Universitat Autònoma de Barcelona

PERSONALITY CHANGES IN PATIENTS WITH DRUG-RESISTANT EPILEPSY AFTER SURGICAL TREATMENT

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Doctoral Thesis

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Doctoral thesis presented by **Elena Iurina**

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Dr. Luis Pintor and Dr. Crisanto Díez certify that they have supervised and guided this doctoral thesis presented by Elena Iurina: “Personality changes in patients with drug-resistant epilepsy after surgical treatment.” They hereby assert that this doctoral thesis fulfils the requirements to be defended.

Directors,

Dr. Luis Pintor

Dr. Crisanto Díez

TABLE OF CONTENTS

ABBREVIATIONS

AED Anti-epileptic Drugs

DRE Drug Resistant Epilepsy

DSM Diagnostic and Statistical Manual of mental disorders

EEG Electroencephalography

fMRI Functional Magnetic Resonance Imaging

HADS The Hospital Anxiety and Depression Scale

HADS-A (HADA) The Hospital Anxiety and Depression Scale Anxiety subscale

HADS-D (HADD) The Hospital Anxiety and Depression Scale Depression subscale

HRQOL Health-related quality of life

IQ Intelligence Quotient

MMPI Minnesota Multiphasic Personality Inventory

NEO FFI-R Revised NEO Five-Factor Inventory

NEO PI-R Revised NEO Personality Inventory

NSF Not Seizure-free

PWE Patients with Epilepsy

QoL Quality of life

QOLIE Quality of life in Epilepsy

RE Refractory Epilepsy

ST Surgical Treatment

SPSS Statistical Package for the Social Sciences

SF Seizure-free

TLE Temporal Lobe Epilepsy

1. PREFACE

This manuscript is presented as a compendium of publications that consists of two peer-reviewed articles published in the course of the research work developed, and one study being under review at the date of thesis presenting.

STUDY 1: Elena Iurina, Eva Bailles, Luis Pintor. Personality changes in patients with refractory epilepsy after surgical treatment: A systematic review. Seizure. 2021 Feb;85:95-101. doi: 10.1016/j.seizure.2020.12.026. Epub 2021 Jan 7. PMID: 33453594.

STUDY 2: Elena Iurina, Eva Bailles, Mar Carreño, Antonio Donaire, Jordi Rumià, Teresa Boget, Núria Bargalló, Xavier Setoain, Pedro Roldan, Estefanía Conde-Blanco, María Centeno, Luis Pintor. Personality changes in patients with drug-resistant epilepsy after surgical treatment: one-year follow-up study. Epilepsy Research, 2021, 106784, ISSN 0920-1211, https://doi.org/10.1016/j.eplepsyres.2021.106784.

STUDY 3: Elena Iurina, Eva Bailles, Mar Carreño, Antonio Donaire, Jordi Rumià, Teresa Boget, Núria Bargalló, Xavier Setoain, Pedro Roldan, Estefanía Conde-Blanco, María Centeno, Luis Pintor: Influence of personality profile in patients with drug-resistant epilepsy on quality of life following surgical treatment: a one-year follow-up study. ***(under review).***

The structure of this manuscript begins with a brief Introduction (3), where a theoretical review of the current state of the art is presented.
The description of the study's Aims and Hypotheses (4) are followed by Materials and Methods (5), then we describe a Statistical analysis (6) performed, and Results (7): a section that consists of a copy of two studies published and one article being under review now with a detail description of the developed work. Finally, Discussion (8) of the main findings and their implication to the clinical and research field is presented, Limitations (9) of the study, and the Conclusions (10) section with the main concluding observations.

2. ABSTRACT

The present work is a doctoral dissertation concerning a systematic review of the current state of the art in the subject as an introduction and two observational prospective cohort studies examining personality changes in patients suffering from drug-resistant epilepsy in 1 -year follow-up after surgical treatment and influence of a personality profile on their postsurgical quality of life (QoL).

In the first study, we aimed to conduct a systematic review of studies evaluated the personality changes in adult patients with drug-resistant epilepsy following surgical treatment to clarify the question of how changing the state of disease by surgical treatment could have an impact on personality in these patients.

In the second work, we examined the changes in dimensions of personality using the Revised NEO Personality Inventory questionnaire in drug-resistant epilepsy patients who underwent surgical treatment, compared to a control group in one-year follow-up.

In the third research we intended to clarify the influence of personality profile in patients with drug-resistant epilepsy on quality of life following surgical treatment, and compare the results with a non-surgical control group at the 1-year follow-up

In the first study, we conducted a systematic review using the Preferred Reporting Items of Systematic Reviews and MetaAnalyses (PRISMA) statement. We searched PubMed, Medline databases, and the Cochrane Controlled Trials Register, with search terms ‘personality’, ‘epilepsy’, and ‘surgery’. Eleven studies were selected. In 7 out of 11 studies, personality changes were more adaptive, with patients experiencing decreased neuroticism, impulsivity, hypochondriasis, psychasthenia. One study showed increased emotional lability. The remainder of the studies showed no changes in personality dimensions. Changes in personality differed according to the localization of the epileptogenic area, depended on seizure status after treatment and duration of follow-up. Seizure freedom as an outcome of surgical treatment influenced the existence of personality changes, and their severity. Adaptive personality changes could be seen from early follow-up assessments even in patients who were not seizure-free, though further follow-ups showed that improvements after 1–2 years were specific to seizure-free patients.

In the second work, we conducted a prospective comparative controlled study, including drug-resistant epilepsy surgery candidates. Demographic, psychiatric, neurological, and psychological data were recorded. Presurgical and 12-months follow-up evaluations were performed. Through the study, the surgical group decreased in neuroticism and increased in agreeableness. The controls increased in consciousness, and these changes were predicted by the earlier age of epilepsy onset and lesser score in The Hospital Anxiety and Depression Scale Depression

subscale (HADS-D) at the baseline. No personality changes were associated with seizure frequency. The presurgical evaluation concluded that both groups had no differences in demographic, psychiatric, or neurological variables with the only exception being for the number of seizures per month, which was higher in the surgical group. Psychiatric comorbidity in patients was associated with their higher degree of neuroticism and agreeableness at the baseline. Comparing control and surgical groups at the one-year follow-up, the agreeableness personality variable was higher in the surgical group, and as expected, HADS scores were higher in the control group, and seizure frequency was also higher in the control group.

In the third research, we conducted a prospective, comparative, controlled study, including refractory epilepsy surgery candidates. Demographic, psychiatric, neurological, and psychological data were recorded at the baseline and at the 1-year follow-up. 70 patients completed the psychological assessment at the 1-year follow-up. High levels of conscientiousness and openness to experience in operated patients at the baseline predicted better post-surgical outcomes in the quality of life scores. Both groups were similar to each other at the presurgical evaluation in demographic, psychiatric, and neurological variables, except the number of seizures per month - this variable was increased in the surgical group comparing to the controls. At the 1-year follow-up, on comparing the control and the surgical groups, we detected differences in the most items of QoL, which were higher in the operated patients. Postoperative changes in QoL in patients suffering from refractory epilepsy were depended on the personality profile at the baseline: patients with high baseline levels of conscientiousness and openness to experience showed better QoL outcomes following surgical treatment at the 1-year follow-up, while high neurotic patients performed worse QoL results. Postoperative changes in QoL were not associated with the seizure frequency, not at the baseline, or with its' differences at the pre/post follow-up.

Taken together, the main results of the present work are the personality may change following surgical treatment, and these changes have adaptive character; postoperative quality of life improvements in patients depend of the personality profile at the baseline.

3. INTRODUCTION

3.1. Drug-resistant epilepsy. Epidemiology and definition.

Epilepsy is one of the most serious and common neurological diseases, affecting approximately 50 million people worldwide (WHO, 2005). Epilepsy is known to be chronic, a potentially disabling, and socially isolating condition, especially in refractory cases.

About thirty percent of epilepsy patients suffer from seizures despite pharmacotherapy (Kwan and Brodie, 2000). The International League Against Epilepsy (ILAE) Task Force proposed that "drug-resistant epilepsy may be defined as failure of adequate trials of two tolerated and appropriately chosen and used AED (anti-epileptic drugs) schedules (whether as monotherapies or in combination) to achieve sustained seizure freedom". Clinical evidence shows that patients who do not respond to two antiepileptic drugs have only a small chance to control their seizures using any other therapies (Kwan et al, 2010). Pharmacoresistance in epilepsy is a multifactorial phenomenon, which can be explained by different hypotheses: genetic, pharmacokinetic, neural network, intrinsic severity, transporter hypothesis (Tang et al, 2017).

Patients suffering from drug-resistant epilepsy carry the greatest burden of treatment of epilepsy. Management strategies of drug-resistant epilepsy fall into three main categories: pharmacotherapy, epilepsy surgery, and alternative treatment strategies including neurostimulation, ketogenic diet, and lifestyle changes (Sisodiya, 2007). Epilepsy surgery is an effective treatment in cases of refractory epilepsies (Engel et al, 2003).

According to the review and meta-analysis (Mashhad et al, 2020), epilepsy surgery is a safe, effective, method for therapy of intractable seizures, which can lead to seizure freedom and has a low level of complications.

3.2. Personality features in epileptic patients.

As a severe disease of the central nervous system, it can influence cognitive functions, affecting attention and memory (Osorio et al, 2017; van Rijckevorsel, 2006). But does epilepsy have an impact on patients' personality?

Personality is defined as the characteristic sets of behavior, cognition, and emotional patterns that develop from biological and environmental factors and determine motivation and psychological interactions with one's environment (Sadock et al, 2017; Corr Philip J and Matthews Gerald, 2009).

The issue of personality changes in epilepsy is quite complex and it has been a matter of debate for decades. According to the studies (Rassart et al, 2020; Tarsitani and Bertolote, 2006; Kanner, 2003) patients with epilepsy (PWE) demonstrated increased anxiety and depression level compared with healthy controls. Some authors also indicate higher levels of neuroticism (Rassart et al, 2020; Rivera Bonet et al, 2019) and aggression (Shehata and Bateh, 2009) in PWE compared to the general population. Not only the state of disease in general but also the localization of the epileptogenic foci can play a role in the specificity of neuropsychiatric disruptions (Novais et al, 2019; Park et al, 2017).

Temporal lobe epilepsy (TLE) can be linked with increased neuroticism, anxiety, and social limitations compared to patients with frontal epilepsy who demonstrate hyperactivity, executive dysfunctions, and addictive behaviors (Helmstaedter, 2001). Focusing on personality disorders and their patterns, studies reported on an association between extratemporal epilepsy (mostly with frontal lobe foci) and cluster B personality features (dramatic/emotional/erratic), whereas temporal epilepsy is associated with cluster C personality patterns (anxious/fearful) (Novais* et al, 2019, Bear and Fedio, 1977).

PWE also have lower scores in the Big Five Personality domain "openness to experience" compared to individuals suffering from non-epileptic seizures, and healthy controls (Leong et al, 2019).

Another recent study (Elbeh et al, 2021) also reported personality changes in epileptic patients, which differs according to the severity of the disease, being more neurotic in drug-resistant epilepsy group compare to patients with controlled epilepsy, and differs from the healthy controls.

Taking into account that some personality features are the result of a continuing interictal process and brain structure damage caused by epileptic activity or side effects of antiepileptic treatment (Hessen et al, 2007), it is expected that achieving seizure freedom may lead to changes in the severity of these personality traits in patients and recovery from several psychiatric symptoms.

3.3 Postsurgical personality changes.

Surgical therapy is the treatment of choice in refractory epilepsy cases, which can lead to a seizure-free outcome.

After analyzing personality changes in patients with drug-resistant epilepsy following successful surgical treatment, the decrease in the expression of pathological personality traits and the reductions of subscales of neuroticism and organic psycho-syndrome were reported (Novais et al, 2019*; Witt et al, 2008). Such pathological personality patterns such as social introversion, paranoia, psychasthenia, hypochondriasis, and schizophrenia significantly decreased following

surgical treatment in patients suffering from drug-resistant epilepsy in observational follow-up studies using the Minnesota Multiphasic Personality Inventory (MMPI) (Meldolesi et al, 2007; Derry et al, 2002; Wachi et al, 2001; Meier and French,1965). In contrast, some researchers revealed no personality changes in patients with epilepsy following surgical treatment (Engman and Malmgren, 2012; King and Tranel, 2017). Epileptic patients show higher neuroticism compared to the general population (Rassart et al, 2019), and some studies focused on this dimension. Some authors reported neuroticism did not change following surgery (Engman and Malmgren, 2012; Rose et al, 1996), but Witt with colleagues demonstrated changes in some subscales of this dimension in their research.

Thus, we can conclude, that some personality dimensions could change following surgery. These changes can differ according to the localization of the epileptogenic area; for example, the insular resection group became more emotionally labile despite seizure freedom, compared to the temporal group who increased in lack of stamina scale (Hébert-Seropian et al, 2017). Seizure freedom as an outcome of surgical treatment can influence the existence of adaptive personality changes and their severity. Favourable personality changes can be seen from early follow-up assessments even in patients who were not seizure-free, though further follow-ups showed that improvements after 1-2 years were specific to seizure-free patients.

3.4 Personality and quality of life in epileptic patients.

Epilepsy is associated with a high burden on health care and a low index of quality of life in patients (Deleo et al, 2020). Not only the disease itself, but the associated stigma, side effects of antiepileptic treatment, high level of psychiatric and other clinical comorbidity contribute to the low level in quality of life scores in patients (Paschal et al, 2007). However, the quality of life is a subjective indicator, and apart from objective factors, it depends on individual perception, which in turn is associated with a person's personality (Ramanaiah et al, 1997).

Some studies reported the individual personality features in epileptic patients have impact on many aspects of their quality of life. Personality profile is associated with QoL in epileptic patients according to the studies (Rassart et al, 2020; Shamsi et al, 2020; Rose et al, 1996). Personality profile of high neuroticism accompanied by low extraversion is associated with poor mood and difficulties with family functioning (Wilson et al, 2009) and covaried with stigma beliefs, and these may be markers of poor social outcomes in epileptic patients (Margolis et al, 2018). Increased neuroticism in epilepsy patients correlates with depression and anxiety and is inversely related to quality of life (Endermann and Zimmermann, 2009). Neuroticism scale scores were significantly correlated with many domains of patient-perceived psychosocial adjustment and health-related QoL regardless of frequency or type of seizures (Rose, 1996). Patients high in neuroticism and low in conscientiousness generally reported a poorer health-

related QoL (Rassart et al, 2020).

Surgical therapy is the treatment of choice in refractory epilepsy cases, which can lead to a seizure-free outcome and improve QoL.

If the personality profile in patients suffering from epilepsy influences their quality of life during the disease, it can also affect the quality-of-life perception following recovery due to surgical treatment. Indeed, preoperative neuroticism has an important influence on postoperative psychosocial adjustment and health-related QoL that was independent of the postoperative seizure outcome (Rose et al, 1996). Patients with high neuroticism and low extraversion were predisposed to greater depression after surgery; high neuroticism was also associated with disrupted family dynamics following surgical treatment (Wilson et al, 2009).

4. AIMS AND HYPOTHESIS

4.1 General hypothesis and aims

Hypothesis. Personality features in patients with drug-resistant epilepsy change following epilepsy surgery, and personality profile at the baseline affects subjective quality of life outcomes following epilepsy surgery.

Objectives. To evaluate personality in patients by the NEO Five Factor Personality Inventory, Revised version, (NEO-FFI-R) comparing surgically treated patients with a control group. And relate the baseline personality profile of each group (surgical and control) with the follow-up changes in the quality of life (QOLIE-31 questionary – Quality of life in Epilepsy).

4.2 STUDY 1.

Hypothesis:

1) Personality changes following surgical treatment.
2) Clinical and sociodemographic factors influences the personality changes.

General Aim:

To conduct a systematic review of studies measuring personality dimensions before and after surgical treatment in patients suffering from refractory epilepsy to clarify the question of how changing the state of disease by surgical treatment could have an impact on personality in these patients.

Secondary aims:

1) To explore if the personality may change following surgical treatment.

2) To determine which factors may influence the personality changes.

4.3. STUDY 2.

Hypothesis:

1) NEO-PI-R is a sensitive tool in order to measure personality changes in epileptic patients' sample who undergone epilepsy surgery.

2) Clinical and sociodemographic factors may influence the personality changes.

General Aim:

To evaluate the changes in dimensions of personality using the NEO-FFI-R questionnaire in drug-resistant epilepsy patients who underwent surgical treatment, compared to a control group in one-year follow-up.

Secondary aim:

To explore whether seizure status, psychopathology (depression and anxiety), clinical and demographic data could predict personality changes.

4.4. STUDY 3.

Hypothesis:

1) The personality profile at the baseline affects subjective quality of life outcomes following epilepsy surgery.

2) Such factors, as mood and seizure frequency, may affect postsurgical quality of life.

General Aim:

To evaluate influence personality profile in patients with drug-resistant epilepsy on quality of life following surgical treatment at the one-year follow-up and compare the results with non-surgical group of patients.

Secondary aim:

To examine whether seizure status, psychopathology (depression and anxiety), clinical and demographic data could predict these changes.

5. MATERIALS AND METHODS

Firstly we did a systematic review of studies in the same subject.

The review was performed according to the recommendations of the Preferred Reporting Items of Systematic Reviews and MetaAnalyses (PRISMA) statement (Liberati et al, 2009).
We conducted this study according to the protocol registered in advance on PROSPERO with ID: CRD42020208243.
A literature search was performed using electronic databases such as PubMed, Medline, and the Cochrane Controlled Trials Register. The keywords used were personality, epilepsy, and surgery. The first search was done in November 2019, and the last search was performed in March 2020. The literature search, screening of abstracts, and selection of included trials was performed independently by two investigators (Iurina E., Pintor L.).
We included studies which evaluated personality changes after surgical treatment (ST) for refractory epilepsy (RE) in adults. Only studies written in English were included. The minimum required quantity of patients in a study was 15 participants in order to take into account only original articles with statistical methodology, and avoid to introduce case reports or small series of cases. We included only observational longitudinal follow-up studies, which were case control studies or cohort studies, both prospective and retrospective. Only studies using personality questionnaires were selected, with a follow-up period greater than 6 months. No other limits were set in the study design.
The data extracted from eligible studies included: the number of participants, in the case of the presence of a control group reasons for comparing were indicated (localization of epileptogenic foci to be resected, seizure outcome postoperatively, and surgical vs non-surgical groups), duration of follow-up period, personality test and particular scales used, and the difference in scores on the personality measure following ST.
After a theoretical part the empirical clinical study was conducted.
We carried out an observational, prospective cohort study, in which a study group of drug-resistant epileptic patients, who underwent surgical treatment, was compared with a control group consisting of patients suffering from drug-resistant epilepsy treated with antiepileptic drugs. Both groups were followed up to 1 year after being included in the study.
This research was conducted at the Hospital Clinic of Barcelona. The study was approved by the Hospital Ethics Committee. Subjects were recruited from the Epilepsy Unit of the Neurology Service, which receives referrals from the whole of Spain. The general evaluation protocol consisted of the following points: all participants signed informed consent; the patients were evaluated to confirm the diagnosis of drug-resistant epilepsy according to the International League Against Epilepsy protocol (Scheffer et al, 2017) and were assessed for the possibility of surgical intervention.
All participants provided written informed consent at the time of their enrollment in the

outpatient setting of the Epilepsy Unit. Drug-resistant epilepsy was diagnosed according to the International League Against Epilepsy protocol. Accepted patients were referred for admission to a neurology ward for a week evaluation. Clinical evaluation included video-electroencephalography (EEG) monitoring, a 3 - Tesla brain magnetic resonance with an epilepsy protocol, functional magnetic resonance imaging (fMRI), positron emission tomography scans to indicate the epileptogenic zone, neuropsychological tests, the psychiatric evaluation. Taking all these results into account the committee board made a decision on the surgery suitability for every patient. The epilepsy committee comprises neurologists, psychiatrists, neurosurgeons, neuroradiologists, neuropsychologists, psychologists, and nuclear medicine specialists. Those who had contraindications for surgical intervention formed the control cohort. Surgical candidates were paired with the same time following patients, who composed the control group and underwent all assessment procedures at the same time interval respectively to the surgical intervention at the baseline and in 1 year after surgery. Non-surgical patients were maintained on a standard medication regimen during the follow-up period.

Inclusion criteria:

1) Age 18+;
2) Diagnosed drug-resistant epilepsy;
3) Signed informed consent to enter the study.

Exclusion criteria:

1) History of serious medical pathology except for epilepsy;
2) Mental retardation: IQ < 70;
3) Presence of severe dementia previously diagnosed;
4) Schizophrenia or other chronic psychosis;
5) Non-epileptic psychogenic seizures;
6) Surgical intervention for control of previous epileptic seizures.

Baseline demographic, clinical, psychiatric, and psychological variables were collected. Demographic data collection form included age, gender, education, occupation, and marital state. Clinical data consisted of information about the age of the epilepsy onset in months, etiology of epilepsy, localization, and laterization of epileptogenic foci, type of epileptic seizures, dichotomic measure of a number of seizures at the baseline (“5 or less per month” or “more than 5 per month”), and a number of seizures per month in the last 6 months. Psychiatric evaluations were performed by a psychiatrist, and they included DSM-IV Axis-I disorders and HADS - depression and anxiety scale.

Evaluation of personality dimensions was performed by using NEO-FFI-R (Aluja et al, 2005). The revised NEO-FFI (NEO Five-Factor Inventory) is a short version of the NEO-PI-R (Revised NEO Personality Inventory) questionnaire and has 60 items (12 per domain) for self-assessing the five major personality dimensions: neuroticism, extraversion, openness to experience, agreeableness, and conscientiousness. The patient must indicate his/her degree of agreement with the statement using a score from 0 to 4 from "total disagreement" to «totally agree» respectively. The minimum score for any domain is 0, and the maximum is 48.

