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Review

Research Progress on the Relationship Between Gastrointestinal Diseases and Neural Nuclei in Animal Models

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Abstract

Gastrointestinal (GI) diseases are manifestations of abnormal brain-gut interactions, which are closely related to brain functions. Systematic sorting of the central mechanisms related to GI functions is of great clinical significance for preventing and treating GI disorders. We therefore conducted a literature search in the PubMed and Web of Science databases, spanning publications from January, 1975 to March 31, 2025. A total of 398 articles were retrieved, with three of these identified through supplementary searches. After screening, 56 animal studies were included for analysis. The findings indicate that central regulation of GI function is primarily mediated by the frontal and cingulate cortices. Subcortical nuclei appear to be more strongly associated with GI activity than cortical regions, particularly nuclei within the hypothalamus, brainstem, hippocampal gyrus, central amygdala, and thalamus. The hypothalamic-pituitary-adrenal axis plays a crucial role in the regulation of GI function via neuroendocrine pathways and has been extensively studied. However, most studies to date have focused on individual brain regions or specific nuclei, with limited investigation into integrated neural circuits or axis-level mechanisms. Recent advances in neuroscience techniques have paved the way for future studies to more comprehensively investigate cortical-subcortical brainstem multilevel neural circuits and cross-organ regulation of central-GI interactions, contributing to a deeper understanding of the underlying mechanisms of GI-brain interactions.

Keywords: gastrointestinal diseases; neural nuclei; neural circuit; brain-gut axis; central nervous system

1. Introduction

Recent years have seen an increase in the prevalence of gastrointestinal (GI) diseases. This has been attributed to changes in lifestyle and dietary patterns, as well as the impact of stress and emotional factors. Epidemiological studies indicate that approximately 2 billion individuals are affected by digestive diseases, accounting for 27.8% of all disease cases. This high prevalence not only adversely affects the physical and mental health of affected patients, but also places a considerable economic strain on society, making it a major public health issue [1,2].

The digestive system receives innervation through its connections with the central nervous system (CNS) and the enteric nervous system (ENS) within the GI tract wall. Regulatory centers located at various levels of the brain and spinal cord modulate GI function after receiving diverse inputs relating to changes in internal and external environments. They integrate these inputs and convey regulatory signals to nerve plexuses in the GI tract via the autonomic nervous system and the neuroendocrine system, or by directly influencing smooth muscle cells in the GI tract. The neural nuclei, as the fundamental unit of the CNS, are crucial for transmitting and processing information within brain regions [3,4].

Despite advances in research on the brain-gut axis, comprehension of the central mechanisms remains considerably constrained. Prior authors have reviewed neuroimaging studies in relation to GI function, identifying both functional and structural brain abnormalities in patients with GI diseases [5–7]. However, the current literature lacks a comprehensive narrative review that integrates and evaluates the regulatory functions of distinct neural nuclei in GI functions. This gap impedes the formulation of a cohesive theoretical framework to explain the complex neural mechanisms governing gut-brain axis interactions. In addition, due to the spatial resolution limitations of techniques such as functional magnetic resonance imaging (fMRI), it is currently difficult to effectively image fine substructure brain regions such as the hypothalamus and brainstem. Therefore, this review aims to systematically explore interactions between the GI tract and brain regions, using small animal models as the research object.

To inform a comprehensive narrative synthesis, this review categorized topics such as “gastrointestinal”, “gas-

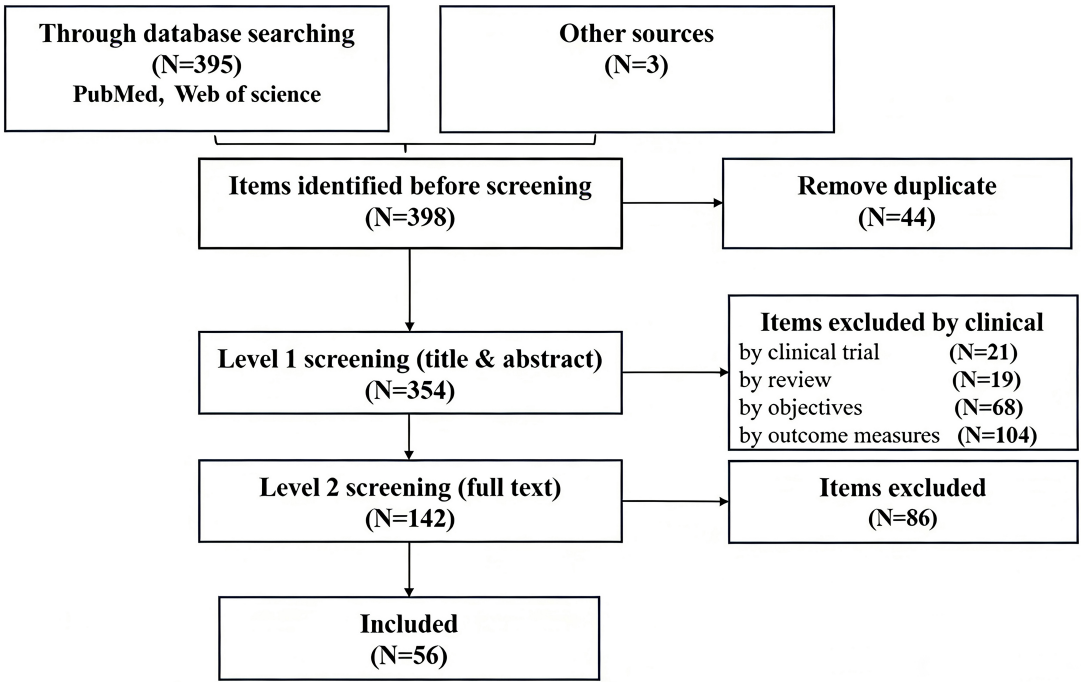

Fig. 1. Flowchart of literature search and screening.

tric dysfunction", "diarrhea", "dyspepsia", "irritable bowel syndrome", "constipation", "vomiting", "reflux esophagitis", "small intestine syndrome", "lactose intolerance", "gastric ulcer", "gastric paresis", "postoperative ileus", "inflammatory bowel disease", "neural nuclei", and "neural circuit". These categories were employed as search fields within the PubMed (https://pubmed.ncbi.nlm.nih.gov/) and Web of Science (https://www.webofscience.com/) databases to identify experimental literature from January 1975 to March 31, 2025. Supplementary searches were also performed to enhance the completeness of the literature review. The inclusion criteria are as follows: (1) the research subjects are GI diseases or GI function; (2) the research involves animal experiments; (3) the observation indicators are related to the neural nuclei. The overall screening process is shown in Fig. 1. A total of 398 documents were retrieved, of which 56 were based on animal experiments and were therefore selected for analysis (Table 1, Ref. [8–63]).

The aims of this review are to (1) identify the important brain regions that regulate GI function and GI diseases, (2) point out the limitations of current research, and (3) make suggestions for future research.

2. Relationship Between Gastrointestinal Disorders and the Cortex

2.1 Frontal Cortex and Cingulate Cortex

The frontal cortex serves as a crucial node within the default mode network (DMN), facilitating the integration of information from peripheral cognitively-regulated pain, and evaluating or responding to the emotional dimensions of pain perception. Individuals with long-term GI disorders may develop chronic symptoms that trigger negative emotions, with the peripheral nervous system transmitting abnormal signals to the frontal cortex. This region coordinates and integrates such information, and prolonged signaling abnormalities may result in structural and functional alterations in the brain [64,65]. The anterior cingulate cortex (ACC), a central component of the frontal cortex network, plays a pivotal role in processing information related to emotions, GI sensory signals, and the regulation of visceral endocrine and pain perception functions [66]. Our previous neuroimaging research identified significant spatial variations in the dorsomedial prefrontal cortex (dmPFC), ventral medial prefrontal cortex (vmPFC), orbital frontal cortex, and the pregenual anterior cingulate cortex (pACC) within the DMN of patients with functional dyspepsia (FD) [67].

An animal study found that anticipatory nausea and vomiting induced c-fos expression in the frontal cortex of male rats [60]. Furthermore, in an animal model of irritable bowel syndrome (IBS), rats exhibited heightened sensitivity to visceral pain following colorectal distension (CRD) stimulation. This was accompanied by up-regulation of P2X3 receptor expression in the prefrontal cortex (PFC), ACC, dorsal root ganglion, and the spinal cord at the L6-S2 segments. P2X receptors are crucial in the formation, transmission, and modulation of visceral pain [68–71], and reduced P2X3 receptor expression has been shown to decrease visceral pain sensitivity. In the cortical network of mice with acute colitis, the middle cingulate cortex (MCC) consistently exhibited high activation in response to both innocuous and noxious mechanical stimulation of the colon. Attenuating MCC activity by reducing excitability of the

Table 1. Experimental details of 56 articles.

Reference	Type of disease	Model induction	Experimental animal information	Neural nuclei/region	Results
Weng *et al*., 2015 [8]	IBS	Either mechanical or chemical colonic irritation between postnatal days 8 and 21	Newborn male Sprague-Dawley rats (5 days old)	Prefrontal cortex, anterior cingulate cortex, dorsal root ganglion, spinal cord (L6-S2 segments)	CRD → the expression levels of the P2X3 receptor in the inter-colonic myenteric plexus, dorsal root ganglion, spinal cord, prefrontal cortex, and the anterior cingulate cortex↓, the sensitivity of the rats to IBS visceral pain↑
Hasegawa *et al*., 2023 [9]	IBS	Treated with TNBS on postnatal days 8. For no inflammation, rats were treated with 50% ethanol	Timed-pregnant female Wistar rats (gestation day 16)	HPA	The time spent in open arms in male MS + TNBS rats was significantly higher than that of TNBS rats. MS and gut inflammation induced an increase in plasma ACTH in female rats but not in male rats at baseline
Chao *et al*., 2021 [10]	IBS	Conditioned stimulus (the special odor of camphor ball) & unconditioned stimulus (rectal distention pressure)	Adult female Sprague-Dawley rats	Hypothalamus, spinal cord lumbar intumescentia	The increasing expression of CRF linked to stress in the hypothalamus and spinal cord
Huang *et al*., 2021 [11]	IBS	Maternal separation	Wistar rats (weight: 280–300 g)	PVN, BNST	MS → firing frequency of CRF neurons in PVN↑, the injection of exogenous GABA into PVN → firing frequency of CRF neurons in PVN↓. GABAergic $BNST_{AV}$-PVN circuit in MS mice↑ → the spontaneous firing frequency of PVN CRF neurons↓, the development of visceral hypersensitivity↓
He *et al*., 2023 [12]	IBS	Water immersion-restraint stress	Male Kunming mice (7–8 weeks, weight: 30–40 g)	CeA, LHA	Chemogenetic activation of GABAergic neurons in the CeA-LHA pathway → anxiety, depression-like behavior, and intestinal motility disorder↓; GABAergic neurons in the CeA-LHA pathway → the expression of orexin-A in the LHA↓
Panteleev *et al*., 2018 [13]	IBS	CRD	Wistar rats (weight: 280–350 g)	VLM	The CRD → VLM neuron activity↑; Buspirone → the CRD-induced neuron responses↓
Chen *et al*., 2017 [14]	IBS	Neonatal maternal separation	Male Sprague-Dawley rats (weight: about 250 g)	Hippocampus	Bilateral intrahippocampal injections of CNQX → the visceral pain in IBS-like rats↓; The expressions of hippocampal GluR2 in IBS-like rats↑
Zou *et al*., 2008 [15]	IBS	Chronic or acute restraint stress	Male Wistar rats (weight: 200 ± 20 g)	Hippocampus, frontal cortex	Chronic and acute stress rats → the Gαi and Gαs expressions in the hippocampus and the cortex of the frontal lobe↓, the protein expression of a2A-AR↓, the protein expression of norepinephrine reuptake transporter↓

Table 1. Continued.

