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Interoceptive inference: from computational neuroscience to clinic

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Abstract

The central and autonomic nervous systems are defined by anatomical, functional and neurochemical characteristics but neither functions in isolation. Fundamental components of autonomically mediated homeostatic processes are afferent interoceptive signals reporting the internal state of the body and efferent signals acting on interoceptive feedback assimilated by the brain. Recent predictive coding (interoceptive inference) models formulate interoception in probabilistic inference terms to explain mechanisms supporting emotion and selfhood. We propose interoception may serve as a way to investigate holistic nervous system function and dysfunction in disorders of brain, body and behaviour. Here, we apply a formal predictive coding framework grounded in the free-energy principle, to describe homeostatic functions of the central and autonomic nervous systems that are bound by interoceptive processes. We do so by (i) firstly describing the application of predictive coding – as circumscribed within the active inference framework – to homeostasis via symbiotic interoceptive and autonomic function, before (ii) secondly describing clinical applications of this framework. Finally, we (iii) describe how this offers an overarching approach to human physiology, particularly autonomically mediated systems, thereby offering a new means to investigate the interaction of the central and peripheral nervous systems in health and disease.

Keywords: active inference, autonomic nervous system, free-energy principle, homeostasis, interoception, interoceptive inference, predictive coding.

1. Introduction

‘Interoception’ refers to afferent sensory information arising from the viscera that underwrites homeostatic functioning (1). The control of interoceptive stability or homeostasis (i.e., autonomic nervous system regulation) can be mapped onto a hierarchical organisation; ranging from basic physiological reflexes to global cortical networks that integrate the function of the central and autonomic nervous systems (2-5). Fundamental components of these homeostatic processes are afferent interoceptive signals reporting the internal state of the body and efferent signals acting on interoceptive feedback (4, 6-8), in the form of homeostatic reflexes that are informed by somatic states represented in the central nervous system. Co-ordinated central and peripheral nervous system function is required, even at lower tiers in the hierarchy, where structures such as the spinal cord, brainstem and hypothalamus mediate autonomic outflows and descending cortical inhibition (9, 10). For example, the periaqueductal gray (PAG), which regulates input/output of nociceptive and visceral signals, is also innervated by descending anterior cingulate cortex (ACC) projections, which can boost or inhibit pain responsivity, selectively (9). Moreover, chemoreceptors in the brain stem monitor arterial carbon dioxide, oxygen and hydrogen ion levels to regulate carbon dioxide, oxygen and pH perfusion via sympathetic and phrenic efferents. More generally, hypothalamic, pontine and medullary sympathetic and parasympathetic nuclei interact with homeostatic representations to generate effector-organ specific autonomic responses (11). In the cardiovascular domain, heart rate changes are related to amygdala and dorsal anterior cingulate cortex (dACC) activity (12) and during stress, amygdala activity predicts systolic contractility (13). The amygdala, ACC and other limbic structures supply descending inputs to the hypothalamus and brainstem for emotion-related autonomic responses (11).

1.1. The functional anatomy of interoception

As key players in the functional anatomy of interoception, the ACC and insula cortex are important for the processing of interoceptive feedback and mediating autonomic responses to

interoceptive information (14, 15). dACC (16) and insula cortex (17, 18) activity reflects engagement of sympathetic nervous system activity coupled to mental and physical behaviours. The anterior and posterior insula show increased neuronal activity during respiration, isometric exercise, cold pressor and Valsalva manoeuvres (19) (20). Increases in blood pressure positively correlate with right dACC activity (17), supporting findings that sympathetic responses are lateralized to the right hemisphere (21), whereas the left insular cortex is involved in parasympathetic nervous system cardiovascular regulation**,** as evidenced by acute left insular stroke disrupting the correlation between heart rate and blood pressure (22).

