Neural Circuits of Interoception

Gary G. Berntson[1,*], **Sahib S. Khalsa**[2,3]

[1]Department of Psychology, Ohio State University, Columbus, OH, USA

[2]Laureate Institute for Brain Research, Tulsa, OK, USA

[3]Oxley College of Health Sciences, University of Tulsa, Tulsa, OK, USA

Abstract

The present paper considers recent progress in our understanding of the afferent/ascending neural pathways and neural circuits of interoception. Of particular note is the extensive role of rostral neural systems, including cortical systems, in the recognition of internal body states, and the reciprocal role of efferent/descending systems in the regulation of those states. Together these reciprocal interacting networks entail interoceptive circuits that play an important role in a broad range of functions beyond the homeostatic maintenance of physiological steady-states. These include the regulation of behavioral, cognitive, and affective processes across conscious and nonconscious levels of processing. We highlight recent advances and knowledge gaps that are important for accelerating progress in the study of interoception.

The Concept of Interoception

The notion of an internal sense of the body (e.g., coenesthesis or somesthesis) dates back centuries, although it was Sherrington (1906) who first introduced the term **interoceptive** (see Glossary) to refer to senses that convey information on the internal state of the body. He included taste among these senses [1]. Sherrington contrasted interoception to exteroceptive sensing, or the sensitivity to stimuli emanating from outside the body (including odors), which could yield **projicience** – an explicit self-referential representation of sensory stimuli occurring far away from the body.

Much has changed in our understanding of interoceptive processes since Sherrington's time. For example, gustation is not always considered to be an interoceptive sense (although lower alimentary receptors may be). Gustation and olfaction, however, are special visceral senses – they share common biochemical markers with general visceral afferents [2], and project to central areas implicated in interoception (section on Ascending Pathways). Gustation and olfaction likely play a role in interoceptive processes [3]. Among the most salient evolutions in our concepts of interoception is the considerable broadening of the meaning of the term [4]. The term **visceroception** could perhaps characterize the classic view. However, interoception is now generally considered to entail far more than only visceroception, and to include the emotional and cognitive sequelae of, and conversely, contributions to, internal

[*]Correspondence: berntson@osu.edu (G.G. Berntson).

bodily states and regulation. Contemporary conceptualizations often consider that interoception entails the integrative interpretation of internal and external stimuli – in the cognitive/emotional context – to derive an overall physiological representation of the state of the body, including conscious and nonconscious aspects [3,5–8].

This review considers the **neural pathways** and **neural circuits** of interoception. We focus on recent developments – and gaps – in our understanding of ascending and descending pathways that are essential for interoceptive processing across human and other animal species. One important focus will be on the interactions between interoceptive afferent signaling and the coupled, reciprocal descending regulatory systems that comprise coherent circuits for adaptive regulation.

Interoceptive Sensors

Although Sherrington considered the adequate stimuli for interoception to be chemical, chemoreceptors represent only one of a myriad of interoceptive sensory transducers. These include chemoreceptors, osmoreceptors, glucoreceptors, mechanoreceptors, and humoral receptors, as well as a range of other transduction signalers, such as free nerve endings which mediate visceral pain and temperature sensation (Figure 1).

Chemoreceptors

Chemoreceptors are widespread and are sensitive to a wide variety of chemical states or substances. A classic example is the carotid body chemoreceptor sensitivity to pCO_2, pH, and to a lesser extent pO_2, in the regulation of respiration and cardiovascular reflexes. This chemosensitivity is likely achieved, at least in part, through specific ion channels, such as the Twik-related acid-sensitive K^+ channels 1 and 3 (TASK1/TASK3), that are sensitive to acidosis and pO_2 [9].

There is also a wide range of chemoreceptors that are sensitive to a variety of body conditions and metabolic states; these include central [10] and peripheral [11] glucoreceptors, thermoreceptors [12], gustatory receptors [13], and osmoreceptors [14]. Both central and peripheral osmoreceptors, for example, that are sensitive to the local osmotic pressure (cellular dehydration), are important in eliciting thirst and other drivers of metabolic adjustments to compensate for body water imbalance. Central sensitivity to metabolic conditions is thus conveyed jointly by both peripheral and central chemoreceptors. Although some central neurons may have inherent chemoreceptive sensitivity, it also appears that brain glial cells (astrocytes), that are chemically (but non-synaptically) coupled to neurons, may mediate the sensitivity to local states such as pCO_2/pH, glucose sensitivity and Na^+ sensitivity that participate in controlling hunger and thirst among other functions [15].

