2 (9.1%)	1 (4.5%)
Lorazepam	1 (3.1%)	1 (3.1%)	1 (4.5%)	1 (4.5%)
Cannabidiol	1 (3.1%)	1 (3.1%)	1 (4.5%)	1 (4.5%)
Vigabatrin	1 (3.1%)	1 (3.1%)	1 (4.5%)	1 (4.5%)
SSRI[1]	4 (12.5 %)	4 (12.5%)	3 (13.6%)	3 (13.6%)
SNRI[2]	1 (3.1%)	1 (3.1%)	1 (4.5%)	1 (4.5%)

Note. T0 = baseline assessment; T1 = short-term assessment; T2 = long-term assessment.
[1] SSRI = Selective Serotonin Reuptake Inhibitor; [2] SNRI = Selective Serotonin and Norepinephrine Reuptake Inhibitor.

Table 4. Evolution in clinical variables from T0 to T1 and from T0 to T2 (mean ± SD or n (%)).

	Study 1 (n = 32)			*Study 2 (n = 22)*		
	T0	T1	*p*	T0	T2	*p*
Number of ASMs[a]	3.25 ± 0.98	2.94 ± 1.05	0.023	3.41 ± 1.05	2.82 ± 1.06	0.009
Total DDD[b] of concomitant ASMs	3.84 ± 1.14	3.25 ± 1.24	0.0001	4 ± 1.18	3.14 ± 1.28	0.001
Total DDD including CNB[c]	---	4.00 ± 1.56	0.360	---	4.10 ± 1.26	0.634
CNB dose (mg/day)	---	172.73 ± 45.58		---	197.73 ± 28.77	
50	----	1 (3.1%)		---	0 (0%)	
100	----	6 (18.8%)		---	0 (0%)	
150	----	6 (18.8%)		---	4 (18.2%)	
200	----	19 (59.4%)		---	15 (68.2%)	
250	----	0 (0%)		---	3 (13.6%)	
Seizures per month	29.53 ± 65.00	17.97 ± 53.63	0.0001	38.32 ± 77.01	20.73 ± 47.49	0.001
Seizure reduction (%)	----	45.13 ± 66.53		---	28.70 ± 83.32	
Seizure changes						
< 25% decrease	----	3 (9.4%)			1 (4.5%)	
≥ 25% decrease	----	23 (71.9%)		---	16 (72.7%)	
≥ 50% decrease	----	19 (59.4%)		---	11 (50.0%)	
≥ 75% decrease	----	14 (43.8%)		---	6 (27.3%)	
100% decrease	----	9 (28.1%)		---	3 (13.6%)	
Increase	----	3 (9.4%)		---	3 (13.6%)	
No changes	----	3 (9.4%)		---	2 (9.1%)	

Note: p for Total DDD including CNB corresponds to the differences between the DDD at T0 (without CNB) and T1 (including CNB; Study 1) and between the DDD at T0 (without CNB) and T2 (including CNB; Study 2).

Abbreviations. [a]ASM = antiseizure medication; [b]DDD = defined daily dose; [c]CNB = cenobamate. T0 = baseline assessment; T1 = short-term assessment; T2 = long-term assessment.

3.2. Differences in cognition, negative affectivity and QOL changes at 3 and 6 months

In Study 1, no significant differences were found in cognitive, emotional or QOL variables. Considering reliable changes from T0 to T1 in terms of global cognitive performance (i.e., contemplating all cognitive variables), 74.3% of patients showed no reliable changes, 16.2% showed an improvement, and 9.5% had a decline.

By cognitive domains, 71.9% of patients showed no reliable changes in visual confrontation naming, while 25% showed an improvement and 3.1% a deterioration. Regarding attention and executive functions, 68.7% of patients showed no changes, followed by 18.8% who showed an improvement and 12.5% who had a deterioration. Concerning immediate memory, 96.9% of patients showed no reliable changes and 3.1% showed an improvement, while in delayed memory 90.6% showed no changes and 6.3% improved.

Concerning negative affectivity, 78.1% of patients had no reliable changes in depressive symptoms, although 6.3% of the patients showed an improvement and 15.6% worsened. Additionally, in trait anxiety, 81.2% of patients had no changes, 12.5% showed an improvement and 6.3% had a decline.

Regarding QOL, 75% of patients showed no changes, followed by 15.6% who experienced a decline, and 9.4% who improved.

Reliable changes from T0 to T1 are shown in Figure 1.

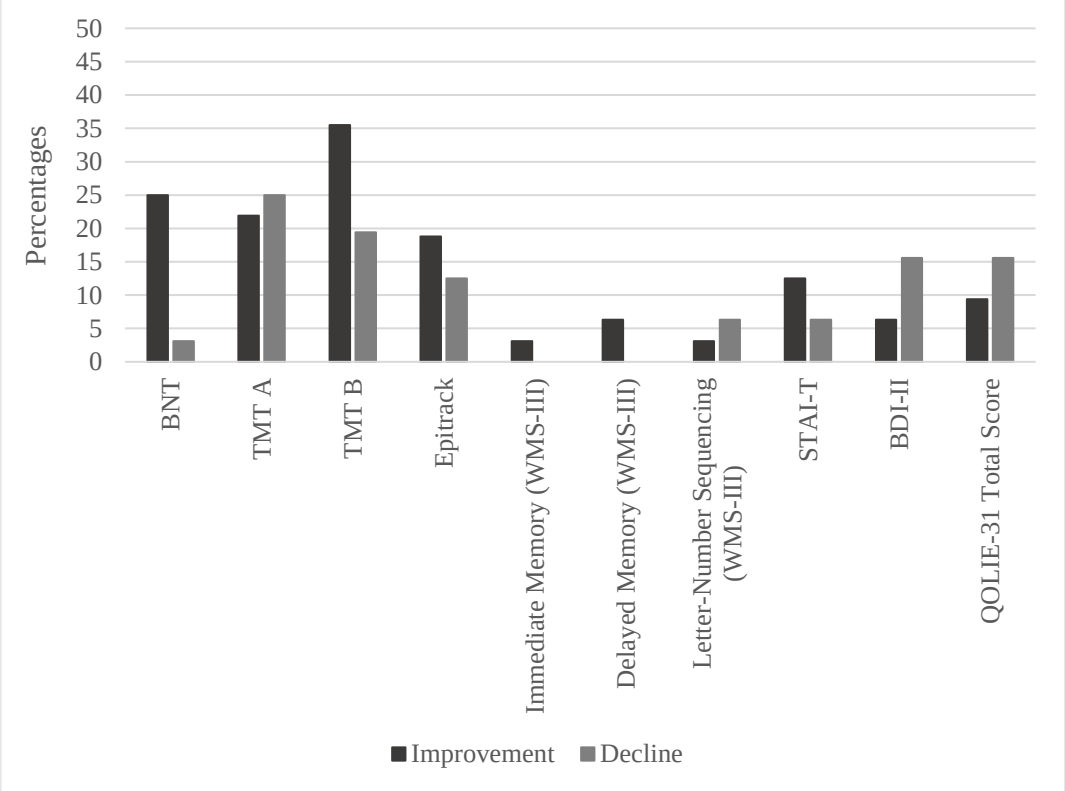

Figure 1. Percentage of patients who showed reliable changes from T0 to T1.

Abbreviations. BNT = Boston Naming Test; TMT = Trail Making Test; WMS-III = Wechsler Memory Scale-III; STAI-T = Trait Anxiety Scale; BDI-II = Beck Depression Inventory-II; QOLIE-31 = Quality Of Life Epilepsy Inventory; QOL = Quality of Life.

Finally, it is noteworthy that the percentage of seizure reduction was not related to the changes in the BDI-II, the STAI-T, or the QOLIE's total scores. Moreover, seizure freedom at T1 did not predict significant change in any cognitive, emotional, or QOL variables.

Regarding Study 2, no significant differences were found in cognition, negative affectivity or QOL. Considering all cognitive measures together, 66.6% of patients showed no reliable changes. However, 24.9% showed an improvement in cognitive performance from T0 to T2, and 8.5% showed a worsening.

Differentiating by domains, 54.6% of patients showed no reliable changes in visual confrontation naming, followed by 45.4% who showed an improvement. Regarding attention and executive functions, 54.5% showed no reliable changes between T0 and T2, 27.3% had an improvement, and 18.2% worsened. In immediate memory, 86.4% showed no changes, and 13.6% had an improvement. Finally, in delayed memory, 86.4% of patients showed no reliable changes and 13.6% of patients showed an improvement.

The mean and SD of the different cognitive variables of Studies 1 and 2 are shown in Table 5.

Table 5. Evolution in cognitive and emotional variables from T0 to T1 and from T0 to T2 (mean ± SD).

	Study 1 (n = 32)			*Study 2 (n = 22)*		
	T0	T1	*p*	T0	T2	*p*
BNT[a]	42.38 ± 12.90	43.97 ± 11.96	0.362	42.05 ± 14.48	44.77 ± 13.70	0.066
Epitrack	27.34 ± 7.81	27.94 ± 7.27	0.282	27.27 ± 8.90	28.59 ± 9.15	0.825
Interference	22.03 ± 11.35	22.25 ± 13.53	0.484	22.32 ± 12.64	23.32 ± 16.89	0.352
TMT[b] A	59.84 ± 74.35	62.00 ± 82.86	0.638	69.73 ± 88.24	75.55 ± 102.70	0.931
TMT[b] B	157.84 ± 95.23	160.87 ±124.62	0.982	147.25 ± 95.80	121.00 ± 90.79	0.525
Maze Test	45.41 ± 34.21	42.59 ± 25.32	0.162	49.09 ± 39.75	51.91 ± 50.62	0.545
Verbal fluency	18.38 ± 9.85	18.91 ± 8.95	0.744	19.18 ± 11.06	20.41 ± 10.56	0.270
Immediate memory	3.53 ± 0.95	3.72 ± 1.05	0.051	3.68 ± 0.95	3.73 ± 1.24	0.936
WMS-III[c]						
Immediate Auditory Memory	13.03 ± 6.64	15.28 ± 5.90	0.764	13.73 ± 6.73	16.73 ± 6.88	0.314
Immediate Visual Memory	14.38 ± 6.98	18.13 ± 10.92	0.697	14.05 ± 7.35	18.50 ± 8.37	0.623
Immediate Memory	27.09 ± 11.78	31.72 ± 12.48	0.540	27.32 ± 12.45	33.82 ± 14.50	0.071
Delayed Auditory Memory	13.81 ± 6.10	15.25 ± 5.66	0.320	14.59 ± 6.27	17.36 ± 5.92	0.233
Delayed Visual Memory	14.69 ± 6.74	16.78 ± 7.93	0.713	14.77 ± 7.03	18.05 ± 8.47	0.938
Delayed Memory	35.53 ± 14.46	39.66 ± 15.17	0.868	37.09 ± 15.48	44.14 ± 17.03	0.637
Delayed Auditory Recognition	7.34 ± 3.54	7.66 ± 3.35	0.177	7.23 ± 3.78	8.77 ± 3.84	0.939
Letter-Number Sequencing	6.69 ± 3.44	6.97 ± 2.91	0.641	6.41 ± 3.65	7.27 ± 3.63	0.438
BDI-II[d]	9.16 ± 8.49	11.94 ± 10.34	0.399	8.62 ± 7.77	9.86 ± 9.31	0.825
STAI-T[e]	25.38 ± 10.62	25.16 ± 13.73	0.948	26.41 ± 10.33	23.41 ± 9.94	0.952
QOLIE-31[f]	57.25 ± 17.45	55.86 ± 18.98	0.182	55.04 ± 16.34	58.56 ± 17.52	0.261
Seizure Worry	46.52 ± 29.88	55.97 ± 26.66	0.656	42.77 ± 31.29	51.32 ± 25.74	0.373
Overall QOL[g]	65.49 ± 21.84	65.31 ± 21.72	0.971	65.24 ± 23.25	66.25 ± 14.78	0.357
Emotional Well-being	65.00 ± 22.44	60.13 ± 23.60	0.432	68.91 ± 21.27	68.00 ± 17.24	0.593
Energy	61.56 ± 18.38	57.19 ± 22.96	0.506	63.86 ± 16.03	61.05 ± 23.70	0.385
Cognition Self-rating	56.46 ± 29.50	52.52 ± 28.83	0.136	52.47 ± 30.01	56.47 ± 30.55	0.120
Medication Effects	56.96 ± 26.22	58.59 ± 27.54	0.268	54.55 ± 25.73	57.44 ± 28.35	0.401
Social Functioning	51.69 ± 24.63	53.50 ± 24.84	0.350	45.55 ± 23.56	50.77 ± 21.22	0.758

Note. [a]BNT = Boston Naming Test; [b]TMT = Trail Making Test; [c]WMS-III = Wechsler Memory Scale-III; [d]BDI-II = Beck Depression Inventory-II; [e]STAI-T = Trait Anxiety Scale; [f]QOLIE-31 = Quality Of Life Epilepsy Inventory; [g]QOL = Quality of Life.
T0 = baseline assessment; T1 = short-term assessment; T2 = long-term assessment.

Regarding negative affectivity and QOL, 71.5% of patients showed no reliable changes in depressive symptoms, 9.5% had an improvement, and 19% worsened. In terms of trait anxiety, no reliable changes were found for 72.8% of patients, followed by 13.6% who showed an improvement, and 13.6% who showed a decline. Finally, for QOL, 63.7% of patients showed

no reliable changes, 22.7% showed an improvement in QOL scores and 13.6% experienced a deterioration.

Reliable changes between T0 and T2 are shown in Figure 2.

In Study 2, no relationships were found between the percentage of seizure reduction and the changes in the BDI-II, STAI-T, and QOLIE's total scores. Furthermore, seizure freedom at T2 also did not predict change in cognitive, emotional, or QOL variables.

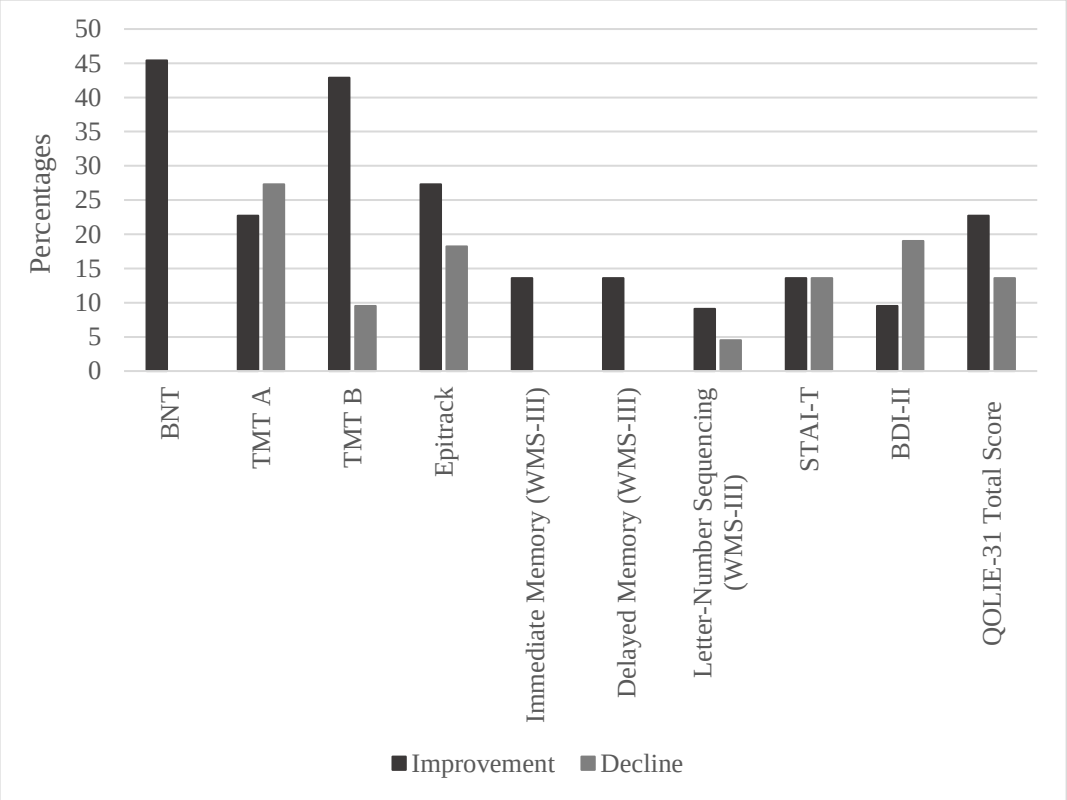

Figure 2. Percentage of patients who showed reliable changes from T0 to T2.

Abbreviations. BNT = Boston Naming Test; TMT = Trail Making Test; WMS-III = Wechsler Memory Scale-III; STAI-T = Trait Anxiety Scale; BDI-II = Beck Depression Inventory-II; QOLIE-31 = Quality Of Life Epilepsy Inventory; QOL = Quality of Life.

4. Discussion

As far as we know, this is the first study to examine the possible effects of CNB on different cognitive domains, as well as on negative affectivity (i.e., anxiety and depression) and QOL in the same sample of patients with epilepsy. Our results suggest that CNB is a safe pharmacological treatment in terms of cognitive performance, negative affectivity, and QOL since no related adverse effects were found after six months of adjunctive treatment.

Regarding cognition, no significant differences were found in attention, executive functions, or visual confrontation naming after CNB treatment, with all patients showing an improvement or no change in their memory scores. These results are of interest to this population, due to the high prevalence of patients with memory deficits (Witt & Helmstaedter, 2017) and considering that some ASMs can reduce memory performance (Motamedi & Meador, 2004). Furthermore, patients remained stable in most cases in both Studies 1 and 2, suggesting that CNB treatment seems not to produce time or dose-dependent effects on cognition variables.

Although there are no studies that comprehensively assess cognition in humans after CNB treatment, Schuetz et al., (2022) explored the effects of CNB on cognition using the Epitrack after three months, showing that most patients remained stable (72%), followed by 16% who improved and 12% who showed a deterioration. Similar results have been found in Study 1, since 68.8% of patients remained stable, 18.8% improved and 12.5% showed a deterioration. Examining whether other variables might be influencing changes in Epitrack, we found that 5 patients out of 8 taking concomitant lamotrigine after three months of CNB administration showed a significant improvement at T2, with only one patient showing a deterioration. Following this result, lamotrigine has been shown to have positive effects on cognition, especially on executive functions (Li et al., 2020). However, concomitant treatment with sodium channel blockers drugs in patients taking CNB is associated with a higher incidence of adverse effects (Chung et al., 2020), so studies with larger samples are needed.

In this regard, it is noteworthy that these changes could be influenced by concomitant ASMs. The DDD of other ASMs significantly decreased in both studies, and previous literature has shown that higher drug load is negatively related to cognitive performance (Helmstaedter et al., 2016; Lozano-García et al., 2021; Witt et al., 2015). Nevertheless, when the CNB load was also considered, the DDD increased from T0 to T1 and T2, but not significantly. Therefore, we suggest that, although decreasing the load of other drugs may have contributed to better

cognitive performance, the cognitive changes are more likely to be due to the introduction of CNB into pharmacological treatment and its clinical effects.

Regarding depressive symptoms, although most patients showed no changes, five patients showed a worsening after three months, and four at six months. Depression is one of the most common comorbidities in epilepsy (Kwon & Park, 2014), being an important variable to be considered in this population. In this line, it has been found that CNB could lead to suicidal behavior and ideation (Food and Drug Administration, 2019), so the monitoring of patients with concomitant antidepressant drugs and CNB treatment has been recommended (Latimer et al., 2021).

In the case of trait anxiety, the percentage of patients who worsened was doubled in Study 2 (13.6%) compared to Study 1 (6.3%). However, as Study 2 had a smaller sample, this difference was due to only one subject. Thus, 19 of the 22 participants in Study 2 showed no change in anxiety level or even an improvement. Congruently, Chung et al. (2020) found in a randomized, double-blind, placebo-controlled study that anxiety was an infrequent adverse event, which was reported only in 0.9% of patients who were taking CNB (Chung et al., 2020).

Concerning QOL, we found a higher percentage of patients who improved their QOL scores in T2 (22.7%) compared to T1 (9.4%). Studying the changes in the different subscales, we found that the most pronounced differences were found in the seizure worry subscale. This suggests that the increase in QOL could be related, at least in part, to the reduction of seizure frequency, since other studies have found that it is a strong predictor of QOL (Baranowski, 2018). Nevertheless, in our study, no significant relationships were found between the percentage of seizure reduction and QOL, which could be due to the limited sample.

In this line, it was found a significant reduction in the seizure number after three and six months of CNB administration. More specifically, the average percentage of seizure reduction in Study 1 was 45.1%, with 28.1% achieving seizure freedom. Analyzing these results over a longer period (i.e., six months), a lower mean seizure reduction rate of 28.7% was observed. However, the percentage of patients with a reduction of at least 50% was quite similar in both studies (59.4% in Study 1 and 50% in Study 2). These results are in line with those obtained in clinical trials, in which 40-69.9% of patients were found to show response rates of $\geq$ 50% at three months,6,9 but also with non-clinical trials, where 42% of patients showed a seizure reduction of at least 50% at three months.14 In the same context, Villanueva et al. (2023) found an average percentage of seizure reduction of 45.9% after three months of CNB treatment,

closely related to our results, with 58.8% of patients with a response rate ≥ 50%, increasing until 65% after six months of treatment.

Given the real-world nature of this study, the results obtained about the effects of CNB are particularly relevant to the clinical setting. However, this study is not exempt from limitations: firstly, the results, especially those of Study 1, should be considered with caution, as many patients were still in the titration period. Therefore, we consider that the results of Study 2 provide more robust data, as patients reached the target dose. Secondly, patients in Study 2 performed the Epitrack three times. However, due to the lack of data to categorize reliable changes based on the results of a third assessment, the proposed criteria for change in the second administration were used. Therefore, improvements in the Epitrack could be related to the fact of having performed this test three times. Thirdly, although intra-subjects differences have been assessed, taking their baseline performance as a reference, a control group would provide more information. Fourth, using three covariates with a limited sample, especially in Study 2, could bias the results. A larger and more homogeneous sample could help also to determine possible significant differences, although 32 patients with two assessments should be enough to detect changes clinically relevant. Finally, although this study comprises a follow-up of half a year, it would be useful to follow up throughout longer periods.

5. Conclusion

In conclusion, CNB adjunctive treatment seems to be an effective ASM without any long-term adverse events in cognition, negative affectivity, and QOL. Specifically, it has been found that the vast majority of patients remained stable in their cognitive performance, as well as in negative affectivity and QOL. Therefore, we conclude that CNB could be an ASM of choice in drug-resistant epilepsy patients, given the apparent safety of the drug and the absence of adverse effects found.

CHAPTER 6

Study 3

Stress phenotypes in epilepsy: impact on cognitive functioning and quality of life[1]

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[1] Published in: Catalán-Aguilar, J., González-Bono, E., Lozano-García, A., Tormos-Pons, P., Hampel, K. G., Villanueva, V., & Cano-López, I. (2023). Stress phenotypes in epilepsy: impact on cognitive functioning and quality of life. *Frontiers in Psychology*, *14*, 1100101.

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1. Introduction

Epilepsy is a disease that affects almost 1% of the general population and is characterized by the recurrence of seizures and its global impact on the individual (Fiest et al., 2017). Seizures have been considered an acute stressor, within the framework of epilepsy as a potentially chronic stress state (Cano-López & González-Bono, 2019). Stress has been defined as "a process in which an individual perceives that demands exceed the organism's regulatory capacity to adapt to a psychological or physiological challenge or stressor" (Cano-López & González-Bono, 2019). The impact of the stress process on the individual can be measured in terms of chronicity or intensity.

Regarding chronicity, seizures are stressful events that lead to the hypersecretion of cortisol in patients with epilepsy (Brandner et al., 2022; Cano-López & González-Bono, 2019). Therefore, prolonged exposure to seizures can lead to a situation of chronic stress. In this regard, the number of years suffering from the disease (i.e. epilepsy duration) is a measure that reflects the chronicity of the stressor (i.e. epilepsy) and it may have implications on different areas of the individual. Longer periods of epilepsy duration have been related to poorer verbal memory functioning in patients with temporal lobe epilepsy (TLE) (Kent et al., 2006), which is the main cognitive concern in this population (Helmstaedter & Kockelmann, 2006; Thompson et al., 2016). Similarly, several studies have found that longer epilepsy duration is related to poorer executive function (Black et al., 2010; Kim et al., 2006; Zamarian et al., 2011). Bonilha et al. (2006) suggested that longer epilepsy duration may imply greater gray matter loss, and this may lead to further cognitive impairment. Nevertheless, the relationship between epilepsy duration and health-related quality of life (QOL) has been found to be inconsistent (Taylor et al., 2011) although several studies have found that longer epilepsy duration is related to poorer QOL (Edefonti et al., 2011; Pauli et al., 2012; Piperidou et al., 2008).

Stress intensity is a more complex factor since it may include seizure frequency and the comorbidities of epilepsy – the presence of which is being increasingly recognized by the International League Against Epilepsy (ILAE) (Scheffer et al., 2017). The difficulty of reliable recording of the seizure frequency should be emphasized, since this information is usually collected by patients and relatives, but patients are not always aware of when they have seizures, or sometimes even forget to write them down (Blachut et al., 2017). For this reason, although this variable offers an approximate value, it cannot be considered a precise variable, especially when the number of seizures is very high. Negative affectivity is considered one of the most

frequent comorbidities in patients with epilepsy (Fiest et al., 2013; Kwon & Park, 2014; Pham et al., 2017) and provides a measure of the interpretation that the individual makes of the stressful event. It has been conceptualized as an exacerbated emotional response to unpredictable seizures (including depression and anxiety), as well as to activity restriction, which in turn leads to low self-esteem, stigma, and social rejection (Kotwas et al., 2017). It has been suggested that negative affectivity would be a more integrative concept than seizure frequency, overlapping with the seizure frequency in some aspects and providing further information even on stressful life events (i.e., factors related and not related to epilepsy) (Kotwas et al., 2017). Specifically, negative affectivity is directly related to clinical variables such as seizure frequency or adverse effects derived from anti-seizure medications (ASMs) (Dehn et al., 2017; Kanner, 2012; Thapar et al., 2009), as well as to other stress variables such as social stigma (Thapar et al., 2009), so it may have an even more important contribution to impaired QOL in this population (Kotwas et al., 2017). Thus, it has been found that stigma is strongly correlated to more depressive symptoms and poorer QOL in people with epilepsy (Tombini et al., 2019). Furthermore, negative affectivity is also linked to other psychosocial processes, being alexithymia (i.e., a subclinical phenomenon involving a lack of emotional awareness) an important concept due to its high prevalence epilepsy (Bewley et al., 2005; Myers et al., 2013; Tojek et al., 2000). Specifically, people with epilepsy with higher levels of anxiety or depression are more likely to experience alexithymia (Choi et al., 2021; Tombini et al., 2020). In this regard, Tombini et al. (2020) suggested that alexithymia could be considered a symptom of depression, or even alexithymia could be considered a risk factor for depression, given the scarcity of coping strategies for dealing with hard-to-identify emotions in these patients. Finally, negative affectivity has also been related to poor cognitive functioning and QOL in patients with epilepsy (Cano López, 2019; Cano-López et al., 2018; Kanner et al., 2010; Tracy et al., 2007) suggesting that this variable holistically affects individuals with epilepsy. Therefore, it is not surprising that patients with epilepsy show lower life satisfaction than people without epilepsy, which could be explained, at least in part, by negative affectivity (Kang, 2023).

