Psychogenic nonepileptic seizures in children - Clinical outcomes, dissociative and psychophysiology characteristics

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Dedication

This dissertation manuscript is dedicated foremost to my wife and partner, Tomoko Kusama. Without her ongoing support my doctorate program and completion of this dissertation would not have been possible. Day after day, she cared for me and our two young children while I labored night after night, weekend after weekend on the various courses, assignments, projects, analyses and revisions. Secondly, this manuscript is dedicated to the many patients with whom I have had the privilege of diagnosing and treating over the recent decade. These individuals presented with a strange and perplexing condition which captivated my scientific interest and curiosity unlike any other clinical disorder. These children and young adults have taught me the very nature of human strength, persistence and capacity to adapt in the face of incredible adversity. Finally, this work is dedicated to my physician and nursing colleagues in the Children's Comprehensive Epilepsy Center (CCEC) at Alberta Children's Hospital, who long ago welcomed me into the world of child epileptology and have continued to support my learning in pediatric medicine.

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MAIN ABSTRACT:

Objective: This dissertation begins with an introduction to the problem posed by psychogenic nonepileptic seizures (PNES), followed by a thorough empirical literature review summarizing and critically evaluating the history of PNES, etiology, diagnosis, theoretical models, neurophysiology, psychophysiology and treatment practices. The chapter concludes with a discussion of the potential role for clinical care models to enhance treatment outcomes in pediatric PNES. Two empirical papers are then presented, the first of which sought to prospectively validate a clinical care pathway for PNES at a child epilepsy center. The second paper sought to determine the psychophysiology and dissociation characteristics of children newly referred for PNES while also exploring the relationship between psychophysiology features and PNES severity, including duration of illness and frequency of events at time of diagnosis. **Methods:** Following Health Research Ethics Board approval at University of Nicosia and University of Calgary (data collection site), a retrospective chart review was conducted that included 43 children sequentially referred, assessed and treated for suspected PNES within a specialized neurology clinic psychology service over a 5-year period. These patients were included as participants in the clinical care pathway validation study. A subset of 33 patients also underwent psychophysiology assessment as part of standardized care and were selected for inclusion in the psychophysiology and dissociation study. **Results:** Age ranged from 6 to 18 years of age at time of diagnosis with the majority of patients being female (n=29, 67%) and adolescent (n=31, 72%) with high level of adherence to the care algorithm (n=34, 84%). Standardized care resulted in high rates of full (n=27, 63%) and partial (n=12, 28%) remission, with 2 patients (5%) continuing to experience less than 50% reduction in

PNES events, as self-reported at discharge (2 patients were lost to follow-up). The entire sample reported an average 96% decrease in monthly frequency of PNES events at discharge and a significant reduction in healthcare utilization related to PNES (74% fewer ambulance calls and 85% fewer emergency department visits). Post hoc analyses demonstrated that duration of PNES illness longer than 12 months (at diagnosis) increased odds of not achieving full remission by discharge (OR=5.94, p=0.019). Among patients included in the psychophysiology and dissociation subset, the majority were found to have autonomic decompensation at baseline (82%), lack of autonomic recovery from a cognitive stressor (58%) and diagnosis of behavioral hypocapnia (85%). Inhibition of normal skin conductance response to laboratory stressor was also associated with longer duration of PNES illness ($\chi 2$=4.47, p=0.035) and elevated heart rate (>90%) at baseline was associated with higher frequency of PNES events in the month preceding diagnosis ($\chi 2$=4.24, p=0.039). Overall high levels of dissociation and hyperventilation symptoms were self-reported by adolescent patients (n=19) and were positively correlated (Kendall's tau=0.35, p=0.04). **Conclusions:** The dissertation findings demonstrate that childhood PNES is characterized by psychophysiology features including baseline autonomic decompensation, increased respiratory CO_2 sensitivity, poor autonomic recovery from stressors and substantial co-morbidity with suppression of the normal stress response. The above studies also demonstrate that standardized care for PNES leads to improved clinical outcomes and reduced healthcare utilization, and that delayed diagnosis and treatment of PNES longer than 12 months is associated with less favorable outcomes in children.

Table of Acronyms:

ACC	Anterior cingulate cortex
ACH	Alberta Children's Hospital
A-DES	Adolescent dissociative experiences scale
AED	Anti-epileptic medication
ANS	Autonomic nervous system
BPD	Borderline personality disorder
CBT	Cognitive behavioral therapy
CCEC	Comprehensive Children's Epilepsy Center
CO_2	Carbon dioxide
DES	Dissociative experiences scale
DLPAG	Dorsolateral periaqueductal grey
DMN	Dorsal motor nucleus
DSM-5	Diagnostic & statistical manual 5th edition
DTI	Diffusion tensor imaging
ED	Emergency department
EEG	Electroencephalogram
EMS	Emergency medical services
EMU	Epilepsy monitoring unit
$ETCO_2$	End tidal carbon dioxide
fMRI	Functional magnetic resonance imaging
FND	Functional neurological disorder
GAF	Global assessment functioning
HPA	Hypothalamus-pituitary-axis
HR	Heart rate
HRV	Heart rate variability
HV	Hyperventilation
ICD-11	International Classification of Disorders (Version 11)
ICM	Integrated Cognitive Model
ILAE	International League Against Epilepsy
LPAG	Lateral periaqueductal grey
MACI	Millon Adolescent Clinical Inventory
mmHg	Millimetres of mercury
MMPI	Minnesota Multiphasic Personality Inventory
MRI	Magnetic resonance imaging
NEAD	Non-epileptic attack disorder
PAG	Periaqueductal grey
PCC	Posterior cingulate cortex
PCO_2	Percutaneous carbon dioxide
PET	Positron emission tomography
PFC	Pre-frontal cortex
PNES	Psychogenic non-epileptic seizures
PTSD	Post-traumatic stress disorder

RCT	Randomized control trial
RPM	Raven's Progressive Matrices
RR	Interval between heart beats
RSA	Respiratory sinus arrhythmia
SCL	Skin conductance level
SMA	Supplementary motor area
TBI	Traumatic brain injury
TMS	Transcranial magnetic stimulation
TPJ	Temporal-parietal junction
VLPAG	Ventrolateral periaqueductal grey
vmPFC	Ventromedial prefrontal cortex

CHAPTER 1: Introduction

Psychogenic non - epileptic seizures (PNES) are observable, abrupt changes in consciousness or behavior that present similar to seizures but are not accompanied by electrophysiological changes. These arise from a psychological etiology (historically categorized under Conversion Disorders) and comprise up to one quarter of referrals to pediatric epilepsy centers. Unfortunately, misdiagnosis is common (up to 7 year delay in adults), results in iatrogenic harm to children by way of antiepileptic drug administration (which does not stop the seizures) and generally the episodes will persist, unless appropriately treated with psychological interventions.

Despite being a very common problem for epilepsy centers worldwide, very little is known about how best to manage PNES in children and youth. While cognitive behavioural therapy (CBT) protocols and administration of selective serotonin reuptake inhibitors (SSRIs) have shown promise in adult studies, there are few that have examined or compared approaches in children. To further add to patient (and healthcare provider) frustration, there is a lack of practical information on how to best initiate and co-ordinate care, once accurate diagnosis has been achieved. Facing a perplexing and often poorly understood diagnosis, patients and their care providers are faced with difficult decisions: 1) How to initiate treatment, where and by whom? 2) What, specifically, are the treatment goals? 3) When PNES events do not abate, at which point should new interventions be considered and at what intensity and cost to the healthcare system? Without a clear ‘roadmap’ to care, patients and their providers may find themselves at a loss to answer the above questions, further reducing patient acceptance and participation in the very treatments most likely to succeed.

1.1 Rationale for the Current Studies

Review of the literature reveals that our understanding of PNES etiology and treatment is still in its infancy, especially as it pertains to children with the disorder. Almost all studies to date have been adult in nature. Another significant limitation of outcome studies is the lack of prospective study designs. While these number only a handful in the adult literature, there are none addressing PNES in children. Prospectively designed studies in child PNES will help to establish causality of interventions that are found to be effective in reducing the frequency of events. Also, the role of psychophysiology abnormalities have been implicated in the etiology of PNES and dissociation (van der Kruijs, Bodde, & Aldenkamp, 2011). Accordingly, many authors have pointed out the need for subjective and objective measures in PNES studies, including psychophysiological measures (Brown et al., 2016). Also, while psychophysiology characteristics have been studied in adult PNES, these have until recently been ignored in children. The role of dissociation has also not been reliably measured in children with PNES, despite an established body of literature suggesting dissociation presents differently across the lifespan (Wherry, Neil, & Taylor, 2009).

The first published clinical care pathway for PNES was developed and implemented at Alberta Children's Hospital (ACH) in 2015. The author and main dissertation supervisor developed the pathway based on results of a retrospective study that sought to characterize pediatric PNES patients and the care they received, with resulting clinical outcomes. This investigation demonstrated positive outcomes at ACH, superior to that of adults (80%, compared with approximately 55% in adult studies), while establishing feasibility of a stepped - care model for PNES in children and youth.

Based on those results, an algorithm for care was developed to serve as a pragmatic guideline for achieving positive outcomes in an existing healthcare setting (Sawchuk & Buchhalter, 2015).

An urgent need for development of PNES care pathways has been identified internationally within the Epilepsy community (Sawchuk, Austin, & Terry, 2017). Highly desirable treatment outcomes of 80% remission were achieved in our original study. Accordingly, our epilepsy center standardized the care pathway for PNES in 2015 to ensure quality of care. Updated to reflect new knowledge and empirical evidence, the current care pathway was instituted to address patient needs within an existing and feasible healthcare framework, while also striving to replicate and improve upon remission rates achieved in our original study. The progression of care approaches in the updated pathway reflect both the author's clinical experience in working with functional neurological disorders as well as recent advancements in the scientific literature regarding PNES etiology, pathophysiology and treatment approaches. New studies describing autonomic nervous system (ANS) features of PNES have opened the way for development of potential diagnostic biomarkers and new treatment targets in children and youth with PNES. The presence of psychological dissociation in PNES populations is also long established in adults but has not been well characterized in pediatric populations. Accordingly, primary changes to the pathway include the following: 1) addition of dissociation measures to battery of psychological tests performed at intake assessment, 2) standardized psychophysiology lab assessment, 3) identification and behavioral correction of hyperventilation employing biofeedback, and 4) specialized CBT

protocol of 6 - 10 sessions (expanded from previous pathway involving unspecified CBT methods and protocols).

1.2 The Research Problem

The studies undertaken during completion of this dissertation project expand on the above line of scientific inquiry. A period of almost three years had elapsed since the care pathway was implemented at ACH. The next logical phase of inquiry into pediatric PNES was to evaluate the clinical outcome of treating patients prospectively using the care pathway, while also continuing to characterize the population based on newly available psychophysiology and dissociation data.

CHAPTER 2: Literature Review

2.1 Introduction

This literature review begins with a comprehensive description of psychogenic non-epileptic seizures (PNES) followed by a review of associated characteristics, neurobiology and etiological theories in children and youth. Contemporary scientific theories will be discussed, followed by identification of dissociation and autonomic nervous system (ANS) arousal correlates in PNES etiology with a focus on potential mechanisms and treatment targets. This is followed by a review of current treatments and known outcomes among children. Finally, clinical care pathways are introduced ending with a review of the Alberta Children's Hospital (ACH) care model for pediatric PNES. The literature review spans early 1900s up until June of 2018 and was conducted utilizing Pubmed and PsychInfo online searches for the following English language search terms

(alone and in combination): psychogenic, nonepileptic seizures, PNES, NES, nonepileptic attack disorder, NEAD, dissociative seizures, dissociation, functional neurological disorder, FND, conversion disorder, psychophysiology and care pathway.

2.2 Defining PNES

PNESs are observable, abrupt changes in consciousness and behavior related to psychological causes that resemble epileptic seizures but are not associated with epileptiform discharges in the brain. Relatively unknown in the public mainstream, PNES is one of the oldest documented medical conditions in man, with descriptions appearing as far back as the Hippocratic works of 1900 B.C. (Micale, 1989). It often presents as subtle motor behavior in younger children while gross motor movements; staring and/or sudden falls characterize phenotypes in adolescents and adults. PNES is among the top three causes of transient loss of consciousness reported at urgent medical centers (Angus-Leppan, 2008). The cause of PNES is not well understood, but events are thought to be caused by emotional processing and autonomic arousal abnormalities (Kozlowska, Chudleigh, et al., 2017; Pick, Goldstein, Perez, & Nicholson, 2019; Reuber & Brown, 2017). These in turn, are thought to trigger transient neurological states during which normal brain functions are altered (Brown & Reuber, 2016; Roberts & Reuber, 2014). PNES has been recognized for several decades in the Diagnostic and Statistical Manual, most recently described as “functional attacks or seizures” (American Psychiatric Association, 2013), a sub-grouping included under the renamed conversion disorder category “functional neurological symptom disorders” (FNDs). PNES has been recognized as well in the International Classification of Disorders (ICD-11) under the term “dissociative seizures”. These differences in terminology reflect somewhat different

views of PNES, with the role of dissociation being emphasized in the ICD-11 while the DSM-5 categorizes PNES under somatization, along with somatic symptom and factitious disorders. Proponents for the latter categorization draw attention to the fact many psychological characteristics and neurophysiological similarities appear to exist between PNES and other somatoform disorders, while detractors point out PNES sufferers appear to have normal physical and neurological functions in between transient states of altered consciousness (Kanaan, Duncan, Goldstein, Jankovic, & Cavanna, 2017).

Although the term "PNES" remains the standardized nomenclature in North America, various other terms continue to be used in the literature, including "pseudoseizures" and "hysterical seizures". Meanwhile, the term "non-epileptic attack disorder (NEAD)" remains the preferred term for PNES in the United Kingdom. Use of terminology in referring to PNES events is not without controversy, as many patients and clinicians find the various terminology confusing or even offensive. Morgan et al. (2015) for example, surveyed 146 caregivers of children being seen in a pediatric clinic, about which terms referring to nonepileptic events were most/least offensive. Their study demonstrated that terms including the words "hysterical" or "psychogenic" were the most offensive to parents or guardians, while the term "nonepileptic events" was perceived as least offensive (Morgan, Dvorchik, Williams, Jarrar, & Buchhalter, 2013).

The prevalence of PNES has been estimated at 2-33 cases per 100,000 (Benbadis & Allen Hauser, 2000) making it nearly as prevalent as worldwide rates of multiple sclerosis and Parkinson's disease (Hirtz et al., 2007). PNES presents frequently to child and adult epilepsy centers alike, where they are seen in up to 50% of adult referrals (Howell, Owen, & Chadwick, 1989) and 20-30% of pediatric referrals for refractory

seizures (Doss & Plioplys, 2018). Onset of PNES appears to be less common in young children and older adults, with 70% of cases occurring in the 2nd to 4th decades of life (Lempert & Schmidt, 1990). PNES has been identified across diverse ethnic groups (An, Wu, Yan, Mu, & Zhou, 2010; Pehlivanturk & Unal, 2002; Sigurdardottir & Olafsson, 1998) with relative consistency in appearance across cultures (A. A. Asadi-Pooya, Valente, Alessi, & Tinker, 2017), suggesting it exists as a universal phenotype.

Scientific interest in PNES has waxed and waned over the last century, receiving significant attention in the late 19th century during the discovery of "hysteria", which all but ceased by the early 20th century at a time when neurologists began focusing more on conditions with demonstrable organic causes. This began to change in the 1970's with development of more reliable electroencephalogram (EEG) technologies, which for the first time provided neurologists a tool to distinguish among epileptic seizures and those not caused by epileptiform activity (Reuber & Brown, 2017). Scientific study of PNES has since proliferated, as demonstrated by a recent PubMed search of "PNES" (Completed May 7, 2018) yielding 320 published articles in the last 5 years, compared with only 180 in the preceding 5-year period.

2.3 Diagnosis

PNES is typically diagnosed based on a sequential activation of healthcare resources following the initiating paroxysmal event. This process usually involves evaluation for epileptic seizures or other neurological disease. The current diagnostic 'gold standard' for PNES is capture of events during simultaneous EEG recording and observation by a trained clinician (LaFrance, Baker, Duncan, Goldstein, & Reuber, 2013). Unfortunately, it can be difficult to capture events in this manner or even

impossible outside epilepsy centers where video EEG monitoring facilities are unavailable. To the trained observer, several diagnostic signs raise the likelihood of PNES, including variable progression of ictal movements, closed eyes and asynchronous limb movements, all of which have high positive predictive values (86-96%) for PNES but not epilepsy. Side-to side head movements, back arching/hip thrusting and full body rotations also increase the likelihood of PNES, with positive predictive values ranging between 47-76% (Goldstein & Mellers, 2012). Diagnosis based on observation alone, however can be precarious, as demonstrated by a recent study showing emergency room physicians were only 44% accurate in diagnosing PNES without event capture on EEG (Wasserman & Herskovitz, 2017).

Once epilepsy is ruled out, differential diagnosis proceeds to considering other potential neurological (e.g. transient ischemia, movement disorder, migraine phenomena) or physiological (e.g. syncope, sleep phenomena, toxicity) causes of sudden impaired movement/awareness. Once medical causes have been confidently ruled out, differential diagnosis can proceed to determining possible psychological or behavioral triggers. These may include evaluation for anxiety-related phenomena (e.g. panic attacks involving impaired awareness), psychotic symptoms (e.g. involving detachment from reality), behavioral factors (e.g. self-stimulation, secondary gain) and even malingering or volitional behaviors.

While a psychological stressor or trigger can sometimes be identified preceding onset of PNES, this is not always the case. Although psychiatric co-morbidities often accompany a diagnosis of PNES, this does little to help in differentiating patients with

epilepsy from PNES (Tellez-Zenteno, Patten, Jette, Williams, & Wiebe, 2007). Further confusing the diagnosis is a relatively high co-occurrence of epilepsy and PNES together, estimated to occur in up to 60% of PNES samples (Sigurdardottir & Olafsson, 1998). A recent study demonstrated only half of such dually-diagnosed patients (and their caregivers) were able to correctly distinguish among their own event types (Gordon et al., 2014). As a result, diagnostic delays of up to 6 years in adults and 3.5 years in North American children have been reported (Patel, Scott, Dunn, & Garg, 2007). The presence of both conditions together can confound or delay diagnosis and treatment significantly, as each disorder requires entirely different management strategies. It is also likely that a large number of patients will remain incorrectly diagnosed with epilepsy over several years or even a lifetime, as suggested by one previous estimate that 10-20% of Americans diagnosed with epilepsy may actually have PNES (Gates, Luciano, & Devinsky, 1991).

2.4 Costs of Misdiagnosis

Failure to make correct diagnosis delays the appropriate treatments being implemented, leading to further progressive physical disability and mental health co-morbidity in child and adult PNES alike. As a result of misdiagnosis, many patients will be inappropriately prescribed anti-epileptic drugs (AEDs), resulting in iatrogenic harm including unwanted side effects, secondary impairments or even death as a result of escalating medication doses being given in response to prolonged events (Reuber, Baker, Gill, Smith, & Chadwick, 2004). In pediatric populations, unnecessary AED usage has ranged from 17% up to 75% of cases (Kotagal, Costa, Wyllie, & Wolgamuth, 2002; Leis, Ross, & Summers, 1992; Sawchuk & Buchhalter, 2015). A second hurdle facing PNES

sufferers is that treatments are often delayed even after receiving an accurate diagnosis (Wyllie et al., 1990). This delay can be up to 5 years in children, further worsening prognosis the longer it goes untreated (Wyllie, Glazer, Benbadis, Kotagal, & Wolgamuth, 1999). Poor outcomes not only affect the child, but also impact family members and parents, who have been shown to experience significant absenteeism from employment (Doss & Plioplys, 2018). All of the above imposes a heavy and potentially avoidable financial burden on healthcare systems across the world, which in the United States alone has been estimated to cost up to US $900 million dollars annually (LaFrance & Benbadis, 2006).

2.5 PNES Characteristics

PNES is associated with a number of clinical and psychological characteristics in children and adults. Demographically, there is a predominance of females after puberty (Chinta, Malhi, Singhi, & Prabhakar, 2008; Irwin, Edwards, & Robinson, 2000; Wyllie et al., 1999) with male predominance before the age of 12 (Kotagal et al., 2002; Sawchuk & Buchhalter, 2015). As a population, adult PNES patients appear to be much younger than those with other FNDs and are also more likely to have suffered traumatic experiences or stressful life events preceding symptom onset (Brown et al., 2016). A recent study at our epilepsy center replicated previous studies demonstrating a significant life stressor precedes PNES diagnosis in the majority (93%) of children and youth with PNES (Sawchuk & Buchhalter, 2015), which is much higher than that reported generally among children from developed countries (Ani, Reading, Lynn, Forlee, & Garralda, 2013; Kozlowska et al., 2007).

A recent study of risk factors for child PNES (Plioplys et al., 2014) reported much higher rates of medical, neurological and psychiatric diagnoses in PNES patients compared with their own siblings. Medication use, increased anxiety sensitivity and solitary emotional expression as a coping mechanism were also much more present in the PNES patients than their siblings. Additional risk factors included increased fearful responding to neutral physical sensations, history of bullying and learning disorders. Although family stress levels were perceived similarly among children with PNES and their siblings, the former were rated by their parents to have higher somatization and somatic complaints (Salpekar et al., 2009). Although sexual abuse was once thought to be a common precursor to development of PNES, this risk factor is not supported empirically. Recent pediatric studies have suggested actual rates of reported abuse range between 15% and 34%, similar to those reported in other mental health disorders such as depression (Doss and Plioplys, 2018; Sawchuk & Buchhalter, 2015; Wyllie et al., 1999).

