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ABSTRACT

Anxiety and depression in epilepsy are strongly documented but post-traumatic stress disorder (PTSD) is underestimated and poorly known. We studied the links between psycho-traumagenic events (TE), onset of epilepsy and severity of PTSD symptoms in patients with epilepsy. The study included 54 patients with epilepsy and 61 controls. We used validated questionnaires to screen for anxiety, depression and PTSD symptoms and we conducted an interview to measure the prevalence of TE. We developed an original exploratory questionnaire to assess the presence of PTSD during inter-ictal and peri-ictal period. The results show that patients reported more exposure to a TE and presented significantly more severe PTSD symptoms than controls. Seventy-eight percent of patients (vs. 52% of controls) had been exposed to a TE, and 26% (vs. 7%) had a score above the diagnostic threshold of the PTSD scale. In addition, 18.6% of patients reported that their epilepsy began at the same time as they began to experience PTSD symptoms following a TE. Patients with high PTSD scores (above the threshold, $n=14$) reported significantly more depression symptoms than patients without PTSD and reported PTSD symptoms both during the ictal and peri-ictal period. Within the whole group of patients, anxiety (72%) and depression (33%) symptoms significantly correlated with PTSD symptoms reported by the scale. This study shows that patients with epilepsy have increased prevalence of self-reported PTSD symptoms. We describe the clinical picture specific to epileptic patients, which may include classical PTSD symptoms but also specific peri-ictal symptoms.

Keywords: Epilepsy, PTSD, anxiety, depression

1. Introduction

Patients with epilepsy are affected by psychiatric comorbidities including anxiety and depression, more frequently than the general population[1,2]. These symptoms may compromise their quality of life[3,4] and are even more frequent in patients with drug resistant epilepsies[5].

There is growing evidence that traumagenic events (TE) are a potential etiologic factor for anxiety and depression. Some studies have suggested that in patients with epilepsy, emotional and sexual abuse in childhood is experienced more often than in the healthy population, and that early maltreatment is a general risk factor for psychiatric comorbidities[6,7]. However, the role of these stressors on epilepsy and psychiatric comorbidities is still poorly understood. In this context, few studies have focused on the relationships between exposure to trauma, post-traumatic stress disorder (PTSD) and epilepsy. Post-traumatic stress disorder is a psychiatric condition that may occur when an individual lives through or witnesses one or more events in which he or she believes that there is a threat to life or physical integrity and safety, and experiences fear, terror, or helplessness. The symptoms are characterized by re-experiencing the traumatic episode, intrusive thoughts, avoidance behaviors, changes in mood and cognition and hypervigilance (American Psychiatric Association, DSM-5, 2013).

To date, there are limited robust data on PTSD symptoms in epilepsy. The majority of studies have focused on the comparison of PTSD symptoms in patients with psychogenic non-epileptic seizures (PNES) and epilepsy[8,9]. PTSD is frequently observed in patients with PNES, with an incidence ranging from 44 to 100%[10]. In contrast, the incidence of PTSD in epilepsy is less well known and, like most psychiatric comorbidities including depression, PTSD is underdiagnosed and undertreated[11]. Studies comparing PNES and epilepsy show that PTSD and depression are more frequent in patients with PNES than in patients with epilepsy[8,12]but also suggest that PTSD could be more frequent in patients with epilepsy

than in the general population[13]. In addition, it has been suggested that individuals with PTSD would be statistically more likely to develop epilepsy[14–17]. Several observational studies have mentioned the development of epilepsy following a TE, suggesting a potential etiological link[18–22]. Corroborating this, experimental animal studies have recently shown that in mature rats, significant stress may induce depression in susceptible animals and may promote the development of epileptogenesis[23,24]. In patients with epilepsy, the temporal relation between epilepsy onset and exposure to a TE is however not specified in most articles, and some previously reported patients may have been exposed to a TE either long before or after the onset of epilepsy.

Another important aspect is that seizures themselves could represent a psychological traumatic event[25,26]. One study showed that patients with epilepsy may develop PTSD following a traumatic seizure, developing typical symptoms such as avoiding thinking about their seizures or elements that could remind them of the seizure (64.7%), and/or re-experiencing traumatic seizures (95.8%), and that these symptoms could be associated with physiological changes (43.7%)[25].

The objective of the present study was to provide a comprehensive description of the spectrum of PTSD symptoms in patients with epilepsy. We explore the prevalence of traumagenic events related to epilepsy onset and PTSD symptoms in comparison with a healthy control group.

2. Materials and Methods

2.1. Participant selection

The study included 54 patients with epilepsy aged 18 to 54 years, 27 females and 27 males from all educational and socio-cultural backgrounds. The study was proposed to consecutive patients hospitalized in the video-EEG monitoring unit of the Epileptology department of La

Timone hospital in Marseille. Patients were recruited during a 6-month period (2018-2019). They were affected by focal (72.2%) or generalized (9.3%) epilepsy, which in the majority was drug-resistant[27]. **All patients who were proposed the study agreed to participate.** No patient included in the study had a recorded PNES during this assessment.