Negative affectivity can be considered a factor involved in stress intensity and as a key variable related to coping with the disease. Risk or protection profiles for coping with the disease have been developed considering emotional and other epilepsy-related variables. An example of this is the model proposed by Ring et al. (2016) using qualitative research methods which differentiate vulnerable and resilient individuals and explain how different

socioemotional and clinical factors influence QOL in patients with epilepsy. Furthermore, Tedrus et al., (2020) suggest that resilience, which can be considered as the ability to cope with a stressful situation satisfactorily (Zapater-Fajarí et al., 2021), is a protective factor for mood disorders in patients with epilepsy. To date, however, this approach has considered the chronicity of the alterations as an extraneous variable to be controlled and not as a measure of the chronicity of the stressor.

Studies focused on the relationship between epilepsy duration and negative affectivity offer heterogeneous results. A recent meta-analysis carried out by Yang et al. (2020) showed that patients with a shorter epilepsy duration had a lower risk of depression. The meta-analysis by Scott et al. (2020) also found that shorter epilepsy duration was associated with a lower prevalence of depressive and anxiety disorders in young people with epilepsy. Brandt et al. (2015), however, found that younger patients with a shorter epilepsy duration were more likely to have anxiety disorders, underlying that an adaptation period is required to develop coping strategies for the stressful situation. These results suggest that there is an interrelationship between epilepsy duration and negative affectivity, and these variables may influence cognition and QOL. However, as far as we know, no studies have summarized stress chronicity and intensity variables in different profiles, nor explored their association with cognition and QOL in the same sample of patients with epilepsy. For this reason, the present study aims to detect phenotypes based on indicators of stress chronicity and intensity (i.e., epilepsy duration, trait anxiety, and depression) in patients with drug-resistant epilepsy, as well as examine differences in cognition and QOL depending on these phenotypes. Although the longer duration of epilepsy and greater negative affectivity may be separately related to poorer cognitive functioning and poorer QOL, we hypothesize that there may be a profile of patients who have adapted adequately to the disease, despite having suffered from it for a long time, presenting moderate levels of negative affectivity. We hypothesize that this profile will be more adaptive at a cognitive and QOL level than the profile of patients with greater negative affectivity.

2. Materials and methods

2.1. Patients

This is a cross-sectional study in which participants were recruited from the Refractory Epilepsy Unit of the Hospital Universitario y Politécnico La Fe between April 2015 and November 2022. The inclusion criteria were: a) patients with a diagnosis of drug-resistant epilepsy, thus ensuring that the disease was chronic; b) candidates for epilepsy surgery to ensure relative homogeneity of the sample (i.e., suspected focal onset seizures); c) a chronological age of at least 18, to ensure cognitive development; d) and a neuropsychological assessment performed before surgery. Excluded were patients who: a) were older than 65, to avoid the possible presence of sensory deficits and fatigue effects; b) in whom the assessment could not be carried out with a minimum of reliability due to their high level of cognitive impairment; and c) had a history of severe psychiatric conditions, since it could affect the results obtained in the neuropsychological evaluation.

2.2. Procedure

The study was conducted following the Declaration of Helsinki and approved by the ethics committee of the hospital. All participants provided informed consent. Our reporting followed STROBE guidelines (Von Elm et al., 2007).

Demographic characteristics (i.e., age, sex, handedness, educational level, academic/employment insertion, and household members), as well as clinical data (i.e., epilepsy type, TLE (yes/no), side of seizure focus, age at epilepsy onset, epilepsy duration, magnetic resonance imaging (MRI) findings, hippocampal sclerosis (HS) (yes/no), number of ASMs, and seizures per month and seizure type) were registered. In this regard and given the objectivity, robustness, and relevance of the variable in this study, epilepsy duration was collected during the interview before the neuropsychological assessment, in which the information provided by the patients was contrasted with the relatives. This variable considered the years elapsed from the time the diagnosis was made until the neuropsychological assessment was performed.

Presurgical assessment included the diagnosis of the epilepsy type and the lateralization of the epileptogenic area based on a comprehensive assessment made by members of a multidisciplinary team. This evaluation included seizure history and semiology, neurologic

assessment, video-electroencephalography monitoring, 3-Tesla MRI, psychiatric assessment, and neuropsychological evaluation. Fluorodeoxyglucose (FDG)- positron emission tomography (PET), single-photon emission computed tomography (SPECT), and intracranial EEG recording were performed selectively. A comprehensive neuropsychological evaluation was carried out for all patients. From this assessment, anxiety, depression, attention, executive functioning, memory, language, and QOL tests were selected for the present study. Furthermore, to ensure that the differences in negative affectivity values in each group were not due to difficulties in emotion recognition, an instrument that assessed the ability to recognize emotional states was administered.

2.3. Neuropsychological assessment

The neuropsychological assessment was designed following the recommendations of the E-PILEPSY consortium (Vogt et al., 2017).

2.3.1. Anxiety

This was assessed using the State-Trait Anxiety Inventory (STAI; Spielberger, 1989). The trait anxiety scale (STAI-T) evaluates relatively stable aspects of anxiety and is composed of 20 items rated on a four-point scale ranging from 0 ("hardly never") to 3 ("almost always"), with higher scores indicating higher anxiety. Cronbach's alpha of the Spanish adaptation of this inventory is 0.94 (Guillén-Riquelme & Buela-Casal, 2011). This instrument was selected since, despite being a test developed for the general population, it is a valid and reliable instrument with acceptable sensitivity and specificity in patients with epilepsy, with a high negative predictive value and a low positive predictive value (Wiglusz et al., 2019; Zingano et al., 2019). It is a strong predictor for QOL in this population (Cano-López et al., 2018; Johnson et al., 2004). Moreover, it is one of the most widely used measures of anxiety in clinical research (Spielberger et al., 1970; Spielberger et al.,1983; Kennedy et al., 2001; Wiglusz et al., 2019), thus enabling us to have a large literature with which to compare our results (Cano-López et al., 2018, 2023; Lima et al., 2021).

2.3.2. Depression

The Beck Depression Inventory-II (BDI-II; Beck et al., 1996) was used to assess depression with 21 items rated on a four-point scale, with higher scores indicating higher depression levels. Cronbach's alpha is 0.89 (Sanz & García-Vera, 2009). This instrument was selected since the E-PILEPSY consortium (Vogt et al., 2017) reported that the BDI was the wide instrument used

by clinicians (60%) to assess mood in patients with drug-resistant epilepsy. Furthermore, it has been shown that BDI-II is a more robust measure than other instruments in patients with epilepsy (Oliveira et al., 2014).

2.3.3. Attention and executive functioning

The Trail Making Test (TMT; Reitan & Wolfson, 1985) was used to measure attention and executive functions (working memory, attention, planning, and set-shifting) that require motor skills and visual-spatial processing. In part A (TMT-A), participants were requested to draw a line to connect 25 circles with successive numbers and in the correct order, whereas in part B (TMT-B) participants must alternate between letters, joining them in the specific order. In this test, longer task completion times indicate poorer performance.

The Wisconsin Card Sorting Test (WCST; Heaton et al., 1993) was used to evaluate cognitive flexibility, abstract conceptualization, and responsiveness to feedback. Higher scores indicated poorer performance in the following indices: number of trials; number and percentage of errors; number and percentage of perseverative responses; number and percentage of non-perseverative errors; trials to complete the first category; and failure to maintain a set. Additionally, higher scores showed better performance in the following indices: correct responses; number and percentage of conceptual level responses; categories completed; and learning to learn.

2.3.4. Memory

The Spanish Complutense Verbal Learning Test (TAVEC; Benedet & Alejandre, 1998) was used to assess episodic verbal memory. This test is a Spanish version of the California Verbal Learning Test (CVLT; Delis et al., 1987). It consists of three shopping lists: a learning list (list A); an interference list (list B); and a recognition list (list C). The following indices were computed: immediate verbal memory; short-term verbal memory; short-term verbal memory with semantic cues; long-term verbal memory; long-term verbal memory with semantic cues; recognition; and discriminability. In all cases, higher scores indicated better performance.

The Rey-Osterrieth Complex Figure test (ROCF; Rey, 1941; Osterrieth, 1944) was used to assess immediate visual memory. It consists of the presentation of a two-dimensional figure that must be copied by the patient, without rotating the model sheet. After 3 min, participants were asked to recall the figure and draw it again without the presence of the model, assessing the immediate visual memory. The scores were computed as the sum of the drawn elements considering the degree of accuracy, deformation, and location. According to this correction

system, each of the 18 elements of the figure received a score of 0, 0.5, 1, or 2 points. The maximum possible score was 36 points.

2.3.5. Language functions

The Boston Naming Test (Kaplan et al., 2001) was used to assess visual confrontation naming. Semantic and phonemic cues were provided in the case of no response or incorrect response. The total score was computed as the number of cards correctly named without phonemic cues and with 60 being the maximum score.

The FAS (Spreen & Benton, 1977) was used to assess phonemic fluency. In this task, participants were requested to say as many words as they can that start with the letters F, A, and S in one minute. The total score was computed as the sum of all admissible words for the three letters.

The Animal Naming Test (ANT; Rosen, 1980) was used to evaluate semantic fluency. In this test, participants were required to name as many animals as possible in 1 min. The total score was computed as the sum of admissible words for this semantic category.

2.3.6. Emotional recognition

The Reading the Mind in the Eyes Test (RMET; Baron-Cohen et al., 2001) was used in its Spanish version (Fernández-Abascal et al., 2013). This test measures the ability to recognize other people's emotions. It consists of 36 photographs of people's gazes, each with four response options. Participants are asked to choose which adjective best describes that look. The test score ranges from 0 to 36, the higher the score, the better the performance. Cronbach's alpha of the Spanish adaptation is 0.63.

2.3.7. QOL

Quality of Life in Epilepsy Inventory (QOLIE-31; Cramer et al., 1998), in its Spanish version (Torres et al., 1999), was used to assess QOL and 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 ranged from 0 to 100, with higher scores indicating better QOL (including seizure worry and medication effects, which were scored on an inverse scale). A QOL composite score was computed using a weighted average of subscales. Cronbach's alpha of the Spanish adaptation of this inventory ranges from 0.55 to 0.92 (Torres et al., 1999).

2.4. Statistical analysis

Outliers were defined as values ± 2.5 SD. We detected three outliers for BDI-II and one for epilepsy duration, and they were winsorized by replacing their values with values equal to the mean ± 2.5 SD to control for the possible effect of extreme values in further analyses (Dixon & Tukey, 1968). A cluster analysis was used to identify groups of participants based on their average *z*-scores across three variables: anxiety; depression; and epilepsy duration. We used Ward's hierarchical clustering method with squared Euclidean distance as the index of the length between patient profiles. This method is one of the most widely used (Govender & Sivakumar, 2020) probably due to its effectiveness at the time of classification (Tufféry, 2011). Ward's method aims to achieve the minimization of intragroup variance and maximizes homogeneity within groups. This analysis provides groups or clusters not defined a priori. Hierarchical clusters provide an output called a dendogram – in which the progressive formation of clusters is shown from n subjects to a single grouping. The R package NbClust was used to check the optimal number of clusters. This package is particularly useful as it provides 23 indices and indicates how many indices support a given number of clusters after varying all combinations of several clusters, distance measures, and clustering methods (Charrad et al., 2012). Dunn's index, which measures the ratio of the minimum inter-cluster distance to the maximum inter-cluster distance, was also calculated. The value of this index ranges from 0 to infinity with higher scores indicating better clustering. Finally, the analyses were replicated with a k-means cluster to observe agreement with the results of the hierarchical cluster. These analyses were made using Rstudio (https://www.r-project.org/, version 4.0.0).

Once the clusters were established, univariate ANOVAs were performed for between-group comparisons based on the cluster and clinical and demographical variables (i.e., age, educational level, age at epilepsy onset, epilepsy duration, number of ASMs, and seizures per month). Moreover, the chi-square test was used to study the differences between frequencies in descriptive variables depending on the cluster (i.e., sex, handedness, academic/employment insertion, household members, epilepsy type, TLE (yes/no), side of seizure focus, MRI findings, HS (yes/no) and seizure type). When significant differences were detected, these demographical and clinical variables were included as covariates in further analyses. Univariate ANOVAs were performed using the z-scores of each variable to determine whether these clusters differed for attention and executive functioning, memory, language, QOL, and emotional recognition. Bonferroni tests were then performed as post hoc analyses. ANOVAs

were performed using SPSS 25.0 and two-tailed tests with *p* set at 0.05 were considered significant. Partial eta squared effect sizes were reported, but this indicator may be difficult to interpret when comparing between studies (Lakens, 2013). Consequently, and considering the recommendation of Preacher & Kelley (2011) of the use of multiple effect size measures, Cohen's *f* statistic was calculated as a local effect size measure using G*Power 3.1.9.7 software, with values near 0.10, 0.25, and 0.40 representing small, medium, and large effect sizes, respectively (Cohen, 1969).

3. Results

3.1. Characteristics of the total sample

The sample was composed of 170 patients (82 men and 88 women; mean age = 38.21, SD = 11.20). The mean age at epilepsy onset was 16.60 (SD = 11.86) and the mean of seizures per month was 20.49 (SD= 44.47). Characteristics of the sample are shown in Table 1.

3.2. Stress phenotypes

Fourteen of the 23 indices from NbClust R package indicated that a three-cluster solution was an optimal number of clusters for portioning the data. The Dunn index for a three-cluster solution was 1.07. When the K-means cluster was performed with a three-cluster solution, the same grouping of patients was obtained for each of the three clusters. Figure 1 shows the Dunn index plot.

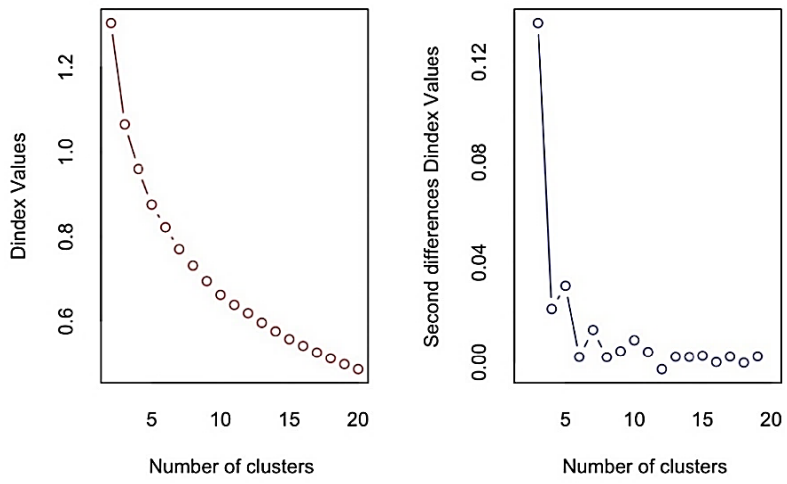

Figure 1. D-index for the determination of the number of clusters. The sharp change in the slope of the D-index second differences plot indicates a significant increase in the value of the measure.

Cluster 1 (i.e., vulnerable phenotype) comprised 26.47% of patients and was characterized by high anxiety and depression, but short epilepsy duration (mean = 14.42 years, SD = 9.07). Cluster 2 (i.e., resilient phenotype) included 27.65% of the patients and was characterized by moderate levels of anxiety and depression, and long epilepsy duration (mean = 40.75 years, SD = 8.77). Cluster 3 (i.e., low-impact phenotype) comprised 45.88% of patients and was considered as a relative control group as patients in this group had low levels of anxiety, depression, and short durations (mean = 14.22 years, SD = 8.72). Mean z-scores and SD for each group are shown in Table 2. As expected, significant differences were found in epilepsy duration, anxiety, and depression depending on the cluster (for all, $p < 0.0001$).

Table 2. Mean and SD of each cluster based on z scores.

	Vulnerable phenotype (n=45)	Resilient phenotype (n=47)	Low-impact phenotype (n=78)	Differences between groups
	Z scores	*Z scores*	*Z scores*	
BDI-II	1.06 ± 0.83	-0.04 ± 0.75	-0.60 ± 0.53	$p < 0.0001$
STAI-R	1.09 ± 0.52	0.07 ± 0.77	-0.65 ± 0.74	$p < 0.0001$
Epilepsy duration	-0.47 ± 0.62	1.32 ± 0.59	-0.49 ± 0.59	$p < 0.0001$

3.3. Patient characteristics depending on stress phenotypes

Patient characteristics depending on stress phenotypes are shown in Table 1. Significant differences depending on stress phenotypes were found for age ($F_{(2,169)} = 35.84$, $p < 0.0001$) with the resilient group being significantly older than the vulnerable and low-impact groups ($p < 0.0001$). Significant differences were also found in age for epilepsy onset ($F_{(2,169)} = 27.33$, $p < 0.0001$), resilient patients having an earlier onset than patients from vulnerable and low-impact phenotypes ($p < 0.0001$); and for educational level ($F_{(2,169)} = 4.72$, $p = 0.01$) with resilient patients showing lower educational levels than the low-impact group ($p = 0.011$). Furthermore, significant differences were found in the number of ASMs ($F_{(2,168)} = 5.34$, $p = 0.006$) with resilient patients taking more ASMs than the other phenotypes (for both, $p \leq 0.036$). Finally, significant differences were found in MRI findings with resilient patients having HS more frequently than the other groups ($p = 0.002$). Age, educational level, number of ASMs, and HS (yes/no) were included as covariates in further analyses to control the possible influence

of these variables. Age of onset of epilepsy was not included as a covariate since it was directly related to epilepsy duration (i.e., the variable of interest in this study). No other significant differences were found in demographical or clinical variables (e.g., seizure frequency).

It should be noted that no differences were found depending on stress phenotypes in the RMET total score. Furthermore, all groups achieved a hit rate of more than 50%, so patients did not seem to have significant difficulties in perceiving and identifying emotions.

Table 1. Characteristics of the total sample and clusters (mean ± SD or n (%))

	Vulnerable phenotype (n=45)	Resilient phenotype (n=59)	Low-impact phenotype (n=66)	Total (n=170)	*p*
Age (years)	36.04 ± 9.88	47.98 ± 8.73	33.58 ± 9.56	38.21 ± 11.20	0.0001
Sex					0.73
Male	24 (53.3%)	22 (46.8%)	36 (46.2%)	82 (48.2%)	
Female	21 (46.7%)	25 (53.2%)	42 (53.8%)	88 (51.8%)	
Handedness					0.48
Right	37 (82.2%)	44 (93.6%)	70 (89.7%)	151 (88.8%)	
Left	5 (11.1%)	2 (4.3%)	4 (5.1%)	11 (6.5%)	
Mixed	3 (6.7%)	1 (2.1%)	4 (5.1%)	8 (4.7%)	
Educational level					0.01
Primary	7 (15.6%)	5 (10.6%)	6 (7.7%)	18 (10.6%)	
Secondary	20 (44.4%)	30 (63.8%)	27 (34.6%)	77 (45.3%)	
Lower university	10 (22.2%)	7 (14.9%)	26 (33.3%)	43 (25.3%)	
University	8 (17.8%)	5 (10.6%)	19 (24.4%)	32 (18.8%)	
Academic/employment insertion					0.06
Yes	19 (42.2%)	21 (44.7%)	48 (61.5%)	88 (51.8%)	
No	26 (57.8%)	26 (55.3%)	30 (38.5%)	82 (48.2%)	
Household members					0.11
Family	16 (35.6%)	9 (19.15%)	34 (43.6%)	59 (34.7%)	
Partner	23 (51.1%)	32 (68.1%)	38 (48.7%)	93 (54.7%)	
Flatmate	2 (4.4%)	0 (0%)	1 (1.3%)	3 (1.8%)	
Living alone	4 (8.9%)	6 (12.8%)	5 (6.4%)	15 (8.8%)	
Epilepsy type					0.51
FLE[a]	6 (13.3%)	11 (23.4%)	16 (20.5%)	33 (19.4%)	
TLE[b]	34 (75.6%)	34 (66.1%)	51 (77.3%)	119 (70%)	
PLE[c]	3 (6.7%)	1 (2.1%)	8 (10.3%)	12 (7.1%)	
OLE[d]	1 (2.2%)	0 (0%)	1 (1.3%)	2 (1.2%)	
ILE[e]	0 (0%)	1 (2.1%)	0 (0%)	1 (0.6%)	
Multifocal	1 (2.2%)	0 (0%)	2 (2.6%)	3 (1.8%)	
TLE[b] (yes/no)					0.46
Yes	34 (75.6%)	34 (72.3%)	51 (65.4%)	119 (70%)	
No	11 (24.4%)	13 (27.7%)	27 (34.6%)	51 (30%)	

Table 1. Continued.

	Vulnerable phenotype (n=45)	Resilient phenotype (n=59)	Low-impact phenotype (n=66)	Total (n=170)	*p*
Side of seizure focus					0.86
Left	23 (51.1%)	23 (48.9%)	34 (43.6%)	80 (47.1%)	
Right	20 (44.4%)	22 (46.8%)	38 (48.7%)	80 (47.1%)	
Bilateral	2 (4.4%)	2 (4.3%)	6 (7.7%)	10 (5.9%)	
Age at epilepsy onset (years)	21.62 ± 11.36	7.23 ± 6.47	19.36 ± 11.56	16.60 ± 11.86	0.0001
Epilepsy duration (years)	14.42 ± 9.07	40.75 ± 8.77	14.22 ± 8.72	21.61 ± 14.76	0.0001
MRI[f] findings					0.009
HS[g]	10 (22.2%)	23 (48.9%)	16 (20.5%)	49 (28.8%)	
FCD[h]	5 (11.1%)	13 (27.7%)	18 (23.1%)	36 (21.2%)	
Tumor	10 (22.2%)	2 (4.3%)	13 (16.7%)	25 (14.7%)	
Heterotopia	2 (4.4%)	0 (0%)	3 (3.8%)	5 (2.9%)	
Cavernona	5 (11.1%)	2 (4.3%)	8 (10.3%)	15 (8.8%)	
Non-especific pathology	13 (28.9%)	7 (14.9%)	20 (25.6%)	40 (23.5%)	
HS[g] (yes/no)					0.002
Yes	10 (22.2%)	23 (48.9%)	16 (20.5%)	49 (28.8%)	
No	35 (77.8%)	24 (51.1%)	62 (79.5%)	121 (71.2%)	
Number of ASMs[i]	2.76 ± 0.88	3.21 ± 0.93	2.71 ± 0.81	2.86 ± 0.89	0.006
Seizures per month	26.05 ± 50.77	22.95 ± 42.62	17.15 ± 42.09	20.49 ± 44.48	0.583
Seizure type					0.498
FAS[j]	1 (2.2%)	0 (0%)	6 (7.7%)	7 (4.1%)	
FIAS[k]	15 (33.3%)	22 (46.8%)	24 (30.8%)	61 (35.9%)	
FBTCS[l]	1 (2.2%)	0 (0%)	2 (2.6%)	3 (1.8%)	
FAS[j]+FIAS[k]	9 (20%)	10 (21.3%)	13 (16.7%)	32 (18.8%)	
FAS[j]+ FBTCS[l]	2 (4.4%)	0 (0%)	3 (3.8%)	5 (2.8%)	
FIAS[k]+FBTCS[l]	13 (28.9%)	10 (21.3%)	23 (29.5%)	46 (27.1%)	
FAS[j]+FIAS[k]+FBTCS[l]	4 (8.9%)	5 (10.6%)	7 (9%)	16 (9.4%)	
RMET[m]	18.81 ± 5.88	18.84 ± 5.42	20.53 ± 4.70	19.62 ± 5.27	0.318

Note. [a] FLE: frontal lobe epilepsy; [b] TLE: temporal lobe epilepsy; [c] PLE: parietal lobe epilepsy; [d] OLE: occipital lobe epilepsy; [e] ILE: insular lobe epilepsy; [f] MRI: magnetic resonance imaging; [g] HS: hippocampal sclerosis; [h] FCD: focal cortical dysplasia; [i] ASM: antiseizure medication; [j] FAS: focal aware seizure; [k] FIAS: focal impaired awareness seizure; [l] FBTCS: focal to bilateral tonic-clonic seizures; RMET[m]: Reading the Mind in the Eyes Test.

3.4. Differences in attention, executive functioning, memory, and language depending on stress phenotypes

Regarding executive functioning (Figure 2), significant differences were also found in the following WCST variables: errors ($F_{(2,168)} = 4.09$, $p = 0.019$, $n^2_p = 0.05$, Cohen's $f = 0.24$); percentage of errors ($F_{(2,168)} = 3.79$, $p = 0.025$, $n^2_p = 0.05$, Cohen's $f = 0.23$); perseverative responses ($F_{(2,168)} = 5.29$, $p = 0.006$, $n^2_p = 0.06$, Cohen's $f = 0.29$); percentage of perseverative responses ($F_{(2,168)} = 5.83$, $p = 0.004$, $n^2_p = 0.07$, Cohen's $f = 0.30$); perseverative errors ($F_{(2,168)} = 6.08$, $p = 0.003$, $n^2_p = 0.07$, Cohen's $f = 0.31$); percentage of perseverative errors ($F_{(2,168)} = 5.99$, $p = 0.003$, $n^2_p = 0.07$, Cohen's $f = 0.31$); percentage of conceptual level responses ($F_{(2,168)} = 3.81$, $p = 0.024$, $n^2_p = 0.045$, Cohen's $f = 0.23$); completed categories ($F_{(2,168)} = 4.61$, $p = 0.011$, $n^2_p = 0.054$, Cohen's $f = 0.24$); and trials to completed the first category ($F_{(2,168)} = 3.54$, $p = 0.031$, $n^2_p = 0.04$, Cohen's $f = 0.23$). In these variables, vulnerable patients had significantly poorer performance than resilient patients (for all, $p < 0.03$). It should be noted that a tendency was also observed on conceptual level responses ($F_{(2,168)} = 2.88$, $p = 0.059$, $n^2_p = 0.03$), specifically vulnerable patients performing worse than resilient patients ($p = 0.056$). Furthermore, the low-impact group performed significantly worse than the resilient group on perseverative responses, percentage of perseverative responses, perseverative errors, percentage of perseverative errors, and completed categories (for all, $p < 0.05$).