A diagnosis of PNES is associated with prominent levels of psychiatric co-morbidity in adults, the most commonly reported being dissociative (up to 91%) and somatoform disorders (up to 84%) followed by posttraumatic, depressive and anxiety disorders (up to 50%). The severity of comorbid disorders also appears to correlate with the severity and frequency of PNES events (Reuber et al, 2008). Similarly in children, a previous investigation by the author found elevated anxiety (21%), depression (55%) and learning disorders (26%) among a group of youth with PNES (Sawchuk & Buchhalter, 2015). PNES also appears to be associated with maladaptive personality traits. In psychological theory, the construct of personality is said to refer to the “container” giving shape to our thoughts, behaviors and actions in response to the environment, including

psychic distress. Among adults, personality scores on the Minnesota Multiphasic Personality Inventory (MMPI) have been shown to accurately differentiate epilepsy and PNES cases by way of elevated hypochondriasis and hysteria scales (Cuthill & Espie, 2005; Schramke, Valeri, Valeriano, & Kelly, 2007). Similarly, classification using the Personality Assessment Inventory (Morey, 1991) in adults was shown to correctly classify PNES diagnosis with 84% sensitivity and 73% specificity, employing a combination of two scales (conversion and health concerns) (Wagner, Wymer, Topping, & Pritchard, 2005). In their summary of the literature on personality traits in PNES, Brown and Reuber (2016) identified what appear to be two reliable and distinct personality categories which they labeled "emotionally dysregulated" (forceful or dramatic patterns) and "emotional over-control" (inhibited, conforming patterns).

Very few studies have examined personality patterns among youth with PNES. Plioplys et al. (2014) compared pediatric patients diagnosed with PNES to their siblings on a variety of measured traits. This study demonstrated increased anxiety, sensitivity, somatization and use of passive coping behaviors (yelling, hitting, crying while alone) in PNES patients compared with their matched siblings. The authors interpreted their results as evidence of increased use of passive/avoidant coping strategies in child PNES (Plioplys et al., 2014). A previous study at our center identified 20 PNES youth having completed personality testing. This sample demonstrated clinically significant, maladaptive personality patterns on the Millon Adolescent Clinical Inventory (MACI) among 85% of the group. The most common of these were inhibited (40%), submissive (40%) and introversive (30%) personality patterns, which co-occurred in 60% of adolescents (Sawchuk & Buchhalter, 2015). Additionally a second, smaller group

comprising 35% of the sample was identified as having significant dramatizing personality patterns in the absence of inhibited, submissive or introversive traits, similar to that proposed by Brown and Reuber (2016). Although the small sample size of this study limited generalizability to other youth with PNES, comparisons with adult studies suggests convergence on two possible PNES subtypes: 1) overly-conforming thoughts/behaviors in individuals who are emotionally over-controlled and, 2) openly non-conforming thoughts/behaviors in those who are emotionally dysregulated. Establishing validity and generalizability of the above findings through larger sample sizes of youth with PNES may have the potential to improve treatment strategies tailored to individual personality phenotypes.

2.6 Neurophysiology Correlates of PNES

Magnetic resonance imaging (MRI) allows for measurement of brain structures including volume of tissue and how different regions are connected. Functional MRI (fMRI) additionally allows for the measurement of brain activity during external stimulation, helping shed light on activation patterns associated with specific stimulus responses. Early investigations of brain imaging in PNES began only at the start of the century, initially with Reuber et al. (2002) who analyzed brain MRI, EEG and neuropsychological testing results among the medical records of 18 PNES patients. These records were compared with that of 60 dually diagnosed (PNES + Epilepsy) cases. Not surprisingly, at least one brain abnormality was identified in 92% of the dually diagnosed sample. By comparison however, 22% of the PNES only sample also had one or more

brain abnormalities, suggesting that structural brain dysfunction may associate with production of PNES events (Reuber, Fernandez, Helmstaedter, Qurishi, & Elger, 2002).

Since the original Reuber et al. (2002) study, the development of diagnostic imaging technologies has increased our ability to study and test hypotheses regarding brain substrates in PNES. Several studies have demonstrated evidence of abnormal neurological structure and function in the adult brains of PNES sufferers, lending considerable support to the theory that PNES episodes are facilitated by an unstable cognitive-emotional-attention system. Multiple studies utilizing matched controls have converged on a number of areas in the brain implicated in PNES etiology. These include the anterior cingulate cortex (ACC) which is involved in mental representation and autonomic arousal, insula (involved in emotion processing, interoception), inferior frontal gyrus (executive control) and precentral sulcus (involved in motor movements). Changes in EEG synchrony have been reported within these cortical brain systems including their interaction with sub-cortical brain structures (Barzegaran, Carmeli, Rossetti, Frackowiak, & Knyazeva, 2016), while other studies have identified reduction or instability in prefrontal EEG synchronization (Barzegaran et al., 2012; Knyazeva, Jalili, Frackowiak, & Rossetti, 2011). Researchers in the above studies have hypothesized the change in communication among cortical and sub-cortical structures may lead to the subjective and observable experience of "losing consciousness" in PNES, as functional disconnection among frontal regions (responsible for volition and awareness) and parietal regions (involved in motor control) has been reliably demonstrated. The above findings have lead authors of those studies to suggest desynchronization may serve as a potential biomarker for PNES in 'at risk' groups while others have suggested behavioral or pharmacological

interventions targeting modulation or prevention of desynchrony, may actually help reduce PNES events (Barzegaran et al., 2016).

2.6.1 Key Substrates

Although a complete neurophysiological model is lacking, imaging studies to date converge on several key substrates that appear to be involved in the production of PNES episodes. These involve brain regions implicated in the modulation of autonomic arousal and internal feedback signals influencing awareness and subjective states. The insula has been implicated in the integration of subjective body and sensory states involving human emotions. Extending 50-60mm in length, neurons located in the insula have a posterior to anterior processing gradient. Ascending sensory pathways, such as cooling sensations or toothaches terminate in the posterior insula, where this information is then re-represented and integrated with other incoming information in the mid then anterior insula, which is believed to play a significant role in human awareness and subjectivity (Craig, 2011). Damage to the insula appears to cause autonomic dysfunction, impaired gustatory, olfactory, auditory and somatosensory perception. Lesions here have also been demonstrated to cause impairment in body awareness, mood, willful action and the ability to experience certain emotions (e.g. disgust). In their review of lesion studies involving the insula, Ibanez et al. (2010) hypothesized it as a multimodal structure serving as a convergence zone involved in coordinating internal and external sensory information while contributing to subjective emotional awareness (Ibanez, Gleichgerrcht, & Manes, 2010).

The anterior insula connects directly to the anterior cingulate cortex (ACC), another key substrate implicated in PNES etiology. Impaired function in the ACC has been associated with altered self-awareness following traumatic brain injuries (TBI). Ham et al. (2014), for example, measured how TBI patients respond to errors during performance and monitor success during tasks. The study utilized fMRI to measure evoked potentials, recorded during standardized protocols in 63 participants with history of TBI. Participants were divided into two groups based on ability to recognize and correct their own errors. The dorsal ACC demonstrated reduced connectivity with the frontal-parietal network during resting state (no task), while the anterior insula demonstrated increased activity following errors in the impaired group (Ham et al., 2014). This study suggests impairments to self-awareness following TBI result from functional breakdown of interactions among the ACC, insula and other regions within the fronto-parietal control network, similar to what has been described in neurophysiological models of PNES episodes (Baslet, 2011). Interestingly, smaller dorsal ACC volumes have also been demonstrated in traumatized adults and children, suggesting ACC involvement in abnormal processing of emotion following traumatic events (Rinne-Albers et al., 2017).

Another key substrate in production of PNES symptoms appears to be the ventromedial prefrontal cortex (vmPFC). This area is involved in internal self-reference processes known to occur during experimental states of rest and disengagement, suggesting involvement in awareness during dynamic interactions with the outer world. The vmPFC is one of many areas that integrate with the ACC and insula to provide autonomic and motivational control, while also enabling complex prediction of others'

behavior in decision-making related to initiation of reciprocal behavior. While the ACC is believed to generate autonomic changes, the insula appears to be involved in mapping visceral responses. Bringing these processes together, it has been hypothesized that interactions between the vmPFC, ACC, insula, and orbitofrontal cortices provide the neural substrate for generation of motivational and affective states central to production of PNES symptoms (Sundararajan, Tesar, & Jimenez, 2016).

2.6.2 Recent Imaging Studies

Newer PNES studies employing fMRI have demonstrated cortical thinning and loss of grey matter volume in a number of cortical areas including the bilateral cerebellum, right precentral and middle frontal gyri, ACC and supplementary motor area (SMA), in comparison with normal controls (Labate et al., 2012). By contrast, cortical increases/thickening have been demonstrated in the left insula, right cingulate cortex and bilaterally in the medial orbitofrontal cortex, compared to a healthy control group (Ristic et al., 2015). Use of another imaging technology, diffusion tensor imaging (DTI), has shed light on neural pathways which are altered in adult PNES, including increased activity in the right-sided uncinate fasciculus (involved in emotion processing). Several studies have demonstrated reduced structural connectivity among frontal and motor/sensory regions, as well as increased abnormal connectivity among regions involved in motor function, emotion regulation and cognitive processes. Lee et al. (2015) for example, demonstrated increased white matter connectivity in PNES patients among several structures including the internal/external capsules, temporal gyrus, uncinated fasciculus and left corona radiata, compared with controls. Brain metabolism also appears to be altered in PNES patients, as demonstrated by positron emission tomography (PET)

studies revealing global decreases in brain activity during acute stress responses. PET studies have also demonstrated reductions in areas involving emotion regulation, awareness of self and environment, implicating reduced metabolism in impaired consciousness among individuals with PNES (McSweeney, Reuber, & Levita, 2017).

2.6.3 Child Imaging Studies in PNES

Almost all PNES imaging studies to date have focused on adults. Accordingly, it has been argued that the neurophysiology findings described above may, in fact reflect long term adaptation to having the condition rather than preceding symptom onset. In order to test this assumption, Kozlowska and colleagues (2017) acquired high-resolution, three-dimensional T1-weighted fMRI images in 25 FND patients ages 10-18 years of age, half of whom had been diagnosed with PNES (n=12). Brain grey matter was quantified in the FND patients using a method called voxel-based morphometry; and compared to 24 healthy age matched controls. Consistent with adult FND studies, the child FND group demonstrated increased grey matter volumes in the left SMA and right superior temporal gyrus, as well as in the right dmPFC. Interestingly, the SMA volumes correlated positively with speed of reaction time to a paradigm involving identification of human emotions. The procedure for the paradigm involved computerized touch screen responses to pictures of human faces expressing one of six different emotions (happy, mad, sadness, fear, disgust & neutral). The authors interpreted their results as evidence that increased vigilance to others' emotional states and enhanced motor readiness to respond reflect reorganization of the brain which may be causal to onset of FND symptoms, including PNES (Kozlowska, Griffiths, et al., 2017).

The above studies demonstrate that despite recent advancements in understanding neurological substrates, the goal of finding a reliable biomarker to aid in diagnosis or treatment for PNES remains elusive (Szaflarski & LaFrance, 2018). As in many other neurological disorders, there appear to be multiple foci involved in the production and maintenance of PNES events, suggesting episodes are likely the expression of time-limited disconnections among neural networks involved in volition, awareness, motor movements, emotion and perception. Accordingly, future studies incorporating an expanded view of relationships among brain regions appear to be required.

2.7 Theoretical Models of PNES Etiology

Historically, various theories have been proposed to elucidate the transitional nature of PNES symptoms. These have ranged from early dissociative explanations for PNES by Freud and Charcot (although they disagreed on treatment), to comparisons with "hard-wired" evolutionary survival mechanisms and cognitive psychology models of the 1970's. More recent exploration and development of etiological theories for PNES have shifted from a focus on early life trauma and personality traits to the role of mammalian threat responses, sympathetic arousal/parasympathetic dysfunction and disordered emotion regulation among specific neurobiological structures (Popkirov et al, 2018).

2.7.1 PNES as a Dissociative Response

Historically, PNES was first considered as a purely dissociative response to intolerable emotions, leading to a time-limited disintegration of conscious awareness of the triggering event. It was the neurologist and psychologist Pierre Janet who initially

hypothesized traumatic memories and emotions lead to dissociation, which he called a "splitting" from conscious awareness leading to autonomous movements without the patient being aware (Janet, 1889). Freud, on the other hand described unconscious conflicts as being symbolically "converted" into somatic symptoms, which he hypothesized served to protect individuals from intense anxiety by making them unaware of psychic distress (Freud, 1953). The theorists were opposed regarding resolution of the dissociated memories and PNES events, the former believing hypnosis to be the cure, whereas Freud advocated for his psychoanalysis in order to bring about restructuring of traumatic memories and emotions. Today, evidence is often cited in support of dissociation's role in PNES, including the high comorbidity of PNES with post-traumatic stress disorder (PTSD), in which proponents have likened PNES to a kind of "venting response" to intolerable emotions and psychosocial stress. Proponents also reference the fact that stressful life events occur with much greater frequency in PNES populations (than controls) in the months preceding symptom onset (Brown et al., 2016).

2.7.1.1 Evidence for Role of Dissociation in PNES

A series of studies by Van der Kruijs et al. (2012, 2014) served as the landmark investigations of mechanisms related to loss of awareness in PNES. These investigations were among the first to examine emotion and information processing abnormalities among PNES patients, in the context of dissociation. The first study (van der Kruijs et al., 2012) matched 11 PNES patients with 12 matched controls. Comparatively, the PNES group demonstrated significantly higher dissociation scores, as measured by the Dissociative Experiences Scale (DES) and lower cognitive performance on a measure of fluid reasoning, the Raven's Progressive Matrices (RPM). A variety of resting state fMRI

tasks were chosen to stimulate suggestibility/dissociation associated with hypnotic induction. Other tasks were chosen based on previously established use in stimulating frontal brain networks involved in volition/intention. Subsequent fMRI "snapshots" of brain activity obtained during administration of the above tasks were used to generate "functional connectivity maps" for both groups. Results of this study showed that among PNES patients, there was increased connectivity between the precentral sulcus (motor cortex, voluntary muscle movement) and insula (emotion regulation, visceral sensory perception, self-awareness). PNES patients additionally had stronger connections among insula and parietal lobe regions responsible for executive control, sensory processing and planning. Functional connectivity between the ACC and inferior frontal gyrus was also increased in the PNES group. Relevant to dissociative theories for PNES, functional connectivity between the precentral sulcus and posterior insula was significantly predicted by DES scores on regression analyses. The cognitive scores (RPM) did not correlate with any of the connectivity values, supporting discriminant validity for the dissociation finding and suggesting that psychological dissociation (but not intelligence) may play a central role in production of PNES episodes. The authors proposed that increased interictal connectivity (between the insula, parietal lobe and precentral sulcus) may represent the neurobiological result of intense emotions influencing executive control, leading to altered motor function states in PNES.

The second study (van der Kruijs et al., 2014) involved resting state fMRI data. Again, higher dissociation and lower cognitive performance scores were demonstrated among the PNES group. Results revealed a correlation between dissociation scores on the DES and level of altered resting state coactivation among the frontal parietal network

(orbitofrontal, insula and subcallosal cortex), executive function network (insula and cingulate) and sensorimotor networks (cingulate gyrus, superior parietal, pre/post central gyri and SMA). By comparison, no significant resting state differences were found within the visual network. Again, connectivity values in the above areas correlated with dissociation scores, suggesting the frontal-parietal network contributes to involuntary movements and altered consciousness experienced during a PNES event.

Additional experimental paradigms have demonstrated interesting correlates among PNES and dissociation. Bakvis and colleagues (2011) for example, published a series of studies examining the role of threat vigilance in PNES populations, theorizing that PNES acts as an avoidant response to protect the individual from re-experiencing stressful memories (Bakvis, Spinhoven, Zitman, & Roelofs, 2011). In their first study, Bakvis and colleagues demonstrated that PNES subjects, in comparison with controls, have faster reaction times to angry faces during an emotional Stroop task (Bakvis, Roelofs, et al. (2009). In their second study, PNES patients were confirmed to have faster reaction times to angry faces (in comparison with epileptic or healthy controls) with the additional finding that salivary cortisol levels correlated positively with the speed of reaction (Bakvis, Spinhoven, & Roelofs, 2009).

In their third study, Bakvis and colleagues (2011) employed a measure of social avoidance, administered before and after administration of a painful stimulus (cold-pressor task) to 12 adult PNES patients and 12 healthy controls. The measure (social approach-avoidance task) involved exposing participants to picture sequences of intermixed angry and happy facial expressions. In response, participants were required to

identify faces as either happy (by extending their arms towards the stimulus screen; described as an "approach" behavior) or angry (by abducting arms inwards to the body; described as an avoidant behavior). The arm movement responses had been previously validated as "emotionally congruent" responses, reflecting normal social behavior in response to negative or positive stimuli, by way of physical proximity to the stimulus. Reaction times to correct responses were measured in seconds. Upon completion, participants repeated the same task but with instructions to "reverse" the learned arm responses, which the authors described as "introducing dissonance". Previous studies have consistently demonstrated the fastest reaction times occur in the angry-congruent condition (arms abducted away from face), which is also associated with the highest levels of salivary cortisol and subjective anxiety report (Bakvis, Spinhoven, et al., 2009). Bakvis et al. (2011) applied the above paradigm to PNES patients and found they reacted differentially (much slower) when approaching angry faces than when avoiding them, an effect which did not occur in the control group. This study appeared to demonstrate that PNES patients have increased avoidance (longer reaction times) to angry faces than controls, and that baseline cortisol levels associate with reaction times. In discussing the implications of their experimental results, the authors proposed that PNES treatments directly addressing fear avoidance and coping strategy use were supported. Further evidence for the role of dissociation in PNES is reviewed under the section "Role of Dissociation in PNES" below.

2.7.2 Cognitive Models of PNES

Following dissociative explanations for PNES-related phenomena, the early cognitive models of PNES conceptualized episodes as an interruption in normal cognitive

processes involving higher cortical areas. These models predicted alterations in the connections among brain regions impacting the functioning of cognitive processes including awareness and volitional control over the body. It was Freud who originally hypothesized that all conversion disorders (PNES included) occur as the result of primary gain (described as suppression of an internal conflict) or secondary gain (defined as receiving care/support or avoidance of unpleasant stressors). More recently, some researchers have proposed at least some types of PNES are a function of reinforcement by others, as a way of deriving secondary gain and avoidance of stressful activities (Brown & Reuber, 2016). In the clinical realm, there have also been anecdotal reports of patients describing subjective experiences during which they "submit" to their attacks (Stone, 2009). Others have suggested secondary gain and more willful submission to attacks among the cognitively compromised, although there appears to be little empirical evidence of this in adults or children (Brown et al., 2016).

The most recent iteration of a cognitive model for PNES comes from Reuber and Brown (2016), who proposed an "Integrated Cognitive Model" (ICM). This model predicts that the subjective experience and observable behaviors of PNES result from an automatic, subconscious activation of previously learned hyperarousal states, combined with "modeling" of previously learned observations or descriptions of epileptic seizure movements. The PNES episode is said to be the result of a conditioned response to an internal or external trigger, in the context of elevated autonomic arousal. The model further predicts episodes occur over time as a result of chronic stress, which gradually disables an individual's ability to inhibit seizure-like responses.

2.7.2.1 Evidence for Integrated Cognitive Models

The finding that traumatic brain injuries (TBI) (usually mild) occur with higher than normal incidence preceding PNES onset has been cited by researchers as implicating cognitive mechanisms in the development of PNES episodes (Brown et al., 2016). It is well established that physiologically "compromised" brains appear to be more vulnerable to PNES, whether resulting from traumatic brain injury, pre-morbid diagnosis of epilepsy or other neurological conditions. Frontal lobe epilepsy especially, for example, appears to increase the risk for comorbid PNES more than that of other focal epilepsies (Pillai & Haut, 2012). Previous studies have also shown a positive association between right hemisphere surgical resection and later development of PNES onset. In attempting to understand the above findings, it may be important to consider previous studies show even mild TBIs can lead to functional network connectivity changes that correlate with psychiatric and cognitive symptoms often accompanying PNES. The evidence suggests it quite possible that ensuing changes post-injury give way to increased dissociation, thereby increasing risk of PNES, a concept termed "dissociogenic brain lesion" (Popkirov, Carson, & Stone, 2018).

While the theory that traumatic brain injury (TBI) may play a causal role in PNES onset is quite compelling, it has not yet been well-validated. Most studies to date have been retrospective and therefore prone to self-report bias. Such bias among individuals recruited for studies may seek an external cause for their PNES and conceivably be expected to recall a previous head injury more than healthy controls. Such a bias may artificially increase the prevalence of historical head injuries in the PNES groups. It is also possible that confounding may result from a recently recognized phenomena

described in the concussion literature, whereby emotional reaction to injurious events themselves appears to alter and negatively impact stress responsivity independent of any actual substrate changes (Silverberg & Iverson, 2011). If less stable autonomic regulation occurs following mild TBI, this could certainly be expected to lead to an increase in risk for PNES. Another explanation for the finding that brain injuries appear to precede onset of PNES is provided by Popkirov et al. (2018), who recently proposed a maladaptive cognitive behavioral response whereby symptoms are learned and internalized through a process of aversive conditioning leading to onset of functional symptoms that may include PNES.

2.7.3 Defense Physiology Model

In contrast with "higher order" explanations given for PNES onset by cognitive psychologists, other theorists have postulated PNES is the result of a "hard-wired", primitive "lower order" reflex mechanism, similar to defense responses observed across animal phylum. Initially proposed based on animal models of predator-prey evolutionary responses, the idea of a PNES as an adaptive, universal response to intolerable stress triggers has endured over many years (since the 1970's). The theory has also persisted despite criticism of being too simplistic to account for all PNES phenomena. Recent advances in neurophysiology, however, converge on neural pathways and structures implicated in production of dissociation and brainstem mediation of nervous system defense responses that may be integral to production of PNES symptoms.

Shauer and Elbert (2010) have proposed dissociation occurs during the autonomic transition from "fight or flight" into passive defense responses, often observed in a

dissociative subtype of PTSD said to comprise 14% of all PTSD cases. The PTSD phenotype is said to be characterized less by hyperarousal and more by submissive defensive responses consisting of immobility, autonomic/emotional blunting and subjective analgesia from pain. Subsequently inspired, Kozlowska and colleagues published a series of studies investigating the conceptualization of functional neurological disorders as a phenotype of the 'defense cascade' in children (Kozlowska, Walker, McLean, & Carrive, 2015). In their papers, the authors draw upon almost a century of scientific inquiry into mammalian evolution and fight-or-flight responses in humans, including Rivers' (1926) description of five sequentially occurring "defense instincts" observed in war veterans (flight, aggression, manipulation, immobility and collapse). In their contemporary model, termed the "defense cascade", Kozlowska and colleagues have described a continuum of universal predator-prey responses across the animal kingdom that are dependent on measurable distance from predator and degree of threat posed. In the mammalian brain, these stages are said to occur sequentially from low to higher threat levels over four physiological states.