As noted earlier, gustatory (taste) receptors have variously been considered as interoceptors or exteroceptors. Gustatory receptors are prototypic chemoreceptors that are tuned to distinct classes of chemical tastant molecules via binding to either G protein-coupled receptors (e.g., sweetness and umami) or directly to ion channel proteins (e.g., saltiness and bitterness). Oral gustatory receptors could be considered to be exteroceptors because they sense stimuli outside the body surface boundary, and that may also be the case for gut gustatory receptors

that lie within the gastric and intestinal wall [16]. However, ingestion (swallowing) marks a decision to move nutrient stimuli into the body, with key implications for homeostasis and survival, perhaps providing a functional demarcation of the transition to an interoceptive signal. It has also been noted that the central projections of gustatory neurons to the nucleus tractus solitarius (NTS) are consistent with other interoceptive pathways. Moreover, functionally significant bitter-taste receptors (TAS2Rs) and olfactory receptors (ORs) have been shown to reside on lung smooth muscle, as well as in other areas such as vascular smooth muscle and central cortical neurons [17]. The ligands for these receptors remain unclear, but may be from both exogenous and endogenous sources (e.g., TAS2Rs may be receptors for acyl-homoserine lactones generated by bacteria, which act to open airways). These and other recent findings suggest the existence of a broad chemoreceptor network that may respond to both endogenous and exogenous ligands. Gustatory receptors, in concert with glucoreceptors, osmoreceptors, hormone receptors (next section) importantly contribute to hunger, thirst, and metabolic homeostasis.

Humoral Receptors

Hormones can have both local paracrine and distant endocrine effects. In the gastrointestinal tract, the classic function of hormones is food intake. Leptin, ghrelin, and cholecystokinin have all been shown to mediate the neural afferent signaling that controls hunger, satiety, and food intake [18,19]. For example, leptin arises (in relation to adipose mass) largely from adipocytes and intestinal enterocytes, and has a hunger-suppressing effect (and other metabolic actions) via a receptor action in the arcuate nucleus of the hypothalamus and other sites. By contrast, ghrelin, arising from gastrointestinal enteroendocrine cells in relation to protein and carbohydrate metabolic status, serves to stimulate hunger and a wide range of other energy homeostatic processes via hypothalamic neuronal receptors in the arcuate nucleus and elsewhere. In addition to central humoral signaling, gut–brain interactions can be mediated by more local hormonal routes at local receptor sites ([18] and the section on Ascending Systems).

Other examples of humoral receptor processes include adrenal hormones (epinephrine, adrenomedullin, and cortisol) that have multiple and diverse actions on both central and peripheral receptor sites, and yield a variety of excitatory/sympathetic effects (adrenaline) and vasoconstrictor and other cardiovascular actions (adrenomedullin [20]). In addition, a wide range of hormonal receptors mediate the actions of central endocrine secretions such as gonadotropin-releasing hormone, luteinizing hormone, growth hormone, vasopressin, oxytocin, among others (section on Descending Systems). Of considerable significance is the presence of a variety of **autonomic nervous system** (ANS) and endocrine receptors on immune cells which now appear to exert powerful influences on immune function and inflammatory reactions, such as those associated with asthma and the vagal anti-inflammatory pathway [21].

Specialized Mechanoreceptors

Baroreceptors are the prototypic interoceptive mechanoreceptors, which are stretch sensitive neurons within the nodose and petrosal ganglia, having receptor processes extending into the aorta and carotid arteries. Stretch of these receptors initiates an afferent volley that in turn

triggers compensatory reflexes (decreases in heart rate, cardiac contractility, and vascular resistance). Although several ion channels support this process, PIEZO1 and PIEZO2 ion channels have received much attention in the mechanoreception literature [22–24]. PIEZO1 and PIEZO2 are expressed in several tissues, including the lungs [25], bladder [26], gastrointestinal tract [27], sensory ganglia and skin [28], and their role in interoception is probably broader than what has been documented so far.

Free Nerve Endings

Signals to elicit pain as well as heat and cold can be detected by free nerve endings associated with Aδ and C fibers projecting largely to lamina I of the spinal cord (further projections are discussed in the section on Ascending Pathways). These free nerve endings can be highly sensitized by a variety of biochemicals, such as prostaglandins, that are commonly associated with tissue injury and immune reactions. However, they may have some inherent thermal [29] or mechanical sensitivity [30]. Nociceptive transduction and signaling may be further enhanced by specialized Schwann (glial) cells that form a mesh-like matrix around free nerve endings. Optogenetic activation/inactivation of these Schwann cells enhances/reduces mechanical pain, respectively [31]. In this regard, these mechanosensitive Schwann cells express a *PIEZO* gene, encoding a mechanoreceptor similar to those discussed above, that may be relevant for their nociceptive mechanosensitivity [31].

