Trends in Cognitive Sciences

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Feature Review

The neurobiology of interoception and affect

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Scholars have argued for centuries that affective states involve interoception, or representations of the state of the body. Yet, we lack a mechanistic understanding of how signals from the body are transduced, transmitted, compressed, and integrated by the brains of humans to produce affective states. We suggest that to understand how the body contributes to affect, we first need to understand information flow through the nervous system's interoceptive pathways. We outline such a model and discuss how unique anatomical and physiological aspects of interoceptive pathways may give rise to the qualities of affective experiences in general and valence and arousal in particular. We conclude by considering implications and future directions for research on interoception, affect, emotions, and human mental experiences.

Highlights

Interoception relies on prediction, like exteroceptive perceptions such as vision.

Unlike the study of vision, cognitive science lacks a clear mechanistic model of how physical energies in the viscera translate into affective experiences.

We outline a model whereby physical energies in the viscera are transduced, transmitted, and compressed within the interoceptive system.

The proposed model can explain why interoceptive sensations are integrated into experiences of affective states.

We speculate on how valence and arousal might emerge from distinct processes in interoceptive pathways.

This model begins to explain how a beating heart is experienced as arousing, unpleasant, and even fearful.

Linking interoception and affect: a neurobiological model

> *Every one of the bodily changes, whatsoever it be, is felt, acutely or obscurely, the moment it occurs… Our whole cubic capacity is sensibly alive; and each morsel of it contributes its pulsations of feeling, dim or sharp, pleasant, painful, or dubious*.
>
> James [1]

> *... stimuli do something more than arouse sensation; they give rise to processes of a different kind, to "feelings" in a special sense; we do not merely take the impressions as they come, but we are affected by them, we feel them.*
>
> Titchener [2]

> *A key feature that distinguishes pain, temperature and other bodily feelings from [external sensations] is their inherent association with emotion.*
>
> Craig [3]

Human beings have an incredible capacity to feel. As conscious beings, we regularly experience **discrete mental states** (see Glossary) that we categorize as 'emotions' (anger, fear, disgust, joy), 'motivations' (engagement, disengagement), or 'somatic' (sensual pleasure, pain, discomfort, hunger, thirst). Even stereotypically 'cognitive' mental states involve feeling: 'memories', 'imagination', 'thoughts', 'decisions', 'attitudes', and 'perceptions' are frequently experienced as varying on dimensions of pleasantness to unpleasantness and activation to quiescence (Figure 1). These dimensions, termed **valence** and **arousal**, respectively, describe **affect**. Although mental states across languages and cultural groups differ in specific meanings, they are nonetheless united by having qualities of valence and arousal [4]. Affect is also thought to be central to human consciousness [5–11] and health [12].

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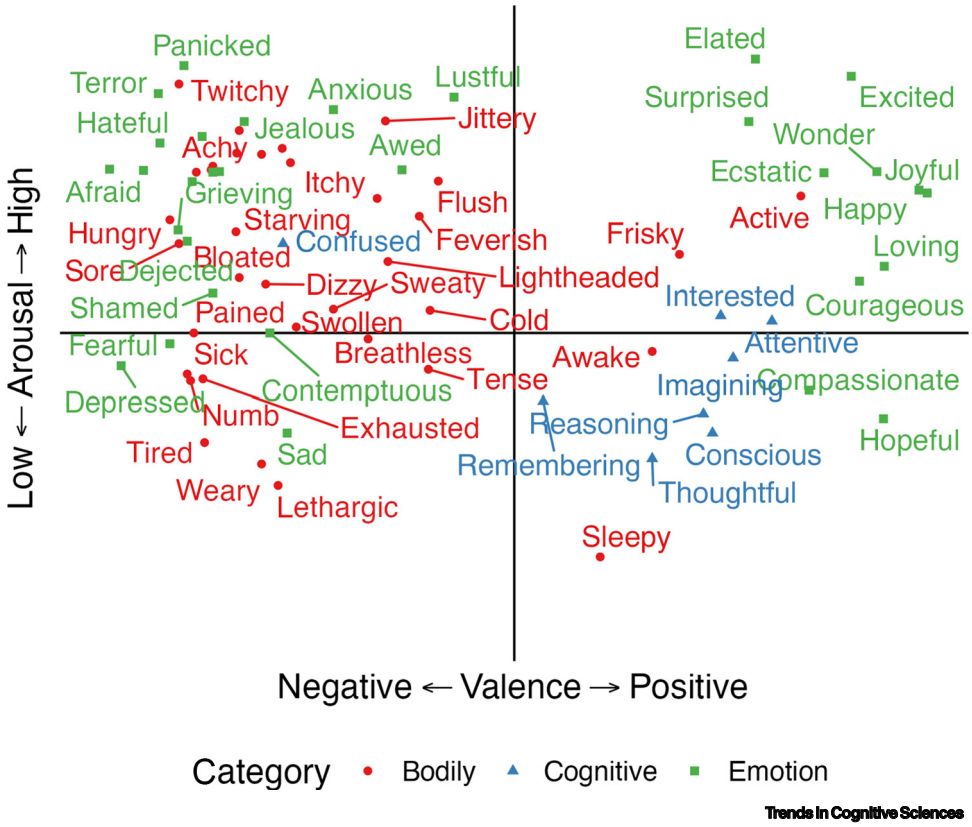

Figure 1. Mental states plotted on the affective circumplex. Different mental states plotted based on valence and arousal norms published in the NRC Valence, Arousal, and Dominance (NRC-VAD) Lexicon [157]. These norms were created using data from human raters and range from 0 (negative valence/low arousal) to 1 (positive valence/high arousal). Words were chosen to exemplify canonical body, cognitive, and emotional states.

Scholars have sought to understand the neurobiological processes that create affect since antiquity. Harkening back to some of the earliest psychological theories [8], decades of affective neuroscience research localize affect within brain systems associated with visceromotor control, viscerosensory representation, and the abstract representation of prior experiences [3,13–15]. Visceral changes, therefore, may not just be a consequence of human feelings, they may also partially constitute them. The brain's representation of visceral activity is called **interoception** (for extended definition, see Box 1). Research on interoception has increased sixfold in just the past decade. This work supports the idea that, in humans, interoception is associated with both the quality and intensity of affective experiences (Box 2). Indeed, it is almost accepted as a scientific fact that interoception is critical to affective experience. Yet important gaps still exist in our understanding of how the affective feelings characterizing mental states such as anger, joy, pleasure, pain, or hunger causally emerge from the confluence of the peripheral and central nervous systems.