With respect memory (Figure 3), significant differences were found in the following TAVEC variables: immediate verbal memory ($F_{(2,168)} = 3.41$, $p = 0.036$, $n^2_p = 0.04$, Cohen's $f = 0.18$); short-term verbal memory ($F_{(2,168)} = 4.86$, $p = 0.009$, $n^2_p = 0.06$, Cohen's $f = 0.22$); short-term verbal memory with semantic cues ($F_{(2,168)} = 3.69$, $p = 0.027$, $n^2_p = 0.04$, Cohen's $f = 0.19$); long-term verbal memory ($F_{(2,168)} = 5.12$, $p = 0.007$, $n^2_p = 0.06$, Cohen's $f = 0.23$); long-term verbal memory with cues ($F_{(2,168)} = 5.81$, $p = 0.004$, $n^2_p = 0.07$, Cohen's $f = 0.24$); recognition ($F_{(2,168)} = 3.18$, $p = 0.044$, $n^2_p = 0.04$, Cohen's $f = 0.19$); and discriminability ($F_{(2,168)} = 3.48$, $p = 0.033$, $n^2_p = 0.04$, Cohen's $f = 0.20$). In these variables, vulnerable patients performed significantly worse than the low-impact group (for all, $p \leq 0.04$), except on recognition, in which the difference did not reach statistical significance ($p = 0.06$). Furthermore, vulnerable patients had lower scores than resilient patients on long-term verbal memory and long-term verbal memory with semantic cues ($p < 0.03$).

Finally, concerning the naming functions (Figure 4), significant differences were found in the number of correct responses ($F_{(2,168)} = 5.14$, $p = 0.007$, $n^2_p = 0.06$, Cohen's $f = 0.24$); the

number of phonemic cues ($F_{(2,168)} = 4.21$, $p = 0.017$, $n^2_p = 0.05$, Cohen's $f = 0.22$); and the total score ($F_{(2,168)} = 5.20$, $p = 0.006$, $n^2_p = 0.06$, Cohen's $f = 0.24$). In these variables, vulnerable patients performed significantly poorer than the low-impact group (for all, $p < 0.04$) and the resilient group (for all, $p < 0.04$, except for the number of phonemic cues, where a tendency was found ($p = 0.059$)). No significant differences were found in other processes (i.e., attention, visual memory, verbal fluency).

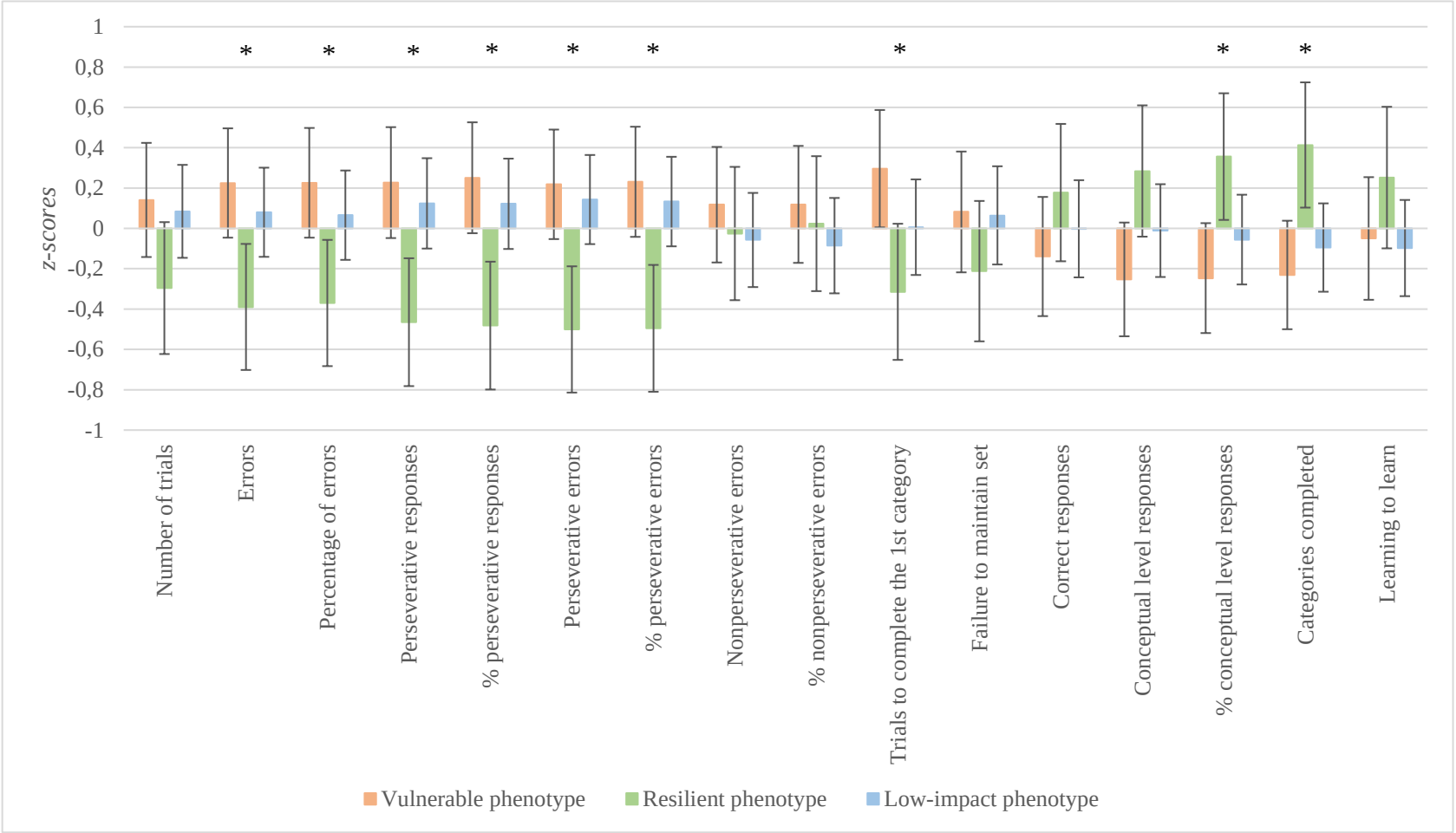

Figure 2. Differences in cognitive flexibility depending on stress phenotypes. * $p < 0.05$; error bars represent 95% confidence intervals. Higher scores indicate poorer performance in most variables (from number of trials to failure to maintain set). However, higher scores indicate better performance in the case of correct responses, conceptual level responses, categories completed, and learning to learn.

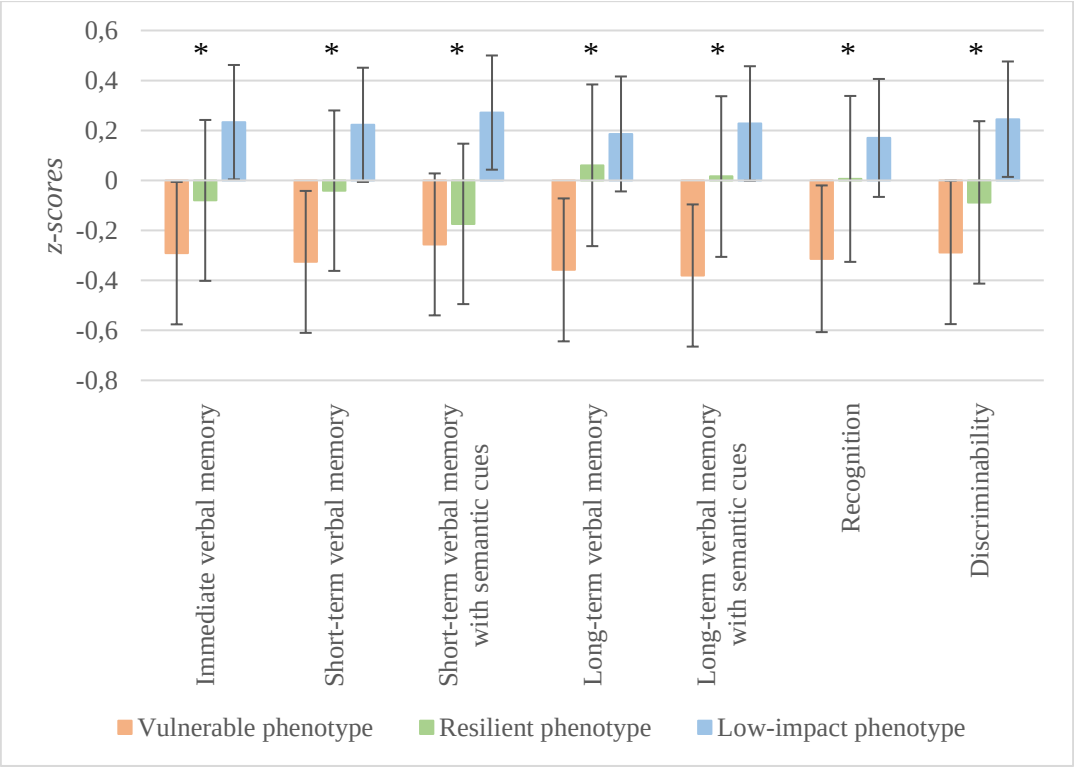

Figure 3. Differences in memory depending on stress phenotypes. * $p < 0.05$; error bars represent 95% confidence intervals.

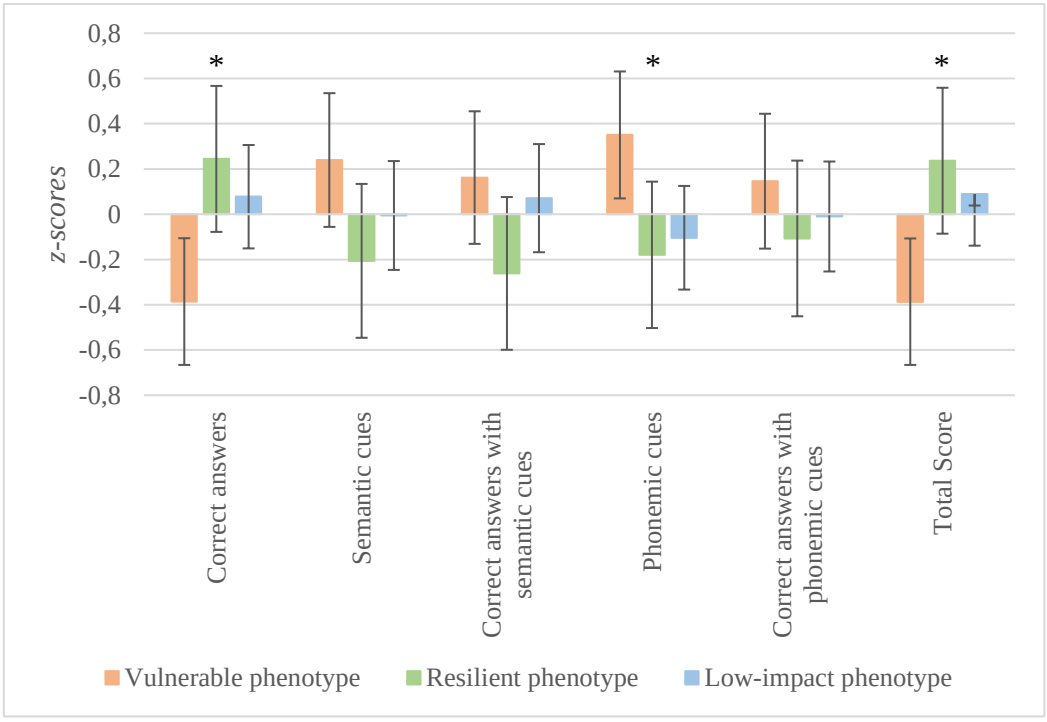

Figure 4. Differences in visual confrontation naming depending on stress phenotypes. * $p < 0.05$; error bars represent 95% confidence intervals.

3.5. Differences in QOL depending on stress phenotypes

Regarding QOL (Figure 5), significant differences were found in overall QOL ($F_{(2,168)}$ = 12.25, $p < 0.0001$, $n^2_p = 0.13$, Cohen's $f = 0.38$); emotional well-being ($F_{(2,168)} = 48.27$, $p < 0.0001$, $n^2_p = 0.37$, Cohen's $f = 0.63$); energy ($F_{(2,168)} = 32.06$, $p < 0.0001$, $n^2_p = 0.28$, Cohen's $f = 0.55$); cognitive self-rating ($F_{(2,168)}$ =15.44, $p < 0.0001$, $n^2_p = 0.16$, Cohen's $f = 0.40$); medication effects ($F_{(2,168)} = 6.80$, $p = 0.001$, $n^2_p = 0.08$, Cohen's $f = 0.29$); social functioning ($F_{(2,168)} = 9.60$, $p < 0.0001$, $n^2_p = 0.11$, Cohen's $f = 0.32$); and QOL composite score ($F_{(2,168)}$ = 39.62, $p < 0.0001$, $n^2_p = 0.33$, Cohen's f = 0.57). Vulnerable patients had significantly poorer QOL than the low-impact group in all these variables (for all, $p \leq 0.005$). Furthermore, resilient patients had significantly lower scores than the low-impact group on overall QOL ($p = 0.024$), emotional well-being ($p < 0.0001$), and energy ($p < 0.0001$). Finally, vulnerable patients showed poorer QOL than resilient patients on emotional well-being ($p = 0.028$), cognitive self-rating ($p < 0.001$), medication effects ($p = 0.008$), social functioning ($p < 0.0001$) and QOL composite score ($p < 0.0001$). It should be noted that a tendency was found for energy, with vulnerable patients having lower scores than resilient patients ($p = 0.052$). No other significant differences were found.

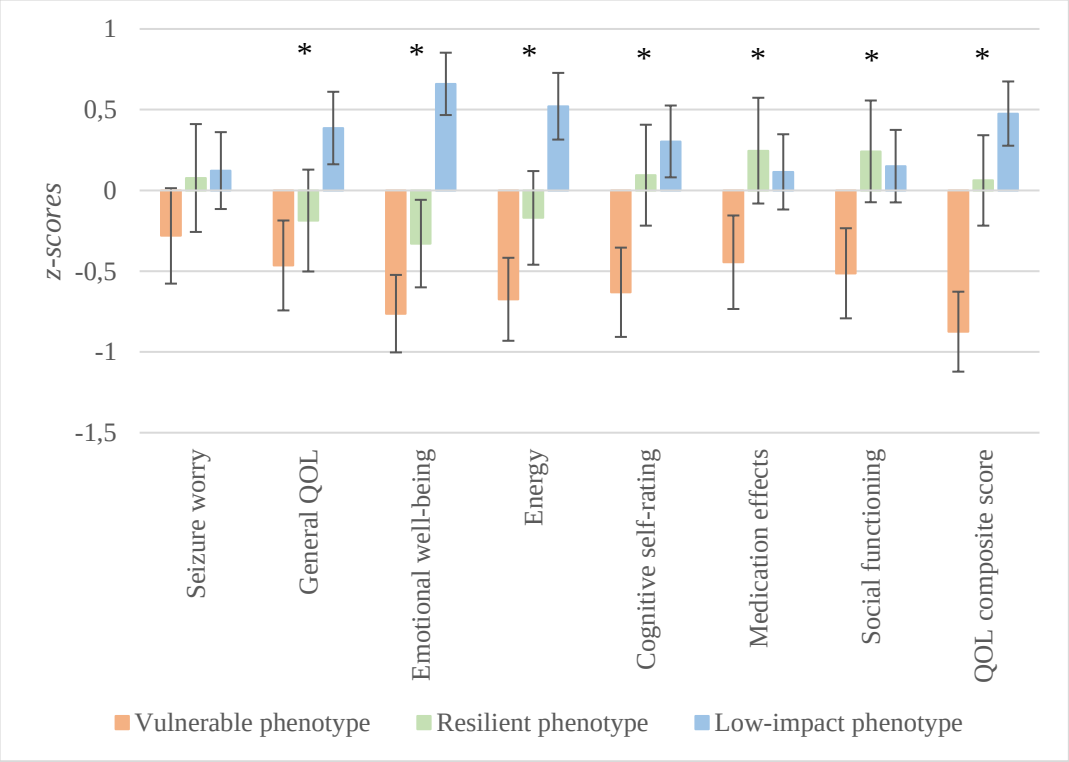

Figure 5. Differences in QOL depending on stress phenotypes. * $p < 0.05$; error bars represent 95% confidence intervals.

4. Discussion

The results of the current study show three stress phenotypes in patients with drug-resistant epilepsy based on indicators of stress chronicity and intensity (i.e., epilepsy duration and negative affectivity): vulnerable; resilient; and low-impact phenotypes. Our findings show that executive function, memory, naming, and QOL differ depending on stress phenotypes. These main findings are discussed below.

4.1. Stress phenotypes in epilepsy: characteristics

The vulnerable phenotype was characterized in our study by shorter epilepsy duration, but high levels of anxiety and depression. The resilient phenotype was characterized by long epilepsy duration and moderate anxiety and depression, suggesting that patients included in this group may have established effective coping strategies or the chronicity of the disease favored compensatory mechanisms that lead to a moderation of negative affectivity. It should be noted that this was the only group to present a long duration for the disease. A low-impact group with low anxiety, depression, and epilepsy duration was also identified. These phenotypes provide us with a new classification of patients with epilepsy in the context of epilepsy as a chronic stress setting. To our knowledge, no previous studies have established phenotypes from a quantitative research perspective considering both stress chronicity and intensity of stress in patients with epilepsy.

Our results showed that stress phenotypes were similar in terms of clinical variables such as epilepsy type, side of seizure focus, and seizure frequency. However, differences were found in MRI findings, with a higher frequency of HS in the resilient group. HS is the most common finding in epilepsy surgery (Malmgren & Thom, 2012) and so the surgery rate is high. Therefore, patients with this condition may be more likely to feel more hopeful about their futures and feel that they have more options and so, therefore, can adopt more resilient behavior. Furthermore, we found that patients in the resilient group had a lower educational level than patients in the low-impact group. The fact that patients from the resilient group had an earlier age of onset of epilepsy (i.e., longer epilepsy duration) could have hindered subsequent academic development in the resilient group with respect to the low-impact group. Furthermore, it should be noted that patients in the low-impact group had lower levels of negative affectivity than the resilient group, and some studies have found that a higher educational level is related

to lower anxiety (Mensah et al., 2007; Peterson et al., 2014), so having low negative affectivity could have acted as a protective factor for educational attainment for the low-impact group.

We also found that resilient patients were significantly older and took more ASMs than the other groups. In samples of people with epilepsy, older patients were found to have healthier coping styles than younger patients (Bautista et al., 2013) and were better adapted to a chronic illness (Canuet et al., 2009). Regarding the number of ASMs, Şenadım et al. (2021) found that focusing on and venting emotions was more frequent in patients with epilepsy who were receiving polytherapy than in those receiving monotherapy (without examining the influence of the specific number of ASMs and so underlying the need for further studies to clarify this relationship). It should be noted that, in our study, most patients (95.3%) received polytherapy. The fact that resilient patients took more ASMs than vulnerable patients may be due to higher chronicity of the disease (i.e., epilepsy duration) and an earlier onset of the disease (Szaflarski et al., 2006; Witt et al., 2020). Together, these results indicate that age and number of ASMs are important factors in understanding stress phenotypes, so they were included as covariates in the further analyses together with educational level and HS.

Due to the high rate of alexithymia in patients with epilepsy (Ricciardi et al., 2015), differences between these groups in emotional recognition were studied. No significant differences were observed among the three groups, with all three presenting a hit rate of at least 50%. This suggests that the differences found in negative affect and QOL in these groups may be not due to possible difficulties in emotional perceiving.

4.2. Differences in attention and executive functioning depending on phenotypes

Significant differences were found in executive functioning between stress phenotypes with the resilient group performing better than the vulnerable and low-impact groups, with small-to-medium effect sizes depending on the variable considered. Although some studies have indicated that longer epilepsy duration is related to poorer performance in executive functions (Black et al., 2010; Kim et al., 2006; Zamarian et al., 2011), other studies have found that duration is a weak predictor of this variable (Thompson & Duncan, 2005; Wang et al., 2011). Some studies have found no relationship between epilepsy duration and executive functioning (Agah et al., 2017; DeGeorge et al., 2021) and our results suggest that negative affectivity, an increasing factor of stress intensity, may be more relevant to explain executive function deficits in patients with epilepsy than stress chronicity.

More detailed vulnerable patients had poorer performance in executive functions than the resilient group, despite the latter group having longer durations of epilepsy. Espinosa et al. (2010) found that WCST performance was related to the severity of depressive disorders in patients with TLE, suggesting that patients with a larger number of total errors were more likely to have depression. This finding is interesting, as significant differences in the total number of errors were only found between the resilient and vulnerable groups, without differences with the low-impact group – who had low negative affectivity despite having the same duration as the vulnerable group. Significant differences were also found in perseverative errors, which has been found to be a predictor of postsurgical BDI score in a sample of TLE patients (Pope et al., 2019). However, there are few studies that address this relationship while considering anxiety. As an exception, Hermann et al. (1991) addressed the relationship between the number of perseverative errors and negative affectivity, including measures of depression and anxiety, and found a significant association between these variables in patients with left TLE, but no significant results in patients with right TLE.

Surprisingly, we also found that the resilient group also performed better in executive function than the low-impact group – with lower perseverative errors and perseverative responses (these variables being measures of cognitive flexibility). These findings are relevant, as patients with a longer history of illness have been found to perform better than those with a shorter duration and lower emotional comorbidity. Cognitive flexibility is a domain related to problem-solving skills and decision-making, that enables the patient to develop different coping strategies to deal with a problem. Some studies that have examined cognitive flexibility with self-report questionnaires have found a positive relationship between resilience and stress coping (Arici-Ozcan et al., 2019; Bonanno et al., 2004; Martin & Anderson, 2001). Soltani et al. (2013) proposed that this relationship may be more complex, and found that cognitive flexibility mediates the relationship of coping styles and resilience with depression. These findings suggest that cognitive flexibility may interfere with the moderate levels of negative affectivity shown in this group.

It should be underlined that, although it cannot be established with certainty that the differences found in executive function tests depending on stress phenotypes were not influenced by other factors, stress phenotypes did not differ in attention functioning, so differences in executive functioning may not be attributed to deficits in this cognitive domain.

4.3. Differences in memory depending on phenotypes

We found significant differences in verbal memory functioning depending on stress phenotypes, with small effect sizes. Specifically, we found poorer memory functioning in the vulnerable group than in the low-impact group. This suggests that negative affectivity is more related to memory impairment than the duration of the disease itself, as both the vulnerable and low-impact groups were equal in epilepsy duration. These results are in line with previous studies that showed that trait anxiety is a predictor of memory functioning (Cano-López et al., 2019) and that patients with epilepsy with depression had cognitive impairments (Arend et al., 2018). Rayner et al. (2016a) suggested that depression may be more strongly linked to deficits in cognitive networks in patients with epilepsy than in cases of primary depression, as there may be mechanisms underlying depression that could affect brain networks in some neurological diseases.

Our results also showed significantly poorer verbal memory functioning in vulnerable patients compared to the resilient group in two subscales (i.e., long-term verbal memory and long-term verbal memory with semantic cues). It should be noted that in our sample resilient patients began to have seizures in childhood and, consequently, have longer epilepsy duration, whereas the vulnerable group began to have seizures in adulthood (with a shorter epilepsy duration). In contrast to our results, it has been found that an early onset of epilepsy may cause changes in brain development characterized by an age-related delay in white matter gain, possibly leading to problems in cognitive development (Hermann et al., 2010), and that epilepsy duration and age of epilepsy onset are predictors of memory failure in children (Menlove & Reilly, 2015) and adults with TLE (Uslu et al., 2019). However, it should be noted that some studies have found memory deficits in patients with a recent diagnosis of epilepsy not treated with ASMs, suggesting that memory impairment in patients with long-standing epilepsy cannot be attributed exclusively to seizure recurrence and the effects of ASMs, and other factors must be explored (Äikiä et al., 2001). It is also possible that the early onset of the resilient group could favor a better performance in the adult stage due to the efficiency of the plasticity and compensatory mechanisms in childhood and adolescence. In our study, vulnerable patients had more negative affectivity than resilient patients, so our results suggest that it is not so much the duration of epilepsy that matters, but how it combines with negative affectivity to explain the differences between the resilient and vulnerable phenotypes in memory functioning.

Rayner et al. (2016b) show that memory failures could be explained depending on the age at epilepsy onset. In this regard, memory failures in patients with early epilepsy onset are mainly explained by neurobiological factors (i.e., the resilient group in our sample), whereas in patients with late-onset these deficits are due to psychological maladaptation (i.e., vulnerable and low-impact groups). Our findings partially agree with this model, as we conclude that in patients with late epilepsy onset, memory failures are mainly related to negative affectivity. In our study, the group with high negative affect and short epilepsy duration (vulnerable group) performed worse than the group with low negative affect and low epilepsy duration (low-impact group) on all memory subscales. Furthermore, these differences were also significant for the long-term memory subscales between the group with moderate levels of negative affect and long epilepsy duration (resilient group) and the vulnerable group (with the vulnerable group showing poorer performance). These results suggest that negative affect is a sensitive factor that may have a stronger effect on memory than epilepsy duration.

It should be noted that no significant differences were found in visual memory depending on stress phenotypes. This could be due to the type of task used to evaluate visual memory, as there are difficulties in finding a 'pure' test of visual memory (Helmstaedter et al., 1995; Vaz, 2004), and patients often use verbal strategies to perform visual tests such as the ROCF (Barr et al., 1997).

4.4. Differences in language functioning depending on phenotypes

Significant differences were found in visual confrontation naming, with small effect sizes. Specifically, the vulnerable group showed poorer performance than the low-impact group and the resilient group. Vulnerable and low-impact groups had similar epilepsy duration, so our results highlight the relevance of negative affectivity in naming and semantic memory processes. Furthermore, the fact that the vulnerable group (i.e., high negative affectivity and short epilepsy duration) had also poorer performance than the resilient group (i.e., moderate negative affectivity and long epilepsy duration) in naming suggests that naming deficits in patients with late epilepsy onset are mainly associated with negative affectivity. These results are in line with those found by Paradiso et al. (2001), showing that patients with TLE and depression had poorer performance than patients with TLE without depression in a neuropsychological evaluation, in which visual naming was assessed. As indicated above,

mechanisms underlying negative affectivity may affect brain networks involved in cognitive functioning (Rayner et al., 2016a).

Decreased naming ability is commonly found in patients with epilepsy, especially in those with TLE, indicating a key role of the medial temporal lobe in this process (Bonelli et al., 2011; Goodglass & Wingfield, 1997; Ogden-Epker & Cullum, 2001; Schefft et al., 2003). It should be noted that stress phenotypes did not differ in verbal fluency, suggesting that the differences found in naming may be attributed to semantic memory functioning and not to other processes such as verbal fluency. Taken together, our results are in line with those found with episodic verbal memory, pointing to an interrelation between semantic and episodic memory (Barrett Jones et al., 2022; Cano-López et al., 2017).

