Seminar in Epileptology

Epileptic Disord 2019; 21 (6): 529-47

The aetiology of psychogenic non-epileptic seizures: risk factors and comorbidities

Stoyan Popkirov [1], Ali A. Asadi-Pooya [2], Roderick Duncan [3], David Gigineishvili [4], Coraline Hingray [5], Andres Miguel Kanner [6], W. Curt LaFrance Jr. [7], Chrisma Pretorius [8], Markus Reuber [9]
on behalf of the ILAE PNES Task Force

[1] Department of Neurology, University Hospital Knappschaftskrankenhaus Bochum, Ruhr University Bochum, Germany
[2] Neuroscience Research Center, Shiraz Medical School, Shiraz University of Medical Sciences, Shiraz, Iran; Jefferson Comprehensive Epilepsy Center, Department of Neurology, Thomas Jefferson University, Philadelphia, USA
[3] Department of Neurology, University of Otago, Christchurch, New Zealand
[4] Department of Neurology & Neurosurgery, Tbilisi State University, Tbilisi, Georgia
[5] Pôle Hospitalo-Universitaire de Psychiatrie d'Adultes du Grand Nancy Centre Psychothérapique de Nancy, Laxou, France; Département de Neurologie, Centre Hospitalier Universitaire de Nancy, Nancy, France
[6] Department of Neurology, Miller School of Medicine, University of Miami, FL, USA
[7] Departments of Neurology and Psychiatry, Brown Medical School, Rhode Island Hospital, Providence, USA
[8] Department of Psychology, University of Stellenbosch, South Africa
[9] Academic Neurology Unit, University of Sheffield, Royal Hallamshire Hospital, Sheffield, UK

Received September 06, 2019; Accepted October 29, 2019

ABSTRACT – Psychogenic non-epileptic seizures (PNES), also known as dissociative seizures, are paroxysms of altered subjective experience, involuntary movements and reduced self-control that can resemble epileptic seizures, but have distinct clinical characteristics and a complex neuropsychiatric aetiology. They are common, accounting for over 10% of seizure emergencies and around 30% of cases in tertiary epilepsy units, but the diagnosis is often missed or delayed. The recently proposed "integrative cognitive model" accommodates current research on experiential, psychological and biological risk factors for the development of PNES, but in view of the considerable heterogeneity of presentations and medical context, it is not certain that a universal model can capture the full range of PNES manifestations. This narrative review addresses key learning objectives of the ILAE curriculum by describing the demographic profile, common risk factors (such as trauma or acute stress) and comorbid disorders (such as other dissociative and functional disorders, post-traumatic stress disorder, depressive and anxiety disorders, personality disorders, comorbid epilepsy, head injury, cognitive and sleep problems, migraine, pain, and asthma). The clinical implications of demographic and aetiological factors for diagnosis and treatment planning are addressed.

Key words: dissociative seizures, psychogenic non-epileptic seizures, aetiology, risk factors, comorbidity

Correspondence:
Stoyan Popkirov
Klinik für Neurologie,
Universitätsklinikum
Knappschaftskrankenhaus Bochum,
In der Schornau 23-25,
44892 Bochum, Germany
<popkirov@gmail.com>

doi:10.1684/epd.2019.1107

Psychogenic non-epileptic seizures (PNES), also known as dissociative seizures, are episodes of altered subjective experience, involuntary movements and reduced self-control that can resemble epilepsy, syncope, or other paroxysmal disorders. However, rather than being caused by neuronal hypersynchronisation (as in epilepsy) or cerebral hypoperfusion (as in convulsive syncope), PNES are the result of complex neuropsychiatric dysfunction. The diagnosis is primarily based on the analysis of seizure experiences and visible manifestations (the patient's history and observable seizure semiology), and is supplemented by the careful exclusion of alternative explanations such as epilepsy (Avbersek and Sisodiya, 2010; LaFrance *et al*., 2013). This narrative review addresses key learning objectives of the ILAE curriculum by describing the demographic profile, common risk factors and comorbid disorders of PNES (Blümcke *et al*., 2019).

While different psychophysiological mechanisms may make variable contributions to the aetiology of PNES in individual patients, a range of predisposing, precipitating and perpetuating factors have been identified across patient populations and integrated into theoretical models (Brown and Reuber, 2016a, 2016b; LaFrance and Bjønæs, 2019). Notably, many possible aetiological contributors defy a simple, dualistic categorization into "psychological" or "physical" factors (*e.g.* childhood abuse affects both brain maturation and social functioning). Within a biopsychosocial framework, it is somewhat arbitrary to discuss disorders which have been defined as being nosologically distinct (*e.g.* panic disorder or post-traumatic stress disorder [PTSD]) as "comorbidities" and not as primary disorders, which include PNES as one manifestation. With this caveat in mind, we discuss risk factors and comorbidities along the lines of the current nosologies in which most PNES are classified as a functional neurological symptom (conversion) disorder according to *Diagnostic and Statistical Manual of Mental Disorders* (*DSM-5*), or dissociative disorder in the International Classification of Diseases 11th edition (Perez *et al*., 2015; Erro *et al*., 2016).

Epidemiology

PNES is a common disorder which is recognised around the world (Kanemoto *et al*., 2017). Major differences in access to diagnostic facilities and expertise mean that there is no reliable epidemiological evidence allowing prevalence comparisons between different countries (Hingray *et al*., 2018). PNES have an annual incidence of at least 1.5-6.17/100,000 (Sigurdardottir and Olafsson, 1998; Szaflarski *et al*., 2000; Duncan *et al*., 2011). This range is likely to be an underestimate of the general population incidence because it only accounts for video-EEG documented diagnoses. In general neurology outpatient clinics, PNES account for 2% of new referrals (Stone *et al*., 2010). In specialised "first seizure" clinics, they comprise 8-12% of presentations (Angus-Leppan, 2008; Duncan *et al*., 2011). Among patients presenting with convulsive seizures to emergency services, PNES are recognised in 11% of cases (Dickson *et al*., 2017). The proportion of those with PNES among patients with apparently refractory epilepsy referred to tertiary epilepsy units is around 30% (Asadi-Pooya and Sperling, 2015). The prevalence of PNES in the general population has been estimated at 2-50/100,000 (Benbadis and Allen Hauser, 2000; Kanemoto *et al*., 2017). Patients with the same disorder also account for about 5% of referrals to specialist syncope services (although their condition is most commonly labelled as "psychogenic syncope" or "pseudosyncope") (Tannemaat *et al*., 2013; Popkirov *et al*., 2014).

PNES cohort studies have identified a number of socioeconomic and demographic risk factors for PNES (McKenzie *et al*., 2010; Duncan *et al*., 2011; Goldstein *et al*., 2019). Women (and girls) make up 60-80% of all patients, although the gender disparity is smaller in older adults and those with intellectual disability (Duncan *et al*., 2006; Duncan and Oto, 2008; Goldstein *et al*., 2019). The mean and median age at onset is around 28 years (although the modal age is 19 years). Young women are at particularly high risk (Asadi-Pooya and Sperling, 2015; Goldstein *et al*., 2019). Like epilepsy, PNES is more commonly diagnosed in individuals from lower socioeconomic groups (Duncan *et al*., 2012), with one large study from the United Kingdom reporting that over 50% of all patients live in areas categorised within the highest deprivation quintile and over two-thirds of patients being unemployed at the point of seeking treatment for PNES (Goldstein *et al*., 2019).

Explanatory frameworks

A number of theoretical models have been proposed and summarized for PNES (LaFrance and Bjønæs, 2019). A recently proposed model, the "integrative cognitive model" (ICM), accommodates current research on experiential, psychological and biological risk factors for the development of PNES, but in view of the considerable heterogeneity of presentations and medical context, it is not certain that a universal model can capture the full range of PNES manifestations (*figure 1*) (Brown and Reuber, 2016b; Reuber and Brown, 2017). In the ICM, PNES are conceptualised as experiential and behavioural paroxysms that result from the activation of a learnt mental representation (akin to a computer programme, *i.e.* the *idea* of

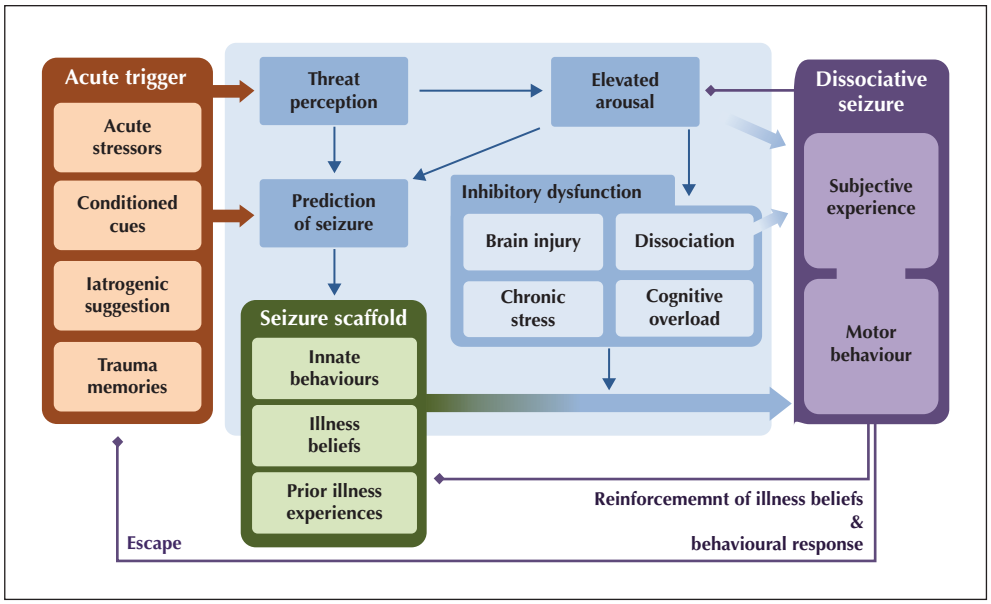

Figure 1. A range of internal and external events can trigger an affective-cognitive-behavioural cascade that culminates in the activation/disinhibition of a "seizure scaffold". Most components of this illness model are "optional", but an awareness of general pathophysiological pathways allows the integration of relevant risk factors and comorbidities on an individual patient level (see case examples).

a seizure, or "seizure scaffold"), often combined with concurrent physiological arousal. The seizure scaffold can contain elements of instinctive automatisms (*e.g.* freezing or thrashing movements), personal illness experiences (*e.g.* syncope or epilepsy) or illness beliefs (*e.g.* derived from witnessed seizures). The activation of the seizure scaffold is triggered by perceived threat and/or conditioned cues, and facilitated by a failure of inhibitory systems. This disinhibition, along with reduced behavioural awareness (or sense of agency), can occur in dissociative states, but also in the context of chronic stress or rumination. The activation of the seizure scaffold (associated with a change in awareness of the self and the environment) ultimately leads to the resolution of a state of distress and parasympathetic activation. This has a physiological component (a calming effect of dissociation through detachment and emotional numbing) and a psychosocial component (an escape from the trigger, *e.g.* through the interruption of interpersonal confrontation, catastrophising thoughts or intrusive memories). The "effective" resolution of the distressed state means that each PNES reinforces the system and makes the next PNES more likely to occur.