The insula has a posterior-to-anterior gradient, with initial sensory afferent information received by the posterior insula, which is then passed to the anterior insula cortex (AIC) – especially the right – where it is integrated with cognitive-affective biases and autobiographical information. This unique integrative structure has led to a variety models relating to the function of the region, ranging from general theories of consciousness and affect to a putative role as a primary viscero-sensory region (23). Accordingly, the AIC modulates homeostatic autonomic and interoceptive function via connections to allostatic centres (24). Reduced baroreceptor tone is associated with ACC, amygdala and AIC function, whereas initiation of baroreflexes increases activity in lateral prefrontal cortex (lPFC) and posterior insula (25). The mid and posterior insula are associated with somatomotor function and representations (26) and the AIC and mid insula cortices, ACC and somatomotor cortex are functionally associated with shifting one's attention to interoceptive signals (27). Bilateral insula cortices are activated during oesophageal stimulation (28) but as stimulation increases to the point of becoming painful, the right AIC is recruited (29), illustrating how increasing interoceptive feedback will ascend the interoceptive hierarchy from bilateral insula to right AIC, as initial reporting of somatic sensory feedback escalates to a violation of homeostasis then to nociception; engaging conscious awareness. More generally, the insula is implicated in the integration of

both interoceptive and exteroceptive inputs, has been proposed to act as a core comparator underlying the generation of a multisensory embodied self (30, 31), which also regulates interactions between the cognitive and affective aspects of pain (32-34).

With respect to descending neural pathways, central efferent signals can drive allostatic changes in autonomic and behavioural function. During rest (35) and exercise (36, 37), perceived changes in skin temperature and thermal discomfort typically induce behavioural modifications before the recruitment of endocrine or autonomic thermostatic mechanisms (38, 39). Behaviour-dependent increases in blood pressure are enabled and moderated by the baroreflex (40, 41) and baroreflex dysfunction causes loss of consciousness due to cerebral hypoperfusion. The baroreflex arc ensures cerebral perfusion by mechanoreceptors in the carotid arteries and aortic arch detecting changes in arterial pressure and constantly feeding back this interoceptive information to the nucleus of the solitary tract (NTS), which synapses with the rostral ventrolateral medulla to set efferent pressor tone. During emotional or cognitive stress, the baroreflex feedback loop is disrupted by top-down cortical influences increasing heart rate and blood pressure during steady-state physiological demands. Specifically, the aberrant cardiovascular up-regulation in the absence of allostatic demand results from suppression of low-order baroreceptor brainstem signalling by the solitary nucleus of the medulla, hippocampus, hypothalamic nuclei and prefrontal cortex (PFC) (42). In summary, although the central and autonomic nervous systems are defined by unique anatomical, functional and neurochemical characteristics, they also interact in a variety of ways to maintain homeostasis. Interoceptive signalling and control spans and integrates central and peripheral homeostatic processes, as well as influencing emotional and cognitive functions (43-45).

In the following, we propose that interoception may serve as a unique window on holistic human nervous system function and dysfunction in disorders of brain, body and behaviour.

Due to the scope of this proposition, we offer a formal framework – grounded in interoceptive inference – that offers a methodological foundation for generating empirical predictions. To this end, we first formulate homeostasis in terms of interoceptive inference; via symbiotic interoceptive and autonomic nervous system function, before describing the clinical application of this approach. We then illustrate how this formulation can offer an overarching approach to human physiology, particularly autonomically mediated systems. Finally, we will review our initial empirical findings and their relationship to interoceptive inference.

1.2. Interoceptive predictive coding – neural correlates for conscious and unconscious processes

Discrepancies between predicted and experienced interoceptive signals have been proposed as a potential cause for anxiety (46). In predictive coding terms, discrepancies between 'top-down' predictions generated by the brain and incoming sensory signals from the periphery are compared to produce a 'prediction error'. Subsequent minimisation of this prediction error corresponds to a Bayes optimal estimation of how sensory signals were caused; this can be seen easily by noting that if descending predictions match sensations exactly, the predictions must have been generated by representations of the world (i.e. expectations) that are, in some sense, veridical. This can be formalised in terms of Bayesian inference, where the evaluation of an expectation about the world is based on prior beliefs and the likelihood of observed data.

The application of predictive coding to perceptual inference involves minimisation of unpredicted or surprising sensory signals (prediction errors) within the cortical hierarchy by the generation of top-down predictions (figure 1). In this setting, the prediction errors at the sensory level play the role of a likelihood (i.e., reporting how unlikely the sensations were given expectations about their causes), while prediction errors at higher levels play the role of

empirical priors (i.e., how unlikely expectations at one level are, given expectations of the level above). It is fairly easy to show that minimising prediction errors at each and every level of the hierarchy produces a set of expectations that constitute a Bayes optimal representation of how sensations are generated. In brief, the minimisation of prediction errors involves reciprocal exchange of signals between hierarchical levels: prediction errors ascend the hierarchy to revise expectations, which generate descending predictions that resolve or suppress prediction errors at the level below.

