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Interictal psychiatric comorbidities of drug-resistant focal epilepsy: Prevalence and influence of the localization of the epilepsy

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ABSTRACT

Psychiatric comorbidities are 2 to 3 times more frequent in patients with epilepsy than in the general population. This study aimed to prospectively assess the following: (i) the prevalence of specific and nonspecific interictal psychiatric comorbidities in a population of patients with drug-resistant focal epilepsy and (ii) the influence of epilepsy lateralization and localization on these psychiatric comorbidities.

In this prospective monocentric study, we collected demographic data, characteristics of the epilepsy, interictal psychiatric comorbidities, mood, anxiety, and alexithymia dimensions. We used criteria from Diagnostic and Statistical Manual of Mental Disorders IV (DSM IV) (Mini International Mental Interview (MINI)), diagnosis criteria for specific comorbidities, and validated mood and anxiety scales (general and specific for epilepsy).

Among the 87 enrolled patients (39 males, 48 females), 52.9% had at least one psychiatric comorbidity. The most common comorbidity was anxiety disorder (28.7% according to the MINI, and 38.4% screening by the Generalized Anxiety Disorder 7 (GAD 7)). Mood disorders were the second most frequent psychiatric comorbidity: 21.8% of our patients had interictal dysphoric disorders (IDDs), 16.1% presented major depressive disorders according to the MINI, and 17.2% screening by the Neurological Disorders Depression Inventory for Epilepsy (NDDIE).

Patients with temporal lobe epilepsy had a higher prevalence of psychiatric comorbidities than patients with extratemporal lobe epilepsy ($p = 0.002$), which is probably related to a higher rate of anxiety disorders in this subgroup ($p = 0.012$). Prevalence of psychiatric disorders prior to epilepsy in patients was higher in right- than in left-sided epilepsy ($p = 0.042$). No difference was found according to limbic involvement at seizure onset.

Overall, this article highlighted a very high proportion of anxiety disorders in these patients with drug-resistant focal epilepsy and the necessity to systematically detect them and thus lead to a specific treatment.

1. Introduction

Lifetime prevalence of psychiatric disorders has been reported in 30 to 80% of patients with drug-resistant focal epilepsy. Many recent epidemiological studies have shown that the prevalence of depression, anxiety, and psychotic disorders was higher in patients with epilepsy than in the general population [1]. Several studies have focused on limited aspects of these various comorbidities, overlooking specific comorbidities such as interictal mood disorders, isolated feelings of persecution, anticipatory anxiety of seizures, or even additional nonspecific comorbidities such as eating behavior disorder [2]. Nonspecific psychiatric disorders can affect everyone whereas specific disorders only affect patients with epilepsy. In addition, many studies have used diagnostic criteria from the international classifications of psychiatric diseases ICD-10 [3] and DSM-IV while numerous disabling psychiatric symptoms reported by patients are often atypical and specific to epilepsy and do not meet the usual criteria of standard classifications [4]. Epilepsy-specific clinical criteria have been recently proposed [5] and validated for rapid detection of depression (e.g., Neurological Disorders Depression Inventory for Epilepsy (NDDIE)) and of anxiety disorder (e.g., Generalized Anxiety Disorder 7 (GAD 7)). Moreover, psychiatric disorders specific to epilepsy such as interictal dysphoric disorder (IDD) have been recently emphasized by the International League Against Epilepsy

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(ILAE) classification of neuropsychiatric disorders of epilepsy [6] according to Blumer's criteria.

These psychiatric comorbidities specifically associated with epilepsy are highly underdiagnosed and thus obviously inadequately treated. They may worsen the course of epilepsy itself, the social exclusion related to the seizures, and the quality of life [7]. Moreover, in active epilepsies, the presence of a depressive syndrome is a stronger predictor of impaired quality of life than the frequency of epileptic seizures [8].

The purpose of this study was to describe the demographic data, the characteristics of epilepsy, and the prevalence of nonspecific and epilepsy-specific psychiatric comorbidities in a population of patients with drug-resistant focal structural epilepsy in the clinical setting of presurgical evaluation.

The secondary objectives were to compare the prevalence and the nature of psychiatric disorders in patients with drug-resistant focal epilepsy in terms of epilepsy lateralization and localization (temporal lobe vs. extratemporal lobe, limbic vs. extralimbic).

The methodology of this current prospective study was unique because of the extensive and comprehensive psychiatric evaluations performed by experienced psychiatrists in a tertiary center for epilepsy.

Our working hypothesis were the following: (i) the prevalence of psychiatric comorbidity was different according to the used diagnostic tool (specific vs. nonspecific international criteria) [9]; (ii) psychiatric comorbidities were more common in patients with temporal lobe epilepsy and in those with limbic epilepsy, and (iii) the prevalence of psychiatric comorbidity was different according to the lateralization of epilepsy.

2. Methods

This epidemiological, observational, and prospective monocentric study collected data from the systematic psychiatric evaluation of patients with drug-resistant focal epilepsy, hospitalized from February 2016 to May 2017 in the epileptology department of Nancy University Hospital for presurgical work-up.

2.1. Inclusion criteria

All consecutive patients undergoing a presurgical work-up in the epileptology unit of the Nancy University Hospital between February 2016 and May 2017 and meeting the following inclusion criteria were proposed to participate:

- Confirmed drug-refractory focal epilepsy diagnosis with video-electroencephalography (video-EEG) recorded seizures, magnetic resonance imaging (MRI), and fluorodeoxyglucose (FDG)-positron emission tomography (PET) (according to the criteria of the ILAE [10]),
- Age 18 years or older,
- French as their native language, and
- Ability to give their consent for the study.

