

Disorders Which Frequently Overlap With Irritable Bowel Syndrome: Can a Shared Neurobiology Explain Their Frequent Association?

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Focus Points

- Irritable bowel syndrome (IBS) is a prevalent functional gastrointestinal disorder.
- IBS frequently overlaps with other functional gastrointestinal disorders.
- IBS frequently co-exists with psychiatric disorders and extraintestinal functional somatic disorders.
- Affective spectrum disorder includes IBS, psychiatric disorders, and functional somatic disorders hypothesized to have shared pathophysiology.
- Disrupted hypothalamic-pituitary-adrenal axis may be one potential link between IBS and several commonly overlapping disorders.

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Abstract

Irritable bowel syndrome (IBS) is a highly prevalent functional gastrointestinal disorder that affects 10% to 27% of the United States population. In most patients with IBS, anxiety, depression, and extraintestinal functional somatic disorders are also present. The etiology of IBS and its non-random association with these disorders is poorly understood. Across these various disorders, disturbed perception of afferent viscerosomatic stimuli, stress vulnerability, and response to antidepressant treatment appear to be common clinical features. This article highlights evidence consistent with the hypothesis that there may be shared pathophysiology linking IBS and disorders that frequently co-occur with it. Evidence for disturbed hypothalamic-pituitary-adrenal axis function resulting in a pro-inflammatory state are presented as one potential neurobiologic model by which the common association of these conditions may be understood.

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Introduction

Irritable bowel syndrome (IBS) is a functional gastrointestinal disorder (FGID) characterized by abdominal pain or discomfort associated with altered defecation patterns.¹ The etiology of IBS is not well understood, but there is general agreement that alterations of pain perception (visceral hyperalgesia), gut reactivity, and dysregulation of the brain-gut axis may be important contributing factors.¹ Other contributing factors include inherited vulnerability, immune dysfunction (post-infectious immune dysregulation), and prior and ongoing psychosocial stress.^{2,3} IBS often overlaps with other FGIDs, which is presumed to reflect a common pathophysiology among them.¹

IBS and functional somatic disorders affect women twice as often as men, are often associated with anxiety and mood disorders, and exhibit pain sensitivity, immune dysfunction, and excess inflammatory activity.^{1,2,4-6} They also have in common onset in early-to-middle life with chronic fluctuation, additive functional impairment, and increased severity when they co-exist.^{1,4,5} Although none have reliably detectable biomarkers, there is a strong correlation between the severity of IBS and the number of extraintestinal symptoms, prior severe physical or sexual abuse, concurrent physical and emotional stressors, and comorbid psychiatric disorders.¹⁻⁷ While no single variable may cause IBS, the interaction of one or more factors may lead to the emergence and persistence of IBS.^{1,4-6}

A history of prior adverse experiences/abuse and ongoing stress clearly exacerbate IBS.^{1,4,6} Stress reactivity is an important but not unique feature of IBS and commonly overlapping disorders. It is paradoxical that the stress response, which promotes successful adaptation to acute stress (survival), may cause negative health effects in the long term if the stress response is not effectively terminated as a result of severe or ongoing stress.⁸ An excess of circulating pro-inflammatory cytokines is thought to be at least one important component in the pathophysiology of various “inflammatory” conditions, including atherosclerosis, coronary artery disease, hypertension, type 2 diabetes, obesity, autoimmune disease, neural sensitization underlying pain, functional somatic disorders, and psychiatric disorders.⁸

This article highlights evidence to support the theoretical concept that disrupted hypothalamic-pituitary-adrenal (HPA) axis homeostasis, which results in a prolonged release of pro-inflammatory stress mediators, may be one important factor in understanding the overlap of IBS with psychiatric and functional somatic disorders.

