
Article:
Reuber, M. orcid.org/0000-0002-4104-6705 and Brown, R.J. (2017) Understanding psychogenic nonepileptic seizures-Phenomenology, semiology and the Integrative Cognitive Model. Seizure, 44. pp. 199-205. ISSN 1059-1311

https://doi.org/10.1016/j.seizure.2016.10.029

Understanding Psychogenic Nonepileptic Seizures – phenomenology, semiology and the Integrative Cognitive Model

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New version 9.12.16 with corrected reference section

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Key words: Aetiology, Cognition, Psychogenic Nonepileptic Seizures, Electroencephalography, functional Magnetic Resonance Imaging

Psychogenic Nonepileptic Seizures – phenomenology, semiology and the Integrative Cognitive Model

Introduction

Psychogenic nonepileptic seizures (PNES) are involuntary experiential and behavioural responses that superficially resemble epileptic seizures (ES) but without the abnormal electrical activity associated with the latter [1]. About one in five patients first presenting to a seizure clinic is diagnosed with PNES [2], which is one of the three most common diagnoses in patients presenting with temporary loss of consciousness [3]. About 75% of patients diagnosed with this condition are female, and PNES disorders most frequently start in late adolescence or early adulthood, although seizures may first manifest in children as young as five and in older people [11, 12].

PNES are not a nosological entity in their own right. Rather, the diagnostic label "PNES" is applied in a range of clinical scenarios in which seizures are thought to have "psychological" causes. Most, but not all presentations, fulfil the diagnostic criteria of Functional Neurological Symptom (Conversion) Disorder in DSM-5 (American Psychiatric Association, 2013), although some may be a feature of another disorder (e.g., Somatic Symptom, Dissociative, Panic, Post-Traumatic Stress) or even be deliberately feigned (as in Factitious Disorder).

Progress in our understanding of PNES has not been linear or continuous. A period in the late 19th and early 20th centuries, when the phenomenon was a key feature of "major hysteria" and attracted a lot of attention, was followed by a long hiatus during which neurologists seemed to focus more on conditions they could attribute to demonstrable structural or physiological changes in the nervous system. Over the same period, psychiatrists noted the disappearance of hysteria from their practice [3] – and, with few exceptions, research on phenomena which would currently be called PNES stopped. This situation changed with the introduction of longer term ambulatory EEG and simultaneous video-EEG recordings to routine clinical practice. From the 1970s, these techniques allowed clinicians to categorise epileptic seizure disorders much more accurately, and to improve their ability to identify patients who might benefit from epilepsy surgery. The availability of these investigations also meant that it was harder for epileptologists to ignore the fact that a substantial group of their patients had seizures that were evidently not caused by epileptic activity.

This, and the realisation that seizure disorders in general were better understood as more complex biopsychosocial phenomena rather than purely "neurological" or "psychiatric" problems, were key motivations for the foundation of the Journal *Seizure* 25 years ago. As founding editor Tim Betts put

it in his editorial heading up the first issue: “this journal is not just about epilepsy, but is about seizures in general” [4].

This paper marks the prominent role played by *Seizure* in the development of our thinking about PNES by exploring how our understanding of the objective and subjective manifestations of PNES has grown since the inaugural issue of the Journal. We begin with a narrative review of studies on neurological comorbidity, visible seizures manifestations, physiological changes and subjective experiences associated with PNES, as well as how patients with PNES talk about their seizures. We then explore how this research fits with recent thinking about the psychological mechanisms of PNES (the *Integrative Cognitive Model;* ICM) [5], and consider how our understanding of PNES may deepen over the next quarter century.

