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The neurobiology of interoception in health and disease

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Abstract

Interoception is the sensing of internal bodily sensations. Interoception is an umbrella term that encompasses; 1) the afferent (body-to-brain) signalling through distinct neural and humoral channels; 2) the neural encoding, representation, and integration of this information concerning internal bodily state; 3) the influence of such information on other perceptions, cognitions and behaviours; and, 4) the psychological expression of these representations as consciously accessible physical sensations and feelings. Interoceptive mechanisms ensure physiological health through the cerebral coordination of homeostatic reflexes and allostatic responses that include motivational behaviours and associated affective and emotional feelings. Furthermore, the conscious, unitary, sense of self in time and space may be grounded on the primacy and lifelong continuity of interoception.

Body-to-brain-interactions influence physical and mental wellbeing. Consequently, systematic investigation of how individual differences, and within-individual changes, in interoceptive processing can contribute to mechanistic understanding of physical and psychological disorders. We present a neurobiological overview of interoception and describe how interoceptive impairments at different levels relate to specific physical and mental health conditions, including sickness and fatigue, depression, eating disorders, autism, and anxiety. We frame these findings in an interoceptive predictive processing framework and highlight potential new avenues for treatments.

1. Introduction

A fundamentally selfish responsibility of the brain is to keep itself, with the rest of the body, alive. The brain coordinates the regulation of vital inner processes, including blood pressure digestion and breathing, by flexibly reacting to external and internal changes. Interoception refers to the sensing of the internal state of the body,¹ providing the afferent channel of the interplay between body and brain that allows homeostasis (i.e. maintenance of physiological stability) through covert reflexes (e.g. baroreflex), motivational drivers (e.g. hunger and thirst) and explicit bodily sensations (e.g. breathlessness, bladder distension or gastric pain). Interoception is differentiated by this inwards bodily focus from exteroceptive senses (e.g. vision, audition)² that process information about the outer world, and more proximate senses (e.g. proprioception, touch, taste) that use the body to describe the external environment and its relation to it. Interoceptive information is communicated through a set of distinct neural and humoral pathways with different modes of signalling, which the brain represents, integrates and prioritises. How these central representations of the inner body are built and interact is an important focus of interoception research, not least because of the implications for a range of processes and disorders. A comprehensive understanding of cognition, emotion, and overall wellbeing must incorporate an understanding of interoception. The same questions are consequently integral to health neuroscience.³ Interoceptive processing has a key role in health and disease, and research is systematically delineating the ways in which brain-body relations can alter a person's wellbeing.

Interoception involves a relatively restricted set of classes and channels of information (e.g., cardiovascular, gastric, respiratory). These differ with respect to the generation of the signal (organ stretching, mechanoreceptive, chemoreception) and their afferent pathway (neural, humoral).⁴ Complexity within interoceptive signalling arises more from the need to parse and integrate of information originating from multiple organs and across wide temporal domains than from the need to differentiate, uniquely characterise and encode complex novel stimuli (even in the generalization of immunological responses). Nevertheless, continuous, dynamic and diverse information about internal bodily function is integrated within shared neural substrates supporting distributed interoceptive representations and associated experiences (feeling states). Together these shape the generative (autonomic or hormonal) control of bodily states and steer adaptive behaviours (e.g. a drop in blood sugar levels leads to foraging). Interoception is not a unitary construct, but can be considered within a conceptual framework encompassing distinct mechanisms and psychological dimensions, characterized for example by processing level (e.g. chemical/neural, behavioural, subjective experiential,

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3 metacognitive), and can be assessed using distinct methodologies (e.g. psychophysiology
4 and brain imaging, behavioural task performance, questionnaire ratings and confidence-
5 accuracy correspondence).^{5, 6} A differentiated, structured view of interoception allows for a
6 fine-grained analysis of concurrent internal processes, how they are represented and
7 communicated to the brain, and how they contribute to health and disease.
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11 One theoretical framework to frame the dynamics and dimensions of interoception is
12 'predictive processing' (PP).⁷⁻⁹ The underlying notion is that the brain makes sense of the
13 potentially overwhelming wealth of incoming sensory data by making a 'best guess' model of
14 the source of sensory information and tests this model against the afferent data. PP centres
15 on the interplay between bottom-up and top-down processes: Within a neural hierarchy,
16 there is constant communication and interaction between lower- and higher-level processes.
17 Higher-order representations of prior information form the basis of predictions (beliefs or
18 priors) about the expected afferent signal. Such predictions can 'cancel out' expected
19 incoming information at lower levels of the hierarchy, permitting 'prediction errors' to ascend.
20 These inform and adjust higher-order representations. Cortical neural hierarchies underpin
21 PP models of exteroceptive sensations, e.g. vision. Interoceptive predictive processing
22 (IPP)^{2, 10, 11} describes the hierarchical processing schemes that underlie the interaction
23 between body and brain. For IPP, where informational parameters are arguably more
24 restricted, yet under more direct neural control, cerebral cortex might dominate only at
25 higher-order representational levels.
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35 In this article, we review the dimensional nature of interoception, approaches to their
36 quantification, discuss the neurobiological basis of interoception, and how these findings can
37 be framed within IPP. Importantly, we offer our perspective on the implications for both
38 physical and mental health, and scrutinize the contributing role of interoception to different
39 health conditions. Finally, we suggest how interoception research can further enhance to
40 Health Neuroscience.
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47 **2. Dimensions of interoception**

