**NourishED Research Foundation (NRFi)**

Stress, Interoception, & Binge Eating Disorder

**Brenna Bray, PhD**

**October, 2024**

[nourished@nourishedrfi.org](mailto:nourished@nourishedrfi.org) | 206-819-9647

1207 Delaware Ave, Wilmington, DE, 19806

1821 Walnut Street, Boulder, CO 80302

[www.nourishedrfi.org](http://www.nourishedrfi.org)

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Part I: Narrative Review

**Stress Regulation of Allostatic Load in Mental Health**

A Narrative Review of how the Glucocorticoid Stress System Regulates the Balance Between External & Internal Stress Load Capacity

**Brenna Bray, PhD1\***

**1**NourishED Research Foundation (NRFi), Boulder, CO, U.S.A. [www.nourishedrfi.org](http://www.nourishedrfi.org).

\*Corresponding Author: Brenna Bray, PhD, brenna@nourishedrfi.org

**Abstract**

This review explores how interoception and the interoceptive system (IS) are linked to adversity/trauma/stress and the hippocampal glucocorticoid stress system. We highlight the roles of glucocorticoid and mineralocorticoid stress receptors as critical interoceptive chemoreceptors and the role of the hippocampus as a critical brain region responsible for relaying, processing, and responding to interoceptive glucocorticoid and mineralocorticoid stress receptor signals and information. We also explore the ways in which adverse stress exposure can result in dysregulated stress and interoceptive signaling responses - with the hippocampus as a possible point of convergence - and how these dysregulations can enable stress to induce its negative impacts on a variety of adverse physical, mental, and behavioral health conditions, including substance use and eating disorders.

The hippocampus is a brain region with high density expression of stress receptors, making it sensitive and responsive to stress and a key system by which stress can modulate a variety of downstream brain processes and functions, through hippocampal connections to a variety of limbic brain regions. The downstream regions and functions that the hippocampus enables stress to modulate include: amygdalar fear conditioning, anxiety-, and post-traumatic stress responses; accumbal reward responses as well as attention, focus, concentration, and motivation; dorsal hippocampal reward cue responses; prefrontal executive functioning and regulatory/inhibitory capabilities, including emotion regulation and goal-oriented decision-making; and hypothalamic stress responses (through feedback onto the hypothalamic-pituitary-adrenal (HPA) axis) and eating behaviors and disorders (EDs)). A variety of literature implicates the hippocampus as an important link between stress and drug-seeking behaviors (e.g., Barr, Bray, Forster, 2017) as well as an important link between interoceptive regulation or modulation of eating behaviors (). Together, these various lines of research implicate the hippocampus as a key brain region involved in stress-induced modulation of interoceptive awareness, deficits, or dysregulation, specifically in reward-related psychological and psychiatric disorders, including substance-related addictive disorders (SRADs) and eating disorders (EDs) like binge eating disorder (BED). Further exploration of this possibility can help create a better understanding of how stress and adversity contribute to eating disorders through their impacts on stress and interoceptive system regulation and response. This can be especially true for BED and EDs that meet the “food addiction” phenotype criteria, as explored through the Yale Food Addiction 2.0 (YFAS 2.0) scale (which adapts the DSM-V diagnostic criteria for substance related addictive disorders to include food/eating as a possibly addictive-type substance or disorder.

**Keywords**: Interoception; Stress; Trauma; Adversity; Hippocampus; Cortisol; Substance Use; Eating Disorder; Substance Related Addictive Disorders; Binge Eating Disorder; Food Addiction

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# 

# Introduction

This review explores how interoception and the interoceptive system (IS) are linked to adversity/trauma/stress and the hippocampal glucocorticoid stress system. We highlight the roles of glucocorticoid and mineralocorticoid stress receptors as critical interoceptive chemoreceptors (Bray, 2018; Schulz & Vögele, 2015) and the role of the hippocampus as a critical brain region responsible for relaying, processing, and responding to exteroceptive and interoceptive information through activation of ventral hippocampal glucocorticoid and mineralocorticoid stress receptors that can mediate and modulate the impacts of functional hippocampal connections to a variety of downstream limbic and \*\*\* brain regions (Barr et al., 2017; Bray, 2018; Bray et al., 2020; Schulz & Vögele, 2015). We also explore the ways in which adverse stress exposure can result in dysregulated stress and interoceptive signaling responses - with the hippocampus as a possible point of convergence - and how these dysregulations can enable stress to induce its negative impacts on a variety of adverse physical, mental, and behavioral health conditions, including substance use and eating disorders.

The hippocampus is a brain region with high density expression of stress receptors, making it sensitive and responsive to stress and a key system by which stress can modulate a variety of downstream brain processes and functions, through hippocampal connections to a variety of limbic brain regions (Barr et al., 2017; Bray, 2018; Bray et al., 2020). The downstream regions and functions that the hippocampus enables stress to modulate include: amygdalar fear conditioning, anxiety-, and post-traumatic stress responses (CITE FORSTER); accumbal reward responses as well as attention, focus, concentration, and motivation (Bagot et al., 2015; Barr et al., 2014; Blaha et al., 1997; Bray, 2018; Bray et al., 2020; Floresco et al., 2001; Taepavarapruk et al., 2014; Taepavarapruk et al., 2000; Taepavarapruk et al., 2008) (Taepavarapruk et al., 2014; Taepavarapruk & Phillips, 2003) (Bray, Weber, et al., 2016; Bray et al., 2017; Floresco, 2014; Pecina & Berridge, 2013); dorsal hippocampal reward cue responses (CITE FORSTER/WATT); prefrontal executive functioning and regulatory/inhibitory capabilities, including emotion regulation and goal-oriented decision-making (CITE FORSTER/WATT); and hypothalamic stress responses (through feedback onto the hypothalamic-pituitary-adrenal (HPA) axis) (CITE HERMANN, SEE BRAY 2018/2020) and eating behaviors and disorders (EDs)).

A variety of literature implicates the hippocampus as an important link between tress and acumbal dopamine responses (Bagot et al., 2015; Barr et al., 2014; Blaha et al., 1997; Bray, 2018; Bray et al., 2020; Floresco et al., 2001; Taepavarapruk et al., 2014; Taepavarapruk et al., 2000; Taepavarapruk et al., 2008) as well as drug-seeking behaviors (Barr et al., 2017; Taepavarapruk et al., 2014; Taepavarapruk & Phillips, 2003; Volkow et al., 2019) as well as an important link between interoceptive regulation or modulation of eating behaviors (Benson et al., 2023; Davidson & Stevenson, 2022; Jones et al., 2021; Parent et al., 2022; Stevenson & Boutelle, 2024) and emotional regulatory responses (Hazelton et al., 2023) that are often associated with eating disorders (Bray, Bray, et al., 2022a, 2022b; Bray et al., 2023). Together, these various lines of research implicate the hippocampus as a key brain region involved in stress-induced modulation of interoceptive awareness, with stress dysregulation resulting in interoceptive dysregulation or deficits in turn (and/or vice versa). This possibility holds particular potential impacts for better understanding eward-related psychological and psychiatric disorders, including substance-related addictive disorders (SRADs) and eating disorders (EDs) like binge eating disorder (BED). Further exploration of this possibility can help create a better understanding of how stress and adversity contribute to eating disorders through their impacts on stress and interoceptive system regulation and response. This can be especially true for BED and EDs that meet the “food addiction” phenotype criteria, as explored through the Yale Food Addiction 2.0 (YFAS 2.0) scale (which adapts the DSM-V diagnostic criteria for substance related addictive disorders to include food/eating as a possibly addictive-type substance or disorder.

# Homeostasis & Allostasis

## Homeostasis & Homeorhesis

**Homeostasis** refers to: (1) the ability of an organism to maintain the internal environment of the body within limits that allow it to survive; (2) self-regulating processes that return critical systems of the body to a set point within a narrow range of operation, consistent with survival of the organism; (3) the body's defensive mechanisms (including protective reflexes against such things as inhaling matter into the lungs, the vomiting reflex as a protection to expel toxic materials from the esophagus or stomach, the eye blink reflex, and the withdrawal response to hot or otherwise pain-ful skin sensations as well as the defense against pathogens through innate and acquired immunity)(McEwen, 2017).

Homeostasis is highly developed and conserved in warm-blooded [e.g., temperature-controlled”] animals, in which the dynamic internal environment (e.g., body temperature, fluid balance, blood pH, and oxygen tension) must be monitored, regulated, and maintained within rather narrow limits, while at the same time balancing oxygen and energy needs across a variety of functions, including homeostatic maintenance, procuring resources (e.g., nutrition for energy) to support homeostatic maintenance, and a variety of additional life-sustaining activities (e.g., locomotion, mating, self-defense, etc.) )(McEwen, 2017).

Contrary to its true intent, the term “homeostasis” literally translates to convey a static (“stasis”) state, “akin to the notion of equilibrium in classical thermodynamics [which assumes a closed system],” rather than conveying the fluid nature of the range of changing set points a living organism - in an open system, in which energy and matter flow in and out – maintains steady state (vs. equilibrium) stability in over a finite period of time (McEwen, 2017). To account for the role of plasticity and the more fluid and dynamic nature of the entire open system, the terms “**hemeoynamics**,” “**homeorheusis**,” and “**rheostasis**” have also been proposed, in which “rheu-sis” (“**something flowing**”) replaces “stasis” (“something static”) and “**rheostasis**” refers to "a condition or state in which, at any one instant, homeostatic defenses are still present but over a span of time there is a change in the regulated level, or set point of a system." (McEwen, 2017).

Among these alterative nomenclatures, the term “rheostasis” has been favored as accounting for “the kinds of physiological plasticity that [are] involved in evolution,” such as the way an organism adjusts to changing seasonal environments by storing body fat or changing reproductive physiology (Mrozovky, 1990 as cited in McEwen, 2017). Over twenty years later, this term proves to be equally appropriate, as it also accounts for the less advantageous ways in which neuroplasticity can facilitate dysregulation of the stress and reward systems at the cellular/molecular (receptor/cell signaling), anatomical (connectivity), epigenetic, whole-system, and inter-systems levels, enabling stress and stress vulnerability to prompt a variety of physical, mental, and behavioral health complications.

Regardless of what nomenclature is used, it is clear that homeostatic processes (a) are dynamic, (b) involve coordination of interoceptive and exteroceptive signaling pathways and systems, (c) involve allostatic mechanisms and information, and (d) likely involve adaptive mechanisms such as NMDA-mediated synaptic plasticity, epigenetic modifications, or other conserved underpinnings of inter- and intra-lifetime adaption (McEwen, 2017).

## Allostasis

**Allostasis** can be defined as “the process of achieving stability through change, wherein the body anticipates and generates biological plans to face future needs,” (Santamaría-García et al., 2024), often accounting for adversity in internal or external conditions.

Allostasis complements homeostasis by describing how the body achieves stability – or, rather, maintains functionality and achieves “an inner calm” through change, particularly in response to stressors, by altering or adapting physiological systems (McEwen, 1998). Thus, allostasis emphasizes the body's active adjustment of its physiological systems in response to stressors, aiming for optimal functioning rather than static equilibrium. It recognizes that the body anticipates challenges and modifies its internal environment accordingly. Allostatic adaptations and process involve rapid coordination of the neuroendocrine and immune systems to meet environmental demands (McEwen, 1998). An example of **allostatic interoception** is the ability of the brain to anticipate the needs of strenuous activity and preparing the muscles with increasing blood glucose and oxygen concentrations and increasing blood flow through vasoconstriction as and increased heart rate.

Allostasis aligns with the alternative nomenclature for homeostasis discussed in section 2.1.1, such as “**homeorheusis**,” (in which “rheu-sis” (“**something flowing**”) replaces “stasis” (“something static”) and “**rheostasis**” (“condition or state in which, at any one instant, homeostatic defenses are still present but over a span of time there is a change in the regulated level, or set point of a system," (McEwen, 2017) that accounts for “the kinds of physiological plasticity that [are] involved in evolution,” (Mrozovky, 1990 as cited in McEwen, 2017)). While allostasis does not confer long-term evolutionary adaptions *per se*, it can result in neuroplastic and epigenetic changes that do confer long-term generational adaptions, particularly in situations of allostatic overload, as is described further below.

## Allostatic Load

***Allostatic Load****represents the cumulative effects of chronic stress on the body, resulting from repeated activation of the allostatic systems (McEwen, 1998). At its essence, allostatic load quantifies the wear and tear on the body from chronic stress exposure, which can lead to significant health consequences (McEwen, 1998) (Santamaría-García et al., 2024).*

***Allostatic load:*** *“The cumulative strain on the body that results from repeated cycles of anticipatory biological changes designed to prepare the body for potential needs and stress. These changes involve necessary energy adjustments that maintain the body’s readiness for imminent biological responses” (Santamaría-García et al., 2024).*

## Allostatic Overload

Over time, a large allostatic (stress) load can lead to detrimental health outcomes, including metabolic, cardiovascular, and psychiatric disorders (Guidi et al., 2021; Ketheesan et al., 2020; Rodriquez et al., 2019; Szanton et al., 2005). Thus, while allostasis is adaptive, excessive demands (e.g., overload) can wear down the body's regulatory systems.

***Allostatic overload:*** *“The amplified and dysregulated activation of anticipatory biological responses to potential needs, which lead to a state of wear and tear on the body. This increases the risk of amplified biological imbalances, which in turn trigger physical and psychological alterations,” (Santamaría-García et al., 2024).*

## Interoception, Allostasis, and Allostatic Load

Interoception, the perception of the body's internal state, is deeply intertwined with allostasis. It involves the brain's processing of internal signals, which is essential for the regulation of physiological states in response to environmental demands. Dysregulation in interoceptive signaling, often stemming from chronic stress or traumatic experiences, can lead to an increased allostatic load. This dysregulation can manifest in various forms, such as heightened sensitivity to stress or diminished awareness of bodily signals, both of which can have profound implications for mental and physical health (Santamaría-García et al., 2024).

**Predictive coding theory:** A framework proposing that perception, cognition, and action are fundamentally influenced by the brain’s predictive mechanisms. The brain continually creates, infers, and updates a model of the body and environment to anticipate sensory input. Predictions about incoming sensory information are continuously compared with actual sensory input to identify and minimize prediction errors. Through active inference, the brain reduces prediction errors through actions that align the environment with its predictions. High-order areas guide anticipation and predictions, and low-order areas guide perceptual processes. High- and low-order areas feed into each other to minimize prediction errors.

**The predictive allostatic interoceptive model:** An active framework suggesting that the body anticipates and generates a model of the environment based on interoceptive inputs to face future needs and respond to external demands. Allostasis and interoception are crucial for maintaining physiological functioning and are believed to influence emotional, cognitive, and behavioral responses in humans.

# Stress Regulation & Dysregulation

## The Glucocorticoid Stress System

### The Hypothalamic-Pituitary-Adrenal (HPA) Axis

At the systemic level, the hypothalamic-pituitary-adrenal (HPA) axis organizes neuroendocrine responses to physical and psychogenic stressors through systemic release of the glucocorticoid hormone cortisol (humans) or corticosterone (rodents) into the bloodstream (**Figure 1**) [92]. Glucocorticoids like cortisol are lipophilic and readily cross the blood bran barrier to act on central tissues (Ulrich-Lai & Herman, 2009). Among the central (brain) tissues that respond to glucocorticoid exposure, the hippocampus is the primary target for glucocorticoid activation in the brain (McEwen et al., 1968). Furthermore, the ventral subiculum of the ventral hippocampus is the primary limbic region that utilizes glucocorticoid feedback to dampen and terminate HPA activity (and stress responses in turn)(Barr et al., 2017; Herman et al., 2003; van Haarst et al., 1997). The hippocampus is also associated with facilitating memory and learning (through receipt, processing, storage, and coordination of stimuli in relation to time – past, present, and future) and regulating processing of- and responses to *internal* (*interoceptive)* and *external* (*exteroceptive)* stimuli, including pleasurable/rewarding, neutral (stimulating), and aversive/stressful stimuli both internally and externally (Barr et al., 2017; Bray, 2018; Bray et al., 2020), as addressed further below (e.g., sections 3.1.2, 3.1.3, **Figure 2, Figure 3**).

Diagram of a diagram of stress

Description automatically generatedFigure 1. The Hypothalamic-Pituitary-Adrenal Axis (HPA) coordinates neuroendocrine stress responses. In response to stress, the paraventricular nucleus of the hypothalamus induces a signaling cascade that ultimately stimulates peripheral secretion of glucocorticoid hormones (cortisol in humans, corticosterone in rodents) into the bloodstream. Glucocorticoids are lipophilic and can readily cross the blood brain barrier to act on central tissues. The hippocampus is the primary target for glucocorticoid activation and the ventral hippocampus is thought to be the primary limbic region that utilizes glucocorticoid feedback to inhibit HPA axis activity through activation of its glucocorticoid and mineralocorticoid receptors. This can dampen and terminate stress responses. Note: the ventral hippocampus is thought to induce inhibition onto the HPA axis by exciting inhibitory projections from the Bed Nucleus of the Stria Terminalis (BNST) via the fimbria/fornix (not shown)(Cullinan et al., 1993). Corticosterone is also thought to inhibit HPA activity at the level the PVN, anterior pituitary, and through other limbic regions (ex: medial prefrontal cortex, not shown), and may excite HPA activity through its actions in the basolateral amygdala (BLA) (Herman et al., 2003; Herman et al., 2016; Herman & Mueller, 2006; Herman et al., 2005)

### The Hippocampus

The hippocampus, a key brain region involved in memory and stress regulation, is particularly sensitive to glucocorticoids. Chronic stress can lead to hippocampal dysfunction, characterized by altered neuronal plasticity and impaired memory. This dysfunction is a hallmark of various neuropsychiatric disorders and underscores the importance of maintaining proper glucocorticoid signaling for cognitive health (Santamaría-García et al., 2024).

#### Hippocampal Dichotomy: Coordinates Interoceptive and Exteroceptive Signals

The ability of the hippocampus to process internal and external cues and coordinate responses related to past, present, and future instances of stress, emotion, reward, and other related behaviors occurs in part due to its unique neuroanatomical dichotomy (**Figure 2**). At the neuroanatomical level, the hippocampus has been conceptually subdivided into posterior/dorsal and anterior/ventral regions based on anatomical connectivity and behavioral outputs observed in rodents and humans respectively (Barr et al., 2017) (**Figure 2**). The posterior/dorsal hippocampus receives *exteroceptive* information (about *external* stimuli) from the entorhinal cortex and has a major role in rapid spatial learning (**Figure 2**) [52]. The anterior/ventral hippocampus receives *interoceptive* information (about *internal* stimuli) through reciprocal connections to limbic regions that modulate motivational and affective states (Barr et al., 2017; Bray, 2018; Bray et al., 2020) (**Figure 2**). Notably, many hippocampal functions involve coordinated processing of both *external/exteroceptive/posterior/dorsal* information *and internal/interoceptive/anterior/ventral* information [55] [56] (Barr et al., 2017). For example, memory formation (which drives learning and behavioral output in turn) involves hippocampal coordination of information from posterior/dorsal neurons that form contextual representations of specific single events and information from anterior/ventral neurons that form representations of multiple events over time (related by a distinct context) [56](Barr et al., 2017).

A diagram of a nervous system

Description automatically generated

Figure 2: Schematic of afferent/efferent connections and functions of the dorsal and ventral hippocampus related to reward and stress processes. Abbreviations: Cx = cortex; HPA = hypothalamic-pituitary-adrenal; PFC = prefrontal cortex; PVN = paraventricular nucleus of the hypothalamus; VTA = ventral tegmental area. Figure obtained with permission from (Barr et al., 2017).

##### Impacts on Reward Responsivity to Internal and External Cues

A variety of literature suggests that in addition to external cue associations, early drug-onset cues (experienced internally) can become associated with the later larger drug effects (Kim et al., 1999). These interoceptive pharmacological cues may overshadow simultaneously present environmental cues and produce conditioned compensatory responses (states of negative affect that are driven by reductions in accumbal shell dopamine levels and oppose the subsequent drug responses). These conditioned compensatory responses are therefore thought to drive tolerance and can reinvigorate drug behaviors (since drug administration can restore the accumbal shell dopamine deficit and thus alleviate the negative affect). It is thought that subjects whose drug administration was not contingent, predictable, or self-controlled may experience stronger drive from interoceptive cues – as opposed to exteroceptive cues – since noncontingent drug experiences lack reliable external predictors by nature. This may result in greater interoceptive cue-driven compensatory conditioned responses that can contribute to greater levels of tolerance in individuals whose drug experience is uncontrollable and unpredictable. Since the ventral hippocampus is associated with relaying *interoceptive* information to the nucleus accumbens shell; whereas the dorsal hippocampus is associated with relaying *exteroceptive* information to the nucleus accumbens core (Barr et al., 2018), the suggestion that greater interoceptive tone mediates tolerance and relapse suggests a possible role for the ventral hippocampus in mediating this process.

A variety of literature exists suggesting that noncontingent models of psychostimulant administration – in which the subject does not have control over drug administration – may result in greater drive from interoceptive cues (novel internal cues that are perfectly contingent with subsequent drug effects and therefore particularly salient). This may result from the fact that exteroceptive clues are limited or lacking in nonocontingent models. This may hold particular relevance to our studies, since the ventral hippocampus is associated with conveying interoceptive information to the nucleus accumbens shell whereas the dorsal hippocampus is more associated with processing exteroceptive cues (and connects to the accumbal core) (Barr et al., 2018).

The interoceptive cues are thought to have greater influence of compensatory conditioned responses that can increase tolerance and produce negative affect states that drive drug behaviors in rats with history of self-administration (who have learned that drug exposure can restore the dopamine deficit associated with the negative affect states); whereas the conditioned compensatory responses can drive drug aversion in rats without a history of self-administration (who have not had the earned experience that drug taking can correct the conditioned compensatory response).

#### Hippocampal Sensitivity to Stress: High Stress Receptor Density

At the cellular and molecular level, the high expression density of glucocorticoid and mineralocorticoid (cortisol) stress receptors in the hippocampus prime it for receiving and relaying information about stress/cortisol and enabling stress to influence downstream neurotransmission and behaviors (Barr et al., 2017; Bray, 2018; Bray et al., 2020). Specifically, the high receptor density make this brain region particularly sensitive and responsive to stress-induced glucocorticoid (cortisol) release, exposure, and receptor activation, identifying it as a neural substrate for stress-induced modification of a variety of different brain, body, and behavioral responses (Barr et al., 2017; Bray, 2018; Bray et al., 2020)).

One impact of glucocorticoid (cortisol) receptor activation in the hippocampus is the ability of the anterior/ventral hippocampus to impose negative feedback onto the HPA axis to terminate stress responses, thus sparing systemic tissue from toxic exposure to glucocorticoid stress hormones and their downstream impacts (as addressed above and in **Figure 1**)(Bray, 2018). Another impact of cortisol in the ventral hippocampus is that it can act on glucocorticoid (cortisol) receptors to stimulate local serotonin release (in the ventral hippocampus) (Barr & Forster, 2011; Bray, 2018; Li et al., 2014). Serotonin has an anxiolytic (anxiety-reducing) effect in the ventral hippocampus (Tu et al., 2014) and has been linked to positive stress coping (Joca et al., 2007; Li et al., 2014; Tu et al., 2014). Additional neural brain and behavioral impacts of glucocorticoid/cortisol receptor activation in the hippocampus can be best understood through a neuroanatomical lens, by first identifying the limbic brain regions the ventral hippocampus connects to (**Figure 3**).

Diagram of a diagram of a complex structure

Description automatically generated with medium confidenceFigure 3. Neural Circuits that Enable Ventral Hippocampal Excitation to Enhance Accumbal Dopamine Output and Mediate Accumbal Excitation/Inhibition. In the midbrain, cells from the medial ventral tegmental area (VTA, shown in blue) send dopaminergic (DA) projections to the medial nucleus accumbens shell (NAcS, shown in purple) that are responsible for NAcS dopamine output (Koob & Volkow, 2010; Pignatelli & Bonci, 2018). The ventral hippocampus (vHipp, yellow) sends separate populations of glutamatergic projection neurons (green) onto the VTA-NAcS dopamine projections; these terminate on the soma within the VTA and onto the dopamine terminals within the NAcS and can increase cell firing (from the VTA) and stimulate terminal dopamine release (within the NAcS) respectively (Britt et al., 2012; Floresco et al., 2001; Geisler et al., 2007; Legault et al., 2000; Tye, 2012; Valenti et al., 2011). A separate population of glutamatergic efferents from the ventral hippocampus that projects to the NAcS is disynaptic and terminates onto excitatory D1- and inhibitory D2 medium spiny neurons (MSNs) within the NAcS and onto feed-forward interneurons. The interneurons target MSNs and tightly regulate the excitatory/inhibitory balance of MSNs locally and create an overall inhibitory “backdrop” within the NAcS in control conditions (Scudder et al., 2018). Dopamine and MSN excitation in the NAcS can also regulate VTA dopamine output reciprocally through direct and indirect pathways (Floresco et al., 2001; Pignatelli & Bonci, 2018). For example, the NAcS sends inhibitory projections to the ventral pallidum (VP, shown in crimson; inhibitory GABAergic projections shown in red) that can disinhibit VTA activity, and the glutamatergic efferents from the ventral subiculum have been functionally linked to this circuit (Floresco et al., 2001). The NAcS also sends two separate populations of direct GABAergic projections to the medial VTA that respond to accumbal shell dopamine and terminate onto VTA dopamine soma or onto feed-forward inhibitory interneurons in the VTA that project onto the VTA dopamine soma, thus enabling accumbal dopamine output to rapidly induce feedback inhibition- or disinhibition onto the VTA directly (Pignatelli & Bonci, 2018; Yang et al., 2018). Finally, the ventral hippocampus sends glutamatergic and GABAergic projections to the basolateral amygdala (BLA, pink) and medial prefrontal cortex (mPFC, gold), both of which send glutamatergic afferents to the NAcS and VTA that enhance NAcS dopamine release in turn (Britt et al., 2012; Carr & Sesack, 1996; Floresco, 2014; Howland et al., 2002; Imperato et al., 1990; Kalivas, 2000; Strange et al., 2014; Tye, 2012; Tye & Deisseroth, 2012; Wanchoo et al., 2009). The mPFC and amygdala also send excitatory projections to the ventral hippocampus, which can regulate NAcS dopamine output and subsequent behaviors indirectly through the ventral hippocampal inputs (Barr et al., 2017; Tye, 2012; Tye & Deisseroth, 2012). In this figure, green projections represent excitatory glutamatergic projections; red projections represent inhibitory GABAergic projection neurons and interneurons. Abbreviations: BLA: Basolateral amygdala; D1: Excitatory type-1 Gs/o dopamine receptor-expressing medium spiny neuron; DA: Dopamine; Glut: Glutamate; mPFC: Medial prefrontal cortex; NAcS: Nucleus accumbens shell; VTA: ventral tegmental area. Figure obtained with permission from. Bray et al., 2020.

#### Hippocampal Connectivity: Links Stress to Limbic Activity and Behaviour

##### Hippocampal-Nucleus Accumbens Connectivity: Modulating Reward and Decision-Making Under Stress

In the brain, hippocampal cortisol modulates accumbal dopamine release (the neurobiological underpinning of motivation, focus, and reward value), enabling stress to modulate the value and priority assigned to specific tasks and stimuli (Bray, 2018; Bray et al., 2020). At the neuroanatomical level, the anterior/ventral subiculum of the anterior/ventral hippocampus sends glutamatergic (excitatory) projection neurons (brain cells) onto the dopaminergic (dopamine-transporting and releasing) projections from the ventral tegmental area (VTA, primary origin of dopamine-releasing neurons (cells) in the brain) to the medial nucleus accumbens shell (NAcS, brain region with high expression of dopamine terminals (e.g., brain cell regions that release dopamine)) that enhance accumbal dopamine output (e.g., dopamine release in the nucleus accumbens)(**Figure 3**)(Bray, 2018; Bray et al., 2020; Koob & Volkow, 2010; Pignatelli & Bonci, 2018). (Bagot et al., 2015; Barr et al., 2014; Blaha et al., 1997; Floresco et al., 2001; Taepavarapruk et al., 2014; Taepavarapruk et al., 2000; Taepavarapruk et al., 2008).

Accumbal dopamine release is associated with reward salience/value (Koob & Volkow, 2010; Pignatelli & Bonci, 2018) and the glutamatergic (excitatory/stimulatory) projections from the hippocamps stimulate the dopaminergic projections from the VTA to the NAc, thus increasing cell firing (from the VTA) and stimulating terminal dopamine release (within the NAcS)(Bray, 2018; Bray et al., 2020; Britt et al., 2012; Floresco et al., 2001; Geisler et al., 2007; Koob & Volkow, 2010; Legault et al., 2000; Pignatelli & Bonci, 2018; Tye, 2012; Valenti et al., 2011).(Bagot et al., 2015; Barr et al., 2014; Blaha et al., 1997; Floresco et al., 2001; Taepavarapruk et al., 2014; Taepavarapruk et al., 2000; Taepavarapruk et al., 2008).

This has been identified as one possible mechanism by which stress can modulate (influence) stimuli *salience/*value (e.g., the value assigned to specific stimuli – whether internal/interoceptive, external/exteroceptive, past-time/memory-related, present, or future-time/goal-seeking/related) (Bray, 2018; Bray et al., 2020). This has also been identified as a possible mechanism by which stress – through its impact on accumbal dopamine release and stimuli/reward salience/value assignment (Pecina & Berridge, 2013) – can influence prioritization and goal-oriented or reward-based decision-making and coordinate goal/salience/value-oriented/directed responses in turn (Bray, 2018; Bray et al., 2020; Floresco, 2014). The aforementioned responses can include *stress/aversion sensitization or desensitization* (and subsequent avoidance, ignorance/persistence, or prioritization) that are thought to occur through cellular, molecular, and epigenetic changes in expression, sensitization, and desensitization of the glucocorticoid (cortisol) receptors in the hippocampus (Bray, 2018; Bray et al., 2020). Conversely, these responses can also include sensitization or desensitization (and subsequent prioritization, hyper-prioritization, and hyperfocus etc.) of reward responses, which are also thought to occur through changes in expression, sensitization, desensitization, and epigenetic modifications of the glucocorticoid (cortisol) receptors in the hippocampus (Bray, 2018; Bray et al., 2020).

Thus, the enhanced corticosterone stress response observed in the ventral hippocampus during amphetamine withdrawal (Bray, Scholl, et al., 2016) paired with the reduced hippocampal GR/MR ratio (Barr & Forster, 2011) may affect hippocampal regulation of accumbal dopamine output and drug salience. The ventral subiculum sends excitatory glutamatergic projects to the medial nucleus accumbens shell that enhance accumbal dopamine output (Bagot et al., 2015; Barr et al., 2014; Blaha et al., 1997; Floresco et al., 2001; Taepavarapruk et al., 2014; Taepavarapruk et al., 2000; Taepavarapruk et al., 2008) and can also reinstate drug behaviors (Taepavarapruk et al., 2014; Taepavarapruk & Phillips, 2003). For example, electrical stimulation of the ventral subiculum was shown to concomitantly enhance dopamine output in the nucleus accumbens shell and reinstate amphetamine self-administration that had previously been extinguished (Taepavarapruk et al., 2014).

Thus, in healthy conditions, stress-induced glucocorticoid (cortisol) release can result in activation of glucocorticoid and mineralocorticoid stress receptors in the ventral hippocampus that can enhance accumbal dopamine output (Bray, 2018; Bray et al., 2020), enabling stress to enhance reward value (Pecina & Berridge, 2013) to promote adaptive goal-oriented behavior (Floresco, 2014). However, prolonged, chronic, or developmental stress exposure can result in dysregulation of the glucocorticoid hippocampal stress system (Bray, 2018; Bray et al., 2020) that can results in dysregulated stress, reward, and stimuli-salience responses in turn (among a variety of additional negative neural and systemic impacts)(Bray, 2018; Bray et al., 2020).

For example, 20 minutes of restraint stress exposure ( a potent psychological stressor (Li et al., 2014; Lukkes et al., 2009; Mo et al., 2008)) results in enhanced glucocorticoid stress hormones (corticosterone in rodents, cortisol in humans) in the ventral hippocampus that peak at ~50% above baseline measures 40 minutes after onset of stress exposure (20 minutes after restraint termination) and return to baseline levels one hour after stress termination in rodents (n=7-9, though these changes were not found to significantly differ statistically from pre-restraint stress exposure levels)(Bray, Scholl, et al., 2016). In contrast, hyper-stimulant exposure and withdrawal stress (e.g., two weeks of daily amphetamine exposure followed by a two-week withdrawal period) followed by 20 minutes of restraint stress exposure during the second week of withdrawal (to mimic acute on prolonged/chronic stress) results in an immediate increase of glucorticoid stress hormone levels in the hippocampus that increase to ~75% above pre-stress baseline levels and post-restraint levels observed in rodents *without* exposure to the hyper-stimulant withdrawal protocol within 20 minutes of restraint stress exposure onset (p<0.05 vs. non-withdrawal group, n=7-9 per group) that peak at ~150% above baseline levels and 100% above non-withdrawal levels at 40 minutes post restraint-onset (p<0.05 vs. baseline levels and non-withdrawal control levels, n=7-9 per group) before returning to baseline and non-withdrawal stress exposure levels at ~100 minutes after restraint onset (Bray, Scholl, et al., 2016).

Corticosterone in the hippocampus can rapidly increase local excitatory activity and induce glutamate release (Karst et al., 2005; Pasricha et al., 2011; Wang & Wang, 2009), and a stress-relevant concentration of corticosterone infused into the ventral hippocampus rapidly enhances dopamine output in the nucleus accumbens shell of drug-naïve rats (Bray, Weber, et al., 2016; Bray et al., 2017). This suggests that corticosterone in the ventral hippocampus may provide a link by which stress can enhance reward value (Pecina & Berridge, 2013) to promote goal-oriented behavior (Floresco, 2014) in the face of stress. Interestingly, the ability of corticosterone in the ventral hippocampus to enhance accumbal dopamine output is lost in amphetamine withdrawal (Bray, Weber, et al., 2016; Bray et al., 2017). In fact, the same stress-relevant infusion of hippocampal corticosterone during amphetamine withdrawal appears to actually *reduce* accumbal dopamine output. Thus, corticosterone in the ventral hippocampus may enable stress to *reduce* reward value, thereby contributing to the dysphoric and anhedonic states that can prompt relapse during psychostimulant withdrawal (Gossop, 2009; Shoptaw et al., 2009). Overall, these findings support a role for hippocampal corticosterone in mediating reward responses to stress, and suggest that dysregulatin of corticosterone signaling in the ventral hippocampus may contribute to stress-induced relapse during psychostimulant withdrawal.

##### Hippocampal-Nucleus Accumbens Pathway: Modulating Baseline Reward and Motivation Under Stress

A separate population of glutamatergic efferents (outgoing neurons) from the ventral hippocampus that projects to the NAcS is disynaptic (has two areas of neutrotransmtter output) and terminates onto excitatory and inhibitory dopamine neurons in the NAc (e.g.,excitatory D1- and inhibitory D2 medium spiny neurons (MSNs)) *and* onto feed-forward interneurons (description of feed-forward interneurons here)(CITATIONS) (Bray, 2018; Bray et al., 2020). The interneurons target MSNs and tightly regulate the excitatory/inhibitory balance of MSNs locally and create an overall inhibitory “backdrop” within the NAcS in control conditions (Scudder et al., 2018) (Bray, 2018; Bray et al., 2020). TRANSLATION HERE OF THE “BACKDROP” (THSE NEURONS REGULATE ‘BASELINE’ DOPAMINE LEVELS, WHICH REGULTE ‘BASLINE AMOUNT OF MOTIVATION/FOCUS AND URGENCY’ SEE CLIFF’S DECISION-MAKING IN DEPRESSION SEMINAR CONTENT OR ASK CLIFF TO COLLABORATE WITH CONTENT HERE).ALSO ADD SENTENCE ON HOW THIS CAN DIRECTLY RELTAE TO INTEROCEPTIVE AWARENESS.

Dopamine and MSN excitation in the NAcS can also regulate VTA dopamine output reciprocally through direct and indirect pathways (Floresco et al., 2001; Pignatelli & Bonci, 2018). For example, the NAcS sends inhibitory projections to the ventral pallidum (VP, shown in crimson; inhibitory GABAergic projections shown in red) that can disinhibit VTA activity, and the glutamatergic efferents from the ventral subiculum have been functionally linked to this circuit (Floresco et al., 2001). The NAcS also sends two separate populations of direct GABAergic projections to the medial VTA that respond to accumbal shell dopamine and terminate onto VTA dopamine soma or onto feed-forward inhibitory interneurons in the VTA that project onto the VTA dopamine soma, thus enabling accumbal dopamine output to rapidly induce feedback inhibition- or disinhibition onto the VTA directly (Pignatelli & Bonci, 2018; Yang et al., 2018). (Bray, 2018; Bray et al., 2020)

##### Hippocampal-PFC Connectivity: Modulating Executive Function Under Stress

The ventral hippocampus also sends glutamatergic and GABAergic projections to the medial prefrontal cortex (mPFC, brain region involved in executive function, including long-term decision-making and planning)(**Figure 3**)(Britt et al., 2012; Carr & Sesack, 1996; Floresco, 2014; Howland et al., 2002; Imperato et al., 1990; Kalivas, 2000; Strange et al., 2014; Tye, 2012; Tye & Deisseroth, 2012; Wanchoo et al., 2009) (Bray, 2018; Bray et al., 2020). Sentence on role ofPFC in executive function and inhibition of basal ganglia (e.g., hippocampus, amygdala, accumbens). The mPFC also sends excitatory projections to the ventral hippocampus, which can regulate NAcS dopamine output and subsequent behaviors indirectly through the ventral hippocampal inputs (Barr et al., 2017; Tye, 2012; Tye & Deisseroth, 2012) (Bray, 2018; Bray et al., 2020).

##### Hippocampal-Basolateral Amygdala Connectivity: Modulating Fear and Anxiety Under Stress

The ventral hippocampus also sends glutamatergic and GABAergic projections to the basolateral amygdala (BLA) (**Figure 3**) (Bray, 2018; Bray et al., 2020; Britt et al., 2012; Carr & Sesack, 1996; Floresco, 2014; Howland et al., 2002; Imperato et al., 1990; Kalivas, 2000; Strange et al., 2014; Tye, 2012; Tye & Deisseroth, 2012; Wanchoo et al., 2009). Sentence on role of BLA in anxiety, panic, fear conditioning, and PTSD. The BLA also sends excitatory projections to the ventral hippocampus, which can regulate NAcS dopamine output and subsequent behaviors indirectly through the ventral hippocampal inputs (Barr et al., 2017; Tye, 2012; Tye & Deisseroth, 2012) (Bray, 2018; Bray et al., 2020).

### Stress Receptor Signalling: Genomic & Non-Genomic MR & GR Dimers

The HPA-axis stress feedback loop (**Figure 1**) and all other downstream stress responses are primarily mediated through glucocorticoid (cortisol) activation of mineralocorticoid (MR) and glucocorticoid (GR) receptors that are both cytosolic (genomic) and membrane-bound (non-genomic) (Groeneweg et al., 2011; Herman et al., 2003; Herman & Mueller, 2006; Karst et al., 2005; van Haarst et al., 1997) (Groeneweg, Karst, de Kloet, & Joels, 2011; Herman et al., 2003; Herman & Mueller, 2006; Karst et al., 2005; van Haarst, Oitzl, & de Kloet, 1997).

Cytosolic MRs (cMRs), with restricted expression (highest in the hippocampus), have ten-fold higher affinity for corticosterone than GRs, and are ~90% occupied under basal conditions [100-103]. They are attributed with regulating HPA inhibition at basal corticosterone levels, and thus determine HPA “set point” [96, 104-108]. cMRs also sustain cellular stability, which maintains stress sensitivity thresholds and preserves limbic network communication [97, 103, 107, 109, 110]. Cytosolic GRs (cGRs) are ubiquitously expressed, with high expression in the hippocampus [95], and regulate delayed feedback inhibition of HPA activity after diurnal corticosterone peaks and acute stress [92, 96, 104-105]. cGRs are also attributed with normalizing neuronal excitability in response to stress and normalizing network activity, which dampens initial stress responses, and promotes adaptive stress coping [107, 109, 110].

