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TITLE: Stress and Functional Neurological Disorders: Mechanistic Insights

AUTHORS:

Roxanne C Keynejad
Section of Women's Mental Health, Health Service and Population Research department, Institute of Psychiatry Psychology & Neuroscience, King's College London, United Kingdom (UK).

Thomas Frodl
Department and Hospital of Psychiatry and Psychotherapy, Otto von Guericke University Magdeburg, Germany.

Richard Kanaan
Section of Cognitive Neuropsychiatry, Institute of Psychiatry Psychology & Neuroscience, King's College London, UK, and Department of Psychiatry, University of Melbourne, Austin Health, Heidelberg, Australia; Florey Institute of Neuroscience and Mental Health, Melbourne, Australia.

Carmine Pariante
Stress Psychiatry and Immunology Lab, Institute of Psychiatry Psychology & Neuroscience, King's College London, UK.

Markus Reuber
Academic Neurology Unit, University of Sheffield, Royal Hallamshire Hospital, Sheffield, UK.

Timothy R Nicholson
Section of Cognitive Neuropsychiatry, Institute of Psychiatry Psychology & Neuroscience, King's College London, UK.

CORRESPONDING AUTHOR:

Dr Roxanne Keynejad

Health Service and Population Research, PO31 David Goldberg Centre, King's College London Institute of Psychiatry, Psychology & Neuroscience, Denmark Hill, London SE5 8AF.
roxanne.keynejad@kcl.ac.uk, 0207 848 8498

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Stress and Functional Neurological Disorders: Mechanistic Insights

ABSTRACT

At the interface between mind and body, psychiatry and neurology, functional neurological disorder (FND) remains poorly understood. Formerly dominant stress-related aetiological models have been increasingly challenged, in part due to cases without any history of past or recent trauma. In this perspective article, we review current evidence for such models, and how research into the role of traumatic stress in other disorders and the neurobiology of the stress response can inform our mechanistic understanding of FND.

First, we discuss the association between stress and the onset or exacerbation of a variety of physical and mental health problems. Second, we review the role of hypothalamic-pituitary-adrenal axis dysfunction in the neurobiology of ill-health, alongside evidence for similar mechanisms in FND. Third, we advocate a stress-diathesis model, in which biological susceptibility interacts with early life adversity, where FND can be precipitated by traumatic events later in life and maintained by psychological responses. We hypothesise that greater biological susceptibility to FND is associated with less severe remote and recent stress, and that FND precipitated by more severe stress is associated with lower biological vulnerability. This would explain clinical experience of variable exposure to historical and recent traumatic stress among people with FND and requires empirical investigation.

A testable, evidence-based stress-diathesis model can inform nuanced understanding of how biological and psychological factors interact at the individual level, with potential to inform personalised treatment pathways. Much-needed research to establish the aetiology of FND will enhance clinical care and communication, facilitate effective treatment and inform prevention strategies.

INTRODUCTION

Functional Neurological Disorder (FND), also known as Conversion Disorder, has been historically conceptualised as the archetypal stress-related condition, but current evidence suggests that historical and precipitating stressors are neither necessary nor sufficient to cause the disorder. The role of stress, particularly severe traumas, in the aetiology of FND remains controversial, but there is consistent evidence that such experiences are major risk factors for, and of mechanistic and therapeutic relevance to, a significant proportion of cases.[1] In this perspective article, we review mechanistic insights into FND provided by the latest neurobiological stress research.

Multifactorial, biopsychosocial models predominate for FND, but details of biological mechanisms remain elusive. However, recent research in other fields, from basic neuroscience to mechanistic studies of other stress-related disorders, is starting to reveal insights into the molecular processes potentially underpinning interactions between biological vulnerability (diathesis) and environmental stressors, as part of a 'stress-diathesis' model. Furthermore, a growing body of literature shows how both early life and precipitating stressors play an aetiological role in physical as well as mental health disorders. Such developments have the potential to shape our understanding of FND's pathogenesis, with wider implications for our understanding of functional disorders affecting other bodily systems. FND is suspected when neurological symptoms arise in the absence of identifiable neuropathology or pathophysiological disease mechanisms. DSM-5 reflects the fact that FND is not a diagnosis of

exclusion, but has distinct 'positive' clinical features differentiating it from other disorders (Box 1).[2] FND is common, often causes severe and chronic disability, but is comparatively under-researched. Many questions about its aetiology await clarification.[1s]

Classical models attributed FND to psychological stressors, particularly historical traumas. So influential was this view that cases without traumatic histories were sometimes ascribed to poor or repressed memories, or even conscious denial. This hypothesis is difficult to prove or disprove, and the possibility that FND can arise in the absence of remote or proximal traumas remains. Recent research supports significantly more severe stressful life events among people with FND than depressed and healthy controls, especially in the month preceding symptom onset; under 20% of aetiologically relevant events were identified in routine clinical practice.[3] However, a significant proportion of people with FND identified no distressing life events, even when best available assessment methods were employed.

