Berntson GG, Gianaros PJ, Tsakiris M (in press). Interoception and the autonomic nervous system: Bottom-up meets top-down. In M. Tsakiris & H. De Preester (Eds.), Mind and Interoception. New York, NY: Oxford University Press.

Interoception and the autonomic nervous system:

Bottom-up meets top-down

Gary G. Berntson

Department of Psychology, The Ohio State University

Peter J. Gianaros

Department of Psychology, University of Pittsburgh

Manos Tsakiris

Lab of Action & Body, Department of Psychology, Royal Holloway

University of London, UK

&

The Warburg Institute, School of Advanced Study, University of London,

UK

Abstract

Although the efferent role of the autonomic nervous system (ANS) in homeostasis has long been recognized, the afferent aspects of the ANS are increasingly recognized to be equally important. Interoception is fundamental to the regulation of internal physiology, particularly as it is coordinated with contextually-determined and adaptive behavioral processes. A cardinal, but often underappreciated, feature of interoception is its complex role in a myriad of integrative cognitive and affective processes in health and disease. We here introduce the concept of interoception and outline its historical origins and applications in multiple domains of psychology and psychobiology. We provide an overview of its peripheral and central neural substrates, and we outline how this construct is best conceptualized within a multi-system and multi-level regulatory framework.

Introduction

Interoception is a multidimensional construct, broadly encompassing the processing of afferent (sensory) information arising from internal organs, tissues, and cells of the body. This afference contributes to the regulation of homeostatic reflexes, and, as we will see below and throughout this volume, more broadly to the generation and regulation of cognitive and emotional behaviors.

Interoception can be encompassed by the broader construct of bodily afference. The latter includes both visceral afference and somatic afference. We use the term visceral afference to refer to the processing of internal sensory information derived from interoceptors that are located in the organs, tissues, and cells of the main cavities of the body (i.e., the viscera), as well as from olfactory and gustatory receptors; all being generally associated with the limbic system and the autonomic nervous system. We use the term somatic afference to refer to the processing of sensory information (e.g., proprioceptive input and tactile sensitivity) derived from components of the somatic system (e.g., muscles, joints, skin). This distinction between somatic and visceral afference does not

imply a complete independence. Indeed, in many cases, there is an integration of multiple modes of bodily or somatosensory information derived, for example, from metabolic changes in active muscle tissue. Hence, the term somatovisceral afference is more appropriately applied to integrated, multimodal, or otherwise nonspecific internal sensory input from within the body (e.g., see Yates & Stocker, 1998). In these regards, the construct of interoception itself is more specifically aligned with that of visceral afference, referring to the processing of sensory information from interoceptors that are located within the visceral organs and from interoceptors located elsewhere in the body that provide for local energy needs. Thus, in contrast to exteroceptors, interoceptors are tuned to sense internal events (Cameron, 2002).

The so-called general visceral afferents (GVAs) that relay internal sensory information from interoceptors are carried by several cranial nerves, the most notable being the vagus nerve. These afferents carry information (e.g. pressor receptor activity) from the gut and the viscera more generally (i.e., organs and tissues located in the thoracic, abdominal, and pelvic cavities, as well as blood vessels and muscles). By comparison, special visceral afferents (SVAs) convey gustatory senses (i.e., taste) and

olfaction (i.e., smell and pheromonal senses). Although the SVAs detect environmental stimuli, they do so by virtue of those stimuli impinging on the internal bodily environment. Hence, they differ from exteroceptors, for example, conveying information related to touch or audition. Furthermore, the visceral senses have common central projections to cell groups in the brainstem, including the nucleus tractus solitarius (NTS), midbrain, and thalamus, that are distinct from those of somatic exteroceptors, and they link anatomically and functionally with a distinct set of central neural systems and processes (Craig, 2014; Saper, 2002). Moreover, they share biochemical markers in common with GVAs afferents and with autonomic neurons (see Squire et al., 2012). There are other classes of sensory systems, such as proprioceptors, that sense joint position, and vestibuloceptors, that sense body orientation in gravitational space. These might be considered interoceptors, as they are internal to the body. Yet, they are closely linked with somatic motor systems anatomically and functionally, and they have biochemical markers more in concert with somatic motor systems. Hence, they are sometimes considered within the unique class of proprioceptors, or otherwise just included within the general class of exteroceptors.

What is important to consider is that both exteroceptive and interoceptive

information can powerfully influence cognitive and emotional processes,

and, importantly, vice versa. Moreover, as will be developed below, visceral

afferents carrying interoceptive information have a constitutional link with

central neural systems underlying cognitive and emotional processes, and

they thus impact these behavioral processes (e.g., Tsakiris and Critchley,

2016a; see also the entire Theme Issue, Tsakiris and Critchley, 2016b).

This is clearly apparent in the positive and negative (e.g., disgust) hedonic

effects of tastes and smells. As detailed in the remaining chapters of this

volume, it is thus doubtful that interoception can be meaningfully parsed or

dissociated from cognitive, emotional, and behavioral processes. Indeed, a

recent meta-analysis of fMRI studies revealed considerable overlap in

systems co-activated by interoceptive signaling, emotional regulation and

low-level social cognition, and convergent results were found for the effects

of lesions (Adolfi et al., 2017).

Historical perspectives

Claude Bernard is generally credited with developing the concept of

the "fixity" or relative stability of the internal fluid matrix (milieu intérieur) as

a necessary condition for what he termed the free and independent life. Walter Cannon, chair of the Department of Physiology at Harvard around the turn of the 20th century, further elaborated on this concept and coined the term homeostasis (Cannon, 1932/1939). He believed that the autonomic nervous system (ANS) plays an important part in maintaining this homeostatic stability. Although Cannon recognized the importance of visceral afferents in homeostatic reflexes, the predominant view of the ANS was as an efferent, lower level, reflexive motor system. Cannon further asserted that the ANS is termed "… 'autonomic' because it acts automatically, without direction from the cerebral cortex" Cannon (1939, p. 250). This misconception was perhaps understandable, as it would be another half century before the existence of direct, monosynaptic projections from cortical and other telencephalic areas to lower brainstem autonomic source nuclei and reflex substrates would be documented (e.g., Barbas et al., 2003; Cechetto & Saper, 1990; Dum et al., 2016; Neafsey, 1990).

<insert Figure 1 about here>
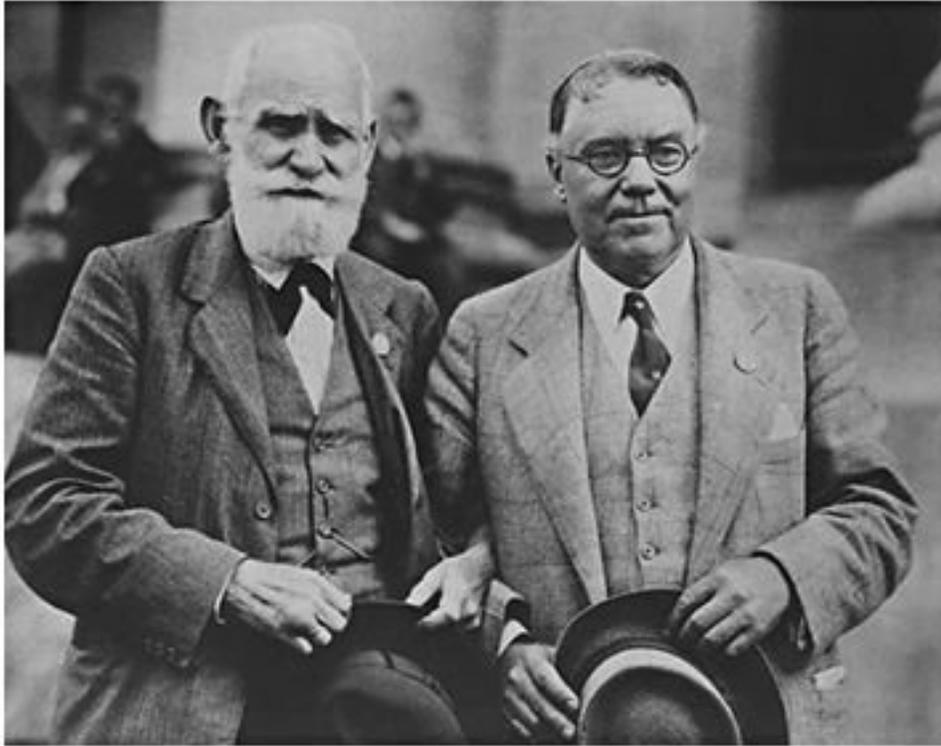
In retrospect, this misconception is also somewhat surprising in view of the work of Cannon's friend, contemporary, and Nobel Laureate, Ivan Pavlov. Here, it is often underappreciated that much of Pavlov's work on learning centered on the modification of an autonomic and homeostatic reflex that involves the processing of interoceptive information in preparation for digestion – the cephalic vagal reflex, or the cephalic phase insulin release to a stimulus which had previously been paired with food. Indeed, this work contributed to a foundation for understanding how interoceptive phenomena can be powerfully related to learning and other

