Psychogenic non-epileptic seizures : a separate disorder or part of a continuum?

Citation for published version (APA):

Bodde, N. M. G. (2013). *Psychogenic non-epileptic seizures : a separate disorder or part of a continuum?* [Doctoral Thesis, Maastricht University]. Maastricht University. <https://doi.org/10.26481/dis.20131031nb>

Document status and date:

Published: 01/01/2013

DOI:

[10.26481/dis.20131031nb](https://doi.org/10.26481/dis.20131031nb)

Document Version:

Publisher's PDF, also known as Version of record

Please check the document version of this publication:

- A submitted manuscript is the version of the article upon submission and before peer-review. There can be important differences between the submitted version and the official published version of record. People interested in the research are advised to contact the author for the final version of the publication, or visit the DOI to the publisher's website.
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Psychogenic non-epileptic seizures

a separate disorder or part of a continuum?

N.M.G. Bodde Psychogenic non-epileptic seizures: a separate disorder or part of a continuum

Layout: Tiny Wouters

Cover design: Painting of "St. Anastasia" by Friedbert Andernach
Permission of the Museum for epilepsy and the history of epilepsy in Kork, Germany

Print: Ipskamp Drukkers, Enschede

ISBN: 978-94-6191-870-3

The printing of this thesis was financially supported by the Nationaal Epilepsie Fonds, the Department of Research and Development Kempenhaeghe and the School for Mental Health and Neurosciences (MHeNS), Maastricht University.

Psychogenic non-epileptic seizures

a separate disorder or part of a continuum?

PROEFSCHRIFT

Ter verkrijging van de graad van doctor aan de Universiteit Maastricht,
op gezag van de Rector Magnificus, Prof. dr. L.L.G. Soete,
volgens het besluit van het College van Decanen,
in het openbaar te verdedigen
op donderdag 31 oktober 2013 om 16.00 uur

door

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Chapter 1

General introduction

General introduction

A psychogenic non-epileptic seizure (PNES) is defined as a clinically observable paroxysmal change in behaviour or consciousness, that resembles an epileptic seizure, but is not accompanied by the typical electrophysiological changes that accompany an epileptic seizure. In these patients there is an absence of any known organic aetiology for the seizures, whereas there is positive evidence or a strong suspicion for the existence of psychogenic factors¹⁻³. The incidence of PNES in the general population is relatively low, estimated at about 1.5/100,000 persons per year^{4,5}. The actual incidence may be higher because of difficulties in epidemiological studies, such as the requirement for detailed neurological examination to confirm PNES, limiting the possibility to carry out large community studies⁶. Tertiary referral centres estimate a much higher incidence rate. Twenty-five to thirty percent of the patients referred to tertiary epilepsy centres for refractory epilepsy are diagnosed with PNES, with or without co-morbid epilepsy⁷.

Although the correct medical differential diagnosis of PNES versus epilepsy can be challenging, the differential diagnosis has greatly improved during the past thirty years with advanced techniques such as video EEG. Differentiating PNES from epilepsy is important, since misdiagnosing PNES as epilepsy may potentially expose patients to unnecessary antiepileptic medication and other iatrogenic consequences of unnecessary medical treatments^{7,8}. However, once the medical diagnosis has been made, patients with PNES comprise a very heterogeneous patient group with regard to the psychological aetiology⁹. It appears not easy to treat these patients adequately and prognosis for at least part of the patients is not that well. With their somatic appearance and underlying psychological or psychiatric problems, PNES patients present on the boundaries of the medical and mental health services. There are potential risks that PNES patients 'shop' through the medical circuit or remain in a 'No Man's Land' without the necessary realization of appropriate psychological or psychiatric treatment^{10,11}. Meanwhile, the impact on daily life is substantial, including not being able to engage in society, leading to psychological burden and substantial economic costs^{12,13}.

The studies in this thesis aim at exploring the psychological aetiology after the medical diagnosis of PNES has been confirmed. A focus that is in line with recent studies of PNES in the international field. Firstly, the research questions focus on finding psychogenic factors that underlie the onset and the prolongation of PNES. Finding underlying psychological mechanisms is essential to engage in treatment. Secondly, the research questions aimed at exploring possible sub-classifications of PNES that may be helpful to specify treatment for subgroups and to establish prognosis. The studies are mostly based on clinical work with PNES patients diagnosed in the

specialised Epilepsy Centre Kempenhaeghe and referred to a multidisciplinary expert team involved in the treatment of PNES.

In **part 1**, introducing the topic, a background for our studies is established by presenting reviews of the existing literature. The first review in chapter 2 focuses specifically on the medical differential diagnosis of PNES and epilepsy. In chapter 3, the review is focused on psychological aetiology, treatment issues and prognosis. Based on these reviews a model is proposed of factors involved in the causation, provocation and prolongation of PNES. This model is used for the interpretation of the findings of subsequent studies. Although this model resembles other models of somatoform disorders, specific factors were added presenting PNES as a unique disorder.

In **part 2** the current status of subsequent treatment interventions is explored. Is there evidence-based treatment for PNES and what is the long term prognosis? Chapter 4 describes a clinical non-randomized study on the long-term outcome of a group of patients diagnosed with PNES in our center, 4 to 6 years after the diagnosis. A Cochrane review on treatment effects is presented in chapter 5. This was a mutual collaboration with the University of Liverpool. Additional information was used for a separate review that is presented in chapter 6.

Considering the above described complications in diagnosis and treatment, **part 3** challenges both the usefulness of the PNES diagnosis for such a heterogeneous patient group and the opinion of PNES as a unique disorder. Patients with PNES may have similar characteristics as patients with other functional neurological symptoms (FNS) or even the broader group of patients with functional somatic symptoms and syndromes (FSSS). In chapter 7 the personality profile of patients with PNES is compared with the profile of patients with insomnia. Chapter 8 includes a descriptive study providing patient characteristics in 90 patients newly referred to the epilepsy center in a 2-year period, including the medical and psychological patient history before seizure onset. Finally, the theoretical model derived from the reviews is used to describe subgroups in a prospective study presented in chapter 9.

In the model that is used in our studies, a specific vulnerability to develop PNES is suggested. This predisposition may involve psychological factors such as personality characteristics. However, biological vulnerability may also be involved in the development of PNES. This is studied in **part 4**. Such a vulnerability may not be the single cause of the symptoms, but may contribute to the development of PNES. This in line with the biopsychological model that is used in somatoform disorders. In chapter 10 a specific review is presented, focusing on psychobiological markers for dissociation, one mechanism or process that may cause psychogenic seizures. In a

final study, described in chapter 11, functional MRI is used to demonstrate such biological vulnerability.

Finally, in chapter 12, general discussion and conclusion, the results of all studies are discussed by attempting to answer some of the recurring questions about PNES. Central focus of the discussion is whether PNES must be viewed as a separate disorder or part of a continuum with other functional somatic (neurological) symptoms.

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Part 1

Setting the scene

Chapter 2

Psychogenic non-epileptic seizures – Diagnostic issues: A critical review

NMG Bodde, JL Brooks, GA Baker, PAJM Boon, JGM Hendriksen, AP Aldenkamp

Clin Neurol Neurosurg 2009;111:1-9

Abstract

In this review we systematically assess our current knowledge about psychogenic non-epileptic seizures (PNES), epidemiology, etiology, with an emphasis on the diagnostic issues. Relevant studies were identified by searching the electronic databases. Case reports were not considered. Articles were included when published after 1980 up till 2005 (26 years). A total of 84 papers were identified; 60 of which were actual studies. Most studies have serious methodological limitations. An open non-randomized design, comparing patients with PNES to patients with epilepsy is the dominant design. The incidence of PNES in the general population is low. However, a relatively high prevalence is seen in patients referred to epilepsy centres (15-30%). Caution is needed in the clinical interpretation of ictal features suggested to be pathognomic for PNES. Video-EEG is widely considered to be the gold standard for diagnosing PNES. Still the differential diagnosis epileptic/non-epileptic seizures can be difficult. Despite the current available technical facilities, the mean latency between onset of PNES and final diagnosis as being non-epileptic and psychogenic is approximately 7 years. One of the reasons for diagnostic delay is that the diagnosis of PNES is often limited to a 'negative' process and consequently PNES is characterized as a 'non-disease' (i.e. 'not epilepsy'). The psychological diagnosis is thus an important, although not a conclusive, 'second phase' aspect of medical decision making. Specific relations between seizure presentation and underlying psychological mechanisms are not conclusive. A classification between major motor manifestations and unresponsiveness is recognized. With respect to psychological etiology, a heterogeneous set of factors have been identified that may be involved in the causation, development and provocation of PNES.

Introduction

Psychogenic non-epileptic seizures (PNES) are paroxysmal changes in behavior that resemble epileptic seizures, have no electrophysiological correlate or clinical evidence for epilepsy, whereas there is positive evidence for psychogenic factors that may have caused the seizure¹⁻³. Improved diagnostic capabilities (especially the video-EEG) have shown that PNES are more common than once believed³. Patients with PNES are often misdiagnosed as suffering from intractable epilepsy, and are thus potentially exposed to unnecessary anticonvulsant medications and other iatrogenic consequences of unnecessary treatments^{4,5}.

Many patients with PNES have a tendency to seek frequently medical attention⁶, and PNES make up a larger share of the workload of neurologists, general physicians and even emergency physicians⁷. In the study by Leis et al.² 69% of the patients with PNES were treated pharmacologically with antiepileptic drugs (AEDs), whereas the maximum duration of AED treatment had been longer than 360 months. AEDs prescribed to PNES patients have potentially serious side effects and may even exacerbate the seizures. Failure to recognize pseudostatus epilepticus has a potential hazard of intubation and its morbidity and mortality: a third of the patients with PNES suffer at least one prolonged seizure that could be mistaken for status epilepticus⁷. The failure to recognize the psychological nature of these seizures also delays implementation of appropriate psychological treatment⁷. Social stigma attached to the diagnosis of epilepsy is considerable and patients that suffer such a stigma for a longer period become hostile when the diagnosis changes from epilepsy to PNES⁸.

The clinical relevance of an early diagnosis of PNES is also unequivocal when looking at secondary outcomes: most patients with PNES have substantial social and personal problems; the majority are not in paid employment^{1,9}. Most apparent are the problems in family-life. Relatives are often as anxious as the patient. Protectiveness may lead to gross restriction and life-long effects on the social position⁹. Studies also show that PNES patients score significantly lower on quality of life subscales (work, driving, social functioning, etc.)¹⁰. Szaflarski et al.¹¹ showed that 'health related quality of life' for patients with PNES may score about 10% lower than patients with refractory epilepsy.

Seizures, erroneously diagnosed as epileptic also have an economic impact. The costs of misdiagnosing and treating PNES are staggering: estimates suggest more than 100,000 dollar per patient¹² to an amount equal to that of intractable epilepsy, which for 1995 was estimated to be as high as \$231,432 per patient¹¹. Martin et al.¹³ evaluated the direct medical costs that were on average \$8000,- per patient for the 6 months period pre-diagnosis. After the diagnoses of PNES was made the costs were \$1300,- for the 6 months period. There was a 84% reduction in total seizure-related medical charges in the 6 months period following the PNES diagnosis.

It is therefore clear that the diagnosis of PNES is clinically relevant. Benbadis¹⁴, however, concludes that in his experience this is a field in which there is a severe

disconnect between the frequency of the problem and the amount of attention (especially scientific attention) devoted to it. In this review we therefore systematically assess our current knowledge about PNES with an emphasis on the diagnosis of PNES.

Methods

Relevant studies were identified by searching the electronic databases psycINFO, EMBASE, MEDLINE, PubMed and Online Contents. Articles included in this review were identified by searching the terms: 'non-epileptic seizures'; 'non-epileptic attack disorder'; 'psychogenic non-epileptic seizures'; 'pseudo-epileptic attack disorder'; 'psychogenic pseudoseizures'; 'psychogenic seizures'; 'dissociative episodes', 'hysterical seizures'. In all cases 'seizures' were also replaced by 'fits' and 'attacks'. Titles of articles and abstracts extracted during the search were reviewed for relevance, and if found to be applicable, the full-text article was retrieved. Articles were included if they were published in English, Dutch or German. Case reports were not considered. Articles were included when published after 1980 up till 2005.

Results

A total of 84 papers were identified; 60 of these were studies and 24 reviews. Table 2.1 provides the main characteristics of the main source articles and Table 2.2 shows the reviews and their topics:

Description of the studies

Some comments on the results in Tables 2.1 and 2.2 are in order. The dominant type of design in studies on PNES is the open non-randomized comparative study. The studies are therefore not protected against the effects of bias, especially selection bias. Patients with epilepsy are mostly used as the comparator. Although this seems obvious in the light of the fact that the symptoms resemble seizures, but is not logical when studying for example the psychopathology or outcomes in daily life in patients with PNES. In many cases patients with PNES have been in the diagnostic process as 'epileptic patient' for many years. The effect may therefore not be different and patients with epilepsy may not be helpful to study the specific effects or etiologies in patients with PNES. The sample size is mostly rather limited; the majority in the range of 20-30 patients. Given the high variability of the symptoms and underlying characteristics in these patients, it is doubtful whether any of the studies achieves sufficient power. Formal power analyses, have however not been performed. The larger studies are retrospective studies and mostly studies on patient files. The only exceptions are postal questionnaire studies with such a high non-response rate that bias can not be excluded.

Table 2.1 Overview of studies on diagnostic issues in patients with PNES.

Reference	Study: design and number of patients
Abukakr et al. ⁸	Open cohort study; 23 patients with PNES; no controls
Abubakr and Wambacq ³²	PNES in the elderly
Al Marzooqi et al. ⁵⁶	Open non-randomized comparative design; 97 patients with PNES compared to 97 patients with epilepsy
Alsaadi et al. ³⁷	Evaluation of video-EEG in 29 patients with PNES
Alving ⁶⁹	Open non-randomized comparative design with 20 patients with PNES and 38 patients with epilepsy
Arnold and Privitera ⁶⁷	Double blind comparative design in 14 patients with PNES and 27 with epilepsy
Bazil et al. ⁷²	Open non-randomized comparative design, comparing 8 patients with PNES with 10 patients with epilepsy; outcome: sleepstructure. PNES in the elderly
Behrouz et al. ³¹	Evaluation of video-EEG in 32 patients with PNES
Benbadis et al. ²¹	Open non-randomized comparative study in 10 patients with PNES and 10 patients with epilepsy
Berkhoff et al. ⁴⁸	Retrospective open clinical follow-up study (2 years) in 128 patients with PNES (46 combined with epilepsy).
Betts and Boden ¹²	Retrospective open non-randomized comparative design, with 96 women with PNES, 132 women with epilepsy and 87 women with a psychiatric diagnosis
Betts and Boden ⁷²	
Binder et al. ⁶⁰	Open non-randomized comparative design, comparing 12 patients with PNES with 31 patients with epilepsy
Bowman and Markand ⁵⁹	Open non-randomized non-controlled study in 45 patients with PNES
Buchanan and Snars ⁶⁴	Open non-randomized clinical retrospective study on outcome in 50 patients with PNES
Cragar et al. ¹⁷	Prospective open non-randomized comparative study with 92 patients with epilepsy, 74 patients with PNES and other small groups.
Dericoglu et al. ⁶⁸	Open non-randomized clinical retrospective study on the effect of provocation in 39 patients with PNES
Galimberti et al. ²⁶	Open non-randomized comparative study in 31 patients with PNES and 38 patients with epilepsy
Gates et al. ⁴¹	Open non-randomized comparative study in 25 patients with PNES and 25 patients with epilepsy
Goodyer and Mitchell ⁶	Open non-randomized comparative study in 23 patients with PNES and 70 patients with psychiatric symptoms
Gould et al. ⁷⁸	Open clinical study in 30 patients (of which some had PNES)
Holmes et al. ²⁵	Open non-randomized comparative study in 84 patients with PNES and 84 patients with epilepsy
Jawad et al. ⁶⁵	Open and non-randomized comparative design in 46 female patients with PNES compared to 50 female patients referred to a psychiatric outpatient clinic
Kanner et al. ⁴⁶	Open non-randomized comparative study on seizure characteristics in 16 patients with PNES and 11 patients with epilepsy.
King et al. ⁵²	Open non-randomized comparative study in 12 patients with PNES and 6 patients with epilepsy
Kuyk et al. ⁴³	Open treatment study using hypnosis as recall technique in six patients with PNES and seven patients with epilepsy
Kuyk et al. ⁴⁵	Open non-randomized comparative study on hypnotic recall in 20 patients with PNES and 17 patients with epilepsy
Kuyk et al. ⁸⁰	Open and non-randomized retrospective comparative design in 60 patients with PNES compared to 25 patients with a combination of epilepsy and PNES
Kramer et al. ²⁸	Open non-controlled and non-randomized study in 27 patients with PNES

Reference	Study: design and number of patients
Krumholz and Niedermeyer ¹	Retrospective follow-up study (5 years) in 34 patients with PNES
Leis et al. ²	Retrospective study of EEG/video and medical records of 47 patients with PNES
Mace & Trimble ⁷⁹	Survey of diagnostic preferences in the UK
Martin et al. ¹³	Open and non-randomized and non-controlled study on the economic outcome in 20 patients with PNES
Marquez et al. ³	Retrospective open non-randomized comparative study looking at BMI in 46 patients with PNES and 46 patients with epilepsy
McDade & Brown ⁷⁴	Open non-controlled and non-randomized treatment study in 18 patients with PNES
Meierkord et al. ⁷³	Open non-randomized non-controlled study in 110 patients with uncertain seizures; EEG analysis.
van Merode et al. ⁸¹	Open non-randomized and non-controlled study in 62 patients with PNES on etiological factors
Mökleby et al. ⁵⁵	Open non-randomized comparative study in 23 patients with PNES, 23 patients with somatoform disorders and 23 normal controls
Moore and Baker ⁷⁷	Retrospective study of psychological factors in patient files for 185 patients with PNES
Müller et al. ¹⁶	Epidemiological retrospective study of 322 medical records of patients referred to an epilepsy centre. 44 (14%) had PNES, some in combination with epilepsy
Parra et al. ³⁶	Open non-randomized comparative study in 39 patients with PNES, 21 patients with epilepsy and 20 patients with combined PNES/epilepsy
Prueter et al. ⁶²	Open non-randomized comparative study in 19 patients with PNES, 20 patients with epilepsy and 21 patients with both epilepsy and PNES
Ramchandani and Schindler ⁷⁶	Open non-randomized non-controlled study of psychiatric symptoms in 20 patients with PNES
Reuber et al. ⁵³	Retrospective study of patient files
Reuber et al. ⁸⁴	Open study on psychogenic factors in 59 patients with PNES on predisposing, precipitating and perpetuating factors
Rusch et al. ²⁰	Open non-randomized non-controlled study in 26 patients with PNES (including 15 patients with PNES and epilepsy)
Saygi et al. ³⁹	Open non-randomized comparative study on seizure characteristics in 12 patients with PNES and 11 patients with epilepsy
Scheepers et al. ⁴⁰	Medical audit assessing patient characteristics in 27 patients with PNES
Shukla et al. ⁷⁰	Serum prolactin levels in 19 patients with PNES
Sigurdardottir and Olafsson ²²	Epidemiology of PNES (Icelandic study)
Stone et al. ⁸⁶	Open non-controlled study for psychiatric symptoms in 20 patients with PNES and 30 patients with motor conversion symptoms
Szafarski et al. ¹¹	Open study on quality of life and mood in 45 patients with PNES and 40 patients with epilepsy
Tojek et al. ⁴⁷	Open non-randomized comparative study assessing psychiatric symptoms in 25 patients with PNES and 33 patients with epilepsy
Vincentis et al. ³⁰	Open non-randomized non-controlled comparative study in 21 patients with PNES and epilepsy with respect to their DSM classification
Vinton et al. ⁵¹	Quantitative EEG mapping in 15 patients with PNES
Wagner et al. ⁵⁰	Open and non-controlled study on the use of personality inventory (PAI) to support a diagnosis of PNES in 61 patients
Wilkus et al. ⁶⁶	Open non-randomized comparative study in 25 patients with PNES and 25 patients with epilepsy
Witgert et al. ⁵	Open non-randomized study in 39 patients with PNES on the frequency of symptoms for panic attacks
Wyllie et al. ²⁷	Open non-randomized comparative study in 18 children with PNES and 20 adults with PNES

Table 2.2 Overview of reviews on diagnostic issues in patients with PNES.

Reference	Review topic
Alper ¹⁵	General update
Barry and Sanborn ⁶³	Psychological factors
Benbadis and Hauser ²¹	Epidemiology of PNES
Benbadis ⁴	Educational approach
Braun ⁸²	Dissociation in PNES
Chabolla et al. ⁵⁸	Classification
Chen et al. ⁷¹	Use of serum prolactin in the diagnosis
Dekkers and van Domburg ⁵⁴	Diagnosis with an emphasis on psychological diagnosis
Devinsky ⁴²	Differential diagnosis
Fejerman ³⁸	PNES imitating idiopathic generalized epilepsies
Fiszman et al. ⁶¹	Traumatic events and PTSD in patients with PNES
Francis and Baker ⁴	Description of PNES in an historic and societal context, terminology, epidemiology, diagnosis and aetiology
Iriarte et al. ¹⁰	Diagnosis of PNES
Kuyk et al. ⁴⁴	Psychological diagnosis
Krumholz ⁴⁹	Diagnosis and management
LaFrance and Devinsky ⁸⁵	Treatment of non-epileptic seizures
LaFrance and Barry ⁵⁷	Update on treatments of PNES
Mackay ³⁴	Diagnosis of PNES in children
Ramani et al. ¹⁹	General update
Reuber and Elger ⁷	Update on diagnosis and outcome of PNES
Reuber and House ⁹	Treatment factors
Riggio ²⁴	Seizure characteristics
Sirven and Glosser ²³	Epidemiology of PNES
Wyllie et al. ²⁹	PNES in children

Epidemiology

The epidemiological data have two sources of origin:

- (a) Data from tertiary centers, such as epilepsy centers. These data provide us an estimate for the proportion of PNES among those patients that are in assessment for possible epilepsy. Abubakr et al.⁸, Alper¹⁵ and Witgert et al.⁵ report that in approximately 25-30% of the patients referred to tertiary epilepsy centers for refractory epilepsy a diagnosis of PNES is obtained. Betts and Boden¹² report 24% with PNES per year in a highly specialized psychiatric ward. Müller et al.¹⁶ report PNES in 14% of the patients in a specialized hospital. Cragar et al.¹⁷ reconfirm the prevalence data of up to 33% of the patients with PNES referred to epilepsy centers, but found this percentage only be true for clinical referrals. Prevalence is much lower (5%) in outpatient units¹⁵.

A complicating observation, especially for the patients referred to specialized epilepsy centers is that between 5 and 40% of the patients with PNES have a concomitant diagnosis of epilepsy or have a past history with epileptic seizures¹⁰. This finding is confirmed in the study by Bendadis et al.¹⁸ in which between 9 and 32% of PNES patients also had epilepsy. It is often claimed¹² that this patient group is the most challenging for diagnosis and treatment^{2,19}, although this claim

is challenged by others²⁰. Müller et al.¹⁶ report that in most patients PNES started years later than the epileptic seizures; in some cases more than a decade later. No other studies have confirmed this.

- (b) Data from population studies, that provide an estimate of the prevalence and incidence of PNES in the general population. Benbadis and Hauser²¹ estimate the point prevalence to be low in the range of one person per 30,000-50,000. In the Iceland population study the incidence of PNES was 1.4 in 100,000 person-years of observation with a maximum age-specific incidence between 15 and 24 years²². Szaflarski et al.¹¹ report an incidence of 3-4.6 per 100,000 subjects. This incidence rate is equivalent to 4% of that of epilepsy. Studies based on patients referred to neurological centers for diagnosis have reported an incidence of 1.5 per 100,000 per year⁷. Although these data are reasonably consistent, Sirven and Glosser²³ point to one specific methodological problem when interpreting these rates. As some patients with PNES may have more or less identical symptoms as other 'movement' or 'conversion-type of symptoms', some patients with PNES are likely to be followed for various other neurologic complaints in a movement disorders centre, headache clinic or chronic-pain program and would be excluded from epidemiologic estimates. They therefore do not exclude the possibility that the current incidence rates underestimate the problem.

When evaluating the specific characteristics, most studies found that 75-80% of the patients with PNES are female^{8,24}. Holmes et al.²⁵, however, suggest that the gender factor may be less pronounced than given by the previous figures. Generally, fewer men than women seek medical attention. This may result in an evaluation of only the most severely affected men. This is in line with some reports that suggest more severe psychogenic factors in men compared to women. The true incidence of men with PNES may thus be significantly unrecognized and underreported. The PNES episodes tend to begin in early adulthood in most patients^{3,8,26}. Wyllie et al.²⁷ have demonstrated that PNES are rare in children under 10 years old. When occurring in the younger age range, the PNES are seldom a 'stand-alone phenomenon' and more often occur as a symptom in a range of other symptoms^{28,29}, mostly mannerisms, parasomnias, hyperventilation attacks, breath-holding spells, syncope or movement disorders³⁰. On the other hand Behrouz et al.³¹ and Abubakr and Wambacq³² have demonstrated that PNES should also be considered as a diagnostic possibility in older patients (60 years of age or older). The actual prevalence of PNES in the elderly is however not known. Moreover a higher incidence is found with lower educational level²⁶. Significant psychiatric co-morbidity is found in at least 70% of the patients, although often the exact definition of the psychiatric disorder is lacking or nonconclusive^{9,14,21}.

Among the conversion types of symptoms, PNES is the second most common conversion symptom category exceeded in frequency only by all forms of movement disturbances, including paralysis, weakness, impaired gait, and tremor¹⁵.

Diagnosis including differential diagnosis

In a first phase PNES must be distinguished from organic non-epileptic seizures, such as syncope, migraine or tension headache, hyperventilation, transient ischemic attacks, hypoglycaemia, benign myoclonia, myasthenia gravis, paroxysmal choreoathetosis, seizures due to alcohol abuse and one of the parasomnias^{7,16,33}. In children especially the parasomnias are a diagnostic challenge^{29,34}. All these conditions require specific diagnostic procedures. Next, attention must be paid to non-epileptic emotionally based states that resemble seizures¹². Especially panic attacks and related anxiety states such as impulse control problems and flashbacks in the context of post-traumatic stress disorder are a major diagnostic confound that must be distinguished from epilepsy^{7,35}. Moreover ictal and postictal fear are reported to be common anxiety states in epilepsy and are reported to occur in approximately 10-15% of the patients with complex partial seizures with a temporal origin¹⁵. Therefore not all anxiety states are non-epileptic by definition.

Most of the attention during this phase must, however, be paid to distinguishing epileptic from non-epileptic seizures. Such differential diagnosis may be challenging in many cases^{14,34-37} and especially in those cases mimicking idiopathic generalized seizures, such as myoclonic or absence seizures³⁸. Various studies demonstrated that many signs that have been considered typical for PNES, appeared not to be specific and can also be found in epileptic seizures, especially in those seizures that originate from the frontal lobe^{3,39}. Hence, caution is needed in the clinical interpretation of ictal features that have been considered pathognomonic for epileptic seizures such as tongue biting, or complex movements^{2,10}. Sometimes injuries are seen as indicative for epilepsy; however, impressive degrees of self-injury can occur in PNES as well. The frequent occurrence of fractures in patients with PNES are in fact evidence for the capacity of some PNES patients for self-inflicted injury and discomfort. This capacity is perhaps explained by the tolerance of pain conferred by dissociation¹⁵, which is one of the most common psychological mechanisms in PNES. Autonomic changes can occur with epileptic seizures, but also with PNES (e.g. coughing, palpitations and pupillary dilatation). Many of these signs are simply part of the generalized arousal response attached to panic or other extreme emotional states^{23,40}.

Many studies have reported that the clinical diagnosis and careful history making is still essential for the differential diagnosis. The following symptoms have found to distinguish epileptic seizures from PNES:

- PNES are more often composed of purposeful, asynchronous, apparently consciously integrated motor activity such as thrashing movements of the entire body, opisthotonic posturing of trunk, out-of-phase limb movements, side-to-side head movements, forward pelvic thrusting^{10,24,37,41}. Sirven and Glosser²³ observed that distinctive patterns of facial muscle activity distinguished PNES from epileptic seizures. PNES patients were more likely to have forceful sustained eye closing at any stage of the seizure and jaw clenching in the tonic phase of convulsive seizures.

- PNES is often accompanied by moaning and crying (ictal weeping) throughout the events¹⁰. However a caveat concerns the existence of ictal fear in epilepsy¹⁵.
- Leis et al.² found in their series that the single most common ictal characteristic of PNES was unresponsiveness without predominant motor manifestations. This is, however, only one seizure type in PNES and hence not a very useful differential characteristic.
- Stereotyped behavior is regarded as more characteristic of epileptic seizures than of PNES^{15,42}. So variability in symptoms is regarded a symptom of PNES.
- Also, patients with PNES often describe fluctuating, but more or less continuous, levels of conscious mental activity during their events without the discrete gaps of missing memory that are characteristic of the impaired consciousness during complex partial epileptic seizures¹⁵. Some studies have tried to use this postictal amnesia as a sign for epileptic seizures, e.g. using hypnosis or a hypnotic recall technique^{43,44,45}.
- Agreement appears to exist regarding increased seizure length²⁴ and a high degree of affect in the vocalization in PNES^{39,46}. Epileptic vocalizations are described as monotonous, with less emotive content than those encountered in PNES¹⁵.
- Self-reported emotional stress bears a somewhat counter-intuitive relationship to epilepsy and PNES¹⁵. Most patients with epilepsy do report having more seizures when they are angry or anxious. Patients with PNES have been reported to more often deny a connection between their events and the subjective experience of emotional stress, possibly because the PNES itself serves to enable psychic discomfort to remain out of conscious awareness^{15,47}.
- More often, PNES occur in the presence of others and have a more gradual onset (slow increase of symptoms)^{19,23} with abrupt recovery¹.
- Pre-ictal pseudosleep, in which the seizure arises while the patient seems to be asleep despite electrographic evidence of wakefulness, has been reported to be specific for PNES²³.

Although such seizure characteristics can be important, Reuber and Elger⁷ warn that often the past medical, social and psychiatric history is more helpful in the differentiation of PNES from epilepsy than the description of the seizures themselves. Others warn that a history with clear psychogenic factors does not protect against developing organic problems such as epilepsy⁴⁸. Therefore such a positive history only has meaning in the context of excluding medical causes for the seizures⁴⁹. Wagner et al.⁵⁰ describe the use of a psychological test (the Personality Assessment Inventory, PAI) as an effective psychological screening tool to aid in the differential diagnosis of epileptic seizures versus PNES prior to hospital admission for VEEG. Cragar et al.¹⁷ conclude that, despite a plethora of research on methods for differentiating PNES from epilepsy, seizure recording with simultaneous video EEG monitoring remains the gold standard for differential diagnosis. However, some studies report that despite the most modern investigatory equipment it sometimes may be impossible to decide

what one is dealing with^{12,45,51}. Parra et al.³⁶ state that during the initial years of video EEG monitoring neurologists were more prone to misdiagnose PNES as epilepsy^{52,46}, but in the last few years clinicians are more likely to suspect and recognize PNES but also ‘overdiagnose’ atypical paroxysmal events as PNES. In their own study they also found that epileptic seizures were misdiagnosed as PNES more frequently than the reverse (57% versus 12%). A worrisome observation is that, despite the current available technical facilities, the mean latency between onset of PNES and final diagnosis as being non-epileptic and psychogenic is approximately 7 years^{7,9,37,53}. Müller et al.¹⁶ therefore conclude that early admission of so-called ‘pharmacoresistent epilepsy’ to an epilepsy centre (establishing a standard work-up and clarifying the medical terminology) will improve diagnosis (and lead to adequate therapy of PNES as well prevent unnecessary drug treatment). They describe a diagnostic algorithm in which video EEG and clinical observation as well as a close review of the general medical and drug history must be considered as a minimal diagnostic standard. One of the reasons for diagnostic delay is outlined by Dekkers and Domburg⁵⁴: the medical diagnosis of PNES is often limited to a ‘negative’ process and consequently PNES is characterized as a ‘non-disease’ (i.e. ‘not epilepsy’, ‘no cardiac disease’, ‘not an anxiety attack’, etc.), which may obstruct a ‘positive diagnosis’, evaluating the exact psychological mechanisms that have caused PNES in an individual patient.

The psychological diagnosis is thus an important, although not a conclusive, ‘second phase’ aspect of medical decision making in which the focus will gradually shift to etiological factors. Iriarte et al.¹⁰ (see also Mökleby et al.⁵⁵) emphasize that the diagnosis of PNES requires a multidisciplinary approach. It is not enough to determine that the seizures have a non-epileptic origin, but also to obtain a comprehensive clinical psychological, psychiatric and neuropsychological evaluation that may shed light on potential psychogenic mechanisms of PNES^{56,57,58}. Bowman and Markand⁵⁹ advise that after PNES are confirmed a complete assessment should be carried out, requiring at least three components: (a) screen for co-existent neurological disorder; (b) psychological examination; (c) assessment of social/interpersonal problems. Three general types of psychological tests have been used to assess PNES: personality inventories, neuropsychological tests and forced choice malingering detection tests. They are useful methods, and each probably contributes to obtaining unique information that can identify patients who should be monitored. Also multiple measures should provide a more accurate prediction of the seizure type than single measures^{23,60}.

Some authors use a classification system for the clinical manifestations of PNES such as the DSM- IV or ICD-10^{20,55,61}. Seizures are then diagnosed as either ‘dissociative disorders’ (ICD-10)⁶² or on the DSM on either axis I, or axis II or both. The most frequent DSM-IV diagnosis for PNES appears to be somatoform disorder (conversion disorder)^{24,63}. The second most common diagnosis was anxiety disorder^{5,64}. It is questionable though, whether the seizures should be ‘relabelled’, since these diagnostic categories on their own tell us comparatively little about the management

of patients with PNES⁶⁵. Wilkus et al.⁶⁶ even used MMPI profiles to distinguish epilepsy from PNES and report a 80% success score. This has never been confirmed, though. Moreover Arnold and Privitera⁶⁷ could not distinguish patients with epilepsy and patients with PNES using the DSM classification in a double blind study. Induction protocols are controversial (e.g. suggestive techniques such as tuning fork or intravenous injection of normal saline solution; Dericioglu et al.⁶⁸) because it may negatively influence the patient-physician relationship, but also because induction tests can also induce epileptic seizures or can even cause PNES in patients who might not have had PNES before^{10,16,44}. The diagnostic accuracy of serum prolactin levels is less than that of provocation with suggestion during video EEG monitoring^{15,69,70}. Although Chen et al.⁷¹ recommend that elevated serum prolactin assay, when measured in the appropriate clinical setting (at 10-20 min after a suspected event) is a useful adjunct for the differentiation of generalized tonic-clonic or complex partial seizure from PNES among adults and older children.

As mentioned before, the coexistence of epileptic and non-epileptic seizures in the same patient presents a specific diagnostic challenge. Some studies have found that there may be relationships between the two types of seizures, such as symptom modeling and the susceptibility to behavioral dysfunction conferred by neurological illness and behavioral toxicity of AEDs¹⁵. Two types of seizures may be especially difficult to differentiate: frontal seizures^{12,39} and minor non-convulsive psychogenic seizures which simulate complex partial epileptic seizures¹. Bazil et al.⁶⁶ suggest that monitoring the sleep structure may be an helpful additional aid in the differential diagnosis. Patients with PNES have a sleep architecture similar to patients with major depression with an increased percentage of REM sleep.

Seizure characteristics

Although PNES can imitate any type of seizure event⁵, Abubakr et al.⁸ suggest a division into two seizure types: (a) major motor manifestations and (b) limpness, unresponsiveness, flaccidity. Sometimes this division is made in parallel with the epileptic seizures that they resemble: 'Major' seizures are defined as attacks that resemble most convulsive-type seizures such as the generalized tonic or clonic seizures. 'Minor' seizures resemble absence-like or short partial seizures¹. A similar division is proposed by Riggio²⁴, distinguishing between: a primary motor component type and the second non-motor type in which the event is often characterized by a change in behavior. Meierkord et al.⁷³ report that 66% of the patients presented with excessive motor manifestations and unresponsiveness is a more seldom reported symptom. This is confirmed by McDade and Brown⁷⁴. Leis et al.², however, caution against such conclusions as unresponsiveness may go undetected more frequently. Betts and Boden^{12,75} distinguish three types of seizures: (a) 'Swoons': a relaxed fall to the ground without injury, followed by lying still without convulsion, with eyes closed for various periods of time and apparently unconscious, usually followed by rapid

recovery with no post-ictal confusion; (b) 'Tantrums': the patient emits a cry, falls, thrashes about with a convulsive struggle if restrained, kicks and may bite (either himself or spectators), and is often noisy, shouting, roaring or crying; (c) 'Abreactive attacks'; there may be initial over-breathing, which may pass unrecognized, followed by sudden movement and stiffening of the body, which is followed by breath holding, gasping, uncoordinated jerking of the body with pelvic thrusting and back arching. There may be screaming or crying, spitting or retching. It bears superficial resemblance to sexual intercourse and may continue for many hours. Alper¹⁵ distinguishes PNES that are conversion symptoms (conversion PNES) from PNES that are non-conversion and are paroxysmal behavioral features of other syndromes (non-conversion PNES). Another important distinction proposed by Alper^{15,35} is that between consciousness/unconsciousness and intentional/nonintentional. This distinction leads to the following subgroups: (a) PNES as conversion disorder: the patient is not consciously aware of intentionally producing symptoms or of the presumed unconscious conflict or unmet need underlying their occurrence. (b) PNES as factitious disorder: patients are consciously aware of intentionally producing symptoms but not consciously aware of their reason for pursuing the sick role as a dominant motivating theme of their lives. (c) Non-epileptic seizures in the context of malingering: the patient is consciously aware of intentional symptom production and clearly understands his or her agenda, which is specifically identifiable in external incentives. Intentional PNES production distinguishes these disorders from other axis I disorders, which may occasionally manifest unintentional paroxysmal behavioral features that may be suspected of being epileptic seizures, such as anxiety, dissociative or impulse control disorders.

Some specific relationships were reported between seizure presentation and underlying psychological mechanisms. Meierkord et al.⁷³ report that pelvic thrusting can occur as prominent feature only in women with a history of childhood sexual abuse. Galimberti et al.²⁶ report that PNES mimicking generalised tonic-clonic seizures was associated with a low educational level. Ramchandani and Schindler⁷⁶ found that patients with pseudo complex partial seizures had dissociative symptoms, whereas patients with pseudo tonic-clonic seizures had their illness developed in the context of longstanding personality disorders. Alper¹⁵ emphasized the importance of distinguishing the subgroup with non-conversion PNES as it may allow identification of a discrete underlying psychiatric disorder, whose specific treatment differs from that of conversion PNES. This is particularly true for axis I disorders that allows specific pharmacotherapeutic approaches such as panic disorder or schizophrenia. Moore and Baker⁷⁷ observed that many of the symptoms described by their patients appear to be anxiety related. Holmes et al.²⁵ found a relationship between seizure presentation and gender. Men were more likely than women to have 'convulsive-like' psychogenic seizures, while women were more likely to have 'non-convulsive' attacks. This semiological difference is attributed to 'a more male form of acting out' during forms of PNES associated with dramatic motor activity.

Psychological etiology

Freud saw PNES as a 'hysterical fit', being the expression of normal sexual desires, repressed from conscious awareness due to the unbearable affects with which they had become associated. The phenomenological similarity of many patients' seizures to movements common in the context of the sexual act was interpreted as evidence that the seizure was the symbolic expression of a repressed unconscious sexual conflict^{4,15,58}. After the abolition of the term 'hysterical neurosis' from the current diagnostic systems, PNES is no longer seen as one discrete disorder ('hysteria') and the term 'hysterical seizures'^{19,78} vanished from the literature, although a survey among British neurologists showed that in 1991 the term hysteria was still used in the 'informal contacts'⁷⁹. Sirven and Glosser²³ conclude that a satisfactory etiologically referenced classification system has been elusive because of many current problems, of which the issue of homogeneity is dominant. PNES are almost infinitely heterogeneous and are quite different from person to person. Even if the PNES behaviors of very different people are morphologically similar, clinical experience reveals that the psychogenic causes may be quite divergent^{20,44,80}. It is helpful when describing psychological etiology also to define the used terms, because one of the major problems is the incoherent use of terminology:

- '*Psychological etiology*' or '*psychogenic factors*' describe the underlying causation of the seizures; factors such as sexual abuse during childhood⁸¹. Such psychogenic factors may be compulsory but not sufficient to cause PNES; not all patients that suffered from sexual abuse will develop PNES, although the risk for developing PNES is clearly increased. Other common examples of such psychological etiology may be personality disorders.
- '*Psychological mechanisms*' are the actual mechanisms that transfer an emotional state into a seizure. One of the most commonly described psychological mechanisms is dissociation^{3,8,15,82}.
- A final frequently used term in this context is '*comorbidity*', specifically '*psychiatric comorbidity*'^{7,55,62}. Some authors describe psychiatric comorbidity as an etiological factor. However the term "comorbidity" refers to different disorders than PNES. In this context PNES is considered a separate disorder and psychiatric comorbidity then refers to psychiatric diseases in the same patient, such as depression. The problem in clinical practice and in scanning the literature is that it is often extremely difficult to clarify the relationship between PNES and such comorbid disorders in terms of causation. Often the resulting psychiatric disorders may be a cause as well as the result of PNES or simply an epiphenomenon. For example a depression could be a result of having psychogenic seizures over a long period of time, but a depression could also be a separate disorder. To define psychiatric comorbidity as an etiological factor therefore seems unjustified.

A wide range of psychogenic factors have been identified that may underlie the occurrence of PNES in individual patients: a history of sexual and physical abuse and post-traumatic stress disorder, malingering, depression or chronic anxiety, dissociation, somatization disorder, including Briquet's syndrome, behaviorally oriented concepts of secondary gain and assumption of the sick role (mainly in intellectually impaired persons), personality disorders, organicity and age^{8,12,15,27,55,61,63,75,77}. Elsewhere⁸³, we propose a model distinguishing 5 different levels. This model is based on the previous mentioned factors specifically found for PNES. (a) *Psychological etiology*: factors that are involved in the causation of PNES, such as sexual abuse; (b) *Vulnerability*: factors that predispose a person to develop psychosomatic symptoms, such as PNES. Many authors have pointed to the specific vulnerability of patients with PNES both in terms of the emotional 'make-up' and their neuropsychological functioning; (c) *Shaping factors*: factors that can specifically shape the symptoms in the form of 'seizures' (in contrast to for example movement disorders or 'headache-like symptoms'). A shaping factor may be a relative with epileptic seizures (symptom modeling); (d) *Triggering factors*: create circumstances or situations that provoke PNES such as factors that refer to primary gain. Also psychological mechanisms that transfer an emotional state into a seizure can be part of these triggering factors such as dissociation; (e) *Prolongation factors*: the previous four factors are specifically important in the development of PNES. Prolongation factors are important in explaining why the seizures persist. Examples are the coping strategy of a patient or secondary gain aspects. This model resembles other models used to explain PNES or other somatisation disorders⁸⁴⁻⁸⁶.

Discussion

In this systematic review we identified papers on diagnostic issues through the period 1980 up to 2005 (26 years), of which 60 were actual studies. The quality of most research is limited, due to serious methodological limitations. Nonetheless, they represent some key data on diagnostic issues related to PNES.

PNES is a condition with a significant burden on the patients involved. First of all, the diagnosis is difficult in many cases; therefore patients with PNES are often misdiagnosed as suffering from intractable epilepsy, and are thus potentially exposed to the iatrogenic consequences of unnecessary treatments. Moreover most patients with PNES have substantial social and personal problems even after a clear diagnosis. In economic terms, the costs of misdiagnosing and treating PNES are staggering: estimates suggest an amount equal to that of intractable epilepsy, which for 1995 was estimated to be as high as \$231,432 per patient.

The incidence of PNES in the general population is low (about 1.5/100,000 persons per year; about 4% of the incidence of epilepsy), with a peak in the young adult age range (15-24 years) predominantly in women with a lower educational level. Point

prevalence rates vary but are probably in the range of one person per 30,000-50,000. However, a much higher prevalence is seen in patients referred to epilepsy centres: 15-30% of patients referred to tertiary epilepsy centres have PNES, which illustrates the complexity of the diagnosis. A further complicating factor is that PNES frequently occurs in patients with the comorbid diagnosis of epilepsy or a past history with epileptic seizures (estimates vary to 5-40% of the patients with PNES).

One factor causing differential diagnostic uncertainty is that caution is needed in the clinical interpretation of ictal features that are suggested to be pathognomic for PNES. Large overlap exists with epileptic phenomena, especially when epileptic seizures originate in the frontal lobe. Therefore video-EEG is widely considered to be the gold standard to confirm a suspected diagnosis of PNES. Two caveats are mentioned in the evaluated studies. Firstly when the medical diagnosis of PNES is only focused on excluding epilepsy, the outcome can be a 'negative' process (it is 'not epilepsy', 'no cardiac problems', 'no metabolic disorders', etc.) and consequently PNES becomes a 'non-disease'. Such a process may frustrate a 'positive diagnosis' evaluating the underlying psychological mechanisms that have caused PNES in an individual patient. Thus medical and psychological diagnosis must be combined in a multidisciplinary assessment protocol for PNES. In such a protocol the medical diagnosis should be the first phase, since the presence of clear psychogenic factors does not exclude the possibility of epilepsy. A second caveat concerns the observations that despite the currently available technical facilities, the mean latency between onset of PNES and final diagnosis as non-epileptic and psychogenic is approximately 7 years. Such long latency periods increase the risk that patients will be treated with antiepileptic drugs for 'refractory epilepsy' which complicates their later acceptance of the seizures as non-epileptic, which is a precondition for psychological treatment.

Attempts to categorize ictal movements into specific patterns (e.g. clonic, tonic, dystonic, in-phase or out-phase, unilateral or bilateral) proved very difficult if not impossible. Also specific relationships between seizure presentation and underlying psychological mechanisms are not conclusive. The only widely recognized classification is between major motor manifestations and unresponsiveness. Moreover a frequent distinction is between patients with PNES that result from a conversion or dissociative disorder who do not appear to have control over their events, in contrast to malingering.

A wide range of psychogenic factors have been identified that may underlie the occurrence of PNES in individual patients. Not all these factors have the same type of impact; some factors are etiological, others modulating or are precipitating, i.e. 'trigger' seizures. Consequently some studies propose a 'multifactor approach': i.e. one factor is not always sufficient to develop PNES. In most patients several of such factors are active and have to interact to develop PNES, such as the presence of a psychopathological disorder and the influence of a 'general trigger mechanism' or an emotional mechanism such as a higher dissociation tendency or a greater vulnerability of the brain for not tolerating conflictual situations.

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Chapter 3

Psychogenic non-epileptic seizures – Definition, etiology, treatment and prognostic issues: A critical review

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Seizure 2009;18:543-53

Abstract

In this review we systematically assess our currently available knowledge about psychogenic non-epileptic seizures (PNES) with an emphasis on the psychological mechanisms that underlie PNES, possibilities for psychological treatment as well as prognosis. Relevant studies were identified by searching the electronic databases. Case reports were not considered. 93 Papers were identified; 65 of which were studies. An open non-randomized design, comparing patients with PNES to patients with epilepsy is the dominant design. A working definition for PNES is proposed. With respect to psychological etiology, a heterogeneous set of factors have been identified. Not all factors have a similar impact, though. On the basis of this review we propose a model with several factors that may interact in both the development and prolongation of PNES. These factors involve psychological etiology, vulnerability, shaping, as well as triggering and prolongation factors. A necessary first step of intervention in patients with PNES seems to be explaining the diagnosis with care. Although the evidence for the efficacy of additional treatment strategies is limited, variants of cognitive (behavioural) therapy showed to be the preferred type of treatment for most patients. The exact choice of treatment should be based on individual differences in the underlying factors. Outcome can be measured in terms of seizure occurrence (frequency, severity), but other measures might be of greater importance for the patient. Prognosis is unclear but studies consistently report that 1/3rd to 1/4th of the patients become chronic.

Introduction

Psychogenic non-epileptic seizures resemble epileptic seizures, have no electro-physiological correlate or clinical evidence for epilepsy, whereas there is positive evidence for psychogenic factors that may have caused the seizure¹⁻³. With their somatic appearance and underlying psychological or psychiatric problems, these seizures appear on the boundaries of the medical and mental health services, although most patients seem to be seen in tertiary epilepsy centres. The incidence of PNES in the general population is relatively low, estimated at about 1.5/100,000 persons per year; about 4% of the incidence of epilepsy^{4,5}. However, data from epilepsy centres estimate a much higher incidence rate. In 25-30% of the patients referred to tertiary epilepsy centres for refractory epilepsy a diagnosis of PNES is obtained^{6,7}. A complicating factor is that between 5 and 40% of these patients with PNES has a concomitant diagnosis of epilepsy or has a past history with epileptic seizures^{8,9}.

