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*EDITORIAL*

# The psyche and the gut

Paul Enck, Ute Martens, Sibylle Klosterhalfen

Paul Enck, Ute Martens, Sibylle Klosterhalfen, University Hospitals Tübingen, Department of Internal Medicine VI, Psychosomatic Medicine and Psychotherapy, Germany
Correspondence to: Professor Paul Enck, University Hospitals Tübingen, Department of Internal Medicine VI, Psychosomatic Medicine and Psychotherapy, Osianderstr. 5, Tübingen72076, Germany. paul.enck@uni-tuebingen.de
Telephone: +49-7071-9387374 Fax: +49-7071-9387379
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## Abstract

Research on gut-brain interactions has increased over the last decade and has brought about a number of new topics beyond "classical" subjects, such as "stress" and "personality", which have dominated the psychosomatic literature on gastrointestinal disorders over the past century. These novel topics include brain imaging of intestinal functions, placebo responses in gastroenterology, learning of gastrointestinal symptoms, quality of life in patients with intestinal complaints, and psychotherapy and familial aggregation of functional intestinal disorders. Currently, these new topics appear with a frequency of 1% to 3% in leading gastroenterological journals, either as data presentation or review papers. Increasing focus underlines the importance of enhancing our understanding on how the psyche and the brain communicate in order to better meet the needs of our patients.



**Key words:** Gut-brain interactions; Psyche; Functional bowel disorders; Irritable bowel syndrome

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## THE PSYCHE AND THE GUT

While the relationship between the psyche and the gastrointestinal tract is reflected in many different medical and scientific topics that address the gut-brain (or brain-gut) axis, this relationship is clearly underrepresented in the history (albeit short history) of the *World Journal of Gastroenterology* (*WJG*). Among the 600 or so articles published in the current volume (Vol. 12, 2006) of the *WJG*, only 7 (approx. 1%) addressed different psychological aspects of gastrointestinal diseases, such as quality of life[1] and psychological impact of chronic gastrointestinal diseases[2], mental problems with hepatitis[3], family occurrence[4] and other psychological aspects[5] of functional bowel disorders. Only 1 paper reported experimental data on brain imaging[6] and only one review paper addressed the psycho-physiological aspects of visceral pain[7]. In comparison, the respective numbers from other journals, such as Gastroenterology and Gut (both approx. 3%), indicate a much higher interest in and devotion to psychological aspects of gastrointestinal (GI) functions and disorders, and the range of reported relationships between the gastrointestinal tract and the brain is much broader. This certainly must and will change with upcoming issues and volumes of the *WJG*.

## ASPECTS OF BRAIN-GASTROINTESTINE COMMUNICATION

The following list of topics, which is certainly far from being complete, represents various aspects of involvement of the psyche in bowel functions and disorders, many but not all of which are related to functional bowel diseases.

### *Psychology and inflammatory bowel disorders*

For many years, inflammatory bowel diseases (e.g., Crohn's disease, ulcerative colitis) have been regarded as among the best examples of truly "psychosomatic disorders", i.e., disorders in which the psyche may play a major role in the pathogenesis of symptoms. This is the case despite the fact that the exact biological nature of all inflammatory bowel diseases (IBDs) has still not been identified and there is serious concern that IBD may not represent a clinical entity at all.

Based on such assumptions, psychotherapeutic approaches with IBD have dominated the discussion for many years, until these approaches failed to show clinical improvement above the rate of spontaneous remission of symptoms[8]. This seemed to have ended this discussion until recent progress in our understanding of how environmental stressors, on the one hand[9], and the personal and genetic background of the individual, on the other hand, can modulate intestinal disease activity *via* psycho-immunologic mechanisms. This has brought about a new understanding of the role of psychological factors, especially stress, in inflammatory and non-inflammatory bowel diseases[10].

The fluctuating interest of the scientific community in

psychological aspects of inflammatory bowel diseases over the last 50 years is well documented in the psychosomatic literature[11], and demonstrates that many of the psychological topics investigated depend on novel insights in pathophysiology and therapy in gastroenterology.

### Family aggregation in functional GI disorders

Functional bowel disorders of the irritable bowel syndrome (IBS) type are among the most frequent disorders in the population, as well at the level of primary care or in gastroenterological outpatient units[12]. Familial aggregation, in which several members of a family are affected by the same disease, has been noted with IBS and has raised the question of whether this reflects a genetic trait or a socially determined learning of gastrointestinal symptoms through reinforcement, e.g. from parents to their children[4,13]. Twin studies, as well as longitudinal epidemiologic surveys, have recently provided strong evidence for the latter[14].

### Stress and the gastrointestinal tract

One of the key features of the autonomic regulation of gastrointestinal functions by the enteric nervous system (ENS) is the fact that it, in part, prevents the GI tract from responding rapidly to environmental stressors and that if such stress responses occur in cases of severe distress, their consequences are excessive[15]. The central mechanisms that mediate these stress responses, *via* the central release of CRF that activates the hypothalamic-pituitary axis, have been elucidated in the past decade and may not only be responsible for functional but also for inflammatory disorders of the gastrointestinal tract[16]. Drugs (astressin) have been developed that counteract or prevent stress-induced autonomic changes[17] and may prove to be useful in the treatment of stress-related disorders such as IBD and IBS.

