UNIVERSIDADE DE LISBOA
FACULDADE DE MEDICINA

Mental Disorders and Refractory Epilepsy

Evidence of a bidirectional relationship

FILIPA ANDREIA LEMOS NOVAIS OLIVEIRA CRUZ

Orientadores:
Prof. Doutora Maria Luísa Caruana Canessa Figueira da Cruz Filipe
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TESE ESPECIALMENTE ELABORADA PARA OBTENÇÃO DO GRAU DE DOUTOR EM MEDICINA
ESPECIALIDADE DE PSIQUIATRIA E SAÚDE MENTAL

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FOREWORD

People with refractory epilepsy suffer from important limitations that may have a severe impact on their personal, family and social functioning. Moreover, they have very high rates of mental disorders, often underdiagnosed and undertreated.

In this thesis, we aimed to investigate the bidirectional relationship between refractory epilepsy and mental disorders. Psychiatrists´ interest in the study of mood and behavior of people with epilepsy dates back to many years ago. However, there is still need to systematize and add scientific evidence to many of the previous theories. We believe that by focusing on these matters we may bring important insights into both epilepsy and mental disorders.

Our plan of work included two parts. First, we studied the impact of epilepsy-related factors and epilepsy surgery on mental disorders. Then, we focused on the impact of mental disorders on the course of epilepsy, after surgery.

We believe that our research may have significant implications for both researchers and clinicians. The investigation of the factors that lead to the worsening or *de novo* psychiatric symptoms may contribute to unravel the neurobiological basis of mental disorders. The interconnection between Psychiatry and Neurosciences is, indeed, fundamental for the comprehension of psychiatric syndromes.

Moreover, the study of the mutual relationship between these disorders will certainly help us to understand them better and how they could have a negative impact on each other. Finally, we hope that this work will also reinforce the importance of recognizing psychiatric disorders in people living with epilepsy and to include psychiatrists in a comprehensive therapeutic approach.

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ACRONYMS

ANT-DBS	Anterior Nucleus of the Thalamus - Deep Brain Stimulation
BPRS	Brief Psychiatric Rating Scale
CRS	Cortical Responsive Stimulation
DSM	Diagnostic and Statistical Manual of Mental Disorders
EEG	Electroencephalography
FLE	Frontal Lobe Epilepsy
GABA	γ-Aminobutyric Acid
GSI	Global Severity Index
HARS	Hamilton Anxiety Rating Scale
HDRS	Hamilton Depression Rating Scale
ICD	International Statistical Classification of Diseases and Related Health Problems
ILAE	International League Against Epilepsy
MMCI-II	Millon Clinical Multiaxial Inventory II
PWE	People with epilepsy
RE	Refractory Epilepsy
RS	Resective Surgery
SCL-90	Symptom Checklist-90
TLE	Temporal Lobe Epilepsy
VNS	Vagus Nerve Stimulation

ABSTRACT

Introduction

Although the relationship between mental disorders and epilepsy has been studied for several years there is a lack of systematization of knowledge in this area. People with epilepsy, particularly those who are refractory to pharmacological treatment, have a high prevalence of psychiatric comorbidities. For these patients, surgical treatment is often proposed; its effects at a psychopathological level may depend on the clinical characteristics of each person and the surgical technique itself. While some epilepsy-related characteristics may contribute to a higher risk of psychiatric disorders, these may also be associated with the prognosis of refractory epilepsy.

Aims

This study focused on the relationship between mental illness and refractory epilepsy. Specifically, our objectives were to study the mutual influence between refractory epilepsy or epilepsy surgery and mental disorders. Moreover, we also aimed to determine if the dysfunction, associated with the epilepsy origin, of a particular lobe or hemisphere influenced the risk or the type of any psychiatric disorder.

Methods

To investigate these questions, we designed one cross-sectional and five ambispective cohort studies, using a sample of people with refractory epilepsy referred to surgery. The participants were accessed before surgery and annually, after that, during a maximum period of three years, by a psychiatrist from the Epilepsy Surgery Group of Hospital de Santa Maria. Assessments included a clinical evaluation and a battery of scales and questionnaires. Different statistical approaches were used according to the aim of each study.

Results

Our results showed that 46% of people with refractory epilepsy had a lifetime history of some psychiatric disorder and the risk seems to be higher in those with an epilepsy originated in the right hemisphere. Regarding personality, 70% had a dysfunctional personality pattern. After epilepsy surgery, this percentage dropped to 58% and the difference was found to be significant. “Avoidant” and “Compulsive” personality patterns were associated with a

temporal epilepsy origin while an extratemporal origin was associated with “Histrionic” and “Antisocial” patterns.

Additionally, our studies allowed us to identify that epilepsy with a multilobar origin and a neuromodulation technique, the Deep Brain Stimulation of the Anterior Thalamic Nucleus (ANT-DBS) were associated with the development of *de novo* psychiatric disorders.

It was also demonstrated that in people with a bilateral epilepsy origin, no remission of epileptic seizures and in those submitted to ANT-DBS there was an increase of psychopathological scores and, consequently, a greater mental suffering, one year after the epilepsy surgery.

Regarding the course of refractory epilepsy, we showed that a history of any mental illness is a predictor of lower seizure control after surgery. In fact, regarding epilepsy surgery outcome this was the most important contributor to the accuracy of a predictive model.

Conclusions

Important conclusions can be drawn from these results. People with refractory epilepsy have high rates of mental disorders and dysfunctional personality adjustment patterns. Regarding the relationship with surgery, people who are subjected to ANT-DBS appear to have an increased probability of either developing new psychiatric syndromes or worsening previous psychopathological symptoms, when compared to conventional resective surgery. Despite the fact that this modality of neuromodulation is relatively recent, this work points to a high risk of psychiatric effects.

Moreover, people with a bilateral or multilobar epilepsy origin also have higher risk of worsening or developing *de novo* psychopathology. Considering these data and our findings regarding the poor reduction after surgery of those with psychiatric disorders present, we hypothesize that there might be a subgroup of people with wider brain dysfunction, leading to a more serious neuropsychiatric disorder and therefore worse global prognosis.

In summary, together these studies allowed us to demonstrate evidence for a bidirectional relationship between refractory epilepsy and mental disorders. Epilepsy-related factors affect the course of mental disorders and mental disorders affect the course of epilepsy after surgery. Similarly, we showed that epilepsy surgery also affects the future course of psychopathological symptoms and dysfunctional behavioural patterns. By demonstrating this relationship, our work emphasized the importance of a close collaboration between neurologists and psychiatrists in the follow-up of people with refractory epilepsy.

Moreover, we showed that the potential dysfunction of a particular zone of the brain, due to the epilepsy origin, may be associated with a higher risk for any mental disorder and an increased probability of developing certain dysfunctional personality characteristics. These findings may add to the investigation of the biological basis of mental illnesses.
Future studies should use bigger samples to confirm our results regarding the psychopathological risks of epilepsy surgery, particularly, ANT-DBS, and explore the hypothesis of a subgroup of patients with a more generalized brain dysfunction and what are the neurobiological mechanisms involved in this dysfunction.

Keywords: refractory epilepsy, mental disorders, epilepsy surgery.

RESUMO

Introdução

Embora a relação entre as doenças mentais e a epilepsia seja estudada desde há vários anos, os dados existentes são ainda controversos e pouco sistematizados. Hippocrates (460-370 BC), terá sido um dos primeiros autores a descrever a existência de perturbações psicopatológicas em pessoas com epilepsia. Já no século XX, Kraepelin (1923) caraterizou alguns destes quadros, tendo descrito quer alterações do humor, nomeadamente as "Disforias Periódicas" quer alterações da personalidade. De facto, estas foram alvo de estudo ao longo de décadas, tendo sido, mais tarde, descrita a síndrome de Gastaut-Geschwind que compreendia um conjunto de caraterísticas do comportamento interictal, designadamente, o aumento de preocupações morais, filosóficas e interesses religiosos, viscosidade, hipergrafia e ausência de sentido de humor. Em Portugal salienta-se o trabalho de Júlio de Matos (1884) acerca da "Loucura Epilética" e de Miguel Bombarda (1896) que se debruçou sobre o estudo desta entidade em "Lições sobre Epilepsia e as Pseudo-Epilepsias".

Estudos mais recentes têm mostrado que as pessoas com epilepsia, particularmente, as que sofrem de epilepsia refratária ao tratamento farmacológico, tem uma elevada prevalência de comorbilidades psiquiátricas. As patologias mais comuns são as Perturbações do humor e ansiedade embora também se encontrem taxas mais elevadas de outras patologias, como as perturbações psicóticas, quando é feita a comparação com a população geral. Estes doentes têm também um maior risco de suicídio, estando esta entre as principais causas de mortalidade precoce nestas pessoas. O impacto das doenças mentais na qualidade de vida destes doentes é muito significativo e alguns estudos parecem apontar, igualmente para a possibilidade de agravarem o curso da própria epilepsia. Contudo, as patologias do foro mental continuam a ser subdiagnosticadas ou, muitas vezes, não tratadas, nestes doentes.

Às pessoas com epilepsia refratária é, muitas vezes, proposto um tratamento cirúrgico cujos efeitos a nível psicopatológico poderão depender das caraterísticas clínicas de cada pessoa e da própria técnica cirúrgica. Para além disso, existem diferentes técnicas cirúrgicas, com intuito curativo ou paliativo, que poderão ser aplicadas de acordo com critérios clínicos e preferência dos doentes e famílias.

Objetivo

Este trabalho focou-se no estudo da influência mútua entre a epilepsia refratária ou a cirurgia da epilepsia e a doença mental. Para além disso, pretendemos, ainda, esclarecer se a disfunção, relacionada com a origem da epilepsia, de um determinado lobo ou hemisfério se associa ao maior risco de desenvolver uma perturbação psiquiátrica ou um tipo específico de perturbação.

Método

Para investigar estas questões, foram projetados um estudo transversal, com o intuito de caraterizar a amostra, e cinco estudos de coorte ambispectivos, usando uma amostra de pessoas com epilepsia refratária encaminhada para cirurgia. Os participantes recrutados a partir do Grupo de Cirurgia de Epilepsia do Hospital de Santa Maria, foram avaliados antes da cirurgia e anualmente, durante um período máximo de três anos, por um dos psiquiatras envolvidos na equipa multidisciplinar deste grupo. As observações incluíram uma avaliação clínica e as seguintes escalas e questionários: *The Brief Psychiatric Rating Scale (BPRS); The Hamilton Depression Rating Scale (HDRS); The Hamilton Anxiety Rating Scale (HARS); The Beck Depression Inventory (BDI); The Montgmomery-Asberg Depression Scale (MADRS); The Symptoms Distress Checklist (SCL-90); The Millon Clinical Multiaxial Inventory-II (MCMI-II); The Temperament Evaluation of Memphis, Pisa and San Diego Autoquestionnaire (TEMPS-A); The Quality of Life in Epilepsy Inventory (QoLIE 31)* e a *The Wechsler Adult Intelligence Scale (WAIS-III)*. Em cada estudo foram utilizados e reportados dados de apenas alguns destes testes de acordo com o objetivo do mesmo. Foram também definidas janelas temporais diferentes em cada trabalho, adequadas ao propósito do mesmo e de acordo com os dados disponíveis. As perturbações psiquiátricas podem ser classificadas, de acordo com a sua relação temporal com as crises epiléticas como pre-ictais ou interictais, tendo a nossa pesquisa incidido sobre este último tipo. Neste trabalho não foram ainda incluídas perturbações consideradas como especificamente associadas à epilepsia como a disforia interictal pela sua falta de validação.

A análise das variáveis em estudo foi feita através da utilização de métodos estatísticos adequados a cada objetivo.

Este estudo foi proposto e aprovado pela Comissão de Ética do Hospital de Santa Maria.

Resultados

Os nossos resultados mostram que 46% das pessoas com epilepsia refratária tem história de pelo menos uma perturbação psiquiátrica, ao longo da sua vida, e o risco parece estar aumentado em pessoas com foco epileptogénico direito. Em relação à personalidade, 70% desta população apresentou um padrão disfuncional de personalidade. Depois da cirurgia, esta percentagem decresceu para 58% e a diferença foi estatisticamente significativa. Os padrões "Evitante" e "Compulsivo" associaram-se a uma origem epilética temporal e os padrões "Histriónico" e "Antissocial" a uma origem extratemporal.

Para além disso, os nossos estudos identificaram como fatores associados ao desenvolvimento de patologia psiquiátrica *de novo* pós cirurgia, designadamente, a zona epileptogénica multilobar e a estimulação cerebral profunda do núcleo anterior do tálamo (ANT-DBS).

Demonstrou-se, ainda, que nas pessoas com origem epilética hemisférica bilateral, sem remissão das crises epiléticas e naquelas submetidas a ANT-DBS houve um agravamento de índices psicopatológicos e, por conseguinte, um maior sofrimento mental, um ano após a cirurgia da epilepsia.

Em relação ao curso da epilepsia, demonstrou-se que a existência de história de doença mental constitui um preditor de menor controlo das crises epiléticas pós cirurgia. De fato, em relação ao resultado da cirurgia de epilepsia, esse foi o fator que mais contribuiu para a precisão de um modelo preditivo do resultado da cirurgia.

Conclusões

Importantes conclusões podem ser retiradas destes resultados. Pessoas com epilepsia refratária têm elevada prevalência de doença mental e de padrões de personalidade associados a um funcionamento mal adaptativo. Fatores relacionados com a epilepsia, tais como a sua topografia de origem, podem contribuir para o aumento desta vulnerabilidade. Considerando a relação com a cirurgia, as pessoas sujeitas a ANT-DBS parecem ter uma probabilidade muito superior, quer de desenvolvimento de síndromes psiquiátricas *de novo*, quer de agravamento de sintomas psicopatológicos prévios, em relação à cirurgia ressetiva convencional. Embora esta modalidade de neuromodulação seja ainda recente, este trabalho aponta para um risco elevado de alterações psiquiátricas.

Adicionalmente, doentes com disfunção mais global do sistema nervoso central, associados à origem epilética bi-hemisférica ou multilobar, apresentam, igualmente, este risco de

agravamento ou de desenvolvimento de psicopatologia *de novo*. Por outro lado, as pessoas com história de doença mental também não respondem de forma tão eficaz à cirurgia, mantendo mais crises, após o procedimento. Estes doentes podem constituir um subgrupo caraterizado por uma patologia neuropsiquiátrica de base mais grave.

Em conclusão, este trabalho permitiu obter evidência acerca da existência de uma relação bidirecional entre a epilepsia e as doenças psiquiátricas. Demonstrou-se que alguns fatores relacionados com a epilepsia afetam o curso e tipo de doenças mentais nesta população e que a as doenças mentais afetam o curso da própria epilepsia. Também se demonstrou que a cirurgia da epilepsia interfere com o curso dos sintomas psicopatológicos e comportamentais após este procedimento. Deste trabalho conclui-se, ainda, que a disfunção de diferentes regiões cerebrais poderá contribuir para a emergência de patologia mental.

Assim, enfatiza-se a importância de uma estreita colaboração entre neurologistas e psiquiatras no acompanhamento das pessoas com epilepsia refratária. Desta colaboração podem ainda ser apontados caminhos para a investigação das bases biológicas das doenças mentais.

Estudos futuros, envolvendo amostras mais amplas, poderão confirmar o risco aumentado de desenvolvimento de novo ou agravamento de sintomas psiquiátricos associados à cirurgia da epilepsia e em particular à ANT-DBS. Deverá ainda ser confirmada a hipótese aqui colocada de um potencial subgrupo, caraterizado por uma disfunção mais generalizada do sistema nervoso central, associado quer à epilepsia refratária de pior prognóstico quer à doença mental, assim como, quais os potenciais mecanismos neurobiológicos que poderão estar na base desta disfunção.

Palavras-chave: epilepsia refratária, doença mental, cirurgia da epilepsia.

PUBLICATIONS LIST

In agreement with *Decreto-Lei* 388/70, art. 8º, the results presented and discussed in this work were published or submitted for publication in peer-review journals, as follows:

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- **Novais F**, Franco A, Loureiro S, Andrea M, Figueira ML, Pimentel J, Pestana LC. Personality patterns of people with Refractory Epilepsy – does the epileptogenic zone matter? Epilepsy & Behavior 2019;97:130–134. doi: 10.1016/j.yebeh.2019.05.049.

- **Novais F**, Pestana LC, Loureiro S, Andrea M, Figueira ML, Pimentel J. Predicting de novo psychopathology after epilepsy surgery: A 3-year cohort study. Epilepsy & Behavior 2019;90:204–8. doi: 10.1016/j.yebeh.2018.11.037.

- **Novais F**, Pestana LC, Loureiro S, Andrea M, Figueira ML, Pimentel J. Clinical determinants of psychopathological outcomes after epilepsy surgery. Epilepsy & Behavior 2019;97:111–117. doi: 10.1016/j.yebeh.2019.04.043.

- **Novais F**, Pestana LC, Loureiro S, Andrea M, Figueira ML, Pimentel J. Psychiatric disorders as predictors of epilepsy surgery outcome. Epilepsy & Behavior 2019;100:106513. doi: 10.1016/j.yebeh.2019.106513. Epub 2019 Oct 19.

- **Novais F**, Pestana LC, Loureiro S, Andrea M, Figueira ML, Pimentel J. Development of a comprehensive model to predict epilepsy surgery outcome. *Submitted for publication.*

CHAPTER I: Introduction and Aims

INTRODUCTION

Historical perspective

The bidirectional relationship between mental disorders and, particularly, depression was suggested, twenty-six centuries ago, by Hippocrates (460-370 BC), when he wrote "melancholics become epileptics and epileptics melancholics", proposing a reciprocal relationship between depression and epilepsy[1]. Not surprisingly, the interest of psychiatrists in epilepsy has a long history. In the XIX century, Esquirol (1772-1840) and Morel (1809-1873) described the tendency of people with epilepsy to social isolation and hyperreligiosity[2]. Kraepelin (1856-1926) explained, in 1923, what he considered to be the most common form of psychiatric disorders in these patients, the "Periodic Dysphorias", which corresponded to changes in mood, with irritability being its cardinal symptom. Additionally, these patients could present depression, anxiety and less common "paradoxistic" euphoric mood states or delusional episodes that he considered to be merely their extension[3]. Kraepelin also suggested that people with epilepsy have certain personality characteristics, he described them as meticulous, slowed, circumstantial, labile, irritable, explosive and prone to religiosity[4]. Again, about 20 years later, Bleuler (1857-1939) described the disorders of mood in people with epilepsy (PWE) according to Kraepelin´s conceptions[3]. Between 1973 and 1984, Norman Geschwind´s, an American neurologist, published an extensive amount of literature concerning interictal behavioral changes in temporal lobe epilepsy (TLE). What was latter called the Gastaut-Geschwind syndrome included increased religious interests, hypergraphia, increased aggression, higher moral and philosophical concerns, viscosity, and seriousness (lack of humor). The same author proposed that these characteristics resulted from a lesion stimulating the limbic system[5]. Later research using the questionnaire developed by Bear and Fedio[6] to evaluate these personality traits in people with TLE did not support the syndrome[7].

In Portugal, some important psychiatrists treated people with epilepsy and wrote about their psychiatric disturbances. Among of the most notable works are those of Julio de Matos (1884) in "*Loucura Epilética*" and Miguel Bombarda (1896) in "*Lições sobre Epilepsia e as Pseudo-Epilepsias*"[8].

Epilepsy and comorbid Mental Disorders

It is estimated that around 25 to 50% of PWE suffer from at least one psychiatric comorbidity. In some groups, such as TLE and Refractory Epilepsy (RE) a prevalence of up to 80% has been reported[9]. Although there are some discrepancies in literature, the most common type of disorders seem to be mood disorders, particularly, major depression, and anxiety[10,11]. The previous work of a Portuguese researcher, Professor Doutor António Palha (1985), focused on the determination of the prevalence of psychiatric disorders in a sample of 90 people with epilepsy. He showed that 63,3% had a history of depressive symptoms, 32,2% had a history of psychotic symptoms and 13,3% patients had severe anxiety symptoms in the past[8]. There is also an increased risk of suicide, particularly in TLE, in patients submitted to surgical treatment and those with psychiatric comorbidities[12].

Mental disorders have an important impact on PWE quality of life, contributing to the global burden and disability associated with epilepsy[13]. In the last decades, psychiatrists were not always involved in the care of these patients and psychiatric disorders are largely underdiagnosed and undertreated in people with neurological disorders[14].

Disturbances of mood and behavior may be defined according to if they have a temporal relationship with seizures as peri-ictal (pre-ictal, post-ictal and ictal) and, if no relation with seizure occurrence can be established, as interictal[15]. Our work focused on interictal disorders, as psychiatric comorbidities are generally considered.