PHENOMENOLOGY AND MANIFESTATIONS

NEUROLOGICAL COMORBIDITY

PNES have been found to be associated with a range of neurological disorders, most importantly with epilepsy: All published case series of patients with PNES that did not exclude patients with a history of epilepsy demonstrate that the prevalence of epilepsy is increased in patients with PNES. Having said that, the most robust studies indicate that no more than 10% of adults with PNES have concurrent epilepsy [6]. In patients with comorbid epilepsy, PNES are almost invariably preceded by the manifestation of epileptic seizures [7]. Although epidemiological data about other comorbid brain problems is less certain, patients with intellectual disabilities or head injuries may also be at increased risk of PNES [8]. However, no clear links between PNES and particular types of structural or functional brain lesions have been found [9, 10]. This suggests that a range of different brain problems may predispose patients to developing PNES and/or that the link between PNES and these problems is mediated by other mechanisms, including iatrogenicity, exposure to seizure models or traumatisation. Likewise, the fact that PNES sometimes stop after successful epilepsy surgery in patients with mixed seizure disorders does not mean that PNES were directly linked to epileptic seizures or interictal epileptic activity [11].

VISIBLE ICTAL OBSERVATIONS

The first two decades after the introduction of seizure observation with simultaneous video-EEG generated a number of studies focusing on visible seizure manifestations [1]. The main focus in many cases was to generate lists of features with differential diagnostic potential. Numerous such signs have been described, with a systematic review indicating that the most reliable indicators of PNES are long duration, occurrence from apparent sleep with EEG-verified wakefulness, fluctuating course, asynchronous movements, pelvic thrusting, side-to-side head or body movement, closed eyes during the episode, ictal crying, memory recall and absence of postictal confusion [12]. No individual observation can provide a firm basis for a diagnosis of PNES in isolation and all of these "typical" features of PNES could, conceivably, be observed in epileptic seizures; nevertheless, these visible seizure manifestations allow experienced clinicians to differentiate between epileptic and nonepileptic seizures with a high level of accuracy if they are able to examine patients during a seizure or see a recording of a typical event [13, 14].

The initial video-EEG studies also established that PNES may manifest in different ways. The most commonly observed semiology involves excessive movement of limbs, trunk and head. In most series, seizures with stiffening and tremor, or seizures with atonia are less frequent [1].

Several more recent studies have suggested that visible (or subjective) semiological elements are not combined randomly but that there may be several distinct PNES types. The most advanced study of (mainly visible) features of PNES focussed on 22 different observations and identified five different PNES types by hierarchical cluster analysis [15]. This semiological typology has been replicated in a very different (Indian) patient cohort [16]. Although other authors have described somewhat different categories, they also found that PNES could be subdivided into a moderate number of discrete semiological groups [17].

While the "meaning" of these different PNES types was not explored in the studies discussed above, other studies have demonstrated links between semiological and other clinical features: One showed that patients with a history of sexual abuse more often have convulsive PNES and a history of nocturnal spells, ictal injuries and incontinence. Patients who had previously been sexually abused were also more likely to report flashbacks and emotional triggers of their PNES or experience seizures prodromes [18]. Another study showed that patients with convulsive PNES had poorer outcomes [19].

Although many authors have claimed that PNES tend to change more over time than epileptic seizures [1], recent research has demonstrated that the semiology of PNES in individual patients is actually quite stereotyped, at least over the short term [17]. Nevertheless, some change in PNES

manifestations is often apparent, especially over the course of the first few events or over the longer term. While there is no published proof for the clinical observation that new seizure elements sometimes become part of the visible seizure manifestations when patients with PNES have been exposed to epileptic seizures (for instance on Epilepsy Monitoring Units), there is some evidence for the idea that symptom modelling may play a role: in one study, patients with PNES were six times more likely to report having witnessed someone in a seizure before experiencing their own first seizure than those with epilepsy (11 versus 66%) [20].

Overall, evidence concerning visible seizure manifestations does not support older notions of PNES as activations of inherent, hard-wired behaviour patterns akin to freeze or startle responses [21]. Rather, the limited typology and the relatively stereotyped but somewhat malleable nature of PNES across different cultures is more consistent with the idea that these seizures have a conditioned, reflex-like element that is embellished by learning and experience.

PHYSIOLOGICAL CHANGES

The first studies of Electrocardiographic (ECG) changes in PNES were published around the launch of *Seizure* 25 years ago. It was recognised that ictal sinus tachycardia was common, but more gradual in onset, less marked and less persistent after PNES cessation than in epileptic seizures [22, 23]. Subsequent studies have demonstrated that a rapid heart rate increase has a high positive predictive value for the identification of epileptic seizures [24, 25].

