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Irritable bowel syndrome: analyzing the brain-gut axis and efficacy of psychological treatment

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Thesis

**IRRITABLE BOWEL SYNDROME: ANALYZING THE BRAIN-GUT AXIS AND
EFFICACY OF PSYCHOLOGICAL TREATMENT**

by

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B.S., University of Wisconsin- Madison, 2014

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requirements for the degree of
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ABSTRACT

Irritable bowel syndrome (IBS) is the most common chronic functional gastrointestinal disorder that affects approximately 11% of the global population with a higher prevalence in women and those under the age of 50. IBS is characterized and diagnosed by the presence of a group of symptoms including abdominal pain, bloating or distension accompanied by altered bowel movements. A positive diagnosis of IBS can be made in the presence of well-defined, validated diagnostic criteria and in addition to the exclusion of organic disease with minimal testing. The lack of specific therapeutic targets makes treatment of IBS very difficult and its management is focused on symptom relief. IBS has a well-established high comorbidity with anxiety, depression, and psychosomatic disorders which contributes significantly to a substantial burden of illness. IBS patients exhibit a markedly decreased quality of life, decreased work productivity and increased absenteeism from work, and increased direct healthcare utilization (such as office visits, medical tests, and specialty referrals), resulting in a large economic burden for society. Despite this, effective pharmacologic and non-pharmacologic treatment options are limited and many patients with IBS do not achieve complete symptom relief long term and continue to suffer from IBS symptoms.

Early pioneering in the study of this disease has called for a biopsychosocial model, a model in which psychological and social factors are also considered in IBS treatment. Through consideration of this model, it has been discovered that the disease has strong ties with early life environment, daily stress, and coping skills. Research in the past decades has established IBS as a disease of neurogastroenterology and involves disturbances in the brain-gut axis, the connection between the central nervous system and enteric nervous system. The brain-gut axis is organized in hierarchies with the first control level consisting of the enteric nervous system (ENS) sensory, muscular, and interneurons, all of which form reflex circuitry to control gastrointestinal (GI) motility and sensation among other functions. The central nervous system (CNS) synapses onto these circuits via vagal and spinal afferents. Information from the luminal GI tract is processed in the higher cortical structures of the brain, particularly in the hypothalamus, amygdala, anterior cingulate cortex (ACC) and prefrontal cortex (PFC). These structures are also important for homeostasis and regulation of attention, emotion, and behavior. Disturbances of these pathways result in peripheral and eventually central sensitization, the subject of this thesis. Sensitization in IBS includes visceral hypersensitivity, increased pain perception, and increased GI motility. Due to the cortical regions where this information is processed, these physical symptoms often have a complex interplay with psychological symptoms including anxiety, fear, and stress. The connection between the physical symptoms and psychological symptoms lies in the pain matrix and emotional motor system. This has been confirmed by many brain imaging studies comparing normal individuals with IBS patients testing visceral, somatic and cutaneous pain as well as anxiety and depression levels. IBS patients, unlike control subjects, have been found to have increased pain perception localizing to all these

regions and they also rate the pain as more unpleasant, a psychological factor, than normal patients. In addition to increased cortical activation, IBS patients have increased corticotropin releasing factor in the amygdala promoting anxiety and increasing stress levels and GI symptoms. Of note is the fact that stress is both a cause and effect of IBS symptoms and often compounds symptoms due to the cyclical nature of stress and chronic pain. Because stress ties in with both the physical and psychological symptoms faced by IBS patients, implementation of psychological treatment in IBS management is of great importance and have demonstrated improved outcomes in IBS patients. Psychological treatments with empirical evidence are discussed in this thesis and include cognitive behavioral therapy, psychodynamic psychotherapy, hypnotherapy, and mindfulness/relaxation exercises. Whether these all treatments tie into the alterations in cortical processing in brain-gut function is a topic that is yet to be explored.

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LIST OF ABBREVIATIONS

AC	Ascending Colon
ACC	Anterior Cingulate Cortex
ACTH	Adrenocorticotrophic Hormone
ANS	Autonomic Nervous System
BGA	Brain Gut Axis
CBT	Cognitive-Behavioral Therapy
CNS	Central Nervous System
CRD	Colorectal Distension
CRH	Corticotrophin Releasing Hormone
CRF	Corticotrophin Releasing Factor
DNIC	Diffuse Noxious Inhibitory Controls
DM	Dorsomedial
EDU	Educational
EMS	Emotional Motor System
ENS	Enteric Nervous System
EPAN	Enteric Primary Afferent Neuron
FBD	Functional Bowel Disorder
FBDSI	Functional Bowel Disorder Severity Index
FC	Functional Constipation
FDr	Functional Diarrhea

FGID	Functional Gastrointestinal Disorder
fMRI.....	Functional Magnetic Resonance Imaging
GHT.....	Gut-Directed Hypnotherapy
GI	Gastrointestinal
HPA.....	Hypothalamic-Pituitary-Adrenal
HRQOL	Health Related Quality of Life
IC.....	Insular Cortex
ICC	Interstitial Cells of Cajal
IPAN.....	Intrinsic Primary Afferent Neuron
LC.....	Locus Coeruleus
MCC	Midcingulate Cortex
pACC	Perigenual Anterior Cingulate Cortex
PAG.....	Periaqueductal Gray
PCC.....	Posterior Cingulate Cortex
PFC.....	Prefrontal Cortex
PHG	Para-Hippocampal Gyrus
PRS.....	Partial Resistant Stress
RSFC	Resting-State Functional Connectivity
SI.....	Small Intestine
SMT.....	Standard Medical Treatment
SSC.....	Somatosensory Cortex
SSS.....	Total Symptom Severity Scale

QOL..... Quality of Life
VMR Visceromotor Response
VPL Ventral Posterior Lateral
WAS Water Avoidance Stress

INTRODUCTION

Irritable bowel syndrome (IBS) is a chronic functional gastrointestinal disorder (FGID) characterized by abdominal pain, bloating or distension along with altered bowel habits in the absence of discernable organic diseases. FGID are characterized by the absence of biomarkers that would allow for a straightforward clinical diagnosis using specific diagnostic testing; rather they are diagnosed and classified by the presence of certain clinical criteria and symptoms as most recently described in the Rome IV criteria (Lacy et al., 2016). As such, these criteria help the clinician to make the diagnosis of a FGID more reliable. In contrast, organic diseases are those which are visible through diagnostic testing because of their distinct pathology; and are classified by organ morphology (Drossman, 2016).

The estimated global prevalence of IBS is 11.2% with geographic variation; the lowest (7.0%) in South Asia and the highest (21.0%) in South America (Lovell and Ford, May 2012). Prevalence is higher in women than men by a difference of 5.1%, with values of 14.0% and 8.9% respectively (Lovell and Ford, July 2012). Global prevalence also varies by age with a 25% higher prevalence in individuals over the age of 50 (Lovell and Ford, May 2012).

IBS represents one of several FGID and falls even further into the functional bowel disorder (FBD) classification, one of the six major classifications for FGIDs in adults (Lacy et al, 2016). There are also pediatric categories of disorder based on age in which IBS can also fall into. FBD is broken up into five categories: irritable bowel syndrome, functional constipation, functional diarrhea, functional abdominal bloating/distension, and unspecified FBD. A new sixth category is opioid-induced constipation (OIC), which clinically manifests similar to functional constipation but can be generally attributed to the use of opioid-based pain therapy. In addition, due to significant overlap in symptoms, the different categories of FBD exist as a spectrum of disorders (**Figure 1**) making them difficult to distinguish between each other. As such, they should not necessarily be thought of as discrete disorders, merely a useful framework for researchers and clinicians (Lacy et al., 2016). For the diagnosis of IBS following the Rome IV criteria, the diagnostic criteria is

“Recurrent abdominal pain, on average, at least 1 day per week in the last three months, associated with two of the following criteria:

1. Related to defecation
2. Associated with a change in frequency of stool
3. Associated with a change in form (appearance) of stool”

(Lacy et al.,1394).

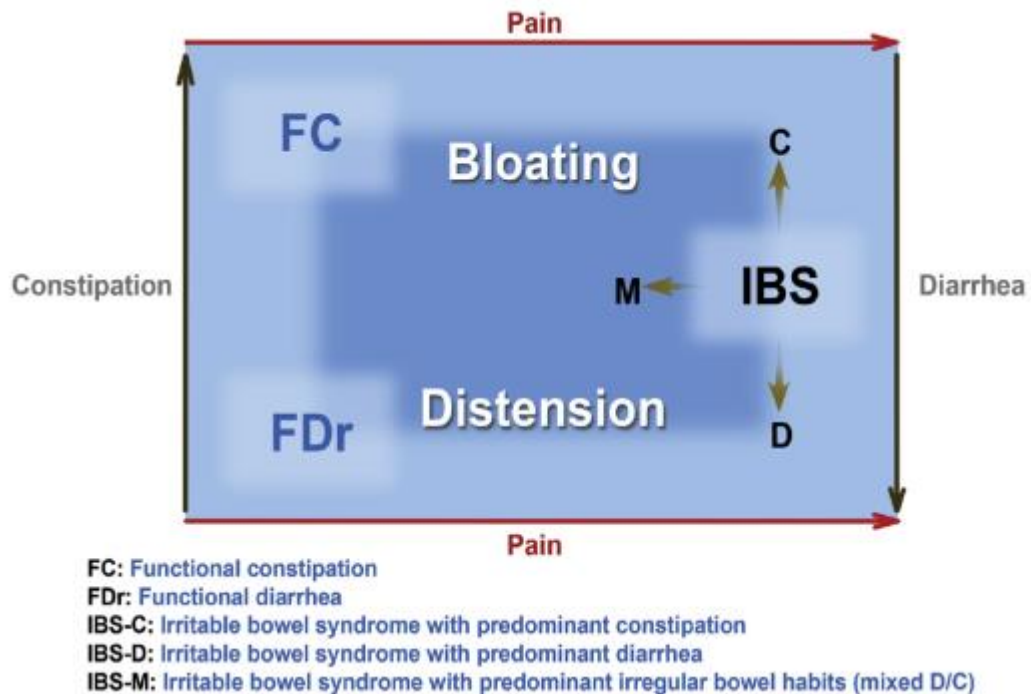


Figure 1. Conceptual framework to explain FBDs. These disorders should be considered as a continuum rather than as discrete disorders. Functional constipation (FC) or Functional diarrhea (FDr) are disorder with altered bowel movements alone (constipation or diarrhea, respectively, without the existence of abdominal pain). When altered bowel movements occur in conjunction with abdominal pain, the disorder is classified as IBS, which is further broken down into its subtypes. Abdominal bloating or distension often occur generally with any FBD. Figure taken from (Lacy et. al, 2016)

It is important to note that IBS is a disorder in which both abdominal pain and altered bowel habits occur. Furthermore, IBS is broken down into four different subtypes based on the predominant type of bowel movement that the patient reports shown in (**Table 1.**). The Bristol stool scale (Lacy et al., 2016) helps the clinician and patient to determine the predominant stool consistency.

IBS-C	IBS with constipation	<ul style="list-style-type: none"> • Hard or lumpy stools at least 25% of the time • Loose or watery stools less than 25% of the time
IBS-D	IBS with diarrhea	<ul style="list-style-type: none"> • Loose or watery stools at least 25% of the time • Hard or lumpy stools less than 25% of the time
IBS-M	Mixed IBS	<ul style="list-style-type: none"> • Hard or lumpy stools at least 25% of the time • Loose or watery stools at least 25% of the time
IBS-U	Unsubtyped IBS	<ul style="list-style-type: none"> • Hard or lumpy stools less than 25% of the time • Loose or watery stools less than 25% of the time

Table 1. IBS Subtypes and Diagnostic Criteria. Adapted from (NIDDK, 2015)

Diagnostic criteria have assisted practicing clinicians greatly to make a positive diagnosis of IBS even though it may overlap or co-exist with other GI disorders, including other FGID. A positive diagnosis of IBS then facilitates the development of a rational treatment plan for the patient. Patients with IBS experience a great deal of substantial, yet variable GI symptoms that lower their quality of life tremendously and result in frequent doctor visits. To manage their predominant

symptoms treatment options are oriented towards lifestyle changes, such as dietary modifications, laxatives or anti-diarrheals, targeted pharmacological treatments, and sometimes psychological support.

The Rome Foundation – Rome IV (May 2016)

The Rome Foundation is a not for profit organization (<http://theromefoundation.org/>) established in the late 1980s to provide support for scientific research and education with the goal of improving current knowledge about FGIDs. This knowledge is useful for diagnosis and treatment in clinical practice as well as in research related to FGID. The Rome Foundation has periodically released compendiums of the gathered data for researchers and clinical practitioners to use. The latest compendium titled, Rome IV (Lacy et al., 2016), was released in May 2016, ten years after the release of Rome III is the most recent reiteration of diagnostic criteria of FGID and the current understanding of their underlying biology. Much of the current knowledge about IBS can be attributed to The Rome Foundation, and the four Rome compendiums that have been released to date will be referenced to in this thesis extensively.

The Biopsychosocial Model

In 1977, a breakthrough moment in medicine came through the reports published by Dr. Engel (Engel, 1977). Dr. Engel called for a revision in the current biomedical model of treatment of disease, arguing that it is reductionist and exclusionist because it requires that disease progression can only be conceptualized and defined by the biological defects in the patient. He continues with the notion that a physician's role in treatment must include the realms of the biological, social, and psychological. Thus, he developed what is called the biopsychosocial model. Disease and medical care are interrelated through this model. He argues that "a medical model must also consider the patient, the social context in which he lives, and the complementary system devised by society to deal with disruptive effects of illness" (Engel, 1977). In disease, there are paradoxical states in which patients test positive for the biological defect but don't feel sick, while other patients who feel very ill test negative for disease. Dr. Engel believes that a biopsychosocial model which is inclusive of both the illness and the patient would accommodate for both circumstances.

The biopsychosocial model has been a helpful lens through which FGIDs, including IBS, can be viewed. Not only because FGIDs are symptom based conditions, but also because severity of symptoms, disease progression, treatment seeking behaviors, and treatment efficacy are so highly variable among individuals. There is no one unifying biochemical defect for IBS, but rather many potential defects and many compounding biological, social and

psychological factors which can contribute to the frequency and chronicity of the disease.

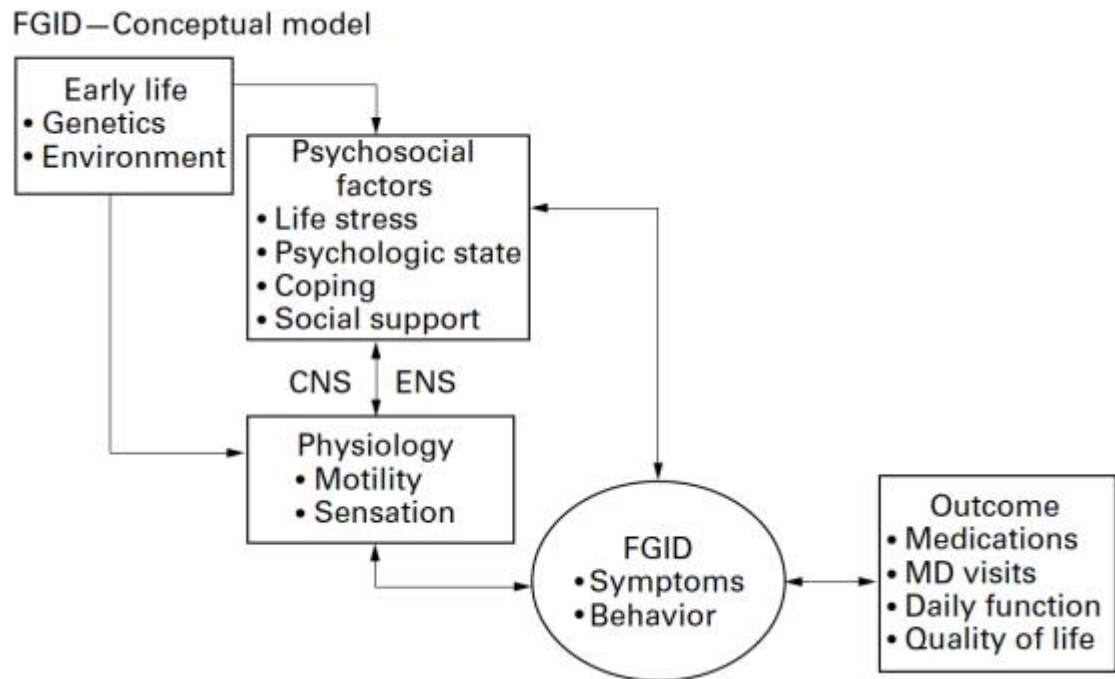


Figure 2. Functional Gastrointestinal Disorders (FGID) – Conceptual Model. FGID manifests through symptoms and behavior that are caused by the combination of early life factors, genetics and environment; psychosocial factors in an individual’s daily life and the sudden changes in physiology. Additionally, the symptoms and behavior feedback the patients’ psychological well-being and social life and can compound the physiological effect and vice versa with the physiological sensation or somatization affecting the individuals psychology. As a result, individuals seek out medication, healthcare and their quality of life becomes impeded and daily function hindered. The frequent healthcare visits and decrease quality of life as well feeds back on psychosocial wellbeing and physiological symptoms in the individual. Figure adapted from (Drossman, 1999).