The first stage of the defense cascade represents initial hypervigilance in response to possible threat, expressed via elevated autonomic arousal and mediated by activation of the limbic forebrain and amygdala. This in turn activates descending hypothalamus pathways, moving down the brain stem and spinal cord into viscera and muscles. The second stage represents an established mammalian "fight-or-flight" response, generating rapid autonomic and physiological arousal, mediated similarly through the hypothalamus but with activation of the lateral periaqueductal grey (LPAG) region, which in turn further activates sympathetic arousal (Kozlowska, Walker, et al., 2015).

The next two stages draw upon the PTSD work of Shauer and Elbert (2010), representing an escalation in survival behaviors to adapt where escape has become impossible. The third stage involves a behavioral "freezing" during which the organism is physically unable to generate a motor response but remains alert. Interestingly, it has been hypothesized this function evolved to decrease detection by predators, while allowing the mammal to scan its environment for escape options. Neurophysiology studies have demonstrated this response is mediated by activation of the vagal pathway via the dorsal motor nucleus (DMN). This in turn results in neural inhibition of the sympathetic response (previously activated in stage 2), while concurrent activation of the lateral and ventrolateral PAG regions inhibits the LPAG (via opioid receptor channels). Interestingly, Kozlowska has reported the successful remediation of the freezing response in children via Naloxone (an opioid antagonist) administration, providing clinical validity for this mechanism in humans. The third stage phenotype is also consistent with our own clinical experience of presentations in a pediatric emergency department at our center.

The fourth and final stage in the defense cascade results in complete loss of consciousness and volitional mobility, termed "tonic immobility" (Kozlowska, Walker, et al., 2015). The evolutionary advantage of this response is said to discourage the predator-killing reflex, as many animal groups do not consume already killed prey (apparently in order to avoid eating contaminated flesh). Evolutionary theorists have also proposed this neurophysiological state may serve to inhibit awareness of pain in an organism about to be consumed. The "tonic immobility" response is mediated by the same neurophysiological pathway described above (limbic forebrain and amygdala activation) but with deactivation of the hypothalamus pathway and concurrent activation of the

vagus nerve via PAG regions. Kozlowska et al. (2015) have suggested this terminus in the defense cascade may account for at least some presentations of PNES.

Kozlowska and colleagues suggest the above 'defense cascade' is primitive, automatic and experienced subjectively as overwhelming and beyond conscious control. The authors conceptualize the defense cascade as manifesting across a variety of psychiatric conditions, including functional neurological disorders, peritraumatic reactions (numbing, dissociation during sexual assaults and following natural disasters) and borderline personality disorder affective states including subjective experience of emotional release during self-harming behavior. The authors also advocate for choosing behavioral and pharmacological interventions targeting each stage described above, including those that lower sympathetic arousal or block opioid receptor pathways involved in the freeze response. They also suggest that de-escalation of the defense response requires reverse activation of each stage in sequence, such that fight-or-flight for example, must be achieved following withdrawal of the freeze response (Kozlowska, Walker, et al., 2015).

In the context of psychosocial development, the defense cascade authors have suggested that early life stressors prime the stress system, comprised of the hypothalamus-pituitary-axis (HPA), autonomic nervous system (ANS), immune-inflammatory system and emotion centers of the brain into a "state of readiness", through repeated activation of immune-inflammatory responses and glial cell development. Subsequent activation of any part of the system (even by mild psychosocial or physiological triggers) triggers the body's stress response resulting in a

neurophysiological “cascade” leading to network wide reorganization prioritizing automatic threat responses. The result is that abnormal connectivity may result among brain regions responsible for arousal, emotion & motor processing. Accordingly, Kozlowska et al. (2015) hypothesize that children with PNES may develop overactivation of the above pathways which are then able to override normal functions mediating motor, sensory and awareness systems following even minor triggering events.

2.7.3.1 Evidence for Defense Cascade in PNES

The Kozlowska et al. (2015) physiology-behavior model is a well-conceived and deeply synthesized formulation incorporating empirically established facets of dissociation, neurophysiology and mammalian behavior in an attempt to account for a number of FND phenotypes including PNES. At present, the model still requires validation and empirical testing of predictions it makes regarding human responses to perceived threat. The model also appears to lack an explanatory framework for the role of higher cortical areas (above the level of limbic forebrain) in producing behavioral threat responses, although the authors may have deferred this issue in part by referring to their model as a “primitive” innate mechanism not involving awareness or volition. The model also does not account for production of seizure-like movements often observed during PNES episodes.

Much of the empirical foundation for the defense cascade model is synthesized from study of substrates implicated in PTSD. The PAG region is located near the brain stem and is responsible for mediating autonomic responses to threatening stimuli. Structurally, the region consists of numerous substructures opposing or inhibiting each

other in function. Bandler et al. (2000) originally established the dorsolateral periaqueductal grey (DLPAG) and lateral periaqueductal grey (LPAG) are responsible for activating the sympathetic nervous system, while the ventrolateral periaqueductal grey (VLPAG) is responsible for opposing this activity via parasympathetic activation. Another study (Adamec, Toth, Haller, Halasz, & Blundell, 2012) demonstrated an association between DLPAG activation and anxiety responses to stress in rodents. The authors established that endocannabinoid administration facilitates further release of cortisol in the creation of an acute stress response. Concurrent activation of the locus coeruleus also appears to induce vasoconstriction of peripheral blood vessels while increasing blood supply to core muscles, enabling the organism to fight a predator (Goadsby, Lambert, & Lance, 1985).

A recent fMRI study tested the hypothesis that PAG regions are involved in modulation of the sympathetic (DLPAG) and passive (VLPAG) defense systems in dissociative PTSD (Harricharan et al., 2016). All PTSD patients in the study (n=60) demonstrated extensive resting functional connectivity between the DLPAG and VLPAG with various areas including the dorsal ACC, orbitomedial prefrontal cortex and bilateral fusiform gyrus when compared with normal controls (n=40). Hyperarousal scores were correlated with connectivity between right fusiform gyrus and the DLPAG but not the VLPAG, providing validity of the DLPAG in generating high arousal. Although PTSD patients demonstrated DLPAG connectivity with areas associated with initiation of autonomic hyperarousal and active coping strategies (dorsal ACC and anterior insula), only dissociative PTSD patients showed activation of the VLPAG and connectivity to areas implicated in passive coping strategies and dissociation (temporoparietal junction

and rolandic operculum). The dissociation group also had higher dissociation scores on scales measuring depersonalization and derealization. The authors interpreted their results as evidence of "defensive posturing" in patients with PTSD and that there is unique connectivity among brain regions involved in dissociative PTSD. Although this study did not measure connectivity in PNES patients, the same structures identified have been implicated in both PTSD and PNES, in relation to emotional reactivity and defensive action (dorsal ACC and anterior insula) as well as dissociation (temporoparietal junction).

2.7.4 Limitations of Theoretical Models in PNES

The three theoretical perspectives described above have endured to some extent as a result of the fact that emerging technologies have allowed scientists to begin associating neural substrates within these frameworks. Many issues require resolution however, before the perspectives can be developed into working models capable of generating testable predictions. All of the above models also draw on similar, non-mutually exclusive constructs including dissociation and somatization, which are often poorly defined or fail to be operationalized on a standardized and clinically relevant level (Brown et al., 2016). In their systematic review, Brown et al. (2017) conclude the current evidence base simply does not allow for firm conclusions to be drawn about which of the above models may be correct or unified in a mutually accommodating way. They argue the solution lies in either: 1) resolving differences between models or, 2) articulating key predictions that can be tested and teased apart in a scientific manner. While much of the theoretical work has yet to guide diagnosis or treatment in any clinically meaningful manner, the gap in our understanding of what psychological mechanisms, neurological substrates and functions are necessary for PNES to occur does appear to be narrowing.

2.8 Role of Psychophysiology in PNES

Psychophysiology science is grounded on the premise that "mental processes influence the physiological state while changes in physiology, in turn, influence thoughts, feelings and motivation" (Critchley, 2009). The study of human psychophysiology tells us that this interaction is necessary to our survival so that motivations arising from a physiology need can be activated. A simple example demonstrates this: If we are thirsty or hungry, the way we behave towards food differs significantly and biases our perceptions, cognitions and memory, thereby driving our feeding behaviors. The exact nature of ANS arousal in PNES is as of yet unclear, but key findings have included increased cortisol and heart rate, as well as decreased heart rate variability (HRV) among adult PNES patients. Abnormal nervous system responses to mental and physiological stimuli have also been demonstrated in children with PNES, including reduced HRV (vagal) recovery, increased rate of cortisol release and increased amplitude of event related potentials in the brain (Kozlowska, Rampersad, et al., 2017). Increased vigilance towards emotion of others has also been demonstrated, in the form of motor reactivity (Bakvis, Roelofs, et al., 2009). Connectivity changes in the brain have been demonstrated among resting state networks suggesting abnormal processing in brain circuits related to emotion, arousal, motor planning/co-ordination and reference to self (Perez et al., 2015). Arousal related impairments have been demonstrated in the prefrontal cortex (Kozlowska, Palmer, Brown, Scher, et al., 2015) and avoidance tendencies have been shown to be increased in response to social threat cues in PNES patients (Bakvis et al., 2011). What is interesting is that all three theoretical models

described above include autonomic arousal as a necessary factor in production of PNES events, regardless of what central nervous system structures and functions are involved.

2.8.1 Skin Conductance & HRV Studies

Skin conductance level (SCL) measurements reflect purely sympathetic neural responses without direct influence from parasympathetic output or circulating factors such as adrenalin (Critchley, Elliott, Mathias, & Dolan, 2000). An fMRI study of SCL responses demonstrated the right orbitofrontal cortex, right anterior insula, left lingual gyrus, right fusiform gyrus, and left cerebellum all covary with SCL increases (Critchley et al., 2000), areas similarly implicated in PNES etiology (Sundararajan et al., 2016). The same study reported a significant association between elicited SCL responses and corresponding activity across the medial visual cortices, cerebellum and left prefrontal cortex. These results suggest areas implicated in emotion and attention are also involved in generating and representing peripheral SCL responses. The authors went on to propose these neurological functions enable integration of adaptive responses in the body (motor readiness, activation) with real-time emotional and attentional states of the organism. Direct stimulation of the amygdala, hippocampus or anterior cingulate areas also result in ipsilateral modulation of SCL. In experimental studies. Mungen (2010) established that time-delayed SCL responses (measured at upper extremities) occur interictally and post-ictally in epileptic patients.

Change in heart rate over time (HRV) occurs as the result of multiple physiological factors including respiratory sinus arrhythmia (RSA). HRV is thought to be a superior measurement of autonomic functioning as it provides a single index of both

sympathetic and parasympathetic function. HRV has become increasingly recognized as a useful measure in studies of medical and psychiatric conditions, including a recent study in depression-prone youth, which demonstrated that childhood adversity predicts less flexibility in RSA changes during sad mood induction among adolescents with major depression. In the study, more recent adversities did not appear to associate with this finding, suggesting RSA is a longer-term marker of stress levels (Daches et al., 2017).

Studies of HRV and SCL have yielded conflicting results among measurements taken during pre, ictal and post-ictal PNES time frames. Mungen et al. (2010) were among the first to study autonomic functions in PNES utilizing SCL and HRV measurements. In their comparative study of adult epileptics versus adults with PNES, only the former were reported to demonstrate any interictal or ictal abnormality. A notable limitation of this study however, was inclusion of only two very specific psychophysiology variables: interval between heart beats (RR) and sympathetic skin response level (SCL) during EMG stimulus testing. In the former, RR interval variations were measured ictally and interictally, both during normal breathing and deep breathing (during rate of 6 breaths/minute). The latter measured latency of sympathetic skin response to stimulus and was delayed in epileptic but not PNES patients. The magnitude of differences between epilepsy and normal control groups however, was minimal. Another limitation of the study was that AED use was not described among the samples so could not be considered as a potential biasing or confounding factor. Based on their results, the authors suggested that autonomic functioning in PNES patients appears normal (Mungen et al., 2010).

Subsequent studies of psychophysiology abnormalities reported conflicting results regarding presence/absence of HRV factors among epilepsy and PNES patients. Reinsberger et al. (2012) reported that an adult ictal heart rate above 130 bpm yielded 97% positive predictive value for epilepsy over PNES. This study also reported that post-ictal heart rate was higher following epileptic versus PNES events (Reinsberger, Perez, Murphy, & Dworetzky, 2012). Using measurements of HRV, Ponnusamy et al. (2012) also reported that epileptics had higher sympathetic tone than PNES at rest and during seizures. In another HRV study however, Van der Kruijs (2016) demonstrated PNES episodes in adults are also preceded by increased sympathetic tone, followed by an increase in parasympathetic tone both during and following the PNES episode. In a retrospective study of 42 adult PNES patients and 46 complex partial seizure patients, Reinsberger et al. (2012) reported that ictal heart rate could not distinguish among epileptic versus PNES events. The authors also reported that significant pre-ictal increase and postictal decrease in heart rate occurred in the PNES but not the epilepsy group. Jeppenson et al. (2016) subsequently reported that sympathetic activity occurred in both groups during ictal events but was higher in epilepsy than PNES patients. The authors also described significant variability in heart rate change which they suggested would limit clinical utility of using of HRV measurements in helping to distinguish among epileptic versus PNES events. Not surprisingly, the above studies lead authors to conclude that future research is required to identify idiosyncratic features of sympathetic changes preceding epilepsy and PNES. A recent review also concluded that use of autonomic nervous system features as biomarker of PNES are not yet recommended,

although some markers, such as prolonged return of HR to baseline post-ictally may help support diagnosis of epilepsy over PNES (Sundararajan et al., 2016).

2.8.2 Role of Hyperventilation in PNES

Hyperventilation (HV) has long been suspected of playing a role in onset of PNES events, with up to 80% of adult patients displaying panic-like symptoms preceding or during their attacks (Hendrickson, Popescu, Dixit, Ghearing, & Bagic, 2014). HV has also been recognized as a common trigger for PNES in adults such that its use is recommended as an acceptable provocation technique in the EMU (Benbadis et al., 2000). Although data in children are sparse, HV has also been recognized to increase the child's susceptibility to triggering a PNES event, possibly more so than in adults as a result of cerebrovascular immaturity and excessive vasoconstrictor response to respiratory CO_2 changes (North, Ouvrier, & Nugent, 1990). Additional studies suggest approximately one quarter of children with PNES experience preictal or ictal HV, implying a potential causal role (Deka, Chaudhury, Bora, & Kalita, 2007; Krishnakumar, Sumesh, & Mathews, 2006).

HV is defined as breathing behaviours in excess of what is needed for metabolic demands and leads to a variety of neurophysiological changes in the nervous system both centrally and peripherally. Clinically, HV presents in many different forms, but can often be observed by laboured breathing patterns in the chest, excessive gasping sounds or appearance of open mouth in conjunction with rapid breathing cycles. The first stage of HV is sympathetic nervous system stimulation, consisting of cortical excitability globally followed by a hypoxic phase resulting in decreased cortical function and inhibition.

Peripherally, HV results in neuronal hypopolarization, leading to increased excitability of sensory and motor axons causing muscle excitability and paraesthesia. Cardiac effects also occur, including vasoconstriction of coronary arteries causing subjective chest pain (Kozlowska, 2013).

Persisting HV leads to cerebral hypoxia resulting in reduced brain function. Sequentially, a physiological cascade follows characterized first by reduced arterial CO_2 which increases arterial pH. Studies have shown that cerebral arteries constrict in children, resulting in reduced blood flow, increased binding of oxygen to haemoglobin and lowered oxygenation as well as metabolism throughout the brain (Engel, Ferris, & Logan, 1947; Hauge, Thoresen, & Walloe, 1980; Yamatani, Konishi, Murakami, & Okuda, 1994). Interestingly, the brain regions most sensitive to this hypoxia begin in higher brain regions including prefrontal cortex and basal ganglia, then hypothalamus and midbrain, followed by the brainstem which is most resistant to these effects. As the higher cortical areas facilitate human consciousness, subjective changes in awareness occur quickly after HV begins. This process results in a "disconnect" of higher cortical and lower brainstem functions that may provide a mechanism for provoking PNES episodes (Kozlowska, Chudleigh, et al., 2017). It is well established that HV results in even more pronounced changes in children and youth than adults, with studies showing greater decreases in cerebral blood flow (Gotoh, Meyer, & Takagi, 1965; Yamatani et al., 1994). Although norms are limited in children, the above symptoms have been well established as occurring in adults at arterial CO_2 levels of 20mmHg or lower (Rafferty, Saisch, & Gardner, 1992).

Kozlowska et al. (2017) measured breathing rate and arterial CO_2 levels in 60 children and adolescents with PNES. This study also employed healthy (n=17), psychiatric (n=25) and epilepsy (n=8) controls as comparison groups (Kozlowska, Rampersad, et al., 2017). The authors found PNES patients demonstrated elevated respiration at baseline, with 69% having rates above the 75th percentile on age-based norms (Fleming et al., 2011). HV was also assessed during administration of a protocol involving rapid breathing over a 5-minute period, as part of typical provocation procedures in the EMU. Analysis variables included: 1) baseline CO_2, 2) total change in CO_2 during challenge, 3) trough or lowest value CO_2 during challenge, 4) rate of CO_2 drop (mmHg/minute) (baseline to trough values), 5) rate of CO_2 recovery following challenge, as well as 6) the final CO_2 value post-assessment. The assessment protocol lasted 35 minutes and consisted of the following conditions: 1) eyes open (3 minutes), 2) eyes closed (2 minutes), 3) photic stimulation, 4) break, and finally 5) the HV protocol. In the PNES group, duration of illness ranged from 1 day to 48 months and 47% had other comorbid functional neurological conditions. All families had reported stressors preceding onset of PNES symptoms. The findings were that PNES patients had higher respiration rates at baseline (25 versus 20 breaths/minute) and 69% had baseline heart rates above the 75th percentile (mean 91 bpm compared with healthy controls mean bpm of 77). Baseline percutaneous CO_2 measured through sensor on skin (PCO_2) showed baseline values of 37mmHg in the PNES group versus 41mmHg in the combined control group and trough (lowest) values of 24mmHg in PNES versus 26mmHg in the controls, both differences of which were significant. Although rate of the drops during HV challenge were not significantly different, recovery time was 1.9mmHg/minute in the

PNES group versus 3.2mmHg in the control group. The post-assessment mean PCO_2 values were also significantly lower in the PNES group (36mmHg compared with 42mmHg in controls). The authors completed a secondary analysis on patients confirmed to have HV provoke their PNES events (determined by direct observation), which numbered 32 out of the 60 PNES patients. This group showed significantly lower mean PCO_2 values throughout the 5-minute HV challenge protocol than controls or other PNES patients. The authors went on to label this group "HV-induced PNES". The authors calculated symptoms of cerebral hypoxia during the HV protocol challenge which were reported to be five times higher in the PNES group than controls (Kozlowska, Rampersad, et al., 2017).

Authors for the above study interpreted their findings as evidence that child PNES occurs in the context of "readiness-for-action", characterized by higher autonomic arousal and increased ventilation in order to meet metabolic demands. They also associated low PCO_2 during baseline and poor recovery as indicative of over-reactivity and dysregulation of the interconnections among motor activity and sympathetic nervous system function. Several limitations were reported in the study. Firstly, the authors described slow diffusion of CO_2 from blood to skin, resulting in a 2-minute delay from the actual blood levels to observed percutaneous readings of CO_2, which may have "blunted" the accuracy of comparisons. Secondly, the authors pointed out a lack of cerebral blood flow measurement during HV, the inclusion of which would have helped establish neurophysiological mechanisms involved in triggering PNES. Thirdly, the authors pointed out they lacked measurement of cortical arousal/reactivity, which also would have helped determine HV effects on the brain. Despite these stated limitations,

the authors concluded their results demonstrate a vital need to identify HV among child PNES populations, in order to target down-regulation of the ANS. They also concluded patients require training to avert HV and resulting PNES episodes, after which they may be better able to focus on psychological interventions addressing stressors and perceived threats involved in initial PNES onset (Kozlowska, Rampersad, et al., 2017).

2.8.3 Suppressed Stress Responses

A more recent development in the study of autonomic characteristics has been the suggestion "suppression" may occur in PNES and other functional neurological disorders. In one study of childhood conversion disorder patients, including a large PNES cohort (Kozlowska, Palmer, Brown, McLean, et al., 2015), the authors noted decreased capacity "to mount an optimal autonomic response". The conclusion followed from the finding that conversion patients, compared with matched controls, did not respond with the same degree of heart rate increases across cognitive tasks. In the study, involving 57 patients with conversion disorder (29 were PNES), the authors applied four different standardized tasks during assessment. Changes in heart rate were compared among PNES and normal controls. The primary result was increased arousal at baseline in the PNES group. Respiratory rates were also estimated from the RSA readouts. PNES patients did not appear to differ from other conversion disorders on measurements, although they did endorse higher somatic symptoms and reports of fatigue, breathlessness, dizziness, or nausea. The authors interpreted their findings as evidence of reduced capacity in conversion disorder to withdraw parasympathetic output. The finding that child PNES patients did not demonstrate normal heart rate increases across cognitive stressors deserves further validation and study. If suppression of the normal autonomic response

can be further demonstrated in PNES, it may serve as a potential index of less efficient autonomic regulation in future studies of PNES.

2.9 Role of Dissociation in PNES

2.9.1 Definition of Dissociation

The psychological concept of dissociation is defined as a heterogeneous construct involving disruption and loss of integration of normal subjective experiences; including consciousness and awareness of the self, memory, perception, intention and voluntary motor control (Krause-Utz, Frost, Winter, & Elzinga, 2017). Dissociation can be considered on a spectrum of intensity ranging from an increased tendency to experience loss of somatic awareness (trait dissociation) to more invasive disruptions involving transient states in and out of awareness (state dissociation). At higher intensities, state dissociation is considered a pathological, primary feature of dissociative disorders included in the DSM-5 (APA, 2013). Pathological dissociative processes are also implicated in a range of psychiatric disorders, including borderline personality disorder (BPD) (during intense affect states) and PTSD (during fear-induced memory recall). Clinical symptoms commonly attributed to psychological dissociation include depersonalization, derealization, emotional numbing, memory fragmentation/intrusion and loss of somatic awareness.

