Section 1 Recognition, Diagnosis, and Impact of Nonepileptic Seizures

Chapter 1

Epidemiology and Classification of Nonepileptic Seizures

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This chapter introduces the differential diagnosis of three seizure groupings for patients presenting with what are commonly referred to as "spells": epileptic seizures, psychogenic nonepileptic seizures (PNES), and physiological nonepileptic events (PNEE). Each grouping has its unique etiologies and treatment approaches. Given the numerous texts published on epilepsy, this book focuses on the latter two groupings, PNES and PNEE. This introductory chapter describes the etiology and classification of PNES. Other chapters describe diagnoses in the differential for PNEE. Treatments for adults and children with PNES are covered later in the book.

Psychogenic Nonepileptic Seizures

Psychogenic nonepileptic seizures are clinically defined as events that alter or appear to alter neurological function, resemble epileptic seizures [1] and are classified in the *Diagnostic and Statistical Manual of Mental Disorders* Fifth Edition (DSM-5) [2] as a conversion disorder (or functional neurological symptom disorder) in the category of Somatic Symptom and Related Disorders (APA). Clinicians have been fairly reliably able to distinguish PNES from epilepsy based on clinical characteristics of the disorder [3], but a definitive distinction between epilepsy and PNES was not possible until an improved diagnostic tool – prolonged video-EEG monitoring (VEEG) – became available. VEEG allowed the correct diagnosis in a considerable percentage of patients with poorly controlled seizures. The diagnosis of PNES, referred to as "hysteroepilepsy" or "pseudoseizures" in the past (see Chapter 24), however, has existed for millennia.

Terminology

A survey of British neurologists in the late 1980s revealed that preferred nomenclature for unexplained neurological symptoms included "functional," "psychogenic," and "hysteria" [4]. Scull cites 15 synonyms for PNES, including, among others, "pseudoseizures" (suggesting that there is something spurious or false about the events), "hysteroepilepsy" (indicating that the uterus is the origin of the nonepileptic events), "hysterical pseudoseizures," "pseudoepileptic seizures," and "psychogenic seizures" [5]; more recently, terms such as PNES, "nonepileptic attack disorder," and "stress seizures" have also been used. The emergence of new, less pejorative labels, such as PNES, indicates an increasing understanding and acknowledgement that the events are very real to the patients, witnesses, and physicians, and that they have different and variable pathophysiology or etiology from epileptic seizures. The term *psychogenic* nonepileptic seizures emphasizes the distinction between psychogenic and *physiological* nonepileptic seizures (or events) as seen in patients with migraine or other neurological conditions, sleep disorders, or cardiac events (see Chapters 6 and 7). Consistent with the first three editions of this book and with research on terminology, we and others in the field believe that the term psychogenic nonepileptic seizures (PNES) is the most appropriate term for this condition, as it moves beyond the pejorative connotation that "pseudoseizure" carries, and we will use this term where appropriate.

Epidemiology of PNES

The diagnosis of PNES is documented with the results of VEEG, while the relevant psychological or psychiatric factors may not be elicited at that time. Typically, monitoring reveals (1) the lack of EEG changes during clinical events that are associated with alteration of consciousness or motor, sensory, and/or autonomic phenomena; (2) normal alpha background rhythm (or no change in background rhythm) with or without the alteration of consciousness; and (3) the non-stereotypic nature of the events; in addition, a sustained response to antiepileptic drugs (AEDs) is

usually not observed. A history consistent with PNES is also used in making the diagnosis [6,7]. Some patients with PNES who have possible or confirmed diagnosis of epilepsy are considered to carry a dual (or mixed) diagnosis of PNES/ES [8].

Until the 1990s, no population-based studies of PNES had been performed, and most estimates of incidence and prevalence of PNES were based on VEEG reports from tertiary care epilepsy centers. By default, the incidence and prevalence reported from such estimates were heavily dependent on referral patterns and on the vigilance of the clinicians evaluating the patients in the outpatient clinics who later referred them for evaluation with VEEG. These estimates were likely to under-report PNES because patients with PNES may not always be evaluated by epilepsy specialists as the nature of their events may be variable and include many other medically unexplained symptoms (MUSs), including those of pain, sleep disorders, movement disorders, multiple sclerosis, or stroke-like events. It is also important to note that many patients do not come to medical attention, as their seizures are temporarily controlled through behavioral, psychological, or pharmacological interventions; hence definitive evaluation is frequently not performed or is delayed until seizures recur. Further, only ~50% of patients are evaluated and treated by neurologists trained in recognizing and managing seizure disorders, while ~40% of patients with seizure disorders have limited access to care, in part owing to cost [9,10]. Thus, it is not surprising that the typical delay in recognizing and making the diagnosis of PNES was approximately 7 to 8 years in the past [1,6,11], although shorter times from onset to diagnosis have been reported recently, indicating increasing recognition of the entity and vigilance of providers [12].

