Feature Review

Visceral Signals Shape Brain Dynamics and Cognition

Damiano Azzalini,1,2 Ignacio Rebollo,1,2 and Catherine Tallon-Baudry1,*

Most research in cognitive neuroscience explores how external stimuli are processed by the brain. However, the brain also receives input from the internal body. We discuss here how the heart and gastrointestinal (GI) tract intrinsically generate their own electrical activity, thereby continuously sending information to the brain. These ongoing ascending signals actively shape brain dynamics at rest, complementing canonical resting-state networks (RSNs). Cardiac signals also influence the processing of external sensory information and the production of spontaneous, internal cognition. These findings are discussed in relation to interpretative frameworks regarding the functional role of visceral inputs. This active field of research offers a unique opportunity to draw new theories blurring the border between cognition, emotion, and consciousness, as well as between mind and body.

A Paradigm Shift in Cognitive Neuroscience

‘The brain is bombarded by information from the environment.’ This sentence, in one form or another, acts as an introduction to many textbooks and articles about perception and cognition (e.g., [1]). Although the internal environment is sometimes mentioned, the vast majority of the experimental work pertains to the processing of external stimuli. This reflects the dominant paradigm in cognitive neuroscience, where an agent collects information from the external environment via the senses and then reacts to this environment by producing actions (Figure 1A). By studying the brain, cognitive neuroscience has been highly successful at providing mechanistic explanations of behavior and at revealing the existence of hidden rules and variables, such as for instance the reward prediction error [2]. In the following we review extensions of this paradigm that include the interplay between the brain and the internal bodily environment (Figure 1B) to account for the neural implementation of cognition. More specifically, we focus on the heart and the gastrointestinal (GI) tract (see Glossary), and refer the reader to [3] for a comprehensive review of other types of somatic influences, including notably humoral and immune factors.

There are several reasons why cardiac and GI inputs might influence brain dynamics and cognition. The first distinctive feature of these two organs is that they generate their own intrinsic oscillatory electrical activity, even when disconnected from the brain, from the first weeks of gestation until death. We will detail later the intrinsic properties of the heart and the GI tract – but consider an isolated heart in a vat, waiting to be transplanted: it is beating. The heart thus differs from respiration, for instance [4]. A respiratory system disconnected from the brain is inert, because breathing commands are generated in the central nervous system (CNS). By contrast, both the heart and the GI tract can be considered as intrinsic oscillators that continuously send information to the brain. Visceral signals can thus be considered as stimuli that influence spontaneous brain dynamics. Second, cardiac and GI signals are characterized by intrinsic time constants in the sub-second (heart) to 20 s range (stomach), compatible with the timescale of cognition. Importantly, these signals reach not only brainstem nuclei but also many subcortical and cortical regions involved in cognitive tasks. Last but not least, monitoring internal visceral variables is a

Highlights

Visceral signals automatically contribute to shaping spontaneous large-scale brain dynamics, even when not consciously experienced. To what extent ascending visceral signals can be consciously perceived remains a matter of debate.

Neural and behavioral responses to external stimuli can be influenced by temporal contingencies between heartbeats and stimuli.

Beyond temporal contingencies, the transient neural response evoked by each heartbeat plays a role in cognitive functions that are usually studied separately, such as emotion, self-related cognition, and also subjective visual perception, calling for new theoretical perspectives.

Neural responses to heartbeats may be involved in the generation of the unified viewpoint of consciousness.
core function of the CNS, and the drive behind many life-sustaining behaviors that are tightly related to high-level sensory and cognitive functions. For instance the basic behavior of searching for food is motivated by internal states such as hunger, and requires visual search, action planning, navigation, and learning and memory.

Given all these features, cardiac and GI signals stand out as a continuous source of information that may influence both brain dynamics and high-level cognition. However, experimental research has so far mostly focused on descending influences from brain to heart, analyzing in particular how pain, stress, physical effort, and emotion affect heart rate or heart-rate variability (HRV). In this article we will focus on ascending pathways from viscera to brain, their impact on resting-state brain dynamics, and their influence not only on emotions but also on perception and cognition.