Given the lack of definitive empirical evidence for the necessity of precipitating stressors in the aetiology of FND, an exclusive focus on stressors in cases with no history of trauma can be counter-productive to clinician-patient relationships. Furthermore, early and more recent stressful life events are relatively common in the general population, so aetiological relevance cannot be assumed when identified. The requirement for a triggering stressor was therefore removed from DSM-5 but retained as a sub-type specifier (Box 1).

Box 1: DSM-5 functional neurological symptom disorder (conversion disorder) diagnostic criteria

A. One or more symptoms of altered voluntary motor or sensory function.
B. Clinical findings provide evidence of incompatibility between the symptom and recognized neurological or medical conditions.
C. The symptom or deficit is not better explained by another medical or mental disorder.
D. The symptom or deficit causes clinically significant distress or impairment in social, occupational, or other important areas of functioning or warrants medical evaluation.

Specify:

- Symptom type: e.g. weakness/paralysis, abnormal movement, attacks/seizures, anaesthesia/sensory loss.
- With/without psychological stressor (associated with symptom onset).
- Acute (< 6 months) or persistent (> 6 months).

Can we therefore reconcile the observation that traumatic experiences appear aetiologically important in some cases, without being identified in all people with FND? Since Briquet in 1859,[2s] the roles of biological susceptibility, difficult life events and precipitating trauma in the aetiology of FND have been recognised. From Bleuler[3s] and Rosenthal's[4s] work on schizophrenia to the Camberwell collaborative depression study[4], 'stress-diathesis' models aim to explain how prior diatheses interact with precipitating stressors to cause psychopathology. In this perspective article, we detail how this model retains contemporary relevance for FND, supported by renewed interest in traumatic stressors.[5s-7s] We first outline the evidence for associations between stress and ill-health, including mental health, functional and physical health disorders. We then summarise the biology of adaptive and maladaptive stress responses and relevant evidence from clinical disorders and animal models. We review advances in the neurobiology of stress-related presentations, such as post-traumatic stress disorder (PTSD), alongside evidence for similar mechanisms in FND. Finally, we propose a research agenda for FND and other functional ('medically unexplained' or somatoform) syndromes.

STRESS AND HEALTH

Mental health and functional disorders

Transient anxiety or distress in response to stress is often adaptive, unlike anxiety disorders and depression, which persist long after the stressor and impact on functioning. Seminal research among women living in Camberwell, UK, demonstrated the association between frequency and type of previous-year stressful life events and subsequent psychopathology. Specifically, stressors categorised as 'severe danger' were associated with independently-diagnosed anxiety, 'severe loss' was associated with later depression, and experiencing both 'severe danger' and 'loss' was associated with mixed anxiety and depression.[5] A large, albeit inconsistent, literature suggests hypothalamic-pituitary-adrenal (HPA) axis dysfunction in anxiety disorders.[8s]

Stress is strongly associated with most psychiatric disorders, both via early life traumas as putative 'vulnerability factors', and later life events preceding symptom onset, as 'precipitating factors'. Childhood abuse is associated with high odds ratios (ORs) for all common psychiatric disorders. For example, the UK household Adult Psychiatric Morbidity Survey of over 7000 individuals reported OR=10 for psychosis,[9s] OR=5 for depression, and OR=12 for phobia among people reporting non-consensual sexual intercourse under 16 years.[6] A recent meta-analysis found a significant correlation between childhood trauma and severity of hallucinations and delusions, and that severity of childhood neglect correlated with negative symptoms of psychosis, such as lethargy and apathy.[7] A meta-analysis[8] found that childhood maltreatment and was associated with significantly more severe and frequent relapses of bipolar affective disorder, higher rates of psychiatric comorbidity and suicide attempts. Structural and functional neuroimaging correlates of childhood maltreatment[10s] (so-called 'limbic scars') have led authors to propose 'ecophenotypes': sub-types of psychopathological phenotypic expression according to early-life adversity.[9]

FND studies show high rates of preceding severe life events, compared to healthy controls and people with depression, with increasing frequency preceding symptom onset.[3] A recent meta-analysis of case-control studies found higher frequency of both childhood and adulthood stressors in people with FND than controls.[1] It reported OR=2.8-4.3 for stressful life events preceding FND symptom onset, with higher ratios in studies using better-quality interview methods. Odds ratios were greatest when people with FND were compared with healthy controls (OR=8.6), compared to neurological (OR=2.5) and mental health (OR=2.0) control participants. A temporal interaction between stress exposure and symptoms is supported by evidence that late-onset (over 55 years) functional seizures are associated with higher rates of severe physical health problems and health-related trauma, whilst younger-onset functional seizures are associated with higher rates of antecedent sexual abuse.[11s]

A systematic review of other functional disorders (including irritable bowel syndrome, chronic pelvic pain and somatisation disorder) also showed significantly increased rates of lifetime abuse in comparison to controls, and an association of abuse with symptom severity.[10] A case control study of chronic fatigue syndrome (CFS) clinic referrals found more severe stressful life events and difficulties in the three months (OR=9) and year (OR=4.3) preceding illness onset, compared to age and sex-matched population controls.[11]

Physical health disorders

The association between stress and the onset or exacerbation of symptoms is acknowledged by the addition of "psychological factors affecting other medical conditions" to DSM-5.[2] Here, we discuss robust findings from dermatology, cardiology and neurology.

