REVIEW

The stress concept in gastroenterology: from Selye to today [version 1; referees: 2 approved]

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v1 **First published:** 19 Dec 2017, **6**(F1000 Faculty Rev):2149 (doi: 10.12688/f1000research.12435.1)
Latest published: 19 Dec 2017, **6**(F1000 Faculty Rev):2149 (doi: 10.12688/f1000research.12435.1)

Abstract

More than eighty years after Hans Selye (1907–1982) first developed a concept describing how different types of environmental stressors affect physiological functions and promote disease development (called the “general adaptation syndrome”) in 1936, we herein review advances in theoretical, mechanistic, and clinical knowledge in stress research, especially in the area of gastroenterology, and summarize progress and future perspectives arising from an interdisciplinary psychoneurobiological framework in which genetics, epigenetics, and other advanced (*omics*) technologies in the last decade continue to refine knowledge about how stress affects the brain-gut axis in health and gastrointestinal disease. We demonstrate that neurobiological stress research continues to be a driving force for scientific progress in gastroenterology and related clinical areas, inspiring translational research from animal models to clinical applications, while highlighting some areas that remain incompletely understood, such as the roles of sex/gender and gut microbiota in health and disease. Future directions of research should include not only the genetics of the stress response and resilience but also epigenetic contributions.

Open Peer Review

Referee Status: ✔ ✔

	Invited Referees 1	2
version 1 published 19 Dec 2017	✔	✔

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Author roles: Elsenbruch S: Conceptualization, Validation, Writing – Original Draft Preparation, Writing – Review & Editing; **Enck P**: Conceptualization, Validation, Writing – Original Draft Preparation, Writing – Review & Editing

Competing interests: No competing interests were disclosed.

How to cite this article: Elsenbruch S and Enck P. **The stress concept in gastroenterology: from Selye to today [version 1; referees: 2 approved]** *F1000Research* 2017, **6**(F1000 Faculty Rev):2149 (doi: 10.12688/f1000research.12435.1)

Grant information: Both authors conducted placebo research as members of a collaborative research unit funded by the German Research Foundation (DFG FOR 1328).

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Introduction

Our review will start with a short historical vignette on Hans Selye's contribution to our current understanding of the concept of environmental stressors on human disease and will bridge to acute research questions driven by progress in neurophysiology ("decade of the brain") and, more recently, microbiology. In three sections, we will then elaborate how stress research has contributed to basic animal studies in gastroenterology (for example, on the role of sex differences and the contribution of the gut microbiota for understanding the stress response and visceral hypersensitivity, in translational research on the commonalities and differences between acute and chronic stress in humans, and on clinical research exploring whether and how stress contributes to functional and other gastrointestinal [GI] disorders, taking both basic [sex and microbiota] and technical [brain imaging] aspects into consideration).

Historical vignettes

In the July issue of the journal *Nature* in 1936, 29-year-old Hans Selye, a Vienna-born Austrian-Hungarian who studied medicine and chemistry in Prague, Paris, and Rome before completing his Ph.D. at Johns Hopkins University and immigrating to Montreal, published his first (!) paper. This short note entitled "A syndrome produced by diverse nocuous agents"[1] was about twice the size of an abstract nowadays, yet the syndrome would later become known as the stress concept, also known as "general adaptation syndrome" (GAS). Although it described the major principle, a global and homogenous three-phase bodily response to a variety of different noxious stimuli, the term "stress" was not mentioned. It also contained no reference that this concept may be of any special relevance to the GI tract, except that Selye noted that "the formation of acute erosions in the digestive tract, particular in the stomach, small intestine and appendix" of the animals (rats) following exposure to noxious agents occurred[1]. Ten years later, Selye published a full account of his experimental findings, entitled "The general adaptation syndrome and diseases of adaptation"[2], that may mark the true beginning of the GAS/stress theory, again remarkable for different reasons: for the fact that this paper was published simultaneously in several journals (*Journal of Allergy, Annales d'Endocrinologie*, *Manpower*, *Piersol's Cyclopedia of Medicine, Surgery and Specialties*, and *Bulletin de Biologie et de Médecine Expérimental de l'U.R.S.S.*), which is entirely impossible to think of nowadays, and for the frequently reproduced figure illustrating the—at that time—unknown pathways connecting the brain to peripheral bodily systems, including the GI tract. Yet it was GI physiology and the search for pathways and their neuroendocrine mediators, including those involved in "stress ulcers" in the gut, that subsequently received the most attention: UCLA's Center for Ulcer Research and Education[3], founded in 1974, was the Mecca for stress research outside its hub in Montreal, Canada. This promoted the idea that central stress causes or contributes to many peripheral diseases—a concept that ever since has been discussed in gastroenterology, much earlier than in other core medical areas and subspecialties. Ulcers are no longer a major focus of stress research in gastroenterology, but, given the detection of *Helicobacter pylori* and its involvement in ulcer formation, stress research in gastroenterology continues to thrive.