In the present review, we build on prior theorizing to suggest that an understanding of how interoception is related to affect requires a broader understanding of how information flows from the brain to the periphery and back again. Studies of so-called '**exteroceptive** senses', such as vision, have made great strides in formulating scientific models of how discrete perceptions (e.g., of faces or objects) that are characterized by phenomenological properties (e.g., color, contour, depth, motion) are achieved by the nervous system (e.g., [16–18]). These models describe

Glossary

Affect: an abstract mental state characterized by valence and arousal.
Allostasis: the brain's predictive regulation of the internal milieu; it is different from homeostasis in that homeostasis is decentralized and reactive, while allostasis is centralized and predictive.
Arousal: the subjective feeling ranging from activation to deactivation; the sense that the body and/or mind are 'being stirred'.
Compression: a form of data reduction in which the size of data is reduced without appreciable loss of information.
Discrete mental state: any mental experience that is foregrounded in consciousness, bounded in time, and experienced as categorically distinct from other mental states (often described with mental state words such as 'emotions', or 'fear').
Exteroception: the sensation and perception of signals from the outside world (most typically associated with vision, audition, gustation, and olfaction).
Granularity: granule cells are a type of neuron that are very small and, in the cortex, typically located within layer 4. Cortex can be differentiated into granular cortex (many granule cells), dysgranular cortex (some but not many granule cells), and agranular cortex (no granular cells) based on the relative density of granule cells. Definition of granularity is largely subjective, with no hard and fast rules about how to differentiate granular from dysgranular cortex, for example. The presence/absence of granular cells is often used to specify lamination, because agranular cortex lacks layer 4.
Informational entropy: in information theory, entropy represents the average uncertainty of outcomes sampled from a probability distribution. A distribution with high entropy means that, on average, outcomes are relatively unpredictable. In the context of perception, informational entropy represents the average uncertainty of sensory signals sampled by the brain.
Integration: the combining of data from different sensory streams within or across sensory modalities.
Interoception: the sensation and perception of the internal state of the body.
Interoceptive pathways: the sensors, spinal tracts, cranial nerves, and neural architectures that support sensation and perception of the internal state of the body.

Box 1. Defining interoception

We follow the majority of existing literature by defining interoceptive pathways as including sensory cells located in the walls, membranes, and surrounding vasculature of visceral organs [158], spinothalamic sympathetic nervous system and vagal parasympathetic nervous system pathways, and brain regions spanning the brainstem, subcortical, limbic, paralimbic, and cortical regions implicated in predicting and representing information from the body [3,41,159,160]. Within this system, key brain regions include the nucleus of the solitary tract and parabrachial nucleus in the brainstem, which receive projections from spinal lamina and the vagus and in turn project to the thalamus. From the thalamus, subcortical–cortical connections link the thalamus to regions within the primary interoceptive cortex (mid- to dorsal posterior insula), and cortico-cortical connections link anterior insula, anterior cingulate cortex, and ventromedial prefrontal cortex [160]. We distinguish these pathways from efferent visceromotor pathways that initiate autonomic activation, which have been extensively reviewed elsewhere [36,159].

However, there is growing criticism of this exclusively autonomic operationalization of interoception. Many scholars have argued for a more broad conceptualization of interoceptive pathways that also include chemical (e.g., signaling via the blood or cerebrospinal fluid [161]), neural, and mixed signaling pathways from other peripheral bodily systems such as the skeletal system, somatic system, enteric system, and even from the immune and endocrine systems [47,54,55,162–167]. Even the utility of basic 'visceral' versus 'somatic' distinctions has been called into question. Some organs contain both 'visceral' and 'somatic' tissues, including aspects of the respiratory, gastrointestinal, and integumentary (i.e., skin) systems (for review, see [47]). Chemical and neural signaling pathways interact at nearly all levels of the neuraxis, and the brain almost certainly integrates information from the skeletal, somatic, enteric, immune, and endocrine systems into its ongoing representation of the state of the body. Furthermore, there is growing evidence that other, traditionally exteroceptive, systems (e.g., vision, olfaction, gustation), are reciprocally linked to subjective affective experiences [121,168–171]. More research must articulate the pathways via which neural, chemical, and mixed signaling from the immune and endocrine systems, skin, muscles, bones, and other somatic tissues might contribute to interoception.

how physical wavelengths of light are **transduced** by retinal cells in the eye, **transmitted** by the optic nerve to the brain, and **compressed** and **integrated** in primary visual cortex and along cortical hierarchies (i.e., dorsal and ventral visual streams). To understand how interoception is related to affect, we likewise need a neurobiological model that traces how mental states (e.g., fear, joy, hunger, pain) characterized by distinct phenomenological properties (e.g., valence and arousal) emerge from the viscera. Doing so requires an understanding of how mechano-, chemo-, and thermo-sensory signals are transduced by receptor cells in and around the viscera, transmitted

Box 2. The correlation between interoception and affect

To date, much of the research on interoception and affect has taken one of two approaches: measuring covariation between individual differences in interoceptive traits and affective experiences, or between brain activation within interoceptive pathways (Box 1) and affective experiences [172]. Relatively little research has causally manipulated interoceptive pathways in humans and tested the outcome on affective experience, although see Box 3.

Interoceptive traits are between-subjective differences in interoceptive tendencies or abilities as measured by either self-report (e.g., [173–177]) or behavior (e.g., [178–183]). Although these self-reported and behavioral indices are often poorly correlated [184], they each predict aspects of subjective affect such that, on the whole, there is convergent evidence linking interoception and subjective affect.

For example, studies show some (albeit mixed) evidence linking self-reported interoceptive traits with anxiety and depression [185–188]. Individual differences in evaluative beliefs about body states also interact with objective peripheral physiological reactivity to predict the intensity of subjective stress [129]. Behavioral interoceptive traits are correlated with the etiology and symptomatology of several common mood disorders (e.g., anxiety, depression, bipolar disorder; reviewed in [12,187–189]), emotion regulation [190,191], and reliably predict the intensity or arousal of emotions in the lab (for review see [129], c.f., [192]) and in daily life [128].

By contrast, research linking interoceptive pathways (Box 1) and affect often focuses on measures of end-organ function (e.g., the heart rate) or individual differences in the structure/function of relevant brain anatomy (e.g., insula). For example, many studies have examined the relationship between autonomic arousal and subjective affect, finding evidence that physiological changes often accompany affective experiences such as emotion [193–195]. Finally, activation in brain regions linked to interoception, such as the anterior insula and dACC, are amongst the most consistently activated brain regions during subjective experiences of unpleasantness and pleasantness [15,196] or emotions such as anger, disgust, fear, happiness, and sadness in humans [111].

Lamination: the layered or laminar structure of the cortex.
Lossy compression: a form of data reduction wherein key information or patterns are retained while other (e.g., redundant or predicted) information is permanently discarded. Different from 'lossless compression'.
Nocebo: nocebo effects occur when one's negative expectations render an innocuous intervention harmful.
Placebo: placebo effects occur when one's positive expectations render an innocuous intervention (e.g., a saline injection or sugar pill) beneficial.
Predictions: patterns of ongoing intrinsic brain activity that serve to anticipate (or simulate) sensorimotor events before they occur.
Prediction error: sensory input that diverges from current predictions (can also be mathematically represented as the degree of divergence between sensory input and current predictions).
Predictive processing: functional mode wherein the brain learns statistical regularities in the body and in the world and encodes these regularities as 'priors' in order to predict impending sensorimotor events before they occur.
Pulse (or pressure) wave: changes in vascular pressure across the body as blood is shunted from the chambers of the heart to the periphery with each beat.
Repetition suppression effect: phenomenon wherein by increasing the predictability of a stimuli, you can attenuate psychoneurobiological reactivity to that stimuli.
Sensorimotor-association heterarchy: principle gradient in the brain anchored on one end by sensorimotor cortices and on the other by heteromodal association cortices.
Transduction: the translation of physical energy (e.g., light, pressure, heat, chemical composition) into electrical impulses within the nervous system.
Transmission: the relay of information between the periphery and brain via central (e.g., spinal tracts) and peripheral (e.g., cranial nerves) pathways of the nervous system.
Valence: the subjective feeling ranging from pleasantness to unpleasantness.

along spinal tracts and the cranial nerves (e.g., the vagus nerve) to the brain, and compressed and integrated in primary interoceptive cortex and along cortical hierarchies. We build on recent research and theorizing [3,5,13,25,37,38,41,42,208] to outline such a model and discuss how unique aspects of these **interoceptive pathways** may give rise to subjective experiences that differ in key ways from those of other sensory systems, such as vision.