The potential role of visceral signals in emotions, perception, and cognition is thought to originate from a common low-level function, homeostatic/allostatic regulation, that would have been harnessed by evolution to develop other, higher-level processes [5]. Homeostasis, a concept
identified by Claude Bernard in the 19th century, refers to the automatic adjustment of physiological variables within a given range. More relevant for cognition, allostatic [5–7] is a process that also aims at physiological stability, but that does so by activating physiological systems in anticipation to bodily needs, as for instance when preparing the body for physical effort. The best-known example of an allostatic regulation is the production of saliva by Pavlov’s dog in response to a sound that the dog has learned to associate with food presentation. Other types of allostatic regulation result in adjustments of the cardiovascular system, for example in situations involving novelty, threat, and stress, or physical effort, with potential long-term consequences on health [8]. Allostatic regulations have been most often studied from the perspective of a descending control from brain to body, for instance a change in heart rate induced by a preparatory cue, and related to arousal. However, ascending inputs are required to inform the brain about current bodily states, as stated for instance in the recent reformulation of allostatic regulations in the predictive coding framework [9–13], where the brain constantly updates an internal model of the likely causes of inputs [14,15].

We begin this article by mapping the theoretical landscape on the putative functional roles of visceral inputs beyond allostatic regulations, and then present the basic physiology of cardiac and gastric signals and ascending anatomical pathways. The remainder of the review is devoted to experimental studies showing the impact of cardiac and gastric signals on spontaneous brain activity, and the different ways cardiac signals influence perception, emotion, cognition, and consciousness.

Mapping the Theoretical Landscape

What could be the functional roles of visceral inputs? Different proposals have been formulated, tapping onto domains ranging from emotions, to bodily self, to first-person perspective.

Emotions

Bodily signals, and in particular visceral signals, have long been associated with emotions. We tend to spontaneously associate different emotions with different combinations of bodily regions in a stereotypical manner, as recently shown in a set of elegant behavioral experiments [16,17]. However, the causal role of visceral signals in the generation of emotions is controversial. To briefly summarize a century-old debate, some [18,19] hold that subjective emotional feelings are consequences of bodily changes that are automatically triggered by emotional stimuli, whereas for others [20] it is the emotion that drives bodily changes. The various models of affective appraisal [21,22] leave open the possibility that changes in bodily states are included, among many other components, in affective responses. It has been suggested [23,24] that visceral signals, and more generally the sense of the physiological state of the body, are integrated with sensory and cognitive inputs in the insula to form a ‘global emotional moment’. In another proposal [25], the self derives from ‘primordial feelings’ that are related to actual or mentally simulated changes in the body. The self here would be directly grounded in the subjective experience of emotions and their associated visceral states, and further enriched by perception and cognition (Figure 1C). Note that all those proposals link the emotional experience to ‘changes’ (actual, simulated or predicted) in bodily states and/or arousal.

Multisensory Integration and Bodily Self

Another line of proposals refers to the notion of the bodily self, viewed as a multisensory construct (Figure 1D) where tactile, proprioceptive, vestibular, and visceral signals are combined to define the sense of body location in space and the sense of body ownership [9,26]. The relative weight given to visceral inputs, compared with other sources of bodily information, varies from moderate, taking into account existing experimental evidence [26], to potentially important, in theoretical proposals linking active inference, body ownership and visceral signals [9,27]. Because the
temporal coincidence between inputs is a key feature of multisensory integration, this hypothesis predicts that the relative timings of visceral and external signals should be relevant.

First-Person Perspective
Our own position is that the neural monitoring of cardiac and GI inputs plays a key role in the generation of first-person perspective by creating a subject-centered frame of reference [28,29]. First-person perspective refers to the unique bodily-centered viewpoint that we have on the environment [30,31] or on our own mental life. It pertains to the unity of consciousness and provides the intrinsic ‘mineness’ of conscious experience [32]. The existence of first-person perspective is often taken for granted (e.g.,[33]), probably because, if there is a perspective at all, then it is mine because it happens in my brain [29]. Nevertheless, a great deal of information processing in the brain is unconscious and thus, by definition, is devoid of first-person perspective – a mechanism explaining how first-person perspective is generated thus becomes necessary.