Seventy years after Selye's account and at the end of the "Decade of the Brain", the September 2015 issue of *Nature Neuroscience* provided state-of-the-art reviews of stress research summarizing the remarkable progress in our understanding of mechanisms involved in central processes and their clinical implications for multiple diseases and health conditions, ranging from psychiatric to cardiovascular and immune-related diseases. Important conceptual developments, especially the concepts of allostasis and allostatic load[4], continue to provide a more refined psychoneurobiological framework to explain the mechanisms and clinical implications of chronic stress and stress-related conditions. These incorporate new aspects such as the role of threat perception, cognitions, coping, and appraisal processes[5,6] with a focus on mental health, individual variability, and resilience[7,8] and their underlying neurobiological mechanisms.

Today, stress research is highly transdisciplinary and has many facets, including research into motivation and reward, plasticity, cognition, and sex differences, to name a few. Some of these topics have found their way into gastroenterological research; others have yet to be incorporated. Although recent work is carried out mostly in the context of visceral pain[9] and the biopsychosocial disease model in functional GI disorders such as irritable bowel syndrome (IBS) and functional dyspepsia (FD), interest in stress and biopsychosocial disease concepts[10,11] has started to extend to other GI conditions such as inflammatory bowel diseases (IBDs)[12,13], liver diseases[14], and celiac disease[15,16].

In the following, we will discuss current facets of stress research both in animal studies and in human research and will outline its relevance for the pathophysiology of GI conditions, either shown or proposed.

Translational approaches to study acute and chronic stress

To reliably produce gastric (stress) ulcers, a simple cold-restraint model was used until the 1980s in most animal studies, for example,[17], but was frequently questioned for its relevance in humans and replaced by other stressors (for example, by noise[18]) when GI functions (motility and secretion) rather than ulcer formation were of interest. But it was not until in 1989, when a truly psychological (that is, non-invasive and non-physical) stress model for rodents—the water avoidance model[19]—was introduced, that animal stress research became truly relevant for the investigation of intestinal functions and dysfunctions in humans. Yet other animal models—neonatal maternal separation[20] and, more recently, limited nesting[21]—sparked the initiation of a large series of studies on the long-term effects of stress on visceral sensitivity and related dysfunctions in animals.

In humans, there are a number of approaches to study the effects of acute and chronic stress and underlying psychological and neurobiological mechanisms. One prominent example of a well-established acute laboratory stress model is the Trier Social Stress Test (TSST), which combines a difficult cognitive task (mental arithmetic) with a public-speaking task in front of an audience. The TSST is a widely established, highly standardized, and purely psychosocial trigger of acute stress responses[22,23] that

reliably induces pronounced yet transient increases in psychological and biological stress markers, including emotional and cognitive responses along with activation of the hypothalamus-pituitary axis and sympathetic nervous system. Several examples for its application in the context of the GI system exist[24–30], while other work in the field[31–34] has implemented alternative approaches to induce psychological stress. Some of these experimental protocols produce weaker, less reliable stress effects (for example, dichotomous listening), incorporate a physical pain component (for example, cold pressure test), or focus primarily on emotional or cognitive aspects (for example, listening to sad music, seeing disturbing pictures, and anticipating electric shock). Pharmacological approaches, such as the administration of corticotropin-releasing hormone (CRH), CRH antagonist, or hydrocortisone, which have recently been accomplished in the GI system[35–38], allow clinicians to specifically assess effects on GI-related functions mediated by the hypothalamic-pituitary-adrenal (HPA) axis but arguably have limited external validity as models of psychological stress in humans given a lack of effects at the subjective level (for example, no increase in subjective stress levels of state anxiety).