There has been some controversy regarding the atypical nature of some mental and behavioral disturbances in epilepsy. An example of this dissidence is the interictal dysforic disorder that has its roots on the syndrome defined by Kraepelin and Bleuler[16]. However, the majority of patients with this disorder also have depression and anxiety that seem to have a much higher impact on quality of life and seizure control[17]. Moreover, dysphoric disorder was never included in diagnostic classifications, it is considered doubtful, lacking diagnostic tools and clinical utility[17]. Other entities such as the interictal personality, formerly known as the Gastaut-Geschwind syndrome and the interictal psychosis were not proven to constitute well characterized and individual syndromes in epilepsy[18,19]. Instead they share common characteristics with the syndromes diagnosed by international classification systems, inherently polymorphic, in patients with and without epilepsy.

In our work, we choose not to include other entities rather than those that could be diagnosed according to the 10th version of the International Statistical Classification of Diseases and Related Health Problems (ICD-10) criteria.

Underlying mechanisms and risk factors

Risk factors for mental disorders in PWE include psychosocial factors such as stigma, poor disease acceptance, anticipatory anxiety associated with the unpredictable nature and outcome of seizures, as well as, the limitations imposed by the disease itself[20]. Pharmacological effects, related to the use of antiepileptics, should also be considered. These may originate from their mechanism of action, involving the regulation of neuronal excitability and potentially the modulation of the serotoninergic, noradrenergic and dopaminergic systems, neural plasticity and neurogenesis, the underlying neurological condition and personal factors[21].

Epilepsy-related factors may, as well, contribute to the increased vulnerability for mental disorders in this population. Epileptogenic activity may induce local or global long-term brain disturbances that increase the risk for the development of psychopathological symptoms and syndromes. In animal models, rats showed a depressive-like pattern of behavior after an induced status epilepticus[22,23]. Additionally, the researchers showed a decrease in serotonin concentration, turnover and release in the hippocampus of these animals[24].

Neurobiological aspects may, in fact, constitute common underlying mechanisms in both epilepsy and psychiatric disorders or, alternatively, these disorders may represent different expressions of the same molecular substrates. These factors may include alterations in the neurotransmission mediated by serotonin, dopamine, norepinephrine, glutamate and γ-aminobutyric acid (GABA) through changes in signal transduction mechanisms. Other suggested contributors are the hyperactivity of the hypothalamic–pituitary–adrenal axis and the central nervous system inflammation, occurring in both epilepsy and mental disorders[25].

Moreover, some studies have pointed out to a shared heritability between some mental disorders, such as, schizophrenia, attention deficit hyper-activity disorder, autism spectrum disorders and epilepsy[26,27].

A commonly cited neurobiological phenomena, is forced normalization, a term coined by Landolt (1958) to explain psychotic symptoms associated with the disappearance of

epileptiform activity on electroencephalograms and seizure remission in PWE[28]. Since then, many clinical cases, corresponding to the initial description, have been reported and some potential explanatory mechanisms have been proposed as well. These include the ability of kindling, initiated by electrical stimuli applied to the mesolimbic system, to produce behavioral changes in animal models[29], and modulation of neurotransmitters such as dopamine, glutamate or GABA produced by antiepileptic drugs[28,30]. However, forced normalization is reported to occur only in 7.8% of PWE[31] and its biological mechanism remains largely unknown.

Two other terms were proposed later: the term *alternative psychosis*, suggested by Tellenbach (1965), that applies to the clinical phenomenon of a reciprocal relationship between abnormal mental states and seizures that did not rely on EEG findings, and *paradoxical normalization*, suggested by Wolf (1991), describing epilepsy that is still active, but it remains subcortical and leads to the development of psychopathological symptoms[32].

People with psychiatric disorders also have an increased risk of developing epilepsy. Some psychiatric disorders such as attention deficit disorder with hyperactivity, major depression and suicidal ideation may precede the onset of epilepsy. Population-based studies found an increased risk of epilepsy from 3.5 to 17 times greater in patients suffering from psychiatric disorders when compared to the general population[33].

Additionally, mental disorders have been associated with clinical refractoriness in PWE[1].

Refractory Epilepsy and Epilepsy Surgery

In 2014, the International League Against Epilepsy (ILAE) defined epilepsy as "a disease of the brain defined by any of the following conditions: (1) at least two unprovoked (or reflex) seizures occurring >24 h apart; (2) one unprovoked (or reflex) seizure and a probability of further seizures similar to the general recurrence risk (at least 60%) after two unprovoked seizures, occurring over the next 10 years; (3) diagnosis of an epilepsy syndrome"[34].

About 60% of PWE have a focal-onset epilepsy, affecting, most frequently, the temporal lobe[35]. Neocortical TLE represents 10% of TLEs and the rest affects mesial structures – the hippocampus and the amygdala[36,37].

About a third of PWE do not respond to pharmacological treatment[38] and are considered to have RE. This is defined as "failure of adequate trials of two tolerated, appropriately chosen and used antiepileptic drug schedules (whether as monotherapies or in combination)

to achieve sustained seizure freedom"[39]. An even higher prevalence of psychiatric disorders has been reported in these patients[40,41]. The potential to lower seizures threshold of some psychotherapeutic drugs such as antidepressants or antipsychotics, as well as structural and functional brain abnormalities and dysfunctional secretion of neurotransmitters, in both pharmacoresistant epilepsy and psychiatric disorders, have been proposed as potential mechanisms underlying this association[42].

Patients with RE may be eligible for resective surgery, a procedure that is effective in the remission of seizures in about 70% of the cases[43]. However, seizure control may depend on several clinical factors including age at surgery, duration of epilepsy and location of the area of the cortex that is necessary and sufficient for initiating seizures and whose removal (or disconnection) is necessary for complete abolition of seizures, called the epileptogenic zone[44–46].

For those whom, by any reason, surgical resection is not feasible, other options may be considered. Namely, neuromodulation interventions, such as Vagus Nerve Stimulation (VNS) or Deep Brain Stimulation, targeting the Anterior Nucleus of the Thalamus (ANT-DBS)[47]. These are palliative procedures with much lower rates of success.

The standard method to report the outcome of epilepsy surgery is the Engel Scale (Table 1)[48]. This instrument was developed by the neurologist Jerome Engel Jr. and was first presented at the Palm Desert Conference on Epilepsy Surgery in 1992[49].

All these techniques have shown positive results in the reduction of seizure frequency, while the resection of the epileptogenic zone is curative.

Although the procedure seems to have a global positive effect also in terms of quality of life and psychopathology, particularly in those who became seizure-free[50–53], these results are still controversial[11,54,55] and up to 20% of these patients may develop *de novo* psychiatric disorders[56]. Differences between studies might be due to the selection of small and different patient samples.

Establishing clinical factors related to both psychiatric and neurological outcomes, after epilepsy surgery, plays an important role in the determination of psychopathological risks and success of surgery. The knowledge of potential success and risks are fundamental to inform both patients and clinicians regarding their decision to proceed to such an invasive procedure. This knowledge also helps to identify patients that might need more frequent psychiatric routine assessments and vigilance.

Furthermore, the research of biological factors associated with specific psychiatric disorders or the general risk for their emergence or aggravation may help to define investigation lines regarding the neurobiological basis of psychiatric disorders.

Table 1 - Engel's Classification of Postoperative Outcome

Class I: Free of disabling seizures[a]
A. Completely seizure free since surgery
B. Nondisabling simple partial seizures only since surgery
C. Some disabling seizures after surgery, but free of disabling seizures for at least 2 years
D. Generalized convulsions with AED discontinuation only
Class II: Rare disabling seizures ("almost seizure free")
A. Initially free of disabling seizures but has rare seizures now
B. Rare disabling seizures since surgery
C. More than rare disabling seizures since surgery, but rare seizures for the last 2 years
D. Nocturnal seizures only
Class III: Worthwhile improvement[b]
A. Worthwhile seizure reduction
B. Prolonged seizure-free intervals amounting to greater than half the followed-up period, but not <2 years
Class IV: No worthwhile improvement
A. Significant seizure reduction
B. No appreciable change
C. Seizures worse

[a] Excludes early postoperative seizures (first few weeks).
[b] Determination of "worthwhile improvement" will require quantitative analysis of additional data such as percentage seizure reduction, cognitive function, and quality of life.

AIMS

Our aims were:

- To study the effect of refractory epilepsy and epilepsy surgery on mental disorders.
- To study the effect of mental disorders on the course of refractory epilepsy after surgery.
- To explore the role of different brain areas on the susceptibility for psychiatric disorders, using epilepsy and epilepsy surgery as a model.

CHAPTER II: General Methodological Considerations

THE STUDY SAMPLE

This work was developed using a consecutive sample of people with refractory epilepsy referred to psychiatric pre-surgical evaluation by the Epilepsy Surgery Group of the Hospital de Santa Maria (CHULN), Lisbon, Portugal. It included people with temporal and extratemporal epileptogenic zones submitted to different surgical techniques (RS, VNS and ANT-DBS).

Patients were accessed before surgery and 6, 12, 24, 36 and 60 months, after surgery.

Collection of data has begun in 1999 and the design of this study was conceived in 2015. Therefore, a retrospective and a prospective component were considered.

All assessments were made by a psychiatrist and a psychologist from the Epilepsy Surgery Group and included a full clinical evaluation and the following instruments adapted from the 1st Steering Committee Meeting Epilepsy Registry:

- The Brief Psychiatric Rating Scale (BPRS);
- The Hamilton Depression Rating Scale (HDRS);
- The Hamilton Anxiety Rating Scale (HARS);
- The Beck Depression Inventory (BDI);
- The Montgmomery-Asberg Depression Scale (MADRS);
- The Symptoms Distress Checklist (SCL-90);
- The Millon Clinical Multiaxial Inventory-II (MCMI-II);
- The Temperament Evaluation of Memphis, Pisa and San Diego Autoquestionnaire (TEMPS-A);
- The Quality of Life in Epilepsy Inventory (QoLIE 31);
- The Wechsler Adult Intelligence Scale (WAIS-III).

CLINICAL SCALES AND QUESTIONNAIRES

Each study involved different data regarding clinical diagnosis and some of the tests and questionnaires, included in the initial battery, according to the objective of the study and the availability of data. Following is a description of those that were included:

The Hamilton Anxiety Rating Scale (HARS)

This rating scale is one of the first being developed to measure severity of anxiety symptoms and is nowadays one of the most widely used. The scale consists of 14 items and measures both phobic anxiety and somatic anxiety[57].

The Hamilton Depression Rating Scale (HDRS)

This is the most widely used rating scale used to access depression. The version used corresponds to the original 17 items version. It was developed to access depression symptoms over the past week. The original scale was developed for inpatients and has a particular focus on melancholic an physical symptoms[58].

Brief Psychiatric Rating Scale (BPRS)

This rating scale is one of the most widely used scales to measure longitudinal changes in psychotic symptoms and it is based on the interview with the patient, his speech and behavior. The scale contains 18 items, each one rated from 1 (absente) to 7 (extremely severe), evaluating positive, negative and affective symptoms[59]. An extended Portuguese version, with 24 items, was adapted by Gusmão, Talina, Xavier and Caldas de Almeida (1996)[60].

Symptom Cheklist-90 (SCL-90)

This multi-dimensional instrument is a 90-item self-report symptom inventory developed to measure psychological symptoms and psychological distress. It has been extensively validated and used in neurological patients. It contains 9 subscales evaluating different symptom dimensions: somatization, obsessive-compulsive, interpersonal sensitivity, depression, anxiety, hostility, phobic anxiety, paranoid ideation and psychoticism. There are also three global indices for the SCL-90: 1) Global Severity Index (GSI), which is the average score of the 90 items of the questionnaire, 2) Positive Symptom Distress Index,

which is the average score of the items scored above zero, and 3) Positive Symptoms Total, which is the number of items scored above zero[61]. The GSI is suggested to be the best single indicator of the current level of the disorder. A Portuguese version was made has been adapted from the revised version of this questionnaire and shown good psychometric results[62].

The Millon Clinical Multiaxial Inventory II (MMCI-II)

The MCMI-II is a psychological assessment toll used to evaluate personality patterns and psychopathology in adults. It includes 13 personality scales and 9 clinical syndrome scales[65]. This questionnaire was developed to evaluate personality prototypes that were included in the Diagnostic and Statistical Manual (DSM). For each personality type patient´s raw scores are converted into Base Rate scores. The presence of a personality trait is indicated by a score of 75 to 84 and a score of 85 or above indicates the persistence of a personality pattern. This version has been validated in clinical samples showing good internal consistency[66].

The Wechsler Adult Intelligence Scale (WAIS-III)

This is a widely used Intelligence Quotient (IQ) test designed to measure intelligence and cognitive ability in adults[67].

CHAPTER III: Research Questions

RESEARCH QUESTIONS AND RESEARCH OUTLINE

In order to achieve these objectives, six different studies were conceived to answer the following research questions:

STUDY 1

Question 1: What is the percentage of people with refractory epilepsy that also have a history of any mental disorder?

Question 2: What are the most frequent psychiatric disorders in people with refractory epilepsy?

Question 3: Are there any epilepsy related factors that may increase the risk for psychiatric disorders?

STUDY 2

Question 4: What is the percentage of people with a dysfunctional personality pattern in those with refractory epilepsy?

Question 5: Does the affection of different brain lobes contribute to different types of personality disorders?

Question 6: Is the epilepsy surgery associated with a reduction on the proportion of people with dysfunctional personality patterns?

STUDY 3

Question 7: What is the percentage of people developing *de novo* psychiatric disorders after epilepsy surgery?

Question 8: Are there any epilepsy or surgery-related factors that could increase the risk for *de novo* disorders?

STUDY 4

Question 9: Considering those who already had some degree of psychiatric symptomatology are there any factors that could predict the worsening or the improvement of their mental symptoms, after surgery?

STUDY 5

Question 10: Does a lifetime history of any psychiatric disorder predicts worse epileptic seizures control after surgery?

STUDY 6

Question 11: What is the relative importance of having a history of any psychiatric disorder in a predictive model of epilepsy surgery outcome?

CHAPTER IV: Refractory epilepsy and epilepsy surgery impact on mental disorders

Study 1: Psychiatric Disorders and their predictors in people with refractory epilepsy

Title The right-side epileptogenic zone as a predictor of psychiatric comorbidity in people with refractory epilepsy.

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Abstract

Objectives The aim of this study was to determine the rate and types of lifetime psychiatric disorders, as well as their predictors, in a sample of people with refractory epilepsy.

Methods Demographic, neurological, psychiatric and neuropsychological data, from people with refractory epilepsy, were registered at the pre-surgical interview. Logistic regression was used to determine predictors.

Results One hundred and ninety-one participants were included. Forty-six percent of our sample had at least one previous psychiatric diagnosis, most frequently depressive (64%), anxiety (10%), substance use (10%) and psychotic disorders (6%). Patients with a right-side epileptogenic zone had an increased risk for these disorders (OR 2.36; CI 1.22-4.56; p=0.01).

Conclusion Specific epilepsy-related factors may raise the risk of developing a psychiatric disorder. Our study adds evidence to support a bidirectional relationship between epilepsy and mental health.

Keywords Refractory epilepsy, epilepsy surgery, epileptogenic zone, personality

1. Introduction

People with epilepsy and particularly those with medically refractory epilepsy have an increased risk of mental disorders and suicide[68,69]. Additionally, psychiatric disorders and their treatment may also increase the risk of developing epilepsy[70,71].

Lifetime psychiatric disorders have been reported in more than 50% of people with refractory epilepsy[72,73]. The most common disorders, in this population, are depression (24-74%), anxiety disorders (10-25%) and psychotic disorders (2-7%)[73].

Psychiatric comorbidity worsens the quality of life[74] of these people and has a negative impact on the course of epilepsy both before[75] and after epilepsy surgery[76]. In fact, according to the new definition of epilepsy, this is not only a disease with recurrent seizures but it is also often associated with cognitive and psychiatric comorbidities[77].

Some factors that may contribute to the high prevalence of psychiatric comorbidities in epilepsy have been proposed. They include psychosocial adverse factors such as stigma and discrimination,

mobility issues and lack of employment opportunities[78].

Little is known about biological risk factors for the development of psychiatric disorders in the context of epilepsy, however, some mechanisms, mainly based on research in animal models, have been proposed. Some are common aspects of both epilepsy and mental disorders, particularly, depression, and comprise hypothalamic–pituitary–adrenal axis hyperactivity, decreased serotonergic neurotransmission and noradrenergic neurotransmission, glutamatergic and GABAergic disturbances and inflammatory processes[79].

Other factors associated with a higher risk of psychiatric disorders in people with epilepsy include malformations of cortical development[80], accumulation of seizure-related damages related to higher number of previous seizures[81], earlier age at epilepsy onset[82], involvement of potentially more sensitive areas and structures such as the those located in the temporal lobe[83] and the use of antiepileptic drugs[84].

Despite the probable important contribution of psychosocial considerations, as epilepsy directly affects the central nervous system, we may assume that some factors related to this direct brain insult may increase the risk of developing psychopathological symptoms.

The aims of this study were the characterization of lifetime psychiatric disorders, in patients with refractory epilepsy, particularly, their prevalence and types, and also to identify epilepsy-related risk factors associated with this comorbidity.

2. Methods

People with refractory epilepsy were recruited, between April 2000 and September 2018, from the Refractory Epilepsy Reference Centre and the Epilepsy Surgery Group from the Department of Neurosciences and Mental Health of our Institution. The diagnosis of refractory epilepsy was made according to the International League Against Epilepsy[85].

For the purpose of this study, we included the presurgical evaluation data from people with temporal and extratemporal epileptogenic zones. This assessment included a video-electroencephalography (EEG) monitoring, a 3-Tesla brain magnetic resonance with epilepsy protocol, functional magnetic resonance imaging (fMRI) and positron emission tomography scans to determine the epileptogenic zone, a neuropsychological and a psychiatric evaluation.

This study has been performed in accordance with the ethical standards of the 1964 Declaration of Helsinki and its later amendments and was approved by the Ethics Committee of our institution.

2.1 Subjects

Participants older than 18 years, with refractory epilepsy were included. Those with other neurological diseases or intellectual disability were excluded from the analysis. Demographic (gender, age, employment status, marital status) and clinical data (etiology of epilepsy, the topography of the epileptogenic zone, the age of onset, time to surgery as well as other relevant data) were collected during interviews and from medical and surgical records at the time of the pre-surgical evaluation.

2.2 Psychiatric Evaluation

Each patient was subjected to a psychiatric evaluation made by an experienced psychiatrist, from our group and center, and included a clinical psychiatric history (demographic data, previous psychiatric history, family history, use of substances as well as other relevant data) collected at the presurgical evaluation. Information from the patient, accompanying person and medical records were taken into consideration.

2.3 Statistical Analysis

The statistical analysis was made using Stata software (version 14.2; StataCorp, Texas, USA). Descriptive statistics were performed to report the analysis of data presented as mean

± standard deviation or median (minimum-maximum). Student's t-test and the Mann-Whitney U test were used for parametric and non-parametric data, respectively. A chi-square test, or the Fisher exact test in case of non-parametric data, was applied to compare categorical variables which were given as the number of cases and proportions.

Using forward selection, each predictor was tested using a logistic regression model and then significant predictors were included in a multivariate model. These variables include age, gender, duration of epilepsy, age of epilepsy onset, location of the epileptogenic focus considering the lobe and lateralization. Within patients with temporal epilepsy, neocortical versus mesial location were also included.

Measures of association were expressed as Odds Ratio (OR) and a p-value ≤0.05 was considered statistically significant.

3 Results

3.1 Demographic and clinical findings.

Two hundred and four consecutive people with RE who were proposed to pre-surgical evaluation were enrolled. Five were secondarily excluded because of intellectual disability, and 1 refused to participate. Thus, a total of 199 individuals were included in the sample. Their demographic and clinical characteristics were illustrated in Table 2. Considering the excluded patients: four had left temporal epileptogenic zones, one had a right temporal epileptogenic zone, and one had a right occipital epileptogenic zone. There was missing information regarding the epileptogenic zone of 8 patients (4%). We assumed this information was missing completely at random and excluded it from the analysis.

Table 2 - Socio-demographical and clinical characteristics of the participants.

AGE, YEARS	**38.8 ± 11.6**
MALES, N (%)	85 (42.7)
EDUCATION, YEARS	10.1 ± 4.5
ACTIVE WORKERS, N (%)	93 (64.6)
UNEMPLOYED, N (%)	39 (21.7)
RETIRED, N (%)	25 (13.9)
MARRIED, N (%)	74 (50.0)
AGE AT ONSET, YEARS	15.9 ± 11.3
DURATION OF EPILEPSY, YEARS	22.7 ± 13.0
TEMPORAL EPILEPTOGENIC ZONE, N (%)	168 (86.6)
• **MESIAL, N (%)**	134 (82)
• **NEOCORTICAL, N (%)**	29 (18)
EXTRATEMPORAL EPILEPTOGENIC ZONE, N (%)	26 (13.4)
• **FRONTAL EPILEPTOGENIC ZONE, N (%)**	13 (6.7)
• **MULTILOBAR EPILEPTOGENIC ZONE, N (%)**	10 (5.2)
• **OCCIPITAL EPILEPTOGENIC ZONE, N (%)**	2 (1.0)

• **PARIETAL EPILEPTOGENIC ZONE, N (%)**	1 (0.5)
SIDE OF THE EPILEPTOGENIC FOCUS	
• **LEFT**	97 (50.8)
• **RIGHT**	84 (44.0)
• **BILATERAL**	10 (5.2)
NUMBER OF ANTIEPILEPTIC DRUGS	**2.3 (0.6)**

3.2 Lifetime psychiatric diagnosis

Seventy-seven people (46%) from our sample were found to have at least one-lifetime psychiatric diagnosis. Among these patients, the most frequent psychiatric disorders were depressive (64%), anxiety (10%), substance abuse (10%) and psychotic disorders (6%).