Corticosterone stress responses that occur too quickly to attribute to genomic effects are credited to activation of non-genomic membrane-bound receptors (mMRs/mGRs) in the hippocampus (and other regions). These membrane receptors have ≥ 10-fold lower affinity for corticosterone than their cytosolic counterparts [97, 103, 108] and thus act as hippocampal “cortico-sensors” [99, 111]. mMRs rapidly and reversibly enhance excitatory glutamatergic transmission in the hippocampus [97, 99, 107]; they contribute to rapid inhibition of HPA activity and activate rapid and reversible behavioral stress responses important for appraisal and coping [99, 110]. mGRs have lower corticosterone affinity than mMRs and augment inhibitory GABAergic interneuronal transmission [112] to suppress excitability; they also promote spinogenesis [97, 113]. Alterations in these receptors’ expression, function, and ratios relative to one another – especially within the hippocampus – can diminish stress responsiveness and coping ability, which is associated with multiple disease states, including depression and psychostimulant withdrawal [113, 114].

Glucocorticoid stress responses in the hippocampus also vary based on hippocampal region (dorsal vs. ventral): acute foot shock rapidly increases corticosterone levels in the dorsal hippocampus, followed by a more delayed elevation in the ventral hippocampus [115]. Also, acute swim stress decreases long-term potentiation (LTP) in the dorsal hippocampus, but increases LTP in the ventral hippocampus [116]. This differential response may temporarily suppress the dorsal hippocampus’ cognitive cortical communication and facilitate ventral hippocampal transmission of emotional information [117].

## Eustress in the Homeostatic System

### Stress Regulation of Homeostasis

Stress can be understood as a perceived or actual threat to an individual’s physiological or psychological integrity, leading to various physiological and behavioral responses. In the context of biomedicine, stress often refers to conditions where adrenal glucocorticoids and catecholamines are elevated due to an experience (McEwen, 2007). Stress is also a subjective experience that may not always align with physiological responses, and the term is commonly used in everyday language to describe both positive (‘good stress’) and negative (‘bad stress’) experiences (Lazarus & Folkman, 1984).

Stress involves both a stressor and a corresponding stress response. Stressors can be physical, such as trauma, injury, or physical exertion beyond the body’s capacity. Other physical stressors include noise, overcrowding, and extreme temperatures. Psychological stressors encompass time-pressured tasks, interpersonal conflicts, unexpected events, frustration, isolation, and traumatic life events. These stressors can trigger behavioral responses and physiological consequences, such as activation of the hypothalamic-pituitary-adrenal (HPA) axis, leading to glucocorticoid (cortisol) secretion. Changes in cortisol levels can affect blood pressure, heart rate, metabolism, inflammation, immune function, gut function, neurocognitive function, self-regulatory capacities, and other bodily processes (Sapolsky, 2004).

Behavioral responses to stressors can either mitigate risk and promote health, such as maintaining a balanced diet and regular exercise, or exacerbate physiological stress consequences through harmful behaviors like smoking, drinking, overeating, or reckless driving. The physiological stress response primarily involves the activation of the autonomic nervous system and the HPA axis, resulting in increased levels of catecholamines and glucocorticoids. These responses can have both protective and damaging effects (McEwen & Wingfield, 2003).

Two critical aspects of the physiological stress response are its activation in response to a challenge and its deactivation when no longer needed. The catecholamines of the sympathetic nervous system and glucocorticoids from the adrenal cortex initiate cellular events that promote adaptive changes in cells and tissues, protecting the organism and enhancing survival. However, excessive stress or inefficient acute stress responses can lead to wear and tear, exacerbating disease processes (Chrousos, 2009).

Individual differences in interpreting and responding to stress, as well as susceptibility to stress-related diseases, are significant. Genetic predispositions can increase the risk of certain disorders. Additionally, developmental factors, such as prenatal stress or nurturing postnatal experiences, influence lifelong behavioral and physiological responses to stressors. Life experiences, combined with genetic and developmental influences, result in substantial variability in how individuals react to stress and the long-term consequences (Heim & Nemeroff, 2001).

### Glucocorticoid Stress System Regulates of Allostatic Load

#### Cortisol: The molecular unit by which the body maintains homeostasis and allostasis

The glucocorticoid stress system mediates and regulates nearly all homeostatic and non-homeostatic (allostatic) conditions, ranges, changes, processes, responses, functions, and systems in the body. In humans, the glucocorticoid stress hormone cortisol is the molecular unit by which the human body maintains homeostasis or pushes itself outside of homeostatic range (into allostasis) in order to adapt to “non-normative” or extreme conditions (experiences and environments). As such, it may not be surprising that the glucocorticoid stress system regulates every single bodily organ, organ system, function, and process in the human body (both in homeostasis and allostasis).

##### Cortisol Regulation of the Life Cycle

Throughout the lifespan, cortisol regulation of serotonin coordinates our birth, development, migration, growth, aging/senescence, and end of life processes.

##### Sleep & Wakefulness

###### Neurobiological (Cognition, Mentation, Sensation, Perception, Emotion, Action)

Cortisol contributes to the transition from sleep to wakefulness. At the **neurobiological level, morning glucocorticoid (cortisol) surges** result in dopamine output surges that assist in the transition from mental/cognitive sleep to wakefulness and provide us with motivation to “seize day” and direct our energy toward specific tasks that are assigned dopaminergic salience (e.g., “value”), ranging from seeking, preparing, and consuming coffee and breakfast, maintaining our social hygiene through washing/bathing and clothing routines, prioritizing, planning, scheduling and implementing our daily and long-term schedules and activities (Bray et al., 2020). Cortisol regulation of the **nigrostriatal dopamine system** enables us to translate our cognitive processes into physical actions (Bray et al., 2018; 2020).

###### Biophysical (Orthostatic Changes, Motion, Movement, Action)

At a more physical/biological level, morning glucocorticoid surges impact our **respiratory and heart rates, blood pressure, and blood glucose levels,** enabling us to transition orthostatically from the supine sleeping position to prone standing and moving positions.

At the end of the day, diminished cortisol levels contribute to the neurobiological and physical transition from wakefulness to sleep and rest.

##### Daily Processes, Functions, & Activities

###### Biophysical (Orthostatic Changes, Motion, Movement, Action)

Cortisol also sustains our physical and mental/neurobiological processes throughout the day. Continued glucocorticoid regulation of **heart and respiratory rate, blood pressure, and metabolism** throughout the day enable us to access and sustain a variety of ranges of motion and movements, including sleeping/resting/napping, sitting, standing, walking, running, coordinating our limbs and appendages for fine-tuned motor skills and functional movement processes.

###### Neurobiological (Cognition, Regulation, Executive Function)

At the neurobiological level, continued glucocorticoid (cortisol) regulation of the **mesolimbic and nigrostriatal dopamine system (as well as nearly all other neurotransmitter systems)** enables us to focus, direct, and redirect our attention to a variety of internal and external stimuli and process, rank/value, coordinate, and enact/implement a variety of internal and external short- and long-term responses to those stimuli ([Bray et al., 2018](https://search-proquest-com.ezproxy.usd.edu/docview/2157998281?accountid=14750); [2020](https://pubmed.ncbi.nlm.nih.gov/31881169/)).

##### Environmental Awareness & Response

###### Interoceptive Awareness: Internal Sensation & Perception

Glucocorticoid modulation of dopamine output associated with interoceptive cues (e.g., cues about changes in our internal environments such as heart rate and blood pressure (as addressed above) as well as thirst, hunger, body temperature, etc.) can dictate the salience (value) of these cues and our conscious awareness of them and sensitivity to them in turn ([Bray et al., 2022](https://pubmed.ncbi.nlm.nih.gov/31881169/); [Schaan et al., 2019](https://pubmed.ncbi.nlm.nih.gov/31681049/); [Schulz & Vögele 2015](https://loop.frontiersin.org/people/31460); [Koehnle & Rinaman, 2010](https://pubmed.ncbi.nlm.nih.gov/20159026/); [Ouzir & Errami, 2016](https://pubmed.ncbi.nlm.nih.gov/27306332/)).

In relation to life sustaining activities (e.g., thirst, hunger, body temperature), stress then enables homeostatic regulation of these activities and active responses when levels become allostatic (non-hoeostatic).

###### Thirst, Hunger, & Hydration/Nutrition- Seeking, Engaging, Appetitive, & Consumption Behaviors

Cortisol regulation of the gastrointestinal and immune systems enable us to take in samples of the external environment in the form of food and metabolize the food into energy, develop immune screening and signaling processes and responses to generate internal signals about our external environment (e.g., its nutritional diversity and safety), fuel life-sustaining microbes that live in our gut and support our many functions, and excrete what is not needed.

###### External Sensation & Perception

Cortisol contributes to the tight regulation of our sensory systems. For example, cortisol enables stress to induce vasoconstriction that reduces the size of our field of vision to prioritize greater far-sided acuity while prolonged cortisol exposure can contribute to the sensitization of a variety of sensory receptors, resulting in heightened sensation that can help us gain awareness and understanding of our external environment. This is important in environments where there is perceived risk for danger (heightened senses of sight, smell, sound, and touch can help us avoid danger and navigate to safety more quickly.

Regulation of the kidneys and liver further regulate vital filtration, detoxification, and excretion systems.

##### Everything

Glucocorticoid regulation of cardiovascular system, respiratory system, musculoskeletal systems, developmental systems and processes, blood and lymph tissues and systems, skin and immune systems and functions, kidney and filtration systems and processes, liver and detoxification systems, adipose tissues (which respond to inflammation), hormone, endocrine, reproductive, and metabolic systems and processes, brain and neurobiological systems and processes, and the psychological (sensation and perception) and behavioral responses in turn.

## Stress Dysregulation (ADD HERE)

Although stress can feel uncomfortable, it plays an important role in mediating a variety of brain and bodily functions (CITATIONS).

Glucocorticoid stress hormones such as cortisol play a crucial role in regulating the body's response to stress (as addressed in section \*\*\*). Under mild stress, glucocorticoids can promote beneficial eustress responses that help the body respond adaptively to acute stress exposure by regulating various physiological processes, including increased metabolism, enhanced immune function and memory consolidation, and increased stress resilience (Sapolsky et al., 2000).

A variety of literature demonstrate that eustress (stress exposure with beneficial outcomes) embodies just one form of stress exposure with a variety of specific contextual factors, including control, predictability, onset, timing, stress response dose and duration, and overall allostatic stress load informing whether stress has positive or negative net impacts on a variety of physical and mental health markers (CITATIONs) (Bray, 2018; Bray et al., 2020).

Stress exposure that deviates from the specific factors associated with eustress include extreme stress (in which glucocorticoid stress responses to a single acute stress exposure are exaggerated or prolonged and result in damaging or toxic cortisol tissue exposure, as occurs in single cases of trauma), uncontrollable and unpredictable stress (which often stimulates extreme stress responses in the brain and body), childhood and developmental stress and adversity (e.g., stress and adversity that occur during development of the systems and processes that regulate stress responses neurobiologically, as occurs during adverse childhood experiences (ACEs, which are also often uncontrollable and thus extreme)), prolonged or chronic stress and adversity (as occur often in adverse life experiences (ALEs), unfavorable living conditions, and chronic disorder and disease states), and acute on chronic stress (CITATIONS). These deviant forms of distress can singularly and independently disrupt the entire glucocorticoid stress system at the cellular/molecular (receptor expression and sensitivity), epigenetic, synaptic (neurogenesis and neuroplasticity), neuroanatomical, and systemic levels, resulting in lifelong dysregulation of the glucocorticoid stress system and subsequent stress responses (CITATIONS)

Severe, developmental, prolonged, and/or acute on chronic stress can result in excessive, cytotoxic, and/or prolonged cortisol receptor & tissue exposure and damage that can result in dysregulation of the entire glucocoritcoid stress system as well as the various functions associated with the over-exposed tissue/organ. The associated negative health outcomes can include pro-inflammatory responses to stress, impaired cognitive function, and increased vulnerability to negative health outcomes an disease (Caratti et al., 2018; Sapolsky et al., 2000).

A variety of preclinical and clinical literature demonstrate that stress exposure, aversive stimuli, and drug stimuli can produce craving (in humans) and negative affect/aversive states (humans and rodents) that are time-locked with immediate reductions in accumbal shell dopamine concentrations and frequency of shell dopamine release (in rodents) (Bray, 2018; Bray et al., 2020) and increases in drug-seeking behavior and hyper-salient food-seeking and binge-eating behavior in humans (CITATIONS). Moreover, these negative affect states and reductions in accumbal shell dopamine levels directly drive and predict drug-taking behavior, hyper-salient food-seeking behavior, and binge eating (in humans and rodents) which alleviates the negative affect (in humans) and immediately restores accumbal shell dopamine levels (in rodents) (Brischoux et al., 2009; Paliwal et al., 2008; Robinson et al., 2014; Roitman et al., 2008; Sinha, 2001, 2007; Sinha et al., 1999; Sinha et al., 2000; Sinha et al., 2006; Sinha et al., 2003; Twining et al., 2009; Twining et al., 2014; Ungless et al., 2004; Weise-Kelly & Siegel, 2001; Wheeler et al., 2011; Wheeler & Carelli, 2009; Wheeler et al., 2008) ADD CITATIONS FOR HYPER-SALIENT FOOD-SEEKING AND BINGE EATING.

Overall, it appears that stress can enhance accumbal shell dopamine output and motivate goal-oriented behavior in normative states (Berridge & Robinson, 2016; Bray, 2018; Bray et al., 2020; Enrico et al., 2013; Floresco, 2014; Hollon et al., 2015). However, stress can reduce accumbal shell dopamine output in dysregulated stress systems (CITATIONS), which can enable stress to facilitate and reinforce psychostimulant drug-seeking, hyper-salient food-seeking, and salient eating behaviors (e.g., binge eating, bulimia, and restriction)(CITATIONS) and relapse during sensitive periods of acute abstinence and withdrawal (Bray, 2018; Bray et al., 2020; Roitman et al., 2008; Twining et al., 2014)ADD CITATIONS FOR FOOD/EATING. Stress-induced reduction in accumbal dopamine release can thereby motivate craving, stimulant seeking and taking of any sort (including drugs and hyper-salient foods and eating behaviors), and relapse during acute and prolonged periods of abstinence (Cleck & Blendy, 2008; Koob et al., 2014; Kwako & Koob, 2017; Paliwal et al., 2008; Sinha, 2007; Twining et al., 2014; Wheeler & Carelli, 2009; Wheeler et al., 2008) (Bray, 2018; Bray et al., 2020)ADD FOOD/EATING CITATIONS.

Ending sentence/paragraph – thus, the hippocampus may be a mechanism by which stress can reduce interoceptive awareness and facilitate maladoptive coping response (including binge eating) in turn.

### Impacts of Stress on the Brain & Body (C/P from other NRFi Stress Doc)

# Interoception and the Interoceptive System

## Interoception & Exteroception

### Interoception & the Interosome

**Interoception** refers to: (1) the ability of an organism to sense/receive, signal/communicate, process, interpret, perceive, integrate, respond, self-regulate, and anticipate sensory information that originate within the body through a variety of sensory receptor (interoceptors) and modalities, providing real-time information about the body’s internal landscape; (2) a variety of processes that enable this capacity; (3) a mechanism that facilitates adaptive responses to both internal and external stimuli essential for maintaining allostasis and thus (4) enables homeostatic and allostatic regulation physically as well as mentally, psychologically, emotionally, and behaviorally (Craig, 2009; Khalsa et al., 2018; Santamaría-García et al., 2024).

Through a variety of internal sensory receptor modalities, the interoceptive system collects a variety of information about our internal environment (the ***interosome***) and relays it through the peripheral and central nervous systems for autonomic (sympathetic, parasympathetic, and enteric, bottom-up) and somatic reflexive and non-reflexive (e.g., integrated, processed, top-down) processing, integration, regulation, and responses. The wide range of interoceptive sensory receptors enable the interoceptive system to collect, relay, process, integrative, coordinate, respond to-, and predict a large array of information about the internal landscape, including heart rate, respiration, blood pressure, local and regional internal body temperature, pH, oxygen and energy availability, metabolism, digestion, hunger, bladder and bowel fullness or emptiness, immune responses, stress responses, and so much more. In exploring the body’s interceptive system, we learn that our bodies are just as interested and attentive to our *internal* physical and psychological environments as they are to our *external* environments, and both environments seem to equally inform our actions and environmental interactions (independently and interdependently).

The totality of an individual’s internal environmental experience over the lifespan, including exposures – including physical conditions and other conditions – across a lifetime that impact health, including toxins, pollutants, diet, and genetic factors” are referred to here as the **interosome** (in the same way the *exposome* is used to describe these factors related to external environmental experiences (Santamaría-García et al., 2024), as described further below).

### Exteroception & the Exposome

Interoception – as described and defined in section 3.1.1 (above) and 3.2 (below), confers the abilities and processes by which the nervous system “senses, integrates, and anticipates bodily signals at both conscious and subconscious levels, providing a moment-to-moment mapping of the body’s internal landscape, (CITAATION). In contrast, **exteroception** describes the process of sensing stimuli originating outside the body (Santamaría-García et al., 2024). It encompasses the perception of *external* environmental stimuli through sensory organs (in the same way interoception does for the internal environment), enabling individuals to interact with their surroundings (Santamaría-García et al., 2024)*.* The totality of an individual’s “environmental physical (i.e., pollution) and social (i.e., socioeconomic conditions) exposures across a lifetime that impact health, including pollutants, diet, lifestyles, social determinants of health, social adversities, and structural inequalities” are referred to as the **exposome** (Santamaría-García et al., 2024).

## The Interoceptive System

The interoceptive system is a complex network that allows organisms to sense and interpret signals from within the body. Interoceptive processing occurs across all major biological systems involved in maintaining bodily homeostasis, including the cardiovascular, respiratory/pulmonary, enteric/gastrointestinal, genitourinary, nociceptive, chemosensory, osmotic, thermoregulatory, visceral, immune, and autonomic systems (Khalsa et al., 2018). The subsections below provide detailed descriptions of the interoceptive process(es), starting from receptor activation and progressing through the various stages of signal transduction, relay, and response.

### Interoceptive Sensory Receptors

**Interoreceptors (interoceptive sensory receptors)** are specialized nerve endings located throughout the body, including in internal organs, muscles, and skin. These receptors detect various physiological states such as hunger, thirst, heart rate, and internal temperature. [When a stimulus (e.g., a change in blood pressure or the presence of a specific chemical) activates these receptors, it triggers a change in the membrane potential of the sensory receptor cells1](https://www.griffinot.com/interoception-explained/).

Interoceptive receptors come in a variety of modalities, just like external sensory receptors. They include **mechanoreceptors** (respond to mechanical forces such as pressure, vibrations, and stretching), **thermoreceptors** (detect changes in temperature), **nocicpetors** (respond to potentially damaging stimuli, often perceived as pain), **photoreceptors** (detect and respond to light), and **chemoreceptors** (respond to specific chemicals). These receptors interact with a variety bodily and organ systems *internally (e.g., inside the body, in the interosome)* – including the cardiovascular, respiratory, enteric/gastrointestinal, genitourinary, nociceptive, chemosensory, osmotic, thermoregulatory, visceral1, immune, and autonomic systems (Khalsa et al., 2018) – and encode a variety of sensory information – about pressure, vibration, stretching, temperature, pH, presence of oxygen and other chemicals, pain and other potentially dangerous stimuli – into electrochemical signals (actions potentials) that are relayed to the brain via **afferent pathways (**relaying signals from the peripheral to the central nervous system, e.g., from the body to the brain).

#### Recetpor Activation Transduction to Action Potentials

The activation of interoceptive receptors leads to the transduction of the stimulus into electrical signals, known as action potentials. This process involves the opening of ion channels in the receptor cell membrane, causing a change in the membrane potential. [When the membrane potential reaches a certain threshold, an action potential is generated and propagated along the sensory neuron2](https://en.wikipedia.org/wiki/Transduction_%28physiology%29)[3](https://bio.libretexts.org/Bookshelves/Introductory_and_General_Biology/General_Biology_%28Boundless%29/35%3A_The_Nervous_System/35.05%3A_How_Neurons_Communicate_-_Nerve_Impulse_Transmission_within_a_Neuron-_Action_Potential).

#### Glucocorticoid and Mineralocorticoid Receptors

A variety of literature implicates glucocorticoid and mineralocorticoid stress receptors (GRs and MRs) in a variety of interoceptive processes (Koning et al., 2019; Nicolaides et al., 2014; Sapolsky et al., 2000) as described further below (**section 4**). While the specific concept of GRs and MRs functioning as interoceptive chemoreceptors has not been addressed in the literature, these receptors (and the glucocorticoid stress system more broadly) *do*  meet the various components of the interoceptive definition provide din part 1 of this review. For example, the glucocorticoid stress system – including glucocorticoid activation of GRs and MRs – (1) are used to encode and communicate information that originates both inside and outside of the body through a variety of sensory modalities, providing real-time information about the body’s internal landscape and this information is signaled/communicated, processed, interpreted, perceived, integrated, regulated, anticipated, and responded to through the interoceptive system (and the various subdivisions of the nervous system that the interoceptive system interacts with; (2) encompass one of the many processes by which the interoceptive system enables an organism to sense/receive, signal/communicate, process, interpret, perceive, integrate, respond, self-regulate, and anticipate sensory information that originate within the body through a variety of sensory receptor (interoceptors) and modalities, providing real-time information about the body’s internal landscape; (3) provide a mechanism that facilitates adaptive responses to both internal and external stimuli essential for maintaining allostasis and thus (4) enable homeostatic and allostatic regulation physically as well as mentally, psychologically, emotionally, and behaviorally (Craig, 2009; Khalsa et al., 2018; Santamaría-García et al., 2024).

### Afferent Pathways

[**Afferent pathways** carry sensory information from the body’s sensory receptors (including interoceptive receptors) to the central nervous system (CNS), which includes the brain and spinal cord1](https://www.varsitytutors.com/ap_biology-help/understanding-afferent-and-efferent-neurons)[2](https://www.osmosis.org/answers/afferent-vs-efferent-neurons). In simpler terms, afferent pathways bring information ***to*** higher levels of processes (generally in the brain)(while efferent pathways send instructions **from** the brain to the body).

Several neural pathways have been implicated in processing interoceptive signals, beginning with a rich interface between **autonomic afferents** and the central nervous system. Table 1 provides a brief overview of relevant anatomical terms and pathways.

Relay pathways involve primarily **spinal, vagal, and glossopharyngeal afferents**, with multiple levels of processing and integration in **autonomic ganglia and spinal cord** (10,19,22,41).

Action potentials encoding interoceptive sensory information travel along **afferent pathways** to the central nervous system. These pathways include the vagus nerve, glossopharyngeal nerve, and spinothalamic tracts. [The signals are transmitted to the brainstem, specifically the Nucleus of the Solitary Tract (NTS), and then relayed to the thalamus4](https://en.wikipedia.org/wiki/Interoception)[5](http://www.scholarpedia.org/article/Interoception). The thalamus acts as a relay station, directing the signals to the appropriate brain regions for further processing.

### Specific Organ System Afferents

#### Dermal/Skin System

Sensory receptors in the skin detect changes in temperature, pressure, and pain, which are interoceptive signals. These signals are transmitted via spinal afferents to the CNS for processing.

#### Musculoskeletal System

Proprioceptors in muscles and joints send interoceptive information about body position and movement through spinal afferents to the CNS.

#### Head and Neck

Sensory receptors in the head and neck, including those in the oral and nasal cavities, transmit interoceptive signals via cranial nerves (e.g., glossopharyngeal nerve) to the brainstem.

#### Postural System

Mechanoreceptors in the vestibular system detect changes in head position and movement, sending interoceptive signals through the vestibulocochlear nerve to the brainstem.

#### Cardiovascular System

Baroreceptors and chemoreceptors in blood vessels detect changes in blood pressure and blood chemistry, transmitting interoceptive signals via the vagus nerve to the NTS.

#### Pulmonary/Respiratory System

Stretch receptors in the lungs and airways send interoceptive information about lung inflation and respiratory rate through the vagus nerve to the brainstem.

#### Gastrointestinal System

Sensory receptors in the gastrointestinal tract detect changes in gut distension and chemical composition, transmitting interoceptive signals via the vagus nerve to the NTS.

#### Endocrine System

Hormone levels are monitored by receptors in various endocrine glands, with interoceptive signals transmitted through neural pathways to the CNS for regulation.

#### Immune System

**I**mmune cells release cytokines that can influence neural activity, with interoceptive signals transmitted through afferent pathways to the CNS for immune response modulation.

#### Autonomic System

Sensory receptors in various organs detect changes in autonomic function, transmitting interoceptive signals through autonomic afferents to the CNS for homeostatic regulation.

By integrating interoceptive signals from these diverse organ systems, the CNS can maintain homeostasis and respond to internal and external changes effectively. This comprehensive mapping of the body’s internal landscape is crucial for maintaining overall health and well-being.

| Table 1: Definitions, Pathways, and Interoceptive Components of the Nervous System | | | |
| --- | --- | --- | --- |
| **Nervous System Component/Division** | **Definition & Explanation** | **Pathways** | **Relationship to Interoceptive System (IS)** | |
| **Autonomic Nervous System (ANS)** | Functional division of the nervous system that has components in both the CNS and PNS and controls the involuntary functions of internal organs, blood vessels, smooth and cardiac muscles to regulate bodily functions (e.g., heart rate, digestion, respiratory rate, pupillary response, urination, and sexual arousal), primarily at the unconscious/ subconscious levels, through its interactions with interoceptive signaling pathways. The ANS is divided into two main branches, SNS and PNS that regulate stressful/aversive and homeostatic/ conservative/ restorative processes respectively. | Afferent\*  Efferent\*  Vagal (Autonomic), Glossopharyngeal (Autonomic) | The ANS and IS are closely intertwined, and work together to ensure the body can adapt to internal and external changes, maintaining a stable and functional internal environment. The relationship between the two systems can be summarized as follows:  1. Afferent Pathways: Interoceptive signals are transmitted to the brain via afferent pathways, including the vagus nerve, which is a key component of the ANS.  2. Central Processing: The brain regions involved in processing interoceptive signals, such as the insular cortex and anterior cingulate cortex, are also involved in regulating autonomic functions.  **3. Efferent Pathways**: The ANS responds to interoceptive signals by adjusting bodily functions to maintain homeostasis. (E.g., if interoceptive signals indicate low blood pressure, the ANS can increase heart rate and constrict blood vessels to raise blood pressure). | |
| Sympathetic Nervous System (SNS) | Part of ANS; activates fight-or-flight response, increasing heart rate and energy availability. | Afferent  Efferent\* | The SNS can influence interoception by modulating bodily states that are sensed interoceptively. For example, during a stress response, the SNS increases heart rate and blood pressure, which are interoceptive signals that the brain processes. The SNS and IS are interconnected ***through the body’s stress responses***, where cortisol plays a crucial role. [Cortisol, acting via glucocorticoid and mineralocorticoid receptors, modulates the SNS by influencing heart rate, blood pressure, and energy mobilization, while also affecting interoceptive processes by altering the perception of internal bodily states1](https://www.frontiersin.org/journals/psychology/articles/10.3389/fpsyg.2015.00993/full)[2](https://www.health.harvard.edu/staying-healthy/understanding-the-stress-response)[3](https://academic.oup.com/jes/article/3/10/1917/5537534). (See sections 2.3.1 and 4 for additional detail). | |
| Parasympathetic Nervous System (PSNS) | Part of ANS; promotes rest-and-digest activities, conserving energy and aiding digestion. | Afferent  Efferent\*  (Vagal (Autonomic)) | The PSNS and the IS are closely related, as both are involved in the regulation of internal bodily states and homeostasis through their interactions with the interosome. [As part of the ANS, the PSNS is responsible for promoting the “rest-and-digest” state, which includes activities such as reducing heart rate, promoting digestion, and conserving energy1](https://www.verywellhealth.com/parasympathetic-nervous-system-8687840) that the IS detects, “reports on” and regulates[2](https://www.psychologicalscience.org/observer/interoception-how-we-understand-our-bodys-inner-sensations). Furthermore, Recent findings suggest [interoceptive awareness can modulate parasympathetic activity, leading to changes in heart rate, digestion](https://www.mdpi.com/2076-3425/13/4/592), and a variety of additional ANS properties[3](https://www.mdpi.com/2076-3425/13/4/592). | |
| **Central Nervous System (CNS)** | Comprises the brain and spinal cord; processes and integrates sensory information and coordinates responses. | Afferent\*  Efferent\*  (Spinal, CNS) |  | |
| **Peripheral Nervous System (PNS)** | Connects CNS to limbs and organs; includes sensory and motor neurons. | Afferent\*  Efferent\* |  | |
| Somatic Nervous System (SoNS) | Part of PNS; controls voluntary muscle movements and processes sensory information from external stimuli. | Afferent  Efferent |  | |
| **Enteric Nervous System (ENS)** | Network of neurons in the gastrointestinal tract; regulates digestion independently of CNS. | Afferent\*  Efferent\* |  | |

Table 1: Definitions, pathways, and interoceptive components of various nervous systems. The interoceptive system involves interoceptive sensory receptor transduction into action potentials that are relayed from their respective locations in the interosome (e.g., inside the body) through afferent signalling pathways in the autonomic nervous system, which has components in both the PNS and CNS, and includes both the SNS and PNS. In this table, column 1 identifies specific components or divisions of the nervous system with indented and non-bolded terms indicating subdivions of a larger component/divison shown in a preceeding row.. Column 2 provides a brief definition or explanation of the nervous system component. Column 3 indicates whether the system’s pathways are afferent (ascending from the PNS to CNS) or efferent (descending from the CNS to the PNS), with an asterisk (\*) used to indicate the direction (afferent or efferent0 of the interoceptive pathways in the system and the specific interoceptive components of those pathways outlined below in parentheses. Column 4 describes the way(s) in which the nervous system division specified in column 1 relate to the interoceptive system. Abbreviations: ANS, autonomic nervous system; CNS, central nervous system; ENS, enteric nervous system; IS, interoceptive system; PNS, peripheral nervous system, SPSNS, parasympathetic nervous system; SoNS, somatic nervous system.

Additionally, here are some components involved in processing interoceptive signals:

| **Component** | **Description** |
| --- | --- |
| **Interoceptors** | Sensory receptors that detect internal bodily sensations such as hunger, thirst, and internal pain. |
| **Brain Regions** | Includes the insula, anterior cingulate cortex, somatosensory cortex, and brainstem, which process interoceptive signals. |

I hope this helps with your review of the interoceptive system! If you need any further details or adjustments, feel free to let me know.

Sure! Here are the definitions and additional systems that complement the autonomic and central nervous systems:

### Reflex Loops and Efferent Pathways

Some interoceptive signals trigger reflex loops that result in immediate, involuntary responses. For example, the baroreceptor reflex helps regulate blood pressure by adjusting heart rate and blood vessel diameter. [These reflexes involve direct communication between sensory and motor neurons in the spinal cord and brainstem8](https://magazine.hms.harvard.edu/articles/making-sense-interoception). Additionally, interoceptive signals can lead to conscious actions through efferent pathways. [The brain sends signals via descending neural pathways, such as the vagus nerve and spinal efferents, to modulate the activity of internal organs and maintain homeostasis9](https://www.nccih.nih.gov/grants/concepts/functional-neural-circuits-in-interoception-science).

### Central Nervous System Processing

THE CNS consists of the brain and spinal cord¹. It is the processing center that manages everything your body does, from thoughts and feelings to movements². The CNS receives sensory information, processes it, and responds with motor output³.

#### Spinal Cord

#### Brain

Several brainstem (nucleus of the solitary tract, parabrachial nucleus, and periaqueductal gray), subcortical (thalamus, hypothalamus, hippocampus, and amygdala), and cortical regions (insula and somato- sensory cortices) represent key afferent processing regions (22,42,43). A complementary set of regions involved in visceromotor actions represents key efferent processing regions, including the **anterior insula, anterior cingulate, subgenual cingulate, orbitofrontal, ventromedial prefrontal, supplementary motor, and premotor areas** (44–46). It is noteworthy that these neural regions coincide closely with other sensory processing systems, especially the nociceptive and affective systems. The degree to which these represent distinct or overlapping systems is currently unclear.

particularly through the **vagus nerve** and **spinal pathways**, ultimately reaching a variety of interoceptive processing regions in the brain, including the **insula** and **anterior cingulate cortex (ACC)** as well as the **hippocampus** and **prefrontal cortex (PFC)**. These regions play a crucial role in the conscious awareness of bodily states, contributing to emotional regulation and decision-making (Khalsa et al., 2018; Santamaría-García et al., 2024).

The insular cortex (**InsCtx**) plays a pivotal role in integrating interoceptive signals, acting as a hub for processing sensory information from the body and predicting future physiological states (Khalsa et al., 2018). The **anterior cingulate cortex (ACC)** and the **prefrontal cortex (PFC)** are also crucial, contributing to the cognitive and emotional aspects of interoception (Khalsa et al., 2018). Additionally, the **brainstem** and **hypothalamus** are involved in autonomic regulation, ensuring homeostasis by modulating bodily functions such as heart rate and respiration (Santamaría-García et al., 2024).

##### Brainstem

Additionally, the **brainstem** and **hypothalamus** are involved in autonomic regulation, ensuring homeostasis by modulating bodily functions such as heart rate and respiration (Santamaría-García et al., 2024).

##### Hypothalamus

The **brainstem** and **hypothalamus** are involved in autonomic regulation, ensuring homeostasis by modulating bodily functions such as heart rate and respiration (Santamaría-García et al., 2024).

##### Anterior Insula & Insular Cortex (InsCtx)

The insular cortex (**InsCtx**) plays a pivotal role in integrating interoceptive signals, acting as a hub for processing sensory information from the body and predicting future physiological states (Khalsa et al., 2018).

The **insula** – along with the **anterior cingulate cortex (ACC)**, **hippocampus**, and **prefrontal cortex (PFC)** – plays a crucial role in the conscious awareness of bodily states, contributing to emotional regulation and decision-making (Khalsa et al., 2018; Santamaría-García et al., 2024).

##### Anterior cingulate (ACC)

The **anterior cingulate cortex (ACC)** and the **prefrontal cortex (PFC)** are crucial components of the IS, contributing to the cognitive and emotional aspects of interoception (Khalsa et al., 2018). Together, the **ACC, insula**, **hippocampus**, and **prefrontal cortex (PFC)** play a crucial role in the conscious awareness of bodily states, contributing to emotional regulation and decision-making (Khalsa et al., 2018; Santamaría-García et al., 2024).

##### Subgenual Cingulate

##### Orbitofrontal Area

##### Prefrontal Cortex

Together, the **ACC, insula**, **hippocampus**, and **prefrontal cortex (PFC)** play a crucial role in the conscious awareness of bodily states, contributing to emotional regulation and decision-making (Khalsa et al., 2018; Santamaría-García et al., 2024).

##### Ventromedial Prefrontal Area/Cortex

##### Supplementary motor Area/Cortex

##### Premotor areas

##### Hippocampus

Effective interoceptive awareness facilitates adaptive responses to both internal and external stimuli, essential for maintaining allostasis (Craig, 2009). Thus it is not surprising that the hippocampus is increasingly recognized as a critical component of interoceptive processing and central to the interoceptive system (Barr et al., 2017)., bridging the gap between bodily signals and cognitive-emotional responses.

Traditionally associated with memory and spatial navigation, the hippocampus also plays a significant role in contextualizing interoceptive sensations. Studies have shown that the hippocampus is involved in encoding the emotional significance of interoceptive signals, allowing individuals to form memories based on bodily states (Barr, Bray, & Forster, 2017). This connection facilitates adaptive responses to internal states, as the hippocampus helps contextualize experiences and integrate them into existing knowledge frameworks. By doing so, it aids in decision-making processes influenced by interoceptive awareness, emphasizing its multifaceted role in emotional and cognitive functioning.

Furthermore, the hippocampus interacts with other brain regions involved in interoception, such as the insula and anterior cingulate cortex, to provide a comprehensive understanding of internal bodily signals. This integration allows for the modulation of emotional responses based on interoceptive feedback, which is crucial for effective emotional regulation and social interactions. Dysfunction in hippocampal activity can impair this integration, leading to heightened anxiety and stress responses, as individuals may struggle to accurately interpret their internal states (Khalsa et al., 2018; Santamaría-García et al., 2024). This highlights the hippocampus not just as a memory center but as a vital player in the complex network governing interoceptive awareness and emotional processing.

Table 1 summarizes the key anatomical components involved in interoception, highlighting their specific roles in sensing and processing internal bodily states. The collaborative functioning of these systems emphasizes the intricate link between bodily awareness and emotional health.

| **Table 2: Components and Functions of the Interoceptive System** | |
| --- | --- |
| **Component** | **Role in Interoception** |
| Interoreceptors | Sensory receptors that exist inside the body |
| Insular Cortex (InsCtx) | Integrates interoceptive signals and predicts future physiological states |
| Anterior Cingulate Cortex (ACC) | Contributes to cognitive and emotional aspects of interoception |
| Prefrontal Cortex (PFC) | Involved in higher-order processing and decision-making related to interoceptive signals |
| Hippocampus |  |
| Brainstem | Regulates autonomic functions such as heart rate and respiration |
| Hypothalamus | Maintains homeostasis by modulating bodily functions |
| Cardiovascular System | Provides feedback on blood pressure and heart rate |
| Respiratory System | Monitors oxygen levels and respiratory rate |
| Gastrointestinal System | Detects gut distension and other digestive processes |

Table 2: Components and Functions of the Interoceptive System. This table summarizes the key components involved in interoception, highlighting their specific roles in sensing and processing internal bodily states. The collaborative functioning of these systems emphasizes the intricate link between bodily awareness and emotional health.

The **insula** is especially important for integrating interoceptive information with emotional experiences, thereby allowing individuals to respond appropriately to their internal states. Other brain areas involved include the **somatosensory cortex** and the **prefrontal cortex**, which further process this information and support higher-order cognitive functions. In addition, the interplay between the brain and peripheral organs underscores the importance of interoception in homeostasis, allostasis, somatosensation and overall physical and emotional well-being. Disruptions in interoceptive processing can lead to a large variety of physical and psychological imbalances and disorders (e.g., alexithymia, allostatic and interoceptive overload, somatosensory dysregulation, and a variety neurodivergences), illustrating the critical role of these systems in maintaining physical and mental health (Khalsa et al., 2018; Santamaría-García et al., 2024).

“Brain structure and function of the allostatic interoceptive network

“The integrated allostatic interoceptive processes are associated with brain structure and function of a set of areas known together as the allostatic interoceptive network (AIN) (47).

“Recent studies have identified the allostatic interoceptive network (AIN)(2-4). This brain network is a neuroanatomical and functional system comprising hubs from the salience network and the default mode network and integrating interoceptive information(2-6). Particularly, the AIN comprises a set of regions, including anterior mid-cingulate cortex, pregenual anterior cingulate cortex, subgenual anterior cingulate cortex, dorsal amygdala, ventral-anterior insula, dorsal mid- insula, and dorsal posterior insula(4). ). [And hippocampus (Barr et al., 2017; Bray, 2018)]

The limbic cortices can be divided cytoarchitectonically into agranular regions which send prediction signals and (dys-)granular regions which receive prediction error signals from the internal milieu(4).

Allostatic interoceptive processes are also determined by interactions between the heart, breath, and the gut-brain axis as well as by epigenetic, metabolic, autonomic, inflammatory, immunological, and microbiota mechanisms (16,44,47,63) (Supplemental Section S2). [And glucocorticoid stress systems regulated by the HPA axis and hippocampus (Barr et al., 2017; Bray, 2018)]

The AIN mediates cognitive processes such as memory, executive function, emotional processing, and cognitive control while also relating to allostatic load(2-6). The AIN also oversees heart-brain communication and peripheral activity, subsequently influencing bodily reactions to environmental stimuli(7). Notably, projections from the limbic cortices to the hypothalamus and brainstem nuclei, considered neuroanatomical routes for predictive signals from limbic cortices, help regulate the neuroendocrine, autonomic, and immune systems(4, 8)[as also reported and others (Barr et al., 2017; Bray, 2018)]. “(Santamaría-García et al., 2024)[Supplementary Material].

### Neuroendocrine Processes: The Glucocortiocid Stress System as a Key Component of the Interoceptive System

A variety of literature implicates glucocorticoid and mineralocorticoid stress receptors (GRs and MRs) in a variety of interoceptive processes (Koning et al., 2019; Nicolaides et al., 2014; Sapolsky et al., 2000). While the specific concept of GRs and MRs functioning as interoceptive chemoreceptors has not been addressed in the literature, a variety of literature highlights the critical role of MR and GR stress receptors in mediating allostatic stress adaptation and homeostatic regulation through a variety of interoceptive alterations. For example, glucocorticoids influence stress responses by integrating permissive, suppressive, stimulatory, and preparative actions (Sapolsky et al., 2000). Additionally, MRs and GRs in the brain have distinct and sometimes opposite effects on cellular physiology, which are crucial for maintaining homeostasis and adapting to stress (Koning et al., 2019).

