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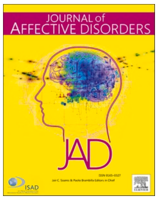

Common threads: Altered interoceptive processes across affective and anxiety disorders

Martina Saltafossi [a,b], Detlef Heck [c,d], Daniel S. Kluger [a,b,1], Somogy Varga [e,*,1]

[a] Institute for Biomagnetism and Biosignal Analysis, University of Münster, Münster, Germany
[b] Otto Creutzfeldt Center for Cognitive and Behavioral Neuroscience, University of Münster, Münster, Germany
[c] Department of Biomedical Sciences, University of Minnesota Medical School, Duluth, MN, USA
[d] Center for Cerebellar Network Structure and Function in Health and Disease, University of Minnesota, Duluth, MN, USA
[e] Department of Philosophy, Aarhus University, Aarhus, Denmark

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ABSTRACT

There is growing attention towards atypical brain-body interactions and interoceptive processes and their potential role in psychiatric conditions, including affective and anxiety disorders. This paper aims to synthesize recent developments in this field. We present emerging explanatory models and focus on brain-body coupling and modulations of the underlying neurocircuitry that support the concept of a continuum of affective disorders. Grounded in theoretical frameworks like peripheral theories of emotion and predictive processing, we propose that altered interoceptive processes might represent *transdiagnostic* mechanisms that confer common vulnerability traits across multiple disorders. A deeper understanding of the interplay between bodily states and neural processing is essential for a holistic conceptualization of mental disorders.

1. Introduction

While the Diagnostic and Statistical Manual of Mental Disorders (DSM) taxonomic system has notably enhanced communication and diagnostic reliability (Dalgleish et al., 2020), it faces criticism for its reliance on symptom clusters that are presumed to delineate distinct disorders (Blashfield et al., 2014). This is particularly evident in affective and anxiety disorders, where, in part due to widespread comorbidities, some have argued for a reevaluation of traditional diagnostic boundaries towards a broader characterization (Brown and Barlow, 1992; Brown et al., 2001; Kessler et al., 1996; Saha et al., 2021). There is increasing acknowledgment that symptoms often align more accurately along continuous dimensions (Brown et al., 2001; Dalgleish et al., 2020), and that diagnostic categories may not predict treatment responses or accurately capture underlying dysfunctional mechanisms (Insel, 2014; Insel et al., 2010).

This new perspective aligns well with research focused on identifying subsystemic contributions to psychiatric disorders that transcend traditional diagnostic categories. A prime example is emerging research showing how altered interoceptive processes, through which the body's nervous system senses and interprets internal physiological states, are implicated in psychiatric disorders. While interoceptive correlates of mental disorders were traditionally considered within specific diagnostic categories (see e.g., Harshaw, 2015 for depression), recent approaches indicate they might represent *transdiagnostic mechanisms* that confer common vulnerability traits across multiple disorders (Khalsa et al., 2018; Nord and Garfinkel, 2022; Nord et al., 2021). Moreover, the growing interest in interoceptive processes is driven by the potential to manipulate interoceptive channels for therapeutic purposes (Schoeller et al., 2024).

In line with such an overall approach, this paper focuses on affective and anxiety disorders and sets out three objectives. First, it synthesizes findings from neuroscientific and behavioral studies on interoceptive processes implicated in psychiatric conditions. Second, using the theoretical framework of predictive processing, we propose a model that explains how altered interoceptive processes may contribute to the development and maintenance of these disorders. Third, we explore how alterations in interoceptive processes connect clinical manifestations and underscore the potential of interoception-based interventions that aim to recalibrate the perception and interpretation of interoceptive signals. Overall, this paper contributes to a growing literature on how altered interoceptive processes can function as transdiagnostic

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[*] Corresponding author at: Jens C. Skousvej 7, 8000 Aarhus, Denmark.
E-mail address: varga@cas.au.dk (S. Varga).
[1] Equal contribution.

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mechanisms. By focusing on shared processes across different disorders rather than specific conditions, we aim to challenge traditional diagnostic boundaries and highlight new therapeutic possibilities.

2. Interoception, emotional processing, and cognition

Recent research has increasingly focused on how interoceptive signals from within the body – such as rhythmic signals from cardiac and respiratory activities – continuously modulate brain processes. New findings have shown that their role extends beyond helping maintain homeostasis, bodily awareness, and influencing emotional and physiological responses. A rapidly growing body of evidence suggests a profound impact of these signals on cognition and emotion (Azzalini et al., 2019; Engelen et al., 2023; Parviainen et al., 2022). While various interoceptive signals may exert similar influences, the following discussion provides a brief overview of some key findings related to signals from cardiac and respiratory activities.

First, interoceptive signals from cardiac rhythms are not just indicators of physical states but seem important to the neural processing of emotionally valenced stimuli (Fig. 1). Results indicate that while systole – the contraction phase of the cardiac cycle – dampens perception of neutral sensory inputs (Al et al., 2020; Birren et al., 1963; Grund et al., 2022; Saltafossi et al., 2023; Sandman et al., 1977), it also amplifies threat processing, e.g. enhancing detection of fearful stimuli (Garfinkel et al., 2014). This is most likely related to the neural encoding of arterial baroreceptor bursts, which propagate from the receiving brain stem nuclei to sensorimotor and cognitive brain areas through extensive thalamocortical networks (Lacey and Lacey, 1978, 1958; Skora et al., 2022). During states of heightened cardiovascular arousal, such as those induced by emotional stress, increased blood pressure and heart rate are thought to facilitate reactions to threatening stimuli by mobilizing a fight or flight-like response (Critchley and Garfinkel, 2017; Garfinkel and Critchley, 2016; Garfinkel et al., 2014). The ability to sense one's own heartbeats is also the basis for measuring interoceptive sensitivity (Garfinkel et al., 2015). This sensitivity is closely linked to emotional experience, suggesting that individuals who accurately detect their bodily states may experience emotions more intensely (Pollatos et al., 2005). Further research is needed to determine whether such heightened sensitivity also correlates with a greater influence of interoceptive inputs on brain activity. However, this appears likely: for example, in individuals with MDD or anxiety, enhanced interoceptive sensitivity may intensify feelings of anxiety or deepen depressive moods, potentially worsening cognitive biases such as the processing of fear cues and negative memory recall. This would suggest a substantial impact of interoceptive signals on brain activity related to cognitive processing.

