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Interventions and Manipulations of Interoception

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Abstract

Interoceptive pathways may be manipulated at various levels to develop interventions to improve symptoms in a range of disorders. Primarily through the lens of the respiratory system, we outline

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various pathways which can be manipulated at neural, behavioral, and psychological levels to change representation of and attention to interoceptive signals, which can alter interconnected physiological systems and improve functioning and adaptive behavior. Interventions can alter interoception via neuromodulation of the vagus nerve, slow breathing to change respiratory rate and depth, or awareness processes such as mindfulness-based interventions. Aspects of this framework may be applied to other physiological systems, and future research may integrate interventions across multiple levels of manipulation or bodily systems.

Keywords

respiration; neuromodulation; mindfulness; interoceptive awareness; PTSD; substance use disorder

Improving health via interventions of interoceptive processing at multiple levels and systems.

Interoceptive pathways and processes offer ripe opportunities for experimental manipulations of mind-body interactions, leading to promising clinical interventions for a wide variety of conditions. Interoceptive pathways include bidirectional interactions between the central nervous system and other physiological systems [1], which provides a moment-by-moment mapping of the body's internal landscape in all states, some of which can be sensed in conscious awareness [2,3]. Many physical and psychiatric clinical disorders are associated with disruptions in interoceptive processes that involve one or more physiological systems as well as interactions among them [4]. Further, interoceptive systems can be studied through many perspectives including cell- and systems-biology, and may be manipulated with techniques at cellular, systems, and psychological levels [4,5]. Investigating interventions of interoception through the lens of the respiratory system, we briefly review research that highlights the ability to manipulate aspects of breathing from perspectives such as systems neuroscience and psychology. Through changes in the respiratory system and its interconnected biological systems (e.g., cardiac, neural, and gut), we outline how interoceptive interventions may improve symptoms in various clinical disorders (such as cardiovascular disease, stress, mood, and substance use disorders), and may be integrated together to optimize outcomes (Figure 1, **Key Figure**).

Interoceptive pathways of breathing.

Biological rhythms entrain physiological activity throughout the body; in the case of breathing, its rhythm impacts cognitive, emotional, and sensory processing [6,7]. Breathing rhythms are generated in the brainstem [8] resulting in periodic movement of inspiratory and expiratory muscles driven by motoneurons in the brainstem and spinal cord. The principal engine for generating breathing rhythm is the preBötzinger Complex, a compact bilateral medullary nucleus, that ultimately drives inspiratory muscles and coordinates with expiratory movements [8]. In addition to driving respiratory movements, breathing-related activity initiated in the preBötzinger Complex affects suprapontine structures, e.g., hippocampus, prefrontal cortex, amygdala, to influence cognitive and emotional function [9,10]. Regulatory breathing is a behavior that regulates blood oxygen necessary for aerobic metabolism and blood carbon dioxide that is a byproduct of aerobic metabolism. Malfunctioning of the respiratory system can produce a multitude of breathing disorders including pulmonary diseases (e.g., asthma, chronic obstructive pulmonary disease, and fibrosis of the lung), sleep apnea, and apnea (asphyxiation) which can occur in the case of opioid drug overdose.

The processes underlying breathing mostly operate unconsciously; however, breathing can enter conscious awareness, particularly when there is change in intensity (e.g., exercise), airway obstruction, or through interoceptive awareness training such as mindfulness meditation. Indeed, respiratory processes are integral to the mind-body connection. Different emotional states, such as fear and anxiety [6], can increase respiratory rate in order to enhance oxygen intake to support the energetic cost of fleeing or fighting threats. Conversely, respiratory challenge elicits sensations that can trigger panic [11]. Just as respiratory processes can influence mental states, conscious processes can be used to change respiratory functioning, for instance by altering respiratory rate or interoceptive awareness of sensations of breathing [12]. Respiration is unique compared to other systems (such as the gastrointestinal one) insofar as conscious regulation can immediately impact respiratory processes, and as sketched above, respiratory processes can affect emotion and cognition. Below, we review various manipulations and interventions that influence the respiratory system at different levels, and offer potential areas for integration of interventions and for future research.