4.5. Differences in QOL depending on phenotypes

In terms of QOL, significant differences with medium-to-large effect sizes (depending on the QOL score considered) were found depending on stress phenotypes. Specifically, we found that the vulnerable group had poorer QOL than the low-impact group in QOL composite score and most QOL subscales. These findings are in line with several studies that showed that depressive symptoms and anxiety are negatively related to QOL (Cano-López et al., 2018; Gur-Ozmen et al., 2017; Kwan et al., 2009; Lima et al., 2021; Micoulaud-Franchi et al., 2016; Scévola et al., 2017; Tombini et al., 2020), with anxiety even being the strongest predictor of QOL in patients with TLE (Cano-López et al., 2018; Lima et al., 2021).

Our results also showed that the resilient group had poorer QOL than the low-impact group in overall QOL, emotional well-being, and energy subscales. Regarding overall QOL, some studies have found that epilepsy duration is related to poorer scores in this subscale in people with epilepsy (Pauli et al., 2017; Shetty et al., 2011). We argue that patients with longer durations may have a more comprehensive affectation of the disease that may affect different areas, and therefore they may have poorer overall QOL. Regarding emotional wellbeing, it should be noted that the low-impact group was taken as a representation of patients who did not yet have emotional alterations associated with epilepsy. However, the resilient group was not completely exempt from these emotional alterations (i.e., having moderate levels of negative affectivity). This may explain why patients from the resilient group, with moderate levels of anxiety and depression, have less QOL related to emotional well-being than the low-impact group. Regarding the energy subscale, our results may be influenced by the longer

epilepsy duration that characterized resilient patients compared to patients from the low-impact group, considering that recurrent exposition to seizures may worsen the signs of fatigue associated with age and chronic illness in patients with epilepsy (Baranowski, 2018).

We also found a significantly poorer QOL in the vulnerable group compared to the resilient group in all the QOL subscales, except for seizure worry and overall QOL (where no differences were found) and energy (where a tendency was found). Regarding emotional well-being, since the vulnerable group had a higher negative affectivity than the resilient group, it was to be expected that they would perceive a lower related QOL. As regards cognitive self-rating, the vulnerable group had poorer objective memory scores than the other groups, but the differences did not reach statistical significance. This suggests that differences between vulnerable and resilient groups are more notable in subjective cognitive performance than in objective cognitive functioning, which is congruent with the high negative affectivity scores of the vulnerable group. In the case of medication effects, we found that the resilient group, despite taking the largest number of ASMs, perceived fewer medication effects than the vulnerable group. This contrasts with studies that showed that the number of ASMs is related to QOL (Lozano-García, et al., 2021) even when depression was considered in this relation (Wang et al., 2022). However, other studies have found that patients with comorbid depression (Josephson et al., 2017) or anxiety (Kanner, 2012) experience greater adverse effects from ASMs. This could explain, at least in part, why patients with higher negative affectivity experience worse adverse effects and, consequently, a poorer related QOL. Regarding social functioning, the vulnerable group had poorer scores than the resilient group. This may be explained by two facts. Firstly, vulnerable patients with a shorter period of adaptation to the disease may feel more stigmatized and may perceive less seizure control and a greater sense of unpredictability, which may be associated with greater social isolation and, therefore, with reduced QOL (Błaszczyk & Czuczwar, 2016; Suurmeijer et al., 2001). Secondly, the vulnerable group had higher negative affectivity, and this could be related to social problems. In this line, a study of patients with TLE found that anxiety was negatively related to both perceived social support and social functioning (Catalán-Aguilar et al., 2022). Furthermore, it has been shown that social support plays an important role as a predictor of negative affectivity in epilepsy (Gandy et al., 2012).

4.6. Strengths and limitations of this study

This study has strengths such as the large and relatively homogeneous sample (i.e., adult patients with drug-resistant epilepsy). Although Ring et al. (2016) differentiated vulnerable and resilient individuals and analyzed how different socioemotional and clinical factors influence QOL in patients with epilepsy using qualitative methods, our study represents an advance over previous studies, since, as far as we know, it is the first to summarize stress chronicity and intensity variables in different profiles from a quantitative research perspective and to explore their association with cognition and QOL in patients with epilepsy. Our findings highlight that it is not so much the epilepsy duration and negative affectivity separately that are relevant, but how these variables combine to form phenotypes. It is worth noting that the anxiety assessed in this study is the anxiety trait and not a scale of clinical anxiety. This enhances the predictive power of this dimension in the detection of vulnerable and resilient individuals since it is not necessary to reach clinical scores. Hermann et al. (2021) recommended that future studies move toward a new taxonomy of epilepsy, in which cognitive and psychological comorbidities become more relevant. Considering this suggestion, we proposed new phenotypes according to emotional comorbidity and epilepsy duration. In addition, to ensure that other comorbidities such as memory deficits, executive functioning impairment, naming difficulties or poor QOL are examined, we show differences depending on stress phenotypes in these variables.

Despite these strengths, some limitations should be considered. First, although our sample was composed of patients with drug-resistant epilepsy sample, different types of epilepsy were included. For this reason, future studies should explore the identified phenotypes with specific types of epilepsy. Second, due to the cross-sectional nature of the data, we cannot conclude causality in the relationships. Third, larger sample sizes could provide more information and ensure statistical power. Fourth, executive function is a complex cognitive domain, so the inference of executive function only from WCST and TMT scores should be considered with caution (Miranda et al., 2020). Fifth, although negative affectivity has been considered in stress phenotypes and may summarize the heightened emotional response to unpredictable seizures, the unpredictability of seizures was not registered, so further studies may design new measurements for this variable. In this line, stress indicators such as cortisol levels or response are also needed to confirm the stress in these three phenotypes and future research in this line must be encouraged. Sixth, although side of seizure focus is a variable of great interest for understanding the idiosyncrasies of epilepsy, it was not considered in determining stress

phenotypes since its relationship with stress processes is inconsistent. Specifically, some studies showed that patients with left temporal lobe epilepsy have higher levels of depression and anxiety (Altshuler et al., 1990), whereas others found a lack of relationships of side of seizure focus with negative affectivity (Cano-López et al., 2019; Devinsky et al., 2005; Sperli et al., 2009) or cortisol response (Cano-López at al., 2019). This highlights the need for further studies to assess the possible relationship between stress and lateralization of epilepsy. Seventh, the group labels of 'resilient', 'vulnerable', and 'low-impact' must be taken cautiously since they are supported by criteria of negative affectivity and duration of epilepsy. This does not mean that resilient patients show better outcomes or vulnerable patients display worse outcomes in all the assessed dimensions. On the contrary, these phenotypes point to the strengths and weaknesses of each type of patient to better outline the necessary interventions. Eighth, although our anxiety and depression scores could be useful for detecting susceptibilities to clinical disorders (Cano-López et al., 2019) they are not diagnostic measures (Kendall et al., 1987). We used the BDI and STAI to evaluate negative affectivity since data collection began in 2015 using these tests and it was decided to continue using the same instruments for reasons of comparability, but future studies should replicate these results with screening tools specifically designed and validated in patients with epilepsy for depressive disorders and anxiety disorders. Finally, to ensure the ability of the participants to recognize one's own emotions, future studies should consider including a measure of alexithymia that allows for the assessment of the possible difficulties in emotional self-recognition.

4.7. Conclusions

The results of the current study contribute to differentiating phenotypes based on stress chronicity and intensity, while considering both epilepsy duration and negative affectivity. Vulnerable patients have poorer memory, naming, and QOL. This group of patients is the most clinically relevant, as it corresponds to a risk profile. This indicates the need to detect non-clinical anxiety and depression in the early years of epilepsy. Patients in the resilient group perform better on executive functions. These patients have experienced epilepsy practically all their lives, adapting the disease to their environment. However, this does not imply better memory functioning and QOL than the low-impact group. Finally, it should be noted that participants from the low-impact group had a low negative affect and a similar level of memory to those from the resilient group, and had a higher QOL than the rest of the groups. These findings show the importance of taking into account negative affectivity and memory

functioning during the early years of the disease, whereas in later stages executive functions become more relevant. Furthermore, these results highlight the relevance of considering epilepsy as a model of interconnected networks, in which comorbidities and clinical and demographic variables interact with each other. In fact, people with epilepsy perceive poor life satisfaction, probably due to the interaction between low perceived QOL, socio-emotional limitations, daily challenges, and the effects of the disease itself (Kang, 2023). Resilience is not a static variable, but a dynamic progress (Hatala et al., 2013; Luthar & Cicchetti, 2000), so our results could be useful for detecting vulnerable or resilient profiles and implementing individualized clinical treatments that are more tailored to patient needs. Wagner et al., (2010) demonstrated the benefits of promoting resilience in patients with epilepsy. Future research with patients with epilepsy should examine stress chronicity and intensity variables together with specific coping instruments, as well as study the relevance of possible modulating factors such as social support. Finally, we encourage assessing the efficacy of interventions designed to enhance resilience in patients with drug-resistant epilepsy.

CHAPTER 7

Study 4

The buffered cortisol response to stress in patients with epilepsy and its relationship with memory functioning and quality of life: preliminary results[1]

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1. Introduction

Epilepsy has been proposed as a model of chronic stress in humans (Cano-López & González-Bono, 2019). The repetition of uncontrollable and unpredictable seizures that put life at risk, mood comorbidities, and the side effects of antiseizure medications (ASMs) affect the quality of life (QOL) of the patients during prolonged periods (Cano-López et al., 2018; George et al., 2015; Sancho et al., 2010). In this setting, glucocorticoids, as the final product of the stress response, increase after seizures (Maguire & Salpekar, 2013), but also seem to play a relevant role in seizure onset (Chameau et al., 2007; Liu et al., 2004).

In the general population, although results are not homogeneus, chronic stress has been related to a buffered cortisol awakening response and responsivity to acute stress (Duan et al., 2013; Lam et al., 2014), mostly interpreted as a sign of loss of adaption to new challenges. Moreover, both acute and chronic stress have been related to mood disorders and cognition. In this regard, a buffered response to acute stress has been proposed as a predictor of future anxiety and depression (for review, see Turner et al., 2020), while chronic stress has been associated with mood disorders (Ross et al., 2017). Regarding cognition, the classic framework that affirmed that stress impairs memory has given way to a more complex reality. Although results are not unanimous, acute mild-intensity stress can enhance encoding and memory consolidation in implicit and declarative memory tasks, but not in the case of acute high-intensity stress (for review, see James et al., 2023). However, certain consensus exists about the pernicious effects of chronic stress on cognition (McEwen & Sapolsky, 1995; Sandi, 2013).

As far as we know, no studies exist about the interaction between chronic status, such as epilepsy, and acute stress response together with its implications on mood and cognition in this population. Potential results could contribute to explaining the mechanisms underlying the interaction between stress and epilepsy. To our knowledge, only two studies have coped with the stress response to psychosocial stressors in persons with epilepsy, although no data on memory or mood are available (Allendorfer et al., 2014; Goodman et al., 2019). In Allendorfer et al. (2014), the cortisol response of 23 patients with left temporal lobe epilepsy (TLE) to the Stress Math Task was compared with those found in 23 healthy controls. The results showed greater cortisol reactivity in patients with epilepsy than in controls, and this response was positively related to seizure frequency in patients with poor seizure control (Allendorfer et al., 2014). These results are in line with those of Goodman et al. (2019), who measured the cortisol

response to a standardized psychosocial stressor, the Montreal Imaging Stress Task (Dedovic et al., 2005).

Although these results represent an important step forward, it should be interesting to examine the responsivity of patients to the Trier Social Stress Test (TSST; Kirschbaum et al., 1993), a well-known standardized psychosocial stressor that has demonstrated a powerful stress response in humans, and its implications in memory, mood, and QOL in this population. With this in mind, the present study aims to check the integrity of the stress response to a standardized psychosocial stressor in patients with epilepsy, and to determine the possible relationship of the magnitude of this response with negative affectivity, memory functioning, and QOL.

2. Methods

2.1. Participants

The sample included three sex-balanced groups: the experimental group (EG) of patients with epilepsy exposed to psychosocial stress, a control group of patients with epilepsy (CG-E) who were not exposed to psychosocial stress, and a second control group of healthy individuals (CG-H) who also were exposed to psychosocial stress.

Patients of the EG and CG-E were recruited from the Refractory Epilepsy Unit, Hospital Universitario y Politécnico La Fe. The inclusion criteria comprised: a) drug-resistant epilepsy with a hypothesis of TLE when the assessment was performed; b) candidates for epilepsy surgery; c) a chronological age of at least 18 years; and d) a neuropsychological assessment performed before surgery. Excluded were patients: a) older than 65 years; b) with severe cognitive impairment (e.g., dementia); c) with severe psychiatric conditions; d) who suffered an endocrine disease; and e) who were not fluent in Spanish. Participants of the CG-H were recruited from the general population using local advertisements. The inclusion criteria comprised an age between 18 and 65 years. The participants with drug prescriptions, severe cognitive impairment (e.g., dementia), and endocrinological or psychiatric conditions were excluded.

2.2. Procedure

This is a cross-sectional study whose reporting followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement guidelines (von Elm et al., 2007).

The protocol was conducted according to the principles of the Declaration of Helsinki and was approved by the Ethics Committee of the Hospital Universitario y Politécnico La Fe. All participants provided informed consent.

Before the assessment session, all the participants were instructed to abstain from eating, consuming food and beverages containing stimulants (e.g., tea or coffee), drinking alcohol, smoking, or brushing their teeth for two hours before the session. After checking these conditions and obtaining informed consent, demographic characteristics were recorded.

A multidisciplinary team collected presurgical data from the patients (groups EG and CG-E) before the assessment session. These data included 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, academic/employment insertion, marital status, household members) and clinical data (i.e., epilepsy duration, age at epilepsy onset, epilepsy type, lateralization of seizure onset, seizures per month, seizure type, total defined daily dose (DDD), number of ASMs, number of failed ASMs, and MRI findings) were registered. Due to the possible effect of ASMs on cortisol levels (Johannessen & Landmark, 2010.; Putignano et al., 1998), the DDD of all ASMs was calculated following the ATC index of the WHO Collaborating Centre for Drug Statistics Methodology (WHO, 2023).

The assessment session was always carried out between 4:00 pm and 8:00 pm to minimize hormonal circadian variations and, for patients, before the epilepsy surgery. This session was different for the three groups. For the EG of patients, a TSST protocol was administered after habituation to the clinical setting, followed by a neuropsychological evaluation. The TSST protocol included the collection of six saliva samples for cortisol determinations before the stressor (C1) and 15 (C2; immediately after the stressor finished), 30 (C3), 45 (C4), 60 (C5), and 75 minutes (C6) after the stress onset. The stress exposure lasted 15 minutes and details are described below. For the CG-H, only the TSST was administered to control stress response and the timing for saliva samples was similar to the EG group of patients. For the CG-E, only the neuropsychological evaluation was carried out to control for clinical epilepsy-related factors

and the effect of the evaluation. During this assessment, six saliva samples (from C1 to C6) were collected to measure cortisol secretion and accurately analyze the cortisol decline in the late afternoon and evening — the circadian trough (Lupien et al., 2005; Kirschbaum et al., 1989). Saliva samples were collected with a mean 15-minute interval between samples, although this interval could vary depending on the duration of tests. Memory assessment was performed between C1 and C6 samples, after habituation to the clinical setting.

The neuropsychological exploration was designed following the recommendations of the E-PILEPSY consortium (Vogt et al., 2017) and included the assessment of attention, executive function, memory, language, and motor function. From this evaluation, memory, state and trait anxiety, state mood, depression, and QOL tests were selected for the present study. No missing data were detected for any variable. State anxiety and mood were evaluated at the beginning and the end of the neuropsychological assessment, while trait anxiety, depression, and QOL were explored at the end of the assessment session.

2.3. Psychosocial stress

Participants of the EG and CG-H were challenged with the TSST (described in detail in Kirschbaum et al., 1993). The TSST mainly consists of a 5-minute preparation task, a 5-minute speech task, and a 5-minute mental arithmetic task in front of an audience. The audience was composed of two reviewers (a man and a woman) who were dressed in smocks. During the 15 minutes of the TSST, a video recording was simulated to enhance the evaluative threat. This stress protocol has been repeatedly shown to induce significant activation of the pituitary-adrenal axis, with 2- to 3-fold increases of free cortisol in healthy men (Kirschbaum et al., 1993).

2.4. Salivary cortisol

Saliva samples were collected using Salivettes (Sarstedt, Nümbrecht, Germany) for cortisol. Participants were instructed to keep the cotton swab in their mouths for two minutes. The samples were centrifuged at 3000 rpm for 15 min, resulting in a clear supernatant with low viscosity that was stored at −80 °C until analyses were performed in the Laboratory of Social Cognitive Neuroscience, Faculty of Psychology (Universitat de València). Salivary cortisol concentrations were determined in duplicate with the salivary cortisol enzyme-immunoassay kit from Salimetrics (Newmarket, UK). Assay sensitivity was <0.007 μg/dL. For each patient, all the samples were analyzed in the same trial. The criterion for measurement replication was

fixed as an 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.

2.5. Neuropsychological assessment

2.5.1. Memory

The Wechsler Memory Scale-Third Edition (WMS-III; Wechsler, 1997), in its Spanish version (Pereña et al., 2004) was used to assess verbal and visual memory. 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, and delayed visual memory), two general memory indices (immediate memory and delayed memory), as well as indices of auditory processes (i.e., single-attempt learning, learning slope, retention, and retrieval). These indices were expressed in age-adjusted scalar scores, with higher values indicating better memory functioning. Test-retest reliability of this instrument is 0.87 (Pereña et al., 2004).

2.5.2. State and trait mood

Mood and anxiety state. The Spanish version (López-Gómez et al., 2015) of the Positive and Negative Affect Schedule (PANAS; Watson et al., 1988) was used for measuring mood state. This is a self-reported questionnaire of 20 items, consisting of two subscales; one that measures positive affect, and another that assesses negative affect, each containing 10 items. A five-point Likert scale was used, in which 1 was 'very slightly or not at all' and 5 was 'extremely'. Cronbach's alpha for the Spanish adaptation of this test was 0.92 for Positive Affect Scale and 0.88 for Negative Affect Scale (López-Gómez et al., 2015). To measure state anxiety, the state anxiety scale was used (STAI-S; Spielberger et al., 1989), which evaluates the current state of anxiety. It consists of 20 items classified on a four-point scale, ranging from 0 ("hardly never") to 3 ("almost always"), with higher scores indicating higher anxiety. Cronbach's alpha of the Spanish adaptation of this inventory is 0.94 (Guillén Riquelme & Buela Casal, 2011).

Trait anxiety. This was assessed using the State–Trait Anxiety Inventory (STAI; (Spielberger, 1989). The trait anxiety scale (STAI-T) evaluates relatively stable aspects of

anxiety and it consists of 20 items rated on a four-point scale ranging from 0 (“hardly never”) to 3 (“almost always”), with higher scores indicating higher anxiety. Cronbach’s alpha of the Spanish version of this inventory is 0.90 (Guillén-Riquelme & Buela-Casal, 2011).

Depression. The Beck Depression Inventory-II (BDI-II; Beck et al., 1996) was used to assess depression with 21 items rated on a four-point scale, with higher scores indicating higher depression levels. Cronbach’s alpha of the Spanish adaptation is 0.89 (Sanz & García-Vera, 2009).

2.5.3. QOL

Quality of Life in Epilepsy Inventory (QOLIE-31; Cramer et al., 1998) in its Spanish version (Torres et al., 1999), was used to assess QOL. It includes 31 items distributed into seven scales: seizure worry; overall QOL; emotional well-being; energy; cognitive self-rating; medication effects; and social functioning. Scores for each subscale ranged from 0 to 100, with higher scores indicating better QOL (including seizure worry and medication effects, which were scored on an inverse scale). A QOL composite score was computed using a weighted average of subscales. Cronbach’s alpha of the Spanish adaptation of this inventory ranges from 0.55 to 0.92 (Torres et al., 1999).

2.6. Statistical analysis

Cortisol levels were log-transformed to ensure the normality of the data distribution, allowing for the application of parametric statistics. Greenhouse-Geisser adjustments for the degree of freedom were performed in all the repeated measures analysis. To estimate the magnitude of the response of cortisol, the area under the curve (AUC) was calculated by two formulas that are widely accepted (Pruessner et al., 2003): the area under the curve with respect to ground (AUC_g) and the area under the curve with respect to baseline or increase (AUC_i).

To test differences in cortisol levels depending on the group, repeated measure ANCOVAS with ‘moment’ as a within-participants factor (5 levels, C2 to C6) and ‘group’ as a between-participants factor (3 groups) was carried out, using C1 as a covariate to control possible between-individual variations in initial cortisol levels (Kirschbaum et al., 1990). To examine the cortisol levels evolution for each group, paired *t*-tests were performed separately. To explore the differences among groups in AUC_g and AUC_i, one-way ANOVAs were carried out. Bonferroni tests were employed as post hoc analyses. These analyses were repeated including

sex (in all cases) and side of seizure focus (for comparing epilepsy groups) as between-participants factors.

For demographic and clinical variables, independent t-tests were performed for the comparisons between groups of patients in the case of quantitative variables (i.e., age, educational level, epilepsy duration, age at epilepsy onset, seizures per month, total DDD, number of ASMs, and number of failed ASMs) and chi-square in the case of the categorial variables (i.e., sex, academic/employment insertion, marital status, household members, epilepsy type, lateralization of seizure onset, seizure type, and MRI findings). For neuropsychological variables, independent *t*-tests were also performed for the comparisons between the scores of both groups of patients. The scores of mood and anxiety states, evaluated before and after the evaluation, were contrasted using repeated measures ANOVAs with 'moment' as a within-participants factor (2 levels) and the 'group' as a between-participants factor (2 groups of patients). Changes in mood and anxiety states were calculated as post-evaluation scores minus pre-evaluation scores. Correlations between cortisol response and clinical and neuropsychological variables were carried out with Spearman correlations.

These analyses were performed using SPSS 28.0 and two-tailed tests with p set at 0.05 were considered significant.

3. Results

3.1. Preliminary analyses

The sample was composed of 147 participants distributed into three sex-balanced groups: the EG, composed of patients with epilepsy exposed to psychosocial stress (n = 38; 19 men and 19 women); the CG-E, a control group of patients with epilepsy who were not exposed to psychosocial stress (n = 50; 26 men and 24 women); and the CG-H, a second control group of healthy individuals who also were exposed to psychosocial stress (n = 59; 25 men and 34 women).

No significant differences were found in sex distribution or age between groups. The mean and standard deviation (SD) of the age of the groups were 38.50 ± 10.92 years for the EG, 39.38 ± 12.38 years for the CG-E, and 40.82 ± 8.55 years for the CG-H. No significant differences were found between patient groups in demographic or clinical variables (Table 1).

Table 1. Characteristics of both groups of patients (mean ± SD or n (%)).

	EG (*n*=38)	CG-E (*n*=50)	*p*
Sex			0.61
Women	19 (50.0%)	24 (48.0%)	
Men	19 (50.0%)	26 (52.0%)	
Educational level			0.84
Primary	16 (42.1%)	20 (40.0%)	
Secondary	10 (26.3%)	16 (32.0%)	
Higher education	12 (31.6%)	14 (28.0%)	
Academic/employment insertion			0.08
Yes	24 (63.2%)	22 (44.0%)	
No	14 (36.8%)	28 (56.0%)	
Marital status			0.49
Single	19 (50.0%)	21 (42.0%)	
Married	18 (47.4%)	25 (50.0%)	
Divorced	1 (2.6%)	4 (8.0%)	
Household members			0.57
Family	12 (31.6%)	16 (32.0%)	
Partner	22 (57.9%)	32 (64.0%)	
Flatmate	1 (2.6%)	0 (0%)	
Alone	3 (7.9%)	2 (4.0%)	
Epilepsy duration (years)	21.55 ± 13.96	23.38 ± 16.32	0.58
Age at epilepsy onset (years)	16.95 ± 12.01	15.99 ± 11.68	0.71
Epilepsy type			0.17
FLE[a]	3 (7.9%)	9 (18.0%)	
TLE[b]	35 (92.1%)	41 (82.0%)	
Lateralization of seizure onset			0.76
Left	17 (44.7%)	24 (48.0%)	
Right	21(56.3%)	26 (52.0%)	
Seizures per month	13.39 ± 36.67	17.27 ± 31.72	0.60
Seizure type			0.46
FAS[c]	0 (0.0%)	2 (4.0%)	
FIAS[d]	14 (36.8%)	21 (42.0%)	
FBTCS[e]	1 (2.6%)	0 (0.0%)	
FAS[c] + FIAS[d]	6 (15.8%)	10 (20.0%)	
FIAS[d] + FBTCS[e]	15 (39.5%)	13 (26.0%)	
FAS[c] + FIAS[d] + FBTCS[e]	2 (5.3%)	4 (8.0%)	
Total DDD[f]	3.43 ± 1.42	3.14 ± 1.25	0.32
Number of ASMs[g]	2.76 ± 0.94	2.80 ± 0.86	0.85
Number of failed ASMs[g]	6.71 ± 3.28	6.7 ± 3.68	0.98
MRI[h] findings			0.36
Hippocampal sclerosis	20 (52.6%)	16 (32.0%)	
Focal cortical dysplasia	3 (12.0%)	9 (18.0%)	
Tumour	3 (7.9%)	9 (18.0%)	
Heterotopia	1 (2.6%)	1 (2.0%)	
Cavernoma	3 (7.9%)	4 (8.0%)	
Non-specific pathology	8 (21.1%)	11 (22.0%)	

Note. [a]FLE: frontal lobe epilepsy; [b]TLE: temporal lobe epilepsy; [c]FAS: focal aware seizures; [d]FIAS: focal impaired awareness seizures; [e]FBTCS: focal to bilateral tonic-clonic seizures; [f] Total DDD: defined daily dose; [g]ASM: antiseizure medication; [h]MRI: magnetic resonance imaging.

3.2. Cortisol response to psychosocial stress

Significant differences among groups were found in cortisol levels before the stressor (C1) ($F_{(2,146)}$ = 14.61, $p < 0.0001$), with EG and CG-E showing higher cortisol levels than healthy controls ($p < 0.0001$ and $p < 0.002$, respectively). Thus, C1 will be a covariate to estimate cortisol response controlling baseline levels.