Afferent/Ascending Pathways and Signaling Systems

Considerable progress has been made since the early 20th century conceptions of visceral regulation, which was considered to be largely composed of low-level reflexive mechanisms. Cannon, for example, viewed the 'interofective' system as 'autonomic' because it acts 'automatically, without direction from the cerebral cortex' [32]. It is now apparent, however, that there are major rostral neural contributions to visceral regulation, which in turn generally receive a wide array of ascending visceral afferents. In addition to the nucleus tractus solitarius (NTS), the classical visceral receiving area in the brainstem [33], visceral afferent information is relayed and/or projects more directly to higher levels of the neuraxis. These areas include the parabrachial nucleus [34,35], thalamus [36], hypothalamus [37], hippocampus [38–40], amygdala [41], insula [42,43], primary and secondary somatosensory cortex [44,45], anterior cingulate cortex [46,47], and the orbitofrontal and medial prefrontal cortices [48,49] (Figure 2). These rostral systems will be further discussed in the Efferent Pathways section.

Interoceptive signals can be conveyed to **central nervous system** (CNS) substrates by sensory afferent pathways and humoral messengers, or may be more directly sensed by central neurons and glia as considered above (e.g., osmoreceptors and glucoreceptors). The vagus nerve is a major conduit for interoceptive signals. Although it also carries parasympathetic efferents, it is primarily an afferent pathway conveying information from body interoceptors. Visceral afferents are also carried in cranial nerves (V, VII, IX) and sacral (S2–S4) dorsal roots. Many interoceptor afferents, especially C and Aδ nociceptor afferents, enter the brain via cervical, thoracic and lumbar dorsal roots, terminating largely

in lamina 1 in the dorsal horn, and are then relayed to higher central target sites such as the thalamus and insula via spinothalamic pathways [50]. A 'direct vagal-ascending vagal-activated pathway' from the NTS to insula and secondary somatosensory cortex was also reported in macaque monkeys [51]. Humoral signaling may entail direct actions on the CNS (e.g., insulin and ghrelin effects on hunger) or may act locally in the periphery to trigger further effects (e.g., prostaglandin sensitization of nociceptors). In some cases, internal states may be signaled by multiple pathways that have different temporal dynamics and perhaps only partially overlapping functional actions. How these multiple signals are integrated into an adaptive circuit is an important issue that needs further exploration. We consider this issue through the illustrative example of gut–brain interactions.

Sensory Transduction from Gut to Brain

The brain senses stimuli from surfaces of the body through innervated epithelial **sensors**. For example, the skin mechanoreceptor, the Merkel cell, synapses with somatosensory afferents, thus allowing us to sense fine textures [52]. Likewise, in the tongue, the chemosensory taste cell synapses with facial and vagal nerves, allowing us to perceive flavor [53]. In the gut lumen, however, stimuli were thought to be conveyed to nerves only via the slow paracrine action of hormones (e.g., cholecystokinin, CCK; serotonin, 5-HT; and peptide YY, PYY). Until 2015, to our knowledge, no direct innervation of an epithelial sensory cell had been described [54].

The source of these neuropeptides is the enteroendocrine cell. In the past 10 years, numerous transgenic mouse models were developed to identify enteroendocrine cells. These models allowed the profiling of chemo-, thermo-, and mechanoreceptors in these cells [55,56]. Enteroendocrine cell models were also a foundation for discovering that, in addition to the classic endocrine function of enteroendocrine cells, these cells function as sensory transducers. Using tools for the study of neural circuits, it was uncovered that these cells form synapses throughout the gastrointestinal tract. Over two-thirds of enteroendocrine cells contact PGP9.5-positive sensory nerves in the intestinal mucosa [57], and in the colon these cells synapse using serotonin to transduce noxious stimuli onto spinal nerves [58]. These epithelial innervated sensors are known as neuropod cells [59].

Neuropod cells recapitulate the connections with peripheral sensory neurons even when isolated from the mouse and cocultured *in vitro* [57]. In 2018, it was discovered that neuropod cells synapse with nodose neurons, forming a neural pathway that connects the intestinal lumen with the NTS via a single vagal synapse [59]. This neural circuit can transduce a luminal stimulus in as little as 60 ms. The neuropod cell–vagal neural circuit is essential for the brain to rapidly recognize glucose stimuli from ingested sugars. The entrance of glucose into the neuropod cell stimulates the release of the neurotransmitter glutamate, that activates vagal ionotropic receptors, providing a molecular basis for rapid gut-to-brain sensory transduction [59] (this innate vagal signaling circuit may be different from those involved in conditioned learning, that are vagus-independent [60,61], and could involve cortical and subcortical **neural networks**).

Several studies have highlighted the function of gut–brain circuits in guiding sugar preferences [62–64], but the intestinal cells that drive this behavior were only discovered in

2020. Specifically, a mouse distinguishes sugars from an artificial sweetener guided by the sensory inputs of intestinal neuropod cells [65]. When neuropod cells are silenced, the animal cannot distinguish between sucrose and sucralose, and when neuropod cells are stimulated the animal consumes sucralose as if it were a regular caloric sugar. The neuropod cell uses two different neurotransmitters, glutamate and ATP, to convey signals from sugars and sweeteners, respectively. The discovery that an innate choice of an animal is driven by a specific sensory cell of the gut – the neuropod cell – provides a neural basis for gut interoception [66].