In biologically plausible versions of the scheme, prediction errors are thought to be encoded by the activity of superficial pyramidal neurons, which compare expectations with predictions descending from deep-layer pyramidal neurons in higher hierarchical levels. The prediction error is then projected (via intrinsic or interlaminar connections) to deep pyramidal cells encoding expectations in the higher cortical level, enabling a more accurate prediction to be reciprocated. This recurrent message passing allows prediction units to produce a more accurate prediction and effectively silence prediction error.

Figure 1 near here

A prediction error's strength or influence on expectations or representations as higher levels depends on its 'precision' or reliability (figure 1). If a prediction error is less reliable, such as vision on a foggy day, more precision or weight will be afforded to prior expectations or beliefs about the environment. This ensures Bayes optimal perception, meaning that precision determines the influence of prediction error on subsequent hierarchical cortical evidence (i.e., prediction error) accumulation. This hierarchical form of estimation for inference necessitates a generative model, in which the expected cause of representations at one level of the

hierarchy become priors for expectations in the subordinate level. The term 'generative model' is used because the model generates the predictions of subordinate causes and ultimately sensations *per se*. When a generative (i.e. internal or forward) model is converted given the data at hand, sensations are explained in terms of the most likely hierarchical causes. These expected causes are constantly updated as new data are successively sampled to provide a biologically plausible form of evidence accumulation for data assimilation (47). Inversion of generative models refers to the deduction of the causes (hidden states of the world) from the consequences of sensory samples that one receives from the world. This inverts the mapping prescribed by the generative model that generates consequences (sensations) from causes (hidden or latent states).

The primate brain is hierarchically structured (48), which suggests the generative model used by the brain must also be hierarchical. This hierarchical architecture allows for the reciprocal message passing of predictions and prediction errors among hierarchical levels described above. Predictive coding models – derived from the 'the free-energy principle' (FEP) (49, 50) – assume the brain endeavours to minimise precision weighted prediction errors throughout and implicitly maximise the evidence for its generative model[1]. This is known as self-evidencing (51), which can be regarded as a generalisation of homoeostasis to every sensory modality predicted by the brain. Crucially, the FEP posits a defining role for homeostatic and allostatic processes in the functioning of the nervous system by casting the homeostatic imperative to stay alive as an innate and very precise prior over physiological states (30).

[1] Free energy can be regarded as the total amount of (precision weighted) prediction error summed over all levels of a hierarchical model.

1.3. Active inference under the free-energy principle

Under the free-energy principle, 'active inference' refers to the bilateral reduction of free-energy when: (i) prediction errors ascend the cortical hierarchy to change predictions, or (ii) prediction errors descend to the periphery to engage motor (or autonomic) reflexes, which change sensations (52). In the sensory system, prediction errors can only be modified by changing predictions, whereas proprioceptive and interoceptive prediction errors can also be modified by engaging reflexes to alter the sensory signal at its point of origin. In short, the prediction error can be reduced by changing the prediction (i.e., perception) or by changing the sensations being predicted (i.e., action). Movements can be initiated by predictions of the sensory consequences of action because the motor system automatically moves the sense organs to meet proprioceptive predictions, thereby shifting the imperative for action from what the individual wants to achieve with the action to what he/she wants to experience (50). An intuitive example of this is the common pain reflex; if a sufficiently precise and unexpected stimulus is received (e.g., placing one's hand on a hot stove), an optimal response would be to immediately alter sensations (e.g., by withdrawing one's hand); rather than to update one's beliefs about the stimulus. This would be the homologue of a homoeostatic reflex. The alternative would be to perceive the stove is too hot and turn down the gas. This would be the homologue of allostasis that calls on deep or hierarchical inference – driven by ascending prediction errors – to regain homeostasis. One can see that the two ways of minimising prediction error depend sensitively on the precision afforded to ascending prediction errors; one can either ignore ascending prediction errors via sensory attenuation to engage reflexes (c.f., homoeostasis) or allow ascending prediction errors to engage adaptive behaviour (c.f., allostasis). In this scenario, the greater the nociceptive prediction error (i.e. the more it deviates from homeostasis), the less it will be allowed to ascend the cortical hierarchy before peripheral reflexes are necessitated. In contrast, a more minor burn (a smaller prediction error) with less precision could ascend to higher-order processes and be integrated with more

complex adaptive behaviours. In what follows, we look more closely at the crucial role of precision in mediating between these two sorts of responses.