Interventions of interoception via vagus nerve stimulation and respiratory-gated auricular vagal afferent nerve stimulation

Neuromodulation is a class of therapeutic interventions defined by the alteration of nerve activity through the delivery of electrical stimulation or chemical agents to targeted sites of the body. Such targets can include known nodes of interoceptive pathways, even cutaneous locations innervated by branches of nerves typically considered as part of the autonomic nervous system (ANS). The vagus nerve is the main parasympathetic conduit of the ANS and is involved in the regulation of cardiovascular, respiratory and gastrointestinal function. Most vagal fibers (~80%) are afferents and carry interoceptive sensory information from the head, neck, abdomen, and thorax to (mainly) the nucleus tractus solitarii (NTS) in the brainstem. NTS signals are then communicated to neuromodulatory brainstem nuclei of diffuse monoamine systems – i.e., locus coeruleus (LC) and raphe nuclei [13,14]. Vagus nerve stimulation (VNS) via electrical pulses (typically 20–30Hz, 0.25–3.5mA, 30–60s ON 5min OFF [15]) is a prototypical and FDA-approved therapeutic intervention that taps into existing interoceptive (i.e. visceroceptive) pathways with demonstrated efficacy for multiple disorders. While the precise mechanisms underlying the effects of VNS are unknown, vagal afference relayed to NTS modulates cortical/subcortical excitability, affecting higher brain structures [16] including via monoaminergic neuromodulatory systems. Importantly, the main brainstem target of the vagus nerve, NTS, also receives somatosensory afference via the purely afferent auricular branch of the vagus nerve (ABVN) [17,18], which innervates the auricle (outer ear), most consistently at the cymba conchae [19]. Non-invasive (transcutaneous) methods of ABVN stimulation (taVNS) have been proposed [20,21], and

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preliminary neuroimaging studies have found that taVNS modulates brainstem and cortical areas (left prefrontal cortex, bilateral postcentral gyrus, left posterior cingulate gyrus, and left insula) similar to ones modulated by classical VNS [22–26]. This VNS approach is much more broadly applicable, due to cutaneous targeting, and commercial taVNS devices have been approved.

Interestingly, the dorsal medullary vagal system (which includes NTS) operates in tune with breathing (e.g. respiratory sinus arrhythmia). Second-order relay neurons in the NTS receive interoceptive afference from pulmonary stretch receptors and aortic baroreceptors, primarily during inhalation. NTS may also receive inhibitory inputs during inhalation, and facilitatory inputs during exhalation from nuclei in the ventral respiratory column or other brainstem nuclei [27–29]. Thus in order to target a phasic window with reduced competing afference and facilitatory, receptive, state, ABVN stimulation gated to exhalation has been proposed (i.e. Respiratory-gated Auricular Vagal Afferent Nerve Stimulation, RAVANS), and has demonstrated, enhanced brainstem targeting [25,26] and therapeutic response [30] for clinical disorders such as chronic pelvic pain and migraine (Figure 1). Such approaches are consistent with existing research showing that biological rhythms entrain physiological activity throughout the body, including the specific impact of the respiratory rhythm on cognitive, emotional, and sensory processing [7,31]. Future research should also explore whether respiratory rhythms can modulate physiological and clinical response to other neuromodulatory approaches, such as spinal cord stimulation, implanted vagus nerve stimulation, and trigeminal nerve stimulation.

Conscious modulation of interoception via mindfulness training and higher-order neural networks.

Interoceptive information is also represented in higher-order neural networks such as the posterior and anterior insula [32], which could potentially be altered by top-down modulation via cognitive and emotional control networks [3]. These executive control networks have been typically studied using exteroceptive information, and may similarly be recruited and applied to interoceptive signals [33]. In the case of respiratory information, neural networks may represent respiratory rate at both unconscious [34] and conscious levels [35]. Representation of interoceptive information may be altered through psychological interventions such as mindfulness meditation, which include training awareness to 1) internal respiratory signals from bodily areas associated with breathing such as the nostrils, throat, lungs, and diaphragm, 2) sensations such as pressure, tingling, movement, and temperature, and 3) cognitive and affective qualities of attention such as sustained focus with a nonjudgmental attitude [36]. For example, in a core practice of focused attention to the breath, interoceptive attention is focused on sensations of the breath, until distracted by other internal or external stimuli, and then nonjudgmentally returned to the breath. Meditation practices may thus strengthen interoceptive focus and stability [2,37], cognitive processes directed towards interoceptive stimuli (including sustained attention, cognitive monitoring, and meta-awareness [38–40]), and emotion regulation (greater acceptance of internal sensory experiences and less reactivity to them [41,42]). In addition, meditation practices may cultivate compassion [43], and kindness in response to pain and suffering, which can be directly applied to sensory experiences [44]. These skills may lead to better monitoring and regulation of physical, emotional, and social processes [45], contributing to improved health-promoting decision-making and behaviors [2,37]. This may be why mindfulness-based interventions may lead to improvements in a broad range of clinical populations such as those with stress [46], pain [47], depression [46,48], anxiety [46], and addiction [49].

