

WJG 20th Anniversary Special Issues (4): Irritable bowel syndrome

Role of negative affects in pathophysiology and clinical expression of irritable bowel syndrome

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Author contributions: Muscatello MRA contributed to the literature search, manuscript writing, and final revision; Bruno A suggested topics to be included and contributed to the writing of the manuscript; Scimeca G managed the literature search and contributed to the writing; Pandolfo G contributed to the literature search and writing of the manuscript; Zoccali RA contributed to the study idea, manuscript writing and final revision of the article.

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Received: September 28, 2013 Revised: January 18, 2014

Accepted: April 2, 2014

Published online: June 28, 2014

gut microbiota, inflammation/immunity, and symptom reporting.

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Key words: Depression; Anxiety; Anger; Mood disorders; Irritable bowel syndrome; Neuroticism; Stress; Brain-gut axis; Microbiota; Hypothalamic-pituitary-adrenal axis

Core tip: This review deals with the role of negative affects in pathophysiology and clinical expression of irritable bowel syndrome (IBS). Depression, anxiety, and anger play a key role in dysregulation of the brain-gut axis, contributing to the majority of pathophysiological and symptomatic correlates of IBS. Research efforts to integrate different knowledge provide further insight into the pathways linking negative psychological states to health and disease, leading to identification of individual vulnerability and susceptibility factors, including subsyndromal conditions, which should be addressed to promote better health in the population and more effective and efficient prevention and treatment of IBS.

Abstract

Irritable bowel syndrome (IBS) is regarded as a multifactorial disease in which alterations in the brain-gut axis signaling play a major role. The biopsychosocial model applied to the understanding of IBS pathophysiology assumes that psychosocial factors, interacting with peripheral/central neuroendocrine and immune changes, may induce symptoms of IBS, modulate symptom severity, influence illness experience and quality of life, and affect outcome. The present review focuses on the role of negative affects, including depression, anxiety, and anger, on pathogenesis and clinical expression of IBS. The potential role of the autonomic nervous system, stress-hormone system, and immune system in the pathophysiology of both negative affects and IBS are taken into account. Psychiatric comorbidity and subclinical variations in levels of depression, anxiety, and anger are further discussed in relation to the main pathophysiological and symptomatic correlates of IBS, such as sensorimotor functions,

Muscatello MRA, Bruno A, Scimeca G, Pandolfo G, Zoccali RA. Role of negative affects in the pathophysiology and clinical expression of irritable bowel syndrome. *World J Gastroenterol* 2014; 20(24): 7570-7586 Available from: URL: <http://www.wjgnet.com/1007-9327/full/v20/i24/7570.htm> DOI: <http://dx.doi.org/10.3748/wjg.v20.i24.7570>

INTRODUCTION

Irritable bowel syndrome (IBS) is a disorder of the lower gastrointestinal tract characterized by a set of gastrointestinal (GI) symptoms such as abdominal discomfort or pain^[1], bloating or feelings of abdominal distension,

alterations in bowel habits (constipation and/or diarrhea), and altered stool passage (urgency or feeling of incomplete evacuation)^[2]. Diagnosis of IBS depends on symptom-based criteria such as the Rome criteria, after excluding the presence of any organic GI diseases^[3]; beyond diagnostic criteria, clinical routine biopsies and examinations have shown that the number of lymphocytes, mast cells, enterochromaffin cells, and nerve fibers are, at least in IBS subtypes, increased^[4,7] and an increased amount of nerve-activating mediators is released from the colonic mucosa in IBS patients^[8]. Estimated prevalence of IBS in the general population varies from 5.8% to 26.1%^[9] and much of the variability in prevalence rates is probably due to different symptom-based diagnostic criteria, sample selection, access to health care, and/or cultural factors. In clinical samples, IBS accounts for approximately 3% of all general practice^[10] and up to 70% of referrals to gastroenterology clinics^[11].

Regarding sex differences, a higher prevalence is found in women, with a female-to-male ratio close to 2^[12]. As predominant bowel pattern, women more commonly report functional constipation, defined as persistent symptoms of difficult, infrequent, or seemingly incomplete defecation^[13], with no other apparent etiology, and abdominal pain^[14]. Furthermore, women are more likely than men to seek medical assistance^[15]. The onset of IBS usually occurs between the ages of 15 and 65 years, and the mean age at presentation is the mid 30s, although in a number of subjects, symptoms may date back to childhood. The course of the illness is chronic, fluctuating, and relapsing; in some cases, symptoms can spontaneously resolve and the syndrome may have a good prognosis, as documented by long-term, follow-up studies^[16,17].

The etiopathogenesis of IBS is complex and not yet completely understood. IBS may be better conceptualized as the resultant of the complex interactions of a number of factors such as abnormal colonic motility, visceral hypersensitivity, enhanced pain perception^[18,19], low-grade inflammation involving mast cells^[20], dietary intolerance^[21], alteration of microbiota, the intestinal microbial community^[22,23], abnormalities in the autonomic nervous system^[24,25], and stress^[26,27].

A major contribution to the understanding of the pathogenesis of IBS has come from the hypothesis of the hyper-reactivity of the brain-gut axis; a model describing bidirectional pathways among central nervous system (CNS), autonomic nervous system (ANS), and enteric nervous system (ENS), thus linking emotional and cognitive areas in the CNS with visceral afferent sensation and intestinal function^[28,29]. A growing body of evidence indicates that IBS is viewed as being caused by dysregulation of the brain-gut axis, involving neural, endocrine and neuroimmune pathways that are affected and often disrupted by psychosocial and environmental stressors, including life events, or by physical stressors (infection/inflammation)^[30,31].

The biopsychosocial model of illness and disease^[32]

has provided a conceptual framework that is helpful for understanding the bidirectional relationship between mind and body, integrating biological science with individual features. According to this model, illness and disease result from simultaneously interacting systems at multiple levels (cellular, tissutal, organismal, interpersonal, and environmental), and research in this field is oriented to determine the ways in which biological, psychological, and environmental factors interact to explain illness onset, course, and outcome^[33]. The biopsychosocial model applied to the understanding of IBS pathophysiology assumes that psychosocial factors, interacting with biological mechanisms such as peripheral/central neuroendocrine and immune changes, may induce and aggravate symptoms of IBS, modulate symptom severity and persistence, influence illness experience and quality of life, and affect treatment response and outcome^[34]. However, it remains unclear which psychological factors are the most relevant in explaining these outcomes.

The natural history and risk factors of IBS suggest that the disease may begin in early life. The quality of the early family environment can provide a main source of strength or vulnerability in later life^[35]. Mothers represent a major source of interaction and regulation of physiological and psychological processes, therefore, maternal care influences the physiological and psychological development of the child, whereas inadequate maternal care is related to developmental problems both in human infants and in rats^[36]. In rodent models it has been shown that the early postnatal stage is a crucial period for the healthy development of pups; alterations in early experiences are thought to have long-lasting consequences for stress responsiveness and emotions^[37]. An extension of this model postulates that adverse events in early life, experimentally reproduced with the use of the maternal separation procedure, are associated with maladaptive behavioral and hormonal responses to stress and may contribute to increase vulnerability to disease in later life. Maternal separation (MS), a model of early life stress, has been used in rodents for understanding the effects of early life stress on the development of the CNS and across a variety of systems including the brain-gut axis^[38].

Thus, the multiple alterations across the regulation of the brain-gut axis animal models provide strong evidence for a deep understanding of stress-related GI disorders also in humans. It has been suggested that problems during the perinatal period may contribute to the susceptibility to develop IBS in humans; events such as prenatal undernutrition and painful experiences might interfere with GI physiological maturation^[39].

Over the past decade the significant interplay among psychopathological factors, psychiatric comorbidity, chronic emotional distress as possible associated features or co-factors in IBS onset, course, and clinical expression has gained attention by research strategies pursued by different specialties, such as psychiatry, psychology, neurobiology, and pain.

In this review we focus on the role of negative affects, including depression, anxiety and anger on the pathophysiology and clinical expression of IBS, taking into account that association between emotions and GI health is bidirectional and effects can accumulate over a long period of time. The focus on affective traits is congruent with the line of research whose effort is to target those basic dispositions relevant to psychopathology that may affect the development, course and outcome of IBS, possibly influencing the search for individualized and integrated treatment strategies oriented to improve individual outcomes.

AFFECTIVE STYLES: POSITIVE VS NEGATIVE AFFECTS

The term affective style refers to a range of individual differences in different parameters of emotional reactivity, involving valence-specific features of emotional reactivity and affective processing and regulation. In keeping with its main role in defining mental health and quality of life, affective style has been studied in detail. From a psychophysiological point of view, several parameters of affective style can be objectively measured including: (1) threshold to response; (2) magnitude of response; (3) rise time to peak of response; (4) recovery function of the response; and (5) duration of response, where the last three parameters refer to different aspects of affective chronometry or the time course of emotional responding^[40].

Evidence from both animal and human neurobiological and brain imaging studies shows that the key brain regions contributing to the supposed emotion processing circuit are the prefrontal cortex (PFC), amygdala and extended amygdala/ventral striatum, including nucleus accumbens, hypothalamus and anterior cingulate cortex (ACC)^[41].

Beyond detection and evaluation of emotionally salient stimuli, emotion processing also involves the experience, regulation and expression of the affective response; the capacity to regulate effectively negative emotions and to decrease the duration of aversive affects is considered one of the key components of affective style^[42].

A large amount of research shows that emotional experience is dominated by two core and broad dimensions accounting for the variability in individual levels of psychological well being and distress: positive affect (PA) and negative affect (NA)^[43,44]. PA can be defined as an affective construct that reflects a level of pleasurable engagement with the environment and that involves both emotional and cognitive components, such as joy, enthusiasm, happiness, high energy levels, interest, motivation, and mental alertness^[45]; low levels of PA are characterized by poor energy and fatigue.

In contrast, NA is a dimension of subjective distress including a range of aversive mood states, such as sadness, anger, disgust, guilt, fearfulness, and depression.

Both PA and NA can be conceptualized either as a transient state or as a trait, defined as individual differences in general affective level. Affective traits are stable dispositions to experience the corresponding mood factors (positive or aversive emotions). Hence, high-trait NA subjects are more likely to experience pervasive and intense states of negative affect, whereas high trait PA individuals report generally higher levels of positive affect, maintaining a generally high activity level. High NA individuals usually experience significant levels of distress and dissatisfaction across time and in everyday life situations, even in the absence of objective stressors; they are also more introspective, suffer from poor self-esteem and tend to focus on the negative side of self, others, and the world in general. Moreover, high NA individual tend to be hyper-reactive in front of stressful events^[46].

More recently, the constructs of PA and NA, along with a dimension defined as physiological hyperarousal (HA), have been included in the tripartite model, which aims to assess distinctive and overlapping features of depression and anxiety. The core assumption of the model is that both disorders share a general distress factor; however, depression should be characterized by a mixed state of high NA and low PA, whereas anxiety should be a state of high NA and HA^[47]. Accordingly, NA is thought to be the underlying construct for both depressive and anxiety disorders.

Whether PA and NA should constitute the extreme and opposite poles of the mood dimension has been a matter of debate in the emotion literature. Although their names seems to suggest that they are opposite poles of the same continuum, PA and NA appear to be highly distinct dimensions; as stated by Zautra *et al*^[48] “most of us believe that positive feelings are the opposite of negative feelings, and that a person who is unhappy is also sad. These statements are truisms in the language of feelings, affects, and emotions. Most of the time, positive and negative feeling states are independent of one another”. This issue has not only theoretical implications, but also impacts on clinical research; as highlighted in a review on the influence of PA on health: “If PA and NA are bipolar ends of the same construct, benefits of PA may merely reflect the absence of NA rather than the presence of positive feelings. Alternatively, should the two be mutually independent, PA could provide benefits independent of NA levels”^[49].

The conceptualization of PA and NA as independent dimensions has received support from neurobiological and brain-imaging studies that have demonstrated the existence of separate cerebral circuits and anatomical systems mediating positive and negative affectivity^[40] and, further, that the propensity toward one or the other type of affect reflects individual dispositions probably grounded in neurobiological differences. In terms of the brain centers involved, the frontal lobes of the right hemisphere have been implicated in NA and behavioral inhibition (withdrawal tendencies), whereas the frontal

lobes of the left hemisphere have been implicated in PA and approach behaviors^[40]. The existence of two separate systems and brain circuits for PA and NA has powerful implications for clinical work, because therapeutic approaches may focus on decreasing negative affective experiences or increasing positive ones.