1.4 Precision and gain control

The precision of ascending prediction errors determines the balance between priors and sensory signals to govern the influence of sensory evidence and prior beliefs (figure 2). In this setting, attention is intimately related to precision; in that attention is thought to increase the precision of prediction errors so that they have a greater influence on perception. Conversely, sensory attenuation is thought to reduce the precision of ascending prediction errors to enable motor reflexes (53). In this process, a vital element of sensory attenuation requires ignoring the consequences of action to be ignored so that precise predictions, to allow intentions to be realised through the releases of reflexive action (54). In this scenario, by allowing predictions to be fulfilled via spinal reflex arcs, sensory attenuation allows movement to occur, meaning that sensory attenuation is therefore crucial for labelling movements as self-generated (55). A key neurobiological issue here is that precision can be associated with the excitability or postsynaptic gain of units encoding prediction error (56). This means that the accentuation or attenuation of precision rests upon neuromodulatory processes and gain control mechanisms mediated by short-term changes in synaptic efficacy. This is an important observation because it speaks to the pathophysiology of several disorders that can usually be traced back to neuromodulatory abnormalities (57).

Figure 2 near here

2. Interoceptive (active) inference in theory and practice

We now briefly describe how active inference may be transferred from the proprioceptive to the interoceptive domain as interoceptive inference. This will help elucidate how interoceptive inputs drive the autonomic nervous system to mediate homeostasis (figure 3). We begin with psychophysiological aspects, such as classical conditioning, the placebo effect and substance abuse and relapse, as well as affective disorders and psychosomatic illness. We then describe how interoceptive inference can offer an overarching methodology to study human physiology; using bladder function and thermoregulation as examples – in addition to the previously described cardiovascular reflex arcs. We conclude with a brief summary of our studies of interoceptive inference.

Figure 3 near here

The free-energy principle has been applied to proprioceptive and exteroceptive sensory domains to elucidate the neurobiology of perception, motor control and attention (58) (59), with applications to autism spectrum disorder (60) and schizophrenia (61, 62). However, its potential role in interoception has only recently been considered (4, 6, 7, 63, 64). It has been suggested that Pavlovian classical conditioning can be viewed an elementary form of interoceptive inference (65). Pavlov demonstrated not only that an unconditioned interoceptive prediction error (food) induces homeostatic autonomic responses (salivation) but that through the encoding of an exteroceptive signal (a bell), the same autonomic reflex can be induced by top-down predictions (66). Recently we have found preliminary empirical support of interoceptive inference by demonstrating that the orienting response, which was first described by Pavlov, is exaggerated during combined emotional aversion and the interoceptive threat (and therefore, increased interoceptive prediction error) of dysautonomic

symptom provocation in patients with the postural tachycardia syndrome and vasovagal syncope – two forms of dysautonomia defined by baroreflex dysfunction (67) (68). These findings provide insights into how interoceptive inference can prescribe autonomic reflexes and the destructive effect of dysautonomia on homeostasis due to the breakdown of autonomic reflex arcs.

Pavlov also foreshadowed the role of predictive coding when noting that previously neutral stimuli conditioned the effects of apomorphine and morphine (69). The implication of the opiate system in the placebo effect (70) further suggests that interoceptive inference can explain how an inert stimulus can induce physiological responses via the attenuation of bottom-up prediction errors (71). Learning theories have underlined the role of prior expectations in the placebo effect, particularly placebo analgesics actual feelings of pain are overridden by the prediction of pain relief (72) (73) (74, 75) (76-79). Functional imaging studies have provided the neural correlates of the interrelated altered precision of peripheral prediction errors, personality, endogenous opioid system engagement and anticipatory changes that scaffold the effects of placebo hypoalgesia, particularly prefrontal suppression of prediction error processing in the ventral striatum.

Recently, separate studies have started to look at the role of prediction error traits (80) (81) and interoception as markers for substance abuse and relapse (82). Using a within subjects placebo design, Gu and colleagues used a computational model of mesolimbic dopamine systems. found that prior beliefs about a smoked cigarette's nicotinic content modulated striatum responses to reward prediction errors, evidencing how beliefs can override a potent neuroactive compound, such as nicotine (81). Although these studies explored prediction error traits and interoception in isolation, we believe that drawing together these cornerstones of interoceptive inference may be useful for future work.

