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BRIEF COMMUNICATION

Correlation between fluorodeoxyglucose positron emission tomography brain hypometabolism and posttraumatic stress disorder symptoms in temporal lobe epilepsy

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Abstract

The relationship between posttraumatic stress disorder (PTSD) and focal epilepsy is poorly understood. It has been hypothesized that there is a complex and reciprocal potential reinforcement of the symptoms of each condition. In this study, we investigated whether there are PTSD-specific brain changes in temporal lobe epilepsy (TLE). Brain fluorodeoxyglucose positron emission tomography (PET) metabolism was compared between controls and two groups of TLE patients: one group of 15 patients fulfilling the criteria for a potential diagnosis of PTSD (TLE-PTSD+), another group of 24 patients without a diagnosis of PTSD (TLE-PTSD-), and a group of 30 healthy control participants. We compared the differences in brain PET metabolism among these three groups, and we studied their correlations with interictal and peri-ictal scales of PTSD symptoms. TLE-PTSD+ patients showed more significant hypometabolism involving right temporal and right orbitofrontal cortex in comparison to TLE-PTSD- patients and healthy subjects. Moreover, degree of reduced metabolism in these brain areas correlated with interictal and peri-ictal PTSD questionnaire scores. PTSD in temporal epilepsy is associated with specific changes in neural networks, affecting limbic and paralimbic structures. This illustrates the close intertwining of epileptogenic and psychogenic processes in these patients.

Fabrice Bartolomei and Eric Guedj contributed equally as last authors of the study.

KEYWORDS
anxiety, PTSD, temporal lobe epilepsy

1 | INTRODUCTION

Posttraumatic stress disorder (PTSD) 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.[1]

To date, the occurrence of PTSD in patients with epilepsy has not been extensively studied. Patients with epilepsy are more exposed to traumatic life events and report more symptoms of PSTD than healthy controls.[2] It has also been shown that in addition to the classical PTSD symptomatology, patients with epilepsy report psychological symptoms during the inter- and peri-ictal period that are specifically related to occurrence of seizures: hypervigilance to seizures, avoidance of all potential seizure triggers, and even traumatic reliving of the ictal period.[2] The relationship between PTSD and epilepsy is therefore complex, with probable reciprocal reinforcement of the symptoms of each condition. Major stresses are likely to accelerate epileptogenesis in animal models,[3] and PTSD has been associated with alterations in brain networks affecting the prefrontal cortex,[4] the amygdala, the hippocampus,[5] or the precuneus.[6] These regions are also likely to be altered in focal epilepsy, especially in temporal lobe epilepsy (TLE).[7] How the combination of epilepsy and PTSD alters brain networks is not known, particularly whether there are metabolic modifications specific to PTSD in patients with TLE. In this work, we explored the relationships between PTSD and epileptogenic networks by correlating brain fluorodeoxyglucose positron emission tomography (18F-FDG-PET) metabolic abnormalities in patients with TLE and PTSD symptoms.

2 | MATERIALS AND METHODS

2.1 | Study population

Patients with drug-resistant TLE were recruited from the Department of Epileptology, Timone Hospital, Marseille, France during 2018–2019. We selected only patients with unilateral TLE with or without a lesion, who had undergone an 18F-FDG-PET scan during the presurgical workup of their epilepsy. The diagnosis of TLE was based on magnetic resonance imaging (MRI) and PET data, interictal electroencephalographic (EEG) data, clinical semiology, and video-EEG recordings of seizures and in some patients stereotactic EEG recordings. All included patients had clear unilateral temporal lobe onset. We controlled the demographic homogeneity of the patients, including sex, age, laterality of epilepsy, and presence of lesion (from MRI). Data are available in Table S1. A female predominance was observed in the PTSD group (73% vs. 33%).