Within the autonomic nervous system (ANS), the sympathetic nervous system (SNS) and parasympathetic nervous system (PSNS) control the body’s “fight, flight, freeze, fawn, or feast ® ” and “rest, digest, restore, conserve” responses that the interoceptive system “reports on” (Schulz & Vögele, 2015; Ueno et al., 2023), in which stress exposure results in activation of the hypothalamic-pituitary-adrenal (HPA) axis, culminating in release of glucocorticoid stress hormones (e.g., cortisol) from the adrenal glands. Glucocorticoid stress hormones (cortisol) are lipophilic, so they can cross a variety of membrane barriers (including the blood-brain barrier and the blood-gut barrier) to activate glucocorticoid and mineralocorticoid stress receptors (GRs and MRs) in a variety of peripheral and central tissues (CITATIONS – see section below or Bray et al., 2018). Activation of GRs and MRs in the ANS tissues and organs regulate a variety of SNS and PSNS responses, including the body’s “fight, flight, freeze, fawn, or feast ® ” and “rest, digest, restore, conserve” responses that the interoceptive system “reports on” (Schulz & Vögele, 2015; Ueno et al., 2023). Thus, the SNS and PSNS have the ability to modify specific conditions of the internal environment (e.g., heart and respiratory rate, vasodilation/constriction, etc.) and the interoceptive system senses and relays information on the internal environmental – including SNS and PSNS responses that induce changes in the internal environment – to higher central processing centers in the brain (Schulz & Vögele, 2015; Ueno et al., 2023). The stress system has the capacity to drive the SNS and PSNS responses and internal environmental changes that the interoceptive system detects, relays, and responds to in turn (Schulz & Vögele, 2015; Ueno et al., 2023).

**Stress-induced cortisol levels can also influence interoceptive processes by affecting how the brain perceives and responds to internal bodily states (Koning et al., 2019; Nicolaides et al., 2014; Sapolsky et al., 2000).** The ability of stress-induced cortisol to influence interoceptive sensitivity and tone may occur at the cellular and molecular level through changes in GR-MR hetero- and homodimerization that alter receptor sensitivity and the direction and magnitude of downstream responses (as has been proposed by Bray et al. (2018, 2020) and others). It may also occur through the ability of GRs & MRs to function as hormone-dependent transcription factors, influencing gene expression and thereby affecting interoceptive processes in turn(Kino & Chrousos, 2004; Koning et al., 2019).

### Descending Pathways and Modulation

Descending pathways play a crucial role in interoception by modulating bodily signals through the autonomic, endocrine, and immune systems. These pathways integrate higher brain functions with bodily regulation to maintain homeostasis. The subsections below describe how they contribute to top-down (descending) interoceptive regulation of homeostasis and allostasis.

#### Autonomic Nervous System (ANS)

The ANS is divided into the sympathetic and parasympathetic nervous systems. Descending pathways from the brain, particularly the hypothalamus and brainstem, regulate the activity of the ANS. For example:

* [**Sympathetic Pathways**: These pathways prepare the body for “fight or flight” responses by increasing heart rate, dilating airways, and mobilizing energy stores1](https://www.frontiersin.org/journals/neuroscience/articles/10.3389/fnins.2022.875200/full).
* [**Parasympathetic Pathways**: These pathways promote “rest and digest” activities by slowing the heart rate, stimulating digestion, and conserving energy1](https://www.frontiersin.org/journals/neuroscience/articles/10.3389/fnins.2022.875200/full).

#### Endocrine System

The hypothalamus and pituitary gland play a central role in the endocrine system. Descending pathways from the hypothalamus regulate the release of hormones that affect various bodily functions. For example:

* [**Hypothalamic-Pituitary-Adrenal (HPA) Axis**: This axis regulates the body’s response to stress by controlling the release of cortisol, a hormone that helps manage stress and maintain homeostasis1](https://www.frontiersin.org/journals/neuroscience/articles/10.3389/fnins.2022.875200/full).

#### Immune System

The nervous system can influence immune responses through descending pathways. For example:

* **Neuroimmune Modulation**: Descending pathways from the brain can modulate immune cell activity, influencing inflammation and immune responses. [This interaction helps the body respond to infections and maintain overall health1](https://www.frontiersin.org/journals/neuroscience/articles/10.3389/fnins.2022.875200/full).

#### Integration with Higher Brain Functions

Descending pathways also integrate higher brain functions with bodily regulation. This integration involves several brain regions, with most rsearch in this area focusing on the role of the prefrontal cortex and limbic system.

* [**Prefrontal Cortex**: Involved in decision-making and emotional regulation, the prefrontal cortex can influence interoceptive processes by modulating autonomic and endocrine responses](https://www.frontiersin.org/journals/neuroscience/articles/10.3389/fnins.2022.875200/full)[2](https://www.frontiersin.org/journals/psychology/articles/10.3389/fpsyg.2024.1244701/full).
* **Limbic System**: Including structures like the amygdala and hippocampus, the limbic system is involved in emotional processing and memory. [It can affect interoceptive signals by modulating stress responses and emotional states](https://www.frontiersin.org/journals/neuroscience/articles/10.3389/fnins.2022.875200/full)[2](https://www.frontiersin.org/journals/psychology/articles/10.3389/fpsyg.2024.1244701/full).

### Maintaining Homeostasis or Allostatic Load

The combined action of ascending and descending pathways ensures that the body maintains homeostasis. [By continuously sensing, integrating, and modulating bodily signals, the nervous system can adapt to internal and external changes, ensuring optimal functioning and health2](https://www.frontiersin.org/journals/psychology/articles/10.3389/fpsyg.2024.1244701/full).

### Additional Systems

#### Peripheral Nervous System (PNS)

This system includes all the nerves outside the CNS. It connects the CNS to the limbs and organs, essentially serving as a communication relay between the brain and spinal cord and the rest of the body¹³.

Peripheral organs and systems, including the **cardiovascular, respiratory, and gastrointestinal systems**, provide continuous feedback to the brain about the body’s internal state. Sensory receptors in these organs detect changes in physiological parameters, such as blood pressure, oxygen levels, and gut distension, and relay this information via afferent pathways to the central nervous system (Khalsa et al., 2018). This intricate communication network allows the brain to maintain homeostasis and respond adaptively to internal and external stimuli (Santamaría-García et al., 2024).

#### Somatic Nervous System (SNS)

A part of the PNS, the somatic nervous system is associated with voluntary control of body movements via skeletal muscles¹².

#### Enteric Nervous System (ENS)

Often referred to as the "second brain," the ENS is a branch of the ANS that operates independently of the CNS. It consists of neurons confined to the gastrointestinal tract and can function autonomously[^10^].

### Heart-brain interactions

Heart-brain interactions have been classically studied via the heart-evoked potential (HEP), an indicator of interoceptive processes and neural responses triggered by cardiac activity (6, 9-18). Multimodal evidence has recently associated the HEP with interoception (11, 12, 19, 20), allostasis (16, 20), and allostatic-interoceptive dynamics (8). An intensified HEP in the resting state has been described as an indicator of allostatic-interoceptive overload (9, 20). HEP involves source generators in interoceptive and allostatic regions, including the insula, anterior cingulate cortex, and amygdala (6). Modulation of the HEP can arise from both bottom-up (i.e., instigated by cardiovascular imbalances and associated error processing) and top-down mechanisms (i.e., deviated interoception with misdirected predictive deductions)(13). Beyond traditional active heartbeat detection tasks, HEP changes measured with amplitude difference, latency, and power occur during non-cardiac monitoring tasks and at rest, and correlate with hypervigilance to interoceptive signals and allostatic overload (21). HEP has been implicated in mental conditions such as insomnia, anxiety, post-traumatic stress disorder, and depression (18), as well as a broad range of neurological (11, 15, 16, 22) neurodegenerative (9, 11, 12, 14, 18, 19, 22) and neurocardiogenic conditions (23).

The brain controls heart activity via the sympathetic and parasympathetic branches of the autonomic nervous system, affecting cardiac function in response to a range of internal and external stimuli (24). This modulation can also be monitored through the heart rate variability index (25). This index is mediated by the integration between top-down mechanisms of prefrontal regions and brainstem nuclei that directly control the heart (26). Heart rate variability has been shown to predict autonomic changes linked to physical stress, cognition, and brain disorders (26).

Given the known links between HRV and a variety of physical and mental health issues that commonly co-occur with eating disorders (e.g., anxiety, depression, trauma/adversity/PTSD, and cardiometabolic syndrome (Bray, Bray, et al., 2022b; Bray et al., 2023)), it would seem reasonable to test whether changes in HRV are associated with BED.

### Respiratory-brain interactions

Respiratory interoception, the ability to sense and regulate breathing, is vital for adapting to external demands(27). Accurate monitoring of respiratory sensations optimizes cardiorespiratory function during activities, acting as a health marker(28, 29). Heightened respiratory awareness is associated with psychiatric conditions including anxiety and panic disorder, and persistent breathlessness has been linked to an increased risk of depression and anxiety (30). Some measures, including breath rate and metacognitive perception, are considered potential allostatic interoception biomarkers (31).

Additionally, Berner et al. have observed altered interoceptive activation before, during, and after aversive breathing load in adult women remitted from anorexia nervosa (RAN)(n=17) vs healthy weight-matched controls (HWCs, n=25) (Berner et al., 2018) and altered anticipation and processing of aversive interoceptive experience (e.g., aversive breathing load) among women remitted from bulimia nervosa (RBN)(n=24) compared to HWCs (n=25)(Berner et al., 2019). During the anticipatory breathing load stage of both parallel studies, relative to respective HWCs, women with RAN showed reduced activation in the right mid-insula (Berner et al., 2018); whereas women with RBN showed *increased* activation in the mid-insula, superior frontal gyrus, putamen, dorsal anterior cingulate, posterior cingulate, and amygdala (Berner et al., 2019). Exploratory analyses indicated that in women with RBN, greater neural activation during breathing load anticipation was associated with past bulimic symptom severity and the duration of symptom remission (Berner et al., 2019). During the aversive breathing load stage in both respective studies, relative to respective HWCs, women with RAN showed increased activity in the striatum and cingulate and prefrontal cortices (PFC) and time course analyses indicated that RAN responses in interoceptive processing regions during breathing load increased more steeply than those of healthy controls (Berner et al., 2018). In contrast, women with RBN showed aberrant decline in activation of the same regions where activity was *increased* during the anticipatory breathing load stage (e.g., the mid-insula, superior frontal gyrus, putamen, dorsal anterior cingulate, posterior cingulate, and amygdala)(Berner et al., 2019). After stimulus offset (in both respective studies relative to respective HWCs), women with RAN showed increased activation in the PFC, bilateral insula, striatum, and amygdala (Berner et al., 2018), with hyperactivation after breathing load associated with markers of past AN severity (Berner et al., 2018).

Together, these findings suggest that in women with RAN, “anticipatory deactivation with a subsequent exaggerated brain response during and after an aversive body state may contribute to difficulty predicting and adapting to internal state fluctuation. Because eating changes our interoceptive state, restriction may be one method of avoiding aversive, unpredictable internal change in AN,” (Berner et al., 2018). In women with RBN, the findings suggest that “an exaggerated anticipatory response and an abnormally decreasing response during aversive homeostatic perturbations may promote hallmark bulimic behaviors [including] binge eating, dietary restriction, and purging,” (Berner et al., 2019). Thus, these findings “support a role for homeostatic instability in BN, and these altered patterns of brain activation may serve as novel targets for pharmacological, neuromodulatory, and behavioral interventions,” (Berner et al., 2019). While AN, BN, and BED are three distinct psychological and neurobiophysiological pathologies, the many shared similarities – especially the binge-eating behavior that is shared in BN and BED – suggests homeostatic instability and dysregulation may exist as a pathological feature of BED that results in altered patterns of brain activation and hallmark disordered eating behaviors (e.g., binge eating). This possibility – if supported -could identify alterations in brain activation patterns as novel targets for pharmacological, neuromodulatory, and behavioral interventions (as suggested for BN in Brenner et al., 2019. However, this possibility, though certainly plausible, requires testing for confirmation.

### Gut-brain-microbiota axis

Gut-brain-microbiota interactions are critical processes guided by predictive allostatic and interoceptive mechanisms (32). The gut-brain axis facilitates bidirectional anticipation and regulation of physiological responses in the presence of external demands (33). Gut-brain- microbiota communication is maintained via a complex network including the salience network, autonomic nervous system, enteric nervous system, hypothalamic–pituitary–adrenal axis, and immune systems (34). Changes in gut-microbiota composition influence this axis, impacting interoceptive awareness, allostatic responses, and brain function related to stress and emotions (29). Diet is one of the critical processes that affect microbiome diversity, impacting gut-brain- microbiome interactions. Moreover, microbes are themselves able to influence eating behavior(35). A balanced gut microbiota supports immune function and intestinal barrier integrity(36).

Axis imbalances may lead to "leaky gut" and inflammatory responses, disrupting allostatic processes(37). Allostatic overload can influence gut microbiota balance (37). Gut microbiota- derived metabolites, like short-chain fatty acids, influence brain function, and affect neurotransmission and functional connectivity. Moreover, cognitive processes including memory, emotion regulation, decision-making, motivated behavior, and circadian process regulation, are shown to be impacted by dysregulations in the gut-brain-microbiome axis (38). Individuals with dysregulation in this axis can exhibit gastrointestinal symptoms, anxiety, depression, avoidance behaviors (39), and poor quality of life (40). Gut-brain-microbiome alterations mediated by inflammatory processes have also been associated with neurodegenerative diseases (41). Critically, microbiome transplants effectively reduced neuroinflammation observed in neurodegeneration (41).

There is also direct evidence supporting desensitization or delay in gastric interoception signaling and reduced myoelectrical power in individuals with BN and BED (n=32 total) relative to age-, sex-, and BMI-matched HCs (n=32) (van Dyck et al., 2020). For example, in a 2-step water load test (WLT-II), individuals with BN or BED drank significantly more water before reporting satiation vs. HWCs and percentage of normal gastric myoelectical power was significantly smaller vs HWCs and negatively correlated to the number of objective binge-eating episodes per week in patients with BN or BED. Power in the bradygastria range was greater in ED than in HC participants. Together, these findings suggest individuals with BED and BN have delayed satiety responses and abnormal gastric myoelectical activity (GMA) relative to weight-matched healthy controls (van Dyck et al., 2020). Whether these abnormalities result from- or contribute to disturbances to gastric motor function warrants further investigation.

ADD PRE/PROBIOtIC WORK HERE (Bray et al., 2024)

### Peripheral biological processes

Allostatic interoception regulates the autonomic nervous system to balance stress responses (42, 43). The autonomic system manages functions like heart and respiratory rate or digestion, modulating responses to environmental stressors. Faced with threats, it activates the "fight or flight" response, while in calm situations, it promotes "rest and digest" activities(42, 43). Key stress biomarkers include arterial pressure (44) and resting heart rate (45).

Metabolic processes convert nutrients into energy essential for growth and repair (46). Allostatic regulation modulates these in response to demands. Under stress, it activates the hypothalamic- pituitary-adrenal axis (HPA(42)), prompting hormone releases. While short-term allostatic responses are both adaptive and protective, long-term elevations can result in health issues (42) including changes in cortisol (47), body mass (48), waist-hip ratio (49), and cholesterol (50).

Allostatic interoception mediates inflammatory responses based on environmental cues, modulating cytokines like tumor necrosis factor-alpha (TNF-α), interleukins (IL; e.g., IL-1β, IL- 6, and IL-10)(51). Elevated cytokine levels during systemic inflammation after stress responses may alter the perception and regulation of inner signals. Although it is an innate defense against threats, persistent inflammation can be harmful (20). Indeed, chronic inflammation is linked to an increased risk of suffering depression, anxiety, and neurodegenerative diseases and is measured by interleukins, cytokines, glial responses, and neurodegeneration markers like neurofilament light chain(48).

### Epigenetics

The interplay between allostatic processes, epigenetic changes, and environmental stressors has recently been highlighted(52). Epigenetics involves gene activity modifications without altering DNA sequences influenced by the exposome. These changes may persist across the lifespan or even across generations(53)(Figure 1D). Allostatic load correlates with these epigenetic alterations, especially in stress-response genes(54). Chronic stress affects the hypothalamic-pituitary-adrenal (HPA) axis, resulting in changes that influence brain development and increase susceptibility to mental disorders(55, 56). Stress-induced shifts in the gut microbiota can also modify neural epigenetics, impacting brain function(57). In addition, recent findings indicate accelerated epigenetic aging due to allostatic overload in older people (52, 58, 59).

## Interoceptive Distinctions

### Interoception & Visceroception

**Visceroception** refers to “the perception of bodily signals arising specifically from visceral organs such as the heart, lungs, stomach, intestines, and bladder, along with other internal organs in the trunk of the body,” (Janig 1996 as cited in Khalsa et al., 2018 Supplementary Material). While interoception is not synonymous with visceroception, it does include (and “subsume”) it (Khalsa et al., 2018). Specifically, interoception describes the perception of bodily signals arising from *all* components of the internal environment and condition, not just those associated with visceral organs (e.g., organs and organ systems located in the trunk of the body, “the viscera”). Thus, organs and organ systems like the skin, musculoskeletal system, immune system, endocrine and neuroendocrine systems, etc. are not included in visceroception but are included in interoception, which relates to *all* physiological tissues that relay a signal to the central nervous system about the current state of the body (not just the viscera) (Khalsa et al., 2018).

### Interoception & Somatosensation

**The somatosensory system,** also known as the **somatic sensory system**, is a part of the sensory nervous system. [It is responsible for processing sensory information from the body, including exteroceptive, proprioceptive, and interoceptive components that include touch, pain, temperature, and body position (proprioception)1](https://en.wikipedia.org/wiki/Somatosensory_system)[2](https://www.biologyonline.com/dictionary/somatosensory-system). This system has two main subdivisions: mechanosensation (e.g., detecting touch and pressure) and nociception (e.g., detecting temperature and pain).

**Somatosensation** refers to the ability of the body’s somatosensory system to sense/detect, process, and perceive ***external stimuli*** from the dermal/skin and musculoskeletal systems (e.g., skin, muscles, joints) through peripheral touch, temperature, pain, and proprioception receptors (e.g., mechanoreceptors, thermoreceptors, proprioreceptors, and nocicpetors), sensory neurons, and brain regions responsible for interpreting these sensory signals to inform perceptions of touch, temperature, pain, and proprioception (e.g., external stimuli and body position) and support interactions with the *external* environment (Cascio, 2010; de Haan & Dijkerman, 2020; Herman et al., 2021; Klingner & Witte, 2018).

The concept of interoception is tightly linked to that of **somatosensation**, (Cascio, 2010; de Haan & Dijkerman, 2020; Herman et al., 2021; Klingner & Witte, 2018).

While interoception and somatosensation both involve sensory processes, they tend to focus on different aspects of sensory perception. For example, both interoception and somatosensation involve the detection and processing of sensory information through neural pathways that transmit sensory information to the brain for sensory processing and perception. However, they differ in the types of stimuli they process, the types of receptors used to process stimuli, and their overall bodily functions.

**Interoception** generally refers to the perception of ***internal bodily sensations***, such as hunger, thirst, heart rate, and internal pain and [involves receptors located in internal organs and tissues](https://med.libretexts.org/Bookshelves/Anatomy_and_Physiology/Human_Anatomy_%28Lange_et_al.%29/13%3A_Somatic_Senses/13.02%3A_Sensory_Modalities_and_General_Senses) (CITE). Interoception involves interoceptors that detect changes within the body’s internal environment, such as blood pressure and visceral pain and plays a crucial role in maintaining homeostasis and regulating bodily functions by providing feedback about the internal state of the body (CITATION).

Recently, somatosensation had gained interest in the field of mental health, with a widespread clinical uptake of somatosensory interventions. These often include mind-body and complementary and integrative health interventions (e.g., yoga, meditation, mindfulness) that demonstrate effectiveness in clinical mental health broadly as well as in eating disorders and binge eating disorder specifically (Bray et al., 2024c.d). The update, exploration, and efficacy of these interventions in the context eating disorders loosely suggests somatic or interoceptive underpinnings for eating disorder and binge eating disorder. This possibility is explored conceptually here and warrants greater clinical exploration through controlled trials.

#### Interoception, Exteroception, & Somatosensation: A Ven Diagram Situation

Interoception and exteroception are both crucial aspects of how we perceive and interact with the world, but they focus on different sources of sensory information:

* [Interoception refers to the perception of internal bodily signals, such as hunger, thirst, heart rate, and internal pain1](https://www.psychologytoday.com/us/blog/explorations-the-mind/202205/the-significance-interoception).
* [Exteroception involves the perception of external stimuli from the environment, such as touch, temperature, and sound1](https://www.psychologytoday.com/us/blog/explorations-the-mind/202205/the-significance-interoception).

Regarding somatosensation and exteroception:

* Somatosensation is a broader term that encompasses the sensory systems responsible for processing information about the body and its environment. [It includes exteroception, proprioception (sense of body position and movement), and interoception2](https://www.amboss.com/us/knowledge/the-somatosensory-system).
* [Exteroception is a subset of somatosensation that specifically deals with external stimuli](https://www.psychologytoday.com/us/blog/explorations-the-mind/202205/the-significance-interoception)[2](https://www.amboss.com/us/knowledge/the-somatosensory-system).

While somatosensation includes exteroception, it also covers other sensory modalities like proprioception and interoception. Exteroception is specifically focused on external sensory information.

## Interoceptive Awareness

The concept of **interoceptive awareness** (IA, capacity for conscious perception of internal bodily sensations/signals and behavioral responsiveness) has been developed into a construct that can be (and is) assessed in research (and clinically) through a variety of subjective and objective measures, including self-report questionnaires (EXAMPLES HERE), behavioral tasks (EXAMPLES HERE), and physiological assessments (e.g., heartbeat detection tasks) (Khalsa et al., 2018; Santamaría-García et al., 2024).

In their 2018 revie of Interoception in Mental Health, Khalsa et al. identify several features of IA, which are reproduced in **Table 3** below.

| **Table 3: Features of Interoceptive Awareness & Assessment Paradigms.** | | |
| --- | --- | --- |
| **Feature** | **Definition** | **Examples of Associated Paradigms** |
| Attention | Observing internal body sensations | **C, GI** (Simmons et al., 2013); **R** (Farb et al., 2013) |
| Detection | Presence or absence of conscious report | **C** (Khalsa et la., 2018; Garfinkel et al., 2013); **R; GI** |
| Magnitude | Perceived intensity | **C, R; GI; U** |
| Discrimination | Localize sensation to a specific channel or organ system and differentiate it from other sensations | **C, R; GI** |
| Accuracy (Sensitivity) | Correct and precise monitoring | **C; C,R; R; GI** |
| Insight | Metacognitive evaluation of experience/ performance (e.g., confidence–accuracy correspondence) |  |
| Sensibility | Self-perceived tendency to focus on interoceptive stimuli (trait measure) |  |
| Self-Report Scales | Psychometric assessment via questionnaire (state/trait measure) |  |

Table 3: Features of Interoceptive Awareness & Assessment Paradigms. The paradigms used to assess the various features of interoceptive awareness span several physiological systems, including the cardiovascular (C), respiratory (R), gastrointestinal (GI), and urinary (U) systems. The paradigms and references listed are obrained from Table S1 in Khalsa et al., 2018 (Khalsa et al., 2018). They are not exhaustive and are provided as illustrative examples only. Many other approaches and paradigms exist, some of which are described elsewhere in this publication.

The anterior insular cortex (AIC) has been implicated in interoceptive awareness (and in awareness more broadly) as well as interoceptive impacts on subjective feelings, in part through its implications (through neuroimaging studies??) in a wide range of conditions and behaviors, ranging from “bowel distension and orgasm, to cigarette craving and maternal love, to decision making and sudden insight,” (Craig, 2009). This region is also associated with neurobiological processes of substance related addictive disorders, withdrawal processes, and eating disorders, including the nonclinical phenomenon of “food addiction” and the clinical diagnosis of binge eating disorder (CITATIONS).

## Interoceptive Load & Overload

Under normal conditions, allostatic interoceptive processes synchronize internal sensing with anticipating external requirements (15,44,64), regulating biological cascades to respond appropriately. However, these processes can become overwhelmed and altered, leading to misreading real and imagined external demands, inaccurate anticipation, and amplified prediction errors (15,25,27,38,44,64). These alterations can trigger dysregulated inflammatory, immune, metabolic, and microbiome cascades, thereby contributing to neurological and psychiatric disorder symptoms (65). Vasovagal syncope exemplifies altered regulatory and anticipatory mechanisms in response to external demands (66) (see Supplemental Section S3).”(Santamaría-García et al., 2024)

Summarize section from (Santamaría-García et al., 2024). Include info from (Khalsa et al., 2018) as needed.

### Interoception & Alexithymia

The concept of interoception is believed to be related in some ways to that of alexithymia, a subclinical phenomenon involving a lack of emotional awareness thought to result from difficulty in identifying and describing one’s feelings and in distinguishing feelings from bodily sensations of emotional arousal (Bray et al., 2023; Nemiah, 1976; Singer & Tusche, 2014). Previously, it has been assumed that alexithymia involves interoceptive deficits that are specific to emotion (Brewer et al., 2016; Nemiah, 1976). However, more recent findings suggest alexithymia is associated with poor non-affective interoception (e.g., somatosensory deficits such as deficits in perceiving heart rate) and increased perceived similarity between affective and non-affective states in both clinical and control populations (Brewer et al., 2016).

Formally, **Alexithymia** is a multidimensional personality trait characterized by difficulties in identifying and describing feelings, distinguishing between feelings and bodily sensations, and an externally oriented cognitive style (Koppelberg et al., 2023). It involves both cognitive and affective deficits, including a lack of emotional awareness and limited imaginative capacity(Koppelberg et al., 2023; Samur et al., 2013).

**Interoception** refers to the ability to perceive internal bodily sensations, such as hunger, thirst, and heartbeat(Butera et al., 2022; Koppelberg et al., 2023). Alexithymia and interoception are related in that both involve the processing of internal states. However, alexithymia specifically pertains to difficulties in recognizing and describing *emotional* states, while interoception encompasses a broader range of bodily sensations (Brewer et al., 2016; Gaggero et al., 2021; Koppelberg et al., 2023). Studies have shown that individuals with alexithymia often have impaired interoceptive accuracy and attention (Gaggero et al., 2021; Koppelberg et al., 2023).

#### Alexithymia and Somatosensation

While alexithymia and somatosensation both involve bodily awareness, alexithymia is more focused on the emotional and cognitive aspects of bodily sensations (Koppelberg et al., 2023; Moriguchi & Komaki, 2013). In contrast, somatosensation is primarily concerned with the physical perception of sensory stimuli (Jones et al., 2004). Neuroimaging studies have shown that alexithymia is associated with altered neural responses to emotional stimuli and enhanced activity in somatosensory regions(Moriguchi & Komaki, 2013).

#### Alexithymia and Eating Disorders

Alexithymia is prevalent in individuals with eating disorders, including anorexia nervosa, bulimia nervosa, and binge eating disorder(Koppelberg et al., 2023; McAtamney et al., 2023). Higher levels of alexithymia have been observed in populations with eating disorders compared to healthy controls (Koppelberg et al., 2023; McAtamney et al., 2023). Alexithymia has been speculated to contribute to the development and maintenance of eating disorders by impairing emotional regulation and increasing vulnerability to stress(Koppelberg et al., 2023; Nowakowski et al., 2013).

#### Alexithymia and Binge Eating Disorder

In the context of **binge eating disorder (BED)**, alexithymia has been associated with difficulties in identifying and managing emotions, which can lead to maladaptive coping strategies such as binge eating (Bray, Bray, et al., 2022b; Bray, Sadowski, et al., 2022; Bray et al., 2023);Koppelberg, 2023 #9107;Nowakowski, 2013 #9115}. BED experts and research suggests that individuals with BED and high levels of alexithymia may use food as a way to regulate their emotions, leading to a cycle of emotional eating and binge episodes (Bray, Bray, et al., 2022a, 2022b; Bray, Sadowski, et al., 2022; Koppelberg et al., 2023; Wallis & Ridout, 2022)

# 

# Stress & Interoception Dysregulation

## Impact of Stress on Interoceptive and Allostatic Interoceptive Processes

Acute and chronic stressors, such as those outlined in **section 3.3** (e.g., ACEs, ALEs, etc.) can profoundly impact (and disrupt or dysregulate) glucocorticoid stress systems as well as interoceptive signaling and awareness (CITE). These experiences can lead to a dysregulated stress response system, where the body's ability to manage stress is compromised, resulting in an **increased allostatic load**. Chronic or prolonged stress, as well as acute on chronic stress, can exacerbate this dysregulation, potentially leading to mental and physical health disorders (Franco-O’Byrne et al., 2024). Santamaría-García et al. (2024) highlight how allostatic interoceptive overload can occur when the demands placed on interoceptive systems exceed their capacity, leading to maladaptive emotional responses and increased vulnerability to mental health disorders. The interplay between environmental demands and biological functions, as modulated by **allostatic interoceptive processes**, is a critical area of research for understanding and treating psychiatric and neurological conditions (Santamaría-García et al., 2024).

Similar to the ways various forms of excess, prolonged, or chronic childhood and lifetime adverse experiences can result in dysregulation of stress responses (e.g, hypersensitization, hypercortisol secretion, blunted disinhibition resulting in prolonged cortisol secretion and exposure), stress-induced interoceptive disruption can manifest as heightened sensitivity to internal signals or reduced awareness, complicating emotion regulation and increasing psychological distress (Schultchen et al., 2019);(Barr et al., 2017; Bray, 2018; Santamaría-García et al., 2024; Schulz & Vögele, 2015). Santamaría-García et al. (2024) note that extreme stress can lead to a feedback loop, where interoceptive overload results in further stress vulnerability, perpetuating a cycle of dysregulation.

## How Stress Modulates Interoceptive Awareness

### Allostatic Interoceptive Overload

Stress can significantly modulate interoceptive awareness by disrupting the body’s ability to accurately perceive and interpret internal signals. Emerging theories emphasize the crucial role of **allostasis** (anticipatory and adaptive regulation of the body’s biological processes) and **interoception** in adjusting physiological responses to environmental and bodily demands (Santamaría-García et al., 2024). Disruptions in **integrated allostatic interoceptive mechanisms** have been observed in psychiatric and neurological disorders, including anxiety, depression, Alzheimer’s disease, and frontotemporal dementia (Santamaría-García et al., 2024). The biological mechanisms associated with allostatic interoception and interoceptive dysregulation include “whole-body cascades” that encompass “brain structure and function of the allostatic interoceptive network, heart-brain interactions, respiratory-brain interactions, the gut-brain-microbiota axis, peripheral biological processes (inflammatory, immune), and epigenetic pathways,” (Santamaría-García et al., 2024). Many of these mechanisms – like the allostatic interoceptive network itself – converge on those implicit in the glucocorticoid stress system.

### Glucocorticoid Stress Dysregulation

#### Cytotxic Glucocorticoid Stress Hormones (e.g., Cortisol) Exposure

Glucocorticoids, particularly cortisol, play a pivotal role in mediating the body's stress responses. Acute stressors may trigger a beneficial response, enhancing resilience and supporting health (eustress). Conversely, chronic stress can lead to maladaptive responses characterized by heightened inflammation and a predisposition to distress (Sapolsky, 2000). Santamaría-García et al. (2024) discuss how glucocorticoid dysregulation can exacerbate interoceptive overload, impacting mental health across various conditions.

#### Hippocampal Dysregulation

Dysregulation of the hippocampal glucocorticoid stress system can significantly impair interoceptive processing. The hippocampus is sensitive to stress hormones, particularly glucocorticoids, which are released during stress responses. Chronic exposure to elevated glucocorticoid levels can lead to hippocampal atrophy and functional impairments, disrupting its ability to integrate interoceptive information effectively (Barr, Bray, & Forster, 2017). This dysfunction can manifest as a reduced capacity to accurately perceive and respond to internal bodily signals, leading to increased anxiety and maladaptive emotional responses. Individuals may find it challenging to interpret sensations such as increased heart rate or gastrointestinal discomfort, which can exacerbate feelings of distress and contribute to a cycle of anxiety.

#### Receptor Dysregulation

A variety of literature implicates glucocorticoid and mineralocorticoid stress receptors (GRs and MRs) in a variety of interoceptive processes (Koning et al., 2019; Nicolaides et al., 2014; Sapolsky et al., 2000). For example, glucocorticoids influence stress responses by integrating permissive, suppressive, stimulatory, and preparative actions (Sapolsky et al., 2000). Additionally, MRs and GRs in the brain have distinct and sometimes opposite effects on cellular physiology, which are crucial for maintaining homeostasis and adapting to stress (Koning et al., 2019).

#### Glucocorticoid Stress Regulations of ANS SNS and PSNS Alteratins ot the Interoceptive Environment

Within the autonomic nervous system (ANS), the sympathetic nervous system (SNS) and parasympathetic nervous system (PSNS) control the body’s “fight, flight, freeze, fawn, or feast ® ” and “rest, digest, restore, conserve” responses that the interoceptive system “reports on” (Schulz & Vögele, 2015; Ueno et al., 2023), in which stress exposure results in activation of the hypothalamic-pituitary-adrenal (HPA) axis, culminating in release of glucocorticoid stress hormones (e.g., cortisol) from the adrenal glands. Glucocorticoid stress hormones (cortisol) are lipophilic, so they can cross a variety of membrane barriers (including the blood-brain barrier and the blood-gut barrier) to activate glucocorticoid and mineralocorticoid stress receptors (GRs and MRs) in a variety of peripheral and central tissues (CITATIONS – see section below or Bray et al., 2018). Activation of GRs and MRs in the ANS tissues and organs regulate a variety of SNS and PSNS responses, including the body’s “fight, flight, freeze, fawn, or feast ® ” and “rest, digest, restore, conserve” responses that the interoceptive system “reports on” (Schulz & Vögele, 2015; Ueno et al., 2023). Thus, the SNS and PSNS have the ability to modify specific conditions of the internal environment (e.g., heart and respiratory rate, vasodilation/constriction, etc.) and the interoceptive system senses and relays information on the internal environmental – including SNS and PSNS responses that induce changes in the internal environment – to higher central processing centers in the brain (Schulz & Vögele, 2015; Ueno et al., 2023). The stress system has the capacity to drive the SNS and PSNS responses and internal environmental changes that the interoceptive system detects, relays, and responds to in turn (Schulz & Vögele, 2015; Ueno et al., 2023).

#### Glucocorticoid Stress Regulations of Interoceptive Tone

**Stress-induced cortisol levels can also influence interoceptive processes by affecting how the brain perceives and responds to internal bodily states (Koning et al., 2019; Nicolaides et al., 2014; Sapolsky et al., 2000).** The ability of stress-induced cortisol to influence interoceptive sensitivity and tone may occur at the cellular and molecular level through changes in GR-MR hetero- and homodimerization that alter receptor sensitivity and the direction and magnitude of downstream responses (as has been proposed by Bray et al. (2018, 2020) and others). It may also occur through the ability of GRs & MRs to function as hormone-dependent transcription factors, influencing gene expression and thereby affecting interoceptive processes in turn(Kino & Chrousos, 2004; Koning et al., 2019).

## Implications for Neurobiology, Psychology, & Psychiatry

Overall, it appears that the dynamic balance between homeostasis, allostasis, and allostatic load, in conjunction with glucocorticoid stress responses and interoceptive processes, forms a complex network that governs the body's reaction to stress. Disruptions in this network can lead to a variety of health challenges, highlighting the need for continued research and intervention strategies to manage stress effectively and maintain overall health and well-being. The interplay among allostasis, allostatic load, interoception, and stress responses is vital for understanding how chronic stress affects mental and physical health. Santamaría-García et al. (2024) provide evidence of how these dynamics contribute to psychiatric and neurological conditions, emphasizing the need for interventions targeting interoceptive awareness and resilience to mitigate the adverse effects of stress. Future studies should aim to further elucidate the intricate connections within this network to better understand the multifaceted nature of stress and its far-reaching implications for human health.

# Role of the Dorsal and Ventral Hippocampus in Eating Disorders

The hippocampus, with its high expression of mineralocorticoid and glucocorticoid receptors, is acutely responsive to stress, making it a key player in the interaction between stress and interoceptive processes, particularly in the context of eating disorders such as binge eating disorder (BED). The hippocampus can be divided into dorsal (posterior) and ventral (anterior) regions, each with distinct functional roles. The dorsal hippocampus is primarily involved in processing exteroceptive cues from the external environment, such as food-related stimuli, while the ventral hippocampus is associated with glucocorticoid stress signaling, emotional regulation, and interoceptive processing (Bray et al., 2020; Barr, Bray, & Forster, 2017). This dichotomy suggests that stress can disrupt the integration of external and internal signals, exacerbating maladaptive eating behaviors often observed in BED.

The dorsal hippocampus relays exteroceptive signals that inform eating behavior based on external cues, while the ventral hippocampus integrates these external signals with internal interoceptive states. This integration is crucial for making informed decisions regarding eating, as individuals with BED often experience a disconnect between their internal bodily cues (like hunger) and external food-related cues (Kullmann et al., 2020). Stress can alter the functional connectivity between these two regions, leading to impaired decision-making and emotional regulation. The coordination between the dorsal and ventral hippocampus is essential for achieving a balanced response to both internal and external stimuli, and disruptions in this network can contribute to the dysregulation of eating behaviors (Bray et al., 2020).

## Functional Connections of the Ventral Hippocampus

### Ventral Tegmental Area (VTA)\*\*:

The ventral hippocampus has reciprocal projections to the VTA, a critical region for dopamine signaling. These connections enable stress to influence the dopaminergic tone, effectively setting a motivational "backdrop" for behavior (Britt et al., 2012). In the context of BED, stress-induced changes in dopamine signaling may enhance cravings for palatable foods, compounding the cycle of emotional eating.

### Nucleus Accumbens (NAc)

Projections from the ventral hippocampus to the NAc facilitate stress-driven dopamine output (Bray et al., 2020). In healthy conditions, this output supports concentration and goal-oriented behavior, whereas in dysregulated states, it can lead to reduced motivation and anhedonia. This is particularly relevant for individuals with BED, as stress may diminish motivation while simultaneously enhancing the desirability of food, fostering binge eating episodes (Eichenbaum, 2017).

#### Impacts on Reward Responses to Internal and External Cues

A variety of literature suggests that in addition to external cue associations, early drug-onset cues (experienced internally) can become associated with the later larger drug effects (Kim et al., 1999). These interoceptive pharmacological cues may overshadow simultaneously present environmental cues and produce conditioned compensatory responses (states of negative affect that are driven by reductions in accumbal shell dopamine levels and oppose the subsequent drug responses). These conditioned compensatory responses are therefore thought to drive tolerance and can reinvigorate drug behaviors (since drug administration can restore the accumbal shell dopamine deficit and thus alleviate the negative affect). It is thought that subjects whose drug administration was not contingent, predictable, or self-controlled may experience stronger drive from interoceptive cues – as opposed to exteroceptive cues – since noncontingent drug experiences lack reliable external predictors by nature. This may result in greater interoceptive cue-driven compensatory conditioned responses that can contribute to greater levels of tolerance in individuals whose drug experience is uncontrollable and unpredictable. Since the ventral hippocampus is associated with relaying *interoceptive* information to the nucleus accumbens shell; whereas the dorsal hippocampus is associated with relaying *exteroceptive* information to the nucleus accumbens core (Barr et al., 2018), the suggestion that greater interoceptive tone mediates tolerance and relapse suggests a possible role for the ventral hippocampus in mediating this process.

A variety of literature exists suggesting that noncontingent models of psychostimulant administration – in which the subject does not have control over drug administration – may result in greater drive from interoceptive cues (novel internal cues that are perfectly contingent with subsequent drug effects and therefore particularly salient). This may result from the fact that exteroceptive clues are limited or lacking in nonocontingent models. This may hold particular relevance to our studies, since the ventral hippocampus is associated with conveying interoceptive information to the nucleus accumbens shell whereas the dorsal hippocampus is more associated with processing exteroceptive cues (and connects to the accumbal core) (Barr et al., 2018).

The interoceptive cues are thought to have greater influence of compensatory conditioned responses that can increase tolerance and produce negative affect states that drive drug behaviors in rats with history of self-administration (who have learned that drug exposure can restore the dopamine deficit associated with the negative affect states); whereas the conditioned compensatory responses can drive drug aversion in rats without a history of self-administration (who have not had the earned experience that drug taking can correct the conditioned compensatory response).

### Prefrontal Cortex

The ventral hippocampus also projects to the prefrontal cortex, influencing executive function, long-term planning, and impulse control (Hasselmo, 2005). Under stress, the ability to regulate impulses related to eating can be compromised, leading to disordered eating patterns. This connection is crucial for moderating the decision-making process regarding food intake, especially in stressful situations (Nusslock & Miller, 2016).