Attention networks of alerting, orienting, and executive control have been typically studied using exteroceptive information such as visual and audio stimuli [50,51]. Less is known about whether these attention networks can be similarly applied to interoceptive information, which is internal and difficult to measure. One neural network which may bridge interoception and executive functioning is the salience network, which is primarily composed of the anterior insula, the ventrolateral PFC, and dorsal ACC, and is involved in detecting events and providing signals to the executive control network to engage in goal-directed activity [52,53]. The anterior insula may serve as an integral hub in mediating dynamic interactions between other large-scale brain networks involved in externally oriented attention and internally oriented cognition [54], where its core function is to mark salient events for additional processing and initiate appropriate control signals [53]. Within the salience network model, insular function can be conceptualized as basic mechanisms of bottom-up detection of salient events, switching between other large-scale networks to facilitate attention and working memory when a salient event is detected, interaction of the anterior and posterior insula to modulate autonomic reactivity to salient stimuli, and strong functional coupling with the anterior cingulate cortex (ACC) to facilitate rapid access to the motor system [53].

Psychological interventions of interoception such as meditation may use executive control networks to increase engagement of interoception and salience networks, which share a key hub of the anterior insula. Studies using functional magnetic resonance imaging (fMRI) show that breath-focused meditation increases activation in networks involved in focused attention and cognitive control (i.e., the Executive Function Network [EFN] including prefrontal cortex [PFC], ACC, premotor cortex [55,56]) as well as interoception (including the insula [37,56]). Findings from electroencephalography (EEG) studies of breath-focused meditation suggest increased alpha in posterior areas and theta in frontal areas [39,57]. Increased frontal theta may indicate a need for cognitive control and call on other brain regions [58], and may also influence white matter [59]. Mindfulness meditation training resulted in greater activation in the posterior insula, a region that is sensitive to respiratory rate and putatively considered primary interoceptive cortex, as well as a posterior limbic and medial parietal network during an interoceptive breath-focused task [60]. Mindfulness training also enhanced insula connectivity with the posterior ventromedial thalamus [60], a relay of the lamina I spinothalamocortical pathway supporting interoceptive afference [32]. In addition, breath-focused meditation practice decreases activation in regions associated with mind wandering and self-referential processing [38,56,61] (i.e., the Default Mode Network including the anterior medial PFC, posterior cingulate cortex, and posterior inferior parietal lobule [62]). These findings suggest that meditators may focus on the breath via increased engagement of neural networks associated with cognitive control and interoception, and disengage from mind wandering and self-referential processing via decreased DMN activation [38,56]. Disengaging from self-related thought is particularly important from clinical perspectives, due to the cognitive and emotional flexibility it cultivates [40,46]. New methodologies are being developed to track these fluctuating neural states of attention to interoceptive signals during meditation, using machine learning to identify participant-specific brain patterns associated with each network, which provides empirical evidence of the neural differentiation between inner states of interoception, mind wandering, and self-referential processing. These neural patterns are then used to estimate the focus of attention during breath-focused meditation, which can be used to assess the percentage time of interoceptive focus on the breath [63].

Studies of exteroceptive visual and auditory processing have been able to precisely measure behavioral and neural mechanisms of alerting (attention in time), orienting (attention in space), and executive control of these representations. Studies of interoception have been more limited in their tools to measure similar processes due to the difficulty in measuring changes in attention to internal stimuli, particularly those that originate from different systems of the body (for instance discrimination between breath or gut sensations). Strides are being made in measuring alerting and orienting to respiratory stimuli. The perceived intensity of respiratory resistance can be parametrically manipulated using a medical device that changes air levels to model anticipation and experience of respiratory threat, which are respectively represented in ventrolateral and lateral periaqueductal gray [64]. Orienting interoceptive attention to different locations in the body (e.g., breath vs. feet) can be distinguished using machine learning applied to fMRI data [63]. Integration of these tasks with executive processing tasks of interoceptive information may better elucidate commonalities and distinctions between the neural mechanisms of interoceptive vs. exteroceptive attention processing, and how interventions may alter these neural and subjective representations using executive control.

Leveraging interoception of breathing to improve sympathetic function.

