

REVIEW ARTICLE

Functional neurological disorder and gut
microbiome: Casual or causal relationship?Alejandro Borrego-Ruiz^{1*}, and Juan J. Borrego²¹Department of Social and Organizational Psychology, National University of Distance Education (UNED), Madrid, Spain²Department of Microbiology, University of Malaga, Malaga, Spain

Abstract

Functional neurological disorder (FND), or conversion disorder, is a psychosomatic condition that affects the voluntary motor and/or sensory functions of the patient. Its origin is not yet fully understood, but the main risk factors related to this disorder include exposure to recent psychological stressors and previous experience of aversive episodes during childhood, such as abuse, family dysfunction, and neglect. The symptoms of FND result from complex interactions involving the central nervous system and also the endocrine and immune systems. In this work, we hypothesized the relationship between the gut microbiome and the pathophysiology of FND because both share several common features, such as the effects of neurotransmitters, the hippocampal expression of brain-derived neurotrophic factor, and the inflammatory responses. Based on these common aspects, we suggested that stress, gut microbiome, and inflammation factors induce chronic and systemic inflammation of the brain causing neurological disorders, including FND. More specific studies are warranted to validate the casual or causal relationship between FND and the gut microbiome.

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1. Introduction

Psychosomatic disorders affect both body and mind, and these conditions are mainly characterized by physical symptoms that result from psychological causes such as stress, anxiety, and depression.¹ In the past decades, there has been a rapid increase in the prevalence rates of psychosomatic disorders as a result of the swiftly changing modern lifestyle of people, as well as due to long-standing emotional, social, and occupational stress.² Historically, the term “psychosomatic” was first used by the German psychiatrist Johann Christian August Heinroth in 1818,³ while the term “psychosomatic medicine” was introduced by Felix Deutsch in 1922.⁴ Sigmund Freud systematically studied the now-famous case of “Anna O,” who suffered from what was then called hysteria.^{5,6} Explaining the mechanisms of the psychosomatic disorder of alexithymia, Nemiah *et al.* stated in 1976 that emotional reactions occur in two dimensions: psychological and vegetative states.⁷

Functional neurological disorder (FND), or conversion disorder, is a psychosomatic condition affecting the voluntary motor or sensory function of the patient,⁸ in which

its symptomatology cannot be explained by any other psychological or physiological condition.⁹ The main symptoms of FND include abnormal movements, aphasia, blindness, deafness, dizziness, localized anesthesia, muscle weakness, paralysis, pseudoseizures, psychogenic non-epileptic seizures, speech difficulties, and tremors.^{10,11}

The origin of this disorder is not yet fully understood, although several predisposing, precipitating, and perpetuating factors have been reported as possible consequences of its etiology.¹² However, there is an association between the development of FND and the life event stressors during childhood that lead to trauma.^{13,14} It is well known that trauma affects salience, emotion processing, and sensorimotor circuitry in the brain.¹⁵ On the other hand, event stressors may be caused by external stimuli, physiological illnesses, or psychological pressures, and regarding these states, there is comorbidity with other neuropsychiatric disorders, including anxiety, dissociative disorders, post-traumatic stress disorder, and depression.^{16,17}

FND symptoms result from complex interactions involving the central nervous system (CNS), endocrine, and immune systems. Especially, the hypothalamic-pituitary-adrenal (HPA) axis plays a crucial role, as its dysfunction is influenced by prolonged psychological stress.¹⁸ As a result, stress hormones, such as cortisol, can have detrimental effects on immune function, inflammation, and overall balance within the organism.¹⁹

There are studies that have investigated the effects of psychological stress on the gut microbiome.²⁰ In addition, the gut microbiome influences brain function and behavior through the gut-brain axis, and its dysbiosis can potentially lead to the development of various psychological and psychiatric disorders.²¹ Therefore, in this work, we hypothesized the relationship between the gut microbiome and the pathophysiology of FND because gut microbiome dysbiosis and FND share several common features, such as the effects of neurotransmitters,²² the hippocampal expression of brain-derived neurotrophic factor (BDNF),²³ and inflammatory responses.²⁴

