An Integrative Neurocircuit Perspective on Psychogenic Non-Epileptic Seizures and Functional Movement Disorders: Neural Functional Unawareness

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Abstract

Functional Neurological Disorder (conversion disorder) is a neurobehavioral condition frequently encountered by neurologists. Psychogenic Non-Epileptic Seizure (PNES) and Functional Movement Disorder (FMD) patients present to epileptologists and movement disorder specialists respectively, yet neurologists lack a neurobiological perspective through which to understand these enigmatic groups. Observational research studies suggest that PNES and FMD may represent variants of similar (or the same) conditions given that both groups exhibit a female predominance, have increased prevalence of mood-anxiety disorders, frequently endorse prior abuse, and share phenotypic characteristics. In this perspective article, neuroimaging studies in PNES and FMD are reviewed, and discussed using studies of emotional dysregulation, dissociation and psychological trauma in the context of motor control. Convergent neuroimaging findings implicate alterations in brain circuits mediating emotional expression, regulation and awareness (anterior cingulate and ventromedial prefrontal cortices, insula, amygdala, vermis), cognitive control and motor inhibition (dorsal anterior cingulate, dorsolateral prefrontal, inferior frontal cortices), self-referential processing and perceptual awareness (posterior parietal cortex, temporoparietal junction), and motor planning and coordination (supplementary motor area, cerebellum). Striatal-thalamic components of prefrontal-parietal networks may also play a role in pathophysiology. Aberrant medial prefrontal and amygdalar neuroplastic changes mediated by chronic stress may facilitate the development of functional neurological symptoms in a subset of patients. Improved biological understanding of PNES and FMD will likely reduce stigma and aid

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the identification of neuroimaging biomarkers guiding treatment development, selection and prognosis. Additional research should investigate neurocircuit abnormalities within and across functional neurological disorder subtypes, as well as compare PNES and FMD to mood-anxiety-dissociative disorders.

Introduction

Functional Neurological Disorder (FND) (conversion disorder) is a neurobehavioral condition at the intersection of neurology and psychiatry, and is closely linked to the origins of both specialties. This disorder was first described in ancient Greece using gynecologic themes (wandering womb)[1] and later framed as demonic possession with the rise of Christianity. FND was introduced into the medical literature as "hysteria" and was considered an acceptable, neurologically diagnosable condition by the French neurologist Jean-Martin Charcot who stated "the neurological tree has its branches; neurasthenia, hysteria, epilepsy, all the types of mental conditions, progressive paralysis, gait ataxia".[2] A reframing occurred through the writings of Sigmund Freud, the Austrian neurologist turned founder of psychoanalysis, who suggested in *Studies on Hysteria* that "the aetiology was to be sought in sexual factors" and coined the term "conversion hysteria" as occurring when "the (intolerable) affective idea is *converted* into a physical phenomenon".[3] Pierre Janet, Freud's contemporary, theorized an important role for dissociation in the psychological underpinnings of conversion disorder rather than emphasizing intolerable (sexual) conflicts.[4]

Modern day clinical neurologists see approximately 30% of outpatients for medically unexplained symptoms (MUS),[5] and approximately 18% of those individuals are diagnosed with functional neurological symptoms.[6] In epilepsy and movement disorder subspecialties, upwards of 20-50% of patients admitted to the epilepsy monitoring units[7] and 20% of patients seen in movement disorder clinics[8] have psychogenic non-epileptic seizures (PNES) or functional movement disorders (FMD) respectively. Despite familiarity with diagnosing PNES or FMD, neurologists find these patients "difficult to help"[9] and lack a neurobiological understanding of this disorder.[10] Given the staggering frequency with which neurologists encounter patients with FND and the limited comfort neurologists and psychiatrists have in caring for patients with these syndromes, authorities in the field including Mark Hallett have suggested that FMD constitutes a "crisis in neurology",[11] a sentiment which should undoubtedly be extended to FND more broadly. While it has been suggested for several decades that neurologists and psychiatrists collaborate to effectively manage PNES patients,[12] it has recently become apparent that increased integration is required across neurology subspecialties and psychiatry. There is emerging evidence that PNES and FMD represent phenotypic variants of similar (or even the same) underlying conditions.[13]

In this perspective article, observational research studies directly comparing PNES and FMD patients will first be discussed. Thereafter, functional and structural neuroimaging studies will be reviewed to characterize systems-level neurocircuit abnormalities associated with these two conditions. Brain-behavior relationships in this cohort will be contextualized by integrating roles for emotional dysregulation, dissociation and early-life psychological trauma. Important brain regions in the neurobiology of PNES and FMD will be highlighted and future research directions will be suggested, including the need to identify neuroimaging biomarkers informing treatment development, selection and prognosis. This article focuses almost exclusively on non-epileptic seizure and movement disorder FND-subtypes to draw out several parallels between patients referred to epilepsy and movement disorder clinics respectively. While we acknowledge that the neuroimaging literature in functional limb weakness/paralysis[14-17] which has been reviewed elsewhere[18,19] is relevant given that patients frequently have multiple functional motor symptoms in parallel (i.e. inconsistent limb strength[20] in the setting of functional hyperkinetic limb movements), a detailed discussion of functional limb weakness is beyond the scope of this article.