The ICM can accommodate much of the aetiological and clinical heterogeneity which characterises PNES. In the following sections, we discuss common aetiological factors and how they could contribute to the predisposition, precipitation and perpetuation of PNES according to the ICM.

Experiential risk factors

Traumatic abuse and stressful life events

The epidemiological association of PNES with previous life adversity and psychological trauma, which has been recognised since the nineteenth century (Breuer and Freud, 1895), continues to be a central element in the current understanding of the condition (Bowman, 2018). Studies have demonstrated increased rates of both childhood maltreatment (including sexual, physical and psychological abuse and neglect) and stressful life events, such as bereavement or illness (Bowman, 2018). A recent systematic review calculated that among 903 patients with PNES across 24 highly heterogeneous studies (compared to 1,023 controls), the odds ratio of retrospective reports of stressors in childhood and adulthood was 3.1 (confidence interval 1.7-5.6) (Ludwig *et al.*, 2018). Of note, different studies identified some patients (14-70%) who reported no severely stressful life events or childhood maltreatment (Ludwig *et al.*, 2018). This means that, although trauma and neglect may occasionally occur too early in life to be explicitly remembered, and the findings may have been affected by poor sensitivity of some of the methods used to capture trauma (Baldwin *et al.*, 2019), an attitude of "there must have been something traumatic" is not justified. Among patients with PNES, trauma is more prevalent in those with more severe psychiatric

comorbidity and stronger dissociative tendencies (Hingray *et al.*, 2011). Patients with PNES reporting sexual trauma also have more severe, and more commonly convulsive seizures, often characterised by emotional triggers and prodromal symptoms (Selkirk *et al.*, 2008) although this was not replicated in one recent study (Asadi-Pooya and Bahrami, 2019). While the identification of these features justifies a more extensive psychiatric exploration, the absence of reported trauma or stress does not contradict a diagnosis of PNES.

Trauma can contribute to the occurrence of PNES in various ways. Firstly, childhood maltreatment and traumatization have a clearly observable impact on brain development and maturation (Perry and Pollard, 1998). Studies have shown reproducible structural and functional changes in the brains of adults who have suffered childhood trauma (Herringa, 2017). Reduced grey matter in limbic and prefrontal areas is consistently found and related to abnormal stress and emotion regulation (Paquola *et al.*, 2016). These effects on frontolimbic structures may be aggravated by reduced functional connectivity between limbic and prefrontal areas as well as increased amygdala reactivity to negative stimuli (Herringa, 2017). Although imaging studies in patients with PNES have so far failed to converge on pathognomonic structural abnormalities across unselected PNES patient populations (Asadi-Pooya, 2015; McSweeney *et al.*, 2017), altered structural frontolimbic connectivity has been demonstrated in some cases (Hernando *et al.*, 2015; Lee *et al.*, 2015; Perez *et al.*, 2017), possibly related to disruption of age-dependent maturation processes (Popkirov *et al.*, 2018a).

The long-term developmental effects of childhood trauma also include changes in various developmentally sensitive allostatic systems relevant to PNES and related disorders (Keynejad *et al.*, 2018). Childhood maltreatment affects inflammatory states in adulthood (Danese *et al.*, 2007) with studies consistently showing chronic alterations independent of psychiatric morbidity (Coelho *et al.*, 2014). Closely connected to functional changes in inflammatory systems are those in the stress response system, and within it the hypothalamic-pituitary-adrenal axis (Roelofs and Pasman, 2016; Keynejad *et al.*, 2018). Limited empirical evidence suggests that basal diurnal cortisol is increased in patients with PNES, especially those with a history of sexual trauma (Bakvis *et al.*, 2010), and correlated with heightened threat perception (Bakvis *et al.*, 2009).

Lastly, traumatic events can also contribute to the manifestation of PNES through their subsequent mental representation, *i. e.* memories (Bowman, 1993). Seizures can be precipitated by trauma cues and ictal experience can include reliving of trauma memories (flashbacks) (Reuber *et al.*, 2011, 2016). The suppression of intolerable memories has long been presumed to be a primary function of dissociation according to Pierre Janet, or, in Freudian terms, the "primary gain" of "conversion" (Bowman, 2018). Studies using functional MRI have shown that the neurophysiology behind wilful memory suppression in general involves activation of the lateral prefrontal cortex which suppresses hippocampal activity (Anderson *et al.*, 2004). Similar network responses to traumatic memories have been observed in patients with dissociative movement disorders ("motor conversion disorder") (Aybek *et al.*, 2014). Furthermore, compared to healthy controls, patients also had accompanying activation of areas involved in motor planning and body schema (supplementary motor area and temporoparietal junction). This kind of motor system activation has been associated with the initiation of previously learnt motor behaviour independent of top-down voluntary control (Voon *et al.*, 2011; Aybek *et al.*, 2014).

Acute and persistent stress

Stress does not have to be severe or traumatic to contribute to the occurrence of PNES. A stress-diathesis model can help explain the variability in trauma and stress history in patients (Keynejad *et al.*, 2018). In individuals with high biological susceptibility to stress-related pathology, even mildly or moderately stressful experiences may precipitate PNES. Conversely, even in the absence of particularly strong innate predispositions, chronic stress or major psychological trauma may lead to PNES or other functional neurological symptoms. Acute stress is frequently cited by patients and (more so) caregivers as a trigger of PNES, and bodily signs of distress are often reported as premonitory or ictal phenomena (Reuber and Rawlings, 2016). What is more, PNES are associated with acute physiological arousal which may be followed by parasympathetic activation as a PNES subsides (Ponnusamy *et al.*, 2012; van der Kruijs *et al.*, 2016). This supports the idea that dissociation in general and PNES in particular can serve as an allostatic mechanism that relieves distress, especially when other coping mechanisms are unavailable or have been overwhelmed (Goldstein and Mellers, 2006; Stone and Carson, 2013; Brown and Reuber, 2016b).

Dysfunctional relationships and attachment

In addition to leading to long-term problems with stress and emotion regulation, childhood trauma is known to be associated with the development of dysfunctional attachment styles in adulthood. In keeping with this, problems in interpersonal functioning

are common among patients with PNES (Brown and Reuber, 2016a). Relationships within the family, with therapists, and in a wider social environment are often characterized by insecure attachment, social anxiety and avoidance. This can be a major source of emotional distress for patients (Green *et al*., 2017; Wardrope *et al*., 2019). In line with the ICM, PNES can remove patients from situations characterised by interpersonal challenges, thus reinforcing an unintentional "escape"-mechanism (Brown and Reuber, 2016b). This is evident in cases when PNES occur during psychotherapy, where stressors such as relationship conflicts and traumatic memories are often addressed (Kemp *et al*., 2018). Aside from the immediate stress relief afforded by a PNES, secondary reinforcement may be provided by the "sick role" conferred upon patients within their social environment.

Illness beliefs, social contagion and iatrogenesis

The power of suggestion in the precipitation of PNES is a well-known phenomenon, which is sometimes used as a diagnostic technique in epilepsy centres (Popkirov *et al*., 2015a). Purely "ideogenic" cases, whereby the conviction that one has a seizure disorder is sufficient to cause seizures, are very rare (Roach and Langley, 2004). Nonetheless, certain illness beliefs can be potent precipitating and perpetuating factors. In military veterans, for example, among 81 patients with PNES, 47% cited (usually mild) traumatic brain injury as a cause of their seizures (possibly influenced by the well-known association of head injury and epilepsy) (Salinsky *et al*., 2018). Misattribution effects like this can be reasonably extrapolated to head injuries in a civilian context (see below), especially with the recent media attention around mild traumatic brain injury (Popkirov *et al*., 2018a).

Another common perpetuator of physician-related illness misattribution is medication. Taking an antiepileptic drug (AED) may contribute to the delay of correcting an epilepsy misdiagnosis (Bahrami *et al*., 2019). While it is conceivable that AEDs could predispose to PNES through (unwanted) physiological effects (Niedermeyer *et al*., 1970; Jabeen *et al*., 2018), the prescription of AEDs is likely to shape illness expectations, and there have even been cases when AED prescribed for a different reason (*e.g.* neuropathic pain) have contributed to the subsequent misinterpretation of seizure-like events as epilepsy (Oto *et al*., 2003). For this reason, once a diagnosis of PNES (and absence of epilepsy) has been established, AEDs given for suspected epilepsy should be tapered immediately, not least to support the change in illness perceptions (Thompson *et al*., 2009; Oto *et al*., 2010). Explaining that AEDs do not treat PNES and removing them can have positive effects on quality of life (Rawlings *et al*., 2017a) and long-term outcome (Duncan *et al*., 2016; Chen *et al*., 2018).

Psychiatric comorbidity

Dissociative and functional disorders

PNES are commonly associated with other dissociative and functional neurological (conversion) symptoms. Other dissociative disorders have been identified in a median of 33% of patients with PNES (Bowman, 2018). Additional functional, or "medically unexplained", symptoms are found in 60-80% of patients with PNES (Bowman and Markand, 1996; Duncan *et al*., 2011; McKenzie *et al*., 2011). Conversely, a study of the first 100 consecutive outpatients evaluated at a speciality clinic for motor functional neurological disorders (FND) reported that 17 patients had PNES combined with a functional movement disorder and/or a functional limb weakness (Matin *et al*., 2017). In another study on 73 patients with motor FND, 17 (23%) also had PNES (Crimlisk *et al*., 1998). In a large series of 65 cases of functional movement disorders, three had coexisting PNES (5%), while 8/157 (5%) patients with PNES from the same study had a coexisting functional movement disorder (Driver-Dunckley *et al*., 2011). In a series of 107 cases of functional limb weakness, eight patients (7%) reported a "non-epileptic attack" at symptom onset (Stone *et al*., 2012). Somatization tendencies, identified by high levels of self-reported physical symptoms correlate positively with greater severity and poor outcome (Reuber *et al*., 2003a, 2003b; Brown and Reuber, 2016a).

Post-traumatic stress disorder (PTSD)

Considering the strong association between trauma and PNES, it is not surprising that PTSD is a common comorbidity. In nine studies on adults with PNES that included PTSD assessment (reviewed by Fiszman *et al*. [2004]), 79/207 (38%) fulfilled diagnostic criteria for current PTSD. Comparable rates are reported in recent studies (reviewed and meta-analysed by Diprose *et al*. [2016]), with a higher rate of 58-64% among military veterans (Salinsky *et al*., 2012; Salinsky *et al*., 2018). It has been suggested that patients with PNES and repeated trauma experience in childhood show symptom overlap across psychological domains with patients with so-called "complex" PTSD (Hingray *et al*., 2017). Patients with both PNES and epilepsy tend to have lower rates of PTSD than those without comorbid epilepsy (D'Alessio *et al*., 2006; Labudda *et al*., 2018), suggesting alternative aetiological routes (see below).

PTSD comorbidity has potential therapeutic implications, as PNES patients with PTSD have higher levels of alexithymia and tend to apply more emotion-focused coping strategies compared to patients without trauma or with trauma but no PTSD (Zeng *et al.*, 2018). Prolonged exposure therapy, a PTSD-specific therapy that relies on guided confrontation with activities, places and situations associated with trauma, has been shown to lead to high rates of seizure remission in patients with PNES and comorbid PTSD (Myers *et al.*, 2017). Eye movement desensitization and processing (EMDR) -another psychotherapeutic technique used for PTSD- has also been suggested for the treatment of traumatized patients with PNES (Chemali and Meadows, 2004).