2. Pathophysiology of FND

Frequent manifestations of FND include functional seizures (also known as dissociative or psychogenic non-epileptic seizures), functional movement disorders (FMDs) (paresis), somatosensory or visual symptoms, and speech disorders.¹² Brain differences (gray matter and basal ganglia volumes) have been found in FND individuals compared to healthy controls.²⁵ FND individuals show increased connectivity between the insula, motor, and parietal areas²⁶ and abnormalities in agency and limbic

networks.²⁷ In recent decades, new hypotheses on the pathophysiology of these disorders have been formulated based on the integration of psychology and neurobiology, taking into account the neuropsychobiological factors that contribute to the development and maintenance of FND.^{28,29}

Few studies have placed the focus on the molecular basis of FND. The current evidence highlights the presence of altered levels of the neurotransmitter glutamate in the limbic system and in the cerebrospinal fluid of patients with FMD, a specific subtype of FND.^{30,31} In addition, another neurotrophin, the BDNF, is involved in the development, survival, maintenance, and plasticity of neurons, and has been related to the pathophysiology of FND,³² as patients with epileptic and psychogenic non-epileptic seizures have decreased serum BDNF levels.³³ More recently, Demartini *et al.*³⁴ reported lower blood levels of glutamate, BDNF, and dopamine in FMD patients compared to healthy controls and concluded that glutamatergic and dopaminergic dysfunction may be involved in the pathophysiology of FMD.

Another factor that may contribute to the pathophysiology of FND is oxidative stress, which provokes damage in the brain through the production of reactive oxygen species (ROS).³⁵ Oxygen derivatives and peroxides have been implicated in the harmful mechanisms of several neuropsychiatric disorders, such as anxiety, depression, and schizophrenia.³⁶ However, various markers of oxidative stress, including ROS, 8-isoprostane, thiols, and nitrite derivatives, have not yet been evaluated in FND.^{37,38}

The potentiality that inflammation plays a role within the pathophysiology of FND may provide feedback regarding how trauma and stressful events during childhood adversely affect the adult's health.³⁹ It is well known that stress provokes inflammation,^{40,41} mainly by causing an imbalance in the homeostatic mechanisms, ultimately leading to the release of glucocorticoids through the HPA axis,⁴² and there is a hyperarousal stress state in the FND motor-related symptoms.⁴³

3. Microbial neurotransmitters and metabolites

Gut microbes regulate several host functions and behavior through chemical interactions with the CNS, including both "direct" and "indirect" communication.⁴⁴ Microorganisms have the ability to produce various neurotransmitters, such as acetylcholine, dopamine, gamma-aminobutyric acid, norepinephrine, and serotonin (Table 1), which can stimulate host production of other neuroactive compounds that regulate gut-brain signaling.⁴⁵ Therefore, dysbiosis

Table 1. Microbial production of neurotransmitters^{21,46,47}

Neurotransmitters	Precursors	Gut microbiota producers
Acetylcholine	Choline	<i>Bacillus</i> , <i>Escherichia</i> , <i>Lactobacillus</i> , and <i>Staphylococcus</i>
Dopamine	Tyrosine, L-DOPA	<i>Bacillus</i> , <i>Escherichia</i> , <i>Serratia</i> , and <i>Staphylococcus</i>
GABA	Acetate	<i>Bacteroides</i> , <i>Bifidobacterium</i> , <i>Escherichia</i> , <i>Eubacterium</i> , <i>Lactobacillus</i> , <i>Parabacteroides</i> , and <i>Pseudomonas</i>
Glutamate	Acetate	<i>Bacteroides</i> , <i>Brevibacterium</i> , <i>Campylobacter</i> , <i>Corynebacterium</i> , and <i>Lactobacillus</i>
Histamine	Histidine	<i>Klebsiella</i>
Noradrenaline or norepinephrine	Tyrosine	<i>Bacillus</i> , <i>Escherichia</i> , and <i>Saccharomyces</i>
Phenylethylamine	Phenylalanine	<i>Staphylococcus</i>
Serotonin	5-hydroxytryptophan, tryptophan	<i>Candida</i> , <i>Clostridium</i> , <i>Enterococcus</i> , <i>Escherichia</i> , <i>Lactobacillus</i> , <i>Staphylococcus</i> , and <i>Streptococcus</i>
Tryptamine	Tryptophan	<i>Clostridium</i> , <i>Ruminococcus</i> , and <i>Staphylococcus</i>
Tyramine	Tyrosine	<i>Providencia</i> and <i>Staphylococcus</i>

of the gut microbiome may disrupt neurotransmitter synthesis and lead to mental disorders.^{46,47}