Prolonged VEEG monitoring is usually performed in patients who experience frequent, prolonged, or medication-resistant events that raise the clinician's suspicion that they are possibly nonepileptic; patients with infrequent or controlled events, even when suspicious in description, do not usually undergo VEEG because of the high cost and low yield of such studies. Frequently, patients with poorly controlled seizures are referred to epilepsy centers for possible surgical evaluation and possible intervention, and are diagnosed with PNES only after the full evaluation, including the VEEG, is completed. Further, many patients undergo multiple VEEG evaluations, as they may be searching for confirmation of a diagnosis, or they may be referred to various centers for second opinion by physicians who are either unaware of the previous evaluations or diagnoses, or who are dubious of the diagnosis of PNES [13]. Finally, many patients undergo outpatient or emergency VEEG monitoring, rather than formal VEEG in an epilepsy monitoring unit (EMU), in the setting of frequent and prolonged seizures necessitating rapid admission via emergency room, and these patients are frequently diagnosed with nonepileptic psychogenic status (NEPS) [12,14,15]. Therefore, epidemiological studies of PNES are challenging and, by definition, can include only patients who underwent full and complete evaluation with VEEG. Estimations based on the results of VEEG are likely to lead to underestimates of the true incidence and prevalence of PNES, as referring patients for VEEG depends on availability of the testing, vigilance of the physician, and frequency of the events.

Incidence of PNES

Incidence is broadly defined as the number of new cases of a disease occurring per unit of time in a specific population. Three epidemiological studies of incidence of PNES have been published to date [6,12,16]. Since the methodologies used in these studies were somewhat different, these studies will be discussed separately.

The first study was performed in Iceland in the mid-1990s. This country has a very stable and homogeneous population, and all patients with new-onset seizures were considered for evaluation with VEEG, which was performed in the country's only available EEG laboratory [16]. The authors of this study identified 14 patients aged 16–54 with definite PNES; the majority of these patients (78.6%) were women. The incidence of PNES was calculated as 1.4 per year per 100,000. The highest incidence of PNES was noted in the 15–24 years age group (3.4/100,000 person-years), with no patients above the age of 55 diagnosed with PNES. The incidence of PNES was highest in female patients 15–24 years of age (5.9/100,000 person-years). The authors estimated that patients with PNES constitute about 5% of all patients with new-onset seizures. For comparison, the authors estimated the incidence of epilepsy in the Icelandic population over 15 years old to be 35/100,000 person-years.

The second study was performed in Hamilton County, Ohio [6]. The authors found the mean

incidence of PNES to be about 3.03/100,000 person-years. The highest incidence in this study was in the 25–44 years age group (4.38/100,000 person-years) with 73% being women, which was a similar gender ratio to the Iceland study and to previous reports [17]. This incidence of PNES was compared with the population incidence of epilepsy in Rochester, Minnesota of 44/100,000 person-years [18]. Interestingly, the incidence of PNES in this study was twice that of the incidence of PNES in the Icelandic population, while the overall incidence of epilepsy in the US study was also higher than that reported by Sigurdardottir and Olafsson in Iceland.

Finally, the most recently published study of the incidence of PNES was conducted in Scotland [12]. The study design was similar to the Icelandic study in that patients who were suspected of having nonepileptic events were evaluated with outpatient or inpatient VEEG monitoring as early as possible in the course of disease, which is reflected in the mean duration of time from seizure onset to diagnosis of only 1.7±3.4 years. The incidence of PNES in this study was 4.9/100,000 person-years (81% of patients were women), which is similar to the previous study from Hamilton County in Ohio [6,12] At the same time, these authors reported that for each patient with PNES there were five to six patients with newly diagnosed epilepsy, indicating fairly similar incidence of epilepsy to the one reported from Rochester, Minnesota [18].

Of interest is that these incidence estimates are similar to a study from the Netherlands in which patients with nonepileptic seizures of non-medical origin (e.g., PNES, panic attacks, hyperventilation) were combined into one group that comprised 18% of all newly evaluated patients with seizures, with the denominator being all patients with first seizure; 67% of patients included in the "non-organic" group were female [19].

The similarities between these studies indicate that the proportion of patients with newly diagnosed PNES may be similar across populations when compared with the overall incidence of epilepsy. Additionally, the results indicate a fairly similar approach to the evaluation of patients with new-onset seizures or spells between the three incidence studies, and a very consistent proportion of patients diagnosed with PNES being female (70–80%). There also may be similar awareness and vigilance of the physicians regarding the possibility of a diagnosis other than epilepsy in patients with new-onset seizures. The study by Szaflarski *et al.* [6] also found increasing incidence of PNES over the study period, indicating higher awareness of clinicians and familiarity with the diagnosis of PNES and possibly improved access to VEEG in the studied region.

