

Stress-related IBS

Kim Outhoff, Senior Lecturer, Department of Pharmacology,
Faculty of Health Sciences, University of Pretoria

Correspondence to: kim.outhoff@up.ac.za

Keywords: stress, allostatic load, irritable bowel syndrome, brain–gut–microbiota axis

Abstract

The gastrointestinal tract is exquisitely sensitive to different physical and psychological stressors. Irritable bowel syndrome (IBS) may be viewed as a disorder caused by stress-induced dysregulation of the complex interactions along the brain-gut-microbiota axis, which involves the bidirectional, self-perpetuating communication between the central and enteric nervous systems, utilising autonomic, psychoneuroendocrine, pain modulatory and immune signalling pathways. An overzealous stress response may significantly alter not only the sensitivity of the central and enteric nervous systems, but also other potentially important factors such as gut motility, intestinal mucosal permeability and barrier functioning, visceral sensitivity, mucosal blood flow, immune cell reactivity and enteric microbiota composition. Symptoms of these (mal)adaptive changes may include constipation, diarrhoea, bloating and abdominal pain, manifesting clinically as IBS. This article briefly reviews the current postulated stress-models of IBS.

© Authors

Reprinted with permission *South African Family Practice* 2016; 58(3)

Stress

In 1936, Hans Selye coined the concept of stress, defining it as “the nonspecific response of the body to any demand made upon it”.¹ Stress was described as a general increase in the need to perform certain adaptive functions and then to re-establish normalcy, independent of the specific activity that caused this rise in requirements. He went on to say that it is even immaterial whether the agent or situation we face is pleasant or unpleasant; all that counts is the intensity of the demand for readjustment or adaptation. He emphasised that stress is a response to a stimulus, which he called a stressor.

Selye’s non-judgemental description of stress has changed somewhat over the years, becoming increasingly defined as any acute threat to the homeostasis of an organism, which may be real or perceived, and elicited by internal or external events.² The distinction between stress and stressor has become blurred. In addition, in many cultures, stress is now synonymous with feelings of overwhelming worry, anxiety or fear, often of uncertainty, loss of control, or perhaps ultimately, death.^{3,4} However one views these transitions in definition, it is agreed that the physiological stress response heroically defends the stability of the internal environment in an attempt at ensuring the survival of the organism.⁵ Maintaining stability or homeostasis through change is known as allostasis, and this reflexive, adaptive, protective and restorative process is mediated by the hypothalamic–pituitary–adrenal (HPA) axis, the autonomic nervous system, as well as cardiovascular, immune and metabolic systems, engaging stress-related and other hormones, neurotransmitters and cytokines, amongst others.^{6,7}

Stressors can be acute or chronic, ranging from mundane irritations to life-threatening events that trigger the fight-flight response. A persistent or untempered stress response significantly increases the cumulative wear and tear on the body, or the adaptive or allostatic load, which may initiate long-term behavioural patterns, physiological reactivity and other bodily changes, thereby causing or exacerbating psychological and physical illnesses, including infectious, cardiovascular and gastrointestinal.^{6,8} In turn, these may serve as additional stressors (“symptom generated stress”), and perpetuate or even amplify the pain/suffering cycle, causing long-term damage, rather than protection.⁹ The clinical manifestations of allostatic overload include undue fatigue, irritability and feelings of demoralisation, occurring against a backdrop of a variety of psychiatric, somatic and visceral complaints.⁷

Stress and IBS

IBS is the most common functional gastrointestinal disorder in developed countries, affecting approximately a tenth of the global population and accounting for roughly half of all visits to GPs for gastrointestinal complaints.¹⁰ Although this is a heterogeneous disorder, symptoms typically include abdominal discomfort or pain, bloating as well as altered bowel habits, which may be remitting, chronic and debilitating.²

There is a strong association between stress and IBS: Risk factors for IBS include genetic susceptibility, early adverse life events and sustained or pathological stress, while trigger factors include psychosocial and physical stressors, including gastroenteritis and antibiotic overuse.² (Figure 1) Psychological or physical stressors

