Trends in Cognitive Sciences

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Review

Interoceptive pathways to understand and treat mental health conditions

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An increasing recognition that brain and body are dynamically coupled has enriched our scientific understanding of mental health conditions. Peripheral signals interact centrally to influence how we think and feel, generating our sense of the internal condition of the body, a process known as interoception. Disruptions to this interoceptive system may contribute to clinical conditions, including anxiety, depression, and psychosis. After reviewing the nature of interoceptive disturbances in mental health conditions, this review focuses on interoceptive pathways of existing and putative mental health treatments. Emerging clinical interventions may target novel peripheral treatment mechanisms. Future treatment development requires forward- and back-translation to uncover and target specific interoceptive processes in mental health to elucidate their efficacy relative to interventions targeting other factors.

Highlights

Patients with neuropsychiatric disorders associated with altered emotional or physical experiences show disruptions in interoception.

Interoception may be an important target of both existing and novel mental health treatments.

Antidepressants modulate aspects of interoception and specific psychological therapies target interoceptive processes, particularly breathing.

Medications for certain physical health conditions are associated with better mental health.

Interoceptive measures could be used to stratify patients for treatment selection.

Body–brain science: from periphery to mainstream

Over a century after the introduction of **peripheral theories of emotion** (see Glossary) [1], the notion that physiological signals influence emotion is widely accepted [2,3]. New techniques that combine peripheral and central signals are driving a rapid increase in research detailing the complex and multifaceted ways in which bodily state can interact with brain to influence cognition and emotion [4]. Recent work shows the nature of this influence ranges from moment-to-moment mapping, such as discrete cardiac cycle effects on emotion [5], to long-term emotional changes arising from chronic alterations, as in the immune system [6,7]. The influence of the body on emotion can be ascribed to two pathways that include bottom–up afferent signalling and/or top–down processing of the body. The body-to-brain axis maps bodily signals onto emotions, generating a patterned relationship between particular bodily states and emotions via neural representations of internal bodily signals. Higher-order paths represent someone's awareness of their bodily signals – for instance, how accurately they sense and interpret bodily information – which likewise contributes to emotional experience. These paths can be also be influenced by higher-order processes that interact with interoceptive signals, for example, appraisals given to undifferentiated bodily arousal [2,8] and strong beliefs about the body that might override veridical input [9].

The role of the body in emotion may be particularly relevant for the treatment of mental health disorders, today the world's leading cause of disability [10]. Recent efforts to characterise the nature of disrupted **interoception** in mental health conditions mirror these two pathways. In the first, direct changes in the body, including resultant neural modulation, might promote vulnerability to poor mental health. Alternatively or additionally, the sensing and perception of bodily signals might be upregulated or downregulated in mental health conditions, and may influence the experience of particular mental health symptoms. Traditionally, interoceptive correlates of mental health have been considered in the context of specific diagnoses. More recently, it has been suggested that they might instead represent 'transdiagnostic' mechanisms conferring a common vulnerability across multiple disorders [11]. Similarly, a range of effective mental health treatments

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alter interoception via effects on bodily physiology or on the perception of bodily processes. Understanding the path from interoception to mental health might reveal peripheral routes that render particular current treatments effective, as well as pave the way for future interventions designed explicitly to target interoceptive processes in mental health disorders.

Initial characterisation of interoception confined it to the visceral organs [12], although more recent definitions tend to encompass a broad set of bodily signals and general feeling states relevant to homeostatic control, physiological needs, and organ integrity [13,14]. For this review, we adopt a broader definition originating from a recent white paper on interoception in mental health: namely, 'the processing of internal bodily stimuli by the nervous system' [15], which includes sensing, interpreting, and integrating signals originating from inside the body, 'providing a moment-by-moment mapping of the body's internal landscape across conscious and unconscious levels' [15]. This is distinct from nervous system processing of signals originating from exteroceptive or proprioceptive information, and also does not describe physiological states *per se*, but rather the processing of internal physiological information. But what counts as an 'internal' stimulus? Some sources of internal information, such as signals originating from the heart, are widely accepted interoceptive mechanisms. Others, such as the influence of the immune system on the nervous system, are more controversial. This review references both accepted and more controversial sources of interoceptive information, but provides a table indicating how widely accepted each source of information is as 'interoceptive' (Figure 1).

How the body shapes emotion

Physiological signatures of emotion

The body's drive for **homeostasis** means our mental response to a glass of water depends acutely on whether we are thirsty or not. Likewise, physiological signals throughout the body have profound effects on emotional experience. How might physiological responses alter emotion experience? Classical models of bodily inference suggest that autonomic nervous system (ANS) activation causes an undifferentiated arousal response which affects nonspecific emotion processing. In this framework, the ANS is mobilised in response to metabolic demands to anticipate particular behaviours, resulting in general emotional arousal [2,16]. Appraisal theories of emotion denote that there is no direct mapping of internal signals to precise emotional feeling states; instead, largely undifferentiated changes in bodily state are 'appraised' to shape emotional feelings. These appraisal processes guide which emotions are experienced, and the appraisals themselves can be influenced by a variety of factors including past memories, external context, dispositional style and cultural context [8]. The theory of constructed emotion [2] posits that the brain constructs instances of emotion, in a context-specific manner, by 'imposing meaning' on noisy and ambiguous data from the body and the world. These theories crucially detail the complex interplay of factors that interact with interoceptive signals to guide emotional experience. While not negating the influence of extraneous factors such as memory, personality, and context on emotion, contemporary empirical findings are furthering our understanding of the ways that internal bodily signals themselves can change emotion.