Reference	Type of disease	Model induction	Experimental animal information	Neural nuclei/region	Results
Wang *et al*., 2006 [16]	IBS	Intragastric instillation of 2.0 mL water at 0–4 °C once a day for 2 weeks	Male Wistar rats (four weeks post-natal, weight: 120–150 g)	Hypothalamus, posterior horn of the spinal cord	IBS model rats → the opacity density of substance P immunoreactive tissues and c-fos protein-positive tissue in the hypothalamus and posterior horn of the spinal cord↑
Zhou *et al*., 2024 [17]	FD	Given 0.2 mL 2,4,6-trinitrobenzenesulfonic acid in 10% ethanol in normal saline	Newborn male rats (ten-day-old)	NTS	Model rats → AVNS/K252a↑-NTS-NGF-TrkA-PLC-γ↓/PLC-γ↓/TRPV1↓ → visceral hypersensitivity↓
Zhang *et al*., 2020 [18]	FD	Received a gavage of 0.2 mL of 0.1% iodoacetamide in 2% sucrose	Male Sprague-Dawley pups (seven-day-old) with mother rats	NTS	Electroacupuncture → normalized restraint stress-induced impairment of gastric slow wave in FD rats; vagal activity↑, improved sympathovagal balance; c-fos-positive cell counts in the NTS↑
Hou *et al*., 2023 [19]	FD	Received 0.2 mL 0.1% iodoacetamide in 2% sucrose	Male Sprague-Dawley rats (five-day-old)	DMV	Model mice with ia treament → AVNS-DMV-vagal nerve↑, acetylcholine↑, NF-κB p65↓ → visceral hypersensitivity↓, gastric emptying↓
Bülbül *et al*., 2016 [20]	Stress-induced GI dysfunction	Restraint stress	Wistar rats	PVN	Stress exposure → hypothalamic PVN apelin and CRF levels↑, which were negatively and positively correlated with gastric emptying and colon transit, respectively
Dong *et al*., 2023 [21]	Stress-induced GI dysfunction	Stress (15 min of tail pinch 34, 45 min of placing individual mice in water)	Male C57BL/6J, ChAT-Cre and Pet1-Cre mice (8–10 weeks)	5-HT^{DRN} → ACh^{DMV} → stomach circuit	Chronic stress+ hypoactivate gastric function → (5-HT^{DRN} → ACh^{DMV} → stomach circuit)↓
He *et al*., 2022 [22]	Stress-induced intestinal dysfunction	Chronic unpredictable stress and acute restraint stress	Male C57BL/6 mice (weight: 25–30 g)	LHA, BLA	The melanin-concentrating hormone neurons of the LHA projected to the BLA
Zhu *et al*., 2012 [23]	Stress gastric mucosal damage	Induction of restraint and water (21 ± 1 °C)-immersion	Adult male Sprague-Dawley rats (weight: 210–230 g)	LHA, FN	Microinjection of Baclofen into FN → the number of GABA positive neurons in the LHA↓ → the expressions of GABAAR β 1 and GABABR1 in LHA↓
Brenner *et al*., 2021 [24]	Acute experimental colitis	Ad libitum access to dextran sulfate sodium in tap water for 5 days	Adult male C57Bl6 mice (12–16 weeks old, weight: 25–30 g)	MCC, PI, ACC	Activity of the MCC↓ → visceral hypersensitivity↓, CRD → the excitability of the PI, somatosensory, and the rostral ACC

Table 1. Continued.

Reference	Type of disease	Model induction	Experimental animal information	Neural nuclei/region	Results
Teratani *et al*., 2020 [25]	Colitis	2% dextran sulfate sodium in drinking water	C57BL/6 (WT) mice, BALB/c mice, Jcl, Ly5.1 mice, Foxp3CreERT2 mice, Cx3cr1GFP/GFP transgenic mice, Rag2-knockout mice and Myd88-knockout mice (6–8 weeks)	NTS	The hepatic vagal sensory afferent nerves → NTS → the vagal parasympathetic nerves and enteric neurons
Sun *et al*., 2018 [26]	NEC	Fed with increasing doses of different types of human donor milk and decreasing doses of parenteral nutrition	Preterm piglets	Hippocampus	Si-NEC and Co-NEC were associated with different hippocampal expressed genes; NEC lesions → the proportion of amoeboid microglial cells
Zhang *et al*., 2024 [27]	NCI	Inject 0.5% acetic acid into the colorectum	Male and female C57BL/6J mice	PVT, IC	NCI → c-fos expression and calcium activity upon CRD in the IC^{Glu}↑ → colorectal visceral pain↑; the PVT^{Glu} → IC^{Glu} → colorectal visceral pain responses
Matisz *et al*., 2022 [28]	Acute gut inflammation	2% DSS or 3% DSS added to the drinking water for 5 days	Male C57BL6J mice (7–8 weeks)	Hippocampus	Dextran sodium sulfate concentration on apical dendrites in the CA1 hippocampus↑ → the proportion of head spines↓
Mumphrey *et al*., 2016 [29]	Anorexia	Roux-en-Y gastric bypass surgery	Male C57BL6J mice	LPBN, NTS, amygdala	Obese mouse model of RYGB → calcitonin gene-related peptide neurons in the external LPBN as well as neurons in the nucleus tractus solitaries, area postrema, and medial amygdala↑
Mishra *et al*., 2024 [30]	Anorexia	LPBN astrocyte activation-induced	Male and female Sprague-Dawley rats (5 weeks)	LPBN	NMDA receptor blockade↓ → LPBN astrocyte activation → food intake↓ → anorexia
Helm *et al*., 2003 [31]	Anorexia	Serotonin or CCK-8 injected in the PVN significantly decreased ipsilateral accumbens DA	Male Sprague-Dawley rats (weight: 350–400 g)	PVN, Accumbens	Serotonin or CCK-8 injected in the PVN → ipsilateral accumbens dopamine; 5-HT plus CCK injected in combination → dopamine↓, extracellular ACh↑
Rinaman, 2003 [32]	Anorexia	CCK-induced	Adult male Sprague-Dawley rats	Hypothalamic, amygdala, VLM, NTS, PVN	Anorexia → Hypothalamic c-fos expression↓, neural activation in the parabrachial nucleus and amygdala appeared normal; VLM activation → CCK-induced c-fos expression in NTS lesions and PVN↓
Alhadeff *et al*., 2015 [33]	Cisplatin-induced anorexia	Cisplatin-induced	Male Sprague-Dawley rats (weight: 250–265 g)	DVC, LPBN, CeA, NTS	Cisplatin treatment → CeA gene expressions of AMPA and NMDA glutamate receptor↑; In animals injected with LPBN fluorogold → c-fos-expressing AP cells in cisplatin-treated animals↑; In the NTS → c-fos-expressing cells in cisplatin-treated animals↑; In the DVC of animals with CeA-injected fluorogold → c-fos-expressing neurons in the NTS of cisplatin-treated rats

Table 1. Continued.

Reference	Type of disease	Model induction	Experimental animal information	Neural nuclei/region	Results
Wang *et al*., 2023 [34]	GD	500 μL of 37 °C saline was injected into the balloon with a rate of 0.5 mL/s	Male C57BL/6J and CRH-Cre mice (8–10 weeks old)	PVN, DMV	GD induced gastric motility disorders → activation of PVN^{CRH} neurons; PVN^{CRH} neurons project into DMV^{ChAT} neurons → regulation of PVN^{CRH} → modulated activity of the PVN^{CRH} → DMV^{ChAT} pathway → gastric motility disorders induced by GD↓
Kim *et al*., 2020 [35]	GD	/	Male and female C57BL/6, Pdyncre/+ and Gt (Rosa)26Sortm14(CAG-tdTomato)Hze/J (Ai14) mice (6 weeks)	PBN	Ingestion and oral and gastric irritation, individual PB^{Pdyn} neurons↑; Signs of GD → vagus nerve → PB^{Pdyn} neurons → appetite suppression signals
Min *et al*., 2011 [36]	GD	Implanted with intra-gastric balloons or intra-gastric catheters	Male Sprague-Dawley rats	Hypothalamus, NTS, hippocampus, amygdala, thalamus, cerebellum, cingulate, insular, motor, and sensory cortices	Gastric distension → BOLD fMRI activity within homeostatic regions (the hypothalamus and NTS), non-homeostatic regions (the hippocampus, amygdala, thalamus, cerebellum, cingulate, insular, motor, and sensory cortices)↑
Horn *et al*., 2014 [37]	Emesis	Subdiaphragmatic vagotomy on $CuSO_4$	Adult musk shrews and adult male Sprague-Dawley rats	DVC, PBN, PVN, BNST	Musk shrews-$CuSO_4$ (++++)- PVN/BNST-NTS/PBN-vagus nerve-AP-emesis
Billig *et al*., 2001 [38]	Emesis	Intraperitoneal injection of lithium chloride (LiCl; 86 mg/kg)	Male ferrets (weight: 1.5–2.0 kg)	DVC, PVT, supraoptic nuclei of the hypothalamus, NTS, CeA, BNST	Intravenous administration of CCK octapeptide → neurons of DVC, PVT, supraoptic nuclei of the hypothalamus, NTS, CeA, and BNST↑
Zhang *et al*., 2021 [39]	Constipation	Loperamide	Adult male Sprague-Dawley rats (6 to 8 weeks old)	DMV, NTS	Model rats-AVNS → the c-fos expression in both NTS and DMV↑, vagal efferent activity↑
Bhagat *et al*., 2015 [40]	HFD	High fat diet	Timed pregnant Sprague-Dawley rat dams	DMV	HFD → the excitability and input resistance of DMV neurons↓, fire action potentials↓; the tonic activation of presynaptic group II metabotropic glutamate receptors on inhibitory nerve terminals↓ → modulation of GABAergic synaptic transmission↓; the size and dendritic arborization of gastric-projecting DMV neurons↑
Alhadeff and Grill, 2014 [41]	Food intake	/	Adult male Sprague-Dawley rats (weight: 250–300 g)	mNTS	MNTS GLP-1 R↑ → intake of a palatable high-fat diet, operant responding for sucrose under a progressive ratio schedule of reinforcement, and the expression of a conditioned place preference for a palatable food↓
Duraffourd *et al*., 2012 [42]	Food intake	/	Adult male Sprague-Dawley rats (6 to 8 weeks, weight: 260–280 g)	DVC, PBN, NTS, PVN, LHA, ARC	C-fos activation took place in the main hypothalamic regions (NTS, PVN, LHA, ARC); Nalox infusion → induction of c-fos in the DVC, NTS, and PBN

Table 1. Continued.