Prevalence

Prevalence is defined as the number of active cases of a disease per unit of population at risk. Obviously, it is difficult to estimate the prevalence of disease when diagnosis is based on VEEG, which is costly, time-consuming, and sometimes difficult to obtain, as compared with clinical criteria. Nevertheless, there are many reports that indicate that the prevalence of PNES among those who are referred to epilepsy centers is between 10% and 20% in children, and between 10% and 58% in adults, with the most frequently quoted numbers between 20% and 30% [20]. One study proposed an estimate of the prevalence of PNES based on a calculation using the known prevalence of epilepsy of 0.5–1%, a proportion of intractable epilepsy among epilepsy patients of 20–30% (with 20–50% of these patients referred to epilepsy centers), and an assumption that 10–20% of patients referred to epilepsy centers would be diagnosed with PNES [21]. Using these available data, the estimated prevalence of PNES was between 1/50,000 and 1/3,000, or 2 to 33 per 100,000. Therefore, PNES is not a rare disorder, and its economic impact related to medication and treatment expenses is estimated to be high, probably similar to the economic impact of epilepsy. Previous research has also documented worse outcomes in patients with PNES than those with ES [22], suggesting comparatively higher individual burden of PNES. Correct diagnosis and appropriate patient education may lead to a better understanding of the disease by patients and physicians and, therefore, may lower the economic impact by 69–97% [23].

Often, patients with prolonged events of nonepileptic origin are labeled as or diagnosed with NEPS [14]. While there are no incidence or prevalence studies of NEPS, studies report that up to 78% of patients with PNES have experienced at least one episode of NEPS [24]. The only difference between the patients with PNES and NEPS identified in this study was a much younger age of the patients who presented with NEPS. An additional two studies that examined a large number of patients with NEPS and PNES did not identify any specific demographic or clinical

differences between groups [15,25]. The distinction, at least at this point, appears to be somewhat artificial, but it is important for clinicians to remember that NEPS should be in the differential diagnosis for patients with prolonged events. Not diagnosing these patients correctly from the beginning may expose them to unnecessary interventions and potential iatrogenic harm, given that these patients have a higher likelihood of presenting via the emergency department and have a higher chance of intensive care unit admission [24,26].

Prevalence of Comorbid Epilepsy and PNES

The reported prevalence of comorbid epilepsy in patients diagnosed with PNES varies considerably and has been reported to be between 9% and 63% [6,27], with the higher number reported in one of the first studies reporting the results of VEEG in patients with medication-resistant epilepsy [27]; in that study, a total of only eight patients with PNES were identified (five had comorbid epilepsy). In the Icelandic study, 50% of patients diagnosed with PNES had comorbid epilepsy [16]. This number also appears to be very high, as other recent studies have reported much lower prevalence of epilepsy in patients with PNES. In the second published incidence study described above, only 16/177 (9%) patients were diagnosed with comorbid PNES and epilepsy [6],which is much closer to a later estimate from a study that found coexisting epilepsy in about 9.4% of patients with PNES [8]. A more recent study from Iran reported the prevalence of comorbid epilepsy in patients with PNES to be 16.6% [28]. Therefore, it appears that about 10–20% of patients with PNES have comorbid epilepsy. Most importantly, in patients with well-characterized epilepsy and abnormal EEG showing epileptiform discharges, PNES are still possible and should be considered if the patient's seizures are not responding to standard treatments.

To summarize, the diagnosis of PNES is not uncommon, with about 5–20% of patients with spells or seizures having nonepileptic events. Clinicians should be vigilant in monitoring the description of events and particularly aware of unusual phenomena that may be atypical in epileptic seizures but suggestive of PNES. Unusual characteristics of seizures or lack of medication response should prompt VEEG evaluation as means of pinpointing the diagnosis and designing an optimal treatment plan.

Social Epidemiology and Social Factors in PNES

The literature emphasizes the importance of cultural and social factors in PNES (see Chapters 12–16 in this volume). However, there has been limited systematic and comprehensive research on the incidence and prevalence of PNES, its determinants, and risk factors for PNES according to social characteristics (e.g., social status or position). Such studies fall into the realm of social epidemiology, referred to by some as the study of social determinants of health [29]. Some of the key social determinants of health are social class or socioeconomic status (education, income, and occupation), age, sex, race, and ethnicity.

Socio demographic factors such as gender and age have been identified as key issues in the diagnosis and treatment of PNES (see Chapters 10, 11, 12 in this volume), but the social underpinnings of their relationships to PNES are not well described. Epidemiological studies tend to report the distribution of PNES by gender and age, but come short of discussing how sex and age (independently and together) may be associated with PNES outcomes. Although biologically determined, sex and age are also social statuses, which influence one's social position and, subsequently, one's health status. For example, the higher rates of PNES among women could be linked to gender inequality and women's generally inferior social position; stress related to gendered social roles and division of labor (e.g., unequal distribution of family and household labor; work–family conflict and strains); or violence against women (e.g., sexual abuse). Schmitz suggests that (1) frustration with gender discrimination may lead to helplessness and anger that manifests in dissociative reactions, and (2) hysterical behavior is more socially appropriate for women than men, who tend to react to stress with substance abuse and/or aggression [30]. Schmitz found that in the studies she examined, gender was treated as a confounding variable rather than a risk factor to study independently of other determinants [30].