All patients had medically intractable focal or multifocal structural epilepsy and were evaluated indeed in the setting of an epilepsy monitoring unit. However, not all patients proceeded to epilepsy surgery.

2.2. Clinical evaluation and data collection

The methodology was designed to comprehensively evaluate nonspecific psychiatric disorders and psychiatric disorders specific to epilepsy, with heteroevaluation and self-assessment tools. This methodology is part of our clinical evaluation protocol, including systematic psychiatric assessment of hospitalized patients with drug-resistant focal epilepsy. In this study, the data were collected prospectively.

Sociodemographic data including way of life, education, and activity were collected.

2.3. Seizure data

Seizure-related variables including seizure frequency and duration, medical history of head injury, febrile seizures, and febrile encephalopathy were recorded and documented by epileptologists. Signs of clinical severity of seizures were sought: cranial trauma, loss of consciousness, tongue biting, or loss of urine during seizures.

Lateralization and localization of seizure foci were based on the recorded seizures during long-term video-EEG monitoring and imagery in all patients and additional video-stereoelectroencephalography (video-SEEG) in 54 out of 87. Seizures were classified as follows: temporal lobe/extratemporal lobe, right/left/bilateral, and limbic/extralimbic based on anatomoelectroclinical correlations. Limbic seizures were defined as seizures with a clear medial temporal lobe onset, either proven on SEEG recordings or on converging findings from phase 1 presurgical work-up: history of childhood febrile seizures, hippocampal sclerosis, exceptional secondary generalization, typical medial temporal lobe seizure semiology involving viscerosensitive symptoms, dreamy-state or déjà-vu, warning, delayed loss of contact, delayed oroalimentary and gestural automatisms, and duration of seizures >1 min [11].

We also collected data about ongoing antiepileptic treatment and reported those with a potentially negative psychotropic effect: levetiracetam, vigabatrin, perampanel, stiripentol, tiagabine, ethosuximide, felbamate, zonisamide, phenobarbital, phenytoin, and topiramate.

2.4. Psychiatric data

Psychiatric disorders were evaluated by 2 psychiatrists with experience in specific epileptic disorders in three dimensions:

- Nonspecific psychiatric disorders evaluated by nonspecific tools,
- Nonspecific psychiatric disorders evaluated by a tool specially validated in population with epilepsy, and
- Specific epilepsy psychiatric disorders.

The chronology of early psychiatric disorders related to the onset of epileptic illness was sought.

2.4.1. Nonspecific psychiatric disorders evaluated by nonspecific tools

Patients were assessed with a structured clinical interview based on the Mini International Neuropsychiatric Interview (MINI) [12] completed with symptom-rating scales that has been validated for clinical use as well as research. For anxiety, state–trait anxiety scale: state (STAI A) and state–trait anxiety scale: traits (STAI B) were used. The STAI A is particularly used to control the level of anxiety at the moment of evaluation and is not a diagnostic instrument. For mood evaluation and depression, heteroscale Beck 21 was used.

Addiction, habit, and eating disorder are explored in detail by the MINI DSM-IV. We add also the search for binge eating disorder according to the criteria from DSM-5.

The presence or absence of diagnosed family psychopathology and past history of psychiatric illness was also recorded.

2.4.2. Nonspecific psychiatric disorders evaluated by a tool specially validated in population with epilepsy

Patients passed specific scales, which include the NDDIE [13]. The NDDIE was developed to evaluate the major depressive disorder (as defined in the DSM-IV) while taking into account the confounding variables in patients with epilepsy, in particular, AED effect and cognitive deficit.

The GAD 7 [14] was used. It evaluates the generalized anxiety disorder according to the DSM-IV and has been validated in patients with epilepsy.

The NDDIE and GAD 7 have been validated as highly sensitive and specific screening tools.

2.4.3. Specific interictal psychiatric comorbidities (no direct chronological relation with the seizure)

These comorbidities were systematically investigated and measured [6]: interictal dysphoria (Blumer syndrome), anticipatory anxiety, situations avoided, and intensity of a nonspecific persecution experience.

Interictal dysphoric disorder (according to Blumer's criteria) can be defined as follows: at least three episodes of a few hours to a few days, grouping together at least three criteria among the following eight: depressed mood, asthenia, atypical pain, insomnia, fear and anxiety, irritability, euphoric mood, and instability of mood.

Anticipatory anxiety was defined as the agonizing fear of seizure. Situations avoided were defined as an activity avoided (social, sports, or daily activity) by the patient because of fear of a seizure. Nonspecific persecution experience was a feeling of persecution criticized and isolated, i.e., without other psychotic elements (disorganization, hallucinations, other delusions, mental automatism) by the patient.

We finally assessed iatrogenic mental health and behavioral disturbances with antiepileptic drug (AED).

2.5. Statistical analyses

We compared demographic data, seizure data, and psychiatric data according to the lateralization and localization of seizure focus (left vs. right; temporal lobe vs. extratemporal lobe) and according to limbic involvement (limbic vs. extralimbic).

Binary variables were analyzed using chi-squared test, and quantitative variables were analyzed using Student's *t*-test with Statistica 10. A p value of less than 0.05 was considered statistically significant.

3. Results

3.1. Overall description of the population studied

3.1.1. Demographic data

Of the 87 patients in the cohort, 39 (44.8%) were men. Sex ratio was 0.8.

The mean age at inclusion was 34.3 years (range: 18–62 years; standard deviation: 11.9).