Although these observations demonstrated less marked acute physiological changes during PNES than epileptic seizures, several more recent studies have highlighted the fact that PNES are also associated with autonomic arousal. One study showed a lower parasympathetic tone and higher sympathetic tone during PNES than at rest, with HRV markers correctly categorising over three quarters of ECG segments from patients with PNES as capturing the ictal or interictal state [26]. A more recent study using a slightly different approach and different time windows demonstrated an increase in heart rate variability (HRV) markers of sympathetic tone just prior to a PNES but suggested that the seizures themselves were associated with parasympathetic activation, consistent with the idea that PNES may provide some relief from heightened arousal or the stimuli giving rise to it [27].

Despite the demonstrable differences in arousal between the seizure and non-seizure states, a number of studies have indicated that PNES themselves should be regarded as the "tip of the iceberg" of a more persistent (interictal) state of hyperarousal. Evidence of this has been provided by HRV studies as well as by a study comparing cortisol day curves in patients with PNES and healthy controls [28-30]. In another study, the elevated resting cortisol levels detected in patients with PNES were found to be positively correlated with increased threat vigilance [31].

Interictal physiological abnormalities have also been found in several small studies exploring brain networks using functional Magnetic Resonance Imaging (fMRI). One comparing patients with PNES and healthy controls suggested that, in the patient group, there was stronger connectivity between areas involved in emotion processing (insula), executive control (inferior frontal gyrus and parietal cortex) and movement (precentral sulcus) which was positively correlated with dissociation scores ($r=0.59$) [32]. In contrast, another study comparing MRI connectivity density maps of patients with PNES and healthy controls found patients with PNES to have reduced Functional Connectivity Density values in frontal, sensorimotor and occipital cortices, cingulate gyrus and insula [33]. In a second study by the same group, resting state fMRI data were combined with Diffusion Tensor Imaging (DTI) tractography. In line with their previous findings, PNES patients showed reduced connectivity compared to healthy controls, suggesting that PNES could be the result of poor integration of emotion processing, executive control and motor networks in the brain. This study also demonstrated a reduced coupling strength of functional and structural connectivity in the PNES population. The measure of coupling strength showed high sensitivity and specificity in the differentiation of individuals with PNES from healthy controls [34].

Studies based on computer-aided scalp EEG analysis have provided further indication of reduced network connectivity in patients with PNES. One small study using a graph theoretical approach and comparing patients with healthy controls described a weakness in local connectivity and skewed balance between local and global connectedness in EEG alpha band. These topological indices were positively correlated with PNES frequency [35]. Another small study comparing PNES patients to healthy controls identified decreased clustering coefficients in the gamma band, a measure thought to be associated with reduced efficiency of information transfer. This finding could reflect reduced prefrontal connectivity and result in impairment of executive control [36]. Reduced connectivity has also been shown to distinguish PNES patients from those with epilepsy with a high level of accuracy [37]. Although a study analysing whole-head surface topography of multivariate phase synchronisation in interictal high-density EEG failed to demonstrate any significant differences between 13 patients with PNES and the same number of age- and gender-matched controls, a

significant correlation was found between decreased prefrontal and parietal synchronisation and PNES frequency in the patient group [38].

SUBJECTIVE EXPERIENCES

Even if a seizure has been captured by video-EEG, diagnoses of epilepsy or PNES can never rely on video-EEG data alone. Patients' subjective seizure symptoms give important clues about the nature and aetiology of the seizures. Compared to a relative wealth of publications about visible or measurable PNES manifestations, very little research was carried out on patients' subjective seizure experiences in the 1980s and 1990s. Since then, several studies have demonstrated that ictal impairment of consciousness is less profound in PNES than in epileptic seizures. For instance, patients with PNES were shown to have greater recall of aspects of an ictal examination than those who were tested after a complex partial epileptic seizures [49]. An increased recall of ictal events under hypnosis also proved to be a useful diagnostic indicator of PNES in one small study [50].