How a unique viewpoint can emerge is not yet known. Information is expressed in the brain in sensory and cognitive maps, each of which has its own frame of reference, or coordinate system – gaze-centered, head-centered, etc. [34–36]. The expression of information in different frames of reference is also a general feature of cognitive maps [37–40]. Despite the multiplicity of coordinate systems in which information is encoded, the conscious experience of the external world and of inner mental life feels unified, as if experienced from a single point of view. The existence of a common input to different maps could facilitate the alignment and coordination of different frames of reference by providing a common reference point. Because visceral signals are constantly present and distributed across a large number of cortical and subcortical areas, they could provide such an input (Figure 1E) and hence help in binding those maps together into the integrated viewpoint of first-person perspective. In this view, visceral signals would play a role not only in emotions and bodily self but also more generally in conscious perception and cognition (Figure 1F).

Common Features and Differences between Theoretical Perspectives
The different perspectives discussed here share common features, and are related to one another. The first-person perspective account can encompass the proposals related to both emotions and bodily self because both are necessarily experienced from the first-person perspective. In addition, the viewpoint from which we experience the world originates from body location, an important component of the bodily self [30]. Finally, the sense of body ownership based on multisensory integration of proprioceptive and vestibular signals probably requires the coordination of different frames of reference, as hypothesized in the first-person perspective account.

However, there are also differences. In the first-person perspective view, and to a lesser extent in the multisensory integration account, visceral state does not matter per se (e.g., whether the heart is beating rapidly or slowly) provided that the viscera send ascending signals. By contrast, emotion-related theories postulate that visceral states directly contribute to emotional feelings. Furthermore, the three proposals target three different aspects of mental life: emotions, bodily self, and subjective experience. Finally, the different accounts use different levels of descriptions and propose different mechanisms: convergence in the insula, multisensory integration, or generation of a subject-centered frame of reference. Before reviewing experimental evidence on the functional role of visceral inputs, it is worth reviewing the known facts – and the many unknowns – about the generation of visceral signals, and their transduction and transmission up to their central representation.

The Heart and the GI Tract as Electrical Pacemakers
Both the heart and the GI tract are endowed with an intrinsic nervous system [41–43] and generate their own electrical rhythm. The heart contains pacemaker cells that initiate cardiac contractions, and that operate autonomously, enabling the heart to beat even when isolated from the
rest of the organism. In normal conditions, the rate of cardiac contractions is regulated by descending influences from the CNS, and by less well described local influences of the intrinsic cardiac nervous system. As a result, the heart rate of healthy participants is highly irregular. This irregularity is tightly related to the integrity of the CNS, and any sign that the heart is becoming too regular is a clinically relevant neurological warning sign. Recent studies showed that HRV provides information about the state of the CNS, and can be efficiently used not only to predict epileptic seizure onset [44] or seizure development [45] but also to detect residual signs of consciousness in noncommunicating patients [46,47]. However, we will set aside descending influences from brain to heart because this review focuses on ascending pathways — from heart to brain. How is the brain informed about the occurrence and strength of a cardiac contraction? This question pertains to **interoception** — the perception of visceral signals by the brain — as initially proposed by Sherrington, who coined the term ‘interoceptor’ [48,49]. The term interoception has later been extended to the sense of the physiological state of the body [24], including for instance information such as temperature.

Cardiac contractions, and resulting pulses of blood in vessels, are transduced into neural signals by numerous mechanoreceptors in the heart itself, both in the **atria** and in the **ventricles**, as well as in blood vessels (aorta, carotid artery, pulmonary and coronary vessels) [50–52]. Most cardiac receptors fire transiently at a given moment in the cardiac cycle, but latencies can vary considerably depending on receptor type and location [51]. Mechanoreceptors often signal the strength of cardiac contraction and blood pressure, but some cardiac receptors instead indicate the occurrence of a contraction, irrespective of cardiac contraction parameters [51]. In addition to cardiac and blood vessel receptors, the occurrence of cardiac contractions is also signaled through other, less well known pathways. The pulse modulates the neural activity of tactile [53] and proprioceptive [54,55] receptors, showing that information about cardiac activity is already present at the most peripheral level in the somatosensory modality. Another intriguing possibility is direct vasculoneuronal coupling in the CNS [56], an effect recently observed in rodent slices [57], where a change in pressure in the vessels modulates neural firing.

