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RESEARCH ARTICLE

Heterogeneity of patients with functional/dissociative seizures: Three multidimensional profiles

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Abstract

Objective: Current concepts highlight the neurological and psychological heterogeneity of functional/dissociative seizures (FDS). However, it remains uncertain whether it is possible to distinguish between a limited number of subtypes of FDS disorders. We aimed to identify profiles of distinct FDS subtypes by cluster analysis of a multidimensional dataset without any a priori hypothesis.

Methods: We conducted an exploratory, prospective multicenter study of 169 patients with FDS. We collected biographical, trauma (childhood and adulthood traumatic experiences), semiological (seizure characteristics), and psychopathological data (psychiatric comorbidities, dissociation, and alexithymia) through psychiatric interviews and standardized scales. Clusters were identified by the Partitioning Around Medoids method. The similarity of patients was computed using Gower distance. The clusters were compared using analysis of variance, chi-squared, or Fisher exact tests.

Results: Three patient clusters were identified in this exploratory, hypothesis-generating study and named on the basis of their most prominent characteristics:

1. A “No/Single Trauma” group (31.4%), with more male patients, intellectual disabilities, and nonhyperkinetic seizures, and a low level of psychopathology;
2. A “Cumulative Lifetime Traumas” group (42.6%), with clear female predominance, hyperkinetic seizures, relatively common comorbid epilepsy, and a high level of psychopathology; and
3. A “Childhood Traumas” group (26%), commonly with comorbid epilepsy, history of childhood sexual abuse (75%), and posttraumatic stress disorder, but also with a high level of anxiety and dissociation.

Significance: Although our cluster analysis was undertaken without any a priori hypothesis, the nature of the trauma history emerged as the most important differentiator between three common FDS disorder subtypes. This subdifferentiation of FDS disorders may facilitate the development of more specific therapeutic programs for each patient profile.

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KEYWORDS

comorbid epilepsy, dissociation, etiopathogenesis, psychological trauma

1 | INTRODUCTION

Functional/dissociative seizures (FDS) are periods of abnormal behavior and experience, typically involving impairment of consciousness and involuntary movements.¹ Their manifestations superficially resemble epileptic seizures, but FDS are not caused by abnormal ictal electrical activity in the brain.^{1,2} The etiology of FDS is usually presumed to be psychogenic, even though this term remains controversial. FDS could be characterized as a physical manifestation of acute or chronic stressors or conflicts.²⁻⁴ Most FDS disorders manifest between the ages of 15 and 35 years; across the age spectrum, women are affected four to five times more commonly than men.^{3,5,6} A meta-analysis of FDS cohort studies has calculated a mean epilepsy comorbidity rate of 22%.⁷

Studies have identified multiple psychiatric, experiential, somatic, cognitive, and medical risk factors for FDS.^{7,8} For instance, psychiatric comorbidity is found in nearly 70% of patients suffering from FDS,^{3,9} and strong associations between FDS and somatoform disorder,¹⁰ dissociative disorder,¹¹ posttraumatic stress disorder (PTSD),¹² depression,¹¹⁻¹³ anxiety disorder,^{12,13} and personality disorder^{11,12} have been described. People with FDS are more likely to report previous traumatic experiences than those with epilepsy or general population controls.^{7,14} Consequently, several studies have explored how these risk factors interact in the development of FDS as predisposing, precipitating, or perpetuating factors.^{3,8,15} Unfortunately, the multifactorial etiology and complex interactions between different factors make it difficult to devise a unitary etiopathological model or to devise treatment manuals.^{3,8,15}

The diagnosis of FDS was long based on the exclusion of epilepsy. Recent texts have emphasized the importance of “positive” diagnostic criteria, emphasizing what characterizes FDS disorders themselves rather than what these disorders lack in comparison to epilepsy.¹⁶ The identification of semiological feature clusters has been a major advance for this positive diagnostic approach.^{15,17,18,19} One study established five subtypes of FDS based on their clinical signs.¹⁷ In addition, a recent systematic review of the semiological classification of FDS proposed three principal groups: motor seizures, nonmotor seizures, and mixed semiology.²⁰ The identification of a broader patient profile also taking account of patients’ subjective and emotional symptomatology would be a further advance, especially while there continue to be many barriers to accessing diagnostic video-electroencephalographic (EEG) monitoring

Key Points

- The nature of trauma history emerged as the most important differentiator between three common FDS disorder subtypes (Group 1, “No/Single Trauma”; Group 2, “Cumulative Lifetime Traumas”; and Group 3, “Childhood Traumas”)
- Distinct etiopathogenic profiles probably contribute to the development of FDS
- The different comorbidities of FDS are not simply associations of the disorder, but are more likely to be manifestations of more complex clinical entities
- This subdifferentiation of FDS disorders may facilitate the development of more specific therapeutic programs for each patient profile

around the world. Several studies have therefore examined the different psychopathological, demographic, and medical backgrounds of FDS patients and have proposed distinctions between subtypes of FDS disorders based on their psychological profiles and their trauma history.^{18,21,22,23} These studies were based on highly selected patient samples with the specific objective of verifying one or more preconceived ideas about FDS disorders. Other studies identified patient subgroups based on previous theories focusing on personality pathology or emotional dysregulation.^{18,23,24,25} As yet, no common agreement on different FDS subtypes has emerged.

The objective of the present explanatory, hypothesis-generating study was to characterize such FDS subtypes based on multidimensional profiles of biographical, trauma, semiological, and psychopathological data, without any a priori hypothesis of which features would best delineate different psychopathological profiles.

