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Psychogenic non-epileptic seizures
in children and adolescents:
Part I – Diagnostic formulations

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Abstract
Psychogenic non-epileptic seizures (PNES) are a nonspecific, umbrella category that is used to collect together a range of atypical neurophysiological responses to emotional distress, physiological stressors and danger. Because PNES mimic epileptic seizures, children and adolescents with PNES usually present to neurologists or to epilepsy monitoring units. After a comprehensive neurological evaluation and a diagnosis of PNES, the patient is referred to mental health services for treatment. This study documents the diagnostic formulations – the clinical formulations about the probable neurophysiological mechanisms – that were constructed for 60 consecutive children and adolescents with PNES who were referred to our Mind-Body Rehabilitation Programme for treatment. As a heuristic framework, we used a contemporary reworking of Janet’s dissociation model: PNES occur in the context of a destabilized neural system and reflect a release of prewired motor programmes following a functional failure in cognitive-emotional executive control circuitry. Using this framework, we clustered the 60 patients into six different subgroups: (1) dissociative PNES (23/60; 38%), (2) dissociative PNES triggered by hyperventilation (32/60; 53%), (3) innate defence responses presenting as PNES (6/60; 10%), (4) PNES triggered by vocal cord adduction (1/60; 2%), (5) PNES triggered by activation of the valsalva manoeuvre (1/60; 1.5%) and (6) PNES triggered by reflex activation of the vagus (2/60; 3%). As described in the companion article, these diagnostic formulations were used, in turn, both to inform the explanations of

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PNES that we gave to families and to design clinical interventions for helping the children and adolescents gain control of their PNES.

**Keywords**
Psychogenic non-epileptic seizures, functional neurological symptom disorder, conversion disorder, dissociative convulsions, stress seizures, dissociation

**Introduction**

Psychogenic non-epileptic seizures (PNES) are time-limited disturbances of motor-sensory control accompanied by an alteration in consciousness, but without ictal activity on electroencephalogram (EEG). PNES commonly present with rhythmic tremor or rigor-like movements: violent thrashing; complex movements such as flexion and extension; myoclonic-like movements; episodes of unresponsiveness; episodes of collapse/swooning; non-epileptic auras; and shuddering, staring and tonic posturing (Morgan & Buchhalter, 2015). Because PNES mimic epileptic seizures, children and adolescents with PNES usually present to neurologists or to epilepsy monitoring units; after a comprehensive neurological evaluation and a diagnosis of PNES, the patient is referred to mental health services for ongoing treatment. This study, Part I of a two-part article, presents the diagnostic formulations – the clinical formulations about the probable neurophysiological mechanisms, known or hypothesized – that were constructed for 60 consecutive children and adolescents with PNES who were referred to our Mind-Body Rehabilitation Programme for treatment. In Part II, we use the formulations presented here to frame discussions with patients and families, and to identify what treatments are most likely to help patients diagnosed with particular subtypes of PNES (Kozlowska, Chudleigh, et al., 2017).

More than a century ago, Janet (1889) proposed a dissociation model in which danger, severe stress, illness or fatigue could destabilize the neural system, disrupt the mental synthesis between ideas, acts, and sensory and motor functions, and cause PNES. Despite this early interest in PNES, the technological advances that allow contemporary researchers to study brain function had yet to be developed. Interest in PNES waned; research came to a halt. Notwithstanding the lack of progress in understanding the neurobiological mechanisms underlying PNES, up to a third of all patients presenting to specialist epilepsy centres continued to be diagnosed with PNES (Uldall, Alving, Hansen, Kibaek, & Buchholt, 2006) and to be referred to mental health services for treatment.

When this study was being established, neurologists and psychiatrists hypothesized that PNES involved a heterogeneous range of neurobiological mechanisms that varied from one patient to another (Baslet, 2011; Goldstein & Mellers, 2012). Figuring prominently in this context was Baslet’s ‘Psychogenic Non-epileptic Seizures: A Model of Their Pathogenic Mechanism’, a contemporary reworking of Janet’s dissociation model of PNES (Baslet, 2011). His model provided an overarching framework in conceptualizing our study, talking about PNES with patients and families, and interpreting our findings. Using the language of contemporary neuroscience, Baslet (2011) suggested that PNES reflect a release or activation of prewired motor programmes secondary to a functional failure in ‘cognitive-emotional executive control circuitry’ (p. 9) in the prefrontal cortex (PFC) and that sudden shifts in arousal (both increases and decreases) play a central role in PNES pathophysiology. Under his model, multiple different mechanisms could result in PFC dysfunction and subsequent destabilization of the neural system, with each mechanism representing a different PNES subgroup.
In parallel, scientists and clinicians working in areas nominally unrelated to PNES identified a broad range of animal and human responses to fear, physiological stressors and danger. These responses resembled, in terms of presentation, what our own team was encountering with PNES patients. That is, the responses were ones that could be understood as explaining some of the presentations that we were seeing clinically.

In the remainder of this section, we provide a brief overview of the broad range of brain-body responses to fear, physiological stressors and danger. Following that, we describe how these brain–body responses can be used to understand the clusters of clinical presentations we encountered in our cohort of 60 consecutive child and adolescent patients with PNES.

### Innate defence responses to danger or to memories of danger

The study of innate defence responses began in the 1800s when Darwin used the terms *feigning death* to describe tonic immobility in fireflies, lizards and spiders (C. Darwin, 1839), and *flight* and *utter prostration* to describe the flight and the collapsed immobility responses in humans (C. Darwin, 1872). Subsequent research with animals and humans identified a continuum of defence responses – freezing, flight, fight, tonic immobility, collapsed immobility and quiescent immobility – termed the *defence cascade*. Two of these defence responses – tonic immobility and collapsed immobility – are discussed in the ‘Introduction’ section of this study because of their relevance to children/adolescents presenting with PNES.