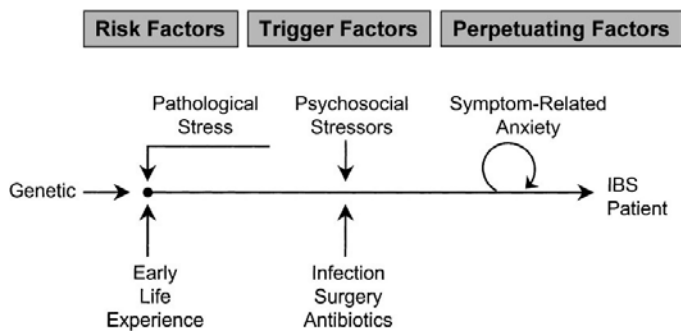


Figure 1: Role of stress in development and modulation of irritable bowel syndrome (IBS) symptoms. Different types of stressors may play a role in the permanent biasing of stress responsiveness, in transient activation of the stress response, and in the persistence of symptoms.⁹

may also lead to flare-ups or exacerbation of complaints, and co-morbidity with other chronic pain conditions as well as stress-associated psychiatric illness, notably depression and anxiety, is common.¹¹

Treatment is usually directed at symptom control, which is important for interrupting the self-perpetuating symptom-related anxiety/stress response circuit. However, symptom-based therapies do not necessarily modify the natural history of the disorder, and a greater appreciation of the postulated pathophysiology may well refine therapeutic approaches.^{2,11}

Brain–gut–enteric microbiota axis

The brain–gut axis

Stressors compel the central nervous system's (CNS) emotional motor system (EMS) to communicate with the gut's enteric nervous system (ENS) in order to mediate a variety of physiological adaptive gastrointestinal responses.⁵ This reciprocal exchange of information is achieved via activation of multiple parallel stress response pathways, notably the autonomic nervous system (ANS), the hypothalamic–pituitary–adrenal axis (HPA), pain modulatory, neuro-endocrine and immune, collectively termed the brain–gut axis.¹¹ Afferent fibres project to integrative CNS structures, while efferent fibres project to smooth muscle, thus allowing signals from the brain to influence motor, sensory and secretory functions of the gut, and visceral messages from the gut to affect brain function, in particular those areas devoted to stress regulation including the hypothalamus. For instance, psychological stress activates release of corticotropin releasing factor (CRF) and hence HPA and sympathetic responses via serotonergic and noradrenergic systems, in effect increasing adrenal cortisol release as well as regulating immune function, while pain-modulating endorphins play an inhibitory role.⁷ Infective agents such as *E-coli* activate the neuro-endocrine response via pro-inflammatory cytokines which activate the hypothalamus directly. Prostaglandin E₂ may also activate the adrenal cortex, stimulating further cortisol release.¹² These intricate and bidirectional interactions are essential for regulating overall gut function in both healthy and diseased states, ultimately modulating secretion, motility, blood flow and gut-

associated immune function appropriate to current conditions.¹³

The enteric nervous system is pivotal in executing these local physiological gut responses prompting the release of various neuropeptides and hormones.⁷ A variety of gut-based cell types, including intrinsic and extrinsic sensory neurons, enteric glia, immune cells and innervated entero-endocrine ("the gut connectome"), enjoy complex relationships at this level.¹¹ However, being at the end, or the beginning, of the regulatory loop, it is potentially the gut flora that may ultimately play one of the more prominent roles in influencing gastro-intestinal (top-down) and psychological (bottom-up) function, respectively.

Microbiota

Within a few days of birth, our internal and external surfaces are rapidly colonised by commensal microorganisms. The total sum of these organisms (microbiota) outnumbers somatic cells by approximately 10:1, while the collective genomes of the microbiota (the microbiome) overshadows the human genome by roughly 100:1.¹⁴ This relationship is therefore significant, benefitting both host and microorganism. In healthy individuals the enteric microbiota comprises approximately 400–1000 different bacterial species, mostly belonging to Firmicutes and Bacteroides phyla, contributing approximately 10¹¹ bacterial cells per gram of colon contents.^{13,15}

There is a delicate balance between the gut microbiota and host epithelium and lymphoid tissue, all of which are important for maintaining homeostasis.¹² Studies have shown that the microbiota influences gut homeostasis directly by regulating bowel motility and modulating intestinal pain, immune responses and nutrient processing.¹³ These non-pathogenic gut microbes may also be critical for the early programming and later responsiveness of the stress system.¹² Homeostasis is maintained by the perfect regulation of microbial load and the immune response generated against it. Any disturbance of the balance between enteric microbiota and host may lead to gastrointestinal pathologies such as IBS, and conversely to psychiatric illness such as anxiety.¹⁶ (Figure 2)