In contrast to acute stress, which induces an adaptive response preparing the organism for "fight-or-flight" and therefore is not harmful per se, chronic stress evokes maladaptive psychophysiological changes which, when severe, can have a multitude of clinical[39] and broad implications[40,41] for the GI system. It is defined as the psychophysiological response to long-term emotional pressures such as adverse life events over which the individual perceives little or no control and typically is measured with validated questionnaires (for example, the Trier Inventory for the Assessment of Chronic Stress [TICS][42] and the Perceived Stress Questionnaire[43]).

Although experimental approaches in animals and humans are divergent and continue to evolve, broad knowledge about centrally mediated effects of stress on GI sensorimotor functions has fundamentally shaped the concept of the brain-gut axis and continues to inspire animal and human studies.

Current animal stress research in the gastrointestinal tract

Visceral hypersensitivity—an abnormally high responsiveness of the gut toward physiological stimuli (for example, distension)—is regarded as a key feature of functional bowel disorders of IBS type[44]. In animals, it can reliably be induced by a temporary (for example, early life) exposure of a gut segment to a noxious but transient stimulus that leaves the segment unaltered morphologically but responsive to low-level stimuli later in life[45] and other, non-GI stimuli (for example, foot-shock) work as well[46]. Visceral hypersensitivity can also be induced in newborn pups when they are exposed to maternal separation (1 hour per day for a week or two) and are retested days, weeks, or months later[20]; this effect appears specific for visceral hypersensitivity but not for other behavioral measures[47]. Such an effect of early life stress is not limited to rodents but also occurs in other mammals, such as in porcine models where it induced chronic functional diarrhea and intestinal barrier defects and increased mast cell activity[48], lasting hypersensitivity of secretomotor neuron function, and upregulation of the cholinergic enteric nervous system[49].

Neonatal maternal separation also changes neurocognitive functions[50] and stress responsiveness in the dams[51]; whether visceral sensitivity of the mothers is altered remains unknown. When pregnant rats are exposed to a gut-sensitizing stimulus, their offspring will also show visceral hypersensitivity[52]. It has been shown that such experimentally induced hypersensitivity will be transmitted across generations[53], indicating "soft" rather than Mendelian inheritance and an epigenetic mechanism for this[54]. Whether transmission of susceptibility occurs via transmission of hormonal concentrations to offspring via lactation[55] or via alterations of the gut microbiota that is transmitted vertically[56] remains an open issue.

Even if gut segments of stress-exposed animals show little or no morphological alterations upon macroscopic or microscopic inspection, they still may behave differently not only *in vivo* but also *ex vivo* when jejunal and colonic segments of animals stressed by restraint for one hour demonstrated decreased motility frequency and increased amplitude *in vitro*[57]. According to the authors, this implies that dysmotility is generated by mechanisms internal to the gut (rather than central), presumably via immune-mediated or neurally mediated changes of the enteric nervous system, because of the short-term nature of the stress-test interval. One putative mediator may be neuropeptide Y (NPY); its receptors play important roles in—among others—stress resilience[58].

The variability of stress responses in different animal strains of the same species—for example, selective breeding-based cholinergic hypersensitivity and hyposensitivity Flinders rat lines[59] or hyperanxious (HAB-M) and hypoanxious (LAB-M) mouse lines[60]—or increased stress responsiveness in Wistar Kyoto rats, as compared with Sprague Dawley rats[61], is well established. The importance of individual vulnerability and resilience factors is increasingly acknowledged both conceptually (for example,[8]) and in mechanistic research and may exhibit a genetic[62] and an epigenetic[63] basis, and this is possibly based on "synaptic rewiring" of stress-sensitive neurons[64]. In all cases, however, it is likely that the "three-hit concept" of vulnerability and resilience persists: a genetic predisposition and early life adverse events are necessary so that a later-in-life stressor can exhibit negative health outcomes, and one or more missing may result in higher resilience[65]. It is of importance to note that resilience has not yet been thoroughly investigated in relation to GI functions in animals (and humans) under stress; it is, however, known that patients with IBS lack resilience, and low resilience was associated with worse IBS severity, lower quality of life, more early life stressful events, and stress hyper-responsiveness[66]. Similarly, in patients with IBD, the role of (maladaptive) coping is only beginning to be unraveled (for example,[67–69]), calling for translational research on individual risk and resilience in patients with GI conditions.

