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Functional/dissociative seizures: Review of its relationship with trauma, dissociation and the neurobiological underpinnings

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ABSTRACT

Functional dissociative seizures (FDS) are paroxysmal and episodic events associated with motor, sensory, mental, or autonomic manifestations, which resemble epileptic seizures but are not caused by epileptogenic activity. FDSs affect approximately 30% of patients attending specialized epilepsy centers and constitute a severe mental health problem. Patients with FDSs also have a high frequency of other psychiatric comorbidities like depression and anxiety disorders, particularly trauma and post-traumatic stress disorder. It has been postulated that FDSs are essentially dissociations that operate as an evitative psychological mechanism to deal with traumas. In this manuscript, we carried out a state-of-the-art review to provide a critical approach to the extensive literature about FDS, focusing on the relationship with trauma, post-traumatic stress disorder, dissociation, and the neurobiology of these phenomena.

1. Introduction

Functional/dissociative seizures (FDS) (formerly known as Psychogenic Non-Epileptic Seizures) are sudden and involuntary episodic events (paroxysm) associated with motor, sensory, mental, or autonomic manifestations without epileptogenic discharge with neither neurological nor medical cause (Asadi-Pooya et al., 2020; Hingray et al., 2022a). Patients with this disorder exhibit functional alteration of the central nervous system and reduced self-control. FDS is often underdiagnosed, undertreated, and confused with epilepsy as they resemble epileptic seizures (ES) (Anzellotti et al., 2020a; Lanzillotti et al., 2021; Popkirov et al., 2019; Beghi et al., 2015a; Anzellotti et al., 2020a; Lanzillotti et al., 2021; Popkirov et al., 2019; Beghi et al., 2015a). Unlike epilepsy and convulsive syncope, FDS is not caused by neuronal hyper synchronization or cerebral hypoperfusion. Instead, it results from a complex neuropsychiatric dysfunction, and it can be diagnosed only when medical causes (epilepsy, syncope, stroke) have been ruled out (Lanzillotti et al., 2021; Baslet, 2011). Some authors suggest some criteria to have a more objective definition (D'Alessio et al., 2006):

1. Presence of atypical paroxysmal behavioral episodes recorded on video-EEG monitoring in the absence of electroencephalographic ictal activity.
2. Absence of other clinical diagnoses or findings suggestive of epilepsy or other neurological or medical disorder in EEG or neuroimaging studies.

It is essential to mention that functional/dissociative seizures do not have a clear place in the current nosography. The International Classification of Diseases 10th edition (ICD-10) classifies FDS as a dissociative disorder. In contrast, the Diagnostic and Statistical Manual of Mental Disorders Fifth Edition (DSM-5) places it under somatoform disorders (Beghi et al., 2015a; American Psychiatric Association).

Current evidence indicates that FDS results from converging genetic, neural, and environmental factors (Psychogenic nonepileptic seizures in adult, 2022). Most of this field's research has focused on the psychosocial correlates of this disorder (Wiseman and Reuber, 2015). Some cohort studies of FDS have identified socioeconomic and demographic risk factors associated with FDS. Women (and girls) constitute 60–80% of all patients, although the gender disparity is smaller in older adults and

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those with intellectual disabilities. The mean and median age of onset is around 28 years (although the modal age is 19 years) (Popkirov et al., 2019).

Patients with FDS are more likely to report previous traumatic experiences than those with epilepsy or general population controls. Consequently, several studies have explored how these risk factors interact in the development of FDS. They found that traumatic experiences involved in the pathogenesis of the FDS were considered predisposing, precipitating, or perpetuating factors (Myers et al., 2013, 2018; Asadi-Pooya and Bahrami, 2019a). Unfortunately, the multifactorial etiology and complex interactions between different factors make it challenging to devise a unitary psychopathological model or a treatment manual (Hingray et al., 2022a). On the other hand, the neurobiology of this disorder has received far less attention. Fortunately, researchers began to be interested in this field, and the use of neuroimaging techniques and functional connectivity studies is helping to understand the organic basis of FDS (Anzellotti et al., 2020a; Asadi-Pooya, 2015). This manuscript aims to review the evidence regarding FDS and its association with trauma. We will focus on epidemiological, psychosocial, and neurobiological variables.

2. Methods

We carried out a state-of-the-art review, narrative type. This review aims to provide a critical approach to the extensive literature about FDS, emphasizing those articles produced in the last decades. The search strategy was made through different scientific databases (PubMed, Medline, PsycInfo), using the following descriptors: "PNES", "psychogenic nonepileptic seizures", OR "pseudoseizures", OR "FDS", "functional/dissociative seizure", "psychiatric comorbidities", "neurobiology", AND "trauma" and "dissociation". The most recent and essential articles were selected through pair debriefing to include the most updated information about each topic. This work will provide helpful information to contribute to a better approach to understanding patients with FDS.