Short-chain fatty acids (SCFAs), including acetate, butyrate, and propionate, are metabolic lipids produced by gut microbes through the fermentation of dietary fiber. The major gut bacterial producers of SCFAs are listed in Table 2.⁴⁸⁻⁵⁰ SCFAs have the ability to influence the host energy balance, hormones, and metabolism, regulating the epigenetics, immune system, and neuroplasticity within the CNS, and they also constitute an important gut-brain signaling pathway through the vagus nerve.⁵¹ Other microbial metabolites, such as alpha-tocopherol, indole, p-aminobenzoate, secondary bile acids, and tyramine, affect the production and secretion of serotonin by the enteroendocrine cells.⁵² The mechanism underlying the production of gut hormones acts through the activation of G protein-coupled receptors by the SCFAs within the colon, which enhance the liberation of peptide YY and glucagon-like peptide 1 from enteroendocrine L-cells.^{53,54} These hormones in turn can affect mood, memory, and learning processes, increasing neuroplasticity and neuroprotection in the hippocampus,⁵⁵ and reducing beta-amyloid plaques and microglial activation.⁵⁶ In addition, ghrelin, leptin, and insulin are other metabolic hormones influenced by SCFAs that affect brain function.⁴⁵

Microbial enzymatic processes can produce the neurotoxins D-lactic acid and ammonium compounds, and other neuroactive metabolites, such as amino acids (tryptophan and tyramine), lipopolysaccharide (LPS), long-chain fatty acids, trimethylamine-N-oxide, and polysaccharide A, which induce peripheral immune cell migration into the brain and cause neuroinflammation,⁴⁴ although it is complicated to directly assess to what extent microbial metabolism affects CNS activity.⁵⁷

4. Gut microbiome dysbiosis and neuroinflammation

The gut microbiome can modulate host immune activity by regulating the production of pro-inflammatory cytokines, which afterward influence the HPA axis to release corticotrophin-releasing hormone, adrenocorticotrophic hormone, and cortisol.⁵⁸ The HPA axis is modulated by diverse stressors such as microbial infection and psychological stress; the toll-like receptors (TLRs) recognize pathogenic microorganisms or adverse conditions leading to an activation of the nuclear factor kappa B pathway, cytokine production, and ultimately HPA response.⁵⁹ Besides, the HPA response mediated by stress can also be regulated by serotonin neurotransmission.⁶⁰

Regarding neuroinflammation, several clinical studies have demonstrated reduced diversity and dysbiosis of the gut microbiome. Nevertheless, it is still unclear whether it is dysbiosis that actively modulates inflammatory processes within the CNS, or whether it is only due to an effect of neuroinflammation itself.⁶¹ It has been demonstrated that dysbiosis increases the permeability of the gut epithelial barrier, exposing the host to greater levels of microbial metabolites and to an increased quantity of cell wall components, such as bacterial extracellular vesicles (BEVs), lipoteichoic acids (LTA), LPS, and various peptidoglycan (PG), which could exert a significant impact on the pathogenesis of neurological diseases.

LPS and LTA can interact with several TLRs expressed by human neurons, and this ligand-receptor interaction triggers the production of inflammatory substances, such as ROS, which can mediate microglial activation.⁶² In addition, neuronal death by caspase-3-dependent apoptosis is promoted by pro-inflammatory cytokines liberated in