Reference	Type of disease	Model induction	Experimental animal information	Neural nuclei/region	Results
Kosugi *et al*., 2021 [43]	Food intake	/	Male and female C57BL/6J mice (3 to 12 months old)	Hippocampus, LS	Food stimulate → (vHip↑/vCA1$^{\rightarrow LS}$↑) → feeding↑; sated mice-food stimulate → (vHip↓/vCA1$^{\rightarrow LS}$↓) → feeding↓
Scott *et al*., 2025 [44]	Food intake	/	C57BL/6J mice	HPA axis	Chemogenetic excitation of NG^{Oxtr} → food and water consumption↓, patterns of brain activity associated with augmented HPA axis activity, and behavioural indices of vigilance. Recurrent excitation of NG^{Oxtr} → food intake and lowers body mass↓
Huang *et al*., 2024 [45]	Food intake	/	Adult male and female Glp1r-ires-Cre, Ai9, Glp1rtm1Ssis and C57BL/6 J mice (8 weeks old)	NTS	NTS^{GLP1R} neurons↑ → satiety in the absence of aversion, AP^{GLP1R} neurons↑ → strong aversion with food intake reduction
Kuo *et al*., 2007 [46]	Appetite	/	Male C57BL/6 mice (16–24 weeks)	ARC, PVT, ventromedial nuclei	Peripheral injection of the orexigenic peptide ghrelin → signal intensity in key appetite-regulatory regions of the hypothalamus (ARC, PVT, and ventromedial nuclei)↑
Fan *et al*., 2023 [47]	Overeating disorders	Consecutive 11-day restriction + stress (R + S) cycles	Female rats	PVT	PVT glutamatergic neurons↓ → abnormal preference for HPF and excessive food intake in overeating disorders mice↓
Qiao *et al*., 2011 [48]	Gastric motility	/	Male and female Sprague-Dawley rats (weight: 250–320 g)	LC, NRM, DMV	LC stimulation → the gastric motility↓, blocking the α receptor on DMV → reverse the effect; NRM stimulation → the amplitude of gastric constriction↓, DMV lesion → abolish the effect
Tebbe *et al*., 2005 [49]	Gastric motility	/	Male Sprague-Dawley rats (weight: 400 $\pm$ 50 g)	ARC, PVN	Microinjection of the non-selective CRF receptor antagonist into the PVN → stimulatory effect of neuronal activation in the ARC by kainate on colonic motor function↓; neurons in the ARC↑ → CRF-receptor-mediated mechanism in the PVN → colonic motility↑
Herman *et al*., 2009 [50]	Gastric motility	/	Adult male Sprague-Dawley rats (weight: 250–350 g)	NTS, DMV	$GABA_A$ receptor blockade in the mNTS → gastric motility↑, local inhibitory signaling by NTS interneurons is interposed between vagal afferent nerve fibers and NTS projection neurons that in turn regulate the activity of DMV neurons
Nasse, 2014 [51]	GI function	/	Sprague-Dawley rat pups with dam	NTS	Sensory, integrative, and motor nuclei that are critical to oromotor and GI function → axonal projections from the NST to the reticular formation and from the reticular formation to the hypoglossal motor nucleus (mXII) persist

Table 1. Continued.

Reference	Type of disease	Model induction	Experimental animal information	Neural nuclei/region	Results
Malloy *et al.*, 2012 [52]	GI rhythms	/	Male wild-type Sv/129 mice	SCN	When animals are presented with food ad libitum, surgical ablation of the SCN → abolishes circadian locomotor, feeding, and stool output rhythms, while restricted feeding reestablishes these rhythms temporarily
Bülbül and Sinen, 2022 [53]	GI dysmotility	Exposed to maternal separation in newborn & exposed to chronic homotypic stress in adulthood	Adult male Wistar rats (weight: 250–300 g)	LC, PVN, CeA, DMV	NPSR expression was detected in CRF-producing cells of PVN and CeA. NPSR was present in ChAT-expressing neurons in DMV, and nucleus ambiguus in addition to the TH-positive neurons in C1/A1, and LC
Hermann *et al.*, 2008 [54]	GI dysmotility	Nanoinjection of SDF-1 into the DVC	Male and female Long–Evans rats (weight: 200–400 g)	DVC, NTS, DMV	Nanoinjection of SDF-1 into the DVC → gastric motility↓, c-fos-activated neurons in the NTS and DMV↑, CXCR4-immunoreactivity is also intense on microglia within the DVC, though not on the astrocytes
Zhang *et al.*, 2017 [55]	GI dysmotility	Glucagon	Rats	Somatic nerve-spinal cord-NTS-DMV-vagus efferent pathway	Electroacupuncture enhanced vagal activity → the number of c-fos positive cells in DMV and NTS↑, → GI dysmotility↓; Spinalization → gastric facilitative response disappeared; Somatic nerve-spinal cord-NTS-DMV-vagus efferent pathway
Arima *et al.*, 2017 [56]	GI failure	Induction of brain micro-inflammation at specific vessels by cytokine injection	C57BL/6 mice	DMH	Model mice → TH+ noradrenergic neurons↑-ATP↑-DMH/third ventricle region/dentate gyrus-vagal nerve-p38/MAPKAPK2↑ → GI failure
Wang *et al.*, 2023 [57]	Gastric motility disorder	Restraint stress combined with irregular feeding	Ai9 (RCL-tdT), GAD2-Cre, and C57BL/6J mice (8–10 weeks)	DVC, CeA	Restraint stress → gastric emptying↓, gastric motility and food intake↓; CeA GABAergic neurons↑; DVC neurons↓; CeA^{GABA} neurons and the CeA^{GABA} → DVC pathway↓ → gastric movement and gastric emptying↑
Zhang *et al.*, 2018 [58]	Visceral pain	Neonatal maternal deprivation	Male Sprague-Dawley rats	Right hemisphere of IC	Expression of P2X3Rs both at mRNA and protein levels in the right hemisphere of IC↑; frequency and amplitude of miniature excitatory postsynaptic current in the right hemisphere of IC↑
Zhang *et al.*, 2024 [59]	Gastric pain	Performing gastric balloon implantation surgery	Male and female C57BL/6J mice (6–8 weeks)	NTS, LPBN, PVT, prelimbic cortex	Gastric distension → NTS → vagus nerve → lateral paraventricular nucleus, PVT → prelimbic cortex

Table 1. Continued.

Reference	Type of disease	Model induction	Experimental animal information	Neural nuclei/region	Results
Bernanke *et al*., 2022 [60]	ANV	A novel context was repeatedly paired with the emetogenic agent LiCl	Male and female Sprague-Dawley rats	Frontal cortex, insula, and PVN of the hypothalamus	ANV → c-fos expression of the frontal cortex, insula, and PVN of the hypothalamus of males↑
Holmes *et al*., 2009 [61]	Gastric tone and esophageal-gastric reflex	CCK-8s microinjected in the DVC or applied on the floor of the fourth ventricle	Male Sprague-Dawley rats (weight: 175–250 g)	DVC	CCK-8s micro-injected in the DVC → gastric tone↓
Fan *et al*., 2018 [62]	Gastric mucosal damage	Restraint water-immersion stress	Male Wistar rats (weight: 220–250 g)	LC	Intracerebroventricular injection of c-fos antisense oligodeoxynucleotides and astrocytic toxin L-a-aminoadipate (L-AA) → the gastric mucosal damage↓ → the activation of neurons and astrocytes in the LC↓
Chang *et al*., 2024 [63]	Gut microbiome and immunity	/	Adult male mice: C57BL/6J, Glp1r-ires-Cre, Glp1r-ires-Cre × Ai148D, Glp1r-ires-Cre × CD63-emGFPl/s/l, Glp1r-ires-Cre × Ai148D × Ai9, Glp1r-ires-Cre × ROSA26iDTR, Glp1r-ires-Cre × Ai148D × ROSA26iDTR, Ai9 × Glp1r-ires-Cre, Glp1r-ires-Cre × CAG-Sun1/sfGFP, B6J.ChAT-ires-Cre: Δneo, $Cckar^{Cre}$ × Ai9, ChAT-ChR2-EYFP line 6	CeA	Chronic stress → CeA activity↓; CeA↑ → Brunner's glands↑, reversed the effects of stress on the gut microbiome and immunity

IBS, irritable bowel syndrome; CRD, colorectal distension; HPA, hypothalamic-pituitary-adrenal; MS, maternally separated; TNBS, trinitrobenzene sulfonic acid; CRF, corticotropin-releasing factor; PVN, paraventricular nucleus; BNST, bed nucleus of the stria terminalis; CeA, central amygdala; LHA, lateral hypothalamic area; VLM, ventrolateral medulla; FD, functional dyspepsia; NTS, nucleus tractus solitarius; AVNS, auricular vagal nerve stimulation; DMV, dorsal motor nucleus of the vagus; GI, gastrointestinal; DRN, dorsal raphe nucleus; BLA, basolateral amygdala; FN, fastigial nucleus; MCC, middle cingulate cortex; PI, posterior insula; ACC, anterior cingulate cortex; NEC, necrotizing enterocolitis; NCI, neonatal colonic inflammation; PVT, paraventricular thalamus; IC, insular cortex; LPBN, lateral parabrachial nucleus; RYGB, Roux-en-Y gastric bypass; NMDA, N-Methyl-D-Aspartate; DVC, dorsal vagal complex; AP, area postrema; LS, lateral septum; GD, gastric dilation; HFD, high fat diet; ARC, arcuate nucleus; LC, locus coeruleus; NRM, nucleus raphe magnus; SCN, suprachiasmatic nucleus; DMH, dorsomedial nucleus of the hypothalamus; ANV, anticipatory nausea and vomiting; ↑, increase or activation; ↓, decrease or inhibition; TrkA, tropomyosin receptor kinase A; PLC-γ, phospholipase C-γ; NGF, nerve growth factor; GABA, γ-aminobutyric acid; CNQX, an AMPAR inhibitor; GluR2, Glutamate receptor 2; K252a, an inhibitor of TrkA; TRPV1, transient receptor potential vanilloid 1; NF-κB p65, nuclear factor kappa B p65; ACh, Acetylcholine; CCK, cholecystokinin; BOLD, blood oxygen level dependent; mNTS, medial nucleus tractus solitarius; GLP-1R, glucagon-like peptide-1 receptor; NPSR, neuropeptide-S receptor; ChAT, choline acetyltransferase.

somatosensory cortex (SI) and the rostral anterior cingulate cortex (rACC) during acute colitis effectively diminished visceral hypersensitivity, anxiety-like behaviors, and visceral motor responses to CRD. These findings highlight the mechanistic role of central cortical circuitry in the manifestation of visceral pain and suggest that plasticity in the cingulate cortex may serve as a therapeutic target for intestinal disorders [8].

2.2 The Insula, Motor, and Sensory Cortices

Prior research has demonstrated that patients with FD exhibit reduced cortical thickness in various brain regions compared to healthy controls, with a significant negative correlation observed between disease duration and cortical thickness in the primary SI [72]. The insular cortex (IC) is intricately associated with the function of the visceral autonomic nervous system and plays a role in digestive muscle movements and autonomic regulation of the GI tract [73]. Blood oxygen level-dependent functional magnetic resonance imaging (BOLD fMRI) studies in humans have highlighted the involvement of higher corticolimbic structures in the satiation effects of gastric distension [74]. Additionally, the IC, SI, and motor cortex, identified as "non-homeostatic" regions, regulate food intake. An animal study utilized brain imaging to observe global spatiotemporal changes in BOLD fMRI signals within the brains of adult male rats during gastric distension, while continuously monitoring blood pressure. Gastric distension was found to elevate BOLD fMRI activity in homeostatic regions, including the IC and the motor and sensory cortices [36]. Additionally, significant upregulation of P2X3 receptor expression was observed at both the mRNA and protein levels in the right hemisphere of the IC in rats experiencing chronic visceral pain. Electrophysiological recordings of synaptic transmission in IC brain slices using the membrane clamp technique revealed a notable increase in the frequency and amplitude of miniature excitatory postsynaptic currents in the right hemisphere of the IC in these rats [58].

3. Relationship Between Gastrointestinal Disorders and Hypothalamus-Related Nuclei

The hypothalamus plays a critical role in maintaining homeostasis by regulating endocrine and autonomic functions, and is also implicated in regulating appetite, weight, mood, and behavior. It is anatomically divided into four central regions: anterior, medial, lateral, and posterior. Dysfunction in any of these specific areas leads to distinct symptoms [75]. The hypothalamus, particularly the paraventricular nucleus (PVN), suprachiasmatic nucleus (SCN), and lateral hypothalamic area (LHA) in the anterior region, is significantly implicated in GI disorders due to its association with appetite regulation and stress-related GI conditions. Additionally, the hypothalamic-pituitary-adrenal (HPA) axis is implicated in the regulation of GI function via neuroendocrine mechanisms, and has also been associated with intestinal inflammation [76,77]. Hyperactivity of the HPA axis has been correlated with synergistic effects between multiple sclerosis and intestinal inflammation [9]. Corticotropin-releasing factor (CRF) serves as a critical regulatory element in the stress response. Increased expression of CRF in the hypothalamus under stress conditions suggests a pivotal role in the mechanisms underlying visceral hypersensitivity signal conduction pathways. Chao *et al.* [10] quantified CRF levels in the spinal cord and brain of rats with IBS. CRF expression was present in the hypothalamus and spinal cord, with a higher positive index observed in IBS rats than in normal rats.