Age also plays a role in PNES, in part because the social position and social roles change throughout the life course. Epidemiological studies discussed previously estimated PNES peaking in adolescence and early and middle adulthood. This could be due to hormonal changes as well as changing social expectations during transition from childhood to adult life stages. In comparison, PNES in children aged 12 years

and lower appear to be reported with school phobia and fear of examinations [30]. Data on the elderly are generally lacking, but high rates of PNES diagnosis among elderly people who have undergone VEEG further signal potential PNES disparities in general populations [31]. PNES in the elderly are often associated with health-related traumatic experiences [30,31], but stress related to declining health status, social isolation, and diminished social activity and self-mastery may be additional factors, which are yet to be further explored.

There are surprisingly few data about the relationship between socioeconomic indicators, such as education, and PNES. Low education has been shown to increase the risk of mental disorders, including major depression and other mood disorders, anxiety, and substance abuse [32]. Considering that PNES reflect a somatic mental illness, frequently comorbid with mood or anxiety disorders, a person's level of education likely has an impact on PNES occurrence, diagnosis, and treatment. In one study, more than a third of the PNES sample had only a high school education or less [33]. The authors suggested that the lower levels of education might be due to the younger age of PNES onset and the possibility that patients with PNES stopped educational pursuit because of the presence or severity of the symptoms (signaling a potential selection effect). There is little information about other socioeconomic factors (e.g., family background or income) and other social statuses (e.g., race) in PNES, although they are likely to play a role. One study reported associations between lower quality of life and social characteristics such as employment status, marital status, religious affiliation, proximity to family supports, and having children (all social determinants of health) in patients with PNES [34].

The social epidemiological perspective has a great potential to further inform understanding of the epidemiology of PNES in various populations. This perspective focuses on the social environment (family, community) and social group memberships as key determining factors in health, and – notably – it engages approaches to studying risk factors and diseases with the goal of fundamentally altering disease etiology and intervention strategies [35]. Thus, further systematic research on social factors in PNES, drawing on sociological and psychosocial theory, is needed to understand the PNES epidemiology more fully and to enhance early identification and treatment of PNES, with a focus on vulnerable social groups.

Clinical Classification Schemes of PNES

Since the introduction of VEEG, epileptologists have had increased diagnostic capability, especially in regard to differentiating between ES and PNES [36]. Studies have identified heterogeneity in the psychological background and profile of patients with PNES. However, commonalities are found in many patients with PNES, including a history of trauma or abuse, psychiatric comorbidities, and family or social dysfunction. Studies have identified and proposed differentiation of discrete subtypes of PNES [37,38]. For example, Gates' introduction to the second edition of this book divided nonepileptic events into a dichotomy – physiological and psychogenic [39]. The ability to classify patients within subtypes of PNES is important because there is evidence that subtypes may be clinically relevant in terms of predicting outcome [38], informing nosology [37,38], and, perhaps most importantly, potentially directing treatment [40,41].

Studies of subtypes of PNES have used a wide range of methodologies and criteria. The following broad categories of subtypes that do not conform to existing psychiatric taxonomy will be reviewed: (1) classifications based on clinical semiology, (2) classifications based on personality testing, (3) classifications based on both semiology and personality testing, and (4) classifications based on suspected psychological mechanism/etiology. In this section, we survey the literature on classifications, as an introduction to further discussions in subsequent chapters, with the caveat that not all investigators recognize these and other classifications and argue instead for a uniform approach to all patients with PNES [42].

Classifications Based on Semiology

Characterizing seizure-like events by their semiology has a long history that can be traced back to initial theorizing about "hysterical" reactions by Charcot and Janet [43]. The earliest classifications of PNES resulting from descriptive accounts of semiology were dichotomous. These classifications were borne out of conceptualizations of PNES as expressions of basic human needs or drives. For example, Kretschmer, following the ideas of Freud, characterized spells as either hypermotor or atonic [44]. As summarized by Blumer and Adamolekun, Kretschmer postulated that PNES appear "…in the form either of a motility storm consisting of regression in a state of terror with hyperkinesis, trembling, and convulsing, or of sham death with

stupor, immobilization, or a hypnoid state" [45, p. 498]. Similarly, Szondi described a polarity of paroxysmal drives oriented around the locus of perceived source of danger. Szondi postulated that PNES represented either a "protective drive," with the epileptiform reaction as a response to perceived internal danger, or a hysteriform reaction in response to perceived danger in the external world [45]. The basic classification of PNES as either hypermotor or atonic has survived within differing terminology ("catatonic" versus "thrashing," "convulsive" versus "nonconvulsive") and underlies modern classification schemes of PNES [38].