We also included 61 control participants, 43 females and 18 males aged between 18 and 50 years, from various educational and socio-cultural backgrounds who were not suffering from any known chronic illness or psychiatric symptoms (*table 1*). They were recruited among the staff and students at Aix Marseille University and Nice Cote d'Azur University. All control participants volunteered for no remuneration. For all inclusions of patients and control participants, questionnaires were supervised by a qualified psychologist. All the procedures and protocols have been approved by the institutional Ethical Committee and were performed after written informed consent by all of the patients. Participants were interviewed and asked to fill out questionnaires and to note whether they had experienced a TE. In the epilepsy group we specified that the event could be either related or unrelated to the epilepsy and seizures. Subjects were asked open-ended questions about the possibility of traumatic events in their lives and their temporal relationship to the onset of their epilepsy. We did not use a specific questionnaire for exploring TE.

2.2.Measurement of psychiatric symptoms

To evaluate symptoms of PTSD, we translated into French the PDS-5 : *Posttraumatic stress disorder diagnostic scale for DSM-5*[28].(*table 2*). This questionnaire was proposed to any participant who felt he/she had been exposed to a TE during his/her lifetime and the scale was completed in relation to the most emotionally salient TE from the person's point of view. This scale was used to assess reexperiencing symptoms (criterion B), avoidance behaviors (criterion C), changes in mood and cognition (criterion D) and hypervigilance (criterion E).

The questionnaire was completed by patients and controls under the supervision of a psychologist.

In line with our research objectives, we developed a questionnaire to assess PTSD symptoms more specifically related to epilepsy. We called it "Posttraumatic Stress Disorder for Epilepsy" (PTSD-E) (*supplementary tables*) and used DSM-5 semiological criteria and theoretical arguments for PTSD.

Through the first items were designed to evaluate the symptoms during the peri-ictal period, we investigated whether seizures could occur in relation to certain thoughts, situation, time of day. Second, we explored whether, during the inter-ictal period, patients adopted avoidance behaviors to specific seizure triggers (memories, thoughts, situations). We also assessed whether they were hypervigilant with regards to the risk of having a seizure (over-alert state). The following items measure whether patients report any manifestations of intrusive thoughts (emotions or memories) during the ictal period. Finally, we assessed the psychological distress that could result from these symptoms in post-ictal period. The items of the questionnaire were scored as categorial variables ranging from 0 (never) at 4 (always) to create a total score and sub-scale scores (*supplementary tables*). A brief description of the two tools used for post-traumatic stress symptoms (PDS-5 and PTSD-E) is available in *table 2*.

For generalized anxiety screening, we used the French version of the GAD-7 scale (*Generalized Anxiety Disorder*) with a cutoff score of 7/21[29]. For major depressive disorder screening, we used the French version of the NDDI-E scale (*Neurological Disorders Depression Inventory for Epilepsy*) with a cutoff score of 15/24[30].

2.3. Statistical analyses

A chi-square test of independence was performed to examine the relation between the traumagenic exposure and experimental group. The severity of PTSD symptoms (PDS-5 score) was compared between the epilepsy and control groups using a *t test*.

Furthermore, we created two subgroups within the epilepsy group, based on the PDS-5 clinical scale: patients with a score above the diagnostic score were attributed to the "PTSD+" subgroup and those with a score under the diagnostic score to the "PTSD-" subgroup. **Based on previous publication[28] we used a cut-off score of 27.5 as a diagnostic threshold..** We analysed differences between these subgroups by *t test* of symptoms of PTSD associated with seizures, reported by the PTSD-E questionnaire. We also compared groups by *t test* with regards to anxiety and depression symptoms using total scores of the relevant screening tools. **Bonferroni correction for multiple comparisons was applied to control for significance (corrected threshold $p < 0.004$ for 12 tests)**

Preliminary data analysis is indicated in supplemental material.

3. Results

The subjective temporal relationship between TE and onset of epilepsy is described in *table 3*. Compared to controls, patients with epilepsy more frequently reported having been exposed to a TE (78% vs. 52%). In the epilepsy group, 26% presented a score above the diagnostic score of the scale compared to 7% in the control group. The proportion of subjects who reported being exposed to a TE is more frequent in the epilepsy group $\chi^2(1, N=107) = 8, p < 0.005$, *table 3*). Patients presented significantly more severe PTSD symptoms ($M=27.3$; $SD=15.4$) than the control group ($M=14.5$; $SD=13.8$) as assessed by the PDS-5 ($t(64) = -3.56, p = 0.001$, *table 3*). Fourteen patients were classified as belonging to the PTSD+ (26%) and 40 the PTSD- (74%) subgroups. Moreover, during their interview, 8 (14%) patients reported that their first seizure occurred following a TE, with epilepsy onset occurring within 6 months following the TE (*table 3*). In addition, two other patients reported repeated exposure to TE during childhood and having developed symptoms of PTSD a few years later, at the same

time of the onset of their epilepsy. Thus, a total of 10 patients (18.5%) reported a temporal relationship between a TE and their epilepsy onset, and/or the development of PTSD symptoms (*table 3*).

