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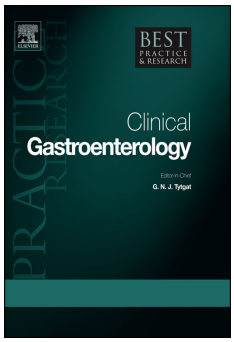

The Stomach - Brain Axis

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Gastric Physiology and Pathogenesis

The Stomach - Brain Axis

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Key words: Brain-gut interactions, stomach, functional gastrointestinal disorders, inflammation, microbiome, stress

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Abstract

The stomach has distinct functions in relation to the ingestion and handling of solids and liquids. These functions include storage of the food before it is gradually emptied into the duodenum, mechanical crushing of larger food particles to increase the surface area, secretion of an acidic enzyme rich gastric juice and mixing the ingested food with the gastric juice. In addition, the stomach 'senses' the composition of the gastric content and this information is passed via the vagal nerve to the lateral hypothalamus and the limbic system, most likely as palatability signals that influence eating behaviour. Other sensory qualities related to the stimulation of gastric tension receptors are satiety and fullness. Receptors that respond to macronutrient content or gastric wall tension influence appetite and meal related hormone responses.

The ingestion of food – in contrast to an infusion of nutrients into the stomach - has distinct effects on the activation of specific brain regions. Brain areas such as thalamus, amygdala, putamen and precuneus are activated by the ingestion of food. Gastric nutrient infusion evokes greater activation in the hippocampus and anterior cingulate. The brain integrates these interrelated neural and hormonal signals arising from the stomach as well as visual, olfactory and anticipatory stimuli that ultimately influence eating and other behavioural patterns. Furthermore, there is now good evidence from experimental studies that gastric afferents influence mood, and animal studies point towards the possibility that gastric dysfunction may be a risk factor for mood disorders such as anxiety and depression. The stomach is also not only colonised by *H. pylori* but a large array of bacteria. While there is sufficient evidence to suggest that *H. pylori* may alter caloric intake and mood, the role of other gastric microbiome for the brain function is unknown. To address this appropriate targeted gastric microbiome studies would be required instead of widely utilised opportunistic stool microbiome studies.

In summary, it is now well established that there are important links between the brain and the stomach that have significant effects on gastric function. However, the stomach also influences the brain. Disturbances in the crosstalk between the stomach and the brain may manifest as functional GI disorders while disturbances in the stomach – brain communication may also result in an altered regulation of satiety and as a consequence may affect eating behaviour and mood. These observations may enable the identification of novel therapies targeted at the gastroduodenum that positively alter brain function and treat or prevent conditions such as obesity or functional gastrointestinal disorders.

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INTRODUCTION

The gastric phase of digestion is complex. The ingestion of food stimulates gastric acid secretion and changes the motility of the stomach. The high acidity of the gastric juice helps to kill potentially harmful bacterial contamination of the ingested food. The acidity of the gastric juice also activates pepsin that helps to digest ingested peptides. At the same time the fundic smooth muscles of the stomach initially relax via a vago-vagal reflex to allow to store the ingested nutrients in the proximal stomach while the distal stomach 'grinds' the gastric content and slowly delivers the chime into the duodenum where it is sensed and duodenogastric reflexes are stimulated that alter gastric function.

Following this initial relaxation (accommodation), the tone of the proximal stomach gradually increases and the ingested food is moved towards the distal stomach. The distal part is able to crush the soft food particles (antral mill) and controls the delivery of food into the duodenum. Thus, while the stomach appears to be a simple hollow dilated muscular organ between the oesophagus and the small bowel it serves important functions. Besides the exposure to the acidic gastric juice it ensures that that the ingested nutrients are delivered into the duodenum at a rate that does not exceed the digestive capacity of the intestine [1-3].