3. General epidemiology and psychiatry comorbidities

According to different studies, the incidence of FDS ranges from 1.4- to 4.9 per 100,000 inhabitants per year (Duncan et al., 2011; Benbadis and Allen Hauser, 2000; Sigurdardottir and Olafsson, 1998; Szaflarski et al., 2000). The prevalence of this disorder in the general population has been estimated to be 2–33/100.000 (Benbadis and Allen Hauser, 2000). In specialized epilepsy centers, the frequency of this disorder ranges from 5 to 10% in outpatient settings and 20–40% in inpatient settings (Alsaadi and Marquez, 2005). FDS represents approximately 30% of all intractable seizure disorders referred to epilepsy centers, and patients are often misdiagnosed as having drug-resistant epilepsy (Lanzillotti et al., 2021; D'Alessio et al., 2006; Duncan et al., 2011; Benbadis and Allen Hauser, 2000). There is a more significant number of female patients among FDS patients (Thomas et al., 2013; Goldstein et al., 2019; NOE et al., 2012). FDS usually presents in adolescence and young adulthood, although seizures can begin at any point in life (Szabõ et al., 2012; Asadi-Pooya and Emami, 2013; Duncan et al., 2006).

Co-occurring psychiatric disorders are widespread in patients with FDS. A study comparing a group of pure FDS patients (without comorbid epilepsy) and a group of mixed FDS patients (with comorbid epilepsy) for different variables, including psychiatric comorbidities, found somatoform disorders to be the most prevalent psychiatric comorbidity in both groups, followed by affective disorders second, and PTSD third. This study also found a greater prevalence of PTSD in the pure FDS group (29% in the pure FDS group vs. 5% in the mixed FDS group) (D'Alessio et al., 2006). A study comparing psychiatric disorders in patients with FDS and patients with drug-resistant epilepsy (DRE) found that the most common psychiatric diagnosis among the FDS group were somatoform disorders (88.57%), followed by dissociative disorders (37.14%) (considering FDS as the core syndrome). In this same study, depression was equally prevalent in both groups, while anxiety disorders, trauma history, and PTSD were more prevalent in the FDS group, and psychosis was more prevalent in the DRE group (Scévola et al., 2013a). Another study comparing history of trauma and presence of psychiatric disorders between patients with pure FDS and mixed FDS showed that while both groups exhibited similarly high rates of psychiatric disorders (79.1% in pure FDS patients and 76.2% in mixed FDS patients), the pure FDS group had a higher rate of PTSD (32.9%) compared to the mixed FDS group (16.7%) (Labudda et al., 2018). A more recent study found the most prevalent psychiatric comorbidity to be depression, present in about 60% of patients with FDS, followed by PTSD, which was found in around 50% of FDS patients, and anxiety disorders, found in 45% of patients (Lanzillotti et al., 2021).

Personality disorders are also highly prevalent among patients with FDS, and the clinical presentation is even more complex when they are present. According to different studies, rates range from 36% to 62%, and cluster B disorders are the most frequent personality disorders among this population (D'Alessio et al., 2006; Baillés et al., 2004; Jawad et al., 1995). Cluster C personality disorders have also been reported among patients with FDS (Lanzillotti et al., 2021).

4. Trauma and FDS

The epidemiological association of FDS with previous life adversity and psychological trauma, recognized since the 19th century, remains a central element in the current understanding of this disorder. Trauma is currently defined as exposure to death, serious injury, or sexual violence, whether actual or threatened, in one or more different ways (American Psychiatric Association).

Studies have shown increased rates of child maltreatment (including sexual, physical, and psychological abuse and neglect) and stressful life events, such as bereavement or illness, in patients with FDS, and trauma history is more prevalent in patients with this disorder with more severe psychiatric comorbidities and dissociative tendencies (Popkirov et al., 2019) (see Table 1).

A review that gathered data from 23 reports, including data from 1123 FDS patients, calculated that the prevalence of psychological trauma varied from 21% to 100%, and the prevalence of sexual or physical abuse varied from 3.5% to 74%. This study also found a stronger association between history of psychological trauma and FDS in Western countries compared to South America and Asia (Beghi et al., 2015a). Another study of 131 patients, including six different patient groups (temporal lobe epilepsy patients, other epilepsy syndromes patients, FDS patients, other nonepileptic syndromes patients, mixed FDS patients, and uncertain diagnosis patients) found a greater prevalence of childhood trauma in the FDS patients' group, as well as overall higher scores on the CTG (Childhood Trauma Questionnaire) (Johnstone et al., 2016a). A recent study comparing different variables, including history of trauma, between patients with FDS (n = 51) and patients with DRE (n = 97) found trauma history to be present in 78.5% of patients with FDS, and only in 26% of patients in the DRE group. The most frequent type of trauma reported in both groups was sexual abuse, but it was higher in the FDS group (Scévola et al., 2021a).