The apelin signaling pathway regulated by the PVN is a potentially novel pharmacological target for treating functional GI disorders. Following both acute stress (AS) and chronic heterogeneous stress (CHeS), elevated hypothalamic apelin and CRF levels were observed in the PVN microdialysis fluid of rats. These levels exhibited negative and positive correlations with gastric emptying and colonic transit, respectively [20]. Activation of the GABAergic bed nucleus of the stria terminalis anteroventral ($BNST_{AV}$)-PVN circuit in maternally separated (MS) mice was shown to reduce the spontaneous firing frequency of PVN CRF neurons, thereby preventing the development of visceral hypersensitivity. GABAergic neurons projecting from the $BNST_{AV}$ to the PVN are implicated in developing MS-induced visceral hypersensitivity, offering new insights into the neural circuit mechanisms underlying chronic visceral pain [11]. Malloy *et al.* [52] showed the SCN is essential for maintaining self-sustaining rhythms in the GI tract. In environments with alternating light-dark cycles and constant darkness, lesions in the SCN of mice disrupt circadian rhythms in locomotor activity, food consumption, fecal counts, and fecal weight.

A recent investigation demonstrated that microinjection of baclofen into the cerebellar parietal nucleus of rats with stress gastric mucosal damage (SGMD) reduced GABA-positive neurons within the LHA, and increased LHA-mediated sympathetic discharges in the ventral tegmentum. This physiological response led to vasoconstriction of the gastric mucosa, thereby exacerbating SGMD and offering novel insights into the roles of the cerebellum and hypothalamus in GI disorders [23]. Another study employing Fluoro-Gold retrograde tracing in conjunction with fluorescence immunohistochemistry reported that GABAergic neurons in the central amygdala (CeA) project to the LHA. Microinjection of a gamma-aminobutyric acid (GABA) receptor antagonist into the LHA of mice with IBS alleviated anxiety, depression-like behaviors, and intestinal motility disorders. In contrast, chemogenetic activation of GABAergic neurons in the CeA-LHA pathway induced anxiety, depression-like behaviors, and intestinal motility disorders in IBS mice, while also inhibiting orexin and its co-expression with GABAA

receptors in the LHA. These findings suggest the CeA-LHA GABAergic pathway may play a role in the pathogenesis of IBS by modulating orexin-A neurons [12].

4. Relationship Between Gastrointestinal Disorders and Brainstem-Associated Nuclei

4.1 Brainstem Vagus Nerve Complex

As the principal center of the autonomic nervous system, the brainstem is integral to regulating internal organ function, and its impairment can result in GI dysfunction. The dorsal vagal complex (DVC) of the brainstem encompasses the vagus nerve afferent terminals in the nucleus tractus solitarius (NTS), visceral efferent motor neurons in the dorsal motor nucleus of the vagus (DMV), and neurons in the area postrema (AP), all of which are responsible for neural regulation of digestive function from the oral cavity to the transverse colon [78,79].

Cholecystokinin (CCK) directly influences brainstem structures, impacting GI function through its involvement in vagal-vagal brainstem circuits that convey effector responses to the GI [80,81]. Microinjection of CCK-8 into the DVC results in an immediate and transient reduction in gastric tone, indicating that application of CCK-8 to the brainstem can stimulate the vagus nerve to mediate gastric relaxation and temporarily reverse the vagal-gastric reflex [61].

The DMV is a primary center for innervating the parasympathetic GI tract, regulating GI activity through vagal efferents. Furthermore, the DMV is interconnected with numerous nuclei in the brainstem, suggesting that various levels of central nuclei within the medulla oblongata may contribute to regulating gastric function through distinct mechanisms involving the DMV [82,83]. The stomach receives acetylcholinergic inputs from the DMV (ACh^{DMV}), which are innervated by serotonergic neurons in the dorsal raphe nucleus ($5\text{-}HT^{DRN}$). The $5\text{-}HT^{DRN} \rightarrow ACh^{DMV} \rightarrow$gastric circuit is inhibited under conditions of chronic stress and gastric hypoplasia. Activation of this circuit reverses gastric dysfunction induced by chronic stress, indicating the $5\text{-}HT^{DRN} \rightarrow ACh^{DMV} \rightarrow$stomach axis is a critical driver of stress-related gastric dysfunction. This finding provides valuable insights into the neural circuitry underlying brain regulation of gastric function [21].

Additionally, the afferent vagus nerve conveys sensory information from the GI and other visceral organs to the brainstem via neuronal synapses in the NTS. Noninvasive auricular vagal nerve stimulation (aVNS) has been shown to enhance colonic transmission in opioid-induced constipated (OIC) rats through pathways involving the NTS, DMV, and vagal efferents [39]. This mechanism is associated with increased c-fos expression in the NTS and DMV, and enhanced vagal efferent activity. NTS acts as the primary central nucleus for pain in harmful gastric distension via the vagus nerve. The prelimbic cortex (PL) is involved in the perception of gastric pain, while the lateral parabrachial nucleus (LPBN) and paraventricular thalamic nucleus (PVT) are key sites for synaptic transmission from the NTS to the PL. Zhang *et al.* [59] reported a four-synaptic neuronal circuit connecting the NTS-LPB-PVT-PL. This circuit transmits gastric injury signals via the vagus nerve.

Nerve growth factor (NGF) is integral to the pathophysiology of GI disorders characterized by visceral hypersensitivity [84]. The expression levels of NGF, tropomyosin receptor kinase A (TrkA), phospholipase C-γ (PLC-γ), and TRPV1 mRNA were found to be markedly elevated in the NTS of rats with FD and gastric hypersensitivity, suggesting disruption of the NGF/TrkA/PLC-γ signaling pathway [17].

4.2 Other Brainstem-Related Nuclei

Other brainstem nuclei, including the locus coeruleus (LC), nucleus raphe magnus (NRM), parabrachial nucleus (PBN), and ventrolateral medulla (VLM), contribute to the regulation of gastric function through their connections with the DVC [85]. The LC processes GI signals from the vagus nerve and the spinal cord, while the NRM modulates gastric motility via its influence on DVC neurons. The PBN receives GI input from the NTS and relays this information to nuclei involved in gastric regulation [48,86]. Furthermore, the NTS maintains fiber connections with the VLM, which modulates visceral function through sympathetic and parasympathetic efferent pathways.

Stimulation of the LC and the NRM was shown to significantly inhibit gastric motility. Destruction of the DMV attenuates this effect, and it can also be reversed by blocking adrenergic α-receptors or $5\text{-}HT_{2A}$ receptors on the DMV. Consequently, the LC may function as a bi-directional regulator of gastric motility via $5\text{-}HT_{2A}$ and α-receptors on the DMV [48]. The LPBN and its astrocytes can modulate feeding behavior. In obese mice, voluntary feeding strongly and selectively activates calcitonin gene-related peptide neurons in the outer LPBN, and neurons in the NTS and AP [29]. LPBN glutamate signaling is a significant factor in anorexia nervosa, and can be triggered by activation of the LPBN [30]. CRD as a pain stimulus enhances VLM neuronal activity and the descending response, while buspirone suppresses CRD-induced neuronal responses. This suggests that buspirone can effectively alleviate abdominal pain symptoms by modulating pain-related VLM neuronal activity [13].

5. Relationship Between Gastrointestinal Disorders and Other Subcortical Nuclei

5.1 Hippocampus

The hippocampus functions as a visceral integration center within the limbic system. It plays a crucial role in the development of chronic visceral pain and is intricately linked to intestinal inflammation and the regulation

of gastric motility [87,88]. α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors are glutamate receptors prevalent throughout the brain. These facilitate the transmission of pain signals, with Glutamate Receptor 2 (GluR2) being one of their subunits [89]. The expression of hippocampal GluR2 was observed to be significantly elevated in rats exhibiting IBS-like symptoms [14]. Furthermore, bilateral intrahippocampal administration of an AMPA receptor inhibitor alleviated visceral pain in these IBS-like rats, thereby contributing to the development of visceral hypersensitivity.

The hippocampus is strongly associated with intestinal inflammation, and mice with colitis have fewer CA1 neurons expressing c-fos [28]. Furthermore, necrotizing enterocolitis (NEC) lesions in the small intestine have been shown to correlate with altered hippocampal gene expression. In pigs with NEC induced by preterm birth, small intestine (Si-NEC) and colon (Co-NEC) were associated with 27 and 12 differentially expressed genes (DEGs) in the hippocampus, respectively. These DEGs include genes related to neuroinflammation and hypoxia, which were upregulated in Si-NEC pigs [26]. Moreover, the hippocampal gyrus is particularly vulnerable to stress-related injury, and the onset of IBS has been linked to diminished expression of G protein and α2A-adrenergic receptor (α2A-AR) in both the hippocampal gyrus and colon. In a rat model that simulates IBS through chronic and acute stress (CAS), the expression of G protein-coupled receptors, such as Gαi and Gαs, in the hippocampus was significantly lower compared to the control group. Moreover, the expression of α2A-AR protein was also reduced in the CAS group relative to the control group [15,90].

5.2 Amygdala

A previous study found that resting-state functional connectivity (rsFC) in the basolateral amygdala and central medial amygdala subregions was significantly elevated in patients with FD compared to healthy individuals [91]. The CeA is an important structure of the limbic system and plays a significant role in controlling fearful emotions [92]. It also regulates GI function and has been implicated in anxiety/stress-related GI dysfunctions [93].

To investigate anterograde tracing of the $CeA^{GABA}\rightarrow$DVC circuit, Wang *et al.* [57] first injected Cre-dependent virus into the unilateral CeA of mice. By employing the membrane clamp analysis technique, these authors found that the $CeA^{GABA}\rightarrow$DVC pathway may be involved in regulating gastric dyskinesia under restraint stress. It was shown that restraint stress delayed gastric emptying (GE), while activating CeA GABAergic neurons and inhibiting DVC neurons. Inhibition of the $CeA^{GABA}\rightarrow$DVC pathway in gastric dyskinesia mice using optogenetic methods enhanced gastric motility and GE. In addition, CeA is a potential response site that mediates the GI side-effects of cisplatin. Notably, the expression of AMPA and N-Methyl-D-Aspartate Receptor (NMDA) glutamate receptor subunits in the CeA was significantly upregulated following cisplatin-induced anorexia. This finding indicates that glutamate receptor signaling in the CeA is crucial for the development of anorexia after cisplatin treatment [33].

5.3 Thalamus

A clinical study of patients with FD identified increased nodal efficiency and nodal degree centrality in the anterior thalamus. The rsFC between the right anterior thalamus and the left nucleus accumbens was significantly associated with scores on the Nepean Dyspepsia Symptom Index and the Nepean Dyspepsia Life Quality Index (NDLQI). Additionally, the nodal efficiency of the right anterior thalamus showed a significant correlation with NDLQI scores [94].

IC is implicated in chronic visceral pain in IBS. The PVT is a crucial relay station for ascending peripheral signals, transmitting visceral pain signals to the IC [95,96]. Neonatal colonic inflammation (NCI) was found to enhance c-fos expression and calcium activity in response to CRD in IC glutamatergic neurons (IC^{Glu}). Modulation of the $glutamatergic^{PVT\text{-}IC}$ pathway through optogenetic, chemogenetic, or pharmacological methods alters colorectal visceral pain responses [27]. Furthermore, selective optogenetic modulation of PVT projections to the IC influences colorectal visceral pain, which can be reversed by chemogenetic manipulation of downstream IC^{Glu}. This study used a mouse model of NCI to identify a novel PVT-IC neural circuit that plays a critical role in colorectal visceral pain.