Personality disorder

A high prevalence of personality disorders among patients with PNES has been noted, with borderline personality disorder (BPD; also known as emotionally unstable personality disorder), or at least borderline personality traits, being a particularly common phenotype (although some studies report cluster C personality disorders [avoidant, dependent, or obsessive-compulsive] at similar rates) (Lacey *et al.*, 2007; Bermeo-Ovalle and Kanner, 2018). Childhood trauma is common in BPD and is associated with higher rates of dissociative symptoms (Popkirov *et al.*, 2018b). Conversely, emotion dysregulation, a hallmark of BPD, is frequently seen in patients with PNES and is likely to be an important factor in seizure pathophysiology (Reuber *et al.*, 2004; Williams *et al.*, 2018; Jungilligens *et al.*, 2019). BPD is further characterised by a marked instability of interpersonal relationships, which is a common and clinically relevant finding in patients with PNES (Holman *et al.*, 2008; Green *et al.*, 2017; Wardrope *et al.*, 2019). Dialectical-behaviour therapy, an intervention that specifically targets emotion dysregulation and interpersonal problems in BPD, can be helpful for patients with PNES (Bullock *et al.*, 2015).

Depression and anxiety

Exact rates vary, but a recent meta-analysis has calculated overall rates of clinical depression of around 40% (Walsh *et al.*, 2018). Comparative studies have revealed higher rates of depressive and anxiety disorders in patients with PNES compared to the general population (Bermeo-Ovalle and Kanner, 2018). Most studies of depression and anxiety disorders also found higher levels of these pathologies in patients with PNES than those with epilepsy (Diprose *et al.*, 2016; Walsh *et al.*, 2018). Compared to patients with epilepsy, depression in patients with PNES tends to manifest more through physical (rather than affective or cognitive) symptoms, is associated more closely with relationship problems (Green *et al.*, 2017), and has a stronger impact on quality of life (Walsh *et al.*, 2018). The frequency of anxiety disorders ranged between 9 and 71% in different studies (Bermeo-Ovalle and Kanner, 2018). In a recent meta-analysis of nine studies, 20% of patients with PNES had a comorbid panic disorder (Indranada *et al.*, 2018). Like PTSD, panic disorder might play a particularly relevant role in the pathophysiology of some PNES (Indranada *et al.*, 2018). Dissociative symptoms are common during panic attacks, and, conversely, anxiety symptoms are sometimes reported during PNES (Rawlings *et al.*, 2017b; Indranada *et al.*, 2018). The causal system underlying panic attacks (perceived threat -arousal- escape) can be found in some patients with PNES (Goldstein and Mellers, 2006; Brown and Reuber, 2016b).

Medical and neurological comorbidity

Epilepsy and epilepsy surgery

The combination of epilepsy and PNES is not uncommon and presents significant diagnostic and therapeutic challenges. When present, epilepsy almost invariably precedes the onset of PNES (Reuber *et al.*, 2003c). In a recent meta-analysis of over 118 studies with a pooled sample size of 17,478 patients, comorbid epilepsy was reported in 22% of cases on average (95% confidence interval: 19-25). The pooled estimate of the prevalence of comorbid PNES in cohorts of patients with epilepsy was 12% (Kutlubaev *et al.*, 2018). However, most studies originated from specialised epilepsy centres, so it is possible that the rate of patients with comorbid epilepsy would be lower in primary care, psychiatric or general neurology settings. In two population-based studies, the pooled rate of comorbid epilepsy was 14% (Kutlubaev *et al.*, 2018). The rate was also lower (below 10%) in studies requiring video-EEG proof of additional epileptic seizures (Lesser *et al.*, 1983; Benbadis *et al.*, 2001). Conversely, the rate of comorbid epilepsy may be higher in particularly selected patient groups, for instance, those with learning disabilities (Duncan and Oto, 2008) or children (Vincentiis *et al.*, 2006). The aetiological role of coexisting epilepsy is manifold, with illness-related chronic stress, psychiatric comorbidity, biological predisposition and symptom modelling all likely to play a role.

New onset of PNES can occur after epilepsy surgery in 2.4-8.8% of patients, with lower rates reported in larger studies (Ney *et al.*, 1998; Glosser *et al.*, 1999; Markoula *et al.*, 2013; Asadi-Pooya *et al.*, 2016). Brain surgery, other than epilepsy surgery, can precipitate

PNES at similar rates (Reuber *et al*., 2002). Peri-operative stress or the change in psychosocial dynamics associated with becoming seizure-free have been considered as potential aetiological factors (Ney *et al*., 1998; Asadi-Pooya *et al*., 2016), as well as lesional changes to brain network connectivity (Popkirov *et al*., 2018a).

Traumatic brain injury (TBI)

A history of head injury has been reported in patients with PNES at rates of 16-83%, with a pooled frequency of 42% among 1,039 adults across 17 studies (Popkirov *et al*., 2018a). This is higher than the rate of 12% found among the general population (Frost *et al*., 2013). The reported injuries are classified as mild TBI in the majority of cases with the distribution of severity approximating that found in the general population (Vincentiis *et al*., 2006). Mild TBI can have various neuropsychiatric consequences that could contribute to the occurrence of PNES (Popkirov *et al*., 2018a). Personal illness beliefs can be structured around a head injury (see above) even in the absence of a biologically plausible pathophysiology (Salinsky *et al*., 2018), and an injury that occurs in association with significant stress (combat, accident, emergency treatment) can contribute to maladaptive learning processes that incorporate acute concussive symptoms into conditioned stress responses (Brown and Reuber, 2016b). Lastly, diffuse axonal injury associated with temporary metacognitive impairments could be relevant in some cases (Popkirov *et al*., 2018a).

Cognitive complaints

Subjective cognitive complaints are reported by a majority of PNES patients (60%), but standard neuropsychology rarely confirms corresponding objective deficits (Driver-Dunckley *et al*., 2011). Lack of effort or task engagement is only very rarely to blame - instead, cognitive problems such as forgetfulness and difficulties with concentration are thought to arise from attentional dysfunction and slower information processing, both strongly correlated with comorbid mood disorders, possibly compounded by medication (see Teodoro *et al*. [2018] for a review of cognitive symptoms and deficit in PNES). This pattern of cognitive problems is not unique to PNES, but can be found in patients with functional movement disorders, fibromyalgia and chronic fatigue syndrome (Teodoro *et al*., 2018) or in isolation as a functional cognitive disorder (Stone *et al*., 2015). Cognitive complaints correlate significantly with quality of life in PNES patients (Myers *et al*., 2012) and should receive special attention. Possible medication effects need to be addressed, and patients need to be educated about the nature of the problems, potential interactions with disordered sleep and mood, and coping strategies. Considering the role of stress and cognitive control in the pathophysiology of PNES, it is easy to see how symptomatic attentional dysfunction in everyday life might contribute to precipitation and perpetuation of PNES in some cases (Brown and Reuber, 2016a).

Sleep disturbance

Patients with PNES more frequently report problems with sleep (Latreille *et al*., 2018) and sleep apnoea symptoms than those with epilepsy (Karakis *et al*., 2014). A history of sleep disorder is noted in a third of patients (Elliott and Charyton, 2014; Latreille *et al*., 2018). Four small polysomnographic studies on a total of 68 patients have been conducted (Bazil *et al*., 2003; Phillips *et al*., 2013; Latreille *et al*., 2019; Popkirov *et al*., 2019). Clinically significant sleep-disordered breathing is found in 14-29% of patients (Phillips *et al*., 2013; Popkirov *et al*., 2019). A probable periodic limb movement disorder was found in 27% of the patients examined (Popkirov *et al*., 2019). Overall sleep quality is compromised, with patients showing a mean sleep onset latency of around 45 minutes, and spending an average of 1-2 hours awake per night after first falling asleep (Latreille *et al*., 2018; Popkirov *et al*., 2019). This might explain why a large proportion of patients take sleep medication (Latreille *et al*., 2019). Sleep disturbances are common symptoms of depressive and anxiety disorders, but the link with PNES may be more than simple comorbidity. Both experimental and clinical studies have suggested that sleep deprivation promotes dissociative tendencies (van der Kloet *et al*., 2012a), and one study on a mixed psychiatric inpatient sample has shown a decrease in dissociative symptoms after sleep normalization (van der Kloet *et al*., 2012b), suggesting that improvement of sleep might be of therapeutic use in patients with PNES.

Chronic pain

Individuals with PNES are much more likely to have chronic pain conditions than epilepsy controls (Benbadis, 2005; Kerr *et al*., 2017), with pain reported by up to 86% of patients (Dworetzky *et al*., 2005; Driver-Dunckley *et al*., 2011; Gazzola *et al*., 2012). Chronic pain is more common in women (Thomas *et al*., 2013), and is often part of a somatic symptom disorder or fibromyalgia (Ettinger *et al*., 1999; Mokleby *et al*., 2002; Benbadis, 2005). A substantial proportion of those with PNES (24-47%) uses regular pain medication, with opioids being used by 14-32% of patients in different case series (Hantke *et al*., 2007), similar

to the levels of analgesic usage among patients with functional motor disorders (O'Connell *et al.*, 2019). Common risk factors may contribute to the emergence of chronic pain and PNES (Ettinger *et al.*, 1999; Mokleby *et al.*, 2002). Alternatively, persistent pain (with or without associated insomnia) and disabilities associated with this symptom can be a source of acute and chronic stress predisposing, precipitating or perpetuating maladaptive coping responses including dissociation. Use (or abuse) of opioid medication could also play a role in the pathophysiology of PNES. Chronic inescapable trauma leads to chronic downregulation of the endogenous opioid system and increased stress-related opioid release, with implications for self-destructive behaviours, social attachment processes, and pain (Lanius *et al.*, 2018). The opioid system has been implicated in defensive "shut-down" responses under conditions of inescapable stress and is thought to mediate alterations of consciousness during dissociative responses (Lanius *et al.*, 2018). Pharmacological antagonism of opioids with naltrexone has been shown to reduce dissociative symptoms in BPD (Schmahl *et al.*, 2012) and has been reported as beneficial in patients with daily refractory PNES undergoing inpatient psychotherapy (Straub and Bohlmann, 2009).

Migraine

About 50-60% of patients with PNES have comorbid migraine (Elliott and Charyton, 2014; Shepard *et al.*, 2016), far exceeding the rate of 15% found in the general population (Steiner *et al.*, 2013). One large study (n = 1,000) from India reported a very high rate of swoon-type reactions accompanying severe migraine attacks in women (13% of girls and 23% of women), but not in men (0% of boys; 1% of men), probably reflecting a culture-associated phenomenon (Chakravarty *et al.*, 2010). Interestingly, patients with PNES report more frequent and longer lasting migraine attacks than those with epilepsy (Shepard *et al.*, 2016). Severe pain, combined with the anxiety of unpredictable attack durations, can serve as a potent trigger (as suggested by the observations by Chakravarty *et al.* [2010]), while sensorimotor and cognitive aura symptoms (common in dissociative seizure patients [Shepard *et al.*, 2016]) could contribute to the seizure scaffold. Neurophysiologically, individuals with migraine consistently show reduced habituation to sensory and noxious stimuli of various modalities, including defensive reflexes such as the blink reflex (Coppola *et al.*, 2013). One speculative interpretation of the high rate of comorbid migraine in patients with PNES is thus that an inability to habituate to *(i.e.* tolerate) distressing interoceptive stimuli or thoughts is compensated through alternative system-wide adaptations such as dissociation (Goldstein and Mellers, 2006; Stone and Carson, 2013). Put simply, as one major adaptive dynamic (habituation) is impaired, other strategies are utilised to deal with persistent/intolerable distress.