From a personality perspective, NA as a trait is the core component of two similar personality constructs, neuroticism, and type D (distressed) personality. Neuroticism, defined as “a broad dimension of individual differences in the tendency to experience negative, distressing emotions and to possess associated behavioral and cognitive traits”^[50], is characterized by overstated reactivity to physiological changes, by emotional instability with overwhelmingly negative emotions. Neuroticism has been related with a broad range of physical health problems, included IBS^[51,52], even when depression and other risk factors are controlled. Type D personality, a concept derived from empirical and theoretical research, is regarded as consisting of two stable broad traits: NA, and social inhibition (SI), which refers to a tendency to suppress and inhibit the expression of emotions^[53,54]. Type D personality seems to confer a specific vulnerability to chronic stress, and it has been associated with high rates of medical comorbidity, unfavorable clinical courses, both medical and psychological, and low subjective and physician-assessed health ratings^[55].

Overall, affective styles, also conceived as personality traits in different theoretical models of personality, represent stable and chronic attributes of individuals and thus they may have predictive value; in this sense, NA is related to long-term emotional distress, general maladjustment, and with a broad range of subjective complaints and reported physical symptoms.

ROOTS OF NA: TEMPERAMENT, EPIGENETICS, AND CHILDHOOD ANTECEDENTS

Temperament has been defined as biologically based individual differences in reactivity and regulation that are almost stable over time; probably in part heritable, it shapes the propensity to approach or withdrawal from novel and unfamiliar situations and, ultimately, the way individuals adapt^[56]. Such individual differences appear early in life, and have been biologically connected with differences in emotional responsivity, as approach tendencies/behavioral activation are related to PA, whereas withdrawal tendencies/behavioral inhibition are linked to NA. Accordingly, infants and children characterized by behavioral inhibition show high NA, and low levels of PA, social interactions, and approach behaviors; moreover, they are fearful in unfamiliar contexts^[57]. Temperament dimensions are normally distributed in the general population, but it is widely accepted that certain temperamental features, such as NA and behavioral inhibition, may have a role in the development of later

psychopathology and affective disorders. As suggested by recent research, behavioral inhibition is recognized as an early temperamental precursor of later anxiety disorders^[58], whereas low PA is an acknowledged risk factor for depression^[59].

It has been hypothesized that, on an inherited temperamental basis that predisposes vulnerability to withdrawal tendencies/behavioral inhibition, the expression of an affective style characterized by preponderant NA is ultimately determined by environment. A number of environmental factors possibly playing a role in the formation of a negative affective style have been identified: negative parenting styles, insecure parent-child attachment, parental anxiety, and adverse life events may interact with behavioral inhibition in maintaining the pathways toward psychopathology and mental distress^[58].

On a neurobiological level, it has been suggested that adverse events in early childhood affect experience-dependent maturation of structures on those brain systems underlying emotional functioning^[60].

A growing line of research is converging on epigenetics, the study of heritable changes in gene expression that occur without changes in DNA sequence. Epigenetic mechanisms can change genome function under exogenous influence; moreover, epigenetic changes allow for the stable propagation of gene activity states for generations afterwards^[61].

From an epigenetic point of view, among environmental factors, early life experiences are associated with different outcomes in life-long health and behavioral pathways both in animals and in humans^[62]. It has been demonstrated that differences in maternal care in rats during the first weeks of life are associated with long-term effects on behavior and brain function persisting into adulthood, mainly *via* alterations in the stress response^[63]. Similarly, in humans, childhood maltreatment is significantly associated with psychopathological outcomes in adult life^[64].

Moreover, maternal emotional states, such as anxiety, psychological distress, and depression, are associated with child health, and parental functioning problems, such as restricted emotional expression, poor emotional supportiveness, and role conflicts, are associated with poorer psychological and physical well being of children with chronic illnesses^[65].

NEGATIVE AFFECTS AND IBS: POTENTIAL LINKS

The effect of negative affects and emotions on health has been long recognized; particularly, the physiological consequences associated with affect and emotion arousal provide one potential mechanism by which emotional states may influence physical health, leading to increased vulnerability to illness^[66]. In general, negative affects are related to unhealthy patterns of physiological functioning, while positive affects are associated with better

health, although the role of other potential mediators of this association, such as healthy lifestyles, stronger social networks, more positive social interactions, frequency of stressful events, and a putative role of PA as stress buffer need to be further investigated^[49].

From a neurobiological point of view, CNS pathways (outflows from cortico-limbic-pontine networks) to gut form the emotional motor system (EMS) that can be viewed as an extension of the limbic system into the gut, involved in the modulation of autonomic and neuroendocrine pathways, and pain^[67]. The tonic modulation exerted by the EMS include serotonergic, noradrenergic and opioidergic descending spinal pathways. The most studied pathways in IBS is the serotonin (5-HT) neurotransmission system, and it has been hypothesized that the co-occurrence of NA and IBS may be related to serotonergic hypofunction both in the ENS and CNS. Thus, affective and emotional symptoms should be considered as specific and integral to the illness, rather than causal factors or consequences of IBS^[68]. We discuss here further mechanisms that may subtend the link between NA and IBS, and in particular the potential roles of autonomic nervous system, stress-hormone system and immune system.

ANS

The ANS can be considered the neural interface conveying top-down and bottom-up signals. The same cerebral regions (amygdala, hippocampus, and prefrontal cortex) implicated in the modulation of gut function are also involved in the regulation of affectivity, mood, and emotions, and, thus, in the development of social behavior and coping strategies^[69]. At the ANS level, a relative hyperfunction of the sympathetic activity along with a relative hypofunction of the parasympathetic activity (low vagal tone) has been described in mood and anxiety disorders^[70]; similar findings have been described in IBS, and increased sympathetic tone has been shown to enhance visceral hypersensitivity^[71]. The processing of sensory information, mainly of noxious stimuli, strongly relies on emotional, motivational, and cognitive components, all of which are likely affected by affective styles. ANS output can be activate by ascending interoceptive signals from the gut, by descending cognitive or emotional influences, or in response to external or internal demands. Depending on the class of stimuli (threats to body homeostasis, severe environmental stressors, as well as strong emotions such as anger, fear, and sadness), ANS output can override local ENS function^[72]. The effect of sympathetic outflow to the gut is inhibitory, thus it slows GI transit and secretion, whereas parasympathetic activity on the gut is excitatory, and also mediates the release of 5-HT from enterochromaffin cells^[73]. Autonomic dysfunction, mainly lower parasympathetic activity, may account for the burden of extraintestinal symptoms and overlapping chronic pain disorders in IBS, such as chronic pelvic pain, headache, fibromyalgia, and psychiatric disorders^[28,30]. An intriguing hypothesis

is that top-down sympathetic and parasympathetic activity from brain to gut is thought to mediate affect-related patterns of regional changes in motor, secretory and perhaps immune activity in the GI tract, and these changes are similar to the changes in facial expressions and body postures induced by emotional states^[72]. Accordingly, long-lasting alterations in ANS output to the gut may induce changes in peripheral target cells (*e.g.*, adrenergic and serotonergic receptors) with subsequent feedback from gut to brain and possible effects on those brain regions that receive this prolonged input, as highlighted by neuroimaging studies^[69]. Thus, the hypothesis of ANS dysfunction may provide a stimulating theoretical frame for better understanding the association between changes in brain-gut signaling and NA.

Stress-hormone system: hypothalamic-pituitary-adrenal axis

With the term “stress”, Selye defined the physiological adaptive responses of the organism to emotional or physical threats (“stressors”), whether real or perceived^[74]. Stress evokes adaptive “fight or flight” responses aimed to maintain the stability of the internal environment and to ensure survival; these responses are driven by the activation of the hypothalamic-pituitary-adrenal (HPA) axis. Corticotropin-releasing factor (CRF) is a crucial neuropeptide in the regulation of the HPA axis, and the final common pathway in the stress response. It has several central effects, including cardiovascular by sympathetic activation leading to increased arousal, alertness, rapid heart rate and respiration, cerebral blood flow regulation, and stress-induced analgesia^[75]. Glucocorticoids and catecholamines secreted in response to stressor represent the primary mediators in the chain of hormonal events triggered in response to stress; cortisol, the hormonal end-product of the HPA axis, is one of the most potent endogenous feedback compound on the pro-inflammatory signal transduction machinery^[76]. Negative feedback involving the activation of neural, neuroendocrine and immune mechanisms limits the stress response, leading the organism back to a state of homeostasis; thus, the “ideal” stress response should be time limited. However, if the stressor persists and becomes chronic, the adaptive system becomes defective or excessive, and the prolonged activation of the HPA axis and ANS lead to alterations in mood and affects, a loss of cognitive and affective flexibility, and inhibition of those vegetative processes that are likely to impede survival of the organism during a life-threatening situation, like appetite control, digestion, sleep, sexual activity, and endocrine programs for growth and reproduction^[75]. Stress is considered a significant factor involved in illness and well-being; stress-induced disorders affect the whole body, including the GI tract, which is a sensitive target^[77], and is strongly related to psychiatric disorders. Regarding depression, research has focused on a central role of a pathologically dysregulated HPA axis; stress-induced hypercortisolemia leads to the central downregulation of glucocorticoid receptors, im-

pairing negative feedback of cortisol and enhancing levels of CRF and adrenocorticotrophic hormone^[78]. Early stressors are thought to predispose individuals to adult-onset depression *via* a stable hyperactivity of the HPA system. It has been demonstrated that individuals with both depression and antecedents of early-life trauma exhibit structural reductions in regions involved in HPA axis regulation, whereas individuals with depression alone do not. A recent study has shown that smaller hippocampal volume is observed before the manifestation of clinical symptoms of depression in at-risk adolescents; particularly in those who experienced high levels of adversity during childhood^[79]. The authors suggested that smaller hippocampal size may be an inherited trait predisposing individuals towards the development of those psychiatric disorders that are triggered or worsened by stress, thus partially mediating the effect of early-life adversity on depression during longitudinal follow-up. Increased HPA-axis activity, documented by cortisol awakening response, is also found in anxious people^[80] and, in healthy adults, it has been associated with changes in experimentally induced NA^[81].

Regarding IBS, a major role of stress in the pathophysiology, symptoms severity, visceral pain, and treatment outcome has been documented^[82]. Similar to that found in depression, epidemiological data have shown that a history of early trauma (sexual or physical abuse, and neglect) in genetically predisposed subjects can be a key predisposing factor for the development of IBS in adulthood; however, it occurs in only a minority of all IBS patients. The mechanisms by which early trauma can affect susceptibility to stress-related disorders are the induction of persistent changes in the responsiveness of HPA axis to further stressors^[83], and possibly, epigenetic changes in glucocorticoid receptor expression^[84]. Important insights on the role of early stress on later development of GI symptoms come from animal models. The impact of maternal separation on the brain-gut axis and on GI function has been extensively studied: separated rats show alterations in both central and peripheral neurotransmitter systems, mainly 5-HT and glutamate, activation of the HPA axis with changes in the CRF system; alterations in pain pathways and visceral hypersensitivity with stress-induced hyperalgesia and increased colonic motility; GI immune changes, with aberrant activation of both colon- and systemic-mediated immunity; intestinal barrier dysfunction, with increased permeability and inflammatory cell infiltration in the lamina propria; and disrupted microbiota persisting into adulthood^[85]. Based on the literature, it appears difficult to determine at which level of the HPA axis the primary dysfunction is located; nevertheless, there is sufficient evidence that, in susceptible individuals, alterations in the central stress circuits mediated by early-life adversity and NA play a major role in the pathogenesis and clinical expression of IBS.