A relationship linking child sexual abuse (CSA) as a risk factor for the development of FDS has been suggested previously in the literature. An extensive study comparing history of childhood abuse in patients who suffered FDS (n = 71) and those who had epilepsy (n = 140) found significantly higher rates of both sexual abuse (24.0% vs. 7.1%) and physical abuse (15.5% vs. 2.9%) in those who had FDS (Alper et al., 1993). Another study comparing patients with FDS only (n = 324), patients with mixed FDS (n = 84), and patients with epilepsy only (n = 281) found history of abuse (sexual or physical) more frequent in the FDS only group (Elliott and Charyton, 2014a). Other recent studies also showed higher rates of childhood trauma in patients with FDS: in one retrospective study of 96 patients with intractable epilepsy and 161 patients

Table 1
Main studies about trauma experiences and PTSD in patients with FDS.

Authors	Title	Study type	Sample	Results
Asadi-Pooya A, Bahrami Z 2019	Sexual abuse and psychogenic nonepileptic seizures	Retrospective database study	n = 314	26 patients (8.3%) had a history of sexual abuse 288 patients (91.7%) denied history of sexual abuse
Hingray C, Ertan D, Reuber M et al. 2022	Heterogeneity of patients with functional/ dissociative seizures: Three multidimensional profiles	Prospective multicenter study	n = 169	Three patient clusters identified: 1. No/Single trauma group: 31.4%. More male patients, intellectual disabilities, low level of psychopathology and nonhyperkinetic seizures 2. Cumulative lifetime trauma group: 42.6%. More female patients, hyperkinetic seizures, high level of psychopathology and comorbid epilepsy 3. Childhood traumas group: 26%. Commonly comorbid epilepsy, history of sexual abuse (75%), PTSD, anxiety and dissociation.
Johnstone B, Velakoulis D, Yuan CY, Ang A, Steward C, Desmond P et al. 2016	Early childhood trauma and hippocampal volumes in patients with epileptic and psychogenic seizures	Cross-sectional study	n = 131	There is a greater prevalence of childhood trauma in FDS patients, as well as overall higher scores on the CTG (Childhood Trauma Questionnaire)
Elliott JO, Charyton C. 2014	Biopsychosocial predictors of psychogenic non-epileptic seizures	Cross-sectional study	n = 689	History of sexual abuse if more frequent in FDS only patients than in patients with mixed FDS or epilepsy only.
Scevola L, Teitelbaum J, Oddo S et al. 2013	Psychiatric disorders in patients with psychogenic nonepileptic seizures and drug-resistant epilepsy: A study of an Argentine population	Cross-sectional study	n = 84	Anxiety disorders, trauma history, PTSD and personality cluster B disorders were more frequent in the group with PNESs. DRE patients had a higher frequency of psychotic disorders. Depression was equally prevalent in both groups.
Scevola L, Wolfzun C, Sarudiansky M et al. 2021	Psychiatric disorders, depression and quality of life in patients with psychogenic non-epileptic seizures and drug resistant epilepsy living in Argentina	Cross-sectional study	n = 148	A history of trauma was present in 78.5% of patients in the PNES group, and only in 26% of patients in the DRE group.

with FDS, the FDS group exhibited significantly higher rates of sexual trauma as “other” trauma (Myers et al., 2019a). A recent review described that history of traumatic events ranges from 44% to 100% in FDS patients, and a history of sexual abuse ranges from 23% to 77% (Lanzillotti et al., 2021). However, a more recent study conducted in Iran where 314 patients with FDS were studied showed different results, with only 12.8% of patients having a history of childhood abuse, 11.8% having a history of physical abuse, and 8.1% having a history of sexual abuse (Asadi-Pooya and Bahrami, 2019a).

Previous studies have suggested a symptom overlap in psychological domains between patients who suffer FDS and experienced repeated childhood traumatic experiences and patients with “complex” PTSD (Hingray et al., 2017). This could be related to the high rates of PTSD observed in FDS patients (as mentioned in the previous section) and suggest that FDS may represent a manifestation of complex PTSD in some cases.

A recent study of 169 FDS patients collected different data (including biographical information, history of childhood or adulthood traumatic experiences, seizure semiology, and psychopathological data) and identified three patient clusters specifically related to the presence (or absence) and the type of trauma. The three clusters identified were a “No/Single Trauma” group (31.4%), a “Cumulative Lifetime Traumas” group (42.6%), and a “Childhood Traumas” group (26%). The first group included only a minority of patients who reported trauma history, and none experienced multiple lifetime traumas. Patients in the second group included those who reported at least one traumatic event both in childhood and adulthood. Patients in the third group included those who reported childhood trauma and most had experienced multiple traumatic events during their childhood. This group (Childhood Traumas) also had the highest rates of history of sexual abuse (75%). Each group differed in epidemiology, seizure semiology, and psychopathology (Hingray et al., 2022a). The results found in the mentioned study suggest that trauma history could play an essential role in the distinction of different subgroups of FDS patients with different epidemiology, comorbidities, and semiology characteristics.