The Spanish version of the QOLIE-31 scale was applied for evaluating the quality of life in the patients (Torres et al, 1999).

Anxiety and depressive symptoms were assessed by Hospital Anxiety and Depression Scale (HADS). The Spanish version of HADS was applied for evaluating depression (HADS - D) and anxiety (HADS-A) (Herrero et al, 2003). It contains 14 items, 7 of which are for self-assessing the level of depression and 7 for anxiety. Every subscale should be scored by the patient from 0 to 3 according to the severity of the item. Accordingly, the patient can score from 0 to 21 points on each scale. More than 10 points out of 21 in every subscale is considered as a probable indicator of clinical anxiety or depression. The clinician version of the Structured Clinical Interview for DSM-IV (SCID-CV; Spanish version) (First et al, 1996) was used to assess DSM-IV Axis-I disorders. We grouped psychiatric comorbidity into two clusters: "yes"/"no". The following psychiatric conditions were evaluated: 1) affective disorders, including major depressive episodes, recurrent depression, dysthymic disorder, affective disorder due to a medical condition or substance disorder, adjustment disorder, and bipolar disorder; 2) anxiety disorders, including panic disorder, phobia, obsessive-compulsive disorder, posttraumatic stress disorder, and other anxiety disorders; 3) schizophrenia or schizoaffective disorder and other psychosis; 4) eating disorders; 5) conduct disorder; and 6) substance use disorder.

, psychological evaluation through the NEO-FFI-R and QOLIE.

The postoperative evaluation 1-year following surgical treatment involved the following procedures: the psychiatric evaluation (HADS), the clinical psychology assessment (NEO-FFI-R) and quality of life assessment (QOLIE-31), and a clinical interview to collect neurological data.

6. STATISTICAL ANALYSIS

Statistical analysis was performed using Version 22 of SPSS for Windows and differences were considered significant at $p < 0.05$. Distributions of variables were examined by Shapiro-Wilk Test according to our sample size and appropriate tests were applied for further analysis. The intention to treat approach was carried out in order to see if the 10 drop-out patients were

different from patients finishing the follow-up. A descriptive analysis of all variables was performed at the baseline. The group of controls and the surgical group were compared to detect initial differences between groups, using a Student's t-test, Pearson's chi-square test, Mann–Whitney U test according to the type of every variable and its distributions. When a difference was found, how it affected personality was examined using Kruskal-Wallis tests and Student's t-test. Also, stepwise multiple regression (ANOVA), Student's t-test, and Spearman correlation analysis was run for all the independent variables to reveal how they are initially associated with the personality profile.

The independent variables included age, gender, type of epilepsy, location, laterality, etiology, age at epilepsy onset, HADS, and mental disorders (existence or absence: yes/no). To evaluate changes in psychological and psychiatric test results from baseline to 1-year follow-up, Student's t-test, within subjects Wilcoxon signed-rank test, and Spearman correlation tests were performed. Adjustments for multiple tests were performed using the Games-Howell procedure. Those variables of personality test that reached statistical significance in 1-year follow-up were introduced into stepwise multiple regression analysis. Multiple regression was used to determine the contribution of each variable at the baseline on the changes in personality dimensions at the 1-year follow-up. Also, such data as seizure frequency at the baseline, seizure frequency at the 1-year follow-up, and the variable reflecting changes in this item in pre/post follow-up period were included in the Spearman correlation tests to be compared with variables indicating changes in personality dimensions.

Those variables of mood and QoL tests, that reached statistical significance at the 1-year follow-up, were introduced into regression analyses. Pearson or Spearman correlation analysis was applied to determine the contribution of each variable of personality in changes in the mood and QoL.

7. RESULTS

Brief results of every study:

STUDY 1: Eleven studies were selected. In 7 out of 11 studies, personality changes were more adaptive, with patients experiencing decreased neuroticism, impulsivity, hypochondriasis, psychasthenia. One study showed increased emotional lability. The remainder of the studies showed no changes in personality dimensions. Changes in personality differed according to the localization of the epileptogenic area, depended on seizure status after treatment and duration of follow-up. Seizure freedom as an outcome of surgical treatment influenced the existence of personality changes, and their severity. Adaptive personality changes could be seen from early

follow-up assessments even in patients who were not seizure-free, though further follow-ups showed that improvements after 1–2 years were specific to seizure-free patients.

STUDY 2 and STUDY 3: A 1-year follow-up was completed by 70 out of 80 patients. The presurgical evaluation concluded that both groups had no differences in demographic, psychiatric, or neurological variables with the only exception being for the number of seizures per month, which was higher in the surgical group. Psychiatric comorbidity in patients was associated with their higher degree of neuroticism and agreeableness at the baseline.

Through the study, the surgical group decreased in neuroticism and increased in agreeableness. The controls increased in consciousness, and these changes were predicted by the earlier age of epilepsy onset and lesser score in HADD at the baseline. At the 1-year follow-up, on comparing the control and the surgical groups, we detected differences in the most items of QoL, which were higher in the operated patients. No personality or QoL changes were associated with seizure frequency. High levels of conscientiousness and openness to experience in operated patients at the baseline predicted better post-surgical outcomes in the QoL scores, while high neurotic patients performed worse QoL results. Comparing control and surgical groups at the one-year follow-up, the agreeableness personality variable was higher in the surgical group, and as expected, HADS scores were higher in the control group, and seizure frequency was also higher in the control group.

Results of the study are presented in publications that consists of three peer-reviewed articles published in the course of the research work developed, detailed below:

7.1. STUDY 1: Elena Iurina, Eva Bailles, Luis Pintor. Personality changes in patients with refractory epilepsy after surgical treatment: A systematic review. Seizure. 2021 Feb;85:95-101. doi: 10.1016/j.seizure.2020.12.026. Epub 2021 Jan 7. PMID: 33453594.

7.2. STUDY 2: Elena Iurina, Eva Bailles, Mar Carreño, Antonio Donaire, Jordi Rumià, Teresa Boget, Núria Bargalló, Xavier Setoain, Pedro Roldan, Estefanía Conde-Blanco, María Centeno, Luis Pintor: Personality changes in patients with drug-resistant epilepsy after surgical treatment: one-year follow-up study, Epilepsy Research, 2021, 106784, ISSN 0920-1211, https://doi.org/10.1016/j.eplepsyres.2021.106784.

7.3. STUDY 3: Elena Iurina, Eva Bailles, Mar Carreño, Antonio Donaire, Jordi Rumià, Teresa Boget, Núria Bargalló, Xavier Setoain, Pedro Roldan, Estefanía Conde-Blanco, María Centeno,

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Personality changes in patients with refractory epilepsy after surgical treatment: A systematic review

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ABSTRACT

Purpose: We aimed to conduct a systematic review to evaluate the personality changes in adult patients with drug-resistant epilepsy following surgical treatment.
Methods: A systematic review was conducted using the Preferred Reporting Items of Systematic Reviews and MetaAnalyses (PRISMA) statement. We searched PubMed, Medline databases, and the Cochrane Controlled Trials Register, with search terms 'personality', 'epilepsy', and 'surgery'.
Results: Eleven studies were selected. In 7 out of 11 studies, personality changes were more adaptive, with patients experiencing decreased neuroticism, impulsivity, hypochondriasis, psychasthenia. One study showed increased emotional lability. The remainder of the studies showed no changes in personality dimensions.
Changes in personality differed according to the localization of the epileptogenic area, depended on seizure status after treatment and duration of follow-up. Seizure freedom as an outcome of surgical treatment influenced the existence of personality changes, and their severity. Adaptive personality changes could be seen from early follow-up assessments even in patients who were not seizure-free, though further follow-ups showed that improvements after 1–2 years were specific to seizure-free patients.
Limitations: The main limitation of our research is the heterogeneity of approaches used to evaluate personality in the included studies. Furthermore, the included studies also had different sample sizes and comparison groups, different designs, and different follow-up durations. We only included studies that were written in English.
Conclusions: The majority of studies reported changes in personality dimensions in patients suffering from refractory epilepsy.

1. Introduction

Epilepsy is one of the most serious and common neurological diseases, affecting approximately 50 million people worldwide [1]. Epilepsy is known to be a potentially disabling, chronic, and socially isolating condition, especially in refractory cases. As a severe disease of the central nervous system, it can influence cognitive functions, affecting attention and memory [2,3]. But does epilepsy have an impact on patients' personality? Personality is defined as the characteristic sets of behavior, cognition, and emotional patterns that develop from biological and environmental factors and determine motivation and psychological interactions with one's environment [4,5]. The issue of personality changes in epilepsy is quite complex and it has been a matter of debate

for decades. According to the current state of the art, personality differences between patients with epilepsy (PWE) and control subjects are usually found to be small and mostly explained by increased anxiety and depression [6–8]. Some authors also indicate higher levels of neuroticism [8,9] and aggression [10] in PWE compared to the general population. Not only the state of disease in general but also the localization of the epileptogenic foci can play a role in the specificity of neuropsychiatric disruptions [11,12]. Temporal lobe epilepsy (TLE) can be linked with increased neuroticism, anxiety, and social limitations compared to patients with frontal epilepsy who demonstrate

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hyperactivity, executive dysfunctions, and addictive behaviors [13].

PWE also have lower scores in the Big Five Personality domain "openness to experience" compared to individuals suffering from non-epileptic seizures, and healthy controls [14]. Thus, we do not observe major personality reorganization in patients due to refractory epilepsy, but changes in some domains of personality, mainly in mood.

Previous studies have demonstrated that epilepsy has an influence on some personality domains. We assume that surgery changes the state of the disease in terms of neurophysiological functioning in patients, and, therefore can also affect their personality.

The current systematic review of studies measuring personality dimensions before and after ST in patients suffering from refractory epilepsy (RE) aims to clarify the question of how changing the state of disease by ST could have an impact on personality in these patients.

2. Materials and methods

The review was performed according to the recommendations of the

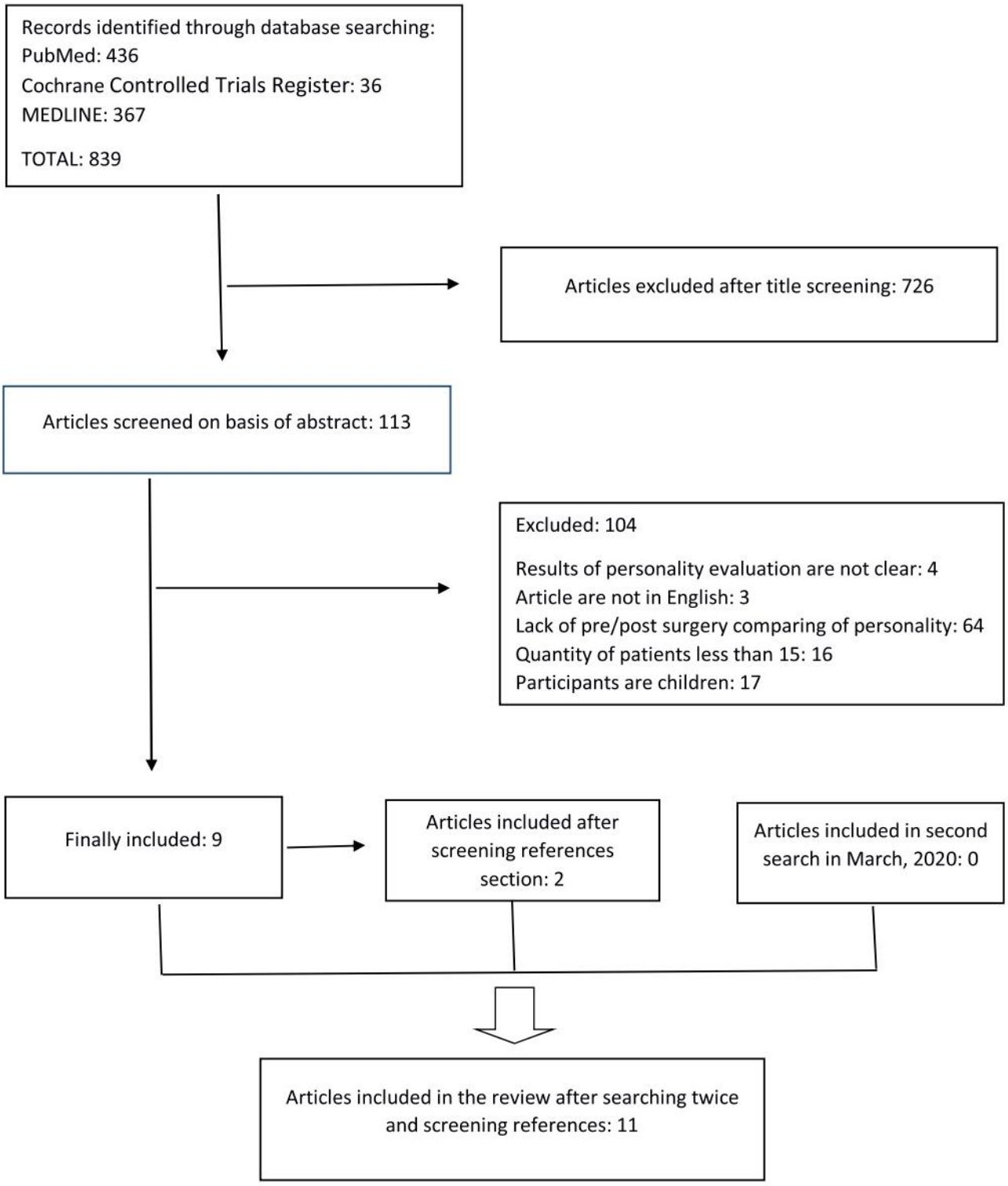

Fig. 1. Chart of studies selected.

Preferred Reporting Items of Systematic Reviews and MetaAnalyses (PRISMA) statement [15].

We conducted this study according to the protocol registered in advance on PROSPERO with ID: CRD42020208243.

2.1. Data sources and search strategy

A literature search was performed using electronic databases such as PubMed, Medline, and the Cochrane Controlled Trials Register. The keywords used were personality, epilepsy, and surgery. The first search was done in November 2019, and the last search was performed in March 2020. The literature search, screening of abstracts, and selection of included trials was performed independently by two investigators (Iurina E., Pintor L.).

2.2. Study selection

We included studies which evaluated personality changes after ST for RE in adults. Only studies written in English were included. The minimum required quantity of patients in a study was 15 participants in order to take into account only original articles with statistical methodology, and avoid to introduce case reports or small series of cases. We included only observational longitudinal follow-up studies, which were case control studies or cohort studies, both prospective and retrospective. Only studies using personality questionnaires were selected, with a follow-up period greater than 6 months. No other limits were set in the study design.

2.3. Data extraction

The data extracted from eligible studies included: the number of participants, in the case of the presence of a control group reasons for comparing were indicated (localization of epileptogenic foci to be resected, seizure outcome postoperatively, and surgical vs non-surgical groups), duration of follow-up period, personality test and particular scales used, and the difference in scores on the personality measure following ST.

3. Results

Initially, 436 publications were identified in Pubmed, 367 in Medline and 36 studies were found in Cochrane Controlled Trials Register. After reviewing the titles, abstracts and removing duplicates, nine studies remained. The references in the studies included from the first round were also reviewed, and two papers were added. Therefore, a total of 11 studies were identified for inclusion in this review. The flowchart shown in Fig. 1 details this process.

A summary of the selected studies is shown in Table 1. In 7 out of 11 studies, after surgery the epileptic patients showed more adaptive personality traits, a decrease in scales of neuroticism, impulsivity, hypochondriasis, paranoidism or increase in control scales. One study showed less appropriate management of emotions. The remaining 3 out of 11 studies showed no changes in personality measures.

8 out of 11 the studies had a comparative group; four studies compared changes in personality according to the localization of epileptogenic area, three studies compared seizure-free (SF) and non seizure-free (NSF) patients, and one study compared surgical and non-operated groups. The sample sizes varied from 24 to 194 participants. The postsurgical follow-up duration ranged from 6 to 24 months. Seven studies applied *The Minnesota Multiphasic Personality Inventory (MMPI)* [16,17], two studies administered *The Iowa Scales of Personality Change* [18], and each of the following measures was used by one study: *The Karolinska scale of personality* [19], *The German personality inventory* [20], and *The Millon Clinical Multiaxial Inventory-II* [21]. *Caudality* was included as an additional scale in one of the studies reviewed, which differentiates frontal from more posterior lesions by MMPI features [22].

Following subsections describe postsurgical personality changes in PWE between groups according to reasons for compare in studies reviewed.

3.1. Influence of localization of epileptic foci to be resected on postsurgical personality changes

One study compared an insular resection group with a TLE cohort [26]. The insular resection group increased in scales of irritability, frugality, anxiety and emotional lability. The TLE group worsened in the "lack of stamina" scale. Another study compared TLE and frontal lobe epilepsy groups, and personality traits remained stable following surgery in both groups [23].

Witt et al. [27] investigated TLE and extra-TLE groups and compared them based on the lateralization of epileptogenic area. There were no deviant differences in these scores, neither pre- nor postoperatively in patients compared with estimated healthy population means. Differences were observed between the subgroups of patients with left and right TLE. The SF left TLE group showed enhanced emotional stabilization, and neuroticism subscale hyperemotionality was decreased, whereas the SF right temporal group showed significantly lower scores in neuroticism items, anxiety and vegetative symptoms postoperatively. The SF right group also showed a decrease in impulsivity – a subscale of organic psycho-syndrome. Meier et al. [28] reported on the improvement in schizoadaptive behavior implications: the right TLE group showed reductions in schizophrenia scale scores, while the left TLE group demonstrated reduced in paranoia and social introversion. Only paranoia item scores changed from being within the clinically significant level to the normal range. Another study comparing TLE and extra-TLE personality changes [8] evaluated the proportion of patients with persistence of any dysfunctional personality pattern pre- and post-surgery. After ST, the proportion of patients with poorly adjusted personality patterns (score above 85 on *The Millon Clinical Multiaxial Inventory-2*) decreased from 70 % to 58 %. The personality patterns with the most significant score reductions were histrionic, narcissistic, antisocial, aggressive, and passive-aggressive. Neither the epileptogenic zone localization nor the lateralization was associated with this decrease.

3.2. Influence of seizure freedom as a surgical outcome on changes in personality

The SF group compare to the NSF decreased in subscales of organic psycho-syndrome and neuroticism following ST in the study of Witt et al. [27]. Another study [29] found a significant decrease in hypochondriasis in the SF group. Changes were seen in the frames of the normal (not deviant) interval of the scores mentioned. Wachi and colleagues in their research [30] concluded that all participants showed decreased scores for infrequency, psychasthenia, hypochondriasis, and schizophrenia in 1 year after ST, without significant differences between the SF and NSF groups. In the study of Wheelock et al. [31] scales depression and psychasthenia were assessed in two postsurgical evaluations: at 2-months and 1-year follow-ups. All patients showed increased above average population scores on both scales at the baseline. The SF group showed a gradual decrease in depression and psychasthenia to levels within the normal range for these traits, whereas NSF patients showed improvement within a short follow-up, but returned to the baseline or even worse within 1 year post-surgery.

3.3. Longitudinal changes in 2 times measured studies

Meldolesi et al. [32] compared the MMPI data obtained at 1- and 2-year follow-ups. Changes were seen within average population interval. Decreases on social introversion and paranoia scales were seen at both time points. In scales used to assess truthfulness, the 'lie' and 'defensiveness' sub-scale scores were increased after surgery, suggesting

Table 1
Summary of method and results of the studies included in the review.

First Author, year of publication, reference	Type of study	Sample	Period of follow-up	Evaluating of personality	Seizure outcome	Changes in personality after surgery
Novais, 2019 [8]	Comparative, loci of epileptic area	N=168, temporal epileptogenic zone N=26, extratemporal epileptogenic zone	1 year	Millon Clinical Multiaxial Inventory-2	N/A	The reduction in the proportion of patients with a dysfunctional personality patterns was observed without association with localization of epileptic area.
Hebert-Seropian, 2017 [26]	Comparative, loci of epileptic area	N=19, insular epilepsy N=19, temporal lobe epilepsy	> 6 months	Iowa Scales of Personality Change	There were no significant differences between groups in seizure outcome by Engel's classification (p=0.12). Average (insular group) meaning= 121; SD=0.54	The insular group demonstrated significant increased scores of Irritability, Lability/ Moodiness, Anxiety and Frugality. TLE group showed significant increased scores of Anxiety, Lack of stamina and Vulnerability to pressure. A significantly higher proportion of patients from the TLE group worsened in Lack of stamina in comparison to the insular group.
King, 2017 [24]	No comparative study.	N=27	>6 months	The Iowa Scales of Personality Change; Minnesota Multiphasic Personality Inventory-2	International League Against Epilepsy (ILAE) seizure outcome classification system ratings averaged 1.89 (SD = 1.22).	Personality and behavior characteristics remained stable.
Engman, 2012 [23]	Comparative, loci of epileptic area	N=39, temporal lobe epilepsy N= 11, frontal lobe epilepsy	2 years	Karolinska Scales of Personality	N/A	Personality features remained stable.
Witt, 2008 [27]	Comparative, loci of epileptic area	N = 26, extratemporal lobe epilepsy (right n=11 left =15); N = 125, temporal lobe epilepsy (right n=65, left =60)	1 year	German personality inventory (Fragebogen zur Persunlichkeitbei zerebralen Erkrankungen).	70.2 % of the patients became seizure-free, i.e. they did not have one single seizure nor any aura within the last 12 months.	All patients showed reduction in Organic Psycho-syndrome and Neuroticism scales.Organic Psycho-Syndrome scale.
Meldolesi, 2007 [32]	No comparative study	N=52, temporal lobe epilepsy	1 year and 2 years	Minnesota Multiphasic Personality Inventory	1-year follow-up outcome: 42 (81 %) completely SF (Engel 1a); 5 (10 %) presented not-disabling auras (Engel 1b); 4 (8%) suffered from rare (1–3 per year) disabling seizures (Engel class 2), 1(2%) - significant improvement in seizure frequency and severity (Engel class 3). Two years after surgery outcome: 43 (83%) -Engel class 1a, 3 (6%) Engel class 1b, and 6 (12%) - Engel class 2.	Patients decreased in the Social Introversion and Paranoia clinical scales scores; and increased in control scales the Lie and Defensiveness in both follow-up evaluations,
Derry, 2002 [29]	Comparative study, outcome of surgery (seizure free or not)	N=12 seizure-free; N=12 not seizure free	2 years	Minnesota Multiphasic Personality Inventory - 2	SF=12 (no auras or simple partial seizures nor any other kind of epileptic symptoms). NSF=12 (seizures per month: M=4.4, SD=3.7)	SF patients decreased in Hypochondriasis scale mean.
Wachi, 2001 [30]	Comparative study, outcome of surgery (seizure free or not)	N=16, seizure-free; N = 10, not seizure free	1 month, 1 year	Minnesota Multiphasic Personality Inventory	SF=16; NSF=10. The SF group included those who did not have any complex partial or grand mal seizures in the year after the surgery. Auras did not exclude patients from the SF group. the seizure frequency was reduced by 90 %. In 2, the seizure frequency decreased by 75–90 %. In 2 patients the seizure frequency remained the same as that before the surgery.	All patients decreased in the scores of Infrequency, Hypochondriasis, Psychasthenia and Schizophrenia in 1-year follow-up.
Rose, 1996 [25]	No comparative study	N=45	1 year	Minnesota Multiphasic Personality Inventory - adapted Neuroticism scale only was assessed.	SF=20, NSF=25	Changes in Neuroticism were not significant.