Some early attempts to classify subtypes of PNES by semiology followed this theorized dichotomy fairly closely. For example, Meierkord *et al.* categorized spells as attacks of collapse and attacks with prominent motor activity [17]. Interestingly, several authors have reported that two-thirds of patients with PNES have the hypermotor type and the remaining one-third of patients have the atonic type of spells [17,46]. Other classifications of PNES included both motor and affective components of PNES. For example, Wilkus and Dodrill categorized PNES as mostly motor/limited affect and limited motor/prominent affect groups [47].

Other semiology-based classifications of PNES introduced finer, but differing, distinctions between types of spells. In an early study of semiology, PNES were characterized into four major patterns associated with the events: bilateral motor, unilateral motor, multiple behavior phenomena, or impaired responsiveness with no observable behavior [48]. By contrast, in a study of whether stereotyped behavior during PNES represents learned behavior, Henry and Drury characterized events as convulsive, hypotonic ("sudden falls, or leaning limply/leans onto a bed or other nearby support"), automatistic ("simple or complex movements that are symmetric or nonconvulsive"), or hypokinetic ("motionless or nearly motionless staring with unchanging posture") [49]. In a study of whether closed eyes during spells indicated psychogenic etiology in the context of seizure provocation, Flugel *et al.* used VEEG to classify patients into the following three semiology-based groups: strong movements particularly of the extremities (similar to a generalized tonic-clonic seizure); spells with mild, less pronounced motor activity; and almost motionless unresponsiveness [50]. In contrast, Gumnit and Gates mention the importance of differentiating PNES that resemble complex partial seizures (CPS) from those that resemble generalized tonic-clonic seizures [51]. In a review of cases described in other studies, van Merode *et al.* categorized PNES as resembling generalized tonic-clonic seizures, resembling CPS, or resembling a combination of both categories [52]. In one of the first studies to use symptom cluster analysis, Groppel *et al.* classified patients with PNES via VEEG into three semiology-based clusters: psychogenic motor seizures, psychogenic minor motor or trembling seizures, and psychogenic atonic seizures [53].

Reuber *et al.*, in an outcome study involving long-term follow-up, classified patients with PNES into the following groups: positive motor, negative motor, and purely sensory [41]. However, a subset of recent studies has excluded PNES characterized exclusively by sensory phenomena from their classification schemes owing to the limited sensitivity of scalp electrodes for detection of simple partial seizures [37,54]. Furthermore, caution is warranted not to misdiagnose PNES in patients with frontal lobe ES, as these may be very bizarre in their appearance and not associated with clear EEG changes [55,56]. These difficulties render the differentiation of ES and PNES, in the case of sensory, bizarre behaviors, or subjective PNES extremely difficult, thus sometimes compromising the accurate designation of these events as PNES versus epilepsy.

More recent studies have further expanded the number and complexity of delineations between types of PNES in order to better understand the natural history and pathogenesis of PNES. For example, Selwa *et al.* introduced a classification of PNES into six types: catatonic, thrashing, automatisms, tremor, intermittent, and subjective. This study was unique in that it focused on the utility of subtype with regard to outcomes, such as remission of seizures and discontinuation of AEDs [38]. Although there are six subtypes in the proposed Selwa *et al.* classification, their study focused on comparisons between catatonic and thrashing, the two most conceptually opposite categories. Griffith *et al.* modified the Selwa scheme to a four-subtype scheme, consisting of catatonic, major motor, minor motor, and subjective [37]. The Griffith *et al.* classification is more parsimonious and resulted in better inter-rater reliability than the Selwa *et al.* scheme [37,38].

Finally, in addition to the previously mentioned study that used "symptom cluster analysis" [53], two recent studies used similar analyses of clinical symptoms [57,58]. In the first of those two studies, visual rather than computational analyses were conducted

to demonstrate six distinct types of events based on semiology clustering: rhythmic motor, hypermotor, complex motor, dialeptic, subjective auras, and mixed PNES types [58]. In the second study, association analysis between semiological categories was conducted to reveal five different clinical subtypes of events associated with PNES – dystonic attacks, paucikinetic attacks, pseudosyncope, hyperkinetic attacks, and axial dystonic attacks [57].

In summary, recent attempts to classify PNES by semiology have expanded upon earlier dichotomous distinctions between, for example, "atonic" and "hypermotor" events, by identifying three to six distinct subtypes of PNES, with the most useful of these schemes demonstrating good inter-rater reliability; these new classification schemes may be related to outcome and help in guiding therapy choices.

Classifications Based on Personality Testing

Some investigators have used psychological testing, especially personality testing, to identify subtypes of patients with intractable seizure disorders. The most commonly used measure of personality and psychopathology in both ES and PNES populations is the Minnesota Multiphasic Personality Inventory (MMPI) [59,60]. Other personality measures have also been used in these populations, including the Personality Assessment Inventory (PAI) [24,59,61]. For example, in a sample of presurgical patients with intractable seizure disorders, a subset of whom (about 20 of 90) were likely to have PNES or both PNES and ES, King *et al.* identified three groups based on personality profiles: (in order of greatest frequency) minimal psychological complaints, generalized clinical elevations (high psychological complaints), and intermediate elevations with a tendency to emphasize somatic complaints or depression [62].

