Symposium

Six Challenges for a Mechanistic Science of Human Interoception

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Human interoception has become a major focus of systems, cognitive, and clinical neuroscience. Work across the past decade has shown that signals originating within the body shape perception, emotion, cognition, behavior, and health. Despite rapid methodological and conceptual progress, which substantially expanded our understanding of how bodily signals are processed and represented, much of the field remains constrained by descriptive methods. As these approaches passively assess bodily signals or subjective awareness, they have limited ability to establish causal mechanisms or translate interoceptive findings into clinically informative frameworks. Here, we identify six challenges and corresponding methodological directions for advancing human interoception research: strengthening integration of animal and human models, developing causal perturbation paradigms, capturing interoception in ecologically valid contexts, standardizing multidimensional measurement across bodily systems, adjudicating between computational accounts, and translating mechanistic insights into clinically informative models of health and disease. These challenges are best understood as linked requirements for moving interoception research from relevance to mechanism. Together, they highlight the need to move beyond predominantly static, passive, and single-modality approaches toward studies that can test how internal bodily signals relate to neural activity, behavior, and health.

Introduction

The past two decades have seen a rapid expansion of the field of interoception—the process by which the nervous system senses, interprets, and integrates internal physiological signals (Khalsa et al., 2018). It has emerged as a central topic across systems and cognitive neuroscience and moved from relative obscurity to common parlance in scientific and clinical communities. The substantial growth of interoception research has transformed our understanding of how bodily signals from multiple organ systems, including cardiovascular, respiratory, gastrointestinal, immune, and endocrine systems, continuously inform the brain about the body's physiological state and thus contribute to perception, emotion, cognition, and health. For example, signals from each of these systems have been shown to influence distinct aspects of behavior, highlighting that internal physiology is not merely regulated by the brain but actively shapes brain function across multiple timescales [see Engelen et al. (2025) for an example of this line of work]. This progress has been driven by increasingly sophisticated behavioral, physiological, and neuroscientific approaches, enabling researchers to characterize interoceptive processes with unprecedented precision across multiple levels of analysis.

These advances have broadened the scope of interoception research to encompass an increasingly diverse range of theoretical frameworks, experimental paradigms, bodily systems of interest, and clinical applications. However, this breadth has also made it increasingly difficult to integrate findings across studies. Different paradigms often probe complementary but distinct dimensions of interoception, providing valuable insights into different aspects of body–brain interactions, yet bodily systems are typically investigated in isolation, and computational theories are rarely rigorously tested against competing predictions. Similarly, findings from animal models, laboratory-based human studies, and clinical research frequently remain disconnected, constraining our ability to develop fully causal, mechanistic explanations with translational potential. Moreover, much of the relevant work continues to develop within domain-specific literature, such as feeding, thirst, satiety, fear, and immunity, rather than under a shared interoceptive framework, limiting communication across fields and slowing synthesis despite growing conceptual overlap. As a result, despite substantial progress, the field still lacks an integrated mechanistic framework that explains how bodily signals influence brain function across contexts, bodily systems, and levels of analysis.

The field of interoception thus faces an important challenge: to shift from describing interoceptive phenomena to explaining the mechanisms through which bodily signals shape behavior, cognition, and health. Accordingly, we argue that the next era of human interoception research will require moving beyond

Received May 26, 2026; revised Aug. 13, 2026; accepted Aug. 17, 2026.

Author contributions: G.A., M.G.A., S.S.K., C.L.N., F.H.P., and L.R. wrote the paper.

We thank Chen Levine and Ye'ela Zair for their valuable contributions to the preparation of this manuscript.

*G.A., M.G.A., S.S.K., C.L.N., F.H.P., and L.R contributed equally to this work.

The authors declare no competing financial interests.

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https://doi.org/10.1523/JNEUROSCI.1178-26.2026

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predominantly static, passive, and single-modality characterizations of bodily awareness toward a more mechanistic science of dynamic, causal, and multisystem regulation embedded in behavior, physiology, and health.

Achieving this goal will require progress across several interdependent levels of inquiry. Here, rather than comprehensively reviewing the recent interoception literature, we outline six key challenges for advancing a more mechanistic science of human interoception, ranging from broad conceptual and theoretical research questions (bridging animal–human, computational modeling) to methodological and experimental advances (causal perturbations, ecological, real-world context and multidimensional measurements) and, ultimately, to the translation of mechanistic insights into clinical settings (Fig. 1). These challenges are presented as complementary requirements for moving the field beyond predominantly descriptive approaches to an increasingly tractable, mechanism-driven clinically relevant science of human interoception.