Significant effects of the 'moment*group' interaction were found on cortisol levels after stress (Figure 1) ($F_{(6.9,492.5)}$ = 5.05, $p < 0.0001$, $\eta^2 = 0.07$, P = 1.0), as well as significant effects of the 'moment' and the 'group' main factors ($F_{(3.4,492.5)}$ = 11.30, $p < 0.0001$, $\eta^2 = 0.07$, P = 1.0; and $F_{(1,143)}$ = 4.43, $p < 0.01$, $\eta^2 = 0.058$, P = 0.75, respectively). The EG showed an abolition of the stress response with lower cortisol levels than healthy participants in all moments, being significant only after 30 minutes (C3) of the stressor beginning ($p < 0.05$). Moreover, non-significant differences were found between both groups of patients, with and without stress. As expected, significant differences were found between the groups CG-E and CG-H, since this latter group was exposed to stress and showed higher cortisol levels than the patients immediately after the stressor (C2) ($p < 0.01$), and at 30 (C3), 45 (C4) and 60 (C5) minutes after the stressor onset ($p < 0.0001$, $p < 0.01$ and $p < 0.05$, respectively). No significant effects of sex or side of seizure focus were found when the analysis included these factors.

Examining the evolution of each group, the EG showed decreases in cortisol levels from baseline (C1) levels to after the stressor, which were significant at C4, C5, and C6 (for all, $p < 0.01$). No significant effects of sex or side of seizure focus were found in this group. The CG-E also showed decreases in cortisol levels from C1 to levels after the stressor, which were significant at C3, C4, C5, and C6 (for all, $p < 0.0001$), as is expected according to circadian rhythm. Both patterns of response strongly contrast with that shown by the CG-H group, which exhibited the expected cortisol response with significant increases in cortisol levels at C2 and C3 (for both $p < 0.0001$), and marginally C4 ($p < 0.06$), no significant changes at C5, and significant decreases at C6 (for all, $p < 0.05$).

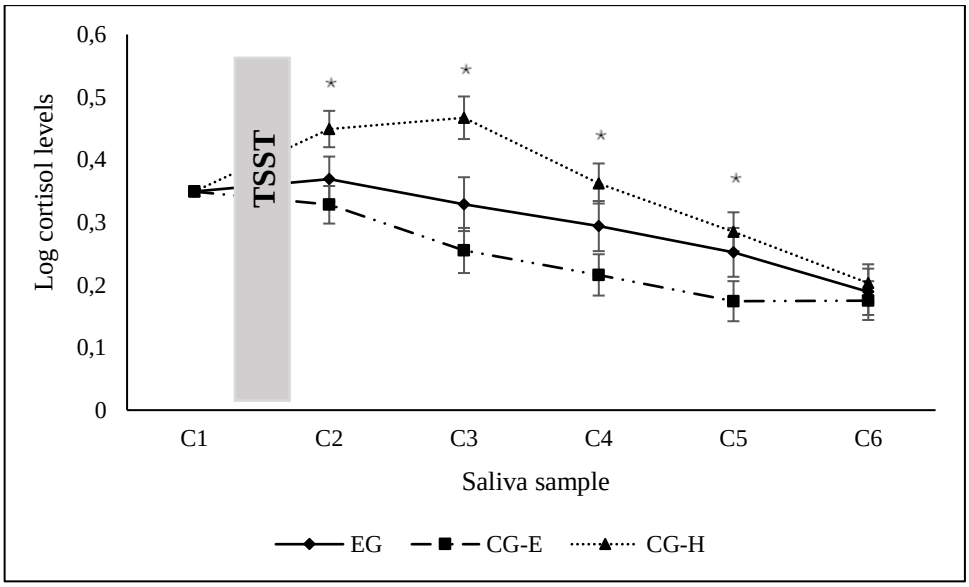

Figure 1. Cortisol levels (in logarithmic data) after exposure to a psychosocial stressor in the three groups with C1 as a covariate. *Note*. TSST: Trier Social Stress Test.

Both stress groups (EG and CG-H) present a high variability in the cortisol levels during the stressor. Considering the absolute criterion of increases of 1.5 nmol/L from baseline as indicative of stress response (Miller et al., 2013), only 6 patients of the EG were responders (15.8% of the group size), while 23 participants were responders in the group of healthy individuals (39% of the group size). When the relative criterion of 15.5% increases from baseline as indicative of stress response was considered (Miller et al., 2013), 14 patients of the EG were responders (36.8% of the group size), while 41 participants were responders in the group of healthy individuals (69.5 % of the group size).

Concerning the magnitude of the response (Figure 2), estimated as AUC (both AUC_g and AUC_i), significant effects were found on AUC_i ($F_{(2,146)} = 9.15$, $p < 0.0001$), but not on AUC_g. A greater response was found in the AUC_i of the CG-H during stress, which contrasts with the decreases in both groups of patients, with and without stress ($p < 0.001$ and $p < 0.003$, respectively).

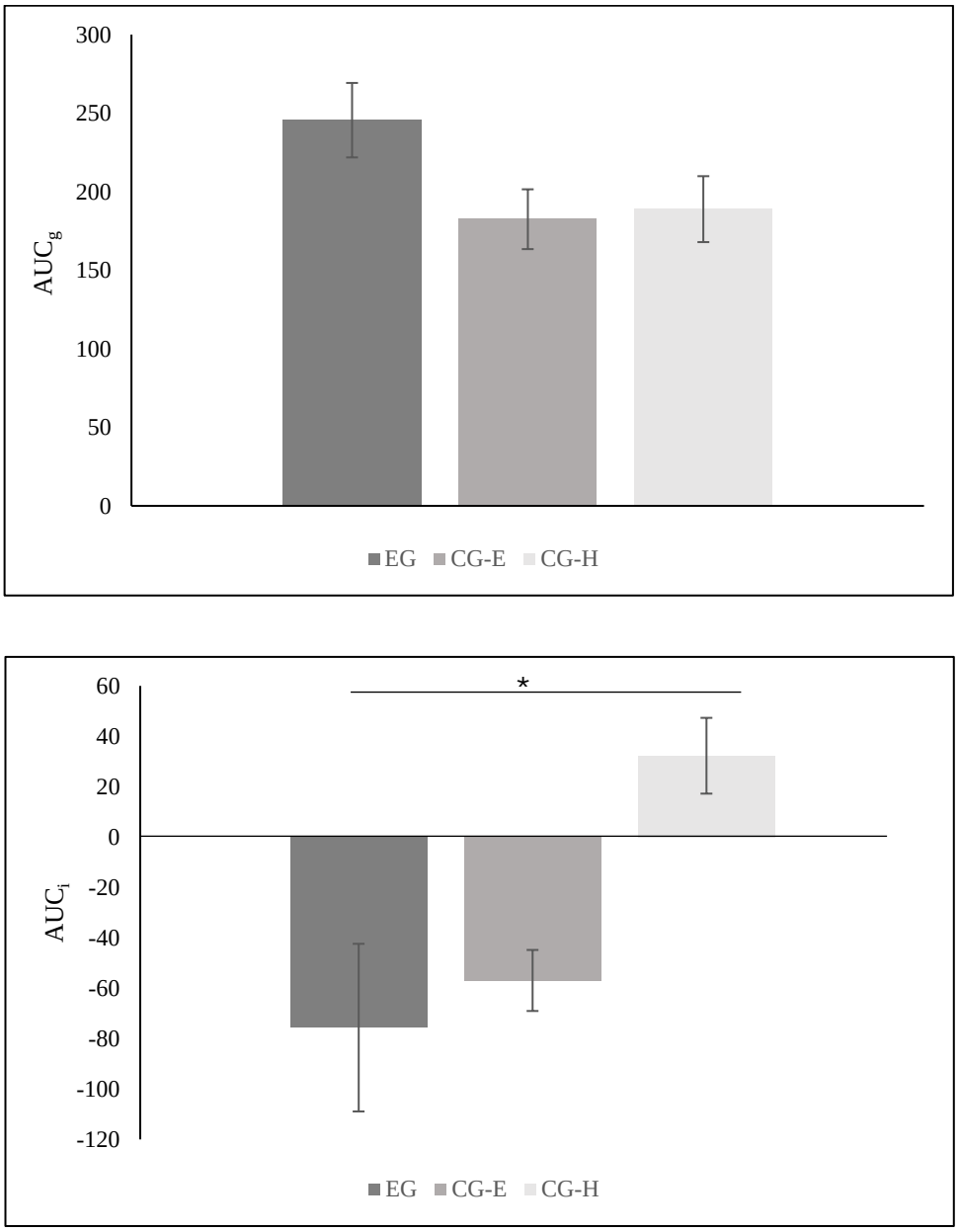

Figure 2. AUC_g and AUC_i for the three groups of participants

3.3. Cortisol response and its relationship with clinical and neuropsychological variables in patients with epilepsy

Before the stressor onset, C1 levels were positively related to epilepsy duration in the total sample (r = 0.37, p < 0.0001). After stress exposure, AUC_i was negatively related to epilepsy duration in the total sample (r = -0.38, p < 0.0001), so lower AUC_i was associated with more

years of suffering seizures. No other significant relationships were found with seizure frequency, age at epilepsy onset, number or DDD of ASMs, or AUC_g. By groups, a unique significant negative relationship was found between AUC_g and seizure frequency in the EG (r = -0.40, $p < 0.02$), not found in the CG-E.

The neuropsychological assessment included memory, mood and anxiety states, trait anxiety, depression, and QOL. No significant differences between groups were found in any of these variables, except for retrieval, with higher scores in the EG than in the CG-E. For mood state, a significant effect of 'moment' was found on positive mood ($F_{(1,86)} = 8.25$, $p < 0.01$, $\eta^2 = 0.09$, P = 0.81) and negative mood ($F_{(1,86)} = 16.42$, $p < 0.0001$, $\eta^2 = 0.16$, P = 0.98), in both cases with decreases after the evaluation respect to baseline scores in the total sample. No significant effects were found in state anxiety. Statistics of these variables for both patient groups are detailed in Table 2.

In the total sample, AUC_i was related to better emotional well-being ($r = 0.28$, $p < 0.01$), but also lower QOL related to medication effects ($r = -0.22$, $p < 0.04$), both subscales of QOL. No other relationships were found with neuropsychological variables or AUC_g. By groups, in the CG-E, AUC_i was positively associated with two subscales of the QOLIE-31, overall QOL and emotional well-being ($r = 0.29$, $p < 0.04$ and $r = 0.34$, $p < 0.02$, respectively), but also with changes in negative mood and state anxiety ($r = 0.28$, $p < 0.05$ and $r = 0.343$, $p < 0.04$, respectively). Significant correlations were not found with AUC_g in this group. By contrast, in the EG patients with stress, AUC_g was positively related to the retrieval of the information (r = 0.43, $p < 0.01$) and the scores on the overall QOL subscale ($r = 0.40$, $p < 0.01$). No significant correlations were found with AUC_i in this group.

In the EG group, only 6 patients were responders to the TSST attending to the absolute criteria, whereas 32 patients did not exhibit the typical stress response. Although this distribution leads to taking the results with caution, comparisons between responders and non-responders were carried out in clinical and neuropsychological variables. To check the criteria, responders showed higher AUC_g and AUC_i than the no responders ($t = 2.85$, $p < 0.01$ and t = 3.61, $p < 0.001$, respectively). They also had an older age at epilepsy onset than the non-responders, although this difference did not reach statistical significance ($t = 1.96$, $p < 0.06$). The responders also showed better performance in delayed auditory memory ($t = 2.10$, $p <$ 0.04), delayed auditory recognition ($t = 2.44$, $p < 0.02$), delayed memory ($t = 2.21$, $p < 0.03$), single-attempt learning ($t = 2.38$, $p < 0.02$) and nearly in immediate auditory memory (t =1.96,

$p < 0.06$) than the non-responders. Regarding negative affect and mood, responders showed lower trait anxiety than non-responders ($t = -2.05$, $p < 0.05$). Finally, concerning QOL, the responders also perceived a better QOL attending to the scores in the subscales of overall QOL and emotional well-being ($t = 3.99$, $p < 0.0001$ and $t = 3.12$, $p < 0.004$, respectively). Descriptive statistics of both groups are shown in Table 3.

Table 2. Memory, mood and anxiety states before and after the neuropsychological assessment, trait anxiety, depression, and QOL in the EG and CG-E of patients (mean ± SD).

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

Note. [a]WMS-III = Wechsler Memory Scale-III; [b]PANAS = Positive and Negative Affect Schedule; [c]STAI = State-Trait Anxiety Inventory; [d]BDI-II = Beck Depression Inventory-II; [e]QOLIE-31 = Quality of Life in Epilepsy Inventory; [f]QOL = quality of life.

Table 3. Descriptive statistics of responders (n = 6) and non-responders (n = 32) of the EG group.

	Responders (*n* = 6)	Non responders (*n* = 32)	*p*
AUC_g	388.43 ± 145.94	218.74 ± 131.81	0.01*
AUC_i	165.10 ± 125.10	-120.75 ± 185.32	<0.01*
Age	38.17 ± 15.41	38.56 ± 10.20	0.93
Epilepsy duration (years)	12.67 ± 9.99	23.21 ± 14.08	0.09
Age at epilepsy onset (years)	25.5 ± 14.43	15.34 ± 11.11	0.06
Seizures per month	4.61 ± 4.41	15.08 ± 39.90	0.53
Number of ASMs[a]	2.67 ± 1.36	2.78 ± 0.87	0.79
Number of failed ASMs[a]	6.33 ± 3.61	6.78 ± 3.27	0.76
Total DDD[b]	2.85 ± 1.96	3.53 ± 1.31	0.29
WMS-III[c] (scalar scores)			
Immediate auditory memory	20.0 ± 5.58	15.22 ± 5.46	0.06
Delayed auditory memory	20.50 ± 5.89	15.09 ± 5.76	0.04*
Delayed auditory recognition	11.50 ± 2.16	8.16 ± 3.20	0.02*
Immediate visual memory	15.67 ± 3.88	14.59 ± 6.04	0.68
Delayed visual memory	14.67 ± 5.12	14.38 ± 5.58	0.91
Immediate memory	35.67 ± 8.89	29.38 ± 10.22	0.17
Delayed memory	51.17 ± 19.97	37.47 ± 12.72	0.03*
Single-attempt learning	21.83 ± 4.07	17.28 ± 4.33	0.02*
Learning slope	22.50 ± 6.68	20.41 ± 5.13	0.39
Retention	20.83 ± 3.92	16.88 ± 5.79	0.12
Retrieval	1.42 ± 2.15	0.69 ± 1.99	0.42
PANAS[d]			
Positive mood change	-0.33 ± 3.88	-2.87 ± 8.11	0.4
Negative mood change	-5.50 ± 2.88	-2.12 ± 7.89	0.31
STAI[e]			
State anxiety change	-2.50 ± 3.33	-2.21 ± 9.51	0.94
Trait anxiety	18.50 ± 10.07	27.47 ± 9.80	0.05*
Trait anxiety (PC)	44.0 ± 32.70	69.31 ± 26.37	0.05*
BDI-II[f]	7.0 ± 7.48	12.28 ± 10.48	0.25
QOLIE-31[g]			
Seizure worry	56.50 ± 15.37	45.59 ± 25.31	0.32
Overall QOL[h]	73.83 ± 3.76	62.0 ± 14.36	<0.01*
Emotional well-being	84.0 ± 9.46	59.63 ± 18.57	<0.01*
Energy	68.50 ± 12.62	59.22 ± 16.61	0.20
Cognition self-rating	53.33 ± 21.76	48.69 ± 25.39	0.68
Medication effects	48.33 ± 30.80	44.81 ± 32.80	0.81
Social functioning	48.67 ± 13.98	49.41 ± 26.71	0.95
QOL composite score	61.67 ± 11.03	52.91 ± 16.60	0.23

Note. [a]ASM: antiseizure medication; [b] Total DDD: defined daily dose; [c]WMS-III = Wechsler Memory Scale-III; [d]PANAS = Positive and Negative Affect Schedule; [e]STAI = State-Trait Anxiety Inventory; [f]BDI-II = Beck Depression Inventory-II; [g]QOLIE-31 = Quality of Life in Epilepsy Inventory; [h]QOL = quality of life.

The relative criteria of 15.5% increase with respect to baseline, less restrictive, resulted in 14 responders and 24 non-responders. In this case, the AUC_i was higher in responders than in non-responders (t = 4.20, $p < 0.0001$), but no differences were found in the AUC_g. The significant differences in clinical or neuropsychological variables were restricted to increases in positive mood during evaluation which contrasts with the decreases in the non-responders (t = 2.08, $p < 0.05$). No other differences were found between these two groups of patients.

4. Discussion

The results of the present study suggest the abolition of stress response to a standardized psychosocial stressor in patients with epilepsy. Additionally, the reactivity to the stressor is related to memory performance (i.e., retrieval of the information) and certain aspects of the QOL in patients.

Considering our data, cortisol levels decreased in patients with epilepsy after a psychosocial stressor, which has demonstrated a well-known and powerful stress response in humans (Kirschbaum et al., 1993). In fact, similar cortisol levels have been found in patients exposed to stressful stimuli than in patients without stressor administration, both groups exhibiting a cortisol profile of progressive decreases, typical of the circadian rhythms of cortisol in the afternoon. The buffered cortisol response of the experimental group strongly contrasts with the typical response to the TSST found in the healthy controls, especially evident at 15 and 30 minutes after the stressor onset, and widely documented in previous studies (for review, see Allen et al., 2017). To our knowledge, only two studies coped with the psychosocial stress response in patients with left TLE epilepsy compared with healthy controls (Allendorfer et al., 2014; Goodman et al., 2019). In those studies, although patients showed higher levels than healthy controls in all moments, before the stressor too, cortisol levels after the stress never were higher than before. However, these results were interpreted by the authors as a higher response in patients than in controls, based on the AUC_g and an index of recovery of the cortisol response which is calculated with the baseline after the stressor (Allendorfer et al., 2014; Goodman et al., 2019). In the present study, a progressive decrease in cortisol levels was also found compared to the baseline, located before the stress. From this view, our results are coherent with those found in adults by Allendorfer et al. (2014) and Goodman et al. (2019), but also with those found in children and adolescents with stress-triggered seizures, after exposure to the TSST (van Campen et al., 2015).

In the present study, AUC_g and AUC_i were calculated considering the baseline before the stress exposure (Pruessner et al., 2003). However, the AUC_g did not show significant differences among groups, and the AUC_i of the EG group showed pronounced decreases, similar to those found in patients without TSST exposure, which contrasts with the increases of the healthy controls. Both indices of the stress response can be associated with different aspects since the AUC_i has been related to perceived stress as an indicator of the sensitivity of the system to produce changes over time, while AUC_g has been associated with physical complaints and total hormonal output (Pruessner et al., 2003). In this line of rationale, our results showed a negative relationship between AUC_g and seizure frequency in the EG, in agreement with the results found by Allendorfer et al. (2014) about patients with poor seizure control.

Several factors could be behind the disparity of the results. First, the patients in the study carried out by Allendorfer et al. (2014) and Goodman et al. (2019) were patients with left TLE. Although we included patients with a hypothesis of TLE when the presurgical assessment was performed, this comprehensive evaluation showed that 34 patients had TLE, three had frontal lobe epilepsy, and the remaining one had frontotemporal epilepsy. Even though the hemisphere lateralization of the stress response cannot be discarded (Ocklenburg et al., 2016), the lack of effects of the side of seizure focus leads us to think that lateralization is not a plausible reason for the discrepancies in the results. It is possible that the four patients with main frontal affectation could overlap effects. Second, only 10 of the patients in Allerdorfer's study had uncontrolled epilepsy and 13 were seizure-free for three months before the study. In the present study, the sample was composed of drug-resistant epilepsy patients who were suffering seizures from a mean higher than 20 years (21.55 ± 2.27 and 23.39 ± 2.31 for EG and CG-E, respectively) with more than 13 seizures per month (13.39 ± 6.03 and 17.27 ± 4.49 for EG and CG-E, respectively). This setting could favor a severe state of chronic stress in these patients. To support this, higher levels of cortisol have been found in both groups of patients than in healthy controls, positively associated with epilepsy duration. This hypercortisolism that characterizes chronic stress regimens may be related to the loss of glucocorticoid feedback control of the hypothalamic-pituitary-adrenal (HPA) axis, which could be associated with decreased glucocorticoid receptors in regions such as the paraventricular nuclei, hippocampus, and prefrontal cortex (Herman et al., 2016). Interestingly, mounting evidence supports the fact that exaggerated as well as blunted stress reactivity of the HPA axis are both related to altered glucocorticoid signaling (Agorastos & Chrousos, 2022). Thus, hypercortisolism could favor a buffered response to acute stress due to a physiological ceiling or starvation of the stress system.

Third, methodological issues for the calculation of responsiveness are different. In the present study, the interpretation of the response has included the consideration of pre-stress cortisol levels as a baseline and the calculation of Pruessner et al. (2003) for the areas under the curve. Finally, the different clinical contexts of the samples of this study and that of Allendorfer's study lead us to think that other factors, such as ASMs influence, could alter the HPA responsiveness to stress differently.

The blunted cortisol response to acute stress has also been described in other samples exposed to chronically stressed scenarios. For example, previous studies from our laboratory showed that family caregivers of patients with long-term diseases exhibited a buffered cortisol response to psychosocial stress (De Andrés-García et al., 2013). This pattern of response has also been observed in patients with panic or post-traumatic stress disorder (von Majewski et al., 2023; Wichmann et al., 2017). In the present study, decreases in the mood state were found in patients with epilepsy. Unfortunately, no data on mood in healthy controls were available to check if these mood changes explain, at least in part, the buffered response.

Despite these results, cortisol levels are highly variable in patients with epilepsy. The classification between responders and non-responders is commonly accepted in healthy individuals, using absolute and relative criteria to determine whether a participant exhibits or not a cortisol response to TSST (Miller et al., 2013). From a conservative viewpoint, the absolute criterion which states an increase of at least 1.5 nmol/L from baseline revealed that only 15.8% of the EG group of patients were responders. This result contrasts with the percentage of responders in the healthy group (39% of the group size) and agrees with the blunted cortisol response in epilepsy patients.

The stress response in patients with epilepsy could have implications for cognitive performance and perceived QOL. In the total sample, AUC_i was related to better emotional well-being, although also with lower QOL related to medication effects. More interestingly, in the CG-E, AUC_i was positively associated with the overall QOL and emotional well-being, but also with changes in negative mood and state anxiety. Significant correlations were not found with AUC_g in this group. Additionally, although results must be taken with caution, the six responders to TSST of the EG group suffered late epilepsy showing better memory performance, higher QOL, and lower trait anxiety than the non-responders. If these results could be replicated, they would suggest that the preservation of the cortisol response to acute stress, from an adaptive view, is associated with other adaptive processes in neurological patients such

as memory, emotional well-being, and QOL. In fact, previous studies in the general population have shown that a buffered cortisol response to stress could reflect a defective HPA-axis response that is accompanied by poorer memory performance (Almela et al., 2014), and that cortisol elevations in response to acute stress had mood-protective effects (Abercrombie et al., 2023). This highlights the adaptative function of cortisol when facing a threat (Dickerson & Kemeny, 2004).

This study has some limitations. First, the study has a cross-sectional design, so it is not possible to establish causal relationships. Longitudinal studies are needed to shed more light on the relationships among these variables. Second, the neuropsychological evaluation could have acted as a stressor for the patients with epilepsy, although it would not be expected that this aspect would differentially influence the two groups of patients with epilepsy (with and without stress), since both were subjected to the same neuropsychological evaluation. Third, no mood data were available for healthy controls, so future studies should include this variable to check if mood changes explain, at least in part, the buffered response of patients with epilepsy compared to healthy controls. Finally, although no differences were found in the ASMs load (neither in terms of the number of drugs nor in terms of DDD), certain ASMs could interact with cortisol levels, as could be suggested by the negative correlation between cortisol and QOL related to medication effects. Thus, future studies should consider the possible effects of pharmacological treatment in more detail.

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

CHAPTER 8

Study 5

The Development and Validation of the Epilepsy Perceived Stress Inventory for Adults (EPSI-A): a Pilot Study[1]

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1. Introduction

Epilepsy is a disease characterized by a predisposition and recurrence of seizures that comprehensively affect the individual (Fisher et al., 2014). About one-third of this population has drug-resistant epilepsy and in these cases antiseizure medications (ASMs) are ineffective for controlling seizures (Sultana et al., 2021). 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 (Cano-López & González-Bono, 2019) with seizures as acute stressors (Cano-López & González-Bono, 2019; van Campen et al., 2014).

Chronic stress has been widely described in the scientific literature as an important factor related to human disease (Cohen et al., 2007). Among definitions of stress, Cohen et al. (1997) described it as 'a process in which environmental demands tax or exceed the adaptive capacity of an organism, resulting in psychological and biological changes that may place persons at risk of disease'. From a more restricted concept, Koolhaas et al. (2011) stated that stress is limited to situations that are unpredictable and uncontrollable (as could be chronic exposition to seizures). Criteria such as duration and frequency of exposure to the stressor differentiate between acute and chronic stress. Therefore, it is not surprising that a bidirectional relationship between stress and epilepsy has been proposed (Cano-López & González-Bono, 2019).

On the one hand, stress has a key role in epileptogenesis (Friedman et al., 2011; van Campen et al., 2014) and is implicated in an increased hyperexcitability of neural circuits that could lead to seizure generation (Gunn & Baram, 2017; Maguire & Salpekar, 2013). Thus, as expected, perceived stress is considered one of the most common seizure precipitants (Lang et al., 2018). Supporting this idea, it has been found that psychological stress is positively associated with seizure frequency (Haut et al., 2007; Jhaveri et al., 2023; Thapar et al., 2009). Furthermore, levels of perceived stress seem to be higher in drug-resistant epilepsy patients than in controlled epilepsy patients (Moon et al., 2016), and also higher than in people with a history of other chronic diseases such as asthma, high blood pressure, or even cancer (Layne Moore et al., 2009).

On the other hand, epilepsy and seizures can influence the activation of the hypothalamic-pituitary-adrenal (HPA) axis that increases secretion of the corticotropin-releasing factor by the hypothalamus and, in turn, triggers the release of corticotropin in the anterior pituitary and the production of cortisol as an outcome of stress response (Charmandari et al., 2005; Galimberti et al., 2005; Maguire & Salpekar, 2013). A systematic review pointed out that in 45% of the

studies explored, people with epilepsy had higher basal cortisol levels than healthy people (Cano-López & González-Bono, 2019). 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 since cortisol levels can increase by 50-75% in the 30 minutes after awakening (Cano-López & González-Bono, 2019; Pruessner et al., 1997).