Research suggests that neural networks may mediate respiratory and interoceptive awareness processes through conscious regulation. This provides pathways through which patients may become active participants in their health by engaging in interventions that consciously regulate respiratory rate or increase interoceptive awareness capacity through mindfulness approaches. Manipulating interoception of breathing may help treat diseases involving dysregulation of the sympathetic nervous system (SNS), a system important for acute and long-term blood pressure regulation. Multiple chronic diseases, including chronic kidney disease [65] and posttraumatic stress disorder [66], are characterized by chronic overactivation of the SNS that contributes to increased cardiovascular disease (CVD) risk. However, treatments to combat SNS overactivation remain limited, particularly because current treatment options (peripheral sympatholytic medications such as β-blockers, α1-blockers, and central α2 agonists) may have side effects such as hypotension, orthostasis, and fatigue [67] as well as metabolic consequences [68]. Development of non-pharmacological treatment modalities to combat SNS overactivity and dysregulation may offer alternative treatment routes.

Behavioral manipulation of respiratory rate: Guided slow breathing.

Increasing interoception of breathing may be one safe and effective nonpharmacologic approach that may have beneficial effects on sympathetic regulation. Slow breathing (or decreasing respiratory rate) is thought to lower blood pressure due to an increase in tidal volume that then leads to activation of cardiopulmonary stretch receptors, resulting in reflex reduction in SNS activation [69]. Slow breathing also improves arterial baroreflex control of SNS activity [70,71]. Respiratory rate can be manipulated using device-guided slow breathing (DGB) in which a biofeedback device guides breathing rates to subphysiologic levels of ~5 breaths/min using musical tones [72] (Figure 1).

One chronic condition in which breathing-based interventions may improve SNS overactivation is posttraumatic stress disorder (PTSD), a mental health condition that is characterized by persistent mental and emotional stress. Multiple epidemiologic studies have shown that PTSD patients are at increased risk of developing hypertension and other cardiovascular diseases [73]. Prior work has shown that veterans with PTSD have augmented SNS reactivity during mental stress, and abnormal regulation of SNS activity characterized by impaired arterial baroreflex sensitivity [66]. Importantly, exaggerated sympathetic reactivity and impaired baroreflex sensitivity are both associated with an increased risk of hypertension and cardiovascular disease [74]. Device-guided slow breathing may acutely reduce blood pressure and muscle sympathetic nerve activity (MSNA) [75], and improve arterial baroreflex sensitivity in veterans with PTSD [75], as well as other chronic conditions characterized by SNS overactivation and impaired baroreflexes [70,71]. In addition, eight weeks of daily device-guided slow breathing ameliorated sympathetic reactivity to mental stress in PTSD patients [76]. Results from a randomized controlled trial showed that mindfulness-based stretching with deep breathing exercise reduces PTSD symptom severity in women with subclinical PTSD [77], although the exact interoceptive mechanisms are unclear. Chronic kidney disease (CKD) is another prevalent disorder characterized by chronic overactivation of the SNS. In a USA cohort of Black men not previously trained in meditation, a single session of mindfulness meditation with a major component of breathing awareness reduced blood pressure and MSNA when compared to the control intervention (health education recording) [78]. While long-term studies are still needed, these findings collectively suggest that increased interoception of breathing with slow breathing may have beneficial effects on SNS activity and symptoms in patients with PTSD and CKD.

Interoceptive awareness skills and increased emotion regulation as potential mechanisms for improved health.

Meditation practice may also decrease respiratory rate even when respiratory changes are not explicitly instructed [60,79]. Additionally, mindfulness-based interventions may result in interoceptive benefits that are over and above those of slow breathing. For example, mindfulness meditation reduced SNS activity and blood pressure in CKD patients; and while mindfulness medication also reduced respiratory rate, slow breathing alone (without the mindfulness component) did not result in the same reductions in SNS activity or blood pressure [78]. Are there additional interoceptive skills that subjects learn during mindfulness-based practices, in addition to the direct or indirect effects on respiration? Mindfulness-based interventions teach subjects to consciously attend to sensations of their bodies with attitudes of nonjudgment, openness, curiosity, and self-compassion [36], thus developing skills of focused inner attention or *interoceptive awareness*. This contrasts with negative, ruminative, and catastrophizing types of reactions, which can increase stress responses and thus lead to worsening of psychological and physical symptoms [80]. In addition to decreasing reactivity to bodily sensations, interoceptive awareness may also cultivate better physical and emotional regulation through understanding the functional significance of bodily sensations. For example, a tightening in the chest may indicate breath obstruction (where coughing would be adaptive) or feelings of anxiety (where self-soothing would be adaptive). Mindfulness interventions may thus promote insight and adaptive action in response to inner bodily signals.