Pathophysiology in IBS

In genetically predisposed individuals, particularly those who have experienced early life adversity, exposure to sustained or overwhelming stress may induce dysregulation of any component of the brain–gut–microbiota axis, which may cause or exacerbate symptoms associated with IBS. The exaggerated brain outputs via the ANS and HPA axis seen in IBS sufferers, have been shown to inappropriately influence intestinal motility and secretion, intestinal epithelial permeability, immune function and gut microbiota composition. Local physical gut factors, in particular dietary factors and intestinal pathogens have an equally important effect on these peripheral gut functions. All of these, and especially immune and microbiota signalling, feed back to the brain, thereby completing and perpetuating the stress response cycle.^{7,11} (Figures 2 and 3)

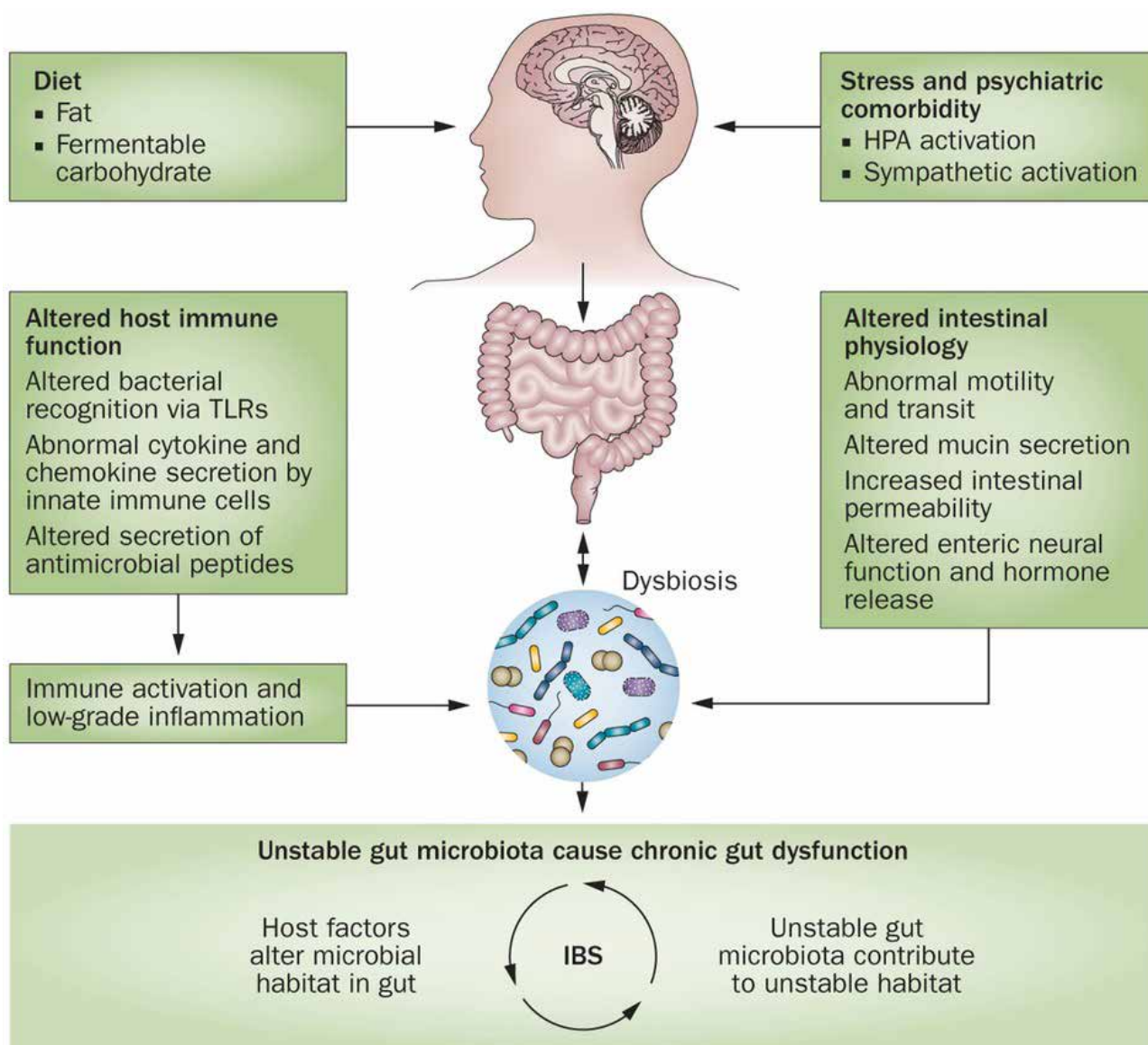


Figure 2: The relationship between dysbiosis and irritable bowel syndrome (IBS). Abbreviations: HPA: hypothalamic–pituitary–adrenal axis; TLRs: Toll-like receptors (innate immune sensors, at the interface of intestinal epithelial barrier, microbiota, and the immune system)¹⁷

Gene expression may be primarily flawed, or may be influenced by early adverse life events through persistent epigenetic mechanisms. Of interest is that the genetic polymorphisms that have been linked to the complex interactions between early environmental factors and relevant IBS-associated dysfunctional brain networks are largely related to regulation of the HPA axis. These include polymorphisms of genes encoding corticotrophin-releasing hormone receptor 1, glucocorticoid receptor, catecholamine and serotonin (5HT) signalling, inflammation related and female sex hormones.¹¹

IBS patients display abnormalities in the functional brain networks linked to emotional arousal, central autonomic control, central executive control, sensorimotor processing and salience detection (i.e. discrimination between real or perceived threat). These may account for the variety of information processing aberrations seen in patients with IBS, such as biased threat appraisal and negative expectations of outcomes, autonomic

hyper-arousal and increased symptom-focused attention.¹¹ IBS sufferers have an increased perception of visceral stimuli and symptom severity, and a propensity to catastrophise the likelihood and severity of future episodes.¹¹ Evidence suggests that patients with chronic and recurring visceral pain or discomfort have functional as well as neuroplastic alterations in the relevant areas of the brain, likely as a result of information-overload along gut-brain pathways.^{7,11}