Efferent/Descending Pathways and Regulatory Systems

Although our primary focus is on interoception, it is difficult to separate afferent interoceptive processes from their reciprocal efferent influences that can change the internal environment and reciprocally impact on interoceptive afference. To fully comprehend the functioning of interoceptive circuits, it will be important to understand feedback interactions between the reciprocal afferent/efferent elements in interoceptive circuits.

The nervous system has numerous descending efferent signaling pathways that can influence the state of internal organ systems. These 'command' signals can be initiated centrally or in a reflexive capacity following homeostatic perturbations of body state. They span every system involved in the afferent transmission of interoceptive signals, including the autonomic, endocrine, and immune systems. Although we know a great deal about the neural connections that link autonomic output from centers in the brainstem and spinal cord to specific organs [67], our understanding of the central neural circuits (e.g., limbic and those in the cerebral cortex) that link higher brain function to autonomic output and organ function is limited. Here we summarize some recent conceptual and empirical developments that expand this frontier with respect to the autonomic, endocrine, and immune systems.

Autonomic Efferent Pathways

The concept of a 'central autonomic network' (CAN) – defined as 'an integral component of an internal regulation system through which the brain controls visceromotor, neuroendocrine, pain, and behavioral responses essential for survival,' [68] – is well established [69]. Major components of the CAN are considered to include the anterior cingulate cortex, insular cortex, thalamus, hypothalamus, amygdala, periaqueductal grey (PAG), parabrachial nucleus, NTS, locus coeruleus, and ventrolateral medulla, and these broadly impact sympathetic and parasympathetic autonomic control of internal states. Recent retrograde rabies virus tracing studies have provided a useful means to track the anatomical connections from organs innervated by the sympathetic and parasympathetic limbs of the ANS back to key nodes of the CAN. This work indicates a much broader descending control of the ANS and the internal environment than was initially recognized.

In monkeys, injections of rabies virus into the adrenal medulla, that produces circulating epinephrine and norepinephrine in response to sympathetic efferent innervation, has revealed three distinct cortical networks on the lateral and medial surface of the prefrontal cortex [70], each of which has a human equivalent that is involved in movement [71], cognition [72,73], and affect [74,75]. These corticoadrenal networks are connected via a series of three

synapses. By contrast, the cortical networks controlling the adrenal gland are more limited in the rat, and these originate mainly from the primary/secondary motor cortex and to a lesser extent from sensory regions including the primary somatosensory cortex and the insula [76]. That is, the cortical areas that are the major source of cognitive control in the monkey appear to be absent in the rat, indicating that the network of brain–body connections is more widespread in primates. It will be of interest to further examine the functional implications of these differences, particularly in terms of their contribution to the higher-order processing of cognitive and affective stressors.

In rats, injections of rabies virus into the stomach have recently identified distinct networks in the brain that are linked to sympathetic and parasympathetic function [49]. Parasympathetically active neurons project from the rostral insula and medial prefrontal cortex to the stomach via a series of three synapses, whereas sympathetically active neurons project from the primary/secondary motor and primary somatosensory cortex via four synapses. This finding suggests that the regulation of gut activity may be executed by distinct cortical networks, and reinforces the likelihood that the homeostatic, motivational, and affective processing of gut signals involves a complex set of sensorimotor feedback loops between the brain and periphery.

The cardiovascular system is also highly influenced by the CAN. Dysfunction of particular regions of this network (notably the insular cortex and PAG) has been associated with pathologically heightened autonomic arousal and several cardiac diseases ([77,78], reviewed in [79]).

The complexity of neural afferent/efferent interactions in guiding circuit functions is not to be underestimated. For example, even in the simpler nervous system of the mouse (relative to humans), adaptive feeding behavior can be flexibly shifted by aversive sensing in the insular cortex [80], a region that shows extensive top-down and bottom-up network connectivity with other subcortical and cortical regions [81,82]. Hunger/thirst-dependent patterns of activity in the insula have also been observed to shift in anticipation of 'expected' satiety of the food/water signals [83], suggesting that mice can generate and modify interoceptive predictions in response to on-going contextual changes in the external environment. Further, the ability to precisely and voluntarily control urinary voiding in mice has been localized using optogenetics to a circuit projecting from Barrington nucleus brainstem neurons to the urinary sphincter via spinal interneurons [84]. Mouse regulation of itch has also been linked to specific GABAergic and glutamatergic neurons in the PAG, and selective encoding of aversiveness has been tied to GABAergic neurons [85]. Collectively, these findings illustrate the reciprocal interactions between the mammalian CNS and peripheral nervous systems that both arise from and impact on visceral afference.