Comparative Clinical Studies of PNES and FMD

Diagnostic guidelines for PNES and FMD have been published in the epilepsy and movement disorder literature respectively (See Table 1).[21,22] Despite these non-overlapping criteria, the Diagnostic and Statistical Manual of Mental Disorders-5 (DSM-5),[23] identifies both conditions under the overarching diagnostic category of Functional Neurological Symptom Disorder (FNSD) (synonymous with FND), with a specific symptom qualifier for distinct phenotypes (i.e. with seizures or abnormal movements). DSM-5 emphasizes "positive" examination findings for a FNSD diagnosis (which moves this disorder away from being considered a diagnosis of exclusion) and does not fundamentally require a temporal association with a psychological stressor. Consistent with a more inclusive framing, it has been observed that upwards of 25% of patients diagnosed with PNES subsequently developed additional MUS.[24] Our own group and others[25] have encountered several patients diagnosed with both PNES and FMD, suggestive that categorical distinctions in the neurological subspecialty literature warrant further considerations. Furthermore, we have observed that a given patient may at times be diagnosed with either PNES or FMD depending on the approach and expertise of the particular clinician.

Several observational cohort studies have compared neuropsychiatric characteristics in patients with PNES and FMD. In a study by Grimaldi and colleagues, 8 PNES patients and 9 clinically established or documented FMD subjects were compared on measures of anxiety (Spielberger State-Trait Anxiety Inventory) and depression (13-item Beck Depression Inventory (BDI-13)).[26] While both groups reported elevated depression symptoms, there was a trend towards increased state and trait anxiety in PNES patients compared to FMD subjects. Both groups also endorsed similar childhood sexual abuse histories (4 PNES; 3 FMD), and chart reviews showed that 5 PNES subjects had a family history of epilepsy, while 3 PMD subjects endorsed a family history of movement disorders.

A retrospective chart review study compared 116 documented PNES patients and 56 clinically definite FMD subjects.[25] Of note, 3 subjects were excluded from the analysis for

having co-existing PNES and FMD. While both groups were predominantly female, patients with PNES were younger (41 vs. 51), began exhibiting symptoms at a younger age, and had fewer years of education. Consistent with the phenotypic differences of each subtype, PNES patients typically had episodic events with loss of consciousness while FMD symptoms were more constant. PNES patients reported a significantly higher rate of prior abuse (including childhood abuse) compared to FMD subjects, although 32% of FMD patients also reported abuse histories and 12 out of 56 FMD charts failed to document this information. Both cohorts also endorsed depression, chronic pain, subjective cognitive complaints, and sleep disorders; FMD patients reported more frequent pre-existing anxiety disorders.

A prospective cohort study collected demographic, clinical and psychometric data on 35 PNES and 104 FMD patients.[27] This study observed that FMD patients were older (47.1 vs. 41.8) and had a greater proportion of male subjects (33.0% vs. 14.3%). Both groups were symptomatic approximately 3 years prior to diagnosis. Unlike the findings of the prior study,[25] both groups had similar educational backgrounds. While 87.7% of PNES subjects had impaired consciousness, it is noteworthy that 31.7% of FMD patients also reported impaired consciousness. Additionally, both cohorts reported similar decreases in quality of life and increases in somatization.

One prospective study compared 20 PNES and 30 patients with functional limb weakness/ paralysis[28]. Similar to comparisons between PNES and FMD subtypes, PNES patients were observed to be younger, more likely unmarried and reported a higher incidence of early-life abuse (incest) compared to individuals experiencing functional limb weakness/paralysis. Also, while there were no between-group gender differences, a higher proportion of PNES subjects met criteria for borderline personality disorder and reported adverse life events in the 12 months before assessment.

Overall these studies, while requiring replication with larger sample sizes, suggest that PNES and FMD patients have similar high rates of depression, anxiety, chronic pain, somatization, and subjective cognitive complaints, although FMD patients may be older, have a lower female:male ratio and potentially report a lower incidence of abuse compared to PNES patients. Given the neuropsychiatric similarities between PNES and FMD, and the suggestion by several authors that these conditions represent different presentations of a single disorder,[13,27] PNES and FMD may share a convergent neurobiology. The following sections review functional magnetic resonance imaging (fMRI), positron emission tomography (PET), single photon-emission computed tomography (SPECT), and quantitative structural MRI neuroimaging studies in PNES and FMD.

Neuroimaging Studies and Related Observations in PNES

Thus far, five neuroimaging studies have been conducted in PNES. van der Kruijs and colleagues performed a series of task-based and resting-state functional connectivity MRI studies. In the first of two studies, 11 PNES patients were compared to 12 healthy subjects.[29] The PNES group was reportedly without comorbid psychiatric disorders or malingering as determined through "extensive (neuro-) psychological assessment" and collateral information. Subjects were administered self-report measures of trait dissociation, and all subjects underwent two resting-state fMRI (rsfMRI) scans, a picture encoding task,

and a Stroop task. There were no statistically significant neural activation differences between PNES and healthy subjects during performance of the cognitive tasks. Based on activation peaks from the two paradigms, 9 region-of-interest ("seed") regions were identified to investigate rsfMRI connectivity differences. Seed-based functional connectivity analyses evaluate the temporal coherence between a region-of-interest and other brain regions. In PNES, enhanced resting-state functional connectivity was observed between brain areas involved in emotional processing (anterior cingulate cortex (ACC), insula), executive control (inferior frontal gyrus, parietal cortex) and movement (precentral sulcus). In particular, increased functional connectivity was observed between the left precentral sulcus seed region and the right perigenual ACC and anterior/posterior insula. Several functional connectivity patterns also correlated with reported trait dissociation, including a positive correlation between Dissociative Experience Scale (DES) scores and precentral sulcus-posterior insula functional connectivity.