The immune system's role in the pathogenesis of IBS is important but only partially understood. It is currently postulated that sympathetic nervous system hyperactivity evoked by either genetic or adverse life events during early development may increase production of immature primed monocytes that traffic into the gut to alter local function and ENS plasticity, and into the brain to affect CNS plasticity, particularly in the structures involved in salience processing and autonomic regulation.¹¹ In this way, the sensitised gut generates repetitive adverse sensory experiences

(symptom flares) to which the overly sensitive brain responds with both greater aversion and increased sympathetic outflow, resulting in increased monocyte production that further alters neural function in both the gut and brain.¹¹

The enteric microbiota's composition and function is subject to influences from a diverse range of factors including diet, antibiotic use, infection and stress. (Figure 2) Sustained activation of any of the brain–gut axis systems may influence gut microbes indirectly (by causing changes in their environment) or directly (by stress related host signalling molecules released into the gut lumen from lamina propria cells of enterochromaffin, neuronal and immune cells) which may have clinical implications in IBS.¹³ There is also some evidence that catecholamines can alter the growth, motility and virulence of pathogenic and commensal bacteria. Stress may thus alter the gut microbiota, causing

imbalance (dysbiosis).⁶ Conversely, the enteric microbiota affects communication between the gut and brain.^{8,10} In early life, enteric dysbiosis may adversely influence the development of the nervous system, the brain's relationship with the intestine, and the HPA axis while in adults, dysbiosis may impact on fully developed circuits. Aberrant signalling is probably enhanced by stress-induced increases in intestinal permeability or mucosal inflammation, ultimately leading to changes in gut–brain communication and subsequently in brain structure and function.^{15,18}

Conclusion

Taken together it is currently proposed that primary genetics as well as epigenetic modifications induced by early stressful life events may cause hyper-responsiveness in certain brain

