Psychogenic Non-Epileptic Seizures

A review of imaging studies and their contribution towards establishing a PNES pathology

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ABSTRACT

Introduction:
Psychogenic nonepileptic seizures (PNES) are episodic, time-limited alterations in motor, sensory, autonomic, and/or cognitive signs and symptoms. PNES are considered to be psychogenically determined and are not caused by epileptiform brain activity. Moreover, PNES are associated with several psychopathological traits, and trauma experience is considered to play a role in the development. However, the neurobiological mechanisms are poorly understood, and diagnosing and treating PNES remains a challenge. This review aims to assemble information from neuroimaging studies on the causality and development of PNES pathology, including key structures and neuronal networks related to PNES.

Methods:
A literature search was performed in PubMed, looking for original neuroimaging studies aiming to identify neuronal structures and networks involved in PNES.

Results:
The literature search yielded a total of 14 original studies using MRI, fMRI, PET and EEG. Alterations were described in neuronal networks mediating emotion processing, attention, executive control and motor function. In particular, abnormalities in the prefrontal cortex are described, as well as possible hyperlinks between insula and motor cortices. Key structures identified include the orbitofrontal cortex, bilateral cerebellum and insula. Plasticity of functional connectivity is considered to be involved in the pathogenesis of PNES.

Discussion:
The study findings are limited by small study populations and possible confounding factors, due to lack of registration of/control for psychopathological traits. However, the preliminary results point at several key regions for further investigation and offer explanatory models to the symptoms experienced in PNES patients. The role of trauma in PNES development also warrants further investigation.
1. INTRODUCTION

1.1. What are psychogenic nonepileptic seizures?

1.1.1. Definition
Psychogenic nonepileptic seizures (PNES) are paroxysmal time-limited motor, sensory, autonomic, and/or cognitive signs and symptoms. Although resembling epileptic seizures, PNES are not caused by ictal epileptiform activity (1). In recent guidelines, PNES are understood to be psychogenically determined (2), and the diagnosis is categorized as a psychiatric disorder. In the Diagnostic and Statistical Manual of Mental Disorders, DSM-IV, PNES is allocated under conversion disorder, while in the ICD-10 PNES is allocated under dissociative disorders, as dissociative convulsions. Other explanatory medical causes must be excluded, and psychological stress factors are considered related to the aetiology (1, 3).

1.1.2. Epidemiology
PNES prevalence is estimated to be 2-33/100,000 (2). It is estimated to be the diagnosis in 5-25% of patients referred to outpatient epilepsy centres, and 25-40% of patients evaluated in inpatient monitoring units for intractable seizures (2). Research on PNES suggests that it is a global condition, not limited to specific regions or cultures, with comparable semiological descriptions (1). Furthermore, PNES is not considered correlated to race, marital status or years of education (2). There is a predominance of female patients (66-99%). Onset of PNES is most frequently observed in the 3rd decade of life, but it has been described in most age groups (2).

1.1.3. Making the diagnosis
To diagnose PNES is a challenge, due to the heterogeneity of the events and lack of specific markers. There are no pathognomonic clinical features for PNES (4). The most common manifestation of PNES is unresponsive behaviour with motor manifestations, mimicking a generalized convulsion or a complex partial seizure, and less than one event per week is considered uncommon. (2). Patients frequently report altered consciousness and loss of self-agency, and PNES is considered to be beyond voluntary control (5). Epilepsy must be excluded, which is complicated by the fact that at least 10% of PNES patients have coexistent epilepsy (6). In particular, frontal lobe epilepsy has similar semiology as PNES.

The average diagnostic delay is 7 years (7), but has been reported as high as 9-16 years (2). The gold standard for diagnosing PNES is long-term video-EEG, with registration of a spontaneous or provoked seizure, agreed upon by the patient and/or observers to be typical for the patient’s events (1). A detailed history of the events from the patient and observers, physical examination and other selected testing methods are also important features in the diagnostic path (2). Misinterpretation of the medical history and/or EEG-data is a common source for misdiagnosing PNES (1).

1.1.4. Related traits
A psychiatric evaluation is recommended, as PNES are associated with other psychopathological conditions which could be in need of treatment (2). Depression, anxiety, dissociative disorders, somatoform disorders, PTSD and personality disorders (cluster B) are all found to be strongly associated with PNES. Other traits, such as alexithymia, arousal tolerance, hypervigilance and avoidance tendencies are also considered to participate in the development (7). In addition, a
history of sexual or physical abuse is described in 33-50% of PNES patients (2), but have been reported as high as 50-77% (7). One study reported a correlation between avoidance strategies and low HRQOL in PNES patients (5).

1.1.5. Treatment and prognosis
Psychiatric interventions remain the hallmark of treatment for PNES, with cognitive behavioural therapy (CBT) showing the most promise in reducing PNES frequency and improve psychosocial functioning (2). The diagnostic delay and misdiagnosis of PNES leads to inappropriate treatment of presumed epilepsy with antiepileptic drug therapy. This entails a significant risk of iatrogenic injury and morbidity to the patient, as well as creating costs to the patient and health care system (1). This also delays instigation of appropriate treatment of PNES and related psychopathology. Patients with PNES have reportedly a lower health related quality of life (HRQOL) than patients with epilepsy (8). Only a minority of patients (25-38%) achieve seizure freedom, while children have better prognosis (70-80%) (2).

1.2. Historical background

PNES is currently categorized together with functional neurological disorders (FND) in the DSM-5, under the heading “Functional neurological symptoms disorders” (9). In regard to causality, there is a tension between a psychogenic and an organic causality model, which spans centuries of medical history. This in particular due to the association between these modern day diagnoses and the historically compelling term hysteria. It is important to note that up until the 17th century and partly after, the term hysteria referred to a large set of symptoms (10). The history of PNES is as such not synonymous to the history of hysteria. However it has implication for the understanding of PNES today. In particular, it is relevant as the history offers different answers to the question of whether or not hysteria is a disease like any other with a treatable cause, or if it is a disease apart (11).

Hysteria itself was introduced in medical literature in the 19th century, then as caption headings added in Emile Littré’s (1801-1881) edition of the Hippocratic corpus (11). The diagnosis of hysteria is however not present in the Hippocratic works (12), but conditions resembling the description of PNES is. It is also present in the earliest known medical records 1900 years BC (13). This period, up to the rise of Christianity, constitutes the first of four paradigms of hysteria, bearing in mind that hysteria here is a modern disease concept, retrospectively added to the medical history (13). Hysteria is in this period considered to be completely organic and a disease like any other. The mechanisms involved were all thought to be connected to the female sexual organs: The womb’s free and wild movements within the female body, named “suffocation of the uterus”, the retention of female semen or the drifting of diverse vapours from the womb (11). Episodes can in these conditions occur where the patient according to the Hippocratic texts “(...)grinds her teeth, saliva runs in the mouth and she resembles the epileptics” (11). According to De re medica, a medical work by Celsus from the first century, this illness caused by the uterus can “sometimes sever the consciousness and cause a collapse like in epilepsy”. Causality factors were usually sexual deprivation, and treatment was marital intercourse, odours and other physical measures to keep the womb in place. The patient was, not surprisingly, exclusively female.

In the second paradigm, in the medieval age from year 500-1300, the causality was no longer organic, it was supernatual and very much a disease not like any other. However, the
main subject for the malady continued to be female. Women with unexplained convulsions, among other manifestations, were considered possessed. Demonology became a new explanatory framework, led by the Church. The causality was no less than a consequence of original sin, and prayers and exorcism were among the treatment options (13).