IBS and Comorbid Functional Somatic Disorders

Although patients may present with symptoms in one organ system, individuals with IBS often report a wide variety of non-intestinal symptoms across multiple organ systems and are twice as likely as patients without IBS to meet criteria for one or more non-gastrointestinal functional somatic disorders (FSDs) such as fibromyalgia, chronic fatigue syndrome (CFS), myofascial disorders, migraine, non-cardiac chest pain, interstitial cystitis, and chronic pelvic pain.^{4,9-16} The non-random association of FSDs with IBS suggests that they may share some common biologic factors. It has been suggested that a more unified, holistic view of these disorders as representing different expressions of some central pathology may allow for a better understanding of their etiology than attempting to understand how different diagnostic entities could commonly appear together.⁹ In an attempt to address the issue of whether IBS is a distinct entity versus part of a more global condition, Whitehead and colleagues¹⁰ critically examined the literature on comorbidity in IBS, noting that there are numerous hypotheses offered to explain the common association of IBS with other functional and psychiatric disorders.⁴ It is suggested that uncomplicated IBS (eg, IBS only) may be more biologically determined, while those with complicated IBS (eg, IBS with high comorbidity) may have more psychological (presumably stress-related) illnesses in which stress reactivity is more apparent and potentially more important. Accumulated evidence supports the concept that these associated disorders are distinct from IBS and each other, although they share certain features.^{4,10} The biopsychosocial model of IBS takes both groups into account so that needs for patient education and treatment are individualized.^{1,4}

The comorbidity of IBS with fibromyalgia has received the most attention of the FSDs. Fibromyalgia is a myofascial disorder which affects approximately 2% of the general population and is characterized by diffusely distributed

musculoskeletal pain with specific tender points which can be elicited on physical examination.^{4,10,11} In the community and clinical sample studies reviewed by Whitehead and colleagues,¹⁰ IBS sufferers had significant comorbidity with fibromyalgia across studies (33% to 66%; median=32.5%). Of those who had a predominant diagnosis of fibromyalgia, a similarly high prevalence rate of IBS was found across studies (33% to 66%; median=48%).^{4,11} Chang and colleagues¹² reported that patients with IBS and concurrent fibromyalgia exhibited somatic hyperalgesia to a greater extent than patients without IBS or those with IBS only (the latter showing tender point hypoalgesia). Individuals with IBS and comorbid FSDs such as chronic pelvic pain also exhibit more somatization and psychiatric distress.^{13-15,17} Since IBS and some FSDs not only overlap, but may interact to change clinical features or IBS severity, future studies should take into account comorbid disorders which may affect relevant outcome measures.^{1,4,12,16} CFS affects <1% of the general population and is characterized by unexplained, persistent fatigue for at least 6 months which confers some functional impairment. IBS co-occurs with CFS in 33% to 66% of patients (median=approximately 50%) and CFS occurs in approximately 14% of IBS patients.^{4,10}

IBS and CoMorbidity Psychiatric Illness

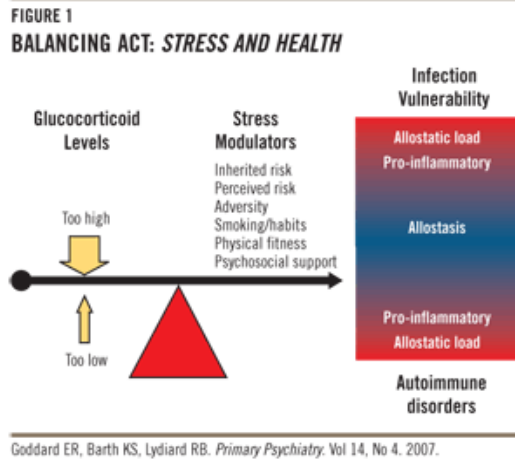
The frequent overlap of IBS with psychiatric disorders is well documented.^{1,4,9,10,16,18-20} Psychiatric disorders, like the FSDs which overlap with IBS, are also associated with a wide variety of unexplained pain and somatic symptoms.¹⁸ In the 1991 National Institute of Mental Health Epidemiological Catchment Area study, respondents seeking consultation for numerous unexplained physical complaints were up to 200 times more likely to have panic disorder than those without such complaints.¹⁸ In primary care, 28% to 40% of patients presenting with unexplained gastrointestinal complaints have panic disorder.¹⁹ Conversely, 25% to 40% of patients with panic disorder meet criteria for IBS.²⁰ A recent study reported that panic disorder patients volunteering for clinical trials met Rome criteria for four (range=2-11) FGIDs.²⁰