(continued on next page)

Table 1 (*continued*)

First Author, year of publication, reference	Type of study	Sample	Period of follow-up	Evaluating of personality	Seizure outcome	Changes in personality after surgery
Wheelock, 1998 [31]	Comparative study, outcome of surgery (seizure free or not)	N=55, seizure-free N=24, not seizure free	2 months; 1 year	Minnesota Multiphasic Personality Inventory - only Depression and Psychasthenia scales were evaluated.	SF=55, NSF=24 reduction in seizures after surgery.	SF group showed improvements at both follow-ups;
Meier, 1965 [28]	Comparative study, surgery group vs non surgery group	N=38, temporal lobe epilepsy, of which: N=15 temporal lobectomy left; N=23 N=40, non-operated control group	1 year	Minnesota Multiphasic Personality Inventory; Two additional measures were included for analysis: the Caudality scale and an Index of Psychopathology.	N/A	Non-surgical group demonstrated no any changes in evaluated scales.

greater social desirability and self-control.

Another study [30] with follow-up periods of 1-month and 1-year reported a gradual decrease in scores for infrequency, hypochondriasis, psychasthenia, and schizophrenia at both evaluations, which only reached statistical significance at the one-year time point, and without changes between SF and NSF groups.

Another study [31] with a similar design, - two measures at 2 months and one year post-surgery - using only psychasthenia and depression scales, and found changes in both SF and NSF groups over time. The SF group showed reduced depression and psychasthenia throughout the entire follow-up, whereas the NSF group improved after 2 months but then returned to baseline after 1 year.

3.4. Neuroticism changes

Two of three evaluating neuroticism studies detected no changes in this personality dimension [25,23], but Witt et al. [27] found decreasing in a few subscales from the neuroticism global scale in SF group only.

4. Discussion

To our knowledge, this is the first systematic review investigating personality changes of PWE following ST. The discussion section is structured by the subsections reflecting personality changes in PWE following ST, according to postsurgical seizure outcome, localization of epileptogenic area to be resected, and duration of follow-up. Also, the neuroticism changes section is presented to focus on this important personality forming dimension which increased scores are linked with epilepsy according to the previous studies.

4.1. Localization of epileptogenic focus to be resected and personality changes

The localization of epileptogenic area influences the state of epilepsy, which might mean differences in neurophysiological outcome following ST. The insula is known to be involved in emotion formation and processing, and insula damage could lead to disruption in these functions. The insula resection group [26] had emotional disturbances postoperatively compared to the temporal cohort.

Three studies [23,8,27] detected no differences in personality features post-surgery when comparing a temporal group with an extra-temporal group. However, there were different personality changes in TLE patients with left compared to right lateralization [27,28]. Both groups demonstrated improvements in the same domains, but on different subscales. Despite the limitations and preoperative differences in neuropsychological features between groups [8], the common outcome seems robust and showed personality changes can depend on lateralization of epileptogenic area and only in the TLE.

4.2. Influence seizure freedom as a surgical outcome on changes in personality

Almost all studies found an association between seizure freedom and changes in the patients' personality. Seizures and interictal epileptic activity influenced epilepsy-specific personality domains such as organic psycho-syndrome and neuroticism [27], hypochondriasis [29], and psychasthenia [31]. Only one study [30] reported no changes between SF and NSF groups. However, despite the fact that the NSF group still had seizures, their seizure frequency was decreased by 75–90 % in 8 of 10 patients in this study. Thus, it could be inferred that reduction in seizure frequency, rather than complete seizure elimination, results in improved neuropsychological functioning in patients. Another study [31] found no difference in psychasthenia scores between SF and NSF groups in a short follow-up: both groups showed significant improvements on this scale meanings at the 1st postsurgical measure (2 months), but afterwards, only the NSF group declined to the baseline after 1 year. The difference between short and long-term data illustrates these personality features require more time to improve.

4.3. Longitudinal changes in studies with 2 time points

Whilst personality trait changes seem to be stable by one year post-surgery, the presence of further changes at two years shows that personality changes may be more gradual, and longer follow-ups may be required. Improvements are observed on both in clinical and truthfulness scales at both follow-up time points [32]. Gradual improvements on personality tests in 1-month and 1-year follow-ups was reported by another study [30]. Seizure freedom was associated with a stable improvement in psychasthenia at both follow-ups, whereas the NSF group improved after 2 months and then returned to the baseline after 1 year [31]. The authors explained these results in the NSF cohort as a consequence of positive expectations of ST and hope for improving seizure status later, despite continuing seizures in a short follow-up. Thus, we can conclude improvement in personality appears within a short follow-up period and the process continues within at least the first 2 years, and is mostly associated with seizure freedom.

4.4. Neuroticism changes

Two out of three measured neuroticism studies detected no changes in this dimension following surgery [25,23]. *Witt et al.* [27] found only a decrease in some subscales of this scale postoperatively in SF patients. The question of whether neuroticism is an epilepsy-driven feature remains open and needs clarifying by further research.

5. Limitations

The main limitation of the current systematic review is due to the different questionnaires that were applied for personality evaluation in

patients. Different approaches were used in the completion of these questionnaires: some studies used responses given by close relatives/friends while others used responses given by the patients themselves. Furthermore, different personality domains were evaluated. Also, both poorly adjusted personality traits and normal personality dimensions were evaluated. Different study designs were also applied: comparative studies, cohort studies, case-control studies. The studies varied widely in sample size and evaluated personality after different length follow-up periods. Finally, only articles written in English were reviewed.

6. Conclusions

Personality dimensions in PWE may change following ST. Personality traits became more adaptive due to decreased impulsivity, hypochondriasis, psychasthenia or increased control scales.

Three studies showed no changes in personality post-surgery, while one showed increased emotional lability, which was characterized as a negative development.

Studies comparing SF and NSF groups after surgery showed a decrease in poorly adjusted personality traits in SF patients, primarily organic psycho-syndrome and neuroticism, hypochondriasis, and psychasthenia.

Development of personality changes may be displayed within a short follow-up in both SF and NSF patients, but at further follow-up these improvements were only maintained in groups that were seizure-free.

What factors can lead to personality changes following ST of RE?

It follows from the definition, that personality is mediated by biological and environmental factors. There are many factors that may affect patients suffering from RE apart from the burden of the disease itself: side effects of medication, stigma, restrictions in social and professional activity, high-risk of complications in pregnancy and many more. Considerable decrease in seizure frequency in patients improves these factors, and decreases distress-level, which together lead to favorable changes in emotional and behavioral domains of personality.

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Declaration of Competing Interest

The authors report no declarations of interest.

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References

[1] World Health Organization. International league against epilepsy, international bureau for epilepsy. Atlas: Epilepsy Care in the World; 2005. Geneva, Switzerland.
[2] Osório CM, Latini A, Leal RB, de Oliveira Thais MER, Vascouto HD, Remor AP, et al. Neuropsychological functioning and brain energetics of drug resistant mesial temporal lobe epilepsy patients. Epilepsy Res 2017;138(December):26–31. https://doi.org/10.1016/j.eplepsyres.2017.10.009. Epub 2017 Oct 12. PMID: 29040828.
[3] van Rijckevorsel K. Cognitive problems related to epilepsy syndromes, especially malignant epilepsies. Seizure 2006;15(June(4)):227–34. https://doi.org/10.1016/j.seizure.2006.02.019. Epub 2006 Mar 24. PMID: 16563807.
[4] Corr Philip J, Matthews Gerald. The Cambridge handbook of personality psychology (1. Publ. ed.). Cambridge: Cambridge University Press; 2009. ISBN 978-0-521-86218-86219.
[5] Sadock Benjamin, Sadock Virginia, Ruiz Pedro. Kaplan and Sadock's comprehensive textbook of psychiatry. Wolters Kluwer; 2017. ISBN 978-1-4511-0047-1.
[6] Kanner AM. Depression in epilepsy is much more than a reactive process. Epilepsy Curr 2003;3(6):202–3. https://doi.org/10.1046/j.1535-7597.2003.03609.x. 2003.
[7] Tarsitani L, Bertolote JM. Major depressive comorbidity in epilepsy as a reactive process to a chronic condition. Epilepsy Behav 2006;8(1):343–4. https://doi.org/10.1016/j.yebeh.2005.08.021. 2006.
[8] Rassart J, Luyckx K, Verdyck L, Mijnster T, Mark RE. Personality functioning in adults with refractory epilepsy and community adults: implications for health-related quality of life. Epilepsy Res 2020;2020(159):106251. https://doi.org/10.1016/j.eplepsyres.2019.106251.
[9] Rivera Bonet CN, Hermann B, Cook CJ, Hwang G, Dabbs K, Nair V, et al. Neuroanatomical correlates of personality traits in temporal lobe epilepsy: findings from the Epilepsy Connectome Project. Epilepsy Behav 2019;98(Pt A):220–7. https://doi.org/10.1016/j.yebeh.2019.07.025. 2019.
[10] Shehata GA, Bateh AE. Cognitive function, mood, behavioral aspects, and personality traits of adult males with idiopathic epilepsy. Epilepsy Behav 2009;14(1):121–4. https://doi.org/10.1016/j.yebeh.2008.08.014. 2009.
[11] Novais F, Loureiro S, Andrea M, Figueira ML, Pimentel J, Câmara Pestana L. May the right-side epileptogenic zone be a predictor of psychiatric comorbidity in people with refractory epilepsy? Laterality 2019;25(3):275–84. https://doi.org/10.1080/1357650X.2019.1662431. 2020.
[12] Park CH, Choi YS, Jung AR, Chung HK, Kim HJ, Yoo JH, et al. Seizure control and memory impairment are related to disrupted brain functional integration in temporal lobe epilepsy. J Neuropsychiatry Clin Neurosci 2017;29(4):343–50. https://doi.org/10.1176/appi.neuropsych.16100216. 2017.
[13] Helmstaedter C. Behavioral aspects of frontal lobe epilepsy. Epilepsy Behav 2001;2(5):384–95. https://doi.org/10.1006/ebeh.2001.0259. 2001.
[14] Leong M, Wang AD, Trainor D, Johnstone B, Rayner G, Kalincik, et al. Personality profiles differ between patients with epileptic seizures and patients with psychogenic non-epileptic seizures. Seizure 2019;2019(73):1–8. https://doi.org/10.1016/j.seizure.2019.10.011.
[15] Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JPA, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. J Clin Epidemiol 2009;62(10):e1–34. https://doi.org/10.1016/j.jclinepi.2009.06.006. 2009.
[16] Hathaway SR, McKinley JC. Minnesota multiphasic personality inventory, manual. New York: Psychological Corporation; 1951.
[17] Butcher J, Dahlstrom W, Graham J, Tellegen A, Kraemer B. Manual for administration and scoring the Minnesota multiphasic personality Inventory-2: MMPI-2. Minneapolis: University of Minnesota Press; 1989.
[18] Barrash J, Anderson SW, Hathaway-Nepple J, Jones RD, Tranel D. The Iowa scales of personality change. Iowa City: University of Iowa College of Medicine, Dept. of Neurology; 1997.
[19] Ortet-Fabregat Generós, Ibáñez Manuel, Llerena Adrián, Torrubia Rafael. The Underlying Traits of the Karolinska Scales of Personality (KSP)The underlying traits of the karolinska scales of personality (KSP). Eur J Psychol Assess 2002. https://doi.org/10.1027//1015-5759.18.2.139.
[20] Helmstaedter C, Gleiner U. Fragebogen Zur Persnlichkeit Bei Zerebralen Erkrankungen. Bonn: University Hospital of Epileptology, Rheinische Friedrich-Wilhelms-Universitat; 1999.
[21] Millon T. Millon clinical multiaxial inventory: I & II. J Couns Dev 1992;70(3):421–6. https://doi.org/10.1002/j.1556-6676.1992.tb01627.x.
[22] Williams HL. The development of a caudality scale for the MMPI. J Clin Psychol 1952;1952(8):293–7. https://doi.org/10.1002/1097-4679(195207)8:3<293::aid-jclp2270080313>3.0.co;2-p.
[23] Engman E, Malmgren K. A longitudinal study of psychological features in patients before and two years after epilepsy surgery. Epilepsy Behav 2012;24(2):221–6. https://doi.org/10.1016/j.yebeh.2012.03.032.
[24] King ML, Tranel D. Stable psychological functioning after surgery for epilepsy: an informant-based perspective. Epilepsy Behav 2017;69:110–5. https://doi.org/10.1016/j.yebeh.2017.01.028.
[25] Rose KJ, Derry PA, McLachlan RS. Neuroticism in temporal lobe epilepsy: assessment and implications for pre- and postoperative psychosocial adjustment and health-related quality of life. Epilepsia 1996;37(5):484–91. https://doi.org/10.1111/j.1528-1157.1996.tb00595.x.
[26] Hébert-Seropian B, Boucher O, Sénéchal C, Rouleau I, Bouthillier A, Lepore F, et al. Does unilateral insular resection disturb personality? A study with epileptic patients. J Clin Neurosci 2017;43:121–5. https://doi.org/10.1016/j.jocn.2017.04.001.
[27] Witt JA, Hollmann K, Helmstaedter C. The impact of lesions and epilepsy on personality and mood in patients with symptomatic epilepsy: a pre- to postoperative follow-up study. Epilepsy Res 2008;82(2–3):139–46. https://doi.org/10.1016/j.eplepsyres.2008.07.011.
[28] Meier MJ, French LA. Changes in MMPI scale scores and an index of psychopathology following unilateral temporal lobectomy for epilepsy. Epilepsia 1965;6(3):263–73. https://doi.org/10.1111/j.1528-1157.1965.tb03794.x.
[29] Derry PA, Harnadek MCS, McLachlan RS, Sontrop J, Blume WT, Girvin JP. A longitudinal study of the effects of seizure symptoms on the Minnesota Multiphasic Personality Inventory-2 (MMPI-2) clinical interpretation. J Clin Psychol 2002;58(7):817–26. https://doi.org/10.1002/jclp.2005.
[30] Wachi M, Tomikawa M, Fukuda M, Kameyama S, Kasahara K, Sasagawa M, et al. Neuropsychological changes after surgical treatment for temporal lobe epilepsy. Epilepsia 2001;42:4–8. https://doi.org/10.1046/j.1528-1157.42.s6.1.x.
[31] Wheelock I, Peterson C, Buchtel HA. Presurgery expectations, postsurgery satisfaction, and psychosocial adjustment after epilepsy surgery. Epilepsia 1998;39(5):487–94. https://doi.org/10.1111/j.1528-1157.1998.tb01410.x.
[32] Meldolesi GN, Di Gennaro G, Quarato PP, Esposito V, Grammaldo LG, Morosini P, et al. Changes in depression, anxiety, anger, and personality after resective surgery

for drug-resistant temporal lobe epilepsy: a 2-year follow-up study. Epilepsy Res 2007;77(1):22–30. https://doi.org/10.1016/j.eplepsyres.2007.08.005.

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Personality changes in patients suffering from drug-resistant epilepsy after surgical treatment: a 1-year follow-up study

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ABSTRACT

Objective: To determine changes in dimensions of personality in a sample of patients suffering from drug-resistant epilepsy at the 1-year follow-up following surgery, compared to non-surgically treated controls.

Methods: We conducted a prospective comparative controlled study, including drug-resistant epilepsy surgery candidates. Demographic, psychiatric, neurological, and psychological data were recorded. Presurgical and 12-months follow-up evaluations were performed. Personality dimensions were measured by the NEO Five-Factor Inventory, Revised version (NEO-FFI-R), anxiety and depression symptoms were assessed by the Hospital Anxiety and Depression Scale (HADS: HADA-Anxiety and HADD-Depression), psychiatric evaluations were performed using the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV) Axis-I disorders classification. Statistical analysis consisted of comparative tests, correlation analysis, and the stepwise multiple regression test (ANOVA).

Results: A 1-year follow-up was completed by 70 out of 80 patients. Through the study, the surgical group decreased in neuroticism and increased in agreeableness. The controls increased in consciousness, and these changes were predicted by the earlier age of epilepsy onset and lesser score in HADD at the baseline. No personality changes were associated with seizure frequency. The presurgical evaluation concluded that both groups had no differences in demographic, psychiatric, or neurological variables with the only exception being for the number of seizures per month, which was higher in the surgical group. Psychiatric comorbidity in patients was associated with their higher degree of neuroticism and agreeableness at the baseline.

Comparing control and surgical groups at the one-year follow-up, the agreeableness personality variable was higher in the surgical group, and as expected, HADS scores were higher in the control group, and seizure frequency was also higher in the control group.

Significance: Higher agreeableness was the most relevant difference in personality dimensions in patients who underwent surgical treatment compared with the non-surgical treatment group. After surgery patients decreased in neuroticism and increased in agreeableness scores.

1. Introduction

Epilepsy is a common neurological disorder affecting more than 50 million people all over the world (Ngugi et al., 2011). There are about 30 % of patients with epilepsy who do not have an adequate response to antiepileptic pharmacotherapy (Kwan and Brodie, 2000). Drug-resistant (or refractory) epilepsy is defined when attempts to choose an appropriate drug treatment are unsuccessful after two different antiepileptic

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drug therapies and uncontrolled seizures continue (Kwan et al., 2010).

Drug-resistant epilepsy is associated with a high burden on health care, patients' low index of quality of life, and high comorbidity, especially with psychiatric diseases (Janson and Bainbridge, 2021; Hitiris et al., 2007). Surgery is the treatment of choice in the case of diagnosed drug-resistant epilepsy, and it aims to achieve a seizure-free outcome and improve the quality of a patient's life (Duncan et al., 2006; Wiebe et al., 2002).

It is known that, compared to the general population, epileptic patients can exhibit specific features of personality; for instance, a high level of aggression (Shehata and Bateh, 2009) and dysfunctional personality patterns (Novais et al., 2019; Bear and Fedio, 1977). As for non-pathological personality dimensions, epileptic patients can show a high level of neuroticism (Rivera Bonet et al., 2019) and a low level of openness to experience (Leong et al., 2019), compared to the general population.

After analyzing personality changes in patients with drug-resistant epilepsy following successful surgical treatment, the decrease in the expression of pathological personality traits and the reductions of subscales of neuroticism and organic psycho-syndrome were reported (Novais et al., 2019; Witt et al., 2008). Such pathological personality patterns such as social introversion, paranoia, psychasthenia, hypochondriasis, and schizophrenia significantly decreased following surgical treatment in patients suffering from drug-resistant epilepsy in observational follow-up studies using the *Minnesota Multiphasic Personality Inventory (*MMPI) (Meldolesi et al., 2007; Derry et al., 2002; Wachi et al., 2001; Meier and French, 1965). In contrast, some researchers revealed no personality changes in patients with epilepsy following surgical treatment (Engman and Malmgren, 2012; King and Tranel, 2017).

Epileptic patients show higher neuroticism compared to the general population (Rassart et al., 2020), and some studies focused on this dimension. Some authors reported neuroticism did not change following surgery (Engman and Malmgren, 2012; Rose et al., 1996), but *Witt with colleagues* (Witt et al., 2008) demonstrated changes in some subscales of this dimension in their research. A recent systematic review (Iurina et al., 2021), studied personality changes in patients with drug-resistant epilepsy following surgical treatment, and came to the conclusion, that some personality dimensions could change following surgery. These changes can differ according to the localization of the epileptogenic area; for example, the insular resection group became more emotionally labile despite seizure freedom, compared to the temporal group who increased in lack of stamina scale (Hébert-Seropian et al., 2017).

Seizure freedom as an outcome of surgical treatment can influence the existence of adaptive personality changes and their severity. Favourable personality changes can be seen from early follow-up assessments even in patients who were not seizure-free, though further follow-ups showed that improvements after 1–2 years were specific to seizure-free patients. Taking into account that pathological personality features are the result of a continuing interictal process and brain structure damage caused by epileptic activity or side effects of antiepileptic treatment (Hessen et al., 2007), it is expected that achieving seizure freedom may lead to changes in the severity of these personality traits in patients and recovery from several psychiatric symptoms. Reviewing current literature revealed a lack of studies to analyse changes in non-pathological personality features following surgery in drug-resistant epilepsy. The present study aimed to evaluate the changes in dimensions of personality using the NEO-FFI-R questionnaire in drug-resistant epilepsy patients who underwent surgical treatment, compared to a control group in one-year follow-up.