The second rsfMRI connectivity study used a data-driven independent component analysis (ICA) approach.[30] ICA allows rsfMRI data to be decomposed into statistically maximally independent functional networks including the default mode network (DMN: a set of regions spontaneously active during passive self-reflective moments[31]), sensorimotor, executive, frontoparietal, and visual processing regions. Using similar inclusion/exclusion criteria as the first study, 21 PNES patients compared to 27 healthy subjects demonstrated abnormalities in several resting-state networks including: increased subgenual ACC, orbitofrontal cortex (OFC), and insula coactivations with the fronto-parietal network; increased ACC and insula coactivation with the executive control network; increased cingulate gyrus, superior parietal lobule, pre- and postcentral gyri, and supplemental motor area (SMA) coactivations with the sensorimotor network; and increased precuneus and cingulate gyrus coactivations with the DMN. PNES subjects also exhibited decreased coactivation of the OFC with the executive control network, and decreased precuneus coactivation with the sensorimotor network. In correlational analyses that combined PNES and healthy subjects, the above functional connectivity patterns positively correlated with trait dissociation scores. Overall, these functional connectivity patterns delineated prominent paralimbic (ACC, OFC, insula), attentional (posterior parietal cortex (PPC)), motor (SMA), and DMN (precuneus) sites of altered resting-state connectivity in PNES.

Another study used rsfMRI and diffusion tensor imaging in 20 PNES subjects compared to 20 healthy subjects to evaluate the organizational structure of brain networks.[32] Exclusion criteria for the PNES group included comorbid psychiatric conditions and malingering, and all patients were medication free for at least two weeks prior to participation. Prior research has shown that healthy subjects demonstrate functional and structural connections exhibiting small-world organizational properties,[33] defined by a limited number of temporally and spatially interconnected brain regions forming distinct networks rather than a construction of random network connections. Specific sites within networks exhibiting particularly robust connections are termed modules and hubs. Compared to healthy controls, PNES subjects exhibited altered network properties indicating a more regular (lattice-like) functional and structural organization pattern in emotional control, attentional, sensorimotor, subcortical, and default mode networks. PNES patients also showed decreased coupling of functional and structural connectivity, potentially suggestive of less efficient neural coordination in

PNES. In a separate article, these same PNES and healthy cohorts were compared using resting state, functional connectivity density mapping (a data-driven approach that delineates the density of short (local) and long range (distant) functional connections across regions).[34] PNES subjects compared to controls exhibited increased short range connections in the left superior and middle frontal gyri, ACC and bilateral middle cingulate gyri, and increased long range connections in bilateral SMA, visual processing regions, right posterior insula, superior temporal gyrus, pre and post central gyri and the left paracentral lobule. Notable decreases in long range connections in PNES subjects compared to controls were noted in the right orbitofrontal and ventrolateral prefrontal cortices and the inferior parietal lobule among other regions. These findings implicate large-scale functional connectivity changes in emotional processing/control (ACC, insula, OFC), sensorimotor (SMA, pre/post central gyri), and default mode networks in PNES.

Structural brain differences have been evaluated using two complementary quantitative techniques (voxel-based morphometry (VBM)[35] and cortical thickness analysis[36]) in 20 PNES subjects compared to 40 healthy subjects.[37] Patients underwent formal neuropsychological and psychiatric assessments, including dimensional anxiety, depression, and dissociation assessments. In VBM analyses, PNES patients exhibited decreased gray matter volumes in the right ACC, SMA, middle frontal gyrus, precentral gyrus, and bilateral cerebellum. A negative correlation was noted between Beck Depression Inventory (BDI) scores and gray matter volume in the right dorsal premotor cortex in PNES patients. Cortical thickness analyses identified thinning of the right paracentral gyrus, precentral gyrus, superior frontal gyrus, and precuneus. Increased BDI scores correlated with thinning of the right OFC, superior frontal, and paracentral gyri; Somatoform Dissociative Questionnaire-20 scores correlated with cortical thickness reductions in the left inferior frontal gyrus and central sulcus.

Taken together, these results suggest that PNES patients exhibit functional and structural alterations in brain networks mediating emotion regulation and awareness (ACC, OFC, insula), executive/cognitive control (inferior frontal gyrus, ACC), attention (PPC), self-referential processing (DMN, particularly the precuneus), and motor (SMA, precentral gyrus, cerebellum) functions. These findings require further clarification in the context of several limitations to the above studies. It is striking that four[29,30,32,34] of the five studies recruited PNES participants reported as free of psychiatric comorbidities, yet three of the studies[29,30,37] did not report performing a Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, Version IV Disorders (SCID-DSM-IV). It is well known that PNES patients have elevated rates of depression, anxiety (particularly panic disorder and post traumatic stress disorder (PTSD)), dissociative disorders, other somatoform disorders, and personality disorders that are potential confounding variables (or important aspects of the disorder itself) that requires specific assessment.[38-41] Similarly, several studies excluded patients with malingering, but given the complexity of formally diagnosing malingering, it remains unclear how this variable was definitively excluded. Surprisingly, task-based fMRI studies using emotionally valenced probes have yet to be performed in this population, and future studies should further characterize coping strategies, personality traits, and the impact of early-life trauma among other variables.