We begin by situating this approach within models of predictive brain function. By these models, the brain issues probabilistic **predictions** about impendeing sensory and motor events before they occur, guiding perception and action in real time. These efferent predictions are corrected *ad hoc* by afferent sensory signals, or **prediction errors**, from the body and from the world [for reviews of predictive processing models, see 13,19, 21–25]. Guided by research on prediction within the motor, visual, auditory, gustatory, and olfactory systems, we next describe how prediction is enacted along interoceptive pathways. We focus on how high-dimensional afferent signals are transduced, transmitted, compressed, and integrated within the brain to produce a low-dimensional representation of the state of the body and highlight instances where structural or functional properties of interoceptive anatomy might serve to explain key features of affective experience. We speculate that, as compared with exteroceptive sensations, interoception may be governed relatively more by the brain's predictions than by actual sensory changes in the body. In this sense, interoception may be relatively less plastic than its 'exteroceptive' counterparts. We also speculate that anatomical features of interoceptive pathways may make affective states relatively difficult to locate in time and space and more likely than other sensory experiences to recede to the background of conscious awareness. We conclude by discussing how interoceptive anatomy and physiology may give rise to the specific phenomenology of valence and arousal. We hope that this review will begin to answer important questions about the neural basis of affect, interoception, and how the two may be related in the brain's construction of mental states.

The predictive brain

Understanding the anatomy and physiology of interoceptive pathways (Box 1) is essential for understanding how they may contribute to affective experience. Yet, this anatomy cannot be studied separately from principles of brain and nervous system function more generally. Contemporary neuroscience models argue that brains have evolved across evolutionary timescales to engage in **predictive processing**. Via predictive processing, the brain uses statistical regularities encoded from within the body and the world around it to represent an internal model of the body in the world [20]. On the basis of ongoing sensory events, this model then generatively predicts what sensory and motor events are most likely or most adaptive, respectively, in the future [21–24].

Sensory data that deviates from predictions serves as a learning signal called prediction error, ascending the neural hierarchy to update future predictions. Sensory data that confirms (or else weakly deviates from) predictions are discarded. Predictive processing increases evolutionary fitness by minimizing **informational entropy** as well as metabolic costs associated with encoding every available sense datum [19,25,26]. Predictive processing also decreases the likelihood of costly and even lethal errors by responding proactively instead of reactively to potential threats [27,28]. Imagine if your brain gave equal weight to the shape, texture, and color of the trees in the forest, the feel of the ground beneath your feet and the breeze on your skin, the sound of the birds and the wind in the trees, and the smell of the pines and the earth, only to realize too late that a cougar was about to pounce on you. Predictive processing helps to solve this challenge.

Predictive processing is well-known to occur in exteroceptive sensory modalities, such as vision, where sensory predictions bias visual perception towards the visual events most likely in a given context [29–31]. For instance, classic research in vision shows that the brain 'fills in' artificially

induced blind spots by using priors drawn from statistical regularities present in the rest of the visual field [32]. Moreover, unpredicted and goal-irrelevant stimuli often go unseen; a classic study showed that perceivers who were focused on watching others pass a basketball back and forth failed to see a person in a gorilla costume pass through the scene [33]. However, when prediction errors are particularly discordant from predictions, they are prioritized for processing. For instance, during induced binocular rivalry, different stimuli are presented to each eye, resulting in discordant prediction error signals from each eye and the conscious visual experience of seeing stimuli that alternate in time and predominance [34]. This is also the case for prediction errors that are particularly relevant to survival goals. Per the earlier example, visual prediction errors caused by the unexpected detection of biological motion in one's vicinity (i.e., a cougar) would inhibit ongoing sensory processing and behavior, re-orient attentional resources toward the unexpected stimulus, and upregulate functional connectivity from visual areas to premotor cortex to coordinate an appropriate motor response [35].

More recently, predictive processing models have been applied to interoception [36,37]. These models describe how the brain predicts the state of the body so that it can effectively satisfy future metabolic needs in relation to both the current state of the body and events in the external world (i.e., to enact **allostasis** [28]). In the service of allostasis, efferent visceromotor sensory predictions from the brain collide with afferent interoceptive sense data from the viscera; this occurs all along the neuraxis, from the brain to the periphery and back again. Interoceptive sense data that strongly deviate from predictions ascend the neuraxis as prediction error to update the brain's internal model of the state of the viscera [38]. For instance, unpredicted gastrointestinal inflammation and discomfort after consuming contaminated food (i.e., food poisoning) is encoded as prediction error by the brain and may shape future predictions about that food and the context it was eaten in, perhaps eliciting conditioned taste and context aversion in the future [39].

To understand how prediction and prediction error in the viscera may be translated into affective experience, we examine how physical energies are transduced, transmitted, compressed, and integrated along the neuraxis. Doing so reveals intriguing hypotheses about the types of mental phenomenology these processes might create, but also important gaps in our understanding of how sensations in the viscera translate into mental experiences.

Information flow through the interoceptive system

In the following sections, we trace how sense data in the peripheral body might ultimately contribute to subjective experiences of affect. Although the nervous system is predictive, with top-down predictions issued by the brain shaping even low-level sensory processing, we follow the traditions of exteroceptive perception that trace sense data from peripheral sense organs to the brain (Figure 2). Starting in early life, these afferent pathways are what seed a brain's developing internal model, laying the basis for future predictions [12,40]. Afferent prediction error is what ultimately serves to update the brain's internal model across the lifespan. We thus begin our discussion by focusing on sense data and tracing its flow up the neuraxis to the brain. We recognize throughout that this sense data is constantly constrained by efferent predictions.

When focusing on exteroceptive sensation and perception, we primarily discuss vision, given both its centrality to human experience and the relative wealth of research on its neurobiological and phenomenal underpinnings. Where applicable, we also discuss other exteroceptive sensations such as olfaction and gustation, given that their neurobiology may be ultimately more akin to interoception than vision [25,41,42].