Under the active inference, anxiogenic traits, such as catastrophizing or somatic hypervigilance can be viewed in terms of the aberrant precision of top-down predictions or bottom-up prediction errors respectively. Therefore, it stands to reason that anxious individuals possess greater interoceptive accuracy (as measured by heartbeat tracking paradigms) (83, 84), on the view that these individuals assign too much precision to ascending interoceptive prediction errors; i.e., a failure to attenuate ascending interoceptive prediction errors. Cornwell and colleagues recently provided support for this by using Bayesian analyses to evidence how anxiogenic stimuli unbalance feedforward signalling that occurs in response to sensory prediction errors. Specifically, dynamic causal modelling described how anxiety-related hypervigilant responses are best explained by the increased postsynaptic gain and modulation of feedforward coupling within a temporo-frontal network {Cornwell, 2017 #125}.

In contrast, clinically depressed subjects have diminished interoceptive accuracy (85-87). Recently, reduced resting state connectivity between attentional and interoceptive networks has been found in melancholia (87), offering an explanation for the impoverished interoception and somatic ideation in these patients. These findings suggest that investigating somatic attention and awareness in anxiety and depression may offer targets for behavioural or pharmaceutical treatment strategies. In particular, an interesting clinical question is whether 'normalising' interoceptive precision can affect affective symptomatology. Furthermore, the focus on synaptic gain in the encoding of precision (and its attenuation) speaks to quantifying pathophysiology in terms of effective connectivity; specifically, the intrinsic excitability of neuronal sources in the interoceptive hierarchy. See (60) for an exemplar study that used dynamic causal modelling to look at the intrinsic excitability of the anterior insular, using an empathy for pain task in normal subjects and autistic spectrum disorder.

In hypochondriasis and somatisation disorders, patients report somatic hypervigilance and interoceptive sensitivity (88-91), indicating aberrant interoceptive precision. Pareés and colleagues (55) report loss of sensory attenuation and a related diminished sense of agency, which is offered as an explanation for functional movement disorder (FMD). This misattribution of agency – regarding voluntary movement – results in FMD patients experiencing the intent to move and actual movement as being simultaneous. Recently, we have applied this paradigm to functional syncope (fainting); i.e., apparent syncope (loss of postural tone and unresponsiveness) during normal blood pressure and heart rate indices that would not cause cerebral hypoperfusion and subsequent loss of consciousness (92). We identified two subgroups that experienced functional syncope during clinical autonomic assessment (93). The first had no undiagnosed form of dysautonomia but a prevalence (41%) of psychiatric illness, presenting as a typical conversion disorder group. The second had undiagnosed postural tachycardia syndrome during orthostatic (upright posture) manoeuvres. Neither group were hypotensive during functional syncopal episodes (figure 4). However, the functional syncope/postural tachycardia syndrome group were typically tachycardic (figure 5) during functional syncopal episodes, which occurred almost entirely during orthostatic stress; i.e., whilst symptomatic with (undiagnosed) orthostatic tachycardia. Some individuals may therefore be prone to impaired sensory attenuation if in a state of undiagnosed sympathoexcitation. One might suppose that the apparent loss of postural tone may reflect a failure to modulate the precision of interoceptive prediction errors during undiagnosed posture-related tachycardia (due to baroreflex dysfunction). This provides a potential explanation for functional syncope in the functional syncope/postural tachycardia syndrome subgroup (94).

Figure 4 and 5 near here

Interoceptive inference offers a new and mechanistic perspective on basic and clinical homeostatic issues. For example, with the context-specific knowledge that polite society generally prefers us to micturate in private, ascending lower urinary tract information reaches the brain via the PAG before relaying to the thalamus and hypothalamus, both of which send bladder-related interoceptive signals to the dACC, AIC and lPFC (95). If the decision is made not to void, then the medial prefrontal cortex (mPFC) inhibits the PAG. If it is decided that voiding should occur, the mPFC disinhibits the PAG, which activates the pontine micturition centre (PMC). The PMC then engages sacral autonomic efferents to relax the urethral sphincter and contract the detrusor (96, 97). This model provides a nice example of how context-specific information about the environment is inferred (from a Bayesian perspective) to mediate and contextualise autonomic and behavioural homeostatic outputs. Crucially, this rests, under interoceptive inference, on properly contextualising (i.e., predicting) the precision or gain of interoceptive prediction errors that underwrite homoeostatic or allostatic behaviour.