3.3 Results from the logistic regression model

Right side epileptogenic zone was a significant predictor of a lifetime psychiatric diagnosis (Crude analysis: OR 2.36; CI 1.22-4.56; p=0.01; Adjusted analysis: OR 2.33; CI 1.17-4.63; p=0.02), independently of the epileptogenic lobe.

Patients with a right-sided epileptogenic zone had increased rates of depression (35% versus 24%), anxiety disorders (7% versus 1%) and psychotic disorders (6% versus 1%).

The other variables tested were not found to constitute significant predictors.

The full results from the logistic regression model are represented in Table 3.

Table 3 - Results from the logistic regression model.

PREDICTORS	OR	STANDARD ERROR	P
Age	1.03	0.02	0.120
Gender	0.55	0.20	0.097
Age at onset	0.99	0.02	0.829
Duration of epilepsy	1.00	0.02	0.979
Temporal epileptogenic zone, n (%)	1.22	1.22	0.839
Extratemporal epileptogenic zone, n (%)	1.90	2.12	0.563
Multilobar epileptogenic zone, n (%)	0.82	0.81	0.839
Side of the epileptogenic focus			
• Left	0.43	0.15	0.016
• Right	2.33	0.82	0.016
• Bilateral	1.62	1.37	0.570

4 Discussion

In our sample, forty-six percent of people had a past history of at least one previous psychiatric disorder. In this order, depressive, anxiety, substance use, and psychotic disorders were the most frequent types of diagnosis.

Studies focusing on the prevalence of psychiatric disorders in people with refractory epilepsy report different prevalence rates, probably, because of differences in the diagnostic criteria and methods and different people samples. However, they all tend to report an increased rate when compared to the general populations and with individuals presenting other neurological or non-neurological conditions[86].

Moreover, our work shows that people with a right epileptogenic zone have more than twice the risk (OR 2.33) of having a psychiatric disorder compared to those with a left epileptogenic zone. In our sample, people with a right-side epileptogenic zone had increased rates of depression, anxiety, and psychosis when compared to left or bilateral epileptogenic focus. This risk is independent of the affected lobe and other demographic and clinical factors related to epilepsy.

Our findings are in line with previous studies, both in epilepsy and in other neurological disorders. Sperli et al. (2009) found that a right side epileptogenic zone was a risk factor for psychiatric comorbidity[87]. More recently, Jansen et al. (2018) also found that people with right-sided epilepsy had a more frequent history of psychiatric disorders prior to epilepsy onset[88].

The right hemisphere has a major role in emotion processing[89], including visuospatial attention and emotional perception, recognition memory for emotional images[90] and facial emotion processing[91]. While some studies suggest that it may have a preponderant role on the processing of negative stimulate, others state that there is a general dominance of the right hemisphere for all emotions, regardless of their affective valence[92,93].

There is an association between right side stroke and depression[94]. Moreover, neuroimaging studies suggest that the right hemisphere has important involvement in depression[95,96]. Right hemisphere function deficits, symmetry breaking, and more random network structure were found in depressive disorders[97]. Therefore, an epileptogenic insult located in this hemisphere may disrupt important networks involved in this function, probably even before the epileptic seizures manifest clinically.

Besides depression, research in other neurological disorders showed that post-stroke psychosis, most frequently, follows unilateral damage of the right hemisphere[98,99]. Bilateral or right traumatic lesions were associated with delusional disorders[100]. It has been suggested that the right hemisphere might have a role in the production of delusional beliefs as it has important roles in pragmatic communication, perceptual integration, attentional surveillance, and anomaly/novelty detection and belief updating[101].

Both primary and secondary psychosis respond to antipsychotics suggesting a common underlying pathological mechanism[98,99].

Research on anxiety and laterality is still scarce, however, recent research showed that the right hemisphere may have a key role in the neuroanatomical basis of Generalized Anxiety Disorder[102].

This study has some limitations. The first was that this was an observational study, with a retrospective component. Different sources of information were considered in order to confirm clinical information and to reduce missing data. Second, as this is a transversal study so causality cannot be determined. Third, lifetime psychiatric disorders may be underestimated because they may be seen as a natural reaction to epilepsy and its limitations, they may not be remembered or be underreported because of the fear of not qualifying for surgery. However, previous clinical reports and family members were consulted to reduce this possibility. Forth, the type of antiepileptic drugs was not controlled and these may have an impact on mood and behavior. Nevertheless, we do not expect to have significant differences in therapeutic schemes between people with different epileptogenic focus as they are mainly determined by their efficacy on the control of epilepsy, regardless of the epileptogenic zone. There were no significant differences in the number of antiepileptics between people with and without previous psychiatric comorbidity.

Notwithstanding these limitations, our results point out important conclusions. Psychiatric comorbidity is much more frequent in people with refractory epilepsy than in the general population and those with a right epileptogenic zone may be at a higher risk.

These data support the bidirectional relationship between epilepsy and mental health. It may also add to the current knowledge of the neurobiological basis of psychiatric disorders.

Future studies should focus on the biological mechanism that may explain this association between right-sided brain dysfunction and psychiatric disorders.

Study 2: Personality in people with refractory epilepsy

Title Personality patterns of people with medically refractory epilepsy – does the epileptogenic zone matter?

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Abstract

Objectives The aims of this study were to determine the rate of dysfunctional personality patterns before and after epilepsy surgery, their types and the importance of the epileptogenic zone in a sample of people with refractory epilepsy.

Methods We conducted an ambispective observational study, including refractory epilepsy surgery candidates. Demographic, psychiatric and neurological data were recorded. Evaluation of personality was made using the Millon Clinical Multiaxial Inventory-II (MCMI-II). Pre-surgical predictors of personality patterns were determined using a logistic regression model. The proportion of patients with dysfunctional personality patterns, before and after surgery, was compared using the Mcnemar´s test. Then a generalized estimating equation model was performed to include predictors of changes in this rate.

Results One hundred and ninety-nine participants were included. Seventy percent had a dysfunctional personality pattern before surgery. After surgery, this percentage dropped to 58%. The difference was statistically significant after adjusting for potential confounders (p=0.013). The most common types were Cluster C personality patterns. Temporal epileptogenic zone was a significant predictor of higher scores of the Avoidant (Coef. 11.8; CI -0.59 23.7; p=0.051) and Compulsive (Coef. 9.55; CI 2.48 16.6; p=0.008) personality patterns and lower scores of Histrionic (Coef. -11.4; CI -21.2 -1.55; p=0.024)

and Antisocial (Coef. -8.4; CI -15.6 -1.25; p=0.022) personality patterns, compared to extratemporal epileptogenic zone.

Conclusion People with refractory epilepsy have high rates of dysfunctional personality patterns. These patterns differ according to the epileptogenic zone.

Keywords Refractory epilepsy, epilepsy surgery, epileptogenic zone, personality

1. Introduction

The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) defines personality disorder as "an enduring pattern of inner experience and behavior the deviates markedly from the expectations of the individual's culture"[103]. This pattern includes impairments in personality (self and interpersonal) functioning and the presence of pathological personality traits, defined as habitual forms of behavior, thought, and emotion that is relatively stable across time and consistent across situations, in each individual[104]. The DSM-5 defines a set of ten types of personality disorders, each one defined by a typical group of dysfunctional personality characteristics or traits. Personality traits, including pathological traits, such as grandiosity, obsessionality, impulsivity or emotional lability, exhibit much higher rates of stability than personality disorders[105]. Personality disorders are organized into 3 clusters: Cluster A (odd/eccentric), including Paranoid, Schizoid, and Schizotypal personality disorders; Cluster B (dramatic/emotional/erratic), including Antisocial, Borderline, Histrionic, and Narcissistic personality disorders; and Cluster C (anxious/fearful), including Obsessive–Compulsive, Avoidant, and Dependent personality disorders[106].

The high prevalence of dysfunctional personality traits among people with epilepsy was noted many decades ago and it has been discussed over the years. Kraepelin(1923) described certain distinctive personality characteristics in these patients, such as meticulousness, slowness, circumstantiality, lability, irritability, explosiveness and a particular proneness to religiosity[4]. Between 1973 and 1986, Norman Geschwind wrote substantially about what was later called the "Geschwind syndrome", in people with temporal lobe epilepsy (TLE). It included increased religious interests, hypergraphia, increased aggression, increased moral and philosophical concerns, viscosity, and seriousness. He also provided an explanation based on the effect of a lesion stimulating the limbic system[5].

Nowadays, some authors still consider the existence of an "interictal personality" in TLE, historically defined as a seizure-based behavioral condition which includes the traits described by Geschwind and it is assessed using the Neurobehavioral Inventory (NBI)[107]. However, this entity is still controversial and it has not been included as a specific type of personality disorder in the standard psychiatric classifications[108,109].

Personality traits and personality disorders have been investigated independently in epilepsy. Recent research has shown that people with epilepsy have certain personality characteristics or traits, such as lower self-consideration and self-esteem[110]. Some personality traits may

be associated with epilepsy-related factors, namely, earlier age of onset, longer duration of epileptic history and higher seizure frequency[111].

Regarding personality disorders, diagnosed according to the DSM or the International Statistical Classification of Diseases and Related Health Problems (ICD), their prevalence ranges between 13 to 35% in people with focal epilepsy (mainly TLE), and from 18 to 42% in surgical candidates or people who have undergone surgery[112]. In comparison, the prevalence of personality disorders in the general population ranges between 4 and 15%[113]. The most prevalent types are not consensual amongst studies. However, cluster C personality disorders, namely Obsessive-Compulsive, Dependent and Avoidant are commonly cited as the most frequent in samples of people with refractory epilepsy[114–116].

Personality disorders in people with epilepsy have been associated with the adaptation or reaction to psychosocial factors, such as stigmatization, low self-esteem or social isolation[112] but also to epileptic seizure-related factors including a temporal epileptogenic zone, earlier age of onset, longer duration of the disease and higher seizure frequency[111]. Moreover, personality disorders may also have an impact on the course of epilepsy, potentially affecting adherence to treatment and interpersonal behavior in medical settings[112]. People with preoperative personality disorders also seem to be less likely to become seizure-free after temporal lobe resection[116].

The association of specific personality patterns to the epileptogenic zone and the role of surgery on the longitudinal course of these patterns have not been clearly established. With this study, we aimed to determine the rate of dysfunctional personality patterns and their types in a sample of people with refractory epilepsy. We also searched for epilepsy-related factors associated with these patterns. Finally, we aimed to evaluate the impact of surgery on the rate of these disorders.

2. Methods

This ambispective cohort study was conducted at the Department of Neurosciences and Mental Health of our Institution, between April 2000 and September 2018. Subjects were recruited from our Refractory Epilepsy Reference Centre and the Epilepsy Surgery Group. The diagnosis of refractory epilepsy was made according to the International League Against Epilepsy [85].

The presurgical evaluation included a video-electroencephalography (EEG) monitoring, a 3-Tesla brain magnetic resonance with an epilepsy protocol, functional magnetic resonance

imaging (fMRI) and positron emission tomography scans to determine the epileptogenic zone, a neuropsychological and a psychiatric evaluation. People with temporal and extra-temporal epileptogenic zones were included.

Demographic (gender, age, employment status, marital status) and clinical data (etiology of epilepsy, the topography of the epileptogenic zone, the age of onset, time to surgery and Engel Class[48]) after surgery, were collected during interviews and from medical and surgical records. Participants were receiving a minimum of two antiepileptic drugs. However, the type and dosages of these drugs were not addressed in this study because there was considerable variability between patients, as it is usual in people with refractory epilepsy.

This study has been performed in accordance with the ethical standards of the 1964 Declaration of Helsinki and its later amendments and was approved by the Ethics Committee of our institution.

2.1 Subjects

Participants older than 18 years, with refractory epilepsy, included as surgery candidates, with at least one year of primary school education were included in the study. Those with other neurological diseases or intellectual disability were excluded from the analysis.

2.2 Psychiatric Evaluation

A psychiatric evaluation was performed by an experienced psychiatrist, before surgery and one year after the procedure. It included a clinical psychiatric history (demographic data, previous psychiatric history, family history, use of substances as well as other relevant data), the determination of a clinical diagnosis of lifetime and current psychiatric disorders, established according to the ICD-10[117], and the following personality and psychopathological tests:

2.2.1 The Millon Clinical Multiaxial Inventory-II (MMCI-II)

The MCMI-II is a psychological assessment tool used to evaluate personality patterns and psychopathology in adults. It includes 13 personality scales, 9 clinical syndrome scales[65] and three validity scales to assess response styles on the instrument[118]. This self-report questionnaire includes 175, yes or no questions, regarding patterns of emotional, cognitive and behavioral response. It was developed to evaluate personality prototypes that were included in the Diagnostic and Statistical Manual (DSM). However, as this is not a

standardized diagnostic instrument based on DSM diagnostic criteria, we opt to use the more conservative term of "personality patterns" to designate the dysfunctional personality types that it evaluates. For each personality type, the patient's raw scores are converted into Base Rate scores. The presence of a personality trait is denoted by a score of 75 to 84 and a score of 85 or above indicates the persistence of a personality pattern. This version has been validated in clinical samples showing good internal consistency[66].

2.2.2 The Hamilton Anxiety Rating Scale (HARS)

The scale consists of 14 items and measures both psychic and somatic anxiety[57].
It is scored according to the following cut-offs: 17 = mild; 18-24 = mild to moderate; 25-30 = moderate to severe anxiety[57].

2.2.3 The Hamilton Depression Rating Scale (HDRS)

The version used corresponds to the original 17 items version. It was developed to access the severity of depressive symptoms[58] and the following scores are generally considered: 0-7 = normal; 8-16 = mild; 17-23 = moderate; >24 = severe depression[119].

2.3 Statistical Analysis

The statistical analysis was performed using Stata software (version 14.2; StataCorp, Texas, USA). Descriptive statistics were performed to report the analysis of data presented as mean ± standard deviation or median (minimum-maximum).

For the study of the predictors, before surgery, the outcome variables were the types of personality patterns according to the MCMI-II, analyzed as continuous variables. For the purpose of this study, the psychopathological scales of MCMI-II were not integrated into the analysis. Predictors included the side of the epileptogenic zone, as a categorical variable (right, left or bilateral), the epileptogenic zone lobe, analyzed as a binary variable (temporal versus extratemporal). Within people with a temporal lobe epileptogenic zone, mesial versus neocortical zones were also included, as a binary variable. A linear regression model was used for the analysis.

The McNemar's test was first used to compare the proportion of patients with a score above 85 at any personality pattern before and after surgery.

Then, to study the longitudinal changes, according to different predictors and potential confounders, a generalized estimating equation model was used including the following

variables: type of surgery and Engel class, as binary variables; HDRS and HARS scores, obtained at the one-year evaluation, as continuous variables.

Measures of association were expressed as Coefficients or Odds-Ratio (OR) and a p-value ≤0.05 was considered statistically significant.

3 Results

3.1 Demographic and clinical findings

One hundred and ninety-nine participants were included in the sample. Their demographic and clinical characteristics are illustrated in Table 4.

Table 4 - Socio-demographical and clinical characteristics of the participants.

AGE, YEARS	**38.8 ± 11.6**
MALES, N (%)	85 (42.7)
EDUCATION, YEARS	10.1 ± 4.5
ACTIVE WORKERS, N (%)	93 (64.6)
UNEMPLOYED, N (%)	39 (21.7)
RETIRED, N (%)	25 (13.9)
MARRIED, N (%)	74 (50.0)
AGE AT ONSET, YEARS	15.9 ± 11.3
DURATION OF EPILEPSY, YEARS	22.7 ± 13.0
TEMPORAL EPILEPTOGENIC ZONE, N (%)	168 (86.6)
• **MESIAL, N (%)**	106 (65)
• **NEOCORTICAL, N (%)**	57 (35)
EXTRATEMPORAL EPILEPTOGENIC ZONE, N (%)	26 (13.4)
• **FRONTAL EPILEPTOGENIC ZONE, N (%)**	13 (6.7)
• **MULTILOBAR EPILEPTOGENIC ZONE, N (%)**	10 (5.2)
• **OCCIPITAL EPILEPTOGENIC ZONE, N (%)**	2 (1.0)
• **PARIETAL EPILEPTOGENIC ZONE, N (%)**	1 (0.5)
LATERALITY OF THE EPILEPTOGENIC FOCUS	
• **LEFT**	97 (50.8)
• **RIGHT**	84 (44.0)
• **BILATERAL**	10 (5.2)
NUMBER OF ANTIEPILEPTIC DRUGS	**2.3 (0.6)**

3.2 Psychiatric Disorders and Personality Patterns

At the pre-surgical evaluation, 33 patients had a current psychiatric diagnosis. Thirty had Major Depression, 1 had a Generalized Anxiety Disorder and another had an Obsessive-Compulsive Disorder.

One hundred patients (70%) had a score above the threshold of 85 in at least one personality pattern, in the pre-surgical evaluation. Regarding their types, most patients (34%) scored above the defined cut-off on more than one pattern. Twenty-three patients scored above the cut-off in 2 types of personality patterns and 26 patients on 3 or more. Most commonly, these patterns corresponded to a mixture of personality types from Cluster C (35%). The second

most frequent pattern was the Obsessive-Compulsive (15%) followed by the dependent personality pattern (9%).

3.3 Predictors of dysfunctional personality patterns before surgery

Temporal epileptogenic zone was a significant predictor of higher scores of the Avoidant (Coef. 11.8; CI -0.59 23.7; p=0.051) and Compulsive (Coef. 9.55; CI 2.48 16.6; p=0.008) personality patterns and lower scores of Histrionic (Coef. -11.4; CI -21.2 -1.55; p=0.024) and Antisocial (Coef. -8.4; CI -15.6 -1.25; p=0.022) personality patterns.

The side of the epileptogenic zone was not found to be a significant predictor of personality. Within people with a temporal epileptogenic zone, mesial and non-mesial locations were also not significantly associated with personality patterns.

3.4 Longitudinal changes in the proportion of patients with pathological personality patterns

After surgery, the percentage of people scoring above 85 dropped to 58%. The difference was marginally significant (OR 4.5; CI 0.93-42.8; p=0.065) in the first analysis. The personality patterns with the most significant score reductions were Histrionic, Narcissistic, Antisocial, Aggressive and Passive-Aggressive.

The multivariate generalized estimating equation model including all considered variables showed a statistically significant reduction in the proportion of patients with a dysfunctional personality pattern (Coef. -1.83; CI -3.26 -0.39; p=0.013) across time. None of the variables included were significantly associated with this decrease.

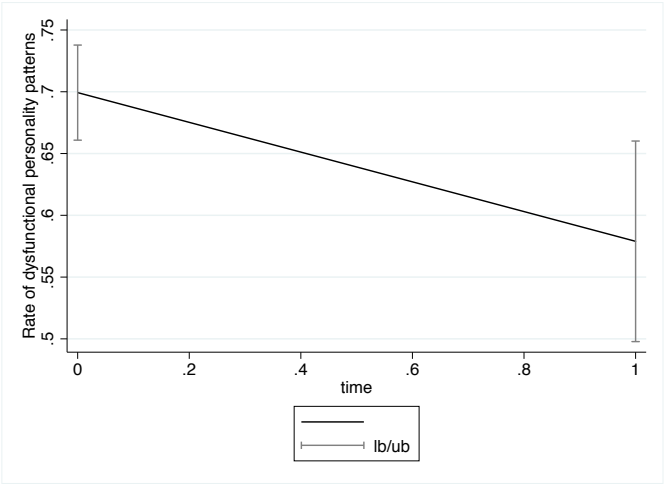
Medium scores and standard deviation of each personality pattern, before and after surgery, were summarized in Table 5.

Table 5 - Clinical personality patterns according to MCMI-II.

	BEFORE SURGERY	ONE YEAR AFTER SURGERY
SCHIZOID	63.2 ± 20.3	67.7 ± 21.5
AVOIDANT	65.4 ± 25.7	69.9 ± 25.8
DEPENDENT	69.8 ± 24.8	69.9 ± 21.9
HISTRIONIC	61.2 ± 21.3	54.8 ± 23.2
NARCISSISTIC	65.0 ± 20.4	56.2 ± 26.9
ANTISOCIAL	62.4 ± 15.5	56.1 ± 17.0
AGGRESSIVE	62.6 ± 20.9	56.2 ± 22.0
COMPULSIVE	75.2 ± 15.3	77.3 ± 11.8
PASSIVE-AGGRESSIVE	55.5 ± 31.2	47.4 ± 30.8
SELF-DEFEATING	62.3 ± 25.5	63.6 ± 27.9
SCHIZOTYPAL	61.2 ± 17.8	60.9 ± 21.2
BORDERLINE	55.3 ± 20.7	54.3 ± 21.3
PARANOID	**65.7 ± 16.1**	**64.5 ± 11.5**

A graphical representation of the rate of dysfunctional personality patterns, before and after surgery, was illustrated in Figure 1.