These patients are part of a cohort of patients included in a previous study investigating the characteristics of PTSD in patients with epilepsy.[2] The diagnosis of PTSD was based on a clinical interview with the same psychologist, using the international screening criteria of the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5).[1] All patients in the PTSD group had a score > 27.5 on the diagnostic scale for PTSD (Posttraumatic Diagnostic Scale for DSM-5 [PDS-5]).[8] A questionnaire specific to PTSD symptoms in epilepsy (in the inter- and peri-ictal period), recently developed by our team, was also completed by the patients (for details, see Table 1). We also asked the patients to fill out questionnaires screening for major depression (Neurological Disorders Depression Inventory for Epilepsy [NDDI-E]) and generalized anxiety disorder (Generalized Anxiety Disorder–7 items [GAD-7]).[9]

We selected a third group of healthy subjects, without neurological/psychiatric symptoms or antecedent diagnosis, and with normal brain MRI, who underwent brain 18F-FDG-PET in the Department of Nuclear Medicine at Timone Hospital, Marseille, France. They were selected from a previous study including 60 age- and sex-matched subjects (NCT00484523; Table S1).

2.2 | 18F-FDG-PET imaging and processing

Brain 18F-FDG-PET scans were acquired at the same center using an acquisition protocol conforming to European guidelines, at resting state, in subjects fasting for at least 4 h with a controlled, normal glycemic level, using an integrated PET/computed tomography (CT) General Electric camera, after an intravenous administration of 150 MBq per 15-min acquisition at 30 min postinjection. Images were reconstructed on a 192 × 192 matrix using the ordered subsets expectation maximization algorithm and

TABLE 1 Posttraumatic stress disorder symptom screening

Instrument	Item description
PDS-5	Criterion A items: Scale for any participant who felt he/she had been exposed to a TE during his/her lifetime Criterion B items: Reexperiencing symptoms Criterion C items: Avoidance behaviors Criterion D items: Changes in mood and cognition Criterion E items: Hypervigilance
PTSD-E	Specificity items (peri-ictal period): Investigation of whether seizures could be expressed in specific ways (occurring in relation to certain thoughts, situation, time of day) Avoidance items (interictal period): Avoidance behaviors to specific seizure triggers (memories, thoughts, situations) Hypervigilance items (interictal period): Hypervigilant with regard to risk of having a seizure (overalert state) Intrusions items (ictal period): Manifestations of intrusive thoughts (emotions or memories) during the ictal period Distress items (postictal period): Psychological distress that could result from all preceding symptoms

Abbreviations: PDS-5, Posttraumatic Diagnostic Scale for DSM-5; PTSD-E, Post-Traumatic Stress Disorder for Epilepsy; TE, traumagenic event.

corrected for attenuation using a CT transmission scan. All PET imaging was performed during the hospitalization for phase 1 of presurgical evaluation. The interictal nature of PET scans was established by clinical observation 15 min prior to FDG administration and during the uptake period of 30 min.

Whole-brain statistical analysis was performed at the voxel level using SPM8 software (Wellcome Department of Cognitive Neurology, University College London) to compare patients to healthy subjects with consideration of their age and sex as covariables.

The PET images were spatially normalized onto the Montreal Neurological Institute atlas. The dimensions of the resulting voxels were 2 × 2 × 2 mm. The images were then smoothed with a Gaussian filter (8 mm full width at half maximum) to blur individual variations in the gyral anatomy and to increase the signal-to-noise ratio. Proportional scaling was performed to give the same global metabolic value to each PET examination. Consequently, the extracted values have no dimension; the default value of 50 for the grand mean value scales the global flow to a physiologically realistic value of 50 ml/dl/min.

As more significant hypometabolism was expected between patients and heathy subjects than between patients with and without PSTD symptoms, the statistical threshold was thus adapted at the analysis level. The SPM(T) PET maps were obtained at an uncorrected height threshold (voxel-level significance) of $p < .005$ between patients with PSTD symptoms and healthy subjects, within an inclusive mask of hypometabolism of patients with PTSD symptoms in comparison to those without PTSD symptoms fixed at $p < .05$ uncorrected. The *T*-score of voxel level corresponded to a threshold of 2.65, and an additional statistical control was applied at the cluster level with a *k* extent higher than those expected by Monte Carlo simulation corresponding to at least 128 voxels. Mean metabolic values of this cluster(s) were extracted using MarsBaR (http://marsbar.sourceforge.net/).

2.2.1 | Standardized protocol approvals, registrations, and patient consents

The institutional review board of the French Institute of Health (IRB15226) approved this study, and written patient consent was obtained.

2.3 | Statistical analysis

We controlled the distribution of the three experimental groups by the Shapiro–Wilk test, and they were normal. We used whole-brain voxel-based analysis to compare brain PET metabolism between the three groups (see above). Pearson correlation coefficients were calculated between the PTSD questionnaire responses and the metabolic cluster that was identified among the three groups. A *p*-value of <.05 was considered significant. We also compared patients with right TLE in the two experimental groups by Student *t* test.