Positive correlations were found between the levels of anxiety or depression symptoms and PTSD symptoms in the whole epilepsy sample (*table 4*). The PTSD+ subgroup ($M=16.86$; $SD=3.53$) scored significantly higher than the PTSD- ($M=11.88$; $SD=4.11$) for the depression scale ($t(52) = 4.04$ $p < 0.001$). Eighty-six percent of PTSD+ reported a score above the cut-off of the NDDI-E scale compared to 33% of PTSD-. For the anxiety scale, 100% of PTSD+ patients reported a score above the cut-off compared to 75% of PTSD- but this difference of GAD-7 scores between the subgroups was not significant ($t(52) = 1.65$ $p = \text{NS}$).

The PTSD-E scale was used to explore the link between PTSD symptoms and seizures. Results are described in *table 5*. Among the patients, 36.2% reported that seizures tended to be triggered by particular thoughts, situations or times of day; 24.4% reported that they adopted avoidance behaviours (criteria C) in order to avoid situations, places or thoughts that could trigger a seizure. In addition, 37.6% reported being hypervigilant (criterion E) at the onset of seizures and 38.8% reported that during their seizure (ictal period) they had relived memories or involuntary emotions. We compared PTSD-E scores between PTSD+ and PTSD- subgroups (*table 5*). PTSD+ reported significantly more PTSD-E items during inter-ictal and peri-ictal periods than PTSD- ($t(52) = 4.53$ $p = < 0.001$, *table 5*). This means that PTSD symptoms associated with seizures were significantly more reported by patients who score above the diagnostic threshold on the PDS-5 clinical scale.

4. Discussion

Here, we investigated PTSD symptoms related to psychiatric comorbidities in a cohort of patients with epilepsy in comparison to a healthy control group. Our main results were: 1/ patients with epilepsy had a higher prevalence of PTSD symptoms than healthy controls; 2/

depression was more frequent in epileptic patients presenting with more marked PTSD symptoms; 3/ PTSD symptoms may occur during inter-ictal and peri-ictal periods and may interact with seizure semiology. From these results emerges a spectrum of PTSD manifestations in epilepsy summarized in Figure 1. This model proposes a dynamic view of the relationships between trauma, seizures, PTSD, anxiety and depression in epileptic patients.

4.1. PTSD symptoms in epileptic patients and their relationships with psychiatric comorbidities

Our results show that patients more frequently reported exposure to TE and reported more symptoms of PTSD than healthy controls. Within the general population, the incidence of traumatic exposure during lifetime is estimated at 70.4% worldwide[31] and 72.2% in France[32]. However, while this frequency is very high, the development of PTSD is far less frequent and is estimated to occur in around 5.6% of people who have been previously exposed to traumatic events[33]. This incidence is close to that observed in our control participants: 52% were exposed to a TE and 7% reported PTSD symptoms exceeding the cut-off score of 27.5 on the PDS-5.

However, we found a higher incidence of PTSD symptoms in our sample of patients, since 78% reported exposure to a TE and 26% exceeded the cut-off score for PTSD symptoms on the PTSD-5 scale. These findings reinforce those obtained in preliminary investigations [13,25].

Moreover, the current results show that patients who reported PTSD symptoms above the cut-off score (PDS-5) also had higher scores of depression (NDDI-E) than patients with PTSD scores below the cut-off. However, generalised anxiety symptoms did not differ significantly between these subgroups. This result suggests that depression in epilepsy may be associated

with exposure to traumatic events and PTSD. The association of depression, PTSD and epilepsy requires future investigations to better decipher the underlying mechanisms.

4.2.Temporal relation between TE, PTSD and epilepsy

Our results suggest 2 main types of temporal relationships between TE and epilepsy onset in our patients (*figure 1, 1.2*). First, some patients developed their epilepsy within 6 months of experiencing a TE or the onset of PTSD symptoms. This temporal relationship was identified in 18.6% of patients and this finding underlines the importance of studying the common pathophysiological pathways between PTSD and epilepsy. Animal experiments have shown that early postnatal stress (maternal separation) may accelerate epileptogenesis in the limbic kindling[35] or in the lithium pilocarpine model[36]. Findings from these animal studies suggest that early life stress in rats may promote the process of epileptogenesis. More recently, major social stress in vulnerable adult animals has been showed to lead to depression and promote the development of epilepsy in the kainate model of limbic seizures[23,24]. Taken as a whole, these results support the hypothesis of a “psychoepileptogenic” process, considering that emotional and physiological processes related to unresolved past stressful events could induce a state of vulnerability to the development of epilepsy[37].

Secondly, for some patients, PTSD and epilepsy have less evident etiological link: 27% of them reported having been exposed to a TE and having developed symptoms of PTSD long before the onset of epilepsy and 31% reported having been exposed to traumagenic events after the onset of epilepsy.