Burden of Illness

It has been well-established that IBS lowers quality of life. In a study conducted in 2000, IBS patients in the US received lower Health Related Quality of Life (HRQOL) scores in all eight of the SF-36 categories; physical function, role limitations- physical, bodily pain, emotional well-being, role limitations- emotional, energy/fatigue, social functioning, and general health (Gralnek, 2000). Similar results have been obtained in populations in universities in the US and in Europe, further validating that IBS lowers quality of life.

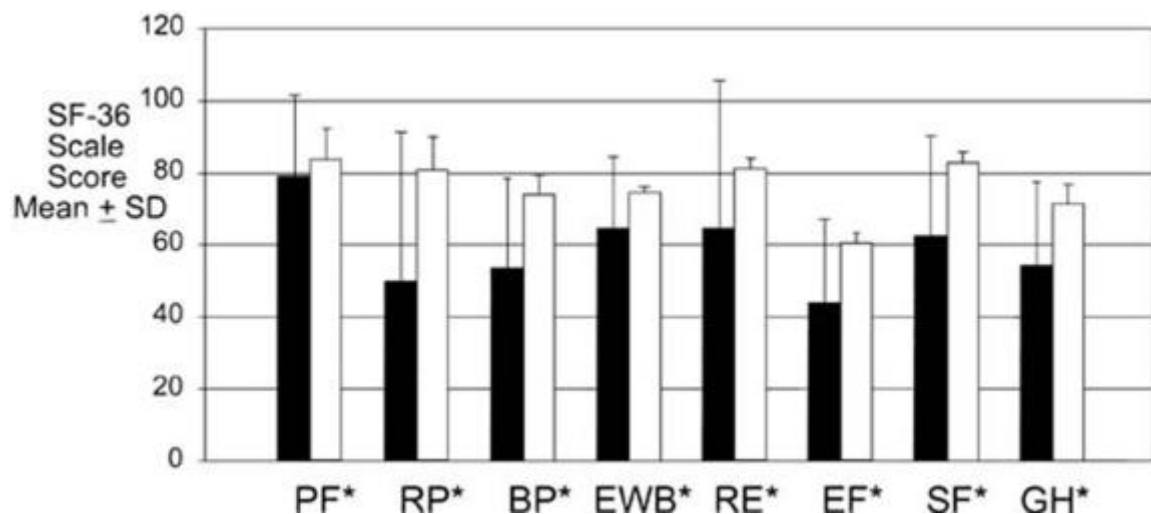


Figure 3. HRQOL Scores. Patients with IBS (black; n = 877) vs. general US population (white, n = 2474) in eight categories: PF- physical function, RP- role limitations physical, BP- bodily pain, EWB- emotional well-being, RE- role limitations emotional, EF- energy/fatigue, SF- social functioning, GH- general health. Figure adapted from (Gralnek, 2000)

IBS also contributes significantly to high amount of health care expenditures. In 2004, there were 3.1 million ambulatory care visits of patients with IBS as the diagnosis and an estimated 5.9 million prescriptions were filled at retail pharmacies (Everhart, 2009). Besides the large healthcare cost to the society at

large, IBS also interferes with work productivity as patients need to take sick days for their physician visits and to cope with their symptoms. IBS symptoms begin presenting most often in young adults, interfering with the lives of many individuals to launching their professional careers. When assessing the clinical determinants for why IBS lowers quality of life (QOL) almost universally among IBS patients, the findings indicated that QOL was lowered due to extraintestinal, systemic symptoms such as fatigue, low energy, feeling tense or nervous, low sexual interest, and “feeling that something is seriously wrong with their body.” Because of these findings, it is suggested that physicians try to focus more on global symptom severity and helping patients cope with anxiety and chronic stress that comes with the disorder (Spiegel, 2004). Due to the chronicity of the disease and often limited therapeutic success, along with the contribution of chronic stress and anxiety lowering QOL which also feed back on physiological factors, the relationship and trust between the healthcare provider and patient is of utmost importance and determines the therapeutic outcome in patients with IBS. Diagnostic evaluation of patients with suspected IBS can be generally minimal without invasive testing and is symptom oriented (Chey et al., 2015). However, because of the previous history with the debate on a biomedical model vs. a biopsychosocial model, providers tended to focus on the assessment of biomedical markers and exclusion of organic diseases which often involved unnecessary invasive testing or treatment modalities, such as colonoscopy and cholecystectomy (Chey et al., 2015). These failures to make a positive diagnosis

of IBS with minimal testing (which is possible using the Rome criteria) and manage symptoms may further frustrate patients and contribute to the stresses that decrease not only their mental HRQOL scores but also their physical ones. The development of a trusting provider patient relationship which makes a positive diagnosis of IBS, emphasizes the explanation of the natural history of IBS, and stating the realistic expectations of symptoms for patients often helps to avoid the use of invasive procedures and diagnostic examinations. It also avoids to a large degree the surmounting healthcare costs incurred by IBS patients. Due to the large interference in the daily lives of patients and the cost to the patient and the society as a whole, it is becoming increasingly important that health care providers find a way to help patients cope with their IBS symptoms based on a trusted relationship.

Specific Aims

Specific aims of this thesis include:

- Characterization of the brain-gut axis hierarchical structure and neuroanatomy
- Assessment of the changes to the brain-gut axis in IBS, specifically in the higher cortical regions with regards to increased sensitivity
- Correlation between anxiety and stress with physical symptoms in IBS

- Analysis of studies conducting different types of psychological treatments as a treatment option and determining relative efficacy of each

BRAIN-GUT AXIS

A central feature in FGID that is becoming increasingly clear in recent years is an alteration to the brain-gut axis (BGA). The brain-gut axis is the connection between the central nervous system (CNS) and enteric nervous system (ENS), and includes communication via neural pathways including the autonomic nervous system (ANS), along with immune and endocrine messengers. Also, feeding into this pathway is the hypothalamic-pituitary-adrenal (HPA) axis. The basic hierarchy of the brain-gut axis is illustrated in figure 4 below.

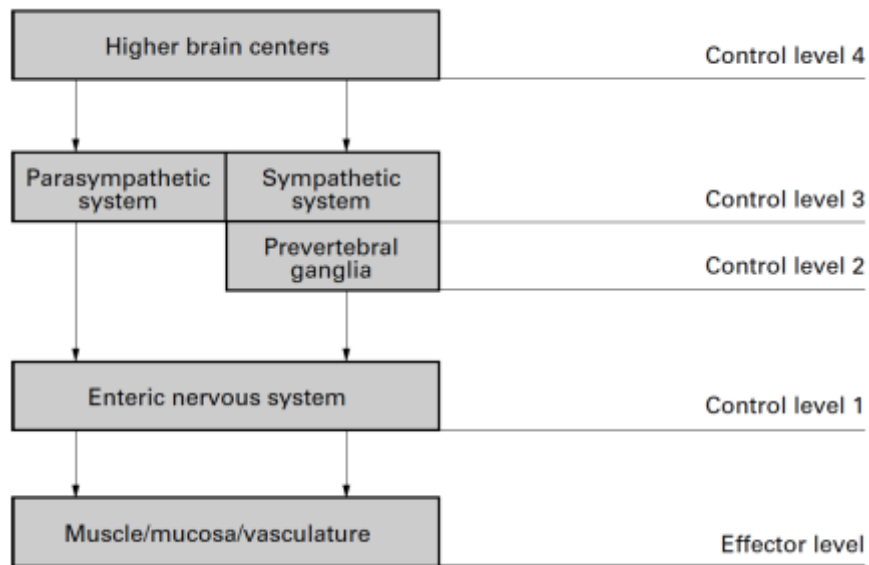


Figure 4. Neural control of the gut. There are four basic levels of integrative organization in the brain gut axis. Level 1 is the ENS acts locally. Level 2 include the prevertebral ganglia containing the postganglionic neurons that innervate the gut. Level 3 and 4 include the CNS with level 3 governing the ANS and higher cortical regions of the brain in level 4. Figure taken from (Wood et al., 1999).

The centers of the brain that connect with the gut are also involved in body homeostasis and emotional regulation, thus stress has been implicated in being

a contributing factor towards IBS symptoms. Additionally, there is a high comorbidity rate of approximately 50% between IBS and common psychiatric illnesses including: major depressive disorder, generalized anxiety disorder, panic disorder, and posttraumatic stress disorder. Assessing dysfunction in the brain-gut axis is an important therapeutic target both pharmacologically and psychologically and has become a major focus in FGID research. Recent evidence also suggests cross-talk between the brain-gut axis and the gut microbiome via neuroimmune messengers secreted in the gut. In the following section, the neurological and neuroimmune pathways of the brain-gut axis will be discussed along with its effects on gut function and symptom perception.

Neuroanatomy of Brain-Gut Axis

The GI system itself has its own nervous system, the ENS, which has some functional similarities with the CNS, but also functions independently. Within the ENS there are sensory, motor, and interneurons that form local reflexes governing the behavior of gut musculature, secretory glands, and vasculature. Musculomotor neurons innervate the musculature and either inhibit or initiate contractile activity. Secretomotor neurons stimulate secretory glands to secrete chloride, bicarbonate, and mucus which maintain the pH and fluid contents of the gut lumen. Together this network determines motility (contractility) and enzyme and fluid secretion in the gut during various digestive and behavioral states (Lacy et al., 2016). Disruption of the intrinsic ENS circuitry may result in various

pathophysiological states. In addition to muscle cells, interstitial cells of Cajal (ICC) are also involved with the regulation of intestinal motility. ICC are non-neuronal pacemaker cells that are connected to each other via electrical syncytial networks around the circumference and longitudinally through the myenteric stomach, small intestine, and large intestine (Takaki, 2003). They generate electrical pacemaker potentials resulting in spontaneous, rhythmic contractile activity in the gut which spread through gap junctions between the cells (Lacy et al., 2016). Sensory information is also relayed through these intrinsic circuits via ENS afferents and efferents. ENS afferents are referred to as EPANs (enteric primary afferent neurons) or IPANs (intrinsic primary afferent neurons). They respond to mechanical alterations of the mucosa and chemicals in the lumen along with radial stretch and muscle tension (Costa et al. 2000). The various neurons of the ENS motor system are shown in the figure 5 below.

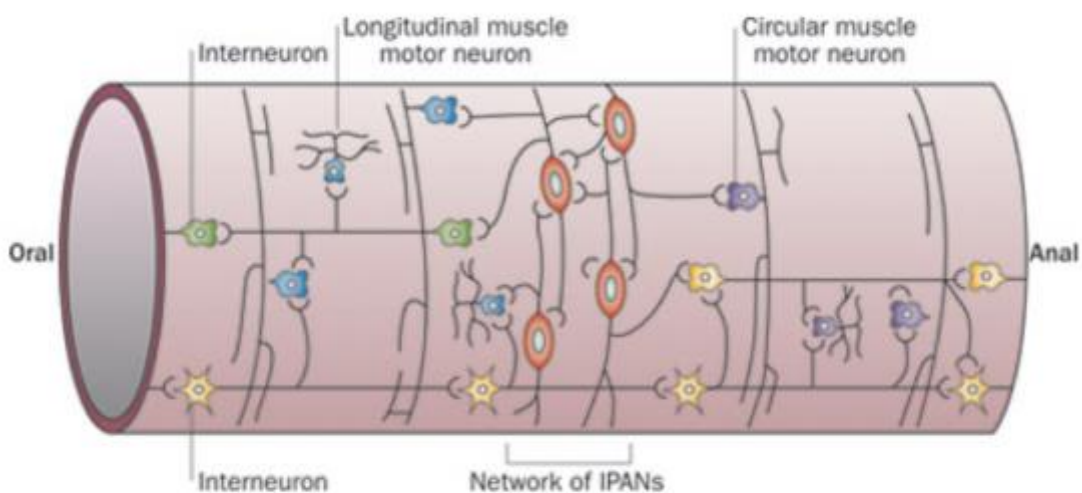


Figure 5. ENS circuitry. IPANS, sensory neurons of the ENS synapse with interneurons which process information and synapse onto musculomotor neurons. The musculomotor neurons innervate longitudinal and circular smooth muscle of the gut; mainly that of the myenteric stomach, small intestine and large intestine. Adapted from (Furness, 2012).

Sensory information is relayed from the GI tract to the CNS via vagal and spinal afferents which are splanchnic and pelvic, respectively. The vagal nerve conducts largely sensory signals (information) such as presence of food, motor activity, and distension of the digestive track to the CNS (Mulak et al., 2004).

Mechanisms by which this sensory information is relayed include mechanotransduction and luminal sensing (Lacy et al., 2016). Vagal efferents innervate the myenteric plexus. Previously, it was believed that the efferent neurons directly innervated the enteric motor neurons in the gut and all the information processing was mediated by the CNS. This classical model has been proven to be false in light of current evidence. It is now known that vagal efferents from the CNS synapse onto the integrative system of the ENS where information on reflexes are stored and information is processed. These interneurons then synapse onto enteric motor neurons and either inhibit or initiate contraction.

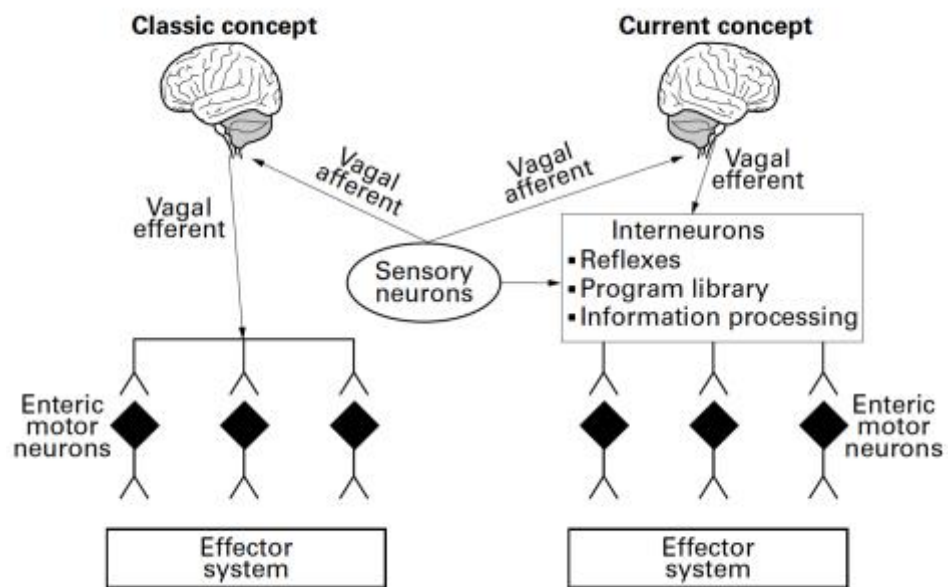


Figure 6. Classical vs. Current Model of Brain-Gut Pathways. In the classical model, vagal efferents synapse directly onto enteric motor neurons. In the current model, vagal efferents synapse onto the ENS integrative network of neurons which then give signals to enteric motor neurons. Figure taken from (Wood et al., 1999).

Sensory endings contain ion channels and receptors that convert various stimuli into action potentials. The ion channels are mechanosensitive and open or close in response to physical changes in the mucosal membrane. The receptors are both ionotropic and metabotropic and respond to messengers released by secondary sensory cells. These cells are in close proximity to the lumen and sense the luminal environment of the gut. Cell types include ICC, enteric neurons, epithelial cells, enteroendocrine cells, mast cells and macrophages.

The structures in the CNS that have been most significantly implicated in brain-gut function include components of the limbic system: hypothalamus, amygdala,

anterior cingulate cortex (ACC) as well as the prefrontal cortex (PFC). The major functions of these regions are shown in Table 2.

Limbic Structure	Functions	Stimulus Response
Hypothalamus	<ul style="list-style-type: none"> • Govern CNS autonomic response • Maintain homeostasis • Generate coordinated emotional response 	Emotional response- anger, fear, curiosity, lethargy, etc.
Amygdala	<ul style="list-style-type: none"> • Process emotions • Form emotional memories 	Changes in emotion and autonomic function
Anterior Cingulate Cortex (ACC)	<ul style="list-style-type: none"> • Integrate visceral, attentional, emotional information • Regulate affect 	Information processing; dispersal of pain inhibition signals
Prefrontal Cortex (PFC)	<ul style="list-style-type: none"> • Represent goals • Behaviors and vigilance to achieve goals • Process effect 	Increased vigilance; Affective processing

Table 2. CNS Structures and Functions. Three of the regions in the limbic system- hypothalamus amygdala, and ACC along with its close connection to the PFC are the major relevant structures to FGID pathophysiology. Their major functions and response when stimulated are listed. Adapted from (Jones et al., 2006).