Although diagnosis can be difficult, the differential diagnosis between PNES and epilepsy has improved in the last thirty years, especially since the introduction of simultaneous video-EEG monitoring^{6,9,10}. Diagnosing PNES is important because of the potential iatrogenic hazards such as potentially serious side effects of anti epileptic drugs and failure to recognize pseudo status-epilepticus with a potential hazard of intubation^{5,11}. The failure to recognize the psychological nature of these seizures also delays implementation of appropriate psychological treatment⁵. Social stigma attached to the diagnosis of epilepsy is considerable and patients that suffer such a stigma for a longer period can become hostile when the diagnosis changes from epilepsy to PNES¹².

The differential diagnosis is thus a very important aspect and a first step in the treatment of PNES. However, when the medical diagnosis is only focused on excluding epilepsy, it can become a pure 'negative' process and consequently PNES becomes a non-disease¹³. A positive diagnosis is necessary in which the underlying psychological mechanisms are evaluated that can be used for treatment aspects. LaFrance and Devinsky¹⁴ call this 'borderland diagnosis' referring to the fact that the diagnosis is best made by neurologists with expertise in clinical neurophysiology, especially long-term monitoring and V-EEG, whereas treatment is best initiated by psychologists whose experience affords them a familiarity with psychological constructs and conflicts. Theories regarding the psychological etiology of PNES are however very diverse. This probably reflects the heterogeneity of the psychogenic etiology of PNES that can be a symptom of various affective and psychiatric factors^{15,16}. Literature is also hindered by variation and inconsistent use of terminology. As yet there is no accepted model to explain the psychogenic features leading to PNES, but there are indications that often more than one factor or psychogenic mechanism operates in PNES¹⁷. Also comparatively little research has been done on treatment and prognosis for patients with PNES.

In this review we therefore systematically assess the current knowledge about PNES with an emphasis on the psychological mechanisms that underlie PNES, psychological treatment, as well as prognosis. We not only aim at identifying relevant factors, which has been done excellently in some other reviews, but also attempt to organize such factors in an explanatory model. Such a model arranges factors in their relationships and can provide options for therapy and research. Although we can learn from other psychosomatic disorders and their theoretical background, such as conversion disorders, PNES are unique in their aspect, especially because of the paroxysmal nature. This implies that models for other psychosomatic disorders can not easily be transferred to PNES.

Methods

Relevant studies were identified by searching the electronic databases psycINFO, EMBASE, MEDLINE, PubMed and Online Contents. Articles included were identified by searching the terms: 'non-epileptic seizures'; 'non-epileptic attack disorder'; 'psychogenic non-epileptic seizures'; 'pseudo epileptic attack disorder'; 'psychogenic pseudoseizures'; 'psychogenic seizures'; 'dissociative episodes', 'hysterical seizures' with regard to etiology and treatment. In all cases 'seizures' were also replaced by 'fits' and 'attacks'.

Titles of articles and abstracts extracted during the search were reviewed for relevance, and if found to be applicable, the full-text article was retrieved. After selecting the articles, the search was expanded by using the PubMed function 'related articles'. In addition, reference lists of all articles that were identified in the electronic investigation were scanned. Further articles and conference papers were identified through hand searches in the library holdings of Kempenhaeghe and Maastricht University. Articles were included if they were published in English, Dutch or German. Case reports were not considered. Articles were included when published after 1980-2005 (26 years).

Results

A total of 93 papers were identified; 65 of these were studies and 28 reviews. Table 3.1 provides the main characteristics of the studies and Table 3.2 shows the reviews:

Table 3.1 Overview of studies on definition, etiology, treatment and prognostic issues in patients with PNES.

Reference	Study: design and number of patients
Abubakr et al. ¹²	Open cohort study; psychological factors in 23 patients with PNES; no controls
Aldenkamp and Mulder ⁹⁴	Open non-randomized comparative design; 45 PNES patients; three treatment conditions
Aldenkamp and Mulder ⁵¹	Open non-randomized comparative design, comparing psychological etiology in 24 PNES with 24 patients with epilepsy
Alper et al. ⁴⁸	Open non-randomized comparative study in which a scale (DES) was tested in 132 patients with conversion-type PNES versus 169 patients with epilepsy (and complex partial seizures)
Arnold and Privitera ¹⁶	Double blind comparative design comparing psychological etiology in 14 patients with PNES and 27 with epilepsy
Barry et al. ⁷⁵	Open and non-randomized non-controlled study in 37 patients with PNES after head injury
Benbadis ⁷⁶	Retrospective study on patient files on the relationship between chronic pain and PNES
Benbadis et al. ⁸	Evaluation of video-EEG in 32 patients with PNES
Betts and Boden ²¹	Retrospective open clinical follow-up study (2 years) in 128 patients with PNES (46 combined with epilepsy).
Betts and Boden ⁴¹	Retrospective open non-randomized comparative design, with 96 women with PNES, 132 women with epilepsy and 87 women with a psychiatric diagnosis
Bewley et al. ⁵⁰	Open non-randomized comparative study on measures of alexithymia in 21 patients with PNES versus controls.
Binder et al. ²⁷	Open non-randomized comparative design, comparing MMPI profiles in 12 patients with PNES with 31 patients with epilepsy
Bowman and Markand ¹⁵	Open non-randomized non-controlled study in 45 patients with PNES; outcome: DSM-III classifications
Buchanan and Snars ⁷⁰	Open non-randomized clinical retrospective study on clinical outcome after individual treatment in 50 patients with PNES
Carton et al. ⁸⁷	Open non-randomized postal questionnaire study on outcome in 84 patients with PNES
Cragar et al. ¹⁰	Prospective open non-randomized comparative study on personality traits in 92 patients with epilepsy, 74 patients with PNES and other small groups.
Drake et al. ⁴⁶	Open non-randomized clinical retrospective study on psychiatric symptoms in 20 patients with PNES
Dworetzky et al. ³⁹	Comparison between 34 patients with epilepsy and 22 patients with PNES, with a focus on seizure semiology
Ettinger et al. ⁸²	Telephone based questionnaire on clinical psychological and psychiatric characteristics in 56 patients with PNES
Fargo et al. ⁷³	Open non-randomized comparative study on neuropsychological and quality of life outcomes in 37 patients with PNES and 45 patients with epilepsy
Farias et al. ⁷⁹	Open non-randomized comparative study on seizure frequency after presenting the diagnosis in 22 patients with PNES and 10 patients with epilepsy
Fleisher et al. ²⁴	Open non-randomized comparative study studying the effect of trauma in 30 patients with PNES and 32 patients with epilepsy
Galimberti et al. ¹⁷	Open non-randomized comparative study on psychological profiles in 31 patients with PNES and 38 patients with PNES and epilepsy
Goldstein et al. ⁸³	Evaluation of cognitive behavioural therapy

Reference	Study: design and number of patients
Jawad et al. ⁶⁵	Open and non-randomized comparative design in 46 female patients with PNES compared to 50 female patients referred to a psychiatric outpatient clinic
Kuyk et al. ³⁶	Open and non-randomized comparative retrospective study on dissociation in 65 patients with PNES and 94 patients with epilepsy
Krumholz and Niedermeyer ¹	Retrospective follow-up study on the natural history and prognosis (5 years) in 34 patients with PNES
Lancman et al. ⁶⁴	Open non-randomized non-controlled study on psychological factors in 93 patients with PNES
Leis et al. ²	Retrospective study of EEG/video and medical records of 47 patients with PNES
Lempert and Schmidt ⁹²	Open non-randomized non-controlled and retrospective follow-up study on natural history and clinical outcome in 50 patients with PNES
Lichter et al. ²⁸	Clinical follow-up of 5 patients with postanesthetic PNES
Lobello et al. ³⁴	Open non-randomized comparative study of results of video evaluation in 91 patients with PNES, 37 with epilepsy and 13 patients with epilepsy and PNES
Marquez et al. ³	Retrospective open non-randomized comparative study looking at BMI in 46 patients with PNES and 46 patients with epilepsy
McDade and Brown ⁹⁰	Open non-controlled and non-randomized treatment study on management and predictive factors of outcome in 18 patients with PNES
Meierkord et al. ⁹³	Open non-randomized non-controlled study on characteristics of video-EEG in 100 patients with PNES
Mökleby et al. ⁵⁵	Open non-randomized comparative study in 23 patients with PNES, 23 patients with somatoform disorders and 23 normal controls
Moore and Baker ¹¹	Retrospective study on psychological characteristics of patients files for 185 patients with PNES
Müller et al. ³⁵	Epidemiological retrospective study of 322 medical records of patients referred to an epilepsy centre. 44 (14%) had PNES, some in combination with epilepsy
O'Sullivan et al. ⁸⁵	Interview study on opinion of general practitioners in 23 patients
Owczarek ⁶¹	Open non-randomized comparative study on MMPI profiles in 66 patients with PNES, 36 patients with epilepsy and 42 patients with combined PNES/epilepsy
Owczarek ⁶²	Open non-randomized comparative study on MMPI profiles in 70 patients with PNES, 42 patients with epilepsy and 40 patients with combined PNES/epilepsy
Owczarek and Jedrzejczak ⁴⁷	Open non-randomized comparative study on MMPI profiles in 38 patients with PNES, 36 patients with epilepsy and 32 patients with combined PNES/epilepsy
Prigatano et al. ³⁰	Non-controlled open treatment study in 9 patients with PNES
Prueter et al. ⁵⁴	Open non-randomized comparative study on dissociative features in 19 patients with PNES, 20 patients with epilepsy and 21 patients with both epilepsy and PNES
Quigg et al. ⁵⁶	Open non-controlled study about quality of life and PNES in 30 patients
Ramchandani and Schindler ⁴³	Open non-randomized non-controlled study on psychiatric factors in 20 patients with PNES
Reuber et al. ⁷⁴	Retrospective study on evidence of brain abnormality of patient files
Reuber et al. ⁴⁹	Open postal questionnaire study on long-term outcome of a retrospective sample of 98 patients with PNES and 66 patients with PNES and epilepsy

Reference	Study: design and number of patients
Reuber et al. ⁵²	Study on psychological outcome in 119 patients with epilepsy and 119 patients with PNES
Reuber et al. ⁵³	Open postal questionnaire study in 85 patients with PNES and 63 with epilepsy
Reuber et al. ⁸⁸	Open postal questionnaire study on long-term outcome. Similar study as Reuber et al. ^{49,52} with different outcomes measures
Rusch et al. ⁸⁶	Open non-randomized non-controlled study on effects of psychological treatment in 26 patients with PNES (including 15 patients with PNES and epilepsy)
Salmon et al. ³⁸	Psychological outcome and etiology in 81 patients with epilepsy and 81 patients with PNES
Sigurdardottir and Olafsson ⁴	Epidemiology of PNES (Icelandic study)
Stewart et al. ⁵⁸	Open non-randomized comparative study in 13 patients with PNES compared to patients with anxiety attacks (n=11) or combined PNES and anxiety attacks (n=13)
Szaflarski et al. ³²	Open non-randomized comparative study on quality of life aspects in 45 patients with PNES and 40 patients with epilepsy
Szaflarski et al. ⁶⁶	Open non-randomized comparative study on quality of life in 53 patients with PNES and 53 patients with epilepsy
Thompson et al. ⁶⁰	Open non-randomized comparative study on psychological etiology in 27 patients with PNES and 22 patients with epilepsy
Tojek et al. ⁴⁵	Open non-randomized comparative study on psychosocial risk factors in 25 patients with PNES and 33 patients with epilepsy
Vanderzant et al. ⁶³	Psychological outcome using the MMPI in 19 patients with PNES
Vincentiis et al. ⁶⁷	Open non-randomized non-controlled comparative study on psychological risk factors in 21 patients with PNES and epilepsy
Walczak et al. ⁸⁹	Open non-randomized and non-controlled study on outcome after diagnosis using telephonic interviews in 51 patients with PNES
Witgert et al. ⁷	Open non-randomized study on frequency of panic symptoms in 39 patients with PNES
Wyllie et al. ⁶⁸	Open non-randomized comparative study on video-EEG in 18 children with PNES and 20 adults with PNES
Zaroff et al. ⁸⁴	Results of psychoeducation and psychotherapy in 10 patients with PNES

Description of the studies

Some comments on the results in Table 3.1 are in order. The dominant type of design is the open non-randomized comparative study. The studies are therefore not protected against the effects of bias, especially selection bias. Patients with epilepsy are mostly used as the comparator. This may seem obvious since the symptoms resemble epileptic seizures, but this is not logical when studying for example the underlying psychopathology or etiology which is presumed to be very different in epilepsy versus PNES. In many cases patients with PNES have been in the diagnostic process as 'epileptic patient' for many years. The effect on daily life may therefore not be different. Also, the sample size is mostly rather limited; the majority in the range of 20-30 patients. Given the high variability of the symptoms and underlying characteristics in these patients, it is doubtful whether any of the studies achieves sufficient power to allow formal conclusions. The larger studies are retrospective

studies and mostly studies on patient files. The only exceptions are postal questionnaire studies. In these studies such a high non-response rate was observed that bias cannot be excluded. The quality of the studies is even more limited when treatment issues are considered. In our Cochrane review, we identified only three studies with a quasi-randomized design¹⁸.

Table 3.2 Overview of reviews on definition, etiology, treatment and prognostic issues in patients with PNES.

Reference	Review topic
Alper ⁶	General update
Alsaadi and Marquez ⁷⁷	PNES: diagnosis, etiology and treatment
Baker et al. ¹⁸	Cochrane review on treatment of PNES
Barry and Sanborn ³⁷	Psychological factors
Betts ⁷⁸	Management of PNES
Bowman ⁵⁹	Indicators for prognosis
Chabolla et al. ²³	Classification
Dekkers and van Domburg ¹³	Diagnosis with an emphasis on psychological diagnosis
Fiszman et al. ⁴⁰	Traumatic events and PTSD in patients with PNES
Francis and Baker ²²	Description of PNES in an historic and societal context, terminology, epidemiology, diagnosis and etiology
Iriarte et al. ⁹	Diagnosis of PNES
Kuyk et al. ³¹	Psychological diagnosis
Krumholz ²⁰	Diagnosis and management
LaFrance and Devinsky ¹⁴	Diagnosis and treatment
LaFrance and Barry ⁴⁴	Update on treatments of PNES
LaFrance et al. ⁴²	Results of an interdisciplinary workshop
Lesser ³³	General update
Massey and Riley ²⁵	General update
Ramani et al. ⁵⁷	General update
Reuber and Elger ⁵	Update on diagnosis and outcome of PNES
Reuber and House ⁷¹	Treatment factors
Riggio ²⁶	Seizure characteristics
Rosenbaum ⁷²	Hypothesis why PNES occur mostly in women
Scull ¹⁹	Terms for PNES
Shen et al. ⁸¹	Protocol for presenting the diagnosis of PNES
Sirven and Glosser ⁶⁹	Epidemiology of PNES
Trimble ²⁹	General update
Wyllie et al. ⁸⁰	PNES in children

Definition and terminology

Several terms are used¹⁹, most frequently the term ‘non-epileptic seizures’ (NES)^{3,12,20}, ‘non-epileptic attack disorder’ (NEAD)^{21,22}, ‘psychogenic non-epileptic seizures’ (PNES)^{10,17,23,24}, ‘pseudoepileptic attack disorder’ (PEAD)¹³, ‘pseudo-seizures’²⁵, ‘psychogenic pseudo-seizures’ (PPS)⁹, ‘psychogenic seizures’^{2,26,27} and ‘dissociative episodes’²⁸. In line with, e.g. Trimble²⁹, Scull¹⁹ and Prigatano et al.³⁰, we prefer terminology that avoids the term ‘pseudo’, a term that tends to imply that the seizures are unreal and can have a pejorative meaning. Moreover, using the term

‘pseudo’ may suggest ‘malinger’. ‘Non-epileptic seizure’ (NES) is a term that is non-judgmental, acceptable to patients and serving descriptive and neutral patterns at the same time. Adding the term ‘psychogenic’ can help to distinguish these seizures from other ‘organic’ based non-epileptic seizures, such as seizures due to cardiac disease. Thus, in our opinion the term ‘psychogenic non-epileptic seizures’ (PNES)^{10,17,31,32} is the preferred term.

Definitions vary widely, but the elements most common are:

- a) an observable abrupt paroxysmal change in behaviour or consciousness¹²; sometimes also defined as episodes of altered movement, sensation, or experience¹⁰ or the internal psychic state¹⁷
- b) the absence of the characteristic electrophysiological changes in the brain, which accompany an epileptic seizure²¹; hence the absence of ictal or postictal EEG changes^{12,14}. The combined EEG and video recordings of seizure events (EEG-video recordings) therefore are considered the gold standard in the diagnosis of PNES^{33,34}
- c) no evidence for other somatic causes for the seizures (such as cardiac disease)^{13,35}
- d) usually the seizure is time limited⁷
- e) and resembles, or is mistaken for, epilepsy or at least mimics epileptic seizures^{17,32}
- f) there is no voluntary control³
- g) the seizures are caused by ‘a psychological process’^{5,10}; ‘a variety of psychogenic processes’⁹. This latter factor refers to the psychological etiology, the psychic causes of the seizures.

A working definition, based on the aforementioned elements could be: a psychogenic non-epileptic seizure is an observable abrupt paroxysmal change in behaviour or consciousness, that resembles an epileptic seizure, but that is not accompanied by the electrophysiological changes that accompany an epileptic seizure or clinical evidence for epilepsy, for which no other evidence is found for other somatic causes for the seizures, whereas there is positive evidence or a strong suspicion for psychogenic factors that may have caused the seizure.

Psychological etiology

Many psychosocial factors and psychological mechanisms have found to be associated with PNES, often in a non-systematic order. We firstly discuss each of these factors as they are presented in literature and subsequently order them in an attempt to develop a model that expresses the relationships between such factors.

Trauma

This factor is most commonly mentioned especially in early studies. A history of sexual or physical abuse or other significant traumas such as significant bereavement and post-traumatic stress disorder (PTSD)^{11,21,24,36-39}. Fiszman et al.⁴⁰ found very high rates (15-40% exceeding the incidence in control) of general trauma (44-100%) and physical or sexual abuse (23-77%). PNES samples also showed a higher prevalence of PTSD than control groups, raising the possibility that PNES may arise as a clinical expression of a hypothetical PTSD subtype. According to Betts and Boden⁴¹ this factor is often underestimated as most patients will not easily disclose a history of abuse ('unspeakable dilemmas'). They see PNES either as a form of acting out of a 'flash back' experience, thus a kind of acting-out the memory of the abuse, or as a 'cut-off phenomenon', an automatic reaction to intrusion into consciousness of unpleasant memories. LaFrance et al.⁴² report that in children 9-18 years old about 32% had a history of sexual abuse, 6% of physical abuse and 44% severe family stressors. Ramchandi and Schindler⁴³ found 'guilt-laden bereavement' to be an important precursor of seizures.

Dissociation

This factor is often discussed in relation to traumatic experiences. Dissociation^{6,12,44} is not a true cause in the sense of an etiological factor, but merely a mechanism, i.e. a disruption of the usually integrated functions of identity, memory, consciousness or perceptions of the environment. Dissociation refers to a loss or altered integration of the continuity of the experience of the self. Its function is probably to spare the normally integrated conscious self from confronting the painful and unendurable by altering conscious experience⁶. Bowman and Markand¹⁵ conclude that PNES patients appeared to express dissociative distress about reported trauma, often sexual abuse⁴⁵. The 'conversion V' profile on the MMPI-2⁴⁶, collectively observed in the PNES patients is compatible with reports that dissociative reactions (dissociation between feelings and thoughts/memories) are common in these patients^{30,47}. Dissociation and conversion are linked to such an extent that the ICD classifies conversion as a dissociative disorder^{6,48}. In addition there are indications that PNES patients are characterized by a relatively high level of hypnotisability as measured with the Stanford Hypnotic Clinical Scale^{31,36}.

Somatisation disorder

Somatisation disorder or high levels of somatisation, including Briquet's syndrome^{6,21,49}, generally present as conversion disorder³⁰. Reuber et al.⁴⁹ found that as a group, PNES patients show a high tendency to express psychosocial distress by producing unexplained somatic symptoms which are brought to medical attention. Bewley et al.⁵⁰ demonstrated a relationship between PNES and certain subscales of an

instrument measuring alexithymia (Toronto Alexithymia Scale, TAS-20). Alexithymia is a concept expressing that patients experience emotions as physiological reactions as opposed to feelings.

Personality factors or disorders^{15,51,52}

A problem in comparing studies on personality factors is that different diagnostic systems are used to describe personality disorders, such as the descriptive use of axis II DSM-IV personality disorders or the more dimensional (structural) categorisation on the basis of psychological tests such as the MMPI-2 or the DAPP Q. Some studies^{10,53} distinguish three types of personality disorders in patients with PNES: a) borderline personality disorder (assumed to be the most common type in patients with PNES); b) overly controlled personality; and c) avoidant personality disorder. According to Alper⁶, dependant personality traits are the dominant type of personality dysfunction in patients with PNES. Reuber et al.⁵³ propose a kind of general characteristic of the personality structure of patients with PNES, described as 'emotional dysregulation'. This broad dimension of personality pathology reflects stable personality vulnerabilities, which put individuals at greater risk of anxiety and depressive symptoms. This has been termed 'general neurotic syndrome' in the past and is characterized by a combination of high trait anxiety/ high arousability combined with poor coping. Thompson et al.⁶⁰ using personality assessments with the MMPI, report that patients with PNES have significantly higher scores on the scales 'hypochondriasis', 'hysteria', 'depression' and 'schizophrenia' than do patients with epilepsy. This was confirmed in the study by Owczarek⁶¹. Binder et al.²⁷ report that PNES patients scored significantly higher on the somatoform MMPI profiles. Owczarek⁶² used personality indices to interpret MMPI results and found that patients with PNES alone or in combination with epileptic seizures scored significantly higher than the epileptic group on anxiety measures. This suggests that the predisposition of PNES is reflected in the anxiety dimensions of the personality profile. Nonetheless, substantial disagreement exists about the sensitivity of the test, regardless of the interpretative algorithms used. Vanderzant et al.⁶³, e.g. found no significant MMPI score differentiating between PNES and epilepsy.

Coping

A special element of personality is coping or the way difficult situations are handled. Some authors report a specific coping style in patients with PNES^{3,10,55,64}, often characterized by hostility (anger and mistrust in other people). It is possible that the hostile coping style may be related to relatively high incidence of physical and sexual abuse and that any subjective experience of 'not being understood' or rejected would increase the hostile behaviour⁵⁵. Measuring defence mechanisms with the DMI (Defence Mechanisms Inventory) Jawad et al.⁶⁵ found that patients with PNES were

characterized by higher scores on the 'reversal' scale and lower scores on the 'turning against self' scale. This indicates that these patients prefer to use denial and repression to perceived threats rather than to confront and solve problems. The authors state that therapists need to recognize the avoidant responses of the patient in dealing with negative life circumstances which have interfered with their ability to engage in deep intimate relationships and prevented them from acquiring effective coping skills. Noteworthy in this case is the study by Marquez et al.³ in which a statistically significant association is found between PNES and high body-mass index. It is possible that the psychopathological processes underlying PNES also contribute to weight problems. PNES and weight deregulation may be two aspects of the PNES patients underlying coping pattern in situations with psychological distress.

Psychiatric comorbidity

Psychiatric disorders have been found, mostly depression^{12,29,58}, panic disorder with or without agoraphobia and affective disorders such as chronic anxiety^{55,64,66}. According to Abubakr et al.¹² depression is the most common comorbid disorder in patients with PNES. In line with this observation, suicide attempts have been reported. Some studies⁷ report that adolescents with PNES may experience a greater frequency of symptoms associated with panic attacks during their typical seizure events than adults. The results raise the possibility that the role of panic disorder in PNES may differ, depending on age of presentation. Psychiatric disorders, may however be the cause or the result of PNES, an epiphenomenon or a different diagnostic term to describe PNES. For example depression may be the result of having PNES for a longer period, it may be the etiological factor causing PNES and it may be a comorbid disorder (unrelated to PNES). Categorization of PNES patients into DSM-IV or ICD-10 diagnoses has been done where these seizures were diagnosed as either 'dissociative disorders' (ICD-10)⁵⁴ or on the DSM on either axis I, or axis II or both^{5,53}. The most frequent DSM-IV diagnosis for PNES appears to be somatoform disorder (conversion disorder)^{10,17,54}. The second most common diagnosis was anxiety disorder^{17,55,56}. For DSM-IV axis II PNES patients showed higher percentages of cluster B personality disorders, being indicative of possible 'acting out' behaviours^{17,57,58}. Nonetheless, specificity of such classification has not been demonstrated⁵⁹. PNES patients had multiple psychiatric diagnoses, including somatoform disorder (89%), dissociative disorder (91%), affective disorder (64%), personality disorder (62%), PTSD (49%) and other anxiety disorders (47%).

Age factors

Children with PNES appear to have a different psychological profile when compared to adults^{37,51}. In children the role of situational stress is more apparent⁶⁷. Adolescence is recognized as a specific risk factor, being a potential time of turmoil and psychological

distress, when self-esteem and important relationships are being developed and the person gains their own identity. These are highly vulnerable processes that in some cases may lead to somatoform reactions such as PNES^{68,69}.

Behavioural modification

Behaviourally oriented concepts of primary and secondary gain and adaptation of the sick role are often the main factor behind the development of PNES in intellectually disabled persons³⁰. Secondary gain may more generally play a role in the prolongation of seizures^{11,12}. The primary gain is the reduction of subjective anxiety and related affects by expressing an underlying conflict or unmet need in the form of a physical symptom. This allows the patient to escape the unpleasant emotions evoked by conscious awareness of the conflict. This is not perceived or experienced consciously. Secondary gain involves clearly identifiable external incentives, i.e. meeting of dependency needs, monetary gain, escape from unpleasant circumstances or role demands, and so on. This gain may or may not be consciously perceived⁶.

Other behaviourally oriented concepts are symptom modelling and the influence of domestic stressors (relationship problems, family dysfunctioning)^{11,38}. Symptom modelling is the process by which the patient may acquire a symptom on the basis of observing a physiologically genuine example of the symptom. This is particularly relevant to patients with both PNES and epilepsy, but also to patients with a relative with epilepsy^{6,51,64}.

Sometimes 'chronic PNES' are distinguished from 'acute' or situational PNES. The latter are generally short-lived, self-limiting and with good prognosis. Most commonly, domestic stressors precede the development of acute PNES⁷⁰.

Malingering is sometimes seen in patients who expect financial compensation^{12,71}; malingering is the only factor with conscious manipulation of the symptoms.

Gender

There is a dominance of the female gender^{12,26}. Reasons for this preponderance are not entirely clear. No specific or consistent difference in the underlying psychopathology between men and women with PNES has been reported. However, some authors speculate that women and men differ in vulnerability to physical or emotional trauma and that at least in the affected women with PNES the attack is a reflection of 'rage, fear, and helplessness' against domination or abuse⁷².

'Organicity'

A specific vulnerability may play a role in the development of PNES, possibly as an extra factor. This factor is often labelled as 'organicity'. In some studies

neuropsychological deficits have been found^{37,73}. Other studies have reported subtle neurologic dysfunction⁷⁴. Also histories of head injury may be a significant provocation factor in patients with PNES in as many as 20-30%^{20,64,75} as well as chronic pain³⁹. Benbadis⁷⁶ found a relationship between PNES and chronic pain or fibromyalgia. Antiepileptic drug toxicity may increase the frequency or cause dramatic changes in the pattern of PNES¹, which is a finding of particular importance in the light of the observed diagnostic delay in these patients. The effect of antiepileptics is in line with the observation that PNES sometimes occur after anaesthesia. A possible explanation for this relationship is that by inducing a state of altered awareness, an anaesthetic agent can initiate dissociative episodes in vulnerable personalities²⁸.

The previously mentioned factors represent a heterogeneous group and each may have a differential impact in the causation, development and prolongation of PNES. Not all factors have a similar impact. Sexual abuse may be an example of a psychogenic factor, an underlying cause for PNES, whereas dissociation may be the actual psychological mechanism that shapes or modulates the seizures. Symptom modelling may simply be a factor that explains why the symptoms take the form of an epileptic seizure and not that of a tremor or movement disorder. Drug toxicity may not cause PNES but lower the threshold for PNES. In line with this, Galimberti et al.¹⁷ suggest that one factor is not always sufficient to develop PNES. In their opinion at least two aspects of a proposed three-factor process must be active to develop PNES, i.e. the presence of a psychopathological disorder and the influence of a 'general trigger mechanism' which leads to increased tendency towards somatisation^{8,51,63}. Also Prigatano et al.³⁰ postulate a two-factor model, based on the fact that many patients with PNES have neuropsychological deficits: one factor is an emotional mechanism such as a higher dissociation tendency in response to experiencing irresolvable situations that they cannot manage as adults; the second factor may be greater vulnerability of the brain for not tolerating conflictual situations. This interaction may well produce some underlying neurophysiological disturbance that disrupts sensorimotor function or consciousness, see also^{63,77}. Reuber and Elger⁵ suggest a model with interacting predisposing, precipitating and perpetuating factors based on other models for psychosomatic disorders.

Based on the above factors we propose a model here, with 5 different layers or levels:

Level 1. Psychological etiology the factors that are involved in the causation of PNES, such as sexual abuse or other traumatic experiences.

Level 2. Vulnerability refers to factors that predispose a person to develop psychosomatic symptoms, such as PNES. Examples are personality factors, gender, neuropsychological impairments and age. Many authors have pointed to the specific vulnerability of patients with PNES both in terms of the emotional 'make-up' and their neuropsychological functioning. Also possible organic factors may play a role here.

Level 3. Shaping factors can specifically shape the symptoms in the direction or form of ‘seizures’ (in contrast to for example movement disorders or ‘headache-like symptoms’). A shaping factor may be a relative with epileptic seizures (symptom modelling) or having epilepsy in the past.

Level 4. Triggering factors create circumstances or situations that provoke PNES such as factors that refer to first gain. Also psychological mechanisms that transfer an emotional state into a seizure can be part of these triggering factors, such as dissociation and somatisation. Such factors explain why seizures occur on a specific day, or in a cluster or why there is a period of remission. This contrasts PNES from conversion states that more or less have a permanent presentation.

Level 5. Prolongation factors. The previous factors are specifically important in the development of PNES. Prolongation factors are important in explaining why the seizures persist and PNES may become a chronic disorder. These factors profile its frequency and its resistance against therapy. Such modulating factors are, e.g. the coping strategy of the patient and secondary gain aspects.

Figure 3.1 Model of psychological factors involved in PNES.

Figure 3.1. describes the assumed relationship between such factors. This model is not conclusive as some factors can interact at several levels of the model. Coping strategies may be involved in the causation of PNES and may have a role in the

vulnerability, whereas family factors may contribute to the prolongation of seizures and not only in the development. This model resembles other models used to explain somatoform disorders.

A comparable approach is seen in some studies that have attempted to distinguish subtypes of PNES, based on some of the previously mentioned factors. An interesting approach of the relationship between PNES and personality disorders is presented by Cragar et al.¹⁰. PNES subtypes have been described on dimensions of psychopathology as measured by the MMPI-2. Three personality clusters emerged. The authors offer tentative descriptions of the clusters: (1) 'depressed neurotics'; (2) 'somatic defenders'; (3) 'activated neurotics'. Clusters 1 and 3 also differ significantly on neurocognitive testing, with cluster 1 patients scoring lower than cluster 3 in memory functioning, while cluster 2 individuals show generally average cognition across domains. Reuber and House⁷¹ distinguish three groups, based on psychiatric comorbidity (present in 70% of the PNES patients in their study): (a) disorders of mood-depression, anxiety, panic and PTSD; (b) somatisation and abnormal illness behaviour; and (c) borderline personality.

Treatment/intervention

Several aspects of treatment and intervention are commonly reported.

a) Explanation

It is often emphasized that this is the necessary first step of intervention^{23,42,77-79}. Important is that the diagnosis of PNES is communicated to the patient in a non-accusative, open way⁸⁰. Betts and Boden²¹ suggest using the term 'emotional attack' in the communication with the patient. A recent international workshop proposed to use the term 'functional seizure'⁴². Different authors mention different kinds of protocols for this phase^{21,81}. Reuber and Elger⁵ report that PNES can stop with an explanation of the problem and no further therapy. This is also demonstrated in the study by Farias et al.⁷⁹. While communicating with the patient, it is imperative to realize that PNES often result from a mismatch of traumatic experience and inability to cope, so simply telling patients that they do not have epilepsy may traumatize them further, especially when they are then abandoned to their fate⁵. In those cases, presenting the diagnosis and its nonorganic etiology may have led some patients to replace PNES with new confounding symptoms or symptom substitution⁸². Patients can understand the concept of emotions/stress causing involuntary physical reactions and that such reactions can be 'pathological'⁵. On the other hand, Alper⁶ warns for an early emphasis on psychogenic factors. In his experience, it is far better that the patient with PNES is being told they do not have epilepsy by the neurologist than to be informed of psychogenesis by the psychiatrist at this stage. Contrary to some reports it has been shown that outcome is better in patients with PNES who believe that they have PNES rather than epilepsy⁸².

b) Additional treatment

Some patients will need a period of additional treatment that has to vary from patient to patient, based on the underlying psychological mechanisms that have triggered PNES^{6,21,77}. Only very few studies have examined the management of PNES. Inspiration has to come from studies looking at similar disorders⁵. Possibilities mentioned in literature are:

- Procedures of behaviour therapy or operant conditioning: the primary focus is attempting to prevent 'rewarding' of seizure activity by ignoring it and deliberately rewarding non-seizure activity by verbal praise and encouragement. The essential principle is to achieve extinction of the PNES as a conditioned response to secondary gain. Behavioural therapy uses progressive relaxation, systematic desensitization, exposure plus response prevention to modify anxiety and allow more adaptive responses⁴⁴. A specific form of behaviour therapy is 'cognitive behaviour therapy' that is aimed at changing dysfunctional thought processes. Behaviour modification may be particularly useful in patients where the production of PNES has been reinforced inadvertently as a means of engaging the attention of others or to evade unwanted activities⁶⁹. The techniques are particularly suited to the management of patients with neuropsychological impairment, psychotic levels of ego disorganization or severe personality disorders^{6,9,21,69}. A recent open pilot study⁸³ of cognitive behavioural therapy for PNES found that participants had a significant reduction in PNES episode frequency and reported improved psychosocial functioning following 12 sessions of treatment. Also special forms of (cognitive behavioural) therapy are mentioned in literature.
- Formal, intensive anxiety or anger management training, aimed at both reducing general tension and also specifically at helping patients to recognize seizure onset and immediately employing relaxation techniques to try to stop it. Prigatano et al.³⁰ hypothesize that if PNES are precipitated by expressions of anger or other intolerable emotions, psychological treatment intended to enhance the awareness of unexpressed negative emotions and to confront ongoing stressors should decrease the frequency of PNES.
- Formal abreaction (mostly hypnotic abreaction) to try to discover how the patients feel during a seizure²¹.
- Formal individual psychotherapy^{26,65}. There are different forms of psychotherapy, ranging from cognitive behavioural therapy to more supportive, practical forms to psychodynamic forms of psychotherapy, depending on the underlying problem and capacities of the patients^{14,21,70,82} (see also overview in⁷⁷). LaFrance and Devinsky¹⁴ call this 'diagnosis-directed psychotherapy'. Reuber and Elger⁵ claim that psychotherapy aims at modulating temperamental extremes, to help patients recognize early signs of crisis, or to disrupt secondary escalation. It may also be directed at the identification of stressors and the

presentation of alternative ways of addressing problems in the social environment which are interacting with personal vulnerability. Also psychotherapy may focus on the original negative event or trauma believed to have precipitated the seizures¹¹. Barry and Sanborn³⁷ refer to the concept of language dysfunction allowing the patient to learn to express distress verbally and to eventually give up somatic preoccupations.

- Some patients benefit from group (psycho)therapy^{6,41,44,84}. Prigatano et al.³⁰ report that because many patients are emotionally or socially isolated many appreciated having a group experience simply because they wanted to know that they were not alone with their problems. Other advantages are summarized by LaFrance and Barry⁴⁴, including explanation, possibly with the use of psychoeducation, support network building, decreasing social isolation, as well as allowing direct experiences witnessing NES and identifying possible causation.
- Family therapy (including couples therapy)^{6,21,44,82}: the family needs to cope with their anxiety about the seizures and learn not to reinforce them. Also in children family stressors are an important target for treatment³⁷.
- Medication (tranquillizers), for a few patients who have PNES at night, medication can be used to prevent the patient waking up during the night for a few weeks^{21,71}. Alper⁶ emphasizes that pharmacotherapy should be especially considered when there is a relation with panic disorder, major mood disorder, ADD or psychoses as these disorders have relatively specific pharmacotherapeutic approaches. LaFrance and Barry⁴⁴ (see also¹⁴) suggest that pharmacotherapy for psychiatric comorbidities of PNES with a selective serotonin reuptake inhibitor (SSRI) or related compounds may be useful. As yet no acute pharmacological treatment has been developed except for stopping seizures with excessive sedation and paralytic agents used in 'pseudo status'. The pharmacotherapy of the dissociative disorders or of somatisation disorder is less well-established.
- For very chronic somatisers 'case-management' may be more appropriate⁷¹. The primary aim is then more limited, i.e. reducing emergency admissions, unnecessary investigations, and treatment⁵. Often the general practitioner has to be involved in such management⁸⁵.

Although variants of cognitive (behavioural) therapy currently form the preferred type of treatment for most patients, the exact choice of treatment should be based on differences in e.g. coping style, anger control style, attitude style and defence style^{9,10}. Ettinger et al.⁸² used for example an eclectic approach with elements of the above. Rusch et al.⁸⁶ found that most of the patients benefited from exposure therapy, which is not surprising, given the considerable avoidance exhibited by these patients. Reuber and Elger⁵ emphasize that if the underlying etiology is an axis I disorder, such as depression, patients may respond to psychological or pharmacological treatments. If, on the other hand patients show evidence of maladaptive personality, chronic somatisation, or dissociation tendencies treatment may more realistically aim at

behaviour modification rather than cure. Some patients may actually benefit from the treatment of their psychiatric comorbidity, such as depression. The experience is that at least 2 years of outpatient treatment is needed⁴¹. Reuber et al.⁵³ emphasize that much of the vulnerability associated with personality pathology in patients with PNES have implications for psychotherapeutic treatment: efforts should focus on change of individual adaptation and coping processes rather than on basic tendencies in personality, which are less likely to change.

Betts and Boden²¹ report that for some patients (particularly post-traumatic or symbolic attacks) treatment in the community from the start is preferable and it may be important not to admit them to hospital. Buchanan and Snars⁷⁰ confirm this approach: taking into account the frequency of domestic stresses in the etiology of PNES, it is not surprising that relapse should be frequent after hospital discharge. Moreover Müller et al.³⁵, report that the observed tendency to refer patients with PNES to a centre of excellence too late (there is an average delay between the onset of PNES and diagnosis of 7 years) is an important obstacle for treatment; most of these patients will have had long periods in which they were treated with antiepileptic drugs for 'refractory epilepsy' which complicates their acceptance of the seizures as non-epileptic⁸⁷.

It is also important to note that treatment can be focused on one level of the underlying psychogenic etiology, disregarding more fundamental problems when these can not be changed. For example, not all patients with trauma and abuse histories did require direct intervention for abuse or trauma memories to achieve cessation of their seizures^{38,86}.

There is little literature on the efficacy of treatment strategies for PNES and no standardized treatment protocols for PNES exist^{9,10}. Ettinger et al.⁸² summarise the methodological problems in most studies. Some of these studies were limited by small sample size, inclusion of patients with both PNES and epileptic seizures, reliance on methods other than video-EEG to make the PNES diagnosis and marked variability in the follow-up durations. Literature only mentions three studies with a randomized or quasi-randomized design which in fact do not allow definite conclusions^{18,44}. In a non-controlled study, Buchanan and Snars⁷⁰, report successful outcomes in 50% of the patients, largely by confronting them with the diagnosis of PNES, 30% with formal psychotherapy and a similar number with ongoing support. Szaflarski et al.³² summarise the results of many studies and case reports and conclude that appropriate diagnosis and management of PNES can lead to remission of PNES in 19-52%^{88,89}, to improvement in 75-95% of the patients and decrease of health care utilization by 69-97%. An important factor is mentioned by Sirven and Glosser⁶⁹: simply using the retrospectively estimated seizure frequency is not likely to produce useful data since the behaviour is plastic and might simply shift to another somatic complaint. Relevant outcome measures might include: health related quality of life indices, employment status, health care utilization rates, physical morbidity and mortality figures⁵⁶. A relationship between seizure outcome and 'quality of life

measures' have been reported. The main finding is that a complete cessation of PNES is required to demonstrate a significantly higher QOL. Neither the rate nor the interval change in the rate of PNES following diagnosis was proportional to QOL indices. This suggests that the goal in treatment of NES should be full remission of PNES rather than a reduction in seizure frequency⁵⁶.

A recent multidisciplinary, international workshop assessed the state of affairs on this field and laid the groundwork to fill the treatment void⁴². They recommend a PNES treatment study that would have 3 arms: a neurological follow-up control group, a cognitive-behavioural therapy (CBT) intervention group, and a psychopharmacological treatment group. Outcomes would include both measures of seizure occurrence (seizure frequency, but also seizure severity), measures assessing aspects of psychological etiology, but also practical measures for social outcome, such as employment.

In the case of coexistence of PNES and epileptic seizures in the same patient, it is particularly important to determine whether patients require adaptation of their AED-treatment. In these patients, it is important that they learn to differentiate between the two types of seizures which make the self reports about seizure frequency more reliable.

Prognosis

Very few reviews have dealt with the prognosis of PNES once the diagnosis had been made. Therefore, our knowledge of prognosis remains sketchy^{21,71}. Previous outcome studies described only small samples with 50 patients or less, had less than 2-year follow-up, focused on the persistence of PNES rather than wider psychosocial criteria or assessed no or few prognostic factors, although all investigators agree that outcome is variable⁵². Iriarte et al.⁹ report that in general 1/3rd of the patients will become seizure free after diagnosis and 50-70% will have improvement in seizure frequency. There are, however, no controlled studies of long-term outcome of PNES patients⁶. Reuber and House⁷¹ claim that a quarter of the patients become chronic. Ettinger et al.⁸² report a mean duration of PNES of 7.79 years with a range of 1-38 years. Betts and Boden²¹ report that although the immediate outcome of treatment measures will be reasonably good (see also⁹⁰), at the 2-year follow-up many patients had seizure relapse. Especially with treatment in the clinic, this can be misleading. In the study by Krumholz and Niedermeyer¹ 56% of the 34 patients were regarded as having poor outcome at 2-year follow-up, with very similar results for the 5-year follow-up period. In the studies of Farias et al.⁷⁹ and O' Sullivan et al.⁸⁵ almost all patients had an initial good response to the diagnosis of PNES, but at follow up at 18 months about 80% of the patients had seizure relapse^{79,85}.

Reuber et al.⁵², report that patients admitted to epilepsy centres have a poor long-term prognosis. After a mean of 11 years after seizure onset and 4 years after diagnosis, two-thirds of the patients continued to have seizures and more than half

were dependent on social security. On the contrary, Bodde et al.⁹¹ report a more favourable prognosis after diagnosis in an epilepsy centre both in terms of seizure frequency and psychological outcome. Such differences are probably caused by differences in study populations and type of diagnostic procedures. Buchanan and Snars⁷⁰ distinguish an 'acute' from a 'chronic' group: 76% of the patients in their study showed improvement of seizure frequency and, on follow up, 80% of the acute group and 28% of the chronic group became seizure free. Wyllie et al.⁶⁸ showed substantially better remission rates for children and adolescents of 73, 75 and 81% after 1, 2 and 3 years follow-up.

Prognosis is different, dependent on the underlying psychological disorder. For some patients, an empathic confrontation with the fact that the seizures are non-epileptic may be enough to stop them⁹¹. Others only resolve with intensive cognitive, behavioural and anxiety management. Those which are probably replays of previous trauma require very intensive and prolonged therapy. In general it is observed that differences in psychopathology may have important implications for prognosis¹⁰. Iriarte et al.⁹ and Reuber and Elger⁵, summarise the characteristics of the patients with favourable prognoses: no or mildly severe psychiatric history¹⁰, short history of PNES/early diagnosis^{41,70,92}, identifiable acute psychological trauma preceding the onset of PNES, living independently, absence of concomitant epilepsy⁹³(although this is debated⁵²), a normal IQ, higher socio-economic class, less dramatic seizures (no positive motor features, no ictal incontinence or tongue biting, no PNES status or admission to intensive care), younger age^{51,68,94}, the absence of a past history of violence⁶, no ongoing use of AED's^{1,87}, and being female not male^{39,59,77}. Outcome appeared to be associated with measures of personality traits. Better outcome is associated with lower scores of the higher order personality dimensions 'inhibitedness', 'emotional dysregulation' and 'compulsivity'⁵². Especially 'inhibitedness' is an important predictor for outcome and thus represents an important factor for prognosis. High scores exhibit reluctant self-disclosure and restricted affective expression of anger and of positive sentiments.

PNES often recur once the patient returns to the community, since he/she is often returning to the very stresses that led to PNES in the first place; relapse particularly of post-traumatic or symbolic PNES usually occurs⁵².

Outcome is nearly always discussed in terms of reduction of seizure frequency. Reuber and House⁷¹ emphasize that other outcomes (such as employment status) may be of greater importance for the patient. In that respect it is important that in some countries and under some conditions patients with PNES are not allowed to keep their driving license which may seriously restrict their occupational possibilities. Sirven and Glosser⁶⁹ found that the longer the PNES continue, the lower the probability that psychosocial morbidity will improve even if the correct diagnosis is later made. Betts and Boden²¹ report that in a substantial number of patients, it seems difficult to completely remove the label of epilepsy. In many patients family pressure appears to lead to re-introduction of anticonvulsant medication. Sirven and

Glosser⁶⁹ demonstrated that if PNES even temporarily decline as a placebo response to AEDs, the belief in the diagnosis 'epilepsy' can be so strong that it can dissuade subsequent physicians from reconsidering the case or discontinuing therapy. Their conclusion is that it may take more courage to stop pharmacotherapy in such patients than to start it.

Discussion

In this systematic review we identified 93 papers through the period 1980 up till 2005 (26 years), of which 65 were actual studies. The quality of most research is limited, due to serious methodological limitations. Nonetheless, they represent some key data on treatment and etiology of PNES.

Although there are several terms used, in this review the non-judgemental term psychogenic non-epileptic seizures (PNES) is the preferred term. In a first phase PNES refer to not having epileptic seizures, but in a second phase it seems important to search for positive evidence for psychogenic factors that may have caused the seizures⁹⁵.

A wide range of psychogenic factors have been identified that may underlie the occurrence of PNES in individual patients ranging from a history of sexual abuse to personality disorders. Such factors do not have a similar impact; consequently some studies propose a 'multifactor approach': i.e. one factor is not always sufficient to develop PNES. In most patients several of such factors would interact to develop PNES in a patient. Examples are the presence of a psychopathological disorder and the influence of a "general trigger mechanism" or an emotional mechanism such as a higher dissociation tendency or a greater vulnerability of the brain for not tolerating conflictual situations. Based on the literature a model is proposed with five different layers: psychological etiology, vulnerability, shaping factors, trigger and prolongation factors. In this model the paroxysmal nature of the seizures is integrated, which is a specific aspect of PNES in comparison to other psychosomatic disorders. Possibly such a model can help in providing options for therapy, explaining therapy results, i.e. prognosis.

This model assumes that PNES is a unique symptom or disorder. Others such as Quigg et al.⁵⁶ state that PNES should not be considered a disorder in itself, but a symptom of an underlying psychological or psychiatric disorder or recent trauma. Therefore PNES can also be considered a symptom very similar to somatoform disorders including somatisation and conversion.

In line with the heterogeneity of factors involved, a plethora of psychological treatment strategies is available ranging from family therapy to hypnosis. Till now, no accepted protocol for the treatment of PNES exists and no randomized clinical trials have been carried out. There is consensus that treatment should be focused on the psychogenic factors that have triggered the PNES in an individual patient, taking into

account also the characteristics of the personality ‘make-up’, i.e. coping style, anger control style, attitude style and defence style. Also outcome can be measured in terms of seizure occurrence, but other measures might include quality of life, employment status and health care utilization. Both diagnosis and treatment seem to profit from a multidisciplinary approach, although not always simultaneously^{9,42,69}.

Again, if PNES is not seen as a unique symptom but simply as one of the many possible symptoms of a somatoform disorder, then the question must be raised whether we should treat PNES as a separate symptom or only focus on the underlying psychogenic factors.

Prognosis is unclear but studies consistently report that 1/3rd to 1/4th of the patients become chronic. Characteristics of the patients with good outcome are: no or mildly severe psychiatric history, short history of PNES, identifiable acute psychological trauma preceding onset PNES, living independently and the absence of concomitant epilepsy. More attention is needed for other outcomes such as employment status that may be of greater importance for the patient. In a substantial number of patients it seems difficult to completely remove the label of epilepsy. In these cases it seems imperative that the patient can recognize the differences between PNES and epileptic seizures. In many patients family pressure appears to lead to re-introduction of anticonvulsant medication. Finally more systematic treatment –effect studies are needed and they probably benefit from a theoretical frame-work about the etiology of PNES. A possible first step might be testing validity of the proposed model for different PNES patients.