One likely transdiagnostic mechanism through which mindfulness training facilitates well-being is by increasing emotion regulation capacity. For example, two studies of Mindful Awareness in Body-oriented Therapy (MABT), a mindfulness-based approach designed to teach interoceptive awareness and related skills for self-care [81], demonstrated significant longitudinal reductions in substance use and related health outcomes such as craving, and emotion dysregulation compared to control conditions among women in treatment for substance use disorder (SUD) [82,83] (Figure 1). In addition, respiratory sinus arrythmia (RSA) and interoceptive awareness skills were improved in MABT vs. control conditions [84], which were maintained through 12-month follow-up [83]. This suggests that the conscious interoceptive skills learned through MABT may feedback to bodily processes such as RSA, a physiological measure of parasympathetic nervous system influence on heart rate [85], where higher RSA predicts greater self-reported regulatory control and decreased negative emotional arousal in response to stressors [86].

MABT involves explicit focus on conscious attention to sensory experience in the body, and involves the integration of experiential (bottom up) and evaluative processes based on somatic experience (top down) processes. This approach explicitly addresses difficulties with interoceptive processing and develops interoceptive awareness in bodily areas that are associated with respiratory and vagal activity such as the chest and abdominal region, as well as areas of the body that are often holding muscular tension such as the shoulders, neck, jaw, and back. Access to self-representations based on embodied sensory experience is thought to support a sense-of-self crucial for interacting with the environment [87]. Compelling evidence across multiple disciplines indicates that interoceptive processes are integral to self-regulation, including regulation of emotions and behavior [37]. Greater accuracy of interoceptive self-representation promotes adaptive responses, whereas dissociation from accurate representation can lead to dysregulation [88]. The capacity to attend to interoceptive experience is important for awareness and evaluation of sensory responses that ultimately motivate human behavior [89]. MABT may aid symptom reduction in conditions that involve disordered interoceptive processing such as in SUD, where unconscious interoceptive signals may increase drug-seeking motivation [90]. Developing interoceptive awareness is thought to reveal and de-automate such conditioning, supporting positive decision-making processes critical for relapse prevention [90]..

Integrative approaches for interventions of interoception.

Interventions of interoception may also be leveraged at multiple pathway points to treat conditions. It may be particularly beneficial to combine manipulations and interventions at both 1) biological levels through exogenous manipulations (i.e. neuromodulation, pharmacotherapy) and 2) psychological levels through active patient participation in altering interoceptive awareness (i.e. slow breathing, mindfulness skills), which may result in synergistic effects. Novel synergistic approaches along these lines have been recently suggested, for instance by combining neuromodulatory RAVANS taVNS (discussed earlier) and mindfulness meditation training, which commonly directs attention to respiratory rhythms. Because bodily systems are interconnected, many clinical conditions involve dysregulation of several systems and may therefore benefit from treatment of multiple interoceptive pathways. As described above, people in treatment for SUD have been shown to benefit from interoceptive awareness training through MABT [83], which decreases craving and substance use, while increasing interoceptive awareness and emotion regulation.

It is also possible that patients with SUD may be treated via manipulations of other interoceptive systems such as the hunger system, given that substance use involves a subjective sense of craving, the latter being a common feature of addiction and recently included as a DSM-5 diagnostic criterion. Indeed, both preclinical and human research indicate an important overlap between neurocircuitry regulating addiction and those regulating hunger, appetite, and pathological eating behaviors [91]. Furthermore, medications approved to treat patients with addiction often have effects on hunger, appetite and food intake [92]. With that in mind, it is particularly intriguing to study hunger-related gut-brain pathways, such as the ghrelin system. The “hunger hormone” (acyl)-ghrelin is a stomach-derived peptide that activates the growth hormone secretagogue receptor 1a (GHS-R1a), also known as the ghrelin receptor. Several rodent studies indicate that deletion of the ghrelin peptide or receptor gene leads to a reduction in alcohol intake and other alcohol-related outcomes [93–95]. Furthermore, ghrelin administration increases alcohol intake, preference, self-administration, conditioned place preference and other alcohol-related outcomes, whereas conversely, GHS R1a blockade reduces these behaviors [93–95]. In humans, observational studies indicate a positive association between endogenous ghrelin concentrations and alcohol craving, alcohol-related subjective effects and brain activity in response to alcohol cues [93–95]. Furthermore, ghrelin administration increases cue-induced alcohol craving but not cue-induced juice craving [96] and increases progressive-ratio alcohol self-administration [94]. Consistent with the preclinical studies mentioned above, preliminary human research also suggests that blocking GHS-R1a may be a potentially promising approach. PF-5190457, a GHS-R1a blocker, has been shown to be safe and tolerable when co-administered with alcohol and may reduce cue-elicited craving for alcohol and food in heavy-drinking individuals [97]. While these findings are encouraging, significant additional work is needed to further test the potential for the ghrelin system to be a target to treat addiction.