processes instantiated in higher brain systems that can jointly influence visceral control, including systems within the cerebral cortex. This includes experience-based acquired responses that can both modulate ongoing visceral processes, as well as anticipate and prospectively guide adaptive autonomic, cognitive and emotional responses (Cameron, 2002; Dworkin, 1993).

Well before the existence of long descending pathways linking brain and viscera had been established, functional studies revealed autonomic representations in multiple higher-level diencephalic and telencephalic areas of the forebrain. The 1949 Nobel Laureate, Walter Hess, for example, had reported striking autonomic responses from telencephalic (e.g., the amygdala and septal area) and diencephalic structures, including the hypothalamus, which Hess considered the head-ganglion of the autonomic nervous system (Hess, 1954; see also Ranson et al., 1935). The Canadian neurosurgeon, Wilder Penfield, also reported autonomic responses to cortical stimulation in conscious human patients (Penfield, 1954). At this point, we recognize a broad central autonomic network comprised of a number of forebrain areas, including the insular cortex, cingulate cortex, medial prefrontal cortex, amygdala, and hippocampus, as

well as caudal cell groups in the midbrain periaqueductal gray, pons, cerebellum, and medulla (Benarroch, 1993; Cechetto & Saper, 1990; Critchley, 2005; Dampney, 2015; Loewy, 1991; Neafsey, 1990; Saper, 2002; Shoemaker & Goswami, 2015). This network highly overlaps and interacts with systems implicated in complex cognitive and affective processes (Annoni et al., 2003 Critchley, 2005; Myers, 2017; Saper, 2002).

Another legacy from the Cannon era that did not survive the test of time is the view that the ANS is primarily an efferent motor system, with minimal visceral afferents necessary to support homeostatic reflex functions. In his influential book, The Wisdom of the Body, Cannon stated "The nerve fibers of the autonomic nervous system, which are mostly efferent, pass out of the central nervous system….." (Cannon, 1939, p. 252). Similarly, John Newton Langley, who coined the term autonomic nervous system[1] (Langley, 1898) viewed the ANS largely as a motor system, although he recognized that one might "consider as afferent autonomic fibers those which give rise to reflexes in autonomic tissues…(but are)… incapable of directly giving rise to sensation" (Langley, 1903, p. 2). As early as the mid-1930s, however, there were quantitative studies demonstrating that the majority of fibers in the vagus are sensory

(Foley & DuBois, 1937; Heinbecker & O'Leary, 1933). This is consistent with contemporary estimates that 70%-90% of vagal fibers, about 2-20% of fibers in the splanchnic (sympathetic) nerves and about 2% in spinal nerves are visceral afferents[2] (Berthoud & Neuhuber, 2000; Cameron, 2002; Jänig & Morrison, 1986).

Historically, there were also notable conceptual challenges to the notion that the ANS is primarily a motor system. In contrast to the view that emotions precede and trigger bodily reactions, William James (1884) proposed that exciting events induce bodily changes (including autonomic responses) and that our subsequent feeling of these changes constitutes the emotion. Shortly thereafter, Carl Lange (1885) independently proposed a vascular theory of emotion, which held that vasomotor responses are the primary effects of affectations, and subjective sensations of emotion arise secondarily. Both of these perspectives converged into a view of visceral afference as fundamental for the generation and experience of emotion.

This view came under severe assault from two notable figures. Walter Cannon (1927, 1931), often considered the "father of the autonomic nervous system" and Sir Charles Sherrington (1900) – a notable turn-of-

the-century physiologist and a recipient of the Nobel Prize in Physiology or Medicine (1932) for "discoveries regarding the functions of neurons." At least the strong form of the James-Lange concept (emotions as the mere perception of visceral feedback) was largely discredited at that time. There were a number of arguments against the James/Lange perspective. Cannon, for example, argued that the viscera have few afferents and are relatively insensate. As noted above, however, it is now recognized that visceral afferents in fact outnumber efferents. Additionally it was argued that 1) visceral responses are too slow to underlie emotion; 2) similar visceral changes may occur across different emotions and even non-emotional states; 3) inducing autonomic responses does not necessarily invoke emotions; and 4) that autonomic denervations of various types do not prevent emotional reactions. None of those are particularly telling arguments unless one wants to assert an identity relationship between visceral afference and emotion. James (1884), in fact, viewed emotions as being multiply determined, and to include cognitive contributions. He stipulated in his 1884 piece that the only emotions that he will "…consider here are those that have a distinct bodily expression" (p. 189) — the so-called 'coarser emotions'. It is well established that there are multi-level hierarchical and heterarchical representations in neurobehavioral systems

and central autonomic networks (see Berntson et al., 2016; Norman et al., 2014), and there are multiple determinants of affective processes. What will become apparent through the chapters of this volume is that there are powerful interactions between cognitive and emotional processes, somatic and autonomic outflows, and interoceptive feedback. Consequently, the effects of interoceptive feedback would not be expected to be invariant, but to show notable brain-state and context dependencies (e.g., see Cacioppo et al., 1992).

A case report

Visceral afference can powerfully modulate cognitive and emotional processes, as illustrated by the following case report on MM (personal communication). MM is a graphic artist and videographer, who was working on a documentary about a historical kidnapping and murder. She had extensively researched and documented the story and had located and interviewed most of the characters involved (except for the perpetrator who had killed himself). The story was ready for filming (January 2007). But, alas, it never happened:

"I handed the story back to the producer when it became clear that I can not work the script (kept repeating the same scenes), as I was able to keep it all in my head for about 3 pages - few minutes, and no amount of colour coordinated storylines and post-it notes was going to save me when I was not able to make a simple decision on spot (calculating what days we had available for shooting whom...etc)."

What lead to this transformation (February, 2007)? It was *endoscopic thoracic sympathectomy* (ETS), the surgical destruction or disabling of the upper spinal sympathetic (autonomic) nerve trunk—for hyperhidrosis (excessive sweating). Thereafter, MM's life (age 39 at the time) was dramatically changed[3]:

"It is my experience that following this surgery there is a shift in personality and how emotions are experienced. It is, however, not only emotional blunting, but also an impaired impulse control and disinhibition (as if a grown up brain has been replaced by a primitive, and at times manic brain, that affects higher functioning). I am not sure how to describe it really... There is an indifference and striking lack of fear.... I witnessed within myself once I got into my car and started driving around, or in

general danger situations, any urbanite encounters. My emotions are blunted, and there is an unsettling deadness and indifference towards my prior life and aspirations, goals. This indifference and emotional blunting was present as soon as I woke up from the surgery and has not left me since…"

"In general, the procedure led to a personality change, in some aspects subtle, in others a profound shift that I find exceedingly difficult to accept - a kind of physiological expression of how I was feeling, zombie-like…"

"I was described by one (video) critic as a human seismograph, recording the finest shifts in mood/tone… (now) I have problems in social settings, where I generally might appear antisocial. I force myself to ask questions and engage in 'banter', but more often I forget. I would say that it has changed how I relate to people: I do not relate..."