Figure 1 - Dysfunctional personality rates before and one-year after surgery.



Medium scores and standard deviation of HARS and HDRS, before and after surgery, were summarized in Table 6.

Table 6 - HDRS and HARS total scale medium scores.

	Before surgery	One year after surgery
HDRS	8.35 ± 7.8	6.36 ± 6.4
HARS	8.74 ± 7.0	7.06 ± 7.2

4 Discussion

In our sample, 70% of people with medically refractory epilepsy displayed a dysfunctional personality pattern before surgery. The most common types were Cluster C personality patterns, which is in line with previous studies[114–116].

One year after surgery, there was a statistically significant reduction in the rate of dysfunctional traits, although of small magnitude. We hypothesize that the removal of the epileptogenic zone or/and the reduction of the interictal epileptic activity might have had a beneficial role. There are very few studies regarding the impact of epilepsy surgery on personality disorders and traits. Previous data using the Minnesota Multiphasic Personality Inventory suggested a decrease in some dysfunctional personality traits, namely, interpersonal sensitivity, irritability, social introversion, hypochondriasis, and psychasthenia, after TLE surgery[120,121].

Additionally, this study showed different personality patterns in people with refractory epilepsy. Those with temporal epileptogenic zones had higher scores in DSM cluster C personality patterns – Avoidant and Compulsive and lower scores in cluster B personality

patterns – Histrionic and Antisocial. Since the comparison was made between temporal and extratemporal patients, this implies that those with extratemporal epileptogenic zones (mostly frontal lobe epilepsies) had higher scores on these cluster B patterns and lower scores on the cluster C patterns.

There is a scarcity of studies focusing on the determination of the neurobiological basis of personality disorders, in people with and without epilepsy. The studies available suggest a link between cluster B personality disorders and frontal lobe dysfunction, while cluster C personality disorders may have an association with temporal lobe dysfunction. In particular, the personality characteristics of "interictal personality" have been associated with mesial epileptogenic zones[5]. More recently, introversion related behaviors and anxiety, that may be seen in cluster C personality disorders, have also been associated with mesial temporal pathology[122]. In our work, no differences were detected between patients with mesial versus neocortical temporal epileptogenic zones. This may be due to potential limbic dysfunction even in neocortical epilepsies, to the importance of other temporal zones for social cognition and interaction[123] or to the inability of the test to detect these differences.

Helmstaedter (2001) stated that people with TLE tend to manifest more anxiety, neuroticism, and social limitations while those with frontal epilepsy show executive dysfunctions, hyperactivity and addictive behaviors[124].

Despite the controversy, some of the classical personality characteristics attributed to people with TLE resemble those found in cluster C personality disorders, namely, hypermoralism, dependency, humorlessness, obsessionalism, viscosity and circumstantiality[6]. On the other hand, people with Juvenile Myoclonic Epilepsy, linked to frontal dysfunction, seem to have more frequent cluster B traits such as impulsive and irresponsible behavior[125]. In a previous study, reversible interictal antisocial behavior was reported in 4 persons with epilepsy involving the prefrontal cortex. All of these patients fulfilled the DSM-IV criteria for Antisocial Personality disorder and these characteristics remitted following seizure control[126].

Moreover, Pizzi et al. (2009), using the Personality Assessment Inventory, reported a similar pattern. In their sample, people with frontal lobe epilepsy had more borderline and antisocial interictal traits than those with a temporal lobe epileptogenic zone[127]. These dysfunctional traits may be related to social cognition deficits, as impaired humor appreciation and decreased ability to detect facial expression[128,129].

A recent study evaluated a patient with crossed obsessive-compulsive personality disorder and impaired theory of mind in temporal lobe epilepsy. The authors found that this patient

revealed impaired interpretation of other people's behavior, mental rigidity, and a tendency to formulate inflexible judgments[130].

The neuroanatomical mechanisms that may contribute to the development of personality disorders have also been investigated in non-epileptic patients. Both the orbital prefrontal cortex (OFC) and the anterior cingulate gyrus (ACG) display important roles in social judgment, control of aggression and other non-sanctioned behavior. Cluster B patients tend to have impairments in these abilities. Disinhibited angry behaviors have been shown both in patients with personality disorders, such as Borderline or Narcissistic and in patients with damage to the prefrontal cortex. This brain area seems to act by inhibiting the amygdala activation, and therefore, inhibiting impulsive aggression[131]. Histrionic personality disorders have been frequently associated with conversion disorders, in particular, psychogenic non-epileptic seizure (PNES)[132]. These disorders also seem to be associated with prefrontal cortex hypoactivation[133]. Raine et al. (2000) showed that prefrontal structural deficit, related to a significant reduction in prefrontal gray but not white matter, may underlie the low arousal, poor fear conditioning, lack of conscience, and decision-making deficits that have been found to characterize cluster B personality patterns[134].

Despite the fact that the neurobiology of Cluster C personality disorders remains mostly unexplored, enlarged striatal and OFC/prefrontal volumes have been shown in patients with obsessive-compulsive traits[106]. We hypothesize that, contrary to cluster B patients, they may have a hypoactivation of the limbic system, both because of excessive inhibition from these cortical areas or dysfunction of important limbic structures such as the amygdala and hippocampus seen in temporal lobe epilepsy.

This study has some limitations. Firstly, this was an observational study, with a retrospective component, and therefore subject to bias. Different sources of information were considered in order to confirm clinical information and to reduce missing data. Secondly, the MCMI-II corresponds to DSM-III which was the most recent version of this questionnaire when the first surgical candidates were assessed and we decided to keep it in order to maintain a homogeneous method of personality evaluation. Most of the personality categories and Millon's conception of personality patterns have prevailed until the publication of DSM-5. Despite the fact that MCMI is an important and widely used instrument to evaluate personality, it has never been used in epilepsy, so we cannot compare our results with other studies. Moreover, we also did not apply the NBI and investigated the characteristics of the "interictal personality" syndrome that could be interesting to compare with our MCMI

results. Thirdly, the type of antiepileptic drugs was not controlled and these may have an impact on mood and behavior.

Despite these constraints, our study showed some important data regarding personality patterns in people with refractory epilepsy, using a tool designed to evaluate personality prototypes from a standard diagnostic classification system. We showed that most of these patients have a Cluster C Personality Disorder pattern, although different epileptogenic zones may contribute to different dysfunctional personality patterns. Epilepsy surgery may also have a potentially beneficial role on the course of these dysfunctional patterns.

These results may contribute to a better understanding of dysfunctional personality in epilepsy and how epilepsy-related factors may contribute to distinctive dysfunctional patterns. The recognition of the most common personality disorders in epilepsy could improve the management of these patients in the setting of multidisciplinary care. This work may also contribute to the elucidation of the neurobiological basis of personality disorders.

Future studies, with more robust samples, are encouraged to deepen the knowledge of the relationship between epilepsy and personality disorders as well as the potential role of surgery in the long-term course of these psychiatric disorders.

Study 3: Predictors of de novo psychopathology after epilepsy surgery

Title Predicting de novo psychopathology after epilepsy surgery: a 3-year cohort study

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Abstract

Objective The aim of this study is to determine potential risk factors for de novo psychiatric syndromes after epilepsy surgery.

Methods Refractory epilepsy surgery candidates were recruited from our Refractory Epilepsy Reference Centre. Psychiatric evaluations were made before surgery and every year, during a 3-years follow-up period. Demographic, psychiatric and neurological data were recorded. The types of surgeries considered were resective surgery (resection of the epileptogenic zone) and palliative surgery (deep brain stimulation of the anterior nuclei of the thalamus (ANT-DBS)). A survival analysis model was used to determine pre and post-surgical predictors of de novo psychiatric events after surgery.

Results One hundred and six people with refractory epilepsy submitted to epilepsy surgery were included. Sixteen people (15%) developed psychiatric disorders that were never identified before surgery. Multilobar epileptogenic zone ($p=0.001$) and DBS of the anterior nucleus of the thalamus ($p=0.003$) were found to be significant predictors of these events.

Conclusion People with more generalized epileptogenic activity and those who are submitted to ANT-DBS seem to present an increased susceptibility for the development of mental disorders, after neurosurgical interventions, for the treatment of refractory epilepsy. People considered to be at higher risk should be submitted to more frequent routine psychiatric assessments.

Keywords Epilepsy; Refractory Epilepsy; Surgery Epilepsy; De novo Psychopathology

1. Introduction

More than 50 million people around the world have epilepsy[135], a debilitating neurological disorder associated with several comorbidities, particularly, psychiatric conditions[136]. Indeed, it is estimated that up to 60% of this population suffer some psychiatric disorder and the risk of death from suicide may be 5.8 times higher than in the general population[137,138].

About one-third of people with epilepsy do not respond to adequate antiepileptic drug treatment[47], they are considered to have refractory epilepsy and may be candidates for epilepsy surgery. Resective surgery is the most common procedure for those who have a well localized epileptogenic zone, and about 70% of those submitted to this procedure became seizure free[43]. The most common type of localized epileptogenic zone affects the temporal lobe, particularly, mesial structures. A smaller proportion affects neocortical zones[36,37].

Those who are not candidates for resective surgery, generally, because of multiple epileptogenic zones or lack of an identifiable epileptogenic zone, may undergo palliative surgery, such as, neuromodulation interventions. Vagus Nerve Stimulation (VNS), or more recently, Cortical Responsive Stimulation (CRS) or Deep Brain Stimulation (DBS), targeting the anterior nucleus of the thalamus (ANT), bilaterally, are currently the most frequently employed techniques

Despite the high rates of success of resective surgery in the control of epileptic seizures, about 20% of people with refractory epilepsy may develop de novo psychopathology after surgery[56], most commonly, adjustment disorders and depression[139].

Few studies have focused on predictors of de novo adverse psychiatric events after resective surgery, such as major depression, mania, and psychosis. Some have found that receiving psychiatric treatment or a history of mental illness, namely, depression or anxiety, before surgery, was a risk factor for psychopathology after resective surgery[140,141]. However, this association may only reflect the natural history of previous disorders. Other potential risk factors include higher prevalence of mood disorder among first- and second-degree relatives[142], preoperative bilateral electroencephalogram (EEG) abnormalities[143], preoperative history of secondary generalized tonic-clonic seizures[144], persistence of seizures after resective surgery, history of fear auras[145] and temporal versus extratemporal surgery[146].

Concerning ATN stimulation, the most common modality of DBS (ANT-DBS), some studies suggest that it might have a positive impact on mood[147,148], while others found worse depression scores after this procedure[149,150].

Establishing potential risk factors for de novo psychopathology would allow clinicians to inform people with refractory epilepsy better before surgery and to be more attentive to those presenting these factors.

We aim to study the potential risk factors for de novo psychopathology following epilepsy surgery, either resective surgery or Deep Brain Stimulation of the anterior thalamus nucleus DBS-ATN.

2. Methods

This ambispective cohort study was conducted at the Neurosciences` Department, that includes the Psychiatric, the Neurological and Neurosurgical Departments, of Hospital de Santa Maria (Lisbon), between May 2004 and May 2018. Subjects were recruited from the Refractory Epilepsy Reference Centre and the Epilepsy Surgery Group of our institution. The considered total follow-up period was 36 months, after surgery, although not all subjects were followed during this entire period because of loss of follow-up. Patients were evaluated by the psychiatrist belonging to both the center and group before surgery and after 12, 24 and 36 months. Follow-up time was measured in months. The diagnosis of refractory epilepsy was made according to the International League Against Epilepsy[39].

Presurgical surgery evaluation, in our group, includes, at least, a video-EEG monitoring, a 3-Tesla brain magnetic resonance with epilepsy protocol, and neuropsychological and psychiatric evaluation. Our reference center includes patients with temporal and extra-temporal epileptogenic zones. The location of the epileptogenic zone is determined using surface preoperative magnetic resonance imaging (MRI), functional magnetic resonance imaging (fMRI) and positron emission tomography scans and video–electroencephalography (EEG). In our institution, the majority of people with refractory epilepsy who underwent surgery are submitted to resective surgery, a smaller proportion of VNS or ANT-DBS. People submitted to VNS will not be included in this study given the lack of enough follow-up data.

Data concerning demographic (gender, age, employment status, marital status, etiology of epilepsy, the topography of the epileptogenic zone, the age of onset, time to surgery), and Engel Class[151] after surgery were collected during interviews and from medical and surgical records. In the pre-surgical period, patients were under, at least, two antiepileptic

drugs, but their type and dosages were not addressed in this study because there was considerable variability between patients as it is usually in people with refractory epilepsy. However, in our center patients keep the same antiepileptic drugs and therapeutic schemes for at least 2 years after surgery.

During follow-up, patients were seen regularly by the members of the Epilepsy Surgery Group and referred to psychiatry if they develop de novo psychopathology after surgery. Information concerning the referral to psychiatry was also registered.

This study has been performed in accordance with the ethical standards of the 1964 Declaration of Helsinki and its later amendments and was approved by the Ethics Committee of Santa Maria Hospital. All participants evaluated prospectively, signed an informed consent.

2.1 Subjects

Participants older than 18 years, submitted to resective surgery or DBS were included in the study. Patients with other neurological diseases or intellectual disability were excluded from the analysis. One hundred and eighty-one consecutive people with refractory epilepsy who were proposed to pre-surgical evaluation were enrolled. Fifteen were secondarily excluded because of intellectual disability (QI<70), 13 because they did not undergo surgery, 44 because of loss of follow-up, 1 because he has undergone VNS; finally, 1 died and 1 refused to participate. Thus, a total of 106 individuals were included in the study.

2.2 Psychiatric evaluation

Psychiatric evaluations include a clinical psychiatric history (demographic data, previous psychiatric history, psychiatric medication, family history, use of substances as well as other relevant clinical data). The evaluation also included the following psychopathological tests:

2.2.1. The Hamilton Anxiety Rating Scale (HARS)

This rating scale was developed to measure the severity of anxiety symptoms consisting of 14 items and measures both phobic anxiety and somatic anxiety[57].

2.2.2. The Hamilton Depression Rating Scale (HDRS)

This is the most widely used rating scale used to access depression. The version used corresponds to the original 17 items version and has a particular focus on melancholic and physical symptoms[58].

2.2.3. Brief Psychiatric Rating Scale (BPRS)

This rating scale is one of the most widely used scales to measure psychotic symptoms and it is based on the interview with the patient, his speech and behavior.

2.2.4. Symptom Checklist-90 (SCL-90)

This multi-dimensional instrument is a is a 90-item self-report symptom inventory developed to measure psychological symptoms and psychological distress. There are three global indices for the SCL-90: the Global Severity Index (GSI), the Positive Symptom Distress Index and the Positive Symptoms Total. The GSI is suggested to be the best single indicator of the current level of the disorder.

After this initial evaluation, people with refractory epilepsy presenting major psychiatric disorder or considered to have a higher risk of developing psychiatric disorder were referred to a psychiatric outpatient clinic of one of the investigators.

De novo major psychiatric disorders were classified according to the International Statistical Classification of Diseases and Related Health Problems (ICD-10)[117]. Lifetime prevalence of psychiatric syndromes was determined using information from patients and family members, accompanying the patient, at the pre-surgical evaluation moment.

2.3 Statistical analysis

The statistical analysis was performed using Stata software (version 14.2; StataCorp, Texas, USA). Descriptive statistics were used to report the analysis of data presented as mean ± standard deviation or number and proportions. Student's t-test and the Mann-Whitney U test were used for parametric and non-parametric data, respectively. As the population studied is an open cohort, person-time variables were taken into account in a time-to-event analysis. Potential risk factors were analyzed using the Cox Proportional Hazards Model.

First, we performed univariate analysis including variables that were considered to have clinical relevance both for epilepsy and psychiatric disorders. These variables include sex, age at surgery, years of education, duration of epilepsy and age at onset of epilepsy, analyzed as continuous variables. Employment and marital status, epileptogenic zone side (right, left or bilateral cerebral hemispheres), epileptogenic zone topography (temporal, extratemporal or multilobar), as categorical variables. As Engel Classes (I, II, III, or IV) reflect progressive stages of prognosis with Class I meaning “Seizure free or no more than a few early, nondisabling seizures; or seizures upon drug withdrawal only” and IV reflecting “No worthwhile improvement; some reduction, no reduction, or worsening are possible”[151]

we treated these variable as continuous in order to increase the power of our analysis. Previous history of other mental disorders, family history of psychiatric disorders, epileptogenic zone concerning one (unilobar) versus more than one lobe (multilobar) and resective surgery vs ANT-DBS, analyzed as binary variables.

The outcome variable, de novo psychopathology, was coded as a binary variable (0=no event; 1=at least one event).

Variables achieving statistical significance as predictors of de novo psychopathology were included in a multivariate analysis.

The assessment of model assumptions was tested using Schoenfeld residuals test.

Measures of association were expressed as hazard ratios. A significant P value from the Cox Proportional Hazards Model was set at ≤0.004, after a Bonferroni correction was made, considering the number of tests performed (14).

Ties were handled using the Efron method for ties.

3. Results

3.1 Demographic and clinical findings of the people with refractory epilepsy with and without de novo psychopathology

The study included 106 persons with refractory epilepsy. Ninety-two (88%) had a temporal epileptogenic zone, 57 (62%) had mesial sclerosis and 34 (37%) other pathologies, 1 had a parietal epileptogenic zone, 7 a frontal epileptogenic zone and 5 had an epileptogenic zone affecting more than one brain lobe (Table 7).

After surgery, the majority of people were considered to be Class Engel I (75%). No statistically significant differences were found, concerning these variables, between patients with and without follow-up.

Regarding lifetime psychiatric history, no statistical differences were found between patients submitted to resective surgery or ANT-DBS. In the first group, 62 patients had no previous psychiatric history, 36 had a history of depression, 6 had a history of an anxiety disorder, 3 had a history of a psychotic disorder, 6 had a history of alcohol or drug abuse and the rest of the sample had other pathologies. In the second group, 3 had no previous diagnosis and 4 had a lifetime history of depression. At the pre-surgical evaluation, patients had a medium HARS score of 8,6±6,9, a medium HDRS score of 8,3±7,7, a medium BPRS of 27,4±8,9 and the medium score of the GSI of SCL-90 was 0,9±0,6. No statistical differences were found concerning surgical groups.

Table 7 - Clinical characteristics and socio-demographical of the participants.

	Clinical and socio-demographical characteristics	
	Mean±SD	Range
Age, years	37.6 ±10.7	18 - 65
Sex/Males, n (%)	40 (37.7)	
Education, years	10.2 ±4.4	1 - 18
Active workers, n (%)	57 (58.8)	
Married, n (%)	49 (49)	
Age at onset, years	14.4±10.1	1 - 58
Duration of epilepsy, years	23.2 ±12.9	3 - 59
Temporal epileptogenic zone, n (%)	92 (87.6)	
Extratemporal epileptogenic zone, n (%)	8 (7.6)	
Multilobar epileptogenic zone, n (%)	5 (4.8)	
The side of the epileptogenic focus		
• Left	50 (47.2)	
• Right	52 (49.1)	
• Bilateral	4 (3.8)	
Number of antiepileptic drugs	2.3±0.6	1 - 4
Type of surgery, n (%)		
• Resective surgery	99 (93.4)	
• Deep brain stimulation	7 (6.6)	

3.2 De novo major psychopathology

After surgery, 16 patients (15%) developed a major psychiatric syndrome that has never been reported before surgery. The incidence rate was 0,005 events per month. The mean time until the first psychiatric event was 13 months and the median was 7 months (ranging from 1 to 36 months). Nine had a de novo depressive episode (F32) (8% of the sample), 6 had an acute and transient psychotic disorder (F23) (6%), 2 had a manic episode (F30) (2%) and 1 patient had a de novo anxiety disorder (F41) (1%). Four patients had 2 events during the follow-up period. Treatment and psychiatric follow-up were offered to all these patients and all improved with treatment.

3.3. Results from the Cox Regression Model

Multilobar epileptogenic zone, bilateral epileptogenic zone, ANT-DBS and higher Engel Class were found to be significant predictors of de novo major psychopathology, after surgery, with hazard ratios of 13.24 (CI 95% 4.22-41.49; p<0,001), 7.68 (CI 95% 1.90-31.01; p=0,004), 7.84 (CI 95% 2.58-25.22; p<0,001) and 2.18 (CI 95% 1.36-3.49; p=0,001), respectively.