In addition to the quantitative functional and structural neuroimaging studies discussed above, evidence from studies utilizing observational EEG and MRI, ictal/interictal and subtraction SPECT, as well as post-surgical onset PNES cases may help elucidate the pathophysiology of this condition. PNES patients exhibit non-specific brain abnormalities on EEG and MRI,[42] and one report suggested a potential association with nondominant right hemispheric lesions.[43] Several patients have experienced PNES events immediately following frontotemporal epileptic seizures,[44,45] potentially linking emotion and/or behavioral disinhibition to the pathophysiology of PNES. Quantitative SPECT, apart from a role in lesion localization for epilepsy surgery, has been used in cases where there is diagnostic uncertainty despite video EEG.[46] While ictal/interictal and subtraction SPECT are typically normal in PNES patients,[47] focal insular hypermetabolism on subtraction ictal SPECT[46] and bilateral frontal and right medial temporal lobe hypometabolism on inter-ictal SPECT[48] have been reported in PNES. Several studies have also described patients developing new-onset PNES or somatoform disorders following epilepsy surgery.[49-53] These studies have identified right hemispheric resections[53] and anterior temporal lobectomy[51] as associated with the development of somatoform illness in post-surgical patients. Interestingly, new-onset FMD (psychogenic tremor and astasia-abasia) has also been described following right temporal lobectomy for medically refractory epilepsy.[54]

Neuroimaging Studies in FMD

Voon, Hallett and colleagues performed a series of fMRI studies evaluating neurocircuit abnormalities in FMD. 8 patients with clinically definite, positional functional (psychogenic) tremor participated in a within-subject fMRI study contrasting positional psychogenic tremor movements to volitional reproductions of their tremor in a distinct position and rest periods.[55] The contrast [Conversion Tremor vs. Rest] × [Volitional Tremor vs. Rest] identified hypoactivation of the right temporoparietal junction (TPJ). Functional connectivity analyses using the right TPJ as a "seed" region showed decreased connectivity between the TPJ and bilateral sensorimotor cortices, subgenual ACC/medial prefrontal cortex, cerebellar vermis, right precuneus/superior parietal cortex, and the left ventral striatum during psychogenic vs. voluntary tremors. This study screened for psychiatric disorders using DSM-IV criteria; two subjects endorsed major depression and three reported generalized anxiety disorder symptoms at symptom onset. One subject was also prescribed antidepressants. The authors' theorized that selective right TPJ hypoactivation (and related decreased connectivity with sensorimotor cortices) during psychogenic movements impaired FMD subjects' awareness of their own movement authorship.[56,57]

One published study to date investigated neurocircuit activations to emotionally valenced stimuli in 16 documented or clinically established FMD patients and 16 healthy subjects using an affectively valenced face-viewing task.[58] Exclusion criteria included current major mental illness, although FMD subjects endorsed remitted past diagnoses of major depression (5), generalized anxiety disorder (4), dysthymia (3), adjustment disorder (2), and panic attacks (2) based on the SCID-DSM-IV. Two FMD subjects also reported childhood sexual abuse, one participant met criteria for generalized anxiety disorder, and four subjects were taking psychotropic medications (benzodiazepine (3); antiepileptic drug (1)). Compared to healthy subjects, FMD subjects did not show preferential amygdalar activation for negative

vs. positively valenced stimuli; FMD subjects showed increased right amygdala activations to happy (and to a lesser extent also for fearful) stimuli in region-of-interest analyses. This differential amygdala finding remained when analyses controlled for state depression and anxiety scores. Also, for fear vs. neutral and happy vs. neutral contrasts, FMD patients exhibited increased functional connectivity between the right amygdala and the right SMA compared to healthy subjects. This latter finding suggested enhanced emotional (amygdalar) influence over brain regions mediating motor planning and behavior.

Another fMRI study evaluated internally and externally generated volitional motor initiation in 11 mixed-phenotype, clinically definite FMD patients compared to 11 healthy subjects.[59] While patients with current major depression were excluded, FMD subjects met SCID-DSM-IV criteria for prior depression (3), generalized anxiety disorder (3), and panic attacks (1). Two FMD subjects were also on benzodiazepines. During both internally and externally generated movements, FMD subjects exhibited lower left SMA activations and greater activations in the right amygdala, left anterior insula, and bilateral posterior cingulate cortex compared to healthy subjects. When comparing internally vs. externally cued movements, left SMA seed-based functional connectivity analyses showed decreased coactivations with bilateral dorsolateral frontal cortex (dlPFC) in FMD subjects. Reduced dlPFC-SMA functional connectivity potentially reflected reduced cognitive control over motor behavior. This study is noteworthy in that it helps delineate abnormal interactions across emotional processing, cognitive control and motor execution brain regions in FMD.

A SPECT imaging study investigated regional cerebral blood flow (rCBF) differences in 5 patients with clinically definite psychogenic tremor, 5 subjects with essential tremor and 5 healthy participants during rest and a tremor-inducing motor task.[60] Focusing on rCBF differences between psychogenic tremor and healthy subjects, FMD subjects showed increased left insula and inferior frontal gyrus activations at rest. During psychogenic tremor movements compared to rest, FMD subjects showed decreased bilateral ventromedial prefrontal cortex (vmPFC) and left perigenual ACC activations along with increased right cerebellar hemisphere and vermis activations. Similar to patterns identified in PNES, these findings suggest neurocircuit abnormalities linked to impaired emotion regulation and awareness, cognitive control/motor inhibition and motor coordination in patients with psychogenic tremor. A resting-state PET case study of an individual with a documented psychogenic tremor showed bilateral hypermetabolism of the medial PPC, potentially also denoting attentional and sensory integration deficits in the neurobiology of psychogenic tremor.[61]