We also noted a separate, distinct profile of PTSD symptoms, also reported in previous studies [25,26], in which PTSD symptoms occurred with regards to of the traumagenic effect of a specific seizure or/and of the repeated occurrence of seizures. This impact of seizures was not directly investigated in our study and is difficult to distinguish it from other sources of

trauma, stress, and anticipatory anxiety. We integrate this profile into a dynamic model (fig 1, 6.), which may act as an isolated factor or be linked with other psychopathological features of epilepsy: for example, symptoms of PTSD may manifest during the peri-ictal period, including during seizure semiology (see below).

4.3. PTSD symptoms specific to epilepsy

We observed that patients with PTSD symptoms reported more PTSD-E items (specifically exploring PTSD features related to epilepsy) during the inter- and peri-ictal periods than patients without PTSD symptoms. So, in addition to the classical symptomatology of PTSD (*fig 1, 3.*), these symptoms could be associated with seizures (*Fig 1, 4.5*). Indeed, during the pre-ictal period, patients with PTSD symptoms may relatively frequently identify personal triggers for seizures, related or not to their traumatic memories, which we called “specific triggers of seizures”. This was in contrast with a low prevalence of this in patients with lower levels of PTSD symptoms. Moreover, patients with PTSD symptoms tended to adopt more avoidance behaviour against seizure-specific triggers and more frequently reported hypervigilance related to seizures in the inter-ictal period. They also reported experiencing more intrusions (thoughts or memories) during the seizure itself (ictal period) than patients without PTSD symptoms. In this way, some case reports have mentioned that epilepsy patients with severe PTSD may have a specific seizure semiology, in that re-experiencing of a traumatic memory may occur during the ictal period[38,39]. These findings presuppose an interaction within limbic networks, particularly involving amygdala hyperactivity that characterizes traumatic memory and epileptogenic networks[22,38,39]. Repeated exposure to seizures can act as a reinforcer of PTSD according to a mechanism similar to fear conditioning, one major axis of neurobiological theories of PTSD[40]. The fact that patients with PTSD symptoms report that their seizures may be triggered in a specific way, *i.e.*, in

relation to personal factors related or unrelated to previous events, may argue in favour of an association between PTSD and epileptic networks. This specificity is moreover in line with the conditioning models of PTSD, where a conditioned emotional response is associated with a specific neutral stimulus at the time of the trauma[40,41]. In this way, even if a seizure was not the original cause of the PTSD, the repeated exposure to seizures might progressively produce a PTSD reaction, that we called here ‘traumatic process of seizure’.

We found that patients with peri-ictal PTSD symptoms had high prevalence of anxiety and depressive symptoms. Since patients with PTSD symptoms also more readily identified their seizure triggers, this could tend to increase hypervigilance and avoidance symptoms during the inter-ictal period, and as such could be strongly associated with the anticipatory anxiety of epileptic seizures[42] and vulnerability to stress as a seizure trigger[22].

5. Conclusion

This study highlights the importance of traumagenic events and the occurrence of PTSD symptoms in a population of patients with epilepsy. In addition, we found a relationship between PTSD and depression. Recognition of these symptoms should lead to specific management in the future in order to improve the care and quality of life of these patients.

6. Limitations

Some methodological limits of the present study should be considered. First, the sample is based mainly on patients with drug resistant epilepsies and is not representative of the whole population of epileptic patients. The younger, predominantly female control group may constitute a statistical bias for comparison. In addition, the results could be more reliable by using a control group with a comparable health status to the epilepsy patients (for example, chronic disease). Regarding the TE, the experiment is self-reported, and it is necessary to

consider that the current psychological state (including depression) may influence the recollection of difficult memories or the accentuation of their negative valence. The proposed PTSD-E was exploratory and not based on existing studies of PTSD symptoms; however, since no suitable tool existed, this was a necessary step. The PDS-5 questionnaire is of acceptable psychometric quality[28], but has not yet validated in the French language. In addition, the results should be viewed with caution because the use of the PDS-5 provides a measure of PTSD symptoms but is not a diagnostic instrument. Similarly, regarding measures of anxiety and depression symptoms, the NDDI-E and GAD-7 are both validated screening tools, but not diagnostic instruments or severity scales.