On the multivariate model, laterality and Engel Class after surgery were not significant predictors. Using backward selection, only variables concerning unilobar versus multilobar

epileptogenic zone and type of surgery were included in the final model with hazard ratios of 9 (CI 95% 2.60-31.19; p=0,001) and 6.81 (CI 95% 1.95-23.78; p=0,003), respectively.
Schoenfeld residuals test showed no statistically significant results allowing us to assume that there is no departure from the proportional hazards assumption.
Multicollinearity was not detected using the Variance Inflation Factor test.
Kaplan-Meier curves showed a much shorter time to event for patients with multilobar compared to unilobar epileptogenic zone (Figure 2) and for those submitted to ANT-DBS comparing to resective surgery (Figure 3).

Figure 2 - Kaplan-Meier estimates of survival comparing multilobar to unilobar epileptogenic zone (p<0.001).

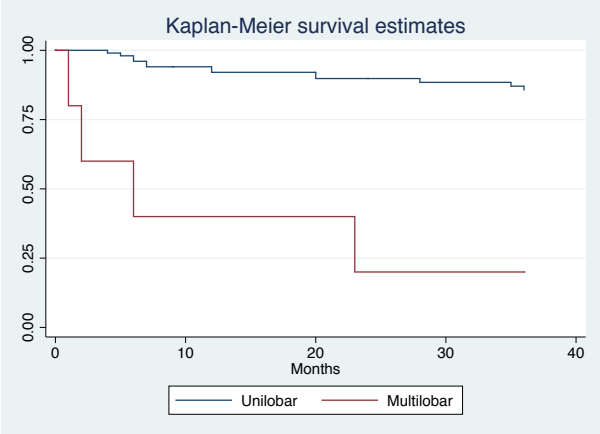
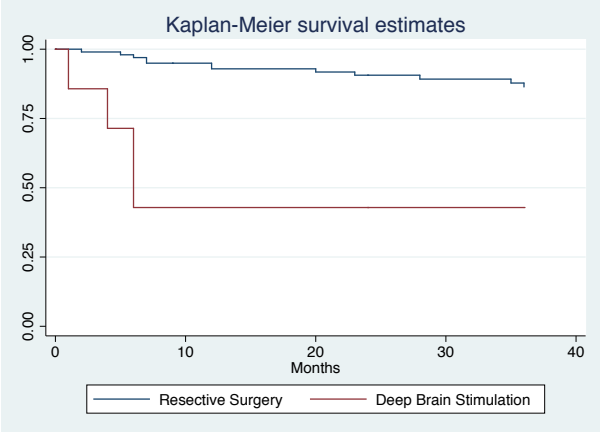


Figure 3 - Kaplan-Meier estimates of survival comparing RS to DBS (p<0.001).



4. Discussion

This cohort study was conducted in a reference center for refractory epilepsy using a sample of people who underwent surgery. Our aim was to identify clinically relevant risk factors for the development of major psychopathology that was not identified, in these patients` life, before surgery.

Forty-two percent of the surgical candidates, of this sample, had a lifetime history of at least one psychiatric disorder. This high prevalence is in line with other studies using a sample of refractory epilepsy patients[152,153].

After the surgical procedure, although the overall quality of life and psychiatric symptomatology improvement have been reported, for the majority of people with refractory epilepsy[154], a significant proportion of patients may develop serious psychiatric episodes[141]. In our sample, 15% of participants developed major psychiatric episodes that were never reported before surgery. However, these events were transient and responded to pharmacotherapeutic intervention. This incidence rate is higher than what would be expected in the general population in the same 3-year period[155,156] and appear to be surgery related as half of the patients with de novo psychopathology had the first event up to 7 months after surgery.

The main predictors of major psychiatric events were an epileptogenic zone affecting more than one lobe and being submitted to ANT-DBS. People with multilobar epileptogenic zone were 9 times more likely to develop new psychiatric events after surgery, and those submitted to DBS were almost 7 times more likely to develop these events.

A multilobar epileptogenic zone reflects a more widespread brain epileptogenicity. This finding is in line with previous studies, showing an association between a more general attainment of the brain such as bilateral functional and structural abnormalities, bilateral interictal discharges and frontal hypometabolism after temporal lobe surgery and the emergence of new psychopathology after surgery[143,157,158].

Generalized epileptiform activity may disrupt important circuits involved in the control of mood and behavior, leaving patients more vulnerable to develop these disorders after a major neurosurgical procedure.

The second significant predictor was the type of intervention. Patients submitted to ANT-DBS have a higher hazard of developing psychiatric disorders after surgery. In previous literature, the stimulation of the ANT, in refractory epilepsy, has been associated with higher rates of self-reported depression[159]. A more recent study, with 22 patients submitted to ANT-DBS, for the treatment of refractory epilepsy, showed that 2 patients, with a history of

depression, developed depressive symptoms and 2 others, with no history of psychosis, developed clear paranoid symptoms and anxiety[160].

Earlier studies concerning DBS use on Parkinson Disease and dystonia have found an association between this procedure and other serious psychiatric events such as hypomania/mania[161], psychotic disorders[162] and suicidal ideation/attempts[163]. There seems to be a different risk of developing mania or depression according to the location of the electrodes[164,165]. Older patients might also be particularly vulnerable to adverse psychiatric events[166].

Patients with refractory epilepsy submitted to this type of surgery may, likewise, be at a higher risk of the same psychiatric adverse events. This can be explained by the fact that although there are different targets, according to the disease that is intended to be treated, these structures participate in circuits that have implications for the control of mood and cognition.

This study has some limitations. It was an observational ambispective study with a retrospective component. There are some missing data and loss of follow-up. To account for this limitation, we used a survival analysis model. Secondly, as only annual evaluations were carried on, inter-evaluation disturbances may have been missed. Notwithstanding, psychiatrists involved were in constant communication with other members of the Epilepsy Surgery Group involved in the follow up of participants, and, every time a psychiatric disturbance was identified, they were promptly referred to a psychiatric consultation. We did not control for the type of antiepileptic drugs or changes in dosages. Some antiepileptics may have different effects on mood and behavior, however, as previously stated, for the majority of patients no changes were made during the follow-up period. Moreover, we didn´t analyze each type of psychiatric episode separately. Although they have different clinical presentations, only major episodes and serious adverse psychiatric events were considered. The occurrence of any of these events is always an important factor that has a major impact on quality of life of people with epilepsy.

Another important limitation is related to the possibility that, during pre-surgical evaluation, patients and families underreport psychiatric symptoms because they may be considered it a "natural reaction" to epilepsy or because of their fear of not being qualified for surgery. This may lead to an overestimation of what could be considered de novo psychopathology. Furthermore, as the sample size is relatively small, there are only a few numbers of events limiting the statistical power and stability of our models.

Despite these constraints, our study allows the identification of clinical variables that could be associated with an increased risk for de novo psychiatric events and a shorter time-to-event, after surgery. Moreover, it may suggest potential biological mechanisms involved in post-surgery psychiatric morbidity. New studies with larger number of patients submitted to DBS and resective surgery for epilepsy are required to confirm these results. Our study also reinforces the need for a comprehensive assessment of patients, the importance of adequate counseling pre-surgery and psychiatric follow-up. We suggest that patients with a multilobar epileptogenic zone and those submitted to invasive procedures for the treatment of epilepsy-like refractory epilepsy, particularly, DBS, should be submitted to more frequent psychiatric routine assessments after surgery.

In conclusion, our study identified two important factors that are highly associated with an increased risk of developing a serious psychiatric event after surgery, a wider epileptogenic zone and thus a more general involvement of different areas and brain circuits and the neurosurgical procedure to which patients are submitted.

Study 4: Determinants of psychopathological outcomes after epilepsy surgery

Title Clinical determinants of psychopathological outcomes after epilepsy surgery

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Abstract

Objectives People with refractory epilepsy submitted to surgery may improve or deteriorate their cognitive and emotional function. The aim of this study is to determine the predictors of longitudinal changes in psychopathological symptomatology, one year after epilepsy surgery, considering clinical and demographic characteristics.

Methods People with refractory epilepsy referred to epilepsy surgery were included in this ambispective study. Psychiatric evaluations were made before surgery and one year after the procedure. Demographic, psychiatric and neurological data were recorded. Linear regression was used to analyze longitudinal data regarding the Global Severity Index and 9 symptom dimensions of Symptom Checklist-90 (SCL-90).

Results Seventy-six people were included. Bilateral epileptogenic zone, lack of remission of disabling seizures and Deep Brain Stimulation, targeting the anterior nucleus of the thalamus (ANT-DBS), were the most important predictors of an increase in SCL-90 scores, after surgery.

Conclusion Some individual factors may have an impact on the development or worsening of the previous psychopathology. This study identifies clinical aspects associated with greater psychological distress, after surgery. These patients may benefit from more frequent psychiatric routine assessments for early detection.

Keywords Refractory epilepsy; epilepsy surgery; psychopathology

1. Introduction

About one-third of people with epilepsy do not respond to adequate antiepileptic drug treatment[47]. These people are considered to have refractory epilepsy, a chronic and debilitating condition with a great impact on patients' quality of life[167,168].

Not surprisingly, previous studies have reported high rates of mental disorders and psychopathological symptoms in people with epilepsy, particularly in those suffering from refractory epilepsy[136,168,169]. The most commonly reported disorders are affective and anxiety syndromes[36,37].

Most people with refractory epilepsy display a well-characterized lesion considered to be the epileptogenic zone. Focal epilepsy affects, most frequently, the temporal lobe, particularly mesial structures – the hippocampus and the amygdala[36,37]. These people may be eligible for resective surgery, a procedure that is effective in the remission of seizures of about 70% of the cases[43]. For those whom, by any reason, surgical resection is not feasible, other options may be considered, namely, neuromodulation interventions, such as Vagus Nerve Stimulation (VNS) or Deep Brain Stimulation, targeting the Anterior Nucleus of the Thalamus (ANT-DBS)[47].

Epilepsy surgery improves quality of life, even in those who are not seizure-free[170] plus may have a positive impact on the severity of depression, anxiety and total psychiatric symptoms[171–173].

Previous studies, focusing on psychopathological dimensions after epilepsy surgery, have reported that psychiatric symptoms tend to decrease over time[171,174]. Although most patients seem to achieve a general improvement, others develop de novo psychopathology or may worsen their previous psychiatric condition[175]. In fact, epilepsy surgery has been associated with a high risk of mortality secondary to suicide[176]. Death from suicide occurs even after successful surgery in which people who became seizure free[177].

Meldolesi et al. have shown a decrease of some state and trait emotional variables, as well as personality variables, such as interpersonal sensitivity, irritability, social introversion, and paranoia, at 1-year and 2-year follow-up evaluations, after surgery[174]. Similarly, Payson et al. reported improvement in some subscales of the Personality Assessment Inventory that differed according to the surgical side and location, highlighting the importance of considering psychological changes according to patient´s clinical characteristics[178].

Regarding ATN-DBS, some studies suggest that it might have a positive impact on mood[147,148], while others found that it could worse depression scores[149,150]. The anterior nucleus of the thalamus has a critical position in the "Papez circuit", a group of brain

regions with an important role on emotional and cognitive control. ATN-DBS may disrupt this circuit. It has been demonstrated that this procedure has deleterious effects on cognitive control and emotion-attention interaction[179]. Consequently, it may lead to dysfunctional mood and cognitive regulation, as well as, to an increased risk of psychopathological symptoms and psychiatric disorders.

While epilepsy surgery seems to have an impact on the psychopathological outcome, some authors suggested that presurgical psychopathology could also have an impact on the neurological outcome[76] suggesting a bidirectional relationship between these entities. However, a recent large cohort study by Altalib et al. (2018) did not confirm this association[180].

Despite the growing interest in psychopathology, both before and after surgery, there is a paucity of studies concerning the influence of different clinical features and surgical procedures on the post-surgical psychopathological symptoms of people with epilepsy. The purpose of this study was to address this issue.

2. Methods

This ambispective observational study was conducted at the Neurosciences` Department, of our institution, between February 2008 and October 2018. Retrospective and prospective data collection started after the study´s approval by our local Ethics committee in 2015. Subjects were recruited consecutively from the Refractory Epilepsy Reference Centre and the Epilepsy Surgery Group. The follow-up period was 12 months after surgery. Participants were evaluated by the psychiatrist belonging to both the Center and Group. The diagnosis of refractory epilepsy was made according to the definition of the International League Against Epilepsy[39].

Presurgical surgery evaluation, in our Group, includes, at least, a video-EEG monitoring, a 3-Tesla brain magnetic resonance with an epilepsy protocol, and a neuropsychological and psychiatric evaluation. Most patients are submitted to resective surgery, a smaller proportion of them undergo ANT-DBS or VNS. Only patients submitted to resective surgery or DBS were enrolled in this study because of a lack of detailed follow-up data of patients submitted to VNS.

Demographic (gender, age, employment status, marital status) and clinical data (etiology of epilepsy, the topography of the epileptogenic zone, the age of onset, time to surgery and Engel Class[151]), registered one month after surgery, were collected during interviews and from medical and surgical records. In the pre-surgical period, people were under, at least,

two antiepileptic drugs, but their type and dosages were not addressed in this study because there was considerable variability between people, as it usually is in this population. However, in our center, people keep the same antiepileptic drugs and therapeutic schemes for at least 2 years after surgery.

A written consent form was obtained from participants evaluated prospectively and the study was approved by the local Ethics Committee.

2.1 Subjects

Participants older than 18, submitted to resective surgery or DBS were included in this study. People with other neurological diseases or intellectual disability were excluded.

2.2 Psychiatric Evaluation

Psychiatric evaluations were performed, before and 12 months after surgery, by one of the 3 psychiatrists from our group (LCP, FN, SL) and include a clinical psychiatric history (demographic data, previous psychiatric history, family history, use of substances as well as other relevant data) and Symptom Checklist-90 (SCL-90). This multi-dimensional instrument is a 90-item self-report symptom inventory developed to measure psychological symptoms and psychological distress. It has 9 subscales evaluating different symptom dimensions: somatization, obsessive-compulsive, interpersonal sensitivity, depression, anxiety, hostility, phobic anxiety, paranoid ideation, psychoticism and a global scale called Global Severity Index (GSI)[67].

2.3 Statistical Analysis

The statistical analysis was performed using Stata software (version 14.2; StataCorp, Texas, USA). Descriptive statistics were presented as mean ± standard deviation or as the number of subjects/cases and proportions.

A paired t-test was used to compare pre and post total medium GSI scores.

For the longitudinal evaluation of SCL-90 subscales and GSI scores, after epilepsy surgery, as outcome variables, we performed Linear Regression. A set of predictor variables, clinically relevant both for epilepsy and psychiatric disorders, were included, as well as the SCL-90 baseline scores as a covariate.

Predictor variables include sex, age at surgery, duration of epilepsy and age at onset of epilepsy, analyzed as continuous variables. Epileptogenic zone side (right, left or bilateral cerebral hemispheres) and epileptogenic zone topography (temporal, extratemporal or

multilobar), and Engel Classes (I, II, III, or IV)[151], as categorical variables. Mesial versus non-mesial temporal epileptogenic zone and resective surgery vs ANT-DBS, analyzed as binary variables.

Normality of residuals was tested for each model.

Measures of association were expressed as coefficients and a p-value ≤0.05 was considered statistically significant.

3 Results

3.1 Demographic and clinical findings

One hundred and eight consecutive people with refractory epilepsy proposed to pre-surgical evaluation were enrolled. Ten were secondarily excluded because of intellectual disability (IQ<70), 18 because they did not undergo surgery, 2 because they underwent VNS; finally, 1 died and 1 refused to participate. Thus, a total of 76 individuals were included in the study. Demographic and clinical characteristics are described in Table 8.

Sixty-three (85%) people had a temporal, 7 a frontal and 4 an epileptogenic zone affecting more than one cerebral lobe, respectively. Regarding participants with temporal epilepsy, 35 (56%) had mesial sclerosis and 28 (35%) other pathologies.

One month after surgery, the outcomes of the majority of people (80%) were classified as Engel Class I.

Table 8 - Demographic and Clinical characteristics of participants

	SOCIO-DEMOGRAPHICAL AND CLINICAL CHARACTERISTICS
AGE, YEARS	39.0 ± 11.7
MALES, N (%)	28 (36.8)
EDUCATION, YEARS	10.6 ± 4.5
ACTIVE WORKERS, N (%)	41 (54.7)
UNEMPLOYED, N (%)	21 (28.0)
RETIRED, N (%)	13 (17.3)
MARRIED, N (%)	37 (49.3)
SINGLE OR DIVORCED, N (%)	38 (49.3)
AGE AT ONSET, YEARS	17.2 ± 11.8
DURATION OF EPILEPSY, YEARS	21.7 ± 14.1
TEMPORAL EPILEPTOGENIC ZONE, N (%)	63 (85.1)
EXTRATEMPORAL EPILEPTOGENIC ZONE, N (%)	7 (9.5)
MULTILOBAR EPILEPTOGENIC ZONE, N (%)	4 (5.4)
SIDE OF THE EPILEPTOGENIC FOCUS	
• **LEFT**	32 (42.7)
• **RIGHT**	38 (50.7)

• **BILATERAL**	5 (6.7)
NUMBER OF ANTIEPILEPTIC DRUGS	2.4 ± 0.6
TYPE OF SURGERY, N (%)	
• **RESECTIVE SURGERY**	69 (90.8)
• **DEEP BRAIN STIMULATION**	**7 (9.2)**

3.2 Analysis of longitudinal changes in GSI of SCL-90 considering the total sample

At the pre-surgical and one-year evaluation, participants had a medium GSI score of 0.82±0.61 and 0.82±0.68, respectively. No significant differences were found considering the total sample.

3.3 Analysis of longitudinal changes in each SCL-90 symptom dimensions scores considering subgroups according to clinical predictors

Some subgroups of patients were found to have increased scores on some of the symptom dimensions and GSI, according to the defined predictors.

Figures 4 to 20 represent all positive findings regarding longitudinal changes in SCL-90 subscales and GSI.

A summary of all positive findings has also been illustrated in Table 9.

Table 9 - Summary of predictors of higher SCL-90 scores one year after surgery

	Predictors of higher SCL-90 scores one year after surgery Coefficients (95% CI)			
	Engel Class II (compared to Engel Class I)	Bilateral epileptogenic zone	Multilobar epileptogenic zone	ANT-DBS
Somatization	1.32 (0.73,1.90)			
Obsessive-Compulsive	1.62 (0.61,2.62)			
Interpersonal sensitivity	0.88 (0.11,1.65)			
Depression	1.60 (0.69,2.51)			
Hostility	0.77 (0.13,1.41)		0.82 (0.05,1.59)	0.59 (0.14,1.05)
Phobic anxiety	0.94 (0.18,1.71)	Left: 0.71 (0.03,1.38) Right: 0.73 (0.08,1.38)		0.62 (0.06,1.19)
Paranoid Ideation	1.44 (0.66,2.23)	Left: 1.24 (0.55,1.94) Right: 1.06 (0.36,1.76)		1.17 (0.62,1.73)
Psychoticism	0.97 (0.22,1.73)			
Global Severity Index	1.19 (0.54,1.85)	Left: 0.65 (0.02,1.29) Right: 0.65 (0.02,1.28)		0.570.02,1.11)

Figure 4 - Longitudinal changes in GSI, according to the epileptogenic zone side.

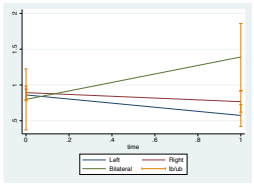


Figure 5 - Longitudinal changes in GSI, according to the Engel class.

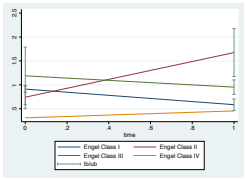


Figure 6 - Longitudinal changes in GSI, according to the type of surgery.

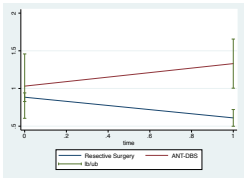


Figure 7 - Longitudinal changes in somatization subscale, according to the Engel class.

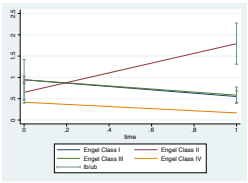


Figure 8 - Longitudinal changes in the obsessive-compulsive subscale, according to the Engel class.

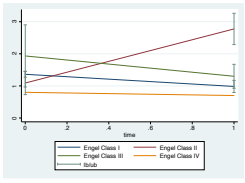


Figure 9 - Longitudinal changes in interpersonal sensitivity subscale, according to the Engel class.

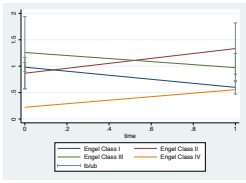


Figure 10 - Longitudinal changes in depression subscale, according to the Engel class.

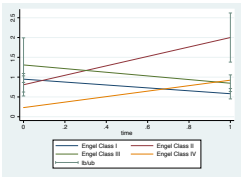


Figure 11 - Longitudinal changes in hostility subscale, according to the epileptogenic zone lobe.