5. Linking the neurobiology of dissociation, trauma, and FDS

5.1. Neurobiology of FDS

Even though many studies have established the importance of psychosocial factors in FDS (Popkirov et al., 2019; Reuber, 2009), the neurobiology of this disorder has received far less attention. Therefore, the neurobiological underpinnings of FDS have been poorly understood (Anzellotti et al., 2020b). However, evidence in this field is growing, and some crucial correlates have been described. Many studies using different techniques explored structural changes in the brain and abnormalities in functioning and connectivity. This section summarizes some of the most relevant findings (see Fig. 1 and Table 2).

To the best of our knowledge, only two studies in the existing literature have evaluated morphological brain changes in FDS patients, exhibiting contradictory results. A study by Labate et al. revealed abnormal cortical thinning of the right premotor and motor regions and cerebellum bilaterally in FDS patients compared to healthy control (Labate et al., 2012). On the other hand, the study by Ristic et al. (Ristić et al., 2015) found increased and decreased thickness in different cortical areas in FDS patients. These patients exhibited increased cortical thickness in the left and right medial-orbitofrontal and left lateral-orbitofrontal cortex, whereas atrophy was found in the left and right precentral, right entorhinal, and right lateral occipital regions when compared to healthy controls.

Several connectivity studies have shown interesting findings regarding structural and functional changes in the brain of patients with FDS (Li et al., 2015a; Ding et al., 2013a, 2014a; Barzegaran et al., 2016). Using diffusion tensor imaging (DTI), Hernando et al. (2015a) found right lateralization of the connectivity of the uncinate fasciculus, a vital tract implicated in the connection between medial prefrontal regions and limbic areas (amygdala, hippocampus) that plays a crucial role in the emotion regulation and memory processes. According to this study, this right lateralization negatively affects emotion regulation. On the contrary, a similar study using DTI found a left lateralization pattern and increased connectivity in other structures, including the left corona radiata, left internal and external capsules and left superior temporal

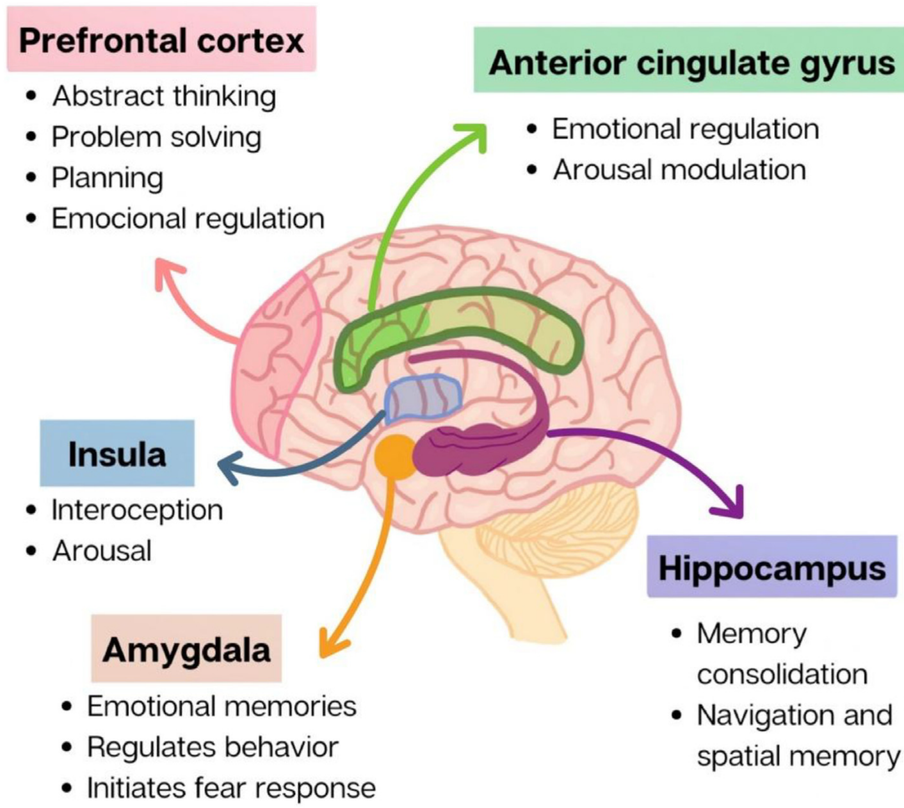

Fig. 1. Brain structures involved in the neurobiology of functional/dissociative seizures (FDS).

Table 2
Main studies showing neurobiological underpinnings of FDS.