Similarly high rates of IBS have been found in patients with obsessive-compulsive disorder (OCD). Masand and colleagues²¹ reported a prevalence rate for IBS of 35% patients with OCD versus 3% of an age-matched control group. Similarly high rates of PTSD in IBS and high rates of IBS in PTSD have been reported.¹⁷

Mood disorders often co-exist with IBS.²²⁻²⁷ Masand and colleagues^{22,23} reported rates of IBS in 60% of outpatients with dysthymia²² and in 27% with major depressive disorder (MDD)²³ versus only 2% to 3% in comparison groups. The severity of MDD appears to increase with the severity of IBS. Miller and colleagues²⁴ inquired about suicidal ideation and attempts in samples of 100 tertiary care (the most severe and refractory group), 100 secondary care, and 100 primary care patients with IBS as well as 100 patients with inflammatory bowel disorders. Levels of depression were highest in the tertiary care samples. The percentages of IBS patients in the tertiary, secondary, and primary care samples who reported having contemplated suicide were 38%, 16%, and 4%, respectively; 15% of the inflammatory bowel patients also endorsed suicidal ideation. Five percent of the tertiary care IBS group had actually attempted suicide. These patients considered hopelessness, inadequacy of treatment, and interference with life as crucial issues related to their gastrointestinal symptoms.

Affective Spectrum Disorder

Affective spectrum disorder (ASD) describes a cluster of disorders and syndromes consisting primarily of psychiatric and functional disorders, including IBS. This term was chosen because all of these conditions improve to some degree from antidepressant treatment. As such, it has been proposed as a model for understanding the link between these frequently overlapping disorders, including mood and anxiety disorders, eating disorders, migraine, premenstrual dysphoric disorder, IBS, fibromyalgia, CFS, and others.²⁵ In addition to their non-random distribution, most are characterized by stress reactivity, pain sensitivity, various non-diagnostic somatic symptoms, functional impairment, and immune dysfunction (Figure 1).

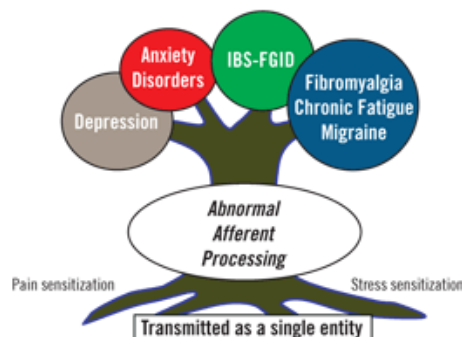


Hudson and colleagues²⁵ interviewed 168 first-degree relatives of 64 probands with MDD versus 152 first-degree relatives of 58 probands without MDD, for the presence of ASDs. They found familial aggregation of ASD with an odds ratio (OR) of 2.5 ($P=.001$) in the relatives of depressed probands versus those of non-depressed probands. The risk for ASDs in pedigrees of first-degree relatives of MDD appeared to travel within the pedigrees as a single entity. Hudson and colleagues²⁶ also examined familial aggregation of ASDs in relatives of probands with fibromyalgia versus relatives of those without fibromyalgia. This study reported an OR of 1.8 ($P=.065$). The authors concluded that ASD aggregates strongly in families and MDD exhibits the strongest familial co-aggregation with other ASDs. These results suggest that forms of ASD may share heritable pathophysiologic features. Based on these findings, the authors hypothesized that the disorders within the ASD spectrum may share some heritable pathophysiologic features.

Is Excessive Inflammatory Activity the Link?