The limbic system is a region of the mammalian brain often referred to as the “visceral” or “emotional brain.” It functions to maintain homeostasis for the organism along mediating emotional responses (Tucker et al., 1995). Because this region of the brain regulates autonomic and neuroendocrine response and sensory perception, regulation of the gut and its pathophysiological states may be a result. The interconnection between the physical homeostasis and emotional motor system (EMS) suggests that emotions would also play a role in

GI pathophysiology. The limbic system is also closely connected to the PFC which is also involved with regulation and communication in the brain-gut axis. The PFC is involved in affective processing and its central role is to represent goals and behave in a way to achieve those goals (Jones et al., 2006).

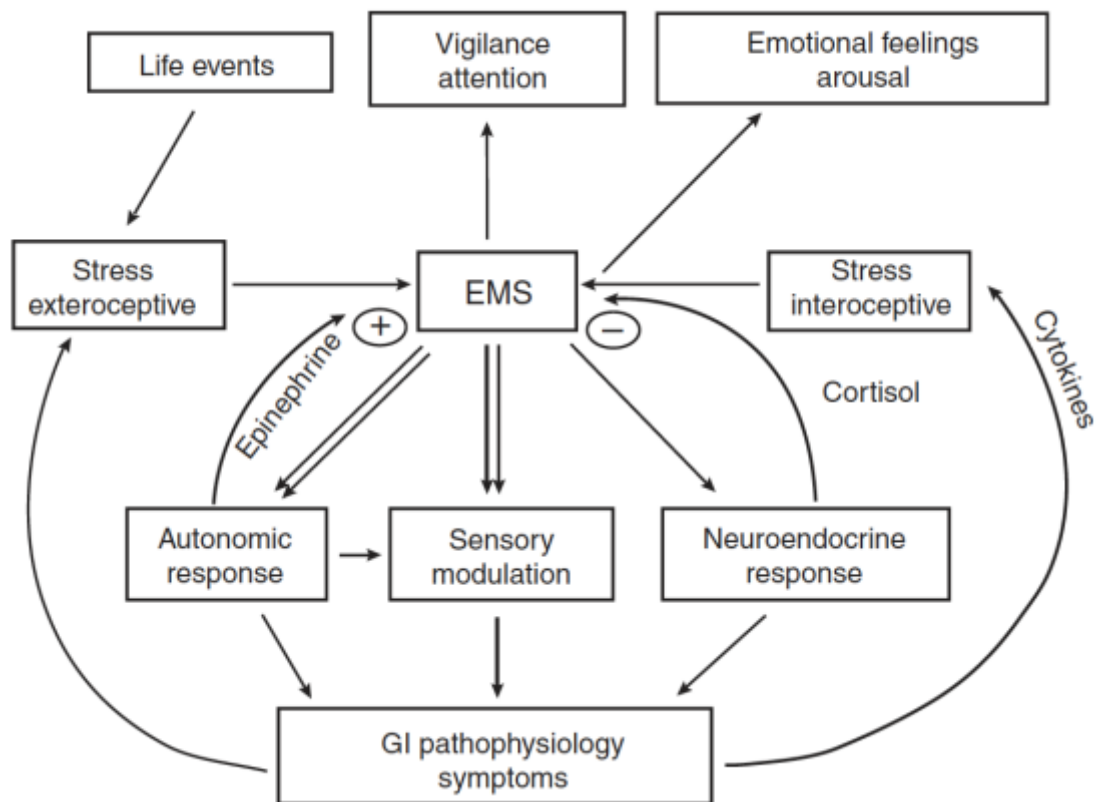


Figure 7. Inputs and Outputs of the Emotional Motor System (EMS). EMS, also known as the limbic system located in the CNS regulates peripheral body systems via autonomic, pain modulatory, and endocrine responses. These responses can act on the gut and form pathophysiological symptoms. EMS also signals to the forebrain (the prefrontal cortex) to modulate attention and emotional arousal. Input to EMS can be exteroceptive (psychological) or interoceptive (physical) stress. GI symptoms can exacerbate stress which further feeds into a pathological feedback loop. Figure taken from (Mayer et al., 2001).

Visceral Hypersensitivity and Pain Perception in Irritable Bowel Syndrome

A hallmark feature in IBS patients is an increased perception of pain in response to visceral stimuli. This phenomenon is known as visceral hypersensitivity. Pain is a potent nonverbal signal prioritized by the CNS. Pain perception involves sensory, emotional and cognitive processing. Visceral pain is relayed to the spinal cord then brain via three pathways: spinothalamic, spinoreticular, and spinomesencephalic (Jones et. al 2006). These signals are then processed by a common network of cortical and subcortical regions referred to as the 'pain matrix'. Regions of the pain matrix include: the mid/anterior insula, subregions of the ACC, PFC, thalamus, and occasionally the dorsal pons and periaqueductal gray (PAG). The pain matrix responds activates slightly differently to somatic and visceral pain (Chang et al., 2005). Two studies have demonstrated differences in somatosensory cortex activation between visceral rectal distension and somatic anal distension (Hobday et al., 2001 & Lotze et al., 1997). Both found greater activation of S1 cortex in somatic anal distension and the latter found increased motor cortex activation as well. Visceral rectal distension was associated with the same regions as somatic anal distension except in the study by Hobday et al., 2001, ACC activation was only found in visceral stimulation. This however, differs from common knowledge that the ACC is activated in both somatic and visceral stimulation. An explanation for this could be that the visceral stimulation was non-painful. However, the correlation between visceral pain and ACC activation is important to note. Another study showed that non-painful rectal distension

showed no activity in the ACC but when replaced with a painful stimulus ACC activation increased by 10.5% (Silverman et al., 1997). ACC activation increased as subjective pain intensity increased in normal individuals.

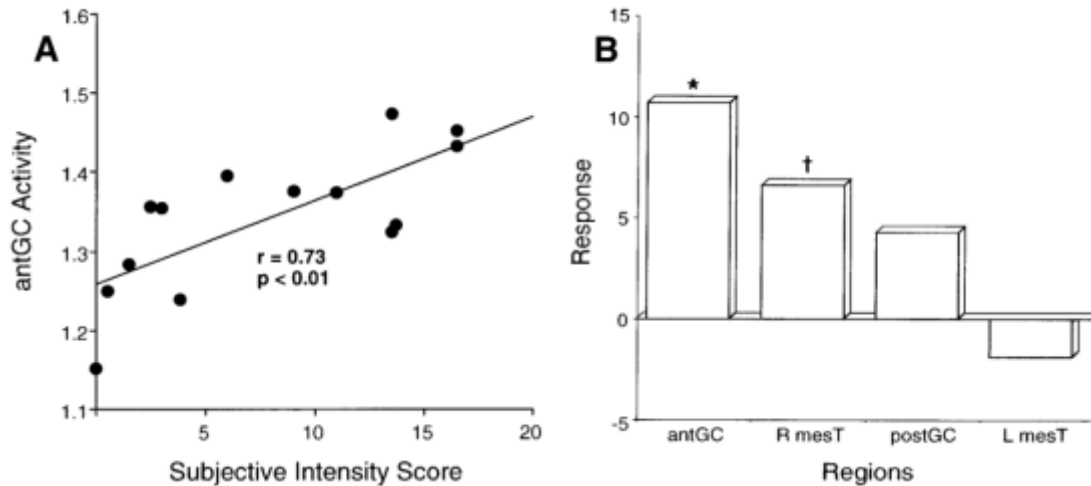


Figure 8. Regional ACC Activity in Response to Perceived Intensity of Painful Stimuli. ACC was activated in anticipation of painful stimuli and activation increased in response to both actual and simulated stimulation. Linear regression of the relationship was statistically significant with a p-value < 0.01. Figure taken from (Silverman et al., 1997).

In a comparison between noxious esophageal distension and cutaneous thermal stimulation, subject intensity did not differ. However, there was a marked difference in unpleasantness with the visceral esophageal pain rated more unpleasant (Strigo et al., 2000). These findings were further validated in another study where results demonstrated that when unpleasantness was matched in visceral and somatic stimulation, the intensity was lower with visceral stimulation (Dunckley et al, 2005). This shows that visceral pain has a psychological component as patients rated it more unpleasant even when pain intensity ratings

were lower. Somatic pain led to activation of regions involved with spatial orientation and exteroception such as the dorsolateral PFC and inferior parietal cortex. Visceral pain, on the other hand led to activation of the right anterior insula which is involved more with processing emotions and interoception (Dunckley et al., 2005). This suggests that processing of visceral pain results in a greater emotional and psychological response than somatic pain which recruits the centers involved with spatial localization and motor response.

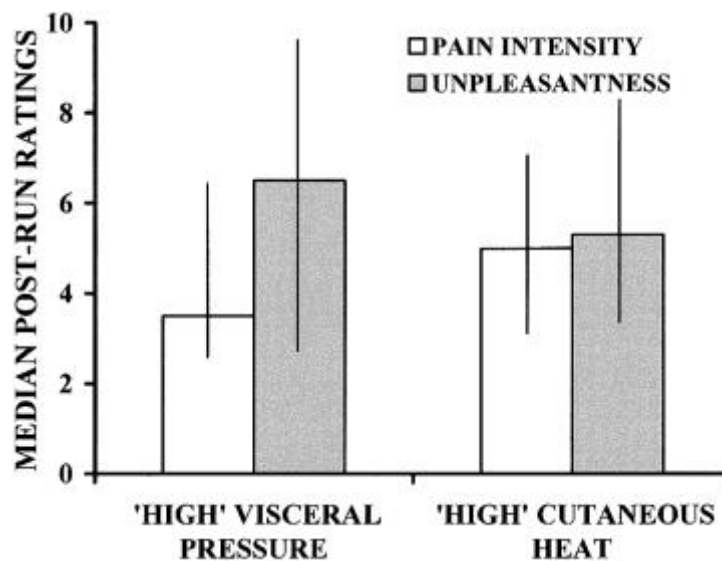


Figure 9. Differences in Pain Intensity and Unpleasantness in Visceral vs. Cutaneous Stimulation. When matched for pain intensity, visceral stimulation was rated as more unpleasant. Figure taken from (Strigo et al., 2000).

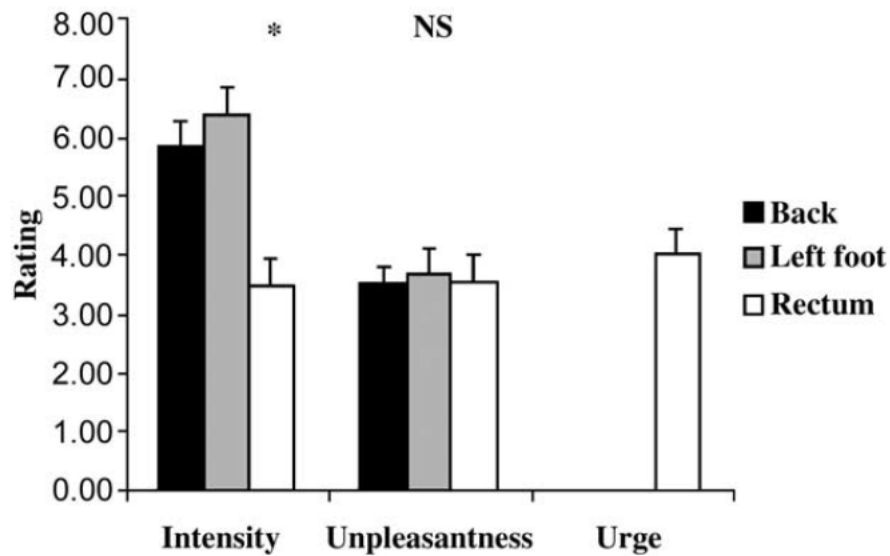


Figure 10. Intensity and Unpleasantness in Painful Somatic (back and foot) vs. Visceral (Rectal) Stimulation. When matched for unpleasantness, physical pain intensity rating was much lower in rectal/visceral stimulation suggesting a psychological component to visceral pain. Figure taken from (Dunckley et al., 2005).

All three of the above-mentioned studies shared a significant feature in common, greater activation of the anterior/rostral portion of the ACC (Silverman et al., 1997, Strigo et al., 2001, Dunckley et al., 2005). The anterior region of the ACC has been associated with attention. This region is also in close proximity and has connections with the rostral limbic system and PFC suggesting that an interplay between these regions is involved in affective pain processing (Devinsky et al., 1995).

Studies on patients with IBS have demonstrated lower pain thresholds, increased visceral hypersensitivity, and activation of regions of the brain involved with

emotions, especially linked with anxiety and fear responses. In a large study consisting of five different cohorts from different countries, similar results on increasing visceral hypersensitivity in conjunction with increasing GI symptoms were found across the board (Simren et al., 2017). Although other studies have showed opposite results with no or negative correlation between GI symptoms and sensitivity, those studies may be either not reproducible or had small sample sizes questioning the statistical validity of the results. In this study, only four of the five cohorts showed the same linear trend but with a p-value < 0.0001 showing statistically robust significance, but do need further confirmation. In addition, IBS patients showed a significant negative linear relationship between symptom severity and pain threshold suggesting that IBS patients have a decreased pain tolerance. When controlling for visceral sensitivity, a significant relationship was found between GI symptom severity and anxiety or depression (Simren et al., 2017).

Cohort	Correlation Coefficient	p-value
1 (n=242)	-0.27	<0.0001
2 (n=243)	-0.20	0.002
3 (n=159)	-0.27	0.001
4 (n=353)	-0.29	<0.0001
5 (n=147)	-0.20	0.02

Table 3. Correlation Between Pain/Discomfort Thresholds and Z Scores of GI Symptom Severity in Five Patient Cohorts. A negative correlation between pain/discomfort threshold and GI symptom severity was found in the five different cohorts located in Belgium, the US, and Sweden. P-values of less than 0.05 were demonstrated in all five of cohorts. Adapted from (Simren et al., 2017).

Another study demonstrated increased visceral and cutaneous sensitivity in IBS patients. Visceral sensitivity was examined using rectal distension and cutaneous sensitivity was tested using thermal stimulation. IBS patients rated visceral and cutaneous intensity as the same but rated visceral stimulation as more unpleasant (Verne et al., 2003).

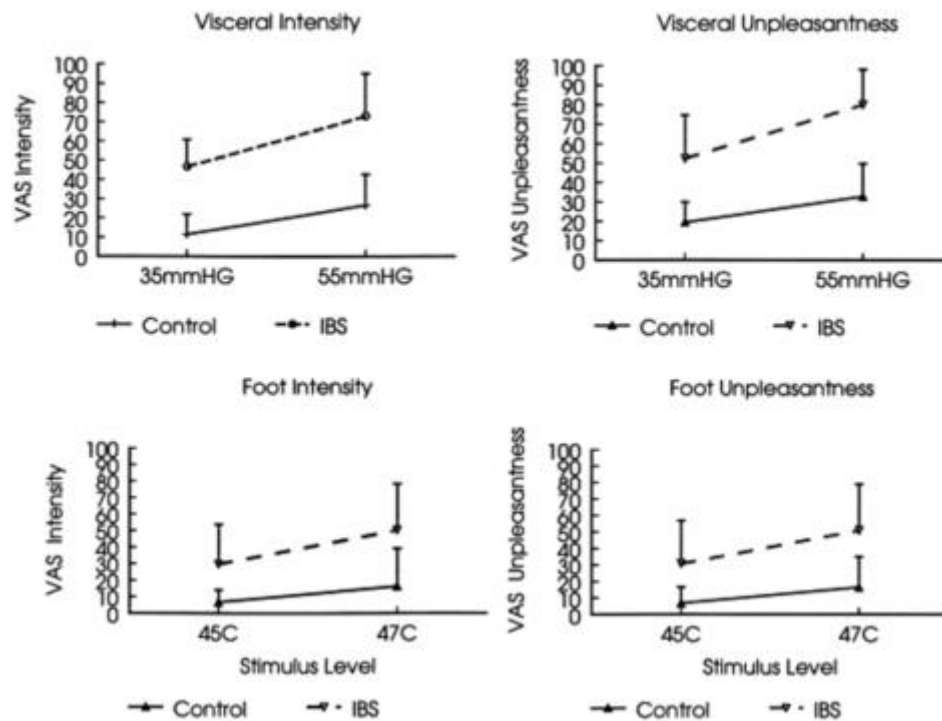


Figure 11. Comparisons Between Control Group and IBS Group in Visceral and Cutaneous Pain Intensity and Unpleasantness. IBS patients reported a significantly higher pain intensity with both visceral (rectal) stimulation and cutaneous stimulation (to the foot). Both groups considered visceral stimulation as more unpleasant. IBS patients considered visceral stimulation to be much more unpleasant despite not considering it more intense. Figure taken from (Verne et al., 2003).

When determining sensory thresholds between IBS patients, patients with abdominal pain of different causes, and healthy controls, IBS patients had a significantly lower pain threshold when compared to the control group and other FGID groups as well (Bouin et al., 2002).