Fifty-five point two percent lived with a partner, 24.1% lived alone, and 20.7% lived with their parents or in institutions. Forty-one point four percent had one or more children. Thirty-five point six percent drove a car regularly. Fifty-eight point six percent had a professional activity or are students while 41.4% of them do not work. Only 12.6% were on sick leave at the time of inclusion. In the cohort, 31% of the patients received state financial assistance.

3.1.2. Characteristics of epilepsy

The average duration of evolution of epilepsy was 18.5 years (standard deviation: 15.8). In 43.7% of the patients, cerebral MRI revealed an epileptogenic lesion. Ninety-seven point seven percent of our patients were taking AED, and 88.5% had at least one AE molecule with a known negative psychotropic effect. The included patients take an average of 2.2 AEDs.

In our study population, 46% had a right-sided epilepsy, 43.7% had a left-sided epilepsy, and 10.3% had a bilateral epilepsy or an unknown epilepsy lateralization. Seventy-two point four percent had temporal lobe epilepsy versus 26.5% with extratemporal lobe epilepsy; 1.1% of our patients had multifocal epilepsy and did not fall into the temporal lobe or extratemporal lobe category. Finally, 48.3% had limbic epilepsy (Table 1).

Table 1
Characteristics of epilepsy.

Evolution time of epilepsy (average (standard deviation))	18.5 (15.8)
Secondarily generalized seizures % (N)	39% (34)
MRI lesions % (N)	43.7% (38)
Antiepileptic drugs % (N)	97.7% (85)
At least one antiepileptic drug with potential negative psychotropic effect % (N)	88.5% (77)
Right-sided epilepsy % (N)	46.0% (40)
Left-sided epilepsy % (N)	43.7% (38)
Bilateral or nonlateralized epileptogenic focus % (N)	10.3% (9)
Temporal lobe epilepsy % (N)	72.4% (63)
Extratemporal lobe epilepsy % (N)	26.5% (23)
Limbic epilepsy % (N)	48.3% (42)
Extralimbic (%) (N)	51.7% (45)

N = number of patient.

3.1.3. Interictal psychiatric disorders

Data are summarized in Table 2.

Fifty-five point two percent had an ongoing or previous psychiatric follow-up, 16.1% had already been hospitalized in the psychiatric department, and 14.9% had attempted suicide at least once.

Sixty point nine percent of our patients had at least one psychiatric history, and 52.9% had an ongoing psychiatric disorder at the time of inclusion.

Forty-two point five percent had a history of psychotraumatism.

The psychiatric disorder preceded the onset of epilepsy in 31% of our patients, and in 58.6%, a psychiatric disorder appeared after epilepsy onset.

3.1.3.1. Mood disorders.

- *Mood disorders evaluated by nonspecific tools.* The MINI revealed that mood disorders (44.8%) represented the most frequent psychiatric history in our cohort but was ongoing in only 16.1% of our patients at the time of evaluation. The results of the Beck 21 confirmed this result: 14.9% had a positive result on this self-questionnaire.
  At the time of evaluation, 17.2% of the patients received antidepressant treatment.
- *Mood disorders screened by a specific tool.* Seventeen point two percent of our patients had a positive NDDIE.
- *Specific mood disorders*. At the time of evaluation, an ongoing IDD was present in 21.8% of our population.
- *Drug-induced mood disorders.* In the cohort, 17.2% had a previous or ongoing drug-induced mood disorder.

3.1.3.2. Anxiety disorders

- *Anxiety disorders evaluated by nonspecific tools.* The MINI revealed that anxiety disorders represented the most frequent psychiatric comorbidity at evaluation: 28.7%. This was confirmed by the results of STAI A (anxiety state) positive in 10.8% of the patients and STAI B (anxiety traits) positive in 18.9% of the patients.
  At that time, only 10.3% of the patients received antianxiety medication.
- *Anxiety disorders screened by tool validated in population with epilepsy.* In our patients, 38.4% had a positive result in GAD 7.
- *Specific anxiety disorders.* Fifty-two point nine percent of the patients had an anticipatory anxiety.
  There was at least one situation avoidance in 39.1% of the patients.
- *Drug-induced anxiety disorders.* There was a drug-induced anxiety disorder in 2.3% of the patients.

3.1.3.3. Psychotic disorders

- *Psychotic disorders evaluated by a nonspecific tool.* The MINI found an ongoing psychotic disorder in 8% of our patients, as well as a history of psychotic disorder in 5.7% of the patients. At the time

Table 2
Interictal psychiatric disorders in drug-resistant focal epilepsy.

Classification of interictal psychiatric disorders	Subcategories	Type		
		Mood disorders % (N)	Anxiety disorders % (N)	Psychotic disorders % (N)
Nonspecific disorder	According to DSM-IV criteria with MINI And nonspecific scales (Beck 21, STAIs A and B)	Major depressive disorder: 12.6% (11) Depression according to a positive score in the Beck 21 scale: 14.9% (13)	Generalized anxiety disorder: 10.3% (9) Obsessive–compulsive disorder: 2.3% (2) Panic disorder without agoraphobia: 12.6% (11) Agoraphobia without history of panic disorder: 6.9% (6) Social phobia: 1.1% (1) Posttraumatic stress disorder: 3.4% (3) Anxiety state evaluated by a positive score in the STAI A: 10.8% (9) Anxiety trait evaluated by a positive score in the STAI B: 18.9% (16)	Psychotic disorders: 8% (7)
	According to specific tool or tool validated in epilepsy	Depression according to a positive score in the NDDIE scale: 17.2% (15)	General anxiety according to a positive score in the scale GAD 7 scale: 38.4% (33)	
Specific disorder		Interictal dysphoric disorder: 21.8% (19)	Anticipatory anxiety: 52.9% (46) At least one avoidance for fear of a seizure: 39.1% (34)	Isolated feeling of persecution: 11.5% (10)
Iatrogenic	Antiepileptic drug-induced	AED-induced mood disorder: 17.2% (15)	AED-induced anxiety symptoms or nervousness or symptoms of increased arousal: 2.3% (2)	AED-induced psychotic disorder: 4.6% (4)

MINI (Mini International Neuropsychiatric Interview); STAI (state trait anxiety scale); NDDIE (Neurological Disorders Depression Inventory for Epilepsy); GAD 7 (Generalized Anxiety Disorder 7); N = number of patient.

of inclusion, 4.6% of the patients were treated with an antipsychotic medication.