3 | RESULTS

Thirty-nine patients with TLE were selected (15 PTSD + and 24 PTSD-). The PTSD+ group had a majority of right temporal lobe epilepsies (11/15, 73%; Table S1). In comparison with healthy controls, patients with TLE exhibited significant hypometabolic brain regions prominent in temporal regions (*p*-voxel < .005; Figure 1A).

TLE PSTD+ patients exhibited significant brain hypometabolism in comparison both to those without PTSD (*p*-voxel < .05 uncorrected) and to healthy subjects (*p*-voxel < .005; uncorrected), involving the right temporal pole and the right orbitofrontal cortex ($k = 1066$; *T*-max = 4.64; *p*-cluster = .007, uncorrected; Figure 1B).

We compared brain metabolism in this cluster between right TLE-PTSD+ and right TLE-PTSD- patients. Right

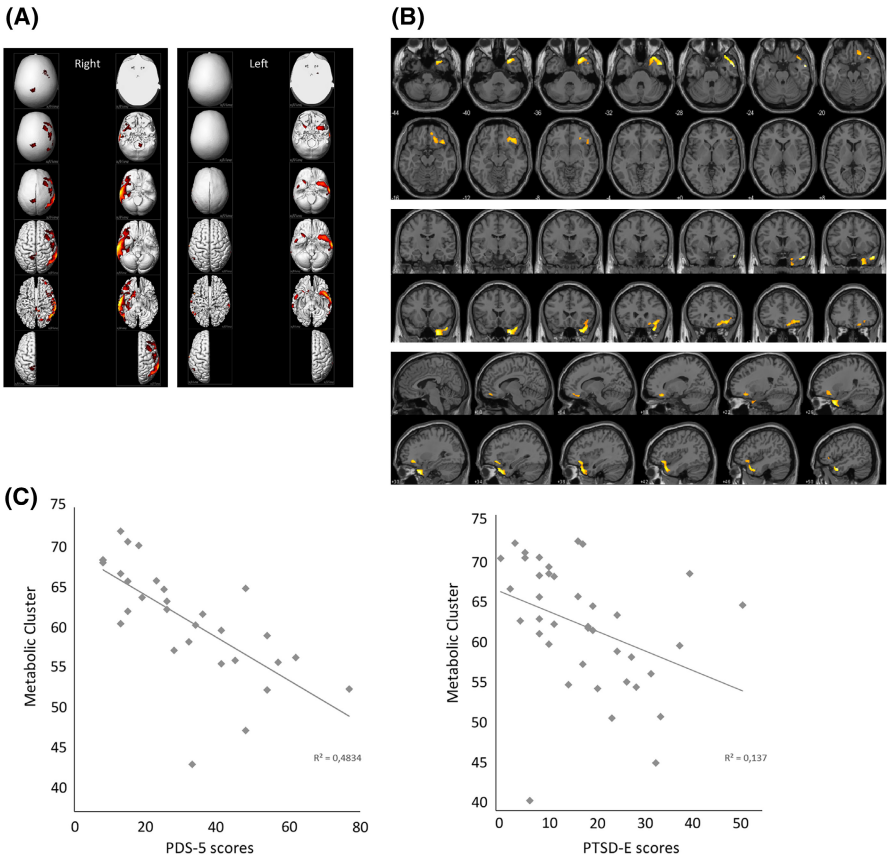

FIGURE 1 Hypometabolism in temporal lobe epilepsy (TLE) patients with posttraumatic stress disorder (PTSD) symptoms. (A) In comparison with healthy controls, patients with TLE exhibited significant hypometabolic brain regions, which was prominent in temporal regions (p-voxel < .005). Right TLE and left TLE are shown. (B) TLE patients with PTSD symptoms exhibited significant brain fluorodeoxyglucose positron emission tomography (18F-FDG-PET) hypometabolism in comparison both to those without PTSD and to the healthy subjects (using inclusive mask), involving the right temporal pole and orbitofrontal cortex. (C) Correlation between the brain 18F-FDG-PET metabolic cluster and the PTSD symptom scores (Posttraumatic Diagnostic Scale for DSM-5 [PDS-5]) and PTSD symptom scores of the inter and peri-ictal periods (Post-Traumatic Stress Disorder for Epilepsy [PTSD-E]).