Dermatological disorders

The historically-recognised association between stress and exacerbations of skin disorders, such as flare-ups of previously dormant psoriasis, is increasingly understood in terms of neuroendocrinology and inflammation.[12s] For example, dysregulation of pro-inflammatory processes and corticotropin-releasing hormone (CRH) have been identified in psoriasis, atopic dermatitis, acne, allergic reactions and alopecia areata.

Cardiovascular disorders

The common belief that cardiovascular disorders can be caused, or at least precipitated, by stress is increasingly supported by evidence. Large prospective cohort and case-control studies of many thousands of participants support an association between ischaemic heart disease and low job control[12], and self-reported work, home, financial and major life stress.[13s]

Rates of life-threatening arrhythmias doubled in the month following the World Trade Center attacks, in New York residents with implantable cardioverter-defibrillators (ICD) not personally affected.[14s] Anger and anxiety are associated with increased rates of ICD shocks,[15s] ameliorated by psychological treatment.[16s] Episodes of atrial fibrillation (AF) increase 2.5-fold after feelings of stress, sadness, anxiety and anger,[17s] and long-term anger, hostility and tension predict AF and coronary heart disease.[18s]

The rare, but severe, and increasingly recognised, Takotsubu cardiomyopathy, known as stress cardiomyopathy or 'broken heart syndrome', is associated with stressful life events.[13] Even impersonal stressors can seemingly provoke cardiac dysfunction: myocardial infarction rates increased three-fold in Germans during their football team's 2006 World Cup matches.[14] Furthermore, PTSD has a complex and bidirectional relationship with cardiovascular disease incidence, although studies exploring causation are lacking.[19s] Finally, robust methods for identifying stressful life events indicate elevated rates of severe events in the year preceding strokes, and strokes preceded by severe stress are associated with less severe hypertension.[20s]

Neurological disorders

A strong association between migraine and stress is reported by patients and observed by clinicians. High rates of childhood maltreatment, especially emotional abuse and neglect, and re-victimisation in adulthood are observed in outpatient clinic attendees diagnosed with migraine.[21s] A systematic review found that stress is self-identified as a precipitant by 58% of people experiencing migraine. However, self-report methods limit interpretation of this study:[22s] sub-clinical prodromal migraine symptoms could explain preceding experiences of stress in a proportion of cases. Evidence that Norwegian adolescents who survived the Utøya mass killings experienced elevated rates of migraine (OR=4.3) and tension-type headache (OR=3.39) compared to matched controls, supports a role for stress and anxiety.[23s]

The association between stress and epilepsy is also well-described. Early-life stress is increasingly acknowledged in the development of mesial temporal lobe epilepsy,[24s] and preceding stress is the most frequently reported epileptic seizure trigger, albeit confounded by sleep deprivation, alcohol and missed medication.[25s] A study of over 4,500 people with epilepsy found that 5 cases per 1,000 arose abruptly after a stressful event.[26s] A review found mixed results from prospective human studies, but more convincing evidence from animal models, of increased epileptic activity and seizures in response to endogenous and exogenous stress mediators. Stress-precipitated epileptic

seizures, with improvement in response to stress management interventions, affect a proportion of people with epilepsy.[27s]

There is accumulating evidence that other neurological disorders are associated with stress, such as Multiple Sclerosis (MS). Elevated rates of severe life events in the six months preceding MS onset identified by case-control studies[28s] have been supported by meta-analysis.[29s] A prospective longitudinal study found that increased conflict and disruption of routine increased the odds of new gadolinium-enhancing (Gd+) brain lesions on MRI, in people with relapsing MS, eight weeks later.[30s] A randomised controlled trial of stress management therapy for MS showed reduced cumulative Gd+ and new T2 brain lesions, and higher rates of Gd+ and new T2 brain lesion-free scans in the treatment group, compared to a waiting list control group, which disappeared at 24 weeks' follow-up.[31s]

Stress may also influence the development and symptom severity of Parkinson's Disease (PD).[32s] Anxiety symptoms and disorders commonly precede and follow development of PD,[33s] and neurotic personality traits are associated with increased risk of PD, attenuated by smoking.[34s] Stress can also worsen motor and non-motor PD symptoms, prompting the theory that age-related HPA axis dysfunction increases dopaminergic neurone susceptibility to the effects of stress.[35s] Finally, tremor syndromes are characteristically worsened by stress and anxiety, and studies suggest higher rates of anxiety and perfectionism in musicians with focal dystonia, than healthy musician controls.[36s]

THE NEUROBIOLOGY OF THE STRESS RESPONSE

Here, we briefly review the HPA axis and how its dysfunction in animal and human populations contributes to neurological and behavioural symptoms.