Thus, well-coordinated gastric motor function is considered critical for the gastric phase of the digestion of food. This complex process is regulated by different and most likely redundant feedback mechanisms: The nutrient stimuli (volume and chemical properties of intraluminal nutrients) are sensed by mechosensory and chemosensory receptors. These receptors trigger either enteric (intrinsic) or vagal and sympathetic (extrinsic) pathways to regulate and control motor and secretory function sensed by specific receptors in the gut wall and initiate reflexes via either the intrinsic (enteric) nervous system or extrinsic (vagal and sympathetic) pathways, to control and coordinate gastric contractile activity [4].

Connections between the brain and the stomach: Gastric sensory functions and the cephalic phase of digestion

The digestive tract - and not only the stomach - senses the gastrointestinal content including nutrients ingested with meals in various ways. Volume or wall tension [5, 6], osmolality, acidity, and macronutrient composition represent the dominant sensory modalities [7, 8]. This sensory information is partly mediated via the enteric nervous system [9] to facilitate secretion, absorption, and motility and does not reach a level of consciousness. Awareness of digestive sensations, such as fullness and satiation, is required to regulate eating behaviour [7].

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On the other hand visualisation of food and the anticipation of eating initiates profound changes of digestive function characterised by a significant increase of gastric acid secretion and the release of a variety of gastrointestinal hormones [10, 11]. This cephalic phase is under cholinergic control [10] and thus can be blunted or even abolished by atropine or vagotomy [12].

1 ASSESSMENT OF STOMACH – BRAIN PATHWAYS

1.1 Standardised gastric distention (mechanical stimulation) to quantitate sensory function

Gastric distension has been used in numerous human studies to assess gastric sensory function. These studies assessed symptom intensities [6, 13-15] or assessed brain activity via functional Magnet Resonance Imaging (fMRI) [16, 17] or Positron Emissions Tomography (PET) [18]. The first perception of balloon distension and the maximal tolerated pressures are significantly correlated suggesting that the same mechanisms and pathways are relevant for perception and pain. Gastric pressure at occurrence of perception and the maximal tolerated pressure have been observed to be not significantly different for the different distension protocols [5]. The high correlation of pressure thresholds at first perception and maximal tolerated distension suggest a single population of gastric mechanoreceptors that mediate first sensation at low intensity stimulation and pain at intense stimulation [5].

1.2 Neuroimaging to study stomach – brain interactions

Functional neuroimaging as a methodology to assess the effects of gastric or visceral stimulation has rapidly emerged in recent years [19]. These studies allow better characterization of the relationship between the central nervous system, sensations such as hunger, satiety, and food intake. Intra-gastric administration of liquid meals revealed different brain responses as compared to mechanical stimulation with gastric balloons suggesting that the central processing of signals reflects more than just the mechanical component of nutrients in the stomach. These studies utilising functional MRI have demonstrated activation of amygdala and insula during gastric distension [19]. Thus, the amygdala – which is part of the limbic system – and the insula are involved in the perception of gastric stimulations.

The group of Tack et al used brain H_2O-Positron Emission Tomography (PET) in relation to upper functional gastrointestinal functional disorders [21]. They found that in patients with

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functional dyspepsia (FD) thresholds for discomfort in response to a balloon distension were lower as compared to controls. PET did not show activation of specific brain regions such as the periventricular anterior cingulate cortex (pACC) in patients with FD. In addition, patients lacked a dorsal pons or amygdala deactivation during distension and sham as compared to controls. Interestingly, anxiety correlated negatively with pACC and midcingulate cortex and positively with dorsal pons activity. Based upon this it was concluded that FD was correlated negatively with activity of pACC and failed to deactivate the dorsal pons during distension. In addition they failed to deactivate the amygdala during sham; this may represent arousal-anxiety-driven failure of pain modulation.