Regional brain metabolism was evaluated in 6 clinically definite, psychogenic dystonia patients compared to 6 DYT1 positive dystonia subjects and 6 healthy individuals using $H_2^{15}O$ PET during rest, fixed right leg posturing and paced ankle movements.[62] Subjects with current major affective or psychotic disorders were excluded, although it is unclear if a structured psychiatric clinical interview was performed. In a combined analysis across all contrasts, individuals with psychogenic dystonia compared to healthy subjects demonstrated increased rCBF in right TPJ, caudate, bilateral dorsal thalamus, left cerebellar hemisphere and vermis; individuals with psychogenic dystonia also showed decreased rCBF in left dorsal ACC, TPJ, primary and supplementary motor regions, inferior parietal lobule,

cerebellar hemisphere, and right inferior frontal gyrus. Comparing paced ankle movements to rest, psychogenic dystonia subjects vs. healthy controls showed increased right dlPFC rCBF in region-of-interest analyses. These findings outlined prominent striatal-thalamic and cerebellar dysfunction in patients with psychogenic dystonia, along with abnormalities in cognitive-control (dorsal ACC, dlPFC, inferior frontal gyrus), self-agency/perceptual awareness (TPJ, inferior parietal lobule) and motor execution.

Dopamine transporter (DAT) SPECT imaging has emerged as a useful adjunct in the diagnosis of neurodegenerative parkinsonism by detecting presynaptic dopaminergic deficits in the striatum, and may have diagnostic value in challenging cases where a psychogenic Parkinsonism is suspected.[63] For example, in 5 patients with clinically established psychogenic Parkinsonism, 2 of 5 subjects showed a pre-synaptic dopaminergic deficit on DAT-SPECT imaging suggestive of a neurodegenerative or dual psychogenic-neurodegenerative etiology. Future ligand-based PET and SPECT neuroimaging studies may elucidate neurochemical abnormalities in FMD and PNES.

In summary, neuroimaging studies in FMD indicate neural alterations in neurocircuits mediating emotional expression, regulation, and awareness (ACC, vmPFC, insula, amygdala, vermis), cognitive control and motor inhibition (ACC, dlPFC, inferior frontal gyrus), motor planning and coordination (SMA, cerebellum), and perceptual awareness (PCC/TPJ). Striatal-thalamic abnormalities in psychogenic dystonia may relate to abnormal automaticity of behavior in prefrontal-subcortical networks.[64] Also, while the FMD neuroimaging studies frequently screened for psychiatric co-morbidities, future research with larger sample sizes and improved dimensional characterization of critical variables (mood, dissociation, early life sexual/physical abuse, coping strategies) will further refine brain-behavior relationships in FMD.

Emotional Dysregulation, Dissociation, and Trauma

To contextualize PNES and FMD neuroimaging findings, it is important to consider roles for emotional dysregulation and psychological trauma. While few studies have directly compared PNES and FMD, several studies have evaluated psychiatric co-morbidities and psychological trauma frequency in both groups. PNES patients have markedly elevated rates of depression, anxiety, other somatoform disorders (including pain syndromes), dissociative disorders, and personality disorders including borderline personality disorder.[38,65-68] Affectively, PNES patients exhibit elevated rates of PTSD[38,39,69] and panic disorder.[70-73] Interestingly, an early study comparing 32 patients with panic attacks to 15 PNES patients showed that 70% of PNES subjects experienced a majority of panic disorder symptoms during a PNES event and approximately 30% of subjects with panic attacks reported having "convulsions" during their panic attacks.[74] Patients with panic disorder have also infrequently endorsed focal neurologic symptoms during their events.[75] Compared to complex partial seizures, PNES events typically present with a greater number of somatic anxiety symptoms during attacks (e.g. autonomic arousal).[76] In a case series of 10 PNES subjects, panic attack-like warning symptoms were noted, poorly tolerated, and tended to decrease in duration over time (with PNES events described as providing relief from the uncomfortable autonomic arousal).[77] These findings suggest synergistic relationships

between mood-anxiety psychiatric co-morbidities and PNES. Psychiatric co-morbidities have been less well studied in FMD, although studies indicate that approximately 50% of patients have been previously diagnosed with a psychiatric condition, most commonly depression, generalized anxiety disorder, and personality disorders.[78-80] It is noteworthy that PNES patients frequently have concurrent paroxysmal panic attacks, while further research is needed to explore a relationship between FMD and generalized anxiety symptoms.

Emotional processing abnormalities have been empirically investigated in PNES and FMD. Bakvis and colleagues compared 19 PNES and 20 healthy subjects using a masked emotional Stroop task and observed a negative attentional bias for angry faces that positively correlated with prior sexual trauma reports.[81] In an affectively valenced approach-avoidance task, PNES patients compared to healthy subjects demonstrated delayed approach behaviors for angry vs. happy faces and exhibited increased cortisol levels. Elevated pre-task cortisol levels correlated with reaction time delays in PNES.[82,83] A subsequent neuroendocrine study showed that PNES subjects, particularly those with sexual trauma histories, had increased diurnal cortisol levels compared to healthy individuals.[84] In a study comparing PNES subjects to individuals with high and low PTSD symptoms using an affectively valenced picture viewing task,[85] PNES subjects rated neutral pictures more intensely than either PTSD-symptom group and rated pleasant pictures more emotionally intense than individuals with low-PTSD symptoms. Emotional processing deficits in FMD have been less well characterized, with one study identifying increased startle eye blink amplitude during both positive and negatively valenced picture viewing in FMD (healthy subjects only showed the expected enhanced eye blink amplitude for negatively valenced pictures).[86] Overall, these findings indicate that PNES subjects show an attentional bias and avoidant behavior for negative emotional stimuli, and have increased hypothalamic-pituitary axis output that is potentially linked to previously experienced sexual trauma. FMD patients, while less well studied, exhibit abnormal interactions between emotional processing and movement that require further characterization.