The dissociation experienced during a traumatic event is considered an adaptive defense mechanism which aids the individual to cope with overwhelming and unescapable threat. The premise of dissociation theory is that subjective detachment states help to create an inner distance from an overwhelming experience by “dampening”

intolerable emotions and reducing awareness of the traumatic memory. A common example is the subjective experience of viewing an event from outside the self. Other examples include subjective reports of being "out of body" and floating above one's body to reduce awareness of physical injury. Disturbing sensory, emotional and cognitive intrusion of awareness during normal daily activities, however, can result from severe trauma experiences.

Dissociation is thought to interfere with coherent cognitive encoding of experiences, leading to fragmentation of memories where cognitive, sensory and emotional aspects of the trauma event are abnormally stored as separate elements in the cognitive network. In this way, it is thought that flashback memories may occur by unintentional activation of these elements during normal cognitive processes. Individuals having experienced dissociation related to previous trauma, also appear more likely to respond in a similar way to traumatic cues later in life. This dissociative response can generalize across situations and even begin to occur in presence of minor stressors (Lanius et al, 2010). In this way, dissociation is recognized as maladaptive while also interfering with treatment.

2.9.2 Dissociation Substrates

Brain structures implicated in PNES onset and maintenance are also thought to be involved in production of dissociative symptoms. Depersonalization, conceptualized as a state of subjective detachment involving emotional numbing, analgesia and hypervigilance, has been linked to increased activity in areas involved in arousal modulation and attention control. These include prefrontal structures (medial and

dorsolateral PFC) and the ACC. Increased activity in these areas "dampens" the amygdala and attenuates automatic responses by shutting down the affective system. Additional research demonstrates that cortical arousal during dissociative experiences leads to secretion of endogenous opioids and cannabinoids that impair functioning in frontal brain areas including the cingulate, insular and orbitofrontal cortices via opioid receptors (Lanius, 2014). The above suggests anesthetic chemicals disrupt the vertical integration of brain functioning among higher cortical areas and lower subcortical brain systems that ordinarily maintain full conscious awareness.(Kozlowska, Chudleigh, et al., 2017).

Studies of patients experiencing chronic depersonalization have demonstrated that insula activity is diminished during dissociative experiences and appears to play an important role in attention modulation, interoceptive awareness, pain perception and encoding of negative emotional content. Alexithymia (lack of subjective emotional awareness) is also associated with altered insula and ACC reactivity to sad facial expressions in these populations. Jay et al. (2015) used fMRI to demonstrate that the ventrolateral prefrontal cortex (VLPFC) abnormally inhibits the insula in adults with depersonalization disorder. The degree of this inhibition also correlates with intensity of dissociation symptoms. The posterior cingulate cortex (PCC) links to the PFC and is implicated in self-referential focus, pain processing and daydreaming. Altered brain metabolism is this area has been demonstrated during dissociative experiences, including in temporal lobe epilepsy patients while subjectively reporting perception of the self as "unreal".

2.9.3 Psychophysiology of Dissociation

A number of associations between dissociation and autonomic correlates have been established. The reduced sense of self and emotional "numbing" associated with depersonalization and derealization disorders is thought to be mediated by abnormal emotional processing, due to biases in self-referent multi-sensory integration. This emotional "numbing" is often accompanied by suppressed autonomic arousal during emotionally provocative stimuli (Dewe, Watson, & Braithwaite, 2016). A recent study of normal subjects (n=118), for example found those predisposed to depersonalization and derealization symptoms had suppressed skin conductance level (SCL) responses to simulated physical threat. Although a reliable reduction in finger temperature was also demonstrated during fear responses, this value was not consistently associated with measures of dissociative experiences (Dewe et al., 2016).

In another study, it was hypothesized that inhibition of the right ventrolateral PFC using repetitive transcranial magnetic stimulation (rTMS) would lead to increased arousal and reduced symptoms in patients with treatment resistant depersonalization disorder (Jay et al, 2018). Here, a total of 17 patients and 20 healthy controls were randomized to receive a single rTMS session of stimulation to either the right ventrolateral PFC or temporal-parietal junction (TPJ). Stimulation of the right ventrolateral PFC resulted in increased skin conductance for the depersonalization group but not healthy controls. Stimulation to either area also lead to reduced dissociative symptoms in the clinical group. The authors concluded their findings support a model whereby increased ventrolateral PFC activity results in physiological arousal, leading to “emotional numbing” in depersonalization disorder. According to this model, the authors suggested

that rTMS treatment of ventrolateral PFC may increase physiological arousal capacity thereby reducing depersonalization symptoms.

2.9.4 Dissociation in PNES

Psychological dissociation has long been implicated as the" fundamental defense mechanism" essential for development of functional neurological disorders, including PNES. In support of this perspective, Tomic et al. (2017) reported patients with functional dystonia had higher dissociation scores and lower extroversion and openness scores, in comparison with organic dystonia patients. Compelling evidence exists for the role of dissociation in PNES from a small number of hypnosis studies demonstrating reversibility of the dissociative amnesia typically occurring during ictal PNES. This paradigm relies on the fact that ability to recall ictal memories after certain types of epileptic events should not be possible. Adult PNES patients also share many common demographic and clinical features with patients having dissociative disorders. These include trauma experiences, increased hypnotizability and symptoms of amnesia, fugue and depersonalization (Masumi et al., 2009). Other studies have suggested very high levels of dissociation among PNES groups, such as Bowmen et al (1999) who found that 91% of 45 adult PNES patients met criteria for a dissociative disorder. Another study found "attachment dissociation" was high in both PNES and dissociative disorders but that "compartmentalization dissociation" was high in PNES only, although the latter result appeared to be accounted for by depression and anxiety scores (Lawton, Baker, & Brown, 2008).

In another study, Masumi et al. (2015) evaluated dissociative experiences in an adult PNES population using the Dissociative Experiences Scale (DES). This study involved three comparison groups including epilepsy (n=50), PNES/epilepsy (n=30) and healthy controls (n=80). The highest mean DES scores were demonstrated in the dual epilepsy and PNES group ($\bar{x}$=29.3); much higher than in the Epilepsy only ($\bar{x}$=13.5) or control group ($\bar{x}$=11.1). Scores meeting criteria for "high" comprised 53% of the dual diagnosis group versus only 12% of epileptics and 6% of the control group. The DES score did not correlate with either the frequency of PNES events or descriptions of severity obtained on Global Assessment of Functioning (GAF) scores (low, moderate, high) from the DSM-V.

Additional literature to date suggests dissociative experiences are elevated in PNES more than in epileptics. The effect is inconsistent however, with differences usually being small. Furthermore, the group mean scores in PNES appear to remain lower than in those meeting criteria for dissociative disorders under the DSM-5. One potential explanation for this inconsistency may be in the way dissociation is measured, as many studies involve self-report scales describing features of dissociation that are phenotypically quite similar to transient epileptic states. In considering PNES dissociation, it is important to understand that dissociative mechanisms can operate in absence of trauma disorders or so called "trait dissociation". In other words, all individuals likely have ability to dissociate without having experienced traumatic events (Brown et al., 2016). In their recent review of dissociation's potential role in PNES etiology, Brown and Reuber (2016) suggest that a general capacity for dissociation is a common correlate of PNES but is "neither necessary nor sufficient to cause or explain

phenomena" on its own (Brown & Reuber, 2016). To date, no measures of dissociation have published in pediatric PNES studies.

2.10 PNES Treatment

Published research has shifted in the last decade from focusing on PNES diagnostic procedures to treatment approaches (Popkirov, Jungilligens, et al., 2018). A wide variety of behavioral, psychotherapy and pharmacotherapy approaches have been studied with reduction in PNES frequency as the primary outcome. Among these however, it is difficult to identify individual therapies that may be effective. A 2014 Cochrane review, for example, found little reliable evidence to support any specific treatment for PNES in adults, including CBT (Martlew et al, 2014). The majority of adult treatment studies are also retrospective in nature, with only two published randomized controlled trials (RCTs) having been undertaken but with small samples. The first of these demonstrated complete resolution of events for 14 out of 15 participants undergoing paradoxical intention therapy (Ataoglu, Ozcetin, Icmeli, & Ozbulut, 2003). The second published RCT involved 34 adults (across three centers) and demonstrated a reduction of 51% of PNES events in those receiving CBT. The addition of Sertraline in another group resulted in event reduction of 59% (LaFrance et al., 2014), compared with standard medical care or Sertraline alone (although latter showed limited to no benefit).

2.10.1 PNES Treatment in Children & Adolescents

While no studies exist which have prospectively measured outcome in pediatric PNES, retrospective studies have demonstrated as much as 60% to 80% of children with PNES achieve symptom improvement or event freedom following treatment periods

lasting several months (Chinta et al., 2008; Irwin et al., 2000; Sawchuk & Buchhalter, 2015; Wyllie et al., 1999) (Reilly, Menlove, Fenton, & Das, 2013). Accordingly, there appear to be more promising outcomes for children and adolescents with PNES than in adults, for reasons which remain unknown. Speculation has ranged from the suggestion that PNES factors may be less chronified in children, or that there is superior neuroplasticity and resilience in children at an earlier age. Treatment targets in PNES research include not only reduction of events, but improvement in underlying mental health and quality of life (Doss & Plioplys, 2018). To date, treatments for PNES in children have mirrored those used in adults, including relaxation training, increasing awareness of triggers, learning adaptive cognitive-behavior responses (counter-conditioning), mindfulness-based intervention for attention "re-training" and increasing tolerance of high arousal states. Hypnotherapy is also frequently listed as promising, but evidence for its' effectiveness is quite limited in both adults and children. Proponents for hypnotherapy in PNES cite there is a similar "decoupling" of frontal attention in highly hypnotizable subjects, which may resemble what occurs during ictal PNES onset.

A multidisciplinary approach to treatment in childhood PNES is thought to be most efficacious (Doss & Plioplys, 2018). It is generally recommended that care include involvement of a neurologist as well as a mental health care team. There is no evidence of pharmacological agents being used to effectively treat pediatric PNES (Babaturk & Sullivan, 2018). While CBT, family therapy and psychodynamic or interpersonal therapies have shown promise in adult treatment studies of PNES; none of these approaches have been adequately studied in children. Creating a response plan for parents and teachers of children with PNES is often recommended (Caplan et al., 2017) and

enhances delivery of short-term management (PNES "first aid"). Individual treatment sessions with the child as well as one or more separate sessions with the parents is also recommended to provide psychoeducation about the role of emotions and autonomic arousal leading to PNES events. Caplan and colleagues (2017) additionally recommend coaching parents to respond to their child with empathy and expectation for gradual increase in return to activities.

For the child with PNES, resuming activities and learning to cope with stressors is a front-line treatment goal. Once coping skills have been evoked, building insight into triggers can begin, while reinforcing positive coping and addressing environmental factors that can be changed. Effectively treating the underlying mental health factors is also important to prevent relapse, and targets frequently include social anxiety or depression. It is also recognized that intensive mental health interventions may be required before resolution of PNES events. Caplan and colleagues (2017) have described criteria for intensive mental health admissions including: 1) daily episodes at home and school, 2) PNES longer than one year, 3) school absence greater than 3 months, 4) severe comorbid mental health conditions, including suicidal thoughts or self-harm and finally, 5) when abuse is present or when home situation is contributing primarily as PNES trigger.

2.10.2 Treatment Outcome Studies

A small number of child PNES treatment outcome studies have been published. Chinta et al. (2008) for example, demonstrated an 82% reduction in events in association with treatment periods ranging from 3-6 months. Intervention involved multidisciplinary

care comprising of joint neurological/psychological assessment, diagnosis, and treatment involving behavioral and psychiatric care. Yadav et al. (2015) retrospectively reviewed 90 patient records of PNES diagnoses in children under the age of 18, over a two-year follow-up period. They reported 36% as having sustained full remission by 6 months, 33% having no remission at two years, with the remaining third went into remission over the remaining treatment period. Unfavorable outcomes were associated with comorbid epilepsy and prolonged duration of symptoms preceding accurate diagnosis. Limitations in this study included retrospective data collection at a single healthcare center, possibly limiting generalizability. As well, 46 out of 136 patients were excluded due to lack of a two-year follow-up; hence there was a strong likelihood of non-responder bias, which may have overestimated proportion of successful outcomes. The authors were also unable to measure the amount or type of treatment received, which was unstandardized. The authors recommended that multi-site, prospective studies are required in order to reliably establish treatment effect in child PNES.

A previous study at our center (n=29) demonstrated partial to full remission in the majority of cases (79%) over a several-month period. Treatment consisted of psychological assessment followed by either brief solution-focused therapy or CBT. The addition of multidisciplinary mental health services (psychiatry, family therapy) was included in more severe cases and a small number received intensive mental health admissions, either by way of day or inpatient programs. Similarly, positive outcomes were achieved among children dually diagnosed with epilepsy and PNES, with loss of only a single case to follow-up. The study also demonstrated that medical and emergency

department utilization reduced, especially among the dually diagnosed patients, in comparison with those having PNES alone.

Kozlowska et al. (2017) examined data for 60 children with PNES having been referred to a mind-body rehabilitation program, which included use of respiratory biofeedback. The authors utilized a broad definition of PNES, described as an umbrella category including multiple pathways by which a destabilized neural system may lead to a release of "prewired motor programs, following functional failure in cognitive-emotional executive control circuitry". Employing Janet's dissociation model of PNES as a framework, the authors sub-grouped their sample into 6 different subgroups by hypothesized mechanism of collapse. Subgrouping was then used to assign specific treatment interventions. Accordingly, the PNES subgroups were: 1) purely dissociative, 2) dissociative (but triggered by HV) and 3) reactions resulting from threat responses (defense cascade, described earlier) including tonic or collapsed immobility (Kozlowska, Chudleigh, et al., 2017). Although three additional categories were described in the paper, these were comprised of a small number of patients having hypoxic seizures, usually not included in PNES definitions employed by other studies. The study demonstrated 75% full recovery from PNES events, while 7% were reported to have refractory PNES events.

Interestingly, the authors conducted post-hoc analyses of vulnerability and risk factors for persisting PNES. Results demonstrated that having had PNES events longer than three months (preceding treatment period) resulted in worse outcomes than those having more recently/acute symptoms. The authors also reported that 4 patients out of 60

did not respond to treatment and that these individuals had prolonged PNES history ranging from 12-34 months. Extent of mental health comorbidity also worsened prognosis. Factors that did not relate to treatment outcome included child IQ, comorbid neurological illness, presence of pain disorder or other functional neurological symptoms.

2.10.3 Treatment by Sub-Grouping

As in the above study, investigators over the years have attempted to account for the variability among PNES semiology by efforts to identify sub-groups among PNES phenotypes. One argument for this approach stems from findings suggesting various factors predispose individuals to PNES (previous trauma, dissociation) but are not a requirement in order to develop the disorder. Along these lines, Reuber (2008) described three "clusters" of adult PNES presentations: the first group characterized by unresponsiveness (combined with large motor movements), while the second group is described as having unresponsiveness (combined with minor motor or trembling motions). The third group is described with events of purely sensory or subjective symptoms, during which full consciousness is preserved (Reuber, 2008).

In another study, Quinn et al. (2008) identified three distinct subgroups based on dissociation scores and trauma history in a sample of adult PNES patients. The first group was characterized by severe and chronic trauma history with disordered attachment (invalidation in relationships, described as 'attachment trauma'). In the remaining groups, PNES appeared to occur in the context of ongoing interruptions to awareness of self and memory (i.e. dissociation) with (Group 2) or without (Group 3) a history of attachment trauma (Quinn, Schofield, & Middleton, 2008).

In the most advanced study of PNES semiology characteristics to date, Hubsch et al. (2011) analyzed video-EEG records of 145 PNES events to determine presence of 22 observable signs among 52 patients. Employing multiple correspondence analysis and hierarchical cluster analysis, they identified 5 clusters based on primary features: 1) dystonic attack with 'primitive' gestural activity (31.6%); 2) 'pauci-kinetic' attack with preserved responsiveness (23.4%); 3) pseudosyncope (16.9%); 4) hyperkinetic, prolonged attacks with HV and auras (11.7%); and 5) axial dystonic, prolonged attack (16.4%) (Hubsch et al., 2011).

In children, Kozlowska et al. have also suggested that PNES is a heterogeneous category. In one study, the authors established attachment profiles in youth diagnosed with any FND (including PNES) via structured interviews and coded subjects based on four attachment types described in the Dynamic-Maturational Model of attachment (Kozlowska, Palmer, Brown, McLean, et al., 2015). While controls demonstrated normative patterns of attachment, the conversion disorder group demonstrated two different "at-risk" attachment groups, which were labelled 'inhibitory' or 'coercive-preoccupied'. The first group was described as children using substantial psychological inhibition to minimize subjective awareness of difficult emotions and memories, while also displaying positive affect appearances to mask inner feelings of ongoing distress. This group was also characterized by high conformity towards parental expectations and well-being being prioritized over their own opinions. This group typically complied with what was expected of them by authority figures and typically worked very hard to ensure the interactions with parental figures were positive and free of conflict. Children in the second group were characterized by exaggerated negative affect and focus on fear, anger

and “desire for comfort”. By contrast with the first group, these children were noted to prioritize their own perspective over that of adults. This “noncompliance” typically took a passive form involving behavioral inhibition of anger/distress, increased helplessness or fear/pain and significant elicitation of comfort/rescue. The FND group as a whole were also characterized on a narrative task by recurring language dysfluencies (disorganized distressing thoughts, feelings and memories) related to traumatic memories, suggesting unresolved loss (Kozlowska, Palmer, Brown, McLean, et al., 2015).

Along similar lines, Myers et al. (2017) have suggested that PNES with comorbid diagnosis of PTSD requires specialized treatment, specifically with a focus on graduated exposure to previous traumatic memories. In their study, prolonged exposure therapy was studied with 6 dually diagnosed PNES + PTSD adult subjects seen over 12-15 weekly sessions. Over the course of treatment, just over half (56%) experienced an event in session and 81% (13 out of 16) experienced full event remission by the conclusion of treatment. No control groups or random assignment was utilized, and sample size was small warranting replication, but results were promising suggesting there may be benefit in “targeted” interventions for specific subgroups of PNES (Myers, Vaidya-Mathur, & Lancman, 2017).

2.10.4 Use of a Care Pathway in PNES

PNES is considered a healthcare problem around the world, with insufficient knowledge and awareness being reported in a recent survey of epilepsy professionals across 63 countries (Hingray et al., 2018). In considering the treatment of PNES, many barriers to care exist including high levels of misdiagnosis, limited clinician knowledge,

lack of access to appropriate treatment, healthcare system inefficiencies and lack of empirical support (Sawchuk et al., 2017). Clinical care pathways are a recent development in western medicine approaches to illness and disease. Originally arising from business quality management practices of the mid-1980's, the purpose of a care pathway is to focus on steps required for attaining intended outcomes (Rooney, 2017). The main goal of a healthcare pathway is to improve quality through reliability, consistency and minimization of wastage. Pathway use in healthcare stems from increasingly complex interventions and rapidly developing knowledge bases within medical research. The use of the care pathway then is to "distill" the available research and evidence for clinicians, offering them a faster, more efficient and predictable means of reaching a planned health outcome. The pathway algorithm involves delivering various nested processes along decision point routes within the care diagram (Rooney, 2017).

The pathway holds together what would otherwise be a collection of uncoordinated and potentially unnecessary procedures giving rise to low quality outcomes and excessive cost or waste, which for PNES patients would be expected to result in longer wait-times and poorer prognosis. The challenge is often in making a pathway general enough so that it can be applied broadly, yet specific enough to be relevant to a specific population within an actual healthcare delivery system. Kinsman et al. (2010) define five specific criteria for a clinical care pathway, defined as an intervention requiring: 1) a structured multidisciplinary plan of care, 2) translation into existing guidelines and healthcare structures, 3) detailed steps included during aa course of treatment, care plan or guideline, 4) has timeframes and/or criteria-based progression set out on the pathway, and 5) strives to standardize care for a specific procedure or

episode of care in a specific patient group (Kinsman, Rotter, James, Snow, & Willis, 2010). Although the implementation of clinical decision tools has not yet been established in PNES, use and development of such pathways have the possibility to improve efficiency, cost and treatment for children and adolescents with PNES (Sawchuk et al., 2017).

The first published clinical care pathway for PNES was developed and implemented at our center in 2015. The pathway was developed based on results of a retrospective study, which sought to characterize pediatric PNES patients and the care they received, with resulting clinical outcomes. The results of that study supported the need for adjunctive psychological assessment prior to commencing therapy, as a high number of co-morbidities were reported in addition to PNES. Results also supported a view of PNES as a "symptom" rather than the "underlying disease" process, as many patients required extensive mental health follow-up beyond remission of PNES events. Our results also provided some early support for the development of care models which progress in accordance with stepped care. This was evidenced by the fact our sample responded, at least in terms of symptom remission at variable levels of care (Sawchuk & Buchhalter, 2015). Based on those results, an algorithm for care was developed pragmatically to serve as a guideline for achieving positive outcomes in an existing healthcare setting. This investigation demonstrated positive outcomes (79%), while establishing feasibility of a stepped-care model for PNES in children and youth (Sawchuk & Buchhalter, 2015).

2.11 Rationale for the current line of inquiry

Despite being a very common problem for epilepsy centers worldwide, very little is known about how best to manage psychogenic non-epileptic seizures (PNES) in children and youth. While CBT protocols and administration of SSRIs have shown promise in adult studies, there are few that have examined or compared approaches in children. To further add to patient (and healthcare provider) frustration, there is a lack of practical information on how to best initiate and co-ordinate care, once accurate diagnosis has been achieved. Facing a perplexing and often poorly understood diagnosis, patients and their care providers are faced with difficult decisions: 1) How to initiate treatment, where and by whom? 2) What, specifically, are the treatment goals? 3) When PNES events do not abate, at which point should new interventions be considered, at what intensity and cost to the healthcare system? Without a clear 'roadmap' to care, patients and their providers may find themselves at a loss to answer the above questions, further reducing patient acceptance and participation in the very treatments most likely to succeed.