Tragically, this outcome was not unique to MM. There is a considerable literature documenting a range of post-sympathectomy complications including cognitive deficits, altered mood, emotional blunting,

fatigue and neuropathic complications (e.g., Furlan et al., 2000; Goldstein, 2012; Mailis & Furlan, 2003). Indeed, a support group, The Sympathetic Association (FfSo), was formed in Karlstad, Sweden, by people who found themselves disabled by serious side effects of sympathectomies (http://home.swipnet.se/sympatiska/index3.htm).

We will return to the case of MM below (General Visceral Afferents).

Central visceral pathways and the visceral cortex

An important integrative site in the forebrain for visceral afference is the insular cortex, which could be considered a primary visceral cortical site. The insula, in turn, is highly interconnected with cortical and subcortical areas involved in cognition, emotion and motivation, including the prefrontal cortex, the cingulate cortex and the amygdala (Allen et al., 1991; Augustine, 1996; Nieuwenhuys, 2012; Oppenheimer and Cechetto, 2016). The insula receives input from all visceral afference, and as will be seen throughout this volume, contributes to the integration of this afference with neurobehavioral processes (Tsakiris and Critchley, 2016a), and

anomalies in insular function are associated with a wide range of cognitive, emotional and behavioral disturbances (Gasquoine, 2014).

Special visceral afferents. The Chemical Senses: Olfaction & Gustation. As noted above, olfaction is a special visceral sense closely linked with both positive and negative hedonics. This is especially true in lower animals where it plays a central role in guiding behavior. The olfactory system is closely linked with a medial central brain network that was historically referred to as the rhinencephalon (nose brain). Paul Broca (1878) referred to the medial central components of the brain as the great limbic lobe (le grand lobe limbique), as they arch around the central encephalon ("limbique" in French translates as "hoop" or "curve"). Papez (1937) proposed that limbic areas and associated structures are an important central network in emotion (often referred to as Papez circuit). This concept was further developed by Paul MacLean (1954) who coined the term 'limbic system' and viewed this system as an evolutionary heritage (the paleomammalian brain) that regulates emotion, motivation, and survival-related behaviors, as well as links these phenomena with vulnerability to chronic health conditions (e.g., hypertension, asthma). Olfactory afferents play an important role in emotion, motivation, and

survival-related behaviors processes. Although the olfactory system more directly projects to a number of cortical areas, olfactory information is also relayed via the thalamus and other cortical areas to the insular cortex (which itself is often considered to be a part of the limbic system). Odors can modulate mood, cognition, and behavior, and many of these effects appear to be mediated by the insula (for reviews, see Miranda, 2012; Saive et al., 2014; Soudry et al, 2011).

The primary gustatory cortex lies in the anterior insula. Gustatory afferents (cranial nerves VII, IX and X) terminate in a medullary nucleus, the nucleus tractus solitarius (NTS), and then are relayed via the midbrain parabrachial nucleus to the ventroposteromedial thalamus, which issues direct projections to the anterior insula (Saper, 2002). A similar functional pattern emerges in the literature to that of olfaction (Rolls, 2015). There are potent insular contributions to the processing of taste hedonics and attentional and memorial processes associated with taste, and insular cortex abnormalities are associated with disturbances in these processes (Frank et al., 2013; Maffei et al., 2012).

General visceral afferents. As is the case with gustatory afferents, all general visceral afferents in cranial nerves project to the nucleus tractus solitaries (NTS) in the brainstem, to the parabrachial nucleus in the midbrain and then via the ventroposteromedial (VPM) nucleus of the thalamus to the insular cortex. In his classic studies, Wilder Penfield reported that electrical stimulation of the insula induced a variety of visceral sensory experiences (Penfield & Jasper, 1954). In addition to cranial nerves, general visceral afferents carrying nociceptive, temperature and chemosensory information from the body enter the spinal cord via dorsal spinal roots and terminate in the dorsal horn (especially in lamina I). Until around the turn of the 21st century, the general belief was that small-diameter nociceptive (i.e., sensory information about tissue damage)/temperature afferents were part of the somatosensory system and were ultimately relayed to the somatosensory cortex in the parietal lobe. Indeed, this view persists. In their 2016 text on Neuroscience, Bear et al. assert that the "Spinothalamic pathway is the major route by which pain and temperature information ascend to the cerebral cortex." (Bear et al., 2016, p. 444). In fact, it is now well established that the small diameter fibers carrying nociceptive, temperature and chemical senses project from the VPM not to the somatosensory cortex but to the insula (Craig, 2015;

Saper, 2002). This accounts for the fact that in Wilder Penfield's studies, patients never reported pain on stimulation of the somatosensory cortex (Penfield & Jasper, 1954). Moreover, surgeons do not extirpate the somatosensory cortex for pain syndromes. In contrast, however, Mazzola et al. (2012) report induced pain with stimulation of the insular cortex, and painful "somatosensory" seizures appear to arise not from the somatosensory cortex, but from the opercular-insular cortex (Montavont, 2015).

This general visceral afference, and the top-down and bottom-up integration of insular cortical systems, underlie the cognitive-emotional processes that reflect the broad integrative contributions of the insula (Tsakiris and Critchley, 2016a; see also chapters 2 and 6, Part I of the present volume). Insula lesions, for example, result in diminished emotional arousal to affective pictures, and a reduced ability to even recognize the affective picture content (Berntson et al., 2011). Although the literature on insular involvement in emotion and emotional processing is quite consistent (Uddin et al., 2017), there appears to be some diversity in the effects of insular lesions[4]. In addition to its role in emotion and motivation, the insula appears to play a pivotal role in the sense of self, agency, and indeed,

consciousness (Craig, 2014; Strigo & Craig, 2016; Tsakiris and Critchley, 2016, see also Chapters 2 & 6, Part I of this volume and Chapter 2, part III of this volume). Thus, insula activation is correlated with the sense of body ownership and agency (Farrer et al., 2003; Tsakiris, 2007; see also Chapter 2, part III of the present volume). In accord, lesions of the insula can lead to a disturbed sense of body ownership, including somatoparaphrenia or the denial of body ownership (Cogliano et al., 2012; Gandola et al., 2012; Karnath and Baier, 2010; Moro et al, 2016).

The findings outlined above and further addressed in the present volume indicate that visceral afferent input to the insula appears to be critical in cognitive and emotional processes. But one may see similar deficits with disrupted visceral afference in the absence of frank insular impairments. Patients with pure autonomic failure, and the associated blunting of autonomic activity and visceral afference have been reported to show deficits in cognitive processing, empathy and emotional reactivity (Chauhan et al., 2008; Critchley et al, 2001; Heims et al., 2006). In this regard, returning to our case study, although MM did not have a direct insular insult, the surgical sympathectomy would have as a necessary consequence a diminution of both sympathetic and parasympathetic

visceral afference, and this may have contributed to the cognitive and emotional sequelae she experienced. Critchley et al. (2001, p 207) asserted that "Body state changes, particularly those mediated by the autonomic nervous system, are crucial to the ongoing emotional experience of emotion", and Goldstein (2012) reported that partial cardiac denervation was associated with fatigue, altered mood, blunted emotion, and decreased ability to concentrate. The findings that meditation can increase insular activity, connectivity, gray and white matter volume raise a question as to a potential therapeutic strategy in visceral denervation syndromes (Gotink et al., 2016; Hernandez et al., 2016; Laneeri et al., 2016).