The GI tract also generates its own rhythm. The GI tract is lined with a specific cell type, the interstitial cells of Cajal, that continuously generate slow pacemaker currents [58,59]. During digestion, the gastric rhythm sets the pace of gastric contractions, but the rhythm itself is generated at all times, even outside digestion [60], and even when the stomach is disconnected from the CNS [61]. Interstitial cells of Cajal form direct synapse-like connections with afferent sensory neurons [62], in a pattern established during embryonic development [63], providing a pathway for ascending information from stomach to brain. In addition, the stomach contains multiples mechanoreceptors, some with multiple receptive fields distributed throughout the stomach [64], that are active when the stomach is distended by food ingestion or when the stomach contracts. Last, the chemoreceptor-like cells lining the gut epithelium were until recently thought to act on nerves only indirectly, through the slow action of hormones. However, it was recently discovered that those receptors can directly synapse with sensory **vagal** neurons [65].

**The Central Representation of Visceral Organs**

Anatomofunctional studies in animals (Box 1 for details and references) suggest a distributed central representation of visceral organs, in which visceral inputs target numerous cortical structures as well as major neuromodulation nuclei (Figure 2). Cortical targets include primary and secondary somatosensory cortices, insula (Box 2), ventromedial prefrontal cortex (vmPFC), and cingulate motor regions. Some puzzling anatomical projections are not represented in Figure 2, such as projections from brainstem nuclei that relay visceral information to the lateral geniculate nucleus [66,67]. These projections are massive, to the point that, based only on connectivity, one could conclude that the function of the (visual) lateral geniculate nucleus is to
Visceral inputs reach the brain via vagal and spinal pathways which target NTS and PBN brainstem relay nuclei (purple). These in turn project to noradrenergic (LC) and serotonergic (RN) nuclei in the brainstem, and to subcortical (red) and cortical (yellow) regions. Note that this schematic representation does not highlight differences between species. Abbreviations: Amy, amygdala; Cer, cerebellum; CM, cingulate motor regions; Hc, hippocampus; Hyp, hypothalamus; Ins, insula; LC, locus coeruleus; NTS, nucleus of the solitary tract; PBN, parabrachial nucleus; RN, raphe nucleus; SI, primary somatosensory; SII, secondary somatosensory; St, striatum; Th, thalamus; vmPFC, ventromedial prefrontal cortex.

Box 1. The Numerous Targets of Visceral Inputs
Signals arising from the heart and GI tract are relayed, through spinal or cranial nerve (mostly vagal but also glossopharyngeal) pathways, to brainstem nuclei (nucleus tractus solitarius, NTS; and parabrachial nucleus, PBN). Ascending sensory fibers represent 80% of the vagus nerve [157]. Visceral and somatosensory inputs converge on the same neurons [158] at different stages (spinal cord, NTS). As described in Figure 2, the brainstem nuclei directly influence both serotonergic (dorsal Raphe nucleus) and noradrenergic (locus coeruleus) pathways, and act as relays for direct thalamocortical pathways. From the thalamus numerous cortical areas receive visceral inputs: primary and secondary somatosensory cortex [159,160], insula [161], ventromedial prefrontal cortex [162], cingulate motor regions [163]. The hippocampus also receives inputs from the NTS via a multisynaptic pathway [164]. In addition, the NTS and PBN reach various subcortical structures, the hypothalamus, the cerebellum, the amygdala, and the striatum, structures that in turn project to several other cortical areas. The relative balance between spinal and vagal inputs, which differ in term of fiber velocity and activation threshold, is not yet known with certainty at the cortical level [163,165]. Furthermore, the core regions of this visceral network are functionally and anatomically connected [166]. Anatomy thus suggests a relatively distributed system, with numerous main cortical targets (also Box 2).

Viscerotopic organization is present in the brainstem relay nuclei [167] as well as in the thalamus and insula [161] (Box 2). Surprisingly, whether S1 shows a viscerotopic organization, and whether and how it merges with the somatotopic representation of the body, has not been extensively studied [160]. Only scarce information is available: bladder distension activates neurons in S1 that also respond to stimulation of the hand [168], and vagus nerve stimulation suggests a GI tract representation close to the mouth region [169].

