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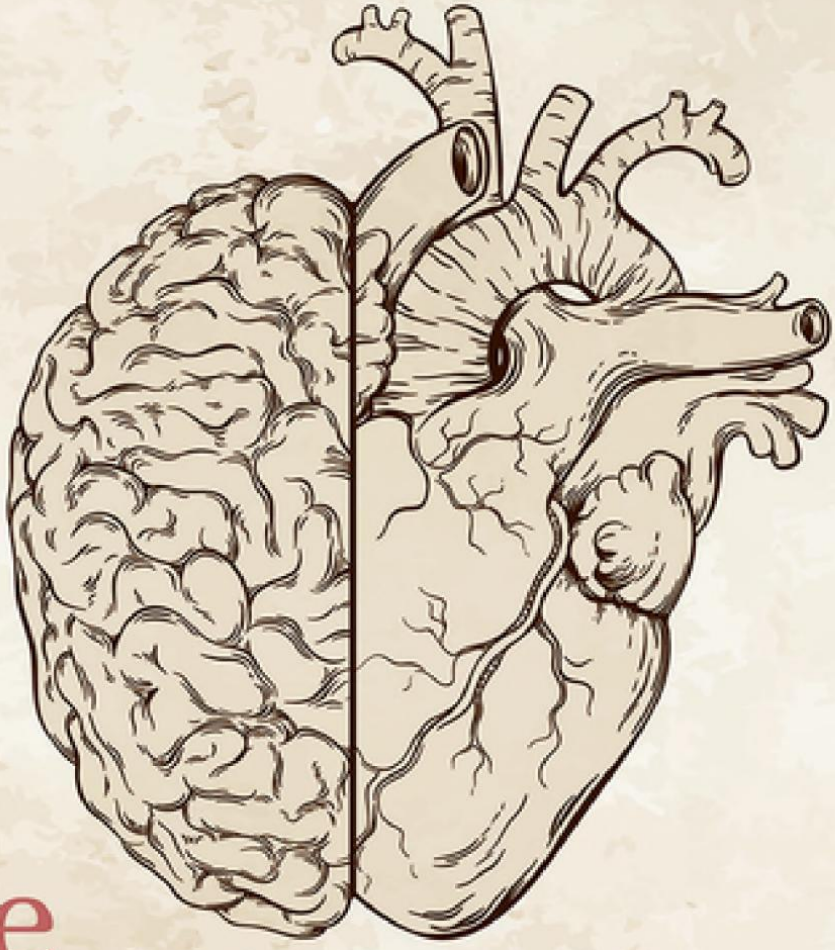

The Interoceptive Mind

From homeostasis to awareness

EDITED BY

Manos Tsakiris & Helena De Preester

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PART I

Introduction

Chapter 1

Interoception and the autonomic nervous system: Bottom-up meets top-down

Gary G. Berntson, Peter J. Gianaros, and Manos Tsakiris

1.1 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 in this chapter 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 and tissues 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 blood vessels) originating 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 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 later in this chapter, 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 & Critchley, 2016a; see also the entire Theme issue, Tsakiris & 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 (functional MRI) 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).

1.2 **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 (Bernard, 1878). Walter Cannon, chair of the Department of Physiology at Harvard around the turn of the twentieth 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, Levinthal, & Strick, 2016; Neafsey, 1990).

In retrospect, this misconception is also somewhat surprising in view of the work of Cannon's friend, contemporary, and Nobel Laureate, Ivan Pavlov (see Figure 1.1). 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

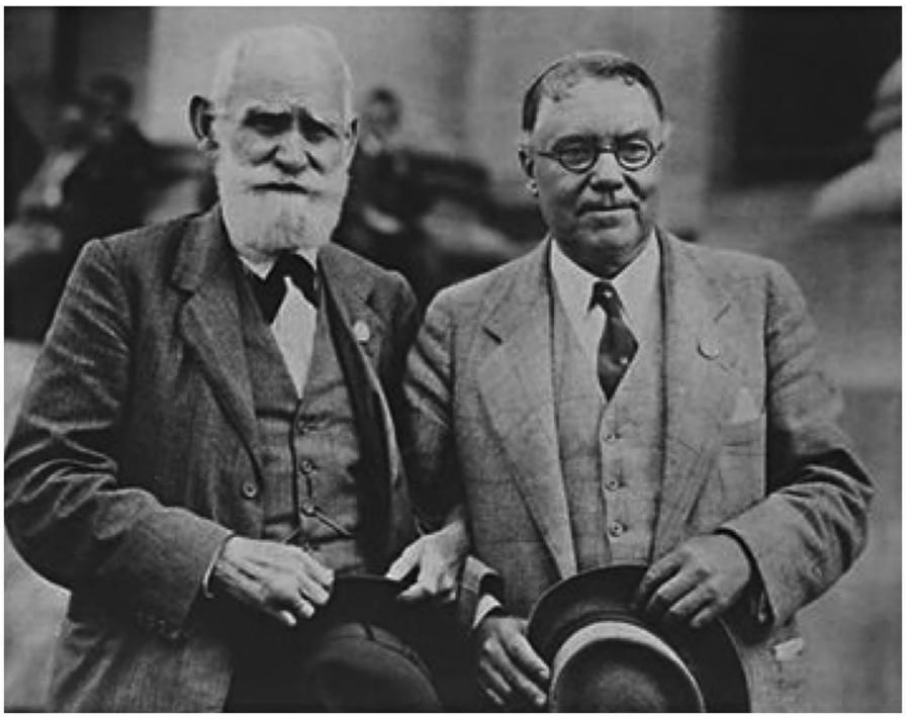

Figure 1.1 Walter B. Cannon with Ivan Pavlov at the 1929 International Physiological Congress. Photograph reproduced with the acquiescence of the curator (Harvard Medical Library in the Francis A. Countway Library of Medicine).