Review of the literature reveals that our understanding of PNES etiology and treatment is still in its infancy, especially as it pertains to children with the disorder. Almost all studies to date have been adult in nature. Another significant limitation of outcome research is the lack of prospective study designs. While these number only a handful in the adult literature, there are none addressing PNES in children. Prospectively designed studies in child PNES will help to establish causality of interventions that are found to be effective in reducing the frequency of events. Also, the role of psychophysiology abnormalities have been implicated in the etiology of PNES and

dissociation (van der Kruijs et al., 2011). Accordingly, many authors have pointed out the need for subjective and objective measures in PNES studies, including psychophysiological measures (Brown et al., 2016). While psychophysiology characteristics have been studied in adult PNES, data on childhood PNES is limited to preliminary results at a single healthcare center (Kozlowska, Chudleigh, et al., 2017). The role of dissociation has also not been reliably measured in children with PNES, despite the fact dissociation is established as presenting differently over the lifespan (Wherry et al., 2009).

An urgent need for development of PNES care pathways has been identified internationally within the Epilepsy community (Sawchuk et al., 2017). Highly desirable treatment outcomes of 80% remission were achieved in our original study. Accordingly, our epilepsy center standardized the care pathway for PNES in 2015 to ensure quality of care. Updated to reflect new knowledge and empirical evidence, the current care pathway was instituted to address patient needs within an existing and feasible healthcare framework, while also striving to replicate and improve upon remission rates achieved in our original study. The progression of care approaches in the updated pathway reflect both the author's clinical experience in working with functional neurological disorders as well as recent advancements in the scientific literature regarding PNES etiology, pathophysiology and treatment approaches. New studies describing autonomic nervous system (ANS) features of PNES have opened the way for development of potential diagnostic biomarkers and new treatment targets in children and youth with PNES. The presence of psychological dissociation in PNES populations is also long established in adults but has not been well characterized in pediatric populations. Accordingly, primary

changes to the pathway include the following: 1) addition of dissociation measures to battery of psychological tests performed at intake assessment, 2) standardized psychophysiology lab assessment, 3) identification and behavioral correction of HV employing biofeedback, and 4) specialized CBT protocol of 6-10 sessions (expanded from previous pathway involving unspecified CBT methods and protocols).

2.11.1 Research Questions / Objectives:

The proposed research project continues with the above line of scientific inquiry. A period of almost three years has elapsed since the new pathway was implemented at ACH. The next logical phase of inquiry into pediatric PNES will be to evaluate the clinical outcome of treating patients prospectively using the care pathway, while also continuing to characterize the population based on newly available data. In addition to describing autonomic and dissociative characteristics in pediatric PNES, it is hypothesized that following a standardized care pathway will further enhance clinical outcomes achieved at our child epilepsy center.

Aim 1.1: Do newly diagnosed PNES patients, receiving multidisciplinary assessment and treatment under the standardized care pathway, achieve outcomes comparable to those achieved in the original 2015 study?

Aim 1.2: Which factors predict treatment responsivity to standardized care under the PNES care pathway?

Aim 2.1: What are the autonomic nervous system characteristics of children and youth newly diagnosed with PNES, as measured using psychophysiology assessment?

Aim 2.2: Do any of the above autonomic characteristics associate with PNES symptoms (duration of illness, frequency of attacks)?

Aim 2.3: Is it feasible to train patients to self-correct respiratory CO_2 levels using behavioral treatment strategies?

Aim 3: What psychological dissociation characteristics are there of children and youth newly diagnosed with PNES and do these associate with symptoms of hyperventilation?

CHAPTER 3. Empirical Papers

3.1 Psychogenic Non-Epileptic Seizures in Children–Prospective Validation of a Clinical Care Pathway & Risk Factors for Treatment Outcome

Psychogenic Non-Epileptic Seizures in Children–Prospective Validation of a Clinical Care Pathway & Risk Factors for Treatment Outcome

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Abstract

Purpose: The purpose of this study was to prospectively validate a care pathway for psychogenic non-epileptic seizures (PNES) in a pediatric setting. The pathway was developed based on a previous study of patients at our center which demonstrated positive treatment outcomes of 80% full or partial remission. Sequentially referred PNES patients in the validation cohort received care prospectively according to the pathway algorithm. It was hypothesized the validation cohort would achieve outcomes similar to that of the development cohort as a result of standardized care. *Method:* We performed a retrospective chart review of 43 children sequentially referred, assessed and treated within a specialized neurology psychology service for suspected PNES over a 5-year period. The majority of patients (n=41, 95%) met diagnostic criteria for probable, clinically established or documented PNES, according to ILAE criteria. *Results:* Ages ranged from 6 to 18 years of age at time of diagnosis, with the majority of patients being female (n=29, 67%) and adolescent (n=31, 72%). There was a high level of adherence to the care algorithm (n=34, 84%). The development and validation cohorts were similar across demographic, clinical and psychological characteristics. Standardized care resulted in high rates of full (n=27, 63%) and partial (n=12, 28%) remission, as self-reported at discharge. A 96% decrease in mean monthly frequency of total PNES events was also observed at discharge, as was a significant reduction in healthcare utilization related to PNES (74% fewer ambulance calls and 85% fewer emergency department visits). Post hoc analyses demonstrated that duration of PNES illness longer than 12 months (at

diagnosis) increased odds of not achieving full remission by discharge (OR=5.94, p=0.02). Developmental period of onset (child versus adolescent), having abnormal EEG result, previous concussion, chronic versus acute stressor, more than one PNES event type or additional functional neurological symptoms did not significantly impact treatment response. *Conclusions:* This study demonstrates, for the first time prospectively in a pediatric setting, that standardized care for PNES leads to improved clinical outcomes and reduced healthcare utilization. Delayed diagnosis and treatment of PNES longer than 12 months also appears to be associated with less favorable outcomes in children.

(*Keywords*: PNES, non-epileptic event, care pathway, treatment, epilepsy, outcomes)

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1. Introduction

Psychogenic nonepileptic seizures (PNES) are sudden changes in consciousness and behavior resembling epileptic seizures, but not associated with ictal epileptiform discharges. Complex biopsychosocial causes underlie PNES onset and events themselves are thought to be caused by emotional processing and autonomic arousal abnormalities triggering transient neurological states (Pick, Mellers, & Goldstein, 2018; Reuber & Brown, 2017; Roberts & Reuber, 2014). Unfortunately, misdiagnosis is common (up to 5-year delay in children) giving way to potential iatrogenic harm as a result of anti-seizure medications (ASM), which are unlikely to improve symptoms. In the absence of effective treatment, the episodes will also generally persist, leading to poor quality of life and escalation of medical interventions that may progress into adulthood.

PNES is considered a world healthcare problem, with insufficient knowledge and awareness about management being reported in a recent survey of epilepsy professionals across 63 countries (Hingray et al., 2018). Additional barriers to successful treatment in PNES include lack of access and poor adherence to appropriate care (Carter et al., 2018). A recent study for example, reported that while 80% of adult PNES patients attended an initial psychiatric visit post-diagnosis, only 14% attended the fourth appointment (Tolchin, Dworetzky, & Baslet, 2018). There is also limited empirical evidence for specific treatment approaches in adults (Beghi, Cornaggia, Beghi, & LaFrance, 2019) or children (Doss & Plioplys, 2018).

Although cognitive behavioral approaches alone and/or in combination with selective serotonin reuptake inhibitors (SSRIs) have shown promise in adults, these have not been empirically tested in childhood PNES. Although a multidisciplinary approach to PNES care has been recommended (Milan-Tomas, Persyko, Del Campo, Shapiro, & Farcnik, 2018), healthcare providers attempting to manage childhood PNES are faced with a lack of guidelines around how to best initiate and co-ordinate care once accurate diagnosis is achieved. Facing a perplexing and poorly understood condition, patients and their care providers are faced with difficult decisions including where to initiate treatment and when to change management approaches when events do not improve.

Clinical care pathways are a relatively recent development in the medical profession, intended to guide approaches to illness and disease. Originally arising from business quality management practices of the mid-1980's, the adoption of healthcare pathways arose from rapidly developing knowledge bases within medical sub-specialties leading to increasingly complex interventions (Rooney, 2014). The purpose of the care pathway is to focus on the steps or stages required to achieve intended outcomes, while also improving care quality through reliability, consistency and minimization of wastage (Kinsman et al., 2010). Application of the pathway involves delivering various nested processes along decision point routes within the algorithm. The pathway holds together what would otherwise be a collection of uncoordinated and potentially unnecessary procedures giving rise to

low quality outcomes and excessive cost or waste, which for PNES patients has the potential to result in longer wait-times and poorer prognoses (Sawchuk et al., 2017). Although the implementation of clinical decision tools has not yet been established in PNES, we believe that use and development of such pathways has the potential to improve efficiency, cost and treatment for children and adolescents with PNES.

The first published clinical care pathway for PNES in children was developed and implemented at Alberta Children's Hospital (ACH), based on the results of a retrospective study characterizing pediatric PNES patients and the care they received (Sawchuk & Buchhalter, 2015). This study demonstrated positive outcomes while also establishing the feasibility of a stepped-care model for PNES in a real-world clinical setting. The care algorithm was subsequently updated and implemented at our center for management of PNES diagnoses, to serve as a guideline for maximizing positive outcomes in a public healthcare system [5].

The primary aim of the current study was to evaluate the clinical outcome of managing patients prospectively under the care pathway, while also characterizing factors potentially impacting treatment response. It was hypothesized that implementing standardized care via a pathway algorithm would further enhance clinical outcomes achieved at our Comprehensive Children's Epilepsy Center (CCEC) while also reducing inappropriate healthcare utilization in child PNES.

2. Methods

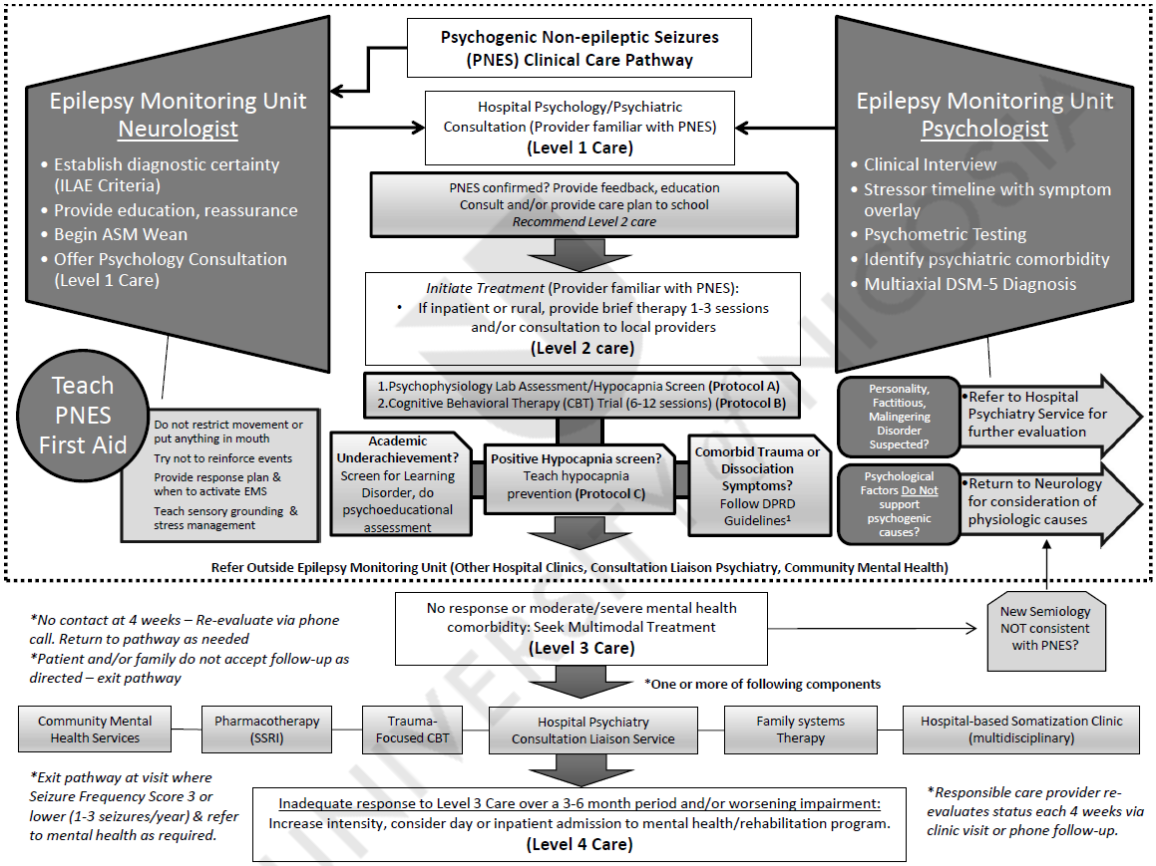
2.1 Study Population

Following approval by the local Conjoint Health Research Ethics Board, a retrospective chart review of children referred to a Neurology Psychology service for suspected PNES was performed. Patients included 67 patients seen consecutively between October 2016 and January 2019, according to the management algorithm displayed in Figure 1. For purposes of the present study, we defined PNES as paroxysmal events of a psychogenic etiology as categorized in the Diagnostic and Statistical Manual (DSM-5) under "functional attacks or seizures" [18]. A total of 19 patients were excluded who did not retain diagnosis of PNES and had exited the pathway. These cases included factitious disorder (n=4), factitious disorder by proxy (n=2), cardiac syncope (n=2), narcolepsy (n=2), other dissociative disorders (n=2), temporal lobe epilepsy (n=2), frontal lobe epilepsy (n=1), generalized epilepsy (n=1), focal epilepsy (n=1), functional diplopia (n=1) and subjective visual phenomena (n=1). An additional 5 patients were excluded who did not attend assessment and subsequently were lost to follow-up.

The remaining patients (n=43) had a final diagnosis of possible, probable, clinically established or documented PNES, as set out by International League Against Epilepsy criteria [17]. Video recordings were used to aid in correlating events with EEG during routine and long-term monitoring in the hospital lab, at discretion of the treating neurologist. Accordingly, typical events were captured during vEEG

monitoring (without ictal epileptiform discharge) in 61% of subjects included in the present study (n=26). The remaining patients (n=17, 39%) had undergone a combination of routine, ambulatory or long-term monitoring without event capture, although episodes were usually observed by an experienced clinician who was present or able to witness a video recording provided by the patient's family.

Figure 1. PNES Clinical Care Pathway



1. Hunter EC, Charlton J, David AS. Depersonalisation and derealisation: assessment and management. BMJ 2017;356: j745.

2.2 Comparison Group

The original 2015 study cohort (used to develop the pathway) was included as a comparison group and has been previously described (Sawchuk & Buchhalter,

2015). The development sample comprised 29 patients with final diagnosis of PNES seen at our center over 2007 to 2013 and had been exposed to the same treatment elements included in the current validation study, with exception of psychophysiology screening and biofeedback training to correct abnormal respiratory CO_2 levels. The purpose of these comparisons was to determine degree of homogeneity among the development and validation cohorts.

2.3 Medical Record Review

Data collection procedures were similar in both the development and validation cohorts. Paper and electronic medical records were accessed to collect data regarding patient characteristics including demographics, medication use, comorbid medical and psychiatric diagnoses, neurological investigations and psychological assessment results. Comorbid psychiatric disorders were identified based on either 1) historical diagnoses indicated on the medical chart or, 2) by new diagnosis at time of psychological assessment and based on criteria set out by the DSM-5. Information regarding PNES episodes was obtained from a standardized neurology consultation note used by neurologists within the epilepsy center program. PNES semiology characteristics, date of onset, event average duration and frequency were also documented using standardized coding practices. For frequency of PNES events, total number of events reported in the previous 30 days at diagnosis and discharge was recorded.

Data regarding stressor history was obtained from a standardized psychological assessment report and was coded by a senior clinical psychologist according to acute (less than 6 months) or chronic (6 months or more) duration. Reported stressors were also categorized according to nine broad areas by the senior clinical psychologist. Acceptance of diagnosis was operationalized as documented description of family acceptance at time of the psychology intake feedback session. Healthcare utilization, including total emergency department (ED) visits, ambulance activations (EMS) and ASM prescriptions related to PNES were obtained from a province-wide electronic database.

2.4 Measurement Tools

All patients underwent similar psychological assessment involving parent ratings and self-report measures including the Behavior Assessment System for Children, Version 2 (Reynolds & Kamphaus, 2004) and Beck Youth Inventory - Version 2 (Beck, 2001). Patients 13 years of age and older were also administered the Millon Adolescent Clinical Inventory (MACI), a self-report assessment tool anchored in contemporary personality theory. Similar to the MMPI, the MACI has been supported for a wide range of uses in adolescent populations and is established as a valid measure of diagnostic categories and maladaptive personality traits in psychiatric adolescent populations (Millon, 1993; Pinto & Grilo, 2004). All patients were encouraged to maintain logs of PNES events leading up to diagnosis but not during the treatment period. At conclusion of treatment, PNES event frequency and

remission status were coded based on self-report by parent and child at either their final clinic visit or phone follow-up at 3 months.

2.5 Care Pathway Algorithm

Management consisted of medical evaluation leading to diagnosis of non-epileptic etiology for events and included initial diagnosis and education around PNES by a neurologist as part of standard clinic practice. Once PNES was confirmed or suspected, patients were referred to a specialized psychology service for comprehensive assessment. Stepped care thereafter was primarily psychological, ranging from several weeks up to 2 years (See PNES Care Pathway, Figure 1).

The first level of care involved clinical psychology assessment and patient feedback, education regarding diagnosis and management recommendations. Progression to level 2 care was usually recommended to patients and their families unless full resolution of events had already been achieved, or patients had already declined. Level 2 care involved attending standardized cognitive behavioral therapy (CBT) therapy trial of 6-12 sessions within the neurology clinic. Where this was not feasible due to distance, individual CBT was attended at local mental health centers with ongoing consultation being provided by a senior clinic psychologist at the epilepsy center. Patients also completed a psychophysiology assessment with subsequent biofeedback training for improving respiratory CO_2 stability, typically lasting from 1-3 treatment sessions. Where this was not feasible due to distance,

local mental healthcare providers were educated regarding CO_2 sensitivity in PNES populations and given behavioral strategies to avoid hyperventilation in session. A psychoeducational assessment was also recommended at this stage if undiagnosed learning disorder was suspected to be significantly contributing to onset of PNES symptoms. Where psychological trauma (e.g. sexual or physical abuse) or dissociative symptoms were identified, primary care guidelines described by Hunter et al. (Hunter, Charlton, & David, 2017) for management of depersonalization/derealization symptoms were followed.

Level 3 care involved making outside referrals for multimodal treatment services, usually to an in-hospital psychiatry or community mental health service where patients were able to access pharmacotherapy, individual/group psychotherapy (including trauma-focused CBT) and/or family systems therapy. Pharmacotherapy usually involved an SSRI and, in some cases, abortive medications including benzodiazepine or quetiapine. In more remote communities, prescriptions were often made by local family physicians receiving consultation from a neurology clinic pharmacist. Another treatment option included referral to a specialized outpatient Somatization Clinic, consisting of comprehensive multidisciplinary assessment and treatment by hospital-based psychiatry, pediatrics and allied health professionals, including a physical exercise program. Lack of adequate response (event reduction) at Level 3 prompted efforts to have patients admitted into inpatient or day patient mental health/rehabilitation programs lasting on average 4-6 weeks (Level 4 Care). Mental health follow-up was provided thereafter as required in the community.

2.6 Statistical Analysis

Demographic and clinical characteristics of patients referred for confirmed or suspected PNES were characterized descriptively through tabulation of data and calculation of frequencies/means, for comparison with the original pathway development cohort. Comparison testing for significant differences across cohorts was accomplished employing Chi Square (χ^2) tests for categorical data (Fisher's Exact Test in case of zero cells) and t-tests for continuous data. For purposes of categorical comparison, outcome at discharge was operationally defined according to the following criteria: 1) complete absence of new PNES events (Full Remission), 2) 50% or greater reduction in frequency of PNES events (Partial Remission), 3) no reduction (or less than 50% reduction) in frequency of events (refractory to treatment) or, 4) lost to follow-up (outcome unknown). The minimum time period required for patients to be included in either full or partial remission status was 3 months. Additional paired t-tests were used to compare monthly seizure counts (means) pre-post treatment. Healthcare utilization data were analyzed descriptively in the year preceding and year following PNES diagnosis and means were compared using paired t-tests. Treatment responsivity factors were assessed by calculating odds ratios for each factor in achieving full remission versus combined partial remission/refractory outcome at time of discharge. A binary variable was generated for duration of PNES illness, using the median value (12 months) to assign patients to short (12 month or under) or longer duration (over 12 months) in the calculation

of odds ratios. P values less than 0.05 were considered significant. All data were analyzed using Stata 12 software (Stata Corp LP, College Station, TX 7745, USA).

3. Results

3.1 Sample Description

A total of 43 individuals with final diagnosis of PNES were identified. Mean age at diagnosis was 13.9 years (sd=2.7) and ranged from 6-18 years. Patients were primarily female (n=29, 67%) and adolescent (n=31, 72%). Average age at PNES onset was 12.4 years (sd=2.8) with a mean illness duration of 21.7 months (sd=46) at time of PNES diagnosis. The majority of patients were of Caucasian ancestry (n=34, 79%) with the remainder being of Middle Eastern, Indian, African or Aboriginal descent. There were no significant age differences between the original pathway development cohort and the validation sample (t=0.53, p=0.60) which were also demographically similar (See Table 1).