On the other hand, the brain response to gastric stimulation is not only defined by the stimulus. Genetic factors may modulate brain responses after gastric stimuli. In one study the activation of the striatal region – which plays a role in consummatory food reward, and striatal dopamine receptors are reduced in obese individuals, relative to lean individuals. This reduction is due to the presence of the A1 allele of the TaqIA restriction fragment length polymorphism. This is associated with dopamine D2 receptor (DRD2) gene binding in the striatum and compromises striatal dopamine signalling [20].

2 ASCENDING AND DESCENDING ANATOMICAL STRUCTURES AND PHYSIOLOGICAL MECHANISMS

2.1 Ascending pathways

The visceral information arising from the stomach and the upper part of the gastrointestinal tract is transmitted primarily via afferent pathways in the vagus nerve and the spinal afferent system [22]. Vagal afferents project to specific brain areas such as the solitary tract nucleus, with secondary projections ascending to the thalamus and directly to other brain structures [23-25]. These pathways are involved in arousal, homeostatic, and emotional behaviours [26] and the regions include the hypothalamus, locus coeruleus, amygdala, and periaqueductal grey. Third-order neurons project from the thalamus to the sensory cortex [23-25].

Afferents arising from the gastrointestinal system including the stomach are important in regulating eating behaviour [27]. For example the hormone ghrelin is a hunger-driving hormone originating from the gastrointestinal tract, mainly found in the mucosa of the proximal stomach [28]. Other neuropeptides such as neuropeptide Y with effects on food intake are regulated by peptide signalling originating from the gastrointestinal tract [29].

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The brain stem sensory apparatus is relevant for nausea and vomiting. Abdominal vagal afferents that detect intestinal luminal contents and gastric tone terminate in the nucleus tractus solitarius. Neurons from the nucleus tractus solitarius project to a central pattern generator, which coordinates the sequence of behaviours which coordinates emesis. These signals are also directly connected to diverse populations of neurons in the ventral medulla and hypothalamus ("vomiting center") [30-32].

2.2 Descending inhibition of afferents

The brain sends inhibitory efferent signals from the anterior cingulate cortex directly and indirectly via opioidergic, serotoninergic, and noradrenergic pathways to the dorsal horn of the spinal cord and inhibit presynaptically afferent pain signals [33, 34]. Because brain regions involved in descending pain inhibition are also implicated in the processing of visceral, attentional, and emotional information, the dispersal of inhibitory efferent messages by these structures may be mediated by cognitive, emotional, and behavioural factors.

3 INFLUENCES OF THE BRAIN ON STOMACH FUNCTION

3.1 Psychological factors and visceral afferents

Brain regions that are involved in the processing of visceral sensory information are integrated with a central neural network also known as the limbic system. The limbic system is critical for the regulation of moods and emotions [35]. It is also involved in the modulation of visceral pain perception and transmission [36]. Interestingly candidate genes such as CACNA1C (rs1006737) relevant for synaptic function appear to be associated with anatomical structures in the brain that are altered in mood disorder [37]. Thus, in humans there is evidence that genetic factors are associated with anatomical structures that are relevant for the central processing of afferents.

Anxiety scores in patients with functional GI disorders are closely correlated with symptom intensities [38, 39]. This demonstrates that central affective and cognitive processes are relevant for the processing of visceral afferents and ultimately may play a role for the manifestation of functional gastrointestinal disorders.

3.2 Experimental induction of motion-sickness

There are very limited data that have systematically assessed CNS stimulation on gastric emptying. In a recent elegant study [40], motion sickness was induced by an optokinetic drum. Volunteers rated the intensity of motion sickness. Antral contractile activity and gastric

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volume retained after a liquid nutrient meal (600 ml) were assessed by magnetic resonance imaging in healthy subjects during two different protocols. Vection significantly delayed gastric emptying. Interestingly, the antral contractile activity initially decreased immediately after onset of drum rotation followed by gradual recovery upon withdrawal of the stimulus. The severity of nausea and inhibition of gastric emptying or antral contractile activity were not significantly associated. Thus, the central stimulus of vection has a distinct effect on gastric motor function but the changes of motor function are not necessarily linked to subjective symptoms.