HPA function and dysfunction

The HPA axis is intimately involved in homeostatic responses to environmental change by regulating metabolic and immune functioning (Figure 1).[15,16] The association of psychiatric symptoms with states of hypocortisolaemia (e.g. depression in Addison's disease) and hypercortisolaemia (e.g. psychosis in Cushing's syndrome or following corticosteroid treatment), and their resolution following endocrine recovery, demonstrate how the HPA axis influences mental as well as physical health.

Allostasis is the healthy process of adaptation to environmental challenges, facilitated by stress hormones, neurotransmitters, cytokines and other mediators. When these processes are insufficient, recurrently activated or persist beyond the stressor, they cause harmful brain and bodily wear and tear – allostatic load or overload,[17] which predispose to disease. Stimulation of one allostatic system frequently triggers a cascade of responses by others.[37s] For example, persistent hypercortisolaemia and elevated inflammation levels may explain the increased risk of cardiovascular disease,[38s] metabolic syndrome[39s] and cognitive decline[40s] in people exposed to chronic stress. The long-term impact of childhood adversity on adult mental health and age-related disease suggests 'biological embedding' of these early experiences in developmentally-sensitive, inter-related allostatic systems.

Inflammatory and stress responses are closely linked. Animal and human studies of acute inflammation triggered by lipopolysaccharide injection and chronic illness (such as obstructive sleep apnoea) have demonstrated disruption of the intrinsic circadian pattern of HPA activity, with widespread effects on glucocorticoid target organs.[18] The Dunedin cohort study showed that

stressors can affect multiple allostatic systems: adults with a history of childhood maltreatment had elevated baseline inflammatory biomarkers, including C-reactive protein (CRP), fibrinogen and white blood cells.[19]

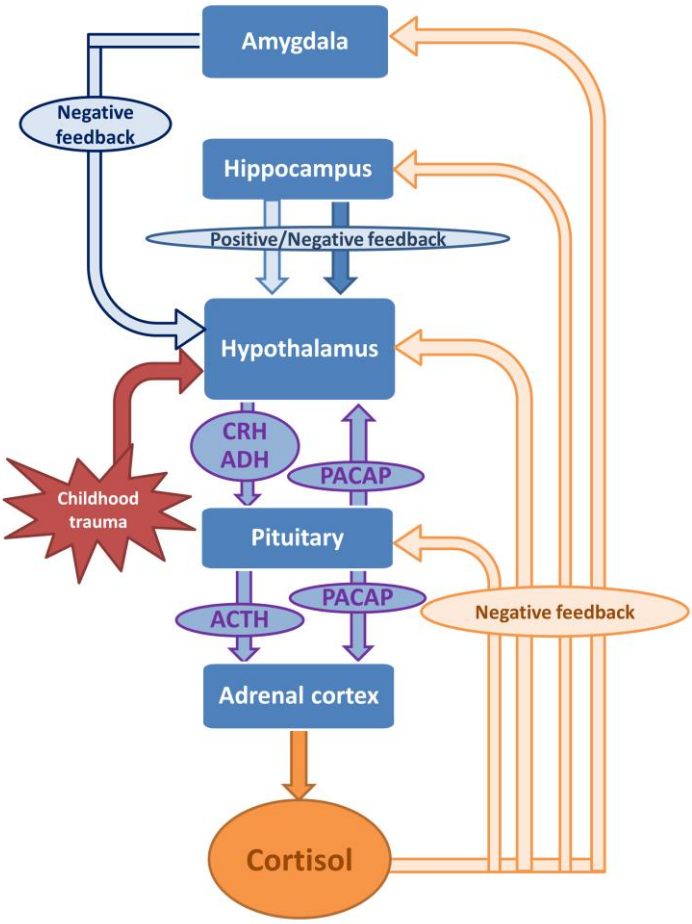

Figure 1: The HPA axis[15]

Corticotropin-releasing hormone (CRH) secretion by the paraventricular nucleus (PVN) of the hypothalamus is traditionally considered the first response to a physical or psychological threat. CRH stimulates pituitary adrenocorticotropic hormone (ACTH) secretion, prompting glucocorticoid release by the adrenal cortex in a feedforward cascade. Cortisol, the main glucocorticoid, is tightly controlled by negative feedback at the pituitary gland, hypothalamus and hippocampus[60]. Pituitary adenylate cyclase-activating polypeptide (PACAP) is thought to modulate the HPA response to acute psychogenic but not systemic stress, via CRH and increased adrenal cortisol secretion.[36]. ADH: Antidiuretic hormone/Arginine Vasopressin.