It has also become apparent that many patients with PNES experience panic symptoms (at least in some of their seizures) and that it can be difficult to distinguish clearly between some PNES and panic attacks [39, 40]. However, it appears that panic symptoms may be experienced differently during PNES. Goldstein and Mellers (2006), for example, found that patients with PNES reported more somatic symptoms of anxiety during their attacks than patients with epilepsy, although they did not seem to experience subjectively higher levels of anxiety during their seizures. As PNES patients reported more agoraphobic-type avoidance behaviour than those with epilepsy, PNES were interpreted as a dissociative response to anxious arousal, that is, "panic without panic" [41]. Other studies have also demonstrated that PNES are more likely to feel "physical" than "psychological" [42, 43], and qualitative research has demonstrated that patients often find doctors' accounts of PNES as a response to stress or other psychosocial triggers unconvincing, even though many (but by no means all) report past or current stressful events. [44, 45].

Nevertheless, one of the largest studies of subjective PNES experiences demonstrated that a simple score of >4/13 panic symptoms predicted a diagnosis of PNES rather than epilepsy with a sensitivity of 83% and a specificity of 65% [46]. Another study achieved similar levels of differential diagnostic accuracy between epilepsy and PNES (77% of cases correctly classified) with a more detailed questionnaire focusing on a wider range of self-reportable symptoms associated with transient loss of consciousness, although the questionnaire differentiated better between syncope and epilepsy (91%) and between syncope and PNES (94%). In that study, patients' relative endorsement of 74

possible TLOC-associated symptoms contributed to five separate experiential factors focusing on the themes “feeling overpowered “, “sensory experience”, “amnesia”, “mind/body/world disconnection” and “catastrophic experience”. The latter two (ictal dissociation- and anxiety-linked) themes differentiated patients with PNES most clearly from the other two groups and are therefore likely to be most characteristic of the PNES experience (typical questions: “In my attacks I see things which are not really there”; “During my attacks I am frightened I am going to die”) [47]. Another study focusing on the relationship between different types of symptoms in the PNES group included in the comparative research described above found that a greater recall of ictal panic symptoms is associated with more common dissociative experiences [48].

INTERACTIONAL REPRESENTATION

In routine practice, subjective experiences are usually captured by history-taking. Despite the fact that the process of eliciting and interpreting the patient’s history is, arguably, the most important contribution clinicians make to the diagnostic process, it has only become a focus of epileptological research over the last two decades. Importantly, in the process of describing their seizures, patients do not just tell the clinician what they experience in their seizures, they also show *how* they deal with the challenge of having to communicate about their seizure experiences interpersonally. The latter observation may provide clinicians with insights into patients’ preferred coping behaviours more generally [49].

Research initially carried out in Germany but then also in the United Kingdom and elsewhere showed that patients with epilepsy tend to focus on their subjective seizure experiences and expend considerable effort to explain exactly how they feel in their seizures; in contrast, those with PNES preferentially focus on the circumstances in which their seizures occurred or the consequences of their seizures [50-53]. The metaphoric conceptualisations of seizure experiences preferred by patients with epilepsy place the linguistic agency with the seizure, which acts independently and often in a hostile fashion (eg. “the seizure knocked me out”). In contrast, patients with PNES prefer metaphors in which the linguistic agency is with the patient and which depict the seizure as a space or place (eg. “I went into the seizure”) [54]. Narratives of patients with epilepsy typically normalise seizure experiences whereas patients with PNES often catastrophise [55]. Patients with epilepsy are happy to call their main symptom a “seizure” whereas those with PNES often avoid labels and prefer pronouns [56]. These observations concur with other data suggesting that many patients with PNES

have an avoidant coping style [57, 58], and that the attacks themselves are often an anxiety-based phenomenon, albeit not one that is always recognised as such by patients.

