STRESS AND SEIZURES: EXPLORING THE ASSOCIATIONS BETWEEN STRESS AND EPILEPTIC AND PSYCHOGENIC NON-EPILEPTIC SEIZURES

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Dědečkovi, s láskou

(To my Grandfather, with love)

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Abstract

Stress is one of the most frequently self-identified seizure precipitants in patients with epilepsy, and psychogenic non-epileptic seizures (PNES) are by definition associated with psychological distress. Stress is a multifaceted phenomenon, yet few studies have systematically examined its different components in patients with seizures. The main aim of this thesis was therefore to assess the association between stress and seizures using a combination of stress measures, and to develop an intervention targeting stress in patients with seizures.

The first study prospectively explored a range of psychological and physiological stress markers in patients undergoing video-telemetry. A diurnal pattern was observed in the physiological measures but, whereas some of the physiological measures were shown to be associated with each other, no close relationship was found with self-reported stress. Notably, none of the stress measures predicted occurrence of epileptic seizures or PNES; however, the occurrence of seizures was found to predict greater self-reported stress and autonomic arousal up to 12 hours after the seizures. A second part of the study assessed implicit attentional responses to stress-related stimuli and suggested patients with epilepsy show heightened vigilance towards threat (especially seizure threat), associated with increased autonomic arousal.

A self-help stress-management intervention, developed as part of the second study, was evaluated in a pilot randomised controlled trial. Results from the pilot demonstrated the intervention was acceptable and provided preliminary evidence for its effectiveness in reducing self-perceived stress. Further evaluation in a larger trial may be justified, although future studies should include measures to reduce the high attrition rates observed in the pilot study.

Ultimately, examination of the role of stress in seizure disorders continues to be an important area for future research. Simple interventions such as the one developed in this thesis could be a useful complementary treatment option for reducing the distress associated with seizures.

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Glossary of Abbreviations

ACT	Acceptance and Commitment Therapy
ACTH	Adrenocorticotropic Hormone
ADR	Adrenaline
AED	Anti-Epileptic Drugs
ANS	Autonomic Nervous System
BRCS	Brief Resilient Coping Scale
CBT	Cognitive Behavioural Therapy
CRH	Corticotropin-Releasing Hormone
CSI	Cardiosympathetic Index
CVI	Cardiovagal Index
D-SI	D-Transformed Stroop Index
DSM-V	Diagnostic and Statistical Manual of Mental Disorders
ECG	Electrocardiography
EEG	Electroencephalography
EMDR	Eye Movement Desensitisation and Reprocessing
EQ-5D	European Quality of Life - 5 Dimensions Scale
fMRI	Functional Magnetic Resonance Imaging
GAD-7	Generalised Anxiety Disorder 7-Item Scale
GSR	Galvanic Skin Response
HIPT	Habit Index of Positive Thinking
HLM	Hierarchical Linear Modelling
HPA	Hypothalamic-Pituitary-Adrenocortical
HRQoL	Health-Related Quality of Life
HRV	Heart-Rate Variability
ICC	Intra-Class Correlation
ICD-10	International Classification of Diseases
ILAE	International League Against Epilepsy
LC-MS/MS	Liquid Chromatography and Tandem Mass Spectrometry
LOT-R	Life Orientation Test - Revised
LSSS-3	Liverpool Seizure Severity Scale - Version 3
MRC	Medical Research Council
NA	Noradrenaline
NDDI-E	Neurological Disorders Depression Inventory for Epilepsy
NEWQOL-6D	Quality of Life in Newly Diagnosed Epilepsy - 6 Dimensions
NHS3	National Hospital Seizure Severity Scale
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
NMDA	N-Methyl D-Asparate
Nmol/L	Nanomoles per Litre
PNES	Psychogenic Non-Epileptic Seizures
PNS	Parasympathetic Nervous System

PSS-4	Perceived Stress Scale - 4 Items
PTSD	Post-Traumatic Stress Disorder
PVN	Paraventricular Nucleus
RCT	Randomised Controlled Trial
RMSSD	Square Root of the Mean of the Sum of Squares of Differences between Adjacent NN Intervals
RT	Response Time
SAM	Sympathetic-Adrenomedullary
SCN	Suprachiasmatic Nucleus
SDNN	Standard Deviation of All NN Intervals
SE	Status Epilepticus
SISE	Single-Item Self-Esteem Scale
SNS	Sympathetic Nervous System
SSAM	Spontaneous Self-Affirmation Measure
SSSI	Smith Stress Symptom Inventory
SWD	Spike-Wave Discharges
TP	Total Power
VAS	Visual Analogue Scale
vEEG/ECG	Video-Electroencephalography/Electrocardiography
VNS	Vagus Nerve Stimulation
WHO	World Health Organisation

Publications

Publications arising from the PhD project

Parts of Chapter 1 and Chapter 2 presented in this thesis were published as detailed below:

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Other related publications

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1. CHAPTER 1

Introduction

1.1 Epilepsy

Epilepsy is one of the most common disabling neurological disorders, characterised by recurrent seizures (Haut et al., 2006). According to the International League Against Epilepsy (ILAE), epilepsy is defined as a disease of the brain diagnosed on the basis of any of the following three criteria: (1) occurrence of at least two unprovoked or reflex seizures more than 24 hours apart, (2) one unprovoked or reflex seizure associated with at least 60% probability of seizure recurrence in the next ten years, or (3) diagnosis of an epilepsy syndrome (Fisher et al., 2014). Epilepsy is a complex disorder with a heterogeneous aetiology and diverse manifestations (Berg et al., 2010). The ILAE proposed a classification system based along five axes that describe (1) the type of seizure (Figure 1.1), (2) focal or generalised seizure onset, (3) epilepsy syndromes (Figure 1.2), (4) aetiology and (5) the associated disability (Duncan et al., 2006). Seizures are events in the brain characterised by hypersynchronous and excessive electrical discharges that can be classified as generalised, focal or unknown (Berg et al., 2010). Generalised seizures arise within and spread across both hemispheres, whereas focal seizures originate in one part of the brain and may or may not spread. Seizures can vary from brief lapses of consciousness, muscle jerks or stiffening to severe convulsions, and can be accompanied by disturbances of sensation, mood or mental function (Duncan et al., 2006). Different types of epilepsy can be grouped into epilepsy syndromes according to the clinical symptoms and characteristics of the disorder (Haut et al., 2006). Based on the underlying aetiology, epilepsies can be divided into genetic epilepsies caused by a genetic deficiency or structural-metabolic epilepsies caused by damage or

disorders of the brain including birth trauma, head injury, brain tumours, brain infection or alcohol abuse. In many cases, the cause remains unknown (Berg et al., 2010).

The overall prevalence of epilepsy is high (between 4 - 15 per 1,000 population per year) and it is associated with a societal and economic burden (Duncan et al., 2006; Ngugi et al., 2010). Epilepsy affects individuals of all ages, across all geographical regions, and is associated with serious impacts on the individual's self-image, self-esteem and health-related quality of life (HRQoL) (Baker et al., 2000; Fisher et al., 2000; Hermann & Jacoby, 2009).

The aim of the treatment of epilepsy is a complete elimination of seizures, as well as the reduction of the associated disability and improvement of HRQoL (Haut et al., 2006). Most patients are offered long-term antiepileptic drug treatment, which stops the attacks in 60 - 65% of patients, however, about one third of patients do not respond to medication (Duncan et al., 2006). Drug-resistant epilepsy can be treated by epilepsy surgery, vagal nerve stimulation (VNS) or other non-pharmacological therapeutic methods including special diets.

Patients may also benefit from psychosocial and educational interventions or alternative medicine (Wolf et al., 2013). In the past these methods were an important part of treatment although lost favour as a result of a biomedical understanding becoming predominant in the second half of the 20th century (Pinikahana & Dono, 2009). Such approaches however, have recently gained renewed interest. This can be partly attributed to the fact that many patients using medication continue to have seizures and may therefore seek alternative treatment options (Wolf, 2002). Another reason may be that unless seizures are controlled altogether, HRQoL in epilepsy is related less to the frequency and severity of seizures than to psychosocial factors, such as social isolation or depression and anxiety, for which people with epilepsy are at higher risk (Kessler et al., 2012).

One of the greatest concerns of people with epilepsy is the unpredictability of seizure events, one example of this is that people can often find it difficult to understand why their

seizures started (Fisher et al., 2000). Given that seizure (ictal) events can be paroxysmal in nature and have been described as highly distressing experiences (Fisher et al., 2000), the recognition and management of seizure triggers is an important area of research with scope for targeted intervention. It should be noted however that there is a difference between risk factors and triggers of epilepsy. Risk factors increase the likelihood that the disorder will develop and therefore explain the vulnerability of an individual to the process of *epileptogenesis* or the initial development of epilepsy (Haut et al., 2006). Triggers, on the other hand, are factors that increase the probability of an attack occurring in an individual who has already developed the disorder and are therefore related to *ictogenesis* or the development of epileptic seizures in the presence of a vulnerability to 'spontaneous' epileptic seizures (Haut et al., 2006).

Figure 1.1. *Classification of seizures by the ILAE Commission on Classification and Terminology (Berg et al., 2010)*

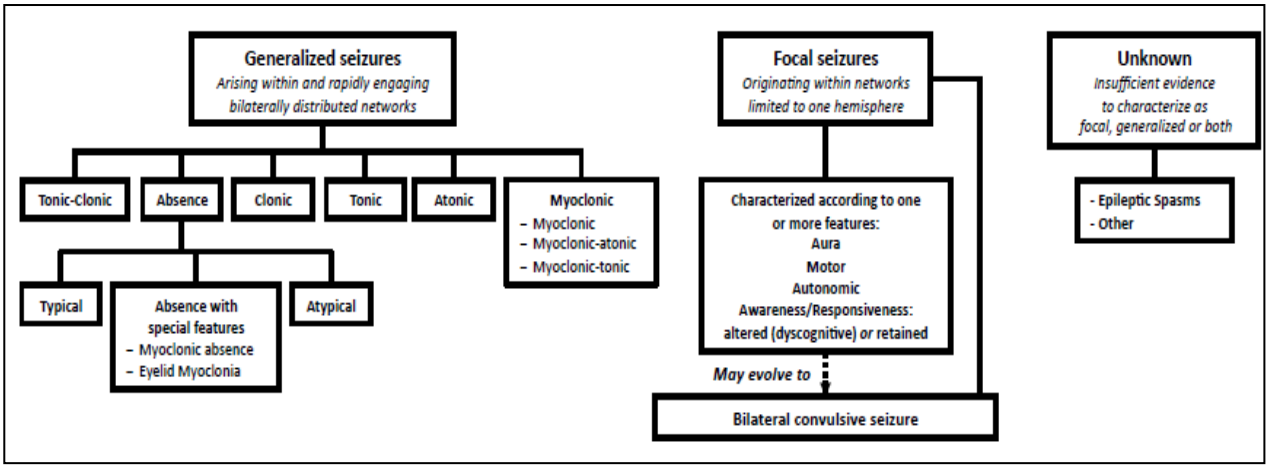
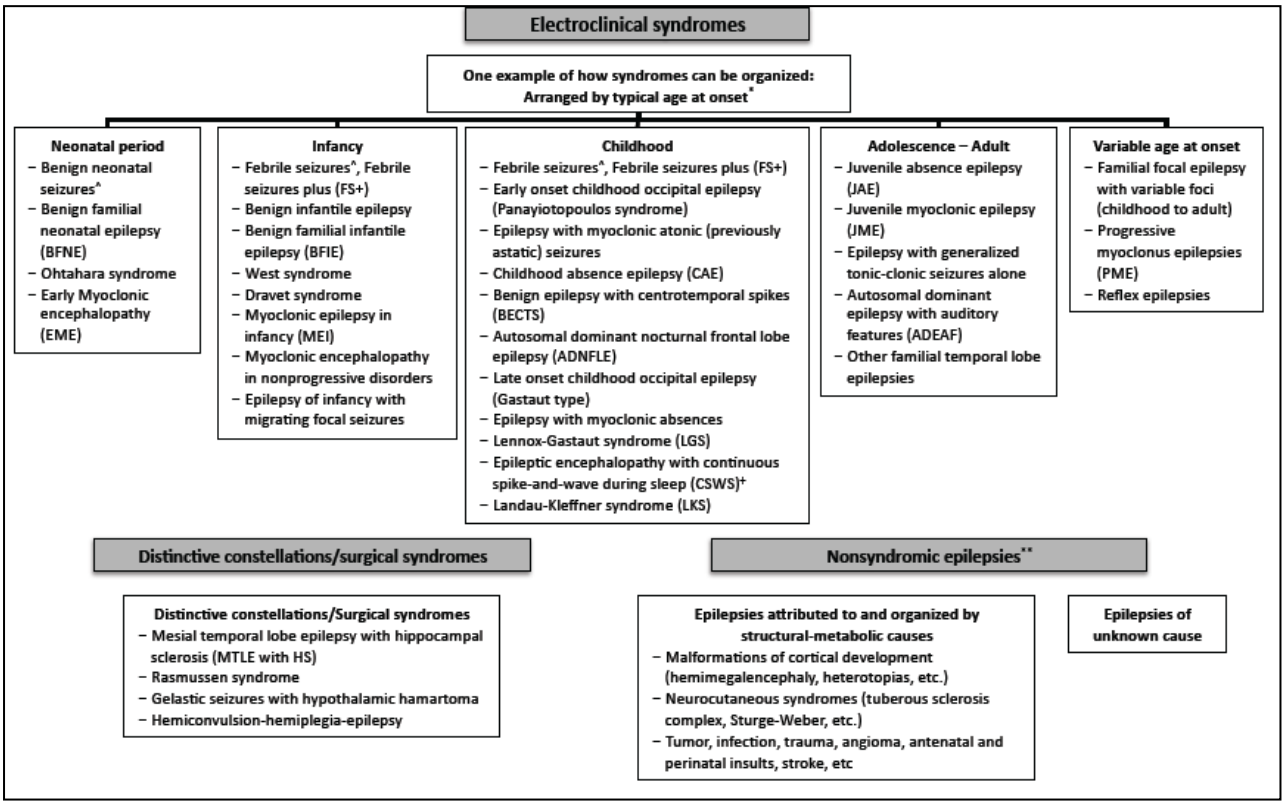


Figure 1.2. *Overview of epileptic syndromes proposed by the ILAE Commission on Classification and Terminology (Berg et al., 2010)*



1.2 Psychogenic Non-epileptic Seizures (PNES)

Psychogenic non-epileptic seizures (PNES) are characterised by episodes of involuntary alteration of consciousness and disturbances of motor, sensory, autonomic, cognitive or behavioural function that superficially resemble epileptic seizures but are not caused by epileptic activity in the brain (Reuber, 2009). PNES are attributed to underlying psychological causes and are classified as a conversion or somatic symptom disorder in the Diagnostic and Statistical Manual of Mental Disorders (DSM-V) (APA, 2013) and as a dissociative disorder in the International Classification of Diseases (ICD-10) (WHO, 1992).

There are multiple predisposing, precipitating and perpetuating factors associated with PNES, and the disorder is often related to a complex interplay of these factors (Reuber, 2009). The predisposing factors may include dysfunctional family environment, childhood

sexual abuse or other traumatic experiences in early life (Salmon et al., 2003). PNES are often precipitated by significant adverse or traumatic life events and are commonly associated with other mental disorders, including anxiety, depression, personality disorders, post-traumatic stress disorder, or other dissociative or somatoform disorders (Bodde et al., 2009). PNES also develop in about 10 - 30% of patients with concurrent epilepsy (Asadi-Pooya & Emami, 2013; Martin et al., 2003; Reuber, 2009). In some patients, physical precipitants, such as minor brain injuries, epilepsy surgery or other neurosurgical procedures can be identified. A number of factors can further exacerbate the disorder, including the concurrent psychiatric disorders or maladaptive coping styles (Reuber, 2009). Similar to epilepsy, it is useful to distinguish between more general risk factors for PNES that predispose, precipitate and maintain the disorder, and more immediate triggers of the individual seizures. Such trigger factors include overwhelming sensory and emotional stimuli, which may play an important role in seizure management (Goldstein & Mellers, 2006).

Of patients newly presenting in seizure clinics with blackouts 10 - 20% have PNES (Angus-Leppan, 2008). The diagnosis of the disorder can be difficult, although a 'gold-standard' can be achieved by the recording of typical seizures with synchronised video-electroencephalography (video-EEG). However, video-EEG is typically only carried out in patients with persistent, frequent or treatment refractory seizures and in the majority of cases, PNES are associated with a delay in diagnosis (Reuber et al., 2002), and are often initially misdiagnosed as epilepsy (LaFrance et al., 2013). This means that, although the recommended treatment method for PNES is psychotherapy, many patients with PNES are inappropriately treated with anti-epileptic drugs, thus increasing the chance of iatrogenic harm (LaFrance et al., 2013; Reuber et al., 2005b). Seizure and social outcomes in patients with PNES are poor if no specific treatment is offered (Reuber et al., 2003).

1.3 The Concept of Stress

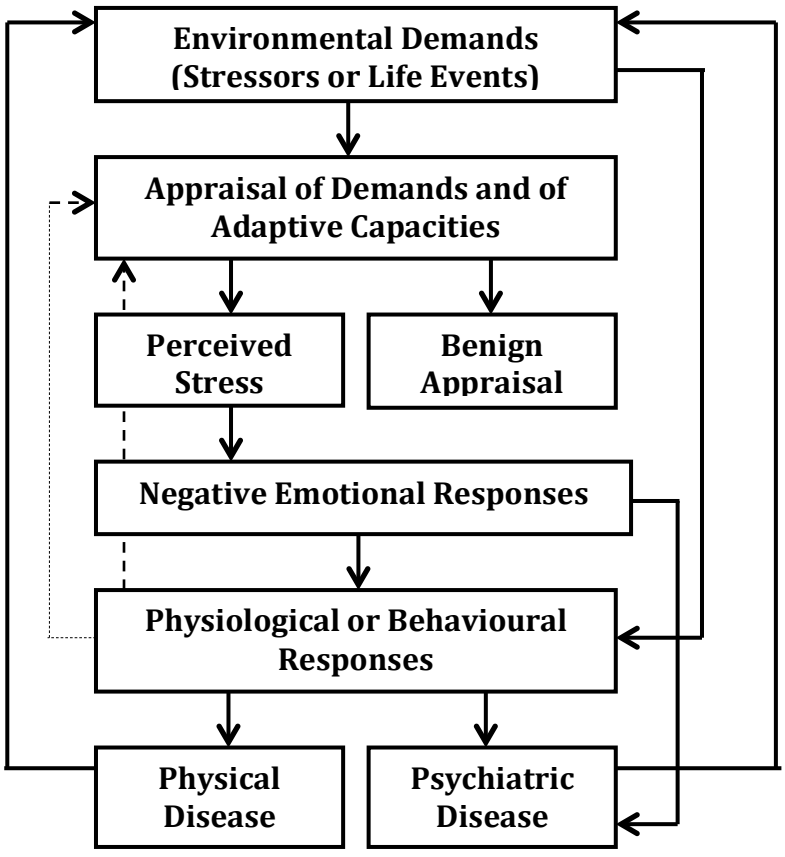
The experience of 'stress' is a common component of everyday life. Stress is a part of an adaptive mechanism that mobilises the organism to respond appropriately to threatening or challenging stimuli (Aldwin, 2000). However, longitudinal research, such as the Whitehall II studies (Carroll et al., 2001), has suggested that the physiological changes associated with stress responses to environmental and psychosocial demands can have adverse effects on people's health, particularly if they are excessive or prolonged.

Stress is a complex phenomenon and its aspects and effects on health have been studied by a number of disciplines (Aldwin, 2000). As a result, there are multiple definitions and methods of measurement which have created considerable confusion and inconsistency (Cohen et al., 1995). Cohen et al. (1995) attempted to integrate the different approaches defining stress as '*a process in which environmental demands tax or exceed the adaptive capacity of an organism, resulting in psychological and biological changes that may place persons at risk of disease*' (p. 3). This encompasses the three main theoretical perspectives on stress: (1) the environmental perspective, concerned with external environmental events that can be objectively considered as stressful; (2) the psychological perspective, focussed on the individual's subjective appraisals of events and his or her capacity to cope with them; and (3) the biological perspective, studying the physiological stress responses, in particular the neuroendocrine and immune processes and their effects on health (Aldwin, 2000). The three perspectives can be unified into an integrative model (Figure 1.3) showing stress as a dynamic process with the environmental, psychological and biological variables mutually influencing each other. The three perspectives place a different emphasis on the subjective and objective experience of stress, and each of them is associated with different measures of stress. Given the interactive nature of the different aspects of the stress process, the most

informative approaches involve combinations of objective and subjective stress measures (Aldwin, 2000).

One of the most challenging questions across all stress approaches is the question of the temporal characteristics of stress (Cohen et al., 1995). For instance, a distinction is commonly made between 'acute' and 'chronic' stress. There is, however, no clearly defined time period for the acute versus chronic stress and the consequences of the temporal characteristics of stress may be different for different health outcomes. Furthermore, evidence shows that individuals may even be affected by prenatal maternal stress through epigenetic mechanisms, for example, animal studies demonstrated that infants of mice who were exposed to a stressor during the gestation period showed memory deficits and increased depressive-like behaviour (Sierksma et al., 2013). Cohen et al. (1995) therefore recommend that the temporal aspects should always be considered in the context of the particular research question and characteristics of the outcome measure.

Figure 1.3. *Integrative model of the environmental, psychological and biological perspectives on stress. Model adapted from Cohen et al. (1995)*



1.4 Stress and Seizures

Stress, epilepsy and PNES are multifaceted conditions, which can interact in complex ways. Epilepsy and PNES are likely to be associated with a great degree of stress, resulting from the disabling effects of living with a chronic condition, as well as the experience of recurrent seizures, each of which can in itself be an acutely stressful event (Goldstein & Mellers, 2006). The relationship also goes in the other direction. Many studies have demonstrated that patients with epilepsy consider stress the most common trigger of their seizures (e.g., Fisher et al., 2000) and the mechanisms by which stress affects the neuroendocrine and immune systems have been proposed to influence the development and exacerbation of epilepsy at various stages of the disorder (Friedman et al., 2011). For instance, a review of animal work has shown that early life stress can contribute to the development of epilepsy and create an increased vulnerability to seizures through alteration of the brain structure, electrophysiology, neurotransmitter and neuroendocrine function (Koe et al., 2009). The neuroendocrine and immune stress responses could also exacerbate the neural damage following an aetiological event, such as traumatic brain injury or an isolated or provoked seizure, which could further contribute to the process of epileptogenesis (Friedman et al., 2011). Finally, by affecting neuronal excitability, stress could also exacerbate the frequency and severity of spontaneous seizures (Friedman et al., 2011).

The effects of stress on PNES are even more notable, as PNES are by definition related to psychological stress factors and the seizures are considered to be behavioural or dissociative responses to emotional, physiological or social distress (Bowman, 2006; Reuber & Mayor, 2012). The development of PNES has been associated with adverse life events (Binzer et al., 2004). Stress and psychophysiological arousal have further been suggested as factors capable of triggering individual seizures (Goldstein & Mellers, 2006). Stress may therefore be both a risk factor for the development of epilepsy and PNES, as well as a trigger

affecting the occurrence and severity of seizures in individuals with existing seizure disorders.

1.5 Aims

The overall aims of this PhD project are to explore the relationships between stress and epileptic and psychogenic non-epileptic seizures and to develop and pilot-test a self-help stress management intervention for patients with seizures. In this thesis, I present two studies that were designed to achieve these aims. The project has a number of specific objectives, as outlined below:

1.5.1 Primary Aims

1.) To provide a narrative literature review of the relationship between stress and epileptic and psychogenic non-epileptic seizures in adults with established seizure disorders

2.) To describe diurnal patterns of psychological and physiological measures of stress in patients with epilepsy and patients with PNES, and explore their relationships to each other and to seizure occurrence

3.) To investigate implicit attentional responses to stress-related stimuli in patients with epilepsy and patients with PNES, compared to healthy volunteers, and to explore their associations to physiological stress measures

4.) To develop a self-help stress management intervention for patients with seizures and assess its feasibility and acceptability in a pilot study of a randomised controlled trial

1.5.2 Secondary Aims

5.) To explore moderating factors of the implicit attentional responses

6.) To test whether the implicit cognitive and/or physiological stress responses can be altered by a self-affirmation intervention

7.) To conduct a preliminary evaluation of the self-help stress management intervention in reducing stress, seizure frequency, anxiety and depression, and improving quality of life in patients with epilepsy and patients with PNES, and provide estimates of effect sizes to facilitate sample size calculations for future RCTs

2. CHAPTER 2

The Role of Stress as a Trigger for Epileptic and Psychogenic Non-Epileptic Seizures: A Narrative Review of Evidence from Human and Animal Studies and Psychological Interventions

Several previous reviews have focused on the role of early life stress and stress in adulthood in epileptogenesis, and the development of PNES. This narrative review concentrates on the relationship between stress in adulthood and seizures in people with established seizure disorders. Taking into an account the different perspectives on stress, both subjective and objective evidence for the relationship between stress and seizures will be reviewed, using human studies of perceived psychological stress and stressful life events, as well as physiological findings from animal and human studies of epilepsy and PNES. Additional evidence from psychological interventions will also be presented and the potential for development of new interventions will be discussed.

2.1 Psychological Stress, Coping and Seizures

Psychological models of stress emphasise the role of the subjective interpretation of a stimulus or an event. According to the dominant model of stress developed by (Lazarus & Folkman, 1984), the stress process consists of four stages: stimulus presentation, primary appraisal, secondary appraisal and the stress reaction. If the stimulus is appraised as threatening (primary appraisal), and the individual's coping resources are appraised as insufficient (secondary appraisal), the individual responds with a stress reaction. This involves negative emotional responses (feeling tense, nervous, irritable or upset), as well as other behavioural reactions, such as changed sleeping or dietary habits (Lazarus, 1993).

Encountering a stressful situation requires emotional, cognitive and behavioural efforts, generally referred to as 'coping'. According to Lazarus and Folkman, there are two broad types of coping, (1) emotion-focused coping, typically directed at regulating the distressing emotions and changing the way the individual attends to and interprets the experience, and (2) problem-focused coping, which involves efforts to take actions to change or improve the situation (Lazarus & Folkman, 1984). The evidence for whether people's perceptions, coping and reactions to stress may have an effect on the occurrence of seizures is discussed below.

2.1.1 Psychological Stress and Epileptic Seizures

2.1.1.1 Self-report studies

There is overwhelming evidence from patient self-reports suggesting that stress is most commonly perceived as a trigger of seizures. Hayden et al. surveyed over 500 patients with epilepsy and found that the aspect people found most worrying about their condition was the unpredictability and lack of control over their seizures. When asked about the predictability of their seizures, 59% of patients believed that stress was related to seizure frequency and 41.2% further independently identified stress as the main factor that increases the likelihood of a seizure (1992). The trend of reporting stress as the main seizure precipitant was later confirmed across large numbers of patients of different nationalities and with various epilepsy syndromes (Hart & Shorvon, 1995; Nakken et al., 2005).

One study pointed out a potential issue common to all of the above studies. Apart from stress, factors including lack of sleep and tiredness are also often reported as seizure precipitants (Frucht et al., 2000). Frucht et al. (2000) found that stress, which was identified as the main precipitant by 30% of the 400 participants, was significantly positively correlated with fatigue and sleep deprivation, forming a cluster of precipitants that may interact to produce the effect on seizures. However, a later study by Haut and colleagues demonstrated

that stress is frequently reported independently of other factors. In their study, 64% of the 89 patients who participated in the study believed that stress was related to at least some of their seizures and this belief was not significantly associated with sleep deprivation (Haut et al., 2003).

Further supporting evidence comes from interview studies. A semi-structured interview study found that out of 100 participants, the majority stated stress or feeling anxious, worried and tense as the main precipitating factors, both in response to open (53%) and closed questions (66%) (Spector et al., 2000). Another interview study asked young patients and their carers about seizure precipitation and found that stress (described as feeling worried, upset, angry, anxious or excited) was the most frequently reported precipitant by both groups (Cull et al., 1996). Moreover, although there was a rather poor agreement between the patients and carers on all other questions, there was a high correspondence for stress as a precipitant.

Another study, which showed that most patients also reported stress as a trigger (55.9%), also highlighted a problem with the retrospective nature of patient self-reports that undermines the reliability and the potential predictive value of the findings (Pinikahana & Dono, 2009). While 86.9% of patients reported they were aware of experiencing initial symptoms and seizure triggers, only 63.6% stated they were able to tell that they were going to have a seizure. This suggests that patients may only recognise or assume what the precipitating event was after the seizure.

A major limitation of the self-report studies is the lack of a clear definition and a standardised, validated assessment of the self-perceived ‘stress’ or its temporal characteristics in relation to seizures. Furthermore, the retrospective nature and cross-sectional design of most of the studies do not allow any conclusions about the actual temporal or causal link between stress and seizure occurrence.

One of the few studies with a longitudinal design that used a validated stress scale showed that stress, measured by the Perceived Stress Scale (PSS) (Cohen et al., 1983), anxiety and depression were all significant predictors of self-reported seizure frequency (Thapar et al., 2009). This provides support for the idea that stress can trigger seizures, but also draws attention to the role of comorbid psychiatric disorders in the relationship between stress and seizures. Another study also found that reporting stress as a seizure precipitant was significantly related to scores on an anxiety scale (Sperling et al., 2008). Depression and anxiety are common comorbidities of epilepsy and there is a complex, bidirectional relationship among the disorders (Kanner, 2009). While epilepsy increases the risk for depression and anxiety, the history of a psychiatric disorder has been found to double the risk for developing epilepsy (Hitiris et al., 2007). There could be a common mechanism underlying the psychiatric disorders, stress and epilepsy that may be involved in triggering seizures. Whether there are physiological links between self-perceived stress and epileptic seizures or not, this perception could have important implications for seizure management and people's quality of life.

2.1.1.2 Prospective diary studies

Although there is compelling evidence from the self-report research, prospective studies of stress and seizures yielded more controversial findings. Analysis of patients' diary data showed that higher levels of stress and anxiety were associated with a higher risk of having a seizure the next day (Haut et al., 2007). Furthermore, higher levels of stress and anxiety were also related to a greater likelihood of a positive seizure prediction. This study does, however, have several limitations. Firstly, stress and anxiety were not defined or assessed by a standardised scale and the measures were only taken once a day, which may not be representative of the levels over the whole day. Secondly, the paper diaries used in the

study are rather unreliable as they allow for retrospective recording and bias in responding (Litt & Krieger, 2007).

Haut et al. later conducted a similar study using a more reliable method of recording through electronic diaries that enabled time tracking to prevent retrospective filling (Haut et al., 2012). Patients were asked to make recordings twice a day and stress was measured both by a self-rating scale and the PSS. In addition, the study also investigated mood and premonitory symptoms, or so-called prodromal states. Epileptic prodromes comprise states and sensations that precede seizures for a prolonged period of time and include disturbances in behaviour, mood or sensation (Mormann & Lehnertz, 2013). Haut et al.'s (2012) study found that the perceived stress levels were not associated with an increased risk of seizures in the following 12 hours, a finding that directly contradicts the results of the earlier study by the same author (Haut et al., 2007). Increased seizure risk was, however, significantly associated with lower mood and higher number of identified premonitory symptoms (Haut et al., 2012).

It seems plausible that there is a relationship between the premonitory symptoms, mood and stress. Haut et al. (2007) found a correlation between stress and positive self-prediction of seizures which could suggest that patients either based their predictions on the awareness of stress being a potential trigger or they may have misinterpreted the premonitory sensations related to a forthcoming seizure as feeling 'stressed', a hypothesis that is supported by the study of Haut et al. (2012). When stress and the prodromal states were assessed separately, prodromes were shown to have a better predictive potential than stress levels indicated by the self-report and the PSS scales. The relationship between prodromal states, stress and other precipitants is nevertheless complex (Haut et al., 2012), and there is a degree of overlap. Furthermore, the diary studies are limited by possible inaccuracy of

seizure reporting. The evidence from these few prospective studies therefore remains inconclusive.

2.1.1.3 Stressful life events

A small body of evidence comes from studies on the impact of environmental stressors on seizure occurrence. There is evidence that external stressors can trigger seizures in people with no previous seizure history (Moshe et al., 2008). The observation that stressors can have epileptogenic effects suggests that they could also affect the frequency of seizures in individuals with existing epilepsy.

Neufeld et al. investigated frequency of seizures during the Persian Gulf War in 1991 (Neufeld et al., 1994). Out of 100 Israelis living in the area, 82 reported experiencing stress during the war period but only 8 reported an increased frequency of seizures. The authors conclude that there may be a weak relationship between stressful events and seizures. Another study examined effects of the experience of an earthquake in Seattle in 2001 and reported that experiencing the earthquake precipitated a seizure within 24 h after the event in 11.5% of patients (Watson et al., 2002). The subjective perceptions of the event as stressful were, however, not assessed. Both studies are limited considerably by its design based on retrospective self-report.

In a prospective study, analysis of diaries from 46 patients showed stressful events to be significantly associated with increased seizure frequency in five participants, but the events were also significantly associated with decreased seizure frequency in two patients (Neugebauer et al., 1994). More compelling evidence for the association was obtained in a controlled study on the effects of a flood evacuation in the Netherlands in 1995 (Swinkels et al., 1998). Swinkels et al. (1998) compared the frequency of seizures from medical records or seizure diaries of a group of 30 evacuees and 30 control patients. The two groups differed significantly in the degree of change of seizure frequency from pre-evacuation period to the

period during evacuation and shortly after, with eight evacuees as opposed to only one control patient showing an increase in seizure frequency. In a follow-up questionnaire, 70% of the evacuees stated that they experienced triggering factors during the evacuation and the majority (91.9%) reported stress being one of them. However, of the evacuees with a change in seizure frequency, only three reported experiencing stress as a trigger.

Although the results show a rather weak relationship, external stress does seem to play a role in seizure frequency - at least in a certain proportion of individuals. There are likely to be important differences in people's subjective appraisal of experiences, which may influence their perception of how stressful a particular event is (for instance, early life and previous illness experiences or mitigating factors during exposure to the acute stressor). There is initial evidence suggesting that people with temporal lobe epilepsy who report experiencing emotional seizure triggers show attention bias toward threat, as demonstrated in an emotional Stroop test and a dot detection paradigm (Lanteaume et al., 2009). The issue is complicated by the fact that stressful experiences may be associated with other potentially seizure-precipitating factors (such as sleep withdrawal). Unfortunately, such possible confounding factors were not prospectively assessed in any of the studies.

2.1.2 Psychological Stress and Psychogenic Non-epileptic Seizures

2.1.2.1 Stressful life events, stress appraisal and coping

While a number of studies focussed on the role of childhood trauma in PNES, fewer studies have looked at the role of other stressful life events and stress in adulthood, and the effects of stress on the occurrence of seizures (Tojek et al., 2000).

Self-report studies of life events suggest that patients with PNES experience more stressful life events than healthy individuals (Frances et al., 1999; Testa et al., 2012) and those with epilepsy (Tojek et al., 2000). In a study that compared the two seizure disorders,

patients with PNES reported higher frequency of stressful life events and rated the events as more stressful than patients with epilepsy (Tojek et al., 2000). Patients with PNES were also found to be subjectively more distressed by negative life events than patients with epilepsy in a study by Testa et al., (2012), although both groups of patients reported an equal number of stressful events.

Frances et al. (1999) suggested that both patients with epilepsy and PNES experience life as more stressful than healthy individuals. However, while the experience of patients with epilepsy may be based on realistic perceptions and concerns related to the unpredictable and disabling nature of their condition and the associated constraints, patients with PNES may have more unrealistic perceptions of situations as threatening and underestimate their coping resources or use maladaptive coping techniques. This may be a consequence of their difficult or traumatic experiences and dysfunctional family environment (Frances et al., 1999). Patients with PNES have indeed been shown to use avoidant coping strategies (Goldstein & Mellers, 2006; Frances et al., 1999), engage in ruminative thinking about their stressful life experiences (Tojek et al., 2000) and use less proactive coping and planning (Testa et al., 2012). In fact, the seizures in patients with PNES can be considered a manifestation of the avoidant coping behaviour and a means to escape or avoid emotional distress. Goldstein & Mellers (2006) explored whether PNES are triggered by stress or anxiety and found that patients with PNES self-reported a higher number of somatic symptoms of anxiety and autonomic arousal during seizures than patients with epilepsy. The study was nevertheless based on patients' retrospective self-reports and does not provide a direct evidence for the link between stress and PNES.

2.1.2.2 Implicit stress responses

In addition to the self-report studies, Bakvis et al. conducted a series of studies looking at implicit or automatic stress responses. Compared to healthy controls and patients

with epilepsy, patients with PNES showed greater vigilance to socially threatening stimuli, demonstrated by a positive attentional bias towards angry faces presented subliminally in an emotional Stroop test (Bakvis et al., 2009a; Bakvis et al., 2009b). Patients with PNES also showed greater automatic avoidance tendencies in a social approach-avoidance task than healthy individuals (Bakvis et al., 2011). Interestingly, these implicit responses were absent in acute stress conditions induced by the Trier Social Stress Test (Bakvis et al., 2009a; Bakvis et al., 2009b; Bakvis et al., 2011). The finding of greater attentional biases at baseline corresponds with the findings by Roberts et al. In their study, patients with PNES, as well as seizure-free individuals with a high number of post-traumatic symptoms (PTS), reported more emotionally intense responses to neutral and pleasant affective pictures than a group of seizure-free individuals with low PTS symptoms but all groups had similar responses to negative affective pictures (Roberts et al., 2012). Roberts et al. (2012) suggest that patients with PNES may exhibit greater vigilance in 'safe' baseline conditions due to their adverse experiences from the past that conditioned them to be vigilant to potential threats in the environment.

The psychological stress mechanism in patients with PNES, therefore, seems to be characterised by greater appraisal of situations as threatening together with implicit hypervigilance to threat and maladaptive, avoidant coping responses to stressors. This may make this group of patients more vulnerable to stress and its negative effects. However, it remains unclear what role (if any) these stress-related responses play in precipitating individual seizures, as no studies have investigated the direct temporal relationship between stress and non-epileptic seizures.

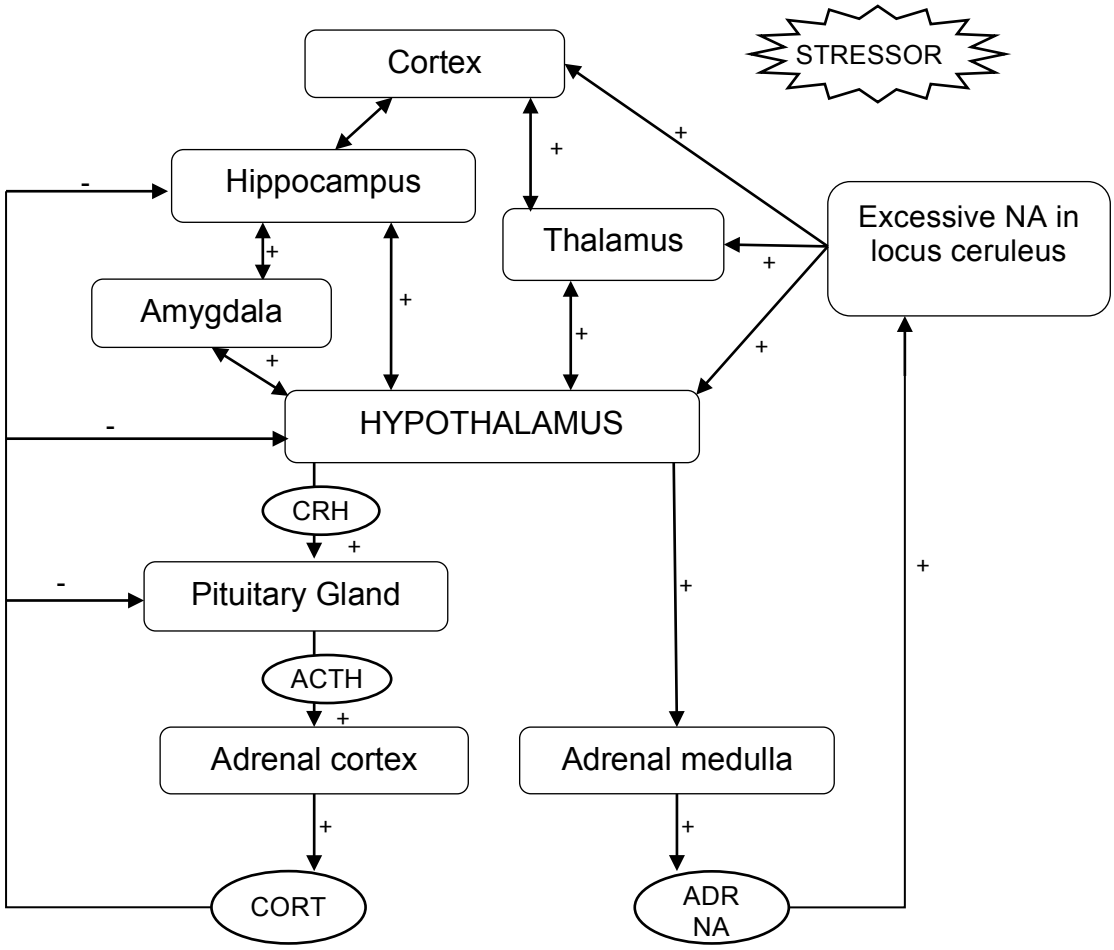
2.2 Physiological Stress and Seizures

The biological stress response is mediated by the neuroendocrine system that initiates activation and subsequent restoration of the organism's functions, in order to adapt to a given stressor (Aldwin, 2000). The two main components involved are the hypothalamic-pituitary-adrenocortical (HPA) axis and the sympathetic-adrenomedullary (SAM) system (Figure 2.1) (Cohen et al., 1995).

2.2.1 The HPA Axis

The activity of the HPA axis is characterised by a three-stage hormonal response (see Figure 2.1). During the first 'alarm stage', the hypothalamus increases secretion of corticotropin-releasing hormone (CRH) through a specialised set of neurons in the paraventricular nucleus (PVN), causing the anterior pituitary gland to release adrenocorticotropic hormone (ACTH), which activates the adrenal cortex to produce corticosteroid hormones (cortisol in humans, corticosterone in animals) (Cohen et al., 1995). After this rapid increase in hormonal secretion, the corticosteroid hormones help to adapt to the stressor and restore the state of the organism during the 'resistance stage'. If exposed to a severe or chronic stressor, the HPA adaptive capacity is impaired and the organism reaches 'exhaustion stage' in which it is no longer able to respond to stressors (Cohen et al., 1995).

Figure 2.1. *The physiological response to stress by the HPA axis and the SAM system and the positive and negative feedback loops.*



2.2.2 HPA Axis Stress Mediators in Epilepsy

As the HPA stress mediators affect excitatory and inhibitory processes in brain areas that are commonly involved in epilepsy, such as the limbic structures (see Figure 2.1), they have been suggested to have the capacity both to facilitate and suppress seizure activity (Myslobodsky, 1993). A few reviews (Joels, 2009; Lai & Trimble, 1997) have summarised the effects of the different HPA hormones. CRH has been found to increase excitability in the hippocampus by, for example, increasing the frequency of spontaneous excitatory postsynaptic currents and the number of action potentials per burst (Hollrigel et al., 1998). CRH can also facilitate inhibition of the hippocampus through suppression of the activity of

N-methyl-D-asparate (NMDA) (Sheng et al., 2008). Similarly, corticosteroid hormones can also enhance excitatory and inhibitory transmission. Corticosterone has been found to increase the amplitude of calcium currents in cells of the CA1 hippocampal area, allowing for greater Calcium influx and thus increased excitation of the CA1 cells (Chameau et al., 2007). It has also been shown to decrease the neuronal firing rate mediated by serotonin receptors (Beck et al., 1996). The effects of ACTH, on the other hand, seem predominantly anticonvulsant (Croiset & Dewied, 1992). The following paragraphs will focus especially on experimental studies of those hormones that could play a role in the exacerbation of seizures.

2.2.2.1 Animal models of epilepsy

The effects of the HPA stress hormones on seizures have not been studied experimentally in humans and most evidence therefore comes from animal studies. In order to gain a better understanding of the findings, it is important to distinguish between the different animal models of epilepsy and what they represent. Models of epilepsy can be divided into 'acute' and 'chronic' models (Loescher, 2002). In acute models, a seizure is induced in a healthy animal by electrical or chemical stimulation and these models therefore provide insights into the process of epileptogenesis.

In chronic models of epilepsy, animals are made epileptic by chemical or electrical induction of status epilepticus (SE) which is a state of a persistent seizure after which recurrent seizures usually occur, or by kindling, which involves initial stimulation by electrical or chemical doses that are not acutely ictogenic but eventually induce seizures after repeated stimulation and may lead to development of spontaneous seizures in the fully-kindled state. Alternatively, mutant animals with inborn epilepsy are used (Loescher, 2002). The chronic models represent fully developed epilepsy and enable investigation of the process of ictogenesis. In stress research, the exogenous administration of a stress mediator

(e.g., corticosterone) or endogenous sources of stress mediators via exposure to a naturalistic stressor (e.g., water immersion) are used in both types of models (Joels, 2009).

Most animal studies of stress and epilepsy focus on the potential of acute and chronic exposure to stress or stress hormones to trigger epilepsy in non-epileptic animals. The main findings have been summarised by recent reviews (Joels, 2009) and as the focus of this review is on the process of ictogenesis, the studies of epileptogenetic effects of stress will not be further discussed here.

2.2.2.2 Ictogenesis in genetic models

One study investigated the effects of exogenous corticosterone administration in a genetic rat model of absence epilepsy, characterised by non-convulsive seizures manifesting as bursts of spike-wave discharges (SWD) detectable by EEG (Schridde & van Luijtelaar, 2004). The study found a 327% increase in the SWD following corticosterone administration.

A study of the effects of a natural stressor on the model of absence epilepsy presented a conflicting finding (Tolmacheva & van Luijtelaar, 2007). Rats exposed to an acute stress in the form of a foot shock showed no change in the SWD following a single shock. However, there was an aggravated increase in SWD over three days of repeated stressor exposure. This suggests possible effects of repeated but not acute stressor on the occurrence of seizures.

However, Tolmacheva et al. later demonstrated that there may be an effect of acute stress which follows a gradual, time-dependent pattern (Tolmacheva et al., 2012). In their study of foot shock in the model of absence epilepsy, the SWD were initially suppressed by the stressor but there was a significant increase within an hour after the exposure. A second experiment confirmed the findings by Tolmacheva & van Luijtelaar (2007) and showed that rats exposed to the foot shock stress on three consecutive days, showed an aggravation of the SWDs, with the SWDs also increasing in anticipation of the foot shock on day 3.

The effects of acute stress were further supported by a study that tested the effects of three different types of stressors using the EL mouse, a genetic model of focal epilepsy (Forcelli et al., 2007). While mice exposed to tail suspension handling exhibited a significant increase in epileptiform EEG activity, no such increase was found for foot shock or a social intrusion stressor. Similar results were obtained by a study that investigated the effects of various environmental factors on seizure susceptibility (Todorova et al., 1999). The study found that handling of mice involving tail suspension induced seizures and further increased seizure susceptibility after one week.

2.2.2.3 Ictogenesis in post-status epilepticus models

There is also limited evidence from the post-status epilepticus model of epilepsy. A recent study examined the effects of repeated corticosterone administration in epileptic mice that had previously been chemically induced to go into SE and had subsequently developed spontaneous seizures (Castro et al., 2012). The corticosterone administration significantly increased the frequency and duration of epileptiform EEG activity, compared to control treatment. However, corticosterone had no effects on the frequency of overt seizures. Nevertheless, the study supports the findings of the previous studies, suggesting that repeated stress exposure may increase seizure vulnerability.

Unfortunately, there is a lack of studies replicating these findings. Another study of the post-SE model found elevated levels of endogenous corticosterone in rats with epilepsy induced by the SE that was not related to the occurrence of spontaneous seizures but was correlated with the presence and severity of behaviour interpreted as depressive (Mazarati et al., 2008). This corresponds with the findings from human clinical studies and suggests a possible mediation of depression and other psychiatric disorders.

2.2.3 HPA Axis Stress Mediators in PNES

The role of HPA axis stress mediators has not been investigated directly in relation to the occurrence of PNES. Nevertheless, there is evidence suggesting the involvement of the HPA axis in the pathology of PNES. Patients with PNES, and especially those with a history of sexual abuse, have been found to have higher levels of cortisol at baseline than healthy individuals (Bakvis et al., 2010). Cortisol levels of patients with PNES were also elevated throughout the avoidance task in the study of automatic avoidance (Bakvis et al., 2011). Furthermore, the levels of baseline cortisol in patients with PNES were also positively correlated to the attentional bias to threatening social stimuli (Bakvis et al., 2009a). The cortisol response to the stressful task in the study by Bakvis et al. (2009b) was, however, not significantly different from that of healthy subjects. These findings seem to support the data from studies of psychological stress, suggesting that patients with PNES may experience a state of cognitive hypervigilance and physiological hyperarousal at baseline. Such elevated cortisol levels at baseline coupled with blunted cortisol response to an acute stressor, which was found in patients with PNES, were also found in patients anxiety and panic disorders (Petrowski et al., 2013) and may reflect an impairment of the adaptive capacity of the HPA axis (or the so-called 'exhaustion stage'), resulting from chronic stress exposure.

2.2.4 The SAM System

While most research on stress and epilepsy focuses on the HPA axis mechanisms (Joels, 2009), less attention has been paid to the role of the SAM system. The SAM system responds to stress via the two branches of the autonomic nervous system (ANS), the sympathetic nervous system (SNS) and the parasympathetic nervous system (PNS) that regulate the homeostatic function of the organism by a mutually antagonistic influence on internal organs (Porges, 1992). Exposure to a stressful stimulus activates the hypothalamus

and the pituitary gland to release hormones that cause the adrenal medulla to secrete adrenaline (ADR) and noradrenaline (NA) (see Figure 2.1). These hormones activate the SNS causing arousal and mobilising the organism to prepare for appropriate action (Aldwin, 2000). This is manifested by an increased heart rate, blood pressure or sweating (Cohen et al., 1995). Porges (1992) argued that the PNS may play an even more important role in the stress reaction. While the SNS is activated in response to external demands, PNS activation, mediated mainly by the tenth cranial nerve, the vagus nerve, is responsible for the on going regulatory and feedback processes. In response to stress, the PNS activation (tone) is decreased and the homeostasis of the organism is disrupted. This can even occur in the absence of SNS activation (Porges, 1992).

2.2.4.1 Patterns of SAM system activity in epilepsy

Seizure (ictal) activity often affects parts of the brain involved in activation of the ANS, such as the limbic system or medulla (Nouri, 2011). As a result, ictal activity can be associated with changes in the SNS and PNS tone that can be detected from the pattern of heart rate monitored by electrocardiogram (ECG) (Nouri, 2011). Since changes of the SNS and PNS tone are part of the body's reaction to a potential stressor, it can be hypothesised that identifying the pattern characteristic of the stress response, i.e., an increased SNS and suppressed PNS tone, during the pre-ictal period, could serve as an evidence for the role of stress in seizure precipitation.

This was indeed found in a study that assessed the PNS and SNS input to the heart by inspecting parameters of the heart rate variability (HRV) calculated from ECG recordings of six patients with epilepsy (Jeppesen et al., 2010). The results showed suppressed PNS activity 10 s before the seizure onset. Similarly, a rapid reduction of the PNS tone was found within 30 s before seizure onset (Novak et al., 1999).

Additionally, a recent study identified significantly reduced HRV during the interictal, resting period, in a group of patients with epilepsy, indicating an overall reduced PNS tone (Ponnusamy et al., 2011). Significantly reduced PNS and increased SNS tone were also found during seizures in patients with epilepsy, but not in patients with PNES (Ponnusamy et al., 2012).

2.2.4.2 Patterns of SAM system activity in PNES

Similar to the limited evidence on the role of HPA axis in PNES, there are no studies exploring the direct links between autonomic stress responses and the occurrence of non-epileptic seizures. There is evidence for reduced HRV in patients with PNES at baseline in the study of automatic avoidance (Bakvis et al., 2010) and HRV was also significantly lower in patients with PNES compared to healthy controls in the study by Bakvis et al. (2009a). In addition, the study by Ponnusamy et al. (2011) showed reduced resting HRV in both patients with epilepsy and PNES.

According to Porges (1992), such a chronically reduced PNS activation found both in patients with epilepsy and PNES could be a manifestation of an impaired ability of the PNS to respond to external stressors and thus greater stress vulnerability. Indeed, decreased HRV has been associated with a range of psychiatric disorders, including post-traumatic stress disorder (Cohen et al., 1999).

2.3 Psychological Interventions

2.3.1 Non-Pharmacological Interventions for Epilepsy

Better understanding, recognition and control of seizure triggers might not only reduce the unpredictability of seizure events, but could also help prevent or even eliminate seizure occurrence (Pinikahana & Dono, 2009). Wolf (2002) proposed a distinction of

interventions into: (1) non-specific seizure prevention, based on identification of factors that facilitate seizure occurrence and development of strategies to combat or prevent them, including a hygienic lifestyle and improvement of coping strategies, (2) specific seizure prevention, used for reflex epilepsy where seizures are consistently triggered by a specific stimulus and can therefore, be prevented by avoidance or other specific techniques targeting the particular trigger, and (3) specific and non-specific seizure arrest. The seizure arrest interventions are based on the recognition of initial warning signs and auras which are the altered sensations immediately preceding seizures, considered part of the actual seizure (Mormann & Lehnertz, 2013), and subsequent interruption of the progressing seizure (Wolf, 2002).

As the seizure arrest techniques involve stopping of a seizure that has already been triggered, they are not directly relevant to the question of stress and seizure precipitation. Similarly, the specific seizure prevention methods only pertain to reflex epilepsy, which is a very rare type of epilepsy. These techniques have recently been discussed elsewhere (Wolf et al., 2013) and will therefore not be considered here. Instead, the focus will be on reviewing the non-specific seizure prevention methods, based on the assumption that interventions targeting stress as a seizure precipitant that show an improvement in seizure control or reduction could serve as an additional evidence for the role of stress in triggering seizures.

2.3.1.1 Educational and self-management interventions

One of the successful educational programmes is the MOSES (Modular Service Package Epilepsy) programme, comprising of nine modules designed to improve knowledge and coping with epilepsy (May & Pfafflin, 2002). A controlled study showed that patients who participated in the course significantly improved their knowledge and coping skills, and reported greater reduction in seizure frequency, measured by a seizure frequency scale, compared to a control group. Although the programme did not directly target stress, one of its

modules focused on the psychological aspects of epilepsy and patients subsequently improved coping with emotions.

Schmid-Schonbein developed and tested a psychological treatment method based on seizure-control, consisting of identification of seizure-facilitating factors and development of counter-measures and coping strategies under the guidance of a therapist (Schmid-Schonbein, 1998). Their study of 16 patients found that psychological stress was identified as the main precipitant in 11 patients. After 3 – 30 months of the therapy, 68% of patients self-reported reduction in seizure frequency.

An intervention that recognised and directly targeted stress as a potential seizure precipitant is the on-line self-management programme WebEase (Epilepsy Awareness, Support, and Education) (Dilorio et al., 2011). This interactive programme contains three modules that address medication, stress and sleep management. A recent study showed a trend toward significance for perceived stress in a group of people with epilepsy who completed all or some of the on-line modules (Dilorio et al., 2011). Unfortunately, the study did not assess the effects on seizure frequency.

2.3.1.2 Andrews/Reiter method

The Andrews/Reiter method is a behavioural technique combining aspects of both the seizure prevention and seizure arrest treatment methods. It consists of techniques aimed at interrupting auras, as well as learning to identify and cope with seizure-provoking situations, in particular emotional stress (Elsas et al., 2011). Michaelis et al. analysed medical diary records of 60 patients who underwent a three-day Andrews/Reiter therapist-guided intervention followed by daily practice of relaxation, breathing, journaling of emotional stressors and other seizure triggers, and practicing strategies to cope with them (Michaelis et al., 2012). Stress was identified as the most common seizure precipitant by 40% of patients and there was more than 50% reduction of seizure frequency in 50% of the patients from

baseline to the last months of the treatment. The retrospective, self-report design of the study, as well as the fact that the exact length of the therapy was not specified are, however, major limitations of the study.

2.3.1.3 Yoga and biofeedback

Practicing behavioural techniques based on biofeedback and relaxation has also been suggested as a therapeutic method for epilepsy. These techniques enable patients to become aware of and subsequently deliberately control autonomic physiological processes that may be involved in triggering and propagation of seizures (Wolf, 2002).

A theory linking the mechanisms of yoga, stress and seizures has recently been proposed (Streeter et al., 2012). Streeter et al. (2012) pointed out that yoga, a traditional Indian technique comprising of breathing exercises, postures and meditation, could influence both the SAM and the HPA mechanisms involved in stress and thus provide for potential stress and seizure reduction. Breathing, which is one of the main ANS functions involving the SNS and PNS pathways, is deliberately controlled during yoga and could therefore influence the ANS activity. It has indeed been demonstrated that yoga can increase the HRV and the PNS tone (Khattab et al., 2007), as well as to reduce levels of cortisol (Kamei et al., 2000).

Evidence from studies of yoga in epilepsy seems to support this hypothesis. A controlled study compared a group of patients treated by yoga with two control groups, one performing exercises mimicking yoga, and the other being followed-up without any treatment or exercise (Panjwani et al., 1996). The study found that 4 of the 10 participants in the yoga group became seizure-free, compared to none in the two control groups, and 9 of the patients in yoga group achieved more than a 50% reduction of seizures, compared to one in the control conditions. Similarly, a study of the effects of yoga and acceptance commitment therapy (ACT) found that yoga significantly reduced seizure frequency, with 50% of patients

becoming seizure-free (Lundgren et al., 2008). However, similar results were found also for ACT, suggesting that the effects may not have been specific to yoga, but rather based on a treatment mechanism common to both types of therapy.

One of the biofeedback methods targeting the ANS pathways through biofeedback from measurement of the galvanic skin response (GSR) may also be of interest. GSR reflects the SNS influence on sweat glands, indicating emotional and attentional arousal (Nagai, 2011). Learning to deliberately alter the GSR (and thus the SNS tone) can reduce cortical potentials that contribute to the regulation of cortical excitability, in particular, the excitation associated with initial orienting response to stimuli (Nagai, 2011). This mechanism could affect both the ANS-mediated stress response and seizures. Indeed, Nagai et al. found that GSR biofeedback training resulted in more than 50% seizure reduction in 6 out of 10 patients with epilepsy (Nagai et al., 2004). The GSR biofeedback has also been found effective as an intervention for highly stressed individuals (Khanna et al., 2007). As the GSR biofeedback is a relatively new method, its mechanisms still remain to be further clarified.