- *Specific psychotic disorders.* In the cohort, 11.5% of the patients had an isolated feeling of persecution. In these patients, the average intensity of the feeling of persecution was 7 (1.6)/10.
- *Drug-induced psychotic disorders.* A drug-induced psychotic disorder affected 4.6% of the patients in the cohort.

3.1.3.4. Addictions and eating disorders

At the time of the evaluation, 28.7% had at least one addiction found in the MINI. The eating disorders at inclusion were present in 1.1% of the study population.

3.2. Interactions between epilepsy lateralization and interictal psychiatric comorbidities

Nine patients had bilateral epilepsy or unknown epilepsy lateralization and were not included in the statistical analyses comparing the effect of right or left epilepsy lateralization.

Forty patients had a right lateralized epilepsy, and 38 had a left lateralized epilepsy.

The groups with left- and right-sided epilepsy did not significantly differ in terms of age at epilepsy onset (respectively 17.6 (13.2) vs. 16 (10.3); $p = 0.552$), mean duration of epilepsy (respectively 15.8 (12.7) vs. 18 (12.9); $p = 0.467$), neurological history (history of cranial trauma, for example, 15% vs. 13.2%; $p = 0.815$), and signs of clinical severity of seizures.

Data are summarized in Table 3.

3.2.1. Psychiatric history

With respect to psychiatric data, the groups with left- and right-sided epilepsy did not differ in terms of previous psychiatric follow-up (respectively 52.5% vs. 60.5%; $p = 0.475$), previous hospitalization in psychiatric department (respectively 10% vs. 23.7%; $p = 0.105$), presence of at least one ongoing psychiatric disorder in the MINI (respectively 52.5% vs. 52.6%; $p = 0.991$), psychiatric history in the MINI (respectively 57.5% vs. 68.4%; $p = 0.318$), psychiatric family history (respectively 32.5% vs. 36.8%; $p = 0.921$), and of personal history of a suicide attempt (respectively 15% vs. 13.2%; $p = 0.577$).

However, patients with right-sided epilepsy had a significantly more frequent history of psychiatric disorder prior to epilepsy onset (respectively 42.5% vs. 21.1%; $p = 0.042$). There was no significant difference between these two groups for psychiatric disorders that appeared after the onset of epilepsy (respectively 52.5% vs. 71.1%; $p = 0.092$).

3.2.2. Mood disorders

- *Mood disorders evaluated by nonspecific tools*. The groups with left- and right-sided epilepsy did not differ in terms of mood disorders defined as the existence of at least one current mood disorder in the MINI (respectively 7.5% vs. 18.4%; $p = 0.149$) or at least one

Table 3
Comparison of the prevalence of mood disorders according to lateralization of epilepsy.

	Epilepsy on the right N = 40% (N)	Epileptogenic focus on the left N = 38% (N)	p
Major depressive disorder	5% (2)	18.4% (7)	0.064
Existence of at least one mood disorder in the MINI	35% (14)	55.3% (21)	0.072
Interictal dysphoric disorder	22.5% (9)	18.4% (7)	0.656
Depression according to a positive score in the Beck 21 scale	17.7% (7)	18.8% (7)	0.908
Depression screened by a positive score in the NDDIE scale	20.6% (8)	24.1% (9)	0.735
Bipolar disorder	0	0	
Drug-induced mood disorder	10% (4)	21.1% (8)	0.176

MINI (Mini International Neuropsychiatric Interview); NDDIE (Neurological Disorders Depression Inventory for Epilepsy); GAD 7 (Generalized Anxiety Disorder 7); N = number of patient.

history of mood disorder in the MINI (respectively 35% vs. 55.3%; p = 0.072), or Beck 21 positive (respectively 17.7% vs. 18.8%; p = 0.908).
They did not differ in terms of antidepressant therapy at the time of evaluation (respectively 12.5% vs. 21.1%; p = 0.311).
Major depressive disorder tended to be more frequent in patients with left-sided epilepsy compared with patients with right-sided epilepsy (respectively 5% vs. 18.4%; p = 0.064).

- *Mood disorders screened by a specific tool.* The groups with left- and right-sided epilepsy did not differ in the NDDIE results (respectively 20.6% vs. 24.1%; p = 0.735).
- *Specific mood disorders.* The groups with left- and right-sided epilepsy did not differ in terms of IDD (respectively 22.5% vs. 18.4%; p = 0.656).
- *Drug-induced mood disorders.* The groups with left- and right-sided epilepsy did not differ in terms of drug-induced mood disorders (respectively 10% vs. 21.1%; p = 0.176).