Challenge 1: Bridging Animal and Human Research

Despite major advances in both animal and human research, the field still lacks frameworks that allow mechanistic discoveries in one domain to translate efficiently into the other

Many of the central questions in interoception, including how internal bodily signals are encoded, integrated, and transformed into perception, emotion, and behavior, require both the mechanistic resolution afforded by animals (Livneh and Andermann, 2021; Pang et al., 2025) and the cognitive, subjective, and clinical insights uniquely accessible in humans (Nord and Garfinkel, 2022; Engelen et al., 2023). Neither approach alone is sufficient. Hence, one of the most pressing challenges in interoception research lies in achieving rigorous and comprehensive translation between animal and human work (Knight and Liberles, 2025). This gap in translation and integration between human and animal findings is increasingly being narrowed by two complementary developments: First, methodological advances in human research, including noninvasive

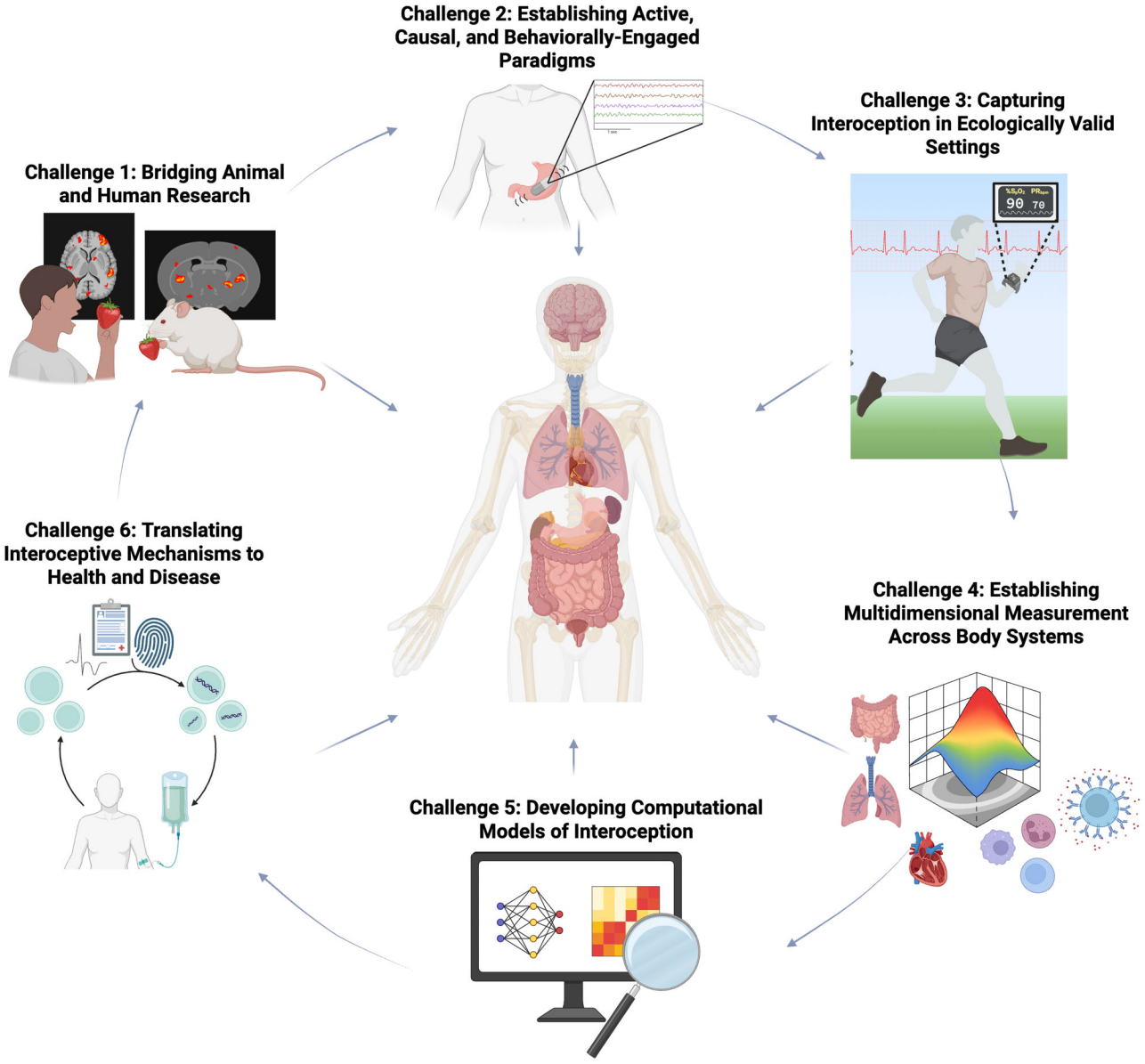


Figure 1. Six key challenges for advancing a mechanistic science of human interoception (Figure created with BioRender.com).

neuromodulation and neuropharmacological techniques (Tyrer et al., 2025), increasingly allow causal interrogation of body–brain pathways in humans (see section on causal interventions in Challenge 2). Second, implementation of computational frameworks allows findings from rodent and human studies to be expressed and tested in shared terms (Petzschner et al., 2017, 2021; Allen, 2020; Allen et al., 2022; Courtin et al., 2025; Weber et al., 2025; Rafael et al., 2026; see Challenge 5 on computational approaches).

Two research domains provide the clearest illustrations of what such integration and alignment between human and nonhuman animal research can achieve, generating mechanistic insights that would not emerge from either approach alone.