There is a lack of measures designed to quantify perceived stress in epilepsy. As far as we know, only Snyder (1993) 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 (Moon et al., 2016; Novakova et al., 2017; Thapar et al., 2009). 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 (Ficker, 2000; Mahler et al., 2018). This is in line with the restrictive definition offered by Koolhaas et al. (2011), which qualifies that stress should be limited to uncontrollable and unpredictable life-threatening experiences. Therefore, the development of a questionnaire to quantify the effects of epilepsy-related factors on stress could be useful. For these reasons, this study develops the Epilepsy Perceived Stress Inventory for Adults (EPSI-A), a self-report questionnaire designed to measure perceived stress in adult patients with drug-resistant epilepsy, and to prove its validation 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 (von Elm et al., 2007). 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 (Scheffer et al., 2017). 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 (Vogt et al., 2017). 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 analyse the cortisol decline in the evening (Kirschbaum & Hellhammer, 1989; Lupien et al., 2005), 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 20 minutes, 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; Spielberger, 1989) 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 (Guillén-Riquelme and Buela-Casal, 2011).

The Beck Depression Inventory-II (BDI-II; Beck et al., 1996) 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 (Sanz & García-Vera, 2009).

2.3.2. QOL

QOL was examined using the Quality of Life in Epilepsy Inventory (QOLIE-31; Cramer et al., 1998), in its Spanish version (Torres et al., 1999). 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 (Torres et al., 1999).

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 4ºC (Chojnowska et al., 2021). 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 minutes 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 (Pruessner et al., 2003). These two formulas provide information on the variation in cortisol levels. Particularly, the AUC_g is a variable related to 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 (Pruessner et al., 2003).

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 (Streiner & Norman, 1995). 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 (Krijnen, 1996). Furthermore, theorizing that our factors would be correlated (Child, 2006), an oblique rotation was used (Jennrich & Sampson, 1966). 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 (Kaiser, 1960). For factor adequacy, considering the number of participants in the study, pattern coefficients equal to or greater than 0.34 were considered salient (Norman & Streiner, 2014). 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 (Costello & Osborne, 2019) and with differences between these loadings of less than 0.1 (Çokluk et al., 2010). 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) (Zumbo et al., 2007). 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).

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.

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%)

Table 1. Continued.

	Mean ± *SD* or n (%)
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
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.

3.2. Conceptual analysis and item selection

Items were selected based on previous literature (e.g., Cano-López & González-Bono, 2019; Koolhaas et al., 2011) and tests that measure related concepts (e.g., Beck et al., 1996; Cramer et al., 1998; Spielberger, 1989). Furthermore, testimonials from people with epilepsy collected in semi-structured interviews and mutual-aid groups were considered, together with the experience of a panel of experts.

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 is shown in Appendix 1.

Items were initially created to have representative data about topics that were theorized to be related to stress in epilepsy, such as epilepsy concerns, controllability of the disease, seizure predictability, frequency, epilepsy severity, disease attribution (differentiating between internal and external attribution), and disease consequences. Nevertheless, no factors were theorized a priori.

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 is shown in Table 2.

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

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.

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 to 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 (2019) and Çokluk et al. (2010) 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 (Appendix 2).

Based on the content of each factor of the last EFA, these factors were termed: 1) *epilepsy concerns* (5 items); 2) *impact on daily performance* (4 items); 3) *social consequences* (3 items); and 4) *epilepsy severity* (3 items). 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.

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			
EPSI-A 2	0.86			
EPSI-A 3	0.60			
EPSI-A 4	0.60			
EPSI-A 5	0.60			
EPSI-A 10				0.67
EPSI-A 11		0.51		
EPSI-A 19				0.38
EPSI-A 21				0.44
EPSI-A 22		0.60		
EPSI-A 24			0.88	
EPSI-A 25			0.83	
EPSI-A 26			0.54	
EPSI-A 27		0.67		
EPSI-A 28		0.94		
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*.

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 (cs = -0.60) and distribution was platykurtic (ck = -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.

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

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

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

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 between this

factor and the current number of ASMs ($r(236) = 0.183$, $p = 0.005$) was found. 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 ($r = 0.277$, $p < 0.001$), and negatively associated with the age at epilepsy onset ($r(236) = -0.182$, $p = 0.005$) and the C7 measure of cortisol ($r(125) = -0.199$, $p = 0.026$).

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 ($r(236) = -0.181$, $p = 0.005$). Furthermore, this factor was negatively 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).

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 ($r(236) = -0.418$, $p < 0.001$). No relationships for this factor with clinical variables were found. However, this factor was negatively 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 ($r(125) = -0.180$, $p = 0.045$).

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 ($r(236) = 0.279$, $p < 0.001$), younger age at epilepsy onset ($r(236) = -0.170$, $p = 0.009$), and lower cortisol levels in the C2 sample ($r(125) = -0.181$, $p = 0.044$).

4. Discussion

The EPSI-A is a self-report instrument developed to assess perceived stress in people with epilepsy. It consists of 15 items organized in 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), as well as with clinical variables and cortisol secretion. From an overall view, higher scores on the EPSI-A were related to increased anxious and depressive symptoms, poorer QOL, and greater epilepsy severity.

Temkin and Davis (1984) 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 (Fisher et al., 2014).

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 ≥ 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 (Janssens et al., 2008), especially for initial developments of instruments (Hair, 2010; Nunnally & Bernstein, 1994). 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 (Cramer et al., 1996, 1999; Torres et al., 1999).

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. Surprisingly, although the *epilepsy concerns* factor was associated with the current

number of ASMs, *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 (Tedrus et al., 2020) with resilient patients showing a higher QOL (Catalán-Aguilar et al., 2023; Ring et al., 2016). 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. These variables have been related on several occasions to measures frequently used to evaluate perceived stress. A higher number of ASMs was associated with higher anxiety (Zhong et al., 2021), higher depressive symptoms (Tombini et al., 2020), and poorer QOL (Alexander et al., 2018; Lozano-García et al., 2021; Moran et al., 2020; Strzelczyk et al., 2023). 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 (Szaflarski et al., 2006).

These variables (i.e., the number of previous ASMs, the number of current ASMs, and the age at epilepsy onset) could be considered as indicators of epilepsy refractoriness, suggesting that the more refractory the epilepsy, the greater the impact on activities of daily life and interpersonal relationships. Baker et al. (1997) 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 related to social support (Karakaş et al., 2022), which is positively associated with perceived epilepsy control (Amir et al., 1999). Epilepsy refractoriness variables can then be associated with social factors, which in turn can be correlated with emotional variables. For example, unemployment or a driving ban, which are among the constraints that most concern this population (Elsharkawy et al., 2009; Fisher et al., 2000), have been proven to impact anxiety and QOL (Cano-López et al., 2023; Catalán-Aguilar et al., 2022; Tombini et al., 2020). Therefore, future studies should explore if 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 to salivary cortisol, which is considered one of the most important biomarkers of stress (Hellhammer et al., 2009). As previous literature suggests (Allendorfer et

al., 2014; Marek et al., 2010), and compared to data provided by the CIRCORT database (Miller et al., 2016), patients with epilepsy in our sample showed a higher mean cortisol level 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 (Hill et al., 2011; Ostrowska et al., 1988; Tuveri et al., 2008) or even no differences (Bakvis et al., 2009; Galli et al., 1996). 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 (van Campen et al., 2016), the type and dose of ASMs (Johannessen & Landmark, 2010; Putignano et al., 1998) or the type and lateralization of epilepsy (Cano-López et al., 2019; Luef & Rauchenzauner, 2009).

Despite the hypercortisolism in our sample, seven of the nine cortisol measures collected correlated negatively with some EPSI-A scale. In this line, Fries et al. (2005) demonstrated that 20-25% of patients with different stress-related disorders may develop hypocortisolism after prolonged periods of stress together with HPA axis hyperactivity, and this decrease in cortisol levels may be a mechanism associated with enhanced stress sensitivity (i.e., greater stress perception). This HPA axis adjustment may act as a protective factor for this vulnerable population, lowering levels to avoid harmful effects through mechanisms (such as the down-regulation of specific receptors at different levels of the axis, reduced biosynthesis or depletion of cortisol, and increased negative feedback sensitivity to glucocorticoids) (Fries et al., 2005). Therefore, considering the negative relationships found between the EPSI-A scale and cortisol levels, our results suggest that those patients who are more vulnerable to stress are those who show lower cortisol levels. 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.

More particularly, the first four cortisol measures were negatively related to the *social consequences* factor of the EPSI-A. Previous literature has suggested that emotions are responsible for mediating the relationship between stress perception and hormonal response (Miller et al., 2007). It has been shown that cortisol levels and shame are positively related in acutely stressful situations (Dickerson & Kemeny, 2004; Gruenewald et al., 2004). However, in chronically stressed populations, such as patients with post-traumatic stress disorder, an inverse relationship has been found, with shame being related to hypocortisolism (Mason et al., 2001). Although this remains speculative, our results suggest that patients with elevated levels

of perceived stress on this factor are likely to have more difficulties in interpersonal relationships, probably influenced by poorer social skills and greater shyness. Therefore, considering that patients with epilepsy suffer from chronic stress, the embarrassment of social interaction could be partly responsible for this relationship, and this situation would not be maintained during the rest of the assessment due to the adaptation to the evaluator. This would support the suggestion by Miller et al. (2007) that shame may be a key factor in mediating perceived stress and cortisol levels. However, future studies should test whether patients with difficulties in social skills score higher on this scale.

Additionally, the last three cortisol measures and AUC_g were negatively associated with the *epilepsy severity* factor of the EPSI-A. Increased severity and uncontrollability of the stressor during prolonged periods have been associated with a decrease in the HPA axis activity (Miller et al., 2007). Therefore, higher epilepsy severity could be related to lower levels of cortisol. Nevertheless, these relationships were found at the end of the assessment. We consider that people with more severe epilepsy could be at greater risk of having fatigue symptoms, and fatigue has been related to hypocortisolism (Brooks & Carter, 2013; Roberts et al., 2010). In support of this idea, epilepsy, as well as some stress-related disorders such as chronic fatigue syndrome or post-traumatic disorder, have some symptoms considered in the hypocortisolism symptom triad (i.e., stress sensitivity, pain, and fatigue) (Heim et al., 2000). Furthermore, higher scores in this factor were related to lower total cortisol output. Patients with chronic fatigue have also shown lower total cortisol production than healthy people (Herane-Vives et al., 2020). Thus, patients with higher perceived stress related to the epilepsy severity could be more vulnerable to fatigue effects and decreases in cortisol levels.

One fact that should be mentioned, given the increased recognition by the International League Against Epilepsy (ILAE) (Scheffer et al., 2017) 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. (2016) 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 (Kwon & Park, 2014; Pham et al., 2017). 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, 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 influence the negative relationship found between perceived stress and hormonal levels. Therefore, having a larger sample and a control group may help us understand the nature of this relationship. Fourth, 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 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 (Helmstaedter & Witt, 2017), so inventories that imply low cognitive load are more appropriate. Secondly, the brevity of the test. Its speed of application enables its use in various contexts (e.g., consultations and waiting rooms) and provides benefits in terms of efficiency. 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 and finally, the use of hormone levels. The possibility of having a correlation with a stress biomarker might add support to the data. 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.

CHAPTER 9

General discussion, limitations and future directions

1. General discussion

As a whole, the main findings of this Thesis highlight that epilepsy can be studied under the stress framework. Considering the SOR model, stressors, individual modulators, and stress response can provide a useful frame to study epilepsy from a more integrative view of the patient. With this approach, the main results will be discussed.

1.1. Stressors in epilepsy and their impact on patients' life

The first aim of this Thesis was to examine the association of a potential social stressor commonly reported by patients with epilepsy (i.e., unemployment) considering other individual variables such as cognitive performance, perceived social support, negative affectivity, and QOL, and clinical variables such as seizure frequency. This aim was addressed in Study 1 and was composed of two specific aims.

Concerning the first of them, the purpose was to determine whether patients with academic/employment insertion differ in depression, anxiety, executive function performance, social support, and QOL from those without insertion. Our results partially agree with hypothesis 1, which stated that patients with academic/employment insertion would show better executive functioning than those without insertion. Although a tendency for higher scores in the group with insertion was shown, no significant differences in executive performance were observed between patients with and without academic/employment insertion. One possible reason could be the cognitive impairment related to epilepsy duration (Gavrilovic et al., 2019). Despite both groups had an onset of epilepsy at similar ages, the group with insertion was younger, suffering epilepsy during a shorter period.

Interestingly, this result reached statistical significance when employment insertion was considered separately from academic insertion. Performance in executive functions has been positively linked to work behavior in other chronically stressed populations (McGurk & Meltzer, 2000). Interestingly, a positive relationship has also been found between executive performance and job complexity in chronically stressed populations (i.e., severe mental disorders) among patients without access to adapted jobs, but not among those with adapted positions (McGurk & Mueser, 2003). Although it may seem speculative, considering these results and given that no significant differences were found between those patients with academic insertion — in which context is more common to find compensatory strategies adapted to the idiosyncrasy of the student —, it is suggested that the dependence of executive performance may not be so much

related to the insertion itself, but to the lack of adequacy of the positions to the patient's needs. Therefore, job adaptations according to the patient's particularities may act as a buffer against the impact of stress in these contexts. Future studies should assess this issue deeply.

Hypothesis 2 was confirmed, which stated that academic/employment insertion would act as a source of social support, as a protective factor against negative affectivity, and as an enhancer of QOL. Patients with TLE with academic/employment insertion showed significantly lower anxiety, higher social support, and better QOL than those without insertion. However, it should be noted that no differences were found in depressive symptomatology and seizure frequency. To our knowledge, no other studies have explored the effect of academic insertion in patients with epilepsy on these variables. Conversely, employment has been more studied, and is related to reduced anxiety and depression, poor social support, and high QOL in patients with epilepsy (Azuma & Akechi, 2014; Mensah et al., 2007; Peterson et al., 2014; Wo et al., 2016). Interestingly, patients with insertion showed higher QOL related to social functioning than those without insertion, which suggests that employment could facilitate coping with the disease through increased social support (McCagh et al., 2009). These results highlight the effect that social insertion may have on the overall impact on the individual, supporting the conceptualization of problems in academic/employment worlds or poor social support as potential stressors in patients with epilepsy.

Regarding the second specific aim, it was focused on exploring the direct association between academic/employment insertion and QOL, as well as its indirect relationship through negative affectivity, executive functioning, and social support. In this regard, it was hypothesized that academic and/or employment insertion would have a direct effect on QOL, but it would be also indirectly associated with QOL through negative affectivity, social support, and cognitive performance (hypothesis 3 of the present Thesis). Our data partially agree with this, since the mediation model showed no significant direct effects, but revealed an indirect effect of academic/employment insertion on QOL. More specifically, results showed that academic/employment insertion was related to higher social support, which was associated with lower anxiety, and this was correlated to better QOL. Furthermore, although executive functioning did not fit this model, it was related to better QOL. These results highlight the complexity and heterogeneity of the networks created through social insertion, providing a new model that allows a comprehensive understanding of QOL in patients with TLE.

In summary, it can be concluded from these results that academic and/or employment inactivity can be considered a stress source in patients with drug-resistant epilepsy and that, to deeply understand their impact, different areas of the individual must be considered. Previous literature has already supported the consideration of difficulties related to the labor market as a source of stress for these patients. Temkin & Davis (1984) stated that the only stressor that was able to predict the occurrence of seizures was attendance at work or school. In the same line, Saengsuwan et al. (2015) found that the main source of stress was work problems (reported by 40% of patients), followed by economic difficulties (34%). These two factors can be considered the result of the same problem (i.e., unemployment), since they are closely related. Considering this, a study conducted by McCann et al. (2021) showed that financial difficulties and food shortages were the events reported as most stressful. Interestingly, difficulties in accessing pharmacological treatment were also considered highly stressful. This exposes the problem of patients living in low-income countries or without public health care. In these contexts, a feedback loop is created where unemployed patients cannot afford the cost of ASMs. This results in inadequate treatment, leading to the worsening of the disease and increased disability, further reducing their capability to work and consequently diminishing their economic income (McCann et al., 2021).

Employment is also a source of social support, expanding networks and increasing the available resources to the individual. In this sense, social support can be contemplated as a protective factor against stress. Although no studies have addressed social support within a framework of stress in epilepsy, some self-reported works have informed about stress sources related to this variable. Haut et al. (2003) observed that family arguments and the loss of a close person were the most self-reported stressors. Interestingly, this last event (i.e., loss of a loved person) was also reported as a stressor by more than half of the patients (54%) in the study carried out by Gélisse et al. (2015), followed by 32% who reported having ended a relationship with someone close. These events predicted seizure occurrence, supporting the need to consider social stress within clinical practice in epilepsy (Gélisse et al., 2015; Haut et al., 2003).

Another factor recognized as a stressor in epilepsy is the occurrence of epileptic seizures. For this reason, seizure frequency was examined during the rest of the studies as a characteristic of the stressor, observing differences between experimental groups or covarying its effect to avoid interference with other stressors. As discussed in previous chapters, seizures are unpredictable, uncontrollable, and health-threatening events (Cano-López & González-Bono,

2019). In addition, seizures entail a great burden for patients, causing challenges to their autonomy (England et al., 2012). Previous literature supports the conceptualization of seizures as acute stressors, showing a positive correlation between the presence of seizures and the levels of perceived stress (Goodman et al., 2019; Haut et al., 2007) and cortisol levels (Bazil et al., 2000; Zhang & Liu, 2008), which is considered a biomarker of stress. The recurrence and maintenance of seizures may promote the chronicity of stress in these patients, as occurs in drug-resistant epilepsy. Hence, epilepsy duration has been considered as an indicator of the chronicity of the stressor in the present Thesis, exploring its characteristics in the studies. All this could explain, at least partially, that patients with epilepsy have higher levels of perceived stress than healthy people (Gargiulo et al., 2022; Moon et al., 2016), but also than patients with well-controlled epilepsy (Aishwarya et al., 2023). Furthermore, patients with epilepsy have hypercortisolemia compared to the general population (Allendorfer et al., 2014; Marek et al., 2010), even controlling the effect of previous seizures (Cano-López et al., 2019).

Although previous studies have identified stressful life events in epilepsy, these are usually limited to the relationship between stress and seizure occurrence, or to the differences in stress levels between populations, as detailed in the systematic review presented in Chapter 2. These reports are certainly of great interest in the field, but they are far from following a complete model of stress, as the consequences of stressors on the different areas of the individual remain unclear.

1.2. Modulator factors in epilepsy

After identifying social stressors and their role, and following the SOR model of stress, the next aim of this Thesis was to identify personal and clinical factors that influence how the stressor is appraised by the organism. To this purpose, the effect of clinical and emotional modulator factors (pharmacological treatment and negative affectivity) was studied, assessing their impact on cognitive and psychological variables in patients with drug-resistant epilepsy. This general objective was composed of two specific aims.

The first specific aim was to analyze the modulator effect of a new ASM, cenobamate, on cognition, negative affectivity, and QOL, after a period of gradual dose increase (i.e., after 3 months) and after achieving a stable dose (i.e., after 6 months), controlling for the impact of age and the consumption of other ASMs and antidepressants, which could interfere in the results. This objective was addressed in Study 2, and was of particular interest given that, in addition to

exploring the modulator role of pharmacological treatment, the effect of a new generation ASM was tested shortly after it came on the market. Therefore, due to the lack of previous real-world research, its study was of great relevance to this population. Our results confirmed hypothesis 4, which stated that attention and executive function performance would remain stable after 3 months of treatment with cenobamate, in line with Schuetz et al. (2022), allowing the extrapolation of this conclusion to other cognitive domains, such as memory and naming. In addition to the absence of cognitive changes, adjunctive treatment with cenobamate had no effects on negative affectivity, and QOL neither after 3 nor after 6 months, while a significant seizure reduction was found at both time points.

The modulating role of the pharmacological treatment of stress in epilepsy can be based on different mechanisms, two of which stand out in this Thesis. First, its ability to interfere with seizure frequency and, second, the impact that side effects can have on other comorbidities and daily live activities. On the one hand, regarding the influence on the occurrence and recurrence of seizures, part of the interest of this article lies in the characteristics of the sample. Within a framework where seizures are considered as stressors, patients of this study were highly vulnerable to stress and epilepsy, due to severe drug resistance and the unfeasibility or ineffectiveness of surgery to achieve seizure control. Therefore, the decrease in both short- and long-term seizure frequency in this population was a major accomplishment. On the other hand, this study also addressed the impact of adjuvant treatment with cenobamate on cognitive performance, negative affectivity, and QOL, showing that it is a safe drug in these terms given the lack of adverse effects. Subsequent studies have supported our results, even showing an improvement in verbal episodic and visuospatial memory scores (Serrano-Castro et al., 2024) and anxious symptomatology after 6 months of treatment (Pietrafusa et al., 2023). Taking all these results together, it is suggested that cenobamate could modulate the stress response in epilepsy, being associated with clinical improvement (i.e., seizure reduction) and an absence of side effects on cognitive performance, mood, and QOL.

Study 3 addressed the second specific aim, which focused on identifying vulnerability or protection profiles to the impact of stress in epilepsy, considering indicators of stressor chronicity (i.e., epilepsy duration) and intensity of impact (negative affectivity), and examining the differences in cognition and QOL depending on these profiles. In this regard, our results partially confirmed hypothesis 5. As expected, a resilient group (i.e., longer epilepsy duration and moderate negative affectivity levels) was found. However, we did not find a group with

longer epilepsy duration and high negative affectivity levels. In addition to the resilient group, two more phenotypes were identified: a vulnerable group (i.e., shorter epilepsy duration and high negative affectivity) and a low-impact group (i.e., shorter epilepsy duration and lower negative affectivity). This latter group served in the study as a reference group, facilitating comparisons and the formulation of conclusions. Furthermore, the identification of a resilient and a vulnerable group aligns with Ring et al. (2016), who proposed a model of resilience in which clinical, psychological, and social variables interact, increasing the vulnerability or resilience of patients. These authors point out that these profiles, far from being static, are dynamic constructs susceptible to the influences of these variables, thereby affecting the patient's QOL (Ring et al., 2016). Remarkably, these groups of patients were similar in terms of seizure frequency. The characteristics of each group support the existence of stress phenotypes in epilepsy, which appear to have a different modulatory effect.

The moderate negative affectivity levels of the resilient phenotype suggest that patients can develop adaptative coping strategies. From a clinical view, these patients could be considered more vulnerable, due to their older age, the earlier epilepsy onset, the greater number of ASMs, and the lower educational level. However, *with age comes wisdom*, so we consider that older age and longer duration of epilepsy could lead to the development of more effective coping mechanisms, explaining, at least in part, these results. Age has been positively related to resilience and healthier coping styles (Baker et al., 2019; Bautista et al., 2013). Furthermore, studies with the general population showed that older adults appraise stimuli as less stressful (Aldwin et al., 1996). Regarding epilepsy duration, more years suffering the disease could be related to a lower severity perception and a greater adaptation to the disease (Kotwas et al., 2017). Nevertheless, given that negative affectivity levels remained moderate, it is proposed that epilepsy may continue to be a source of stress, although perceived as less intense than in those patients who have suffered from the disease for a shorter period of time.

Hypothesis 6 was confirmed, which stated that the group of patients with moderate levels of negative affectivity would show better cognitive performance and QOL than those with high negative affectivity. The resilient group performed better on executive functions, visual confrontation naming, and long-term memory performance than the vulnerable group. It might be assumed that epilepsy duration could be responsible for these differences between groups. However, previous literature has shown a negative relationship between cognitive performance and years of suffering epilepsy (Black et al., 2010; Uslu et al., 2019; Zagaria et al., 2021), so,

following this line, the resilient group should have worse cognitive performance. Notwithstanding, the resilient group was also the only one with an epilepsy onset in childhood. Therefore, although some studies have associated a younger age at epilepsy onset with cognitive decline (Hermann et al., 2010; Menlove & Reilly, 2015), an earlier onset could favor more efficient brain plasticity and compensatory mechanisms (Loring et al., 2008).

Significant differences were also found between the vulnerable and the low-impact group in naming and memory performance (the vulnerable group with lower scores). Since these groups were equal in epilepsy duration, and considering that the resilient group dealt with the disorder for the longest period (despite having better scores than the vulnerable group, with a shorter duration), it could be hypothesized that, more than the duration of epilepsy, these differences could be due to negative affectivity. In this regard, depression and anxiety have been related to poor cognitive functioning in patients with epilepsy (Arend et al., 2018; Cano-López et al., 2019; Espinosa et al., 2010; Wang et al., 2019), being strong predictors of cognitive performance (Bingaman et al., 2023; Cano-López et al., 2019; Jarčušková et al., 2020; Miller et al., 2016; Tang et al., 2013). Hence, this emphasizes the importance of considering the combination of clinical and emotional variables and highlights how each phenotype can modulate the impact of stress on cognitive performance.

Additionally, the resilient group had better executive functioning than the low-impact group (i.e., shorter epilepsy duration and lower negative affectivity). Therefore, these differences could not be attributed to negative affectivity. Greater resilience has been related to better cognitive performance (Tedrus et al., 2020). Furthermore, in this particular case, it is proposed that resilience could be related to cognitive flexibility, which is defined as a dynamic process of adaptation (Arici-Ozcan et al., 2019). This subdomain of executive functions is responsible for developing different strategies to deal with a given situation, so it seems to be a basic requirement for having resilient behavior. Therefore, it is suggested that cognitive flexibility could be a relevant variable in the stress process. However, further studies to clarify this question are needed.

Regarding QOL, the low-impact group had better scores than both, the resilient and the vulnerable group. Furthermore, the resilient group showed better QOL than the vulnerable group. In other words, QOL scores were higher in the group with the lowest negative affectivity, decreasing in the group with moderate negative affectivity, and reaching the lowest scores in the group with high negative affect. This is in line with studies that have shown the relationship

between negative affectivity and poor QOL (Cano-López et al., 2018, 2023; Lima et al., 2021; Scévola et al., 2017; Taylor et al., 2011; Tombini et al., 2020).

Thus, it can be concluded that negative affectivity may act as a modulator in the stress process in people with epilepsy, considering the chronicity of the stressor, and underlying the relevance of other variables in resilience behavior, such as age or cognitive flexibility. In line with this, Thapar et al. (2009) identified the influence of negative affectivity in the relationship between stress and changes in seizure recency, showing a stronger effect of depression compared to anxiety. These results highlight the need to assess the negative affectivity in patients with patients with epilepsy and high levels of stress.

Despite that more research is needed, based on the results found in Study 3, we suggest that negative affectivity may have a strong modulator effect regardless of the epilepsy duration. The strength of its impact is also observed in the study of stress predictors. In this regard, Moon et al. (2016) pointed out that depression was the strongest predictor of perceived stress, followed by sleep problems, anxiety, and seizure control (in that order). Therefore, emotional variables had a stronger effect even than the epilepsy-related variable (i.e., seizure control). According to the diathesis-stress paradigm, one of the factors most linked to stress vulnerability is personality components, which are related to the ability to regulate mood. Given this, the importance of depression in the field of stress is not surprising. Even though most reports have focused on the role of stress as a predictor of depression (Hammen, 2015; Lee et al., 2010, 2022), others have suggested that depressive symptomatology may also increase sensitivity to stress (Gotlib & Joormann, 2010; Monroe et al., 2009), probably due to dysregulation of the HPA axis (Burke et al., 2005; Heim et al., 2008). However, these studies are restricted to the consideration of depression as a primary problem, and not as a comorbid condition.