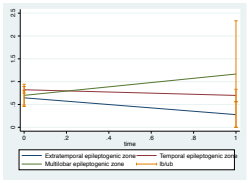


Figure 12 - Longitudinal changes in hostility subscale, according to the Engel class.

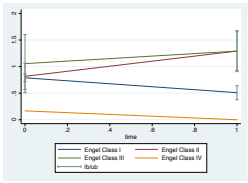


Figure 13 - Longitudinal changes in hostility subscale, according to the type of surgery.

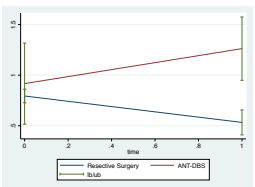


Figure 14 - Longitudinal changes in phobic anxiety subscale, according to the Engel Class.

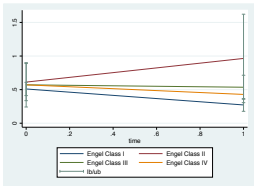


Figure 15 - Longitudinal changes in phobic anxiety subscale, according to the type of surgery.

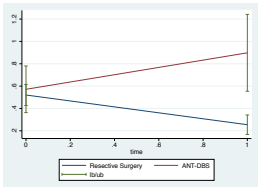


Figure 16 - Longitudinal changes in phobic anxiety subscale, according to the epileptogenic zone side.

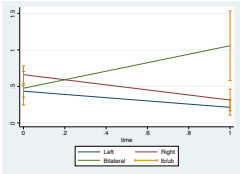


Figure 17 - Longitudinal changes in paranoid ideation subscale, according to the Engel Class.

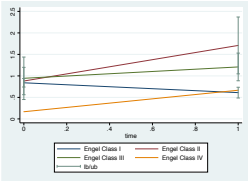


Figure 18 - Longitudinal changes in paranoid ideation subscale, according to the epileptogenic zone side.

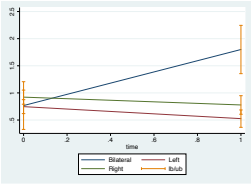


Figure 19 - Longitudinal changes in paranoid ideation subscale, according to the type of surgery.

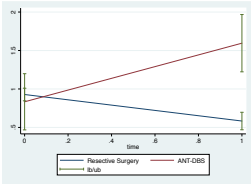
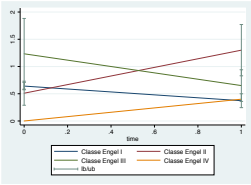


Figure 20 - Longitudinal changes in psychoticism subscale, according to the Engel class.



4 Discussion

Considering the total sample, no significant differences were found regarding GSI, before and one year after surgery, although most of these patients have been free of seizures.

However, our study showed that some clinical factors may contribute to worse GSI scores, reflecting a post-surgery more severe general psychopathological profile in some subgroups of patients: those with a bilateral epileptogenic zone, those submitted to ANT-DBS and those whose outcome was classified as Engel Class II.

Having an Engel Class II compared to Engel Class I was a predictor of higher scores one year after surgery, affecting all SCL-90 domains, as well as the GSI. This data is in line with previous studies showing an association between lack of seizure control after surgery and increased psychopathological symptoms[158,181].

Some hypothesis may explain this association, namely, the unmet expectations of patients and families. A mismatch between anticipated and real results, particularly, in those that do not become seizure free, may lead to family and individual distress and frustration. Patients with seizure recurrence may become significantly disappointed or have a sense of "failure", these negative feelings may be reinforced by surgery complications or de novo psychiatric disorders[182,183].

Continued epileptogenic activity, after a major neurosurgical procedure, may also have a role in the increased psychological stress of patients without seizure remission. Abnormal electric activity may affect, directly or indirectly, brain circuits that have important roles in the control of emotions and cognition[158,181].

After surgery, a bilateral epileptogenic zone was associated with increased phobic anxiety and paranoid ideation scores whereas multilobar epileptogenic zone was associated with higher hostility scores.

These two characteristics could reflect more diffuse epileptogenicity, and are in accordance with previous findings, suggesting that a more generalized brain dysfunction could be associated with an increased risk for post-operative mental symptoms. Such findings also include a preoperative history of secondary generalized tonic-clonic seizures[144], frontal hypometabolism in temporal lobe epilepsy[184] and preoperative bilateral independent spike discharges[158]. Dysfunctionality in different brain areas and circuits probably constitutes an important risk factor for the emergence of psychopathological symptoms after a major biological stressor such as epilepsy surgery.

Finally, the type of surgery, namely, being submitted to ANT-DBS in comparison to resective surgery, also contributed to the increased scores, after surgery, in the hostility, the phobic anxiety, and the paranoid ideation domains, as well as in the global scale. There are few studies reporting psychopathological outcomes after ANT-DBS for the treatment of refractory epilepsy. Findings include an increased risk of depression, paranoid and anxiety symptoms after surgery[159,160]. It is uncertain into what extent this procedure may contribute to the disruption of important circuits involved in mood regulation.

A meta-analysis of psychiatric and neuropsychiatric adverse events associated with DBS, including different sites of stimulation, reported mixed findings regarding mood and behavior measured with the mentation, behavior, and mood (MBM) subscale of the unified Parkinson's disease rating scale. About half of the studies reported an improvement, 33% reported a worsening of symptoms and 11% reported no changes[185]. The fact that the majority of studies included in this analysis reported an improvement in psychopathological scores contrasts with our findings. However, this study includes many different stimulation sites and indications including depression and obsessive-compulsive disorder. Moreover, many of the studies did not report any outcomes regarding psychopathological outcomes. Interestingly, thalamus stimulation was associated with a higher risk of suicide, suggesting that this might be a particularly vulnerable structure[185]. Clearly, there is a need for further studies examining the psychopathological outcome after ANT-DBS.

This study has some limitations. The first is that this was an observational ambispective study with an important retrospective component. Missing information may introduce bias; however, different information sources were consulted to minimize the lack of data.

Epilepsy and psychiatric pharmacological treatments were not controlled and might have an impact on participant psychopathological symptoms. Nonetheless, all patients with clinically significant mental symptoms were referred to a psychiatrist and submitted to treatment. We do not expect that the predictors found in our models would influence the probability of being treated.

Finally, the sample size is relatively small, increasing the risk of a type II error.

Despite these constraints, important conclusions may be drawn from our study. Our findings suggest that the lack of complete seizure remission, more global epileptogenicity, and ANT-DBS are associated with more psychological distress after surgery. This research also offers some insights into what may constitute potential biological mechanisms involved in the development of psychiatric disorders and should be enhanced by prospective studies with more robust samples.

CHAPTER V: Mental disorders impact on the course of refractory epilepsy

Study 5: Psychiatric disorders as predictors of epilepsy surgery outcome

Title Psychiatric disorders as predictors of epilepsy surgery outcome.

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Abstract

Objectives Our aim was to determine if a history of a mental disorder predicts a worst neurological outcome for patients undergoing epilepsy surgery.

Methods We conducted an ambispective observational study including people with refractory epilepsy who underwent resective surgery. Demographic, psychiatric and neurological data were collected, before and one year after surgery. Pre-surgical interviews included a psychiatric evaluation and the determination of prevalent and lifetime psychiatric diagnosis. The one-year post-surgical outcome was classified according to the Engel Outcome Scale. Predictors of post-surgical Engel class were determined using an ordered logistic regression model.

Results A lifetime history of any mental disorder was a significant predictor of a higher Engel Class (p=0.017).

Conclusion This study shows that psychiatric lifetime diagnoses are associated with worse surgical outcome and highlighted the importance of the inclusion of these diagnoses in the evaluation of the potential success of the surgery.

Keywords Refractory Epilepsy; Surgery Epilepsy Outcome; Lifetime Psychiatric Disorders

1 Introduction

Psychiatric comorbidity is frequent in people with epilepsy[41,186,187]. There is an association between these type of disorders concerning their severity and probability of occurrence[188–191]. Psychiatric disorders can precede, co-occur, or follow the diagnosis of epilepsy[188]. Previous studies have suggested that there is a bidirectional relationship between mental disorders and epilepsy[192,193].

Some aspects that may explain this association have been postulated. Psychosocial factors may partially explain the high prevalence of depression and anxiety in people with epilepsy. These factors include stigma, poor disease acceptance, and anticipatory anxiety associated with the unpredictable nature and outcome of seizures and the limitations imposed by the disease itself[194]. However, common biological factors may also explain this bidirectional association. Psychiatric disorders and epilepsies may share common genetic mechanisms, such as copy number variants, which seem to act as a non-specific risk factor for both epilepsy and schizophrenia, autism spectrum disorders and attention deficit hyperactivity disorders[26]. A hyperactive hypothalamic–pituitary–adrenal axis has been suggested as another putative mechanism, as an abnormal dexamethasone suppression test has been demonstrated in both primary major depression and in people with epilepsy without depression[193]. Elevated glucocorticoid levels might damage neuronal and cortical function, thereby increasing the synaptic glutamate levels[193]. Dysfunction of glutamate transporter proteins, serotonin, dopamine, and y-aminobutyric acid transporters, together with reduced levels of serotonin and noradrenaline, might also play a role in the pathogenesis of depression and epilepsy**[193,195–197]**.

People suffering from mental disorders and epilepsy might have a more global dysfunction of brain networks, neurotransmitter or neuroendocrine systems, or some other general mechanism. Widespread brain abnormalities have been identified in both focal epilepsy and some psychiatric disorders, such as schizophrenia, bipolar disorder and major depression[15–19].

About one-third of people living with epilepsy do not respond to pharmacological treatment[38], and they are considered to have refractory epilepsy[39]. They have an even higher risk for psychiatric disorders[40,41]. Some of these patients may be submitted to surgery (resective or palliative) with different neurological outcomes. Clinical characteristics, such as a history of presurgical secondarily generalized convulsive seizures, learning disability, an extratemporal epileptogenic zone, bilateral hippocampal sclerosis and bi-temporal interictal epileptiform discharge, as well as palliative procedures, have been

shown to increase the probability of recurrence of seizures after surgery[44,76,203]. Inversely, higher age at onset and a shorter duration of epilepsy have been associated with a better post-surgery seizure control[204,205].

Some previous studies have suggested that a lifetime history of psychiatric disorders is also associated with a poor post-surgical seizure outcome[76,206,207]; however other studies did not confirm this finding[208,209]. Hence, we believe that this important subject deserves further investigation.

People suffering from mental disorders and epilepsy might have a more global dysfunction of brain networks, neurotransmitter or neuroendocrine systems and potentially a more serious disorder. Widespread brain abnormalities have been identified in both focal epilepsy and some psychiatric disorders, such as schizophrenia, bipolar disorder and major depression[198–202].

Considering this hypothesis, the present study postulates that a pre-surgical lifetime history of mental disorders may be an important predictor of a worst postoperative seizure control.

2 Methods

This ambispective cohort study was conducted at the Neurosciences and Mental Health Department of the Hospital de Santa Maria, between April 2000 and September 2018. Subjects were recruited from both the Refractory Epilepsy Reference Centre and the Epilepsy Surgery Group. Participants were evaluated, before surgery and after 12 months, by one of the psychiatrists belonging to both the Center and the Group. The diagnosis of refractory epilepsy was based on the definition of the International League Against Epilepsy[39].

Presurgical evaluation routinely included at least a video-electroencephalography (EEG) monitoring, a 3-Tesla brain magnetic resonance with an epilepsy protocol, a neuropsychological and a psychiatric evaluation. All patients underwent resective surgery.

Data pertaining to demographic (gender, age, employment status, marital status, etiology of epilepsy, the topography of the epileptogenic zone, the age of onset, time to surgery), and Engel Class[210] after surgery, were collected during the interviews and from the patient`s medical and surgical records. In the pre-surgical period, patients were taking, at least, two antiepileptic drugs. However, the type, number, and dosages of the medications were not addressed in this study because of the usually broad variability among this population. Nonetheless, patients usually, continue to take the same drugs and maintain the same therapeutic schemes for at least 2 years, after surgery, if they stop having seizures.

This study was performed in accordance with the ethical standards of the 1964 Declaration of Helsinki, and its later amendments, and it was approved by the Ethics Committee of the Hospital de Santa Maria (CHULN).

2.1 Subjects

Participants older than 18 years, submitted to resective surgery, with a minimum of one year of education were included in the study. Participants that underwent Deep Brain Stimulation (DBS) or Vagus Nerve Stimulation (VNS), and those with other neurological diseases or intellectual disability, were excluded.

A total of 196 consecutive people with refractory epilepsy, who were proposed for pre-surgical evaluation, were enrolled in the study. Of those, 15 were secondarily excluded because of intellectual disability (QI<70), 48 were excluded because they did not undergo surgery, 12 were excluded because they underwent DBS or VNS, 1 refused to participate, and 1 died. Thus, a total of 124 individuals were included in the study.

2.2 Psychiatric Evaluation

Psychiatric evaluations included a clinical psychiatric history (demographic data, previous psychiatric history, family history, use of substances, as well as, other relevant data) and the following psychopathological tests:

2.2.1 The Hamilton Anxiety Rating Scale (HARS)

This scale consists of 14 items and measures both psychic and somatic anxiety[57].

It is scored according to the following cut-offs: 17 = mild; 18-24 = mild to moderate; 25-30 = moderate to severe anxiety[57].

2.2.2 The Hamilton Depression Rating Scale (HDRS)

The version used corresponds to the original 17 items version. It was developed to access the severity of depressive symptoms[58] and the following scores were considered: 0-7 = normal; 8-16 = mild; 17-23 = moderate; >24 = severe depression[119].

2.2.3 Brief Psychiatric Rating Scale (BPRS)

This rating scale is used to measure the change in psychiatric symptoms, particularly, psychotic symptoms. It contains 18 items, each one rated from 1 (absent) to 7 (extremely

severe), evaluating positive, negative and affective symptoms[59]. It ranges from 18 to 126[211].

2.2.4 Symptom Checklist-90 (SCL-90)

This multi-dimensional instrument is a 90-item self-report symptom inventory developed to measure psychopathological symptoms and psychological distress. It has been extensively validated. There are three global indices for the SCL-90: 1) Global Severity Index (GSI), which is the average score of the 90 items of the questionnaire; it is the best single indicator of the current level of the disorder, 2) Positive Symptom Distress Index, which is the average score of the items scored above zero, and 3) Positive Symptoms Total, which is the number of items scored above zero[61]. A cut-off of 0.57 was proposed[212].

Lifetime psychiatric disorder diagnostics were established according to the International Statistical Classification of Diseases and Related Health Problems (ICD-10)[117], including information provided by the patient and the family member who accompanied the pre-surgical evaluation.

2.3 Statistical Analysis

The statistical analysis was conducted using Stata software (version 14.2; StataCorp, Texas, USA). Descriptive statistics were performed to report the analysis of data presented as mean ± standard deviation or median (minimum-maximum). Student's t-test and the Mann-Whitney U test were used for the parametric and non-parametric data, respectively. A chi-square test, or the Fisher exact test in case of non-parametric data, was used to compare the categorical variables, which were given as the number of cases or proportions.

The outcome variable considered was the Engel Class, registered 12 months, after surgery. Because this is an ordinal variable, an ordered logistic regression model was used for the univariate and multivariate analysis.

First, a model was developed including lifetime psychiatric diagnosis, analyzed as a binary variable (at least one lifetime diagnosis versus no lifetime diagnosis); then as a categorical variable was created, according to the following diagnostic groups: no history of previous mental disorders, history of psychoactive substance use, any psychotic disorder, any mood disorder, any anxiety disorder, any other mental disorder.

Measures of association were expressed as Odds Ratio (OR); and a p-value ≤ 0.05 was considered to be statistically significant.

3 Results

3.1 Demographic and clinical findings considering the existence of a lifetime psychiatric diagnosis versus no history of such diagnosis

Comparing patients with and without a history of a lifetime psychiatric disorder, significant differences were found regarding their employment status. Those with a history of some psychiatric disorder had a lower probability of being active workers (p= 0.009). Approximately half of them were unemployed or had retired early. They also tended to have a right epileptogenic zone (p=0.007), a longer duration of disease (p=0.03), and a worse outcome after surgery (p=0.01). Other demographic and clinical characteristics are described in Table 10.

Table 10 - Socio-demographical and clinical characteristics of the participants.

	No lifetime psychiatric disorders N = 67	At least one lifetime psychiatric disorder N = 57	p-value
Age, years	36.9 ± 11.8	40.4 ± 11.7	0.10
Males, n (%)	29 (43.3)	21 (36.8)	0.47
Education, years	11.0 ± 4.4	9.7 ± 4.6	0.11
Active workers, n (%)	53 (79.1)	28 (52.8)	0.009
Married, n (%)	35 (52.2)	27 (49.1)	0.29
Age at onset, years	17.1 ± 11.2	15.3 ± 10.9	0.35
Duration of epilepsy, years	19.9 ± 12.3	25.0 ± 13.7	0.03
Temporal epileptogenic zone, n (%)	61 (91.0)	50 (89.3)	0.74
• Mesial	53 (86.9)	43 (86.0)	
• Neocortical	8 (13.1)	7 (14.0)	
Extratemporal epileptogenic zone, n (%)	6 (9.0)	6 (10.7)	
Side of the epileptogenic lesion			
• Left	39 (58.2)	19 (33.9)	0.007
• Right	28 (41.8)	37 (66.0)	
Type of epileptogenic lesion			0.68
• Sclerosis	40 (65.6)	31 (62.0)	
• Tumors	13 (21.3)	9 (18.0)	
• Dysplasia	2 (3.3)	3 (6.0)	
• Gliosis	2 (3.3)	1 (2.0)	
• Cavernous angioma	2 (3.3)	2 (4.0)	
• Other	2 (3.3)	4 (8.0)	
Number of antiepileptic drugs	2.3 ± 0.6	2.2 ± 0.6	0.39
Epileptic crises per month	6.8 ± 8.6	9.2 ± 16.9	0.48
Engel I	58 (92.1)	39 (75.0)	0.01
Engel II, III and IV	5 (7.9)	13 (25.0)	

3.2 Lifetime history of mental disorders

Before surgery, a total of 57 candidates (46%) had a lifetime history of at least one mental disorder. The number of patients per diagnosis category is represented in Table 11.

Table 11 - Socio-demographical and clinical characteristics of the participants.

No previous diagnosis, n (%)	67 (54.0)
Depressive disorders, n (%)	36 (29.0)
Anxiety disorders, n (%)	6 (4.8)
Psychoactive substance use, n (%)	6 (4.8)
Psychotic disorders, n (%)	3 (2.2)
Other diagnosis, n (%)	6 (4.8)

3.3 Psychopathology at the moment of pre-surgical evaluation

At the pre-surgical evaluation, surgical candidates had a medium HDRS total score of 7.69±7.56, a medium HARS total score of 8.32±7.09, a medium GSI total score of 0.88±0.56, and a medium BPRS total score of 27.5±9.15.

According to the defined cut-off for HDRS, 7 people had moderate depression and 13 people had severe depression at the moment of evaluation. Two patients had moderate to severe anxiety according to the HARS.

3.4 Results from the univariate analysis

The lifetime history of any mental disorder was a predictor of higher Engel Class scores one year after surgery (OR 3.83; CI 95% 1.27-11.59; p=0.017).

Considering each group of disorders separately, a previous diagnosis of a psychotic disorder (OR 35.18; CI 95% 2.84-436.15; p=0.006) and any substance use disorder (OR 15.94; CI 95% 2.89-87.93; p=0.001) were significant predictors of higher Engel Class scores.

4 Discussion

This cohort study was conducted in a reference center for refractory epilepsy using a sample of people who underwent epilepsy surgery. Our aim was to confirm that lifetime psychiatric disorders or psychopathology, detected at the pre-surgical evaluation, predict a worse post-operative seizure outcome.

Our data showed that 46% of epilepsy surgery candidates had a previous history of mental disorders. This high percentage tracks with previous studies[152,213] and argues for a close relationship between epilepsy and psychiatric disorders.

Further, this study showed that patients with a history of mental disorders tend to have lower levels of success in the control of seizures after surgery. Depression, psychotic disorders and substance use disorders may have a higher negative impact.

Previous researchers have also investigated the relationship between pre-operative psychopathology or major psychiatric disorders and the probability of seizure remission after epilepsy surgery. However, the results were controversial. Koch-Stoecker et al. (2017) concluded that a lifetime diagnosis of psychosis, major depression, or personality disorders diminished the probability of complete seizure remission[214]. Additionally, Kanner et al. (2009) studied presurgical lifetime history of mood, anxiety, attention deficit hyperactivity, and psychotic disorders as independent predictors of seizure outcome and suggested that a lifetime psychiatric history may predict worse post-operative seizure control[206]. Adams et al. (2012) found no association between psychiatric history and seizure outcome on patients with mesial sclerosis. These contradictions, however, may be due to the analysis of a small sample (n=72). Another potential explanation was provided by the authors, namely that the association found in previous literature may be due to the inclusion of patients with other diseases besides mesial sclerosis in their samples. Lifetime psychiatric disorders would predict worse outcomes in this group of people but not in mesial sclerosis patients[208]. Our sample includes both patients with and without mesial sclerosis. Lackmayer et al. (2013) also found that pre-operative depressive symptoms were not predictors of post-operative seizure control in people with temporal lobe epilepsy. However, their sample size was also small (n=45)[209].