Authors	Title	Sample	Methods	Results
Ding J, An D, Liao W et al. 2013	Altered Functional and Structural Connectivity Networks in Psychogenic Non-Epileptic Seizures	n = 37	Resting-state functional MRI DTI	FDS patients showed altered small-worldness in both functional and structural networks and shifted towards a more regular (lattice-like) organization.
Din J, An D, Liao W et al. 2014	Abnormal functional connectivity density in psychogenic non-epileptic seizures	n = 38	MRI with functional connectivity density mapping	FDS patients showed abnormal functional connectivity density (FCD) in the frontal cortex, cingulate gyrus, insula, and occipital cortex. Occipital cortex FCD correlated with duration of disease. Patients also showed disrupted functional connectivity between all these regions.
Li R, Liu K, Ma X et al. 2015	Altered Functional Connectivity Patterns of the Insular Subregions in Psychogenic Nonepileptic Seizures	n = 38	Resting-state functional MRI	FDS patients showed significantly stronger functional connectivity between insular subregions and sensorimotor networks, lingual gyrus, superior parietal gyrus and putamen.
Van Der Kruijs S, Bodde N, Vaessen M et al. 2012	Functional connectivity of dissociation in patients with psychogenic non-epileptic seizures	n = 23	Functional MRI	FDS patients showed increased functional connectivity values between insula, inferior frontal gyrus, parietal cortex, and precentral sulcus.
Li R, Li Y, An D et al. 2015	Altered regional activity and inter-regional functional connectivity in psychogenic non-epileptic seizures	n = 38	Resting-state functional MRI	FDS patients exhibited increased functional connectivity in dorsolateral prefrontal cortex (DLPFC), sensorimotor and limbic system, and decreased functional connectivity in the ventrolateral prefrontal cortex. FDS patients also showed increased fractional amplitude of low-frequency fluctuations (fALFF) in the DLPFC, parietal cortices and motor areas, and decreased fALFF in the triangular inferior frontal gyrus.
Hernando K, Szaflarski J, Ver Hoef L et al. 2015	Uncinate fasciculus connectivity in patients with psychogenic nonepileptic seizures: A preliminary diffusion tensor tractography study	n = 16	MRI DTI	FDS patients showed a greater number of uncinate fasciculus streamlines in the right hemisphere tract than in the left hemisphere.
Arthuis M, Micoulaud-Franchi J, Bartolomei F et al. 2015	Resting cortical pet metabolic changes in psychogenic non-epileptic seizures (FDS)	n = 32	18FDG-PET	FDS patients exhibited significant PET hypometabolism in the right inferior parietal and central region, and bilaterally in the anterior cingulate cortex. FDS patients also showed significant increase in metabolic correlation between right inferior parietal/ central region and bilateral cerebellum, and between bilateral anterior cingulate cortex and left parahippocampal gyrus.

gyrus, some of which are involved in motor functions (Lee et al., 2015).

A study using DTI and resting-state fMRI (rs-fMRI) was the first to explore the topological organization in FDS. Results showed that patients with FDS present decreased structural and functional connectivity strength in brain areas involved in attention and sensorimotor processing, subcortical regions, and areas of the Default Mode Network (Ding et al., 2013a). In a follow-up study using the same data and density mapping (Ding et al., 2014a), researchers found that patients with FDS showed abnormal function connectivity density regions. The sensorimotor cortex, frontal cortex, cingulate gyrus, insula, and occipital cortex were mainly altered. These findings support the hypothesis that FDS is associated with alterations in attention, emotion, and sensorimotor networks (Ding et al., 2014a).

Li et al. investigated the functional connectivity of insular subregions in these patients (Li et al., 2015b). Results demonstrated that patients with FDS, compared to healthy controls, exhibited more robust functional connectivity between insular subregions and sensorimotor networks, lingual gyrus, superior parietal gyrus, and putamen. These findings suggest a hyperlink pattern of insular subregions involved in abnormal cognitive processes, motor function, and emotional regulation in FDS. Later, the same group conducted a follow-up study to re-analyze the dataset (Li et al., 2015a). Results demonstrated that patients with FDS show increased synchronous activity mainly in the dorsolateral prefrontal cortex, parietal, and motor regions and decreased activity in the right triangular inferior frontal gyrus. This brain structure is part of the ventrolateral prefrontal cortex and has a role in the modulation of response inhibition (Li et al., 2015a).

A study using Positron-Emission Tomography (PET) compared FDS patients to healthy controls. According to the results, patients with FDS exhibit hypometabolism in the right inferior parietal and central region and the bilateral anterior cingulate cortex (Arthuis et al., 2015a). These findings also support the idea that many pathophysiological mechanisms might produce FDS. Emotion dysregulation could be related to decreased functioning in the anterior cingulate cortex. On the other hand, altered self-awareness/consciousness processes might be associated with hypometabolism in the right inferior parietal cortex (Anzellotti et al., 2020b).