Disrupted hypothalamic-pituitary-adrenal (HPA) axis has been demonstrated in IBS and several commonly overlapping disorders.^{5,8,9,27-30} Either excessive cortisol or insufficient cortisol production has been frequently but not universally associated with IBS. Several of the commonly overlapping disorders may be one underlying mechanism resulting in the HPA axis dysfunction. Inflammatory states associated with persistent stress may result either from excessive pro-inflammatory cytokine production or subnormal production of anti-inflammatory cytokines and have been reported in psychiatric and functional disorders including IBS (Figure 2).^{8,20,22-34}

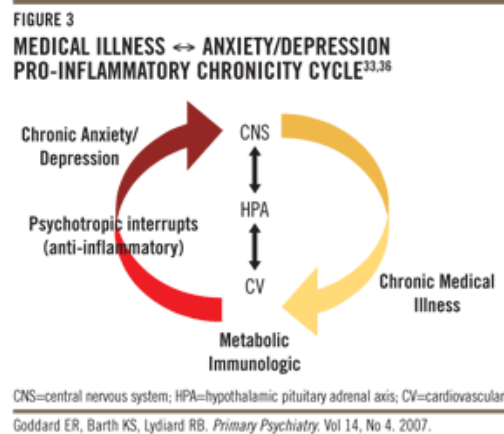
FIGURE 2
AFFECTIVE SPECTRUM DISORDERS: STRESS-REACTIVE DISORDERS WITH SHARED PATHOPHYSIOLOGY²⁵



IBS=irritable bowel syndrome; FGID=functional gastrointestinal disorder.
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There is a delicate homeostatic balance between neural, neuroendocrine, and immune function, which together regulate the brain and body. The stress response is an adaptive, innately programmed cascade of physiologic, immune, metabolic, sensory, and musculoskeletal actions triggered by a real or perceived threat to the homeostasis (safety and health) of the individual.³⁵ Activation of the HPA axis system triggers the release of stress mediators such as cortisol, catecholamines, and pro-inflammatory cytokines (interleukins^{1,3,8} and tumor necrosis factor- α). ASD aggregates strongly in families, and MDD displays a significant familial coaggregation with other forms of ASD, taken collectively. These results suggest that forms of ASD may share heritable pathophysiologic features.

Stress-related disruption of HPA-axis homeostasis may contribute to allostatic load or the “wear and tear” which results from repeated activation of the HPA axis. Over time, the accrued allostatic load contributes to the risk for adverse health consequences (eg, metabolic syndrome) mediated by stress mediators including excessive pro-inflammatory activity.^{8,29,31-33} The clinical observation that stress exacerbates and worsens the outcome of chronic medical (eg, cardiovascular, endocrine), psychiatric, and functional somatic disorders suggests that there may be interaction of comorbid pro-inflammatory states underlying the increased severity and relative treatment resistance of various combinations of comorbidity (Figure 3).^{34,36} Following successful adaptation to the threat, cortisol plays a critical anti-inflammatory role in terminating the stress response by binding the glucocorticoid receptors in the hypothalamus, hippocampus, pituitary, and other key brain areas. Paradoxically, pro-inflammatory cytokines and other humoral mediators of inflammation potentially stimulate the HPA axis and extra-hypothalamic corticotropin releasing factor (CRF) release. This acts to promote neural sensitization at multiple levels, which lead to amplification of the CRF and pro-inflammatory cytokine response to each successive stressor.^{8,31}



Pro-inflammatory cytokines antagonize glucocorticoid receptor function, thereby interfering with the glucocorticoid receptor-mediated feedback inhibition necessary to shut off CRF release.²⁹ Under prolonged conditions of repeated or persistent stress, the ability to muster an effective, adaptive stress response may eventually diminish due to reduced glucocorticoid receptor sensitivity to glucocorticoids or, in some situations, insufficient cortisol production.²⁹ In either case, the net effect is unopposed CRF hyperactivity, sympathetic arousal, and release of pro-inflammatory cytokines. In this way, a self-promoting pro-inflammatory cycle could be initiated and maintained.