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References

- [1] LaFrance WC, Kanner AM, Hermann B. Chapter 20 Psychiatric Comorbidities in Epilepsy. *Int Rev Neurobiol* 2008;83:347–83. [https://doi.org/10.1016/S0074-7742\(08\)00020-2](https://doi.org/10.1016/S0074-7742(08)00020-2).
- [2] Kwon OY, Park SP. Depression and anxiety in people with epilepsy. *J Clin Neurol* 2014;10:175–88. <https://doi.org/10.3988/jcn.2014.10.3.175>.
- [3] Erica.K. J, Jana.E. J, Michael. S, Bruce.P. H. The Relative Impact of Anxiety, Depression, and Clinical Seizure Features on Health-related Quality of Life in Epilepsy. *Epilepsia* 2004;45:544–50.
- [4] Kanner AM, Barry JJ, Gilliam F, Hermann B, Meador KJ. Anxiety disorders, subsyndromic depressive episodes, and major depressive episodes: Do they differ on their impact on the quality of life of patients with epilepsy? *Epilepsia* 2010;51:1152–8. <https://doi.org/10.1111/j.1528-1167.2010.02582.x>.
- [5] Fiest KM, Patten SB, Jetté N. Screening for Depression and Anxiety in Epilepsy. *Neurol Clin* 2016;34:351–61. <https://doi.org/10.1016/j.ncl.2015.11.003>.
- [6] Labudda K, Illies D, Herzig C, Schröder K, Bien CG, Neuner F. Current psychiatric disorders in patients with epilepsy are predicted by maltreatment experiences during childhood. *Epilepsy Res* 2017;135:43–9. <https://doi.org/10.1016/j.eplepsyres.2017.06.005>.
- [7] Lee I, Strawn JR, Dwivedi AK, Walters M, Fleck A, Schwieterman D, et al. Epilepsy & Behavior Childhood trauma in patients with self-reported stress-precipitated seizures. *Epilepsy Behav* 2015;51:210–4. <https://doi.org/10.1016/j.yebeh.2015.07.019>.
- [8] Diprose W, Sundram F, Menkes DB. Epilepsy & Behavior Psychiatric comorbidity in psychogenic nonepileptic seizures compared with epilepsy. *Epilepsy Behav* 2016;56:123–30. <https://doi.org/10.1016/j.yebeh.2015.12.037>.

- [9] Myers L, Trobliger R, Bortnik K, Zeng R, Saal E, Lancman M. Psychological trauma, somatization, dissociation, and psychiatric comorbidities in patients with psychogenic nonepileptic seizures compared with those in patients with intractable partial epilepsy. *Epilepsy Behav* 2019;92:108–13. <https://doi.org/10.1016/j.yebeh.2018.12.027>.
- [10] Fiszman A, Alves-Leon SV, Nunes RG, D'Andrea I, Figueira I. Traumatic events and posttraumatic stress disorder in patients with psychogenic nonepileptic seizures: A critical review. *Epilepsy Behav* 2004;5:818–25. <https://doi.org/10.1016/j.yebeh.2004.09.002>.
- [11] Mula M. Depression in epilepsy. *Curr Opin Neurol* 2017;30:180–6. <https://doi.org/10.1097/WCO.0000000000000431>.
- [12] Walsh S, Levita L, Reuber M. Comorbid depression and associated factors in PNES versus epilepsy: Systematic review and meta-analysis. *Seizure* 2018;60:44–56. <https://doi.org/10.1016/j.seizure.2018.05.014>.
- [13] Rosenberg HJ, Rosenberg SD, Williamson PD, Wolford GL 2nd. A comparative study of trauma and posttraumatic stress disorder prevalence in epilepsy patients and psychogenic nonepileptic seizure patients. *Epilepsia* 2000;41:447–52.
- [14] Chen YH, Wei HT, Bai YM, Hsu JW, Huang KL, Su TP, et al. Risk of Epilepsy in Individuals with Posttraumatic Stress Disorder: A Nationwide Longitudinal Study. *Psychosom Med* 2017;79:664–9. <https://doi.org/10.1097/PSY.0000000000000463>.
- [15] Zeber JE, Copeland LA, Amuan M, Cramer JA, Pugh MJ V. The role of comorbid psychiatric conditions in health status in epilepsy. *Epilepsy Behav* 2007;10:539–46. <https://doi.org/10.1016/j.yebeh.2007.02.008>.
- [16] Kessler RC, Lane MC, Shahly V, Stang PE. Accounting for comorbidity in assessing the burden of epilepsy among US adults: Results from the National Comorbidity Survey Replication (NCS-R). *Mol Psychiatry* 2012;17:748–58. <https://doi.org/10.1038/mp.2011.56>.
- [17] Rehman R, Kelly PR, Hcm MBA, Husain AM, Tran TT. Characteristics of Veterans diagnosed with seizures within Veterans Health Administration. *J Rehabil Res Dev* 2015;52:751–62.
- [18] Shibahara I, Osawa S, Kon H, Morita T, Nakasato N. Increase in the number of patients with seizures following the Great East-Japan Earthquake. *Epilepsia* 2013;54:49–53. <https://doi.org/10.1111/epi.12070>.
- [19] Sledjeski EM, Speisman B, Dierker LC. Does number of lifetime traumas explain the relationship between PTSD and chronic medical conditions? Answers from the