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Part 2

Lessons from current treatment

Chapter 4

Factors involved in the long-term prognosis of psychogenic non-epileptic seizures

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J Psychosom Res 2007;62:545-51

Abstract

Introduction

Information on the long-term effects of psychogenic non-epileptic seizures (PNES) is limited. We therefore reassessed 22 patients 4-6 years after the initial diagnosis of PNES in a tertiary referral epilepsy centre. The diagnosis was confirmed using clinical description and additional electroencephalogram (EEG) investigations in 1998, 1999 and 2000. Patients with epilepsy and PNES as comorbid symptoms were not included. Reassessments were aimed at seizure reduction and possible psychogenic factors.

Methods

Three psychological tests were used at baseline at the time of diagnosis and repeated at end point. These three tests assessed different “levels” of psychological function [i.e., complaints (The Symptoms Check List Revised), coping strategy (The Dissociation Questionnaire), and personality factors/psychopathology (The Dutch-language short version of the Minnesota Multiphasic Personality Inventory-2)].

Results

Twenty-two patients were included. Seizure frequency showed statistically significant reduction. At the time of diagnosis, none of the patients was seizure-free or had only yearly seizures, whereas at end point 7, of 22 patients were completely in remission and 3 patients had only occasional seizures. The number of patients with daily seizures dropped from nine to two. It has not been fully clarified which factors caused this improvement, but the common denominators are that a definitive expert diagnosis in a tertiary centre was made and all possible efforts were made to inform the patient in a respectful manner about this diagnosis.

In addition to seizure reduction, there was improvement on different levels of psychological function, showing reduction in psychological distress, reduction in dissociative features such as amnesia, increase in self-control, reduction in feelings of dissatisfaction and passive avoidant behavior, and a more active attitude towards social contact.

Conclusion

In the long term, the patients with PNES who were included in our study have more self-control and approach social contact with a more self-confident attitude. This does not necessarily reflect a causal relationship with the observed seizure reduction. Nonetheless, it is noteworthy that, post aut propter, the eradication of a symptom (i.e., seizures) with social consequences is followed by or is associated with a more confident social attitude. This opens possibilities for treatment strategies.

Introduction

Psychogenic non-epileptic seizures (PNES) are a relatively frequently reported symptom. For example, 7-10% of patients referred to a specialized epilepsy center in The Netherlands have PNES¹ and, internationally, estimates of up to 33% have been mentioned². In theory, the distinction between epileptic seizures and PNES is evident³. Epileptic seizures are the clinical manifestation of a sudden abnormal change in brain function, accompanied by excessive electrical discharge of brain cells. PNES are defined as a sudden disruptive change in a person's behavior, which is usually time-limited and resembles or is mistaken for epilepsy but is not accompanied by abnormal paroxysmal discharges on electroencephalogram (EEG) and occurs as a symptom of emotional disturbances, personality factors, or present or historical social circumstances⁴⁻⁶. Although diagnosis can be difficult, diagnostic features have been better characterized in recent years. Diagnosing PNES is important because of potential iatrogenic hazards. Patients may be diagnosed as suffering from intractable epilepsies and may be overtreated⁷. There are indications that prognosis in the long term may be worse in such cases⁸. In addition, long periods of uncertainty of the diagnosis may have a negative impact on social development and occupational opportunities⁹, which again may have long-lasting effects. Comparatively little research has been done on long-term prognosis after the diagnosis¹⁰⁻¹². Validated treatments and controlled trials are lacking¹³. Furthermore, follow-up period is mostly relatively short, varying from 3 months to a year after diagnosis^{14,15}.

The definition of PNES is hindered by a diversity of conflicting terminologies, such as hysterical seizures, psychogenic seizures, non-epileptic seizures, and functional seizures^{16,17}. In the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*, PNES is classified as a "Conversion disorder with seizures or convulsions." This variation in terminology represents a variety of models proposed to explain PNES. In fact, theories regarding the causes of these seizures are probably as diverse as the phenomenology of this type of seizure. Using *Diagnostic and Statistical Manual of Mental Disorders, Third Edition* criteria, Stewart et al.¹⁸ were able to uncover several forms of psychopathology in patients with PNES, with a clear tendency for the combination of borderline and antisocial personality disorders. A remarkable finding was that hysteria was not a common diagnosis. The synonym "hysterical seizure" for PNES is, therefore, not correct. The variety of theoretical models explaining PNES probably reflects the heterogeneity of the psychogenic etiology of PNES, which can be a symptom of various affective and psychiatric factors^{19,20}. As yet, there is no accepted model explaining the psychogenic factors leading to PNES. There are indications that, often, more than one factor or psychogenic mechanism operates in PNES^{15,21}.

Some attempts have been made to classify patients with PNES into distinct groups requiring different types of interventions and with different prognosis²². For example, persisting seizures are expected to occur in patients with personality disorders^{8,23}, whereas, patients who have PNES because of recently experienced extreme stressors

are considered relatively easy to treat and may, therefore, have PNES only as a temporary symptom²⁴. The outcome may, therefore, help us to identify some psychogenic mechanisms. We lack, however, knowledge about the prognosis of PNES, as most studies are cohort studies that only report on the diagnosis but do not provide follow-up data. Long-term outcome may also help us to distinguish between “subtypes” of PNES, as patients with persistent seizures over time may have different psychogenic mechanisms in comparison to patients with full seizure remission.

With regard to outcome, there are different studies suggesting that seizure control alone is not a comprehensive measure of good medical or psychosocial outcome in PNES^{11,25}. Several studies have shown that other outcomes, such as employment status²⁶, may be of greater importance for patients. A consensus report on PNES treatment emphasized that if an intervention improved seizure control without changing the hypothesized etiology, the validity of the treatment could be called into question¹³.

In this study, we will therefore reassess patients diagnosed with PNES 4-6 years after the initial diagnosis in a tertiary referral epilepsy center. Reassessments will be aimed at seizure frequency and possible psychogenic outcomes.

Methods

Design

Patients were consecutively included when:

1. They had a diagnosis of PNES. Patients with epilepsy and PNES as comorbid symptoms were not included.
2. The diagnosis had been confirmed in a tertiary referral epilepsy center using clinical description and additional EEG investigations (such as EEG video telemetry). The type of EEG investigation was based on clinical indications such as patient history and seizure semiology.
3. Diagnosis was made in the period 1998-2000.
4. Normal intelligence was assessed clinically.
5. Outcomes of neurological examination (including EEG data) and psychological assessments were present.

All patients were then reevaluated 4-6 years later. This time interval was chosen to focus on long-term outcomes – thus a period definitely outside the diagnostic phase but without coming into life-phase changes.

Patients

In total, 28 patients were selected; 5 patients did not provide informed consent. Thus, in total, 23 patients were included in the study. One patient could not be scheduled for assessments, therefore, 22 patients participated in the study.

Instruments

Recordings for seizure frequency, using standardized seizure diaries, are based on self-reports and by-proxy reports. The same method was used at baseline and at end point. In our study, seizure remission was defined as full-year remission.

Three personality inventories were used at baseline at the time of diagnosis and repeated at end point. These tests assess different “levels” of psychological function:

1. Level of complaints: The Symptoms Check List Revised (*SCL-90-R*) is used to assess symptoms (levels) and psychological distress on the global severity index (indicates the overall level of psychological distress)²⁷.
2. Level of coping strategy: The Dissociation Questionnaire (*DIS-Q*) is used. This is a scale based on the Dissociative Experiences Scale²⁸, the Perceptual Alteration Scale²⁹, and the Questionnaire of Experiences of Dissociation³⁰ adapted from the Dutch language^{31,32}. This scale was used to analyze dissociative features and has four subscales:
 - (a) *DIS-Q d1*: identity confusion and depersonalization
 - (b) *DIS-Q d2*: self-control
 - (c) *DIS-Q d3*: amnestic and dissociation features
 - (d) *DIS-Q d4*: concentration “absorption” of environmental input.
3. Level of personality factors/psychopathology: The Dutch-language short version of the Minnesota Multiphasic Personality Inventory ([*MMPI*] is used^{33,34}. The shortened Dutch version of the *MMPI* (*NVM*) contains 83 items, comprising five scales. Each item contains a statement for which the patient decides on appropriateness to one’s case. The five *NVM* scales are as follows.
 - (a) Negativism (22 items): items referring to passive avoidant behavior, feelings of dissatisfaction and grudge regarding daily life events, and aggressive behavior. Individuals with a high score show a negative, dissatisfied, and hostile attitude toward other people, and tend to react with grumbling and complaining for feelings of discomfort. They often feel tense and behave self-defensively. In persons with a low score, this is not the case. This scale is related to the psychopathic deviate, hypomania, lie, depression, masculinity-femininity, and schizophrenia scales of the *MMPI*.
 - (b) Somatization (20 items): items connected with vague physical complaints. Persons with a high score tend to react to psychological stress with physical symptoms. Individuals with a low score do not. This scale is related to the hypochondriasis, hysteria, and depression scales of the *MMPI*.

(c) Shyness (15 items): items reflecting feelings of shyness and difficulties in interpersonal contacts. People with a high score indicate that they feel shy often and regard this as a problem. They are reserved, introverted, silent, and less sociable. Persons with a low score do not feel shy and are jovial and talkative. This scale is related to the social introversion, hysteria, and psychopathic deviate scales of the MMPI.

(d) Psychopathology (13 items): items connected with delusional feelings, paranoid thoughts, and bizarre experiences. These are present in persons with a high score. Low and average scores should be considered normal. This scale is related to the paranoia, fake (F), and schizophrenia scales of the MMPI.

(e) Extraversion (13 items): items reflecting an active and energetic attitude toward various social contacts. Persons with a high score are extraverted, and persons with a low score are not. This scale provides no indication for introversion. It is related to the social introversion and depression scales of the MMPI.

Statistical analysis

Data were included in a data matrix through two independent inclusions. All data were analyzed with SPSS (Version 13). On the first step, frequencies and descriptions were calculated for all clinical and demographical variables. On the second step, a comparison was made (using *t* test for dependent groups). Finally, linear regression was carried out to find personality characteristics that are predictors of seizure reduction in this group.

Results

Table 4.1 shows the most important clinical and demographic characteristics of the study sample. The average age of the patient sample is 30.4 years (S.D.=10.7; range, 15-49 years). Age had a normal distribution. The vast majority of patients in the sample were female (86.4%). Personal situation varied considerably: 31.8% of patients were living with parents, whereas almost 40.9% of patients were married or were living together. A smaller part of the sample was divorced and single. Lower secondary school (40.9%) and secondary school (40.9%) were the highest educational levels for the majority of patients. The age of seizure onset was below 16 years for about a quarter of patients (23.8%), and a group of similar size experienced onset during adolescence (16-20 years). Most patients, though (33.3%) had their first seizure at the ages of 21–30 years. The rest of the sample (19.1%) had their first seizure above the age of 30 years. The age at which seizures were diagnosed as PNES was more equally spread and Table 4.1 shows that, in general, there was a >7-year delay between seizure onset and time of diagnosis (7.2 years).

Table 4.1 Clinical and demographic characteristics of the study sample of 22 patients with PNES at diagnosis.

Gender [<i>n</i> (%)]	
Male	3 (13.6)
Female	19 (86.4)
Age in years [mean (S.D.)]	30.4 (10.7)
Demographical characteristics [<i>n</i> (%)]	
Living with parents	7 (31.8)
Single	1 (4.5)
Married/living together	9 (40.9)
Divorced and single	4 (18.3)
Divorced and new partner	1 (4.5)
Children [<i>n</i> (%)]	
0	12 (54.5)
1	3 (13.6)
2	6 (27.4)
3	1 (4.5)
Maximum educational level [<i>n</i> (%)]	
Primary school	3 (13.7)
Lower secondary school	9 (40.9)
Secondary school	9 (40.9)
Higher education	1 (4.5)
Age at seizure onset [<i>n</i> (%)]	
< 16 years	5 (23.8)
16-20 years	5 (23.8)
21- 30 years)	7 (33.3)
> 30 years	4 (19.1)
Mean (S.D.)	23.2 (12.5)
Age at diagnosis [<i>n</i> (%)]	
15-20 years	5 (22.7)
21-30 years	6 (27.3)
31-40 years	6 (27.3)
41-50 years	5 (22.7)
Mean (S.D.)	30.4 (10.7)
Seizure type [<i>n</i> (%)]	
Tonic-like	1 (4.5)
Clonic-like	2 (9.1)
Absence-like	10 (45.5)
Periods of disorientation/fugues	6 (27.3)
Atonic-like	3 (13.6)
Seizure frequency at diagnosis [<i>n</i> (%)]	
Seizure-free	0 (0)
Yearly	1 (4.5)
Monthly	5 (22.7)
Weekly	7 (31.8)
Daily	9 (41.0)
Consciousness during seizure [<i>n</i> (%)]	
Normal	1 (4.5)
Disturbed or lower consciousness	21 (95.5)
Preceding sensations of seizures (such as dizziness) [<i>n</i> (%)]	
No	13 (59.1)
Yes	9 (41.9)

Table 4.1 (continued)

Epilepsy in the family [<i>n</i> (%)]	
No epilepsy	16 (72.7)
First-degree relative	4 (18.2)
Second-degree relative	2 (9.1)
Preceding treatments/therapies [<i>n</i> (%)]	
None	9 (40.9)
Psychological and psychiatric treatments	7 (31.8)
Other medical treatment	6 (28.3)
Antiepileptic medication [<i>n</i> (%)]	
No medication	19 (87.5)
AEDs	3 (13.5)
Type of assessment used to diagnose PNES [(<i>n</i> (%)]	
Reevaluation of EEGs plus routine EEG	2 (9.1)
24-h EEG, sleep-deprivation EEG, or seizure recordings	20 (81.9)
MRI	3 (13.5)
Comorbid medical disorders (%)	
None	100

Most of the PNES mimicked “absences” in their presentation (45.5%). Periods of disorientation (fugue-like seizures) were also quite common (27.3% of the patient group). Less common were atonic-like seizures (sudden drop attacks) (13.6%), clonic-like (9.1%) and tonic-like seizures (4.5%). Seizure frequency was high. At the time of diagnosis, most patients had daily seizures (41.0%), 31.8% had weekly seizures, and 22.7% of the patient group reported monthly seizures. Only one patient reported a yearly frequency at time of diagnosis. None of the patients was seizure-free. All patients, except one, experienced disturbed or lower consciousness during seizure. A substantial group of patients (41.9%) had preceding sensations, although the presentation varied considerably, ranging from visual sensations to nausea. The vast majority of patients (72.7 %) did not have a familial history of epilepsy. Four patients had a first-degree relative with epilepsy, whereas two patients had a second-degree relative. One third of the patient group (31.8%) had psychological or psychiatric treatment before seizures were diagnosed. Most patients were not on antiepileptic drug (AED) treatment at the time of diagnosis; three patients used AEDs at moderate doses. No complicating etiology predisposing to developing epilepsy was observed. Only one patient had no EEG (reevaluation of the EEG was made in another hospital); one patient had routine EEG; all other patients needed 24-h EEG, seizure recording, or sleep-deprivation EEG. In three patients, magnetic resonance imaging (MRI) was performed.

Figure 4.1 shows seizure frequency at baseline (at diagnosis) and at end point. The average time between diagnosis and end point was 4.7 years (S.D.=1.3). Seizure frequency was reduced statistically significant ($P \leq 0.001$): 10 patients were seizure-free or had only occasional seizures per year, whereas none of the patients fell into these categories at the time of diagnosis.

Figure 4.1 Seizure frequency of PNES at baseline (diagnosis) and at end point.

No relationship was found between reduction in seizure frequency and seizure type, age at onset, familial history of epilepsy, former treatment, use of AEDs, existence of preceding sensations, age, or gender. This was, however, at least partly due to the fact that the majority of the patients had a reduced seizure frequency; thus, variation was limited (all P values >0.05).

A comparison of the personality inventories, assessed at baseline (diagnosis) and at end point, is presented in Table 4.2 and shows statistically significant changes for:

1. SCL-90: ($P=0.001$)- indicates significant reduction in psychological distress at end point compared to that at baseline
2. DIS-Q d1: identity confusion ($P=0.01$)- indicates that less complaints regarding identity confusion and depersonalization exist at end point
3. DIS-Q d2: loss of control ($P\leq 0.001$)- indicates an increase in self-control at end point compared to that at baseline
4. DIS-Q d3: amnesia ($P=0.007$)- indicates less amnesic/dissociation features at end point
5. NVM: negativeness ($P=0.036$)- indicates reduction in passive avoidant behavior and feelings of dissatisfaction
6. NVM: extraversion ($P=0.005$)- reflects a more active and energetic attitude toward social contacts.

Table 4.2 Changes in psychological inventories from baseline assessment (at the time of diagnosis) to end point assessments.

	At diagnosis (baseline)	At reevaluation (end point)	<i>P</i>
SCL-90 (psychoneurotic complaints)	169.25 (43.8)	134.50 (47.8)	0.001
DIS-Q <i>d1</i>	1.6185 (0.77)	1.2462 (0.40)	0.01
DIS-Q <i>d2</i>	2.2877 (0.59)	1.6092 (0.56)	0.000
DIS-Q <i>d3</i>	2.1400 (0.70)	1.7169 (0.83)	0.007
DIS-Q <i>d4</i>	1.8915 (0.57)	1.6023 (0.61)	0.098
NVM negativeness	4.60 (1.30)	3.87 (1.25)	0.036
NVM somatization	6.13 (1.56)	5.47 (1.69)	0.173
NVM shyness	4.93 (1.87)	4.73 (1.83)	0.595
NVM psychopathology	4.13 (1.69)	3.20 (1.42)	0.084
NVM extraversion	4.27 (1.94)	3.00 (1.70)	0.005

Statistically significant values ($P \leq 0.05$) are presented in bold.

In all comparisons, the scales at end point show less complaints/problems compared to baseline. Improvement on seizure frequency is thus associated with a larger improvement of function in these patients, specifically a reduction in psychological distress, and patients report a reduction in dissociative features such as amnesia, increase in self-control, reduction in feelings of dissatisfaction and passive avoidant behavior, and a more active attitude towards social contact.

Linear regression analysis was performed with seizure improvement as dependent variable. We used a digital variable for this analysis: "improvement or not" was rated as 1 (*any reduction in seizure frequency from baseline to end point*) or 0 (*either no change from baseline to end point or worsening of seizure frequency*). Scores on the personality inventories (SCL, NVM, DIS-Q) at baseline were used as possible predictors. This analysis tests for possible psychogenic predictors for favorable or worse prognosis. The analysis shows a statistically significant relationship with two variables: psychopathology (NVM) on the first step ($P=0.04$) and negativism (NVM) on the second step ($P=0.04$), explaining 55.2% of the variance (hence, these are dominant factors explaining more than half of the variance of seizure improvement). The relationship can be interpreted as follows: with higher psychopathology, chances of seizure improvement are reduced; with lower negativism (self-avoidant behavior), chances of seizure improvement are increased.

In a second regression analysis, we evaluated which personality traits can be seen as predictors of seizure frequency at baseline. The results show that all scores on the personality inventories combined explain 87% of the variance, but that none of the separate scores is statistically significant.

Discussion

Whereas none of the patients was seizure-free at diagnosis, a substantial portion of this group was in complete remission at end point. Although group size was limited, the results were convincing: at the time of diagnosis, none of the patients was seizure-free or had only yearly seizures, whereas at end point, 7 of 22 patients were completely in remission and 3 patients had only occasional seizures. The number of patients with daily seizures dropped from nine to two. It has not been fully clarified which factors caused this improvement as all patients had different procedures, but the common denominators were that a definitive and expert diagnosis was made in a tertiary center and that all possible efforts were made to inform the patient in a respectful manner about this diagnosis. Apparently, this is a sufficient procedure (although, in many patients, this is followed by a variety of treatment and counseling procedures) to reduce seizure frequency or to fully stop the seizures. Although many patients followed some form of treatment or counseling procedures, these types of intervention were individualized and showed a broad range. Maybe presenting the diagnosis is a kind of first phase for every patient. A second phase only follows when necessary and when the patient is open to the investigation of underlying psychological mechanisms. An important aspect of the presentation is focused on achieving the patients' acceptance of the diagnosis.

In a recent international interdisciplinary workshop that aimed to discuss the development of treatments for patients with non-epileptic seizures, it was stated that a major obstacle to treatment is the patients' refusal to accept the diagnosis. Therefore, the presentation of the diagnosis is considered pivotal in the acceptance of the diagnosis¹³.

Since these are patients with PNES only, part of the expert diagnosis was also to convince the patient to stop taking AEDs. Current taking of AEDs might, on a attribution level, be a sign for the patient that he or she does have an organic disease such as epilepsy. Reuber et al.¹², in their long-term follow up study, found that 40.7% of patients with PNES only were taking anticonvulsants. They also found a relatively poor prognosis for this group.

In addition to seizure reduction, there is an improvement on different levels of psychological function. At the level of complaints, there is a reduction in psychological distress. At the level of coping strategy, there is a reduction in dissociative features such as amnesia and an increase in self-control. With regard to personality factors, there is a reduction in feelings of dissatisfaction and passive avoidant behavior, and a more active attitude towards social contact. The patients, therefore, seem to have more self-control and approach social contact with a more self-confident attitude. This does not necessarily reflect a causal relationship (i.e., these factors are not necessarily psychogenic mechanisms underlying PNES). Nonetheless, it is noteworthy that, post aut propter, the eradication of a symptom (i.e., seizures) with social consequences is followed by or is associated with a more confident social attitude.

Given the fact that only a minority of these patients had complex psychotherapeutic interventions, it is tempting to assume that, here, the psychological changes follow seizure reduction.

When the actual improvement of seizure frequency per patient was tested in linear regression analysis, the level of psychopathology and the tendency for passive avoidance behavior (NVM negativism) at the time of diagnosis were the strongest predictors. This indicates that the level of psychopathology is a negative predictor for prognosis and that a lower level of negativism (self-avoidant behavior) is a positive predictor for prognosis. The first finding may be helpful in clinical practice in identifying patients for treatment; the second finding may help us in finding adequate types of treatment for patients. We must still be careful in interpreting these data as the level of psychopathology and negativism explain improvement of seizure frequency, but not the actual seizure frequency at baseline, at the time of diagnosis. The second regression analysis shows that, at the time of diagnosis, many other psychological factors are involved, suggesting a multifactorial origin of the seizures. It is remarkable that the psychological factors combined account for almost 90% of seizure variance at baseline. Thus, other factors (or a more complex pattern of psychogenic influences) may be responsible for seizure onset rather than for seizure recurrence.

An additional finding that is worth mentioning is that there is still an average delay of 7.2 years between the reported seizure onset and the diagnosis of PNES. This has been reported in other studies in the past³⁵, and this long delay still seems valid. In the light of the possible stigma of seizures, uncertainty about the diagnosis, and the impact of seizures on social functioning and occupational possibilities, this period must be shortened. In the light of this lengthy delay, the small number of patients on AED treatment is remarkable. In addition, the relatively limited number of patients (about one third of the sample) who had preceding psychological or psychiatric treatment is noteworthy. Possibly, there is a long “silent period” in which the patients do have PNES that occur infrequently or without serious impact on daily life, which may delay proper referral for diagnosis. Another reason for the observed diagnostic delay may be sampling bias. It is possible that patients with PNES who were referred to a tertiary referral epilepsy center have difficult-to-detect seizures or difficult-to-classify seizures. This may explain why the majority of the patients needed laborious EEG recordings, such as seizure recordings or sleep EEGs. This may also be an explanation for the fact that most of the patients had seizures mimicking “absences” or “periods of disorientation”. Several authors, such as Meierkord et al.³⁶, report that the majority of patients present with excessive motor manifestations and that unresponsiveness is a more seldom symptom. However, other authors, such as Leis et al.³⁷, caution against such conclusions, as unresponsiveness may go undetected more frequently. Possibly because of closer observations in a tertiary center, these symptoms dominate in this sample.

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Chapter 5

Treatments for non-epileptic attack disorder: a Cochrane Review

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Cochrane Database of Systematic Reviews 2007, Issue 1. Art. No.: CD006370

Abstract

Background

Psychogenic non-epileptic seizures (NES) have the outward appearance of epilepsy in the absence of physiological or electroencephalographic correlates. Non-epileptic seizures can occur in isolation or in combination with epileptic seizures. The development and maintenance of non-epileptic seizures has been well documented and there is a growing literature on the treatment of NES which includes non-psychological (including anti-anxiety and antidepressant pharmacological treatment) and psychological therapies (including cognitive behavioural therapy (CBT), hypnotherapy and paradoxical therapy). Various treatment methodologies have been tried with variable success. The purpose of this Cochrane review was to establish the evidence base for treatment of NES.

Objectives

To assess whether treatments for NES result in a reduction in frequency of seizures and/or improvement in quality of life, and whether any treatment is significantly more effective than others.

Search strategy

We searched the Cochrane Epilepsy Group's Specialised Register (September 2005), the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* Issue 3, 2005), and PsycINFO (1806 to July 2005). No language restrictions were imposed. We checked the reference lists of retrieved studies for additional reports of relevant studies.

Selection criteria

Randomised or quasi-randomised studies were included that assessed one or more types of psychological or non-psychological interventions for the treatment of NES. Studies of childhood NES were excluded from our review.

Data collection and analysis

Three review authors independently assessed the trials for inclusion and extracted data. Outcomes included reduction in seizure frequency and improvements in quality of life.

Main results

Three small studies met our inclusion criteria and were of poor methodological quality. Two assessed hypnosis and the other paradoxical therapy. There were no detailed reports of improved seizure frequency or quality of life, and these trials provide no reliable evidence of a beneficial effect of these interventions.

Authors' conclusions

In view of the methodological limitations and the small number of studies, we have no reliable evidence to support the use of any treatment including hypnosis or paradoxical injunction therapy in the treatment of NES. Randomised studies of these and other interventions are needed.

Plain language summary

There is no reliable evidence to support the use of any interventions for people with non-epileptic seizures.

There has been extensive investigation of the aetiology of non-epileptic seizures. However, the literature on the treatment of such seizures is less well defined. We conducted a review of randomised controlled trials of interventions for non-epileptic seizures. We found only three studies and from these no conclusive results can be drawn.

Background

Much research has been devoted to the aetiology of non-epileptic seizures. Significant links have been found between certain life events and the occurrence of non-epileptic seizures. In particular there have been consistent findings of co-occurrence of experiences of abuse in childhood or early adulthood and the development of non-epileptic events (Francis 1999a; Reilly 1999).

Psychological factors such as anxiety, stress, anger and other emotions as well as by mental tasks and thoughts (Francis 1999b) can trigger an attack, as can physiological states such as over-exertion and pain (Stone 2004). It is on the basis of such studies that much literature has evolved regarding potential treatments. Various psychological and non-psychological interventions such as Cognitive Behaviour Therapy (CBT), eye movement desensitization and reprocessing, and neurofeedback have been used alone or in combination in the treatment of non-epileptic seizures to reduce attack frequency and improve quality of life. Potential treatments include the following.

Eye movement desensitization and reprocessing (EMDR)

Chemali 2004 reported on the use of EMDR in the treatment of psychogenic seizures. This was a single case study involving a 48 year old female with post-traumatic stress disorder and psychogenic seizures that lasted for many hours. After 18 months of EMDR treatment (weekly sessions) the patient was described as "event-free". Follow up three months later confirmed she was still seizure free.

Group psychoeducation

An open-ended group psychotherapy program was given to 10 patients with NES by Zaroff 2004. This program included a "disorder-specific psychoeducation treatment

component". Only 7 of the 10 completed the majority of psychoeducational sessions. Seizure frequency was measured pre- and post-treatment. Four patients had no change in seizure frequency but three of these were seizure free at treatment initiation. Two patients had a reduction in seizure frequency and one an increase. The authors concluded that there was a non-significant trend towards improved quality of life (as measured by the QOLIE-31(Quality Of Life In Epilepsy) questionnaire). They also note that seizure remission following diagnosis supports the hypothesis that education about the disorder is effective in its treatment.

Neurofeedback plus psychotherapy

Swingle 1998 trained three patients presenting with non-epileptic events in the use of electroencephalographic (EEG) feedback between one and three times a week. Neurofeedback therapy is used in an effort to reduce general levels of arousal. The hypothesis is that high arousal levels are implicated in the development and or maintenance of attacks and reducing these levels may have an impact on attack frequency and/or severity. This neurofeedback therapy was used to reduce the EEG theta/sensorimotor rhythm (SMR) ratio. This treatment was used in conjunction with psychotherapy. The aim of the treatment protocol was to reduce the ratio of theta to sensorimotor rhythm (SMR). The author concluded that reductions in the theta/SMR ratio brought about by neurofeedback were associated with reductions in seizure behaviour. Swingle also added the use of EEG feedback training. He commented on the absence of a control group and the limitations this puts on the generalisability of his findings.

Psychotherapy

In their retrospective study Aboukasm 1998 divided 61 patients into four groups: (a) those receiving comprehensive epilepsy program (CEP) psychotherapy; (b) those only under CEP neurologist care; (c) those receiving non-CEP psychotherapy; and (d) those with no feedback or intervention. There were no details about the type of psychotherapy used. The authors reported that group D had significantly less desirable NES clinical outcomes than the other three groups and less improvement in QOL. They concluded that psychotherapy and feedback by CEP professionals experienced in epilepsy and NES was beneficial compared to other or no interventions.

Cognitive behavioural psychotherapy

In a paper by Rusch 2001 psychotherapeutic intervention focused on one of six symptom patterns: acute anxiety/panic; impaired affect regulation and interpersonal skills; somatization/conversion; depression; post-traumatic stress disorder; and reinforced behaviour pattern. Patients were treated according to the symptom

pattern e.g. those in the acute anxiety/panic group received cognitive therapy with exposure; those in the reinforced behaviour pattern group received behavioural management strategies involving family or significant other participation to directly modify reinforcement patterns. Twenty-six of 33 patients completed treatment and of those, 21 were event-free by the end of treatment; the remaining five showing a significant reduction in frequency.

Combined interventions

Psychotherapy, occupational therapy and minimal attention within in-patient setting

McDade 1992 diagnosed 18 patients in an in-patient setting with NES; nine were solely experiencing NES and nine were experiencing a combination of NES and epilepsy. This group of clients poses a significant management problem as often the treating physician, the client and the family may have difficulty differentiating between seizures and non-epileptic events. Individual programmes were developed for each patient, but each programme included psychotherapy (orientation not specified), occupational therapy, and minimal attention being paid to the seizures. Sixteen of the patients completed the programme. Eight became seizure free, three had occasional NES and five were unchanged. At one year follow up, seizure patterns were reported to be similar and patients were also reporting an improvement in social functioning. The authors conclude that prognosis for NES is good when management takes place in a specialist unit with a multi-disciplinary approach and a team familiar with this patient group.

Confrontation with diagnosis, psychotherapy and continuing clinical care

In this study, the authors described outcome in 50 patients (including adults and children) with NES (Buchanan 1993). They divided their group into those with acute (18) and those with chronic NES (32). In the acute group direct communication of the diagnosis was the only intervention for 12/18, six received formal psychotherapeutic support, one had barbiturates withdrawn, and one had family therapy. In terms of outcome, 15/18 (83%) were seizure free at follow up and the remaining three had a marked improvement. The chronic group also had various psychiatric/psychological problems such as personality disorder, anxiety disorder, abnormal illness behaviour, major depression, somatisation disorder and Munchausen's syndrome. In this group various management approaches were used and some patients had more than one approach which included confrontation with the diagnosis, exploratory formal and/or supportive psychotherapy, continuing clinical care and firm management with limit

setting. With regard to outcome in the chronic group, 9/32 were seizure free, 11/32 were significantly improved and 8/32 had no change at all.

Operant conditioning

Betts 1992a report on a group of 128 patients diagnosed with NES over a five year period (46 had the additional diagnosis of epilepsy, 82 had NES only). A variety of management strategies were offered; these included anxiety management, abreaction, psychotherapy/counselling, family therapy and medication (major tranquillizers). Most patients received more than one treatment and almost all were treated by operant conditioning. This was described by the authors as attempting to prevent rewarding of seizure activity by ignoring it and deliberately rewarding non-seizure activity by verbal praise and encouragement. At discharge it was reported that 63% (76) of patients no longer had NES and 24% (29) had a partial resolution the remainder had either no change or were worse. At two year follow up, seizures had returned in 34% (41) or partially returned 14% (17) while 31% (37) were still seizure free. In 8% (10) the diagnosis of NES was found to be incorrect. The authors comment that inpatient treatment results may be misleading. Once the patient returns to the community and the stresses that may have led to the attack disorder, NES may return.

Retrospective follow-up studies

An exploration of reaction to diagnosis and treatment subsequently offered was undertaken by Riaz 1998. They retrospectively collected data regarding 91 patients admitted to an inpatient facility. Of those 25 were diagnosed with NEAD and 15 of these were included in the final analysis. The authors also collected follow-up data by semi-structured interviews. They reported that a comparison of seizure frequency from admission to follow up (one to two years) indicated 27% of the sample were still seizure free, 40% had a greater than 50% reduction, and 13% had experienced an increase in seizure frequency. With regard to treatment, 20% had been seen by a psychiatrist, 40% had been followed up in epilepsy clinics and 40% had received no contact with specialist services. Unfortunately, this paper does not indicate whether those who became seizure free were mainly those who had received some form of intervention.

Objectives

To assess whether treatments for NES result in a reduction in frequency of seizures and/or improvement in quality of life, and whether any treatment is significantly more effective than others.

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs) or quasi-randomised studies (e.g. where randomisation is according to the day of the week or date of birth). The studies may be single or double blind or unblinded.

Types of participants

Adult male or female with any type of non-organic non-epileptic seizures, with or without learning disabilities.

Types of interventions

Any psychological or behaviour modification therapies such as use of cognitive behaviour therapy, relaxation therapy, bio-feedback, counselling, hypnotherapy, conditioning, physical therapies, massage, aromatherapy.

Exclusion criteria

Studies restricted to children.

Types of outcome measures

Primary outcome measures

Seizure reduction

- (a) Fifty per cent or greater reduction in seizure frequency.
- (b) Seizure free.
- (c) Percentage change in seizure frequency.

Secondary outcome measures

- (a) Quality of life (QOL).
- (b) Seizure severity - provided a standardized and validated scale is used.

Search methods for identification of studies

See: Cochrane Epilepsy Group methods used in reviews.

We searched the Cochrane Epilepsy Group's Specialised Register (12 September 2005). This register contains reports of trials identified from regular searches of the Cochrane Central Register of Controlled Trials (CENTRAL) and of MEDLINE. Relevant

reports are also identified by handsearching selected journals and conference proceedings. A more detailed description of this activity can be seen by clicking on the link above and selecting 'Specialised Register'.

In addition, we carried out searching as follows:

Electronic databases

We searched the following databases using the strategies described. There were no language restrictions.

(1) The Cochrane Central Register of Controlled Trials

(CENTRAL) (*The Cochrane Library* Issue 3, 2005) was searched using similar terms to those outlined in (2) below.

(2) MEDLINE (Ovid) (1966 to July 2005)

1. exp SEIZURES/ or Seizure\$.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
2. epilep\$.ab,ti.
3. non-epileptic attack\$.mp.]
4. non-epileptic seizure\$.mp.
5. (psychogenic and attack\$).mp.
6. (psychogenic and seizure\$).mp.
7. pseudoseizure\$.mp.
8. functional seizure\$.mp.
9. NEAD.mp.
10. non-epileptic attack disorder.mp.
11. hysterical seizure\$.mp.
12. somatoform disorder\$.mp. or exp somatoform disorders/
13. psychophysiologic\$ disorder\$/ or exp psychophysiologic disorders/
14. exp dissociative disorders/ or dissociative disorder\$.mp.
15. exp conversion disorder/ or conversion disorder\$.mp.
16. (somatisation or somatization).mp.
17. or/1-16
18. psychotherapy.mp. or exp PSYCHOTHERAPY, MULTIPLE/ or exp PSYCHOTHERAPY/ or exp PSYCHOTHERAPY, GROUP/ or exp "IMAGERY (PSYCHOTHERAPY)"/ or exp PSYCHOTHERAPY, BRIEF/ or exp PSYCHOTHERAPY, RATIONAL-EMOTIVE/
19. assertive therapy.mp.
20. aromatherapy.mp. or exp AROMATHERAPY/
21. art therapy.mp. or exp Art Therapy/
22. autogenic training.mp. or exp Autogenic Training/

23. abreaction.mp. or exp ABREACTION/
24. aversive therapy.mp. or exp Aversive Therapy/
25. acceptance commitment therapy.mp.
26. exp Behavior Therapy/ or behav\$ therapy.mp.
27. Behav\$ modification.mp.
28. biofeedback.mp. or exp "Biofeedback (Psychology)"/
29. bibliotherapy.mp. or exp BIBLIOTHERAPY/
30. cognitive therapy.mp. or exp Cognitive Therapy/
31. cognitive behav\$ therapy.mp.
32. cognitive analytical therapy.mp.
33. counsel\$ing.mp or exp COUNSELING/
34. catharsis.mp. or exp CATHARSIS/
35. colo\$r therapy.mp. or exp Color Therapy/
36. crisis intervention.mp. or exp Crisis Intervention/
37. couples therapy.mp. or exp Couples Therapy/
38. conditioning.mp. or exp "Conditioning (Psychology)"/
39. classical conditioning.mp. or exp Conditioning, Classical/
40. operant conditioning.mp. or exp Conditioning, Operant/
41. exp DESENSITIZATION, PSYCHOLOGIC/ or desensitization.mp.
42. dance therapy.mp. or exp Dance Therapy/
43. family therapy.mp. or exp Family Therapy/
44. free association.mp. or exp Free Association/
45. hypnosis.mp. or exp HYPNOSIS/
46. gestalt therapy.mp. or exp Gestalt Therapy/
47. humanistic therapy.mp.
48. flooding.mp. or exp Implosive Therapy/
49. implosive therapy.tw
50. autosuggestion therapy.mp.
51. music therapy.mp. or exp Music Therapy/
52. marital therapy.mp. or exp Marital Therapy/
53. nondirective therapy.mp. or exp Nondirective Therapy/
54. directive therapy.mp.
55. milieu therapy.mp. or exp Milieu Therapy/
56. meditation.mp. or exp MEDITATION/
57. play therapy.mp. or exp Play Therapy/
58. psychotherapeutic processes.mp. or exp Psychotherapeutic Processes/
59. psychodrama.mp. or exp PSYCHODRAMA/
60. exercise therapy.mp. or exp Exercise Therapy/
61. exp psychotherapy, rational-emotive/ or rational emotive therapy.mp.
62. residential treatment.mp. or exp Residential Treatment/
63. reality therapy.mp. or exp Reality Therapy/
64. exp Suggestion/ or suggestion therapy.mp.

65. socioenvironmental therapy.mp. or exp Socioenvironmental Therapy/
66. systemic therapy.mp.
67. exp Systems Theory/ or systems therapy.mp.
68. stress management.mp. or exp Adaptation, Psychological/
69. psychoanalytic therapy.mp. or exp Psychoanalytic Therapy/
70. transactional analysis.mp. or exp Transactional Analysis/
71. therapeutic community therapy.mp.
72. patient centred therapy.mp.
73. client centred therapy.mp.
74. exp "EARLY INTERVENTION (EDUCATION)"/ or exp CRISIS INTERVENTION/ or exp INTERVENTION STUDIES/
75. therapy.mp.
76. treatment outcome.mp. or exp Treatment Outcome/
77. outcome.mp.
78. or/18-77
79. randomized controlled trial.pt.
80. controlled clinical trial.pt.
81. exp Randomized Controlled Trials/
82. exp Random Allocation/
83. exp Double-Blind Method/
84. exp Single-Blind Method/
85. clinical trial.pt.
86. exp Clinical Trials/
87. (clin\$ adj trial\$).ab,ti.
88. ((singl\$ or doubl\$ or trebl\$ or tripl\$) adj (blind\$ or mask\$)).ab,ti.
89. exp PLACEBOS/
90. placebo\$.ab,ti.
91. random\$.ab,ti.
92. exp Research Design/
93. or/79-92
94. (animals not human).sh.
95. 93 not 94
96. 17 and 78 and 95

(3)PsycINFO (Ovid)

(1806 to July 2005) was searched using similar terms to those outlined in (2) above.

References from published studies

We reviewed the reference lists of retrieved studies to search for additional reports of relevant studies.

Methods of the review

Trials were independently assessed for inclusion by five review authors (JB, GB, AA, NB, LG) with disagreements resolved by mutual discussion.

The same five review authors independently extracted the following data and again any differences of opinion were resolved by mutual discussion:

- (1) Study methods:
 - (a) design (e.g. parallel or crossover design);
 - (b) randomisation method (allocation concealment and list generation);
 - (c) blinding method;
 - (d) quality of allocation concealment (A, adequate; B, unclear; C, inadequate).
- (2) Participants:
 - (a) number (total/per group);
 - (b) age and sex distribution;
 - (c) exclusions withdrawal;
 - (d) type of seizures;
 - (e) duration of attack disorder;
 - (f) aetiology of attack disorder;
 - (g) presence or absence of learning disability.
- (3) Type of intervention and control.
- (4) Duration of follow up.
- (5) Outcome data (as described earlier).

We intended to assess the results of each intervention separately. As only three randomised controlled clinical trials were found that used differing methodologies, no meta-analysis was undertaken but results for individual studies are given in tables.

Description of studies

Hypnosis and non-epileptic seizures

One study investigated the effects of hypnosis on non-epileptic seizures (Moene 2002). This study included 45 adult in-patients with conversion disorder. Seven experienced paroxysmal myoclonic outbursts and eight had seizures or convulsions. Twenty four were allocated randomly to the experimental group and 21 to the control group. The average duration of conversion disorder was 3.9 years (range two months to 22 years; standard deviation [SD] 4.5 months). Forty per cent (18) of the 45 had acute onset (within three days). Sixty two per cent (28) (an undisclosed proportion of whom had acute onset) developed conversion symptoms in connection with a previous physical complaint or affliction in the relevant part of the body. Thirty-two (72.7%) of the patients used medication (benzodiazepines (43.2%), medication for somatic complaints (45.5%) and painkillers (44.4%) most frequently). No discussion of withdrawal of medication or otherwise was included.

Patients in both treatment and control groups followed a group therapy programme with the aim of increasing problem-solving skills. This programme consisted of group psychotherapy, social skills training, formulating and evaluating treatment goals, creative therapy and sports. In addition, conversion patients also had physiotherapy, individual exercise sessions and bed rest. The experimental group had the addition of hypnotic treatment. This involved one preparatory session followed by eight weekly sessions lasting one hour. Part of this treatment involved the patients learning self-hypnosis and they were instructed to practice each day for 30 minutes. In the control group, instead of hypnosis, a treatment aimed at optimising non-specific or common therapy factors was implemented. This involved a preparatory session followed by eight weekly session lasting one hour.

The primary outcome measure used was the Video Rating Scale for Motor Conversion Symptoms (VRMC). Follow up in this study was eight months after pre-treatment assessment.

A further study by Moene 2003 included 44 adult outpatients with conversion disorder (motor type) or somatisation disorder (with motor conversion symptoms). Of the 44, six experienced paroxysmal myoclonic outbursts and two had seizures or convulsions. Twenty were randomly allocated to the treatment group and 24 to the waiting list control group. The treatment group received one preparatory session followed by 10 weekly sessions. Two hypnotic strategies were used: (1) direct symptom alleviation used suggestions designed to alter conditioned cues to motor symptoms; (2) emotional expression/insight involved age regression to explore factors implicated in the development of the symptoms. Self hypnosis was also taught and patients were asked to practice the symptom alleviation strategies for 30 minutes a day. A waiting list control group was used.

Average duration of conversion disorder was 3.7 years (range two months to 16.7 years; SD 4.7 months). In terms of onset, 37.2% (16) patients had acute onset (within three days) and 47.8% (21) developed conversion symptoms in connection with a previous physical complaint or affliction in the relevant part of the body. Twenty-one (48.8%) of the patients used medication (benzodiazepines (14%), medication for somatic complaints (30.2%) and painkillers (34.8%) most frequently). No discussion of withdrawal of medication or otherwise was included.

Primary outcome measure used was the VRMC. Follow up for the treatment group was at six months after their tenth session. No follow up was arranged for the waiting list control group.

It is noted that preliminary data on eight adults with motor conversion symptoms (one described as having pseudo-epileptic seizures) was published by Moene in 1998 (Moene 1998).

Paradoxical intention and non-epileptic seizures

We found one randomised controlled clinical trial investigating the effects of paradoxical intention on non-epileptic seizures (Ataoglu 2003). This study included 30 adults with conversion disorder, specifically pseudoseizures. Fifteen were randomly allocated to the experimental group and 15 to the control group after exclusions for abnormal EEG, organic disease, previous psychiatric treatment etc. In the experimental group, patients were hospitalised and given two paradoxical intention treatment sessions per day. During sessions, patients were encouraged to imagine anxiety provoking situations and/or experiences. The aim was to help the patients to re-experience their traumas and experience their conversion attacks. After three weeks, patients were discharged. Three weeks post discharge, a re-assessment took place and comparisons of anxiety and conversion scores were made. In the control group, patients were prescribed diazepam as outpatients (5-15mgs) they were given appointments at 10, 20, 30, and 45 days to review their progress and also were reviewed at the end of treatment for anxiety and conversion symptoms.

The overall mean duration of conversion disorder for the whole sample was 42 days (experimental group 34 days; control group 48 days). There was no discussion of medication use in these groups. The aetiology was not detailed; however anxiety provoking situations and experiences, and traumatic events were mentioned. The primary outcome measure was anxiety score as measured by the Hamilton Rating Scale for Anxiety (HRSA). Follow up in this study was three weeks after the study finished. The study duration was six weeks therefore follow up was approximately two months after the start of the study.

It is noted that an earlier account of this research was published by Ataoglu, in 1998 (Ataoglu 1998).

Methodological quality of included studies

Hypnosis and non-epileptic seizures

Moene 2002 used block randomisation (block sizes: 3 x 4, 2 x 6, 2 x 8, 2 x 4 and 2 x 2) to allocate patients to treatment conditions. This was concealed from the therapist and assessors. The assessors rating the outcomes were blinded to treatment allocation. Further details of randomisation or blinding method are not provided. In terms of methodological weaknesses, of the 45 patients with conversion symptoms, eight were reported to have seizures or convulsions and seven were reported to have

paroxysmal myoclonic outbursts, however patients could have more than one symptom so the exact number is unclear. There was no detail regarding seizure frequency or change in seizure frequency, nor were there measures of quality of life or seizure severity.

Moene 2003 used block randomisation (unspecified) to assign patients to experimental (hypnosis) or control (waiting list) conditions. The assessors rating the outcomes were blinded to treatment allocation. No further details of randomisation or blinding method were provided. In terms of methodological weaknesses, only two of the patients with conversion symptoms were documented as having seizures or convulsions, although six were reported to have paroxysmal myoclonic outbursts (patients may have more than one symptom so the exact number is unclear). There was no detail regarding seizure frequency or change in seizure frequency, nor were there measures of quality of life or seizure severity.

Paradoxical intention and non-epileptic seizures

In this study (Ataoglu 2003), random allocation was effected by a computerised system; no further information is provided. All patients were assessed by a psychiatrist who was blinded as to the patients' group throughout the study. There were some methodological weaknesses in the study design: absence of a placebo control group and the two groups received their interventions in different settings – inpatient and outpatient.

Results

Hypnosis and non-epileptic seizures

Moene 2002 provided no results specific to non-epileptic seizures. It is stated that frequency and duration of seizures was noted by staff and patients throughout the study. From this they calculated the mean percentage change in frequency and duration which was converted to a representative score on the VRMC rating scale. However, none of these scores were provided in the paper.

The authors analyses were time and condition by time interactions. Their outcome measures were the VRMC, SCL-90 (Symptom Checklist-90; Dutch version) a self report measure of psychoneuroticism, the ICIDH (International Classification of Impairments, Disabilities and Handicaps) subscale for physical activities), and the ICIDHP (the perceived problems subscale). The authors reported significant symptom reduction in patients with a conversion disorder of the motor-type; however this was independent of the treatment condition. They reported no significant condition effects and no significant condition-by-time interactions for any of the outcome measures. However,

a significant main effect for time was reported on all of the outcome measures (VRMC, $F(2, 82)=28.07$, $P=0.001$; SCL-90, $F(3, 126)=3.37$, $P=0.05$; ICIDH, $F(3, 123)=12.76$, $P=0.000$; ICIDHP, $F(3, 123)=8.97$, $P=0.000$). The authors concluded that the addition of hypnosis to the treatment programme did not affect outcome.

Moene 2003 provided no results specific to NES. As with their 2002 study, the outcome measures were VRMC, SCL-90 and ICIDH. The authors reported significant treatment results for a hypnosis-based treatment in patients with a conversion disorder, motor type. There was a statistically significant difference between the mean VRMC scores (treatment group 5.9, SD 1.3; control group 3.8, SD 1.4; $t=5.065$, $P=0.001$). The analysis of the ICIDH results indicated that the treatment group improved more than controls on this interview measure of general motor impairment (treatment group $t=3.63$, $P<0.01$; control group $t=1.074$, $P=0.29$). The authors found no significant effect of treatment on the SCL-90 (main effects: group $F(1, 41)=0.385$, $P=0.54$; time $F(3, 126)=3.636$, $P=0.064$. interaction: $F(1, 41)=0.345$, $P=0.56$). At six-month follow up the authors reported that improvement was maintained.