AN INTEGRATIVE AETIOLOGICAL MODEL: "STATE OF THE ART" AND FUTURE DIRECTIONS

AN INTEGRATIVE COGNITIVE MODEL OF PNES

At the time that *Seizure* first went into publication, the two predominant models suggested somewhat vaguely that PNES were either a manifestation of dissociation or somatization [1, 59]. We recently reviewed the evidence pertaining to these and other, more recent, models of PNES, encompassing research on life adversity, dissociation, anxiety, suggestibility, attentional dysfunction, family/relationship problems, insecure attachment, defense mechanisms, somatization/conversion, coping, emotion regulation, alexithymia, emotional processing, symptom modelling, learning and expectancy in patients with PNES [5, 58].

Leaving aside questions about the quality of this research, which has numerous limitations [58], it was evident that none of the available models (which interpret PNES variously as the activation of dissociated material, a physical manifestation of emotional distress, hard-wired reflex responses, or learned behaviours [58]), could provide a complete explanation of the semiology and phenomenology of PNES, or account for all of the available research data on the phenomenon. In order to address these limitations, we described an Integrative Cognitive Model (ICM) that brings together existing theories within a single explanatory framework, leading to a number of novel hypotheses [5]. Based on an established theory of "medically unexplained symptoms" (MUS) [60], the ICM suggests that the observable and subjective elements of PNES result from the automatic execution of a learnt mental representation (broadly speaking, "idea") of seizures (the "seizure scaffold"), typically in the context of a high level inhibitory dysfunction resulting from chronic stress, arousal and other factors that compromise high level processing.

Insert figure 1 near here

The seizure scaffold consists of a sequence of perceptions and motor activities initially formed by experiences such as inherent reflexes (eg. freeze, startle), physical symptoms (eg. of pre-syncope /

dissociation / hyperventilation / head injury), but also personal knowledge or modelling. The perceptions may be triggered by sensory inputs but are generated by pre-existing expectations and are at odds with the patients' actual internal or external environment (readers keen to convince themselves how sensory experience can be "trumped" by expectations are advised to look up the rubber hand illusion and the McGurk effect). This sequence of perceptions and actions is relatively stable but not completely fixed. As such, it has much in common with the key constituents of a conditioned reflex.

Like a conditioned reflex, the seizure scaffold can be triggered by a range of internal or external stimuli. This often occurs in response to elevated autonomic arousal, although it can become divorced from abnormal autonomic and emotional activity and may be triggered by thoughts or perceptions which are, objectively, quite neutral. Triggering of the seizure scaffold often disrupts the individual's (full) awareness of distressing material. The seizure scaffold is more likely to be triggered in the presence of dysfunctional inhibition, which could be due to chronic stress but also have "physical" causes such as illness or the effects of medication. The launch of the seizure scaffold is usually experienced as non-volitional although patients may be able to inhibit it by willed action. This is in keeping with the observation that there may be times when patients "wilfully submit" to the dissociation associated with their PNES by a withdrawal of active inhibition subjectively perceived as volitional [61]).

The reflex-like nature of PNES described in this model is consistent with the observation of a limited number of PNES-types and the relatively stable experiential and behavioural semiology of seizures in individual patients. However, the ICM can accommodate the clinical and psychological heterogeneity evident from so many of the studies discussed above, while indicating how factors such as previous traumatic experiences, current life adversity and physical health problems may contribute to PNES. Importantly, however, none of these factors is essential for the development or maintenance of the disorder, even though they may be of central importance in specific cases.

TESTING THE ICM

To date, the vast majority of studies of psychological mechanisms relevant in PNES have used self-report methods, although there are obvious conceptual limitations to using self-report in research

about a process that evidently involves some unconscious elements. Having said that, our understanding of psychological mechanisms underpinning PNES has also been enhanced by experimental approaches, such as those used by Bakvis and colleagues mentioned already. Although relatively small in scale, these studies have provided important corroborating evidence that differences between patients with PNES and healthy controls (or controls with epilepsy) are not limited to the seizure state, and the first objective demonstration of heightened avoidance tendencies and abnormal working memory in patients with PNES [62, 63]. What is more, the heightened arousal, and the experimental cognitive findings likely to be associated with impaired inhibition are in keeping with the ICM.