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 elicited by stimulation of 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, Kabat, & Magoun, 1935). The Canadian neurosurgeon, Wilder Penfield, also reported autonomic responses to cortical stimulation in conscious human patients (Penfield & Jasper, 1954). At this point, we recognize a broad central autonomic network comprising 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, skeletomotor, 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

[1] "We propose 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 & Häbler, 1995). They are general visceral afferents that are not strictly coupled to an autonomic branch.

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. However, it is now recognized that visceral afferents in fact outnumber efferents. Additionally, it was argued that (a) visceral responses are too slow to underlie emotion; (b) similar visceral changes may occur across different emotions and even non-emotional states; (c) inducing autonomic responses does not necessarily invoke emotions; and (d) 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 article 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, Cacioppo, & Bosch, 2016; Norman, Berntson, & Cacioppo, 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, Berntson, & Klein, 1992).

1.3 **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, filming never happened:

> I handed the story back to the producer when it became clear that I could not work the script (kept repeating the same scenes), as I was able to keep it all in my head for only about 3 pages—few

> minutes, and no amount of colour coordinated storylines and Post-It notes were 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 led 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 (she was 39 years old 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, Mailis, & Papagapious, 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 in section 1.4.2.

1.4 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

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

motivation, including the prefrontal cortex, the cingulate cortex, and the amygdala (Allen et al., 1991; Augustine, 1996; Nieuwenhuys, 2012; Oppenheimer & 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 & Critchley, 2016a), and anomalies in insular function are associated with a wide range of cognitive, emotional, and behavioral disturbances (Gasquoine, 2014).

1.4.1 Special visceral afferents: The chemical senses—Olfaction and gustation

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*) because 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 behavioral 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, Royet, & Plailly, 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 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, Kullmann, & Veit, 2013; Maffei, Haley, & Fontanini, 2012).

1.4.2 General visceral afferents

As is the case with gustatory afferents, all GVAs in cranial nerves project to the 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; Penfield & Faulk, 1955). In addition to cranial nerves, GVAs 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 twenty-first 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 textbook on neuroscience, Bear, Connors, and Paradiso assert that the "spinothalamic pathway is the major route by which pain and temperature information ascend to the cerebral cortex" (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, 2014; 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; Penfield & Faulk; 1955). Moreover, surgeons do not extirpate the somatosensory cortex for pain syndromes. In contrast, however, Mazzola and colleagues (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 et al., 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 & Critchley, 2016a). 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, Nomi, & Hébert-Seropian, 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 & Critchley, 2016a, b; see also Chapters 2, 3, and 16 in the present volume). Thus, insula activation is correlated with the sense of body ownership and agency (Farrer, Franck, & Georgieff, 2003; Tsakiris et al., 2007). 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 & Baier, 2010; Moro et al., 2016).

These findings and further results addressed in the present volume indicate that visceral afferent input to the insula appears to be critical in cognitive and emotional processes.

[4] Garcia and colleagues (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 and colleagues (2017) report consistent socio-emotional deficits with insular lesions, but they also emphasize the considerable functional heterogeneity in this brain region.

However, 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, Mathias, & Critchley, 2008; Critchley, Mathias, & Dolan, 2001; Tsakiris 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 and colleagues (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; Laneri et al., 2016).

1.5 Current applications and implications

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 hardwired 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, Cacioppo, & Bosch, 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 and Eyer (1988) and later Schulkin (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. However, deviations from homeostasis may not always entail simply an altered setpoint level. Berntson, Cacioppo, and Bosch (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 long-standing attention because of their presumptive relationships with aspects of physical and mental health across the lifespan (Cohen , Gianaros, & 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, Kraynak, Fisher,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 non-human 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 & Wager, 2015). To elaborate, stressors are thought to engage higher neural substrates of the CAN, including the insula and anterior cingulate cortex (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 most 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 & Jennings, 2018). 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 & Simmons, 2015).

Understood in this way, "mismatches" 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 40 mmHg 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 & Jennings, 2018).

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 & Jennings, 2018; see also Chapter 17 in 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 & Critchley, 2016; see also Chapter 7 in 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.

1.6 From interoception to interoceptive awareness

The multiple reciprocal links between interoception and psychological function, as highlighted in the preceding sections, 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 (Schandry, 1981), respiration (Daubenmier et al., 2013), or feelings of fullness and gastric sensitivity (Herbert et al., 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 favor 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, Tajadura-Jiménez, and Costantini (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 and colleagues (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 et al., 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 et al., 2017; Park et al., 2017; Ronchi et al., 2017; Schauder et al., 2015; Sel, Azevedo, & Tsakiris, 2016; Shah, Catmur, & Bird, 2017; Suzuki et al., 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 (see also Chapter 2 in the present volume). Across different domains, from emotion processing (Dunn et al., 2010; Pollatos et al. 2007) to body image (see Badoud & Tsakiris, 2017 for a review), and social cognition (Shah et al. 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).

1.7 Future perspectives

The complexity of the central autonomic network, its vast interconnectivity with other brain systems, and the broad functional impact of visceral afference all 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 is most likely to require the consideration of multiple parameters and physiological patterns, from a multisystem, 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: (a) visceral responses are too slow to underlie emotion; (b) similar visceral changes may occur across different emotions and even non-emotional states; (c) inducing autonomic responses does not necessarily invoke emotions; and (d) 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 heartbeat-to-heartbeat 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 earlier, the effects of visceral afference are likely to be varied and brain-state dependent (e.g. see also Chapter 10 in the present volume). 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, and attentional focus, in the same way that classic visual illusions (e.g. the old woman/young woman illusion; Boring, 1930) 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.

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