It is conceivable that the effectiveness of vagus nerve stimulation (VNS) therapy is also, at least in part, mediated by alterations of ANS activation, although the exact mechanism of VNS is not yet fully understood. The treatment involves implantation of a stimulator into the chest cavity, which generates electrical signals that are carried by electrodes to stimulate the vagus nerve (Schachter & Saper, 1998). VNS has not only been shown to be effective for refractory epilepsy, but has also been used to treat depression (Bonaz et al., 2013). Animal and human studies suggest that VNS is associated with alterations in the activity of the structures of the central autonomic system, which are also involved in the stress response (Henry, 2002).

2.3.2 Psychological Interventions for PNES

Although psychological treatment is accepted as the treatment of choice for PNES (Reuber et al., 2005), there is only limited evidence for the effectiveness of different psychological treatment approaches, and even less so in the relation to stress and seizures. There is currently no standardised treatment protocol for PNES and various types of therapy have been used, including cognitive behavioural therapy (CBT), group and family therapies, eye movement desensitisation and reprocessing (EMDR), neurofeedback or hypnosis; however, there is a lack of randomised controlled trials (RCT) assessing their outcomes (Martlew et al., 2007).

In an uncontrolled study of an in-patient treatment programme based on cognitive behavioural techniques, which included strategies for stress management and improvement of coping skills, 81% of 16 patients who took part in the study have been shown to achieve over 50% seizure reduction and there was an improvement in coping skills and psychiatric symptoms (Kuyk et al., 2008). Two methodologically stronger studies showed support for the effectiveness of CBT. LaFrance et al. developed a CBT programme for PNES, based on modifying cognitive distortions and identifying seizure triggers and demonstrated seizure cessation in 11 out of 17 patients in a small pilot RCT (LaFrance et al., 2009). The therapy included examination of external stressors and internal seizure triggers and development of relaxation skills. The CBT approach has also been shown to be effective for seizure reduction and health service use in a larger pilot RCT (Goldstein et al., 2010).

There is also some evidence for beneficial effects of therapies with psychodynamic focus. An uncontrolled study of long-term effects of a brief augmented psychodynamic interpersonal therapy, which covers identification of stressors, stress reduction techniques and improvement of coping behaviours, found seizure cessation in 25.5% of the 47 patients and further 40% of patients achieved over 50% seizure reduction. There was also a

considerable reduction in health care utilisation (Mayor et al., 2010). Another uncontrolled pilot study assessed a group therapy with a psychodynamic focus emphasising the development of coping strategies including exploration of seizure precipitants (Barry et al., 2008). This study found improvement on all the outcome measures, including seizure frequency, severity of somatic symptoms and depression (Barry et al., 2008).

These studies are, however, methodologically weak and no research assessing stress reduction as an outcome measure have been conducted to date. There is a clear need for more RCTs in the future (Martlew et al., 2007).

2.4 Self-Affirmation as an Intervention for Stress and Seizures

2.4.1 Self-Affirmation Theory

Self-affirmation is a psychological mechanism that may be relevant to the management of the damaging effects of stress. According to self-affirmation theory, the individual's self-system comprises different domains that are important to them (e.g., roles, goals, values or belief systems). One function of this self-system is to maintain an overall positive self-image and sense of 'self-integrity' or perception of oneself as adaptively and morally adequate (Steele, 1988). When an important part of the self-system is threatened, people are motivated to respond in ways that restore their sense of self-integrity. These responses can often be defensive and maladaptive; for example, smokers may ignore or denigrate threatening health messages, instead of using the information to attempt to quit (Sherman & Cohen, 2006). Self-affirmation is a mechanism that can reduce the defensive responses to threat. It is an alternative way of restoring global self-integrity through affirmation of important aspects of the self-system other than the one under threat, for example, reflecting upon an important personal value or characteristic (Steele, 1988).

Self-affirmation has been found to be effective in a range of cognitive and social domains and there is a growing evidence for its beneficial effects on health (Harris & Epton, 2009; Sherman & Cohen, 2006). Self-affirmed individuals have been found to be more accepting of threatening health information (Armitage et al., 2008) and to express more intention to change their risky health behaviours (Harris & Napper, 2005).

2.4.2 Self-affirmation and Stress Management

Importantly, self-affirmation has been shown to buffer psychological and physiological responses to stress. Experimental studies have shown that self-affirmed participants had significantly lower cortisol levels in response to a laboratory stress task than a group of controls (Creswell et al., 2005) and self-affirmation has also been found to attenuate the epinephrine (adrenaline) response to an academic stressor (Sherman et al., 2009). Self-affirmation also buffered psychological responses to stress by reducing ruminative thinking that can further exacerbate the effects of stress (Sherman et al., 2009). Self-affirmation therefore seems to be a promising technique that could have the potential to improve the effectiveness of stress management interventions. Indeed, it has been found that patients with end-stage renal disease who were given a self-affirming intervention involving writing about their most important value reported significantly reduced perceptions of stress (Estevez, 2002).

2.5 Questions Arising From the Literature Review

The reviewed studies have many limitations and raise issues that will require further clarification. The current evidence suggests that stress may exacerbate the epileptiform activity (or its effects) in the brain, and play a role in triggering overt spontaneous seizures at least in a certain proportion of individuals with epilepsy. However, factors including the

subjective perceptions of stress, and individual differences in psychological and physiological vulnerability, and resilience to stress in people with epilepsy deserve further investigation.

Stress appraisal and the cognitive, physiological and coping stress responses also seem to play an important role in PNES. It is conceivable that the experience of stress could precipitate PNES, however, no studies have examined the relationship directly. It may be the case that repeated stress exposure increases the risk of future stress to precipitate both epileptic and non-epileptic seizures, which are, in turn, associated with a degree of stress and further exacerbate the stress vulnerability. This bidirectional relationship clearly needs to be explored further.

Many of the discussed studies were limited by cross-sectional, retrospective design and reliance on self-reports. Importantly, the experience of 'stress' is complex and multi-faceted, however, very few studies have taken an integrative approach and measured both the psychological and the physiological aspects of stress, and the conclusions that can be drawn from such studies are therefore somewhat incomplete.

The review of evidence from non-pharmacological interventions showed that psychological treatment focused on helping patients to identify seizure-provoking factors, including stress, and to develop strategies better to cope with them was demonstrated to reduce seizures in some individuals. None of these interventions have, however, specifically targeted stress or directly assessed whether the reduced seizure frequency was achieved through stress reduction. The results of the intervention studies therefore suggest a potential for development and empirical evaluation of new non-pharmacological treatment methods targeting stress as a seizure-facilitating factor. Such treatment approaches could incorporate and assess the self-affirmation technique, which has been shown to reduce both psychological and physiological responses to stress.

This thesis therefore sets out further to explore the different components of the stress process, their interactions and their relationships to epileptic and non-epileptic seizure occurrence, using a prospective design and integrating a range of psychological (self-report and implicit) as well as physiological measures of stress. As there is a potential for development of new psychotherapeutic interventions and a lack of randomised controlled trials assessing the outcomes of psychological treatment for seizure disorders, the PhD project also includes the development and pilot evaluation of a new self-help intervention specifically targeting stress in patients with seizures.

3. CHAPTER 3

Study 1a: Exploring the Links between Stress and Epileptic or Psychogenic Non-epileptic Seizures

3.1 Study Introduction

The literature discussed in the literature review (Chapter 2) suggests that many patients with epilepsy believe their seizures are more likely to happen when they are feeling stressed (Nakken et al., 2005). Psychogenic non-epileptic seizures (PNES) are by definition caused by psychological distress and have been interpreted as behavioural responses to overwhelming psychophysiological arousal (Goldstein & Mellers, 2006). However, there is a lack of prospective studies investigating the link between stress and seizure occurrence directly and the temporal relationship between stress and seizures therefore remains unclear. It is conceivable that repeated or chronic stress exposure creates a greater predisposition for further stress experiences to trigger both epileptic seizures and PNES. Such a predisposition could also be affected by the stress associated with seizures themselves.

A number of the studies discussed were limited by their retrospective, self-report design and the few available prospective studies provide rather inconclusive evidence. Furthermore, 'stress' is complex and multifaceted phenomenon comprised of a range of autonomic, endocrine, immune, cognitive, affective and behavioural processes, yet very few studies have measured the different aspects of stress in combination.

This study therefore explored the patterns of physiological stress measures (HRV parameters extracted from video-electroencephalographic/electrocardiographic (video-EEG/ECG) recordings and levels of salivary cortisol) and self-reported measures of

perceived stress across the day and the interrelationships between these measures. The study also prospectively assessed the association between stress and seizures, using both objective measures of physiological stress responses and a self-report measure of subjective psychological stress.

3.2 Study Aims

1. To describe the patterns of the daily self-reported and physiological (cortisol, HRV) measures of stress in patients with epilepsy and patients with PNES.
2. To explore the associations between daily self-report and physiological (HRV, cortisol) measures of stress.
3. To explore the relationship of the daily self-report, HRV and cortisol stress measures to seizure occurrence (number and timing of seizures during video-EEG/ECG).

3.3 Methodology

3.3.1 Participants and Design

The study is a prospective assessment of the daily levels of physiological and psychological stress and their relationship to seizure occurrence in patients undergoing in-patient video-EEG/ECG monitoring. Adult patients with refractory (epileptic or non-epileptic) seizures admitted for diagnostic or pre-surgery video-EEG/ECG monitoring in the video telemetry unit at the Royal Hallamshire Hospital in Sheffield were recruited into the study. The diagnosis (epilepsy or PNES) was confirmed by the analysis of the video-EEG recording of at least one typical seizure by a trained Neurophysiologist. Where no typical seizure was recorded during the video-EEG assessment, a clinical diagnosis was established based on the expert opinion of the patient's Consultant Neurologist and a second opinion

from a Consultant specialised in epilepsy. Patients whose diagnosis of epilepsy or PNES remained uncertain after completion of video-EEG monitoring were excluded from further analyses.

The formal inclusion criteria for the study were as follows:

1. Clinically firm diagnosis of epilepsy (and no additional PNES) or PNES (and no additional epilepsy) supported by two experts in the diagnosis and treatment of patients with seizures.
2. Over the age of 16 years
3. Able to complete the self-report questionnaires without help
4. Able to give informed consent

The formal exclusion criteria for the study were as follows:

1. Patients with possible or definite mixed seizure disorders (epileptic seizures and PNES)
2. People who were unable to give informed consent
3. People who were unable to complete the self-report questionnaires unaided
4. People whose diagnosis remained uncertain

3.3.2 Outcome Measures

3.3.2.1 Baseline measures

3.3.2.1.1 Self-report questionnaires

The validated self-report questionnaires compiled for this study were piloted in the neurology outpatient clinic ($N = 5$) at the Royal Hallamshire Hospital.

3.3.2.1.1.1 Demographic questionnaire

The demographic questionnaire was developed as part of the project to collect information about age, gender, employment status and level of education. Participants who were in full-time education, employed or self-employed were classed as 'economically active', patients who were unemployed, retired or on disability benefits were classed as 'economically inactive'. See Appendix 1 for the full questionnaire.

3.3.2.1.1.2 Perceived Stress Scale – 4 Items (Cohen et al., 1983)

The PSS-4 is a short version of the original PSS-14 developed to measure the degree to which situations in people's lives are perceived as stressful (see Appendix 2). The scale is a global measure of non-specific stress over the course of the past month (e.g., "In the last month, how often have you felt difficulties were piling up so high that you could not overcome them?"), rated on a 5-point scale ("Never", "Almost never", "Sometimes", "Fairly often", "Very often"). Reliability coefficients range between 0.84 and 0.86 for the original PSS-14 and between 0.72 and 0.79 for the reduced 4-item version (Karam et al., 2012). The validity of the PSS-14 is supported by significant correlations ($p < .001$) with the number and impact of stressful life-events. The PSS-4 has been used and validated as a measure of perceived stress in patients with epilepsy (Haut et al., 2012; Thapar et al., 2009). The scale had good internal consistency reliability in the present sample (4 items; alpha = 0.79).

3.3.2.1.1.3 Liverpool Seizure Severity Scale – Revised (Scott-Lennox et al., 2001)

The LSSS-3 is a newly-revised version of the LSSS-2 (Baker et al., 1998). The LSSS-3 is a 12-item inventory designed to quantify the severity of patient's seizures (see Appendix 3). The items are rated on 4 to 6-point scales (e.g., "After my most severe seizures: I always feel sleepy", "I usually feel sleepy", "I sometimes feel sleepy", "I never feel sleepy"). It provides a single-unit weighted scale that measures the severity of the most severe seizures

the patient has experienced during the past 4 weeks. Reliability of the LSSS-3 has been demonstrated (alpha > 0.71) and validity of the scale is supported by correspondence with physician-rated seizure severity (Scott-Lennox et al., 2001). The internal consistency reliability of the LSSS-3 in the sample was good (12 items; alpha = 0.85).

3.3.2.1.1.4 Quality of Life in Newly Diagnosed Epilepsy - 6 Dimensions (Mulhern et al., 2012)

The NEWQOL-6D was used as an epilepsy-specific measure of the health-related quality of life (HRQoL) (see Appendix 4). The NEWQOL-6D assesses the HRQoL on six dimensions, including worry about attacks, depression, memory, concentration, control, and stigma. Each dimension consists of one item with four response levels (e.g., the control dimension item: "How much control do you feel you have over things that happen to you?"; response levels: "I have complete control", "I have some control", "I have little control", "I have no control"). The scoring is based on obtaining a unique health state by combining one level from each of the six dimensions (e.g., state 111111 indicates no problems on any of the six dimensions, while state 444444 indicates serious problems on all six dimensions). A single utility value between 0 (poor health) and 1 (perfect health) can then be derived for each health state based on a formula developed by the authors (Mulhern et al., 2012). The original NEWQOL has acceptable internal consistency reliability (0.58 – 0.97), as well as test-retest reliability (0.76 – 0.91). The measure was also found to have high concurrent validity (0.60 – 0.90) (Abetz et al., 2000).

3.3.2.1.1.5 Life-Orientation Test – Revised (Scheier et al., 1994)

The Life Orientation Test Revised (LOT-R) is a 10-item scale designed to assess generalized optimism (e.g., "In uncertain times, I usually expect the best") (see Appendix 5). The items are rated on a 5-point bipolar scale ("Strongly disagree", "Disagree", "Neutral",

"Agree", "Strongly agree"). Only six items of the questionnaire are scored, four items are filler items. Internal consistency of the scale has been found adequate (alpha = 0.69 – 0.78), as has test-retest reliability (Hirsch et al., 2010; Scheier et al., 1994). Criterion validity of the scale has been supported by significant negative correlation with hopelessness (r = 0.62) and depression (r = 0.60) (Hirsch et al., 2010) and significant positive correlation with life satisfaction (r = 0.45) (Glaesmer et al., 2012). The LOT-R has been used in a number of behavioural, affective and health-related studies (for a review, see Scheier et al., 2010). The internal consistency reliability in the sample was good (6 items; alpha = 0.83).

3.3.2.1.1.6 Spontaneous Self-Affirmation Measure (Harris et al., In preparation)

The SSAM is an instrument under on-going development that has been designed to measure the natural tendency to self-affirm. A short, 15-item, version of the measure was used in the current study (see Appendix 6). This measure consists of two scales, a measure assessing the tendency to engage in positive self-thought (the Habit Index of Positive Thinking; HIPT) and the tendency to self-affirm in the face of threat (the Spontaneous Self-Affirmation Measure; SSAM). The SSAM consists of 10 items (e.g., "When I feel threatened or anxious by people or events I find myself thinking about my values") rated on a 7-point bipolar scale with labelled end-points ("Disagree completely", "Agree completely"). Preliminary evidence showed adequate reliability and validity of the measure and further validation of the measure was part of this study. Internal consistency reliability of the HIPT (5 items; alpha = 0.97) and the SSAM (9 items; alpha = 0.91) in our sample was excellent.

3.3.2.1.1.7 Single-Item Self-Esteem Scale (Robins et al., 2001)

The SISE is a single-item measure of global self-esteem, scored on a 5-point Likert scale (see Appendix 6). The mean test-retest reliability of the scale was 0.78 (Robins et al., 2001). Construct validity has been demonstrated by a number of studies, showing significant

correlations with the Rosenberg Self-esteem Scale, r = 0.72 – 0.76, as well as the Texas Social Behaviour Inventory, r = 0.58 (Robins et al., 2001).

3.3.2.1.1.8 Brief Resilient Coping Scale (Sinclair & Wallston, 2004)

The BRCS is a 4-item measure designed to assess resilient coping, or tendencies to cope with stressful situations in an adaptive manner (e.g., "I believe I can grow in positive ways by dealing with difficult situations"), rated on 5-point bipolar scales with labelled end-points ("Not true of me at all", "Very true of me") (see Appendix 7). The BRSC has been found to have adequate internal consistency reliability (alpha = 0.64 – 0.76) and test-retest reliability (r = 0.71) and has demonstrated sensitivity to changes associated with cognitive-behavioural interventions (Sinclair & Wallston, 2004). The internal consistency reliability in this study was good (4 items; alpha = 0.79).

3.3.2.1.1.9 Neurological Disorders Depression Inventory for Epilepsy (Gilliam et al., 2006)

The NDDI-E is a 6-item inventory developed to detect depression in patients with epilepsy (see Appendix 8). The six items represent common symptoms of depression experienced in the past two weeks that can be differentiated from adverse effects of anti-epileptic drugs (e.g., "Everything is a struggle") (Gilliam et al., 2006). Each item is rated on a 4-point scale ("Always or often", "Sometimes", "Rarely", "Never"). The inventory was found to have internal consistency reliability of 0.85 and test-retest reliability between 0.78 (Gilliam et al., 2006) and 0.82 (Margrove et al., 2011). A score of more than 15 on the NDDI-E had 90% specificity, 81% sensitivity and a predictive value of 0.62 for a diagnosis of major depression (Gilliam et al., 2006). The inventory had good internal consistency reliability in this sample (6 items; alpha = 0.80).

3.3.2.1.1.10 Generalised Anxiety Disorder 7-item Scale (Spitzer et al., 2006)

The GAD-7 assesses anxiety symptoms experienced over the course of the past two weeks (e.g., "Feeling anxious, nervous or on edge") (see Appendix 9). The items are rated on 4-point scales indicating the frequency of experiencing each symptom ("Not at all", "Several days", "Over half the days", "Nearly every day"). Internal consistency reliability of GAD-7 was found to range between 0.86 - 0.91 in both the general population and patients with psychopathology (Dear et al., 2011; Lowe et al., 2008). The scale was found to have test-retest reliability of 0.82 (Delgadillo et al., 2012). The GAD-7 has been validated by significant positive correlations with a number of anxiety measures, including the Hamilton Anxiety Scale (r = 0.85) and Beck Anxiety Inventory (r = 0.72) (Spitzer et al., 2006). The GAD-7 has previously been used as a screening tool in epilepsy (Rakesh et al., 2012). The internal consistency reliability in this sample was excellent (7 items; alpha = 0.91).

3.3.2.2 Daily measures

3.3.2.2.1 Self-report measures

3.3.2.2.1.1 Smith Stress Symptoms Inventory (Piiparinen & Smith, 2003)

The SSSI is a 35-item measure of commonly reported stress symptoms (e.g., "I have a nervous stomach") (see Appendix 10). The inventory comprises 6 sub-scales encompassing different symptom categories, including worry/negative emotion, attentional deficits, striated muscle tension, autonomic arousal/anxiety, depression, and interpersonal conflict/anger. A total score can be calculated from all 35 items to indicate overall level of stress symptomatology. Each item is rated on a 4-point scale ("Doesn't fit me at all", "Fits me a little", "Fits me moderately well", "Fits me very well"). A version of the scale assessing current stress symptoms ("right now at the present moment") was used in this study. Internal consistency reliability of the scale ranges from 0.76 to 0.89 (Piiparinen & Smith, 2004).

Validity of the scale has also been demonstrated (Piiparinen & Smith, 2004). For further confirmation of validity of the scale, a single-item 7-point scale assessing how stressed the subject feels at the present moment was used in addition to the SSSI. There was a strong positive correlation between the 7-point scale and the total SSSI score in this sample (r = .83, p < .001) and the consistency reliability of the SSSI was excellent (35 items; alpha = 0.97).

3.3.2.2.2 Heart rate variability

Heart-rate variability reflects the dynamic influences of the parasympathetic (or vagal) and sympathetic nervous system tone on the heart. There are many different measures of the short- and long-term HRV that can be obtained from the ECG recordings. The main distinction of the HRV metrics is between the time- and frequency-domain parameters. The time-domain parameters include direct statistical or geometric measures of the beat-to-beat or inter-beat intervals (*NN* intervals), whereas the frequency-domain parameters are based on power spectral density analysis (Allen et al., 2007). In addition, non-linear HRV metrics can also be calculated using a method developed by Toichi (Toichi et al., 1997). This method is based on constructing a Lorenz plot, in which the fluctuation of the beat-to-beat intervals of the ECG recording is transformed into points distributed on a two-dimensional plane, with two axes – a transverse axis (T), which is vertical to the plane, and a longitudinal axis (L), which is parallel to the plane. According to this method, a measure of the parasympathetic nervous system (PNS) activity, called the cardiovagal index (CVI), is calculated from the Lorenz plot as $\log_{10}(T \times L)$. A measure of the sympathetic nervous system (SNS) tone, called the cardiosympathetic index (CSI), is calculated from the Lorenz plot as L/T.

The HRV measures of overall variability and those capturing the PNS activity tend to be highly correlated with each other and negatively related to parameters reflecting the SNS activity (Allen et al., 2007). Nevertheless, despite the close relationship between the measures, no single parameter has been identified as the optimal measure and it is therefore

recommended to use a combination of measures to get a sense of the patterns of variability, as each measure has its advantages and disadvantages (Task Force Of The European Society Of Cardiology And The North & Society Of Pacing And, 1996).

For the analysis of HRV, three- to ten-minute samples of resting ECG free of muscle artefact or ectopic beats were selected. The HRV parameters calculated from the ECG recordings and used in the analyses are presented in Table 3.1.

Table 3.1. *The types of heart-rate variability measures used in the study*

ANS tone measured by the HRV metric	**Type of HRV metric**			
	Time-domain metrics		**Non-linear metrics**	
Combined PNS and SNS tone	SDNN	*Standard deviation of all NN intervals*		
PNS (vagal) tone	RMSSD	*Square root of the mean of the sum of squares of differences between adjacent NN intervals*	CVI	*Cardiovagal index*
SNS tone			CSI	*Cardiosympathetic index*

3.3.2.2.3 Salivary cortisol

Salivary cortisol is one of the most informative markers of the stress response. It can be easily and non-invasively collected using commercially available saliva collection device Salivette. Measures of salivary cortisol are commonly used in stress research (Bakvis et al., 2009b; Creswell et al., 2005) and salivary cortisol has been shown accurately to reflect the levels of cortisol in the blood (Kirschbaum & Hellhammer, 1994), with validated liquid chromatography and tandem mass spectrometry (LC-MS/MS) providing the highest level of precision in measurement (Perogamvros et al., 2009).

Cortisol levels can be used both as an indicator of acute stress reactivity as well as to measure exposure to long-term stress. Elevated cortisol levels were found to reliably reflect increased stress reactivity (Steward & Seeman, 2000). Cortisol secretion is characterised by a distinct diurnal pattern regulated by the brain's pacemaker of the HPA axis, located in the suprachiasmatic nucleus (SCN) of the hypothalamus (Debono et al., 2009). A number of

physiological and psychological processes in humans are mediated by circadian rhythms regulated by the cells of the SCN but these circadian rhythms are most robustly established for melatonin, the core body temperature and cortisol production (Hofstra & de Weerd, 2009). The circulating levels of cortisol are typically highest within 1 hour of awakening and decline throughout the day to reach the lowest point at around the sleep onset, after which they being to increase again between 2.00 – 4.00am (Debono et al., 2009). Chronic stress exposure associated with chronically elevated cortisol levels leads to a diminution of the natural diurnal fluctuation of cortisol levels (Herbert, 2013; Ockenfels et al., 1995). Disrupted circadian rhythm of cortisol has also been found in conditions such as depression or chronic fatigue, leading to increased cardiovascular risk (Debono et al., 2009; Herbert, 2013).

In this study, saliva was sampled as one of the physiological stress measures each morning at approximately 9am and each evening at 10pm. Cortisol levels were assessed separately in the morning and evening, and the diurnal pattern was also explored by examining cortisol deltas, calculated as the difference between the morning and evening cortisol levels. Lower cortisol delta reflects smaller difference between the morning and evening cortisol and therefore indicates a diminished diurnal cortisol change. Factors that influence levels of cortisol, including smoking, food intake or consumption of drinks with low pH were controlled for. The samples were analysed using the LC-MS/MS method described by Perogamvros et al (2009), which is based on converting the saliva molecules into a charged (ionised) state and subsequently analysing the ions of interest (cortisol) on the basis of their mass-to-charge ratio (Perogamvros et al., 2009; Pitt, 2009).

In addition, the daily cortisol measures collected as part of the study were compared to a normative sample provided by collaborators at the Department of Human Metabolism, University of Sheffield.

3.3.2.2.4 Seizure occurrence and seizure severity

3.3.2.2.4.1 Seizure occurrence

Occurrence of seizures was monitored throughout the video-ECG/EEG monitoring period. Seizures are routinely recorded by the patient and the EEG Technicians overseeing the patients' care on the ward. Additionally, I asked patients about the number and timing of any seizures experienced each day during a daily interview. The number, timing and type of seizures experienced were later reviewed and confirmed by inspection of the video-ECG/EEG.

3.3.2.2.4.2 National Hospital Seizure Severity Scale (O'Donoghue et al., 1994)

The NHS3 is a scale that contains seven seizure-related factors and yields a score of 1 – 27. The scale is administered by a health professional during an interview with a patient and a witness of the seizures to assess the severity of the most common seizure types in a given time frame. The scale has demonstrated test-retest reliability of 0.90 and its validity has been confirmed by compatibility of the scale measures with seizure severity perceived by patients (O'Donoghue et al., 1994). A modified version of the scale that can be applied to individual seizures was used to assess the severity of each seizure that occurred during the video-ECG/EEG monitoring (example item: "Has the patient had a generalised convulsion during this seizure") (Appendix11). Under supervision from a Senior Clinical Neurophysiologist, I completed the scale for each seizure based on a review of the video-ECG/EEG recording and a video-ECG/EEG monitoring report routinely produced for each patient by the EEG Technicians and a Consultant Clinical Neurophysiologist.

3.3.3 Procedure

3.3.3.1 Recruitment

Potential participants were identified from a list of patients scheduled for admission to the inpatient video-telemetry ward at the Royal Hallamshire Hospital for vEEG/ECG monitoring. All potential participants were sent an invitation letter with an enclosed information sheet about the study one week before admission. Patients are routinely admitted to the video-telemetry ward for two- to five-day diagnostic or pre-surgery monitoring, commencing on Monday morning or on Wednesday afternoon and ending on Wednesday mid-day or on Friday afternoon. On the day of their admission to the video-telemetry ward (either Monday morning or Wednesday afternoon), I approached potential participants and gave them an opportunity to ask questions about the study. Individuals who expressed interest in participating in the study were screened using the inclusion and exclusion criteria detailed above and asked to provide a written informed consent.

3.3.3.2 Baseline assessment

Patients who consented to take part in the study were asked a set of questions related to their medical and seizure history in a brief interview. This included questions about any diagnosis of diabetes, renal failure, cardiac disorders, or neurological disorders with neuropathy, chronic smoking or alcohol use, current medication use (including anti-epileptic drugs and any other medication), duration of their seizure disorder, a brief description of their typical seizures, presence of any seizure triggers and the date and time of their last seizure (if remembered).

Participants were then asked to complete a set of baseline self-report questionnaires (see Figure 3.1). The baseline questionnaires included the demographic questionnaire, Perceived Stress Scale – 4 Item (PSS-4) (Cohen et al., 1983), Liverpool Seizure Severity

Scale – Revised (LSSS-3) (Scott-Lennox et al., 2001), questionnaires assessing psychological resilience including the Quality of Life in Newly Diagnosed Epilepsy – 6 Dimensions (NEWQOL-6D; Mulhern et al., 2012), Life-Orientation Test – Revised (LOT-R; Scheier et al., 1994), Spontaneous Self-Affirmation Measure (SSAM; Harris et al., in preparation), Single-Item Self-Esteem measure (SISE; Robins et al., 2001) and Brief Resilient Coping Scale (BRCS; Sinclair & Wallston, 2004), plus questionnaires assessing psychopathology, including the Neurological Disorders Depression Inventory for Epilepsy (NDDI-E; Gilliam et al., 2006), and the Generalised Anxiety Disorder 7-item Scale (GAD-7; Spitzer et al., 2006).

3.3.3.3 Daily data collection

After completion of the baseline questionnaires, the stress data collection procedure for each day was explained to the participants. They were asked to follow the same procedure every evening at 10pm and every morning at 9am. They were asked first to complete the daily Smith Stress Symptom Inventory. Having completed the questionnaire, participants were instructed to lie down in a supine position and rest without moving for ten minutes, trying to breathe normally, in order to obtain a resting ECG recording for the extraction of HRV parameters, free of movement artefact and with a constant respiration rate. After they have rested for 10 minutes, participants were asked to provide a sample of their saliva using a Salivette saliva collection tube and to note down the exact time of the saliva collection. I demonstrated how to use the Salivette tube and further instructed the participants to avoid smoking, eating, and drinking anything but water for one hour before taking the saliva sample (i.e., between 9 – 10pm in the evening and between 8 – 9am in the morning).

Participants were provided with two envelopes, one labelled ‘Evening’, which contained the materials for data collection in the evening of the same day, and one labelled ‘Morning’, which contained materials for the following morning. Each envelope included a detailed instruction sheet explaining the data collection procedure for each day, the daily

stress questionnaire (the SSSI), and the Salivette saliva collection tube (Figure 3.2). Participants were also given an additional brief summary sheet to keep by their bedside, highlighting and reminding them of the main steps to take each evening and each morning. All participants were further provided with an alarm clock set for 10pm to remind them to complete the evening measures and they were asked to re-set it for 9am after they have completed the evening procedure. In addition to the daily stress measure collection, participants were asked to keep a record of any seizures they may experience in a diary routinely provided to them as part of the vEEG/ECG monitoring.

After the initial visit on the day of the admission, I visited the participants in the ward every morning just after 9am to check they had completed the morning measures and to collect the completed evening and morning questionnaires and saliva tubes. Participants were provided with a new set of materials for the evening and the following morning and their alarm clock was re-set for 10pm to remind them to complete the evening measures. As part of each morning's visit, I also asked the participants whether they experienced any seizures since the last visit and if so, to provide the time and a brief description of the type and duration of each seizure. On the morning of the final day of the vEEG/ECG monitoring, after the relevant study materials were collected, participants were thanked for their help and their participation in the study was completed.

Figure 3.1. *Flow-chart representing the data collection procedure*

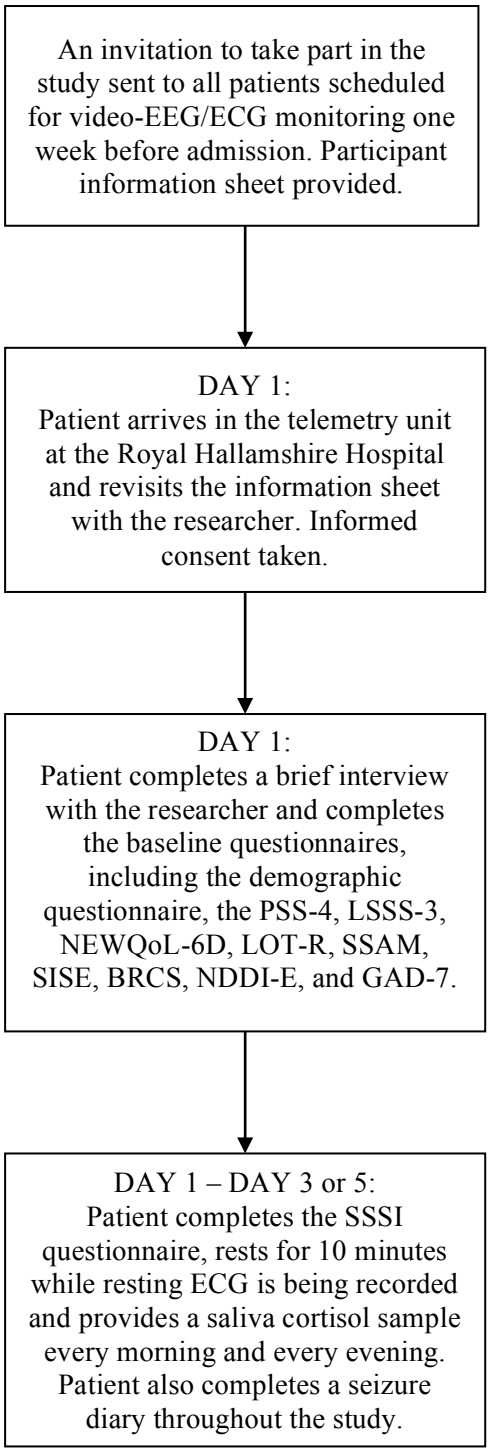
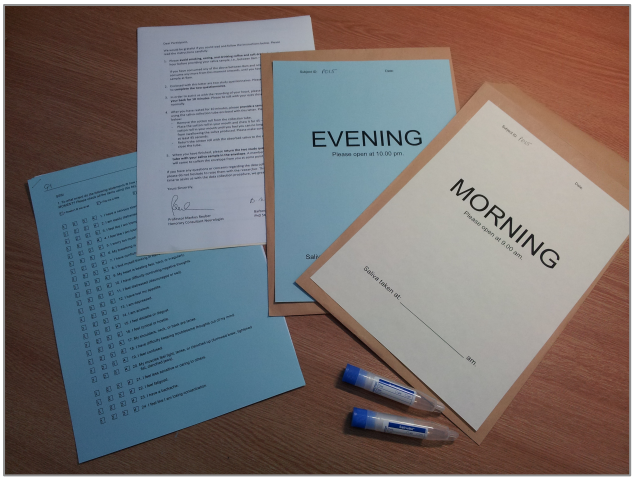


Figure 3.2. *Data collection set*



3.3.4 Data Preparation

3.3.4.1 Review of video-EEG/ECG recordings

After the patient's discharge from the video-telemetry ward, their video-EEG/ECG recordings were reviewed using the XLTEK EEG software, in order to check the timing of the morning and evening data collection and whether the participants followed the procedure as instructed, as well as to confirm the timing and severity of seizures that occurred during the video-telemetry monitoring, and to extract the resting ECG recordings. Where the video recording revealed that the participant failed to complete the questionnaires or take the saliva sample on the given day or did so more than two hours before or after the specified time, the data were excluded from the analysis. Saliva samples were also excluded if the recordings showed that the participant consumed food or drinks less than 30 minutes before taking the saliva sample.

3.3.4.2 Heart rate variability data

Three to ten-minute resting evening and morning ECG recordings were selected. The selected samples were visually inspected to ensure the recordings were free of muscle artefact

and ectopic beats. The ECG samples recorded by the XLTEK EEG system were exported as text files, the sampling rate used to record the ECG was identified (256, 512, or 1024 Hz), and the files were subsequently manually converted into corresponding time-data series (Ponnusamy et al., 2011; Ponnusamy et al., 2012). The HRV parameters were calculated from the data series using the Matlab based Kubios HRV software (Tarvainen et al., 2014) for Mac (version 2.2, 2014) (Figure 3.3).

Figure 3.3. *Kubios HRV software user interface. The software uses a QRS detection algorithm to compute time-domain, frequency-domain and non-linear HRV parameters from the ECG data*

3.3.4.3 Seizure occurrence and severity data

The number and timing of seizures were reviewed using the XLTEK EEG software and the patients' video-ECG/EEG monitoring report. Each seizure was scored for severity using the modified NHS3 scale. The review of seizure timings as well as the scoring of seizure severity was conducted under the supervision of a Clinical Neurophysiologist.

3.3.4.4 Saliva samples

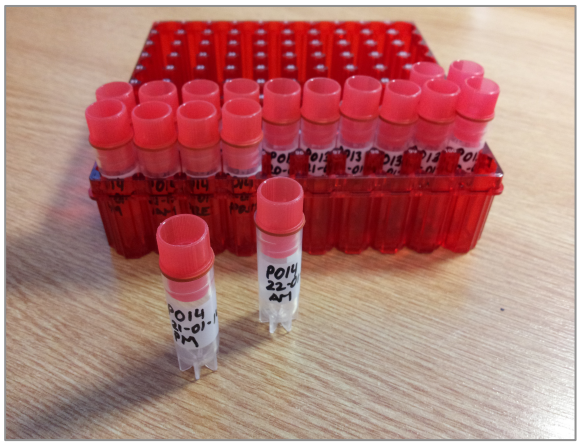
The collected salivary samples were stored in a cold room at 4°C during the week the participant spent in the video-telemetry ward and subsequently centrifuged at the end of each week at 1000 x g for 2 minutes (Kirschbaum & Hellhammer, 1994) (Figure 3.4). The obtained clear salivary supernatant was pipetted from the Salivette tubes (Figure 3.5a) into 2ml cryovial tubes (Figure 3.5b). The samples were then frozen and stored at - 20°C until they were sent for the LC-MS/MS analyses at the Department of Clinical Biochemistry, University Hospital of South Manchester.

Figure 3.4. *Centrifuge used for saliva sample preparation*

Figure 3.5.

(a) *Salivette saliva collection device*

(b) *Saliva samples stored in cryovial tubes*



3.3.4.5 Questionnaire data

All questionnaire data were scored and missing data handled following the instructions in the relevant questionnaire manuals. Where no formal instruction was available on how to treat missing data and where no more than 10% of scores were missing, the missing scores were replaced by the mean of completed items for the given scale or sub-scale. Questionnaires with more than 10% of scores missing were excluded from the analyses.

3.3.5 Statistical Analyses

The baseline data were analysed using the Statistical Package for the Social Sciences (SPSS; version 22 for Mac; SPSS Inc., Chicago, IL, U.S.A.). The daily stress and seizure data have a multi-level structure and some of the questions related to the daily data were therefore explored by multi-level regression analyses using the HLM 7.01 software (Student Edition) for hierarchical linear modelling (Raudenbush, 2011). Before analysis, all measures were checked for normality using the Shapiro-Wilk test. Measures that were non-normally distributed were normalised using natural log-transformation.

The results of the analyses are organised into four sections. First, the baseline demographic, clinical and psychological characteristics of the patients are summarised and examined using Chi-square and independent-samples *t*-test analyses.

The second section contains a description of the key daily self-report and physiological stress measures as well as the seizures recorded during the video-EEG/ECG monitoring (Aim 1). Each of the stress measures was compared using a series of two-way analyses of variance (ANOVA). Cortisol deltas were calculated and compared between the two patient groups using an independent-samples *t*-test. In addition, the cortisol data were

compared to the normative dataset provided by collaborators from the University of Sheffield.

In the third section, the associations between the daily self-reported and physiological stress measures were explored using Pearson's product-moment correlation analyses (Aim 2).

In the final section, the relationships between the daily stress measures and the seizure occurrence were explored using the multi-level modelling approach (Aim 3).

3.4 Results

3.4.1 Description of Baseline Demographic and Clinical Characteristics

A total of 55 patients were recruited for the study. Of these, 22 patients received a definitive diagnosis of epilepsy (13 females, 59.1%). A diagnosis of epilepsy based on a video-EEG recording of a typical seizure was available for 15 patients; in the remaining seven patients the diagnosis was based on expert clinical assessment by two epilepsy specialists. A definitive diagnosis of PNES was established for 23 patients (eight females, 34.8%). Seventeen patients received a diagnosis of PNES confirmed by video-EEG; the diagnosis for the remaining six patients was based on expert clinical consensus. A further five patients were diagnosed as having a mixed disorder (all females, 100%), with three of those being confirmed by video-EEG and two based on expert clinical assessment. For five patients the diagnosis remained uncertain (four females, 80%). Patients with mixed disorder and those with an uncertain diagnosis were excluded from the analyses. This resulted in a final sample of 45 patients.

The demographic and clinical characteristics of the 45 patients as well as their baseline psychological questionnaire measures are summarised in Table 3.2. Of the 22 epilepsy patients, eight patients (36.4%) were surgery candidates; the remaining 14 epilepsy

patients had been admitted for diagnostic video-telemetry. As seen in Table 3.2, the majority of the epilepsy patients had focal epilepsy.

Baseline differences between patients with epilepsy and patients with PNES were established by comparing the groups on the demographic, clinical and psychological measures. Chi-square analyses revealed there were no significant differences between the groups in gender distribution, $X^2(1, N = 45) = 2.67$, $p = .102$, economic activity, $X^2(1, N = 44) = 3.38$, $p = .066$, or medication use, $X^2(1, N = 45) = 0.31$, $p = .577$.

An independent samples *t*-test showed there was a significant difference in the duration of the seizure disorder. Patients with epilepsy reported a longer history of seizures than patients with PNES, $t(38) = 2.09$, $p = .043$. There were no other significant differences on clinical, demographic or self-report measures between patients with epilepsy and those with PNES (see Table 3.2 for further demographic and clinical information).

Table 3.2. *Baseline demographic, psychological, and clinical characteristics*

Characteristic	Epilepsy (N = 22) Mean (*SD*)	PNES (N = 23) Mean (*SD*)	*P*-value
Gender (N female (%))	13 (59.1%)	8 (34.8%)	.102
Age	39.00 (16.05)	43.74 (11.97)	.266
Education (years)	14.55 (2.70)	13.28 (2.32)	.125
Economically active (N (%))	12 (54.5%)	6 (26.1%)	.066
PSS-4	7.14 (3.04)	7.13 (3.09)	.995
GAD-7	8.68 (5.72)	10.81 (5.90)	.226
NDDI-E	14.36 (3.03)	15.48 (3.73)	.279
SSAM	4.17 (1.38)	4.57 (1.51)	.380
HIPT	3.79 (1.56)	3.82 (1.80)	.952
BRCS	12.64 (3.63)	11.52 (3.75)	.317
LOT-R	11.86 (4.47)	12.70 (5.15)	.562
SISE	3.23 (1.34)	3.00 (1.31)	.573
NEWQOL-6D	0.77 (0.10)	0.71 (0.13)	.104
Seizure duration (years)	14.75 (14.60)	7.15 (7.05)	**.043**
Seizure frequency (seizures/month)	15.19 (24.16)	18.10 (37.27)	.766
Seizure severity (measured by LSSS-3)	48.09 (21.07)	50.40 (21.38)	.740
Medication use total (N (%))	21 (95.5%)	21 (91.3%)	.577
AED Monotherapy	5 (22.7%)	9 (39.1%)	-
AED Polytherapy	16 (72.7%)	4 (17.4%)	-
Anti-anxiety/Anti-depressants/Beta-blockers	7 (31.8%)	11 (47.8%)	-
Any other medication	8 (36.4%)	15 (65.2%)	-
Epilepsy type (N (%))			
Idiopathic generalised epilepsy	1 (4.6%)	n/a	-
Focal epilepsy	14 (63.6%)	n/a	-
Unclassifiable epilepsy	7 (31.8%)	n/a	-

Note. *SD* = standard deviation; *PSS-4* = Perceived Stress Scale; *GAD-7* = Generalised Anxiety Disorders 7-item Scale, *NDDI-E* = Neurological Disorders Depression Inventory for Epilepsy; *SSAM* = Spontaneous Self-Affirmation Measure; *HIPT* = Habit Index of Positive Thinking; *BRCS* = Brief Resilient Coping Scale; *LOT-R* = Life Orientation Test-Revised; *SISE* = Single-Item Self-Esteem Scale; *NEWQOL-6D* = Quality of Life in Newly Diagnosed Epilepsy – 6 Dimensions; *AED* = anti-epileptic drugs.

3.4.2 Description of Diurnal Variability of Daily Stress Measures (Aim 1)

Of the 45 patients included in the analyses, 30 patients (66.7%) experienced seizures during the video-EEG/ECG monitoring. A total of 83 seizures were recorded (Table 3.3). A Mann-Whitney *U* Test was performed to examine differences between patients with epilepsy and patients with PNES in the number of seizures they experienced and the seizure severity.

The test showed there were no significant differences between the two groups in the number of seizures experienced during the monitoring, $U = 210.00$, $p = .315$. Unfortunately, seizure severity ratings were not available for all of the seizures recorded, as some seizures were too brief to be rated and some were not visible on the camera. The severity ratings were only available for 27 out of the 34 epileptic seizures and for 21 out of the 49 PNES. Comparison of seizure severity ratings from all epileptic and non-epileptic seizures for which the seizure severity ratings were available showed that, overall, the non-epileptic seizures were rated as more severe than the epileptic seizures, $U = 173.50$, $p = .021$.

Table 3.3. *Summary of length of hospital stay and seizure occurrence in the two patient groups*

	Epilepsy ($N = 22$)	PNES ($N = 23$)	*P*-value
Days spent in hospital *(Mean (SD))*	4.18 (1.01)	3.61 (0.94)	.056
Number of seizures recorded	34	49	.315
Occurrence of seizures during vEEG/ECG			
Patients with no seizures (*N* (%))	9 (40.9%)	6 (26.1%)	-
Patients with one seizure (*N* (%))	5 (22.7%)	5 (21.7%)	-
Patients with multiple seizures (*N* (%))	8 (36.4%)	12 (52.2%)	-
Severity of all seizures recorded *(Median (IQR))**	4.00 (5.00)	7.00 (4.00)	**.021**

Note. *N* = sample size; *SD* = standard deviation.; *IQR* = inter-quartile range. *The seizure severity ratings are based on seizures for which scores were available (epileptic seizures *N* = 27; PNES *N* = 21).

The initial summary and description of the daily stress measures was only performed at the person level using aggregated measures from each patient. The measures were aggregated using each person's mean morning and mean evening self-reported stress, means of the equivalent morning and evening HRV measures and means of their morning and evening cortisol values. Table 3.4 summarises the mean morning and mean evening stress measures and cortisol deltas. The evening and morning HRV and cortisol measures were non-normally distributed and the values were therefore log-transformed before analysis. A descriptive summary of the log-transformed values on which the analyses are based is presented in Table 3.5. Differences in the stress measures were explored for each measure separately using a series of two-way ANOVAs for mixed designs with diagnostic group

(epilepsy vs. PNES) as between-participants independent variable and time of day (morning vs. evening) as within-participants independent variable.

Table 3.4. *Mean morning and mean evening stress measures in the two patient groups*

Stress Measure	Epilepsy			PNES		
	N	Morning *M* (*SD*)	Evening *M* (*SD*)	*N*	Morning *M* (*SD*)	Evening *M* (*SD*)
Self-reported stress	21	1.57 (0.50)	1.64 (0.50)	22	1.88 (0.83)	1.88 (0.77)
HRV parameters	20			21		
SDNN		37.78 (19.78)	39.12 (20.73)		31.07 (23.84)	36.39 (25.25)
RMSSD		38.34 (23.17)	45.30 (31.22)		27.52 (27.51)	39.17 (34.23)
CVI		2.96 (0.44)	2.98 (0.47)		2.65 (0.57)	2.86 (0.54)
CSI		1.83 (0.51)	1.68 (0.60)		2.38 (0.60)	1.87 (0.59)
Cortisol levels (nmol/L)	22	5.10 (1.99)	1.19 (0.68)	22	4.65 (2.16)	0.98 (0.42)
Cortisol delta (nmol/L)	21	3.54 (2.80)		18	3.81 (2.22)	

Note. *M* = mean; *SD* = standard deviation; Variation in sample sizes indicates missing data for certain variables.

Table 3.5. *Mean morning and mean evening HRV and cortisol measures in the two patient groups after log-transformation*

Stress Measure	Epilepsy			PNES		
	N	Morning *M* (*SD*)	Evening *M* (*SD*)	*N*	Morning *M* (*SD*)	Evening *M* (*SD*)
HRV parameters	20			21		
LogSDNN		1.52 (0.21)	1.52 (0.22)		1.40 (0.27)	1.47 (0.25)
LogRMSSD		1.51 (0.24)	1.54 (0.28)		1.30 (0.32)	1.46 (0.31)
LogCVI		0.47 (0.06)	0.47 (0.07)		0.41 (0.10)	0.48 (0.08)
LogCSI		0.24 (0.12)	0.20 (0.15)		0.36 (0.12)	0.25 (0.13)
LogCortisol	22	0.64 (0.18)	0.02 (0.17)	22	0.60 (0.22)	-0.04 (0.12)

Note. *M* = mean; *SD* = standard deviation; Variation in sample sizes indicates missing data for certain variables

3.4.2.1 Self-reported stress

The ANOVA showed there were no significant main effects of time, group, or time by group interactions for self-reported stress (*p's* > .05), suggesting that the mean levels of self-reported stress were comparable in the mornings and in the evenings in both patients with epilepsy and patients with PNES.

3.4.2.2 Heart-rate variability

The ANOVA revealed there was a significant main effect of time of day on RMSSD, $F(1, 35) = 6.46$, $p = .019$. Figure 3.6 shows that RMSSD was higher in the evening than in the morning in both patient groups.

The analysis also revealed a significant main effect of time of day on CSI, $F(1, 35) = 11.45$, $p = .002$. Overall, CSI was higher in the morning than in the evening. There was also a significant main effect of patient group, $F(1, 35) = 5.31$, $p = .027$. As shown in Figure 3.7, CSI was higher in patients with PNES than in patients with epilepsy.

There were no significant main effects or interactions for SDNN or CVI (p's > .05), suggesting there was no difference between morning and evening SDNN or CVI and no difference between the two patient groups in these measures.

Figure 3.6. *Morning and evening log-transformed RMSSD in the two patient groups*

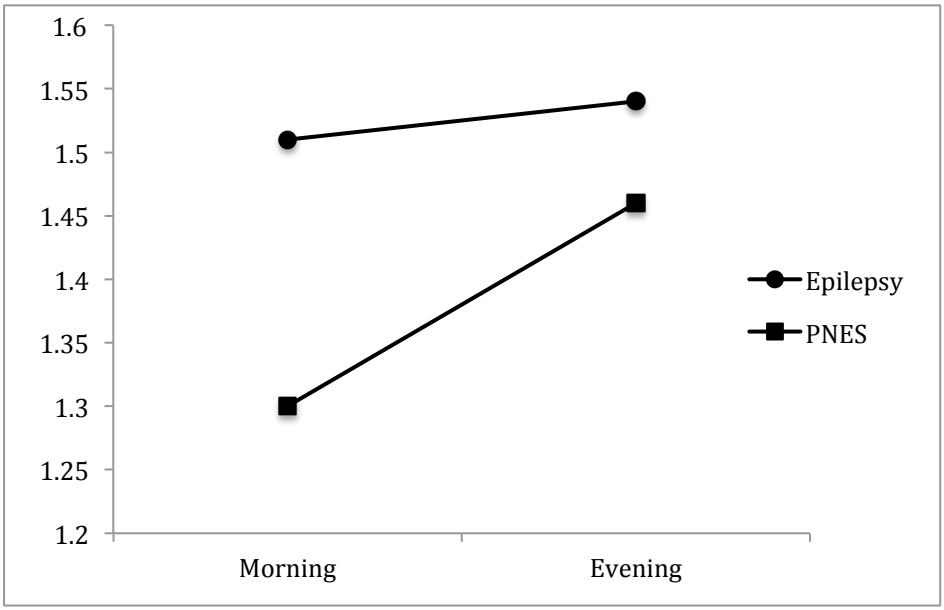
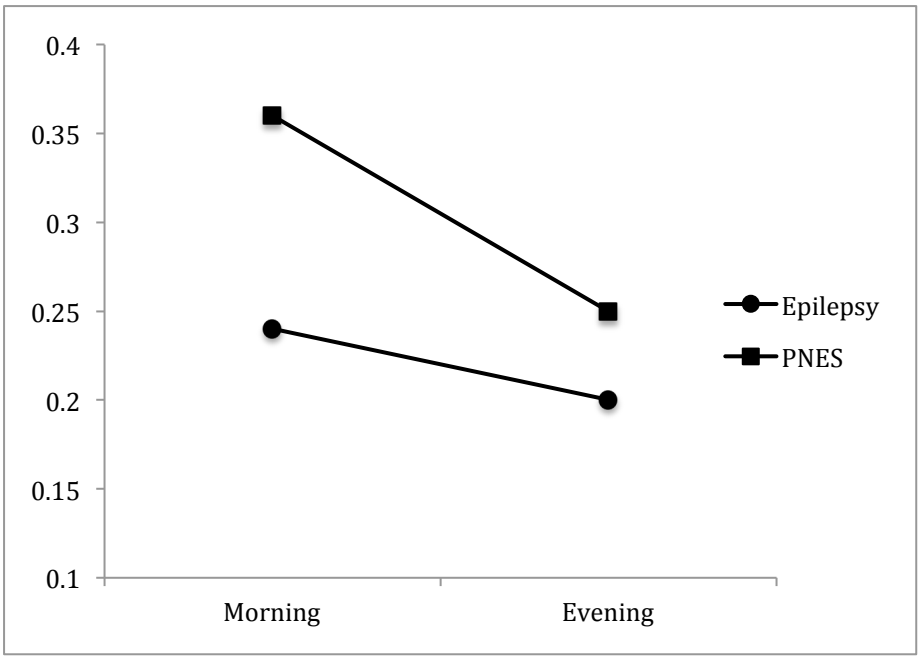


Figure 3.7. *Morning and evening log-transformed CSI in the two patient groups*



3.4.2.3 Salivary cortisol

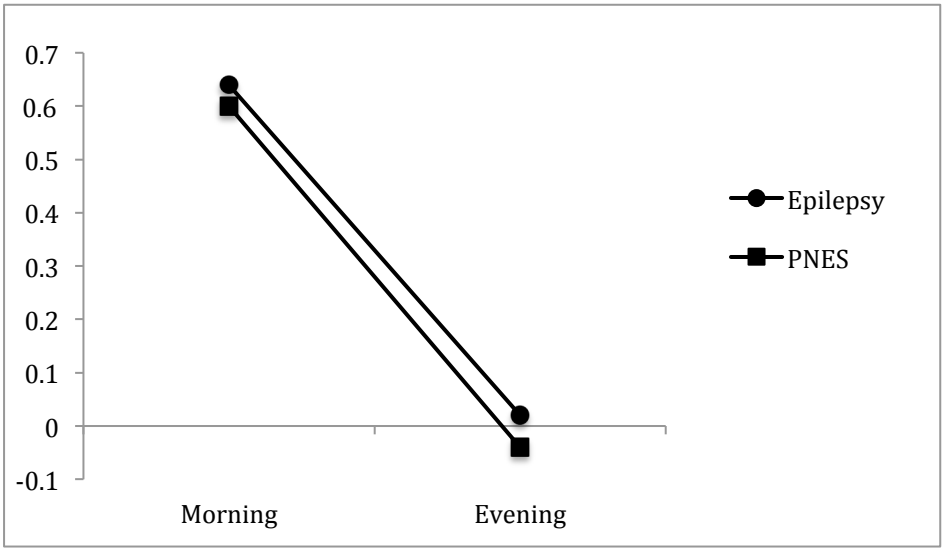
Examination of the morning and evening cortisol showed there was a significant main effect of time of day on the levels of cortisol, $F(1, 40) = 317.79$, $p < .001$. As can be seen in Figure 3.8, cortisol levels were higher in the morning than in the evening in both patient groups. There were no significant main effects of patient group and no significant interactions (*p's* > .05).

An independent-samples *t*-test was further performed to examine the differences between patients with epilepsy and patients with PNES in their mean cortisol delta values. No significant difference was found between the two patient groups, $t(37) = -0.33$, $p = .740$, suggesting the diurnal cortisol changes were similar in patients with epilepsy and patients with PNES.

In addition, the cortisol data were compared to normative salivary cortisol data from 14 healthy volunteers (all male; age $M = 32.86$, $SD = 11.24$) collected at the same time points (at 9am and 10pm), using two-way ANOVAs for the morning and evening measures, and

one-way ANOVA for the cortisol deltas. The analyses showed no significant differences between the three groups in the morning or evening cortisol levels or the cortisol deltas (*ps* > .05). For a summary of the normative cortisol values see Appendix 12.

Figure 3.8. *Morning and evening log-transformed cortisol levels in the two patient groups*



3.4.3 Associations among Daily Stress Measures (Aim 2)

Correlations between the morning measures and between the evening measures were explored both at the time-point level using all available data points from all patients and at the person level using the aggregate (mean) values for each patient.

3.4.3.1 Time-point level correlations

The correlation matrix in Table 3.6 shows the correlation coefficients between the morning measures using all available data points for self-reported stress, salivary cortisol and the heart-rate variability parameters. There were no significant correlations between self-reported stress and any of the physiological measures, including cortisol and HRV (*p's* > .05).

However, there was a significant negative correlation between salivary cortisol and SDNN (p = .012), as well as between salivary cortisol and RMSSD (p = .027). This suggests that higher morning cortisol levels were associated with lower overall heart-rate variability (as indicated by the SDNN) and lower vagal tone (as indicated by the RMSSD). It is also worth noting that all the morning HRV parameters were significantly correlated with each other (see Table 3.6).

Table 3.6. *Correlations between the morning stress measures in both patient groups combined*

	1	2	3	4	5	6
1 Self-reported stress (N = 113)						
2 LogCortisol (N = 110)	.002					
3 LogSDNN (N = 80)	-.053	-.288*				
4 LogRMSSD (N = 80)	-.079	-.253*	.941**			
5 LogCVI (N = 80)	-.053	-.225	.975**	.964**		
6 LogCSI (N = 80)	.102	.068	-.352**	-.646**	-.469**	

Note. *Correlation is significant at .05 level. ** Correlation is significant at .01 level.

The correlations between the evening measures are shown in Table 3.7. No significant correlations were found between self-reported stress and cortisol or between self-reported stress and any of the HRV measures (p's > .05). There were also no significant correlations between cortisol and the HRV parameters (p's > .05). Similarly to the morning measures, the evening HRV parameters were significantly correlated with each other (see Table 3.7).

Correlations between the morning and evening measures were also examined separately in patients with epilepsy and patients with PNES. The correlation patterns were similar in the two groups, with the only significant correlations being among the HRV parameters in both patient groups. For the correlation matrices, see Appendix 13.

Table 3.7. *Correlations between the evening stress measures in both patient groups combined*

	1	2	3	4	5	6
1 Self-reported stress (*N* = 103)						
2 LogCortisol (*N* = 106)	.061					
3 LogSDNN (*N* = 94)	-.053	.058				
4 LogRMSSD (*N* = 94)	-.047	.057	.943**			
5 LogCVI (*N* = 94)	-.045	.067	.980**	.969**		
6 LogCSI (*N* = 94)	.018	-.016	-.434**	-.706**	-.538**	

Note. *Correlation is significant at .05 level. ** Correlation is significant at .01 level.