Several lines of published research pointed to the clinical relevance of tonic and collapsed immobility in understanding PNES: case reports of soldiers and war veterans who went into states of collapse in response to fear during military action or in response to memories of military action (Kardiner, 1941; Mosso, 1896); reports of rape victims who experience what is referred to as *rape-induced paralysis* (Galliano, Noble, Travis, & Puechl, 1993; Moller, Sondergaard, & Helstrom, 2017); Stefan Bracha’s (2004) work on fainting in response to fear; Bruce Perry’s accounts of long periods of unresponsiveness in maltreated children (Perry & Szalavitz, 2006); and Stephen Porges’ (2011) work on the role of the defensive vagus in shut-down states. Based on the clinical descriptions contained in this literature, we realized that in our tertiary care hospital, some of the children/adolescents that neurologists had referred to us with a diagnosis of PNES were actually experiencing tonic immobility or collapsed immobility in response to some sort of threat.

In our effort to understand the neurobiology of tonic immobility and collapsed immobility, we collaborated with the tenth author (P.C.), a neuroscientist, to develop a neurobiological model of the innate defence responses (Kozlowska, Walker, McLean, & Carrive, 2015). According to that model, innate defence responses are hard-wired, automatically activated motor, autonomic and sensory responses mediated by subcortical neural circuits. Each defence response has a signature neural pattern – a somatomotor component (which involves either activation or loss of tone of skeletal muscle), an autonomic/viscero-motor component (which involves sympathetic, defensive parasympathetic (vagal), or mixed activation of the viscera) and a pain-processing component (opioid system). High states of arousal are necessary for innate defence responses to be activated. Children/adolescents who activate *tonic* immobility will present immobile, with closed eyes or an unfocused gaze, with or without tremors in the extremities, and will be unresponsive to external stimuli, including pain stimuli. Children/adolescents who activate *collapsed* immobility will present with sudden collapse (fainting) that involves a loss of consciousness, a loss of muscle tone and sometimes a loss of continence. Because the neural signatures of tonic and collapsed immobility include activation of the opioid system, some clinicians have utilized naloxone – which blocks opioid receptors – to disrupt the neural pattern and to terminate the tonic/collapsed immobility response (Bruce Perry, personal communication, June 2016).1
Hyperventilation in response to stress or danger

The autonomic system\(^2\) (which mediates changes in arousal) is tightly coupled with the skeletomotor system (which mediates changes in muscle tone and muscle activity, including increased activity of muscles responsible for respiration (Dum, Levinthal, & Strick, 2016). Because of this coupling, when a threat is perceived, increases in arousal are accompanied by increases in respiration: the body prepares itself for action. When ventilation exceeds metabolic demand, hyperventilation (HV) occurs, and in susceptible individuals, HV can change brain neurophysiology in powerful ways.

In our clinical work with children/adolescents with PNES, we had observed that our patients typically presented in a state of high arousal. This clinical observation was confirmed in our research with children/adolescents with functional neurological symptoms, which identified increases in physiological arousal (Kozlowska, Palmer, et al., 2015), increases in cortical arousal (Kozlowska, Melkonian, Spooner, Scher, & Meares, 2017) and a state of motor readiness to emotional signals (Kozlowska, Brown, Palmer, & Williams, 2013). We had also observed that many of our patients with PNES hyperventilated in and around the time of their PNES, and that HV appeared to trigger their PNES. We formally tested this hypothesis in the scientific arm of this study – the PNES Hyperventilation Study (Kozlowska, Rampersad, et al., 2017). We found that nearly half of the children/adolescents with PNES (26 of 60) had difficulty in regulating CO\(_2\) during a HV-challenge, and that over half those with PNES (32 out of 60) appeared to trigger their events with HV.

The PNES Hyperventilation Study indicated that HV was one of the mechanisms by which PFC function could be disrupted – triggering, in turn, PNES. HV can disrupt brain function and trigger PNES through two potential processes (see Kozlowska, Rampersad, et al., 2017 for review). In the first, cortical arousal phase of HV, it causes increased excitability in widely distributed networks and can therefore, via the arousal mechanisms, contribute to the functional failure of executive control circuitry (i.e. loss of horizontal integration of brain function). In the second hypoxic phase of HV, prolonged HV causes cerebral hypoxia due to constriction of cerebral arteries and can contribute to a functional disconnect between the cortex and lower brain structures (i.e. loss of vertical integration in brain function); hypoxia disrupts the signals from the brain stem that ordinarily maintain both consciousness and muscle tone. Whether the two above processes should be conceptualized as an example of dissociation, hypoxia or mixed dissociation-hypoxia process is an open question. What is clear, however, is that in vulnerable individuals, HV appears to disrupt PFC function in significant ways and can result in a release of subcortical motor programmes: PNES (for a clinical example see Chandra et al., 2017).

Non-Hyperventilation-related hypoxia in response to threat

From the established medical literature, we were aware that in addition to HV-induced hypoxia, non-epileptic seizures could occur as a function of hypoxia secondary to disruptions of the breathing cycle or by reflex activations of the defensive vagus (Gastaut, 1974; Stephenson, 1990). Concretely, as part of an atypical response to stress, some individuals will experience hypoxia-induced non-epileptic seizures because they occlude their airway (via vocal cord adduction, holding the breath or the valsalva manoeuvre, all in response to distress) or because activation of the defensive vagus results in decreased blood flow to the brain (via reflex activations of the defensive vagus in response to fear, pain or exposure to blood). We were also aware that this group of non-epileptic seizures involved an unacknowledged conceptual overlap between what neurologists typically conceptualized a ‘physiologic’ non-epileptic seizures (those caused by a known physiological mechanisms)
and ‘psychogenic’ non-epileptic seizures (those caused by distress or underlying psychological conflicts or stressors; Engelsen, Gramstad, Lillevåg, & Karlsen, 2013). That is, the neurophysiological mechanisms that caused hypoxia-induced non-epileptic seizures could also be triggered by distress, fear, panic, sudden fright or pain.