2. Methods

2.1. Design

We carried out an observational, prospective cohort study, in which a study group of drug-resistant epileptic patients, who underwent surgical treatment, was compared with a control group consisting of patients suffering from drug-resistant epilepsy treated with antiepileptic drugs. Both groups were followed up to 1 year after being included in the study.

2.2. Setting and participants

This research was conducted at the Hospital Clinic of Barcelona. The study was approved by the Hospital Ethics Committee. Subjects were recruited from the Epilepsy Unit of the Neurology Service, which receives referrals from the whole of Spain.

The general evaluation protocol consisted of the following points: all participants signed informed consent; the patients were evaluated to confirm the diagnosis of drug-resistant epilepsy according to the International League Against Epilepsy protocol (Scheffer et al., 2017) and were assessed for the possibility of surgical intervention. Patients with one or more of the clinical conditions listed below were excluded from the current study:

1) history of serious medical pathology except for epilepsy;
2) mental retardation: IQ < 70;
3) presence of severe dementia previously diagnosed;
4) schizophrenia or other chronic psychosis;
5) non-epileptic psychogenic seizures;
6) surgical intervention for control of previous epileptic seizures.

Those, who met the inclusion criteria of the study, but had contraindications for surgery according to the Epilepsy Committee report, constituted the control group.

2.3. Clinical assessments

Demographic, clinical, psychiatric, and psychological variables were collected. Demographic data collection form included age, gender, education, occupation, and marital state. Clinical data consisted of information about the age of the epilepsy onset in months, etiology of epilepsy, localization, and laterization of epileptogenic foci, type of epileptic seizures, dichotomic measure of a number of seizures at the baseline ("5 or less per month" or "more than 5 per month"), and a number of seizures per month in the last 6 months. Psychiatric evaluations were performed by a psychiatrist, and they included DSM-IV Axis-I disorders and HADS – depression and anxiety scale. Evaluation of personality dimensions was performed by using NEO-FFI-R (Aluja et al., 2005). The revised NEO-FFI (NEO Five-Factor Inventory) is a short version of the NEO-PI-R (Revised NEO Personality Inventory) questionnaire and has 60 items (12 per domain) for self-assessing the five major personality dimensions: neuroticism, extraversion, openness to experience, agreeableness, and conscientiousness.

The patient must indicate his/her degree of agreement with the statement using a score from 0 to 4 from "total disagreement" to «totally agree» respectively. The minimum score for any domain is 0, and the maximum is 48. The average scores of each variable in the Spanish population are: Neuroticism: Mean = 23.48, SD = 9.04; Extraversion: Mean = 29.73, SD = 7.50; Openness to experience: Mean = 30.66, SD = 7.22; Agreeableness: Mean = 36.15, SD = 6.63; Conscientiousness: Mean = 33.38, SD = 7.66. Neuroticism is a disposition to experience negative effects, such as anger, irritability, emotional instability, anxiety, and depression. Extraversion is characterized by sociability, assertiveness, high activity level, positive emotions, and in search of stimulation. Openness trait involves being creative, curious, interested in new experiences and being emotionally and artistically sensitive. Agreeableness is the domain of emphatic emotion, expressing the ability to help and cooperate for the well-being of society. Conscientiousness reflects the tendency to be responsible, strong willed, persistent, organized, goal-directed, and adherence to rules and ethical principles.

Anxiety and depressive symptoms were assessed by Hospital Anxiety and Depression Scale (HADS). The Spanish version of HADS was applied for evaluating depression (HAD - D) and anxiety (HAD - A) (Herrero et al., 2003). It contains 14 items, 7 of which are for self-assessing the level of depression and 7 for anxiety. Every subscale should be scored by the patient from 0 to 3 according to the severity of the item. Accordingly, the patient can score from 0 to 21 points on each scale. More than 10 points out of 21 in every subscale is considered as a probable indicator of clinical anxiety or depression.

The clinician version of the Structured Clinical Interview for DSM-IV (SCID-CV; Spanish version) (First et al., 1996) was used to assess DSM-IV Axis-I disorders. We grouped psychiatric comorbidity into two clusters: "yes"/"no". The following psychiatric conditions were evaluated: 1) affective disorders, including major depressive episodes, recurrent depression, dysthymic disorder, affective disorder due to a medical condition or substance disorder, adjustment disorder, and bipolar disorder; 2) anxiety disorders, including panic disorder, phobia, obsessive-compulsive disorder, posttraumatic stress disorder, and other anxiety disorders; 3) schizophrenia or schizoaffective disorder and other psychosis; 4) eating disorders; 5) conduct disorder; and 6) substance use disorder.

2.4. Procedure

All participants provided written informed consent at the time of their enrollment in the outpatient setting of the Epilepsy Unit. Drug-resistant epilepsy was diagnosed according to the International League Against Epilepsy protocol. Accepted patients were referred for admission to a neurology ward for a week evaluation.

Clinical evaluation included video-electroencephalography (EEG) monitoring, a 3 - Tesla brain magnetic resonance with an epilepsy protocol, functional magnetic resonance imaging (fMRI), positron emission tomography scans to indicate the epileptogenic zone, neuropsychological tests, the psychiatric evaluation, and a psychological evaluation through the NEO-FFI-R. Taking all these results into account the committee board made a decision on the surgery suitability for every patient. The epilepsy committee comprises neurologists, psychiatrists, neurosurgeons, neuroradiologists, neuropsychologists, psychologists, and nuclear medicine specialists.

Those who had contraindications for surgical intervention formed the control cohort. Surgical candidates were paired with the same time following patients, who composed the control group and underwent all assessment procedures at the same time interval respectively to the surgical intervention at the baseline and in 1 year after surgery. Non-surgical patients were maintained on a standard medication regimen during the follow-up period. The postoperative evaluation 1-year following surgical treatment involved the following procedures: the psychiatric evaluation (HADS), the clinical psychology assessment (NEO-FFI-R), and a clinical interview to collect neurological data.

2.5. Statistical analysis

Statistical analysis was performed using Version 22 of SPSS for Windows and differences were considered significant at $p < 0.05$.

Distributions of variables were examined by Shapiro-Wilk Test according to our sample size and appropriate tests were applied for further analysis.

The intention to treat approach was carried out in order to see if the 10 drop-out patients were different from patients finishing the follow-up. A descriptive analysis of all variables was performed at the baseline. The group of controls and the surgical group were compared to detect initial differences between groups, using a Student's *t*-test, Pearson's chi-square test, Mann–Whitney *U* test according to the type of every variable and its distributions. When a difference was found, how it affected personality was examined using Kruskal-Wallis tests and Student's *t*-test. Also, stepwise multiple regression (ANOVA), Student's *t*-test, and Spearman correlation analysis was run for all the independent variables to reveal how they are initially associated with the personality profile. The independent variables included age, gender, type of epilepsy, location, laterality, etiology, age at epilepsy onset, HADS, and mental disorders (existence or absence: yes/no).To evaluate changes in psychological and psychiatric test results from baseline to 1-year follow-up, Student's *t*-test, within-subjects Wilcoxon signed-rank test, and Spearman correlation tests were performed. Adjustments for multiple tests were performed using the Games-Howell procedure.

Those variables of personality test that reached statistical significance in 1-year follow-up were introduced into stepwise multiple regression analysis. Multiple regression was used to determine the contribution of each variable at the baseline on the changes in personality dimensions at the 1-year follow-up. Also, such data as seizure frequency at the baseline, seizure frequency at the 1-year follow-up, and the variable reflecting changes in this item in pre/post follow-up period were included in the Spearman correlation tests to be compared with variables indicating changes in personality dimensions.

3. Results

Of 80 eligible patients, 70 completed the neuropsychiatric assessment at the 1-year follow-up, 28 underwent surgery, and 42 were not suitable for surgery (control group). In the intention to treat approach, no statistical differences in sociodemographic, clinical, or neuropsychiatric variables were revealed between patients who completed the study and patients who were lost to 1-year follow-up ($n = 10$).

3.1. Descriptive analysis at baseline and comparison between groups

Sociodemographic, clinical, and neuropsychiatric variables at the baseline in the whole sample and the differences between groups are shown in Table 1.

Given that we found the baseline differences in the number of seizures at the basal time (per month), we analyzed this variable affection on the personality dimensions. Thus, in Table 2, we compared personality dimensions according to the basal seizure frequency dichotomized, and no differences between both groups were observed. Tables 3A and 3B presents the analysis of how personality dimensions were associated with all the independent sociodemographic and clinical variables at the baseline.

3.2. Longitudinal analysis of one-year follow-up outcomes

Table 4 shows longitudinal changes in personality, mood, and seizure frequency in the surgical and non-operated group through the study, as well as differences between groups at the one-year follow-up. Significant differences between basal and 1-year meanings in the surgical group were observed in decreased neuroticism (Mean = 4.46, SD = 6.05, $p = 0.001$*), and increased agreeableness scores (Mean=-2.16, SD = 4.20, $p = 0.011$*). Conscientiousness increased in the control group through the 1-year follow-up: Mean=-2.36, SD = 4.71, $p = 0.002$*.

The comparison of control and surgical groups revealed the only significant difference in agreeableness personality variable, being higher in the operated group ($p = 0.007$*).

The number of seizures diminished significantly in the surgical group only (Mean = 26.04, SD = 37.52, $p = 0.000$**). Differences were observed in the number of seizures per month comparing both groups of patients at the one-year follow-up, with higher scores in the controls: $z=-5.394$, $p = 0.000$**.

We evaluated how the variable, reflected personality changes from the baseline to the 1-year after surgery, depended on the number of seizures at the one-year follow-up and pre-post differences in seizures frequency: no statistically significant associations with these variables were observed either in the surgical group or the control group.

Table 5 demonstrates changes in mood and differences between

Table 1
Sociodemographic and clinical variables at baseline and differences between groups.

	Whole sample group (n = 70)			Surgical group (n = 28)			Control group (n = 42)			Differences between surgical and control group, p-value
	%	Mean	SD	%	Mean	SD	%	Mean	SD	
Sociodemographic										
Age		36.94	10.93		35.00	8.49		38.24	12.22	0.195
Gender:										0.728
Women	55.7			53.6			57.1			
Men	44.3			46.4			42.9			
Education:										0.768
Basic education	45.7			46.4			45.2			
Secondary education	37.1			39.3			35.7			
Higher education	17.1			14.3			19			
Occupation:										0.073
Inactive	28.6			14.3			38.1			
Housewife/student	21.4			21.4			21.4			
Active	50			64.3			40.5			
Marital status:										0.519
Married	57.1			64.3			52.4			
Separated/widowers	12.9			7.1			16.7			
Single	28.6			28.6			28.6			
No data	1.4			0			2.4			
Neurologic										0.819
Idiopathic etiology	60.0			64.3			57.1			
Type of seizures:										0.599
No seizures	1.4			0			2.4			
Focal onset impaired awareness seizures	50.0			57.1			45.2			
Other focal onset seizures	15.7			14.3			16.7			
Unknown onset tonic- clonic seizures	20			14.3			23.8			
Generalized seizures	10.0			14.3			7.1			
Locus:										0.571
Temporal	57.1			64.3			52.4			
Extratemporal	24.3			25.0			23.8			
Unestablished	15.7			10.7			19			
Hemisphere:										0.400
Right	44.3			42.9			45.2			
Left	37.1			46.4			31			
Bilateral	12.9			7.1			16.7			
Unknown	1.4			0			2.4			
Age (months) of epilepsy onset		193.6	180.34		139.57	120.77		229.62	204.46	0.068
Number of seizures at the basal time (per month)		21.11	35.71		26.04	37.52		17.83	34.52	0.040*
Psychiatric assessment:										
Psychiatric comorbidity	37.1			50			12			
HADS scale:										
HAD-Depression		3.93	3.41		4.59	4.09		3.49	2.86	0.308
HAD-Anxiety		6.59	3.52		7.16	3.87		6.18	3.21	0.203
Clinical psychology assessment										
NEO personality:										
Neuroticism		25.53	6.85		26.66	6.90		24.78	6.77	0.254
Extraversion		26.61	5.90		25.87	6.30		27.10	5.65	0.395
Openness to experience		27.55	6.27		27.46	6.51		27.60	6.19	0.923
Agreeableness		32.73	5.07		33.82	5.36		32.00	4.79	0.141
Conscientiousness		32.48	5.90		33.45	6.95		31.84	5.86	0.265

HADS scoring for each variable: Normal: 0–7; Borderline abnormal (borderline case): 8–10; Abnormal (case):11–21.
The average scores of each NEO-FFI-R variable in the Spanish population are: Neuroticism: Mean = 23.48, SD = 9.04; Extraversion: Mean = 29.73, SD = 7.50; Openness to experience: Mean = 30.66, SD = 7.22; Agreeableness: Mean = 36.15, SD = 6.63; Conscientiousness: Mean = 33.38, SD = 7.66.

surgical and control groups at the 1-year follow-up. HADA and HADD scores were higher in the control group, comparing to the surgical group at the 1-year follow-up ($p = 0.044^*$ and $p = 0.018^*$ relatively for anxiety and depression scores). The number of seizures diminished significantly in the surgical group only (Mean = 26.04, SD = 37.52, $p = 0.000^{**}$). Differences were observed in the number of seizures per month comparing both groups of patients at the one-year follow-up, with higher scores in the controls: $z=-5.394$, $p = 0.000^{**}$.

We evaluated how the variable, reflected personality changes from the baseline to the 1-year after surgery, depended on the number of seizures at the one-year follow-up and pre-post differences in seizures frequency: no statistically significant associations with these variables were observed either in the surgical group or the control group.

3.3. Predictive analysis from baseline variables to one-year follow-up outcomes

The surgical group increased in neuroticism and agreeableness, which was not predicted by any baseline variables of interest.

The controls increased in consciousness; these changes were

Table 2
Association of NEO-FFI personality dimensions and seizure frequency (intervals) at the baseline (presurgical evaluation) in a 70 drug-resistant epilepsy patients' sample.

	Seizure frequency	N of patients	Mean	SD	Differences between groups, p-value
Neuroticism	5 or less per month	30	24.94	6.87	p = 0.532
	More than 5 per month	40	25.98	6.88	
Extraversion	5 or less per month	30	26.99	4.68	p = 0.634
	More than 5 per month	40	26.33	6.72	
Openness to experience	5 or less per month	30	26.37	6.36	p = 0.174
	More than 5 per month	40	28.43	6.14	
Agreeableness	5 or less per month	30	32.59	4.35	p = 0.846
	More than 5 per month	40	32.83	5.59	
Conscientiousness	5 or less per month	30	32.93	5.82	p = 0.589
	More than 5 per month	40	31.15	6.02	

Personality was not associated with the seizure frequency in our sample.

predicted by the earlier age of epilepsy onset and lower depression scores at the baseline (R^2 = 27.8 %, p = 0.002, beta = - 0.363 and – 0.302 respectively). Also, the controls increased in HADS scores, which was not predicted by any baseline variables of interest.

4. Discussion

It was revealed that personality traits in patients with drug-resistant epilepsy change following surgical and pharmacological antiepileptic treatment at the 1-year follow-up, but in a different way depending on whether or not surgical treatment is carried out. This is the most important outcome of our study. These personality changes were not associated with seizure status. The most relevant features in our study were a decrease in neuroticism and an increase in agreeableness in the surgical group through the follow-up, and higher agreeableness in the surgical group compared with the control group one year after surgery.

Decrease in neuroticism one year after surgical treatment in epileptic patients was presented in another study (Witt et al., 2008) with 151 epileptic patients, with a mean age of 37.1 years. However, the German personality inventory was used for personality assessment in this case instead of being performed with the NEO-FFI-R as we did. The German personality inventory (*Fragebogen zur Persunlichkeit bei zerebralen Erkrankungen)* aims to identify behavioral and personality patterns in non-psychiatric patients with central nervous system disorders and epilepsy in particular. The scale of neuroticism corresponds to the identically named trait of the Big Five Personality Inventory, but includes some reflected pathological features subscales: vegetative symptoms, anxiety, somatization, hyperemotionality, reduced drive, obsession, and other-determination. Additionally, they reported on the personality changes in seizure-free patients only. With reference to somatic and psychic anxiety as items of the neuroticism-related scale, another study (Engman and Malmgren, 2012) also found a decrease in these features evaluated by the Karolinska Scale of Personality in 57 epileptic patients, with a mean age of the participants similar to ours, after surgical treatment. These neuroticism-related subscales are quite similar to the NEO - neuroticism item, but these items are part of a wider neuropsychological feature in the Karolinska Scale of Personality - from scales related to neuroticism and anxiety proneness. Personality changes were revealed in seizure-free patients only (Engel I). In another study (Rassart et al., 2020) with 53 patients, and a mean age of 30 years the shortened Dutch version of the Big Five Inventory was used to evaluate personality. The Liverpool Seizure Severity Scale was used to assess seizure frequency and severity. The association of a high level of neuroticism and a low level of agreeableness with seizure frequency in epileptic patients was detected in that research. In contrast, in our analysis, we found no association of these personality changes with the number of seizures per month neither pre- nor pre/post changes in seizure frequency variables. Wachi et al. (2001) reported no differences between seizure-free and non-seizure-free groups in personality changes in a small sample of 26 epileptic patients following surgical treatment. But patients from the non-seizure-free group showed a reduction in seizure frequency of up to 90 % from a preoperative level. The authors applied the MMPI questionnaire for personality assessment in their study and reported a decrease in the scores of infrequency, hypochondriasis, psychasthenia,

Table 3A
Association of personality dimensions with neurological and sociodemographic variables at the baseline (presurgical evaluation) in a 70 drug-resistant epilepsy patients' sample.

	Age	Gender	Etiology	Type of the seizures	Locus	Hemisphere (right vs left vs bilateral)	Age (month) of epilepsy onset	Number of seizures at basal time (per month)
Neuroticism	Pearson Correlation = 0.040p = 0.743	F = 0.530t=-1.109df = 68p = 0.271	F = 0.108t = 0.369df = 65p = 0.694	F = 1.535p = 0.214	F = 0.310p = 0.735	F = 0.366p = 0.695	Correlation coefficient = 0.238p = 0.047*	Correlation coefficient = 0.074p = 0.543
Extraversion	Pearson Correlation=-0.218p = 0.070	F = 1.753t=-1.413df = 68p = 0.162	F = 0.064t = 0.800df = 65p = 0.925	F = 0.745p = 0.529	F = 0.282p = 0.755	F = 0.346p = 0.709	Correlation coefficient=-0.273p = 0.022*	Correlation coefficient=-0.038p = 0.755
Openness to experience	Pearson Correlation=-0.014p = 0.907	F = 0.000t=-0.806df = 68p = 0.423	F = 0.025t = 1.017df = 65p = 0.313	F = 0.833p = 0.480	F = 2.114p = 0.129	F = 0.504p = 0.606	Correlation coefficient=-0.102p = 0.401	Correlation coefficient = 0.139p = 0.252
Agreeableness	Pearson Correlation=-0.106p = 0.382	F = 0.256t=-2.383df = 68p = 0.020* (W > M)	F = 0.003t=-1.467df = 65p = 0.313	F = 0.263p = 0.852	F = 0.407p = 0.668	F = 3.898p = 0.025* (R > L > B)	Correlation coefficient=-0.59p = 0.626	Correlation coefficient = 0.146p = 0.228
Conscientiousness	Pearson Correlation = 0.189p = 0.117	F = 0.356t=-3.512df = 68p = 0.001** (W > M)	F = 0.029t = 0.535df = 65p = 0.595	F = 0.819p = 0.488	F = 0.835p = 0.439	F = 0.880p = 0.420	Correlation coefficient=-0.029p = 0.810	Correlation coefficient=-0.039p = 0.750

W: women; M: men; R: right, L: left; B: bilateral.
Age of the epilepsy onset, hemisphere of the epileptogenic focus, and gender were associated with personality in our sample.
* p < 0,05.
** p < 0.001.

Table 3B
Association of personality dimensions and mood and psychiatric comorbidity at the baseline (presurgical evaluation) in the sample of 70 drug-resistant epilepsy patients.

	HAD-Depression	HAD-Anxiety	Psychiatric comorbidity (yes/no)
Neuroticism	Correlation coefficient = 0.441 p = 0.000 **	Correlation coefficient = 0.528 p = 0.000 **	F = 0.297, t=-2.444, df = 68, p = 0.017* (Neuroticism is higher in patients with psychiatric comorbidity)
Extraversion	Correlation coefficient=-0.501 p = 0.000 **	Correlation coefficient=-0.080 p = 0.518	F = 4.926, df = 38.674, t = 1.895, p = 0.066
Openness to experience	Correlation coefficient=-0.278 p = 0.022 *	Correlation coefficient=-0.141 p = 0.252	F = 1.202, t = 0.228, df = 68, p = 0.821
Agreeableness	Correlation coefficient=-0.235 p = 0.054	Correlation coefficient = 0.095 p = 0.439	F = 0.801, t=-2.357, df = 68, p = 0.021* (Agreeableness is higher in patients with psychiatric comorbidity)
Conscientiousness	Correlation coefficient=-0.101 p = 0.413	Correlation coefficient = 0.101 p = 0.411	F = 0.031, t=-0.008, df = 68, p = 0.993

Psychiatric comorbidity and mood were associated with personality in our sample.
* $p < 0,05$.
** $p < 0.001$.

and schizophrenia in patients following surgical treatment. Thus, the improvement in pathological personality traits can be observed even in the case of reduction in seizure frequency, rather than complete seizure elimination.