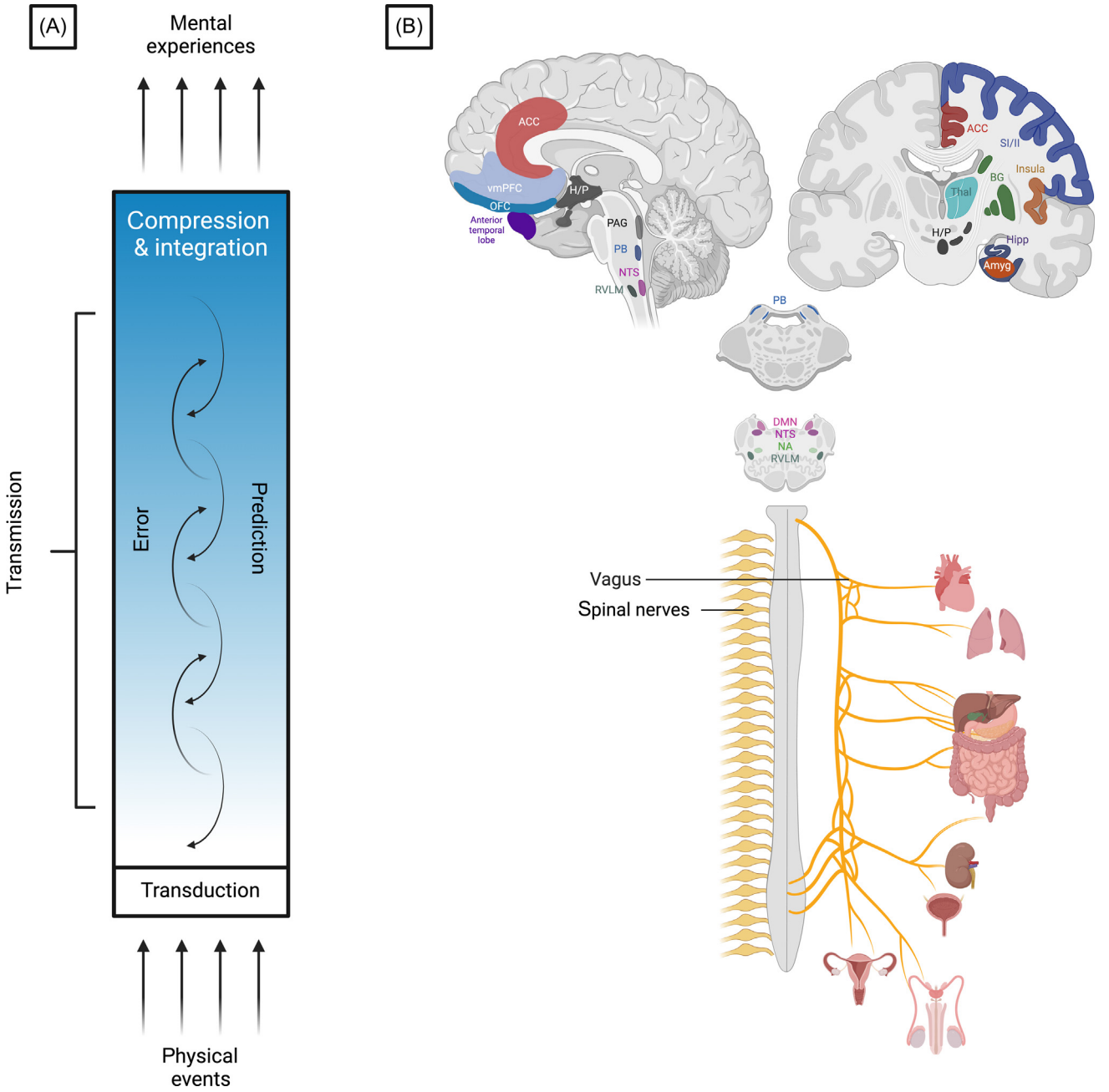

Figure 2. Neurobiological model linking physiological events and mental experience. (A) Depicts a schematic of how physical events are transduced, transmitted, compressed, and integrated within the nervous system to produce mental experiences. (B) Depicts relevant anatomy for understanding these processes with respect to interoception and affect. Interoception begins when information about a physical event in the periphery (e.g., a beating heart) is transduced by sensory receptors (e.g., baroreceptors in the aortic arch) and propagated along transmission pathways of the central (e.g., spinal tracts) and peripheral (e.g., cranial nerves such as the vagus) nervous system. As sensory information is transmitted from the periphery to the brain, it interacts with descending sensory predictions from higher up in the nervous system heterarchy. Sensory information that is adequately consistent with predictions is not propagated further up the neuraxis. Sensory information that is inconsistent with predictions (i.e., prediction error) is fed back up the neural heterarchy to inform future predictions. As information is transmitted, sensory signals become smaller in size, or compressed, integrated, and abstracted into lower-dimensional representations that increasingly integrate across sensory modalities. These processes begin in the periphery but escalate in the brain. Ultimately, compressed, low-dimensional interoceptive representations give rise to mental experiences and

(Figure legend continued at the bottom of the next page.)

When focusing on interoception, we primarily discuss the heartbeat. The heartbeat is a prototypical example of an interoceptive signal and with good cause. The heart is thought to have an important co-dependency with the brain vis a vis its role in transporting oxygen, nutrients (e.g., vitamins, minerals, sugars, fats, and proteins), hormones, immune cells, and waste products to and from other organs. The brain is especially subject to damage if it does not receive oxygen and nutrients from a functioning circulatory system. This co-dependency may even develop *in utero* insofar as the heart is the first organ to differentiate in a developing embryo and provides important oxygen and nutrients to the developing brain via the liver and umbilical cord [43–45]. From the moment a human can locomote, the cardiac system is also critical to initiating adaptive visceromotor responses to threats and challenges in the outside world [46]. For these and more pragmatic reasons (Box 3), the heartbeat has been the most extensively studied interoceptive sensation [47–50]. Correspondingly, there is a tradition of focusing on autonomic sympathetic neurobiological pathways in interoception [3,41,51]. Nonetheless, we caution that a bias towards studying the heartbeat has likely obscured the importance of other organ systems (e.g., the lungs or gut [52,53]) in interoception as well as other physiological pathways (e.g., the immune or endocrine systems [54,55]) (Box 1).

Sensation in interoceptive pathways

We begin by examining how an interoceptive sensation such as a heartbeat might contribute to affective experience by focusing on the sensations that are produced in the viscera when the heart beats. The physical energies associated with the heartbeat must first be registered, or transduced, by the peripheral nervous system. Transduction is the translation of physical energies by specialized sensory receptor cells into electrical signals that can, ultimately, be represented by the brain.

In vision, physical wavelengths of light are transduced by photoreceptors in the retina. In gustation, chemical compounds are transduced by chemoreceptors in the oral cavity and upper gastrointestinal tract. Interoception, by contrast, is unique insofar as it relies on myriad sensor types (mechano-, chemo-, thermo-, and multimodal receptors), that are spread across the entire body. When the heart beats, it produces multiple changes in physical energy throughout the body in a phenomenon known as the **pulse (or pressure) wave** [56]. The pulse wave is coordinated by the sinoatrial node, a small cluster of specialized pacemaker cells, that generates the electrical impulses that cause the heart musculature to contract. Each contraction of the heart in turn is associated with changes in blood flow and, consequently, with changes in the pressure and resistance of blood vessels branching throughout the body. The pulse wave also elicits subtle changes in skin temperature and local changes in the density of chemicals transported by the blood to and from other organs. As a result, the heartbeat can ultimately be transduced by a combination of mechano-, chemo-, and thermo-receptors in the heart, across the body (e.g., in the skin and peripheral vasculature), and even by receptors within the brain itself [57]. These sensors collectively register phasic changes in physiological phenomena such as arterial volume, blood oxygenation, glucose density, and temperature.