### Brain imaging of intestinal functions

Progress in our understanding of the contribution of central processing of visceral functions has been brought about by the recent application of brain imaging technology (positron emission tomography, PET; functional magnetic resonance imaging, fMRI; magnetoencephalography, MEG) to gastroenterology, both for the investigation of basic mechanisms, such as the cortical topography of visceral functions and the distinction between visceral and somatic pain[18] and the modulatory effects of emotions on intestinal functions[19], and for our understanding of the pathogenesis of functional bowel disorders[20] and the efficacy of medical therapy[21]. Other applications include the assessment of differences between inflammatory and functional bowel disorders[22], and the recovery of intestinal sensory functions in patients with complete spinal cord injury[23].

### Placebo responses in gastroenterology

Placebo responses in clinical trials with IBS, but also with IBD patients, have waxed and waned in recent years, presumably due to changes in the designs of clinical trials and to altered expectancies of both patients and researchers; the exact mechanisms by which placebo responses occur are still a matter of debate[24]. Brain imaging studies of the placebo response under experimental and clinical conditions have shown that different psycho-biological mechanisms are involved, including Pavlovian conditioning and signal detection[25], and a genetic trait to become a placebo responder cannot be excluded[26]. The future will require new and innovative research designs to overcome these types of problems in the development of new drugs to treat these conditions.

### Learning of GI symptoms: The example of nausea

Pavlovian conditioning and learning have been shown to be in effect with nausea-associated symptoms, such as occur with cancer chemotherapy[27], and with behavioral treatment modalities, such as latent inhibition and overshadowing, which have been shown to be effective in the prevention and reduction of anticipatory nausea and vomiting (ANV)[28]. Experimental nausea research, e.g. with motion sickness paradigms, has further explored the underlying mechanisms of NV, and have demonstrated significant racial and gender effects both in conditioned and unconditioned nausea and in the ability to profit from respective therapies[29].

### Psychological burden of food intolerances in GI disorders

Patients with functional upper and lower GI symptoms not only report nausea and eating-associated problems, such as early satiety and abdominal fullness and distension, but also food intolerances to many different kinds of foodstuff[30]. However, when tested for true food allergies, the data indicate that this only occurs in a minority of cases, and this is not different from population studies[31]. Irrespective of the nature of food intolerances, many patients must significantly restrict their diet and they experience a significant impact on their quality of life[32]. This may also have an impact on their responsiveness and compliance to other medical and psychological therapies.

However, the presence of increased concentrations of histamine, mast cells, neuropeptides, and other pro-imflammatory mediators[33] in intestinal biopsies from patients with functional bowel disorders may also indicate a pathomechanism of IBS and related diseases, which has been named "post-infectious IBS"[34]. It refers to the fact that many of these patients report a past episode of gastroenteritis that marked the onset of their bowel complaints. Patients with post-infectious IBS have been verified in prospective field studies[35] as a significant subgroup of patients. Psychological factors (e.g., stress, anxiety, depression) have been named as relevant factors in predicting who will become an IBS patient and who will not in the case of severe enteric inflammation[36].

### Psychotherapy in functional disorders

With only a few drugs available that have been shown to be effective in the treatment of functional bowel disorders[37], psychotherapy has become a major therapeutic option under many clinical conditions, especially with severely impaired patients. Psychotherapy, irrespective of the type of treatment, e.g., hypnotherapy, behavioral intervention, cognitive modulation, psychodynamic therapy, or

psychoeducative approaches, has been shown to be more effective than conventional treatment alone in most cases[38]. However, why and how many patients are motivated to accept psychotherapy, while others are not, and whether this determines the efficacy of psychotherapy has remained obscure[39].

### *Acupuncture treatment in gastrointestinal diseases*

As with psychotherapy, acupuncture has occasionally been offered to patients with functional and organic bowel disorders and has been shown to achieve variable success. When acupuncture was adequately controlled for placebo effects, with the so-called "Streitberger" needle[40], no difference in symptom improvement was found between acupuncture and sham acupuncture in patients with IBS[41]. This suggests that acupuncture effects may be placebo responses. However, when we tested changes in autonomic variability (heart rate) and neuro-endocrine control (circadian profile of salivary cortisol), it became evident that acupuncture, but not sham acupuncture, improved symptoms *via* its effects on the parasympathetic control of gut sensations and functions[42].

### *Psychopharmacology of intestinal functions*

Since many patients with IBS and IBD suffer from significant psychiatric co-morbidity, such as depression and anxiety, psychotropic drugs that have been used to treat these conditions have been found to affect the gastrointestinal symptoms as well[43]. Today it is common knowledge that serotonergic drugs, which have a central target, may elicit their beneficial effects also in the GI tract, provided the respective receptors are peripheral, due to the fact that most serotonin is released in the ENS. Antidepressant drugs such as serotonin-reuptake inhibitors (SSRIs) are therefore, in principle, able to modulate gastrointestinal functions as well[44]. It has also been shown that polymorphisms of the serotonin-transporter gene system are not only associated with significant psychiatric morbidity, but also co-determine the efficacy of drugs acting on the GI tract[45].

## THE PSYCHE AND THE GUT: A SUMMARY

The above listed topics, which have been the subject of research on gut-brain interactions over the last decade, represent only a fraction of relevant themes that need to be addressed. Some of these studies will find their way into the *WJG*, either as data or review papers, as has been happening with increasing frequency in other leading gastroenterologic journals. We need to enhance our understanding of how the psyche and the brain communicate in order to better meet the needs of our patients, both with functional disorders and those with diseases of organic origin.

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