Immune system

The immune system is highly connected with other

physiological systems and susceptible to the effects of hormones, neurotransmitters, and other mediators. Direct anatomical and functional links between the CNS and the immune system provide a biological pathway by which affects, emotions, and psychological distress may influence immunity. Chronic stress is associated with altered immunity and an increased susceptibility to a number of diseases^[86], and there is emerging evidence that positive affects can moderate the negative impact of stress on immunity. PA as a trait has been associated with increased cellular immune competence, greater NK cell cytotoxicity, and increases in secretory IgA responses to antigen challenge, increased number of helper T cells, and antibody levels^[87]. Conversely, a growing body of research has found that negative affects and emotions are associated with immunological dysregulation in experimental paradigms aimed to evoke transient mood changes. NA as a stable personality dimension with related coping styles such as repression, rejection, and sensitivity, has been associated with altered leukocyte counts in peripheral blood and dysregulated cellular immune function^[88]. Individuals high in hostility, a stable personality disposition derived from anger, exhibit significant increases in NK cell cytotoxicity when compared with those who are low on hostility^[89]. The relationship between depression and immunity is complex, because depression has been alternatively associated with both immune suppression and immune activation. A recent study has shown that depression and melancholia are associated with activation of cell mediated immunity (CMI); the linked CMI and inflammatory responses are also associated with the onset of depression and with the melancholic cluster symptoms of depression. Exposure to previous depressive episodes seems to amplify the size of CMI responses, possibly increasing the recurrence of depressive episodes^[90]. However, markers of impaired cellular immunity, mainly diminished NK cell cytotoxicity, have also been associated with depression^[91]. Nevertheless, the significant associations of findings of both immune suppression and immune activation with depression raise serious questions concerning the validity of the construct of depression as a homogeneous disorder.

The associations between immunity and GI function are unequivocal, because up to 80% of the immune cells of the whole organism are contained within the gut mucosa and the gut-associated lymphoid tissue^[78]. Accordingly, the gut represents a key structure in maintaining the balance between tolerance and immunity^[78], but it also is a target for unbalanced immune processes. There is increasing evidence suggesting a role for immune activation in IBS^[92].

Findings from a study aimed to examine associations between depression, fatigue, and immunity in IBS patients *vs* healthy controls demonstrate that IBS samples are characterized by higher numbers of mast cells in the gut lamina propria compared to controls; moreover, fatigue and depression ratings are correlated with mast cell counts^[93]. Evidence for a low-grade inflammatory state

in both IBS, depression, and anxiety is discussed in the section related to inflammation as a feature of IBS.

Based on the literature, it is clear that dysfunctional affective and behavioral patterns are main factors in the activation of immune pathways linking to IBS, taking into account that communication between the brain, immune system and gut is bidirectional.

PSYCHIATRIC COMORBIDITY, NEGATIVE AFFECTS AND IBS: WHAT IS THE EVIDENCE?

The issue of comorbidity among psychiatric disorders and IBS is well documented. The prevalence of psychiatric disorders in IBS patients is high, with up to 60% of patients diagnosed as having a comorbid psychiatric disorder^[94]. Results from a prospective, randomized controlled trial aimed to investigate the relationship between bowel symptoms, psychological variables and rectal sensitivity in severe IBS, showed that 44% of IBS patients had psychiatric comorbidity^[95]. The higher rates of comorbidity refer to patients seen in referral centers, and it remains unknown whether those rates of psychiatric disorders are as high in the community of non-consulters, or whether they apply exclusively to those subjects who have sought treatment^[2]. Other authors have suggested that excess comorbidity characterizes only a subset of IBS patients who show a tendency to noticing somatic sensations and a lower threshold for consulting a physician; although, psychopathological factors in IBS have been considered to be related to inducing illness behavior rather than being causally related to the condition itself^[96]. Nevertheless, there is a growing body of evidence supporting an association between psychological distress, environmental stress, and IBS.

A population-based nested case-control study^[97] demonstrated that psychosocial distress was significantly associated with the presence of a functional GI disorder, although it was not explained by health-care utilization. Studies conducted on university students have highlighted the role of depression and anxiety in predicting IBS status^[98], and in community subjects, depression, anxiety, sleep disorders, and somatic symptoms such as headache, and backache were more frequently associated with IBS independent of other variables such as age, sex, education level, marital status, smoking, alcohol use, and BMI^[99].

No specific psychiatric disorder has been associated with IBS, but mood disorders (major depression and dysthymia), anxiety, and somatoform disorders have been the most frequently diagnosed conditions^[100]. In some authors' opinion, high rates of psychiatric disorders in IBS probably reflects referral bias^[96], although recent evidence has shown that psychiatric comorbidity is not only present in tertiary care, but also in primary care^[101] and in non-help-seeking community-based patients^[102]. A random community-based telephone survey

aimed to investigate the prevalence, comorbidity and risk correlates of IBS and generalized anxiety disorder (GAD) in a general population ($n = 2005$) showed that about one in six people with IBS in the community had comorbid GAD that added to the severity and impairment of IBS, also associated with core depressive symptoms^[103]. It is also recognized that patients with IBS or other functional GI disorders tend to have additional functional disorders in various other organ systems (*e.g.*, unexplained pain, weakness, and sexual complaints), and complaints of multiple drug sensitivities and allergies. Moreover, they make twice as many health-care visits per year as age-matched controls, undergo excessive diagnostic tests and surgical procedures, use many over-the-counter and prescription medications, and become refractory to treatment^[104]. Thus, the implications for health economics are significant: IBS patients incur substantially more direct health-care costs than non-IBS patients, and 66% of these excess costs are for non-GI indications, and mainly for psychiatric comorbidity^[105].

It must be stressed that the comorbidity between IBS and psychiatric disorders seems to be bidirectional; also, the prevalence of IBS in psychiatric patients who seek treatment is high, with a prevalence of 19% in schizophrenia, 29% in major depression, and 46% in panic disorder among other disorders^[106]. The prevalence rate of IBS is particularly high in patients diagnosed with double depression (major depressive episode plus dysthymia, a chronic depressive condition), and 57.6% of patients with double depression met the criteria for IBS when compared with controls^[107]. These patients are also more likely to complain of symptoms of weakness, nocturnal bowel movements, and GI symptoms related to stress^[107]. Furthermore, in 50% of patients, the psychiatric disease preceded the onset of the bowel disease, whereas in 37.5% of patients the bowel symptoms appeared first; significantly more patients with double depression also reported a family history (61.5% *vs* 22.5%) of IBS than controls did^[107]. Anxiety sensitivity and illness attitudes and intrusiveness are predictive of elevated IBS symptoms^[108].

Maladaptive affective experiences are distinguished from their adaptive counterpart by several indexes, such as frequency, intensity, duration, and inappropriateness^[109]. Although they represent a main part of psychiatric disorders (*e.g.*, depressed mood is fundamental to clinical depression, as well as anxiety, and is the main symptom of GAD), they should be not be considered identical^[109].

As underlined in the previous sections, symptoms of depression and anxiety, related emotional disorders, individual differences in the tendency to experience negative affect, and related personality traits may reflect a chronic psychological characteristic rather than a discrete, identifiable psychiatric condition. This distinction is important because diagnosable psychiatric disorders, characterized by full, severe symptoms, occur occasionally in the population, whereas subclinical affective symptoms and personality traits involving depression and anxiety,

besides being more common, may be associated with worse health outcomes, and with increased susceptibility to illness just as the full-blown affective disorders^[110].

Here, we summarize research that has evaluated negative affects or affective symptoms in IBS, specifically addressing depression, anxiety and anger. These constructs overlap substantially with more general constructs such as psychological distress and with trait features of negative affect.

Although it may seem rather obscure, from a psychopathological point of view, depressive and anxious affects are included in the same section, because the vast majority of clinical-based research and review papers have not investigated these two affective dimensions separately. Plausible explanations are that depression and anxiety are the most common mental disorders in the general population, often comorbid and overlapping conditions, and mainly, they are categorical psychiatric disorders with a precise set of diagnostic criteria. In contrast, anger, despite its wide diffusion in the general population, has received little attention from psychiatry and clinical psychology, and anger has not been studied in as much depth in its connection to IBS.

ROLE OF DEPRESSION, ANXIETY AND ANGER IN IBS

In the following sections we review the research that has examined the negative affects depression, anxiety and anger in relation to the main pathophysiological and symptomatic correlates of IBS such as sensorimotor functions, gut microbiota, inflammation and immunity, and symptoms reporting.

Visceral and pain hypersensitivity and abnormal colonic motility

Perceptual hypersensitivity to experimental and physiological gut signals in IBS patients has been systematically demonstrated since the first studies on this issue^[111,112], and it has been proposed as a reliable biological marker of the illness. Nevertheless, it is not clear whether this may reflect a true hypersensitivity or rather a central affective alteration of the processing of normal or even reduced gut signals^[72].

Recent studies have shown that the hypersensitivity for rectal distension in IBS is largely determined by hypervigilance for visceral stimuli, anticipation, and a marked tendency to label visceral sensations as painful rather than being a true hypersensitivity; namely an enhanced detection of visceral stimuli^[113]. Recent studies on IBS patients have directly assessed hypervigilance by the use of the emotional Stroop test - a measure of emotional interference and attentional bias - and results have shown that IBS patients present attentional biases to GI pain-related, and social threat words^[114]. A good deal of research has increased knowledge about the strong influence of negative affects, cognitive processes,

arousal, and conditioning on visceral hypersensitivity and pain sensitivity, not only in subjects with IBS, but also in those with subtle GI symptoms within the general population. Anxiety and depression scores are elevated in subjects who report abdominal pain and are positively correlated with pain duration^[115]. Moreover, subjects with abnormal anxiety and depression scores have generally a higher burden of abdominal pain, and this association is most prominent in women^[115]. The influence of depressive symptoms on rectal sensitivity in different subtypes of IBS patients (diarrhea/constipation-predominant *vs* alternating subtypes) has also been investigated. Depression levels are negatively correlated with rectal pain threshold, but only in the alternating subtype of IBS, suggesting that depression might affect pain thresholds differently according to the subtype of IBS^[116]. Other authors have not found a relationship between rectal sensitivity and negative affects, anxiety, depression, and neuroticism^[117].

Attempting to elucidate to what extent affective disturbances contribute to disturbed neural responses to visceral stimuli, brain imaging findings in healthy subjects have documented increased brain activity during negative affects in posterior cingulate cortex, thalamus and somatosensory cortex in the rectal distension paradigm^[118]. It has indeed become clearer that the emotional context affects the neural processing of visceral stimuli even in healthy subjects^[119]. Brain imaging studies^[119] have shown that IBS patients, in response to visceral pain stimulation, present differential brain activations in ACC and insular regions, and in prefrontal and limbic regions, such as the amygdala and hippocampus; brain regions that play a major role in the central pain matrix, besides being involved in the affective component of pain. A functional magnetic resonance imaging study^[120] has demonstrated that patients with IBS experience significantly more pain and discomfort upon rectal distension, despite unaltered rectal sensory thresholds. Depression and anxiety scores are associated with subjective stimulus ratings, but not with rectal sensory thresholds. Furthermore, depression symptoms are correlated with activation of the PFC and cerebellar areas, whereas anxiety scores are significantly associated with pain-induced activation of the anterior mid-cingulate cortex and pregenual anterior cingulate cortex. The above brain regions are involved in the processing of visceral afferent information, in emotional arousal and in cortical modulation. This study was particularly interesting because the examined sample of IBS patients was characterized by relatively minor psychopathological symptoms, although intriguing implications about the role of negative affects rather than that of psychiatric disorders can be inferred. Depression, anxiety, stress, anticipation, and the recall of painful memories can enhance the perception of visceral pain, whereas relaxation and distraction can decrease it^[29].

Intestinal motility patterns, such as enhanced gastrocolic reflex, altered gastric emptying, increased small

intestinal transit, and small bowel contractions following stressful events are present in 25%-75% of patients with IBS^[100]. Patients with diarrhea-predominant IBS (IBS-D) have shorter small-bowel and colonic transits than those with constipation-predominant IBS (IBS-C), who exhibit slowed whole-gut transit. Psychological distress can elicit an enhancement of colonic motility and diarrhea^[15]. This effect is particularly pronounced in IBS patients, who tend to have a greater colonic motor response to both psychological and physical stress in comparison to healthy controls. In a large sample ($n = 1021$) of university students, participants with IBS were more likely to have clinical anxiety and reported higher levels of anxiety sensitivity, neuroticism, and trait worry than their asymptomatic counterparts^[121]. In this group, anxiety was specific to visceral sensations, and this measure was the strongest predictor of IBS diagnostic status^[121]. The authors have suggested that IBS may reflect a vicious cycle of anxiety response in which fears and negative beliefs about GI sensations lead to increased vigilance toward bodily sensations, and in turn, the visceral sensations themselves may further increase as a result of anxiety. Taken together, these results suggest that while predisposing vulnerability factors such as NA or neuroticism and enhanced stress responsiveness contribute to the development of anxiety problems, they may also predispose the individual to anxiety-related visceral sensations, thereby increasing IBS risk. A recent study comparing the distribution of symptoms and psychological parameters in adult patients with different functional GI disorders has demonstrated that depression and anxiety are related to the anatomical extent of the problem, such as the number of sites of complaint^[122]. Moreover, sex differences were found: in male subjects, the extent of sites of functional GI disorder is strongly related to trait anxiety, whereas in female subjects it is strongly related to depression^[122].