The first domain is gut–brain reward. In rodents, hypothalamic circuits governing hunger and thirst are modulated both by predictive sensory cues (Chen et al., 2015; Mandelblat-Cerf et al., 2015; Zimmerman et al., 2016) and by rapid postingestive feedback from the gut (Beutler et al., 2017; Zimmerman et al., 2019), revealing an architecture in which homeostatic state is continuously updated through the integration of prediction and visceral feedback. Further work identified vagal pathways through which postingestive nutrient signals are relayed to dopaminergic reward circuits (de Araujo et al., 2008, 2020; Han et al., 2018; Kaelberer et al., 2018; Tan et al., 2020; Grove et al., 2022). Together, these studies fundamentally shifted the view of reward, demonstrating that primary reinforcement signals arise from internal physiological state rather than external sensory cues alone (Dayan, 2022; Weber et al., 2025). A parallel program of human research has translated several of these principles. Striatal responses to calorie-predictive flavors track plasma glucose rather than hedonic ratings (de Araujo et al., 2013), and decoupling sweetness from caloric content disrupts metabolic responses, consistent with sweetness functioning as a predictive cue (Veldhuizen et al., 2017). Importantly, human research uniquely allows these mechanisms to be linked to subjective experience, showing how flavors previously associated with calorie-dense food, shape neural and metabolic responses as well as affective evaluation (Fleming et al., 2026b). This cross-species convergence has begun to reshape the understanding of obesity, where the postingestive reward signaling is selectively blunted and is not restored by weight loss, suggesting a specific deficit in interoceptive reinforcement rather than in hedonic processing per se (van Galen et al., 2023). Together, these findings illustrate how animal studies identified the underlying biological mechanisms, whereas human studies established their cognitive and clinical relevance.

The second domain concerns cardiac afference and its contribution to affective regulation. Recent work in rodents has established the insula and medial prefrontal cortex as key regions integrating cardiac afferent signals in a context-dependent manner to construct emotional state, such as regulation of learned fear or anxiety (Klein et al., 2021; Hsueh et al., 2023; Malezieux et al., 2026). Human work has begun to converge on this architecture using complementary approaches. Functional MRI and intracranial recordings confirmed cardiac and respiratory representations within the human insular cortex (Critchley et al., 2004; Hassanpour et al., 2018; Park et al., 2018; Harrison et al., 2021), with a layer-specific topography (Müller-Schrader et al., 2025) consistent with subregional specialization of visceral processing. Furthermore, behavioral and clinical studies have linked cardiac signaling to fear responses (Garfinkel et al., 2014) and have linked abnormal insular and prefrontal activity to anxiety disorders (Paulus and Stein, 2006; Teed et al., 2022; Steinhäuser et al., 2023). Together, these findings point to a conserved insular–prefrontal architecture through which cardiac afferent signals may shape affective responses, with animal studies providing causal circuit-level evidence and human studies employing high-resolution neuroimaging methods to probe this same mechanism and linking it to subjective emotional experience and affective disorders.

Importantly, successful translation does not imply direct equivalence between species, as rodents, nonhuman primates, and humans differ in many dimensions (e.g., physiology, behavior, cortical organization). Rather than seeking one-to-one correspondence, the goal is to develop shared mechanistic frameworks that generate testable predictions across species while acknowledging species-specific adaptations and constraints [see Charbonneau et al. (2026) for a comparative review of insula across species].

Progress will likely depend on developing shared hypotheses that can be tested across species using complementary methodologies. A "roving lens" approach, in which multidisciplinary teams apply distinct and complementary methodologies to cross-species investigations, may allow mechanistic discoveries, computational models, and human phenomenology to iteratively inform one another [see Verdonk et al. (2025) for a review of this concept].

Challenge 2: Establishing Active, Causal, and Behaviorally Engaged Paradigms

Most human interoception research remains observational, even though interoception is inherently active and supports the regulation of bodily state

The most common forms of methodological inquiry in human interoception research have involved the passive assessment of internal bodily signals: participants are typically asked to attend to their heartbeats or gut rumble (Savage et al., 2025), monitor breathing (Nikolova et al., 2022), rate a sensation, or report their awareness of sensation while remaining still in a controlled lab setting. These paradigms have been invaluable for characterizing basic perceptual phenomena (Jones, 1994; Brener and Ring, 2016), but they may capture only a limited aspect of how interoceptive systems operate in everyday life (Khalsa et al., 2009b).

However, interoception is typically argued to support adaptive regulation in a body that is constantly changing, moving, predicting, and acting on the world rather than merely supporting the monitoring of bodily signals. This view is reflected in contemporary frameworks such as predictive processing and allostasis, which conceptualize interoception as part of a regulatory system that continuously anticipates and responds to bodily needs (Barrett and Simmons, 2015; Friston et al., 2016; Owens et al., 2018; Allen, 2020). Paradigms that capture participants' responses to spontaneously occurring bodily signals rather than actively manipulating them leave the system unprobed: they reveal how the brain responds to whatever signals happen to arise, but not how it responds when those signals are systematically altered (Khalsa and Lapidus, 2016). Hence, they capture only a restricted aspect of a process that is, by its nature, agentive. This conceptual shift has an important methodological implication. Given that interoception fundamentally contributes to a reactive regulatory process (i.e., homeostasis), the challenge for the field is to develop paradigms that reflect and can capture this perturbation. The emerging frameworks and methodological tools suggest that such paradigms are now becoming feasible in

humans [for a few examples, see Hassanpour et al. (2016) and Mayeli et al. (2023)].