Current applications and implications

As noted above, the central autonomic network (CAN) and neurobehavioral substrates more generally, become re-represented and elaborated with the evolutionary development of higher-level neural systems (Jackson, 1884). This has significant implications for the functional understanding of the autonomic nervous system, visceral afference, and the multi-level representations in the CAN. To elaborate, lower-level

autonomic reflexes, such as those studied by Cannon, are relatively hard-wired and highly regulated by local visceral afference contributing to the feedback regulation of homeostasis. The baroreceptor reflexes, for example, are visceral homeostatic control loops that constrain short-term variations in blood pressure via rapid autonomic adjustments. The afferent limb of the baroreflexes encompasses interoceptors positioned in the heart and great arteries. Increases in blood pressure cause a distortion of their free nerve endings, leading to an increase in afferent firing and associated afferent input to the NTS. Via relays in the rostral and caudal ventrolateral medulla, this NTS afferent input results in a subsequent reflexive reduction in sympathetic and an increase in parasympathetic control of the heart and cardiovascular system, culminating in an associated compensatory reduction in blood pressure. The sensitivity of the homeostatic baroreceptor-heart rate reflex can be quantified by the slope of the function relating heart rate to blood pressure. This slope reflects in part the servocontrol of blood pressure by heart rate decreases with increasing blood pressure (decreasing cardiac output) and heart rate increases with decreasing blood pressure (increasing cardiac output). It was Cannon's student, Philip Bard, however, who noted that the slope of the baroreflex function could be decreased (flattened) by a typical laboratory stressor

(reflecting a decrease in sensitivity of the baroreflex). That is to say, stressors 'inhibit' the homeostatic control over blood pressure by the baroreflex, which presumably enables heart rate and blood pressure to rise simultaneously and rapidly to provide hemodynamic and metabolic support for adaptive action or stressor coping. Although stressor-evoked effects on the baroreflex have been widely seen across species, such effects raise a number of basic questions insofar as they reflect 'anti-homeostatic' actions that appear to be implemented by higher levels of the CAN. That is, while homeostasis is an important contribution of the ANS, ANS effects are not always homeostatic across behavioral states (see Berntson et al., 2016). Indeed, it may be maladaptive to maintain a "fixity" of the internal milieu by lower reflex substrates of the CAN. In this way and in the face of adaptive challenges, higher levels of the CAN may modulate or 'reset' lower substrates for reflex control to implement contextually appropriate, anticipatory, or otherwise 'adaptive' increases in both blood pressure and heart rate (Dampney, 2017).

Sterling & Eyer (1988) and later Shulkin (2003) introduced the concept of allostasis to reflect the fact that homeostasis is not necessarily static, but can assume different regulatory levels (setpoints), to adapt to

survival challenges. An example of this is fever, which unlike the 'anti-homeostatic' baroreflex effects of stress, represents a true adoption of a higher regulatory setpoint, which is monitored and actively defended both physiologically and behaviorally. Bruce McEwen (2012) subsequently introduced the concept of allostatic load to reflect the fact that while short-term allostatic adjustments may be adaptive, sustained, long term allostatic adjustments may have cumulative and deleterious health consequences. But deviations from homeostasis may not always entail simply an altered setpoint level. Berntson et al. (2016) advanced the concept of heterodynamic regulation, in which higher level CAN and neurobehavioral substrates, integrating somatovisceral afference, cognitive and emotional processing, can dynamically regulate autonomic outflows and therefore somatovisceral afference in a flexible, dynamic fashion to achieve more optimal adaptive outcomes that are appropriate to given behavioral contexts.

These considerations suggest that classical concepts of the autonomic nervous system, which focus on autonomic reflexes and homeostasis, are inadequate for a full understanding of the contributions of the ANS and its afference to neurobehavioral processes. An illustration of

the latter point is evident in contemporary perspectives on the role of interoceptive processes in physiological stress reactivity and recovery. More precisely, physiological stress reactivity and recovery have received widespread and longstanding attention because of their presumptive relationships with aspects of physical and mental health across the lifespan (Cohen, Gianaros, and Manuck, 2016). For example, people with phenotypes to exhibit exaggerated and prolonged rises in heart rate and blood pressure that are mediated by the autonomic nervous system are at elevated risk for hypertension, stroke, myocardial infarction, and early death (Ginty et al., 2017).

The central substrates for such patterns of stressor-evoked physiological reactivity and recovery have been studied for over a century in human and nonhuman animal studies. Notwithstanding, a historically neglected dimension of these substrates is how they are influenced by stressor-evoked interoceptive information encoded in peripheral physiology (Gianaros and Wager, 2015). To elaborate, stressors are thought to engage higher neural substrates of the CAN, including the insula and ACC, which may appraise stressors and in turn issue descending visceral motor commands for rapid autonomic adjustments to cardiovascular physiology.

These centrally determined and stressor-evoked adjustments may entail simultaneous rises in blood pressure and heart rate, with accompanying modifications to the baroreflex, to provide metabolic support for behavioral action and stressor coping (Gianaros et al., 2012). This central linkage of behavior with metabolically supportive changes in cardiovascular physiology is exemplified in the cardiac-somatic coupling hypothesis of Obrist (1981) and the 'central command hypothesis' within the field of exercise physiology (Fisher et al., 2015). More recent perspectives on this linkage now emphasize that central substrates for peripheral stress reactivity likely issue visceral motor commands in a predictive fashion, providing metabolic support for behavior that is anticipated in the future (Ginty et al., 2017; Gianaros and Jennings, under review). Moreover, these substrates may also predict patterns of expected visceral (interoceptive) feedback in a way that serves to calibrate peripheral physiology with behavior and the metabolic demands of a given context (Barrett and Simmons, 2015; see also Part II, Chapter 1 of the present volume).

Understood in this way, 'mis-matches' between actual and predicted metabolic demands can be viewed as visceral prediction errors. These errors may manifest in the magnitude or patterning of stressor-evoked

changes in peripheral physiology. For example, a rise in blood pressure in excess of 40mmHg in preparing for a public speech can be seen as a visceral prediction error—insofar as it is a hemodynamic change that is disproportionate to the actual metabolic needs of the context. Likewise, sustained or prolonged changes in cardiovascular physiology that far outlast the ending of a given stressor can be viewed as metabolically disproportionate or otherwise contextually unnecessary and inappropriate. Visceral prediction errors of these types may be quantified by integrating laboratory stress reactivity testing with methods of exercise physiology, wherein changes in cardiovascular physiology that are in excess of oxygen consumption and metabolic requirements of a context can be computed (see Ginty et al., 2017; Gianaros and Jennings, under review).

The presumptive bases for visceral prediction errors may partly involve the resetting or modulation of homeostatic functions by substrates of the central autonomic network, allowing for context-dependent changes in visceral control via the autonomic nervous system. Visceral prediction errors underlying observable patterns of stress physiology may also involve insensitivity to interoceptive and visceral feedback as well (Ginty et al., 2017; Gianaros and Jennings, under review; see also Leder, part III,

chapter 5 of the present volume). For example, as a result of such insensitivity, the visceral feedback provided by baroreceptors about 'exaggerated' and stressor-evoked rises in blood pressure may not serve to minimize future visceral prediction errors that manifest as exaggerated stress reactivity. Moreover, interoceptive information from stressor-evoked changes in cardiovascular physiology (e.g., relayed by the baroreceptors) is capable of powerfully shaping the appraisal of threatening and painful information (Garfinkel and Critchley, 2016; see also Quadt, Garfinkel, and Critchley, this volume). Put simply, stressor-evoked changes in peripheral physiology do not happen in a vacuum, having 'bottom-up' effects on higher neural substrates. Open questions in this domain extend to other parameters of physiology beyond the cardiovascular system that change with stress (e.g., immune and neuroendocrine functions), as well as how visceral feedback from multiple physiological parameters are integrated by higher neural substrates to shape behavioral states as they unfold across contexts.

From interoception to interoceptive awareness

The multiple reciprocal links between interoception and psychological function, as highlighted above, do not necessarily imply a conscious awareness or intervention. However, several research strands across psychological sciences and cognitive neuroscience have recently focused on our ability to become aware of interoceptive states and the importance that such states of interoceptive awareness have for the awareness of the self and of others. Earlier psychological research has shown how higher levels of interoceptive accuracy, that is typically quantified in behavioral tasks that require participants to pay attention to interoceptive states such as heartbeats (Shandry, 1981), respiration (Daubenmier et al., 2013) or feelings of fullness and gastric sensitivity (Herbert, Muth, Pollatos, & Herbert, 2012) influence emotional processing. For example, higher levels of interoceptive accuracy are associated with more intense emotional experiences and better emotion-regulation (see Critchley & Harrison, 2013)

Capitalizing on such findings, more recent studies have expanded their focus to ask questions about the role that interoceptive awareness may play for body-representations (for reviews see Craig, 2009; Tsakiris, 2010). Historically, the perception of one's own body from the outside (e.g., self-recognition) and the perception of the body from within (e.g., of signals coming from the visceral organs) have largely been studied independently.

