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The gut and its microbiome as related to central nervous system functioning and psychological wellbeing: Introduction to the Special Issue of *Psychosomatic Medicine*

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Abstract

Accumulating evidence indicates bidirectional associations between the brain and the gut microbiome with both top-down and bottom-up processes. This article describes new developments in brain-gut interactions as an introduction to a special issue of *Psychosomatic Medicine*, based on a joint symposium of the American Psychosomatic Society and the American Gastroenterological Association. Literature review articles indicate that several psychiatric disorders are associated with altered gut microbiota, whereas evidence linking functional gastrointestinal disorders and dysbiosis has not been firmly established. The association between dysbiosis with obesity, metabolic syndrome and type II diabetes mellitus is still inconclusive, but evidence suggests that bariatric surgery may favorably alter the gut microbial community structure. Consistent with the literature linking psychiatric disorders with dysbiosis is that life adversity during childhood and certain temperaments that develop early in life are associated with altered gut microbiota, particularly the Prevotella species. Some studies reported in this issue support the hypothesis that brain-gut interactions are adversely influenced by reduced functional activation of the hippocampus as well as autonomic nervous system dysregulation. The evidence for the effects of probiotics in the treatment of C. difficile colits is relatively well-established, but effects on mental health and psychophysiological stress reactivity is either inconclusive or still in progress. To conceptualize brain-gut interactions, a holistic, systems-based perspective on health and disease is needed, integrating gut microbial with environmental ecology. More translational research is needed to examine the mental and physical health effects of pre- and probiotics, in well-phenotyped human populations with sufficiently large sample sizes.

The American Psychosomatic Society and the American Gastroenterological Association convened a symposium titled “Brain Gut Interactions and the Intestinal Microenvironment” held in New York City on September 25–26, 2015, which brought together an international, interdisciplinary group of researchers and clinicians to assess the status of this rapidly emerging field, identify gaps in our knowledge and propose necessary research to fill these gaps. Following the symposium, presenters at the symposium and interested parties who did

The authors of this article served as Guest Editors of this special issue of Psychosomatic Medicine on “Brain-Gut Interactions and the Intestinal Microenvironment.”

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not participate in the meeting were invited to submit original and review articles pertinent to the topic of the microbiome-gut-brain axis. Thirteen such articles were selected by peer review to be published in this special issue of *Psychosomatic Medicine*.

The first article by Aroniadis et al. [1] is a white paper summarizing the information presented at the aforementioned symposium and gives an comprehensive overview of the current evidence supporting a role for the intestinal microbiome in the pathogenesis of medical and psychiatric disorders. The review highlights the bidirectional communication between the brain, the gut and its microbiome, and emphasizes the importance of early life events in programming this interaction in ways that affect the life of the individual. It briefly reviews the evidence supporting a role for pre- and probiotics and for fecal microbial transplantation in treating dysbiotic states. The overview concludes by highlighting the challenges and barriers to advancing our understanding of brain-gut microbiome interactions in health and disease.

The role of alterations in gut microbial composition ("dysbiosis") in the pathophysiology of inflammatory and functional gastrointestinal (GI) disorders has been a topic of great interest to Gastroenterology. Sundin and co-authors [2] review this topic and conclude that while evidence for dysbiosis has been reported in some studies when comparing patient populations to healthy controls, and in subsets of patients, no uniform disease pattern and no evidence for causality of gut microbial signaling to the brain has emerged so far. For example, subsets of IBS patients that exhibit identical symptoms have been reported to display normal or abnormal gut microbial composition across different studies. Several factors could explain the heterogeneity of reported results, including patient selection, site-related differences in collection, analytical parameters, dietary differences and heterogeneity of patients based on gastrointestinal motility and secretion, duration of disease and genetic factors. Finally, observed dysbiotic states in functional GI disorders may not be a primary factor in the pathophysiology, but may be secondary to altered autonomic nervous system outflow to the gut.