Other dissociative brain processes in the face of threat

Finally, four additional bodies of research contribute to our understanding of other stress-induced, dissociative brain processes at work in patients who present with PNES. This additional research involves (1) methodological advances in analysing EEG and brain-imaging data, specifically in studies with patients with PNES, (2) the emerging literature about changes that occur in the brain as a function of cortical arousal, (3) the literature on dissociation and (4) arousal-related priming, activation, and proliferation of glial cells, which increases the individual’s sensitivity to stress. Taken together, these four bodies of work identify brain processes that are likely to contribute to dissociation – a loss of connectivity between brain areas that typically work together – which cannot be understood or conceptualized by any of the mechanisms described earlier in this section.

Neurophysiological studies with adult patients with PNES have been reviewed exhaustively by Perez and colleagues (Perez et al., 2015; Perez & LaFrance, 2016). In a nutshell, neurophysiological studies suggest that functional failures of executive control circuitry reflect alterations in connectivity in resting-state brain networks involved in the following: emotion regulation and arousal, cognitive control, self-referential processing, and motor planning and coordination. Studies in adults and adolescents show that functional failures also include changes in EEG synchrony, both within cortical brain systems and between cortical and subcortical brain systems (Barzegaran, Carmeli, Rossetti, Frackowiak, & Knyazeva, 2016; Umesh, Tikka, Goyal, Sinha, & Nizamie, 2017).

In parallel, an emerging body of work has examined how changes in cortical arousal facilitate shifts in network organization – to weaken cortical networks and to strengthen subcortical ones – as part of the brain’s response to threat (Arnsten, 2015; de Kloet, Joels, & Holsboer, 2005; Hermans et al., 2011). Exposure to acute, uncontrollable stress causes catecholamine release in the PFC and impairs both PFC function and connectivity within cortical networks (Arnsten, 2015), causing a disruption (dissociation) of horizontal integration of brain function.

Research on dissociation suggests that, on the molecular level, cortical arousal also involves secretion of endogenous opioids, endogenous cannabinoids and other anaesthetic neurochemicals (Lanius, 2014) that can likewise impair function in frontal areas – the cingulate cortex, orbitofrontal cortex and insula cortex, all of which have high levels of opioid receptors (Lanius, 2014). Anaesthetic neurochemicals may also disrupt the vertical integration of brain function – the normal relationship between the cortex and subcortical brain systems – thereby interfering with signals from the brain stem that ordinarily maintain consciousness, and leading to changes in the individual’s level of consciousness (Lanius, 2014).

Finally, recent advances have found that glial cells – the cells that surround neurones and that support and interact with them – are involved in the brain’s response to stress (Ji, Chamesessian, & Zhang, 2016; von Bernhardi, Eugenin-von Bernhardi, Flores, & Eugenin Leon, 2016; Wu, Dissing-Olesen, MacVicar, & Stevens, 2015). In restorative mode, glial cells stabilize and regulate neural networks, suppress inflammation and promote healing. In response to stress, they switch into defensive mode. In defensive mode, they proliferate and secrete pro-inflammatory neurochemicals that excite neurones and that disrupt brain function by interfering with the homeostatic regulation of synapses. In this way, glial cells play a major role in priming the brain’s sensitivity to stress and in stress-related changes in network organization. Glial cells also induce stress-related neuroplastic...
changes that maintain chronic pain (Ji et al., 2016). Similar, stress-induced glial-mediated neuroplastic changes are implicated in patients whose PNES (and other functional neurological symptoms) become chronic.

Taken together, the above bodies of work provide us with a basic understanding of the broad range of dissociative brain processes’ that are triggered in the brain in response to increases in cortical arousal, and that disrupt brain function and connectivity. In daily life, a broad range of stressors – illness, injury, emotional distress secondary to adverse life events, or psychological trauma – can activate cortical arousal mechanisms (catecholamine release, secretion of anaesthetic neurochemicals and network reorganization) and, in susceptible individuals, shift brain organization into a defensive state. In this defensive state, the brain switches from reflective voluntary control of behaviour to reflexive modes of behaviour. Salient emotional signals are prioritized, and motor control is modulated by emotion-processing regions (Arnsten, 2015; Blakemore, Sinanaj, Galli, Aybek, & Vuilleumier, 2016; Hermans et al., 2011). An unwanted by-product of this process may be the emergence of functional neurological motor symptoms, including PNES. Whereas functional motor symptoms, both positive and negative (abnormal gait, functional tremor, functional tics, motor weakness and limb paresis), appear to reflect a relatively stable reorganization of neural networks in response to stress, PNES appear to reflect transient disruptions of neural networks – disruptions that affect the vertical integration of brain function and that cause a disconnect between cortical and subcortical systems (Barzegaran et al., 2016). The result is a temporary ‘glitch’ in top-down executive control over the motor regions in a time-limited release of motor programmes in the basal ganglia, midbrain and brain (PNES).

Aims of the study

As we have seen above, PNES is an umbrella category that incorporates a range of atypical neurophysiological responses to emotional distress, physiological stressors and danger. In the sections below, our goal is to determine the extent to which these mechanisms can be clinically incorporated, on a case-by-case basis, into diagnostic formulations that identify distinct subgroups of patients with PNES. We use the expression diagnostic formulations to refer to working hypotheses that take into account and synthesize all available information about the child/adolescent’s presentation, including information obtained from the child/adolescent, family and neurologist, complemented by the team’s clinical knowledge and its own study of the scientific and clinical literature. The diagnostic formulation provides both a shared understanding of the problem and a roadmap for the journey of treatment (Gordon, Riess, & Waldinger, 2005; Kozlowska, 2013).