A subset of bodily signals are now thought to be associated with specific emotions or subsets of emotions. For example, perception of 'core' disgust stimuli (e.g., faeces) elicits a shift in the electrical activity of the stomach [18,19], which can be targeted pharmacologically to reduce disgust avoidance [17]; this electrical activity is distinct from physiological changes associated with other subcategories of disgust (e.g., bodily violence) [18,19]. Classical models of bodily influence on emotional experience may have disregarded effects with relatively fast or slow temporal characteristics. Experiments on the consequences of different aspects of the cardiac cycle have demonstrated the role of baroreceptors in emotion intensity and detection. For example, fear stimuli

Glossary

Alexithymia: a transdiagnostic construct relating to impairments in emotion processing, traditionally characterised by difficulties identifying and describing one's own emotions.
Back-translation: methods that reverse the traditional translational pipeline, working from therapy to mechanism to determine the mechanistic action of efficacious therapeutic interventions.
Exteroception: a sensation that results from stimuli located outside the body, including vision, hearing, touch, or pressure.
Functional neurological disorder (FND): a condition that is defined by the presence of motor and sensory symptoms (e.g., seizures, paralysis, movement disorder) that are not caused by identifiable neurological origins.
Homeostasis: the ability of organisms to maintain a stable internal bodily environment.
Hypertension: a condition characterised by persistently elevated arterial blood pressure.
Interoception: the process by which the nervous system senses, interprets, and integrates signals originating from within the body, providing a moment-by-moment mapping of the body's internal landscape across conscious and unconscious levels.
Interoceptive accuracy: correct and precise monitoring, that is, the correspondence between objectively measured physiological events and individuals' reported experience of those events, ascertained through behavioural tests.
Interoceptive insight: metacognitive evaluation of experience/performance, for example, the correspondence between accuracy during an interoceptive task, and (self-reported) perceived accuracy or confidence during the task.
Peripheral theories of emotion: theories that emotions arise at least in part due to physiological signals originating in the body.
Posttraumatic stress disorder (PTSD): a mental health condition that occurs following a traumatic event and is characterised by intrusive memories, flashbacks, and avoidance behaviour, among other anxiety- and stress-related symptoms.
Precision medicine: stratified treatment of patients within (or across)

Cardiovascular	Sherrington, C. (1906) [12]
Gastrointestinal (oesophageal, gastric, intestinal, colorectal)	Sherrington, C. (1906) [12]
Bladder	Sherrington, C. (1906) [12]
Respiratory	Sherrington, C. (1906) [12]
Visceral pain	Sherrington, C. (1906) [12]
Hunger	Craig, A.D. (2002) [13]
Thirst	Craig, A.D. (2002) [13]
Fatigue	Khalsa, S.S. *et al.,* (2018) [15]
Blood/serum (pH, osmolality, glucose)	Khalsa, S.S. *et al.,* (2018) [15]
Internal temperature	Craig, A.D. (2002) [13]
Muscle tension	Khalsa, S.S. *et al.,* (2018) [15]
Itch	Craig, A.D. (2002) [13]; Khalsa, S.S. *et al.,* (2018) [15]
Tickle	Craig, A.D. (2002) [13]; Khalsa, S.S. *et al.,* (2018) [15]
Affective touch	Craig, A.D. (2002) [13]; Crucianelli, L. *et al.,* (2018) [129]; Björnsdotter, M. et al., (2010) [130]
Inflammation	Khalsa, S.S. *et al.,* (2018) [15]
Inflammatory / mechanical joint pain	Khalsa, S.S. *et al.,* (2018) [15]
Skin temperature	Craig, A.D. (2002) [13]; Khalsa, S.S. *et al.,* (2018) [15]

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Figure 1. The varying recognition of organs and senses as interoceptive. The classification of bodily organs and senses as interoceptive varies according to different definitions, with varying degrees of broad acceptance and controversy within the field. Green indicates organs and senses universally recognised as interoceptive: visceral organs included under Sherrington's original conceptualisation of interoception. Light green indicates those widely recognised as interoceptive today, although absent from the original conceptualisation. Yellow indicates potential sources of interoceptive information which have been recognised more recently or less consistently across definitions. Red indicates more controversial potential interoceptive sources, which are considered by some researchers to be interoceptive but are often excluded from traditional definitions. Example (i.e., nonexhaustive) references provided. See [12,13,15,129,130].

clinical conditions according to individual measures (e.g., biomarkers that predict treatment response).

Respiratory sinus arrhythmia: the phenomenon by which heart rate varies according to respiration phase.

Selective serotonin reuptake inhibitors (SSRIs): common drugs for the treatment of depression and are also prescribed for anxiety in addition to other mental health conditions.

presented concurrently with baroreceptor activation (i.e., at cardiac T wave, when the heart–brain channel is active) can facilitate the encoding of fear memories, indexed by elevated next-day fear recall [20]. This has implications for the nature of body state (i.e., high arousal, when the heart is beating stronger and faster) and how it might heighten subsequent fear memories.