3.3 Sham feeding (cephalic phase) and gastric function

It is well established that nutrients in the gut stimulate gastric acid secretion and gastrointestinal motility [7]. However, sham feeding also increases gastric, and pancreatic secretion and inhibits the occurrence of an interdigestive antroduodenal motility pattern [10]. These effects were abolished by atropine. In contrast the cholecystokinin receptor antagonist loxiglumide did not attenuate pancreatic enzyme response but reduced the sham feeding induced antral motor response and the release of pancreatic polypeptide. As a consequence it is reasonable to assume that the effects of sham feeding are at least partly mediated by the vagal nerve.

3.4 Psychological stressors or relaxation and stomach function

Numerous studies have explored the effects of psychological stressors on gastrointestinal functions [41]. The first systematic observational approach was published in 1833 by the American surgeon William Beaumont. In a monograph on the physiology of digestion, he reported his observations of digestive (gastric) function in Alexis St. Martin, a Canadian who suffered at the age of 19 years a gun-shot wound and developed a permanent gastric fistula that allowed to observe the gastric mucosa and assess gastric secretion. Beaumont studied for a decade gastric physiology in his volunteer and published key aspects of the digestive process. In this context Beaumont noted on various occasions changes of gastric physiology induced by emotional factors [42].

Well controlled experimental studies in healthy subjects have demonstrated that acute mental stressors such as mental arithmetic had no significant effect on mean (unstimulated) gastric acid secretion while the occurrence of interdigestive Phase III complexes was delayed and pancreatic enzyme secretion was also reduced [43]. Similarly, acute mental stress does not alter meal stimulated acid secretion [44]; however, there was remarkable individual variability in relation to the response to the stressor and the individual response

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related to personality traits such as impulsivity as measured using standardised personality tests [44].

Focussing on acid related symptoms, McDonald-Haile [45] assessed in subjects with documented gastroesophageal reflux disease the effects of a psychologically neutral or stressful task followed by relaxation. While the stressful task induced cardiovascular responses no effects on objective acid exposure were observed. In contrast relaxation lowered objective parameters of oesophageal acid exposure, reduced symptom ratings and anxiety scores with stressful tasks relative to neutral tasks. Stressful tasks also caused significant increases in blood pressure, subjective ratings of anxiety, and reports of reflux symptoms as compared to the control setting.

3.5 Psychological factors and epigastric symptoms

There is good evidence from epidemiologic studies that psychological distress as manifest by anxiety and depression is associated with functional gastrointestinal disorders [39, 46, 47]. In a recent study depression, somatization, and FGID symptoms were measured using self-report questionnaires. In addition barostat studies were used to determine visceral sensory thresholds. Confirmatory factor analysis (CFA) was used to analyse associations between Rome III symptom-based subgroups and to assess relationships of the symptom factors with gastric sensorimotor function, depression, and somatization. A relatively large cohort of 259 tertiary care patients with functional dyspepsia were included and this study confirmed the existence of the Rome III subgroup postprandial distress syndrome (PDS) and observed that gastric sensitivity and depression are associated with meal related symptoms (PDS) and nausea and vomiting [48].

3.6 Modulation of brain function and influence on gastric acid secretion

Subjects were hypnotized and instructed to imagine all aspects of eating various delicious meals. In response to this acid output increased significantly. In random order the volunteers were also instructed under hypnosis to imagine deep relaxation and remove their thoughts from hunger. Compared to the control condition of no hypnosis this significantly reduced unstimulated and even pentagastrin-stimulated peak acid secretion [49].