Reciprocal Control of the Endocrine System

The hypothalamus is a key region that controls numerous functions crucial for survival, including energy metabolism, thermoregulation, feeding and digestion, fluid and electrolyte balance, sleep– wake cycling, and reproductive and stress endocrine responses [37]. It contains a collection of highly diverse cell populations connected via numerous pathways. Each survival function engages a distinct set of nuclei and pathways within the

hypothalamus, and these are in turn influenced by a broader set of pathways in the brain and viscera. The parabrachial nuclei (PBN), that receives numerous inputs from visceral, including nociceptive, afferents and the NTS, are key relay stations to the hypothalamus that provide ascending interoceptive information and descending feedback/control signals [37].

The neuroendocrine cells of the hypothalamus control the release of hormones directly into the hypophysial bloodstream or indirectly via regulation of hormone-producing cells of the anterior pituitary gland through a complex series of tonic and pulsatile interactions [86]. The sheer scope of functions governed by hypothalamic signaling can be appreciated based on the range of hormones involved – including corticotropins [hypothalamic–pituitary–adrenal (HPA) stress hormone responses], gonadotropins (urogenital and reproductive maturity), thyrotropins (brain and bone development), somatotropins (metabolic and muscle activity), and lactotropes (milk production).

Hypothalamic control of homeostasis is classically viewed as reactive. However, there is growing appreciation that the hypothalamus can exert both reactive and predictive forms of control [87], although this concept is mostly based on non-neuroendocrine functions. Identification of a predictive hypothalamic controller of homeostatic endocrine function would require rethinking of the impact of this brain region on allostatic processes.

Reciprocal Control of the Immune System

There is a reflexive control mechanism by which the CNS regulates the immune system, both in terms of immune responses and inflammatory disease progression. Many neuroimmunomodulatory nodes have been identified through the use of peripheral inflammatory probes to elicit afferent immune signals in the periphery while recording the activity of the CNS. According to this model, peripheral inflammation induces afferent neural signals that converge through the vagus nerve onto the NTS [88]. As mentioned earlier, the NTS has numerous ascending projections to the hypothalamus, amygdala, striatum, cingulate cortex, and insular cortex. The precise role of these regions in regulating immune function and their relationship to interoceptive signaling is unclear [89]. The NTS also has lateral projections through intermediaries to vagal motor neurons in the dorsal vagal motor nucleus (DMN) and the nucleus ambiguus (NA), as well as the rostral ventrolateral medulla (RVLM), which represent the efferent limbs of the pathway. Stimulation of the mouse RVLM [90] or of mouse vagal efferents [91] results in suppression of innate immune responses and downregulation of proinflammatory cytokines in the spleen via a cholinergic mechanism. Humoral pathways can also directly activate regions of the CNS. For example, some inflammatory mediators (e.g., interferon α, interleukin 6) and immune cells (e.g., stress-induced myocytes) can enter the nervous system directly through the circumventricular organs (e.g., area postrema) to exert effects directly on the brain [92].

There is also direct neural coupling between microglial and monocyte activation and neural effector systems (e.g., CNS, ANS, endocrine, and behavioral). For example, exposure to homeostatic threats such as repeated stress leads to microglial activation and macrophage recruitment to the brain, and has been linked to changes in mood and behavior [93]. Neuronal activity related to exteroceptive and interoceptive input also directly regulates microglial dynamics. A recent mouse study found that reducing sensory neuronal activity

globally via general anesthesia or locally via whisker trimming led to increased brain microglial process surveillance [94]. Microglial surveillance was directly controlled by noradrenergic signaling to microglial β-adrenergic receptors and required the mice to be awake, potentially indicating key roles in arousal and environmental processing. It is worth emphasizing that the perspective presented here represents a limited view of the neural regulation of immune function ([95] for comprehensive overview).

Integration of Interoceptive Signals with Higher-Level Processes

Conscious Awareness

Interoceptive processes typically occur beneath the level of conscious awareness, and humans rarely have high-resolution access to what is happening in the body at any moment [96]. Instead, conscious perceptions of interoceptive signals usually arise when body homeostasis is perturbed (e.g., when breathing quickens, the heartbeat surges, or the bladder is full), or when something goes wrong within the body (e.g., when we feel an internal threat such as angina, nausea, or a kidney stone). This parallels aspects of processing by somatic sensory systems, much of which are also nonconscious (e.g., postural reflex control). Subjectively, it seems to be very different from exteroceptive sensory systems, many of whose functions often rely on conscious or wakeful processing (e.g., visual navigation or speech processing). **Interoceptive awareness** thus allows conscious interpretation of self-relevant signals and adaptive regulatory behaviors, such as urination to obtain relief or help seeking to ameliorate sickness symptoms. However, there are multiple features of interoceptive awareness [7,97], of which perceptual accuracy is only one component (Figure 1). There are prominent clinical examples of individual differences in conscious awareness, such as sex differences in the detection of angina triggered by myocardial infarction [98]. There are also some functions that humans never gain awareness of (e.g., liver or kidney). Finally, there are currently no animal models of interoceptive awareness, but, given the homology between cortical regions such as insular cortex in humans and non-human primates [42], this may be worthy of exploration.