Asthma

Asthma has been reported in a third of patients with PNES (de Wet *et al.*, 2003; Elliott and Charyton, 2014). As with other common comorbidities, the recurrent distress of asthma attacks and the anxiety associated with an unpredictable and potentially life-threatening disorder can contribute to the emergence of PNES. The high prevalence of reported asthma in PNES patients could, however, have a different explanation. Vocal cord dysfunction (VCD), a functional respiratory disorder, is often misdiagnosed as asthma, although it typically presents with inspiratory dyspnoea and stridor (rather than the expiratory dyspnoea observed in asthma) accompanied by panic and agitation (Gimenez and Zafra, 2011). It shares several risk factors with PNES (anxiety, depression, history of abuse, female gender), and involves a vicious cycle of anxiety, hyperventilation, dysfunctional breathing and enhanced laryngeal reflexes (Bardin *et al.*, 2017). The diagnosis of asthma / VCD in patients with PNES is complicated by the fact that all of these conditions are often associated with a tendency to hyperventilate (de Wet *et al.*, 2003). A meta-analysis of seven studies examining ictal phenomena in patients with PNES has shown that 68% (CI: 55.4-79.5%) of patients had symptoms which could be related to hyperventilation (feeling dizzy or light-headed) (Indranada *et al.*, 2018). Furthermore, intentional and unintentional hyperventilation can precipitate or accompany PNES and deliberate hyperventilation is an effective provocation procedure for PNES during video-EEG recordings (Popkirov *et al.*, 2015b; Indranada *et al.*, 2018).

Critical appraisal of the literature

The nature and direction of the relationship between PNES and most of the comorbidities reviewed here cannot be derived from correlational or epidemiological studies. Comorbidities may be coincidental without any pathophysiological inter-relation; they can directly or indirectly contribute to PNES (*e.g.* concurrent epilepsy); they can be caused by PNES (*e.g.* secondary social phobia); they can have a bidirectional causal association (*e.g.* depression); or be associated with each other through shared risk factors (*e.g.* other functional neurological disorders). Furthermore, in some cases, PNES cannot be clearly separated

from a "comorbid" condition - either pathophysiologically or clinically (*e.g.* when PNES develop out of a classic panic attack or represent an embodied flashback in PTSD). In addition to these conceptual considerations, the methodological limitations of the available literature have to be considered. The rates of occurrence of most risk factors and comorbidities reviewed above have been reproduced in reasonably-sized populations. However, different definitions and classifications have been used, especially in relation to psychiatric comorbidities. Many studies rely on subjective symptom reporting rather than clinical diagnoses. The association with potential risk factors has typically relied on retrospective recall of such factors rather than prospective longitudinal research. Findings are usually not adjusted for socioeconomic status, although there is evidence that PNES are more common among poorer individuals who may have different rates of trauma and comorbidities relative to control populations with a different socioeconomic background (Sigurdardottir and Olafsson, 1998; Szaflarski *et al.*, 2000; Duncan *et al.*, 2011; Goldstein *et al.*, 2019). Many published patient series were recruited in specialist settings where patients with more complex disorders may be over-represented, for instance those with a higher rate of comorbid epilepsy (Kutlubaev *et al.*, 2018). Finally, (under-reported) cultural differences may play an important role, such as the high incidence of PNES accompanying migraine attacks in Indian women (Chakravarty *et al.*, 2010). The cultural aspects of PNES aetiology tend to be neglected in academic research, but they can be of substantial explanatory, diagnostic and therapeutic value in clinical practice. Seizure semiology could be shaped by culturally established gestures and other idioms of distress (*e. g.* shielding of the face), and social situations and family dynamics need to be seen through the lens of culture, religion and politics to understand their psychosocial impact (Kanemoto *et al.*, 2017; Martínez-Taboas *et al.*, 2019).

Risk factors and comorbidities in clinical practice

Diagnostic value of risk factors and comorbidities

The mainstay of diagnosis of PNES is the semiological seizure analysis (clinical features can have a cumulative predictive value approximating 100% [Avbersek and Sisodiya, 2010]) supported, when necessary and possible, by ictal video-EEG (LaFrance *et al.*, 2013; Popkirov *et al.*, 2017). While at group level PNES are associated with a comorbidity profile, which differs from that associated with epilepsy, comorbidities and risk factors alone are not sufficient to make the diagnosis of PNES and may in fact be misleading. However, the diagnostic process does not end with the label "PNES" (and much less with that of a "non-epileptic event"): the ultimate diagnostic goal is to understand the biopsychosocial aetiology of the condition in an individual patient. Of course, neurologists do not face this task alone, but they need to be aware of how major risk factors and comorbidities can interact with seizures in those with PNES. Neither nosology nor nomenclature currently provide an appropriate reflection of the heterogeneity of PNES, so an individualised understanding of the patient's condition requires careful consideration of how risk factors and comorbidities interact in each particular case.

Competencies and learning points

Learning objective: "Describe the epidemiology, psychiatric and experiential risk factors of PNES":
- Describe the incidence and estimated prevalence of PNES and its importance as one of the most common causes of transient loss of consciousness.
- Describe the prevalence and importance of common experiential risk factors and how they can interact with PNES pathophysiology.
- Describe common medical and psychiatric comorbidities, and how they can relate to PNES.
- Describe how risk factors and comorbidities influence the diagnostic workup and individual treatment planning.

Risk factors and comorbidities for choice of treatment

Manualized treatments exist for PNES (Reiter *et al.*, 2015), addressing not only the seizures, but also the risk factors and comorbidities, illustrating that individual aetiological factors need to be considered when planning treatment for PNES (LaFrance and Bjønæs, 2019). There is an increasing body of evidence supporting the therapeutic value of a range of psychotherapeutic interventions for PNES. A recent meta-analysis demonstrated that a pooled mean of 47% of patients treated became free of PNES after intervention and 82% experienced a greater than 50% improvement in seizure frequency (Carlson and Nicholson Perry, 2017). Irrespective of modality, indispensable components of treatment are: communicating the diagnosis with sufficient regard for the patient's understanding and acceptance; involving carers and devising strategies for acute seizures; involving therapists early; and treating medical comorbidities in appropriate and complementary ways (Reuber, 2019). □

Key points

- PNES are episodes of impaired awareness and behavioural control that can resemble epilepsy or other paroxysmal disorders, although they have neuropsychiatric underpinnings.
- PNES are commonly misdiagnosed as epilepsy or syncope (the opposite diagnostic error occurs as well, but is less frequent).
- PNES are the result of complex and heterogeneous neurocognitive dysfunction often involving elements of abnormal stress responses and emotion processing combined with attentional and metacognitive problems.
- Psychiatric comorbidities are common, particularly dissociative, depressive, anxiety and posttraumatic stress disorders, and personality disorders (especially borderline pattern).
- A history of trauma and stressful life events are frequently but not invariably reported, and interpersonal relationships are often characterized by insecure attachment.
- Comorbid epilepsy (almost invariably preceding the development of PNES) occurs in roughly 10% of adults and up to 30% of children with PNES, and may present an important diagnostic and therapeutic challenge.
- Various comorbidities such as chronic pain, sleep problems, migraine, asthma, and history of head injury are found at higher rates in patients with PNES than in the general population.
- In an individual patient, it is difficult to establish whether a co-occurring condition is a true comorbidity, a predisposition, or an underlying cause of PNES.
- The identification of risk factors and comorbidities of PNES alone does not allow a reliable distinction from other causes of transient impairment of awareness and self-control, but their characterisation and consideration are crucial in the planning of individual treatment.
- There are evidence-based treatments for PNES which address underlying risk factors and comorbidities.

Case studies

Case 1

A 23-year old man presents to the epilepsy-monitoring unit (EMU) with suspected pharmacoresistant post-traumatic epilepsy. Eight months ago, he was involved in a serious road traffic accident (RTA). In the RTA he suffered a concussion (loss of consciousness for about 15 minutes and peritraumatic amnesia), but sustained no further injuries. CT and MRI revealed no abnormalities at the time. Since then, he has experienced high levels of anxiety, low mood, fatigue, nightmares, disturbed sleep, intrusive memories and irritability. He has stopped driving his car and avoided traffic in general. Four months ago, he started having seizures which were usually preceded by palpitations, a sensation of a lump in the throat, and feeling "spaced out". He would then become unresponsive and develop slight symmetrical shaking of his limbs. Attacks would last between two and 20 minutes and occur between one and six times a month. When seizures lasted for more than a few minutes, the patient's family called the emergency services. His past medical history includes asthma in childhood and migraine without aura (currently four attacks/month). After the onset of the seizures, he was started on levetiracetam for suspected epilepsy and zopiclone for his sleeping problems.

On Day 2 of the EMU monitoring, the patient becomes unresponsive shortly after hyperventilation has been performed and a typical seizure is observed. The patient later reports having experienced his usual prodromal warning signs. Based on the characteristic semiology (and the absence of epileptic activity on the EEG), PNES are diagnosed. Since only one type of seizure is reported, the epilepsy diagnosis is reversed. A psychiatric evaluation confirms the diagnosis of post-traumatic stress disorder.

The patient and his family are informed about the diagnoses and potential treatments. Levetiracetam is discontinued and the irritability is markedly reduced. He is started on venlafaxine (as a treatment for PTSD and migraine). The neurologist discusses emergency strategies regarding future seizures, explains a few simple "grounding" techniques, and the patient is referred for cognitive-behavioural therapy (*figure 2*).

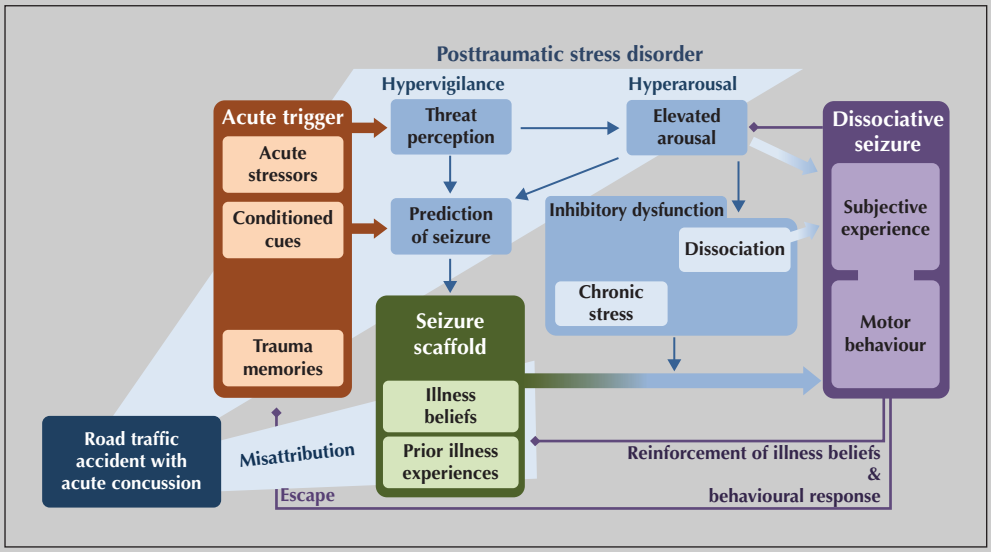

Figure 2. Summary of Case 1.