Sex differences in rodents and humans

Gender differences in the prevalence of chronic visceral pain, especially a female preponderance of functional gastrointestinal disorders (FGIDs), are well established. Further support for a role of sex-related factors comes from mechanistic human and animal research showing sex differences in visceral pain processing in animal models, healthy individuals, and patients with FGIDs[70,71]. The putative connection linking gender/sex and sex hormones to stress and pain is undoubtedly highly complex yet intriguing and in need of more dedicated research in animal models, healthy humans, and patients[70,72] with attention to effects across the life span[73]. After all, many sex differences exist in the central and peripheral response to stress because of dimorphic brain development[73]. During gestation, sex differences in embryonic responses to maternal and environmental stress are well documented, and males are at higher risk for negative outcomes. In humans, this is associated with higher incidences of neurological disorders (attention-deficit/hyperactivity disorder, among others); in animals, stress during pregnancy predominantly affects male offspring[74]. During childhood, in contrast, stress appears to increase the risk for affective disorders, and here women are at higher risk, especially during their reproductive years. Whether this explains the higher incidence of functional (GI) disorders remains an open issue, as this is dependent also on the effects of prenatal and perinatal stress on the development of intestinal functions that have rarely been investigated in this context.

Preliminary data suggested a strong sex difference in some of the reported consequences of stress on intestinal functions, and females were more resilient in general than males. Both chronic and intermittent stress models (for example, limited nesting) have profound consequences on the offspring with minimal external intervention from the investigator[75]. Limited nesting of rat dams increased gut permeability predominantly in female Wistar pups, but overall stress-decreased diversity of the gut microbiota was similar between sexes[56]; in another study from the same group, offspring male pups showed increased gut permeability but female pups did not[76]. Water-avoidance stress reduced the visceral motor response to colorectal distension immediately after the stressor, and this analgesic effect was opioid-dependent (naloxone-sensitive) in females but insensitive to naloxone in males, and repeated stress induced hyperalgesia in females only[77]. Sexual dimorphism was also found in mast cell responses to stress, with female mice "exhibiting increased clinical scores, hypothermia, and serum histamine levels in response to stress and greater intestinal permeability and serum histamine responses"[78]. In the above-cited porcine model[48,49], responses in females overall were larger than in male animals.

The role of stress in patients

Patients with FGIDs report higher levels of chronic stress and more adverse life events, and the proportion of patients who present with a history of early life stress or trauma is considerable[79,80]. In prospective studies, chronic stress has been identified as one of the psychological risk factors for the development of an FGID later in life or for post-infectious IBS; in IBD, chronic stress prospectively increases the risk of relapse[12], but the connection between GI symptom (reports), intestinal inflammation, and stress remains to be clarified[81]. Importantly, stress and other psychological disturbances such as depression or anxiety symptoms can both precede the manifestation of chronic GI complaints and occur as a consequence of the GI condition[82], supporting a complex interplay between psychological changes and GI symptoms in terms of a vicious cycle.

The ability of acute stress, acute negative emotions, or HPA-axis mediators to influence both upper and lower GI sensorimotor processes and central pain processing has been extensively documented in healthy humans[79]. In patients with FGID, knowledge is not as extensive, but stress effects appear to be altered, especially in patients with hypersensitivity. For example, in patients with FD, state anxiety at the time of testing was associated with impaired gastric accommodation[83] and correlated negatively with gastric discomfort and pain thresholds and with gastric compliance in hypersensitive FD[84]. Mental stress failed to produce the normal reduction in antral motility in patients with FD[30,85]. The neurobiological mechanisms underlying these effects remain incompletely understood, especially in patients, but likely involve both brain mechanisms and top-down neuroendocrine and autonomic pathways and may include mast cell-dependent effects on permeability[30,79,86].