Early examples of the importance of this shift are already emerging. Rather than treating variation in interoceptive state as experimental noise to be minimized, recent studies provide compelling evidence as to why such variation should be experimentally leveraged to understand behavior. For example, gastric physiology has been observed to covary with emotional experience (Porciello et al., 2024), whereas metabolic state has been linked to reinforcement learning, affect, and decision-making (Nord et al., 2021; Fleming et al., 2026a,b). These findings align with theoretical and computational frameworks proposing that bodily signals contribute directly to reinforcement learning, decision-making, and active inference, extending the role of interoception beyond perception to the control of adaptive behavior (Petzschner et al., 2021; Allen et al., 2022; Brændholt et al., 2023; Weber et al., 2025). Together, these findings highlight the value of paradigms in which participants act, adapt, and learn in response to interoceptive feedback in real time (Azzalini et al., 2021; Williams et al., 2026).

Developing paradigms that move beyond passive observation toward active engagement and causal intervention is methodologically demanding but is increasingly within reach. Progress toward this goal has been driven by methods that experimentally perturb body–brain signaling, enabling direct tests of the causal relationships between bodily state, neural activity, perception, and behavior. These approaches fall into three broad categories: pharmacological manipulations, direct perturbation of peripheral interoceptive signals, and neuromodulation of body–brain pathways.

Pharmacological approaches provide one of the most direct means of experimentally perturbing body–brain signaling (Khalsa et al., 2009b, 2018; Harrison et al., 2021). For example, bolus isoproterenol infusions, a peripheral beta-adrenergic agonist similar to adrenaline, can induce acute elevations in cardiorespiratory sensation, with effects on cortical substrates linked to interoception (e.g., insula, prefrontal cortex, amygdala; Khalsa et al., 2009a,b, 2016; Hassanpour et al., 2018; Nord et al., 2021). Pharmacological manipulations can also be used to dissect the mechanisms underlying interoceptive processing. Recent evidence indicates that beta-adrenergic blockade can differentially enhance cardiac perceptual sensitivity and respiratory perceptual precision, revealing distinct adrenergic contributions to interoception across organ systems (Tyrer et al., 2025). By comparing the centrally penetrating, nonselective beta-blocker propranolol with the minimally brain-penetrant, cardioselective beta-blocker bisoprolol, the study demonstrated that peripheral adrenergic blockade was sufficient to enhance cardiac interoception. These findings illustrate how pharmacological manipulations can dissociate peripheral and central mechanisms, enabling the causal testing and identification of pathways supporting different facets of interoceptive processing.

Pharmacological interventions can also probe interoceptive pathways beyond the cardiovascular system. For example, GLP-1 receptor agonists act on both peripheral and central GLP-1 receptors, providing a timely example of how modulation of endogenous satiety signaling influences appetite, motivation, and behavior through designated body-to-brain communication pathways (van Bloemendaal et al., 2014; Müller et al., 2019; Gill et al., 2026). The clinical use of such pharmacological substances (beta-adrenergic receptor blockers, GLP-1 receptor agonists) creates a unique opportunity to examine how targeted perturbations of interoceptive pathways influence behavior, decision-making, and health outside the laboratory. Beyond therapeutic relevance, these interventions illustrate how molecular perturbations are powerful tools for probing interoceptive function.

A second class of causal approaches nonpharmacologically perturbs peripheral interoceptive signals, enabling controlled manipulation of body–brain communication in different physiological systems. Some methods act directly on peripheral interoceptive pathways. In the gastrointestinal domain, ingestible vibrating capsules provide nonpainful mechanosensory stimulation to the gut wall, enabling simultaneous assessment of brain, gastric, and perceptual responses (Mayeli et al., 2023). In the respiratory domain, inspiratory resistance paradigms similarly allow controlled perturbation of breathing-related afferent signals while measuring perception, learning, and prediction (Faull et al., 2018; Harrison et al., 2021; Nikolova et al., 2022). Other approaches seek to modify interoceptive processing through biofeedback. For example, preliminary work suggests that gastric biofeedback, in which participants learn to align electrogastrogram activity with a visualized normogastric rhythm, may influence some self-reported aspects of gastric interoception and intuitive eating in nonclinical samples (Tiemann et al., 2025).

A third class of causal approaches aims to directly modulate the neural pathways through which interoceptive information reaches and is processed by the brain. Vagus nerve stimulation has been shown to modulate stomach–brain coupling (Müller et al., 2022) and has also been suggested to enhance performance on heartbeat detection tasks while modulating cortical markers of interoceptive processing [Richter et al., 2021; though see Klein et al. (2021)]. More recently, low-intensity focused ultrasound neurostimulation has demonstrated that activity within interoceptive cortical regions, including the insula, can be modulated noninvasively, with preliminary evidence that this may alter physiological as well as cognitive processes (Legon et al., 2024, 2025; Strohman et al., 2024a,b). As these methods mature, they may permit increasingly focal and mechanistically informative causal interrogation of specific interoceptive circuits.

Finally, interoceptive processing can also be perturbed indirectly by altering the sensory (exteroceptive) context in which interoceptive signals are experienced. Floatation-REST, which minimizes exteroceptive stimulation by suspending participants in thermoneutral salt water, reduces external sensory input, thereby amplifying cardiorespiratory sensations and producing measurable effects on interoceptive awareness and anxiety (Feinstein et al., 2018; Choquette et al., 2023).