Interoceptive inference proposes that interoceptive predictions and prediction errors can be suppressed by modifying predictions or demarcating these predictions as reference points for autonomically mediated reflexes (6). As with the urinary or cardiovascular systems, thermoregulation can be modelled within the active inference framework. Hypothermia and hyperthermia represent profound deviations from thermostasis; with increasingly complex endocrine, autonomic and behavioural homeostatic reflexes engaged as one's core temperature rises or falls from its homoeostatic set point of 37°C (i.e., as prediction error increases) (98). During this process, thermoceptive prediction errors will have greater precision on subsequent central signalling, as glutamatergic, cool-sensitive neurons synapse with GABAergic interneurons in the median preoptic area to initiate thermoregulatory autonomic or motor reflexes (99). Depending on whether temperature must be increased or decreased, the processing of thermoregulatory prediction error can also result in the inhibition of action potentials in warm-sensitive neurons of the medial preoptic subnucleus, which

mediates autonomic control of cutaneous vasoconstriction as well as motor control of shivering and thermogenic brown adipose tissue (BAT) (100, 101). As interoceptive inference dictates efferent homeostatic changes, BAT neuromodulators, such as glutamate, serotonin and vesicular glutamate transporter 3 will be released to control BAT sympathetic outflow and thermogenesis (99, 102).

Under interoceptive inference, descending predictions can only elicit autonomic responses if the ascending prediction error has been attenuated. Without this functional change in gain, prediction errors would lead to revised predictions rather than action (103). We recently examined the relationship between measures of cardiac interoception and autonomic cardiac control in healthy controls and patients with forms of cardiovascular dysautonomia defined by baroreflex dysfunction (the postural tachycardia syndrome and vasovagal syncope) to (i) seek empirical support for interoceptive inference and (ii) delineate if this relationship was sensitive to increased interoceptive prediction error in patients during head-up tilt/symptom provocation (104) (105). Compared to controls, interoceptive accuracy (as measured using a heartbeat tracking task) was reduced in both postural tachycardia syndrome and vasovagal syncope groups. Healthy controls' interoceptive sensibility (subjective confidence in interoceptive accuracy) positively correlated with low-and-high frequency heartrate variability (HRV) whilst supine (table 1). Conversely, both the postural tachycardia syndrome and vasovagal syncope groups' interoceptive awareness (a metacognitive measure of the degree to which objective interoceptive accuracy relates to interoceptive sensibility) negatively correlated with high-frequency HRV during head-up tilt. Our pilot study offers initial empirical evidence for interoceptive inference and supports our previous findings (106) that postural tachycardia syndrome and vasovagal syncope cohorts share a central pathophysiology underlying interoceptive deficits expressed across distinct cardiovascular autonomic pathophysiology. From a predictive coding perspective, postural tachycardia syndrome and vasovagal syncope patients' data indicates a failure to attenuate/modulate ascending interoceptive prediction

errors, reinforced by the concomitant failure to engage autonomic reflexes during head-up tilt. Our findings also define how both central and autonomic processes are ultimately implicated in dysautonomia.

Table1 near here

Activation of the right AIC is positively correlated with interoceptive accuracy in healthy controls during heartbeat perception paradigms, with the right insula making inferences about internal bodily states, that can be accessed during conscious interoception (27). The AIC has 2 major roles in interoceptive inference: (i) integrating top-down predictions from high-level cortical regions with bottom-up prediction error and (ii) cascading descending predictions that are a reference point for autonomic mediation of homeostasis (6, 65). This functional architecture accounts for the recent findings that the degree of damage to the anterior insula is positively correlated with acquired alexithymia levels (107), reflecting the interoceptive contribution to inference about emotional states (43). The AIC contains a significant number of 'von Economo neurons', which are large bipolar, spindle-shaped projection neurons (108). Von Economo neurons are prevalent in humans and are mainly situated in layer Vb of the ACC and the frontoinsular cortex (i.e., the junction of AIC and posterior orbitofrontal cortex) and are specifically associated with interoception (109). In comparison to controls, autism spectrum disorder subjects have a significantly greater ratio of von Economo neurons to pyramidal neurons (110), which may be of particularly relevance to the common interoceptive sensitivity reported in autism spectrum disorder (7, 111).