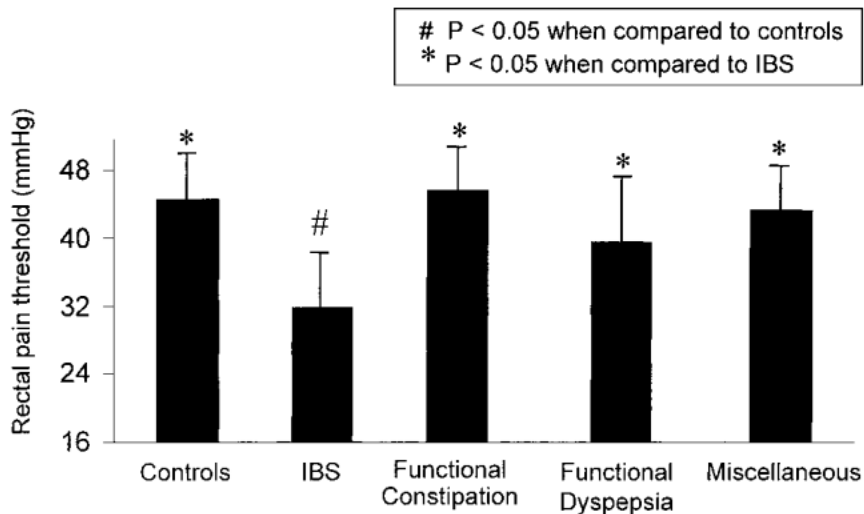


Figure 12. Rectal Pain Thresholds in Control vs IBS vs Groups with Abdominal Pain from Other Sources. IBS patients had a significantly lower pain threshold when compared to all the groups, even groups with other FGIDs. Figure taken from (Bouin et al., 2002).

Altered Pain Processing in Irritable Bowel Syndrome

Current hypotheses to explain the increase in pain perception in IBS patients include an increase in afferent processing and increases in activation of certain cortical regions, and disturbances in pain inhibitory mechanisms. Although it has not yet been determined which mechanism is the initial cause of hypersensitivity, studies show slight differences in terms of activation of some regions, however, and further controlled testing need to be conducted. The two CNS regions that have been consistently found have increased activation in IBS patients in response to visceral pain are the dorsal ACC and insula. Other regions with increased activities include the thalamus, posterior cingulate cortex (PCC), somatosensory cortex (SSC), prefrontal cortex (PFC). IBS patients also have altered cerebral activity in response to anticipated but not actually received visceral stimulation, especially in subcortical regions with emotional processing function like the hypothalamus, amygdala and dorsal pons (Chang et al., 2005). The table below shows a summary of findings in previous publications. There are differences in data suggesting that CNS processing or cortical activity may not be the only cause of hypersensitivity, or that the etiology is heterogeneous.

Study	Modality	Methods	ACC	Insula	Brainstem	PFC	Amyg	Thalamus	PCC	SSC
Verne <i>et al.</i> ⁸⁶ Ctrls = 9 IBS = 9	fMRI	Rectal distension	↑	↑	na	↑	na	↑	↑	↑
Chang <i>et al.</i> ⁸⁷ IBS = 10 IBS + FM = 10	PET	Cutaneous heat Rectal distension Cutaneous mechanical pressure	↑ mACC ↑ mACC*	↑ nd nd	na nd nd	↑ nd nd	na nd nd	↑ nd nd	↑ nd nd	↑ nd nd
Mertz <i>et al.</i> ⁸⁸ Ctrls = 16 IBS = 18	fMRI	Rectal distension	↑	na	na	na	na	↑	na	na
Naliboff <i>et al.</i> ⁸⁹ Ctrls = 12 IBS = 12	PET	Anticipated and delivered rectal distension	↓ pACC ↑ rostral ACC	na	↓	↓	na	↓	↑	na
Silverman <i>et al.</i> ⁹⁵ Ctrls = 6 IBS = 6	PET	Anticipated rectal distension†	↓ pACC	na	na	↑	na	na	na	na
Berman ⁹¹ IBS = 37	PET	Anticipated and delivered rectal distension pre-/post-alosetron	↓ pACC	↑	↓ pons	↓ vmPFC ↑ vlPFC	↓	↑	na	na
Morgan ⁹² IBS = 19	fMRI	Rectal distension with hi/lo acoustic stress pre-/postamitriptyline	↓ pACC	nd	nd	nd	nd	nd	nd	↓
Lackner ⁹⁰ Ctrls = 6 IBS = 6	PET	Rectal distension pre-/postcognitive therapy	↓ pACC	nd	nd	↓	↓	nd	↓	nd

Table 4. Summary of Brain Activity Findings in Control vs. IBS Patients Before and After Rectal Stimulation. There is a large variance in findings so it is difficult to make universal claims on brain activity and afferent processing in IBS and visceral pain. This area needs to be researched more. A possible reason for the heterogeneity is a host of other factors in the ENS that can disrupt neural processes. Table taken from (Jones et al., 2005).

Three selected studies discussed had similar results using three different brain activity analysis techniques. In the study conducted by Verne et al., functional, structural, and angiographic images were acquired using a functional magnetic resonance imaging (fMRI) imaging technique to detect brain activity. Image slices were overlaid on top of each other to create a 3D anatomic image of the brain and areas of increased brain activity were highlighted.

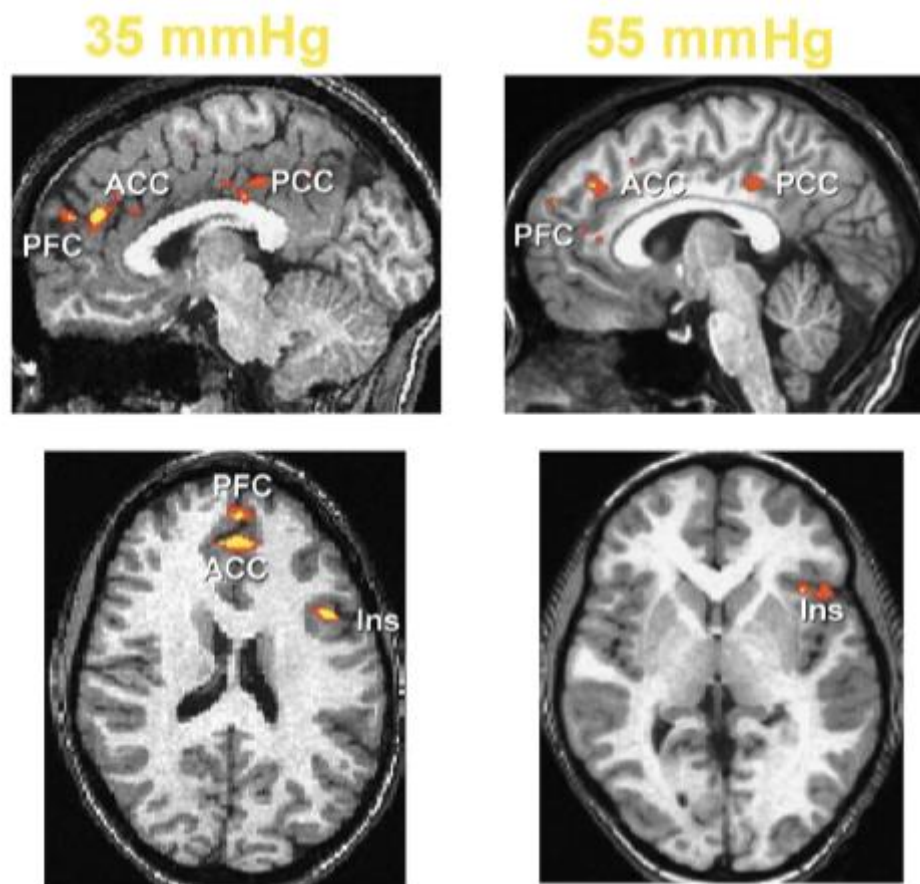


Figure 13. 3D Anatomic Representation of Electrical Brain Scans in IBS Patients. Patients with IBS had an increase in brain activity in the ACC, PCC, PFC, and insula in both non-painful (35 mm Hg) and painful (55 mm Hg) rectal stimulation. Figure taken from (Verne et al., 2003).

In this study, they also discovered that IBS patients had increased activation of the ventral posterior lateral (vpl) and dorsomedial (dm) thalamus, insula, SSC, and PFC in response to rectal stimulation. Another study using fMRI technique to record brain activity during rectal distension was conducted by Mertz et. al.

Patients with IBS experienced greater activation of the ACC and insular cortex

(IC) during painful rectal distension than during nonpainful rectal distension. Compared to controls, IBS patients tended to have greater activation of the ACC and IC during painful stimulation as well (Mertz et al., 2001). The ACC has been implicated in forming memories with chronic pain and regulates arousal and attention providing an explanation as to why IBS patients have a such a marked sensitivity towards painful stimuli and why they find the stimulation to be so much more unpleasant (Wilder-Smith et al., 2004).

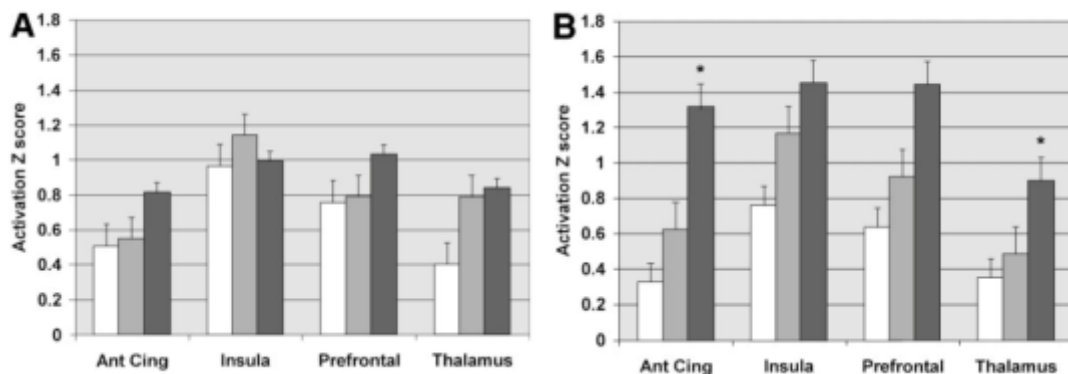


Figure 14. Controls (A) vs IBS Patients (B) in Regional Brain Activity During Non-Painful (white and gray) and Painful (black) Rectal Distension. IBS patients had a significant increase in ACC and thalamic activity in response to painful stimulation over non-painful stimulation. There was also a trend towards greater activity in these regions in IBS patients vs. control, however the difference was marginally significant and the test should be repeated to validate the claim. Figure taken from (Mertz et al., 2000).

In comparison to painful visceral stimulation, non-painful stimulation seems to activate different afferent pathways and results in differences in cortical activation as well. When comparing anticipated and received non-painful rectal distension

in IBS patients vs. control, IBS patients did not show an increased pattern of activity in the thalamus and PFC (Naliboff et al., 2001). Because these regions are involved with emotional and cognitive processing, the results suggest that the presence of visceral pain rather than visceral stimulation can result in increased pain perception. Activation of the rostral aspects of the ACC and the medial PFC is common in anticipation of aversive stimulation and has also been associated with increased activation in both normal and pathological anxiety (Drevets, 2001). Since IBS patients have greater activation of these regions in anticipation to pain, it can be theorized that at a resting state they are more anxious.

Besides the increased activation of the pain matrix, IBS patients lack the ability to inhibit activated pathways and thus are not able to properly downregulate pain response. A study testing visceral and thermal cutaneous pain showed that IBS patients exhibit a decreased ability to modulate and downregulate pains when counter measures are performed to reduce pain intensity and unpleasantness. Counter-irritation in the form of a cold bath was used to help downregulate pain between thermal stimulations. The method of counter-irritation using an ice bath is an example of diffuse noxious inhibitory controls (DNIC). IBS patients were found to not benefit from this and could not decrease pain intensity from thermal stimulation. There is also a correlation between visceral sensitivity and pain inhibition ability where a decreased visceral pain tolerance (visceral hypersensitivity) decreased the patients' pain inhibitory function. (Piche et al.,

2010). This suggests that pain inhibition is diminished broadly in IBS patients and the visceral hypersensitivity from the gut has caused a sensitization and the CNS level. Other studies have also demonstrated this diminished pain inhibition using visceral, cutaneous, and somatic stimulation as well (Song et al., 2006).

Deficiency of DNIC mechanisms has been exhibited in various chronic pain states including chronic headaches, fibromyalgia, and IBS suggesting it to be an important area of research for FGID characterized by chronic pain and resulting in central sensitization (King et al., 2009).

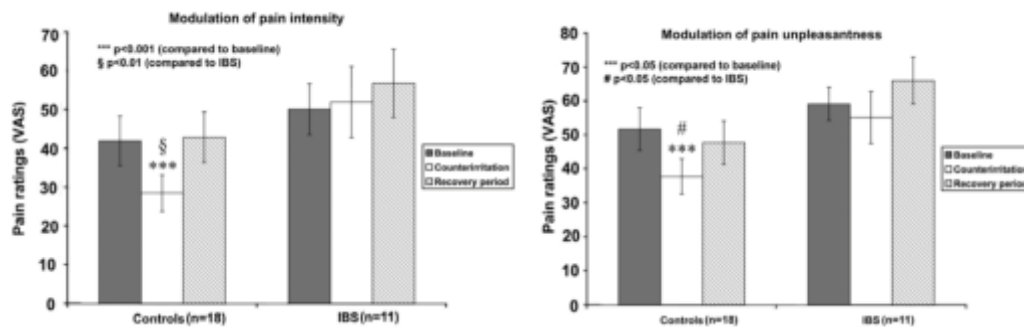


Figure 15. Control vs IBS Patients Modulation of Pain Intensity and Unpleasantness. IBS patients had a diminished ability to modulate both pain intensity and pain unpleasantness to a significant degree.

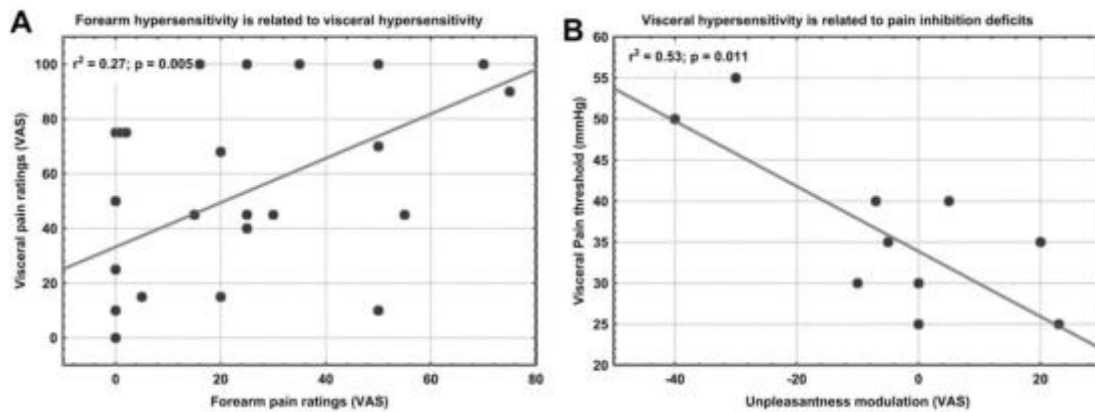


Figure 16. Thermal Sensitivity and Pain Inhibition. IBS patients showed increasing sensitivity to thermal pain in correlation to increasing levels of visceral hypersensitivity. A decreasing threshold of visceral pain resulted in a deficit in pain inhibitory mechanism suggesting a strong correlation between the disease state and altered CNS function.

One mechanism by which the brain sends inhibitory efferent signals is via activation of the perigenual ACC (pACC). The pACC sends direct and indirect efferent signals via the amygdala to the ponto-medullary networks which include: the periaqueductal gray (PAG), rostral ventral medulla and raphe nuclei (Vogt et al, 1995). This decrease in pACC activity could be indicative of a diminished pain inhibition causing the increased pain response and visceral hypersensitivity. Abnormal modulation of pain was found in 70-85% of IBS patients and increasing clinical symptom intensity correlated with increasing abnormal modulation. Descending modulation is conducted by efferents through brainstem and spinal pathways and are modulated by cortical processes involved with cognition and emotion which further supports the idea that altered pain processing can be

attenuated by psychological circumstances (Wilder-Smith, 2011). Currently, few studies are available on brain imaging to provide a biological basis for decreased endogenous pain modulation in IBS patients, but given the consistent results showing IBS patients have altered endogenous pain modulation, this area can be very useful in gaining a better understanding of the correlation between altered cortical processing and IBS symptoms.

Increased Anxiety and Fear Responses in Irritable Bowel Patients

IBS patients have been found to have increased activation of the amygdala resulting in increased anxiety and fear in response to pain and symptoms.

Psychological co-morbidities including anxiety and depression have been found to exacerbate symptoms in patients as well, creating a feedback loop between psychological health and physical IBS symptoms. Both treatment seeking and non-treatment seeking IBS patients have higher rates of clinically diagnosed anxiety disorder suggesting a strong link between the two disorders (Lydiard & Falsetti, 1999).