Paradoxical intention and non-epileptic seizures

No specific non-epileptic attack frequency or severity results were provided by Ataoglu 2003 as the primary outcome measure in this study was anxiety score. However, the authors noted percentage of the sample in each group who showed no conversions symptoms in the last two weeks at follow up: Experimental group 14 (93.3%); Control group 9 (60%). There was a significant improvement in recovery rate in the PI group when compared than the diazepam-treated group ($t=2.27$, $P=0.034$).

The authors analysed anxiety scores on the HRSA before and after treatment. There was no significant difference between pre-treatment anxiety scores. Both groups recorded significantly decreased anxiety scores by the end of treatment (diazepam-treated group $z=3.24$, $P=0.0012$; PI group ($z=3.41$, $P=0.0007$). A greater degree of significance was found in the PI group when comparing the difference between pre- and post-treatment anxiety scores ($z=2.43$, $P=0.015$).

Discussion

Patients with non-epileptic seizures represent a heterogeneous group with diverse psychological problems against a background of longstanding physical, psychological or sexual abuse, inadequate social skills and chronic adjustment problems (Devinsky 1998; Francis 1999a; Reilly 1999; Rusch 2001). Consequently, non-epileptic seizures represent a serious problem for the patient, the family and the treating clinician. The costs to society can be significant with reported costs in the US of US\$100,000 per

year per patient (Martin 2003). The challenge for the treating clinician relates to providing an accurate diagnosis and an effective treatment. The evidence for how best to manage and treat patients with this condition however is scarce. The available evidence relies on clinical case studies or studies that lack scientific rigour. A number of authors have recognised the benefits of CBT, including Betts 1993; Lesser 2003; and Ramani 1993. There is a clear recognition that patients with non-epileptic seizures would benefit from cognitive behavioural treatment and this should be in the context of a multidisciplinary team (Betts 1993; Lesser 2003; Ramani 1993).

This review, like previous reviews (Rusch 2001) clearly highlights that there is a lack of well-designed trials to inform treating physicians as to what therapeutic treatments exist and how effective they may be with this condition. According to Reuber and colleagues (Reuber 2005) lessons however can be drawn from the treatment of similar types of psychopathology (somatoform disorder, post-traumatic stress disorder and hypochondria), where cognitive behavioural treatment is considered the psychological treatment of choice. Finally it is difficult to disagree with the view of Devinsky who comments that while "our ability to diagnose NES has advanced significantly in the past two decades, our understanding of its pathophysiology and our ability to provide effective treatment has progressed in small tentative steps in the past century" (Devinsky 1998). It would seem that the status quo remains.

Authors' conclusions

Implications for practice

There is currently no sound evidence base on which to base treatment decisions for people with non-epileptic attacks.

Implications for research

Consensus is required regarding appropriate outcome measures, including measures of NES frequency and quality of life measures.

Pragmatic randomised clinical trials are required to assess the effectiveness of potential interventions.

Tables

Characteristics of included studies

Study	Ataoglu 2003
Methods	Method of randomisation: computerised Blinding: psychiatrist blinded to treatment group Treatment duration: 6 weeks.
Participants	Diagnosis: Pseudoseizures / Conversion Disorder using DSM IV criteria N=30. Participants: 29 female, mean age 27 (range 18-35). History: no information provided regarding previous seizures or comorbid conditions. Setting: Department of psychiatry, Turkey.
Interventions	Paradoxical Intention group (N=15): Inpatient treatment in psychiatric ward, 2 sessions a day for 3 weeks. Diazepam group (N=15): Outpatient treatment (5-15mg/day). Appointments at 10, 20, 30 & 45 days.
Outcomes	Hamilton Rating Scale for Anxiety before and after treatment. Frequency of conversion attacks in past week noted for each patient with changes in these scores converted to percentages. Leaving the study early.
Notes	
Allocation concealment	B – Unclear
Study	Moene 2002
Methods	Method of randomisation: block. Blinding: therapists and assessors blind. Treatment duration: 8 months.
Participants	Diagnosis: Conversion Disorder (motor type) or Somatisation Disorder (with motor conversion symptoms) using DSM IIIR criteria N=45. Participants: 34 female, mean age 36.8 years (sd 11.31, range 18-56 years). History: mean age of onset = 32.6 years (sd 10.9 years, range 16-54 years). Mean symptom duration = 3.9 years (sd 4.5 months, range 2 months-22 years). Acute onset, 18. Previous outpatient treatment, 33. Previous inpatient treatment, 18. 32 used medication. 37 used technical aids. Setting: outpatient psychiatric departments in The Netherlands.
Interventions	Both groups consisted of inpatient treatment programme (group work, individual physiotherapy, exercise and bed rest). Treatment group (N=26) included an introductory session followed by 1 hour per week for 8 weeks of hypnosis. Also encouraged to practice self hypnosis for ½ hour per day with audiotape. Control group (N=23) included 8 weeks of 1 hour sessions encouraging patients to talk about their experience and homework to write about sessions.
Outcomes	Video Rating Scale for Motor Conversion Symptoms. D(is)abilities code items from the International Classification of Impairments, Disabilities and Handicaps. Symptom Checklist-90. Stanford Hypnotic Clinical Scale for Adults. Patient expectations of treatment outcome. Leaving the study early.
Notes	
Allocation concealment	B - Unclear

Characteristics of included studies

Study	Moene 2003
Methods	Method of randomisation: block. Blinding: assessors blind. Treatment duration: 3 months (follow up at 6 months for treatment group).
Participants	Diagnosis: Conversion Disorder (motor type) or Somatisation Disorder (with motor conversion symptoms) using DSM IIR criteria N=44. Participants: 75% female, mean age 36.6 years (sd 11 years, range 18-61 years). History: Mean age of onset, 33.8 years (sd 11.3 years, range 15-59 years). Mean symptom duration, 3.7 years (sd 4.7 months, range 2 months -16.7 years). Previous history of same or other conversion symptoms, 18. Sudden onset, 16. Identifiable stressor reported, 12. Previous psychiatric care, 32 (9 as inpatient). 21 used medication. 16 used technical aids. Setting: Outpatient psychiatric departments in The Netherlands.
Interventions	Treatment group (N=24) 1 hour introductory session explaining rationale for using hypnosis followed by hypnosis sessions 1 hour per week for 10 weeks. Also encouraged to practice self hypnosis for ½ hour per day with audiotape. Control group (N=25) waiting list for hypnosis.
Outcomes	Video Rating Scale for Motor Conversion Symptoms. D(isabilities) code items from the International Classification of Impairments, Disabilities and Handicaps. Symptom Checklist-90. Stanford Hypnotic Clinical Scale for Adults. Patient expectations of treatment outcome. Leaving the study early.
Notes	
Allocation concealment	B - unclear

Characteristics of excluded studies

Study	Reason for exclusion
Aboukasm 1998	Not RCT: retrospective, non-randomised.
Betts 1992a	Not RCT: retrospective, non-randomised.
Betts 1992b	Not RCT: retrospective, non-randomised.
Bhattacharyya 1971	Not RCT: no control group.
Bleichhardt 2004	RCT for CBT of multiple somatoform symptoms but no indication of the symptoms of the sample; therefore no indication that people with non-epileptic attacks were included in the sample.
Buchanan 1993	Not RCT: retrospective, non-randomised.
Chemali 2004	Not RCT: case report.
Couprie 1995	Not RCT: case report.
Dickes 1974	Not RCT: allocation, no control group.
Dickinson 2003	RCT for care recommendation letter intervention for somatization in primary care but no indication of the symptoms of the sample; therefore no indication that people with non-epileptic attacks were included in the sample.
Farias 2003	Not RCT: no control group for people with non-epileptic attacks.
Ford 1977	No indication that people with non-epileptic attacks were included in the sample.
Goldstein 2004	Not RCT: open trial of the effectiveness of CBT on treatment of non-epileptic attacks.
Hellman 1990	RCT for behavioural medicine interventions for people with psychosomatic complaints. No indication that people with non-epileptic attacks were included in the sample.
Hiller 2003	Neurological symptoms indicated but non-epileptic attacks not specified.

Characteristics of excluded studies

Study	Reason for exclusion
Jongsma 1999	Not RCT: follow-up study.
Kolk 2004	RCT: no indication that people with non-epileptic attacks were included in the sample
Krull 1990	Not RCT: no control group.
Larisch 2004	RCT: no indication that people with non-epileptic attacks were included in the sample.
Lehmann 1984	RCT: no indication that people with non-epileptic attacks were included in the sample.
Lempert 1990	Not RCT: retrospective data collection.
Lidbeck 1997	RCT: no indication that people with non-epileptic attacks were included in the sample.
Lyles 2003	RCT: no indication that people with non-epileptic attacks were included in the sample.
McDade 1992	Not RCT: no control group.
Menza 2001	Not RCT: not randomised, no control group, no indication that people with non-epileptic attacks were included in the study.
Muller 2001	RCT: no indication that people with non-epileptic attacks were included in the study.
Noyes 1998	Not RCT: not randomised and no control group. No indication that people with non-epileptic attacks were included in the study.
Peters 2002	RCT: No indication that people with non-epileptic attacks were included in the study.
Prigatano 2002	Not RCT: no control group.
Pu 1986	Not RCT: no control group.
Ramani 1982	Not RCT: no control group.
Riaz 1998	Not RCT: retrospective study.
Rost 1994	RCT: no indication that people with non-epileptic attacks were included in the study.
Rusch 2001	Not RCT: no control group and no randomisation.
Shapiro 1997	Not RCT: no control group.
Shapiro 2004	Not RCT: no indication that people with non-epileptic attacks were included in the study.
Sheehan 1980	RCT: no indication that people with non-epileptic attacks were included in the study.
Skupin 1975	Not RCT: no indication that people with non-epileptic attacks were included in the study.
Smith 1986	RCT: no indication that people with non-epileptic attacks were included in the study.
Speckens 1995	RCT: no indication that people with non-epileptic attacks were included in the study.
Speed 1996	Not RCT: no control group and no indication that people with non-epileptic attacks were included in the study.
Sumathipala 2000	RCT: no indication that people with non-epileptic attacks were included in the study.
Swingle 1998	Not RCT: no control group and no randomisation.
Volz 2000	RCT: no indication that people with non-epileptic attacks were included in the sample.
Volz 2003	RCT: no indication that people with non-epileptic attacks were included in the sample.
Wilkinson 1994	Not RCT: no control group, no randomisation and no indication that people with non-epileptic attacks were included in the sample.
Williams 1979	Not RCT: no control group and no randomisation.
Zaroff 2004	Not RCT: no control group.

Cover sheet

Title	Treatments for non-epileptic attack disorder
Author(s)	Baker GA, Brooks JL, Goodfellow L, Bodde N, Aldenkamp A
Contribution of author(s)	<p>Baker, G.A (guarantor of the review) was involved in the following: conceiving the review, designing the review, coordinating the review, data collection for the review, screening search results, screening retrieved papers against inclusion criteria, appraising quality of papers, interpretation of data, performing previous work that was the foundation of current study, providing general advice on the review, writing the review, providing a methodological perspective, providing a clinical perspective, providing a policy perspective, providing a consumer perspective.</p> <p>Brooks, J was involved in the following: designing the review, coordinating the review, data collection for the review, screening search results, organizing retrieval of papers, screening retrieved papers against inclusion criteria, appraising quality of papers, abstracting data from papers, writing to authors of papers for additional information, providing additional data about papers, obtaining and screening data on unpublished studies, data management for the review, interpretation of data, providing a methodological perspective, providing a clinical perspective, providing a policy perspective, providing a consumer perspective, writing the review.</p> <p>Goodfellow, L. was involved in: data collection for the review, screening search results, organising retrieval of papers, screening retrieved papers against inclusion criteria, appraising quality of papers, abstracting data from papers, data management for the review.</p> <p>Bodde, N. was involved in: conceiving the review, designing the review, appraising quality of papers, abstracting data from papers, providing a methodological perspective, providing a clinical perspective, providing general advice on the review.</p> <p>Aldenkamp, A.P. was involved in: conceiving the review, designing the review, appraising quality of papers, abstracting data from papers, providing a methodological perspective, providing a clinical perspective, providing general advice on the review, performing previous work that was the foundation of current study.</p>

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Chapter 6

Nondrug treatments for psychogenic non-epileptic seizures: what's the evidence?

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Epilepsy Behav 2007;11:367-77

Abstract

Objective

The purpose of this Cochrane review was to establish the evidence base for treatment of psychogenic non-epileptic seizures.

Methods

Six hundred eight references were identified using a search strategy designed with the support of the Cochrane Review Epilepsy Group library. The search employed Medline and PsychInfo, and included hand searches of relevant journals (Seizure, Epilepsia, Epilepsy & Behavior, Epilepsy Research).

Results

Three studies were found that met the inclusion criteria; two used hypnosis and one used paradoxical therapy. None included detailed reports of improved seizure frequency or quality of life, although reduction in seizure frequency was mentioned. All three studies concluded that the intervention used was beneficial in the treatment of psychogenic non-epileptic seizures.

Conclusions

The limited number of studies and poor methodology preclude these results from being generalizable. There is a need for well- designed clinical trials to identify the most suitable treatments for this population.

Introduction

Although much research has been devoted to the etiology of psychogenic non-epileptic seizures^{1,2}, little attention has been given to the systematic evaluation of treatment programs, although there have been various reviews of the research literature over the years³⁻⁷. Patients with psychogenic non-epileptic seizures represent a heterogeneous group with diverse psychological problems against a background of long-standing physical, psychological, or sexual abuse, inadequate social skills and chronic adjustment problems^{1,2,8}. Consequently, psychogenic non-epileptic seizures (PNES) represent a serious problem for the patient, the family, and the treating clinician. The costs to society can be significant, with reported costs in the United States of US\$100,000 per year per patient⁹. The challenge for the treating clinician relates to providing an accurate diagnosis and an effective treatment. The evidence for how best to manage and treat patients with this condition, however, is scarce. The available evidence relies on clinical case studies or studies that lack scientific rigor. In addition, there is no overall theoretical framework for the understanding of PNES on which to base the development of treatment strategies and research protocols. Various psychological and nonpsychological interventions, such as cognitive behavior therapy (CBT)^{4,10,11}, eye movement desensitization and reprocessing¹³, and neurofeedback¹⁴, have been used alone or in combination in the treatment of PNES to reduce attack frequency and improve quality of life.

In the studies, there was variable detail provided regarding how the diagnosis of PNES was given, although diagnosis is usually through exclusion of epilepsy and other paroxysmal conditions. Expert analysis of video-telemetry recordings can result in identification of PNES as the result of seizure-like physical activity in the absence of any EEG correlates. More details regarding how these diagnoses are made are given in Reuber's 2005 article¹⁵. In some cases, because the diagnosis of conversion disorder was the focus, rather than the more specific PNES, DSM-IV criteria were used¹⁶.

Several studies have attempted to document the treatment outcomes of various types of intervention. McDade and Brown reported on the outcomes of treatment using psychotherapy, occupational therapy, and minimal attention within an inpatient setting. The authors concluded that prognosis for PNES is good when management takes place in a specialist unit with a multidisciplinary approach and a team familiar with this patient group¹⁷. In the same year, Betts and Boden reported on a group of 128 patients diagnosed with PNES over a 5- year period¹⁸. A variety of management strategies were offered; these included anxiety management, abreaction, psychotherapy/counseling, family therapy, and medication (major tranquillizers). At discharge it was reported that 63% (76) of patients no longer had PNES and 24% (29) had a partial resolution; the remainder had either no change or were worse. At 2- year follow up, seizures had returned in 34% (41) and partially returned 14% (17) while 31% (37) were still seizure free. In 8% (10) the diagnosis of PNES was found to be incorrect. The authors commented that inpatient treatment

results may be misleading. Once the patient returns to the community and the stresses that may have led to the attack disorder, PNES may return¹⁸.

Confrontation with diagnosis, psychotherapy and continuing clinical care were the main components of a study by Buchanan and Snars, who reported that 9 of 32 became seizure free, 11 of 32 significantly improved, and 8 of 32 exhibited no change at all¹⁹. A later study involved combining neurofeedback with psychotherapy¹⁴. The author concluded that reductions in the theta/SMR ratio brought about by neurofeedback were associated with reductions in seizure behavior. Swingle also added the use of EEG feedback training. He commented on the absence of a control group and the limitations this puts on the generalizability of his findings.

In their retrospective study, Aboukasm et al. divided 61 patients into four groups: (A) those receiving comprehensive epilepsy program (CEP) psychotherapy; (B) those only under a CEP neurologist's care; (C) those receiving non-CEP psychotherapy; and (D) those with no feedback or intervention. There were no details about the type of psychotherapy used. The authors reported that Group D had significantly less desirable PNES clinical outcomes than the other three groups and less improvement in quality of life (QOL). They concluded that psychotherapy and feedback by CEP professionals experienced in epilepsy and PNES were beneficial compared with other or no interventions²⁰. Rusch et al. described how the psychotherapeutic interventions focused on one of six symptom patterns: acute anxiety/panic; impaired affect regulation and interpersonal skills; somatization/conversion; depression; posttraumatic stress disorder; and reinforced behavior pattern. Patients were treated according to the symptom pattern; for example, those in the acute anxiety/panic group received cognitive therapy with exposure; those in the reinforced behavior pattern group received behavioral management strategies involving family or significant other participation to directly modify reinforcement patterns. Twenty-six of thirty-three patients completed treatment, and of those, 21 were event free by the end of treatment, the remaining 5 showing a significant reduction in frequency³.

An open-ended group psychotherapy program was published by Zaroff et al. This treatment was given to 10 patients with PNES and included a "disorder-specific psychoeducation treatment component". Only 7 of the 10 completed the majority of psychoeducational sessions. Seizure frequency was measured pre- and post-treatment. Four patients had no change in seizure frequency, but three of these were seizure free at treatment initiation. Two patients had a reduction in seizure frequency, and one, an increase. The authors concluded that there was a nonsignificant trend toward improved QOL (as measured by the Quality of Life in Epilepsy-31 Inventory [QOLIE-31]). They also note that seizure remission following diagnosis supports the hypothesis that education about the disorder is effective in its treatment²².

Many of these studies, however, were plagued by methodological difficulties, and none were randomized controlled clinical trials. Randomized controlled clinical trials (RCTs) represent the gold standard for evaluating the clinical effectiveness of treatment. The aim of this article is to systematically review RCTs that have evaluated

the outcomes of treatment for patients with PNES. The excluded studies are summarized in Table 6.1.

The main objectives of the review were to assess whether RCTs of treatments for PNES result in a reduction in frequency of seizures and/or improvement in QOL and to assess if any treatment is significantly more effective than others. Treatments included CBT, hypnotherapy, and paradoxical therapy. Medication trials were not included specifically in this review as our focus was noninvasive, nondrug treatments for PNES. Primary outcome measures were seizure frequency and percentage change in seizure frequency. Secondary outcome measures were QOL and seizure severity measures.

A formal systematic review has been completed as part of *The Cochrane Library* series.

Table 6.1 Characteristics of excluded studies.

Study	Reason for exclusion
Aboukasm et al., 1998 ³⁵	Not RCT: retrospective, nonrandomized
Betts and Boden, 1992 ³⁶	Not RCT: retrospective, nonrandomized
Betts and Boden, 1992 ³⁷	Not RCT: retrospective, nonrandomized
Bhattacharyya and Singh, 1971 ³⁸	Not RCT: no control group
Bleichhardt et al., 2004 ³⁹	RCT for CBT of multiple somatoform symptoms, but no indication of the symptoms of the sample; therefore, no indication that people with non-epileptic attacks were included in the sample
Buchanan and Snars, 1993 ⁴⁰	Not RCT: retrospective, nonrandomised
Chemali et al., 2004 ¹³	Not RCT: case report
Couprie et al., 1995 ⁴¹	Not RCT: case report
Dickes, 1974 ⁴²	Not RCT: allocation, no control group
Dickinson et al., 2003 ⁴³	RCT assessing the impact of a care recommendation letter intervention for somatization in primary care, but no indication of the symptoms of the sample; therefore, no indication that people with non-epileptic attacks were included in the sample
Farias et al., 2003 ⁴⁴	Not RCT: no control group for people with non-epileptic attacks
Ford and Long, 1977 ⁴⁵	No indication that people with non-epileptic attacks were included in the sample
Goldstein et al., 2004 ⁴⁶	Not RCT: open trial of the effectiveness of CBT in treatment of non-epileptic attacks
Hellman et al., 1990 ⁴⁷	RCT for behavioral medicine interventions for people with psychosomatic complaints; no indication that people with non-epileptic attacks were included in the sample
Hiller et al., 2003 ⁴⁸	Neurological symptoms indicated, but non-epileptic attacks not specified
Jongsma et al., 1999 ⁴⁹	Not RCT: follow-up study
Kolk et al., 2004 ⁵⁰	RCT: no indication that people with non-epileptic attacks were included in the sample
Krull and Schifferdecker, 1990 ⁵¹	Not RCT: no control group
Larisch et al., 2004 ⁵²	RCT: no indication that people with non-epileptic attacks were included in the sample

Table 6.1 (Continued)

Study	Reason for exclusion
Lehmann et al., 1984 ⁵³	RCT: no indication that people with non-epileptic attacks were included in the sample
Lempert and Schmidt, 1990 ⁵⁴	Not RCT: retrospective data collection
Lidbeck, 1997 ⁵⁵	RCT: no indication that people with non-epileptic attacks were included in the sample
Lyles et al., 2003 ⁵⁶	RCT: no indication that people with non-epileptic attacks were included in the sample
McDade and Brown, 1992 ⁵⁷	Not RCT: no control group
Menza et al., 2001 ⁵⁸	Not RCT: not randomized, no control group, no indication that people with non-epileptic attacks were included in the study
Muller et al., 2001 ⁵⁹	RCT: no indication that people with non-epileptic attacks were included in the study
Noyes et al., 1998 ⁶⁰	Not RCT: not randomized and no control group; no indication that people with non-epileptic attacks were included in the study
Peters et al., 2002 ⁶¹	RCT: no indication that people with non-epileptic attacks were included in the study
Prigatano et al., 2002 ⁶²	Not RCT: no control group
Pu et al., 1986 ⁶³	Not RCT: no control group
Ramani and Gumnit, 1982 ⁶⁴	Not RCT: no control group
Riaz et al., 1998 ⁶⁵	Not RCT: retrospective study
Rost et al., 1994 ⁶⁶	RCT: no indication that people with non-epileptic attacks were included in the study
Rusch et al., 2001 ³	Not RCT: no control group and no randomization
Shapiro Teasell, 1997 ⁶⁷	Not RCT: no control group
Shapiro and Teasell, 2004 ⁶⁸	Not RCT: no indication that people with non-epileptic attacks were included in the study
Sheehan et al., 1980 ⁶⁹	RCT: no indication that people with non-epileptic attacks were included in the study
Skupin and Franzke, 1975 ⁷⁰	Not RCT: no indication that people with non-epileptic attacks were included in the study
Smith et al., 1986 ⁷¹	RCT: no indication that people with non-epileptic attacks were included in the study
Speckens et al., 1995 ⁷²	RCT: no indication that people with non-epileptic attacks were included in the study
Speed, 1996 ⁷³	Not RCT: no control group and no indication that people with non-epileptic attacks were included in the study
Sumathipala et al., 2000 ⁷⁴	RCT: no indication that people with non-epileptic attacks were included in the study
Swingle, 1998 ⁷⁵	Not RCT: no control group and no randomization
Wilkinson and Mynors-Willis, 1994 ⁷⁶	Not RCT: no control group, no randomization, and no indication that people with non-epileptic attacks were included in the sample
Williams et al., 1979 ⁷⁷	Not RCT: no control group and no randomization
Volz et al., 2000 ⁷⁸	RCT: no indication that people with non-epileptic attacks were included in the sample
Volz et al., 2003 ⁷⁹	RCT: no indication that people with non-epileptic attacks were included in the sample
Zaroff et al., 2004 ⁸⁰	Not RCT: no control group

Methods

Studies were included in the review if they were RCTs or quasi-randomized studies (e.g., where randomization is according to the day of the week or date of birth). The studies may be single or double blind or unblinded. Participants were described as adult male or female with any type of non-organic PNES, with or without learning disabilities. With respect to interventions, any psychological or behavior modification therapies, such as CBT, relaxation therapy, biofeedback, counseling, hypnotherapy, conditioning, physical therapies, massage, and aromatherapy, were included. Studies were excluded if they did not follow RCT methodology and/or used children in the study.

Search strategy

The search strategy was designed with support from the Cochrane Review librarian. The search used Medline and PsychInfo (searches conducted on 12 September 2005 using the search strategy detailed in Table 6.2) and included hand searches of relevant journals (*Seizure*, *Epilepsia*, *Epilepsy & Behavior*, *Epilepsy Research*). We searched the Cochrane Epilepsy Group's Specialized Register (7 September 2005), the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2005, issue 3), and cross-references from identified publications. We checked the reference lists of retrieved studies for additional reports of relevant studies.

We identified any cross- references from relevant articles and contacted colleagues to ask if they were aware of any studies that we had missed. Of the 608 references identified, most had to be excluded as they did not refer to the treatment outcomes and did not include people with psychogenic non-epileptic attacks. Of the remaining studies relating specifically to treatment outcomes, an additional 48 were excluded from this review. The identified abstracts were independently checked by five review authors (J.B., G.B., A.A., N.B., and L.G.) to assess the relevance for inclusion in the review.

Trials were independently assessed for inclusion by five review authors (J.B., G.B., A.A., N.B., L.G.), with disagreements resolved by mutual discussion. The same authors independently extracted the following data, and again, any differences of opinion were resolved by mutual discussion:

1. Study methods
 - a. Design (e.g. parallel or crossover design)
 - b. Randomization method (allocation concealment and list generation)
 - c. Blinding method
 - d. Quality of allocation concealment (A, adequate; B, unclear; C, inadequate)

2. Participants
 - a. Number (total/per group)
 - b. Age and sex distribution
 - c. Exclusions withdrawal
 - d. Type of seizures
 - e. Duration of attack disorder
 - f. Etiology of attack disorder
 - g. Presence or absence of learning disability
3. Type of intervention and control
4. Duration of follow up
5. Outcome data (as described earlier)

Table 6.2 Database search strategy.

Database: Ovid MEDLINE (R) <1966 to July Week 4 2005>	
Search Strategy	
1	exp SEIZURES/ or Seizures.mp. (61960)
2	non-epileptic attacks.mp.(48)
3	non-epileptic seizures.mp. (89)
4	(psychogenic and attack) \$. mp. [mp=title, original title, abstract, name of substance word, subject heading word] (129)
5	(psychogenic and seizure) \$. mp. [mp=title, original title, abstract, name of substance word, subject heading word] (348)
6	pseudoseizures.mp. (329)
7	functional seizure\$.mp.(5)
8	NEAD.mp.(14)
9	non-epileptic attack disorder.mp. (19)
10	hysterical seizure\$.mp. (38)
11	somatoform disorder\$.mp. or exp Somatoform Disorders/ (8769)
12	psychophysiologic\$ disorder\$.mp. or exp Psychophysiologic Disorders/ (15269)
13	dissociative disorders\$.mp. or exp Dissociative Disorder/ (2185)
14	conversion disorder\$.mp. or exp Conversion disorder/ (1528)
15	somatisation.mp. (216)
16	somatization.mp. (1829)
17	psychotherapy.mp. or exp PSYCHOTHERAPY, MULTIPLE/ or exp PSYCHOTHERAPY/ or exp PSYCHOTHERAPY, GROUP/ or exp "IMAGERY (PSYCHOTHERAPY)"/ or exp PSYCHOTHERAPY, BRIEF/ (98665)
18	psychotherapy.mp. or exp PSYCHOTHERAPY, MULTIPLE/ or exp PSYCHOTHERAPY/ or exp PSYCHOTHERAPY, GROUP/ or exp "IMAGERY (PSYCHOTHERAPY)"/ or exp PSYCHOTHERAPY, BRIEF/ or exp PSYCHOTHERAPY, RATIONAL-EMOTIVE/ (98665)
19	assertive therapy.mp. (0)
20	aromatherapy.mp. or exp AROMATHERAPY/ (362)
21	art therapy.mp. or exp Art Therapy/(804)
22	autogenic training.mp. or exp Autogenic Training/(960)
23	abreaction.mp. or exp ABREACTION/ (349)
24	aversive therapy.mp. or exp Aversive Therapy/(778)
25	acceptance commitment therapy.mp. (6)
26	exp Behavior Therapy/ or behavior therapy.mp. (31538)
27	Behavior therapy.mp. (737)
28	Behavior modification.mp. (2014)

Table 6.2 Database search strategy (continued)

Search Strategy	
29	biofeedback.mp. or exp "Biofeedback (Psychology)"/(5261)
30	bibliotherapy.mp. or exp BIBLIOTHERAPY/ (214)
31	cognitive therapy.mp. or exp Cognitive Therapy/(5580)
32	Cognitive Behav\$ therapy.mp. (1857)
33	Cognitive analytical therapy.mp. (1)
34	exp Counseling/ or counselling.mp. (28136)
35	catharsis.mp. or exp CATHARSIS/(239)
36	colo\$r therapy.mp. or exp Color Therapy/(33)
37	crisis intervention.mp. or exp Crisis Intervention/(4413)
38	couples therapy.mp. or exp Couples Therapy/(194)
39	conditioning.mp. or exp "Conditioning (Psychology)"/(53717)
40	classical conditioning.mp. or exp Conditioning, Classical/(12046)
41	operant conditioning.mp. or exp Conditioning, Operant/ (12748)
42	exp DESENSITIZATION, PSYCHOLOGIC/ or desensitization.mp. (18562)
43	dance therapy.mp. or exp Dance Therapy/ (114)
44	family therapy.mp. or exp Family Therapy/(6184)
45	free association.mp. or exp Free Association/ (477)
46	hypnosis.mp. or exp HYPNOSIS/ (8807)
47	gestalt therapy.mp. or exp Gestalt Therapy/(146)
48	humanistic therapy.mp.(2)
49	flooding.mp. or exp Implosive Therapy/(1388)
50	autosuggestion therapy.mp.(0)
51	music therapy.mp. or exp Music Therapy/(1274)
52	marital therapy.mp. or exp Marital Therapy/ (1151)
53	nondirective therapy.mp. or exp Nondirective Therapy/(262)
54	directive therapy.mp.(16)
55	milieu therapy.mp. or exp Milieu Therapy/(2619)
56	meditation.mp. or exp MEDITATION/(1069)
57	play therapy.mp. or exp Play Therapy/(745)
58	psychotherapeutic processes.mp. or exp Psychotherapeutic Processes/(7579)
59	psychodrama.mp. or exp PSYCHODRAMA/(2016)
60	exercise therapy.mp. or exp Exercise Therapy/(14019)
61	relaxation therapy.mp. or exp Relaxation Techniques/(4887)
62	exp Psychotherapy, Rational-Emotive/ or rational emotive therapy.mp. (182)
63	residential treatment.mp. or exp Residential Treatment/(2366)
64	reality therapy.mp. or exp Reality Therapy/(263)
65	exp Suggestion/ or suggestion therapy.mp.(2194)
66	socioenvironmental therapy.mp. or exp Socioenvironmental Therapy/(20276)
67	systemic therapy.mp. (2780)
68	systems therapy.mp.(53)
69	exp Systems Theory (1491)
70	stress management.mp. or exp Adaptation, Psychological/(59888)
71	psychoanalytic therapy.mp. or exp Psychoanalytic Therapy/(10970)
72	transactional analysis.mp. or exp Transactional Analysis/(306)
73	therapeutic community therapy.mp.(0)
74	patient centred therapy.mp.(1)
75	client centred therapy.mp.(4)
76	exp "EARLY INTERVENTION (EDUCATION)"/ or intervention.mp. or exp CRISIS INTERVENTION/ or exp INTERVENTION STUDIES/(131763)
77	therapy.mp.(895506)
78	treatment outcome.mp. or exp Treatment Outcome/(235916)

Table 6.2 Database search strategy (continued)

Search Strategy	
79	outcome.mp.(477298)
80	epilepsy.ab,ti.(35348)
81	seizure.ab,ti.(23884)
82	2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 80 or 81 (75146)
83	17 or 18 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68 or 69 or 70 or 71 or 72 or 74 or 75 or 76 or 77 or 78 or 79 (1515468)
84	82 and 83 (19512)
85	limit 84 to humans (18794)
86	randomized controlled trial.pt. (203331)
87	controlled clinical trial.pt. (68803)
88	exp randomized controlled trials/ (38162)
89	exp random allocation/ (53379)
90	exp double-blind method/ (82258)
91	exp single-blind method/ (9092)
92	86 or 87 or 88 or 89 or 90 or 91 (345903)
93	(animals not human).sh. (3767480)
94	92 not 93 (318672)
95	clinical trial.pt. (409893)
96	exp clinical trials/ (167519)
97	(clin\$ adj trial) \$.ab,ti. (87420)
98	((singl\$ or doubl\$ or trebl\$ or tripl) \$ adj (blind\$ or mask)) \$.ab,ti.(78813)
99	exp placebos/ (23823)
100	placebo\$.ab,ti. (89523)
101	random\$.ab,ti. (312954)
102	exp research design/ (193141)
103	95 or 96 or 97 or 98 or 99 or 100 or 101 or 102 (764959)
104	(animals not human).sh. (3767480)
105	103 not 104 (667712)
106	94 or 105 (669322)
107	106 and 85 (2572)
108	2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 (25881)
109	17 or 18 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68 or 69 or 70 or 71 or 72 or 74 or 75 or 76 or 77 or 78 or 79 (1515468)
110	108 and 109 (8086)
111	limit 110 to humans (8068)
112	106 and 111 (608)

Results

We reported the results of each intervention separately. As only three RCTs were found, no meta-analysis was undertaken, but results for individual studies are given. Results have been tabulated rather than combined in a meta-analysis.

Hypnosis and psychogenic non-epileptic seizures

Moene and colleagues²³ investigated the effects of hypnosis on PNES. This study included 45 adult inpatients with conversion disorder. Seven experienced paroxysmal myoclonic outbursts and eight had seizures or convulsions. Twenty-four were allocated randomly to the experimental group and 21 to the control group. The average duration of conversion disorder was 3.9 years (range, 2 months- 22 years; SD, 4.5 months). In 18 of 45 (40%), the onset was acute (within 3 days). Twenty-eight (62%) (an undisclosed proportion of whom had acute onset) developed conversion symptoms in connection with a previous physical complaint or affliction in the relevant part of the body. Thirty-two (72.7%) patients used medication (benzodiazepines, 43.2%; medication for somatic complaints, 45.5%; and painkillers, 44.4% most frequently). No discussion of withdrawal of medication or otherwise was included.

Patients in both treatment and control groups followed a group therapy program with the aim of increasing problem-solving skills. This program consisted of group psychotherapy, social skills training, formulation and evaluation of treatment goals, creative therapy, and sports. In addition, patients with conversion disorder had physiotherapy, individual exercise sessions, and bed rest and, in the experimental group, hypnotic treatment also. The hypnotic treatment involved one preparatory session followed by eight weekly 1-hour sessions, each. As part of this treatment, the patients learned self-hypnosis and were instructed to practise each day for 30 minutes. In the control group, instead of hypnosis, a treatment aimed at optimizing non-specific or common therapy factors was implemented. This involved a preparatory session followed by eight weekly 1-hour sessions.

The primary outcome measure used was the Video Rating Scale for Motor Conversion Symptoms (VRMC). Follow-up in this study occurred 8 months after pretreatment assessment.

Another study by the same authors²⁴ included 44 adult outpatients with conversion disorder (motor type) or somatization disorder (with motor conversion symptoms). Of the 44, six experienced paroxysmal myoclonic outbursts and two had seizures or convulsions. Twenty were randomly allocated to the treatment group and 24 to the waiting list control group. The treatment group received one preparatory session followed by 10 weekly sessions. Two hypnotic strategies were used: (1) In direct symptom alleviation, suggestions were designed to alter conditioned cues to motor symptoms. (2) Emotional expression/insight involved age regression to explore factors implicated in the development of the symptoms. Self-hypnosis was also taught and patients were asked to practice the symptom alleviation strategies for 30 minutes a day. A waiting list control group was used.

Average duration of conversion disorder was 3.7 years (range, 2 months-16.7 years; SD, 4.7 months). In terms of onset, 16, (37.2%) patients had acute onset (within 3 days) and 21 (47.8%) developed conversion symptoms in connection with a previous

physical complaint or affliction in the relevant part of the body. Twenty-one (48.8%) patients used medication (benzodiazepines, 14%; medication for somatic complaints, 30.2%; and painkillers, 34.8%, most frequently). No discussion of withdrawal of medication or otherwise was included.

The primary outcome measure used was the VRMC. Follow-up for the treatment group occurred 6 months after their tenth session. No follow-up was arranged for the waiting list control group.

Preliminary data on eight adults with motor conversion symptoms (one described as having pseudo-epileptic seizures) were published by Moene et al.²⁵.

Paradoxical intention and psychogenic non-epileptic seizures

We found one RCT investigating the effects of paradoxical intention on PNES by Ataoglu et al.¹⁶. This study included 30 adults with conversion disorder, specifically pseudo-seizures. Fifteen were randomly allocated to the experimental group and 15 to the control group after exclusions for abnormal EEG, organic disease, previous psychiatric treatment, and so on. In the experimental group, patients were hospitalized and given two paradoxical intention treatment sessions per day. During sessions, patients were encouraged to imagine anxiety-provoking situations and/or experiences. The aim was to help the patients to reexperience their traumas and experience their conversion attacks. After 3 weeks, patients were discharged. Three weeks postdischarge, a reassessment took place, and anxiety and conversion scores were compared. In the control group, patients were prescribed diazepam as outpatients (5-15 mg); they were given appointments at 10, 20, 30, and 45 days to review their progress and also were reviewed at the end of treatment for anxiety and conversion symptoms.

The overall mean duration of conversion disorder for the whole sample was 42 days (experimental group, 34 days; control group, 48 days). Medication use in these groups was not discussed. Etiology was not detailed; however, anxiety-provoking situations and experiences and traumatic events were mentioned. The primary outcome measure was anxiety score as measured by the Hamilton Rating Scale for Anxiety (HRSA). Follow-up in this study occurred 3 weeks after completion of the study. As the study lasted 6 weeks; follow-up was approximately 2 months after the start of the study. An earlier account of this research was published by Ataoglu et al. in 1998²⁶.

Methodological quality of included studies

Hypnosis and psychogenic non-epileptic seizures

Moene et al.²³ used block randomization (block sizes: 3 x 4, 2 x 6, 2 x 8, 2 x 4 and 2 x 2) to allocate patients to treatment conditions. This was concealed from the therapist and assessors. The assessors rating the outcomes were blinded to treatment allocation. Further details on randomization or blinding method were not provided. In

terms of methodological weaknesses, of the 45 patients with conversion symptoms, 8 were reported to have seizures or convulsions and 7 were reported to have paroxysmal myoclonic outbursts; however, as patients could have more than one symptom, the exact number is unclear. There were no details on seizure frequency or change in seizure frequency, nor were there measures of QOL or seizure severity.

Moene et al.²⁴ used block randomization (unspecified) to assign patients to the experimental (hypnosis) or control (waiting list) condition. The assessors rating the outcomes were blinded to treatment allocation. No further details of randomization or blinding method were provided. In terms of methodological weaknesses, only two of the patients with conversion symptoms were documented as having seizures or convulsions, although six were reported to have paroxysmal myoclonic outbursts (patients may have more than one symptom so the exact number is unclear). There were no details on seizure frequency or change in seizure frequency, nor were there measures of quality of life or seizure severity.

Paradoxical intention and psychogenic non-epileptic seizures

In this study by Ataoglu et al.¹⁶, random allocation was effected by a computerized system; no further information was provided. All patients were assessed by a psychiatrist who was blinded as to the patients' groups throughout the study. There were some methodological weaknesses in the study design: there was no placebo control group, and the two groups received their interventions in different settings – inpatient and outpatient.

Results of included studies

Hypnosis and psychogenic non-epileptic seizures

Moene et al.²³ provided no results specific to PNES. They stated that the frequency and duration of seizures were noted by staff and patients throughout the study. From this they calculated the mean percentage change in frequency and duration, which was converted to a representative score on the VRMC rating scale. However, none of these scores were provided in the article.

Moene and colleagues' compared outcome measures across the experimental and control groups. They also looked at comparisons of outcome measures from pre-treatment assessment, mid-treatment, post-treatment and follow-up assessments. Their outcome measures were the VRMC, Symptom Checklist-90 (SCL-90, Dutch version), a self-report measure of psychoneuroticism; the International Classification of Impairments, Disabilities and Handicaps (ICIDH, subscale for physical activities); and the ICIDHP (perceived problems subscale). The authors reported significant symptom reduction in patients with a conversion disorder of the motor-type; however, this was independent of the treatment condition. They reported no significant condition effects and no significant condition x time interactions for any of the outcome

measures. However, a significant main effect for time was reported on all of the outcome measures (VRMC, $F(2, 82)=28.07$, $P=0.001$; SCL-90, $F(3, 126)=3.37$, $P=0.05$; ICIDH, $F(3, 123)=12.76$, $P=0.000$; ICIDHP, $F(3, 123)=8.97$, $P=0.000$). The authors concluded that the addition of hypnosis to the treatment program did not affect outcome.

Moene et al.²⁴ provided no results specific to PNES. As with their 2002 study, the outcome measures were the VRMC, SCL-90, and ICIDH. The authors reported significant treatment results for a hypnosis-based treatment in patients with a conversion disorder, motor type. There was a statistically significant difference between the mean VRMC scores (treatment group: 5.9, SD 1.3; control group: 3.8, SD 1.4; $t=5.065$, $P=0.001$). Analysis of the ICIDH results indicated that the treatment group improved more than controls on this interview measure of general motor impairment (treatment group $t=3.63$, $P<0.01$; control group $t=1.074$, $P=0.29$). The authors found no significant effect of treatment on the SCL-90 (main effects: group $F(1, 41)=0.385$, $P=0.54$; time $F(3, 126)=3.636$, $P=0.064$. interaction: $F(1, 41)=0.345$, $P=0.56$). At 6-month follow-up the authors reported that improvement was maintained.

Paradoxical intention and psychogenic non-epileptic seizures

No specific psychogenic non-epileptic attack frequency or severity results were provided by the authors¹⁶, as the primary outcome measure in this study was anxiety score. However, the authors noted percentage of the sample in each group who manifested no conversions symptoms in the last 2 weeks at follow-up: experimental group, 14 (93.3%); control group, 9 (60%). There was a significant improvement in recovery rate in the paradoxical intention group when compared with the diazepam-treated group ($t=2.27$, $P=0.034$).

The authors analyzed anxiety scores on the HRSA before and after treatment. There was no significant difference between pretreatment anxiety scores. Both groups recorded significantly decreased anxiety scores by the end of treatment (diazepam-treated group: $z=3.24$, $P=0.0012$; paradoxical intention group: $z=3.41$, $P=0.0007$). A greater degree of significance was found in the PI group when comparing the difference between pre- and post-treatment anxiety scores ($z=2.43$, $P=0.015$). The included studies are summarized in Table 6.3.

Table 6.3 Characteristics of included studies.

Study	Methods	Participants	Interventions	Outcomes	Allocation concealment
Ataoglu et al., 2003 ¹⁶	Randomization: computerized Blinding: psychiatrist blinded to treatment group Treatment duration: 6 weeks	Diagnosis: Pseudoseizures / Conversion Disorder using DSM-IV criteria Participants: N=30, 29 female, mean age 27 (range 18-35) History: no information provided regarding previous seizures or comorbid conditions Setting: Department of psychiatry, Turkey	Paradoxical intention group (N=15): inpatient treatment in psychiatric ward, 2 sessions a day for 3 weeks Diazepam group (N=15): Outpatient treatment (5-15mg/day); appointments at 10, 20, 30 & 45 days	Hamilton Rating Scale for Anxiety before and after treatment Frequency of conversion attacks in past week noted for each patient, with changes in these scores converted to percentages Leaving the study early	Unclear
Moene et al., 2002 ²³	Randomization: block Blinding: therapists and assessors blind Treatment duration: 8 months	Diagnosis: Conversion Disorder (motor type) or Somatization Disorder (with motor conversion symptoms) using DSM-III-R criteria Participants: N=45; 34 female; mean age 36.8 years (SD 11.31, range 18-56 years) History: Mean age of onset = 32.6 years (SD 10.9, range 16-54); mean symptom duration = 3.9 years (SD 4.5 months, range 2 months-22 years); acute onset, 18; previous outpatient treatment, 33; previous inpatient treatment, 18; 32 used medication; 37 used technical aids Setting: Outpatient psychiatric departments in The Netherlands	Both groups consisted of inpatient treatment program (group work, individual physiotherapy, exercise and bed rest) Treatment group (N=26): included an introductory session followed by 1 hour per week for 8 weeks of hypnosis; also encouraged to practice self hypnosis for ½ hour per day with audiotape Control group (N=23): included 8 weeks of 1-hour sessions encouraging patients to talk about their experience and homework to write about sessions	Video Rating Scale for Motor Conversion Symptoms: D(abilities) code items from the International Classification of Impairments, Disabilities and Handicaps Symptom Checklist-90 Stanford Hypnotic Clinical Scale for Adults Patient expectations of treatment outcome Leaving the study early	Unclear
Moene et al., 2003 ²⁴	Randomization: block Blinding: assessors blind Treatment duration: 3 months (follow-up at 6 months for treatment group)	Diagnosis: Conversion Disorder (motor type) or Somatization Disorder (with motor conversion symptoms) using DSM-III-R criteria Participants: N=44, 75% female; mean age 36.6 (SD 11, range 18-61 years) History: Mean age of onset, 33.8 years (SD 11.3, range 15-59); mean symptom duration, 3.7 years (SD 4.7 months, range 2 months-16.7 years); previous history of same or other conversion symptoms, 18; sudden onset 16; identifiable stressor reported, 12; previous psychiatric care, 32 (9 as inpatient); 21 used medication; 16 used technical aids Setting: Outpatient psychiatric departments in The Netherlands	Treatment group (N=24): 1-hour introductory session explaining rationale for using hypnosis followed by hypnosis sessions 1 hour per week for 10 weeks; also encouraged to practice self hypnosis for ½ hour per day with audiotape. Control group (N=25): Waiting list for hypnosis	Conversion Symptoms: D(abilities) code items from the International Classification of Impairments, Disabilities and Handicaps Symptom Checklist-90 Stanford Hypnotic Clinical Scale for Adults Patient expectations of treatment outcome Leaving the study early	Unclear

Discussion

This review, in line with previous reviews³, clearly highlights that there is a lack of well-designed trials to inform treating physicians as to what therapeutic treatments exist and how effective they may be for this condition. An overall theoretical framework for understanding the development of PNES would provide a foundation on which to develop treatment strategies and research protocols. Various frameworks have been proposed in an effort to elucidate the development of PNES. They include models based on biopsychosocial^{27,28}, psychodynamic²⁹, cognitive^{30,31}, and learning theory³² approaches. Although such theoretical models have been discussed^{33,34}, no dominant theoretical framework has thus far emerged. According to Reuber and colleagues⁷, lessons can be drawn from the treatment of similar types of psychopathology (somatoform disorder, posttraumatic stress, and hypochondria), for which the frameworks are, on the whole, better developed and CBT is considered the psychological treatment of choice.

The area would benefit from much clearer outcomes including measurement of the number of events, the improvement in the QOL associated with treatment, and the improvement in psychological and social skills. There is a need for pragmatic RCTs to demonstrate the efficacy of the different treatment options for this group of patients. The absence of well-designed clinical trials represents a failure to provide evidence of what treatment of choice should be offered to patients with PNES. More scientifically rigorous research is warranted.

Finally, it is difficult to disagree with Devinsky⁸, who comments that although "our ability to diagnose PNES has advanced significantly in the past two decades, our understanding of its pathophysiology and our ability to provide effective treatment has progressed in small tentative steps in the past century". It would seem that the status quo remains.

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Part 3

Patient characteristics and psychogenic aetiology

Chapter 7

MMPI-2 personality profiles of patients with psychogenic non-epileptic seizures

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Epilepsy Behav 2011;20:674-80

Abstract

This comparative study explored whether psychogenic non-epileptic seizures (PNES) are a unique disorder with distinctive personality characteristics or (seen from the personality profile) PNES are allied with the domain of a general functional somatic symptom and syndrome (FSSS). We compared the Minnesota Multiphasic Personality Inventory 2 (MMPI-2) results for 41 patients with newly diagnosed PNES and 43 patients with newly diagnosed insomnia. There were no statistically significant quantitative scoring differences on the main clinical scales, indicating that there is no substantial difference in “personality make-up” between the two groups with a FSSS. Additional subscale analysis indicated that patients with PNES reported significantly more somatic complaints (Hysteria 4) and bizarre sensory experiences (Schizophrenia 6). Further profile analysis revealed that the personality pattern of patients with PNES was characterized by a strong tendency toward “conversion V, a lack of control pattern and less excessive worries” as compared with patients with insomnia. Patients with PNES are characterized by a stronger tendency toward somatization and externalization, which has treatment implications.