2 | MATERIALS AND METHODS

2.1 | Patients

This multicenter cohort study (Nancy, Reims, Dijon, Tours) was conducted prospectively, over 24 months, between January 2014 and June 2017. The study included patients older than 18 years in whom a diagnosis of FDS had been established through the video-EEG recording of

spontaneous or hyperventilation-triggered seizures, similar to those previously described by patients and seizure witnesses. Patients were only included if they had had at least three episodes of FDS, at least 24 h apart, over the past 2 years and at least one episode within the past 3 months. Patients were informed about their diagnosis in a standardized manner following the strategy described by Hall-Patch.²⁶ All participants provided written informed consent. Data were collected during semistructured face-to-face interviews by a psychiatrist or neuropsychologist. An epileptologist at each participating center provided the neurological data. This study was approved by an independent ethics committee (2012-A01580-43).

2.2 | Data

2.2.1 | Biographical data

Data on sex, age at inclusion, relationship status (single/couple), employment status (currently in paid work or fulltime education), state assistance related to their seizures, learning disability (if the patients had attended a special education institute), and level of education were collected. The level of education was categorized into no diploma, entry-level diploma, high school diploma or equivalent, and higher education diploma (Figure S1).

2.2.2 | Seizure characteristics

We collected data on age at FDS onset and diagnosis, comorbid epilepsy, treatment with antiseizure medicine (ASM), unjustified or unwarranted ASM at the time of the study, and self-identified FDS triggers (spontaneously reported or in response to prompting during doctor interview).

FDS were categorized using the classification proposed by Hubsch et al.¹⁷ distinguishing five different semiological profiles. These profiles were simplified to establish three groups based on categories most frequently used in the previous literature: hyperkinetic seizures, paucikinetic seizures, and syncopelike events. For some analyses, we used an even simpler dichotomous categorization into hyperkinetic versus nonhyperkinetic seizures (paucikinetic seizures and syncopelike events).

2.2.3 | Trauma history

Childhood trauma information was sampled using the 28-item Childhood Trauma Questionnaire,²⁷ which distinguishes five subcategories of maltreatment (emotional neglect, emotional abuse, physical neglect, physical

abuse, and sexual abuse). We retained three forms of traumas: sexual, physical (including neglect or abuse), and emotional traumas (including neglect or abuse). The presence of trauma exposure was determined by the total score above the threshold score. Participants reporting at least two forms of childhood traumas were categorized as having been exposed to multiple childhood trauma experiences.

Adulthood trauma data were collected using a life events checklist inspired by the LEC-5.²⁸ Events were categorized into three forms of traumas: sexual, physical, and emotional trauma (e.g., the experience of violent or brutal death in the patient's immediate social environment, serious illness, emotional abuse). Participants reporting at least two forms of adulthood trauma were classed as having had multiple adulthood trauma experiences.

For the purpose of the cluster analysis, we identified a pattern of cumulative lifetime traumas if participants had reported at least one form of trauma in both childhood and adulthood.

2.2.4 | Psychopathological data

For psychiatric comorbidities, the Mini-International Neuropsychiatric Interview (MINI) was used to establish current mental health diagnoses (major depressive disorder, dysthymia, generalized anxiety disorder (GAD), agoraphobia panic disorder, PTSD)²⁹; the Montgomery-Åsberg Depression Rating Scale (MADRS)³⁰ measured depression severity (pathological threshold score was set at 15); and the Hamilton Anxiety Assessment Scale (HAMA)³¹ evaluated anxiety symptoms (pathological threshold score was set at 20).

Dissociative tendencies were assessed using the Dissociation Experience Scale (DES).³² This is a self-report questionnaire with 28 items divided into three dimensions: absorption into the imaginary, depersonalization/derealization, and dissociative amnesia. Clinical dissociative disorders are expected if the score is 30 or more.³³

The Toronto Alexithymia Scale (TAS-20)^{34,35} was used to measure alexithymia. The three dimensions of alexithymia identified are: difficulty identifying and/or describing one's own emotions and focusing attention on the outside rather than on inner sensations. A score of <51 eliminates alexithymia, a score between 52 and 60 suggests possible alexithymia, and a score of >60 confirms alexithymia.

2.3 | Statistical analysis

Missing data were imputed by sampling from a fully conditional multivariate model.³⁶ Specifically, the model

estimated a conditional density for each variable containing missing data, and five iterations of sampling were conducted from this conditional density to determine the most plausible value for the missing data.

For cluster identification, the similarity of participants was computed using Gower distance.³⁷ For each possible participant pair, the contribution to Gower distance was calculated using a distinct method for categorical and continuous data. For categorical data, the contribution to Gower distance was 0 if the patients had the same value for the variable, and 1 otherwise. For continuous data, the contribution to the distance was equal to the difference between the values of each participant, divided by the maximum distance observed in the data. For each pair of participants, the total distance was calculated as the sum of all contributions to the distance for continuous and categorical variables. The contributions for each variable were equally weighted. Clusters were identified by using the Partitioning Around Medoids (PAM) method.³⁸ This method identifies clusters of participants based on the dissimilarity of each participant from typical observations in each group. In contrast to the k-means algorithm, the PAM algorithm does not rely on centroids, which do not correspond to actual observations in the variable space.

The variables used for the calculation of the distance matrix were: sex, age, absence of diploma (yes/no), studies completed up to higher education diploma (yes/no), employment/student status (yes/no), recipient of state assistance for seizures (yes/no), learning disability (yes/no), estimated age at FDS onset, time to FDS diagnosis (months), associated epilepsy (yes/no), psychotropic treatment (yes/no), seizures induced by frustration (yes/no), seizures induced by anxiety (yes/no), existence of an identified trigger (yes/no), number of lifetime traumas, history of any lifetime trauma (yes/no), history of childhood trauma (yes/no), sexual childhood trauma (yes/no), emotional childhood trauma (yes/no), history of adult trauma (yes/no), multiple lifetime traumas (yes/no), PTSD (yes/no), suicide attempts (yes/no), number of current psychiatric disorders, number of past psychiatric disorders, DES score, TAS score, alexithymia score ≥ 61 , MADRS score, HAMA score, panic disorder (yes/no), agoraphobia (yes/no), generalized anxiety (yes/no), and simplified seizure classification.

The number of clusters to be presented was determined by an expert review of the clinical relevance of the profiles obtained by the classification algorithm.