The glucocorticoid cascade hypothesis proposes that excess cortisol secretion in response to stress causes hippocampal damage, which in turn reduces negative feedback on CRH, resulting in uncontrolled secretion and further damage. Hypercortisolaemia is associated with altered synaptic plasticity, reduced neurogenesis, neuronal atrophy and excess secretion of excitatory neurotransmitters such as glutamate, triggering hippocampal changes which can lead to cell death.[20] Neurobiological studies of these processes in clinical populations and animals provide potential insights into the mechanisms underlying stress-related disorders, including FND and PTSD.

HPA dysfunction in animal studies

The 'stress inoculation hypothesis'[21] proposes that early-life exposure to stressors over which the juvenile exerts control is associated with appropriate hormonal and behavioural responses to stress in adulthood. Animal studies consistently show that prenatal, early life and adult stress are associated with increased activity of phagocytic microglia in the hippocampus and prefrontal cortex.[22]

Research into degu rodents suggests impaired dendritic development following early life stress caused by maternal separation.[23] This supports a 'two hit' hypothesis, whereby microglia and dendrites are primed by early life adversity to be more sensitive to future stress. The evolutionary 'match/mismatch' theory argues that mismatch between early life stress and the adult environment predisposes to non-communicable, including mental health, disorders.[24] Microglial and dendritic pathology are hypothesised to mediate the relationship between stress and mental disorders; this could also apply to functional disorders.

Rat studies support epigenetic mechanisms for childhood influences on adult behaviour. Rat pups receiving low maternal nurturing show increased methylation of the glucocorticoid receptor (GR) gene promoter at a hippocampal nerve growth factor binding site, resulting in lifelong reduced GR expression from the first week of life.[25] By contrast, pups of high-nurturing mothers lack this methylation, have greater hippocampal GR expression, are less anxious adults and more nurturing mothers to their own pups.

Different regions of the human brain undergo synaptic proliferation, pruning and myelination at different stages of development. Animal studies can experimentally manipulate early life and adult stress, to test clinical hypotheses about sensitive periods.[41s] Inter-species variation in brain development and vulnerability to early life adversity means that human studies must test hypotheses derived from animal models.[42s]

For example, animal research has studied the evolution of the autonomic nervous system, from the primitive, unmyelinated vagus to the mammalian, myelinated vagus.[26] In the case of seizure-variant FND (also known as psychogenic, non-epileptic or dissociative seizures), chronically reduced resting vagal tone has been hypothesised to underlie recurrent 'fight or flight' responses to stressors, as further reduction of vagal tone to appraise the stressor (a 'vagal break') is not possible when sympathetic activity (indicated by low heart rate variability) is low at baseline.[27]

HPA dysfunction in clinical populations

The relationship between trauma, HPA, neuroanatomical and clinical pathology is highly complex. In recent studies,[28] childhood maltreatment was associated with HPA axis dysfunction, epigenetic regulation of HPA axis-related genes, and also with structural and functional brain alterations suggesting a relationship between these factors. Findings from psychiatric disorders like depression might also apply to stress-associated disorders like PTSD and FND. For example, preliminary evidence suggests increased methylation of the oxytocin receptor gene (OXTR) promoter in people with functional motor symptoms, compared with matched controls.[29] The glucocorticoid cascade hypothesis can be expanded to incorporate recent advances in our understanding of genetic, epigenetic, personality and time-dependent factors, including evidence from animal studies, with benefits for psychiatric research.[20]

Recurrence of depression is associated with reduced hippocampal volume, moderated by age of onset,[43s] whilst chronic depression and relapses over three years' follow-up are associated with

reduced amygdala and dorsomedial prefrontal cortex volumes.[30] In contrast to the evidence of hypercortisolism in depression and psychosis which prompted the glucocorticoid cascade hypothesis, hypocortisolism[44s] and increased GR binding and function in PTSD suggest hypersensitivity of negative feedback.[31] Prospective studies suggest low baseline cortisol could be a risk factor for PTSD[32] and that hydrocortisone administration post-trauma could be protective,[45s] by interfering with traumatic memory retrieval.[46s]

PTSD is the archetypal stress-related disorder, and genetic research suggests potential mechanisms through HPA dysfunction. For example, FKBP5 is a 'co-chaperone' protein, which regulates the effects of cortisol on gene expression. Studies in general medical clinics found that specific FKBP5 and CRH receptor 1 single nucleotide polymorphisms (SNPs) interact with severity of childhood abuse to predict adult symptoms of PTSD[33] and depression.[34] Exposure to childhood adversity in individuals with these same FKBP5 risk alleles is associated with epigenetic changes,[35] increased dorsal amygdala reactivity[36] and attentional bias to threat.[37]

Pituitary adenylate cyclase-activating polypeptide (PACAP) is thought to modulate the HPA response to acute psychogenic but not systemic stress, via CRH and increased adrenal cortisol secretion.[38] With its selective PAC1 receptor, PACAP is associated with glucocorticoid secretion and anxiety in response to stress in mouse models.[39] In women only, PACAP levels correlate with PTSD diagnosis and symptom severity, and a PAC1 gene SNP predicts PTSD diagnosis and symptoms.[40] The location of this SNP in a proposed oestrogen receptor element of the gene suggests that oestrogen may influence its expression, which may explain the female preponderance of PTSD (also observed in FND.[47s])