Introduction

Psychogenic non-epileptic seizures (PNES) resemble epileptic seizures, but have no electrophysiological correlate or clinical evidence for epilepsy, whereas there is positive evidence that psychogenic factors may have caused the seizures¹⁻³. With their somatic appearance and underlying psychological or psychiatric problems, the patients with these seizures present on the boundaries of the medical and mental health services. The incidence of PNES in the general population is relatively low, estimated at about 1.5/100,000 persons per year⁴⁻⁶. Tertiary referral centers estimate a much higher incidence rate⁷. Twenty-five to thirty percent of the patients referred to tertiary epilepsy centers for refractory epilepsy are diagnosed with PNES^{8,9}.

In the diagnostic process two phases can be identified. First, the medical diagnosis requires excluding epilepsy and other somatic causes ("negative" diagnosis). Second is the "positive" diagnosis, for which the underlying psychological mechanisms are evaluated that can be used in treatment^{10,11}. Over the years many psychological mechanisms have been suggested¹²⁻¹⁷. Also, attempts have been made to classify possible subgroups of PNES based on different psychogenic etiological factors^{18,19}. Recent studies have shown that PNES are caused by the interaction of multiple factors, not all of which have a similar impact in different patients. Elsewhere we proposed a theoretical model comprising the different etiological factors that may be involved in the causation, development, and provocation of PNES^{11,20}. Although this model resembles other models^{6,21}, mostly derived from other psychosomatic symptoms, there are also specific factors, especially because of the paroxysmal nature of the seizures. An example is the distinction of triggering factors that create circumstances or situations that provoke PNES. These factors differentiate PNES from other conversion disorders, such as conversion paralyses, that more or less are permanent. Therefore, in this model PNES are considered a unique disorder^{11,20}. Others, however, such as Quigg et al.²², state that PNES should not be considered a disorder in itself, but a symptom of an underlying psychological or psychiatric disorder or recent trauma. In this approach PNES are considered a symptom very similar to other functional somatic symptoms and syndromes (FSSS)^{23,24}. Studies increasingly show the high tendency of patients with PNES to somatize²⁵ and to have other somatoform disorders in their patient history. For example, Mökleby et al.²⁶ showed that 43% of the patients with PNES in their study had somatoform pain disorders and 30% had an undifferentiated somatoform disorder. O' Sullivan et al.¹⁶ reported that 34% of their patients with PNES in a tertiary referral centre exhibited more than one other potential somatoform symptom.

Although, as yet, there is no accepted model to explain PNES, all studies agree that personality factors are an important "modulating" factor in the development of PNES²⁷. Personality traits characterize a person's typical manner of thinking, feeling, perceiving, and relating to others across a wide range of situations²⁸. In some cases

personality traits or personality patterns can be so maladaptive that they constitute a personality disorder²⁹. It is suggested that although only a minority of the general population is diagnosed with a personality disorder, many individuals have a personality pattern that is referred to as a “personality dysfunction” or “difficult personality”. The latter increases their vulnerability to develop a serious mental disorder or psychosomatic symptoms^{20,30}. Personality factors may explain why one patient is able to restore psychological balance after a trauma, whereas other patients develop severe psychosomatic symptoms. Specific personality factors may contribute to different psychosomatic symptoms²⁰.

The Minnesota Multiphasic Personality Inventory 2 (MMPI-2) is one of the most frequently used assessment tools for psychopathology. The MMPI-2 has previously been used in studies in of patients with PNES. However, most of those studies used the MMPI-2 in the first phase of diagnosis, as an extra tool to try to differentiate PNES from epilepsy³¹⁻³⁴. The results of the majority of these studies confirmed the clinical utility of the MMPI-2 as a diagnostic aid in the differentiation of PNES³⁵⁻³⁸. Most studies that used the MMPI-2 to assess underlying psychopathology in the second phase, after the non-epileptic diagnosis was confirmed, used patients with epilepsy as a control group^{19,39}. Few studies have attempted to find differences between the personality profiles of patients with PNES and patients with other functional somatic symptoms with a psychogenic origin. The comparison of patients with PNES and patients with epilepsy can be criticized on two grounds. First, epilepsy is not a mental disorder. Second, many patients with PNES have been through the diagnostic process as an “epileptic patient” for many years. The effect may therefore not be different and patients with epilepsy may not be the ideal population to study the role of personality factors in the psychogenicity of PNES.

Our research question is whether we must consider PNES as a unique disorder with distinctive personality characteristics or as (seen from the personality profile) allied to the domain of a general FSSS, in line with other symptoms such as tension headache, irritable bowel syndrome, chronique fatigue and insomnia^{23,24}. Functional somatic symptoms are defined as physical symptoms that may suggest a general medical condition, but for which after extensive medical assessment no organic cause and bodily mechanisms are identified. Psychogenic factors are supposed to play a role in the etiology^{23,40-42}. We therefore did not use patients with epilepsy as the control group, but instead included patients with insomnia. Insomnia is a broad concept that can be divided into several subdiagnoses, several of which have no organic causes and hence are a somatoform symptom or FSSS^{23,43}. A crucial etiological factor in such disorders is dysfunction of personality^{44;45}. Some of the patients have a “symptomatic” insomnia based on comorbid psychiatric disorders, such as a mood disorder. Our study included only those patients with insomnia for which no organic cause for the sleeping problems was found and the insomnia was not exclusively related to another mental disorder⁴⁰. The MMPI-2 was used in these patients for additional assessment of the psychogenic cause and subsequent psychological treatment.

In this study we analyzed whether the MMPI-2 profile of patients with PNES is specific to PNES or is a more general characteristic of FSSS. The clinical relevance is obviously whether specific treatment or referral to general institutions for mental health is sufficient for people with PNES.

Methods

Participants

Consecutive patients diagnosed with PNES or insomnia in a tertiary referral epilepsy and sleep medicine center during 2006 and 2007 were included in this study. All patients were referred by the neurologist or sleep physician for additional assessment of the psychogenic cause and subsequent psychological treatment. The assessment involved extensive history taking, DSM-IV diagnosis, and personality inventories. This type of selection method precluded a count of the number of patients excluded based on the study criteria. Furthermore, patients were excluded if they could not adequately complete the personality inventory because they had low intelligence or were illiterate. The study was approved by the local medical ethics committee. All participants gave informed consent.

For the diagnosis of PNES, clinical descriptions and additional EEG investigations (such as EEG video telemetry) were used. The type of EEG investigation was based on clinical indications such as patient history and seizure semiology. Patients with PNES were excluded from the study if they showed evidence of comorbid epilepsy. The insomnia group included only those patients with sleep disorders for which no organic cause had been found and for which psychological factors were dominant. Also, sleep disorders resulting exclusively from a diagnosable DSM-IV mental disorder⁴⁰, that is, a “symptomatic” insomnia, were excluded. Thus, the patients with insomnia could have other complaints, such as depressive symptoms, as long as the sleeping problems were not based exclusively on a depressive disorder.

Eventually, 43 referred patients were included in the psychogenic insomnia group and 41 patients in the PNES group. All MMPI-2 profiles were screened on validity and reliability using the information of the validity scales, described under Results. The profiles of all patients were shown to be reliable and valid^{46,47}.

Measures and procedure

In this comparative cohort study, all patients completed the MMPI-2. This objective self-report personality inventory contains 567 items, distributed among four scales: Validity, Clinical, Content, and Supplementary scales. Internal consistency reliability coefficients (Cronbach's α) of the clinical scales ranged from 0.37 to 0.86⁴⁸.

This study focused on the main clinical scales (370 items), in addition to the 31 subscales, which consist of the 28 Harris-Lingoes subscales and the 3 Social Introversion subscales. The main clinical scales measure the following constructs: (1) Hypochondriasis (Hs), (2) Depression (D), (3) Hysteria (Hy), (4) Psychopathic Deviate (Pd), (5) Masculinity/Femininity (Mf), (6) Paranoia (Pa), (7) Psychasthenia (Pt), (8) Schizophrenia (Sc), (9) Hypomania (Ma) and (10) Social Introversion (Si). Patients were asked to identify whether a given statement applied to them or was not (true/false items).

The MMPI-2 is widely used for personality assessment and has been employed in many previous studies to assess pathological personality features⁴⁷. The MMPI-2 has also been used in studies of patients with PNES^{35,49-51}. In general, the MMPI-2 is considered to be robust for changes over time⁴⁸. Because of this the MMPI-2 was conceptualized to be a measure of stable traits³⁹. The interpretation of the MMPI-2 is based on clinical experience rather than on one or more underlying theories⁵². In addition to analysis of the absolute scores on the main clinical scales, the relative contribution of the specific subscales to the total score is interpreted by using the Harris-Lingoes subscales and the Social Introversion subscales. The clinical scales represent a relatively heterogeneous content. Systematic analysis of the subgroups of items within these scales may supplement and enhance the interpretation of the MMPI-2^{48,53}.

The differences and relationships between scores are compared using profile analysis^{52,54}. Since the development of the initial MMPI, researchers have emphasized the need to interpret the configurations of scores on the clinical scales in addition to absolute scores⁴⁶. There is a vast amount of previous research that aimed to describe or differentiate patient groups based on their MMPI profiles^{37,55,56}. Specifically, this study focuses on possible differences in patterns that might be observed.

Statistical analysis

All data were analyzed with SPSS Version 13 (SPSS, Inc, Chigaco, IL, USA). First, frequencies and descriptives were calculated for the main clinical and demographic variables for each group separately. Chi-square testing was used to evaluate whether the patient groups differed significantly on the clinical and demographic variables. Subsequently, the two patient groups were compared using the independent-sample *T* test. The purpose was to find any differences on the MMPI-2 clinical and subscales that might indicate a difference in underlying personality structure. To correct for multiple testing, only *P* values <0.01 were considered to represent statistically significant differences.

Results

The main demographic characteristics of the two groups are summarized in Table 7.1, separately for patients with PNES ($n=41$) and patients with insomnia ($n=43$). Eighty-four patients participated in this study. Mean age was 35 years ($SD=12$), and the majority of the participants were females (72.6%). The two groups appeared to be comparable with respect to most characteristics, except employment status ($X^2 [3,84]=14.40$, $P=0.002$). Fewer patients with PNES were employed compared with patients with insomnia, because of the larger number of patients with PNES unemployed with disability status.

Table 7.1 Demographic characteristics of the patients with PNES ($N=41$) and patients with insomnia ($N=43$).

Variable	Patients with PNES	Patients with insomnia
Gender (%)		
Male	17.1%	37.2%
Female	82.9%	62.8%
Age in years, mean (SD)	33.41 (12.52)	38.30 (11.15)
Marital status		
Single	41.5%	30.2%
Married/cohabiting	53.7%	67.4%
Divorced/single	4.9%	2.3%
Maximum educational level		
Primary school	14.6%	2.3%
Secondary school	63.4%	62.8%
Higher education	22.0%	34.9%
Employment status		
Unemployed	24.4%	23.3%
Unemployed after disability	36.6%	16.3%
Employed	17.1%	53.5%
Attending school	22.0%	7.0%

Validity scales

A cutoff score of 10 (69T) was used on the L and K scales as well as the VRIN (Variable Response Inconsistency) and TRIN (True Response Inconsistency) scales^{46,47}. All profiles included were reliable and valid and no patients had to be excluded because of this. There were no significant differences on the validity scales between patients with PNES and those with insomnia. Both patient groups are characterized by relatively mild elevations on the so-called infrequency scales (F and F-back), with overall mean F-scale scores of 64.44 (20.5) for patients with PNES and 57.66 (13.8) for patients with insomnia, and F-back-scale scores of 64.66 (22.1) for patients with PNES and 59.48 (19.1) for those with insomnia. This indicates that both patient groups did not have a tendency to exaggerate their responses (no “cry for help”).

Comparison of the MMPI main clinical scales

None of the scores on the main clinical scales differed statistically significantly between the two groups. Two clinical subscales showed statistically significant differences. Patients with PNES reported more somatic complaints such as headaches, dizziness, and balance problems on subscale Hy4 ($M=70.12$, $SD=13.34$) than patients with insomnia ($M=58.65$, $SD=13.35$) ($t=3.939$, $P<0.001$). Moreover, patients with PNES reported more bizarre sensory experiences, such as absence-like states, hallucinations, and unusual thoughts. They also more often reported abnormal physical sensations (Sc6) ($M=74.20$, $SD=17.83$) than the patients with insomnia ($M=61.42$, $SD=14.68$) ($t=3.592$, $P=0.001$).

Profile analysis

Main clinical scales

Two observations could be made based on the profile derived from the scores on the main scales (see Figure 7.1). The first observation concerns the so-called “conversion valley pattern”, or conversion V, a “neurotic triad configuration” that was found in the PNES profile and not the insomnia profile. According to Wilkus et al.¹², “conversion V” is a profile characterized by elevated scores on scales 1 and 3 (both >59) and a score on scale 2 that is at least 10 points lower. For the patients with PNES, the 10-point criterion was reached for the scale 3 versus 2 comparison and was almost reached for the scale 1 versus 2 comparison. We therefore do not have a true conversion V, but a tendency toward such a pattern. This pattern represents the tendency for patients with PNES not only to report psychosomatic complaints, but also to pursue a medical explanation for their symptoms as well as to be reluctant to accept that psychological factors may underlie their symptoms. This is characteristic of “classic conversion symptoms” and of a somatoform disorder diagnosis⁴⁸. In this configuration, the relative elevations of scales 1 and 3 are also important. In the PNES group, scale 3 scores are relatively higher than scale 1 scores.

In contrast, in the insomnia group scale 2 was elevated compared with scales 1 and 3, indicating that these patients, in general, tend to be more open to a psychological explanation for their symptoms and tend to suffer more.

A second observation was based on the comparison between the last two main clinical scales: scale 9 (Ma) and scale 0 (Si). A pattern characterized by substantially higher scores on scale 9 than scale 0 was observed for the patients with PNES. This represents a “lack of control” pattern.

Figure 7.1 Mean scores on the Main Clinical Scales:
 (1) Hs, Hypochondriasis; (2) D, Depression; (3) Hy, Hysteria; (4) Pd, Psychopathic Deviate; (5) Mf, Masculinity-Femininity; (6) Pa, Paranoia; (7) Pt, Psychastenia; (8) Sc, Schizophrenia; (9) Ma, Hypomania; (0) Si, Social Introversion.

Subscales

Patients with insomnia scored higher on scale 2 (Depression) subscales than patients with PNES, with the exception of the third subscale (D3) which measured physical malfunctioning. The patients with insomnia more often reported feelings such as being sad, depressed, unhappy, and pessimistic about the future. Although very high scores on scale 2 (exceeding a *T* score of 70) indicate clinical depression, more moderate high scores tend to be indicative of a personality style⁴⁸. This is the case for the patients with insomnia.

On the scale 3 (Hy) subscales, both patient groups reported similar average scores. They differed only on the Somatic Complaints subscale (Hy4), and this difference was significant (see Figure 7.2). A difference was also observed for the Self-Alienation subscale (Pd 5), on which subjects diagnosed with insomnia scored considerably higher than individuals with PNES (see Figure 7.3). Patients with insomnia more often reported feeling unhappy, having problems with concentration, and having a bleak perspective on life in general. A statistically significant difference was also found on the Bizarre Sensory Experiences subscale (Sc6), on which patients with PNES scored significantly higher than those with insomnia (see Figure 7.4).

Other large differences between the two groups could be noted on the Lack of Ego Mastery (Cognitive) (Sc3) and Lack of Ego Mastery (Defective Inhibition) (Sc5) subscales. Although patients with insomnia scored higher on Sc3, patients with PNES had higher scores on Sc5. Patients with insomnia more often reported having concentration and attention problems and the fear of losing their mind. Patients with PNES more often reported that they did not feel in emotional control, felt restless, and felt irritable. On the scale 9 (Ma) subscales, two differences between the groups could be observed. Patients with PNES scored higher on the Amoralism (Ma1) and

Imperturbability (Ma3) subscales (see Figure 7.5). Patients with PNES tended to see others as unfair and denied having social fears. They more often reported being impatient and short-tempered toward others. However, on the Psychomotor Acceleration (Ma2) subscale, patients with PNES scored lower. They did not report overactive thought processes or excessive motor activity. In contrast, the patients with insomnia tended not to see others as selfish and unfair, but reported feeling tense and restless and having problems with overactive thought processes and excessive motor activity. A last difference could be observed on the Social Avoidance scale (Si2) (see Figure 7.6). Although individuals with PNES scored lower on all three Social Introversion subscales than patients with insomnia, the contrast was most obvious on the second subscale measuring Avoidance (Si2). The patients with insomnia tended to withdraw more from social groups and to avoid the cooperation with others.

Figure 7.2 Mean score on the clinical subscales of scale 3, Hy (Hysteria): Hy1, Denial of Social Anxiety; Hy2, Need for Affection; Hy3, Lassitude-Malaise; Hy4, Somatic Complaints; Hy5, Inhibition of Aggression.

Figure 7.3 Mean scores on the clinical subscales of scale 4, Pd (Psychopathic Deviate): Pd1, Familial Discord; Pd2, Authority Problems; Pd3, Social Imperturbability; Pd4, Social Alienation; Pd5, Self-alienation.

Figure 7.4 Mean scores on the clinical subscales of scale 8, Sc (Schizophrenia): Sc1, Social Alienation; Sc2, Emotional Alienation; Sc3, Lack of Ego Mastery (Cognitive); Sc4, Lack of Ego Mastery (Conative); Sc5, Lack of Ego Mastery (Defective Inhibition); Sc6, Bizarre Sensory Experiences.

Figure 7.5 Mean scores on the clinical subscales of scale 9, (Ma (Hypomania): Ma1, Amorality; Ma2, Psychomotor Acceleration; Ma3, Imperturbability; Ma4, Ego Inflation.

Figure 7.6 Mean scores on the clinical subscales of scale 0, SI (Social Introversion): Si1, Shyness/Self-consciousness; Si2, Social Avoidance; Si3, Self/Other Alienation.

Discussion

The MMPI-2 showed no statistically significant quantitative scoring differences on the clinical main scales between the patients with PNES and the patients with insomnia included in this study. The first conclusion, therefore, is that in terms of the main personality characteristics, there is no substantial difference in “personality make-up” between the two groups with a FSSS. This indicates that, as seen from the personality profile, PNES do not constitute a specific, unique syndrome, but are part of “the family” of FSSS. In this interpretation, it is rather arbitrary which symptom is presented. This is in line with Quigg et al.²², who reported that PNES are not a disorder in themselves, but a symptom of an underlying psychological or psychiatric disorder or recent trauma.

When the results were analyzed on a more detailed level, that is, on the level of subscale and profile analysis, differences between the two groups emerged. These differences do not change the overall conclusion, but may have important implications for treatment.

1. The patients with PNES manifested higher variability in somatic complaints than the patients with insomnia. This indicates a tendency to react with a variation of somatoform symptoms and a tendency to shift more easily from symptom to symptom. In contrast, patients with insomnia tended to report more dejected feelings such as “being sad”, “being unhappy”, “feeling depressed”, and “being pessimistic about their life and future”. Thus, the patients with insomnia expressed more feelings indicating that they suffer from the symptoms.
2. The patients with PNES reported significantly more unusual sensory experiences, probably reflecting the manner in which they experienced their psychogenic seizures.
3. The patients with PNES more often reported feeling of irritable, restless, and out of emotional control. These feelings are projected toward the social environment (“acting out”). In contrast, the patients with insomnia tended to report more cognitive symptoms such as attention and concentration problems.

Overall, these findings indicate that patients with insomnia are more acutely aware of their symptoms and are more likely to acknowledge the presence of distress. Patients with PNES may suffer as much or more from their symptoms, but they seem to lack the psychological awareness of the causes and consequences of their psychological dysfunction.

4. Looking further into interaction patterns with their environment there is, again on a subscale level, a tendency for patients with PNES to see others as “selfish and unfair” and to experience themselves as having an open, but impatient attitude toward others with no social fears. On the contrary, the patients with insomnia

showed a tendency to experience themselves as tense and ignored and they tended to withdraw from social groups.

5. Finally, looking at the profile analysis, the two groups had different profiles. The patients with PNES showed a tendency toward the so-called “conversion V” pattern, which represents the tendency to report psychosomatic complaints with a strong preference for a medical explanation. In contrast, the insomnia group did not show this pattern; in general, they were more open to a psychological explanation for their disorder.

In summarizing the profiles it is clear that there are relative differences regarding the extent of somatization and externalization between the patient groups. The patients with PNES had a greater tendency to manifest psychosomatic symptoms and also to shift more easily between symptoms. Although patients with PNES suffered from their symptoms, they more frequently projected the burden of their symptoms to the environment. They tended to have great difficulty in acknowledging the presence of psychological distress and had a strong preference for a medical explanation for their symptoms.

The aforementioned stronger somatization tendency has been reported in other studies of patients with PNES^{19,25, 57-59}. Somatization seems to play a central role in the PNES population, although the causality of somatization as an etiological factor is difficult to establish^{6,57}. Somatization is probably an important mechanism by which emotional problems are externalized. The function is mostly the avoidance of full awareness of the emotional burden and the escape from full responsibility for the emotional problems^{11,18}. Also, there may be a lack of coping strategies to resolve psychological problems in another way⁶. Attribution of the symptoms to a medical cause has also been reported in other PNES studies. A number of studies found that the difficulty in accepting a psychogenic diagnosis also results from an inability of patients with PNES to link the experienced symptoms to specific causes (“I never feel stressed when I have the seizures”)⁶⁰⁻⁶². The resulting confusion seems to enhance the critical view of patients with PNES towards an underlying psychogenic explanation.

Although the sleeping problems of the patients with insomnia we assessed were also related to psychological factors, somatization and externalization seemed to play a less important role. The finding that patients with insomnia show more intrinsic distress about their symptoms has been reported in other studies as well; patients with insomnia obviously suffer from their symptoms^{56,63}. In particular, the cognitive worrying we observed is characteristic of many patients referred to mental health institutions⁶⁴.

These results also have prognostic and treatment implications. The combination of somatization and externalization might explain the difficulty that patients with PNES have in accepting their diagnosis and being motivated for nonmedical treatment. In addition, difficulty in creating a positive patient relationship after the diagnosis of PNES is explained is often described^{30,65}. This is problematic, as studies consistently

report that one-third to one-fourth of the patients become chronic^{20,66}. It has been illustrated that a good therapeutic relationship is crucial for a favorable long-term outcome of PNES^{67,68}. Patients with PNES often find the idea that psychogenic factors are responsible for their physical symptoms unacceptable and counterintuitive^{60-62,69}. They thus persist in viewing their seizures as having an organic origin. Consequently they go to the physician with the expectation that some tests will be performed, a diagnosis will be made, and a medical treatment will be prescribed as with any other medical illness^{44,70}. “Are you sure all necessary investigations have been performed and none of them showed any signs of epilepsy?” is one of the most frequently asked questions by patients in our clinical practice.

Moreover, as was pointed out by Green et al.⁶¹, society still seems to hold views that organic illnesses are genuine and legitimate whereas psychological conditions are not. Therefore, people who are told that their illness has a psychological origin are more likely to feel rejected by doctors and believe that they are viewed as being malingers or attention-seekers^{61,65}. This reinforces their tendency to seek medical responsibility for these symptoms. This pattern, in combination with the previous interaction factors (feeling they are viewed as attention seekers, etc.) may explain why “hostile coping” is a frequently reported coping style among patients with PNES^{20,26}.

What all this means is that treatment decisions require a cautious approach in patients with PNES. The fundamental factor in a good therapeutic relationship is trust^{30,67,71}. Given the tendency of patients with PNES toward somatization and attribution of their symptoms to a medical cause, trust in a psychological treatment will improve when treatment starts within a medical center, instead of direct referral to a mental health institution. Some studies support this conclusion, postulating that strongly somatizing patients are not willing to accept referral for treatment to a psychological institution that has no contact with the institution that currently provides their medical care^{14,65,66,69}. Aboukasm et al.⁶⁹ compared four treatment programs and found that the best outcome occurred after the so-called “comprehensive” treatment program given in a specialized tertiary epilepsy center. This is in line with the suggestion that patients with PNES should preferably be treated in or in alliance with a medical center also treating epilepsy⁶⁵.

Finally, there are limitations to this study that are worth mentioning. One reason for the lack of differences on the main clinical scales is that multiple factors are involved and that structural personality factors alone are not sufficient to generate a specific somatoform disorder^{11,20,27}. In other words, by restricting ourselves to personality profiles alone, no real differences could have been found. Second, generalization of the results may be restricted by selection bias. Both the patients with PNES and those with insomnia were referred to a tertiary referral center and therefore probably represent the more complicated cases. Furthermore, we included only patients who were referred by the neurologist or sleep physician for further psychological

assessment and treatment. This selection method precluded a count of the number of patients excluded on the basis of the study criteria. Future research should include this information to better estimate base rate information in relation to selection ratio for both groups. Furthermore, we did not use a control group without symptoms. Also, it is not expected that patients with insomnia represent all patients with different somatoform symptoms. So, ideally, two other control groups would have been needed to improve generalizability. Finally, future research comparing patients with PNES with other FSSS is recommended.

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Chapter 8

Patients with psychogenic non-epileptic seizures referred to a tertiary epilepsy centre: Patient characteristics in relation to diagnostic delay

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Clin Neurol and Neurosurg 2012;114:217–222

Abstract

Objective

This clinical study examines patient and seizure characteristics of patients with psychogenic non-epileptic seizures (PNES) in a tertiary epilepsy centre. The main focus was whether a new subgroup of PNES patients emerged with a relatively short referral time and possible specific characteristics.

Methods

All PNES patients referred to a specialist program in our centre between mid 2007 and mid 2009 were consecutively included. This yielded a study cohort of 90 patients.

Results

The majority of the patients have a patient history with many medical symptoms and they were or had been in treatment by a medical specialist. Furthermore diffuse psychological/psychiatric symptoms and subsequent treatments are also remarkably common, in general without a clear psychological diagnosis. The average time between seizure onset and referral to an epilepsy centre is remarkably low (4.29 years). About 50% of the patients were referred within 2 years of seizure onset. This 'active high speed referral group' had significantly more previous psychological complaints, significantly more previous psychological/psychiatric treatments and a trend towards more previous medical investigations.

Conclusion

There seems to be a new subgroup of PNES patients with a short referral time, characterized by a more active attitude towards examination of the symptoms in combination with an active attitude to apply for treatment. However, the PNES cohort as a whole is characterized by having somatoform symptoms based on a process of somatization.

Introduction

Psychogenic non-epileptic seizures (PNES) are sudden paroxysmal changes in behaviour or consciousness, that resemble epileptic seizures, but are not accompanied by the electrophysiological changes that characterize an epileptic seizure. Also, there is no clinical evidence of other organic disease that may explain the seizures, whereas there is positive evidence for psychogenic factors that may have caused the seizures¹⁻³. The incidence of PNES in the general population is about 1.5/100,000 persons per year. This is equivalent to about 4% of the incidence of epilepsy^{2,4,5}. However, the prevalence of PNES in patients referred to epilepsy centres is estimated to be about 15-30%^{2,6,7}. Apparently a group of these patients have such severe or difficult-to-diagnose symptoms that referral to a tertiary epilepsy centre is needed⁸. A complicating observation, especially for the patients referred to specialized epilepsy centres, is that between 5-40% of the patients with PNES have a concomitant diagnosis of epilepsy or have a past history with epileptic seizures^{9,10}. In diagnosing PNES two consecutive phases can be identified^{3,11}. Initially, organic factors must be excluded. This is a necessary first step, since the presence of clear psychogenic factors does not exclude the possibility of epilepsy¹². The diagnosis of PNES is based on history taking, seizure observations and EEG recordings^{2,5,13}. The differential diagnosis can be challenging¹⁴⁻¹⁶. Also, various studies demonstrated that many signs that have been considered typical for PNES, appeared not to be specific and can also be found in epileptic seizures, especially in those seizures that originate from the frontal lobe^{2,14,17}.

The second phase aims at obtaining a 'positive diagnosis' in which the underlying psychological mechanisms are evaluated that can be used for treatment^{3,18}. Theories regarding the psychological etiology of PNES are diverse. This probably reflects the heterogeneity of the psychogenic etiology of PNES^{19,20}. Recent studies showed that PNES are caused by an interaction of multiple factors in which not all factors may have a similar impact in an individual patient^{3,21,22}. Attempts are made to organize different etiological factors in a descriptive model. Also several studies have tried to classify possible subgroups of PNES based on different etiological factors²³⁻²⁵.

Over the years several patient and seizure characteristics about PNES have been consistently reported^{2,3}. In general, there is a predominance of the female gender (of about 75-99%)^{6,26}. Age at onset is at about 20-30 years^{5,7,27}. A higher incidence of PNES has been found in patients with a lower educational level²². At time of diagnosis a majority of the patients report a relatively high seizure frequency (daily or weekly seizures)^{28,29}. Meierkord et al.³⁰ revealed that the majority of patients (66%) had seizures with major motor manifestation (resembling tonic-clonic seizures). Seizures in the category "unresponsiveness" ('absence-type seizures') are a less frequent reported symptom. However, Leis et al.¹ have demonstrated that unresponsiveness may often remain undetected so they warn against such conclusions.

Although PNES patients constitute a heterogeneous group, psychiatric co-morbidity or even multiple psychiatric diagnoses, have also consistently been reported^{19,22,31}. Especially mood disorders (mostly depression)^{32,33}, anxiety disorders^{31,34}; and personality disorders³⁵ are frequently mentioned^{5,7,11,29,36-38}. Often the exact definition of the psychiatric disorder is however lacking or nonconclusive, due to differences in methodology, the selection criteria or missing information².

An additional consistent finding is the long delay of approximately 7 years between seizure onset and the (final) diagnosis of PNES, at least in those patients that have been referred to tertiary centres. This finding has been reconfirmed and still seems valid over the years^{2,5,7,19,28,39-41}. Reuber and Elger⁵ argue that a potential reason for this diagnostic delay could be that patients often present their seizures to generalists, physicians in emergency care departments a.o. instead of experts in the assessment and treatment of seizures. Non-expert physicians may act 'better safe than sorry' when they are faced with seizures and treat these seizures as organic although they are uncertain about the diagnosis. Several studies showed that a large number of patients who were referred to tertiary epilepsy centres with 'intractable epilepsy' or with an uncertain diagnosis, were later diagnosed as having PNES^{15,18,41,43}. Also, it is possible that patients with PNES referred to a tertiary epilepsy centre are exactly those patients in whom the seizures are difficult to detect or difficult to classify^{8,28}. The diagnostic delay is seen as worrisome since diagnosing PNES is essential for adequate therapy and can prevent unnecessary drug treatment^{3,42,44}.

Although this delay is consistently reported and seems stable around 7 years, our recent experience in clinical practice suggests that for some patients the time between onset of seizure symptoms and referral to a tertiary centre seems to be much shorter. There is no change in referral guidelines in our country so our assumption is that this is related to patient characteristics. As this has not yet been reported, we analyzed the patient characteristics of a non-selective group of PNES patients referred to our tertiary epilepsy centre. Our main focus is on assessing patient characteristics of a possible 'new' subgroup of PNES patients with a relative short referral time.

Methods

Participants

All patients aged >12 years referred to the epilepsy centre between mid 2007 and mid 2009 were consecutively included in the study after a final diagnosis of PNES was made. Epilepsy as concomitant disorder was not an exclusion criterion. The study was approved by the local Medical Ethics Committee.

Procedure

This study is an open non-controlled clinical cohort study. Patients were included after the diagnostic phase was completed and the patients were referred to an expert team. The PNES diagnosis had to be confirmed in the tertiary epilepsy centre by an experienced neurologist/epileptologist, using clinical description and additional EEG investigations (also EEG video telemetry). The type of EEG investigation was based on clinical indication such as patient history and seizure semiology.

Statistical analyses

Statistical analyses were performed using SPSS 16.0. (SPSS, Inc, Chicago, IL). For relevant variables parametric *t*-tests or non-parametric statistics were used (Mann-Whitney *U* tests). The significance level was set at 5%. In addition a non-parametric correlation analysis was performed.

Results

Table 8.1 shows the main demographical and clinical characteristics of the 90 patients included. There is a dominance of the female gender and mean age at referral was 31.71 years. Most patients have a lower educational level, such as special education, primary school or lower vocational education. Most patients solely have PNES, although about one third of the patients had PNES in combination with epilepsy. Only in one patient there was doubt about comorbidity with epilepsy, but no doubt about PNES.

A large part of the patients does not live independent, but with their parents (35.6%). The mean age of this home living group is 20 years, but 30% is older than 21 years. Furthermore, about half of the patients reports having a complicated family background, such as divorced parents or a family breakdown due to external circumstances such as a deceased parent. In 20% of the patients epilepsy or other types of seizures occurred in the first line (parents or siblings) or second line (grandparents and friends). The mean age of onset of the seizures is 26.5 years, with a standard deviation of 12.9 years. The youngest patient was 5 years at seizure onset and the oldest patient was 63 years old. At time of referral to the epilepsy centre almost half of the patients (46%) used AED medication. AED polytherapy was used in 26% of the patients; 20% of the patients used AED monotherapy. Furthermore, psychotropic medication is used in 20% of the patients and 7% used sleep medication. 27% Of the patient group used other medication such as medication for the heart. Only 36% of the patients did not use any medication at the time of referral.

Table 8.1 Patient characteristics.

	Number	Percentage
Number of patients	90	100
Gender		
Male	22	24.4
Female	68	75.6
Age at time of diagnosis		
Minimum age	13.92	
Maximum age	63.33	
Mean	31.71 (SD = 12.59)	
Median	29.17	
Education		
Special education	11	12
Primary school	13	14
Lower secondary school	25	27.5
Middle level secondary school	25	27.5
Higher education	10	12
Unknown	6	7
Also epilepsy?		
No	64	71
Yes	25	28
Doubt	1	1

Table 8.2 summarizes seizure frequency and seizure type at time of diagnosis in the epilepsy centre. Most of the patients had daily or weekly seizures. Seizures types were divided into different categories, based on the classification proposed by Betts and Boden³³. Most of the patients had ‘twilight state’ symptoms, which are characterised by sudden episodes of loss of consciousness and psychic symptoms. A second common seizure type is ‘the tonic-clonic like seizure’, that resembles epileptic seizures with a tonic phase and clonic movements. Other frequent seizure types were ‘clonic-like’ or ‘atonic-like’ (drop attacks). ‘Absence-like’ seizures were uncommon in this cohort.

These different seizures types can also be divided into two different broad categories^{2,30}, i.e. ‘major motor manifestation’ and ‘unresponsiveness, flaccidity’. This classification is based on either seizures that involve movements and jerks or falling (major motor manifestation) or without any movement (unresponsiveness). The categories are equally common in our cohort (39% major motor manifestations versus 46% unresponsiveness). Some patients (14%) have more than one seizure type.

Table 8.2 PNES frequency and seizure type at time of diagnosis.

Seizure frequency	% of the study group	Seizure Type	% of the study group*
Daily	21	'Twilight state'	34
Weekly	44	'Tonic-clonic like'	24
Monthly	13	'Clonic-like'	11
Yearly	10	'Atonic-like'	10
Seizure free	2	'Clonic and twilight state'	5
Unclear	10	'Tonic-like'	2
		'Clonic and Stupor-like'	2
		'Absence-like'	2
		Unknown	1
		Other types	9

* Some patients have more than one seizure type.

Table 8.3a shows that only a minority of this cohort has no general medical complaints in the patient history before referral. The vast majority of the patients reports frequent medical and physical complaints.

In line with this finding, Table 8.3b shows that only a minority of 21% of the patient group had no previous history of medical treatments before referral to our tertiary epilepsy centre. The majority of the patients had been in treatment for one or more medical diseases or problems. These were treatments by a medical specialist, such as a neurologist or medical specialist for internal medicine.

Table 8.3 History of medical symptoms and medical treatment before referral.

a. Medical symptoms	Percentage of the study group	b. Previous medical treatment for	Percentage of the study group
No medical complaints	28	Suggested head injury	34
Chronic headache	16	Chronic diseases (a.o. diabetes mellitus, asthmatic bronchitis, tumour and pulmonary embolism)	22
Sleeping problems	12	Neurological disorders	21
Chronic fatigue	11	General medical problems	21
Chronic pain	10	Seizure-like symptoms	18
Addiction problems	4	Epilepsy	8
Hyperventilation	4	No medical treatments	21
Hypertension	4		
Menstrual complaints	3		
Memory complaints	2		
Heart complaints	2		
Physical disability/ wheelchair bound	2		
ADHD	1		
Obesity	1		

Table 8.4a shows that most of the patients have no confirmed previous psychological or psychiatric disorder or clearly defined and diagnosed symptoms. Despite this lack of confirmed psychological or psychiatric diagnosis, Table 8.4b shows that about two third of the patient group had previous psychological or psychiatric treatments before they were referred to the epilepsy centre.

Table 8.4 History of psychological/psychiatric symptoms and subsequent treatments before referral.

a. Previously confirmed psychological/psychiatric symptoms or disorders	Percentage of study group	b. Previous psychological and/or psychiatric treatments	Percentage of study group*
No confirmed psychological/psychiatric disorder	72.5	Psychological treatment of longer duration	47
Depression	11	Psychiatric treatment of longer duration	24
Suicide attempt(s)	5.5	Counseling by a social worker	8
Borderline personality disorder	3	Acute admission for psychiatric treatment	6
Eating disorder	2	Single psychological or psychiatric consultation	8
Anxiety attacks	2	Family counselling	7
Self mutilation	2	No psychological/psychiatric interventions	37
Asperger syndrome	2		
Mood swings	1		

* Some patients have more than one symptom or treatment.

Figure 8.1 shows on the horizontal axis the patients and on the vertical axis the number of years between seizure onset and referral to the epilepsy centre. This shows that the average time between seizure onset and referral to the tertiary centre is 4.29 years (SD=6.44 years). However, the relatively high standard deviation illustrates that there is a large range. The minimum time between the first seizure and a referral was 1 month and the maximum time was 25 years and 4 months. The blue line in Figure 8.1 shows the time for each individual patient between seizure onset and referral to the tertiary epilepsy centre. The red line represents the average time of this study group. Globally about 50% of the patients were referred within two years of the seizure onset. The other 50% of the patient group is referred around the average period (30%) or were referred after a very long period from seizure onset. About 20% of the patients were referred after 9 years or longer from seizure onset.

We compared these groups for differences. In general, differences were limited. Naturally, the first group has a much shorter referral delay. Furthermore, this group had significantly more previous psychological complaints (Mann-Whitney U 793,000, $P=0.034$), more previous psychological or psychiatric treatments (Mann-Whitney U

23,000, $P=0.03$) and a trend towards more previous medical investigations (Mann Whitney U 19,500, $P=0.06$).

Further analyses of the referral patterns of all patients showed that most patients (41%) were referred for 'diagnostic uncertainty' or for a second opinion (13%). Other referral questions were unsatisfactory seizure control and/or side-effects of the antiepileptic drugs (15%) or 'recurrent seizures' (10%). In a mere 4% of the patients a clear suspicion of PNES was the actual referral reason. Furthermore 53% of the patients were referred by a neurologist from a general hospital or by a family doctor (40%). Only 1% of the patients was referred by an psychiatrist.

Figure 8.1 Time between seizure onset and referral to the tertiary epilepsy centre.
* n=8 missing values for diagnostic delay because of no record in the patient file

Discussion

This clinical study was aiming at exploring characteristics of patients with PNES, referred between mid 2007 and mid 2009 to and diagnosed in a tertiary epilepsy centre. We were particularly interested in the patient characteristics of a possible new subgroup of PNES patients with a relative short referral time.

Some of the consistently reported characteristics of PNES patients^{2,3,5,6,22} were also found in our cohort: a predominance for the female gender (75.6%) and a lower educational level. Approximately one third of the patients does not live independent, but with their parents. 30% of this 'home living' group is older than 21 years, which

could represent a higher tendency towards dependency. Also about half of the cohort report complications in the family of origin, such as divorced parents or problematic relationship(s) within the family. About 20% of the patients had relatives in first or second line with seizures. This is lower than expected as we have suggested^{2,3} that patients with PNES must have had models for seizures in their direct environment. As reported in other studies^{28,29}, seizure frequency at time of diagnosis is high: 65% of the patients had weekly or daily seizures. A broad distinction of the seizures into 'major motor manifestation' and 'unresponsiveness, flaccidity'³⁰ reveals that both types are equally common in occurrence (39% versus 46%). The relatively high percentage of unresponsiveness is in line with Leis et al.¹ demonstrating that unresponsiveness may often remain undetected by the referring institute. It may be these patients that are referred to and diagnosed in a tertiary centre²⁸. In accordance with a study by Bodde et al.³, most patients had only PNES, although about one third of the patients had PNES and epilepsy as comorbid disorder. Only 4% of the patients were referred with a clear suspicion of PNES. Diagnostic uncertainty or unsatisfactory seizure control were the main referral reasons. This corresponds with the observation that apparently a group of PNES patients have such frequent or difficult-to-diagnose symptoms that referral to a tertiary epilepsy centre is needed. Almost half of the patients (46%) used antiepileptic drugs at time of referral. This is in accordance with other studies^{29,45}, although the high percentage of patients on polytherapy in our cohort (26%) is remarkable. Only one third of the patients did not use any medication at time of referral.

The majority of the patients (about 70%) report other medical symptoms in their patient history prior to referral to the epilepsy centre. Especially chronic headache, sleeping disorders, chronic fatigue and chronic pain are frequently mentioned. These are symptoms that are difficult to confirm objectively. In line with these medical symptoms, the vast majority of the patients were or had been in treatment for one or more medical diseases by a medical specialist. Only a minority (18%) had no previous history of medical treatments at time of diagnosis in our centre. If compared with the general population about 30% will consult a specialist (source: Statistics Netherlands⁴⁶). Especially head injury was reported by about one third of the patients. Kuyk⁴⁷ and Benbadis⁴⁸ also found that some of the PNES patients had a history of head injury. Similar results have also been reported for other conversion patients⁴⁹. The relationship between this finding and the development of PNES or other conversion symptoms is unknown.

In addition to the large amount of former medical symptoms and treatment, more or less elusive psychological/psychiatric symptoms and subsequent treatments are also remarkably common. Patients reported for example stress at work, performance anxiety and mood swings in their patient history. These types of psychological symptoms seem to be difficult to verify since only 19% of these patients had a diagnosed and confirmed psychological or psychiatric disorder such as a depressive disorder. This implies that in the vast majority of the patients (81%) previous

psychological and psychiatric treatments were initiated without a clear diagnosis, but based on indistinct, equivocal complaints or symptoms.

Summarizing these findings, our cohort is characterized by having a patient history with many medical and psychological/psychiatric symptoms and an active drive towards seeking subsequent treatment for them. In general there is a lack of clear diagnoses. These findings seem to indicate the presence of somatoform symptoms and a process of somatization in PNES patients. In somatization, physical symptoms occur in the absence of any identifiable bodily mechanism. Patients experience and communicate somatic distress, have a somatic explanation for their symptoms and look for medical treatment^{50,51}. Patients with somatoform symptoms mostly do not have clear psychological /psychiatric disorders, but they have vague, indistinct and difficult to verify complaints, generally somatically defined such as chronic headache etc. In line with this somatic definition, they are not referred by psychiatrists but by neurologists and family practitioners⁵². We also found this reference pattern in our patient cohort.

The most striking finding in this study is the relatively low average time between seizure onset and referral to a tertiary epilepsy centre of 4.29 years. This is different from most of the reports that have demonstrated an average of approximately 7 years^{2,3,5,7,15,19,28,40,41}. Furthermore, the standard deviation was high (6.44 years). Almost 50% of the patients were referred within 2 years after seizure onset.

According to our hypothesis we analyzed this so-called 'active high speed referral group' on specific characteristics. In contrast with the findings of O'Sullivan et al.⁵³, who found a shorter diagnostic delay for patients with PNES alone, we did not find delay differences between PNES patients only and PNES patients with comorbid epilepsy. We did find that our active high speed referral group had significantly more previous psychological/psychiatric complaints and more previous psychological/psychiatric treatments in their patient history. Furthermore, there is a strong trend towards more previous medical investigations. So this active group is characterised by a stronger drive for medical examinations and treatment of mostly indistinct, equivocal symptoms.

Nonetheless, this does not indicate a specific subgroup with specific distinctive features. Our cohort as a whole is characterized by having many diffuse psychological/psychiatric and/or medical symptoms. This is in line with the consistent finding of psychiatric comorbidity and the tendency to somatize in PNES patients^{13,20,31,39, 54,55}. For example O' Sullivan et al.⁵³ report that 34% of their PNES patients in a tertiary referral centre (Cork University Hospital) exhibited multiple potential somatoform symptoms. They also state that they feel this is an underestimation of the co-occurrence of other potential somatoform disorders. It therefore seems more likely that there is a continuum of somatization in the PNES patients referred to an epilepsy centre, in which a group of patients has a more active attitude towards medical investigations and treatment of these symptoms.

Currently, it is not possible to clarify whether this continuum of somatization might differentiate PNES patients based on the DSM-IV classification system of somatoform disorders. The DSM-IV distinguishes seven different types of somatoform disorders: somatization disorder, undifferentiated somatoform disorder, conversion disorder, pain disorder, hypochondriasis, body dysmorphic disorder and somatoform disorder not otherwise specified. In most cases, PNES is classified as a conversion disorder, since the seizures present as a 'pseudo neurological symptom', affecting voluntary or sensory function and suggesting dysfunction of the nervous system (DSM-IV)⁵⁶. However, given the elusive symptoms in the patient history, other classifications types may also be considered, especially a somatization disorder (SD). A SD is characterized by having symptoms affecting different medical area's; so pain symptoms, gastrointestinal symptoms and sexual symptoms have to be reported as well. In order to confirm such a diagnosis often additional physical examinations and diagnostic tests are required to exclude organic disorders. Such investigations are costly and often not available in the patient history⁵¹. Furthermore, autobiographic memory of past medical or psychiatric symptoms is often unreliable. Patients seem to forget or fail to report previously reported symptoms that are no longer troublesome^{57,58}. Also, clinicians need to systematically discuss former symptoms⁵¹. For these reasons, the actual prevalence of a SD may be substantially higher than literature suggests⁵¹. Remarkably, even in the 'high speed referral group', which is characterized by more medical investigations and treatments, a SD according to DSM criteria was not significantly more confirmed than in patients who were referred much later. A potential explanation might be that physicians are 'better safe than sorry' in diagnosing a SD. Furthermore, in the Dutch system patients are referred to different specialists for different symptoms, so a specialist may lose track on the whole patient history.

Our study does not provide reasons for this high speed referral pattern in a subgroup of the PNES patients. It may be the changed position of the epilepsy centres, which are now widely known to have specific expertise in diagnosing and treating PNES. Also the topic of 'somatically unexplained symptoms' seems to get more attention in hospitals^{59,60}. However, there are no strong indications that these changes have led to a different referral pattern. It may also be failure of institutions for psychological and psychiatric treatment to cope with these strongly somatizing patients. In general, the shorter the diagnostic delay, the better. However, if these 'active high speed referral' patients are constantly referred for (medical) investigation of changing symptoms, this will also prevent appropriate treatment. Only cooperation between hospitals or tertiary referral centres and institutions for mental health might prevent this kind of 'medical shopping'. Furthermore Ettinger et al.³⁹ suggested that future investigations should determine what effect revealing a PNES diagnosis has on the frequency and severity of other symptoms, such as headache and other pain symptoms. In some patients the resolution of the PNES may be followed by the development of substitute symptoms. Also PNES may not be the most serious manifestation of a SD.

Finally, in our study we analysed descriptive characteristics of patients with PNES. Our focus was not on assessing personality traits. It is possible that using psychological tests could differentiate patients from the 'high speed referral group' at a different level. Especially at the level of coping mechanisms changes can be hypothesized. Coping styles refer to the way people act upon a setback, such as having symptoms, in their lives. Changes might be found between more active or passive coping styles^{3,61,62}. The search for possible subgroups for PNES remains important to improve tailored treatment for this heterogeneous group of patients.

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Chapter 9

Subgroup classification in patients with psychogenic non-epileptic seizures

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Epilepsy Behav 2012;26:279-89

Abstract

Introduction

In this open non-controlled clinical cohort study, the applicability of a theoretical model for the diagnosis of psychogenic non-epileptic seizures (PNES) was studied in order to define a general psychological profile and to specify possible subgroups.

Methods

Forty PNES patients were assessed with a PNES “test battery” consisting of eleven psychological instruments, e.g., a trauma checklist, the global cognitive level, mental flexibility, speed of information processing, personality factors, dissociation, daily hassles and stress and coping factors.

Results

The total PNES group was characterized by multiple trauma, personality vulnerability (in a lesser extent, neuropsychological vulnerabilities), no increased dissociation, many complaints about daily hassles that may trigger seizures and negative coping strategies that may contribute to prolongation of the seizures. Using factor analysis, specific subgroups were revealed: a ‘psychotrauma subgroup’, a ‘high vulnerability somatizing subgroup’ (with high and low cognitive level) and a ‘high vulnerability sensitive personality problem subgroup’.

Conclusion

Using a theoretical model in PNES diagnosis, PNES seem to be a symptom of distinct underlying etiological factors with different accents in the model. Hence, describing a general profile seems to conceal specific subgroups with subsequent treatment implications. This study identified three factors, representing two dimensions of the model, that are essential for subgroup classification: psychological etiology (psychotrauma or not), vulnerability, e.g., the somatization tendency, and sensitive personality problems/characteristics (‘novelty seeking’). For treatment, this means interventions could be tailored to the main underlying etiological problem. Also, further research could focus on differentiating subgroups with subsequent treatment indications and possible different prognoses.