Second, somewhat similar to the influences of cardiac rhythms, it is widely recognized that interoceptive signals from respiration also entrain large-scale brain dynamics and neural signaling. This occurs through multiple mechanisms and pathways with respiration-locked olfactory bulb activity as the main driving force among respiration-coupled sensory inputs (Ito et al., 2014). Sensory pathways carrying respiration-locked activity play a major role in effectively synchronizing brain activity with breathing (Allen et al., 2023; De Falco et al., 2024; Heck et al., 2016; Ito et al., 2014; Karalis and Sirota, 2022; Kluger and Gross, 2021, 2020; Kluger et al., 2023; Tort et al., 2018). However, there are also direct influences from brain stem respiratory pattern-generating nuclei to brain areas linked to arousal and emotion and vice versa. For example, Liu and colleagues recently showed that opioid-receptor expressing neurons in the lateral parabrachial nucleus have direct projections to the amygdala and the preBötzinger complex and are crucial for linking breathing with pain perception and anxiety (Liu et al., 2022). Another study by Yackle and colleagues showed a direct influence of respiratory brain stem pattern-generating neurons in the preBötzinger complex on arousal via direct projections to noradrenergic neurons in the locus coeruleus (Yackle et al., 2017). While this review focuses on the role of interoception, direct intrinsic interactions between brain areas controlling respiratory rhythm, arousal and emotions are likely significant contributors to coupling breathing with arousal and emotion albeit via very different neuronal mechanisms that do not depend on interoception.

Relatedly, cognitive, sensory, and motor-related functions are coupled to the respiratory rhythm (Arshamian et al., 2018; Brændholt et al., 2024; Grund et al., 2022; Heck and Varga, 2023; Heck et al., 2022; Johannknecht and Kayser, 2022; Kluger et al., 2021; Park et al., 2020; Perl et al., 2019; Varga and Heck, 2017). In the same vein, respiration is closely linked to the limbic system and corresponding affective processing, influencing the processing of emotionally valenced stimuli (Fontanini and Bower, 2006; Heck et al., 2022; Zelano et al., 2016). For

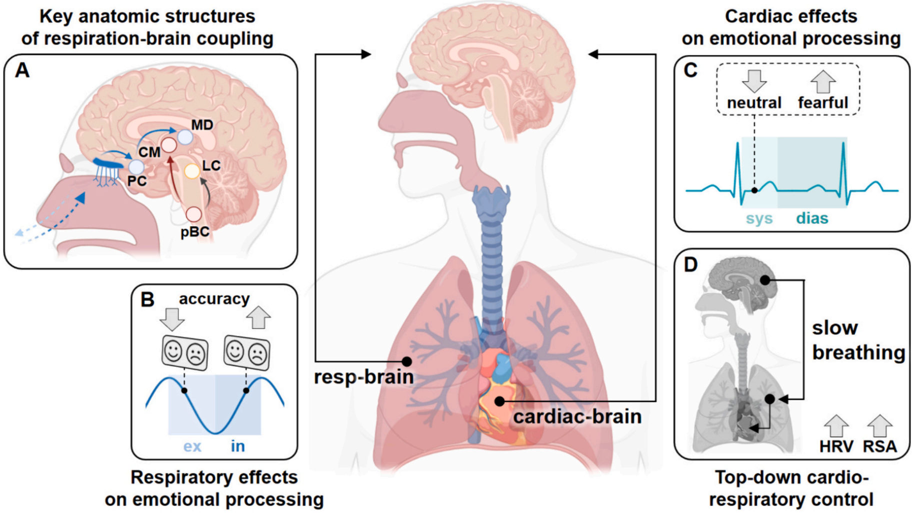

Fig. 1. Cardiorespiratory coupling to brain function and behaviour. **A,** During nasal respiration, airflow stimulates mechanoreceptors linked to the olfactory bulb, generating slow oscillations that influence the piriform cortex (PC), mediodorsal thalamus (MD), and cortical areas through phase-amplitude coupling. Meanwhile, respiratory pattern generators in the brainstem (preBötzinger complex, pBC) project to cortical areas via the centromedial thalamus (CM) and locus coeruleus (LC), a critical modulator of arousal. Adapted from Kluger et al. (2024b). **B,** Behavioral evidence suggests that respiratory phase impacts emotional processing, with inspiration enhancing performance accuracy. **C,** A similar phase dependency for emotional processing exists in the cardiac cycle: Systole boosts detection of fearful faces. **D,** The respiratory rhythm is coupled with the cardiac rhythm through respiratory sinus arrhythmia (RSA), where the heart rate increases during inspiration. Consequently, slow breathing techniques can enhance heart rate variability (HRV), promoting a parasympathetic state and relaxation.