The cardiac cycle is associated with patterns of respiration, as indexed by **respiratory sinus arrhythmia**. Respiratory phase (inspiration/expiration) also alters emotion processing. Nasal inspiration, but not expiration, improves reaction times to fearful (but not surprising) faces, potentially due to the influence of respiratory phase on limbic brain regions [21]. Respiratory entrainment of amygdalar local field potential activity predicted emotion identification performance in one patient with implanted intracranial electrodes [21]. Rate of breathing also alters valence processing: the autonomic state induced by slow breathing preferentially modulates positive affect, while the autonomic state induced by fast breathing preferentially modulates negative affect [22]. Likewise, slow breathing reduces heat pain intensity and unpleasantness, ameliorating negative affect [23]. Slow breathing influences physiology via respiratory, cardiovascular,

and autonomic mechanisms. Within the autonomic domain, parasympathetic mechanisms are thought to be the principle driver of affective change following slow breathing [23]. This is particularly relevant for clinical conditions thought to involve a relative deficit of parasympathetic activity and its downregulation of negative affect [23]. By contrast, slow breathing 'enhances' parasympathetic afferent activation via bronchiopulmonary vagal afferents, increasing parasympathetic tone, also reflected in increased heart rate variability [23,24]. Slower breathing may be a useful intervention to reduce pain, and potentially, regulate affect [23]. These mechanisms may underpin a number of therapeutic applications of breathing regulation for mental health (discussed later).

At a much slower physiological timescale, the immune system can evoke motivational reorientation away from positive- and towards negative-valence information [25]. In rats, injection of potent immune system activators like endotoxin induce marked anhedonia and other depression-like symptoms, which can be attenuated or completely blocked by chronic antidepressant administration [26]. In studies using typhoid vaccination as a model of immune system activation, mood deterioration correlates with enhanced activation in the subgenual anterior cingulate during emotional face processing, and related coactivation between the subgenual anterior cingulate cortex (sgACC) and other regions involved in affect processing [27]. This may be coupled with shifts in learning: typhoid injection also enhances behavioural punishment (versus reward) sensitivity [25]. This could represent an adaptive reallocation of resources during acute sickness, away from learning to perform reward-associated actions, towards learning to avoid potentially punitive actions. Motivational reorienting explains the ability of sickness to induce negative affect, as well as more severe mental health symptoms.

Emotional experience is a complex interplay between internal and external factors. Non-interoceptive factors contribute substantially to emotional experience, including cultural context (see [28] for a broader review of theories of emotion). Cognitive mechanisms, such as memory, reward, and attention, are also known to impact mental health (reviewed elsewhere, e.g., [29]), although these cognitive processes have the potential to also be shaped by dynamic changes in visceral physiology and interoceptive processes [4,30]. Even identical, highly differentiated physiological signals might not induce precisely the same subjective phenomena in two people. Therefore, emotion experience is shaped not only by our physiological responses, but also by our individual capacity to sense bodily signals [31]. Quantifying the sensing of internal bodily signals is key to understanding the role of the body in emotion processing.

Interoceptive dimensions as mediators of emotional experience

Perception of the body's internal state, a core aspect of interoception [14], arises via a diverse set of physiological mechanisms. Anatomically, interoceptive signals are thought to ascend spinal laminar 1 spinothalamic tract via unmyelinated and lightly myelinated afferents [14]. Interoception can be subdivided into particular sources of information, or channels (for instance, mechanoreceptor-derived signals ascending a particular afferent pathway), and measured by probing various different dimensions of interoception, for example, **interoceptive accuracy** or **interoceptive insight** (Box 1). Each of these channels and dimensions represent specific ways of quantifying individual differences in interoceptive experience [32]. Individual differences may underlie important variation in emotional experience in the population.

Visceral perception plays a role in the intensity of our emotional experiences. In one experiment, people with better interoceptive accuracy, as measured by the heartbeat discrimination task (one of the most frequently used method for quantifying interoceptive accuracy, though note limitations [33]), reported more intense affect (amusement, anger, and fear) while viewing an emotionally intense film [31]. Heightened affective experience might represent a generally improved

Box 1. Dimensions of interoception and their clinical relevance

Interoception is delineated across different dimensions [14,15]. Interoceptive dimensions are differentially altered in mental health conditions, and by pharmacological, psychological, and behavioural interventions. Here, we provide illustrative examples of relevant conditions and treatments affecting interoceptive dimensions.

Interoceptive attention

Anxiety and related conditions increase self-focus, a bias of attention towards internal cues, including on the body and interoceptive sensations [113,114]. Therapeutic strategies such a 'behavioural activation' increase engagement in external activities, which may induce attentional shifts away from the self.

Interoceptive attribution

Attribution of bodily signals varies across clinical conditions; for example, catastrophic interpretations of cardiovascular signals (such as a signalling a heart attack) are more common in panic disorder, while patients with somatoform disorders show reduced emotional awareness [115], suggesting a potential disposition for physical interpretations. Interventions such as cognitive behavioural therapy (CBT) incorporate strategies to alter the nature of interoceptive attributions.

Interoceptive insight

Interoceptive insight (also termed interoceptive metacognition and interoceptive awareness [70]), operationalised as confidence–accuracy correspondence during tests to assess interoceptive accuracy, and/or the alignment of interoceptive beliefs with veridical bodily state, can be altered in clinical conditions such as FND [9]. Preliminary evidence suggests SSRIs might enhance interoceptive insight [86]. Long-term meditation may align interoceptive self-report and accuracy [104].

Interoceptive self-report

Interoception can be assessed with self-report measures, such as questionnaires. Conditions such as autism and anxiety are associated with a tendency to report being more 'aware' of bodily sensations [114,116].

Interoceptive accuracy

Interoceptive accuracy can be quantified in different bodily axes, including heartbeat detection tests and respiratory resistance tests. Conditions such as alexithymia [117] and schizophrenia [118] show impaired interoceptive accuracy. Enhancing interoceptive accuracy may aid capacity for autonomic regulation and anxiety reduction [106].