Fecal microbial transplantation (FMT) was already used in Traditional Chinese Medicine some 1,500 years ago to treat gastrointestinal disorders. However, it has become increasingly popular in modern medicine since the first report about its effectiveness in pseudomembraneous colitis was published in 1958. Brandt [3], one of the pioneers in the use of fecal microbial transplantation in the treatment of C. difficile colits, provides an overview of the use of fecal microbiota transplant in the treatment of this serious disease, the only gastrointestinal disorder for which such therapy has proven safe and highly effective to date. Important issues to be addressed with microbiota transplant are the long-term safety of the treatment, the possibility of obtaining similar therapeutic effects with a consortium of gut microbes, and the mechanisms underlying its therapeutic benefits.

Based on mouse models, and microbiota transplant experiments from obese individuals into germfree mice, there is strong evidence for a role of the gut microbiome in obesity and metabolic diseases, in particular metabolic syndrome and type II diabetes. There is also good experimental evidence to show that gut microbial metabolites such as short chain fatty acids can stimulate the release of satiety hormones from enteroendocrine cells in the distal small

bowel. But as pointed out in the review article by de Clercq and co-authors [4], reported findings in obese subjects are inconsistent and there is no clear evidence for causality between gut microbial composition and energy homeostasis in humans. For example, while FMT from obese humans to germfree mice, and between mice of different body weight strongly supports such a role, few therapeutic applications of this knowledge to treat human obesity have been reported to date.

Sanmiguel and colleagues [5] report results from a study performed in obese women undergoing bariatric surgery, evaluating the effects of this intervention on body weight and BMI, ingestive behavior and gut microbial composition. Interestingly, the observed reductions in BMI, food intake and hedonic eating were associated with several microbial genera, and 5 bacterial genera discriminated between pre- and post-surgery results. Even though these results do not prove causality between gut microbes and ingestive behavior, they clearly demonstrate the involvement of certain gut microbes in surgery-induced weight loss.

Early life stress associated with separation of infant monkeys from the mother is a major psychological stressor and has previously been shown to be associated with transient reductions in Lactobacilli and Bifidobacteria. While these earlier observations were obtained with culture techniques, Amaral and co-authors [6] examine how microbiota community composition is affected in infant monkeys following their separation from the mother and assignment to groups of peers. The gut microbiota of group members were more similar to each other than those between groups. The major taxa of the infant gut microbiota differed from that of very young infants still breastfeeding, and were similar to those observed in adult monkeys, with a predominance of Prevotella species.

The existence of bidirectional interactions between the brain and the gut microbiome is well supported by studies performed in rodents, with limited evidence coming from human studies. There is general agreement that the early life period is crucial for the programming of both the gut microbiome and the brain. Based on this model, Kim et al. [7] aimed to test the hypothesis that temperament (composed of individual trait tendencies in reaction to emotional stimuli) is associated with the composition of the gut microbiome in a small group of healthy Korean women. Consistent with previous reports, they identified two “enterotypes” based on the prevalence of the taxa Bacteriodacea (enterotype I), and Prevotellacea (enterotype II), respectively. The temperament dimensions Novelty Seeking and Reward Dependence differed between the two enterotypes, being lower in the Prevotella predominant enterotype. Though not conclusive, these findings are consistent with the concept of an interaction between the gut microbiome and the brain, possibly shaped early during development of the brain and gut microbiome.

K. Tillisch and co-authors [8] provide evidence for an association between brain structure, white matter connectivity, functional brain and emotional responses to a negative emotional task and gut microbial community structure. Structural and anatomic brain parameters accurately classified a Prevotella-predominant and a Bacterioides-predominant cluster. Subjects in the Prevotella-predominant cluster showed more negative emotional responses to viewing negative images, and this subjective response was associated with a reduced

functional activation of the hippocampus, a brain region exerting inhibitory influences on the emotion generating circuits in the brain (among other critical neurocognitive functions). Even though the number of participants in the study was relatively small, the findings are consistent with an important association between gut microbial features and brain structure and function.