However, genetic findings are limited by studies focusing on single candidate polymorphisms, given the polygenic nature of the HPA axis, and small sample sizes compared with much current genetic research. Whilst promising, polygenic approaches[48s] remain in their infancy and require replication, given the small effect sizes of common genetic variants, heterogeneity between patients, difficulties in robustly measuring stressful experiences in large samples and ascertaining the temporal relationship between trauma and symptoms. Recent, rapid improvements in technological affordability, coupled with greater collaboration between research centres, mean that genetics may become increasingly informative for unifying our understanding of FND's pathogenesis.[49s]

NEUROBIOLOGY OF FUNCTIONAL DISORDERS

Aetiological and mechanistic theories of FND have focused on interactions between biological, psychological and social factors, although biological evidence is particularly limited. We focus here on empirical evidence from fields of most relevance to stress response dysfunction in FND. These perspectives are not mutually exclusive and may each represent different mechanistic levels of the same, or overlapping, aetiological processes.

HPA axis dysregulation

The limited literature investigating stress biomarkers in FND has yielded conflicting findings from relatively small samples. One study comparing 18 medication-free participants with seizure-variant FND with well-matched healthy controls, found significantly increased basal diurnal cortisol levels.[41] Elevated basal cortisol was associated with a history of sexual trauma,[50s] which was in turn associated with attentional bias for angry faces on a masked emotional Stroop task.[42] The same group found that participants with seizure-variant FND showed higher 'approach-avoidance congruency' for angry faces on a computerised task in comparison to controls, which correlated with

basal salivary cortisol.[51s] Another study of 33 patients with functional movement disorders found no significant differences from healthy controls in salivary cortisol, but over half were taking variable doses of psychotropic mediations, with potentially sedative or anxiolytic effects capable of influencing the HPA response.[43] A recent study found that participants with motor FND had higher background salivary cortisol and (sympathetic) alpha amylase than controls, associated with the number and impact of stressful life events they had experienced. Another study found that people with FND reported higher stress, despite no biomarker differences from controls, during and after the Trier social stress test. This mismatch between subjective and biological stress responses supports a role for impaired interoception in FND.[44]

Neuroimaging research found that reduced regional volumes including the left hippocampus and left anterior insula (women only) correlated with severity of childhood abuse and lifetime trauma, but not self-reported FND symptoms.[45] FND case series indicate that symptoms develop in a proportion after brain injury, including post-neurosurgery.[46] However, this association may not indicate causative lesions; post-surgical or post-injury stress, or 'abreaction' following anaesthesia could contribute. Furthermore, studies describing brain lesions in FND have failed to show consistent patterns of lateralisation or localisation supporting a direct aetiological link. The few structural neuroimaging studies to date are limited by small sample sizes, diagnostic heterogeneity, comorbidities and cross-sectional designs. Preliminary findings suggest a potential aetiological role for trauma-specific neuroplasticity in FND but require further investigation.

Allostatic load

Although the relationship between FND and disorders such as CFS remains controversial, several studies have investigated biomarker profiles in participants with a range of so-called 'medically unexplained' diagnoses. A review found that the evidence of exposure to acute and chronic stress, endocrine, autonomic and inflammatory biomarkers in irritable bowel syndrome, fibromyalgia, and CFS was inconclusive, frequently contradictory and focused on single systems.[47] A study of 182 patients with CFS measured an 'allostatic load index' comprising 11 biomarkers of metabolic, cardiovascular, inflammatory, HPA axis and sympathetic nervous system activity. An angiotensin-1 converting enzyme (ACE) SNP was associated with higher interleukin-6, CRP and lower cortisol levels in women, independent of age, sex, BMI and fatigue levels, which could support a stress-diathesis model.[48] Clinical heterogeneity is likely to reflect multiple potential aetiologies in different patients, in different combinations. Wide-ranging environmental influences on non-specific biomarkers mean that simultaneous assessments of stress, endocrine, autonomic and immune systems in large longitudinal samples, ideally alongside genetic and neuroimaging data, are required to establish the relevance of these findings to FND.

Freeze/Hide response

A developmental perspective proposes that functional symptoms arise from innate responses to threat, part of a 'defence cascade' from arousal to (in extreme cases) collapsed immobility.[49] Two threat responses relevant to FND are freezing (which inhibits negative emotions), and hiding (which internally appeases distress).[50] In addition to approach-avoidance of angry faces,[42] participants with FND have been shown to have increased periaqueductal grey matter (involved in the freeze response to fear) and supplementary motor area (SMA, involved in self-awareness and motor control) activation in response to sad faces, in addition to the amygdala activation also seen in people with depression, PTSD and childhood maltreatment.[51]

Darwinian concepts of stress [52] propose that a balance of genetic traits has been preserved across species, favouring a mixture of individuals with high ('hawks') and low ('doves') levels of aggression.