Clusters were visualized using the t-SNE method (Supplemental Material).^{39,40}

Comparison of clusters, continuous variables are presented as mean and SD, categorical data as frequencies and percentages. For exploratory analyses, clusters were

compared using analysis of variance, the chi-squared test or Fisher exact test as appropriate. As the tests were exploratory, there was no need to correct for multiple analyses. Effect sizes were calculated with eta-squared for numeric variables and Cramér V for nominal variables. Effect size was interpreted as small (0–.19), medium (.20–.39), relatively large (.40–.59), and large (.60–1) with Cramér V, and as small (0–.38), medium (.39–.55), and large (.56–1) with eta-squared.

Silhouette widths were calculated to estimate the degree of resemblance of each patient to the other patients in their cluster and to help with the determination of the number of clusters.⁴¹ Average silhouette widths were calculated for each group and for all patients.

Analyses were carried out using R software version 3.5.2 (www.R-project.org).⁴²

3 | RESULTS

Our complete sample consisted of 169 FDS patients (137 women) with a mean age of 34.0 years. The median age at seizure onset was 24 years (Q1, Q3 = 9.00, 84.00). An exploratory analysis generated three profiles according to traumatic, psychopathological, and semiological similarities of the participants.

An analysis of the average silhouette width provided us with three possible candidates for the number of clusters: two (highest silhouette width: .214), three (next highest: .133), or five clusters (.120; higher than other neighboring average silhouette widths; Figure 1). The analysis with five clusters was eliminated, because the size of the different clusters was too small to draw reliable conclusions about their psychological or clinical characteristics.

Although the choice of three clusters provided a lower average silhouette width than that of two, this allowed for a more refined characterization of the subgroup profiles and was considered by the authors to be the best compromise between within-cluster homogeneity and our ability to deliver a clinically relevant subgroup characterization. Figure 2 presents a visualization of the three clusters of FDS.

From a statistical point of view, participants' trauma history pattern emerged as the strongest discriminating feature between these three profiles. Based on our semantic interpretation of the three profiles, we therefore named the identified patient subtypes according to their trauma history: Group 1, "No/Single Trauma"; Group 2, "Cumulative Lifetime Traumas"; and Group 3, "Childhood Traumas."

A full description of our cohort with its three subgroups is presented in four separate tables focusing on biographical characteristics (Table 1), seizure characteristics (Table 2), trauma variables and history (Table 3), and

psychopathological characteristics (Table 4). Data without specific explanation represent percentages.

3.1 | Common, nondiscriminating characteristics of the whole cohort

Relationship status, employment/studying status, and receipt of state assistance for seizures did not contribute to the separation of the three patient clusters identified.

Diagnostic delay was generally long (mean delay = 78.7 months, SD = 123.9 months; $p = .33$), with large disparities within each group. Although the difference between the clusters in terms of ASM did not achieve statistical significance, patients in Cluster 2 (Cumulative Lifetime Traumas) received more treatment (Cluster 1, mean = 15.1; Cluster 2, mean = 27.8; Cluster 3, mean = 11.4; $p = .06$). There were also no clear differences between the clusters in terms of the semiological seizure category, although some between-cluster differences reached statistical trend level (see next section).

Each variable relating to trauma and psychopathology contributed to the differentiation between patient clusters, with the exception of the MINI diagnosis of obsessive–compulsive disorder, bulimia, addiction, and psychotic disorder. Psychopathology therefore made a significant contribution to the separation between FDS patient subtypes.

3.2 | Discriminating characteristics

The following paragraphs provide a synthetic description of the most distinctive characteristics distinguishing these

three patient groups. A summary of these three types of profiles is given in Table 5.

3.2.1 | Group 1, No/Single Trauma (31.4%, $n = 53$)

Biographically, this group was characterized by an overrepresentation of men and the highest ratio of patients with learning disability. There was a statistical trend for patients in this group to have a lower level of education.

Concerning their seizures, a majority did not identify any trigger factors, and, in contrast to the other two groups, frustration was reported to precipitate seizures slightly more frequently than anxiety. These patients mostly presented with nonhyperkinetic seizures, with a majority of paucikinetic seizures (42.2%). As in the Childhood Traumas Group, comorbid epilepsy was quite common in this group (43.4%).

A trauma history was reported by only a minority of participants in this group, and none had experienced multiple lifetime traumas. The most frequent type of single trauma reported in this subgroup was adult emotional trauma (13.5%), followed by physical trauma (11.5%). Current PTSD was virtually nonexistent in this group.

Psychopathology levels and the average number of comorbid mental disorders per participant were lower than in the other two groups (mean = .87, SD = 1.00; $p < .001$). Less than one quarter of patients in this cluster were found to have a current depressive or generalized anxiety disorder on the MINI. Dissociative tendencies were low and not pathological (mean DES score = 16.8, SD = 15.0; $p < .001$). Patients also had relatively low alexithymia