In rodent studies, the ingestion of certain probiotic strains has been shown to positively affect brain function and behavior, and human studies have shown a reduction of the stress response, leading to the concept of “psychobiotics”. Möllerand colleagues [9] aimed to test the hypothesis that short term intake of a multi-strain, multi-species probiotic affects resting and stress stimulated cardiovascular response in healthy subjects. This well designed RCT did not confirm the hypothesis, as the probiotic group did not show significant differences in any of the endpoints, including resting or stress-induced cardiovascular function, recovery from stress, or psychological reactions to stress. Possible explanations for the negative results include the nature and short duration of the stress paradigm used in the study.

Two of the pioneers of brain-gut microbiome research, Dinan and Cryan, reviewed the literature on this topic as it relates to psychiatry [10]. They emphasize that the great majority of existing studies have been performed in experimental animals with only a small number of clinical studies addressing the translational relevance. One exception may be four recently published studies (including one of their own) in patients with clinical depression, all of which have shown alterations in the gut microbiome. In two of these studies a fecal microbiota transplant into either germ free or antibiotic-treated mice resulted in altered emotional behaviors in the animals. However, the cause for the dysbiotic state in these patient populations remains to be determined. As depression-like behavior develops in mice undergoing chronic stress, and this behavior can be transferred to germ free mice, it is conceivable that the observed dysbiosis in humans with depression is the consequence rather than the cause of altered stress responses.

Michels and co-authors [11] report results from a study performed in 113 healthy children to determine possible associations between emotional measures, perceived stress, biological markers of stress and gut inflammation and fecal microbial metabolites (short chain fatty acids). They found significant associations between self-reported emotional problems and several short chain fatty acids, and a negative correlation between parasympathetic tone and valerate levels. Neither stress measures, hair cortisol, or short chain fatty acid levels were correlated with fecal calprotectin levels. This study demonstrates that chronic stress can affect gut microbial metabolite levels, presumably mediated by sympathetic nervous system effects on the gut. Such gut microbial measures are stronger biological correlates of chronic stress than cortisol levels or immune activation in the gut.

In a study by Hemmings et al. [12] results from a small study are reported comparing gut microbial differences between PTSD-affected individuals and a comparison group of asymptomatic trauma-exposed individuals. While there was no detectable difference between the groups in terms of several microbial diversity measures, they identified three phyla that distinguished the PTSD affected individuals. A decrease in the abundance of these taxa was associated with higher subjective PTSD scores.

This special issue of *Psychosomatic Medicine* concludes with a conceptual paper by Maier and al'Absi [13] proposing a holistic, systems-based view of human health, in which gut microbial and environmental ecology are essential components. The authors propose that similar to the paradigm shift that occurred with the introduction of the biopsychosocial model, the proposed ecological framework will usher in another major change in our understanding of human health and disease. Such a change will require novel, more integrative treatment approaches to chronic disorders not only of the gut but of all aspects of body and mind.

In summary, this special issue provides an overview of the emerging understanding of the interactions between the mind, the brain, the gut and its microbiome. The evidence provided here supports both top-down and bottom-up modes of communication between the gut microbiome and the brain, although more research is needed to demonstrate causality in these interactions. The articles provide support for a role of the brain in modifying the community structure of the gut microbiota, a fact that is often neglected in the literature. The science of brain-gut microbiome interactions is a new area of research in a field that is rapidly evolving, with progress driven largely by technological and analytical advances. Following the pioneering initial studies performed in mouse models, the field most importantly needs well-designed clinical studies performed in well-phenotyped human populations. In order to clearly identify a role of the gut microbiota, larger studies, using standardized quantification and characterization of both gut microbial community structure as well as microbial metabolite levels in stool and plasma are needed.

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Abbreviations

BMI	body mass index
FMT	fecal microbial transplantation
GI	gastrointestinal