With the dawning of the renaissance at the end of the medieval period, the causality was again shifting towards an organic explanation. This period, entering into the modern era, offers the third paradigm with a neurologic explanatory framework. Neurology and psychology was itself coined as a term by Thomas Willis (1621-1675) in the late 17th century (13). Around the same time, the head was proposed as the origin of hysteria. This opened up for the possibility that hysteria also could apply to men (13). Thomas Sydenham (1624-1689) provided what can be considered the first neuropsychological explanation, observing that seizures were triggered by sudden and violent emotions. The strong emotions were thought to cause an imbalance in the distribution of animal spirits between the body and the brain (13). Sydenham was also allegedly the first to state that hysteria imitates culture (12), thus addressing the heterogenic manifestations of hysteria.

In the late 18th/early 19th century however, a reintroduction of the uterine theory of hysteria took place. This is thought to be a consequence of the contemporary botanical and zoological taxonomic works by Carl Linnaeus (1707-1778) and Comte de Buffon (1707-1788), and a subsequent interest for the classification of diseases. Again, the disease was exclusively female, but now caused by sexual indulgence rather than deprivation as in the first paradigm. The ovulation process was discovered in 1840, offering a new ovarian theory of hysterical disease (13). Treatment options consisted of local physiological procedures, and the occasional amputative and extirpative gynaecological surgeries.

Convinced that hysteria had an organic cerebral cause (14), Jean Martin Charcot (1825-1893) was a prominent person in the neurological paradigm, introducing the term "hystéro-épileptique" (11). He was convinced that hysteria had an organic cause, making it a disease like any other, related to a not yet discovered dysfunction in the central nervous system. He believed hereditary predisposition to be of importance, together with nervous degeneration and environmental "agents provocateurs" (13). As such, he had little belief in an effective cure, only treatment to alleviate symptoms. He hosted the famous Tuesday lessons on "the grand neurosis" at Pitié-Salpêtrière in Paris, where the classical manifestations of hysteria were demonstrated. The patient, most often female, would scream and go pale with a loss of consciousness, then fall to the ground with a stiff body, before a clonic phase began. In this phase, the iconic arc-en-cercle/arch of hysteria could be witnessed. The seizures would resolve with a phase of laughter, sobbing and tears (11).

The organic lesion did not prove easy to find, and Charcot's theories were later contradicted, in particular by the Nancy school, as being partly founded on suggestion mechanisms. This introduced the fourth paradigm: the psychological model. Again, the condition is considered as a disease apart, it is psychogenic and not due to a anatomical lesion. The Nancy school considered hysteria as an exaggerated psychological reaction, and given the right circumstances, anyone could become hysterical (13). Pierre Janet (1859-1947), a student of Charcot, agreed with the Nancy-school in that hysteria was a mental malady. He focused on the unusual altered states of consciousness associated with hysteria, and proposed that these psychological phenomena were the result of emotional traumas that had weakened the synthesizing abilities of the healthy human psyche (13). He further theorized an important role for dissociation in conversion disorder (9). Sigmund Freud (1856-1939), also a visitor at the Tuesday lessons at Salpêtrière, claimed that hystrogenesis rested in the repression of traumatic
memories. These memories where then subconsciously converted into somatic manifestations, which he labelled conversion hysteria. First, he assumed that the repressed pathogenic material consisted of unconscious memories of childhood sexual traumas. This view was however changed towards the material consisting of sexual desires and fantasies, retained in the unconscious for purposes of self-defence. He popularised and developed the psychoanalytical approach, which dominated the first half of the 20th century (13).

By the 21st century, medical terms have evolved along the Freudian terms to conversion disorders, somatisation disorders and dissociative disorders, via terms such as convulsive hysteria and hysterical seizures. The term hysterical seizures is today discouraged, together with terms such as pseudoseizures, as these have negative connotations and lack precision. 'Functional disorders of the brain' was introduced in the 19th century (10), and the term 'functional' has lasted up until current medical literature, being perceived more positively than 'psychogenic' (15). PNES has largely remained a psychological and psychiatric state, and as such considered apart from other organic diseases. This does not exclude that PNES might be a disease like any other disease - but it stresses that the organ responsible for it, the central nervous system, is not an organ like any other. This applies in particular to highly complex brain functions such as emotional processing and consciousness, which are reported altered during PNES. The development of neuroscience and functional neuroimaging techniques opens up for the investigation of this complex physiopathology. In particular, the 20th century concept of homeostasis could be relevant for understanding the PNES mechanism. In the recent classification system DSM-5, conversion disorder criteria (F44.5) are changed to highlight positive examinations findings, without requiring temporal association with a psychological stressor. By making this change, the PNES-diagnosis is moved away from being an exclusion diagnosis, marking a possible new development towards looking at these events in terms of a biological, functional and brain based disorder (9). In the duality between organic and psychogenic however, it is worth referencing Horatio Bryan Donkin (1845-1927), who in 1892 stated in a debate on the word 'functional' the following: "...it being well understood, that with every change in nervous functions, whether normal or abnormal, there is a corresponding molecular change in nervous structure".

1.3. Aim

In this review, I aim to assemble information from neuroimaging studies on the causality and development of PNES pathology. In doing so, the goal is to identify key structures and neuronal networks related to PNES manifestations and its development. I also aim to identify areas where further investigation could be directed. I do not aim to address questions related to gender, nor to lateralisation. I do not attempt to explain related PNES-diagnosis, such as functional movement disorders, although recent research suggests a mutual benefit in adjoining research on these multifactorial conditions (9).

2. METHODS

For the purpose of this review, I initially performed a scoping search on PNES and pathophysiology to establish MeSH-terms, relevant terminology and find key articles. This was
followed by a more specific search in PubMed, built with the aid of a librarian at the medical library, Ullevål University Hospital, Oslo. Key words included psychogenic nonepileptic seizures and related disorders, neuroimaging techniques and pathophysiology. No MeSH-terms are currently established for PNES. For the study methods, abbreviations were chosen over MeSH-terms, to include the most recent articles not yet indexed. No timeframe for the search was set. The search conducted was as follows:

(((((((((voxel-based morphometry) OR cortical thickness) OR cortical thickness analysis) OR EEG) OR ((fMRI) OR MRI)) OR fMRI) OR SPECT) OR (PET) OR "Positron-Emission Tomography"[Mesh])) AND ((("functional movement disorder*") OR ("psychogenic non-epileptic seizures") OR pnes)) OR "psychogenic movement disorder") OR (("psychogenic non-epileptic seizures") OR pnes)) OR "psychogenic movement disorder") OR ("physiopathology" [Subheading])) OR (((((("functional movement disorder*") OR ("psychogenic non-epileptic seizures") OR pnes)) OR "psychogenic movement disorder") OR ("physiopathology" [Subheading]))))

The search yielded 442 results. Of these, 115 articles did not contain references to neuroimaging, but provided useful background and review articles on PNES. The remaining 327 articles were scanned on the level of title, then abstract followed by a full length-evaluation. Related citations where investigated, as well as reference lists in key articles, without yielding new relevant articles. In total, 14 original study-articles were selected, relevant to the search criteria. Of these were two retrospective studies and 13 case-control studies (one study included both a retrospective part and a case-control study), of which six was based on fMRI, six on EEG, one on PET and one on MRI and EEG. Initial inclusion criteria consisted of PNES-patients and healthy controls, two articles were however included: one included PNES patients and epilepsy patients as controls, and one included PNES-patients, epilepsy patients and healthy controls. Inclusion was based on the studies’ focus on physiopathology. The search included psychogenic movement disorders, but due to the scope of this article, these were not included. The selected articles are naturally grouped after investigation methods; MRI, fMRI, PET, EEG, and are presented chronologically.