### Amygdala

Projections to the amygdala from the ventral hippocampus enhance anxiety and fear conditioning, which are often heightened during stress (Liu et al., 2012). This increased emotional response can trigger maladaptive eating behaviors as individuals may turn to food as a coping mechanism to alleviate negative emotions associated with anxiety and fear.

### Insular Cortex

The ventral hippocampus also has connections to the insular cortex, a region involved in interoceptive awareness and emotional experience (Kong et al., 2013). These projections enable the integration of interoceptive signals with emotional context, facilitating a more accurate perception of bodily states. Dysregulation in this pathway may contribute to the impaired body awareness often seen in BED.

### Anterior Cingulate Cortex (ACC)

Projections to the ACC further enhance emotional regulation and cognitive control over eating behaviors (Shackman et al., 2011). The ACC is critical for assessing the emotional significance of interoceptive signals. Dysregulation in this pathway can lead to an inability to respond appropriately to internal cues, thereby exacerbating binge eating tendencies in response to stress (Harrison et al., 2010).

## Conclusions

Through these interconnected pathways, the ventral hippocampus serves as a crucial node in integrating stress responses, interoceptive awareness, and behavioral regulation, thereby influencing the development and maintenance of eating disorders such as binge eating disorder. The complex interplay between these systems highlights the importance of addressing both psychological and physiological factors in the treatment of BED.

Moreover, this dysregulation may also affect the connectivity between the hippocampus and other key areas involved in interoception, such as the insula and prefrontal cortex. Impaired signaling within this network can lead to a disconnect between bodily sensations and emotional responses, fostering interoceptive dysregulation. Consequently, individuals may struggle with conditions such as panic disorder, where misinterpretation of bodily signals can trigger overwhelming fear and anxiety (Khalsa et al., 2018; Santamaría-García et al., 2024). This underscores the importance of the hippocampus not only in memory and context but also in maintaining the integrity of interoceptive processes, emphasizing the need for targeted interventions to address stress-related dysregulation in these systems.

Part II: Brief Narrative & Literature Review

**Stress Regulation of Interoceptive Allostatic Load in Binge Eating Disorder**

A Narrative Review of how Glucocorticoid Stress System Dysregulation Mediates an Imbalance Between External & Internal Stress Load Capacity in Eating Disorders

**Juliet Nadershahi1, Brenna Bray, PhD1\***

**1**NourishED Research Foundation (NRFi), Boulder, CO, U.S.A. [www.nourishedrfi.org](http://www.nourishedrfi.org).

\*Corresponding Author: Brenna Bray, PhD, brenna@nourishedrfi.org

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# Abstract

Interoception, the process by which the nervous system senses, interprets, and integrates signals originating from within the body, has gained significant attention in recent years due to its implications for mental health and eating disorders. This narrative review aims to explore the role of interoceptive awareness (IA) in binge eating disorder (BED), examining how stress modulates interoception, the relationship between interoception and other eating disorders, and the links between interoception and neurodivergent conditions such as autism and alexithymia. By synthesizing findings from 34 publications, this review highlights the importance of interoception in understanding and treating BED and other related conditions. Future research directions and potential therapeutic interventions targeting interoceptive deficits are also discussed.

# Introduction/Background

Interoception refers to 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 (Khalsa et al., 2018). Interoceptive awareness (IA) is the conscious perception of these internal bodily signals and is typically measured using self-report questionnaires, behavioral tasks, and physiological assessments (e.g., heartbeat detection tasks). SENTENCE ON ALEXITHYMIA

Recent research has shown that IA plays a crucial role in emotional regulation, cognitive processing, and overall well-being (Brewer et al., 2016; Dunn et al., 2010; Khalsa et al., 2018; Kim et al., 1999; Weng et al., 2020). In the context of eating disorders, deficits in IA have been linked to disordered eating behaviors, such as binge eating, anorexia nervosa, and bulimia nervosa (Jenkinson et al., 2018; Martin et al., 2019). Understanding and improving IA may offer new therapeutic avenues for treating these conditions.

# Interoception in Binge Eating Disorder (BED)

## General Overview

Binge eating disorder (BED) is characterized by recurrent episodes of eating large quantities of food, often rapidly and to the point of discomfort, accompanied by a sense of loss of control. Interoceptive deficits have been associated with BED, suggesting that individuals with BED may have difficulty accurately perceiving and responding to internal bodily signals related to hunger and satiety (Martin et al., 2019).

## Specific Studies and Findings

* **Wiss & Avena (2020)**: This chapter discusses the biological basis of binge eating and the role of food addiction. It highlights the neurobiological vulnerabilities and controversies surrounding food addiction and its public health implications.
* **van Dyck et al. (2020)**: This study investigates gastric interoception and gastric motility in patients with bulimia nervosa and BED. It finds that patients with these disorders have a delayed response to satiation and abnormal gastric myoelectrical activity.
* **Romano et al. (2020)**: This research examines the association between somatic symptoms and binge eating in women’s daily lives. It suggests that somatic symptoms may serve as momentary correlates or proximal antecedents of binge eating behavior.
* **Vinai et al. (2015)**: This study evaluates psychopathology in obese patients with and without BED, finding that BED patients exhibit higher levels of psychopathology, including drive for thinness, bulimia, body dissatisfaction, and interoceptive awareness.
* **Martin et al. (2019)**: This systematic review explores the relationship between interoception and disordered eating. It finds that deficits in interoception are observed across various types of disordered eating and interoceptive modalities, suggesting that interoception may be a transdiagnostic feature of disordered eating.
* **Khalsa et al. (2018)**: This review highlights the role of interoception in mental health, including its contributions to the maintenance of homeostatic functioning, body regulation, and survival. It discusses the challenges and future directions for interoceptive research in mental health.

## Stress & Interoception Disruption

### How Stress Modulates Interoceptive Awareness

Stress can significantly modulate interoceptive awareness by disrupting the body’s ability to accurately perceive and interpret internal signals. Emerging theories emphasize the crucial role of allostasis (anticipatory and adaptive regulation of the body’s biological processes) and interoception in adjusting physiological responses to environmental and bodily demands (Santamaría-García et al., 2024). Disruptions in integrated allostatic interoceptive mechanisms have been observed in psychiatric and neurological disorders, including anxiety, depression, Alzheimer’s disease, and frontotemporal dementia. These disruptions can lead to altered brain structure and function, heart-brain interactions, respiratory-brain interactions, and gut-brain-microbiota axis, among other processes.

## Interoception in Other Eating Disorders

### Mixed EDs and EDNOS

Deficits in interoception have been observed across various types of disordered eating, suggesting that interoception may be a transdiagnostic feature of disordered eating (Martin et al., 2019). This includes mixed eating disorders (EDs) and Eating Disorder Not Otherwise Specified (EDNOS), which included BED before the publication of the DSM-V in 2013.

## Neurodivergence in Eating Disorders and Binge Eating Disorder

### Connections to Conditions like Alexithymia and Autism

Interoceptive deficits have also been linked to neurodivergent conditions such as autism and alexithymia. Alexithymia, characterized by difficulties in identifying and describing one’s own emotions, has been associated with poor interoceptive ability (Brewer et al., 2016). This suggests that interoceptive deficits may play a role in the emotional and cognitive challenges faced by individuals with these conditions.

* **Pruccoli et al. (2023)**: This case series reports on children and adolescents with comorbid feeding and eating disorders (FEDs) and neurodevelopmental disorders (NDDs), such as autism spectrum disorder (ASD) and attention-deficit/hyperactivity disorder (ADHD). The study highlights the impact of NDDs on the diagnosis and treatment of FEDs.
* **Solmi et al. (2021)**: This study investigates the trajectories of autistic social traits in childhood and adolescence and their association with disordered eating behaviors. It suggests that greater autistic social traits in childhood could represent a risk factor for the development of disordered eating in adolescence.
* **Nickel et al. (2019)**: This systematic review explores the overlap between eating disorders, ASD, and ADHD. It highlights the frequent association between these conditions and the need for further research to understand the underlying mechanisms.
* **Dell’Osso et al. (2019)**: This study investigates the prevalence and features of sub-threshold autistic traits (ATs) among adults, suggesting that ATs may be associated with specific personality features and higher vulnerability towards psychopathology.
* **Nazar et al. (2016)**: This study examines the prevalence of ADHD in obese women with binge eating and bulimic behaviors, finding a higher rate of ADHD in this population and a significant correlation with more severe disordered eating patterns.

## Future Directions for Research

Future research should focus on examining particular dimensions of interoception to provide insights into the specific interoceptive deficits associated with disordered eating. This could lead to the development of improved therapies targeting interoceptive awareness and its role in eating disorders (Martin et al., 2019). Additionally, longitudinal studies are needed to better understand the causal relationships between interoceptive deficits and disordered eating behaviors. Investigating the role of stress and its impact on interoception in different populations could also provide valuable insights for developing targeted interventions.

## Conclusions

Interoception plays a crucial role in the understanding and treatment of binge eating disorder and other related conditions. Deficits in interoceptive awareness have been linked to disordered eating behaviors, stress, and neurodivergent conditions such as autism and alexithymia. By synthesizing findings from 34 publications, this narrative review highlights the importance of interoception in understanding and treating BED. Future research should focus on developing improved therapies targeting interoceptive deficits and exploring the underlying mechanisms of interoception in different populations.

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Part III: Narrative & Literature Review Resources

**Interoception & Neurodivergence in Binge Eating Disorder**

A Narrative Review of Existing Literature

**Juliet Nadershahi1, Brenna Bray, PhD1\***

**1**NourishED Research Foundation (NRFi), Boulder, CO, U.S.A. [www.nourishedrfi.org](http://www.nourishedrfi.org).

\*Corresponding Author: Brenna Bray, PhD, brenna@nourishedrfi.org

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# Abstract

# Interoception in Mental Health

#### Santamaría-García, H., et al. (2024). "Allostatic Interoceptive Overload Across Psychiatric and Neurological Conditions." Biol Psychiatry.

1. Abstract

Emerging theories emphasize the crucial role of allostasis (anticipatory and adaptive regulation of the body's biological processes) and interoception (integration, anticipation, and regulation of internal bodily states) in adjusting physiological responses to environmental and bodily demands. In this review, we explore the disruptions in integrated allostatic interoceptive mechanisms in psychiatric and neurological disorders, including anxiety, depression, Alzheimer's disease, and frontotemporal dementia. We assess the biological mechanisms associated with allostatic interoception, including whole-body cascades, brain structure and function of the allostatic interoceptive network, heart-brain interactions, respiratory-brain interactions, the gut-brain-microbiota axis, peripheral biological processes (inflammatory, immune), and epigenetic pathways. These processes span psychiatric and neurological conditions and call for developing dimensional and transnosological frameworks. We synthesize new pathways to understand how allostatic interoceptive processes modulate interactions between environmental demands and biological functions in brain disorders. We discuss current limitations of the framework and future transdisciplinary developments. This review opens a new research agenda for understanding how allostatic interoception involves brain predictive coding in psychiatry and neurology, allowing for better clinical application and the development of new therapeutic interventions.

1. Intro

As a species, we regularly encounter a variety of environmental challenges, including infections, pollution, physical stress, socioeconomic disparities, and trauma. These factors influence our overall well-being (1). Our adaptive capacity is shaped by the intensity of these threats and our inherent biological pre- dispositions (2). Moreover, this adaptation relies on different regulatory physiological mechanisms that anticipate, mediate, and respond to the complexity of environmental and biological interactions (3,4). These regulatory physiological mechanisms can foster successful resilience or result in physical, neurological, and psychiatric disorders (5). Although previous evidence has focused on how our biological systems respond to external stressors, leading to either adaptability or the emergence of diseases (6), significant gaps in our knowledge persist.

Therefore, the mechanisms through which external challenges (e.g., insufficient income) and internal alterations (e.g., dysregulation of the hypothalamic-pituitary-adrenal [HPA] axis) combine to induce psychiatric or neurological pathological outcomes remain unclear (7). Limited evidence details how stressors instigate disease by impacting various biological pathways (2,8). Predominant frameworks, such as diathesis- stress models, overlook the many biological processes that such threats may influence (9–12).

Emerging models could offer new perspectives. Recent studies have underscored the significance of anticipatory bio- logical reactions to upcoming external challenges, or allostasis (13,14), and the perception, regulation, and modulation of in- ternal states, or interoception (10,11,15,16) (Figure 1). Effectively coordinating anticipation of environmental demands and regulating internal bodily demands is crucial for adaptation. Conversely, dysregulation in this coordination is associated with psychiatric and neurological disorders. This dysregulation oc- curs when there is a mismatch between the anticipated energy expenditure and the actual energy required to cope with stressors, leading to physiological alterations due to overload (17–19). A deeper understanding of allostasis and interoceptive processes could elucidate the mechanisms that govern adapt- ability or vulnerability to psychiatric and neurological disorders (4,7,15,17,20), thereby offering an innovative framework for diagnosis, characterization, and intervention.

This review explores the allostatic interoceptive framework in psychiatric and neurological disorders, drawing on an extensive search of MEDLINE, Embase, and Web of Science databases for literature published from January 1, 1998, to June 30, 2023. The search utilized keywords related to external demands, biological processes, allostasis, interoception, and the disorders in question (see Supplemental Section S1). The review is divided into 4 main sections: 1) an overview of integrative models emphasizing allostatic interoception; 2) a detailed examination of allostatic interoceptive processes in disorders such as depression, anxiety, Alzheimer’s disease (AD), and behavioral- variant frontotemporal dementia (bvFTD); 3) an analysis of the

1. Figure 1 Legend

Figure 1. Allostatic interoception regulates environmental and biological interactions across the life span. The left panel outlines predictive allostatic interoceptive processes. The allostatic interoceptive system (A) is supported by the allostatic interoceptive network, which includes principal hubs such as the anterior midcingulate cortex (aMCC), pregenual anterior cingulate cortex (pACC), subgenual anterior cingulate cortex (sgACC), dorsal amygdala (dAmy), ventral-anterior insula (vaIns), dorsal midinsula (dmIns), and dorsal posterior insula (dpIns). The limbic cortices can be divided cytoarchitectonically into agranular regions that send prediction signals and (dys)granular regions that receive prediction error signals from the internal milieu, initiating psychological responses. Allostatic interoceptive processes, which are rooted in brain-body interactions including brain-heart, brain-respiratory, and brain-gut-microbiome systems, facilitate anticipation and guide responses to internal and external demands and threats, which may vary across the life span (B). Various biological predispositions can either dampen or amplify allostatic interoceptive processes, including the functioning of cardiovascular, metabolic, inflammatory, and stress-hormone systems (C). The degree of responses to external stimuli are influenced by genetic-epigenetic predispositions toward adaptive behaviors related to disease risks (D). Visuals in (A–C) are illustrative examples and do not represent actual data. GWAS, genome-wide association study.

Allostatic Interoception in Psychiatry and Neurology framework’s role in elucidating neurological and psychiatric diseases across the life span, including its interaction with the spatiotemporal dynamics of brain function; and 4) a discussion of the research and clinical implications of this framework.

We anticipated empirical support for the presence of allo- static and interoceptive alterations in psychiatric disorders (mainly depression and anxiety) and neurological disorders (mainly AD and FTD). We also expected that these alterations would be associated with the core clinical features of these disorders. Additionally, we hypothesized that pathophysio- logical mechanisms within the allostatic interoceptive frame- work could help explain the neurocognitive and behavioral alterations that we observed. Finally, we elaborate on how the allostatic interoceptive framework interacts with complemen- tary models to explain further normality and the emergence of psychiatric and neurological disorders.

1. ALLOSTASIS, ALLOSTASIS LOAD, AND INTEROCEPTION

Across the life span, humans face different environmental demands such as physical threats, air pollution, infections, and stress, as well as social determinants of health, including social disparities and adversities, which together are known as the exposome (21–23). In adaptative situations, exposomes acti- vate physiological mechanisms to ensure survival and maintain internal equilibrium (14,24,25). Allostasis, which refers to the anticipatory and adaptive regulation of the body’s physiolog- ical processes, is central to adaptation (13). Allostasis is modulated by different biological processes, including genetic and epigenetics, that impact cardiovascular, inflammatory, and metabolic functioning (11,13,14) (Figure 1 and Box 1).

The cost of responding to external demands is known as allostatic load (15,16,20,26). When the exposome or internal bodily needs exceed an individual’s coping ability, allostatic overload ensues (26). Different triggers, including social dis- parities, adversities, lifestyles, and chronic stress, as well as dysregulated internal bodily processes, can result in a state of allostatic overload (24–30). Allostatic overload may trigger neurobiological changes, including oxidative stress; chronic inflammation (31); insulin resistance (32); reduced volume of the hippocampus, amygdala, and prefrontal cortex (19,24); and an imbalance in neurotransmission (33). As such, this state predisposes the organism to chronic diseases

1. Box 1. Glossary

* Interoception: The process by which the nervous system senses, integrates, and anticipates bodily signals at both conscious and subconscious levels, providing a moment-to-moment mapping of the body’s internal landscape. Interoceptive skills encompass sensitivity (accurate detection of internal bodily signals), awareness (ability to be conscious of internal sensations), and metacognition (ability to reflect upon, infer, and evaluate one’s interoceptive skills), among other domains. Descending pathways play a crucial role in interoception by modulating these bodily signals through autonomic, endocrine, and immune systems, integrating higher brain functions with bodily regulation and maintaining homeostasis.
* Exteroception: The process of sensing stimuli originating outside the body. It encompasses the perception of environmental stimuli through sensory organs, enabling individuals to interact with their surroundings.
* Exposome: The totality of an individual’s environmental physical (i.e., pollution) and social (i.e., socioeconomic conditions) exposures across a lifetime that impact health, including pollutants, diet, lifestyles, social determinants of health, social adversities, and structural inequalities.
* Allostasis: The process of achieving stability through change, wherein the body anticipates and generates biological plans to face future needs. An illustrative example of allostatic interoception is how the brain anticipates the need for strenuous activity and prepares the muscles by increasing blood flow.
* Allostatic load: The cumulative strain on the body that results from repeated cycles of anticipatory biological changes designed to prepare the body for potential needs and stress. These changes involve necessary energy adjustments that maintain the body’s readiness for imminent biological responses.
* Allostatic overload: The amplified and dysregulated activation of anticipatory biological responses to potential needs, which lead to a state of wear and tear on the body. This increases the risk of amplified biological imbalances, which in turn trigger physical and psychological alterations.
* Predictive coding theory: A framework proposing that perception, cognition, and action are fundamentally influenced by the brain’s predictive mechanisms. The brain continually creates, infers, and updates a model of the body and environment to anticipate sensory input. Predictions about incoming sensory information are continuously compared with actual sensory input to identify and minimize prediction errors. Through active inference, the brain reduces prediction errors through actions that align the environment with its predictions. High-order areas guide anticipation and predictions, and low-order areas guide perceptual processes. High- and low-order areas feed into each other to minimize prediction errors.

The predictive allostatic interoceptive model: An active framework suggesting that the body anticipates and generates a model of the environment based on interoceptive inputs to face future needs and respond to external demands. Allostasis and interoception are crucial for maintaining physi- ological functioning and are believed to influence emotional, cognitive, and behavioral responses in humans. (14,24,26,28,33–35), such as cardiovascular and metabolic conditions (32,36), accelerated aging (34,37,38), and neuro- psychiatric disorders (27,28,39).

Critically, allostasis processes are also determined by the prediction and integration of internal bodily states known together as interoception (10,11,15). Interoception refers to the process of sensing, integrating, and modeling internal body signals, providing a moment-to-moment mapping of the body’s internal landscape. Different domains constitute the interoceptive capacities, including sensitivity (the ability to detect internal bodily signals accurately), awareness (the ability to be aware of internal sensations in the body), and meta- cognition (the ability to reflect upon and infer one’s intero- ceptive skills) (11,15–17).

Interoception involves complex interactions between afferent (ascending) and efferent (descending) pathways that regulate the internal environment. Interoception allows us to anticipate and regulate sensory signals from innervated visceral organs, including cardiovascular, respiratory, and gastrointestinal systems (40). Interoception also involves che- mosensation, changes in the endocrine system (41), immune system (42), temperature, and affective touch (43). Interoceptive pathways are mediated and regulated by autonomic pro- cesses; integration of ascending and descending neural information (8,16,44); and visuomotor and motor control pathways (17,45–48). On the functional level, interoception influences decision making, emotion regulation, memory, and social interaction (49).

Descendent pathways of interoception, which span the autonomic, endocrine, and immune systems, can originate centrally or reflexively in response to homeostatic disruptions. The central autonomic network, including regions like the anterior cingulate cortex, insular cortex, thalamus, hypothalamus, amygdala, periaqueductal gray, parabrachial nucleus, nucleus tractus solitarius, locus coeruleus, and ventrolateral medulla, broadly impacts sympathetic and para- sympathetic autonomic control of internal states, all responses essential for survival (50–53). These pathways influence organ function, modulate immune responses, and interact with higher brain functions, thereby integrating cognitive and affective processes with bodily regulation (11,50–56).

1. THE INTEGRATED ALLOSTATIC INTEROCEPTIVE FRAMEWORK

The allostatic interoception framework refers to the anticipa- tion and modeling of external demands based on perception, integration, and regulation of inner biological states. Allostatic interoceptive processes allow for the modulation of different biological processes that lead to adaptation or disease (15,16,20,26,57) (see Figure 1A). This framework is consistent with predictive coding, which states that the brain anticipates and models external demands based on internal cues and demands (16,20,58,59). A prediction error is generated when an anticipated modeled signal differs from the actual input. Prediction errors help refine future anticipations and adapt to new challenges (47,59). Discrepancies between predicted and actual signals can trigger dysfunctional responses (7,15,16,20,45,47,60). The Bayesian brain concept extends this idea, suggesting that the brain operates as a Bayesian infer- ence machine, wherein priors—preexisting information, con- straints, or knowledge biologically determined or learned (61)—are continuously updated with new sensory evidence to optimize perception and action (62). Thus, some biological priors, such as genetically encoded modulations or developmental patterns (4), play a crucial role in shaping these predictions.

The integrated allostatic interoceptive processes are asso- ciated with brain structure and function of a set of areas known together as the allostatic interoceptive network (AIN) (47), which include the anterior midcingulate cortex, pregenual anterior cingulate cortex, subgenual anterior cingulate cortex, dorsal amygdala, ventral-anterior insula, dorsal midinsula, and dorsal posterior insula (47). Allostatic interoceptive processes are also determined by interactions between the heart, breath, and the gut-brain axis as well as by epigenetic, metabolic, autonomic, inflammatory, immunological, and microbiota mechanisms (16,44,47,63) (Supplemental Section S2).

Under normal conditions, allostatic interoceptive processes synchronize internal sensing with anticipating external re- quirements (15,44,64), regulating biological cascades to respond appropriately. However, these processes can become overwhelmed and altered, leading to misreading real and imagined external demands, inaccurate anticipation, and amplified prediction errors (15,25,27,38,44,64). These alter- ations can trigger dysregulated inflammatory, immune, meta- bolic, and microbiome cascades, thereby contributing to neurological and psychiatric disorder symptoms (65). Vaso- vagal syncope exemplifies altered regulatory and anticipatory mechanisms in response to external demands (66) (see Supplemental Section S3).

1. THE INTEGRATED ALLOSTATIC INTEROCEPTIVE FRAMEWORK IN PSYCHIATRY AND NEUROLOGY

In psychiatry, a wide array of multigenic factors is recognized, but these are nonspecific due to pleiotropy (one gene linked to multiple traits) and cannot solely account for the onset of psychiatric disorders (67). Theoretical and empirical evidence instead points to complex interactions between environmental and biological factors as being fundamental to psychiatric diseases. Disruptions in anticipatory and regulatory mecha- nisms, particularly predictive allostatic interoceptive pro- cesses, are crucial in various psychiatric disorders, especially anxiety and depression. Evidence from interventions that target these processes further underscores their significance in the development of common psychiatric conditions (see Supplemental Section S4 and Figure 2) (68–73).

1. Anxiety

Anxiety is a complex emotional response encompassing fear, apprehension, and worry. It often arises in response to stress or perceived threats, whether real or imagined (74). Anxiety is an adaptative, natural human experience. When chronic or overwhelming, however, anxiety may interfere with daily functioning and lead to anxiety disorders (74). Anticipatory allostatic interoceptive processes are associated with anxiety symptoms and disorders (27,75).

Previous studies suggest heightened allostatic load in pa- tients with anxiety disorders like panic and generalized anxiety (26). This encompasses increases in proinflammatory cyto- kines, sympathetic dominance, altered HPA axis function, and elevated biogenic amines during fear reactions (24,33,36). Dysfunctions in the anterior insula and anterior cingulate cor- tex, key regions for allostatic processing, have been tied to

anxiety disorders (76). Allostatic overload manifests as symp- toms like autonomic discharges in panic disorders, appre- hensive anticipation, and somatic symptoms in generalized anxiety disorders (26,76,77).

Anxiety is also linked to heightened interoception and misinterpretation of bodily signals, causing symptoms like overmonitoring of physical responses, tension, tiredness, insomnia, heightened startle reflexes, and anxious affect (27,75,78). The discrepancy between expected and actual bodily signals can perpetuate anxiety and maintain a chronic stress response (60). Such alterations have been observed across panic disorders, phobias, and generalized anxiety dis- orders (27,75,78–81).

Although the evidence is not yet conclusive (77), some studies have indicated brain-heart desynchronization, altered heartbeat evoked potential (HEP) index (77,79,82), and heightened cardiac and respiratory interoceptive sensitivity in anxiety (83) and obsessive-compulsive disorder (77,80,84). This increased sensi- tivity may predispose individuals to anxiety disorders by leading them to interpret typical cardiac and respiratory symptoms as catastrophic and triggering different anxiety symptoms.

1. Depression

Depression is a mental health disorder characterized by persistent feelings of sadness, anhedonia, depressive thoughts, motor alterations, tiredness, fatigue, changes in appetite and sleep patterns, and alteration of daily functioning (85). Previous studies have studied depression as an allostatic load disorder (15,17,45,46,86) marked by irregularities in various biological processes (87), including metabolic imbal- ances (88) with abnormal HPA axis activity, proinflammatory states (10), and skewed autonomic processes (45,46,86). Chronic stress, a primary driver of allostatic load and depres- sion risk, induces changes in emotion- and memory-regulating brain structures like the hippocampus and amygdala (45,46).

Numerous studies have also indicated anomalies in intero- ceptive processing in depression, which often manifest as feelings of bodily disconnection or misjudgment of internal states (10,45,89). Evidence suggests altered interoceptive awareness in those patients (90–92). These interoceptive dis- turbances relate to emotion dysregulation and a negative attentional bias (93). Additionally, these deficits are correlated with structural and functional changes in the insula and other brain regions vital for interoceptive awareness (90,94).

Interoceptive changes can influence the allostatic system, contributing to depressive symptoms (45,46,95). Persistent ru- minations and abulia have been linked to disruptions in cardiac and gastric interoceptive feedback, impacting anticipatory allo- static processes (45,46,94,95). Depression’s hallmark symp- toms, such as anhedonia and fatigue, are related to heightened body awareness, reduced body trust, and attentional issues (92,93). Recent reviews indicate that moderate to severe depression is tied to interoceptive alterations affecting decision making and emotion regulation, regardless of comorbidities or treatments like selective serotonin reuptake inhibitors (89).

1. Explanatory Models

The connections between the allostatic interoceptive frame- work and psychiatric disorders are primarily based on correlational studies (96), which are valuable in cognitive neuroscience despite potential confounders and challenges in reproducing causal models (96). Association studies sup- port the framework’s relevance in depression and anxiety. In depression, the locked-in brain hypothesis suggests ineffi- cient energy regulation and insensitivity to prediction errors, leading to mood changes, reduced motivation, and difficulty engaging in activities (45). This is linked to changes in the subgenual anterior cingulate cortex, which regulates auto- nomic control and energy, contributing to depressive symptoms (45,97). Temporary changes in behaviors like eating, sleeping, or exercising can also lead to transient changes in energy regulation, thereby contributing to episodic depression (45).

Anxiety involves unadjusted allostatic interoceptive pro- cesses, altered predictions, and dysregulated energy expen- diture (20,60,77,98,99). This leads to overactivation of biological processes in response to perceived threats (99). Persistent stress can disrupt the HPA axis, elevate cortisol levels, and damage mood-regulating brain areas (18,99,100). Dysregulated interoceptive mechanisms exacerbate anxiety by leading to misinterpretation of bodily cues, which leads to emotional distress and defensive behaviors (18). This is mediated by the altered activity and dynamics of the AIN, salience, and executive control networks (14,45–47,101).

1. PREDICTIVE ALLOSTATIC INTEROCEPTION IN NEUROLOGICAL DISORDERS

Studies of allostatic interoception in neurological conditions have been mainly focused on neurodegenerative disorders (Table 1; Tables S1 and S2). Allostatic overload can heighten sensitivity to future stressors, resulting in a state of hypervig- ilance (24). Such a state can induce chronic stress, leading to inflammation, metabolic imbalances, and increased neurotox- icity, which in turn can cause neural damage. Over time, these detrimental effects may contribute to cognitive and behavioral decline and raise the risk of developing dementia (8,24,102) (Figure 2).

1. CONTRASTS BETWEEN THE ALLOSTATIC INTEROCEPTIVE PROCESSES AND OTHER MODELS OF DISEASE

The allostatic interoceptive framework offers a unique perspective compared with the diathesis-stress (128) and traditional homeostatic models (129). The diathesis-stress model links inherent biological vulnerabilities and external stressors to disorders, while the homeostatic model focuses on maintaining internal balance affected by predispositions and external factors. However, these models have limitations, such as in depression related to external stressors and spo- radic AD (105) and in failing to account for dynamic biological responses to various exposures (14,130).

In contrast, the allostatic interoceptive framework empha- sizes the dynamic interaction between biological factors and external threats based on internal sensing processes (17,47,64). This approach is consistent with enactive frame- works that view disease as changes in interactions between biological agents and the environment rather than merely as brain diseases (131). This enhances the understanding of multietiologic diseases from dimensional and transdiagnostic perspectives and helps to better explain altered cognitive and behavior patterns, consistent with frameworks such as the Research Domain Criteria and the Hierarchical Taxonomy of Psychopathology (Box 2).

1. NEW PERSPECTIVES OF THE ALLOSTATIC INTEROCEPTIVE FRAMEWORK IN PSYCHIATRY AND NEUROLOGY

The allostatic interoceptive framework opens new research avenues in psychiatry and neurology by examining how pre- dictive allostatic interoception processes are crucial during critical neurodevelopmental periods. Alterations in these pro- cesses have been linked to conditions like autism (132), attention disorders (132–135), depression, anxiety (8,11,15,102,136), and neurodegenerative diseases (8,44,47,63,109). Current research highlights gaps, such as the impact of neurodevelopmental changes and external threats, on these mechanisms (Box 3).

The proposed framework also interacts with brain spatio- temporal dynamics, where different time scales affect inter- oception and cognitive processes (137,138). For example, in depression, altered time scale processing affects anticipatory and interoceptive functions, leading to symptoms like reduced speed in processing prediction errors (139). Similarly, besides the allostatic interoceptive failure in bvFTD (63,102,109,111), patients with bvFTD exhibit impaired brain temporal dynamics with 2-fold transient altered temporal states leading to slow (apathy) or fast (disinhibition) neural states (44). Moreover, conditions like autism and schizophrenia (140,141) show de- viations in predictive oscillatory patterns that affect neural synchronization and responses to environmental challenges

(140,141) (Box 4). Despite the mentioned findings (140,141), current evidence on the role of an allostatic interoceptive framework on other disease models, including autism and schizophrenia, is still under debate (140,141). Future research should focus on generating contrastive and comparative studies on how the allostatic interoceptive framework and spatiotemporal approaches better explain the neurobiology and clinical manifestations observed in psychiatric disorders (for a further review of new perspectives of the allostatic interoceptive framework, see Supplemental Section S5).

1. DISCUSSION

The current scoping review highlighted the role of allostatic and interoceptive processes in integrating environmental and biological factors under normal and neuropsychiatric condi- tions. We gathered evidence showing how these processes are altered and directly impact clinical and neurocognitive profiles in depression, anxiety, AD, and FTD, as well as other

neuropsychiatric disorders (see Tables S1 and S2). Our review provides support for a more comprehensive understanding of multilevel biological alterations observed in psychiatric and neurological disorders in this model, compared with other approaches, such as the diathesis-stress model.

Our review identified proposed pathophysiological mecha- nisms altered in allostatic interoceptive processes that contribute to psychiatric and neurological disorders. These include disruptions in energy regulation, unadjusted prediction processes, impaired generation of internal and external models in response to environmental demands, and altered brain- biological systems underlying allostatic interoceptive pro- cesses in the context of neurodegeneration. These alterations stem from regulatory processes determined by the AIN and disrupted energy regulation and predictive processes at various biological levels, leading to cognitive and behavioral changes associated with clinical repertoires in psychiatry and neurology.

Current findings recognize that allostatic interoceptive dysregulations are intertwined with the cognitive, affective, and emotional symptoms of psychiatric (45,46) and neurological conditions (102,109,111). Core evidence in depression and bvFTD support this view. Depression has been described as a systemic dysregulation of the body’s internal mechanisms in response to stress (90,93). Individuals with depression often display altered interoceptive processes. These alterations are associated with specific dysexecutive and emotional dysre- gulation in patients with depression (45,90). In bvFTD research, the alteration of allostatic interoceptive processes, as gauged by HEP modulation and altered connectivity in AIN, has been associated with executive dysfunction, behavioral distur- bances, and impaired emotion and social cognition (102,109,111).

Temporary changes in allostatic interoceptive processes and their impacts on biological cascades could explain the episodic symptomatic phases of psychiatric disorders, particularly in the presence of intense external demands (142).

In contrast, in neurodegenerative disorders, a more chronic, persistent, and accumulated dysregulation of the allostatic interoceptive mechanisms that affect the biology-environment interactions is expected (8,59). These dysfunctions could affect other mechanisms, including oxidative stress processes, mitochondrial breakdown, and altered protein recycling and aggregation (2,8,34,37,63,102,143). The precise mechanisms that lead to neurodegeneration or the temporary imbalances observed in psychiatric conditions remain unclear. New studies are required to explore the potential biological and environmental mechanisms that trigger temporary or chronic changes in psychiatric and neurological conditions.

1. NOVELTY OF THIS STUDY

Current evidence on an allostatic interoceptive framework for psychiatry and neurology faces essential caveats. Although some studies have analyzed combined alterations in allostatic interoceptive processes associated with behaviors (8,59,64) and psychiatric (45,46) and neurological (8,16,63,102,109,111,144) disorders, most research has focused on interoceptive impairments or allostatic overload in isolation. With some exceptions (102,109,111), studies have also focused on specific disorders, lacking dimensional alter- ations observed in psychiatric and neurological disorders. The current study bridges these gaps by analyzing the relationship between allostatic interoceptive mechanisms and biological, neurocognitive, and clinical changes in psychiatric and neurological conditions. It transcends traditional categorical approaches, integrating dimensional frameworks in neuro- psychiatry. It also shows how these processes evolve across the life span, impacting brain health, and interact with brain spatiotemporal dynamics.

New studies should implement specific metrics to capture allostatic and interoceptive processes in psychiatric and neurological disorders. These metrics should include allostatic load indices (27), which measure various biological levels affected by allostatic load processes, and assessments of interoception sensitivity and awareness (102,145,146). As- sessments of brain activity related to interoceptive processes, such as the HEP and the AIN dynamics, and their interaction with other networks could reveal the role of integrated allo- static interoceptive processes in these disorders (45,109). This

is consistent with recent calls for including interoception as a critical construct in neuropsychiatric disorders (54,134).

Evaluating multiple biological levels associated with allo- stasis and interoception will enhance the understanding of intervention impacts on reducing allostatic interoceptive overload (15). Nonpharmacological interventions focusing on respiration, body scanning, and relaxation techniques have shown promise in reducing allostatic interoceptive load, thus alleviating symptoms of anxiety, depression, and somatic is- sues (41,147,148).

Current studies have begun to explore the impact of spatiotemporal brain dynamics on regulating allostatic intero- ceptive processes (44). Different biological processes, including interoception, exteroception, and cognition, occur at varying spatiotemporal dynamics (44,139,149,150). New research could investigate spatiotemporal brain dynamics in altered allostatic interoceptive processes and associate these metrics with specific spatiotemporal brain patterns using whole-brain modeling and other relevant methods.

1. LIMITATIONS OF THE CURRENT FRAMEWORK

Our research underscores the significance of allostatic inter- oceptive processes in psychiatry and neurology, but significant challenges remain. Few studies have combined the effects of allostasis and interoception on these disorders, with most examining them separately. This has resulted in an under- standing based largely on correlations, highlighting the need for comprehensive studies that focus on longitudinal in- teractions between the environment and biology. There is also a notable lack of multilevel analyses, causal modeling, and complexity approaches in existing research.

1. CONCLUSIONS

This review emphasizes the crucial role of allostatic intero- ceptive processes in managing responses to environmental and biological interactions, leading to adaptive or dysregulated outcomes in psychiatric and neurological disorders. We pro- vide evidence of allostatic and interoceptive changes in con- ditions such as anxiety, depression, AD, and bvFTD. These changes can predict various physiological, neurocognitive, and clinical features across disorders. Advancing research in allostatic interoception is vital for developing more in-depth studies on its role in brain health and disease, leading to the implementation of new insights in clinical settings and personalized treatment strategies.

#### Khalsa, S. S., et al. (2018). "Interoception and Mental Health: A Roadmap." Biological Psychiatry: Cognitive Neuroscience and Neuroimaging 3(6): 501-513.

1. Abstract

Interoception refers to 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 signaling has been considered a component process of reflexes, urges, feelings, drives, adaptive responses, and cognitive and emotional experiences, highlighting its contributions to the maintenance of homeostatic functioning, body regulation, and survival. Dysfunction of interoception is increasingly recognized as an important component of different mental health conditions, including anxiety disorders, mood disorders, eating disorders, addictive disorders, and somatic symptom disorders. However, a number of conceptual and methodological challenges have made it difficult for interoceptive constructs to be broadly applied in mental health research and treatment settings. In November 2016, the Laureate Institute for Brain Research organized the first Interoception Summit, a gathering of interoception experts from around the world, with the goal of accelerating progress in understanding the role of interoception in mental health. The discussions at the meeting were organized around four themes: interoceptive assessment, interoceptive integration, interoceptive psychopathology, and the generation of a roadmap that could serve as a guide for future endeavors. This review article presents an overview of the emerging consensus generated by the meeting.

###### Intro

Interoception refers collectively to the processing of internal bodily stimuli by the nervous system. Parcellation of the nervous system’s processing of sensory signals into inter- oception, proprioception, and exteroception began more than 100 years ago (1), although it was predated by interest in linking body–brain interactions with conscious experience (2,3). Scientific interest in interoception has fluctuated (Figure 1A). During the 1980s, biological psychiatry was inundated with observations of interoceptive disturbances in panic disorder (4–7), although the trend receded after it became clear that the etiological mechanism was broader than a single molecular receptor target (8). Recent years have witnessed a surge of interest on the topic of inter- oception due in part to findings highlighting its integral role in emotional experience, self-regulation, decision making, and consciousness. Importantly, interoception is not limited to conscious perception or even unique to the human spe- cies. From this perspective, interdisciplinary efforts to un- derstand different features of interoception have been essential for advancing progress in cognitive and clinical neuroscience (Figure 1B).

###### ASSESSMENT

###### Body Systems of Interoception

Interoceptive processing occurs across all major biological systems involved in maintaining bodily homeostasis, including the cardiovascular (9,10), pulmonary (11), gastrointestinal (12,13), genitourinary (14), nociceptive (15), chemosensory (16), osmotic (17), thermoregulatory (18), visceral1 (19), immune (20,21), and autonomic systems (22,23) (Table 1). There has been relatively little focus overall on the integration across bodily systems; thus, it is not surprising that most in- vestigations of the topic have been siloed within distinct research areas or scientific disciplines [see (24,25) for note- worthy exceptions].

###### Features of Interoception

Interoception is not a simple process but rather has several facets (26). The act of sensing, interpreting, and integrating information about the state of inner body systems can be related to different elements such as interoceptive attention, detection, discrimination, accuracy, insight, sensibility, and self-report (Table 2). However, most interoceptive processes occur outside the realm of conscious awareness. Consciously experienced elements are measured clinically via subjective report, and there are few observable interoceptive signs (e.g., heart rate, respiration rate, pupillary dilation, flushing, perspi- ration, piloerection, nociceptive reflexes) (Table 3). Experi- mental approaches can quantify different body systems and features of interoceptive processing. Nevertheless, these measures are only partially overlapping and likely reflect somewhat distinct neural processes (27). Access to the full range of interoceptive signals often involves invasive ap- proaches, which tend to elicit physiological perturbations and index more objectively measurable features (28). However, many insights have been gained by the application of nonin- vasive approaches within neuroscience and psychological assessment contexts (29) (see “Eavesdropping on Brain–Body Communication” section below).