While stress responses have traditionally emphasized heightened autonomic arousal and increased amygdalar activity in fight or flight behaviors, dissociation is a distinct stress reaction also implicated in the neurobiology of functional neurologic symptoms. Dissociation can be conceptualized as a fragmentation and compartmentalization of one's self-perception and body-schema (depersonalization) and/or perception of the external world (derealization) such that an individual experiences a sense of detachment and estrangement. Dissociative experiences are common in panic disorder, PTSD, somatoform disorders, dissociative disorders, and borderline personality disorder among other conditions. A considerable literature has identified a positive association between dissociative experiences and PNES,[38,87,88] including links between increased dissociation and poor prognosis[89] and diminished quality of life.[90] Similar to the paucity of research studies investigating emotional processing abnormalities in FMD, dissociative symptoms in FMD have been understudied. In one sample of 64 clinically-definite FMD subjects compared to 38 healthy individuals, no differences were found in self-reported dissociation using the DES. While a detailed review of the neurobiology of dissociation is beyond the scope of this article and reviewed elsewhere,[91-93] research in primary dissociative disorders and in PTSD populations with prominent dissociation delineate abnormal brain activations in

hippocampal-based declarative and amygdalar-based emotional memory systems,[94,95] PPC/angular gyrus regions mediating multimodal sensory integration and perceptual awareness,[94-96] and medial prefrontal cortex regions (e.g. ACC) engaged in emotion regulation.[97-99]

Approximately 20-50% of PNES subjects endorse prior sexual-physical abuse and/or neglect.[66,100-103] A particular relationship between early-life childhood sexual abuse and PNES has been demonstrated in the literature,[101,104] and prior psychological trauma in PNES has also been linked to the development of other MUS.[102] In a large cohort of 176 subjects with definite PNES, prior sexual abuse was associated with early symptom onset, greater diagnostic delay, more severe spells typically of a "convulsive type," emotionally triggered events, and flashbacks among other symptoms.[105] While a subset of FMD patients also endorse prior sexual-physical abuse,[25,79] further research is required.

Convergent basic science and translational research studies have identified an important association between early-life stress and maladaptive structural brain changes.[106] Animal models of chronic stress show that the medial prefrontal cortex (including the ACC), hippocampus and amygdala undergo neuroplastic changes in response to prolonged stress.[107] The medial prefrontal cortex and the hippocampal CA3 region exhibit dendritic spine density reductions following repeated stress; amygdalar experience-dependent changes, while less well studied, have also been described. Recent large-scale volumetric analyses in human subjects observed ACC, OFC, insula, hippocampal, and caudate gray matter reductions associated with a history of childhood trauma.[108] Early-life interpersonal stress also predisposes to insecure adult attachment, which has been linked to amygdala and striatal dysfunction[109] and hypothalamic-pituitary-adrenal axis dysregulation.[110] Importantly, these findings overlap with neurocircuits implicated in PNES, FMD, and other medically unexplained somatoform illnesses.[111]

Important Neural Circuits in PNES and FMD

Based on neuroimaging findings in PNES and FMD, prefrontal-insular-amygdalar, PPC/TPJ, and premotor areas are some of the key regions implicated in the convergent pathophysiology of these disorders (See Figure 1). The medial prefrontal cortex, particularly the ACC, exhibits functional and structural brain alterations in PNES[29,30,34,37] and FMD.[55,60,62] The ACC has been classically subdivided into a ventral affective component and a dorsal cognitive component[112], and is also implicated in motivational states and visceral-somatic nociceptive processing.[113] More recent ACC structure-function parcellations implicate subgenual and perigenual subregions in emotion regulation and fear extinction, while dorsal ACC regions are engaged in emotional appraisal, expression and cognitive control.[114] ACC-subcortical connections include the nucleus accumbens/ventral caudate, ventral globus pallidus, and mediodorsal and ventral anterior thalamic nuclei. The subgenual and perigenual ACC are reciprocally connected to the amygydala, while the dorsal ACC (particularly posterior areas) is connected to dorsal and lateral prefrontal regions (including the SMA and dlPFC).[115] Hypoactivation of the subgenual and perigenual ACC as depicted in several FMD neuroimaging studies suggests diminished top-down regulatory

control of amygdalar activity. This would be consistent with increased amygdalar activation observed in FMD patients during both affectively valenced[58] and motor tasks.[59]

In contrast to FMD subjects, preliminary neuroimaging results in PNES potentially link trait dissociation to increased resting-state perigenual ACC activations.[29,30] This is noteworthy given the frequency of early life trauma, dissociation, and PTSD symptoms in PNES patients, and is consistent with heightened perigenual ACC activations seen in the dissociative subtype of PTSD.[92] Task-based, emotionally valenced neuroimaging studies in PNES would help clarify if this increased ACC activity is a static or dynamic finding; PTSD patients may exhibit both hyperarousal, re-experiencing symptoms and severe dissociation at distinct instances.[116] Similar to the identification of PTSD subtypes (hyperarousal, re-experiencing vs. dissociative),[92] distinct PNES subtypes may also be identified based on variables such as the degree of co-occurring dissociation. From a structural perspective, the only published study evaluating volumetric brain abnormalities in PNES subjects with motor-related events, showed reduced gray matter volumes in the posterior-dorsal aspects of the ACC and SMA, and decreased cortical thickness in paracentral and precentral gyri.[37] While further research is required, dorsal ACC-SMA structural alterations may lead to abnormal behavioral expression. Reciprocal ventral and dorsal ACC connections may mediate interactions between impaired emotion regulation and emotion expression.