These differences between our and other studies may occur due to the different inventories applied to assess personality and seizure frequency. We did not have a "seizure-free" group in our analysis: we indicated the number of seizures for every patient or 2 groups according to the seizure frequency ("5 or less per month" and "more than 5 per month") for different statistical calculations.

In our research, the control group increased in consciousness at the one-year follow-up, which was predicted by an earlier age of epilepsy onset and lower depression symptoms measured by HADD at the baseline.

Consciousness is defined as an individual's organization, persistence, and motivation in achieving a goal (Roberts et al., 2009). Increase in this complex trait of character in a control group appears as an adaptive process and psychologically tackling disease-associated stress, which goes better in more emotionally stable individuals, who are less depressed.

Conscientiousness and agreeableness were significantly higher in women than in men at the baseline in our sample. We cannot completely confirm or deny the idea of personality gender differences in epileptic patients vs the general population, as there are different results reported in the literature. Some general population studies (Chapman et al., 2007; Costa et al., 2001) indicated women being higher in agreeableness and neuroticism scores than men; one research (Weisberg et al., 2011) reported on higher extraversion additionally to the features mentioned above. Nostro et al. (2017) reported that neuroticism and consciousness were higher in women than in men in the general population. According to the research of Mac Giolla and Kajonius (2019) women typically score higher than men in all five trait factors in the general population. All the above-mentioned studies reported women being more neurotic than men in the general population. However, this differs from our results which revealed no significant gender differences in the neuroticism scores. It could be due to the fact that epilepsy is associated with increased neuroticism in patients compared with the general population regardless of gender (Rivera Bonet et al., 2019), so epileptic men become more neurotic compared with men without epilepsy.

Agreeableness was lower in the bilateral epileptogenic foci localization subgroup in comparison to the right and left hemispheres. There are no personality differences between the right and left localized epilepsy foci, which is in line with another epileptic patient's study results

Table 4
Changes in NEO-FFI-R dimensions and seizure frequency at the one-year follow-up in the surgical and control groups of drug-resistant epilepsy patients.

	Surgical group					Control group					
	Results		Differences (basal-1 year)			Results		Differences (basal-1 year)			Differences between groups, p-value
	Mean	SD	Mean	SD	p	Mean	SD	Mean	SD	p	
NEO-FFI-R:											
Neuroticism	22.19	9.50	4.46	6.05	0.001**	23.97	9.05	0.81	7.42	0.484	0.433
Extraversion	27.37	6.62	−1.49	6.83	0.258	27.27	7.08	−0.16	4.72	0.826	0.954
Openness to experience	28.22	8.12	−0.77	5.70	0.484	28.03	6.20	−0.42	5.51	0.624	0.909
Agreeableness	35.98	5.27	−2.16	4.20	0.011*	32.17	5.92	−0.17	5.12	0.828	0.007*
Conscientiousness	35.36	6.18	−1.91	5.53	0.079	34.19	6.60	−2.36	4.71	0.002*	0.460
Seizure frequency	0.96	2.99	26.04	37.52	0.000**	15.56	21.21	2.68	25.54	0.866	0.000**

Personality and seizure frequency changed in both groups of patients at the 1-year follow-up.
* $p < 0,05$.
** $p < 0,001$.

Table 5
Changes in HADS at the one-year follow-up in the surgical and control groups of drug-resistant epilepsy patients.

	Surgical group					Control group					
	Results		Differences (basal-1 year)			Results		Differences (basal-1 year)			Differences between groups, p-value
	Mean	SD	Mean	SD	p	Mean	SD	Mean	SD	p	
HADS scale:											
HAD-Depression	3.08	3.24	1.51	3.33	0.146	5.15	3.97	−1.66	4.17	0.015*	0.018*
HAD-Anxiety	5.60	4.42	1.56	4.14	0.072	7.73	4.42	−1.55	3.64	0.010*	0.044*

Control group increased in depression and anxiety levels at the 1-year follow-up.
* $p < 0,05$.

(Leong et al., 2019). According to the results of two studies with healthy participants, special anatomic areas were associated with high agreeableness: larger areas in the left superior temporal gyrus (Li et al., 2017) or larger regional gray matter volume right orbitofrontal cortex (Kapogiannis et al., 2013). Our research did not provide enough data for a detailed discussion on this topic, but it seems that anatomical and functional brain features in epileptic patients, who have bilateral localization of epileptogenic foci, can negatively influence agreeableness.

Neuroticism and agreeableness were higher in patients with psychiatric comorbidities at the baseline in our research. The neuroticism domain presented a positive correlation with psychiatric symptoms in both mesial temporal lobe epilepsy related to hippocampal sclerosis in 100 patients and also in a study with 100 juvenile myoclonic epilepsy patients (Alonso et al., 2019).

Agreeableness dimension scores negatively correlated with psychiatric diseases in studies with non-epileptic participants: in a non-clinical sample of 3147 subjects between 17 and 25 years old, who had a psychotic experience in the past (Shi et al., 2018); in 3785 patients between 21 and 46 years old suffering from addictive disorders (Dash et al., 2019); and in a sample of 6140 patients with borderline personality disorder (Distel et al., 2009). Our patients suffering from drug-resistant epilepsy showed a high level of agreeableness in the subgroup with psychiatric comorbidities, and this result does not correspond to the other non-epileptic studies, which evaluated the association of personality and psychiatric disorders.

The most prevalent psychiatric comorbidity in epileptic patients associated with high neuroticism is mood disorders. Our sample showed that neuroticism was associated with higher HADS scores. The higher the neuroticism is, the more depressive and anxious the patient is; which is in line with many previous studies with both epileptic patients and healthy participants (Rivera Bonet et al., 2019; Lee et al., 2018; Kim et al., 2016; Endermann and Zimmermann, 2009; Wilson et al., 2009). Extraversion and openness to experience personality dimensions were negatively associated with depression scores in our research, which is in line with previous studies with healthy participants (Kim et al., 2016), and with neurologic diseases subjects (Magyar et al., 2017).

Our study shows the association between earlier onset of epilepsy and higher conscientiousness scores. Also, a significant correlation between the neuroticism level and the age of epilepsy onset was revealed, indicating that the later in age epilepsy begins, the higher the neuroticism is. Seizure onset during infancy was associated with lower neuroticism scores in adulthood comparing to the group with adolescent seizure onset in another study (Wilson et al., 2009). It may reflect that these individuals became accustomed to living with the disease from an early age and did not have to adapt to epilepsy limitations. Also, earlier epilepsy onset was associated with an increase in conscientiousness in the control group in the 1-year follow-up, which illustrates more flexible adaptive ability in these patients.

Thus, in our sample, the earlier epilepsy onset predicts more favorable personality development and more flexible adaptive ability, compared to the patients with a later age of the disease manifestation. The findings of the study inform clinical psychologists, psychiatrists, and patients, that some personality features and mood can favorably change following surgical treatment. These improvements can have a positive impact on future psychological functioning in patients.

5. Strengths

Our study is one of the few that were carried out with a control group, while most of the studies to date did not have controls. Personality traits were measured by a standardized and validated tool such as NEO-FFI-R.

6. Limitations

The main limitation of this study occurs due to the small sample size. Due to ethical reasons the distribution for groups of surgical treatment or controls depended on patient suitability and was not randomized, which could cause bias in our sample. Furthermore, one of the limitations of the study was the lack of an instrument which could inform about various pathological personality traits. Only through this assessment (and consequent statistical analysis) could we talk about "normal/pathological" personality traits. There are instruments capable of measuring pathological personality, such as DAPP-BQ or NBI.

7. Conclusion

This study demonstrates that personality traits in patients with drug-resistant epilepsy change following surgery at the 1-year follow-up. Agreeableness was the most relevant difference between the surgical and control group, being higher in the former.

The surgical group became less neurotic and increased in agreeableness scores, while the control group increased in the consciousness scale, especially if a patient was young at the onset of epilepsy and was not depressed according to the baseline presurgical evaluation. The changes in personality dimensions were not associated with the seizure frequency, either at the baseline or at the follow-up.

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Declaration of Competing Interest

None of the authors has any conflict of interest to disclose. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

References

Alonso, N.B., de Albuquerque, M., Vidal-Dourado, M., Cavicchioli, L.H., Mazetto, L., de Araújo Filho, G.M., et al., 2019. Revisiting personality in epilepsy: differentiation of personality in two epilepsies starting in adolescence. Epilepsy Behav. 97 (August), 75–82. https://doi.org/10.1016/j.yebeh.2019.05.004. Epub 2019 Jun 10. PMID: 31195327.

Aluja, A., García, O., Rossier, J., García, L.F., 2005. Comparison of the NEO-FFI, the NEO-FFI-R and an alternative short version of the NEO-PI-R (NEO-60) in Swiss and Spanish samples. Pers. Individ. Differ. 38, 591–604.

Bear, D.M., Fedio, P., 1977. Quantitative analysis of interictal behavior in temporal lobe epilepsy. Arch. Neurol. https://doi.org/10.1001/archneur.1977.00500200014003.

Chapman, B.P., Duberstein, P.R., Sörensen, S., Lyness, J.M., 2007. Gender differences in five factor model personality traits in an elderly cohort: extension of robust and surprising findings to an older generation. Pers. Individ. Differ. 43 (6), 1594–1603. https://doi.org/10.1016/j.paid.2007.04.028.

Costa, P.T., Terracciano, A., McCrae, R.R., 2001. Gender differences in personality traits across cultures: robust and surprising findings. J. Pers. Soc. Psychol. 81 (August (2)), 322–331. https://doi.org/10.1037/0022-3514.81.2.322. PMID: 11519935.

Dash, G.F., Slutske, W.S., Martin, N.G., Statham, D.J., Agrawal, A., Lynskey, M.T., 2019. Big five personality traits and alcohol, nicotine, cannabis, and gambling disorder comorbidity. Psychol. Addict. Behav. 33 (June (4)), 420–429. https://doi.org/10.1037/adb0000468. Epub 2019 May 16. PMID: 31094546; PMCID: PMC7269105.

Derry, P.A., Harnadek, M.C.S., McLachlan, R.S., Sontrop, J., Blume, W.T., Girvin, J.P., 2002. A longitudinal study of the effects of seizure symptoms on the Minnesota Multiphasic Personality Inventory-2 (MMPI-2) clinical interpretation. J. Clin. Psychol. 58 (7), 817–826. https://doi.org/10.1002/jclp.2005.

Distel, M.A., Trull, T.J., Willemsen, G., Vink, J.M., Derom, C.A., Lynskey, M., et al., 2009. The five-factor model of personality and borderline personality disorder: a genetic analysis of comorbidity. Biol. Psychiatry 66 (December (12)), 1131–1138. https://doi.org/10.1016/j.biopsych.2009.07.017. Epub 2009 Sep 12. PMID: 19748081.

Duncan, J.S., Sander, J.W., Sisodiya, S.M., Walker, M.C., 2006. Adult epilepsy. Lancet 367 (April (9516)), 1087–1100. https://doi.org/10.1016/S0140-6736(06)68477-8. PMID: 16581409.

Endermann, M., Zimmermann, F., 2009. Factors associated with health-related quality of life, anxiety and depression among young adults with epilepsy and mild cognitive

impairments in short-term residential care. Seizure 18 (3), 167–175. https://doi.org/10.1016/j.seizure.2008.08.013.

Engman, E., Malmgren, K., 2012. A longitudinal study of psychological features in patients before and two years after epilepsy surgery. Epilepsy Behav. 24 (2), 221–226. https://doi.org/10.1016/j.yebeh.2012.03.032.

First, M., Spitzer, R., Miriam, Gibbon, Williams, Janet B.W., 1996. Structured Clinical Interview for DSM-IV Axis I Disorders, Clinician Version (SCID-CV). Washington, DC Am. Internet. cited 2016 Feb 25; Available at: https://scholar.google.es/scholar?cluster=6807271620914188016&hl=es&as_sdt=2005&sciodt=0,5#0.

Hébert-Seropian, B., Boucher, O., Sénéchal, C., Rouleau, I., Bouthillier, A., Lepore, F., et al., 2017. Does unilateral insular resection disturb personality? A study with epileptic patients. J. Clin. Neurosci. 43, 121–125. https://doi.org/10.1016/j.jocn.2017.04.001.

Herrero, M.J., Blanch, J., Peri, J.M., De Pablo, J., Pintor, L., Bulbena, A., 2003. A validation study of the hospital anxiety and depression scale (HADS) in a Spanish population. Gen. Hosp. Psychiatry 25 (July-August (4)), 277–283. https://doi.org/10.1016/s0163-8343(03)00043-4. PMID: 12850660.

Hessen, E., Lossius, M.I., Reinvang, I., Gjerstad, L., 2007. Slight improvement in mood and irritability after antiepileptic drug withdrawal: a controlled study in patients on monotherapy. Epilepsy Behav. 10 (May (3)), 449–455. https://doi.org/10.1016/j.yebeh.2007.01.014. Epub 2007 Mar 9. PMID: 17350342.

Hitiris, N., Mohanraj, R., Norrie, J., Sills, G.J., Brodie, M.J., 2007. Predictors of pharmacoresistant epilepsy. Epilepsy Res. 75 (July (2-3)), 192–196. https://doi.org/10.1016/j.eplepsyres.2007.06.003. PMID: 17628429.

Iurina, E., Bailles, E., Pintor, L., 2021. Personality changes in patients with refractory epilepsy after surgical treatment: a systematic review. Seizure 85 (February), 95–101. https://doi.org/10.1016/j.seizure.2020.12.026. Epub 2021 Jan 7. PMID: 33453594.

Janson, M.T., Bainbridge, J.L., 2021. Continuing burden of refractory epilepsy. Ann. Pharmacother. 55 (March (3)), 406–408. https://doi.org/10.1177/1060028020948056. Epub 2020 Aug 14. PMID: 32795085.

Kapogiannis, D., Sutin, A., Davatzikos, C., Costa Jr., P., Resnick, S., 2013. The five factors of personality and regional cortical variability in the Baltimore longitudinal study of aging. Hum. Brain Mapp. 34 (November (11)), 2829–2840. https://doi.org/10.1002/hbm.22108. Epub 2012 May 19. PMID: 22610513; PMCID: PMC3808519.

Kim, S.E., Kim, H.N., Cho, J., Kwon, M.J., Chang, Y., Ryu, S., et al., 2016. Direct and indirect effects of five factor personality and gender on depressive symptoms mediated by perceived stress published correction appears in PLoS One. 2016; 11 (6): e0157204. PLoS One 11 (4), e0154140. https://doi.org/10.1371/journal.pone.0154140. Published 2016 Apr 27.

King, M.L., Tranel, D., 2017. Stable psychological functioning after surgery for epilepsy: an informant-based perspective. Epilepsy Behav. 69, 110–115. https://doi.org/10.1016/j.yebeh.2017.01.028.

Kwan, P., Brodie, M., 2000. Early identification of refractory epilepsy. N. Engl. J. Med. 342, 314–319.

Kwan, P., Arzimanoglou, A., Berg, A.T., Brodie, M.J., Allen Hauser, W., Mathern, G., et al., 2010. Definition of drug resistant epilepsy: consensus proposal by the ad hoc task force of the ILAE commission on therapeutic strategies. Epilepsia 51 (6), 1069–1077.

Lee, S.A., Jeon, J.Y., No, S.K., Park, H., Kim, O.J., Kwon, J.H., et al., 2018. Factors contributing to anxiety and depressive symptoms in adults with new-onset epilepsy. Epilepsy Behav. 88, 325–331. https://doi.org/10.1016/j.yebeh.2018.10.005.

Leong, M., Wang, A.D., Trainor, D., Johnstone, B., Rayner, G., Kalincik, et al., 2019. Personality profiles differ between patients with epileptic seizures and patients with psychogenic non-epileptic seizures. Seizure. https://doi.org/10.1016/j.seizure.2019.10.011.

Li, T., Yan, X., Li, Y., et al., 2017. Neuronal correlates of individual differences in the big five personality traits: evidences from cortical morphology and functional homogeneity. Front. Neurosci. 11, 414. https://doi.org/10.3389/fnins.2017.00414. Published 2017 Jul 18.

Mac Giolla, E., Kajonius, P.J., 2019. Sex differences in personality are larger in gender equal countries: replicating and extending a surprising finding. Int. J. Psychol. 54 (December (6)), 705–711. https://doi.org/10.1002/ijop.12529. Epub 2018 Sep 11. PMID: 30206941.

Magyar, M., Gonda, X., Pap, D., Edes, A., Galambos, A., Baksa, D., et al., 2017. Decreased openness to experience is associated with migraine-type headaches in subjects with lifetime depression. Front. Neurol. 8, 270. https://doi.org/10.3389/fneur.2017.00270. Published 2017 Jun 22.

Meier, M.J., French, L.A., 1965. Changes in MMPI scale scores and an index of psychopathology following unilateral temporal lobectomy for epilepsy. Epilepsia 6 (3), 263–273. https://doi.org/10.1111/j.1528-1157.1965.tb03794.x.

Meldolesi, G.N., Di Gennaro, G., Quarato, P.P., Esposito, V., Grammaldo, L.G., Morosini, P., et al., 2007. Changes in depression, anxiety, anger, and personality after resective surgery for drug-resistant temporal lobe epilepsy: a 2-year follow-up study. Epilepsy Res. 77 (1), 22–30. https://doi.org/10.1016/j.eplepsyres.2007.08.005.

Ngugi, A.K., Kariuki, S.M., Bottomley, C., Kleinschmidt, I., Sander, J.W., Newton, C.R., 2011. Incidence of epilepsy: a systematic review and meta-analysis. Neurology 77 (September (10)), 1005–1012.

Nostro, A.D., Müller, V.I., Reid, A.T., Eickhoff, S.B., 2017. Correlations between personality and brain structure: a crucial role of gender. Cereb. Cortex 27 (July (7)), 3698–3712. https://doi.org/10.1093/cercor/bhw191. PMID: 27390020; PMCID: PMC6059198.

Novais, F., Franco, A., Loureiro, S., Andrea, M., Figueira, M.L., Pimentel, et al., 2019. Personality patterns of people with medically refractory epilepsy – does the epileptogenic zone matter? Epilepsy Behav. 97, 130–134. https://doi.org/10.1016/j.yebeh.2019.05.049.

Rassart, J., Luyckx, K., Verdyck, L., Mijnster, T., Mark, R.E., 2020. Personality functioning in adults with refractory epilepsy and community adults: implications for health-related quality of life. Epilepsy Res. 159 (January), 106251 https://doi.org/10.1016/j.eplepsyres.2019.106251.

Rivera Bonet, C.N., Hermann, B., Cook, C.J., Hwang, G., Dabbs, K., Nair, V., et al., 2019. Neuroanatomical correlates of personality traits in temporal lobe epilepsy: findings from the Epilepsy Connectome Project. Epilepsy Behav. https://doi.org/10.1016/j.yebeh.2019.07.025.

Roberts, B.W., Jackson, J.J., Fayard, J.V., Edmonds, G., Meints, J., 2009. Conscientiousness. In: Leary, M.R., Hoyle, R.H. (Eds.), Handbook of Individual Differences in Social Behavior. The Guilford Press, pp. 369–381.

Rose, K.J., Derry, P.A., McLachlan, R.S., 1996. Neuroticism in temporal lobe epilepsy: assessment and implications for pre- and postoperative psychosocial adjustment and health-related quality of life. Epilepsia 37 (5), 484–491. https://doi.org/10.1111/j.1528-1157.1996.tb00595.x.

Scheffer, I.E., Berkovic, S., Capovilla, G., Connolly, M.B., French, J., Guilhoto, L., et al., 2017. ILAE classification of the epilepsies: position paper of the ILAE commission for classification and terminology. Epilepsia 58, 512–521.

Shehata, G.A., Bateh, A.E., 2009. Cognitive function, mood, behavioral aspects, and personality traits of adult males with idiopathic epilepsy. Epilepsy Behav. https://doi.org/10.1016/j.yebeh.2008.08.014.

Shi, J., Yao, Y., Zhan, C., Mao, Z., Yin, F., Zhao, X., 2018. The relationship between big five personality traits and psychotic experience in a large non-clinical youth sample: the mediating role of emotion regulation. Front. Psychiatry 9, 648. https://doi.org/10.3389/fpsyt.2018.00648.

Wachi, M., Tomikawa, M., Fukuda, M., Kameyama, S., Kasahara, K., Sasagawa, M., et al., 2001. Neuropsychological changes after surgical treatment for temporal lobe epilepsy. Epilepsia 42, 4–8. https://doi.org/10.1046/j.1528-1157.42.s6.1.x.

Weisberg, Y.J., Deyoung, C.G., Hirsh, J.B., 2011. Gender differences in personality across the ten aspects of the big five. Front. Psychol. 2, 178. https://doi.org/10.3389/fpsyg.2011.00178. Published 2011 Aug 1.

Wiebe, S., Matijevic, S., Eliasziw, M., Derry, P.A., 2002. Clinically important change in quality of life in epilepsy. J. Neurol. Neurosurg. Psychiatry 73 (August (2)), 116–120. https://doi.org/10.1136/jnnp.73.2.116. PMID: 12122166; PMCID: PMC1737966.

Wilson, S.J., Wrench, J.M., McIntosh, A.M., Bladin, P.F., Berkovic, S.F., 2009. Personality development in the context of intractable epilepsy. Arch. Neurol. 66 (1), 68–72. https://doi.org/10.1001/archneurol.2008.532.

Witt, J.A., Hollmann, K., Helmstaedter, C., 2008. The impact of lesions and epilepsy on personality and mood in patients with symptomatic epilepsy: a pre- to postoperative follow-up study. Epilepsy Res. 82 (2–3), 139–146. https://doi.org/10.1016/j.eplepsyres.2008.07.011.