###### Importance of an Interoceptive Taxonomy

There is no generally agreed-on taxonomy for interoception science. Variable definitions have made it difficult to identify the features under investigation, let alone evaluate the quality of the findings. Based on the number of physiological systems involved, it could be questioned whether the terms “inter- oception” and “interoceptive awareness” are too broad. Interoceptive awareness is an umbrella term that was first used to describe a self-report subscale (30), but it has subsequently been used to encompass any (or all) of the different inter- oception features accessible to conscious self-report. Re- searchers from different fields developed definitions that only partially overlapped, reflecting the need for operationalization in neuroscience (31,32) and clinical practice (33,34). Here we develop a more coherent nomenclature for its various com- ponents (Table 2), mirroring developments in other fields, especially pain (35). One key aspect is the importance of dis- tinguishing sensation (i.e., the raw signals conveyed by bodily sensors) from perception (36,37). We return to this theme below.

###### Multilevel Investigations

While interoception research to date has typically focused on single organ systems, an expanded approach that assesses multiple interoceptive organ systems and/or elements is needed. Examples include targeting numerous interoceptive features simultaneously and employing different tasks that converge on the same feature (e.g., combining top-down assessments of interoceptive attention with bottom-up perturbation approaches in the same individual) (Figure 2A).

###### Sensing Perturbations

The inner and outer worlds of the body constantly fluctuate. The nervous system monitors these environmental changes and responds adaptively in order to maintain a homeostatic balance and promote survival. Because psychiatric disorders often promote or reflect the development of chronic ho- meostatic and allostatic disturbances (38), there is a need for methods capable of eliciting homeostatic perturbations in controlled settings, especially those assessing subjective and behavioral responses to valence and arousal deviations. However, interoception is not simply about afferent pro- cessing. The brain’s constant monitoring of the body occurs in service of optimizing homeostatic regulation. This efferent limb is understudied (39), and paradigms that can effectively measure visceromotor outputs will be critical to establish sensitive assays of dysfunctional interoception and homeo- static regulation (e.g., detection of visceromotor-efferent neural signals controlling baroreflex sensitivity during modu- lation of visceral-afferent input by sympathetic drugs). The reliability and validity of methods should be rigorously established.

###### INTEGRATION

###### Interoception and Domain Specificity Within the Brain

There are fundamentally differing ways to interpret the evolu- tion of brain and body signaling in humans. The processing of interoceptive input could be domain specific, with modular processing occurring in specialized, encapsulated neural cir- cuits [e.g., cardiac, respiratory, urinary, genital, chemical, hormonal; see (40) for a review of domain specificity] or func- tionally coupled (e.g., cardiorespiratory, genitourinary, che- mohormonal) and integrated within a single neural circuit. Understanding the adaptive origins and functions of intero- ceptive domain specificity (if present) could tell us how the implementation and deployment of interoceptive signals by the nervous system contributes to disordered mental health. Because interoceptive signaling involves afferent and efferent inputs across multiple hierarchies within the autonomic and central nervous systems, identifying where and how informa- tion processing dysfunctions negatively affect mental health represents a challenging problem.

###### Neural Pathways of Interoception

Several pathways have been implicated in the neural pro- cessing of interoceptive signals, beginning with a rich interface between autonomic afferents and the central nervous system. Relay pathways involve primarily spinal, vagal, and glossopharyngeal afferents, with multiple levels of processing and integration in autonomic ganglia and spinal cord (10,19,22,41). Several brainstem (nucleus of the solitary tract, parabrachial nucleus, and periaqueductal gray), subcortical (thalamus, hypothalamus, hippocampus, and amygdala), and cortical regions (insula and somato- sensory cortices) represent key afferent processing regions (22,42,43). A complementary set of regions involved in visceromotor actions represents key efferent processing regions, including the anterior insula, anterior cingulate, subgenual cingulate, orbitofrontal, ventromedial prefrontal, supplementary motor, and premotor areas (44–46). It is noteworthy that these neural regions coincide closely with other sensory processing systems, especially the nocicep- tive and affective systems. The degree to which these represent distinct or overlapping systems is currently unclear.

###### Linking Paradigms Across Units of Analysis

A particular challenge when examining interoception is the fact that afferent sensory signals are integrated on several levels (peripherally, within the spinal cord, and supraspinally) to form sets of interoceptive maps across different body systems. The brain appears to integrate information representing particular states of multiple systems simultaneously (cardiac, respiratory, chemical, hormonal, nociceptive, etc.) (41), and it is imperative to be able to model and comparatively evaluate such map- pings (Figure 2B). This poses many challenges. One approach might be to apply measures that assess multiple organ sys- tems or interoceptive features simultaneously [see (42,47,48)] or to record activity across the brain, spinal cord, and peripheral organs (49). However, it is also possible that multisystem as- sessments may reduce specificity for certain disorders and therefore may be unnecessary. For example, some patients with panic disorder may experience dyspnea but not palpita- tions. Localizing and then targeting the dysfunctional intero- ceptive domain would become more useful than broad multisystem interventions.

###### Timing and Rhythm in Interoceptive Circuits

The physiological timescales and amplitudes of interoceptive signaling vary dramatically (e.g., heart rate [0.5–3.3 Hz], res- piratory rate [0.08–1 Hz], gastric contractility [0.05–0.1 Hz], urinary frequency [0.000045–0.00012 Hz]), with even slower changes in humoral mediators (50) (Figure 2C, D). They also vary across individuals, and over the life span (e.g., increased heart rates in infants/children). Despite the variance, the brain tracks such changes in similar subregions, including the insula, somatosensory cortices, cingulate, amygdala, thal- amus, and brainstem (42,43,51–53). Temporal synchrony or dyssynchrony between these systems may affect interocep- tive experiences, affect, and behavior, although the exact mechanisms require further study (54). Repetitive events are

another important element for learning, and while there are numerous classic studies on visceral learning at the periph- eral organ system level (55,56), we know little about the central mapping of learned visceral memories, especially in psychiatric disorders (57).

###### PSYCHOPATHOLOGY Interoceptive Psychopathology

Several conceptual and heuristic models have linked dys- functions of interoception to mental health conditions. Spe- cifically, mood and anxiety disorders have been linked to failures to appropriately anticipate changes in interoceptive states (97). Eating disorders show behavioral and neural

abnormalities in interoceptive processing, particularly in the context of caloric anticipation (72,98–100), although it remains unclear whether this is due to altered afferent signaling, altered central sensory processing, abnormal temperament, and/or metacognition. Drug addiction, another condition marked by interoceptive disturbances, has an overlapping neural circuitry and abnormal responses to interoceptive cues (101–104). Interoceptive dysfunction also likely plays a role in conditions such as posttraumatic stress disorder and somatic symptom disorders (33). Other disorders also have interoceptive symp- tom overlap; however, the specific feature involved may differ according to the disorder or affected individual [e.g., chronic pain (105,106), Tourette’s syndrome and other tic disorders, borderline personality disorder, obsessive-compulsive disor- der, autism spectrum disorder (107), functional developmental disorders (108)]. Table 3 lists diagnostic symptoms and clinical signs indicative of interoceptive dysfunction in several psychi- atric disorders. Conditions that have a psychiatric component include fibromyalgia, chronic fatigue syndrome, irritable bowel syndrome, and functional disorders within medicine (e.g., noncardiac chest pain, functional dysphagia) as well as certain medical disorders (e.g., gastroesophageal reflux, asthma).

Alternatively, one can use a dimensional psychopathology approach to link processes underlying interoceptive dysfunc- tion to psychiatric disorders. Transdiagnostic perspectives such as those provided by the Research Domain Criteria (109) may be particularly helpful in identifying the potential role played by various interoceptive processes because several of these might not be readily identified at the symptom report

level relied on by clinicians and, accordingly, might not have entered into the diagnostic specifications for DSM. This would allow for identification of mechanistic dysfunctions across units of analyses and might bridge the biological gap in current diagnostic classification frameworks by directly probing the links between physiological and psychological dysfunctions. Interoceptive investigations in mental health populations might reveal evidence of 1) attentional bias (e.g., hypervigilance), 2) distorted physiological sensitivity (e.g., blunted or heightened magnitude estimation in response to a perturbation), 3) cognitive bias (e.g., catastrophizing in response to an antici- pated stimulus), 4) abnormal sensibility (e.g., tendency to label one’s experiences in a particular way), and 5) impaired insight (e.g., poor confidence–accuracy correspondence on a task).

Determining whether interoceptive processes are a cause or consequence of developmental psychopathology, and which factors might affect this development (such as early life stress or pain), will be an important area for future research. Such studies may benefit from the examination of younger (110,111) or older (112,113) samples and premorbid identification and longitudinal tracking of individuals (114). Investigating the role of social cognition/theory of mind in clinically relevant intero- ceptive inference generation represents another ripe opportu- nity (115).

Interoceptive Tests and/or Biomarkers

Because interoception is fundamentally a process linking body and brain, it is conceivable that objective measures of this process could serve as biological indicators of disease states. However, there is currently limited evidence for interoceptive predictors of diagnostic, prognostic, or treatment status (33,116,117). Biomarkers, such as those derived from neuro- imaging or blood measurements, should be sensitive, specific, and unaffected by cognitive and emotional influences. How- ever, it seems conceivable that the most clinically sensitive interoceptive measures might derive from probes that perturb physiological functions to engage specific metacognitive be- liefs and/or expectations about bodily states. Such measures could facilitate differential diagnosis testing by revealing the presence of interoceptive dysfunction of biological (within a physiological system or systems), psychological (e.g., overly precise expectations about bodily states), or metacognitive (e.g., discrepant self-efficacy beliefs with regard to homeo- static/allostatic regulation) origin (37). This approach could be seen as analogous to a cardiac stress test, such that adequate engagement of the system under ecologically valid conditions is required in order to measure its dysfunction.

The most common application of interoceptive evaluation in current clinical practice occurs during interoceptive exposure psychotherapy for panic disorder (118). During this procedure, patients self-induce varieties of interoceptive symptoms via low-arousal manipulations (e.g., hyperventilation, performing jumping jacks, spinning in a chair, breathing through a straw) while the clinician monitors their subjective distress level. Unfortunately these manipulations often fail to adequately reproduce the fear response, possibly because the patient retains full control over the stimulation (the patient can quit at any time) and the perturbation remains predictable with mini- mal uncertainty, raising the question of whether modulating

both physiological homeostasis and the perception of controllability might further improve the ecological validity and efficacy of interoceptive exposures (119). A test to verify suc- cessful interoceptive exposure therapy for panic disorder in- volves completion of a standardized behavioral avoidance paradigm (120). In this setting, the degree of tolerance to being enclosed in a small dark chamber for 10 minutes might provide behavioral evidence verifying tolerance to triggers of intero- ceptive dysregulation. There is also experimental evidence that pharmacological interoceptive exposure therapy can reduce anxiety disorder symptom severity either as monotherapy (7,121–123) or as an augmentative approach (124). However, there are few studies of these procedures to date, the impact of such interventions on longer term outcomes (e.g., 6 months or beyond) are unknown, and none of these approaches has translated into clinical practice.

###### Current Treatments Relevant to Interoception

Among the currently available therapies with an interoceptive basis are pharmacotherapies directly modulating interoceptive physiology. Examples include adrenergic blockade (e.g., pro- pranolol) or agonism (e.g., yohimbine), stimulants (e.g., methyl- phenidate), benzodiazepines, muscle relaxants, and opioids. A second example is cognitive behavioral therapy with exposure and response prevention to reverse or attenuate conditioned fears or form new learned associations. It is helpful in ameliorating cognitive biases in numerous disorders, including depression, obsessive-compulsive disorder, posttraumatic stress disorder (specifically prolonged exposure therapy), irritable bowel syn- drome, and chronic pain. Interoceptive exposure is a special example demonstrated to be effective in specific disorders (especially panic disorder). Behavioral activation therapy for depression sometimes includes exposure to experiences with positive interoceptive value. A third example is capnometry- assisted respiratory training. Based on the assumption that sustained hypocapnia resulting from hyperventilation is a key mechanism in the production and maintenance of panic, carbon dioxide capnography-assisted therapy aims to help patients voluntarily increase end-tidal partial pressure of carbon dioxide and tolerate physiological variability associated with panic at- tacks (125,126). As a fourth example, mindfulness-based stress reduction, yoga, and other meditation/movement-based treat- ments may be aimed at improving metacognitive awareness of mind–body connections by systematically attending to sensa- tions of breathing, cognitions, and/or other modulated body states (e.g., muscle stretching) (127).

###### Interoceptive Treatments on the Horizon

Several emerging technologies may have relevance for inter- oception and mental health, including Floatation-REST (reduced environmental stimulation therapy) and perturbation approaches.

###### Floatation-REST.

This intervention, which systematically attenuates exteroceptive sensory input to the nervous system, also appears to noninvasively enhance exposure to intero- ceptive sensations such as the breath and heartbeat (128). Preliminary data suggest that a single 1-hour session has a short-term anxiolytic and antidepressant effect in patients with

###### ROADMAP

###### The Road Ahead

Beyond the issues outlined previously, progress in determining the relevance of interoception for mental health relies on emphasizing the features that distinguish it from other sensory modalities. Interoception seemingly involves a high degree of connectivity within the brain (135). It appears to be tightly linked to the self and survival through homeostatic mainte- nance of the body, and by helping us to represent how things are going in the present with respect to the experienced past and the anticipated future. These computations may depend on what has occurred to shape the body’s internal landscape, and it is in this regard that learning, and malleability of repre- sentations over time, could play important roles.

The conceptual framework for investigating interoception may overlap with other processes, including emotion (136) and pain (137), because each is integral for maintaining bodily homeostasis. An important endeavor may involve the identification of which neural systems for interoception, emotion, cognition, and pain are overlapping, interdigitating, or even possibly identical. Additional effort is needed to define the neurophysiological nomenclature, core criteria, common features, developmental aspects, modulating fac- tors, functional consequences, and putative pathophysio- logic mechanisms of interoception in mental health disorders.

The current work offers some conceptual distinctions and some mutually agreed-on terminology, with many others still needed. Several low-hanging fruits, as well as promising emerging technologies and tools, have been mentioned. Further empirical work will be critical to delineate how inter- oception can be mapped to mental health measures, models, and approaches, and benchmarks for success/failure need to be established. Models of interoceptive processing that improve on the traditional stimulus, sensorimotor processing, and response function concepts have been described, but these models remain theoretical and await further testing. Therefore, the current document is best viewed as a work in progress.

#### Brewer, R., et al. (2016). "Alexithymia: a general deficit of interoception." R Soc Open Sci 3(10): 150664.

Alexithymia is a sub-clinical construct, traditionally characterized by difficulties identifying and describing one's own emotions. Despite the clear need for interoception (interpreting physical signals from the body) when identifying one's own emotions, little research has focused on the selectivity of this impairment. While it was originally assumed that the interoceptive deficit in alexithymia is specific to emotion, recent evidence suggests that alexithymia may also be associated with difficulties perceiving some non-affective interoceptive signals, such as one's heart rate. It is therefore possible that the impairment experienced by those with alexithymia is common to all aspects of interoception, such as interpreting signals of hunger, arousal, proprioception, tiredness and temperature. In order to determine whether alexithymia is associated with selectively impaired affective interoception, or general interoceptive impairment, we investigated the association between alexithymia and self-reported non-affective interoceptive ability, and the extent to which individuals perceive similarity between affective and non-affective states (both measured using questionnaires developed for the purpose of the current study), in both typical individuals (n = 105 (89 female), mean age = 27.5 years) and individuals reporting a diagnosis of a psychiatric condition (n = 103 (83 female), mean age = 31.3 years). Findings indicated that alexithymia was associated with poor non-affective interoception and increased perceived similarity between affective and non-affective states, in both the typical and clinical populations. We therefore suggest that rather than being specifically associated with affective impairment, alexithymia is better characterized by a general failure of interoception.

#### Dunn, B. D., et al. (2010). "Listening to your heart. How interoception shapes emotion experience and intuitive decision making." Psychol Sci 21(12): 1835-1844.

Theories proposing that how one thinks and feels is influenced by feedback from the body remain controversial. A central but untested prediction of many of these proposals is that how well individuals can perceive subtle bodily changes (interoception) determines the strength of the relationship between bodily reactions and cognitive-affective processing. In Study 1, we demonstrated that the more accurately participants could track their heartbeat, the stronger the observed link between their heart rate reactions and their subjective arousal (but not valence) ratings of emotional images. In Study 2, we found that increasing interoception ability either helped or hindered adaptive intuitive decision making, depending on whether the anticipatory bodily signals generated favored advantageous or disadvantageous choices. These findings identify both the generation and the perception of bodily responses as pivotal sources of variability in emotion experience and intuition, and offer strong supporting evidence for bodily feedback theories, suggesting that cognitive-affective processing does in significant part relate to "following the heart."

# Stress, Mental Health, Eating Disorders, & Interoceptive Deficits

## Stress in Interoceptive Awareness

#### Santamaría-García, H., et al. (2024). "Allostatic Interoceptive Overload Across Psychiatric and Neurological Conditions." Biol Psychiatry.

Emerging theories emphasize the crucial role of allostasis (anticipatory and adaptive regulation of the body's biological processes) and interoception (integration, anticipation, and regulation of internal bodily states) in adjusting physiological responses to environmental and bodily demands. In this review, we explore the disruptions in integrated allostatic interoceptive mechanisms in psychiatric and neurological disorders, including anxiety, depression, Alzheimer's disease, and frontotemporal dementia. We assess the biological mechanisms associated with allostatic interoception, including whole-body cascades, brain structure and function of the allostatic interoceptive network, heart-brain interactions, respiratory-brain interactions, the gut-brain-microbiota axis, peripheral biological processes (inflammatory, immune), and epigenetic pathways. These processes span psychiatric and neurological conditions and call for developing dimensional and transnosological frameworks. We synthesize new pathways to understand how allostatic interoceptive processes modulate interactions between environmental demands and biological functions in brain disorders. We discuss current limitations of the framework and future transdisciplinary developments. This review opens a new research agenda for understanding how allostatic interoception involves brain predictive coding in psychiatry and neurology, allowing for better clinical application and the development of new therapeutic interventions.

### Stress in Physical & Mental Health

Feletti ACES

#### The Ventral Hippocampus Relays Interoceptive Cues to the Nucleus Accumbens and is Sensitive to Stress

The hippocampus is a brain region associated with mediating and moderating stress responsiveness (Barr et al., 2017; Bray, 2018; Bray et al., 2020). At the cellular and molecular level, it has a high density of glucocorticoid and mineralocorticoid stress receptors, making it sensitive and responsive to stress-induced glucocorticoid (cortisol) release (see citations in (Barr et al., 2017; Bray, 2018; Bray et al., 2020)). The hippocampus has been subdivided into posterior/dorsal and anterior/ventral regions based on anatomical connectivity and behavioral output in rodents and humans respectively (Barr et al., 2017). The posterior/dorsal hippocampus receives *exteroceptive* information from the entorhinal cortex and has a major role in rapid spatial learning (**Figure 1**) [52]. The anterior/ventral hippocampus receives *interoceptive* information through reciprocal connections to limbic regions that modulate motivational and affective states (Barr et al., 2017). Other limbic brain regions involved include the nucleus accumbens, amygdala, medial prefrontal cortex, and hypothalamus (**Figure 1**) [50–54] (Barr et al., 2017; Bray, 2018; Bray et al., 2020). Notably, both regions of the hippocampus are involved in memory formation [55]; posterior/dorsal neurons form contextual representations of specific single events while anterior/ventral neurons form representations of multiple events (related by a distinct context) over time [56].

A diagram of a nervous system

Description automatically generated

The subiculum, the major output structure of the hippocampus, provides projections to the nucleus accumbens, which also receives input from anterior/ventral tegmental area (VTA) dopamine terminals [34, 57–59](Barr et al., 2017; Bray, 2018; Bray et al., 2020) (Fig 1-3 used with permission from Bray, 2018). The nucleus accumbens integrates affective and motivational information to produce goal-directed behavioral output [60–62]. Thus, the hippocampus – through its interactions with the mesoaccumbal dopamine system – is poised to play an important role in mediating the effects of drugs of abuse (e.g., psychostimulants)(Barr et al., 2017) as well as the effects of other salient stimuli, including emotional responses to environmental experiences and cues *and* reward/distress responses to food and eating, including responses to highly processed food consumption and/or binge eating-, bulimic-, or restrictive eating behaviors.

Diagram of a diagram of a complex structure

Description automatically generated with medium confidence***Figure 1-3. Neural Circuits that Enable Ventral Hippocampal Excitation to Enhance Accumbal Dopamine Output and Mediate Accumbal Excitation/Inhibition.*** *In the midbrain, cells from the medial ventral tegmental area (VTA, shown in blue) send dopaminergic (DA) projections to the medial nucleus accumbens shell (NAcS, shown in purple) that are responsible for NAcS dopamine output (Koob & Volkow, 2010; Pignatelli & Bonci, 2018). The ventral hippocampus (vHipp, yellow) sends separate populations of glutamatergic projection neurons (green) onto the VTA-NAcS dopamine projections; these terminate on the soma within the VTA and onto the dopamine terminals within the NAcS and can increase cell firing (from the VTA) and stimulate terminal dopamine release (within the NAcS) respectively (Britt et al., 2012; Floresco et al., 2001; Geisler et al., 2007; Legault et al., 2000; Tye, 2012; Valenti et al., 2011). A separate population of glutamatergic efferents from the ventral hippocampus that projects to the NAcS is disynaptic and terminates onto excitatory D1- and inhibitory D2 medium spiny neurons (MSNs) within the NAcS and onto feed-forward interneurons. The interneurons target MSNs and tightly regulate the excitatory/inhibitory balance of MSNs locally and create an overall inhibitory “backdrop” within the NAcS in control conditions (Scudder et al., 2018). Dopamine and MSN excitation in the NAcS can also regulate VTA dopamine output reciprocally through direct and indirect pathways (Floresco et al., 2001; Pignatelli & Bonci, 2018). For example, the NAcS sends inhibitory projections to the ventral pallidum (VP, shown in crimson; inhibitory GABAergic projections shown in red) that can disinhibit VTA activity, and the glutamatergic efferents from the ventral subiculum have been functionally linked to this circuit (Floresco et al., 2001). The NAcS also sends two separate populations of direct GABAergic projections to the medial VTA that respond to accumbal shell dopamine and terminate onto VTA dopamine soma or onto feed-forward inhibitory interneurons in the VTA that project onto the VTA dopamine soma, thus enabling accumbal dopamine output to rapidly induce feedback inhibition- or disinhibition onto the VTA directly (Pignatelli & Bonci, 2018; Yang et al., 2018). Finally, the ventral hippocampus sends glutamatergic and GABAergic projections to the basolateral amygdala (BLA, pink) and medial prefrontal cortex (mPFC, gold), both of which send glutamatergic afferents to the NAcS and VTA that enhance NAcS dopamine release in turn (Britt et al., 2012; Carr & Sesack, 1996; Floresco, 2014; Howland et al., 2002; Imperato et al., 1990; Kalivas, 2000; Strange et al., 2014; Tye, 2012; Tye & Deisseroth, 2012; Wanchoo et al., 2009). The mPFC and amygdala also send excitatory projections to the ventral hippocampus, which can regulate NAcS dopamine output and subsequent behaviors indirectly through the ventral hippocampal inputs (Barr et al., 2017; Tye, 2012; Tye & Deisseroth, 2012). In this figure, green projections represent excitatory glutamatergic projections; red projections represent inhibitory GABAergic projection neurons and interneurons.* ***Abbreviations:*** *BLA: Basolateral amygdala; D1: Excitatory type-1 Gs/o dopamine receptor-expressing medium spiny neuron; DA: Dopamine; Glut: Glutamate; mPFC: Medial prefrontal cortex; NAcS: Nucleus accumbens shell; VTA: ventral tegmental area.*

Importantly, the posterior/dorsal and anterior/ventral hippocampus may differentially regulate accumbal activity [60, 63], since the anterior/ventral subiculum projects to the medial shell of the nucleus accumbens while the posterior/dorsal subiculum projects to the more lateral accumbens and core (**Figure 1**) [51, 54, 64]. The posterior/dorsal and anterior/ventral hippocampus also influences accumbal activity indirectly, via multi-synaptic projections to the VTA (**Figure 1,1-3**) [65–67]. Consequently, glutamatergic output from the hippocampus facilitates dopaminergic activity in the mesolimbic dopamine pathway [34, 57, 68, 69]. In the nucleus accumbens shell, this communication is vital for forming place-reward associations [70–72] and mediating reward salience [63]. Thus, context-related processing within the hippocampus may drive reward-related processes mediated by the nucleus accumbens.

The hippocampus also regulates anxiety and avoidance behaviors. Anxiety is an innate response coordinated to protect an animal from potential harm, which is linked to maximizing chances of reward in approach-avoidance conflict situations. The hippocampus has been proposed to underlie anxiety behaviors by detecting novelty or uncertainty [73, 74] and then increasing attention and behavioral inhibition [75, 76]. However, maladaptive changes to the circuits underlying this response can constrain normal functioning and lead to a disruptive pathological state.

The *anterior/ventral* hippocampus in particular plays a predominant role in mediating anxiety/avoidance behaviors. For example, glutamatergic activation of the anterior/ventral hippocampus is important for expressing anxiety-like behaviors [77, 78] and lesioning the anterior/ventral—but not posterior/dorsal—hippocampus reduces innate avoidance behavior in unconditioned anxiety tests, and reduces

Since the anterior/ventral hippocampus is associated with relaying *interoceptive* information to the nucleus accumbens shell; whereas the posterior/dorsal hippocampus is associated with relaying *exteroceptive* information to the nucleus accumbens core (Barr, Bray, Forster, 2018; Bray et al., 2018, 2020).

# Neurobiology of Binge Eating Disorder

#### Frank, G. K. W., et al. (2019). "The Neurobiology of Eating Disorders." Child Adolesc Psychiatr Clin N Am 28(4): 629-640.

Eating disorders are severe psychiatric illnesses with a typical age of onset in adolescence. Brain research in youth and young adults may help us identify specific neurobiology that contributes to onset and maintenance of those disorders. This article provides a state-of-the-art review of our current understanding of the neurobiology of anorexia nervosa and bulimia nervosa. This includes brain structure and function studies to understand food restriction, binge-eating or purging behaviors, cognitive and emotional factors, as well as interoception. Binge-eating disorder and avoidant restrictive food intake disorder are also discussed, but the literature is still very small.

#### Martin, E., et al. (2019). "Interoception and disordered eating: A systematic review." Neurosci Biobehav Rev 107: 166-191.

Deficits in interoception have been associated with disordered eating but there has been no systematic review of whether the interoceptive deficits are observed across all types of disordered eating and across interoceptive modalities. There has also been no evaluation of whether deficits in interoception play a causal role in the development of disordered eating. Nor has there been a review of the moderating/mediating factors of the relationship between interoception and disordered eating. To address these gaps we conducted a systematic review using PRISMA guidelines. 104 studies with 32883 participants were included. Deficits in interoception were observed across disordered eating types and interoceptive modalities suggesting that interoception may constitute a transdiagnostic feature of disordered eating. There is currently limited evidence on the causal role of interoception in the development of disordered eating and no studies have formally analysed the moderators/mediators. Future mechanistic research examining particular dimensions of interoception will provide insights into the specific interoceptive deficits associated with disordered eating and could lead to the development of improved therapies.

#### Frank, G. K. (2015). "Advances from neuroimaging studies in eating disorders." CNS Spectr 20(4): 391-400.

Over the past decade, brain imaging has helped to better define eating disorder-related brain circuitry. Brain research on gray matter (GM) and white matter (WM) volumes had been inconsistent, possibly due to the effects of acute starvation, exercise, medication, and comorbidity, but newer studies have controlled for such effects. Those studies suggest larger left medial orbitofrontal gyrus rectus volume in ill adult and adolescent anorexia nervosa after recovery from anorexia nervosa, and in adult bulimia nervosa. The orbitofrontal cortex is important in terminating food intake, and altered function could contribute to self-starvation. The right insula, which processes taste but also interoception, was enlarged in ill adult and adolescent anorexia nervosa, as well as adults recovered from the illness. The fixed perception of being fat in anorexia nervosa could be related to altered insula function. A few studies investigated WM integrity, with the most consistent finding of reduced fornix integrity in anorexia and bulimia nervosa-a limbic pathway that is important in emotion but also food intake regulation. Functional brain imaging using basic sweet taste stimuli in eating disorders during the ill state or after recovery implicated repeatedly reward pathways, including insula and striatum. Brain imaging that targeted dopamine-related brain activity using taste-reward conditioning tasks suggested that this circuitry is hypersensitive in anorexia nervosa, but hyporesponsive in bulimia nervosa and obesity. Those results are in line with basic research and suggest adaptive reward system changes in the human brain in response to extremes of food intake-changes that could interfere with normalization of eating behavior.

# Interoception in Craving and Reward-Based Decision-Making

#### Kim, J. A., et al. (1999). "Drug-onset cues as signals: intra-administration associations and tolerance." J Exp Psychol Anim Behav Process 25(4): 491-504.

On the basis of a conditioning analysis of drug tolerance, drug-associated cues become associated with the drug effect. These cues elicit conditional compensatory responses and modulate the expression of tolerance. Although there are many findings consistent with the conditioning analysis of tolerance, there also are contrary findings. The results of these experiments suggest that some of the apparently contradictory findings result because interoceptive pharmacological cues, as well as exteroceptive environmental cues, are paired with a drug effect. That is, within each administration, early drug-onset cues may become associated with the later, larger drug effect, and these pharmacological cues may overshadow simultaneously present environmental cues. We demonstrate the contribution of such intraadministration associations to tolerance to the analgesic effect of morphine and to the expression of conditional compensatory hyperalgesia.

# Interoception in Eating Disorders

## General

#### Khalsa, S. S., et al. (2018). "Interoception and Mental Health: A Roadmap." Biological Psychiatry: Cognitive Neuroscience and Neuroimaging 3(6): 501-513.

Interoception refers to 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 signaling has been considered a component process of reflexes, urges, feelings, drives, adaptive responses, and cognitive and emotional experiences, highlighting its contributions to the maintenance of homeostatic functioning, body regulation, and survival. Dysfunction of interoception is increasingly recognized as an important component of different mental health conditions, including anxiety disorders, mood disorders, eating disorders, addictive disorders, and somatic symptom disorders. However, a number of conceptual and methodological challenges have made it difficult for interoceptive constructs to be broadly applied in mental health research and treatment settings. In November 2016, the Laureate Institute for Brain Research organized the first Interoception Summit, a gathering of interoception experts from around the world, with the goal of accelerating progress in understanding the role of interoception in mental health. The discussions at the meeting were organized around four themes: interoceptive assessment, interoceptive integration, interoceptive psychopathology, and the generation of a roadmap that could serve as a guide for future endeavors. This review article presents an overview of the emerging consensus generated by the meeting.

#### Martin, E., et al. (2019). "Interoception and disordered eating: A systematic review." Neurosci Biobehav Rev 107: 166-191.

Deficits in interoception have been associated with disordered eating but there has been no systematic review of whether the interoceptive deficits are observed across all types of disordered eating and across interoceptive modalities. There has also been no evaluation of whether deficits in interoception play a causal role in the development of disordered eating. Nor has there been a review of the moderating/mediating factors of the relationship between interoception and disordered eating. To address these gaps we conducted a systematic review using PRISMA guidelines. 104 studies with 32883 participants were included. Deficits in interoception were observed across disordered eating types and interoceptive modalities suggesting that interoception may constitute a transdiagnostic feature of disordered eating. There is currently limited evidence on the causal role of interoception in the development of disordered eating and no studies have formally analysed the moderators/mediators. Future mechanistic research examining particular dimensions of interoception will provide insights into the specific interoceptive deficits associated with disordered eating and could lead to the development of improved therapies.

###### 3.2. Characteristics of included articles

Across the 104 studies included, the total number of participants was 32,883 with a minimum number of eight participants (Matsumoto et al., 2006) and a maximum number of 5139 participants (Kim et al., 2018). The majority of studies (n = 77, 74%) recruited women parti- cipants only. The remaining studies comprised 26 studies that included both men and women, and one study that recruited men only (Ussery and Prentice-Dunn, 1992). Of the 26 studies that recruited both men and women, the percentage of women participants ranged from 50 to 93%. The majority of studies (n = 93) recruited adult participants (mean age of participants = > 18). Ages of the participants across all samples ranged from 9 years (Koch and Pollatos, 2014) to 60 years (Fassino et al., 2004). Publication dates of the articles ranged from 1974 (Garfinkel, 1974) to 2018 (e.g. Berner et al., 2018; Romano et al., 2018). The majority of studies used a cross-sectional design (n = 78), nine used longitudinal observational designs, seven used quasi-experi- mental pretest-posttest designs (one of which only ran a cross-sectional comparison of interoception), seven used an experimental design, and two used a cross-sectional family-based design.

The majority of the studies assessed interoception using ques- tionnaire measures (n = 66). Other methods employed were heartbeat perception tasks (n=9), pain detection and threshold paradigms (n=15), and neuroimaging, with tasks and conditions including comparisons of hungry/full, pain perception, and trials consisting of focussing on internal sensations (n=11). One study used a drug to elicit interoceptive state changes, one compared the sensation of gastric fullness with gastric volume, and one compared pre- and post-meal aversion to glucose.

Thirty-one studies in this systematic review presented data relevant to the association between AN and interoception; 17 studies presented data relevant to the association between BN and interoception; 6 stu- dies measured interoception in participants with clinical binge eating disorder; 26 studies collected data from participants with AN and par- ticipants with BN as part of a mixed ‘eating disorder group’ and 24 studies presented data relevant to the association between subclinical disordered eating behaviours and interoception.

###### 3.5. Interoception in binge eating disorder

The results of four cross sectional studies on patients with active illness are reported here. No studies in this systematic review measured interoception in participants recovered from binge eating disorder and there were no studies using neuroimaging.

###### 3.5.1. Active illness

All four cross sectional studies assessing interoception in binge eating disorder recruited participants with active binge eating disorder and found significant impairments in interoception. Three of these studies (Aloi et al., 2017; Ramacciotti et al., 2008; Vinai et al., 2015) used self-report measures and one measured mechanical pain threshold (Raymond et al., 1995).

###### 3.6. Interoception in mixed diagnosis groups

There were twenty-four cross sectional studies. The majority of these studies collected data from groups including participants with both AN and BN (e.g. Ciccolo and Johnsson, 2002 Halmi and Sunday, 1991), with the exception of Rossiter et al. (1989) and Laessle et al. (1989) who included participants with BN and ‘restrained’ participants. In studies including participants with BN and participants with AN, 8 studies also reported on additional eating disorder groups including binge eating disorder or eating disorder not otherwise specified (EDNOS) (Eshkevari et al., 2014; Fassino et al., 2004; Kim et al., 2018; Nevonen et al., 2006; Nyman-Carlsson et al., 2015; Preyde et al., 2016; Solmi et al., 2018; Van Dyck et al., 2016). There were no studies in participants recovered from eating disorders and no neuroimaging studies.

Overall, of the 24 cross sectional studies reporting data relevant to the association between a mixed eating disorder sample and inter- oception, 22 showed impairments in at least one measure of inter- oception. The methods employed in these studies included self-report (n = 18), pain perception (n = 3) and reporting of gastric sensations across eating episodes (n = 1). One study assessed differences in ac- ceptance and clarity of interoceptive processing in eating disorders (Merwin et al., 2010) and found mixed results, with neither the ac- ceptance nor clarity interoception subscales predicting bulimia and only ‘lack of clarity’ predicting restraint. One study (Eskevari et al., 2014) found no difference in interoceptive processing in an eating disorder sample using a heartbeat detection paradigm, however 83% of participants were ‘poor’ detectors of heartbeat, which may explain the null results.

###### 3.7. Interoception in subclinical disordered eating behaviours/non-clinical samples

Twenty studies were cross sectional and none used neuroimaging techniques. The range of disordered eating behaviours in studies in- cluded in the current systematic review were emotional eating (e.g. Koch and Pollatos, 2014; Young et al., 2017), external eating (e.g. Koch and Pollatos, 2014), subclinical binge eating (e.g. Brown et al., 2010), restraint (e.g. Tylka and Wilcox, 2006) and mixed/composite measures from questionnaires (e.g. Anderson et al., 2016; Myers and Crowther, 2008).

All of the twenty cross sectional studies reporting data relevant to the association between disordered eating behaviour and interoception, found impairments in at least one measure of interoception. The ma- jority of these studies (n = 18) used self-report methods and the two remaining studies used heartbeat counting and detection tasks. One study found results which were somewhat mixed: once anxiety and depression were controlled for, a significant relationship remained for only two measurements out of four: confidence in heartbeat counting, and the relationship between heartbeat perception and self-reported interoceptive impairments (Young et al., 2017, Study 1).

###### 3.8. Interoceptive modalities

A range of interoceptive modalities were investigated in the studies included in this systematic review including cardiac, respiratory, gas- tric, pain and touch interoception. The most commonly measured in- teroceptive modalities were gastric, cardiac and pain, with measure- ments of these modalities comprising 101 out of the 104 studies.

###### 3.8.1. Gastric interoception

Gastric interoception was the most common modality measured in studies assessing interoception in disordered eating. Seventy-four stu- dies included in the systematic review measured gastric interoception, 19 of these studied gastric interoception in AN, 7 in bulimia, 4 in binge eating disorder, 20 in mixed eating disorder groups and 24 in sub- clinical disordered eating. Of these studies, 72 found significant dif- ferences in gastric interoception associated with disordered eating. The most commonly used methods to measure gastric interoception (n = 68) were self-report questionnaire measures. These included the Interoceptive Awareness subscale of the Eating Disorders Inventory (Garner et al., 1983) and the Intuitive Eating Scale (Tylka, 2006). One study compared gastric volume with self-reported hunger and fullness found at each given stomach volume (Bluemel et al., 2017). Partici- pants with AN reported higher fullness and lower hunger than control participants, however participants with AN had a slower gastric emp- tying rate, which may account for this difference. Five studies used neuroimaging methods and found that dysfunctional gastric inter- oceptive processing was associated with disordered eating. Two studies (De Caro and Di Blas, 2016; Heilbrun and Worobow, 1991) did not find that gastric interoception was associated with disordered eating.

###### 3.8.2. Cardiac interoception

Twelve studies measured detection of cardiac interoceptive signals. Six of these studies assessed cardiac interoception in participants with AN, 2 in participants with BN, 1 in a mixed eating disorder sample, and 3 in subclinical/ disordered eating behaviour. The most common method used to measure cardiac interoceptive signals was heartbeat detection which was used in 9 studies with significant impairments found in 7 studies. Of the two studies that did not show a significant association between cardiac interoception and disordered eating, one used a straightforward heartbeat counting paradigm (Ambrosecchia et al., 2017) and one used a heartbeat-detection paradigm, which re- quired participants to discriminate their heartbeat from an auditory tone (Eshkevari et al., 2014). Eshkevari et al. (2014) reported that 83% of their participants were poor at detecting their heartbeat, which may explain this null result.

Two studies (Kerr et al., 2106; Kerr et al., 2017) used fMRI to assess interoceptive processing of cardiac signals and both found differences in neural processing of interoception in patients recovered from AN and healthy controls. One study (Khalsa et al., 2015) used infusions of isoproterenol (a non-selective β adrenoceptor agonist) to elicit changes in cardiac activity and found that participants with AN reported in- creased cardiac sensations under low arousal states.

###### 3.8.3. Pain interoception

Seventeen studies measured pain-related responses. Seven of these studies measured pain interoception in participants with AN, five in BN, one in binge eating disorder, four in a mixed eating disorder sample and one in binge eating disorder. The majority of methods used to elicit pain were either temperature-based (utilising the application of either cold or hot stimuli to cause pain n = 11), or mechanical (utilising pressure to cause pain, n = 4). Two studies (Girdler et al., 1998; Stein et al., 2003) used submaximal effort tourniquet tests to measure ischemic pain. Fourteen out of the 17 studies found dysfunctional pain proces- sing in participants with disordered eating.