6. Discussion

The “brain-gut axis” refers to signaling pathways between the CNS and GI. GI diseases often manifest as disruptions in brain-gut interactions, which are intricately linked to brain function. Therefore, elucidating the central mechanisms associated with the GI system is of paramount importance. In this review, 56 animal studies that specifically targeted neural nuclei were analyzed and categorized. Current research is predominantly focused on isolated brain regions or functions, with a notable lack of investigation into the systemic framework and neural circuits. GI dysfunction is generally not attributable to a single brain region or circuit. Instead, it may result from an imbalance in the regulatory hierarchy of the “cortical-subcortical-brainstem” axis. The present study highlights that central regulation involving GI centers is primarily mediated by the cerebral cortex, particularly the frontal and cingulate cortices. These are involved in the emotional integration and cognitive modulation of GI function. Compared to the cortex, subcortical nuclei exhibit a closer association with GI function, in particular the hypothalamus-related nuclei (e.g., PVN, LHA), brainstem-related nuclei (e.g., DVC, DMV, NTS, LC, NRM, PBN, VLM), as well as the hippocampal gyrus,

CeA, thalamus, and other relevant brain regions. These act as a hub that receives cortical signals and relays them to the brainstem (Fig. 2). The brainstem, comprising nuclei such as the DMV and NTS, serves as the primary regulatory center that directly interfaces with GI effectors. The regulation of GI function can thus be conceptualized as following a comprehensive conduction pathway: cortical-subcortical-brainstem multilevel neural circuits.

Moreover, the HPA axis plays a crucial role in regulating GI function via neuroendocrine mechanisms, and has been the focus of significant attention in prior research. Additionally, the sensory, motor, endocrine, and feeding circuits of the GI system are interconnected networks. For instance, the NTS serves not only as a central transmission hub for visceral sensations such as pain, but also as a critical center for regulating vagus nerve activity. It receives projections from the hypothalamus and exhibits advanced integrative functions. Functional circuits within this system can exert reciprocal influences on one another. The CRF neurons located in the PVN and the HPA axis play a role in the development of visceral hypersensitivity and pain [97]. During stress, activation of the HPA axis inhibits appetite-promoting neurons in the arcuate nucleus while enhancing appetite-suppressing neurons, resulting in decreased appetite among patients with GI disorders [98]. Consequently, an imbalance in the hierarchical regulation between cortical and subcortical brainstem structures may lead to cross-circuit dysfunctions in sensory, motor, endocrine, and feeding pathways. Functional abnormalities in key regulatory nodes may serve as pivotal hubs for multi-circuit disorders.

The autonomic nuclei function as the central hub and regulatory center for complex communication between the brain and the GI tract. Key structures, such as the NTS and DMV, are essential components of this brain-gut interaction. It has been reported that puerarin can decrease fat absorption and body weight by shortening jejunal microvilli through the DMV vagal pathway [99]. The therapeutic effects of electroacupuncture at ST 36 on glucagon-induced GI motility disorders are mediated via the somatic motor-spinal-NTS-DMV pathway [55]. The regulatory impact of GI diseases on autonomic nuclei can be conceptualized as forming a maladaptive “brain-gut” positive feedback loop. Aberrant signaling triggers the activation of neuronal and glial cells within the NTS, leading to central sensitization and disrupted information processing. The sensitized NTS then conveys inaccurate signals to the DMV, and simultaneously receives atypical descending inhibition from limbic and stress-associated brain regions. Consequently, this leads to diminished and disorganized efferent activity of the DMV, thereby compromising vagal regulation of GI function. The spinal cord is integral to neural regulation of GI function, serving as a crucial conduit between higher brain centers and GI effectors, as well as functioning as a lower reflex center. Its various segments exhibit distinct functional and anatomical divisions. The thoracic region primarily facilitates inhibitory regulation of the sympathetic nervous system, with its visceral nerves modulating stress responses by inhibiting GI motility, secretion, and inducing vasoconstriction [100]. However, research has shown that the spinal cord, specifically from T8 to T10, is not involved in the transduction of vomiting signals [37]. The dorsal horn of the lumbosacral segment is implicated in sympathetic innervation of the pelvic and upper intestinal tracts, providing innervation to the distal colon and rectum via the pelvic nerve. Studies have reported a pronounced local inflammatory response within the spinal cord in IBS models, which correlates with the inflammatory status of both the intestine and higher brain regions. This provides crucial molecular pathological insights into the mechanisms underlying chronic pain and sensory abnormalities associated with IBS [8,10]. Consequently, the localization of spinal cord segment injuries is intricately linked to the specific type of GI dysfunction observed. Such segment-specific relationships form the foundational basis for understanding GI management strategies, patterns of visceral pain involvement, and GI manifestations of autonomic nervous system disorders following spinal cord injury.

This narrative review provides a systematic examination of the roles played by several key brain regions in GI diseases. However, certain pertinent areas are insufficiently addressed within the current scope of discussion. Clinical trials have demonstrated that basal ganglia nuclei, including the putamen, caudate nucleus, and globus pallidus, are involved in appetite regulation and can influence GI hormone levels. Nonetheless, there is a paucity of animal studies investigating the specific mechanisms by which these nuclei operate within the brain-gut axis. The neural circuitry foundations, signaling pathways, and dynamic interactions with peripheral metabolic indicators require further comprehensive investigation. Future research should incorporate circuit-specific manipulation, *in vivo* recording, and multimodal molecular monitoring in animal models to elucidate the cellular and neural circuit mechanisms that link these neural nuclei to GI disorders. Such investigations may identify novel therapeutic targets for interventions in related metabolic and GI diseases [101]. Furthermore, the microbiota-gut-brain (MGB) axis represents a complex system that facilitates bidirectional communication and dynamic regulation between the gut microbiota and host. The gut microbiota produces a range of metabolites and interacts with the host via neural, immune, and metabolic pathways, thereby influencing brain function and maintaining systemic homeostasis [102]. A growing body of research has highlighted the significant role of the MGB axis in Alzheimer’s disease [103], stroke [104], depression, anxiety [105], and neurodevelopmental disorders [106]. Modulation of the MGB axis has been shown to mitigate depressive behaviors in stress-induced depressed rats, reduce brain tissue damage, and restore cognitive function

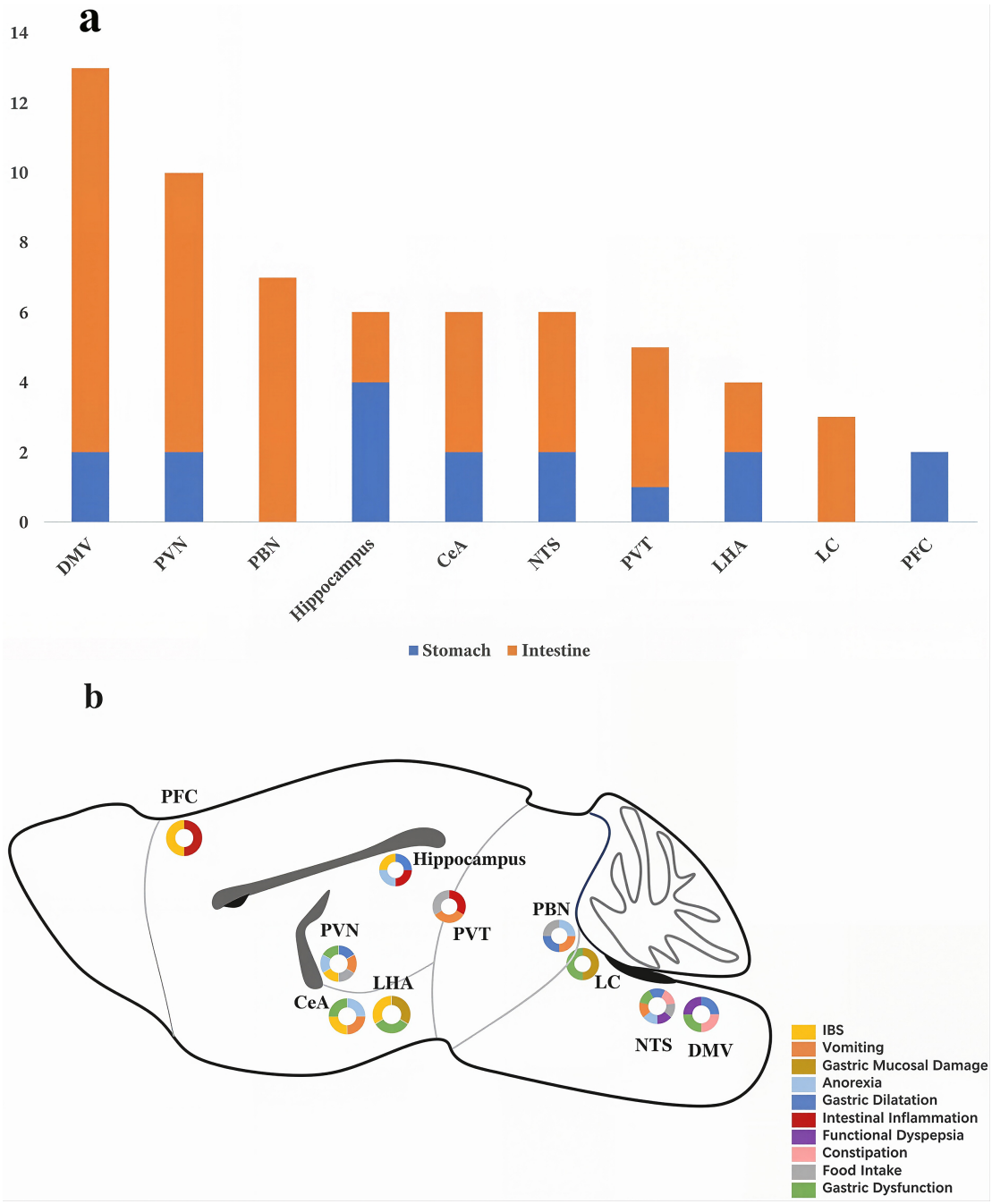

Fig. 2. Major neural nuclei associated with gastrointestinal function. (a) The correspondence between neural nuclei and stomach or intestine. (b) The correspondence between neural nuclei and gastrointestinal function. PFC, prefrontal cortex.

[107]. Consequently, the MGB axis is pivotal in regulating metabolism, immune homeostasis, and CNS function.

The majority of studies reviewed here utilized rodent models (rats and mice), with a minority employing other mammals such as piglets, musk shrews, and snow foxes. There is currently a substantial gap in knowledge regarding the interaction between neural nuclei and GI diseases, and more specifically, there is under-utilization of non-human primate models. Rodent models are indispensable for elucidating the fundamental physiological functions and initial mechanisms of neuronal-gut interactions, offering invaluable insights. However, the structural and social behavioral complexities of rodent nervous systems differ markedly from those of humans, thereby constraining the exploration of certain advanced integrative mechanisms. Primates, such as macaques, are more closely related to humans in terms of systematics, cortical complexity, and cognitive function, particularly in regions associated with advanced integrative brain functions such as the prefrontal cortex, ACC, and insula. Consequently, it is imperative that non-human primate models are employed in research aimed at understanding the integration mech-

anisms of advanced cognitive functions or complex emotions with GI symptoms. This research paradigm can be closely integrated with methodologies such as fMRI, calcium imaging, and detailed behavioral analysis, all of which are essential for successful clinical translation. Future studies should aim to systematically include cross-species comparisons and validations. The establishment of multi-level evidence chains spanning from rodents to primates should help mitigate potential biases arising from model singularity. This approach is anticipated to significantly improve the reliability and success rate for translating fundamental mechanistic insights derived from animal models into therapeutic strategies for human GI diseases.

Epidemiological data show that the incidence of GI diseases is markedly higher in women compared to men. Nonetheless, a pronounced disparity exists in the sex selection of animal models used in current research. Analysis of the 56 animal studies reviewed here revealed that the majority utilized exclusively male rodents. Only a minority of studies incorporated rodents from both sexes, and even fewer studies employed specifically female animals. This predominance of male-focused experimental designs is often justified by concerns that female hormonal cycles may introduce confounding variables. However, this approach systematically underestimates the influence of sex on physiological and pathological GI processes. Consequently, future research should systematically integrate sex as a biological variable in the experimental design, ensuring equal representation of females and males in the animal models. Furthermore, the effect of sex hormone fluctuations on the regulation of the gut-brain axis should also be investigated. The establishment of more gender-balanced experimental systems will improve the validity of clinical extrapolation of research findings. This should in turn provide a more comprehensive understanding of the pathogenesis of GI diseases and offer crucial evidence for the development of sex-specific therapeutic strategies.