48 Interoception is defined by both its origin within, and reference to, the inner state of the body.
49 This single term generalises communication through multiple distinct physical axes, and
50 representations that unfold at different anatomical and psychological levels, on different
51 timescales. Interoception is a concept that implicitly suggests the integration of different
52 types of sensory information. However, inconsistency within the physiological and
53 psychological literature regarding the definition of interoception, and use of terms such as
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3 interoceptive awareness, led to proposed dimensional frameworks for understanding and
4 studying this set of senses.^{5, 12} Within such a framework, interoception can be described
5 from the physical responses in body and brain representation up to (and beyond)
6 interoceptive metacognitive insight and conscious awareness.
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9 The first dimension refers to the afferent, interoceptive signal that is communicated to the
10 brain from one or more internal organ, which can be measured, for example, by evoked
11 changes in central neural activity, for example as a change in neuroimaging signal or
12 heartbeat evoked potential (HEP).¹³ HEPs refer to a change in neural activity (measured
13 using magnetoencephalography (MEG), electroencephalography (EEG) or intracranial
14 neural recordings) that occurs after a heartbeat. Interestingly, HEP amplitude typically
15 correlates with the ability of an individual to detect and report their heartbeats.¹⁴
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19 The second dimension reflects the impact of visceral afferent signals on other forms of
20 central sensory or cognitive processing and behaviours. This level does not necessitate (or
21 preclude) perceptual awareness (i.e. consciousness) of the interoceptive signal or the other
22 processes. Illustrations of this interoceptive dimension are found, for example, in cardiac
23 timing experiments where afferent heartbeat signals impact decisions, emotional processing
24 and memory.¹⁵⁻¹⁷
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29 Three 'psychological' dimensions refer more directly to the perception of interoceptive
30 signals: Interoceptive accuracy, sensibility and awareness.¹² These dimensions developed
31 from the use of tests of interoceptive sensitivity/ability, such as heartbeat detection tasks.
32 These tasks are designed to rate individuals according to differences in their ability to sense
33 internal bodily signals, which might account for variation in emotional temperament or
34 psychosomatic vulnerability.¹⁸ Typically, an interoceptive task requires a participant, at rest,
35 to report 'felt' interoceptive sensations (e.g. the timing of a heartbeat): Interoceptive accuracy
36 refers to objective performance on such behavioural tests, e.g. how accurately they perform
37 a heartbeat tracking task.¹⁹ Next, interoceptive sensibility describes subjective belief about
38 one's own ability to consciously perceive bodily signals, ascertained via self-report measures
39 such as questionnaires (e.g. body perception questionnaire (BPQ))²⁰, or reflected in their
40 rated confidence in their performance accuracy on an interoceptive task. Since some people
41 think they are good, but in fact are objectively very poor, at reporting bodily sensations (and
42 conversely), this level of conscious insight can be quantified: Metacognitive interoceptive
43 awareness expresses this insight into interoceptive performance aptitude, and can be
44 derived from confidence-accuracy correspondence.²¹ This metacognitive dimension of
45 interoception is a most appropriate use of the word 'awareness' in the context of
46 interoception.
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3 A further 'executive' dimension on this interoceptive dimensional framework attempts to
4 capture the degree to which an individual is able to flexibly attend to, and utilize,
5 interoceptive information or can adaptively switch between interoceptive and exteroceptive
6 representations.⁵
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9 **3. The neurobiology of interoception**