Conclusion

Stress vulnerability and the biologic and environmental variables contribute to loss of homeostatic control of the HPA axis homeostasis, and may be a common link between IBS and commonly overlapping disorders. The proposed model of excessive pro-inflammatory cytokine production is proposed as one potentially shared pathophysiologic mechanism by which they are linked.^{1,3,5,8-12,18,28,30-34} This is consistent with the known anti-inflammatory effects of antidepressants across IBS and related functional disorders, even (in IBS) in the absence of concurrent psychiatric disorders.³⁷ Further research into the interacting effects of comorbidity; inherited vulnerability; neuroendocrine, neuroimmune, and neuroinflammatory aspects of IBS; and psychiatric and functional disorders provide a basis for

hypothesis-testing research which may enhance our understanding of and lead to improved new treatments for these common and sometimes debilitating disorders. **PP**

References

1. Drossman DA, Camilleri M, Mayer EA, Whitehead WE. AGA technical review on irritable bowel syndrome. *Gastroenterology*. 2002;123(6):2108-2131.
2. Longstreth GF, Thompson WG, Chey WD, Houghton LA, Mearin F, Spiller RC. Functional bowel disorders. *Gastroenterology*. 2006;130(5):1480-1491. Erratum in: *Gastroenterology*. 2006;131(2):688.
3. Chang L, Toner BB, Fukudo S, et al. Gender, age, society culture, and the patient's perspective in the functional gastrointestinal disorders. *Gastroenterology*. 2006;130(5):1435-1446.
4. Palsson OS, Whitehead WE. Comorbidity associated with irritable bowel syndrome. *Psychiatr Ann*. 2005;35(4):320-324.
5. Chang L. Neuroendocrine and neuroimmune markers in IBS, pathophysiology or epiphenomenon. *Gastroenterology*. 2006;130(2):596-600.
6. Drossman DA. The functional gastrointestinal disorders and the Rome III process. *Gastroenterology*. 2006;130(5):1377-1390.
7. Drossman DA, Li Z, Leserman J, Toomey TC, Hu YJ. Health status by gastrointestinal diagnosis and abuse history. *Gastroenterology*. 1996;110(4):999-1007.
8. Charmandari A, Kino T, Chrousos G. Glucocorticoids and their actions: an introduction. *Ann N Y Acad Sci*. 2004;1024(11):1-8.
9. Tan S, Tillisch K, Mayer E. Functional somatic syndromes: emerging biomedical models and traditional chinese medicine. *Evid Based Complement Alternat Med*. 2004;1(1):35-40.
10. Whitehead WE, Palsson O, Jones KR. Systematic review of comorbidity of irritable bowel syndrome other disorders: what are the causes and implications? *Gastroenterology*. 2002;122(4) 1140-1156.
11. Sperber AD, Atzmon Y, Neumann L, et al. Fibromyalgia in the irritable bowel syndrome: studies of prevalence and clinical implications. *Am J Gastroenterol*. 1999;94(12):3541-3546.
12. Chang L, Mayer EA, Johnson T, FitzGerald LZ, Naliboff B. Differences in somatic perception in female patients with irritable bowel syndrome with and without fibromyalgia. *Pain*. 2000;84(2-3):297-307.
13. Williams RE, Hartmann KE, Sandler RS, Miller WC, Savitz LA, Steege JF. Recognition and treatment of irritable bowel syndrome among women with chronic pelvic pain. *Am J Obstet Gynecol*. 2005;192(3):761-767.
14. Longstreth GF. Irritable bowel syndrome and chronic pelvic pain. *Obstet Gynecol Surv*. 1994;49(7):505-507.
15. Azpiroz F, Dapoigny M, Pace F, et al. Nongastrointestinal disorders in the irritable bowel syndrome. *Digestion*. 2000;62(1):66-72.
16. Palsson O, Drossman DA. Psychiatric and psychological dysfunction in irritable bowel syndrome and the role of psychological treatments. *Gastroenterol Clin N Am*. 2005;34(2):281-303.
17. Leserman J. Association of sexual and physical abuse with functional gastrointestinal and pelvic pain. *Primary Psychiatry*. 2007;14(4):58-63.
18. Simon GE, VonKorff M. Somatization and psychiatric disorders in NIMH Epidemiologic Catchment Area study.