Several authors have emphasized the heterogeneity of personality profiles among patients with PNES [59,62,63]. For example, studies have found that a majority of patients with PNES have personality abnormalities on psychometric tests [46,64], but there is not a single characteristic personality profile that can be attributed to these patients [65]. Barrash *et al.* analyzed MMPI profiles of patients with PNES and identified seven discrete personality clusters: histrionic, depressed, non-affective serious psychopathology, disinhibited, decompensated, somatisizers, and asymptomatic [66]. In another study involving personality testing with the MMPI, Gumnit and Gates analyzed interviews, MMPI, and projective testing results among patients with PNES. They found five underlying etiology-based subtypes based on suspected etiology or function of PNES: psychological distress-emotional conflict; inappropriate coping mechanisms; misinterpretation of normal physiological stimuli; psychotic behavior; and an epileptic aura or seizure followed by PNES. They also reported that these subtypes were useful for selecting patients for appropriate treatments [51].

Of note, the model employed by the *Diagnostic and Statistical Manual of Mental Disorders* (DSM) has been criticized by some authors [46,67,68]. For example, Reuber *et al.* criticized the categorical model of the DSM in favor of a dimensional system that would consider personality disorders as extremes on a continuum of common personality traits. These authors also noted considerable symptomatic and behavioral overlap and poor inter-rater reliability between DSM personality disorders [46]. In addition, Reuber *et al.* and other investigators have criticized the use of the MMPI for categorizing personality subtypes, especially among inpatient groups. The same authors stated that the MMPI is difficult to interpret because it simultaneously measures both personality characteristics and psychopathological syndromes, such as hypochondriasis and conversion [46]. In contrast to studies utilizing the MMPI, Reuber *et al.* used the Dimensional Assessment of Personality Pathology-Basic Questionnaire (DAPP-BQ) [69] as a measure of personality in patients with PNES as compared with patients with ES and healthy subjects. They found three distinct "typical pathological personality profiles" via cluster analysis (in order of size): similar to borderline personality disorder, overly controlled personality, and similar to avoidant personality disorder.

There has been increasing attention in behavioral medicine paid to the importance of measuring "normal" personality traits. Cragar *et al.* emphasized the relationships of normal personality traits to health status, health outcomes, and behavior patterns [40]. Moreover, normal personality traits, such as optimism and pessimism, have been found to be relevant to investigations of etiology and outcome in both medical and psychological disorders [70,71]. Cragar *et al.* studied "normal" personality in patients with PNES by means of personality dimensions derived from the "Big 5" as measured by the Revised NEO Personality Inventory (NEO-PI-R) [72]. Using cluster analysis of

both MMPI and NEO-PI-R results, Cragar *et al.* found three clusters of patients with PNES: depressed neurotics, somatic defenders, and activated neurotics [40].

Several recent investigations focused on the use of PAI rather than MMPI for the evaluation of personality trait in patients with PNES. In one of the initial reports, Wagner *et al.* indicated that PAI was able to distinguish personalities of patients with PNES from ES with good specificity and sensitivity, and that patients with PNES had much higher somatization indices in addition to the previously observed differences between the groups [73]. These authors went further and created the "NES Indicator" (based on the PAI Somatization scale) which was 84% sensitive and 73% specific for correctly diagnosing PNES. However, further testing of this indicator on a larger sample of patients showed that it was no more useful than the conversion subscale of PAI [74,75].Finally, one study compared the diagnostic accuracy of MMPI and PAI [61]. These authors found that both scales were similar in their ability to correctly diagnose PNES, but combining them into one measure produced the best predictive model, with 87% sensitivity and 82% specificity.

It is, therefore, clear that classification of PNES by personality testing has underscored the heterogeneity of personality profiles in patients with PNES. Although some earlier work focused on pathological personality profiles, a more recently employed approach has been to investigate normal personality traits or dimensions that have been related to the etiology and outcome of a range of medical disorders, and to examine the ability of such testing to distinguish between PNES and ES. Unfortunately, the heterogeneity of PNES and of the psychological psychiatric comorbidities and the similarities in those domains between PNES and ES constitute a major obstacle in developing reliable methods of differentiating the two conditions based purely on psychometric measures.

Classifications Based on Both Semiology and Personality Testing

A few studies have combined personality, psychological testing and semiology in identifying subtypes of PNES. In perhaps the best example of this approach, Wilkus and Dodrill classified patients with PNES into the following groups: (1) mostly motor and limited/none affect; and (2) limited motor/prominent affect. These two PNES subgroups had different composite MMPI profiles; moreover, 76% of patients in the study could be classified into one of these two groups [47].