- National Comorbidity Survey-Replication (NCS-R). *J Behav Med* 2008;31:341–9.
<https://doi.org/10.1007/s10865-008-9158-3>.
- [20] Christensen J, Li J, Vestergaard M, Olsen J. Stress and epilepsy: A population-based cohort study of epilepsy in parents who lost a child. *Epilepsy Behav* 2007;11:324–8.
<https://doi.org/10.1016/j.yebeh.2007.06.003>.
- [21] Gélisse P, Genton P, Coubes P, Tang NPL, Crespel A. Can emotional stress trigger the onset of epilepsy? *Epilepsy Behav* 2015;48:15–20.
<https://doi.org/10.1016/j.yebeh.2015.05.010>.
- [22] Lanteaume L, Guedj E, Bastien-toniazzo M, Magalahaes A, Mundler O, Bartolomei F. Cognitive and metabolic correlates of emotional vulnerability in patients with temporal lobe epilepsy. *J Neurol Neurosurg Psychiatry* 2012;83(5):522–8.
<https://doi.org/10.1136/jnnp-2011-301219>.
- [23] Becker C, Bouvier E, Ghestem A, Siyoucef S, Claverie D, Camus F, et al. Predicting and treating stress-Induced vulnerability to epilepsy and depression. *Ann Neurol* 2015;78:128–36. <https://doi.org/10.1002/ana.24414>.
- [24] Becker C, Mancic A, Ghestem A, Poillerat V, Claverie D, Bartolomei F, et al. Antioxidant treatment after epileptogenesis onset prevents comorbidities in rats sensitized by a past stressful event. *Epilepsia* 2019;60:648–55.
<https://doi.org/10.1111/epi.14692>.
- [25] Cheung M, Allen RD, Dennis I. The impact of self-efficacy, alexithymia and multiple traumas on posttraumatic stress disorder and psychiatric co-morbidity following epileptic seizures: a moderated mediation analysis. *Psychiatry Res* 2013;210:1033–41.
<https://doi.org/10.1016/j.psychres.2013.07.041>.
- [26] Labudda K, Illies D, Bien CG, Neuner F. Epilepsy & Behavior Postepileptic seizure PTSD : A very rare psychiatric condition in patients with epilepsy. *Epilepsy Behav* 2018;78:219–25. <https://doi.org/10.1016/j.yebeh.2017.08.043>.
- [27] Kwan P, Arzimanoglou A, Berg AT, Brodie MJ, Hauser WA, Mathern G, et al. Definition of drug resistant epilepsy: Consensus proposal by the ad hoc Task Force of the ILAE Commission on Therapeutic Strategies. *Epilepsia* 2010;51:1069–77.
<https://doi.org/10.1111/j.1528-1167.2009.02397.x>.
- [28] Foa EB, Mclean CP, Zang Y, Zhong J, Powers MB, Kauffman BY, et al. Psychometric Properties of the Posttraumatic Diagnostic Scale for DSM – 5 (PDS – 5) 2016;28:1166–71.
- [29] Micoulaud-Franchi JA, Lagarde S, Barkate G, Dufournet B, Besancon C, Trébuchon-

- Da Fonseca A, et al. Rapid detection of generalized anxiety disorder and major depression in epilepsy: Validation of the GAD-7 as a complementary tool to the NDDI-E in a French sample. *Epilepsy Behav* 2016;57:211–6.
<https://doi.org/10.1016/j.yebeh.2016.02.015>.
- [30] Micoulaud-franchi J, Barkate G, Fonseca AT, Vaugier L. *Epilepsy & Behavior* One step closer to a global tool for rapid screening of major depression in epilepsy : Validation of the French NDDI-E. *Epilepsy Behav* 2015;44:11–6.
<https://doi.org/10.1016/j.yebeh.2014.12.011>.
- [31] Kessler RC, Aguilar-Gaxiola S, Alonso J, Benjet C, Bromet EJ, Cardoso G, et al. Trauma and PTSD in the WHO World Mental Health Surveys. *Eur J Psychotraumatol* 2017;8. <https://doi.org/10.1080/20008198.2017.1353383>.
- [32] Husky, M M, Lépine J-P, Gasquet I, Kovess-Masfety V. Prevalence and Psychological Correlates of Complicated. *J Post Trauma Stress* 2015;20:251–62.
<https://doi.org/10.1002/jts>.
- [33] Koenen KC, Ratanatharathorn A, Ng L, McLaughlin KA, Bromet EJ, Karam EG, et al. Posttraumatic stress disorder in the world Mental Health Surveys. *Psychol Med* 2018;47:2260–74. <https://doi.org/10.1017/S0033291717000708>.Posttraumatic.
- [34] Chopra MP, Zhang H, Ph D, Kaiser AP, Ph D, Moye JA, et al. PTSD Is a Chronic , Fluctuating Disorder Affecting the Mental Quality of Life in Older Adults. *Am J Geriatr Psychiatry* 2014;22:86–97. <https://doi.org/10.1016/j.jagp.2013.01.064>.
- [35] Salzberg M, Kumar G, Supit L, Jones NC, Morris MJ, Rees S, et al. Early postnatal stress confers enduring vulnerability to limbic epileptogenesis. *Epilepsia* 2007;48:2079–85. <https://doi.org/10.1111/j.1528-1167.2007.01246.x>.
- [36] Lai MC, Holmes GL, Lee KH, Yang SN, Wang CA, Wu CL, et al. Effect of neonatal isolation on outcome following neonatal seizures in rats - The role of corticosterone. *Epilepsy Res* 2006;68:123–36. <https://doi.org/10.1016/j.epilepsyres.2005.10.005>.
- [37] Bernard C. The diathesis-epilepsy model: How past events impact the development of epilepsy and comorbidities. *Cold Spring Harb Perspect Med* 2016;6.
<https://doi.org/10.1101/cshperspect.a022418>.
- [38] Zijlmans M, van Campen JS, de Weerd A. Post traumatic stress-sensitive epilepsy. *Seizure* 2017;52:20–1. <https://doi.org/10.1016/j.seizure.2017.09.010>.
- [39] Biran I, Admon R, Gazit T, Fahoum F. Interaction of Temporal Lobe Epilepsy and Posttraumatic Stress Disorder : Network Analysis of a Single Case Past and Current History 2020;11:1–7. <https://doi.org/10.3389/fpsyg.2020.01010>.