3.4.3.2 Person level correlations

The between-subject correlations among the patients' mean morning and mean evening measures in both patient groups combined are presented in Tables 3.8 and 3.9. Pearson's product-moment correlation analyses showed that there were no significant correlations between the mean morning self-reported stress and salivary cortisol or between self-reported stress and the HRV parameters (*p's* > .05). There were, however, significant correlations between the morning HRV parameters (see Table 3.8).

Table 3.8. *Between-subject correlations among the mean morning measures*

	1	2	3	4	5	6
1 Self-reported stress (*N* = 43)						
2 LogCortisol (*N* = 42)	.063					
3 LogSDNN (*N* = 38)	-.030	-.272				
4 LogRMSSD (*N* = 38)	-.077	-.260	.948**			
5 LogCVI (*N* = 38)	-.040	-.233	.979**	.964**		
6 LogCSI (*N* = 38)	.161	.106	-.338*	-.620**	-.438**	

Note. *N* = number of patients. *Correlation is significant at .05 level. ** Correlation is significant at .01 level

Similarly, no significant correlations were found between the mean evening measures of self-reported stress and any of the physiological stress measures or between cortisol and any of the HRV parameters. The evening HRV parameters were significantly related to each other (Table 3.9).

Examination of the between-subject correlations among the mean morning and mean evening measures in the two patient groups separately revealed a similar pattern of correlations, with the only significant relationships found among the HRV parameters.

Table 3.9. *Between-subject correlations among the mean evening measures*

	1	2	3	4	5	6
1 Self-reported stress (*N* = 42)						
2 LogCortisol (*N* = 44)	-.053					
3 LogSDNN (*N* = 40)	.014	-.042				
4 LogRMSSD (*N* = 40)	.017	-.065	.951**			
5 LogCVI (*N* = 40)	.031	-.041	.986**	.974**		
6 LogCSI (*N* = 40)	-.014	.100	-.489**	-.733**	-.581**	

Note. *N* = number of patients. *Correlation is significant at .05 level. ** Correlation is significant at .01 level

3.4.4 Relationships between Stress and Seizure Occurrence (Aim 3)

The data have a multi-level structure with time-points (Level 1) nested within patients (Level 2), therefore a series of multi-level regression analyses with maximum likelihood estimation was used to explore the relationships. The relationships were examined in two different ways. Firstly, a series of multi-level models was tested to investigate whether any of the daily stress measures predicted the occurrence of seizures in the next 12 hours. Secondly, another series of models was tested to examine whether the occurrence of seizures in the past 12 hours predicted the levels of self-reported stress, cortisol or HRV at each time point.

3.4.4.1 Do any of the daily stress measures predict seizure occurrence?

To answer this question, a series of multi-level regression models was constructed with the number of seizures occurring in the next 12 hours as the outcome in the models. The daily self-reported stress, cortisol and HRV measures as well as time of day (coded as morning = 0, evening = 1) and the number of seizures occurring in the past 12 hours were used as Level 1 predictors in the models. Patient group (coded as PNES = 0, epilepsy = 1) and the mean self-reported stress, cortisol and HRV measures for each person were used as

Level 2 predictors. All missing data were removed before analysis using the HLM software, which resulted in a final sample of $N = 153$ at Level 1 and $N = 39$ at Level 2.

To test for significant predictors of seizure occurrence, each stress measure was examined separately by comparing four models: (1) a null model predicting seizures in the next 12 hours with an intercept only; (2) a daily stress model, adding a fixed effect of daily self-reported stress/cortisol/HRV at Level 1; (3) a model with added fixed effects of time of day and seizures in the past 12 hours at Level 1 and the diagnostic group at Level 2; and (4) a full model, adding the mean self-reported stress/cortisol/HRV at Level 2 to test for patient-level effects.

3.4.4.1.1 Self-reported stress predicting seizure occurrence

The model parameters and the significance level of each predictor in each model are shown in Table 3.10. For comparison purposes, a null model without any predictors was created (Table 3.10). The intra-class correlation (ICC) was calculated from the null model by dividing the Level 2 variance by the sum of the total variance (Level 1 + Level 2). The ICC for the number of seizures in the next 12 hours was 0.154, suggesting that 15.4% of variance in this outcome was between Level 2 units, i.e., at the patient level.

Model fit for each model was assessed with likelihood ratio tests based on the deviance statistic (deviance is calculated by the HLM software as -2 x log likelihood). For a model with a better fit, the likelihood ratio test should show a significant reduction in deviance.

To test the daily stress model (Model 1), daily self-reported stress (as measured by the SSSI) alone was added as a fixed parameter to the null model. As seen in Table 3.10, self-reported stress was not a significant predictor of seizure occurrence and the likelihood ratio test showed that adding this parameter did not provide significant improvement in deviance compared to the null model, $X^2(1) = 0.01$, $p = .904$.

To check for any effects of the time of day, whether or not seizures occurred in the 12 hours before each stress measurement, and diagnostic group (i.e., whether the occurrence of seizures was different in patients with epilepsy or those with PNES), these parameters were added to the daily stress model (Model 2). As can be seen in Table 3.10, none of these additional parameters were significant predictors of seizures. The likelihood ratio test showed that this model did not provide a significant reduction in deviance compared with the null model, X^2 (4) = 1.26, p = .867, or compared with Model 1, X^2 (3) = 1.25, p = .741.

Finally, to check for the patient-level effects of self-reported stress, the aggregate (mean) self-reported stress was added as a Level 2 predictor (Model 3). As can be seen in Table 3.10, the aggregate self-reported stress was not a significant predictor of seizures and did not affect the significance of any of the other model parameters. The likelihood ratio test showed that adding the aggregate self-reported stress at Level 2 did not provide a significant reduction in deviance compared with the null model, X^2 (5) = 2.17, p = .825, or compared with Model 2, X^2 (1) = 0.91, p = .340.

Table 3.10. *Summary of multi-level regression models for self-reported stress (SSSI) as a predictor of seizure occurrence, with time-points (Level 1: N = 153) nested within patients (Level 2: N = 39) with random intercept and fixed slopes for all predictors*

	Null Model		Model 1			Model 2			Model 3		
Parameter	*B*	*SE*	*B*	*SE*	*p*	*B*	*SE*	*p*	*B*	*SE*	*p*
Level 1 predictors											
Intercept	0.22	0.05	0.20	0.16	.206	0.27	0.17	.131	0.33	0.19	.087
SSSI	-	-	0.01	0.09	.902	0.02	0.09	.867	0.26	0.26	.329
Time of day	-	-	-	-	-	-0.01	0.08	.865	-0.02	0.08	.759
Seizures in past 12 hrs	-	-	-	-	-	-0.03	0.05	.556	-0.05	0.06	.401
Level 2 predictors											
Diagnostic group	-	-	-	-	-	-0.11	0.11	.318	-0.12	0.11	.286
Aggregate SSSI	-	-	-	-	-	-	-	-	-0.27	0.28	.338
Deviance	230.00		229.99			228.74			227.83		
Parameters	3		4			7			8		

Note. B = coefficient; SE = standard error; SSSI = Smith Stress Symptom Inventory as a measure of self-reported stress.

3.4.4.1.2 Salivary cortisol predicting seizure occurrence

The parameters for the cortisol models are displayed in Table 3.11. To test the model with daily salivary cortisol alone (Model 1), daily cortisol values were added as a Level 1 fixed parameter to the null model. As can be seen in Table 3.11, salivary cortisol was not a significant predictor of seizure occurrence and the likelihood ratio test showed that adding this parameter did not provide significant reduction in deviance compared to the null model, X^2 (1) = 0.10, p = .748.

Next, time of day, seizures occurring in the 12 hours before each stress measurement and the diagnostic group were added to the daily cortisol model (Model 2). The likelihood ratio test showed that this model did not provide a significant reduction in deviance compared with the null model, X^2 (4) = 1.31, p = .859, or compared with Model 1, X^2 (3) = 1.21, p = .751.

Finally, to check for the patient-level effects of cortisol, the aggregate cortisol was added as a Level 2 predictor (Model 3). Aggregate cortisol was not a significant predictor of seizures (Table 3.11). The likelihood ratio test showed that adding this parameter did not provide a significant improvement in deviance compared with the null model, X^2 (5) = 3.45, p = .631, or compared with Model 2, X^2 (1) = 2.14, p = .144.

Table 3.11. *Summary of multi-level regression models for salivary cortisol as a predictor of seizure occurrence, with time-points (Level 1: N = 153) nested within patients (Level 2: N = 39) with random intercept and fixed slopes for all predictors*

	Null Model		Model 1			Model 2			Model 3		
Parameter	*B*	*SE*	*B*	*SE*	*p*	*B*	*SE*	*p*	*B*	*SE*	*p*
Level 1 predictors											
Intercept	0.22	0.05	0.21	0.06	.001	0.26	0.15	.091	0.37	0.17	.033
Cortisol	-	-	0.03	0.10	.748	0.05	0.20	.785	0.17	0.21	.416
Time of day	-	-	-	-	-	0.02	0.15	.883	0.09	0.16	.572
Seizures in past 12 hrs	-	-	-	-	-	-0.03	0.05	.549	-0.03	0.05	.581
Level 2 predictors											
Diagnostic group	-	-	-	-	-	-0.11	0.11	.316	-0.08	0.11	.452
Aggregate cortisol	-	-	-	-	-	-	-	-	-0.63	0.43	.151
Deviance	230.00		229.90			228.69			226.55		
Parameters	3		4			7			8		

3.4.4.1.3 Heart-rate variability parameters predicting seizure occurrence

Because the HRV parameters were all correlated among each other, in order to avoid the issue of multicollinearity as well as to avoid having too many variables in the model, the models were constructed separately for the four HRV parameters. The model parameters and their significance levels are summarised in Tables 3.12 – 3.15.

As shown in Table 3.12, the daily SDNN alone (Model 1) was not a significant predictor of seizures. The likelihood ratio test showed that adding this parameter did not significantly improve the model, compared to the null model, X^2 (1) < .001, p = .993. Adding the time of day, seizures in past 12 hours and diagnostic group to the model (Model 2) did not provide a significant reduction in deviance either, compared to the null model, X^2 (4) = 1.25, p = .870, or compared to Model 1, X^2 (3) = 1.25, p = .741. Adding the aggregate SDNN at Level 2 (Model 3) to examine the patient-level effects of SDNN showed that aggregate SDNN was not a significant predictor (see Table 3.12) and adding this parameter to the model did not significantly reduce the deviance, compared to the null model, X^2 (5) = 3.30, p = .654, or compared to Model 2, X^2 (1) = 2.05, p = .152.

Table 3.12. *Summary of multi-level regression models for SDNN as a predictor of seizure occurrence, with time-points (Level 1: N = 153) nested within patients (Level 2: N = 39) with random intercept and fixed slopes for all predictors*

	Null Model		Model 1			Model 2			Model 3		
Parameter	*B*	*SE*	*B*	*SE*	*p*	*B*	*SE*	*p*	*B*	*SE*	*p*
Level 1 predictors											
Intercept	0.22	0.05	0.22	0.28	.435	0.26	0.29	.366	-0.08	0.38	.834
SDNN	-	-	-0.001	0.17	.992	0.02	0.19	.912	-0.30	0.29	.306
Time of day	-	-	-	-	-	-0.01	0.08	.864	-0.001	0.08	.988
Seizures in past 12 hrs	-	-	-	-	-	-0.03	0.05	.571	-0.05	0.06	.339
Level 2 predictors											
Diagnostic group	-	-	-	-	-	-0.11	0.11	.316	-0.14	0.11	.218
Aggregate SDNN	-	-	-	-	-	-	-	-	0.56	0.39	.155
Deviance	230.00		230.00			228.75			226.70		
Parameters	3		4			7			8		

Similarly, the daily RMSSD was not a significant predictor of seizures (Model 1) and adding this parameter to the null model did not significantly reduce the deviance, X^2 (1) = 0.34, p = .560 (Table 3.13). Adding the time of day, seizures in past 12 hours and diagnostic group (Model 2) did not provide significant reduction in variance, compared to the null model, X^2 (4) = 1.90, p = .755, or compared to Model 1, X^2 (3) = 1.56, p = .669. The aggregate RMSSD was not a significant predictor (Model 3) and did not provide significant reduction in deviance either, compared to the null model, X^2 (5) = 4.10, p = .536, or compared to Model 2, X^2 (1) = 2.20, p = .138.

Table 3.13. *Summary of multi-level regression models for RMSSD as a predictor of seizure occurrence, with time-points (Level 1: N = 153) nested within patients (Level 2: N = 39) with random intercept and fixed slopes for all predictors*

	Null Model		Model 1			Model 2			Model 3		
Parameter	*B*	*SE*	*B*	*SE*	*p*	*B*	*SE*	*p*	*B*	*SE*	*p*
Level 1 predictors											
Intercept	0.22	0.05	0.09	0.22	.680	0.12	0.23	.594	-0.16	0.30	.581
RMSSD	-	-	0.09	0.15	.559	0.13	0.16	.415	-0.13	0.23	.567
Time of day	-	-	-	-	-	-0.03	0.08	.762	-0.003	0.08	.967
Seizures in past 12 hrs	-	-	-	-	-	-0.03	0.05	.602	-0.05	0.05	.359
Level 2 predictors											
Diagnostic group	-	-	-	-	-	-0.13	0.11	.259	-0.16	0.11	.157
Aggregate RMSSD	-	-	-	-	-	-	-	-	0.47	0.31	.141
Deviance	230.00		229.66			228.10			225.90		
Parameters	3		4			7			8		

Examination of the models for the CVI showed that the daily CVI alone (Model 1) was not a significant predictor of seizures (see Table 3.14) and adding this parameter did not provide a significant reduction in deviance compared to the null model, X^2 (1) = 0.07, p = .797. Adding the time of day, seizures in the past 12 hours and diagnostic group (Model 2) did not significantly reduce the deviance compared to the null model, X^2 (4) = 1.44, p = .836, or compared to Model 1, X^2 (3) = 1.38, p = .710. Adding the aggregate CVI at Level 2 (Model 3) showed the aggregate CVI was not a significant predictor and did not provide

significant reduction of deviance (Table 3.14), compared to the null model, X^2 (5) = 3.63, p = .604, or compared to Model 2, X^2 (1) = 2.18, p = .140.

Table 3.14. *Summary of multi-level regression models for CVI as a predictor of seizure occurrence, with time-points (Level 1: N = 153) nested within patients (Level 2: N = 39) with random intercept and fixed slopes for all predictors*

	Null Model		Model 1			Model 2			Model 3		
Parameter	*B*	*SE*	*B*	*SE*	*p*	*B*	*SE*	*p*	*B*	*SE*	*p*
Level 1 predictors											
Intercept	0.22	0.05	0.16	0.25	.534	0.18	0.25	.473	-0.15	0.34	.669
CVI	-	-	0.14	0.55	.797	0.26	0.57	.647	-0.67	0.84	.427
Time of day	-	-	-	-	-	-0.02	0.08	.824	-0.002	0.08	.978
Seizures in past 12 hrs	-	-	-	-	-	-0.03	0.05	586	-0.05	0.05	.355
Level 2 predictors											
Diagnostic group	-	-	-	-	-	-0.12	0.11	.288	-0.16	0.11	.177
Aggregate CVI	-	-	-	-	-	-	-	-	1.71	1.14	.143
Deviance	230.00		229.93			228.55			226.37		
Parameters	3		4			7			8		

As shown in Table 3.15, the daily CSI alone was not a significant predictor of seizures (Model 1) and adding this parameter to the null model did not provide a significant reduction in deviance, X^2 (1) = 2.50, p = .114. However, when the effects of time of day, seizures in the past 12 hours and diagnostic group were added to the model (Model 2), the daily CSI became a significant predictor of seizures in the next 12 hours (see Table 3.15), although this model did not provide a significant reduction in deviance, compared to the null model, X^2 (4) = 5.10, p = .277, or compared to Model 1, X^2 (3) = 2.60, p = .457. To examine the patient-level effects of CSI, the aggregate CSI was added at Level 2 (Model 3). As shown in Table 3.15, when aggregate CSI was added, the daily CSI lost its significance again, suggesting that the variance in seizures occurring in the next 12 hours was not explained by daily CSI when the patients' aggregate CSI was accounted for. The aggregate CSI itself was not a significant predictor of seizures and adding this parameter to the model did not provide

significant reduction in deviance compared to the null model, X^2 (5) = 7.36, p = .195, or compared to Model 2, X^2 (1) = 2.26, p = .132.[1]

Table 3.15. *Summary of multi-level regression models for CSI as a predictor of seizure occurrence, with time-points (Level 1: N = 153) nested within patients (Level 2: N = 39) with random intercept and fixed slopes for all predictors*

	Null Model		Model 1			Model 2			Model 3		
Parameter	*B*	*SE*	*B*	*SE*	*p*	*B*	*SE*	*p*	*B*	*SE*	*p*
Level 1 predictors											
Intercept	0.22	0.05	0.34	0.09	<.001	0.50	0.14	<.001	0.64	0.16	<.001
CSI	-	-	-0.47	0.29	.110	-0.63	0.31	**.047**	-0.19	0.42	.635
Time of day	-	-	-	-	-	-0.06	0.08	.502	-0.03	0.08	.694
Seizures in past 12 hrs	-	-	-	-	-	-0.03	0.05	.552	-0.04	0.05	.425
Level 2 predictors											
Diagnostic group	-	-	-	-	-	-0.15	0.11	.165	-0.19	0.11	.089
Aggregate CSI	-	-	-	-	-	-	-	-	-0.93	0.62	.139
Deviance	230.00		227.51			224.91			222.64		
Parameters	3		4			7			8		

3.4.4.2 Does seizure occurrence predict daily stress levels?

Another set of multi-level models was constructed to explore the question of whether seizure occurrence can predict any of the daily stress measures. Four multi-level regression models were compared for each stress measure as an outcome: (1) a null model predicting the self-reported stress/cortisol/HRV with an intercept only, (2) a model with the number of seizures in the past 12 hours as a Level 1 predictor, (3) a model adding the fixed effects of time of day (coded as morning = 0, evening = 1) at Level 1 and diagnostic group (coded as PNES = 0, epilepsy = 1) at Level 2, and (4) a model in which the sum of seizures for each patient (i.e., the total number of seizures the patient experienced during the video-EEG recording) was added as a Level 2 predictor to check for patient-level effects of seizure occurrence.

[1] Additionally, to check whether the Level 1 parameters for all the models reported in section 3.4.4.1 varied differently between patients, the Level 1 slopes were made to vary at random at Level 2. Making the slopes random did not significantly reduce the deviation (p > .05), suggesting the parameters did not vary differently between patients and there were not likely to be any cross-level interactions.

3.4.4.2.1 Seizure occurrence predicting self-reported stress

The summary of the model parameters is provided in Table 3.16. The intra-class correlation for self-reported stress calculated from the null model was 0.924, suggesting that 92.4% of variance in self-reported stress was between the Level 2 units (i.e., at the patient level).

The number of seizures occurring in the past 12 hours (Model 1) was a significant predictor of daily self-reported stress. One unit increase in the number of seizures occurring in the past 12 hours was associated with a 0.06 increase in the self-reported stress score. The likelihood ratio test showed that this model provided a significant reduction in deviance compared to the null model, X^2 (1) = 7.34, p = .007. Estimation of the modelled variance was derived using the formula proposed by Raudenbush and Bryk (Raudenbush & Bryk, 2002). The model accounted for an estimated 7% of the within-participants variance in daily self-reported stress. Seizures remained a significant predictor when the fixed effects of time of day and diagnostic group were introduced in the model (Model 2). Adding these parameters did not significantly reduce the deviance compared to Model 1, X^2 (2) = 2.25, p = .325. Finally, the sum of seizures was added as a Level 2 predictor (Model 3). This parameter was not a significant predictor of self-reported stress and the model did not provide a significant improvement in deviance compared to Model 2, X^2 (1) = 1.83, p = .176.

Table 3.16. *Summary of multi-level regression models for number of seizures predicting self-reported stress, with time-points (Level 1: N = 153) nested within patients (Level 2: N = 39) with random intercept and fixed slopes for all predictors*

	Null Model		Model 1			Model 2			Model 3		
Parameter	*B*	*SE*	*B*	*SE*	*p*	*B*	*SE*	*p*	*B*	*SE*	*p*
Level 1 predictors of SSSI											
Intercept	1.70	0.10	1.68	0.10	<.001	1.69	0.14	<.001	1.81	0.15	<.001
Seizures in past 12 hrs	-	-	0.06	0.02	**.007**	0.06	0.02	**.011**	0.06	0.02	**.007**
Time of day	-	-	-	-	-	0.04	0.03	.146	0.04	0.03	.150
Level 2 predictors of SSSI											
Diagnostic group	-	-	-	-	-	-0.07	0.19	.717	-0.10	0.19	.608
Sum of seizures	-	-	-	-	-	-	-	-	-0.06	0.04	.179
Deviance	31.32		23.98			21.74			19.90		
Parameters	3		4			6			7		

3.4.4.2.2 Seizure occurrence predicting salivary cortisol levels

The model parameters are presented in Table 3.17. The ICC for salivary cortisol calculated from the null model was 0.0002, suggesting that only 0.02% of the variance in cortisol was at the patient level. As shown in Table 3.17, the number of seizures in the past 12 hours alone (Model 1) was not a significant predictor of salivary cortisol levels and this model did not provide a significant improvement compared to the null model, X^2 (1) = 0.29, p = .592. Next, the time of day and the diagnostic group were added to the model (Model 2). Time of day was found to be a significant predictor of salivary cortisol. In line with the findings reported in section 3.4.2, cortisol levels in the morning (coded 0) were higher than the levels in the evening. The model provided a significant reduction in deviance compared to Model 1, X^2 (2) = 187.53, p < .001, accounting for an estimated 74.5% of the within-participants variance in salivary cortisol. Introducing the sum of seizures at Level 2 (Model 3) did not provide further significant improvement in deviance compared to Model 2, X^2 (1) = 0.39, p = .530.

Table 3.17. *Summary of multi-level regression models for number of seizures predicting salivary cortisol, with time-points (Level 1: N = 153) nested within patients (Level 2: N = 39) with random intercept and fixed slopes for all predictors*

	Null Model		Model 1			Model 2			Model 3		
Parameter	*B*	*SE*	*B*	*SE*	*p*	*B*	*SE*	*p*	*B*	*SE*	*p*
Level 1 predictors of cort											
Intercept	0.29	0.03	0.29	0.03	<.001	0.62	0.04	<.001	0.59	0.04	<.001
Seizures in past 12 hrs	-	-	-0.02	0.04	.593	0.02	0.02	.419	0.01	0.03	.699
Time of day	-	-	-	-	-	-0.65	0.03	**<.001**	-0.65	.0.03	**<.001**
Level 2 predictors of cort											
Diagnostic group	-	-	-	-	-	0.01	0.05	.873	0.01	0.04	.861
Sum of seizures	-	-	-	-	-	-	-	-	0.01	0.01	.528
Deviance	146.10		145.81			-41.72			-42.11		
Parameters	3		4			6			7		

3.4.4.2.3 Seizure occurrence predicting HRV parameters

The intra-class correlations for the HRV parameters calculated from the null models are summarised in Table 3.18. The models for the four HRV parameters are summarised in Tables 3.19 – 3.22.

Examination of the models for SDNN showed that the number of seizures in the past 12 hours alone (Model 1) was a significant predictor of SDNN (Table 3.19) and this model provided a significant improvement in deviance compared to the null model, X^2 (1) = 4.19, p = .041, accounting for an estimated 4.9% of the within-participant variance in daily SDNN. One unit increase in the number of seizures in the past 12 hours was associated with a 0.04 per cent reduction in SDNN. Seizures remained a significant predictor when the effects of time of day and diagnostic group were added to the model (Model 2) and this model was not a significant improvement compared to Model 1, X^2 (2) = 0.68, p = .409. Similarly, the number of seizures in the past 12 hours remained a significant Level 1 predictor when the sum of seizures was introduced at Level 2 (Model 3) and this model did not provide a significance reduction in deviance, X^2 (1) = 2.74, p = .100.

Table 3.18. *Intra-class correlation estimates for the HRV parameters*

HRV Parameter	Intra-Class Correlation (ICC)
SDNN	0.630 (63.0%)
RMSSD	0.611 (61.1%)
CVI	0.605 (60.5%)
CSI	0.478 (47.8%)

Table 3.19. *Summary of multi-level regression models for number of seizures predicting SDNN, with time-points (Level 1: N = 153) nested within patients (Level 2: N = 39) with random intercept and fixed slopes for all predictors*

	Null Model		Model 1			Model 2			Model 3		
Parameter	*B*	*SE*	*B*	*SE*	*p*	*B*	*SE*	*p*	*B*	*SE*	*p*
Level 1 predictors of SDNN											
Intercept	1.67	0.04	1.48	0.04	<.001	1.43	0.05	<.001	1.38	0.06	<.001
Seizures in past 12 hrs	-	-	-0.04	0.02	**.039**	-0.04	0.02	**.025**	-0.05	0.02	**.010**
Time of day	-	-	-	-	-	0.05	0.03	.072	0.05	0.03	.066
Level 2 predictors of SDNN											
Diagnostic group	-	-	-	-	-	0.06	0.07	.410	0.07	0.07	.318
Sum of seizures	-	-	-	-	-	-	-	-	0.03	0.02	.102
Deviance	-66.67		-70.87			-74.86			-77.60		
Parameters	3		4			6			7		

As shown in Table 3.20, seizures in the past 12 hours were not a significant predictor of RMSSD (Model 1) and this model did not provide a significant reduction in deviance compared to the null model, X^2 (1) = 2.06, p = .151. Introducing the effects of time of day and diagnostic group in the model (Model 2) showed that the time of day was a significant predictor of RMSSD. In line with the results reported in section 3.4.2, RMSSD was likely to be lower in the morning (coded as 0) than in the evening. This model provided a significant reduction in deviance compared to Model 1, X^2 (2) = 10.79, p = .005. Interestingly, when the sum of seizures was added at Level 2 (Model 3), the number of seizures in the past 12 hours at Level 1 became a significant predictor of RMSSD. The model suggested that when the patient's total number of seizures was controlled for, one unit increase in the number of seizures in the past 12 hours was associated with a 0.06 per cent decrease in daily RMSSD. The overall sum of seizures was a significant Level 2 predictor, suggesting that in patients

who experienced more seizures during the video-EEG monitoring period, the RMSSD levels were higher. The time of day also remained a significant predictor, as shown in Table 3.20. This model provided a significant improvement in deviance compared to Model 2, X^2 (1) = 4.65, p = .031, accounting for an estimated 10.3% of the within-participants variance in RMSSD.

Table 3.20. *Summary of multi-level regression models for number of seizures predicting RMSSD, with time-points (Level 1: N = 153) nested within patients (Level 2: N = 39) with random intercept and fixed slopes for all predictors*

	Null Model		Model 1			Model 2			Model 3		
Parameter	*B*	*SE*	*B*	*SE*	*p*	*B*	*SE*	*p*	*B*	*SE*	*p*
Level 1 predictors of RMSSD											
Intercept	1.44	0.04	1.45	0.04	<.001	1.35	0.06	<.001	1.28	0.07	<.001
Seizures in past 12 hrs	-	-	-0.04	0.02	.148	-0.04	0.02	.076	-0.06	0.03	**.022**
Time of day	-	-	-	-	-	0.10	0.03	**.003**	0.10	0.03	**.002**
Level 2 predictors of RMSSD											
Diagnostic group	-	-	-	-	-	0.11	0.09	.218	0.12	0.08	.135
Sum of seizures	-	-	-	-	-	-	-	-	0.04	0.02	**.034**
Deviance	4.98		2.92			-7.87			-12.52		
Parameters	3		4			6			7		

The model parameters for CVI are summarised in Table 3.21. The number of seizures in the past 12 hours alone was not a significant predictor of CVI (Model 1) and adding this parameter did not provide a significant improvement in deviance compared to the null model, X^2 (1) = 2.39, p = .121. Adding the effects of time of day and diagnostic group to the model (Model 2) showed that time of day was a significant predictor of CVI, suggesting that CVI in the morning (coded 0) was likely to be lower than in the evening. This model provided a significant reduction in deviance compared to Model 2, X^2 (2) = 6.92, p = .032, accounting for an estimated 7.3% of the within-participants variance in CVI. The time of day remained a significant predictor when the sum of seizures was added at Level 2 (Model 3). Furthermore, when the sum of seizures was included in the model, the number of seizures in the past 12 hours became a significant predictor of CVI at Level 1, suggesting that when the patients'

overall number of seizures was held constant, a one unit increase in the number of seizures in the past 12 hours was associated with 0.02 per cent reduction in CVI. However, adding these parameters did not provide a significant reduction in deviance compared to Model 2, X^2 (1) = 3.54, p = .060.

Table 3.21. *Summary of multi-level regression models for number of seizures predicting CVI, with time-points (Level 1: N = 153) nested within patients (Level 2: N = 39) with random intercept and fixed slopes for all predictors*

	Null Model		Model 1			Model 2			Model 3		
Parameter	*B*	*SE*	*B*	*SE*	*p*	*B*	*SE*	*p*	*B*	*SE*	*p*
Level 1 predictors of CVI											
Intercept	0.45	0.01	0.45	0.01	<.001	0.42	0.02	<.001	0.41	0.02	<.001
Seizures in past 12 hrs	-	-	-0.01	0.01	.118	-0.01	0.01	.078	-0.02	0.01	**.027**
Time of day	-	-	-	-	-	0.02	0.01	**.022**	0.02	0.01	**.020**
Level 2 predictors of CVI											
Diagnostic group	-	-	-	-	-	0.03	0.03	.212	0.03	0.02	.144
Sum of seizures	-	-	-	-	-	-	-	-	0.01	0.01	.064
Deviance	-389.74		-392.13			-399.05			-402.60		
Parameters	3		4			6			7		

Examination of the models for CSI showed that the number of seizures in the past 12 hours alone was not a significant predictor of CSI (Model 1) and this model did not provide a significant improvement in deviance compared to the null model, X^2 (1) = 0.31, p = .575.

Introducing the effects of time of day and diagnostic group (Model 2) showed that time of day was a significant predictor of CSI. As shown in Table 3.22, the model suggests that CSI in the morning (coded as 0) was likely to be higher than in the evening, which is consistent with the findings reported in section 3.4.2. This model provided a significant improvement in deviance compared to Model 1, X^2 (2) = 17.70, p < .001. Finally, the sum of seizures was added at Level 2 (Model 3). The sum of seizures was a significant predictor of CSI, suggesting that one unit increase in the overall number of seizures a patient experienced was associated with 0.02 per cent reduction of CSI. When this parameter was included in the model, the diagnostic group also became a significant predictor of CSI, suggesting that when

the overall number of seizures was held constant, patients with PNES (coded as 0) had higher CSI than patients with epilepsy (see Table 3.22). The time of day also remained a significant predictor of CSI. This model provided a further significant reduction in deviance, X^2 (1) = 5.43, p = 0.020, and accounted for an estimated 10.4% of the within-participants variance in CSI. [2]

Table 3.22 *Summary of multi-level regression models for number of seizures predicting CSI, with time-points (Level 1: N = 153) nested within patients (Level 2: N = 39) with random intercept and fixed slopes for all predictors*

	Null Model		Model 1			Model 2			Model 3		
Parameter	*B*	*SE*	*B*	*SE*	*p*	*B*	*SE*	*p*	*B*	*SE*	*p*
Level 1 predictors of CSI											
Intercept	0.26	0.02	0.26	0.02	<.001	0.33	0.03	<.001	0.36	0.03	<.001
Seizures in past 12 hrs	-	-	-0.01	0.01	.575	-0.004	0.01	.776	0.01	0.01	.566
Time of day	-	-	-	-	-	-0.07	0.02	**<.001**	-0.07	0.02	**<.001**
Level 2 predictors of CSI											
Diagnostic group	-	-	-	-	-	-0.07	0.04	.083	-0.07	0.03	**.041**
Sum of seizures	-	-	-	-	-	-	-	-	-0.02	0.01	**.021**
Deviance	-184.36		-184.67			-202.37			-207.05		
Parameters	3		4			6			7		

3.5 Discussion

The main objective of this exploratory study was prospectively to capture a range of psychological and physiological stress measures in patients with epilepsy and those with PNES, to describe the daily patterns of these measures, their associations with each other, and their relationships with seizure occurrence.

The first aim of this chapter was to provide a description of diurnal variability in the different daily stress measures. The summary of the morning and evening data from both patient groups revealed that levels of self-reported stress were comparable in the mornings

[2] In addition, all models reported in section 3.4.4.2 were also run with random slopes at Level 2. Making the slopes random to check for random effects did not significantly reduce the deviation (p > .05), suggesting there were no cross-level interactions.

and in the evenings in both patient groups. In contrast, the physiological stress measures showed a circadian pattern.

The HRV parameter reflecting the parasympathetic nervous system tone (RMSSD) was lower in the morning and higher in the evening, whereas the parameter reflecting sympathetic nervous system tone (CSI) showed an opposite pattern, with values being higher in the morning and lower in the evening. The sympathetic metric was also higher overall in patients with PNES than in patients with epilepsy. This is in contrast to the findings of Ponnusamy et al. (2011) who found no differences in resting parasympathetic or sympathetic HRV parameters between patients with epilepsy and patients with PNES. In terms of the circadian patterns of HRV, a day-night pattern has been reported in healthy individuals, with a peak of the vagal tone at night, decrease towards a sympathetic dominance in the morning and a plateau throughout the day (Bonnemeier et al., 2003). Most studies of the cardiac and autonomic changes in epilepsy examined heart-rate variability in relation to the risk of sudden unexpected death in epilepsy (SUDEP). Several studies reported HRV alterations in patients with epilepsy, with reduced vagal tone both ictally and interictally, compared to healthy controls, particularly in refractory epilepsy (Brotherstone & McLellan, 2012; Jeppesen et al., 2010; Lotufo et al., 2012; Nei, 2009; Ponnusamy et al., 2012; Pradhan et al., 2011). However, not many researchers have examined the diurnal patterns of HRV in patients with epilepsy and the evidence is even more limited for patients with PNES. One study found suppressed circadian HRV characterised by attenuation of the normal night time increase of HRV in patients with temporal lobe epilepsy, compared to healthy controls (Ronkainen et al., 2005). In contrast, the results of the present study suggest that the circadian changes in both patients with epilepsy and patients with PNES follow the normal day – night pattern. The results are consistent with the findings of a doctoral thesis on the autonomic function in epilepsy, which assessed 24-hour HRV in 66 patients with intractable epilepsy and found a

similar diurnal pattern of HRV changes, with high vagal tone (RMSSD) at night and lower vagal tone in the morning and throughout the day but no significant differences in the overall HRV (SDNN) between day and night time (Adjei, 2011). Nevertheless, both the present study and the study conducted by Adjei lack a control group of healthy participants, and it is therefore possible that whilst there are detectable differences between the morning and evening vagal tone in the patient sample, these differences may not be as pronounced as they are in healthy individuals and/or that the HRV in the patients may be reduced overall.

Similarly to the patterns found in heart-rate variability, the results of the present study showed a distinct pattern in the levels of salivary cortisol, with high values in the morning and lower levels in the evening. This pattern is consistent with the well-established circadian rhythm of cortisol and it was similar in both patients with PNES and patients with epilepsy. No differences were found between the groups in their cortisol deltas either (morning cortisol minus evening cortisol). Interestingly, when the cortisol measures were compared to data from healthy volunteers collected at the same time points (9am and 10pm), there were no significant differences in the morning, evening or cortisol delta levels between patients and healthy individuals. This would suggest that the normal cortisol rhythm was preserved in the two patient groups and that they did not have significantly altered levels of morning or evening cortisol and did not show a blunted cortisol delta, compared to the normative data. This is rather surprising, considering the presence of factors that may have been expected to reduce diurnal cortisol fluctuation, such as the use of enzyme-inducing anti-epileptic drugs and psychological disturbances related to comorbid depression. Nevertheless, this finding seems to parallel the results of studies that found no differences in baseline cortisol levels between patients with epilepsy and healthy controls (Hofstra & de Weerd, 2009; Pritchard, 1991).

The evidence for the diurnal levels of cortisol in patients with PNES is mixed. A few studies reported no difference between patients with PNES and healthy controls (Bakvis et al., 2009b; Tunca et al., 1996) whilst later studies by the same authors found increased cortisol levels in patients compared to controls (Bakvis et al., 2010; Tunca et al., 2000). One reason for the discrepancy between the findings of the latter study by Bakvis and colleagues and the results of the present study may be the time of measurement. Bakvis and colleagues found significant differences in cortisol levels between patients and controls at 12pm, 2pm, 4pm, 6pm and 8pm but, similarly to the present study, the groups in the Bakvis study were not significantly different at 10am or at 10pm (Bakvis et al., 2010). This suggests that patients and healthy individuals may not differ significantly at the extreme points, i.e., in the morning when the cortisol levels are the highest and late in the evening when the cortisol levels are very low, but that there may be differences in the day curve of cortisol. The lack of multiple saliva collection points throughout the day that would allow for construction of cortisol day curves is a limitation of the current study. Another reason for the findings of the study by Bakvis and colleagues may be that their group of patients included a high proportion of individuals who experienced sexual trauma. These patients had higher cortisol levels in the study by Bakvis et al. than patients with PNES but no history of sexual trauma. History of sexual trauma was not assessed as part of the present study and it is therefore not possible to determine whether it may have had any influence on the patients' cortisol levels. However, it is worth noting that the PNES group in the present study consisted predominantly of male participants, in whom the likelihood of a previous experience of sexual abuse is lower than in females (Bowman & Markand, 1999; Duncan & Oto, 2008).

As part of the second aim of this chapter, the relationships between these measures were examined both at the person level using mean measures for each patient and at the time-point level, using all available data points. No significant relationships were found between

the self-reported stress and any of the physiological measures. As would be expected from the patterns found in the physiological measures, there was a significant negative relationship between the HRV and cortisol measures in the morning. No relationships were found between the evening measures, which may be largely related to the very low cortisol levels in the evening. As found in previous studies of HRV, most of the HRV parameters were closely related to each other both in the morning and in the evening (Allen et al., 2007; Stalder et al., 2011). Data on the relationship between the HPA axis and the HRV are limited. A study of a group of healthy psychology students showed a significant negative association between cortisol awakening response and resting HRV later in the day but no associations between awakening-induced changes in cortisol and awakening-induced changes in HRV (Stalder et al., 2011). A study of healthy medical students found no correlation between cortisol and HRV at rest but correlation was found under stressful conditions on an examination day (Lucini et al., 2002). Similarly, a study of healthy nurses during working shifts suggested that the two systems might function relatively independently during everyday situations characterised by low levels of stress but the cortisol and HRV response becomes closely correlated in highly stressful situations (Looser et al., 2010). It could be speculated that the correlation of morning HRV and cortisol observed in the patients in the present study is more similar to a correlational pattern found in healthy individuals in stressed rather than non-stressed states.

Overall, the pattern of the HRV and cortisol measures and their relationships in the current study suggest that the physiological stress markers in patients with seizures follow a diurnal pattern characterised by higher physiological arousal in the morning and lower levels of arousal in the evening. This pattern is not reflected in the subjectively reported levels of stress, which suggests some discrepancy between the more objective physiological measures and the subjectively self-reported measures. This discrepancy has been noted in other studies.

For example, in Stalder et al. (2011), cortisol, heart rate and HRV were not associated with self-reported measures of either perceived stress or emotional regulation. Furthermore, both patients with epilepsy and patients with PNES tend to have relatively high levels of alexithymia (i.e., difficulty in identifying, understanding and describing own emotions), which can cause further inaccuracies in their self-reports (Bewley et al., 2005; Myers et al., 2013). This highlights the complexity of the experience of stress and the difficulty of its assessment in patients with seizures, as patients' subjective perceptions may not always match or reliably reflect the underlying physiological processes. However, it is also possible that self-report stress measures, particularly the momentary version of the SSSI questionnaire used in the present study, may be better at capturing acute changes in stress levels. Despite the fact that the patients in the present study experienced seizures during the monitoring period and were undergoing various diagnostic and other medical procedures, the morning and evening stress measurements were mostly conducted during the interictal, resting state.

The third aim of this chapter was to explore the relationships between the daily psychological and physiological stress measures and seizure occurrence using a multi-level analysis approach. The results indicate that, in the current study, the occurrence of epileptic or psychogenic non-epileptic seizures was not predicted by any of the daily self-report, cortisol or heart-rate variability measures. Stress has been described as a seizure precipitant in patients with epilepsy by many cross-sectional and self-report studies (Ferlisi & Shorvon, 2014; Nakken et al., 2005; Privitera et al., 2014; Sperling et al., 2008; Wassenaar et al., 2014). However, to date, only two studies have examined the links between stress and seizure occurrence prospectively in adult epilepsy and their findings were mixed (Haut et al., 2012; Haut et al., 2007). As discussed in the Literature Review, the first study, which used paper diaries completed once a day, found that stress, anxiety and sleep deprivation increased the likelihood of seizure occurrence in the next 24 hours (Haut et al., 2007). In contrast, the later

study, in which electronic diaries with morning and evening alarm prompts were used and which assessed a wider range of precipitating factors and premonitory symptoms, did not find stress to be a significant precipitant of seizures (Haut et al., 2012). Instead, mood and so-called premonitory symptoms were associated with increased likelihood of seizure occurrence over the following 12-hour period. There are currently no prospective studies of the links between stress and seizure occurrence in patients with PNES. The present study extends the previous diary studies by including physiological stress markers, in addition to self-reported stress. Similarly to the latter study by Haut and colleagues, the present study did not find self-reported stress to be a significant predictor of seizures. The present study did not assess the premonitory seizure symptoms described in the study by Haut and colleagues, which were found to be significant predictors of seizure occurrence. However, the Smith Stress Symptom Inventory used to assess the daily stress in the present study does include a range of somatic and cognitive symptoms that would fit the definition of some of the premonitory symptoms in the study by Haut and colleagues, such as feeling irritable, feeling emotional, experiencing headaches or having trouble concentrating (Haut et al., 2012). Furthermore, the present study assessed physiological arousal using biological markers of both the HPA axis and the autonomic nervous system. Yet, none of these measures were found to be predictive of the number of seizures occurring in the subsequent 12 hours. One possible explanation for the discrepancy between the studies may be the different environments in which the diary data were collected (naturalistic home environment in the study by Haut et al., versus inpatient video-telemetry ward in the present study). A further limitation of the present study, compared to the study by Haut and colleagues, is the considerably smaller number of data points, as the present data were collected over a 3 – 5 day period, whereas the participants in the Haut study kept diaries for 12 – 14 weeks.

The examination of whether the occurrence of seizures can predict any of the daily stress measures over the following 12 hours revealed that seizures were predictive of self-reported stress as well as some of the heart-rate variability measures. However, seizures did not predict the levels of salivary cortisol in either patient group. Cortisol was better predicted by time of day, which accounted for a large proportion of the within-participants variance. This is consistent with the earlier finding of a distinct diurnal pattern characterised by high cortisol levels in the morning and low levels in the evening.

Occurrence of seizures was associated with higher levels of self-reported stress and reduced overall heart-rate variability (as measured by the SDNN parameter) in both patient groups. The relationship was maintained when time of day and the overall number of seizures were accounted for in the more complex models. Although the within-subject variance in self-reported stress and SDNN explained by the number of seizures in the previous 12 hours was relatively small (7% and 4.9% respectively), this finding seems to suggest that at least some of the daily variance in these stress measures was accounted for by seizure occurrence. This is perhaps not surprising, as both epileptic and non-epileptic seizures are distressing events, associated with a range of psychological and physiological changes. Patients with PNES were previously found to report high levels of somatic symptoms of anxiety during their attacks (Goldstein & Mellers, 2006) and a number of studies demonstrated ictal alterations of HRV during epileptic seizures (Brotherstone & McLellan, 2012; Ponnusamy et al., 2012). A previous study of 31 surgical candidates with epilepsy found post-ictal disturbance in heart-rate variability lasting for up to 5 – 6 hours after the seizure (Toth et al., 2010).

The relationships between seizure occurrence and the other HRV parameters were more complex. The multi-level analyses confirmed the earlier findings and showed that the parasympathetic (RMSSD, CVI) and sympathetic (CSI) parameters were significantly

predicted by time of day, with lower parasympathetic and higher sympathetic nervous system tone in the morning and higher PNS and lower SNS tone in the evening. There was a discrepancy in terms of the effects of time of day on the CVI parameter. While the multi-level analyses suggested that CVI was lower in the morning and higher in the evening, the earlier analysis in section 3.4.2 did not detect a significant difference between the mean morning and the mean evening CVI. This could be explained by the fact that the multi-level analyses used both time-level and person-level data rather than person-level mean measures and as such are therefore likely to provide a more accurate estimate of the relationships.

When the overall number of seizures the patient experienced during the monitoring was held constant, seizures in the past 12 hours were also a significant predictor of RMSSD. Occurrence of seizures in the previous 12-hour period was associated with reduced RMSSD, indicating a decrease in the parasympathetic (vagal) tone after seizures. However, the overall number of seizures was also a significant predictor of RMSSD but in the opposite direction. The results seem to suggest that patients who experienced more seizures overall had higher RMSSD. Similarly, the overall number of seizures was a significant predictor of CSI, with patients who experienced more seizures overall having lower CSI, i.e., lower sympathetic nervous system tone. The reasons for this seemingly contradictory finding are not entirely clear. When the overall number of seizures was held constant, the diagnostic group was also a significant predictor of CSI, suggesting that CSI was higher in patients with PNES than in patients with epilepsy, which is consistent with the earlier analysis.

Taken together, the findings about the relationship between stress and seizure occurrence in this exploratory study seem to suggest that, whereas the experience of seizures may be associated with increased perceived stress and autonomic arousal observable for up to 12 hours after the seizure, neither the subjectively perceived stress nor the physiological stress markers are reliable predictors of seizure occurrence. This is not consistent with the

findings of the large number of studies in which patients reported stress as the main seizure precipitant. Considering the lack of correlation between the physiological and self-reported stress measures in the present study, it could be speculated that patients may be unable to reliably assess their subjective stress symptoms or that their subjective experience does not necessarily match their physiological stress responses. Either way, it is conceivable that when thinking about their seizures, which are experiences that are associated with increased subjective and physiological stress, patients may misattribute seizures to stress as a trigger in retrospective self-reports. Similarly, it is also possible that their post-seizure appraisal of pre-seizure events may characterise these events as more stressful in retrospect than they were experienced at the time. Recent perspectives on patients' self-reports indeed suggest that retrospective self-report questionnaires tap into the 'remembering' self, which is linked to default and long-term memory networks and is functionally and neuroanatomically different from the conscious, 'experiencing' self, which is more connected to the salience network and bodily sensations (Conner & Barrett, 2012). While patients' subjective memories, perceptions and beliefs about their seizures and seizure precipitants are important, the results of the present study suggest that they may not be a reliable seizure prediction tool. However, it is important to remember that this is a single exploratory study with a number of limitations (discussed below), and more data will be needed to establish the relationships with more certainty.

3.5.1 Limitations

The study has a number of limitations. The main limitations are related to its exploratory nature and its correlational design, which does not provide evidence about causal links among the variables. Due to the exploratory nature of the study, a number of tests have been performed without making adjustments for multiple testing, which may have increased

the risk of Type 1 error. Furthermore, although the sample size is comparable to that of similar previous studies, there were a relatively limited number of data-points available for analysis, particularly for patients admitted for only 3 days and those with a lot of missing data. The findings of this study therefore need to be interpreted with caution and taken as preliminary bases for future well-powered studies rather than conclusive evidence.

Another limitation is the environment in which the study took place. The levels of acute stress are likely to be somewhat different in the hospital setting than in patients' home environment. It is possible that some individuals may experience the hospital environment as well as the daily diagnostic procedures as generally stressful. On the other hand, being away from the context of common everyday demands and hassles and stressful or dysfunctional family relationships and interactions may reduce stress for some patients.

This is related to another limitation of the study, namely the fact that it only accounted for a limited range of factors that may affect the stress that patients experience and its effect on seizures. There is a range of other factors that could be considered in future studies, including stressful or traumatic experiences in early life and other major life events throughout adulthood, significant interpersonal relationships or even the influence of genetic factors. Although there were no major differences between the two patient groups on their baseline measures, the groups were nevertheless heterogeneous, with different patients taking different medication and experiencing different seizure types. There were patients who did not experience any seizures during the video-EEG monitoring and there were patients in the PNES group whose seizures did not involve loss of consciousness, which means that although two expert clinical opinions were obtained to establish the diagnosis, some patients may still have been misdiagnosed. Given the heterogeneity of these patients and the complexity of the relationship between stress and seizures, it is possible that there may be a sub-group of patients who may be more vulnerable to stress and/or its effects on seizures than

others. One mechanism that could underlie this vulnerability is the cognitive bias to stress-related stimuli, explored and discussed in Chapter 4. However, the relatively small sample size in this study and the limited number of seizures experienced during the monitoring did not allow for performance of sufficiently powered sub-group analyses.

Another limitation is the possible effect of antiepileptic medication. The patients in this study were taking different anti-epileptic (and other) drugs and some subjects had their medication temporarily withdrawn or reduced during the stay in the telemetry unit, which may have affected their psychological and physiological state. Hepatic enzyme-inducing medications (such as some of the most commonly used antiepileptic drugs) may have significant effects on salivary cortisol levels (Hofstra & de Weerd, 2009). Antiepileptic drugs may also affect HRV measures (Hofstra & de Weerd, 2009; Sevcencu & Struijk, 2010). However, there is currently no available literature to provide comprehensive guidance on possible exclusion criteria for particular AEDs. The fact that the cortisol levels did not differ significantly between patients or from the normative data from healthy individuals seems to suggest that the medication did not cause any significant alterations in cortisol levels in patients. However, this cannot be determined with certainty.

A further issue is related to the temporal dynamics and relationships between the variables. As mentioned previously, the daily assessment was performed twice. As a result, the time period between the stress assessments and seizure occurrence was variable, with some seizures occurring within a few hours of the morning/evening stress measurement but others occurring nearly 12 hours later. It also meant that it was not possible to explore cortisol day curves or assess these measures at fixed times before and after seizures. Furthermore, certain events during the course of the day that may have caused increased or acute stress to patients may have been missed. Therefore, the lack of a relationship between

stress and subsequent seizure occurrence may be explained by the fact that the time-window of 12 hours was too large.

3.5.2 Future Research

The results of this exploratory study highlight the complexity of the experience of stress and the relationship of its different components to each other and to seizures. Further examination of these relationships is therefore warranted. For example, future studies could include a control group of healthy participants, in order to compare the diurnal patterns of physiological stress measures between patients with seizures and healthy individuals.

The present study could be replicated with a larger sample of patients and with more data collection points throughout the day and before and after seizures. It would also be interesting to examine the effects of seizure severity on the levels of stress, which is something that was not feasible as part of the present study, due to the significant proportion of missing seizure severity data.

A sufficiently powered study with a larger sample could also perform sub-group analyses to explore factors that may make certain sub-groups of patients particularly vulnerable to the effects of stress or the effects of stress on their seizures, such as past experience of trauma or a range of individual vulnerability or resilience factors. A recent study of childhood epilepsy ($N = 64$), which used both retrospective reports and diaries found a positive relationship between acute stress and seizures in 62% of the children (van Campen et al., 2015). The study further found that children with such stress-related seizures showed blunted cortisol response to an acute stressor, compared to children without stress-precipitated seizures or healthy controls, although the groups did not differ in their sympathetic stress response or in their baseline cortisol levels. Immediate responses to acute stressors were not assessed in the present study. Therefore, a design similar to that of the van

Campen study could be replicated in adult epilepsy and the effects of acute versus more chronic stress on seizures could be further explored by prospective longitudinal studies with more frequent assessment points. Based on the finding of a diurnal pattern of both cortisol and HRV reported in this chapter, future cortisol and HRV-based studies in patients with seizures will need to take into consideration the time of when the study was conducted,

3.5.3 Implications and Conclusions

To conclude, this exploratory study assessed a combination of physiological and psychological stress measures and prospectively assessed their relationships to each other as well as to seizure occurrence. Despite the limitations of the study, the present findings contribute to previous studies of the diurnal patterns of physiological stress measures in patients with seizures, particularly in those with PNES, where these measures have not previously been assessed prospectively. The study also expands on the findings of previous diary studies of the relationships between stress and seizures by including physiological measures of stress. The results of the present study indicate that there may be a discrepancy between patients' physiological responses and their subjective perceptions, and that whereas the experience of seizures seems to be associated with increased self-reported stress and physiological arousal, the effects of the physiological and self-reported stress on seizure occurrence are less clear.

4. CHAPTER 4

Study 1b: Exploring Implicit Attentional Responses to Stress-Related Stimuli Using the Emotional Stroop Test

4.1 Study Introduction

A large body of psychological research has focused on studying implicit cognition as a way of assessing and understanding processes that are not accessible to introspection and therefore not easily captured by self-report (Wiers et al., 2007). Implicit cognition comprises processes involving attention, memory, learning, or social cognition that are automatic, outside of conscious awareness, and are believed to have important effects on behaviour and physiological responses (Dimaro et al., 2014; Egloff et al., 2002; Wiers et al., 2007). It has been demonstrated that biased implicit attitudes can influence decision making, for example in the context of shortlisting members of ethnic minorities for academic positions (Beattie et al., 2013). As another example, in a study of healthy participants undertaking a speech stress test, an implicit attention task predicted heart rate and blood pressure reactivity to the speech test (Egloff et al., 2002). These implicit processes have also been suggested to be more reliable predictors of psychological and behavioural outcomes than explicit measures and self-reports (Beattie et al., 2013; Cox et al., 2002; Dimaro et al., 2014; Nock et al., 2010). For example, Nock et al. (2010) found that implicit associations between the self and death/suicide in individuals attending a psychiatric emergency department were a significantly better predictor of the patients making a suicide attempt than known risk factors such as depression or the clinicians' and patients' predictions. Implicit cognitive processes may also play an important role in the aetiology and maintenance of psychopathology (Wiers et al., 2007; Williams et al., 1996).

One common paradigm used to study implicit attention is the Stroop test. The Stroop test is a measure of attentional bias and response automaticity (Stroop, 1935). It demonstrates that more automatic responses can cause interference in situations where the individual is required to attend selectively to a less automatic task. In the traditional colour word Stroop test, the task is to name the colour of the ink in which a word is written, ignoring the meaning of the word itself, which creates a conflict between the more automatic tendency to read the word and the colour naming. The conflict, or the so-called Stroop effect, is reflected in slower response times. The emotional version of the Stroop test is based on the notion that people with affective disorders have a greater sensitivity to stimuli and information related to their concern. This sensitivity causes them to automatically selectively attend to negative emotional stimuli, which is associated with further exacerbation and maintenance of the disorders (Williams et al., 1996). Such attentional bias has indeed been demonstrated in individuals with post-traumatic stress disorder (PTSD), anxiety, panic or depression, who consistently show slower response times to emotional words related to their psychopathology than to emotionally neutral words in an emotional Stroop test (Buckley et al., 2002; Mitterschiffthaler et al., 2008). There is also some evidence suggesting an attentional bias towards threat may exist in patients with epilepsy (Lanteaume et al., 2009; Zeitlin et al., 1995) and patients with PNES (Bakvis et al., 2009a).

In the current study, the emotional Stroop test was used to assess attentional bias to different types of stress-related stimuli in patients with epileptic seizures and patients with PNES, compared to healthy individuals, as such bias could play an important role in the patients' stress responsiveness and vulnerability and could be a target for psychological interventions. To explore how such attentional biases may relate to the underlying stress physiology, the associations between attentional biases and physiological stress measures were also explored as part of the study.

Additionally, to explore individual characteristics that may make patients more or less vulnerable to attentional hypervigilance other than the seizure disorder itself, as a secondary outcome, the study also examined whether the attentional biases in the two patient groups are moderated by overall levels of self-perceived stress and individual differences in optimism and resilient coping. While heightened attentiveness towards stress-related information may be associated with more frequent stress responses, and may increase vulnerability to emotional distress (Lanteaume et al., 2009), experiencing long-term stress may, in turn, be one of the factors contributing to the development and further exacerbation of attentional biases. Long-term self-perceived stress reported by the patients was therefore explored as one of the possible moderating factors. At the same time, personal resources that contribute to psychological resilience could serve as protective factors, making individuals less vulnerable to developing maladaptive attentional biases. Psychological resilience refers to the individual's ability to adapt to and recover from significant stressors and is associated with personality traits such as optimism, self-efficacy and self-esteem, as well as emotional, cognitive and behavioural processes such as resilient coping, characterised by tendencies to cope with stressors in an active and adaptive manner (Sinclair & Wallston, 2004). Likewise, optimism, which is a personality trait characterised by holding positive beliefs and expectancies about the future, has been linked to less reactivity to stressful experiences and therefore less vulnerability to psychological problems and better subjective wellbeing and quality of life in both healthy populations and patients with medical and psychiatric conditions including coronary heart disease (Carver et al., 2010), epilepsy (Pais-Ribeiro et al., 2007), or PNES (Griffith et al., 2008). Higher optimism is also associated with better adjustment to chronic neurological conditions such as multiple sclerosis (de Ridder et al., 2000) and it has been linked to proactive, engagement coping and lower levels of avoidance (Carver & Connor-Smith, 2010). For example, optimism in patients undergoing coronary

artery bypass surgery was associated with information seeking and goal-setting for recovery (Scheier et al., 1989), and a number of studies of breast cancer patients reported that optimism was related to greater acceptance of the diagnosis, less cognitive avoidance and less helplessness, which in turn led to reduced distress and better quality of life (Carver et al., 1993; Schou et al., 2005). Individual coping style also plays an important role in psychological resilience and there are a number of types of coping including problem- and emotion-focussed coping, engagement and disengagement coping, and proactive and avoidant coping (Carver & Connor-Smith, 2010). In this study, optimism and a resilient coping style were examined as possible moderating factors that could make patients more resilient to attentional biases.

Finally, the effectiveness of a brief self-affirmation intervention in reducing any attentional biases was tested as an additional secondary outcome, in order to explore whether attentional biases in the patients could be altered by this psychological intervention.

4.2 Study Aims

4.2.1 Primary Aims

1. To investigate implicit attentional biases towards/away from stress-related stimuli in patients with epilepsy and patients with PNES, compared to healthy volunteers
2. To test associations between attentional biases and physiological stress measured by heart-rate variability and salivary cortisol within each of the groups

4.2.2 Secondary Aims

3. To examine the moderating effects of self-reported stress, optimism and resilient coping on attentional biases in the two patient groups

4. To test whether attentional biases and/or physiological stress responses can be altered by a brief self-affirmation intervention

4.3 Methodology

4.3.1 Development of the Stroop Test

4.3.1.1 Pre-selection of emotional and neutral words

The selective attentional bias in the emotional Stroop test is characterised by a highly disorder-specific response (Becker et al., 2001). Testing responses to specific types of threat in patients with epilepsy and PNES could therefore provide insights into the mechanisms underlying their psychophysiological stress responses. Based on a review of literature, four categories of threat were identified: (1) seizure-related threat, (2) social threat, (3), somatic threat, and (4) general threat.