Together, these approaches illustrate that interoceptive function can be causally interrogated through multiple complementary strategies, by manipulating bodily signals, neural pathways, or the sensory context in which those signals are experienced. Furthermore, they highlight that interoceptive processes are most clearly identified under conditions of challenge, modulation, and action. Passive paradigms will remain useful, but they are unlikely to be sufficient.

Challenge 3: Capturing Interoception in Ecologically Valid Settings

A central challenge is to understand interoception not as a static trait measured under controlled conditions, but as a dynamic process that varies across time, bodily state, and real-world contexts

Closely related to the question of behavioral engagement is the broader challenge of ecological validity: the degree to which laboratory measures reflect how interoception functions in real-world settings. Laboratory paradigms necessarily trade

representativeness for experimental control and rigor, and this trade-off carries costs. Interoceptive experience during social threat, physical illness, or metabolic stress (i.e., allostatic load; Paulus et al., 2019) is unlikely to be fully captured by performance on a brief laboratory task conducted at rest. Yet the relationship between laboratory interoceptive performance and real-world interoceptive experience remains poorly characterized, making ecological validity a major challenge for the field.

A related issue is that physiological states, such as inflammation, metabolic challenge, autonomic arousal, hunger, or fatigue, fluctuate continuously within individuals. However, interoception is often measured as a stable individual characteristic, and therefore most laboratory paradigms provide only a snapshot of interoceptive processing. Remarkably little is known about how these changing physiological states alter interoceptive processing over time and how interoceptive representations are updated accordingly [but see Small et al., 2001; Livneh et al., 2020; Livneh and Andermann, 2021]. Most existing paradigms are not designed to capture such within-person changes. Addressing it requires moving from single-session, single-modality measurements toward approaches that can track how brain–body interactions evolve as physiological states and environmental contexts change.

Progress toward this goal is beginning to emerge from studies treating brain–body coupling as dynamic rather than static. Work examining how gastric electrical signals couple with large-scale functional brain networks across time offers a model for this approach, revealing structured variation that would be averaged away in static designs (Rebollo et al., 2021; Levakov et al., 2023; Tallon-Baudry et al., 2026; Zair and Avidan, 2026). These brain–stomach interactions are also shaped by ongoing environmental context. Viewing food-related stimuli (disgusting and appetizing) elicits differential gastric electrical signals, possibly reflecting a preparatory physiological response (Oseran et al., 2026). Together these findings illustrate that brain–body interactions vary systematically across time and contexts. These dynamic interactions also carry clinically relevant information. Stronger stomach–brain coupling in frontoparietal networks has been associated with dimensional measures of anxiety, depression, and stress (Banellis et al., 2025). Beyond concurrent clinical associations, computational modeling of gut mechanosensory stimulation induced via vibrating capsules showed that gastrointestinal interoception was associated with future relapse in anorexia nervosa, suggesting potential prospective value (Verdonk et al., 2026). Together, these directions suggest that the state dependence of interoception is not a nuisance to be controlled but a meaningful signal to be measured for concurrent and prospective insight.

A key implication of this dynamic view is that attention directed toward the body's internal state, namely, interoceptive attention, may itself involve a regulatory process rather than simply a means of observing bodily signals. Interoceptive attention refers to the allocation of attentional resources toward internal bodily signals. Directing attention inward may reshape the precision or weighting assigned to those signals and thereby change the neural representation of that bodily state (Avery et al., 2014; Stewart et al., 2020). This raises the possibility that interoceptive attention may provide a mechanism through which cognition dynamically modulates ongoing brain–body interactions, thereby shaping downstream regulatory processes. Some emerging evidence supports this possibility. Directing attention toward immune-related bodily sensations has been recently shown to causally alter the magnitude and temporal dynamics of acute inflammatory responses (Mizrachi et al., 2026), suggesting that interoceptive attention can feed back onto the physiological processes it monitors. This positions interoceptive attention as a candidate mechanism linking top–down cognitive processes to ongoing physiological regulation, highlighting that brain–body interactions are shaped not only by changing physiological states but also by ongoing cognitive states. Whether similar regulatory effects extend across physiological systems and translate into clinically meaningful outcomes remains an important open question.

Interoceptive attention is not only experimentally manipulable, but it also fluctuates spontaneously in everyday life. Multidimensional experience sampling demonstrates that "body-wandering" or mind-wandering about the visceral body constitutes a dominant mode of self-generated thought and correlates with both neurovisceral connectivity and symptoms of depression and anxiety (Banellis et al., 2026a).

Capturing these dynamics both in the laboratory and outside is now increasingly feasible. Wearable or ingestible physiological sensors (Porciello et al., 2024), ecological momentary assessment via apps, and ambulatory neuroimaging offer the means to track interoceptive signals and their behavioral correlates in daily life. Beyond improving ecological validity, repeated real-world measurements may also provide the longitudinal data needed to constrain and validate computational models that cannot be adequately parameterized from single laboratory sessions alone (see Challenge 5). The principal challenge is therefore not collecting more real-world bodily data but knowing what such data mean: when they reflect adaptive bodily monitoring, when they reflect maladaptive vigilance, and when they identify mechanisms relevant to symptoms or behavior.