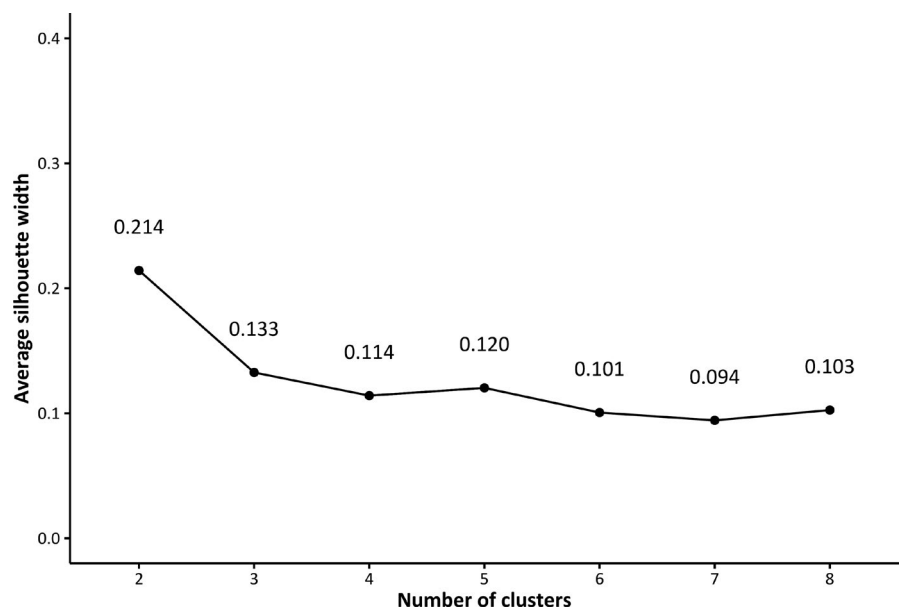


FIGURE 1 Silhouette widths for different numbers of clusters

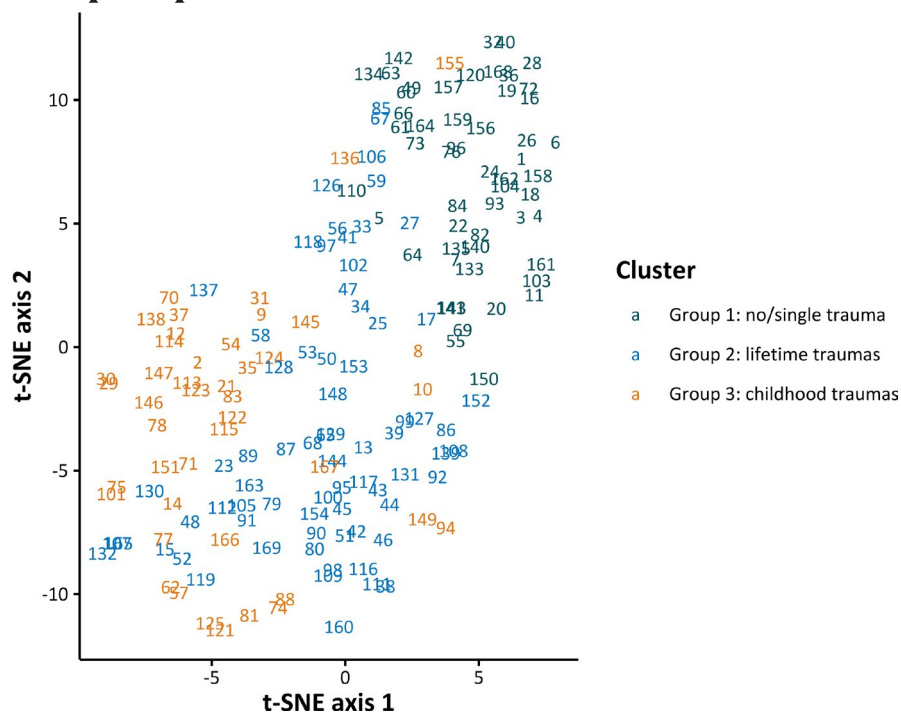


FIGURE 2 t-SNE (t-distributed stochastic neighbor embedding) visualization of the three clusters of functional/dissociative seizure patients in the active variable space

scores (mean TAS-20 score = 51, SD = 13.3; $p < .001$), and only 21.2% of patients in this group would be classed as alexithymic (TAS-20 score > 61).

3.2.2 | Group 2, Cumulative Lifetime Traumas (42.6%, $n = 72$)

Biographically, this group (91.7% female) had achieved relatively high levels of education.

Concerning their seizures, most participants in this subgroup could identify triggering factors (86.1%), with anxiety reported in eight of 10 and frustration in one of two cases. Hyperkinetic seizures were the most common semiology, and comorbid epilepsy was rare (16.7%). However, many individuals in this group received inappropriate ASM.

In terms of trauma, there was an overrepresentation of multiple lifetime traumatic antecedents. Emotional trauma was reported most commonly and also represented the most common type of trauma in adulthood. One third of individuals reported having been raped as adults, and one third had a current diagnosis of PTSD.

The psychopathological profile of patients in this subgroup was often disturbed (87.5%), but the level of psychopathology was lower than in the Childhood Traumas group (mean = 3.20, SD = 1.97). One third of the patients in this group had made a suicide attempt. Patients were more commonly using psychotropic treatments than those in the Childhood Traumas group (66.7%). In this group, the majority of patients had depressive disorders/dysthymia. MINI

diagnoses of anxiety disorder were made in more than one half (55.1%), and of GAD in one third of this group. Dissociation scores were particularly high but lower than among the Childhood Traumas group, and evidence of alexithymia was recorded in approximately one half of the members of this group (51.4% had TAS-20 scores > 61).

3.2.3 | Group 3, Childhood Traumas (26%, $n = 44$)

Biographically, the Childhood Traumas group predominantly included women (86.4%) and was youngest at the time of inclusion. This group mainly comprised patients with an intermediate level of education. The proportion of those with higher education diplomas was lower than in the other two groups.

Concerning their seizures, the members of this group were youngest at seizure onset and had the highest rate of comorbid epilepsy (52.4%). Most could identify triggering factors (86.4%), identifying anxiety (84.1%) more frequently than frustration (31.8%). The seizure semiology was evenly divided between hyperkinetic and nonhyperkinetic seizures (50.0 vs. 50.0%).

In relation to trauma, except for a single patient, all patients in this subgroup had reported childhood trauma. Most individuals in this group had experienced multiple traumatic events in their childhood. A large majority of participants had experienced both child sexual abuse and emotional trauma. The PTSD prevalence was highest in this group (63.6%).