Preconscious impact of afferent signals

Bodily state alters stimulus processing, at both slow (e.g., immune state) and rapid timescales (e.g., with each heartbeat). For example, cardiovascular signals can increase fear processing, an effect heightened in anxious individuals [20]. Blood pressure medications (e.g., losartan) can enhance the extinction of fear memories [89].

Neural processing interoception

Neural activation in key areas subserves interoception. Disruption of dorsal mid-insula activation during interoception is found across a range of mental health disorders [11]. Pharmacological interventions, such as SSRIs, are associated with changes in insula activation during affective processing [84].

Afferent signal

Autonomic signatures are linked to emotional state. Afferent signals such as heartbeats increase in frequency/intensity during heightened anxiety states. Medication, such as beta-adrenoreceptor blockers, can dampen afferent signals, reducing anxiety [119].

detection of bodily signals. This could be adaptive in certain contexts. For example, participants with heightened cardiac interoceptive accuracy are better at regulating their emotions in response to negative affect [34–36]. Accurate moment-by-moment estimation of bodily state might facilitate downregulation of unpleasant bodily or emotional states.

Emotional and interoceptive experience are intertwined not just under normative conditions, but also during disruptions to either emotional or affective systems, or both. Conditions that involve disrupted bodily processing are often comorbid with mental health conditions: for instance, asthma is marked by reduced respiratory interoceptive accuracy [37,38] as well as a high

instance of anxiety disorders [39,40]. Poor respiratory accuracy is associated with higher levels of anxiety [40]. Conversely, across mental health conditions, there are disruptions in both physiological states and interoceptive access to physiological signals.

The body in mental health disorders

Mental health disorders have an unknown aetiology and myriad risk factors, including genetic, epigenetic, brain injury [41], and social contributors [41–43]. Cognitive changes in mental health disorders have largely been attributed to alterations in 'hot' (reward or emotion related) and/or 'cold' (nonemotional) neurocognitive systems [29]. This framework has also been dominant in evaluating cognitive mechanisms of mental health treatments, both pharmacological [44] and non-pharmacological [45,46].

Cognitive models of mental health conditions do not traditionally include a role for bodily processes. Nevertheless, input from the periphery into the central nervous system has causal effects on various aspects of cognition (e.g., [25,27,47]), and interoceptive mechanisms in the brain overlap with emotion processing [14]. Peripheral influences (and interoception specifically) may therefore represent a third neurocognitive contributor to poor mental health.

Physiological changes in almost every bodily system are associated with mental health disorders [15,48]. Medical conditions involving disruptions to certain organ systems also correspond to poor mental health – for instance, the prevalence of depression in patients with cardiovascular disease is threefold higher than in the general population [49]. This relationship echoes patterns observed with a number of other physical conditions, such as between **posttraumatic stress disorder (PTSD)** and **hypertension**, along with an increased risk for stroke and heart attack, where shared incidence is again high [50].

Immune system dysfunction and mental health

Pharmacologically mimicking the effects of acute infection on the immune system using interferon-alpha administration causes almost half of people to develop major depression within 12 weeks [51], implying that there is likely a causal role of immunological factors in postviral-associated mental health conditions. Immune system dysfunction is commonly found in patients with current mental health disorders, including psychosis [52], trauma- and stressor-related disorders [53], and depression [54]. Crucially, increased peripheral inflammation can induce central nervous system inflammation via humoral and neural mechanisms, including recruitment of activated monocytes into the brain following cerebral microglial activation [55], which may be one cause of central neuroinflammation in psychiatric disorders [56].

Immunological changes can cause symptoms falling at the juncture of physical and mental health, as in postinfectious syndromes. In a prospective study, 12% of patients experienced disabling fatigue, depression, pain, and neurocognitive difficulties 6 months after acute infection with Epstein–Barr virus, Q fever, or Ross River virus [57]. Many patients experience similar long-term postviral symptoms following acute infection with the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) virus [58]. 'Long coronavirus disease (COVID)', like other postinfectious syndromes, may be driven in part by peripheral inflammatory changes (with potential subsequent effects on central neuroinflammation), which are sustained in the absence of infection, causing fatigue and other neuropsychiatric symptoms. This is an essential area for future research. A large body of evidence suggests that patients with depression also have immune system dysfunction, which may precipitate depressive episodes [59–62]. Patients with major depressive disorder show increased blood levels of inflammatory proteins [such as interleukin-6 (IL-6) and C-reactive protein (CRP)] and increased expression of immune-related genes [59–62].

The role of the immune system may contribute to heterogeneity within a single diagnostic category, and possibly represent a transdiagnostic disruption across a number of neuropsychiatric disorders. A recent study employed data-driven multivariate mixture modelling of immune cell counts to identify four subgroups of patients with major depression (two of which were characterised by increased inflammatory proteins and more severe depressive symptoms, but differing from one another in terms of myeloid and lymphoid cell counts) [54]. A caveat of cross-sectional work is uncertain causality; it is essential to also test causal contributions of particular inflammatory markers in depression. In one recent example combining large datasets from the UK and the Netherlands, heightened levels of two different inflammatory markers – IL-6 and CRP – were each associated with homeostatic symptoms of depression (e.g., fatigue, sleep). But a causal Mendelian randomisation approach showed that in fact only IL-6 could be causally linked to depression (i.e., SNPs in the IL-6-R gene were associated with either later serum IL-6 concentration or CRP concentration, likely as a downstream readout of IL-6) [63].