Several more recent experimental studies have focussed on aspects of emotion processing. In one study, PNES patients reported greater emotional intensity of neutral pictures but less positive emotional behaviour in response to pleasant pictures than a control group without seizures but with similar levels of previous trauma [64]. Another study testing affect perception and theory of mind demonstrated that, compared to healthy controls, patients with PNES were characterised by increased alexithymic traits and, impaired mentalizing skills while basal facial expression recognition were found to be normal [65]. Finally, in an experimental study focussing on attention to emotion, patients with PNES reappraised their cognitions less frequently and showed impairment in their ability to switch attention between emotion and non-emotion face categorisations [66].

There is also some initial experimental evidence demonstrating how PNES may serve a functional purpose. One of the studies of HRV changes during PNES already mentioned above suggested that the preictal rise of sympathetic activation was stopped by the dissociation from the adverse experience causing PNES or associated with having a seizure and replaced by parasympathetic activation in the ictal and postical phase of a PNES [27]. If confirmed in larger studies, this findings would provide strong support for the ICM. Another study compared explicit (self-report) and implicit (reaction-time dependent) psychological measures in patients with PNES or epilepsy and in healthy controls. Only the PNES group showed discrepancies between explicitly reported high anxiety and the implicitly recorded measures. One possible explanation of these findings is that PNES enable patients to dissociate “successfully” from adverse emotions and not to think of themselves as anxious individuals [67].

While it would be premature to draw any firm conclusions from these small experimental studies (or the physiological research mentioned above), the ICM provide a basis for hypothesis-driven research. These small studies demonstrate how we can use experimental methods to further our

understanding of PNES in the future.

Conclusions

Over the last 25 years we have gained a much better understanding of the clinical phenomenology of PNES as well as the physiological and psychological factors characterising and contributing to this disorder. This research has demonstrated that patients do not only have PNES, but also more persistent problems likely to affect their emotional well-being, social functioning and ability to cope with life challenges in between seizures. Although the PNES patient population is aetiologically and experientially heterogeneous it may be possible to define a moderate number of different subtypes and clinical subpopulations characterised by differences in seizure experience and semiology, psychological and psychiatric profile. Physiological and hypothesis-driven experimental studies have begun to make contributions to a better-grounded understanding of the neurobiological foundations to this disorder, although the evidence emerging from studies using relatively novel methods (such as resting state fMRI or quantitative EEG analysis) currently remains inconclusive.

Although the ICM embraces the evidence discussed above better than traditional accounts, it is important to point out that the model is intrinsically a psychological theory. While invoking processes such as threat perception or response inhibition, which are clearly linked to neurobiological mechanisms, it does not map directly onto particular anatomical structures in its current form. Indeed, many of the factors included in the model could involve different centres or networks in the brain. However, the lack of anatomical or mechanistic precision is a strength and not a weakness of the ICM: The representation of PNES as the result of dysfunction of a range of interacting neuronal networks allows the model to account for the numerous interindividual differences described above, as well as for changes in the relative importance of different factors in one particular patient as a PNES disorder turns from an acute to a chronic problem, or as PNES stop in response to therapeutic intervention. What is more, the ICM can help psychotherapists put together individualised formulations of the aetiology of a particular patient's PNES disorder and devise effective treatment strategies targeting specific elements of the model.

Last but not least, the ICM provides a clear basis for future hypothesis-driven phenomenological, psychological and experimental research. If the model is correct, future research will have to combine phenomenological data with methods probing particular PNES mechanisms to account for the heterogeneity of the disorder. Researchers can make the most of the phenomenological variability of PNES by pursuing correlational approaches or by selecting subgroups of patients, but

our understanding of PNES is unlikely to advance much further without a more differentiated approach to disorder. This means that future aetiological research will need to involve larger numbers patients with PNES. The impressive recruitment success of the multicentre CODES study in the United Kingdom (a randomised controlled Cognitive Behaviour Therapy treatment trial to which over 500 patients have been recruited so far [68]) demonstrates that these sort of studies are feasible if researchers collaborate and funders can be persuaded to invest in the improvement of a common, costly and under-researched disorder.

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