Introduction

About 25-30% of the patients referred to tertiary epilepsy centers or specialized hospitals have psychogenic non-epileptic seizures (PNES)¹⁻⁴. A psychogenic non-epileptic seizure is defined as a clinically observable paroxysmal change in behavior or consciousness that resembles an epileptic seizure but is not accompanied by the typical electrophysiological and behavioral changes that accompany an epileptic seizure. There is also an absence of any known organic etiology for the seizures, whereas there is positive evidence or a strong suspicion for the existence of psychogenic factors^{3,5-7}.

Earlier research in the field of PNES has mainly focused on the differential diagnosis with epileptic seizures. The correct medical diagnosis of PNES remains a challenge, but since the introduction of simultaneous video EEG-monitoring, the differential diagnosis of PNES-epilepsy has greatly improved^{1,8-11}. The true challenge in the diagnostic process of PNES, however, is not only to exclude epilepsy and other organic factors but also to avoid that PNES becomes a 'nondisease'¹². A subsequent positive diagnosis is required involving the underlying psychological mechanisms^{7,9,13,14}. There is consensus that in most patients, multiple underlying psychogenic factors or mechanisms are involved in different combinations and with variable effects on prognosis^{15,16}.

In a small group of PNES patients, the communication of the PNES diagnosis in a clear, empathic way will result in seizure reduction^{7,17-19}. However, patients with PNES comprise a very heterogeneous patient group²⁰⁻²⁴. Several studies report that for many PNES patients, the long-term prognosis is not good. In about 1/3rd to 1/4th of the patients, PNES become chronic^{7,25}. Patients often show 'medical shopping' in a search for second opinions. Also, symptom characteristics may shift from seizures to other psychosomatic symptoms mimicking e.g. movement disorders^{26,27}. As a result, the patients remain in a purely medical environment and are not referred to appropriate psychological therapy^{28,29}.

To achieve optimal therapeutic outcome, the choice of treatment should be adjusted to the individual patient's combination of underlying etiological factors^{7,9,15,29,30}. Recently, we have proposed a theoretical model distinguishing five different levels representing specific underlying psychogenic factors (see Figure 9.1)^{6,7}. This model was derived from a literature search on psychological etiology and PNES. The model resembles other models with predisposing, precipitating and perpetuating factors to explain somatoform disorders^{16,31-33}, but more specific factors have been added in relation to PNES. *Level 1, psychological etiology*, refers to factors involved in the causation of PNES, such as sexual abuse or other traumatic experiences^{34,37}. However, not all people who have had traumatic experiences develop PNES^{38,39}. Many authors have pointed to the specific vulnerability of PNES patients both in terms of their emotional profile and their neuropsychological functioning. Examples are personality factors, gender and age^{9,26,29,40-44}. Also, possible organic factors such as head trauma,

may induce higher vulnerability⁴⁵⁻⁴⁷. *Level 2, vulnerability*, therefore, refers to characteristics that predispose a person to develop psychosomatic symptoms, such as PNES. *Level 3, shaping factors*, refers to factors that explain why the symptoms are 'seizures' and not for example functional movement disorders, sleep disorders or 'headache-like symptoms'. A shaping factor may be a close friend or relative with epileptic seizures (symptom modeling) (see^{20,48}) or having had epilepsy in the past. *Level 4, triggering factors*, refers to factors that create circumstances or specific situations that provoke a seizure at a specific moment, such as PNES during school break or after a marital quarrel^{49,50}. Also, psychological mechanisms that transfer an emotional state into a seizure can be part of these triggering factors, such as dissociation and somatization^{1,14,21,51,52}. Such factors explain why seizures occur on a specific day, or in a cluster or why there is a period of remission. This distinguishes PNES from conversion states that generally have a more permanent presentation. *Level 5, prolongation*, refers to factors that are important in explaining why the seizures persist over time and PNES may become a chronic disorder. These factors determine its frequency and its resistance against therapy. Such modulating factors are, e.g., the coping style of the patient and secondary gain aspects^{9,49,53}.

Figure 9.1 Diagnostic model of psychogenic factors involved in psychogenic non-epileptic seizures^{6,7}.

Figure 9.1 describes the assumed relationship between the factors. The model is not conclusive as some factors can interact at different levels. Coping strategies may be involved in the causation of PNES and may have a role in the vulnerability, whereas family factors may contribute to the prolongation of seizures and not only in the development⁵⁴.

The current study focuses on the applicability of this model in the diagnosis of PNES. Relevant and available tests covering the different factors of the model were used to identify dominant factors for the total group and for specific subgroups. There was a focus on subgroups since many factors have been related to PNES but seldom account for the patient group as a whole^{7,23,24,52,55,56}. Recent studies increasingly focus on finding criteria to differentiate subgroups in PNES, using PNES phenomenology⁵⁷, descriptive patient characteristics⁵⁸, personality factors and/or cognitive functioning^{9,24}. As yet, these criteria were not investigated using a diagnostic model. In this study, tests used in clinical practice were integrated in the diagnostic model in order to systematically assess relevant factors and subgroups.

Methods

Participants

Patients were consecutively included when:

1. The PNES diagnosis had been confirmed in the tertiary referral epilepsy centre using clinical description and additional EEG investigations (such as video-EEG monitoring). The type of EEG investigation was based on clinical indications, such as patient history and seizure semiology.
2. The diagnosis was confirmed in the period 2009-2010.
3. They were >15 years old.
4. They had a normal intelligence. Mental retardation was an exclusion criterion.
5. They did not have major psychiatric comorbidity, such as major clinical depression.

In total, 40 patients were selected that met the inclusion criteria.

Procedure

This study was an open non-controlled clinical cohort study. All patients were psychologically assessed by trained clinical psychologists. The history of all patients was taken, and a DSM-IV classification was made. The different levels of the theoretical model were assessed using a psychological PNES “test battery”. In this battery, eleven psychological tests/instruments were selected that met the criteria for validity and reliability and had norm scores. For level 1, no norm scores were

available, but we could use a trauma checklist. Also, level 3, shaping, mostly refers to symptom modeling for which no normed psychological test is available. Since dissociation is supposed to modulate between level 3 and 4, we used the dissociation questionnaires for this level.

The following tests were selected:

Level 1 'psychological etiology':	Trauma: TEC (Traumatic Experiences Checklist)
Level 2 'vulnerability':	A) Neuropsychological factors <ul style="list-style-type: none"> • Global Cognitive level: Raven (Raven Progressive Matrices) • Mental flexibility: TMT (Trail Making Test) • Speed of information processing: CVST (Computerized Visual Searching Task) B) Personality factors <ul style="list-style-type: none"> • Short TCI (Dutch language short version of the Temperament and Character Inventory) • Short MMPI (Dutch language short version of the Minnesota Multiphasic Personality Inventory)
Level 3 'shaping':	Dissociation <ul style="list-style-type: none"> • DIS Q (Dissociation Questionnaire) • SDQ-20 (Somatoform Dissociation Questionnaire)
Level 4 'triggering':	Daily hassles and stress: EPCL (Everyday Problem Checklist)
Level 5 'prolongation':	Coping <ul style="list-style-type: none"> • UCS (Utrecht Coping Scale) • CERQ (Cognitive Emotion Regulation Questionnaire)

An extensive description of the instruments is attached in Appendix A.

Statistical analysis

Statistical analyses were performed using SPSS 16.0. (SPSS, Inc, Chigaco, IL). The individual results were converted to z-scores to allow comparability among the tests. In a first step of the analyses, we explored whether the scores on the profile of the total group differed significantly from the 'norm z-value' of 0 that represents no difference with the norm population. Secondly, we performed subgroup analysis. In a univariate approach, relevant factors were inspected separately. However, this

approach ignores the intercorrelations between the different tests and levels of the model. Subsequently, we, therefore, used a multivariate correlational approach with factor analysis. The significance level was set at 5%.

Results

Table 9.1 shows the main demographical and clinical characteristics of the 40 patients. There was a dominance of the female gender, and mean age during assessment was 30 years. Most patients had only PNES, although about one-third of the patients had PNES in combination with epilepsy. Most patients had at least monthly seizures, and four patients were seizure free in the past three months. Thirteen patients reported no or only a mild impact of the seizures on their daily functioning, whereas eighteen patients reported frequent to severe impact on their daily living. Most patients lived with their parents or with a partner, and only two patients lived alone. Sixteen patients were unemployed or disabled to go to school or work.

Table 9.1 Demographical and clinical characteristics of the study group.

N	40
Gender (male:female)	8:32
Mean age (years)	30
Age range (years)	15.7–63
Additional epilepsy (no:yes)	30:10
PNES frequency	
- Currently seizure free	4
- Less than monthly	2
- Monthly	3
- Weekly	15
- Daily	10
Impact of PNES on daily functioning	
- No impact	3
- Occasionally	10
- Frequently	9
- Seriously	6
- Completely	3
Social status	
- Living with parents	18
- Living alone	2
- Married/living with partner	19
Education/work	
- School	11
- Unemployed	6
- Disabled	10
- Employed	9
- School and employment	3

A. Profile analysis of the total PNES group

Figure 9.2 shows the profile of the total group in z-scores for the different levels in the model: 0 is the average report in the general population; based on reference values, scores of -1 and -2 show deviation of respectively 1 standard deviation and 2 standard deviations from the reference. Vice versa scores of + 1 and + 2 show scores higher than reference value. Statistically significant differences with the norm scores are provided in the figure.

Figure 9.2 Profile of scores of the total PNES group normalized by using z-scores.
* = Statistically significant differences with norm scores.

Level 1: 'psychological etiology'

For the TEC (Traumatic Experiences Checklist), no norm scores are defined; therefore, z-values cannot be reported. The TEC was, therefore, not included in the profile. One can argue that any trauma may have an effect and is not 'normal'. Seventy percent of our patients did report a traumatic event, and 52% reported multiple traumas. These percentages seem to deviate from 'the normal situation'. However, the TEC allows reports over a whole range of situations, some of which actually are more common in the general population, such as 'emotional neglect'. If we only inspect the variables in the TEC 'threat of body/life', 'sexual harassment' and 'sexual abuse' than 42.5% of our patients reported such traumas. Breslau et al.¹⁰⁰ reported that traumas that result in a Post Traumatic Stress Disorder (PTSD), generally associated with severe trauma, occurred in only 8% of the population.

Level 2: 'vulnerability'

a. *Neuropsychological function.* Global cognitive level (Raven) was not significantly different from normal, but PNES patients showed greater rigidity and lacked planning skills (TMT; $t=2.063$; $P=0.046$). Moreover, they were characterized by slowing of central information processing speed (CVST; $t=4.329$; $P\leq 0.001$).

b. *Emotional profile/personality factors.* Significant differences on the short TCI (short version of the Temperament and Character Inventory) with the reference values were found on three 'temperament dimensions', e.g., higher 'harm avoidance' ($t=0.837$; $P=0.001$), lower 'reward dependence' ($t=2.057$; $P=0.046$) and higher 'persistence' ($t=3.140$; $P=0.003$) and on one 'dimension of character': lower 'self transcendence' ($t=4.265$; $P\leq 0.001$). These results characterized the PNES patients as having a careful, anxious attitude, being vigilant for potential danger (high harm avoidance) in combination with a practical approach of situations and being insensitive for social signals (low reward dependence). The total PNES group were shown to be diligent and perfectionistic despite setbacks (high persistence). They had difficulty tolerating ambiguity and uncertainty and a strong need to control (low self-transcendence).

On the short MMPI (short version of the Minnesota Multiphasic Personality Inventory), PNES patients scored relatively high in 'somatization' ($t=8.416$; $P=0.001$) and 'shyness' ($t=2.558$; $P=0.015$). This indicated a strong tendency to react with (psycho)somatic complaints on psychological distress and also a tendency to be introverted, to be less sociable and to attempt to internally control emotions.

Level 3 'shaping'

No statistically significant differences were found with the reference values for the SDQ-20 (Somatoform Dissociation Questionnaire) and the DIS-Q (Dissociation Questionnaire). The PNES group as a whole did not show increased scores for both forms of dissociation.

Level 4 'triggering'

The EPCL (Everyday Problem Checklist) showed a statistically significant higher number of 'total complaints' ($t=4.497$; $P\leq 0.001$), 'subject dependent complaints' ($t=5.516$; $P<0.001$) and 'situations beyond control of the subjects' ($t=3.066$; $P=0.004$). The PNES group as a whole reported having many daily hassles and chronic stressors during the past two months within several life domains.

Level 5 'prolongation'

The UCS (Utrecht Coping Scale) showed a higher tendency towards a passive, 'wait and see' attitude ($t=3.129$; $P=0.003$) when confronted with problems or events requiring adjustment. Furthermore, on a behavioral coping level, the patients tended to avoid problems and tended to avoid looking for social support.

The CERQ (Cognitive Emotion Regulation Questionnaire) showed statistically significant higher scores for 4 areas: 'acceptance' ($t=2.510$; $P=0.016$), 'positive refocusing' ($t=2.689$; $P=0.010$), 'self blame' ($t=2.665$; $P=0.011$) and 'rumination' ($t=2.423$; $P=0.020$).

B. Subgroup analysis: univariate approach and factor analysis

Some of the total group results were remarkable, such as the lack of dissociation. We, therefore, investigated whether the overall results merely represented an average concealing specific subgroups. The subgroups were inspected by dividing the total group into subgroups based on a) psychological etiology, b) the tendency to dissociate, c) the tendency to report daily hassles, d) the cognitive level and e) psychopathology.

a) Subgroups based on psychological etiology

The profile was inspected separately for patients who reported a psychotrauma on the TEC total score and patients who did not report a trauma, which is presented in Figure 9.3. Patients with a reported trauma ($n=28$) differed from patients without reported trauma ($n=12$) on level 2 with more mental slowing on the CVST ($t= -2.690$; $P=0.011$). The short MMPI showed more 'negativism', indicating more suffering from their problems ($t=2.030$; $P=0.049$), and more 'shyness', indicating attempting to internally control emotions ($t= -2.891$; $P=0.006$). The short TCI showed more 'harm avoidance' ($t= -2.304$; $P=0.027$) and less 'self-directedness' ($t=2.343$ $P=0.024$) for the patients with reported trauma. This showed this subgroup to be more anxious and being vigilant for potential danger (high harm avoidance) in combination with being fragile/immature and having difficulties pursuing meaningful personal goals and values in their lives (low self-directedness). On level 3, patients with trauma showed increased psychoform dissociation, e.g., scale d1: 'identity confusion and

depersonalization', than did patients without trauma ($t = -2.166$; $P = 0.037$). On level 4, no differences were found. On level 5, there was an increased score on the coping subscale 'blaming others' ($t = -2.490$; $P = 0.018$), referring to having a cognitive coping strategy of holding other people responsible.

Figure 9.3 Profile comparison of patients with a reported trauma versus patients without a reported trauma.

* Statistically significant differences between the two groups.

When the group was divided into two subgroups, a) patients with no or one trauma and b) patients with multiple traumas, a similar pattern was found, though less pronounced. Patients with multiple traumas ($n = 21$) differed from patients with no or a

single trauma ($n=19$) on level 2 with more 'shyness' ($t=-2.153$; $P=0.038$) on the short MMPI. On level 3, increased dissociation was found for scale d1: 'identity confusion and depersonalization' ($t=-2.487$; $P=0.019$). On level 4, no differences were found, and on level 5, there was again an increased score on the subscale 'blaming others' ($t=-2.632$; $P=0.012$).

b) Subgroups based on dissociation

As the average profile did not show increased scores on the dissociation scales, it was explored whether two subgroups would exist. The patients were consequently divided into scores (based on the cut-off score provided by the SDQ-20 manual) that represent higher dissociation tendency (scores >25 ; $n=17$) and lower dissociation tendency ($n=23$). Patients with higher dissociation showed on level 2 increased somatization ($t=-2.293$; $P=0.027$) on the short MMPI. On level 3, obviously, the dissociation subscales 'loss of control' ($t=-2.980$; $P=0.005$) and 'amnesia' ($t=-2.485$; $P=0.023$) of the DIS-Q were increased. On level 4, 'total complaints' ($t=-2.743$; $P=0.012$) and 'subject dependent complaints' ($t=-2.694$; $P=0.012$) on the EPCL were increased in patients with higher dissociation tendency. On level 5, patients with higher dissociation tendency showed increased scores on the subscale 'blaming others' ($t=-2.128$; $P=0.042$).

c) Subgroups based on the tendency to report daily hassles and stressors

As increased levels of daily hassles and complaints on the EPCL were dominant in the average profile, we distinguished patients that reported an extremely high number of complaints over the past two months (scores on the EPCL $>z$ -score 1 ($n=14$) from the remaining patients. This revealed that patients with a high level of complaints showed on level 2 a higher tendency on the short MMPI towards 'negativism' ($t=2.661$; $P=0.11$) and on the short TCI increased 'harm avoidance' ($t=1.997$; $P=0.04$), less 'persistence' ($t=-2.917$; $P=0.006$) and less 'self-directedness' ($t=-6.692$; $P\leq 0.001$). On level 3, all dissociation scales were increased in the patients with a high level of complaints (SDQ-20 $t=3.440$; $P=0.001$; Dis-Q d1: 'identity confusion and depersonalization' $t=3.701$; $P=0.001$; Dis-Q d2: 'self-control' $t=3.921$; $P\leq 0.001$; Dis-Q d3: 'amnesic and dissociation features' $t=2.910$; $P=0.006$; Dis-Q d4: 'concentration 'absorption' of environmental input' $t=2.212$; $P=0.033$).

d) Subgroups based on global cognitive level

The patients were also divided by those scoring average or higher on the Raven and patients scoring below average. Patients scoring below average showed decreased 'persistence' on the short TCI ($t=2.299$; $P=0.03$) on level 2 and increased 'positive refocusing' ($t=2.175$; $P=0.043$) on level 5.

e) Subgroups based on psychopathology

A division based on psychopathology (> or < than the z-score 0 on the subscale psychopathology of the short MMPI) did not reveal any significant differences, which may be caused by the fact that only 10 patients had scores higher than z-score 0.

The former step suggests that the total group of PNES patients consisted of subgroups with differential patterns with regard to the factors presented in the model (Figure 9.1). In a second step of the subgroup analysis, we used a multivariate correlational approach with factor analysis. Seven variables were entered in the factor analysis. The choice for these variables was based on the highest correlating variables as well as a representation of each level. Therefore we entered the following:

- Level 1: TEC total score (1)
- Level 2: Neuropsychological: CVST (2)
Personality: short TCI novelty seeking (3) and short MMPI somatization (4)
- Level 3: SDQ-20 norm score (5)
- Level 4: EPCL total complaints (6)
- Level 5: CERQ self blame (7).

Factor analysis was used, based on principal component analysis. In four steps, the cut-off score of eigenvalue <1 was reached. At that point, a satisfactory 80% of the variance was explained. This implicates that the seven variables have sufficient (80%) explaining power for the variation in the investigated sample. A four-factor solution was achieved (presented in Table 9.2).

Table 9.2 Results of the factor analysis.

		Component			
		Factor 1	Factor 2	Factor 3	Factor 4
Level 1	TEC	<u>.586</u>	<u>-.650</u>	-.017	.096
Level 2	short MMPI somatization	.041	<u>.663</u>	-.111	<u>.654</u>
	Short TCI novelty seeking	-.356	.342	<u>.746</u>	-.182
	CVST	-.388	<u>-.417</u>	<u>.401</u>	<u>.639</u>
Level 3	SDQ-20 norm score	<u>.800</u>	-.018	.043	.237
Level 4	EPCL total complaints	<u>.661</u>	<u>.569</u>	.071	-.078
Level 5	CERQ self blame	<u>.511</u>	-.094	<u>.693</u>	-.073

High loadings on a factor (> .40) are underlined and in bold.

Factor 1 shows a subgroup characterized by a psychotraumatic origin of PNES without any involvement of level 2 vulnerability. These patients were not necessarily predisposed to develop somatization symptoms based on increased vulnerability; the reported trauma is essential. There was a high level of somatoform dissociation, complaints in daily life and cognitive coping problems (self blame), which is in line

with the results of the former profile analysis. This subgroup may be characterized as the '*psychotrauma subgroup*'. This factor alone is valid for 28% of the study population, so it may represent between 1/4 and 1/3 of the population.

Factor 2 has a high negative loading for the TEC indicating that psychotrauma had no essential role in the psychogenic origin of PNES in these patients. There was, however, on level 2 a high vulnerability with respect to personality factors: a high tendency for somatization. The CVST indicated an undisturbed level of cognitive function. On level 4, there was a high level of complaints in daily life. This factor can be characterized as '*high vulnerability somatization subgroup*' representing patients with a strong tendency to react with (psycho)somatic complaints on psychological distress (without a clear psychotraumatic origin) because of a personality vulnerability. This factor is valid for 21% of the population.

Factor 3 also shows no loading on psychotrauma. There was again on level 2 a high vulnerability on personality factors, however not focusing on somatization. This factor shows a high loading for 'novelty seeking' on the short TCI, indicating a strong tendency to react impulsively and to have quick tempers. They also loaded on 'self blame' on the CERQ and had mental slowing/rigidity as cognitive style on the CVST. This factor can be characterized as the '*high vulnerability sensitive personality problem subgroup*' and represents 17% of this population.

Factor 4 shows a combination of a high somatization tendency with a rigid and slow cognitive style on level 2 and no stress in daily life. This factor (representing 14% of this population) seems to be a low cognitive level variant of factor 2 with patients that easily develop somatization symptoms, however, without the burden of daily hassles; the '*high vulnerability somatization subgroup with a low cognitive level*'.

In fact, factor analysis shows two dimensions that are essential: the psychological etiology (psychotrauma or not) and the vulnerability e.g., the somatization tendency and the sensitive personality problems ('novelty seeking'), resulting in three subgroups. Subgroups 2 and 4 are similar, except for their cognitive level and for the burden they experience in daily life.

Discussion

A. Profile analysis of the total PNES group

The diagnostic profile of the total group showed some remarkable findings. On level 1 ('psychological etiology'), 70% of the patients did report one or more traumatic experiences before the age of 18. Although this percentage was relatively high, it seemed comparable with other studies on PNES^{21,37}. The psychological instrument we used, the TEC, allowed reports over a whole range of traumatic experiences. When we specifically focused on physical and sexual abuse, than 42.5% of the patients reported such traumas. To compare, Breslau et al.¹⁰⁰ reported that traumas resulting in a

posttraumatic stress disorder occurred in 8% of the general population. Hence, physical and sexual abuse during childhood is an important etiological factor in PNES. Level 2 effects ('vulnerability') showed that the neuropsychological impairments were mostly related to a defensive 'avoidance type' of cognitive style (slow, rigid). These effects may be seen as a consequence of personality characteristics and the burden of the seizures rather than as a causal factor. This is line with the fact that similar neuropsychological impairments in epilepsy and PNES have been reported for many years¹⁰¹⁻¹⁰³. Drane et al.¹⁰⁴ also pointed to 'cognitive style characteristics' when they raised the possibility that PNES patients may often make an inadequate effort in taking the tests so their findings may not be trustworthy. Also, Hill and Gale⁵⁶ mentioned that abnormal neuropsychological functioning in PNES patients has been attributed to psychological and motivational factors. Hence, neuropsychological impairments do not seem to contribute to an increased vulnerability for PNES.

The assessment of personality factors on level 2 showed an increased tendency of somatization, referring to reacting with (psycho)somatic symptoms on psychological distress, a finding that is often reported in recent PNES studies^{14,26,51}. The personality profile showed, in a lesser degree, also increased shyness on the short MMPI, referring to being less sociable and to attempt to internally control emotions. The short TCI showed a personality profile of having an anxious, practical and perfectionistic attitude with difficulties tolerating ambiguity and a strong need to control.

Remarkable was the absence of increased scores on tests for level 3 ('shaping'), indicating that dissociation was not increased in the average profile. This is in line with other studies (e.g.,^{51,81,105,106}) showing that although dissociation scores were higher in PNES patients, these scores did not indicate severe significant dissociative tendencies for the group as a whole.

On level 4 ('triggering'), the total PNES group reported many complaints about possible burdens in daily life in the past two months that may trigger seizures.

Level 5 ('prolongation') showed coping problems that may contribute to prolongation, such as a passive and/or avoidant attitude when confronted with problems. These coping problems have been found in other studies as well^{105,107,108}.

Although these findings are useful in describing PNES patients as a group, the results might simply represent a 'grand average' concealing specific subgroups. Lally et al.³⁹ formulated this different, e.g. there may be no "one fits all" in terms of theory application (see also Mazza⁵²) and subgroup analysis might reveal more specific characteristics.

B. Subgroup analysis

Univariate analysis, using dichotomization in low and high scores, showed that subgroups indeed exist. The subgroup of patients with severe (physical and sexual) trauma was characterized by more mental slowing and significantly more 'negativism',

more 'shyness', more 'harm avoidance' and less 'self-directedness'. This subgroup, who suffered more from their problems, was more introverted and was trying hard to internally control emotions. These patients had an anxious attitude and were being vigilant for potential danger. The low 'self-directedness' referred to being immature, fragile and sensitive for external pressure, which can make it difficult to pursue meaningful personal goals and values. Also, in this subgroup, we found a higher tendency for psychoform dissociation on the level of identity confusion. The absence of increased dissociation was, therefore, an average characteristic of the total group but was not true for patients with a reported trauma. Other studies found subgroups in PNES exhibiting more dissociative tendencies related to trauma as well¹⁰⁹ even in non-clinical samples¹¹⁰. It is remarkable though that somatoform dissociation was not increased in this subgroup, especially since the PNES represent a psychosomatic symptom. The crucial factor is whether there was a reported trauma or not. When the variable 'multiple trauma' was included, the observed pattern did not change. The psychological profile seemed directly linked to the traumatic experiences, and the patients suffered from the consequences. The combination of a high level of distress and an identifiable link to an etiological factor may help these patients to benefit from psychological therapy and to accept the diagnosis since it can be integrated into their personal history¹¹¹.

Subgroup division based on dissociation did not provide new information. This was possibly a result of the high relationship between dissociation and other factors in the model⁸¹. Similarly, a division based on cognitive level did not show new information. The cognitive results primarily reflected a slow and rigid cognitive style and were, therefore, closely related to other factors in the model. This may conceal its effect on subgroup division. Also, psychopathology was not an essential factor. This was probably an effect of sampling bias and test selection, combined with a statistical effect. Severe and/or acute psychiatric comorbidity was an exclusion criterion. Moreover and as a consequence of the previous factor, only 10 patients had a z-score higher than 0 ('normal'), which did not allow sufficient power to detect differences. One other factor showed new information: reporting daily hassles and complaints, a level 4 ('triggering') factor. Patients with an extreme high level of complaints revealed more 'passive type' of personality characteristics (e.g., increased 'harm avoidance', less 'persistence' and less 'self directedness') on the short TCI and an increased tendency to dissociate on both somatoform and psychological forms of dissociation. Taken as a whole, these univariate analyses suggested that the investigated patients with PNES had some characteristics in common but that a subgroup approach provides more information. Especially, the importance of an underlying traumatic psychological etiology was shown. The effect of other factors was possibly concealed by high intercorrelations between the factors. We, therefore, used a multivariate correlational approach with factor analysis. This generated 4 factors that characterized subgroups of patients:

- a) A psychotrauma subgroup; about ¼ and 1/3 of the investigated patients.
- b) A high vulnerability somatization subgroup; about 1/5 of the patients.
- c) A high vulnerability sensitive personality problem subgroup; less than 1/5 of the patients.
- d) A high vulnerability somatization, low cognitive level subgroup with no stress in daily life.

This group is a variation of group b with low cognitive level; a small group of 14% of the investigated patients.

We concluded that in our study, two dimensions are essential: the psychological etiology (psychotrauma or not) and the vulnerability e.g., the somatization tendency and the sensitive personality problems ('novelty seeking'), resulting in three subgroups. The fact that the first two factors in our model (Figure 9.1) were dominant is in line with the model in which the etiology starts at levels one and two, and subsequent factors are secondary factors.

The concept of subgroups is in line with recent other PNES studies^{7,24,25,56} in which the chosen classification was based on seizure characteristics and/or psychological criteria. Unfortunately, the distinguished subgroups were not easy to compare since different criteria and psychological tests were used. However, more studies found traumatic experiences and dissociation, cognitive functioning and personality factors, especially somatization, to be discriminatory variables in defining subgroups (see^{44,112}). An interesting approach was to define subgroups based on the relationship between PNES and personality disorders, previously presented by Cragar et al.⁹. Psychogenic non-epileptic seizure subtypes had been described on dimensions of psychopathology as measured by the MMPI-2. Three personality clusters emerged. The authors offered tentative descriptions of the clusters: (1) 'depressed neurotics'; (2) 'somatic defenders'; and (3) 'activated neurotics'. Clusters 1 and 3 also differed significantly on neurocognitive testing, with cluster 1 patients scoring lower than cluster 3 in memory functioning, while cluster 2 individuals showed generally average cognition across domains. Reuber and House²⁵ distinguished three groups, based on psychiatric comorbidity (present in 70% of the PNES patients in their study): (a) disorders of mood-depression, anxiety, panic and PTSD; (b) somatization and abnormal illness behavior; and (c) borderline personality. Furthermore, Hill and Gale⁵⁶ recently found two PNES subgroups based on differences in cognitive functioning and seizure semiology. The PNES two-subgroup model (nonmotor and motor), in comparison to patients with temporal lobe epilepsy (TLE), showed a trend towards superior performance across nearly all cognitive measures for the nonmotor NES subgroup. Conversely, the subgroup with motor PNES symptoms showed performance generally comparable to TLE patients. Finally, a very recent study of Magaudda et al.¹¹² specifically focused on patients with a combination of both epilepsy and PNES. They showed that this so called "mixed PNES group" could be divided in three subgroups based on epilepsy type, mental level, comorbid psychiatric

disorders, and history of traumatic experiences. In line with our results in their 'group 3', the PNES etiology was not related to epilepsy but to the psychic trauma.

Our study showed that two dimensions are essential and constitute three subgroups. This is important in clinical practice. In the psychotrauma group, there is the overwhelming impact of psychotrauma, possibly followed by psychological aftermath 'gone wrong', leading to functional somatic symptoms. In this case, there is no specific vulnerability, and the emotions caused by the psychotrauma might be simply too distressing to find another than a somatic channel, leading partially to dissociation. Treatment should focus on the psychotrauma, and in fact these patients seem to be highly comparable with patients with Posttraumatic Stress Disorder. So, although in most patients PTSD cannot be diagnosed (see Bailles et al.⁵⁵), the role of trauma in this subgroup may be as important. Fiszman et al.³⁷ already suggested that PNES may arise as a clinical expression of a hypothetical PTSD subtype, the core symptoms of which are dissociative. For further research, it would be interesting to compare this trauma PNES group (without PTSD) with PTSD patients. Selkirk et al.¹¹³ also differentiated PNES patients reporting sexual abuse from PNES patients not reporting a sexual abuse history. Bakvis et al.¹¹⁴ also found also differences on biological level; basal hypercortisolism was more pronounced in traumatized patients with PNES as compared to nontraumatized PNES patients.

The second and fourth groups are patients with a specific personality vulnerability. They are prone to react with somatic symptoms to emotional overload. Here, treatment should not only focus on symptom control but also on providing patients more effective coping strategies to handle critical emotional situations. This is of course more challenging in the fourth subgroup. Finally, the third subgroup has PNES as part of their personality problems, which has been extensively discussed in previously published work²⁶.

Appendix A. Description of instruments

Level 1: 'Psychological etiology'

* *The Traumatic Experiences Checklist (TEC)*⁵⁹

The TEC is a 29-item self-report questionnaire retrospectively assessing potential childhood traumatic experiences in the period of 0 to 18 years of life. The TEC was developed as self-report scale as some patients may be less inhibited to report traumatic experiences on self-report measures than in the context of face-to-face trauma interviews⁶⁰. The TEC includes a wide range of potentially traumatic experiences that are not necessarily traumatizing to every individual. However, experiences that are not traumatic to most individuals can be quite traumatic to others⁵⁹. The TEC has a total score and distinguishes 5 subscales: emotional neglect; emotional abuse; threat of body/life; sexual harassment and sexual abuse. Psychometric analysis shows satisfactory reliability⁶¹ and validity⁵⁹.

Level 2 'Vulnerability'

a. Cognitive functions (neuropsychological testing)

* *Global cognitive level. The Raven Progressive Matrices* (Raven) was used. This non-verbal instrument includes multiple choice tests of abstract reasoning. An assessment with the Raven yields a total and a percentile score⁶². Reliability studies, covering a very wide age range, many cultural groups, and clinical as well as healthy populations, show a good reliability, internal consistency and retest reliability^{62,63}.

* *Trail Making Test (adult version)*. This test consists of two parts, A and B, and is a test for mental flexibility and planning. In fact, this test measures executive function, which is a key cognitive function⁶⁴. Especially, trail B is a good predictor of brain impairment. Although there is a practice effect when the test is administered repeatedly in the same subject, alternate forms of trails A and B have been developed and shown to be reliable⁶⁵. In this study, the test was only administered once to the same patient. Furthermore, normative data used nowadays take into account factors such as age and level of education, which makes interpreting the scores very reliable over different patient groups⁶⁶⁻⁶⁸.

* *Central (mental) information processing speed: The Computerized Visual Searching Task (CVST)*: The CVST is an adaption of Goldstein's Visual Searching Task and gives an indication of the speed of information processing. The test score is the total average searching time of correct answers in seconds⁶⁹.

b. Emotional profile (Personality factors)

* *The Dutch language short version of the Temperament and Character Inventory TCI (short TCTI, Dutch: VTCTI).* The short and Dutch version of the TCI was used, including only the main scales⁷⁰⁻⁷². The short TCI is based on the psychobiological theory of personality of Cloninger⁷³⁻⁷⁵ in which both normal and deviant variations in personality are described. The short TCI has 4 dimensions of temperament: 'novelty seeking'; 'harm avoidance'; 'reward dependence' and 'persistence' and three dimensions of character: 'self-directedness', 'cooperativeness' and 'self-transcendence'. Reliability and validity are acceptable^{76,77}.

* *The Dutch language short version of the Minnesota Multiphasic Personality Inventory (short MMPI, Dutch: NVM)*^{78,79}. The five short MMPI scales are as follows:

- *Negativism (22 items):* items referring to passive avoidant behavior, feelings of dissatisfaction and grudge regarding daily life events, and aggressive behavior. This scale is related to the psychopathic deviate, hypomania, lie, depression, masculinity-femininity, and schizophrenia scales of the MMPI.
- *Somatization (20 items):* items connected with vague physical complaints. This scale is related to the hypochondriasis, hysteria, and depression scales of the MMPI.
- *Shyness (15 items):* items reflecting feelings of shyness and difficulties in interpersonal contacts. This scale is related to the social introversion, hysteria, and psychopathic deviate scales of the MMPI.
- *Psychopathology (13 items):* items connected with delusional feelings, paranoid thoughts, and bizarre experiences. This scale is related to the paranoia, fake (F), and schizophrenia scales of the MMPI.
- *Extraversion (13 items):* items reflecting an active and energetic attitude towards various social contacts. This scale is related to the social introversion and depression scales of the MMPI.

Level 3 'Shaping'

Dissociation

Dissociation is a broad concept that involves both psychological manifestations, such as disturbances of consciousness and/or identity or an altered perception of the environment, as somatoform manifestations, specifically referring to a lack of the normal integration of sensorimotor components of experience, e.g., hearing, speaking and moving⁸⁰. Not all types seem to be related to PNES^{81,82}. Therefore, two types of

dissociation scales were included: the DIS-Q measuring more psychological forms of dissociation, and the SDQ-20 specifically measuring somatoform types of dissociation.

* *The Dissociation Questionnaire (DIS-Q)*. This scale is based on the Dissociative Experiences Scale (DES)⁸³, the Perceptual Alteration Scale (PAS)⁸⁴ and the Questionnaire of Experiences of Dissociation (QED)⁸⁵, and it has been adapted for the Dutch language^{86,87}. The scale has four subscales: Dis-Q d1: identity confusion and depersonalization; Dis-Q d2: self-control; Dis-Q d3: amnesic and dissociation features; Dis-Q d4: concentration 'absorption' of environmental input. The DIS-Q is extensively assessed psychometrically. All psychometric studies suggest that the DIS-Q is reliable and is able to differentiate persons with dissociative disorders from other groups⁸⁷.

* *Somatoform Dissociation Questionnaire (SDQ-20)*^{88,89}. This self-report questionnaire evaluates the severity of somatoform dissociation. The items pertain to negative (e.g., analgesia) and positive (e.g., site-specific pain) dissociative phenomena³⁹. Several studies showed that the psychometric characteristics of the scale to be very satisfactory^{88,90-93}.

Level 4 'Triggering'

* *The Everyday Problem Checklist (EPCL, dutch: APL)* [94]. This self-report questionnaire measures the frequency and the intensity of daily hassles and chronic stressors experienced during the past two months within several life domains^{94,95}. Two subscales can be distinguished: 1) EPCL-DEP (Dutch: APL-AFH) consisting of items representing events and conditions that are caused by the subjects themselves (subject dependent); and 2) EPCL-IND (Dutch: APL-ONA) containing items referring to situations beyond control of the subject. There is also a total score (TOT-score) indicating the subjective experience of psychosocial stress in the past two months. Test-retest reliability is qualified as satisfactory [94].

Level 5 'Prolongation'

* *The Utrecht Coping Scale (UCS); coping with problems and events (Dutch: UCL)*⁹⁶. This scale aims at defining characteristic coping behavior confronted with problems or events requiring adjustment. The UCS scales seem to take an intermediate position between "trait" and "state", conforming to the theoretical view on coping as a personality style⁹⁷. There are six subscales: 'actively addressing'; 'palliative reaction'; 'avoiding/ waiting'; 'looking for social support'; 'passive reaction pattern'; 'expression of emotions'; and 'using reassuring and comforting thoughts'. Reliability of the UCS is studied in different subject groups and shows sufficient results^{96,97}.

* *Cognitive Emotion Regulation Questionnaire (CERQ)*. The CERQ is a multidimensional questionnaire constructed to identify the cognitive coping strategies someone uses after having experienced negative events or situations. The questionnaire refers exclusively to thoughts (a cognitive level) after having experienced a negative event⁹⁸. The nine conceptually separate emotion regulation strategies described are 'self-blame'; 'acceptance'; 'rumination'; 'positive refocusing'; 'refocus on planning'; 'positive reappraisal'; 'putting into perspective'; 'catastrophizing' and 'blaming others' Garnefski et al.⁹⁸ showed that the subscales can be grouped into adaptive and less adaptive regulation strategies. Reliability of the scales for divers populations and validity of the CERQ are mentioned as good up to very good^{98,99}.

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Part 4

Somatic vulnerability

Chapter 10

Psychophysiological biomarkers of dissociation in psychogenic non-epileptic seizures

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Acta Neurol Belg 2011;111:99-103

Abstract

Misdiagnosis of patients with psychogenic non-epileptic seizures (PNES) as having epilepsy is a clinical relevant problem. Considerable problems for the patients, such as unnecessary anticonvulsant medication use and delay of suitable therapy, as well as a considerable economic burden are involved. Furthermore, after the diagnosis of PNES is confirmed, there is a lack of scientific evidence about the most efficient treatment for PNES. Evaluation of contributing factors is necessary. These factors should be implemented in explanatory models for the occurrence of PNES, which should be employed in diagnosis and treatment. Recent evidence suggests a role of deficiencies in neuronal information processing in multiple mental conditions. Although the focus in PNES research over the last two decades primarily has been on differential diagnosis and psychological and environmental factors, abnormalities in psychophysiological characteristics might also be involved in PNES. This review focuses on neurobiological substrates of PNES and dissociation, a trait which is often associated with PNES, to explore whether deviant information processing is involved in the aetiology of PNES. All studies examining the relationship between psychophysiological parameters and PNES have an exploratory character. However, the results suggest that neurophysiological characteristics, such as brain activity as visualized by functional MRI (fMRI), cardiovascular measurements and neuroendocrine functioning, may be abnormal in patients with PNES. Future investigations should therefore elucidate the exact role of neurophysiological abnormalities in the aetiology of PNES.

Introduction

Psychogenic non-epileptic seizures (PNES) are epilepsy-like episodes of movement, sensations or behaviours that resemble epileptic seizures, but are not accompanied by epileptiform brain activity as seen on electroencephalogram (EEG). The underlying cause is assumed to be psychological; the episodes may be the somatic manifestations of emotional distress¹. PNES is one of the most important differential diagnoses of epilepsy, and most patients with PNES are initially misdiagnosed as having epilepsy. The average period between the onset of seizures and the diagnosis of PNES is typically more than 6 years². Misdiagnosis as epilepsy for patients with PNES has serious consequences for the patient, such as exposure to unnecessary anticonvulsant medication, and considerable delay to start the appropriate psychological therapy. In addition, a substantial economic burden is involved, as erroneous treatments for intractable epilepsy are expensive³. Evaluating the information described above, it is clear that differential diagnosis of PNES is clinically relevant. However, if the emphasis is only on excluding epilepsy, PNES may become a non-disease⁴. A positive diagnosis is necessary for appropriate treatment, therefore, the underlying mechanisms must be evaluated and results must be implemented in treatment. To gain more insight in the underlying mechanisms of psychogenic seizures, it is necessary to identify not only causal factors, such as traumatic experiences, but also predisposition factors, which elucidate why certain persons develop PNES symptoms after trauma and others do not. Such predisposition factors may be of influence in the stages of vulnerability, shaping, provocation and prolongation of PNES pathology, and have to be identified in order to organize an explanatory model of PNES.

An important predisposing factor for PNES is the tendency to dissociate^{1,5}. The process of dissociation is a disruption of the usually integrated functions of identity, memory, consciousness or perceptions of the environment. It is regarded as a psychological defence mechanism from stressful events, by altering conscious experience⁶. Others assume dissociation to be a constitutional mental weakness that is activated by adverse events⁷. Dissociation is closely related to the process of hypnosis and essentially shows the ability to take distance from reality. People differ in their tendency to dissociate. The tendency to easily dissociate is considered an important factor in the provocation and possibly also the prolongation of PNES⁸.

Because the tendency to dissociate is such a prominent trait of a substantial group of PNES patients, investigation of biological correlates of dissociation is an important step in the attempt to generate an explanatory model for PNES. The psychophysiological mechanism underlying dissociation still remains to be elucidated. This review focuses on neurobiological substrates of PNES and dissociation associated with PNES, to explore whether deviant information processing is involved in the aetiology of PNES.

Methods

Relevant studies were identified by searching the electronic databases PubMed and ScienceDirect. Articles included in this review were identified by searching the terms “MRI PNES”, “fMRI PNES”, “fMRI psychiatry”, “fMRI hypnosis”, “HRV PNES”, and “cortisol PNES”. Titles of articles and abstracts extracted during the search were reviewed for relevance, and if found to be applicable, the full-text article was retrieved. Case reports were not considered. Articles were included when published after 1980 up till 2010.

Results

Structural MRI abnormalities

Magnetic Resonance Imaging (MRI) of the brain provides the opportunity to investigate cerebral changes in a number of fundamentally different ways⁹. Structural MRI is one of the techniques most often employed for detection of anatomical brain abnormalities. Some investigations have related PNES with structural MRI abnormalities. For example, Reuber et al.¹⁰ found structural brain abnormalities more commonly in PNES patients than in the general population. They investigated the proportion of PNES patients having neurological abnormalities on structural magnetic resonance imaging, and found that 27% of PNES patients and 78% of patients with PNES and epilepsy showed anatomical irregularities. A wide variety of abnormalities was found in the PNES only group, including – in order of frequency - postoperative defects, arachnoid cyst, posttraumatic changes, generalized atrophy, gliotic change, white matter lesions, hippocampal sclerosis, and venous angioma. Abnormalities in the PNES plus epilepsy group included hippocampal sclerosis, postoperative defects, migration disorders, signs of previous stroke, gliosis, posttraumatic changes, hemiatrophy, white matter lesions, tumor, cavernoma, and venous angioma.

Devinsky et al.¹¹ even report 65 percent of their sample of PNES patients (without comorbid epilepsy) having structural abnormalities on MRI. In their sample, neurological features also varied widely, but showed to be significantly more present in the right hemisphere of PNES patients compared to the distribution of pathologies in the brains of epilepsy patients. These results suggest that right hemisphere dysfunction may form a predisposition factor to development of PNES symptoms. This finding is consistent with previous evidence for right hemisphere dominance in emotional regulation and conversion reactions^{12,13}. Thus, it is possible that neuropathology influences the neuropsychological performance of patients with PNES, and both may, in interaction, constitute the vulnerability factor in PNES patients. More research is needed to identify the exact role of structural brain abnormalities in the aetiology of PNES.

Functional MRI abnormalities

Quantitative information about structural brain abnormalities provides minimal insight into functional organization and reorganization in patients with PNES. To investigate whether deviations in functional brain architecture are predictive of dissociation in patients with PNES, functional imaging is essential. Functional Magnetic Resonance Imaging (fMRI) is a technique frequently used to explore the relationship between brain activation and cognitive functioning. It measures changes in the blood-oxygen-level dependent (BOLD) signal, which are assumed to accompany neural activity in the brain¹⁴. fMRI abnormalities have been demonstrated to be related to abnormal information processing in several mental conditions, for example schizophrenia^{15,16}, panic disorders¹⁷, and bipolar disorder¹⁸.

Until now, fMRI techniques have not extensively been used to explain deviant neuronal processing in patients with PNES. However, some investigations have explored the relationship between hypnosis, a process closely linked to dissociation, and altered fMRI characteristics. In a fMRI investigation of McGeown et al.¹⁹, the authors demonstrate that induction of hypnosis in highly suggestible individuals causes decreased cerebral blood flow in the anterior parts of the default mode network during rest. Other authors, for example Egner et al.²⁰ and Raz et al.²¹, have also associated decreased activation of frontal structures such as the anterior cingulate cortex (ACC) with high suggestibility. Because the process of hypnosis appears to be related to dissociation, similar activation patterns may be observed in patients with PNES with a high tendency to dissociate.

Brain network abnormalities

Cognitive and emotive functions result from the interactions of a number of differently localized brain regions rather than single (isolated) regions. In this context, novel brain connectivity analyses, which examine the integrity of cerebral networks, are most appropriate in evaluating information processing deficits of patients with psychiatric conditions such as PNES²². For example, fMRI facilitates the assessment of the functional connectivity of regional brain activity, based on correlations in dynamic spontaneous fluctuations²³. This analysis can be applied both on task-related fMRI data, as well as on resting state fMRI (rs-fMRI) data where no explicit stimuli are presented²⁴. In addition, network analysis of diffusion tensor imaging (DTI) data, using measures of water directionality and diffusivity, can provide information regarding the integrity of structural connectivity of the entire brain²⁵.

Cardiovascular dysfunctioning

It is hypothesized that patients with PNES (almost) continuously experience high levels of emotional stress. Emotional stress has been proven to be accompanied by physiological changes like increased heart rate, blood pressure, respiration rate and

muscle tension, and decreased heart rate variability (HRV)^{26,27}. HRV in particular is a measure of interest, because it reflects the functioning of the parasympathetic autonomic nervous system, the system responsible for stimulation of activities that occur when the body is at rest. HRV may be decreased in patients with PNES, suggesting a state of hypervigilance. Indeed, Bakvis et al.²⁸ have examined the cardiovascular functioning of patients with PNES, and found that patients with PNES show lower HRV during baseline and recovery of stress compared to healthy controls. However, their study had an experimental design; ambulatory measurements during daily life (comprising psychogenic non-epileptic seizures) would provide additional and ecological valid information about the level of emotional arousal and cardiovascular condition of patients with PNES.

Abnormal neuroendocrine functioning

An increased state of threat vigilance was also confirmed with endocrinal measurements by Bakvis et al.²⁹, who confirmed a state of hypercortisolism in patients with PNES. Increased cortisol levels are assumed to reflect greater activity of the hypothalamic-pituitary-adrenal (HPA) axis, a major part of the neuroendocrine system that controls reactions to stressors and regulates many body processes including mood and emotions^{30,31}. The HPA-axis has been proven to be involved in the neurobiology of mood disorders such as anxiety disorder^{32,33}, bipolar disorder^{34,35}, post-traumatic stress disorder³⁶, borderline personality disorder³⁷, and major depressive disorder^{38,39}. Antidepressants, which are routinely prescribed for many of these disorders, serve to regulate HPA axis function⁴⁰. Recently, a pilot randomized controlled trial with Sertraline (a serotonin selective reuptake inhibitor) suggests this pharmacotherapy to be effective for seizure reduction, confirming involvement of the HPA-axis in the aetiology of PNES⁴¹.

Conclusion

To explore whether deviant information processing is involved in the aetiology of PNES, this review focused on neurobiological substrates of PNES and of dissociation associated with PNES. Demonstration of a relationship between PNES and deviant information processing would have substantial implications for the understanding of PNES aetiology. Better understanding of the mechanisms underlying PNES development could eventually improve the clinical management of PNES diagnosis and treatment. Nowadays, the time interval between seizure onset and PNES diagnosis still is more than 6 years on average, during which the patient is treated as having refractory epilepsy, which forms a heavy burden on the patient and society. Early recognition of vulnerability factors such as dissociation would offer a possibility

of earlier diagnosis of PNES, diminishing delay of suitable therapy and unnecessary medical charges for epilepsy treatment.