3.2.3. Anxiety disorders

- *Anxiety disorders evaluated by nonspecific tools.* The patients with left- and right-sided epilepsy did not differ in terms of the presence of at least one current anxiety disorder in the MINI (respectively 32.5% vs. 28.9%; p = 0.734), at least one history of anxiety disorder in the MINI (respectively 32.5% vs. 18.4%; p = 0.155), as well as in terms of the results of STAI A (respectively 8.8% vs. 12.5%; p = 0.628) and STAI B (respectively 20.6% vs. 15.6%; p = 0.601). The groups did not differ either in terms of ongoing anxiolytic treatment at inclusion (respectively 7.5 vs. 10.5; p = 0.640).
- *Anxiety disorders screened by tool validated in population with epilepsy.* The groups with left- and right-sided epilepsy did not differ in terms of depression according to a positive score in the GAD 7 scale (respectively 37.2% vs. 40%; p = 0.903).
- *Specific anxiety disorders.* There is no difference in terms of anticipatory anxiety (respectively 47.5% vs. 44.7%; p = 0.807) neither for avoidance resulting from anxiety (respectively 45% vs. 47.4%; p = 0.834).
- *Drug-induced anxiety disorders.* Similarly, the two groups did not differ according to the existence of drug-induced anxiety disorder (respectively 0% vs. 2.6%; p = 0.302).

3.2.4. Psychotic disorders

- *Psychotic disorders evaluated by a nonspecific tool.* The groups with left- and right-sided epilepsy did not differ in terms of psychotic histories in the MINI (respectively 5% vs. 7.9%; p = 0.602) and current psychotic symptoms such as the presence of hallucinations (respectively 0% vs. 2.6%; p = 0.302) or psychic disorganization.
  The two groups did not differ in terms of ongoing antipsychotic treatment (respectively 5% vs. 5.3% p = 0.958).
- *Specific psychotic disorders.* The two groups did not differ in terms of the presence of an isolated feeling of persecution (respectively 12.5% vs. 7.9%; p = 0.503).
  However, the intensity of this feeling quantified on an imaginary scale graduated from 0 to 10 (0 being the absence of persecution feeling and the most intense persecution feeling possible) is significantly higher in patients with left-sided epilepsy (p = 0.012). Indeed, the intensity of the persecution experience was, on average, 7.8 (0.8)/10 for patients with left-sided epilepsy compared with 5.8 (1.1)/10 for patients with right-sided epilepsy (p = 0.012).
- *Drug-induced psychotic disorders.* The two groups did not differ in terms of drug-induced psychosis (respectively 2.5% vs. 7.9%; p = 0.280).

3.2.5. Addictions and eating disorders

The groups with left- and right-sided epilepsy did not differ in terms of addictive or dietary behaviors.

3.3. Interaction between epilepsy localization (temporal lobe vs. extratemporal lobe) and interictal psychiatric comorbidities

Sixty-three patients had temporal lobe epilepsy, and 23 had extratemporal lobe epilepsy. One patient with multifocal epilepsy was excluded from statistics concerning this lobar location of epilepsy.

Patients with extratemporal lobe epilepsy were significantly younger than patients with temporal lobe epilepsy (respectively 27.7 vs. 36.5 years; p = 0.002). The groups with temporal lobe epilepsy and extratemporal lobe epilepsy did not differ in terms of disease duration (respectively 20.3 (SD: 16.8) vs. 13.7 (SD: 12.6); p = 0.089), perinatal neurological history (respectively 7.9% vs. 0%; p = 0.164), or the presence of a MRI-visible epileptogenic lesion (respectively 38.1% vs. 60.1%; p = 0.169).

Nevertheless, patients with extratemporal lobe epilepsy took significantly more AEDs than patients with temporal lobe epilepsy (respectively 2.1 (SD: 0.9) vs. 2.6 (SD: 0.8); p = 0.012) (Table 4).

3.3.1. Psychiatric history

A history of psychiatric follow-up was more frequent in patients with temporal lobe epilepsy than patients with extratemporal lobe epilepsy (respectively 63.5% vs. 30.4; p = 0.006). The existence of at least one psychiatric disorder after the onset of epilepsy was significantly higher in the group with temporal lobe epilepsy than in the group with extratemporal lobe epilepsy (respectively 69.8% vs. 34.8%; p = 0.002) as well as the existence of at least one psychiatric history in the MINI (respectively 69.8% vs. 30.4%; p = 0.003), of an ongoing psychotropic treatments at inclusion (respectively 25.4% vs. 4.3%; p = 0.014), and number of ongoing psychotropic treatments (respectively 0.37 (0.7) vs. 0.04 (0.2); p = 0.040).

3.3.2. Mood disorders

- *Mood disorders evaluated by nonspecific tools.* The two groups did not differ in terms of the presence of a current mood disorder in the MINI (respectively 15.9% vs. 13%; p = 0.746) and of depression according to a positive score in the Beck 21 scale (respectively 18.8% vs. 10%; p = 0.623).
- *Mood disorders screened by a specific tool.* The groups with temporal lobe epilepsy and extratemporal lobe epilepsy did not differ in terms of depression according to a positive score in the NDDIE scale (respectively 27.5% vs. 5.3%; p = 0.113).
- *Specific mood disorders.* For IDD (respectively 25.4 vs. 8.7; p = 0.092), there is no difference.
- *Drug-induced mood disorders.* The two groups did not differ in terms of the presence of a drug-induced mood disorder (respectively 14.3% vs. 21.7%; p = 0.407).

3.3.3. Anxiety disorders

- *Anxiety disorders evaluated by nonspecific tools.* A current anxiety disorder according to the MINI (respectively 36.5% vs. 8.7%; p = 0.012), a history of anxiety disorder in the MINI (respectively 30.2% vs. 8.7%; p = 0.040), as well as a positive result in STAI A (respectively 11.3% vs. 5%; p = 0.011) were more frequent in the group with temporal lobe epilepsy.
- *Anxiety disorders screened by tool validated in population with epilepsy.* The groups with temporal lobe epilepsy and extratemporal lobe epilepsy did not differ in terms of anxiety generalized according to a positive score in the GAD 7 scale (respectively 36.5% vs. 17.4%; p = 0.139).