Integration

Interoception is increasingly viewed as a bidirectional process between the brain and body, in which multiple feedback and feedforward loops lead to an internal representation of the body. The precise contribution of interoceptive signals (particularly during periods of perturbation) to the perceptual, affective, and cognitive components of these representations is presently unclear, although it is likely to be rooted in constructs such as arousal, attention, motivation, memory, cognition, emotion, language, and culture [99–102]. Relatively little is known about the influence of interoceptive circuits on body regulation signals, their subsequent translation into action, and the ensuing impact on body homeostasis. Determining the relative contributions of bottom-up versus top-down signals to interoception and body regulation is thus an important challenge facing the field. It can be approached by manipulating one system and observing responses in the other (for example, by increasing interoceptive input [103,104], by dampening exteroceptive input [105], by synchronizing exteroceptive stimuli with interoceptive input [106,107], or by directly stimulating relevant circuits [108–110]). In some cases, illusory perceptions can be triggered without even

manipulating interoceptive signals at all – by providing false feedback [111] or by manipulating environmental context [112]. However, perceptual sensitivity for one signal may not generalize to others [113], and it is possible that interoceptive signal processing can impact on exteroceptive perception [114], suggesting that a better understanding of how multiple sensory signals are integrated will be essential to progress further [115]. A purely reductionistic approach may not suffice given the complexity involved; instead, progress may be informed by approaches that take into account both the individual components and the interactions between them, namely a dynamic systems approach [116]. Charting the neural basis of interoception and body regulation will ultimately provide a foundation for meaningfully integrating the different perspectives (emotional/affective, cognitive, behavioral, motivational, and even the philosophy of self) on the function and dynamics of interoception in determining health [117].

Concluding Remarks

Interoception involves a wide range of afferent signaling processes spanning sensors, pathways, systems, and circuits. These signaling routes have different temporal dynamics and patterns of interactions, and these will be important to document. Of additional importance is the recognition of afferent signal modification by reciprocal efferent pathways which can impact on the organism's internal environment and, in turn, modulate subsequent afferent signaling. Interoceptive regulatory systems are probably best conceived of as a set of reciprocal afferent/efferent circuits that are engaged in a continuous circular loop of interaction. Future research should be addressed at (i) further elaborating the multisynaptic pathways and circuits connecting the CNS with the internal organs of the body, (ii) clarifying the ascending interoceptive pathways linking the NTS and spinal afferents with higher order regions of the CNS, (iii) understanding how interactions between the neural pathways and circuits of interoception are optimized to integrate information from all incoming sensory signals, and (iv) identifying how the neural mechanisms that affect signal processing determine whether interoceptive signals reach or trigger conscious awareness (see Outstanding Questions).

Acknowledgments

Glossary

Autonomic nervous system (ANS)
a system composed of two populations of nerve cells – sympathetic and parasympathetic – that are connected to peripheral organ systems, to each other, and to the CNS

Central nervous system (CNS)
a system composed of many interconnected populations of nerve cells located in the brain and spinal cord

Interoception

the overall process of how the nervous system (central and autonomic) senses, interprets, and integrates signals originating from within the body, providing a moment-by-moment mapping of the internal landscape of the body across conscious and nonconscious levels

Interoceptive awareness

the act of consciously sensing, interpreting, and integrating information about the state of inner body systems

Neural circuit

a network of anatomically interconnected nerve cells that work together to dynamically guide specific functions

Neural network

a group of anatomically interconnected nerve cells that are categorized according to function

Neural pathway

a series of anatomical connections between nerve cells that enable transmission of a signal from one region to another

Projicience

an explicit sensory representation that is projected onto an object or state in the environment

Sensor

a structure that receives biophysical impulses and transmits a signal reflecting the characteristics of these impulses

Viscoception

the sensory (conscious or nonconscious) recognition of the status of the internal body systems

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Highlights

The nervous system receives ascending communication of interoceptive signals originating from the periphery via chemoreceptor, mechanoreceptor, and osmoreceptor pathways, several of which were discovered only recently.

Visceral systems and associated interoceptive signals are regulated in part by descending central nervous system (CNS) control of the autonomic nervous system, yielding a reciprocal circuit that regulates bodily organs and a wide array of motor, cognitive, and affective processes.