TLE-PTSD+ (n = 11) patients showed hypometabolism on this cluster compared to right TLE-PTSD- (n = 12; t [21] = −3.17; p = .005/U = 21; p = .004).

The metabolism of this cluster was negatively correlated with the level of PTSD symptoms (PDS-5; r = −.695; p < .001) and inter- and peri-ictal PTSD symptoms (PTSD-E, Post-Traumatic Stress Disorder for Epilepsy; r = −.370; p < .020; Figure 1C). We also found a significant correlation between this metabolic cluster and NDDI-E scores (r = −433; p = .015), but there was no correlation with anxiety scores measured by the GAD-7 (r = −338; p = not significant).

4 | DISCUSSION

Epilepsy patients have an increased incidence of emotional trauma[10] and a likely increased incidence of PTSD.[2] In a cohort of epilepsy patients, we recently showed that 26% (vs. 7% of controls) had a score above the diagnostic threshold of the PTSD-5 scale.[2] In this study, we looked at whether TLE patients with PTSD had differences in metabolism compared to TLE patients without PTSD. The main result of this study was to show that in comparison with TLE-PTSD-, the group of patients with TLE-PTSD+ presented significant hypometabolism in the right temporal pole and the right orbitofrontal cortex. This result is in agreement with previous studies dealing with neurofunctional alterations in PTSD patients, affecting the temporolimbic system and the prefrontal cortex.[4] Recently, it has been shown that the volume of the right temporal pole of PTSD patients was significantly smaller than that of healthy and psychiatric control groups.[11] The temporal pole is part of the paralimbic system, as are the anterior cingulate cortex, orbitofrontal cortex, and insula. Considered a node of the paralimbic cortex, the temporal pole is thought to play a key role in social and emotional processing.[12]

The right laterality of this hypometabolism can be compared with the right predominance of epilepsy in

this group of patients (73%). The hypometabolism of the right temporal polar region could simply be related to the right predominance of the epilepsy in patients with PTSD. However, we observed that this hypometabolic cluster persists when comparing only right temporal epilepsies (PTSD+ vs. PTSD- groups). The pathological role of this hypometabolic cluster is reinforced by the strong linear correlation between the degree of hypometabolism and the PTSD scores: the lower the cerebral metabolism of the temporal pole and orbitofrontal cortex, the greater the PTSD symptomatology. This right-sided predominance warrants further investigation to understand why patients with PTSD likely more often have a right-sided epilepsy. It is possible that the interaction between PTSD and epileptogenesis promotes this lateralization, but this remains to be demonstrated in a larger cohort of patients.

Hypometabolism is a characteristic of epileptogenic networks and may be associated with hyperexcitability of some of the involved brain regions. Thus, hypometabolism of paralimbic regions in the PTSD+ group could be associated with a decrease in interictal metabolism but would have the property of being hyperexcitable in the ictal period or in the case of PTSD during the manifestations of symptoms. Several studies support this paradoxical effect, showing a decrease in interictal metabolism but amygdala hyperexcitability during ictal periods.[13] This could reflect dysfunction of networks subserving emotional regulation, as has been observed in PTSD, in which hypofunctionality of the prefrontal cortex could favor the emergence of PTSD symptoms, particularly fear response.[14–16]

It is worth noting that our study has some limitations, including small sample sizes, heterogeneity in the etiology, and lack of clinical covariation.

5 | CONCLUSIONS

This study shows that TLE patients with PTSD are characterized by metabolic alteration at the group level, specifically affecting the right temporal pole and the right orbitofrontal region. This metabolic alteration is correlated with the severity of PTSD symptoms. These results illustrate the close intertwining of epileptogenic and psychogenic processes and suggest that specific cerebral network changes are associated with interictal psychiatric phenomena in epilepsy.

AUTHOR CONTRIBUTIONS

F.B., L.-D.S., E.G., and S.F. contributed to the design and implementation of the research. E.G. and T.H. performed PET data analysis. L.-D.S. performed the psychological measurements and analyzed the data. S.B. and A.M. aided in interpreting the results and worked on the manuscript. All authors discussed the results and commented on the manuscript.

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CONFLICT OF INTEREST

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

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