example, in a seminal study by Zelano et al. (2016), participants identified fearful faces more quickly during nasal inspiration than expiration. Correspondingly, since respiration is under volitional control (Herrero et al., 2018; McKay et al., 2003), the influence can also be reciprocal. Herrero et al. (2018) showed that successfully focusing on each breath as is commonly practiced in traditional meditation or anxiolytic breathing exercises, enhances the influence of breathing on neuronal activity (see also Fincham et al., 2023). By consciously focusing on and regulating their breathing patterns, individuals can effectively modulate their emotional state (Arch and Craske, 2006; Doll et al., 2016). Linking both cardiac and respiratory effects outlined above, slow breathing techniques can promote autonomic changes, specifically through increased heart rate variability (HRV) and respiratory sinus arrhythmia (RSA; Berntson et al., 1993; Zaccaro et al., 2018). These changes ultimately result in reductions of heat pain intensity, unpleasantness, and negative affect ratings (Strigo and Craig, 2016; Zautra et al., 2010). In contrast, upregulation of the breathing rate leads to shifts towards sympathovagal dominance, thereby exacerbating negative emotions (Strigo and Craig, 2016).

This brief overview of signals from cardiac and respiratory activities indicates that they play an active role in shaping emotions and cognition through modulation of underlying brain networks (Feldman et al., 2024). Historically, this notion has its roots in *peripheral theories* of emotion, which claim a profound intertwining of the salience of bodily states and emotions generation (Barrett, 2006a, 2006b; Nord and Garfinkel, 2022). The influential James-Lange theory postulates that feelings arise directly from the perception of rather heterogeneous sets of bodily symptoms, with emotion resulting from awareness of physiological arousal (James, 1884; Lange and James, 1922). Similarly, *appraisal theories* incorporate the context and categorization of these visceral-based emotional states, suggesting that cognitive processes also play a crucial role in shaping our emotional experiences (Schachter and Singer, 1962). Despite the diverse perspectives offered by different approaches, contemporary neuroimaging studies converge on the shared neural underpinnings of interoception and emotion (Craig, 2002; Strigo and Craig, 2016; Tsakiris and De Preester, 2018). The insular cortex in particular appears to be consistently involved in this crosstalk (Adolfi et al., 2017; Tsakiris and Critchley, 2016). The posterior section of the insula relays visceral and nociceptive information via inputs from the thalamus and bidirectional connections with the primary somatosensory cortex (Quadt et al., 2018). The anterior insula is involved in representing and integrating interoceptive signals with exteroceptive, motivational, and emotional information (Critchley et al., 2004, 2002; Damasio et al., 2000). This integration is facilitated by the anterior insula's connections with the posterior insula and the anterior cingulate cortex, forming a network with the amygdala and ventromedial/orbitofrontal cortex (Quadt et al., 2018).

3. Interoception, anxiety, and affective disorders

Alterations within this interoceptive brain network are increasingly linked to psychiatric disorders in the literature (Barrett and Simmons, 2015; Barrett et al., 2016). Collectively, these findings across a wide variety of psychiatric disorders may be taken to challenge the DSM's nosological boundaries underlying clinical diagnoses today. Instead, the universality of peripheral involvement in psychiatric conditions and the well-established neural circuits underlying (dys-)functional brain-body coupling suggest that aberrant interoceptive processing might be a transdiagnostic mechanism and a useful marker of psychiatric conditions (Critchley et al., 2019; Dalgleish et al., 2020; Nord et al., 2021; Tumati et al., 2021). In line with our overall focus on signals from cardiac and respiratory activities, the following discussion provides a brief overview of key findings related to these areas.

First, recent work on MDD clarifies the role of interoceptive signals from cardiac activity in disorders. Studies assessing interoceptive accuracy in MDD report atypical insular activity during heartbeat perception tasks and find that difficulties in decision-making are associated with reduced interoceptive accuracy (Eggart et al., 2019). While attending to their own heartbeats, patients with MDD exhibited decreased hemodynamic activity within multiple hubs of the interoceptive circuitry (dorsal mid-insula cortex, orbitofrontal cortex, and amygdala; Fig. 2A) compared to healthy controls, with insular responses correlating negatively with symptom severity (Avery et al., 2014). Conversely, a positive relationship between subjective symptoms and both accuracy of interoceptive perception and mean activity in the right anterior insula/opercular cortex was evident for individuals experiencing anxiety (Critchley et al., 2004; Fig. 2B). Causal evidence supporting the role of the insular cortex is provided by Hsueh et al. (2023), who demonstrated that optogenetic inhibition of the posterior insular cortex attenuates anxiety-like behaviors in mice. These behaviors were induced by optical cardiac pacing in a risky context. In humans, a comprehensive meta-analysis by Nord et al. (2021) reported convergent alterations of neural activity in the left dorsal mid-insula during various interoceptive probes (i.e., both top-down interoceptive attention to specific organ systems and bottom-up perturbation of bodily signals) across patients not only with MDD, but also with bipolar disorder, anxiety, anorexia, and schizophrenia.