The evidence that proinflammatory interventions like interferon cause one-quarter of patients to experience a depressive episode [64], in combination with evidence that acute inflammatory challenge leads to motivational reorienting [25] also provides causal evidence for the role of proinflammatory cytokines in 'sickness behaviour': cognitive, behavioural, and physiological changes induced by systemic infection and commonly seen in depression or depressive-like states [6,47,65–67]. Immune differences may also interact with other peripheral systems such as the gut microbiome to contribute to depression-like behaviour in animals [68].

Measuring dimensions of interoception in mental health

Interoception can be assessed across different dimensions, including interoceptive accuracy, insight, and other higher-order measures including interoceptive attention and interoceptive attribution [32] (see Box 1 for examples of these interoceptive dimensions and their putative role in mental health). The extent to which interoception is shared across different bodily axes is still under investigation. Initial work suggests that interoceptive measures/dimensions in one axis do not necessarily correspond to better measurement in another. For instance, while there appears to be a good correspondence between cardiac and gastric interoceptive accuracy [69], cardiac interoceptive accuracy and respiratory interoceptive accuracy are dissociated [40]. However, interoceptive insight (meta-cognition) appears correlated across cardiac and respiratory channels [40]. An important direction for future clinical work is a comprehensive multiaxis assessment of different interoceptive dimensions [32] across both basic and higher-order interoceptive measures, to establish the specificity of differences in interoception in a particular disorder.

Exteroception helps us navigate the world. Provided exteroceptive cues are attended to, and surpass a certain perceptible threshold, exteroception largely has the capacity to be coupled to conscious access. By contrast, interoceptive signals are continuously processed centrally but these signals rarely, by comparison, break through to consciousness awareness. As such, accuracy at interoceptive tasks is less likely to correspond to confidence measures relative to an exteroceptive task [40], and beliefs about interoceptive aptitude do not necessarily align with actual interoceptive accuracy or precision [70]. This decoupling of interoception from metacognitive insight potentially renders interoception more vulnerable to the influence of strong priors or beliefs [71], especially in the context of weak or imprecise interoceptive representation.

This may be particularly relevant for various clinical conditions (see Box 2 for the example of **alexithymia**). Here we draw particular attention to those clinical conditions with beliefs about the body which potentially deviate from veridical input, such as **functional neurological**

Box 2. The case of alexithymia

Sensing, interpreting, and integrating signals from the body is altered across disorders that involve different emotion experience. Here we will focus on the case of alexithymia. Some interoception research using classic heartbeat perception tests converges to suggest that alexithymia is associated with impaired interoceptive accuracy [120]. Alexithymia is also associated with worse interoceptive ability in non-cardiac domains, including a reduced propensity to use interoceptive cues to gauge respiratory output, reduced taste sensitivity, and reduced effort on tasks of muscular effort [121]. This is consistent with the principle that sensing bodily changes informs emotional experience, where it follows that an impaired capacity to accurately sense bodily signals is associated with difficulties identifying and detecting feelings. Alexithymia is also associated with the somatisation of emotions, where emotional states are more likely to be attributed to a physical rather than an emotional origin. In addition to altered attribution, poor interoceptive precision could reduce the capacity for emotional granularity [122] and thus increase the probability of somatic rather than emotional interpretations of bodily sensations.

A relationship between alexithymia and interoception might also explain disrupted interoception in clinical conditions. For instance, alexithymia is highly comorbid with autism, and many autistic individuals have difficulties understanding their own emotions and the emotions of others [123]. Previous research suggests that individuals on the autistic spectrum may also have impaired interoceptive accuracy [116,124], though work specifically differentiating autism and alexithymia indicates that it may be comorbid alexithymia, rather than autism *per se*, that drives impaired interoceptive accuracy [117]. However, this research was primarily assessed using a self-report measure of interoception (TAS) in combination with cardiac interoception tests. Sensory alterations are well established in autism and more nuanced interoceptive tests are needed across a variety of axes to better understand the nature of altered interoceptive sensory processing in autism, where changes in temperature perception, slow affective touch, and gastric processing are documented (see [125] for a review).

Other studies find no relationship between alexithymia and worse cardiac interoceptive accuracy [126] or better cardiac interoception in high alexithymia participants [127]. These inconsistent findings can be explained by a quadratic relationship between alexithymia and interoceptive accuracy; although many individuals with heightened alexithymia show low interoceptive accuracy, a subset of individuals with heightened alexithymia show abnormally high interoceptive accuracy in specific domains [128]. This may also speak to different subtypes of alexithymia, underscored by either attenuated or noisy augmented afferent signals. Further research is needed to better understand the complex relationship between alexithymia, interoception, and somatisation.

disorder (FND) and somatoform disorders. FND has been associated with impaired interoceptive accuracy [9], including following induced dissociation [72] and sham (placebo) brain stimulation [73]. Interoceptive errors in FND are related to the frequency of functional (nonepileptic) seizures [9]. These errors can be characterised by discrepancies between interoceptive precision (i.e., interoceptive accuracy) and self-report interoceptive measures, conceptualised as interoceptive beliefs or 'priors'. Similarly, somatoform disorders are associated with reduced interoceptive accuracy [74], and may be characterised by a mismatch between prior expectations of symptoms and sensory input from the body [75]. Together, this research highlights that the nature of interoceptive beliefs and predictions could be key for understanding a variety of neuropsychiatric conditions, particularly when top–down beliefs differ from perceived afferent signals. This perspective is consistent with our adopted definition of interoception [15], which includes both the sensing of bodily signals and their 'integration', for example, integration with higher-order beliefs and predictions in the brain. Our perspective is also aligned with contemporary computational approaches to interoception, such as those founded on predictive coding, where brain areas at higher levels of an interoceptive hierarchy send predictions about expected sensory input to lower levels, and mismatches between predicted and actual input are processed as prediction errors [76].