Challenge 4: Establishing Multidimensional Measurement across Body Systems

What exactly are we measuring when we measure interoception, and how can these measurements provide a foundation for mechanistic understanding across different bodily systems and interoceptive sources?

A central challenge for mechanistic interoception research is determining what our measurements capture. Interoception has been recognized as a multidimensional construct, encompassing multiple dissociable processes, including the accuracy with which individuals detect internal bodily signals (Unal et al., 2021), the beliefs they hold about their own interoceptive ability, and the degree to which confidence tracks actual accuracy. These dimensions can dissociate sharply, and growing evidence suggests they have distinct neural substrates, developmental trajectories, and clinical profiles (Suksasilp and Garfinkel, 2022). Conflating them has generated a literature in which findings fail to replicate across paradigms, not because the underlying biology is inconsistent, but because different measures are indexing different processes. Such dissociations are evident even in populations expected to show superior interoceptive abilities. For example, experienced meditators report heightened bodily awareness yet do not consistently outperform controls on heartbeat perception tasks (Khalsa et al., 2020), underscoring the distinction between subjective beliefs, attentional styles, and objective performance. This example illustrates why progress depends on distinguishing between different dimensions of interoception rather than treating them as interchangeable measures of a single construct.

The measurement problem is further compounded by the modality specificity of interoceptive processing. Although the

cardiac domain has historically dominated interoception research for reasons of methodological convenience rather than theoretical priority, recent work has progressively moved beyond single-organ paradigms, from early comparisons of cardiac and respiratory interoception (Garfinkel et al., 2016) to multimodal psychophysical batteries integrating cardiac, respiratory, and gastric measures within a common experimental framework (Eimer et al., 2026; Banellis et al., 2026b). These studies demonstrate that interoceptive performance is largely modality specific, with performance in one bodily domain failing to reliably predict performance in another. Moving beyond single-organ paradigms also requires integrating methods for characterizing what each task measures. For example, Bayesian psychophysical approaches that properly decompose perceptual sensitivity, metacognitive efficiency, and affective dimensions across modalities have begun to expose how much the field's conclusions depend on which task and which bodily system it chose to measure (Khalsa et al., 2018; Allen et al., 2022). Importantly, these approaches may become even more informative when combined with perturbation-based paradigms (as discussed in Challenge 2; Tyrer et al., 2025; Verdonk et al., 2026), which provide a means of testing how interoceptive measures change in response to experimentally controlled alterations in bodily state. These findings highlight that conclusions about interoception depend not only on how it is measured but also on which bodily system is being measured.

What is needed are multilevel assay batteries that simultaneously probe interoceptive accuracy, metacognition, and prediction, using both attentional and perturbation-based methods within the same individual (ideally, across multiple visceral systems, and using multiple forms of neural interrogation; Adamic et al., 2024; Verdonk et al., 2024). A further dimension, largely absent from current paradigms, is behavioral: if visceral states contribute to reinforcement signals (Weber et al., 2025), then interoceptive assays should also capture how well individuals update behavior based on visceral feedback, for example, by adapting decisions, learning rates, or reward expectations as a function of changing bodily states. Ultimately, the goal is to connect subjective interoceptive reports to measurable biological processes, asking not only whether someone perceives their body accurately but what exactly is being measured and how it relates to behavior, physiology, and health. Such assays will provide the empirical foundation needed to interpret causal manipulations (Challenge 2), develop and test computational theories (Challenge 5), and ultimately improve translation to clinical settings (Challenge 6).

Challenge 5: Developing Computational Models of Interoception

Computational frameworks offer a common language for linking bodily signals, behavior, neural circuits, and clinical phenomena, but realizing this promise requires stronger empirical tests

Concrete mathematical formulations have long been put forward to describe how organisms acquire, represent, and exploit internal models of the world to guide perception and action. These frameworks have proven explanatorily powerful in the exteroceptive domain, accounting for perceptual illusions, multimodal integration, and the influence of prior expectations on sensory inference (Sutton and Barto, 1998; Rao and Ballard, 1999; Knill and Pouget, 2004; Körding and Wolpert, 2004; Friston, 2005; Petzschner et al., 2015). Unlike descriptive frameworks, computational models make explicit, quantitative predictions that can be experimentally tested, providing a common language for linking physiology, neural circuits, behavior, and ultimately clinical phenomena. A central theoretical development of the past decade has been the extension of these computational frameworks to interoception, recognizing that the body constitutes a second sensory and regulatory environment whose signals are inferred, weighted, and acted upon by the same neural machinery that supports exteroceptive perception (Barrett and Simmons, 2015; Pezzulo et al., 2015; Stephan et al., 2016; Petzschner et al., 2017, 2021; Allen and Friston, 2018; Unal et al., 2021; Müller-Schrader et al., 2025). Despite this increasing theoretical line of study, the empirical work that would test those predictions remains comparatively thin. Computational models are uniquely positioned to address several of the challenges discussed throughout this review, including animal–human translation (Challenge 1), causal perturbation (Challenge 2), multidimensional measurement (Challenge 4), and clinical heterogeneity and translation (Challenge 6). At the same time, progress on computational models is itself dependent on progress in these other challenges. Developing optimal models, for instance, first requires identifying measures that are tractable and reliable enough to formulate computationally. Closing the gap between computational theory and empirical validation is one of the most pressing challenges for the next decade.