Am J Psychiatry. 1991;148(11):1494-1500.

19. Roy-Byrne PP, Wagner AW, Schraufnagel TJ. Understanding and treating panic disorder in the primary care setting. *J Clin Psychiatry*. 2005;66(suppl 4):16-22.
20. Lydiard RB. Increased prevalence of functional gastrointestinal disorders in panic disorder: clinical and theoretical implications. *CNS Spectr*. 2005;10(11):899-908.
21. Masand PS, Keuthen NJ, Gupta S, Virk S, Yu-Siao B, Kaplan D. Prevalence of irritable bowel syndrome in obsessive-compulsive disorder. *CNS Spectr*. 2006;11(1):21-25.
22. Masand PS, Kaplan DS, Gupta S, Bhandary AN. Irritable bowel syndrome and dysthymia. Is there a relationship? *Psychosomatics*. 1997;38(1):63-69.
23. Masand PS, Kaplan DS, Gupta S, et al. Major depression and irritable bowel syndrome: is there a relationship? *J Clin Psychiatry*. 1995;56(8):363-367.
24. Miller V, Hopkins L, Whorwell PJ. Suicidal ideation in patients with irritable bowel syndrome. *Clin Gastroenterol Hepatol*. 2004;2(12):1064-1068.
25. Hudson JI, Mangweth B, Pope HG Jr, et al. Family study of affective spectrum disorder. *Arch Gen Psychiatry*. 2003;60(2):170-177.
26. Hudson JI, Arnold LM, Keck PE Jr, Auchenbach MB, Pope HG Jr. Family study of fibromyalgia and affective spectrum disorder. *Biol Psychiatry*. 2004;56(11):884-891.
27. Vierck CJ Jr. Mechanisms underlying development of spatially distributed chronic pain (fibromyalgia). *Pain*. 2006;124(3):242-263.
28. Demitrack MA, Crofford LJ. Evidence for and pathophysiologic implications of hypothalamic-pituitary-adrenal axis dysregulation in fibromyalgia and chronic fatigue syndrome. *Ann N Y Acad Sci*. 1998;840:684-697.
29. Raison CL, Miller AH. When not enough is too much: the role of insufficient glucocorticoid signaling in the pathophysiology of stress-related disorders. *Am J Psychiatry*. 2003;160(9):1554-1565.
30. Heim C, Ehlert U, Hanker JP, Hellhammer DH. Psychological and endocrine correlates of chronic pelvic pain associated with adhesions. *J Psychosom Obstet Gynaecol*. 1999;20(1):11-20.
31. Anisman H, Merali Z. Cytokines, stress and depressive illness: brain-immune interactions. *Ann Med*. 2003;35(1):2-11.
32. Hayley S, Poulter MO, Merali Z, Anisman H. The pathogenesis of clinical depression: Stressor- and cytokine-induced alterations of neuroplasticity. *Neuroscience*. 2005;135(3):650-678.
33. Tuglu C, Kara SH, Caliyurt O, Vardar E, Abay E. Increased serum tumor necrosis factor-alpha levels and treatment response in major depressive disorder. *Psychopharmacology (Berl)*. 2003;170(4):429-433.
34. Kenis G, Maes M. Effects of antidepressants on the production of cytokines. *Int J Neuropsychopharmacol*. 2002;5(4):401-412.
35. Jarcho JM, Mayer EA. Stress and irritable bowel syndrome. *Primary Psychiatry*. 2007;14(4):74-78.
36. Kiecolt-Glaser JK, McGuire L, Robles TF, Glaser R. Psychoneuroimmunology and psychosomatic medicine: back to the future. *Psychosom Med*. 2002;64(1):15-28.
37. Lydiard RB. Psychopharmacology in the treatment of irritable bowel syndrome. *Primary Psychiatry*. 2007;14(4):40-42,45-49.

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