Concluding remarks and future perspectives.

Here, we outline a framework where interventions may manipulate interoceptive processing at various levels to improve clinical symptoms and functioning. Using respiration as a case system, we describe interventions that can alter interoceptive processing via neuromodulatory (e.g., taVNS), behavioral (slow breathing), and psychological means (mindfulness-based approaches). This framework brings together multiple perspectives and levels of analysis, which may be applied to other interoceptive systems (and associated organs) such as the gut and digestion (stomach, intestines), cardiovascular (heart), and urinary (bladder) systems. Although not all systems can be as readily consciously manipulated as the respiration system, interoceptive awareness skills may be applied to recognize bodily sensations or symptoms that are important for regulating health-related behaviors (see Outstanding Questions Box for summary of inquiries to move research forward). For example, patients experiencing craving may be taught to recognize interoceptive cues within the gut and other relevant areas of the body, and engage in adaptive regulatory behaviors. Importantly, the quality of interoceptive attention matters (such as being sustained and nonjudgmental), and may be an important determinant in the outcome of treatments as it allows patients to understand their bodily signals and become active participants in managing their health. Depending on the health condition, patients can become aware of relevant signals from the gut, heart, bladder, or other organs, and learn to engage in regulatory health behaviors. For example, those with diabetes can be taught to recognize changes in their blood sugar through changes in physical sensations, and know when to engage in behaviors to manage symptoms [98]. Interventions of interoception may potentially be integrated with computational modeling [5] to understand how interoceptive representations may be altered within specific clinical conditions. Other mind-body interventions involving active physical movements and breath regulation (e.g., exercise, yoga, pranayama, and Tai Chi) may also be studied using this framework. As described earlier, different clinical conditions may also be treated by modulating multiple interoceptive systems, such as combinations of respiratory and gut systems in SUD. Finally, interoceptive processes occur within each individual’s specific social and environmental context, which may produce unique interoceptive cues and associations [99]. For example, social interoception frameworks suggest that an individual’s patterns of physiological responding may change depending on their relationship to another individual [100,101]. Clinical phenomena may also be tied to interoceptive signaling conditioned with specific visual and social cues. For example, seeing a whiskey bottle at a party may be conditioned to sensations of craving for a substance user and increase risk of relapse. The framework discussed in this article may be extended to various interoceptive systems, mind-body interventions, and clinical conditions so that more integrated cross-disciplinary solutions may emerge.

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Glossary

Aerobic metabolism
A chemical process that uses oxygen to convert carbohydrates and fats into energy

Autonomic nervous system (ANS)
A part of the peripheral nervous system that regulates involuntary functions of the body such as heart rate, respiratory rate, and digestion

Baroreflex
A homeostatic mechanism that helps regulate blood pressure changes through a rapid negative feedback loop

Discrimination
Localize sensation to a specific channel or organ system and differentiate it from other sensations

Meta-awareness
A state of deliberate attention to the contents of conscious thought, serving as an appraisal of consciousness awareness

Monoaminergic systems
A group of systems that use monoamine neurotransmitters, such as serotonin, dopamine, norepinephrine, epinephrine, and/or histamine, to influence processes such as emotion, arousal, and memory

Motoneuron
Another term for a motor neuron, a type of efferent neuron that conveys motor impulses from the brain or spinal cord to a muscle or gland

Progressive-Ratio
A schedule of conditioning in which an increase in response is required for the delivery of a reinforcement in successive sessions

Suprapontine
Above the pons. The pons is part of the brain stem

Sympatholytic medication
A type of medication that attenuates the downstream effects of postganglionic functioning in organs innervated by the sympathetic nervous system

Transcutaneous auricular Vagus Nerve Stimulation (taVNS)
a non-invasive form of VNS which uses cutaneous or percutaneous electrodes to electrically stimulate the auricular branch of the vagus nerve at the ear