These features of interoceptive transduction likely have implications for the experience of interoception and, by extension, affect. First, the rhythmicity of interoceptive sensations makes them unique from other sense data. Many physiological processes have some inherent

help to inform human behavior. Abbreviations: ACC, anterior cingulate cortex; Amyg, amygdala; BG, basal ganglia (including striatum and caudate); DMN, dorsal motor nucleus; Hipp, hippocampus; H/P, hypothalamus and pituitary; insula, insular 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; Thal, thalamus; vmPFC, ventromedial prefrontal cortex. Panel (B) adapted, with permission, from Berntson and Khalsa [41]. Figure created with BioRender.com.

Box 3. Future directions for establishing a causal link between interoception and affect

Unlike vision, the study of interoception lacks the same wealth of stimulation, lesion, pharmacological, clinical, and cross-species research to guide causal inference. The little stimulation, lesion, pharmacological, clinical, and cross-species work that is available is suggestive, however, that interoceptive pathways play a role in affect. Electrical stimulation of sites throughout the insula causes affective experiences [197]. Cases of patients with bilateral insula lesions show some preserved affective experience (especially positive affect) but the findings suggest there may be disruptions in the incidence and timing of negative affect [198]. Blunting peripheral signaling pathways using a beta-blockade (e.g., propranolol) attenuates the intensity and arousal of healthy adults' emotions during acute stress [199]. The neurodegenerative condition, pure autonomic failure, which is characterized by denervation of peripheral autonomic nerves, shows a similar pattern of attenuation during stress in patients suffering from it [200]. Finally, there is some evidence that individuals with high spinal cord injury show decrements in affective experience [201]. See [119] for a review of such findings.

Nonetheless, the findings are mixed and complex in many such studies and with good reason. First, it is notoriously difficult to manipulate and measure peripheral processes non-invasively in humans, causing most studies to rely on passive measurement of pulsatile signals from the heart, lungs, and gut via surface electrodes. Novel methods for manipulating and measuring tissue function via deep brain or transcutaneous nerve stimulation offer exciting future directions in this regard (e.g., [202]). Second, although clinical models have been integral to our understanding of interoceptive and affective processes, some of the most relevant conditions remain exceedingly rare (e.g., brain stem lesions, sympathectomy, vagotomy, familial dysautonomia, or pure autonomic failure). Even when studies do accrue a number of patients, sample sizes remain quite small and often do not contain optimal measurements for explicitly testing the role of interoception in affect (see [119]). Finally, cross-species differences in cortical cytoarchitecture and connectivity suggest meaningful differences in how information is processed in the brains of mammals and thus might limit the utility of some types of non-human models. For example, while there have been several cutting-edge neurophysiology and neuroimaging studies conducted on interoception in mice [203–205], there are substantial differences in nervous system anatomy (including in insular cortex) between humans and rodents [151,206]. However, there are homologies between the insular cortex of non-human primates and humans. More non-human primate and human-subject research is needed that probes the extent to which peripheral receptors, transmission pathways, and brainstem, subcortical, and cortical regions are necessary or sufficient for subjective interoceptive and affective experiences. Recent evidence that rhesus macaque monkeys can detect their own heartbeats [207] offers future pathways for causal manipulation of those pathways in the non-human primate brain.

rhythmicity, which affords them predictability [41,43,58]. For instance, the sensory events associated with the heartbeat have a period on the order of milliseconds due to the sinoatrial node's pacemaking, whereas other visceral physiology, such as hormone concentrations or body temperature, exhibit circadian or circalunar rhythms regulated by other biological clocks. Collectively, this rhythmicity may afford interoceptive sense data predictability and precision. Predictable stimuli are known to elicit **repetition suppression effects**, whereby activation within sensory brain regions representing prediction error is suppressed as the predictability of sense data increases [59,60]. Repetition suppression effects have also been extended to explain the suppression of internally generated stimuli. For example, scholars have used these insights to explain the reduced perceptual intensity of self-initiated (and thereby predicted) sensations such as tickling one's own skin or listening to one's own voice [61,62]. Internally generated interoceptive data may work similarly, insofar as internally generated interoceptive sensations are often suppressed from conscious awareness unless they are extreme. High predictability and precision when combined with the suppression of prediction error might explain the power of **placebo** and **nocebo** effects relative to objective tissue damage in pain [63,64], as well as the relative impenetrability of an affective state once a person is experiencing it. Indeed, there is evidence that the most effective forms of emotion regulation involve explicitly changing one's predictions (e.g., via cognitive reappraisal [65]) or inducing strong prediction errors in the body (e.g., via direct change to the physiological state via exercise, ingestion of chemicals, or a large shift in the external context [66–68]).

Second, the spatial distribution of visceral sensory receptors differs from those of exteroceptive systems like vision, with implications for the experience of affect. Visceral sensory receptors are widely distributed across organ systems, but they are sparsely distributed within most organs (the skin is a notable exception [69]). This spatial distribution is thought to contribute to visceral sensations that are poorly localized and often referred to the skin [69,70]. For instance, the

precise localization of visceral pain is notoriously difficult. Affect too, seems not to be localized to a spot in the body, even if affective experiences are experienced as having inherently bodily qualities [71]. Collectively, these features of interoceptive transduction may help us understand why, even from initial transduction, interoceptive sensations often proceed in the backdrop of conscious experience and are experienced as somewhat vague and diffuse.

Transmission in interoceptive pathways

In order for a heartbeat to contribute to interoception and affective experience, the sense data associated with its physiology must travel from primary sensory receptors to sensory neurons and, ultimately, to the brain. This process is called transmission. Since transmitting massive amounts of sensory data is metabolically demanding, evolution has fostered a tradeoff between information transfer pace and metabolic efficiency during the transmission of sense data [72–74]. Sensory neurons with thinner axons are more metabolically efficient than thicker axons because they can send more information per energy unit (ATP) and per axon volume. However, these thinner axons have increased channel noise from the stochastic opening and closing of voltage-gated sodium channels, which disrupts the precise timing of action potentials [75]. Since any given sodium channel has a greater influence on membrane potential in thinner axons, such channel noise can produce spontaneous action potentials that decrease the fiber's overall signal-to-noise ratio [75]. In contrast, thicker fibers are less metabolically efficient but can convey more information per unit of time and are less susceptible to channel noise [72,73].

In vision, wavelengths of visible light are transmitted by short, thick axons which evolved to process sense data with an inherently quick rate of change (i.e., the visual light spectrum has a frequency range of between 400 and 800 THz) [72,76]. Being able to process dynamic visual stimuli afforded substantial survival benefits to animals that hunted during daylight, making short thick axons adaptive despite their metabolic costs [72]. By contrast, the sensory neurons of the interoceptive system that innervate organs and synapses on spinal tracts and cranial nerves transmit sensory data that occurs with relatively slow frequency (e.g., the average adult human heart rate is about 65 beats/minute or 1.08 Hz; gastric and urinary frequencies are even slower; [41,77], c.f. [78]). This data must also travel relatively long distances from the periphery to the brain. As such, interoceptive neurons likely evolved to be thinner than other types of sensory neurons on average ([72], c.f. [74]) because they minimize metabolic costs associated with information transfer over long distances. As we discussed earlier, and will discuss later, features of interoceptive sense data may be inherently more predictable than visual sense data, making the downsides associated with thinner axons less impactful within the interoceptive system than in the visual system.