A gap in our understanding of how interoceptive signals are relayed through the CNS from the body centers on inputs to the nucleus tractus solitarius and higher relay pathways.

The neural circuits of interoception are important for behavioral, cognitive, and emotional regulation across conscious and nonconscious levels of processing.

Outstanding Questions

What are the multisynaptic pathways that connect circuits from the CNS with the internal organs of the body (e.g., lungs, stomach, intestine, spleen, heart)?

How do the ascending interoceptive pathways linking the NTS and higher-order regions of the CNS differ between humans and other species?

How are the interactions between the circuits of interoception optimized to integrate information from all incoming sensory signals and to perform the operations necessary to effectively regulate body functioning?

How do the neural mechanisms that affect signal processing determine whether interoceptive signals reach or trigger conscious awareness?
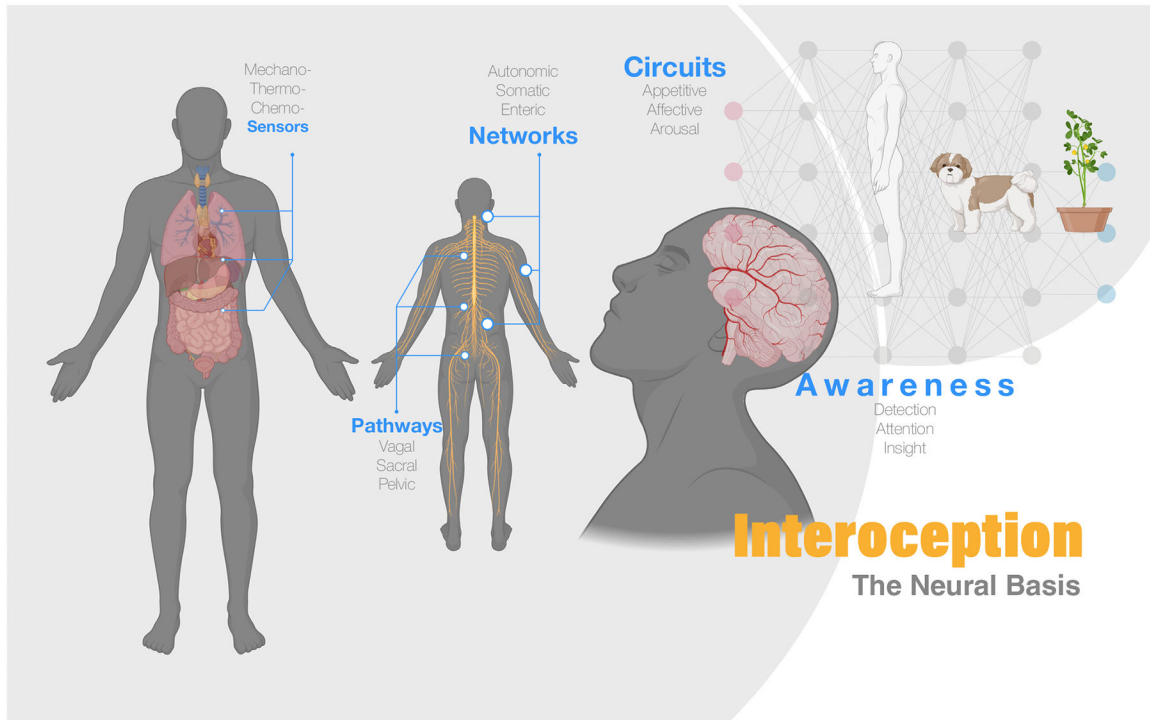
Figure 1. The Continuum of Interoception.
Interoception is a neural process that traverses sensors (e.g., mechanoreceptors, thermoreceptors, chemoreceptors, osmoreceptors, humoral receptors, glucoreceptors, and free nerve endings), pathways (e.g., vagal, cranial, sacral, spinothalamic, and somatosensory), networks (e.g., central and peripheral autonomic, enteric, thalamocortical, hypothalamic, limbic, sensorimotor, salience, and default), circuits (e.g., appetitive, affective, arousal, thermal, nociceptive, cognitive, social, and threat), and awareness (e.g., detection, attention, insight, magnitude, discrimination, accuracy, and sensibility). Each component contributes to the next, although most processing of interoceptive