Methods

Participants

The study was approved by the Sydney Children’s Hospital Network Ethics Committee. Participants and their legal guardians provided written informed consent in accordance with the Australian National Health and Medical Research Council guidelines.

The participants of the study consisted of 60 consecutive children and adolescents – 42 girls and 18 boys, aged 8–17.67 years (mean = 13.45; standard deviation (SD) = 2.61) – who were referred to Psychological Medicine for treatment of PNES after assessment in the Department of Neurology during a 5-year period (April 2011–March 2016). The time from onset of PNES ranged from 1 day to 48 months (median = 2 months). In 28 cases (47%), the PNES presented alongside other functional neurological symptoms; in 10 cases (17%), the PNES presented alongside a chronic pain presentation; and in 22 cases (36.7%), the PNES were the primary presenting symptom. All families reported antecedent stressors (range = 1–12; mean = 4.63; median = 4; see Table 1). Comorbid symptoms and
diagnoses are documented in Table 1. Other clinical characteristics, intelligence quotient, comorbid neurological conditions and the semiology of PNES are documented in Tables 2 and 3. All children in the study participated in the PNES Hyperventilation Study, which provided neurophysiological data and HV-challenge profiles (Kozlowska, Rampersad, et al., 2017). Eight children/adolescents were excluded from the previous study because of partial pressure of carbon dioxide (PCO2) data were not collected, and four because PCO2 data were inadequate (technical difficulties or child’s lack of cooperation during the HV challenge).

### Procedure

All patients with PNES completed a comprehensive neurology assessment, were diagnosed with PNES and were referred to Psychological Medicine for treatment. The Psychological Medicine assessment involved a comprehensive family assessment (Kozlowska, English, & Savage, 2013). The team
made its diagnostic formulation, based on all available information, at the completion of the family assessment and provided an explanation about the child/adolescent’s PNES – the lay version of the diagnostic formulation – to the child/adolescent and family. Baseline respiratory rates were recorded at the beginning of the child’s individual assessment, which included a determination whether the child/adolescent was capable of using a biofeedback tool called MyCalmBeat. The formulation/explanation was updated if new information came to light during the inpatient treatment admission.

Data analysis

The data analysis was qualitative. The diagnostic formulations – our clinical formulation about the probable neurophysiological mechanisms underlying particular presentations – are clustered below into subgroups of similar patients (PNES subgroups, see Figure 1). Normal reference ranges were used to evaluate elevated baseline respiratory rate and heart rate (Fleming et al., 2011).

To make the qualitative data clinically relevant to mental health clinicians, we provide a clinical vignette for each PNES subgroup. With the consent of the patients and parents, Vignettes 1, 2, 5 and 6 describe individual patients in particular PNES subgroups. Vignettes 3 and 4 are amalgams put together from similar cases.

### Table 2. Comorbid neurological conditions and intelligence quotient.

| Comorbid neurological conditions and intelligence quotient | n   | %   |
|-----------------------------------------------------------|-----|-----|
| **Current comorbid neurological condition**               |     |     |
| Epileptic seizures (one was part of a congenital syndrome, see below) | 7   | 11.67 |
| Congenital condition with neurological manifestations (neurofibromatosis Type 1 with hydrocephalus, epilepsy and ocular gliomas; chromosome deletion 8 with spontaneous intraventricular bleeds, hydrocephalus and ventriculo-peritoneal shunting procedures) | 2   | 3.33 |
| Left cerebral atrophy of unknown cause (unchanging over time) | 1   | 1.67 |
| Cerebral palsy | 1   | 1.67 |
| Hereditary angioedema | 1   | 1.67 |
| Tuberous sclerosis | 1   | 1.67 |
| Cerebellopontine angle cavernoma | 1   | 1.67 |
| Migraine (one child’s migraines were accompanied by hemiplegia) | 2   | 3.33 |
| **Past history of a neurological insult to the central nervous system** |     |     |
| Past history of viral meningitis | 2   | 3.33 |
| Past history of chemotherapy | 1   | 1.67 |
| **Other conditions or vulnerabilities** |     |     |
| Type 1 diabetes | 1   | 1.67 |
| The past history of Bell’s palsy | 1   | 1.67 |
| Hypermobility | 4   | 6.67 |
| Fainting secondary to orthostatic stress (2 girls, 1 boy) | 3   | 5   |
| Postural tachycardia syndrome (POTTS) | 5   | 8.33 |
| **Intelligence quotient estimate (from school reports and school assessments)** |     |     |
| Superior | 7   | 11.7 |
| Average | 43  | 71.7 |
| Borderline | 8   | 13.33 |
| Developmental delay | 2   | 3.33 |
Results: PNES subgroups

PNES subgroup 1: dissociative PNES

Diagnostic formulation. One-third of patients (23/60; 38%) were clustered into subgroup 1: dissociative PNES (see Figure 1). As discussed in the introduction, our diagnostic formulation in this
scenario is that a broad range of stressors have activated cortical arousal mechanisms and have shifted brain organization into a defensive state. An unwanted by-product of this process is the emergence of functional neurological motor symptoms, including PNES.

In this dissociative PNES subgroup \( (n = 23) \), 14 patients had PNES comorbid with other functional neurological symptoms (see Figure 2), 7 had PNES alone and 2 had PNES in the context of a chronic pain presentation. On clinical measures of arousal and motor readiness, 39\% of patients (9/23) had baseline heart rates above the 75th percentile, and 58\% (11/19) had baseline respiratory rates above the 75th percentile. A handful of patients (4/23; 17\%) had skewed HV profiles. On clinical assessment, patients typically reported that their PNES occurred suddenly, without warning. If warning signs were present, they included motor agitation (e.g. jiggling legs), sudden headache and a sense of ‘spacing’ or ‘vagueing’ out. Although we did not observe these patients to hyperventilate before the PNES – or to precipitate their PNES via HV – some patients were sometimes, but not always, observed to hyperventilate during the PNES.