Collectively, the anatomical features of interoceptive transmission pathways allow a large amount of information covering a large amount of space to be efficiently transmitted over a long distance. However, these features may compound the already low spatial specificity of interoceptive sense data. Because sensory neurons within the interoceptive system skew thin, they lack the temporal resolution of other sensory neurons, such as those supporting vision. This feature may explain why interoceptive sense data is experienced with less temporal precision than other types of sense data and why affective states are typically experienced as relatively diffuse and slow-moving.

Compression and integration in interoceptive pathways

As sense data encoding the heartbeat are transmitted along the neuraxis, they are progressively altered to further maximize the efficiency of information transfer [79]. This process involves both phenomena called '**lossy compression**' (hereafter 'compression') [79,80] and integration of different sources of sense data. In compression, some sense data are retained, whereas other sense data are permanently discarded. In integration, sense data from different pathways and

even modalities are combined to form lower-dimensional summary representations [25,38,42]. Compression and integration occur iteratively in the peripheral nervous system and then again in the brain.

In vision, compression and integration begin in retinal ganglion cells. Retinal photoreceptors sensitive to short, medium, and long wavelengths of light synapse onto a smaller number of retinal ganglion cells. These ganglion cells compress and integrate signals to begin to represent color perception [17]. As in vision, compression and integration in the interoceptive system likely begin in peripheral transmission pathways. For example, substantial research documents somato-visceral integration in the spinal cord [81–85] and recent work on the vagal trunk of pigs and humans reveals merging fascicular bundles that are thought to contribute to the integration of visceral data into viscerotopic representations of peripheral organs [86,87].

In the cortex, sense data flows along a **sensorimotor-association heterarchy** anchored on one end by regions involved in primary sensory representation and on the other by heteromodal association cortices [25,38,88–90] (Figure 3). Note that unlike a hierarchy, in a heterarchy the flow of information is multidirectional and sometimes nonlinear [91]. The flow of information along the sensorimotor-association heterarchy is afforded by variation in the cytoarchitecture of brain regions; The extent to which areas are **granulated** and **laminated** seem to be of particular importance for this sort of information processing [13,25,92]. Barbas and colleagues' 'structural model' of brain function [92] suggests that prediction error is generated by relatively more granular and more highly laminated brain tissue. For instance, primary visual cortex (V1) is granular and highly laminated (i.e., has six well-defined layers). These features allow it to support largely unimodal, high-dimensional representations that unfold with a quicker rate of change [93–95].

By contrast, predictions are initiated further up the heterarchy within more agranular and dysgranular cortical regions, which tend to have fewer layers of cortex [92]. It is thought that these brain regions' structure is a product of neuronal migration during the expansion of brain tissue along the rostrocaudal axis during both evolutionary and ontogenetic development [94]. As a result, many of these structures are in anterior or medial regions of the brain and include anterior temporal lobe, anterior cingulate cortex, ventromedial prefrontal cortex, ventral anterior insula, and posterior medial orbitofrontal cortex. Many of these regions are also known as 'heteromodal association regions', and are capable of representing low-dimensional (i.e., compressed) and multimodal (i.e., integrated) representations that are abstracted from primary high-dimensional sense data [25,89,94] (Figure 3). Perhaps not surprisingly, many of these regions have been associated with human 'autobiographical memory' and 'semantic representation' [96–98]. In other traditions [99–101], these regions are considered limbic, paralimbic, and motor and thereby 'emotional'.

In vision, compression and integration are achieved as predictions interact with sense data all along ventral and dorsal visual streams, processing circuitry originating in primary visual cortex and extending through the occipital lobe into either the temporal (ventral stream) or parietal lobe (dorsal stream) (e.g., [102,103]). Here, visual sense data is progressively compressed and integrated into lower-dimensional representations that ultimately form the basis of visual features such as edges, contour, and motion [18,88,104]. Further up the heterarchy, visual sense data is integrated with other modalities such as auditory and somatosensory data; it ultimately is processed within ventromedial prefrontal cortex and produces, for instance, perceptions of colored objects moving in space [31] (Figure 3).

The flow of interoceptive sense data along the sensorimotor-association heterarchy differs from visual sense data in a couple of key ways. First, before reaching primary interoceptive cortex (I1) in the mid- and dorsal posterior insula, interoceptive sense data go through initial compression