Table 4
Comparison of interictal psychiatric disorders according to localization of epilepsy.

		Temporal N = 63% (N)	Extratemporal N = 23% (N)	p
Mood disorders	Existence of at least one current mood disorder in the MINI	15.9% (10)	13% (3)	0.746
Anxiety disorders	Existence of at least one current anxiety disorder in the MINI	36.5% (23)	8.7% (2)	**0.012**
	Existence of at least one history of anxiety disorder in the MINI	30.2% (19)	8.7% (2)	**0.040**
	Anxiety state evaluated by a positive score in STAI A	11.3% (7)	5% (1)	**0.011**
	Anxiety trait evaluated by a positive score in STAI B	20.8% (13)	10% (2)	0.065
	General anxiety according to a positive score in the GAD 7 scale	44.2% (28)	20% (5)	0.139
Psychotic disorders	Existence of at least one current psychotic disorder in the MINI	9.5% (6)	4.3% (1)	0.437

MINI (Mini International Neuropsychiatric Interview); STAI (state trait anxiety scale); N: number of patient. Bold values indicates significance at $p < 0.05$.

- *Specific anxiety disorder.* There was no difference for anticipatory anxiety (respectively 54% vs. 47.8%; $p = 0.614$) and avoidance resulting from anxiety (temporal: 55.6% vs. extratemporal: 47.8% $p = 0.525$).
- *Drug-induced anxiety disorders.* The two groups did not differ concerning the existence of a drug-induced anxiety disorder (respectively 3.2% vs. 0%; $p = 0.387$).

3.3.4. Psychotic disorders

- *Psychotic disorders evaluated by a nonspecific tool.* The groups with temporal lobe epilepsy and extratemporal lobe epilepsy did not differ in terms of the existence of at least one current psychotic disorder in the MINI (respectively 9.5% vs. 4.3%; $p = 0.437$), of the existence of at least one antecedent psychotic in the MINI (respectively 7.9% vs. 0%; $p = 0.164$), and of antipsychotic treatment (respectively 6.3% vs. 0%; $p = 0.216$).
- *Specific psychotic disorders.* The two groups did not differ in terms of the existence of a feeling of patient persecution (respectively 9.5% vs. 4.3%; $p = 0.203$) and the intensity of persecution (respectively 7.1 (SD: 1.5) vs. 7 (SD: 0); $p = 0.955$).
- *Drug-induced psychotic disorders.* The two groups did not differ regarding drug-induced psychotic disorders (respectively 4.8% vs. 4.3%; $p = 0.936$).

3.3.5. Addictions and eating disorder

Groups with temporal lobe epilepsy and extratemporal lobe epilepsy did not differ in terms of addictions and eating disorders.

3.4. Effect of limbic vs. extralimbic epilepsy localization

Forty-two out of 87 patients had a limbic epilepsy.

Patients in the group with limbic epilepsy were significantly older than those in the group with extralimbic epilepsy (respectively 36.6 vs. 31.5 years old in average; $p = 0.044$). Patients from the group with limbic epilepsy had a significantly longer duration of epilepsy (respectively 21.1 (14.4) vs. 13.9 (10.9); $p = 0.011$) and a more frequent history of febrile seizures (respectively 21.7% vs. 5.1%; $p = 0.007$). Regarding the other characteristics of epilepsy, they did not differ from the group with extralimbic epilepsy.

Patients with limbic epilepsy took significantly less antiepileptic treatments with known negative psychotropic effects (respectively 1.29 (SD: 0.72) vs. 1.57 (SD: 0.95); $p = 0.044$) (Table 5).

3.4.1. Psychiatric history

Groups with limbic and extralimbic epilepsy did not differ in terms of the presence of at least one psychiatric history in the MINI (respectively 64.6% vs. 56.4%; $p = 0.437$), at least one current psychiatric pathology in the MINI (respectively 51.2% vs. 53.8%; $p = 0.870$), and psychiatric disorders before the onset of epilepsy (respectively 29.2% vs. 33.3%; $p = 0.676$) and after the onset of epilepsy (respectively 64.6% vs. 51.3%; $p = 0.210$).

3.4.2. Mood disorders

- *Mood disorders evaluated by nonspecific tools.* Groups with limbic and extralimbic epilepsy did not differ in terms of mood disorders data evaluated in the MINI and depression according to a positive score in the Beck 21 scale (respectively 19.4% vs. 15.8%; $p = 0.680$).
- *Mood disorders screened by a specific tool.* There is no difference in depression according to a positive score in the NDDIE scale (respectively 29.4% vs. 13.5%; $p = 0.101$).
- *Specific mood disorders.* The two groups did not differ in terms of IDD (respectively 29.1% vs. 12.8%; $p = 0.066$).
- *Drug-induced mood disorders.* Groups with limbic and extralimbic epilepsy did not differ in terms of drug-induced mood disorders (respectively 18.5% vs. 15.4%; $p = 0.679$).

3.4.3. Anxiety disorders

- *Anxiety disorders evaluated by nonspecific tools.* Groups with limbic and extralimbic epilepsy did not differ in terms of the existence of

Table 5
Comparison of interictal psychiatric disorders according to limbic involvement of epilepsy.