**Vignette 1: dissociative PNES.** Fiona, a 14-year-old girl, experienced a painful, twitching left foot following a tumble turn in a swimming competition, after which she presented to hospital and had a neurological assessment. After 3 weeks, new symptoms emerged. Fiona experienced PNES – tonic- and clonic-like movements lasting up to an hour – followed by an inability to speak or to move her limbs. After each PNES, for periods lasting up to a week, she also did not remember recent events and did not recognize family and friends. In addition to the pain and twitching, she developed pins and needles in her left foot and fluctuating dystonia of the third, fourth and fifth left toes. She experienced intermittent dystonia or twitching of other body parts (head, neck and shoulders).

Fiona and her older brother lived at home with their estranged parents. For many years, Fiona had witnessed high levels of conflict between her brother and her mother, including episodes of physical violence towards her mother. Although Fiona and her father resided in the same house, she had not had a conversation with her father for 6 years.
Fiona and her family did not want to engage with the Psychological Medicine team. They attended the family assessment during Fiona’s second admission to the neurology ward, when Fiona had begun to suffer from PNES and when she could no longer recognize her parents. The family accepted, though somewhat reluctantly, the explanation pertaining to the PNES and functional neurological symptoms. Fiona’s mother and brother became very upset that the stress in the family could have affected Fiona’s body in such a severe way. From that point on, Fiona’s brother ceased his angry outbursts at home.

Treatment in hospital included pharmacotherapy for down-regulating arousal, stabilizing sleep and terminating excessively long PNES (melatonin 6 mg and clonidine 50 mcg at bedtime; fluoxetine 20 mg and olanzapine 5 mg if the PNES lasted more than an hour). It also included individual work with Fiona to help her track body state, to identify warning signs (sudden headache, feeling hot, sweating), and to use progressive muscle relaxation, guided-imagery recordings or slow breathing to avert PNES. As part of a family intervention, the unresolved issues within the family system were discussed explicitly; the family decided that repair of the estrangement between them was not possible. Fiona engaged in 18 months of outpatient treatment, during which she began to explore her anxiety in relation to school work and her home life. Her PNES now occurred very intermittently – once every 3 months – when she was sleep deprived or stressed.

**PNES subgroup 2: dissociative PNES triggered by Hyperventilation**

**Diagnostic formulation.** In total, 32 patients (32/60; 53%) were clustered into PNES subgroup 2 (see figure 1). Clinically, this subgroup was indistinguishable from subgroup 1 except that the children/adolescents’ PNES were typically triggered by HV (Kozlowska, Rampersad, et al., 2017). As discussed in the introduction, our working formulation for this patient cluster was that when these patients became stressed, they activated their respiratory motor system (alongside the autonomic nervous system and cortical arousal systems) and inadvertently hyperventilated, thereby disrupting brain function and triggering PNES.

In this HV-induced subgroup (n = 32), 13 patients had PNES comorbid with other functional neurological symptoms (see Figure 3), 12 had PNES alone and seven had PNES in the context of a chronic pain presentation. In this last group, four also experienced transient functional motor-sensory symptoms. On clinical measures of arousal and motor readiness, 53% of patients (17/32) had baseline heart rates above the 75th percentile; 75% (21/28) had baseline respiratory rates above the 75th percentile; and 72% (23/32) had skewed HV profiles (see black line in Figure 4). On clinical assessment, many patients reported that their PNES were typically preceded by warning signs, including ‘breathing too fast’, ‘heart beating’, sweatingness, nausea, feeling dizzy, blurry vision, visual blackout, sudden headache, tight band around the head, wobbly legs and a feeling of foginess and being unable to think clearly. The visual and cognitive symptoms described by these patients are prototypical symptoms of HV. Paroxysmal increases in ventilation – probable HV – occurred immediately prior to PNES episodes and were observed in all 32 cases during the assessment or treatment admission.

Further sequencing work with these patients and their families suggested that HV events (and subsequent PNES) were triggered by psychological distress in 26 cases, by pain in four cases and by exercise in two cases. The sources of psychological distress were very broad, ranging from anticipatory anxiety about commonplace daily stressors, such as scholastic expectations at school, to adverse life circumstances such as illness worries, family conflict, loss events or bullying, to intrusive memories of the past sexual abuse by a parent or grandparent. For all four patients whose PNES were triggered by pain, the pain occurred in the context of chronic pain conditions. For both patients whose PNES were triggered by exercise, the relevant sports activities took place during a
Figure 4. Hyperventilation profiles in children and adolescents assessed for PNES and in controls in the scientific arm of the current study – the PNES Hyperventilation Study (Kozlowska, Rampersad, et al., 2017).

The shaded blue area depicts the homeostatic range for arterial CO2. The top blue line depicts controls. Controls showed a clear pattern of PCO2 changes during the HV task: a baseline PCO2 within the homeostatic range, a steep drop in PCO2 during HV, and a prompt return to homeostasis during recovery. The middle red line depicts the 60 children and adolescents with PNES who participated in the study (and in the current study). Children and adolescents with PNES showed a downwardly skewed HV-challenge profile suggesting difficulties with PCO2 regulation. The bottom black line depicts the subgroup of 32 children and adolescents whose PNES were typically preceded by – ‘triggered by’ – HV.
period of increased stress at school, with the consequence that the children/adolescents were unable to down-regulate following exercise (resulting in HV and then PNES).