In addition to specific changes across distinct interoceptive channels, there may be some commonalities in interoceptive dysfunction in mental health disorders across interoceptive channels. A recent neuroimaging meta-analysis of interoceptive neural processing in patients with bipolar disorder, anxiety, major depression, anorexia, and schizophrenia found a common disruption in dorsal mid-insula activation during various interoceptive probes (e.g., pain, hunger, interoceptive attention) [11]. Similarly, in a large transdiagnostic sample, measures of cardiac physiology [heart rate and heart rate variability (HRV)], objective interoceptive influences on perception, and

subjective (self-report) sensitivity to interoceptive signals differed across patients with mental health conditions, with particular distinct differences in schizophrenia that merit further investigations [77]. These may be linked to autonomic dysfunction: reduced vagal modulation and loss of cardiovascular signal complexity have been reported in patients with schizophrenia [78], and their first-degree relatives [79], representing a potential risk factor for cardiac disease. Bayesian modelling applied to a sample of patients with depression, anxiety, eating, and substance use disorders found a transdiagnostic failure to increase precision of ascending cardiac signals during an interoceptive perturbation (breath hold) [80]. Together, this suggests that differences in physiological systems and interoceptive experience represent targets for interventions – and already are targeted by a number of evidence-based treatments for mental health (Box 1).

Treating mental health via the body

The most common treatments for affective disorders, cognitive behavioural therapy and **selective serotonin reuptake inhibitors (SSRIs)**, are thought to alter emotion processing via two distinct routes [81,82]. Cognitive therapies may alter affective processing via attention and awareness of affective state via proximal changes in the medial prefrontal cortex, while antidepressant medication might modify visceromotor state itself via proximal changes in serotonergic receptors in the amygdalae [83], both relevant for interoceptive processing. In addition, some interventions may directly perturb peripheral physiology, and downstream affect neural mechanisms, contributing to mental health treatment.

Common treatment strategies for mental health disorders may alter interoceptive processing, either via direct physiological effects on the body or by changes to interoceptive perception, including differences in interoceptive accuracy, interoceptive insight, or the (self-reported) perception of internal signals (Figure 2, Key figure and Table 1). There is evidence for putative central and peripheral effects of SSRIs on interoceptive-related processes. For example, subchronic SSRI administration attenuated insula activity during affective anticipation [84], but has also been found to alter oesophageal mechanosensitivity and chemosensitivity, decreasing oesophageal discomfort during the balloon distention paradigm and increasing the duration to first perception in the acid perfusion test [85]. Emerging evidence suggests that a single dose of an SSRI may enhance interoceptive awareness, specifically enhancing the metacognitive insight dimension of interoception [86]. This provides preliminary support that serotonergic medication, the most common class of medication for mental health disorders, may alter interoceptive processes via central or peripheral mechanisms. Similarly, propranolol, a β-adrenergic receptor antagonist and common medication for panic disorder, alters cardiovascular function via its effects on the sympathetic nervous system, where it improves autonomic regulation [87] but also has central effects on the noradrenaline system of the brain. In general, treatments could alter interoceptive processing via peripheral effects on the autonomic, neuroendocrine, and immune systems (i.e., indirectly altering interoception), as well as via central effects on interoceptive systems in the brain, or indeed via a combination of the two.

Pharmacologically targeting interoceptive mechanisms

Inspired by basic research, novel approaches are being devised to probe peripheral targets directly for mental health treatment. The renin–angiotensin system is involved in cardiovascular regulation and hypertension is commonly treated via pharmacological inhibition of this system. In a large community sample, individuals taking blood pressure medication that acts on the renin–angiotensin system [e.g., angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs)] were less likely to have PTSD symptoms [88]. Blood pressure medications targeting different pathways, including β-blockers, calcium channel blockers, and diuretics, were not associated with reduced PTSD symptoms. Complementing this, preclinical work causally demonstrated that

Key figure

Examples of interoceptive targets of existing or putative mental health treatments