TABLE 1 Biographical characteristics

Characteristic	Total, <i>n</i> = 169	Group 1, No/Single Trauma, <i>n</i> = 53	Group 2, Cumulative Lifetime Traumas, <i>n</i> = 72	Group 3, Childhood Traumas, <i>n</i> = 44	<i>p</i>	Association η^2 or Cramér V^a
Biographic data						
Women, %	81.1	62.3	91.7	86.4	<.001 ^b	.329
In relationship, %	52.1	49.0	48.6	61.4	.36	.078
Age, years (SD)	34.5 (12.4)	36.81 (13.1)	35.95 (12.2)	29.35 (10.6)	.005 ^b	.061
Education, %						
No diploma	17.4	23.5	15.3	13.6	.37	.077
Entry-level vocational diploma	44.9	45.1	34.7	61.4	.02 ^b	.152
High school diploma	37.7	31.4	50.0	25.0	.01 ^b	.159
Higher education diploma	15.6	13.7	20.8	9.1	.22	.095
Learning disability	23.4	33.3	12.5	29.5	.01 ^b	.159
Economic status, %						
Employment/student	63.5	64.7	59.7	68.2	.64	.051
State assistance for seizures	23.2	26.9	22.2	20.5	.73	.043

^aEta-squared ranges from -1 to $+1$, with zero being no effect ($0-.38$: small effect size; $.39-.55$: medium effect size; $.56-1$: large effect size).

^bStatistically significant.

TABLE 2 Seizure characteristics

Characteristic	Total, <i>n</i> = 169	Group 1, No/Single Trauma, <i>n</i> = 53	Group 2, Cumulative Lifetime Traumas, <i>n</i> = 72	Group 3 Childhood Traumas, <i>n</i> = 44	<i>p</i>	Association η^2 or Cramér V^b
Seizure history						
Age at FDS onset, years, mean (SD)	27.18 (13.0)	30.87 (12.9)	28.27 (13.2)	20.96 (10.8)	<.001 ^b	.088
FDS diagnosis time, months, mean (SD), median [Q1, Q3]	78.65 (123.9), 24.00 [9.00, 84.00]	65.18 (125.1), 24.00 [7.56, 49.44]	82.74 (124.1), 24.00 [9.25, 84.00]	88.60 (123.7), 36.00 [12.00, 123.24]	.33	.001
Associated epilepsy, %	34.1	43.4	16.7	52.4	<.001 ^b	.231
Antiseizure medicine, %						
Antiseizure medicine	50.9	52.8	44.4	59.1	.29	.121
Unwarranted antiseizure treatment	19.5	15.1	27.8	11.4	.06	.183
Triggering factors, %						
No trigger factor identified	26.0	52.8	13.9	13.6	<.001 ^b	.413
Frustration influencing seizure	40.8	35.8	50.0	31.8	.10	.164
Anxiety influencing seizure	64.5	30.2	77.8	84.1	<.001 ^b	.488
Seizure type, %						
Nonhyperkinetic seizures (pseudosyncope + paucikinetic)	51.0	64.4	42.4	50.0	.07	.124
Hyperkinetic seizures	49.0	35.6	57.6	50.0	.23	
Pseudosyncope	19.7	22.2	18.2	19.4		.129
Paucikinetic	31.3	42.2	24.2	30.6		

Abbreviation: FDS, functional/dissociative seizures.

^aEta-square ranges from -1 to $+1$, with zero being no effect (0–.38: small effect size; .39–.55: medium effect size; .56–1: large effect size).

^bStatistically significant.

TABLE 3 Trauma variable and history

	Total, <i>n</i> = 169	Group 1, No/Single Trauma, <i>n</i> = 53	Group 2, Cumulative Lifetime Traumas, <i>n</i> = 72	Group 3, Childhood Traumas, <i>n</i> = 44	<i>p</i>	Association η^2 or Cramér V^a
Lifetime traumas [life event checklist & CTQ]						
Current PTSD, %	32.5	1.9	33.3	63.6	<.001	.485
History of PTSD, %	24.8	7.7	21.7	52.5	<.001	.272
At least one trauma in life, %	78.1	34.0	98.6	97.7	<.001	.509
Number of trauma histories in life, mean, SD	2.06 (1.7)	.49 (.8)	2.93 (1.6)	2.52 (1.5)	<.001	.476
Multiple traumas [at least one in childhood, one in adulthood], %	39.6	0	70.0	41.9	<.001	.423
Childhood traumas [CTQ], %						
At least one trauma	65.7	15.1	83.3	97.7	<.001	.535
Sexual trauma	38.2	3.8	41.4	74.4	<.001	.398
Emotional trauma	50.6	5.7	72.2	69.8	<.001	.448
Physical trauma	31.5	9.4	43.1	39.5	<.001	.243
Multiple traumas	40.8	1.9	54.2	65.9	<.001	.402
Adulthood traumas [life event checklist], %						
At least one trauma	49.7	19.2	81.4	34.9	<.001	.19
Sexual trauma	17.6	3.8	32.9	9.3	<.001	.244
Emotional trauma	36.4	13.5	58.6	27.9	<.001	.297
Physical trauma	26.7	11.5	40.0	23.3	.002	.194
Multiple traumas	22.4	7.7	34.3	20.9	.002	.19

Abbreviations: CTQ, Childhood Trauma Questionnaire; PTSD, posttraumatic stress disorder.

^aEta-square ranges from -1 to +1, with zero being no effect (0-.38: small effect size; .39-.55: medium effect size; .56-1: large effect size).