Finally, only one study using fMRI has evaluated functional connectivity changes in response to external stimuli in patients with FDS (van der Kruijs et al., 2012). Interestingly, patients with this condition exhibited stronger connectivity values between areas involved in emotion regulation, executive control, and movement (insula, inferior frontal gyrus, parietal cortex, and precentral sulcus, respectively), which were significantly associated with higher dissociation scores. These results support the idea that FDS patients have a higher tendency to dissociate.

5.2. *Neurobiology of dissociation and trauma*

Many specialists have proposed dissociation as one of the fundamental mechanisms in this disorder since people with FDS often present dissociative symptoms (Pick et al., 2017). Dissociation is a broad construct that includes a variety of conditions such as amnesia, depersonalization/derealization, identity fragmentation, and somatoform symptoms. Current neurobiological studies define dissociation as a disturbance in the integration of thought, memory, emotion, feelings, sense of self, body awareness, and perception of the external environment. Some authors have proposed that dissociative disorders, altogether with borderline personality, PTSD, and conversion and somatoform disorders, constitute the spectrum of trauma-related disorders. Thus, the effects of traumatic events would go beyond PTSD (del Río-Casanova et al., 2016).

During development, childhood traumatic experiences can be crucial since they may alter the neurobiological structure and function of the brain. Alterations occur mainly in stress-sensitive areas, such as the amygdala, prefrontal cortex (PFC), and hippocampus. These changes are a result of the interaction between chronic and repeated activation of the physiological stress response (activation of the hypothalamic-pituitary-adrenal (HPA) axis) and genetic and epigenetic factors during sensitive periods of development (Sierra et al., 2002; Brown and Reuber, 2016). Therefore, chronic exposure to stress can cause impairment in these structures, leading to maladaptive responses to stressful situations (Pant et al., 2022).

Neurobiological findings in dissociative disorders do not show a unitary pattern (del Río-Casanova et al., 2016). For example, in psychogenic amnesia, there is a hyperactivation of the prefrontal areas and hypoactivation of the amygdala with an increase in inhibitory experiences (van der Kruijs et al., 2014a). However, evidence is contradictory since the opposite correlates have also been found (Kikuchi et al., 2010).

Research in patients with PTSD has provided substantial evidence regarding the neural basis of dissociation. Lanius et al. used functional MRI (fMRI) and found that patients with PTSD, predominantly related to childhood abuse, presented two response patterns. 70% of the subjects showed a predominant re-experiencing/hyperarousal pattern with increased heart rate, while 30% of the sample presented a dominant secondary dissociative response, consisting of depersonalization and derealization states without increased heart rate (Lanius et al., 2006).

In the study mentioned above, researchers found that patients who experienced what they called “primary dissociation” (re-experiencing and hyperarousal) exhibited abnormally low activation in the medial prefrontal cortex and the anterior cingulate cortex. These brain areas are crucial in emotion regulation and arousal modulation (Lanius et al., 2006). Increased amygdala activation has been reported in PTSD patients after exposure to traumatic reminders and fearful masked faces (Etkin and Wager, 2007). In this way, primary dissociation symptoms can be conceptualized as a result of emotional under-modulation (or under-regulation) since there is a failed prefrontal inhibition of reactive limbic regions (see Fig. 2).

Findings regarding secondary dissociation symptoms (depersonalization/derealization and analgesia) are quite different. Another study carried out by Lanius et al. (2010) revealed that patients with PTSD experiencing these symptoms presented abnormally high activation in the anterior cingulate cortex (ACC) and the medial prefrontal cortex. Therefore, PTSD dissociative subtype results from an emotional over-modulation of traumatic memories caused by increased activation of the medial prefrontal structures and hyperinhibition of limbic areas, such as the amygdala (see Fig. 2). This constitutes the so-called corticolimbic inhibition model. Several studies showed results in the same direction and provided further evidence to support this theory (Felmingham et al., 2008; Röder et al., 2007).

This information has led to the hypothesis that neurobiological underpinnings in conversion disorder would vary according to the type of symptoms the patient presents. According to some authors, there are two types of conversion symptoms. On the one hand, the negative type includes sensorimotor deficits such as paralysis, aphonia, blindness, deafness, and sensory loss (Rió-Casanova et al., 2016). These manifestations have been linked to emotional over-regulation (Sierra et al., 2002). On the other hand, positive conversion symptoms are characterized by excessive activity manifested by tremors, aberrant moments, and psychogenic seizures, among others, resulting from emotional under-regulation (Rió-Casanova et al., 2016).

6. Discussion

This manuscript carried out a state-of-the-art review to provide a critical approach to the extensive literature about FDS, focusing on describing the epidemiology, the association with trauma, and reviewing the neurobiological underpinnings and associations of FDS, trauma, and dissociation.

