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Orbitofrontal cortex dysfunction in psychogenic non-epileptic seizures. A proposal for a two-factor model

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ABSTRACT

Psychogenic nonepileptic seizures (PNES) often mimic epileptic seizures and occur in both people with and without epilepsy. Pathophysiology of conversion disorders such as PNES remains unclear though significant psychological, psychiatric and environmental factors have been correlated with a diagnosis of PNES. Many clinical signs that have been considered typical for PNES can also be found in frontal epileptic seizures. Given the resemblance of seizures and affective changes from Orbitofrontal cortical dysfunction to PNES like events and correlation of psychological and environmental stress to conversion disorders such as PNES, we propose a two-factor model for the pathogenesis of PNES. We hypothesize that patients with PNES could have a higher likelihood of having both Orbitofrontal cortical dysfunction and a history of psychological stressors rather than a higher likelihood of having either one or the other. We further explore the implications of this two-factor model, including possible therapies.

Introduction

Psychogenic nonepileptic seizures (PNES) are a behavior pattern mimicking epileptic events without the concomitant EEG pattern of an electrical seizure. The prevalence of PNES in the US has been estimated to be 33 per 100,000 people [1], occurring in both persons with and without epilepsy [2]. The mean incidence of three per 100,000 people per year of PNES is closer to that of multiple sclerosis in the US at 4.2 [1,3]. PNES is therefore a major health concern in need of effective treatment. In this light it is striking that the pathophysiology of conversion disorders such as PNES remains unclear [4].

We propose here a two-factor hypothesis for the development of PNES to focus research efforts towards arriving at a clinically testable model for PNES. We anticipate that this effort would make major factors underlying PNES explicit, leading to increased consistency in the identification and clinical diagnosis of PNES. With the availability of new investigative tools in neuropsychological testing and neuroimaging, it is possible that pursuit of these avenues could be fruitful in the future.

Two-factor hypothesis of the development of PNES

In patients with underlying orbitofrontal cortex (OFC) dysfunction related to self-appraisal of affective stimuli, subsequent psychological stressors mediate the development of PNES symptoms.

Comorbidity of PNES with epilepsy

The diagnosis of PNES is fraught with challenges, as no single pathognomonic clinical feature for PNES exists [5]. Coexisting PNES and epilepsy is noted in about 10–13% of cases reviewed [6]. Further, despite the widespread use of video-EEG, difficulties remain as PNES and epileptic seizures share many similar features: for example, both of these disorders can be associated with convulsions and/or alterations in behavior and consciousness. Auras that are considered a classic feature of epileptic syndromes are also frequently reported in PNES and may be a more common symptom than in epilepsy [19–21]. Many signs such as ictal pelvic thrusting, rocking of body, side-to-side head movements or rapid postictal recovery that have been considered typical for PNES appear not to be specific to it, but can also be found in epileptic seizures, especially in those seizures that originate from the frontal lobe [5,22,23]. Bizarre, hyperactive, frontal lobe seizures or complex partial seizures of frontal lobe origin with complex motor behaviors have often been mistaken for PNES [24]. In an earlier crucial study we noted that during Video-EEG monitoring, patients having

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epilepsy and concomitant PNES, frontal seizures are more commonly noted in patients with epilepsy and concomitant PNES than in those with epilepsy alone [25].

Within the frontal lobes there is significant functional heterogeneity in sub-regions, and these differences are often reflected in frontal seizure semiology [26]. Localization of frontal seizures to sub regions of the frontal cortex are often challenging due to difficulty in accessibility to recording electrodes. It is therefore difficult to currently assess if underlying common shared neural mechanisms exist, between frontal seizures and PNES to explain shared semiology or if the similarities noted are incidental. Despite this, it is worth noting that some published case series point to the propensity of seizures arising from a few frontal areas to mimic PNES phenomena [24,27–29]. Seizures characterized by general motor agitation are known to be associated with lesions of the OFC and frontopolar cortices [27]. Tonic seizures originating in the supplementary motor area have been misinterpreted as being psychogenic as they present with brief bilateral tonic activity without the loss of consciousness [24]. PNES have been noted to occur almost immediately after epileptic seizures, suggesting that the experience of having a seizure can in susceptible individuals provoke PNES [28,29].

Among both epilepsy and PNES patients, an early age of onset and more frequent 'seizure events' correlates with the severity of frontal executive deficits [30]. PNES subjects have also been noted to have higher emotional dysregulation and compulsivity personality traits than healthy controls. Similar behavioral correlates of hyperactivity, obsession, and addiction can also be seen in frontal lobe epilepsy [6,7,12,31]. These findings prompt us to consider reasons why PNES and epilepsy populations share many common markers of neural dysfunction relating to the frontal lobe.