TABLE 4 Psychopathological characteristics

Characteristic	Total, <i>n</i> = 169	Group 1, No/Single Trauma, <i>n</i> = 53	Group 2, Cumulative Lifetime Traumas, <i>n</i> = 72	Group 3, Childhood Traumas, <i>n</i> = 44	<i>p</i>	Association η^2 or Cramér V^b
General psychopathology						
Current psychiatric pathologies, %	78.7	56.6	87.5	90.9	<.001	.366
Number of current psychiatric pathologies, mean (SD)	1.95 (1.7)	.87 (1.0)	1.97 (1.5)	3.20 (1.9)	<.001	.271
Psychotropic treatment, %	47.9	39.6	66.7	27.3	<.001	.336
History of suicide attempts, %	31.9	15.2	34.5	50.0	.004	.182
Depression						
MADRS, mean (SD)	14.8 (9.9)	9.84 (7.3)	16.01 (9.9)	18.44 (10.6)	<.001	.099
Depressive disorder [MDE or dysthymia], %	44.1	21.1	56.5	44.7	.002	.192
Anxiety						
Hamilton, mean (SD)	18.96 (9.9)	14.49 (9.2)	18.86 (9.8)	24.21 (8.7)	<.001	.134
Current panic disorder, %	19.3	10.5	14.5	36.8	.01	.184
Current agoraphobia, %	28.3	15.8	24.6	47.4	.01	.174
Current generalized anxiety disorder, %	35.2	23.7	26.1	63.2	<.001	.229
Existence of at least one anxiety disorder, %	59.3	44.7	55.1	81.6	.003	.186
Dissociation, mean (SD)						
Total DES score	24.05 (16.8)	16.77 (15.0)	25.12 (16.0)	30.54 (17.2)	<.001	.129
Absorption in imaginary	31.37 (19.1)	24.23 (17.4)	31.09 (18.1)	40.01 (19.6)	<.001	.096
Depersonalization derealization	22.10 (17.3)	15.02 (16.4)	24.07 (17.2)	26.89 (16.2)	<.001	.101
Dissociative amnesia	17.44 (15.8)	10.69 (12.6)	18.05 (15.4)	24.11 (16.9)	<.001	.129
Alexithymia, mean (SD)						
TAS	58.12 (11.7)	52.08 (13.2)	58.76 (10.3)	63.91 (8.5)	<.001	.146
Difficulty identifying feelings	21.54 (5.8)	18.55 (6.0)	22.22 (5.7)	23.79 (4.3)	<.001	.085
Difficulty describing feelings	16.15 (4.27)	14.31 (4.4)	16.67 (4.1)	17.40 (3.7)	.001	.125
Externally oriented thinking	20.46 (4.67)	19.22 (4.8)	19.88 (4.3)	22.86 (4.3)	<.001	.098

Abbreviations: DES, Dissociative Experience Scale; MADRS, Montgomery-Åsberg Depression Rating Scale; MDE, major depressive episode; TAS, Toronto Alexithymia Scale.

^aEta-square ranges from -1 to +1, with zero being no effect (0-.38: small effect size; .39-.55: medium effect size; .56-1: large effect size).

TABLE 5 Biological, seizure, psychological, and trauma characteristics of the various FDS profiles

	Group 1, No/Single Trauma, 31.4%	Group 2, Cumulative Lifetime Traumas, 42.6%	Group 3, Childhood Traumas, 26%
Biographic	Higher ratio of men Low education level (with exceptions)	Very high ratio of women High education level	High ratio of women Intermediate education level
Seizures	Triggering factor not well identified 40% comorbid epilepsy Majority of nonhyperkinetic seizures	Low rate of comorbid epilepsy but with a high rate of unjustified ASM treatment High ratio of hyperkinetic seizures	Early FDS onset (<20 years old) One of two has comorbid epilepsy
Trauma	Low rate of trauma (0% experienced multiple lifetime trauma) No PTSD	Multiple lifetime traumas Childhood emotional abuse (72%) Adulthood sexual abuse (32.9%)	Childhood trauma: 75% sexual abuse 70% emotional abuse
Psychopathology	The least disturbed psychopathology profile (number and intensity) No dissociation Moderate alexithymia	High psychopathology Most likely to be treated High levels of depression	Most disturbed psychopathological profile Low psychotropic treatment rate High rates of anxiety disorder Very high dissociative tendencies and high rates of alexithymia

Abbreviations: ASM, antiseizure medicine; FDS, functional/dissociative seizures; PTSD, posttraumatic stress disorder.

The FDS patients in this group had the most disturbed psychopathology profile; 90.9% had psychiatric comorbidities, with a median of three different diagnoses ($p < .001$). However, this group was receiving less psychotropic treatment (72.7% did not receive any treatment, $p < .001$). The attempted suicide rate was higher than in the other groups. Anxiety was the most prominent manifestation of psychopathology. At least one anxiety disorder was presented in 81.6% of childhood trauma patients (including GAD in 63.2%, agoraphobia in 47.4%, and panic disorder in 36.8%). Depressive spectrum disorders were identified in 44.7% of the members of this group. Dissociation scores were extremely high in this subgroup (mean = 30.5, SD = 17.2), with high scores in all DES dimensions. Amnesia differentiated most clearly between this subgroup and the two others (mean dissociative amnesia score = 24.1, $p < .001$). The mean alexithymia scores were highest in this group (mean TAS score = 63.9, $p < .001$), and 67.4% were above the usual alexithymia threshold (TAS-20 score > 61).

4 | DISCUSSION

This study explored demographic, clinical, and psychopathological parameters in 169 patients with FDS with no a priori hypothesis. We identified three large subgroups defined by clusters of parameters showing significant between-group differences. The presence, nature, and pattern of traumatic experiences—in particular of a background of childhood trauma—emerged

as such an important distinguishing criterion that we named the groups according to their respective experiences: No/Single Trauma, Cumulative Lifetime Traumas, and Childhood Traumas. The strength of an association proved especially high for trauma-related factors, confirming that the pattern of an individual's trauma history is a particularly important factor in the distinction of FDS disorder subtypes.