Methods of quantifying pain included both the measurement of pain threshold (e.g. time taken for a stimulus to first cause a painful sensa- tion) and the measurement of pain tolerance (e.g. time taken for a participant to withdraw from a painful stimulus). Three studies com- bined pain measurement with neuroimaging measures (Strigo et al., 2013; Bär et al., 2013, 2015) and all three of these studies found dys- functional pain processing associated with disordered eating. Three studies that assessed pain threshold and tolerance did not find a dif- ference in pain in disordered eating (Goldzak-Kunik et al., 2011; Krieg et al., 1993; Schmahl et al., 2010). In the study by Goldzak-Kunik et al., 2011, neither threshold nor tolerance was assessed, instead participants completed Visual Analogue Scales of cold, unpleasantness and pain during application of an ice pack, which may explain the null effects since application of an ice pack is a non-standard test. Both the studies by Schmahl et al., 2010 and Krieg et al., 1993 used a thermal pain stimulus which suggests that the type of pain stimulus used may be important.

###### 3.8.4. Other interoceptive modalities

Two studies measured other interoceptive modalities using fMRI, and both were in participants recovered from AN. One measured re- spiratory interoception (Berner et al., 2018) and the other measured touch (Bischoff-Grethe et al., 2018) and found significant differences in interoceptive processing between participants recovered from AN and healthy controls. The study by Khalsa and colleagues (2015) that in- volved infusions of isoproterenol showed that participants with AN reported increased breathing sensations under states of low arousal.

###### 3.9. Onset/maintenance

We found only nine studies that used prospective designs. Of these studies, all but one reported an association between interoceptive awareness and disordered eating risk/scores. De Caro and Di Blas (2016) found no significant relationship between interoception and bulimic tendencies over a seven month period but the sample size was a small group of self-selected teenagers. Most studies recruited non-clin- ical population-based samples of teenagers and assessed the factors predicting eating disorder risk at a later time point (e.g. Leon et al., 1999). Three studies recruited from clinical samples and examined predictors of changes in disordered eating over time (Amianto et al., 2017; Bär et al., 2006; Bizeul et al., 2001). One study compared the baseline scores for girls asymptomatic at baseline who continued to be asymptomatic at follow-up with a group that developed partial syn- drome (Kileen et al. 1996; average age at baseline 14.9 years). These authors reported that girls developing partial syndrome had higher scores on lack of interoceptive awareness at baseline. On the other hand, Koch and Pollatos (2014) reported that external and emotional eating in children with obesity, but not lean participants, predicted lack of interoceptive awareness at follow-up but not the other way round.

Two studies measured interoception in the relatives of individuals with disordered eating. These studies provide insight into whether disturbed interoception is a heritable feature that might predispose someone towards developing an eating disorder. One study assessed interoception in family members of women with bulimia (Lilenfeld et al., 2000). This study found higher interoceptive impairments in first- degree relatives who had also experienced an eating disorder, but no significant difference between interoceptive impairments in never-ill relatives of bulimia patients and relatives of healthy controls. The second study that assessed interoception in family members recruited a sample of women recovered from AN and their relatives (Casper, 1990). There was no significant difference in interoceptive impairments be- tween relatives of recovered patients and either recovered patients or healthy controls.  
Seven studies in this systematic review used a quasi-experimental

pretest-posttest design to assess changes in interoceptive processing over the course of therapy. Six studies reported improvements in in- teroceptive processing over the course of treatment. However, Fischer et al. (2016) found a cross-sectional influence of interoception on dis- ordered eating (women with AN scored higher than healthy controls at every time point on lack of interoceptive awareness), but there was no significant improvement in disordered eating over time in a small group of women with AN undergoing cognitive behaviour therapy.

###### 3.10. Quality of included studies

Inter-rater agreement for quality assessment was good (kappa: 0.64, SE of kappa: 0.156, 95% CI: 0.34 to 0.947). Quality ratings varied significantly across studies. Most of the studies included were of either moderate (n = 44) or low (n = 48) quality. The remaining twelve studies were high quality (see Fig. 2 for a summary). Small sample sizes and poor or no control for potential confounds were the main limita- tions. Most of the questionnaire studies were not designed specifically to assess interoception but rather were validation studies of specific measures that happened to include a subscale relevant to interoception.

###### 4. Discussion

To the best of our knowledge this is the first paper to systematically review the literature on interoception across the broad spectrum of disordered eating behaviours and interoceptive modalities. One hun- dred and four studies were included in the review and we find that all types of disordered eating behaviour are associated with impairments in interoceptive function across several modalities.

There was consistent evidence for a relationship between dysfunc- tional interoception and AN, with 92% of studies finding impaired in- teroceptive function in AN. Similarly, 93% of studies measuring inter- oception in a mixed group of eating disorders (e.g. AN, BN and BED/ EDNOS) reported impairments in interoception relative to controls. Ninety-five percent of studies assessing a variety of disordered eating behaviours reported impaired interoception on at least one measure. The evidence to support the relationship between BN and interoceptive abilities was more mixed but still supportive of dysfunctional inter- oception associated with BN, with just over 80% of studies showing significant impairment in interoception. The strength of evidence is moderate because the majority of studies were limited by methodolo- gical issues, in particular the use of small sample sizes and poor control for confounds.

It is difficult to rule out that the association between interoceptive functioning and disordered eating is due to the confounding influence of comorbid psychiatric disorders such as anxiety and depression, which are known to influence interoceptive capabilities (Pollatos et al., 2009) and are found in the majority of individuals with eating disorders (Kaye et al., 2004; Bulik et al. (1997). Indeed, for many of the studies reviewed, the eating disorder group had comorbid psychiatric disorders whereas the presence of psychiatric conditions was an exclusion cri- terion for the control groups. In studies that did control for potential confounds of comorbid disorders (Ambrosecchia et al., 2017; Lavagnino et al., 2014; Pollatos et al., 2008; Pollatos and Georgiou, 2016; Matsumoto et al., 2006 Young et al., 2017), or that reported no sig- nificant differences in depression scores between participant groups (Strigo et al., 2013), the results were mixed. In some cases, where an- xiety and depression were controlled for, no significant differences were found between disordered eating groups and controls (e.g. Ambrosecchia et al., 2017; Young et al., 2017). However, in other studies (e.g. Pollatos et al., 2008) when controlling for anxiety and depression, the association between eating disorders and interoception remained significant, suggesting that the relationship between inter- oception and disordered eating is not fully accounted for by depression/ anxiety. This conclusion is supported by the finding that depression was not a significant predictor of effect size in the meta-analysis conducted by Jenkinson and colleagues (2018). Future research might employ a propensity score matching approach by including additional control groups matched for levels of comorbidities. Alternatively, studying the relationship between interoception and disordered eating in non-clin- ical samples that have reduced prevalence of co-morbidities would also be informative.

###### 4.1. Disordered eating/eating disorder types

In line with the findings from a recent meta-analysis of the data on self-reported interoceptive impairments in eating disorders using the Eating Disorder Inventory (Jenkinson et al., 2018), we find that inter- oceptive impairments exist across the spectrum of disordered eating from subclinical populations with emotional eating and binge eating to individuals with clinically diagnosed eating disorders including AN and BN and binge eating disorder (BED). The finding that interoceptive impairments occur in different types of eating disorders/disordered eating suggests interoception may constitute a transdiagnostic feature of eating disorders (Fairburn et al., 2003).

The role of interoception in disordered eating could be investigated further by adopting a dimensional research framework, such as that advocated by the National Institute of Mental Health Research Domain Criteria (RDoC) initiative which argues for the study of fundamental components of behaviour (domains) using different units of analysis that link brain and behaviour (Insel et al., 2010). Studies of inter- oceptive processes in both clinical and subclinical populations using validated instruments that assess self-report, behaviour, physiology, neural circuits and genetics could provide novel insights into the nature of the relationship between interoception and disordered eating and identify potential biomarkers relevant to the diagnosis and treatment of eating disorders.

###### 4.2. Interoceptive modalities

To assess the specificity of interoceptive impairments in disordered eating, we stratified our findings by the interoceptive modality that was measured. The modality in which impairments were most consistently associated with disordered eating was gastric interoception, with 96% of studies measuring gastric interoception reporting impairments as- sociated with disordered eating. This finding may be a result of the characteristics of disordered eating itself, as gastric interoception is strongly associated with eating. However, it is also important to note that gastric interoception was measured using self-report methods more often than any other modality. Hence, it is possible that the association between gastric interoception and disordered eating reflects a specific problem in conscious processing of interoceptive signals measured using self-report tools. In addition, it should also be noted that studies of gastric interoception may predominate due to a perception by re- searchers that interoception is most easily studied by assessing gastric function.

A number of studies assessed pain and cardiac interoception in disordered eating. In both of these modalities, just over 80% of studies reported aberrant processing associated with disordered eating, sug- gesting that these modalities are also affected. Although heartbeat counting tasks are commonly used to assess interoception due the ease of measurement it should be noted that there are methodological lim- itations to this approach (Brener and Ring, 2016). For example, knowledge of one’s resting heart rate influences the accuracy on heat beat counting tasks (Murphy et al., 2018). In addition, only around a third of participants can accurately count their own heat beat at rest, which opens up the possibility that floor effects may explain some null findings (Khalsa & Lapidus 2016). In relation to pain processing, variability of the results might be explained by a lack of consistency of measures across studies e.g. the use of heat vs. cold stimuli. The finding that impaired interoception is seen across different modalities could be explained by aberrant signalling within an afferent neural system that represents all aspects of interoception (Craig, 2009). Indeed, for cardiac and gastric signalling there are partially overlapping cortical representations within the mid insula and so it is possible that aberrant insula activity and functional connectivity may contribute to interoceptive dysfunction across modalities in eating disorders. The extent to which interoception is served by a unitary system remains unclear at present, although most models emphasize the role of func- tionally coupled circuits rather than modular processing in specialised domain specific systems (e.g. Craig, 2009; Quattrocki and Friston, 2014). Further investigation of the neurobiological mechanisms that underpin interoceptive dysfunction in disordered eating could shed further light on this issue.

###### 4.3. Onset/maintenance

Our review found evidence that impairments in interoception are present in individuals who have recovered from an eating disorder (e.g. Khalsa et al., 2015; Klabunde et al., 2013), which suggests that pro- blems with interoception are not solely explained by features associated with an active illness, such as severe calorie restriction or binge-purge behaviours. These data imply that dysfunctional interoception might be a predisposing factor for the onset of disordered eating. This proposal is supported by data from prospective longitudinal studies indicating that problems with interoception predict changes in eating disorder risk (e.g. Leon et al., 1999). Although it should be noted that there is cur- rently only a small number of population based studies that have as- sessed the role of interoception in illness onset.

The suggestion that problems with interoception might predispose an individual to develop an eating disorder is supported by data from studies that have linked dysfunctional interoception to specific genetic variants (Frieling et al., 2006). However, there are also reports that impaired interoception is reversed as a result of successful therapy (e.g. Matsumoto et al., 2006), which implies that at least some of the pro- blems with interoception might be a complication of the eating disorder that resolves with treatment rather than constituting a predisposing factor. In fact, it is possible the problems with interoception that are observed in recovered patients might reflect an enduring change in interoception or a scarring effect of having experienced an eating dis- order (e.g. Klabunde et al., 2013; Stein et al., 2003). Such an inter- pretation is supported by evidence, albeit currently limited, from family studies (Lilenfeld et al., 2000; Casper, 1990), which have found that family members of patients, without a history of eating disorders, do not show impairments in interoception. These data suggest that inter- oceptive dysfunction does not constitute a heritable trait or en- dophenotype that is observable in non-affected first degree relatives of people with eating disorders.

One interpretation that could explain the existing data is that dys- functional interoception might predispose an individual towards the development of disordered eating but once disordered eating behaviour patterns become established, problems with interoception are accen- tuated. However, there is currently limited evidence on the causal role of interoception in the development of disordered eating. Prospective longitudinal studies that include a pre-morbid baseline assessment provide the most rigorous test of whether or not dysfunction in inter- oception plays a causal role in the development of disordered eating but these are costly and difficult to implement since very large sample sizes are required due to the relatively small number of individuals who go on to develop an eating disorder. An alternative is to use a high-risk design in which the incidence of a diagnosis at follow-up is increased by following individuals already deemed high-risk for future eating dis- orders (Stice and Desjardins, 2018).

###### 4.4. Gaps in knowledge and directions for future research

This review has highlighted a lack of research on the moderators and mediators of the relationship between interoception and disordered eating. Not all individuals with dysfunction in interoceptive processing will develop disordered eating and so identifying potential moderators will be an important avenue for future research. For example, there may be personality factors such as impulsivity or obsessive–compulsive traits that interact with interoceptive dysfunction, and the presence or absence of these traits may determine the likelihood of interoceptive dysfunction leading to disordered eating.

Future research should also address the mechanisms mediating the relationship between interoception and disordered eating behaviours/ eating disorders. Interoceptive states may influence eating behaviours via changes in the reward value of food. Information about the state of the body is passed to areas of the brain involved in computing the in- centive salience of a food so that its motivational value is increased when in a state of food deprivation and decreased in a replete state (Cabanac, 1971). Dysfunction in interoceptive signalling might reduce the motivating effect of food deprivation on behaviour as has been observed in women who are in remission from AN (Wierenga et al., 2015). Furthermore, a failure to downregulate food reward with food consumption might promote overeating once eating has begun, which could facilitate binge like eating as has been observed in BN (Ely et al., 2017). Thus, future studies could examine the potential mediating role of reward responsiveness in the relationship between interoception and disordered eating. In addition, problems with interoceptive processes could result in bodily signals related to nutrient ingestion or nutrient deficits not being factored into more complex decision making pro- cesses that mediate food consumption and food choices (Higgs, 2008). In this case, decisions are more likely to be influenced by other inputs e.g. external cues. Thus, overeating or undereating might occur de- pending on the predominant influences on the food-related decision making at any one time for an individual, which might be weight concerns, emotional concerns or hedonic goals. Such links between interoceptive capabilities and responses to different types of external cues have yet to be fully explored. Finally, problems with interoception might also promote disordered patterns of eating via dysfunctional body perception/evaluation which could lead to disordered eating through body dissatisfaction (Badoud, and Tsakiris, 2017).

There have also been fewer studies to date on the role of inter- oception in binge eating disorder than in AN and BN. BED was in- troduced as an eating disorder category in the Diagnostic and Statistical Manual of Disorders, Fifth Edition (DSM-5) in 2013 (American Psychiatric Association, 2013). It is the most prevalent form of eating disorder and one of the primary chronic illnesses among adolescents (Nicholls and Barrett, 2015). Hence further investigation of the role of interoception in binge eating disorder is advised.

The current systematic review considered ‘interoception’ in general due to the broad focus of research to date, but a number of separate facets of interoceptive insight have been described (Khalsa et al., 2018). In order to further understand of the role of interoception in disordered eating it will be necessary delineate different aspects of interoception (Khalsa et al., 2018). Interoception encompasses functioning at many different levels including physical responses in the body, the neural representations of these responses and their perception, as well as in- sight and conscious awareness of these responses. Three psychological dimensions of interoception that relate to the perception of inter- oceptive responses have been distinguished: interoceptive accuracy, sensibility, and awareness (Garfinkel et al., 2015). Interoceptive accu- racy refers to the process of detecting and counting internal bodily sensations and is measured using methods such as heartbeat counting. Interoceptive sensibility refers to self-evaluated interoceptive capability and is usually assessed by questionnaire measures. Interoceptive awareness refers to the correspondence between interoceptive accuracy and insight into one’s own interoceptive performance and so represents a metacognitive aspect of interoception. An additional dimension of interoceptive awareness has been suggested recently which describes a person’s ability to flexibly attend to, and utilize, interoceptive in- formation or to adaptively switch between interoceptive and ex- teroceptive representations (Quadt et al., 2018).

At present it is unknown whether dysfunctional interoception as- sociated with disordered eating is due to dysfunctional afferent sig- nalling, central sensory processing of interoceptive stimuli or percep- tion or insight into interoceptive performance. It is possible that there is no dysfunction in afferent interoceptive signalling (e.g. the presence and magnitude of signals is detected), but there may be dysfunction in signal monitoring (accuracy) and/or the tendency to focus on signals (sensibility). A small number of studies in this systematic review mea- sured more than one dimension of interoception (e.g. Ambrosecchia et al., 2017; Young et al., 2017), and some of these assessed the asso- ciation between dimensions (e.g. Pollatos et al., 2008). Interestingly, some studies found impairment in one dimension of interoception (e.g. sensibility), but no impairment in another dimension (e.g. accuracy). For example Ambrosecchia et al. (2017) found that participants self- reported poorer interoceptive sensibility, but had interoceptive accu- racy that was comparable to healthy controls. Similarly, Pollatos et al. (2008) found no association between interoceptive awareness and sensitivity. However, it should be noted that these studies assessed in- teroceptive accuracy in the cardiac domain and sensibility using the Interoceptive subscale of the Eating Disorders Inventory (EDI) rather than assessing accuracy and sensibility within the same modality. In addition, while the EDI has been shown to discriminate between in- dividuals with eating disorders and healthy controls, it is not a measure that was designed specifically to assess visceral interoceptive sensi- bility. Future systematic studies that assess interoception across a range of modalities and include measures of neural signalling, behavioural performance, and self-evaluated interoceptive capability, alongside metacognitive measures both within and between modalities, are re- quired to uncover the specific nature of the interoceptive dysfunction associated with disordered eating.

The evidence reviewed here from studies that assessed neuronal activation using fMRI suggests that disordered eating is associated with dysfunction in the neural processing of interoception compared with individuals without disordered eating. The majority of the studies linked differences in neural responses in the insula to dysfunctional interoception. However, it should be noted that an issue with the fMRI methods used in a number of studies in this systematic review is the reliance on reverse inference, which is using specific patterns of acti- vation to infer the engagement of specific mental processes e.g. in- ferring that activation of the insula is related to interoceptive proces- sing because the insula has been previously implicated in such processes. The reliance of a study’s conclusion on reverse inference depends on the paradigm used (Poldrack, 2011). For example several studies (Wierenga et al., 2015, 2017 and Holsen et al., 2012) altered the fullness of the stomach and inferred that the differences in brain re- sponses between a AN group and the control group was due to differ- ences in interoception. However, interoception defined as accuracy in sensing the internal state of the body was not measured directly and so these studies rely on reverse inference. To address the issue of reverse inference, predictive modelling techniques (Varoquaux and Poldrack, 2019) may be valuable to identify a neural signature for interoception that predicts interoceptive capability and hence could be used as a biomarker in future studies. In addition, the interpretation of the re- lationship of the reported neural activity to interoceptive abilities is not straightforward since reduced activity in the insula for example could represent more efficient processing of interoceptive signals or reduced inputs. Nevertheless, the fMRI data reviewed here suggest that neural signalling in the insula depends upon the specific context in which that activity is assessed (e.g. Berner et al., 2018; Bischoff-Grethe et al., 2018). In particular, there is evidence that patients recovered from AN show increased neural activation in insula in anticipation of i nteroceptive events but decreased activation during an aversive in- teroceptive event (e.g. Berner et al., 2018; Strigo et al., 2013). For ex- ample, during anticipation of pain, patients recovered from AN showed greater activation in right anterior insula than did healthy controls but showed significantly decreased posterior insula activation during pain processing (Strigo et al., 2013). This pattern of responses may indicate heightened interoceptive responses in anticipation of pain but poorer processing of interoceptive stimuli. However, other studies have re- ported an opposite pattern of results, whereby recovered AN patients had a reduced activation in right mid-insula in the anticipatory period but increased bilateral, anterior, mid-, posterior insula activation during and after an aversive breathing load task (Berner et al., 2018). One possibility is that some interoceptive problems in AN arise from a mismatch between predictions about how the body should feel and the information coming from the body, which has been referred to as an interoceptive prediction error. Such prediction errors have also been hypothesized to account for aberrant interoceptive functioning in an- xiety disorders (Paulus and Stein, 2010) and are a core feature of pre- dictive coding accounts of interoception (Barrett and Simmons, 2015; Seth and Critchley, 2013).

Predictive processing Merwin et al. (2010) is a theoretical model of neural functioning (Friston, 2010) that has recently been applied to the study of interoception. Rather than assuming that interoceptive per- ceptions are linked directly to internal bodily sensations, predictive processing accounts suggest that perceptions arise from a comparison between representations of anticipated sensations and current inter- oceptive signals. Interoceptive perceptions are thought to mainly reflect the anticipated state of the body based on what is predicted given past experience, but, incoming sensory information about the actual state of the body provides a check on the accuracy of these predictions (Barrett and Simmons, 2015; Seth and Critchley, 2013). If a mismatch between actual and predicted states, or a prediction error, is detected then this error may be used to update the predictions, and possibly change per- ceptions, or trigger changes in the body that fulfil those predictions. This account is similar to that proposed by Higgs (2005) who has ar- gued that feelings of satiety are cognitively constructed in the brain; a process that involves integrating current internal state cues with in- formation in memory about recent eating to predict the effects of fur- ther consumption.

Within a predictive/constructive interoceptive framework, dys- functional interoception could arise if the incoming sensory signals are noisy or unreliable (see Paulus et al., 2019 for a recent review). In such circumstances, predictions (and perceptions) might be strongly influ- enced by external sources of information or beliefs that are not updated by prediction error. For example, the perception of the body as it relates to food deprivation or repletion in patients with eating disorders might be influenced by beliefs that are not updated by incoming interoceptive signals. A similar situation might arise from a failure to integrate in- coming sensory signals with anticipated states. Further research guided by the predictive/constructive framework is needed to test these hypotheses.

###### 4.5. Strengths and limitations of the current systematic review

We conceptualized disordered eating as a continuum ranging from normal eating to eating disorders and considered studies using a range of interoceptive modalities which enabled a large number of studies to be systematically reviewed. However, there may be a language and a publication bias, as the search was limited to studies written and published in the English language. However, the number of non-English language studies identified was only four. The majority (77%) of studies in the current systematic review recruited women only. Therefore, the results should be applied to males with caution, particularly as one longitudinal study suggested that sex may moderate the relationship between interoception and disordered eating. This finding highlights the need for more research into interoception and disordered eating behaviour in males. In addition, many studies published in this area were not designed to explore an association between interoception and disordered eating. For example, most studies comparing self-rated in- teroceptive sensibility were designed as questionnaire validation stu- dies, which resulted in suboptimal study designs and the potential for biased results. Finally, due to the heterogeneity of the studies, parti- cularly with respect to the methodologies and outcomes used, a meta- analysis was not considered feasible.

###### 4.6. Clinical implications

If further research confirms that interoceptive dysfunction predis- poses individuals to the development of eating disorders then assess- ment of interoception may be useful in identifying those at risk of de- veloping eating disorders and hence could be valuable for prevention programmes. There is evidence that interoceptive function can change over time and be modified by treatment (see results from this review and that of Khalsa et al., 2018) and so interoceptive dysfunction could also be a useful focus for the treatment of eating disorders and other conditions with comorbid eating disturbances such as Attention Deficit Hyperactivity Disorder (ADHD) (Kaisari et al., 2017, 2018) and de- pression (Simmons and Deville, 2017). There are opportunities for treatments based on stimulating afferent interoceptive signalling e.g. vagus nerve stimulation (De Couck et al., 2017) or flotation therapies that reduce exteroceptive signals allowing enhanced exposure to in- teroceptive signals (Feinstein et al., 2018). Future work could also ex- amine the potential for using drug therapies to target interoceptive dysfunction in patients with eating disorders. There is growing interest in the role of the hormone oxytocin in interoception (Betka et al., 2018; Quattrocki and Friston, 2014) and given that oxytocin has already been found to improve some of the symptoms of AN (e.g. Kim et al., 2014), future studies could examine whether intranasal administration of oxytocin improves interoception in disordered eating.

###### 4.7. Conclusions

The majority of studies included in the current systematic review reported significant impairments in interoceptive processes associated with disordered eating behaviour and eating disorders. Impairments were observed across eating disorder types and interoceptive modalities suggesting that interoception may constitute a transdiagnostic feature of eating disorders that is related to dysfunction in a common neural system which underpins the processing of different types of interoceptive signals. There is currently limited evidence on the potential causal role of interoception in the development of disordered eating and on the moderating and mediating mechanisms. Future research that examines specific dimensions of interoception in both clinical and subclinical populations at different levels of analysis may provide novel insights into the underlying dysfunction in interoception associated with disordered eating and which could potentially lead to the development of improved therapies for eating disorders.

#### Jenkinson, P. M., et al. (2018). "Self-reported interoceptive deficits in eating disorders: A meta-analysis of studies using the eating disorder inventory." J Psychosom Res 110: 38-45.

###### Abstract

OBJECTIVE: An impairment of the ability to sense the physiological condition of the body - interoception - has long been proposed as central to the onset and maintenance of eating disorders. More recent attention to this topic has generally indicated the presence of interoceptive deficits in individuals with an eating disorder diagnosis; however, possible links with specific diagnosis, BMI, age, illness duration, depression, and alexithymia remain unclear from individual studies. This meta-analysis aimed to provide a necessary quantitative overview of self-reported interoceptive deficits in eating disorder populations, and the relationship between these deficits and the previously mentioned factors. METHODS: Using a random effects model, our meta-analysis assessed the magnitude of differences in interoceptive abilities as measured using the Eating Disorder Inventory in 41 samples comparing people with eating disorders (n = 4308) and healthy controls (n = 3459). Follow-up and moderator analysis was conducted, using group comparisons and meta-regressions. RESULTS: We report a large pooled effect size of 1.62 for eating disorders with some variation between diagnostic groups. Further moderator analysis showed that BMI, age and alexithymia were significant predictors of overall effect size. CONCLUSION: This meta-analysis is the first to confirm that large interoceptive deficits occur in a variety of eating disorders and crucially, in those who have recovered. These deficits may be useful in identifying and distinguishing eating disorders. Future research needs to consider both objective and subjective measures of interoception across different types of eating disorders and may fruitfully examine interoception as a possible endophenotype and target for treatment.

###### Intro

Eating disorders (EDs) are characterised by an ongoing disturbance of eating or eating-related behaviour, which leads to changes in the consumption or absorption of food, and significantly impaired physical health or psychosocial functioning [3]. EDs are a pervasive psychiatric disturbance, associated with severe negative consequences, including significant distress, depression, suicide, substance abuse and even death [5,74,75]. As such, EDs represent a major clinical challenge, and priority for research to identify their aetiology, and develop effective treatments. Unfortunately, the cause of EDs remains poorly understood, with several biological, social and psychological factors identified as important in the onset and maintenance of different EDs [22].

The task of identifying the causal mechanisms underlying EDs is complicated by the fact that a different combination of factors may contribute to various subtypes of ED. The current Diagnostic and

Statistical Manual (DSM-5; APA 2013) identifies three primary ED di- agnoses: Anorexia Nervosa (AN; characterised by restrictive eating, severe weight loss, and an intense fear of gaining weight), Bulimia Nervosa (BN; characterised by a preoccupation with body weight and shape, normal body weight, and episodes of binge eating with com- pensatory behaviours such as purging), and Binge Eating Disorder (BED; characterised by frequent binge eating with feelings of loss of control, but no use of compensatory behaviours). Two further cate- gories (Other Specified Feeding or Eating Disorder (OSFED), and Unspecified Feeding or Eating Disorder (UFED)1), also exist to classify EDs that do not more accurately fit into AN, BN, or BED, such as aty- pical presentations of the above or other feeding and eating disorders.

Notably, early clinical descriptions of EDs highlighted “disturbances in accuracy of perception or cognitive interpretation of stimuli arising from the body” ([12], p. 189). These dual aspects have been examined under the modern-day concepts of interoception (i.e. the ability to sense t he physiological condition of the body [19], and alexithymia (i.e. difficulty identifying and describing feelings/emotions; see [80]). Such difficulties in perceiving signals arising from the body and/or identi- fying and interpreting emotional states have since been established as a core psychopathological element of several ED [32,80].

Difficulties with somatic perception/awareness may contribute to EDs because individuals incorrectly interpret bodily signals referring to hunger and satiety cues [12]. A difficulty perceiving hunger cues may result in skipped meals, or the restriction of food intake until intense feelings of hunger occur. By contrast, difficulty in detecting normal levels of fullness could cause binging or overeating [32,50]. In addition, deficits in identifying emotional states may contribute to difficulties with emotional regulation; a multidimensional construct characterised by flexible modulation strategies, behavioral control, emotional awareness and distress tolerance [43,52]. ED patients may confuse their internal bodily signals with emotions, and have difficulties experien- cing and differentiating different emotions, or modulating or attenu- ating their intensity [15,52]. Such maladaptive emotion regulation or

emotional dysregulation is a key psychological problem in EDs, related to mood instability, impulsivity, recklessness, anger and self-destructive- ness [52].

The majority of data concerning interoceptive deficits in EDs is based on self-reports obtained from the Eating Disorder Inventory (EDI; [42]), which primarily assesses the interpretative component of inter- oceptive deficits rather than somatic awareness. The EDI includes an “Interoceptive Awareness” subscale, comprising 10 questions reflecting “a lack of confidence in recognising and accurately identifying emo- tions and sensations of hunger or satiety” ([42], p. 18). Using the EDI and subsequent revisions (EDI-2, [40], EDI-2, [41]; EDI-VS, [58]), self- reported interoceptive deficits of this interpretative kind have been found consistently across patients with various EDs [32,52].

Importantly, although interoceptive deficits are widely reported as being a core psychopathological component of several EDs, it is not known whether the effect size is the same across the spectrum of EDs, or whether a particular diagnosis is associated with greater interoceptive deficits. In addition, several variables are known to interact and overlap with interoceptive processing and EDs, such as age, disease duration, Body Mass Index (BMI), depression and alexithymia [4,44,45,57,64,67,76]. However, these factors have not consistently been taken into account when examining interoceptive processes in patients with ED. Taking these factors into consideration, and identi- fying to what extent and how deficits in the interpretation of signals arising from the body contribute to different EDs, might allow for more targeted and effective interventions to be administered. Therefore, the current study first aimed to compare the magnitude of interoceptive deficits (as measured using the EDI) across different types of ED. Sec- ondly, we aimed to examine whether age, illness duration, BMI, de- pression, and alexithymia serve as moderators for any interoceptive deficits observed in ED overall, and whether these were further specific to different subtypes of ED. We did not have any a-priori predictions regarding the directionality of interoceptive deficits across different ED subtypes, or how these deficits might be moderated by the factors mentioned above, since individual studies have often not specifically examined or had statistical power to address such questions in an ED population, have used different measures to assess interception, or have produced contradictory results in healthy and ED populations (e.g. see [57] for interesting work on the relationship between interoception and alexitymia); as such, our meta-analyses represent a novel, quantitative exploration into these questions.

###### 3. Results

The analysis included 29 studies and 41 samples, providing a total sample of 4308 eating disorder participants and 3459 controls (7746 when controls are repeated in separate comparisons, see Table 1). The first, main analysis revealed significantly greater interoceptive deficits in the ED patients (SMD = 1.62: 95% CI = 1.46 to 1.77, p < 0.001)2 compared with healthy controls, indicating an 87% chance that a person picked at random from the ED group will have a greater inter- oceptive deficit than a person picked at random from the control group (probability of superiority). The studies were heterogeneous, (Q (40) = 386.10, p < 0.001) with an I2 value of 89.64. The high level of heterogeneity validated the suitability of a random-effects model and suggested the possible existence of moderating variables contributing to heterogeneity that required further investigation. Examination for publication bias Using Duval and Tweedie's [26] Trim and Fill method highlighted two potentially missing studies, though it made no sub- stantive difference to the effect size (SMD = 1.57: 95% CI = 1.41 to 1.73, p < 0.001).

###### 3.1. Interceptive deficits in different types of ED

Moderator analysis was undertaken to examine the impact of ED type on interoceptive deficit effect size (see Fig. 2). The initial analysis included all 29 studies and 41 samples. The samples comprised: AN (k=12), BN (k=10), BED (k=5), EDNOS (k=3), Mixed ED (k=9) and participants recovered from AN or BN (k = 2). A significant difference in pooled effect size was found amongst the various diagnostic groups (Q(5) = 50.30, p < 0.001).

We subsequently compared the size of interoceptive deficits across different ED diagnoses (see Fig. 2 for individual forest plots). In ac- cordance with the minimum study criteria for moderator analysis spe- cified above (k≥4), patients with EDNOS (k=3) and participants recovered from AN or BN (k = 2) were not analysed as part of sub- sequent comparisons. In addition, as the mixed group combined several types of ED (including AN, BN and BED) it could not be meaningfully compared with the separate ED subtypes, and was not included in follow-up comparisons. The remaining comparisons between AN, BN and BED indicated that patients with BN report the greatest deficit overall, with interoceptive awareness being significantly lower in BN than BED (Q(1) = 41.72, p < 0.001), but not compared with AN (Q (1)=2.57, p=0.11. In addition, patients with AN showed a sig- nificantly greater interoceptive deficit compared with BED (Q (1) = 25.27, p = 0.001). The level of heterogeneity (I2) was lower in each of these separate ED subsamples (AN = 77.91%, BN = 71.17%, BED=38.31%) compared to when all ED types were grouped and analysed together (89.64%), as might be expected; however, the rela- tively high level of heterogeneity remaining in these sub-samples sug- gests that there may still be other unidentified sources of heterogeneity. We explored these factors in further moderator analyses below.

###### 3.2. Further moderator analysis

The influence of age, illness duration, BMI, depression, and alex- ithymia on interoceptive awareness were analysed using meta-regres- sion. As indicated above, meta-regressions were not run with sub- samples fewer than six or in mixed samples. In addition, analyses were not run where the target measure was not reported or sufficiently variable for analyses to be run on the sample. Table 1 provides a summary of the meta-regressions conducted.

###### 3.2.1. Age

Meta-regression revealed greater interoceptive deficits in younger samples when samples of all ED subtypes were included in the analyses (k = 28). However, sub-analysis of patients with BN (k = 6) and AN (k = 9) separately indicated that interoceptive deficits were, contrast- ingly, significantly larger in older groups.

###### 3.2.2. Illness duration

There were too few samples to run regression analysis on illness duration.

###### 3.2.3. BMI

Across 17 samples that included all types of ED diagnoses, sig- nificantly greater interoception deficits occurred in samples with lower mean BMI.

###### 3.2.4. Depression

Depression was recorded in 8 ED samples which included the di- agnoses AN, BN, EDNOS and BED. Meta-regression of these samples revealed that average depression score was not a significant predictor of effect size.

###### 3.2.5. Alexithymia

A meta-regression of 6 samples which included the diagnoses AN, BN and BED found significantly greater interoception deficits in sam- ples with lower mean alexithymia scores (i.e. less alexithymia/better at identifying and labelling emotions).

###### 4. Discussion

The aim of the current meta-analysis was to investigate the extent of self-reported interoceptive deficits in EDs, and examine how various factors (i.e. ED diagnosis, age, illness duration, BMI, depression and alexithymia) may influence interoceptive deficits in ED. We identified 41 ED samples comprising 4308 people with various types of ED (in- cluding AN, BN, BED, and EDNOS), and compared these with 3459 healthy controls. A significant interoceptive deficit was found across this ED sample, with a very large effect size (SMD) of 1.62. This equates to there being approximately 87% chance that a person picked at random from the ED group will have a greater interoceptive deficit compared with a person picked at random from the control group. Furthermore, comparison across different ED subtypes revealed the novel finding that interoceptive deficits appear to exist on a continuum in EDs, with BN and AN patients experiencing significantly more pro- nounced interoceptive deficits compared to patients with BED. Our analyses also revealed that interoceptive deficits are greater in ED pa- tients with a lower BMI and younger age. Separate moderator analyses of BN and AN patients, however, revealed a contrasting pattern in which interoceptive deficits are greater in older patients. Finally, we found that interoceptive deficits across several EDs were not related to levels of depression; however, individuals with lower levels of alex- ithymia report greater interoceptive deficits. We discuss these findings in greater detail below.

Our first, overall finding of an interoceptive deficit in patients with ED is consistent across samples and studies, and accords with the long proposed disturbance of interoception in EDs [12]. More importantly, we document for the first time that a large and significant interoception deficit occurs across a wide range of eating disorders. Analysis of spe- cific EDs revealed large effect sizes in each group: AN (SMD = 1.71), BN (SMD = 1.96), BED (SMD = 0.76); EDNOS (SMD = 1.72), mixed diagnoses (SMD = 1.71) and those who had recovered from eating disorders (SMD = 0.76). We also present the hitherto unreported finding that BN and AN samples experience the greatest impairment of interoceptive abilities, whereas BED samples were found to report the smallest. Interestingly, even recovered AN and BN samples displayed a large effect size (Fig. 2F). The observation that substantial interoceptive deficits remain after recovery suggests a relative trait stability of such deficits and may have clinical implications for defining recovery from an eating disorder. For example, recovery of interoceptive abilities may not be a useful indicator for assessing ED recovery; however, the modest number of recovered samples (K = 2) means this finding should be interpreted cautiously.

Our finding that significant interoception deficits occur in all ED diagnoses lends support to a continuum or transdiagnostic approach to ED, which supposes that ED lie on a spectrum of dieting and weight concerns rather than being qualitatively distinct [23,71]. The core symptomology of EDs is the same, but can be expressed differently through the varying severity and kinds of eating behaviours displayed throughout the course of the disorder [30]. In line with this approach, we found that although interoceptive deficits are consistent across all EDs, significant inter-diagnostic differences emerge in the degree of impairment. Previous research has explored a variety of en- dophenotypes3 in EDs (for a discussion see [14,77]) and the accumu- lated evidence presented here points to interoception deficits as a candidate endophenotype for EDs. However, it remains unclear whe- ther these deficits play a role in the onset and maintenance of the disorders, or are caused in some way by the disorder and its symptoms. In this context, Lilenfeld et al. [55] posit an interesting distinction

3 “Endophenotypes are considered to be measureable biological markers for a disease which are associated with the illness in the general population, are observable regardless of whether the illness is active, are observed in unaffected family members of probands at a higher rate than in the general population, and are heritable” ([77], p. 4).

regarding traits that persist after recovery from an eating disorder and in particular to whether such traits reflect either “...a potential vul- nerability factor contributing to the development of the ED or a ‘ scar’ (i.e. consequence) of the illness.” (p. 1400). Lilenfeld et al. found di- minished interoceptive awareness amongst previously eating-dis- ordered relatives of bulimic probands when compared to their never-ill relatives. They interpret this as consistent with their “scar” model, i.e. that having had an eating disorder leaves a “scar”; however, as they later note “...it is impossible to definitively determine which may be ‘scar effects’ and which may be predisposing factors at the present time” ([56], p. 313). Nonetheless, a large prospective study of junior high and high school students found that poor interoceptive awareness (from the EDI) predicted risk of eating disorders one year later [54]. Thus, a next step to further explore this line of thinking would be for future studies to assess interoception in the unaffected first degree relatives of those with EDs.

We found that mean age was a significant predictor of interoception deficit, being greater in younger samples; however separate analyses of AN and BN samples revealed contrastingly greater interoceptive deficits in older samples. The separate analysis of age and interoceptive deficit in BN patients included only a small number of samples, and this limits the conclusions that can be drawn regarding this finding. It is possible that the overall analysis may have been influenced by diagnosis, as BED samples typically had a higher average sample age and were found to have significantly smaller effect sizes, which may explain the difference in direction of the relationship found in the overall and sub-analyses. Unfortunately, there were too few samples to also analyse the effect of illness duration on interoceptive deficits, and so it is not possible to determine whether the link between age and interoceptive deficit is simply a result of the illness length, or if interoceptive deficits are a stable trait that do not change over time. In order to draw such con- clusions, future studies are needed that record illness duration.

We also found that individuals with lower BMIs have significantly greater interoceptive deficits; however, the finding of a negative re- lationship between effect size and BMI may have again been influenced by ED subtype. Unfortunately, it was not possible to carry out further analysis of individual ED subtypes because of limitations in the re- corded range of BMI and/or too few studies reporting BMI for meta- regression to be performed. Nevertheless, we note that the samples with larger BMIs were those with a BED diagnoses, which were also found in the current analyses to have significantly smaller interoceptive deficits than samples with BN or AN. Our attempts to analyse BMI and inter- oceptive deficits in EDs highlights potential difficulties in examining the influence of BMI across ED samples more generally. The link be- tween interoceptive deficits, BMI and EDs may be more complex than is currently understood based on the limited evidence available, and ad- ditional research, which includes a range of BMIs and weight-recovered AN patients, is needed to examine these relationships.