In another study Bresnick et al [50] tested the effect of dichotomous listening to induce stress and a control condition on gastric acid output in healthy controls and patients with (inactive) duodenal ulcer. While the stressor did not alter gastric acid secretion in healthy subjects, the authors report a significant increase of acid secretion during emotional stress in

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the duodenal ulcer patients as compared to the control situation. This implies that in patients with an acid related disease the stress response is different. While it is now accepted that peptic ulcer disease is closely associated with a gastric *H. pylori* colonisation, *H. pylori* has substantial effects on gastrointestinal physiology. It is well established that the release of gastrointestinal hormones such as gastrin are influenced by *H. pylori* colonisation [51, 52]. Thus, it is unclear if the different response of patients with peptic ulcer disease is a consequence of the *H. pylori* infection or perhaps a distinct response pattern to stress in combination with *H. pylori* that is a risk factor for peptic ulcer disease.

3.7 Influence of brain activity on gastric function

In healthy volunteers light sedation with propofol did not influence gastric emptying as measured by plasma acetaminophen (paracetamol) levels after oral intake of the medication [53]. On the other hand, in patients and controls undergoing minor gynaecologic surgery anaesthesia induced with either propofol alone, propofol and the morphine analogue alfentanil or propofol and fentanyl (and maintained with intermittent propofol and 66% nitrous oxide in oxygen), gastric emptying was delayed significantly in all patient groups when compared with healthy volunteers [54]. Thus the effect on gastric emptying was not simply mediated by the stimulation of peripheral opioid receptors.

4. ALTERATION OF BRAIN FUNCTION BY GASTRIC STIMULATION

Information from the digestive tract influences behaviour (e.g. via sensation such as hunger or satiety that alter behaviour). On the other hand it is widely accepted that the ingestion of food may influence mood. In a rat model of subdiaphragmatic vagal deafferentation (which is the most complete and selective vagal deafferentation method) effects of the vagal afferents on innate anxiety, conditioned fear, and neurochemical parameters in the limbic system were tested [26]. These studies found that innate anxiety and learned fear are both modulated by visceral (vagal) afferents. These effects are most likely modulated via the limbic system. Thus, it is not only the brain that alters gut function but the stomach and gastric afferents that alter brain function and moods.

Gastric pacing or electrical stimulation changes gastric function such as gastric emptying [55] and has been used to treat patients with functional abdominal pain and gastroparesis [56]. In dogs gastric electrical stimulation of the stomach activated brain stem regions, the amygdala and the occipital lobe regions. However, this did not influence apomorphine induced emesis and gastric dysrhythmia [32].

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Another well-established mode to induce gastric symptoms or pain is gastric distention. The role of concomitant electrical gastric stimulation was studied by Ouelaa et al. [57]. The pain response was assessed by measuring the pseudo-affective reflex response (blood pressure variation) while neuronal activation was determined using c-fos immunohistochemistry in the central nervous system and phosphorylation of ERK1/2 in dorsal root ganglia. Gastric distension reduced the variation of blood pressure. The electrical stimulation prevented the gastric distension induced phosphorylation of ERK1/2 in dorsal root ganglia and the activation of the nucleus of the solitary tract and the hypothalamic paraventricular nucleus. Thus, electrical stimulation of the stomach appears to suppress central pain responses most likely due to direct modulation of gastric spinal afferents.

Gastric inflammation leads to anxiety- and depression-like behaviours in female (but not male) rats via the neuroendocrine (Hypothalamic-Pituitary-Adrenal (HPA) axis) pathway [58]. This suggests that GI inflammation can impair normal brain function and induce changes in psychological behaviour through the GI-to-brain signalling.

In the neonatal period a transient gastric irritation can induce a long lasting increase in depression- and anxiety-like behaviours and an increased sensitivity of the HPA axis to stress [59]. These findings have potential implications for the pathogenesis of psychological co-morbidity in patients with functional bowel disorders. Based upon these findings it is evident that gastric afferents do not only transiently alter brain function but gastric afferents may also have long lasting effects on brain function.