- [40] Brewin CR, Holmes EA. Psychological theories of posttraumatic stress disorder. *Clin Psychol Rev* 2003;23:339–76. [https://doi.org/10.1016/S0272-7358\(03\)00033-3](https://doi.org/10.1016/S0272-7358(03)00033-3).
- [41] Engert F, Bonhoeffer T. Synapse specificity of long-term potentiation breaks down at short distances. *Nature* 1997;388:279–84. <https://doi.org/10.1101/lm.451507>.
- [42] Hingray C, McGonigal A, Kotwas I, Micoulaud-Franchi JA. The Relationship Between Epilepsy and Anxiety Disorders. *Curr Psychiatry Rep* 2019;21. <https://doi.org/10.1007/s11920-019-1029-9>.

Legends of figure and tables

Figure 1: Post-traumatic Stress Disorder spectrum in epilepsy: clinical picture model

Symptoms of post-traumatic stress disorder (PTSD) can result from: **1.** exposure to a traumatic event over the lifetime before or after the onset of the epilepsy **2.** Traumatic effects characteristic of the seizure or a particularly psychologically significant seizure.

3. Symptoms may subsequently occur in daily life, in accordance with the classical semiological criteria referred to in the DSM 5.

4. Symptoms may also merge with epileptic activity, manifesting during pre-ictal and peri-ictal periods and become more severe during this period, depending on the severity of the PTSD.

5. Seizures that may occur in a specific context in relation to the contextual elements of the trauma (fear conditioning theory) may increase hypervigilance and avoidance behaviors to the seizures during inter-ictal and pre-ictal periods.

6. The PTSD symptoms during the peri-ictal period that cause fear of seizures can thus in turn reinforce the trauma associated with the seizures, which we call “the traumatic process of seizures” (*i.e.* patients who have been exposed to a traumatic event in everyday life may also develop symptoms of PTSD because of seizures, related to exposure to traumatic factors during the peri-ictal period).

7. The hypervigilance and avoidance behaviors against specific triggers of seizures during inter-ictal and peri-ictal periods that are characteristic of PTSD are thus accentuated by the unpredictable and anxiety-provoking nature of seizure occurrence, increasing anticipatory seizure anxiety and post-traumatic symptoms of seizures.

8. The complex pattern of PTSD profiles in epilepsy thus increases anxiety and depressive disorders and has a negative impact on quality of life and, in accordance with previous studies, probably on seizure frequency.

Table 1: Patients Epilepsy and control group descriptive factors

Table 2: PTSD Symptoms screening

Table 3: Post-traumatic Stress Disorder symptoms in epilepsy.

Descriptive report of exposure to a traumagenic event (TE) and of post-traumatic stress disorder (PTSD) symptoms in epilepsy and control groups.

Abbreviations: TE, traumagenic event; PTSD, post-traumatic stress disorder; PDS-5, Post-traumatic stress disorder diagnostic scale for DSM-5.

*PDS-5's cut-off.

^aBonferroni's correction <0.004; * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

Table 4: Anxiety and depression symptoms in patients with post-traumatic stress disorder symptoms.

Abbreviations: GAD-7, Generalized Anxiety Disorder 7-item; NDDI-E, Neurological Disorders Depression Inventory for Epilepsy; PTSD-E, Post-traumatic Stress Disorder for Epilepsy.

Table 5: Post-traumatic stress disorder symptoms in ictal and peri-ictal periods

Description scores for Epilepsy, PTSD+ and PTSD- groups and Independent Samples T-Test between PTSD+ and PTSD- groups for PTSD-E score on sub-scales and total score.

Abbreviations: GAD-7, Generalized Anxiety Disorder 7-item; NDDI-E, Neurological Disorders Depression Inventory for Epilepsy; PTSD-E, Post-traumatic Stress Disorder for Epilepsy.

Declaration of competing interest

The authors have no conflict of interest to declare.