For example, the question of how the brain produces the experience of body-ownership has focused mainly on multisensory integration. In the Rubber Hand Illusion (RHI), one of the most influential experimental models of embodiment, watching a rubber hand being stroked synchronously with one's own unseen hand causes the rubber hand to be experienced as part of one's body (Botvinick & Cohen, 1998; Tsakiris, 2010). These results speak in favour of an exteroceptive model of the self, within which self-awareness is highly malleable, subject to the perception of the body from the outside. However, exteroceptive input represents only one set of channels of information available for body-awareness. We are also interoceptively aware of our body.

To address how interoceptive signals are integrated with exteroceptive signals to create an integrated sense of the bodily self, Tsakiris et al. (2011) measured and quantified Interoceptive Accuracy (IAcc) with the heartbeat counting task and compared this with the change in body-ownership caused by multisensory stimulation, using the RHI as a paradigmatic case of the exteroceptive self. Participants with lower IAcc

experienced a stronger illusory sense of body-ownership, suggesting that in the absence of accurate interoceptive representations one's model of self is predominantly exteroceptive. While others had shown how a change in the body-ownership during RHI affects homeostatic regulation (Moseley et al., 2008), we now had evidence showing that both the experience of body-ownership, and subsequent changes in homeostatic regulation, depend partly on levels of IAcc. Consistent with these behavioral findings, neuroimaging and neuropsychological observations on the critical role of the insular cortex for body-awareness support the view that the ways in which we perceive our body from the inside interact with our perception of the body from the outside. Right anterior insula activity correlates with performance in interoceptive accuracy tasks (Critchley et al., 2004). A rare single-case study shows that heartbeat awareness decreased after insular resection (Ronchi et al., 2015), and Couto et al. (2015) report impaired interoceptive awareness with insular cortical or white matter lesions. Right mid-posterior insula activity correlates with the body-ownership experienced during the Rubber Hand Illusion, a paradigm that uses exteroceptive input (e.g., vision and touch) to study, in a controlled way, the bodily self (Tsakiris, Hesse, Boy, Haggard, & Fink, 2007). This same area seems to be the critical lesion site for somatoparaphrenia – a striking loss

of body-ownership (Karnath & Baier, 2010). These findings suggest that the interoceptive and the exteroceptive representations of the body are integrated from the posterior to anterior subregions across the insular cortex (Farb, Segal, & Anderson, 2013; Simmons et al., 2013). Moreover, this integration appears to underpin the experience of my body as mine - an experience that is the hallmark of the bodily self (Gallagher, 2000).

Such approaches paved the way for a large number of psychophysiological and neuroimaging studies (Aspell et al., 2013; Blefari et al., 2017; Crucianelli, Krahé, Jenkinson, & Fotopoulou, 2017; Park et al., 2017; Ronchi et al., 2017; Schauder, Mash, Bryant, & Cascio, 2015; Sel, Azevedo, & Tsakiris, 2016; Shah, Catmur, & Bird, 2017; Suzuki, Garfinkel, Critchley, & Seth, 2013; Tajadura-Jiménez & Tsakiris, 2014) that corroborate the basic hypothesis about the crucial psychological role that interoception plays for self-awareness and awareness of other people. Across different domains, from emotion-processing (Dunn et al, 2010; Pollatos, Gramman & Schandry, 2007) to body-image (see Badoud & Tsakiris, 2017 for a review), and social cognition (Shah, Catmur & Bird, 2017), the representation that one has of her internal body seems to be

crucial for the representation of the "material me", as Sherrington would put it, in relation to others (Fotopoulou & Tsakiris, 2017).

Future perspectives

The complexity of the central autonomic network, its vast interconnectivity with other brain systems, and the broad functional impact of visceral afference, pose challenges to progress in the interoceptive canon. Although there may certainly be a place for studies of single interoceptive dimensions or measures, a full understanding will likely require the consideration of multiple parameters and physiological patterns, from a multi-system, multi-level interacting (top-down and bottom up) perspective. Thus, important directions for the future include a focus on multiple interoceptive dimensions, interdisciplinary perspectives (cognitive/behavioral, neural, physiological, etc.) and interactions among interoceptive processes and a broader range of affective-cognitive processes. An illustration of this point comes from the literature on autonomic specificity of emotions, and the role of visceral afference.

Consider Cannon's arguments against the James-Lange view, that: 1) visceral responses are too slow to underlie emotion; 2) similar visceral changes may occur across different emotions and even non-emotional states; 3) inducing autonomic responses does not necessarily invoke emotions; and 4) that autonomic denervations of various types do not prevent emotional reactions. There clearly is not a simple isomorphism between autonomic responses and emotions, but that really should not be expected—there are multiple determinants of emotion and multiple levels of organization in affective substrates and the central autonomic network. Emotions can be triggered cognitively, as well as from external stimuli and context. These may well have different patterns of activation within central networks. The arguments that visceral responses are too slow and that autonomic denervations do not eliminate emotions, would only be arguments against the view that visceral afference is the only determinant of emotion. We now know this not to be the case. Moreover, visceral afference is also likely to be 'fast' enough to exert influences along the lines of what James and Lange envisioned. Neurally mediated baroreflex influences on heart rate and blood pressure control, for example, happen within milliseconds. These influences extend to the processing of and

reactivity to affective and nociceptive stimuli on a heart-beat to heart-beat basis (Garfinkel and Critchley, 2016).

Canon's two remaining arguments, that autonomic arousal may not lead to emotional states and that similar autonomic responses may be associated with different emotions, are also not compelling. As noted above, the effects of visceral afference are likely to be varied and brain-state dependent (e.g. see Ibanez et al., Part II, chapter 3). A given pattern of visceral afference in one context (be that environmental, psychological, or neurophysiological) may well have quite distinct effects. How we perceive a stimulus or context is very much determined by expectations, goals, attentional focus, in the same way that classic visual illusions (e.g., the Boring, 1930; old woman/young woman illusion) depend on attentional focus, expectations, priming or other variables.

A given pattern of visceral afference, for example, may be functionally perceived, and have different outcomes depending on the context or neurobiological or neurobehavioral (brain) state. This has been termed the somatovisceral model of emotion (SAME) wherein the same pattern of visceral afference may be associated with different emotions (see

Cacioppo et al., 1992; Norman et al., 2014). As with research on interoception, there is consensus that research on interoceptive awareness must develop a wider and more grounded measurement model, a richer theoretical framework that is at the same time biologically plausible and psychologically meaningful, and a fuller characterization of the links between different interoceptive systems and across interoceptive and exteroceptive systems. This contextual and brain-state dependency needs to be considered in interpreting and understanding visceral afference and our awareness of it, across different fields, from basic research to clinical applications and from theoretical and computational perspectives. The chapters included in this volume intend to address at least some of these aims.

Footnotes

[1]"Wepropose the term 'autonomic nervous system,' for the sympathetic system and the allied nervous system of the cranial and sacral nerves, and for the local nervous system of the gut" (p. 270).

[2]Although some of these afferents run with parasympathetic and sympathetic efferents, it is not appropriate to consider them "parasympathetic" and "sympathetic" afferents (Freire-Maia & Azevedo,1990; Jänig & Habler, 1995). They are general visceral afferents that are not strictly coupled to an autonomic branch.

[3]There was no pre-surgical history of psychophathology. The patient elected the procedure to reduce excessive sweating, and to some extent, tis was achieved. However, as is common with ETS (Furlan et al., 2000), she did experience periodic "compensatory" sweating.

[4]Garcia et al. (2016) report minimal cognitive or socio-emotional deficits in a single case report after extensive vascular lesion damage, including the insular cortex. The authors, however, emphasize how unusual this case was, as there were also minimal disturbances in sensorimotor and other functions. The literature on disgust, especially, is quite variable, but Uddin et al. (2017), report consistent socio-emotional deficits with insular lesions, but they also emphasize the considerable functional heterogeneity in this brain region.