3. RESULTS

3.1. MRI
In one of the earliest studies conducted to investigate whether physical brain disorder is associated with increased risk of PNES, Reuber et al. retrospectively studied data from 329 patient files from the year 1991-2001 (16). The data consisted of registrations of epileptiform EEG-changes, MRI-studies and neuropsychological deficits (NPD). The initial inquiries also aimed to discover whether markers for physical brain abnormality have a predilection for the right hemisphere. Inclusion criteria consisted of PNES confirmed by video-EEG, and patient
groups were divided on a basis of PNES alone or PNES with concurrent epilepsy. A complete set of studies (MRI, EEG and NDP) were obtained from 18 PNES only patients, and from 60 PNES patients with concurrent epilepsy. In total, at least one marker of brain abnormality was found in 22.3% of the PNES only patients, but the actual number is estimated as higher, as only 35.9% of PNES patients underwent MRI and only 16% underwent neuropsychological testing. In patients with PNES and epilepsy, evidence of physical brain abnormality was detected in 91.9%. The figures presented make an association of PNES and physical brain dysfunction probable. No predilection for the right hemisphere was found.

3.2. Functional MRI

In 2011, van der Kruijjs et al. began their neuroimaging approach to PNES. In the first of two studies, the group investigated possible alterations in emotion- and information processing, through task-based and resting-state functional connectivity (FC) MRI studies (17). Dissociation was emphasized in the theoretical foundations as an important mechanism in PNES, with loss of integration of conscious functioning. 11 patients with PNES and 12 age- and gender matched healthy controls were included in the study, after exclusion of psychiatric and neurologic comorbidities. The PNES-diagnosis was set by a specialist, based on clinical description. Video-EEG, considered the gold standard for PNES-diagnosis, was only done when available. PNES-patients were also selected on the basis of their tendency to dissociate. Three of the patients were on or had recently taken anti-epileptic drugs, one patient had recently taken tricyclic antidepressants, and two patients were on benzodiazepines. All participants answered questionnaires for evaluation of dissociative traits and global cognitive performances (Raven’s matrices), which all but one PNES patient completed. PNES patients scored significantly lower on global cognitive performance, and had significantly higher dissociation tendency than the healthy controls. For the imaging, four sets of fMRI was done, beginning and ending with a resting state fMRI. The final rsfMRI was taken to examine possible dissociative traits brought on by the attentional effort in the two previous task-related fMRI. The tasks chosen for the trfMRI consisted of 1) a picture encoding task, to stimulate the process of suggestibility, and 2) Stroop colour naming task, as dissociation is associated with hypnotic induction, which has been related to Stroop performance and FC changes in the frontal attention system. There were no significant differences between PNES patients and healthy controls in the activation maps generated from the two task-related fMRI, nor in the two sets of rsfMRI. 9 regions of interest (ROI) were created based on average activation in the two trfMRI, enabling an investigation of temporal coherence between ROIs and other brain regions. Functional connectivity maps in PNES patients showed abnormal functional correlations between the precentral sulcus (motor cortex, voluntary muscle movement) and the insula (emotion regulation, visceral sensory perception, self awareness). Significantly stronger correlations were found between the insula and the parietal lobe (executive control, processing of sensory information and subsequent action organisation). The FC value between the anterior cingulate cortex (emotional processing) and inferior frontal gyrus (executive control) was significantly higher in the PNES group, also related to dissociative traits. Relevant to the study’s focus on dissociation, the FC value of the precentral sulcus - posterior insula showed significant correlation with the scores of dissociation (DES). The DES score was through linear regression found to be a significant predictor, whereas test scores on Raven’s matrices was not. This implies that dissociation, and not intelligence, is an important mechanism in the abnormal FC-values observed in PNES. The study findings reaffirm dissociation as a
mechanism in PNES. The higher functional connectivity in rsfMRI between insula (emotion processing), parietal lobe (executive control) and precentral sulcus (movement) provide a possible hyperlink for emotions to influence executive control and lead to altered motor function, as seen in PNES.

In van der Krujs et al.’s second study from 2013, a data-driven independent component analysis (ICA) was performed on resting state fMRI-data (18). This method investigates whole-brain networks, and permits the data from the rsfMRI to be decomposed into statistically maximally independent functional networks. Out of ten identified networks, four networks were chosen on the basis of their relevance to dissociation: 1) executive control, 2) fronto-parietal network, 3) sensimotor network and 4) default mode network. Lastly, the visual network was included as this was considered unlikely to be affected by PNES and thus gave a basis for examining change in the other four networks. 21 PNES patients and 27 age- and gender matched healthy controls was included by the same inclusion and exclusion criteria as in their first study. No participants took anti epileptic drugs at the time of inclusion or throughout the investigations. No remark was noted on the use of other drugs, such as benzodiazepines and antidepressants. The same questionnaires for dissociative traits and global cognitive performance was administered and completed in all but one PNES patient. In line with the previous study, significantly higher dissociation scores and lower global cognitive performances were found in the PNES patient group. In the rsfMRI-studies, PNES patients showed altered coactivation in many of the networks, compared to healthy controls. Increased coactivation was found in the orbitofrontal, insular and subcallosal cortex in the fronto-parietal network; the cingulate and insular cortex in the executive control network; the cingulate gyrus, superior parietal lobe, pre- and postcentral gyri and supplementary motor cortex in the sensorimotor network; and the precuneus and (para-) cingulate gyri in the default mode network. Decreased coactivation was found in the orbitofrontal cortex in the executive control network, and in the precuneus in the sensorimotor network. No significant differences were found in the visual network between the PNES group and control group. Connectivity values were correlated with dissociation scores. Several of the alterations, e.g. in the fronto-parietal network and the default mode network, can contribute to the mechanism of involuntary movements and alteration of consciousness, which are often experienced by patients with PNES.

20 patients with PNES and 40 healthy controls were enrolled in a study by Labate et al., to investigate key brain networks in PNES pathology (19). PNES was in this study understood as strongly connected to conversion disorders. Pathology was therefore expected to be found in prefrontal and sensorimotor circuits. The study was performed by using two complementary quantitative techniques, voxel-based morphometry (VBM) and cortical thickness analysis. The latter describes the columnar architecture of the cortex, and the VBM gives a general measure of grey matter volume. Patients were included upon video-EEG diagnosis of PNES and exclusion of other psychiatric or neurologic comorbidities, substance abuse and use of antipsychotic drugs. Controls were enrolled from staff at the research university, and demonstrated no psychiatric or neurologic comorbidities. All patients completed neuropsychological and psychiatric questionnaires, including forms for evaluating traits of depression, anxiety and dissociation. In the VBM analysis, PNES patients showed significant loss of grey matter volume in the bilateral cerebellum, the right precentral gyrus, right middle frontal gyrus, the anterior cingulate cortex and supplementary motor area. Grey matter volume in the right dorsal premotor cortex was further negatively correlated to depression scores. In the analysis of cortical thickness, the study demonstrated significant thinning in the right precentral gyrus, right superior frontal gyrus, right precuneus and right paracentral gyrus. Significant association was also established
between increasing depression scores and the thinning of the right superior frontal gyrus and the right paracentral gyrus.