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11 Convergent evidence identifies insular cortex as the brain substrate underpinning higher-
12 order interoceptive representations: for example, left posterior insula cortex is reliably
13 engaged when attention is directed to one's heartbeat, relative to an exteroceptive focus.²²
14 Also, anterior insular cortex activity predicts objective performance accuracy on interoceptive
15 tasks. In particular, right anterior insular cortex (AIC) functional reactivity predicts
16 interoceptive accuracy on a heartbeat discrimination task and its volume predicts
17 interoceptive sensibility.¹ The insular cortex is buried between the adjacent frontal and
18 temporal lobes. The architecture of insula changes (including progressive loss of the granule
19 cell layer) from posterior to anterior insular cortex, with other sub-regional differences in
20 cellular organization. Insular cortices are bi-directionally connected to cingulate, prefrontal,
21 parietal, and medial temporal cortices and subcortically to basal ganglia.²³ AIC is strongly
22 connected with anterior cingulate cortex (ACC), arguably forming a functional unit with
23 amygdala and ventromedial/ orbitofrontal cortex (VMPFC/OFC), to which they are mutually
24 linked. Posterior insula has stronger reciprocal connections to second somatosensory cortex
25 (SII), and receives direct afferent input from interoceptive thalamus (posterior ventromedial
26 nucleus, which has a lighter corollary projection to anterior cingulate cortex), relaying
27 interoceptive and nociceptive information. Interoceptive information is projected within insula
28 form posterior insula (i.e. primary viscerosensory cortex implicated in primary, objective
29 representations of bodily signals), and rostrally to AIC, which serves to re-represent and
30 integrate interoceptive signals with exteroceptive and motivational information.²⁴
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42 The higher-order representation of interoceptive information within AIC and its projection
43 regions underpin consciously accessible feelings that inform emotions and motivate
44 behaviours. This representation also shapes the operational functioning of the brain, as the
45 brain continuously receives and responds to such homeostatic afferent signals. An important
46 aspect of this higher-order representation is the integration across distinct categories of
47 signals that possess distinct temporal response characteristics and encode hormonal,
48 metabolic, thermal, immunological, nociceptive and visceromotor information. This
49 information reaches the brain through humoral and neural pathways.²⁵ Microglial
50 transduction pathways additionally inform about, and even engage the brain in, inflammatory
51 status, where inflammatory mediators lead to waves in microglial activation that is
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3 propagated across the brain.²⁶ However, loss of anatomical specificity, temporal structure
4 and perceptual distinctiveness may be obligatory characteristics of a dynamic higher-order
5 integrative interoceptive representation, from which may emerge an amorphous affective
6 feeling state that is the predictive platform for motivational behaviour, emotional experience,
7 and internal homeostatic control.
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11 Nevertheless, well before insular cortex, conscious access, and affective feeling states,
12 afferent viscerosensory information is processed within subcortical and brainstem regions
13 supporting homeostasis. The nucleus of the solitary tract (NTS) is the main region where
14 visceral neural (spinal laminar 1 and vagus nerve) inputs converge within brainstem,²⁷ and is
15 of critical importance for the control of physiological state (e.g., blood pressure control). NTS
16 consists of a series of purely sensory nuclei and is organized viscerotopically, where
17 neurons that receive input from distinct organs and types of visceral receptor are in close
18 proximity. This specific organization hints to early integration of viscerosensory signals
19 across related modalities.²⁸ NTS projects to hypothalamus, ventrolateral medulla and
20 parabrachial nucleus, and through these regions provides a first level of control of hormonal,
21 immune, and autonomic outputs. Chemicals circulating in the blood stream access the brain
22 via specialist circumventricular organs (area postrema, organum vasculosum of laminae
23 terminae and subfornical organ). The humoral information is projected to hypothalamus and
24 NTS, contributing the negative feedback control and cross-modal homeostatic responses
25 mediated through pituitary hormones and the autonomic nervous system.
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28 The NTS receives from spinal visceral afferent neurones with cell bodies in the dorsal root
29 ganglion contain motivational information from cranial nerves, notably the vagus nerve:
30 Viscerosensory inputs with cell bodies in vagus nerve ganglia terminate in the NTS and
31 project onto the pontine parabrachial nucleus, and periaqueductal grey (PAG) before an
32 obligatory relay within posterior ventromedial thalamus. These pre-thalamic midbrain
33 pathways project further to hypothalamus and amygdala, and complement the main
34 viscerosensory thalamocortical projection to insular cortex (and ACC). Nevertheless, all
35 levels of the neuroaxis representing interoceptive information are implicated in the
36 autonomic control of internal physiological state and processes that shape emotions,
37 feelings, behaviour and cognition.^{10, 24, 25, 29-32} Ultimately, the interplay of body and brain
38 depends on bi-directional signal messaging, where higher-level brain regions might influence
39 bodily processes in a top-down manner, and afferent signals influence brain processes from
40 the bottom-up. This complex and dynamic interaction is theoretically captured by an
41 increasingly prominent framework, predictive processing (PP), or, more specifically,
42 interoceptive predictive processing (IPP).
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4. Interoceptive Predictive Processing (IPP)

General predictive processing

Predictive processing (PP)^{7, 8} is an algorithmic theory about how the brain makes sense of the world and the body it is embedded in. The rationale is that the brain has no direct access to the states of the external world and body, but is instead confronted with an excess of sensory signals. Moreover, each signal has multiple possible causes, so the brain needs to *infer* the most probable hidden cause of the sensory information it receives.

The external world we live in is full of causal regularities of different spatial and temporal timescales, such as ‘what goes up must go down’.⁹ However, these occur alongside noise and irregularities, including unpredictable, surprising events or disturbances in signals. For the brain to use sensory information and to steer the health and behaviour of the organism in an adaptive manner, it must filter out regularities and deal with the noise. PP offers an account about how a neural system finds these regularities. PP suggests that the brain generates a prediction about which input is most likely to arrive next. If this is wrong, a prediction error/mismatch occurs. This error signal can be used in two ways: it can improve and update the model, perhaps generating a perception, (i.e. *perceptual inference*), or it can lead to a change in behaviour so that the next incoming input fits the prediction better (resulting in action, i.e., *active inference*). In this way, sensory signals from the outside shape and fundamentally alter predictive representations in the brain; the causal regularities of brain-external matter are ‘folded into’ predictions. This is an important point of PP, as it allows for both the external world and bodily actions to influence the workings of the brain. In other words, it allows for the influence of both environmental, social and cultural factors from the top-down, alongside individual factors, for example genetic dispositions, hormone levels and prior experiences from the bottom-up.

Although PP integrates these brain-external components into its theoretical horizon, it is mainly an account of how the brain works. The basic assumption is that there is a neural and functional hierarchy in the brain that implements generative models. These models are ‘generative’ because they generate predictions about the most likely state of the level below. The cortical hierarchy implements predictions that range from highly abstract regularities (e.g. ‘what goes up must come down’) at higher levels to basic, concrete sensory properties of incoming signals at lower levels. Higher levels putatively operate at slower timescales, while timescales get faster as one goes down the hierarchy.³³ Along this hierarchical organization, predictions are passed down and compared to the actual state of the level below, all the way down to the sensory input. The discrepancy between prediction and signal is propagated back up the hierarchy, where it is used to change generative models to improve their predictive power. This process of prediction error minimization (PEM) lies at