Case 2

A 36-year-old teacher with long-standing temporal lobe epilepsy undergoes right selective amygdalohippocampectomy. After surgery, she remains seizure-free (outcome Engel Class IA), but complains of memory impairments that make teaching very stressful. Six months after the operation, she insists on reducing her topiramate, hoping to improve her memory performance, and is explicitly warned that seizures could recur. Shortly after reducing the dose, she suffers a seizure. She reports having first felt slight dizziness and a dry mouth, and was then "simply not there" for a few minutes. Her sister reports that the patient had tears in her eyes immediately following the seizure. This kind of seizure started to occur about once a month despite the reversal of the topiramate dose reduction. During a five-day EMU stay, no seizure can be recorded until one is elicited using verbal suggestion on the sixth day. The ictal video is shown to the patient and her sister, and both confirm that this is the "new kind" of seizure. Ictal EEG shows no epileptic activity.

The patient is diagnosed with new-onset PNES. After a long discussion with the neuropsychologist, she realizes that her attacks are usually preceded by worries about "the epilepsy coming back" and anxiety related to work. She declines cognitive-behavioural therapy, explaining she'll try to "figure it out" herself first. On follow-up, six months later, she reports no further seizures since the diagnosis (*figure 3*).

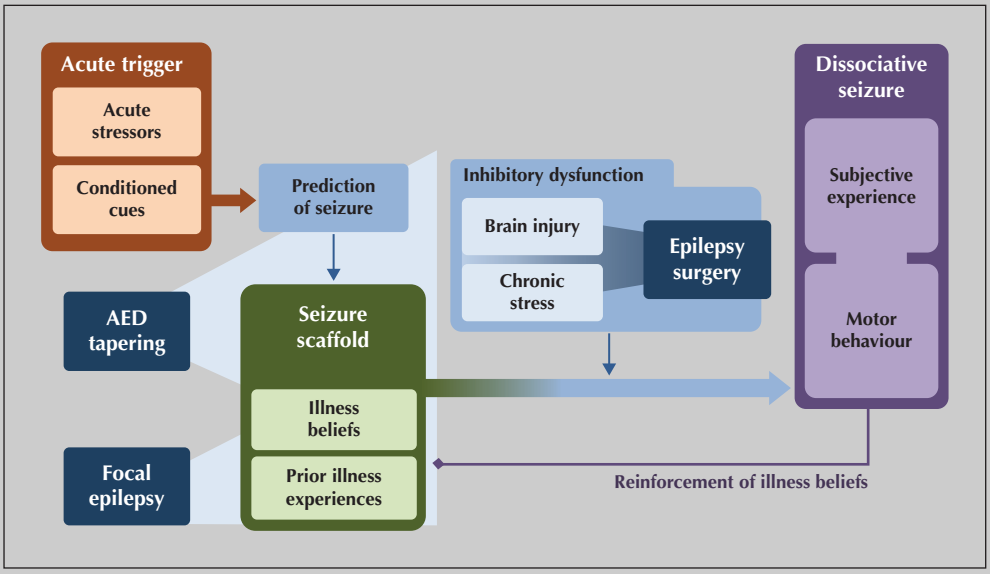

Figure 3. Summary of Case 2.

Case 3

A 19-year-old woman is brought to the emergency department (ED) with a convulsive seizure. According to the emergency personnel, the seizure began after an altercation with her boyfriend. At the time of arrival in the ED, the seizure has lasted approximately 30 minutes and is ongoing. The patient's eyes are tightly shut, there are continuous thrashing movements of all limbs of variable amplitude and stable frequency, and her back is arched intermittently. Two doses of intravenous lorazepam (2x4 mg) administered by the receiving ED doctor, on the basis of a misdiagnosis of status epilepticus, aggravate the seizure manifestations. A neurologist and anaesthetist are called. Before the patient can be sedated and ventilated, the neurologist arrives and makes the correct diagnosis of a prolonged PNES. The neurologist asks the patients' relatives to step out and the ED treatment team to step back from the patient. He addresses the patient by her name, explains that she is in a safe place and that she is experiencing a non-epileptic seizure. He reassures her that this seizure will stop shortly and will not damage her brain. The neurologist tells the patient that he would like to explain more about non-epileptic seizures once the seizure is over. The seizure manifestations subside over a further five minutes.

When she recovers sufficiently, the patient reports that she has been having these kinds of seizures with increasing frequency over the last year, and that they are currently occurring twice a week. Sometimes she is partially aware of what is happening in the seizures. They seem to occur at any time and she does not recognise specific triggers although they have been more frequent at times when she has felt stressed. A doctor has suggested antiepileptic drug treatment but she was not convinced that she had epilepsy. Her medical records reveal a history of severe childhood abuse, previous self-harm, recurrent syncope, and asthma.

The diagnosis of PNES is explained to the patient and her boyfriend. The verbal explanation is supported by a leaflet about PNES and information about a PNES website. The patient is referred to a psychiatrist for further evaluation (*figure 4*).

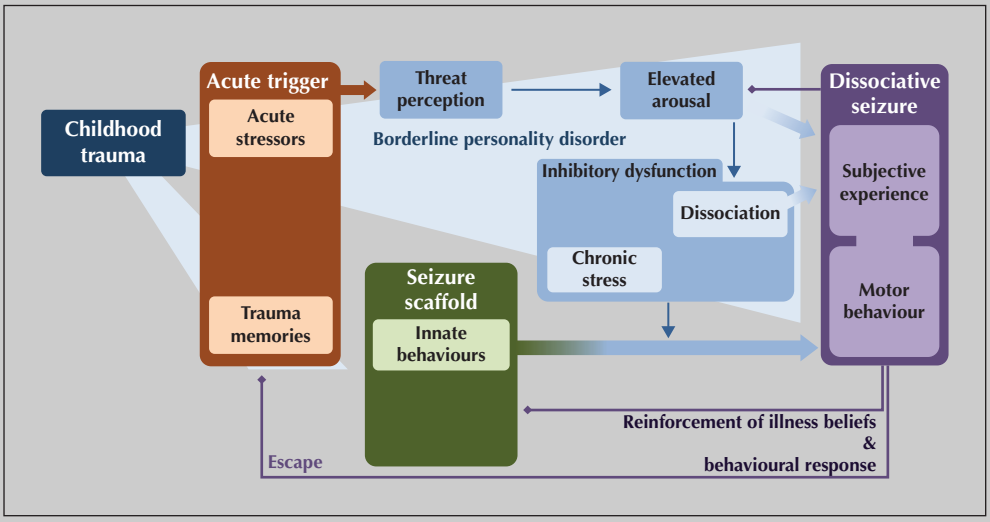

Figure 4. Summary of Case 3.

Recommended references

Asadi-Pooya AA, Sperling MR. Epidemiology of psychogenic nonepileptic seizures. *Epilepsy Behav* 2015; 46: 60-5.

Avbersek A, Sisodiya S. Does the primary literature provide support for clinical signs used to distinguish psychogenic nonepileptic seizures from epileptic seizures? *J Neurol Neurosurg Psychiatry* 2010; 81(7): 719-25.

Popkirov S, Carson AJ, Stone J. Scared or scarred: could 'dissociogenic' lesions predispose to nonepileptic seizures after head trauma?*Seizure* 2018; 58: 127-32.

Reuber M, Brown RJ. Understanding psychogenic nonepileptic seizures-Phenomenology, semiology and the Integrative Cognitive Model. *Seizure* 2017; 44: 199-205.

Schachter SC, LaFrance JWC. *Gates and Rowan's nonepileptic seizures*. 4th Ed. Cambridge: Cambridge University Press, 2019.

Supplementary data.
Summary didactic slides are available on the www.epilepticdisorders.com website.

Acknowledgements and disclosures.
SP has received a speaking fee from Novartis. *AA-P* has received honoraria from Cobel Darou and RaymandRad; Royalty: Oxford University Press (Book publication). *RD* has received an honorarium from UCB PHARMA. *DG* reports no disclosures. *CH* has no disclosures relative to PNES. *AMK* received honoraria from Eisai laboratories for participating on the Scientific advisory Board, from Neuropace for participation in symposia, and from the Epilepsy Foundation of America, for being co-Editor-In-Chief of Epilepsy.com. None have a conflict with the topic of this manuscript. *WCL* has served on the editorial boards of Epilepsia, Epilepsy & Behavior, Journal of Neurology, Neurosurgery and Psychiatry, and Journal of Neuropsychiatry and Clinical Neurosciences; receives editor's royalties from the publication of Gates and Rowan's Non-epileptic Seizures, 3rd ed. (Cambridge University Press, 2010) and 4th ed. (2017); author's royalties for Taking Control of Your Seizures: Workbook and Therapist Guide (Oxford University Press, 2015); has received research support from the NIH (NINDS 5K23NS45902 [PI]), Department of Defense (W81XWH-17-0169 [PI]), Rhode Island Hospital, the American Epilepsy Society (AES), the Epilepsy Foundation (EF), Brown University and the Siravo Foundation; serves on the Epilepsy Foundation Professional Advisory Board; has received honoraria for the American Academy of Neurology Annual Meeting Annual Course; has served as a clinic development consultant at University of Colorado Denver, Cleveland Clinic, Spectrum Health and Emory University; and has provided medico legal expert testimony. *CP* reports no disclosures. *MR* has benefited from an educational grant from UCB Pharma and has accepted speaker's fees from Eisai, UCB Pharma and LivaNova. He receives royalties for "In our words: Personal Accounts of Living with Non-epileptic Seizures", "Epilepsy Explained" and "Borderlands of Epilepsy Revisited" from Oxford University Press and is paid for his work as Editor-in-Chief of "Seizure - European Journal of Epilepsy" by Elsevier.

Disclaimer.
This report was written by experts selected by the International League Against Epilepsy (ILAE) and was approved for publication by the ILAE. Opinions expressed by the authors, however, do not necessarily represent the policy or position of the ILAE.

References

Anderson MC, Ochsner KN, Kuhl B, *et al*. Neural systems underlying the suppression of unwanted memories. *Science* 2004; 303(5655): 232-5.

Angus-Leppan H. Diagnosing epilepsy in neurology clinics: a prospective study. *Seizure* 2008; 17(5): 431-6.

Asadi-Pooya AA. Neurobiological origin of psychogenic nonepileptic seizures: a review of imaging studies. *Epilepsy Behav* 2015; 52(Pt A): 256-9.

Asadi-Pooya AA, Sperling MR. Epidemiology of psychogenic nonepileptic seizures. *Epilepsy Behav* 2015; 46: 60-5.

Asadi-Pooya AA, Bahrami Z. Sexual abuse and psychogenic nonepileptic seizures. *Neurol Sci* 2019; 40(8): 1607-10.

Asadi-Pooya AA, Asadollahi M, Tinker J, Nei M, Sperling MR. Post-epilepsy surgery psychogenic nonepileptic seizures. *Epilepsia* 2016; 57(10): 1691-6.