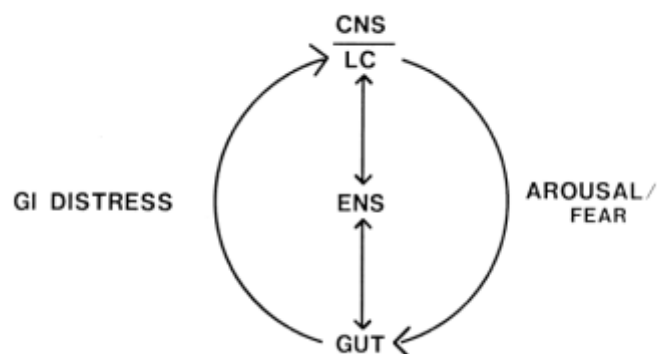


Figure 17. Brain-Gut Loop. GI distress modulates CNS function including increasing anxiety and fear which can then act on the gut and cause further gut dysfunction. Figure taken from (Lydiard & Falsetti, 1999).

In a one year follow-up study, researchers found that subjects that did not have IBS but a high level of anxiety or depression had an increased incidence of IBS development in the one year follow-up. Similarly, the subjects who did have IBS had increased anxiety and depression levels in the one year follow-up (Koloski et al., 2016). This illustrates a strong association of anxiety/depression and IBS where one compounds the other and vice versa, albeit a causal relationship is possible but not proven.

Measure	Baseline FGID	Follow-up IBS Odds ratio* (95% CI), P value
Anxiety	Negative	1.31 (1.06–1.61), 0.01
	Positive	1.05 (0.87–1.27), 0.6
Depression	Negative	1.54 (1.29–1.83), <0.001
	Positive	0.94 (0.78–1.13), 0.5

Table 5. Prediction of IBS at Follow-Up with Anxiety or Depression as a Predictor. Subjects with anxiety and depression who had no baseline FGID symptoms (negative) had a significantly higher chance of getting IBS at the one year follow-up. Table taken from (Koloski et al., 2016).

Measure	Baseline psychological status	Follow-up anxiety Difference between means* (95% CI), P value	Follow-up depression Difference between means* (95% CI), P value
IBS	Normal	0.34 (0.13–0.55), 0.002	0.81 (0.47–1.15), <0.001
	Elevated	0.44 (–0.02–0.89), 0.06	0.84 (–0.85–2.54), 0.3
FD	Normal	0.38 (0.14–0.63), 0.002	0.92 (0.57–1.27), <0.001
	Elevated	0.50 (0.07–0.94), 0.02	1.08 (–0.32–2.48), 0.1

Table 6. Prediction of Anxiety or Depression at Follow-Up with IBS as a Predictor. Subjects with IBS had an increased likelihood of developing anxiety or depression at the one year follow-up. Table taken from (Koloski et al., 2016).

IBS patients exhibited significantly higher anxiety ($p < 0.001$) and fear ($p < 0.004$) in response to visceral pain than the control group. Between visceral and cutaneous stimulation, IBS patients reported much higher anxiety and fear over visceral pain than cutaneous despite rating the pain intensity equally in both (Verne et al., 2003). Not only visceral pain, but IBS patients also exhibited increased anxiety in response to thermal cutaneous pain (King et al., 2009).

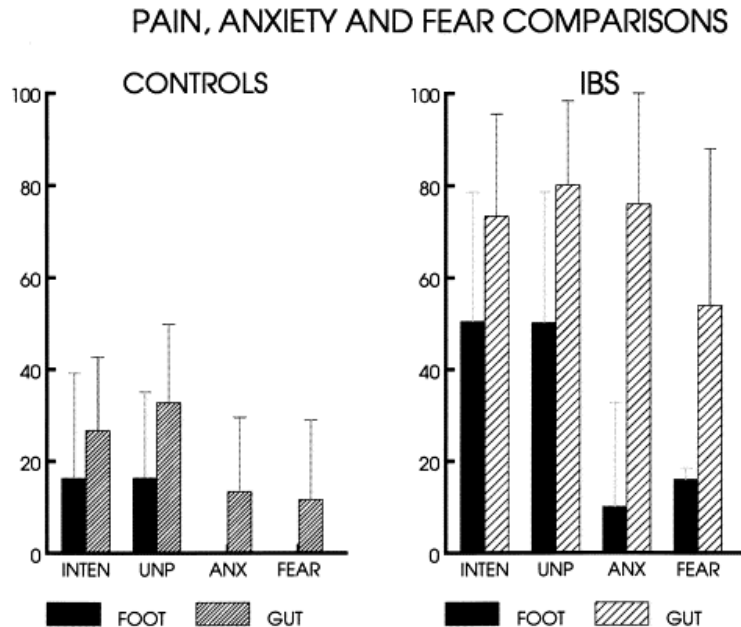


Figure 18. Pain, Anxiety, and Fear in IBS Patients During Visceral and Cutaneous Stimulation. IBS patients exhibited a markedly increased response to pain and unpleasantness during both visceral and thermal stimulation. They had increased anxiety and fear to both types of stimulation with especially high

levels of anxiety and fear during visceral stimulation. Figure taken from (Verne et al., 2003).

The link between anxiety and IBS symptoms lies in the amygdala. IBS patients have higher resting-state functional connectivity (RSFC) of the amygdala with various connections in the brain. A study by Qi et al., 2016 found that IBS patients had a higher RSFC in amygdala-insula, amygdala-midbrain, amygdala-para-hippocampal gyrus (PHG) and amygdala-sensorimotor regions. The insula, as mentioned previously is part of the pain matrix suggesting the amygdala has a role in increased pain. The amygdala-midbrain connection IBS patients has been implicated in processing of visceral information related to emotional stimuli suggesting a role in IBS patients' increased pain perception. PHG is involved with coding long-term emotional memories suggesting that the negative emotions felt during visceral pain may be coded in IBS patients. The connection with sensorimotor regions illustrates that sensitization becomes widespread into the somatic and cutaneous domain suggesting widespread central sensitization (Qi et al., 2016). IBS patients have also demonstrated increased amygdala activity along with the pain matrix during rectal distension (Naliboff et al., 2003, Wilder-Smith et al., 2004). These studies show that amygdala activity is both hyperactivated in IBS patients at a resting state and is also further hyperactivated during pain processing.

In an animal model, the amygdala was stimulated with stereotaxic delivery of corticosterone to determine its effects on the GI tract. It was revealed that the increased amygdala activity via corticosterone resulted in increased abdominal contractions in rats with nonsensitized and sensitized colons undergoing rectal distension (Greenwood-Van Meervald et al., 2001).

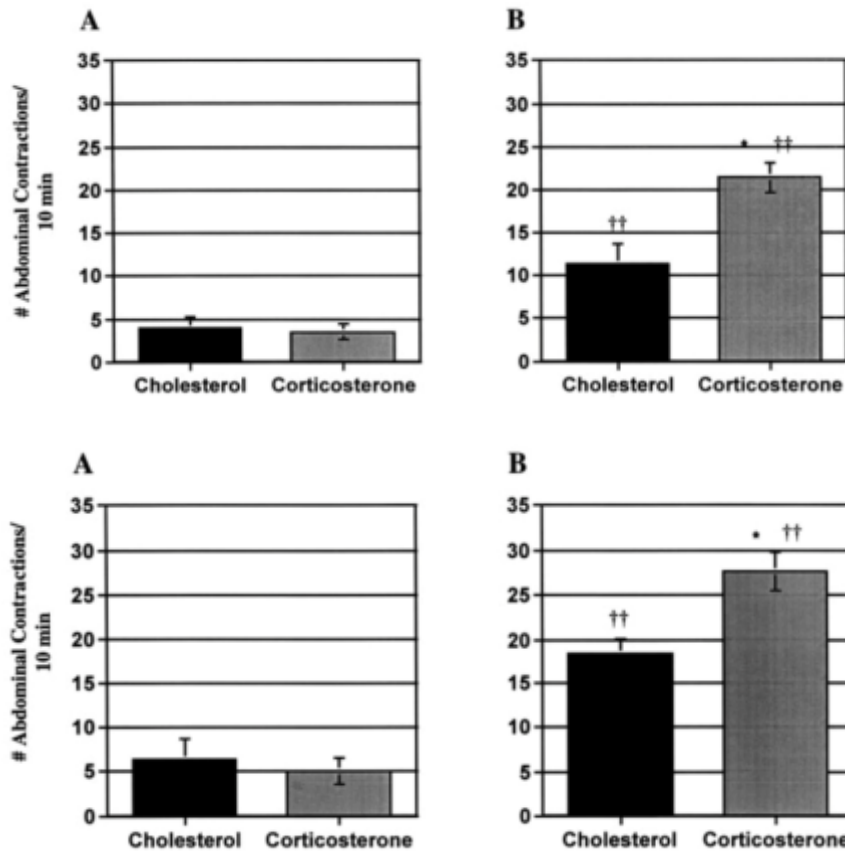


Figure 19. Effect of Corticosterone (Activation of Amygdala) on Abdominal Contractions. The rats with nonsensitized colons are shown in the top two graphs while the ones with colons are illustrated in the bottom two graphs. Rectal

distension resulted in increased abdominal contractions in both types of subjects with administration of corticosterone having a significantly enhanced effect on motility. Figure taken from (Greenwood-Van Meerveld et al., 2001).

These findings tie in with a previous study conducted by the same group that demonstrated that delivery of corticosterone to the amygdala also resulted in increased anxiety. Further evidence for the role of the amygdala comes from studies which show that increasing fear conditioning, an adaptive response facilitated by the amygdala, results in increased colonic sensitivity and motility. Fear conditioning was conducted on mice via electrical shock and cecocolonic spikes were measured to determine motility. The results demonstrated increased colonic motility (Gue et al., 1991). Another study of interest tested predictable vs. unpredictable odor shock in neonate mice and response to colorectal distension was measured in adulthood. Anxiety was assessed via light-dark emergence and the results showed longer emergence times indicating increased anxiety in the rats that received unpredictable shocks as pups. When neonates were exposed to unpredictable shocks (fear conditioning in early life), they showed increased sensitivity to rectal distension in adulthood (Tyler et al., 2007). This suggests that the anxiety induced by early life trauma leads to increased GI sensitivity in adulthood.

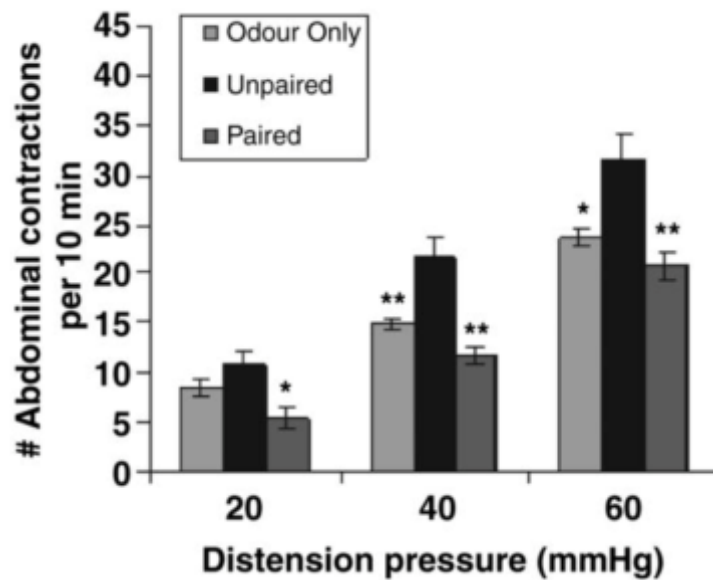


Figure 20. Abdominal Contractions During Colorectal Distension in Adult Rats with Unpaired (unpredictable) vs. Paired (predictable) Odor-Shock as Neonates. Unpaired odor-shock resulted in increased number of abdominal contractions indicating increased GI sensitivity in adulthood when exposed to early-life trauma. Figure taken from (Tyler et al., 2007).

The amygdala facilitates both autonomic and endocrine responses to stress. One way this is done is through increasing corticotrophin releasing factor (CRF) expression and influencing the HPA to release adrenocorticotrophic hormone (ACTH) and cortisol. The amygdala has also been linked to enteric functions such as gastric emptying and colonic motility. Overall, the role of the amygdala is wide and far-reaching with networks of projections reaching various brain regions including: PAG, raphe nuclei, parabrachial nucleus, locus coeruleus (LC), Barrington's nucleus, etc., (Myers and Greenwood-Van Meervald, 2009). The proposed projections and effects on GI, pain, and anxiety are illustrated in the

figure below. Due to the large body of evidence regarding the link of anxiety with IBS symptoms and the evidence of increased amygdala activity facilitating this process, treatment modalities focusing on this aspect of the disorder should be considered for effective IBS management.

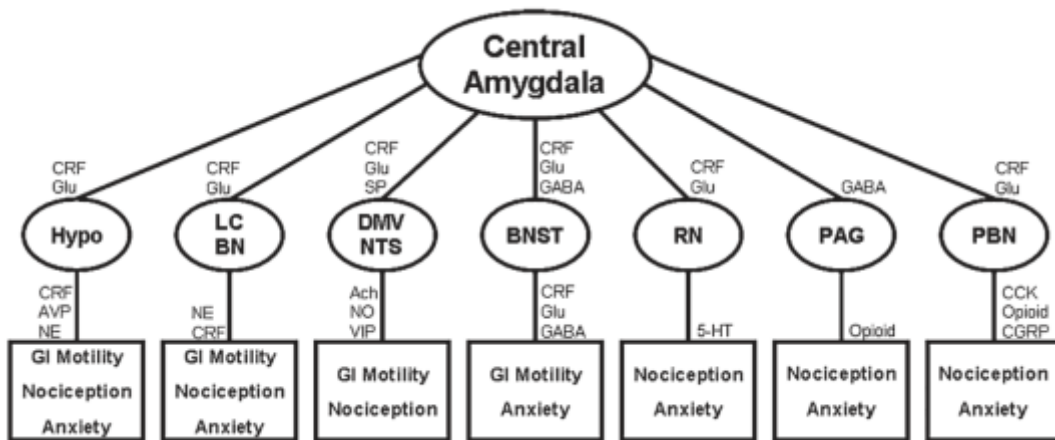


Figure 21. Mechanisms for Amygdala-Mediated Integration of GI Motility, Nociception (Pain), and Anxiety. The amygdala contains a series of projections through various regions of the brain and facilitates activity via CRF, Glutamate, GABA, and other neurogenic molecules. CRF has been implicated in stress and IBS as well. Figure taken from (Myers and Greenwood-Van Meerveld, 2009).

Role of Stress in Irritable Bowel Syndrome

Stress is known to play a large role in many chronic conditions. Stress is a physical, mental, or emotional factor that causes bodily or mental tension.

Stressors can be either internal as result of illness or medical procedure or external from the environment and/or psychological and social situations

(<http://www.medicinenet.com>). Various studies have demonstrated that daily stress increases the intensity and severity of visceral pain (Moloney et al., 2016). A clinically relevant model demonstrated that three days of forced swim (FS) stress resulted in visceral hypersensitivity that lasted for months and IBS-like symptoms, mainly due to central sensitization. Additionally, this study showed that the combination of estrogen and FS stress produced significantly higher visceral hypersensitivity which may account for the female preponderance of IBS (Traub et al., 2014). It is generally accepted that stress disrupts the bi-directional communication between the brain and the gut via activation of homeostatic systems, particularly the HPA via release of CRF from the hypothalamus (Vanner et al., 2016).

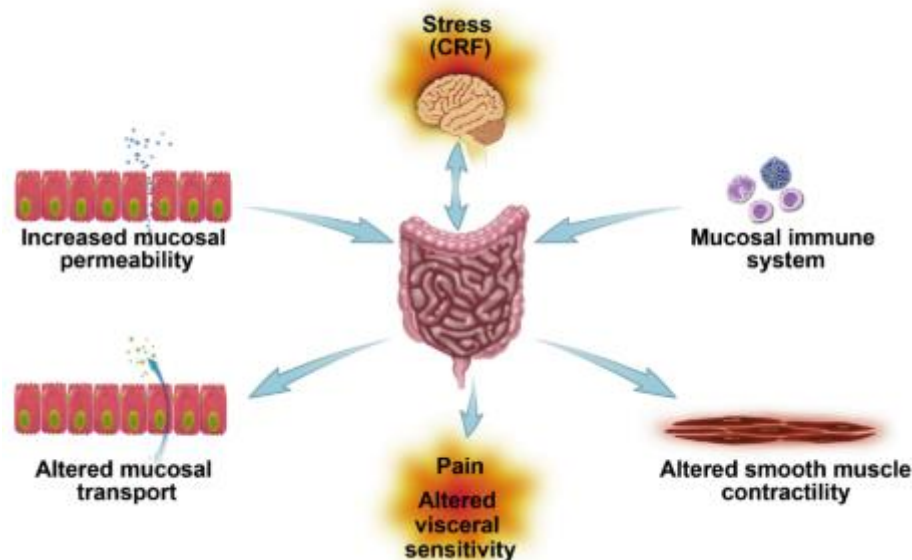


Figure 22. Effects of Stress on GI Function. Proposed mechanism of how stress can affect the bi-direction brain-gut axis. CRF from the CNS influences the mucosa, pain, visceral sensitivity, and smooth mucosal contractility. The mucosa and immune system in the gut can cause central sensitization and further compound symptoms. Figure taken from (Vanner et al., 2016).