Second, recent work on anxiety underscores the role of interoceptive signals from respiratory activity in psychiatric disorders. Given the high subjective salience of respiratory changes, one method to investigate pathological interoceptive alterations involves experimentally inducing resistive loads during inspiration. These loads are hypothesized to elicit interoceptive threat, especially in individuals suffering from anxiety and panic disorder (Alius et al., 2013; Chan et al., 2012; von Leupoldt et al., 2011). Electrophysiological evidence from inspiratory occlusion paradigms shows that high anxiety levels are associated with attenuated respiratory sensory gating as indexed by greater magnitudes of the respiratory-related evoked potential (RREP) components and their oscillatory counterpart (Chan et al., 2015, 2014, 2012; Liang et al., 2024; von Leupoldt et al., 2011; Fig. 2B). In other words, individuals with anxiety cannot filter out redundant respiratory stimuli, which results in sensory flooding and cognitive overload (Liang et al., 2024). Parallel structural and functional magnetic resonance imaging (MRI/fMRI) studies offer some further evidence that negative emotions in psychiatric conditions partially arise from distorted respiratory interoception (Nikolova et al., 2024; Harrison et al., 2021; Jelinčić and von Leupoldt, 2021). Showing that the neural correlates of respiroception map onto key interoceptive structures, Nikolova et al. (2024) found that distinct cortical microstructure patterns in the insular, cingulate, and primary sensory cortices correlate with perceptual sensitivity and precision in detecting inspiratory loads, while affective responses to these loads were associated with the primary somatosensory cortex myeloarchitecture.

Clearly, the preliminary evidence linking interoceptive signals to psychiatric disorders requires further validation within a robust theoretical framework of brain function. Advanced explanatory models such as predictive processing are now being expanded to integrate interoceptive processes more comprehensively. In the ensuing section, we will delineate some fundamental components of predictive processing frameworks and explore their application in interpreting the emerging evidence on interoceptive contributions to psychiatric disorders.

4. Interoception and mental disorder: the predictive processing framework

Interoception research has significantly benefited from computational modelling. Predictive processing accounts (Friston, 2018; Rao and Ballard, 1999) rank among the most influential frameworks of brain function and continue to provide the theoretical backdrop for interactions between brain and periphery. In short, neural computation is cast as the bidirectional processing of top-down probabilistic predictions (e.g. of brain or bodily states) and bottom-up prediction errors (i.e. the