signals occurs beyond the conscious awareness of the organism. Further, interoceptive awareness relies on circuit-based representations of the internal bodily self (e.g., 'my body': manikin at top right) and differs substantially from other circuit-based representations of other living objects (e.g., 'dog', 'plant' etc.)
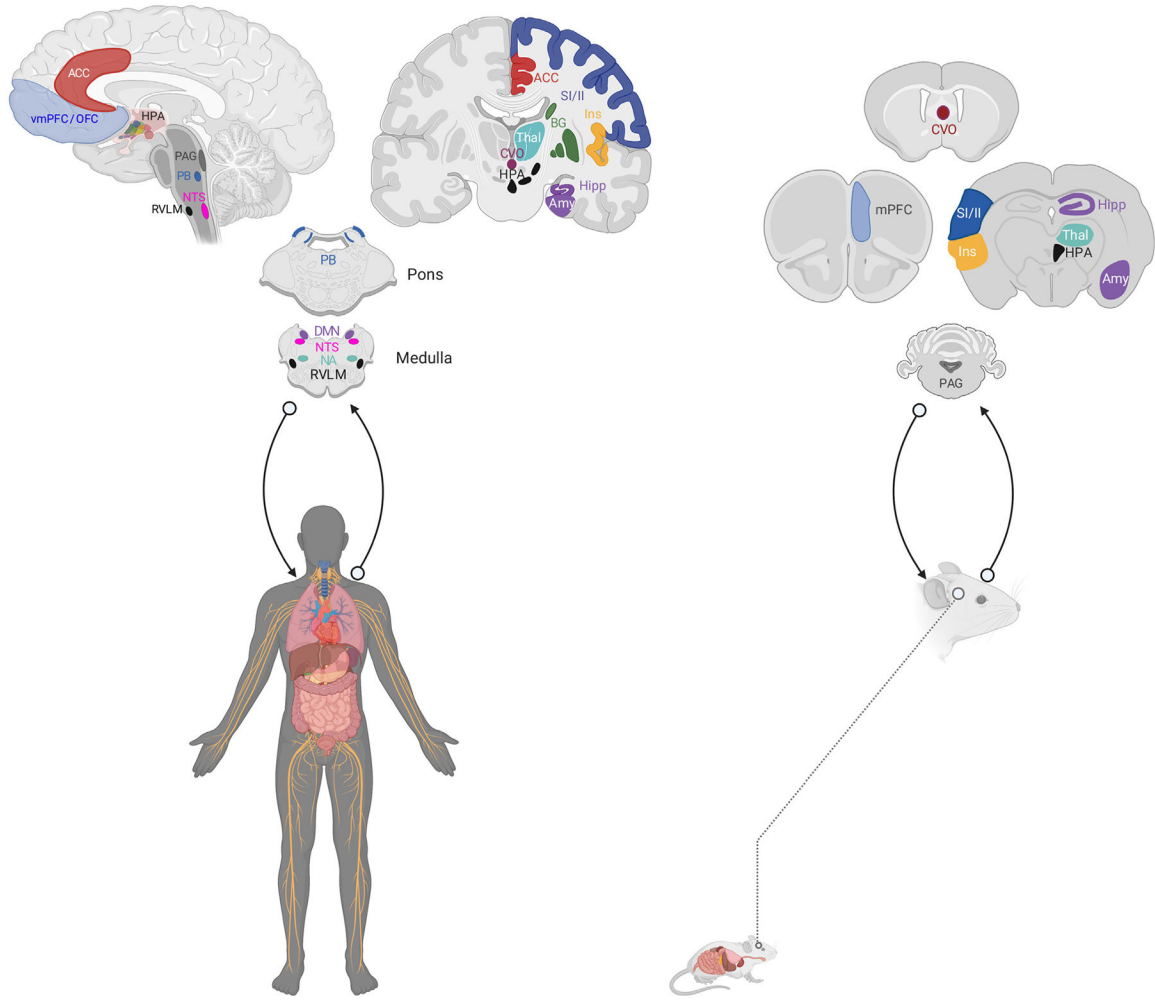
Figure 2. Brain Regions Involved in Interoceptive Processing.
There is a cross-species gap in our understanding of how interoceptive signals are relayed through the central nervous system from the body. In humans, the role of cortical and limbic regions is well characterized, with less emphasis on the transmission of interoceptive signals from the body to brainstem regions (e.g., NTS, PB). In animal models including rodents (as illustrated here), the role of interoceptive signal transmission from the body to brainstem regions (e.g., NTS) is well detailed, with less emphasis on the role of signal transmission to higher cortical regions. Ascending arrows denote afferent signal transmission; descending arrows denote efferent signal transmission. Abbreviations: Amy, amygdala; BG, basal ganglia (including striatum and caudate); CVO, circumventricular organs including the subfornical organ (SFO), organum vasculosum of the lamina terminalis (OVLT), and the area postrema (AP); DMN, dorsal motor nucleus; Hipp, hippocampus; HPA, hypothalamus and pituitary; Ins, insular cortex; mPFC, medial prefrontal cortex (including infra- and pre-limbic cortex); NA, nucleus ambiguus; NTS, nucleus tractus solitarius; OFC, orbitofrontal cortex; PAG, periaqueductal grey; PB, parabrachial nucleus; RVLM, rostral ventrolateral medulla; SI/II, primary and secondary somatosensory cortex; vmPFC, ventromedial prefrontal cortex.