In recent years, advancements in neuroscience technology, such as the development and refinement of fluorescent micro-optical sectioning tomography (fMOST) three-dimensional imaging [108], real-time, ultra-large-scale, high-resolution 3D mesoscope (RUSH3D) *in vivo* microimaging [109], viral cis- and retrograde tracing, and photochemical genetic modulation, have paved the way for future research. This progress enables a more comprehensive investigation of cortical-subcortical-brainstem multi-level neural circuits, as well as the cross-organ regulation of central-GI interactions, thereby facilitating a deeper understanding of the underlying mechanisms of GI-brain interactions. Future research should focus on developing real-time monitoring technologies to simultaneously record intestinal metabolites and EEG activity, employing single-cell sequencing technologies to analyze the microbial response mechanisms of specific cell types within the gut-brain axis, integrating microbiome, metabolome, and neuroimaging markers, and establishing risk prediction models for brain and intestinal diseases. Additionally, advancements in identifying specific microbial strains or metabolites as therapeutic targets hold the potential for the development of personalized intervention strategies.

7. Conclusions

In summary, the central mechanisms of GI diseases are rooted in the complex, multi-layer neural network of the brain-gut axis. This review demonstrates that GI function is regulated by a "cortical-subcortical-brainstem" hierarchical structure, in which subcortical and brainstem nuclei represented by the hypothalamus, NTS, and DMV play a central hub role. Abnormalities of these nuclei can trigger central sensitization, disrupt autonomic nervous system balance, and trigger neuroimmune inflammation, leading to a vicious cycle and forming the pathological basis of various GI symptoms.

The limitations of current research are highlighted by insufficient exploration of system level neural circuits and microbial interactions, as well as species and sex biases in animal models. Looking ahead, further advances in this field will rely on the integration of cutting-edge neuroscience technologies, the adoption of multispecies comparative research paradigms, and the implementation of sex-balanced experimental designs. Only through this multidimensional, integrated research strategy can the fine mechanisms of brain-gut interactions be fully decoded, allowing basic research findings to be translated into precise and effective new treatments for GI diseases.

Author Contributions

JX drafted the manuscript and prepared the tables and figures. JKZ and XD identified appropriate references and drafted the manuscript. DW and YFL participated in the literature search and selection. ZXH designed the literature retrieval strategy, reviewed the manuscript, and obtained funding. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

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Conflict of Interest

The authors declare no conflict of interest.

References

[1] GBD 2017 Disease and Injury Incidence and Prevalence Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet (London, England). 2018; 392: 1789–1858. https://doi.org/10.1016/S0140-6736(18)32279-7.

[2] Zhou M, Wang H, Zeng X, Yin P, Zhu J, Chen W, *et al*. Mortality, morbidity, and risk factors in China and its provinces, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet (London, England). 2019; 394: 1145–1158. https://doi.org/10.1016/S0140-6736(19)30427-1.

[3] Chang X, Zhang H, Chen S. Neural circuits regulating visceral pain. Communications Biology. 2024; 7: 457. https://doi.org/10.1038/s42003-024-06148-y.

[4] Parker CG, Dailey MJ, Phillips H, Davis EA. Central sensorymotor crosstalk in the neural gut-brain axis. Autonomic Neuroscience: Basic & Clinical. 2020; 225: 102656. https://doi.org/10.1016/j.autneu.2020.102656.

[5] Khalil M, Zhang Z, Engel MA. Neuro-Immune Networks in Gastrointestinal Disorders. Visceral Medicine. 2019; 35: 52–60. https://doi.org/10.1159/000496838.

[6] Dong XH, Yin T, Yu SY, He ZX, Chen Y, Ma PH, *et al*. Neural Responses of Acupuncture for Treating Functional Dyspepsia: An fMRI Study. Frontiers in Neuroscience. 2022; 16: 819310. http://doi:10.3389/fnins.2022.819310.

[7] Yin T, Teng YK, Zeng F. Neuroimaging in acupuncture research: current status and perspectives. Chinese Bulletin of Life Sciences. 2022; 34: 517–524. https://doi.org/10.13376/j.cbls/2022060. (In Chinese)

[8] Weng ZJ, Wu LY, Zhou CL, Dou CZ, Shi Y, Liu HR, *et al*. Effect of electroacupuncture on P2X3 receptor regulation in the peripheral and central nervous systems of rats with visceral pain caused by irritable bowel syndrome. Purinergic Signalling. 2015; 11: 321–329. https://doi.org/10.1007/s11302-015-9447-6.

[9] Hasegawa R, Saito-Nakaya K, Gu L, Kanazawa M, Fukudo S. Maternal separation and TNBS-induced gut inflammation synergistically alter the sexually differentiated stress response in rats. BioPsychoSocial Medicine. 2023; 17: 7. https://doi.org/10.1186/s13030-022-00258-x.

[10] Chao G, Wang Z, Chen X, Zhang S. Cytokines in the colon, central nervous system and serum of irritable bowel syndrome rats. European Journal of Medical Research. 2021; 26: 7. https://doi.org/10.1186/s40001-021-00479-w.

[11] Huang ST, Song ZJ, Liu Y, Luo WC, Yin Q, Zhang YM. $BNST_{AV}{}^{GABA}$-PVN^{CRF} Circuit Regulates Visceral Hypersensitivity Induced by Maternal Separation in Vgat-Cre Mice. Frontiers in Pharmacology. 2021; 12: 615202. https://doi.org/10.3389/fphar.2021.615202.

[12] He X, Ji P, Guo R, Ming X, Zhang H, Yu L, *et al*. Regulation of the central amygdala on intestinal motility and behavior via the lateral hypothalamus in irritable bowel syndrome model mice. Neurogastroenterology and Motility. 2023; 35: e14498. https://doi.org/10.1111/nmo.14498.

[13] Panteleev SS, Sivachenko IB, Lyubashina OA. The central effects of buspirone on abdominal pain in rats. Neurogastroenterology and Motility. 2018; 30: e13431. https://doi.org/10.1111/nmo.13431.

[14] Chen A, Chen Y, Tang Y, Bao C, Cui Z, Xiao M, *et al*. Hippocampal AMPARs involve the central sensitization of rats with irritable bowel syndrome. Brain and Behavior. 2017; 7: e00650. https://doi.org/10.1002/brb3.650.

[15] Zou N, Lv H, Li J, Yang N, Xue H, Zhu J, *et al*. Changes in brain G proteins and colonic sympathetic neural signaling in chronic-acute combined stress rat model of irritable bowel syndrome (IBS). Translational Research: the Journal of Laboratory and Clinical Medicine. 2008; 152: 283–289. https://doi.org/10.1016/j.trsl.2008.10.002.

[16] Wang WF, Yang YS, Peng LH, Sun G. Alternation of substance P-containing neural pathways in a rat model of irritable bowel syndrome with rectal distension. Chinese Journal of Digestive Diseases. 2006; 7: 211–218. https://doi.org/10.1111/j.1443-9573.2006.00273.x.

[17] Zhou JZ, Chen H, Xu WL, Fu Z, Zhou S, Zhu WJ, *et al*. Auricular Vagal Nerve Stimulation Inhibited Central Nerve Growth Factor/Tropomyosin Receptor Kinase A/Phospholipase C-Gamma Signaling Pathway in Functional Dyspepsia Model Rats With Gastric Hypersensitivity. Neuromodulation: Journal of the International Neuromodulation Society. 2024; 27: 273–283. https://doi.org/10.1016/j.neurom.2023.01.007.

[18] Zhang S, Liu Y, Li S, Ye F, Foreman RD, Chen JDZ. Effects of electroacupuncture on stress-induced gastric dysrhythmia and mechanisms involving autonomic and central nervous systems in functional dyspepsia. American Journal of Physiology. Regulatory, Integrative and Comparative Physiology. 2020; 319: R106–R113. https://doi.org/10.1152/ajpregu.00256.2019.

[19] Hou L, Rong P, Yang Y, Fang J, Wang J, Wang Y, *et al*. Auricular Vagus Nerve Stimulation Improves Visceral Hypersensitivity and Gastric Motility and Depression-like Behaviors via Vago-Vagal Pathway in a Rat Model of Functional Dyspepsia. Brain Sciences. 2023; 13: 253. https://doi.org/10.3390/brainsci13020253.

[20] Bülbül M, İzgüt-Uysal VN, Sinen O, Birsen İ, Tanrıöver G. Central apelin mediates stress-induced gastrointestinal motor dysfunction in rats. American Journal of Physiology. Gastrointestinal and Liver Physiology. 2016; 310: G249–G261. https://doi.org/10.1152/ajpgi.00145.2015.

[21] Dong WY, Zhu X, Tang HD, Huang JY, Zhu MY, Cheng PK, *et al*. Brain regulation of gastric dysfunction induced by stress. Nature Metabolism. 2023; 5: 1494–1505. https://doi.org/10.1038/s42255-023-00866-z.

[22] He X, Li Y, Zhang N, Huang J, Ming X, Guo R, *et al*. Melanin-concentrating hormone promotes anxiety and intestinal dysfunction *via* basolateral amygdala in mice. Frontiers in Pharmacology. 2022; 13: 906057. https://doi.org/10.3389/fphar.2022.906057.

[23] Zhu JZ, Fei SJ, Zhang JF, Zhu SP, Liu ZB, Li TT, *et al*. Lateral hypothalamic area mediated the aggravated effect of microinjection of Baclofen into cerebellar fastigial nucleus on stress gastric mucosal damage in rats. Neuroscience Letters. 2012; 509: 125–129. https://doi.org/10.1016/j.neulet.2011.12.057.

[24] Brenner L, Zerlin L, Tan LL. Functional disruption of cortical cingulate activity attenuates visceral hypersensitivity and anxiety induced by acute experimental colitis. Scientific Reports. 2021; 11: 2103. https://doi.org/10.1038/s41598-021-81256-x.

[25] Teratani T, Mikami Y, Nakamoto N, Suzuki T, Harada Y, Okabayashi K, *et al*. The liver-brain-gut neural arc maintains the T_{reg} cell niche in the gut. Nature. 2020; 585: 591–596. https://doi.org/10.1038/s41586-020-2425-3.

[26] Sun J, Pan X, Christiansen LI, Yuan XL, Skovgaard K, Chatterton DEW, *et al*. Necrotizing enterocolitis is associated with acute brain responses in preterm pigs. Journal of Neuroinflammation. 2018; 15: 180. https://doi.org/10.1186/s12974-018-1201-x.