Table 2. SCFAs and their corresponding bacterial producers⁴⁸⁻⁵⁰

SCFAs	Bacterial phyla	Bacterial genera
Acetate (C2)	Actinomycetota	<i>Bifidobacterium</i>
	Bacillota	<i>Acetobacterium</i> <i>Blautia</i> <i>Clostridium</i> <i>Eubacterium</i> <i>Ruminococcus</i> <i>Streptococcus</i> <i>Thermoanaerobacter</i>
	Bacteroidota	<i>Bacteroides</i> <i>Prevotella</i>
	Verrucomicrobiota	<i>Akkermansia</i>
Propionate (C3)	Actinomycetota	<i>Propionibacterium</i>
	Bacillota	<i>Anaerostipes</i> <i>Coprococcus</i> <i>Dialister</i> <i>Eubacterium</i> <i>Faecalibacterium</i> <i>Megasphaera</i> <i>Phascolarctobacterium</i> <i>Roseburia</i> <i>Veillonella</i>
	Bacteroidota	<i>Bacteroides</i>
	Pseudomonadota	<i>Salmonella</i>
Butyrate (C4)	Bacillota	<i>Acidaminococcus</i> <i>Anaerostipes</i> <i>Clostridium</i> <i>Coprococcus</i> <i>Eubacterium</i> <i>Faecalibacterium</i> <i>Peptostreptococcus</i> <i>Roseburia</i>
	Fusobacteriota	<i>Fusobacterium</i>

Abbreviation: SCFAs: Short-chain fatty acids.

response to LPS, LTA, and PG.⁶³ Neurons in certain brain areas, such as the cerebellum, hippocampus, and prefrontal cortex, express elevated levels of PG recognition protein 2 (PGLYRP2), which enables them to identify and discern muropeptides emanating from both Gram-positive and Gram-negative bacteria.⁶⁴ PGLYRP2 connects to the bacterial cell wall to cleave the stem peptide, leading to the generation of pro-inflammatory cytokines (interleukin-1 β , interleukin-6, and tumor necrosis factor).⁶⁵

Interestingly, there is an alternative direct communication network between bacteria and their host that involves the liberation of bacterial-derived functional molecules through BEVs.⁶⁶ The BEVs (exosomes and microvesicles) are enriched in lipids, nucleic acids, metabolites, proteins, and virulence factors, and they are released by both pathogenic and symbiotic bacteria,

although their content may differ according to the bacterial species and the growth conditions. BEVs play a pivotal role in bacterial adaptation, communication, and virulence, but recent evidence also suggests a pathophysiological role of BEVs in the interactions involving bacteria among themselves and bacteria with their host.^{67,68} Moreover, BEVs have been shown to activate innate immune cells, such as dendritic cells, macrophages, and microglia, as well as adaptive immune T and B cells in distant organs at the time BEVs are administered into the systemic circulation,⁶⁹ in addition to propagating inflammation in CNS tissues.⁷⁰ Once in the brain, BEVs possess the ability to directly alter neurological function and induce pathological variations.⁷¹ Activation of astrocytes and microglia by virulence factors such as LPS, PG, and proteins provided by BEVs induces the release of inflammatory chemokines and cytokines.⁷²

The gut microbiome can also alter the cytokines through the microbial metabolites by commanding the dynamics of pro- and anti-inflammatory T cells. This leads to changes in TLR signaling,⁷³ to the induction and proliferation of Treg cells and TH17 cells,⁷⁴ and to the dampening of intestinal epithelial cell responses.⁷⁵ The proposed role of the microbiome in regulating inflammatory cytokine concentrations makes the microbiome a critical factor in dictating the dynamics related to the immune response.

5. Conclusion

Psychosomatic medicine studies the interactions of biological, psychological, and social factors that regulate the balance between health and disease, emphasizing the holistic nature of human health and recognizing that cognitive and emotional states can significantly influence physical outcomes and vice versa. This illustrates the complex yet close interaction between mind and body, which is notably modulated by different intrinsic mechanisms, such as the autonomic nervous system, the HPA, and the immune responses. Moreover, the interplay between genetic predispositions and environmental stressors is a critical aspect that offers insights into personalized approaches to prevention and treatment. For instance, individuals with genetic vulnerability to certain mental health conditions may suffer exacerbated symptoms when exposed to major life stressors. This understanding has led to the development of interventions that address both biological and psychosocial constituents, such as cognitive-behavioral therapy combined with pharmacological treatment and lifestyle modifications. In this regard, the progress in neuroimaging and psychophysiological assessments (e.g., functional magnetic resonance imaging and positron emission tomography scans) have allowed researchers to observe

brain activity in real-time, facilitating the identification of the specific neural correlates of psychosomatic symptoms. Besides, other kinds of psychophysiological evaluations, including measures of heart rate variability and galvanic skin response, provide additional data on how the body reacts to stress and emotional stimuli. In fact, advances in scientific methods have been widely applied in the study of psychosomatic disorders, facilitating the exploration of their underlying causal mechanisms and the examination of correlations between brain function and clinical manifestations.⁷⁶