That is, hawks are hypothesised to favour fight-flight responses to stressors, and doves favour a freeze-hide strategy, with trade-offs in health and disease. This model suggests that sickness responses, including fatigue, anorexia and depression, could result in 'freeze-hide' behaviour, as an evolved behavioural strategy potentially mediated by immunological and neuroendocrine cascades.[53]

Relatedly, people with FND causing limb paralysis are more likely to report 'escapable' life events, especially immediately preceding the onset of symptoms, than controls.[3] When recalling life events with escape potential, people with FND have significantly higher left dorsolateral prefrontal cortex activity and lower left hippocampal activity, with increased activity in the right SMA and temporoparietal junction, than when recalling similarly threatening life events from the same period.[54] Whilst recalling life events, FND participants did not demonstrate the right inferior frontal cortex activation seen in controls, but did show enhanced connectivity between the amygdala, SMA and cerebellum. These findings support an association between abnormal emotional and memory processing of life events, and changes in motor areas pertaining to symptoms and body schemata.

Attentional hypotheses

One mechanistic account of FND[55] proposes that aberrant functional connectivity between the limbic system and SMA activates a 'previously mapped conversion motor representation': conditioned movements, originally triggered by a situation of physical illness or injury, and emotional arousal.[56] The inability of people with FND to consciously suppress their symptoms, is thus explained by impaired connectivity between the SMA and inhibitory areas, such as the prefrontal cortex. Bayesian concepts have been used to elaborate this model, which proposes that the relationship between sensory evidence and prior beliefs is mediated by bodily attention, expectations of symptoms, physical and emotional experience and beliefs about illness.[57] This model proposes that a previously mapped functional motor representation (perhaps adaptively generated during adverse early life experiences) creates abnormally strong top-down predictions ('priors') in FND, which overwhelm contradictory, bottom-up sensory evidence.

The Bayesian hypothesis shares with an Integrative Cognitive Model (ICM) of FND the prediction that symptoms will occur in situations when they are expected. Applying a more general model of 'medically unexplained symptoms' to seizure-variant FND, the ICM emphasises the roles of chronic and acute arousal, which are relieved by dissociation.[58] This model proposes that chronic stress and arousal, caused by a range of exposures including traumatic life events and physical illness, predispose to the high level processing dysfunction which enables a 'seizure scaffold' (a dynamic mental representation shaping expectations) to be activated.

Predictive coding

The process by which dissociation may result from stress in FND is outlined by the predictive coding model of symptom perception, which posits a continuous process of automatic, unconscious 'hypothesis testing', whereby prior expectations are recurrently refined against new sensory inputs, to minimise prediction error. This yields symptom experiences which 'compromise' between priors and prediction error, which in turn feed back, adjusting the prior. In functional disorders, impaired threat processing, attention, sensitivity to contextual cues, and interoception, all of which can be influenced by early life and recent stress, reduce the precision with which sensory cues are processed. These factors predispose the individual to erroneous symptom experiences, such as those arising from fleeting symptoms of arousal.[59] Similarly, functional seizures would arise from re-activation in response to recent stress, of prior dissociative motor and perceptual representations, in part formed during early life adversity, in susceptible individuals.[58]

Such models generate hypotheses about the neurobiological processes by which functional motor representations are formed and how their re-activation can be treated therapeutically, through a biopsychosocial approach.

IMPLICATIONS FOR FND

The wealth of recent research into the role of stress in health and disease prompts hypotheses pertaining to FND, whose implications are summarised in a stress-diathesis model (Figure 2). Combinations of risk and protective factors are likely to influence an individual's cumulative susceptibility to FND, operating at various levels, from endocrine (e.g. HPA response) to neurophysiological (e.g. motor planning/initiation, interoception) and psychological (e.g. somatosensory and/or threat attention) levels. Our underlying hypothesis, that high biological susceptibility requires minimal childhood maltreatment and mild recent stress to precipitate FND, whilst low biological susceptibility requires more significant childhood maltreatment and recent stress to precipitate FND, must be interrogated through biopsychosocial investigation. Growing research focus on sensitive periods of brain development at which maltreatment may exert greater harm, predisposing to psychopathology,[9] will inform our understanding of how traumatic stressors interact with biological susceptibility in FND. However, the quality of research which recognises the key role played by stress, is often limited by methodological issues such as self-report questionnaires and recall bias.[1] Detailed interview techniques, which blind-rate a range of experiences, contextualised to the person's life, remain the gold standard, but require considerable time and training, and cannot fully objectify (at least partially) subjective stress experiences. In the absence of predisposing or precipitating stressors, unacknowledged iatrogenic stress induced by recurrent healthcare contact without identification of underlying pathology may influence recovery from FND. Since people with FND are less likely than matched neurological controls to agree that stress is a possible cause of their symptoms,[60] our model could facilitate clinical dialogue and therapeutic engagement.