		Limbic N = 42% (N)	Extralimbic N = 45% (N)	p
Psychiatric disorder	History of psychological follow-up	52.1% (22)	58.9% (27)	0.520
	Existence of at least one psychiatric disorder before onset of epilepsy	29.2% (12)	33.3% (15)	0.676
	Existence of at least one current psychiatric disorder in the MINI	52.1% (22)	53.8% (24)	0.870
	Existence of at least one psychiatric history in the MINI	64.6% (27)	56.4% (25)	0.437
	Personal history of attempts of suicide	12.5% (5)	15.4% (7)	0.488
Mood disorders	Existence of at least one current mood disorder in the MINI	16.7% (7)	15.4% (7)	0.871
	Interictal dysphoric disorder	29.1% (12)	12.8% (6)	0.066
	Antidepressant treatment in progress	16.7% (7)	17.9% (8)	0.875
Anxiety disorders	Existence of at least one current anxiety disorder in the MINI	27.1% (11)	30.8% (13)	0.706
	Anxiolytic treatment in progress	14.6% (6)	5.1% (2)	0.150
Psychotic disorders	Isolated feeling of persecution	12.5% (5)	10.3% (5)	0.744
	Antipsychotic treatment in progress	8.3% (4)	0	0.065

MINI (Mini International Neuropsychiatric Interview); N: number of patient.

at least one current anxiety disorder in the MINI, at least one history of anxiety disorder in the MINI, anxiety state according to a positive score in the STAI A scale (respectively 8.3% vs. 13.2%; p = 0.504) and anxiety trait according to a positive score in the STAI B scale (respectively 22.2% vs. 15.8%; p = 0.480).
- *Anxiety disorders screened by tool validated in population with epilepsy.* The two groups did not differ in terms of anxiety generalized according to a positive score in the GAD 7 scale (45.7% vs. 31.6%; p = 0.214).
- *Specific anxiety disorder.* The two groups did not differ in terms of anticipatory anxiety (respectively 52.1% vs. 53.8%; p = 0.870) neither for avoidance resulting from anxiety (respectively vs. 43.6 vs. 35.4; p = 0.564).
- *Drug-induced anxiety disorders.* Groups with limbic and extralimbic epilepsy did not differ in terms of drug-induced anxiety disorders (respectively 2.1% vs. 5.2%; p = 0.439).

3.4.4. Psychotic disorders

- *Psychotic disorders evaluated by a nonspecific tool.* Groups with limbic and extralimbic epilepsy did not differ in terms of psychotic disorders. However, patients with limbic epilepsy tended to take antipsychotic treatment more frequently than patients with extralimbic epilepsy (respectively 8% vs. 0%; p = 0.065).
- *Specific psychotic disorders.* The two groups did not differ in terms of the existence of a feeling of persecution of patients (respectively 12.5% vs. 10.3%; p = 0.744) and the intensity of persecution (respectively 1.1 (SD: 2.6) vs. 0.8 (SD: 2.4); p = 0.490).
- *Drug-induced psychotic disorders.* The two groups did not differ in terms of drug-induced psychosis (respectively 4.2% vs. 5.1%; p = 0.831).

3.4.5. Addictions and eating disorders

Groups with limbic and extralimbic epilepsy did not differ in terms of addictive behaviors, eating disorders, and drug-induced appetite disorders (respectively 20.9% vs. 35.9%; p = 0.118).

4. Discussion

Our study aimed to prospectively assess and describe the interictal psychiatric comorbidities in a homogenous cohort of patients with refractory focal epilepsy in the clinical setting of a tertiary epilepsy monitoring unit. This was based on a systematic psychiatric assessment, heteroevaluation, and self-assessment tools. We also wanted to study the influence of the diagnostic criteria (nonspecific vs. specific for epilepsy), the lateralization, and localization of epilepsy on the prevalence of these comorbidities.

Anxiety disorders and mood disorders had been described as the two main psychiatric comorbidities in many studies [15]. Our results on the overall population were similar to those of literature, with 2/3 of the patients having a psychiatric history according to the MINI (Mini International Neuropsychiatric Interview) and more than half with an ongoing psychiatric disorder in the MINI [2,16–18].

The prevalence of possible depression associated with chronic epilepsy based on a specific screening tool such as the NDDIE scale (17.2%) was consistent with the prevalence reported in the literature [2]. This specific screening scale (NDDIE) was more sensitive than the nonspecific scale (for example, the Beck 21 scale: 14.9%) in our cohort. These findings were consistent with the literature regarding patients with all types of epilepsy [19–21]. It is important to note that this prevalence in the present study was calculated on a specific population of patients with drug-resistant focal epilepsy. The NDDIE scale has been scarcely used so far in this population, despite its simplicity and rapidity of use. This finding supports the recommendation to use NDDIE for better detection of depression in these patients with refractory focal epilepsy.

Our clinical approach focused on specific psychiatric comorbidities associated with epilepsy such as IDD that was found in 21.8% of our cohort.

This prevalence was higher than the rate of mood disorder diagnosed according to the MINI (16.1%) but consistent with previous studies [5,9]. This was mainly related to the duration criteria for IDD that is shorter than in the MINI (less than 15 days). This may lead to underdiagnosis and undertreatment. Considering the strong correlation between mood disorders and quality of life in active epilepsies [22], it is essential to actively look for this disorder with specific clinical tools in patients with refractory focal epilepsy so that they can benefit from appropriate treatment and an improved quality of life.

Similarly, the use of a specific screening scale for anxiety disorders in patients with epilepsy (GAD 7) yielded a higher prevalence of anxiety (38.4%) than the scales with nonspecific criteria (28.7% of the patients in the MINI, 10.8% in the STAI A, and 18.9% in the STAI B).