Finally, there are numerous interspecies differences. For instance, the ratio between the different types of cardiac mechanoreceptors can vary by a factor of 1–10 between cats, dogs, and monkeys [51], and the direct projections from PBN to insula and to ventromedial prefrontal cortex in rats [170] seem to be absent in monkeys [171]. The overall picture of anatomical pathways presented in this article is a composite view derived from studies in different animal species that differ between themselves and that probably also differ from humans.

relay visceral information to the cortex [68]. In addition, because the monitoring of visceral inputs is a life-sustaining function, one would expect visceral pathways to be evolutionary ancient and preserved throughout evolution. However, there are many differences between mammalian species (see Box 1 for examples).
Neither anatomical tracing from visceral organs to brain nor well-controlled purely ascending nerve stimulations are available in humans. Nonetheless, brain imaging studies during cardiovascular adjustments [69–72] point to the involvement of the vmPFC, insula, and hippocampal formation, as well as a dorsal anterior cingulate cortex (ACC) region compatible with cingulate motor regions. Note that in these studies it is difficult to distinguish between

**Box 2. The Insula in Interoception and Beyond**

The insula is more and more often presented as ‘the’ primary visceral cortex in the literature on interoception. Although there is no doubt that the insula is involved in visceral processing, whether it represents the main entry point of visceral signals, or only one of the possible entry points (Figure 2), can be debated.

The insula has been labeled ‘the’ primary visceral cortex [172] because it contains a viscerotopic map [161]. However, studies from the 1950s show that primary and secondary somatosensory cortices also represent visceral information [159], and proposed to rename them somatovisceral cortices [173]. The viscerotopic organization of primary somatosensory cortex has scarcely been explored since then, and whether other cortical areas, for instance prefrontal or cingulate regions, are viscerotopically organized is not known.

The insula has been highlighted in experiments on explicit interoception. A pioneering study [81] revealed that attention to heartbeats increases activity in a distributed network, but the anterior insula was the only region where activity correlated with performance. Although a meta-analysis confirmed the involvement of the anterior insula [174], the necessity of the insula for explicit interoception has been questioned. A patient with insular lesions could perform well at interoceptive tasks provided that cardiac-related inputs mediated by the skin were available [175], but see also [176]. In addition, functionally relevant HERs were observed predominantly outside the insula in several experiments [111,128,130,131,135] (Figure 5).

The insula has been highlighted in experiments on explicit interoception. A pioneering study [81] revealed that attention to heartbeats increases activity in a distributed network, but the anterior insula was the only region where activity correlated with performance. Although a meta-analysis confirmed the involvement of the anterior insula [174], the necessity of the insula for explicit interoception has been questioned. A patient with insular lesions could perform well at interoceptive tasks provided that cardiac-related inputs mediated by the skin were available [175], but see also [176]. In addition, functionally relevant HERs were observed predominantly outside the insula in several experiments [111,128,130,131,135] (Figure 5).

The insula is a very large region, of which viscerosensory and visceromotor representations occupy only a portion – in the mid- to posterior insula. Establishing the functional and structural organization of the insula with higher precision is a very active field of research [177–180]. The insula is also one of the most frequently activated regions across numerous imaging experiments [181,182]. Figure I highlights the overlap in the anterior insula of activations related to seemingly very disparate functional terms. The apparent convergence of very different functions in the insula might be due to the limited spatial resolution of standard fMRI. However, there might also be unexpected crosstalk between functions that are not usually considered together. In the cognitive neuroscience literature, the insula is more often associated with saliency [183] than with interoception. Because novelty detection alters heart rate in a systematic manner [46,113], the saliency-related function of the insula might be tightly intertwined with its visceral role. The insula could also be systematically informing value-based choices about the internal state of the body [184]. Conversely, insular activation in interoceptive tasks might be related to general cognitive functions that are not specific to interoception, such as saliency.

**Figure I. Meta-Analytic Activation of the Insula.** (A) Pain (516 studies), (B) memory (2744), (C) selective attention (146), (D) heart rate (72), (E) autonomic (117), (F) cognitive control (598), as retrieved from NeuroSynth [181], December 2018, using the uniformity test and default settings. The green crosshair corresponds to Montreal Neurological Institute (MNI) coordinates (36, 22, −4) in all panels.
ascending and descending signals. In addition, the primary somatosensory cortex displays electrophysiological responses to heartbeats [73], as will be detailed later. Other experimental paradigms based on mechanical distension of various parts of the GI tract [74], and/or on patients with GI disorders [75,76], reveal the involvement of somatomotor regions, insula, vmPFC, and mid-cingulate, as well as disconcerting modulations of activity in occipital regions [77,78]. Although some of those studies were careful to control for pain (e.g., [77,79]), the experimental set-up, with the insertion of inflatable balloons, is at best uncomfortable and stressful, and in any case nonecological. Noninvasive induction of gastric distention can be experimentally obtained by asking participants to drink moderate to large amounts of water [80], but it has not yet been used to map gastric distension with brain imaging. Nevertheless, both cardiovascular adjustments and artificial stimulation of the GI tract reveal in humans the activation of a network compatible with the anatomical pathways described in animals.