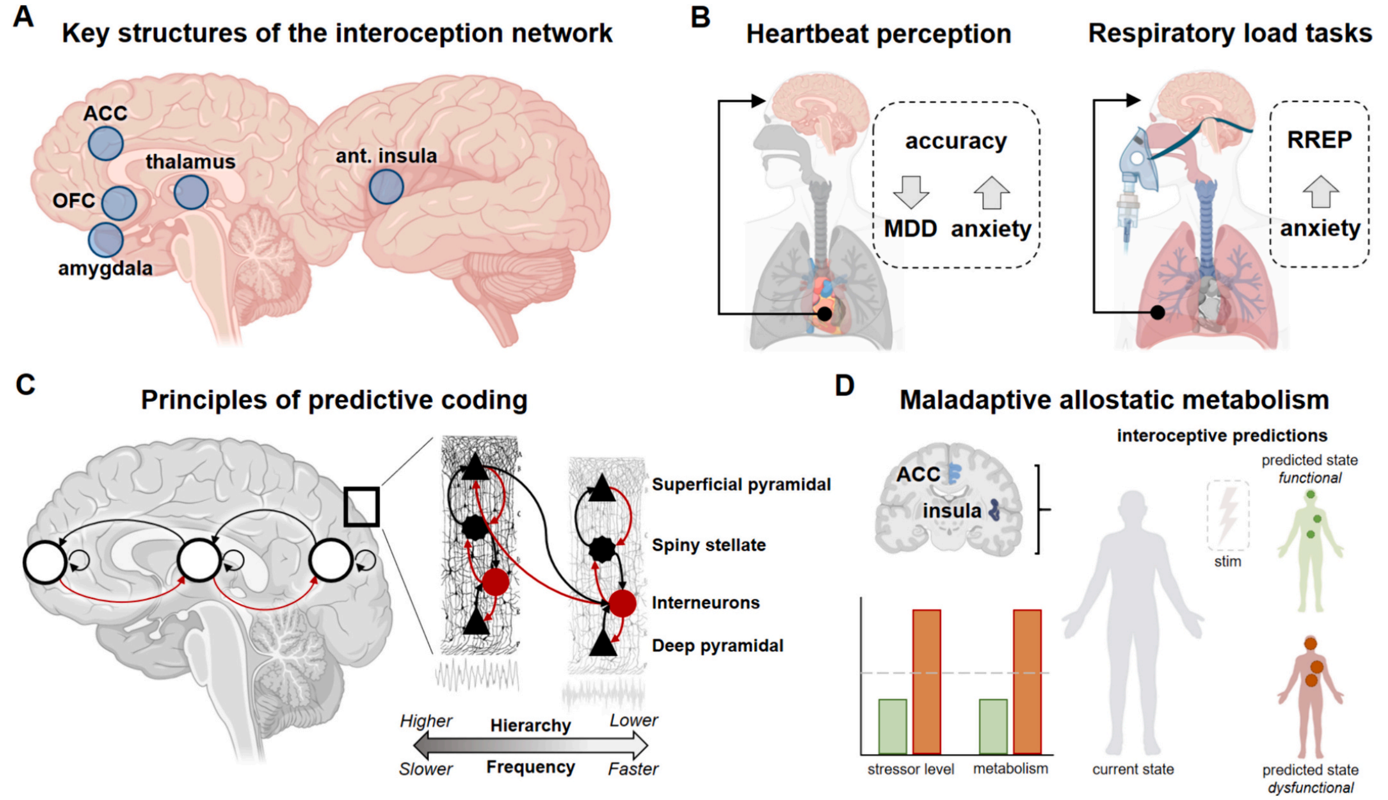

Fig. 2. Predictive accounts of interoception. **A,** Among the key hubs of the interoception brain network are the anterior cingulate cortex (ACC), orbitofrontal cortex (OFC), amygdala, thalamus, and anterior insula. The predictive processing model of interoception integrates these structures, mapping them onto second-order processes such as conscious perception and metacognitive control of lower-level sensory information. **B,** Dysfunctional brain-body coupling manifests in affective disorders as decreased interoceptive sensitivity in heartbeat perception tasks among patients with major depressive disorder (MDD), while patients with anxiety disorders exhibit heightened responsiveness to heartbeats and inspiratory loads (measured as the respiratory-related evoked potential, RREP). **C,** Schematic hierarchical architecture of neural oscillations within the predictive coding framework. Feed-forward predictions shown in red, feed-back prediction errors in red. Within individual canonical microcircuits (right), specific cell populations encode predictions (deep pyramidal cells), prediction errors (superficial pyramidal cells), or precision (inhibitory interneurons). These units form a natural predictive hierarchy with prediction error cells driving successively faster rhythms as one ascends the hierarchy. Adapted from Brændholt et al. (2023). **D,** Aberrations in ACC and insular cortex activity contribute to dysfunctional interoceptive predictions. Everyday stimuli are perceived as stressors, which leads to predictions of upregulated physiological responses and a long-term metabolism increase within ACC/insula. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

extent to which actual sensorimotor perception matches these predictions; Fig. 2C). Specifically, brain-body applications of predictive processing (Ainley et al., 2016; Seth, 2013) offer a theoretical framework to explore the potential role of altered interoceptive processes in psychiatric disorders.

Because breathing rhythm is uniquely under conscious voluntary control, respiratory predictive processing has received special attention (Allen et al., 2023; Corcoran et al., 2018; Faull et al., 2017). The integration of rhythmic and homeostasis-related information, along with the relative saliency of the breathing signal, enables the brain to predict respiratory states with high precision and to easily recognize disturbances (as in the respiratory load experiments mentioned above). The concept of *active sensing* (Schroeder et al., 2010) views the respiratory rhythm as a means to actively coordinate the timing of sensory information sampling with ongoing internal brain and body dynamics.

Based on such a theoretical framework, we and others have previously suggested that dysfunctional alterations of respiration-brain coupling – as conceptualized by predictive processing frameworks – may play a critical role in both the development and the course of psychiatric disorders. For example, affective disorders like MDD (Zamoscik et al., 2018) and anxiety (Grassi et al., 2013) have been characterized by long-term changes of respiratory patterns, with hyperventilation during acute panic attacks being a particularly prominent example (Goodwin et al., 2002). On the neural level, these alterations coincide with distinctive changes in brain activity within the interoceptive network outlined in the previous sections. Predictive processing accounts provide a joint explanatory model of how dysfunctional interoception may contribute to disorders. For example, in anxiety, altered respiratory rhythms could increase the frequency of feed-forward neural oscillations carrying visceral expectations (i.e., predictions about interoceptive signals). Evidence showing aberrant alpha oscillations patterns, may reflect this bias towards priors (Brændholt et al., 2023; Eidelman-Rothman et al., 2016; Fig. 2C). Increasingly strong prediction errors will eventually require a shift in prior expectations to minimize prediction errors. The incorrect inference ‘there must be an external threat causing my faster breathing’ leads to an allostatic shift, where the body's regulatory processes and physiological responses designed to deal with danger adjust to cope with this mistakenly perceived threat. Over time, the allostatic shift might contribute to the agent's increasing endorsement of negative expectations (Hakamata et al., 2010), and, if breathing becomes more and more aberrant, this feedback loop will result in a surge of arousal and negative emotions (see Brændholt et al., 2023).

Within the predictive processing framework, Paulus et al. (2019) developed two main hypotheses about how altered interoceptive processes contribute to both anxiety and mood disorders. First, they identify *hyperprecise priors* (i.e., exceedingly strong expectations about situations that elicit bodily changes) as one key alteration of interoception in psychiatric disorders. Second, they propose that *context rigidity* (i.e., difficulties adjusting these prior expectations in the face of changes within the internal or external environment) might contribute to the persistent occurrence of somatic prediction errors. Under normal circumstances, homeostatic balance is restored by adjusting expectations or engaging in regulatory actions that align the physiological state with interoceptive expectations. However, in non-adaptive individuals, prolongation of somatic error could eventually lead to a turbulent reference state (Paulus and Stein, 2010, 2006), dysfunctional learning about bodily states over time (Van den Bergh et al., 2017), and ultimately psychophysiological alterations (Santamaría-García et al., 2024).

These allostatic shifts manifest in various ways (see Ibanez and Northoff, 2024). Hallmarks of anxiety disorders are exaggerated fear, apprehension, and worry accompanied by somatic symptoms including fatigue, irritability, sleep disturbance, racing heart rate, shortness of breath, and hyperventilation (Tumati et al., 2021; Klein and Klein, 1988). A critical component of these disorders is the misinterpretation of bodily states (Paulus and Stein, 2010; Santamaría-García et al., 2024). For instance, in patients with panic disorder, negative feelings associated with respiratory sensations become conditioned interoceptive cues (Bouton et al., 2001; Maisto et al., 2021), causing severe panic attacks in response to ventilatory stimulants like increased CO_2 concentration (Nardi et al., 2009). This heightened response reflects the brain's maladaptive attempt to adapt internal states to external demands, a process that has been linked to dysfunction in the anterior insula and anterior cingulate cortex (ACC) (Paulus and Stein, 2006, 2010). According to the *embodied predictive interoception coding* (EPIC) model proposed by Barrett and Simmons (2015), these regions are responsible for encoding interoceptive predictions and integrating prediction errors (Barrett and Simmons, 2015; Barrett et al., 2016; Petzschner et al., 2021; Seth, 2013; Paulus et al., 2019; Fig. 2D). Fittingly, neurobiological changes following allostatic overload particularly affect limbic-interoceptive structures, including the amygdala (Lenart-Bugla et al., 2022; Santamaría-García et al., 2024). Recent research has recognized the amygdala's pivotal role in the *Apnea-induced Anxiety* model (AiA; Feinstein et al., 2022; Ritz, 2022). This model predicts that apneic episodes, and thus fear and avoidance behaviors, are triggered by amygdala-driven inhibition of brainstem respiratory centers (Feinstein et al., 2022). Additionally, threat valence regarding the expectation of breathing resistance scales more strongly with anterior insula deactivation in individuals with low trait anxiety (compared to high trait anxiety; Harrison et al., 2021).