In order to assess the responses directly related to the experience of having seizures, a category of seizure-related words was created. Due to the lack of studies specifically investigating the effects of seizure-relevant words, only a small set of words was available, from a study by Zeitlin et al. (1995), including words such as *epilepsy, seizure* and *toxic*. An additional set of candidate words (e.g., *convulsion, blackout, fit*) was identified from a publication of personal accounts of individuals living with seizures (Schachter, 1993).

Given the perceived stigma associated with epilepsy (Baker et al., 2000; Hayden et al., 1992) and the implicit responses to socially threatening images in patients with PNES (Bakvis et al., 2009a), a category of socially threatening words was also included. The word stimuli for this category (e.g., *foolish, humiliated, inferior)* were taken from previous studies of social anxiety (Johnson-Laird & Oatley, 1989; Martin et al., 1991; Mattia et al., 1993).

To explore the role of somatisation in PNES, a further category of illness-related or somatic symptom words (e.g., *sick, medication, aches*) was included. Word stimuli used in

studies of somatoform disorders (Moss-Morris & Petrie, 2003; Witthoft et al., 2009) and panic (McNally et al., 1990) were selected for this category, as were a set of medical words used in a study of epilepsy patients (Zeitlin et al., 1995). A small number of words associated with somatic symptoms identified by the researcher (e.g., *illness, pain, pills*) were also added.

Finally, to explore the effect of generally threatening stimuli, a category of generally threatening words (e.g., *murder, massacre, rape*) that have previously been tested in patients with temporal lobe epilepsy (Lanteaume et al., 2009) was included in the study.

A list of 100 word stimuli was compiled (25 words in each of the four categories of threat) and the words were then matched in frequency, length and semantic category (where possible) with emotionally neutral counterparts. The matching was based on the CELEX Lexical Database (Baayen et al., 1995), using the N-Watch programme for psycholinguistic statistics (Davis, 2005). This resulted in a final list of 25 threat words and 25 neutral words in each of the four categories (200 words in total).

4.3.1.2 Word-rating survey

In order to test the validity of these words for patients with epilepsy and PNES, a survey was conducted using two on-line questionnaires, one asking participants to rate each word in terms of the level of threat and the other to rate them in terms of perceived relevance to seizures.

4.3.1.3 Survey participants

Members of the on-line communities of epilepsy organisations including Epilepsy Action and Fable were approached. Additional participants were recruited in the outpatient clinic at the Royal Hallamshire Hospital in Sheffield. Patients with epilepsy and non-epileptic seizures were included. A total of 21 participants (eight males), aged 24 – 64 years (M = 43.52, SD = 12.49) provided ratings of the level of threat. Seizure-relevance ratings were

obtained from 20 participants (eight males), aged 21 – 73 years (M = 38.95, SD = 14.60). Four participants who did the threat ratings also completed the seizure-relevance questionnaire.

4.3.1.4 Materials and procedure

Two online questionnaires were constructed using Survey Gizmo questionnaire software. A web-link that randomly allocated participants to either the threat or the seizure-relevance rating questionnaire was circulated via online forums of the named epilepsy organisations. Participants were presented with the 200 words in random order and asked to provide ratings of the level of threat *('Please indicate how threatening you find each of the following words'*) or the relevance to seizures *('Please indicate how much you think about each of the following words as being related to seizures'*) on a 7-point Likert scale *('Not at all threatening/Extremely threatening'* or *'Not related to seizures/Very closely related to seizures'*). Participants recruited in the outpatient clinic completed paper versions of the questionnaires.

4.3.1.5 Survey results

The main aim of the analyses was to determine whether the pre-selected threat words were indeed relevant to patients with seizures and to select the most threatening set of stimuli for each category. The analyses were also designed to validate the category of seizure-related words, as the words in this category had not been used in previous studies.

A series of independent-samples t-tests were performed to compare the level of threat of the different word categories. Overall, there was a significant difference between the threat words and the neutral words ($p < .001$) and a significant difference was also found between the neutral words and each of the four threat categories (Table 4.1) ($p < .001$). These findings

confirmed that the threat words were perceived as significantly more threatening than the neutral words by patients with epileptic or non-epileptic seizures.

Table 4.1. *Mean ratings of the level of threat for the neutral and threatening words overall and in each category.*

	Threat Words *M (SD)*	Neutral Words *M (SD)*	P- values Threat vs. Neutral
Overall	2.99 (1.37)	1.32 (0.48)	< .001
General threat words	3.47 (1.53)		< .001
Social threat words	2.87 (1.58)		< .001
Somatic threat words	2.68 (1.58)		< .001
Seizure threat words	2.92 (1.46)		< .001

Note. *M* = mean, *SD* = standard deviation.

Ten words from the general, social and somatic threat category with the highest threat ratings were identified. Almost all of these words fell within the highest quartile; four were among the highest-rated words in the second quartile.

The ten words for the seizure threat category were selected on the basis of the seizure relatedness ratings. The majority of words rated as most closely related to seizures were the words from the pre-selected seizure category. Interestingly, a number of words from the general, social and somatic threat category were also rated as relatively closely related to seizures. There was a particular overlap with the somatic words, with three words from the original pool of somatic threat words being rated among the ten most closely related to seizures. These three words were moved into the seizure threat category.

Each of the selected threat words was paired with its neutral counterpart and the neutral words were then checked for ratings of threat and seizure relatedness. Neutral words that had rather high ratings were replaced by neutral words with lower ratings, matched as closely as possible in frequency and length ($N = 5$). The final list of the 80 words that was used in the experiment is presented in Table 4.2.

Table 4.2. *Threat and neutral words selected for the Stroop experiment with mean threat and seizure relatedness ratings*

General Threat			**Social Threat**		
	Threat Rating	Seizure Rating		Threat Rating	Seizure Rating
Threat	*M (SD)*	*M (SD)*	*Threat*	*M (SD)*	*M (SD)*
RAPE	4.76 (2.12)	2.30 (2.18)	STRESSED	3.76 (2.30)	4.50 (1.88)
MASSACRE	4.57 (2.27)	2.10 (1.92)	FAILURE	3.43 (2.10)	3.35 (2.37)
MURDER	4.52 (2.27)	2.35 (2.18)	PANICKY	3.33 (1.88)	4.05 (2.04)
TERROR	4.38 (2.09)	4.00 (2.60)	HUMILIATED	3.29 (2.00)	3.40 (2.28)
BOMB	4.29 (2.17)	2.60 (2.19)	FEARFUL	3.24 (2.26)	3.95 (2.44)
RAGE	4.14 (1.77)	3.45 (2.61)	INSECURE	3.19 (1.97)	3.30 (2.36)
KILL	4.10 (2.41)	2.55 (2.44)	INADEQUATE	3.10 (2.36)	3.00 (2.34)
HOSTAGE	4.10 (2.23)	2.53 (2.27)	RIDICULE	3.05 (2.00)	2.60 (2.23)
HOSTILE	3.86 (2.10)	2.65 (2.01)	ISOLATED	3.00 (1.90)	3.42 (2.19)
ASSASSIN	3.81 (2.50)	1.85 (1.50)	FAIL	3.00 (2.00)	2.65 (2.21)
Neutral			*Neutral*		
TALE	1.38 (0.92)	1.25 (0.79)	STREAMS	1.33 (1.00)	1.45 (1.47)
MUSICIAN	1.24 (0.70)	1.10 (0.45)	FLOWERS	1.05 (0.22)	1.16 (0.50)
DETAIL	1.57 (1.47)	1.75 (1.71)	ORBITAL	1.10 (0.32)	1.00 (0.00)
BUTTER	1.19 (0.68)	1.10 (0.45)	LANDSCAPES	1.05 (0.22)	1.00 (0.00)
BOWL	1.10 (0.44)	1.25 (1.12)	LUGGAGE	1.57 (1.57)	1.30 (1.34)
KNEE	1.29 (0.78)	1.26 (0.65)	ADJACENT	1.62 (1.57)	1.45 (1.47)
SEAT	1.33 (0.91)	1.20 (0.62)	HOUSEHOLDS	1.38 (1.07)	1.25 (1.12)
HAIRCUT	1.33 (0.58)	1.20 (0.70)	BANANA	1.10 (0.30)	1.05 (0.22)
FORESTS	1.10 (0.30)	1.30 (0.92)	INTERIOR	1.24 (0.70)	1.40 (1.39)
SCISSORS	1.90 (1.30)	1.65 (1.53)	SMOOTH	1.10 (0.30)	1.05 (0.22)
Somatic Threat			**Seizure Threat**		
	Threat Rating	Seizure Rating		Threat Rating	Seizure Rating
Threat	*M (SD)*	*M (SD)*	*Threat*	*M (SD)*	*M (SD)*
PARALYSIS	3.95 (2.48)	3.20 (2.07)	SEIZURE	3.57 (2.58)	6.25 (1.62)
FAINTNESS	3.25 (2.05)	4.45 (1.82)	EPILEPSY	4.05 (2.40)	6.05 (1.76)
ILLNESS	3.14 (1.88)	4.05 (2.26)	BLACKOUT	3.33 (2.33)	5.60 (1.70)
DISEASE	3.05 (2.21)	2.15 (1.90)	HEADACHE	2.52 (2.04)	5.25 (1.97)
SICKNESS	3.05 (2.25)	3.40 (2.46)	CONFUSION	2.91 (2.05)	5.10 (1.80)
BREATHLESS	3.00 (2.03)	3.20 (2.07)	FORGETFUL	3.24 (2.27)	5.00 (2.13)
SHAKY	2.91 (2.05)	3.45 (2.31)	MEDICATION	2.33 (1.65)	5.00 (2.29)
SICK	2.91 (1.97)	3.40 (2.26)	FALL	2.86 (1.98)	4.75 (2.00)
PAIN	2.86 (1.98)	3.80 (2.04)	FATIGUE	3.00 (2.14)	4.75 (2.27)
ILL	2.81 (1.63)	4.50 (1.88)	COLLAPSE	3.38 (2.09)	4.75 (2.40)
Neutral			*Neutral*		
EQUATIONS	1.38 (1.07)	1.25 (0.91)	PEANUTS	1.14 (0.48)	1.15 (0.49)
BILLBOARD	1.05 (0.22)	1.10 (0.45)	PLATYPUS	1.19 (0.68)	1.10 (0.45)
BOTTLES	1.10 (0.30)	1.50 (1.48)	LANTERNS	1.05 (0.22)	1.05 (0.22)
CAPTAIN	1.05 (0.22)	1.00 (0.00)	NOTEBOOK	1.19 (0.51)	1.25 (0.79)
PAVEMENT	1.33 (0.97)	1.25 (0.91)	DOCUMENTS	1.48 (1.12)	1.45 (1.23)
PROGRAMMED	1.24 (0.77)	1.30 (0.92)	READERSHIP	1.38 (0.92)	1.15 (0.49)
SILKY	1.05 (0.22)	1.05 (0.22)	STATIONERY	1.33 (1.32)	1.10 (0.45)
PARK	1.10 (0.30)	1.00 (0.00)	CENT	1.19(0.68)	1.05 (0.22)
LIST	1.67 (1.56)	1.25 (0.91)	DRAWERS	1.14 (0.48)	1.10 (0.45)
BAG	1.05 (0.22)	1.05 (0.22)	CATEGORY	1.14 (0.36)	1.45 (1.15)

Note. *M* = mean, *SD* = standard deviation.

4.3.2 Selection of Self-Affirmation Intervention

A literature search for existing self-affirmation manipulations suitable for use in this Stroop experiment yielded two possible manipulations: a kindness self-affirmation manipulation (Reed & Aspinwall, 1998) and a self-affirmation task based on the Values in Action Strengths scale (Peterson & Seligman, 2003) developed by Napper and colleagues (Napper et al., 2009).

The kindness self-affirmation manipulation is a ten-item self-report questionnaire designed to elicit affirmative responses by asking participants about past acts of kindness (e.g., *'Have you ever attended to the needs of other person?'*). Based on evidence that kindness is a highly desirable personal value, self-affirmation is achieved through affirming the self as possessing this important characteristic.

The Values in Action (VIA) self-affirmation manipulation is a 32-item self-report questionnaire adapted from the original 250-item Values in Action Strengths scale. The self-affirming effects of the questionnaire are achieved through focussing participants' minds on important personal values and strengths (e.g*., 'I always try to keep my word.'*). The items are rated on a 5-point scale (*very much like me / like me/ neutral / unlike me / very much unlike me*).

These manipulations were selected because they are simpler to use than, for example, the frequently used Allport-Vernon-Lindzey Scales (Vernon & Allport, 1931), which require either pre-screening of participants or later allocation of participants to a particular sub-scale. The two selected manipulations are also less demanding than essay-based self-affirmation manipulations, which involve writing an essay about an important value or characteristic.

4.3.2.1 Self-affirmation intervention selection study

In order to make an informed decision about which one of the two manipulations was more suitable for the experiment and for people with seizures, the manipulations were tested and evaluated by members of the local Sheffield branch of the Epilepsy Action.

4.3.2.2 Participants

Six individuals (four males) aged 46 – 68 years (M = 56.00, SD = 8.85) volunteered to take part in the selection study. Four volunteers suffered from epileptic seizures, one volunteer from PNES and one volunteer experienced both epileptic and non-epileptic seizures.

4.3.2.3 Outcome Measures

The self-affirming effects of the two interventions were assessed using the scales developed by Napper et al. (2009). Seven items rated on bipolar scales (scored 0 – 6) were used to assess self-appraisal (e.g., *'The task made me think about positive aspects of myself'*), two items rated on unipolar scales (scored 0 – 4) assessed awareness of the self and values (*'The task made me aware of who I am'* and *'The task made me aware of my values (the principals and standards by which I try to live my life'*).

In addition, a brief interview was conducted with each participant, in order to find out about clarity of the instructions, possible problems with either of the interventions and recommendations regarding the suitability of the interventions for the purposes of the study.

4.3.2.4 Procedure

Members of the Epilepsy Action group in Sheffield were approached by email distributed by the branch officer. Interested volunteers were invited for a one-hour session at the Royal Hallamshire Hospital. Further recruitment was undertaken in person during one of the monthly meetings of the Epilepsy Action Sheffield branch.

Individuals who agreed to participate obtained an information sheet summarising the background and purposes of the study, as well as the purpose and procedure of the session. Participants had an opportunity to ask questions and they agreed to take part by signing a consent form. Participants were asked to complete a brief demographic questionnaire and the two self-affirmation manipulations, first the kindness then the VIA manipulation, each followed by the Napper et al. (2009) rating scales.

After completing the questionnaires, each participant was briefly interviewed about the clarity of instructions and appropriateness of the interventions and asked for additional feedback and comments.

4.3.2.5 Results

A series of paired-samples *t*-tests were performed to test for differences between the self-affirming effects of the two interventions. Table 4.3 shows that the kindness affirmation produced slightly higher ratings on self-appraisal and awareness of self and values. However, the difference between the two interventions was not significant in the elicited sense of self-appraisal ($t = 2.01$, $p = .100$) or awareness of self and values ($t = .67$, $p = .530$).

Table 4.3. *Mean ratings for the kindness self-affirmation and the VIA self-affirmation manipulations*

	Kindness Affirmation *M (SD)*	VIA Affirmation *M (SD)*	P-values
Self-Appraisal	3.69 (0.95)	3.12 (1.26)	*n.s.*
Awareness of Self and Values	3.17 (0.93)	3.00 (0.55)	*n.s.*

Note. *M* = mean, *SD* = standard deviation, *n.s.* = not significant.

Verbal feedback from participants suggested that both self-affirmation manipulations were comprehensible and there were no significant problems with completing either. With regard to the self-affirming effects of the manipulations, participants' responses seemed to

correspond with results of the quantitative ratings. Three participants felt that the kindness manipulation was more thought provoking than the VIA manipulation and that having to write particular examples of past acts of kindness elicited more self-reflection. Two participants preferred the VIA manipulation and found it more personally relevant. One participant had no preference and found both self-affirmation manipulations equally challenging. Overall, the self-affirming effects of the two manipulations seem comparable, although the kindness affirmation may be slightly more effective. As the kindness manipulation is also shorter and has more established support in the literature (Armitage, 2012; Armitage et al., 2008; Epton & Harris, 2008), it was eventually selected for use as the self-affirmation manipulation for the experiment (Appendix 14).

4.3.3 Experimental Design

The Stroop experiment assessed participants' performance on the emotional Stroop test at two time points, before and after the self-affirmation intervention, in order to assess and compare their attentional biases towards/away from stress-related stimuli and to evaluate their responsiveness to psychological intervention.

4.3.4 Participants

4.3.4.1 Patients

Patients admitted for inpatient video-EEG/ECG recruited for Study 1a were approached to take part in the Stroop experiment. Patients were recruited on the basis of the inclusion/exclusion criteria described in Chapter 3.

4.3.4.2 Healthy volunteers

In addition to the patient participants, healthy volunteers were recruited to undertake the emotional Stroop experiment as a control group. Healthy volunteers were recruited

through a volunteer mailing list of the University of Sheffield. All potential participants were sent an email invitation to the study with a link to an online screening questionnaire, which included detailed information about the study and questions about past history of any neurological or psychiatric disorders, age, and gender. This enabled matching of the control group with patients by age and sex and screening for past neurological and psychiatric history. Volunteers with no history of neurological or psychiatric disorders matched in age and gender to the patient participants were invited for the study appointment.

4.3.5 Outcome Measures

4.3.5.1 Self-report measures

A selection of self-report measures completed by all patients at baseline was used for this part of the study. These questionnaires included the demographic questionnaire, Perceived Stress Scale – 4 Item (PSS-4) (Cohen et al., 1983), Liverpool Seizure Severity Scale – Revised (LSSS-3) (Scott-Lennox et al., 2001), Life-Orientation Test – Revised (LOT-R) (Scheier et al., 1994), Spontaneous Self-Affirmation Measure (SSAM) (Harris et al., In preparation), Brief Resilient Coping Scale (BRCS) (Sinclair & Wallston, 2004), and questionnaires assessing psychopathology, including the Neurological Disorders Depression Inventory for Epilepsy (NDDI-E) and the Generalised Anxiety Disorder 7-item Scale (GAD-7) (Spitzer et al., 2006). A detailed description of these measures is provided in Chapter 3.

4.3.5.2 Attentional biases

Implicit attentional biases were investigated by comparing the participants' response times (RTs) to neutral versus threatening words. Slower response times to threatening words, as compared to neutral words, indicate greater attentional bias towards threatening or stress-related stimuli and therefore suggest a cognitive hyper-vigilance towards threat that could increase the vulnerability to stress.

Mean RTs were calculated for the threatening and neutral words overall, as well as for the different word categories. Error trials and trials in which the RT was below or above 2 SD of the participant's mean RT were removed. In order to control for variability in response times between individuals, a D-transformation procedure was used to standardise the scores on the basis of within-participant variability (Greenwald et al., 2003). A D-transformed Stroop Index (D-SI) was calculated as a measure of attentional bias using the following equation:

$$\text{D-SI} = \frac{(\text{mean RT for threatening words} - \text{mean RT for neutral words})}{\text{pooled SD for threatening and neutral words}}$$

4.3.5.3 Heart-rate variability parameters

Patients' ECG was recorded using the ECG channel of the XLTEK EEG system (XLTEK, Ontario, Canada) as is used routinely for video-EEG/ECG monitoring. Healthy participants' ECG recording was obtained using a portable R-R interval recording device (Firstbeat Bodyguard 2) with two chest electrodes. Heart-rate variability parameters were extracted from resting ECG recordings taken at four time-points, immediately before and immediately after each of the Stroop tests. For the analysis of HRV, 3-5 minute samples of resting ECG free of muscle artefact or ectopic beats were selected. The selected samples were visually inspected to ensure the recordings were artefact-free. Patients' ECG samples were recorded by the XLTEK EEG system described in Chapter 3. The ECG samples from healthy participants were extracted from the Firstbeat Bodyguard device using the Firstbeat Uploader software, and saved in an R-R interval data series format (sampled at 1000 Hz). HRV parameters were extracted using the Kubios HRV software, following the procedure detailed in Chapter 3.

The following HRV parameters were used: SDNN as a time domain metric of overall HRV, RMSSD as a time domain parasympathetic metric, total power (TP) as a frequency domain metric of overall HRV, CVI as a non-linear parasympathetic metric, and CSI as a non-linear sympathetic metric.

4.3.5.4 Salivary Cortisol

In this part of the study, saliva was sampled as one of the physiological stress measures at two time points, just before the Time 1 Stroop test and just after the Time 2 Stroop test. The samples were collected using the Salivette collection device (Sarstedt Ltd). Factors that influence levels of cortisol, including smoking, food intake or consumption of drinks with low pH were controlled for. The salivary samples were prepared for analysis, stored and analysed using the same procedure described in Chapter 3.

4.3.6 Procedure and Data Collection Tools

Patients completed the experiment on one of the days they spent in the in-patient video-telemetry ward. Most patients completed the experiment on the first or second day of their stay in the ward. An attempt was made to perform the experiment on days when no seizures had occurred prior to the Stroop test (i.e., since midnight on that day). For patients for whom this was not possible ($N = 7$), the experimenter ensured that the Stroop experiment was completed at least one hour after the seizure occurrence. Healthy volunteers were invited to the Royal Hallamshire Hospital for a 2-hour appointment, during which they underwent the same procedure as the patient participants with the same experimenter.

All participants were asked to complete a set of baseline self-report questionnaires after consenting to participate in the study (see Chapter 3 for the questionnaire description). Only the questionnaires of interest to this part of the study are reported in this chapter. These questionnaires include the demographic questionnaire, the PSS-4, the LSSS-3, the LOT-R,

the SSAM, the BRCS, the NDDI-E and the GAD-7. Completion of these questionnaires took about 30 minutes.

The main part of this study was completion of the emotional Stroop test. The test was performed at two time points: before (Time 1) and after the kindness self-affirmation intervention (Time 2). The experiment was carried out on a laptop computer (13-inch MacBook Pro, OS X 10.8.5, 2012) using software developed specifically for this experiment in the C++ programming language by a research fellow at the Department of Medical Physics and Clinical Engineering, Sheffield Teaching Hospitals NHS Foundation Trust.

Participants sat on a bed or a chair, approximately 50 cm from the laptop screen, which was placed on a hospital table (patients) or a desk (healthy participants). At Time 1, participants were presented with a set of emotionally threatening and matched emotionally neutral words, and asked to indicate the colour of each word by pressing a corresponding key on the laptop keyboard marked with a coloured sticker ('F' = red, 'G' = blue, 'H' = green, 'J' = black). The experimental trials were preceded by 20 practice trials. The following instructions were presented on the laptop screen: *"You will be presented with a set of words written in RED, BLUE, GREEN or BLACK colour. Your task is to indicate the colour of each word by pressing the corresponding key on the keyboard. Please ignore the meaning of the word and identify the colour as quickly as you can without making any errors. You will have a chance to familiarise yourself with the task in a short practice trial before the real test begins. Keep your eyes fixated on the black cross in the middle of the screen and respond to each word as fast as possible."*

Each trial consisted of a black fixation cross display for 500ms, followed by the word stimulus presentation until response was given. The stimuli consisted of the four categories of threatening words described above: (1) general threat words, (2) social threat words, (3) words related to somatic symptoms and (4) words related to the experience of seizures, and a

matched set of neutral counterparts. There were 5 threat words and 5 matched neutral words in each category, adding up to 20 threatening and 20 neutral words in total. Each word was presented singly in the middle of the computer screen, four times, once in each of the four colours (red, blue, green, black), which resulted in a total of 160 trials. Presentation of the word stimuli was randomised for each participant.

Afterwards, participants completed the kindness self-affirmation intervention (Reed & Aspinwall, 1998). After the intervention, patients were asked to perform the emotional Stroop test again (Time 2), using a different set of randomly presented 20 threatening and 20 neutral words taken from the four identified word categories. The order of presentation of the two word-sets used in the Time 1 and Time 2 Stroop tests was counter-balanced across participants.

Participants' resting ECG was recorded for analysis before as well as after the Time 1 and Time 2 Stroop test. For this purpose, participants were asked to lie still in a supine position and breathe normally for 3 - 5 minutes.

In addition, salivary samples were collected from participants for analysis of the levels of free cortisol as a marker of physiological stress. Saliva was sampled at two time points, just before the Time 1 Stroop test and just after the Time 2 Stroop test. The whole experiment took between one and two hours.

4.3.7 Statistical Analyses

The data were analysed using SPSS (version 22; SPSS Inc., Chicago, IL, U.S.A.). Distribution of scores was assessed for normality using the Shapiro-Wilk test. The results are organised into five sections. In the first section, descriptive and inferential statistics including Chi-square and one-way ANOVA with the group (epilepsy vs. PNES vs. healthy controls) as

between-participants independent variable were used to describe and compare the demographic and clinical characteristics of the three groups.

In the second section, the attentional biases in the first Stroop test are explored. The D-SI scores were normally distributed. One-sample *t*-tests were used to explore the attentional biases in each group. A two-way ANOVA for mixed designs with group as a between-participant independent variable (epilepsy vs. PNES vs. healthy controls) and word category as a within-participant independent variable (general vs. seizure vs. social vs. somatic threat words) was performed to examine attentional bias differences between the groups. Differences between the groups were further explored using Tukey's Honestly Significant Difference (HSD) post-hoc tests.

In the third section, associations between attentional biases and physiological measures are examined. The cortisol data and the HRV parameters were non-normally distributed and the distribution was therefore normalised using natural log-transformation prior to analysis and subsequently analysed using parametric tests. A series of one-way ANOVAs were used to first explore the differences in the physiological stress measures including salivary cortisol and HRV between the groups. The relationships between physiological stress measures and the attentional biases were subsequently examined using Pearson's Product-Moment Correlation.

In the fourth section, the moderating effects of self-reported stress, optimism and resilient coping are explored by moderated multiple regression and tests of simple slopes, using the PROCESS for SPSS macro programme (Hayes, 2013).

In the final section, the effects of the self-affirmation intervention are explored. A three-way ANOVA for mixed designs with group (epilepsy vs. PNES vs. healthy controls) as a between-participants independent variable and time (pre- versus post-intervention Stroop test) and word category (general vs. seizure vs. social vs. somatic threat words) as within-

participants independent variables was conducted to examine the effects on attentional biases. The changes in the HRV parameters were examined using a two-way ANOVA for mixed designs with group (epilepsy vs. PNES vs. healthy controls) as a between-participants independent variable and time (before Time 1 Stroop vs. after Time 1 Stroop vs. before Time 2 Stroop vs. after Time 2 Stroop) as a within-participants independent variable. Changes in salivary cortisol measured between the Time 1 Stroop test and after the Time 2 Stroop test were explored using a two-way ANOVA for mixed designs with group (epilepsy vs. PNES vs. healthy controls) as a between-participants independent variable and time (pre- vs. post-Stroop test) as a within-participants independent variable.

In view of the fact that this is an exploratory study, no adjustments were made for multiple comparisons (Goeman & Solari, 2011). Two-tailed *p*-values of <0.05 were considered statistically significant.

4.4 Results

4.4.1 Demographic, Clinical and Psychological Characteristics

Of the 55 patients recruited for Part 1 of the study, 54 patients completed the Stroop experiment. Of these, 22 patients had a diagnosis of epilepsy (13 females, 59.1%), 22 patients had a diagnosis of PNES (eight females, 36.4%), and further five patients had a mixed seizure disorder (all females, 100%). For the remaining five patients, the diagnosis remained uncertain after their admission and expert review (four females, 80%). Patients with mixed disorder and those with an uncertain diagnosis ($N = 10$) were excluded from the analyses, which resulted in a final sample of 44 patients. In addition to the patient participants, 22 healthy adults with no history of a neurological or a psychiatric disorder, matched in age and gender to the patients were recruited for the study as a control group. As one participant later withdrew, the final control group consisted of 21 healthy volunteers (15 females, 71.4%).

Table 4.4 summarises the demographic and psychological characteristics of the participants. Chi-square analysis showed there was no significant difference in gender distribution between the three groups, $X^2(2, N = 65) = 5.53$, $p = .063$. A series of one-way ANOVAs showed there were no significant differences between the groups in age, $F(2, 62) = 0.53$, $p = .591$) or spontaneous self-affirmation, $F(2,58) = 0.67$, $p = .516$. However, there were significant differences in years spent in full-time education, $F(2, 62) = 15.42$, $p = < .001$, levels of self-perceived stress, $F(2, 62) = 7.81$, $p = .001$, anxiety, $F(2, 62) = 7.34$, $p = .001$, depression, $F(2, 62) = 6.11$, $p = .004$, resilient coping, $F(2, 62) = 5.11$, $p = .009$, and optimism, $F(2, 62) = 7.55$, $p = .001$, between the groups. Tukey's HSD post-hoc tests showed that both patients with epilepsy and patients with PNES spent fewer years in full-time education, had higher levels of self-perceived stress, anxiety and depression, and lower levels of optimism than healthy volunteers (p's < .05*)*. Patients with PNES but not patients with epilepsy had lower levels of resilient coping than healthy participants ($p = .007$). A significant difference was found between the groups in their medication use, $X^2(2, N = 65) = 33.18$, $p < .001$. As seen from Table 4.4, a significantly higher proportion of patients were on medication, compared to healthy participants. There were no significant differences between patients with epilepsy and patients with PNES in the duration of their disorder, seizure frequency, or seizure severity (p's > .05).

Table 4.4. *Demographic, psychological and clinical characteristics*

Characteristic	Epilepsy (N = 22) Mean (*SD*)	PNES (N = 22) Mean (*SD*)	Healthy Controls (N = 21) Mean (*SD*)
Gender (N female (%))	13 (59.1%)	8 (36.4%)	15 (71.4%)
Age	39.00 (16.05)	43.68 (12.25)	40.24 (18.07)
Education (years)	14.55 (2.70)	13.29 (2.39)	17.95 (2.98)
PSS-4	7.14 (3.04)	7.14 (3.17)	4.14 (3.24)
GAD-7	8.68 (5.72)	10.62 (5.97)	4.29 (4.84)
NDDI-E	14.36 (3.03)	15.36 (3.77)	11.95 (2.96)
SSAM	4.17 (1.38)	4.56 (1.55)	4.63 (1.17)
BRCS	12.64 (3.63)	11.59 (3.83)	14.81 (2.40)
LOT-R	11.86 (4.47)	12.78 (5.26)	17.24 (4.76)
Seizure duration (years)	14.75 (14.60)	7.27 (7.22)	n/a
Seizure frequency (seizures/month)	15.19 (24.16)	20.76 (41.00)	n/a
Seizure severity (measured by LSSS-3)	48.09 (21.07)	50.44 (22.24)	n/a
Medication use total (N (%))	21 (95.5%)	20 (90.9%)	5 (23.8%)
AED Monotherapy	5 (22.7%)	9 (40.9%)	n/a
AED Polytherapy	16 (72.7%)	3 (13.6%)	n/a
Anti-anxiety/Anti-depressants/Beta-blockers	7 (31.8%)	11 (50.0%)	0
Any other medication	8 (36.4%)	14 (63.6%)	5 (23.8%)

Note. *SD* = standard deviation.

4.4.2 Attentional Biases (Aim 1)

The attentional biases towards/away from stress-related stimuli in the three groups were explored using the D-SI measures in the Time 1 Stroop test (pre-intervention). Table 4.5 summarises the mean overall score as well as the scores for the four word categories in the three groups.

Table 4.5. *Pre-intervention D-transformed Stroop Index (D-SI) in the patient groups and healthy volunteers for the different word categories*

Word Category D-SI (milliseconds)	Epilepsy (N = 22) Mean (*SD*)	PNES (N = 22) Mean (*SD*)	Healthy Controls (N = 21) Mean (*SD*)
Overall D-SI	87.04 (144.21)	23.96 (152.92)	-30.59 (183.14)
General Threat D-SI	65.77 (279.28)	31.15 (292.82)	-70.03 (342.94)
Seizure Threat D-SI	155.35 (304.43)	3.44 (250.13)	49.62 (249.36)
Social Threat D-SI	16.06 (308.72)	26.56 (253.59)	-75.99 (320.67)
Somatic Threat D-SI	131.66 (332.82)	16.56 (328.92)	-17.11 (285.34)

Note. D-SI = D-transformed Stroop Index, *SD* = standard deviation.

The one-sample *t*-tests used to explore the patterns of responses in each group showed that in patients with epilepsy, the overall D-SI, $t(21) = 2.83$, $p = .010$, as well as the D-transformed Stroop Index for the seizure-related threat category, were significantly different from zero, $t(21) = 2.39$, $p = .026$, indicating a significant positive bias towards threatening words. The Stroop responses in patients with PNES and in healthy controls were not significantly different from zero (p's > .05).

The two-way ANOVA used to compare the responses between the groups revealed that the main effect of group (epilepsy vs. PNES vs. healthy controls) was significant, $F(2, 62) = 3.28$, $p = .044$, whereas the main effect of word category (general vs. seizure vs. social vs. somatic threat) was not significant, $F(3, 62) = 0.98$, $p = .405$. The interaction between group and word category was not significant either, $F(2, 62) = 0.47$, $p = .828$. The main effect of group was further investigated using Tukey's HSD post-hoc tests. These tests showed that patients with epilepsy had significantly higher D-SI scores than healthy controls in each word category ($p = .036$). The differences between patients with PNES and healthy controls, as well as between patients with epilepsy and patients with PNES were not significant (p's > .05).

4.4.3 Associations between Attentional Biases and Physiological Stress Measures (Aim 2)

4.4.3.1 Associations between attentional biases and salivary cortisol

Before exploring the associations between the measures, differences between the three groups in salivary cortisol measured before the Time 1 Stroop test were assessed. The mean log-transformed salivary cortisol values for the three groups from samples collected before the Time 1 Stroop test are displayed in Table 4.6. The one-way ANOVA showed there was

no significant difference between the groups in cortisol, although the result approached significance, $F(2, 51) = 2.92$, $p = .063$.[3]

Pearson's product-moment correlation showed there were no significant correlations between salivary cortisol and the Stroop responses overall or in any of the word categories in patients with epilepsy or patients with PNES (p's = .087 – .966; r^2 < .001 – .16). However, significant positive correlations were found in the healthy controls between salivary cortisol and the overall D-SI, $r(13) = .53$, $p = .042$, $r^2 = .28$ (28% variance explained), and between salivary cortisol and the social threat category D-SI, $r(13) = .62$, $p = .014$, $r^2 = .38$ (38% variance explained).

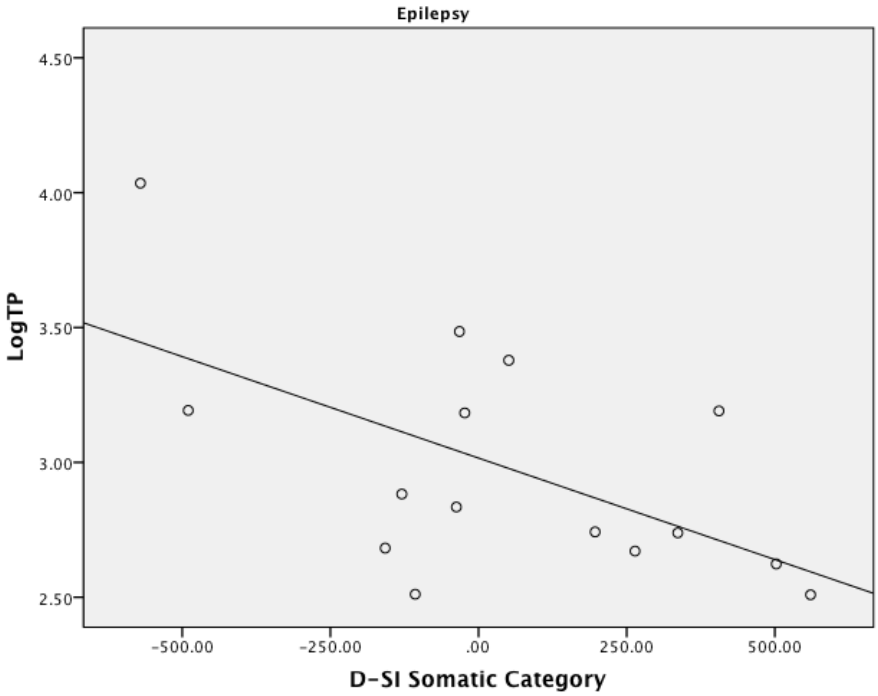
4.4.3.2 Associations between attentional biases and HRV

The heart-rate variability parameters extracted from the resting ECG recording taken just before the Time 1 Stroop are displayed in Table 4.6. First, differences in the HRV parameters between the three groups were explored. The analysis revealed significant differences in SDNN, $F(2, 52) = 5.57$, $p = .006$, TP, $F(2, 52) = 5.35$, $p = .008$, RMSSD, $F(2, 52) = 3.72$, $p = .031$, and CVI, $F(2, 52) = 5.23$, $p = .009$. No significant difference was found in CSI ($F(2, 52) = 0.04$, $p = .957$) between the groups. Tukey's HSD post-hoc tests showed the significant differences were between patients with PNES and healthy controls. Patients with PNES had significantly lower overall measures of HRV than healthy controls, namely the SDNN ($p = .005$) and TP ($p = .006$), as well as lower measures of vagal tone, including RMSSD ($p = .024$) and CVI ($p = .007$), indicating increased autonomic arousal. There were no significant differences between patients with epilepsy and patients with PNES or between patients with epilepsy and healthy controls.

[3] Given the diurnal fluctuations in salivary cortisol discussed in Chapter 3 and the fact that participants performed the Stroop test at various times of the day and the samples were therefore collected at different times, the effects of the cortisol collection time were checked by adding the saliva collection time (samples collected before 12pm versus those collected after 12pm) into the ANOVA. The analysis yielded no significant main effect of collection time and no significant interaction between group and collection time (p's > .05), suggesting that collection time did not significantly affect the cortisol levels in any of the groups.

Next, the associations between the attentional biases measured by the Time 1 Stroop test and the HRV parameters measured prior to the Time 1 Stroop test were examined. In patients with epilepsy, a significant negative correlation was found between the D-SI for somatic words and the total power, $r(13) = -.58$, $p = .022$, $r^2 = .34$ (34% variance explained) (Figure 4.1). There was also a negative correlation between the D-SI for somatic words and SDNN which approached significance, $r(13) = -.49$, $p = .064$, $r^2 = .24$ (24% variance explained). No other significant relationships were found between any of the Stroop responses and the HRV parameters in any of the groups (p's = .072 - .947). The associated effect sizes were small and varied from $r^2 < .001$ (less than 0.1% variance explained) to $r^2 = .17$ (17% variance explained).

Figure 4.1. *Scatterplot representing the correlation between total power and D-transformed Stroop Index for the somatic threat category in patients with epilepsy*



4.4.3.3 Associations between salivary cortisol and HRV

There were no significant correlations between any of the HRV parameters and salivary cortisol in any of the three groups (p's = .191 - .995). Effect sizes were small, varying from r^2 < .001 (less than 0.1% variance explained) to r^2 = .10 (10% variance explained).

Table 4.6. *Physiological stress measures in the three groups taken before Time 1 Stroop*

Physiological Measure	Epilepsy		PNES		Healthy Controls	
	N	Mean (*SD*)	N	Mean (*SD*)	N	Mean (*SD*)
Median cortisol level (nmol/L)*	20	0.55 (0.30)	19	0.38 (0.30)	15	0.35 (0.24)
HRV parameters*						
SDNN	15	1.51 (0.21)	20	1.36 (0.23)	20	1.61 (0.26)
TP	15	2.98 (0.43)	20	2.67 (0.46)	20	3.15 (0.52)
RMSSD	15	1.52 (0.25)	20	1.37 (0.26)	20	1.61 (0.31)
CVI	15	0.47 (0.06)	20	0.42 (0.08)	20	0.49 (0.08)
CSI	15	0.22 (0.15)	20	0.21 (0.15)	20	0.22 (0.13)

Note. *Log-transformed values. Variation in sample sizes indicates missing data for certain variables.

4.4.4 Moderation of Attentional Biases in the Two Patient Groups (Aim 3)

Table 4.7 shows zero-order correlations between attentional biases in the Time 1 Stroop test in the two patient groups and the self-reported psychological measures. To test whether the attentional biases in the two patient groups were affected by self-reported stress, optimism, or resilient coping, a series of moderated multiple regression analyses were conducted, with patient group (patients with epilepsy vs. patients with PNES) as an independent variable and self-reported stress/optimism/resilient coping as moderators. The self-reported stress, optimism, and resilient coping scores were mean-centred prior to analysis.

Table 4.7. *Correlations between the Time 1 Stroop test D-SIs and the self-reported psychological measures in the two patient groups combined*

	1	2	3	4	5	6	7	8	9	10	11
1 Overall D-SI											
2 General D-SI	.492**										
3 Seizure D-SI	.640**	.113									
4 Social D-SI	.419**	.071	.042								
5 Somatic D-SI	.419**	-.135	.121	-.235							
6 PSS-4	-.072	-.043	-.096	.150	-.182						
7 GAD-7	-.235	-.079	-.361*	.018	-.120	.655**					
8 NDDI-E	-.192	-.075	-.390**	.190	-.146	.615**	.773**				
9 LOT-R	.276	.090	.203	.009	.245	-.527**	-.488**	-.544**			
10 BRCS	.142	.137	.170	-.194	.184	-.445**	-.431**	-.391**	.461**		
11 SSAM	-.125	-.215	.041	-.159	.078	-.267	-.005	-.115	.470**	.378*	

Note. $N = 44$. *Correlation is significant at 0.05 level. **Correlation is significant at 0.01 level.

4.4.4.1 Self-reported stress

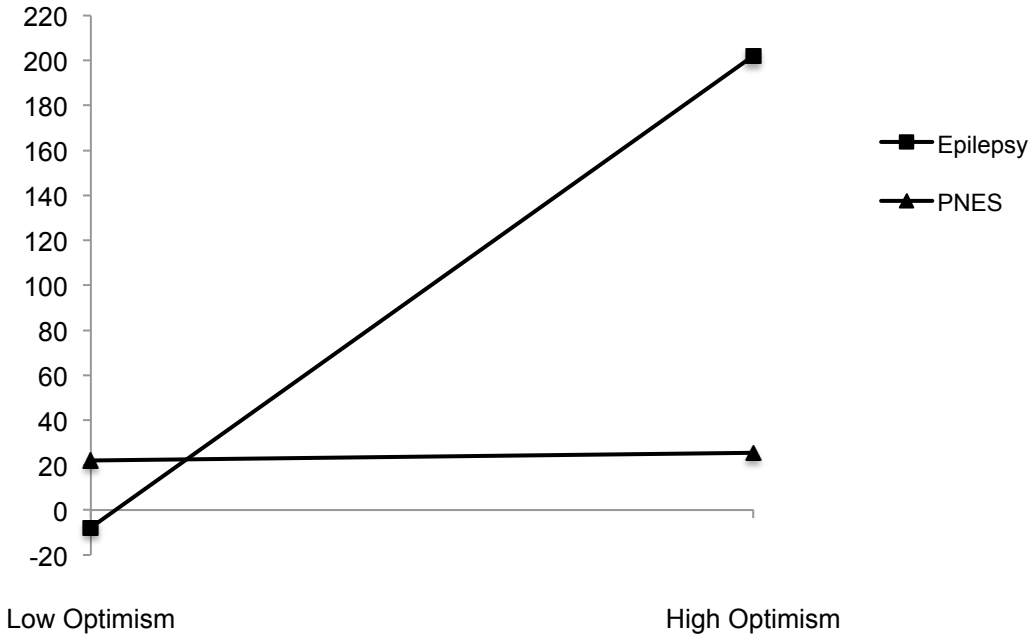
The regression models for the overall Stroop index, general, seizure, social and somatic threat categories were not significant (*p*'s > .05). There were no significant main effects of self-reported stress, group or their interaction (*p*'s > .05).

4.4.4.2 Optimism

The regression model for the overall Stroop index was significant, $F(3, 44) = 9.05$, $p < .001$. There was a significant main effect of optimism, $\beta = 42.98$, $p < .001$; the higher optimism scores the patients reported, the greater their overall attentional bias. There was also a significant interaction between optimism and patient group, $\beta = -21.30$, $p = .006$. The interaction was decomposed using simple slopes analysis at high (one standard deviation above the mean) and low (one standard deviation below the mean) levels of optimism. The simple slopes analysis revealed that patient group was significantly predictive of the overall

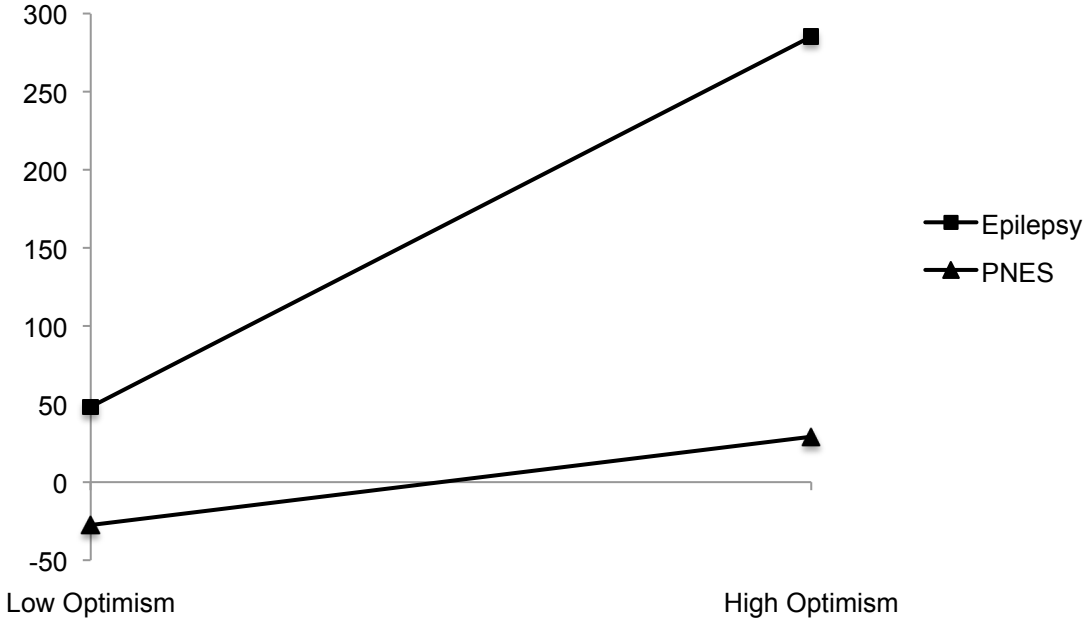
attentional bias for patients high in optimism, β = -176.44, p = .005, but not those low in optimism, β = 29.83, p = .551. As shown in Figure 4.2, among those scoring high in optimism, patients with epilepsy showed greater overall attentional bias (indicated by the overall D-SI score) than patients with PNES.

Figure 4.2. *Interaction between patient group and optimism on the overall D-transformed Stroop Index scores. Simple slopes for patient groups at high and low levels of optimism*



The model was also significant for the seizure threat category, F(3, 44) = 3.32, p = .019. There was a significant main effect of optimism, β = 87.15, p = .008; the higher the patients scored on optimism, the greater their attentional biases toward seizure-related threat. There was also a significant interaction between optimism and group, β = -43.65, p = .024. Simple slopes analysis at high and low levels of optimism again showed that patient group was significantly predictive of attentional bias towards seizure-related threat in patients who scored high on optimism, β = -346.55, p = .013, but not those who scored low on optimism, β = 76.18, p = .570. The attentional bias towards seizure-related threat was greater in patients with epilepsy than in patients with PNES among patients high in optimism (Figure 4.3).

Figure 4.3. *Interaction between patient group and optimism on the D-transformed Stroop Index scores for seizure-related threat. Simple slopes for patient groups at high and low levels of optimism*



4.4.4.3 Resilient coping

The models for the overall Stroop index, general, seizure and somatic threat category were non-significant (*p'*s> .05). There were no significant main effects of resilient coping or group, and there were no significant resilient coping by group interactions (*p'*s> .05). The overall model for social threat category was significant, $F(3, 44) = 3.16$, $p = .035$; however, there were no significant main effects of resilient coping or group and no significant interaction (*p'*s > .05).

4.4.5 Effects of the Self-Affirmation Intervention (Aim 4)

4.4.5.1 Effects on the attentional biases

The post-intervention D-SI scores are summarised in Table 4.8. One-sample *t*-tests used to explore the post-intervention Stroop response patterns in each group showed that the post-intervention D-SIs did not significantly differ from zero in any of the three groups.

The three-way ANOVA conducted to examine the effects of the self-affirmation intervention on the attentional biases showed there were no significant main effects of time, $F(1, 62) = 0.25$, $p = .621$, group, $F(2, 62) = 0.92$, $p = .406$, or word category, $F(3, 62) = 0.62$, $p = .606$. There were no significant interactions between time and group, $F(2, 62) = 1.96$, $p = .149$, word category and group, $F(6, 62) = 0.73$, $p = .622$, or between time and word category, $F(3, 62) = 0.62$, $p = .606$. The three-way interaction between group, time and word-category was not significant either, $F(6, 62) = 0.54$, $p = .779$.

Table 4.8. *Post-intervention D-SI in the patient groups and healthy volunteers for the different word categories*

Word Category D-SI (milliseconds)	Epilepsy (N = 22)	PNES (N = 22)	Healthy Controls (N = 21)
	Mean (*SD*)	Mean (*SD*)	Mean (*SD*)
Overall D-SI	27.17 (175.87)	51.46 (202.43)	51.17 (171.14)
General Threat D-SI	-52.66 (281.88)	92.82 (299.18)	0.48 (348.99)
Seizure Threat D-SI	42.51 (335.54)	65.61 (290.50)	33.25 (334.49)
Social Threat D-SI	24.82 (328.13)	35.80 (330.15)	119.57 (357.52)
Somatic Threat D-SI	100.41 (323.86)	3.43 (306.02)	43.28 (313.93)

Note. D-SI = D-transformed Stroop Index, *SD* = standard deviation.

4.4.5.2 Changes in heart rate variability

The HRV parameters taken at the four different time points (before and after the Time 1 and Time 2 Stroop tests) are summarised in Table 4.9. The two-way ANOVA showed there was a main effect of group for SDNN, $F(2, 52) = 3.73$, $p = .032$, for CVI, $F(2, 52) = 3.33$, $p = .045$, and for TP, $F(2, 52) = 3.85$, $p = .029$. Further post-hoc Tukey's HSD tests showed that patients with PNES had significantly lower SDNN, CVI and TP than healthy controls (p's $< .05$) across the four time points. No significant main effect of group was found for RMSSD or CSI. There were no main effects of time for any of the HRV parameters and no significant time by group interactions (p's $> .05$).

Table 4.9. *Heart-rate variability parameters after Time 1 and before and after Time 2 Stroop Test*

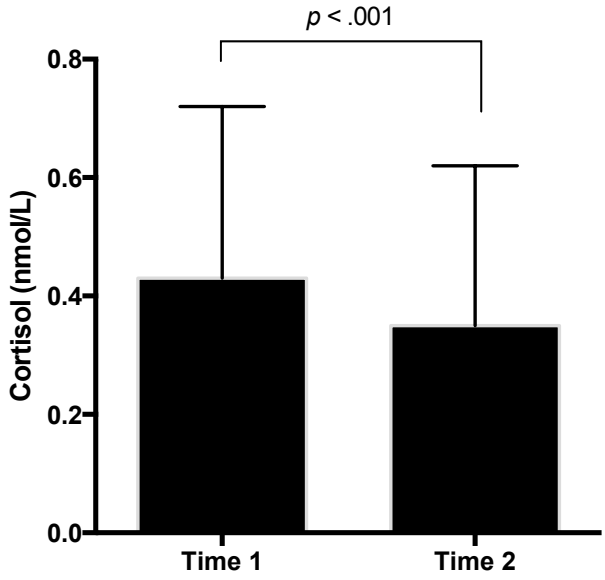
	After Time 1 Stroop Test *Mean (SD)*			Before Time 2 Stroop Test *Mean (SD)*			After Time 2 Stroop Test *Mean (SD)*		
HRV parameters*	Epilepsy	PNES	Control	Epilepsy	PNES	Control	Epilepsy	PNES	Control
SDNN	1.52 (0.22)	1.42 (0.25)	1.60 (0.25)	1.55 (0.22)	1.42 (0.24)	1.59 (0.24)	1.55 (0.23)	1.39 (0.16)	1.52 (0.23)
TP	3.02 (0.45)	2.80 (0.51)	3.21 (0.47)	3.05 (0.47)	2.76 (0.51)	3.13 (0.51)	3.06 (0.42)	2.76 (0.51)	3.18 (0.50)
RMSSD	1.54 (0.29)	1.42 (0.30)	1.56 (0.31)	1.56 (0.30)	1.42 (0.29)	1.57 (0.29)	1.55 (0.29)	1.38 (0.22)	1.60 (0.32)
CVI	0.47 (0.07)	0.43 (0.08)	0.49 (0.08)	0.48 (0.07)	0.43 (0.08)	0.48 (0.07)	0.48 (0.07)	0.43 (0.05)	0.49 (0.07)
CSI	0.20 (0.13)	0.22 (0.17)	0.28 (/15)	0.20 (0.16)	0.21 (0.16)	0.25 (0.16)	0.22 (0.18)	0.25 (0.15)	0.25 (0.15)

Note. *N* Epilepsy = 11; *N* PNES = 16; *N* Control = 18. *Log-transformed values.

4.4.5.3 Changes in salivary cortisol

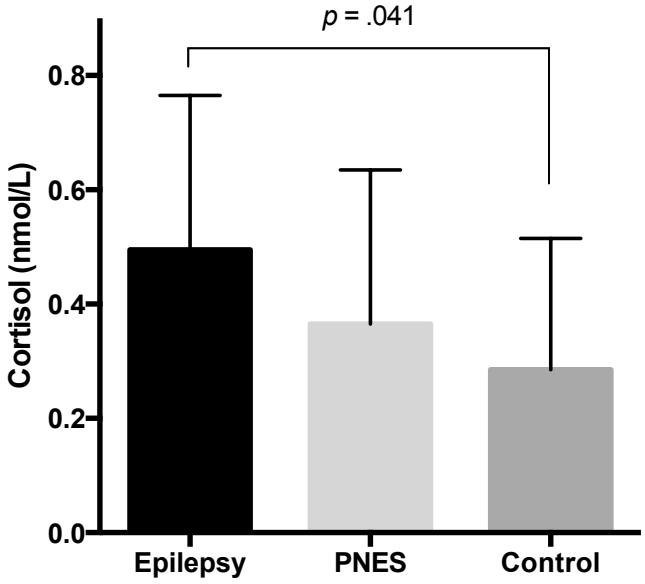
The mean difference between the sampling time of cortisol collected before the Time 1 and after the Time 2 Stroop test in all three groups combined was 41.50 minutes. The two-way ANOVA used to assess changes in salivary cortisol revealed that there was a significant main effect of time, $F(1, 50) = 13.86$, $p < .001$. Salivary cortisol was significantly higher before the Time 1 Stroop test ($M = 0.43$, $SD = 0.29$) than after the Time 2 Stroop test ($M = 0.35$, $SD = 0.27$) across all the three groups (see Figure 4.4).

Figure 4.4. *Mean log-transformed salivary cortisol levels before Time 1 Stroop test (Time 1) and after Time 2 Stroop test (Time 2) in the three groups combined.*



There was also a significant main effect of group, $F(2, 50) = 3.28$, $p = .046$ (Figure 4.5). Tukey's HSD post-hoc tests revealed that across the two time points, patients with epilepsy had significantly higher levels of cortisol than healthy controls ($p = .041$). The interaction between time and group was not significant, $F(2, 50) = 2.19$, $p = .122$.

Figure 4.5. *Mean log-transformed salivary cortisol levels in patients with epilepsy, patients with PNES and healthy controls at the two time points combined*



4.5 Discussion

This chapter described the development and results of an emotional Stroop experiment designed to explore attentional biases towards/away from stress related stimuli in patients with epilepsy and patients with PNES, compared to healthy individuals. As part of the Stroop experiment, the relationships between attentional biases and physiological stress measures were also explored. In addition, the moderating effects of self-reported stress, optimism and resilient coping on attentional biases in the two patient groups were examined as a secondary outcome to explore factors underlying vulnerability and resilience to

attentional biases in these patients. The study also explored whether the attentional biases and/or any of the physiological stress measures could be altered by a self-affirmation intervention.

The findings of the study revealed that patients with epilepsy showed a significant positive attentional bias towards threatening words overall as well as towards seizure-related threat words specifically, as indicated by a positive Stroop index, which was significantly different from zero. In patients with PNES, the overall Stroop index, as well as the Stroop indexes for the four word categories were also positive, suggesting a bias towards threatening rather than neutral words, although this was less marked than in patients with epilepsy and did not reach statistical significance. Conversely, in the healthy control group, the Stroop indexes were predominantly negative, suggesting a bias towards neutral rather than threatening words, although this bias was not statistically significant. Previous studies of attentional biases in patients with seizures and in healthy individuals interpret a negative attentional bias seen in healthy participants as a preconscious avoidance or orienting away from the threatening stimuli (Bakvis et al., 2009a; Bakvis et al., 2009b). Such attentional avoidance has been described as appropriate, as avoiding threat and harm is an adaptive response (van Honk et al., 2000).

Comparison of the three groups among each other revealed that patients with epilepsy exhibited significantly greater bias across the different word categories than healthy volunteers but did not differ significantly from patients with PNES. The differences between patients with PNES and healthy controls were not significant. This suggests that in this study patients with epilepsy but not patients with PNES were highly vigilant towards threat related stimuli and particularly towards information related to the seizure disorder itself. This would fit with the findings by Jones et al. who found that seizure severity was a more significant contributor to anxiety symptoms in patients with epilepsy than in patients with PNES, in

whom attachment style and relationship quality contributed more (Jones et al., Manuscript in preparation).

With regard to epilepsy, this finding seems consistent with the emotional Stroop literature, in which a disorder-specific Stroop response is typically found in patients with a range of disorders, including depression, anxiety or PTSD (Williams et al., 1996). The findings are also in line with those of Zeitlin et al. (1995) who found attentional biases towards seizure-related words in patients with epilepsy who reported a high number of seizure-related fears, as well as the results from the study by Lanteaume et al. (2009) who showed attentional biases towards threat in a sub-group of patients with temporal lobe epilepsy who reported experiencing emotional seizure triggers. However, the patients in the Lanteaume et al. (2009) study showed an attentional bias towards generally threatening words, whereas patients in the current study were biased towards threatening words across the four categories and towards seizure-related threat words in particular. Contrary to the Lanteaume et al. (2009) study, the sample of patients who participated in the current study included patients with different epilepsy types and both patients who did and those who did not endorse stress as a seizure trigger[4]. The findings from the current study therefore seem to suggest that the increased attentional vigilance towards threat in patients with epilepsy may not be limited to those with temporal lobe epilepsy or those who subjectively experience stress-related or emotional triggers. Interestingly, the attentional vigilance towards seizure-related threat found in patients with epilepsy in the present study also fits with the findings of a qualitative study of patients' seizure metaphors, in which patients with epilepsy but not patients with PNES described their seizures as hostile, external entities of which they are a victim (Plug et al., 2009).