By simultaneously considering both behavioral and affectual aspects of the presentation of PNES, the classification by both semiology and personality testing may represent an important evolution in the classification of PNES.

Classifications Based on Etiology or Suspected Psychological Mechanism

Some investigators have classified patients with PNES via behavioral and interpersonal factors believed to contribute to the development of PNES – in other words, by etiology or suspected psychological mechanism. On a patient-by-patient basis, PNES may have a single-factor or multifactorial etiology; that is to say, in a given patient, PNES are believed to manifest from one or more of several distinct causal pathways [76,77]. Ford identified several factors that may individually or jointly contribute to the etiology of somatoform disorders, including: secondary gain, behavioral manifestations of ineffective communication/inability to adequately identify and express strong emotion, and disturbed family systems [78].

Studies of patients with PNES have produced similar findings related to etiological factors (i.e., interpersonal, communication, and/or family problems). For example, Lesser summarized the etiological factors of PNES described in the literature as follows: (1) interpersonal, (2) intrinsic emotional problems or internalized conflicts (e.g., somatization, dissociation, posttraumatic stress), (3) psychosis, (4) personality disorder, and (5) cognitive difficulties or history of head trauma [77]. Similarly, Alsaadi and Marquez classified PNES by suspected psychological causal pathway, while emphasizing that all PNES function as a coping mechanism [76]. They classified the etiology of PNES as follows: (1) caused by misinterpretation of physical symptoms, (2) the result of psychopathological processes (e.g., somatization, dissociation), (3) response to acute stress (in patients with absence of psychopathology), and (4) reinforced behavior pattern in cognitively impaired patients.

On the other hand, some authors have conformed more closely to psychodynamic theory in classifying patients with PNES by etiology. For example, one group of authors described four "psychodynamic pathways" to PNES: (1) history of childhood physical or sexual abuse, (2) recent sexual assault, (3) multiple life

stresses that overwhelm coping abilities, and (4) panic attacks mistaken for PNES [79,80]. These authors noted that for all these categories, the manifestation of PNES was often triggered by recent trauma. Other studies conformed more closely to formal psychological diagnostic categories and processes. For example, one study identified six categories, or "symptom patterns," of patients with PNES, based in part on the most effective psychotherapeutic interventions used with each group [81]. Rusch *et al.*'s findings were reformulated by LaFrance and Devinsky as the following: (1) anxious, (2) abused (subclassified into 2a – abused [borderline personality disorder], and 2b – afraid [as in posttraumatic stress disorder]), (3) somatic, (4) dysthymic/depressed, and (5) mentally retarded (now referred to as intellectual disability) [82].

In general, the model for PNES development and maintenance includes abnormalities in biological (e.g., disruption in the function of the limbic system and its connections), psychological (e.g., problems related to emotion regulation), and/or social domains (e.g., limitations in social functions), with the PNES phenotype thought to result from one or more abnormalities in these domains. Thus, classification of PNES by suspected etiology brings into focus common pathogenic factors, such as trauma, and the multifactorial nature of the development and maintenance of PNES. Consideration of the differential effectiveness of psychotherapeutic interventions with subgroups of patients with PNES is one intriguing method of improving our understanding of nosology with a direct implication for improving treatment.

Neurological Events Mimicking PNES

There is no single diagnostic test that allows certain differentiation of PNES, ES, PNEE, and/or other types of psychiatric diagnoses. Even VEEG, the gold standard in distinguishing between PNES and epilepsy, does not always yield the correct diagnosis when used in isolation, as it may be difficult to distinguish, for example, between bizarre ictal behaviors associated with frontal lobe/supplementary motor seizures and PNES [55,56]. Certainly, VEEG, in association with other tests and clinical observation(s), is a valuable tool in differentiating PNES from other neurological or non-neurological conditions. But before such testing is scheduled, as with all patients presenting for initial evaluation or follow-up, a detailed general history is essential for correct diagnosis. A focused, symptom-oriented approach alone may lead to incorrect diagnosis. Description of the events obtained from the patient may be very sketchy or plainly inaccurate. Therefore, a detailed description of the event(s) from witnesses is of significant value. The International League Against Epilepsy (ILAE) NES Task Force published diagnostic criteria used to establish diagnostic levels of certainty for PNES, and the combination of history, semiology, and event captured on VEEG consistent with PNES allows for a level of Documented PNES [83].

As noted, semiologic descriptive elements are key data points for aiding the diagnosis. Information about duration of the events may be the first clue to the correct diagnosis, as PNES frequently have longer duration than typical ES and may be prolonged, lasting sometimes more than 30 minutes, as in, for example, NEPS [14,49]. Further, seizure precipitants and the presence or absence of certain phenomena, such as prolonged waxing and waning course of the events, screaming, hearing but not being able to respond, ictal eye closure, crying/whimpering, asynchronous or asymmetric extremity movements, and pelvic thrusting, may be helpful in coming to the right diagnosis. Further, the presence of EEG abnormalities including epileptiform discharges is not necessarily indicative of epilepsy [84].