Interestingly, gender also appears to interfere with the stress process, particularly in the perception of stressful stimuli. In this regard, gender differences are observed both in patients with epilepsy (Koutsogiannopoulos et al., 2009) and in the general population (Matud, 2004), with men more frequently reporting work-related problems as stressors, and women reporting more often aspects related to social support, such as family disputes. This underlines the complexity of the stress network, having interrelated modulators of different natures influencing the stress process.

In conclusion, it can be assumed that clinical and emotional variables can modulate the individual's stress levels in drug-resistant epilepsy, probably by regulating physiological and

psychological mechanisms involved in stressor appraisal. These results may be of great interest in clinical practice, by detecting risk profiles and favoring an earlier intervention. Therefore, we conclude that these results may be relevant when establishing cognitive and emotional prognoses, and facilitating the implementation of personalized treatments.

1.3. Stress response

Having identified stressors and studied the effect of some modulators, the last point of the present Thesis was to explore the stress response in epilepsy. Given the dysregulation of the functioning of the HPA axis in people with epilepsy (Cano-López & González-Bono, 2019), it was considered appropriate to study the hormonal response to stress. Thus, the first specific aim was to explore the cortisol response to the presence of an acute psychosocial stressor, the TSST, in patients with drug-resistant epilepsy. In particular, differences in the cortisol response between patients with epilepsy and healthy individuals were explored, as well as differences in the cortisol response in patients with epilepsy who underwent the stressor and those who did not.

The results found in Study 4 were contrary to hypothesis 7, since a hyporesponsiveness of cortisol to stress was found in patients with epilepsy compared to the healthy population. The two studies that assessed cortisol reactivity to acute stressors in adults concluded that there was a greater response in patients with left TLE compared to healthy controls (Allendorfer et al., 2014; Goodman et al., 2019). However, in these studies, cortisol levels were never higher than those before the stressor. Therefore, we consider that these authors interpreted an index of recovery as reactivity, and that the differences compared to the control group might be due to the higher baseline cortisol levels of patients with epilepsy. Supporting our results, van Campen et al. (2015) showed that children and adolescents with stress-triggered seizures had a decreased cortisol response after exposure to the TSST, suggesting that the sensitivity of seizures to stress could be associated with a downregulation of the HPA axis.

Higher cortisol levels before the stressor were found in patients with epilepsy than in the general population, in agreement with the previous literature (Allendorfer et al., 2014; Cano-López et al., 2019; Goodman et al., 2019; Marek et al., 2010). Furthermore, baseline cortisol level was positively related to epilepsy duration. These results are consistent with the conceptualization of epilepsy within a framework of chronic stress, and point to a dysregulation of the HPA axis (Cano-López & González-Bono, 2019), which could be related to factors such

as the presence of hippocampal atrophy or seizures, leading to elevated cortisol secretion (Allendorfer et al., 2014; Bazil et al., 2000; Zhang & Liu, 2008).

Contrary to hypothesis 8, we found that patients with epilepsy had the same levels of cortisol production in both groups of patients, regardless of whether they were subjected to the stressor or not. In the general population, an increase in cortisol production has been observed after exposure to the TSST (Het et al., 2012), which is considered one of the most effective stressors in eliciting a response in humans (Dickerson & Kemeny, 2004). Some mechanisms could explain these results. On the one hand, a hyper- or hyporesponsiveness of the HPA axis to stress has been linked to altered glucocorticoid signaling (Agorastos & Chrousos, 2022), suggesting that this buffered response to stress could be due to a ceiling effect caused by hypercortisolism. On the other hand, chronic exposure to stress could lead to adaptive changes in the organism. Therefore, cortisol hyporesponsivity to acute stressors may have a protective role in particularly vulnerable populations to stress, desensitizing the HPA axis (Ostrander et al., 2006). Supporting this idea, our results showed that longer epilepsy duration was related to higher cortisol levels before the stressor and lower cortisol response to acute stress.

A buffered cortisol response to stressors has also been observed in animal models (Ostrander et al., 2006), but also in humans subjected to chronic stress conditions (i.e., posttraumatic disorder and panic disorder) after TSST exposure (Petrowski et al., 2010; Pierrehumbert et al., 2009; Wichmann et al., 2017). However, although the bulk of the research points to these data, there is some heterogeneity in the results, even in other chronically stressed populations (Abelson et al., 2007; Elzinga et al., 2003; Gola et al., 2012). This suggests that the cortisol responsiveness to acute stressors may be sensitive to other variables, such as the type and dose of ASMs (Johannessen & Landmark, 2010; Putignano et al., 1998), the presence of interictal epileptiform discharges (van Campen et al., 2016), the type and lateralization of epilepsy (Cano-López et al., 2019; Luef & Rauchenzauner, 2009), or the sex (Liu et al., 2017).

The second specific aim was to explore the relationships between cortisol levels and memory, mood, and QOL, In this regard, we found that in patients with epilepsy who were not exposed to the stressor, the AUC_i — which is more related to the sensitivity of the system— was positively associated with QOL (in particular, emotional well-being and overall QOL) and change in mood and anxiety (i.e., post-assessment values minus pre-assessment values). As far as we know, this is the first study to assess the relationship between cortisol production and QOL in patients with epilepsy. Although no studies exists exploring potential relationships between

cortisol response to psychosocial stress and affective variables, other studies have examined the association between basal cortisol levels and negative affectivity. In this regard, Cano-López et al. (2019) showed no significant correlations, while Busch et al. (2012) found that higher cortisol levels were associated with higher anxiety, but no relationship was found with depressive symptomatology. Finally, in patients from the experimental group (i.e., those exposed to the TSST), the AUC_g — which is a measure of the total quantity of cortisol released — was positively related to memory retrieval and overall QOL. These results represent a new advance in the understanding of the mechanisms underlying the interaction between stress and epilepsy.

Remarkably, only six patients in the experimental group responded to TSST. These patients had later epilepsy onset, better memory performance, lower trait anxiety, and better QOL than the non-responders patients. Nevertheless, these results should be taken with caution due to the limitations of the sample. However, although it may seem speculative, it is suggested that the preservation of the stress response may be related to the lower severity of the disease, supporting that this response could be related to other adaptative processes in epilepsy, which in turn could affect the patient's autonomy.

To conclude, Study 4 provides further insight into the stress response in patients with epilepsy, highlighting a cortisol hyporesponsivity to an acute psychosocial laboratory stressor and hypercortisolemia in these patients compared to healthy subjects. This suggests a dysregulation of the HPA axis in patients with epilepsy due to persistent and continuous exposure to stress. Furthermore, the relationships found between higher cortisol production and memory, mood, and QOL emphasize the need for further research addressing this topic.

1.4. Transactional results

Our findings show that the stress process in epilepsy involves certain particularities related to the disease and its impact, showing differences with the general population in the type of stressors and their consequences, in how factors modulate their perception and management, and, finally, in the hormonal stress response. These findings support the framing of epilepsy within a chronic stress model, which could provide a more holistic view of the disease and more accurate clinical care.

To our knowledge, only Snyder (1993) designed a tool for measuring the frequency with which specific stressors are experienced, as well as the degree of stress generated (i.e. the ESI-

R). However, although this tool certainly responded to a clinical need, some limitations can be observed. First, its validation was performed with a limited sample (n = 25), and, to our knowledge, no factor analysis was carried out to observe the structure and relevance of the factors in measuring perceived stress. Second, this tool consists of 22 specific items, such as "difficulties in getting insurance", so the likelihood of patients having experienced them is lower. More general items assessing the individual's perception of stress related to a particular area (e.g., work problems) might provide more useful information. Finally, the ESI-R is designed for the general epilepsy population. Patients with drug-resistant epilepsy are more vulnerable to stress, due to the unpredictability, repeatability, and severity of seizures. Therefore, a specific tool for this population, including items on seizure severity, could be highly useful.

These may be some of the reasons why this tool has been scarcely used by previous studies. As can be seen in Chapter 2, most studies employed the Perceived Stress Scale (Cohen et al., 1983). This test is a useful measure, but it was designed for the general population. Therefore, factors that may interfere with the results, such as specific stressors or modulators of stress in epilepsy, are ignored. Others, instead, used visual analog scales or interviews, which can provide interesting information, but they are not validated tools. Therefore, to respond to this need in clinical and research practice, the last objective of the present Thesis was to develop a specific measure to assess perceived stress in adults with drug-resistant epilepsy (i.e., the EPSI-A scale), analyzing its relationship with clinical, psychological, and hormonal variables (i.e., salivary cortisol levels). This aim was addressed in Study 5.

Hypothesis 9 was confirmed, since the developed instrument showed adequate values, demonstrating its validity in measuring perceived stress in this population. In addition, it was positively related to anxious and depressive symptomatology and negatively related to QOL. The test was structured in four factors: *epilepsy concerns*, *impact on daily performance*, *social consequences*, and *epilepsy severity*. Interestingly, these factors encompass the current definition of epilepsy, considering clinical aspects, but also the impact in their daily lives (Fisher et al., 2014).

Concerning hypothesis 10, our results partially agree. Higher scores in the EPSI-A were related to a higher number of previous failed ASMs, a higher number current number of ASMs, and a younger age at epilepsy onset. These variables can be considered a measure of refractoriness, so we suggest that patients with more severe epilepsy may be at risk for higher levels of perceived stress, in line with previous literature that has addressed this question

(Aishwarya et al., 2023). However, given that several studies point toward hypercortisolemia in patients with epilepsy (Allendorfer et al., 2014; Cano-López et al., 2019; Marek et al., 2010), it was hypothesized that higher perceived stress scores would be positively related to cortisol levels. Despite the hypercortisolism in our sample, seven of the nine cortisol measures were negatively associated with some EPSI-A scale. In this regard, patients with some stress-related disorders may develop hypocortisolism after prolonged stress, and this decrease in cortisol levels could act as a protective factor to avoid harmful effects on the organism (Fries et al., 2005). Therefore, we concluded that patients more vulnerable to stress may have lower cortisol levels. Further research is needed to clarify to what extent cortisol response to stress could be associated with perceived stress.

Future reports should provide more detailed information on the usefulness of this tool, answering questions about its sensitivity to measure perceived stress in patients with well-controlled or generalized epilepsy, or its relationship with other variables of interest in clinical practice (e.g. effects of treatments, impact of epilepsy or social changes, etc.). Nonetheless, we consider that this tool may be appropriate for this population, given its easy implementation and brevity (15 items), and its psychometric properties, which offer promising results.

1.5. Clinical implications

The results of the present Thesis provide a comprehensive perspective of epilepsy within a stress theoretical framework (see Figure 2). This approach is novel in this field and encompasses stressors, modulators, and responses. First, the role of social stressors in epilepsy is corroborated and their relationship with other cognitive, emotional, and QOL variables is explored. This offers a new model that helps to understand QOL from a more comprehensive perspective and allows the detection of risk factors that may interfere with the prognosis and impact of the disease. Furthermore, it can be useful for designing programs that promote academic/employment reinsertion, considering socioemotional and cognitive aspects. Second, it studies the effect of stress modulators on epilepsy, advancing at the same time in the knowledge of the impact of a new ASM. This helps to implement treatments appropriate to the patient's idiosyncrasies, and favors the detection of vulnerable or protective stress profiles, allowing an earlier intervention. Third, the response to an acute psychosocial stressor in patients with epilepsy is examined, compared with healthy populations and people with epilepsy not subjected to an acute stressor. This answers questions that remained unresolved, such as the action of the HPA axis in response

to the TSST or the impact of cortisol production in memory, negative affectivity, and QOL. Finally, the development of a new measure to assess perceived stress in epilepsy allows a more reliable and appropriate assessment for this population, optimizing the identification of patients at risk and the study of the relationship with other variables, thus facilitating a more comprehensive view of epilepsy.

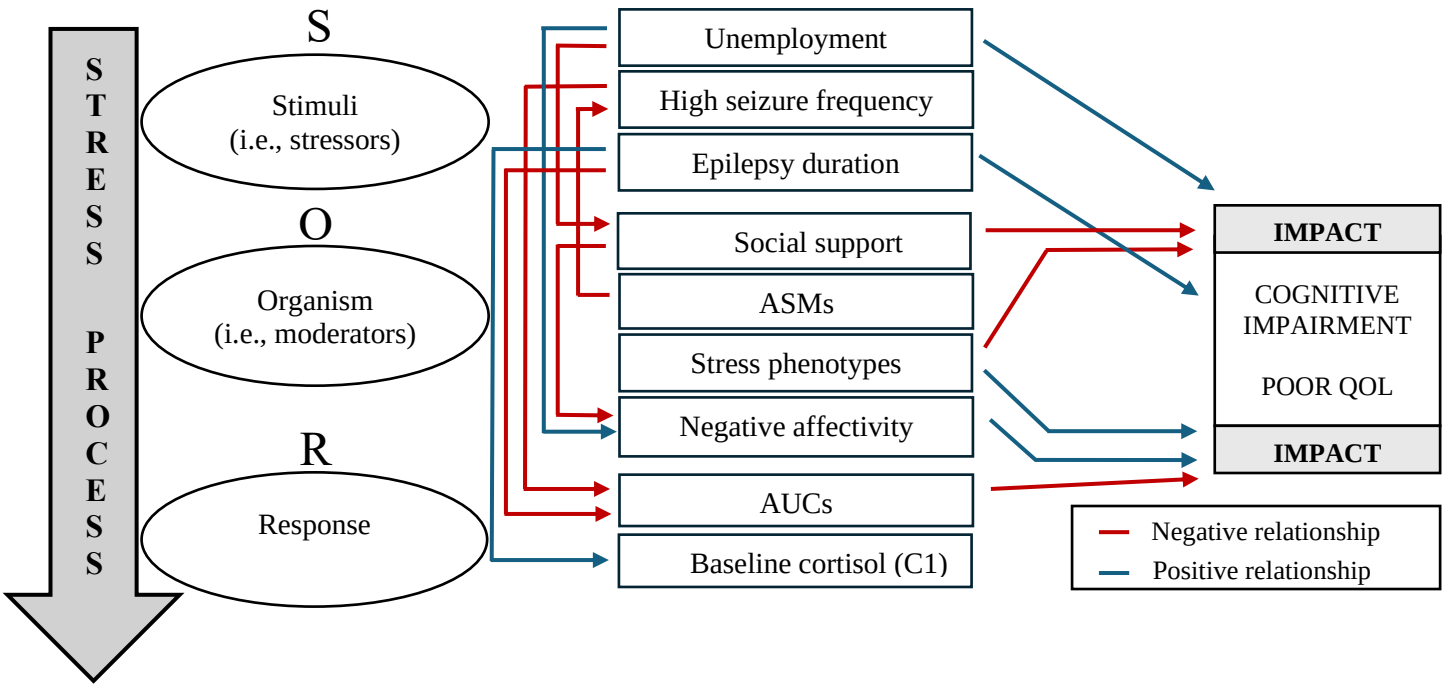

Figure 2. Stress model in patients with drug-resistant epilepsy based on the results of the Thesis.

2. Limitations

Although the specific limitations of each study have been addressed in the respective discussion section, some of them are generalized to several of the studies and their nuance is necessary for understanding the results. First, the sample size was relatively small in some studies, especially in Study 2. Given the lack of research on a promising new ASM, there was an urgent need to share knowledge with the scientific community. However, working with larger samples would ensure statistical power and allow more information to be obtained. Secondly, except for Study 1, conducted with TLE patients, the samples were composed of patients with different types of epilepsy and seizures. A more homogeneous sample would allow more accurate and reliable information. Third, the studies in the present Thesis, except for Study 2, were cross-sectional in nature. Longitudinal studies would provide a more detailed view of how stress affects patients with epilepsy throughout the life cycle, considering changes

in the evolution of the disease and daily life activities that could interfere with the stress process. Fourth, since cortisol levels could be influenced by clinical variables, such as seizure recency or type and dose of ASMs, future studies should replicate these results by controlling these variables. Finally, the ESI-R was not considered for the convergent validation of the EPSI-A, due to the scarce use of this instrument in the research field and clinical practice.

3. Future directions

The present Thesis advances the understanding of epilepsy within the context of stress. However, some questions remain unresolved, and others are emerging.

First, the identification of other stressors in epilepsy is necessary. This would allow the anticipation of possible harmful effects and the design and implementation of strategies to help buffer the stress effect. Although seizures have been considered acute stressors in previous literature, the interrelationship between stress, seizures, and their impact on the individual has not yet been addressed in the same sample, which could help to understand the underlying networks from a holistic perspective.

Second, the results show the modulatory role of ASMs (i.e., cenobamate) and negative affectivity. However, it has also been observed that other variables may play an important role in the stress process, such as age or cognitive flexibility, so further studies assessing their implication could obtain promising results.

Third, it would be interesting to include other indicators to explore the acute stress response, both at psychological and physiological levels. Furthermore, further studies should assess the possible differences after undergoing effective treatments in seizure control, as well as between drug-resistant epilepsy and well-controlled patients.

Fourth, future reports should consider the limitations presented in this Thesis, conducting longitudinal studies with larger and more homogeneous samples, to advance the knowledge of stress in epilepsy. This would allow the examination of potential factors to explain individual differences such as age or gender.

Finally, this Thesis has demonstrated the importance of stress in the prognosis and consequences of epilepsy. Therefore, the next step in clinical practice would be the design of therapeutic programs aimed at reducing stress levels and providing effective tools to mitigate its effects.

CHAPTER 10

Main conclusions

1. Main conclusions

The following main conclusions can be obtained from the studies included in this Thesis:

1. Patients with employment insertion have better executive function performance than those unemployed. However, these differences are not found depending on academic insertion.
2. Patients with academic/employment insertion have higher social support, lower trait anxiety, and better QOL than those without insertion.
3. Academic/employment insertion has indirect effects on QOL through its relationship with global social support and trait anxiety.
4. Patients receiving adjunctive treatment with cenobamate for 3 and 6 months showed a seizure frequency reduction, with no changes in cognitive performance, negative affectivity, or QOL in respect to baseline.
5. Stress phenotypes in epilepsy can be identified in terms of chronicity (i.e., epilepsy duration) and intensity (i.e., negative affectivity). These phenotypes are categorized as resilient (i.e., longer epilepsy duration and moderate negative affectivity), vulnerable (i.e., shorter epilepsy duration and higher negative affectivity) and low-impact (i.e., shorter epilepsy duration and lower negative affectivity).
6. The impact of stress differs across phenotypes, with the vulnerable group showing poorer cognitive performance and QOL than the other groups. The resilient group has better executive performance than both, the vulnerable and low-impact groups, and better QOL than the vulnerable group. The low-impact group has the better QOL.
7. Patients with epilepsy have a buffered cortisol response to TSST exposure compared to healthy people. Furthermore, these patients have higher levels of cortisol before the stressor compared to healthy people.
8. Patients with epilepsy show a buffered stress response to the TSST, with no differences in cortisol levels between patients exposed to the TSST and those who do not. Furthermore, although tentative, higher cortisol response to acute stress is associated with better information retrieval, an increase in mood and anxiety during a neuropsychological assessment, and better QOL in patients with epilepsy.
9. The EPSI-A is a new useful, reliable, and valid measure to assess perceived stress specifically in people with epilepsy, which is related to clinical and psychological variables.
10. Lower cortisol levels are related to *social consequences* and *epilepsy severity* scores from the EPSI-A.

CHAPTER 11

General summary in Spanish

1. Introducción

La epilepsia es un trastorno neurológico caracterizado por una predisposición a presentar crisis epilépticas recurrentes que impacta de forma integral en el individuo (Fisher et al., 2017). El tratamiento de primera elección de la epilepsia incluye el uso de fármacos antiepilépticos (FAEs) para controlar la aparición y la frecuencia de las crisis. Aunque este tratamiento es eficaz para la mayoría de los pacientes (Kwan et al., 2011), en aproximadamente un tercio de esta población los FAEs no consiguen controlar las crisis, sufriendo lo que se conoce como epilepsia farmacorresistente (Sultana et al., 2021).

Las personas con epilepsia farmacorresistente sufren la sobrecarga de la epilepsia de manera severa (Jacoby y Baker, 2008). Estos pacientes experimentan cuadros clínicos más graves, probablemente debido al pobre control de las crisis epilépticas (López-González et al., 2015). Así, las personas con epilepsia farmacorresistente tienen un mayor riesgo de mortalidad (Tomson et al., 2005), peor rendimiento cognitivo (Monteagudo-Gimeno et al., 2020), una mayor variedad de comorbilidades (Scheffer et al., 2017), y una mayor probabilidad de experimentar efectos adversos de los FAEs (Jacoby y Baker, 2008) que las personas con epilepsia bien controlada. Además, estos pacientes parecen tener un perfil vulnerable a los efectos psicológicos de la epilepsia, mostrando mayores niveles de depresión y ansiedad (Gilliam et al., 2004; Micoulaud-Franchi et al., 2016). Por último, la epilepsia farmacorresistente se ha relacionado con un deterioro en la función social, con más dificultades laborales (Majkowska-Zwolińska et al., 2012), menor apoyo social (Amir et al., 1999), mayor estigma percibido (Deleo et al., 2020) y una menor calidad de vida (CV) (Akdemir et al., 2016).

Las comorbilidades en la epilepsia pueden afectar a su evolución (Keezer et al., 2016) y repercutir en la CV (Cano-López et al., 2018, 2023; Pauli et al., 2017). En este sentido, las comorbilidades del estado de ánimo han sido ampliamente estudiadas en esta población debido a las altas tasas de prevalencia (Josephson et al., 2017). Alrededor del 30% de las personas con epilepsia las presentan (Mula et al., 2021), siendo las más frecuentes los trastornos depresivos y de ansiedad, con prevalencias del 35.0% y 25.6%, respectivamente (Lu et al., 2021). Estas comorbilidades pueden afectar al pronóstico de la enfermedad, mostrando una relación positiva con variables clínicas, como la frecuencia de crisis (Dehn et al., 2017), los efectos secundarios de los FAEs (Kanner et al., 2012; Josephson et al., 2017) y la duración de la epilepsia (Scott et al., 2020; Yang et al., 2020).

El deterioro cognitivo es otra de las comorbilidades más frecuentes en la epilepsia, que afecta entre al 70% y el 80% de los pacientes (Helmstaedter y Witt, 2017; Ives-Deliperi y Butler, 2021). Este deterioro responde a un conjunto de interacciones multifactoriales interrelacionadas, donde variables demográficas, clínicas, morfológicas y de tratamiento influyen en el rendimiento cognitivo del paciente (Helmstaedter y Witt, 2017), siendo especialmente sensibles la memoria, la atención, las funciones ejecutivas y el lenguaje (Wang et al., 2019).

Además de la recurrencia de las crisis, los pacientes con epilepsia se enfrentan a desafíos en la vida social. Tradicionalmente, estos pacientes han sido objeto de un estigma social que solía estar ligado a la ausencia o sesgo en la información disponible para la población. El estigma social se refleja en determinados indicadores demográficos, como las menores ratios de empleo, los niveles de estudios o las tasas de nupcialidad, así como el bajo apoyo social (Stavem et al., 2000; Kinariwalla y Sen, 2016). Este entorno puede comprometer la autoestima y la autonomía de las personas con epilepsia, afectando a la CV (Jacoby y Austin, 2007; Marinas et al., 2011) y siendo incluso mejores predictores de esta que las variables clínicas (Tombini et al., 2021).

El desempleo es una de las mayores preocupaciones para estos pacientes. Las tasas de desempleo entre las personas con epilepsia son más altas que en la población general (de Souza et al., 2018; Viteva, 2013), y se ha relacionado con una peor afectividad negativa (Gandy et al., 2015; Wo et al., 2016). Los principales predictores de desempleo propuestos son la cronicidad de la epilepsia, la aparición de crisis durante el último año y la politerapia; siendo la incontrolabilidad de las crisis el predictor más potente (Majkowska-Zwolińska et al., 2012; Marinas et al., 2011).

El impacto del desempleo en la epilepsia afecta a todas las áreas del individuo. En primer lugar, afecta negativamente a la economía del paciente, lo que en algunos países puede limitar el acceso a la atención médica y al tratamiento adecuado. En segundo lugar, el desempleo en personas con epilepsia se ha relacionado con una menor autoestima (Lee, 2005; Schachter et al., 1993). Finalmente, la inserción laboral se asocia con un mayor apoyo social (Wo et al., 2016).

El apoyo social es un factor esencial en el estudio de las enfermedades crónicas, ya que promueve el bienestar y amortigua los efectos negativos de otras comorbilidades (Wang et al., 2015). Además, el apoyo social está relacionado con una mayor CV (Charyton et al., 2009). La CV es un concepto multidimensional que abarca el bienestar del individuo, y que va más allá

de la dicotomía entre salud y enfermedad. La CV en la epilepsia se ha conceptualizado dentro del modelo de Baker et al. (1993), que comprende variables físicas, psicológicas y sociales. Este marco teórico está respaldado por la evidencia científica, que encuentra relaciones directas entre la CV y estas variables. Por ello, el correcto manejo y tratamiento de la epilepsia debe incluir aspectos más allá del control de las crisis, promoviendo la detección precoz de aquellos pacientes especialmente vulnerables a las consecuencias de la epilepsia.

A este respecto, el estrés es uno de los factores que deben tenerse en cuenta. El estrés es un proceso que se desencadena tras la presentación de un estímulo que es percibido por el organismo como nocivo para la homeostasis y que provoca una respuesta para restablecer el equilibrio. Puede conceptualizarse dentro del modelo Estímulo-Organismo-Respuesta (EOR; Woodworth, 1918). Según este marco teórico, la percepción de un estímulo y su consiguiente procesamiento por parte del organismo como amenazante inducirán una respuesta de estrés (Zhang et al., 2021). Esta respuesta puede estar influida por diferentes factores, siendo especialmente relevantes la duración del estresor y las características individuales (Radley et al., 2011). La duración del estresor lleva a diferenciar entre los conceptos de "estrés agudo" y "estrés crónico". Desde el punto de vista de la salud, el estrés crónico se ha conceptualizado como el proceso en el que las demandas del entorno superan la capacidad del individuo para hacerles frente de manera continuada, lo que provoca impactos psicológicos y fisiológicos, y aumenta el riesgo de enfermedad (Cohen et al., 2007; O'Connor et al., 2021). No obstante, este impacto también puede verse modulado por las características individuales, como las experiencias previas o la predisposición genética (Radley et al., 2011). En este sentido, la resiliencia surge como un factor protector frente al estrés (Ong et al., 2006).