[4] Comparison of patients with epilepsy and patients with PNES who endorsed versus those did not endorse stress to be a possible seizure trigger using a two-way ANOVA for independent designs yielded no significant differences in the Stroop responses between the groups.

Based on previous studies suggesting implicit attentional vigilance towards threat to be a maladaptive response, associated with the maintenance and exacerbation of various psychopathologies, the assumption of the present study was that such attentional biases in patients with seizures could contribute to their vulnerability towards greater and/or more frequent stress responses. However, it is worth considering whether the attentional vigilance may in fact be an expected or not necessarily a maladaptive response in patients with epilepsy. In their review of emotional Stroop test studies, Williams et al (1996) discuss the possible role of exposure to certain types of stimuli in the emotional Stroop interference. For example, there is a possibility that the greater attentional bias towards negative words such as *'gloomy'* in individuals with depression may be caused by the fact that depressed individuals tend to often dwell on such concepts and the Stroop interference for depressive words could therefore reflect mere extended exposure or practice in processing this type of information (Williams et al., 1996). Likewise, patients with refractory epilepsy are likely to be frequently exposed to information related to seizures and this could perhaps prime them to automatically attend to such information. However, while this could be true for the attentional vigilance towards the seizure-related stimuli, the fact that patients exhibited significantly greater attentional bias towards threatening words across all the different word categories compared to healthy volunteers suggests that the attentional vigilance towards threat in the epilepsy patients is more generalised and therefore more likely to be a maladaptive or a hyper-vigilant attentional response. Furthermore, Williams et al (1996) argue that the disorder-specific attentional bias seen in various psychological disorders is not likely to be only due to extended practice, as therapeutic studies show that reduction of symptoms or recovery from the disorder following therapy is also associated with alleviation of the attentional bias – something that would not be expected if the bias was caused purely by repeated exposure.

In terms of attentional biases in patients with PNES, although the PNES patients showed a somewhat different pattern of responses than the healthy volunteers, the differences in the responses between the groups did not reach statistical significance, unlike in the study conducted by Bakvis et al., who reported a significant attentional bias towards angry stimuli in patients with PNES, compared to healthy controls (Bakvis et al., 2009a). When interpreting responses to emotional stimuli, several modulating factors need to be considered, including characteristics of the individual, characteristics of the stimulus and characteristics of the environment such as task and situational demands (Okon-Singer et al., 2013). While the main aims of this study were to examine the effects of having a seizure disorder and the associated physiological and psychological characteristics of the patients on the attentional responses to stress-related stimuli, the effects of the stimulus properties and the testing environment should also be addressed. One possible explanation for the discrepancy between the findings of the current study and that of Bakvis et al. (2009a) may be the type of emotional stimuli used in the two studies. While the current study used word stimuli, Bakvis and colleagues used pictures of angry faces. Pictures of faces and real-life scenes may be more salient stimuli than words (Okon-Singer et al., 2013). Faces in particular are considered to be significant social and biological stimuli processed through dedicated neural circuits that may be different to those used to process word stimuli (Okon-Singer et al., 2013). Furthermore, PNES are often associated with a history of interpersonal trauma (Kaplan et al., 2013) and the attentional bias towards angry faces in the Bakvis et al. (2009a) study was indeed positively related to levels of self-reported sexual trauma. It is therefore conceivable that the angry facial stimuli in the Bakvis et al. study elicited stronger responses than the word stimuli used in the present study. Alternatively, the attentional biases identified in the Bakvis et al. study may have been a feature of those patients who experienced sexual trauma, which is something that has not been specifically assessed in the PNES patients who took

part in the current study. Furthermore, as described in Chapter 3, the majority of the PNES patients in this study were male and therefore less likely to have a history of sexual abuse (Bowman & Markand, 1999; Duncan & Oto, 2008). Apart from the different stimuli used, the current study also used a different mode of stimuli presentation. While the Bakvis et al. study used masked stimuli, the word stimuli in the current study were unmasked, although participants were instructed to focus on the colour of the words rather than their meaning. It is therefore possible that the study by Bakvis et al. captured preconscious attentional biases that were not captured by the longer and unmasked presentation of the stimuli in the current study.

Examination of the physiological stress measures and their relationships to the attentional biases revealed that there were no differences between the groups in their levels of salivary cortisol measured before the first Stroop test. The salivary cortisol levels were not related to attentional biases in either of the patient groups but there was a positive association between salivary cortisol and the overall Stroop index, as well as the Stroop index for the social category in healthy participants. This would suggest that healthy volunteers who were physiologically more aroused were more vigilant towards threat. Considering the higher levels of medication use, depression, anxiety, and possible seizure-related physiological changes in the two patient groups compared to the healthy individuals, it could be speculated that these factors may have affected the cortisol levels in the two patient groups and this could have obscured possible relationships between cortisol levels and attentional biases.

Interestingly, a previous study that investigated baseline cortisol levels from samples taken before a masked emotional Stroop test in patients with PNES, patients with epilepsy and a healthy control group and their association with attentional biases towards angry faces, found no significant differences in cortisol levels between the groups, similarly to the results of the current study (Bakvis et al., 2009b). However, unlike in the present study, the study by

Bakvis et al. found a positive relationship between cortisol and attentional bias towards threat in patients with PNES (Bakvis et al., 2009b). It is important to note that patients with PNES in the study by Bakvis et al were all unmedicated, whereas patients in the present study were taking a range of different medications. The lack of a relationship between cortisol and attentional biases in the present study could therefore be attributed to possible medication effects, as mentioned above, although the finding that morning and evening cortisol levels or cortisol deltas in the patients in the present study did not differ from a normative sample of healthy individuals would argue against significant medication effects. Furthermore, a later study by Bakvis and colleagues found that baseline cortisol levels in patients with PNES were higher in those who reported sexual trauma than in those with no history of sexual abuse (Bakvis et al., 2010). As discussed earlier, the likelihood of sexual abuse in the PNES group in the present study is low, although this was not formally assessed.

In terms of heart rate variability, patients with PNES but not patients with epilepsy had significantly reduced overall heart rate variability as well as lower vagal tone than healthy controls, indicating greater physiological stress vulnerability. This physiological vulnerability in the PNES group was also indicated by the findings reported in Chapter 3, as patients with PNES had higher sympathetic nervous system tone, reflected by higher CSI, than patients with epilepsy. Similar findings were reported by Bakvis et al. (2009a) who found reduced HRV in patients with PNES, compared to healthy controls. This finding is also partly in line with a previous HRV study, which showed a pathologically reduced resting HRV in patients with PNES, in keeping with heightened level of autonomic arousal (Ponnusamy et al., 2011). However, Ponnusamy et al. (2011) also found reduced HRV in patients with epilepsy, compared to healthy individuals, which was not replicated in the current study. Other studies of HRV parameters in epilepsy have found variable results. Although most studies show altered HRV in patients with epilepsy compared to controls

(Lotufo et al., 2012), there are studies that found no difference between patients with epilepsy and controls (Persson et al., 2007).

Examination of the relationships between HRV and attentional biases showed a negative association between the total power (a measure of overall HRV) and attentional bias towards somatic threat words in patients with epilepsy, suggesting that patients with lower overall HRV show greater vigilance towards somatic threat. This finding could be explained in the context of the neurovisceral integration model (Thayer & Lane, 2000). According to this model, the neural networks involved in emotional and cognitive regulation, including the anterior cingulate, the insula, the ventromedial prefrontal cortices, the amygdala, or the paraventricular nuclei of the hypothalamus, among others, are also involved in the regulation of cardiac autonomic activity that can be measured by HRV (Thayer & Lane, 2000). The model proposes that these neural systems are responsible for making adaptive and flexible cognitive, emotional and autonomic responses to environmental demands. Disruption of regulation in these systems can lead to prolonged activation of excitatory sympathetic nervous system responses and defensive cognitive and behavioural mechanisms, put a strain on the autonomic nervous system, and lead to a range of psychopathologies (Thayer & Lane, 2000). Indeed, while higher resting HRV was found to be related to more adaptive cognitive processing of emotional stimuli and therefore more effective emotion regulation, lower resting HRV is associated with more hyper-vigilant responses to emotional stimuli and maladaptive regulation of emotions, which can be detrimental to psychological wellbeing (Park & Thayer, 2014). In the patients with epilepsy in the current study, diminished HRV could therefore be associated with exacerbated, maladaptive attentional responses to threatening stimuli. In turn, this attentional hypervigilance could make these patients more likely to notice and focus on threatening information in their environment and therefore more

prone to more frequent autonomic responses to such stimuli, which can further alter their autonomic nervous system functioning and flexibility.

The examination of the relationship between cortisol and HRV showed these two physiological markers were not significantly correlated in any of the groups. Considering the findings of the diurnal pattern in these measures reported in Chapter 3, the lack of association between HRV and cortisol measured as part of the Stroop test could be explained by the different times of day at which the experiment was conducted. As suggested by previous studies discussed in Chapter 3 (Looser et al., 2010), it is also possible that under resting conditions, these two physiological systems function relatively independently.

The attentional responses towards stress-related stimuli in the two patient groups were further explored by examining the moderating effects of self-reported stress, optimism and resilient coping on attentional biases. Although both patient groups reported higher levels of self-perceived stress than the healthy volunteers and patients with PNES reported lower levels of resilient coping in the baseline questionnaires, self-reported stress and resilient coping were not found to be significant moderating factors.

There was, however, a significant moderating effect of optimism. The optimism by group interaction revealed that the patient group was significantly predictive of the attentional response in patients who scored high in optimism, namely, among those with epilepsy, people higher in optimism had significantly greater attentional bias, whereas in patients with PNES optimism did not moderate the degree of attentional bias. This is a rather counter-intuitive finding, suggesting that, for patients with epilepsy, being optimistic was associated with being overall more vigilant towards threat and particularly vigilant towards seizure-related information. There is mixed evidence in the literature for the relationship between optimism and attentional bias towards negative and positive stimuli. One study found that healthy participants with high health-related optimism paid more attention to

health-related threat than pessimists, particularly if the threat was perceived as self-relevant (Aspinwall & Brunhart, 1996). The finding of the current study that patients with epilepsy high in optimism had greater attentional bias towards seizure-related threat would seem to corroborate the finding of the study by Aspinwall and Brunhart. The lower attentional vigilance towards threat-related stimuli in epilepsy patients who were low in optimism would on the other hand suggest attentional avoidance of the threat stimuli. However, the Aspinwall and Brunhart study did not assess whether or how the attentional biases were related to coping responses or levels of stress or general psychological wellbeing and it is therefore difficult to establish whether such biases served an adaptive or a maladaptive function in the study participants. Several later studies found the opposite pattern, showing that optimists were more vigilant towards positive pictures and more avoidant of negative pictures compared to those low in optimism (Isaacowitz, 2005; Luo & Isaacowitz, 2007). It is also worth noting that the effects of optimism may differ between healthy individuals and people with disorders, as well as between different types of disorders. A study of patients with Parkinson's disease and patients with multiple sclerosis showed that patients with multiple sclerosis benefited more from being optimistic than those with Parkinson's disease (de Ridder et al., 2000). That study also suggested a possible curvilinear effect of optimism on adjustment and coping, whereby having medium levels of optimism may be more adaptive than being high or low in optimism (de Ridder et al., 2000).

The effectiveness of the kindness self-affirmation intervention was assessed by comparing the participants' Stroop responses in the Time 1 and Time 2 Stroop test and by comparing the physiological stress measures taken across the experiment. The results suggest that the intervention was not associated with any significant changes in attentional responses in any of the three groups.

The heart rate variability patterns also remained unchanged throughout the experiment, although it should be noted that due to the relatively small sample in the present study, the tests might not have been sufficiently powered to achieve significance. Patients with PNES showed lower HRV compared to healthy volunteers across all four time-points, which is consistent with the findings of Bakvis et al. (2009a).

There was, however, a significant change in salivary cortisol, with cortisol being lower after the second Stroop test than before the first Stroop test across all groups. In addition, when averaged across the two time-points, patients with epilepsy had higher levels of cortisol than healthy controls, perhaps suggesting a greater overall arousal in this patient group. The cortisol changes are difficult to interpret due to poor temporal resolution of the cortisol response, with studies of the salivary cortisol response typically sampling cortisol at a number of time points with intervals ranging from between five to 35 minutes (Kirschbaum & Hellhammer, 1994). Cortisol was only sampled at two time points in the current study, immediately before and immediately after the whole experiment. The reduction in cortisol from before the first Stroop test to after the second Stroop test could therefore have several different interpretations. The observed reduction in cortisol may be an indication of the desired positive effects of the self-affirmation intervention, which was performed before the second Stroop test, approximately 10 – 20 minutes prior to the second saliva sample collection. This would be consistent with previous studies in which a self-affirmation intervention was shown to reduce cortisol, epinephrine and norepinephrine responses to acute stressors (Creswell et al., 2005; Sherman et al., 2009). However, the cortisol reduction in the current study may also reflect a mere reduction in arousal throughout the experiment, regardless of the intervention, or it could have been affected by the diurnal fluctuation observed in the cortisol levels in Chapter 3. The participants were perhaps more aroused prior to performing the Stroop test for the first time and calmed down throughout the experiment.

This is somewhat unlikely, as studies showed that performing the Stroop test may be associated with a certain degree of stress (Renaud & Blondin, 1997). Although the emotional Stroop experiment in the current study was not designed to function as a stressor per se, it seems more likely that the evaluative nature of the task where participants were required to give fast and accurate responses would lead to increase rather than decrease in arousal. However, it is also possible that the decrease in arousal occurred during the second Stroop test as a result of habituation to the task rather than the effects of the intervention. Whether the change in cortisol was a result of the intervention effects, reduction of arousal throughout the experiment, habituation to the task or a combination of these effects is not possible to determine with certainty.

4.5.1 Limitations

The study has a number of limitations. The major limitation is the small sample size in each of the groups. Although the sample size is comparable to some of the previous studies exploring attentional biases in patients with seizures (Bakvis et al., 2009a; Lanteaume et al., 2009), it is nevertheless possible that some effects were undetected by the current study due to its low statistical power.

A further limitation is related to the heterogeneity of the two patient groups. Both patients with epilepsy and patients with PNES reported high levels of comorbid depression and anxiety and the majority of patients were taking anti-epileptic as well as other medication, many of which could have possible effects on the levels of cortisol (Hofstra & de Weerd, 2009). As the levels of depression and anxiety varied systematically between the groups, it was not possible to control for the effects of these disorders using analysis of covariance (Field, 2009) and the small group sizes did not allow for meaningful sub-group comparisons. Given that high levels of psychiatric comorbidity are typically found in these

patients (Kanner, 2009; LaFrance et al., 2013), the fact that patients in this study were not excluded on the basis of comorbid psychiatric disorders may make the results more generalisable. Furthermore, on a biological level, there are likely to be close multi-lateral relationships between epilepsy, PNES and comorbid psychiatric disorders such as depression or anxiety (for example, through the HPA axis) and it is therefore difficult to make a clear conceptual distinction between these conditions. Both epilepsy and PNES are bio-psycho-socially determined conditions with a wide range of neuropsychiatric manifestations, which interact in complex ways (Elliott & Richardson, 2014; Kanner, 2009; LaFrance et al., 2008; Reuber, 2009), and it is therefore questionable whether it is desirable or appropriate to 'control' for the associated psychopathology.

Nevertheless, it is possible that the presence of anxiety, depression, or the effects of medication confounded some of the identified differences between patients and healthy volunteers in attentional biases and the physiological measures and the results therefore need to be interpreted with caution. In addition, previous studies identified at least two clusters of patients with PNES that may differ in their psychological characteristics and levels of psychological impairment (Brown et al., 2013; Uliaszek et al., 2012). It is therefore conceivable that the patterns of attentional biases may differ between different sub-groups of patients with PNES.

Although an attempt was made to control the conditions during the Stroop experiment as much as possible, the environment in the telemetry ward in which the patients performed the test were nevertheless suboptimal. Due to the various medical and other procedures carried out in the ward, the Stroop test had to be performed at various times of the day and at various stages of the patients' stay in the hospital (although most patients performed the test on the first or second day of their stay). In light of the findings reported in Chapter 3, which suggested that the experience of seizures may be associated with increased autonomic arousal

and self-perceived stress, it is also important to note that while most patients performed the Stroop experiment on days when no seizures had occurred prior to the experiment and the few patients who had experienced a seizure prior to the experiment completed the Stroop test at least one hour or more after the seizure, it is nevertheless possible that the experience of seizures could have had an influence on the Stroop test performance in some patients. Furthermore, the Stroop test was performed in a hospital bay, which was shared with other patients and although an attempt was made to keep any distractions to the minimum by having the bed curtains closed and asking the medical staff and visitors in the ward not to disturb the participant for the duration of the experiment, the environment was nevertheless relatively noisy and potentially distracting. In contrast, healthy volunteers performed the test in a quiet experimental room with no distractions.

4.5.2 Implications and Conclusions

Despite its limitations, this exploratory study presents novel findings about the patterns of attentional responses to stress-related stimuli in patients with epilepsy and patients with PNES and their relationships with physiological measures of stress including salivary cortisol and heart-rate variability. The attentional vigilance towards threatening stimuli, including stimuli related to seizures, and its association with reduced HRV found in the epilepsy patients in this study may represent a pattern of maladaptive cognitive and autonomic responses that contribute to the stress vulnerability of these patients. However, future studies could explore to what extent these attentional biases are indeed maladaptive, as well as whether and how they relate to the patients' stress responses. For example, it would be interesting to examine whether greater attentional vigilance towards threat is associated with heightened endocrine, autonomic, cognitive or self-reported responses to an experimental stressor.

The fact that the attentional biases were not related to or moderated by levels of self-reported stress could reflect the discrepancy between the more subjective self-report and the more objective cognitive and physiological stress measures, described in Chapter 3. This further emphasises the complexity of the stress-related vulnerability in this patient group and the importance of using a combination of implicit and explicit measures. One of the implications of these findings for future research in this area may be that simple self-reports cannot be used as a proxy of attentional biases or physiological arousal, which may still have significant effects on the life experience and functioning of patients with epilepsy and PNES.

If we assume that the biased attentional responses are maladaptive, then these biases could be a target of information processing training interventions designed to refocus the attention away from factors that may be triggering stress responses. A few studies documented a successful application of such attention training programmes in individuals with anxiety disorders (Mathews et al., 2007; Schmidt et al., 2009). The feasibility of using such interventions for patients with epilepsy may be an interesting area for future research. Future studies could also further explore the role of optimism in the responses to emotional stimuli in this patient group.

The current study failed to replicate the findings of previous studies that identified attentional biases in patients with PNES (Bakvis et al., 2009a; Bakvis et al., 2009b). Perhaps future studies could investigate attentional biases in these patients using a larger sample, comparing different types of stimuli (e.g., words versus pictures), different modes of stimuli presentation (masked versus unmasked), and examining sub-groups of patients, based on different levels of trauma or psychopathology.

Although the self-affirmation intervention used in this study was not found to be effective in altering the attentional biases, it may have had some effects on the levels of

salivary cortisol. The effects of an intervention associated with the self-affirmation technique on a range of outcomes are further investigated and discussed in Chapter 5.

5. CHAPTER 5

Study 2: A Pilot Study of a Self-Help Stress Management Intervention for Patients with Seizures

5.1 Study Introduction

This study focuses on a simple stress intervention designed to help patients with seizures presenting to neurologists cope with stress – regardless of whether the seizures are epileptic or non-epileptic in nature.

With the exception of epilepsy surgery (which is only suitable for a small minority of patients with epilepsy) there are presently no truly 'anti-epileptic' treatments for epilepsy. Treatments used in clinical practice are mostly 'anti-convulsant' (i.e., anti-ictal), which means they merely control some of the manifestations but do not cure the disorder. As discussed in Chapter 2, many patients with epilepsy experience a high degree of stress, suffer from comorbid psychiatric conditions or struggle with the perceived or real stigma associated with epilepsy. All of this has a negative impact on the patients' quality of life, and suggests that these patients could benefit from complementary psychosocial interventions (Kessler et al., 2012). Indeed, the latest National Institute for Health and Care Excellence (NICE) guidelines for the management of epilepsy recommend the use of psychological therapies in combination with other treatments (NICE, 2015).

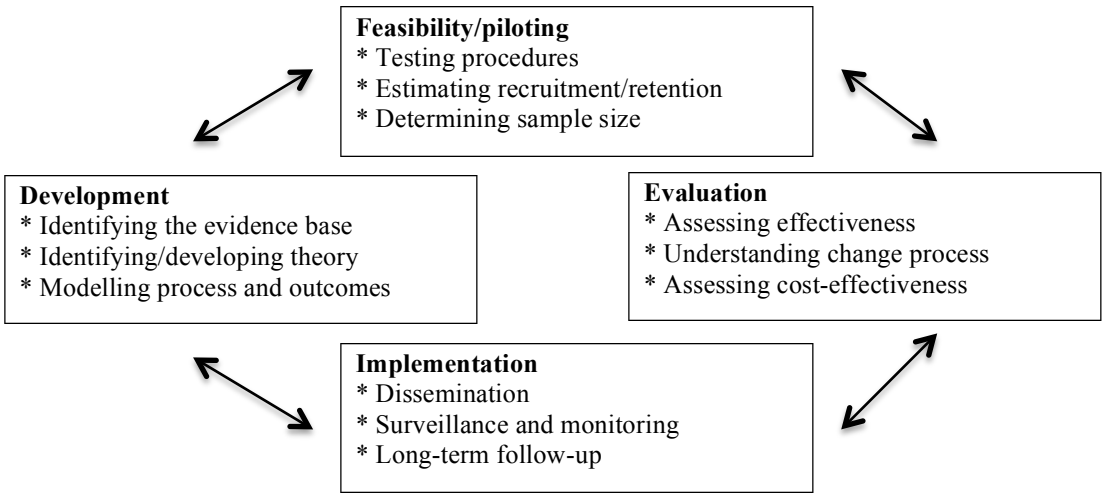
For patients with PNES, psychotherapy is the accepted treatment of choice (LaFrance et al., 2013). Although psychosocial interventions for epilepsy and PNES have been described and tested, only a minority of patients with these seizure disorders currently gain access to targeted psychological therapies and therefore the psychological and social problems associated with epilepsy and PNES often remain neglected (Mittan, 2009; Reuber

et al., 2005a). Furthermore, there is a lack of empirical studies evaluating the effectiveness of the available psychotherapeutic programmes (Mittan, 2009). The latest Cochrane reviews concluded that, due to methodological limitations and a low number of participants in the studies currently available, no firm conclusions can be drawn and more randomised controlled trials (RCTs) are necessary to provide a reliable evidence base for the effectiveness of different psychosocial treatments for epilepsy and PNES (Martlew et al., 2007; Ramaratnam et al., 2008). Another limitation is that many studies have used outcome measures incapable of capturing the broader range of possible positive outcomes (Mittan, 2009). Moreover, few of the programmes shown to be effective in research studies have been put into general use, presumably because perceived economic constraints and staffing implications associated with these interventions have outweighed expectations of patients benefit, raising questions about their more widespread utility in clinical services (Mittan, 2009). There are a number of possibly more cost-effective interventions in the form of self-help leaflets, books and Internet resources, which could provide standardised, low-intensity psychological treatment that patients could work through independently. However, these have not been evaluated by RCTs.

An empirically tested, simple and widely applicable self-help intervention that would help people with epilepsy and PNES manage the stress they experience would be relatively easy to implement in NHS settings and could have positive effects on how stressed patients feel, the frequency of the patients' seizures and their overall quality of life. The Medical Research Council (MRC) have developed a framework to provide guidance for development and evaluation of complex interventions, i.e., interventions comprising a number of interacting components (Craig et al., 2008). As shown in Figure 5.1, according to this framework, the process of developing and testing new interventions should have four main stages, including the development of the intervention based on appropriate evidence and

theory, assessment of feasibility and piloting of the methodology, evaluation of effectiveness, cost-effectiveness and change processes, and finally, publication and implementation of the intervention in clinical practice.

Figure 5.1. *Main stages in the development and evaluation process of complex interventions (taken from the MRC guidelines by Craig et al. (2008))*



In accordance with this framework, a self-help intervention targeting stress in patients with seizures was developed as part of this study, as the first stage of the process outlined above. The intervention was assessed in a pilot trial in order to determine whether an evaluation in a larger randomised controlled trial would be justified. It is worth noting that, to date, there is a lack of consensus about the difference between 'feasibility' and 'pilot studies' (Lancaster, 2015). While the MRC guidelines use the terms more or less interchangeably, the National Institute for Health Research (NIHR) provide separate definitions for feasibility and pilot studies. According to the NIHR, feasibility studies are, *'pieces of research done before a main study in order to answer the question "Can this study be done?" They are used to estimate important parameters that are needed to design the main study'*, whereas a pilot study is *'a smaller version of the main study used to test whether the components of the main study can all work together. It is focussed on the processes of the main study, for example to*

ensure that recruitment, randomisation, treatment, and follow-up assessments all run smoothly' (Lancaster, 2015). Recent reviews highlight the fact that there is a major concern regarding the appropriate objectives of pilot studies. While these should primarily be focused on assessing feasibility and acceptability, testing the data collection and randomisation procedures, estimating rates of recruitment/retention, providing initial estimates for sample size calculations, and selecting appropriate outcome measures, the emphasis is often inappropriately placed on hypothesis-testing (Arain et al., 2010; Lancaster, 2015). It is therefore recommended that estimates of treatment effectiveness in pilot studies should be treated as preliminary and included as a secondary objective.

In light of these recommendations, the present study was designed as a pilot of a randomised controlled trial (based on the NIHR definition), which aimed to assess the feasibility of the self-help intervention, to estimate recruitment and retention rates, and to assess the perceived acceptability and usefulness of the intervention by the study participants. The secondary aim of this pilot study was to provide a preliminary estimate of effect sizes to guide future larger scale RCTs and to assess possible effectiveness of the intervention in reducing levels of stress, improving the quality of life and reducing seizures in patients with epilepsy and those with PNES.

5.2 Study Aims

5.2.1 Primary Aims

1. To develop a theory-based self-help intervention targeting stress in patients with epileptic and psychogenic non-epileptic seizures
2. To assess feasibility and acceptability of the intervention in a pilot of a randomised controlled trial

5.2.2 Secondary Aims

3. To provide estimates of effect sizes for power calculations to guide a future randomised controlled trial
4. To provide preliminary evidence of effectiveness of the intervention in improving the patients' quality of life, and reducing levels of self-reported stress, anxiety, depression and seizure frequency

5.3 Methodology

5.3.1 Development of the Intervention

5.3.1.1 Theoretical framework

The structure and content of the intervention were guided by the MRC and NICE guidelines. These emphasise that the key points to be considered at the development stage of a new intervention are awareness of relevant theory and existing evidence for what is likely to be effective, as well as understanding of the desired outcomes and the likely processes and mechanisms of change (Craig et al., 2008; NICE, 2007).

The rationale for the development of the intervention was the fact that there is currently a lack of interventions targeting stress, developed specifically for and empirically tested in patients with seizures. Therefore, the aim was to compile a selection of simple, theory-guided techniques and strategies that are likely to work for this patient group, either based on previous studies and existing interventions for stress management, modified to be relevant to seizures, or techniques previously used in patients with seizures. The intervention has a number of different components, based on five theoretical approaches discussed below.

5.3.1.1.1 Integrative model of stress

The overall framework for the structure of the intervention was based on the integrative model of stress presented in Chapter 1. According to the model, the experience of 'stress' comprises interactions between environmental demands (stressors and life events), appraisal of demands and adaptive capacities, the resulting perceived stress, and the associated emotional, cognitive, behavioural and physiological stress responses (Cohen et al., 1995). The intervention therefore includes techniques targeting all the different components of the model, i.e., strategies aimed at identifying stressors, a section addressing the appraisal of the stressors and coping skills, and a range of techniques targeting the different stress responses, including strategies for tackling negative thoughts and worries, relaxation and breathing techniques for reduction of negative emotions and physiological arousal, and strategies for overcoming maladaptive stress-related behaviours. The intervention suggests two different approaches to coping with stressors on the basis of their controllability. Based on the theory developed by Lazarus and Folkman, problem-focused coping is considered appropriate for more controllable stressors, whereas for stressors that are outside the individual's control, emotion-focused coping is more appropriate (Lazarus & Folkman, 1984).

5.3.1.1.2 Core cognitive-behavioural techniques

The specific techniques were selected on the basis of a review of literature about design of self-help and stress management interventions (Bergsma, 2008; Cuijpers & Schuurmans, 2007; Fledderus et al., 2013; Hasson et al., 2005; Lewis et al., 2012; Reeves & Stace, 2005; van Straten et al., 2008; Williams et al., 2011), as well as printed and on-line stress management materials. The core techniques and strategies selected for the intervention were mostly based on the cognitive-behavioural approach, which is at present the most empirically founded approach for stress and anxiety management (Cuijpers & Schuurmans,

2007; Kaczkurkin & Foa, 2015; NICE, 2011). The cognitive-behavioural techniques typically involve cognitive restructuring by learning to identify and challenge irrational or maladaptive thinking patterns, and behaviour modifications to reinforce adaptive behaviours and reduce levels of arousal (e.g., exposure, goal-oriented problem-solving strategies, applied relaxation, or changing levels of activity). These techniques are practical, as they tend to be relatively simple and can be broken down into easy steps (Cuijpers & Schuurmans, 2007).

There is also promising preliminary evidence for the effectiveness of cognitive-behavioural therapy (CBT) interventions for patients with epilepsy (Gandy et al., 2013; Goldstein et al., 2003; McLaughlin & McFarland, 2011) and PNES (Goldstein et al., 2010; Goldstein et al., 2004). These interventions include the additional use of behavioural and cognitive counter-measures to identify and avoid seizure triggers or to stop impending seizures from progressing (e.g., sensory grounding or breathing techniques), as well as strategies to reduce behavioural avoidance and minimise other maladaptive behaviours that may exacerbate seizures (as well stress), for example reducing alcohol consumption or promoting regular sleeping and eating habits (Goldstein et al., 2004; Goldstein et al., 2003).

5.3.1.1.3 Psycho-education

Psycho-education is a recognised treatment option for a range of mental health problems, based on improving patients' understanding and self-management of their condition through education. Psycho-educational approaches and programmes have previously been described as potentially beneficial for patients with epilepsy (Laybourne et al., 2015; May & Pfafflin, 2002), as well as patients with PNES (Mayor et al., 2013). A brief psycho-educational section about stress and seizures was therefore included in the current intervention to provide greater insight into what stress is, its manifestations and symptoms and the different ways in which it may be related to both epileptic seizures and PNES.

5.3.1.1.4 Self-affirmation

As discussed in Chapter 2, self-affirmation is a psychological technique that has been shown to have positive effects on both acute and chronic psychological and physiological stress responses as well as a range of other health-related behaviours (Creswell et al., 2013; Creswell et al., 2005; Epton & Harris, 2008; Sherman et al., 2009). A self-affirmation exercise was therefore included to enhance the effects of the intervention. The possible mechanism of action could be two-fold. Firstly, as discussed by Sherman and colleagues, reflecting on valued domains of the self may put the stressors the person experiences in a different perspective and thereby alter stress appraisal by changing its perceived significance and reducing the person's additional concerns (e.g., negative ruminations, fear of failure) that may exacerbate the stress experience (Sherman et al., 2009). Secondly, as an alternative mechanism of restoring one's self-integrity when faced with new information that threatens pre-existing beliefs, self-affirmation has been shown to decrease defensiveness and increase openness towards threatening information (Armitage et al., 2008; Griffin & Harris, 2011). The inclusion of a self-affirmation exercise could therefore make patients more receptive to, and accepting of, the information and advice presented in the booklet.

The self-affirmation exercise was based on the traditional values-based self-affirmation techniques (Creswell et al., 2005; Vernon & Allport, 1931), modified to be more interactive (i.e., involved drawing of a spider-diagram representing the person and their most important values and then writing a few sentences about one of the values, see Table 5.1/Appendix 18).

5.3.1.1.5 Implementation intentions

Implementation intentions are simple, goal-oriented 'if-then' plans, designed to increase behavioural change by encouraging people to mentally link critical situations with desired behavioural responses (e.g., *"If situation X arises, then I will perform goal-directed*

behaviour Y!") (Gollwitzer, 1999; Gollwitzer & Sheeran, 2006). A wealth of studies show that people's goals and intentions do not easily translate into action, and this can be further exacerbated in people with mental health problems (Toli et al., 2015). The theory behind implementation intentions is that forming an implementation intention plan, which specifies when, where and/or how the goal-directed behaviour will be initiated, will lead to the relevant behavioural responses being elicited automatically when the critical situation is encountered in real life (Gollwitzer & Sheeran, 2006).

The implementation intention technique has previously been found to enhance the effectiveness of self-help interventions (Varley et al., 2011) and has been successfully used in conjunction with the self-affirmation technique (Armitage et al., 2011). Implementation intentions have also previously been used to increase medication adherence in patients with seizures (Brown et al., 2009). Forming a brief implementation intention plan was therefore included in the present intervention to encourage patients to translate the stress management strategies they learn as part of the intervention into action.

5.3.1.2 Description of the intervention

The intervention is an unguided self-help intervention that takes the form of a brief, 26- page A5 booklet (see Appendix 18). The booklet also includes a Compact Disc with two audio recordings (male and female voice) of a guided muscle relaxation taken from the Non-epileptic Attacks website, with the permission of the authors (http://nonepilepticattacks.info). The booklet has six main parts, as detailed in Table 5.1.

Previous studies of self-help interventions suggest that, in addition to the use of theory-guided strategies, effective interventions are characterised by simplicity and use a self-paced approach. In order to ensure simplicity of the intervention and to make it as accessible to patients with seizures as possible, the intervention was written in simple language and divided into sections, which were organised as a set of steps to follow (see

Table 5.1 and Appendix 18). The text and instructions were presented as bullet points, tables and diagrams. Where possible, interactive exercises with spaces for patients to write in were included. To encourage self-pacing, patients were instructed to go through the intervention and select and focus on the most relevant and helpful strategies.

The booklet design and structure were discussed with and reviewed by a Cognitive Behavioural Therapist specialised in working with patients with seizures who suggested including a sensory grounding exercise, which was added to Section 4 of the booklet.

To obtain initial indication of acceptability and relevance of the intervention, the design of the booklet was further discussed with service users attending the outpatient seizure clinics at the Royal Hallamshire Hospital. Nine patients (4 male) were approached and agreed to read through the booklet in the following week and provide feedback over telephone. Six of these patients responded to the telephone call. Of these, three patients confirmed they read the booklet and thought it was acceptable, comprehensible and relevant. The three remaining patients stated they did not read the booklet due to lack of time (N = 1) or lost interest in providing feedback (N = 2). The low response rate to this initial feedback alerted the researcher to the risk of high dropout rate and it was decided to include additional screening criteria (described in section 5.3.3) to ensure patients recruited in the pilot study felt stress is relevant to them and their seizures and were motivated to complete the study.

Table 5.1. *Structure of the self-help booklet*

Booklet section	Rationale/Aims of section	Techniques and strategies
Section 1 'Step 1: Understand stress'	Psychoeducational information aimed at increasing the understanding of stress, its effects and its interactions with seizures	• Information about what is stress • Information about what causes stress • Information about the symptoms of stress • Information about how stress is related to seizures • The vicious cycle of stress diagram
Section 2 'Step 2: Spot the stressors in your life'	A section based on the idea that patients may find it difficult to identify the sources of stress in their lives, aimed at increasing awareness of the degree of stress experienced and helping to identify and tackle stressors	• Life events checklist with ratings of stressfulness • Writing down minor everyday stressors and hassles
Section 3 'Step 3: Clarify your values and priorities'	A value-based self-affirmation exercise aimed at clarifying and reflecting on valued life domains in order to put stressors into perspective and reduce defensiveness	• Drawing a value diagram • Identifying and writing down the most important value • Writing a few sentences about the identified value
Section 4 'Step 4: Cope more effectively'	An explanation of two different ways of appraising and coping with stressors, depending on whether or not it is possible to change, control or avoid the sources of stress	• For stressors that can be controlled or avoided, a problem-focused coping approach is recommended • For stressors that are not possible to control or avoid, an acceptance based, emotion-focused coping approach is recommended
o Ways of coping	Goal/action-oriented, problem-focused coping strategies based on the CBT approach	• Problem-solving exercise based on identifying the problem, listing all possible solutions, choosing the best one and breaking it down into steps • Time-management exercise to give shape to one's day • Practicing to say 'No'
o Coping with stressful thoughts	CBT based techniques for cognitive restructuring by identifying and challenging stress-related negative cognitions	• Learning to spot stressful thoughts using a checklist of common cognitive errors • Challenging thoughts • Taking control of worries
o Coping with stressful feelings	CBT and relaxation based techniques to reduce physiological arousal, negative emotions, and prevent impending seizures.	• Learning to relax using a progressive muscle relaxation with guided audio instructions • Controlled breathing technique • Taking time out • Sensory grounding exercise • Taking a break and engaging in enjoyable activities • Connecting with others and seeking social support
o Coping with a stressful lifestyle	Basic advice and information about life hygiene aimed at encouraging a healthy lifestyle and reducing maladaptive stress related behaviour	• Techniques for improving sleep • Techniques for improving diet and reducing alcohol consumption • Engaging in safe levels of exercise
Section 5 'Step 5: Take action'	Implementation intention based goal plan aimed at encouraging patients to translate the coping techniques into action	• Selecting the most helpful coping strategy from a list of the coping techniques introduced in the booklet • Forming a goal plan (*'If I feel stressed, tensed or worried, then I will use my X technique to help me cope!')*
Section 6 'Step 6: Getting more help'	A list of additional resources and contact details for relevant support services	• Books and CDs • Online resources • Useful contacts

5.3.2 Design of the Pilot Study

The study was a pilot of a prospective randomised controlled trial. Participants were randomised to two groups, (1) an immediate intervention group who received the self-help intervention immediately after completion of a baseline assessment and (2) a delayed intervention group who received the intervention at one-month follow-up and served as a control group in the initial period, from baseline to one-month. Participants in both groups were assessed at baseline and subsequently followed up after one and after two months.

5.3.3 Participants

Consecutive patients were recruited in the Neurology Outpatient Clinic and the Specialist Epilepsy Nurse Clinics at the Royal Hallamshire Hospital, Sheffield. Adult patients with a clinical diagnosis of epilepsy or PNES were approached to participate in the study. Individuals who expressed interest in participating in the study were further screened and recruited on the basis of the criteria specified below.

Inclusion Criteria:

1. Clinically firm diagnosis of epilepsy, PNES or mixed (epileptic and non-epileptic) seizures
2. Over the age of 16 years
3. Able to complete the self-report questionnaires without help
4. Able to give informed consent
5. At least some of the seizures are perceived to be precipitated by stress
6. Currently experiencing a degree of stress and willing to try techniques to reduce stress

Exclusion Criteria:

1. Patients who were unable to give informed consent
2. Patients who were unable to complete the self-report questionnaires and diary measure unaided
3. Patients who have not experienced a seizure within the last 12 months
4. Patients whose diagnosis was uncertain
5. Patients who did not perceive stress to be relevant to their seizures and/or were not willing to try techniques to reduce stress

The patients' diagnosis was initially obtained from their medical notes and later confirmed by their consultant neurologists, all of whom were specialised in the treatment of seizure disorders. The diagnosis was considered 'clinically firm' if the consultant neurologist was sufficiently certain of the diagnosis based on the patient's history, description of a typical seizure by a seizure witness and/or, where available, a video-EEG recording of a typical seizure. The additional inclusion criteria number 5 and 6 were added on the basis of the initial experience of the pre-pilot, in which a number of patients took the booklet but failed to engage further. An attempt was made to ensure that the recruited participants were motivated and committed to the study, as such a sample is more likely to represent the real-life population that would benefit from the intervention.

5.3.4 Outcome Measures

5.3.4.1 Telephone feedback questionnaire

Patients were contacted by telephone one week after receiving the self-help intervention booklet and interviewed using a questionnaire developed as part of the study (Appendix 15). The questionnaire was designed to assess compliance with the instructions and to collect feedback on the acceptability and usefulness of the booklet. Compliance with

the instructions was assessed by a question asking whether or not the patient read through the booklet in the past week and if not, identifying reasons for not working through the booklet (the response options included, *'I have not had time to do it', 'I have forgotten about it', 'I have lost the booklet', 'The booklet was too long', 'The booklet was too complicated', 'I have lost interest in the study'*, and *'Other reasons'*).

Feedback on the booklet was obtained through a set of rating scales and open-ended questions. The questionnaire included four questions rated on five-point rating scales, assessing (1) the overall helpfulness of the booklet (from *'Not at all helpful'* to *'Very helpful'*), (2) whether or not the participant went through each of the nine sections of the booklet (*'Yes'* or *'No'*) and if so, the usefulness of each of the sections (*'Not at all useful'* to *'Very useful'*), (3) the participant's likelihood of using at least one of the techniques introduced in the booklet in the future (*'Very unlikely'* to *'Very likely'*), and (4) how much they would recommend the booklet to other people with seizures (*'Definitely not recommend'* to *'Definitely recommend'*). There were also three open-ended questions asking (1) what the participant liked the most about the booklet, (2) what they liked the least about the booklet, and (3) which particular coping technique they liked the most. In addition, the questionnaire included a final open-ended question giving the participant an opportunity to provide any further feedback or comments about the booklet.

5.3.4.2 Self-report questionnaires

A sub-set of the self-report questionnaires described in Chapter 3 was used for the baseline and follow-up assessments in this study. The questionnaires used in this study included a demographic questionnaire with questions about age, gender, education, employment status, duration of the seizure disorder, current medication, the nature of the seizures, the date of the last seizure, and whether the patient was currently receiving any psychological or psychiatric treatment. Patients also completed the Quality of Life in Newly

Diagnosed Epilepsy – 6 Dimensions Scale (NEWQOL-6D; (Mulhern et al., 2012), the Liverpool Seizure Severity Scale (LSSS-3; Scott-Lennox et al., 2001), a generalised rather than the momentary version of the Smith Stress Symptom Inventory assessing the 35 stress symptoms in the past month (SSSI; (Piiparinen & Smith, 2003), the Neurological Disorders Depression Inventory for Epilepsy (NDDI-E; Gilliam et al., 2006), the Generalised Anxiety Disorder 7-item Scale (GAD-7; Spitzer et al., 2006), the Single-Item Self-Esteem scale (SISE; Robins et al., 2001), and the Spontaneous Self-Affirmation Measure with the Habit Index of Positive Thinking scale (SSAM and HIPT; Harris et al., in preparation). In addition, the European Quality of Life – 5 Dimensions Scale (EQ-5D; Brooks, 1996) described below was used as a generic HRQoL measure. The questionnaire sent to patients at one- and two-month follow-up included an additional question about changes in medication since the last assessment.

5.3.4.2.1 European Quality of Life – 5 Dimensions Scale (Brooks, 1996)

The EQ-5D is a standardised, generic measure of quality of life applicable to a range of health conditions and treatments (see Appendix 16). It consists of 5 descriptive items, including mobility, self-care, usual activities, pain/discomfort, and anxiety/depression, rated on 5-point scales (e.g., *"I have no problems walking about", "I have slight problems walking about", "I have moderate problem walking about", "I have severe problems walking about", "I am unable to walk about"*). The measure also includes a visual analogue scale (VAS), which records the respondent's health on a 20 cm vertical 100-point scale with end-points labeled *"the best health you can imagine"* and *"the worst health you can imagine"*.

Similarly to the NEWQOL-6D, the scoring is based on obtaining a unique health state by combining one level from each of the 5 descriptive items. There are a total of 3125 possible health states, each of which is referred to in terms of a 5-digit code. For example, state 11111 indicates no problems on any of the 5 dimensions, while state 12345 indicates no

problems with mobility, slight problems with washing or dressing, moderate problems with doing usual activities, severe pain or discomfort and extreme anxiety or depression. Each of these health states can be converted into a single index value between 0 (poor health) and 1 (perfect health). The VAS produces a single score ranging from 0 – 100. The EQ-5D has been translated into a number of languages and validated in a diverse patient population (Greiner et al., 2003; Shaw et al., 2005). The EQ-5D was included in the current study to enable possible future comparisons with other studies of different patient groups.

5.3.4.3 Seizure diary

The number of seizures experienced during each month was assessed by a simple seizure diary, previously used in a study of a psycho-educational intervention for patients with PNES (Mayor et al., 2013). For a copy of the seizure diary, see Appendix 17.

5.3.5 Study Procedure

5.3.5.1 Recruitment

Patients attending the Neurology Outpatient and the Specialist Epilepsy Nurse Clinics to see a Neurologist or an Epilepsy Nurse for help with seizures were sent an invitation letter with an information sheet concerning the purposes and procedures of the study together with their appointment letter, approximately 2 - 6 weeks before their scheduled clinic visit. On the day of their appointment, I approached patients in the waiting room and gave them an opportunity to ask questions and revisit the information sheet. Interested participants were screened for their suitability to take part in the study on the basis of the exclusion/inclusion criteria described above and their motivation to participate. Recruitment took place over a 5-month period between December 2014 and April 2015.

5.3.5.2 Baseline assessment and randomisation

Patients identified as suitable for the study were asked to sign a consent form and complete the set of baseline questionnaires described above. Patients were also asked to keep a seizure diary throughout the duration of the study.

Patients were subsequently randomly allocated to the immediate or delayed intervention groups. Each participant was assigned a consecutive study participation number, which had been randomised to either the immediate or the delayed intervention at the start of the study using an online randomisation tool (https://www.sealedenvelope.com/simple-randomiser/v1/lists). Patients allocated to the immediate intervention group were provided with an envelope containing a detailed instruction letter, a seizure diary for the following month, and the self-help stress management booklet. They were encouraged to read and work through the booklet over the following week and I arranged to contact them by telephone approximately one week after the baseline assessment for a brief interview using the feedback questionnaire designed to check on their progress and to obtain feedback on the booklet. Patients in the delayed intervention group received an envelope with an instruction letter and the seizure diary but without the self-help booklet. They were informed that the self-help booklet would be sent to them by post as part of the one-month follow-up assessment and I arranged to contact them for the telephone interview approximately one week after they had received the one-month follow-up materials and had had a chance to work through the self-help booklet.

5.3.5.3 Telephone interview

Patients in the immediate intervention group were contacted by telephone one week after the baseline assessment. They were interviewed using the Telephone Feedback Questionnaire described above and their responses were recorded in the questionnaire sheet.

Responses to the open-ended questions were transcribed verbatim or paraphrased as closely as possible if the participant provided more information than was possible to transcribe. Participants who did not answer the call on the arranged date were contacted again or a message was left for them if they had previously given permission for this. Participants who did not respond to any of the two phone calls were sent the feedback questionnaire by post and asked to send it back using an enclosed prepaid envelope.

5.3.5.4 One-month follow-up

The first follow-up was arranged for both groups at one month after the initial assessment in the clinic. Participants were sent the follow-up materials by post. The follow-up assessment involved completing the NEWQOL-6D and EQ-5D, the LSSS-3, NDDI-E, GAD-7, and SSSI questionnaires and submitting the seizure diary for the past month. Patients were also provided with a new seizure diary sheet to keep in the following month. Patients in the delayed intervention group received the self-help intervention booklet as part of the first follow-up assessment and were encouraged to use the booklet in the following week. Patients in the delayed intervention group were then further contacted by telephone one week after receiving the follow-up materials with the intervention booklet and asked to provide feedback on the booklet. The telephone interview was conducted following the same procedure as described above.

5.3.5.5 Two-month follow-up

Both groups were contacted again by post for the final follow-up assessment two months after the baseline assessment in the clinic. The two-month follow-up pack included the NEWQOL-6D and EQ-5D, the LSSS-3, NDDI-E, GAD-7, and SSSI questionnaires Participants were asked to return the questionnaires and the seizure diary they had been keeping in the past month using an enclosed prepaid envelope.

Participants who failed to return either of the one- or two-month follow-up materials within two weeks were contacted by telephone. Two telephone reminders were made and participants who did not respond to the calls or who failed to return the materials even after being reminded by telephone were sent a reminder letter explaining to them the importance of completing and returning the follow-up materials as soon as possible, and encouraging them to contact the research team if they had not received or if they had misplaced any of the study materials.

5.3.6 Data Preparation and Statistical Analyses

The questionnaires were scored according to their relevant scoring instructions. Where no formal instruction was available on how to treat missing data and where no more than 10% of scores were missing, the missing scores were replaced by the mean of completed items for the given scale. Mean replacement was performed on the SSSI ($N = 7$), GAD-7 ($N = 2$), SSAM ($N = 2$), and HIPT ($N = 3$) questionnaires.

All data were analysed using SPSS (Version 22 for Mac; SPSS Inc., Chicago, IL, U.S.A.). As the main aims of this pilot study were to assess feasibility and acceptability of the intervention, the focus was on descriptive statistics to present the recruitment and retention rates and the baseline self-report measures. The distribution of the data was assessed using the Shapiro-Wilk test. Although the data on a number of outcome measures, including the EQ-5D, NEWQOL-6D, SSSI, GAD-7, HIPT, SISE, and the LSSS-3 were non-normally distributed, parametric tests were used throughout and means and standard deviations are reported. All analyses were also run using non-parametric tests and any differences this made to the outcomes are highlighted. Where group comparisons were made, Chi-square analyses were used for categorical variables and *t*-tests were performed for continuous variables.

5.4 Results

5.4.1 Participants

5.4.1.1 Recruitment and retention rates

Figure 5.2 shows the recruitment and retention rates in the study. A total of 429 patients attending the clinics were approached and screened for eligibility. Of these, 178 patients (41.5%) were not interested in participating in the study, and further 169 patients (39.4%) did not meet the eligibility criteria. This resulted in a sample of 82 interested, eligible patients (19.1%) who consented to taking part in the study and were randomised to one of the two intervention groups.

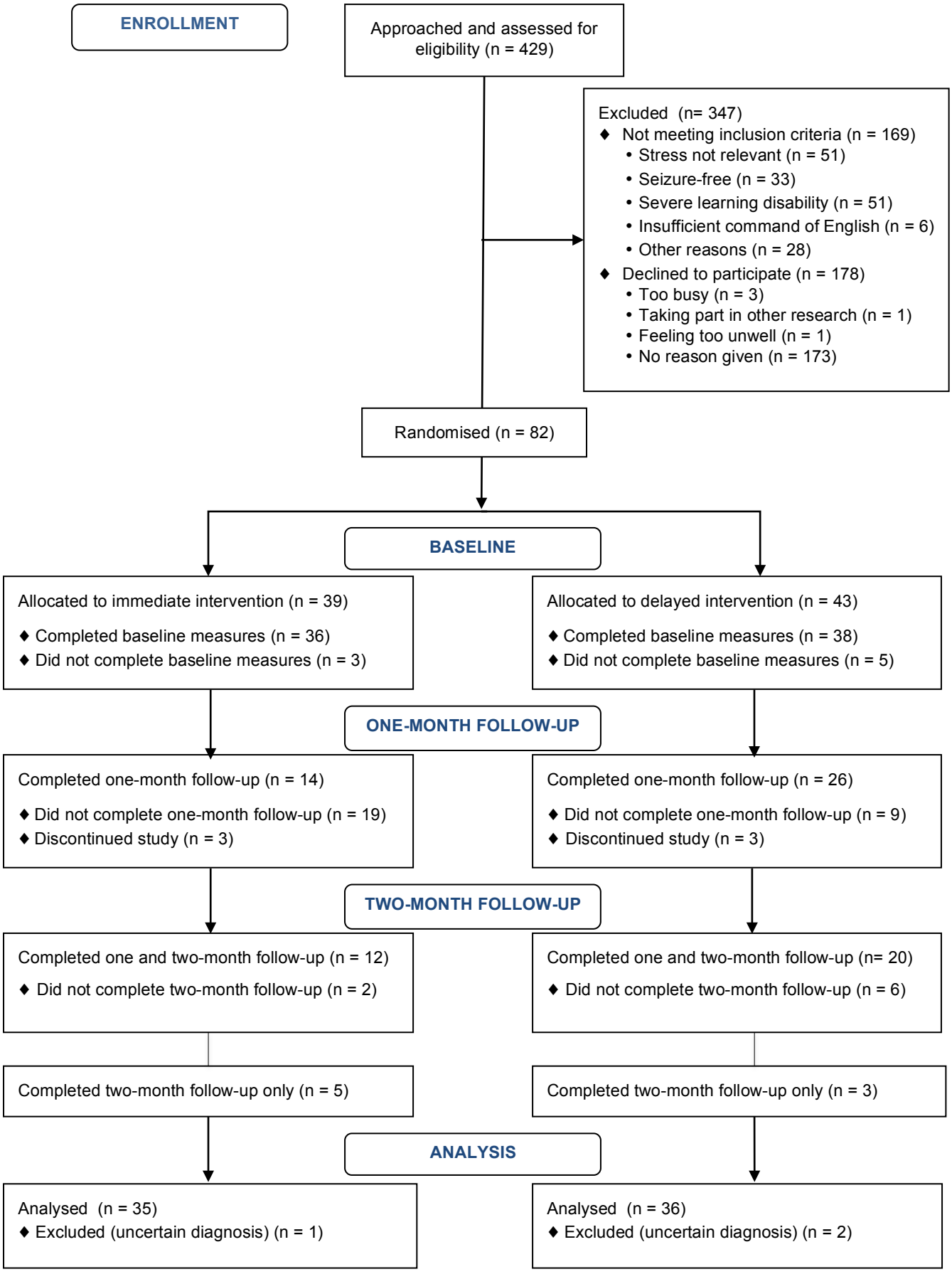
Thirty-nine patients were randomised to the immediate intervention group, of whom 36 completed the baseline assessment. The remaining three patients did not have enough time to complete the questionnaires in the clinic and said they would complete and send the materials back by post but failed to do so. Of the 36 patients who completed the baseline assessment, 14 (38.9%) completed and returned the one-month follow-up materials; 19 (52.8%) did not return the one-month materials and did not respond to telephone and postal reminders; and three patients (8.3%) informed the researcher they wished to withdraw from the study. Twelve patients (33.3%) who completed the one-month follow-up also completed and returned the two-month follow-up questionnaires (i.e., completed the full study); two further patients (5.6%) dropped out at this stage. Five patients who did not return the one-month questionnaires did complete and return the two-month follow-up questionnaires.

Forty-three patients were allocated to the delayed intervention group and out of these, 38 patients completed the baseline questionnaires. Of these 38 patients, 26 (68.4%) returned the one-month follow-up materials; nine (23.7%) failed to return the materials and did not respond to reminders; and three patients (7.9%) withdrew from the study. Twenty patients

(52.6%) who completed the one-month follow-up also returned the two-month follow-up materials (i.e., completed the full study); six further patients (15.8%) were lost to the second follow-up. Three patients who did not complete the one-month follow-up completed and returned the two-month follow-up only (see Figure 5.2).

The patients' diagnosis was later confirmed by their consultant neurologists. A diagnosis of epilepsy was confirmed in 57 patients, 12 patients had PNES, and two patients had both epileptic and psychogenic non-epileptic seizures. Patients whose diagnosis was uncertain were excluded from the analysis ($N = 3$).

Figure 5.2. *Flow diagram of patient recruitment and retention in the study*



5.4.1.2 Randomisation check

The baseline demographic, clinical and psychological measures in the two intervention groups are summarised in Table 5.2. A series of Chi-square analyses for categorical variables and independent-samples *t*-tests for continuous variables showed there were no baseline differences between the immediate and the delayed intervention groups (*p's* > .05).

Table 5.2. *Baseline demographic and clinical characteristics of the two intervention groups*

Characteristic	Immediate Intervention Group (*N* = 35) Mean (*SD*)	Delayed Intervention Group (*N* = 36) Mean (*SD*)	*P*-value
Age	40.49 (12.59)	43.22 (13.99)	.390
Gender (*N* female (%))	23 females (65.7%)	27 females (75.0%)	.391
Years in education	13.66 (2.84)	13.88 (2.43)	.735
Economically active (*N* active (%))	19 active (54.3%)	17 active (47.2%)	.552
Diagnosis (*N* (%))			.747
Epilepsy	26 (74.3%)	31 (86.1%)	
Idiopathic generalised epilepsy	7	5	
Focal epilepsy	18	22	
Unclassifiable epilepsy	1	4	
PNES	7 (20.0%)	5 (13.9%)	
Mixed epilepsy and PNES	2 (5.7%)	0	
Seizure disorder duration (years)	17.88 (16.84)	16.25 (13.51)	.654
Median seizure frequency (seizures/month)	3.00 (16.00)	2.00 (4.00)	.492
Seizure severity	55.20 (21.65)	56.72 (18.14)	.757
AED use (N (%))			.199
None	5 (15.2%)	1 (2.9%)	
AED Monotherapy	15 (45.5%)	19 (54.3%)	
AED Polytherapy	13 (39.4%)	15 (42.9%)	
SSAM	3.77 (1.54)	4.19 (1.69)	.285
HIPT	3.34 (1.57)	3.92 (1.96)	.176
SISE	2.46 (1.15)	3.00 (1.39)	.082
NEWQOL-6D index value	0.70 (0.14)	0.74 (0.14)	.194
EQ-5D index value	0.69 (0.23)	0.64 (0.30)	.448
EQ-5D visual analogue scale	70.03 (15.61)	63.56 (20.10)	.139
SSSI	2.47 (0.66)	2.37 (0.64)	.530
GAD-7	9.74 (6.29)	9.25 (6.26)	.747
NDDI-E	15.23 (3.66)	15.08 (4.22)	.639

Note. *SD* = standard deviation; *AED* = anti-epileptic drugs; *SSAM* = Spontaneous Self-Affirmation Measure; *HIPT* = Habit Index of Positive Thinking*; SISE* = Single-Item Self-Esteem Scale; *NEWQOL-6D* = Quality of Life in Newly Diagnosed Epilepsy – 6 Dimensions; European Quality of Life-5 Dimension; *SSSI* = Smith Stress Symptom Inventory; *GAD-7* = Generalised Anxiety Disorders 7-item Scale, *NDDI-E* = Neurological Disorders Depression Inventory for Epilepsy.

5.4.1.3 Baseline measures in completers versus non-completers

Considering the high dropout rate, the baseline characteristics were compared between those participants who completed the whole study ('completers'; $N = 29$) and those who dropped out or withdrew from the study ('non-completers'; $N = 42$). The baseline measures are summarised in Table 5.3.

A series of Chi-square and independent-samples *t*-test analyses were performed to examine whether there were any baseline differences between completers and non-completers. The analyses revealed that there was a significant difference in age, $t(69) = -2.83$, $p = .006$. As can be seen in Table 5.3, participants who completed the study were older than those who did not complete it. There were no other significant differences between the groups in any of the other variables.