One emerging line of work has begun to directly test whether interoceptive perception conforms to the architecture predicted by hierarchical predictive-processing accounts. These accounts propose that the brain encodes interoceptive predictions and prediction errors in distinct cortical compartments, weights these signals by their estimated precision, and updates beliefs about visceral state through Bayesian inference (Barrett and Simmons, 2015; Petzschner et al., 2021). Several empirical findings are now beginning to test these predictions. Computational modeling of respiratory perception during 7 T fMRI has identified neural representations of both predictions and prediction errors in the anterior insula, with individual differences in anxiety modulating the prediction-related signal in line with framework expectations (Harrison et al., 2021). Attention to cardiac signals modulates the heartbeat-evoked potential and engages the anterior insula in a manner consistent with precision-weighting of interoceptive signals (Critchley et al., 2004; García-Cordero et al., 2017; Petzschner et al., 2019; Verdonk et al., 2024), and psychophysical tasks for cardiac and respiratory perception are beginning to dissociate sensory precision from prior expectations in individual participants (Smith et al., 2020; Harrison et al., 2021; Legrand et al., 2022). Layer-resolved 7 T fMRI is starting to map interoceptive attention onto specific compartments of the insular cortex, of relevance to hierarchical accounts that assign feedforward prediction error and feedback prediction signals to distinct laminar populations (Müller-Schrader et al., 2025). At the level of population coding, the mouse insular cortex maintains representations not only of current physiological state but of anticipated future states, with cue-evoked activity transiently shifting toward the predicted satiety state (Livneh et al., 2020; Livneh and Andermann, 2021; Rafael et al., 2026).

These studies illustrate that computational theories are becoming experimentally testable. However, despite this progress, translating these computational frameworks into paradigms capable of rigorously distinguishing between competing theoretical accounts is still rare. Only a handful of studies fit generative models to interoceptive data at the parameter level (Li et al., 2025), and direct model comparison between related

predictive accounts is largely absent. In addition, core framework predictions, such as the quantitative coupling of interoceptive precision to autonomic state, the laminar segregation of predictions from prediction errors, and the mapping of psychiatric phenotypes onto identifiable parameter regimes, remain to be tested in most interoceptive domains beyond cardiac and respiratory signals. A further imbalance compounds the gap: these frameworks have largely inspired human research, where invasive access to circuit-level variables is limited, whereas animal models, despite enabling cell-type–specific perturbations and chronic measurements of the physiological variables that the models predict, have been used far less often to test their computational claims. Closing this human–animal gap is likely to provide the most decisive parameter-level tests of interoceptive predictive processing (see Challenge 1).

Indeed, one of the best examples of animal–human research synergy presented in Challenge 1 also represents an evolution of computational models of reward. This emerges from the fact that primary reinforcing signals sustaining ingestive behavior are not delivered at the sensory periphery but arise postorally, from the body's own monitoring of energy, nutrient, and hydration state (Tellez et al., 2016; Han et al., 2018; de Araujo et al., 2020; Grove et al., 2022). This understanding has begun to reshape how reinforcement and pavlovian conditioning are conceptualized computationally: reward is no longer treated as an externally defined quantity attached to a stimulus but as an internally generated signal whose magnitude depends on physiological state, and dopaminergic responses that were once interpreted as a unitary reward prediction error are increasingly understood as a cascade of distinct signals tied to anticipation, consumption, and delayed postingestive feedback (Dayan, 2022; Weber et al., 2025).

Finally, a further computational complexity arises from the rhythmic nature of interoceptive signals originating from different bodily systems and their coupling with neural rhythms (Tallon-Baudry et al., 2026). Computational models must consider the timing and precision of brain coupling to one or multiple of these rhythms, and this, in turn, will enable further understanding of what functions they serve and how different rhythms are integrated (Engelen et al., 2023, 2025). Hence, future work in both human (De Falco et al., 2024) and animal (even at a cellular level; Magaña et al., 2026) models would necessitate multiorgan recordings combined with neural and behavioral (Banellis et al., 2026b) recordings that will then be applied to computational models. Such knowledge has implications also for the translational challenge we outline below (Challenge 6).

Challenge 6: Translating Interoceptive Mechanisms to Health and Disease

The challenge is no longer to demonstrate that interoception is relevant to health and disease but to identify when, how, and for whom specific interoceptive mechanisms matter

The sixth challenge for human interoception research is real-world translation. The hurdle is to determine how specific interoceptive mechanisms can meaningfully inform clinical understanding, assessment, and intervention. Clinical implementation remains limited because the field still too often moves from broad associations to broad interventions, without specifying whether the relevant mechanism is altered afferent signaling, biased perceptual inference, maladaptive attention, disrupted affective valuation, impaired learning, or failed regulatory control at the individual level. Translational progress will require clinically interpretable assays that can stratify patients, identify modifiable mechanisms, and test whether changing those mechanisms alters a person's symptoms, function, or disease course.