Uno de los principales mediadores de la relación entre estrés y salud es el eje hipotálamo-hipofiso-adrenal (HHA), que se activa en situaciones de estrés, desencadenando la secreción de cortisol por las glándulas suprarrenales (Charmandari et al., 2005). Sin embargo, en condiciones de estrés crónico, como algunas patologías de larga duración, puede observarse una desregulación del eje HHA. En este sentido, la evidencia apoya que las personas con epilepsia muestran niveles basales de cortisol más altos en comparación con personas sanas (Cano-López y González-Bono, 2019).

En cuanto a la respuesta de cortisol al estrés en pacientes con epilepsia, solo dos estudios han explorado el impacto de la exposición a estresores psicosociales agudos, concluyendo que los pacientes con epilepsia tenían una mayor reactividad del cortisol que el grupo control (Allendorfer et al., 2014; Goodman et al., 2019). Interesantemente, la responsividad del cortisol

se relacionó positivamente con la frecuencia de crisis en pacientes con epilepsia con pobre control (Allendorfer et al., 2014).

Las crisis epilépticas se han considerado factores de estrés agudo en la epilepsia farmacorresistente, debido a su repetibilidad, incontrolabilidad y por suponer una amenaza para la salud (van Campen et al., 2014; Sander y Bell, 2004). Por lo tanto, la epilepsia se ha propuesto como un modelo de estrés crónico en humanos (Cano-López y González-Bono, 2019). La estrecha relación entre estrés y epilepsia apoya la conceptualización de la epilepsia dentro de un marco de estrés. Este vínculo parece ser bidireccional, ya que el estrés puede aumentar el riesgo de crisis epilépticas, pero la epilepsia en sí también puede elevar los niveles de estrés, debido a la condición crónica de la enfermedad y la recurrencia de las crisis (Novakova et al., 2013; Ponnusamy et al., 2012).

Estos resultados ponen de manifiesto la particularidad del proceso de estrés en la epilepsia, desde los estímulos considerados como estresores hasta la propia respuesta de estrés. Sin embargo, a pesar de ello, pocos estudios han abordado la epilepsia desde el marco del estrés. La aproximación de las principales dificultades de estos pacientes y el impacto global sobre el individuo desde esta perspectiva podría ayudar a comprender de forma integral los determinantes de su CV y lograr un mejor manejo de la enfermedad.

2. Objetivos e hipótesis

La presente Tesis incluye una revision sistemática y cinco estudios experimentales dirigidos a explorar el proceso de estrés en la epilepsia siguiendo el modelo EOR. Por ello, el objetivo 1 se centró en estudiar el impacto de un estresor social (i.e., desempleo) sobre variables cognitivas, emocionales y la CV. El objetivo 2 fue explorar el rol modulador de variables clínicas y emocionales del individuo (i.e., fármacos como el cenobamato y el afecto negativo). El objetivo 3 se focalizó en examinar la respuesta del cortisol a la exposición de un estresor psicosocial agudo. Y, por último, en el objetivo 4 se propuso desarrollar y validar una herramienta para medir el estrés percibido en pacientes con epilepsia farmacorresistente. Por lo tanto, los objetivos generales y las hipótesis para cada uno de ellos fueron:

Objetivo general 1. Examinar la asociación de un potencial estresor social comúnmente informado por los pacientes con epilepsia (i.e., el desempleo) con el rendimiento cognitivo, el apoyo social, la afectividad negativa y la CV. Además, se tuvieron en cuenta variables clínicas

como la frecuencia de las crisis. Se hipotetizó que los pacientes con inserción académica/laboral mostrarían un mejor funcionamiento ejecutivo que aquellos sin inserción, debido al impacto en la reserva cognitiva (Vance et al., 2016). Además, con base en la literatura previa, se esperó que la inserción académica/laboral actuara como fuente de apoyo social, como factor protector frente a la afectividad negativa (Wo et al., 2016) y como potenciador de la CV (Azuma y Akechi, 2014). Por último, se hipotetizó que, además de su efecto directo sobre la CV, la inserción académica y/o laboral tendría un efecto indirecto sobre la CV a través del rendimiento cognitivo, el apoyo social y la afectividad negativa.

Objetivo general 2. Identificar los factores personales y clínicos que influyen en la forma en la que el estresor es valorado por el organismo. Para ello, se estudió el efecto de factores moduladores clínicos y emocionales (tratamiento farmacológico y afectividad negativa), valorando su impacto sobre la función cognitiva y variables psicológicas en pacientes con epilepsia farmacorresistente.

En concreto, en el objetivo específico 2.1. se propuso analizar el efecto de la introducción en el tratamiento farmacológico de un FAE de nueva generación, el cenobamato, sobre la cognición (i.e., atención, funciones ejecutivas, denominación y memoria), la afectividad negativa y la CV, tras un periodo de incremento gradual de la dosis (i.e., a los 3 meses) y tras alcanzar una dosis estable (i.e., a los 6 meses), controlando el impacto de la edad y el consumo de otros FAEs y antidepresivos. Atendiendo al único trabajo publicado sobre este aspecto, se planteó la hipótesis de que la atención y el rendimiento de la función ejecutiva se mantendrían estables tras el tratamiento con cenobamato (Schuetz et al., 2022).

Asimismo, el objetivo específico 2.2. se centró en identificar perfiles vulnerables o protectores al impacto del estrés en epilepsia, considerando indicadores de intensidad del estrés (i.e., sintomatología ansiosa y depresiva) y cronicidad del estresor (i.e., duración de la epilepsia), y examinando las diferencias en el rendimiento cognitivo (i.e., atención, funciones ejecutivas, memoria y lenguaje) y CV entre estos perfiles. Hasta donde sabemos, no hay estudios que hayan establecido perfiles relacionados con el estrés específicos en epilepsia. Sin embargo, la literatura previa que ha abordado el efecto de la resiliencia sobre la afectividad negativa en esta población nos permitió hipotetizar sobre la existencia de dos fenotipos: uno caracterizado por una larga duración de la epilepsia y niveles moderados de afectividad negativa, sugiriendo una adaptación a la enfermedad; y otro grupo con larga duración de la epilepsia, pero niveles de sintomatología ansiosa y depresiva más altos (Ring et al., 2016). Se

esperó que el grupo de pacientes con niveles moderados de afectividad negativa mostraran un mejor rendimiento cognitivo y CV que aquellos con alta afectividad negativa, basándonos en estudios que evaluaron la relación entre afectividad negativa, cognición y CV (Taylor et al., 2011; Wang et al., 2019).

Objetivo general 3. Estudiar si la respuesta de estrés del cortisol a un estresor psicosocial agudo de laboratorio difiere entre pacientes con epilepsia y personas sanas. Para controlar los factores relacionados con la epilepsia, se incluyó un segundo grupo control de pacientes con epilepsia no expuestos al estresor. Por último, se examinó la posible relación entre la magnitud de la respuesta del cortisol con el rendimiento de la memoria, la afectividad negativa y la CV. Basándonos en la interpretación de los resultados de estudios previos sobre la respuesta del cortisol a un estresor psicosocial agudo (Allendorfer et al., 2014; Goodman et al., 2019), y junto aquellos estudios que abordan la dinámica de la respuesta del cortisol a estresores agudos en la población general (Dickerson y Kemeny, 2004), se planteó la hipótesis de que los pacientes con epilepsia mostrarían una mayor reactividad del cortisol a un estresor agudo psicosocial que en las personas sanas (Allendorfer et al., 2014; Goodman et al., 2019). Además, se hipotetizó que las personas con epilepsia sometidas a un estresor agudo de laboratorio tendrían una mayor producción de cortisol que las no expuestas, atendiendo a los hallazgos en la población general (Dickerson y Kemeny, 2004).

Objetivo general 4. Desarrollar un instrumento específico para evaluar el estrés percibido en adultos con epilepsia farmacorresistente, analizando sus propiedades psicométricas y explorando la relación del estrés percibido con variables clínicas, psicológicas y hormonales. Los criterios utilizados para el diseño de los ítems y los resultados de estudios que han explorado la relación entre el estrés percibido (medido mediante cuestionarios desarrollados para la población general) y la afectividad negativa y la CV (Endermann et al., 2013; Lee et al., 2022; Nakamura et al., 2023), nos llevaron a hipotetizar que el instrumento desarrollado sería válido para medir el estrés percibido en esta población, relacionándose con otros instrumentos psicológicos relacionados. Además, considerando la epilepsia dentro de un marco de modelo de estrés crónico, y teniendo en cuenta el hipercortisolismo encontrado en estos pacientes en la literatura previa, hipotetizamos que puntuaciones más altas en la escala de estrés percibido se asociarían con una mayor gravedad de las condiciones clínicas del paciente, así como con

niveles más altos de cortisol (Allendorfer et al., 2014; Cano-López et al., 2019; Marek et al., 2010).

3. Estudios experimentales realizados

3.1. Estudio 1

Este estudio tuvo como objetivo examinar el impacto de la inserción académica y/o laboral sobre el rendimiento cognitivo, el apoyo social percibido, la afectividad negativa y la CV, así como variables clínicas tales como la frecuencia de las crisis. Para este propósito, cincuenta y nueve pacientes con epilepsia del lóbulo temporal (edad media = 39.49 años) fueron clasificados en dos grupos: con inserción académica/laboral y sin inserción. Los pacientes fueron sometidos a una evaluación neuropsicológica en la que se examinaron las funciones ejecutivas, el apoyo social percibido, la sintomatología depresiva y ansiosa, y la CV. Los resultados mostraron que el grupo con inserción presentó una tendencia a tener puntuaciones más altas en funcionamiento ejecutivo que el grupo sin inserción, aunque las diferencias no fueron estadísticamente significativas. Sin embargo, este resultado alcanzó la significación estadística cuando se consideró la inserción laboral independientemente de la inserción académica. Además, los pacientes con inserción académica/laboral tuvieron significativamente mejor apoyo social, menor ansiedad rasgo y mayor CV, no observándose diferencias significativas en la sintomatología depresiva y la frecuencia de crisis. Por último, se llevó a cabo un modelo mediacional que indicó que, a pesar de que la inserción no mostró efectos directos significativos, tuvo un efecto indirecto de sobre la CV. Más concretamente, los resultados mostraron que la inserción académica/laboral se relacionó con un mayor apoyo social, el cual se asoció con una menor ansiedad, que a su vez correlacionó con una mejor CV. Además, aunque el funcionamiento ejecutivo no encajó en este modelo, se relacionó con una mejor CV. Estos resultados destacan la complejidad y heterogeneidad de las redes creadas a través de la inserción social, proporcionando un nuevo modelo que permite una comprensión más comprehensiva de la CV en pacientes con epilepsia del lóbulo temporal.

3.2. Estudio 2

El objetivo de este estudio fue analizar el efecto modulador de un nuevo FAE, el cenobamato, sobre la cognición, la afectividad negativa y la CV, tras un periodo de aumento gradual de la dosis (i.e., a los 3 meses) y tras alcanzar una dosis estable (i.e., a los 6 meses), controlando el impacto de la edad y el consumo de otros FAEs y antidepresivos, en una muestra

de pacientes con epilepsia farmacorresistente. Para ello, se realizaron dos estudios prospectivos de cohortes. En el Estudio 1, 32 pacientes (22 hombres y 10 mujeres) se sometieron a una evaluación neuropsicológica basal y a corto plazo (i.e., 3 meses). En el Estudio 2, 22 pacientes (16 hombres y 6 mujeres) de la muestra inicial se sometieron a una evaluación basal y otra de seguimiento 6 meses después de la evaluación basal. En cuanto a los resultados obtenidos, no se encontraron diferencias significativas en las variables cognitivas, la afectividad negativa y la calidad de vida ni a los 3 ni a los 6 meses. Del mismo modo, teniendo en cuenta el índice de cambio fiable, la mayoría de los pacientes no presentaron cambios significativos en estas variables. No obstante, cabe señalar que sí se encontró mejoría significativa en la frecuencia de crisis. Tomando todos estos resultados en conjunto, se sugiere que el cenobamato podría modular el estrés asociado a la epilepsia, propiciando una mejoría clínica (es decir, una reducción de las crisis) y una ausencia de efectos adversos sobre el rendimiento cognitivo, el estado de ánimo y la CV.

3.3. Estudio 3

Este estudio pretende establecer fenotipos en función de cómo afrontan los pacientes una condición estresante (i.e., epilepsia) y examinar las diferencias en el funcionamiento cognitivo y la CV en función de estos fenotipos. Se planteó la hipótesis de que existiría una interrelación entre la duración de la epilepsia y la afectividad negativa, y que estas variables influirían en la cognición y la CV. Un total de 170 pacientes (82 hombres y 88 mujeres) se sometieron a una evaluación neuropsicológica en la que se evaluó el rendimiento cognitivo (i.e., atención y funciones ejecutivas, memoria verbal y visual, lenguaje, y reconocimiento emocional), la sintomatología depresiva, la ansiedad rasgo, y la CV. Se realizó un agrupamiento jerárquico utilizando puntuaciones z para tres variables: ansiedad rasgo; sintomatología depresiva; y duración de la epilepsia. Se encontraron tres fenotipos: vulnerable (alta afectividad negativa y corta duración); resiliente (afectividad negativa moderada y larga duración); y grupo de bajo impacto (baja afectividad negativa y corta duración). Los resultados mostraron que el grupo vulnerable tenía peor funcionamiento cognitivo y CV que los otros grupos. En concreto, el grupo vulnerable mostró peores puntuaciones que el grupo de bajo impacto en memoria verbal, denominación por confrontación visual y CV (excepto en lo que respecta a la preocupación por las crisis). Además, los pacientes resilientes obtuvieron mejores puntuaciones que el grupo de bajo impacto en las variables de flexibilidad cognitiva, aunque también puntuaciones más bajas en algunas subescalas de CV (i.e., CV general, bienestar emocional y energía). Por último, el

grupo vulnerable obtuvo peores puntuaciones que el grupo resiliente en funcionamiento ejecutivo, la denominación y la CV. Estos resultados sugieren que el manejo del estrés en pacientes con epilepsia está relacionado con el funcionamiento cognitivo y la CV. Estos resultados subrayan la relevancia de considerar las comorbilidades en la epilepsia para detectar perfiles vulnerables o resilientes como factores de riesgo o protección para el deterioro cognitivo y de la CV.

3.4. Estudio 4

El objetivo de este estudio fue comprobar la integridad de la respuesta de estrés ante un estresor psicosocial estandarizado en pacientes con epilepsia y examinar la relación de la magnitud de esta respuesta con la memoria, el estado de ánimo y la CV. La muestra estaba compuesta por 147 participantes distribuidos en tres grupos: el grupo experimental (GE) de pacientes con epilepsia expuestos al *Trier Social Stress Test* (TSST) que se sometieron a una evaluación neuropsicológica (n = 38), un grupo control de pacientes con epilepsia (GC-E) no expuestos al TSST que se sometieron a una evaluación neuropsicológica (n = 50), y un grupo control de individuos sanos (GC-S) expuestos al TSST (n = 59). Se recogieron seis muestras de saliva para determinar el cortisol. Se encontraron efectos significativos de la interacción 'momento*grupo' sobre los niveles de cortisol. El GE mostró una abolición de la respuesta de estrés con niveles de cortisol más bajos que los participantes sanos. No se hallaron diferencias significativas entre los grupos GE y GC-E. El grupo GC-S mostró niveles de cortisol más elevados que el GC-E tras el estresor. El área bajo la curva del cortisol con respecto a los niveles basales fue mayor en el GC-S que en el GE y el GC-E. Sólo el 16% de los pacientes del GE fueron respondedores al estrés, frente al 39% del GC-S. En el GE, los respondedores mostraron un mejor funcionamiento de la memoria, una mayor CV general y bienestar emocional, así como un menor rasgo de ansiedad que los no respondedores. Nuestros hallazgos sugieren que una amortiguación de la respuesta del cortisol al estrés agudo en pacientes con epilepsia, y que la reactividad al estresor está relacionada con el funcionamiento de la memoria y la CV. Estos resultados podrían contribuir a clarificar los mecanismos subyacentes de las interacciones entre estrés y epilepsia.

3.5. Estudio 5

Este estudio tuvo como objetivo desarrollar y validar el Inventario de Estrés Percibido por Epilepsia para Adultos (EPSI-A por sus siglas en inglés), un inventario de autoinforme diseñado

para cuantificar el estrés percibido en pacientes con epilepsia farmacorresistente. La muestra consistió en 236 pacientes con epilepsia farmacorresistente que se sometieron a una evaluación neuropsicológica en la que se registró la depresión, la ansiedad y la CV. Además, se recogieron 9 medidas de cortisol en saliva durante la evaluación en 125 pacientes de la muestra total. El EPSI-A constó de 15 ítems, las puntuaciones más altas indicando una mayor percepción de estrés. El análisis factorial exploratorio mostró una solución de cuatro factores: *preocupaciones por la epilepsia* (5 ítems); *impacto en el rendimiento diario* (4 ítems); *consecuencias sociales* (3 ítems); y *severidad de la epilepsia* (3 ítems). Estos factores explicaban el 63.3% de la varianza total. La fiabilidad de consistencia interna medida con los coeficientes omega de McDonald y alfa de Cronbach fue satisfactoria, con valores ≥ 0.78 (excepto para la *severidad de la epilepsia*, cuyos valores fueron 0.59 y 0.58, respectivamente). La validez de constructo quedó demostrada por su correlación con varias escalas psicológicas, variables clínicas y niveles de cortisol. Los resultados mostraron que el EPSI-A es una herramienta fiable y válida para evaluar el estrés percibido en personas con epilepsia. Su concisión, rapidez de administración y especificidad lo convierten en un instrumento adecuado para esta población.

4. Conclusiones principales

De los estudios incluidos en esta Tesis se pueden obtener las siguientes conclusiones principales:

1. Los pacientes con inserción laboral presentan un mejor rendimiento de la función ejecutiva que los desempleados. Sin embargo, estas diferencias no se encuentran en función de la inserción académica.

2. Los pacientes con inserción académica/laboral tienen mayor apoyo social, menor ansiedad rasgo y mejor CV que aquellos sin inserción.

3. La inserción académica/laboral tiene efectos indirectos sobre la CV a través de su relación con el apoyo social global y la ansiedad rasgo.

4. Los pacientes que recibieron tratamiento adyuvante con cenobamato durante tres y seis meses mostraron una reducción de la frecuencia de las crisis, sin cambios en el rendimiento cognitivo, la afectividad negativa (ansiedad y depresión) o la CV con respecto a los valores basales.

5. Los fenotipos de estrés en la epilepsia pueden identificarse en términos de cronicidad (i.e., duración de la epilepsia) e intensidad (i.e., afectividad negativa). Estos fenotipos se clasifican en resilientes (i.e., mayor duración de la epilepsia y afectividad negativa moderada),

vulnerables (i.e., menor duración de la epilepsia y mayor afectividad negativa) y de bajo impacto (es decir, menor duración de la epilepsia y menor afectividad negativa).

6. El impacto del estrés difiere según el fenotipo: el grupo vulnerable muestra un peor funcionamiento cognitivo y una peor CV que los demás grupos. El grupo resiliente presenta un mejor funcionamiento ejecutivo que los grupos vulnerable y de bajo impacto, y una mejor CV que el grupo vulnerable. El grupo de bajo impacto tiene una mejor CV que el resto de grupos.

7. Los pacientes con epilepsia tienen una respuesta de cortisol amortiguada a la exposición al TSST en comparación con las personas sanas. Además, estos pacientes tienen niveles más altos de cortisol antes del estresor en comparación con las personas sanas.

8. Los pacientes con epilepsia muestran una supresión de la respuesta de estrés al TSST, sin mostrar diferencias en los niveles de cortisol entre los pacientes expuestos al TSST y los que no. Además, aunque de forma tentativa, una mayor respuesta de cortisol al estrés agudo se asocia a una mejor recuperación de la información, un incremento en el estado de ánimo negativo y la ansiedad durante una evaluación neuropsicológica, y una mejor CV en pacientes con epilepsia.

9. El EPSI-A es una nueva herramienta útil, fiable y válida para evaluar el estrés percibido en personas con epilepsia farmacorresistente, que se relaciona con variables clínicas y psicológicas.

10. Los niveles más bajos de cortisol están relacionados con puntuaciones más altas en los factores de *consecuencias sociales* y *severidad de la epilepsia* del EPSI-A.

5. Implicaciones clínicas

Los resultados de la presente Tesis ofrecen una perspectiva integral de la epilepsia dentro de un marco teórico del estrés. Este enfoque es novedoso en este campo y abarca estresores, moduladores y respuesta al estrés. En primer lugar, se corrobora el papel de los estresores sociales en la epilepsia y se explora su relación con otras variables cognitivas, emocionales y de CV. Esto ofrece un nuevo modelo que ayuda a entender la CV desde una perspectiva más global y permite detectar factores de riesgo que pueden interferir en el pronóstico y el impacto de la enfermedad. Además, puede ser útil para diseñar programas que promuevan la reinserción académica/laboral, considerando aspectos socioemocionales y cognitivos. En segundo lugar, estudia el efecto de los moduladores del estrés en la epilepsia, avanzando al mismo tiempo en el conocimiento del impacto de un nuevo FAE. Esto ayuda a la implementación de tratamientos adaptados a la idiosincrasia del paciente, y favorece la detección de perfiles de estrés

vulnerables o protectores, permitiendo una intervención más temprana. En tercer lugar, se examina la respuesta a un estresor psicosocial agudo en pacientes con epilepsia, en comparación con personas sanas y personas con epilepsia no sometidas a un estresor agudo. Esto responde a cuestiones que permanecían sin resolver, como la acción del eje HHA en respuesta al TSST o el impacto de la producción de cortisol en la memoria, la afectividad negativa y la CV. Finalmente, el desarrollo de una nueva medida para evaluar el estrés percibido en epilepsia permite una evaluación más fiable y adecuada para esta población, optimizando la identificación de pacientes en riesgo y el estudio de la relación con otras variables, permitiendo así una visión más integral de la epilepsia.

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Appendices

Appendix 1. Initial version of the Epilepsy Perceived Stress Inventory for Adults (EPSI-A) (Spanish).

A continuación, se presenta una lista de afirmaciones. Por favor, rodee con un círculo el número que mejor refleje su grado de acuerdo con estas afirmaciones. No deje ningún enunciado de la lista sin contestar. Muchas gracias por su colaboración.

0	1	2	3	4
Totalmente en desacuerdo	En desacuerdo	Ni de acuerdo ni en desacuerdo	De acuerdo	Totalmente de acuerdo

1. Estoy preocupado/a por tener otra crisis	0	1	2	3	4
2. Tengo miedo de sufrir otra crisis en el próximo mes	0	1	2	3	4
3. Me preocupa dañarme a mí mismo/a durante una crisis	0	1	2	3	4
4. Me preocupa la incomodidad o los problemas sociales que puede generarme tener una crisis	0	1	2	3	4
5. Me resulta molesto tener una crisis	0	1	2	3	4
6. Realizo procedimientos eficaces que me permiten controlar mis crisis	0	1	2	3	4
7. Reconozco síntomas que señalan la aparición de una crisis	0	1	2	3	4
8. Soy capaz de predecir la aparición de una crisis	0	1	2	3	4
9. Tengo crisis diarias	0	1	2	3	4
10. Durante las crisis pierdo la conciencia	0	1	2	3	4
11. Mis crisis interfieren mis actividades diarias	0	1	2	3	4
12. Algunas de mis crisis duran más de 30 minutos	0	1	2	3	4
13. Atribuyo mi enfermedad a algún acontecimiento de mi infancia	0	1	2	3	4
14. Atribuyo mi enfermedad a alguna experiencia traumática (por ejemplo, un accidente, un episodio triste, etc.)	0	1	2	3	4
15. Atribuyo mi enfermedad a algo que yo hago (costumbres, hábitos, etc.)	0	1	2	3	4

Appendix 1. Continued.

16. Atribuyo mi enfermedad a algo que puedo evitar	0 1 2 3 4
17. Pienso que la causa de mi enfermedad es genética (herencia familiar)	0 1 2 3 4
18. Tengo miedo de tener hijos con epilepsia	0 1 2 3 4
19. Mis crisis han puesto en peligro mi vida	0 1 2 3 4
20. Mis crisis me producen alteraciones físicas o psicológicas importantes	0 1 2 3 4
21. Tengo problemas de memoria tras sufrir una crisis	0 1 2 3 4
22. Tengo problemas laborales a causa de la epilepsia	0 1 2 3 4
23. Tengo problemas económicos a causa de la epilepsia	0 1 2 3 4
24. Tengo problemas en la vida de pareja a causa de la epilepsia	0 1 2 3 4
25. Tengo problemas en la vida familiar a causa de la epilepsia	0 1 2 3 4
26. He perdido amistades a causa de la epilepsia	0 1 2 3 4
27. He tenido dificultades en las actividades de la vida cotidiana (conducir, cocinar, etc.) a causa de la epilepsia	0 1 2 3 4
28. He tenido dificultades para realizar algunas actividades de ocio que me gustan a causa de la epilepsia	0 1 2 3 4

Appendix 2. Final version of the Epilepsy Perceived Stress Inventory for Adults (EPSI-A) (Spanish).

A continuación, se presenta una lista de afirmaciones. Por favor, rodee con un círculo el número que mejor refleje su grado de acuerdo con estas afirmaciones. No deje ningún enunciado de la lista sin contestar. Muchas gracias por su colaboración.

0	1	2	3	4
Totalmente en desacuerdo	En desacuerdo	Ni de acuerdo ni en desacuerdo	De acuerdo	Totalmente de acuerdo

1. Estoy preocupado/a por tener otra crisis	0	1	2	3	4
2. Tengo miedo de sufrir otra crisis en el próximo mes	0	1	2	3	4
3. Me preocupa dañarse a mí mismo/a durante una crisis	0	1	2	3	4
4. Me preocupa la incomodidad o los problemas sociales que puede generarme tener una crisis	0	1	2	3	4
5. Me resulta molesto tener una crisis	0	1	2	3	4
6. Durante las crisis pierdo la conciencia	0	1	2	3	4
7. Mis crisis interfieren mis actividades diarias	0	1	2	3	4
8. Mis crisis han puesto en peligro mi vida	0	1	2	3	4
9. Tengo problemas de memoria tras sufrir una crisis	0	1	2	3	4
10. Tengo problemas laborales a causa de la epilepsia	0	1	2	3	4
11. Tengo problemas en la vida de pareja a causa de la epilepsia	0	1	2	3	4
12. Tengo problemas en la vida familiar a causa de la epilepsia	0	1	2	3	4
13. He perdido amistades a causa de la epilepsia	0	1	2	3	4
14. He tenido dificultades en las actividades de la vida cotidiana (conducir, cocinar, etc.) a causa de la epilepsia	0	1	2	3	4
15. He tenido dificultades para realizar algunas actividades de ocio que me gustan a causa de la epilepsia	0	1	2	3	4