Table 5.3. *Baseline demographic and clinical characteristics of completers and non-completers*

Characteristic	Completers (*N* = 29) Mean (*SD*)	Non-completers (*N* = 42) Mean (*SD*)	*P*-value
Age	47.00 (13.76)	38.00 (11.88)	**.006**
Gender (*N* female (%))	23 females (79.3%)	27 females (64.3%)	.173
Years in education	14.15 (2.60)	13.50 (2.64)	.330
Economically active (*N* active (%))	12 active (41.4%)	24 active (57.1%)	.192
Diagnosis (*N* (%))			.694
Epilepsy	23 (79.3%)	34 (81.0%)	
PNES	4 (13.8%%)	8 (19.0%)	
Mixed epilepsy and PNES	2 (6.9%)	0	
Seizure disorder duration (years)	19.16 (15.80)	15.61 (14.71)	.335
Median seizure frequency (seizures/month)	3.00 (14.00)	2.00 (4.50)	.224
Seizure severity	50.38 (22.08)	59.59 (17.57)	.065
AED use (N (%))			.854
None	2 (7.1%)	4 (10.0%)	
AED Monotherapy	15 (53.6%)	19 (47.5%)	
AED Polytherapy	11 (39.3%)	17 (42.5%)	
SSAM	4.30 (1.51)	3.77 (1.67)	.185
HIPT	3.94 (1.67)	3.44 (1.86)	.266
SISE	3.07 (1.18)	2.52 (1.35)	.087
NEWQOL-6D index value	0.75 (0.13)	0.70 (0.15)	.114
EQ-5D index value	0.69 (0.28)	0.64 (0.26)	.474
EQ-5D visual analogue scale	66.54 (21.15)	66.81 (16.26)	.951
SSSI	2.39 (0.61)	2.44 (0.68)	.732
GAD-7	9.61 (6.10)	9.41 (6.41)	.895
NDDI-E	15.11 (3.79)	15.43 (4.10)	.740

5.4.1.4 Baseline measures in patients with epilepsy and patients with PNES

The baseline measures were further explored in patients with epilepsy and patients with PNES (Table 5.4). For the purposes of the baseline comparisons, patients with mixed seizures were included in the PNES group, as previous studies suggested that the psychological profile of these patients is more similar to those of patients with PNES (Galimberti et al., 2003). Analysis showed that higher proportion of patients with epilepsy were taking at least one anti-epileptic drug, compared to patients with PNES, X^2 (2) = 27.85, p <. 001. A series of independent-samples *t*-tests suggested that patients with PNES had lower quality of life as measured by the NEWQOL, $t(67) = 2.66$, p = .010 and the EQ-5D $t(67) = 2.40$, $p = .019$), and higher levels of self-reported depression as indicated by the NDDI-E, $t(68) = -2.00$, $p = 0.49$. There were no other differences between patients with epilepsy and patients with PNES in the baseline measures[5].

Table 5.4. *Baseline demographic and clinical characteristics of the two patient groups*

Characteristic	Epilepsy ($N = 57$) Mean (*SD*)	PNES ($N = 14$) Mean (*SD*)	*P*-value
Age	42.39 (12.54)	39.79 (16.37)	.516
Gender (*N* female (%))	40 female (70.2%)	10 female (71.4%)	.145
Years in education	13.92 (2.72)	13.15 (2.15)	.348
Economically active (*N* active (%))	30 active (52.6%)	6 active (42.9%)	.132
Seizure disorder duration (years)	18.55 (15.59)	10.98 (11.83)	.094
Median seizure frequency (seizures/month)	2.00 (4.50)	3.00 (14.00)	.549
Seizure severity	55.16 (20.93)	59.55 (14.00)	.493
AED use (N (%))			**<.001**
None	0	6 (42.9%)	
AED Monotherapy	31 (54.4%)	4 (28.6%)	
AED Polytherapy	25 (43.9%)	3 (21.4%)	
SSAM	4.15 (1.64)	3.21 (1.34)	.070
HIPT	3.80 (1.79)	2.90 (1.66)	.113
SISE	2.84 (1.31)	2.25 (1.22)	.154
NEWQOL-6D index value	0.74 (0.13)	0.63 (0.14)	**.010**
EQ-5D index value	0.70 (0.25)	0.51 (0.29)	**.019**
EQ-5D visual analogue scale	68.40 (16.38)	59.23 (24.14)	.102
SSSI	2.36 (0.67)	2.67 (0.52)	.101
GAD-7	8.83 (5.99)	12.39 (6.68)	.063
NDDI-E	14.86 (3.81)	17.23 (4.10)	**.049**

[5] Comparison of the baseline measures between patients with epilepsy and patients with PNES using a series of non-parametric Mann-Whitney *U*-tests additionally suggested that patients with PNES also had lower levels of spontaneous tendency to self-affirm as measured by the SSAM ($U = 214.00$, $p = .050$).

5.4.2 Participants' Feedback

Forty-four patients provided telephone feedback on the booklet (20 in the immediate intervention group, 24 in the delayed intervention group). Overall, the feedback received from participants who worked through the booklet and responded to the questionnaire was positive, with most participants finding the booklet helpful and informative. A more detailed analysis of the responses to the rating scales and the open-ended questions is provided below.

5.4.2.1 Usefulness ratings

Of the 44 patients who responded to the feedback questionnaire, 40 provided feedback on each of the separate sections of the intervention. Table 5.5 summarises the numbers of patients who reported reading through the relevant section of the booklet and their ratings of the perceived usefulness of the booklet overall as well as each of the different booklet sections. The ratings were further broken down into three categories, based on whether people rated the booklet as very useful/useful (rating of 5 or 4), neutral (rating of 3), or not useful/not at all useful (rating of 2 or 1).

Table 5.5. *Usefulness ratings of the different parts of the intervention*

Booklet Section	***N*** **read**	**Mean usefulness rating (*SD*)**	***N*** **(%) useful (rated 4 or 5)**	***N*** **(%) neutral (rated 3)**	***N*** **(%) not useful (rated 1 or 2)**
Booklet overall	44	3.84 (0.94)	28 (63.6%)	14 (31.8%)	2 (4.6%)
Section 1 Understand stress	39	4.03 (1.04)	28 (71.8%)	8 (20.5%)	3 (7.7%)
Section 2 Spot the stressors	40	4.20 (0.85)	31 (77.5%)	8 (20.0%)	1 (2.5%)
Section 3 Clarify your values	37	3.86 (1.00)	23 (62.2%)	12 (32.4%)	2 (5.4%)
Section 4 Cope more effectively					
4.1 Ways of coping	38	3.71 (1.10)	21 (55.26%)	11 (28.9%)	6 (15.8%)
4.2 Coping with thoughts	38	4.00 (0.96)	25 (65.8%)	11 (28.9%)	2 (5.3%)
4.3 Coping with feelings	37	3.95 (0.97)	27 (73.0%)	6 (16.2%)	4 (10.8%)
4.4 Coping with lifestyle	35	3.91 (0.85)	25 (71.4%)	8 (22.9%)	2 (5.7%)
Section 5 Take action	27	3.96 (0.90)	18 (66.7%)	8 (29.6%)	1 (3.7%)
Section 6 Getting more help	24	4.29 (0.81)	19 (79.2%)	5 (20.8%)	0 (0%)

5.4.2.2 Ratings of likelihood of future use and recommendation to others

Forty patients responded to the question *'How likely are you to use at least one of the coping techniques from the booklet in the future?'* The mean likelihood rating was 4.45 (SD = 0.78), with 33 patients (82.5%) reporting being likely or very likely to use at least one of the techniques in the future (rating of 4 or 5), seven patients (17.5%) being neutral or undecided (rating of 3), and no patients being unlikely or very unlikely to use at least one of the techniques (rating of 1 or 2).

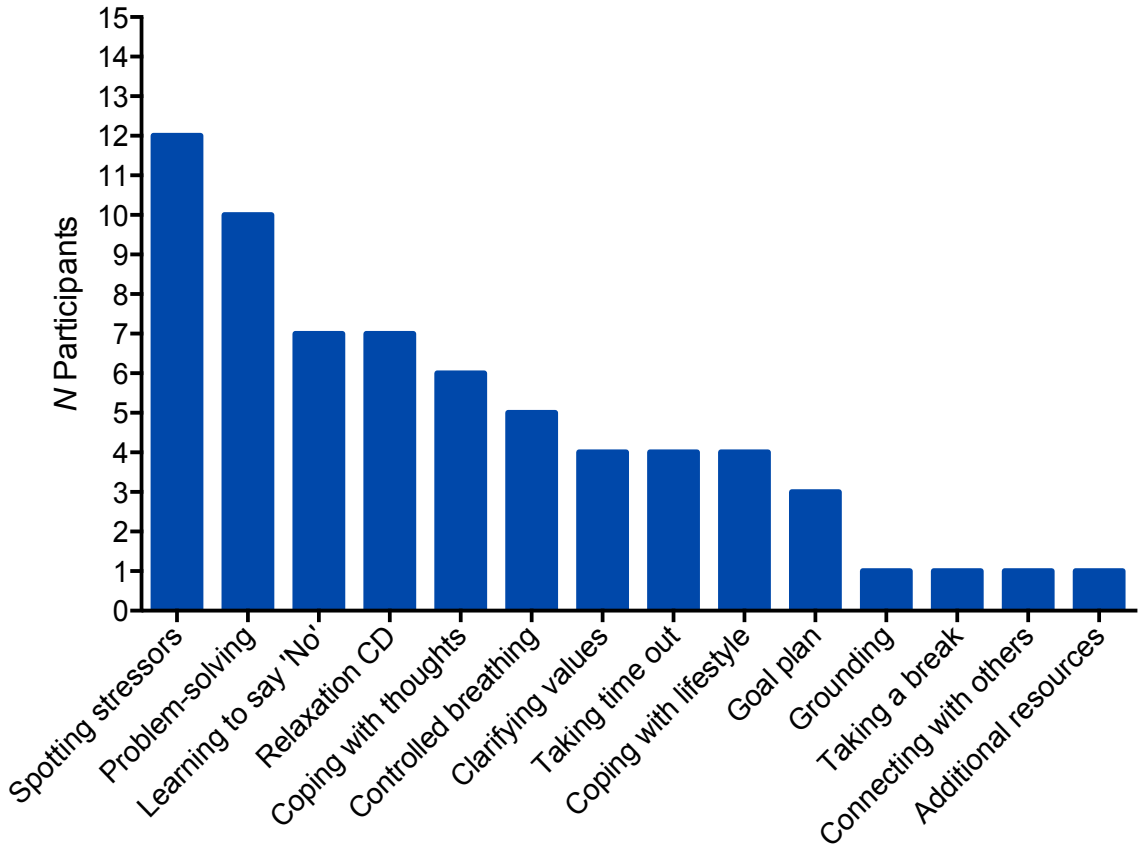
The question *'Would you recommend the booklet to other people with seizures?'* was answered by 42 patients. The mean rating was 4.54 (SD = 0.71), with 37 patients (88.1%) stating they would recommend or definitely recommend the booklet (rating of 4 or 5) and 5 patients (11.9%) being neutral or undecided. No patients stated they would not recommend or definitely not recommend the booklet to other people with seizures (rating of 1 or 2).

5.4.2.3 Feedback from open-ended questions

The three open-ended questions asked about the coping technique or section of the booklet that people liked the most, as well as what people generally liked the most about the booklet and what they liked the least.

Figure 5.3 shows the most popular coping techniques. As can be seen from the graph, the most frequently mentioned techniques included the identification of stressors (preferred by 12 out of the 44 patients), the problem-solving exercise (10 out of 44 patients), practising to say 'No' and the audio-guided muscle relaxation exercise (7 out of the 44 patients).

Figure 5.3. *The most frequently mentioned coping techniques*



5.4.2.3.1 Positive aspects

Several common points emerged from people's comments on the most and least liked aspects of the booklet. From the positive comments, the aspects people appreciated the most included the material being explained in a way that was easy to understand and written in an informal, 'friendly' language (mentioned by 8 patients). One of the patients commented, "*It is written in a really sympathetic language, it makes you feel you're not on your own. It's friendly and informative"*. Another patient stated, *"It's more worldly and comforting than other booklets, less formal"* and one patient said, *"It was written in a language that we can understand. It would encourage you to follow the advice."*

Another positive aspect people mentioned was the way the intervention enabled them to self-assess their stressors and thoughts and to respond in a proactive, constructive way

rather than getting overwhelmed (mentioned by 8 patients). One patient said they liked *"Being able to self-assess my thought patterns and activities, put things into perspective and analyse them and tackle them one by one rather than worrying about them and being overwhelmed"*; another person appreciated *"Prioritising the stress and the worries, writing things down rather than having it all in your mind."*

A number of people also felt the intervention increased their understanding of stress and/or the links between stress and seizures (mentioned by 6 patients). One patient said they liked *"The ways it helped me realise what stress was all about"*. Another patient said, "*All of it was useful, especially the point about the stress and seizure link"*.

People also felt that the intervention introduced new information and techniques and gave them a new perspective (mentioned by 5 patients). One patient said, *"It has given me a few things and techniques to try. The 'take time out' is very good for sleepless nights, something I didn't know about before"*. Other comments included, *"It makes you think"* or *"It gives you a different perspective"*.

Another common positive comment was that the booklet was a good point of reference and included useful resources (mentioned by 5 patients). One participant said, *"This is a great help. I have written useful parts down and carry it around with me and I recommended ideas and techniques to others already"*.

People also mentioned they liked the fact that the intervention was comprehensive, relevant to people with seizures, practical, interactive with enough space for writing notes and that it was possible to select and focus on different sections.

5.4.2.3.2 Negative aspects

With regard to the least liked aspects, most people said that there were no particular things they disliked about the intervention (29 participants). However, some participants felt the intervention was too detailed and complex (mentioned by 5 patients) and that there was a

lot of text and the font was too small (mentioned by 3 patients). One participant felt, *"There may be too much information, it's too complex and ambitious"*. One participant who hadn't worked through the whole booklet at the time of the interview said, *"I will go through it more carefully but I was put off by the amount of information, it could be daunting for people"*.

On the other hand, a number of people said that some of the information was not new to them and that the booklet covered material they were already familiar with (mentioned by 3 patients). One patient said, *"A lot of it is similar to the CBT materials I came across before but it's a good thing to remember and be reminded of"*. Another patient commented, "*It wasn't new to me, it was information I already knew instead of suggestions that are different or new. It's more for people who don't know anything about the triggers of stress. It would be good for a lot of people but it would be nice to have something a bit more advanced for people who already have the basic knowledge."*

Two people felt that the intervention or some of the material was not personally relevant to them, for example, one of them said, *"It was not relevant for me. I have a lot of support from my family and I have my ways of coping when I am stressed out. It might be useful for other people but not me"*. Two people also mentioned that although the intervention was useful in terms of coping with stress, they did not feel it had an impact on their seizure frequency.

5.4.2.3.3 Patients' suggestions and recommendations

When asked about any further general feedback, two participants suggested it would have been helpful to have someone to guide them through the intervention and help them work through the exercises, for example, an epilepsy nurse or an occupational therapist. There was also a recommendation to make the booklet into a two-step intervention, with an initial brief introduction to the basic material and a more advanced version with more

detailed and complex information. One participant further pointed out that it might be useful to include more information about the effects of anti-epileptic medication.

5.4.3 Preliminary Evaluation of Effectiveness

As a secondary aim of this pilot study, a preliminary test of the effectiveness of the intervention was conducted and the effect sizes were estimated. Given the low retention rate in the study, the pre- and post-intervention outcome measures from the two intervention groups were combined and compared using a paired-samples *t*-test, in order to maximise the sample size. The effects are reported both with and without Bonferroni correction for multiple tests. The tests were only performed for a selection of the main outcome measures of interest, including quality of life measured by the EQ-5D index value, self-reported stress measured by the SSSI, anxiety measured by the GAD-7, depression measured by the NDDI-E, and seizure frequency reported in the LSSS-3. Before combining, the baseline versus one-month follow-up measures were compared in the delayed intervention group to assess whether any spontaneous changes occurred during this control (i.e., no intervention) period.

Cohen's d_z measure of effect size was calculated using a power analysis software G*Power (Erdfelder et al., 1996). The Cohen's d_z is a standardised mean difference effect size appropriate for paired-samples *t*-test analyses, as it accounts for the correlation coefficient between the paired measures (Lakens, 2013). It is calculated as:

$$\text{Cohen's } d_z = \frac{M_{diff}}{\sqrt{\frac{\Sigma(X_{diff}-M_{diff})2}{N-1}}}$$

Where the numerator M_{diff} is the mean of the difference scores and the denominator is the standard deviation of the difference scores.

5.4.3.1 Spontaneous changes in the delayed intervention group

The outcome measures at baseline (T0) and at one-month follow-up (T1) in the delayed intervention group are summarised in Table 5.6. A series of paired-samples *t*-tests revealed that there were no significant differences between any of the baseline and the one-month follow-up measures (*p's* > .05). This indicates that there were no statistically significant spontaneous changes in these measures during the no-intervention period.

Table 5.6. *Mean outcome measures at baseline and at one-month in the delayed intervention group*

Outcome Measure (*N* = 24)	Baseline (T0) Mean *(SD)*	One-month (T1) Mean *(SD)*	*P*-value	Cohen's d_z
EQ-5D index value	0.65 (0.29)	0.70 (0.26)	.422	0.195
SSSI	2.45 (0.65)	2.42 (0.78)	.675	0.069
GAD-7	10.58 (6.07)	9.21 (6.93)	.167	0.288
NDDI-E	16.04 (3.71)	15.96 (4.37)	.909	0.023
Seizure frequency	16.13 (56.50)	9.46 (17.41)	.439	0.161

5.4.3.2 Comparison of the pre- versus post-intervention outcome measures

Table 5.7 summarises the pre- and post-intervention outcome measures from patients in both intervention groups combined (i.e., the baseline (T0) versus the one-month follow-up (T1) measures in the immediate intervention group, and the one-month follow-up (T1) versus the two-month follow-up (T2) measures in the delayed intervention group), as well as the associated effect sizes.

As shown in Table 5.7, there was a significant reduction in self-reported stress from pre- to post-intervention, $t(28) = 2.74$, $p = .011$. Applying Bonferroni correction for the five tests would lead to an adjusted significance level of .01 (.05/5), which would mean this effect

would still approach significance[6]. The associated effect size was $d_z = 0.509$, indicating a medium effect size.

There were no significant improvements in quality of life, anxiety, depression, or seizure frequency ($p's > .05$) and the associated effect sizes were small, as can be seen in Table 5.7.

Table 5.7. *Mean pre- and post-intervention outcome measures and associated effect sizes*

Outcome Measure	*N*	Pre-intervention Mean *(SD)*	Post-intervention Mean *(SD)*	*P*-value	Cohen's d_z
EQ-5D index value	29	0.72 (0.24)	0.71 (0.21)	.767	0.056
SSSI	29	2.32 (0.65)	2.12 (0.59)	**.011**	0.509
GAD-7	30	9.10 (6.43)	8.30 (4.87)	.334	0.179
NDDI-E	30	15.00 (3.95)	15.20 (3.23)	.659	0.082
Seizure frequency	31	18.81 (51.10)	13.58 (25.34)	.302	0.188

5.4.4 Analysis Plan and Sample Size Calculation for a Future Randomised Controlled Trial

Based on the estimate of effect size reported above, a preliminary sample-size calculation was performed, in order to determine the sample size that would be needed for an appropriately powered randomised controlled trial of the intervention. One possible way of analysing the data would be to perform a series of 2 x 2 analyses of covariance (ANCOVAs) for mixed designs for each of the five main outcome measures, with the intervention group (immediate versus delayed intervention group) as a between-participants independent variable, time (one-month follow-up versus two-month follow-up) as a within-participants independent variable and the relevant outcome measure at baseline as a covariate. If the intervention was effective, a significant group by time interaction would be expected, with

[6] Comparison of the pre- versus post-intervention self-reported stress using non-parametric Wilcoxon signed-rank test yielded a significant difference, $Z = -2.60$, $p = .009$, which would remain significant even after applying the Bonferroni correction for multiple tests.

the immediate intervention group scoring significantly better than the delayed intervention group at one-month follow-up, and with the two groups having comparable scores at two-month follow up.

The G*Power software was used to calculate the sample size required to achieve sufficient power using a series of ANCOVAs. In order to reduce the risk of Type 1 error, a Bonferroni correction was applied to correct for the five tests of the five main outcome measures and an adjusted significance level of 0.01 was used for the sample size calculation. Using a significance level of 0.01 and assuming a small to medium effect size, the total sample size needed to achieve 80% power with an analysis of covariance would be $N = 191$. This means approximately 96 participants in each intervention group. However, taking into an account the high dropout rate observed in the present study, future studies should expect dropout rates of at least 50%. In order to allow for such level of attrition, the sample recruited into the RCT would need to be at least $N = 382$ (i.e., 191 participants in each intervention group).

5.5 Discussion

This chapter described the theoretical rationale for and the development of a self-help intervention designed to help patients with seizures cope with stress. The intervention was assessed in a pilot of a randomised controlled trial, aimed at testing the feasibility of the study procedures, estimating rates of recruitment and retention, and assessing the acceptability of the intervention. In addition, the study provided a preliminary evaluation of the effectiveness of the intervention and the associated effect sizes as a basis for an estimate of sample size for a potential future RCT.

In terms of feasibility of the study procedures, recruitment and retention in this pilot study posed a significant challenge, due to the short recruitment period and relatively high

proportion of patients who were not eligible or interested in taking part in the study. Some of the reasons for not wanting to take part mentioned by the patients included being too busy, taking part in other research or not feeling well enough; however, most patients did not provide a reason and were not specifically asked about it, which is something that could be further explored in future research. Similar recruitment challenges have previously been reported in a pilot study of a self-management programme for epilepsy, conducted in a similar setting of a specialist outpatient epilepsy service (Pramuka et al., 2007).

Nevertheless, the fact that out of all the patients who were screened and approached by the researcher, 19.1% fulfilled the screening criteria, which required them to consider stress to be a relevant factor for their seizures and to be motivated enough to attempt to reduce their stress, suggests that stress is an important issue for many patients with seizures. However, this real world number of people who are willing to engage in an intervention targeting stress seems lower than the percentages of patients with seizures who report stress to be a potential trigger for their seizures, which have been reported in previous studies (Nakken et al., 2005; Privitera et al., 2014).

Despite the relatively strict screening criteria and an attempt to recruit motivated individuals, there was a high dropout rate among those who consented to participate in the study. Comparison of the two intervention groups at baseline suggested that the randomisation procedure did not lead to any significant differences between the two intervention groups at the start of the study. There were also no apparent baseline differences between those who completed and those who did not complete the study. However, it should be noted that the statistical power of the tests was relatively low. The only identified difference between completers and non-completers was age, with older participants being more likely to complete the study. The reason for this is unclear and the evidence for predictors of retention in studies of self-help interventions is mixed, with some studies

reporting older age to be one of the predictors of higher retention while others reporting younger age to be associated with higher retention (Christensen et al., 2009; Lange et al., 2003; Reeves & Stace, 2005).

Importantly, the levels of attrition were different in the two intervention groups. While only 38.9% of patients in the immediate intervention group responded to the first follow-up, the retention rate in the delayed intervention group was 68.4%. Similarly, while only one third of patients (33.3%) in the immediate intervention group completed the whole study, more than half of the patients (52.6%) in the delayed intervention group completed the whole study. Differential attrition in randomised trials where participants do not differ at baseline is likely to be associated with some aspect of being allocated to the intervention versus the control condition, and can pose a problem for the internal validity of the study. However, the understanding of differential attrition in RCTs is limited (Crutzen et al., 2015).

One reason for the differential dropout rate in the current study could be the expectations of receiving the intervention in those randomised to the delayed intervention group. It is conceivable that the anticipation of receiving and benefiting from the intervention served as an incentive for participants in the delayed intervention group to stay in the study and respond to the first follow-up, as opposed to patients in the immediate intervention group who did not have to wait and received the booklet as part of the baseline assessment. Another possible explanation, suggested by a recent systematic review of differential attrition in health behaviour change trials, is that participants in the immediate intervention group may have also had expectations about the benefits of the intervention, which were not met by the intervention and therefore led to reduced motivation to complete the follow-up (Crutzen et al., 2015). Alternatively, it is possible that a higher proportion of patients in the immediate intervention group dropped out early on due to the initial demands of having to complete the baseline assessment, work through the intervention and provide feedback within the first

week of enrolment into the study. The demands on participants associated with the study intervention have been proposed as one of the challenges of retention in clinical trials (Gul & Ali, 2010), and it would also be supported by the findings of a previous study of a self-help treatment programme for individuals with post-traumatic stress disorder, which showed that participants were more likely to drop out during the initial, most intense phase of the treatment programme (Lange et al., 2003). Although there is a great variability in the recruitment and retention rates of different self-help intervention studies, this pattern of dropout is consistent with a number of previous studies. Two systematic reviews of self-management interventions for anxiety, depression, and psychological distress report that in many of the reviewed studies dropout rates were lower in the control group than in the intervention group (Christensen et al., 2009; Matcham et al., 2014). However, the reasons for this have not been addressed in-depth in any of the reviews.

Overall, the dropout rate of approximately 50 – 70% found in the present study is comparable to other similar studies of self-help interventions. Dropout rates greater than 50% have been found in studies of self-help programmes for affective disorders (Christensen et al., 2009; Reeves & Stace, 2005; Spek et al., 2007). This level of dropout also seems to reflect the interest in and engagement with psychological treatment in patients with non-epileptic seizures. For example, a feasibility study of a psychoeducational intervention for patients with PNES reported a 45% completion rate (Mayor et al., 2013). In contrast, a recent RCT of an online CBT-based intervention for depression in patients with epilepsy reported completion rate of 72% (Schroder et al., 2014). The relatively low dropout in the Schroder et al. study could be explained by the mode of recruitment, as the participants were recruited from epilepsy-specific online forums and it is therefore likely that the sample included proactive individuals who independently seek help and support online. Such participants are likely to be more motivated than the convenience sample of patients attending outpatient

neurology clinics recruited for the present study. Furthermore, the study by Schroder and colleagues used fewer outcome measures, and the fact that the whole study and data collection was conducted online may have made it easier for the participants to complete the study.

Regarding the acceptability of the self-help intervention in the present study, the feedback collected from patients in the telephone interview suggested that, overall, the booklet was perceived as being acceptable, with more than half of the participants rating the booklet as helpful or very helpful. The majority of patients also reported they intended to continue using at least one of the techniques introduced in the booklet in the future, and stated they would recommend the booklet to other people with seizures. The content and format of the intervention seemed acceptable as well and a number of participants commented positively on the language and tone in which the booklet was written, as well as the relevance of the information about stress and seizures and the usefulness of the coping techniques introduced in the booklet. A number of patients appreciated the constructive, problem-focused approach, which allowed them to identify their problems and tackle them in a systematic fashion. This was also reflected by the preference for the identification of stressors and the problem-solving techniques, indicated by patients when asked about their favourite coping strategy. Patients also seemed to find the advice on learning to say 'No' helpful, as well as the relaxation exercise, the strategies for coping with negative thoughts and worries and the controlled breathing technique. Interestingly, the order of preference for the specific coping techniques more or less reflected the order in which these techniques were presented in the booklet, which suggests that people's preferences may have been affected by order effects. It is also possible that some participants only read the first few sections of the booklet, although most participants reported reading through most sections.

Although the overall feedback was positive, it is important to note that there may be a degree of bias, as it is possible that the booklet was not perceived to be helpful by those participants who dropped out, withdrew from the study or did not respond to the feedback questionnaire.

With regard to possible improvements to the intervention, the main negative feedback on the booklet was related to the amount of information and text in the booklet, which was perceived as daunting by some participants. A few participants also expressed an interest in receiving more guidance and having someone to introduce and work through the intervention with them. Based on these comments and suggestions, there are a number of practical ways in which the intervention could be improved. For example, it may be desirable to re-print the booklet using larger font to make it easier to read and perhaps improve the aesthetic appeal of the booklet by adding pictures or photos. In addition, providing more guidance on the use of the booklet could enhance its effectiveness. Indeed, previous studies suggest that guided self-help interventions tend to be more effective than unguided self-help for the management of affective disorders (Cuijpers & Schuurmans, 2007; Gellatly et al., 2007; Lewis et al., 2012). While this would increase the time and staffing resources required, it should be relatively simple for someone with minimal psychological training or experience, for example, an epilepsy nurse, or an occupational therapist to administer the intervention.

The secondary objective of this study was to provide preliminary evidence of effectiveness of the intervention. The high dropout rate and the resulting low number of participants who responded to and completed all of the outcome measures compromised the statistical analysis of the data, as it was not feasible to perform the analysis using data from all the three assessment points. Nevertheless, the preliminary analysis of the data revealed promising findings. The results suggested that the intervention was associated with reduction in self-perceived stress and the effect size of this change was moderate. Considering the self-reported importance of stress and stress management for patients with seizures, this

preliminary finding is encouraging. There are no previous studies of self-help interventions targeting stress management in patients with seizures but the effect size found in the present study seems comparable to other interventions aimed at reducing the symptoms of emotional disorders including depression and anxiety, which reported effect sizes ranging from d = 0.41 – 0.96 (Cuijpers & Schuurmans, 2007; Gellatly et al., 2007; Lewis et al., 2012).

No changes were found in depression, anxiety or quality of life. The reasons for this could be the lack of statistical power to detect changes in these measures or the fact that the intervention was designed to specifically target stress, rather than anxiety or depression. There were also no improvements in seizure frequency, suggesting that while the intervention may be helpful for the management of perceived stress, it may not necessarily be effective in reducing seizures. Indeed, some participants commented that they found the intervention useful in terms of stress but did not feel it had a direct effect on the frequency of their seizures. One reason for this may be the relatively low baseline seizure frequency of the participants in the current study. While there was a great variability between patients, the median seizure frequency at baseline was only 2 – 3 seizures per month. Most intervention studies of anti-epileptic medication typically require patients to experience at least 3 seizures per month (Fertig et al., 2014), whereas the only exclusion criterion in the present study was seizure freedom in the past 12 months. The evidence for effectiveness of psychological interventions on the reduction of seizures is mixed (Ramaratnam et al., 2008). In consideration of the findings of Study 1 of this thesis, the role of stress in directly triggering seizures remains uncertain and it may therefore be rather ambitious to expect a self-help stress management intervention to directly reduce seizure frequency, particularly in patients with small numbers of seizures. However, the occurrence of seizures in patients in Study 1 seemed to be associated with increased levels of self-perceived stress and autonomic arousal, and patients with epilepsy also exhibited increased attentional vigilance towards stress-

related stimuli. Reducing the perceived stress associated with the experience of seizures is therefore valuable in itself. Furthermore, a number of studies emphasised that the complex psychosocial complications associated with having a seizure disorder can be equally or even more disabling than the seizures themselves and it is therefore important to develop treatments targeting all the different difficulties associated with the disorders (Elliott & Richardson, 2014; Hermann & Jacoby, 2009; Lu & Elliott, 2012).

Additionally, as discussed in previous chapters, there may be a sub-group of patients in whom stress does directly trigger seizures. While the present study was not powered to explore sub-groups of patients, this is something that could be further investigated in future studies. There is evidence for the potential of stress management interventions to lead to improvements not only on a psychological but also on a biological level, for example, a RCT of a stress management therapy for patients with multiple sclerosis was found to be associated with a reduction of formation of new brain lesions (Mohr et al., 2012). It would therefore be interesting to test whether the stress management intervention developed as part of the present study could have direct effects on seizure reduction in patients with stress-precipitated seizures.

5.5.1 Limitations

This pilot study has a number of limitations. One of the main limitations was the low retention rate, which was further hindered by the limited time available for data collection within the time frame of the PhD project, resulting in a small sample size. This study was designed as a pilot study and the evaluation of the intervention effectiveness was a secondary aim. The small sample size and the lack of statistical power mean that although the results seem promising, they cannot be confidently generalised at this point.

There are further inherent limitations associated with self-help interventions. In addition to the risk of a high proportion of patients not finishing the treatment, there is also a lack of professional assessment and a limited opportunity to monitor patients' adherence to the intervention. This means that patients may not complete the intervention or may apply the treatment inappropriately. Apart from asking patients which sections of the booklet they read through as part of the telephone interview, adherence was not formally assessed in this pilot study. It is therefore unclear to what extent patients actually read through the different booklet sections and in what way they used the content of the intervention. One way of assessing this, which was considered at the design stage of the study, would be to ask participants to return the booklet to the research team once they have read through it and to examine how many of the interactive exercises they completed. However, it was decided this was not feasible, as it is likely that many patients would not return the booklet and it would not be possible to reliably assess how much of the non-interactive parts of the intervention patients read through. It would also mean that patients would not be able to keep the booklet for future reference. Another option would have been to ask participants to record their use of the intervention as part of their seizure diary; however, this would have further increased the burden of the study and thereby further reduced the retention rates. A better way of assessing adherence would be to convert the booklet into an online intervention and electronically monitor how many sections people accessed and completed. In an on-line version of the intervention it would perhaps also be desirable to assess whether the order in which participants accessed and completed the different sections affected their preferences for the different coping strategies or their effectiveness.

Another limitation is that the feedback provided by patients in the telephone interview was not audio-recorded or formally transcribed and the responses to the open-ended questions were not analysed using a formal qualitative analysis. Furthermore, patients'

responses were assessed by one researcher who was not blinded to the intervention group or the identity of the patients, and who is likely to have been perceived by the patients as the author of the intervention. While undertaking a qualitative analysis was not an aim of this study and while every effort was made to transcribe and evaluate the responses as objectively as possible, there may have nevertheless been a certain degree of bias.

A video-EEG confirmed diagnosis was not required for this study and in most cases, the diagnosis was established clinically by the patient's consultant neurologist. Although patients for whom there was clinical uncertainty about the diagnosis were excluded from the analyses and although the patients were recruited from a specialist neurology service and diagnosed by experienced epileptologists, it is possible that some patients may have received an incorrect diagnosis. However, the intervention was designed for both patients with epilepsy and those with PNES and the diagnostic distinction was therefore not an essential part of this pilot study. Having said that, it would be interesting to explore the effects of the intervention in patients with epilepsy and patients with PNES separately, particularly considering that the patients with PNES in this study reported higher levels of depression, and lower quality of life. Unfortunately, the number of patients with PNES recruited in this pilot study was too low to perform any meaningful sub-group comparisons.

Similarly to the patient groups in Study 1, the majority of patients in the current study were taking a number of anti-epileptic and other medications and a number of patients were suffering from a range of comorbid psychological problems. Patients were not excluded on the basis of their medication use or comorbid psychological conditions, as doing so would mean that the sample would not be representative of the clinical reality of this patient population. The study was not powered to control for these variables and it is therefore not possible to determine whether these factors had any confounding effects on the intervention. Nevertheless, any possible confounding effects were partly controlled for by the randomised

design of the study, the fact that the two intervention groups did not differ on any of these baseline characteristics, and the observation that there was no significant change in the delayed intervention group during the no-intervention period.

Finally, a further limitation of the study is its reliance on self-report measures. Although a selection of standardised, well-established measures was used in the study, the self-report questionnaires are still prone to a number of recall and response biases, particularly in patients with epilepsy and PNES who may have limited emotional insight, as discussed in the previous chapters.

5.5.2 Future Research

Based on the findings of this pilot study, a larger-scale randomised controlled trial of the intervention would require a considerably larger sample size and would need to account for a high dropout rate of at least 50% or more. There are a number of approaches to the statistical analysis of the data, including complete observations analyses or more complex modelling approaches, which could account for the missing data or differential attrition rates, such as an intention to treat analysis with the last observation carried forward or multiple imputation techniques (Christensen et al., 2009; Dziura et al., 2013). Considering the risk of high levels of attrition, it would be important to carefully consider the most appropriate approach if a future RCT was to be conducted.

There are also ways in which the recruitment and retention in the study could be maximised, including a longer recruitment period, extending the recruitment to multiple sites or employing a wider range of recruitment methods in different settings, for example, through online forums or epilepsy and PNES support groups. As discussed above, providing an initial guidance on the intervention or embedding the booklet in an epilepsy nurse-led intervention could enhance the retention in the study and the impact of the intervention itself.

As suggested by the MRC guidelines, future research should also assess the cost-effectiveness of the intervention and include a longer follow-up period, in order to assess long-term benefits of the intervention. It may also be desirable to monitor adherence to the intervention and examine the relationship between the degree of adherence and the treatment outcomes. It would also be interesting to explore the mechanisms of change and possible moderators of improvement, for example individual resilience factors, as well as to examine the effects of the intervention separately in patients with epilepsy and those with PNES, or in a sub-group of patients in whom stress is directly linked to their seizure occurrence.

5.5.3 Implications and Conclusions

In conclusion, despite its limitations, this pilot study provided a description of the development of a theory-based intervention specifically targeting stress in patients with seizures, and demonstrated its acceptability and perceived helpfulness to patients. Furthermore, the preliminary results of the study suggest that this simple intervention may have potential beneficial effects on the reduction of perceived stress – one of the main self-reported seizure precipitants in patients with seizures. While an appropriately powered randomised controlled trial of the intervention is needed to provide definitive evidence for its effectiveness and cost-effectiveness, this pilot study suggests that in motivated individuals who perceive stress to be a factor contributing to their seizures, this self-help intervention could offer a useful tool to help them manage their stress better. Given the current lack of targeted stress-management interventions for patients with seizures, the booklet could be a relatively low-cost, low-threshold complementary treatment option that could be easily integrated into existing services and offered to patients who do not require intensive psychotherapy or as a first step before a more complex intervention and it could also be helpful to patients for whom psychological help may not be readily accessible.

6. CHAPTER 6

Summary and Conclusions

The relationship between stress and epilepsy has received scientific attention in recent years; however, most research to date has focused on the role of stress in epileptogenesis or on stress caused by epileptic seizures. Similarly, stressful life events have been studied as a risk factor for the development of PNES but fewer studies have considered the role of stress as an immediate trigger for non-epileptic seizures, although a close link between PNES and acute arousal has been hypothesised (Goldstein & Mellers, 2006). The evidence presented in Chapter 2 showed that the question whether, how or in whom stress facilitates seizures in patients with existing epilepsy or PNES is important. Many patients consider stress to be a trigger of their seizures and the identification and effective elimination of stress could reduce seizure frequency, as well as the uncertainty and distress surrounding seizure occurrence. The overall objective of this PhD programme was therefore further to explore the relationship between stress and seizures, and to develop and pilot-test a simple psychological self-help intervention that could reduce the stress patients experience and have potential beneficial effects on seizure occurrence and health-related quality of life.

6.1 Key Findings

Study 1a of this PhD project aimed to explore the links between stress and seizure occurrence using prospective assessment of a combination of subjective measures of self-perceived stress and objective measures of physiological stress markers, including levels of salivary cortisol and HRV parameters. As part of the study, the diurnal patterns of these stress

measures and the relationships among them were also examined, in an attempt to provide further insight into the complex interactions of the different stress markers.

The results showed a diurnal pattern in the physiological measures in both patients with epilepsy and those with PNES, similar to that typically found in healthy individuals, with high cortisol levels, high sympathetic nervous system tone and low parasympathetic (vagal) tone in the morning, and lower levels of cortisol, lower sympathetic tone and higher vagal tone in the evening. No diurnal fluctuation was found in self-reported stress in any of the two patient groups.

Notably, no differences were found in the diurnal levels of cortisol between patients with epilepsy, patients with PNES, and a normative sample of healthy volunteers, suggesting there were no abnormalities in the cortisol levels or the cortisol circadian rhythm in the epilepsy and PNES patients in the present study. Normative diurnal HRV data were not available but comparison of the HRV between patients with epilepsy and patients with PNES suggested that patients with PNES had higher sympathetic tone than patients with epilepsy. This is consistent with a number of previous studies (Bakvis et al., 2009a; Bakvis et al., 2011; Roberts et al., 2012) and suggests patients with PNES may have high levels of autonomic arousal even in baseline or resting states.

Exploration of the relationships among the measures showed that cortisol was correlated with some of the HRV parameters in the morning in both patient groups combined. No correlations were found between the physiological measures in the evening, which is something that would be expected, considering the very low levels of nocturnal cortisol. There were no relationships between the physiological measures and self-reported stress in any of the two patient groups. These correlational patterns suggest a degree of association between the endocrine and autonomic stress markers that is not reflected in self-perceived experience. This may indicate a discrepancy between the subjective and objective measures,

previously reported in patients with PNES (Dimaro et al., 2014; Dimaro et al., 2015), which is perhaps partly attributable to the relatively high levels of alexithymia found in both patients with epilepsy and patients with PNES (Myers et al., 2013). However, as discussed previously, it is also plausible that the different components of the stress system function relatively independently under resting conditions and may become more synchronised in highly stressful situations, under heightened arousal or when there has been any other relatively sudden or acute change in stress levels. The finding in study 1a that the occurrence of seizures was associated with both increased self-reported stress and autonomic arousal indicated by reduced HRV in the 12 hours after a seizure is consistent with this idea.

Importantly, the examination of the link between stress and seizure occurrence showed that none of the physiological or self-reported stress measures predicted seizure occurrence in the subsequent 12 hours in any of the two patient groups. Instead, occurrence of seizures was predictive of increased autonomic arousal and higher self-perceived stress, indicating that the experience of seizures was associated with increased stress for up to 12 hours after the seizure in both patient groups. While the 12-hour window may have been too long to capture more immediate pre-ictal stress changes leading up to the seizures, these findings seem to suggest that, at least in the patients who participated in this study, stress was not a reliable seizure predictor. Based on this and the discrepancy found between the patients' daily physiological stress measures and their subjective self-reports, it could be hypothesised that people's retrospective appraisals of pre-ictal events may be inaccurate and possibly influenced by the post-ictal distress associated with the seizure itself. This could explain the disparity between studies in which a large percentage of patients reported stress as the main trigger for their seizures, and the mixed evidence for a direct link between stress and seizures found in prospective studies and in animal experiments. It is also possible that there may be a sub-group of patients with stress-precipitated seizures or with a greater susceptibility for

stress to trigger their seizures, which was not detected or examined as part of this study due to the small sample size.

In order to provide as comprehensive evidence as possible within the scope of this exploratory study, study 1b experimentally assessed implicit attentional responses to stress-related stimuli, which have previously been studied in patients with PNES and epilepsy (Bakvis et al., 2009a; Bakvis et al., 2009b; Bakvis et al., 2011; Lanteaume et al., 2009), as well as their relation to the physiological stress markers in patients with seizures compared to a group of healthy volunteers. Attentional bias towards threat has been proposed to reflect cognitive hyper-vigilance that can contribute towards exacerbation and maintenance of a number of affective disorders, and could therefore play a role in stress vulnerability. In addition, the experiment also examined whether implicit attentional responses in any of the three groups were moderated by self-perceived stress, optimism or resilient coping, and tested whether the attentional responses or any of the physiological measures could be altered by a simple intervention based on the self-affirmation technique.

An emotional Stroop test was developed to assess the attentional biases, using a selection of threatening words from seizure-related, somatic, social and general threat categories, which had been evaluated as part of the study and demonstrated to be perceived as threatening and relevant to patients with seizures. The findings from the Stroop experiment revealed significant positive attentional bias towards seizure-related words compared to neutral words in patients with epilepsy, and patients with epilepsy also had significantly greater attentional biases towards threatening words across all the word categories when compared to healthy volunteers. Although not statistically significant, a similar positive attentional bias pattern towards threatening words was also seen in patients with PNES but this was not significantly different from healthy volunteers or from patients with epilepsy. The responses in healthy volunteers were characterised by a negative attentional bias,

suggesting avoidance of, rather than vigilance towards the threatening stimuli. The attentional bias towards somatic threat in patients with epilepsy was further related to reduced HRV, indicating a possible alteration in the networks involved in the regulation of cognitive, emotional, and autonomic regulation. Abnormalities in this pathway characterised by emotional and cognitive hyper-vigilance and over-excitability, defensive behavioural responses, and impaired ANS flexibility have been previously linked to a range of psychopathologies (Park & Thayer, 2014). This may represent a mechanism that may contribute to the vulnerability to maladaptive stress responses in patients with epilepsy whereby attentional hypervigilance to threat could make these patients more prone to noticing and focusing on threatening information in their environment and therefore more susceptible to more frequent autonomic arousal responses, which could in turn alter their ANS functioning and flexibility. This could be further explored in future studies and targeted by interventions focused on information processing training. Interestingly, the attentional biases in patients with epilepsy were moderated by optimism, suggesting that patients with high self-reported optimism were more prone to attentional biases. The role of optimism in the responses to and coping with stress in patients with epilepsy remains to be investigated in future studies.

The self-affirmation intervention tested as part of the Stroop experiment was not found to be effective in reducing attentional biases or improving HRV in any of the three groups, however the intervention was associated with reduction in salivary cortisol when all three groups were combined. While this cannot be confidently attributed to the effects of the intervention alone, it may be interesting to further examine the effects of self-affirmation on the reduction of cortisol in a larger patient sample.

The results of previous studies of psychological and other non-pharmacological interventions for epilepsy and PNES suggest a potential for development and evaluation of

psychological interventions targeting stress as a trigger for both epileptic seizures and PNES. Consequently, in study 2, a self-help intervention in a form of a short booklet was developed, based on the integrative model of stress and incorporating theory and techniques from cognitive-behavioural, psycho-educational, self-affirmation and implementation-intention approaches to target stress as a seizure-facilitating factor. A pilot study of the intervention revealed that 19% of the 429 patients approached to take part in the study felt stress was relevant to them and their seizures and were prepared to try to improve their coping strategies and reduce stress using the intervention. As discussed in Chapter 5, this number is lower compared to the studies summarised in Chapter 2, where more than half of the patients with epilepsy identified or endorsed stress to be one of the main triggers for their seizures (Hart & Shorvon, 1995; Nakken et al., 2005). It is plausible that many people are likely to report stress as a seizure trigger when asked in a survey or a self-report questionnaire, however, the real world number of patients who are also willing to take steps to reduce the stress they experience by engaging with a study that requires completing an intervention and providing follow-up data and is therefore more demanding, is much lower. In the light of this, the fact that 19% of patients in the study reported in this thesis were motivated enough to enrol in the study indicates that stress is still important to many people with seizures. Nevertheless, the retention in the study was a major challenge and a high dropout of 50-70% was observed, particularly in the immediate intervention group. Feedback from patients who did complete the intervention was positive overall, with most patients rating the booklet as helpful, and stating they planned to continue using some of the coping techniques in the future and that they would recommend it to others with seizures. While most of the feedback was favourable, a few patients felt the booklet contained too much text and information and that it would have been useful to receive more guidance on how to complete it. These results indicate that a future RCT of the intervention would need to maximise recruitment and

retention and that there is a scope for further improvement of the intervention itself, including possible changes to the design and/or mode of delivery.

A preliminary evaluation of effectiveness undertaken as part of the pilot study yielded promising findings, suggesting that the intervention was associated with reduction of self-perceived stress and the effect size of this change was moderate. An appropriately powered trial would be necessary to determine possible effects of the intervention on other outcome measures not found to be affected by the intervention in the present pilot study, including reduction of seizure frequency, anxiety, depression, and improvement of quality of life. Based on the effect sizes and attrition rates estimated as part of the pilot, a sample size calculation for a future RCT was performed, indicating that a sample of at least 382 patients would be needed to achieve sufficient power. Given the encouraging results of the pilot study, if the challenges of recruitment and retention demonstrated in the pilot study were appropriately addressed and accounted for, a future RCT of the intervention developed as part of this PhD programme may be justified. Such future study may need to consider using a different recruitment and/or data collection method, including monitoring of adherence, for example, by converting the booklet into an on-line intervention, and perhaps using a different mode of delivery, such as guided self-help with follow-up phone calls to discuss effectiveness and adherence.

6.2 Limitations

As discussed in the relevant chapters, the studies conducted as part of this PhD programme had several limitations. To highlight the major weaknesses, despite being the largest studies of this kind to date, both studies presented in this thesis were limited by small sample sizes, which may have compromised the power of the statistical tests performed and the results therefore need to be interpreted cautiously. Despite collecting a large amount of

data across multiple days, study 1a was limited by relatively small number of data points, which did not allow for more precise assessment of the dynamic changes in the different stress measures, the effects of acute events occurring throughout the day or the exact temporal relationships between the stress measures at various time periods before and after seizures. Furthermore, due to the lack of prospective studies in this area, the study was exploratory in nature and as such was not designed to test a specific hypothesis; however, the findings and effect sizes presented in this thesis should enable researchers to formulate and test directional hypotheses and/or assess the relationships using experimental designs in the future.

Both studies also included heterogeneous samples of patients with different seizure types, greatly variable seizure frequencies, taking a range of anti-epileptic and other medication, and reporting varying degrees of concurrent anxiety and depression, all of which may have affected the measures and outcomes in different ways. While the effects of these factors were not systematically assessed as part of the this thesis, considering the heterogeneity of patients with seizures and the complexity of the experience of stress, future studies should examine these variables more closely and explore different sub-groups of patients.

6.3 Strengths

Despite their limitations, the studies reported in this thesis contribute valuable exploratory work to the study of the role of stress in ictogenesis, where most evidence to date has come from anecdotal, self-report and retrospective studies or animal research. A particular strength of the two studies is the use of an integrative approach to stress, taking into an account the complexity and the multi-faceted nature of the 'stress' experience and assessing and targeting its different components, including endocrine markers of the HPA

axis, autonomic measures of the SAM system, implicit cognitive responses, and subjective appraisals, in order to contribute to a more complete understanding of the relationships between stress and seizures.

The prospective assessment of the links between stress and seizure occurrence conducted as part of the first study of this thesis adds to two previous diary studies, which investigated the links in patients with epilepsy (Haut et al., 2012; Haut et al., 2007), and expands on them by including physiological stress markers, examining the relationship in both patients with epilepsy and patients with PNES, and by exploring the relationship in both directions. Study 1a of this thesis yielded an interesting finding about the direction of the relationship, suggesting that it is more likely for seizures to cause self-perceived stress and increase autonomic arousal than it is for increased stress to directly trigger seizures, although the limitations of the study, particularly related to the limited number of data collection points, need to be taken into consideration. This finding facilitates a generation of a number of hypotheses to test this further, for example by more frequent assessment of the different stress measures before and after seizure occurrence.

The first study presented in this thesis also provided a description of the diurnal patterns of the different stress measures and how they relate to each other, which has not been systematically assessed before. The finding of the diurnal pattern of cortisol and HRV in both patients with epilepsy and patients with PNES merits further investigation by more frequent or on-line assessment of the measures throughout the day and examining day curves, ideally in a controlled study, which would allow for direct comparisons with a matched group of healthy volunteers to identify any abnormalities in patients.

Implicit attentional responses have previously been studied in both patients with epilepsy and patients with PNES, with a focus on a particular type of threat, such as angry faces (Bakvis et al., 2009a) or generic threat words (Lanteaume et al., 2009). The emotional

Stroop test in the study reported in this thesis assessed a broader range of different categories of threat, all relevant to patients with seizures. The finding of a significant attentional bias towards all categories of threat and seizure-related stimuli in particular in patients with epilepsy, as well as the relationship of the biases to HRV contributes further evidence for mutually interdependent cognitive an autonomic vulnerability to stress in these patients. The Stroop study also yielded a novel finding about the potential moderating effects of optimism, suggesting that the role of different individual characteristics and traits in the susceptibility to stress may be worth exploring further.

Finally, as part of the second study, a novel, theory-based intervention specifically targeting stress in patients with seizures has been developed and an initial stage of its empirical evaluation has been undertaken. The pilot study showed a potential for the intervention to reduce patients' self-perceived stress and the effect size estimates and sample size calculation provided as part of the study can serve to facilitate future assessment of the intervention in a larger trial. Furthermore, if the intervention proved effective in a sufficiently powered RCT, it could have application in clinical practice and it could be offered to patients as a low-cost, stand-alone self-help tool or be incorporated into other psychotherapeutic or epilepsy nurse-led treatment programmes.

6.4 Implications for Future Research

Some ideas for further research were presented in the relevant chapters, however some additional ideas are highlighted here. The findings of the studies presented in this thesis further emphasise the complexity of stress and its multi-faceted nature and it is therefore clear that future studies should attempt to employ a more integrative and interdisciplinary methodological approach rather than rely on patients' self-reports. Future research could further explore the causal and temporal links between the psychological and physiological

stress and seizures in studies with more frequent assessment points or with an experimental design. It would be desirable for future studies to assess the measures over a longer monitoring period than the 3-5 days in study 1 of this thesis, and to account for stressful events occurring during the day. As discussed previously, prospective stress and seizure monitoring could be combined with an experimental assessment of the endocrine, autonomic, cognitive and self-perceived responses to an acute laboratory stressor, for example the commonly used Trier Social Stress Test (Kirschbaum et al., 1993). Based on the finding of the diurnal fluctuations of the physiological measures, it will be important for future studies to carefully consider the timing of the study procedures. Our research team is currently planning further refinement of the HRV parameter analysis using shifting time-windows to enable more precise and dynamic examination of the peri-ictal states, which may have the potential to clarify the relationships further. This methodology has recently been used as a seizure-detection tool in patients with epilepsy (Jeppesen et al., 2015).

The attentional responses and their role in the susceptibility to stress should also be investigated further, particularly in patients with epilepsy and in relation to their interactions with the autonomic nervous system. As discussed, the emotional words used in this thesis may not be the most salient threat stimuli and different implicit cognition paradigms could therefore be employed, for example, using emotional faces previously used in the study by Bakvis and colleagues (Bakvis et al., 2009a), or other emotional images (Roberts et al., 2012), or video clips previously used in other patient groups (Park & Thayer, 2014), or using tests such as the task-switching paradigm (Gul & Ahmad, 2014). It may also be interesting to assess the possible cognitive, affective and autonomic responsiveness and regulation in these patients within the framework of the neurovisceral integration model (Thayer & Lane, 2000). For example, the underlying physiological processes could be further explored by additional examination of the structural and functional brain networks using electroencephalography or

neuroimaging methods. Several recent studies have demonstrated abnormalities in the functional connectivity in brain areas involved in emotional, attentional and sensorimotor regulation in patients with PNES, using scalp EEG (Barzegaran et al., 2012) and functional magnetic resonance imaging (fMRI) (Ding et al., 2013; van der Kruijs et al., 2014) and it may be interesting to explore these in relation to stress responsiveness in both patients with PNES and patients with epilepsy.

Future researchers may also want to consider combining quantitative and qualitative research methodology. Although the direct links between stress and seizures may presently seem unclear and while there seem to be discrepancies between patients' subjective perceptions and their underlying physiological responses, 'stress' does seem to be subjectively important for many patients with seizures. Considering the complexity of the stress and seizure experience and their interactions, it may therefore be desirable to attempt to gain a more in-depth understanding of what patients with epilepsy and those with PNES mean by 'stress' and how they think about their seizure triggers. Previous studies demonstrated differences in the metaphors patients with epilepsy and patients with PNES use to describe their seizures (Plug et al., 2009) and interesting work has been done in these patients using conversational analysis, interpretative phenomenological analysis or thematic content analysis (Dickinson et al., 2011; Monzoni & Reuber, 2009; Thompson et al., 2009). Future studies could therefore include qualitative analyses of patients' narratives.

On a related note, future studies should also attempt to account for a broader range of possible moderating factors, examining stress susceptibility within the bio-psycho-social context of epilepsy and PNES. As discussed previously, future studies could explore the relationships between stress and seizures in patients with different seizure types, seizure frequency or seizure severity, further examine the role of anti-epileptic and other medication, and examine the role of stress in patients with different psychological profiles, accounting for

different levels of concurrent anxiety, depression, other psychiatric comorbidity, history of sexual or other trauma, or avoidant coping, as well as protective or resilience factors previously suggested to play a role in these disorders and in the resilience to stress, such as self-esteem (Dimaro et al., 2015), or attachment style (Brown et al., 2013; Smeets, 2010). Specific clusters of patients with PNES as well as patients with different epilepsy sub-types have previously been suggested (Brown et al., 2013; Magaudda et al., 2011; Uliaszek et al., 2012) and it may be interesting to explore these sub-groups further. It would also be interesting, for example, to investigate the underlying genetic factors that may predispose individuals to be more vulnerable to the pathological effects of stress. Focus of further research and intervention may then be narrowed down to a specific group of patients identified as particularly vulnerable.

Based on the sample size calculations provided as part of the pilot study of the self-help intervention, a larger RCT could be run to further confirm its clinical utility. There is also scope for further development of different types of interventions targeting the different components of 'stress' in patients with seizures. For example, a recent proof-of-concept study of skin conductance biofeedback for patients with self-reported stress-precipitated temporal lobe seizures demonstrated reduction in seizure frequency through training patients to alter their sympathetic nervous system tone in order to reduce cortical excitability (Micoulaud-Franchi et al., 2014). A large multi-centre randomised controlled trial of a stress management intervention for epilepsy (Stress Management Intervention for Living with Epilepsy; the SMILE study), run by researchers at the University of Cincinnati who previously studied stress in patients with epilepsy using self-report surveys and stress and seizure diaries (Haut et al., 2012; Privitera et al., 2014), is also currently under way. Their study involves an observational phase, during which stress and seizures are monitored using smart phones, and an intervention phase, based on focused-attention and relaxation exercises (Privitera, 2015).

It will be interesting in the future to compare and integrate the results of the SMILE trial with the findings reported as part of this thesis. More broadly, there is a growing emphasis on the importance of complementary psychosocial interventions and promotion of self-management in patients with seizures (Edward et al., 2015), and further investigation of the role of stress in seizure disorders and interventions targeting stress in patients with seizures therefore continues to be an important area for future research.

6.5 Conclusions

Overall, this thesis investigated the relationships between physiological and psychological stress markers and the occurrence of epileptic and psychogenic non-epileptic seizures, and developed a targeted intervention aimed at reducing stress, seizures and improving patients' quality of life. The findings of the studies presented throughout the thesis highlight the complexity of the different components of stress, and suggest that these do not always correlate with each other. While none of the examined stress measures were found to predict seizure occurrence, the occurrence of seizures was predictive of increased psychological stress and autonomic arousal in both patients with epilepsy and those with PNES. Patients with epilepsy were further found to be cognitively and physiologically vulnerable to heightened responses to stress-related stimuli, which could make them more vulnerable to the pathological effects of stress. The pilot study of the self-help intervention developed as part of this thesis showed that many patients consider stress to be related to their seizures, and are willing to learn strategies to reduce their stress. Preliminary evaluation of the intervention suggested that self-perceived stress could indeed be reduced in motivated individuals using a simple self-help tool tailored for people with seizures, which could be easily implemented within the NHS at a relatively low cost.

7. CHAPTER 7

Bibliography

Abetz L, Jacoby A, Baker GA, McNulty P. (2000) Patient-based assessments of quality of life in newly diagnosed epilepsy patients: Validation of the NEWQOL. *Epilepsia* 41:1119-1128.