Another way to probe the visceral network is to ask participants to explicitly pay attention to visceral signals. This approach has been mostly used with heartbeats (Box 3), and shows that attention to heartbeats increases brain activity in a distributed network compatible with the known anatomy of visceral ascending pathways (somatosensory cortex, insula, mid-cingulate, and pre-motor regions), and decreases brain activity in occipital regions [81].

Dynamics of Viscera–Brain Coupling during Resting-State

Spontaneous brain activity is spatially and temporally structured, and offers a window into the basic functional organization of the brain. Spontaneous brain activity is typically studied in participants at rest, without any task or experimental stimulation, and is thus sometimes called ‘intrinsic’. However, because ascending cardiac and GI signals are continuously generated, and reach numerous subcortical and cortical targets, these visceral signals can sometimes become the object of conscious perception, resulting in explicit interoception. Sensitivity to internal signals in everyday life, as assessed through self-report questionnaires [185,186], appears to be altered in psychiatric disorders [3,187,188], notably in anxiety and depression [189], as well as in autism spectrum disorder [190].

Beyond questionnaires, the accuracy of cardiac interoception can be more objectively measured in experimental tasks. One paradigm that has been widely used is the heartbeat counting task [191], which consists of mentally tracking heartbeats without relying on external cues. It was recently pointed out that this paradigm has several limitations. The accuracy score negatively correlates with heart rate and is driven by heartbeat underestimation [192], it is biased by participants’ belief about their heart rate [193,194], and counting heartbeats might rely more on somatosensory than on interoceptive signals [175,195]. To overcome some of these limitations, other paradigms use simultaneity judgments between heartbeats and either visual or auditory stimuli. A method of constant stimuli [196,197] was developed that involves presenting auditory stimuli at multiple latencies with respect to the R-peaks. Cardiac interoceptive accuracy is derived from participants’ consistency in simultaneity judgments, and thus accommodates interindividual differences in the latency at which heartbeats may be perceived. Given the important methodological differences between the two paradigms, it is not surprising that the concordance in the results is only partial [195,198,199].

Whether and how self-report questionnaires relate to objective measures of interoceptive accuracy is not clear. For example, meditation practice, which encourages paying attention to bodily signals, increases participants’ subjective confidence about interoceptive judgments, but not their objective accuracy [200–202].

To conclude, this currently very active field of research should soon propose more robust and standardized paradigms to measure explicit interoception. This should in turn help to quantify not only the relevance of cardiac interoception in psychiatric disorders but also interindividual differences in objective performance, subjective experience, and confidence judgments.
signals could act as internal stimuli that contribute to the organization of spontaneous brain activity.

**Viscera–Brain Coupling Reveals New RSNs**

In humans, spontaneous brain activity has been often studied with fMRI, and this revealed the existence of RSNs [82]. An RSN comprises a set of anatomically distinct regions with correlated slow fluctuations of brain activity. This approach has been extended to correlated fluctuations between brain and HRV (Figure 3A) ([70,71] for review). The HRV network (Figure 3B) is relatively extended and includes notably cingulate regions, insula, and hippocampal formation, and also the precuneus and motor cortex. Functional connectivity also fluctuates with heart rate [83,84] and pulse rate [85]. Because HRV is largely driven by the brain, these findings are thought to reflect descending influences from brain to heart. Note that it remains an experimental challenge to distinguish heart- and pulse-related physiological noise from neural signals that covary with cardiovascular changes [86–88].