In this model, a key mediator in stress-induced disruption of the brain-gut axis is CRF. The HPA axis is activated by stress and the hypothalamus releases CRF into the hypophyseal portal circulation where it reaches the anterior pituitary. The anterior pituitary releases adrenocorticotrophin releasing hormone into the systemic circulation. ACTH travels through the bloodstream and reaches its receptors on the adrenal cortex which then releases glucocorticoid hormone, cortisol in humans and corticosterone in rats (Vanner et al., 2016). Cortisol is a well-known hormone because of its role as the primary stress hormone. Its main function is to increase blood glucose, it increases the brain's use of glucose, and increases availability of endogenous compounds important for tissue repair. Additional functions are to reduce nonessential functions during stressful or flight-or-fight periods such as to alter immune response and suppress digestive, reproductive and growth processes. Cortisol also communicates with the brain to control motivation, fear and mood (Mayo Clinic Staff, 2016).

As mentioned in the previous section, administering corticosterone to the amygdala of rats resulted in increased corticotrophin releasing hormone (CRH) expression. (CRH is another term for CRF). Another study conducted by Gue et al., involved a series of experiments on rats involving physical stress, administration of CRH and a CRH antagonist was used to evaluate the effects of

stress on visceral hypersensitivity. In the first experiment, results showed that abdominal contractions in response to colorectal distension (CRD) was increased in rats that had undergone partial resistant stress (PRS) compared to controls (Gue et al., 1991). The second set of experiments involved administering a CRH antagonist before subjecting the rats to PRS. The results showed that blocking CRH binding to its receptor via the antagonist decreased abdominal contractions from rectal distension compared to rats that did not receive the antagonist. The third set of experiments demonstrated increased abdominal contraction in response to rectal distension even in the absence of PRS, confirming the role of CRH in stress-induced visceral hypersensitivity (Gue et al., 1997).

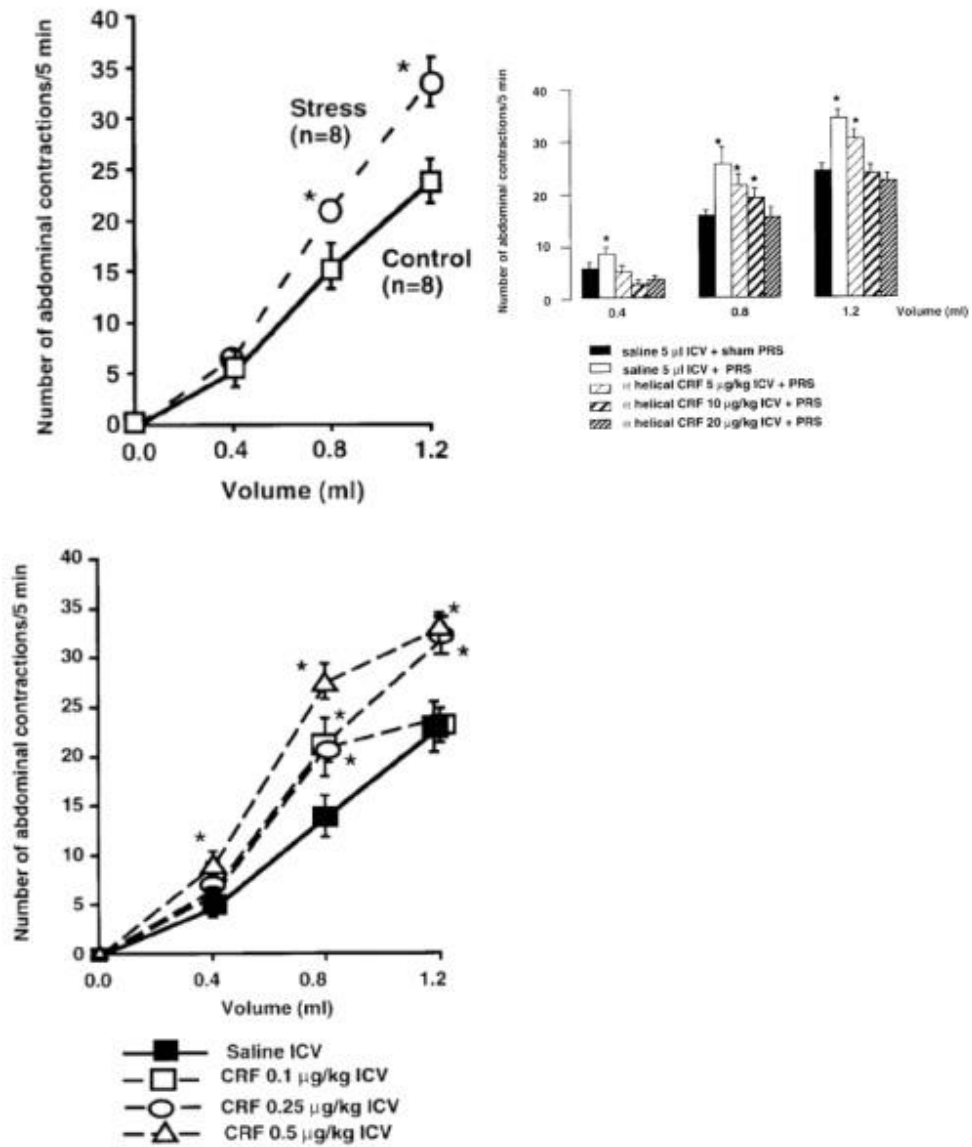


Figure 23. Effects of Stress on Abdominal Contractions in Response to Rectal Distension (Visceral Hypersensitivity) Using Rats. Rats that were subjected to PRS had significantly higher number of abdominal contractions than controls (top left). When given alpha-CRH, a CRH antagonist before PRS the number of abdominal contractions decreased (top right). CRH administered without PRS had the same effect as PRS and rats had increased abdominal contractions with increasing dosage (bottom left). Figures taken from (Gue et al., 1997).

Another study used daily water avoidance stress (WAS) in rats to determine the effects of chronic stress in visceromotor response (VMR). After 10 days of WAS, the rats had an increased VMR in response to CRD illustrating stress-induced visceral hypersensitivity (Bradesi et al. 2005).

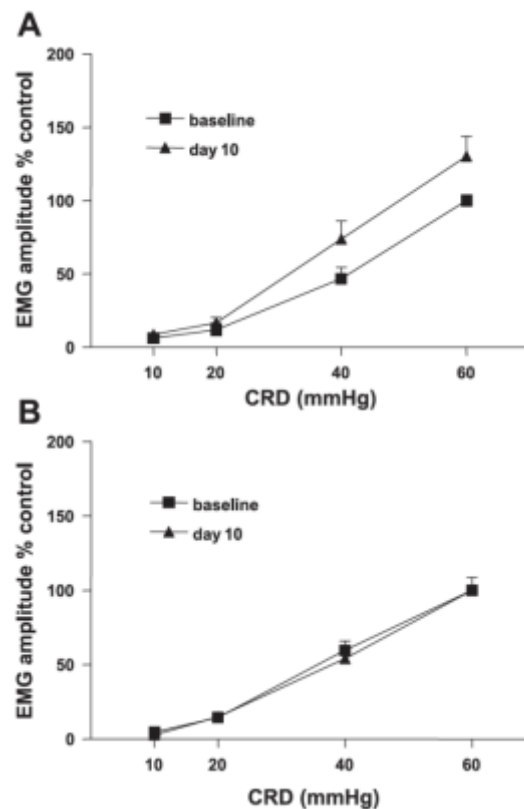


Figure 24. Visceromotor Response to CRD between Rats with chronic 10-Day WAS Treatment vs. Control. VMR was increased in rats that went through 10 days of WAS (A) compared to controls undergoing sham stress (B) providing further evidence that chronic stress increases visceral hypersensitivity. Figure taken from (Bradesi et al., 2005).

Experiments studying the effect of stress on the small bowel and colon have been conducted on humans as well and the results have mimicked typical IBS

symptoms. Psychological stress results in altered transit through GI in which mouth-to-cecum transit time was significantly faster in subjects exposed to stress by listening to a stressful recording (Cann et al., 1983). CRH has been associated with peripheral GI functions such as delaying gastric and small intestinal (SI) emptying and increasing transit through the colon (Williams et al., 1987). Researchers found that administering CRH and immersion of hand into a cold water bath resulted in small intestine (SI) constriction and CRH caused the ascending colon (AC) to increase in volume. Overall, this results in faster transit from the SI to the colon where water is not absorbed fast enough causing diarrhea like patients with diarrhea-predominant IBS (IBS-D) (Pritchard et al, 2015). Another study found the same results with SI constriction and AC volume after CRH was administered. It was also found that CRH resulted in fructose malabsorption but the reasons why remain still unclear (Murray et al., 2016).

The effects of CRH on gastric and colonic motility are more pronounced in IBS patients. CRH administered to IBS patients resulted in greater descending colon motility than CRH administered to controls. 40% of IBS patients exhibited duodenal dysmotility. Abdominal symptoms resulting from CRH lasted longer in IBS patients and plasma ACTH levels were significantly higher (Fukudo et al., 1998).

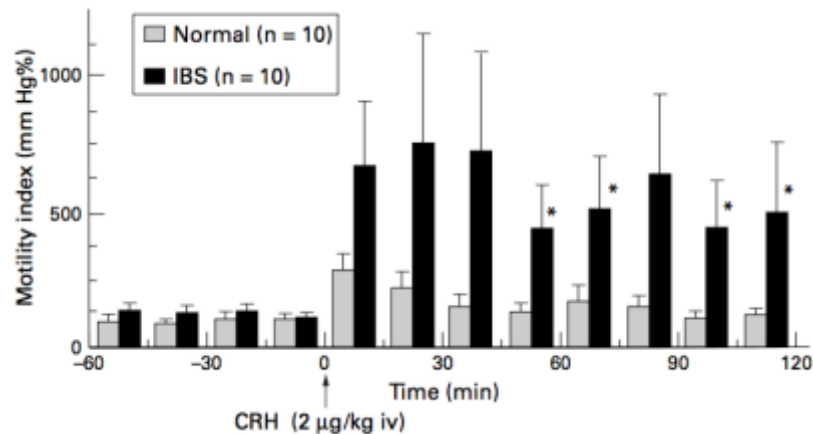


Figure 25. Colonic Motility After Administering CRH in IBS Patients vs. Controls. CRH resulted in increased descending colonic motility in both groups and the effect was significantly greater in IBS patients. Figure taken from (Fukudo et al., 1998).

Increased plasma ACTH levels are indicative of HPA axis dysregulation. IBS patients that demonstrated an exaggerated stress response illustrated via increased ACTH and cortisol levels following CRH infusion also had increased levels of pro-inflammatory cytokines IL-6 and IL-8. IL-6 is a potent HPA activator and increased levels in IBS patients could be a possible link to enhanced HPA responsiveness seen in these patients (Dinan et al., 2006). IL-6 and expression of its receptor in peripheral nerves, dorsal root ganglia, and the spinal cord, has also been shown to be increased during pain episodes (De Jongh et al., 2003) suggesting a possible role in IBS patients' increased pain perception. These results further demonstrate the exaggerated stress response and resulting intestinal motility abnormalities and visceral hypersensitivity in IBS patients.

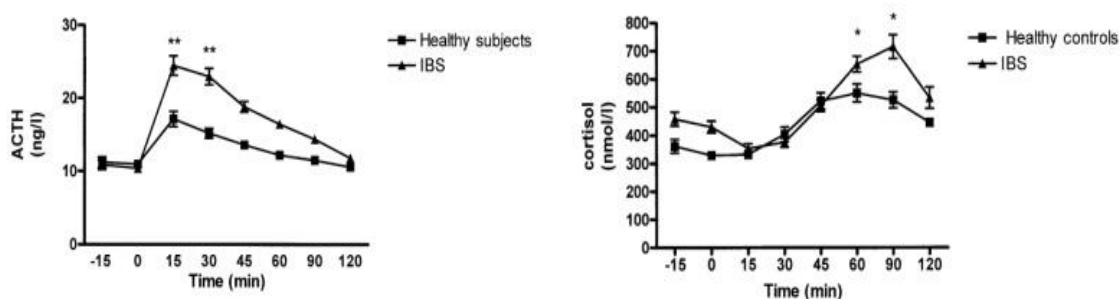


Figure 26. Increased ACTH and Cortisol Levels Following CRH Infusion in IBS Patients vs. Control. IBS patients had a significantly higher increase in ACTH (left) and cortisol (right) levels after CRH infusion compared to controls. Figures taken from (Dinan et al., 2006).

In addition to increased visceral hypersensitivity and increased colonic transit, CRH has been implicated in increased intestinal permeability. CRH receptors type 1 and type 2 have been found in the ileum and colon. Their ligand-specific activation results in increased intestinal permeability, mimicking the effects of stress and symptoms found typically in IBS patients (Larauche et al., 2009). IBS patients, specifically IBS-D patients, have increased intestinal permeability and this abnormality is even more pronounced in IBS patients without a prior history of gastrointestinal infection (Dunlop et al., 2006). Inflammation and altered mucosal permeability has been mainly associated with postinfectious-IBS (patients in which IBS occurs after a gastrointestinal infection; i.e. bowel habits never return back to a normal baseline) suggesting that nonpostinfectious-IBS patients have a similar underlying pathophysiology mechanism. Another study found the same results in all IBS patients when measured as lactulose/mannitol

ratios. Increased lactulose/mannitol ratios indicated the presence of increased intestinal permeability. This study also found that increasing intestinal permeability correlated with increasing symptom severity in IBS patients as determined by functional bowel disorder severity index (FBDSI) scores (Zhou et al., 2009).

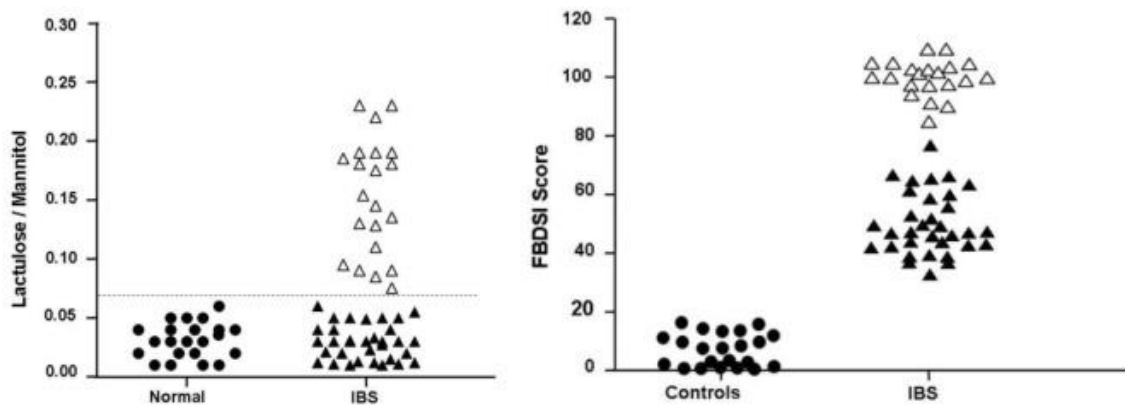


Figure 27. Increased Intestinal Permeability in IBS Patients. IBS patients have increased intestinal permeability in the small intestine demonstrated by the increased lactulose/mannitol ratios (left). Increasing intestinal permeability correlated with increasing severity of IBS symptoms using FBDSI score (right). Figures taken from (Zhou et al., 2009).

IBS patients also exhibit an increased basal level of norepinephrine in the blood and exaggerated motor and sensory responses to controlled stress. These stressors include fear, aggression, unexpected environmental changes, social isolation, and other pathological conditions (O'Malley et al., 2011). In a study assessing stress mediator levels before, during, and after stress, IBS patients

demonstrated higher ratings for stress, a significant increase in CRH and ACTH levels during stress, and had an increased basal level of norepinephrine. The stress delivered to patients and controls in this study was acute mental stress via the Stroop test and the results illustrated the exaggerated neuroendocrine response found in IBS patients (Posserud et al., 2004). Another study found that urine catecholamines were higher both in the morning and afternoon in women with IBS, along with increased epinephrine and cortisol (Heitkemper et al., 1996). Increased cortisol levels have been found in female IBS patients in another study, especially upon waking in the morning, however other studies have showed conflicting results when taking into consideration patients who have undergone emotional abuse (Sugaya et al., 2015).