Table 1. Sample Demographics

	Development Cohort (n=29)	**Validation Cohort (n=43)**	**Chi² (df=1)**
	n (%)	n (%)	χ^2 *(p)*
Female	22 (76%)	29 (67%)	0.59 (0.441)
Caucasian	23 (79%)	34 (79%)	0 (1)
Age<13 years	4 (14%)	12 (28%)	2.0 0.158)

Note: Bold indicates statistically significant difference (p<.05)

Table 2. Clinical Characteristics

	Development Cohort (n=29)	**Validation Cohort (n=43)**	**Chi² (df=1)**
Comorbid Psychiatric Diagnosis[1]	*n (%)*	*n (%)*	*χ^2 (p)*
Depressive Disorder/Mood	15 (52%)	18 (42%)	0.68 (.410)
Anxiety (Any type)	6 (21%)	25 (58%)	**9.91(.002)**
Post-Traumatic Stress Disorder	0 (0%)	3 (7%)	2.11 (.268)*
Dissociative Disorder	1 (4%)	11 (26%)	**6.11(.014)**
Attention/Learning Disorder	11 (38%)	8 (19%)	3.33 (.068)
Pervasive Developmental Disorder	2 (7%)	1 (2%)	0.91 (.341)
Self-Harm/Suicidality	6 (21%)	2 (5%)	**4.51(.034)**
Comorbid Medical Condition[1]			
Epilepsy	7 (24%)	16 (37%)	1.36 (.243)
Other	20 (69%)	23 (54%)	1.73 (.189)
Anti-seizure Medication	13 (45%)	24 (56%)	0.84 (.360)
Observed/Reported Semiology[1]			
Fluctuating ictal course	15 (33%)	14 (33%)	2.65 (.104)
>3 minutes in duration	13 (28%)	32 (74%)	**6.47 (.011)**
Pelvic thrusting	3 (7%)	12 (28%)	3.23 (.072)
Asynchronous movements	7 (15%)	22 (51%)	**5.26 (.022)**
Side-to-side head/body movement	4 (9%)	9 (21%)	0.60 (.440)
Ictal crying	1 (3%)	5 (12%)	1.52 (.218)
Eyes closed	3 (7%)	30 (70%)	**24.63 (<.001)**

** Probability calculated using Fisher's Exact Test*
1 - Not mutually exclusive
Note: Bold indicates statistically significant difference (p<.05)

3.2 Clinical Characteristics

Clinical characteristics of both cohorts are listed in Table 2. Comorbid psychiatric diagnoses were common (>50%) and similar in both samples, although anxiety (58%) and dissociative disorders (26%) were more often diagnosed in the validation cohort. Self-harm and suicidality also occurred less frequently in the validation cohort (5% versus 21%). Comorbid epilepsy occurred in 37% (n=16) of the validation cohort and over half the sample (n=24, 56%) were taking an ASM at time of PNES diagnosis. Comorbid medical conditions were also common comprising over half the sample (n=23, 54%). Medical comorbidity was not statistically different among the cohorts. Semiology characteristics were similar among the cohorts with a few exceptions. These included ictal duration longer than 3 minutes (n=32, 74%), asynchronous limb movements (n=22, 51%) and ictal eye closure (n=30, 70%) which were more frequently reported in the validation cohort (See Table 2).

3.3 Psychological & Psychosocial Characteristics

Parent ratings of withdrawal behaviors were slightly more elevated in the development versus validation cohorts (25% versus 8%), which was significant (χ^2=4.02, p=0.05). There were otherwise no significant psychometric differences across cohorts. Both cohorts were characterized psychometrically by low self (<23%) and parent (<37%) reported mental health symptoms for patients, whereas personality testing among adolescents frequently suggested high levels of

depressive affect (>50%) and anxious feelings (>65%). Personality patterns were also similar among cohorts and characterized by submissive (35-53%), inhibited (23-40%), conforming (30%) and introversive (27-30%) responses to psychological distress. Peer insecurity as measured by personality testing was the most commonly elevated expressed concern (35-40%).

Table 3. Psychosocial Stressors

	Development Cohort (n=27)	**Validation Cohort (n=42)**	**Chi² (df=1)**
Stressor Chronicity	n *(%)*	*n (%)*	χ^2 *(p)*
Acute <6 months	6 (21%)	6 (14%)	0.65 (.422)
Chronic ≥6 months	21 (76%)	36 (86%)	0.52 (.471)
Stressor Type			
Peer Insecurity/Social Anxiety	12 (44%)	13 (30%)	1.14 (.287)
Family Conflict	11 (39%)	18 (42%)	0.07 (.797)
Physical/Sexual Abuse	4 (15%)	5 (12%)	0.10 (.755)
Bullying	6 (22%)	6 (14%)	0.65 (.422)
Loss/Grief	1 (4%)	2 (5%)	0.05 (.818)
Parental Separation	4 (15%)	4 (9%)	0.40 (.526)
Learning Difficulty/Disability	7 (26%)	4 (9%)	3.30 (.069)
Medical Anxiety	4 (15%)	2 (5%)	2.09 (.148)
Chronic Pain	0 (0%)	2 (5%)	1.39(.512)*
Other (Finances, Community)	2 (7%)	1 (2%)	1.00 (.318)

**Probability calculated using Fisher's Exact Test*
1 – Borderline/obsessive-compulsive personality disorder, gender dysphoria, gaming addiction, tics, disorder
Note: Bold indicates statistically significant difference (p<.05)

Psychosocial stressors were identified in the majority of patients (n=42, 98%), which was similar to the development cohort (n=27, 93%) and not statistically significant (χ^2=0.91, p=.341). Stressor characteristics are listed in Table 3. The cohorts were similar in terms of stressor duration and type, being primarily chronic (76% versus 86%) and most often related to peer insecurity (30% versus 44%) or family conflict (39% versus 42%).

Table 4. Patient Management & Outcome

	Development Cohort (n=29)	**Validation Cohort (n=43)**	**Chi² (df=3)**
Maximum Level of Care Received	*n (%)*	*n (%)*	*χ^2 (p)*
Level 1 – Psychology consultation	2 (7%)	3 (7%)	1.33 (.722)
Level 2 – EMU Psychological treatment	14 (48%)	16 (37%)	
Level 3 – Multidisciplinary outpatient	11 (38%)	22 (51%)	
Level 4 –Inpatient or Day patient	2 (7%)	2 (5%)	
Outcome at Discharge			
Remission	17 (59%)	27 (63%)	2.31 (.512)
Partial remission	6 (21%)	12 (28%)	
Refractory	2 (7%)	2 (5%)	
Unknown	4 (14%)	2 (5%)	

Note: Bold indicates statistically significant difference (p<.05)

3.4 Clinical Outcomes

Outcomes for both cohorts are listed in Table 4. Similar to the development cohort, over half of patients (n=27, 63%) achieved complete event remission by conclusion of treatment. Partial remission was achieved in an additional 28% of patients (n=12) while only 2 remained refractory to treatment with minimal to no sustained reduction in PNES events over the treatment period (5%). In both cases, refractory patients lived several hours away from the epilepsy center by car and were not able to complete CBT or psychophysiology lab treatments. Only one patient had access to local but limited mental health services.

Average monthly frequency of PNES events was 44 events at time of diagnosis (sd=65) and 1.7 events at time of discharge (sd=5), which was statistically significant in paired t-test analyses ($t=4.19$, $p<0.001$). While 8 patients with final diagnosis of PNES (no epilepsy) were receiving an ASM at time of diagnosis, none of these patients were taking an ASM by conclusion of the treatment period. Although categorical outcomes were slightly superior in the validation cohort (91% versus 80% combined full/partial remission), these differences were not statistically different on Chi^2 tests ($\chi^2=2.31$, $p=.512$). Length of time in remission status however, was much longer in the validation cohort with an average follow-up period of 13.4 months (sd=11.7), compared with only 3 months in the original development cohort study (sd=2.8) (Sawchuk & Buchhalter, 2015).

3.5 Healthcare utilization

Length of treatment on the care pathway varied from 1 to 24 months, with an average treatment duration of 7.8 months (sd=5.7). Treatment consisted of CBT for 72% of patients (n=31), psychophysiology lab assessment/treatment for an equal number (n=31, 72%) and SSRI prescription (n=21, 49%). Overall, patients attended an average of 3 psychophysiology lab sessions (sd=2) and 5 CBT sessions (sd=6) during their episode of care on the pathway. Most patients underwent at least one brain MRI or CT scan related to PNES symptoms (n=32, 74%), while only one patient received an additional scan following treatment onset.

Data regarding ED and EMS encounters in the year preceding and subsequent to the psychology assessment date were analyzed for the validation cohort. A total of 99 PNES-related ED encounters preceded diagnosis ($\bar{x}$=1.95, sd=1.65) followed by 14 encounters following diagnosis ($\bar{x}$=0.33, sd=0.17), a difference which was significant in paired t-tests (t=6.54, p<.001) and resulting in an 86% reduction. PNES-related EMS encounters totaled 42 ambulance calls preceding diagnosis ($\bar{x}$=0.98, sd=1.5) but only 14 once treatment was initiated ($\bar{x}$=0.26, sd=0.85), also significant in paired t-tests translating into a 74% reduction in EMS encounters (t=3.93, p<.001).

3.6 Treatment Responsivity

Factors associated with incomplete treatment response (i.e. less than full remission) are listed in Table 5. Comorbid epilepsy, adolescent onset, abnormal EEG, previous concussion, multiple PNES event types and additional functional neurological

symptoms were not associated with increased odds of poorer outcome. Delayed diagnosis/duration of PNES illness greater than 12 months, however, was associated with a 6 times greater likelihood of incomplete treatment response (OR=5.94, p=0.02).

Table 5. Risk Factors for Partial Remission/Refractory Treatment Response (n=41)

Risk Factor	Odds Ratio (95% Confidence Interval)	p
Previous Concussion	2.14 (0.43 – 10.23)	0.269
Comorbid Epilepsy	0.40 (0.06 – 2.06)	0.216
Multiple PNES Event Types	0.40 (0.06 – 2.06)	0.216
PNES Illness >12 months	5.94 (1.19 – 32.67)	**0.02**
Additional Functional Symptoms	0.68 (0.12 – 3.26)	0.588
Abnormal EEG	0.52 (0.12 – 2.31)	0.326
Adolescent Onset	1.44 (0.33 – 6.50)	0.585

Note: Bold indicates statistical significance (p<.05)

4. Discussion

4.1 Care Pathway Validation

Clinical care pathways are intended to refine available research and evidence for clinicians, providing faster, more efficient and predictable means of reaching a desired health outcome (Rooney, 2014). Kinsman et al (Kinsman et al., 2010) define five specific criteria required for a clinical care pathway: 1) structured multidisciplinary plan of care, 2) translation into existing guidelines and healthcare structures, 3) detailed steps taken during a course of treatment or decision

guideline, 4) timeframes and/or criteria-based progression set out on the pathway, and 5) standardized care for a specific procedure or episode of care for each specific patient group. One challenge to implementing care pathways is making them general enough to be applied broadly, while retaining adequate specificity for the relevant population within a pragmatic healthcare system. Another challenge in the case of childhood PNES is a lack of high-quality studies to help inform which interventions might lead to superior results. While these are lacking, a recent global review by an expert and stakeholder consensus board concluded that PNES management for children and adults should be multidisciplinary, including CBT as front-line treatment and pharmacotherapy for comorbid anxiety and depression (Gasparini et al., 2019).

The primary significance of our results lies in the fact we were able to prospectively validate use of a clinical care pathway algorithm meeting the above criteria, while achieving a high level of treatment adherence (84%) and positive combined outcomes in 39 out of 43 patients (91%) among a pediatric PNES population. The pathway included treatment components with at least some level of evidence among children or adult PNES, including patient education (LaFrance, Reuber, & Goldstein, 2013), CBT (Goldstein et al., 2010; Goldstein et al., 2015; LaFrance et al., 2009), group therapy (Barry et al., 2008), family therapy (Kozlowska, Chudleigh, Elliott, & Landini, 2016), SSRIs (LaFrance et al., 2014), biofeedback (Kozlowska et al., 2018; Kozlowska, Palmer, Brown, McLean, et al., 2015; Kozlowska, Rampersad, et al., 2017), trauma-based CBT (Myers et al., 2019; Myers et al., 2017) and

multidisciplinary care (Chinta et al., 2008; Yadav, Agarwal, & Park, 2015) including inpatient treatment programs for childhood PNES (Kozlowska et al., 2018). The secondary significance is that we were able to demonstrate successful implementation of a stepped-care approach in a real-world, publicly funded healthcare system. In this regard, our findings demonstrate a small number of patients (7%) achieved positive outcomes as the result of joint diagnosis and patient education by a neurologist and psychologist in the EMU (Level 1 Care). This was followed by favorable response in another third of patients (n=16, 37%) receiving specialized psychology treatment within the EMU combining standardized CBT and psychophysiology assessment/training protocols (Level 2 Care). Not surprisingly, half of patients (n=22, 51%) required multi-modal care beyond our epilepsy center, involving addition of psychiatric medication and outside mental health care providers for group, family and school-based therapies (Level 3 Care). Finally, a small number of patients (n=2, 5%) required intensive mental health or rehabilitation treatment admissions (Level 4 Care), which in both cases, resolved with complete remission of their PNES events. Several rural patients were also seen at Level 3 Care who completed CBT with local mental health care providers (n=7, 16%). In these cases, therapists were supported via consultation with the EMU psychologist regarding PNES treatment and an added SSRI. Outcomes in these cases were similarly positive, with 4 rural patients achieving partial remission, 2 full remission and one remaining refractory, largely as a result of lacking access to mental health admission.

The development cohort was chosen as a comparison group in order to ensure homogeneity among the samples for supporting validity of demonstrated outcomes. In this case, the samples appeared quite similar in terms of demographics, medical/psychiatric comorbidity and psychosocial history. A small number of statistically significant differences were observed, including higher incidence of anxiety and dissociative disorders in the validation cohort but less suicidality. The validation cohort also had higher incidence of event duration above 3 minutes, asynchronous movements and ictal eye closure. While these findings might suggest some increased severity of PNES events in the validation cohort, we suspect that these differences likely resulted from random variability given small sample sizes and the fact our validation cohort was 48% larger (an additional 14 patients) than the development cohort.

Another interesting finding in our study was the relatively high number of patients referred for pediatric PNES who received care according to the pathway algorithm but were ultimately diagnosed with causes other than PNES (n=19/62, 31%). Here, the largest diagnostic group related to factitious symptoms (6/19, 32%) followed by true epilepsy (5/19, 26%). Upon reviewing specific cases, we were able to determine that diagnosis of factitious disorder required lengthy periods of observation and re-assessment during pathway care, typically lasting several months. This finding underscores the necessity for clinicians working in the EMU to be familiar with warning signs and management strategies when factitious disorder

or factitious by proxy is suspected (Bursch, Emerson, & Sanders, 2019; Taskforce, 2017). Similarly, patients ultimately diagnosed with a sole epileptogenic cause for their events typically underwent care on the pathway for several weeks, during which a combination of factors triggered new long-term vEEG monitoring at our center. These factors included: 1) lack of expected response to treatment on the pathway, 2) psychological/psychophysiology assessment results inconsistent with PNES (lack of objective anxiety markers) and 3) new semiology features suggesting epilepsy (e.g. nocturnal onset, incontinence). In most cases, additional scrutiny of captured events, which previously had not correlated with discharges on surface-EEG, were found to originate in deep frontal or temporal cortical structures. These findings offer a compelling argument for maintaining epilepsy care in patients newly diagnosed with PNES, as well as the potential benefit of managing PNES care according to a care algorithm. A stepped-care approach to pediatric PNES in our study thus appeared to heighten diagnostic accuracy while also ensuring maximum delivery of the appropriate resources for the right patients at the right time. Future study may lead to development of additional algorithm parameters that provide direction in clinical decision making about when to return PNES patients for additional or repeat vEEG monitoring.

4.2 Pathway Outcomes

Our results demonstrate, for the first time in a prospective pediatric PNES study, that positive outcomes are achieved following a standardized stepped-care model.

Our combined outcome of 91% full or partial remission meets or exceeds demonstrated outcomes in previous retrospective treatment studies showing 60% to 80% improvement in childhood PNES over several months (Chinta et al., 2008; Irwin et al., 2000; Reilly et al., 2013; Sawchuk & Buchhalter, 2015; Wyllie et al., 1999). Our study also demonstrated relatively stable positive outcomes, given the average follow-up period was over 13 months. This is an important factor given PNES remission status in children is thought to vary with environmental and seasonal changes (e.g. school routines, family holidays)(Luthy, Moss, Torok, McLeod, & Wilson, 2018).

Our results mirror those of a previous outcome study involving 57 youth with conversion disorders, many of them having PNES and treated through an inpatient multimodal treatment program (Kozlowska, Palmer, Brown, McLean, et al., 2015). Here, patients underwent a number of similar interventions included in our care algorithm but at a uniformly intensive level of care involving pharmacotherapy, cognitive-behavior therapy, sleep and biofeedback interventions, family therapy and a daily exercise program. Outcomes in this retrospective study were positive: 61% full recovery (n=35), 17.5% partial recovery (n=10), 2% refractory (n=2), 2% lost follow-up (n=2) and 16% “transformation” to another chronic illness (n=9). By contrast, our results demonstrated similar outcomes involving a variable intensity of care that in most cases did not involve significant costs associated with inpatient admission.

Our results also support the inclusion of a number of treatment recommendations in the case of child PNES. A recent literature review recommended a multidisciplinary approach to PNES care in children, including involvement of a neurologist and mental health care team (Doss & Plioplys, 2018). The development of a response plan for parents and teachers of children with PNES has also been recommended (Caplan, Doss, Plioplys, & Jones, 2017) and was also included in our care algorithm at time of diagnosis and psychoeducation (Level 1). Our study also appears to support previously described criteria for intensive mental health admissions among childhood PNES patients, including: 1) daily episodes at home and school, 2) PNES longer than one year, 3) school absence greater than 3 months, 4) severe comorbid mental health conditions, including suicidal thoughts or self-harm and, 5) when abuse is present or when home situation is contributing primarily as the PNES trigger (Caplan et al., 2017). Future development of care algorithms for PNES may provide further addition and validation of factors determining need for increased intensity of care.

4.3 Treatment Responsivity

In our study, having duration of PNES illness over one year was associated with six time's greater likelihood of not achieving full remission at conclusion of treatment. These results are consistent with previous studies, including Yadav et al. who studied 90 child PNES patients over a 2 year treatment period and found

unfavorable outcomes associated with prolonged duration of symptoms (Yadav et al., 2015). In another study of 60 children treated through a mind-body rehabilitation program, Kozlowska et al. reported that pre-treatment PNES illness duration longer than three months also resulted in worse outcomes (Kozlowska, Chudleigh, et al., 2017). Anecdotally, the authors commented that all treatment non-responders in their study (n=4) had illness durations exceeding 12 months, which was also true for our non-responders (n=2). Also, while odds ratios could not be calculated in our study for acute versus chronic psychosocial stressors, we observed that all patients with acute stressors (n=6) had full remission at discharge, compared with only 59% (n=20) of 34 patients reporting a chronic stressor at diagnosis. Another important finding in our study is that the only two refractory cases were rural patients with limited access to either our center or local mental health resources, which likely contributed to both duration of their illness at PNES diagnosis and subsequent poor outcome. The above responsivity factors deserve further study employing larger samples, including with adults who consistently demonstrate worse outcomes compared with children (Ali A. Asadi-Pooya et al., 2019; Reilly et al., 2013), possibly as a result of delayed diagnosis and treatment.

4.4 Limitations

We acknowledge several factors in our study that limited the quality of evidence for our intervention. First, we did not include a comparison group with random assignment of participants to alternative treatments or care pathway algorithms.

Doing so would have helped establish superiority of a specific sequence or combination of interventions. Random assignment would also have controlled for unknown variables contributing to outcome, including spontaneous remissions or improvements as a result of non-treatment factors (e.g. change in environmental stressors or seasonal patterns). Another limitation potentially impacting interpretation of our results is that while a high level of diagnostic certainty was achieved in the validation cohort (61% documented, with typical event capture during vEEG), 39% of the sample did not have PNES events confirmed in this manner. This raises the possibility that non-PNES causes may have confounded outcome results to some degree, either by artificially contributing to lack of treatment response (if unknown conditions were not being treated) or increased positive outcome as a result of factors not associated with pathway care (e.g. other treatments, spontaneous resolution).

Our results are also limited in generalizability by the manner in which outcome was determined, which in our case extended to self-report remission status, monthly frequency of events and healthcare utilization. Future studies should strive to include additional measures of patient functioning, including quality of life and adaptive measures. Additional information on outcomes such as school days/parent workdays missed would also help characterize positive benefits to patients and their families as a result of participating in treatment.

Finally, while we found a significant contribution of duration of illness on treatment responsivity, we may have been unable to detect meaningful contributions by other factors as a result of low statistical power. Future, larger studies of childhood PNES populations might further help to determine the relevant clinical and historical factors impacting choice of treatment and expected treatment response.

5. Conclusions

Our study prospectively validated a clinical care pathway resulting in high rates of positive outcome through implementation of a standardized care model combining a modest scale of psychology service specialization with other community mental health resources available in most urban areas. A substantial reduction in unnecessary ASM use and healthcare utilization was also achieved. Our results underscore the importance of early detection and diagnosis of PNES in the pediatric EMU, as longer duration of PNES illness appears to have detrimental effect on odds of full remission. Implementation of these and other clinical decision tools will help establish the development of effective healthcare services that improve efficiency, cost and treatment for children and adolescents with PNES while also averting the severe burden of this disorder on children, their families and society.

Conflict of Interest/Disclosure

1. Tyson Sawchuk: No disclosures or conflicts of interest
2. Jeffrey Buchhalter: Has received compensation as a consultant for UCB, the Epilepsy Study Consortium, Eisai Inc, Upsher-Smith Laboratories and Lundbeck.
3. Birgit Senft: No disclosures or conflicts of interest

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3.2 Psychogenic Non-Epileptic Seizures in Children – Psychophysiology & Dissociative Characteristics

Psychogenic Non-Epileptic Seizures in Children – Psychophysiology & Dissociative Characteristics

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Summary

Objective: The purpose of this study was to determine psychophysiology and dissociative characteristics of psychogenic non-epileptic seizures (PNES) in a clinical pediatric setting. We additionally sought to determine the incidence of abnormal autonomic features at baseline and their relationship with duration/severity of PNES illness in youth. We also report on the success of teaching patients to successfully improve respiratory carbon dioxide (CO_2) levels with the aid of biofeedback training. *Methods:* A retrospective chart review was conducted over a 5-year period that included children meeting criteria for probable, clinically established or documented PNES as set out by the International League Against Epilepsy (ILAE) criteria. Of these, 33 patients (81%) underwent psychophysiology assessment as part of standardized care and were selected for study inclusion. *Results:* Ages ranged from 10 to 17 years inclusive (70% female). The majority of patients were found to have some form of autonomic decompensation at baseline (82%), lack of autonomic recovery from a cognitive stressor (58%) and diagnosis of behavioral hypocapnia (85%). Presence of any type of baseline decompensation (χ^2=4.76, p=0.029) or inhibition of normal skin conductance response to laboratory stressor was associated with longer duration of PNES illness (χ^2=4.47, p=0.035). Elevated heart rate (>90%) at baseline was also associated with higher frequency of PNES events in the month preceding diagnosis (χ^2=4.24, p=0.039). Overall high levels of dissociation and hyperventilation symptoms were self-reported by adolescent patients (n=19) and were positively correlated (Kendall's tau=0.35, p=0.04). The majority of patients (89%) were taught to correct respiratory CO_2 levels during a single biofeedback training session. *Conclusions:* Child PNES populations appear to be characterized by psychophysiology markers including baseline ANS decompensation, hyperventilation upon provocation, poor recovery from cognitive stressor and substantial co-morbidity with suppression of the normal stress response. We also conclude that hyperventilation

behaviors can be effectively targeted for treatment, potentially resulting in positive outcomes for this difficult to treat population.