Brain mechanisms

Brain imaging studies have started to delineate the neural mechanisms underlying the effects of stress and other psychological variables on visceral sensation and central pain processing[79,87–89]. For example, acute stress or negative mood demonstrably alters distension-induced neural activation in multiple brain regions, including the insula, cingulate cortex, and prefrontal areas, in healthy individuals and patients with IBS[90,91]. In FD, anxiety during scanning reportedly contributes to group differences between patients and healthy controls[92]. In IBS, effects of acute stress on central pain processing were more pronounced in specific brain regions[25]. Changes in central nervous pain processing in IBS have further been shown to be associated with anxiety symptoms and depression[91], symptoms which are distinct from chronic stress but illustrate the broad role of both chronic and acute psychological factors. Interestingly, patients with IBS also exhibit altered brain activation during pain anticipation[89]. Such anticipatory responses—mainly in brain areas linked to attention, threat detection, and emotion regulation—reflect pain-related fear resulting from associative learning processes[37,93], which influence the processing of visceral stimuli even in healthy humans[94]. In patients with IBD, brain imaging studies have only recently begun to emerge[95,96], including studies addressing effects of acute stress[97,98], laying the foundation for much-needed research on putative similarities and differences in structure-function relationships along the brain-gut axis in IBD and IBS.

Pain-related learning and memory processes

Stress may contribute to impaired pain-related learning and extinction processes and thereby play a role in the transition from acute to chronic pain or the maintenance of chronic symptoms or both. The conceptual basis for this assumption is evidence that functional and structural brain alterations involved in the pathophysiology of chronic pain overlap with brain circuits involved in emotion regulation and stress[99] and with regions mediating fear expression and recovery[100]. From a learning perspective, recurrent painful episodes induce associative and instrumental learning processes. The putative clinical relevance is supported by evidence that learning-based treatment approaches, particularly of exposure-based interventions, are efficacious in IBS[101,102] and other chronic pain conditions[103]. Based on mechanistic work, it has been proposed that conditioning may lower pain thresholds[104] or promote sensitization[105,106] and thus contribute to hyperalgesia or hypervigilance or both, impair perceptual discrimination acuity[107], enhance fear generalization[108], or interfere with normal habituation processes[109], but some of these suggestions come from studies implementing somatic rather than visceral stimuli. To unravel the mechanisms engaged in pain-related associative learning, new research studies have implemented innovative experimental paradigms with visceral stimuli such as unconditioned stimuli or conditioned stimuli (or both) in healthy individuals and patients with IBS[93], some of them using brain imaging techniques to address underlying neural mechanisms[37,110]. However, virtually nothing is known about the possible roles of affective comorbidity and stress in shaping disturbed acquisition or impaired extinction of pain-related fear. Applying existing findings regarding the effects of stress or HPA-axis mediators such as cortisol on memory consolidation and reconsolidation to the field of GI, one could postulate that stress results in a reactivation of the pain-related memory trace or facilitates its reconsolidation or both, ultimately making the pain-related fear memory more lasting. This process may contribute to the maintenance of pain-related fear and hypervigilance and thereby to maladaptive avoidance behavior as part of a vicious circle maintained by stress and fear[111]. Furthermore, research into interactions between affective comorbidity, acute stress, and memory processes may contribute to elucidating individual risk and vulnerability factors and neuropharmacological treatment options for chronic pain[112]. In addition to the many options available to modify stress responses at the central level via medical and psychological strategies, nutritional interventions have recently found increased attention.

Stress and microbiota

Stress induces alterations of the fecal microbiota, and manipulation of the gut microbiota alters stress responses, in both humans and animals. Experimental stress in animals showed sustained alterations of the gut microbiome across species[113]. Stress in pregnant mice disrupted that natural patterning of the gut microbiota during pregnancy. The disruption was observed not only in the gut microbiota but also in the vaginal microbiota[114]; gut microbiota disruption may influence maternal nutritional status and thus change the energy supplies available to the brain of the developing offspring. The development of sexual dimorphism, discussed above, is presumably driven by sex differences in the gut microbiome–brain axis across the life span[115].