Moreover, finding a neurobiological substrate of dissociation in PNES would change the concept of psychogenic seizures into being a psychophysiological phenomenon. This change of concept has implications for the development and evaluation of treatment, although direction of causality has to be examined in more detail. It will be difficult to position psychophysiological abnormalities definitely as a predisposition factor, because such abnormalities may both be the cause and the consequence of dissociation and psychogenic non-epileptic seizures. Longitudinal studies should clarify the exact contribution and interaction of dissociation and psychophysiological disturbances in PNES.

The most promising clinical consequence of such studies, in addition to improving knowledge about the aetiology of PNES, is the possibility of using neuroimaging data or other psychophysiological findings to identify subgroups of patients, which could allow treatments to be tailored.

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Chapter 11

Functional connectivity of dissociation in patients with psychogenic non-epileptic seizures

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J Neurol Neurosurg Psychiatry 2012;83:239-47

Abstract

Introduction

Psychogenic non-epileptic seizures (PNES) resemble epileptic seizures, but lack epileptiform brain activity. Instead, the cause is assumed to be psychogenic. An abnormal coping strategy may be exhibited by PNES patients, as indicated by their increased tendency to dissociate. Investigation of resting-state networks may reveal altered routes of information and emotion processing in PNES patients. The authors therefore investigated whether PNES patients differ from healthy controls in their resting-state functional connectivity characteristics and whether these connections are associated with the tendency to dissociate.

Methods

11 PNES patients without psychiatric comorbidity and 12 healthy controls underwent task-related paradigms (picture-encoding and Stroop paradigms) and resting-state functional MRI (rsfMRI). Global cognitive performance was tested using the Raven's Matrices test and participants completed questionnaires for evaluating dissociation. Functional connectivity analysis on rsfMRI was based on seed regions extracted from task-related fMRI activation maps.

Results

The patients displayed a significantly lower cognitive performance and significantly higher dissociation scores. No significant differences were found between the picture-encoding and Stroop colour-naming activation maps between controls and patients with PNES. However, functional connectivity maps from the rsfMRI were statistically different. For PNES patients, stronger connectivity values between areas involved in emotion (insula), executive control (inferior frontal gyrus and parietal cortex) and movement (precentral sulcus) were observed, which were significantly associated with dissociation scores.

Conclusion

The abnormal, strong functional connectivity in PNES patients provides a neurophysiological correlate for the underlying psychoform and somatoform dissociation mechanism where emotion can influence executive control, resulting in altered motor function (eg, seizure-like episodes).

Introduction

Psychogenic non-epileptic seizures (PNES) are paroxysmal episodes that resemble epileptic seizures, but are not based on epileptiform brain activity as recorded by EEGs and have no clinical evidence for epilepsy. Furthermore, no evidence has been found for other somatic causes of the seizures. Instead, psychogenic factors are assumed to cause the seizures¹.

PNES is one of the most important differential diagnoses of epilepsy. Although the differential diagnosis has been facilitated by the introduction of video EEG, there are as yet no real positive ictal features suggested to be pathognomonic for PNES. Most patients with PNES are initially misdiagnosed as having epilepsy, which has serious consequences for the patient, such as exposure to unnecessary anticonvulsant medication and considerable delay in starting the appropriate psychological therapy². In addition, misdiagnosis of PNES as epilepsy has a substantial economic burden, as erroneous treatments for intractable epilepsy are expensive³.

More knowledge of PNES aetiology is needed to facilitate the process of PNES diagnosis and decide the nature of treatment⁴. Existing theories regarding the underlying psychological mechanisms of PNES are diverse and involve multiple factors that may play a role in the development and prolongation of PNES. One factor that is considered particularly important in most theories for PNES⁵ and other functional symptoms^{6,7} is dissociation. Dissociation is a broad concept that involves a variety of manifestations. In the literature on somatoform disorders, psychological and somatoform dissociation are often distinguished, but they can be seen as related constructs⁸. The process of psychological dissociation is a disruption of the integration of a person's conscious functioning by severing the connection to thoughts, memories, feelings and sense of identity. Somatoform dissociation involves the loss of integration of somatic experiences, functions and responses⁹. Dissociation is postulated to be closely related to the process of hypnosis¹⁰ and is regarded as a coping strategy in the context of acute or chronic traumatization when the individual lacks the capacity to integrate adverse experiences¹¹. PNES patients often demonstrate dissociative symptoms¹² and high hypnotisability¹³, and dissociative disorders have been reported in over 90% of the PNES patients¹⁴. In fact, PNES may be considered as somatoform symptoms resulting from dissociated mental organization¹¹. Accordingly, the DSM-IV-TR and ICD-10 classifications of PNES as, respectively, conversion disorder and dissociative disorder are still a matter of debate¹⁵.

Since the tendency to dissociate is considered such an important mechanism in the aetiology of PNES, a better understanding of the neurobiological mechanism of dissociation might shed light on the pathophysiology of PNES and lead to more specific treatments. It might explain how information in patients with PNES or other functional symptoms is processed differently compared with non-affected individuals. A previous functional MRI (fMRI) study in patients with a motor conversion disorder

identified abnormal functional connectivity (FC) between regions involved in emotion and motor preparation¹⁶. fMRI may identify a similar abnormality in patients with PNES, providing evidence for alternative neuronal routes of information and emotion processing in patients with PNES that probably result in dissociative seizure-like episodes^{4,17,18}. As yet, no fMRI study has been performed in patients with PNES.

We hypothesize that functional connections between networks involved in emotion, sensorimotor, and cognitive processes are abnormal in patients with PNES. Additionally, these abnormal connections are associated with the tendency to dissociate. To test these hypotheses, we performed an fMRI study in patients with PNES and healthy controls.

Materials and methods

Participants

Patients were selected by their clinical psychologist or neurologist (>10 years and >9 years experience, respectively), on the basis of their seizure characteristics⁵, tendency to dissociate, and the absence of mental retardation and comorbid psychiatric disorders (e.g., mood and anxiety disorders, schizophrenia and psychosis, and substance-related disorders), which were determined through (hetero-) anamnesis and extensive (neuro-) psychological assessment. Individuals with neurological comorbidity (including epilepsy) and malingering patients were excluded. Patients were only included after the PNES diagnosis was confirmed in a tertiary epilepsy centre by an experienced neurologist/epileptologist, using clinical description and, when available, additional (video) EEG investigations.

The total study population included 13 patients with PNES and 13 healthy volunteers. Two patients with PNES did not complete the study and one healthy control demonstrated periventricular heterotopia on MRI, because of which these patients were excluded from the analysis. The other subjects did not have clinically significant MRI abnormalities (Table 11.1). Analyses were performed on the data obtained from 11 patients and 12 healthy volunteers. All participants gave informed consent to participate in the investigation, which received ethical approval by the Medical Ethical Committee of Maastricht University (ref. 10-3-045).

Table 11.1 Participant demographics and characteristics.

ID	Age	Gender	PNES duration (years)	No. of attacks in previous month	Type of Symptoms *	Medication	MRI remarks
1	39	F	1	3	Unresponsiveness	-	
2	40	F	13	0	Major motor manifestations	-	
3	50	F	6	5	Major motor manifestations	-	
5	25	F	3	1	Major motor manifestations	-	
6	52	M	13	1	Major motor manifestations	Amitriptyline, Rosuvastatin, Oxazepam	Cerebral atrophy
8	28	M	14	0	Major motor manifestations	Diazepam	
9	37	M	3	8	Unresponsiveness	2008-2010 Valproic acid, Topiramate.	
						Sumatriptan and Naratriptan	
10	36	F	27	2	Unresponsiveness	-	
11	20	M	1	2	Unresponsiveness	-	
12	28	F	2	0	Major motor manifestations & Unresponsiveness	-	
13	18	M	1	0	Major motor manifestations	October 2009 – April 2010 Valproic acid	Asymmetrical ventricular system
C1	55	M				-	Diffuse white matter abnormalities
C2	52	F				-	
C3	29	F				-	Small aspecific white matter abnormality
C4	27	F				-	
C5	24	M				-	Small lacunar lesion and slight atrophy
C6	39	F				-	
C7	37	F				-	
C8	37	F				-	Somewhat plump ventricular system
C10	32	M				-	
C11	25	F				-	Small arachnoidal cyst right temporal pole
C12	23	F				-	
C13	23	M				-	

For ID, C = Healthy control; * Seizure types were classified according to Abubakr et al.¹⁹; PNES, psychogenic non-epileptic seizures.

Questionnaires and neuropsychological investigation

All participants were asked to complete questionnaires to evaluate their dissociation tendency. These questionnaires included the Dissociation Questionnaire (DIS-Q), Dissociative Experiences Scale (DES) and the Somatoform Dissociation Questionnaire (SDQ-20)²⁰. Both the psychological forms of dissociation (DES and DIS-Q) and somatoform dissociation (SDQ-20) were assessed. Global cognitive performance was tested using the Raven's Progressive Matrices Test²¹. We obtained completed questionnaires from 10 patients with PNES and 12 healthy controls, as one patient did not return the questionnaires.

Neuroimaging

MRI was performed on a 3.0-tesla unit equipped with an 8-channel head coil (Philips Achieva, Philips Medical Systems, Best, The Netherlands). For anatomic reference, a T1-weighted 3D turbo field echo was acquired with the following parameters: repetition time (TR) 8.2 ms, echo time (TE) 3.7 ms, flip angle 8°, matrix 240x240, field of view (FOV) 256x256x180 mm³, 1 mm adjacent reconstructed coronal slices. fMRI data were acquired using a whole-brain single-shot multi-slice blood oxygen level-dependent echo-planar imaging sequence, with TR 2 s, TE 35 ms, flip angle 90°, voxel size 2x2x4 mm³, matrix 128x128, 32 contiguous slices per volume and 195 volumes per acquisition.

For fMRI, four different scans were performed: (1) first resting-state fMRI (rsfMRI) session, (2) picture encoding, (3) Stroop colour naming, and (4) second rsfMRI session. During the rsfMRI sessions, subjects were instructed to close their eyes and think of nothing in particular. The rationale for including a second resting-state session after two task-related paradigms was that attentional effort may provoke dissociative phenomena,²²⁻²⁵ which thus may provoke dissociation during the second rsfMRI session.

The picture-encoding task was included in an attempt to stimulate the process of suggestibility by presenting pictures with a high positive sentimental value. During this task, subjects viewed five images of real-life outdoor scenes prior to the fMRI scans during acquisition of the T1-weighted scan²⁶. Each picture was presented 25 times for 3 s. After approximately half an hour, an fMRI examination was performed while variable-length epochs of new pictures (new condition) were demonstrated mixed among variable-length epochs of the five old pictures (old condition). The epochs were mixed into a run of 195 stimuli. A total of 120 new pictures were shown. With each picture, the subjects had to decide whether it was old or new. The activation during the task was contrasted with the resting-state activation for further analysis. Previous studies with this task showed activation of the bilateral medial temporal lobes and other limbic structures²⁶.

The Stroop task was selected because susceptibility to hypnotic induction (associated with dissociation), has previously been related to Stroop performance and FC changes in the frontal attention system.^{27, 28} In the covert variation of the Stroop test,^{29,30} a word stimulus is presented in green, blue, yellow or red colour on a black background. Subjects were instructed to think of the colour in which the word was displayed. For example, the word 'blue' was written in red letters; the subject had to think 'red'. Each word was presented for 2s. In the baseline condition, subjects focused on a cross-hair. The paradigm consisted of seven baseline rest condition blocks (30s each) alternated with six activation blocks, consisting of 15 words. In total, 24 congruent and 66 incongruent stimuli were presented in random order. The contrast between the baseline condition and the activation condition was used for further analysis³⁰.

Neuroimaging analysis

Structural MRI scans were reviewed by an experienced neuroradiologist (>10 years experience). fMRI data analysis was performed in MATLAB (Mathworks, Natick, Massachusetts, USA) using the statistical parametric mapping software package (SPM8) (Wellcome Department of Cognitive Neurology, London, UK). Task-related paradigms were analyzed using brain activation contrasts according to the general linear model. The blood oxygen level-dependent images were realigned, transformed into the standardized Montreal Neurological Institute space and smoothed with an 8-mm Gaussian kernel. In the general linear model, a standard discrete cosine set was used to correct for (low-frequency) signal drift. Additionally, the paradigms were convolved with the haemodynamic response function. To explore differences in activation between the PNES and control group, a random-effects analysis was performed. Results were thresholded at the $P < 0.05$ level (corrected for family-wise multiple comparisons).

Subsequently, regions of interest with strong activation were defined (of approximately 300 voxels), based on the activation patterns during the tasks averaged for all subjects. This way, we ensured that the created masks were specific for this population, which is preferred over mask definitions available from the literature.³¹ The masks were created in MRICro³².

For the resting-state FC analysis, the signal time-course data were filtered by applying a bandpass filter (0.01-0.1 Hz) and corrected for head movement effects by using the six motion correction parameters as a covariate. Seed time courses for each region and subject were then generated by averaging the signal within the region of interest at each time point. Each seed time course then was regressed against all brain voxel time courses to obtain an FC map, which was subsequently transformed using the Fisher-Z transformation³¹. Multiple regression was then performed with subject type (patient or control) and rsfMRI session (first or second) as covariates. The resulting contrasts were thresholded at the $p < 0.05$ level (corrected for multiple comparisons using regional FDR³³). Regions with significant differences in FC between patients and

controls (called FC regions hereafter) were identified, and corresponding masks were created in MRICro³². Subsequently, for these regions individual functional connectivity values (called FC values hereafter) were computed by averaging the FC values over all voxels within each mask.

Statistical analysis

Statistical data analyses on summary values were performed in SPSS (PASW Statistics V.18.0, Chicago: SPSS Inc.), whereas analyses on a voxel-by-voxel level were performed in MATLAB (see previous section). Descriptive statistics of relevant variables were obtained, and Mann-Whitney U tests were performed to examine differences between patients with PNES and controls. Additionally, correlation coefficients between dissociation scores, intelligence scores and FC values were obtained over all subjects using the non-parametric Spearman rank-correlation test. Finally, to gain insight into the predictive value of the tested variables for relevant significant correlations from the latter analysis, a linear regression was performed with FC as a dependent variable and dissociation and intelligence scores as independent variables. Statistical significance is denoted as $P < 0.05$.

Results

Clinical and neuropsychological assessments

The study population comprised of 11 patients with PNES (6 women, 5 men, age 34 ± 11 years, number of seizures in previous month 2.0 ± 2.5), and 12 healthy volunteers (8 women, 4 men, age 34 ± 11 years) (Table 11.1). The patients displayed significantly lower performance on the Raven's Progressive Matrices test, and significantly higher dissociation tendency on the dissociation questionnaires, as assessed with Mann-Whitney U tests ($P < 0.05$). The patients displayed high scores for both psychological and somatoform dissociations ($P < 0.05$).

Neuroimaging analysis

For both the PNES and control groups, the picture-encoding paradigm yielded significant activation within both hippocampi, the left lateral frontal cortex, the parahippocampal gyrus and fusiform gyrus. The Stroop paradigm activated the inferior frontal, precentral and parietal cortices. These results for both groups are typical activation maps, in accordance with the literature.^{26,30,34} Figure 11.1 displays the average activation for the picture-encoding and Stroop paradigms for both groups. The random-effects analysis did not reveal any significant differences for picture-encoding and Stroop colour-naming activation maps between controls and patients with PNES.

Figure 11.1 Group averaged fMRI activation maps superimposed on a normalized T1-weighted MR image. Mean activation patterns for PNES patients are shown in A and D and for healthy controls in B and E. Averaged activation patterns over all subjects are shown in C and F. For the picture encoding paradigm the characteristic hippocampal activation is shown on coronal (A-B), and axial (C) slices. For the Stroop paradigm (D-F) the characteristic prefrontal activation is shown on coronal (D, E, F) slices. The bar on the top right indicates the t-value of the activation level. Slice positions are specified in the MNI coordinate system: $y=-24$ mm for A and B; $z=-18$ mm for C, and $y=6$ mm for D, E, and F.

Based on the average activation for the task-related paradigms, nine seed regions of interest were created (Figure 11.2): left parahippocampal gyrus and right parahippocampal gyrus (based on the encode paradigm), and right inferior frontal gyrus, left inferior frontal gyrus, right intraparietal sulcus, left intraparietal sulcus, left supramarginal gyrus, anterior cingulate cortex, and left precentral sulcus (based on Stroop paradigm). The FC maps based on the seed regions left inferior frontal gyrus, left intraparietal sulcus, left supramarginal gyrus and left precentral sulcus yielded significant group differences in connectivity values ($P<0.05$, corrected) (Table 11.3, Figure 11.3). The right intraparietal sulcus yielded similar results as the left intraparietal sulcus (data not shown). The other four seed regions did not yield significant differences in FC values. Multiple regression did not yield statistical significant differences between the two rsfMRI sessions ($P>0.12$).

Compared with healthy controls, patients had several significantly stronger functional correlations in the following FC regions: the anterior insular cortex, posterior insular cortex, central sulcus, posterior cingulate cortex, anterior cingulate cortex and parietal occipital fissure (Table 11.2). Interestingly, most FC regions were significantly different in FC maps from more than one seed region (Table 11.3). For example, the posterior insular cortex showed significantly higher correlation values with the precentral sulcus, the supramarginal gyrus as well as the intraparietal sulcus in PNES patients

than in controls (average Fisher-Z transformed connectivity values: 0.37 ± 0.12 vs 0.25 ± 0.10 , 0.31 ± 0.15 vs 0.15 ± 0.13 and 0.30 ± 0.15 vs 0.17 ± 0.13 , respectively).

Figure 11.2 Seed regions obtained from the activation maps from the picture encoding (8,9) and Stroop paradigms (1-7), superimposed on a normalized T1-weighted MR image. 1, right inferior frontal gyrus; 2, left inferior frontal gyrus; 3, right intraparietal sulcus; 4, left intraparietal sulcus; 5, left supramarginal gyrus; 6, anterior cingulate cortex; 7, left precentral sulcus; 8, right parahippocampus; 9, left parahippocampus. MNI coordinate system: $z=+46$ mm for A, $y=+6$ mm for B and $y=-42$ mm for C. MNI, Montreal Neurological Institute.

Table 11.2 Maximal Z-score and (cluster size) of regions with significant (positive) differences in FC between PNES patients and controls

	FC REGION(<i>x,y,z</i>)					
	Anterior insula (R) (-38,6,-12)	Posterior insula (R) (-46,-12,6)	Central sulcus (R) (-44,-20,30)	Posterior cingulate gyrus (R) (-2,-58,46)	Anterior cingulate gyrus (R) (-4,40,0)	Parietal occipital fissure (R) (-24,-56,14)
SEED REGION						
(<i>x,y,z</i>)						
Inferior frontal gyrus (L) (44,4,46)			4.26 (250)	4.09 (890)	4.13 (579)	5.17 (723)
Precentral sulcus (L) (46,6,26)	4.51 (64)	5.33 (210)	4.59 (55)		4.28 (789)	4.49 (634)
Supramarginal gyrus (L) (46,-40,50)		6.20 (512)		5.01 (897)		6.30 (713)
Intraparietal sulcus (L) (28,-58,50)		4.86 (313)	5.29 (79)	6.90 (795)	4.40 (653)	4.99 (806)

MNI coordinates are given in *italics* (*x,y,z*). FC, functional connectivity value; L, left; MNI, Montreal Neurological Institute; PNES, psychogenic non-epileptic seizures; R, right.

Figure 11.3 Regions of significant higher functional correlation for seed regions left precentral sulcus (A-C) and left inferior frontal gyrus (D) for PNES patients compared with controls during resting-state fMRI, overlaid on an average normalized T1-weighted MR image generated using MRICro (A,B,D) or projected on an inflated right hemisphere surface map generated in Freesurfer (MGH, Massachusetts, USA) (C). Contrast is visible in the central sulcus (CS), anterior insular cortex (ICa), posterior insular cortex (ICp), anterior cingulate cortex (ACC), posterior cingulate cortex (PCC), and parietal occipital fissure (POF). The bar on the top right indicates the t-value of the FC map. MNI coordinate system: $x=-44$ mm for A, $y=+8$ mm for B and $y=50$ mm for D. FC, functional connectivity value; MNI, Montreal Neurological Institute; PNES, psychogenic non-epileptic seizures.

Table 11.3 Spearman's correlation coefficients (over all subjects) between FC values and scores on DIS-Qs and Raven's test.

	DES	DIS-Q	SDQ-20	Raven
FC precentral sulcus – anterior insula	0.47 *	0.51 *	0.39	-0.48 *
FC precentral sulcus – posterior insula	0.56 **	0.46 *	0.42	-0.56 *
FC supramarginal gyrus – posterior insula	0.45 *	0.54 **	0.45 *	-0.38
FC intraparietal sulcus – posterior insula	0.34	0.45 *	0.37	-0.32
FC inferior frontal gyrus – central sulcus	0.54 **	0.46 *	0.39	-0.24
FC precentral sulcus – central sulcus	0.58 **	0.39	0.34	-0.27
FC intraparietal sulcus – central sulcus	0.64 **	0.53 *	0.43 *	-0.30
FC supramarginal gyrus – PCC	0.46 *	0.39	0.39	-0.50 *
FC intraparietal sulcus – PCC	0.59 *	0.53 *	0.50 *	-0.54 **
FC inferior frontal gyrus – ACC	0.43 *	0.39	0.40	-0.41
FC intraparietal sulcus – ACC	0.54 **	0.43 *	0.49 *	-0.47 *
FC inferior frontal gyrus – PO fissure	0.40	0.39	0.46 *	-0.57 *
FC precentral sulcus – PO fissure	0.38	0.20	0.55 **	-0.43 *
FC supramarginal gyrus – PO fissure	0.52 *	0.46 *	0.63 **	-0.48 *
FC intraparietal sulcus – PO fissure	0.37	0.28	0.44 *	-0.55 *

* Two-tailed p value is statistically significant at the 0.05 level. **Two-tailed p value is statistically significant at the 0.01 level. ACC, anterior cingulate cortex; DES, dissociative experiences scale; DISQ, dissociation questionnaire; FC, functional connectivity value (Fisher-Z transformed); PCC, posterior cingulate cortex; PO, parieto-occipital; SDQ, somatic dissociation questionnaire.

Correlation analysis

As the two rsfMRI sessions did not differ, FC values were averaged over the two sessions. Significant correlations ($P < 0.05$) were found between the abnormal FC values and DES, DISQ, SDQ and Raven scores (Table 11.3). We would like to highlight two correlations that were identified as related to dissociation, especially relevant from the perspective of PNES: precentral sulcus-anterior insula and precentral sulcus-posterior insula. For example, the FC value of the precentral sulcus-posterior insula correlated significantly with the DES (Spearman's $P = 0.56$, $P = 0.007$; Figure 11.4). The FC value of the precentral sulcus-posterior insula connection also negatively correlated significantly with the Raven performance (Spearman's $P = -0.56$, $P = 0.005$). A linear regression for this FC value as a dependent variable and DES and Raven test scores as independent variables yielded DES score as significant predictor ($\beta = 0.066$, $P = 0.046$). Raven test score was not a significant predictor ($P = 0.37$).

Figure 11.4 Scatter plot of distribution of the left precentral sulcus - right posterior insular FC values and DES scores in the whole population. Healthy controls are depicted by black dots, PNES patients are depicted by white dots (Spearman's $\rho = 0.56$, $p = 0.007$). DES, Dissociative Experiences Scale; FC, functional connectivity value; PNES, psychogenic non-epileptic seizures.

Discussion

In this study, we investigated resting-state networks in PNES patients and healthy controls to potentially reveal PNES-associated neurophysiology in terms of altered routes of information and emotion processing. First, a significantly higher dissociation tendency was observed in patients with PNES. Furthermore, an abnormal functional correlation was observed between the precentral sulcus, which resides in the motor cortex controlling voluntary muscle movement, and the insula, which is part of the limbic system and involved with emotion regulation, visceral sensory perception and self-awareness³⁵. Additionally, significantly stronger correlations were found between the parietal lobe, which is involved in processing of sensory information and subsequent action organization³⁶, and the insula. Moreover, a positive relationship between FC values and dissociation scores was found.

Dissociation and PNES

Our results reconfirm that patients with PNES have in general a higher tendency for dissociation than healthy individuals. This is a general effect concerning both psychological and somatoform dissociation^{14,28,37}.

Dissociation and fMRI

The functional connections of the ACC are of interest as the ACC is an area that has been identified to be involved in dissociation and hypnosis³⁸. The FC value of the IFG with ACC was significantly higher in the PNES group. Furthermore, the strength of this connection was significantly related to DES scores. This might have clinical relevance in PNES, as this connection has been associated with cognitive integration and dissociation²⁷.

Outside the domain of PNES, previous studies have related dissociation with fMRI outcomes. For example, Veltman et al.³⁹ have demonstrated increased activation of the dorsolateral and ventrolateral prefrontal cortices, parietal cortex and supplementary motor area during working memory tasks in healthy, high-dissociative participants. Similarly, Elzinga et al.⁴⁰ reported increased activation in anterior, dorsolateral and ventrolateral prefrontal cortices and parietal cortex during a working memory task in patients with dissociative disorder. These results suggest that dissociation is associated with an altered working-memory network.

In contrast, the results of the current study do not reveal differences in activation maps of the encoding task (working memory), or in FC based on seeds relevant to memory (hippocampi), between healthy controls and highly dissociative PNES patients. Also, although the picture encoding task employed emotional stimuli, the activation was related to processes of working memory instead of suggestibility. However, we did find abnormalities in FC in highly dissociative patients with PNES

based on seed regions obtained by the Stroop task. Previous studies in patients with PNES did indicate only a modest working memory deficiency⁴¹. We propose that the PNES pathology affects the neurobiology of executive control, which underlies dissociation, rather than the networks involved in memory processes.

Dissociation and cognition in PNES

Subjects with lower performance on the Raven's test scored significantly higher on the dissociation scales, which is in accordance with previous literature⁴². Dissociation might exert a perturbing action on individuals, which can negatively influence cognitive performance.

The FC values also correlated significantly with global cognitive functioning scores, as assessed using the Ravens' test. Previously, we showed in patients with chronic epilepsy that FC values, as assessed with fMRI, were strongly correlated with intelligence (i.e., performance on word fluency and text-reading tests). We hypothesized that a reduced performance was related to a reduced synchronization of activity in the brain⁴³. In the current study, we observed the opposite effect, namely, a negative correlation of FC values with global cognitive performance. However, a linear regression analysis showed that global cognitive performance (i.e., intelligence) was not a significant predictor for FC values, whereas dissociation was. This emphasizes that dissociation, and not intelligence, is a key mechanism underlying abnormal FC values as observed in patients with PNES (Figure 11.4).

Conversion disorders and fMRI

It has been suggested that PNES share a pathophysiological mechanism with other conversion disorders^{4,18}. An fMRI study in patients with motor conversion revealed that patients have a higher FC between the amygdala and the supplementary motor area during processing of positive and negative emotional stimuli¹⁶. It was suggested that this abnormal FC hints at a greater influence of limbic regions over motor preparatory regions¹⁸. Similarly, in dissociative amnesia, the relationship between memory-related areas and executive control areas may be affected,^{18,44} which also hints at a 'faulty' connection between executive control and areas specifically affected by dissociation.

As we found in PNES, higher FC values between regions involved in emotion and self-perception (insula) and motor preparation (precentral and the sulcus) between these two regions might underlie the pathophysiology for conversion disorders in general, including PNES⁴. The existence of such an unstable cognitive-emotional-motor 'hyperlink' is further supported by the fact that PNES is often accompanied by many diffuse psychological, psychiatric and somatoform symptoms^{18,45}. In addition to the connection pair 'insula-precentral sulcus', we also identified other combinations of seed regions and FC regions (originating in the frontal, parietal and limbic cortices)

with higher FC values for patients. The presence of higher FC in these regions strengthens the assumption that the whole network involved in sensory processing, executive control and emotion regulation in patients with PNES is abnormal. Figure 11.5 displays a schematic representation of the underlying dysfunctioning in this network in patients with PNES.

Figure 11.5 Schematic overview of the circuitry involved in cognitive-emotional executive control. In this study, we found significantly higher functional connectivity strengths between regions involved in emotion (insula) and motor planning (precentral sulcus) for patients with PNES. It appears that healthy controls can control their motor functions without strong influence of emotions, whereas in patients with PNES emotions can bypass executive control and cause involuntary movement. PNES, psychogenic non-epileptic seizures.

Clinical implications

Demonstration of a relationship between dissociation and deficient neuronal processing in PNES has substantial implications for the understanding of the aetiology. Dissociation is one of the mechanisms through which an emotional state can influence executive control, resulting in a seizure-like episode^{17,18} (Figure 11.5). Furthermore, the high FC identified in the current study has potential for the use of functional imaging to aid the differential diagnosis between PNES and epilepsy.

More knowledge of PNES aetiology is necessary for the clinical management of PNES diagnosis and treatment⁴. As such, a higher tendency to dissociate, associated with the hyperlink between regions involved in emotion (insula) and motor preparation (precentral sulcus), may be seen as an increased vulnerability to develop PNES. Moreover, identifying a neurobiological substrate of dissociation in PNES changes the concept of psychogenic seizures into being a biopsychological phenomenon, where a

psychogenic aetiology collides with a specific neurological vulnerability. This has implications for the development and evaluation of treatment, and may eventually improve the clinical management of PNES diagnosis. Moreover, it might aid the patient in accepting diagnosis of PNES. However, it is difficult to consider network abnormalities purely as a predisposition factor, as a diseased network connectivity could either be the cause or the consequence of dissociation and PNES.

Study limitations and future considerations

This study had a limited number of patients. However, even in this small population, statistically significant deviations were demonstrated. These findings should be validated in larger studies, to be able to identify the direction of causality between abnormalities in FC and dissociation and PNES.

Another limitation is that the effect of PNES cannot be disentangled from the effect of dissociation. All of our patients had both PNES and a high dissociation score. To resolve this problem, future studies should include a control group of PNES patients who are not highly dissociative and/or a control group of healthy normal subjects with a high dissociation.

Furthermore, it is not known whether FC abnormalities are accompanied by microstructural (white matter) abnormalities.

Conclusion

The abnormal strong FC found in patients with PNES hints at an underlying psychoform and somatoform dissociation mechanism where emotion can influence executive control, resulting in altered motor function (e.g., seizure-like episodes). Future studies should clarify the exact contribution and interaction of the process of dissociation and network disturbances in PNES.

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Chapter 12

General discussion

General discussion

The quest towards a better understanding of the group of patients with PNES, specifically focussing on psychogenic aetiology and subgroups, has provided some answers, but also raised new questions. The key issue is whether PNES must be viewed as a separate disorder or, whether PNES are part of a continuum with other functional neurological symptoms (FNS) or even with the wider, related domain of functional somatic syndromes and symptoms (FSSS). The study findings in this thesis allow attempting answering some of the recurrent questions about PNES, focussing also on the relevance for clinical practice.

1) Is the diagnosis ‘psychogenic non-epileptic seizures’ a valid diagnosis?

There is consensus in literature that the differential diagnosis PNES versus epilepsy has greatly improved during the last thirty years and that video EEG is the golden standard (chapter 2 and 3). However, diagnosing ‘non epilepsy’ remains a clinical diagnosis and not in all cases video EEG is possible, for example due to infrequent seizures. PNES are – similar to epileptic seizures – paroxysmal events that may evade observation and recording. Also, seizures detected with video EEG in the clinic may not be typical for the seizures occurring in daily life. The patient group with PNES can be diagnostic non-compliant and many patients will not have seizures when they are in the EEG recording unit. As yet, there are no real positive ictal features suggested to be pathognomonic for PNES. This together implies that there may be no 100% guarantee for a PNES diagnosis. The same uncertainty also exists for other functional neurological symptoms (FNS). However, using advanced techniques in combination with the experience of a specialized epileptologist improves the accuracy of the diagnosis. An important misunderstanding, that often confuses the diagnosis, is the interpretation of results of psychological assessment. Once the diagnosis of PNES is firmly established, such assessment may provide insights in the specific psychogenic aetiology. This cannot be reversed; the existence of psychogenic factors (i.e. personality problems, emotional distress, a psychotrauma in the history) cannot be interpreted as evidence for PNES. Finding psychological or psychiatric problems does not eliminate having (comorbid) epilepsy.

The search for better techniques to diagnose PNES continues. Recent research approaching possible bioemotional factors (such as heart-rate variability) and neurobiological substrates for mechanisms involved in PNES (such as dissociation) may be useful for further improvement of the validity of the diagnosis. The findings of the fMRI study in this thesis (chapter 11) and other recent work by our group¹ show that changes in brain activation and neuronal organisation may predispose to dissociation, a mechanism involved in the development of PNES. The abnormal, strong

functional connectivity found in PNES patients provides a neurophysiological correlate for the underlying dissociation mechanism where emotion can influence executive control, resulting in altered motor function (e.g. seizure-like episodes). Heart-rate variability EEG and (functional) MRI seem to be sensitive methods to detect physiological changes related to dissociation and dissociative disorders such as FNS, and can possibly provide more information about the triggering factors involved. The use of such measures could eventually provide biomarkers for earlier identification of patients at risk and appropriate treatment of dissociative conditions¹. However, up till now it is difficult to position psychophysiological abnormalities because they may be both the cause and the consequence of PNES.

In clinical practice it may be helpful to focus on possible subgroups in the differential diagnostic process. In some subgroups of PNES the diagnosis is more certain than in other groups, in which the neurologist has to work with a 'probability diagnosis'. This is in line with the classification of many other neurological disorders. Especially in patients with a complicated combined (frontal) epilepsy and PNES, distinguishing the seizures can be very difficult. In frontal epilepsy the lack of interictal epileptiform EEG activity may result in false negative conclusions. These difficult to diagnose groups of patients are often excluded from research. Pillai en Haut² recently focused specifically on the group of patients with both diagnoses: PNES and epilepsy. They found that frontal lobe epilepsy was more common in patients with epilepsy and concomitant PNES than in patients with epilepsy alone. The results suggest that at least in the subgroup of comorbid epilepsy patients, PNES symptoms may be often associated with frontal seizures.

In general there is consensus in research on FNS that the risk to underdiagnose is probably larger than to overdiagnose. For clinicians, the potential misdiagnosis of an organic disorder is often a concern leading to reluctance in making a FNS diagnosis³. However, diagnostic accuracy is of great importance for therapeutic management^{4,5}. A systematic review found that the frequency of misdiagnosis had been consistent and approximately 4% since 1970⁶. In the differential diagnosis epilepsy versus PNES overinterpretation of the EEG is an important reason why seizures are misdiagnosed as epilepsy so commonly^{5,7}.

2) How are PNES defined?

Before the term PNES was more generally used, psychogenic seizures were labeled in relation to aetiological constructs such as conversion disorder and specifically hysteria. Both labels have a long history, even back to the ancient Greek. In the 20th century psychodynamic visions, especially the psychoanalytic theory of Freud, were of great influence⁸. Freud considered PNES as a 'hysterical fit', being the expression of normal sexual desires, repressed from conscious awareness due to the unbearable

affects with which they had become associated. The phenomenological similarity of many patients' seizures to movements common in the context of the sexual act was interpreted as evidence that the seizure was the symbolic expression of a repressed unconscious sexual conflict. After the abolition of the term 'hysterical neurosis' from the current diagnostic systems, PNES is no longer seen as related to one discrete disorder ('hysteria'). The term 'hysterical seizures' vanished from the literature, although a survey among British neurologists showed that in 1991 the term hysteria was still used in the 'informal contacts' (chapter 2).

In subsequent years the most common label for PNES used in epilepsy centres was "no epilepsy" ("pseudo seizures", "non epileptic attack disorder"). Nowadays, it is known that patients are not helped when presented with a "non-disease" or a "pseudo disease". The more neutral term 'psychogenic non-epileptic seizures' (PNES) is mostly used, avoiding the label pseudo, that may suggest that patients simulate the seizures. However, the term PNES is only used in the field of neurology, especially by neurologists involved in diagnosing epilepsy in general hospitals or specialized epilepsy centres. At least in the Netherlands a diagnosis of PNES is not well known in the broader context of medical practice (such as by general practitioners) or in mental health institutes. Also, the PNES definition clearly describes the somatic appearance of the seizures and the exclusion of other organic causes for the seizures. The underlying psychological or psychiatric problems are less well described, whereas patients with PNES are known to comprise a very heterogeneous group. The central question is whether the underlying pathology can be described in classification systems used in mental health care, such as the DSM-IV or the ICD 10, or that PNES are a unique and separate disorder or symptom unclassifiable in existing systems? Is PNES similar to other FNS or even the broader concept of FSSS, although the presentation of the symptoms is different, or is PNES a separate disorder?

In this thesis we found indications for both similarities and differences with related disorders described in the classification systems for mental health care. The study on personality factors using the MMPI-2 (chapter 7) showed no substantial difference in the personality profile of patients with PNES and patients with insomnia. There were relative differences in the extent of somatization and externalization; PNES patients seemed most similar to patients with a conversion disorder in general. This indicated that, seen from the personality profile, PNES do not substitute a unique disorder, but are part of the family of FSSS. The study on patient characteristics in relation to diagnostic delay (chapter 8) showed similarities between patients with PNES and patients with (different types of) a somatoform disorder such as classified in the DSM-IV or patients described as having "medically unexplained physical symptoms". The majority of the patients with PNES had a patient history with many medical and diffuse psychological symptoms not limited to neurological disorders. It was hypothesized that especially the occurrence of a potential somatization disorder in PNES might be underestimated [see also ⁹]. In the study on subgroups (chapter 9) a

psychotrauma subgroup was identified with dissociative disorders, indicating similarity with the dissociation disorder (ICD10) and/or with a (subgroup of) post traumatic stress disorder (PTSD). The other two subgroups described in chapter 9 showed more similarity with FSSS (the high vulnerability somatising subgroup) and possible personality disorders (the high vulnerability sensitive personality problem subgroup). Describing a general profile seemed to conceal specific subgroups.

The results show, in line with other research, that there may be no term that fits all. PNES seem to be a general term concealing very diverse forms of underlying psychological and psychiatric problems. Characteristics found in some subgroups classify these in the continuum of FSN, FSSS and PTSD. In the forthcoming editions of ICD and DSM there will be revisions in this domain³, reflecting recent research on this area.

However, the type of symptom is of course important and different symptoms may have different impacts for both the patients and the family network. Having sleeping problems has probably a less profound impact on the social environment than seeing a PNES patient falling down at work. Not being able to walk because of conversion paralysis and arriving in a wheelchair has another impact than having sudden, unexpected seizures with the risk of falling down in dangerous places. The impact of having PNES in daily life is probably more similar to having epilepsy. Although similarities exist between PNES and other disorders in mental health care with respect to the underlying psychopathology, PNES also has unique characteristics due to the type of symptom, i.e. seizures. Furthermore, some specific elements in PNES are, as yet, not well understood. For example, the triggering factor, formulated in the theoretical model, to explain what triggers a seizure at a specific moment remains poorly understood. There may be a challenge for neurobiological research in here as mentioned before. There are indications that changing the “psychogenic” into “psychophysiological” seizures may be more suitable for some subgroups of patients with PNES.

3) Treatment of PNES

a) What is the role for epilepsy centres or specialized hospitals?

Many patients with PNES describe a medical history of having had epilepsy or having to deal with contradictory and/or unclear diagnoses, often indirectly sensing that some specialists were doubting an organic cause for the seizures. At the same time neurologists often consider PNES (and in general FNS) patients as “the most difficult to help”³. Since epilepsy centres have the facilities and expertise for the (complicated) medical PNES diagnosis, there seem to be a natural role for them in the subsequent diagnosis, referral and short-term treatment of PNES.

In this thesis two consecutive phases are described in the diagnostic process of PNES. These phases include carefully timed multidisciplinary involvement, although not always simultaneously (chapter 3). In the first phase, the medical diagnosis “no epilepsy” must be established, including the exclusion of other organic factors. This is followed by a first intervention consisting of careful explaining the PNES diagnosis to the patient and her/his family. There is an important role here for the neurologist/epileptologist (chapter 3). For a small group of patients this is sufficient to reduce seizure frequency or even to become seizure free (chapter 4). Clinical practice shows the importance of engaging PNES patients and their families in the diagnostic and treatment process as soon as possible. Without cooperation of the PNES patient, the diagnostic process can become very difficult; for example, the patient has no seizures during the clinical admission. This is also essential when antiepileptic medication is withdrawn. Also, timing of interventions is important. During the medical diagnosis a relatively short diagnostic delay is preferable. Diagnostic delay is still approximately about 6 years, although there are indications that there is an “active high speed referral group”, who is referred within 2 years after seizure onset (chapter 8). However, patients also need time to get used to the idea of possible psychogenic factors playing a role in their seizures. Alper¹⁰ warned already in 1994 for a too early emphasis on psychogenic factors. In his experience it is far better that the PNES patient is told they do not have epilepsy by the neurologist than to be informed of psychogenesis by the psychologist in this first stage (chapter 3).

The second phase aims at establishing a positive diagnosis in which the underlying psychological and social factors are evaluated that can be used for treatment. This phase often involves thorough clinical (neuro)psychological assessment. Not only the first phase can be challenging, this second phase may be complicated as well. Clinical practice shows that this second phase cannot be entered without the consent of the patient to cooperate in the exploration of psychogenic factors. For many PNES patients this agreement can be difficult; they may need time to think this over. In line with the conversion reaction, most PNES patients do not experience a link between the medical symptoms and underlying emotional problems; they seem to be (partly) disconnected from their emotional experience. They may eventually accept the PNES diagnosis at a rational level, but probably feel emotional ambivalent. It may be hard to integrate the diagnosis in their self-image. Common statements in clinical practice are “this is not like me, I am a very stable and straightforward person, I’m not a stressful person”.

After this second phase treatment indications can be determined. Some PNES patients can be directly referred for psychological assessment and treatment in mental health care. However, many patients need the medical environment and specific seizure experience of an epilepsy centre in this second phase. In this stage most patients still have to cope with many seizures which have an impact on their daily life and their

social environment. Although symptom reduction is potentially possible after a clear diagnosis, depending on the complexity of the underlying pathology, seizures will continue during the process of assessment and start of subsequent therapy. Reducing the impact of the seizures on daily life by interventions aimed at school, work and/or the family is also important to break a potential vicious circle of prolongation factors. Other disciplines such as a social worker or educational specialist may be involved in coping with the symptoms on a practical level as well. Furthermore, many PNES patients need recognition for the helplessness they experience of not being able to control the seizures. They may have negative experiences in their social environment, for example when dealing with people that think they simulate. In focussing on symptom treatment, coping with seizures, there are many similarities in dealing with epilepsy in daily life.

In the Netherlands there seem to be different perspectives on the role of epilepsy centres in PNES. Perspectives range from no function at all (patients are confronted with the diagnosis “no epilepsy” and send back to their referrers) to a limited function with brief interventions after the PNES diagnosis to long-term inpatient treatment. Research consistently shows that presenting patients with the negative diagnosis of “no epilepsy” is not enough to guarantee consent with treatment. In fact, patients can experience this negative diagnosis as a denial of their symptoms (chapter 3, chapter 8).

On the other hand, long periods of inpatient treatments in the epilepsy centre may keep the patient in medical care too long, unintentionally confirming the medical attributions of the patients. Furthermore, the underlying psychogenic problems are so diverse that an epilepsy centre does not have all the necessary facilities available in specialized mental health care institutes. During the referral process for subsequent psychological treatment, neurologists face a number of obstacles [see ¹¹]. Access of treatment often is restricted in many areas and there may be long waiting periods or intervals between treatment sessions. Also, patients fail to engage, because they do not understand the relevance of psychological treatment for symptoms they perceive as physical. Referring PNES patients to mental health services too soon can have a high risk of drop out for further treatment and starting a new loop of searching for medical help (medical shopping) or even symptom shifts¹¹⁻¹⁴.

Finding an optimized stepped care management pathway for patients with PNES is essential. In this way both the unique aspects of PNES are taken into account as well as the similarities with other FNS and FSSS. In this pathway the specific expertise of an epilepsy centre can be used in the diagnosis of PNES and the first management steps. PNES patients can be helped to pursue for treatment of the underlying pathology by referring them to mental health care institutes in their own social environment. Especially for the subgroup of patients with combined PNES and epilepsy, the role of the epilepsy centre may be more extended. Also, there may be a more extended consultancy role during the follow up treatment elsewhere, for example, when seizure

type changes and/or there is a renewed uncertainty about a possible somatic cause of the seizures. Quick consultation may prevent unnecessary worries for the patient or extensive new medical investigations, diverting attention of the psychological treatment.

Recent research of Baxter et al.¹¹ showed that even in this (more or less) intermediant function it is important to recognize subgroups in the epilepsy centre to carefully tailor the intervention package to individual needs. Also, cooperation between different professionals is important. In the Dutch system having a good working relationship with the general practitioner is specifically important. The general practitioner can help to motivate for follow up treatment and can help to prevent redundant medical investigations after symptom substitution or symptom shift¹⁵.

b) What is the current status of adequate follow-up treatment of the underlying pathology?

Since the underlying pathology of PNES is very diverse there is no standard psychological treatment for all PNES patients. Treatment interventions range from individual psychotherapy, hypnosis, to intensive multidisciplinary group-psychotherapy. The Cochrane review in this thesis (chapter 5) showed there is no evidence-based support for the use of any specific treatment. However, there is consensus that variations of cognitive behavioral therapy showed to be the preferred type of treatment. In clinical practice this therapeutic background seems particularly important during the first phases of intervention. The associated directive and guiding attitude fits the needs of many patients with FNS or FSSS, often still in doubt about possible organic causes for their seizures and seeking advice. The exact choice of subsequent treatment should be based on individual differences and subgroups. In this thesis a theoretical model is proposed, which can be used for treatment indications. PNES seems to be a symptom of different underlying aetiological factors with specific accents in the model. Treatment is preferably focused on the bottom of the model, the underlying aetiology. The study on subgroups found for example the psychotrauma subgroup, having a clear underlying aetiological factor such as formulated in the diagnostic model. Subsequent treatment would be trauma processing. However, not everyone experiencing a trauma, develops seizures; other factors are important as well. Not all factors may be open for treatment, even when the underlying aetiology is clear. For many patients with PNES treatment in a first phase is focused on stress in daily life and extending coping strategies. Testa et al.¹⁶ recently confirmed that PNES patients have elevated levels of perceived distress and fewer action strategies to reduce the impact of a stressor.

In order for a referral from the epilepsy centre to a mental health institute to be effective, active commitment of the patient is essential. Clinical practice shows the importance of discussing treatment alternatives with PNES patients and strengthen

the importance of making an own decision [see also ¹⁵]. The experienced uncontrollability of the seizures is often one of the most difficult aspects for patients to handle. For some patients this may be related to major life events, in which they were not able to control or change their situation¹⁷. Giving patients with PNES control over alternatives, can help them direct their lives and take responsibility for it. For some patients clinical practice has shown this means choosing 'to learn to live with seizures' and make a well-considered decision to no longer engage in further treatment of underlying factors. This is in line with the consensus that effect measures of subsequent treatment should not only be seizure reduction, but also having less somatic symptoms in general, less medical consumption, improvement of the underlying pathology and quality of life.

In general, treatment settings and professionals with experience in and affinity with the treatment of FNS or FSSS are preferable for subsequent treatment. They can recognize and cope with recurring somatising tendencies, including the temporary return of PNES, which is 'normal' during the treatment process, but can interfere with on-going treatment if not handled properly. It is becoming increasingly clear that networks are necessary to form pathways for patients with FSSS. In the Netherlands there is an initiative to integrate both treatment and research from the perspective of NUMS (Network Unexplained Medical Symptoms, in Dutch NOLK). In the United Kingdom there was an initiative to discuss FNS within the country.

C) What do the findings mean for future research?

The major attention of scientific research has shifted from a focus on the differential diagnosis of PNES from epilepsy to a focus on finding subgroups with regard to the underlying psychological aetiology and treatment. It is widely recognized that evidence-based treatment research is very necessary, but difficult to accomplish. There are several complications for treatment research.

Firstly, most PNES research is initiated from a medical perspective, especially in tertiary epilepsy centres. Generalization of the findings may be limited to a tertiary-care population¹⁸. Secondly, many PNES patients are eventually referred to other institutes and professionals for subsequent (psychological) treatment. As yet, treatment research focuses on the effect of interventions shortly after the PNES diagnosis in the epilepsy centres. For example, in 2010 Goldstein and colleagues¹⁹ published a pilot study with class III evidence of the additional effect of cognitive behavioral therapy compared to standard care. Baxter et al. (2012) also showed the results of a brief intervention pathway after the diagnosis of PNES. More fundamental treatment research on PNES should involve long term follow up research after finishing additional treatment (see also chapter 4). Only when the underlying pathology is treated, the long term effects on PNES and psychological and social

wellbeing will be clear. A long term follow up period is also necessary to prevent an exclusive focus on PNES reduction, whereas there may be symptom substitution or symptom shift to other disorders in the continuum of FNS and FSSS. Studying short term interventions may only illustrate a Pyrrhus victory, since the patient has no more seizures, but has developed other symptoms for which medical help is already sought in another circuit. For research this means collaboration with different institutes involved in the management pathway, such as NOLK.