References

Adolfi, F., Couto, B., Richter, F., Decety, J., Lopez, J., Sigman, M., Manes, F. & Ibáñez, A. (2017). Convergence of interoception, emotion, and social cognition: A twofold fMRI meta-analysis and lesion approach. *Cortex*. 88, 124-142. doi: 10.1016/j.cortex.2016.12.019.

Allen, GV, et al. (1991), Organization of visceral and limbic connections in the insular cortex of the rat. *J Comp Neurol*. 311:1-16.

Annoni JM, Ptak R, Caldara-Schnetzer AS, Khateb A, Pollermann BZ. (2003). Decoupling of autonomic and cognitive emotional reactions after cerebellar stroke. *Ann Neurol*. 53:654-8.

Aspell, J. E., Heydrich, L., Marillier, G., Lavanchy, T., Herbelin, B., & Blanke, O. (2013). Turning Body and Self Inside Out: Visualized Heartbeats Alter Bodily Self-Consciousness and Tactile Perception. *Psychological Science*, *24*, 2445–2453. https://doi.org/10.1177/0956797613498395

Augustine, JR. (1996). Circuitry and functional aspects of the insular lobe in primates including humans. *Brain Res Rev*. 22:229-244.

Badoud D & Tsakiris M (2017) From the body's viscera to the body's image: Is there a link between interoception and body image concerns? *Neurosci Biobehav Rev.* 77:237-246. doi: 10.1016/j.neubiorev.2017.03.017. Barbas, H, Saha, S, Rempel-Clower, N, & Ghashghaei, T. (2003). Serial pathways from primate prefrontal cortex to autonomic areas may influence emotional expression. *BMC Neurosci*. 4, 25.

Barrett LF, Simmons WK. (2015) Interoceptive predictions in the brain. Nature Reviews Neuroscience.16:419-429.

Bear, MF, Connors, BW & Paradiso, MA. (2016). *Neuroscience: Exploring the Brain.* Philadelphia: Wolter Kluwer.

Benarroch, EE. (1993). The central autonomic network: Functionla organizqtion, dysfunction, and perspective. *Mayo Clnic Proc.* 68:988-1001.

Bernard, C. (1878). *Les Phénomènes de la Vie*. Paris: Balliere.

Berntson, GG, Bechara, A, Damasio, H, Tranel, D, Norman, GJ & Cacioppo JT. (2011). The insula and evaluative processes. *Psychol. Sci.* 22:80-86.

Blefari, M. L., Martuzzi, R., Salomon, R., Bello-Ruiz, J., Herbelin, B., Serino, A., & Blanke, O. (2017). Bilateral Rolandic operculum processing underlying heartbeat awareness reflects changes in bodily self-consciousness. *European Journal of Neuroscience*, *45*(10), 1300–1312. https://doi.org/10.1111/ejn.13567

Boring, EG (1930). A new ambiguous figure. *Am J Psychol*. 42:444.

Botvinick, M., & Cohen, J. (1998). Rubber hands "feel" touch that eyes see. *Nature*, *391*(February), 756. doi:10.1038/35784

Boucher, O., Rouleau, I., Lassonde, M., Lepore, F., Bouthillier, A. & Nguyen, D.K. (2015). Social information processing following resection of the insular cortex. *Neuropsychologia*. 71, 1-10. doi:10.1016/j.neuropsychologia.2015.03.008.

Broca, P. (1878) Anatomie comparée des circonvolutions cérébrales: le grande lobe limbique et la scissure limbique dans la série des mammifères. *Review D'Anthropology*.1:385–498.

Cacioppo, JT, Berntson, GG & Klein, DJ. (1992). What is an emotion? The role of somatovisceral afference, with special emphasis on somatovisceral "illusions". *Review of Personality and Social Psychology,* 14: 63-98.

Cameron, OG. (2002). *Visceral Sensory Neuroscience: Interoception*. Oxford: Oxford University Press.

Cannon, WB. (1927). The James-Lange theory of emotions: a critical examination and an alternative theory. *American Journal of Psychology,* 39:106-124.

Cannon, WB. (1931). Again, the James-Lange and the thalamic theory of emotion. *Psychological Review,* 38:281-295.

Cannon, WB. (1932/1939). *The Wisdom of the Body*. London: Kegan Paul, Trench, Trubner & Co.

Cechetto, DF & Saper, CB. (1990). Role of the cerebral cortex in autonomic function, in Loewy, AD & Spyer, KM (eds.) *Central Regulation of Autonomic Functions.* (pp 208-233). NY: Oxford University Press.

Chauhan, B, Mathias, CJ & Critchley HD. (2008). Autonomic contributions to empathy: evidence from patients with primary autonomic failure. *Auton Neurosci*. 140, 96-100.

Cogliano, R et al. (2012). Chronic somatoparaphrenia: A follow-up study on two clinical cases. *Cortex*, 48:758-767

Cohen S, Gianaros PJ, Manuck SB (2016). A stage model of stress and disease. Perspectives on Psychological Science, 11, 456-63.

Couto, B., Adolfi, F., Sedeño, L., Salles, A., Canales-Johnson, A., Alvarez-Abut, P., Garcia-Cordero, I., Pietto, M., Bekinschtein, T., Sigman, M.,

Manes, F. & Ibanez A. (2015). Disentangling interoception: insights from focal strokes affecting the perception of external and internal milieus. *Front Psychol*. 6, 503. doi: 10.3389/fpsyg.2015.00503

Craig, A. D. (2009). How do you feel-now? The anterior insula and human awareness. *Nature Reviews Neuroscience*, *10*, 59–70

Craig, AD. (2014). *How Do You Feel? An Interoceptive Moment with Your Neurobiological Self*. Princeton: Princeton University Press.

Critchley, HD. (2005). Neural mechanisms of autonomic, affective, and cognitive integration. *Journal of Comparative Neurology*. 493:154–166.

Critchley, H. D., & Harrison, N. A. (2013). Visceral influences on brain and behavior. *Neuron*, *77*, 624–38. ttps://doi.org/10.1016/j.neuron.2013.02.008

Critchley, HD, Mathias CJ & Dolan RJ. (2001). Neuroanatomical basis for first- and second-order representations of bodily states. *Nat Neurosci*. 4, 207-12.

Critchley, H. D., Wiens, S., Rotshtein, P., Ohman, A., Dolan, R. J., Öhman, A., & Dolan, R. J. (2004). Neural systems supporting interoceptive awareness. *Nature Neuroscience*, *7*(2), 189–195. https://doi.org/10.1038/nn1176

Crucianelli, L., Krahé, C., Jenkinson, P. M., & Fotopoulou, A. (Katerina). (2017). Interoceptive ingredients of body ownership: Affective touch and cardiac awareness in the rubber hand illusion. *Cortex*. https://doi.org/10.1016/j.cortex.2017.04.018

Daubenmier, J., Sze, J., Kerr, C. E., Kemeny, M. E., & Mehling, W. (2013). Follow your breath: respiratory interoceptive accuracy in experienced meditators. *Psychophysiology*, *50*(8), 777–89. https://doi.org/10.1111/psyp.12057

Dampney, RA. (2015). Central mechanisms regulating coordinated cardiovascular and respiratory function during stress and arousal. *Am J Physiol Regul Integr Comp Physiol*. 309, R429-43.

Dampney, R.A. (2017). Resetting of the Baroreflex Control of Sympathetic Vasomotor Activity during Natural Behaviors: Description and Conceptual Model of Central Mechanisms. Front. Neurosci., 15 August 2017. https://doi.org/10.3389/fnins.2017.00461

Dum RP, Levinthal DJ, Strick PL. (2016). Motor, cognitive, and affective areas of the cerebral cortex influence the adrenal medulla. Proc Natl Acad Sci, 113(35):9922-7.

Dunn, B. D., Galton, H. C., Morgan, R., Evans, D., Oliver, C., Meyer, M., … Dalgleish, T. (2010). Listening to your heart. How interoception shapes emotion experience and intuitive decision making. *Psychological Science*, *21*(12), 1835–1844. https://doi.org/10.1177/0956797610389191

Dworkin, BR. (1993). *Learning and Physiological Regulation* (The John D. and Catherine T. MacArthur Foundation Series on Mental Health). Chicago: University of Chicago Press.