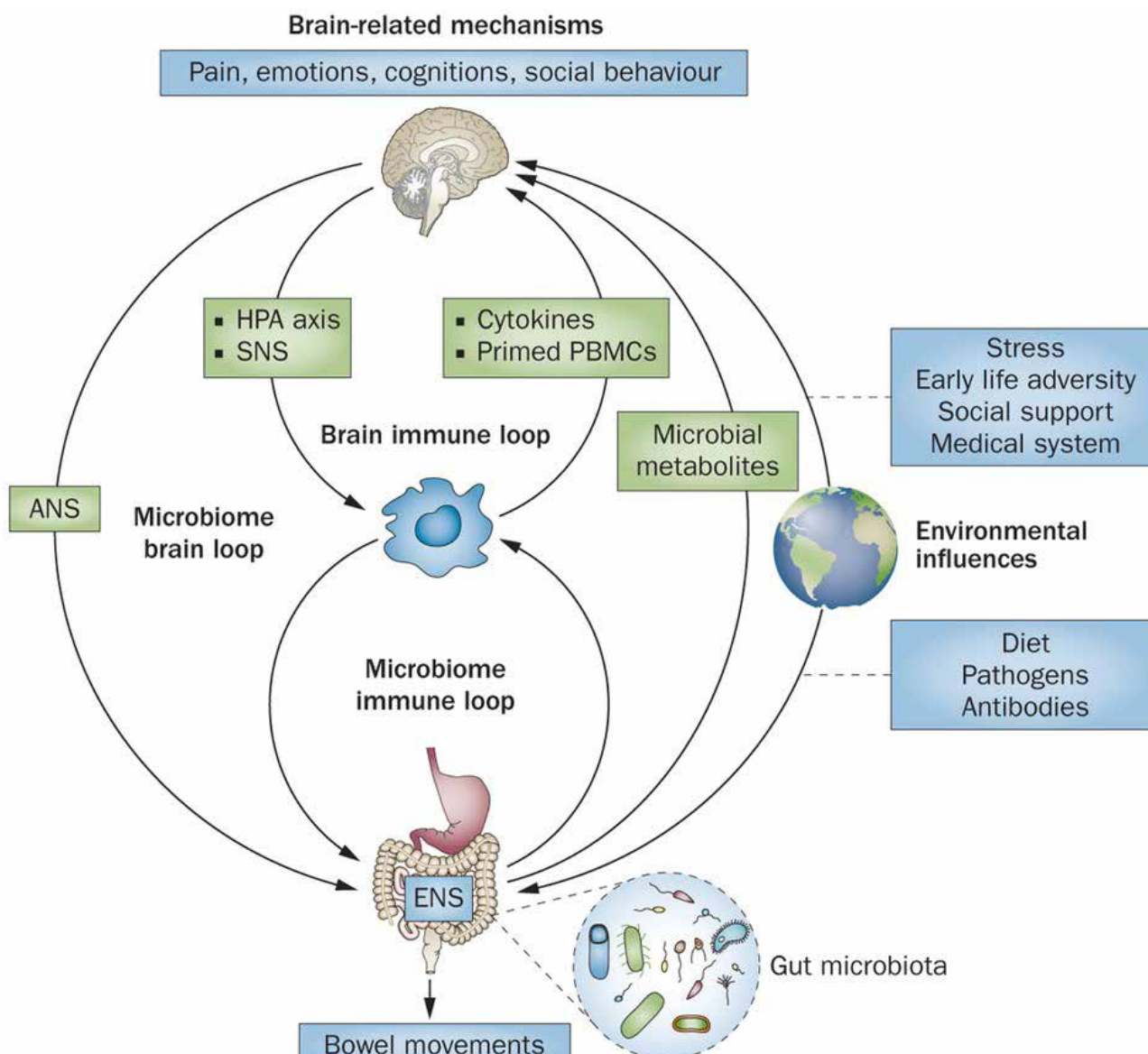


Figure 3: Schematic of the brain–gut axis, including inputs from the gut microbiota, the ENS, the immune system and the external environment. The model includes both peripheral and central components, which are in bidirectional interactions. Bottom-up influences are shown on the right side, top-down influences on the left side of the graph. Abbreviations: ENS: enteric nervous system; HPA: hypothalamic–pituitary–adrenal; PBMC: peripheral blood mononuclear cell; SNS: sympathetic nervous system.¹¹

networks. This hypersensitivity may also be secondary to increased sensory input from the gut, originating from any of the cells (including microbial) of the gut connectome. The altered central brain networks generate upregulated signals to the peripheral gut through hyperactive ANS, HPA and descending dorsal horn pathways. Chronic signalling results in remodelling of peripheral cells in the immune system, gut epithelium and in microbiota composition. These all contribute to sensitising visceral afferent pathways and increase viscera-sensory feedback to the brain, thereby completing the stress response loop.¹¹