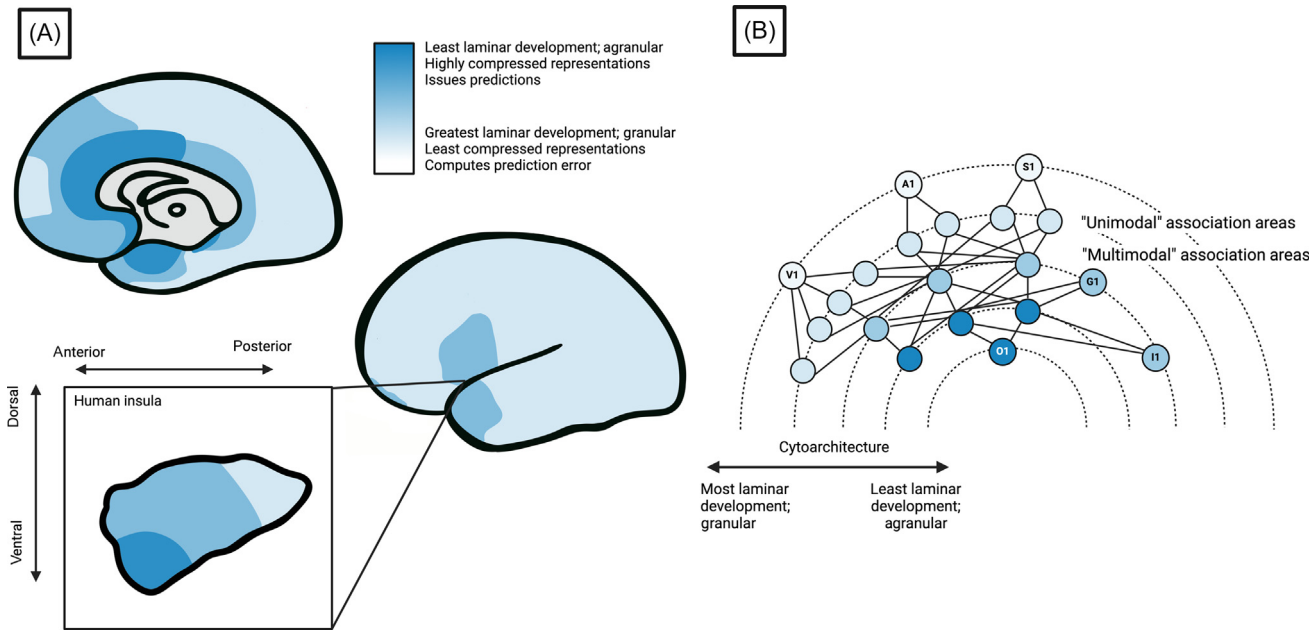

Figure 3. Lamination of brain tissues. Brain regions differ in their degree of lamination (i.e., number of layers) and cytoarchitecture (e.g., presence and number of granule cells, relative numbers of glia, etc.); these structural features have implications for function. Depicted in (A) are differences in lamination of brain tissues. Darker blues indicate less laminated agranular regions (e.g., including cortical limbic areas surrounding the corpus callosum) and lighter colors indicate more laminated granular regions. Prediction signals are thought to flow along laminar gradients from agranular and dysgranular regions with less lamination to granular regions with greater lamination. Prediction errors are thought to flow in the opposite direction. The human insula (inset), which sits under the lateral sulcus, contains a dorsal posterior-to-ventral anterior laminar gradient, wherein predictions emanate from ventral anterior regions and prediction error from dorsal posterior regions. Interoceptive sense data is thus thought to become increasingly compressed and integrated as it moves from posterior to mid- to anterior insula. However, primary sensory areas also differ in their relative degree of lamination and granularity, which means they are situated in different locations within the brain's predictive heterarchy. Depicted in (B) are primary sensory regions for vision (V1), audition (A1), somatosensation (S1), gustation (G1), interoception (I1), and olfaction (O1). V1, A1, and S1 are composed of tissues with the greatest laminar development and granule cells. These brain regions are the furthest away geographically in the brain's predictive heterarchy from lower-lamination agranular and dysgranular regions that generate predictions. The implication is that V1, A1, and S1 may have greater capacity and more opportunity to incorporate prediction error into representations of sense data. Primary regions for interoception (I1), olfaction, (O1), and gustation (G1), by comparison, are composed of tissues with relatively less laminar development and are geographically closer to regions that generate predictions within the heterarchy. As a result, these regions may represent highly compressed, low-dimensional data and may have fewer opportunities for incorporating prediction error into sensory representations. Panel (A) adapted, with permission, from Barrett [13]. Panel (B) adapted, with permission, from Chanes and Barrett [25]. Figure created with BioRender.com.

and integration within the brainstem and midbrain [e.g., within the nucleus of the solitary tract (NTS), periaqueductal gray (PAG), ventrolateral medulla, and parabrachial nucleus] [105]. At least in non-primate mammals, these integration sites map sense data along a gradient representing the rostro-caudal organization of organs in the body [3,106–109; see 42 for a discussion]. For instance, the PAG unites sense data from the periphery to somatotopically represent the face and body [110]. Since regions such as the PAG also generate autonomic visceromotor efferents, this level of spatial differentiation in afferent signals may support the subcortical regulation of autonomic reflex arcs in response to specific somatovisceral changes (e.g., changes in heart rate or respiration during cutaneous pain) without the need to first propagate that information up to the cortex [3,41,111].

From the midbrain parabrachial nucleus, interoceptive sense data forming the basis of somatic states such as hunger, thirst, the urge to breathe, temperature, burning pain, prickling pain, muscle pain, itch, pleasurable touch, and bladder and bowel distension are projected to primary interoceptive cortex in the dorsal posterior insula via the ventromedial nuclei of the thalamus [3,106]. Yet, separate from other studied mammals, the primate brain possesses additional direct pathways from the spinal I lamina and vagus to the ventromedial nuclei of the thalamus; these

pathways may allow the primate brain to circumvent brainstem and midbrain centers to integrate prediction errors from the viscera directly into a summary representation of the internal body within primary interoceptive cortex [3,106]. This structural feature may be one means by which the primate brain creates a global representation of the state of the body as it relates to the current environment, or what Shaffer *et al*. [42] refer to as 'allostatic ensembles'. Although speculative, these pathways may even contribute to human affective experiences. For instance, although traditionally linked to visceral sensations such as pain, meta-analyses reveal that the posterior insula is also consistently activated in human emotional experiences such as anxiety and anger [112,113].

Within the insula itself, interoceptive sense data is progressively compressed and integrated into lower-dimensional representations as information propagates from the dorsal posterior to the ventral anterior of the structure [5,114–116]. The insula transitions from granular cortical tissue with four layers in its most posterior extent (I1), to dysgranular cortex (with a rudimentary layer IV) in its middle extent, to agranular cortical tissue with three layers in its most ventral and anterior extent (Figure 3). According to the Embodied Predictive Interoceptive Coding (EPIC) model [36], dorsal and posterior insula receive predictions from agranular and dysgranular visceromotor control regions of the brain, including ventral anterior insula, mid-cingulate cortex and anterior cingulate cortex, posterior ventromedial prefrontal cortex, and orbitofrontal cortex [13]. These predictions are known as 'efferent copies' (or corollary discharge [117,118]) and represent the predicted sensory consequences of the efferent visceromotor predictions issued by those same brain regions [36]. In this sense, they represent the brain's best guess of what it will feel like when it, say, increases heart rate and cardiac output for the purpose of avoiding a threat or pursuing a reward (see [25]). As with predictions throughout the rest of the neuraxis, these are an important, or even possibly a necessary, foundation for conscious experience and are only updated if they are sufficiently different from prediction errors represented by the dorsal and posterior insula.

Collectively, these architectural features of the interoceptive sensorimotor-association heterarchy have at least two important consequences for interoception and, correspondingly, affective experience. First, unlike visual perception, the fact that interoceptive sensations are represented in cortical regions with little granulation and few layers has implications for their experience. These regions have a structure more akin to the multimodal integration regions that comprise the second level of the visual sensorimotor-association heterarchy [25] (Figure 3). These structural features may mean that interoceptive sense data are already inherently more compressed and integrated than initial visual sense data. Second, the fact that interoceptive predictions proceed directly from agranular, three-layered to more granular four-layered cortex in humans means that interoceptive sense data transverse fewer processing steps in the brain than, say, vision, which transverses cortex ranging from three to six layers (Figure 3). Interestingly, primary interoceptive cortex has structure features more akin to primary olfactory (O1) and gustatory cortex (G1), which should motivate additional research into their structural and functional similarities and differences. The result of their position within the sensori-motor association heterarchy is that there may be fewer opportunities to integrate prediction errors into these senses when compared with vision (for discussion, see [25]). This fact has led scholars to argue, again, that interoception may rely more heavily on predictions than some other sensory systems.

From interoception to subjective affective experience

Scholars have argued for centuries that affective states 'emerge from' or have at their 'core' representations of the state of the body [119]. Our review of the path of efferent visceromotor predictions and afferent interoceptive sense data through the nervous system begins to shine important light on how the state of the body might contribute to affective experiences. Throughout, we have suggested that links between interoception and affect can be better appreciated by

considering what is known about how information flows through interoceptive pathways in the nervous system. We have discussed: (i) how interoceptive sensations have properties such as rhythmicity that make them predictable, (ii) that interoceptive sensory cells are broadly distributed and sparsely concentrated, (iii) that interoceptive transmission channels consist of long-range thin fibers that sometimes split and/or merge, and (iv) that in the brain, signals continue to converge into lower-dimensional multimodal representations along cortical tissues that afford fewer opportunities for computing prediction error than other exteroceptive senses like vision. Collectively, we have suggested that these features may give rise to mental states that lack spatiotemporal precision and rely heavily on prediction versus prediction error and, as a result, often fade into the background of conscious awareness.