Avbersek A, Sisodiya S. Does the primary literature provide support for clinical signs used to distinguish psychogenic nonepileptic seizures from epileptic seizures? *J Neurol Neurosurg Psychiatry* 2010; 81(7): 719-25.

Aybek S, Nicholson TR, Zelaya F, *et al*. Neural correlates of recall of life events in conversion disorder. *JAMA Psychiatry* 2014; 71(1): 52-60.

Bahrami Z, Homayoun M, Asadi-Pooya AA. Why is psychogenic nonepileptic seizure diagnosis missed? A retrospective study. *Epilepsy Behav* 2019; 97: 135-7.

Bakvis P, Spinhoven P, Roelofs K. Basal cortisol is positively correlated to threat vigilance in patients with psychogenic nonepileptic seizures. *Epilepsy Behav* 2009; 16(3): 558-60.

Bakvis P, Spinhoven P, Giltay EJ, *et al*. Basal hypercortisolism and trauma in patients with psychogenic nonepileptic seizures. *Epilepsia* 2010; 51(5): 752-9.

Baldwin JR, Reuben A, Newbury JB, Danese A. Agreement between prospective and retrospective measures of childhood maltreatment: a systematic review and meta-analysis. *JAMA Psychiatry* 2019; 76(6): 584-93.

Bardin PG, Low K, Ruane L, Lau KK. Controversies and conundrums in vocal cord dysfunction. *Lancet Respir Med* 2017; 5(7): 546-8.

Bazil CW, Legros B, Kenny E. Sleep structure in patients with psychogenic nonepileptic seizures. *Epilepsy Behav* 2003; 4(4): 395-8.

Benbadis SR. A spell in the epilepsy clinic and a history of "chronic pain" or "fibromyalgia" independently predict a diagnosis of psychogenic seizures. *Epilepsy Behav* 2005; 6(2): 264-5.

Benbadis SR, Allen Hauser W. An estimate of the prevalence of psychogenic non-epileptic seizures. *Seizure* 2000; 9(4): 280-1.

Benbadis SR, Agrawal V, Tatum WO 4th. V. How many patients with psychogenic nonepileptic seizures also have epilepsy? *Neurology* 2001; 57(5): 915-7.

Bermeo-Ovalle A, Kanner AM. Comorbidities in psychogenic nonepileptic seizures. In: *Gates and Rowan's nonepileptic seizures*. Cambridge University Press, 2018: 245-56.

Blümcke I, Arzimanoglou A, Beniczky S, Wiebe S. Roadmap for a competency-based educational curriculum in epileptology: report of the Epilepsy Education Task Force of the International League Against Epilepsy. *Epileptic Disord* 2019; 21(2): 129-40.

Bowman ES. Etiology and clinical course of pseudoseizures. *Psychosomatics* 1993; 34(4): 333-42.

Bowman ES. Posttraumatic stress disorder, abuse, and trauma. In: *Gates and Rowan's nonepileptic seizures*. Cambridge University Press, 2018: 231-44.

Bowman ES, Markand ON. Psychodynamics and psychiatric diagnoses of pseudoseizure subjects. *Am J Psychiatry* 1996; 153(1): 57-63.

Breuer J, Freud S. *Studien über Hysterie*. F Deuticke, 1895.

Brown RJ, Reuber M. Psychological and psychiatric aspects of psychogenic non-epileptic seizures (PNES): a systematic review. *Clin Psychol Rev* 2016a; 45: 157-82.

Brown RJ, Reuber M. Towards an integrative theory of psychogenic non-epileptic seizures (PNES). *Clin Psychol Rev* 2016b; 47: 55-70.

Bullock KD, Mirza N, Forte C, Trockel M. Group dialectical-behavior therapy skills training for conversion disorder with seizures. *J Neuropsychiatry Clin Neurosci* 2015; 27(3): 240-3.

Carlson P, Nicholson Perry K. Psychological interventions for psychogenic non-epileptic seizures: a meta-analysis. *Seizure* 2017; 45: 142-50.

Chakravarty A, Mukherjee A, Roy D. Migraine, epileptic seizures and psychogenic non-epileptic seizures: observations in Indian patients in a clinic-based study. *Neurol India* 2010; 58(4): 631-3.

Chemali Z, Meadows ME. The use of eye movement desensitization and reprocessing in the treatment of psychogenic seizures. *Epilepsy Behav* 2004; 5(5): 784-7.

Chen DK, Majmudar S, Ram A, *et al*. Change in illness perception is associated with short-term seizure burden outcome following video-EEG confirmation of psychogenic nonepileptic seizures. *Epilepsy Behav* 2018; 83: 186-91.

Coelho R, Viola TW, Walss-Bass C, Brietzke E, Grassi-Oliveira R. Childhood maltreatment and inflammatory markers: a systematic review. *Acta Psychiatr Scand* 2014; 129(3): 180-92.

Coppola G, Di Lorenzo C, Schoenen J, Pierelli F. Habituation and sensitization in primary headaches. *J Headache Pain* 2013; 14: 65.

Crimlisk HL, Bhatia K, Cope H, David A, Marsden CD, Ron MA. Slater revisited: 6 year follow up study of patients with medically unexplained motor symptoms. *BMJ* 1998; 316(7131): 582-6.

D'Alessio L, Giagante B, Oddo S, *et al*. Psychiatric disorders in patients with psychogenic non-epileptic seizures, with and without comorbid epilepsy. *Seizure* 2006; 15(5): 333-9.

Danese A, Pariante CM, Caspi A, Taylor A, Poulton R. Childhood maltreatment predicts adult inflammation in a life-course study. *Proc Natl Acad Sci USA* 2007; 104(4): 1319-24.

de Wet CJ, Mellers JD, Gardner WN, Toone BK. Pseudoseizures and asthma. *J Neurol Neurosurg Psychiatry* 2003; 74(5): 639-41.

Dickson JM, Dudhill H, Shewan J, Mason S, Grunewald RA, Reuber M. Cross-sectional study of the hospital management of adult patients with a suspected seizure (EPIC2). *BMJ Open* 2017; 7(7): e015696.

Diprose W, Sundram F, Menkes DB. Psychiatric comorbidity in psychogenic nonepileptic seizures compared with epilepsy. *Epilepsy Behav* 2016; 56: 123-30.

Driver-Dunckley E, Stonnington CM, Locke DE, Noe K. Comparison of psychogenic movement disorders and psychogenic nonepileptic seizures: is phenotype clinically important? *Psychosomatics* 2011; 52(4): 337-45.

Duncan R, Oto M. Psychogenic nonepileptic seizures in patients with learning disability: comparison with patients with no learning disability. *Epilepsy Behav* 2008; 12(1): 183-6.

Duncan R, Oto M, Martin E, Pelosi A. Late onset psychogenic nonepileptic attacks. *Neurology* 2006; 66(11): 1644-7.

Duncan R, Razvi S, Mulhern S. Newly presenting psychogenic nonepileptic seizures: incidence, population characteristics, and early outcome from a prospective audit of a first seizure clinic. *Epilepsy Behav* 2011; 20(2): 308-11.

Duncan R, Oto M, Wainman-Lefley J, Pelosi A. Mortality in a cohort of patients with psychogenic non-epileptic seizures. *J Neurol Neurosurg Psychiatry* 2012; 83(7): 761-2.

Duncan R, Anderson J, Cullen B, Meldrum S. Predictors of 6-month and 3-year outcomes after psychological intervention for psychogenic non epileptic seizures. *Seizure* 2016; 36: 22-6.

Dworetzky BA, Strahonja-Packard A, Shanahan CW, Paz J, Schauble B, Bromfield EB. Characteristics of male veterans with psychogenic nonepileptic seizures. *Epilepsia* 2005; 46(9): 1418-22.

Elliott JO, Charyton C. Biopsychosocial predictors of psychogenic non-epileptic seizures. *Epilepsy Res* 2014; 108(9): 1543-53.

Erro R, Brigo F, Trinka E, Turri G, Edwards MJ, Tinazzi M. Psychogenic nonepileptic seizures and movement disorders: a comparative review. *Neurol Clin Pract* 2016; 6(2): 138-49.

Ettinger AB, Devinsky O, Weisbrot DM, Goyal A, Shashikumar S. Headaches and other pain symptoms among patients with psychogenic non-epileptic seizures. *Seizure* 1999; 8(7): 424-6.

Fiszman A, Alves-Leon SV, Nunes RG, D'Andrea I, Figueira I. Traumatic events and posttraumatic stress disorder in patients with psychogenic nonepileptic seizures: a critical review. *Epilepsy Behav* 2004; 5(6): 818-25.

Frost RB, Farrer TJ, Primosch M, Hedges DW. Prevalence of traumatic brain injury in the general adult population: a meta-analysis. *Neuroepidemiology* 2013; 40(3): 154-9.

Gazzola DM, Carlson C, Rugino A, Hirsch S, Starner K, Devinsky O. Psychogenic nonepileptic seizures and chronic pain: a retrospective case-controlled study. *Epilepsy Behav* 2012; 25(4): 662-5.

Gimenez LM, Zafra H. Vocal cord dysfunction: an update. *Ann Allergy Asthma Immunol* 2011; 106(4): 267-74.

Glosser G, Roberts D, Glosser DS. Nonepileptic seizures after resective epilepsy surgery. *Epilepsia* 1999; 40(12): 1750-4.

Goldstein LH, Mellers JD. Ictal symptoms of anxiety, avoidance behaviour, and dissociation in patients with dissociative seizures. *J Neurol Neurosurg Psychiatry* 2006; 77(5): 616-21.

Goldstein LH, Robinson EJ, Reuber R, *et al*. Demographics of 698 patients with dissociative seizures participating in a UK multi-centre treatment study. *Epilepsia* 2019; 60(11): 2182-93.

Green B, Norman P, Reuber M. Attachment style, relationship quality, and psychological distress in patients with psychogenic non-epileptic seizures versus epilepsy. *Epilepsy Behav* 2017; 66: 120-6.

Hantke NC, Doherty MJ, Haltiner AM. Medication use profiles in patients with psychogenic nonepileptic seizures. *Epilepsy Behav* 2007; 10(2): 333-5.

Hernando KA, Szaflarski JP, Ver Hoef LW, Lee S, Allendorfer JB. Uncinate fasciculus connectivity in patients with psychogenic nonepileptic seizures: a preliminary diffusion tensor tractography study. *Epilepsy Behav* 2015; 45: 68-73.

Herringa RJ. Trauma, PTSD, and the developing brain. *Curr Psychiatry Rep* 2017; 19(10): 69.

Hingray C, Maillard L, Hubsch C, *et al*. Psychogenic nonepileptic seizures: characterization of two distinct patient profiles on the basis of trauma history. *Epilepsy Behav* 2011; 22(3): 532-6.

Hingray C, Donne C, Cohn A, *et al*. Link between psychogenc nonepileptic seizures and complex PTSD: a pilot study. *Eur J Trauma & Dissociation* 2017; 1(2): 131-6.

Hingray C, El-Hage W, Duncan R, *et al*. Access to diagnostic and therapeutic facilities for psychogenic nonepileptic seizures: an international survey by the ILAE PNES Task Force. *Epilepsia* 2018; 59(1): 203-14.