Evidence of the association of anger and IBS symptoms is incomplete, although this negative affect seems to have a role in altering colonic motility. IBS patients exposed to experimentally induced anger-provoking conditions became angrier than healthy controls and have increased colonic motor activity^[123]. A further study by the same research group has shown that, during anger-provoking paradigms, IBS patients show a decrease of antral motor activity, whereas in controls the same activity is increased^[124]. Suppression of anger, namely the cognitive and behavioral efforts to restrain angry feelings, is associated with prolonged gastric emptying and delayed gut transit in IBS patients^[125]. Moreover, there is an association between anger control or repression and IBS symptoms such as abdominal pain and increased postprandial colonic motility^[126]. A study by our research group has shown no significant differences in anger and defense mechanisms between IBS patients and controls, and thus we suggest that anger experience and expression, as well as defensiveness, do not seem to play a critical role in IBS patients who do not manifest a con-

current psychiatric disorder or emotional disturbance^[127]. Nevertheless, a subsequent study of depression, anxiety and anger in subtypes of IBS subjects has shown that patients with IBS-C compared with IBS-D are characterized by higher levels of trait anger; a stable dispositional feature that includes a general tendency to experience and express anger, along with higher levels of depression and anxiety^[68]. Findings from a study aimed to compare levels of self-reported trait and suppressed anger and recalled childhood abuse in patients with IBS ($n = 75$) or Crohn's disease ($n = 76$) showed that IBS patients were more prone to experience and suppress anger in everyday situations than patients with Crohn's disease^[128]. However, only trait anger remained elevated in IBS patients after controlling for other psychological variables; moreover, childhood sexual abuse was more prevalent in IBS than Crohn's disease patients but it was unrelated to trait anger^[128].

Together, these studies highlight the contribution of negative affects in mediating the pain experience and altered bowel motility in IBS.

Abnormal gut microbiota

The GI microbiota is a rich microbial ecosystem crucial to health and disease; it colonizes the human gut immediately after birth, and plays a key role in maintaining physiological functions of the host, such as digestion and metabolism, trophism, and the development of the mucosal and systemic immune systems^[129]. A link between the intestinal microbiota and IBS has been suggested; the composition (reduction in lactobacilli and bifidobacteria) and temporal stability of the GI microbial community is altered in IBS patients compared with controls^[130]. Furthermore, several IBS symptoms, such as abdominal pain and bloating may be related to excessive production of gas by bacterial fermentation in the distal bowel and colon. In previous studies, small intestinal bacterial overgrowth (SIBO), characterized by the presence of an abnormally high number of bacteria in the small bowel, has been associated with IBS, although with conflicting results. In a sample of IBS patients scoring significantly higher on psychological distress variables including depression, anxiety, and somatization, there were no differences in psychological distress between SIBO⁺ and SIBO⁻ patients; the authors concluded that a possible influence of psychological distress on the association between SIBO and bowel symptoms was unlikely^[131].

Recently, the construct of the brain-gut axis has been recently expanded to include gut microbiota in a bidirectional way^[132], and knowledge in this field is rapidly expanding.

In rodents, a putative role of the gut microbiota in emotional behavior has been hypothesized, even though little is known about the possible mediating signaling mechanisms. The induction of depression- and anxiety-like behaviors influences the composition of the microbiota by enhanced activation of the stress response and disruption of the microbial habitat *via* alterations in

colonic motility^[133]. Although there appears to be some conflicting findings, preclinical data indicate that an altered or absent microbiota can influence the development and functioning of the CNS, and modulate behavior. Beyond the evidence, it seems premature to translate preclinical work on animal models to the clinic. A recent study^[134] on a large cohort of IBS subjects showed that the majority of IBS patients presented changes in microbiota composition when compared with controls; however, some of the IBS samples had no microbial abnormalities. This latter subsample showed a prevalence of 40% depression, which was significantly higher than the overall rate of 22% found in the study. Moreover, the depression rate in the IBS cohort with altered microbiota was comparable to that of the general population. The hypothesis of the possible association between altered microbiota composition and NA actually relies on animal models, and further clinical studies will allow us to better understand the putative role of microbiota in the gut-brain axis in humans.

Inflammation and immunity

In physiological conditions, the gut is in a chronic state of inflammation, with a balance between commensal microbes and the immune system. Although colonic biopsy specimens are usually normal in IBS patients, direct evidence for a role of inflammation and immune activation in IBS has been provided^[3]. It is estimated that postinfectious IBS may represent up to 30% of all IBS cases^[135], and sustained immune activation has been found in this sub-group of patients^[9]. Furthermore, low-grade immune activation in IBS patients in the absence of an episode of acute gastroenteritis is reported^[136].

Inflammatory mediators, including cytokines, prostaglandins, bradykinins, nerve growth factors, adenosine, and serotonin (5-hydroxytryptamine), are all substances involved in visceral hypersensitivity, alterations in motility, increased gut secretion, and possibly contributing to diarrhea^[2]. Studies focusing on cytokine measurements have shown increased levels of the proinflammatory cytokines interleukin (IL)-6 and IL-8 in IBS patients, whereas the presence of extraintestinal comorbidity, including depressive states, is associated with increased levels of IL-1 β and tumor necrosis factor- α ^[137]. A recent study of the correlation between anxiety-depression status and cytokines in a small sample of patients with IBS-D has shown that IBS-D patients who meet the anxiety-depression criteria have increased IL-1 β levels, and decreased levels of IL-10, an anti-inflammatory cytokine, when compared with controls^[138]. The authors have suggested that anxiety-depression status may cause changes in the IL-1 β and IL-10 levels of IBS patients, resulting in an imbalance of the proinflammatory and anti-inflammatory cytokines, thus leading to aggravation of IBS^[138]. The sample size (IBS-D group: $n = 12$; anxiety-depression IBS-D group: $n = 16$; control group: $n = 15$) does not permit us to make robust inferences from the findings, which need to be replicated in larger

samples. Nevertheless, this study is particularly interesting because it was the first to report the influence of negative affects (depression and anxiety) on inflammatory parameters in IBS-D.

Negative affects have recognized common pathways with inflammatory conditions and confer increased risk for disorders with an inflammatory etiology^[139]. Depressed mood has been linked with increased levels of proinflammatory cytokines and other inflammatory mediators, such as acute phase proteins, cellular adhesion molecules, and chemokines^[140]. Cytokine production is associated with the so-called sickness behavior, due to the impact of proinflammatory cytokines on the brain, and characterized by a number of behavioral symptoms such as weakness, depressed mood, anhedonia, lethargy, loss of appetite, feelings of depression, and cognitive deficits. The strict similarity between sickness behavior and depression has led to the cytokine hypothesis of depression, whose main assumption is that both psychosocial and internal stressors may trigger depression *via* inflammatory processes *via* changes in neuroendocrine and neurotransmitter systems^[91].

In contrast with the large body of research examining the association between depression and inflammation, less is known about the relationship between anxiety, anger and inflammation. Anxious subjects have higher levels of the proinflammatory cytokine IL-6^[141]. Higher levels of IL-6 and C-reactive protein (CRP) among individuals with high anger and lower levels of the same inflammation markers among those with high anger control have been found^[142]. Moreover, trait anger and hostility vary positively with levels of CRP and IL-6^[143], suggesting that angry tendencies may confer much of the variability in inflammation associated with negative emotions.

Health care-seeking behavior

From an epidemiological point of view, GI symptoms are remarkably frequent in the general population, with up to 70% of individuals reporting one or more symptoms^[15]. Moreover, only a percentage of individuals affected by IBS in the general population ever seek the attention of the health care system for their symptoms. Part of the variation in rates of health care-seeking behavior is possibly attributable to characteristics associated with the health care system of a particular country or region, and another explanation might be due to social learning in early childhood^[2]. In psychological terms, social learning of illness behavior takes place through reinforcement, when parents respond to abdominal complaints of their children with increased attention, or through modeling, when parents affected by IBS behave in a way that reveals a concern with illness. The effects of social learning on illness behavior in IBS have been highlighted: children of mothers with IBS have more non-GI as well as GI symptoms, more school absence, and attend more medical examinations for GI symptoms than children of non-IBS mothers^[144]. Beyond

accessibility to the health care system, and social learning, psychological distress, psychiatric comorbidity, and NA have been indicated as significant factors in use of health care by IBS adults. It has been shown that in adult IBS patients, health-care-seeking behavior and treatment outcome are adversely associated with anxiety, chronic social stress, acute stressors, and maladaptive coping style^[145]. The majority of IBS patients who seek medical advice for GI problems have an associated affective disorder. Anxiety in particular has been designated as an important determinant of medical consultation among patients with IBS^[146]. In contrast, it has been suggested that negative emotions may not always facilitate care-seeking. The co-occurrence of nonspecific physical symptoms and stressful life events may lead to the misattribution of symptoms to the stressor, and thus, to delay the decision to seek medical attention^[147]. A recent study on a community sample of university students with IBS-like symptoms compared with a non-IBS reference group has shown that health care utilization is mainly associated with IBS symptom severity, and not with emotional distress^[148]. As reviewed in previous sections, rates of negative affects and psychiatric comorbidity in IBS patients are higher than in the general population^[94]. Moreover, these high rates are not encountered only in health-care-seeking IBS patient samples, but also in community-based samples, suggesting that affective disturbances in IBS patients are involved in the pathophysiology of the illness rather than merely a determinant of health care use^[99]. Furthermore, the timing of onset of psychological factors, the shared assumption that NA encompasses temperamental features and stable personality traits, and the bio-psychosocial frame in which IBS is actually viewed, further suggest the influence of NA in IBS development that goes beyond a possible role only in the use of health services^[149]. It seems plausible that health-care-seeking behavior in IBS patients might be influenced by many factors; among these, symptom severity, especially pain, duration of illness, and somatization may have some role^[150].

INTERPLAY BETWEEN GUT AND BRAIN: TREATMENT IMPLICATIONS

Current treatments for IBS are based on symptom representation and comorbid conditions such as lifestyle, diet and stress disorders. Dietary changes, such as a step-wise food exclusion approach, as well as fiber and/or probiotic supplementation, have been proposed when symptoms are mild. For moderate symptoms, pharmacological treatments, including antispasmodics, prokinetics (5-HT₃ antagonists and/or 5-HT₄ agonists, dopamine antagonists), antibiotics, and bulking agents, can be considered. Medications are mainly symptom directed, because the pathophysiological mechanisms for development of IBS are complex and multifactorial.

It is well known from the literature that the efficacy of pharmacotherapy for IBS is weak. Despite the wide

range of available drugs and the high prevalence of the disease, to date, no single drug or particular combination strategy has been shown to be superior to the others^[151].

Severe IBS, characterized by high levels of pain, diminished quality of life, and/or comorbidity with mood and anxiety disorders is frequently resistant to first- and second-line therapies^[152].

Within the frame of the bio-psychosocial model of IBS, and taking into account the bidirectional communication between the brain and the gut, centrally acting treatments, such as psychopharmacological or psychological treatments, can be used to reduce the impact of the GI symptoms.

Psychotropic drugs, mainly antidepressants, are commonly prescribed for IBS.

The rationale for prescribing tricyclic antidepressants (TCAs) is that these drugs have demonstrated efficacy in modulating pain perception *via* central regulatory mechanisms, and for this effect they are also used to treat chronic neuropathic pain and other chronic pain conditions^[153]. Selective serotonin reuptake inhibitors (SSRIs) have a lower side effect profile than TCAs, although their efficacy as antinociceptive agents is questionable^[2]. Moreover, the prokinetic effect of SSRIs (*e.g.*, stimulation of small-intestinal motility and induction of nausea) can intensify certain IBS symptoms^[154].