Nine children/adolescents were diagnosed with HV-induced PNES but had HV profiles indistinguishable from controls. This phenomenon brought to our attention that the manner in which a particular patient hyperventilates during the HV-challenge may be different from the manner in which that same patient hyperventilates during real-life scenarios. In this context, a normal – or almost normal – HV-challenge profile did not necessarily exclude the possibility of HV-induced PNES. What characterized these nine patients was the paroxysmal nature of their HV in real-life situations: severe HV occurred in response to specific triggers. Two patients who had been sexually abused by close family members (father and grandfather, respectively) demonstrated extreme HV only when experiencing vivid intrusive memories of the past abuse. The other seven patients hyperventilated intermittently in the context of daily stressors, recent adverse life events or memories of the past bullying. At other times, they did not manifest any symptoms associated with increases in ventilation.

**Vignette 2: HV-triggered PNES.** Danae was a 14-year-old adolescent girl with left cerebral atrophy of unknown origin (unchanging over time) and a history of absence seizures well controlled with medication. She presented with a new type of seizure event – twitching and tonic- and clonic-like movements – for which there was no electrical correlate on video EEG (vEEG). PCO₂ readings during the HV component of the vEEG showed that Danae was hypocapnic (34 mmHg) prior to formal HV, that her PCO₂ level dropped to 20 mmHg with HV, and that it failed to recover (32 mmHg at 15 minutes post-HV). During the family assessment in Psychological Medicine, and as various school stressors were being explored (the key source of distress for Danae), her breathing rate reached 40 per minute (= HV), precipitating what was, for her, a typical PNES. Danae was unable to slow down her breathing (to a normal rate of <20 breaths per minute), and her PNES continued, on and off, over 30 minutes. The explanation to the family included an explanation of HV as the underlying mechanism and a clear expectation that Danae would be able to control her episodes with breath training and treatment of her anxiety. The intervention included breath training using a biofeedback tool (MyCalmBeat), treatment of anxiety with a selective serotonin reuptake inhibitor and quetiapine (37.5 mg at night) and cognitive-behavioural therapy.

Roughly a year later (after being well for some time), at a time that school examinations were overwhelming her with fear and anxiety, Danae re-presented with a different type of PNES – namely, of sudden fainting accompanied by incontinence (of urine; see section of innate defence behaviours below). This presentation was followed by a family intervention that helped Danae’s parents to modify their expectations of academic achievement and to support a choice of career in which Danae could flourish free of PNES.

**PNES subgroup 3: innate defence responses presenting as PNES**

**Diagnostic formulation.** Six patients (6/60; 10%) – four boys and two girls – were clustered into PNES subgroup 3 because we assessed their PNES as reflecting activation of innate defence responses (tonic immobility or collapsed immobility) (see Figure 1). Triggers for the episodes included highly arousing imaged memories or thoughts pertaining to any of the following: sexual abuse by a parent, emotional and physical abuse by a parent, exposure to domestic violence between parents, memories of a deceased father who had suddenly died from cancer, war trauma, and, in a neurologically compromised adolescent girl, extreme fear of school examinations (see end of Vignette 2). Two patients presented with episodes of collapsed immobility alone. Of these, one had baseline heart and respiratory rates above the 75th percentile, and both had normal
HV-challenge profiles. Three patients presented with collapsed immobility episodes and also PNES triggered by HV, and one with collapsed immobility episodes, tonic immobility episodes and PNES triggered by HV. Of these four, three had baseline heart rates above the 75th percentile; four had baseline respiratory rates above the 75th percentile; and four had skewed HV-challenge profiles. These four patients were also included in data reported in subgroup 2 (see Figure 1).

**Vignette 3: innate defence responses presenting as PNES.** Jasmine was an 8-year-old girl who was attending therapy with her adoptive mother for unpredictable shifts in mood and behaviour. Jasmine had been subjected to extreme physical abuse prior to her adoption; for example, once when she was angry, her biological mother had tried to cut off one of Jasmine’s toes. In therapy, when the therapist was discussing examples of what made Jasmine angry or distressed, Jasmine was unable to manage the conversation. At first she seemed not to be hearing the therapist, and she had a blank look on her face. Then she went pale and limp, and was unresponsive to the therapist’s voice and touch. The collapsed state lasted for 40 minutes. Jasmine’s adoptive mother mentioned that this happened often at home. Jasmine was hypersensitive to changes in tone of voice, and if her adoptive mother raised her voice in any way, Jasmine would become nonresponsive, sometimes going pale and limp. Stories about how the animal the opossum responds to threat – by becoming limp and unresponsive – helped reframe Jasmine’s behaviour as reflecting an innate stress response.

**PNES subgroup 4: PNES associated with syncope triggered by vocal cord adduction in the context of distress**

**Diagnostic formulation.** One patient (1/60; 2%) was clustered into PNES subgroup 4 (see Figure 1). The diagnosis of vocal cord adduction was confirmed by the respiratory team’s direct visualization of the vocal cords while the patient was having symptoms that led to a non-epileptic seizure. On clinical measures of arousal and motor readiness, the patient had a baseline heart and respiratory rates >75th percentile. The HV-challenge profile was normal.

Whereas vocal cord adduction in anxious children with chronic asthma – or misdiagnosed as chronic asthma – is documented in the literature (Ibrahim, Gheriani, Almohamed, & Raza, 2007; Silberg, 2001), non-epileptic seizures following vocal cord adduction have not previously been documented. Despite signs of marked respiratory distress, hypoxia (measured by pulse oximetry) during vocal cord adduction is rare (Brugman, Howell, Rosenberg, Blager, & Lack, 1994). By the same token, non-epileptic seizures associated with vocal cord adduction triggered by distress are also rare.