One obstacle to translation is that interoceptive measures may index different clinical levels of explanation. Recent studies using tightly controlled multimodal interoceptive psychophysics in hundreds of participants have reported limited associations between performance-based cardiac or respiratory interoceptive measures and mental health, despite more consistent relationships between self-reported interoceptive difficulties and psychopathology (Desmedt et al., 2022; Wolters et al., 2022; Banellis et al., 2026b). This dissociation should not be treated as a simple measurement failure. Performance-based tasks, physiological recordings, computational parameters, and self-report measures may capture distinct aspects of interoception, including sensory sensitivity, attention, confidence, appraisal, symptom interpretation, and beliefs about bodily vulnerability. Evidence from adjacent physiological domains, including perceived immunity and self-rated health, further suggests that subjective representations of bodily state can predict health outcomes even when they do not map straightforwardly onto objective physiological measures (Idler and Benyamini, 1997; Mizrachi et al., 2025; Mizrachi and Rozenkrantz, 2026). Translation will therefore require matching measures to mechanisms: identifying which interoceptive dimension is relevant to a given symptom, patient subgroup, intervention target, or clinical outcome.

These challenges are particularly evident in psychiatry, where interoceptive disruptions have been reported across depression, anxiety disorders, psychosis, and eating disorders (Dunn et al., 2007; Paulus and Stein, 2010; Khalsa et al., 2018; Jeganathan et al., 2024; Moccia et al., 2025). Yet findings remain inconsistent and often depend on the bodily domain, task, and interoceptive dimension being measured. Anxiety disorders provide a useful example: studies have reported enhanced, diminished, or unchanged interoceptive accuracy, often using cardiac tasks that capture only a narrow part of a multidimensional construct (Ehlers and Breuer, 1996; Willem Van der Does et al., 2000; Bogaerts et al., 2005; Brewer et al., 2021; Adams et al., 2022). This pattern suggests that inconsistency may reflect not only weak effects or methodological noise but also a mismatch between broad diagnostic categories and the specific interoceptive processes being assessed.

Even with improved measurement, however, translation will remain difficult if interoceptive mechanisms are mapped only onto diagnostic categories. The same mechanism may cut across disorders, differ across individuals with the same diagnosis, or be obscured by comorbidity and multimorbidity. Progress will therefore require moving beyond diagnosis-level associations toward transdiagnostic, mechanism-based models that identify which interoceptive processes are relevant to specific symptoms, patient subgroups, intervention targets, and outcomes. This logic also extends beyond psychiatry, where interoceptive mechanisms may contribute to metabolic, inflammatory, pain, fatigue, and other body–brain conditions that do not fit cleanly within traditional divisions between mental and physical health (Quadt et al., 2018).

One way to address this problem is to adopt data-driven techniques that identify symptom dimensions independently of formal diagnostic categories (Wise et al., 2023). Novel transdiagnostic dimensions can be mapped onto underlying mechanisms, an approach which has proven successful in linking psychopathology to other cognitive domains such as decision-making

(Gillan et al., 2016; Rouault et al., 2018). Similar efforts are beginning to emerge in interoception (e.g., stomach–brain coupling in mental health; Banellis et al., 2025). However, a challenge of this approach is that data-driven dimensions are not inherently mechanistic. They can improve the fit between symptoms and biology, but they can also produce unstable, sample-specific patterns that are difficult to replicate, interpret, or use clinically.

A complementary strategy is to use theory-driven models to identify interoceptive metrics that map onto specific symptoms or behavioral phenotypes rather than diagnoses. For example, interoceptive markers could be linked to anhedonia, effort-based decision-making, fatigue, or metabolic dysregulation in ways that cut across psychiatric and medical conditions. This may be especially important for domains where bodily state and mental health are tightly coupled, including metabolic interoception and fatigue. Computational frameworks offer one route for making these links more mechanistically precise by decomposing interoceptive dysfunction into interpretable processes such as altered priors, precision, prediction error, learning, or regulatory control.

For translation, however, these models must be tested causally. Perturbation-based approaches that experimentally alter bodily states are needed to test whether interoceptive differences contribute to symptoms and whether they can be modified. Reverse translation is equally important: effective pharmacological, psychological, and neuromodulatory interventions should be examined to determine which interoceptive dimensions they change (Challenge 2). Forward translation then becomes possible when causal studies identify interoceptive processes that are plausible treatment targets. The central barrier is patient-target matching: interoceptive disturbances cut across diagnoses and body systems, but patients cannot yet be reliably matched to the mechanism or intervention most relevant to their symptoms. Translation will therefore require integrating causal perturbation, ecological assessment, multidimensional measurement, computational modeling, and animal–human work into a framework that can specify what to target, in whom, and why.

Conclusions

The challenges outlined in this review are not separate obstacles but linked requirements for a more mechanistic science of interoception. Animal–human integration, causal perturbation, ecological assessment, multidimensional measurement, computational modeling, and clinical translation each address a different part of the same problem: understanding how bodily signals are generated, represented, interpreted, and used to guide behavior and health. The critical next step is to move beyond demonstrating that interoception matters—and toward specifying which mechanisms matter, under what conditions, for whom, and with what consequences—for changing symptoms, behavior, and clinical outcomes.

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