Farb, N. a S., Segal, Z. V., & Anderson, A. K. (2013). Attentional modulation of primary interoceptive and exteroceptive cortices. *Cerebral Cortex*, *23*(1), 114–126. https://doi.org/10.1093/cercor/bhr385

Fisher JP, Young CN, Fadel PJ. (2015). Autonomic adjustments to exercise in humans. Comprehensive Physiology. 5:475-512.

Foley, JO & DuBois, FS. (1937). Quantitative studies of the vagus nerve in the cat. I. The ratio of sensory to motor fibers. *J. Comp. Neurol.* 67:49-64.

Fotopoulou A & Tsakiris M (2017) Mentalizing homeostasis: the social origins of interoceptive inference. *Neuropsychoanalysis*, 19, 3-28

Freire-Maia L. & Azevedo, AD. (1990. The Autonomic Nervous System is not a Purely Efferent System. Medical Hyporheses 32:91-99.

Furlan AD et al. (2000). Are we paying a high price for surgical sympathectomy? A systematic literature review of late complications. *J Pain*, 1:245-57.

Gandola, M. et al. (2012). An anatomical account of somatoparaphrenia. *Cortex*, 48:1165-1178.

Gallagher, S. (2000). Philosophical conceptions of the self: Implications for cognitive science. *Trends in Cognitive Sciences*, *4*, 14–21.

Garfinkel SN, Critchley HD. (2016). Threat and the body: How the heart supports fear processing. *Trends in Cognitive Science*. 20, 34-46.

García, A.M., Sedeño, I., Murcia, E.H., Couto, B. & Ibáñez, A. (2016). A Lesion-Proof Brain? Multidimensional Sensorimotor, Cognitive, and Socio-Affective Preservation Despite Extensive Damage in a Stroke Patient. *Front Aging Neurosci*. 8, 335.

Gasquoine, P.G. (2014). Contributions of the insula to cognition and emotion. *Neuropsychol Rev*. 24, 77-87.

Gianaros PJ, Jennings JR (resubmitted). Host in the machine: A neurobiological perspective on psychological stress and cardiovascular disease. American Psychologist.

Gianaros PJ, Onyewuenyi IC, Sheu LK, Christie IC, Critchley HD. (2012). Brain systems for baroreflex suppression during stress in humans. Human Brain Mapping. 2012;33:1700-1716.

Gianaros PJ, Wager TD. (2015). Brain-body pathways linking psychological stress and physical health. *Current Directions in Psychological Science*. 24:313-321.

Ginty AT, Kraynak TE, Fisher JP, Gianaros PG. Cardiovascular and autonomic reactivity to psychological stress: Neurophysiological substrates and links to cardiovascular disease. Autonomic Neuroscience. 2017. doi: 10.1016/j.autneu.2017.03.003

Goldstein, DS. (2012). Neurocardiology. *Cardiovascular Therapeutics* 30 e89–e106.

Gotink, RA, Meijboom, R, Vernooij, MW, Smits, M & Hunink, MG. (2016). 8-week Mindfulness Based Stress Reduction induces brain changes similar

to traditional long-term meditation practice - A systematic review. *Brain Cogn*. 108:32-41.

Heims, HC, Critchley, HD, Martin, NH, Jäger, HR, Mathias, CJ & Cipolotti, L. (2006). Cognitive functioning in orthostatic hypotension due to pure autonomic failure. *Clin Auton Res*. 16:113-20.

Heinbecker, P & O'Leary, J. (1933). The mammalian vagus nerve—afunctional and histological study. *Amer. J. Physiology*, 106: 623-646.

Herbert, B. M., Muth, E. R., Pollatos, O., & Herbert, C. (2012). Interoception across Modalities: On the Relationship between Cardiac Awareness and the Sensitivity for Gastric Functions. *PLoS ONE*, 7(5), e36646.

Hernández, SE, Suero, J, Barros, A, González-Mora, JL & Rubia, K. (2016). Increased Grey Matter Associated with Long-Term Sahaja Yoga Meditation: A Voxel-Based Morphometry Study. *PLoS One*. 11(3).

Hess, WR. (1954). *Diencephalon: Autonomic and extrapyramidal functions*. New York: Grune & Stratton.

Jackson, JH. (1884). On the evolution and dissolution of the nervous system. Croonian Lectures 3, 4 and 5 to the Royal Society of London. *Lancet,* 1:555–739.

James, W.. (1984). What is emotion. *Mind.* 9:188-205.

Jänig W., & Häbler, H.-J. (1995). Visceral-autonomic integration. In G.F. Gebhart (Ed.). Visceral pain. Progress in pain research and management, vol. 4 (pp. 31 l-348). Seattle: IASP Press.

Jänig, W., & Morrison, J.F.B. (1986). Functional properties of spinal visceral afferents supplying abdominal and pelvic organs with special emphasis on visceral nociception. In F. Cervero and J.F.B. Morrison (Eds.). Visceral sensation. Progress in Brain Research, 67, 87- 114.

Frank, S, Kullmann, S & Veit, R. (2013). Food related processes in the insular cortex. *Front Hum Neurosci*. 7:499.

Farrer, C et al. (2003). Modulating the experience of agency: a positron emission tomography study. *Neuroimage*. 18:324-33.

Karnath, H.-O., & Baier, B. (2010). Right insula for our sense of limb ownership and self-awareness of actions. *Brain Structure and Function*, *214*(5–6), 411–417. https://doi.org/10.1007/s00429-010-0250-4

Lange, CG. (1885). Om Sindsbevaegelser. et psycho. *Frysiolog. studie*. Copenhagen: KrØnar.

Laneri, D, Schuster, V, Dietsche, B, Jansen, A, Ott, U & Sommer, J. (2016). Effects of Long-Term Mindfulness Meditation on Brain's White Matter Microstructure and its Aging. *Front Aging Neurosci*. 7:254.

Langley, JN. (1898). On the Union of Cranial Autonomic (Visceral) Fibres with the Nerve Cells of the Superior Cervical Ganglion. *J Physiol*. 23:240-270.

Langley, JN. (1903) The autonomic nervous system. *Brain*. 26:1-26.

Loewy, AD. (1991) Forebrain nuclei involved in autonomic control. *Progress in Brain Research*. 87: 253-268.

Maffei, A, Haley, M & Fontanini, A. (2012). Neural processing of gustatory information in insular circuits. *Curr Opin Neurobiol*.22:709–716.

Maffei, AM, Haley, M, Fontanini, A & Miranda, MI. (2012). Taste and odor recognition memory: the emotional flavor of life. *Review of Neuroscience*. 23:481-99.

Mailis A & Furlan A (2003). Sympathectomy for neuropathic pain. *Cochrane Database Syst Rev.* (2):CD002918.

Mazzola, L, Isnard, J, Peyron, R & Mauguière, F. (2012). Stimulation of the human cortex and the experience of pain: Wilder Penfield's observations revisited. *Brain,* 135; 631-640.

McEwen, BS. (2012). Brain on stress: how the social environment gets under the skin. Proc Natl Acad Sci USA. 16;109 Suppl 2:17180-5.

Montavont, A, Mauguière, F, Mazzola, L, Garcia-Larrea, L, Catenoix, H, Ryvlin, P & Isnard J. (2015). On the origin of painful somatosensory seizures. *Neurology*, 84:594-601.

Moro, V et al. (2016). Motor versus body awareness: Voxel-based lesion analysis in anosognosia for hemiplegia and somatoparaphrenia following right hemisphere stroke. *Cortex*, 83:62-77.

Moseley, G. L., Olthof, N., Venema, A., Don, S., Wijers, M., Gallace, A., & Spence, C. (2008). Psychologically induced cooling of a specific body part caused by the illusory ownership of an artificial counterpart. *Proceedings of the National Academy of Sciences of the United States of America*, *105*(35), 13169–73. https://doi.org/10.1073/pnas.0803768105

Myers, B. (2017). Corticolimbic regulation of cardiovascular responses to stress. *Physiol Behav*. 172:49-59.