FND, a psychosomatic disorder, has a multifactorial etiology, and the main risk factors for this disorder in adults comprise the exposition to psychological stressors as well as the previous experience of aversive episodes during childhood, while in children, the risk factors include abuse, bullying victimization, family dysfunction, neglect, and perceived peer pressure.^{77,78} FND often co-occurs with other psychological conditions, such as anxiety, depression, and post-traumatic stress disorder, as well as cluster B personality traits.⁷⁹ FND is also related to other functional somatic disorders, including chronic pain and irritable bowel syndrome, which suggest the overlapping risk factors or mechanisms shared by their comorbidities.⁸⁰

Undoubtedly, FND is a very peculiar health condition that presents an important challenge for both the clinical and social ambits due to the lack of a clear understanding of its etiology and pathophysiology. The absence of an identifiable neurological cause complicates its diagnosis and treatment; this uncertainty not only makes clinical approaches difficult but also perpetuates the stigma associated with mental disorders since the symptoms of individuals suffering from FND may be mistakenly perceived as feigned or illusory. In social terms, this deeply affects individuals who suffer from this disorder, who often face barriers in seeking support and understanding, thereby negatively impacting their quality of life. Thus, recognizing these implications and promoting a multidisciplinary approach are pivotal. In this respect, the study of the gut microbiota of patients with FND could constitute a promising way to address this disorder, as well as the administration of psychobiotics as a treatment could improve the related symptoms and comorbid health conditions. Psychobiotics, including probiotics, prebiotics, synbiotics, postbiotics, and parabiotics, are used to treat various neuropsychiatric and psychological disorders. Their mechanisms of action involve immunomodulation, modifying the HPA axis, synthesizing neurotransmitters, regulating BDNF, interacting with the vagus nerve, maintaining or improving intestinal barrier function,

suppressing microbial pathogens, and configuring neural networks. These effects are partly mediated by the secretion of SCFAs, which regulate metabolic processes such as intestinal homeostasis, energy acquisition, colonocyte activity, immune system performance, and other physiological functions.⁸¹ Despite significant advancements in understanding the role of psychobiotics in treating mental disorders, several questions remain unanswered, including how factors such as diet, genotype, sex, and age influence their effects, whether psychobiotics alter gut microbiota architecture, if their effects are short term or long term, their potential side effects on the CNS, the factors that modulate their impact, and how they interact with psychotropic agents. On the other hand, a promising therapeutic intervention that could be considered to address FND symptoms is fecal microbiota transplantation, which involves introducing fecal matter from a healthy donor into the recipient's intestinal tract to restore the microbiota. Fecal microbiota transplantation has shown effectiveness in treating recurrent *Clostridioides difficile* infections and is recognized as a viable option for various inflammatory and mental diseases.⁸²

In summary, gut microbes influence both the enteric and CNS through the production of microbial metabolites and neurotransmitters. In addition, the human microbiome is involved in neuroinflammation processes. Thus, changes in the microbiome, particularly that of the human gut, may exert a subtle impact on the cognitive and behavioral levels of individuals, as well as on their brain health.⁸³ The variations in the activity of diverse brain areas in response to modifications in the microbiome point that the human microbiota and its associated products are crucial determinants for neuronal coordination, an aspect involved in the pathophysiology of FND. Therefore, based on these common aspects, we postulated that stress, gut microbiome, and inflammation factors may alter the integrity of the two pivotal barriers within the gut microbiota-brain axis – the gut barrier and the blood–brain barrier – inducing chronic and systemic inflammation of the brain, and causing neurological disorders, including FND.

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Conflict of interest

The authors declare that they have no competing interests.

Author contributions

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