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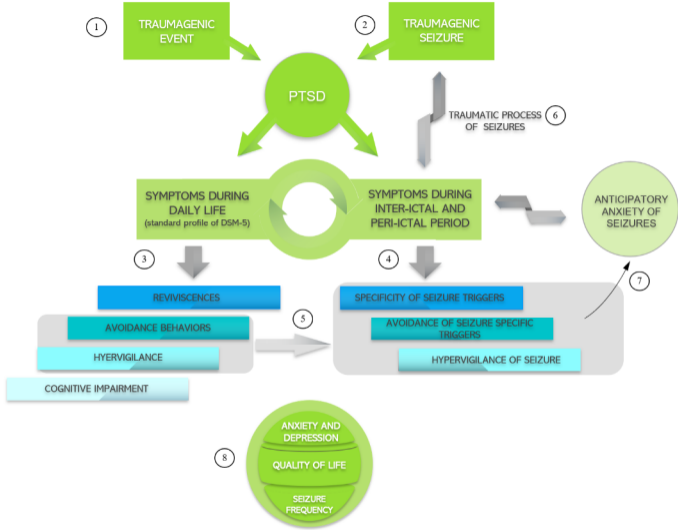


Table 1

	Epilepsy group	Control group	<i>p</i>
<i>N</i>	54	61	
<i>M/F</i>	27/27	18/43	0.025
Age	<i>M</i> =37.11; <i>SD</i> = 9.56	<i>M</i> =26.54; <i>SD</i> =6.52	0.001
Age at seizure onset	<i>M</i> =18.6; <i>SD</i> = 10.7		
Localization of epilepsy			
<i>Generalized</i>	5		
<i>Temporal</i>	30		
<i>Parietal</i>	1		
<i>Frontal</i>	8		
<i>Other</i>	10		

Table 2

<i>Instruments</i>	<i>Items Description</i>
Post-traumatic stress disorder diagnostic scale for DSM-5(PDS-5)	<p>Criterion A items: <i>Scale for any participant who felt he/she had been exposed to a traumagenic event (TE) during his/her lifetime.</i></p> <p>Criterion B items: <i>Reexperiencing symptoms</i></p> <p>Criterion C items: <i>Avoidance behaviors</i></p> <p>Criterion D items: <i>Changes in mood and cognition</i></p> <p>Criterion E items: <i>Hypervigilance</i></p>
Post-traumatic Stress Disorder for Epilepsy (PTSD-E)	<p>Specificity items (peri-ictal period): <i>Investigation if seizures could be expressed in specific ways (occurring in relation to certain thoughts, situation, time of day).</i></p> <p>Avoidance items (inter-ictal period): <i>Avoidance behaviors to specific seizure triggers (memories, thoughts, situations).</i></p> <p>Hypervigilance items (inter-ictal period): <i>Hypervigilant with regards to risk of having a seizure (over-alert state).</i></p> <p>Intrusions items (ictal period): <i>Manifestations of intrusive thoughts (emotions or memories) during the ictal period.</i></p> <p>Distress items (post-ictal period): <i>Psychological distress that could result from all preceding symptoms.</i></p>

Table 3

	Epilepsy group (N=54)	Control group (N=61)	<i>p</i>
Exposure to TE	42 (78%)	32 (52%)	0.005*
Prior to the onset of epilepsy			
More than 6 months before onset of epilepsy	15 (27%)		
Less than 6 months prior to onset of epilepsy	10 (18.5%)		
<i>Within a few days</i>	6		
<i>Within a few weeks</i>	1		
<i>Within a few months</i>	1		
PTSD developed at the same time of seizure onset <i>following earlier exposure to TE</i>	2		
After epilepsy onset	17 (31%)		
PDS-5' score > 27.5*	14 (26%)	4 (7%)	
<i>PDS-5 Total score</i>	<i>M=27.3; SD=15.4</i>	<i>M=14.5; SD=13.8</i>	< 0.001****a

Table 4

Correlation matrix between psycho-emotional measures in Epilepsy group.

		PTSD-E	PDS-5	NDDI-E	GAD-7
PTSD-E	Pearson's r	—	0.529	0.359	0.288
	<i>p-value</i>	—	<0.001	0.008	0.035
PDS-5	Pearson's r		—	0.444	0.356
	<i>p-value</i>		—	0.009	0.039
NDDI-E	Pearson's r			—	0.379
	<i>p-value</i>			—	0.005

Table 5

	Group	Specificity	Avoidance	Hypervigilance	Intrusion	Distress	Total score
M; SD	Epilepsy	4.06; 2.96	3.11; 3.1	3.33; 2.80	2.24; 2.31	4.81; 4.27	17.56; 11.4
	PTSD+	6.29; 3.10	5.36; 4.14	4.64; 2.76	3.57; 2.28	7.86; 3.74	27.7; 11.9
	PTSD-	3.27; 2.51	2.33; 2.03	2.88; 2.70	1.77; 2.17	3.75; 3.95	14.0; 8.92
%	Epilepsy	32.6%	24.4	37.6	26.4	38.8	
%	PTSD+	22.6%	17.8%	24.3%	17.2%	27.7%	–
%	PTSD-	10%	6.6%	13.3%	9.2%	11.1%	–
<i>t</i>		3.63	3.59	3.59	2.64	3.40	4.53
df		52.0	52.0	52.0	52.0	52.0	52.0
<i>p</i>		<0.001	<0.001	0.041	0.011	0.001	<0.001