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Diurnal patterns and relationships between physiological and self-reported stress in patients with epilepsy and psychogenic non-epileptic seizures

Barbora Novakova [a,*], Peter R. Harris [b], Markus Reuber [a]

[a] Academic Neurology Unit, University of Sheffield, Royal Hallamshire Hospital, Glossop Road, Sheffield, S10 2JF, UK
[b] School of Psychology, University of Sussex, Sussex House, Falmer, Brighton BN1 9RH, UK

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ABSTRACT

Purpose: Patients with epilepsy and those with psychogenic non-epileptic seizures (PNES) experience high levels of stress and stress is one of the most frequently self-identified seizure precipitants. Although stress is a multifaceted phenomenon, few studies have systematically examined its different components in patients with seizures. The aim of this study was therefore 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 in order to improve our understanding of the mechanisms underlying stress and seizure occurrence in these patients.
Method: A range of stress markers including self-reported stress, salivary cortisol, and heart rate variability (HRV) were explored in adult patients with refractory epilepsy ($N = 22$) and those with PNES ($N = 23$) undergoing three- to five-day video-telemetry.
Results: A diurnal pattern was observed in the physiological measures, characterized by higher levels of physiological arousal in the mornings and lower levels at night in both patients with epilepsy and PNES. The physiological measures (cortisol and HRV) were associated with each other in patients with epilepsy; no close relationship was found with self-reported stress in either of the two patient groups.
Conclusion: The findings contribute to and expand on previous studies of the patterns of stress in patients with seizures. The results also indicate a discrepancy between patients' physiological responses and their subjective stress perceptions, suggesting that simple self-reports cannot be used as a proxy of physiological arousal in patients with seizures and stress. Stress in these patient groups should be studied using a combination of complementary measures.

1. Introduction

Epilepsy, characterized by recurrent seizures, is one of the commonest disabling neurological disorders [1]. Long-term antiepileptic drug treatment controls seizures in 60–65% of patients; however, seizures in about one-third of patients do not respond to medication [2]. Unless seizures are controlled altogether, patients' quality of life is related less to the frequency and severity of seizures than to psychosocial factors, such as social isolation, depression, and anxiety [3].

Psychogenic non-epileptic seizures (PNES) are episodes of involuntary alteration of consciousness and disturbance of motor, sensory, autonomic or cognitive functioning that superficially resemble epileptic seizures but that are not caused by epileptic activity in the brain [4]. PNES are interpreted as an experiential and behavioral reaction to arousal triggered by internal or external stimuli [5]. Ten to twenty percent of patients newly presenting in seizure clinics with transient loss of consciousness have PNES [6]. Most patients with PNES meet the diagnostic criteria of conversion or functional neurological symptom disorder in the Diagnostic and Statistical Manual of Mental Disorders (DSM-V) [7] and dissociative disorder in the International Classification of Diseases (ICD-10) [8].

High levels of self-perceived stress have been found in both epilepsy and PNES [9,10]. This may be due to elevated rates of psychiatric comorbidities such as depression and anxiety and the disabling effects of living with a chronic condition, but may also be related to the experience of recurrent ictal events and the significant physiological arousal associated with epileptic or non-epileptic seizures [11–14]. Many studies have demonstrated that patients with epilepsy report stress as the commonest trigger of their seizures [15], and it is biologically plausible that the pathophysiological effects of stress on the neuroendocrine and immune systems contribute to the development and exacerbation of epilepsy [16]. Stress should be even more relevant in PNES, if PNES are a behavioral or dissociative response to emotional, physiological or social distressing triggers [17,18].

Stress is a complex and multifaceted phenomenon comprising a range of interacting autonomic, endocrine, immune, cognitive, affective, and

* Corresponding author.
E-mail address: barborkanovakova@gmail.com (B. Novakova).

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behavioral processes. The physiological stress response is mediated by the neuroendocrine system, with its two main components, the hypothalamic–pituitary-adrenocortical (HPA) axis and the sympathetic-adrenomedullary (SAM) system [19]. The activity of the HPA axis is characterized by a hormonal response in which the hypothalamus increases secretion of corticotropin-releasing hormone (CRH), 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). Cortisol levels are one of the most frequently used markers of acute stress reactivity as well as a measure of exposure to long-term stress [20]. Cortisol secretion has a well-established circadian pattern, with circulating levels of cortisol typically highest within 1 h of awakening and declining throughout the day to reach very low or undetectable levels around night-time sleep onset. Cortisol levels then begin to increase again between 2.00 and 4.00 am [21]. Long-term exposure to stressors is associated with a chronic elevation of cortisol and a diminution of this natural diurnal fluctuation [22,23]. Disruption of the circadian cortisol rhythm has also been found in conditions such as depression and chronic fatigue, and is associated with increased cardiovascular risk [21,22].

The effects of corticosteroid hormones on seizure occurrence have mostly been investigated in animal models, suggesting that physiological stress as reflected by elevated corticosteroid levels may exacerbate epileptiform activity (or its effects) in the brain [15,24]. There is only limited evidence about the interactions between epilepsy and the circadian rhythms of cortisol. A number of studies have investigated cortisol levels in patients with epilepsy and found elevated cortisol levels postictally but no differences in baseline levels between patients and healthy controls [25].