Adjei P. (2011) Autonomic function in epilepsy *Institute of Neurology, Faculty of Brain Sciences*, University College London, UCL Discovery Open Access Publication, p. 161.

Aldwin CM. (2000) *Stress, Coping and Development*. The Guilford Press, New York.

Allen JJB, Chambers AS, Towers DN. (2007) The many metrics of cardiac chronotropy: A pragmatic primer and a brief comparison of metrics. *Biological Psychology* 74:243-262.

Angus-Leppan H. (2008) Diagnosing epilepsy in neurology clinics: A prospective study. *Seizure-European Journal of Epilepsy* 17:431-436.

APA. (2013) *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*. American Psychiatric Publishing, Arlington, VA.

Arain M, Campbell MJ, Cooper CL, Lancaster GA. (2010) What is a pilot or feasibility study? A review of current practice and editorial policy. *Bmc Medical Research Methodology* 10:7.

Armitage CJ. (2012) Evidence that self-affirmation reduces body dissatisfaction by basing self-esteem on domains other than body weight and shape. *Journal of Child Psychology and Psychiatry* 53:81-88.

Armitage CJ, Harris PR, Arden MA. (2011) Evidence That Self-Affirmation Reduces Alcohol Consumption: Randomized Exploratory Trial With a New, Brief Means of Self-Affirming. *Health Psychology* 30:633-641.

Armitage CJ, Harris PR, Hepton G, Napper L. (2008) Self-affirmation increases acceptance of health-risk information among UK adult smokers with low socioeconomic status. *Psychology of Addictive Behaviors* 22:88-95.

Asadi-Pooya AA, Emami M. (2013) Demographic and clinical manifestations of psychogenic non-epileptic seizures: The impact of co-existing epilepsy in patients or their family members. *Epilepsy & Behavior* 27:1-3.

Aspinwall LG, Brunhart SM. (1996) Distinguishing optimism from denial: Optimistic beliefs predict attention to health threats. *Personality and Social Psychology Bulletin* 22:993-1003.

Baayen RH, Piepenbrock R, Gulikers L. (1995) The CELEX Lexical Database (CD-ROM) *Linguistic Data Consortium, University of Pennsylvania*, PA.

Baker GA, Brooks J, Buck D, Jacoby A. (2000) The stigma of epilepsy: A European perspective. *Epilepsia* 41:98-104.

Baker GA, Smith DF, Jacoby A, Hayes JA, Chadwick DW. (1998) Liverpool Seizure Severity Scale revisited. *Seizure-European Journal of Epilepsy* 7:201-205.

Bakvis P, Roelofs K, Kuyk J, Edelbroek PM, Swinkels WAM, Spinhoven P. (2009a) Trauma, stress, and preconscious threat processing in patients with psychogenic nonepileptic seizures. *Epilepsia* 50:1001-1011.

Bakvis P, Spinhoven P, Giltay EJ, Kuyk J, Edelbroek PM, Zitman FG, Roelofs K. (2010) Basal hypercortisolism and trauma in patients with psychogenic nonepileptic seizures. *Epilepsia* 51:752-759.

Bakvis P, Spinhoven P, Roelofs K. (2009b) Basal cortisol is positively correlated to threat vigilance in patients with psychogenic nonepileptic seizures. *Epilepsy & Behavior* 16:558-560.
Bakvis P, Spinhoven P, Zitman FG, Roelofs K. (2011) Automatic avoidance tendencies in patients with Psychogenic Non Epileptic Seizures. *Seizure* 20:628-634.
Barry JJ, Wittenberg D, Bullock KD, Michaels JB, Classen CC, Fisher RS. (2008) Group therapy for patients with psychogenic nonepileptic seizures: A pilot study. *Epilepsy & Behavior* 13:624-629.
Barzegaran E, Joudaki A, Jalili M, Rossetti AO, Frackowiak RS, Knyazeva MG. (2012) Properties of functional brain networks correlate with frequency of psychogenic non-epileptic seizures. *Frontiers in Human Neuroscience* 6:13.
Beattie G, Cohen D, McGuire L. (2013) An exploration of possible unconscious ethnic biases in higher education: The role of implicit attitudes on selection for university posts. *Semiotica* 197:171-201.
Beck SG, Choi KC, List TJ, Okuhara DY, Birnstiel S. (1996) Corticosterone alters 5-HT1A receptor-mediated hyperpolarization in area CA1 hippocampal pyramidal neurons. *Neuropsychopharmacology* 14:27-33.
Becker ES, Rinck M, Margraf J, Roth WT. (2001) The emotional Stroop effect in anxiety disorders - General emotionality or disorder specificity? *Journal of Anxiety Disorders* 15:147-159.
Berg AT, Berkovic SF, Brodie M, Buchhalter J, Cross JH, Boas WV, Engel J, French J, Glauser TA, Mathern GW, Moshe SL, Nordli D, Plouin P, Scheffer IE. (2010) Revised Terminology and Concepts for Organization of Seizures and Epilepsies: Report of the ILAE Commission on Classification and Terminology, 2005-2009. *Aktuelle Neurologie* 37:120-130.
Bergsma A. (2008) Do self-help books help? *Journal of Happiness Studies* 9:341-360.
Bewley J, Murphy PN, Mallows J, Baker GA. (2005) Does alexithymia differentiate between patients with nonepileptic seizures, patients with epilepsy, and nonpatient controls? *Epilepsy Behav* 7:430-437.
Binzer M, Stone J, Sharpe M. (2004) Recent onset pseudoseizures - clues to aetiology. *Seizure* 13:146-155.
Bodde NMG, Brooks JL, Baker GA, Boon P, Hendriksen JGM, Mulder OG, Aldenkamp AP. (2009) Psychogenic non-epileptic seizures-Definition, etiology, treatment and prognostic issues: A critical review. *Seizure-European Journal of Epilepsy* 18:543-553.
Bonaz B, Picq C, Sinniger V, Mayol JF, Clarencon D. (2013) Vagus nerve stimulation: from epilepsy to the cholinergic anti-inflammatory pathway, *J Neurogastroenterol Motil*; doi:doi: 10.1111/nmo.1207.
Bonnemeier H, Wiegand UKH, Brandes A, Kluge N, Katus HA, Richardt G, Potratz J. (2003) Circadian profile of cardiac autonomic nervous modulation in healthy subjects: Differing effects of aging and gender on heart rate variability. *Journal of Cardiovascular Electrophysiology* 14:791-799.
Bowman ES. (2006) Why conversion seizures should be classified as a dissociative disorder. *Psychiatric Clinics of North America* 29:185-+.
Bowman ES, Markand ON. (1999) The contribution of life events to pseudoseizure occurrence in adults. *Bulletin of the Menninger Clinic* 63:70-88.
Brooks R. (1996) EuroQol: The current state of play. *Health Policy* 37:53-72.
Brotherstone R, McLellan A. (2012) Parasympathetic alteration during sub-clinical seizures. *Seizure-European Journal of Epilepsy* 21:391-398.

Brown I, Sheeran P, Reuber M. (2009) Enhancing antiepileptic drug adherence: A randomized controlled trial. *Epilepsy & Behavior* 16:634-639.
Brown RJ, Bouska JF, Frow A, Kirkby A, Baker GA, Kemp S, Burness C, Reuber M. (2013) Emotional dysregulation, alexithymia, and attachment in psychogenic nonepileptic seizures. *Epilepsy Behav* 29:178-183.
Buckley TC, Blanchard EB, Hickling EJ. (2002) Automatic and strategic processing of threat stimuli: A comparison between PTSD, panic disorder, and nonanxiety controls. *Cognitive Therapy and Research* 26:97-115.
Carroll D, Smith GD, Shipley MJ, Steptoe A, Brunner EJ, Marmot MG. (2001) Blood pressure reactions to acute psychological stress and future blood pressure status: A 10-year follow-up of men in the Whitehall II study. *Psychosom Med* 63:737-743.
Carver CS, Connor-Smith J. (2010) Personality and Coping *Annual Review of Psychology*, Annual Reviews, Palo Alto, pp. 679-704.
Carver CS, Pozo C, Harris SD, Noriega V, Scheier MF, Robinson DS, Ketcham AS, Moffat FL, Clark KC. (1993) HOW COPING MEDIATES THE EFFECT OF OPTIMISM ON DISTRESS - A STUDY OF WOMEN WITH EARLY-STAGE BREAST-CANCER. *Journal of Personality and Social Psychology* 65:375-390.
Carver CS, Scheier MF, Segerstrom SC. (2010) Optimism. *Clinical Psychology Review* 30:879-889.
Castro OW, Santos VR, Pun RYK, McKlveen JM, Batie M, Holland KD, Gardner M, Garcia-Cairasco N, Herman JP, Danzer SC. (2012) Impact of Corticosterone Treatment on Spontaneous Seizure Frequency and Epileptiform Activity in Mice with Chronic Epilepsy. *Plos One* 7:9.
Chameau P, Qin YJ, Spijker S, Smit G, Joels M. (2007) Glucocorticoids specifically enhance L-type calcium current amplitude and affect calcium channel subunit expression in the mouse hippocampus. *J Neurophysiol* 97:5-14.
Christensen H, Griffiths KM, Farrer L. (2009) Adherence in Internet Interventions for Anxiety and Depression: Systematic Review. *Journal of Medical Internet Research* 11:16.
Cohen H, Matar MA, Kaplan Z, Kotler M. (1999) Power spectral analysis of heart rate variability in psychiatry. *Psychother Psychosom* 68:59-66.
Cohen S, Kamarck T, Mermelstein R. (1983) A global measure of perceived stress. *J Health Soc Behav* 24:385-396.
Cohen S, Kessler RC, Underwood-Gordon L. (1995) Strategies for Measuring Stress in Studies of Psychiatric and Physical Disorders. In Cohen S, Kessler RC, Underwood-Gordon L (Eds) *Measuring Stress: A guide for health and social scientists*, Oxford University Press, New York.
Conner TS, Barrett LF. (2012) Trends in Ambulatory Self-Report: The Role of Momentary Experience in Psychosomatic Medicine. *Psychosomatic Medicine* 74:327-337.
Cox WM, Hogan LM, Kristian MR, Race JH. (2002) Alcohol attentional bias as a predictor of alcohol abusers' treatment outcome. *Drug and Alcohol Dependence* 68:237-243.
Craig P, Dieppe P, Macintyre S, Michie S, Nazareth I, Petticrew M. (2008) Developing and evaluating complex interventions: the new Medical Research Council guidance. *British Medical Journal* 337:5.
Creswell JD, Dutcher JM, Klein WMP, Harris PR, Levine JM. (2013) Self-Affirmation Improves Problem-Solving under Stress. *PloS one* 8:e62593.
Creswell JD, Welch WT, Taylor SE, Sherman DK, Gruenewald TL, Mann T. (2005) Affirmation of personal values buffers neuroendocrine and psychological stress responses. *Psychol Sci* 16:846-851.

Croiset G, Dewied D. (1992) ACTH - A structire-activity study on pilocarpine-induced epilepsy. *Eur J Pharmacol* 229:211-216.
Crutzen R, Viechtbauer W, Spigt M, Kotz D. (2015) Differential attrition in health behaviour change trials: A systematic review and meta-analysis. *Psychology & Health* 30:122-134.
Cuijpers P, Schuurmans J. (2007) Self-help interventions for anxiety disorders: an overview. *Current psychiatry reports* 9:284-290.
Cull CA, Fowler M, Brown SW. (1996) Perceived self-control of seizures in young people with epilepsy. *Seizure* 5:131-138.
Davis CJ. (2005) N-Watch: A program for deriving neighborhood size and other psycholinguistic statistics. *Behavior Research Methods* 37:65-70.
de Ridder D, Schreurs K, Bensing J. (2000) The relative benefits of being optimistic: Optimism as a coping resource in multiple sclerosis and Parkinson's disease. *British Journal of Health Psychology* 5:141-155.
Dear BF, Titov N, Sunderland M, McMillan D, Anderson T, Lorian C, Robinson E. (2011) Psychometric Comparison of the Generalized Anxiety Disorder Scale-7 and the Penn State Worry Questionnaire for Measuring Response during Treatment of Generalised Anxiety Disorder. *Cognitive Behaviour Therapy* 40:216-227.
Debono M, Ghobadi C, Rostami-Hodjegan A, Huatan H, Campbell MJ, Newell-Price J, Darzy K, Merke DP, Arlt W, Ross RJ. (2009) Modified-Release Hydrocortisone to Provide Circadian Cortisol Profiles. *Journal of Clinical Endocrinology & Metabolism* 94:1548-1554.
Delgadillo J, Payne S, Gilbody S, Godfrey C, Gore S, Jessop D, Dale V. (2012) Brief case finding tools for anxiety disorders: Validation of GAD-7 and GAD-2 in addictions treatment. *Drug and Alcohol Dependence* 125:37-42.
Dickinson P, Looper KJ, Groleau D. (2011) Patients diagnosed with nonepileptic seizures: Their perspectives and experiences. *Epilepsy & Behavior* 20:454-461.
Dilorio C, Bamps Y, Walker ER, Escoffery C. (2011) Results of a research study evaluating WebEase, an online epilepsy self-management program. *Epilepsy Behav* 22:469-474.
Dimaro LV, Dawson DL, Roberts NA, Brown I, Moghaddam NG, Reuber M. (2014) Anxiety and avoidance in psychogenic nonepileptic seizures: The role of implicit and explicit anxiety. *Epilepsy Behav* 33:77-86.
Dimaro LV, Roberts NA, Moghaddam NG, Dawson DL, Brown I, Reuber M. (2015) Implicit and explicit self-esteem discrepancies in people with psychogenic nonepileptic seizures. *Epilepsy & Behavior* 46:109-117.
Ding JR, An DM, Liao W, Li JM, Wu GR, Xu Q, Long ZL, Gong QY, Zhou D, Sporns O, Chen HF. (2013) Altered Functional and Structural Connectivity Networks in Psychogenic Non-Epileptic Seizures. *Plos One* 8:10.
Duncan JS, Sander JW, Sisodiya SM, Walker MC. (2006) Adult epilepsy. *Lancet* 367:1087-1100.
Duncan R, Oto M. (2008) Predictors of antecedent factors in psychogenic nonepileptic attacks - Multivariate analysis. *Neurology* 71:1000-1005.
Dziura JD, Post LA, Zhao Q, Fu Z, Peduzzi P. (2013) Strategies for Dealing with Missing Data in Clinical Trials: From Design to Analysis. *Yale Journal of Biology and Medicine* 86:343-358.
Edward KL, Cook M, Giandinoto JA. (2015) An integrative review of the benefits of self-management interventions for adults with epilepsy. *Epilepsy & Behavior* 45:195-204.
Egloff B, Wilhelm FH, Neubauer DH, Mauss IB, Gross JJ. (2002) Implicit Anxiety Measure Predicts Cardiovascular Reactivity to an Evaluated Speaking Task. *Emotion* 2:3-11.

Elliott JO, Richardson VE. (2014) The biopsychosocial model and quality of life in persons with active epilepsy. *Epilepsy & Behavior* 41:55-65.
Elsas SM, Gregory WL, White G, Navarro G, Salinsky MC, Andrews DJ. (2011) Aura interruption: The Andrews/Reiter behavioral intervention may reduce seizures and improve quality of life - A pilot trial. *Epilepsy & Behavior* 22:765-772.
Epton T, Harris PR. (2008) Self-Affirmation Promotes Health Behavior Change. *Health Psychology* 27:746-752.
Erdfelder E, Faul F, Buchner A. (1996) GPOWER: A general power analysis program. *Behavior Research Methods Instruments & Computers* 28:1-11.
Estevez RF. (2002) *Psychosocial Factors and Self-Affirmation in End-Stage Renal Disease Psychology*, Tufts University, Ann Arbor.
Ferlisi M, Shorvon S. (2014) Seizure precipitants (triggering factors) in patients with epilepsy. *Epilepsy & Behavior* 33:101-105.
Fertig E, Fureman BE, Bergey GK, Brodie MA, Hesdorffer DC, Hirtz D, Kossoff EH, LaFrance WC, Versavel M, French J. (2014) Inclusion and exclusion criteria for epilepsy clinical trials-Recommendations from the April 30, 2011 NINDS workshop. *Epilepsy Research* 108:825-832.
Field A. (2009) *Discovering Statistics Using SPSS*. SAGE Publications Ltd, London.
Fisher RS, Acevedo C, Arzimanoglou A, Bogacz A, Cross JH, Elger CE, Engel J, Forsgren L, French JA, Glynn M, Hesdorffer DC, Lee BI, Mathern GW, Moshe SL, Perucca E, Scheffer IE, Tomson T, Watanabe M, Wiebe S. (2014) ILAE Official Report: A practical clinical definition of epilepsy. *Epilepsia* 55:475-482.
Fisher RS, Vickrey BG, Gibson P, Hermann B, Penovich P, Scherer A, Walker S. (2000) The impact of epilepsy from the patient's perspective I. Descriptions and subjective perceptions. *Epilepsy Res* 41:39-51.
Fledderus M, Bohlmeijer ET, Fox JP, Schreurs KMG, Spinhoven P. (2013) The role of psychological flexibility in a self-help acceptance and commitment therapy intervention for psychological distress in a randomized controlled trial. *Behaviour Research and Therapy* 51:142-151.
Forcelli PA, Orefice LL, Heinrichs SC. (2007) Neural, endocrine and electroencephalographic hyperreactivity to human contact: A diathesis-stress model of seizure susceptibility in El mice. *Brain Res* 1144:248-256.
Frances PL, Baker GA, Appleton PL. (1999) Stress and avoidance in Pseudoseizures: testing the assumptions. *Epilepsy Research* 34:241-249.
Friedman AR, Cacheaux LP, Ivens S, Kaufer D. (2011) Elucidating the Complex Interactions between Stress and Epileptogenic Pathways. *Cardiovasc Psychiatry Neurol* 2011:461263.
Frucht MM, Quigg M, Schwaner C, Fountain NB. (2000) Distribution of seizure precipitants among epilepsy syndromes. *Epilepsia* 41:1534-1539.
Galimberti CA, Ratti MT, Murelli R, Marchioni E, Manni R, Tartara A. (2003) Patients with psychogenic nonepileptic seizures, alone or epilepsy-associated, share a psychological profile distinct from that of epilepsy patients. *Journal of Neurology* 250:338-346.
Gandy M, Sharpe L, Perry KN. (2013) Cognitive behavior therapy for depression in people with epilepsy: A systematic review. *Epilepsia* 54:1725-1734.
Gellatly J, Bower P, Hennessy S, Richards D, Gilbody S, Lovell K. (2007) What makes self-help interventions effective in the management of depressive symptoms? Meta-analysis and meta-regression. *Psychological Medicine* 37:1217-1228.
Gilliam FG, Barry JJ, Hermann BP, Meador KJ, Vahle V, Kanner AM. (2006) Rapid detection of major depression in epilepsy: a multicentre study. *Lancet Neurol* 5:399-405.

Goeman JJ, Solari A. (2011) Multiple Testing for Exploratory Research. *Statistical Science* 26:584-597.
Goldstein LH, Chalder T, Chigwedere C, Khondoker MR, Moriarty J, Toone BK, Mellers JDC. (2010) Cognitive-behavioral therapy for psychogenic nonepileptic seizures A pilot RCT. *Neurology* 74:1986-1994.
Goldstein LH, Deale AC, Mitchell-O'Malley SJ, Toone BK, Mellers JDC. (2004) An evaluation of cognitive behavioral therapy as a treatment for dissociative seizures: a pilot study. *Cognitive and behavioral neurology : official journal of the Society for Behavioral and Cognitive Neurology* 17:41-49.
Goldstein LH, McAlpine M, Deale A, Toone BK, Mellers JDC. (2003) Cognitive behaviour therapy with adults' with intractable epilepsy and psychiatric co-morbidity: preliminary observations on changes in psychological state and seizure frequency. *Behaviour Research and Therapy* 41:447-460.
Goldstein LH, Mellers JDC. (2006) Ictal symptoms of anxiety, avoidance behaviour, and dissociation in patients with dissociative seizures. *J Neurol Neurosur Ps* 77:616-621.
Gollwitzer PM. (1999) Implementation intentions - Strong effects of simple plans. *American Psychologist* 54:493-503.
Gollwitzer PM, Sheeran P. (2006) Implementation intentions and goal achievement: A meta-analysis of effects and processes. In Zanna MP (Ed) *Advances in Experimental Social Psychology, Vol 38*, Elsevier Academic Press Inc, San Diego, pp. 69-119.
Greenwald AG, Nosek BA, Banaji MR. (2003) Understanding and using the implicit association test: I. An improved scoring algorithm. *Journal of Personality and Social Psychology* 85:197-216.
Greiner W, Weijnen T, Nieuwenhuizen M, Oppe S, Badia X, Busschbach J, Buxton M, Dolan P, Kind P, Krabbe P, Ohinmaa A, Parkin D, Roset M, Sintonen H, Tsuchiya A, de Charro F. (2003) A single European currency for EQ-5D health states. Results from a six-country study. *The European journal of health economics : HEPAC : health economics in prevention and care* 4:222-231.
Griffin DW, Harris PR. (2011) Calibrating the Response to Health Warnings: Limiting Both Overreaction and Underreaction With Self-Affirmation. *Psychological Science* 22:572-578.
Griffith NM, Smith KM, Schefft BK, Szaflarski JP, Privitera MD. (2008) Optimism, pessimism, and neuropsychological performance across semiology-based subtypes of psychogenic nonepileptic seizures. *Epilepsy & Behavior* 13:478-484.
Gul A, Ahmad H. (2014) Cognitive deficits and emotion regulation strategies in patients with psychogenic nonepileptic seizures: A task-switching study. *Epilepsy & Behavior* 32:108-113.
Gul RB, Ali PA. (2010) Clinical trials: the challenge of recruitment and retention of participants. *Journal of Clinical Nursing* 19:227-233.
Harris PR, Epton T. (2009) The Impact of Self-Affirmation on Health Cognition,Health Behaviour and Other Health-Related Responses:A Narrative Review. *Social and Personality Psychology Compass* 3:962-978.
Harris PR, Napper L. (2005) Self-affirmation and the biased processing of threatening health-risk information. *Personality and Social Psychology Bulletin* 31:1250-1263.
Harris PR, Napper L, Griffin DW, Schuez B, Stride C. (In preparation) *Developing a measure of spontaneous self-affirmation*, Manuscript in preparation.
Hart YM, Shorvon SD. (1995) The nature of epilepsy in the general population. 1. Characteristics of patients receiving medication for epilepsy. *Epilepsy Research* 21:43-49.

Hasson D, Anderberg UM, Theorell T, Arnetz BB. (2005) Psychophysiological effects of a web-based stress management system: A prospective, randomized controlled intervention study of IT and media workers ISRCTN54254861. *Bmc Public Health* 5:14.
Haut SR, Bigal ME, Lipton RB. (2006) Chronic disorders with episodic manifestations: focus on epilepsy and migraine. *Lancet Neurology* 5:148-157.
Haut SR, Hall CB, Borkowski T, Tennen H, Lipton RB. (2012) Clinical features of the pre-ictal state: Mood changes and premonitory symptoms. *Epilepsy Behav* 23:415-421.
Haut SR, Hall CB, Masur J, Lipton RB. (2007) Seizure occurrence - Precipitants and prediction. *Neurology* 69:1905-1910.
Haut SR, Vouyiouklis M, Shinnar S. (2003) Stress and epilepsy: a patient perception survey. *Epilepsy Behav* 4:511-514.
Hayden M, Penna C, Buchanan N. (1992) Epilepsy: patient perceptions of their condition. *Seizure* 1:191-197.
Hayes AF. (2013) *Introduction to Mediation, Moderation, and Conditional Process Analysis: A Regression-Based Approach*. The Guilford Press, London.
Henry TR. (2002) Therapeutic mechanisms of vagus nerve stimulation. *Neurology* 59:S3-S14.
Herbert J. (2013) Cortisol and depression: three questions for psychiatry. *Psychological Medicine* 43:449-469.
Hermann B, Jacoby A. (2009) The psychosocial impact of epilepsy in adults. *Epilepsy Behav* 15:S11-S16.
Hirsch JK, Britton PC, Conner KR. (2010) Psychometric Evaluation of the Life Orientation Test-Revised in Treated Opiate Dependent Individuals. *International Journal of Mental Health and Addiction* 8:423-431.
Hitiris N, Mohanraj R, Norrie J, Sills GJ, Brodie MJ. (2007) Predictors of pharmacoresistant epilepsy. *Epilepsy Research* 75:192-196.
Hofstra WA, de Weerd W. (2009) The circadian rhythm and its interaction with human epilepsy: A review of literature. *Sleep Medicine Reviews* 13:413-420.
Hollrigel GS, Chen K, Baram TZ, Soltesz I. (1998) The pro-convulsant actions of corticotropin-releasing hormone in the hippocampus of infant rats. *Neuroscience* 84:71-79.
Isaacowitz DM. (2005) The gaze of the optimist. *Personality and Social Psychology Bulletin* 31:407-415.
Jeppesen J, Beniczky S, Fuglsang-Frederiksen A, Sidenius P, Jasemian Y. (2010) Detection of epileptic-seizures by means of power spectrum analysis of heart rate variability: a pilot study. *Technol Health Care* 18:417-426.
Jeppesen J, Beniczky S, Johansen P, Sidenius P, Fuglsang-Frederiksen A. (2015) Detection of epileptic seizures with a modified heart rate variability algorithm based on Lorenz plot. *Seizure-European Journal of Epilepsy* 24:1-7.
Joels M. (2009) Stress, the hippocampus, and epilepsy. *Epilepsia* 50:586-597.
Johnson-Laird NP, Oatley K. (1989) Language of Emotions: An analysis of a semantic field. *Cognition & Emotion* 3:81 - 123.
Jones R, Norman P, Reuber M. (Manuscript in preparation) Attachment, relationship quality, and psychological distress in patients with psychogenic non-epileptic seizures compared to those with epilepsy.
Kaczkurkin AN, Foa EB. (2015) Cognitive-behavioral therapy for anxiety disorders: an update on the empirical evidence. *Dialogues Clin Neurosci.* 17:337 - 346.

Kamei T, Torui Y, Kimura H, Ohno S, Kumano H, Kimura K. (2000) Decrease in serum cortisol during yoga exercise is correlated with alpha wave activation. *Percept Mot Skills* 90:1027-1032.
Kanner AM. (2009) Psychiatric issues in epilepsy: The complex relation of mood, anxiety disorders, and epilepsy. *Epilepsy Behav* 15:83-87.
Kaplan MJ, Dwivedi AK, Privitera MD, Isaacs K, Hughes C, Bowman M. (2013) Comparisons of childhood trauma, alexithymia, and defensive styles in patients with psychogenic non-epileptic seizures vs. epilepsy: Implications for the etiology of conversion disorder. *Journal of Psychosomatic Research* 75:142-146.
Karam F, Berard A, Sheehy O, Huneau MC, Briggs G, Chambers C, Einarson A, Johnson D, Kao K, Koren G, Martin B, Polifka JE, Riordan SH, Roth M, Lavigne SV, Wolfe L, Comm OR. (2012) Reliability and validity of the 4-item perceived stress scale among pregnant women: Results from the OTIS antidepressants study. *Research in Nursing & Health* 35:363-375.
Kessler RC, Lane MC, Shahly V, Stang PE. (2012) Accounting for comorbidity in assessing the burden of epilepsy among US adults: results from the National Comorbidity Survey Replication (NCS-R). *Molecular Psychiatry* 17:748-758.
Khanna A, Paul M, Sandhu JS. (2007) A study to compare the effectiveness of GSR biofeedback training and progressive muscle relaxation training in reducing blood pressure and respiratory rate among highly stressed individuals. *Indian journal of physiology and pharmacology* 51:296-300.
Khattab K, Khattab AA, Ortak J, Richardt G, Bonnemeier H. (2007) Iyengar yoga increases cardiac parasympathetic nervous modulation among healthy yoga practitioners. *J Evid Based Complementary Altern Med* 4:511-517.
Kirschbaum C, Hellhammer DH. (1994) SALIVARY CORTISOL IN PSYCHONEUROENDOCRINE RESEARCH - RECENT DEVELOPMENTS AND APPLICATIONS. *Psychoneuroendocrinology* 19:313-333.
Kirschbaum C, Pirke KM, Hellhammer DH. (1993) THE TRIER SOCIAL STRESS TEST - A TOOL FOR INVESTIGATING PSYCHOBIOLOGICAL STRESS RESPONSES IN A LABORATORY SETTING. *Neuropsychobiology* 28:76-81.
Koe AS, Jones NC, Salzberg MR. (2009) Early life stress as an influence on limbic epilepsy: an hypothesis whose time has come? *Front Behav Neurosci* 3:16.
Kuyk J, Siffels MC, Bakvis P, Swinkels WAM. (2008) Psychological treatment of patients with psychogenic non-epileptic seizures: An outcome study. *Seizure-European Journal of Epilepsy* 17:595-603.
LaFrance WC, Kanner AM, Hermann B. (2008) Psychiatric comorbidities in epilepsy. *Epilepsy in Women: the Scientific Basis for Clinical Management* 83:347-383.
LaFrance WC, Miller IW, Ryan CE, Blum AS, Solomon DA, Kelley JE, Keitner GI. (2009) Cognitive behavioral therapy for psychogenic nonepileptic seizures. *Epilepsy & Behavior* 14:591-596.
LaFrance WC, Reuber M, Goldstein LH. (2013) Management of psychogenic nonepileptic seizures. *Epilepsia* 54:53-67.
Lai CW, Trimble MR. (1997) Stress and epilepsy. *J Epilepsy* 10:177-186.
Lakens D. (2013) Calculating and reporting effect sizes to facilitate cumulative science: a practical primer for t-tests and ANOVAs. *Frontiers in Psychology* 4:12.
Lancaster G, A. (2015) Pilot and feasibility studies come of age! *Pilot and Feasibility Studies* 1:1 - 4.
Lange A, Rietdijk D, Hudcovicova M, van de Ven JP, Schrieken B, Emmelkamp PMG. (2003) Interapy: A controlled randomized trial of the standardized treatment of

posttraumatic stress through the Internet. *Journal of Consulting and Clinical Psychology* 71:901-909.
Lanteaume L, Bartolomei F, Bastien-Toniazzo M. (2009) How do cognition, emotion, and epileptogenesis meet? A study of emotional cognitive bias in temporal lobe epilepsy. *Epilepsy Behav* 15:218-224.
Laybourne AH, Morgan M, Watkins SH, Lawton R, Ridsdale L, Goldstein LH. (2015) Self-management for people with poorly controlled epilepsy: Participants' views of the UK Self-Management in epILEpsy (SMILE) program. *Epilepsy Behav* 52:159 - 164.
Lazarus RS. (1993) From psychological stress to the emotions: A history of changing outlooks. *Annu Rev Clin Psychol* 44:1-21.
Lazarus RS, Folkman S. (1984) Coping and Adaptation. *Gentry, W. D. (Ed.). Handbook of Behavioral Medicine. Xvi+575p. the Guilford Press: New York, N.Y., USA; London, England. Illus*:282-325.
Lewis C, Pearce J, Bisson JI. (2012) Efficacy, cost-effectiveness and acceptability of self-help interventions for anxiety disorders: systematic review. *British Journal of Psychiatry* 200:15-21.
Litt B, Krieger A. (2007) Of seizure prediction, statistics, and dogs: A cautionary tail. *Neurology* 68:250-251.
Loescher W. (2002) Animal models of epilepsy for the development of antiepileptogenic and disease-modifying drugs. A comparison of the pharmacology of kindling and post-status epilepticus models of temporal lobe epilepsy. *Epilepsy Res* 50:105-123.
Looser RR, Metzenthin P, Helfricht S, Kudielka BM, Loerbroks A, Thayer JF, Fischer JE. (2010) Cortisol Is Significantly Correlated With Cardiovascular Responses During High Levels of Stress in Critical Care Personnel. *Psychosomatic Medicine* 72:281-289.
Lotufo PA, Valiengo L, Bensenor IM, Brunoni AR. (2012) A systematic review and meta-analysis of heart rate variability in epilepsy and antiepileptic drugs. *Epilepsia* 53:272-282.
Lowe B, Decker O, Muller S, Brahler E, Schellberg D, Herzog W, Herzberg PY. (2008) Validation and standardization of the generalized anxiety disorder screener (GAD-7) in the general population. *Medical Care* 46:266-274.
Lu B, Elliott JO. (2012) Beyond seizures and medications: Normal activity limitations, social support, and mental health in epilepsy. *Epilepsia* 53:e25-e28.
Lucini D, Norbiato G, Clerici M, Pagani M. (2002) Hemodynamic and autonomic adjustments to real life stress conditions in humans. *Hypertension* 39:184-188.
Lundgren T, Dahl J, Yardi N, Melin L. (2008) Acceptance and Commitment Therapy and yoga for drug-refractory epilepsy: A randomized controlled trial. *Epilepsy Behav* 13:102-108.
Luo J, Isaacowitz DM. (2007) How optimists face skin cancer information: Risk assessment, attention, memory, and behavior. *Psychology & Health* 22:963-984.
Magaudda A, Gugliotta SC, Tallarico R, Buccheri T, Alfa R, Lagana A. (2011) Identification of three distinct groups of patients with both epilepsy and psychogenic nonepileptic seizures. *Epilepsy & Behavior* 22:318-323.
Margrove K, Mensah S, Thapar A, Kerr M. (2011) Depression screening for patients with epilepsy in a primary care setting using the Patient Health Questionnaire-2 and the Neurological Disorders Depression Inventory for Epilepsy. *Epilepsy & Behavior* 21:387-390.
Martin M, Williams RM, Clark DM. (1991) DOES ANXIETY LEAD TO SELECTIVE PROCESSING OF THREAT-RELATED INFORMATION. *Behaviour Research and Therapy* 29:147-160.

Martin R, Burneo JG, Prasad A, Powell T, Faught E, Knowlton R, Mendez M, Kuzniecky R. (2003) Frequency of epilepsy in patients with psychogenic seizures monitored by video-EEG. *Neurology* 61:1791-1792.

Martlew J, Baker GA, Goodfellow L., Bodde N., A. A. (2007) Behavioural treatments for non-epileptic attack disorder., *Cochrane Database of Systematic Reviews*; doi:DOI: 10.1002/14651858.CD006370.

Matcham F, Rayner L, Hutton J, Monk A, Steel C, Hotopf M. (2014) Self-help interventions for symptoms of depression, anxiety and psychological distress in patients with physical illnesses: A systematic review and meta-analysis. *Clinical Psychology Review* 34:141-157.

Mathews A, Ridgeway V, Cook E, Yiend J. (2007) Inducing a benign interpretational bias reduces trait anxiety. *Journal of Behavior Therapy and Experimental Psychiatry* 38:225-236.

Mattia JI, Heimberg RG, Hope DA. (1993) THE REVISED STROOP COLOR-NAMING TASK IN SOCIAL PHOBICS. *Behaviour Research and Therapy* 31:305-313.

May TW, Pfafflin M. (2002) The efficacy of an educational treatment program for patients with epilepsy (MOSES): Results of a controlled, randomized study. *Epilepsia* 43:539-549.

Mayor R, Brown RJ, Cock H, House A, Howlett S, Smith P, Reuber M. (2013) A feasibility study of a brief psycho-educational intervention for psychogenic nonepileptic seizures. *Seizure-European Journal of Epilepsy* 22:760-765.

Mayor R, Howlett S, Grunewald R, Reuber M. (2010) Long-term outcome of brief augmented psychodynamic interpersonal therapy for psychogenic nonepileptic seizures: Seizure control and health care utilization. *Epilepsia* 51:1169-1176.

Mazarati A, Siddarth P, Baldwin RA, Shin D, Caplan R, Sankar R. (2008) Depression after status epilepticus: behavioural and biochemical deficits and effects of fluoxetine. *Brain* 131:2071-2083.

McLaughlin DP, McFarland K. (2011) A randomized trial of a group based cognitive behavior therapy program for older adults with epilepsy: the impact on seizure frequency, depression and psychosocial well-being. *Journal of Behavioral Medicine* 34:201-207.

McNally RJ, Riemann BC, Kim E. (1990) SELECTIVE PROCESSING OF THREAT CUES IN PANIC DISORDER. *Behaviour Research and Therapy* 28:407-412.

Michaelis R, Schonfeld W, Elsas SM. (2012) Trigger self-control and seizure arrest in the Andrews/Reiter behavioral approach to epilepsy: A retrospective analysis of seizure frequency. *Epilepsy Behav* 23:266-271.

Micoulaud-Franchi JA, Kotwas I, Lanteaume L, Berthet C, Bastien M, Vion-Dury J, McGonigal A, Bartolomei F. (2014) Skin conductance biofeedback training in adults with drug-resistant temporal lobe epilepsy and stress-triggered seizures: A proof-of-concept study. *Epilepsy & Behavior* 41:244-250.

Mittan RJ. (2009) Psychosocial treatment programs in epilepsy: A review. *Epilepsy Behav* 16:371-380.

Mitterschiffthaler MT, Williams SCR, Walsh ND, Cleare AJ, Donaldson C, Scott J, Fu CHY. (2008) Neural basis of the emotional Stroop interference effect in major depression. *Psychological Medicine* 38:247-256.

Mohr DC, Lovera J, Brown T, Cohen B, Neylan T, Henry R, Siddique J, Jin L, Daikh D, Pelletier D. (2012) A randomized trial of stress management for the prevention of new brain lesions in MS. *Neurology* 79:412-419.

Monzoni C, Reuber M. (2009) Conversational displays of coping resources in clinical encounters between patients with epilepsy and neurologists: A pilot study. *Epilepsy & Behavior* 16:652-659.
Mormann F, Lehnertz K. (2013) Epileptic Prodromes. In Reuber M, Schacter SC (Eds) *Borderland of Epilepsy Revisited*, Oxford University Press, New York.
Moshe S, Shilo M, Chodick G, Yagev Y, Blatt I, Korczyn AD, Neufeld MY. (2008) Occurrence of seizures in association with work-related stress in young male army recruits. *Epilepsia* 49:1451-1456.
Moss-Morris R, Petrie K, J. (2003) Experimental evidence for interpretative but not attention bias towards somatic information in patients with chronic fatigue syndrome. *British Journal of Health Psychology* 8:195 -208.
Mulhern B, Rowen D, Jacoby A, Marson T, Snape D, Hughes D, Latimer N, Baker GA, Brazier JE. (2012) The development of a QALY measure for epilepsy: NEWQOL-6D. *Epilepsy & Behavior* 24:36-43.
Myers L, Matzner B, Lancman M, Perrine K. (2013) Prevalence of alexithymia in patients with psychogenic non-epileptic seizures and epileptic seizures and predictors in psychogenic non-epileptic seizures. *Epilepsy Behav* 26:153-157.
Myslobodsky MS. (1993) Proconvulsant and anticonvulsant effects of stress - the role of neuroactive steroids. *Neurosci Biobehav Rev* 17:129-139.
Nagai Y. (2011) Biofeedback and Epilepsy. *Curr Neurol Neurosci Rep* 11:443-450.
Nagai Y, Goldstein LH, Fenwick PBC, Trimble MR. (2004) Clinical efficacy of galvanic skin response biofeedback training in reducing seizures in adult epilepsy: a preliminary randomized controlled study. *Epilepsy Behav* 5:216-223.
Nakken KO, Solaas MH, Kjeldsen MJ, Friis ML, Pellock JM, Corey LA. (2005) Which seizure-precipitating factors do patients with epilepsy most frequently report? *Epilepsy Behav* 6:85-89.
Napper L, Harris PR, Epton T. (2009) Developing and Testing a Self-affirmation Manipulation. *Self and Identity* 8:45-62.
Nei M. (2009) CARDIAC EFFECTS OF SEIZURES. *Epilepsy Currents* 9:91-95.
Neufeld MY, Sadeh M, Cohn DF, Korczyn AD. (1994) Stress and epilepsy: the Gulf war experience. *Seizure* 3:135-139.
Neugebauer R, Paik M, Hauser WA, Nadel E, Leppik I, Susser M. (1994) Stressful life events and seizure frequency in patients with epilepsy. *Epilepsia* 35:336-343.
Ngugi AK, Bottomley C, Kleinschmidt I, Sander JW, Newton CR. (2010) Estimation of the burden of active and life-time epilepsy: A meta-analytic approach. *Epilepsia* 51:883-890.
NICE. (2007) Behaviour Change at Population, Community and Individual Levels. NICEPublic Health Guidance., National Institute for Health and Clinical Excellence, London.
NICE. (2011) Generalised anxiety disorder and panic disorder in adults: management, National Institute for Health and Care Excellence, London.
NICE. (2015) The epilepsies: the diagnosis and management of the epilepsies in adults and children in primary and secondary care, *National Institute for Health and Care Excellence.* , London.
Nock MK, Park JM, Finn CT, Deliberto TL, Dour HJ, Banaji MR. (2010) Measuring the Suicidal Mind: Implicit Cognition Predicts Suicidal Behavior. *Psychological Science* 21:511-517.
Nouri S. (2011) Epilepsy and the Autonomic Nervous System. In Benbadis SR (Ed) *MedScape Reference*.

Novak V, Reeves AL, Novak P, Low PA, Sharbrough FW. (1999) Time-frequency mapping of R-R interval during complex partial seizures of temporal lobe origin. *J Auton Nerv Syst* 77:195-202.
O'Donoghue MF, Duncan JS, Sander JWAS. (1994) The development and evaluation of a new seizure severity scale: The National Hospital Seizure Severity Scale (NHS3). *Epilepsia* 35:151.
Ockenfels MC, Porter L, Smyth J, Kirschbaum C, Hellhammer DH, Stone AA. (1995) EFFECT OF CHRONIC STRESS ASSOCIATED WITH UNEMPLOYMENT ON SALIVARY COLTISOL - OVERALL CORTISOL-LEVELS, DIURNAL RHYTHM, AND ACUTE STRESS REACTIVITY. *Psychosomatic Medicine* 57:460-467.
Okon-Singer H, Lichtenstein-Vidne L, Cohen N. (2013) Dynamic modulation of emotional processing. *Biological Psychology* 92:480-491.
Pais-Ribeiro J, da Silva AM, Meneses RF, Falco C. (2007) Relationship between optimism, disease variables, and health perception and quality of life in individuals with epilepsy. *Epilepsy & Behavior* 11:33-38.
Panjwani U, Selvamurthy W, Singh SH, Gupta HL, Thakur L, Rai UC. (1996) Effect of Sahaja yoga practice on seizure control and EEG changes in patients of epilepsy. *Indian J Med Res* 103:165-172.
Park G, Thayer JF. (2014) From the heart to the mind: cardiac vagal tone modulates top-down and bottom-up visual perception and attention to emotional stimuli. *Frontiers in Psychology* 5:8.
Perogamvros I, Owen LJ, Newell-Price J, Ray DW, Trainer PJ, Keevil BG. (2009) Simultaneous measurement of cortisol and cortisone in human saliva using liquid chromatography-tandem mass spectrometry: Application in basal and stimulated conditions. *Journal of Chromatography B-Analytical Technologies in the Biomedical and Life Sciences* 877:3771-3775.
Persson H, Ericson M, Tomson T. (2007) Heart rate variability in patients with untreated epilepsy. *Seizure-European Journal of Epilepsy* 16:504-508.
Peterson C, Seligman MEP. (2003) Character strengths before and after September 11. *Psychological Science* 14:381-384.
Petrowski K, Wintermann G-B, Schaarschmidt M, Bornstein SR, Kirschbaum C. (2013) Blunted salivary and plasma cortisol response in patients with panic disorder under psychosocial stress. *International journal of psychophysiology : official journal of the International Organization of Psychophysiology* 88:35-39.
Piiparinen R, Smith JC. (2004) Stress symptoms one year after 9/11/01: A follow-up. *Perceptual and Motor Skills* 99:577-580.
Piiparinen RA, Smith JC. (2003) Stress symptoms of two groups before and after the terrorist attacks of 9/11/01. *Perceptual and Motor Skills* 97:360-364.
Pinikahana J, Dono J. (2009) The lived experience of initial symptoms of and factors triggering epileptic seizures. *Epilepsy Behav* 15:513-520.
Pitt JJ. (2009) Principles and applications of liquid chromatography-mass spectrometry in clinical biochemistry. *The Clinical biochemist. Reviews / Australian Association of Clinical Biochemists* 30:19-34.
Plug L, Sharrack B, Reuber M. (2009) Seizure metaphors differ in patients' accounts of epileptic and psychogenic nonepileptic seizures. *Epilepsia* 50:994-1000.
Ponnusamy A, Marques JLB, Reuber M. (2011) Heart rate variability measures as biomarkers in patients with psychogenic nonepileptic seizures: Potential and limitations. *Epilepsy Behav* 22:685-691.

Ponnusamy A, Marques JLB, Reuber M. (2012) Comparison of heart rate variability parameters during complex partial seizures and psychogenic nonepileptic seizures. *Epilepsia* 53:1314-1321.
Porges SW. (1992) Vagal tone - A physiological marker of stress vulneranbility. *Pediatrics* 90:498-504.
Pradhan C, Sinha S, Thennarasu K, Jagadisha T. (2011) Quantitative analysis of heart rate variability in patients with absence epilepsy. *Neurology India* 59:25-29.
Pramuka M, Hendrickson R, Zinski A, Van Cott AC. (2007) A psychosocial self-management program for epilepsy: A randomized pilot study in adults. *Epilepsy & Behavior* 11:533-545.
Pritchard PB. (1991) THE EFFECT OF SEIZURES ON HORMONES. *Epilepsia* 32:S46-S50.
Privitera M. (2015) The SMILE Study, Retrieved from http://ucepilepsycenter.com/research/the-smile-study/, University of Cincinnati Epilepsy Center.
Privitera M, Walters M, Lee I, Polak E, Fleck A, Schwieterman D, Haut SR. (2014) Characteristics of people with self-reported stress-precipitated seizures. *Epilepsy & Behavior* 41:74-77.
Rakesh SP, Ramesh R, Rachel P, Chanda R, Satish N, Mohan VR. (2012) Quality of life among people with epilepsy: A cross-sectional study from rural southern India. *The National medical journal of India* 25:261-264.
Ramaratnam S, Baker GA, Goldstein LH. (2008) Psychological treatments for epilepsy. *Cochrane Db Syst Rev*:37.
Raudenbush SW, Bryk AS. (2002) *Hierarchical linear models: Applications and data analysis methods*. Sage, Thousand Oaks, CA.
Raudenbush SWB, A.S. Cheong, A.S.Fai, Y.F.Congdon, R.T.du Toit, M. (2011) *HLM 7: Hierarchical linear and nonlinear modeling*. Scientific Software International, Lincolnwood, IL.
Reed MB, Aspinwall LG. (1998) Self-affirmation reduces biased processing of health-risk information. *Motivation and Emotion* 22:99-132.
Reeves T, Stace JM. (2005) Improving patient access and choice: Assisted Bibliotherapy for mild to moderate stress/anxiety in primary care. *Journal of psychiatric and mental health nursing* 12:341-346.
Renaud P, Blondin JP. (1997) The stress of Stroop performance: physiological and emotional responses to color-word interference, task pacing, and pacing speed. *International Journal of Psychophysiology* 27:87-97.
Reuber M. (2009) The Etiology of Psychogenic Non-Epileptic Seizures: Toward a Biopsychosocial Model. *Neurol Clin* 27:909-924.
Reuber M, Fernandez G, Bauer J, Helmstaedter C, Elger CE. (2002) Delays in the diagnosis of psychogenic non-epileptic seizures. *Journal of Neurology Neurosurgery and Psychiatry* 73:224-224.
Reuber M, Howlett S, Kemp S. (2005a) Psychologic treatment of patients with psychogenic nonepileptic seizures. *Expert review of neurotherapeutics* 5:737-752.
Reuber M, Mayor R. (2012) Recent progress in the understanding and treatment of nonepileptic seizures. *Current Opinion in Psychiatry* 25:244-250.
Reuber M, Mitchell AJ, Howlett S, Elger CE. (2005b) Measuring outcome in psychogenic nonepileptic seizures: How relevant is seizure remission ? *Epilepsia* 46:1788-1795.
Reuber M, Pukrop R, Bauer J, Helmstaedter C, Tessendorf N, Elger CE. (2003) Outcome in psychogenic nonepileptic seizures: 1 to 10 year follow-up in 164 patients. *Ann.Neurol.* 53:305-311.

Roberts NA, Burleson MH, Weber DJ, Larson A, Sergeant K, Devine MJ, Vincelette TM, Wang NC. (2012) Emotion in psychogenic nonepileptic seizures: Responses to affective pictures. *Epilepsy Behav* 24:107-115.
Robins RW, Hendin HM, Trzesniewski KH. (2001) Measuring global self-esteem: Construct validation of a single-item measure and the Rosenberg self-esteem scale. *Personality and Social Psychology Bulletin* 27:151-161.
Ronkainen E, Ansakorpi H, Huikuri HV, Myllyla VV, Isojarvi JIT, Korpelainen JT. (2005) Suppressed circadian heart rate dynamics in temporal lobe epilepsy. *Journal of Neurology Neurosurgery and Psychiatry* 76:1382-1386.
Salmon P, Al-Marzooqi SM, Baker G, Reilly J. (2003) Childhood family dysfunction and associated abuse in patients with nonepileptic seizures: Towards a causal model. *Psychosomatic Medicine* 65:695-700.
Schachter SC. (1993) Brainstorms: Epilepsy in our words: Personal accounts of living with seizures. *Brainstorms: Epilepsy in our words: Personal accounts of living with seizures*:xvii+104p.
Schachter SC, Saper CB. (1998) Vagus nerve stimulation. *Epilepsia* 39:677-686.
Scheier MF, Carver CS, Bridges MW. (1994) DISTINGUISHING OPTIMISM FROM NEUROTICISM (AND TRAIT ANXIETY, SELF-MASTERY, AND SELF-ESTEEM) - A REEVALUATION OF THE LIFE ORIENTATION TEST. *Journal of Personality and Social Psychology* 67:1063-1078.
Scheier MF, Magovern GJ, Abbott RA, Matthews KA, Owens JF, Lefebvre RC, Carver CS. (1989) DISPOSITIONAL OPTIMISM AND RECOVERY FROM CORONARY-ARTERY BYPASS-SURGERY - THE BENEFICIAL-EFFECTS ON PHYSICAL AND PSYCHOLOGICAL WELL-BEING. *Journal of Personality and Social Psychology* 57:1024-1040.
Schmid-Schonbein C. (1998) Improvement of seizure control by psychological methods in patients with intractable epilepsies. *Seizure* 7:261-270.
Schmidt NB, Richey JA, Buckner JD, Timpano KR. (2009) Attention Training for Generalized Social Anxiety Disorder. *Journal of Abnormal Psychology* 118:5-14.
Schou I, Ekeberg O, Ruland CM. (2005) The mediating role of appraisal and coping in the relationship between optimism-pessimism and quality of life. *Psycho-Oncology* 14:718-727.
Schridde U, van Luijtelaar G. (2004) Corticosterone increases spike-wave discharges in a dose- and time-dependent manner in WAG/Rij rats. *Pharmacol Biochem Behav* 78:369-375.
Schroder J, Bruckner K, Fischer A, Lindenau M, Kother U, Vettorazzi E, Moritz S. (2014) Efficacy of a psychological online intervention for depression in people with epilepsy: A randomized controlled trial. *Epilepsia* 55:2069-2076.
Scott-Lennox J, Bryant-Comstock L, Lennox R, Baker GA. (2001) Reliability, validity and responsiveness of a revised scoring system for the Liverpool Seizure Severity Scale. *Epilepsy Research* 44:53-63.
Sevcencu C, Struijk JJ. (2010) Autonomic alterations and cardiac changes in epilepsy. *Epilepsia* 51:725-737.
Shaw JW, Johnson JA, Coons SJ. (2005) US valuation of the EQ-5D health states - Development and testing of the D1 valuation model. *Medical Care* 43:203-220.
Sheng H, Zhang YM, Sun JH, Gao L, Ma B, Lu JQ, Ni X. (2008) Corticotropin-releasing hormone (CRH) depresses N-methyl-D-aspartate receptor-mediated current in cultured rat hippocampal neurons via CRH receptor type 1. *Endocrinology* 149:1389-1398.

Sherman DK, Bunyan DP, Creswell JD, Jaremka LM. (2009) Psychological Vulnerability and Stress: The Effects of Self-Affirmation on Sympathetic Nervous System Responses to Naturalistic Stressors. *Health Psychology* 28:554-562.
Sherman DK, Cohen GL. (2006) The psychology of self-defense: Self-affirmation theory. In Zanna MP (Ed) *Advances in Experimental Social Psychology, Vol 38*, Elsevier Academic Press Inc, San Diego, pp. 183-242.
Sierksma ASR, Prickaerts J, Chouliaras L, Rostamian S, Delbroek L, Rutten BPF, Steinbusch HWM, van den Hove DLA. (2013) Behavioral and neurobiological effects of prenatal stress exposure in male and female APPswe/PS1dE9 mice. *Neurobiology of Aging* 34:319-337.
Sinclair VG, Wallston KA. (2004) The development and psychometric evaluation of the brief resilient coping scale. *Assessment* 11:94-101.
Smeets T. (2010) Autonomic and hypothalamic-pituitary-adrenal stress resilience: Impact of cardiac vagal tone. *Biological Psychology* 84:290-295.
Spector S, Cull C, Goldstein LH. (2000) Seizure precipitants and perceived self-control of seizures in adults with poorly-controlled epilepsy. *Epilepsy Res* 38:207-216.
Spek V, Cuijpers P, Nykicek I, Riper H, Keyzer J, Pop V. (2007) Internet-based cognitive behaviour therapy for symptoms of depression and anxiety: a meta-analysis. *Psychological Medicine* 37:319-328.
Sperling MR, Schilling CA, Glosser D, Tracy JI, Asadi-Pooya AA. (2008) Self-perception of seizure precipitants and their relation to anxiety level, depression, and health locus of control in epilepsy. *Seizure* 17:302-307.
Spitzer RL, Kroenke K, Williams JBW, Lowe B. (2006) A brief measure for assessing generalized anxiety disorder - The GAD-7. *Arch Intern Med* 166:1092-1097.
Stalder T, Evans P, Hucklebridge F, Clow A. (2011) Associations between the cortisol awakening response and heart rate variability. *Psychoneuroendocrinology* 36:454-462.
Steele C. (1988) The Psychology of Self-Affirmation: Sustaining the integrity of the self. In Leonard B (Ed) *Adv Exp Soc Psychol*, Academic Press, New York, pp. 261-302.
Steward J, Seeman T. (2000) Salivary Cortisol Measurement, *The MacArthur Research Network on Socioeconomic Status and Health*.
Streeter CC, Gerbarg PL, Saper RB, Ciraulo DA, Brown RP. (2012) Effects of yoga on the autonomic nervous system, gamma-aminobutyric-acid, and allostasis in epilepsy, depression, and post-traumatic stress disorder. *Medical Hypotheses* 78:571-579.
Stroop JR. (1935) Studies of interference in serial verbal reactions. *Journal of Experimental Psychology* 18:643-662.
Swinkels WAM, Engelsman M, Trenite D, Baal MG, de Haan GJ, Oosting J. (1998) Influence of an evacuation in February 1995 in the Netherlands on the seizure frequency in patients with epilepsy: A controlled study. *Epilepsia* 39:1203-1207.
Tarvainen MP, Niskanen JP, Lipponen JA, Ranta-aho PO, Karjalainen PA. (2014) Kubios HRV - Heart rate variability analysis software. *Computer Methods and Programs in Biomedicine* 113:210-220.
Task Force Of The European Society Of Cardiology And The North A, Society Of Pacing And E. (1996) Heart rate variability: Standards of measurement, physiological interpretation, and clinical use. *European Heart Journal* 17:354-381.
Testa SM, Krauss GL, Lesser RP, Brandt J. (2012) Stressful life event appraisal and coping in patients with psychogenic seizures and those with epilepsy. *Seizure-European Journal of Epilepsy* 21:282-287.