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3 the heart of PP and is thought to be the brain's primary task – improving it's guesses about
4 what is going on outside the skull, so it can steer behaviour in the most efficient way.
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6 Interoceptive Inference

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8 Interoceptive inference,^{2, 10} or interoceptive predictive processing (IPP) takes up the general
9 PP framework and applies it to describe internal body-brain interactions. Here, high-level
10 predictions about the internal state of the body are generated within cortex (AIC is most
11 strongly implicated) within a neural hierarchy, proximately involving posterior insula.
12 Descending predictions are compared against incoming afferents, creating an error signal
13 that serves to improve predictions and reduce subsequent prediction error through both
14 perceptual inference (change in feeling state) and active inference (autonomic and
15 behavioural response). These generative predictions cascade to earlier levels of control
16 (including brainstem autonomic centres, which operate along similar negative control
17 feedback principles), ultimately serving to keep bodily states within their expected range for
18 adaptive behaviour, thereby keeping the physiological integrity.
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26 The Embodied Predictive Interoceptive Coding (EPIC) model² relates IPP and prediction
27 error minimization more specifically to cortical architecture. By analogy to predictive coding
28 within the motor system, EPIC proposes that interoceptive predictions originate in the deep
29 layers of agranular (i.e., less laminar differentiation) visceromotor regions within prefrontal
30 (caudal VMPFC/OFC), anterior / mid cingulate cortices and AIC. Back-projecting predictions
31 are proposed to terminate within the superficial layers of dysgranular and granular cortical
32 columns, where they alter ongoing pattern of activity by changing the firing range of neurons
33 in anticipation of viscerosensory sensory input. These interoceptive inputs ascend from the
34 NTS, parabrachial nucleus, via thalamus to primary dysgranular and granular regions of mid-
35 and posterior insular cortex. There, it is proposed that cortical prediction errors are computed
36 (i.e. difference between predicted and actual signal). The resulting prediction error signal is
37 then projected onto the deep layers of agranular visceromotor cortices, where the prediction
38 originated. At this point the error signal can trigger the generation of new descending
39 predictions that are ultimately expressed as autonomic/visceromotor outputs. This process is
40 interoceptive active inference minimising future prediction error through generating
41 interoceptive inputs that confirm predictions. Alternatively, the error may trigger a reduction
42 of further signal sampling to reduce further prediction error (impacting feeling state). Lastly,
43 another option is that the error signal adjusts the precision of prediction units within
44 visceromotor cortices thereby modulating sensory sampling and viscerosensory input
45 through adjusting the gain on thalamocortical communication.
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3 The EPIC model of interoceptive predictive processing also suggests, in line with the general
4 principle of predictive processing, that interoceptive sensations are largely driven by
5 predictions. This means that the perception of bodily signals is weighted toward mostly top-
6 down, rather than a bottom-up, cortical processes. The perception of bodily sensations is
7 thus determined by predictions that are informed by prior experience and kept in check by
8 actual bodily states. The extent to which these predictions lead to perception also depends
9 on precision-weighting (instantiated at one level as attention) across the interoceptive
10 hierarchy, where precision units reflect both the reliability of prediction and prediction errors
11 to increase or decrease the gain on error signals in order to change predictions. A well-
12 functioning precision-weighting system is paramount for healthy functioning, as will become
13 more obvious in later parts of this paper.

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15 Interoceptive predictions interact with other sensory modalities, projecting onto visual,
16 auditory and somatosensory networks, to provide an embodied representational context for
17 perception cognition and action. This way, interoceptive representations modulate responses
18 across the brain, which serves as a reference for exteroceptive process and enable a
19 dynamic multisensory representation of the body in its environment. What we perceive and
20 how we behave is thus ultimately influenced by interoceptive predictions and is steered
21 towards keeping ourselves alive and well. Agranular cortices, the putative origin of
22 interoceptive predictions, are less constrained by incoming signals from the body,² this in
23 turn may permit predictions to be abstract and directed towards the future, enabling
24 allostasis in place of the reactive maintenance of homeostasis. IPP therefore encapsulates
25 the flexible interplay between top-down and bottom-up processes that support stable, yet
26 dynamic, internal environment.

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28 In a healthy brain, predictions are informed by prior experience, situational context and state
29 of the system, the comparison between prediction and actual incoming bodily signal, and
30 precision estimation that results in a well-balanced interaction of brain and body. The goal of
31 this complex process is to keep bodily states within a functional that permits flexibly
32 adaptation to both internal changes and external challenges. The interoceptive system
33 balances anticipated demands and deviations, efficiently regulating needs and resources.
34 This process was conceptualized as 'allostasis' or 'predictive regulation'³⁴ and is underpins
35 the well-being of body and mind.

51 **5. Interoception and physical health**

52 The processing of interoceptive signals in the brain informs central control processes
53 involved in maintaining physiological integrity. Interoception is tightly related to the predictive
54 control of bodily signals that contribute to a system being able to maintain homeostatic set-
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3 points, and the flexible allostatic regulation of more complex demands. When the system
4 fails to respond to demands in an adaptive manner, or when predictive fluctuations fail to
5 foresee necessary demands, the organism may reach allostatic overload and succumb to
6 sickness and disease.
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9 Sickness behaviours