Stress has very important implications in GI function in both healthy individuals and patients with IBS. IBS patients have often presented with stress axis dysfunction and exaggerated response to stress which have exacerbated their symptoms. Because stress is a daily part of life and unpredicted events are bound to occur in one's lifetime, finding ways to cope are crucial in maintaining healthy gut function. Mechanisms of coping with stress should be incorporated into treatment plans for IBS patients stress can either cause or compound their symptoms and their symptoms can feedback and cause even greater stress, creating a harmful cycle. The table below summarizes stress-induced physiologic changes in IBS.

Function	Findings in IBS vs. Controls
GI Motility	<ul style="list-style-type: none"> • Suppressed antral and small bowel motor activity and enhanced colonic motor activity
Visceral Perception	<ul style="list-style-type: none"> • Decreased rectal non-painful and pain thresholds to distension and electrostimulation during psychological stress in IBS but not controls • Higher stress, anxiety, and anger ratings in IBS vs. controls
Intestinal Permeability and Secretion	<ul style="list-style-type: none"> • Increased SI and colonic permeability demonstrated in IBS but not measured in response to stress • Net water flux significantly lower in healthy women with moderate stress compared to those with low stress • Chloride secretion was lower and albumin was higher in moderate stress vs. low stress but not statistically significant
Autonomic Tone	<ul style="list-style-type: none"> • Increases in blood pressure and heart rate shift to lower cardiosympathetic/vagal balance after mental stress in IBS and controls but no group differences
HPA axis	<ul style="list-style-type: none"> • <i>Increased basal levels of cortisol in IBS vs. controls</i> • Two studies show increased HPA axis response and one shows blunted response to hormone stimulation in IBS vs. controls • Most studies report lack of a response to a meal and/or mental stressor in IBS • HPA axis response varies depending on the type of physical stressor

Table 7. Stress-Induced Differences in IBS vs. Controls. Results show variance between studies, but generally stress results in different body function and responses for IBS patients compared to controls. IBS patients have suppressed small bowel activity but enhanced colonic activity. They also have decreased pain thresholds to visceral pain, increased anxiety, stress, and anger, increased HPA axis activation, and increased basal cortisol levels. Table modified from (Chang, 2011).

EFFICACY OF PSYCHOLOGICAL TREATMENTS

Due to the multifactorial underlying pathomechanisms in IBS, the role of stress, environmental factors, and co-morbidities with other disorders, the best clinical management of patients with IBS often involves multiple treatment modalities aiming to achieve symptom relief. Pharmacological treatment and dietary intervention often yield only partial symptom remission. Therefore, it is almost self-evident that treatment of a FGID such as IBS warrants a broad range of interventions, including specific management of the predominant GI symptoms (such as abdominal pain, bloating, and diarrhea or constipation) and a change in lifestyle and coping skills. Various treatment options now also include psychological interventions to supplement immediate symptom relief strategies. These improvements of patient care are hypothesized to be due to modulation of the stress response, ANS balance restoration, and changes in brain activation pattern in response to visceral stimuli (Koob and Heinrichs, 1999), though conclusive scientific evidence of this is currently limited. The three categories of psychotherapy with empirical evidence are: cognitive-behavioral therapy (CBT), psychodynamic therapy, and hypnotherapy (Blanchard et al., 2007). Other techniques include relaxation exercise and mindfulness meditation (Sinagra et al., 2012). Programs regarding long-term implementation of self-management have also been studied. Psychological interventions, at both cognitive and

behavioral level, have been found to increase symptom relief in both short-term and long-term follow ups, three months and one year respectively (Singara et al., 2012). The following section will review the results of different psychotherapies observed in clinical trials.

Cognitive-Behavioral Therapy

Cognitive-behavioral therapy (CBT) has been proven to decrease IBS symptoms and improve the mental health of the IBS patient. It is the most studied of the psychotherapies for IBS. The CBT model involves the relationship between situations, thoughts, behaviors, physical reactions and emotions and patients learn to recognize the patterns and intervene when necessary. A visual representation of the model focused around IBS symptoms is shown in the figure below.

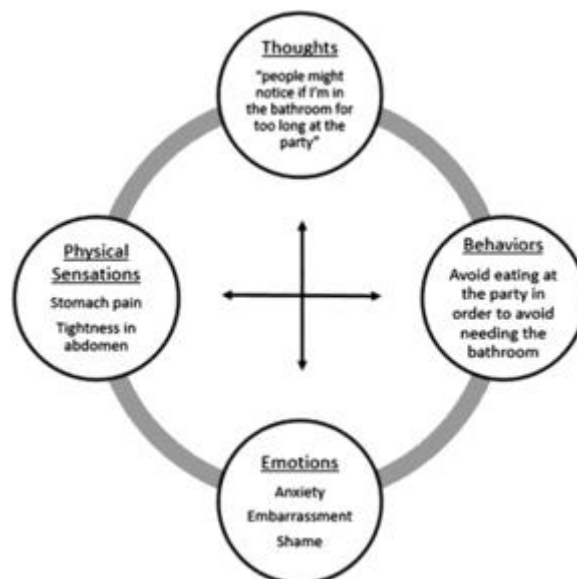


Figure 28. Hypothetical CBT Model for IBS Patient. The CBT model centers around the relationship between situations, thoughts, behaviors, physical reactions, and emotions. For an IBS patients, physical sensations may lead to avoiding social situations involving food causing isolation, embarrassment and shame. The stress induced by these thoughts and feelings may exacerbate symptoms. Figure taken from (Ballou & Keller, 2017).

The CBT model for treating IBS has three major components: psychoeducation about the stress response and its relationship to GI symptoms, building insight into cognitive and behavioral responses to IBS symptoms and/or fear of symptoms, and modifying those responses to decrease distress related to IBS and physical reactivity to stress (Ballou & Keefer, 2017).

An early study followed 25 IBS patients receiving CBT and 20 in the waiting list control group. The experimental group received eight 2-hour group sessions over a period of three months. These patients had significantly reduced abdominal complaints compared to the control group. In addition to GI symptom relief, patients in the treatment group had an increase in successful coping strategies and decrease in avoidance behavior. These outcomes were continued in long-term follow-up averaging about 2.25 years later (van Dulmen et al., 1996). In another study with female FBD patients, CBT was found to be more effective than educational (EDU) sessions alone over a 12-week long period consisting of weekly hour long sessions with the same therapist (Drossman et al., 2003).

CBT vs. EDU		
CBT group (n = 118)	EDU group (n = 50)	P
0.51 (0.01)	0.43 (0.02)	0.001
73/100 (73.0)	19/46 (41.3)	0.0002

Figure 29. Outcome Score for CBT vs. EDU Group. CBT had significantly increased benefit compared to educational sessions alone with a p-value of 0.001. Outcome score is a composite of four clinically relevant outcome variables: satisfaction with treatment, IBS-QOL, global well-being, and McGill Pain Questionnaire. Figure taken from (Drossman et al., 2003).

When CBT is administered in addition to traditional pharmacological therapy, the effects were greater than pharmacological treatment alone. One study combined CBT with mebervine, an antispasmodic drug used to treat IBS. The combination therapy produced greater symptom relief with a reduction in total symptom severity scale (SSS) by 37 points and a decrease in global outcome score by 14.4 points. This improvement persisted even six months after treatment, but the improvement was reduced after 12 months. Work and social adjustment improved with CBT as well, which continued 12 months after treatment (Kennedy et al., 2005).

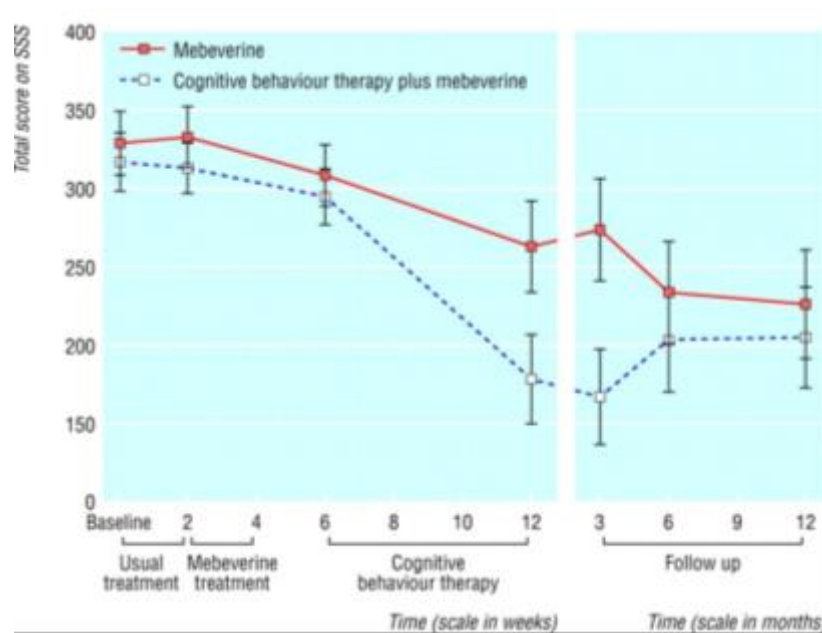


Figure 30. Mean Scores on IBS Symptom Severity Scale. Treatment effect of CBT on total symptom severity scale and global outcome. CBT combined with mebeverine produced greater symptom relief than mebeverine alone, though the effects were less pronounced 12 months after treatment. Figure taken from (Kennedy et al., 2005).

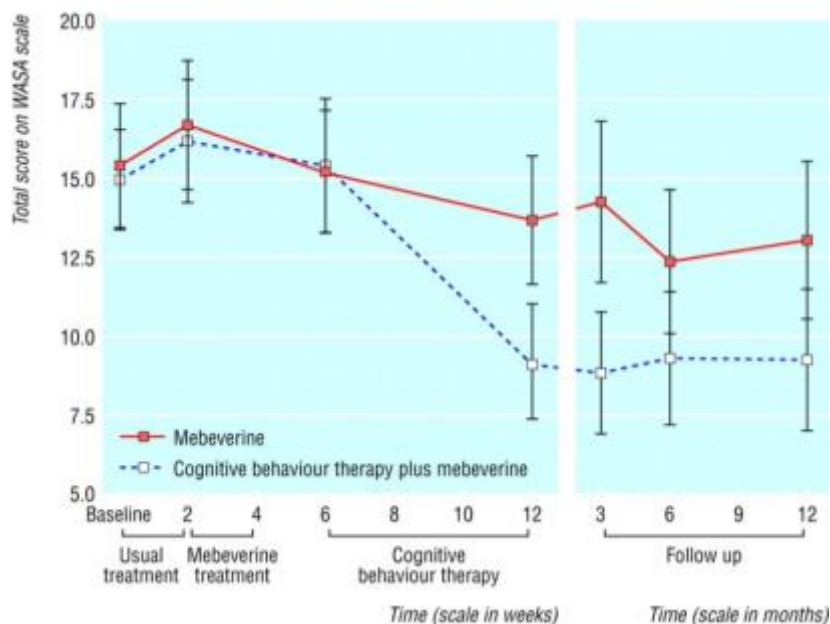


Figure 31. Mean Scores on Work and Social Adjustments Scale. CBT reduced work and social adjustment scale score by 3.4 points over one year. The effect declined overtime but scores were still reduced at 12 months. Figure taken from (Kennedy et al., 2005).

Due to the decline in efficacy, “booster” therapy sessions have been suggested to maintain initial improvement (Kennedy et al., 2005). These results were again replicated using the ROME-II scale to evaluate IBS symptom severity in a case study. IBS patients were separated into medical treatment alone and medical treatment plus CBT groups. The medical treatment consisted of loperamide, lomotil, dimethicon, metoclopramide, amitriptyline, which were prescribed by the patients’ gastroenterologists. Both groups were assessed by the ROME-II for IBS physical symptoms and the SCL-90-R questionnaire to evaluate mental health and psychological symptoms both pre- and post-treatment. The scores did not significantly differ pre-treatment, however at post-treatment, the intervention group showed significantly superior scores (p -value < 0.001). CBT administered alongside prescribed pharmacological treatments produced greater symptom relief and improved mental health in IBS patients, further validating the claim that combination therapy is more effective (Mahvi-Shirazi et al., 2012).

Stages	Group	Mean	SD	Lewin test		Value of <i>t</i>	df	Value of <i>p</i>
				F ratio	<i>p</i>			
Pre-test	Case	10.85	2.13	1.238	0.271	0.089	48	0.930
	Control	10.80	1.78					
Post-test	Case	4.00	1.83	2.527	0.118	6.900	48	0.001
	Control	8.10	2.24					
Pre-test and post-test	Case	6.85	0.30	1.672	0.202	6.860	48	0.001
	Control	2.70	-0.46					

Table 8. Rome-II Questionnaire Scores Pre-Test and Post-Test. The case group is IBS patients receiving CBT and standard medical treatment while the control group is IBS patients receiving medical treatment alone. Scores were similar between the two groups pre-test and then were considerably reduced for the case group post-treatment showing statistically significant results at a p-value < 0.001. Table taken from (Mahvi-Shirazi et al., 2012).

Although CBT has been proven to provide symptom relieve and improve the mental well-being of patients, it has thus far not shown demonstrable effects on the perception of pain. CBT does improve gastrointestinal, visceral and psychiatric symptoms but did not reduce the patients' perception of pain in a recently conducted study using barostat measurements to determine actual and perceived rectal pain both with and without CBT. This seems to suggest that the effect of CBT is more central rather than a direct alteration of visceral afferents of the gut. Symptom relief arises most likely from improved psychological coping by the patients, which in turn results in reduced stress (Edebol-Carlman et al., 2017), a factor that has been implicated in central sensitization as discussed in the previous section.

Psychodynamic Psychotherapy

Psychodynamic psychotherapy is an umbrella term for treatment modalities that operate on a continuum of supportive-interpretive psychotherapeutic interventions. Interpretive interventions aim to enhance patient insight into repetitive conflicts contributing to patients' problems. Supportive interventions aim to strengthen the abilities inaccessible to patients due to stress or that have not developed sufficiently in their lifetime (Leichsenring & Leibing, 2007). The most interpretive is insight-enhancing interpretation while the most supportive techniques include advice, praise, and affirmation. Falling in the middle of the spectrum are confrontation, clarification, and empathic validation (Leichsenring et al., 2006). Psychodynamic therapy also includes interpersonal therapy, a type of therapy geared towards helping individuals solve dilemmas or problems in their relationships and family life. When assessing psychodynamic therapy specifically in the realm of interpersonal problems, researchers found that interpersonal problems led to longer disease durations, and change in interpersonal problems led to change in pain mediated by changes in psychological distress. Change in interpersonal problems was a predictor of improved health status in a long-term (fifteen-month) follow up (Hyphantis et al., 2009).

With respect to IBS, the aim of psychodynamic psychotherapy is to help the patient identify problem areas in their relationships and understand how it affects

their bowel movements. As a result, the patient is helped to make changes to improve emotional status and relationships (Guthrie & Whorwell). There are relatively few studies with data on psychodynamic therapy, but those few contain convincing data on efficacy in IBS symptom management and mental health. The first study to test the effects of psychotherapy on IBS patients was conducted by Svedland et al., 1983. 101 patients received medical therapy with or without psychotherapy for a period of three months. During the treatment period, symptom improvement was greater in the group that received psychotherapy along with medical treatment compared to the control group which received only medical treatment. In a one year follow-up, improvement continued in the psychotherapy group while symptoms recurred in the control group back to the pre-treatment initial state (Svedland et al., 1983). Another study by Guthrie et al., 1991 confirmed these results with a similar sized sample group of 102 IBS patients. 53 were placed in the treatment group and 49 in the control. There were no significant differences between the two groups in terms of age, social class, marital status, severity or duration of IBS, and proportion with psychiatric diagnoses. All the patients had received six months of standard medical treatment prior to the beginning of the study which they continued during the study. The experimental treatment group received dynamic psychotherapy where their bowel and psychiatric symptoms were assessed and their feelings about the illness and emotional problems were explored. They had one initial interview followed by six follow-ups and received a relaxation tape to use regularly at

home. At three months, the treatment group displayed a significantly improved total severity score for their IBS symptoms, and their own rating of their symptoms showed significant improvement as well. The treatment group also exhibited significantly improved anxiety and depression scores and changes in psychiatric symptoms were highly correlated with changes in bowel scores. These improvements were maintained even at a one year follow-up. Psychiatric treatment was also associated with a significant decrease in outpatient visits during that year.

An interesting discovery in this study was that patients who were aware of stress or psychiatric symptoms relating to their pain showed symptom improvement. These patients have discernable episodes of pain and when they recognized these episodes were caused by stress, anxiety or depression, were amenable to improvement via psychiatric treatment. On the other hand, patients who received psychiatric treatment but had chronic pain with no discernable episodes did not show improvement (Guthrie et al., 1991). This seems to suggest that an awareness of psychology and its effect on body functions plays an important role in a chronic condition with a pain component such as IBS. This represents a clinical manifestation of concepts explored in the previous section and provides further evidence regarding the benefits of psychiatric treatment modalities and educating patients on coping skills.