The gastric rhythm is another interesting candidate for the study of brain–viscera coupling because its frequency falls in the same frequency range as RSNs. The gastric rhythm can be recorded noninvasively by placing cutaneous electrodes on the abdomen (Figure 3C) to record the electrogastrogram (EGG) [89,90]. In humans, the EGG spectral signature is sharp, with a peak at around 0.05 Hz corresponding to one cycle every 20 s (Figure 3D). Gastric–brain phase coupling at rest [91] reveals a network (Figure 3E) comprising several primary targets of visceral inputs, such as the primary and secondary somatosensory cortices, and mid-cingulate areas. This network unfolds over time, and a temporally structured sequence of neural events is locked to the gastric cycle. Within the gastric network, several regions are known to contain body maps: these include somatosensory regions and also cingulate motor regions that contain body maps activated by movement, as well as the extrastriate body area that is activated by viewing bodies and body parts [92]. The fact that a common gastric input reaches these different body maps might facilitate the coordination of the different frames of reference employed in touch, action, and vision, but this hypothesis remains to be experimentally tested. Nevertheless, current results indicate that the stomach, and probably more generally the entire GI tract [93], is coupled with the brain at rest in a novel, delayed-connectivity RSN, cutting across canonical RSNs.

**Viscera–Brain Coupling and Spontaneous Brain Rhythms**

Brain rhythms, as revealed by electrophysiological recordings, are another ubiquitous feature of neural activity. The dominant rhythm at rest is the alpha rhythm, ~10 Hz, but brain rhythms take place at numerous frequencies. An important organizing principle of rhythmic brain activity is phase–amplitude coupling [94], where the phase of the lower-frequency oscillation constrains the amplitude of the high-frequency oscillation (Figure 3F). Gastric–brain phase–amplitude coupling, as measured with electroencephalogram (EEG) and magnetoencephalography (MEG) [95], occurs selectively in the alpha frequency range, explaining 8% of alpha variance, and takes place in the parieto-occipital sulcus and right anterior insula (Figure 3E). Directionality analysis indicates that information flows from stomach to brain, supporting the view of a causal role of the gastric rhythm over alpha rhythm power fluctuations. Interestingly, although the stomach seems to contribute to the regulation of alpha amplitude, another study suggests that alpha peak frequency is related to heart rate [96], with a positive correlation between heart rate and occipital alpha peak frequency during wakefulness. During deep sleep, that is characterized by large-amplitude slow oscillations reflecting alternating states of hyperpolarization and depolarization of thalamocortical networks, heartbeats were more likely to occur at the beginning of the depolarization phase.
The coupling between cardiovascular, GI tract and brain activity has consequences for arousal and transition to sleep. Early observations in animals showed how artificially stimulating the mechanoreceptors of the carotid sinus induced immobility and then sleep in dogs and monkeys [97]. In cats, the mechanical distension of the carotid sinus, which causes baroreceptor activation, induces progressive reductions in cortical activity and the appearance of slow waves [98]. These results suggested that blood pressure is “just as important a factor in maintaining the waking state, as the continuous inflow to the brain of proprioceptive and exteroceptive stimuli” [98].
These cardiovascular-related changes in cortical activity and behavior are mediated via modulation of noradrenergic activity in the locus coeruleus [99,100]. The GI tract also seems to be involved in the regulation of arousal. The stimulation of the GI tract induces sleep onset, electroencephalogram (EEG) synchronization, and an increase in slow-wave sleep duration [101], but whether this is mediated by inhibition of locus coeruleus activity is unknown. More generally, whether and how the spontaneous streams of heart and GI tract activity modulate serotonin and noradrenaline release is an important open question. The link between baroreceptor activation and sleep led to the so-called baroreceptor hypothesis, fully developed later, stating that under normal physiological conditions the transient activation of baroreceptors at each cardiac cycle leads to a transient dampening in cortical processing.

The relationship between cardiac/GI activity and sleep seems to go beyond sleep induction. During slow-wave sleep, the electrical activity of the duodenum is coupled with neuronal spiking activity in the cat visual cortex [102]. Furthermore, brain responses to heartbeats in humans (Box 4) decrease during sleep [96].

**Viscera–Brain Coupling during Resting State: Conclusions**

Taking into account the constant stream of visceral inputs stimulating the brain opens new avenues for understanding the nature and organization of spontaneous brain activity. This new source of variance of brain activity has not yet been included in biologically plausible models of spontaneous brain activity but might prove to be an important feature to further refine large-scale models of brain dynamics [103]. Similarly, brain–viscera interactions might constitute an interesting lead to understand the nature of ‘background noise’ in spontaneous neural firing [104], at least in the brain regions of the cardiac and gastric networks.