Unlike previous studies [2] (Scott et al., 2017), anxiety disorders at inclusion were more frequent than mood disorders. This may be related to different factors: (i) the variability of the clinical tools used to assess anxiety. A recent meta-analysis indeed underlined the variability of the anxiety disorder according to the diagnostic tools, by using a structured clinical interview (Scott et al., 2017); (ii) neurologists' greater sensitivity towards mood than anxiety disorders. In fact, neurology teams are more sensitive to mood disorders than anxiety disorders, which could lead to a general underestimation of anxiety disorders in the studies; (iii) the specific population of patients with refractory focal epilepsy; and (iv) the specific context of psychiatric assessment during presurgical evaluation, for some patients eligible for surgery, that may, in itself, be a cause of increased anxiety.

It is essential, however, not to underestimate anxiety, a pathology that can potentially be complicated by suicide, and that reemerges as a psychiatric emergency.

This highlights the need to generalize the use of the GAD 7 questionnaire among neurologists taking care of patients with epilepsy. The GAD 7 self-questionnaire is indeed a specific, fast, and reliable screening tool that has been validated for anxiety disorders in epilepsy in different languages [23–25].

Epilepsy is associated with an increased onset of psychiatric disorders and suicide attempts before and after epilepsy diagnosis. These relations suggest common underlying pathophysiological mechanisms that both lower seizure threshold and increase risk of psychiatric disorders and suicide [26]. Thus, considering this bidirectional link between psychiatric disorders and epilepsy, the question of a common cerebral pathophysiological substrate and of anatomoclinical correlations in epilepsy-associated psychiatric comorbidities has been long addressed.

We, therefore, looked for interactions between lateralization and localization of epilepsy on the one hand, and prevalence of specific psychiatric comorbidities on the other hand.

We found a more frequent psychiatric history preceding epilepsy onset in patients with right lateralized epilepsy. This is an interesting finding, which is consistent with the bidirectional relation between epilepsy and psychiatric comorbidity, perhaps with some difference according to the localization. However, this point needs to be replicated. We did not find a higher prevalence of psychiatric comorbidities in right lateralized epilepsy in contrast with the findings of previous studies. In our study, we even found a tendency for more frequent major depressive disorders and a significantly higher intensity of persecution experience in patients with left lateralized epilepsy. The higher prevalence of language and memory deficits in refractory left lateralized epilepsy may explain these unexpected findings through the bidirectional link between cognitive impairment, stigma, and psychiatric disorder. Indeed, in addition to having chronic and disabling seizures, patients with left lateralized epilepsy may have more difficulties in understanding and adjusting to the surrounding world because of more frequent

cognitive disturbance. It would be relevant for future studies to focus on this potential link between left-sided epilepsy and psychiatric disorders.

Previous studies emphasized the higher prevalence of psychiatric disorders in temporal lobe epilepsy [26–28]. Other authors, however, challenged these findings and stressed the multifactorial hypothesis for the occurrence of psychiatric symptoms [29]. Our findings may reconcile these contradictory studies. We found, indeed, a higher prevalence of nonspecific psychiatric comorbidities, especially anxiety disorders, but not of specific psychiatric comorbidities in temporal lobe epilepsy.

We did not find a higher prevalence of psychiatric comorbidities in limbic epilepsy, regardless of the specificity of the diagnostic tools. This was rather unexpected because the limbic system is known to play a very important role in the regulation of emotions such as fear and pleasure and in the control of emotionally driven behaviors. There was, however, a strong trend towards higher prevalence of antipsychotic drug intake in patients with limbic epilepsy in our series, suggesting a higher prevalence of associated psychosis in this subgroup. The 8% prevalence of chronic antipsychotic treatment in limbic epilepsy is extremely high considering the 2% prevalence of psychosis in the general population. Another explanation could be that this classification was based on the identification of the epileptogenic zone, in other words, the area of seizure initiation. During the interictal phase, the area of functional disturbance as assessed, for example, by interictal FDG-PET is usually larger than the epileptogenic zone and involves both the epileptogenic and the propagation zone [30]. In cases of lateral temporal lobe epilepsy (extralimbic according to our definition), it is very likely that the medial temporal lobe structures were functionally disturbed because they are almost systematically involved in the propagation zone. Those cases were therefore classified as extralimbic whereas an interictal disturbance of limbic structures was very likely. This may explain why temporal lobe and not limbic epilepsy according to our definition was associated with higher prevalence of psychiatric comorbidities.

These heterogeneous results strongly support the concept that the expression of psychiatric symptoms in patients with epilepsy is the result of a complex interaction between sociodemographic, clinical, iatrogenic, and neurobiological factors.

Finally, the absence of correlations between addictive disorders and characteristics of epilepsy may be related to the lack of power of our cohort considering the low prevalence of these disorders in our cohort.

5. Conclusion

Despite the abovementioned inherent selection bias related to the recruitment in a tertiary epilepsy center, the high frequency of psychiatric disorders in this cohort and the specificity of the symptomatology underline the importance of an extended, specialized, and specific psychiatric evaluation for these patients with active refractory focal epilepsy.

The second important finding of our study was the high rate of anxiety disorders in patients with drug-resistant focal epilepsy, which were probably more often underdiagnosed than mood disorders. It is important to remember that there is an important link between anxiety disorders and control of epileptic seizures. This link is bidirectional as a patent anxiety disorder has a pejorative effect on the frequency of seizures, and the repetition of seizures maintains anxiety.

It is necessary to use a specific screening methodology to be able to highlight these anxiety disorders, treat them, and improve the quality of life of patients.

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