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11 The human immune system communicates immunological and inflammatory states to the
12 brain via interoceptive pathways.²⁵ Peripheral states of infection and inflammation are
13 transmitted to the brain via vagus nerve pathways, cytokines that circulate humorally, and
14 via immune cells.²⁵ Responses to these insults include the activation of cardiovascular and
15 gastrointestinal reflexes, the regulation of peripheral immune reactions,³⁵ and also a
16 stereotyped pattern of responses called 'sickness behaviours'.³⁶ These entail fatigue,
17 reduced calorie and fluids intake, social isolation, anhedonia, and fever.³⁷ Sickness
18 behaviours are thought to facilitate counteracting responses to infection and inflammation by
19 inducing behavioural patterns that reduce bodily strain (e.g. fatigue motivates rest), and risk
20 of additional infection (e.g. social isolation). This narrow repertoire of behaviours is evoked
21 as a response to a wide range of infectious and inflammatory conditions, which suggests
22 that they may form a coordinated general physiological and motivational reaction to a
23 particular type of interoceptive challenge for the protection of the body's integrity.³⁸
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26 Experimentally these mechanisms can be explored by administration of substances that
27 cause a brief spike in inflammation, e.g. typhoid vaccine,³⁹ infusion of endotoxin,⁴⁰ or
28 inhalation of antigens.⁴¹ A neurally-mediated interoceptive pathway, recruiting basal and
29 posterior ventromedial thalamus, and dorsal mid- and posterior insula, is activated after
30 typhoid vaccination.⁴² Specific components of sickness behaviour are associated with
31 functional changes within interoceptive brain regions, including mid-insula (fatigue),⁴²
32 subgenual cingulate (mood change),³⁹ and the midbrain substantia nigra (psychomotor
33 slowing).⁴³ The insula is further implicated in the expression of inflammation-induced
34 subjective experiences of fatigue, malaise and social disconnect.⁴⁴ Increase in right anterior
35 insula metabolism tracks the loss of interest in social interaction,⁴⁵ while heightened
36 connectivity between anterior insula and mid-cingulate cortex predict subjective malaise and
37 discomfort after induction of inflammation.⁴⁶ These findings indicate a role for the insula in
38 mediating the experiential side of sickness behaviours, a hypothesis that is in line with the
39 theoretical proposal and emerging evidence implicating insular cortex in subjective
40 experience of conscious motivational and emotional states arising from interoceptive
41 predictive processing.^{31, 47}
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3 The same brain regions that support emotions and affective regulation are thus involved in
4 sickness behaviours (and their origin in IPP), highlighting a connection between
5 inflammation, sickness behaviour and mood disorders.⁴⁴ Changes in motivation are a
6 hallmark of both sickness behaviours and major depressive disorder.⁴⁸ Low motivation to
7 move can be adaptive in the context of physical illness, as it enables energy conservation
8 while prioritizing resources for fighting off inflammation and infection. In the case of
9 prolonged or very severe inflammation, however, these motivational changes can mark the
10 onset of a depressive episode.⁴⁴ Motivational changes ultimately impact processing of
11 reward-stimuli,^{18, 19} correspondingly response to reward outcomes is altered following
12 inflammation. This is reflected on both the neural and behavioural level; reactivity within the
13 ventral striatum, a centre of (predictive) reward processing⁴⁹ is decreased, and both
14 subjective and objective measures of anhedonia (the absence of reactivity to positive stimuli)
15 are increased.⁴⁰ Social withdrawal is another symptom that sickness behaviours and
16 depression share. Not participating in social interaction often leads to feelings of isolation
17 and loneliness, and contributes to the maintenance of depressed mood.⁵⁰ Inflammation,
18 through interoception, thus facilitates processes that underlie and enhance feelings of social
19 isolation; induce feelings of social disconnect,⁵¹ and impair the processing of social cues,⁵²
20 Taken together, sickness behaviours illustrate how perturbation of internal bodily states
21 impact neural representations, emotional states, and executive behaviours. These reactive
22 patterned responses are mediated via interoceptive pathways that typically support adaptive
23 social emotional and motivational behaviours.
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34 35 Fatigue

36 Fatigue is a disorder that is characterized in the ICD-10 as a long-term condition that
37 includes severe and constant feelings of tiredness, trouble concentrating and carrying out
38 daily activities, generalized aches and pains, fever, and sleep disturbances.⁵³ It can be part
39 of sickness behaviours, and as such have adaptive effects in that it prioritizes rest to save
40 resources and may facilitate the role of fever in fighting off infections.⁵⁴ Fatigue can also
41 appear on its own as a chronic condition (chronic fatigue syndrome)⁵⁵, which affects
42 approximately 20% of the general population.⁵⁶ Its prevalence increases to 50%, however,
43 as a symptom in conditions that are associated with a compromised immune system,⁵⁷ such
44 as cancer,⁵⁸ autoimmune diseases like multiple sclerosis,⁵⁹ and fibromyalgia.⁶⁰ Fatigue is
45 strongly associated with depression,⁶¹ and listed in both DSM-5 and ICD-10 as a core
46 criterion for major depression.^{53, 62}
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54 Fatigue is a multi-dimensional construct that involves both impairment of motor and cognitive
55 processes, and the subjective experience of fatigue.⁶³ Research on fatigue emphasises
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3 approaches that associate the condition with peripheral inflammation and its influence on
4 brain structures involved in steering immunological responses.^{37, 64} Brain structures involved
5 in fatigue include insula and the frontostriatal network, most notably the ventral striatum.⁶⁵ In
6 this context, signals of peripheral inflammation reach the frontostriatal network via immune-
7 to-brain communication pathways that involve activation of microglia. This network underlies
8 response to reward, which supports anticipation and motivation, both of which are reduced in
9 fatigue.⁶⁶ An altered frontostriatal network due to inflammation is thus one strong candidate
10 for the neurobiology of fatigue.⁶⁵ AIC has been associated with the experiential quality of
11 emotions and feelings, and is thought to play a key role in the experience of fatigue.⁶⁷ After
12 the experimental induction of inflammation via typhoid vaccine, fatigue was predicted by
13 altered reactivity within mid- and posterior insula and ACC.³⁹ This suggests that interoceptive
14 signalling of inflammatory states, and their impact on brain regions that are associated with
15 processing interoceptive input, is an important factor in subjective experience of fatigue and
16 vitality/agency. Newly emerging views on fatigue are turning towards approaches that not
17 only consider the bottom-up effects leading to fatigue, but that also take into account
18 possible top-down influences.⁶⁸ Further research is needed to determine if distinct levels of
19 interoceptive processing accuracy are compromised in individuals with high levels of fatigue.
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30 **6. Interoception and Mental Health**