Anxiolytic agents, particularly the benzodiazepines (BZDs), combined with antispasmodics, have been one of the most common treatment strategies for IBS patients. However, such therapies have not received supportive evidence from high-quality clinical trials^[155], and the potential role of BZDs in the treatment of IBS needs further evaluation^[156], taking into account the risk of tolerance, the potential for dependency, and rebound after withdrawal.

Considering the partial benefits of pharmacotherapy, a significant amount of research has evaluated psychological and psychosocial treatments for IBS. The effect of various techniques of psychotherapy, such as cognitive behavioral therapy, interpersonal psychotherapy, hypnotherapy, and relaxation/stress management on IBS has been evaluated. Nevertheless, as demonstrated by a recent meta-analysis^[157], psychological interventions are not superior to placebo, and there is no convincing evidence that treatment effects are sustained in long-term follow-up. IBS treatment thus requires complex and multidisciplinary management, and the establishment of a positive and empathic doctor-patient relationship to provide individualized treatment and the education and support needed to help patients to deal with what is often a lifelong disorder.

CONCLUSION

Previous research has suggested that negative emotions and attitudes have detrimental effects on health, and a number of behavioral and biological mechanisms could underlie these associations.

Growing evidence supports the hypothesis that negative affects are a major component of the biopsychosocial model of IBS, because they play a key role in dysregulation of the brain-gut axis, contributing to the majority of pathophysiological and symptomatic correlates of IBS. Beyond temperament and affective dispositions, there is strong support, both from preclinical and clinical studies, for the psychosocial role of the environment in altering behavior and influencing nervous, autonomic and immune functions. Furthermore, early life adversity produces epigenetic changes in those brain regions that influence behavior, affective attitudes, and process information about potentially threatening or harmful environments.

As highlighted in the present review, major contributions to advancing our understanding of the role of NA in IBS have come from different research disciplines, such as gastroenterology, stress medicine, psychiatry, psychology, and neurobiology. Future focus in this research field should move towards the development of integrative research strategies involving these apparently divergent, yet complementary disciplines. In our opinion, efforts aimed to integrate different fields of knowledge will provide further insight into the pathophysiological pathways linking negative psychological states to health and disease, leading to the identification of individual vulnerability and of those susceptibility factors, including subsyndromal conditions, that should be addressed to promote better health in the population and more effective and efficient efforts at prevention and treatment of IBS.

REFERENCES

- Longstreth GF, Thompson WG, Chey WD, Houghton LA, Mearin F, Spiller RC. Functional bowel disorders. *Gastroenterology* 2006; **130**: 1480-1491 [PMID: 16678561 DOI: 10.1053/j.gastro.2005.11.061]
- Talley NJ, Spiller R. Irritable bowel syndrome: a little understood organic bowel disease? *Lancet* 2002; **360**: 555-564 [PMID: 12241674 DOI: 10.1016/S0140-6736(02)09712-X]
- Clarke G, Quigley EM, Cryan JF, Dinan TG. Irritable bowel syndrome: towards biomarker identification. *Trends Mol Med* 2009; **15**: 478-489 [PMID: 19811951 DOI: 10.1016/j.molmed.2009.08.001]
- Spiller RC. Postinfectious irritable bowel syndrome. *Gastroenterology* 2003; **124**: 1662-1671 [PMID: 12761724 DOI: 10.1016/S0016-5085(03)00324-X]
- Guilarte M, Santos J, de Torres I, Alonso C, Vicario M, Ramos L, Martínez C, Casellas F, Saperas E, Malagelada JR. Diarrhoea-predominant IBS patients show mast cell activation and hyperplasia in the jejunum. *Gut* 2007; **56**: 203-209 [PMID: 17005763]
- Akbar A, Yiangou Y, Facer P, Walters JR, Anand P, Ghosh S. Increased capsaicin receptor TRPV1-expressing sensory fibres in irritable bowel syndrome and their correlation with abdominal pain. *Gut* 2008; **57**: 923-929 [PMID: 18252749 DOI: 10.1136/gut.2007.138982]
- Barbara G, Cremon C, Carini G, Bellacosa L, Zecchi L, De Giorgio R, Corinaldesi R, Stanghellini V. The immune system in irritable bowel syndrome. *J Neurogastroenterol Motil* 2011; **17**: 349-359 [PMID: 22148103 DOI: 10.5056/jnm.2011.17.4.349]
- Buhner S, Li Q, Vignali S, Barbara G, De Giorgio R, Stanghellini V, Cremon C, Zeller F, Langer R, Daniel H, Michel K, Schemann M. Activation of human enteric neurons by supernatants of colonic biopsy specimens from patients with irritable bowel syndrome. *Gastroenterology* 2009; **137**: 1425-1434 [PMID: 19596012 DOI: 10.1053/j.gastro.2009.07.005]
- Gwee KA. Irritable bowel syndrome in developing countries--a disorder of civilization or colonization? *Neurogastroenterol Motil* 2005; **17**: 317-324 [PMID: 15916618 DOI: 10.1111/j.1365-2982.2005.00627.x]
- Thompson WG, Heaton KW, Smyth GT, Smyth C. Irritable bowel syndrome in general practice: prevalence, characteristics, and referral. *Gut* 2000; **46**: 78-82 [PMID: 10601059 DOI: 10.1136/gut.46.1.78]
- Whitehead WE, Schuster MM. Gastrointestinal disorders: behavioral and physiological basis for treatment. Orlando: Academic Press, 1985: 256-303
- Saito YA, Schoenfeld P, Locke GR. The epidemiology of irritable bowel syndrome in North America: a systematic review. *Am J Gastroenterol* 2002; **97**: 1910-1915 [PMID: 12190153 DOI: 10.1111/j.1572-0241.2002.05913.x]
- Thompson WG, Longstreth GF, Drossman DA, Heaton KW, Irvine EJ, Müller-Lissner SA. Functional bowel disorders and functional abdominal pain. *Gut* 1999; **45** Suppl 2: II43-II47 [PMID: 10457044 DOI: 10.1136/gut.45.2008.ii43]
- Adeyemo MA, Spiegel BM, Chang L. Meta-analysis: do irritable bowel syndrome symptoms vary between men and women? *Aliment Pharmacol Ther* 2010; **32**: 738-755 [PMID: 20662786 DOI: 10.1111/j.1365-2036.2010.04409.x]
- Drossman DA, Li Z, Andruzzi E, Temple RD, Talley NJ, Thompson WG, Whitehead WE, Janssens J, Funch-Jensen P, Corazziari E. U.S. householder survey of functional gastrointestinal disorders. Prevalence, sociodemography, and health impact. *Dig Dis Sci* 1993; **38**: 1569-1580 [PMID: 8359066 DOI: 10.1007/BF01303162]
- Hahn B, Watson M, Yan S, Gunput D, Heuvelink J. Irritable bowel syndrome symptom patterns: frequency, duration, and severity. *Dig Dis Sci* 1998; **43**: 2715-2718 [PMID: 9881504 DOI: 10.1023/A:1026663613695]
- Janssen HA, Muris JW, Knotterus JA. The clinical course and prognostic determinants of the irritable bowel syndrome: a literature review. *Scand J Gastroenterol* 1998; **33**: 561-567 [PMID: 9669623 DOI: 10.1080/00365529850171783]
- Mayer EA, Aziz Q, Coen S, Kern M, Labus JS, Lane R, Kuo B, Naliboff B, Tracey I. Brain imaging approaches to the study of functional GI disorders: a Rome working team report. *Neurogastroenterol Motil* 2009; **21**: 579-596 [PMID: 19646070 DOI: 10.1111/j.1365-2982.2009.01304.x]
- Elsenbruch S. Abdominal pain in Irritable Bowel Syndrome: a review of putative psychological, neural and neuro-immune mechanisms. *Brain Behav Immun* 2011; **25**: 386-394 [PMID: 21094682 DOI: 10.1016/j.bbi.2010.11.010]
- Philpott H, Gibson P, Thien F. Irritable bowel syndrome - An inflammatory disease involving mast cells. *Asia Pac Allergy* 2011; **1**: 36-42 [PMID: 22053295 DOI: 10.5415/apalergy.2011.1.1.36]
- Atkinson W, Sheldon TA, Shaath N, Whorwell PJ. Food elimination based on IgG antibodies in irritable bowel syndrome: a randomised controlled trial. *Gut* 2004; **53**: 1459-1464 [PMID: 15361495 DOI: 10.1136/gut.2003.037697]
- Jeffery IB, Quigley EM, Öhman L, Simrén M, O'Toole PW. The microbiota link to irritable bowel syndrome: an emerging story. *Gut Microbes* 2012; **3**: 572-576 [PMID: 22895081 DOI: 10.4161/gmic.21772]
- Aziz Q, Doré J, Emmanuel A, Guarner F, Quigley EM. Gut microbiota and gastrointestinal health: current concepts and future directions. *Neurogastroenterol Motil* 2013; **25**: 4-15 [PMID: 23279728 DOI: 10.1111/nmo.12046]
- Aggarwal A, Cutts TF, Abell TL, Cardoso S, Familoni B, Bremer J, Karas J. Predominant symptoms in irritable bowel syndrome correlate with specific autonomic nervous system