5 ALTERATIONS OF STOMACH – BRAIN INTERACTIONS IN THE CLINICAL SETTING

5.1 Alterations of Mechanosensory Gastric Afferents (sensory function)

Abnormal visceral mechano-sensory function has been reported in 50% of non-ulcer (functional) dyspepsia patients [6, 14, 15, 60]. Overall, thresholds for first perception appear to be significantly lower in dyspeptic subjects compared with asymptomatic controls. However, a key feature of patients is that they lack an adaptation (increase of thresholds after repeated distension [6].

On the other hand neuroimaging studies have shown local brain aberrations in functional dyspepsia patients. In addition, abnormal brain functional connections were mainly identified within or across the limbic/paralimbic system, the prefrontal cortex, the tempo-parietal areas and the visual cortex. These functions were associated with the patients' dyspepsia symptoms, the self-rating depression scale and scores on the self-rating anxiety scale [61].

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However, these dysfunctional connections may be epiphenomena rather than causative factors in FD, and further work is required to better characterise these alterations.

5.2 Altered brain function in response to gastric stimulation

A history of abuse is frequently associated with IBS and other functional GI disorders [62]. In a study from Belgium it was reported that abuse and in particular sexual abuse, appeared to influence gastric sensitivity and motor function [63]. There is evidence that neural plasticity during development appears as an adaptive brain response in a regionally highly specific manner. Such plastic reorganization may be protective, but cause other problems later in life such as behavioural abnormalities [64, 65].

5.3 Brain injury and gastric emptying

Brain injury with or without increased intracerebral pressure might be a model for the effects of the brain on gastric emptying. In a study in 21 brain injured patients gastric emptying was not associated with the initial Glasgow Coma Score. However, increased intracranial pressure was associated with delayed gastric emptying [66].

5.4 Surgical interventions at the stomach and effects on brain function

It is now well accepted that in the hypothalamus, the stimulation of receptors for growth hormone secretagogue (ghrelin) receptor-GHSR, leptin receptor-b (LEPRb), Melanocortin-4 receptor (MC4R) and Cannabinoid-1 receptor (CB1R) are critical for energy homeostasis and body weight [67, 68]. Gastric sleeve operations are well accepted as a measure to treat obesity [69, 70]. In obese rats gastric sleeve operations significantly reduced body weight. In the remnant stomach mRNA levels of preproghrelin and ghrelin O-acyltransferase were reduced and this was correlated with long-term decreases in CB1R mRNA. In parallel, in the hypothalamus, increases in GHSR and decreases in CB1R and LEPRb 30 days after the operation followed by further downregulation of CB1R and an increase in MC4R by 90 days. Based upon these data it appears that sleeve gastrectomy induces changes of the stomach – brain axes; acyl-ghrelin initiates molecular events in the gut-brain axis that are likely relevant for the weight loss and may also suggest that cannabinoid pathways may contribute to these therapeutic effects [71].

5.5 Visceral sensation attributed to the stomach

There are a number of more or less distinct sensations that are attributed to the stomach. Fullness or satiety, discomfort or pain and nausea are distinct ‘gastric sensations [5].

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Nausea is a noxious, uncomfortable feeling usually located in the epigastrium. The pathophysiology of nausea encompasses brain-gut and gut-brain interaction. Nausea might be associated is associated with myoelectrical dysrhythmias of the stomach, an objective marker in the periphery. In experimental studies nausea can be induced with Illusory self-motion, the infusion of drugs such as apomorphine or ingestion of excessive amounts of water or nutrients. Utilising these centrally or peripherally acting stimuli, nausea is associated with gastric dysrhythmias such as tachygastrias (3.75-10 cpm) and bradygastrias (1.0-2.5 cpm) [72].