The association between pre-operative psychiatric lifetime diagnosis and seizure outcome could, as mentioned, be related to psychological factors or common biological mechanisms. Long-lasting refractory epilepsy may cause more brain dysfunction and contribute to both psychiatric disorders and a reduced probability of seizure remission.

Our study has some limitations. This was an observational study with a retrospective component, so some data were missing. Different sources of information were considered in order to confirm clinical information and to complete data as much as possible. Another limitation was that lifetime psychiatric diagnosis may not have been reported for several reasons, some including the fact that some psychopathological symptoms may be considered as a “natural reaction” to epilepsy or because of their fear of not being qualified for surgery. Consequently, this may have affected our results. However, information was, whenever possible, confirmed with family members and other accompanying persons. We did not control for the type of antiepileptic drugs; these may have an impact on mood and behavior. Nevertheless, we do not expect to have significant differences in therapeutic schemes between patients with and without psychiatric comorbidities as they are mainly determined by their efficacy on the control of epilepsy regardless of this type of comorbidity. We also

did not include in our analysis the use of psychiatric medications, although we might expect that all patients with moderate to severe symptomatology were medicated. Finally, we considered the 12-month outcome; while a 24-months assessment would be more adequate to evaluate seizure outcome.

Despite these constraints, our study shows a clear relationship between epilepsy and mental disorders, arguing for a bidirectional relationship. Patients with psychiatric disorders and epilepsy may represent a group with more generalized brain dysfunction and a potentially more serious disorder. Previous psychiatric history should always be identified and included in an evaluation protocol that would help clinicians and surgery candidates to have a more accurate prediction of the potential success of the surgery.

Unfortunately, until recent years, psychiatric comorbidities were frequently not considered or treated. The recognition of their impact on the quality of life and on the clinical course of epilepsy has highlighted the need for early identification and treatment of psychiatric disorders[215].

Future studies should focus on the impact of pharmacological or psychosocial treatment of psychiatric comorbidities on the post-surgical course of epilepsy.

Study 6: Development of a predictive model for epilepsy surgery

Title: Development of a comprehensive model to predict epilepsy surgery outcome.

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Abstract

Objectives The aim of this study was to build a predictive model for epilepsy surgery outcome including epilepsy-related and psychiatric predictors.

Methods We conducted an ambispective observational study with the inclusion of people who underwent resective surgery, Deep Brain Stimulation (DBS) or Vagus Nerve Stimulation (VNS). Participants were evaluated before and one-year after surgery to collect data regarding their neurological and psychiatric history. The one-year postsurgical outcome was classified according to the Engel Outcome Scale. Predictors of post-surgical Engel class were included in a multivariate logistic regression model. Then the accuracy of different predictive models combining different predictive factors was tested.

Results Predictors of higher Engel Class were a lifetime history of any mental disorder (OR 3.96; CI 95% 1.36-11.46; p=0.011), an extratemporal epileptogenic zone (OR 4.12; CI 95% 1.12-15.11; p=0.033) and DBS or VNS (OR 83.69; CI 95% 13.62-514.04; p<0.001). A model including gender, duration of epilepsy, age at the beginning of epilepsy, type of surgery and history of any lifetime psychiatric disorder achieved an area under the ROC curve of 0.81. The single most important contributor to the accuracy of the model was a history of any lifetime mental disorder.

Conclusion Simple predictors may be used to predict epilepsy surgery outcome with a good accuracy. Psychiatric lifetime diagnoses are important predictors of a worst surgical outcome and should be included in the decision-making process to determine the potential success of the surgery.

Keywords Refractory epilepsy, epilepsy surgery, outcome, psychiatric disorders

1 Introduction

Epilepsy surgery may be a potential life-changing treatment for those living with refractory epilepsy. In focal epilepsies, the gold-standard is the resective surgery[216]. Up to 80% of patients may achieve seizure freedom patients after the resection of the epileptogenic zone [217]. Mesial temporal sclerosis is the most common form of focal epilepsy; therefore, the majority of these patients undergo temporal resection[218]. The goal of this procedure is to remove the epileptogenic zone completely without any subsequent permanent neurological damage[218].

About a third of those with refractory epilepsy are not suitable for resective surgery, this may be due to clinical factors, such as the type of seizure and location of the epileptogenic zone [219]. These patients may benefit from other types of surgery, also called, palliative procedures, such as the stereotactic surgery or the neuromodulation techniques, including the Vagus Nerve Stimulation and the Deep Brain Stimulation. Despite a seizure-free outcome is not expected, benefits in terms of seizure frequency and severity have been reported[220,221].

Considering the outcome of resective surgery, some prognostic factors have been identified. Abnormalities in the pre-operative Magnetic Resonance Imaging (MRI), complete surgical resection, presence of tumor or mesial temporal sclerosis, right-side resection, history of febrile seizures, and unilateral spikes are some of the factors associated with a better prognosis[222]. No evidence was found regarding other factors such as the presence of post-operative discharges or a history of head injury[222]. Poorer prognosis may be predicted by other clinical characteristics such as bilateral Positron Emission Tomography (PET) abnormalities and acute post-operative seizures[223].

Nonetheless, despite the identification of multiple prognostic factors and the development of some prognostic models, the accuracy of the prediction of epilepsy surgery outcome, using clinical judgment or published statistical tools, is still low[217].

Besides epilepsy related features, other factors such as the presence of a psychiatric lifetime disorder has been identified as an important predictor of epilepsy surgery outcome[116]. Still, none of the multi-variable prognostic models that have been published included this clinical factor or considered its relative importance for the accuracy of the model.

More accurate and comprehensive models, including both clinical and nonclinical variables, are needed to guide the decision-making process[217]. In our work we developed different predictive models, including lifetime psychiatric diagnosis as well as other surgery and epilepsy-related factors to determine its relative importance to the accuracy of the model.

2 Methods

We conducted an ambispective cohort study at the Neurosciences and Mental Health Department of our Institution, between April 2000 and September 2018. Adults with a diagnosis of refractory, according to the definition of the International League Against Epilepsy [39], were included, consecutively, from both our Refractory Epilepsy Reference Centre and Epilepsy Surgery Group. Those with other neurological diseases or intellectual disability were excluded.

The pre-surgical assessment included a video-electroencephalography (v-EEG) monitoring, a 3-Tesla brain magnetic resonance with an epilepsy protocol, a neuropsychological and a psychiatric evaluation. The determination of the epileptogenic zone was made by consensus. Invasive techniques and other exams such as PET were used when the routine assessment was considered insufficient. Most patients underwent resective surgery and a smaller proportion was treated with Deep Brain Stimulation of the anterior nucleus of the thalamus (ANT-DBS) or Vagus Nerve Stimulation (VNS). Demographic and clinical data (gender, age, employment status, marital status, etiology of epilepsy, the topography of the epileptogenic zone, the age of onset, time to surgery), as well as Engel Class[210] one-year after surgery, were collected during interviews and from medical and surgical records. Psychiatric assessment was performed by one of the psychiatrists from the Refractory Epilepsy Reference Centre and Epilepsy Surgery Group. Lifetime psychiatric disorder diagnostics were established according to the International Statistical Classification of Diseases and Related Health Problems (ICD-10)[117]. This study was approved by the Ethics Committee of Hospital de Santa Maria. Methods have been described in detail elsewhere(cit.).

2.1 Statistical Analysis

The statistical analysis was executed using Stata software (version 14.2; StataCorp, Texas, USA). Descriptive statistics were presented as mean ± standard deviation. Student's t-test and the Mann-Whitney U test were used for parametric and non-parametric data, respectively. A chi-square test, or the Fisher exact test in case of non-parametric data, was used to compare categorical variables.

We performed a multivariate logistic regression model for the analysis of predictors and model development.

The outcome variable was the Engel Class registered 12 months, after surgery. As it should be binary, a new variable was generated for the Engel Class - Engel class 1 versus Engel II, III or IV.

Predictors included duration of disease and age of onset of epilepsy, analyzed as continuous variables; gender, temporal versus extratemporal epileptogenic zone and type of surgery (resective surgery versus VNS or ANT-DBS), analyzed as binary variables; laterality of the epileptogenic zone, analyzed as a categorical variable.

Finally, we compared the area under the receiver operating characteristics curve (AUC of ROC) and used the Delong method to test the performance of the predictive models. The best performance was searched using backward selection for each of the chosen predictors. Measures of association were expressed as Odds Ratio (OR) and a p-value ≤ 0.05 was considered statistically significant.

3 Results

3.1 Demographic and clinical findings considering the existence of a lifetime psychiatric diagnosis versus no history of such diagnosis

One hundred and ninety-six consecutive people with refractory epilepsy were enrolled. Fifteen were secondarily excluded because they had intellectual disability, 48 did not underwent surgery, 1 died and 1 refused to participate. Thus, a total of 136 individuals were included in this study. Demographic and clinical characteristics of the sample were described in Table 12.

Table 12 - Socio-demographical and clinical characteristics of the participants.

AGE, YEARS	**38.2 ± 11.7**
MALES, N (%)	67 (42.4)
EDUCATION, YEARS	10.2 ± 4.5
ACTIVE WORKERS, N (%)	93 (64.6)
MARRIED, N (%)	74 (50.0)
AGE AT ONSET, YEARS	15.5 ± 11.1
DURATION OF EPILEPSY, YEARS	22.8 ± 13.2
TEMPORAL EPILEPTOGENIC ZONE, N (%)	139 (89.1)
• **MESIAL**	96 (86.5)
• **NEOCORTICAL**	15 (13.5)
EXTRATEMPORAL EPILEPTOGENIC ZONE, N (%)	17 (10.9)
SIDE OF THE EPILEPTOGENIC FOCUS	
• **LEFT**	74 (47.1)
• **RIGHT**	76 (48.4)
• **BILATERAL**	7 (4.5)
NUMBER OF ANTIEPILEPTIC DRUGS	2.3 ± 0.6
TYPE OF SURGERY, N (%)	
• **RESECTIVE SURGERY**	145 (91.8)

• **DBS OR VNS**	13 (8.2)
ENGEL I	98 (79.0)
ENGEL II, III AND IV	**26 (21.0)**

3.2 Results from the multivariate analysis

The factors associated with a higher Engel Class were a lifetime history of any mental disorder (OR 3.96; CI 95% 1.36-11.46; p=0.011), having an extratemporal epileptogenic zone (OR 4.12; CI 95% 1.12-15.11; p=0.033) and being submitted to ANT-DBS or VNS (OR 83.69; CI 95% 13.62-514.04; p<0.001).

3.2 Results from the prediction models

Without the inclusion of the variable lifetime psychiatric history, the model showed an area under the ROC curve of 0.71 showing poor accuracy. However, when lifetime psychiatric history was included, this area improved to 0.76, considered a fair accuracy.

These results were confirmed using the DeLong method.

After testing for different models combining the variables, the best performance was achieved eliminating laterality and location of the epileptogenic focus and keeping all the other predictors. The area under the ROC curve of the final model was 0.81, showing good accuracy.

The single most important contributor to the accuracy of the model, showing a greater improvement of the ROC area, was the history of a lifetime psychiatric diagnosis.

Figure 21 and 22 illustrates the model with and without the inclusion of lifetime psychiatric diagnosis.

Figure 21 - Area under the Receiver Operating Characteristic (ROC) curve of the model without the inclusion of a psychiatric lifetime history.

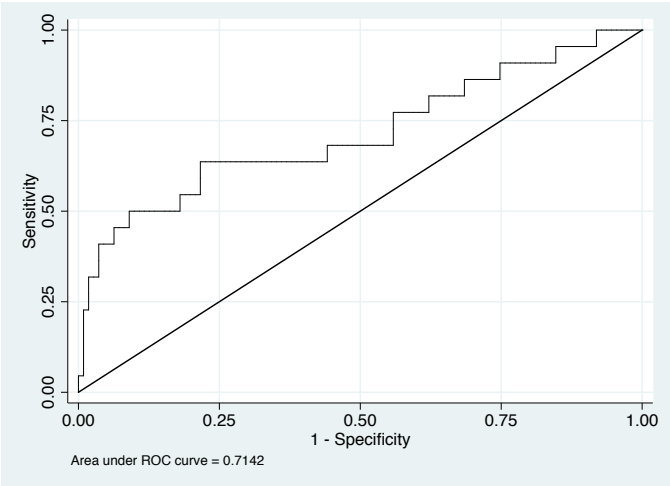


Figure 22 - Area under the ROC curve of the model with the inclusion of a psychiatric lifetime history.

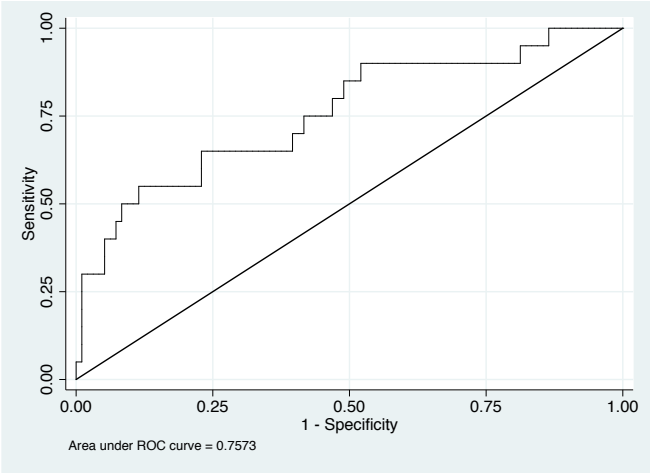


Figure 23 illustrates the comparison of ROC area in both models using the DeLong method.

Figure 23 - Comparison of models using the DeLong method.

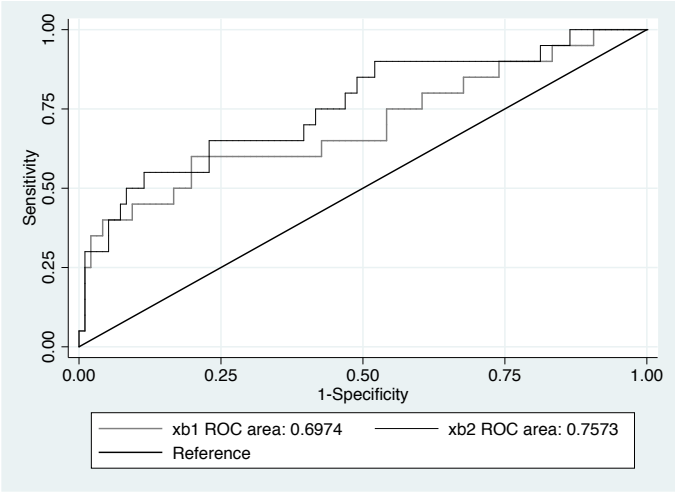
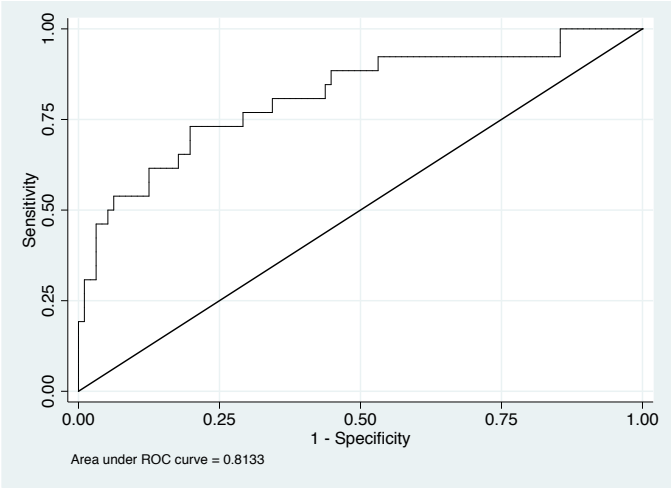


Figure 24 illustrates the final model.

Figure 24 - Final model including gender, duration of epilepsy, age at the beginning of epilepsy, type of surgery and history of any lifetime psychiatric disorder as predictors of Engel Class.



4 Discussion

This cohort study allowed the development of a predictive model that showed good discrimination between those with a better outcome (Engel I) and those with a poorer outcome (Engel II to IV) using simple clinical and demographical characteristics. These variables included the gender, the duration of epilepsy, the age at the beginning of epilepsy, the type of surgery and the existence or not of any lifetime psychiatric disorder.

The most significant predictors of a poorer seizure outcome were a lifetime history of any mental disorder, an extratemporal epileptogenic zone and the type of surgery being ANT-DBS or VNS.

A lifetime psychiatric history was recently found to constitute a predictor of epilepsy surgery outcome[116] (Novais et al. 2019), however, it has not been included in prognostic models yet. Our study shows that this is an important contributor to the accuracy of the outcome prediction and, although it should not preclude the surgery, a psychiatric disorder history must be included in the multidisciplinary discussion regarding the potential outcome of epilepsy surgery.

People with refractory epilepsy and psychiatric comorbidity may have more widespread brain abnormalities such as the dysfunction of glutamate, serotonin, dopamine, and y-aminobutyric acid transporters[1,22,25]. These abnormalities may be secondary to the epileptogenic activity, to the psychiatric disorder or constitute a common ground for both. Due to this generalized dysfunction, a targeted intervention focused on the epileptogenic

zone may not lead to seizure freedom as we would expect in other patients with the same characteristics but without a psychiatric history.

Regarding the type of surgical procedure, as we expected, ANT-DBS and VNS were associated with higher Engel classes. These neuromodulation techniques, considered as palliative procedures, are linked with considerably lower rates of seizure control when compared to resective surgery[224].

Additionally, in our sample, the extratemporal epileptogenic zone was correlated with a lower probability of disabling seizures remission. This result also confirms previous findings[203,225].

Recently, Gracia et al. (2019) compared the accuracy of clinical judgment in predicting epilepsy surgery outcome to two previously published statistical tools, the Epilepsy Surgery Nomogram (ESN) and the modified Seizure-Freedom score (m-SFS)[217]. Using a ROC curve analysis for the prediction of seizure control at 2 and 5 years, these authors found that the AUC curves were approximately 0.48 and 0.47, respectively, when the clinicians´ judgment was considered. The m-SFS, that included the variables: preoperative seizure frequency, history of generalized tonic-clonic seizures, brain magnetic resonance imaging (MRI), and epilepsy duration[226], showed an AUC of, approximately, 0.54, at both time points. While the ESN, witch considered the following predictors: sex, seizure frequency, secondary seizure generalization, type of surgery, pathological cause, age at epilepsy onset, age at surgery, epilepsy duration at time of surgery, and surgical side[227], showed an AUC curve of, approximately, 0.53, also at both time points[217]. The authors found no statistical differences between the ESN and the clinicians or between m-SFS and the ESN and they all showed a very poor ability to predict the surgery outcome, reinforcing the need for better predictors[217]. The variables chosen in our model allowed the development of a model with an AUC curve of 0.81 including only some of the available predictors and the presence of any lifetime psychiatric disorder. Therefore, we were able to identify the predictors that might contribute the most to the prediction of epilepsy surgery outcome.

Moreover, the fact that we used a broad clinical sample allowed us to identify predictors that apply to patients with very different clinical characteristics.

Some limitations of this work must be considered. This work has a retrospective component, so some data were lost. We believe that they are missing completely at random, also different sources of information were used to complete information as much as possible. Lifetime psychiatric diagnosis may not have been reported because of some reasons that include the fact that some psychopathological symptoms may be considered as a “natural reaction” to

epilepsy or because of their fear of not being qualified for surgery. To address this potential problem, information was, whenever possible, confirmed with family members and other accompanying persons. We also did not include in our analysis if patients have been treated or not for their psychiatric condition, therefore we do not have information whether treating these conditions would have an impact on epilepsy course. Lastly, we also did not test or include in our model other predictors of epilepsy surgery outcome that have been identified in previous literature. However, despite their identification as potential predictors, their relative contribution to the accuracy of a predictive model has not been determined. Our study shows that, in fact, a good accuracy may be achieved with simple, although more inclusive, predictors.

Epilepsy surgery may be more or less invasive but there are always potential harms to consider. It is imperative for both doctors and patients to be able to take an informed decision about whether or not to proceed. Predictive models and the development of predictive tools may help epilepsy teams to have a more precise estimate of the seizure outcome after surgery.

Future studies, with bigger samples, should test this model and potentially develop simple tools based on these predictors for clinicians to use in order to predict epilepsy surgery outcome.

CHAPTER VI: Main Findings and Reliability of Questionnaires

SUMMARY OF THE MAIN FINDINGS

STUDY 1

Question 1: *What is the percentage of people with refractory epilepsy that also have a history of any mental disorder?*

Question 2: *What are the most frequent psychiatric disorders in people with refractory epilepsy?*

Question 3: *Are there any epilepsy related factors that may increase the risk for psychiatric disorders?*

Forty-six percent of our sample had at least one previous psychiatric diagnosis, most frequently depressive (64%), anxiety (10%), substance use (10%) and psychotic disorders (6%).