These findings not only speak to a crucial continuum between health and disease states, but also align with previous research showing anterior cingulate cortex activation during anticipation of inspiratory loads and breathlessness (Stoeckel et al., 2018). Consequently, from this perspective, one potential factor underlying a continuum of affective disorders is the failure to update models of body states, as indicated by altered activation patterns in visceromotor regions. Critically, in MDD, these aberrant interoceptive predictions lead to a chronically hyperactive metabolism in structures like the anterior insula and the ACC, based on the pathological perception of everyday events as stressors whose demands must be met by the organism in order to maintain homeostasis (Barrett and Simmons, 2015).

Another mechanism proposed for the case of MDD is a relative insensitivity to prediction errors which contributes to a 'locked-in' brain state where outdated models and predictions are not updated, perpetuating a cycle of negative expectations (Barrett et al., 2016; for a review, see Gilbert et al., 2022). Resulting allostatic change manifests as inefficient energy regulation, characterized by a combination of the above-mentioned hyperactive and attenuated sympathetic responses, fatigue, insensitivity to context and reward, motor retardation, and related persistent negative affect (Arnaldo et al., 2022; Barrett et al., 2016; Lamers et al., 2013; Nemeroff and Goldschmidt-Clermont, 2012; Paulus et al., 2019; Santamaría-García et al., 2024; Ibanez and Northoff, 2024). These symptoms are not merely due to metabolic imbalances in isolated brain structures like the amygdala (Ottowitz et al., 2002), anterior cingulate cortex, and insula (Avery et al., 2014; Barrett et al., 2016; Drevets et al., 1997; Dunlop et al., 2015; Mayberg et al., 1999); rather, they reflect a broader dysfunction (Ibanez and Northoff, 2024; Shaffer et al., 2022; Northoff and Hirjak, 2024). Context insensitivity and rumination, among others, may be understood as an overemphasis on bodily states at the expense of external information, a pattern reflected in altered intra- and inter-connectivity within the default mode (DMN) and salience networks (SN) (Shaffer et al., 2022).

In the case of bipolar disorder, disturbances within fronto-limbic circuits are also a key characteristic, likely affecting all levels of the interoceptive hierarchy (Perry et al., 2019). In particular, dysfunctions involving higher levels might be responsible for producing maladaptive internal models with the inferior frontal gyrus encoding the precision of interoceptive beliefs leading some researchers to describe manic episodes as "psychosis of interoception" (Perry et al., 2019; Sherman et al., 2016). Moreover, similar to psychotic features like hallucinations or delusions, mania may be comprehended in terms of prediction biases stemming from a poorly calibrated precision weighting mechanism that erroneously defines exteroceptive stimuli as salient, rewarding, or threatening (Green et al., 2007; Jones et al., 2005; Perry et al., 2019).

In sum, the predictive processing framework provides a theoretical foundation for understanding the role of altered interoceptive processes in psychiatric conditions. Beyond theoretical insight, it is particularly crucial from a clinical standpoint to understand how these findings can be effectively used to improve patient outcomes. For this reason, in the remainder of this paper we will suggest a way forward along two main dimensions. First, as a methodological contribution, we will apply the recent proposal of *brain-body states* to the case of affective disorders. Second, we will provide a brief outlook on how interoception-focused interventions may help stabilize potentially aberrant interoceptive processes in psychiatric disorders.

5. Brain-body states and embodied precision neuroscience

One way in which the field of clinical neuroscience can enhance our understanding of psychiatric disorders is through the development of methods designed to identify contributing factors. A recently introduced framework of *brain-body states* suggests capturing whole-brain, whole-body dynamics (Kluger et al., 2024a; Fig. 3A). In short, this approach aims to describe health and disease states as a trajectory within a high-dimensional space of both internal (e.g. genetic predisposition, brain/body dynamics) and external factors (e.g. environment, training). Both internal and external variables can be considered at arbitrary complexity, so that the observed space is of such high dimensionality that a meaningful analysis in its entirety becomes impossible. Methodological advances in the realm of dimensionality reduction and feature selection (Schneider et al., 2023), however, can be exploited to reduce data complexity down to a tractable subspace of lower dimensionality. This is possible because not all dimensions carry meaningful information (Ponce-Alvarez et al., 2020), and the main challenge lies in the identification of a constrained set of dimensions which are actually informative with regard to the question at hand. Emerging computational algorithms like representation learning or Hidden Markov Modelling can be used to extract low-dimensional representations (so-called "manifolds"; Gao et al., 2021). Following this dimensionality reduction, psychiatric diagnoses as well as subsequent therapeutic interventions can then be informed by selecting and interpreting meaningful individual features, independently of discrete criteria from diagnostic manuals.