4.1 | Trauma

Several previous studies have attempted to identify FDS patient subgroups on the basis of differences in trauma experiences; however, most of these studies were hypothesis-driven. A previous study by our team²¹ compared FDS patients according to trauma history and found that those who reported a history of trauma had significantly more psychiatric comorbidities and stronger dissociative tendencies. Likewise, Quinn et al.⁴³ divided patients with FDS into three groups according to their trauma experience backgrounds and psychiatric comorbidities on the basis of a literature review. In their first group, the seizures appeared to be a response to severe and chronic trauma. These patients presented with an early attachment disorder, linked to physical or sexual abuse and exposure to violence or abuse and neglect during childhood. In their second group, FDS appeared to occur in the context of disruption of awareness and memory caused by neurological events. In their third group, seizures manifested in the

absence of a trauma history, in the context of acute stress or interpersonal conflict, and patients had no significant psychiatric comorbidities. Another observational study of 40 patients⁴⁴ distinguished between different FDS patient groups based on several different parameters. Three FDS profiles were identified: “Psychotraumatized,” “Strong Tendency to Somatization,” and “Greater Vulnerability to Present a Sensitive Personality Disorder.” It is a particular strength of our current study that it confirmed the importance of differences in trauma experiences as a distinguishing factor between different FDS patient subgroups by purely statistical means and without predetermined assumptions about the role of trauma.

In our present study, 78.1% of patients (with a clear female predominance), reported a history of major emotional trauma, a rate similar to those reported in previous studies.⁴⁵⁻⁴⁸ In the No/Single Trauma group, none of the patients had experienced multiple lifetime traumas. The most frequent form of single trauma reported in this subgroup was adult emotional trauma (13.5%). If this type of trauma is isolated and occurs in adulthood, it is likely to be associated with fewer psychopathological sequelae. In contrast, only one patient in the Childhood Traumas group and one in the Cumulative Lifetime Traumas group did not report a history of trauma.

It is worth noting that the distribution and type of traumas differed between the Childhood Traumas and Cumulative Lifetime Traumas groups, although childhood traumatic experiences were reported in both groups. Sexual abuse was reported by three quarters of members of the Childhood Traumas group but by only 41.4% of the Cumulative Lifetime Traumas group. It is well recognized that childhood sexual abuse is type of trauma associated with a high risk of adverse long-term consequences.^{49,50} The high prevalence of this type of trauma may well explain the higher levels of psychopathology observed in this group. It may not be necessary to accumulate further adverse life events after experiences of childhood sexual abuse to develop a serious disorder like FDS. Childhood sexual abuse is often a marker of more profound family dysfunction, and therefore is particularly harmful.⁵¹ Despite the strong association between childhood sexual abuse and the other features observed among members of this group, we cannot affirm a direct relationship. Childhood sexual abuse could be a marker of a broader range of adverse childhood experiences contributing to causal links but not captured in our dataset.

In the Cumulative Lifetime Traumas group, the childhood traumas reported were more varied, including traumatic emotional, physical, or sexual experiences. In adulthood, sexual abuse was particularly common in this group. The history of recurrent traumatization in this group may have been associated with a progressive

increase in the level of psychopathology. FDS in this group could be the tip of an iceberg of psychological disturbance. Emotional trauma was highly prevalent in both the Childhood Traumas and the Cumulative Lifetime Traumas groups. This type of trauma often affects attachment styles and is also closely linked to a range of mental disorders.⁵² In summary, our data suggest that the type and pattern of trauma as well as the age of occurrence are relevant to the distinction between FDS subgroups.

The Childhood Traumas group presented with the most disturbed psychopathology profile. This group raises questions about the relationship between traumatic experiences in early life and the manifestation of psychopathology in later phases of life, for instance at the time of FDS manifestation. Might trauma during brain maturation result in the establishment of long-lasting pathological defense systems and, in particular, increased dissociative tendencies? Several studies⁵³⁻⁵⁵ have shown that the immaturity of the central nervous system makes children's brains more sensitive to the effects of stress and therefore to trauma exposure, mainly through excessive cortisol secretion. Trauma-related structural changes in the brain could result from neuronal death in certain areas of the brain (such as the limbic prefrontal cortex and the hippocampus), causing focal brain volume reduction and atrophy.⁵⁵ There is an increasing body of work describing long-term biological effects of traumatization (some of which may even be transmitted epigenetically to subsequent generations).⁵⁶ In addition, early life trauma could also be expected to leave a lasting imprint on the functioning of people's psychic defenses. A maladjusted defense system could endure into adulthood and result in the more severe clinical expression of FDS. These considerations may be relevant not only to the Childhood Traumas but also the Cumulative Lifetime Traumas group, as many individuals in this subgroup have experienced traumatic events during childhood as well as in their later lives.

4.2 | Psychopathology

The majority of patients with FDS have previously been shown to have comorbid mental health disorders.^{7,12} Several studies^{57,58} have shown that FDS patients who report previous sexual abuse are at particularly high risk of additional mental health problems including depression. Our findings for the Childhood Traumas and Cumulative Lifetime Traumas groups are in keeping with this. Patients with FDS may have higher levels of psychopathology than those with other functional neurological symptoms. In a study comparing patients with FDS with those with functional movement disorders, a higher rate of antecedent sexual abuse was reported by those with seizures

than those with functional movement disorders, and the patients with seizures had higher levels of alexithymia, dissociative symptoms, and neuroticism than those with functional motor problems. FDS patients also had more symptoms of depression and anxiety.⁵⁹

In the present study, the highest levels of dissociation and alexithymia were found in the Childhood Traumas group. The psychopathology profile of this subgroup resembled that of the first of two FDS disorder subtypes described in a previous study, in which trauma data were not available.⁶⁰ This previous study described a first FDS group characterized by higher levels of psychopathology, somatization, alexithymia, and emotional dysregulation, and a second by higher levels of somatization and depression, with normal levels of alexithymia and emotional regulation. Our No/Single Trauma group shared many characteristics of the second group described in this previous study.⁶⁰

One previous study⁶¹ explored a possible association between educational achievements and the risk of developing FDS and showed that patients with higher levels of education are more likely to report a history of sexual abuse and to have an earlier age of FDS onset. These studies match our findings in the Cumulative Lifetime Traumas group.

Duncan and Oto⁶² explored clinical differences between FDS patients with or without traumatic antecedent factors. Binary logistic regression analysis demonstrated that an absence of traumatic antecedents was predicted by male sex, learning difficulties, circumstantial triggering of spells, and associated epilepsy. These results reflect the profile of our No/Single Trauma group. It seems that the cognitive impairment characterizing this subgroup makes these patients fundamentally different from others with FDS.