31 Interoception research is increasingly demonstrating that, in addition to physical health, the
32 signalling and detection of internal bodily signals is important for mental wellbeing.⁶⁹
33 Interoceptive and emotional processes share underlying neural substrates,⁵ and prominent
34 theories of emotion even suggest that emotional feeling states arise through the sensing of
35 bodily signals.^{47, 70-72} Emotional impairments accompany the majority of mental disorders,⁷³
36 acting as one potential route linking interoception to mental health.
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43 **Depression**

44 Major depressive disorder is associated with affective symptoms such as low mood, and
45 negative cognitions such pervasive negative thoughts and intense feelings of
46 hopelessness.⁷⁴ In addition, somatic symptoms including aches and pains, disordered sleep,
47 loss of appetite and fatigue are just as frequent, and occur universally across cultures.^{75, 76}
48 Recognition that somatic alterations are an important factor for changes in emotion and
49 cognition has grown over the past decade.^{77, 78} Depression is associated with autonomic
50 dysfunction, manifesting as decreased baroreflex sensitivity,^{79, 80} reduced phasic skin
51 conductance responses,^{81, 82} and reduced heart rate variability.⁸¹ In addition to autonomic
52 alterations, signs of heightened inflammation have been documented in depression.⁸³ In a
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3 subset of individuals with depression, cumulative meta-analyses demonstrate raised
4 inflammatory markers, particularly IL-6 and C-reactive protein.⁸⁴ Disturbances in brain
5 function are linked to increases in peripheral inflammatory markers, where, for example,
6 reduced functional connectivity of corticostriatal reward circuitry is observed in depressed
7 individuals with elevated C-reactive protein.⁸⁵
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11 Impaired interoceptive accuracy may lead to reduced emotional experience, and indeed,
12 'feeling nothing' is often reported by depressed individuals. Healthy controls demonstrate a
13 correlation between accuracy and intensity of experienced emotions, where better accuracy
14 leads to more intense feelings,¹⁸ raising the possibility of a potential impairment in
15 interoceptive accuracy in depression. However, experiments detailing altered patterns of
16 altered interoceptive accuracy associated with depression, present a more complex
17 relationship.⁷⁷ The ability to accurately perceive one's heartbeat is negatively correlated with
18 depression symptoms in healthy controls, an effect only found to manifest when coupled with
19 high anxiety.⁷⁸ In an experiment which contrasted interoceptive accuracy across three
20 groups (healthy controls, community sample with moderate depression and a more severely
21 depressed clinical sample), only the moderately depressed sample had significantly impaired
22 interoception.⁷⁷ Interestingly, and counter to predictions, the more depressed group
23 displayed levels of interoceptive accuracy that were comparable to the control group.⁷⁸
24 though this effect may have been influenced, in part, by medication status.⁸⁶ Increasingly,
25 nuanced investigation of interoceptive behavioural impairments linked to specific clusters of
26 symptoms (e.g. differentiating negative effect from emotional numbness) may reveal clearer
27 associations in depression.
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38 Decreased heartbeat perception accuracy is accompanied by significantly reduced heart
39 beat evoked potential (HEP) amplitudes in depressed individuals.⁸⁷ The neurocircuitry
40 underlying attention to visceral interoceptive sensations was assessed in unmedicated
41 individuals with major depressive disorder (MDD) relative to controls. Activity in the dorsal
42 mid-insula as well as a network of brain regions involved in emotion and visceral control,
43 were decreased in the MDD group. Moreover, resting state functional connectivity between
44 the amygdala and the dorsal mid insula cortex was increased in MDD and predictive of
45 depression severity.⁸⁸ Together these results suggest that the brain representation of
46 interoceptive focus may be altered in MDD.
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53 From a theoretical approach, IPP (including the EPIC model) provide insight into depressive
54 mechanisms, extending to the hypothesis that structural abnormalities, and dysfunctional
55 metabolism within agranular visceromotor cortices may be underlying causes of depressive
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3 states, particularly when associated with inflammation and sickness behaviours.²
4 Visceromotor cortical dysfunction causes imbalance between demand and response through
5 over-predicting metabolic energy-demands. This may engender overactivity of the
6 hypothalamus-pituitary-adrenal (HPA) axis and thereby increasing levels of pro-inflammatory
7 cytokines,⁸⁹ causing concomitant alterations in the immune and endocrine system.⁹⁰ This
8 aberrant process will compromise dependent coupling of interoceptive predictions and inputs
9 at the thalamocortical level, leading to a speculated increase in interoceptive prediction
10 errors. Down-regulation of these noisy error signals by precision units leaves them less able
11 to influence and inform predictions. To further reduce prediction errors, the interoceptive
12 network is left with two principle options; maintaining the dysfunctional predictions, or
13 generating afferents that match these predictions. The latter is thought to lead to noisier
14 signals, setting them up to still not be able to change predictions. This insensitivity to
15 prediction errors might mean that faulty predictions will maintain metabolic energy demand,
16 until the endocrine and immune system have reached their limit. Depression ensues when
17 the error signals can finally no longer be ignored and must be reduced, enlisting sickness
18 behaviours to conserve energy.² The insensitivity to prediction errors in combination with
19 ever-more demanding predictions is hypothesised to lead to a 'locked-in' (attractor state)
20 brain that maintains a vicious cycle of faulty predictions and noisy error signals.⁹¹ Inefficient
21 energy-regulation may underlie negative affect, biasing the system more towards avoidance
22 behaviours and social withdrawal.⁹² An IPP model of depression (and fatigue) thus connects
23 aberrant allostatic processes to imbalanced affective processing, driving both somatic and
24 experiential emotional symptoms of depression.
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38 Autism Spectrum Conditions