In total, this study demonstrates that PNES patients display abnormal cortical thinning of the motor and premotor regions in the right hemisphere and the cerebellum bilaterally. These findings, especially the increased depression score correlating to premotor cortical atrophy, might indicate a pathological PNES mechanism involving adaptive cortical-subcortical plasticity within these regions. This places the abnormal brain structure as secondary to the psychopathology, with psychogenic causation as important in the development of PNES.

The same study population was used in the following three fMRI-studies by Ding et al and Li et al. This population has a lower mean age than the two previous studies (19 years ± 7.56 years vs 34 ± 12 years), but displays approximately the same gender distribution (65% vs 62% female). The PNES diagnosis was given after confirmation on video-EEG. Exclusion criteria included neurologic and psychiatric comorbidities; the latter investigated by structured interviews. All drugs were discontinued at least 2 weeks prior to MRI examination. Median PNES frequency was 2.5/month.

To analyse the organizational structure of brain networks in PNES patients, Ding et al. combined data from fMRI and diffusor tensor imaging of functional and structural connectivity networks (20). The structural network represents anatomical integrity of white matter tracts, while functional network displays the temporal coherence of brain regions. In healthy people, these two networks are thought to exhibit small-world architecture, which provides an optimal balance between information integration and segregation. In this organizational form, there is high local clustering between neighbouring nodes, but short path length between any pair of nodes. Nodes that are highly connected are called hubs. fMRI studies have suggested that this topology is shifted towards more random organization in diseases, e.g. partial and generalized epilepsy, and could also be altered in PNES patients. 17 patients with PNES and 20 age- and gender matches controls were enrolled in the study. Graph theoretical analysis was used on the rsfMRI and diffusor tensor imaging data, to construct the functional and structural connectivity networks. These were then coupled. A small-world organization for both networks was found both in the PNES patients and in the control group. However, in the PNES-group, the organization was altered in both modalities, with increased local specialization and decreased global integration. This indicates a more regular (lattice-like) organization in large-scale brain networks which is associated with a less optimal topological organization. This particular finding can point towards a new neuroimaging marker to distinguish PNES from epilepsy. Several regional characteristics were also altered in structural connectivity networks, involving attention-, sensorimotor-, default mode- (all three decreased) and subcortical networks (increased). In particular, decreased nodal characteristics were found relating to attention, working memory and emotion: the insula and the opercular part of the frontal gyrus (attention) and the middle frontal gyrus and orbital part of frontal gyrus (working memory and emotion). The coupling-strength of functional-structural connectivity was significantly decreased in PNES patients. This finding seems to provide high sensitivity and specificity to differentiate PNES-patients from healthy controls. In addition, it suggests a loss of coalescence of functional and structural connectomes, and thus an abnormal mechanism of brain networks in PNES patients.

In the second study, Ding et al. investigated map changes in resting state brain functional connectivity (21). Functional connectivity density mapping is a voxelwise data-driven method that creates local and global functional connectivity density maps. This allows for the density in short range (local) and long range (distant) functional connections to be mapped, and highly connected brain regions (functional hubs) to be detected. In the same study population of 18
PNES and 20 healthy controls, the study’s aim was to find regions with altered functional connectivity density in the PNES patient group, and possibly correlations between brain changes and the duration of PNES. Only the cerebral alterations were investigated, and the cerebellum thus excluded. Functional connectivity density maps were created on the image data obtained, clusters with significant differences were further investigated by regions of interest (ROI) analysis. PNES patients displayed increased short range connections in the left middle-, superior frontal- and medial part of the superior frontal gyrus, anterior cingulate gyrus, supplementary motor area and bilateral median cingulate gyrus. They also displayed increased long range connections in the bilateral calcarine fissure, lingual gyrus and left paracentral lobule. Decreased short range functional connectivity density was found in the right middle occipital gyrus, and in the long range, in the right medial prefrontal cortex, middle frontal gyrus, triangular and opercular parts of the inferior frontal gyrus, superior frontal gyrus, medial part of the superior frontal gyrus, supramarginal gyrus and inferior parietal gyrus. Increased short range functional connectivity density in the left frontal and cingulate cortex indicates a altered cognitive-emotional attention system in PNES. Increased long range functional connectivity density in the insula, sensorimotor and occipital cortex further strengthens that PNES is characterized by impaired function of emotion and cognition, in addition to the sensorimotor cortex. In the seed-voxel correlations, hyperconnectivity was demonstrated between the insula and the supplementary motor area, as well as between the sensorimotor and cingulate cortex, which supports abnormal connectivity density between emotional and sensorimotor networks in PNES. The increased long range functional connectivity density in the calcarine fissure and lingual gyrus was correlated to the duration of PNES, and might represent adaption in PNES patients for long-term hypervigilance and increased response to external stimuli. Decreased functional connectivity was found between the right frontal cortex, which is related to social cognition and emotions, and the parietal cortex. The fronto-parietal networks are associated with attentional control, and these findings might indicate an impaired function of this network. This might lead to a dysfunction of cognitive attention and executive control in PNES.

Narrowing the search in the third study on this population group, Li et al. performed a study on functional connectivity patterns of insular subregions (22). Insula has been reported as an important locus in PNES pathology, related to emotion-, cognitive- and sensorimotor processes. It is however a region with high heterogeneity, and a division into functional subregions has been proposed: a ventral anterior region (chemosensory and socio-emotional processing), a dorsal anterior region (higher cognitive processing) and a posterior region (pain and sensorimotor). The intrinsic resting-state functional connectivity patterns in the insula could provide useful information on PNES pathology. A functional connectivity analysis was performed on 18 PNES patients and 20 controls, between insular subregions and the whole brain. This was done by constructing functional connectivity maps from resting state fMRI and structural connectivity maps from diffusor tension imaging. Regions of interest (seeds) was selected for the left and right insular subregions. Cluster analysis demonstrated three subregions in the left and right seeds: ventral anterior insula, dorsal anterior insula and posterior insula. Overall, a distinct functional connectivity pattern of the insular subregions was demonstrated for both groups. Compared to the controls, the PNES patients showed stronger connectivity in the superior parietal gyrus, the postcentral gyrus, the lingual gyrus and the bilateral supplementary motor area. The left ventral anterior insula-seed (emotional processing) showed stronger functional connectivity in the right lingual gyrus, left post-central gyrus and bilateral supplementary motor area (sensorimotor network). This might indicate that patients with PNES are more likely to respond to emotional upset with involuntary behavioural patterns,
and that this subregion in particular is important in the pathology behind PNES. FC values between the ventral anterior insular seed and the bilateral supplementary motor area showed a positive correlation with PNES-frequency. The right posterior insula demonstrated increased functional connectivity to putamen. High functional connectivity was observed between the left superior parietal gyrus and the right dorsal anterior insula. This could provide a pathway for sensory information to influence cognitive and executive control. An increased functional connection was also found between the ventral anterior insula and the right lingual gyrus. This might demonstrate the plasticity of functional connectivity and an adaption for long term social threat cues and increased response and greater attention to negative emotional stimuli. No direct fiber tracts were detected passing through the insular subregions to the altered PF regions in either group.