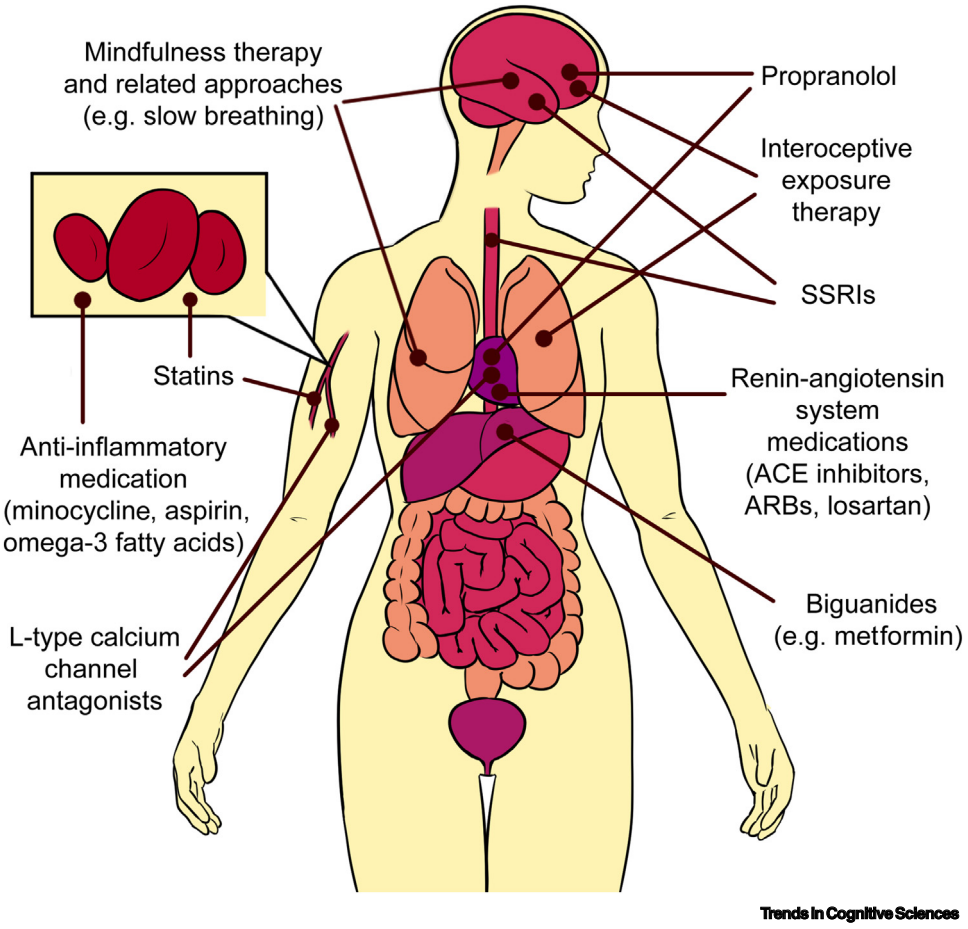

Figure 2. Figure depicting the various potential neural and physiological interoceptive targets of existing (e.g., propranolol; SSRIs; mindfulness) and putative (e.g., statins; losartan; biguanides) mental health treatments. Includes examples of both psychological and pharmacological treatments, some of which target both neural and peripheral mechanisms (e.g., the respiratory and neural effects of slow breathing; the cardiovascular and neural effects of propranolol). Abbreviations: ACE, angiotensin-converting enzyme; ARBs, angiotensin II receptor blockers; SSRIs, selective serotonin reuptake inhibitors.

administration of the selective angiotensin II type 1 (AT_1) receptor antagonist losartan (commonly used in humans for blood pressure regulation) enhanced the extinction of fear memory [89].

Anti-inflammatory medications are increasingly administered for a range of mental health conditions. A systematic review incorporating an amalgamated analysis of 26 randomised control trials for the treatment of depression suggests that anti-inflammatory agents are effective in reducing depressive symptoms relative to placebo [90]. One suggestion is that around one-third of individuals with depression have a subtype characterised by elevated inflammation [91]. Future interventions using **precision medicine** to match the action of specific treatments

Table 1. Examples of interoceptive targets of existing or putative mental health treatments

Treatment	Example target systems	Relevant disorders
SSRIs	Neural interoceptive; respiratory mechanosensation/chemosensation	Major depression; anxiety disorders
Beta-adrenoceptor blockers	Cardiovascular	Anxiety disorders; panic disorders
Angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, losartan	Renin–angiotensin system	Trauma and stress-related disorders
Statins	Cardiovascular; immune	Psychotic disorders; bipolar disorder
L-type calcium channel inhibitors		Psychotic disorders; bipolar disorder
Biguanides	Liver (glucose production)	Psychotic disorders; bipolar disorder
Anti-inflammatory agents (minocycline, omega-3 fatty acids, aspirin)	Immune system	
Interoceptive exposure therapy	Chemoreception (carbon dioxide); respiratory; cardiovascular	Panic disorder
Mindfulness	Neural interoception	Mood and anxiety disorders; eating disorders
Slow breathing	Respiratory; cardiovascular	Mood and anxiety disorders

to the pathophysiology of particular subtypes of patients may prove to be effective – for example, anti-inflammatory treatments administered to individuals with biomarkers indicative of elevated inflammation. Anti-inflammatory strategies for treating schizophrenia are also gaining traction, with the advent of clinical trials assessing the efficacy of anti-inflammatory agents as adjuvants to antipsychotic treatment [92]. Adjuvant anti-inflammatory strategies may be beneficial in relieving psychotic symptoms and treating cognitive deficits in patients with schizophrenia [92], using a variety of anti-inflammatory methods, including aspirin (which inhibits COX enzymes), minocycline (a tetracycline antibiotic), and omega-3 fatty acids (which have anti-inflammatory properties).

There is also evidence that existing treatments for physical conditions may improve outcomes in serious mental health conditions. In a recent demonstration of this in 142 691 patients with bipolar disorder, schizophrenia, or nonaffective psychosis, exposure to hydroxylmethyl glutaryl coenzyme A reductase inhibitors (statins, used to reduce cholesterol and heart disease), L-type calcium channel antagonists (used to reduce blood pressure), and biguanides (used to treat diabetes) were all associated with reduced rates of psychiatric hospitalisation, and in some cases reduced rates of self-harm compared with unexposed periods [93]. These effects may be due to modulation of key physiological systems, for example, statins have anti-inflammatory effects on levels of IL-1β, IL-6, tumour necrosis factor, and CRP [18,19,93–95] in addition to significant effects on the cardiovascular system.