[27] Zhang FC, Wei YX, Weng RX, Xu QY, Li R, Yu Y, *et al*. Paraventricular thalamus-insular cortex circuit mediates colorectal visceral pain induced by neonatal colonic inflammation in mice. CNS Neuroscience & Therapeutics. 2024; 30: e14534.

https://doi.org/10.1111/cns.14534.
[28] Matisz CE, Semenoff N, Ahmed ASF, Griffin L, Wallace LE, McNabb P, *et al*. Acute gut inflammation reduces neural activity and spine maturity in hippocampus but not basolateral amygdala. Scientific Reports. 2022; 12: 20169. https://doi.org/10.1038/s41598-022-24245-y.
[29] Mumphrey MB, Hao Z, Townsend RL, Patterson LM, Münzberg H, Morrison CD, *et al*. Eating in mice with gastric bypass surgery causes exaggerated activation of brainstem anorexia circuit. International Journal of Obesity (2005). 2016; 40: 921–928. https://doi.org/10.1038/ijo.2016.38.
[30] Mishra D, Richard JE, Maric I, Shevchouk OT, Börchers S, Eerola K, *et al*. Lateral parabrachial nucleus astrocytes control food intake. Frontiers in Endocrinology. 2024; 15: 1389589. https://doi.org/10.3389/fendo.2024.1389589.
[31] Helm KA, Rada P, Hoebel BG. Cholecystokinin combined with serotonin in the hypothalamus limits accumbens dopamine release while increasing acetylcholine: a possible satiation mechanism. Brain Research. 2003; 963: 290–297. https://doi.org/10.1016/s0006-8993(02)04051-9.
[32] Rinaman L. Hindbrain noradrenergic lesions attenuate anorexia and alter central cFos expression in rats after gastric viscerosensory stimulation. The Journal of Neuroscience: the Official Journal of the Society for Neuroscience. 2003; 23: 10084–10092. https://doi.org/10.1523/JNEUROSCI.23-31-10084.2003.
[33] Alhadeff AL, Holland RA, Nelson A, Grill HJ, De Jonghe BC. Glutamate Receptors in the Central Nucleus of the Amygdala Mediate Cisplatin-Induced Malaise and Energy Balance Dysregulation through Direct Hindbrain Projections. The Journal of Neuroscience: the Official Journal of the Society for Neuroscience. 2015; 35: 11094–11104. https://doi.org/10.1523/JNEUROSCI.0440-15.2015.
[34] Wang XY, Chen XQ, Wang GQ, Cai RL, Wang H, Wang HT, *et al*. A neural circuit for gastric motility disorders driven by gastric dilation in mice. Frontiers in Neuroscience. 2023; 17: 1069198. https://doi.org/10.3389/fnins.2023.1069198.
[35] Kim DY, Heo G, Kim M, Kim H, Jin JA, Kim HK, *et al*. A neural circuit mechanism for mechanosensory feedback control of ingestion. Nature. 2020; 580: 376–380. https://doi.org/10.1038/s41586-020-2167-2.
[36] Min DK, Tuor UI, Chelikani PK. Gastric distention induced functional magnetic resonance signal changes in the rodent brain. Neuroscience. 2011; 179: 151–158. https://doi.org/10.1016/j.neuroscience.2011.01.051.
[37] Horn CC, Meyers K, Lim A, Dye M, Pak D, Rinaman L, *et al*. Delineation of vagal emetic pathways: intragastric copper sulfate-induced emesis and viral tract tracing in musk shrews. American Journal of Physiology. Regulatory, Integrative and Comparative Physiology. 2014; 306: R341–R351. https://doi.org/10.1152/ajpregu.00413.2013.
[38] Billig I, Yates BJ, Rinaman L. Plasma hormone levels and central c-Fos expression in ferrets after systemic administration of cholecystokinin. American Journal of Physiology. Regulatory, Integrative and Comparative Physiology. 2001; 281: R1243–R1255. https://doi.org/10.1152/ajpregu.2001.281.4.R1243.
[39] Zhang Y, Lu T, Meng Y, Maisiyiti A, Dong Y, Li S, *et al*. Auricular Vagal Nerve Stimulation Improves Constipation by Enhancing Colon Motility via the Central-Vagal Efferent Pathway in Opioid-Induced Constipated Rats. Neuromodulation: Journal of the International Neuromodulation Society. 2021; 24: 1258–1268. https://doi.org/10.1111/ner.13406.
[40] Bhagat R, Fortna SR, Browning KN. Exposure to a high fat diet during the perinatal period alters vagal motoneurone excitability, even in the absence of obesity. The Journal of Physiology. 2015; 593: 285–303. https://doi.org/10.1113/jphysiol.2014.282806.
[41] Alhadeff AL, Grill HJ. Hindbrain nucleus tractus solitarius glucagon-like peptide-1 receptor signaling reduces appetitive and motivational aspects of feeding. American Journal of Physiology. Regulatory, Integrative and Comparative Physiology. 2014; 307: R465–R470. https://doi.org/10.1152/ajpregu.00179.2014.
[42] Duraffourd C, De Vadder F, Goncalves D, Delaere F, Penhoat A, Brusset B, *et al*. Mu-opioid receptors and dietary protein stimulate a gut-brain neural circuitry limiting food intake. Cell. 2012; 150: 377–388. https://doi.org/10.1016/j.cell.2012.05.039.
[43] Kosugi K, Yoshida K, Suzuki T, Kobayashi K, Yoshida K, Mimura M, *et al*. Activation of ventral CA1 hippocampal neurons projecting to the lateral septum during feeding. Hippocampus. 2021; 31: 294–304. https://doi.org/10.1002/hipo.23289.
[44] Scott KA, Tan Y, Johnson DN, Elsaafien K, Baumer-Harrison C, Méndez-Hernández R, *et al*. Mechanosensation of the heart and gut elicits hypometabolism and vigilance in mice. Nature Metabolism. 2025; 7: 263–275. https://doi.org/10.1038/s42255-024-01205-6.
[45] Huang KP, Acosta AA, Ghidewon MY, McKnight AD, Almeida MS, Nyema NT, *et al*. Dissociable hindbrain GLP1R circuits for satiety and aversion. Nature. 2024; 632: 585–593. https://doi.org/10.1038/s41586-024-07685-6.
[46] Kuo YT, Parkinson JRC, Chaudhri OB, Herlihy AH, So PW, Dhillo WS, *et al*. The temporal sequence of gut peptide CNS interactions tracked in vivo by magnetic resonance imaging. The Journal of Neuroscience: the Official Journal of the Society for Neuroscience. 2007; 27: 12341–12348. https://doi.org/10.1523/JNEUROSCI.2391-07.2007.
[47] Fan S, Guo W, Xiao D, Guan M, Liao T, Peng S, *et al*. Microbiota-gut-brain axis drives overeating disorders. Cell Metabolism. 2023; 35: 2011–2027.e7. https://doi.org/10.1016/j.cmet.2023.09.005.
[48] Qiao H, An SC, Xu C. The relationships among raphe magnus nucleus, locus coeruleus and dorsal motor nucleus of vagus in the descending regulation of gastric motility. Zhongguo Ying Yong Sheng Li Xue Za Zhi = Zhongguo Yingyong Shenglixue Zazhi = Chinese Journal of Applied Physiology. 2011; 27: 124–128. (In Chinese)
[49] Tebbe JJ, Pasat IR, Mönnikes H, Ritter M, Kobelt P, Schäfer MKH. Excitatory stimulation of neurons in the arcuate nucleus initiates central CRF-dependent stimulation of colonic propulsion in rats. Brain Research. 2005; 1036: 130–138. https://doi.org/10.1016/j.brainres.2004.12.034.
[50] Herman MA, Cruz MT, Sahibzada N, Verbalis J, Gillis RA. GABA signaling in the nucleus tractus solitarius sets the level of activity in dorsal motor nucleus of the vagus cholinergic neurons in the vagovagal circuit. American Journal of Physiology. Gastrointestinal and Liver Physiology. 2009; 296: G101–G111. https://doi.org/10.1152/ajpgi.90504.2008.
[51] Nasse JS. A novel slice preparation to study medullary oromotor and autonomic circuits in vitro. Journal of Neuroscience Methods. 2014; 237: 41–53. https://doi.org/10.1016/j.jneumeth.2014.08.023.
[52] Malloy JN, Paulose JK, Li Y, Cassone VM. Circadian rhythms of gastrointestinal function are regulated by both central and peripheral oscillators. American Journal of Physiology. Gastrointestinal and Liver Physiology. 2012; 303: G461–G473. https://doi.org/10.1152/ajpgi.00369.2011.
[53] Bülbül M, Sinen O. Centrally Administered Neuropeptide-S Alleviates Gastrointestinal Dysmotility Induced by Neonatal Maternal Separation. Neurogastroenterology and Motility. 2022; 34: e14269. https://doi.org/10.1111/nmo.14269.
[54] Hermann GE, Van Meter MJ, Rogers RC. CXCR4 receptors in the dorsal medulla: implications for autonomic dysfunction. The European Journal of Neuroscience. 2008; 27: 855–864. https://doi.org/10.1111/j.1460-9568.2008.06058.x.

[55] Zhang NN, Zhang SG, Zhang H, Jiang LQ, Yin JY, Chen JD. Somatic-spinal-vagal pathway involved in the ameliorating effect of electroacupuncture on gastrointestinal dysmotility in rats. Gastroenterology. 2017; 152: S924. https://doi.org/10.1016/S0016-5085(17)33154-2.

[56] Arima Y, Ohki T, Nishikawa N, Higuchi K, Ota M, Tanaka Y, *et al*. Brain micro-inflammation at specific vessels dysregulates organ-homeostasis via the activation of a new neural circuit. eLife. 2017; 6: e25517. https://doi.org/10.7554/eLife.25517.

[57] Wang H, Liu WJ, Wang XY, Chen XQ, Cai RL, Zhang MT, *et al*. A central amygdala input to the dorsal vagal complex controls gastric motility in mice under restraint stress. Frontiers in Physiology. 2023; 14: 1074979. https://doi.org/10.3389/fphys.2023.1074979.

[58] Zhang PA, Zhu HY, Xu QY, Du WJ, Hu S, Xu GY. Sensitization of P2X3 receptors in insular cortex contributes to visceral pain of adult rats with neonatal maternal deprivation. Molecular Pain. 2018; 14: 1744806918764731. https://doi.org/10.1177/1744806918764731.

[59] Zhang FC, Weng RX, Li D, Li YC, Dai XX, Hu S, *et al*. A vagus nerve dominant tetra-synaptic ascending pathway for gastric pain processing. Nature Communications. 2024; 15: 9824. https://doi.org/10.1038/s41467-024-54056-w.

[60] Bernanke A, Sette S, Hernandez N, Zimmerman S, Murphy J, Francis R, *et al*. Male and female rats exhibit comparable gaping behavior but activate brain regions differently during expression of conditioned nausea. Behavioural Pharmacology. 2022; 33: 291–300. https://doi.org/10.1097/FBP.0000000000000676.

[61] Holmes GM, Tong M, Travagli RA. Effects of brain stem cholecystokinin-8s on gastric tone and esophageal-gastric reflex. American Journal of Physiology. Gastrointestinal and Liver Physiology. 2009; 296: G621–G631. https://doi.org/10.1152/ajpgi.90567.2008.

[62] Fan F, Li L, Liu W, Yang M, Ma X, Sun H. Astrocytes and neurons in locus coeruleus mediate restraint water immersion stress-induced gastric mucosal damage through the ERK1/2 signaling pathway. Neuroscience Letters. 2018; 675: 95–102. https://doi.org/10.1016/j.neulet.2018.03.054.

[63] Chang H, Perkins MH, Novaes LS, Qian F, Zhang T, Neckel PH, *et al*. Stress-sensitive neural circuits change the gut microbiome via duodenal glands. Cell. 2024; 187: 5393–5412.e30. https://doi.org/10.1016/j.cell.2024.07.019.

[64] Wang J, Liu G, Xu K, Ai K, Huang W, Zhang J. The role of neurotransmitters in mediating the relationship between brain alterations and depressive symptoms in patients with inflammatory bowel disease. Human Brain Mapping. 2023; 44: 5357–5371. https://doi.org/10.1002/hbm.26439.

[65] Lu HC, Hsieh JC, Lu CL, Niddam DM, Wu YT, Yeh TC, *et al*. Neuronal correlates in the modulation of placebo analgesia in experimentally-induced esophageal pain: a 3T-fMRI study. Pain. 2010; 148: 75–83. https://doi.org/10.1016/j.pain.2009.10.012.

[66] Margulies DS, Kelly AM, Uddin LQ, Biswal BB, Castellanos FX, Milham MP. Mapping the functional connectivity of anterior cingulate cortex. Neuroimage. 2007; 37: 579–588. https://doi.org/10.1016/j.neuroimage.2007.05.019.

[67] Liu P, Zeng F, Zhou G, Wang J, Wen H, von Deneen KM, *et al*. Alterations of the default mode network in functional dyspepsia patients: a resting-state fmri study. Neurogastroenterology and Motility. 2013; 25: e382–e388. https://doi.org/10.1111/nmo.12131.