3.3. PET

Only one study has been conducted on PNES patients using positron emission tomography (PET), in order to detect metabolic changes. Arthuis et al. included 16 PNES patients after a retrospective search in patient files, coupled with 16 healthy controls (23). The patients were diagnosed with PNES following video-EEG. Neurologic and psychiatric comorbidities were excluded by expert opinion, not by structured clinical interview. No information was provided regarding medication status. Interictal brain metabolism was studied under the same conditions in all participants, by fluorine-18 solution and subsequent resting state PET. In the PNES group, PET hypometabolism was found within the right inferior parietal and central region, and in the bilateral anterior cingulate cortex. No significant hypermetabolism was found in the PNES group compared to the control group. Further studies of the metabolic connectivity in the two clusters found a significant increase in metabolic correlation between 1) the right inferior parietal and central region and the bilateral cerebellum, and 2) the bilateral anterior cingulate cortex and left parahippocampal cortex. These changes might reflect interictal disturbances in the brain networks underlying PNES. No correlation was found between the two hypometabolic clusters and sociodemographical characteristics. Hypometabolism in the anterior cingulate cortex has in previous studies been described related to psychiatric conditions, e.g. PTSD and anxiety. Due to the lack of structured acquisition of data on psychiatric traits in this study, this parameter cannot be controlled for and therefore cannot be excluded as a possible cause for this particular finding. It is none the less an important finding, in regard to the role of the anterior cingulate cortex in emotional regulation. The hypometabolism in the right inferior parietal cortex is interesting, considering the role of the parietal cortex role in the neural basis of consciousness and the reported altered level of contact and loss of self-agency in the PNES patient group.

3.4. EEG

Interictal EEG abnormalities are a frequent source for wrongly diagnosing PNES as epilepsy, and for delays in PNES diagnosis. Focusing on this challenge, Reuber et al. retrospectively reviewed 187 PNES patient files from 1995-2003 (24). From the EEG-registrations, all of the 187 patients were diagnosed with PNES. 57 had coexistent epilepsy. PNES and epilepsy was diagnosed by video-EEG or/and by expert epileptologist using neuroimaging modalities. However, 19.8% of the participants did not undergo video-EEG before being diagnosed. Of the remaining 130 PNES
patients, 50 patients met the inclusion criteria for a blinded multirater comparison on EEG-data, and were matched with 50 healthy age and gender matched controls. Exclusion criteria for both groups included medical problems with possible effects on the EEG, and use of drugs with potential EEG-effects. No other note on psychiatric or neurologic comorbidities was made. The analysis from the blinded comparison showed that EEG-abnormalities were found 1.8 times more frequently in the PNES patient group compared to healthy controls. Significance could not be proven. In total, 92.9% of patients with PNES and epilepsy, and 53.8% of patients (n=130) with PNES alone had at least one abnormal EEG-report. The rate of reported epileptiform EEG-changes in PNES-only group, 12.3%, was significantly higher than in the general population. Affirming that the presence of brain dysfunction is more prevalent in PNES population, the study suggests that the presence of EEG-changes in isolation, in particular if they are non-specific, should not be considered evidence of epilepsy and should not be used as an argument to start or continue inappropriate antiepileptic treatment.

Knyazeva et al. investigated whole-head multivariate phase synchronisation (MPS), to establish whether PNES is accompanied by changes in regional EEG synchronisation (25). This type of study allows for the assessment of cooperation between cortical network, and with multivariate measures the whole-head topography of synchronisation can be reconstructed. The method was applied to interictal EEG-registrations from 13 PNES patients, matched with 13 healthy controls. Patients were included after video-EEG, normal brain imaging and exclusion of epilepsy had confirmed the PNES-diagnosis. No note was made on concurrent psychiatric conditions. Controls were age- and gender matched, with no history of psychiatric or neurologic comorbidity, however no standardized investigation in this regards was done. 46% of PNES patients used benzodiazepines, 13% used no medication. The remaining 41% used antiepileptic agents and/or antidepressants. No note of discontinuation or use of drugs prior to EEG-recordings was noted in the article. In the course of analysing EEG-data, multivariate phase synchronisation-values were correlated to monthly attack frequency, which was considered a quantitative index of disease severity. Age and disease duration parameters were controlled for. No specific interictal abnormalities were discovered for PNES. PNES-patients did show a consistent hypersynchronisation pattern, but this could be due to benzodiazepine medication as this difference was found also within the PNES-group between those under benzodiazepine medication and those not. Although patchy reductions in neighbourhood synchronisation in the prefrontal region could be seen, in total, no reliable hyposynchronisation pattern in PNES patients could be demonstrated. An inverse correlation between seizure frequency and multivariate phase synchronisation-values in frontal and parietal locations was found. This suggests a location for a brain dysfunction, and the study group proposes that prefrontal dysfunction exerts downstream effects triggering a predisposition to manifest a range of "seizures". Being components of the default-mode network related to alertness, the frontal and parietal association might contributes to the experience of losing consciousness, as frequently reported by PNES-patients. The prefrontal hyposynchronisation may reflect a dysfunction in PNES, and with the correlation between multivariate phase synchronisation values and PNES attack frequency, a reduction or instability in prefrontal EEG synchronisation could be a marker of increased risk for PNES manifestations in populations at risk.

Building on the results from the previous study, Barzegaran et al. went further in investigating a possible cerebral basis for a PNES predisposition (26). This was done by graph theoretical modelling of EEG-based functional networks obtained from the same study population of 13 PNES patients and 13 controls as used in the study from 2010. Notably, possible confounding factors from the high percentage of participants on benzodiazepines...
(46%) and antidepressants and/or antiepileptic drugs (41%) at the time of the EEG is also present in this study. Interictal resting EEG data obtained from the participants were used for further construction of the topology of functional brain networks. This was done using graph theoretical modeling, with calculation of small-world topology, clustering coefficients and global efficiency. Graph theory metrics considers the electrodes as nodes, and measure their degree of connectivity by how many neighbours they have. No systematic significant difference in local connectivity was found between PNES patients and the healthy controls, but the clustering coefficient showed inverse correlation with the frequency of PNES episodes for broad range of density values in the alpha-band and for low density in the beta-band. This could indicate that frequent attacks are associated with poor local connectivity in the cortical networks. The small-world index did not differentiate PNES patients from the healthy controls, but it was significantly inverse correlated to PNES-frequency for all densities in the alpha-band, suggesting that the lower the SW-index, the more frequent the PNES-events. Assortativity values, a measure of brain network resilience, were generally higher in PNES-patients than the controls, and correlated directly with the PNES-frequency in the beta-band. Global efficiency did not vary between the two groups and was not correlated to PNES-frequency. Regarding topography, PNES condition was found to affect the nodes in the prefrontal and posterior areas differently, with loss of prefrontal and left-posterior hubness, while the right hemisphere posterior hubs increased, especially for high-density networks. In total, the study revealed that deficits in local connectivity and/or altered balance between local and global connectivity correlate with PNES-frequency. Strengthening of local connectivity might therefore be a target for therapeutic interventions.

Utilizing advanced statistical analysis of the dynamics of scalp-EEG, Krishnan et al. conducted a study including five patients diagnosed with epilepsy and six patients diagnosed with PNES (27). The researchers have demonstrated in previous studies that epileptic seizures are not abrupt transitions into and out of an abnormal ictal state, but follow a dynamical transition over minutes and hours. In this process, several regions of the brain increasingly approach a similar dynamic state. The preictal entrainment is then reset by the epileptic seizure, in a disentrainment phase. This dynamical resetting is specific and sensitive to epileptic seizures, and scalp-EEG might provide a method to distinguish epileptic seizures from PNES. The article does not fully account for the initial PNES-diagnosis nor inclusion and exclusion criteria. All participants underwent comprehensive neuropsychological testing before inclusion. However, psychiatric comorbidities were not an exclusion criteria. 3 patients were reported with depression, 3 with mild cognitive inefficiency, 3 with conversion disorder, 1 with somatization, and 1 with PTSD. Long-term scalp EEG recording was undertaken, and data subsequently statistically analysed for estimations of entrainment power (SEP) and resetting power (SRP). This was done by analysing the convergence between critical brain sites. The study found that PNES patients, in comparison to ES patients, showed lower levels of dynamic entrainment and resetting at events. Specifically, seizures in patients with PNES did not reset the brain dynamics, while epileptic seizures did (in 4 out of the 5 ES patients included in this study), indicating a less certain function of the seizures in PNES than in epilepsy.

