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Psychophysiological biomarkers of dissociation in psychogenic non-epileptic seizures

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Abstract

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

Key words: Psychogenic non-epileptic seizures; Dissociation; (Functional) Magnetic Resonance Imaging; Cardiovascular functioning; HPA-axis.

Introduction

Psychogenic non-epileptic seizures (PNES) are epilepsy-like episodes of movement, sensations or behaviours that resemble epileptic seizures, but are not accompanied by epileptiform brain activity as seen on electroencephalogram (EEG). The underlying cause is assumed to be psychological; the episodes may be the somatic manifestations of emotional distress (1). PNES is one of the most important differential diagnoses of epilepsy, and most patients with PNES are initially misdiagnosed as having epilepsy. The average period between the onset of seizures and the diagnosis of PNES is typically more than 6 years (2). Misdiagnosis as epilepsy for patients with PNES has serious consequences for the patient, such as exposure to unnecessary anticonvulsant medication, and considerable delay to start the appropriate psychological therapy. In addition, a substantial economic burden is involved, as erroneous treatments for intractable epilepsy are expensive (3). Evaluating the information described above, it is clear that differential diagnosis of PNES is clinically relevant. However, if the emphasis is only on excluding epilepsy, PNES may become a non-disease (4). A positive diagnosis is necessary for appropriate treatment, therefore, the underlying mechanisms must be evaluated and results must be implemented in treatment. To gain more insight in the underlying mechanisms of psychogenic seizures, it is necessary to identify not only causal factors, such as traumatic experiences, but also predisposition factors, which elucidate why certain persons develop PNES symptoms after trauma and others do not. Such predisposition factors may be of influence in the stages of vulnerability, shaping, provocation and prolongation of PNES pathology, and have to be identified in order to organize an explanatory model of PNES.

An important predisposing factor for PNES is the tendency to dissociate (1, 5). The process of dissociation is a disruption of the usually integrated functions of identity, memory, consciousness or perceptions of the environment. It is regarded as a

psychological defence mechanism from stressful events, by altering conscious experience (6). Others assume dissociation to be a constitutional mental weakness that is activated by adverse events (7). Dissociation is closely related to the process of hypnosis and essentially shows the ability to take distance from reality. People differ in their tendency to dissociate. The tendency to easily dissociate is considered an important factor in the provocation and possibly also the prolongation of PNES (8).

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

Methods

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

Results

Structural MRI abnormalities

Magnetic Resonance Imaging (MRI) of the brain provides the opportunity to investigate cerebral changes in a number of fundamentally different ways (9). Structural MRI is one of the techniques most often employed for detection of anatomical brain abnormalities. Some investigations have related PNES with structural MRI abnormalities. For example, Reuber *et al*. (10) found structural brain abnormalities more commonly in PNES patients than in the general population. They investigated the proportion of PNES patients having neurological abnormalities on structural magnetic resonance imaging, and found that 27 percent of PNES patients and 78 percent of patients with PNES and epilepsy showed anatomical irregularities. A wide variety of abnormalities was found in the PNES only group, including – in order of frequency – postoperative defects, arachnoid cyst, posttraumatic changes, generalized atrophy, gliotic change, white matter lesions, hippocampal sclerosis, and venous angioma. Abnormalities in the PNES plus epilepsy group included hippocampal sclerosis, postoperative defects, migration disorders, signs of previous stroke, gliosis, posttraumatic changes, hemiatrophy, white matter lesions, tumor, cavernoma, and venous angioma.

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

Functional MRI abnormalities

Quantitative information about structural brain abnormalities provides minimal insight into functional organization and reorganization in patients with PNES. To investigate whether deviations in functional brain architecture are predictive of dissociation in patients with PNES, functional imaging is essential. Functional Magnetic Resonance Imaging (fMRI) is a technique frequently used to explore the relationship between brain activation and cognitive functioning. It measures changes in the blood-oxygen-level dependent (BOLD) signal, which are assumed to accompany neural activity in the brain (14). Functional MRI abnormalities have been demonstrated to be related to abnormal information processing in several mental conditions, for example schizophrenia (15, 16), panic disorders (17), and bipolar disorder (18).

Until now, functional MR imaging techniques have not extensively been used to explain deviant neuronal processing in patients with PNES. However, some investigations have explored the relationship between hypnosis, a process closely linked to dissociation, and altered functional MRI

characteristics. In a functional MRI investigation of McGeown *et al*. (19), the authors demonstrate that induction of hypnosis in highly suggestible individuals causes decreased cerebral blood flow in the anterior parts of the default mode network during rest. Other authors, for example Egner *et al*. (20) and Raz *et al*. (21), have also associated decreased activation of frontal structures such as the anterior cingulate cortex (ACC) with high suggestibility. Because the process of hypnosis appears to be related to dissociation, similar activation patterns may be observed in patients with PNES with a high tendency to dissociate.

Brain network abnormalities

Cognitive and emotive functions result from the interactions of a number of differently localized brain regions rather than single (isolated) regions. In this context, novel brain connectivity analyses, which examine the integrity of cerebral networks, are most appropriate in evaluating information processing deficits of patients with psychiatric conditions such as PNES (22). For example, fMRI facilitates the assessment of the functional connectivity of regional brain activity, based on correlations in dynamic spontaneous fluctuations (23). This analysis can be applied both on task-related fMRI data, as well as on resting state fMRI (rs-fMRI) data where no explicit stimuli are presented (24). In addition, network analysis of diffusion tensor imaging (DTI) data, using measures of water directionality and diffusivity, can provide information regarding the integrity of structural connectivity of the entire brain (25).

Cardiovascular dysfunctioning

It is hypothesized that patients with PNES (almost) continuously experience high levels of emotional stress. Emotional stress has been proven to be accompanied by physiological changes like increased heart rate, blood pressure, respiration rate and muscle tension, and decreased heart rate variability (HRV) (26, 27). Heart rate variability in particular is a measure of interest, because it reflects the functioning of the parasympathetic autonomic nervous system, the system responsible for stimulation of activities that occur when the body is at rest. Heart rate variability may be decreased in patients with PNES, suggesting a state of hypervigilance. Indeed, Bakvis *et al*. (28) have examined the cardiovascular functioning of patients with PNES, and found that patients with PNES show lower HRV during baseline and recovery of stress compared to healthy controls. However, their study had an experimental design; ambulatory measurements during daily life (comprising psychogenic non-epileptic seizures) would provide additional and ecological valid information about the level of emotional arousal and cardiovascular condition of patients with PNES.

Abnormal neuroendocrine functioning

An increased state of threat vigilance was also confirmed with endocrinal measurements by Bakvis *et al*. (29), who confirmed a state of hypercortisolism in patients with PNES. Increased cortisol levels are assumed to reflect greater activity of the hypothalamic-pituitary-adrenal (HPA) axis, a major part of the neuroendocrine system that controls reactions to stressors and regulates many body processes including mood and emotions (30, 31). The HPA-axis has been proven to be involved in the neurobiology of mood disorders such as anxiety disorder (32, 33), bipolar disorder (34, 35), post-traumatic stress disorder (36), borderline personality disorder (37), and major depressive disorder (38, 39). Antidepressants, which are routinely prescribed for many of these disorders, serve to regulate HPA axis function (40). Recently, a pilot randomized controlled trial with Sertraline (a serotonine selective reuptake inhibitor) suggests this pharmacotherapy to be effective for seizure reduction, confirming involvement of the HPA-axis in the aetiology of PNES (41).

Conclusion

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

Moreover, finding a neurobiological substrate of dissociation in PNES would change the concept of

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

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

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