In addition to the ACC and the amygdala, increased right insular resting-state functional connectivity has been observed in PNES,[29,30,34] and FMD patients showed increased left insular resting-state[60] and task[59] activations in neuroimaging studies. Anatomically, the posterior insula receives visceral-somatic sensory afferents from the thalamus and provides an interoceptive representation of the physiological condition of the body.[117] The mid-insula is an integrative zone where affectively and motivationally valenced information from the ACC, amygdala, and OFC influence sensory processing. Visceral-somatic, affective, and motivational information converge onto the anterior insula, and together with the ACC, the anterior insula (right > left) has been linked to emotional awareness.[118] The right ventral anterior insula is specifically functionally connected to the perigenual ACC at rest,[119] and these regions share large spindle-shaped von Economo neurons linked to social-emotional cognition. Insular structure-function relationships, contextualized using PNES and FMD neuroimaging findings, suggest that impaired interoception and emotional unawareness potentially contribute to the pathophysiology of functional neurologic symptoms.

The PPC, including the TPJ, is another site of prominent functional alterations in PNES[29,30,34] and FMD.[55,59,61,62] This heteromodal cortex has been implicated in motor intentional awareness and self-agency,[120] alien hand syndrome[121], misattributions in neuropsychiatric disorders including delusions of control,[18,122,123] and impairments in body-self integration (i.e. out-of-body experiences, nihilistic delusions).[124,125] PNES and FMD patients report that their symptoms are beyond their control, and at times minimize links between psycho-social stressors and their symptoms. Given the roles of the ACC, insula, and PPC/TPJ in emotional, perceptual and intentional awareness, abnormalities in these regions likely contribute to a neural *Functional Unawareness* in PNES and FMD.[18] Striatal-thalamic connections, particularly in prefrontal-subcortical circuits,[64] have been

implicated in non-conscious automaticity of behavior and may help integrate cortical and subcortical sites of dysfunction.

In addition to the regions outlined, abnormalities in brain areas mediating motor inhibition (inferior frontal gyrus[29,32,34,59,60,62]), episodic memory retrieval (precuneus[30,55,61]), motor coordination (cerebellar hemisphere, lobules I-V,VIII[60,62]), and dysmetria of emotion (vermis[55,60,62]) have been described in PNES and/or FMD patients. The inferior frontal gyrus is a critical node for behavioral inhibition,[126] which is noteworthy given previously characterized motor response inhibition deficits in FMD.[127] Also, while the cerebellum has historically been framed as mediating coordinated movements, evidence increasingly links the cerebro-cerebellar system to cognitive and affective functions.[128,129] Topographic cortico-ponto-cerebellar projections connect paralimbic regions (e.g. ACC) and heteromodal association cortices (e.g. PPC) to specific cerebellar subregions, and the posterior vermis (limbic cerebellum) has been linked to affective lability and panic attacks.[130]

Limitations, Future Directions, and Conclusions

There are several limitations to address regarding the integrative neurocircuit perspective for PNES and FMD put forth in this article. Both PNES and FMD are likely heterogeneous conditions with multiple subtypes within each condition (i.e. major motor vs. atonic PNES events; tremor vs. dystonia; hyperkinetic vs. hypokinetic movements; with vs. without additional psychiatric symptoms[40]) that require future large subject neuroimaging studies to help delineate neurocircuit patterns within and across distinct subtypes. Symptom-specific within-subject analyses may also prove useful in elucidating the biological basis of FND. Future FND research should look to compare not only across FND subtypes but also compare FND cohorts to psychiatric controls (i.e. panic disorder, PTSD, borderline personality disorder) to allow for an investigation of convergent and symptom-specific neurobiological mechanisms. Additional research should also incorporate genetic-epigenetic influences, and the neuroimaging based systems-level approach taken in this article should be further refined with other system-level modalities including electrophysiology techniques[131]. It should be noted that system-level measures of brain function, which may be associated with complex mental states and behaviors, are not necessarily inheritantly causative of specific abnormal symptoms; this highlights the continued need for integrative multi-level research efforts in PNES, FMD and FND more broadly.

While neuroimaging investigations in PNES and FMD are in their early stages, this important line of research is needed to further elucidate the pathophysiology of these conditions. Improved understanding of the biological mechanisms underlying these conditions (and disorder subtypes) will improve recognition that these patients suffer from a biological, functional brain-based disorder and will help reduce stigma associated with this diagnostic category. Functional and structural neuroimaging studies in PTSD have identified preserved perigenual ACC gray matter and cortical thickness as positive predictors of cognitive-behavioral therapy (CBT) treatment response[132] and prognosis[133] respectively, while increased subgenual ACC and amygdalar activations to negatively valenced stimuli have been linked to poor CBT outcomes[134]. The identification of neuroimaging biomarkers for treatment selection and prognosis would be critical in PNES, FMD, and FND more

broadly, as this will facilitate the development of improved treatments and the assignment of specific therapies to particular patients who will most likely benefit from a given intervention. Further neuroimaging and non-imaging studies should investigate similarities and differences across FND subtypes as well as compare FND to trauma related and mood-anxiety-dissociative disorders. Studies probing associations between autonomic measures, neuroendocrine profiles and neuroimaging findings will also advance our biological understanding of FND.