To further establish the role of altered brain connectivity in patients with PNES, Xue et al. conducted a study with scalp-EEG. 15 PNES patients were included, matched with 15 healthy controls (28). Inclusion criteria for both groups consisted of no significant MRI abnormalities or central nervous dysfunction, no drugs 2 months prior to diagnosis/study and right-handedness. The controls had no history of seizures/epilepsy and were matched for age, gender and educational background. For PNES patients, diagnosis was established by video EEG-recordings...
examined by specialists. Exclusion criteria included neurological comorbidity, malingering, current or previous systemic disease or head trauma, alcohol- or substance abuse and psychosis. All participants underwent full medical history, systematic and neurological examinations, psychiatric evaluation, MRI and video-EEG. PNES patients scored significantly higher on questionnaires for anxiety (SAS), somatoform dissociation (SDQ-20) and depression (SDS), but there was no difference in mini-mental state examination. Graph theory was utilized on the EEG-data acquired, and brain networks with network properties constructed. In the statistical analysis, shortest path length for different thresholds was established, with corresponding clustering coefficients and global efficiency measures. Patients with PNES demonstrated significantly decreased clustering coefficients in the gamma band, in addition to decreased long linkage between the frontal region and posterior areas. This suggests a possible pathophysiological mechanism for PNES, as decreased clustering coefficients are associated with low local efficiency of information transfer. Synchronization of the gamma-band (30-70Hz) underlies binding, attention and consciousness. Prefrontal connectivity dysfunction may contribute to the impairment of executive control and hence the uncontrolled movements experienced in PNES. No correlations were found between clustering coefficients and SAS, SDS or SDQ-20, making it possible that the decreased clustering coefficients and subsequent low local information transfer efficiency are related to PNES itself and not to psychiatric comorbidity traits.

In a study from 2014, Xu et al. investigated the use of resting scalp EEG to differentiate between PNES and epilepsy (29). The analyses were based on statistical properties of common spatial patterns extracted from brain network topology (SPN). This method is based on network analysis, where local information processing and global information efficiency can be represented quantitatively by statistical measurements, i.e. clustering coefficients and shortest path length. These are determined by the spatial network topology. Common spatial patterns analysis makes it possible to extract abnormal components from EEGs, and this analysis on the brain network topology might provide insight to the different mechanisms of epilepsy and PNES. 15 patients with PNES, 15 healthy controls and 10 patients with focal epilepsy were included in the study. Inclusion criteria for the PNES group included PNES diagnosis on video-EEG monitoring, with exclusion of comorbid epilepsy. Patients with epilepsy were included after confirmed epilepsy on both EEG and MRI. Healthy controls were included after exclusion of EEG-abnormalities and a negative history of seizures. Neither psychiatric evaluation nor MRI was undertaken in the screening of the participants for the study. Continuous EEG-recording data was obtained from all participants and weighted brain networks constructed. Network properties, clustering coefficients and shortest path length, was subsequently used to measure the local and global information processing abilities of the brain. The results were compared for all three groups in the four EEG-bands. The first analysis did not find differences in brain network properties between patients with PNES and patients with epilepsy, but both groups differed from the control group; patients with epilepsy and PNES had decreased clustering coefficients and an increased shortest path length in frequency bands of interest. This may indicate impaired local information processing and global information integration in these two groups. For diagnostic aims, the proximity in network properties in PNES and epilepsy patients results in a very low differentiation strength. Another way to differentiate these two groups is by rather looking at network topology structure than network properties. In this way, the spatial differentiation can be captured. PNES patients in this study demonstrated stronger linkages between the frontal area and the temporal and occipital areas than the epilepsy patients. A classification is then possible, based on the developed common brain network topology. This
method extracts the inherent spatial information in the resting network. The highest classification potential was 92% accuracy, 100% sensitivity, and 80% specificity, measured from 6 SNP-features in the beta-band.

4. DISCUSSION

Through different methods and techniques, all of the included articles shed light on the neural substrates of PNES. The heterogeneity in techniques makes it difficult to compare the study findings directly. Nonetheless, several observations point to neural networks associated with emotional processing, executive control and sensorimotor functioning. Although preliminary, these findings could be important for the understanding, diagnostic options and treatment of PNES. The theoretical frameworks and choice of methods are well documented; however, there are several limitations in study design.

4.1. Limitations

4.1.1. Population and controls

In the 14 articles, there are 11 study populations in total. In the 13 case-control studies, the number of included patients varies between 5 and 21. The retrospective studies conducted by Reuber et al have larger populations, 206 (2001) and 187 (2002). All of the study populations have female predominance, in line with previous literature (2). PNES onset is most frequently between the age of 20 and 30. The studies conducted by Ding et al. 2013, 2014 and Li et al. 2014 have a younger median age of 19.56, including 4 participants aged 13. This might contribute to a selection bias, as children have better prognosis, with 70-80% achieving seizure remission (30). PNES-events are often frequent, rarely less than one event per week. These same articles stand out with a reported seizure occurrence at 2,5 per month. This also applies to van der Krujs et al. 2012 with 1.7 per month. In three of the articles (Labate et al. 2011, Xu et al. 2013, Xue et al. 2014), seizure frequency was not reported. Heterogeneity is however a challenge in PNES, and it poses constraints on small study populations. Healthy controls were in all studies matched with the patient group in regard to age and gender, in one study (Xue et al. 2013) also in educational years. Education is not considered to influence PNES-prevalence, but lower educational level and lower IQ are associated with worse prognosis (2). In eight studies, participants were recruited from own staff and among medical students (Xue et al. 2013, Xu et al. 2014, Knyazeva et al. 2010, Barzegaran et al. 2012, Ding et al. 2013, 2014, Li et al. 2014, Labate et al. 2011). Education might present a selection bias among these controls. Van der Krujs et al. 2014 reported controls found through advertisement. Reuber et al. 2001 did not include controls, Krishnan et al. 2011 was a comparison between PNES and epilepsy without controls, and three of the articles did not account for where the controls where included from, (Reuber et al. 2002, Arthuis et al. 2014, van der Krujs et al. 2012), which makes further demographic correlations impossible to perform.

4.1.2. Blinding

Only 2 of the studies (Labate et al. 2012, Reuber et al. 2002) report blinded interpretation of the data-registrations. Blinding of control/PNES-patient group could strengthen the study design and prevent information bias.
4.1.3. Psychopathological traits and physical/sexual trauma
As mentioned in the introduction, PNES is associated with depression, anxiety, PTSD, dissociative- and somatoform disorders, as well as cluster B-personality disorders. Schizophrenia and depression with major psychosis is however uncommon (2). Physical and/or sexual abuse, notably in early life, is frequently reported (30-50%) in PNES. Most articles refer to several of these traits, both in the introduction and in the discussion part. It is therefore remarkable that none of the articles have included screening for early life physical/sexual abuse, such as the Traumatic Experience Checklist used in other PNES studies (3). Other psychopathological traits are in general inadequately accounted for. To some extent, this can be explained by limited resources and by the study focus, but for many of the studies these traits represent possible confounding factors. There is a high degree of heterogeneity in both exclusion-criteria, method of screening for psychopathological traits and the data-registration on these traits after inclusion. First, considering pre-inclusion screening, four studies reported comprehensive/extensive neuropsychological testing, but without reporting further which methods were used (van der Kruijfs et al. 2012, 2014, Arthuis et al. 2014, Krishnan et al. 2011). The degree of formal is therefore unknown. Four studies used a formal neuropsychiatric investigation approach in line with DSM-IV (Labate et al. 2011, same population: Ding et al. 2013, 2014, Li et al. 2014). Six studies did not report on method for exclusion of psychopathological traits. Five of these seemingly did not take it into account (Knyazeva et al. 2010, Barzegaran et al. 2012, Xu et al. 2014, Reuber et al. 2001, 2002).