Satiety is a sensation which is attributed to the stomach. Interventricular injections of GLP-1 inhibits food intake, independent of the presence of food in the stomach or gastric emptying. Peripherally administered GLP-1 also affects the central regulation of satiety and hunger. It is therefore the synergistic actions of GLP-1 in the gut and brain, acting on both central and peripheral receptors that seem responsible for the effects of the hormone on satiety [73]. In addition, in animal studies intracisternal -injection of GLP-1 also significantly delayed gastric emptying. This effect was partly reversed by celiac ganglionectomy but not by atropine or N(G)-nitro-l-arginine methyl ester (L-NAME) [74]

5.6 The brain, personality and response to therapy in functional dyspepsia

It is well recognised that only a proportion of patients with functional dyspepsia – a condition with symptoms localised in the epigastrium and referred to the upper gut – respond to medical therapy. In a prospective, placebo-controlled study, patients were treated with an acid inhibition and the response to the therapy assessed. In this study 25 out of 75 were categorized as responders. Anxiety and somatisation were predictors for response while dysmotility-like symptoms were associated with an unfavourable response [75].

5.7 Influence of gastric bacterial colonisation or gastric inflammation on brain function, mood and behaviour

It is now well recognised that even in highly developed countries more than 20% of the population might be infected with *H. pylori* and in developing countries this may approach 100% [76]. However, it needs to be noted that the stomach is also colonised by many other bacteria [77]. It is widely unknown how these bacteria interact. However, the widely used shotgun approach to study stool microbiome in large cohorts of health subjects and patients is unlikely to provide relevant information [78].

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There is now good evidence that systemic inflammation is linked to anxiety and depression and this holds true for functional gastrointestinal disorders [79] as well as for inflammatory bowel disorders [80] or even hepatitis [81]. The most frequent cause of gastric inflammation is *H. pylori* [82].

Whether Gastric inflammation would impact on mood and psychiatric conditions is not well established. However, animal studies suggest that gastric inflammation leads to anxiety- and depression-like behaviours in female but not male rats via the neuroendocrine (HPA axis) pathways. This may suggest that gastric inflammation can impair normal brain function and induce changes in psychological behaviour in a gender-related manner through the GI-to-brain signalling [58]. However, studies in healthy subjects suggest that the gastric *H. pylori* infection is indeed correlated with state and trait anxiety when measured with the Spielberger State and Trait anxiety inventory [83].

There is now good evidence from an ecologic study that the prevalence of obesity and gastric colonization with Helicobacter pylori is inversely correlated [84]. This may suggest that gastric inflammation caused by *H. pylori* influences caloric intake most likely via a variety of (humoral) factors [85-88]. Thus, behaviour and in particular eating behaviour might be affected by a gastric mucosal inflammation via central mechanisms.

6 SUMMARY

The stomach–brain axis as part of the gut-brain axis affects a number of physiological processes that result in satiety, food intake, the regulation of glucose and fat metabolism. In addition there is now also emerging evidence that signals arising from the stomach have effects on psychological wellbeing and moods. While new technologies have provided novel insights into these regulatory mechanisms; the full potential in relation to therapeutic interventions remains to be explored.

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Any Conflict of Interest:

Both authors do not have any conflicts of interest to declare

Practice points:

- The ingestion of food has distinct effects on specific brain regions. This is a response to interrelated neural and hormonal signals arising from the stomach as well as visual, olfactory and anticipatory stimuli.
- The central processing of afferent information ultimately influences eating and other behavioural patterns.
- The role of gastric infection with *H. pylori* or the gastric microbiome remains to be elucidated

Research Points:

- The role of disturbances in the crosstalk between the stomach and the brain for the manifestation of functional gastrointestinal disorders needs to be further explored.
- Further studies are necessary to explore targeted modulation of brain – stomach and stomach – brain communication in relation to the prevention and treatment of obesity or functional gastrointestinal disorders

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Table 1: Modulation of gastric afferents and afferents and relation to stomach or CNS function