FDS still constitutes a serious mental health unresolved problem. The interdisciplinary approach involving different mental health professionals is essential for the proper diagnosis and treatment of patients with FDS (Duncan et al., 2011; Benbadis and Allen Hauser, 2000; Brown

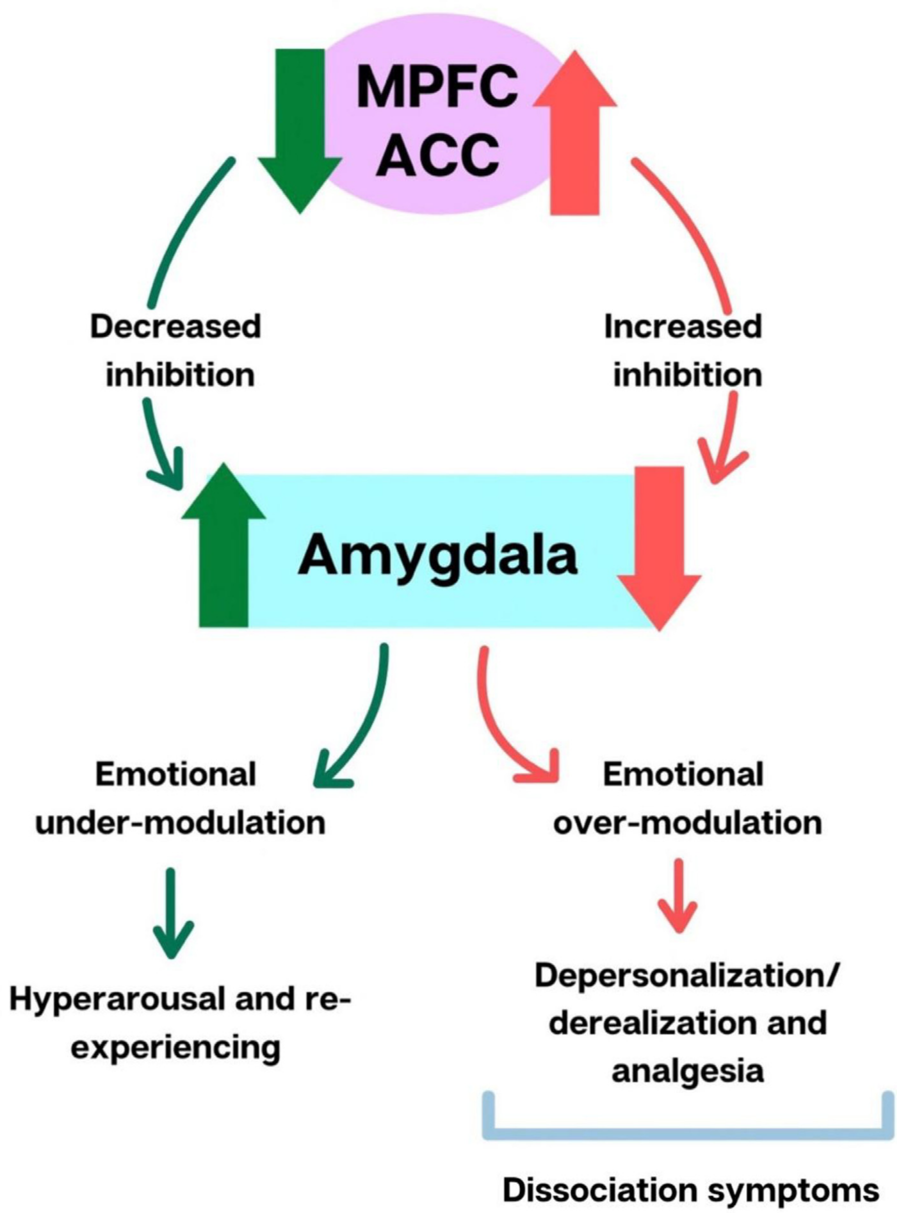

Fig. 2. Mechanisms involved in emotional modulation of FDS patients.

and Reuber, 2016; Neurology, 2002). Furthermore, there is a delay of several years to reach FDS diagnosis in different countries, which is still too long and too late to implement the correct treatment (Scévola et al., 2013a; Neurology, 2002; Reuber et al., 2002).

Most patients with FDS present at least one current and recognizable psychiatric disorder, and many studies showed high rates of somatization, conversion, and dissociative disorders, combined with other comorbid disorders such as depression. The history of sexual abuse, trauma, and posttraumatic stress disorder (PTSD) have been considered etiopathogenic factors (Popkirov et al., 2019; D'Alessio et al., 2006; Scévola et al., 2013a; Baillés et al., 2004; Bowman and Markand, 1996; Galimberti et al., 2003; Fiszman et al., 2004).