Secondly, after inclusion, four studies report on data-registration of psychopathological traits scores: Van der Kruijfs et al. 2012 and 2014 administered 3 questionnaires on dissociation (Dissociation questionnaire, Dissociative experience Scale, Somatoform Dissociation Questionnaire) in addition to a global cognitive performance test, but none on other of the mentioned traits. In the 2012 study, patients are included also on their tendency to dissociate, which creates a selection bias. Labate et al. 2011 undertakes an assessment using Dissociative Experience Scale, Somatoform Dissociation Questionnaire-20, Beck Depression Inventory, State-Trait Anxiety Inventory including the MINI-questionnaire for DSM-IV axis 1 disorders, current and life-time prevalence. Krishnan et al. 2011 reports that among the included PNES-patients, 3 had depression, 3 had mild cognitive inefficiency, 3 with conversion, 1 with somatization and 1 with PTSD. Xue et al. 2013 report a screening of the included patients, including Mini Mental State- Examination, Self-Rating Anxiety Scale, Self-Rating Depression Scale and Somatoform Questionnaire-20.

In total, psychopathological traits known to be strongly associated with PNES are only poorly accounted for in these studies and thus present possible confounding factors. Where it is accounted for, it represents a strength, as in Xue et al. Including these traits also opens up for comparison with other psychopathological disorders where functional imaging-studies have been undertaken.

4.1.4. Medications, head trauma and somatic co-morbidities
Medications and certain diseases can affect the outcome of functional neuroimaging studies, in particular EEG. While all studies excluded epilepsy and several exclude mental retardation, only one of the studies (Reuber et al. 2002, EEG) systematically excluded all participants with medical conditions which might lead to abnormal EEG-changes (thyroid disease, uncontrolled HT, head injury with loss of consciousness, stroke, intracranial surgery). This is also the only study who excludes patients on medicaments with possible effect on EEG-changes, such as
anticonvulsants, anxiolytics, narcotics, antidepressants and beta-blockers. In four of the studies, three with EEG (Reuber et al. 2001, Krishnan et al. 2011, Xu et al. 2014) and one PET (Arthuis et al. 2014), there is no mentioning of medications. In the three Chengdu-based MRI-articles, all drugs were discontinued for minimum two weeks before the MRI (Ding et al. 2013, 2014, Li et al. 2014). Xue et al. 2013 reported that all patients were medication-free for two months before diagnosis. Although having excluded patients with substance-related disorders, in van der Kruis et al. 2012, one on the patients were taking tricyclic antidepressants and benzodiazepines, and one patient were taking benzodiazepines only. In their study from 2014, no patients were taking anti-epileptic drugs at the moment of inclusion, but other medication with possible effect was not mentioned. Labate et al. 2011 mentions that none of the patients were taking antipsychotic drugs at the time of the investigation, but no other types of medicaments were accounted for. In Knyazeva et al. 2010 and Barzegaran et al. 2012, medicaments are accounted for and present a possible confounding factor for their findings, as mentioned in the results section. While 31% did not take any medicaments, 46% were taking benzodiazepines and the remaining 41% were taking anti-epileptic drugs and/or antidepressants. None of the studies screened participants for previous head trauma.

4.2. FINDINGS

Despite the modest sample size in the functional neuroimaging studies, significant findings were demonstrated. Together, they strengthen theories proposed in previous literature, where dysfunction in emotion processing mediated by the limbic system and parietal regions produce the various manifestestations of PNES, in absence of prefrontal inhibition/control and thus outside of the patients sense of volition.

4.2.1. Neural circuits associated to PNES

4.2.1.1. General topological organization characteristics

Several of the studies addressed characteristics of brain network organization in PNES patients. Ding et al. 2013 found altered small world topology, with increased local specialization and decreased global integration, itself an indicator of a less optimal topological organization, with a disturbance in the normal balance in functional and structural connectivity networks. Knyazeva et al. 2010 found no systematic significant differences in local connectivity in PNES patients, and the follow up study from Barzegaran et al. 2012 could not establish a specific EEG hypo- or hypersynchronisation pattern in PNES patients. It did however find several characteristics in brain network correlated to PNES-frequency: 1) The small world-index was significantly inversely correlated to PNES frequency, indicating that the lower the small-world-index, the higher the PNES frequency, 2) PNES patients appeared to have reduced brain network flexibility, where values for resilience in the brain networks were directly correlated to PNES frequency, and 3) Clustering coefficients showed inverse correlation with PNES frequency, something which could mean that poor local connectivity in the cortical networks is associated to frequent PNES. Xue et al. 2013 found low local efficiency of information transfer. Xu et al. 2014 found that patients with epilepsy and patients with PNES both had decreased clustering coefficients and increased shortest path length, compared to healthy controls, which is associated with impaired local information processing and global information integration.

4.2.1.2. Key regions
Labate et al. 2011 found abnormal cortical thinning in the motor and premotor regions in the right hemisphere and the cerebellum bilaterally. Further abnormalities found in the cerebellum promotes this region as a node in the neural network underlying subjective experience of emotion in addition to being involved in cognitive and emotional functions. Arthuis et al. 2014 found an increase in metabolic correlation between the bilateral cerebellum and the right inferior parietal and central region, and between the bilateral anterior cingulate cortex and left parahippocampal cortex. The study also demonstrated hypometabolism in the right inferior parietal cortex, which could be related to patient’s experience of altered consciousness and loss of self-agency.

The orbitofrontal cortex is associated with functions such as emotional recognition, integration of emotionally coloured stimuli and subsequent appropriate choice of action. As such, it is important for behavioural flexibility (31). Decreased coactivation of this region in the executive control network and increased in the sensimotor-network, as found by van der Kruijs et al. 2014, could imply a dysfunction in the prefrontal integration of emotional stimuli, resulting in disturbances in choice of action. Precuneus also showed decreased coactivation in the sensimotor network. Given its association with consciousness, connected to its role as a small-world network hub between prefrontal and parietal regions (demonstrated by displaying deactivation during anaesthetic-induced loss of conscience (32)), this could represent a dysfunction in the consciousness-circuits during sensorimotor functioning.

Insula is involved in many of the alterations demonstrated between PNES patients and controls. It has reciprocal connections to the thalamus, amygdala and the temporal, parietal and frontal cortex and is an important neocortical part of the limbic system and thus in processing and regulation of emotion and awareness. Insula is a part of the salient network, which together with the prefrontal cortex and gyrus cinguli have a paramount role in attention and regulation of behaviour and mental processing (31). The study articles described increased functional connectivity to several regions, among them the precentral sulcus, right lingual gyrus, left postcentral gyrus, bilateral supplementary area, left superior parietal gyrus. It showed increased coactivation in the fronto-parietal network and the executive control network, and decreased nodal characteristics in structural networks related to attention. In particular, the study from Li et al. 2014 highlights important alterations in insular subregions, with possible hyperlink-alterations affecting emotion regulation, cognitive processes and motor function.