The primary motor cortex (M1) is predominantly comprised of agranular neurons and issues motor predictions to the spinal cord to engage motor responses and reflexes (112). M1 simultaneously sends somatosensory predictions to S1 to model the sensory consequences of the predicted action. The predictions propagated to S1 are efferent copies of motor

predictions or commands. We have found that (103, 113) S1 also attenuates sensory gain during self-initiated movement; thereby reducing prediction error signalling to M1, which receives little direct ascending sensory input. This means predictions descending via M1 to the spinal cord are relatively immune to correction by prediction error. This makes sense if we consider elementary movements are executed in a largely open loop fashion. However, S1 generates predictions about sensory afferent signals that are probabilistic and continuously updated by prediction errors, and changes in the gain of S1 responses are linked to both predictability and attention-driven modulation of felt pain (114).

The functionality of this interoceptive hierarchy can be seen in studies of oesophageal stimulation (28), where mild stimulation activates secondary somatosensory cortex. Then, as stimulus intensity escalates, interoceptive inference engages primary somatosensory, bilateral insula, ACC and right premotor structures. These results may reflect how escalating interoceptive-to-nociceptive input augments the precision of ascending prediction errors, with subsequent activation of the somatosensory network. If we consider the aberrant interoceptive precision of anxious individuals, this sort of finding may shed light on the fine detail of the neural correlates of irritable bowel syndrome (115); particularly in consideration of autonomic (e.g., postprandial) stressors that may augment interoceptive prediction errors in anxious subjects (116).

3. Viscero-sensory integration, interoceptive self-inference and metacognitive deficits

Reflecting the function of the most central or highest level of the interoceptive hierarchy, metacognitive ability for conscious introspection is frequently disrupted in a variety of psychopathological disorders (117). Such metacognitive failures; for example, in the case of addiction and posttraumatic stress disorder (PTSD) have been linked to altered arousal (118, 119) that is often highly specific and independent of first-order perceptual or cognitive deficits.

Although metacognition has traditionally been cast in terms of signal detection theory as depending solely on the feed-forward recollection of decision-related evidence (120, 121), recent advances suggest that conscious self-reflection may be better considered as a form of 'interoceptive self-inference', in which hierarchically deep, supramodal predictions of expected precision (or representational stability) enforce interactions between subjective confidence in the interoceptive and exteroceptive domains. For example, we have recently shown that unexpected changes in autonomic arousal reverse the biasing impact of sensory noise (or precision) on subjective confidence, independently of decision accuracy (122). In a pharmacological follow-up study, we further demonstrated that noradrenaline blockade via the beta-adrenoceptor antagonist, propranolol, specifically improves metacognition for perception (123). More generally, confidence for exteroceptive judgements is linked to heart rate increases (122). This is consistent with the hypothesis that metacognition reflects interoceptive-self inference, which not only models the quality of ascending sensory inputs, but also their regulation by the ascending and descending visceromotor processes reviewed above. In this case, metacognitive beliefs are better cast as 'experiential predictions' (e.g., I expect to see an apple with high precision and I expect to 'feel' good about it), rather than the output of a strictly feedforward sensory process. This view suggests that maladaptive interoception may cause adjustments in metacognitive beliefs and first-order perception, ultimately resulting in disorders such as functional and chronic pain, social anxiety (in which neutral social stimuli are evaluated as threatening): see also (124). Likewise, deficits in perceptual ability may result in an alteration in autonomic tone, leading to maladaptive decision-making and systematically biased confidence. Collectively, this view motivates empirical investigations into the possibility of a domain-general neural mechanism linking interoceptive and metacognitive inference, raising the importance of measuring visceral-sensory and cognitive deficits using both first and second-order (metacognitive) measures.

4 Conclusions

A decade ago, it was proposed that interoceptive prediction errors could be a bottom-up source of anxiety. Predictive coding models, as assumed under the FEP, propose the brain must recognise the likely cause(s) of afferent sensory input at any given time to support adaptive responses via probabilistic (Bayesian) inference. This review provides a framework and supportive evidence suggesting that interoceptive inference can elucidate autonomic control of peripheral effector organs, cognitive-affective function, motor control, consciousness and dissociative symptoms. Insights into the neuroanatomy, neurochemistry, neurophysiology and psychophysiology of active inference, precision and precision-weighting are now beginning to suggest how interoceptive signals inform predictions about the state of the body. This review suggests that interoceptive prediction errors can not only be a bottom-up source of anxiety but may also drive autonomic, metacognitive, motor homeostatic and allostatic systems. A key theme that emerges from this treatment is the role of neuromodulation and synaptic gain control in contextualising the use of ascending prediction errors for interoception and autonomic reflexes respectively – and how subtle deficits in the attenuation of ascending prediction errors can lead to pernicious and diverse pathology.