For illustrative purposes, consider the case of a young man whose genetic predisposition for depression manifests as a trait of heightened stress sensitivity. This trait makes him particularly vulnerable to experiencing intense stress responses to any traumatic life events, such as personal losses, professional setbacks, or serious health issues. Both external factors (e.g., socioeconomic instability, limited access to healthcare, and a lack of social support) and internal factors (hormonal imbalances, cognitive style, nutritional deficiencies) might exacerbate

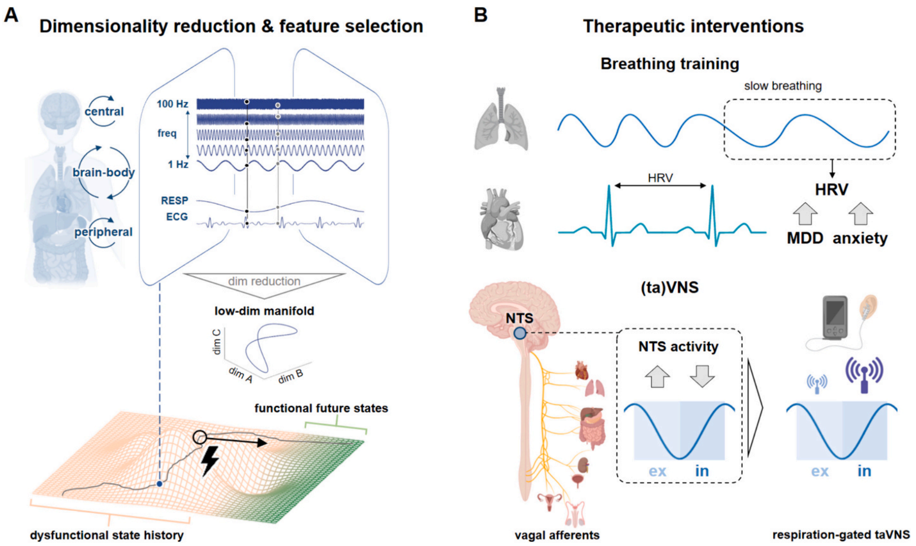

Fig. 3. Use of high-dimensional data for therapeutic interventions. **A,** Multimodal signals from brain and body dynamically interact on various timescales, which we can characterize as transient *brain-body states*. With algorithms like Hidden Markov Modelling (HMM) or supervised learning techniques, these high-dimensional data can be reduced to a subspace (*manifold*) of observable states. As some of these states can be experienced as pathological or dysfunctional, therapeutic interventions can help drive the individual trajectory towards functional future states. Adapted from Kluger et al. (2024a). **B,** Due to the direct cardio-respiratory link through RSA and HRV, breathing training (e.g. slow breathing) can be used to increase HRV in MDD and anxiety patients. Non-invasive vagus nerve stimulation targets the auricular branch of the vagus nerve, a key pathway for afferents from multiple organ systems. A central role in processing these inputs in the brain is ascribed to the nucleus of the solitary tract (NTS) whose activity systematically waxes and wanes during inspiration and expiration, respectively. Respiration-gated taVNS with increased stimulation strength during inspiratory phases holds great potential for therapeutic interventions.

these responses. Heightened stress sensitivity is likely to impact most of his organ systems, including the nervous, cardiorespiratory, and immune systems, triggering alterations in interoceptive processes, which, in turn, further destabilizes his emotional state and exacerbates his psychological distress. Furthermore, disruptions in the sequence of sleep stages are likely to affect synaptic plasticity processes, setting him on a trajectory towards a more persistent depressive state. This cycle may intensify his susceptibility to depressive episodes, illustrating a complex interplay between traits, environmental stressors, cognitive styles, and interoception.

Along with findings cited in previous sections, this framework underscores the role of interoception not only as the endpoint of physiological states, but also as a contributing factor and means to intervene into brain-body dynamics. This ‘active’ role of interoception is a core assumption of many therapeutic approaches, which we will briefly introduce in the final section.

6. Therapeutic implications

Acknowledging the transdiagnostic significance of interoceptive alterations, there has been a surge of interest in exploring targeted interoceptive therapeutic interventions (Heim et al., 2023; Jenkinson et al., 2024; Khalsa et al., 2018; Schoeller et al., 2024; Weng et al., 2021). Brain-body dynamics and inferential processes can indeed be experimentally manipulated in various ways in order to induce affective, cognitive, and behavioral changes. A recent review has extensively outlined current interoceptive techniques suited to achieve such therapeutic effects (Schoeller et al., 2024). By operating at various levels of the interoceptive hierarchy, some of these techniques aim to restore adaptive precision control. While respiration offers a unique way to alter precision weighting through active inference (Allen et al., 2023; Boyadzhieva and Kayhan, 2021), some interoception-based treatment protocols intervene on cardiorespiratory rhythms, thereby inducing negative feelings. These controlled stimulations are assigned a low level in the hierarchy and have been termed *artificial sensations* (Schoeller et al., 2024).