- abnormalities. *Gastroenterology* 1994; **106**: 945-950 [PMID: 8143999]
- 25 **Berman S**, Suyenobu B, Naliboff BD, Bueller J, Stains J, Wong H, Mandelkern M, Fitzgerald L, Ohning G, Gupta A, Labus JS, Tillisch K, Mayer EA. Evidence for alterations in central noradrenergic signaling in irritable bowel syndrome. *Neuroimage* 2012; **63**: 1854-1863 [PMID: 22917679 DOI: 10.1016/j.neuroimage.2012.08.028]
 - 26 **Dinan TG**, Clarke G, Quigley EM, Scott LV, Shanahan F, Cryan J, Cooney J, Keeling PW. Enhanced cholinergic-mediated increase in the pro-inflammatory cytokine IL-6 in irritable bowel syndrome: role of muscarinic receptors. *Am J Gastroenterol* 2008; **103**: 2570-2576 [PMID: 18785949 DOI: 10.1111/j.1572-0241.2008.01871.x]
 - 27 **Konturek PC**, Brzozowski T, Konturek SJ. Stress and the gut: pathophysiology, clinical consequences, diagnostic approach and treatment options. *J Physiol Pharmacol* 2011; **62**: 591-599 [PMID: 22314561]
 - 28 **Mulak A**, Bonaz B. Irritable bowel syndrome: a model of the brain-gut interactions. *Med Sci Monit* 2004; **10**: RA55-RA62 [PMID: 15260348]
 - 29 **Mach T**. The brain-gut axis in irritable bowel syndrome-clinical aspects. *Med Sci Monit* 2004; **10**: RA125-RA131 [PMID: 15173682]
 - 30 **Mayer EA**, Tillisch K. The brain-gut axis in abdominal pain syndromes. *Annu Rev Med* 2011; **62**: 381-396 [PMID: 21090962 DOI: 10.1146/annurev-med-012309-103958]
 - 31 **Ohman L**, Simrén M. New insights into the pathogenesis and pathophysiology of irritable bowel syndrome. *Dig Liver Dis* 2007; **39**: 201-215 [PMID: 17267314 DOI: 10.1016/j.dld.2006.10.014]
 - 32 **Engel GL**. The clinical application of the biopsychosocial model. *Am J Psychiatry* 1980; **137**: 535-544 [PMID: 7369396]
 - 33 **Tanaka Y**, Kanazawa M, Fukudo S, Drossman DA. Biopsychosocial model of irritable bowel syndrome. *J Neurogastroenterol Motil* 2011; **17**: 131-139 [PMID: 21602989 DOI: 10.5056/jnm.2011.17.2.131]
 - 34 **Surdea-Blaga T**, Băban A, Dumitrascu DL. Psychosocial determinants of irritable bowel syndrome. *World J Gastroenterol* 2012; **18**: 616-626 [PMID: 22363132 DOI: 10.3748/wjg.v18.i7.616]
 - 35 **Kerber KJ**, de Graft-Johnson JE, Bhutta ZA, Okong P, Starrs A, Lawn JE. Continuum of care for maternal, newborn, and child health: from slogan to service delivery. *Lancet* 2007; **370**: 1358-1369 [PMID: 17933651 DOI: 10.1016/S0140-6736(07)61578-5]
 - 36 **Caldji C**, Diorio J, Meaney MJ. Variations in maternal care in infancy regulate the development of stress reactivity. *Biol Psychiatry* 2000; **48**: 1164-1174 [PMID: 11137058 DOI: 10.1016/S0006-3223(00)01084-2]
 - 37 **Champagne FA**, Francis DD, Mar A, Meaney MJ. Variations in maternal care in the rat as a mediating influence for the effects of environment on development. *Physiol Behav* 2003; **79**: 359-371 [PMID: 12954431 DOI: 10.1016/S0031-9384(03)00149-5]
 - 38 **O'Mahony SM**, Marchesi JR, Scully P, Codling C, Ceolho AM, Quigley EM, Cryan JF, Dinan TG. Early life stress alters behavior, immunity, and microbiota in rats: implications for irritable bowel syndrome and psychiatric illnesses. *Biol Psychiatry* 2009; **65**: 263-267 [PMID: 18723164 DOI: 10.1016/j.biopsych.2008.06.026]
 - 39 **Mayer EA**, Collins SM. Evolving pathophysiologic models of functional gastrointestinal disorders. *Gastroenterology* 2002; **122**: 2032-2048 [PMID: 12055608 DOI: 10.1053/gast.2002.33584]
 - 40 **Davidson RJ**. Affective neuroscience and psychophysiology: toward a synthesis. *Psychophysiology* 2003; **40**: 655-665 [PMID: 14696720 DOI: 10.1111/1469-8986.00067]
 - 41 **Dalgleish T**. The emotional brain. *Nat Rev Neurosci* 2004; **5**: 583-589 [PMID: 15208700 DOI: 10.1038/nrn1432]
 - 42 **Phillips ML**, Drevets WC, Rauch SL, Lane R. Neurobiology of emotion perception I: The neural basis of normal emotion perception. *Biol Psychiatry* 2003; **54**: 504-514 [PMID: 12946879 DOI: 10.1016/S0006-3223(03)00168-9]
 - 43 **Watson D**, Clark LA. Negative affectivity: the disposition to experience aversive emotional states. *Psychol Bull* 1984; **96**: 465-490 [PMID: 6393179 DOI: 10.1037/0033-2909.96.3.465]
 - 44 **Watson D**, Tellegen A. Toward a consensual structure of mood. *Psychol Bull* 1985; **98**: 219-235 [PMID: 3901060 DOI: 10.1037/0033-2909.98.2.219]
 - 45 **Clark LA**, Watson D, Leeka J. Diurnal variation in the positive affects. *Motiv Emot* 1989; **13**: 205-234 [DOI: 10.1007/BF00995536]
 - 46 **Suls J**. Affect, stress and personality. In Forgas JP. Handbook of affect and social cognition. Mahwah, NJ: Erlbaum, 2001: 392-409
 - 47 **Clark LA**, Watson D. Tripartite model of anxiety and depression: psychometric evidence and taxonomic implications. *J Abnorm Psychol* 1991; **100**: 316-336 [PMID: 1918611 DOI: 10.1037/0021-843X.100.3.316]
 - 48 **Zautra AJ**, Potter PT, Reich JW. The independence of affects is context-dependent: An integrative model of the relationship between positive and negative affect. In Powell Lawton M, Warner Schaie K. Annual Review of Gerontology and Geriatrics. Berlin: Springer, 1997: 75-102
 - 49 **Pressman SD**, Cohen S. Does positive affect influence health? *Psychol Bull* 2005; **131**: 925-971 [PMID: 16351329 DOI: 10.1037/0033-2909.131.6.925]
 - 50 **Costa PT**, McCrae RR. Neuroticism, somatic complaints, and disease: is the bark worse than the bite? *J Pers* 1987; **55**: 299-316 [PMID: 3612472 DOI: 10.1111/j.1467-6494.1987.tb00438.x]
 - 51 **Farnam A**, Somi MH, Sarami F, Farhang S, Yasrebinia S. Personality factors and profiles in variants of irritable bowel syndrome. *World J Gastroenterol* 2007; **13**: 6414-6418 [PMID: 18081232 DOI: 10.3748/wjg.13.6414]
 - 52 **Tayama J**, Nakaya N, Hamaguchi T, Tomiie T, Shinozaki M, Saigo T, Shirabe S, Fukudo S. Effects of personality traits on the manifestations of irritable bowel syndrome. *Biopsychosoc Med* 2012; **6**: 20 [PMID: 23110762 DOI: 10.1186/1751-0759-6-20]
 - 53 **Denollet J**. Type D personality. A potential risk factor refined. *J Psychosom Res* 2000; **49**: 255-266 [PMID: 11119782 DOI: 10.1016/S0022-3999(00)00177-X]
 - 54 **Denollet J**. DS14: standard assessment of negative affectivity, social inhibition, and Type D personality. *Psychosom Med* 2005; **67**: 89-97 [PMID: 15673629 DOI: 10.1097/01.psy.0000149256.81953.49]
 - 55 **Chapman B**, Duberstein P, Lyness JM. Personality traits, education, and health-related quality of life among older adult primary care patients. *J Gerontol B Psychol Sci Soc Sci* 2007; **62**: P343-P352 [PMID: 18079419 DOI: 10.1093/geronb/62.6.P343]
 - 56 **Rothbart MK**, Bates JE. Temperament in children's development. In Eisenberg n, Damon W, Lerner RM. Handbook of child psychology (6th ed.). Social, emotional, and personality development. New York: John Wiley & Sons, 2006: 99-166
 - 57 **Kagan J**. Temperament and the reactions to unfamiliarity. *Child Dev* 1997; **68**: 139-143 [PMID: 9084130 DOI: 10.1111/j.1467-8624.1997.tb01931.x]
 - 58 **Muris P**, van Brakel AM, Arntz A, Schouten E. Behavioral Inhibition as a Risk Factor for the Development of Childhood Anxiety Disorders: A Longitudinal Study. *J Child Fam Stud* 2011; **20**: 157-170 [PMID: 21475710 DOI: 10.1007/s10826-010-9365-8]
 - 59 **Wood AM**, Joseph S. The absence of positive psychological (eudemonic) well-being as a risk factor for depression: a ten year cohort study. *J Affect Disord* 2010; **122**: 213-217 [PMID: 20444444 DOI: 10.1016/j.jad.2010.01.014]

- 19706357 DOI: 10.1016/j.jad.2009.06.032]
- 60 **Cirulli F**, Laviola G, Ricceri L. Risk factors for mental health: translational models from behavioural neuroscience. *Neurosci Biobehav Rev* 2009; **33**: 493-497 [PMID: 19415818 DOI: 10.1016/j.neubiorev.2009.01.006]
 - 61 **Probst AV**, Dunleavy E, Almouzni G. Epigenetic inheritance during the cell cycle. *Nat Rev Mol Cell Biol* 2009; **10**: 192-206 [PMID: 19234478 DOI: 10.1038/nrm2640]
 - 62 **Suderman M**, McGowan PO, Sasaki A, Huang TC, Hallett MT, Meaney MJ, Turecki G, Szyf M. Conserved epigenetic sensitivity to early life experience in the rat and human hippocampus. *Proc Natl Acad Sci USA* 2012; **109** Suppl 2: 17266-17272 [PMID: 23045659 DOI: 10.1073/pnas.1121260109]
 - 63 **Francis D**, Diorio J, Liu D, Meaney MJ. Nongenomic transmission across generations of maternal behavior and stress responses in the rat. *Science* 1999; **286**: 1155-1158 [PMID: 10550053 DOI: 10.1126/science.286.5442.1155]
 - 64 **Gilbert R**, Widom CS, Browne K, Fergusson D, Webb E, Janson S. Burden and consequences of child maltreatment in high-income countries. *Lancet* 2009; **373**: 68-81 [PMID: 19056114 DOI: 10.1016/S0140-6736(08)61706-7]
 - 65 **Tojek TM**, Lumley MA, Corlis M, Ondersma S, Tolia V. Maternal correlates of health status in adolescents with inflammatory bowel disease. *J Psychosom Res* 2002; **52**: 173-179 [PMID: 11897236 DOI: 10.1016/S0022-3999(01)00291-4]
 - 66 **Rosmalen JG**, Neeleman J, Gans RO, de Jonge P. The association between neuroticism and self-reported common somatic symptoms in a population cohort. *J Psychosom Res* 2007; **62**: 305-311 [PMID: 17324681 DOI: 10.1016/j.jpsychores.2006.10.014]
 - 67 **Holstege G**, Bandler R, Saper CB. The Emotional Motor System. In: Jones EG, Peters A. Progress in brain research Vol. 107. Amsterdam: Elsevier, 1996: 3-6
 - 68 **Muscatello MR**, Bruno A, Pandolfo G, Micò U, Stilo S, Scafidi M, Consolo P, Tortora A, Pallio S, Giacobbe G, Familiari L, Zoccali R. Depression, anxiety and anger in subtypes of irritable bowel syndrome patients. *J Clin Psychol Med Settings* 2010; **17**: 64-70 [PMID: 20094761 DOI: 10.1007/s10880-009-9182-7]
 - 69 **Seminowicz DA**, Labus JS, Bueller JA, Tillisch K, Naliboff BD, Bushnell MC, Mayer EA. Regional gray matter density changes in brains of patients with irritable bowel syndrome. *Gastroenterology* 2010; **139**: 48-57.e2 [PMID: 20347816 DOI: 10.1053/j.gastro.2010.03.049]
 - 70 **Brown TA**, Chorpita BF, Barlow DH. Structural relationships among dimensions of the DSM-IV anxiety and mood disorders and dimensions of negative affect, positive affect, and autonomic arousal. *J Abnorm Psychol* 1998; **107**: 179-192 [PMID: 9604548 DOI: 10.1037/0021-843X.107.2.179]
 - 71 **Ng C**, Malcolm A, Hansen R, Kellow J. Feeding and colonic distension provoke altered autonomic responses in irritable bowel syndrome. *Scand J Gastroenterol* 2007; **42**: 441-446 [PMID: 17454853 DOI: 10.1080/00365520600965749]
 - 72 **Mayer EA**. Gut feelings: the emerging biology of gut-brain communication. *Nat Rev Neurosci* 2011; **12**: 453-466 [PMID: 21750565 DOI: 10.1038/nrn3071]
 - 73 **Stephens RL**, Tache Y. Intracisternal injection of a TRH analogue stimulates gastric luminal serotonin release in rats. *Am J Physiol* 1989; **256**: G377-G383 [PMID: 2493198]
 - 74 **Selye H**. A syndrome produced by diverse noxious agents. 1936. *J Neuropsychiatry Clin Neurosci* 1998; **10**: 230-231 [PMID: 9722327]
 - 75 **Swaab DF**. The human hypothalamus. Basic and clinical aspects. Part I: Nuclei of the hypothalamus. In: Aminoff MJ, Boller F, Swaab DF. Handbook of Clinical Neurology, vol. 79. Amsterdam: Elsevier, 2003: 1-476
 - 76 **Rivest S**. How circulating cytokines trigger the neural circuits that control the hypothalamic-pituitary-adrenal axis. *Psychoneuroendocrinology* 2001; **26**: 761-788 [PMID: 11585678 DOI: 10.1016/S0306-4530(01)00064-6]
 - 77 **Stengel A**, Taché Y. Corticotropin-releasing factor signaling and visceral response to stress. *Exp Biol Med* (Maywood) 2010; **235**: 1168-1178 [PMID: 20881321 DOI: 10.1258/ebm.2010.009347]
 - 78 **Nestler EJ**, Barrot M, DiLeone RJ, Eisch AJ, Gold SJ, Monteggia LM. Neurobiology of depression. *Neuron* 2002; **34**: 13-25 [PMID: 11931738 DOI: 10.1016/S0896-6273(02)00653-0]
 - 79 **Rao U**, Chen LA, Bidesi AS, Shad MU, Thomas MA, Hammen CL. Hippocampal changes associated with early-life adversity and vulnerability to depression. *Biol Psychiatry* 2010; **67**: 357-364 [PMID: 20015483 DOI: 10.1016/j.biopsych.2009.10.017]
 - 80 **Wardenaar KJ**, Vreeburg SA, van Veen T, Giltay EJ, Veen G, Penninx BW, Zitman FG. Dimensions of depression and anxiety and the hypothalamo-pituitary-adrenal axis. *Biol Psychiatry* 2011; **69**: 366-373 [PMID: 21030010 DOI: 10.1016/j.biopsych.2010.09.005]
 - 81 **Buchanan TW**, al'Absi M, Lovallo WR. Cortisol fluctuates with increases and decreases in negative affect. *Psychoneuroendocrinology* 1999; **24**: 227-241 [PMID: 10101730]
 - 82 **Chang L**, Sundaresh S, Elliott J, Anton PA, Baldi P, Licudine A, Mayer M, Vuong T, Hirano M, Naliboff BD, Ameen VZ, Mayer EA. Dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis in irritable bowel syndrome. *Neurogastroenterol Motil* 2009; **21**: 149-159 [PMID: 18684212 DOI: 10.1111/j.1365-2982.2008.01171.x]
 - 83 **Drossman DA**. Abuse, trauma, and GI illness: is there a link? *Am J Gastroenterol* 2011; **106**: 14-25 [PMID: 21139573 DOI: 10.1038/ajg.2010.453]
 - 84 **Chrousos GP**. Stress and disorders of the stress system. *Nat Rev Endocrinol* 2009; **5**: 374-381 [PMID: 19488073 DOI: 10.1038/nrendo.2009.106]
 - 85 **O'Mahony SM**, Hyland NP, Dinan TG, Cryan JF. Maternal separation as a model of brain-gut axis dysfunction. *Psychopharmacology* (Berl) 2011; **214**: 71-88 [PMID: 20886335 DOI: 10.1007/s00213-010-2010-9]
 - 86 **Kemeny ME**, Schedlowski M. Understanding the interaction between psychosocial stress and immune-related diseases: a stepwise progression. *Brain Behav Immun* 2007; **21**: 1009-1018 [PMID: 17889502 DOI: 10.1016/j.bbi.2007.07.010]
 - 87 **Dockray S**, Steptoe A. Positive affect and psychobiological processes. *Neurosci Biobehav Rev* 2010; **35**: 69-75 [PMID: 20097225 DOI: 10.1016/j.neubiorev.2010.01.006]
 - 88 **Kiecolt-Glaser JK**, McGuire L, Robles TF, Glaser R. Psychoneuroimmunology: psychological influences on immune function and health. *J Consult Clin Psychol* 2002; **70**: 537-547 [PMID: 12090368 DOI: 10.1037/0022-006X.70.3.537]
 - 89 **Christensen AJ**, Edwards DL, Wiebe JS, Benotsch EG, McKelvey L, Andrews M, Lubaroff DM. Effect of verbal self-disclosure on natural killer cell activity: moderating influence of cynical hostility. *Psychosom Med* 1996; **58**: 150-155 [PMID: 8849632 DOI: 10.1007/s12160-008-9041-z]
 - 90 **Maes M**, Mihaylova I, Kubera M, Ringel K. Activation of cell-mediated immunity in depression: association with inflammation, melancholia, clinical staging and the fatigue and somatic symptom cluster of depression. *Prog Neuropsychopharmacol Biol Psychiatry* 2012; **36**: 169-175 [PMID: 21945535 DOI: 10.1016/j.pnpbp.2011.09.006]
 - 91 **Blume J**, Douglas SD, Evans DL. Immune suppression and immune activation in depression. *Brain Behav Immun* 2011; **25**: 221-229 [PMID: 20955778 DOI: 10.1016/j.bbi.2010.10.008]
 - 92 **Clarke G**, Fitzgerald P, Hennessy AA, Cassidy EM, Quigley EM, Ross P, Stanton C, Cryan JF, Dinan TG. Marked elevations in pro-inflammatory polyunsaturated fatty acid metabolites in females with irritable bowel syndrome. *J Lipid Res* 2010; **51**: 1186-1192 [PMID: 19965606 DOI: 10.1194/jlr.P000695]
 - 93 **Piche T**, Saint-Paul MC, Dainese R, Marine-Barjoan E, Ian-