(*Keywords*: PNES, non-epileptic, dissociative seizure, psychophysiology, dissociation, children)

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Table of Acronyms:

PNES	Psychogenic non-epileptic seizures
CO2	Carbon dioxide
ILAE	International League Against Epilepsy
EEG	Electroencephalogram
EMU	Epilepsy monitoring unit
DSM-5	Diagnostic & statistical manual 5th edition
SCL	Skin conductance level
ETCO2	End tidal carbon dioxide
A-DES	Adolescent dissociative experiences scale
ANS	Autonomic nervous system
FND	Functional neurological disorder
HV	Hyperventilation
GAF	Global assessment functioning

Key Points

- Among 33 patients with pediatric PNES, baseline autonomic decompensation was observed in 82% of cases, while the majority (85%) met criteria for behavioral hypocapnia ($ETCO_2$<30mmHg) at baseline assessment.
- Suppression of the normal psychophysiology stress response was observed in 23% of cases, while another 58% of patients demonstrated lack of autonomic recovery following administration and resolution of a cognitive stressor.
- Baseline autonomic decompensation or inhibition of normal stress responses was associated with longer duration of PNES illness, while elevated heart rate at baseline was associated with higher frequency of PNES events in the preceding month.
- Overall high levels of dissociation were self-reported by adolescent patients (n=19) and were positively associated with severity of self-reported hyperventilation symptoms.
- The majority of patients (89%) were taught to normalize their respiratory CO_2 levels by the end of a single biofeedback training session.

1. Introduction

Psychogenic nonepileptic seizures (PNES) are abrupt changes in awareness and behavior that resemble epileptic seizures but are not caused by ictal epileptiform discharges. Although the cause of PNES is not well understood, the events themselves appear to be triggered by heightened emotional processing and autonomic arousal abnormalities (Kozlowska, Chudleigh, et al., 2017; Pick et al., 2018; Reuber & Brown, 2017) leading to transient neurological states during which normal brain functions are altered (Brown & Reuber, 2016; Pick et al., 2019; Roberts & Reuber, 2014). Far from being a rare phenomenon, PNES comprises 20-30% of pediatric referrals for refractory seizures (Doss & Plioplys, 2018). Despite this, very little is known about how to effectively manage PNES in children and youth. Further exacerbating the problem, almost all empirical studies of PNES are based on adult patients, yielding results and conclusions that may not be generalizable to managing this disabling condition in child sufferers.

There has been a recent proliferation of published studies describing emotional and autonomic nervous system (ANS) correlates of PNES(Pick et al., 2018). Studies thus far have converged upon evidence of autonomic hyperarousal including increased cortisol levels (Bakvis et al., 2011), increased tonic skin conductance levels (SCL)(Pick, Mellers, & Goldstein, 2016b) and increased heart rate(Kozlowska, Palmer, Brown, McLean, et al., 2015)/decreased heart rate variability (HRV)(Bakvis, Roelofs, et al., 2009) among adult PNES patients. Additionally, several studies suggest that PNES episodes are preceded by increased sympathetic output and followed by increased parasympathetic output during and/or following an event(Jeppesen et al., 2016; Ponnusamy, Marques, & Reuber, 2011; Reinsberger et al., 2012; van der Kruijs et al., 2016). Although child PNES studies are limited in number, a recent study of psychophysiology characteristics in youth with functional neurological disorders (FND) demonstrated patients with PNES had higher baseline heart rates than normal controls (Kozlowska, Palmer, Brown, McLean, et al., 2015).

Hyperventilation (HV) has been associated with PNES (Hendrickson et al., 2014) with several studies suggesting a potential causal role for HV in triggering PNES events in children (Barker, Ng, Rittey, Kandler, & Mordekar, 2012; Deka et al., 2007; Kozlowska, Rampersad, et al., 2017; Krishnakumar et al., 2006). Defined as breathing behaviours in excess of what is needed for metabolic demands, HV leads to a variety of neurophysiological changes in the nervous system both centrally and peripherally, which have been argued to increase the child brain's susceptibility to triggering a PNES event, possibly as result of cerebrovascular immaturity and or excessive vasoconstrictor response (North et al., 1990). Kozlowska and colleagues (Kozlowska, Rampersad, et al., 2017) measured respiratory functions in 60 children and adolescents with PNES, while also including healthy controls (n=17), psychiatric controls (n=25) and epilepsy controls (n=8) as comparators . HV was measured by administering a protocol involving induction of CO_2 decreases through rapid breathing over 5-minute periods as part of their video-EEG procedure in the epilepsy monitoring unit (EMU). The authors reported that PNES patients had higher respiration rates (25 versus 20 breaths/minute) and heart rates (91 bpm versus healthy controls mean bpm of 77) at baseline. Baseline percutaneous CO_2 (PCO_2) at baseline was 37mmHg in the PNES group versus 41mmHg in the combined control group. The trough (lowest) values in the PNES were also much more pronounced at 24mmHg in the PNES group versus 26mmHg in the controls, a finding that was statistically significant. Although rate of the CO_2 decompensation during HV challenge was not significantly different among groups, recovery time was much more delayed, being 1.9mmHg/minute in the PNES group versus 3.2mmHg in the control group. The post-assessment mean PCO_2 values were also significantly lower in the PNES group (36mmHg compared with 42mmHg in controls). The authors additionally reported symptoms of cerebral hypoxia during the HV protocol challenge that were five times higher in the PNES group than controls (Kozlowska, Rampersad, et al., 2017).

Psychological dissociation has been implicated in the production of transient abnormal neural states in PNES that may be the result of increasing or chronic autonomic hyperarousal (Brown & Reuber, 2016; Pick et al., 2019; Roberts & Reuber, 2014). Adult PNES patients share many common demographic and clinical features with patients having dissociative disorders, including trauma experiences, increased hypnotizability and symptoms of amnesia, fugue or depersonalization (Ito, Adachi, Okazaki, Kato, & Onuma, 2009). Other studies have suggested high levels of dissociation among PNES groups. Bowmen and colleagues (1999) for example, found that 91% of 45 adult PNES patients met criteria for a dissociative disorder. Despite significant investigation of dissociation in adult PNES populations, we are not aware of any objective measurement of this construct in pediatric PNES populations.

The above studies point to autonomic abnormalities which have been largely unexplored as potential treatment targets in PNES. Interestingly, a number of adult studies have suggested there is a pronounced discrepancy between PNES patients' subjective awareness of their autonomic status and objective psychophysiological measurement (Pick et al., 2018; Roberts & Reuber, 2014; Spinhoven, Onstein, Sterk, & Le Haen-Versteijnen, 1993). These results support the role of PNES as an adaptive mechanism, which helps to resolve an untenable physiological state brought about by increasing autonomic hyperarousal in the absence of subjective awareness (Kozlowska, 2017; Kozlowska, Chudleigh, et al., 2017; Kozlowska, Walker, et al., 2015; Pick, Mellers, & Goldstein, 2016a; Pick et al., 2016b). It follows that improved interoceptive awareness of autonomic arousal (and the ability to mitigate hyperarousal) may help patients to gradually gain control over PNES events (Kozlowska, Palmer, Brown, McLean, et al., 2015; Pick et al., 2018). Interventions along these lines have shown promise with conditions similar to PNES (Schaefer, Egloff, Gerlach, & Witthoft, 2014) and the feasibility of training adults to improve CO_2 homeostasis has already been successfully demonstrated in clinical and non-clinical populations (Szulczewski, 2019a, 2019b, 2019c; Tolin, McGrath, Hale, Weiner, & Gueorguieva, 2017).

While studies describing autonomic features of PNES have opened the way for development of potential diagnostic biomarkers, the exact role of autonomic arousal in pediatric PNES remains unclear (Reinsberger et al., 2015). It also remains to be established that autonomic abnormalities can be successfully targeted for treatment in child PNES. Accordingly, the objectives of this study were to determine: 1) the incidence of abnormal autonomic values at baseline in youth diagnosed with PNES, 2) the incidence of abnormal stress responses (to a standardized cognitive stressor), 3) the relationship between psychophysiology responses to stress and severity of PNES symptoms, 4) the relationship between self-reported hyperventilation and dissociation symptoms and finally, 5) whether patients demonstrating abnormal CO_2 sensitivity could be feasibly taught to correct respiratory CO_2 levels with the aid of biofeedback training.

2. Methods

2.1 Study Population

Following approval by the local Conjoint Health Research Ethics Board, a retrospective chart review of children referred to a Neurology Clinical Psychology service for suspected PNES was performed. Patients included 67 consecutive referrals seen between October 2016 and January 2019. All patients had undergone a full psychological assessment consisting of clinical interview and standardized psychometric testing previously described at our center (Sawchuk & Buchhalter, 2015). A total of 19 patients who did not retain diagnosis of PNES were excluded. An additional 7 patients were excluded due to lost follow-up. Among the remaining 41 patients, 4 patients did not undergo lab assessment given early treatment response to psychoeducation and/or a limited number of individual therapy sessions with a clinical psychologist embedded within the EMU. Another 4 patients were directly discharged to their home communities several hundred kilometers away and were unable to return for lab assessment.

A total of 33 patients (81%) were retained for study inclusion. All patients had final diagnosis of probable, clinically established or documented PNES, as set out by International League Against Epilepsy criteria (LaFrance, Baker, Duncan, Goldstein, & Reuber, 2012). Video recordings were used to aid in correlating events with EEG during routine and long-term monitoring in the hospital lab, at discretion of the treating neurologist. Accordingly, typical events were captured during vEEG monitoring (without ictal epileptiform discharge) in 55% of subjects included in the present study (n=18). The remaining patients (n=15, 45%) had undergone a combination of routine, ambulatory or long-term monitoring without event capture. In all cases however, typical episodes were directly observed by an experienced clinician who was present or able to witness a video recording provided by the patient's family.

2.2 Medical Record Review

Medical records were reviewed for demographic information, clinical characteristics at PNES diagnosis (medications, medical and psychological investigations, PNES semiology, comorbid diagnoses) and psychophysiology characteristics at diagnosis obtained during standardized laboratory assessment. Date of onset for the first PNES event was derived from a standardized neurology consultation note, as were event semiology and characteristics, average event duration and frequency (in the preceding month). Comorbid medical and psychiatric disorders were identified based on either 1) historical diagnoses indicated on the medical chart or 2) by new diagnosis at time of psychological assessment based on criteria set out by the DSM-V. Data regarding stressor history was obtained from a standardized psychological assessment report and was coded by a senior clinical psychologist according to acute or chronic duration, being defined based on a cutoff period of 6 months, as self-reported by patient and/or family.

2.3 Psychophysiology Measurement

All psychophysiology measurements were recorded using a Biograph Infiniti Flexcomp software/hardware system (Thought Technology Co.). Physiological data included peripheral index finger temperature (Fahrenheit), respiration rate (per minute) via pneumography strap across the abdomen, finger electrodermograph (SCL in micro Siemens, μS) measured via two finger electrodes (constant voltage of 0.5 Volts, sampled at rate of 256 samples/second, smoothed with [first order, low pass] filter at 0.2 Hz), heart rate (beats per minute) and heart rate variability (low frequency percentage, calculated via fast-Fourier transformations) measured via index finger blood volume pulse sensor. Criteria for designating psychophysiology values as low or high arousal were set according to previously established criteria in the psychophysiology literature (Fleming et al., 2011; Schwartz & Andrasik, 2003). Specifically, high arousal was defined by hand temperature below 90 degrees Fahrenheit, SCL above 5 μS and heart rate above 90th percentile. In order to ensure time of day did not covary with baseline hand temperature measurements (due to circadian variation), mean temperatures for morning (85.35 degrees) and afternoon (85.53 degrees) were compared employing a t-test, which was not significant (p=0.94).

Subjects also underwent end tidal carbon dioxide ($ETCO_2$) and oxygen saturation monitoring via handheld capnograph/pulse oximeter (Nellcor Puritan Bennett NPB-75) and single use nasal cannula. For the purposes of our study, hypocapnia was operationally defined as any mean CO_2 value below 30 millimeters of mercury (mmHg) during assessment. Assessment data were documented in a standardized psychophysiology assessment report placed on the patient's health record, which was used for clinical purposes including the provision of feedback to patients and their families.

2.4 Psychophysiology Assessment Protocol

Medical charts were reviewed for results of standardized psychophysiology lab assessments, which were usually conducted 1-2 weeks following PNES diagnosis. The assessment protocol has been

previously described (Benore et al., 2014). The protocol consisted of 5 behavioral conditions, including baseline autonomic values at rest (5 minutes) followed by a period of self-guided relaxation (5 minutes). Next, patients were instructed to follow a breathing pacer, displayed on a computer screen and set at rate of 6 breaths per minute (2 minutes). After being allowed to recover to baseline values, patients were administered a standardized laboratory stressor (2 minutes). This involved being instructed to count backwards aloud in serial 7's from 986, "as fast as you can". During the task, patients were continually told to increase speed of verbal responses by a lab assistant who did not offer assistance. The stressor was followed by a recovery period during which patients were instructed the math task was complete and to "relax as deeply as you can". The lab assistant then left the room (5 minutes).

Psychophysiology variables included baseline mean values for all domains, elevated heart rate above 90th percentile and decompensation on any domain at baseline. Stress response variables included lack of SCL reactivity to laboratory stressor (threshold set at 5 μS) or when normal stress response was achieved, the absence of recovery to baseline (below 5 μS). Hyperventilation variables included a standardized hyperventilation symptom rating scale, established as having high sensitivity (91%) and specificity (95%) for clinical diagnosis of hyperventilation syndrome (van Dixhoorn & Duivenvoorden, 1985). Additional variables included end-tidal carbon dioxide (CO_2) measurements taken during the assessment and clinical diagnosis of behavioral hypocapnia made during the lab assessment. Biofeedback training outcomes were examined for evidence of increased hypocapnia control/avoidance and coded according to ability of patients to correct $ETCO_2$ values to a value of 30mmHg or more by the end of a single biofeedback training session.

2.4 Dissociation Data

Dissociation was measured via self-report for children 12-18 years of age, using the Adolescent Dissociative Experiences Scale (A-DES)(Armstrong, Putnam, Carlson, Libero, & Smith, 1997). The A-

DES is a 30 item self-report measure of dissociative experiences modeled after the well-established Dissociative Experiences Scale (DES) for adults (Armstrong et al., 1997). Studies of adult PNES have demonstrated high scores on the DES, similar to levels obtained by patients with dissociative disorders [8-10]. Previous studies have demonstrated that the A-DES is a reliable and valid measure of pathological dissociation in adolescents [7]. Item content in the A-DES surveys depersonalization, derealization, dissociative amnesia, absorption, imaginative involvement, confusion between reality/fantasy and identity change. Overall mean scores range from 0-10, with a mean score of 4 or above signifying pathological dissociation [11].

The A-DES has good internal reliability and validity [12], approximating the DES score divided by 10. Adolescents with Dissociative Identity Disorder typically score between 4 and 7. Internal consistency of the A-DES is high with a demonstrated Cronbach's alpha of .94 (Farrington et al. 2001). Total score on the A-DES is reliable (test–retest) with good internal consistency and concurrent validity with other measures of trait dissociation [7]. The A-DES has also demonstrated good discriminant validity, accurately differentiating among abused and non-abused youth as well adolescents with and without dissociative disorders [13, 14]. A total of 20 adolescent patients had completed the A-DES at time of initial psychological assessment as part of standard medical care for PNES.

2.5 Statistical analysis

Descriptive statistics including percentages and cross-tabulations were used to generate data tables and psychophysiology profiles. One-way analysis of variance and Bonferroni post-hoc tests were used to determine significant differences in mean respiratory CO_2 levels across lab assessment. Two binary outcome variables were generated from self-reported PNES history: 1) duration of illness (time in months since onset) and 2) event frequency (per month). The relationship between psychophysiology baseline values and autonomic response patterns, in relation to the outcome variables, was assessed utilizing Chi Square (χ^2) analyses. Post-hoc contingency coefficients and

effect sizes were calculated to determine the strength of significant differences. The relationship between self-report measures of hyperventilation and dissociation symptoms was assessed employing Kendall's Tau correlation. In order to determine role of potential confounding among psychophysiology measurements as a result of concurrent medication use (SSRI, AED), means were compared across modalities (respiration, $ETCO_2$, hand temperature, SCL, heart rate & HRV) employing t-tests. Probability values of less than 0.05 were considered significant. Data were analyzed using Stata 12 software (Stata Corp LP, College Station, TX 7745, USA).

3. Results

3.1 Sample Description

A total of 33 individuals with final diagnosis of PNES who had undergone psychophysiology lab assessment were identified, the majority of which were 13 years of age or older (n=26, 79%) and female (n=23, 70%). Mean age of the sample was 14.4 years (sd=1.9) with a range of 10 to 17 years inclusive. About one-third of the sample included patients diagnosed with epilepsy and PNES (n=10, 30%). Diagnostic certainty of PNES in the sample was high as over half (55%) had undergone video-EEG with capture of their typical event without epileptiform correlation. A comorbid psychiatric diagnosis was present in the majority of cases (n=32, 97%). Psychosocial stressors, identified in all but one case during psychological clinical interview, were chronic (>6 months duration) in all but 2 cases (n=30, 94%). Almost half the sample (46%) had an additional functional symptom other than PNES (e.g. functional weakness) and about a third (30%) had presented with more than one type of PNES event according to semiology descriptions. Clinical characteristics are listed in Table 1.

3.2 *Psychophysiology Characteristics*

Baseline psychophysiology measurements are displayed in Table 2. Concurrent SSRI or AED use did not significantly impact mean psychophysiology values (all t-test comparisons p>0.05). Overall,

borderline low respiratory CO_2, low hand temperature and high SCL were observed, with hand temperature being most decompensated (below 90 degrees Fahrenheit).

Table 1. Clinical Characteristics (total n=33)

Clinical Features	**% (n)**
Epilepsy	
Comorbid Epilepsy	30% (10/33)
Level 4 Diagnostic Certainty (ILAE Criteria) [1]	55% (18/33)
Current Antiepileptic Medication	43% (13/33)
Psychiatric	
Chronic versus Acute Stressor? [2]	94% (30/32)
Comorbid Anxiety Disorder	67% (22/33)
Comorbid Depressive Disorder	42% (14/33)
Comorbid Post-traumatic stress disorder	6% (2/33)
Additional Functional Symptoms	46% (15/33)
More than one PNES event type	30% (10/33)
Current Selective Serotonin Reuptake Inhibitor	21% (7/33)

1. *"Documented" requires capture of event in question without epileptiform correlate*
2. *Operationally defined as psychosocial stressor reported by patient/family as occurring longer than 6 months preceding diagnosis*

Table 2. Baseline Psychophysiology Values

Modality	**Mean (sd)**
Respiration Rate (Per Minute)	14.5 (1.9)
End Tidal CO_2 (mmHg)	34.2 (3.5)
Hand Temperature (Fahrenheit)	85.3 (6.1)
Skin Conductance (micros Siemens, µS)	4.7 (4.1)
Heart Rate (beats per minute)	84.5 (6.1)
Heart Rate Variability (Low Frequency %)	0.6 (0.2)

Psychophysiology assessment was present in most patients (82%). Inhibition of SCL in reaction to the stressor (defined as lack of increase above 5 micro Siemens), occurred in a quarter of the sample (7/31, 23%). Over half the sample (18/31, 58%) demonstrated normal SCL reactivity in SCL but did not return to baseline levels following a 5-minute recovery period. Elevated heart rates (>90th percentile (Fleming et al., 2011) at baseline occurred in 18% of the sample (6/33).

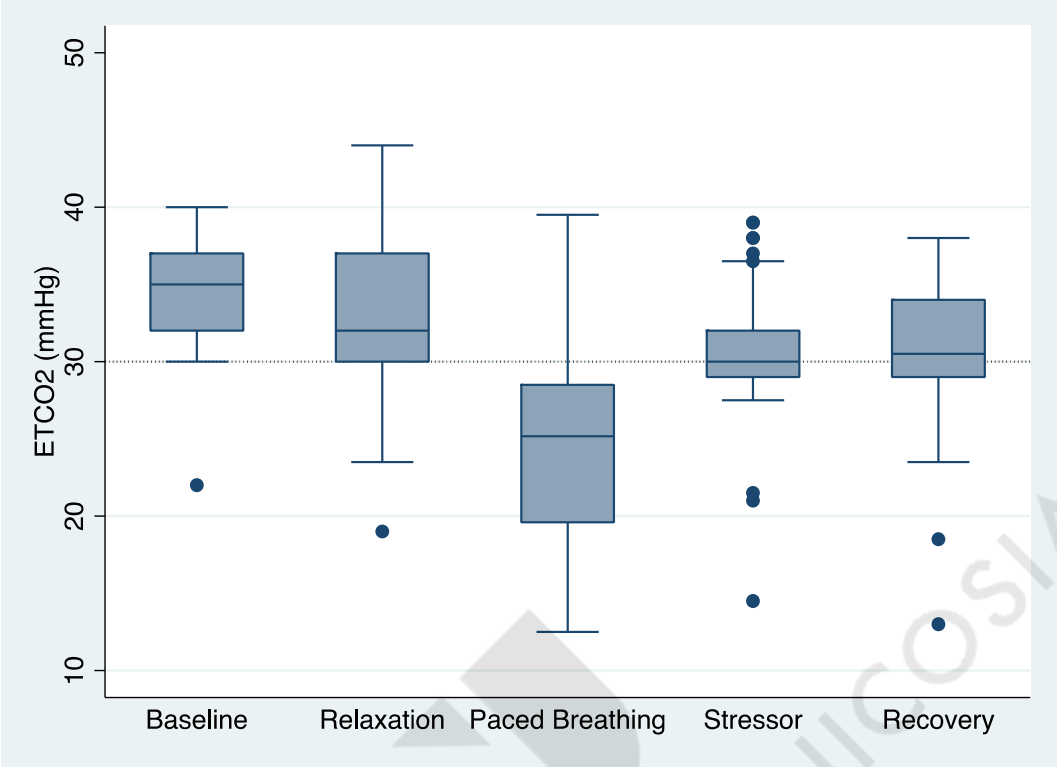
Table 3. Psychophysiology Features

	% (n)
Autonomic Features	
Decompensation at Baseline	82% (27/33)
Stress Response Inhibition	23% (7/31)
Lack of Recovery following stressor	58% (18/31)
Heart rate >90th percentile (Fleming et al, 2011)	18% (6/33)
Hyperventilation	
Nijmegen Score >20 (Severe Hyperventilation)	67% (20/30)
Hypocapnia Diagnosed	85% (28/33)
PNES Prodrome Provoked[1]	55% (18/33)
Taught to Normalize $ETCO_2$ Levels	89% (25/28)

1. *Based on patient self-report during assessment. In most cases these were dizziness/light-headedness, tingling in extremities (paresthesia) or central frontalis headache. In two cases, the actual PNES events had occurred.*

HV symptoms were commonly reported, with 20 patients (67%) obtaining self-report scores in the high severity range. The majority of patients (28/33, 85%) were also clinically diagnosed with behavioral hypocapnia, supported by objective $ETCO_2$ levels below 30mmHg. Mean respiratory CO_2 levels across lab assessment conditions are displayed in Figure 1.