For example, hyperventilation and hypocapnia can be used to induce panic attack-like episodes in both healthy and anxious patients (Roy-Byrne et al., 2006; Schoeller et al., 2024; Tural and Iosifescu, 2021; Van den Hout and Griez, 1984). Through repeated exposure to interoceptive cues (e.g. increased heart rate or heavy breathing) in an environment perceived as safe, patients are able to weaken the conditioned association between bodily symptoms and paired aversive emotional experience (Boettcher et al., 2016). Interoceptive exposure (IE) techniques are based on the principles of fear extinction and inhibitory learning, where conditioned stimuli form new competing associations in the absence of escape or avoidance (Boettcher et al., 2016; Craske et al., 2014, 2008). Although IE-based interventions have been traditionally applied for the treatment of panic disorder (Lee et al., 2006; Schmidt and Trakowski, 2004), post-traumatic stress disorder (PTSD; Wald and Taylor, 2008, 2007), and social anxiety disorders (Collimore and Asmundson, 2014; Dixon et al., 2015), targeting somatic symptoms in patients with MDD holds promise for enhancing coping strategies and reducing the risk of a bodily-driven spiral into negative mood states (Boettcher et al., 2016; Boswell et al., 2014). Alterations in the emotional feedback may disrupt the maladaptive attribution of precision (Schoeller et al., 2024).

A more engaging intervention is breathing retraining, which typically entails taking deep and regular breaths to lower the respiratory rate (Fig. 3B). Recently, this practice has been integrated into biofeedback protocols in which respiratory rate is adjusted online to reach an optimal frequency (<10 breaths per minute) using exteroceptive cues (Sharma et al., 2011; Weng et al., 2021). Slow breathing has a beneficial effect on sympathetic-parasympathetic balance in psychiatric conditions (French et al., 2024; Sevoz-Couche and Laborde, 2022; Zaccaro et al., 2018). Notably, studies have documented increased HRV in patients with anxiety and MDD following this kind of therapy (French et al., 2024; Jester et al., 2019; Kikuchi et al., 2009; Lin et al., 2019; Tatschl et al., 2020). Interestingly, these psychophysiological adjustments can occur without the patients' awareness. According to Schoeller et al. (2024), *interoceptive illusions*, in which interoceptive or exteroceptive cues modify top-down predictions (Iodice et al., 2019; Parrotta et al., 2023; Pezzulo et al., 2018), potentially synchronizing with peripheral signals (Ferrer and Helm, 2013), can entrain bodily rhythms. An example employing a virtual reality paradigm demonstrated that participants visually exposed to an avatar body, whose breathing pattern was systematically manipulated, resolved the visuo-interoceptive conflict by adjusting their respiration rate (Czub and Kowal, 2019).

Interventions on the parasympathetic branch can be effectively enhanced through neuromodulation techniques. Vagus nerve stimulation (VNS) specifically targets the key communication channel connecting the periphery with the brain. The vast majority of vagal fibers are afferents and carry interoceptive information up to the brainstem enabling the regulation of the cardio-respiratory function (Thayer et al., 2011; Weng et al., 2021). A number of studies have established the efficacy of VNS in treating mood disorders, particularly benefiting patients with depression (Bottomley et al., 2019; Nemeroff et al., 2006; Rush et al., 2000; Sackeim et al., 2001). While traditional VNS requires surgical implantation of an electric device near the nerve fibers in the chest (Giordano et al., 2017), non-invasive brain stimulation offers a safer and more accessible method for altering neural signaling in psychiatric conditions (Austelle et al., 2022). Transcutaneous auricular vagus nerve stimulation (taVNS) achieves therapeutic effects by targeting the somatosensory innervation of the outer ear via the auricular branch of the vagus nerve (Hilz, 2022). Similar to VNS targets (Conway et al., 2012; Nahas et al., 2007), non-invasive interventions have been shown to modulate multiple brain areas involved in the pathogenesis of mood disorders and to significantly improve clinical questionnaire scores (Liu et al., 2016; Rong et al., 2016; Fang et al., 2016). Although the precise mechanisms underlying vagal stimulation are not fully understood, the nucleus of the tractus solitarius (NTS) appears to play a central role. It receives inputs from the abdominal vagal nerve and both direct and indirect interoceptive signals from the respiratory system (Napadow et al., 2012). The NTS is influenced by convergent ascending signals from pulmonary stretch receptors and aortic baroreceptors, as well as descending input from medullary respiratory centers. Consequently, NTS activity is downregulated during inspiration and upregulated during expiration (Baekey et al., 2010; Miyazaki et al., 1999, 1998). This has led to growing interest in respiration-gated auricular vagal afferent nerve stimulation, a technique that leverages such expiratory-phase related optimization and has already demonstrated positive outcomes for chronic pelvic pain and migraine (Garcia et al., 2017; Napadow et al., 2012; Sclocco et al., 2019; Weng et al., 2021). However, its effects on affective disorders remain unexplored, and future research is needed to evaluate whether combination of different interventions might improve therapeutic effects (Szulczewski, 2022).

7. Conclusion

This paper has focused on affective and anxiety disorders, synthesizing emerging research that reveals how altered interoceptive processes—the body's nervous system's ability to sense and interpret internal physiological states—are implicated in psychiatric disorders. Building on the theoretical framework of predictive coding, the paper has explored how this model can explain the role of altered interoceptive processes in the development and maintenance of affective and anxiety disorders. These processes are proposed as transdiagnostic mechanisms that confer common vulnerability traits across various disorders, aligning with the recognition that dimensions of psychopathology transcend traditional nosological boundaries. Furthermore, the paper has examined how these alterations in interoceptive processes could amplify the potential of interoception-based interventions, presenting promising new directions for therapeutic strategies in mental health.

CRediT authorship contribution statement

Martina Saltafossi: Writing – review & editing, Writing – original draft, Conceptualization. **Detlef Heck:** Writing – review & editing, Writing – original draft, Conceptualization. **Daniel S. Kluger:** Writing – review & editing, Writing – original draft, Conceptualization. **Somogy Varga:** Writing – review & editing, Writing – original draft, Conceptualization.

Declaration of competing interest

There are no conflicts of interest.

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