Neafsey, EJ. (1990). Prefrontal cortical control of the autonomic nervous system: anatomical and physiological observations. *Prog Brain Res.* 85:147-165.

Nieuwenhuys, R. (2012). The insular cortex: a review. *Prog Brain Res*,195:123-63.

Norman, GJ, Berntson, GG & Cacioppo, JT. (2014). Emotion, Somatovisceral Afference and Autonomic Regulation. *Emotion Review,* 6:113-123.

Obrist PA. (1981). Cardiovascular Psychophysiology: A Perspective. New York, NY: Plenum Press.

Oppenheimer, SM & Cechetto, DF. (2016). Insular cortex and the regulation of cardiac function. *Comphrehensive Physiology*, 6:1081-133.

Park, H.-D., Bernasconi, F., Salomon, R., Tallon-Baudry, C., Spinelli, L., Seeck, M., … Blanke, O. (2017). Neural Sources and Underlying Mechanisms of Neural Responses to Heartbeats, and their Role in Bodily Self-consciousness: An Intracranial EEG Study. *Cerebral Cortex*, *116*, 1–14. https://doi.org/10.1093/cercor/bhx136

Penfield, W & Faulk, ME. (1955). The insula; further observations on its function. *Brain*. 78:445-70.

Penfield, W & Jasper, H. (1954). *Epilepsy and the functional anatomy of the human brain*. NY: Little, Brown & Co.

Pollatos, O., Gramann, K., & Schandry, R. (2007). Neural systems connecting interoceptive awareness and feelings. *Human Brain Mapping*, *28*(1), 9–18. https://doi.org/10.1002/hbm.20258

Ranson, SW, Kabat, H & Magoun, HW. (1935). Autonomic responses to electrical stimulation of hypothalamus, preoptic region and septum. *Arch NeurPsych.* 33: 467-477.

Rolls, ET. (2015). Taste, olfactory, and food reward value processing in the brain. *Prog Neurobiol*. 127-128:64-90.

Ronchi, R., Bello-Ruiz, J., Lukowska, M., Herbelin, B., Cabrilo, I., Schaller, K., & Blanke, O. (2015). Right insular damage decreases heartbeat awareness and alters cardio-visual effects on bodily self-consciousness.

Neuropsychologia, *70*, 11–20.

https://doi.org/10.1016/j.neuropsychologia.2015.02.010

Ronchi, R., Bernasconi, F., Pfeiffer, C., Bello-Ruiz, J., Kaliuzhna, M., &

Blanke, O. (2017). Interoceptive signals impact visual processing: Cardiac

modulation of visual body perception. *NeuroImage*, *158*, 176–185.

https://doi.org/10.1016/j.neuroimage.2017.06.064

Saive, A-L, Royet, J-P & Plailly, J. (2014). A review on the neural bases of

episodic odor memory: from laboratory-based to autobiographical

approaches. *Frontiers in Behavioral Neuroscience*. 8: 240.

Saper, CB. (2002). The Central Autonomic Nervous System: Conscious

Visceral Perception and Autonomic Pattern Generation. *Annual Review of

Neuroscience.* 25:433-469.

Schandry, R. (1981). Heart beat perception and emotional experience.

Psychophysiology, *18*(4), 483–488.

Schauder, K. B., Mash, L. E., Bryant, L. K., & Cascio, C. J. (2015). Interoceptive ability and body awareness in autism spectrum disorder. *Journal of Experimental Child Psychology*, *131*, 193–200. https://doi.org/10.1016/j.jecp.2014.11.002

Schulkin, J. (2003). *Rethinking homeostasis : allostatic regulation in physiology and pathophysiology*. Cambridge, MA: MIT Press.

Sel, A., Azevedo, R. T., & Tsakiris, M. (2016). Heartfelt Self: Cardio-Visual Integration Affects Self-Face Recognition and Interoceptive Cortical Processing. *Cerebral Cortex*. https://doi.org/10.1093/cercor/bhw296

Shah P, Catmur C, Bird G. (2017) From heart to mind: Linking interoception, emotion, and theory of mind. Cortex. Apr 28. pii: S0010-9452(17)30060-6. doi: 10.1016/j.cortex.2017.02.010

Sherrington, CS. (1900). Experiments on the value of vascular and visceral factors for the genesis of emotion. *Proceedings of the Royal Society (London) B,* 66:390-403.

Shoemaker, JK & Goswami, R. (2015). Forebrain neurocircuitry associated with human reflex cardiovascular control. *Front Physiol.* 6, article 240.

Simmons, W. K., Avery, J. a., Barcalow, J. C., Bodurka, J., Drevets, W. C., & Bellgowan, P. (2013). Keeping the body in mind: Insula functional organization and functional connectivity integrate interoceptive, exteroceptive, and emotional awareness. *Human Brain Mapping*, *34*, 2944–2958. https://doi.org/10.1002/hbm.22113

Soudry, YC Lemogne, D Malinvaud, SM Consoli & Bonfils, P. (2011). Olfactory system and emotion: common substrates. *European Annals of Otorhinolaryngol Head Neck Dis.* 128:18-23.

Squire, L, Berg, D, Bloom, FE, du Lac Anirvan, S, Nicholas, G & Spitzer, C. (2012). *Fundamental Neuroscience*. Oxford: Elsevier.

Sterling, P & Eyer, J (1988). *Allostasis: A new paradigm to explain arousal pathology*. In Fisher S & Reason JT (2003). *Handbook of life stress, cognition, and health.* NY: Wiley.

Strigo, IA & Craig, AD. (2016). Interoception, homeostatic emotions and sympathovagal balance. *Philos Trans R Soc Lond B Biol Sci*. 371:1708.

Suzuki, K., Garfinkel, S. N., Critchley, H. D., & Seth, A. K. (2013). Multisensory integration across exteroceptive and interoceptive domains modulates self-experience in the rubber-hand illusion. *Neuropsychologia*, *51*, 2909–2917. https://doi.org/10.1016/j.neuropsychologia.2013.08.014

Tajadura-Jiménez, A., & Tsakiris, M. (2014). Balancing the "inner" and the "outer" self: Interoceptive sensitivity modulates self-other boundaries. *Journal of Experimental Psychology: General*, *143*(2). https://doi.org/10.1037/a0033171

Tsakiris, M., Hesse, M. D., Boy, C., Haggard, P., & Fink, G. R. (2007). Neural signatures of body ownership: A sensory network for bodily self-consciousness. *Cerebral Cortex*, *17*, 2235–2244.

Tsakiris, M. (2010). My body in the brain: A neurocognitive model of body-ownership. *Neuropsychologia*, *48*(3), 703–712. https://doi.org/10.1016/j.neuropsychologia.2009.09.034

Tsakiris, M., Tajadura-Jiménez, A., & Costantini, M. (2011). Just a heartbeat away from one's body: interoceptive sensitivity predicts malleability of body-representations. *Proceedings. Biological Sciences / The Royal Society*, *278*, 2470–2476. https://doi.org/10.1098/rspb.2010.2547

Tsakiris, M & Critchley, H. (2016a). Interoception beyond homeostasis: affect, cognition and mental health. *Philos Trans R Soc Lond B Biol Sci*. 371:1-6.

Tsakiris, M & Critchley, H. (Eds.) (2016b). Theme issue 'Interoception beyond homeostasis: affect, cognition and mental health'. *Philos Trans R Soc Lond B Biol Sci*. 371, issue 1708.

Uddin, L.Q., Nomi, J.S., Hébert-Seropian, B., Ghaziri, J. & Boucher O. (2017). Structure and Function of the Human Insula. J Clin Neurophysiol. 34, 300-306. doi: 10.1097/WNP.0000000000000377.

Yates, BJ & Stocker, SD. (1998). Integration of somatic and visceral inputs by the brainstem: functional considerations. *Exp Brain Res*. 119:269-75.

Figure Legends

Figure 1. Walter B. Cannon with Ivan Pavlov at the 1929 International Physiological Congress. Photograph reproduced with the acquiescence of the curator (*Harvard Medical Library in the Francis A. Countway Library of Medicine).*