- nelli A, Montoya ML, Peyron JF, Czerucka D, Cherikh F, Filippi J, Tran A, Hébuterne X. Mast cells and cellularity of the colonic mucosa correlated with fatigue and depression in irritable bowel syndrome. *Gut* 2008; **57**: 468-473 [PMID: 18194987 DOI: 10.1136/gut.2007.127068]
- 94 **Folks DG**. The interface of psychiatry and irritable bowel syndrome. *Curr Psychiatry Rep* 2004; **6**: 210-215 [PMID: 15142474 DOI: 10.1007/s11920-004-0066-0]
 - 95 **Guthrie E**, Creed F, Fernandes L, Ratcliffe J, Van Der Jagt J, Martin J, Howlett S, Read N, Barlow J, Thompson D, Tomenson B. Cluster analysis of symptoms and health seeking behaviour differentiates subgroups of patients with severe irritable bowel syndrome. *Gut* 2003; **52**: 1616-1622 [PMID: 14570732 DOI: 10.1136/gut.52.11.1616]
 - 96 **Whitehead WE**, Palsson OS, Levy RR, Feld AD, Turner M, Von Korff M. Comorbidity in irritable bowel syndrome. *Am J Gastroenterol* 2007; **102**: 2767-2776 [PMID: 17900326 DOI: 10.1111/j.1572-0241.2007.01540.x]
 - 97 **Locke GR**, Weaver AL, Melton LJ, Talley NJ. Psychosocial factors are linked to functional gastrointestinal disorders: a population based nested case-control study. *Am J Gastroenterol* 2004; **99**: 350-357 [PMID: 15046228 DOI: 10.1111/j.1572-0241.2004.04043.x]
 - 98 **Shen L**, Kong H, Hou X. Prevalence of irritable bowel syndrome and its relationship with psychological stress status in Chinese university students. *J Gastroenterol Hepatol* 2009; **24**: 1885-1890 [PMID: 19780881 DOI: 10.1111/j.1440-1746.2009.05943.x]
 - 99 **Choung RS**, Locke GR, Zinsmeister AR, Schleck CD, Talley NJ. Psychosocial distress and somatic symptoms in community subjects with irritable bowel syndrome: a psychological component is the rule. *Am J Gastroenterol* 2009; **104**: 1772-1779 [PMID: 19491833 DOI: 10.1038/ajg.2009.239]
 - 100 **Drossman DA**, Chang L. Psychosocial factors in the care of patients with GI disorders. In: Yamada T. Textbook of gastroenterology. Philadelphia: Lippincott-Raven, 2003: 636-654
 - 101 **Mussell M**, Kroenke K, Spitzer RL, Williams JB, Herzog W, Löwe B. Gastrointestinal symptoms in primary care: prevalence and association with depression and anxiety. *J Psychosom Res* 2008; **64**: 605-612 [PMID: 18501261 DOI: 10.1016/j.jpsychores.2008.02.019]
 - 102 **Haug TT**, Mykletun A, Dahl AA. Are anxiety and depression related to gastrointestinal symptoms in the general population? *Scand J Gastroenterol* 2002; **37**: 294-298 [PMID: 11916191 DOI: 10.1080/003655202317284192]
 - 103 **Lee S**, Wu J, Ma YL, Tsang A, Guo WJ, Sung J. Irritable bowel syndrome is strongly associated with generalized anxiety disorder: a community study. *Aliment Pharmacol Ther* 2009; **30**: 643-651 [PMID: 19552631 DOI: 10.1111/j.1365-2036.2009.04074.x]
 - 104 **North CS**, Hong BA, Alpers DH. Relationship of functional gastrointestinal disorders and psychiatric disorders: implications for treatment. *World J Gastroenterol* 2007; **13**: 2020-2027 [PMID: 17465442]
 - 105 **Levy RL**, Whitehead WE, Von Korff MR, Feld AD. Intergenerational transmission of gastrointestinal illness behavior. *Am J Gastroenterol* 2000; **95**: 451-456 [PMID: 10685749 DOI: 10.1111/j.1572-0241.2000.01766.x]
 - 106 **Garakani A**, Win T, Virk S, Gupta S, Kaplan D, Masand PS. Comorbidity of irritable bowel syndrome in psychiatric patients: a review. *Am J Ther* 2003; **10**: 61-67 [PMID: 12522523 DOI: 10.1097/00045391-200301000-00014]
 - 107 **Masand PS**, Kaplan DS, Gupta S, Bhandary AN. Relationship between irritable bowel syndrome (IBS) and double depression (dysthymia plus major depression). *Depression* 1995; **3**: 303-308 [DOI: 10.1002/depr.3050030608]
 - 108 **Gros DF**, Antony MM, McCabe RE, Swinson RP. Frequency and severity of the symptoms of irritable bowel syndrome across the anxiety disorders and depression. *J Anxiety Disord* 2009; **23**: 290-296 [PMID: 18819774 DOI: 10.1016/j.janxdis.2008.08.004]
 - 109 **Santor DA**, Coyne JC. Evaluating the continuity of symptomatology between depressed and nondepressed individuals. *J Abnorm Psychol* 2001; **110**: 216-225 [PMID: 11358016 DOI: 10.1037/0021-843X.110.2.216]
 - 110 **Cohen S**, Rodriguez MS. Pathways linking affective disturbances and physical disorders. *Health Psychol* 1995; **14**: 374-380 [PMID: 7498107 DOI: 10.1037/0278-6133.14.5.374]
 - 111 **Ritchie J**. Pain from distension of the pelvic colon by inflating a balloon in the irritable colon syndrome. *Gut* 1973; **14**: 125-132 [PMID: 4696535]
 - 112 **Mayer EA**, Bradesi S, Chang L, Spiegel BM, Bueller JA, Naliboff BD. Functional GI disorders: from animal models to drug development. *Gut* 2008; **57**: 384-404 [PMID: 17965064 DOI: 10.1136/gut.2006.101675]
 - 113 **Dorn SD**, Palsson OS, Thiwan SI, Kanazawa M, Clark WC, van Tilburg MA, Drossman DA, Scarlett Y, Levy RL, Ringel Y, Crowell MD, Olden KW, Whitehead WE. Increased colonic pain sensitivity in irritable bowel syndrome is the result of an increased tendency to report pain rather than increased neurosensory sensitivity. *Gut* 2007; **56**: 1202-1209 [PMID: 17483191 DOI: 10.1136/gut.2006.117390]
 - 114 **Chapman S**, Martin M. Attention to pain words in irritable bowel syndrome: increased orienting and speeded engagement. *Br J Health Psychol* 2011; **16**: 47-60 [PMID: 21226783 DOI: 10.1348/135910710X505887]
 - 115 **Walter SA**, Jones MP, Talley NJ, Kjellström L, Nyhlin H, Andreasson AN, Agréus L. Abdominal pain is associated with anxiety and depression scores in a sample of the general adult population with no signs of organic gastrointestinal disease. *Neurogastroenterol Motil* 2013; **25**: 741-e576 [PMID: 23692044 DOI: 10.1111/nmo.12155]
 - 116 **de Medeiros MT**, Carvalho AF, de Oliveira Lima JW, Dos Santos AA, de Oliveira RB, Nobre E Souza MA. Impact of depressive symptoms on visceral sensitivity among patients with different subtypes of irritable bowel syndrome. *J Nerv Ment Dis* 2008; **196**: 711-714 [PMID: 18791434 DOI: 10.1097/NMD.0b013e318183f896]
 - 117 **van der Veek PP**, Van Rood YR, Masclee AA. Symptom severity but not psychopathology predicts visceral hypersensitivity in irritable bowel syndrome. *Clin Gastroenterol Hepatol* 2008; **6**: 321-328 [PMID: 18258487 DOI: 10.1016/j.cgh.2007.12.005]
 - 118 **Rosenberger C**, Elsenbruch S, Scholle A, de Greiff A, Schedlowski M, Forsting M, Gizewski ER. Effects of psychological stress on the cerebral processing of visceral stimuli in healthy women. *Neurogastroenterol Motil* 2009; **21**: 740-e45 [PMID: 19368654 DOI: 10.1111/j.1365-2982.2009.01295.x]
 - 119 **Tillisch K**, Labus JS. Advances in imaging the brain-gut axis: functional gastrointestinal disorders. *Gastroenterology* 2011; **140**: 407-411.e1 [PMID: 21167161 DOI: 10.1053/j.gastro.2010.12.014]
 - 120 **Elsenbruch S**, Rosenberger C, Enck P, Forsting M, Schedlowski M, Gizewski ER. Affective disturbances modulate the neural processing of visceral pain stimuli in irritable bowel syndrome: an fMRI study. *Gut* 2010; **59**: 489-495 [PMID: 19651629 DOI: 10.1136/gut.2008.175000]
 - 121 **Hazlett-Stevens H**, Craske MG, Mayer EA, Chang L, Naliboff BD. Prevalence of irritable bowel syndrome among university students: the roles of worry, neuroticism, anxiety sensitivity and visceral anxiety. *J Psychosom Res* 2003; **55**: 501-505 [PMID: 14642979 DOI: 10.1016/S0022-3999(03)00019-9]
 - 122 **Bouchoucha M**, Hejnar M, Devroede G, Babba T, Bon C, Benamouzig R. Anxiety and depression as markers of multiplicity of sites of functional gastrointestinal disorders: a gender issue? *Clin Res Hepatol Gastroenterol* 2013; **37**: 422-430 [PMID: 23270854 DOI: 10.1016/j.clinre.2012.10.011]
 - 123 **Welgan P**, Meshkinpour H, Beeler M. Effect of anger on colon motor and myoelectric activity in irritable bowel syn-