Personality and Mental Health

Influence of personality profile in patients with drug-resistant epilepsy on quality of life following surgical treatment: a one-year follow-up study

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1. Introduction

Epilepsy is associated with a high burden on health care and a low index of quality of life (QoL) in patients (Deleo et al, 2020). Not only the disease itself, but the associated stigma, side effects of anti-seizure medications, high level of psychiatric and other clinical comorbidity contribute to the low level in quality of life scores in patients (Paschal et al, 2007).

However, quality of life depends on individual perception, which in turn is associated with an individual's personality (Ramanaiah et al, 1997).

Personality profile is associated with QoL in patients suffering from epilepsy according to the literature (Rassart et al, 2020; Shamsi et al, 2020; Rose et al, 1996).

Surgical therapy is the treatment of choice in refractory epilepsy cases, which can lead to a seizure-free outcome and improve QoL. If the personality profile in patients suffering from epilepsy influences their quality of life during the disease, it can also affect the quality-of-life perception following recovery due to surgical treatment.

Indeed, preoperative neuroticism has an important influence on postoperative psychosocial adjustment and health-related QoL which was independent of the postoperative seizure outcome (Rose et al, 1996). Patients with high neuroticism and low extraversion were predisposed to greater depression after surgery; high neuroticism was also associated with disrupted family dynamics following surgical treatment (Wilson et al, 2009).

Personality psychologists believe that there are five basic dimensions of personality, often referred to as the "Big Five" personality traits: neuroticism, extroversion, openness to experience, agreeableness, and conscientiousness.

This study aims to determine the possible contribution of personality profile in patients with drug-resistant epilepsy to changes in the QoL following surgical treatment and to compare the results with the non-surgical control group at the 1-year follow-up.

2. Methods

2.1. Design

A prospective, comparative, controlled study was carried out in which a surgical group of drug-resistant epilepsy patients was compared with a control group, composed of refractory epilepsy patients treated with anti-seizure medications. Both groups were followed up 1 year after being included in the study.

2.2. Setting and participants

This study was conducted at the Hospital Clinic of Barcelona and was approved by the Hospital Ethics Committee. Subjects were recruited from our Epilepsy Unit of the Neurology Service, which receives referrals from the whole of Spain.

The general evaluation protocol consisted of the following points: all participants signed informed consent; the patients were evaluated to confirm the diagnosis of refractory epilepsy according to the International League Against Epilepsy protocol (Scheffer et al, 2017) and were assessed for the possibility of surgical intervention. Inclusion criteria were age 18 years or older, no history of neurosurgery, a full-scale IQ score of 70 or higher, absence of serious medical pathology except epilepsy, including dementia, schizophrenia or other chronic psychosis, and non-epileptic psychogenic seizures. Those, who met the inclusion criteria of the study, but had contraindications for the surgical treatment according to the decision of the multi-disciplinary team of the Epilepsy Committee, formed the control group.

2.3. Clinical assessments

Demographic, clinical, psychiatric, and psychological variables were collected. The demographic data collection sheet included age, gender, education, occupation, marital state; clinical data included information about etiology of epilepsy, localization, and lateralization of epileptogenic foci, number of seizures at the beginning of the disease, number of seizures in the last 6 months, and age of the epilepsy onset. The Spanish version of HADS was applied for evaluating depression (HAD - D) and anxiety (HAD-A) (Herrero et al, 2003). It contains 14 items, 7 of which are for self-assessing the level of depression and 7 for anxiety. Every subscale should be scored by the patient from 0 to 3 according to the severity of the item. Accordingly, the patient can score from 0 to 21 points on each scale. More than 10 points out of 21 in every subscale is considered as a probable indicator of clinical anxiety or depression.

Evaluations of personality dimensions and quality of life were performed by a clinical psychologist using NEO-FFI-R (Aluja et al, 2005) and the Spanish version of the QOLIE-31 scale was applied to evaluate the quality of life in the patients (Torres et al, 1999).

The revised NEO-FFI (NEO Five-Factor Inventory) is a short version of the NEO-PI-R (Revised NEO Personality Inventory) questionnaire and has 60 items (12 per domain) for self-assessing

the five major personality dimensions: neuroticism, extraversion, openness to experience, agreeableness, and conscientiousness. The patient must indicate his/her degree of agreement with the statement using a score from 0 to 4 from "total disagreement" to «totally agree» respectively. The minimum score for any domain is 0, and the maximum is 48.

The QOLIE-31 is a valid and reliable measure of QoL in patients with epilepsy. It is a self-reported questionnaire comprising two factors (emotional and psychological effects, and medical and social effects), seven sub-scales, and 31 items. Items are measured on 4- to 6- point Likert scales, with a maximum total score of 100. Higher scores indicate a better QoL.

These measures were given during routine clinical follow-up as part of psychological and psychiatric assessment at 12 months.

2.4. Procedure.

Patients with diagnosed refractory epilepsy, who wished to be operated on, were referred for admission to the neurology ward for a 1-week evaluation. After presurgical evaluation, the committee board made a decision on the suitability or not of surgical intervention.

Those, who had contraindications for surgical intervention, formed the control group. Surgical candidates were paired with patients from the control group for follow up and underwent all assessment procedures at the same time intervals respectively to the surgical intervention group at the baseline and 1 year after surgery. During the follow-up period, patients were maintained on a stable medication regimen. The postoperative evaluation at the 1-year follow-up involved psychiatric evaluation (HADS) and clinical psychology assessment (QOLIE). Postsurgical seizure outcome was determined during the follow-up visits by the treating neurologist 1 year after surgical intervention.

3. Statistical analysis

Statistical analysis was performed using Version 22 of SPSS for Windows and differences were considered significant at $p < 0.05$.

Distributions of variables were examined by Kolmogorov–Smirnov test for the whole sample and by Shapiro-Wilk Test for each group. Appropriate tests were applied for further analysis. Data were analyzed with an intention-to-treat approach to see if drop-out patients were different from the patients who finished the follow-up. Descriptive analysis of all variables was performed at the baseline. The group of controls and the surgical group were compared to detect initial differences between groups, using a Student's t-test, Pearson's chi-square test, and Mann–Whitney U-test, according to the type of every variable and its distributions. Also, both groups were compared at the 1-year follow-up in HADS, QoL, and seizure frequency. Changes in mood, QoL, and seizure frequency at the 1-year follow-up were evaluated by Student's t-test or Mann–

Whitney U-test. Those variables of mood and QoL tests, that reached statistical significance at the 1-year follow-up, were introduced into regression analyses. Pearson or Spearman correlation analysis was applied to determine the contribution of each variable of personality in changes in mood and QoL.

4. Results

Of 80 eligible patients, 70 completed the neuropsychiatric assessment at the 1-year follow-up. There were no statistical differences in sociodemographic, clinical, and neuropsychiatric variables between included patients and patients who did not complete the 1-year follow-up (n = 10). The final sample consisted of 28 patients who underwent surgery and 42 patients who were not suitable for the surgical treatment (control group).

4.1. Descriptive analysis at baseline and comparison between groups

Sociodemographic, clinical, and neuropsychiatric variables at the baseline in the whole sample and the differences between groups are shown in **Table 1**: groups are similar to each other in presurgical evaluation in demographic, psychiatric, and neurological variables, except the number of seizures per month - this variable was higher in the surgical group (Mean=26.06, SD=37.52) compared to the controls (Mean=17.83, SD=34.52; p=0.040*).

As differences in the number of seizures at the baseline (per month) were found, a comparison was made whether this variable affects the QoL. No correlations between QoL items and the seizure frequency were found in both groups of patients at the baseline**.**

Table 2 shows association of personality and QoL at the baseline in whole sample of patients: a higher score of Neuroticism was associated with worse QoL, and higher scores in Extraversion and Openness to experience connected with better QoL.

Table 3 demonstrates association between HADS and QoL at the baseline in the whole sample**:** higher scores of HADS were associated with worse QoL.

4.2. Changes in 1-year follow-up and their associations with mood, personality, and seizure frequency

The baseline/1 year follow-up changes in QoL, HADS and seizure frequency for each group were described (surgical and nonsurgical) independently. Also, these variables were compared between our groups of patients. The results are shown in **Table 4.**

Table 4 shows, that at the 1-year follow-up comparing the control and the surgical group, we detected differences in most items of QoL, which were higher in postoperative patients. HADS scores were higher in the control group, compared to the surgical group at the 1-year follow-up. Differences were observed in the seizure frequency between our groups of patients with higher scores in the controls. Analyses were performed to explore the associations of QoL changes and personality at the baseline **(Tab. 5)**.

Table 5 shows, a high baseline level of Conscientiousness in postoperative patients predicted a better outcome in three of eight QoL subscales (Overall quality of life: r=-0.530, p=0.004**,

Social functioning: r=-0.418, p=0,030*; Total quality of life: r=-0.499; p=0.008**) and high baseline level of Openness to experience scale predicted better outcome to one subscale (Medication effects: r=-0.500, p=0,008**); high baseline score of Neuroticism predicted worse QoL outcome in one of eight QoL subscale (Overall quality of life: r=0,382; p=0.049*).

A comparison was made to show whether significant changes in QoL or HADS from the baseline measurement to the 1-year time point were depended on the seizure frequency at the baseline, at the 1-year follow-up, and pre-post differences seizures frequency **(Tab. 6).**

Table 6 demonstrates, that a postsurgical increase in HADA in the control group correlated with seizure frequency in the 1-year follow-up (r=-0.318; p=0.046*). The surgical group increased in the majority of scales of QoL; some of which correlated with seizure variables. An increase in item Seizure worry negatively correlated with seizure frequency at the 1-year follow-up (r=-0.394; p=0.042*); positive changes in Energy/fatigue were negatively correlated with the seizure frequency at the baseline (r=-0.383; p=0.048*). Also, an increase of this subscale was associated with good postsurgical seizure outcome (we used a variable that indicated a difference in the seizure frequency from the baseline to the 1-year follow-up): r=-0.423, p=0.028*. Favorable changes in the subscale Medication effects negatively correlated with the seizure frequency at the 1-year follow-up (r =0.437, p=0.023*).

5. Discussion

The present study aims to determine a possible influence of the personality profile in patients with drug-resistant epilepsy on quality of life following surgical treatment and to compare the results with the non-surgical control group at the 1-year follow-up.

The most important outcome of our study was that patients with high baseline levels of Conscientiousness and Openness to experience showed better QoL outcomes following surgical treatment at the 1-year follow-up, while patients with high levels of neuroticism performed worse in the postsurgical QoL results.

Studying the influence of personality (MMPI-2 and Neuroticism dimension only from the NEO questionnaire were applied) in patients with drug-resistant epilepsy on changes in the quality of life following surgery, the authors (Derry and Wiebe, 2000; Rose et al, 1996) reported that the neuroticism negatively influenced the QoL after surgery. These results are in the line with our research. We also find that Neuroticism was a predictor of a poor postsurgical QoL.

A higher score of Neuroticism was associated with a worse QoL in patients at the baseline in our research. These results correlated with the results obtained by the other researchers in studies with people with epilepsy (Margolis et al, 2018; Rose et al, 1996).

Why do people with high levels of neuroticism show low scores of QoL?

High levels of neuroticism are typically associated with pessimism, vulnerability to stress, and high negative affectivity (Afshar et al, 2015). Neurotic patients frequently use maladaptive coping strategies in dealing with illness-related challenges, such as avoidant or passive coping strategies.

It seemed that some personality traits, such as conscientiousness, openness to experience, extroversion, and agreeableness protect the QoL in patients, and potentially favorable attributes can sometimes reinforce negative tendencies.

Indeed, according to the researches with healthy people, individuals high in Openness and Conscientiousness tend to engage in more adaptive and flexible coping in the face of stress (Lee-Baggley et al, 2005; Watson and Hubbard, 1996). People high in conscientiousness may achieve more goals, as they tend to persist when faced with illness-related constraints, potentially resulting in a better quality of life. In addition, people high in conscientiousness are typically described as attentive, organized, and planful. Surgical treatment in particular, and the burden of the disease in general – suppose an increase in stress, and high levels of these personality features are predictors of good coping with stress in a longitudinal period.

These characteristics might make it more difficult for patients to cope with epilepsy-related factors like social isolation, restrictions in work and study activities, stigma, and many others, and affect the QoL significantly.

This is confirmed by our results that QoL at the baseline was associated with personality and HADS, but not with the seizure frequency. Research (Endermann and Zimmermann, 2009) also reported, that neuroticism had more impact on the QoL than seizure frequency in people with epilepsy.

Some authors reported on the association of QoL with seizure frequency and HADS (Mehta et al, 2014; Villeneuve, 2004). But some studies reported weak (Johnson et al, 2004) or no association (Gilliam, 2002) in seizure frequency and subscales of QoL in patients suffering from epilepsy.

Thus, it seems that the QoL depends more on the individual perception of stress, and coping strategies, which is mediated by the personality characteristics and mood, than on objective clinical factors in patients suffering from severe chronic diseases; for example, seizure frequency in patients with refractory epilepsy.

6. Limitations

The main limitation of this study occurs due to the small sample size. Due to ethical reasons, the distribution for groups of surgical treatment or controls depended on the patient's suitability and was not randomized. All psychological and psychiatric data were self-reported.

7. Conclusion

People with epilepsy with high baseline levels of Conscientiousness and Openness to experience showed better QoL outcomes following surgical treatment at the 1-year follow-up, while patients high in Neuroticism showed a worse QoL. The findings of the study show clinical psychologists, psychiatrists, and patients that some personality features can have an impact on postsurgical QoL. Collection and analysis of personality data alongside QoL measures may be helpful in health policy evaluation.

8. Conflict of Interest

None of the authors has any conflict of interest to disclose.

9. References

Afshar H, Roohafza HR, Keshteli AH, Mazaheri M, Feizi A, Adibi P. The association of personality traits and coping styles according to stress level. J Res Med Sci. 2015;20(4):353-358.

Aluja A, García O, Rossier J, García LF. Comparison of the NEO-FFI, the NEO-FFI-R and an alternative short version of the NEO-PI-R (NEO-60) in Swiss and Spanish samples. *Personal Individ Differ.* 2005;38:591–604.

Deleo F, Quintas R, Pastori C, Pappalardo I, Didato G, Di Giacomo R, et al. Quality of life, psychiatric symptoms, and stigma perception in three groups of persons with epilepsy. Epilepsy Behav. 2020 Sep;110:107170. doi: 10.1016/j.yebeh.2020.107170. Epub 2020 Jun 5. PMID: 32512366.

Derry PA, Wiebe S. Psychological adjustment to success and to failure following epilepsy surgery. Can J Neurol Sci. 2000 May;27 Suppl 1:S116-20; discussion S121-5. doi: 10.1017/s0317167100000779. PMID: 10830338.

Endermann M, Zimmermann F. Factors associated with health-related quality of life, anxiety and depression among young adults with epilepsy and mild cognitive impairments in short-term residential care. Seizure. 2009 Apr;18(3):167-75. doi: 10.1016/j.seizure.2008.08.013. Epub 2008 Sep 26. PMID: 18823801.

Gilliam F. Optimizing health outcomes in active epilepsy. Neurology. 2002 Apr 23;58(8 Suppl 5):S9-20. doi: 10.1212/wnl.58.8_suppl_5.s9. PMID: 11971128

Herrero MJ, Blanch J, Peri JM, De Pablo J, Pintor L, Bulbena A. A validation study of the hospital anxiety and depression scale (HADS) in a Spanish population. *Gen Hosp Psychiatry*. 2003 Jul-Aug;25(4):277-83. doi: 10.1016/s0163-8343(03)00043-4. PMID: 12850660.

Johnson EK, Jones JE, Seidenberg M, Hermann BP. The relative impact of anxiety, depression, and clinical seizure features on health-related quality of life in epilepsy. Epilepsia. 2004 May;45(5):544-50. doi: 10.1111/j.0013-9580.2004.47003.x. PMID: 15101836.

Lee-Baggley D, Preece M, Delongis A. Coping with interpersonal stress: role of big five traits. J Pers. 2005 Oct;73(5):1141-80. doi: 10.1111/j.1467-6494.2005.00345.x. PMID: 16138869.

Margolis, S.A., Nakhutina, L., Schaffer, S.G., Grant, A.C., Gonzalez, J.S. Perceived epilepsy stigma mediates relationships between personality and social well-being in a diverse epilepsy population. Epilepsy Behav. 2018 ;78, 7–13. https://doi.org/10.1016/j. yebeh.2017.10.023.

Mehta S, Tyagi A, Tripathi R, Kumar M. Study of Inter-relationship of Depression, Seizure Frequency and Quality of Life of People with Epilepsy in India. Ment Illn. 2014 Mar 4;6(1):5169. doi: 10.4081/mi.2014.5169. PMID: 25478138; PMCID: PMC4253398.

Paschal AM, Hawley SR, St Romain T, Liow K, Molgaard CA, Sly J, et al. Epilepsy patients' perceptions about stigma, education, and awareness: preliminary responses based on a community participatory approach. Epilepsy Behav. 2007 Nov;11(3):329-37. doi: 10.1016/j.yebeh.2007.06.007. Epub 2007 Sep 10. PMID: 17827072.

Ramanaiah NV, Detwiler FR, Byravan A. Life satisfaction and the five-factor model of personality. Psychol Rep. 1997 Jun;80(3 Pt 2):1208-10. doi: 10.2466/pr0.1997.80.3c.1208. PMID: 9246886.

Rassart J, Luyckx K, Verdyck L, Mijnster T, Mark RE. Personality functioning in adults with refractory epilepsy and community adults: Implications for health-related quality of life.

Epilepsy Res. 2020 Jan;159:106251. doi: 10.1016/j.eplepsyres.2019.106251. Epub 2019 Dec 9. PMID: 31862480.

Rose KJ, Derry PA, McLachlan RS. Neuroticism in temporal lobe epilepsy: assessment and implications for pre- and postoperative psychosocial adjustment and health-related quality of life. Epilepsia. 1996 May;37(5):484-91. doi: 10.1111/j.1528-1157.1996.tb00595.x. PMID: 8617178.

Scheffer IE, Berkovic S, Capovilla G, Connolly MB, French J, Guilhoto L et al. ILAE classification of the epilepsies: position paper of the ILAE commission for classification and terminology. *Epilepsia*. 2017;58:512–21

Shamsi, A., Tohidi, R. S., Shamekhi, M., Amirifard, H., Ansarimoghadam, A. The relationship between personality characteristics and the quality of life in patients with epilepsy. *Psychiatria*, 2020; *17*(2), 66-70.

Torres X, Arroyo S, Araya S, de Pablo J. The Spanish Version of the Quality-of-Life in Epilepsy Inventory (QOLIE-31): translation, validity, and reliability. Epilepsia. 1999 Sep;40(9):1299-304. doi: 10.1111/j.1528-1157.1999.tb00861.x. PMID: 10487195.

Villeneuve N. Quality-of-life scales for patients with drug-resistant partial epilepsy. Rev Neurol (Paris). 2004 Jun;160 Spec No 1:5S376-93. French. PMID: 15331986.

Watson, D., & Hubbard, B. Adaptational style and dispositional structure: Coping in the context of the five-factor model. Journal of Personality, 1996; 64, 737–774

Wilson SJ, Wrench JM, McIntosh AM, Bladin PF, Berkovic SF. Profiles of psychosocial outcome after epilepsy surgery: the role of personality. Epilepsia. 2010 Jul;51(7):1133-8. doi: 10.1111/j.1528-1167.2009.02392.x. Epub 2009 Nov 3. PMID: 19889018.

Table 1. Sociodemographic variables at baseline and differences between groups.

	Whole sample group (n=70)			Surgical group (n=28)			Control group (n=42)			Differences between surgical and control group, p-value
	%	Mean	SD	%	Mean	SD	%	Mean	SD	
Sociodemographic										
Age		36.94	10.93		35.00	8.49		38.24	12.22	0.195
Gender:										0.728
Women	55.7			53.6			57.1			
Men	44.3			46.4			42.9			
Education:										0.768
Basic education	45.7			46.4			45.2			
Secondary education	37.1			39.3			35.7			
Higher education	17.1			14.3			19			
Occupation:										0.073
Inactive	28.6			14.3			38.1			
Housewife/student	21.4			21.4			21.4			
Active	50			64.3			40.5			
Marital state:										0.519
Married	57.1			64.3			52.4			
Separated/widow/ers	12.9			7.1			16.7			
Single	28.6			28.6			28.6			
No data	1.4			0			2.4			
Neurologic										0.819
Idiopathic etiology	60.0			64.3			57.1			
Type of seizures:										0.599
No seizures	1.4			0			2.4			
Focal onset impaired awareness seizures	50.0			57.1			45.2			
Other focal onset seizures	15.7			14.3			16.7			
Unknown onset tonic-clonic seizures	20			14.3			23.8			
Generalized seizures	10.0			14.3			7.1			
Locus:										0.571
Temporal	57.1			64.3			52.4			
Extratemporal	24.3			25.0			23.8			
Unestablished	15.7			10.7			19			
Hemisphere:										0.400
Right	44.3			42.9			45.2			
Left	37.1			46.4			31			
Bilateral	12.9			7.1			16.7			
Unknown	1.4			0			2.4			
Age (month) of epilepsy onset		193.6	180.34		139.57	120.77		229.62	204.46	0.068
Number of seizures at the baseline (per month)		21.11	35.71		26.04	37.52		17.83	34.52	0.040*
Psychiatric assessment										
HADS scale:										
HADS-Depression		3.93	3.41		4.59	4.09		3.49	2.86	0.308
HADS-Anxiety		6.59	3.52		7.33	3.89		6.10	3.21	0.203

Psychological assessment:									
QOLIE:									
Seizure worry	45.65	9.67	45.17	9.51	45.72	10.05	0.734		
Overall quality of life	45.78	8.33	44.06	8.91	46.76	7.95	0.157		
Emotional well-being	46.08	10.01	46.41	10.83	45.68	9.68	0.824		
Energy/fatigue	50.45	8.34	49.12	8.50	50.89	8.02	0.277		
Cognitive function	47.17	11.64	44.56	11.54	48.65	11.70	0.125		
Medication effects	48.40	9.33	47.78	9.37	48.73	9.67	0.647		
Social functioning	42.67	9.39	40.82	10.15	43.68	8.82	0.179		
Total quality of life	44.40	9.77	42.26	10.12	45.90	9.49	0.140		
NEO:									
Neuroticism	25.53	6.85	26.66	6.90	24.78	6.77	0.264		
Extraversion	26.61	5.90	25.87	6.30	27.10	5.65	0.395		
Openness to experience	27.55	6.27	27.46	6.51	27.60	6.19	0.923		
Agreeableness	32.73	5.07	33.82	5.36	32.00	4.79	0.141		
Conscientiousness	32.48	5.90	33.45	6.95	31.84	5.86	0.267		

**p< 0,05*
***p<0.001*
Groups are similar to each other in presurgical evaluation in demographic, psychiatric, neurological, and neurosurgical variables, except the number of seizures per month - this variable was higher in the surgical group.