39 Autism spectrum conditions (ASCs) are classified as neurodevelopmental conditions that are
40 associated with stereotypical and restricted behavioural patterns, altered sensory reactivity,
41 and social and emotional impairments.⁹³
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45 Research is currently investigating the nature of interoceptive deficits associated with ASCs.
46 Work in children is divergent, with one study suggesting interoceptive accuracy is intact in
47 children and adolescents (aged 8-17) with ASCs⁹⁴ while a subsequent study found that
48 interoceptive accuracy, ascertained using heartbeat tracking, was markedly impaired in a
49 comparable child and adolescent autistic sample.⁹⁵ Impaired interoceptive accuracy has also
50 been shown in adults with ASCs, demonstrated using the heart beat tracking task, where
51 significantly lower interoceptive accuracy scores were observed relative to a matched control
52 group.⁶ One study, however, demonstrates data to suggest that autism per se does not
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3 necessarily lead to interoceptive impairments, but instead alexithymia, which is highly co-
4 morbid with ASCs, is associated with reduced interoceptive accuracy.⁹⁶ Alexithymia is a sub-
5 clinical condition characterized by a reduced capacity to detect and identify emotions in
6 oneself and others,⁹⁷ and thus the emotion processing deficits in autism, characterised by
7 high alexithymia, may be the principle driver for interoceptive impairments in ASC. Other
8 studies in non-autistic populations have demonstrated a link between high alexithymia and
9 impairments in interoceptive accuracy,⁹⁸ Together these results suggest that interoceptive
10 accuracy may be impaired in individuals with autism, and that this may be particularly
11 coupled with emotion processing deficits.
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18 In contrast to behavioural performance on interoceptive tests, interoceptive sensibility,
19 assessed via self-report questionnaires, is elevated in adults with ASCs, despite these same
20 individuals demonstrating a relative impairment in interoceptive accuracy.⁶

21 This is in line with research documenting that interoceptive aptitude ascertained using self-
22 report does not necessarily predict actual performance measures.¹² Moreover, it suggests
23 that these interoception dimensions may further diverge in clinical populations, with ASC
24 individuals having an overinflated belief in their interoceptive aptitude relative to their
25 performance accuracy. This enlarged discrepancy between objective and subjective
26 interoceptive performance denotes potential poor interoceptive sensory precision in ASCs
27 and is in line with accounts of autism conceptualized as a condition with an imbalance of the
28 precision ascribed to sensory evidence relative to prior beliefs.⁹⁹
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36 Altered Insula reactivity has been observed in individuals in ASC across a variety of distinct
37 emotion processing tasks, including response inhibition of emotional stimuli,¹⁰⁰ processing
38 of bodily expressions,¹⁰¹ and the processing of incongruent emotional information.¹⁰² ASC is
39 also associated with altered intrinsic functional connectivity of anterior and posterior insula
40 regions and specific brain regions involved in emotion and sensory processing.¹⁰³ Together,
41 these results suggest that altered sensory precision marked by reduced interoceptive
42 accuracy underscored by aberrant insula activity and functional connectivity may contribute
43 to emotion processing deficits observed in ASC and alexithymia more generally.
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49 Anxiety Disorders

50 Anxiety disorders include panic disorder, agoraphobia, social anxiety, generalized anxiety
51 disorder (GAD), and specific phobias.⁶² Investigations into interoceptive alterations in anxiety
52 disorders are mixed, reflecting the diversity of anxiety conditions and also the range of
53 methodological approaches.¹⁰⁴ Studies have reliably found that interoceptive sensibility, i.e.
54 self-report measures of interoception, are elevated in individuals with a variety of anxiety
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3 related conditions.^{105, 106} In accordance with this, interoceptive accuracy is also frequently
4 elevated in individuals with anxiety, indexed by heightened performance on heartbeat
5 perception tests in patients with anxiety and elevated occurrence of trait anxiety symptoms
6 with heightened interoceptive accuracy in non-clinical cohorts.^{77, 107} However, a straight-
7 forward relationship between elevated interoception in anxiety is challenged by a number of
8 studies which either do not show a relationship,^{108, 109} or reveal a reverse relationship, with
9 higher levels of anxiety related to reduced interoceptive accuracy.¹¹⁰ Recent work partly
10 reconciles these divergent findings, by demonstrating that it is the relationship between
11 subjective and objective measures of interoception which predict anxiety symptomatology (in
12 both an autistic population and in healthy controls). Specifically, individuals with an elevated
13 interoceptive trait prediction error, derived from a propensity to believe one is interoceptively
14 proficient despite relatively poor interoceptive accuracy, had heightened trait anxiety
15 scores.¹¹¹ This interoceptive predictive error is potentially consistent with theoretical work
16 that has posited that the pathogenesis of anxiety is related to noisy interoceptive input in
17 combination with noisily amplified self-referential interoceptive predictive belief states.¹¹²
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27 Eating Disorders