Is there a common focus of neuronal dysfunction in PNES?

Epilepsy is related to neuronal dysfunction, while PNES is thought to have psychological and environmental causes. The high prevalence of depression in epilepsy patients has prompted an interest in elucidating whether underlying neurochemical abnormalities make some neuroanatomical structures more vulnerable to the development of a seizure disorder [32]. The occurrence of PNES in many cases almost immediately after epileptic seizures [28,29] also suggests shared neuronal vulnerabilities that could potentially trigger PNES. Shared vulnerabilities between frontal lobe seizures and PNES have also been noted across many studies [5,22–26,31]; a higher frequency of frontal seizures is reported in patients with epilepsy and concomitant PNES [25], a close correspondence of PNES seizure semiology to frontal seizures [5,22–24], and similarities in the psychological and personality profile of frontal lobe seizures and PNES [31].

Furthermore, on neuropsychological tests, patients with PNES have performed worse than normal healthy controls but roughly the same as patients with epilepsy with known neuronal pathology [33]. Even as there is a lack of consensus over the years in the literature regarding specific neuropsychological profile differences between patients with PNES and those with epilepsy [34–37], it has been suggested that this conclusion could be due to many methodological confounds including small numbers of subjects, concomitant use of medications, and/or the presence of additional medical or psychological stressors [38]. However, more recent studies have reported relative deficits in frontal lobe functions of attention and working memory for women with PNES compared to those with left temporal lobe epilepsy [38]. In addition, poor performance on executive function tasks has been observed with an increase in lifetime seizure load among both PNES and epilepsy subjects [30].

Even as previous studies of interictal EEG among PNES subjects have noted nonspecific abnormalities relative to controls [39], a recent small study of interictal EEG noted a prefrontal hypo-synchronisation, suggesting a regional neural dysfunction in patients with PNES [40]. These results raise the question, whether a shared focal frontal neural dysfunction is a common factor in PNES.

Role for environmental and psychological stressors

PNES patients often have a history of developmental insults or trauma that may cause psychological stress exceeding an individual's coping (for reviews, see [4–7]. Stressors causing conversion disorder are thought to underlie PNES [4,6]. Multiple studies have demonstrated a strong correlation between psychological and environmental factors and PNES (for reviews, see [4,6]). Early life trauma and associated post traumatic stress disorder (PTSD) have a higher prevalence in PNES than controls [8], and PNES patients appeared to express dissociative distress about reported trauma [6,9]. A high tendency has also been noted among PNES patients to express psychosocial distress by producing unexplained somatic symptoms that are brought to medical attention [10]. In patients with dissociative disorders, regional cerebral blood flow (rCBF) is decreased in the OFC regions bilaterally suggesting a role for focal neural dysfunction in the OFC as a possible underlying etiology [41].

Psychiatric and personality disorders in PNES

Psychiatric comorbidities including depression, panic disorder with or without agoraphobia, and affective disorders such as chronic anxiety have been observed among PNES subjects. However, it has been noted previously that these psychiatric disorders could be postulated to be either the cause or the consequence of PNES, an epiphenomenon, or a different diagnostic term to describe PNES [6]. The prevalence of borderline personality disorder has also shown to be significantly higher in patients with PNES than in either those with epilepsy or healthy controls [11,12]. Some common traits observed in both PNES and borderline personality disorder subjects include higher prevalence rates of sexual trauma, PTSD, dissociative disorders, somatoform disorders, depressive disorders, and suicide attempts [11–15]. Several behavioral and emotional traits of borderline personality disorder have been observed in patients with PNES. These include anger problems, hostile coping styles, interpersonal problems, emotional instability and dissociation [6,12]. This correspondence between symptoms in these two groups has prompted investigators to suggest that borderline personality disorder might be a possible underlying etiological factor for PNES [9]. As we attempt to examine personality disorders at a neural level, consistent differences from normal controls are now starting to be described in neuropsychological and imaging studies of patients with borderline personality disorder [16]. It is thought that orbitofrontal cortex (OFC) dysfunction may contribute to some core characteristics of borderline personality disorder, in particular impulsivity [17,18]. The OFC appears as a common region of interest in the related conditions of PNES, dissociative disorder and borderline personality disorder.

Positing a role for orbitofrontal dysfunction in PNES

The possible presence of an underlying frontal lobe dysfunction has been suggested in multiple studies on PNES (e.g. [4–6,25,40]). Changes in the fronto-striatal circuits have been postulated earlier to explain some of the neuropsychological deficits seen in PNES patients who share a neuropsychological profile with other