Targeting interoceptive mechanisms with psychological therapies

Select components of psychological treatments for mental health disorders alter physiological and subjective aspects of interoception. Classic cognitive models of panic disorder that emphasise misinterpretation of bodily signals inspired treatments based on interoceptive exposure

[96,97] such as carbon dioxide inhalation, which reduces panic attacks more effectively than propranolol [98]. Evidence also suggests that 'third-wave' therapies such as mindfulness-based treatments (a popular therapy for depression [99] and eating disorders [100], among others) might directly modulate interoceptive processing (depending on the interoceptive state). Many in this class of therapies involve consciously slowing breathing [101], a physiological alteration which experimental work suggests induces an autonomic state that reduces negative affect [23] and increases insula activation during exposure to positive affective stimuli [22] – this contrasts with fast breathing, which increases neural activation during negative image viewing. Mindfulness-based treatments increase activity in the insula during focused respiration [102], while attenuating insula responses to aversive interoceptive experience (aversive breathing load) [103]. While long-term meditation practices and short-term mindfulness interventions are not necessarily associated with enhanced interoceptive accuracy in the cardiac domain [104,105], targeted interoceptive training has been shown to both increase interoceptive accuracy and be an effective intervention for reducing anxiety in an autistic population [106].

Concluding remarks

Together, emerging results across a variety of neuropsychiatric conditions suggest that a 'healthy' interoceptive profile is one with varied and adaptive afferent signals that are perceived with precision, to aid regulation when necessary [80,106]. In a healthy state, integrated signals from body-to-brain can be modulated by attention; this pattern suggests an attentional focus that is on the external world which adaptively and temporarily reorientates to the body when necessary [107–110]. Crucially, bodily attributions should be noncatastrophic [111], and beliefs and predictions about the body should be aligned to the nature of bodily signals [112]. Future research is needed to determine whether these principles hold for all neuropsychiatric conditions, and to devise ways to optimise targeted interoceptive interventions in different conditions, for different individuals.

Interventions that target interoceptive mechanisms may be pivotal for the efficacious treatment of clinical conditions, highlighting a possible central role of interoception in mental health. Interoception across different timescales and levels can shape emotion processing. Empirical research converges to suggest that clinical conditions characterised by emotion disturbance, such as anxiety and depression, are associated with altered interoception. Immunological changes are also evident in a range of physical and mental health conditions, such as fatigue, schizophrenia, and depression. A renewed focus on the body, and interoception specifically, as a treatment mechanism for mental health could be transformative: capacity to alter specific aspects of interoceptive processing may be key for underpinning treatment efficacy. Many existing pharmacological and psychological interventions for mental health conditions alter interoceptive processing, as do treatments for physical health with serendipitous effects on mental health. Recent work has outlined the clinical potential of medications or psychological therapies developed to target interoception directly. However, to benefit from the ability of existing and novel treatments to target interoception, an improved understanding of how a given treatment works is needed. This requires **back-translation** to illuminate the mechanisms of existing treatments, and the incorporation of interoceptive measures into clinical trials for novel treatments. To be comprehensive, such measures need to probe different interoceptive axes (e.g., gastric, respiratory, cardiac) across different neural, behavioural, and subjective levels (see Outstanding questions).

Progress in the treatment of mental health will also rely on nuanced approaches based on individual differences; specific interoceptive changes are unlikely to underpin clinical symptoms in all patients, and some individuals might find interoception-targeting interventions unhelpful or even detrimental. In addition to an improved understanding of disorder-specific changes in interoception, the field

Outstanding questions

To what extent do existing pharmacological and psychological therapies for mental health conditions act via interoceptive mechanisms? This question necessitates back-translational work, from therapy to mechanism, investigating putative interoceptive targets of different therapeutic approaches.

How can cause and effect be distinguished for interoception and mental health? This question can be approached via forward-translation: augmenting interoceptive mechanisms directly in the context of novel or augmentative treatments, potentially combining existing psychological therapies with targeted interoceptive interventions, using either behavioural or neural strategies to alter interoception.

How should we measure dimensions of interoception across different bodily axes? Interoception can span different levels (neural representation of afferent signals, interoceptive accuracy, insight, and subjective report measures) in different bodily axes (e.g., cardiac, respiratory, gastric). This is an essential first step to characterising shifts in interoception associated with better or worse mental health, but optimised tests to assess different dimensions across a range of bodily axes are needed to identify generalised and specific alterations in different clinical groups and their treatment with existing or putative interventions.

To what degree do different dimensions of interoception in different bodily axes map on to diagnostic categories, and to what degree do they represent transdiagnostic processes in mental health conditions?

Are novel interventions designed to target interoceptive mechanisms efficacious for the treatment of different mental health disorders? Approaches including pharmacological, psychological, and somatic treatments have the capacity to target interoceptive processes. Future work should delineate patients most likely to benefit from interoceptive-targeting treatments in a precision medicine framework.

requires a better understanding of heterogeneity within disorders and common transdiagnostic mechanisms across disorders. Interoceptive alterations are likely to be heterogeneous between and even within disorders; an ideal interoceptive treatment would be targeted towards patients showing particular interoceptive disruptions. For example, only those patients with disrupted autonomic regulation (irrespective of clinical diagnosis) would receive autonomic training, such as biofeedback. Augmented and combination therapies should take a similar approach, adding an interoceptive modulation (whether pharmacological, behavioural, or somatic) to poor or non-responders to existing therapies. This could eventually enable a precision medicine approach, targeting treatment towards patients with particular interoceptive disturbances.

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Declaration of interests

No interests are declared.

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