Physiological Nonepileptic Events

We briefly introduce some of the main PNEE diagnoses which are included in the differential diagnosis of PNES. These are usually paroxysmal events with physiological explanation. These etiologies include syncope, nonepileptic myoclonus, dysautonomia, and various sleep disorders (parasomnias), including sleepwalking, confusional arousals, and rapid eye movement (REM) sleep behavior disorders. This list also includes other neurological phenomena, including transient ischemic phenomena and migraine, and non-neurological phenomena such as organic hallucinations and psychosis-related symptoms, such as may be due to medication or substance toxicity (see Chapters 4–7 and 10, 11).

Syncope, especially convulsive syncope, is likely the most frequent physiological phenomenon that is confused with PNES. Overall, convulsive syncope is a relatively common event. In one study of unselected blood donors, convulsive syncope occurred in 0.03%. The donors frequently experienced convulsive tonic extensor spasm(s); other epileptic phenomena

simulating an epileptic seizure occurred less frequently [85]. Further, the authors did not find any significant differences between the "early" and the "delayed" responses [85]. In another VEEG study, 10 of 22 syncopal episodes precipitated by cardiac arrhythmias were associated with regular or irregular tonic movements. Although generalized EEG changes were observed in some patients (usually generalized slowing), no ictal or interictal epileptiform discharges were noted [86]. Therefore, in patients with syncope or when the description of events is not clear, a detailed cardiac evaluation, including 24-hour Holter monitoring or more prolonged cardiac event monitoring, should be considered. Figure 1.1 depicts the EEG and ECG of a patient who experienced vasovagal syncope in response to hyperventilation. Generalized EEG changes are noted in response to central nervous system (CNS) hypoperfusion.

Transient ischemic events that may mimic epilepsy include not only transient ischemic attack (TIA) but also migrainous phenomena. As these events are fairly frequent, and migrainous sensory phenomena that are not associated with headache may sometimes be difficult to distinguish from simple partial sensory seizures, clinicians need to utilize detailed clinical history to reach the diagnosis. With approximately 83 TIAs per 100,000 per year [87] and the incidence of migraine averaging in males between 6.6/1,000 and 10.1/1,000 person-years and in females between 14.1/1,000 and 18.9/1,000 person-years [88], there is a high probability that neurologists will encounter several patients per year who have somewhat unusual presentations of these conditions that will require differentiation from epilepsy or PNES.

Physiological events that require differentiation from PNES/epilepsy are further described in Chapters 6 and 7. Thus, it is very important for the practicing clinician not to assume that patients with unusual events have PNES without proper evaluation, as there are many other clinical entities that mimic epilepsy and PNES that need to be excluded based on thorough clinical history and supplementary testing.

Classification of PNES via Existing Psychiatric Schemes

Consensus on a descriptive nosology of PNES has been elusive. A well-accepted descriptive nosology fosters meaningful classification, facilitates differential diagnosis, and may aid in the understanding of the etiology of a disorder, thereby aiding the selection and development of treatments. However, despite repeated and ongoing attempts to classify PNES as psychiatric phenomena, the classification of PNES within existing psychiatric taxonomies continues to be controversial [89–91]. The classification of PNES is difficult because patients with PNES do not fall into a single, distinct psychopathological category. In fact, researchers have suggested that PNES is not a unitary disorder, but instead may have multiple etiologies and manifestations [65]. Moreover, the etiology of PNES is multifaceted and includes the interaction of predisposing, precipitating, and perpetuating factors [82,92,93].

Sources of Confusion Underlying Classification of PNES

Detailed review of the literature reveals several interrelated sources of controversy that complicate the diagnosis and classification of PNES. The reality of the diagnostic process in clinical practice is that PNES are often diagnosed based on the nature of presenting symptoms and the exclusion of nonpsychogenic etiologies, rather than the identification of relevant psychological factors with histories consistent with conversion or dissociative disorders and documentation of non-neuroanatomical findings on exam. The result is that PNES often are diagnosed negatively ("not ES") as opposed to positively ("is PNES"). This contributes to uncertainty as to the diagnostic features that constitute PNES. Moreover, the classification of PNES is hampered by several unresolved philosophical and semantic dilemmas concerning the nature and underlying causes of PNES. These include: (1) whether somatization or dissociation is the primary underlying etiology of PNES, (2) a descriptive vs. etiological approach to psychiatric classification, and (3) whether PNES should be conceptualized and classified as a symptom of psychiatric disorder or as a separate entity.

Somatization versus Dissociation as the Primary Underlying Etiology of PNES

Disagreement as to whether PNES should be characterized as primarily a somatoform or dissociative disorder complicates the classification of PNES [78,89,94]. Several reviews have examined the differential role and impact of dissociation and somatization in PNES [65,90]. The results of these studies