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Figure 1. This schematic illustrates the message passing implicit in predictive coding based on the generative model described (mathematically) on the lower left. Sensory input is conveyed to visual cortex via ascending prediction errors from the lateral geniculate nucleus. Posterior expectations, encoded by the activity of deep pyramidal cells in primary visual cortex, are driven by ascending prediction errors while, at the same time, they are subject to lateral interactions – with second level prediction errors – that mediate (empirical) priors. These constraints are modulated by top-down predictions of their precision (blue arrows). These predictions are based upon expectations about precision in the highest level that are effectively driven by the variance or power of prediction errors at the lower level. Heuristically, expectations about precision release posterior expectations from constraints in the vicinity of an inferred object and allow them to respond more sensitively to ascending geniculate input.

Figure 2. This schematic details putative laminar-specific connections that are consistent with the precision-based predictive coding scheme in the main text. This architecture conforms roughly to the known neuroanatomy and physiology of canonical microcircuits and laminar specificity of extrinsic connections. The key aspect of this figure is the inclusion of deep pyramidal cells encoding the amplitude of prediction error (squared) that inform posterior expectations about precision in the (matrix cells) of the pulvinar. These cells reciprocate descending projections to modulate the gain of superficial pyramidal cells in cortex. Forward connections are in red and descending (backward) connections are in black. First-order streams are shown as full lines and second-order (precision related) streams are shown as broken lines.

Figure 3. This schematic extends the pulvinar example to provide a rough sketch of equivalent precision or gain control in interoceptive and proprioceptive systems. The architecture and anatomical designations should not be taken too seriously. However, there may be homologous architectures for exteroceptive, proprioception and interoception. Here, we have indicated this by assigning the pulvinar, basal ganglia and amygdala a common role; namely to provide precision control or contextual guidance to interoceptive (insular), proprioceptive (sensorimotor) and exteroceptive (visual) cortex respectively. In addition, each of these systems has been associated with a specific neuromodulator; namely noradrenaline, dopamine and acetylcholine in the ensuing regulation of autonomic arousal, action selection and attentional selection, respectively. Crucially, in a hierarchical setting, all these domain specific systems are integrated at the levels of the hierarchy (here attributed to the anterior cingulate and prefrontal cortex). Note that the recurrent or reciprocal message passing means that changes in the precision or postsynaptic gain in one (e.g., interoceptive) system, will necessarily effect processing in the others (e.g., exteroceptive). This is a necessary consequence of Bayes optimal inference in the sorts of hierarchical models. Note that the only way that this inference can act upon the world is through autonomic or motor reflexes. This means that exteroceptive processing has to be hierarchically integrated with proprioceptive and interoceptive inference – so that it can contextualise behaviour **LC**, locus coeruleus. **VTA**, ventral tegmental area. **NBM**, Nucleus Basalis of Meynert. **VPL**, ventral posterolateral thalamus. **ACC**, anterior cingulate cortex. **PFC**, prefrontal cortex.

Figure 4. Baseline and functional syncope episode blood pressure data in the functional syncope only (FS only) and functional syncope/postural tachycardia syndrome (FS/PoTS) cohorts

Figure 5. Baseline and functional syncope episode heart rate data in the functional syncope only (FS only) and functional syncope/postural tachycardia syndrome (FS/PoTS) cohorts

Interoceptive inference correlations	Supine HRV	Head-up tilt HRV
Healthy controls	Interoceptive sensibility/LF-HRV (r_s= .816, p=.001) Interoceptive sensibility/HF-HRV (r_s= .676, *p*=.002)	
Postural tachycardia syndrome		Interoceptive awareness/HF-HRV (r_s= -.457, *p*=.043)
Vasovagal syncope		Interoceptive awareness/HF-HRV (r_s= -.658, *p*=.015)

Table 1. Overview of how interoceptive inference may subjugate autonomic reflexes, as measured by high frequency (HF-HRV) and low frequency heart rate variability (LF-HRV). Correlations between cardiac interoceptive measures and autonomic cardiac control were found in healthy controls whilst supine and orthostatic intolerance patient groups during increased interoceptive prediction error (head-up tilt). Interoceptive accuracy is an objective interoceptive measure gained from the subject's performance during a heartbeat tracking task. Interoceptive sensibility represents subjective confidence in one's own interoceptive accuracy. Interoceptive awareness is a metacognitive measure of the degree to which objective interoceptive accuracy relates to interoceptive sensibility