Table 2. Association of personality and QoL at the baseline. Whole sample.

Pearson or Spearman correlation.

	Neuroticism	Extraversion	Openness to experience	Agreeableness	Consciousness
Seizure worry	r=-0,170 p=0,161	r=0,165 p=0,175	r=0,085 p=0,488	r=0,148 p=0,226	r=-0,179 p=0,141
Overall quality of life	r=-0,118 p=0,334	r=0,197 p=0,104	r=-0,192 p=0,114	r=0,059 p=0,630	r=-0,015 p=0,901
Emotional well-being	r=-0,393 p=0,001**	r=0,064 p=0,600	r=0,270 p=0,025*	r=0,102 p=0,404	r=0,184 p=0,130
Energy/fatigue	r=-0,362 p=0,002*	r=0,185 p=0,129	r=-0,120 p=0,324	r=-0,062 p=0,613	r=0,069 p=0,576
Cognitive function	r=-0,358 p=0,002*	r=0,222 p=0,067	r=0,108 p=0,377	r=0,114 p=0,352	r=0,159 p=0,193
Medication effects	r=-0,229 p=0,058	r=0,120 p=0,324	r=-0,075 p=0,540	r=0,075 p=0,540	r=0,059 p=0,628
Social functioning	r=-0,389 p=0,001**	r=0,269 p=0,025*	r=-0,007 p=0,956	r=0,116 p=0,344	r=-0,006 p=0,958
Total QoL	r=-0,460 p=0,000**	r=0,291 p=0,015*	r=0,078 p=0,523	r=0,125 p=0,307	r=0,064 p=0,601

**p <0,05*
***p <0.001*

A higher score of Neuroticism was associated with worse QoL, and higher scores in Extraversion and Openness to experience connected with better QoL.

Table 3. Association between HADS and QoL at the baseline. Whole sample.

	Seizure worry	Overall quality of life	Emotional well-being	Energy/fatigue	Cognitive function	Medication effects	Social functioning	Total QoL
HADS-Anxiety	r=-0,365** p=0,002	r=-0,049 p=0,696	r=-0,420** p=0,000	r=-0,367** p=0,002	r=-0,277* p=0,023	r=-0,214 p=0,082	r=-0,341** p=0,005	r=-0,435** p=0,000
HADS-Depression	r=-0,328** p=0,007	r=-0,051 p=0,685	r=-0,250* p=0,041	r=-0,286* p=0,019	r=-0,432** p=0,000	r=-0,213 p=0,084	r=-,435** p=0,000	r=-0,483** p=0,000

**p <0,05*
***p <0.001*
Higher scores of HADS were associated with worse QoL.

Table 4. Quantitative changes in variables of interest at the 1-year follow-up.

	Surgical					Control					Differences between groups, p-value
	Results		Differences (baseline-1 year)			Results		Differences (baseline-1 year)			
	Mean	SD	Mean	SD	p	Mean	SD	Mean	SD	p	
QOLIE:											
Seizure worry	57.93	8.23	-13.07	11.28	0.000**	48.72	12.45	-2.75	10.83	0.121	0.003**
Overall quality of life	53.37	10.84	-9.74	12.86	0.001**	43.55	11.95	2.93	13.39	0.180	0.002**
Emotional well-being	52.89	11.22	-6.39	11.63	0.005**	44.51	12.01	1.38	12.89	0.507	0.008**
Energy/fatigue	56.19	9.61	-7.18	11.10	0.002*	49.39	9.19	1.74	12.20	0.378	0.007**
Cognitive function	48.35	10.62	-3.35	10.32	0.104	47.43	12.48	1.20	9.94	0.457	0.813
Medication effects	52.69	7.96	-5.10	9.27	0.008**	48.09	10.48	0.87	10.95	0.621	0.059
Social functioning	49.52	9.24	-9.22	9.66	0.000**	43.83	10.09	-0.79	9.64	0.960	0.034*
Total QoL	53.31	11.14	-10.19	10.86	0.000**	44.47	11.94	1.10	11.10	0.539	0.012*
HADS scale											
HADS-Depression	3.53	3.32	1.36	3.47	0.146	5.28	3.99	-1.68	4.29	0.015*	0.018*
HADS-Anxiety	5.35	4.08	1.9	4.23	0.116	7.93	4.39	-1.51	3.78	0.016*	0.037*
Seizure frequency	0.96	2.99	26.04	37.52	0.000*	15.56	21.21	2.68	25.54	0.866	0.000**

*p <0,05

**p <0.001

At the 1-year follow-up comparing the control and the surgical group, we detected differences in most items of QoL, which were higher in the patients who underwent surgery. HADS scores were higher in the control group, compared to the surgical group at the 1-year follow-up. Differences in the seizure frequency between our groups of patients were observed, with higher scores in the controls.

Table 5. Association of personality profile at the baseline and changes in subscales of QoL in the surgical group.

	Neuroticism	Extraversion	Openness to experience	Agreeableness	Consciousness
Changes in Seizure worry baseline/1 year follow-up	r=-0,171 p=0,395	r=-0,119 p=0,555	r=0,218 p=0,276	r=0,141 p=0,484	r=-0,354 p=0,070
Changes in Overall quality of life baseline/1 year follow-up	r=0,382* p=0,049	r=-0,201 p=0,314	r=-0,085 p=0,673	r=-0,167 p=0,405	r=-0,530** p=0,004
Changes in Emotional well-being baseline/1 year follow-up	r=0,150 p=0,456	r=-0,130 p=0,517	r=-0,014 p=0,943	r=0,000 p=0,999	r=-0,107 p=0,595
Changes in Energy/fatigue baseline/1 year follow-up	r=0,209 p=0,295	r=-0,158 p=0,432	r=-0,310 p=0,116	r=-0,306 p=0,120	r=-0,258 p=0,194
Changes in Cognitive function baseline/1 year follow-up	r=-0,030 p=0,881	r=-0,155 p=0,439	r=-0,171 p=0,394	r=-0,171 p=0,395	r=-0,449 p=0,019*
Changes in Medication effects baseline/1 year follow-up	r=-0,144 p=0,474	r=0,079 p=0,695	r=-0,500** p=0,008	r=0,038 p=0,850	r=-0,081 p=0,689
Changes in Social functioning baseline/1 year follow-up	r=-0,161 p=0,421	r=0,106 p=0,597	r=0,024 p=0,904	r=-0,059 p=0,769	r=-0,418* p=0,030
Changes in Total QoL baseline/1 year follow-up	r=0,043 p=0,832	r=-0,125 p=0,536	r=-0,118 p=0,558	r=-0,141 p=0,483	r=-0,499** p=0,008

*p <0,05

**p <0.001

Patients with high baseline levels of Conscientiousness and Openness to experience showed better QoL outcomes following surgical treatment at the 1-year follow-up, while patients high in Neuroticism showed worse QoL.

Table 6. Association of significantly changed variables of interest and seizure frequency variables at the 1-year follow-up

Control group

Spearman correlation

	Seizure frequency at the baseline	Seizure frequency at the 1-year follow-up	Changes in seizure frequency baseline/1 year follow-up
Changes in HADA baseline/1 year follow-up	r=-0.154; p=0.342	r=-0.318; p=0.046*	r=0.269; p=0.193
Changes in HADD baseline/1 year follow-up	r=-0.286; p=0.073	r=-0.270; p=0.092	r=-0.373; p=0.066

Surgical group

	Seizure frequency at the baseline	Seizure frequency at the 1-year follow-up	Changes in seizure frequency baseline/1 year follow-up
Changes in Seizure worry baseline/1 year follow-up	r=0.131; p=0.515	r=-0.394; p=0.042*	r=-0.053; p=0.792
Changes in Overall quality of life baseline/1 year follow-up	r=-0.131 p=0.515	r=0.260 p=0.190	r=-0.199 p=0.320
Changes in Emotional well-being baseline/1 year follow-up	r=-0.250 p=0.208	r=0.119 p=0.556	r=-0.333 p=0.089
Changes in Energy/fatigue baseline/1 year follow-up	r=-0.383 p=0.048*	r=0.232 p=0.243	r=-0.423 p=0.028*

Changes in Medication effects baseline/1 year follow-up	r=-0.015 p=0.941	r=0.437 p=0.023*	r=-0.134 p=0.505
Changes in Social functioning baseline/1 year follow-up	r=-0.097 p=0.631	r=0.246 p=0.215	r=-0.198 p=0.322
Changes in Total QoL baseline/1 year follow-up	r=-0.201 p=0.314	r=0.307 p=0.119	r=-0.324 p=0.099

$p < 0.05$

$^{**}p < 0.001$

An increase in HADA in the control group correlated with seizure frequency in the 1-year follow-up. The surgical group increased in the majority of scales of QoL; some of which correlated with seizure variables.

8. DISCUSSION

Firstly, we conducted a systematic review to describe the state of the art in personality changes in epilepsy following surgery. Eleven studies were included in our analysis. We concluded personality changes depend on postsurgical seizure outcome, localization of epileptogenic area to be resected, and duration of follow-up.

The localization of epileptogenic area influences the state of epilepsy, which might mean differences in neurophysiological outcome following ST. The insula is known to be involved in emotion formation and processing, and insula damage could lead to disruption in these functions. The insula resection group (Hébert-Seropian et al, 2017) had emotional disturbances postoperatively compared to the temporal cohort. Three studies (Rassart et al, 2020; Engman and Malmgren, 2012; Witt et al, 2008) detected no differences in personality features post-surgery when comparing a temporal group with an extratemporal group. However, there were different personality changes in temporal lobe epilepsy (TLE) patients with left compared to right lateralization (Witt et al, 2008; Meier and French, 1965). Both groups demonstrated improvements in the same domains, but on different subscales. Despite the limitations and preoperative differences in neuropsychological features between groups (Rassart et al, 2020), the common outcome seems robust and showed personality changes can depend on lateralization of epileptogenic area and only in the TLE.

Almost all studies found an association between seizure freedom and changes in the patients' personality. Seizures and interictal epileptic activity influenced epilepsy-specific personality domains such as organic psycho-syndrome and neuroticism (Witt et al, 2008), hypochondriasis (Derry et al, 2002), and psychasthenia (Wheelock et al, 1998). Only one study (Wachi, 2001) reported no changes between seizure free (SF) and not-seizure-free (NSF) groups. However, despite the fact that the NSF group still had seizures, their seizure frequency was decreased by 75–90 % in 8 of 10 patients in this study. Thus, it could be inferred that reduction in seizure frequency, rather than complete seizure elimination, results in improved neuropsychological functioning in patients. Another study (Wheelock et al, 1998) found no difference in psychasthenia scores between SF and NSF groups in a short follow-up: both groups showed significant improvements on this scale meanings at the 1st postsurgical measure (2 months), but afterwards, only the NSF group declined to the baseline after 1 year. The difference between short and long-term data illustrates these personality features require more time to improve.

Whilst personality trait changes seem to be stable by one year post surgery, the presence of further changes at two years shows that personality changes may be more gradual, and longer follow-ups may be required. Improvements are observed on both in clinical and truthfulness scales at both follow-up time points (Meldolesi, et al, 2007). Gradual improvements on

personality tests in 1-month and 1-year follow-ups was reported by another study (Wachi, 2001). Seizure freedom was associated with a stable improvement in psychasthenia at both follow-ups, whereas the NSF group improved after 2 months and then returned to the baseline after 1 year (Wheelock et al, 1998). The authors explained these results in the NSF cohort as a consequence of positive expectations of ST and hope for improving seizure status later, despite continuing seizures in a short follow-up. Thus, we can conclude improvement in personality appears within a short follow-up period and the process continues within at least the first 2 years, and is mostly associated with seizure freedom.

It was revealed in our empirical clinical study with patients with drug-resistant epilepsy that personality traits change following surgical and pharmacological antiepileptic treatment at the 1-year follow-up, but in a different way depending on whether or not surgical treatment is carried out. This is the most important outcome of our study. Interestingly, these personality changes were not associated with seizure status. Also, seizure status was not associated with positive changes in QoL following ST.

The most relevant features in our study were a decrease in neuroticism and an increase in agreeableness in the surgical group through the follow-up, and higher agreeableness in the surgical group compared with the control group one year after surgery. Decrease in neuroticism one year after surgical treatment in epileptic patients was presented in another study (Witt et al, 2008). However, the German personality inventory was used for personality assessment in this case instead of being performed with the NEO-FFI-R as we did. Additionally, they reported on the personality changes in seizure-free patients only.

With reference to somatic and psychic anxiety as items of the neuroticism-related scale, another study (Engman and Malmgren, 2012) also found a decrease in these features evaluated by the Karolinska Scale of Personality. Personality changes were revealed in seizure-free patients only (Engel I). In another study (Rassart et al, 2020) the shortened Dutch version of the Big Five Inventory was used to evaluate personality. The Liverpool Seizure Severity Scale was used to assess seizure frequency and severity. The association of a high level of neuroticism and a low level of agreeableness with seizure frequency in epileptic patients was detected in that research. In contrast, in our analysis, we found no association of these personality changes with the number of crises per month neither pre- nor pre/post changes in seizure frequency variables. Wachi et al reported no differences between seizure-free and non-seizure-free groups in personality changes after surgical treatment. But patients from the non-seizure-free group showed a reduction in seizure frequency of up to 90% from a preoperative level. The authors applied the MMPI questionnaire for personality assessment in their study and reported a decrease in the scores of infrequency, hypochondriasis, psychasthenia, and schizophrenia in patients

following surgical treatment. Thus, the improvement in pathological personality traits can be observed even in the case of reduction in seizure frequency, rather than complete seizure elimination. These differences between our and other studies may occur due to the different inventories applied to assess personality and seizure frequency. We did not have a "seizure-free" group in our analysis: we indicated the number of seizures for every patient or 2 groups according to the seizure frequency ("5 or less per month" and "more than 5 per month") for different statistical calculations. In our research, the control group increased in consciousness at the one-year follow-up, which was predicted by an earlier age of epilepsy onset and lower depression symptoms measured by HADD at the baseline. Increase in this trait of character in a control group appears as an adaptive process and psychologically tackling disease-associated stress, which goes better in more emotionally stable individuals, who are less depressed. Conscientiousness and agreeableness were significantly higher in women than in men at the baseline in our sample. We cannot completely confirm or deny the idea of personality gender differences in epileptic patients vs the general population, as there are different results reported in the literature. Some general population studies (Chapman et al, 2007; Costa et al, 2001) indicated women being higher in agreeableness and neuroticism scores than men; one research (Weisberg et al, 2011) reported on higher extraversion additionally to the features mentioned above. Nostro et al reported that neuroticism and consciousness were higher in women than in men in the general population. According to the research of Mac Giolla and Kajonius, women typically score higher than men in all five trait factors in the general population. All the above-mentioned studies reported women being more neurotic than men in the general population. However, this differs from our results which revealed no significant gender differences in the neuroticism scores. It could be due to the fact that epilepsy is associated with increased neuroticism in patients compared with the general population regardless of gender (Rivera Bonet et al, 2019), so epileptic men become more neurotic compared with men without epilepsy. Agreeableness was lower in the bilateral epileptogenic foci localization subgroup in comparison to the right and left hemispheres. There are no personality differences between the right and left localized epilepsy foci, which is in line with another epileptic patient's study results (Leong et al, 2019). According to the results of two studies with healthy participants, special anatomic areas were associated with high agreeableness: larger areas in the left superior temporal gyrus (Li et al, 2017) or larger regional gray matter volume right orbitofrontal cortex (Kapogiannis et al, 2012). Our research did not provide enough data for a detailed discussion on this topic, but it seems that anatomical and functional brain features in epileptic patients, who have bilateral localization of epileptogenic foci, can negatively influence agreeableness.

Neuroticism and agreeableness were higher in patients with psychiatric comorbidities at the

baseline in our research. The neuroticism domain presented a positive correlation with psychiatric symptoms in both mesial temporal lobe epilepsy related to hippocampal sclerosis in a study with 100 juvenile myoclonic epilepsy patients (Alonso et al, 2019). Agreeableness dimension scores negatively correlated with psychiatric diseases in studies with nonepileptic participants: in a non-clinical sample, who had a psychotic experience in the past (Shi et al, 2018); in addictive disorders patients (Dash et al, 2019); and in a borderline personality disorder sample (Distel et al, 2009). Our patients suffering from drug-resistant epilepsy showed a high level of agreeableness in the subgroup with psychiatric comorbidities, and this result does not correspond to the other non-epileptic studies, which evaluated the association of personality and psychiatric disorders. The most prevalent psychiatric comorbidity in epileptic patients associated with high neuroticism is mood disorders. Our sample showed that neuroticism was associated with higher HADS scores. The higher the neuroticism is, the more depressive and anxious the patient is; which is in line with many previous studies with both epileptic patients and healthy participants (Rivera Bonet et al, 2019; Lee et al, 2018; Kim et al, 2016; Endermann and Zimmermann, 2009; Wilson et al, 2009). Extraversion and openness to experience personality dimensions were negatively associated with depression scores in our research, which is in line with previous studies with healthy participants (Kim et al, 2016), and with neurologic diseases subjects (Magyar et al, 2017). Our study shows the association between earlier onset of epilepsy and higher conscientiousness scores. Also, a significant correlation between the neuroticism level and the age of epilepsy onset was revealed, indicating that the later in age epilepsy begins, the higher the neuroticism is. Seizure onset during infancy was associated with lower neuroticism scores in adulthood comparing to the group with adolescent seizure onset in another study (Wilson et al, 2009). It may reflect that these individuals became accustomed to living with the disease from an early age and did not have to adapt to epilepsy limitations. Also, earlier epilepsy onset was associated with an increase in conscientiousness in the control group in the 1-year follow-up, which illustrates more flexible adaptive ability in these patients. Thus, in our sample, the earlier epilepsy onset predicts more favorable personality development and more flexible adaptive ability, compared to the patients with a later age of the disease manifestation.

Analyzing the influence of personality profile at the baseline on the postsurgical QoL, we concluded that patients with high baseline levels of Conscientiousness and Openness to experience showed better QoL outcomes following surgical treatment at the 1-year follow-up, while high neurotic patients performed worse in the postsurgical QoL results. Seizure status don’t affect QoL changes in our study.

Studying the influence of personality (MMPI-2 and Neuroticism dimension only from the NEO questionnaire were applied) in patients with drug-resistant epilepsy on changes in the quality of

life following surgery, the authors (Derry and Wiebe, 2000; Rose et al, 1996) reported that the neuroticism negatively influenced the QoL after surgery. These results are in the line with our research, - we also find that the Neuroticism was a predictor of a poor postsurgical QoL. A higher score of Neuroticism was associated with a worse QoL in patients at the baseline in our research. These results correlated with the results obtained by the other researchers in studies with epileptic patients (Margolis et al, 2018; Rose et al, 1996). Why do people with high levels of neuroticism show low scores of QoL? High levels of neuroticism are typically associated with pessimism, vulnerability to stress, and high negative affectivity (Afshar et al, 2015). Neurotic patients used to use maladaptive coping strategies in dealing with illness-related challenges, such as avoidant or passive coping strategies. It seemed that some personality traits, such as conscientiousness, openness to experience, extroversion, and agreeableness protect the QoL in patients, and potentially favorable attributes can sometimes reinforce negative tendencies. Indeed, according to the researches with healthy people, individuals high in Openness and Conscientiousness tend to engage in more adaptive and flexible coping in the face of stress (LeeBaggley et al, 2005; Watson and Hubbard, 1996). People high in conscientiousness may achieve more goals, as they tend to persist when faced with illness-related constraints, potentially resulting in a better quality of life. In addition, people high in conscientiousness are typically described as attentive, organized, and planful. Surgical treatment in particular, and the burden of the disease in general – are supposed to increase stress, and high levels of these personality features are predictors of good coping with stress in a longitudinal period.

These characteristics might make it more difficult for patients to cope with epilepsy-related factors like social isolation, restrictions in work and study activities, stigma, and many others, and affect the QoL significantly. This is confirmed by our results that QoL at the baseline was associated with personality and HADS, but not with the seizure frequency. Research (Endermann and Zimmermann, 2009) also reported, that neuroticism had more impact on the QoL than seizure frequency in epileptic patients. Some authors reported on the association of QoL with seizure frequency and HADS (Mehta et al, 2014; Villeneuve, 2004). But some studies reported weak (Johnson et al, 2004) or no association (Gilliam, 2002) in seizure frequency and subscales of QoL in epileptic patients. Thus, it seems that the QoL depends more on the individual perception of stress, and coping strategies, which is mediated by the personality characteristics and mood, than on objective clinical factors in patients suffering from heavy chronic diseases; for example, seizure frequency in patients with drug-resistant epilepsy.