Figure 1. Mean Respiratory CO_2 Levels (n=33)



While most patients demonstrated CO_2 levels above 30mmHg at baseline ($\bar{x}$=34.2, sd=3.5), a substantial mean reduction in respiratory CO_2 to hypocapnic levels was observed during the paced breathing task ($\bar{x}$=25.2, sd=6.6). This result was significant in one-way analysis of variance testing (F=13.77, p<.001) and Bonferroni post-hoc tests (paced breathing lower than all other conditions, p≤.001). Over half of patients (n=18, 55%) subjectively reported experience of prodromal PNES symptoms during decompensated CO_2 levels, usually during the paced breathing task. A substantial number of patients (n=25, 89%) were able to correct their $ETCO_2$ values above 30mmHg following a 10-20 minute period of biofeedback training employing visual display of their breathing waveform, rate and CO_2 level, with the assistance of a trained clinician.

3.3 Duration & Frequency of PNES Events

Average duration of PNES illness in the sample was 20 months (sd=18 months) following patients' first self-reported PNES events. The shortest illness duration at diagnosis was one month while the longest duration reported was 72 months. Frequency of PNES attacks in the month preceding diagnosis was quite high at an average of 46 events (sd=70). In order to investigate the relationship among psychophysiology features at baseline assessment and duration of illness, the mean duration value of 19 months was chosen as criterion for distinguishing among short versus longer duration PNES symptoms. While elevated heart rate, lower HRV, poor SCL recovery and hypocapnia were not associated with duration of PNES symptoms, presence of any baseline autonomic decompensation ($\chi^2 = 4.77$; p=0.03) or inhibition of stress response ($\chi^2 = 4.47$; p=0.04) was significantly associated with a longer duration of PNES symptoms (See Table 4). The resulting effect sizes were relatively small for both variables, with a contingency coefficient of 0.36 (w=0.14). Frequency of PNES events in the month preceding diagnosis was similarly compared employing a median cutoff of 20 events per month to assess low versus high event frequency in the sample. In this case, elevated heart rate at baseline had a significant association with higher frequency of events ($\chi^2 = 4.24$; p=0.04), suggesting increased cardiac sympathetic output in patients with higher frequency of PNES events (Table 5). Again, the effect size for this relationship was relatively small with a contingency coefficient of 0.34 (w=0.13).

3.4 *Dissociation Characteristics*

Self-report dissociation scores were available for adolescents in the sample (n=20) who had completed the A-DES. Levels were elevated overall in the sample with a mean score of 2.8 (sd=1.8). Of these, 5 patients (25%) obtained scores above the criterion established for dissociative disorder in previous studies(Farrington, Waller, Smerden, & Faupel, 2001), suggesting a quarter of our sample was experiencing clinically significant dissociative symptoms at the time of PNES diagnosis. The

relationship between A-DES scores and Nijmegen scores was analyzed employing Kendall's tau-a test for continuity correction, resulting in a significant positive correlation of r=0.35 (p=0.038).

Table 4. Duration of Illness & Psychophysiology Markers (Chi-Square Tests)

Psychophysiology Marker	**1-18 Months (n = 20)**	**19-72 Months (n = 13)**	**χ^2 (P value)**
Baseline Decompensation	14 (70%)	13 (100%)	**4.76 (0.029)**
Stress Response Inhibition	4 (21%)	7 (58%)	**4.47 (0.035)**
Lack of Stress Recovery	12 (71%)	7 (78%)	0.16 (0.694)
Low HRV LF% (<68%)	12 (60%)	4 (31%)	2.70 (0.101)
Elevated Heart Rate (>90th %ile)	4 (20%)	2 (15%)	0.16 (0.737)
Hypocapnia	18 (90%)	11 (85%)	0.22 (0.643)

Bold indicates statistical significance

Table 5. PNES Event Frequency & Psychophysiology Markers (Chi-Square Tests)

Psychophysiology Marker	**0-20 (n=18)**	**21-60 (n=15)**	**χ^2 (P value)**
Baseline Decompensation	15 (83%)	12 (80%)	0.06 (0.805)
Stress Response Inhibition	5 (28%)	6 (46%)	1.11 (0.291)
Lack of Stress Recovery	11 (73%)	8 (73%)	0.001 (0.973)
Low HRV LF% (<68%)	10 (55%)	6 (40%)	0.79 (0.373)
Elevated Heart Rate (>90th %ile)	1 (6%)	5 (33%)	**4.24 (0.039)**
Hypocapnia	15 (83%)	14 (93%)	0.77 (0.381)

Bold indicates statistical significance

4. Discussion

4.1 Psychophysiology Characteristics

The first aim of our study was to characterize autonomic functioning in youth newly diagnosed with PNES. A previous study reported higher baseline heart rates in youth diagnosed with FND or PNES in comparison with healthy controls. Additionally, both the PNES and FND patients demonstrated decreased ability to regulate heart rate responses during experimental tasks. Based on their findings, the authors proposed that the central and autonomic nervous systems are "mobilized defensively" in youth with PNES, as reflected by increased cortisol levels, higher than normal respiration and heart rates leading to decreased ability to mount a threat response (Kozlowska, 2017). Our results similarly demonstrated a high incidence of baseline autonomic decompensation (82%), often characterized by low peripheral (hand) temperature and elevated resting heart rates.

Very little has been reported in the literature regarding the concept of "stress suppression" in PNES, but analogies can be drawn with other findings in the dissociation literature. Dewe et al. for example reported suppressed SCL responses (but not hand temperature response) to pantomimed body threat (the appearance they were about to donate blood) in individuals measured as being predisposed to dissociative symptoms including depersonalization and derealization (Dewe et al., 2016). Additional studies have demonstrated suppressed autonomic responding to aversive stimuli in similar populations experiencing high levels of dissociation (Sierra et al., 2002; Sierra, Senior, Phillips, & David, 2006). We also found a decreased or impaired ability to normally regulate SCL in most of our sample, with 23% failing to mount an SCL response to a laboratory stressor and another 58% failing to normally recover from the stress afterwards over a 5-minute period. Taken together, the above findings suggest there is a loss of adaptability in the ANS of PNES patients.

Although no studies have directly compared adult versus child PNES samples in terms of SCL or other autonomic measurements, comparison of our mean SCLs at baseline (mean=4.7, sd=4.1) were much

higher than that obtained in a previous study measuring SCL in adult PNES patients (mean=1.07, sd=1.31), whom did not differ from SCL in normal controls at baseline (Pick et al., 2018). These findings raise the possibility that autonomic hyperarousal may be much more pronounced in youth versus adult PNES populations. This possibility is supported by a recent multicenter study which compared PNES event frequency across child, adolescent and adult subpopulations. Here, a significantly higher incidence of monthly PNES events was observed in the transitional period from childhood to adolescence (11-14 years) compared with other age groups (Sawchuk et al., 2019). Taken together, these findings suggest frequency of PNES events may be closely tied with increased sympathetic output at pubertal onset. Another interesting result in our study was that baseline autonomic decompensation or inhibition of the SCL response was moderately associated with longer duration of having had a PNES illness. An elevated heart rate at baseline was also strongly associated with higher frequency of PNES attacks, supporting the role of heightened sympathetic activity in contributing to PNES attacks. It would be interesting in future studies to identify whether similar psychophysiology associations are present in adults or whether these are specific only to pediatric PNES populations.

4.2 Hyperventilation Characteristics

We are aware of only one previous study measuring HV objectively in a pediatric PNES population with CO_2 readings (Kozlowska, Rampersad, et al., 2017). Our study found mean CO_2 levels which were surprisingly similar to this study (34 versus 37mmHg) and much lower than that study's control group mean of 41mmHg. This replication of data is significant, as it is well-established that HV sequelae are much more pronounced in youth, than in adults with PNES. Physiological studies have demonstrated HV results in even more pronounced cerebral blood flow decreases in children and youth than in adults(Gotoh et al., 1965; Yamatani et al., 1994). Hypoxia has also been demonstrated foremost among higher brain regions (e.g. prefrontal cortex, basal ganglia) most thought to be

involved in human consciousness. It may be that the proposed “disconnection” of higher cortical and lower brainstem functions is exacerbated or promoted by HV providing a mechanism for provoking PNES episodes(Szaflarski & LaFrance, 2018) (Kozlowska, Chudleigh, et al., 2017) that is especially invoked in younger patients.

4.3 Psychological Dissociation

An aim of our study was to characterize objectively the levels of dissociation displayed in a youth PNES sample. We found elevated dissociation scores overall for our sample with one quarter scoring above 4, the cutoff reported for identifying youth with dissociative identity disorder (Armstrong et al., 1997) The measure used in our study (A-DES) is modeled on the adult version (DES) which has been found to discriminate among adults with dually diagnosed epilepsy and PNES versus epilepsy only and normal control groups. In that study, high DES scores were found in 58% of the epilepsy/PNES group compared with 12% in the epilepsy group. Interestingly, dissociation is thought to involve similar brain structures implicated in PNES onset and maintenance, including the higher brain regions also impacted by HV sequelae. The fact that we found a significant positive association between self-reported symptoms of dissociation and HV in our study lends support for the idea that these factors (and their corresponding brain substrates) contribute and may combine in some way to the production of PNES symptoms.

4.4 Limitations

We acknowledge several factors in our study that may have limited the impact and generalizability of our results. First, the small sample size did not allow for more advanced statistical analyses. It would have been interesting, for example, to undertake multivariate regression in an effort to determine the degree psychophysiology features might predict PNES severity in children. The small sample size also hindered our ability to detect other potential associations among the data, due to low statistical

test power. Another significant limitation of our study was the absence of comparison groups on measures of psychophysiology and dissociation. It would have been interesting, for example to have compared these measurements with an epilepsy only group, given sympathetic overactivation has also been reported among adults with epilepsy (van der Kruijs et al., 2016) and elevated dissociation scores may also occur with some types of epileptic seizures (Hara et al., 2015). Future studies would be significantly enhanced by including normal controls as well as psychiatric groups not experiencing functional symptoms. Another limitation in our study was the use of a single composite measure of dissociation (A-DES), which does not provide any additional information on type of dissociative symptoms. Adult PNES studies, for example have reported differential associations between PNES and various dissociation symptom sub-types, including psychological versus somatoform and detachment versus compartmentalization symptoms (Holmes et al., 2005).

Several factors may also have contributed to selection bias in our study design. This includes the fact our final sample excluded a small number of patients (n=4) who did not undergo lab assessment given early resolution of PNES following diagnosis. This opens the possibility our final sample was biased by inclusion of individuals who were more severe and less responsive to PNES interventions. Another factor which may have impacted our results is the heterogeneity of diagnostic certainty in our sample, which included patients dually diagnosed with PNES and Epilepsy (30% of sample). Also, while the majority of our patients (55%) were diagnosed with a high degree of certainty for PNES (event capture on vEEG), we cannot firmly rule out possibility of misdiagnosis with the same certainty among the remaining patients (45%). Both of these diagnostic factors in our sample may have contributed to some degree of selection bias.

4.5 Future Directions

Our study represents one of only a small number of investigations to date into the potential role of autonomic correlates in childhood onset PNES. Our study adds new findings with regards to

association between autonomic functioning and severity of PNES symptoms. It would be interesting to determine in follow-up studies if prognosis or response to treatment is also predicted by these markers. Our study is also the first to demonstrate that behavioral hypocapnia dysfunction can be effective targeted in a PNES population and corrected. Future studies should be conducted to determine if such interventions help hasten or improve treatment response in both adult and child PNES samples. It would also interesting to determine if successful recovery from PNES, including reduction of events is associated with improved psychophysiology function through follow-up standardized assessment.

5. Conclusions

Based on a modest but representative sample of PNES patients tested at our pediatric epilepsy center, we conclude that child PNES populations at diagnosis can be characterized by sympathetic overactivation, CO_2 sensitivity and poor recovery from cognitive stressors suggesting loss of autonomic adaptability to daily life events. We also conclude that baseline hyperarousal and lack of ability to mount a threat response are at least partially associated with longer duration of having had PNES illness, reflecting further loss of autonomic adaptability over time. We additionally conclude that elevated heart rate at diagnosis may serve as an indicator of increased chronic activation of the sympathetic nervous system, pre-disposing PNES sufferers to more frequent attacks. These results support an integral role for sympathetic overactivation in helping produce PNES episodes in children. The finding of high dissociation levels that are also associated with HV symptoms in child PNES sufferers, suggests autonomic hyperactivity may help predispose patients to psychological dissociation as an adaptive coping response to chronic hyperarousal thereby increasing risk of developing PNES. Finally, we also conclude that at least one component of this psychophysiology profile, proneness to HV, can be effectively targeted for treatment, potentially resulting in positive outcomes for this difficult to treat population.

Ethical Publication Statement

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

Conflict of Interest/Disclosure

4. Tyson Sawchuk: No disclosures or conflicts of interest
5. Jeffrey Buchhalter: Has received compensation as a consultant for Eisai Inc, Upsher-Smith Laboratories and Lundbeck.
6. Birgit Senft: No disclosures or conflicts of interest

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CHAPTER 4: Conclusion

This dissertation began with an empirical overview of the available literature pertaining to the history, etiology, diagnosis and treatment of psychogenic non-epileptic seizures (PNES). The literature review then went on to describe neurophysiological correlates of PNES, theoretical models and associated psychophysiology and dissociation findings in children and adults. The review concluded with a discussion of the potential role for clinical care models to enhance treatment outcomes in pediatric PNES patients.

The research aims of this dissertation foremost sought to prospectively validate a clinical care pathway developed and in use at the Alberta Children's Hospital, Comprehensive Children's Epilepsy Center (CCEC). The rationale for this aim was to address a major gap in the literature: limited study of childhood PNES treatment and lack of prospective outcome studies. Another aim of the dissertation was to newly characterize psychophysiology and dissociation characteristics in children newly referred for PNES, including respiratory CO_2 levels and electrodermal skin response to a standardized laboratory stressor. Rationale for this latter aim was to address a lack of data regarding psychophysiology characteristics in childhood PNES.

Secondary aims of this dissertation included exploring what historical factors might predict response to treatment on the clinical care pathway and what psychophysiology features might associate with severity of childhood PNES, including duration of illness and frequency of events at time of diagnosis. An additional secondary aim was to establish feasibility of a behavioral intervention for PNES patients identified

as having respiratory CO_2 sensitivity and to explore the relationship, if any among psychophysiology and dissociation measures.

4.1 Empirical Findings

The first empirical study prospectively validated the PNES clinical care pathway (originally developed by the author and main supervisor in 2015) by demonstrating a high rate of full (63%) and partial (28%) remission from PNES events, as a result of patient enrollment in the care algorithm over an average duration of 8 months. Care on the pathway also resulted in a notable increase in diagnostic accuracy, as 28% of all new PNES referrals were re-diagnosed with other medical or psychiatric "mimics". This result has significant and meaningful implications for patients, families and healthcare providers as it demonstrates the importance of retaining PNES patients for psychological treatment within a specialized epilepsy unit during early stages of care. This study also established inferred healthcare cost savings as a result of 96% reduction in PNES events, 74% reduction in ambulance activations and 85% fewer emergency room visits. These results further help to establish economic feasibility and benefit to healthcare systems as a result of implementing a care pathway for child PNES. Finally, the finding that duration of PNES beyond 12 months significantly reduced odds of achieving full remission by completion of treatment, underscores the importance of early identification and management of childhood PNES in attaining optimal outcomes.

The second empirical study achieved a number of research goals. In addition to providing empirical replication of autonomic hyperarousal in children with PNES (elevated heart rate and increased CO_2 sensitivity), this study further demonstrated

decompensated hand temperature at baseline and abnormal electrodermal skin conductance (SCL) responses (inhibition or lack of recovery) to stress induction. All of the above suggests loss of resilience in the child's autonomic nervous system which has been hypothesized as a contributing factor in PNES onset and maintenance (Kozlowska, 2017). The additional finding of an association between specific autonomic parameters (SCL inhibition, elevated heart rate) and PNES severity (duration, frequency) adds further to a developing body of research supporting role of autonomic dysregulation in PNES onset/maintenance and has implications for the development of future treatments in childhood PNES. This study additionally demonstrated a high incidence of respiratory CO_2 sensitivity among childhood PNES patients, suggesting hyperventilation may be common mechanism for triggering of PNES events themselves. The fact this study demonstrated most patients could be taught to recover their CO_2 levels to normal levels behaviorally and without medical intervention also has significant implications for development of effective interventions for childhood PNES.

The second empirical paper also established that, similar to adults, there is an elevated level of psychological dissociation among childhood PNES patients. Quantification of dissociation levels also demonstrated the magnitude of this finding, with one quarter of our sample having achieved levels above the clinical threshold for dissociative disorders in youth. The finding of an association between self-reported hyperventilation and dissociation scores also provides one of the first links among the historical models of PNES etiology, supporting the theory that dissociation may occur as a result of untenable sympathetic output reflected not just in the peripheral nervous

system but the central brain regions responsible for protecting the patient from perceived threats.

4.2 Limitations

There were a number of limitations to the research design and methods encountered during completion of this dissertation research that have implications for future studies. In the case of clinical outcomes, while the pragmatic use of a clinical care pathway in a healthcare setting helped established feasibility and practicality of the care received, lack of comparison groups also limited the empirical rigor which would have resulted from random assignment of patients to multiple treatment arms. Doing so may have helped to establish superiority of one specific intervention or combination of interventions over others, including waitlist controls. Diagnostic certainty is another factor which may have impacted validity of both outcome and psychophysiology study results. While diagnostic certainty achieved in our sample was certainly high, 39% of the main group did not have what is considered "documented" PNES according to ILAE criteria (i.e. capture of typical event on vEEG). The study sample also included patients with dually diagnosed epilepsy and PNES. The empirical implications are that we could not establish with 100% certainty that our PNES sample was pure, opening up the possibility that other factors (such as comorbid epilepsy) may have unintentionally confounded results. Finally, another limitation encountered during completion of the outcome research was that we had not measured additional outcomes to more accurately reflect the complex burden of a childhood illness. Additional information regarding child and parent quality of life through self-report measures, coding of school/workdays

absent, and functional impairment would have shed additional light on important treatment results. It would be useful to include such measures in future outcome studies.

In the case of the psychophysiology study, lack of additional comparison groups such as epilepsy only or psychiatric controls meant we were not able to determine specificity of the autonomic abnormalities to only PNES. Having done so would have helped establish whether the autonomic decompensation or loss of stress response encountered in the study also characterizes other child populations exposed to the stress of having chronic illness or other psychopathology. Additional comparison of baseline and paced breathing respiratory CO_2 levels among youth with panic disorder, for example, would have been interesting and help establish whether there are similar etiologies to both types of paroxysmal conditions. Similarly, it would have been interesting to have studied dissociation findings in the context of comparison with childhood epilepsy patients on the A-DES. Doing so, would have helped establish that the measured variable in PNES patients was in fact diverging in an expected way from results in epilepsy patients. All of the above deserves further study, in order to build upon the current dissertation results.

4.3 Future Research

In conclusion, a number of future directions are suggested by what has been achieved in the current dissertation project. The recently validated care pathway will continue to be implemented at ACH in the foreseeable future and may be enhanced as new evidence arises regarding treatment in childhood PNES. The addition of other behavioral treatments such as structured exercise programs, for example, may additively

contribute to normalization of the ANS and further enhance outcomes. Another area of future study raised by the current dissertation findings lies in the development of a diagnostic pathway for pediatric PNES. There are two reasons for this possibility: 1) the fact that no diagnostic pathways have yet been developed for empirical testing in child PNES and 2) the fact that care on our pathway appears to have significantly enhanced diagnostic accuracy leading to appropriate treatment reassignment for almost a third of the sample. While a current state of the art for diagnostic procedures already exists (as described in the literature review), little has been published regarding "PNES mimics" and how these may be delineated from actual PNES causes in an EMU or hospital clinic. A future study of the current dataset achieved in the completion of this dissertation may yield diagnostic clues (e.g. specific semiology patterns, psychometric profiles or treatment response factors) that can be designed into an algorithm and subjected to empirical validation with a new sample at our center.

Another intriguing possibility lies in the adaptation of the currently validated care pathway for use in other functional neurological disorders, as these are also lacking empirical study in pediatric populations and occur with similar high incidence in child neurology centers around the world. Literature reviewed in the introduction suggests similar autonomic abnormalities may occur in child FND as a whole. The current psychophysiology findings also open up possibilities for new behavioral interventions targeting PNES, especially in children where it appears sympathetic output encountered during pubertal onset may play a more crucial factor in onset and maintenance of the disorder. Such interventions could be geared towards not just improved

regulation/recovery of respiratory CO_2 but also biofeedback interventions addressing other aspects of ANS dysregulation in response to stressors.

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