FDS patients present alterations in functional connectivity of brain regions, especially in networks involved in attention, emotion processing, memory processes, self-awareness, and sensory and motor functions. These abnormalities result in an aberrant sensorimotor process that occurs without the conscious and voluntary control of the individual (Anzellotti et al., 2020b). This evidence supports the idea that this disorder is produced by altered brain mechanisms (behavior, emotion processing, and cognition) that may result from life experiences, mainly adverse life events and maladaptive experiential learning (Li et al., 2015a). Altogether with the morphological changes, these findings may provide the missing neurobiological correlations that would help to explain the complex mechanisms underlying FDS, including how emotion can affect executive control and result in seizure-like episodes. However, it is crucial to consider that some of these findings have modest clinical relevance. Moreover, it is still unclear whether they are found explicitly in FDS or can instead be associated with other frequent comorbidities, such as traumatic brain injury and depression.

The neurobiological findings in all dissociative disorders are still unclear, albeit some evidence converges in explaining emotional under and over-regulation mechanisms. The concept of trauma-related disorders proposed by some authors (del Río-Casanova et al., 2016) may be beneficial in classifying disorders that present dissociative symptoms. According to this model, at one end of the axis, we could find disorders related to emotion under-modulation (PTSD with hyperarousal, BPD, dissociative and conversion disorders with positive symptoms), while at the opposite end would include those where over-modulation predominates (somatoform disorders, dissociative and conversion disorders with negative symptoms). It is essential to clarify that emotional regulation strategies may coexist in most disorders.

Many of the studies reported in this review had some limitations that should be mentioned. First, many of them used small a sample size, which may decrease statistical power (Ding et al., 2013b, 2014b; Li et al., 2015c, 2015d; Arthuis et al., 2015b; van der Kruijs et al., 2014b; Ding et al., 2013b, 2014b; Li et al., 2015c, 2015d; Arthuis et al., 2015b; van der Kruijs et al., 2014b). Hence, further studies using larger samples may be necessary to replicate and support these findings. Also, many studies are based on third-level centers (Myers et al., 2019b; Scévola et al., 2013b, 2021b; Johnstone et al., 2016b), leaving out a group of FDS patients diagnosed in second-level or first-level centers and not represented.

Some of the abovementioned research excluded patients with psychiatric comorbidity (Ding et al., 2013b, 2014b; Li et al., 2015c). Even though this could be important to evaluate neurobiological findings specific to FDS, psychiatric comorbidity tends to be the rule and not the exception in these patients. This reinforces the need to replicate studies using larger samples since this may help investigate findings in more heterogenous FDS samples, carrying out subgroup analyses according to the different comorbidities.

Regarding connectivity studies, two of the cited studies used deterministic-DTI-based tractography, a technique with certain limitations. Since the tracking procedure stops when it reaches regions with fiber crossings, the sensitivity might be reduced (Ding et al., 2013b; Li et al., 2015c; Hernando et al., 2015b). To address this issue, future studies should consider probabilistic tractography techniques.

Another limitation of these studies is the difficulty of discussing and measuring trauma. Frequently, studies rely on self-administered questionnaires (Johnstone et al., 2016b; Hingray et al., 2022b) or self-report of traumatic experiences (Myers et al., 2019b; Asadi-Pooya and Bahrami, 2019b; Elliott and Charyton, 2014b) without a formal psychological evaluation, which can be too subjective. Since trauma can be associated with embarrassment, stigmatization, and fear of social prejudice, it can be difficult for patients to disclose it. Besides, patients might be amnestic about traumatic experiences leading to recall bias. Therefore, there might be a greater prevalence of trauma history than reported.

Something worth mentioning is that most studies in this review regarding trauma and FDS are based in urban Western populations (Myers et al., 2019b; Scévola et al., 2013b, 2021b; Johnstone et al., 2016b). Exceptions include one study carried out in Iran, which reported lower rates of sexual abuse (Asadi-Pooya and Bahrami, 2019a), and one review that included studies from Eastern populations, where lower rates of trauma were found compared to studies from Western populations (Beghi et al., 2015b). This difference could be related to greater stigmatization and less willingness to discuss trauma history in Eastern cultures than in Western cultures. The definition and acceptance of trauma, mainly sexual, can be conditioned by cultural factors, which normalize certain experiences that, despite cultural acceptance, can still be traumatic. This might be the case in the Irani study, where the reported level is clearly odd. However, there could be biological and social differences among different populations, and further research could provide notable contributions, including FDS patients from other cultures, races, and ethnicities.

The literature mentioned above highlights the heterogeneity of the population affected by FDS. Trauma presence or history seems to be an essential characteristic of the psychopathology of these patients. The studies cited in this review support the hypothesis that distinct etiopathogenic profiles contribute to the development of FDS, and trauma and PTSD seem to play an important role. A better understanding of these entities may allow us to develop more specific diagnostic and better therapeutic approaches (Hingray et al., 2022a).

Disclosure

The authors reported no conflicts of interest for this work.

Declaration of competing interest

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