9. LIMITATIONS

The main limitation of the **systematic review** is due to the different questionnaires that were applied for personality evaluation in patients. Different approaches were used in the completion of these questionnaires: some studies used responses given by close relatives/ friends while others used responses given by the patients themselves. Furthermore, different personality domains were evaluated. Also, both poorly adjusted personality traits and normal personality dimensions were evaluated. Different study designs were also applied: comparative studies, cohort studies, case-control studies. The studies varied widely in sample size and evaluated personality after different length follow-up periods. Finally, only articles written in English were reviewed.

The main limitation of **our empirical studies** occurs due to the small sample size. Due to ethical reasons, the distribution for groups of surgical treatment or controls depended on the patient's suitability and was not randomized. All psychological and psychiatric data were self-reported.

10. CONCLUSIONS

Our theoretical research resulted that personality dimensions in PWE may change following ST. Personality traits became more adaptive due to decreased impulsivity, hypochondriasis, psychasthenia or increased control scales. Three of 11 studies included in the literature review showed no changes in personality post-surgery, while one showed increased emotional lability, which was characterized as a negative development. Studies comparing SF and NSF groups after surgery showed a decrease in poorly adjusted personality traits in SF patients, primarily organic psycho-syndrome and neuroticism, hypochondriasis, and psychasthenia. Development of personality changes may be displayed within a short follow-up in both SF and NSF patients, but at further follow-up these improvements were only maintained in groups that were seizure-free. Our empirical study demonstrates that personality traits in patients with drug-resistant epilepsy change following surgery at the 1-year follow-up and personality profile at the baseline affects postsurgical quality of life outcome. The changes in personality dimensions and in QoL were not associated with the seizure frequency, either at the baseline or at the follow-up.

Agreeableness was the most relevant difference between the surgical and control group, being higher in the former in 1 year follow-up assessment. The surgical group became less neurotic and increased in agreeableness scores, while the control group increased in the consciousness scale, especially if a patient was young at the onset of epilepsy and was not depressed according to the baseline presurgical evaluation.

Epileptic patients with high baseline levels of conscientiousness and openness to experience showed better QoL outcomes following surgical treatment at the 1-year follow-up, while patients high in neuroticism showed a worse QoL.

The findings of the study inform clinical psychologists, psychiatrists, and patients, that some personality features and mood can favorably change following surgical treatment and personality profile at the baseline can affect a postsurgical perception of QoL despite of seizure outcome. Systematic collection and analysis of personality data alongside HRQOL measures may be helpful in medical research, clinical practice, and health policy evaluation.

11. REFERENCES

Afshar H, Roohafza HR, Keshteli AH, Mazaheri M, Feizi A, Adibi P. The association of personality traits and coping styles according to stress level. J Res Med Sci. 2015;20(4):353-358.

Alonso NB, de Albuquerque M, Vidal-Dourado M, Cavicchioli LH, Mazetto L, de Araújo Filho GM et al. Revisiting personality in epilepsy: Differentiation of personality in two epilepsies starting in adolescence. Epilepsy Behav. 2019 Aug;97:75-82. doi: 10.1016/j.yebeh.2019.05.004. Epub 2019 Jun 10. PMID: 31195327.

Aluja A, García O, Rossier J, García LF. Comparison of the NEO-FFI, the NEO-FFI-R and an alternative short version of the NEO-PI-R (NEO-60) in Swiss and Spanish samples. Personal Individ Differ. 2005;38:591–604.

Bear, D. M., & Fedio, P. (1977). Quantitative Analysis of Interictal Behavior in Temporal Lobe Epilepsy. *Archives of Neurology*. https://doi.org/10.1001/archneur.1977.00500200014003

Chapman BP, Duberstein PR, Sörensen S, Lyness JM. Gender Differences in Five Factor Model Personality Traits in an Elderly Cohort: Extension of Robust and Surprising Findings to an Older Generation. Pers Individ Dif. 2007;43(6):1594-1603. doi:10.1016/j.paid.2007.04.028

Corr Philip J, Matthews Gerald. The Cambridge handbook of personality psychology (1. Publ. ed.). Cambridge: Cambridge University Press; 2009. ISBN 978-0-521-86218-86219.

Costa PT, Terracciano A, McCrae RR. Gender differences in personality traits across cultures: robust and surprising findings. J Pers Soc Psychol. 2001 Aug;81(2):322-331. doi: 10.1037/0022-3514.81.2.322. PMID: 11519935.

Dash GF, Slutske WS, Martin NG, Statham DJ, Agrawal A, Lynskey MT. Big Five personality traits and alcohol, nicotine, cannabis, and gambling disorder comorbidity. Psychol

Addict Behav. 2019 Jun;33(4):420-429. doi: 10.1037/adb0000468. Epub 2019 May 16. PMID: 31094546; PMCID: PMC7269105.

Deleo F, Quintas R, Pastori C, Pappalardo I, Didato G, Di Giacomo R, et al. Quality of life, psychiatric symptoms, and stigma perception in three groups of persons with epilepsy. Epilepsy Behav. 2020 Sep;110:107170. doi: 10.1016/j.yebeh.2020.107170. Epub 2020 Jun 5. PMID: 32512366.

Derry PA, Wiebe S. Psychological adjustment to success and to failure following epilepsy surgery. Can J Neurol Sci. 2000 May;27 Suppl 1:S116-20; discussion S121-5. doi: 10.1017/s0317167100000779. PMID: 10830338

Derry, P. A., Harnadek, M. C. S., McLachlan, R. S., Sontrop, J., Blume, W. T., Girvin, J. P. A longitudinal study of the effects of seizure symptoms on the Minnesota Multiphasic Personality Inventory-2 (MMPI-2) clinical interpretation. Journal of Clinical Psychology.2002; 58(7), 817–826. https://doi.org/10.1002/jclp.2005

Distel MA, Trull TJ, Willemsen G, Vink JM, Derom CA, Lynskey M et al. The five-factor model of personality and borderline personality disorder: a genetic analysis of comorbidity. Biol Psychiatry. 2009 Dec 15;66(12):1131-8. doi: 10.1016/j.biopsych.2009.07.017. Epub 2009 Sep 12. PMID: 19748081.

Elbeh, K.A.M., Elserogy, Y.M., Hamid, M.F. *et al.* Personality traits in patients with refractory versus non-refractory epilepsy. *Middle East Curr Psychiatry* **28,** 27 (2021). https://doi.org/10.1186/s43045-021-00106-8

Endermann M, Zimmermann F. Factors associated with health-related quality of life, anxiety and depression among young adults with epilepsy and mild cognitive impairments in short-term residential care. Seizure. 2009 Apr;18(3):167-75. doi: 10.1016/j.seizure.2008.08.013. Epub 2008 Sep 26. PMID: 18823801.

Engel JJ, Wiebe S, French J, et al. Practice parameter: temporal lobe and localized neocortical resections for epilepsy: report of the Quality Standards Subcommittee of the American Academy of Neurology, in association with the American Epilepsy Society and the American Association of Neurology. *Neurology* 2003;60:538–547.

Engman, E., Malmgren, K. A longitudinal study of psychological features in patients before and two years after epilepsy surgery. Epilepsy and Behavior.2012; 24(2), 221–226. https://doi.org/10.1016/j.yebeh.2012.03.032

First M, Spitzer R, Gibbon Miriam, Williams, Janet BW (1996) Structured Clinical Interview for DSM-IV Axis I Disorders, Clinician Version (SCID-CV). Washington, DC Am. Internet. cited 2016 Feb 25; Available at: https://scholar.google.es/scholar?cluster=6807271620914188016&hl=es&as_sdt=2005&sciodt=0,5# 0

Gilliam F. Optimizing health outcomes in active epilepsy. Neurology. 2002 Apr 23;58(8 Suppl 5):S9-20. doi: 10.1212/wnl.58.8_suppl_5.s9. PMID: 11971128

Hébert-Seropian, B., Boucher, O., Sénéchal, C., Rouleau, I., Bouthillier, A., Lepore, F., et al. Does unilateral insular resection disturb personality? A study with epileptic patients. Journal of Clinical Neuroscience. 2017; 43, 121–125. https://doi.org/10.1016/j.jocn.2017.04.001

Helmstaedter C. Behavioral aspects of frontal lobe epilepsy. Epilepsy Behav 2001;2 (5):384–95. https://doi.org/10.1006/ebeh.2001.0259. 2001.

Herrero MJ, Blanch J, Peri JM, De Pablo J, Pintor L, Bulbena A. A validation study of the hospital anxiety and depression scale (HADS) in a Spanish population. Gen Hosp Psychiatry. 2003 Jul-Aug;25(4):277-83. doi: 10.1016/s0163-8343(03)00043-4. PMID: 12850660.

Johnson EK, Jones JE, Seidenberg M, Hermann BP. The relative impact of anxiety, depression, and clinical seizure features on health-related quality of life in epilepsy. Epilepsia. 2004 May;45(5):544-50. doi: 10.1111/j.0013-9580.2004.47003.x. PMID: 15101836

Joudi Mashhad, M., Harati, H., Parooie, F. *et al.* Epilepsy surgery for refractory seizures: a systematic review and meta-analysis in different complications. *Egypt J Neurol Psychiatry Neurosurg* **56,** 35 (2020). https://doi.org/10.1186/s41983-020-00168-1

Kanner AM. Depression in epilepsy is much more than a reactive process. Epilepsy Curr 2003;3(6):202–3. https://doi.org/10.1046/j.1535-7597.2003.03609.x. 2003.

Kapogiannis D, Sutin A, Davatzikos C, Costa P Jr, Resnick S. The five factors of personality and regional cortical variability in the Baltimore longitudinal study of aging. Hum Brain Mapp. 2013 Nov;34(11):2829-40. doi: 10.1002/hbm.22108. Epub 2012 May 19. PMID: 22610513; PMCID: PMC3808519.

Kim SE, Kim HN, Cho J, Kwon MJ, Chang Y, Ryu S, et al. Direct and Indirect Effects of Five Factor Personality and Gender on Depressive Symptoms Mediated by Perceived Stress published correction appears in PLoS One. 2016;11(6):e0157204 . PLoS One. 2016;11(4): e0154140. Published 2016 Apr 27. doi:10.1371/journal.pone.0154140

King, M. L., Tranel, D. Stable psychological functioning after surgery for epilepsy: An informant-based perspective. Epilepsy and Behavior.2017; 69, 110–115. https://doi.org/10.1016/j.yebeh.2017.01.028

Kwan P, Arzimanoglou A, Berg AT, BrodieMJ, Allen HauserW, Mathern G, et al. Definition of drug resistant epilepsy: consensus proposal by the ad hoc task force of the ILAE commission on therapeutic strategies. Epilepsia 2010;51(6):1069–77

Kwan P, Brodie M. Early identification of refractory epilepsy. N Engl J Med 2000;342: 314-9.

Lee SA, Jeon JY, No SK, Park H, Kim OJ, Kwon JH, et al. Factors contributing to anxiety and depressive symptoms in adults with new-onset epilepsy. Epilepsy Behav. 2018;88:325-331. doi:10.1016/j.yebeh.2018.10.005

Lee-Baggley D, Preece M, Delongis A. Coping with interpersonal stress: role of big five traits. J Pers. 2005 Oct;73(5):1141-80. doi: 10.1111/j.1467-6494.2005.00345.x. PMID: 16138869

Leong M, Wang AD, Trainor D, Johnstone B, Rayner G, Kalincik, et al. Personality profiles differ between patients with epileptic seizures and patients with psychogenic non-epileptic seizures. Seizure 2019;2019(73):1–8. https://doi.org/ 10.1016/j.seizure.2019.10.011.

Leong, M., Wang, A. D., Trainor, D., Johnstone, B., Rayner, G., Kalincik, et al. (). Personality profiles differ between patients with epileptic seizures and patients with psychogenic non-epileptic seizures. Seizure, 2019; https://doi.org/10.1016/j.seizure.2019.10.011

Li T, Yan X, Li Y, et al. Neuronal Correlates of Individual Differences in the Big Five Personality Traits: Evidences from Cortical Morphology and Functional Homogeneity. Front Neurosci. 2017;11:414. Published 2017 Jul 18. doi:10.3389/fnins.2017.00414

Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JPA, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. J Clin Epidemiol 2009;62(10):e1–34. https://doi.org/10.1016/j.jclinepi.2009.06.006. 2009.

Mac Giolla E, Kajonius PJ. Sex differences in personality are larger in gender equal countries: Replicating and extending a surprising finding. Int J Psychol. 2019 Dec;54(6):705-711. doi: 10.1002/ijop.12529. Epub 2018 Sep 11. PMID: 30206941.

Magyar M, Gonda X, Pap D, Edes A, Galambos A, Baksa D, et al. Decreased Openness to Experience Is Associated with Migraine-Type Headaches in Subjects with Lifetime Depression. Front Neurol. 2017; 8:270. Published 2017 Jun 22. doi:10.3389/fneur.2017.00270

Margolis SA, Nakhutina L, Schaffer SG, Grant AC, Gonzalez JS. Perceived epilepsy stigma mediates relationships between personality and social well-being in a diverse epilepsy population. Epilepsy Behav. 2018 Jan;78:7-13. doi: 10.1016/j.yebeh.2017.10.023. Epub 2017 Dec 22. PMID: 29161631.

Mehta S, Tyagi A, Tripathi R, Kumar M. Study of Inter-relationship of Depression, Seizure Frequency and Quality of Life of People with Epilepsy in India. Ment Illn. 2014 Mar 4;6(1):5169. doi: 10.4081/mi.2014.5169. PMID: 25478138; PMCID: PMC4253398.

Meier, M. J., French, L. A. Changes in MMPI Scale Scores and an Index of Psychopathology following Unilateral Temporal Lobectomy for Epilepsy. Epilepsia. 1965; 6(3),263–273. https://doi.org/10.1111/j.1528-1157.1965.tb03794.x

Meldolesi, G. N., Di Gennaro, G., Quarato, P. P., Esposito, V., Grammaldo, L. G., Morosini, P., et al. Changes in depression, anxiety, anger, and personality after resective surgery for drugresistant temporal lobe epilepsy: A 2-year follow-up study. Epilepsy Research. 2007; 77(1), 22–30. https://doi.org/10.1016/j.eplepsyres.2007.08.005

Nostro AD, Müller VI, Reid AT, Eickhoff SB. Correlations Between Personality and Brain Structure: A Crucial Role of Gender. Cereb Cortex. 2017 Jul 1;27(7):3698-3712. doi: 10.1093/cercor/bhw191. PMID: 27390020; PMCID: PMC6059198.

Novais F, Loureiro S, Andrea M, Figueira ML, Pimentel J, Cˆ amara Pestana L. May the right-side epileptogenic zone be a predictor of psychiatric comorbidity in people with refractory epilepsy? Laterality 2019;25(3):275–84. https://doi.org/ 10.1080/1357650X.2019.1662431. 2020.

Novais*, F., Franco, A., Loureiro, S., Andrea, M., Figueira, M. L., Pimentel, J., & Pestana, L. C. (2019). Personality patterns of people with medically refractory epilepsy – Does the epileptogenic zone matter? *Epilepsy and Behavior, 97*, 130–134. https://doi.org/10.1016/j.yebeh.2019.05.049

Osorio ´ CM, Latini A, Leal RB, de Oliveira Thais MER, Vascouto HD, Remor AP, et al. Neuropsychological functioning and brain energetics of drug resistant mesial temporal lobe

epilepsy patients. Epilepsy Res 2017;138(December):26–31. https://doi.org/10.1016/j.eplepsyres.2017.10.009. Epub 2017 Oct 12. PMID: 29040828.

Park CH, Choi YS, Jung AR, Chung HK, Kim HJ, Yoo JH, et al. Seizure control and memory impairment are related to disrupted brain functional integration in temporal lobe epilepsy. J Neuropsychiatry Clin Neurosci 2017;29(4):343–50. https://doi.org/10.1176/appi.neuropsych.16100216. 2017.

Paschal AM, Hawley SR, St Romain T, Liow K, Molgaard CA, Sly J, et al. Epilepsy patients' perceptions about stigma, education, and awareness: preliminary responses based on a community participatory approach. Epilepsy Behav. 2007 Nov;11(3):329-37. doi: 10.1016/j.yebeh.2007.06.007. Epub 2007 Sep 10. PMID: 17827072.

Ramanaiah NV, Detwiler FR, Byravan A. Life satisfaction and the five-factor model of personality. Psychol Rep. 1997 Jun;80(3 Pt 2):1208-10. doi: 10.2466/pr0.1997.80.3c.1208. PMID: 9246886.

Rassart J, Luyckx K, Verdyck L, Mijnster T, Mark RE. Personality functioning in adults with refractory epilepsy and community adults: implications for healthrelated quality of life. Epilepsy Res 2020;2020(159):106251. https://doi.org/ 10.1016/j.eplepsyres.2019.106251.

Rivera Bonet CN, Hermann B, Cook CJ, Hwang G, Dabbs K, Nair V, et al. Neuroanatomical correlates of personality traits in temporal lobe epilepsy: findings from the Epilepsy Connectome Project. Epilepsy Behav 2019;98(Pt A):220–7. https://doi.org/10.1016/j.yebeh.2019.07.025. 2019.

Rose, K. J., Derry, P. A., McLachlan, R. S. Neuroticism in temporal lobe epilepsy: Assessment and implications for pre- and postoperative psychosocial adjustment and health-related quality of life. Epilepsia. 1996; 37(5), 484–491. https://doi.org/10.1111/j.1528-1157.1996.tb00595.x

Sadock Benjamin, Sadock Virginia, Ruiz Pedro. Kaplan and Sadock's comprehensive textbook of psychiatry. Wolters Kluwer; 2017. ISBN 978-1-4511- 0047-1.

Scheffer IE, Berkovic S, Capovilla G, Connolly MB, French J, Guilhoto L et al. ILAE classification of the epilepsies: position paper of the ILAE commission for classification and terminology. Epilepsia. 2017;58: 512–21.

Shamsi, A., Tohidi, R. S., Shamekhi, M., Amirifard, H., Ansarimoghadam, A. The relationship between personality characteristics and the quality of life in patients with epilepsy. Psychiatria, 2020; 17(2), 66-70.

Shehata GA, Bateh AE. Cognitive function, mood, behavioral aspects, and personality traits of adult males with idiopathic epilepsy. Epilepsy Behav 2009;14 (1):121–4. https://doi.org/10.1016/j.yebeh.2008.08.014. 2009.

Shi, J., Yao, Y., Zhan, C., Mao, Z., Yin, F., Zhao, X. The Relationship Between Big Five Personality Traits and Psychotic Experience in a Large Non-clinical Youth Sample: The Mediating Role of Emotion Regulation. Frontiers in psychiatry. 2018; 9, 648. https://doi.org/10.3389/fpsyt.2018.00648

Sisodiya S. Etiology and management of refractory epilepsies. *Nat Clin Pract Neurol* (2007) 3:320–30. doi:10.1038/ncpneuro0521

Tang F, Hartz AMS, Bauer B. Drug-Resistant Epilepsy: Multiple Hypotheses, Few Answers. Front Neurol. 2017 Jul 6;8:301. doi: 10.3389/fneur.2017.00301. PMID: 28729850; PMCID: PMC5498483.

Tarsitani L, Bertolote JM. Major depressive comorbidity in epilepsy as a reactive process to a chronic condition. Epilepsy Behav 2006;8(1):343–4. https://doi.org/ 10.1016/j.yebeh.2005.08.021. 2006.

Torres X, Arroyo S, Araya S, de Pablo J. The Spanish Version of the Quality-of-Life in Epilepsy Inventory (QOLIE-31): translation, validity, and reliability. Epilepsia. 1999 Sep;40(9):1299-304. doi: 10.1111/j.1528-1157.1999.tb00861.x. PMID: 10487195.

van Rijckevorsel K. Cognitive problems related to epilepsy syndromes, especially malignant epilepsies. Seizure 2006;15(June(4)):227–34. https://doi.org/10.1016/ j.seizure.2006.02.019. Epub 2006 Mar 24. PMID: 16563807.

Villeneuve N. Quality-of-life scales for patients with drug-resistant partial epilepsy. Rev Neurol (Paris). 2004 Jun;160 Spec No 1:5S376-93. French. PMID: 15331986.

Wachi, M., Tomikawa, M., Fukuda, M., Kameyama, S., Kasahara, K., Sasagawa, M., et al. Neuropsychological Changes After Surgical Treatment for Temporal Lobe Epilepsy. Epilepsia. 2001; 42, 4–8. https://doi.org/10.1046/j.1528-1157.42.s6.1.x

Watson, D., & Hubbard, B. Adaptational style and dispositional structure: Coping in the context of the five-factor model. Journal of Personality, 1996; 64, 737–774

Weisberg YJ, Deyoung CG, Hirsh JB. Gender Differences in Personality across the Ten Aspects of the Big Five. Front Psychol. 2011;2:178. Published 2011 Aug 1. doi:10.3389/fpsyg.2011.00178

Wheelock I, Peterson C, Buchtel HA. Presurgery expectations, postsurgery satisfaction, and psychosocial adjustment after epilepsy surgery. Epilepsia 1998;39 (5):487–94. https://doi.org/10.1111/j.1528-1157.1998.tb01410.x

Wilson SJ, Wrench JM, McIntosh AM, Bladin PF, Berkovic SF. Personality development in the context of intractable epilepsy. Arch Neurol. 2009 Jan;66(1):68-72. doi: 10.1001/archneurol.2008.532. PMID: 19139301.

Witt, J. A., Hollmann, K., Helmstaedter, C. The impact of lesions and epilepsy on personality and mood in patients with symptomatic epilepsy: A pre- to postoperative follow-up study. Epilepsy Research. 2008; 82(2–3), 139–146. https://doi.org/10.1016/j.eplepsyres.2008.07.011

World Health Organization. International league against epilepsy, international bureau for epilepsy. Atlas: Epilepsy Care in the World; 2005. Geneva, Switzerland.