Hypnotherapy

Hypnotherapy involves the induction of the patient into a state of relaxation or trance and then making suggestions on improvement in their condition. Gut-directed hypnotherapy (GHT) is a specific type of therapy aimed at normalizing gastrointestinal function. The first two sessions are geared towards getting the patient acquainted with the hypnosis process. Focus on the gut is introduced from the third session onward and patients receive audios to take home and practice with (Whorwell, 2005). Treatment usually lasts for 7-12 sessions in which patients are led through scripted gut-focused imageries and hypnotic suggestions in each session (Ballou & Keefer, 2017). There are currently two standardized hypnotherapy protocols: the Manchester approach (Gonsalkorale, 2006) and the North Carolina approach (Palsson, 2006), which last twelve and seven weeks, respectively.

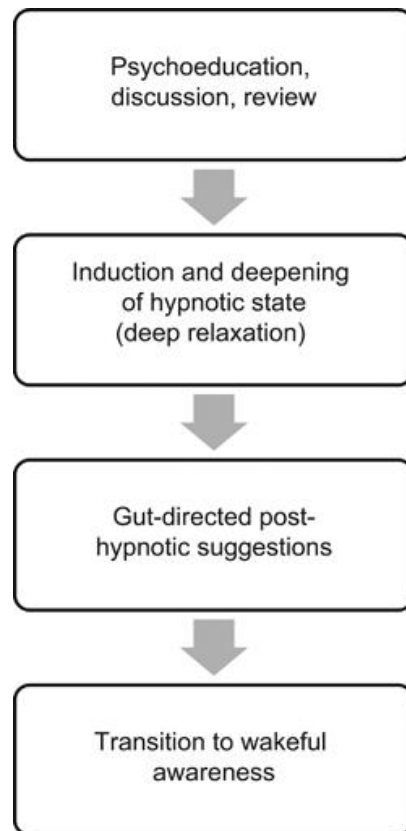


Figure 32. Gut-Directed Hypnotherapy. The first two sessions involve educating and assisting the patient with the hypnotherapy process and inducing a hypnotic state. The next sessions involve induction and deepening of the hypnotic state followed by scripted gut-directed suggestions and finally a transition to wakeful awareness. Figure taken from (Ballou & Keefer, 2017).

GHT has been shown to be effective in IBS treatment. A systematic review of literature regarding hypnotherapy use in IBS treatment from 1970 to 2005 showed that all studies that met inclusion criteria demonstrated improvement in of all major IBS symptoms, extra-colonic symptoms, quality of life, anxiety and depression (Gholamrezaei et al., 2006). The first controlled study testing hypnotherapy on IBS was conducted in 1984 by Whorwell's group. 30 patients

with severe refractory IBS were placed into groups with either hypnotherapy, psychotherapy, or placebo. Psychotherapy patients showed a small but significant improvement in abdominal pain, distension, and general well-being. Hypnotherapy patients showed a dramatic improvement in the same categories and additionally in bowel habits. These improvements lasted into the three-month follow-up without relapse (Whorwell et al., 1984). A follow-up study by the same group seems to suggest, however, that hypnotherapy is more effective for specific sub-groups of patients with IBS including those under the age of 50 and those with more classical cases of IBS (Whorwell et al., 1987). When assessing the durability of hypnotherapy as a treatment option it was found that its positive effects, including IBS symptom scores and extra-colonic symptoms, decrease anxiety and increase quality of life, lasted up to 5 years (Gonsalkorale et al., 2003).

Years since HT	N	Pre-HT*	Follow up*	Pre-HT/follow up†
1<2	37	283.8 (13.9)‡	161.2 (16.1)§	122.7 (95.5 to 149.8)¶
2<3	25	330.8 (18.2)	197.6 (21.4)	133.2 (94.3 to 172.1)
3<4	36	328.4 (14.1)	183.8 (16.8)	145.1 (105.8 to 184.5)
4<5	32	319.5 (16.6)	168.5 (16.9)	151.0 (107.5 to 194.5)
≥5	15	298.8 (23.3)	147.5 (18.0)	151.3 (93.1 to 209.6)

Table 9. Overall IBS Scores for Responders According to Time Lapsed After Treatment. IBS symptom severity scores were significantly diminished in

1, 2, 3, 4, and 5+ years after hypnotherapy treatment. Figure taken from (Gonsalkorale et al., 2003).

Furthermore, a large study of 1000 adult patients provided further evidence of the effectiveness of hypnotherapy in patients with treatment-refractory IBS. Again, the improvement in IBS symptom severity scores, non-colonic symptom scores and quality of life were replicated. Anxiety and depression scores fell after hypnotherapy as well. The overall scores in each category showed significant improvement as well as each of the sub-categories shown in figure 32. Overall, all sub-groups showed significant improvements, whereby improvement was preferentially observed in female patients and those patients with anxiety. The improvement of symptoms in patients with anxiety suggests (by the authors) that the mechanism by which hypnotherapy improves IBS symptoms is psychological (Miller et al., 2015).

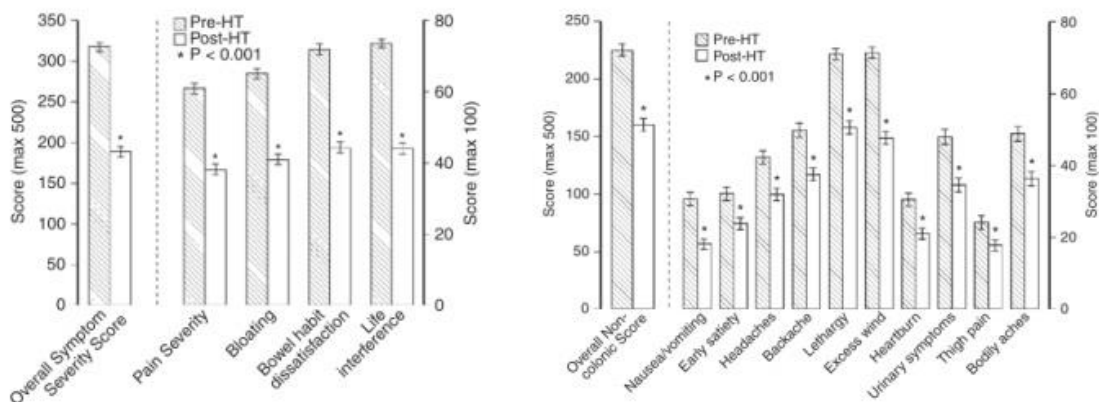


Figure 33. IBS Symptom Severity Score and Overall Non-Colonic Score Pre- and Post-Hypnotherapy. IBS score and non-colonic score significantly decreased following hypnotherapy with p-values <0.001. Each of the individual

subcategories in overall IBS symptom score and non-colonic score had significant decrease as well.

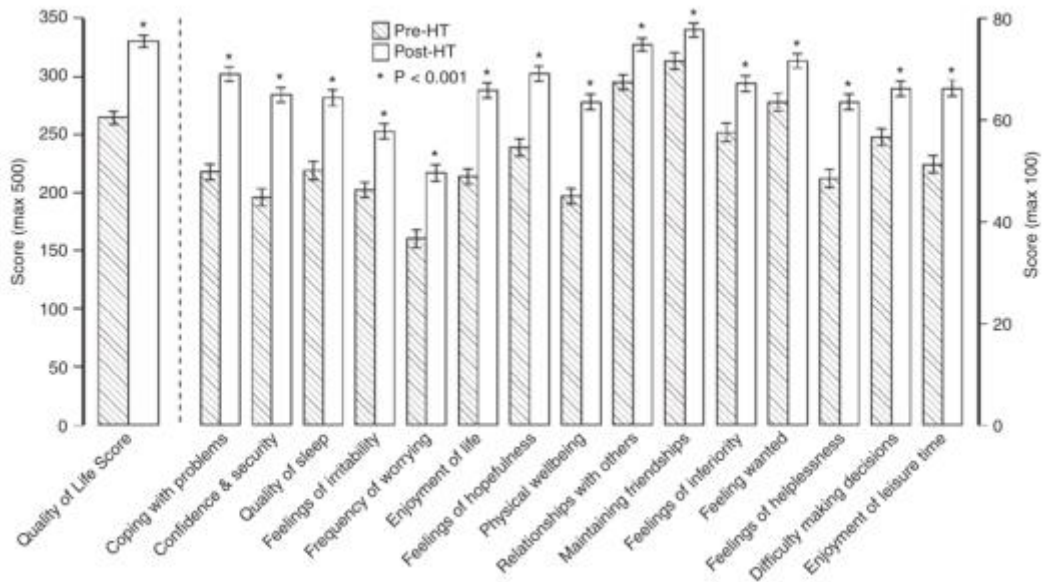


Figure 34. Quality of Life Score Pre- and Post-Hypnotherapy. Overall quality of life increased significantly with a p-value < 0.001. The subcategories of the quality of life questionnaire also exhibited significant improvement.

More standardized studies have been conducted comparing the efficacy of standard medical treatment (SMT) alone vs. standard medical treatment combined with GHT in terms of quality of life. Immediately following treatment, 60.8% of the GHT + SMT group improved while 40.9% of the SMT only group improved. In a 15 month follow-up the difference was even greater with 54.3% of GHT + SMT showing improvement vs. 25% of SMT alone. SMT, when supplemented with GHT, has a more robust effect on quality of life improvement as well as a more long-lasting one (Moser et al., 2013). The significant effect of

GHT on psychological well-being seems to suggest a psychological mechanism involved. Another study conducted by Whorwell's group assessed the effect of hypnotherapy on emotional and physiological responses. Hypnotic induction of three emotional states, excitement, anger and happiness were compared with resulting changes in colonic motility. Out of the three, happiness decreased colonic motility while anger and excitement increased colonic motility. Hypnosis alone decreased colonic motility and a decrease in colonic motility was accompanied by decreased pulse and respiratory rate. This demonstrates the importance of positive emotions on gut symptoms and the way in which hypnosis can be used as treatment (Whorwell et al., 1992).

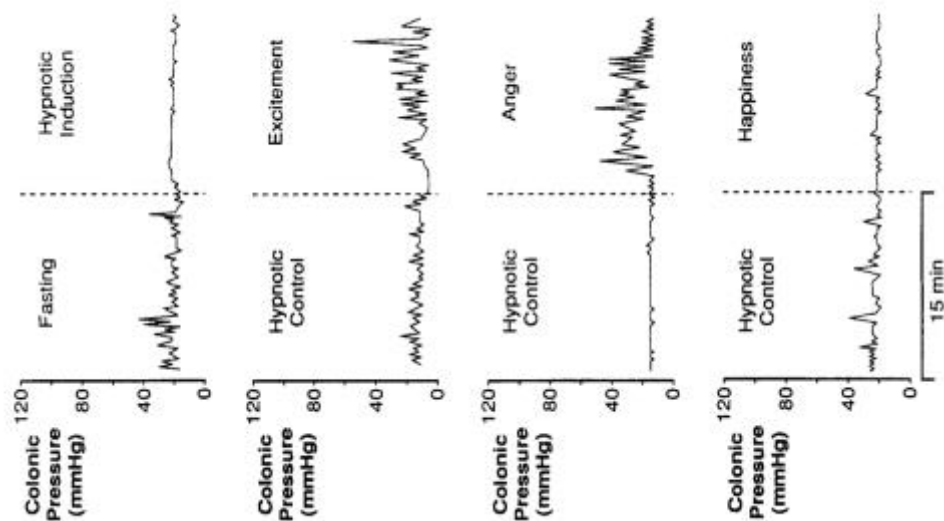


Figure 35. Distal Colonic Motility Before and After Hypnosis and During Hypnotic Induction of Three Emotional States. Hypnosis on its own decreased colonic motility while induction of excitement and anger increased colonic motility. Hypnotic induction of happiness decreased colonic motility to its lowest point. Figure taken from (Whorwell et al., 1992).

Further studies have attempted to demonstrate the direct effect of hypnosis on symptoms associated with IBS. An initial study compared the effect of hypnotherapy on disordered rectal sensitivity threshold in IBS patients. The study consisted of ten hypersensitive patients, seven hyposensitive patients, and six normal sensitivity patients. The hypersensitive patients exhibited an increased pain threshold in response to hypnotherapy compared with lower than standard threshold levels prior to therapy. Similarly, hyposensitive patients with a higher than normal pain threshold exhibited decreased pain threshold after hypnotherapy, albeit with lower significance than the hypersensitive group. The normal group remained unchanged. These results suggest that hypnotherapy plays a role in normalizing abnormal pain threshold and perception in IBS patients (Lea et al., 2003).

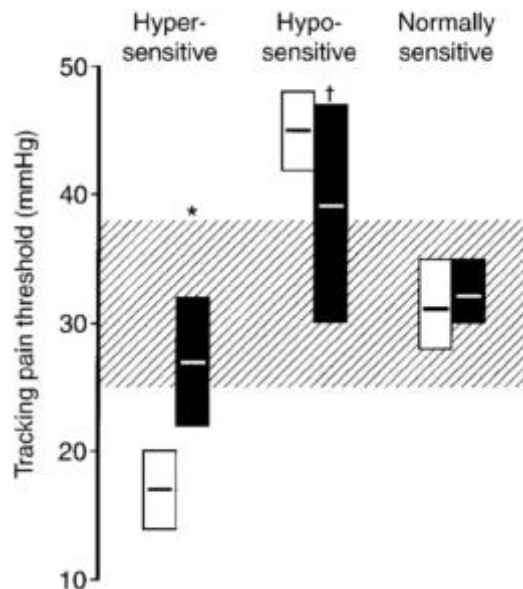


Figure 36. Pain Thresholds Before and After GHT. Pain thresholds were lower than standard in hypersensitive patients and following GHT increased back within a normal range with a p-value < 0.04. Pain thresholds were higher than standard in hyposensitive patients and declined to normal range levels after GHT with a p-value 0.19 (less significant than with hypersensitive patients. GHT did not change pain thresholds in already normal sensitivity patients. Figure taken from (Lea et al., 2003).

As increased rectal sensitivity is a hallmark of IBS and central sensitization, studies have been conducted to assess the effects of hypnotherapy on central processing of pain. In a study assessing cortical region activation, subjects were split into three groups: hypnotherapy, education, and healthy controls. Compared to healthy controls, the IBS patients had higher activation of the PFC, midcingulate cortex (MCC) and ACC. The patients who responded to either treatment, both hypnotherapy and education, had decreased activation of these regions during rectal distension. When comparing the hypnosis responders vs. the education responders, those who received hypnosis showed decreased activation of the anterior insula and the posterior insula when hypnosis responders were compared with healthy controls. This decreased activation is consistent with reduced spinal afferent input to the brain. The observed decrease was not different during the different distensions suggesting a change in central processing rather than a visceral change (Mats B.O. et al., 2013).

Overall, the three psychological therapies discussed have universally affected IBS symptoms and quality of life positively. Further research may be needed to

standardize these results as there are many compounding variables and limitations to the studies. Additionally, it may be of importance to search for a link between psychological treatment and physiological changes, a field that is currently lacking in studies and data. Although CBT is the most widely researched therapy for IBS, there is limited data on whether CBT has a physiological effect. Psychodynamic psychotherapy has the least studies of the three and needs further investigation. Interpersonal psychodynamic therapy, though, has provided a link between personal distress in relationships and more severe IBS symptoms. Hypnotherapy produced many consistent results including changes in central processing, and provides a link between emotions and GI symptoms. However, there still exists a mysticism surrounding hypnotherapy and this may be a barrier that needs to be broken down.

CONCLUSION

Understanding the brain-gut axis is crucial to learning more about the underlying mechanisms of IBS. Increased visceral sensitivity and pain perception are hallmark features of functional gastrointestinal disorder and reduction of these symptoms may be an important target of potential symptom relief. The cortical regions of the pain matrix are closely tied to emotional regulation and body homeostasis. There is repeated evidence of increased anxiety, fear, depression and stress associated with increased IBS symptoms. The biopsychosocial model suggests that these events are interrelated and cyclical in nature with one causing the other and vice versa. As such it is crucial to find ways to regulate psychological symptoms in order to alleviate the physical symptoms.

Psychological treatment of patients with IBS has been shown to provide symptom relief in the short and long term, both in the realms of IBS symptom severity and mental health scores. One link that has yet to be established, however, is the link between altered cortical processing and psychological symptoms. Further evidence for the efficacy of psychological treatment may come in this form. When IBS symptoms are improved, the pain matrix will return to a less hyperactive state. Whether psychological treatment can cause this physiological response is yet to be determined. Future research should focus on this question as it will provide even more convincing data for the efficacy of psychological treatment. Another area of interest is treatment delivery via the

internet. Psychological treatments are now being delivered through internet-based therapy. While this delivery method has been initially tested for efficacy in IBS treatment future clinical trials are needed to firmly establish this novel modality as routine treatment. As technology progresses further, internet-based psychotherapy may become a preferred method of treatment for many patients as it saves time and travel expense. Determining if internet-delivery of psychological treatments have the same effect on IBS symptom relief is another broad realm for further research.

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CURRICULUM VITAE