Modulation	Pathways	Effects	References
Cephalic stimulation	Vagal nerve	Increase of gastric acid secretion	Katschinski et al[10] Taylor & Feldman [11]
Gastric mechanical stimulation	Not formally assessed in study	Compared to healthy controls PET did not show activation of specific brain regions (pACC) in FD patients. Patients showed no dorsal pons and amygdala deactivation during distension and sham.	Geeraets et al [21]
Gastric electrical stimulation	Vagal	Activates brain stem regions, the amygdala and the occipital lobe regions Electrical stimulation of the stomach appears to suppress central pain responses most likely due to direct modulation of gastric spinal afferents	Yu et al [32] Ouelaa et al. [57].
Psychological stress	Not formally assessed in study	No effect on basal gastric acid secretion, or inhibition of interdigestive phase III Meal stimulated gastric acid secretion: no change of mean response but personality traits associated with individual response. High impulsivity scores as measured by a standardised test were associated with an increase of acid secretion.	Holtmann et al [43] Holtmann et al [44]
Relaxation	Not formally assessed in study	Deep relaxation induced by hypnosis reduced basal and pentagastrin-stimulated peak acid secretion was reduced significantly by more than 10%	Klein & Spiegel [49].
Sedation or general anaesthesia	Not formally assessed in study	Light sedation with propofol did not influence gastric emptying as measured by plasma paracetamol levels after oral intake of the medication. Patients and controls undergoing minor gynaecologic surgery, anaesthesia induced with either propofol alone, propofol and the morphine analogue alfentanil or propofol and fentanyl (and maintained	Hammas et al [53]

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		with intermittent propofol and 66% nitrous oxide in oxygen), gastric emptying was delayed significantly in all patient groups when compared with volunteers.	
		Anaesthesia induced with either propofol alone, propofol and the morphine analogue alfentanil or propofol and fentanyl (and maintained with intermittent propofol and nitrous oxide in oxygen), significantly delayed gastric emptying.	Bennett et al [54].

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Figure 1: Summary of effects of gastric stimulation on brain function, and the effects of the brain on gastric function

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Electric stimulation of stomach

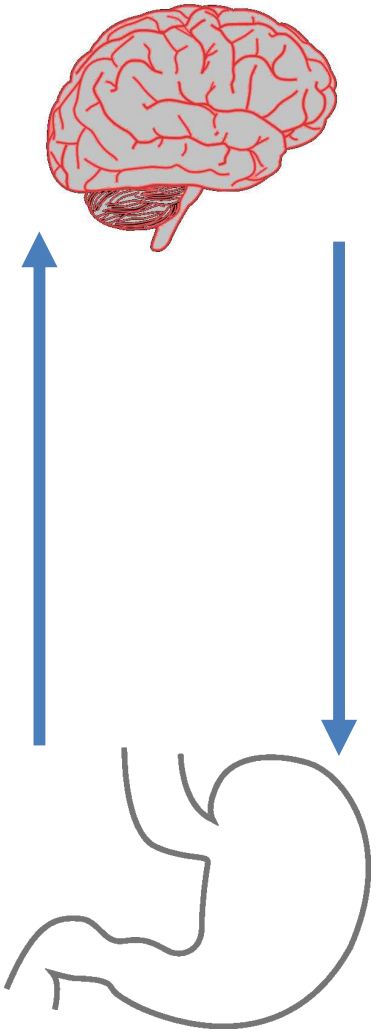
- *Activates brain stem regions, the amygdala and the occipital lobe regions*
- *suppress central pain responses*

Mechanical stimulation (balloon distension)

- *anterior cingulate cortex sends inhibitory efferent signals (via opioidergic, serotoninergic, and noradrenergic systems to the dorsal horn of the spinal cord) inhibiting ,afferent pain signals.*

Noxious luminal content

- *activation of nucleus tractus solitaries, induction of emesis,ventral medulla and hypothalamus*



Cephalic stimulation

- *Increases acid secretion*

Psychological stress

- *Inhibition of interdigestive Phase III complexes*
- *No effect on basal acid secretion*
- *Meal stimulated responses variable (linked to personality traits)*

Relaxation (hypnosis)

- *Reduction of stimulated acid secretion*

Anaesthesia

- *Inhibition of gastric emptying*