Since subgroup analysis is considered important, criteria are needed to distinguish these subgroups and to replicate treatment-studies internationally. As yet comparing the results of different subgroup studies is difficult, because of the different psychological variables involved. Definition of terms can also be a problems. Terms such as “somatization” and “dissociation” can be too comprehensive to operationalize. Psychological tests are not always internationally used and comparable and are mostly assessed through self-report. In this thesis both patient characteristics and psychological variables were used to explore possible PNES subgroups. Seizure characteristics were also tested as a classification criterion, focusing on differences between major motor manifestations of PNES versus unresponsiveness. In line with other research on PNES semiology (chapter 9)²⁰ this was less useful.

Ideally, further treatment research should focus on well-designed randomized clinical trials using stratification techniques to identify the most suitable treatment for subgroups in the PNES population. To further entangle the continuum of PNES, FNS and FSSS, preferably control groups should be used with patients with other functional neurological and/or somatic symptoms in addition to “normal” controls. The results of the MMPI-2 study (chapter 7) suggest that patients with other conversion disorders might be an interesting first control group, having much similarities with PNES. Also, for subgroup research a comparison of the patients of the ‘psychotrauma subgroup’ with patients with an PTSD is recommendable.

Finally, the patient inclusion requires attention, especially the common exclusion of patients with comorbid epilepsy and/or patients in which the PNES diagnosis is very plausible but difficult to diagnose more firmly. Maybe subgroups of these types of patients should be involved in future research as well. Interesting for the combined group of epilepsy and PNES patients is research focusing on a possible connection between stress and epilepsy. Still, treatment research remains clinical work with the methodological and ethical complications. Most research is retrospectively and for convenience epilepsy patients are easily used as a control group. It is becoming increasingly clear that randomised clinical treatment trials regarding PNES as a unique disorder are not possible neither very helpful. Also, the efficacy of treatment needs a long follow up period from the scientific point of view, but there may ethical and

treatment considerations not to contact PNES patients after they were referred to another institute, since this might interfere with their on-going treatment process.

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Summary

Summary

A psychogenic non-epileptic seizure (PNES) is defined as a clinically observable paroxysmal change in behaviour or consciousness, that resembles an epileptic seizure, but is not accompanied by the typical electrophysiological changes that accompany an epileptic seizure. In these patients there is an absence of any known organic aetiology of the seizures, whereas there is positive evidence or a strong suspicion for the existence of psychogenic factors. The incidence of PNES in the general population is relatively low, estimated at about 1.5/ 100,000 persons per year. The actual incidence may be higher because of difficulties in epidemiological studies. Tertiary referral centres, especially epilepsy centres, estimate a much higher incidence rate. Twenty-five to thirty percent of the patients referred to tertiary epilepsy centres for refractory epilepsy are diagnosed with PNES, with or without (comorbid) epilepsy.

Although the correct medical differential diagnosis of PNES versus epilepsy can be challenging, in the past thirty years the differential diagnosis has greatly improved. Differentiating PNES from epilepsy is important, since misdiagnosing PNES as epilepsy may potentially expose patients to unnecessary antiepileptic medications and other iatrogenic consequences of unnecessary medical treatments. However, once the medical diagnosis has been made, it appears not easy to treat these patients adequately and prognosis for at least part of the patients is not that well. With their somatic appearance and underlying psychological or psychiatric problems, PNES patients present on the boundaries of the medical and mental health services. There are potential risks that PNES patients 'shop' through the medical circuit or remain in a 'No Man's Land' without the necessary realization of appropriate psychological or psychiatric treatment. Meanwhile, the impact on daily life is substantial, including not being able to engage in society, leading to psychological burden and economic costs.

The studies in this thesis aim at exploring the psychological aetiology after the medical diagnosis of PNES has been confirmed. A focus that is in line with recent studies of PNES in the international field. Firstly, the research questions focus on finding psychogenic factors that underlie the onset and the prolongation of PNES. Finding underlying psychological mechanisms is essential to engage in treatment. Secondly, the research questions aim at exploring possible sub-classifications of PNES that may be helpful to specify treatment for subgroups and to establish prognosis. The studies are mostly based on clinical work with patients with PNES diagnosed in the specialised Epilepsy Centre Kempenhaeghe and referred to a multidisciplinary expert team involved in the treatment of PNES.

Part 1 gives an overview of the existing knowledge in this field. In **chapter 2** we review the literature on the medical differential diagnosis of PNES and epilepsy. There is consensus in literature that the differential diagnosis PNES versus epilepsy has greatly

improved and that video EEG is the golden standard. However, diagnosing ‘non epilepsy’ remains a clinical diagnosis and not in all cases video EEG is possible. An important misunderstanding, that often confuses the diagnosis, is the interpretation of results of psychological assessment. Once the diagnosis of PNES is firmly established, such assessment (and especially personality assessment) may provide insights in the psychogenic aetiology. This cannot be reversed; the existence of psychogenic factors cannot be interpreted as evidence for PNES. Finding psychological or psychiatric problems does not eliminate having (comorbid) epilepsy. In addition, in **chapter 3** the review is focused on psychological aetiology, treatment issues and prognosis. PNES patients comprise a very heterogeneous patient group with regard to the psychological aetiology. It appears not easy to treat these patients adequately and prognosis for at least part of the patients is not that well. Based on these reviews a model is proposed of factors involved in the causation, provocation and prolongation of PNES. This model helped to interpret the findings of the later studies. Although this model resembles other models of somatoform disorders, specific factors, such as “triggering factors”, were added presenting PNES as a unique disorder.

In **part 2** the current status of subsequent treatment of PNES is explored. **Chapter 4** describes a clinical non-randomized study on the long-term outcome of a group of 22 patients diagnosed with PNES in the epilepsy centre, 4 to 6 years after the diagnosis. Seizure frequency shows statistically significant reduction. It cannot be fully clarified which factors caused this improvement, but one may speculate that a definitive expert diagnosis made in a tertiary center and the efforts to inform the patient in a respectful manner about the diagnosis are crucial factors. However, in addition to seizure reduction, there is improvement on different levels of psychological function, showing reduction in psychological distress, reduction in dissociative features, increased self-control, reduction in feelings of dissatisfaction and passive avoidant behavior, and a more active attitude towards social contact. This does not necessarily reflect a causal relationship with the observed seizure reduction. Nonetheless, it is noteworthy that, post aut propter, seizure remission is associated with a more confident social and personal attitude. **Chapter 5** and **chapter 6** present the results of a Cochrane review on treatment effects in collaboration with the University of Liverpool. The main results show that only three small treatment studies met the Cochrane inclusion criteria at that moment, and these studies are of poor methodological quality. Two studies assessed hypnosis and the other study paradoxical therapy as treatment for PNES. The conclusion is that, in view of the methodological limitations and the small number of studies, there is at that moment no reliable evidence to support the use of any specific treatment, including hypnosis or paradoxical injunction therapy, in the treatment of PNES. Randomized studies of these and other interventions are needed.

Part 3 challenges both the usefulness of the PNES diagnosis for such a heterogeneous patient group and the opinion of PNES as a unique disorder. Patients with PNES may have similar characteristics as patients with other functional neurological symptoms (FNS) or even the broader group of patients with functional somatic symptoms and syndromes (FSSS). In **chapter 7** the personality profile of 41 PNES patients is compared with the profile of 43 patients with insomnia. The personality profile was assessed with the Minnesota Multiphasic Personality Inventory 2 (MMPI-2). The MMPI-2 profile showed no statistically significant quantitative scoring differences on the main clinical scales, indicating that there is no substantial difference in "personality make-up" between these two groups. Additional subscale analysis indicated that patients with PNES reported significantly more somatic complaints and bizarre sensory experiences. Further profile analysis revealed that the personality pattern of patients with PNES was characterized by a strong tendency toward "conversion V, a lack of control pattern and less excessive worries", as compared with patients with insomnia. Patients with PNES are characterized by a stronger tendency towards somatization and externalization, which has treatment implications. **Chapter 8** includes a descriptive study providing patient characteristics in 90 PNEA patients newly referred to the epilepsy centre in a 2-year period, focusing on the medical and psychological patient history before seizure onset. The majority of the patients showed a patient history with many medical symptoms (other than seizures) and they were or had been in treatment by other medical specialists than neurologists. Furthermore, diffuse psychological or psychiatric symptoms and subsequent treatments were also remarkably common, in general without a clear psychological diagnosis. The average time between seizure onset and referral to an epilepsy centre was relatively short (4.29 years), compared to data in literature. About 50% of the patients were referred within 2 years of seizure onset. This 'active high speed referral group' had significantly more previous psychological complaints, significantly more previous psychological/psychiatric treatments and a trend towards more previous medical investigations. The conclusion is that there possibly is a new subgroup of PNES patients, characterized by a relative more active attitude towards examination of symptoms in combination with an active attitude to apply for treatment. The PNES cohort as a whole is characterized by having somatoform symptoms based on a process of somatization.

In **chapter 9** the theoretical model derived from the reviews is used to describe subgroups in a prospective study. The results showed that the total PNES group (n=40) was characterized by multiple trauma, personality vulnerability (in a lesser extent, neuropsychological vulnerabilities), no increased dissociation, many complaints about daily hassles that may trigger seizures, and negative coping strategies that may contribute to prolongation of the seizures. Using factor analysis, three specific subgroups were revealed: a 'psychotrauma subgroup', a 'high vulnerability somatizing subgroup' (with high and low cognitive levels) and a 'high vulnerability sensitive personality problem subgroup'. The conclusion is that using a theoretical model, PNES seem to be a symptom of distinct underlying aetiological factors with different

accents in the model. Hence, describing a general profile seems to conceal specific subgroups with subsequent treatment implications. This study identified three factors, representing two dimensions of the model, that are essential for subgroup classification: psychological etiology (psychotrauma or not) and vulnerability, e.g., the somatization tendency, and sensitive personality problems/characteristics ('novelty seeking'). For treatment this means that interventions could be tailored to the main underlying etiological problem. Also, further research could focus on differentiating subgroups with subsequent treatment indications and possible different prognoses.

In the model a specific vulnerability to develop PNES is suggested. This predisposition may involve psychological factors, such as personality characteristics. However, biological vulnerability may also be involved in the development of PNES. This is studied and described in **part 4**. Such a vulnerability may not be the single cause of the symptoms, but may contribute to the development of PNES. This is in line with the perspectives of the biopsychological model in somatoform disorders. In **chapter 10** a specific review is presented, focusing on psychobiological markers for dissociation, one mechanism or process that may cause psychogenic seizures. In a final study, described in **chapter 11**, functional MRI is used to demonstrate such biological vulnerability. The findings of the fMRI study show that changes in brain activation and neuronal organisation may predispose to dissociation, a mechanism involved in the development of PNES. The abnormal, strong functional connectivity found in PNES patients provides a neurophysiological correlate for the underlying dissociation mechanism where emotion can influence executive control, resulting in altered motor function (e.g., seizure-like episodes). Heart-rate variability (HRV) measures, EEG and (functional) MRI seem to be sensitive methods to detect physiological changes related to dissociation and dissociative disorders such as FNSS, and can possibly provide more information about the specific biological vulnerability. The use of such measures could eventually provide biomarkers for earlier identification of patients at risk and appropriate treatment of dissociative conditions. However, up till now it is difficult to position psychophysiological abnormalities, because they may be both the cause and the consequence of dissociation and PNES.

Finally, in **chapter 12**, general discussion, the results of all studies are discussed by attempting to answer some of the recurring questions about PNES. Central focus of the discussion is whether PNES must be viewed as a separate disorder or part of a continuum with other functional somatic (neurological) symptoms. Also, the discussion is focused on the implication of the study findings, together with clinical practice experience, for the role of epilepsy centres in the diagnosis and treatment of PNES.

Samenvatting

Samenvatting

Een psychogene niet epileptische aanval (PNEA) wordt gedefinieerd als een klinisch observeerbare paroxysmale verandering in gedrag of bewustzijn, die lijkt op een epileptische aanval, maar die niet samengaat met de typische elektrofysiologische veranderingen die samengaan met een epileptische aanval. Bij deze patiënten is geen sprake van een organische etiologie voor de aanvallen, terwijl er positief bewijs is voor of een sterk vermoeden op de aanwezigheid van psychogene factoren. De incidentie van PNEA in de algemene bevolking is relatief laag en wordt geschat op ongeveer 1,5 / 100.000 personen per jaar. De werkelijke incidentie kan hoger zijn, omdat epidemiologische studies moeilijk uitvoerbaar zijn. Tertiaire instellingen, en met name epilepsiecentra, schatten een veel hogere incidentie in. Vijfentwintig tot dertig procent van de patiënten die verwezen worden naar tertiaire epilepsie centra voor refractaire epilepsie, worden gediagnostiseerd met PNEA, met of zonder (comorbide) epilepsie.

Hoewel het stellen van een goede medische differentiaal diagnose van PNEA versus epilepsie gecompliceerd kan zijn, is deze differentiaal diagnostiek in de afgelopen dertig jaar zeer verbeterd. Het differentiëren tussen PNEA en epileptische aanvallen is belangrijk. Een verkeerde diagnose van PNEA als epilepsie stelt patiënten namelijk potentieel bloot aan onnodige anti-epileptische medicatie en kan andere iatrogene consequenties hebben van onnodig medisch handelen. Echter, wanneer de medische diagnose is gesteld, blijkt het niet gemakkelijk deze patiënten adequaat te behandelen. Ook is de prognose, op z'n minst voor een deel van de patiënten, minder goed. Door de somatische verschijningsvorm enerzijds en de onderliggende psychologische of psychiatrische problemen anderzijds, presenteren PNEA patiënten zich op de grenzen van zowel de medische als de geestelijke gezondheidszorg instellingen. Er zijn potentiële risico's dat PNEA patiënten gaan "shoppen" door het medische circuit of in een "niemandsland" verblijven, zonder dat de noodzakelijke adequate psychologische of psychiatrische behandeling wordt ingezet. Ondertussen is de impact op het dagelijks leven aanzienlijk, inclusief niet in staat zijn deel te nemen aan de maatschappij, hetgeen kan leiden tot psychologische belasting en onnodige economische kosten.

De studies in dit proefschrift hebben als doel het onderzoeken van de psychogene factoren, nadat de medische diagnose PNEA is bevestigd. Dit doel komt overeen met recente internationale studies naar PNEA. Ten eerste richten de onderzoeksvragen zich op het vinden van psychogene factoren, die ten grondslag liggen aan het ontstaan en het persisteren van PNEA. Het vinden van onderliggende psychologische mechanismen is essentieel voor het kunnen inzetten van adequate behandeling. Ten tweede hebben de onderzoeksvragen tot doel mogelijke PNEA subgroepen te verkennen, hetgeen behulpzaam kan zijn bij het specificeren van behandeling voor

subgroepen en het vaststellen van daarbij horende prognoses. De studies zijn overwegend gebaseerd op de klinische praktijk met PNEA patiënten, die gediagnostiseerd zijn in het gespecialiseerde epilepsiecentrum Kempenhaeghe en die verwezen zijn naar een multidisciplinair expert team dat zich bezig houdt met de behandeling van PNEA.

Deel 1 geeft een theoretische samenvatting van de literatuur over dit onderwerp. **Hoofdstuk 2** is een review van de literatuur over de differentiaal diagnostiek PNEA versus epilepsie. De review laat zien dat consensus bestaat dat de diagnose-mogelijkheden van PNEA – met het video-EEG als gouden standaard- aanzienlijk verbeterd zijn. Echter, ‘niet-epilepsie’ blijft een klinische diagnose en niet in alle omstandigheden is het video-EEG mogelijk. Een belangrijk misverstand, vaak leidend tot misinterpretaties, is de interpretatie van de resultaten van psychologisch onderzoek. Wanneer eenmaal de diagnose PNEA is bevestigd, heeft psychologisch onderzoek (en dan met name persoonlijkheidsdiagnostiek) een essentiële rol bij het vaststellen van onderliggende psychogene factoren. Deze volgorde kan echter niet omgedraaid worden. Het bestaan van psychogene factoren is geen bewijs dat sprake is van PNEA. Het vinden van psychologische of psychiatrische problemen sluit immers niet uit dat sprake is van (comorbide) epilepsie. In aanvulling hierop richt **hoofdstuk 3** zich op de literatuur over psychologische etiologie, behandelingen en prognose. Patiënten met PNEA vormen een zeer heterogene patiëntengroep met betrekking tot de psychologische etiologie. Het blijkt niet gemakkelijk deze patiënten adequaat te behandelen. Ook is de prognose voor minstens een deel van de patiënten niet goed. Gebaseerd op de reviews is een model opgesteld, waarin de verschillende factoren zijn opgenomen, die verantwoordelijk zijn voor het veroorzaken van PNEA, het uitlokken van de aanvallen en het in stand houden van de symptomen. Dit model wordt ook gebruikt om de resultaten van de vervolgstudies te interpreteren. Het model komt overeen met modellen die ook gebruikt worden bij de verklaring van andere somatoforme stoornissen, maar is door het invoegen van bepaalde factoren, bijvoorbeeld “trigger” factoren, uniek voor PNEA.

Deel 2 richt zich op de huidige kennis over de behandeling van PNEA. **Hoofdstuk 4** beschrijft een klinische studie, waarin de langere termijn effecten van de diagnose PNEA, vastgesteld in een epilepsiecentrum, werden geëvalueerd. Een groep van 22 patiënten met PNEA werd onderzocht, 4 tot 6 jaar nadat de diagnose was vastgesteld. De analyse toont een significante verlaging van de aanvalsfrequentie. Het is niet geheel duidelijk welke factoren hebben bijgedragen aan dit resultaat. Mogelijk heeft de duidelijke diagnose bijgedragen, evenals het feit dat die vastgesteld werd door een expertteam in een expertise centrum. Mogelijk is ook de manier waarop de diagnose met de patiënt is gecommuniceerd van belang, met veel aandacht voor respectvolle communicatie. Naast de aanvalsvermindering is ook sprake van verbetering van verschillende onderzochte psychische functies. Het psychologisch onderzoek toont

vermindering van psychische stress, verminderde neiging tot dissociatie, toename van zelfcontrole, afname van gevoelens van onvrede en van passief vermijdend gedrag en een meer actieve sociale houding. Deze studie heeft niet vastgesteld of de reductie in aanvalsfrequentie veroorzaakt werd of gevolgd werd door de verbetering in psychisch functioneren. Ondanks deze onduidelijkheid is het echter opmerkelijk dat het verdwijnen van een symptoom (aanvallen) met sociale consequenties geassocieerd is met een verbeterde sociale en persoonlijke attitude. **Hoofdstuk 5** en **hoofdstuk 6** presenteren de resultaten van een Cochrane review over behandel-effecten, tot stand gekomen in samenwerking met de universiteit van Liverpool. De resultaten tonen aan dat slechts drie studies op dat moment voldeden aan de Cochrane inclusie criteria. Alle drie de studies hebben ernstige methodologische tekortkomingen. Twee studies onderzochten het effect van hypnose en één studie het effect van paradoxale behandeling op PNEA. De analyse van de gehele literatuur leidt tot de conclusie dat er op dat moment geen ‘evidence-based’ aanbevelingen te geven zijn over het gebruik van specifieke behandelingen bij PNEA. Gerandomiseerde interventiestudies zijn nodig.

Deel 3 richt zich op de zinvolheid van de diagnose PNEA als dé overkoepelende term voor een zeer heterogene aandoening. Bovendien wordt ingegaan op de vraag of PNEA gezien kan worden als een aparte stoornis of dat sprake is van een stoornis in een continuüm van psychische aandoeningen. PNEA patiënten hebben mogelijk vergelijkbare kenmerken met patiënten met andere functionele neurologische symptomen (FNS) of zelfs vergelijkbare kenmerken met de grotere groep van patiënten met functionele somatische symptomen en syndromen (FSSS). In **Hoofdstuk 7** wordt het persoonlijkheidsprofiel van 41 patiënten met PNEA vergeleken met het profiel van 43 patiënten met insomnie. Het persoonlijkheidsprofiel werd vastgesteld met de Minnesota Multiphasic Personality Inventory 2 (MMPI-2). Het MMPI-2 profiel toonde geen statistisch significante kwantitatieve verschillen op de scores op de hoofdschalen, hetgeen betekent dat de ‘personality make-up’ van deze twee groepen niet wezenlijk verschillend is. Aanvullende analyses van de subschalen toonden wel enkele verschillen. De patiënten met PNEA rapporteerden significant meer somatische klachten en bizarre zintuiglijke ervaringen. Een profiel analyse toonde verder voor de patiënten met PNEA een sterke neiging tot “het karakteristieke ‘conversie V’ profiel, een patroon van gebrek aan controle en minder overmatige zorgen” in vergelijking met patiënten met insomnie. In het algemeen kan gezegd worden dat de patiënten met PNEA een sterkere neiging blijken te hebben tot somatisatie en externalisatie, hetgeen van belang is voor de behandeling van deze patiënten. **Hoofdstuk 8** beschrijft een klinische studie naar de patiënt karakteristieken van 90 PNEA patiënten, die gedurende een 2-jarige periode verwezen werden naar het epilepsiecentrum Kempenhaeghe en die gezien waren door een expertteam. Ook de medische en psychologische voorgeschiedenis van deze patiënten werd in de studie onderzocht. De meerderheid van de patiënten had een voorgeschiedenis met

veel medische symptomen (anders dan de aanvallen) en was in behandeling (geweest) bij andere medische specialisten dan neurologen. Verder waren vrij diffuse psychische en psychiatrische symptomen algemeen voorkomend, inclusief daarop gerichte behandelingen. Daarbij viel op dat veel psychische behandelingen gestart waren zonder duidelijke psychologische diagnose. De gemiddelde periode tussen het debuut van de aanvallen en de verwijzing naar een epilepsiecentrum was relatief kort in deze groep (gemiddeld 4.29 jaar), althans in vergelijking met de gepubliceerde data over deze 'diagnostic delay'. Ongeveer 50% van de patiënten was zelfs zeer snel verwezen (binnen 2 jaar na het aanvalsdebuut). Deze snel verwezen groep ("the active high speed referral group") werd gekarakteriseerd door een voorgeschiedenis met significant meer psychische klachten dan de overige patiënten. Tevens hadden zij in hun voorgeschiedenis significant meer psychische/psychiatrische behandelingen ondergaan en toonden zij een sterke tendens tot het verzoeken om medische onderzoeken. Er wordt geconcludeerd dat mogelijk sprake is van een nieuwe subgroep van PNEA patiënten, gekenmerkt door een relatief actieve houding ten opzichte van het laten onderzoeken van symptomen in combinatie met een actieve houding behandeling aan te vragen. Het gehele PNEA cohort wordt gekenmerkt door het hebben van somatoforme symptomen gebaseerd op een proces van somatisatie. Het eerder beschreven theoretische model is in **hoofdstuk 9** gebruikt voor een prospectieve vergelijkende studie naar subgroepen van PNEA patiënten. De resultaten toonden dat de groep als totaal (n=40) werd gekenmerkt door meervoudige psycho-traumata, kwetsbaarheid door persoonlijkheidsfactoren (in mindere mate een neuropsychologische kwetsbaarheid), geen toegenomen dissociatie, veel klachten over dagelijkse zorgen, die aanvallen kunnen triggeren en negatieve coping strategieën, die kunnen bijdragen aan het in stand houden van de aanvallen. Factor analyse toonde drie subgroepen: een 'psycho-trauma subgroep', 'een 'somatisatie subgroep' (met een hoog en laag cognitief niveau) en een subgroep gekenmerkt door 'persoonlijkheidsproblemen' ('sensitiviteit'). De conclusie is, dat door gebruik te maken van het gehanteerde theoretische model, PNEA een symptoom is van verschillende onderliggende etiologische factoren met verschillende accenten in het model. Het beschrijven van een algemeen profiel lijkt te verhullen dat sprake is van specifieke subgroepen met daarop toegespitste behandelmogelijkheden. De studie identificeerde drie essentiële factoren voor subgroep classificatie, die twee dimensies van het model vertegenwoordigen: psychologische etiologie (psychotrauma of niet) en kwetsbaarheid (voor somatiseren en voor het ontwikkelen van persoonlijkheidsproblemen). Voor behandeling betekent dit dat interventies specifiek gericht kunnen worden op het belangrijkste onderliggende etiologische probleem. Ook zou verder onderzoek aan te raden zijn, gericht op het differentiëren van subgroepen met daarbij passende behandelindicaties en mogelijk andere prognoses.

In het gehanteerde model wordt verondersteld dat PNEA mede kan ontstaan door een specifieke kwetsbaarheid of predispositie. Predisponerende factoren kunnen

persoonlijkheidskenmerken zijn, maar ook biologische factoren zouden een rol kunnen spelen in de ontwikkeling van PNEA. Dit is bestudeerd en de resultaten worden beschreven in **deel 4**. Biologische predisposities zullen nooit de enige oorzaak zijn voor PNEA, maar kunnen de kans verhogen dat zich gedurende het leven PNEA ontwikkelt. Ook voor andere somatoforme stoornissen zijn zulke biopsychologische modellen geopperd. **Hoofdstuk 10** bevat de review gericht op psychobiologische factoren die van invloed zijn op een belangrijk proces of mechanisme dat kan bijdragen aan het ontstaan van PNEA, namelijk dissociatie. In een laatste studie, beschreven in **hoofdstuk 11**, wordt functional MRI gebruikt om een dergelijke biologische kwetsbaarheid aan te tonen. De resultaten tonen een dergelijke psychobiologische marker in de vorm van specifieke kenmerken van de neuronale functionele connectiviteit bij patiënten met PNEA. De aangetoonde netwerk veranderingen verhogen de kans op dissociatie en kunnen verklaren waarom emoties bij deze patiënten sneller kunnen leiden tot een motorische reactie (in dit geval een aanval). Het gebruik van deze methode, maar mogelijk ook heart-rate variability (HRV) maten (cardiale signalen gerelateerd aan stress) en EEG, kunnen eveneens biomarkers vormen die aangeven welke mensen een verhoogd risico vormen dissociatieve stoornissen en uiteindelijk ook PNEA te ontwikkelen. Een groot probleem met de huidige maten is het post aut propter dilemma, waardoor geen causale relaties gelegd kunnen worden.

Tenslotte bevat **hoofdstuk 12** de discussie. Gepoogd is de resultaten van de verrichtte studies, maar ook de praktijkervaring, te gebruiken om te proberen enkele van de klinisch relevante vragen – die ook keer op keer opduiken – te beantwoorden. Eén van de centrale vragen is of we PNEA moeten beschouwen als een unieke aandoening of dat het zich laat rangschikken in een continuüm met andere functionele somatische (of neurologische) symptomen. Ook op de rol van de epilepsiecentra in de diagnose en behandeling van PNEA wordt ingegaan.

Dankwoord

Dankwoord

Op het moment van schrijven van dit dankwoord overheerst nog het niet te bevatten gevoel dat na al die jaren dit proefschrift tot een afronding is gekomen. En tegelijkertijd merk ik nog lang niet uitgekeken te zijn op zowel het wetenschappelijk onderzoek als de patiëntenzorg bij mensen met psychogene niet-epileptische aanvallen. Het blijft een uitdaging te proberen de diagnostiek en behandeling steeds beter vorm te geven en we zijn er nog niet.

Het schrijven van het proefschrift, uitwerken van data, is in het geheel iets wat zich solitair afspeelt. Echter, wanneer je onderzoek doet op een breed terrein dat diverse disciplines omvat, betekent dit ook veel samenwerken, netwerken en je verdiepen in de bijdragen van andere specialisten. Mede vanuit mijn achtergrond binnen de GGZ en door de postdoctorale opleiding was ik al doordrongen van het belang van multidisciplinaire samenwerking. Het bleek een goed uitgangspunt voor de huidige werkzaamheden. Deze constatering vormt tevens een excuus dan wel verantwoording voor het lange dankwoord dat gaat volgen.

Te beginnen met de mensen met psychogene niet-epileptische aanvallen die de afgelopen jaren hebben meegewerkt aan het wetenschappelijk onderzoek. Het viel me op hoeveel patiënten daartoe uiteindelijk bereid bleken te zijn. Dit terwijl de aard van het onderzoek, zoals deelnemen aan een fMRI studie, niet voor alle patiënten, met bijvoorbeeld een traumatische achtergrond, even gemakkelijk was. Verschillende mensen gaven aan dat zij de deelname als een erkenning ervaren hebben voor hun aanvallen. Wij leerden er vervolgens van nog meer gebruik te maken van patiënt ervaringen binnen de behandeling van PNEA patiënten. Hartelijk dank aan alle deelnemers aan het onderzoek, ook de vrijwillige controle personen, zonder wie dit proefschrift niet tot stand gekomen was.

Een speciaal woord van dank gaat uit naar degenen die mijn promotie begeleid hebben.

Allereerst prof. dr. R.J. van Oostenbrugge, hoogleraar Neurologie, MUMC, beste Robert. Hartelijk dank dat je later in het promotietraject wilde instappen en de essentiële voorwaarden hebt gecreëerd om daadwerkelijk te kunnen promoveren in Maastricht. Ik heb je kordate, betrokken handelen en kritische feedback met veel gevoel voor (cynische) humor erg gewaardeerd. Dat heeft ook gemaakt dat ik mij goed voorbereid voel voor de promotiedag.

Prof. dr. K.E. Vonck, hoogleraar Epileptologie UZ Gent, beste Kristl. Hartelijk dank voor de waardevolle ondersteuning en zorgvuldige terugkoppeling op de artikelen in de afgelopen jaren. Ik heb veel geleerd van de creatieve manier waarop jij het PNEA onderwerp benadert en je faciliteert wetenschappelijk onderzoek op inspirerende

wijze. De samenwerking met Gent is heel belangrijk gebleken, ook voor de vervolgstudies die momenteel lopen. Hartelijk dank daarvoor.

Dr. R.H.C. Lazeron, dienst Neurologie Kempenhaeghe, beste Richard. Hartelijk dank voor de zeer precieze en kritische feedback op de manuscripten van dit proefschrift. De afgelopen jaren hebben we intensief samengewerkt binnen zowel de patiëntenzorg als het wetenschappelijk onderzoek. Vele patiënten hebben we samen gezien. Het heeft mij gesteund dat we hierin op beide fronten goed hebben kunnen samenwerken, met alle ruimte voor een open discussie. Ik waardeer je integriteit en betrokkenheid zeer.

Dr. A.J.A. de Louw, medisch diensthoofd Neurologie Kempenhaeghe, beste Anton. Veel dank voor de support, vaak met een kwinkslag, en de gedegen terugkoppeling in de afgelopen periode. Je gaf niet alleen feedback op de manuscripten, maar bent ook zeer betrokken bij de inhoudelijke discussies over de manier waarop de patiëntenzorg voor PNEA binnen Kempenhaeghe nog beter vorm gegeven kan worden. Dank ook voor het creëren van de faciliteiten om deze zorg te verbeteren.

Prof. dr. P.A.J.M. Boon, diensthoofd Neurologie UZ Gent, directeur Onderzoek & Ontwikkeling Kempenhaeghe, beste Paul. Hartelijk dank voor alle ondersteuning, de intellectuele uitdaging en stimulans in de afgelopen jaren, hetgeen mij ook geholpen heeft een aantal moeilijke hobbels tijdens het traject te nemen. Het is geen promotie in Gent geworden, maar je bijdragen hebben essentiële accenten op dit proefschrift gelegd.

Prof. dr. A.P. Aldenkamp, hoogleraar Epilepsie & Neuropsychologie MUMC, diensthoofd Gedragswetenschappelijke Dienst (GWD), Kempenhaeghe. Beste Bert, je bent de initiator geweest van dit onderzoek en tevens steeds een drijvende kracht in het blijven volhouden van alle studies, zoeken naar oplossingen bij tegenslag en bedenken van interessante en creatieve invalshoeken. Ik heb daar veel van geleerd en ervaren dat het daar in onderzoek doen ook vaak omgaat. Heel veel dank daarvoor.

Ook wil ik graag speciale dank betuigen aan de leden van de beoordelingscommissie voor de tijd en energie, die zij gestoken hebben in de beoordeling van dit proefschrift. Dank aan prof. dr. F.R.J. Verhey, hoogleraar Neuropsychiatrie en Ouderenpsychiatrie, MUMC (voorzitter); prof. dr. G.A. Baker, professor of Clinical Psychology and Neuropsychology of epilepsy, University of Liverpool, UK; prof. dr. E. Thiery, emeritus hoogleraar Neuropsychiatrie en Neuropsychologie, Universiteit Gent, België en dr. M.C.G. Vlooswijk, dienst Neurologie, Maastricht MUMC.

Dank ook aan het expertisecentrum Kempenhaeghe, de leden van de raad van bestuur, ir. N. Bomer en dr. M. Chatrou, voor het stimuleren van wetenschappelijk

onderzoek ten dienste van het verbeteren van de patiëntenzorg, inclusief het creëren van goede faciliteiten hiervoor. Ook de twee betrokken onderzoekscholen wil ik bedanken. De School for Mental Health and Neuroscience, Maastricht University (MHeNS UM) en de sector Onderzoek & Ontwikkeling vanuit Kempenhaeghe. In het bijzonder de betrokken managers, die hebben bijgedragen aan het organiseren van een goed onderzoeks- en wetenschappelijk klimaat met ruimte voor het volgen van specifieke cursussen. Dank aan Laurent Louwies, Managing Director MHeNS UM en Laura Gottmer-Welschen, manager Onderzoek & Ontwikkeling Kempenhaeghe. Ook dank aan de voorganger, Juliette Duisterwinkel. Juliette, je hebt nog een sleutel van me te goed, vanuit een poging het schrijven te stimuleren op een meer afgezonderde plek in de Boondert!

Dr. J.G. Hendriksen, eerste psycholoog GWD, Kempenhaeghe. Beste Jos, dank je voor de support bij het creëren van voorwaarden voor het uitvoeren van wetenschappelijk werk (het moest soms stevig met mij afgesproken worden). Dank ook voor je zorgvuldige wetenschappelijke bijdragen aan de reviews.

Dank ook aan alle andere betrokken coauteurs voor de waardevolle bijdragen aan de artikelen in dit proefschrift. Tiny Wouters, bedankt voor het zorgvuldig omzetten van het manuscript naar een proefschrift. En Geke Overvliet, bedankt voor de goede tip!

Dr. A.M.A.J. Janssen, drs. C. Theuns en dhr. J.F. Vanhoutvin. Beste Guus, Cees en Jos, jullie vormen de basis van de huidige multidisciplinaire samenwerking op het gebied van PNEA; jullie waren het eerste "PNEA" team binnen Kempenhaeghe. Ik heb veel van jullie kunnen leren in de intensieve gesprekken, die we over de PNEA patiënten voerden, onder andere over het belang van duidelijke communicatie van de diagnose en het betrekken van het systeem. Dank daarvoor. Jullie zijn niet meer werkzaam op Kempenhaeghe, maar we houden contact.

Richard Lazeron, Renée Dabekaussen-Spiering, Jacqueline van Nes, Nora de la Parra, Trudy Beijl en Aleida Smits-van de Velden, de huidige leden van het multidisciplinaire PNEA team in Kempenhaeghe. Veel dank voor de fijne samenwerking en de ondersteuning bij de totstandkoming van dit proefschrift. Samen patiënten zien, bespreken, nadenken over vervolgstrategieën, vormt voor mij een heel leuk en ondersteunend onderdeel van de patiëntenzorg. De wekelijkse vergaderingen verlopen vaak met veel humor en extraatjes en worden door ons allen trouw bezocht.

Sandra Boelen en opnieuw Jacqueline en zeker ook Nora, dank jullie wel voor het overnemen van intakes, andere patiëntencontacten, vergaderingen, op momenten dat er echt even doorgewerkt moest worden aan het proefschrift. Het bleek voor mij in de praktijk niet altijd makkelijk tijd te maken voor de wetenschap binnen de vaak intensieve patiëntenzorg, die gepaard kan gaan met veel telefoontjes, spoed-

aanvragen e.d. Veel dank dat jullie mij daarin hebben bijgestaan. En Nora, mijn enthousiaste 'overbuurvrouw', wat zou ik het leuk vinden wanneer je zou kunnen starten met die (gecombineerde) specialistische opleidingsplek!

Dimona Bartelet, José Wirken, Els van der Horst en Dominique IJff. Tijdens jullie stage- en opleidingsperioden zijn jullie ook bij mij ingesprongen om data te bewerken voor dit proefschrift. Dimona en José hebben er zelfs een scriptie aan gewijd. Veel dank voor jullie hulp.

Dr. Jane Brooks, dr. Laura Goodfellow and prof dr. Gus Baker, thank you for the inspiring cooperation and your hard work on the (Cochrane) Reviews. I enjoyed the visits to Liverpool and it was an educational experience to participate in your non-epileptic attack clinic. The language was different, but there were many similarities in the presentation and difficulties we encounter in diagnosing and treating these patients.

Dr. O. Mulder, gepensioneerd neuroloog en psychotherapeut, een bijzondere combinatie. Beste Olaf, hartelijk dank voor de discussies over PNEA, de samenwerking bij de review en de stimulerende woorden. Je hebt, samen met prof. dr. Aldenkamp, aan de voet gestaan van deze promotiestudie.

Beste Sylvie Kolfschoten van der Kruijs, vanuit je achtergrond als neurowetenschapper ben jij een meer "technisch" promotietraject binnen PNEA gestart naar biofysiologische parameters. Het is erg leuk en stimulerend om samen vanuit verschillende invalshoeken op te trekken. Tijdens de fMRI studie zaten we vaak samen achter de scan met dr. Jaap Jansen en Remco Berting, MRI laborant. Het was in het begin spannend hoe dat zou gaan lopen bij deze patiëntengroep. Zou men niet direct een aanval krijgen tijdens de scan? Het bleek allemaal boven verwachting goed te gaan. Ik heb het als heel gezellig en leerzaam ervaren om met jullie samen te werken. Dank daarvoor! En Sylvie, veel succes met de afronding van je eigen promotie.

Collega's binnen de GWD, psychologen en psychologisch assistenten, dank jullie wel voor jullie belangstelling en steun in de afgelopen jaren. Caroline van der Linden, jouw humor en energie helpen bij elke tegenslag. Misschien kunnen we onze Koefnoen sketches nog eens gaan uitschrijven, anoniem uiteraard! Dank ook voor je hulp bij de feestelijke organisatie rondom de promotie. Lisette, mijn kamergenoot, Debby, Els, Lianne en ook de andere en nieuwe collega's, dank voor de aanhoudende belangstelling en bemoedigende woorden bij het schrijven van dit proefschrift.

Annemarie, Christie en Thérèse en zeker ook Aleida: mijn agenda beheren, dat valt niet mee, maar gelukkig zijn jullie flexibel. Dank voor alle ondersteuning, ook al omdat

jullie het eerste contact zijn voor de patiënten als zij persoonlijk of telefonisch contact zoeken.

De gehele neurologienstaf binnen Kempenhaeghe, zoals o.a. mijn copromotoren, dr. Mariette Debeij-van Hall, dr. Marian Majoie, Saskia Ebus en Inge Gommans, met wie ik de afgelopen jaren veel heb samengewerkt op het gebied van PNEA, epilepsie en het verbeteren van de patiëntenzorg. Dank voor jullie ondersteuning en voor de open houding ten opzichte van multidisciplinair werken.

Mijn praktijkopleiders en supervisoren tijdens de opleiding, in het bijzonder drs. C. de Haan en drs. M. Cluysenaer-Lauwers. Beste Cor en Miriam, ik was nog relatief jong toen ik aan de postdoctorale opleiding begon, maar toch gaven jullie mij de kans en daarvoor ben ik jullie zeer dankbaar. Beiden hebben jullie ook altijd aangegeven dat een combinatie met wetenschap voor mij geschikt zou kunnen zijn. En zie daar, vele jaren later, blijkt dat inderdaad het geval en dan ook nog binnen de affiniteiten, die er altijd al lagen, multidisciplinair werken met "moeilijke mensen". Dank voor jullie begeleiding en de essentiële basis, die jullie voor mijn beroepsuitoefening hebben gelegd. Ook dank aan Ingeborg Hopman, destijds supervisor en "baas", zij leerde me de fijne kneepjes van de gedragstherapie. Altijd hebben we contact gehouden.

Ook de opleidingsgroep tot klinisch psycholoog en psychotherapeut, de "KP 95-club", wil ik bedanken. Marianne, Sylvie, Rolf, Ingrid, Hans, Larissa, Marian, Suzan, Ellen, Mirjam en Jan, we hebben een intensieve periode met elkaar opgetrokken en dat schept een band; we delen een zelfde opleidingsachtergrond en begrijpen elkaars werkzaamheden en positie. We zijn uitgewaaid over het land, maar houden ook altijd weer contact.

Carol en Ronnet, we gaan inmiddels al lang terug. Trouw zijn we aan onze etentjes, waarbij Utrecht zo ongeveer het midden voor ons is, en we alles kunnen delen wat er op ons levenspad komt. We hebben zelfs een vaste stek in "Het Zuiden" weten te bemachtigen. Jullie vertegenwoordigen mijn roots binnen de (klinische) psychotherapie (een intense leerperiode), maar inmiddels ook zoveel meer dan dat. Jullie hebben erg meegeleefd tijdens het promotietraject. Ik ben heel blij dat jullie mijn paranimfen willen zijn!

Anja en Isolde, als vriendinnen gelukkig al heel lang in mijn leven. We startten ieder met een totaal andere studie in Nijmegen, maar smeedden een band voor het leven. Jullie waren getuigen op ons huwelijk. Dank jullie wel voor de mij dierbare vriendschap en de ondersteuning tijdens het promotietraject en de vele leuke momenten, die we samen, maar ook met onze gezinnen beleven. Dat er nog vele van zulke momenten mogen volgen.

De jaarclubgenoten, Marjan, Ilse, Iris, Ellis, Marit en Sabina wil ik bedanken voor hun steun, belangstelling en gezelligheid. Marjan en Ellis, jullie weten hoe het is om te promoveren. De jaarclubnaam verzwijgen we al jaren, dat was in de jaren 80, maar altijd weer volgen er leuke etentjes en uitstapjes. En wat heb ik daar nu weer tijd voor...!

Maria, vriendin, oud collega en coauteur, dank je wel voor alle ondersteuning en de plezierige gezamenlijke ontmoetingen, ook met onze beide gezinnen, hier of in Spanje.

Ook alle andere vrienden en kennissen wil ik danken voor zowel de steun als soms ook broodnodige afleiding. Door de verschillende verhuizingen is ons netwerk erg verspreid over het land, maar gelukkig staat de moderne techniek voor niets (toegeven, ik ben ik niet de allerhandigste technneut, maar leer wel bij...!)

Tineke, Ingrid en Marioline, zonder jullie hulp zou het in dit drukke leven niet mogelijk geweest zijn te kunnen promoveren. Dankzij jullie weet ik dat het thuis goed geregeld is wanneer ik er niet ben. De kinderen zijn ook dol op jullie. Veel dank daarvoor. Dat geldt ook voor alle gezellige en steunende contacten in onze kinderrijke buurt, waar het mede daardoor heel fijn wonen is. In het bijzonder mijn kordate "buurvrouw" Natalie, die ondertussen het nodige afweet van promoveren. En ook Annelyn, de flexibele grote zus en oppas. Die avondvierdaagse lopen komt nog wel een keer!

Familie en schoonfamilie. Doorzettingsvermogen, nieuwsgierigheid en de behoefte je verder te ontwikkelen heb ik als kind goed meegekregen. En eerlijk is eerlijk, dat kwam tijdens dit proces goed van pas. Mijn ouders hebben mij mede gebracht waar ik nu sta. Zonder mijn vader was de hele vacature in Kempenhaeghe mij aanvankelijk waarschijnlijk ontgaan. Hij heeft een goed inzicht gehad in wat mij zou passen. Inmiddels heb ik er een grote, warme (schoon)familie bij gekregen, met de grote broers Arnoud en Adrian, Annelyn, neven en nichten, waarbij ik ook mijn schoonouders niet kan missen. Dat heeft mijn leven verrijkt en al vele leuke momenten gebracht. Dank jullie wel voor jullie belangstelling, support en doortastende, doch confronterende, vragen (Anneke en Erica, jarenlang, liefst tijdens het kerstdiner: "kunnen we al vragen wanneer de promotiedatum is...?!"). Hopelijk volgen er nog vele mooie momenten.

Mijn basis, mijn alles, lieve Bert, Edar, Julien en Anna. Ik houd heel veel van jullie en kan me geen leven zonder jullie voorstellen. Jullie hebben het vele werken voor mij in een ander perspectief geplaatst, al is het werk van mama wel moeilijk uit te leggen ("ze praat een beetje en dan worden de mensen beter toch..?!"). Bert, jij hebt altijd vertrouwen gehouden, mij uitgedaagd met je intellect en humor en veel geduld gehad. Ik kan je niet genoeg bedanken! We gaan een feestje vieren!

Curriculum Vitae

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Nynke Maria Gerharda Bodde werd geboren op 16 september 1971 te Geldrop. In 1989 behaalde zij het atheneum diploma aan het Van der Puttlyceum te Eindhoven. Aansluitend startte zij met de studie psychologie aan de Radboud Universiteit Nijmegen. In 1990 behaalde zij het propedeuse diploma cum laude. Vervolgens volgde zij de doctoraal opleiding vanuit de afstudeerrichtingen Gerontologie en Klinische Psychologie. Als student assistent leidde zij ondersteuningsgroepen voor ouderen en deed vrijwilligerswerk in het verzorgingstehuis. Tijdens de lange stage periode binnen de psychiatrische - en opname afdelingen van Pro Persona GGZ raakte zij toenemend geïnteresseerd in diagnostiek en behandeling van complexe psychologische en psychiatrische problematiek. In juni 1995 rondde zij cum laude de psychologie opleiding af. In datzelfde jaar startte zij met de postdoctorale specialistische opleiding tot klinisch psycholoog en psychotherapeut, eveneens vanuit de Radboud Universiteit Nijmegen. Vanuit deze postdoctorale opleiding was zij verbonden aan diverse opleidingscentra. Zij startte binnen de eerstelijnspraktijk, allereerst Psychologenpraktijk Derksen & Klein Herenbrink te Bommel en later Hopman Praktijk voor Cognitieve Gedragstherapie te Nijmegen. Ook was zij werkzaam op de Psychiatrische Deeltijdbehandeling verbonden aan GGNet te Apeldoorn, de Angstpolikliniek vanuit Pro Persona GGZ te Nijmegen en tot slot het Centrum voor Psychotherapie (deeltijd klinische - en klinische afdelingen) te Lunten, inmiddels eveneens verbonden aan Pro Persona GGZ. In 2001 behaalde zij de BIG registraties tot GZ psycholoog, klinisch psycholoog en psychotherapeut. Ook werd zij in dat jaar geregistreerd als cognitief gedragstherapeut bij de Vereniging voor Gedragstherapie en Cognitieve Therapie (VGCT). Zij vervolgde haar werkzaamheden als hoofdbehandelaar binnen de Psychotherapeutische Deeltijdbehandeling verbonden aan de GGZ in Breda. In 2003 trad zij in dienst van Kempenhaeghe, Expertisecentrum voor epileptologie, slaapgeneeskunde en neurocognitie. Zij is verbonden aan de Gedragswetenschappelijke Dienst. De afgelopen jaren heeft zij een functie binnen de patiëntenzorg gecombineerd met een promotietraject gericht op psychogene niet epileptische aanvallen. In deze functie komen de eerdere interesses samen met het uitdagende gebied van de medisch onverklaarde somatische klachten.

Nynke Maria Gerharda Bodde was born on September 16th 1971 in Geldrop, the Netherlands. In 1989 she finished her secondary school at the Van der Puttlyceum in Eindhoven. Subsequently, she started studying psychology at the Radboud University Nijmegen in the Netherlands. In 1990 she finished her Bachelor psychology cum laude. She then followed the Masters training psychology in both Gerontology and Clinical Psychology. As a student assistant she led support groups for elderly and she was a volunteer in an elderly home. During a long internship in a psychiatric ward and admission centre of "Pro Persona GGZ", she became interested in the diagnosis and

treatment of complex psychological and psychiatric problems. In June 1995 she graduated cum laude as a psychologist. In the same year she enrolled the Postdoc Education towards Clinical Psychologist and Psychotherapist, again at the Radboud University Nijmegen. During this training she worked at several training institutes. Starting within the so called primary care, the Psychology Practice Derksen & Klein Herenbrink in Bommel and, later at Hopman Practice for Cognitive Behavioral Therapy in Nijmegen. She also worked at the Psychiatric Treatment Unit of "GGNet" in Apeldoorn, the Treatment Unit for Anxiety Disorders of "Pro Persona GGZ" in Nijmegen and finally the Centre for Psychotherapy in Lunten, also of "Pro Persona GGZ". In 2001 she is enlisted in the registry as healthcare psychologist, clinical psychologist and psychotherapist. In the same year she was also registered as a cognitive behavioral therapist at the Dutch Association for Behavioral and Cognitive Therapy (VGCT). She subsequently worked as a leading counsellor in the Psychotherapeutic Treatment Centre of the "GGZ" in Breda. In 2003 she joined Kempenhaeghe, Centre of expertise in epileptology, sleep medicine and neurocognition. She is working at the Department for Behavioural Sciences. In the past years she combined a function in patient care with a PhD program focussed at psychogenic non-epileptic seizures. In this function the former interests combine with the challenging field of medically unexplained somatic symptoms.