4.3 | Comorbid epilepsy

One study²² primarily focused on the comorbid epilepsy in those with FDS to subdivide different FDS populations. The authors included patients with mixed seizure disorders (involving epilepsy and FDS) and distinguished between three different patient groups. Their first group was characterized by drug-resistant epilepsy, normal cognition, and the presence of comorbid anxiety and depression. In such cases FDS were thought to be secondary to epilepsy. Their second group of patients had comorbid intellectual disability and dependent personality traits. In their third group, the patients had normal cognition, greater psychiatric comorbidities, and a history of emotional trauma. In this last group, FDS were interpreted as posttraumatic.²² The description of this last group

resonates with the clinical profile of our Childhood Traumas group. Studies exploring differences in clinical semiology between patients with FDS and patients with both FDS and epilepsy found that those with FDS only were significantly more likely to have automatic symptoms and signs compared to patients with mixed (FDS and epileptic) seizure disorders,⁶³ whereas total lack of responsiveness was significantly higher in patients with mixed seizures compared to those with FDS only.⁶⁴ One study found that patients with mixed seizure disorders tended to have an earlier age of FDS onset compared to patients with FDS only.⁶⁵ Similarly, we found that comorbid epilepsy was most common in our Childhood Traumas group, the group with the earliest age at FDS onset.

4.4 | Seizure semiology

In terms of FDS semiology, our results suggest a link between a history of trauma (in adulthood or childhood) and a higher probability of hyperkinetic seizure manifestations (57.6% and 50%, respectively). A link between childhood traumas and the occurrence of motor manifestations has been suggested previously.⁵ One study⁵⁷ showed that patients with FDS who had a history of sexual abuse experienced “convulsive” nonepileptic seizures more often and that their seizures also had more severe motor manifestations. Another study⁶⁶ showed a link between minor motor seizures and particular psychiatric comorbidities (i.e., hypochondriasis). In our study, the absence of a trauma was associated with a higher probability of paucikinetic seizures (42.2%).

4.5 | Limitations

Our study has a number of limitations. The modest size of the participant group and the many datapoints collected mean that there is a risk of false positive findings. The limited number of participants also explains why we were unable to explore associations between the five semiological types described by Hubsch et al.¹⁷ and particular other feature profiles. We had to simplify this classification into three groups: hyperkinetic, paucikinetic, and syncopelike, as usually recognized in the literature. The identification of our three clusters should be validated in separate, larger cohorts, ideally across different cultures.

We also acknowledge uncertainties around the reliability of the retrospective trauma data. Reluctance among some patients to talk about their traumatic experiences may have led to a slight underestimation. Participants may also have been amnesic for their traumatic experiences.

Likewise, it is possible that some traumatic experiences were overreported because the diagnostic process had directed the attention of participants to possible links of their condition with traumatic experiences. The statistical associations described in this study raise the possibility of causal relationships (i.e., causal link between childhood sexual abuse and high levels of psychopathology) rather than proving causality. Several studies have proposed a distinction in FDS patient subgroups based on the presence or absence of emotional dysregulation.⁶⁷ In our study, we did not use specific tools to evaluate this aspect, which explains why it is not featured in our profiles. Moreover, some other potentially relevant features were not included in our methodology (i.e., neuroimaging abnormalities, other magnetic resonance imaging characteristics, cognitive measures other than educational achievement).

The traumatic event definition has varied between studies. In our research, we used the definition provided in the Diagnostic and Statistical Manual of Mental Disorders, 5th edition: “Exposure to actual or threatened death, serious injury, or sexual violence in one (or more) of the following ways: directly, witnessing, learning that the traumatic event(s) occurred to a close family member or close friend or experiencing repeated to aversive details of the traumatic event(s).” Based on this definition, we found that up to 78.1% of our population had experienced at least one trauma in their life. However, the number of traumatic events reported in studies using the broader concept of a “stressful” or “negative life” event has been higher (up to 90%).^{14,68}

5 | CONCLUSIONS

The results of the current study particularly highlight the heterogeneity of the population affected by FDS. Although we started the exploration of our dataset with no a priori hypothesis, the nature of the patients’ trauma history emerged as an important distinguishing characteristic. Sex, comorbid epilepsy, cognitive impairment, and triggering factors also contributed to our distinction between three FDS patient subgroups. The prevalence and severity of psychopathology differed between the three groups.

Our findings could help clinicians to develop an individually adapted, positive management approach to FDS. Our findings provide further support for the hypothesis that distinct etiopathogenic profiles contribute to the development of FDS. The three distinct profiles we have described provide food for thought. Our explanatory analysis allows us to describe three clusters of patients with FDS. These profiles allow us to consider different comorbidity profiles not simply as associations of the disorder but as manifestations of more complex

clinical entities. A better understanding of these entities may allow us to develop more specific clinical, diagnostic, and most importantly therapeutic approaches. These subpopulations differ in terms of their treatment needs. They may also differ in their response to treatment. The development of a therapeutic program addressing each profile may represent a better way forward than a one size fits all approach. In the No/Single Trauma group, a primary focus on the identification of triggering factors may be most appropriate. Moreover, the behavioral aspects of cognitive behavioral therapy (CBT) may be more relevant in this subgroup than the cognitive aspects of CBT, because of the significant cognitive difficulties of these patients. The Cumulative Lifetime Traumas group may benefit most from initial psychoeducation followed by complex trauma-focused psychotherapy, in particular interventions for complex PTSD. Furthermore, the therapeutic approach for patients in this group may need to include measures to reduce the risk of new interpersonal trauma and revictimization. The Childhood Traumas group may derive benefit from psychotherapy focusing on attachment and from additional trauma-focused interventions. Ideally, future studies would include longitudinal and treatment data, so that differences in the evolution and prognosis between the FDS subtypes could be observed.

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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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SUPPORTING INFORMATION

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