In humans, stress-associated disorders have been characterized by altered microbiota profiles—for example, in post-traumatic stress disorder[116], IBS[117], depression[118], eating disorders such as anorexia nervosa[119], and other psychiatric or neurological central nervous system (CNS)-related disorders[120]. Acute exercise affects the microbiota via mitochondrial mediation[121], and long-term stress exposure altered intestinal permeability and microbial composition[122]. Professional athletes show moderately altered microbiota profiles but significantly increased metabolic activity (short-chain fatty acids, acetate, and butyrate) compared with sedentary adults[123], and similar differences were found between an active and a sedentary lifestyle in women[124]. A correlation between cardiovascular fitness and microbiota composition was also found in breast cancer survivors[125].

We have recently reviewed the literature on probiotic effects in CNS functions in animals and humans[126] and found rather inconsistent results. The effects depended on, among other things, the bacterial species applied and the CNS function under investigation, and some positive effects in animals with a specific strain[127] were not replicable in humans with the same strain[128]. When the probiotic *Lactobacillus rhamnosus* JB-1 was applied locally in *ex vivo* gut segments, it reversed restraint stress-induced gut dysmotility[57]. In addition, similar strains may exhibit different responses; for example, the *Lactobacillus pentosus* strain S-PT84 showed anti-stress activity and ameliorated stress-induced immune suppression in mice[129], while another *Lactobacillus* strain, *Lactobacillus casei* 54-2-33, might have anxiogenic effects in mice[130]. Yet another *Lactobacillus* strain reversed stress-induced cognitive, behavioral, and biochemical alterations in rats[131], but a similar effect was seen with strain-unspecific dietary interventions (for example, with polyunsaturated fatty acids)[132]. In chronically stressed mice, restoring stress-decreased *Lactobacillus* abundance in the gut microbiota reversed behavioral alterations[133], and oral intake of *Bifidobacteria* significantly increased the number of resilient mice compared with vehicle-treated mice in another stress model[134]. Also, prebiotic pretreatment of animals prolonged stress-induced visceral analgesia following colorectal distension[135], and this was associated with a reduction of cecal content of isobutyrate and total butyrate. It had anxiolytic effects and reversed the impact of chronic stress in mice[136]. However, it should be kept in mind that these experiments were frequently performed in germ-free animals colonized by single bacterial species, or complex microbiota transplanted from other animals, or "humanized" with fecal microbiota from healthy or diseased humans. Germ-free mice by themselves are questionable models for regular human gut ecology, and elimination or distortion of the gut microbiota by antibiotics is feasible only in animals, except with the locally

acting antibiotic rifaximin that exerted stress-reducing effects in healthy volunteers[137] in a stress paradigm mimicking social isolation[138].

Some *Bifidobacteria* exert strain-specific beneficial effects on stress-related behavior[139] and cognitive functions in mice[140] and in healthy humans[141] and may be potential candidates for the management of patients with IBS[142]. In healthy humans, the *L. casei* strain Shirota preserved the diversity of the gut microbiota and relieved abdominal dysfunction in healthy medical students exposed to academic stress[143,144], and this was similar to other studies[145,146] with the same strain. A probiotic containing seven different bacterial strains was not effective in reducing stress in healthy petrol workers[147,148]. Whether and to what extent specific bacterial strains exert convergent and synergistic effects on the (GI) stress response when combined[149] are open and unsolved issues. Another is the fact that probiotic consumption may exert differential effects in men and women depending on nutritional habits on the one hand and microbiota composition on the other[150], together with sex differences in the stress response, as discussed above. Whether probiotic consumption or nutritional habits are capable of preventing stress vulnerability or increasing stress resilience (or both) is currently unknown but warrants further investigation.

Closing remarks

Figure 1 is an attempt to summarize current knowledge from animal and human studies and condense it into a scheme of where, when, and how different types of stress may affect central and peripheral functions, mediated by the enteric nervous system or the CNS or both along the gut-brain axis[151].