Our meta-regression of alexithymia indicated that individuals with poor emotional awareness do not necessarily have poor interoception. Surprisingly, we found that greater levels of alexithymia (i.e. poorer ability to identify/label emotions/feelings) predicted fewer self-re- ported interoception deficits (i.e. better interoception). This finding is based on the results of only six studies and samples with relatively high levels of alexithymia overall (the mean across our samples ranged be- tween 54.1 and 67.05, and a TAS-20 score of 61 or above indicates high levels of alexithymia; [7]), and so should be interpreted with care and/ or limited to individuals with relatively high alexithymia. Nevertheless, the analysis included several types of ED, and confirms the high oc- currence of alexithymia in EDs [80]. Moreover, this finding is parti- cularly notable given similarities between the interpretative aspect of interoception (as measured by the EDI) and alexithymia (see [28]). Our result provides further insight into current debates and contrasting findings regarding the relationship between alexithymia and inter- oception (see [57,81]). The findings are consistent with previous re- search suggesting that greater levels of alexithymia are related to better interoception (i.e. individuals with poor emotional awareness report greater somatic awareness; [27,57]). This seemingly counterintuitive relationship can be explained by the suggestion that paying attention to interoceptive sensations (i.e. high interoception) may hamper the in- terpretation of one's emotional feelings (i.e. high alexithymia), and contribute to somatoform disorders via the misinterpretation of phy- sical sensations [57].

Finally, we found that depression, as measured by the BDI [8], was not a significant predictor of interoception deficit effect size. Indeed, the association between depressive symptoms and interoceptive abil- ities has not always been consistent in previous research. For example, Dunn et al. [25] found a significant difference in interoception (as measured using a heartbeat perception task; see [72]) between in- dividuals with moderate depression and controls, but no significant difference between severely depressed individuals and controls. Pol- latos et al. [69] found evidence of a significant negative relationship between depression and scores on a heartbeat perception measure of interoception in healthy participants, however also found a significant interaction with anxiety, where this relationship only remained sig- nificant at high levels of anxiety. Therefore, both the severity of de- pressive symptoms and levels of anxiety in the samples used in this analysis may have had an influence over the relationship between de- pression symptoms and effect size, and may explain why no significant relationship was found. The average BDI scores of the samples analysed were also within the minimal-to-moderate range according to estab- lished BDI cut-offs. This limited variability in depression scores ne- cessarily limits the generalisability of our findings to individuals with mild to moderate depression.

###### 4.1. Limitations and recommendations

An important caveat of our findings is that the conclusions drawn relate only to self-reported interoceptive deficits measured by the Interoceptive Awareness subscale of the Eating Disorder Inventory (EDI). This leads to two potential limitations. Firstly, the EDI has been criticised as an assessment of interoception, as it primarily considers the interpretative, emotional aspect of interoception [28], and fails to dif- ferentiate between a confusion or lack of clarity regarding internal experiences and non-acceptance of affective arousal [60]. Moreover, it is possible that, despite self-reporting more interoceptive deficits, in- dividuals with certain types of ED lack insight and consequently un- derreport the true extent of their interoceptive deficits. This would, for example, be consistent with the differing symptomology of AN and BN, where patients with AN often lack insight into or deny their illness and symptoms, whereas patients with BN are typically more motivated to recover [51]. This difference in awareness may, therefore, account to some extent for the differences found in interoceptive deficits between AN and BN patients.

Second, recent research distinguishes between different types or levels of interoceptive ability [38], with interoceptive sensibility referring to the subjective, self-evaluation of interoceptive ability; interoceptive accuracy referring to an individual's objective accuracy in detecting and tracking internal bodily sensations; and interoceptive awareness referring to the a meta-cognitive measure of the correspondence between the objective and subjective measures (see also [16] for discussion of the origin and development of interoception as a concept). As mentioned above, Bruch [12] also distinguished between two kinds of inter- oceptive ability in ED (perception vs. interpretation of body signals). Importantly, the different dimensions of interoception may be distinct and dissociable [37,39]. Unfortunately, our systematic search identified only three studies that examined interoceptive ability objectively in an ED sample [33,50,68], using a heartbeat detection task [72], and so it was not possible to include these in our meta-analysis and/or conduct any meaningful comparisons. Therefore, an important aim for future ED research should be to include both objective and subjective measures of interoceptive ability, to look at awareness across different modalities

(e.g. cardiovascular, gastrointensinal, pain and pleasant touch; see [20,21,46] for examples), and to see how deficits relate to body image and ownership (see [6,20,21]). Although no “gold standard” measure of interoception exists, new methods have been developed to capture the multidimensional nature of interoception (see [38,57,61,62]), and va- lidated in a clinical eating disorder sample (e.g. [11]).

The current review also highlighted how most existing ED studies have assessed samples of AN and BN, with only three samples of EDNOS, despite this being the most common eating disorder seen in outpatient settings [29]. Our review also identified only a limited number of studies involving recovered and BED samples, again high- lighting a clear gap in the current literature. Understandably, fewer studies have focused on BED in comparison to other diagnoses, since it was only recently introduced as a diagnostic category in DSM-5 [3]. A particular focus is required on future studies with recovered eating disorder samples, EDNOS and BED in order to more accurately de- termine the pathogenesis of these EDs, and to assess the validity of introception as an endophenotype.

Finally, in additional to the limited number of studies looking at certain ED subtypes, our review of the literature identified that im- portant clinical variables, such as illness duration and BMI, were not always reported by existing studies. Our meta-analysis was unable to examine the potentially important relationships between illness dura- tion, overall disorder severity and interoceptive abilities, as the ma- jority of studies did not report on the illness duration or severity of their samples. Overall, these issues highlight the need for future research to consistently report on key clinical variables, as well as the need for more research to examine the relationship between the variables and interoception directly using multiple measures.

###### 5. Conclusion

We confirm the existence of a substantial, self-reported inter- oceptive deficit in all types of EDs examined. Impaired interoception may, therefore, be considered a transdiagnostic characteristic of EDs and a possible endophenotype. The degree of interoceptive deficit varies across ED subtypes and may provide a useful distinguishing feature of different EDs. They may also play a maintenance role in eating disorders, and consequently be an appropriate target for treat- ment or prevention. The extent of interoceptive deficit may be influ- enced by several factors, such as age, BMI, and alexithymia; however, further evidence is needed to substantiate these conclusions, with fu- ture studies reporting these factors as well as illness duration, and employing both objective and subjective measures in direct examina- tions of interoceptive process across all types of EDs.

#### Lattimore, P., et al. (2017). "‘I can’t accept that feeling’: Relationships between interoceptive awareness, mindfulness and eating disorder symptoms in females with, and at-risk of an eating disorder." Psychiatry Res 247: 163-171.

Mindfulness based therapies (MBTs) for eating disorders show potential benefit for outcomes, yet evidence is scarce regarding the mechanisms by which they influence remission from symptoms. One way that mindfulness approaches create positive outcomes is through enhancement of emotion regulation skills. Maladaptive emotion regulation is a key psychological feature of all eating disorders. The aim of the current study was to identify facets of emotion regulation involved in the relationship between mindfulness and maladaptive eating behaviors. In three cross-sectional studies, clinical (n=39) and non-clinical (n=137 & 119) female participants completed: 1) the Eating Disorder Inventory (EDI) eating specific scales (drive-for-thinness and bulimia) and the EDI psychological symptom scales (emotion dysregulation and interoceptive deficits); and 2) mindfulness, impulsivity, and emotion regulation questionnaires. In all samples mindfulness was significantly and inversely associated with EDI eating and psychological symptom scales, and impulsivity. In non-clinical samples interoceptive deficits mediated the relationship between mindfulness and EDI eating specific scales. Non-acceptance of emotional experience, a facet of interoceptive awareness, mediated the relationship between mindfulness and eating specific EDI scores. Further investigations could verify relationships identified so that mindfulness-based approaches can be optimized to enhance emotion regulation skills in sufferers, and those at-risk, of eating disorders.

#### Fitzgibbon, M. L., et al. (2003). "A test of the continuity perspective across bulimic and binge eating pathology." International Journal of Eating Disorders 34(1): 83-97.

Abstract: Objective: This article examines the continuity/discontinuity perspective of eating pathology among 375 women seeking treatment. Methods: Participants were categorized into five separate groups: obese nonbingers, subthreshold binge eating disorder (BED), BED, subthreshold bulimics, and bulimics. We tested whether differences in core eating pathology (drive for thinness, body dissatisfaction, current body image, body image ideal) and psychiatric symptoms (depression, interoceptive awareness) differentiated the groups quantitatively (supporting the continuity perspective) or qualitatively (supporting the dis- continuity perspective). Results: Our results, overall, supported the continuity perspective of eating pathology. A discriminant function analysis using the eating pathology and psychiatric symptom variables as predictor variables found that one primary factor differentiated the five groups on both core eating pathology and psychiatric variables. Discussion: The impli- cations of testing this model within a treatment-seeking sample are discussed. # 2003 by Wiley Periodicals, Inc. Int J Eat Disord 34: 83–97, 2003.

## Interoception in Binge Eating Disorder

### Meta-Analyses

#### Jenkinson et al., 2018

In 2018, Jenkinson et al. conducted a meta-analysis of studies assessing self-reported interoceptive deficits in eating disorders using the eating disorder inventor (EDI) (Jenkinson et al., 2018) (**Table 1**). The authors identified 29 studies and 41 samples that met the inclusion criteria, including 5 samples of individuals with binge eating disorder in 4 different studies (Aloi et al., 2017; de Zwaan et al., 1994; Ramacciotti et al., 2008; Vinai et al., 2015). These four studies included 149 patients with adult binge eating disorder (Aloi et al., 2017; de Zwaan et al., 1994; Ramacciotti et al., 2008; Vinai et al., 2015), 36 patients with subclinical binge eating disorder (Aloi et al., 2017; de Zwaan et al., 1994), 15 patients with overeating (de Zwaan et al., 1994), 42 obese controls (Aloi et al., 2017; de Zwaan et al., 1994; Ramacciotti et al., 2008), and 61 healthy controls (Vinai et al., 2015). The overall analysis revealed the largest effect of interoceptive deficits in patients with anorexia nervosa (SMD = 1.71), followed by individuals with bulimia nervosa (SMD = 1.96) and binge eating disorder (SMD = 0.76). Although historically, alexithymia has been suggested to be related to depression (Brewer et al., 2016; Nemiah, 1976), Jenkinson et al. (2018) did not find a statistically significant correlation between interoceptive deficits and levels of depression. Rather, interoceptive deficits were found to be greater in participants with higher levels of alexithymia (less ability to identify, label, and describe one’s feelings and emotions) as well as in those with lower BMI and younger age. Notably, causation was not tested in these relationships. Thus, conclusions cannot be drawn about the nature of the relaltionship between emotion and interoceptive awareness (e.g., wither one causes/contributes to the other). Additionally, findings of associations between greater interoceptive deficits and lower BMI must be interpreted in the context of the study’s meta-regression, which included samples of individuals with anorexia nervosa, bulimia nervosa, and binge eating disorder. These individuals had BMIs ranging from 15.7 to 44.82 across all pooled samples (k = 17, Q = 57.92, p < 0.001). Although BMI has recently received scrutiny as a health measure for a variety of limitations (Nuttall, 2015), a “healthy BMI” is considered to be 18.5 – 24.9, with BMIs below 18.5 considered “underweight”, BMIs of 25.0 – 29.9 considered “overweight,” and BMIs of ≥30 considered obese(CDC, 2020a, 2020b). Therefore, Jenkinson et al.’s 2018 findings cannot necessarily be interpreted to suggest that in normal healthy populations lower BMI is associated with higher levels of alexithymia. Rather, their findings can only be interpreted to suggest that in populations of individuals with eating disorders, in which BMIs range from “underweight” to “morbidly obese,” lower – and possibly underweight – BMIs have higher associations with interoceptive deficits. That is, individuals with less ability to identify, label, and describe their feelings and emotions (higher alexithymia scores) and lower BMIs tend to have less confidence in their ability to recognize and identify emotions and sensations related to hunger and satiety (interoceptive deficits), in the context of individuals with anorexia nervosa, bulimia nervosa, and binge eating disorder.

Overall, Jenkinson et al. (2018) interpreted their findings to suggest that interoceptive deficits exist on a continuum in eating disorders, with individuals with anorexia nervosa and bulimia nervosa experiencing significantly more pronounced interoceptive deficits relative to those with binge eating disorder. The authors suggest the significant inter-diagnostic differences in the degree of interoceptive impairment observed across all eating disorders supports a transdiagnostic view of eating disorders (Fairburn et al., 2009), suggesting eating disorders exist on a spectrum rather than being qualitatively distinct, with similar or overlapping core symptomatology that may be expressed differently throughout the course of the disorder (Fairburn et al., 2009). The authors also interpret their findings to suggest interoception deficits as a candidate endophenotype for eating disorders (in line with the work of Cynthia Bulik and others (Bulik et al., 2007)) and a potential treatment target warranting further research.

Jenkinson et al (2018) did note that the binge eating disorder samples generally had higher mean sample age and significantly smaller effect sizes, which may have resulted in diagnosis influencing the overall analysis. Further, the authors acknowledge that the nature of the relationship between interoceptive deficit and eating disorder diagnosis remains unexplored. Therefore, it is currently unclear whether interoceptive deficits contribute to the onset and/or maintenance of an eating disorder or whether they result from eating disorder pathology and symptomatology.

### Systematic Reviews

#### Martin et al., 2019

##### See c/p above

##### BB Commentary

In 2019, Martin et al. conducted a systematic review of studies assessing interoception and disordered eating, focusing on whether interoceptive deficits play a causal role in the development of disordered eating and whether any factors moderate or mediate the relationship between interoception and disordered eating (Martin et al., 2019). The authors identified 104 studies that met the inclusion criteria, comprising 32,883 participants with various forms of eating disorders and 4 cross-sectional studies assessing interoception in 106 adult participants with active binge eating disorder (Aloi et al., 2017; Ramacciotti et al., 2008; Vinai et al., 2015), 27 participants with obesity and adult binge eating disorder (Raymond et al., 1995), 16 participants with subclinical binge eating disorder (Aloi et al., 2017), 98 obese controls (Aloi et al., 2017; Ramacciotti et al., 2008; Raymond et al., 1995), and 105 healthy controls (Raymond et al., 1995; Vinai et al., 2015) ((Aloi et al., 2017; Ramacciotti et al., 2008; Raymond et al., 1995; Vinai et al., 2015)). Of these four studies, three ((Aloi et al., 2017; Ramacciotti et al., 2008; Vinai et al., 2015)) were included in Jenkins et al.’s 2018 meta-analysis (described above) (Jenkinson et al., 2018) and used self-report measures of interoceptive deficits in eating disorders (using the EDI). The fourth study assessed interoception using mechanical pain threshold (Raymond et al., 1995). All four studies observed significant impairments in interoception (relative to controls). Additionally, all four studies found significant differences in gastric interoception associated with binge eating disorder and Ratymond et al. (1995) observed significantly elevated mean pain detection thresholds in individuals with obesity and binge eating disorder relative to healthy controls (F(2, 101) = 4.12, p = 0.019), Tukey’s post hoc p < 0.05) with no significant difference in mean pain tolerance thresholds (PTTs).

The positive correlations between interceptive deficits, alexithymia, and binge eating disorder – as observed by Jenkinson et al (2018) (Jenkinson et al., 2018) and Martin et al. (2019) (Martin et al., 2019) – suggest a possible mechanistic that can explain the comorbidity between eating disorders and autism spectrum disorder, which is gaining recognition more recently(Björk et al., 2021; Dell'Osso et al., 2019; Nazar et al., 2016; Nickel et al., 2019; Price, 2022; Pruccoli et al., 2023; Solmi et al., 2021). In peer-reviewed literature, for example, a 2023 case series reported on the cases of 11 children and adolescents with comorbid feeding and eating disorders and neurodevelopmental disorders, included three cases of children and adolescents with autism spectrum disorder comorbid with ARFID (n = 2) or anorexia nervosa (n = 1). The two patients with ARFID and ASD had additional comorbidities including Goldehnar syndrome and intellectual disabilities in one and a specific learning disorder and epilepsy in the other (Pruccoli et al., 2023). The authors note that “the onset of feeding and eating disorder-related psychopathology was preceded, sometimes undiagnosed, by altered neurodevelopmental features leading to specific comorbid neurodevelopmental disorder diagnoses (autism spectrum disorder-ASD; attention-deficict/hyperactivity disorder-ADHD; specific learning disorder-SLD),”(Pruccoli et al., 2023). Higher levels of evidence also identify comorbidities between feeding and eating disorders and autism spectrum disorder in pediatric and young adult patients. For example, SOLMI AND BJORK HERE. Dell’Osso et al’s 2019 editorial note that autistic traits “seem highly prevalent in a broad variety of clinical groups (e.g., among patients with eating disorders…),” and “the ASD phenotypes are the tip of the iceberg of several possible clinical expressions (e.g., …eating disorders…) underlying the autism spectrum,” (Dell'Osso et al., 2019)

#### Nickel et al., 2019

##### See c/p above

##### BB Commentary

In a systematic review, Nickel and colleagues highlighted that ASD is most commonly diagnosed among patients with anorexia nervosa (AN), especially the restrictive subtype, while ADHD more frequently occurs in patients with bulimia nervosa (BN) or binge- purging AN(Nickel et al., 2019). Furthermore, the association between BN and binge-eating disorder (BED) with ADHD has been repeatedly proven (Nazar et al., 2016).

##### Discussion: Interoception as a Transdiagnostic Feature of Eating Disorders

The transdiagnostic- and endophenotypical views of eating disorders addressed by Jenkinson et al., (2018) are also addressed in Bray et al., 2023 (Bray et al., 2023), in which 71% of binge eating disorder experts interviewed (10/14) expressed views of binge eating disorder as a heterogenous diagnosis that may encompass several different subsets or phenotypes and 64% of experts (9/14) spontaneously identifying or referencing a total of 19 possible endophenotypes of binge eating disorder, which included a mood or emotion dysregulation-driven endophenotype (spontaneously identified by 2/14 participants, 15%) and depression-mediated and nonspecific gastrointestinal/inflammatory endophenotypes (spontaneously identified by 1/14 participants each, 7% each). The possibility of interoceptive deficits as a possible endophenotype was not addressed or inquired in Bray et al., 2023 (Bray et al., 2023).

Overall, Martin et al’s 2019 findings and conclusions mirrored those expressed in Jenkins et al’s 2018 meta-analysis – that the interoception deficits observed across disordered eating types and interoceptive modalities suggest interoception may constitute a transdiagnostic feature of disordered eating.

However, there is currently limited evidence on the causal role of interoception in the development of disordered eating .

Khalsa et al., 2022 recently published a narrative review of evidence of gastrointestinal interoceptive dysfunction in eating disorders (Khalsa et al., 2022). [The review emphasizes the importance of understanding gastrointestinal interoception through the lens of predictive processing, whereby the nervous system is engaged in predicting upcoming states in relation to current states, and refining these predictions via error signaling 1](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8898253/).

#### Romano, K. A., et al. (2020). "Somatic symptoms and binge eating in women's daily lives." J Psychosom Res 135: 110161.

1. Abstract

OBJECTIVE: The present study aimed to determine whether the momentary severity of women's somatic symptoms was concurrently and prospectively associated with their engagement in binge eating in naturalistic settings. METHOD: Thirty women (M(age) = 34.13, SD = 13.92) who had engaged in binge eating at least once over the month prior to study entry completed a 14-day ecological momentary assessment (EMA) protocol. During each of the 14 days, participants received five semi-random surveys via text message that assessed momentary somatic symptom severity (i.e., headaches, stomachaches/pain, chest/heart pain, faintness/dizziness, shortness of breath, fatigue) and disordered eating behaviors. Generalized estimating equations were used to determine whether momentary somatic symptoms were concurrently and prospectively (i.e., by participants' next assessment) associated with the occurrence of binge eating behavior, while controlling for age and body mass index. RESULTS: At the within-person level, more severe stomachaches/pain, faintness/dizziness, shortness of breath, and fatigue were concurrently associated with an increased likelihood of engaging in binge eating. Further, at the between-person level, more severe stomachaches/pain, chest/heart pain, shortness of breath, and fatigue in general were associated with binge eating across the EMA protocol. Momentary stomachache/pain severity also prospectively predicted women's engagement in binge eating behavior at the next assessment. CONCLUSIONS: The present results provide initial evidence that multiple somatic symptoms may serve as momentary correlates or proximal antecedents of binge eating behavior in women's daily lives. Somatic symptoms may consequently prove useful to target in eating disorder treatments, perhaps via interoceptive exposure interventions.

1. Introduction

Binge eating is prevalent among adult women and is a well-estab- lished correlate of multiple physical and mental health concerns, in- cluding somatic and psychosomatic symptoms (i.e., physical health concerns that are incited or exacerbated by psychosocial factors) [1,2]. Indeed, individuals who frequently engage in binge eating commonly exhibit symptoms that have both psychogenic and physiological ori- gins, such as gastrointestinal concerns (e.g., stomachaches or pains), chest and heart pain, headaches, faintness, shortness of breath, and fatigue [1,3–6]. Given that individuals may be more likely to report somatically-based versus disordered eating symptoms to healthcare

providers [7], enhancing the current understanding of the interplay between binge eating and somatic comorbidities may help improve current screening efforts for binge eating pathology and facilitate in- dividuals' connection with treatment.

1. Somatic symptoms and binge eating

Existing research examining somatic symptoms and binge eating has largely focused on identifying how between-person differences in par- ticular somatic symptoms are associated with binge eating pathology [1,3–6]. For example, in a large sample of Swedish individuals with lifetime binge eating disorder and healthy controls, those with binge eating disorder were more likely to report various neurologic (e.g., headaches, migraines), gastrointestinal, respiratory, and circularity system concerns [6]. Although informative, little is known about so- matic symptom-binge eating comorbidities beyond bivariate between- person associations of this nature. However, more generally, in- dividuals with binge eating symptoms commonly exhibit interoceptive deficits [8–11], or dysfunction in the ability to sense and process visceral bodily experiences and states such as pain, hunger, satiety, and heartbeat sensations [12]. Such difficulties in effectively connecting with internal experiences can translate to individuals' engagement in adverse health behaviors like binge eating as a means of experiential avoidance. This can serve as an impediment to adequate body regula- tion that is integral to maintaining health and well-being [9].

Of note, although between-person research consistently suggests that interoceptive processes are skewed among individuals with eating disorders characterized by binge eating [8–11], the nature of this dys- function is equivocal. For example, some research suggests that in- dividuals with binge eating pathology exhibit hypersensitivity and others hyposensitivity to certain interoceptive signals [9]. This equi- vocality poses different implications for individuals' responses to their internal bodily signals. Hypersensitive or exaggerated responses to in- ternal sensations can lead to subsequent binge eating wherein, for ex- ample, internal signals of depleted energy that are sensed by the body (e.g., fatigue, faintness, hunger) promote behaviors such as binge eating that are designed to address these cues and are maintained over time via reinforcement-based processes [11,13]. In contrast, hyposensitive or blunted responses to interoceptive signals, such as stomachaches/ pain or satiety, can propagate subsequent binge eating via the body's inability to signal the significance of these somatic cues and, in turn, prevent individuals' engagement in this adverse health behavior [13].

1. Ecological Momentary Assessment (EMA)

Existing between-person findings on interoceptive processes can be extended and the evidence-base's equivocality potentially clarified by examining whether various somatic symptoms serve as momentary correlates or proximal triggers of binge eating behavior. EMA is a particularly well-suited methodology that can aid in determining how somatic symptom-binge eating patterns manifest in individuals' daily lives. To date, however, between-person cross-sectional and, to a lesser degree, traditional longitudinal methods have strictly been used to examine somatic symptom and binge eating associations [1,3–6]. These two methods provide limited information about the functionality of these associations and are subjected to retrospective recall bias that can decrease the validity of ensuing results [15]. In contrast, EMA permits the examination of psycho-behavioral factors in individuals' daily lives via brief repeated assessments. Given this, EMA minimizes the influence of recall bias inherent within cross-sectional survey research, increases ecological validity, and enables the examination of novel research questions that address the temporal sequencing of psycho-behavioral factors in naturalistic settings [15].

Although no existing research has examined naturalistic associa- tions between somatic symptoms and binge eating behavior, a growing body of research has used EMA to examine how internal bodily signals such as affect and hunger are associated with binge eating [16–18]. Regarding the latter, meta-analytic evidence suggests that individuals' hunger levels are generally lower prior to binge eating episodes when compared to normative eating episodes [18]. This finding aligns with between-person cross-sectional research that suggests that individuals who engage in binge eating exhibit hyposensitive interoceptive re- sponses to somatic cues [13,14]. However, it remains unknown whe- ther this result generalizes from internal hunger sensations to somatic symptoms and whether there are variations in these associations as a function of somatic symptom type.

1. Results

There were 1558 EMA recordings across the 14-day assessment period. On average, participants responded to 51.93 prompts (SD = 13.49; range = 16–70) and compliance, defined as individuals' average number of completed prompts divided by the total number of possible prompts, was good (78.3%). At baseline, the average number of objective binge eating episodes reported in the past 28 days via the EDE interview was 12.27 (SD=13.78; Range=1–76). Participants endorsed binge eating during 13.7% (213 episodes) of the survey prompts. The number of EMA recordings completed was unrelated to demographic variables. Further, across ratings, participants' somatic symptom severity was generally low, with the average headache pain severity rating being 1.69 (SD = 1.08), as well as 1.60 (SD = 1.01) for stomachaches/pains, 1.08 (SD = 0.35) for chest/heart pains, 1.31 (SD = 0.71) for faintness/dizziness, 1.16 (SD = 0.55) for shortness of breath, and 2.48 (SD = 1.41) for fatigue.

Tables 2 and 3 present the concurrent and prospective (i.e., time- lagged) models for somatic symptom and binge eating associations, respectively. Regarding the concurrent results, significant within- and between-person effects were found for associations between experien- cing stomachaches/pain, shortness of breath, and fatigue relative to binge eating. That is, at times over the hours following participants' previous assessments when they reported more severe stomachaches/ pains, shortness of breath, and fatigue than their averages, they were more likely to concurrently report binge eating episodes. Further, par- ticipants who generally experienced more extreme stomachaches/

pains, shortness of breath, and fatigue than others engaged in more binge eating behavior throughout the EMA protocol. In addition, a significant within- but not between-person effect was found for faint- ness/dizziness and a between- but not within-person effect was found for chest/heart pain severity as correlates of concurrent binge eating behavior. More specifically, at times when participants indicated that they experienced higher levels of faintness/dizziness than they nor- mally did, they were more likely to report having engaged in binge eating and, further, participants who generally experienced more se- vere chest/heart pain than others were more likely to engage in binge eating across assessments.

Regarding the time-lagged analyses, which examined associations between individuals' somatic symptoms at a given assessment and their reports of binge eating at their next assessment, significant within- and between-person effects were found for stomachache/pain severity. In particular, at times when participants experienced more severe sto- machaches/pain than they normally did, they were more likely to en- gage in binge eating by their next survey prompt. Further, participants who generally experienced more severe stomachaches/pains than others were more likely to engage in binge eating by their next as- sessments across the EMA protocol. Significant time-lagged, between- person effects were also found for chest/heart pain severity and shortness of breath, such that participants who typically experienced more severe chest/heart pain and shortness of breath than others were more likely to binge eat by their next assessments across the EMA protocol. All concurrent and prospective associations between head- ache severity and binge eating were not significant.

1. Discussion

Although existing between-person research has consistently found that various somatic symptoms are associated with elevated binge eating severity [1,3–6], no prior studies have examined whether these symptoms serve as concurrent correlates or proximal antecedents of binge eating behavior when assessed in ecologically valid settings. To address this research gap, the present study was the first to use EMA to examine whether women's somatic symptom severity (headaches, sto- machaches/pain, chest/heart pain, faintness/dizziness, shortness of breath, fatigue) at a given moment was independently associated with their engagement in binge  
and prospectively (i.e., by  
indicated that, at the within-person level, more severe gastrointestinal and pulmonary somatic symptoms, alongside signs of depleted energy (faintness/dizziness, fatigue), were concurrently associated with a greater likelihood of engaging in binge eating and that, at the between- person level, an increased severity of most of these symptoms plus chest/heart pain were concurrently associated with a higher probability of binge eating across assessments. Further, intraindividual differences in stomachache/pain severity were also prospectively associated with women's increased likelihood of engaging in binge eating. Considered together, these results provide initial evidence that visceral sensations that span across various domains of bodily functioning may serve as concurrent correlates or proximal antecedents of binge eating and prove useful to target in existing eating disorder treatments.

1. Hypersensitive responses to somatic symptoms

That experiencing more severe somatic symptoms was generally associated with an increased likelihood of concurrent binge eating in the present study aligns with existing between-person research de- monstrating that individuals who engage in binge eating may exhibit hypersensitive responses to interoceptive signals [9,13]. The present within-person findings extend this literature by suggesting that at times when women with elevated binge eating severity experience more se- vere gastrointestinal and pulmonary symptoms, as well as internal cues related to depleted energy (faintness/dizziness, fatigue), than they ty- pically do, they are more vulnerable to engaging in binge eating be- havior at that time. Notably, given that the parameters for these con- current within-person somatic symptom-binge eating associations were generally comparable in size, there appears to be little differentiation in the strength of these associations as a function of somatic symptom type. Consequently, the assessed symptoms appear to be similarly im- pactful.

That within-person differences in concurrent associations between most somatic symptoms and binge eating did not generally differ as a function of somatic symptom type may reflect a negative attribution style that women with elevated binge eating severity have in response to interoceptive signals in general or serve as a marker of emotion dysregulation that commonly manifests in this population [25]. Binge eating may consequently serve as a form of experiential avoidance, wherein women engage in this behavior in an attempt to distance themselves from and quell these adversely perceived internal cues and, instead, experience rewarding and reinforcing effects that are asso- ciated with binge eating in the short-term [9,13]. Previous between- person neuropsychological research has supported this perspective by demonstrating how internal signs of depleted energy (e.g., faintness/ dizziness, fatigue) relate to elevated binge eating pathology, and the present findings extend this work by showing that similar processes occur across somatic symptoms not strictly related to diminished energy reserves at the momentary level of analysis. This prior research centers on the concept of positive alliesthesia [26], which suggests that hy- persensitive responses to indications of low energy incite visceral-be- havioral responses that help the body achieve a state of homeostasis and maintain health. Individuals' motivation to consume food increases during times when their energy is low due, in part, to the rewarding properties associated with such consumption. In those vulnerable to binge eating, the motivational salience of food heightens via re- inforcement-based processes and, in turn, increases individuals' sus- ceptibility to eating beyond their energy needs at a given moment [11]. As an important extension of the present study, it will prove useful for future research to merge this prior evidence with the current findings via multi-modal assessment. Specifically, such work should examine whether objective differences in neural activity in cortical areas asso- ciated with reward, motivation, interoception, and impulsivity mod- erate momentary associations between self-reported somatic symptoms and binge eating behavior

1. Gastrointestinal and cardiovascular somatic symptoms

Elevated stomachache/pain severity was the only within-person effect that was prospectively associated with an increased risk of binge eating at a subsequent timepoint. This suggests that, when compared to other somatic symptoms, experiencing adverse gastrointestinal sensa- tions at a given time may uphold a particularly harmful and enduring role in promoting subsequent binge eating. It is unclear why this so- matic symptom, in particular, appears to subsist. Given that the sto- mach may be more centrally implicated in body image than somatic sensations in other body areas (e.g., headaches, fatigue), it is possible that experiencing elevated gastrointestinal pain may simultaneously heighten women's awareness of their stomachs at large and, in turn, propagate an increase in negative body image and negative affect. Considering that negative body image and negative affect serve as disordered eating behavior triggers [16,27], these psychologically- based concerns may consequently account for or otherwise influence the present prospective associations between elevated stomachache/ pain severity and binge eating behavior. Thus, these constructs warrant assessment as mediators and/or moderators of these associations in future research.

A strength of EMA includes the method's ability to permit the se- paration of within- and between-person effects [15,24]. This helps de- termine whether associations among psycho-behavioral factors exist at times when individuals experience higher levels of various symptoms than they typically do and/or reflect differences in aggregate levels of symptoms that vary between participants. In this regard, it is note- worthy that the between-, but not within-, person association between elevated chest/heart pain severity and an increased likelihood of binge eating was significant and larger than all other assessed concurrent and prospective somatic symptom-binge eating associations. These findings align with prior between-person research that found that various cir- culatory system diseases associated with chest/heart pain exhibit some of the strongest associations with binge eating symptoms [1,5,6]. It is plausible that the present findings similarly reflect individual differ- ences in cardiac-based somatic morbidities that are associated with elevated binge eating behavior. Indeed, as within-person differences in

chest/heart pain severity were not also associated with concurrent binge eating in the present study, this symptom does not appear to serve as a concurrent correlate or a prospective antecedent of binge eating and, instead, appears to reflect trait-level interindividual differences. Future research that controls for cardiac-based somatic morbidities is needed to determine whether this factor accounts for the observed chest/heart pain-binge eating associations.

1. Clinical implications

The present findings can help inform existing eating disorder treatments focused on decreasing individuals' binge eating symptoms. Specifically, the present findings suggest that women's experiences of various somatic symptoms are associated with hypersensitive inter- oceptive responses that are concurrently and, for stomachache/pain severity, prospectively linked to binge eating behavior. Incorporating interoceptive exposure interventions and interventions that more broadly target emotion dysregulation into existing treatment protocols can help encourage individuals to identify and sit with adversely per- ceived internal cues of this nature, rather than attempt to temporarily quell them by engaging in binge eating [28]. Given that stomachache/ pain severity was shown to exhibit a precipitating role in inciting this behavior, addressing adversely perceived internal signals in the sto- mach area may serve as a particularly important somatic symptom to target. In session, this may include directing individuals' attention to stomach pains and tight clothing, associated thoughts, feelings, and sensations that arise, and urges to engage in avoidance strategies (e.g., binge eating) as an (ineffective) means of lessening the sensations in the short-term [28]. Psychoeducation on the role of neural plasticity fol- lowing the normalization of individuals' eating patterns in creating new brain pathways that promote effective, rather than over-active, re- sponses to somatic symptoms can also serve as a viable adjunctive treatment component.

1. Limitations

Although strengths of the current study include the use of EMA with women with elevated binge eating pathology, certain limitations war- rant mention. First, the present sample was all female and most parti- cipants identified as White. Future research with a more gender and racially diverse sample is needed to increase the generalizability of our findings. Second, although EMA studies commonly use single-item questions to examine disordered eating behaviors and correlates of such [16] as a means of decreasing participant burden owing to the heigh- tened frequency of EMA reports, the use of a single-item variable to assess individuals' binge eating behavior in the present study may not have fully captured this construct when compared to multi-item mea- sures. Further, the concurrent models attest to participants' reported somatic symptoms and binge eating behavior over the hours since their last assessment. Consequently, the temporal ordering of these symptom experiences is unclear (i.e., somatic➔binge eating, binge eating➔so- matic). Future research using event-contingent reports and that which examines whether binge eating prospectively predicts somatic symptom severity could help clarify the directionality of these associations. In addition, the present study included 30 participants. Although the use of repeated sampling increased our power to test the present study aims, this is a relatively small between-persons sample size and these findings should be replicated with a larger sample. In addition, al- though all participants needed to report recent objective binge eating to be included in the present study, there was some variation in partici- pants' ED symptom patterning. Consequently, future research with a larger sample is needed to examine whether ED diagnostic differences influences the assessed somatic symptom-binge eating associations. Finally, although the six assessed somatic symptoms have been con- sistently shown to adversely impact individuals with binge eating pa- thology [1,4–6], it would be informative for future studies to examine the momentary impact of additional gastrointestinal symptoms beyond stomachaches/pain alone (e.g., bloating, diarrhea) on women's binge eating.

1. Conclusions

The present study was the first to use EMA to examine whether women's somatic symptoms (headaches, stomachaches/pain, chest/ heart pain, faintness/dizziness, shortness of breath, fatigue) at a given moment were independently associated with their engagement in binge eating behavior both concurrently and prospectively (i.e., by their next assessment). The present results indicated that more severe experiences of all assessed somatic symptoms apart from headache severity were concurrently associated with an increased likelihood of engaging in binge eating behavior at the within- and/or between-person levels. Intraindividual differences in stomachache/pain severity were also prospectively associated with women's increased likelihood of engaging in binge eating. The present results provide initial evidence that mul- tiple visceral sensations may serve as momentary correlates or proximal antecedents of binge eating and prove useful to target in existing eating disorder treatments.

### Narrative Review

#### Khalsa, S. S., et al. (2018). "Interoception and Mental Health: A Roadmap." Biological Psychiatry: Cognitive Neuroscience and Neuroimaging 3(6): 501-513.

Interoception refers to 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 signaling has been considered a component process of reflexes, urges, feelings, drives, adaptive responses, and cognitive and emotional experiences, highlighting its contributions to the maintenance of homeostatic functioning, body regulation, and survival. Dysfunction of interoception is increasingly recognized as an important component of different mental health conditions, including anxiety disorders, mood disorders, eating disorders, addictive disorders, and somatic symptom disorders. However, a number of conceptual and methodological challenges have made it difficult for interoceptive constructs to be broadly applied in mental health research and treatment settings. In November 2016, the Laureate Institute for Brain Research organized the first Interoception Summit, a gathering of interoception experts from around the world, with the goal of accelerating progress in understanding the role of interoception in mental health. The discussions at the meeting were organized around four themes: interoceptive assessment, interoceptive integration, interoceptive psychopathology, and the generation of a roadmap that could serve as a guide for future endeavors. This review article presents an overview of the emerging consensus generated by the meeting.

### Cross-Sectional Studies

#### van Dyck, Z., et al. (2020). "Gastric interoception and gastric myoelectrical activity in bulimia nervosa and binge-eating disorder." Int J Eat Disord.

OBJECTIVE: Identifying factors that control food intake is crucial to the understanding and treatment of eating disorders characterized by binge eating. In healthy individuals, stomach distension plays an important role in the development of satiation, but gastric sensations might be overridden in binge eating. The present study investigated the perception of gastric signals (i.e., gastric interoception) and gastric motility in patients experiencing binge-eating episodes, that is, bulimia nervosa (BN) and binge-eating disorder (BED). METHOD: Twenty-nine patients with BN or BED (ED group) and 32 age-, sex-, and BMI-matched healthy controls (HC group) participated in the study. The onset of satiation and stomach fullness were assessed using a novel 2-step water load test (WLT-II). Gastric myoelectrical activity (GMA) was measured by electrogastrography (EGG) before and after ingestion of noncaloric water. RESULTS: Individuals in the ED group drank significantly more water until reporting satiation during the WLT-II. The percentage of normal gastric myoelectrical power was significantly smaller in the ED group compared to HC, and negatively related to the number of objective binge-eating episodes per week in patients with BN or BED. Power in the bradygastria range was greater in ED than in HC participants. DISCUSSION: Patients with EDs have a delayed response to satiation compared to HC participants, together with abnormal GMA. Repeated binge-eating episodes may induce disturbances to gastric motor function.

#### Aloi, M., et al. (2017). "Social Cognition and Emotional Functioning in Patients with Binge Eating Disorder." Eur Eat Disord Rev 25(3): 172-178.

OBJECTIVE: This study aims to evaluate the theory of mind ability in a sample of obese patients with and without binge eating disorder (BED) and to explore the correlations between emotional and clinical assessments. METHODS: Overall, 20 non-BED, 16 under-threshold BED and 22 BED obese patients completed a battery of tests assessing social cognition and eating disorder psychopathology. RESULTS: Binge eating disorder, non-BED and under-threshold-BED obese patients showed similar ability to recognise others' emotions, but BED obese patients exhibited a deficit in recognising their own emotions as demonstrated by more impaired levels of alexithymia and interoceptive awareness and were more depressed. High positive correlations were evident between binging, depression, interoceptive awareness and alexithymia. CONCLUSIONS: Binge eating disorder patients have a comparable ability to understand others' emotions but a more impaired capacity to understand and code their own emotions compared with non-BED obese patients. This impairment is highly correlated with depression. Copyright © 2017 John Wiley & Sons, Ltd and Eating Disorders Association.

#### Lattimore, P., et al. (2017). "‘I can’t accept that feeling’: Relationships between interoceptive awareness, mindfulness and eating disorder symptoms in females with, and at-risk of an eating disorder." Psychiatry Res 247: 163-171.

Mindfulness based therapies (MBTs) for eating disorders show potential benefit for outcomes yet evidence is scarce regarding the mechanisms by which they influence remission from symptoms. One way that mindfulness approaches create positive outcomesis through enhancement of emotion regulation skills. Maladaptive emotion regulation is akey psychological feature of all eating disorders. The aim of the current study was to identify facets of emotion regulation involved in the relationship between mindfulness and maladaptive eating behaviours. In three cross-sectional studies, clinical (n=39) and non-clinical (n=137 & 119) female participants completed: 1) the Eating Disorder Inventory (EDI) eating specific scales (drive-for-thinness and bulimia) and the EDI psychological symptom scales (emotion dysregulation and interoceptive deficits); and 2) mindfulness, impulsivity, and emotion regulation questionnaires. In all samples mindfulness was significantly and inversely associated with EDI eating and psychological symptom scales, and impulsivity. In non-clinical samples interoceptive deficits mediated the relationship between mindfulness and EDI eating specific scales. Non-acceptance of emotional experience, a facet of interoceptive awareness, mediated the relationship between mindfulness and eating specific EDI scores. Further investigations could verify relationships identified so that mindfulness based approaches can be optimised to enhance emotion regulation skills in sufferers, and those at-risk, of eating disorders.