Thapar A, Kerr M, Harold G. (2009) Stress, anxiety, depression, and epilepsy: Investigating the relationship between psychological factors and seizures. *Epilepsy Behav* 14:134-140.
Thayer JF, Lane RD. (2000) A model of neurovisceral integration in emotion regulation and dysregulation. *Journal of Affective Disorders* 61:201-216.
Thompson R, Isaac CL, Rowse G, Tooth CL, Reuber M. (2009) What is it like to receive a diagnosis of nonepileptic seizures? *Epilepsy & Behavior* 14:508-515.
Todorova MT, Burwell TJ, Seyfried TN. (1999) Environmental risk factors for multifactorial epilepsy in EL mice. *Epilepsia* 40:1697-1707.
Toichi M, Sugiura T, Murai T, Sengoku A. (1997) A new method of assessing cardiac autonomic function and its comparison with spectral analysis and coefficient of variation of R-R interval. *Journal of the Autonomic Nervous System* 62:79-84.
Tojek TM, Lumley M, Barkley G, Mahr G, Thomas A. (2000) Stress and other psychosocial characteristics of patients with psychogenic nonepileptic seizures. *Psychosomatics* 41:221-226.
Toli A, Webb T, Hardy G. (2015) Does forming implementation intentions help people with mental health problems to achieve goals? A meta-analysis of experimental studies with clinical and analogue samples. *Br J Clin Psychol.*:1 - 22.
Tolmacheva EA, Oitzl MS, van Luijtelaar G. (2012) Stress, glucocorticoids and absences in a genetic epilepsy model. *Horm Behav* 61:706-710.
Tolmacheva EA, van Luijtelaar G. (2007) The role of ovarian steroid hormones in the regulation of basal and stress induced absence seizures. *J Steroid Biochem Mol Bioly* 104:281-288.
Toth V, Hejjel L, Fogarasi A, Gyimesi C, Orsi G, Szucs A, Kovacs N, Komoly S, Ebner A, Janszky J. (2010) Periictal heart rate variability analysis suggests long-term postictal autonomic disturbance in epilepsy. *Eur J Neurol* 17:780-787.
Tunca Z, Ergene U, Fidaner H, Cimilli C, Ozerdem A, Alkin T, Aslan BU. (2000) Reevaluation of serum cortisol in conversion disorder with seizure (pseudoseizure). *Psychosomatics* 41:152-153.
Tunca Z, Fidaner H, Cimilli C, Kaya N, Biber B, Yesil S, Ozerdem A. (1996) Is conversion disorder biologically related with depression? A DST study. *Biological Psychiatry* 39:216-219.
Uliaszek AA, Prensky E, Baslet G. (2012) Emotion regulation profiles in psychogenic non-epileptic seizures. *Epilepsy Behav* 23:364-369.
van Campen JS, Jansen FE, Pet MA, Otte WM, Hillegers MHJ, Joels M, Braun KPJ. (2015) Relation between stress-precipitated seizures and the stress response in childhood epilepsy. *Brain* 138:2234-2248.
van der Kruijs SJM, Jagannathan SR, Bodde NMG, Besseling RMH, Lazeron RHC, Vonck KEJ, Boon P, Cluitmans PJM, Hofman PAM, Backes WH, Aldenkamp AP, Jansen JFA. (2014) Resting-state networks and dissociation in psychogenic non-epileptic seizures. *Journal of Psychiatric Research* 54:126-133.
van Honk J, Tuiten A, van den Hout M, Koppeschaar H, Thijssen J, de Haan E, Verbaten R. (2000) Conscious and preconscious selective attention to social threat: different neuroendocrine response patterns. *Psychoneuroendocrinology* 25:577-591.
van Straten A, Cuijpers P, Smits N. (2008) Effectiveness of a web-based self-help intervention for symptoms of depression, anxiety, and stress: Randomized controlled trial. *Journal of Medical Internet Research* 10:10.
Varley R, Webb TL, Sheeran P. (2011) Making Self-Help More Helpful: A Randomized Controlled Trial of the Impact of Augmenting Self-Help Materials With

Implementation Intentions on Promoting the Effective Self-Management of Anxiety Symptoms. *Journal of Consulting and Clinical Psychology* 79:123-128.
Vernon PE, Allport GW. (1931) A test for personal values. *Journal of Abnormal and Social Psychology* 26:231-248.
Wassenaar M, Trenite D, de Haan GJ, Carpay JA, Leijten FSS. (2014) Seizure precipitants in a community-based epilepsy cohort. *Journal of Neurology* 261:717-724.
Watson NF, Doherty MJ, Dodrill CB, Farrell D, Miller JW. (2002) The experience of earthquakes by patients with epileptic and psychogenic nonepileptic seizures. *Epilepsia* 43:317-320.
WHO. (1992) *ICD-10 Classifications of Mental and Behavioural Disorder: Clinical Descriptions and Diagnostic Guidelines*, World Health Organisation Press, Geneva.
Wiers RW, Teachman BA, De Houwer J. (2007) Implicit cognitive processes in psychopathology: An introduction. *Journal of Behavior Therapy and Experimental Psychiatry* 38:95-104.
Williams JMG, Mathews A, MacLeod C. (1996) The emotional stroop task and psychopathology. *Psychological Bulletin* 120:3-24.
Williams RA, Gatien G, Hagerty B. (2011) Design element alternatives for stress-management intervention websites. *Nursing Outlook* 59:286-291.
Witthoft M, Rist F, Bailer J. (2009) Abnormalities in cognitive-emotional information processing in idiopathic environmental intolerance and somatoform disorders. *Journal of Behavior Therapy and Experimental Psychiatry* 40:70-84.
Wolf P. (2002) The role of nonpharmaceutic conservative interventions in the treatment and secondary prevention of epilepsy. *Epilepsia* 43:2-5.
Wolf P, Lin K, Nikanorova M. (2013) Non-Pharmacological Therapy of Epilepsy. In Shorvon S, Guerrini R, Cook M, Lhatoo SD (Eds) *Oxford Textbook of Epilepsy and Epileptic Seizures*, Oxford University Press, Oxford, pp. 135-143.
Zeitlin SB, Bradburn DO, Lawsonkerr K. (1995) SELECTIVE PROCESSING OF EPILEPSY-RELATED CUES IN PATIENTS WITH HIGH FEAR OF SEIZURES. *Journal of Epilepsy* 8:16-22.

Appendices

Appendix 1. Demographic Questionnaire

Personal Information
Please answer the following questions about yourself. The information you are giving us will be treated as confidential and will be anonymised. Do not put your name on the questionnaire.

Subject ID: …… *(to be completed by the investigator)*

1. Today's date: ……..

2. Date of birth: ……..

3. Gender: *(please tick the correct option)*

   ☐ Male ☐ Female

4. Work: *(please tick the correct option)*

   ☐ I am at school/college
   ☐ I am at university
   ☐ I am employed
   ☐ I am self-employed
   ☐ I am unemployed
   ☐ I receive disability benefits
   ☐ I have retired on health-grounds
   ☐ I receive an old-age pension.

5. For how many years in total did you go to school/college/university? …… years

6. Have you ever felt that some of your seizures occur as a result of stress? *(please tick)*

   ☐ YES ☐ NO

Appendix 2. Perceived Stress Scale 4-Item (PSS-4)

PSS- 4

The questions in this scale ask you about your feelings and thoughts during the last month. In each case, please indicate with a check how often you felt or thought a certain way.

1. In the last month, how often have you felt that you were unable to control the important things in your life?

___0=never ___1=almost never ___2=sometimes ___3=fairly often ___4=very often

2. In the last month, how often have you felt confident about your ability to handle your personal problems?

___0=never ___1=almost never ___2=sometimes ___3=fairly often ___4=very often

3. In the last month, how often have you felt that things were going your way?

___0=never ___1=almost never ___2=sometimes ___3=fairly often ___4=very often

4. In the last month, how often have you felt difficulties were piling up so high that you could not overcome them?

___0=never ___1=almost never ___2=sometimes ___3=fairly often ___4=very often

Appendix 3. Liverpool Seizure Severity Scale (LSSS-3)

LSSS

So we can better understand the severity of your seizures, please complete the following questionnaire thinking about the most severe seizure you experienced during the past 4 weeks. (This may be different for each individual, but is based on your most severe seizures over the past 4 weeks).

How may seizures have you experienced during the past 4 weeks? _____ seizures

Note: Please enter '0' if you have not experienced seizures in the last 4 weeks and do not complete the remainder of the questionnaire. If you cannot remember the exact number of seizures you've experienced, please estimate based on the number you usually had during a single day or week.

Please answer each question based on the most severe seizure you have experienced in the past 4 weeks. Circle only one answer for each question.

1. I feel that my most severe seizures have mostly been:

Very severe 0
Severe 1
Mild 2
Very mild 3

---

2. Most commonly when I blank out/lose consciousness:

I blank out for less than 1 minute 1
I blank out for between 1 and 2 minutes 2
I blank out for between 3 and 5 minutes 3
I blank out for more than 5 minutes 4
I never blank out lose consciousness 0

---

3. When I have my most severe seizures, I smack my lips, fidget, or behave in an unusual way:

Always 0

Usually 1

Sometimes 2

Never 3

---

4. After my most severe seizures:

I feel very confused 0

I feel fairly confused 1

I feel slightly confused 2

I do not feel confused at all 3

---

5. After my most severe seizures my confusion lasts for:

Less than 1 minute 1

Between 1 and 5 minutes 2

Between 6 minutes and 1 hour 3

1 to 2 hours 4

More than 2 hours 5

I never feel confused 0

---

6. When I have my most severe seizures:

I always fall to the ground 0

I usually fall to the ground 1

I sometimes fall to the ground 2

I never fall to the ground 3

---

7. After my most severe seizures:

I always have a headache 0

I usually have a headache 1

I sometimes have a headache 2

I never have a headache 3

8. After my most severe seizures:

I always feel sleepy 0

I usually feel sleepy 1

I sometimes feel sleepy 2

I never feel sleepy 3

---

9. After my most severe seizures:

I always find that I have wet myself 0

I usually find that I have wet myself 1

I sometimes find that I have wet myself 2

I never find that I have wet myself 3

---

10. After my most severe seizures:

I always find that I have bitten my tongue 0

I usually find that I have bitten my tongue 1

I sometimes find that I have bitten my tongue 2

I never find that I have bitten my tongue 3

---

11. After my most severe seizures:

I always find that I have injured myself (other than biting my tongue) 0

I usually find that I have injured myself (other than biting my tongue) 1

I sometimes find that I have injured myself (other than biting my tongue) 2

I never find that I have injured myself (other than biting my tongue) 3

---

12. After my most severe seizures I can usually return to what I am doing in:

Less than 1 minute 0

Between 1 and 5 minutes 1

Between 6 minutes and 1 hour 2

1 to 2 hours 3

More than 2 hours 4

Please check that you have answered **all** the questions.

Appendix 4. Quality of Life in Newly Diagnosed Epilepsy – 6 Dimensions (NEWQOL-6D)

Please select the option that applies to you by ticking one of the boxes for each question.

1. **How worried are you that you might have another attack?**

- ☐ I am not worried at all
- ☐ I am a little worried
- ☐ I am fairly worried
- ☐ I am very worried

2. **How often do you have problems with depression?**

- ☐ I never have problems with depression
- ☐ I rarely have problems with depression
- ☐ I sometimes have problems with depression
- ☐ I always or often have problems with depression

3. **Thinking about your memory:**

- ☐ I never have problems with my memory
- ☐ I rarely have problems with my memory
- ☐ I sometimes have problems with my memory
- ☐ I always or often have problems with my memory

4. **Thinking about your concentration:**

- ☐ I have no problem concentrating for more than a short period of time
- ☐ I have mild problems concentrating for more than a short period of time
- ☐ I have moderate problems concentrating for more than a short period of time
- ☐ I have serious problems concentrating for more than a short period of time

5. **How much control do you feel you have over things that happen to you?**

- ☐ I have complete control over things that happen to me
- ☐ I have some control over things that happen to me
- ☐ I have little control over things that happen to me
- ☐ I have no control over things that happen to me

6. **How much do you feel people treat you as an inferior person?**

- ☐ I do not feel that people treat me like an inferior person
- ☐ I feel that some people maybe treat me like an inferior person
- ☐ I feel that some people probably treat me like an inferior person
- ☐ I feel that some people definitely treat me like an inferior person

Appendix 5. Life Orientation Test – Revised (LOT-R)

LOT-R

Please be as honest and accurate as you can throughout. Try not to let your response to one statement influence your responses to other statements. There are no "correct" or "incorrect" answers. Answer according to your own feelings, rather than how you think "most people" would answer.

A = I agree a lot
B = I agree a little
C = I neither agree nor disagree
D = I DISagree a little
E = I DISagree a lot

1. In uncertain times, I usually expect the best.	A	B	C	D	E
2. It's easy for me to relax.	A	B	C	D	E
3. If something can go wrong for me, it will.	A	B	C	D	E
4. I'm always optimistic about my future.	A	B	C	D	E
5. I enjoy my friends a lot.	A	B	C	D	E
6. It's important for me to keep busy.	A	B	C	D	E
7. I hardly ever expect things to go my way.	A	B	C	D	E
8. I don't get upset too easily.	A	B	C	D	E
9. I rarely count on good things happening to me.	A	B	C	D	E
10. Overall, I expect more good things to happen to me than bad.	A	B	C	D	E

Appendix 6. Spontaneous Self-Affirmation Measure (SSAM) and Single-Item Self-Esteem Scale (SISE)

1. When we think about ourselves, our thoughts are sometimes negative and sometimes positive. In this study we are interested in the POSITIVE thoughts you have about yourself.
For each of the following statements, circle the number that indicates how much you agree or disagree with the statement.

Thinking POSITIVELY about myself is something ...

	disagree completely						agree completely
... I do automatically.	1	2	3	4	5	6	7
... that feels sort of natural to me.	1	2	3	4	5	6	7
... I do without further thinking.	1	2	3	4	5	6	7
... I would find hard not to do.	1	2	3	4	5	6	7
... that's typically "me".	1	2	3	4	5	6	7

2. Sometimes when we face difficulties, challenges or problems in our daily lives we can find ourselves thinking about ourselves. We are interested in how often you find yourself thinking about yourself when things start to bother you.

When I feel threatened or anxious by people or events I find myself …

	disagree completely						agree completely
...thinking about my strengths.	1	2	3	4	5	6	7
...thinking about my values.	1	2	3	4	5	6	7
...thinking about my principles.	1	2	3	4	5	6	7
...thinking about what I stand for.	1	2	3	4	5	6	7
...thinking about my family.	1	2	3	4	5	6	7
...thinking about my friends.	1	2	3	4	5	6	7
...thinking about the things I am good at.	1	2	3	4	5	6	7
...thinking about the things I like about myself.	1	2	3	4	5	6	7
...thinking about my failings.	1	2	3	4	5	6	7
...thinking about the people I love	1	2	3	4	5	6	7

I have high self-esteem.

Not very true of me	1	2	3	4	5	*Very true of me*

Appendix 7. Brief Resilient Coping Scale (BRCS)

BRCS

Consider how well the following statements describe your behaviour and actions on a scale from 1 to 5, where 1 means the statement does not describe you at all and 5 means it describes you very well.

1. **I look for creative ways to alter difficult situations.**

   1 2 3 4 5
   Not true of me at all *Very true of me*

2. **Regardless of what happens to me, I believe I can control my reaction to it.**

   1 2 3 4 5
   Not true of me at all *Very true of me*

3. **I believe I can grow in positive ways by dealing with difficult situations**

   1 2 3 4 5
   Not true of me at all *Very true of me*

4. **I actively look for ways to replace the losses I encounter in life.**

   1 2 3 4 5
   Not true of me at all *Very true of me*

Appendix 8. Neurological Disorders Depression Inventory for Epilepsy (NDDIE)

NDDI-E

Please choose the answer that best describes you within the past few weeks, including today.

1. **Everything is a struggle**

☐ Always or Often ☐ Sometimes ☐ Rarely ☐ Never

2. **Nothing I do is right**

☐ Always or Often ☐ Sometimes ☐ Rarely ☐ Never

3. **Feel guilty**

☐ Always or Often ☐ Sometimes ☐ Rarely ☐ Never

4. **I'd be better off dead**

☐ Always or Often ☐ Sometimes ☐ Rarely ☐ Never

5. **Frustrated**

☐ Always or Often ☐ Sometimes ☐ Rarely ☐ Never

6. **Difficulty finding pleasure**

☐ Always or Often ☐ Sometimes ☐ Rarely ☐ Never

Appendix 9. Generalised Anxiety Disorder Scale 7-Item (GAD-7)

GAD-7

Over the last 2 weeks, how often have you been bothered by the following problems?	Not at all	Several days	Over half the days	Nearly every day
1. Feeling nervous, anxious, or on edge	0	1	2	3
2. Not being able to stop or control worrying	0	1	2	3
3. Worrying too much about different things	0	1	2	3
4. Trouble relaxing	0	1	2	3
5. Being so restless that it's hard to sit still	0	1	2	3
6. Becoming easily annoyed or irritable	0	1	2	3
7. Feeling afraid as if something awful might happen	0	1	2	3

Appendix 10. Smith Stress Symptom Inventory (SSSI)

1. To what extent do the following statements fit how you feel RIGHT NOW at the PRESENT MOMENT? Please check all the items using this key.

1 = Doesn't fit me at all 2 = Fits me a little 3 = Fits me moderately well 4 = Fits me very well

1	2	3	4	1. I have a nervous stomach.
1	2	3	4	2. I am easily distracted.
1	2	3	4	3. I feel like I am losing my memory and forgetting things.
1	2	3	4	4. I feel like I am losing sleep.
1	2	3	4	5. I worry too much about things that do not really matter.
1	2	3	4	6. My breathing is hurried, shallow, or uneven.
1	2	3	4	7. I have conflicts with others.
1	2	3	4	8. I find myself thinking in narrow, rigid ways.
1	2	3	4	9. My heart is beating fast, hard, or irregularly.
1	2	3	4	10. I have difficulty controlling negative thoughts.
1	2	3	4	11. I feel distressed (discouraged or sad).
1	2	3	4	12. I have lost my appetite.
1	2	3	4	13. I am depressed.
1	2	3	4	14. I am anxious.
1	2	3	4	15. I feel distaste or disgust.
1	2	3	4	16. I feel cynical or hostile.
1	2	3	4	17. My shoulders, neck, or back are tense.
1	2	3	4	18. I have difficulty keeping troublesome thoughts out of my mind.
1	2	3	4	19. I feel confused.
1	2	3	4	20. My muscles feel tight, tense, or clenched up (furrowed brow, tightened fist, clenched jaws).
1	2	3	4	21. I feel less sensitive or caring to others.
1	2	3	4	22. I feel fatigued.

1	2	3	4	23. I have a backache.
1	2	3	4	24. I feel like I am losing concentration.
1	2	3	4	25. I am afraid.
1	2	3	4	26. My mouth feels dry.
1	2	3	4	27. I feel like I might make mistakes.
1	2	3	4	28. I perspire or feel too warm.
1	2	3	4	29. I feel disorganised.
1	2	3	4	30. I feel the need to go to the restroom unnecessarily.
1	2	3	4	31. I find myself thinking unimportant, bothersome thoughts.
1	2	3	4	32. I have a headache.
1	2	3	4	33. I feel less cooperative with others.
1	2	3	4	34. I feel restless and fidgety.
1	2	3	4	35. I feel irritated or angry.

2. On a scale from 0 to 6, where 0 means not at all stressed and 6 means very stressed, how stressed do you feel RIGHT NOW? Please circle as appropriate.

Not at all stressed Very stressed

0	1	2	3	4	5	6

Appendix 11. Adjusted National Hospital Seizure Severity Scale (NHS3)

NHS3

Patient's Name:

Date:

Instructions for completion:

1. Define how many types of seizure occur (e.g. aura, complex partial, generalized convulsion…). Call these type 1-3 arbitrarily.

2. Apply questions 2-8 to each seizure type separately. As the NHS3 indicates current seizure severity, define the time frame: e.g. 1-3 months or time since the last clinic visit. Use clinical judgment whether each factor occurs in the seizure type (i.e. the physician decides if there is a convulsion after questioning the patient). Allow the patient to judge the frequency of each event. Then tick the box opposite the response options. The number in the box is the score for that question.

Note:
Q.3. Only actual are recorded i.e. if the seizures could cause falls but have not because they all occurred while in bed, then the score is 0.

Q.7. refers to the time until the patient feels fully functional.

Note the specific scoring instructions for Q4. and 6.

3. The column totals give the seizure severity score.

		Type 1	Type 2	Type 3
1. Record the name of the seizure types that occur under headings "type 1, 2, 3…."				
2. Has the patient had a generalized convulsion during this type of seizure?				
	Yes	4	4	4
	No	0	0	0
3. Has the patient fallen to the ground in this type of seizure?				
	Yes	4	4	4
	No	0	0	0
4. Has this type of seizure caused any of the following? (score only the worst)				
	Burns, scalds, deep cuts, fractures	4	4	4
	Bitten tongue or severe headache	3	3	3
	Milder injuries or mild headaches	2	2	2
	No injuries	0	0	0
5. Has the patient been incontinent of urine in this type of seizure?				
	Yes	4	4	4
	No	0	0	0
6. If the seizure caused loss of consciousness, was there a warning long enough for the patient to protect him/herself? (no loss of consciousness or seizures only while asleep scores 0)				
	No	2	2	2
	Yes	0	0	0
7. How long was it until the patient was really back to normal after the seizure?				
	Less than 1 minute	0	0	0
	Between 1 and 10 minutes	1	1	1
	Between 10 minutes and 1 hour	2	2	2
	Between 1 and 3 hours	3	3	3
	More than 3 hours	4	4	4
8. Have the following events occurred in this type of seizure?				
	Seriously disruptive automatisms (e.g. shouting, wandering, undressing)	4	4	4
	Mild automatisms or focal jerking	2	2	2
	None	0	0	0
Add 1 point to each column		1	1	1
TOTAL SCORE FOR EACH SEIZURE TYPE				

Appendix 12. Normative salivary cortisol values before and after log-transformation

Healthy controls salivary cortisol (N = 14)	Morning (9am) *Mean (SD)*	Evening (10pm) *Mean (SD)*	Cortisol delta *Mean (SD)*
Cortisol levels (nmol/L)	4.19 (1.55)	0.95 (0.46)	3.23 (1.58)
Log-transformed cortisol levels (nmol/L)	0.59 (0.16)	-0.05 (0.14)	0.47 (0.20)

Appendix 13. Time-point level correlations between morning and evening stress measures in patients with epilepsy and patients with PNES

Time-point level correlations between the morning self-reported stress (N = 63), salivary cortisol (N = 63) and HRV parameters (N = 42) measures in patients with epilepsy

	1	2	3	4	5	6
1 Self-reported stress						
2 LogCortisol	.027					
3 LogSDNN	.127	-.349*				
4 LogRMSSD	.145	-.255	.917**			
5 LogCVI	.137	-.305	.986**	.963**		
6 LogCSI	-.052	-.080	-.196	-.570**	-.336*	

Note. *Correlation is significant at .05 level. ** Correlation is significant at .01 level

Time-point level correlations between the evening self-reported stress (N = 57), cortisol (N = 60), and HRV parameters (N = 51) measures in patients with epilepsy

	1	2	3	4	5	6
1 Self-reported stress						
2 LogCortisol	.063					
3 LogSDNN	.197	-.054				
4 LogRMSSD	.244	-.076	.940**			
5 LogCVI	.244	-.055	.983**	.971**		
6 LogCSI	-.174	.091	-.453**	-.729**	-.562*	

Note. *Correlation is significant at .05 level. ** Correlation is significant at .01 level

Time-point level correlations between the morning self-reported stress (N = 50), cortisol (N = 47), and HRV parameters (N = 38) in patients with PNES

	1	2	3	4	5	6
1 Self-reported stress						
2 LogCortisol	.000					
3 LogSDNN	-.136	-.225				
4 LogRMSSD	.184	-.228	.957**			
5 LogCVI	.125	-.158	.978**	.965**		
6 LogCSI	.217	.154	-.385*	-.636**	-.468**	

Note. *Correlation is significant at .05 level. ** Correlation is significant at .01 level

Time-point level correlations between the evening self-reported stress (N = 46), salivary cortisol (N = 46), and HRV parameters (N = 43) in patients with PNES

	1	2	3	4	5	6
1 Self-reported stress						
2 LogCortisol	.111					
3 LogSDNN	-.197	.147				
4 LogRMSSD	-.224	.168	.947**			
5 LogCVI	-.197	.153	.980**	.969**		
6 LogCSI	.177	-.127	-.382*	-.657**	-.487**	

Note. *Correlation is significant at .05 level. ** Correlation is significant at .01 level

Appendix 14. Kindness Self-Affirmation Intervention

Personal Attributes Inventory

*Please indicate whether you have ever performed each of the behaviours described below by circling either '**YES**' or '**NO**'. If your answer is 'yes' to any of the behaviours, please provide a brief example of when you performed it.*

1. Have you ever forgiven another person when they have hurt you? **YES** **NO**

If yes, please provide an example……

……

2. Have you ever been considerate of another person's feelings? **YES** **NO**

If yes, please provide an example……

……

3. Have you ever been concerned with the happiness of another person?

YES **NO**

If yes, please provide an example……

……

4. Have you ever looked out for another person's interests before your own?

YES **NO**

If yes, please provide an example……

……

5. Have you ever been generous and selfless to another person?

YES **NO**

If yes, please provide an example……

……

6. Have you ever attended to the needs of another person? **YES** **NO**

If yes, please provide an example……

……

7. Have you ever tried to not hurt the feelings of another person? **YES** **NO**

If yes, please provide an example……

……

8. Have you ever felt satisfied when you've helped another person? **YES** **NO**

If yes, please provide an example……

……

9. Have you ever gone out of your way to help your friend even at the expense of your own happiness? **YES** **NO**

If yes, please provide an example……

……

10. Have you ever found ways to help another person who is less fortunate than yourself?

YES **NO**

If yes, please provide an example……

……

Appendix 15. Telephone Feedback Questionnaire

Patient ID: ……..

Date: …….. First contact / Second Contact

1. Have you had a look at the self-help booklet in the past week?
   YES / NO
   (If 'YES', skip to question 2.)

   1.1 What were the reasons for not reading the booklet?
   - A. I have not had time to do it.
   - B. I have forgotten about it.
   - C. I have lost the booklet.
   - D. The booklet was too long.
   - E. The booklet was too complicated.
   - F. I have lost interest in the study.
   - G. Other reason(s):

     ……..

   1.2 Do you intend to read the booklet? Please tell me how much you intend to read the booklet on a scale from 1 to 5, where 1 means you definitely do not intend to read the booklet and 5 means you definitely intend to read it.

Definitely do not intend to				*Definitely intend to*
1	2	3	4	5

   1.3 Will you be able to read the booklet in the next week? If so, can we contact you again in a week's time? When is the best time to contact you?
   YES / NO
   Best time to contact:…….

2. Overall, how **helpful** did you find the booklet on a scale from 1 to 5, where 1 means not helpful at all and 5 means very helpful?

Not at all helpful				*Very helpful*
1	2	3	4	5

3. Now please think about the different parts of the booklet. For each part, please tell me whether you have read it and how useful you found it, on a scale from 1 to 5, where 1 means not useful at all and 5 means very useful.

Booklet section	Read the section	Usefulness rating
'Understanding Stress'	YES/NO	1 2 3 4 5
'Spot the stressors in your life'	YES/NO	1 2 3 4 5
'Clarify your values and priorities'	YES/NO	1 2 3 4 5
'Ways of coping'	YES/NO	1 2 3 4 5
'Coping with stressful thoughts'	YES/NO	1 2 3 4 5
'Coping with stressful feelings'	YES/NO	1 2 3 4 5
'Coping with a stressful lifestyle'	YES/NO	1 2 3 4 5
'Take action'	YES/NO	1 2 3 4 5
'Getting more help'	YES/NO	1 2 3 4 5

4. What did you like the most about the booklet?

……

……

5. What did you like the least about the booklet?

……

……

6. Which particular coping technique did you like the most?

……

……

7. How likely are you to **use at least one of the coping techniques from the booklet in the future** on a scale from 1 to 5, where 1 means you are very unlikely to use any of the techniques and 5 means you are very likely to use at least one of the techniques in the future?

Very unlikely				*Very likely*
1	2	3	4	5

8. Would you **recommend the booklet** to other people with seizures? Please tell me how much you would recommend it on a scale from 1 to 5, where 1 means you would definitely not recommend the booklet and 5 means you would definitely recommend it to other people with seizures.

Definitely not recommend				*Definitely recommend*
1	2	3	4	5

9. Do you have any other comments or feedback about the booklet?

……

……

……

……

……

……

Appendix 16. European Quality of Life – 5 Dimensions Scale (EQ-5D)

EQ – 5D

Under each heading, please tick the ONE box that best describes your health TODAY

MOBILITY

I have no problems in walking about ❑
I have slight problems in walking about ❑
I have moderate problems in walking about ❑
I have severe problems in walking about ❑
I am unable to walk about ❑

SELF-CARE

I have no problems washing or dressing myself ❑
I have slight problems washing or dressing myself ❑
I have moderate problems washing or dressing myself ❑
I have severe problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

PAIN / DISCOMFORT

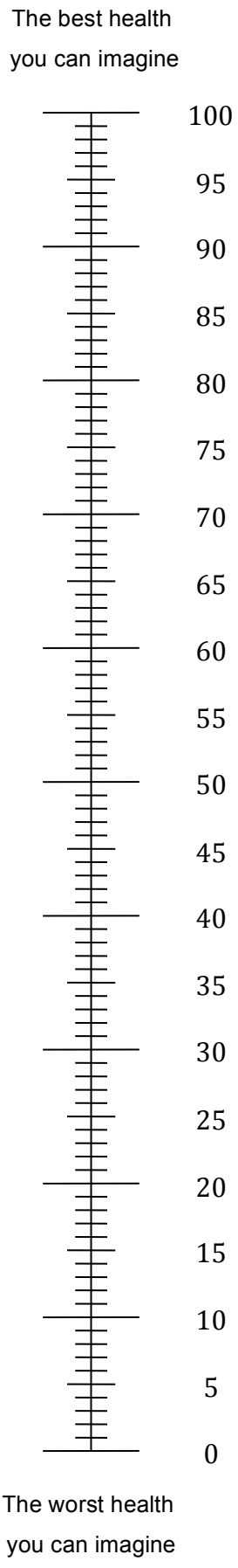
I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



Appendix 17. Seizure Diary

Seizure Diary

Instructions: Please complete the first line of this diary with the name of the month and year. Mark each seizure you have with a cross on the appropriate date. (Example: write "January" and "2014" in the grey box at the top of the table and make the mark "XX" in line 5 if you have had two seizures on January 5th 2014).

Please return this diary to us together with the next set of questionnaires, which will be sent to you by post in one month's time.

Month: **Year:**	**Month:** **Year:**
1	**1**
2	**2**
3	**3**
4	**4**
5	**5**
6	**6**
7	**7**
8	**8**
9	**9**
10	**10**
11	**11**
12	**12**
13	**13**
14	**14**
15	**15**
16	**16**
17	**17**
18	**18**
19	**19**
20	**20**
21	**21**
22	**22**
23	**23**
24	**24**
25	**25**
26	**26**
27	**27**
28	**28**
29	**29**
30	**30**
31	**31**

The University Of Sheffield.

COPING WITH STRESS

A brief self-help guide for people with seizures

This booklet was developed by Barbora Novakova, Professor Peter Harris and Professor Markus Reuber

INTRODUCTION

Everyone has experienced *'stress'* or felt *'stressed'* at some point. Living with seizures can be particularly stressful and people with seizures sometimes find it difficult to cope with the stress in their lives. Too much stress not only has negative effects on physical and mental health in general, it may also make seizures worse.

This booklet provides information and advice about stress and seizures. It will help you:

- Understand more about what stress is, what causes it, how it relates to seizures and what can keep stress going
- Recognise whether stress may be a problem for you and identify the causes of stress in your life
- Overcome your stress by learning new and better ways of dealing with stress

There is no method of managing stress that will work for everyone in every situation. We suggest that you go through the booklet step-by-step, give the different strategies a try and keep going with those that work best for you.

At the end of this booklet, you will find a list of books and websites where you can find additional information about stress and how to handle it. There are also contact details of organisations that can offer further help and support with stress and stress-related problems.

Step 1: UNDERSTAND STRESS

What is stress?

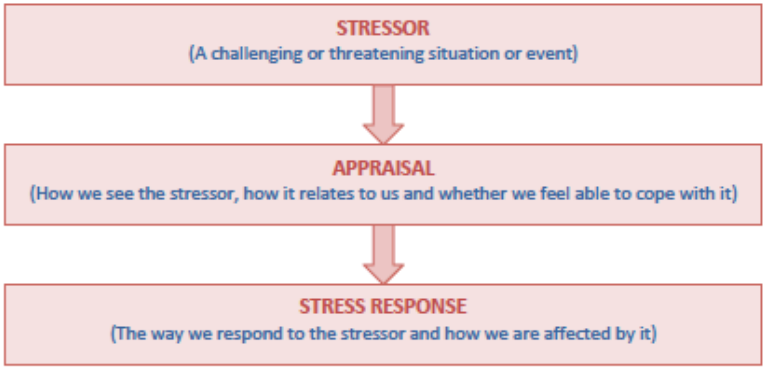
Stress is our response to challenges, threats or pressures. When we are faced with a difficult situation, our brain and glands in our body produce 'stress hormones'. These hormones quickly prepare body parts like the heart, brain and muscles for action. This process is quite normal. The 'fight or flight' response helps us to get ready for the things life throws at us. The 'fight or flight' response is vital for survival.

Of course, these days our survival does not depend so much on fighting or running away. However, the stress response also enables us to stay focused and motivated. Stress only has bad effects on our health when the stress response is too strong or goes on for too long. This sort of harmful stress has been linked to an increased risk of heart disease, stomach and bowel problems, a weakened immune system, anxiety, depression and other health problems.

What causes stress?

People react differently to different situations. The extent to which we experience stress depends on factors in our environment (like how easily we can get help), remote or recent life events (such as the loss of a loved person, divorce or retirement), as well as more minor hassles in our daily lives. In addition, factors like the strategies we use to cope with difficulties, our awareness and understanding of our environment, our mood and health have an effect on how stressed we get.

One important factor, which affects how 'stressed' we feel about something, is what sense we make of it and what it means to us. The process of making sense of the things life throws at us is called 'appraisal'. The model below shows the role of appraisal in stress:



What are the symptoms of stress?

The stress response can take many different forms. It affects our body, the way we feel, the way we think and the way we behave. Any of the following symptoms may be caused by stress:

Your body	Your feelings
• Palpitations • Tense muscles • Hot flushes • Shortness of breath • Sweating • Butterflies in stomach or indigestion • Diarrhoea or constipation	• Crying • Feeling: Irritable or angry Tired Low or depressed Anxious or tense Overwhelmed Emotionally numb
Your thinking	**Your behaviour**
• Trouble concentrating and thinking clearly • Trouble making decisions, poor judgement • Problems with memory • Constant worrying • Being critical and "beating yourself up"	• Increased alcohol or drug use • Changed sleeping habits • Changes in appetite • Isolating yourself from others • Neglecting care of yourself • Snapping at people • Nail biting

How is stress related to seizures?

1. Seizures can cause stress

Seizures can cause stress for different reasons: the seizures themselves can cause a stress response in the body, and living with a chronic illness (such as seizures that keep happening) can be disabling and frustrating. Studies have shown that people with seizures tend to experience more psychological distress than people who do not have to cope with seizures.

2. Stress may cause seizures

It is not clear that stress alone can cause seizures. However, there are a number of ways in which stress can contribute to starting seizure disorders like epilepsy or Non-Epileptic Attack Disorder (NEAD). For instance, it has been shown in animals that early life stress increases the likelihood of developing seizures in later life and some reports suggest that epilepsy and NEAD can develop after stressful or traumatic experiences, such as war or sexual abuse.

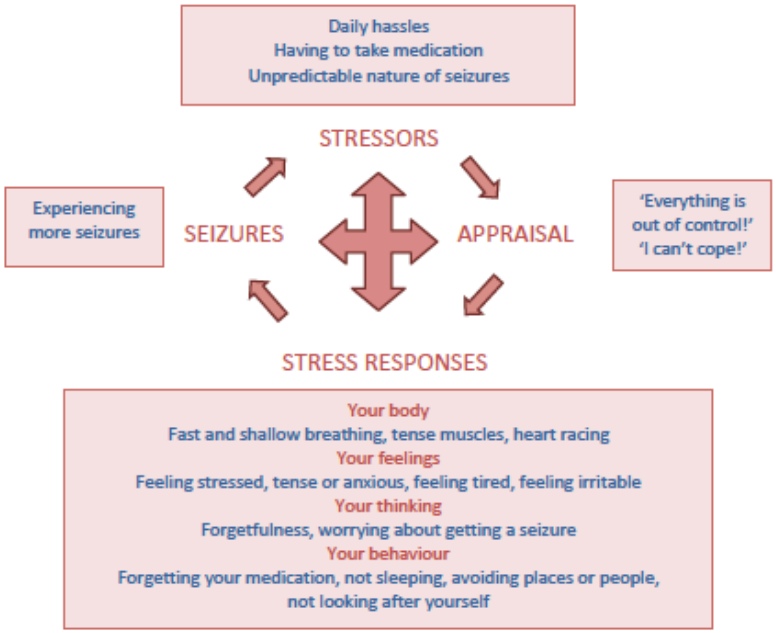
3. Stress can make seizures more likely

Many people who have a seizure disorder think that stress is the most important trigger of their seizures. Indeed, studies have suggested that stressful experiences can increase the number of seizures in some people who have a seizure disorder already.

The way in which stress may cause seizures is not fully understood, but the parts of the brain that regulate the stress response are also often involved in producing seizures, and it is therefore not difficult to imagine how stress could act as a seizure trigger. Many seizures also trigger a stress response in the body. So people may get into a vicious cycle of stress causing seizures, seizures causing stress and so on. In addition, stress is associated with a range of problems that can contribute to seizures, such as lack of sleep, increased alcohol use, anxiety or depression.

People who are stressed appraise the difficulties they face differently. This means that they may not be able to cope with situations when they are stressed which they could handle quite easily when not stressed.

The vicious cycle of stress



Step 2: SPOT THE STRESSORS IN YOUR LIFE

If you want to reduce stress you need to find out where stress comes from in your life. Some people find it difficult to recognise the causes of stress or whether stress is a problem for them. Stress can be associated with major life events and minor everyday hassles.

Are you affected by life events?

Here are some life events that people can find stressful. You will see that not all the events are negative – even pleasant events such as Christmas may be stressful! Read through the list and indicate by ticking the 'I have experienced this' box if you experienced the event in the past year. Also tick whether you found it *stressful* or *very stressful*. You can add your own events at the end of the list.

Life event	I have experienced this	I found this stressful	I found this very stressful
1. Financial difficulties			
2. Pregnancy			
3. Divorce			
4. Separation from partner			
5. Marital/partner problems			
6. Retirement			
7. Unemployment			
8. Made redundant or fired from work			
9. Sexual problems			
10. Serious health problem/injury			
11. Caring for a person with health problem			
12. Illness in a family member			
13. Imprisonment			
14. Ending a relationship			
15. Puberty			
16. Engagement			
17. Broken engagement			
18. Getting back together with partner			
19. Working more than 37.5h a week			
20. Moved house			

Life event	I have experienced this	I found this stressful	I found this very stressful
21. Changes in financial status			
22. Problems with friends			
23. Death of someone close			
24. Problems with relatives			
25. Work-related problems			
26. Birth of a baby			
27. Important achievement			
28. Child started nursery/school			
29. Increased mortgage			
30. Change of job			
31. Difficult relationship			
32. Changed responsibility at work			
33. Going into debt			
34. Legal problem			
35. Going on holiday			
36. Christmas			
37. Change in medication			
38. Experience of seizures in public			
39. Hospital admission			
40. Experience of seizure causing injury			
41. Side effects of medication			
Other important events not listed above			
42.			
43.			
44.			
45.			
Number of **stressful** events I experienced:			
Number of **very stressful** events I experienced:			

Now look at the events that you identified as stressful and very stressful. This can give you some idea about the type of things that may have been a source of stress for you and the number of stressful events that you have had to cope with. Using this booklet can help you improve how you cope with stressful events in your life.

What is causing stress in your life now?

It is not only big life events that can cause stress in your life. Smaller everyday hassles and on-going stressors can be just as stressful. Spend a few moments thinking about what other factors are currently causing you stress, including minor everyday events, and list them below:

Current stressors in my life:

Step 3: CLARIFY YOUR VALUES AND PRIORITIES

The same stressors affect different people in different ways. Research has shown that people who are aware of their values and principles and who know what really matters to them get less stressed about the problems life throws at them. Before you learn more about how you can manage your stress better, spend a few minutes thinking about your values and priorities.

One way to think about your values is to draw a 'value diagram'. (This may seem like an odd thing to do, but several studies have shown that this little exercise really works.)

- Draw a circle with yourself in the centre.
- Then think of your important values. Focus on the things that really matter to you in life, such as your work, your family or friends, your political or religious beliefs, artistic or athletic skills, and link them to the circle.

Example:

Your value diagram:

- Now think about which of these things is most important to you and write it down.

  What's most important to me is: _____

- Try to write one or two sentences about this in the space below. Below are some prompts that may help you.

Why is it important to you?
Can you describe how it makes you feel about yourself?
Can you describe a time when you said or did something that shows how much it really matters to you?

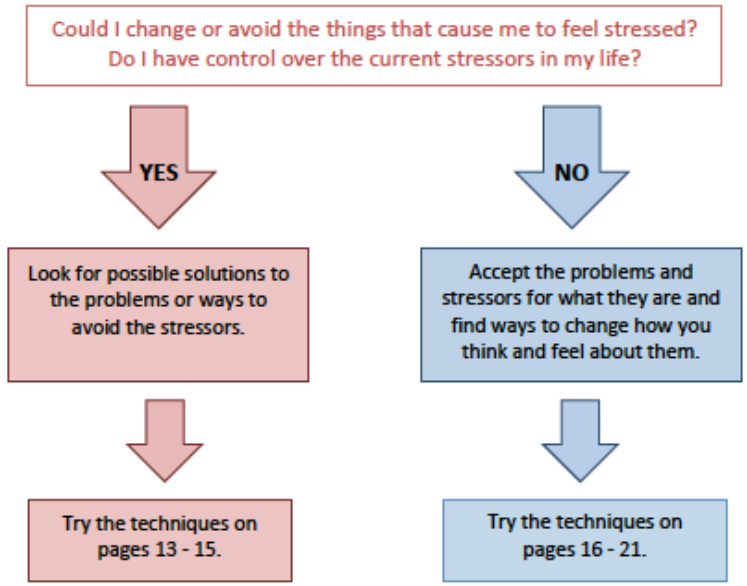
Step 4: COPE MORE EFFECTIVELY

Stress is inevitable. However, you often have some control over the way you deal with it. There are many different ways of coping. Everything that you do in response to a stressful situation is part of how you cope with it (even pulling your hair out!).

Some ways of coping are healthier and work better than others. There are many different strategies and you will need different coping strategies for different situations. Nevertheless, all coping strategies require *action* and *change* - you can either change the stressful situation or stressor, or change your reaction to it.

Could you start making some changes today?

In the following sections, you will find a number of coping strategies that can help you deal with the stresses in your life and your responses to them. To help you decide which strategies might work best for you, think about the current stressors in your life that you have listed on page 9 and ask yourself the following questions:



WAYS OF COPING

When we are having problems that we can't get on top of, we often feel worried or low, instead of looking for solutions. Taking small steps towards dealing with your problems one by one, and coping with the stressors you face can make you feel better and more confident.

Here we suggest some things that can help you to work through your problems, to help you avoid getting overwhelmed.

Strategy 1: Problem-solving

You can improve the way you approach your problems by following the steps below.

1. What is the problem?
Start by writing down what the problem is. Be as clear as you can. If your problem seems too big or complex, break it into smaller problems.
My problem:

2. What could I do about the problem?
Write down every possible solution you can think of, even if it seems silly. Think about how you dealt with similar problems in the past.
Possible solutions:

3. Which solution shall I choose?
Think about advantages and disadvantages of each solution and then choose one to try out.
Solution I will try out:

4. Make a plan
Break your solution down into small steps and plan when and how you will carry them out.
The steps I will take:

5. Take the first step
Try out your solution step-by-step, even if you can only take the first step to solving the whole problem.
The first step I will take is:

6. Take the next steps
What are the next steps that you need to take to reach the chosen solution to your problem?
The next steps I will take:

7. Check whether the plan has worked
Did you manage to solve the problem – are you moving in the right direction? If not, think about what went wrong – do you need to try a different solution? Even if you haven't solved your problem, you are at least facing it and that is likely to lead to a solution eventually!

Strategy 2: Give shape to your day

Having shape to your day can stop your life from feeling chaotic and stressful and will give you a sense of control. Introduce some routine to your day:

- Try getting up and going to bed at the same time every day.
- Find your best time of the day. Are you a morning or an evening person? Do important tasks that need most energy and concentration at the time of the day when you work best.
- Plan ahead. Make a list of things that you need to do the next day or over the next week to stop things from piling up. Try the steps below:
  - Write down everything that comes to mind as a task that needs to be done
  - Think about how important each of the tasks is. What needs to be done today? What can wait? What's the priority?
  - Re-organise your list according to importance. Use a highlighter to mark tasks that are urgent.
  - Look over your list at the end of every day and tick off what you did.

Strategy 3: Practice saying 'No'

Some people feel under a lot of pressure because they are always busy helping others and look after everyone else but not themselves. If you think this may apply to you, think about taking some of the pressure off:

- It is not selfish to sometimes say 'no' when someone asks for help. You have the right to be in control of your life.
- There is no shame in asking for support or help. Wanting to do everything yourself can sometimes make you manage less well.
- Think about giving some of the tasks to others. Can other people at work help with some of the things? Can your partner or children help?

COPING WITH STRESSFUL THOUGHTS

Some problems don't have an easy answer or any answer at all. There are some stressors and stressful situations that just cannot be avoided or managed by being well organised.

In the first part of this booklet we talked about 'appraisal' and how it plays an important role in making people stressed. Even if you can't change or avoid the stressor, you can change how you think about it and reduce negative thoughts that lead to worry and stress. Below are some tips on how to manage stressful thoughts.

Strategy 1: Learn to spot stressful thoughts

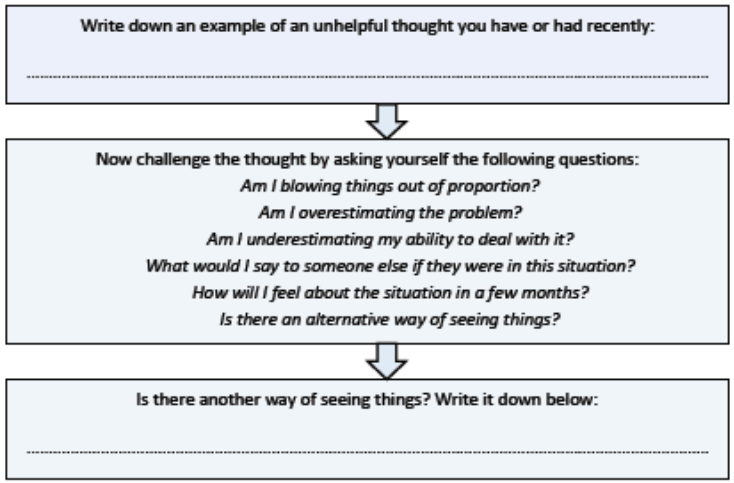
Stress often causes people to have negative thoughts. *'I can't cope with this!' 'Things never go right for me.' 'This won't work out!'* Such thoughts come to our mind automatically and can be quite persistent. They may seem so believable that we don't question them, but they are often unfair and overly critical and only make us feel worse.

The first step in managing unhelpful negative thoughts is to spot them.
Do you recognise any of the patterns below in your own thinking? Put a tick in the 'YES' box next to each one that sounds familiar to you.

Unhelpful patterns of thinking I have experienced		YES
Black and white thinking	Thinking that everything is either perfect or a complete failure.	
Overgeneralising	Believing that if one small thing goes wrong, it must mean that everything else is wrong or that it will go wrong in the future.	
Fortune-telling and catastrophising	Always thinking the worst will happen, blowing things out of proportion and expecting the worst possible outcome.	
Focussing on the negative	Only thinking about negative things, not noticing good things, which have happened to you, or turning them into bad things.	
Mind-reading	Taking things personally, assuming that what another person is thinking about you is bad.	
Should's and must's	Setting standards for yourself which are too high and feeling guilty when you can't live up to them.	

If you have spotted any of these unhelpful thoughts, the next step is to try changing them. You can use the technique below to challenge your bad thoughts.

Strategy 2: Challenge your thoughts



Use this exercise whenever you spot negative thoughts popping into your head. It may be helpful to write the questions from the middle box onto a small piece of paper and carry it with you to look at whenever you start feeling stressed.

Strategy 3: Take control over your worries

Experiencing stress as well as having seizures and the uncertainty that surrounds them can make you worry too much. This in turn causes more stress and anxiety. Use a similar technique to the one above to deal with your worries. Check for unhelpful negative thoughts. Are you fortune-telling and expecting catastrophes?

- Challenge your worries by asking yourself:
  - *How often have I had a worrying thought and it turned out not to be true?*
  - *What are the chances of this worry actually coming true?*
  - *What are other possible outcomes apart from bad things?*
- Set aside one time of day for worrying; don't spend the whole day doing it.
  - When you notice you're worrying, tell yourself you will worry about it later.
  - Choose a time when you allow yourself to worry for 15 minutes, not longer.
  - Only spend the time worrying if you still feel you need to worry.

COPING WITH STRESSFUL FEELINGS

Strategy 1: Learn to relax

We can get 'wound up' and tense when we are feeling stressed. Some people find that they are more likely to get a seizure when they are feeling tense. Regular relaxation can release some of the tension. One effective relaxation technique involves tensing and releasing different muscles.

- You can use the audio CD enclosed with this booklet to practice this muscle relaxation technique. You should aim to practice it everyday to improve your overall level of relaxation and reduce any stress you may be feeling.
- You should listen in a familiar place where there are no distractions. You should be sitting comfortably. An armchair is ideal. Sit with both hands in your lap. The exercise will take about fifteen minutes. At the end of the exercise, take a few moments to 'wake up' by moving and stretching hands, arms fingers and toes.
- You can choose between two different voices that will talk you through the relaxation exercises. One voice is male, the other female. Please use the voice you are most comfortable with.

Please note: Occasionally relaxation makes some people feel anxious or restless, if this occurs do not worry. Try to wake yourself up and stop using the relaxation CD.

Strategy 2: Controlled breathing

When we are stressed, our breathing becomes quick and shallow. This can cause us to feel anxious and it can also increase the likelihood of a seizure. Deep controlled breathing is a way of getting control over your breathing to help you calm down. Practice this exercise and use it whenever you start to feel stressed or when you might go into a seizure.

- Use a comfortable, quiet room.
- Count 'one, two, three' as you breathe in. Think 'relax' as you breathe out.
- Focus your attention on breathing and counting.
- Use a normal rate and depth of breathing.
- Keeping your chest relatively still, expand the bottom of your stomach (below your navel) as you breathe in and pull your stomach in as you breathe out, trying to breathe all the air out of your lungs.
- Count up to 10 breaths and then count backward down to 1.

If at any time you feel 'funny' or dizzy, you should stop practicing straight away.

Strategy 3: Take time out

You can use this method in any situation that makes you feel stressed or anxious. Try taking a few moments out of the stressful situation to go to a relaxing place in your mind:

- Think about a place you have been where you felt happy and relaxed. It might be somewhere you have been on holiday or a special place in your home. It should be somewhere where you have felt calm and at peace.
- Picture that place clearly and think about what you can see there, what you can hear and how it smells. Get the image fixed in your mind so you can call it up whenever you like.
- Whenever you are in a stressful situation, imagine yourself opening a door, which takes you to this place. In your mind picture yourself stepping into this place and soak up the atmosphere, feel the relaxation wash over you.
- You just need to do this for a few moments, and then return to where you were or what you were doing before.

Strategy 4: Grounding exercise

This exercise can help you calm down and stay focused when you are feeling overwhelmed by stress. Use this technique whenever your feelings start getting out of control or when you feel a seizure is about to start.

- Say the following aloud:
  'Right now I am feeling .....'
  (Insert the name of the current emotion, e.g., anxious, angry, overwhelmed)
  'And I am sensing in my body .....'
  (Name at least 3 sensations, e.g., sweaty hands, thumping heart, tense muscles)
- Then concentrate on rubbing something rough or textured with your hands. Use your sense of touch to really focus on the sensations in your fingers and thumbs as you rub. At the same time be aware of how the ground feels solid under your feet or the chair you are sitting on feels beneath you.
- Look around and describe to yourself in detail some of the things you can see.
- Listen to the sounds around you and describe to yourself any sounds you can hear.

Strategy 5: Take a break

It is important to make time for yourself and the things you enjoy. Try going for a walk, listening to music, anything that will distract you from the negative feelings.

Strategy 6: Connect with others

Spend time with people who can support you. Talking to people about your feelings and the things you are finding difficult can give you a great relief.

COPING WITH A STRESSFUL LIFESTYLE

Stress causes changes in our behaviour, including problems with sleep or changes in appetite. People drink alcohol or use other drugs to help them deal with stress. This often causes more stress and can increase the risk of seizures. In the long run, people can develop unhelpful habits to help them cope with stress, which can then be difficult to change. However, even small steps towards a healthier lifestyle can greatly reduce your stress levels, have a positive impact on your seizures and make you feel more in control.

Strategy 1: Improve your sleep

Problems with sleep are among the most upsetting effects of stress. Here we offer some tips that can help you cope with bad sleep.

- Before you go to bed:

  Adjust your room. Making your room quiet and peaceful makes you more likely to fall asleep peacefully. Make sure the room is quiet and adjust the temperature so that it's not too cold or too hot. It can also help to keep the room clean, rather than full of clutter.

  Avoid TV and Computers before going to bed. Watching TV or something on your computer before you go to sleep may be relaxing but the bright light from the screen keeps the brain awake.

  Have a bedtime ritual. Many people find it helpful to have a bedtime ritual. It can be just getting into nightclothes, getting into bed with a good book or doing a relaxation exercise.

- When you are lying in bed and struggle to fall asleep:

  Don't panic. Sleeping difficulties can lead to worrying thoughts such as, *'Oh no, if I don't sleep, I won't be able to function tomorrow!'* Worrying, checking the clock and thinking about the hours of sleep you missed will only make you feel more panicky and less likely to fall asleep. Try to remind yourself that you can in fact cope with much less sleep than you think.

  Distract your mind. When you start worrying, it is helpful to distract your mind. Simply counting sheep may not be enough, the distraction needs to be somewhat challenging. Try one of the following:
  - Count backwards from 102 in 3s
  - Recite a poem or a song
  - Choose a colour and list as many things as you can that are of that colour. List them in categories: foods, animals, objects in your house, etc.

  Get up. If you still cannot fall asleep, try getting up. Doing a simple, repetitive activity such as ironing can help make you feel tired again.

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Step 5: TAKE ACTION

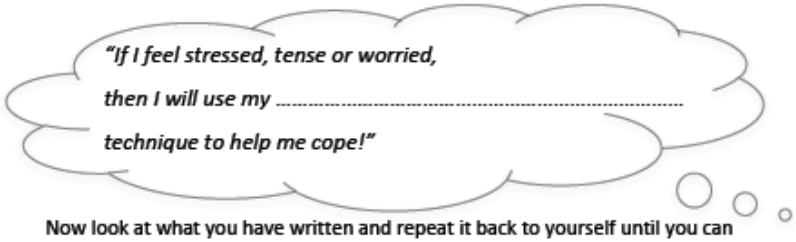
We have suggested a lot of different ways to help you manage your stress and hope that you find at least some of them useful. Changing the way you cope with stressful events can take time and you may find it hard at first to put your new coping activities into practice.

Studies show that you are more likely to succeed if you make a plan for yourself. Below is a list of the coping techniques introduced in this booklet. Pick the one that you found most helpful and write it in the goal plan below the table.

Type of strategy	Techniques	Page
Ways of coping	Problem solving	13
	Give shape to your day	15
	Practice saying 'NO'	15
Coping with stressful thoughts	Learn to spot stressful thoughts	16
	Challenge your thoughts	17
	Take control over your worries	17
Coping with stressful feelings	Learn to relax	18
	Controlled breathing	18
	Take time out	19
	Grounding exercise	19
	Take a break	19
	Connect with others	19
Coping with a stressful lifestyle	Improve your sleep	20
	Watch your diet and alcohol consumption	21
	Exercise	21

Your Goal Plan

Here is an example of a goal plan. Complete the plan by filling the blank space with the coping technique you have chosen from the list above.



Now look at what you have written and repeat it back to yourself until you can remember it word for word without having to read it. This is now your goal plan.

Step 6: GETTING MORE HELP

To get more information about stress or support with emotional and stress-related problems, look at the list below.

If your problems continue despite the use of this booklet and the things listed here, or if you think that you may be depressed, suffering from an anxiety disorder or you have thoughts about harming yourself, please consider discussing your concerns with a health professional. Your GP, your consultant or nurse will be able to offer further support.

Books and CDs

Stress Management: A comprehensive guide to wellness
Edward A. Charlesworth & Ronald G. Nathan
Ballantine Books
A comprehensive guide that helps you to identify the specific areas of your life that are the most stressful and suggests techniques to deal with them

Mindfulness: A practical guide to finding peace in a frantic world (includes a CD)
Mark Williams & Danny Penman
Rodale Books
A book based on the principles of Mindfulness-Based Cognitive Therapy containing a set of simple practices that can be incorporated in daily life to help reduce stress, anxiety, unhappiness and mental exhaustion

The Relaxation and Stress Reduction Workbook
Martha Davis, Elizabeth Robbins Eshelman & Matthew Mc Kay
New Harbringer
A source of stress reduction strategies and step-by-step techniques for calming the body and mind

Applied Relaxation Training (Audio CD)
Matthew Mc Kay & Patrick Fanning
New Harbringer
An audio program that offers a set of techniques you can use to relax in the face of daily stressors: when driving, while working or anywhere else you develop tension during the day

Thoughts and Feelings: Taking control of your moods and your life
Matthew Mc Kay, Martha Davis & Patrick Fanning
New Harbringer
A mental health workbook that provides you with 20 techniques based on cognitive behavioural therapy (CBT) that can be combined into a personalised plan for

overcoming emotional and behavioural concerns and regaining control over your moods and emotions

Overcoming Stress: A self-help guide using Cognitive Behavioural Techniques
Lee Brosan & Gillian Todd
Robinson
A guide based on CBT methods that can help you recognise the common sources of stress, what happens when under stress and how to change the way you think, feel and act so that your life becomes more enjoyable and effective

Why Zebras Don't Get Ulcers
Robert M. Sapolsky
St. Martin's Press
A comprehensive guide to stress, stress-related diseases and coping, which uses insights from scientific research to explain the responses to stress and their effects on physical and mental functioning. It also provides practical advice and guidance on how to control and manage our stress responses

On-line resources

Mind Tools – www.mindtools.com
A website containing simple techniques and practical skills to help you become more effective - includes a section on stress management with a lot of useful information about stress and a number of different coping strategies

GET Self Help - www.getselfhelp.co.uk
A website offering self-help information, resources and worksheets based on CBT to help with a range of mental health problems, including stress

Mood-Juice - www.moodjuice.scot.nhs.uk
A website with regularly updated self-help guides on mental and emotional health problems, including stress, sleeping problems, anxiety, panic, depression, or addiction. Some of the materials are based on Cognitive Behavioural Therapy principles

WebEase (Web Epilepsy, Awareness, Support and Education)
www.webease.org/Overview.aspx
An interactive on-line self-management program for epilepsy consisting of modules focused on stress, medication and sleep management that includes online journal to track your seizures, stress, medication and sleep patterns, and provides personalised feedback

Non-epileptic Attacks - www.nonepilepticattacks.info
A website containing information for people with non-epileptic attacks and their families, including a section with useful self-help tips and strategies.

NHS Website – www.nhs.uk
The 'Live Well' section of the NHS Choices website, as well as the 'Change4Life' pages offer detailed information about healthy lifestyle, including:

- Food and diet
  http://www.nhs.uk/LiveWell/Goodfood/Pages/goodfoodhome.aspx
  http://www.nhs.uk/Change4Life/Pages/healthy-eating.aspx
- Alcohol
  http://www.nhs.uk/Livewell/alcohol/Pages/Alcoholhome.aspx
  http://www.nhs.uk/Change4Life/Pages/drink-less-alcohol.aspx
- Fitness
  http://www.nhs.uk/Livewell/olympics/Pages/Trainingtips.aspx
  http://www.nhs.uk/Change4Life/Pages/be-more-active.aspx
- Sleep
  http://www.nhs.uk/Livewell/insomnia/Pages/bedtimeritual.aspx

Useful Contacts

NHS Direct
Tel: 0845 46 47
Website: www.nhsdirect.nhs.uk

Mind, the mental health charity
Tel: 0300 123 3393
Website: www.mind.org.uk

Samaritans
Tel: 08457 90 90 90
Website: www.samaritans.org

Breathing Space
Tel: 0800 83 85 87
Website: www.breathingspacescotland.co.uk

International Stress Management Association (ISMA)
Tel: 0845 680 70 83
Website: http://www.isma.org.uk

FINAL POINT TO REMEMBER

Remember that you are less likely to get stressed if you are clear about your values and principles and the things you really care about.

Look at your value diagram and your answers on pages 10 - 11 of this booklet and remind yourself of the things that really matter in your life.

Reminding yourself of your most important values when you are feeling stressed can help you put the stressors you face into perspective.