Holman N, Kirkby A, Duncan S, Brown RJ. Adult attachment style and childhood interpersonal trauma in non-epileptic attack disorder. *Epilepsy Res* 2008; 79(1): 84-9.

Indranada AM, Mullen SA, Duncan R, Berlowitz DJ, Kanaan RAA. The association of panic and hyperventilation with psychogenic non-epileptic seizures: a systematic review and meta-analysis. *Seizure* 2018; 59: 108-15.

Jabeen SA, Gaddamanugu P, Cherian A, Mridula KM, Kumar DU, Meena AK. Levetiracetam-associated psychogenic non-epileptic seizures; a hidden paradox. *J Popul Ther Clin Pharmacol* 2018; 25(2): e1-11.

Jungilligens J, Wellmer J, Schlegel U, Kessler H, Axmacher N, Popkirov S. Impaired emotional and behavioural awareness and control in patients with dissociative seizures. *Psychol Med* 2019. doi: 10.1017/S0033291719002861. [Epub ahead of print].

Kanemoto K, LaFrance Jr. WC, Duncan R, *et al*. PNES around the world: where we are now and how we can close the diagnosis and treatment gaps -an ILAE PNES Task Force report. *Open Epilepsia* 2017; 2(3): 307-16.

Karakis I, Montouris GD, Piperidou C, Luciano MS, Meador KJ, Cole AJ. Patient and caregiver quality of life in psychogenic non-epileptic seizures compared to epileptic seizures. *Seizure* 2014; 23(1): 47-54.

Kemp S, Graham CD, Chan R, Kitchingman H, Vickerman K, Reuber M. The frequency and management of seizures during psychological treatment among patients with psychogenic nonepileptic seizures and epilepsy. *Epilepsia* 2018; 59(4): 844-53.

Kerr WT, Janio EA, Braesch CT, *et al*. Identifying psychogenic seizures through comorbidities and medication history. *Epilepsia* 2017; 58(11): 1852-60.

Keynejad RC, Frodl T, Kanaan R, Pariante C, Reuber M, Nicholson TR. Stress and functional neurological disorders: mechanistic insights. *J Neurol Neurosurg Psychiatry* 2018; 90(7): 813-21.

Kutlubaev MA, Xu Y, Hackett ML, Stone J. Dual diagnosis of epilepsy and psychogenic nonepileptic seizures: systematic review and meta-analysis of frequency, correlates, and outcomes. *Epilepsy Behav* 2018; 89: 70-8.

Labudda K, Frauenheim M, Illies D, *et al*. Psychiatric disorders and trauma history in patients with pure PNES and patients with PNES and coexisting epilepsy. *Epilepsy Behav* 2018; 88: 41-8.

Lacey C, Cook M, Salzberg M. The neurologist, psychogenic nonepileptic seizures, and borderline personality disorder. *Epilepsy Behav* 2007; 11(4): 492-8.

LaFrance WC, Bjønæs H. Designing treatment plans based on etiology of psychogenic nonepileptic seizures. In: Schachter SC, LaFrance JWC. *Gates and Rowan's nonepileptic seizures*. 4th Ed. Cambridge: Cambridge University Press; 2019: 283-99.

LaFrance Jr. WC, Baker GA, Duncan R, Goldstein LH, Reuber M. Minimum requirements for the diagnosis of psychogenic nonepileptic seizures: a staged approach: a report from the International League Against Epilepsy Nonepileptic Seizures Task Force. *Epilepsia* 2013; 54(11): 2005-18.

Lanius RA, Boyd JE, McKinnon MC, *et al*. A review of the neurobiological basis of trauma-related dissociation and its relation to cannabinoid- and opioid-mediated stress response: a transdiagnostic, translational approach. *Curr Psychiatry Rep* 2018; 20(12): 118.

Latreille V, Baslet G, Sarkis R, Pavlova M, Dworetzky BA. Sleep in psychogenic nonepileptic seizures: time to raise a red flag. *Epilepsy Behav* 2018; 86: 6-8.

Latreille V, Dworetzky BA, Baslet G, Pavlova M. Sleep disturbances in patients with psychogenic non-epileptic seizures: is it all subjective? A prospective pilot study of sleep-wake patterns. *Seizure* 2019; 65: 124-8.

Lee S, Allendorfer JB, Gaston TE, *et al*. White matter diffusion abnormalities in patients with psychogenic non-epileptic seizures. *Brain Res* 2015; 1620: 169-76.

Lesser RP, Lueders H, Dinner DS. Evidence for epilepsy is rare in patients with psychogenic seizures. *Neurology* 1983; 33(4): 502-4.

Ludwig L, Pasman JA, Nicholson T, *et al*. Stressful life events and maltreatment in conversion (functional neurological) disorder: systematic review and meta-analysis of case-control studies. *Lancet Psychiatry* 2018; 5(4): 307-20.

Markoula S, de Tisi J, Foong J, Duncan JS. De novo psychogenic nonepileptic attacks after adult epilepsy surgery: an underestimated entity. *Epilepsia* 2013; 54(12): e159-62.

Martínez-Taboas A, Lewis-Fernández R, Sar V. Cultural aspects of psychogenic nonepileptic seizures. In: Schachter SC, LaFrance JWC. *Gates and Rowan's nonepileptic seizures*. 4th Ed. Cambridge: Cambridge University Press, 2019: 137-49.

Matin N, Young SS, Williams B, *et al*. Neuropsychiatric associations with gender, illness duration, work disability, and motor subtype in a US functional neurological disorders clinic population. *J Neuropsychiatry Clin Neurosci* 2017; 29(4): 375-82.

McKenzie P, Oto M, Russell A, Pelosi A, Duncan R. Early outcomes and predictors in 260 patients with psychogenic nonepileptic attacks. *Neurology* 2010; 74(1): 64-9.

McKenzie PS, Oto M, Graham CD, Duncan R. Do patients whose psychogenic non-epileptic seizures resolve, 'replace' them with other medically unexplained symptoms? Medically unexplained symptoms arising after a diagnosis of psychogenic non-epileptic seizures. *J Neurol Neurosurg Psychiatry* 2011; 82(9): 967-9.

McSweeney M, Reuber M, Levita L. Neuroimaging studies in patients with psychogenic non-epileptic seizures: a systematic meta-review. *Neuroimage Clin* 2017; 16: 210-21.

Mokleby K, Blomhoff S, Malt UF, Dahlstrom A, Tauboll E, Gjerstad L. Psychiatric comorbidity and hostility in patients with psychogenic nonepileptic seizures compared with somatoform disorders and healthy controls. *Epilepsia* 2002; 43(2): 193-8.

Myers L, Lancman M, Laban-Grant O, Matzner B, Lancman M. Psychogenic non-epileptic seizures: predisposing factors to diminished quality of life. *Epilepsy Behav* 2012; 25(3): 358-62.

Myers L, Vaidya-Mathur U, Lancman M. Prolonged exposure therapy for the treatment of patients diagnosed with psychogenic non-epileptic seizures (PNES) and post-traumatic stress disorder (PTSD). *Epilepsy Behav* 2017; 66: 86-92.

Ney GC, Barr WB, Napolitano C, Decker R, Schaul N. New-onset psychogenic seizures after surgery for epilepsy. *Arch Neurol* 1998; 55(5): 726-30.

Niedermeyer E, Blumer D, Holscher E, Walker BA. Classical hysterical seizures facilitated by anticonvulsant toxicity. *Psychiatr Clin (Basel)* 1970; 3(2): 71-84.

O'Connell N, Nicholson T, Blackman G, Tavener J, David AS. Medication prescriptions in 322 motor functional neurological disorder patients in a large UK mental health service: a case control study. *Gen Hospital Psychiatry* 2019; 58: 94-102.

Oto M, Russell AJ, McGonigal A, Duncan R. Misdiagnosis of epilepsy in patients prescribed anticonvulsant drugs for other reasons. *BMJ* 2003; 326(7384): 326-7.

Oto M, Espie CA, Duncan R. An exploratory randomized controlled trial of immediate versus delayed withdrawal of antiepileptic drugs in patients with psychogenic nonepileptic attacks (PNEAs). *Epilepsia* 2010; 51(10): 1994-9.

Paquola C, Bennett MR, Lagopoulos J. Understanding heterogeneity in grey matter research of adults with childhood maltreatment -a meta-analysis and review. *Neurosci Biobehav Rev* 2016; 69: 299-312.

Perez DL, Dworetzky BA, Dickerson BC, *et al*. An integrative neurocircuit perspective on psychogenic nonepileptic seizures and functional movement disorders: neural functional unawareness. *Clin EEG Neurosci* 2015; 46(1): 4-15.

Perez DL, Williams B, Matin N, *et al*. Corticolimbic structural alterations linked to health status and trait anxiety in functional neurological disorder. *J Neurol Neurosurg Psychiatry* 2017; 88(12): 1052-9.

Perry BD, Pollard R. Homeostasis, stress, trauma, and adaptation. A neurodevelopmental view of childhood trauma. *Child Adolesc Psychiatr Clin N Am* 1998; 7(1): 33-51.

Phillips MC, Costello CA, White EJ, *et al*. Routine polysomnography in an epilepsy monitoring unit. *Epilepsy Res* 2013; 105(3): 401-4.

Ponnusamy A, Marques JL, Reuber M. Comparison of heart rate variability parameters during complex partial seizures and psychogenic nonepileptic seizures. *Epilepsia* 2012; 53(8): 1314-21.

Popkirov S, Gronheit W, Schlegel U, Wellmer J. Recurrent loss of consciousness despite DDD pacing: psychogenic pseudosyncope in a 19-year-old man. *Clin Res Cardiol* 2014; 103(9): 755-7.

Popkirov S, Gronheit W, Wellmer J. A systematic review of suggestive seizure induction for the diagnosis of psychogenic nonepileptic seizures. *Seizure* 2015a; 31: 124-32.

Popkirov S, Gronheit W, Wellmer J. Hyperventilation and photic stimulation are useful additions to a placebo-based suggestive seizure induction protocol in patients with psychogenic nonepileptic seizures. *Epilepsy Behav* 2015b; 46: 88-90.

Popkirov S, Jungilligens J, Gronheit W, Wellmer J. Diagnosing psychogenic nonepileptic seizures: video-EEG monitoring, suggestive seizure induction and diagnostic certainty. *Epilepsy Behav* 2017; 73: 54-8.

Popkirov S, Carson AJ, Stone J. Scared or scarred: could 'dissociogenic' lesions predispose to nonepileptic seizures after head trauma? *Seizure* 2018; 58: 127-32.

Popkirov S, Flasbeck V, Schlegel U, Juckel G, Brune M. Childhood trauma and dissociative symptoms predict frontal EEG asymmetry in borderline personality disorder. *J Trauma Dissociation* 2018: 1-16.

Popkirov S, Stone J, Derry CP. Abnormal sleep in patients with epileptic or dissociative (non-epileptic) seizures: a polysomnography study. *Eur J Neurol* 2019; 26(2): 255-60.

Rawlings GH, Brown I, Reuber M. Predictors of health-related quality of life in patients with epilepsy and psychogenic nonepileptic seizures. *Epilepsy Behav* 2017a; 68: 153-8.

Rawlings GH, Jamnadas-Khoda J, Broadhurst M, *et al*. Panic symptoms in transient loss of consciousness: frequency and diagnostic value in psychogenic nonepileptic seizures, epilepsy and syncope. *Seizure* 2017b; 48: 22-7.