#### Vinai, P., et al. (2015). "Psychopathological characteristics of patients seeking for bariatric surgery, either affected or not by binge eating disorder following the criteria of the DSM IV TR and of the DSM 5." Eat Behav 16: 1-4.

We evaluate whether there are any significant differences in psychopathology between severe obese patients affected by Binge Eating Disorder diagnosed following both the DSM IV TR and the DSM5 criteria, and severe obese patients not having an eating disorder. METHOD: 118 severe obese patients seeking treatment at a center for bariatric surgery in northern Italy were asked to take part in the current study for a period of six months. Average participant age was 44.27 years, SD 12.42. Age ranged from 18 to 67 years. Average patient BMI was 45.03, SD 7.11, ranging from 32.14 to 66.16 kg/m(2). Seventy seven of the patients (65.3%) were females and 41 (34.7%) were males. BED diagnosis was determined following the diagnostic criteria of both the DSM IV TR and the DSM 5. The presence of other eating disorders was excluded through a clinical screening using the Eating Disorder Inventory (EDI). Patient eating habits and the presence of emotional eating were appraised using the Three-Factor Eating Questionnaire. Levels of depression and anxiety were evaluated using the Beck Depression Inventory and the State Trait Anxiety Inventory. RESULTS: 57 out of 118 patients were found to be affected by BED following the DSM 5 criteria; among them 24 followed those of the DSM IV TR. BED patients scored higher on four subscales of the Eating Disorders Inventory: Drive for thinness (DT), Bulimia (B), Body dissatisfaction (BD) and Interoceptive awareness (IA) on the STAI and on the Disinhibition and Hunger subscales of the TFEQ. DISCUSSION: The results confirm the presence of high levels of psychopathology among patients diagnosed with BED, even if they have been diagnosed following the criteria of the DSM 5. There is a great overlap in psychopathology between BED patients diagnosed following the DSM IV TR and the DSM 5 criteria.

#### Lammers, M. W., et al. (2015). "Predictors of outcome for cognitive behavior therapy in binge eating disorder." European Eating Disorders Review 23(3): 219-228.

The aim of this naturalistic study was to identify pretreatment predictors of response to cognitive behavior therapy in treatment-seeking patients with binge eating disorder (BED; N = 304). Furthermore, we examined end-of-treatment factors that predict treatment outcome 6 months later (N = 190). We assessed eating disorder psychopathology, general psychopathology, personality characteristics and demo- graphic variables using self-report questionnaires. Treatment outcome was measured using the bulimia subscale of the Eating Disorder Inventory 1. Predictors were determined using hierarchical linear regression analyses. Several variables significantly predicted outcome, four of which were found to be both baseline predictors of treatment outcome and end-of-treatment predictors of follow-up: Higher levels of drive for thinness, higher levels of **interoceptive awareness**, lower levels of binge eating pathology and, in women, lower levels of body dissatisfaction predicted better outcome in the short and longer term. Based on these results, several suggestions are made to improve treatment outcome for BED patients. Copyright © 2015 John Wiley & Sons, Ltd and Eating Disorders Association.

#### Ramacciotti, C. E., et al. (2008). "Shared psychopathology in obese subjects with and without binge-eating disorder." Int J Eat Disord 41(7): 643-649.

OBJECTIVE: To investigate obese people with/without binge-eating Disorder (BED) in terms of shared psychopathological features pertaining to spectrum of eating disorders. METHOD: One-hundred obese adult patients with a BMI > 30 kg/m(2) referred to an Eating Disorder Unit and/or hospital weight-loss programs were administered the BED Clinical Interview, the Eating Disorder Inventory, and the Structured Clinical Interview for Anorexic-Bulimic Spectrum, Self-Report. RESULTS: Twenty-seven subjects satisfied DSM-IV research criteria for current BED; compared to nonbingeing obese subjects, BED ones were characterized by greater weight-shape concerns influencing self-esteem (p = .05), overall impairment due to the overweight condition (p < .005), psychological distress leading to professional help (p < .001), dichotomous reasoning (p = .01) and secondary social phobia due to the overweight condition (p < .005). Compared to the other group, BED obese subjects scored higher at the following EDI subscales: bulimia (p < .0001), ineffectiveness (p < .01), interoceptive awareness and social insecurity (p < .05). CONCLUSION: The results of this study highlight the role of cognitive mechanisms such as dichotomous reasoning and weight-shape concerns unduly influencing self-esteem as a hallmark of BED in obese patients, and the importance of investigating eating disorder psychopathology by adopting a dimensional perspective, rather than strictly focusing on categories when dealing with obese patients.

#### Fassino, S., et al. (2004). "Clinical, psychopathological and personality correlates of interoceptive awareness in anorexia nervosa, bulimia nervosa and obesity [and BED]." Psychopathology 37(4): 168-174.

Objective: To determine the levels of interceptive awareness (IA), which measures the ability of an individual to discriminate between sensations and feelings, and between the sensations of hunger and satiety, in eating disorder patients and to identify the clinical, psycho- pathological and personal variables correlated with IA. Sampling and Methods: Sixty-one restrictor anorectics, 61 binge-purging anorectics, 104 purging bulimics, 49 obese subjects with **binge eating disorder (BED)** and 47 obese subjects without BED were compared. They were assessed with the Eating Disorder Inventory-2, the Temperament and Character Inventory, and the Beck Depression Inventory, and their clinical and sociodemographic features were recorded. Results: In all patients, the levels of lA were higher than the 'normal' ones; in bulimia nervosa, they were higher than in anorexia nervosa and obesity. Similar personal features and eating attitudes are shared by patients with bulimia nervosa and BED. In the total sample, the following variables independently correlate with IA: the Beck Depression Inventory, self-directedness and persistence. Conclusions: The importance of an altered Al in eating disorders is supported. Both depression and a perfectionist and poorly self- directive personality can lead to greater difficulties in discriminating hunger and satiety.

#### Fitzgibbon, M. L., et al. (2003). "A test of the continuity perspective across bulimic and binge eating pathology." International Journal of Eating Disorders 34(1): 83-97.

Abstract: Objective: This article examines the continuity/discontinuity perspective of eating pathology among 375 women seeking treatment. Methods: Participants were categorized into five separate groups: obese non-binge-eaters, subthreshold binge eating disorder (BED), BED, subthreshold bulimics, and bulimics. We tested whether differences in core eating pathology (drive for thinness, body dissatisfaction, current body image, body image ideal) and psychiatric symptoms (depression, **interoceptive awareness**) differentiated the groups quantitatively (supporting the continuity perspective) or qualitatively (supporting the dis- continuity perspective). Results: Our results, overall, supported the continuity perspective of eating pathology. A discriminant function analysis using the eating pathology and psychiatric symptom variables as predictor variables found that one primary factor differentiated the five groups on both core eating pathology and psychiatric variables. Discussion: The impli- cations of testing this model within a treatment-seeking sample are discussed. # 2003 by Wiley Periodicals, Inc. Int J Eat Disord 34: 83–97, 2003.

#### Raymond, N. C., et al. (1995). "Pain thresholds in obese binge-eating disorder subjects." Biol Psychiatry 37(3): 202-204.

#### de Zwaan, M., et al. (1994). "Eating related and general psychopathology in obese females with binge eating disorder." Int J Eat Disord 15(1): 43-52.

One hundred obese women with a mean age of 39.2 years, and a mean body mass index (BMI) of 35.9 kg/m2 were evaluated before entering a treatment study for weight reduction. According to the results of a structured interview, subjects were divided into four groups: (1) no overeating episodes, (2) episodic overeating episodes without the feeling of loss of control, (3) overeating plus the sense of loss of control (binge eating), and (4) full diagnostic criteria for binge eating disorder (BED). One-way analyses of variance (ANOVAs) revealed significant positive associations between binge eating and eating/weight-related characteristics such as a history of frequent weight fluctuations, the amount of time spent dieting, drive for thinness, and a tendency for disinhibition of eating. Furthermore, subjects exhibited more feelings of ineffectiveness, stronger perfectionistic attitudes, more impulsivity, less self-esteem, and less interoceptive awareness the more problems with binge eating they reported. The results support the idea that binge eaters might be a distinct subgroup among the obese population, and corroborate the utility of a diagnosis of BED in identifying the most disturbed obese subjects with regard to the variables tested.

## Interoception in Other Eating Disorders

### “Mixed EDs” (which can include BED)

(Dancyger & Garfinkel, 1995)

#### Dancyger, I. F. and P. Garfinkel (1995). "The relationship of partial syndrome eating disorders to anorexia nervosa and bulimia nervosa1." Psychol Med 25(5): 1019-1025.

A variety of sociocultural, familial and individual features associated with the eating disorders were examined in subjects with full syndrome (FS) and partial syndrome (PS) eating disorders and in normal high school students. The EAT-26 was administered to 995 high school students. This was followed by individual interviews with those who scored in the symptomatic range. Fifty-one students with PS eating disorders, 57 students without eating disorders (normal controls) and 30 hospital patients with FS, anorexia nervosa or bulimia nervosa were compared on subscales of the Eating Disorder Inventory, the Diagnostic Survey for Eating Disorders and the Beck Depression Inventory. The three groups displayed statistically significant differences on dimensions of EDI subscales Ineffectiveness and Interoceptive Awareness and also with respect to depression, history of being overweight and past history of emotional problems, as well as having mothers with medical illnesses. On these characteristics, the FS subjects displayed higher levels than the PS subjects, who in turn were higher than the NC subjects. The PS subjects displayed elevations on Body Dissatisfaction (EDI subscale), past medical illnesses, and mother's over-concern with eating and weight. These data support a continuum model of the eating disorders, but a continuum of multiple associated features rather than of dieting.

### “EDNOS” (“Eating Disorder Not Otherwise Specified,” which included BED before publication of the DSM-V in 2013).

(Herraiz-Serrrano et al., 2015; Nevonen et al., 2006; Nyman-Carlsson et al., 2015)

#### Nyman-Carlsson, E., et al. (2015). "Eating Disorder Inventory-3, validation in Swedish patients with eating disorders, psychiatric outpatients and a normal control sample." Nordic Journal of Psychiatry 69(2): 142-151.

*Background:* The Eating Disorder Inventory-3 (EDI-3) is designed to assess eating disorder psychopathology and the associated psychological symptoms. The instrument has been revised and has not yet been validated for Swedish conditions in its current form. *Aims:* The aim of  
this study was to investigate the validity and reliability of this inventory and present national norms for Swedish females. *Methods:* Data from patients with eating disorders (*n*292), psychiatric outpatients (*n*140) and normal controls (*n*648), all females, were used to study the internal consistency, the discriminative ability, and the sensitivity and specificity of the inventory using preliminary cut-offs for each subscale and diagnosis separately. Swedish norms were compared with those from Denmark, USA, Canada, Europe and Australian samples. *Results:* The reliability was acceptable for all subscales except Asceticism among normal controls. Analysis of variance showed that the EDI-3 discriminates significantly between eating disorders and normal controls. Anorexia nervosa was significantly discriminated from bulimia nervosa and eating disorder not otherwise specified on the Eating Disorder Risk Scales. Swedish patients scored significantly lower than patients from other countries on the majority of the subscales. Drive for Thinness is the second best predictor for an eating disorder. The best predictor for anorexia nervosa was Interoceptive Deficits and Bulimia for the other diagnoses. *Conclusions/clinical implications:* The EDI-3 is valid for use with Swedish patients as a clinical assessment tool for the treatment planning and evaluation of patients with eating-related problems. However, it still exist some uncertainty regarding its use as a screening tool.

#### Herraiz-Serrrano, C., et al. (2015). "Parental rearing and eating psychopathology." Actas Esp Psiquiatr 43(3): 91-98.

**Introduction.** The aim of the study was to identify the relationship between perceived rearing styles and the clini- cal expression of Eating Disorders (ED).

**Methods.** One hundred and ninety-six patients diag- nosed of an ED and 127 healthy student as controls selected from the Nursing College were evaluated for general psy- chopathology (STAI, BDI II, RSE), and for abnormal eating attitudes (EAT, EDI-II, BITE). The EMBU (‘my memories of up- bringing’) was administered for the assessment of perceived parental rearing styles and was used a questionnaire to as- sess familial variables.

**Results.** In relation to the control group, patients with ED perceived greater rejection, overprotection and less warmth than the controls. Patients who perceived greater paternal favoritism, maternal overprotection and low pater- nal emotional warmth, showed higher levels of anxiety. Pa- ternal affection and maternal attitudes of rejection, over- protection and favoritism were related to lower self-esteem. Regarding abnormal eating attitudes, body dissatisfaction inversely correlated with paternal emotional care and ma- ternal favoritism. The EDI subscales: ineffectiveness, perfec- tionism and ascetism were associated to parental rejection. Maternal rejection also related with drive for thinness, in- teroceptive awareness and impulse regulation. Perceived emotional warmth was related with perfectionism. Bulimia subscale and BITE scores were inversely associated to pater- nal overprotection and affection, and scored significantly higher in paternal favoritism and rejection from both par- ents.

**Conclusions.** Perceived parental bonding is different in the various subtypes of EDs. Patients diagnosed of Bulimia Nervosa or Eating Disorders Not Otherwise Specified perceived greater rejection, less affection and a greater overprotection than Anorexia Nervosa patients and controls.

#### Nevonen, L., et al. (2006). "Validating the EDI-2 in three Swedish female samples: eating disorders patients, psychiatric outpatients and normal controls." Nordic Journal of Psychiatry 60(1): 44-50.

The aim of the current study was to validate the Eating Disorders Inventory 2 (EDI-2) in a Swedish population by investigating how it discriminates between three female samples aged 18 to 50 years: patients with eating disorders (n /978), psychiatric outpatients (n /106) and normal controls (n/602), as well as between different eating disorder diagnoses. The internal consistency of the EDI-2 was above 0.70 for most subscales. The EDI-2 discriminated well between patients with eating disorders and normal controls on all subscales. On the symptom- related subscales, eating disorder patients scored highest followed by psychiatric controls and normals. All subscales except Perfectionism, Interoceptive awareness and Asceticism discrimi- nated eating disorder patients and psychiatric controls. Bulimia patients scored higher than anorexics on the symptom subscales. It is concluded that the EDI-2 discriminates well between eating disorder patients and both psychiatric and normal controls.

# Autism in BED

(Björk et al., 2021; Dell'Osso et al., 2019; Nazar et al., 2016; Nickel et al., 2019; Price, 2022; Pruccoli et al., 2023; Solmi et al., 2021)

#### Pruccoli, J., et al. (2023). "Food and Development: Children and Adolescents with Neurodevelopmental and Comorbid Eating Disorders-A Case Series." Behav Sci (Basel) 13(6).

The impact of psychiatric comorbidities in the diagnosis and treatment of feeding and eating disorders (FEDs) represents an emerging research topic. The current literature, nonetheless, lacks studies investigating the developmental paths of individuals with FEDs and comorbid neurodevelopmental disorders (NDDs). Here, we report 11 cases of children and adolescents with comorbid FEDs and NDDs, as assessed along the neuropsychological, psychopathological, and nutritional developmental pathways. The onset of FED-related psychopathology was preceded, sometimes undiagnosed, by altered neurodevelopmental features leading to specific NDD diagnoses (autism spectrum disorder-ASD; attention-deficit/hyperactivity disorder-ADHD; specific learning disorder-SLD). NDDs appeared to influence the diagnoses and treatments of FEDs, frequently with an impact on socio-relational and emotional premorbid features, and on the possibility to receive and attend FED-targeted treatments. Further studies should longitudinally contribute to assessing the experiences of care and neurodevelopmental pathways of children with FEDs and specific NDD comorbidities.

#### Price, D. (2022). Unmasking Autism: Discovering the New Faces of Neurodiversity. NY, Harmony Books.

For every visibly Autistic person you meet, there are countless “masked” Autistic people who pass as neurotypical. Masking is a common coping mechanism in which Autistic people hide their identifiably Autistic traits in order to fit in with societal norms, adopting a superficial personality at the expense of their mental health. This can include suppressing harmless stims, papering over communication challenges by presenting as unassuming and mild-mannered, and forcing themselves into situations that cause severe anxiety, all so they aren’t seen as needy or “odd.”

In Unmasking Autism, Dr. Devon Price shares his personal experience with masking and blends history, social science research, prescriptions, and personal profiles to tell a story of neurodivergence that has thus far been dominated by those on the outside looking in. For Dr. Price and many others, Autism is a deep source of uniqueness and beauty. Unfortunately, living in a neurotypical world means it can also be a source of incredible alienation and pain. Most masked Autistic individuals struggle for decades before discovering who they truly are. They are also more likely to be marginalized in terms of race, gender, sexual orientation, class, and other factors, which contributes to their suffering and invisibility. Dr. Price lays the groundwork for unmasking and offers exercises that encourage self-expression, including:

• Celebrating special interests

• Cultivating Autistic relationships

• Reframing Autistic stereotypes

• And rediscovering your values

It’s time to honor the needs, diversity, and unique strengths of Autistic people so that they no longer have to mask—and it’s time for greater public acceptance and accommodation of difference. In embracing neurodiversity, we can all reap the rewards of nonconformity and learn to live authentically, Autistic and neurotypical people alike.

#### Solmi, F., et al. (2021). "Trajectories of autistic social traits in childhood and adolescence and disordered eating behaviours at age 14 years: A UK general population cohort study." J Child Psychol Psychiatry 62(1): 75-85.

BACKGROUND: Some people with eating disorders have difficulties with social communication. However, no longitudinal evidence regarding the direction of this association exists. We investigated trajectories of autistic social traits across childhood and adolescence in adolescents with and without disordered eating behaviours in early adolescence. METHODS: We used data from the Avon Longitudinal Study of Parents and Children. Our disordered eating measure indicated presence of any, monthly and weekly disordered eating (fasting, purging, dieting, binge eating) at age 14 years. Autistic social traits were reported by mothers using the Social and Communication Disorders Checklist (SCDC) at age seven, 11, 14 and 16 years. We modelled SCDC score trajectories using multilevel negative binomial models adjusting for a number of child- and maternal-level confounders. RESULTS: Of the 5,381 adolescents included in our sample, 421 (7.8%) experienced one or more disordered eating behaviours, and 148 (2.8%) weekly episodes. Adolescents with disordered eating had a 20% increase in SCDC scores (relative risk (RR) 1.23, 95% confidence interval (CI):1.14, 1.32) compared to those without disordered eating. This association was particularly apparent for those reporting weekly (RR 1.43, 95%CI: 1.27, 1.61) as opposed to monthly disordered eating (RR 1.12, 95%CI: 1.01, 1.22). CONCLUSIONS: Greater autistic social traits in childhood could represent a risk factor for the development of disordered eating in adolescence. Although mechanisms of this association need to be elucidated, clinicians should be aware that autistic social traits could have predated the eating disorder when managing people with these conditions.

#### Björk, A., et al. (2021). "High prevalence of neurodevelopmental problems in adolescents eligible for bariatric surgery for severe obesity." Acta Paediatr 110(5): 1534-1540.

AIM: To assess the prevalence of neurodevelopmental problems in adolescents with severe obesity and their associations with binge eating and depression. METHODS: Data were collected at inclusion in a randomised study of bariatric surgery in 48 adolescents (73% girls; mean age 15.7 ± 1.0 years; mean body mass index 42.6 ± 5.2 kg/m(2) ). Parents completed questionnaires assessing their adolescents' symptoms of attention-deficit/hyperactivity disorder and autism spectrum disorder and reported earlier diagnoses. Patients answered self-report questionnaires on binge eating and depressive symptoms. RESULTS: The parents of 26/48 adolescents (54%) reported scores above cut-off for symptoms of the targeted disorders in their adolescents, but only 15% reported a diagnosis, 32% of adolescents reported binge eating, and 20% reported symptoms of clinical depression. No significant associations were found between neurodevelopmental problems and binge eating or depressive symptoms. Only a third of the adolescents reported no problems in either area. CONCLUSION: Two thirds of adolescents seeking surgical weight loss presented with substantial mental health problems (reported by themselves or their parents). This illustrates the importance of a multi-professional approach and the need to screen for and treat mental health disorders in adolescents with obesity.

#### Nickel, K., et al. (2019). "Systematic Review: Overlap Between Eating, Autism Spectrum, and Attention-Deficit/Hyperactivity Disorder." Front Psychiatry 10: 708.

Background: Links between eating disorders (EDs) [e.g., anorexia nervosa (AN), bulimia nervosa (BN), and binge eating disorder (BED)] and the major neurodevelopmental disorders of autism spectrum disorder (ASD) and attention-deficit/hyperactivity disorder (ADHD) have been repeatedly highlighted. In both ASD and ADHD, these links range from an elevated risk for EDs to common symptomatic overlaps and etiological commonalities with EDs. Methods: We performed a systematic literature search (through July 2019) with Medline via Ovid for epidemiological data on EDs (AN, BN, and BED) in combination with both ASD and ADHD. Results: The reviewed studies showed that, on average, 4.7% of patients with certain ED diagnoses (AN, BN, or BED) received an ASD diagnosis. Reliable data on the prevalence of EDs in ASD samples are still scarce. Comorbid ASD is most commonly diagnosed in patients with AN. The prevalence of ADHD in EDs ranged between 1.6% and 18%. Comorbid ADHD was more often reported in the AN-binge eating/purging subtype and BN than in the AN restrictive subtype. The prevalence of EDs in ADHD ranged between no association and a lifetime prevalence of 21.8% of developing an ED in women with ADHD. Conclusions: Studies on the prevalence rates of EDs in ADHD and ASD and vice versa are heterogeneous, but they indicate frequent association. While there is growing evidence of clinical overlaps between the three disorders, it remains difficult to determine whether overlapping characteristics (e.g., social withdrawal) are due to common comorbidities (e.g., depression) or are instead primarily associated with EDs and neurodevelopmental disorders. Furthermore, prospective studies are required to better understand how these disorders are related and whether ADHD and ASD could be either specific or nonspecific predisposing factors for the development of EDs.

#### Dell'Osso, L., et al. (2019). "Autistic Traits and Illness Trajectories." Clin Pract Epidemiol Ment Health 15: 94-98.

In the framework of increasing attention towards autism-related conditions, a growing number of studies have recently investigated the prevalence and features of sub-threshold Autistic Traits (ATs) among adults. ATs span across the general population, being more pronounced in several clinical groups of patients affected by psychiatric disorders. Moreover, ATs seem to be associated with specific personality features in non-clinical population, implying both a higher vulnerability towards psychopathology and extraordinary talents in specific fields. In this framework, the DSM-5's Autism Spectrum Disorder (ASD) presentations may be considered as the tip of an iceberg that features several possible clinical and non-clinical phenotypes. Globally, the autism spectrum may be considered as a trans-nosographic dimension, which may not only represent the starting point for the development of different psychopathological trajectories but also underlie non-psychopathological personality traits. These different trajectories might be shaped by the specific localization and severity of the neurodevelopmental alteration and by its interaction with the environment and lifetime events. In this wider framework, autistic-like neurodevelopmental alterations may be considered as a general vulnerability factor for different kinds of psychiatric disorders, but also the neurobiological basis for the development of extraordinary abilities, eventually underlying the concept of geniality. Moreover, according to recent literature, we hypothesize that ATs may also be involved in the functioning of human mind, featuring the peculiar sense of "otherness" which can be found, with different grades of intensity, in every human being.

#### Nazar, B. P., et al. (2016). "ADHD Rate in Obese Women With Binge Eating and Bulimic Behaviors From a Weight-Loss Clinic." Journal of Attention Disorders 20(7): 610-616.

Objective: Few studies have demonstrated a possible association between ADHD and obesity in adults. The aim of this study was to investigate the prevalence of ADHD in a sample of obese women seeking treatment, and its relations with binge eating and bulimic behaviors. Method: We performed a cross-sectional study in a clinical sample of one hundred fifty-five women, with a mean age of 38.9 (+10.7) years and a mean body mass index (BMI) of 39.2 (+5.29). Participants were evaluated with semistructured interviews and completed self-report psychiatric rating scales. Results: The rate of ADHD in the sample was of 28.3%. The presence of ADHD was significantly correlated with more severe binge eating, bulimic behaviors, and depressive symptomatology. Conclusion: Similar to previous studies, a higher than expected rate of ADHD was observed among obese women. ADHD in obese individuals may be a risk factor for greater severity of disordered eating patterns.

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# NOTES

Recent research has shown that IA plays a crucial role in cognitive processing, self-regulation, including emotional regulation, and regulating reward responses, decision-making, reward-seeking and stimulant-seeking behaviors, and overall well-being (Brewer et al., 2016; Dunn et al., 2010; Khalsa et al., 2018; Kim et al., 1999; Weng et al., 2020).

* (O’Donnell et al., 1999)” as cited in Pignatelli et al., 2018
* Taste reactivity = affected by conditioned stimuli that engage sensory modalities independent of taste (Delamater et al., 1986;” as cited in Hurley et al., 2017

In the context of eating disorders, deficits in IA have been linked to disordered eating behaviors, such as binge eating, anorexia nervosa, and bulimia nervosa (Jenkinson et al., 2018; Martin et al., 2019). Understanding and improving IA may offer new therapeutic avenues for treating these conditions.

Research on interoception in adult binge eating disorders is relatively limited, though gaining traction more recently (**Table 1**). The majority of information on interoceptive deficits in eating disorders broadly and binge eating disorder specifically are based on findings from the Eating Disorder Inventory’s **(EDI)** “Interoceptive Awareness” **(IA)** subscale(Jenkinson et al., 2018), which includes 10 questions focusing mostly on assessing confidence in recognizing and identifying emotions and sensations related to hunger or satiety (Garner et al., 1983; Jenkinson et al., 2018). The EDI and its IA subscale have undergone several revisions since their conception (Garner, 1991) but remain the most popular tool for IA assessment and consistently identify IA deficits across various samples of patients with eating disorders.

## OTHER/NOTES

“emotional eating (e.g. Koch and Pollatos, 2014; Young et al., 2017), external eating (e.g. Koch and Pollatos, 2014), subclinical binge eating (e.g. Brown et al., 2010), restraint (e.g. Tylka and Wilcox, 2006) and mixed/composite measures from questionnaires (e.g. Anderson et al., 2016; Myers and Crowther, 2008).

All of the twenty cross sectional studies reporting data relevant to the association between disordered eating behaviour and interoception, found impairments in at least one measure of interoception. The ma- jority of these studies (n = 18) used self-report methods and the two remaining studies used heartbeat counting and detection tasks. “

“A range of interoceptive modalities were investigated in the studies included in this systematic review including cardiac, respiratory, gas- tric, pain and touch interoception. The most commonly measured in- teroceptive modalities were gastric, cardiac and pain, with measure- ments of these modalities comprising 101 out of the 104 studies. “

with no significant differences in interoception observed between individuals with eating disorders and healthy controls (47), and limited evidence supporting a causal role of interoception in the development of eating disorders (Martin et al., 2019).

Future research investigating possible relationships between alexithymia, emotion regulation, and negative affect and urgency in binge eating disorder would be both interesting and impactful.

This all aligns with a variety of neuroimaging findings that associate binge eating disorder with alterations in the insula (associated with interoception as well as decision-making, taste perception, and feeding regulation), among other brain regions (Kessler et al., 2016).

A recent comprehensive review discusses brain regions that are altered in both BED and

SUDs: (1) ventral striatum (goal-seeking behaviors, motivation, reward sensitivity), (2) dorsal striatum (habitual and compulsive behaviors), (3) prefrontal cortex (PFC) (executive functioning), and (4) insula (interoception, decision-making, taste perception, and feeding regulation) (Kessler et al. 2016).

# Table 4. Existing literature on interoception in adult binge eating disorder.

| Study Author (Year) | Study Design & Limitations | Patient Population and Demographics | Interoception Assessment Methods | Main Findings | Conclusions |
| --- | --- | --- | --- | --- | --- |
| Meta-Analyses | | | | | |
| Jenkinson et al., (2018)(Jenkinson et al., 2018)  Country: UK | Meta-Analysis | Total k = 29 (41 ED samples, N = 4,308)  BED: k = 5a (N = NR; Na = 149)  sBED: n = 36\*  OE: n = 15\*  OB-CNTRL: 42\*  HC: n = 124  [N = 3,459; 7,746 when controls are repeated in separate comparisons]  EDNOS: k = 3\*  Mixed ED: k = 9\*  Other:  AN: k = 12  BN: k = 10  Recovered AN or BN: k = 2  Pooled effect size across diagnostic groups: Q(5) = 50.30, *p* < 0.001)  Heterogeneity across studies: Q(40) = 386.10, *p* < 0.001, I2 = 89.64  Sex/Gender:  \*\*\*  Mean Age:  \*\*\*  Comorbidities:  NR | Disordered Eating:  BES and clinical interview  Interoception:  EDI-IA (majority) | Significantly greater deficits in IA in ED patients vs HCs (SMD = 1.62: 95% CI = 1.46 to 1.77, p < 0.001)  87% greater probability that an individual randomly selected from the ED group will have a greater IA deficit vs control group.  IA deficit in BN significantly grater than that observed in BED (Q(1) = 41.72, *p* < 0.001) but not AN (Q(1) = 25.27, *p* = 0.001). | Interoceptive deficits (IDs) exist on a continuum in EDs and are more pronounced in AN and BN vs. BED. The inter-diagnostic differences and degree of observed ID across all EDs supports a transdiagnostic view of eating disorders (Fairburn et al., 2009).  IDs may be useful in identifying EDs and future research should investigate whether IDs constitute an ED endophenotype and possible treatment target. |
| Systematic Review | | | | | |
| Martin et al., (2019)(Martin et al., 2019)  Country: UK | Systematic Review | Total k = 104 studies (N = 32,883 participants with EDs)  AN: 31 studies (12 active AN  BED: 6 studies (k = 4):  BED: n = 106  OB + BED: n = 27  sBED: n = 16  OB Controls: n = 98  HCs: n = 105  Other:  BN: 17 studies  AN and BN: 26 studies  Subclinical disordered eating: 24 studies  Sex/Gender:  \*\*\*  Mean Age:  \*\*\*  Comorbidities:  NR | Disordered Eating:  BES and clinical interview  Interoception:  EDI-IA (majority)  Mechanical Pain Threshold (MPT) (Raymond et al., 1995) | Significant impairment in interoception observed across all 4 studies containing populations of individuals with BED (relative to control populations).  Significant differences in gastric interoception associated with BED across all 4 studies (vs controls). | Interoceptive deficits (IDs) exist on a continuum in EDs and are more pronounced in AN and BN vs. BED. The inter-diagnostic differences and degree of observed ID across all EDs supports a transdiagnostic view of eating disorders (Fairburn et al., 2009).  IDs may be useful in identifying EDs and future research should investigate whether IDs constitute an ED endophenotype and possible treatment target. |
| Cross-Sectional, Observational Studies | | | | | |
| Aloi et al., (2017)(Aloi et al., 2017)  Country: Italy | Study Design:  Cross-sectional, observational, single-center study.  Major limitations:  Small sample size, lack of normal weight control group, cross-sectional (vs. longitudinal) measures | Subjects were adult patients with obesity referred to an Italian outpatient unit for ED treatment.  N = 58  BED: 22  sBED: 16  OB Control: 20  Sex/Gender:  62% female  Mean Age:  BED: 44 yrs.  sBED: 43 yrs.  OB Control: 51 yrs.  Comorbidities:  BED and sBED groups had higher BDI scores than OB controls | Disordered Eating:  BES and clinical interview  Interoception:  EDI-IA | IA deficit scores were higher in BED vs. OB  BED obese patients higher levels of IA impairment, alexithymia, and depression.  High positive correlations existed between binging, IA, alexithymia, and depression | Patients with obesity and BED have comparable abilities to understand others’ emotions but impaired abilities to understand their own feelings and emotions, which is correlated to depression. |
| De Zwann et al., (1995)(de Zwaan et al., 1994)  Country: Austria | Study Design:  Cross-sectional, observational sample study.  Major limitations:   * All female weight-loss-seeking participants with overweight (not representative of those with BED), * Self-select/ response bias in recruitment, cross-sectional | Subjects were responders to an advertisement for a study testing a treatment for weight and binge eating. “The treatment study consisted of a supplemented fast plus group therapy.”  N = 100  BED: 43  sBED: 20  OE: 15  OB Controls: 22  Sex/Gender:  100% female  Mean Age:  39.2 yrs.  (no statistically significant differences in age between groups)  Comorbidities:  NR | Disordered Eating:  SCID (with proposed DSM-IV criteria for BED), EDI, and BES  Interoception:  EDI-IA | IA scores were greater in BED (4.2 ± 5.2) vs overeating (2.3 ± 4.1), healthy controls (1.7 ± 3.1), and binge eating (1.4 ± 1.6), though the difference was not statistically significant (F = 3.1, p = 0.029). | Self-reported problems with binge eating correlated positively with less IA and self-esteem and more feelings of ineffectiveness, perfectionistic attitudes, and impulsivity.  BED may be a distinct subgroup among the obese population |
| Ramacciotti et al., (2008)(Ramacciotti et al., 2008)  Country: Italy | Study Design:  Cross-sectional, observational/naturalistic study.  Major limitations:   * Cross-sectional assessment does not allow inferences about causal factors * Recruitment sources may have enhanced differences observed between BED vs non-bingeing controls with obesity (OB Controls). | Subjects were adult patients with obesity referred to an Italian ED unit and/or hospital weight-loss and ED program  N = 90  DSM-IV BED: 27  OB Controls: 63  Sex/Gender:  DSM-IV BED: 87.5% female  OB Controls: 91.6% female  Mean Age:  DSM-IV BED: 37 yrs  OB Controls: 42 yrs  Comorbidities:  NR | Disordered Eating:  DSM-IV BED clinical interview, structured clinical interview for anorexic-bulimic spectrum  Interoception:  EDI-IA | IA deficit scores were higher in DSM-IV BED vs. OB Controls (*p* < 0.05)  Individuals with BED scored higher than OB Controls on measures of IA (*p* < 0.05), ineffectiveness (*p* < 0.01), social insecurity (*p* < 0.05), influence of weight-shape concerns and condition on self-esteem (*p* = 0.05) and social phobia (*p* < 0.005), overall impairment from overweight condition (*p* < 0.005), and dichotomous reasoning (*p* < 0.01). | These results support a dimensional/ transdiagnostic view of eating disorder psychopathology in obese individuals.  Cognitive mechanisms such as weight-shape concerns and dichotomous reasoning may influence low self-esteem as a core feature of BED among individuals with obesity. |
| Raymond et al., (1995)(Raymond et al., 1995)  Country: USA (Minnesota) | Study Design:  Cross-sectional, observational study.  Major limitations:   * All female participants * Self-select/ response bias in recruitment, * Cross-sectional * Use of MPT to imply vagus nerve function, based on hypothesis that abnormal satiety response observed in BN is related to abnormal vagus nerve function | Subjects were recruited through newspaper advertisements  N = 104  OB + DSM-IV BED: 27  OB – BED: 33  OB + sBED: 18  OB – BED: 15  HC: 44  100% female  Age range: 19 – 50 yrs.  Comorbidities:  NR | Disordered Eating:  DSM criteria  Interoception:  Mechanical pain threshold (MPT) | Mean pain detection thresholds (PDT) in response to noxious pressure stimulus were elevated in OB+BED vs. HCs (*F*(2, 101) = 4.12, *p* = 0.019), Tukey’s post hoc *p* < 0.05) with no significant difference in mean pain tolerance thresholds (PTTs).  PDT and PTT were significantly higher in OB + BED and OB + sBED groups compared to OB – BED and HC groups (*F*(2, 100) = 4.56, *p* = 0.12), Tukey’s post hoc *p* < 0.05) | Findings suggest significant elevated pain detection thresholds in individuals with obesity and BED relative to healthy controls and obesity alone. These differences are not due to global somatosensory abnormalities.  Electrical stimulation/activation of vagus afferents may be involved in reflexive production of antinociceptive response.  Elevated pain detection thresholds resulting from abnormal nociceptive processing may be related to abnormal satiety response in women with BN and/or BED. |
| Vinai et al., (2015)(Vinai et al., 2015)  Country: Italy | Study Design:  Cross-sectional, observational study.  Major limitations:   * All female participants * Self-select/ response bias in recruitment, * Cross-sectional | N = 118  BED: 57a  HC: 61  Sex/Gender:  BED: 75% female  HC: 56% female  Mean Age:  BED: 44 yrs  HC: 45 yrs  Comorbidities:  BED participants had higher scores of depression and anxiety vs HCs. | Disordered Eating:  Diagnosis made by ED professional  Interoception:  EDI-IA | IA deficit scores were higher in BED vs. HCs |  |
| Narrative Review | | | | | |
| Khalsa et al. (2022)(Khalsa et al., 2018)  Country: N/A (Interoception Summit 2016 participants) | Study Design:  N/A –  Narrative Review  Major limitations:   * All female participants   Self-select/ response bias in recruitment | N/A | N/A – Narrative Review | **Recent Findings** Eatingisacomplexprocessthatbeginswellbeforeandendswellafterfoodconsumption.Abnormalpredic- tion and prediction-error signals may occur at any stage, resulting in aberrant gastrointestinal interoception and dysregulated gut sensations in eating disorders. Several interoceptive technologies have recently become available that can be paired with computational modeling and clinical interventions to yield new insights into eating disorder pathophysiology. | Abstract  **Purpose of Review** Abnormalinteroceptionhasbeenconsistentlyobservedacrosseatingdisordersdespitelimitedinclusion in diagnostic conceptualization. Using the alimentary tract as well as recent developments in interoceptive neuroscience and predictive processing as a guide, the current review summarizes evidence of gastrointestinal interoceptive dysfunction in eating disorders.  **Summary** Illuminating the neurobiology of gastrointestinal interoception in eating disorders requires a new generation of studies combining experimental probes of gut physiology with computational modeling. The application of such techniques within clinical trials frameworks may yield new tools and treatments with transdiagnostic relevance. |
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| **Table Legend:** TABLE DESCRITION HERE**.** All values reported in the table are those that were reported in the respective publications. Any possible instances in which the publication reporting may have been inaccurate have been noted in footnotes below.  \*Not included in the study’s systematic review or meta-analysis  \*\*Not included in this review.  **a**In Jenkinson 2018, k is reported as 5. Two of these five samples come from the same publication (Vinai et al., 2015), in which one sample included bariatric patients with a DSM-V diagnosis of BED (reported in Vinai et al., 2015 as n = 57) and one sample included bariatric patients with a DSM-IV-TR diagnosis of BED (reported in Vinaoi et al., 2015 as n = 24). However, the 24 participants with a DSM-IV-TR diagnosis of BED were also included in the sample of 57 participants with a DSM-V diagnosis of BED..  **Abbreviations:** 95% CI = 95% confidence interval; AN = anorexia nervosa; BED = binge eating disorder; BES = binge eating scale; BN = bulimia nervosa; DSM-IV = Diagstostic Statistical Manual, 4th edition (published 2002); DSM-V = Diagnostic Statistical Manual, 5th Edition (published 2013); ED = eating disorder; EDI = Eating Disorder Inventory; EDI-IA = Interoceptive Awareness sub scale of the Eating Disorder Inventory; HC = healthy control; IA = interoceptive awareness; ID = interoceptive deficit; K = number of studies; MPT = mechanical pain threshold; N = population size (entire population); n = sample size (specific portion of the population); Na = population size (entire population) as calculated by the authors; N/A = not applicable; NR = not reported; OB = obesity; OB-CNTRL: control with obesity; OE = overeating; P = p-value, probability value; PDT = pain detection threshold; PTT = pain tolerance threshold; Q = Cochran’s Q/heterogeneity statistic, a measure of heterogeneity among study effects in a meta-analysis; sBED = subclinical BED; SCID = structured clinical interview for DSM-IV; SMD = standardized mean difference; UK = United Kingdom; USA = United States of America; vs. = versus; yr(s). = year(s). | | | | | |

1 jenkinson 2018 – meta-analysis

3 – Marin 2019 – Systematic review

4 – Raymond 1995 – study

5 – Aloi 2017 – study

6 – de Zwaan 1994 – study

7 – Ramacciotti 2008 – study

8 – Vinai 2015 – study

9 – Khalsa 2018 – narrative review

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