4.2.1.3. Key networks
Van der Kruijs et al. 2012 found increased functional connectivity between insula (emotional processing) and the parietal lobe (part of the central-executive network, action decision-making) and the precentral sulcus (motor cortex), which might represent a stronger connection between emotion processing and movement generation, facilitating PNES. Ding et al. 2014 found increased long range functional connectivity in the insula, sensorimotor (bilateral supplementary motor area, right precentral and postcentral gyrus) and occipital cortex (bilateral calcarine fissure and lingual gyrus), also suggestive of impaired functions of cognition, emotion and sensorimotor-processing. In addition, the same study found decreased functional connectivity between the right frontal cortex and the parietal cortex. This might indicate alterations in the fronto-parietal network and abnormal emotional-processing with dysfunction in attention and movement generation, without inhibitory prefrontal activity. Increased short range functional connectivity in the left frontal and cingulate cortex also indicates altered cognitive-emotional attention system in PNES. The view is further supported by Li et al 2014 where stronger functional connectivity was found between the left ventral anterior insula,
involved in emotional processing, and the right lingual gyrus, left post-central gyrus and bilateral supplementary motor area. The dorsal anterior insula showed high functional connectivity to the left superior parietal gyrus, which might function as a pathway for sensory information to influence cognitive and emotional control. Knyazeva et al. 2010 found patchy reductions in synchronisation in the prefrontal region, together with an inverse correlation between seizure frequency and multivariate phase synchronisation values in frontal and parietal locations. This could mediate the experience of losing consciousness, as these regions are connected to alertness/consciousness. There was also decreased long linkage between the frontal region and posterior areas found by Xue et al. 2013, proposing that prefrontal connectivity dysfunction contributes to impairment of executive control and subsequent uncontrolled movements.

4.2.1.4. Psychopathological traits, intelligence and brain abnormality
Van der Kruis 2012 found increased functional connectivity between the inferior frontal gyrus and the anterior cingulate cortex, which were correlated to DES-scores. These scores were found to be a predictor for PNES, while Global Performance scores were not, indicating that dissociation and not intelligence is important in PNES mechanism. Labate et al. 2012 found that increased depression scores correlated significantly to 1) premotor cortical atrophy, and 2) thinning of right paracentral gyrus and right superior frontal gyrus, while 3) grey matter volume loss in the right dorsal premotor cortex was negatively correlated to depression scores. Xue et al. 2014 found that PNES patients scored significantly higher on questionnaires for depression, anxiety and dissociation, but none of these scores were correlated to their study findings. Reuber et al. 2001 found that 22.3% of PNES patients in their study had at least one marker of brain abnormality, demonstrated on MRI, EEG or neuropsychological testing. The article proposes that physical brain disease plays a role in PNES. Due to heterogeneity in the examination methods of the patient, where only 18 of 206 PNES patients were screened with all three modalities, the figure is not a controlled estimate. No controls were included, which makes the finding even less valid for clinical use.

4.2.1.5. PNES and development: functional connectivity plasticity
Ding et al. 2014 found increased long range connection values in the bilateral calcarine fissure and lingual gyrus, correlated to the duration of PNES. The lingual gyrus is related to visual memory and facial recognition. This might represent adaption in PNES patients for long-term hypervigilance and increased response to external stimuli. A similar finding was done by Li et al. 2014 where functional connection values between the ventral anterior insula and the lingual gyrus could represent plasticity of the functional connectivity. This implies a possible adaption to long term social threat cues and increased response and greater attention to negative emotional stimuli. The finding is supported by a study demonstrating increased allocation of attentional resources to social threat in PNES patients (3). Labate et al. 2012’s finding of abnormal cortical thinning in motor- and premotor regions in the right hemisphere and the cerebellum bilaterally, correlated to depression scores, implies a mechanism involving adaptive cortical-subcortical plasticity within these regions.

4.2.1.6. Diagnostic implications
Although not their main focus, several of the study findings expand the field of options for diagnosing PNES. Both similarities and differences potentially contributing to misdiagnosing PNES for epilepsy are demonstrated. Ding et al. 2013 found that the coupling-strength of
functional-structural connectivity was significantly decreased in PNES patients. This finding provides high sensitivity and specificity to differentiate PNES-patients from healthy controls. More importantly, previous fMRI-studies on people with epilepsy have demonstrated a shift towards more randomness in brain organization. With the finding of more regular brain organization in PNES-patients, this finding can provide a new neuroimaging marker to distinguish PNES from epilepsy. Knyazeva et al 2010 found that reduction in prefrontal EEG synchronisation could be a marker of increased risk for PNES. Krishnan et al 2011 found that while epileptic seizures reset brain dynamics, PNES does not, and patients with PNES display lower levels of entrainment and resetting at events. This makes scalp-EEG with measurements of these values a possible diagnostic measure to exclude epilepsy. Network topology described by Xu et al 2014 demonstrated that PNES patients have stronger linkages between the frontal area and the temporal- and occipital areas than patients with epilepsy, with a classification potential at 92% accuracy, 100% sensitivity and 80% specificity.

4.2.1.7. Therapeutic implications
To successfully treat PNES is to decrease the PNES frequency, ultimately to complete remission. With a multifactorial pathogenesis, focuses for intervention should be manifold, but not many are proposed in the study articles. Increasing local connectivity is proposed by Barzegaran et al. 2012, by selective modulation of functional connectivity. Anti-epileptic treatment holds no place in the treatment. Reuber et al. 2002 found that EEG-abnormalities were 1,8 times more frequent in PNES patients, with epileptiform EEG-changes in 12,6% of the patients, much higher than in the general population. The finding was not statistically significant, but it provides an argument against initiation or continuation of anti-epileptic drugs based on interictal EEG-changes alone.

5. CONCLUSION

The findings in this review indicate that PNES patients have alterations in functional connectivity in brain networks mediating emotion processing, awareness, attention, executive control and motor function. The altered inhibitory function of the prefrontal cortex could play a central role, impairing executive functions and the feeling of self-agency. Increased functional connections between the limbic system and sensimotor regions, operating as possible "hyperlinks", can explain the abnormal emotional processing with subsequent altered consciousness and involuntary movements. Overall, brain network organization has been described to have reduced flexibility and impaired global information integration, with loss of optimal organization seen in small-world topology. The orbitofrontal cortex, the bilateral cerebellum, the insula and the fronto-temporal network in particular are highlighted as important structures. However, the findings are affected by small study populations and poor documentation of psychopathological traits, and the specific neural substrates of PNES remains to be proven. The relation to previous trauma also warrants further studies. Although not a focus in all articles, it is worth highlighting that PNES-development is not considered related to intelligence. Few remarks are made in regards to pathogenesis, but plasticity of functional connectivity is thought to play an important role, in response to stimuli perceived as threats. This latter finding is relevant to inappropriate avoidance tendencies observed in PNES patients, which provides one target for therapy. Other proposed therapy measures include selective strengthening of functional connectivity, in particular in the prefrontal cortex. Markers aiding in differential diagnosis from epilepsy have been demonstrated, related to small-world
organization and resetting values of brain dynamics. Further investigation of PNES pathology is needed, with sufficient sample sizes and a blinded study design. Psychopathological traits and trauma-experience must be controlled for. A multidisciplinary approach might be best suited, involving the fields of psychiatry, neuroscience and neurology.

REFERENCES