Vagus Nerve Stimulation (VNS)
an invasive (surgical) form of neuromodulation that applies electrical stimulation to interoceptive pathways that direct afference from visceral organs to the brain

Visceroception

A form of interception that is characterized by awareness of bodily signals originating from the viscera: the heart, lungs, stomach, bladder, and other internal organs in the trunk of the body

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Outstanding Questions Box

- What clinical conditions respond to interoceptive therapies?
- Is the development of interoceptive awareness a key component for longitudinal gains in health?
- What are the physiological and/or psychological mechanisms underlying clinical improvements in response to interventions designed to manipulate interoception?
- Can therapies targeting interoception be combined with current pharmacologic approaches in a synergistic manner to improve health?
- What interoceptive mechanisms should be targeted for future intervention development?
- Are there certain areas of the body, or types of sensations, where interoceptive attention may be applied to better manage specific clinical conditions?
- How can therapies targeting interoception be improved or augmented for maximal health benefits?
- What are the steps and/or barriers for implementing interoceptive therapies at a clinical level?
- Can information driven from interoceptive mechanisms serve towards the development of precision medicine approaches?

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Highlights

- Neuromodulation can tap into known interoceptive pathways for clinical benefit
- Meditation with sustained interoceptive focus on breath sensations increases neural activation of interoception networks (including insula) and decreases engagement of the Default Mode Network which supports self-referential processing.
- While sympatholytic medications often have intolerable side effects, interoceptive interventions may be a safe and well-tolerated modality to improve sympathetic regulation and thereby reduce risk of hypertension and cardiovascular disease.
- Recent findings highlight possible underlying mechanisms of improved interoceptive awareness skills and emotion regulation in mindfulness-based interventions for the treatment of physical and mental health conditions.

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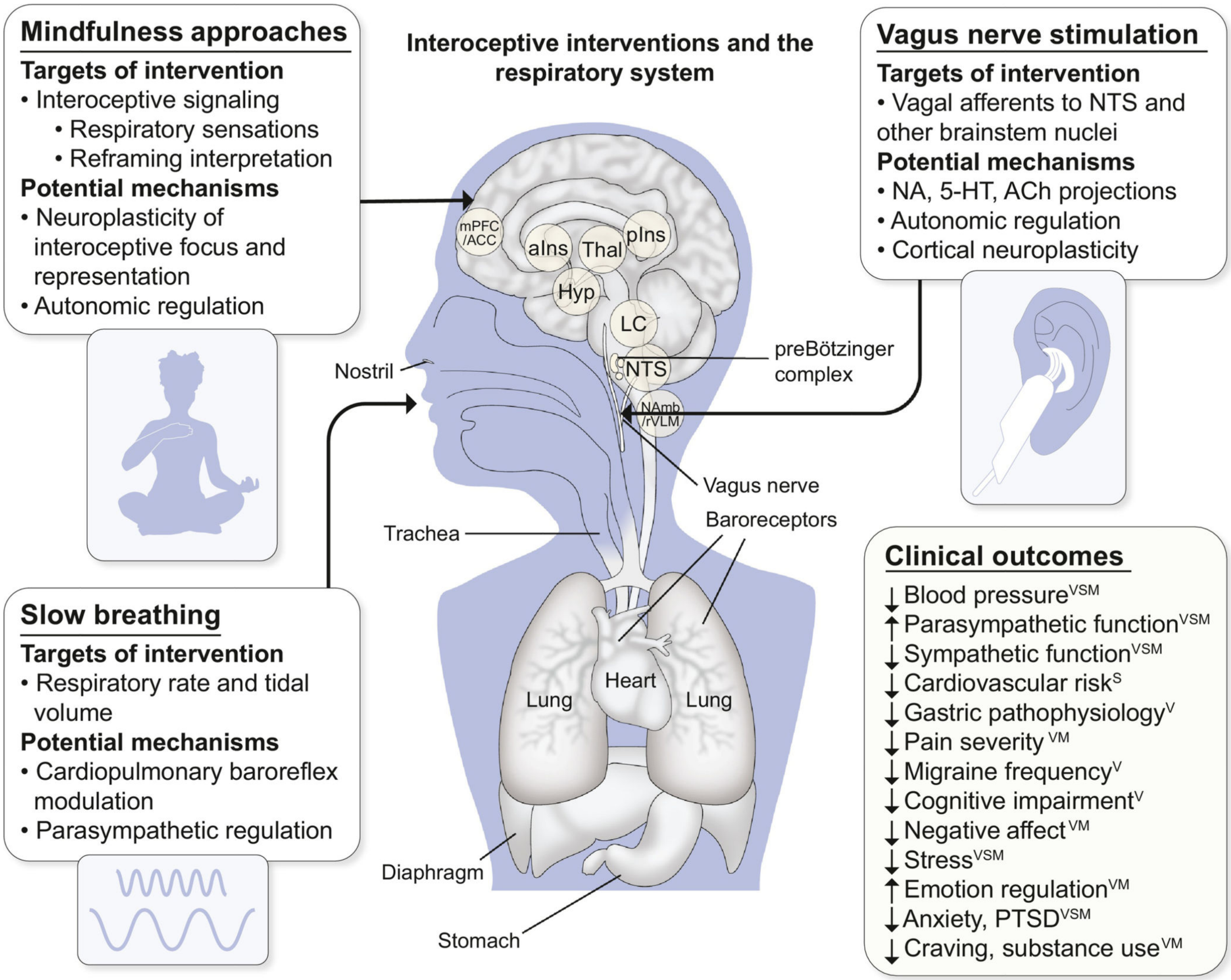