Based on the existing data, we join others in suggesting that these mental states may constitute affect [3,13,120,121], and that the mental representation of affect, in turn, may be the brain's low-dimensional predictions about the physiological state of the body in a given context [13,38]. Affect is often described as having features of valence and arousal, but just because they are often experienced together as a unified psychological state does not mean that they emerge from the same neurobiological mechanisms. Increasingly, researchers have theorized that subjective arousal may be more closely tied to interoception *per se* than valence. Arousal, by these accounts, is thought to indicate the mobilization of energetic resources to minimize future prediction error through action or information gathering (i.e., upweighting precision of ascending sensory evidence) [19,122,123]. By contrast, valence may be a relatively more abstracted, and thus more multimodal and context-dependent, representation of overall goodness-of-fit of the brain's predictive model [122,124–127]. These hypotheses are consistent with the fact that studies evaluating interoception and affect find more consistent links between interoceptive acuity and subjective arousal (relative to valence) [128] (e.g., [129–134]). These hypotheses are also consistent with evidence that subjective arousal is consistently linked to activation within brain regions associated more directly with visceromotor control (e.g., the amygdala) and the representation of afferent visceral signals (e.g., the insula), whereas valence is consistently linked to heteromodal regions associated with integrating multimodal information (e.g., abstraction), context, prior experiences, and concept knowledge such as the ventromedial prefrontal cortex [15,135,136]. More experimental research is needed to confirm such claims, but they offer new hypotheses for testing the link between interoception and facets of affective experience.

If low-dimensional interoceptive representations do give rise to subjective affect, then the evidence we have reviewed introduces novel hypotheses and areas for future research. For example, given the amount of multimodal integration within the insula and other brain regions higher up in the sensorimotor-association heterarchy, it is likely that affect is not solely informed by predictions about the viscera, but rather that affect also incorporates information about other systems of the body (e.g., somatomotor) and about the external environment [137]. As just suggested, this may be particularly true for affective valence as opposed to arousal.

As another example, the idea that affect may be more beholden to predictions (i.e., less subject to updating via prediction error) than vision may help explain why it often feels as if affect happens 'to us' without our control. This may be one reason that throughout Western history affect has been pitted against states that are experienced as more within our conscious control such as willful 'rational' thought [138,139].

Of course, humans do not exclusively experience interoceptive sensations as affect, they also experience discrete sensations in their body such as a racing heart, stomach rumblings, sweaty palms, sore muscles and joints, uterine contractions, and gonadal arousal [69,70]. Reports of

those sensations indicate that they are, at times, available to consciousness and are relatively localized. Thus, sometimes interoception merely results in the experience of a somatic state. Yet, there are also many examples in which prediction error from the body is erroneously experienced as part of another mental state. People feel romantic attraction when aroused on a high suspension bridge, misattribute hunger as anger in the face of an annoyance, and experience people as more aversive when having an immune reaction [130,140–142]. How and when people experience interoception as somatic sensations versus emotions or cognitions is interesting and should be explored further.

Research from affective science may be able to weigh in on such questions and generate new hypotheses. For example, according to theories of constructed emotion (for review, see [143,144]), mental states such as emotions emerge when sensory input from the body and world are categorized using concept knowledge acquired through one's culture and life experiences [13,145]. The distinction between an instance of, say, fear, and a more general feeling of unpleasantness, then, is that a mental state called 'fear' names a specific set of visual, auditory, visceromotor, skeletomotor, and interoceptive predictions based on prior experiences of threat or danger. This type of perception requires abstract knowledge about the types of situations that might cause harm or threat to the body or one's social standing [146]. There is now much evidence that instances of fear, anger, sadness, and joy in humans involve brain activation spanning heteromodal association regions that sit atop the heterarchy we have discussed (Figure 2) [15,147], as well as regions along the temporal parietal junction, lateral temporal cortex, and parahippocampal gyrus more commonly associated with semantic knowledge [97]. Indeed, it is activation in these regions that allow pattern classifiers performed on brain activation to differentiate experiences of fear, anger, sadness, and joy from one another (for review, see [135]). Of course, subcortical and brainstem structures associated with conserved behavioral repertoires (e.g., freezing, fleeing, attack) are also involved and are important to human emotional experiences; these structures certainly show differential activation during human emotional experiences [148,149]. However, as the predictive architecture outlined herein reveals, association cortices may be driving such subcortical activation on the basis of predictions, rather than merely regulating or representing states generated subcortically after the fact. Association cortex (e.g., orbitofrontal cortex) is also associated with context-specific defensive behavior in rats [150], suggesting that its role in issuing predictions is unlikely uniquely human (although it is likely that the relative abstractness of the predictions issued is distinct across species [151]).

These insights from the study of emotion suggest that culture and socialization may also play a more instrumental role in interoception than is typically assumed in most psychological theorizing. To the extent that many types of mental states are socially constructed categories, socialization of culture-specific categories might also shape how states of the body are experienced and regulated. For instance, individuals born in Asian countries are more likely to experience physiological sensations as bodily symptoms (e.g., such as illness), whereas individuals born in the USA are more likely to experience such sensations as emotions [152]. Even within a culture, individuals differ in the tendency to experience their physiological states as emotional versus purely somatic. In Western contexts, individuals high in the trait of alexithymia, who have difficulty labeling and differentiating their emotions, tend to report relatively more somatic complaints than individuals low in alexithymia. These findings imply that individuals high in alexithymia may experience interoceptive sensations as somatic, but not emotional (see [153]).

Finally, whether sensory representations are constructed into discrete mental states at all is largely a function of attentional deployment. When attention is directed outward (instead of inward), these representations may also produce a kind of perceptual realism, imbuing the

world around us with affective properties. For example, when experiencing elevated cardiovascular reactivity, individuals with poorer interoceptive acuity are more likely to perceive social targets as more aggressive and judgmental and less warm and competent than individuals with better interoceptive acuity [141]. Differences in socialization may additionally shape how attention is deployed. For example, in the USA and some Western countries, women and girls reliably express emotions and physical symptoms more often than men and boys [154,155]. In contrast, men and boys appear more likely to externalize their affective experience [156]. A better understanding of interoception's contribution to mental states in health and disease ought to consider these types of situational-, individual-, and cultural-level differences.

Concluding remarks

There has been a sixfold increase in research on interoception in just the last decade and great advances have been made in understanding its neurobiology and its association with affective experiences. However, the field has lacked a mechanistic model for understanding how activation in the viscera comes to be experienced as unpleasant, arousing, or even fearful. Herein we built on prior work, especially that using principles of predictive processing, to articulate how interoceptive sense data is transduced, transmitted, and compressed and integrated by the nervous system to ultimately result in subjective affective experiences. This framework opens many more questions than it answers (see Outstanding questions) and we hope it will be generative for future work. For instance, if affective experience is ultimately a product of predictions seeded within brain regions associated with meaning-making, semantics, and memories, then this would open avenues via which prior experiences, social learning, and culture can ultimately influence interoceptive and affective states. We look forward to this and other questions about how the brain, body, and social world ultimately shape the mind.

Outstanding questions

How are other bodily signals, including those from the enteric nervous system, somatic nervous system, neuroendocrine and immune systems, compressed and represented by the brain and are these pathways distinct from those traditionally associated with interoception?

How does the neuroanatomy and thus structure–function mapping of the interoceptive system differ across species (including humans versus non-human primates versus other mammals)?

Where does compression begin in the peripheral nervous system and what are the consequences for processing distinct visceral sensations and subjective affective experience?

How are valence and arousal differentially influenced by interoception?

How are valence and arousal differentially represented in the predictive hierarchy?

How do individual differences in the biology or enculturation of predictive models impact interoception?

How do individual differences in the biology or enculturation of predictive models impact the extent to which interoception contributes to affective states?

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Declaration of interests

No interests are declared.

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