There is some evidence suggesting the involvement of the HPA axis in the pathology of PNES. Patients with PNES, especially those with a history of sexual abuse, have been found to have higher levels of cortisol at baseline than healthy individuals [26]. Cortisol levels of patients with PNES were also elevated in a study of automatic avoidance [27]. Furthermore, levels of baseline cortisol in patients with PNES were positively correlated with an attentional bias to threatening social stimuli [28].

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 [29]. Exposure to a stressful stimulus activates the SNS via release of adrenalin and noradrenalin, causing physiological arousal. Activation of the PNS, mediated mainly by the vagus nerve, is responsible for on-going regulatory and feedback processes. In the initial response to stress, PNS tone is decreased while the most appropriate response to a particular stressor is selected. Because of its accessibility and high temporal resolution, heart rate variability (HRV) is an increasingly utilized marker of ANS activity. Heart rate variability reflects the dynamic influences of PNS and SNS tone on the heart and can be obtained non-invasively from electro-cardiographic (ECG) recordings.

Several studies reported HRV alterations in patients with epilepsy. Compared to healthy controls, patients with epilepsy (especially when seizures are refractory) have been found to have reduced vagal tone both ictally and interictally [12,30–34]. However, few researchers have examined the diurnal patterns of HRV in patients with epilepsy. One study found suppressed circadian HRV characterized by attenuation of the normal night time increase of HRV in patients with temporal lobe epilepsy, compared to healthy controls [35].

The evidence is even more limited for patients with PNES. The previously mentioned study of automatic avoidance demonstrated reduced HRV in patients with PNES at rest [26]. Heart rate variability was also significantly lower in patients with PNES compared to healthy controls in a study of attentional biases [36]. In addition, Ponnusamy and colleagues showed that resting HRV is reduced in both patients with epilepsy and PNES [37].

There is a lack of studies measuring the different modalities of stress in combination or exploring how different physiological and psychological stress measures relate to each other in patients with seizures. Better knowledge of these relationships would be valuable and improve our understanding of the mechanisms underlying stress and seizure occurrence in these patients. This could have useful implications for seizure detection or forecasting as well as the design of therapeutic interventions to reduce stress or seizures. The current study was intended to explore the patterns of physiological and self-reported stress measures across the day and the interrelationships between the different measures.

2. Methods

2.1. Participants and design

This study prospectively assessed daily levels of physiological and psychological stress in consecutive patients undergoing three- to five-day in-patient video-electroencephalographic/electrocardiographic (video-EEG/ECG) monitoring. We recruited adult patients with refractory seizures (epilepsy or PNES) admitted for diagnostic or pre-surgical video-EEG/ECG monitoring at the Royal Hallamshire Hospital in Sheffield. 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. When a seizure had been recorded, the patient's consultant was asked to confirm that the recorded seizure was typical of habitual events and that it matched the patient's ultimate diagnosis, taking account of all clinical information available. Where no typical seizure was recorded, diagnoses were established clinically on the basis of a case review by two consultants specialized in epilepsy, taking account of all available clinical information. All patients in the PNES group had seizures involving impairment of awareness or responsivity (i.e., episodes which could not have represented misclassified panic attacks). Patients whose diagnosis remained uncertain or patients thought to have mixed disorders with epileptic and non-epileptic seizures were excluded from further analyses. The study received ethical approval by the North East Research Ethics Committee Yorkshire & The Humber (August 2013).

2.2. Outcome measures

2.2.1. Baseline measures

Perceived Stress Scale — 4 Items [38] is a short scale developed to measure the degree to which situations in people's lives are perceived as stressful. The scale is a global measure of non-specific stress over the course of the past month, rated on a 5-point scale. The PSS-4 has been used and validated in patients with epilepsy [39,40]. A previous longitudinal study by Thapar et al. used the PSS-4 to measure stress in a large cohort of patients with epilepsy to examine whether stress, anxiety, and depression predict seizure frequency and seizure recency [40]. The mean baseline PSS-4 score in this study was 5.43 (SD = 3.56). The PSS-4 scale demonstrated good internal consistency in the present sample (4 items; alpha = 0.79).

Liverpool Seizure Severity Scale — Revised [41] is a 12-item inventory designed to quantify the severity of patient's seizures. It provides a single-unit weighted scale that measures the severity of the severest seizures the patient has experienced during the past four weeks. The internal consistency in our sample was good (12 items; alpha = 0.85).

Neurological Disorders Depression Inventory for Epilepsy [42] is a 6-item inventory developed to detect depression in patients with epilepsy by assessing common symptoms of depression experienced in the past two weeks that can be differentiated from adverse effects of anti-epileptic drugs. A score of more than 15 on the NDDI-E has 90% specificity and 81% sensitivity for a diagnosis of major depression [42]. The inventory had good internal consistency in this sample (6 items; alpha = 0.80).

Generalized Anxiety Disorder 7-item Scale [43] assesses anxiety symptoms experienced over the course of the past two weeks The GAD-7 has