Reiter JM, Andrews D, Reiter Jr. C, Curt LaFrance W. *Taking control of your seizures workbook*. Oxford University Press, 2015.

Reuber M. Dissociative (non-epileptic) seizures: tackling common challenges after the diagnosis. *Pract Neurol* 2019; 19(4): 332-41.

Reuber M, Rawlings GH. Nonepileptic seizures - subjective phenomena. *Handb Clin Neurol* 2016; 139: 283-96.

Reuber M, Brown RJ. Understanding psychogenic nonepileptic seizures-phenomenology, semiology and the Integrative Cognitive Model. *Seizure* 2017; 44: 199-205.

Reuber M, Kral T, Kurthen M, Elger CE. New-onset psychogenic seizures after intracranial neurosurgery. *Acta Neurochir (Wien)* 2002; 144(9): 901-7.

Reuber M, House AO, Pukrop R, Bauer J, Elger CE. Somatization, dissociation and general psychopathology in patients with psychogenic non-epileptic seizures. *Epilepsy Res* 2003a; 57(2–3): 159-67.

Reuber M, Pukrop R, Bauer J, Helmstaedter C, Tessendorf N, Elger CE. Outcome in psychogenic nonepileptic seizures: 1 to 10-year follow-up in 164 patients. *Ann Neurol* 2003b; 53(3): 305-11.

Reuber M, Qurishi A, Bauer J, *et al*. Are there physical risk factors for psychogenic non-epileptic seizures in patients with epilepsy? *Seizure* 2003c; 12(8): 561-7.

Reuber M, Pukrop R, Bauer J, Derfuss R, Elger CE. Multidimensional assessment of personality in patients with psychogenic non-epileptic seizures. *J Neurol Neurosurg Psychiatry* 2004; 75(5): 743-8.

Reuber M, Jamnadas-Khoda J, Broadhurst M, *et al*. Psychogenic nonepileptic seizure manifestations reported by patients and witnesses. *Epilepsia* 2011; 52(11): 2028-35.

Reuber M, Chen M, Jamnadas-Khoda J, *et al*. Value of patient-reported symptoms in the diagnosis of transient loss of consciousness. *Neurology* 2016; 87(6): 625-33.

Roach ES, Langley RL. Episodic neurological dysfunction due to mass hysteria. *Arch Neurol* 2004; 61(8): 1269-72.

Roelofs K, Pasman J. Stress, childhood trauma, and cognitive functions in functional neurologic disorders. *Handb Clin Neurol* 2016; 139: 139-55.

Salinsky M, Evrard C, Storzbach D, Pugh MJ. Psychiatric comorbidity in veterans with psychogenic seizures. *Epilepsy Behav* 2012; 25(3): 345-9.

Salinsky M, Rutecki P, Parko K, *et al*. Psychiatric comorbidity and traumatic brain injury attribution in patients with psychogenic nonepileptic or epileptic seizures: a multicenter study of US veterans. *Epilepsia* 2018; 59(10): 1945-53.

Schmahl C, Kleindienst N, Limberger M, *et al*. Evaluation of naltrexone for dissociative symptoms in borderline personality disorder. *Int Clin Psychopharmacol* 2012; 27(1): 61-8.

Selkirk M, Duncan R, Oto M, Pelosi A. Clinical differences between patients with nonepileptic seizures who report antecedent sexual abuse and those who do not. *Epilepsia* 2008; 49(8): 1446-50.

Shepard MA, Silva A, Starling AJ, *et al*. Patients with psychogenic nonepileptic seizures report more severe migraine than patients with epilepsy. *Seizure* 2016; 34: 78-82.

Sigurdardottir KR, Olafsson E. Incidence of psychogenic seizures in adults: a population-based study in Iceland. *Epilepsia* 1998; 39(7): 749-52.

Steiner TJ, Stovner LJ, Birbeck GL. Migraine: the seventh disabler. *J Headache Pain* 2013; 14: 1.

Stone J, Carson A, Duncan R, *et al*. Who is referred to neurology clinics? -the diagnoses made in 3781 new patients. *Clin Neurol Neurosurg* 2010; 112(9): 747-51.

Stone J, Warlow C, Sharpe M. Functional weakness: clues to mechanism from the nature of onset. *J Neurol Neurosurg Psychiatry* 2012; 83(1): 67-9.

Stone J, Carson AJ. The unbearable lightheadedness of seizing: wilful submission to dissociative (non-epileptic) seizures. *J Neurol Neurosurg Psychiatry* 2013; 84(7): 822-4.

Stone J, Pal S, Blackburn D, Reuber M, Thekkumpurath P, Carson A. Functional (psychogenic) cognitive disorders: a perspective from the neurology clinic. *J Alzheimers Dis* 2015; 48(1): S5-17.

Straub H-B, Bohlmann K. Naltrexone in the treatment of nonepileptic psychogenic (dissociative) seizures. *Epilepsia* 2009; 50: 138.

Szaflarski JP, Ficker DM, Cahill WT, Privitera MD. Four-year incidence of psychogenic nonepileptic seizures in adults in hamilton county, OH. *Neurology* 2000; 55(10): 1561-3.

Tannemaat MR, van Niekerk J, Reijntjes RH, Thijs RD, Sutton R, van Dijk JG. The semiology of tilt-induced psychogenic pseudosyncope. *Neurology* 2013; 81(8): 752-8.

Teodoro T, Edwards MJ, Isaacs JD. A unifying theory for cognitive abnormalities in functional neurological disorders, fibromyalgia and chronic fatigue syndrome: systematic review. *J Neurol Neurosurg Psychiatry* 2018; 89(12): 1308-19.

Thomas AA, Preston J, Scott RC, Bujarski KA. Diagnosis of probable psychogenic nonepileptic seizures in the outpatient clinic: does gender matter? *Epilepsy Behav* 2013; 29(2): 295-7.

Thompson R, Isaac CL, Rowse G, Tooth CL, Reuber M. What is it like to receive a diagnosis of nonepileptic seizures? *Epilepsy Behav* 2009; 14(3): 508-15.

van der Kloet D, Merckelbach H, Giesbrecht T, Lynn SJ. Fragmented sleep, fragmented mind: the role of sleep in dissociative symptoms. *Perspect Psychol Sci* 2012a; 7(2): 159-75.

van der Kloet D, Giesbrecht T, Lynn SJ, Merckelbach H, de Zutter A Sleep normalization and decrease in dissociative experiences: evaluation in an inpatient sample. *J Abnorm Psychol* 2012b; 121(1): 140-50.

van der Kruijs SJ, Vonck KE, Langereis GR, *et al*. Autonomic nervous system functioning associated with psychogenic nonepileptic seizures: analysis of heart rate variability. *Epilepsy Behav* 2016; 54: 14-9.

Vincentiis S, Valente KD, Thome-Souza S, Kuczinsky E, Fiore LA, Negrao N. Risk factors for psychogenic nonepileptic seizures in children and adolescents with epilepsy. *Epilepsy Behav* 2006; 8(1): 294-8.

Voon V, Brezing C, Gallea C, Hallett M. Aberrant supplementary motor complex and limbic activity during motor preparation in motor conversion disorder. *Mov Disord* 2011; 26(13): 2396-403.

Walsh S, Levita L, Reuber M. Comorbid depression and associated factors in PNES versus epilepsy: systematic review and meta-analysis. *Seizure* 2018; 60: 44-56.

Wardrope A, Green B, Norman P, Reuber M. The influence of attachment style and relationship quality on quality of life and psychological distress in carers of people with epileptic and nonepileptic seizures. *Epilepsy Behav* 2019; 93: 16-21.

Williams IA, Levita L, Reuber M. Emotion dysregulation in patients with psychogenic nonepileptic seizures: a systematic review based on the extended process model. *Epilepsy Behav* 2018; 86: 37-48.

Zeng R, Myers L, Lancman M. Post-traumatic stress and relationships to coping and alexithymia in patients with psychogenic non-epileptic seizures. *Seizure* 2018; 57: 70-5.

TEST YOURSELF

(1) Which statement regarding the prevalence of psychogenic non-epileptic seizures (PNES) is correct?
A. PNES is diagnosed in over 20% of patients referred to epilepsy units with apparently refractory epilepsy.
B. PNES account for less than 1% of convulsive seizures that present to emergency departments.
C. PNES that look like syncope ("pseudosyncope") are found in about 50% of patients with recurrent syncope of unknown cause.
D. Over 50% of patients with PNES have additional epilepsy.

(2) Which statement regarding PNES and psychological trauma is correct?
A. Psychological traumatization through abuse or stressful life events is very common amongst patients with PNES.
B. Childhood trauma can have both biological and psychosocial long-term effects that predispose to PNES.
C. Although it is common, psychological trauma is not always found in all patients with PNES.
D. All of the above are true.
E. None of the above are true.

(3) In cases when a previous epilepsy diagnosis is revised to PNES,
A. antiepileptic medication should be continued in case additional epilepsy was missed.
B. antiepileptic medication should be continued in order to reassure the patient.
C. antiepileptic medication should be withdrawn because it is ineffective and can cause harm.
D. antiepileptic medication should be changed to a substance with mood-stabilizing effect (*e.g.* valproic acid or lamotrigine).

(4) PNES occurring in the context of post-traumatic stress disorder (PTSD)
A. confirm the diagnosis; PNES exclusively occur in the context of PTSD.
B. contradict the PTSD diagnosis because the two diagnoses are mutually exclusive.
C. always involve so-called "flashback" experiences relating to the trauma.
D. can be alleviated through PTSD-specific treatment approaches.

(5) The following feature(s) can be found in both borderline personality disorder patients and in patients with PNES:
A. Emotion dysregulation.
B. High rates of childhood trauma.
C. Unstable interpersonal relationships.
D. All of the above.

(6) Which one of the following statements regarding the comorbidity of epilepsy and PNES is true?
A. Epilepsy and PNES usually start at the same time.
B. Epilepsy almost always precedes the onset of PNES.
C. PNES invariably start only once epilepsy has resolved through medication or surgery.
D. In patients that have both PNES and epileptic seizures it is always easy to differentiate the two.

(7) A history of mild traumatic brain injury in patients with seizures
A. suggests that seizures are most likely epileptic.
B. is relatively common in patients with PNES.
C. is always pathophysiologically irrelevant.
D. is always indicative of deep psychological traumatization associated with the injury.

(8) Which of the following comorbidies is not particularly common in patients with PNES?
A. Cancer.
B. Migraine.
C. Sleep disturbances.
D. Epilepsy.

(9) Which statement regarding cognitive complaints in patients with PNES is correct?
A. Cognitive complaints are usually the result of reduced effort or malingering.
B. PNES patients almost always have some degree of intellectual disability.
C. Cognitive problems are often due to attentional dysfunction.
D. Dissociative amnesia is very common amongst patients with PNES.

(10) Careful assessment of risk factors and comorbidities serves primarily to:
A. Conclusively diagnose seizures as either PNES or epilepsy.
B. Devise individual treatment plans.
C. Refer patients to another, more relevant specialty.
D. Prove to the patient that there is no "organic" disease.

Note: Reading the manuscript provides an answer to all questions. Correct answers may be accessed on the website, www.epilepticdisorders.com, under the section "The EpiCentre".