These arguments are of necessity circular, reflecting the self-amplifying relationship between different stressors, the stress response and IBS. Deconstructing the stressed-brain-gut-microbiota network is important, ironically in order to appreciate that each of the components cannot possibly act in isolation, being intertwined and dependent on upstream or downstream events and thereby ultimately functioning as an integrated whole. It appears that the over-reactive, super-sensitive, irritable bowel is merely an extension and mirror image of the stressed, anxious, hypervigilant brain, and vice versa. Treating only one aspect of this stress-induced syndrome therefore becomes untenable. Avoiding all environmental and internal stressors is ridiculous. Rather, holistic therapeutic approaches ranging from mitigating the exaggerated stress response at one end of the axis (strong social support, self-relaxation, mindfulness based stress reduction, cognitive behavioural therapy, etc) to restoring gut flora balance at the other end are warranted. Sequential desensitisation of the entire stress response circuit may thus be achieved, one lap at a time.

References

1. Selye H. The Evolution of the Stress Concept: The originator of the concept traces its development from the discovery in 1936 of the alarm reaction to modern therapeutic applications of syntoxic and catatonic hormones. *American Scientist*. 1973;61(6):692–9.
2. Konturek P, Brzozowski T, Konturek S. Stress and the gut: pathophysiology, clinical consequences, diagnostic approach and treatment options. *J Physiol Pharmacol*. 2011;62(6):591–9.
3. Kabat-Zinn J. Full catastrophe living, revised edition: how to cope with stress, pain and illness using mindfulness meditation: Hachette UK; 2013.
4. Hollis J. Finding meaning in the second half of life: How to finally, really grow up: Penguin; 2005.
5. Mayer E. The neurobiology of stress and gastrointestinal disease. *Gut*. 2000;47(6):861–9.
6. McEwen BS. Central effects of stress hormones in health and disease: Understanding the protective and damaging effects of stress and stress mediators. *European Journal of Pharmacology*. 2008;583(2):174–85.
7. Chang L. The role of stress on physiological responses and clinical symptoms in irritable bowel syndrome. *Gastroenterology*. 2011;140(3):761.
8. O'Mahony SM, Marchesi JR, Scully P, et al. Early life stress alters behavior, immunity, and microbiota in rats: implications for irritable bowel syndrome and psychiatric illnesses. *Biological Psychiatry*. 2009;65(3):263–7.
9. Mayer EA, Naliboff BD, Chang L, et al. Stress and irritable bowel syndrome. *American Journal of Physiology-Gastrointestinal and Liver Physiology*. 2001;280(4):G519–G24.
10. Kennedy P, Clarke G, O'Neill A, et al. Cognitive performance in irritable bowel syndrome: evidence of a stress-related impairment in visuospatial memory. *Psychological Medicine*. 2014;44(07):1553–66.
11. Mayer EA, Labus JS, Tillisch K, et al. Towards a systems view of IBS. *Nature Reviews Gastroenterology & Hepatology*. 2015;12(10):592–605.
12. Dinan TG, Cryan JF. Regulation of the stress response by the gut microbiota: implications for psychoneuroendocrinology. *Psychoneuroendocrinology*. 2012;37(9):1369–78.
13. Rhee SH, Poehoullakis C, Mayer EA. Principles and clinical implications of the brain-gut-enteric microbiota axis. *Nature reviews Gastroenterology & Hepatology*. 2009;6(5):306–14.
14. Wang Y, Kasper LH. The role of microbiome in central nervous system disorders. *Brain, Behavior, and Immunity*. 2014;38:1–12.
15. Foster JA, Neufeld K-AM. Gut-brain axis: how the microbiome influences anxiety and depression. *Trends in Neurosciences*. 2013;36(5):305–12.
16. Enck P, Aziz Q, Barbara G, et al. Irritable bowel syndrome. *Nature Reviews Disease Primers*. 2016;2:16014.
17. Collins SM. A role for the gut microbiota in IBS. *Nature Reviews Gastroenterology & Hepatology*. 2014;11(8):497–505.
18. Mayer EA, Tillisch K, Gupta A. Gut/brain axis and the microbiota. *Journal of Clinical Investigation*. 2015;125(3):926.