**Vignette 4: vocal cord adduction.** Mika was a 9-year-old child with a history of chronic treatment-resistant asthma and weekly presentations to hospital. He was referred to neurology for vEEG after a seizure-like event. Subsequently, another event was witnessed during lung-function testing. Mika became anxious and began to cough intermittently and to take in huge, noisy gulps of air. Suddenly, the noisy breathing stopped. Mika’s eyes rolled back, and he slumped to the side and was incontinent of urine. A blue tinge around his lips signalled a hypoxic state. Following the event, he did not remember what had happened. Similar events occurred while Mika was still in hospital. Some were followed by tonic- and clonic-like movements. The speech therapy component of the intervention involved Mika being taught to use the sounds *shh, sss* and *fff* to open his vocal cords when he felt tightness in his chest. The psychological intervention addressed anxiety and involved a range of relaxation, visualization, self-talk and vocalization techniques. The *shh, sss* and *fff* sounds were embedded into Mika’s visualization and relaxation exercises.
Subgroup 5: non-epileptic seizures associated with syncope triggered by activation of the valsalva manoeuvre in the context of distress

Diagnostic formulation. One patient (1/60; 2%) was clustered into PNES subgroup 5. Subsequent to presentation, this patient also developed non-epileptic seizures triggered by HV (see Figure 1). On clinical measures of arousal and motor readiness, the patient had baseline heart and respiratory rates >75th percentile and a skewed HV-challenge profile. The valsalva manoeuvre involves forced expiration against a closed airway, either by closing one’s mouth and pinching one’s nose shut, or by exhaling against a closed glottis. The manoeuvre increases intrathoracic pressure, which leads to decreased cardiac output and decreased cerebral circulation even as the available oxygen itself decreases. Because respiration is driven primarily by the level of carbon dioxide, decreasing that level by hyperventilating prior to breath-holding enables individuals to hold their breath for longer periods of time.

A loss of consciousness associated with the valsalva manoeuvre is well documented in adolescents and young men, who use it as a means of group entertainment (Howard, Leathart, Dornhorst, & Sharpey-Schafer, 1951), and in divers, where it is associated with high rates of mortality (Kumar & Ng, 2010). In children, however – and especially in children with developmental delay – the valsalva manoeuvre may be used habitually as a means of eliciting pleasant sensations (Gastaut, Zifkin, & Rufo, 1987; Lai & Ziegler, 1983) or managing feelings of distress. We – the authors of this study – have also seen this presentation in children/adolescents who have been maltreated in infancy. Like all hypoxic events, the loss of consciousness caused by the valsalva manoeuvre can involve hypoxia-related movements that can look like a seizure.

Vignette 5: non-epileptic seizure associated with the valsalva manoeuvre. Lizzy was a 9-year-old girl of average intelligence with a 1-month history of collapse episodes. She had a history of exposure to drugs in utero and of severe neglect and abuse from birth to 4 years of age. Since that time she was looked after by her grandparents, who became her primary attachment figures. Following the death of her grandfather, Lizzy began to experience episodes of collapse. EEG telemetry over a 24-hour period captured a number of events (including one collapse), all of which were associated with EEG slowing and no changes in heart rate. Lizzy would become distressed, take a breath and grimace as she held the breath against a closed mouth. The key treatment intervention was a slow breathing exercise that, with the help of her grandmother, Lizzy implemented when distressed. Individual work with a psychologist helped soften Lizzy’s grief.

Subgroup 6: non-epileptic seizures associated with syncope triggered by reflex activation of the vagus

Diagnostic formulation. Two patients (2/60; 3%) were clustered into PNES subgroup 6 (see Figure 1). On clinical measures of arousal and motor readiness, one patient had a baseline heart rate >75th percentile and both had a baseline respiratory rate >75th percentile. The HV-challenge profile was skewed in one patient and normal in the other. Syncope triggered by reflex activation of the vagus is common across the lifespan and is well described in the literature (Pavri, 2014). The vagus can be activated by pain and other noxious stimuli, the sight of blood, orthostatic stress (and activation of heart mechanoreceptors) or C-fibre mechanoreceptors located in the lungs, oesophagus, bladder and rectum, associated with coughing, swallowing or vomiting, micturition or defaecation, respectively. In all of these scenarios, reflex activation of the defensive vagus leads to bradycardia or asystole, which causes cerebral hypoxia. As in all cases of cerebral hypoxia, hypoxia-induced loss of consciousness can involve hypoxia-related movements that can look like an epileptic seizure.
In one patient, a 16-year-old girl, non-epileptic events appeared to be triggered by acute pain flare-ups (see Vignette 6). In the other patient, a 14-year-old girl with chronic anxiety (and HV) and established orthostatic syncope, the collapse events typically occurred after meals and appeared to reflect an unusual presentation of postprandial syncope.

**Vignette 6: non-epileptic seizures triggered by reflex activation of the vagus.** Siew was a 16-year-old girl with a 6-month history of complex regional pain syndrome following a sprain injury. A more recent injury had aggravated the pain, causing Siew to experience sudden sharp spikes of pain. Siew began to present to accident and emergency weekly with episodes of fainting or of fainting followed by tonic- and clonic-like movements, which looked just like epileptic seizures. During one such event, Siew sustained significant bruising to her head. After multiple neurology reviews and EEG/vEEG studies, all of which were normal, Siew was diagnosed with PNES. Unable to leave home on her own, Siew became increasingly anxious, weak physically and illness focused, and developed a broad range of other nonspecific somatic symptoms (insomnia, nausea, abdominal pain and loss of appetite). Management included an explanation of the probable underlying mechanism – a reflex activation of the vagus by pain. Incremental physical exercise (while Siew wore a protective helmet) enabled Siew to regain her natural level of fitness. Training in mind-body strategies enabled her to better manage her anxiety, work through pain flare-ups and manage her other somatic symptoms. Her chronic pain symptoms also continued to improve.