Trends in Neurosciences

Figure 1. Interoceptive interventions of the Respiratory System.

Interventions of a given interoceptive system can be understood through four main domains: the intervention type, target(s), potential mechanisms, and clinical outcomes. The target(s) of an interoceptive intervention may include neural entry points that can impact upstream sensory or psychological functioning (e.g., the vagus nerve), or behavioral or psychological entry points which can impact downstream functioning (e.g., respiration rate and depth, interoceptive awareness and interpretation of respiratory sensations). The framework outlined here refers to the respiratory system and may be extended to aspects of other interoceptive systems. **Mindfulness Approaches** (top left). Mindfulness approaches may improve interoceptive awareness by cultivating attention to bodily sensations that is sustained and nonjudgmental. Mindfulness-ofbreath exercises engage neural networks involved in interoception (aIns, pIns), executive function, and emotion regulation (mPFC/ACC). **Slow Breathing** (bottom left). Slow breathing (or decreasing respiratory rate to ~5 breaths/min) is thought to activate cardiopulmonary baroreceptors, leading to reflex reductions in sympathetic nerve activity, resulting in lowered blood pressure. **Vagus Nerve Stimulation (VNS)** (top right). VNS is a form of neuromodulation where electrical stimulation is applied to the main trunk or peripheral receptors of the vagus nerve (such as through non-invasive auricular stimulation, targeting the auricular branch of the vagus nerve). Interoceptive afference can impact clinical outcomes via multiple physiological mechanisms, some of which are already well understood. For instance, afference that reaches conscious perception may also be linked with known baroreflex mechanisms which regulate heart rate. Additionally, parasympathetic vago-vagal reflexes that regulate stomach function involve signaling from the stomach that can reach interoceptive awareness. Such pathways may also be regulated by external input to the constitutive brainstem nuclei via interventions such as transcutaneous auricular vagus nerve stimulation, leading to plasticity in neural circuits both in the brainstem and higher brain centers. Note: the brainstem breathing central pattern generator is a complex network of interacting sites, here represented by its essential engine, the preBötzinger Complex. See [8] for more details. **Clinical outcomes** (bottom right) largely overlap among the three interventions due to targeting the respiration system at different levels of processing, and include ameliorated symptoms in cardiovascular functioning, pain, and psychiatric disorders. Further, interventions can have similar effects because they are inter-related; for example, mindful interoceptive awareness of breath sensations can result in slow breathing. This framework also highlights that interventions may be integrated and optimized by targeting multiple points in interoceptive pathways (such as VNS coupled with Mindfulness approaches). The “Clinical Outcomes” inset indicates which interventions are associated with which outcomes: V, Vagus Nerve Stimulation; S, Slow Breathing; M, Mindfulness approaches. Abbreviations: 5-HT, Serotonin; ACh, Acetylcholine; aIns, Anterior insula; Hyp, Hypothalamus; LC, Locus Coeruleus; mPFC/ACC, Medial prefrontal cortex / Anterior cingulate cortex; pIns, Posterior insula; NA, Noradrenaline; Namb/rVLM, Nucleus ambiguous / Rostral ventrolateral medulla; NTS, Nucleus Tractus Solitarii; PTSD, Post Traumatic Stress Disorder; Thal, Thalamus.