In conclusion, PNES and FMD demonstrate multiple clinical and phenotypic similarities, including increased rates of mood-anxiety-dissociative disorders and early-life abuse. Although neuroimaging research has been limited in PNES and FMD to date, convergent preliminary findings suggest alterations in neurocircuits mediating emotional processing, regulation, and awareness (ACC, vmPFC, insula, amygdala, vermis), behavioral inhibition and cognitive control (inferior frontal gyrus, dlPFC, dorsal ACC), self-referential processing and perceptual awareness (PCC/TPJ, precuneus), and motor preparation and coordination (SMA, cerebellum). The neural Functional Unawareness construct may be a helpful way in which to begin to conceptualize brain-behavior relationships in FND. Future FND research should investigate imaging and non-imaging biomarkers of diagnosis and treatment responses to aid improved biological understanding of this enigmatic and important disorder at the interface of neurology and psychiatry.

Acknowledgments

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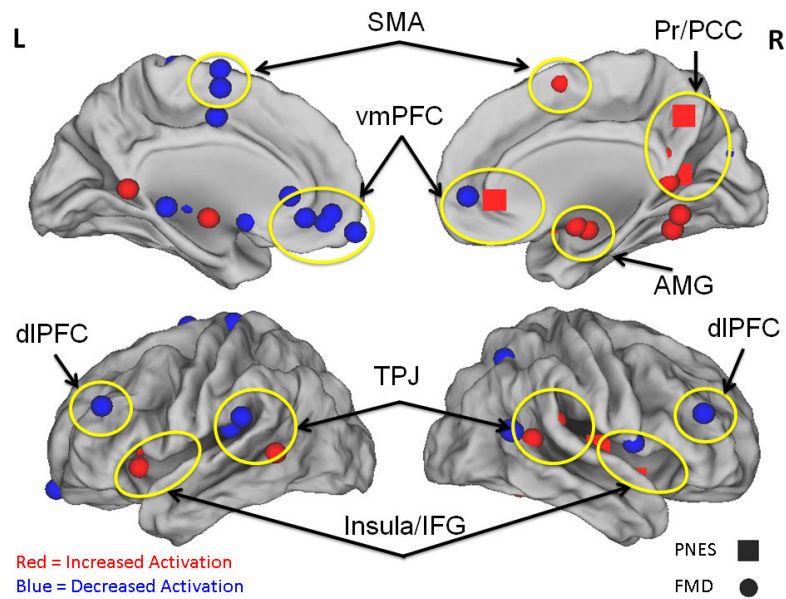
Figure 1.
Display of task univariate and "seed" based functional connectivity (multivariate) activation foci in patients with Psychogenic Non-Epileptic Seizures (PNES) or Functional Movement Disorders (FMD).[29,55,58-60,62] While functional neuroimaging studies have been limited to date in PNES and FMD, inspection of these activation foci suggests alterations in regions mediating emotional processing, regulation, and awareness (perigenual anterior cingulate cortex/ventromedial prefrontal cortex (vmPFC), insula, amygdala (AMG)), cognitive control (dorsolateral prefrontal cortex (dlPFC), dorsal anterior cingulate cortex, inferior frontal gyrus (IFG)), self-referential processing (temporoparietal junction (TPJ)/posterior cingulate cortex (PCC)/precuneus (Pr)), and motor planning (supplementary motor area (SMA)). Only main contrasts were displayed using Caret 5,[135] and cerebellar activation foci are not shown.

Table 1

Summary of diagnostic guidelines for Psychogenic Non-Epileptic Seizure and Functional Movement Disorder.[8,21,22]

Psychogenic Non-Epileptic Seizure	Functional Movement Disorder
Documented	**Documented**
Event observed on video EEG by clinician experienced in diagnosis of seizure disorders showing typical PNES semiology and no epileptiform activity in the peri-ictal period.	Remittance with suggestion, physiotherapy, psychotherapy, placebos, or 'while unobserved.'
Clinically Established	**Clinically Established**
Event observed on video or in-person by clinician experienced in seizure disorder diagnosis showing typical PNES semiology with event NOT captured on EEG. No epileptiform activity in a routine or ambulatory EEG of a typical PNES that would be expected to show epileptiform activity during equivalent epileptic seizures.	Inconsistent over time/incongruent with clinical condition + other manifestations: other 'false' functional neurologic signs (i.e. give-way weakness, non-anatomical somatosensory deficits), multiple somatizations, concurrent psychiatric disturbance.
Probable	**Probable**
Event observed in-person or on video by clinician showing typical PNES semiology. No epileptiform activity on routine or sleep-deprived EEG.	Inconsistent/incongruent movements with no other features or consistent/congruent + 'false' neurological signs or consistent/congruent + multiple somatizations.
Possible	**Possible**
Event described by witness or self-report/description and no epileptiform activity on routine or sleep-deprived EEG.	Consistent/congruent movements + obvious emotional disturbance.