**Limitations**

The scientific arm of this study – the PNES Hyperventilation Study (Kozlowska, Rampersad, et al., 2017) – included a thorough discussion of the study limitations. An additional limitation in the clinical arm (this study) is that we did not have funding to pursue further ambulant electrocardiography (ECG) and EEG monitoring (to document heart rate changes or hypoxia-associated EEG slowing) in patients clustered into PNES subgroups 3 and 6.

**Conclusion**

In conclusion, PNES is a nonspecific, umbrella category that is used to collect together a range of atypical neurophysiological responses to emotional distress, physiological stressors and danger. Recent advances in neuroscience, neurophysiology and the field of dissociation provide us with a richer framework for thinking about PNES. In this study, we used our review of brain–body responses to fear, physiological stressors and danger as the basis for clustering our child and adolescent patients under distinct diagnostic formulations – clinical formulations about the probable neurophysiological mechanisms – that explained their PNES. In Part II – the companion study – we describe how we used the formulations presented here to frame the explanations that we gave to patients and families, and to inform the treatment interventions (within each subgroup) that we used to help our patients gain control of their PNES (Kozlowska, Chudleigh, et al., 2017). As the knowledge about the neurobiology of PNES expands, and as new diagnostic tools become available, the framework offered in this study will need to be updated, expanded and revised to keep abreast of developments in the field. This clinical study highlights the complex interplay among neural, physiological and emotional phenomena; it challenges dualistic thinking and practice; and it emphasizes an integrated mind-body approach, one that links brain, psyche and soma.
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Notes
1. Dr Bruce Perry, who is known for his work with maltreated children and adolescents, has used naloxone or naltrexone in more than 10 cases of children or adolescents presenting with extended immobility and unresponsiveness assessed to reflect the tonic/collapsed immobility response.
2. Physiologists refer to the autonomic system as the visceromotor system because it provides the motor innervation to the viscera. Using this terminology, they would refer to coupling between the two motor systems: visceromotor and skeletomotor.
3. Porges (2011) has written extensively about the defensive vagus and refers to the defensive vagus as the vegetative vagus, the unmyelinated vagus or the unmyelinated vagal system.

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**Author biographies**

Kasia Kozlowska, a Child and Adolescent Psychiatrist and a Clinician Researcher in the area of functional somatic symptoms, runs a multidisciplinary consultation-liaison team committed to the close integration of research findings and clinical practice. In collaboration with the Physiotherapy Department, Adolescent Medicine Department, and Hospital School, she also directs an inpatient Mind-Body Rehabilitation Programme for children and adolescents with functional somatic symptoms. Because research with these children/adolescents shows activation of the stress system, the multidisciplinary team uses a stress-system model to understand and treat functional somatic symptoms.
Catherine Chudleigh is a Clinical Psychologist and a member of the multidisciplinary team. Alongside other clinicians in the team she has developed a range of child-friendly interventions that help children and adolescents with functional somatic symptoms to become aware of body states and to manage states of high arousal.

Catherine Cruz is a Clinical Nurse Consultant and a member of the multidisciplinary team. She engages in ongoing support and education of nursing staff and new graduates ensuring that nursing staff who work in the Mind-Body Programme are well educated about PNES (and other functional somatic symptoms), that they manage these children/adolescents with calm competence and that they relate to patients and their families with understanding and empathy.

Melissa Lim is a Clinical Psychologist—and a member of the multidisciplinary team—who has particular skills in using mind-body strategies when working with children with non-epileptic seizures and their families. Melissa uses Somatic Experiencing in her work.

Georgia McClure is a Clinical Psychologist—and a member of the multidisciplinary team—whose ideas and buoyant enthusiasm serves to maintain team morale. Georgia uses EMDR in her work.

Blanche Savage is a Clinical Psychologist—and a member of the multidisciplinary team—who grounded steadfastness serves to maintain team stability. Blanche uses hypnosis in her work.

Ubaid Shah is a Paediatric Neurologist. Ubaid’s training included a rotation in Psychological Medicine, where he was involved in the treatment of many children and adolescents with functional neurological symptoms. Ubaid is now disseminating his knowledge and skills about functional neurological symptoms and their treatment at the Lady Cliento Hospital in Queensland, Australia.

Averil Cook is a Clinical Psychologist and a previous member of the multidisciplinary team. Averil has extended the team’s family therapy skills and strengthened the team’s systemic perspective. Averil now runs a community child and adolescent service in which she is helping community mental health clinicians accept children and adolescents with functional somatic symptoms as part of their clinical brief.

Stephen Scher has degrees in philosophy and law, and has an ongoing appointment in psychiatry at Harvard Medical School. He has particular interests in clinical ethics, health policy, and philosophical dimensions of medicine. Stephen has supported the clinician team involved in the current project by helping them articulate objections to traditional, but counterproductive, medical terminology (e.g., the term psychogenic) and to distinctions, such as the mind-body split, that undercut efforts to understand and explain PNES and other functional somatic symptoms. He has also supported the current team in their efforts to develop and maintain an ethical, collaborative stance in working with families, and to disseminate their results through publication.

Pascal Carrive is a Neuroscientist who works with animals in a basic science setting. Pascal has done cutting-edge research on the brain stem systems that are involved in fear responses. He has mentored the clinical team to ensure that their understanding of patient physiological and neuroanatomy is informed by basic science research.

Deepak Gill is a Paediatric Neurologist who runs the epilepsy service at The Children’s Hospital at Westmead, NSW, Australia. Deepak’s training also included a rotation in Psychological Medicine. He has promoted close collaboration between the Neurology and Psychiatry Departments.