28 Eating disorders (EDs) are characterized by atypical food intake (e.g., restriction in anorexia
29 nervosa, or bingeing and purging in bulimia nervosa), and are often accompanied by an
30 distorted body image.¹¹³ Poor interoception has been linked to body image concerns,¹¹⁴ and
31 a number of empirical findings converge to suggest potential disturbances in the processing
32 of interoceptive signals in individuals with EDs. Interoceptive self-report in this population
33 has been primarily probed using the Eating Disorder Inventory (EDI)¹¹⁵ which assesses the
34 subjectively reported ability to discriminate sensations of hunger and satiety, and to respond
35 to emotional states. Patients with EDs report impairments in these abilities,¹¹⁶ which could
36 reflect a generalized deficit in interoceptive processing. Empirical findings support this in
37 part, with studies demonstrating impaired interoceptive accuracy in anorexia nervosa
38 patients relative to matched controls using a heartbeat perception test.^{117, 118} Other studies,
39 however, fail to show impaired interoceptive accuracy in anorexia nervosa,¹¹⁹ and instead
40 document enhanced reported detection of interoceptive sensations.
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48 To date, only few studies have investigated whether interoception is compromised in bulimia
49 nervosa, although it is suggested that interoceptive processing deficits drive the symptoms
50 and associated behaviours in bulimia.¹²⁰ One study investigating interoceptive accuracy in
51 woman with a current diagnosis of bulimia nervosa observed no differences in heartbeat
52 tracking task performance when correcting for the presence of co-varying comorbid
53 alexithymia, depressive symptoms and anxiety.¹²¹ In contrast, women who had recovered
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3 from bulimia nervosa (without a prior diagnosis of anorexia nervosa) demonstrated
4 significantly reduced interoceptive accuracy compared to controls.¹²²
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7 Neural representation of bodily state is altered in EDs. During an interoceptive attention task
8 (focusing on the heart, stomach and bladder) individuals with anorexia nervosa display
9 significantly reduced activation in the anterior insula during heart perception, and
10 significantly reduced activation in the dorsal mid-insula during stomach interoception, relative
11 to a matched control group.¹²³ Individuals with anorexia nervosa display reductions in
12 functional connectivity in the thalamo-insula subnetwork, thought to reflect changes in the
13 propagation of sensations that convey homeostatic imbalances.¹²⁴ Bulimia nervosa is
14 associated with increased gray matter volumes within the ventral anterior insula,¹²⁵ and
15 binge eating disorder is associated with increased insula activity when viewing food images
16 after an overnight fast.¹²⁶
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23 Interestingly, altered interoception is not only found in patients who are currently suffering
24 from an eating disorder. Impairments in interoceptive self-report, as measured by the EDI,
25 predicts vulnerability to the development of EDs, as revealed in longitudinal studies.¹²⁷⁻¹²⁹ It
26 is not yet known whether other dimensions of interoception, such as interoceptive accuracy
27 or neural processing of bodily state, would also demonstrate pre-morbid alterations.
28 Nevertheless, interoceptive measures, as least ascertained via self-report, may serve as a
29 marker for ED vulnerability, facilitating potential early intervention.
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35 The exact nature of interoceptive impairment in EDs remains unclear, as it varies across
36 types of eating disorder, and studies often do not take into account co-morbidities such as
37 anxiety, depression and alexithymia, which are also associated with aberrant
38 interoception.^{97, 130} Differences in methodology also potentially contribute to further
39 ambiguity, with objective and subjective dimensions of interoception being used
40 interchangeably, and the interoceptive axis (e.g. cardiac vs. gastric) also requiring further
41 differentiation and systematic evaluation. Behavioural, neuroimaging, and
42 psychophysiological studies nonetheless show that several dimensions of interoception are
43 affected in different types of EDs. Further research with terminological and methodological
44 consistency could help to create a more differentiated account of how interoception
45 contributes to, and maybe even predicts, the occurrence of eating disorders.
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7. Conclusion

There is increasing evidence that the signalling, sensing and detection of bodily states are implicated in physical and mental wellbeing.^{69, 131} Interoception research contributes an important dimension to Health Neuroscience, by providing powerful explanatory understanding into the dynamic interactions between body, brain and mind that underlie pathophysiological disturbances across physical and mental disorders. Capitalising of strengthening theoretical frameworks, including IPP, further research needs to extend systematic interoceptive investigation across different bodily axes, and include measures of interoception that cover neural signalling, objective behavioural performance, subjective experiences and beliefs, alongside metacognitive measures, to delineate comprehensively interoceptive predictors of specific symptoms. Understanding the precise nature of interoceptive deficits has important clinical implications, as insight into interoceptive mechanisms may reveal new therapeutic targets to promote novel interventions.

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