Patients with a right-side epileptogenic zone had an increased risk for these disorders (OR 2.36; CI 1.22-4.56; p=0.01).

STUDY 2

Question 4: *What is the percentage of people with a dysfunctional personality pattern in those with refractory epilepsy?*

Question 5: *Does the affection of different brain lobes contribute to different types of personality disorders?*

Question 6: *Is the epilepsy surgery associated with a reduction on the proportion of people with dysfunctional personality patterns?*

Seventy percent of the participants of the study had a dysfunctional personality pattern before surgery. After surgery, this percentage dropped to 58%. The difference was statistically significant after adjusting for potential confounders (p=0.013).

The most common types were Cluster C personality patterns.

Temporal epileptogenic zone was a significant predictor of higher scores of the Avoidant (Coef. 11.8; CI -0.59 23.7; p=0.051) and Compulsive (Coef. 9.55; CI 2.48 16.6; p=0.008) personality patterns and lower scores of Histrionic (Coef. -11.4; CI -21.2 -1.55; p=0.024) and Antisocial (Coef. -8.4; CI -15.6 -1.25; p=0.022) personality patterns, compared to extratemporal epileptogenic zone.

STUDY 3

Question 7: *What is the percentage of people developing de novo psychiatric disorders after epilepsy surgery?*

Question 8: *Are there any epilepsy or surgery-related factors that could increase the risk for de novo disorders?*

Sixteen people (15%) developed psychiatric disorders that were never identified before surgery. Multilobar epileptogenic zone (p=0.001) and DBS of the anterior nucleus of the thalamus (p=0.003) were found to be significant predictors of these events.

STUDY 4

Question 9: *Considering those who already had some degree of psychiatric symptomatology are there any factors that could predict the worsening or the improvement of their mental symptoms, after surgery?*

Bilateral epileptogenic zone, lack of remission of disabling seizures and Deep Brain Stimulation, targeting the anterior nucleus of the thalamus (ANT-DBS), were the most important predictors of an increase in SCL-90 scores, after surgery.

STUDY 5

Question 10: *Does a lifetime history of any psychiatric disorder predicts worse epileptic seizures control after surgery?*

A lifetime history of any mental disorder was a significant predictor of a higher Engel Class (p=0.017).

STUDY 6

Question 11: *What is the relative importance of having a history of any psychiatric disorder in a predictive model of epilepsy surgery outcome?*

A model including gender, duration of epilepsy, age at the beginning of epilepsy, type of surgery and history of any lifetime psychiatric disorder achieved an area under the ROC curve of 0.81. The most important contributor to the accuracy of the model was a history of any lifetime mental disorder.

RELIABILITY OF QUESTIONNAIRES

We calculated the Cronbach's alpha from both SCL-90 (Table 13) and MCMI-II (Table 14), the two questionnaires used in our studies. This is a widely used an accepted statistical measure that allows the determination of the internal consistency of a test. It measures the pairwise correlations between items. Negative values show that the within-subject variability is higher than between-subject variability. Values from 0.7 to 0.8 show an acceptable internal consistency, from 0.8 to 0.9 it is considered good and above 0.9 the test shows an excellent internal consistency[63,64].

Table 13 – SCL-90 Cronbach's alpha

Personality scales	Cronbach's alfa		Number of items
	Pre-surgery	1-year after surgery	
Somatization	0.87	0.89	12
Obsessive-compulsive	0.86	0.94	10
Interpersonal sensitivity	0.83	0.85	9
Depression	0.88	0.94	13
Anxiety	0.81	0.92	10
Hostility	0.70	0.75	6
Phobic Anxiety	0.80	0.84	7
Paranoid Ideation	0.76	0.81	6
Psychoticism	0.81	0.88	10
Global Severity Index	0.97	0.99	90

Table 14 – MCMI-II Cronbach's alpha

Personality scales	Cronbach's alfa	Number of items
Schizoid	0.99	35
Avoidant	0.99	41
Dependent	0.99	37
Histrionic	0.99	40
Narcissistic	0.99	48
Antisocial	0.99	45
Aggressive	0.99	45
Self-defeating	0.99	40
Schizotypal	0.99	44
Borderline	0.99	62
Paranoid	0.99	43
Compulsive	0.99	38

CHAPTER VII: Discussion and Conclusion

DISCUSSION

The study of mental disorders in PWE began many decades ago, since then there was a sense of connection between these two types of disorders that has yet to be fully determined.
There is an established high prevalence of psychiatric disorders in epilepsy[9] and apparently a higher risk of epilepsy[33] in people with psychiatric disorders.
In this work, we searched for evidence of a bidirectional relationship. Many approaches could be used to study this theme. We opt to divide our work in to two parts; on our first four studies, in order to determine the influence of epilepsy-related features and epilepsy surgery on mental disorders, we focused on the study of the predictors and risk factors for mental disorders in RE people, before and after epilepsy surgery. Then, in our last two studies, we aimed to determine the influence of mental disorders on the course of epilepsy studying them as a potential determinant of the post-surgical course of epilepsy and its role on a predictive model.
In the first study of this thesis we intended to characterize lifetime psychiatric diagnosis identified at the pre-surgical interviews and their epilepsy-related predictors. We found that forty-six percent of our sample had at least one previous psychiatric diagnosis, most frequently depressive (64%), anxiety (10%), substance use (10%) and psychotic disorders (6%). These data are in line with previous literature and reinforce the fact that this is a frequent comorbidity in refractory epilepsy[86]. Moreover, we identified that an epileptogenic zone located on the right cerebral hemisphere doubles the risk for this comorbidity, reinforcing previous literature that points to an important role of the right hemisphere on emotional processing[89].
In study 2, we focused in the personality patterns of patients with RE. For this analysis we used the Millon Clinical Multiaxial Inventory II (MCMI-II) that defines 13 personality profiles. Our objective was to determine if the epileptogenic zone was a predictor of the personality profiles of surgical candidates. Many of the previous studies, focusing the personality patterns in PWE, aimed to determine if there was a distinguished personality profile similar to the one described by Geschwind, using Bear and Fedio questionnaire[7] or other different questionnaires[228,229]. Many also used mixed samples of people with temporal and extratemporal epilepsy[230]. There is a high variability in these studies and a consistent pattern of personality has not been found yet[231].

Our results showed that 70% had a score higher than the cut-off value of 85, in at least one of the personality patterns, meaning that there was a persistence of dysfunctional traits in a high percentage of our sample. The majority of them had a mixed pattern of traits from different personality patterns, most commonly, corresponding to personality types from the Cluster C of the DSM-5.

After surgery, only 58% had a score above the cut-off value, suggesting that the surgery might have some protective effect, possibly due to the reduction of epileptogenic discharges or the removal of dysfunctional brain areas.

Moreover, we showed that surgery candidates have a distinct profile pattern according to their epileptogenic zone. Those with temporal epileptogenic zones had higher scores of two personality patterns corresponding to the DSM cluster C personality patterns – "Avoidant" and "Compulsive" and those with extratemporal epileptogenic zones had higher scores in personality patterns corresponding to cluster B personality patterns – "Histrionic" and "Antisocial". Despite their heterogeneity, some previous data may be in line with these findings. Our extratemporal group was manly constituted by people with a frontal epileptogenic zone that has been associated with impulsivity and antisocial behavior, while the so-called "interictal personality disorder", associated with people with a temporal lobe epileptogenic zone, has some resemblance with the cluster C personality disorders, described in the DSM-5[232–235].

The objective of study 3 was to determine predictors of *de novo* psychiatric syndromes during a follow-up period of 3-years. For this analysis, we used a survival model examining time-to-event and defined the event as being the first major psychiatric syndrome in people without any history of those type of disorders, before surgery.

Our results showed that 15% of our sample developed *de novo* events. This relatively high rate of psychiatric adverse events is superior to the majority of other secondary events[222] and should always be taken into account when discussing the risks of the surgery with patients. The mean time until the first psychiatric event was 13 months and the median was 7 months, showing that there is a highest risk in the first year, after the procedure.

Moreover, we showed that those with a multilobar epileptogenic zone and those submitted to ANT-DBS had a much higher risk of developing new psychiatric disorders and tend to develop them earlier.

Epilepsy surgery is a treatment that has the potential to modify significantly the course of epilepsy and may be even curative. However, an invasive procedure, such as epilepsy surgery, causes some degree of injury inflicted on the normal and functional brain while

dissecting the pathological tissue. This causes at least some transitory neuroinflammation and axotomy[236]. After the procedure, some reorganization of brain cells and circuits probably take place. These processes may cause some degree of distress increasing the risk for post-surgical psychopathology. However, other potential explanations should be considered. Recently, Salpekar(2019), in a paper dedicated to the analysis of our study 3, addresses the difficulties faced by researchers regarding the study of this theme and proposes three mechanisms that may explain *de novo* psychopathology[237]. The first is, as we also stated, that psychiatric disorders may be underreported at the first assessment. The second is that the occurrence of epileptic seizures interrupted by the surgery could have some previous therapeutic effect. For example, in the case of depressive and psychotic symptoms, a phenomenon already discussed by other authors and consistent with the theory of forced normalization. Finally, the possibility that, after the removal of the epileptogenic focus, "depressogenic" tissues may be left untouched. The author also proposes that psychiatric illnesses may be inherent or a constituent part of epilepsy[237]. This suggestion is consistent with our findings.

Our study was the first to include a sample of RE people submitted to RS and ANT-DBS. The use of DBS for the treatment of RE is relatively recent and its risk of psychiatric adverse events, when compared to more conventional methods such as the RS, was not yet clarified. There are some studies showing that there might be some risk of worsening depressive symptoms but results are controversial and generally focused only on mood changes. Fisher et al. (2010) showed that more patients submitted to ANT-DBS report depression, when compared to control subjects, however, they referred that the difference was not reflected in the neuropsychological tests used[238]. Järvenpää et al. (2018) stated that the majority of patients did not had adverse psychiatric events in their group of 22 people submitted to ANT-DBS, however, 2 patients with no previous history developed clear paranoid symptoms after the procedure[239]. In an eleven year follow-up study, 17% of patients developed depression, about 7% had suicidal ideation and 1 patient committed suicide but this was not considered to be "device-related"[240].

Tröster et al. (2017), from the SANTE study group, reported no significant worsening of depression scores during 7 years of follow-up[149]. However, in the same cohort, a rate of 37.3% of depression events was reported and 11.8% had suicidal ideation, at some point, during the first 5-years of follow-up. No other adverse psychiatric events are described[241]. We showed that, in comparison to the more conventional RS, there is an about 7 times higher risk of developing psychiatric disorders, after surgery. In our sample, 40% of those submitted

to DBS developed some major psychiatric disorder that was never identified before surgery, all during the first 6 months after surgery. Showing a higher rate compared to what was previously reported and a considerable risk of psychiatric adverse events, after this type of procedure, when compared to conventional surgery. This difference may be due to the fact that all patients, from our center, are closely followed by psychiatrists while in centers were this is not the rule there might be some degree of underreporting. Other potential reasons may be related to differences in the execution of the technique, modulation parameters or other uncontrolled factors. The fact that most of the samples are small also leads to higher variation among them.

The study 4, lead us to conclude that this neuromodulation technique is not only is a risk factor for *de novo* psychiatric syndromes but is also associated with worst psychopathological scores, measured by SCL-90, a widely used instrument that allows the evaluation of an inclusive group of symptom dimensions. This study focused on the determination of clinical predictors of psychopathological outcomes, one year after surgery. Considering the entire group of patients, no significant differences were found. However, when we did our subgroup analysis, we verified that while some patients improved other specific groups increased their scores. These differences were explained by clinical factors. The most important, with an impact in all symptom dimensions, was Engel Class II when compared to Engel Class I. No significant results were found considering class III and IV probably because of lack of power to detect these differences as very few patients were in these groups.

Although there are very few studies evaluating psychiatric outcomes after RS and even fewer after ANT-DBS, our results are in line with previous data regarding RS and show that patients without seizures remission suffer from higher psychological distress after surgery[158,242]. Some explanatory hypothesis may be considered. An Engel Class II means that the patient continues to have disabling seizures, although, less frequently than before surgery. So, one problem might be the unmet expectations of the patient when they keep having seizures after the procedure, that may lead to feelings of frustration, anxiety and sadness. The first year after surgery is a difficult time as patients have to adapt emotionally and functionally. A good psychosocial outcome is not necessarily dependent just on a good seizure outcome, instead, a “successful” surgery should be a combination of both an acceptable and expected seizure status as well as the individual's perception of improvements in quality of life. The concept of “burden of normality” reflects the idea that a patient might face difficulties while abandoning sick roles and adapting his identity and environment after

the attenuation or cessation of a chronic illness, such as epilepsy[243]. Biological phenomena such as forced normalization[244], continued interictal epileptogenic discharges after the brain surgery, or post-injury neural response cascade, a phenomena that denotes the period of hypometabolism that occurs soon after and persists for a period, after a brain injury[245], may also constitute vulnerability factors for the development or worsening of psychopathological symptoms.

This study also showed that both a multilobar and a bilateral epileptogenic zone were associated with higher scores in many SCL-90 dimensions. Therefore, in patients with an epileptogenic zone that is not confined to a unilateral and single lobe and there is a potentially wider dysfunction of the central nervous system, the removal of a particular brain area may not eliminate the risk and potentially even increase it because of the transitory neuroinflammation and axotomy caused by the surgery.

In the second part of this thesis we focused on the determination of the influence of psychiatric disorders in the course of epilepsy after surgery.

In our fifth study we aimed to determine if a lifetime history of any mental disorder might constitute a predictor of the epilepsy surgery outcome. For this purpose, we included the same cohort from our RE Center and used an ordered logistic regression model. We also included other potential determinants of outcome in our model.

Predictors of higher Engel Class were, as expected, an extratemporal epileptogenic zone, cited by many authors as a predictor of worst outcome[203,225] and ANT-DBS or VNS, considered palliative procedures[224]. More interestingly, a pre-surgical history of mental disorders was a predictor of higher Engel class after surgery, confirming our hypothesis.

Considering the findings from our study 3 and study 4, showing that a potential multilobar or bilateral dysfunction, associated with the epileptogenic zone, lead to a higher risk of psychopathology, after surgery, we may hypothesize that there is a subgroup of patients with a more serious neuropsychiatric disorder, associated with more widespread brain dysfunction. These people may have more psychiatric disorders and worse course of epilepsy leading to a poorer global prognosis. The mechanisms underlying this dysfunction may cause both disorders or can be subsequent to one of them. We may even hypothesize that both conditions are part of the same neuropsychiatric disorder manifesting itself with different symptoms in the course of time.

Then, we developed a sixth study to determine the relative importance of psychiatric disorders as a predictor of epilepsy surgery outcome in a comprehensive model. To access this question predictors of post-surgical Engel Class were included in a multivariate logistic

regression model. Then we tested the accuracy of some predictive models combining different factors potentially associated with the surgery outcome.

The best accuracy model found included gender, duration of epilepsy, age at the beginning of epilepsy, type of surgery and history of any lifetime psychiatric disorder, as predictors. The most important contributor to the accuracy of the model was a history of any lifetime mental disorder. Therefore, this study shows that this is an important contributor to the accuracy of the outcome prediction and, although it should not preclude the surgery, a psychiatric disorder history must be included in the multidisciplinary discussion regarding the potential outcome of epilepsy surgery. According to our knowledge, this was the first study to include mental disorders as a predictor in a predictive model for epilepsy surgery. Furthermore, considering this variable, we were able to develop a model with a much superior accuracy than other recently published models and clinical judgment only[217].

General Limitations

Besides the limitations discussed in each study, we consider that there were some general limitations of our work that we would like to point out.

Firstly, it was based on observational and ambispective studies, with an important retrospective component. The main reason for this was the fact that, at our center, more than a half of the operated people are children which means that less adults would be available to be included in prospective studies. Since we needed a sample considered large enough to test our hypothesis, we decided to use also retrospective data. Different sources of information were reviewed in order to achieve the most complete and accurate data.

Secondly, in our research we used 6 standardized instruments, namely, the Hamilton Anxiety Rating Scale (HARS), the Hamilton Depression Rating Scale (HDRS), the Brief Psychiatric Rating Scale (BPRS), the Symptom Checklist-90 (SCL-90), the Millon Clinical Multiaxial Inventory II (MCMI-II) and The Wechsler Adult Intelligence Scale (WAIS-III). This battery was defined according to the 1st Steering Committee meeting Epilepsy Registry and has been applied to every adult surgery candidate since 1999. Since then, more recent versions of BPRS, SCL-90 and MCMI-II have been developed, however, we decided to keep the same version in order to have a comparable test across all sample. Although they have been widely used to evaluate clinical samples, there isn´t any published validation of these scales and questionnaires and this is an important limitation. There is a scarcity of validated instruments, in Portugal, for the evaluation of psychopathology in medical patients and many of those that have been validated were published after the beginning of the assessments of

this sample. Despite, the lack of validation, both SCL-90 and MCMI-II showed good internal consistency measures as shown in the results section of this thesis.

Thirdly, despite its paramount importance on the development of mental disorders, psychosocial factors were not measured or included in the analysis. However, we believe that the amount of personal, family and social burden is probably equally distributed in the sample. Also, despite the fact that, in the initial protocol, there was a questionnaire that should evaluate quality of life it was not included in our studies because of incompleteness and lack of data. Future studies should definitely include these types of variables.

Finally, another limitation was that some subgroups had few patients limiting the power to detect differences in some studies.

General Strengths and Scientific Interest

The most important strengths of our work were that it was based on a Portuguese clinical sample, collected in the setting of usual medical care, in a Reference Center for the treatment of RE. It also comprised a broad sample constituted by surgical candidates with distinct clinical characteristics and submitted to different types of surgical interventions, adequately controlled, allowing for the transposition of these results to clinical practice.

We used adequate methods and new analytic approaches to explore new questions or poorly investigated ones.

We also showed innovative results that may have clinical implications and contributed to the clarification of some previously investigated but still controversial questions. In general, our results showed evidence to support the bidirectional relationship between refractory epilepsy and mental disorders according to our initial objective. We showed that there is an increased risk of psychiatric disorders when the right hemisphere is affected and the distinctive patterns of personality according to the epileptogenic zone. We also identified that a more widespread brain dysfunction contributes to psychopathology, as well as, continued disabling seizures, after surgery. Moreover, we demonstrated that ANT-DBS is not as benign, from the psychopathological point of view, as it seemed in the first studies reporting the use of this technique. Rather it has an important risk of *de novo* psychiatric syndromes and worsening of previous psychopathology, including not only depression but also psychotic and manic syndromes. Finally, we showed the need to include lifetime psychiatric history as a predictor of surgery outcome

We believe that our results appeal to the interest of psychiatrists, neurologists and neurosurgeons and more importantly may help to improve the care of people with RE.
We also believe that this research could add information to the current knowledge of the neurobiological basis of psychiatric disorders.

CONCLUSION

The work presented in this thesis follows a coherent line of research in order to clarify the bidirectional relationship between mental disorders and refractory epilepsy.

Some main conclusions may be drawn from our study. Firstly, there is a high prevalence of psychiatric disorders in people with refractory epilepsy and the right-sided epileptogenic zone seems to be a risk factor. Secondly, the lobe where the epileptogenic zone is located does have an influence on dysfunctional personality patterns of patients with ER and that surgery might have a positive impact on the improvement of these patterns. Thirdly, ANT-DBS and a multilobar epileptogenic zone increase the risk of worsening of previous psychopathology, regarding certain symptom dimensions and *de novo* psychiatric syndromes. Fourthly, people with bilateral epileptogenic zones and those with Engel class II, in comparison to class I, suffer from higher psychological distress after surgery. These patients should be warned about these potential secondary effects and should also benefit from more frequent routine assessments.

Fifthly, a history of any mental disorder is an important determinant of the success of surgery regarding the control of epileptic seizures and should be considered as an epilepsy surgery outcome predictor. Although mental disorders are not considered to constitute contraindications for surgery, we suggest that when deciding to proceed for surgery this variable should be taken in account.

Overall these findings support the idea of a bidirectional relationship between psychiatry and refractory epilepsy and reinforces the need of the presence of psychiatrists in centers were RE patients are treated. Unfortunately, this is not the rule for many centers in the developed countries[14].

Future studies should include more robust samples to confirm our results. They should should focus in all kinds of psychiatric events and the aggravation of psychopathological symptoms after epilepsy surgery, and particularly, ANT-DBS and in the treatment options for these patients. The clarification of the hypothesis of a subgroup of patients with a more generalized dysfunction and a more serious neuropsychiatric disorders, as well as, the mechanisms underlying this potential syndrome should also be approached by forthcoming research.

CONTRIBUTION OF THE CANDIDATE TO THE RESULTS OF THIS WORK

The candidate was responsible for:

- Evaluation and application of questionnaires and scales in part of the sample
- Collection of all clinical data and building databases
- Definition of all clinical hypothesis
- Design of each study
- Statistical analysis of all data
- Writing first manuscript drafts of all papers

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