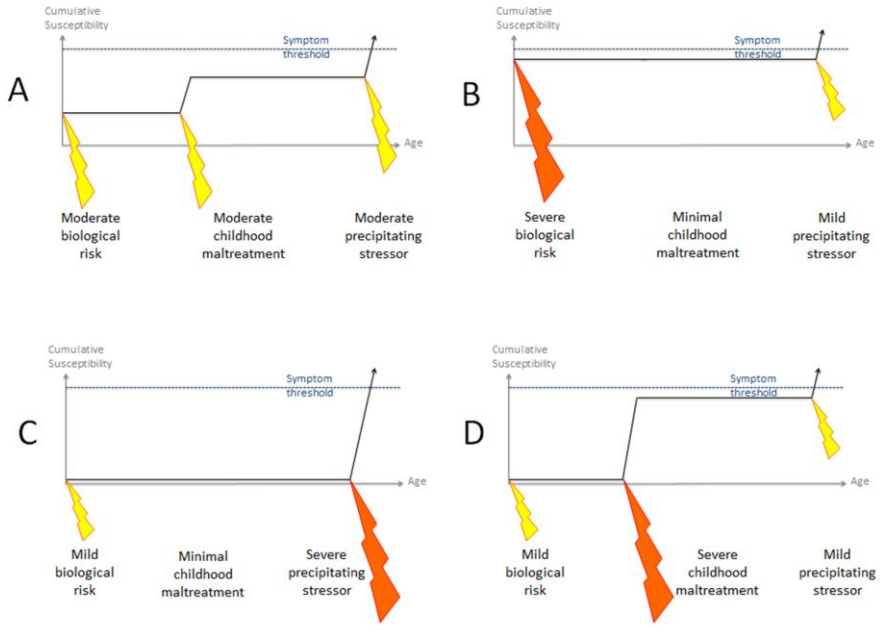

Figure 2: A stress-diathesis model of FND

A: In a person with moderate biological (e.g. genetic) risk exposed to moderate childhood maltreatment, including traumatic experiences, a moderate stressor may be sufficient to precipitate FND; B: in a person with severe biological risk but minimal exposure to childhood maltreatment, a mild stressor may be sufficient to precipitate FND; C: in a person with mild biological risk, exposed to minimal childhood maltreatment, a severe stressor would be required to precipitate FND; D:

in a person with mild biological risk, exposed to severe childhood maltreatment, a mild stressor may be sufficient to precipitate FND.

Box 2: Implications of a stress-diathesis model of FND

Research:

- Genetic research should sub-stratify participants according to identified stressors, with the hypothesis that genetic risk variants will be more prevalent, and therefore more easily detected, in those with low or minimal histories of precipitating stressors (Figure 2).
- Research into biological mechanisms of FND should explore multiple, potentially interacting, pathways operating at different levels, including genetic/metabolic (e.g. HPA response), neurophysiological (e.g. motor planning, interoception), and psychological (e.g. threat, somatosensory attention) levels.
- Research into interventions, including psychological and physical therapies, should explore the potential for evidence-based biomarkers of severity and improvement.

Treatment:

- Personalised treatments could be tailored to each person's combination of protective and risk factors, once identified.
- In the future, preventative interventions could also be explored for individuals at significant (genetic or environmental) risk, identified by screening those with known exposures, or genetic loads confirmed by biomarker or neuropsychological profiling. These measures could be used to monitor responses to treatment and preventative strategies.

FUTURE DIRECTIONS

FND has, until recently, been relatively neglected by psychiatric and neurological research. This review demonstrates the potential for studies of stress biology across diagnostic groups to enhance our understanding of the mechanisms underlying FND. Important developments in biological and cognitive psychiatry mean that we are in a better position than ever to apply well-validated methods to testing this hypothesised model (Box 2).

Key questions raised, requiring interventional research, include: do effective psychological therapies for FND (targeting aberrant threat or attention processing) cause corresponding neurobiological improvements? Are such effects observed where no history of childhood or precipitating stress is identified (arising from high hypothesised biological susceptibility)? Does therapeutic conscious exploration of aetiologically-relevant distal and proximal stressors have corresponding neurobiological effects? Do these differ from effects caused by effective physiotherapy without reference to stress? If so, such research might yield preliminary biomarkers of severity and improvement, enhancing the assessment, treatment and study of FND and other medically-unexplained syndromes. Future research should explore commonalities and differences between FND and other disorders strongly associated with stressful life events, such as PTSD. Answers to how biological and cognitive changes in response to stress operate in FND could furthermore elucidate other equally common and disabling functional disorders.

COMPETING INTERESTS

The authors declare no competing interests.

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AUTHOR CONTRIBUTIONS

Roxanne Keynejad wrote the first draft of this review and led the writing and coordination of subsequent edits.

Thomas Frodl reviewed drafts, provided comments, edits and amendments leading to the final submission.

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Carmine Pariante reviewed drafts, provided comments, edits and amendments leading to the final submission.

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