As is evident from the amount of literature published in the last few years, the stress concept (or GAS) has not only survived in gastroenterology, especially the rise of *Helicobacter pylori* as a *conditio sine qua non* mediator of (stress) ulcer formation, but also gained even wider acceptance than in the times of Hans Selye, not the least through his pupils and successors and ongoing research. It is arguably the major concept to explain the cause and course of functional bowel disorders of IBS type (that is, for visceral hypersensitivity and hypervigilance). Translational animal stress models used nowadays simulate much better than ever before the stressors that affect human health in general and GI functions specifically, explain sex differences as they are found in epidemiological data on functional GI disorders, and pave the way for a better understanding of how stress affects the brain in health and disease. As was pointed out recently, "the gastrointestinal system is an ideal model to analyze the interaction between our genes, emotions and the gut microbiota. … an integrated

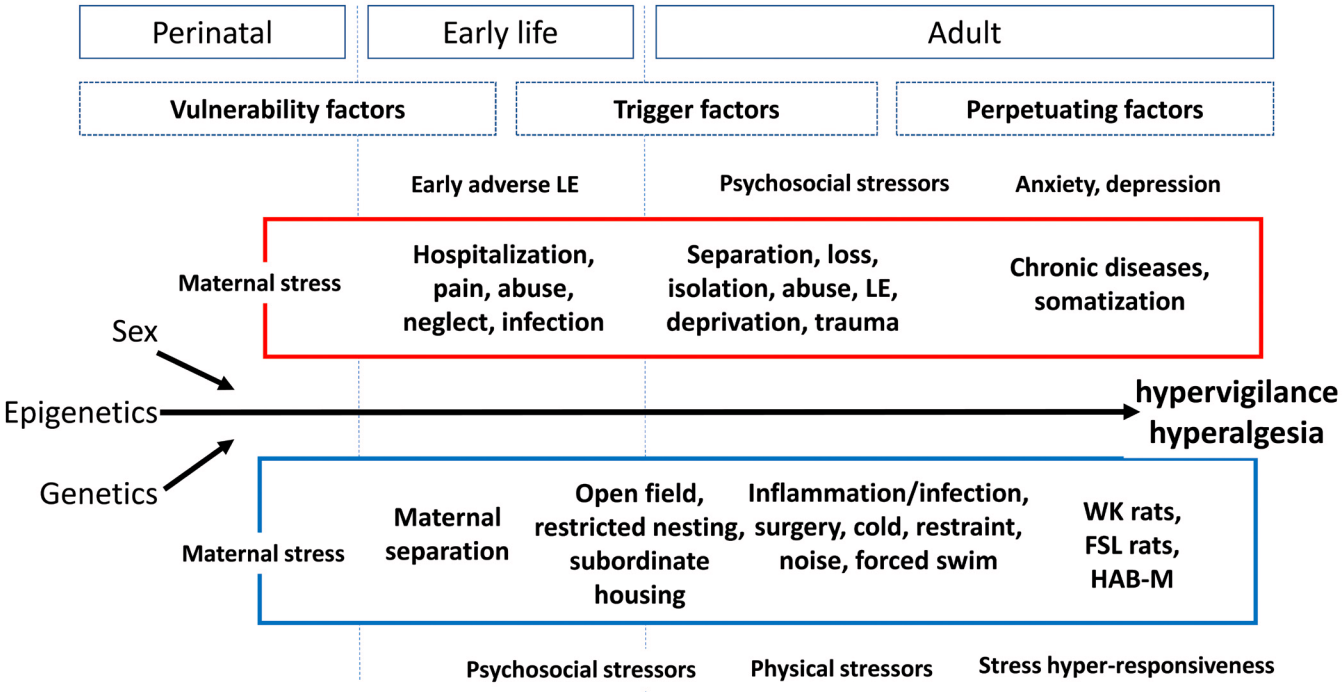

Figure 1. Human (red) and animal (blue) models of stress-induced modulation of visceral sensitivity throughout the life span and for different phases of life (from perinatal to adulthood), together with contributions from genetics/epigenetics and sex FSL, Flinders Sensitive Line; HAB-M, high-anxiety-related-behavior mice; LE, life events; WK, Wistar Kyoto.

approach … is the next frontier that awaits the gastroenterologist to prevent and treat GI disorders"[152].

Competing interests

The authors declare that they have no competing interests.

Grant information

Both authors conducted placebo research as members of a collaborative research unit funded by the German Research Foundation (DFG FOR 1328).

The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

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Version 1

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Competing Interests: No competing interests were disclosed.

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Competing Interests: No competing interests were disclosed.