- drome. *Gastroenterology* 1988; **94**: 1150-1156 [PMID: 3350284]
- 124 **Welgan P**, Meshkinpour H, Ma L. Role of anger in antral motor activity in irritable bowel syndrome. *Dig Dis Sci* 2000; **45**: 248-251 [PMID: 10711433 DOI: 10.1023/A:1005487821063]
 - 125 **Bennett EJ**, Evans P, Scott AM, Badcock CA, Shuter B, Höschl R, Tennant CC, Kellow JE. Psychological and sex features of delayed gut transit in functional gastrointestinal disorders. *Gut* 2000; **46**: 83-87 [PMID: 10601060 DOI: 10.1136/gut.46.1.83]
 - 126 **Evans PR**, Bennett EJ, Bak YT, Tennant CC, Kellow JE. Jejunal sensorimotor dysfunction in irritable bowel syndrome: clinical and psychosocial features. *Gastroenterology* 1996; **110**: 393-404 [PMID: 8566585 DOI: 10.1053/gast.1996.v110.pm8566585]
 - 127 **Zoccali R**, Muscatello MR, Bruno A, Barillà G, Campolo D, Meduri M, Familiari L, Bonica M, Consolo P, Scaffidi M. Anger and ego-defence mechanisms in non-psychiatric patients with irritable bowel syndrome. *Dig Liver Dis* 2006; **38**: 195-200 [PMID: 16500602]
 - 128 **Beesley H**, Rhodes J, Salmon P. Anger and childhood sexual abuse are independently associated with irritable bowel syndrome. *Br J Health Psychol* 2010; **15**: 389-399 [PMID: 19691916 DOI: 10.1348/135910709X466496]
 - 129 **Collins SM**, Bercik P. The relationship between intestinal microbiota and the central nervous system in normal gastrointestinal function and disease. *Gastroenterology* 2009; **136**: 2003-2014 [PMID: 19457424 DOI: 10.1053/j.gastro.2009.01.075]
 - 130 **Codling C**, O'Mahony L, Shanahan F, Quigley EM, Marchesi JR. A molecular analysis of fecal and mucosal bacterial communities in irritable bowel syndrome. *Dig Dis Sci* 2010; **55**: 392-397 [PMID: 19693670 DOI: 10.1007/s10620-009-0934-x]
 - 131 **Grover M**, Kanazawa M, Palsson OS, Chitkara DK, Gangarosa LM, Drossman DA, Whitehead WE. Small intestinal bacterial overgrowth in irritable bowel syndrome: association with colon motility, bowel symptoms, and psychological distress. *Neurogastroenterol Motil* 2008; **20**: 998-1008 [PMID: 18482250 DOI: 10.1111/j.1365-2982.2008.01142.x]
 - 132 **Reigstad CS**, Kashyap PC. Beyond phylotyping: understanding the impact of gut microbiota on host biology. *Neurogastroenterol Motil* 2013; **25**: 358-372 [PMID: 23594242]
 - 133 **Park AJ**, Collins J, Blennerhassett PA, Ghia JE, Verdu EF, Bercik P, Collins SM. Altered colonic function and microbiota profile in a mouse model of chronic depression. *Neurogastroenterol Motil* 2013; **25**: 733-e575 [PMID: 23773726 DOI: 10.1111/nmo.12153]
 - 134 **Jeffery IB**, O'Toole PW, Öhman L, Claesson MJ, Deane J, Quigley EM, Simrén M. An irritable bowel syndrome subtype defined by species-specific alterations in faecal microbiota. *Gut* 2012; **61**: 997-1006 [PMID: 22180058 DOI: 10.1136/gutjnl-2011-301501]
 - 135 **Al-Khatib K**, Lin HC. Immune activation and gut microbes in irritable bowel syndrome. *Gut Liver* 2009; **3**: 14-19 [PMID: 20479895 DOI: 10.5009/gnl.2009.3.1.14]
 - 136 **Chadwick VS**, Chen W, Shu D, Paulus B, Bethwaite P, Tie A, Wilson I. Activation of the mucosal immune system in irritable bowel syndrome. *Gastroenterology* 2002; **122**: 1778-1783 [PMID: 12055584 DOI: 10.1053/gast.2002.33579]
 - 137 **Scully P**, McKernan DP, Keoghane J, Groeger D, Shanahan F, Dinan TG, Quigley EM. Plasma cytokine profiles in females with irritable bowel syndrome and extra-intestinal co-morbidity. *Am J Gastroenterol* 2010; **105**: 2235-2243 [PMID: 20407431 DOI: 10.1038/ajg.2010.159]
 - 138 **Gao J**. Correlation between anxiety-depression status and cytokines in diarrhea-predominant irritable bowel syndrome. *Exp Ther Med* 2013; **6**: 93-96 [PMID: 23935726 DOI: 10.3892/etm.2013.1101]
 - 139 **Toker S**, Shirom A, Shapira I, Berliner S, Melamed S. The association between burnout, depression, anxiety, and inflammation biomarkers: C-reactive protein and fibrinogen in men and women. *J Occup Health Psychol* 2005; **10**: 344-362 [PMID: 16248685 DOI: 10.1037/1076-8998.10.4.344]
 - 140 **Howren MB**, Lamkin DM, Suls J. Associations of depression with C-reactive protein, IL-1, and IL-6: a meta-analysis. *Psychosom Med* 2009; **71**: 171-186 [PMID: 19188531 DOI: 10.1097/PSY.0b013e3181907c1b]
 - 141 **O'Donovan A**, Hughes BM, Slavich GM, Lynch L, Cronin MT, O'Farrelly C, Malone KM. Clinical anxiety, cortisol and interleukin-6: evidence for specificity in emotion-biology relationships. *Brain Behav Immun* 2010; **24**: 1074-1077 [PMID: 20227485 DOI: 10.1016/j.bbi.2010.03.003]
 - 142 **Boylan JM**, Ryff CD. Varieties of anger and the inverse link between education and inflammation: toward an integrative framework. *Psychosom Med* 2013; **75**: 566-574 [PMID: 23766379 DOI: 10.1097/PSY.0b013e31829683bd]
 - 143 **Marsland AL**, Prather AA, Petersen KL, Cohen S, Manuck SB. Antagonistic characteristics are positively associated with inflammatory markers independently of trait negative emotionality. *Brain Behav Immun* 2008; **22**: 753-761 [PMID: 18226879 DOI: 10.1016/j.bbi.2007.11.008]
 - 144 **Levy RL**, Whitehead WE, Walker LS, Von Korff M, Feld AD, Garner M, Christie D. Increased somatic complaints and health-care utilization in children: effects of parent IBS status and parent response to gastrointestinal symptoms. *Am J Gastroenterol* 2004; **99**: 2442-2451 [PMID: 15571594 DOI: 10.1111/j.1572-0241.2004.40478.x]
 - 145 **Videlic EJ**, Adeyemo M, Licudine A, Hirano M, Ohning G, Mayer M, Mayer EA, Chang L. Childhood trauma is associated with hypothalamic-pituitary-adrenal axis responsiveness in irritable bowel syndrome. *Gastroenterology* 2009; **137**: 1954-1962 [PMID: 19737564 DOI: 10.1053/j.gastro.2009.08.058]
 - 146 **Koloski NA**, Talley NJ, Boyce PM. Predictors of health care seeking for irritable bowel syndrome and nonulcer dyspepsia: a critical review of the literature on symptom and psychosocial factors. *Am J Gastroenterol* 2001; **96**: 1340-1349 [PMID: 11374666 DOI: 10.1111/j.1572-0241.2001.03789.x]
 - 147 **Cameron L**, Leventhal EA, Leventhal H. Seeking medical care in response to symptoms and life stress. *Psychosom Med* 1995; **57**: 37-47 [PMID: 7732157]
 - 148 **Gulewitsch MD**, Enck P, Schwille-Kiuntke J, Weimer K, Schlarb AA. Mental Strain and Chronic Stress among University Students with Symptoms of Irritable Bowel Syndrome. *Gastroenterol Res Pract* 2013; **2013**: 206574 [PMID: 23843782 DOI: 10.1155/2013/206574]
 - 149 **Van Oudenhove L**, Aziz Q. Recent insights on central processing and psychological processes in functional gastrointestinal disorders. *Dig Liver Dis* 2009; **41**: 781-787 [PMID: 19665954 DOI: 10.1016/j.dld.2009.07.004]
 - 150 **North CS**, Downs D, Clouse RE, Alrakawi A, Dokucu ME, Cox J, Spitznagel EL, Alpers DH. The presentation of irritable bowel syndrome in the context of somatization disorder. *Clin Gastroenterol Hepatol* 2004; **2**: 787-795 [PMID: 15354279 DOI: 10.1016/S1542-3565(04)00350-7]
 - 151 **Quarero AO**, Meineche-Schmidt V, Muris J, Rubin G, de Wit N. Bulking agents, antispasmodic and antidepressant medication for the treatment of irritable bowel syndrome. *Cochrane Database Syst Rev* 2005; **(2)**: CD003460 [PMID: 15846668 DOI: 10.1002/14651858.CD003460.pub2]
 - 152 **Grover M**, Drossman DA. Centrally acting therapies for irritable bowel syndrome. *Gastroenterol Clin North Am* 2011; **40**: 183-206 [PMID: 21333907 DOI: 10.1016/j.gtc.2010.12.003]
 - 153 **Rahimi R**, Nikfar S, Rezaie A, Abdollahi M. Efficacy of tricyclic antidepressants in irritable bowel syndrome: a meta-analysis. *World J Gastroenterol* 2009; **15**: 1548-1553 [PMID: 19340896 DOI: 10.3748/wjg.15.1548]
 - 154 **Beattie DT**, Smith JA. Serotonin pharmacology in the gastrointestinal tract: a review. *Naunyn Schmiedeberg Arch Pharmacol* 2008; **377**: 181-203 [PMID: 18398601 DOI: 10.1007/

s00210-008-0276-9]

- 155 **Mayer EA**, Tillisch K, Bradesi S. Review article: modulation of the brain-gut axis as a therapeutic approach in gastrointestinal disease. *Aliment Pharmacol Ther* 2006; **24**: 919-933 [PMID: 16948804 DOI: 10.1111/j.1365-2036.2006.03078.x]
- 156 **Salari P**, Abdollahi M. Systematic review of modulators of benzodiazepine receptors in irritable bowel syndrome: is

there hope? *World J Gastroenterol* 2011; **17**: 4251-4257 [PMID: 22090780 DOI: 10.3748/wjg.v17.i38.4251]

- 157 **Zijdenbos IL**, de Wit NJ, van der Heijden GJ, Rubin G, Quatero AO. Psychological treatments for the management of irritable bowel syndrome. *Cochrane Database Syst Rev* 2009; (1): CD006442 [PMID: 19160286 DOI: 10.1002/14651858.CD006442.pub2]

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