[68] Burnstock G. Introduction and perspective, historical note. Frontiers in Cellular Neuroscience. 2013; 7: 227. https://doi.org/10.3389/fncel.2013.00227.

[69] Xu GY, Shenoy M, Winston JH, Mittal S, Pasricha PJ. P2X receptor-mediated visceral hyperalgesia in a rat model of chronic visceral hypersensitivity. Gut. 2008; 57: 1230–1237. https://doi.org/10.1136/gut.2007.134221.

[70] Soares-Bezerra RJ, Calheiros AS, da Silva Ferreira NC, da Silva Frutuoso V, Alves LA. Natural Products as a Source for New Anti-Inflammatory and Analgesic Compounds through the Inhibition of Purinergic P2X Receptors. Pharmaceuticals (Basel, Switzerland). 2013; 6: 650–658. https://doi.org/10.3390/ph6050650.

[71] Burnstock G, Nistri A, Khakh BS, Giniatullin R. ATP-gated P2X receptors in health and disease. Frontiers in Cellular Neuroscience. 2014; 8: 204. https://doi.org/10.3389/fncel.2014.00204.

[72] Liu P, Wang G, Zeng F, Liu Y, Fan Y, Wei Y, *et al*. Abnormal brain structure implicated in patients with functional dyspepsia. Brain Imaging and Behavior. 2018; 12: 459–466. https://doi.org/10.1007/s11682-017-9705-z.

[73] Karaivazoglou K, Aggeletopoulou I, Triantos C. Interoceptive Processing in Functional Gastrointestinal Disorders. International Journal of Molecular Sciences. 2024; 25: 7633. https://doi.org/10.3390/ijms25147633.

[74] Tomasi D, Wang GJ, Wang R, Backus W, Geliebter A, Telang F, *et al*. Association of body mass and brain activation during gastric distention: implications for obesity. PloS One. 2009; 4: e6847. https://doi.org/10.1371/journal.pone.0006847.

[75] Barbier M, Croizier S, Alvarez-Bolado G, Risold PY. The distribution of Dlx1-2 and glutamic acid decarboxylase in the embryonic and adult hypothalamus reveals three differentiated LHA subdivisions in rodents. Journal of Chemical Neuroanatomy. 2022; 121: 102089. https://doi.org/10.1016/j.jchemneu.2022.102089.

[76] Newport DJ, Stowe ZN, Nemeroff CB. Parental depression: animal models of an adverse life event. The American Journal of Psychiatry. 2002; 159: 1265–1283. https://doi.org/10.1176/appi.ajp.159.8.1265.

[77] Karakan T, Ozkul C, Küpeli Akkol E, Bilici S, Sobarzo-Sánchez E, Capasso R. Gut-Brain-Microbiota Axis: Antibiotics and Functional Gastrointestinal Disorders. Nutrients. 2021; 13: 389. https://doi.org/10.3390/nu13020389.

[78] MacDonald AJ, Ellacott KLJ. Astrocytes in the nucleus of the solitary tract: Contributions to neural circuits controlling physiology. Physiology & Behavior. 2020; 223: 112982. https://doi.org/10.1016/j.physbeh.2020.112982.

[79] Browning KN, Travagli RA. Plasticity of vagal brainstem circuits in the control of gastric function. Neurogastroenterology and Motility. 2010; 22: 1154–1163. https://doi.org/10.1111/j.1365-2982.2010.01592.x.

[80] Viard E, Zheng Z, Wan S, Travagli RA. Vagally mediated, nonparacrine effects of cholecystokinin-8s on rat pancreatic exocrine secretion. American Journal of Physiology. Gastrointestinal and Liver Physiology. 2007; 293: G493–G500. https://doi.org/10.1152/ajpgi.00118.2007.

[81] Wan S, Coleman FH, Travagli RA. Cholecystokinin-8s excites identified rat pancreatic-projecting vagal motoneurons. American Journal of Physiology. Gastrointestinal and Liver Physiology. 2007; 293: G484–G492. https://doi.org/10.1152/ajpgi.00116.2007.

[82] Browning KN, Travagli RA. Plasticity of vagal brainstem circuits in the control of gastrointestinal function. Autonomic Neuroscience: Basic & Clinical. 2011; 161: 6–13. https://doi.org/10.1016/j.autneu.2010.11.001.

[83] Travagli RA, Anselmi L. Vagal neurocircuitry and its influence on gastric motility. Nature Reviews. Gastroenterology & Hepatology. 2016; 13: 389–401. https://doi.org/10.1038/nrgastro.2016.76.

[84] Jiang L, Ye B, Wang Y, Yu T, Xu H. Effect and mechanisms of sacral nerve stimulation on visceral hypersensitivity medi-

ated by nerve growth factor. Journal of Cellular and Molecular Medicine. 2019; 23: 8019–8024. https://doi.org/10.1111/jcmm.14660.

[85] Wang H, Shen GM. Is dorsal vagal complex the key nucleus of acupuncture regulation of gastric function? Zhongguo Zhen Jiu = Chinese Acupuncture & Moxibustion. 2020; 40: 89–95. https://doi.org/10.13703/j.0255-2930.20181220-k0002. (In Chinese)

[86] Karimnamazi H, Travers SP, Travers JB. Oral and gastric input to the parabrachial nucleus of the rat. Brain Research. 2002; 957: 193–206. https://doi.org/10.1016/s0006-8993(02)03438-8.

[87] Minami M. Neuronal mechanisms underlying pain-induced negative emotions. Brain and Nerve = Shinkei Kenkyu no Shinpo. 2012; 64: 1241–1247.

[88] Hsu TM, Hahn JD, Konanur VR, Noble EE, Suarez AN, Thai J, *et al*. Hippocampus ghrelin signaling mediates appetite through lateral hypothalamic orexin pathways. eLife. 2015; 4: e11190. https://doi.org/10.7554/eLife.11190.

[89] Song I, Huganir RL. Regulation of AMPA receptors during synaptic plasticity. Trends in Neurosciences. 2002; 25: 578–588. https://doi.org/10.1016/s0166-2236(02)02270-1.

[90] North RA, Surprenant A. Inhibitory synaptic potentials resulting from alpha 2-adrenoceptor activation in guinea-pig submucous plexus neurones. The Journal of Physiology. 1985; 358: 17–33. https://doi.org/10.1113/jphysiol.1985.sp015537.

[91] Zeng F, Sun R, He Z, Chen Y, Lei D, Yin T, *et al*. Altered Functional Connectivity of the Amygdala and Sex Differences in Functional Dyspepsia. Clinical and Translational Gastroenterology. 2019; 10: e00046. https://doi.org/10.14309/ctg.0000000000000046.

[92] Torres-Garcia VM, Rodriguez-Nava E, Roldan-Roldan G, Katz DB, Morin JP. The Role of Basolateral Amygdalar Cholinergic Neuromodulation in Emotional Learning. Journal of Integrative Neuroscience. 2025; 24: 26868. https://doi.org/10.31083/JIN26868.

[93] Becker JJ, Carrasquillo Y. Projections, where art thou: the state and future of the central amygdala. The Journal of Physiology. 2019; 597: 365–366. https://doi.org/10.1113/JP277196.

[94] Zhang P, He Z, Mao Y, Sun R, Qu Y, Chen L, *et al*. Aberrant resting-state functional connectivity and topological properties of the subcortical network in functional dyspepsia patients. Frontiers in Molecular Neuroscience. 2022; 15: 1001557. https://doi.org/10.3389/fnmol.2022.1001557.

[95] Larsson MBO, Tillisch K, Craig AD, Engström M, Labus J, Naliboff B, *et al*. Brain responses to visceral stimuli reflect visceral sensitivity thresholds in patients with irritable bowel syndrome. Gastroenterology. 2012; 142: 463–472.e3. https://doi.org/10.1053/j.gastro.2011.11.022.

[96] Guleria A, Karyampudi A, Singh R, Khetrapal CL, Verma A, Ghoshal UC, *et al*. Mapping of Brain Activations to Rectal Balloon Distension Stimuli in Male Patients with Irritable Bowel Syndrome Using Functional Magnetic Resonance Imaging. Journal of Neurogastroenterology and Motility. 2017; 23: 415–427. https://doi.org/10.5056/jnm16148.

[97] Zhang G, Yu L, Chen ZY, Zhu JS, Hua R, Qin X, *et al*. Activation of corticotropin-releasing factor neurons and microglia in paraventricular nucleus precipitates visceral hypersensitivity induced by colorectal distension in rats. Brain, Behavior, and Immunity. 2016; 55: 93–104. https://doi.org/10.1016/j.bbi.2015.12.022.

[98] Bazhan N, Zelena D. Food-intake regulation during stress by the hypothalamo-pituitary-adrenal axis. Brain Research Bulletin. 2013; 95: 46–53. https://doi.org/10.1016/j.brainresbull.2013.04.002.

[99] Lyu Q, Xue W, Liu R, Ma Q, Kasaragod VB, Sun S, *et al*. A brain-to-gut signal controls intestinal fat absorption. Nature. 2024; 634: 936–943. https://doi.org/10.1038/s41586-024-07929-5.

[100] Holmes GM, Blanke EN. Gastrointestinal dysfunction after spinal cord injury. Experimental Neurology. 2019; 320: 113009. https://doi.org/10.1016/j.expneurol.2019.113009.

[101] Iven J, Biesiekierski JR, Zhao D, Deloose E, O'Daly OG, Depoortere I, *et al*. Intragastric quinine administration decreases hedonic eating in healthy women through peptide-mediated gut-brain signaling mechanisms. Nutritional Neuroscience. 2019; 22: 850–862. https://doi.org/10.1080/1028415X.2018.1457841.

[102] Lin X, Yu Z, Liu Y, Li C, Hu H, Hu JC, *et al*. Gut-X axis. IMeta. 2025; 4: e270. https://doi.org/10.1002/imt2.270.

[103] Xie J, Van Hoecke L, Van Wonterghem E, Van Imschoot G, Andries V, Vereecke L, *et al*. The gut-brain axis in Alzheimer's disease is shaped by commensal gut microbiota derived extracellular vesicles. Gut Microbes. 2025; 17: 2501193. https://doi.org/10.1080/19490976.2025.2501193.

[104] Khan R, Di Gesù CM, Lee J, McCullough LD. The contribution of age-related changes in the gut-brain axis to neurological disorders. Gut Microbes. 2024; 16: 2302801. https://doi.org/10.1080/19490976.2024.2302801.

[105] Wang X, Hu M, Wu W, Lou X, Gao R, Ma T, *et al*. Indole derivatives ameliorated the methamphetamine-induced depression and anxiety via aryl hydrocarbon receptor along "microbiota-brain" axis. Gut Microbes. 2025; 17: 2470386. https://doi.org/10.1080/19490976.2025.2470386.

[106] Wang Q, Yang Q, Liu X. The microbiota-gut-brain axis and neurodevelopmental disorders. Protein & Cell. 2023; 14: 762–775. https://doi.org/10.1093/procel/pwad026.

[107] Zhou J, Zhao Y, Li Y, Li J, Huang J, Liu L, *et al*. Jasmine tea extract prevents CUMS-induced depression-like behaviors through the modulation of microbiota-gut-brain axis. Food Research International (Ottawa, Ont.). 2025; 209: 116214. https://doi.org/10.1016/j.foodres.2025.116214.

[108] Zhong Q, Li A, Jin R, Zhang D, Li X, Jia X, *et al*. High-definition imaging using line-illumination modulation microscopy. Nature Methods. 2021; 18: 309–315. https://doi.org/10.1038/s41592-021-01074-x.

[109] Zhang Y, Wang M, Zhu Q, Guo Y, Liu B, Li J, *et al*. Long-term mesoscale imaging of 3D intercellular dynamics across a mammalian organ. Cell. 2024; 187: 6104–6122.e25. https://doi.org/10.1016/j.cell.2024.08.026.