**The Different Ways That Cardiac Signals Influence Perception and Cognition**

Both the cardiac and gastric signals constrain brain activity at rest, but do they play a role in perception and cognition? Evidence for a link between the gastric rhythm and cognition is scarce (but see [80,105,106]), but the contribution of cardiac signals to cognition has been more extensively studied. Experimental studies on cardiac contribution to cognition can be grouped into three categories: neural responses to heartbeats, temporal contingencies between external stimuli and heartbeats, and heart-rate changes.

Before describing the rationale and methods in these three different approaches, it is worth reminding the reader of some basic facts about cardiac activity [107]. The different waves of the electrocardiogram (ECG) are labeled with conventional names (Figure 4A) corresponding to atrial (P wave) and ventricular (QRS complex) contractions, followed by ventricular relaxation (T wave). The part of the cardiac cycle where the heart muscles are active, contracting and ejecting blood, is called systole. It is followed by a phase in which the heart is relaxed, filling in with blood and where the ECG is more quiescent, called diastole (Figure 4B).

Neural responses to heartbeats (heartbeat evoked responses, HERs) are transient brain responses time-locked to heartbeats obtained by using noninvasive electrophysiological recordings such as magnetoencephalography and electroencephalography (M/EEG) as well as intracranial recordings (iEEG and electrocorticography, ECoG) (Figure 4D–G and Box 4). HERs are computed in the same way as standard evoked responses, by aligning and averaging brain activity to the occurrence of heartbeats [108]. HERs are considered to be responses evoked by the preceding heartbeat rather than being anticipatory of the next heartbeat. Indeed, because the intervals between successive heartbeats are variable, typically between 600 and 1300 ms in a healthy subject, an anticipatory command would be locked to the next heartbeat rather than to the preceding one. HERs are most likely related
to the activity of the different types of mechanoreceptors responding to cardiac contractions. However, the relative contributions of cardiac versus blood vessel mechanoreceptors, and of the pulse-sensing somatosensory and proprioceptive receptors, is not yet known. Because the various types of mechanoreceptors respond at different phases of the cardiac cycle, response latencies are difficult to predict. Last but not least, cardiac parameters, such as the volume of blood ejected at each heartbeat and the heart rate, can influence HER amplitude [109,110]. Knowledge about the physiological basis of HERs thus so far remains very limited compared with the precise description of evoked responses in other sensory modalities, where evoked responses can be used to track the cascade of activation from periphery to brainstem and cortex, and where variations in response amplitude and latency with input parameters are well documented. Links between HERs and cognition are reviewed in detail the next section.
Figure 4. Electrocardiogram (ECG) and Heartbeat Evoked Responses (HERs). (A) Example of an ECG. Letters indicate the main components of a cardiac cycle. IBI is the inter-beat interval, computed between R-peaks. (B) Systole (red), when the heart contracts and ejects blood, and diastole (blue), when the heart relaxes and refills, superimposed on a standard ECG. Stimuli presented during systole and diastole are sometimes processed differently. (C) The fate of stimuli presented synchronously with respect to heartbeats (locked to R peak or T wave for instance) can be different from the fate of stimuli presented asynchronously. (D) Raw magnetoencephalographic (MEG) signal contaminated by the cardiac field artefact. (E) The cardiac field artefact (left, timecourse; right stereotypical topography) is extracted by independent component analysis (ICA). (F) MEG data after removal of the cardiac artefact ICA component. (G) The HER from intracranial data in the human somatosensory cortex. (Left) Several occurrences of responses to single heartbeats (HB); (middle) average HER; (right) electrode location.
A second way to probe the interaction between the neural processing of cardiac signals and the neural processing of an external stimulus is to test whether the occurrence of an external sensory stimulus at a specific moment in the cardiac cycle affects how this stimulus is processed (Figure 4C). For instance, a visual stimulus presented simultaneously with the R-peak might be processed differently than the same visual stimulus presented later in the cardiac cycle, or than a stimulus presented at random moments. There are several such examples, that we present later.

The third approach used to study brain–heart interplay is to measure heart-rate changes following a perceptual, cognitive, emotional, or motor event. Such changes are relatively systematic, even in nonemotional, nonstressing experimental paradigms such as detecting visual gratings [111] or auditory stimuli [46]. Because we focus here on ascending pathways from heart and GI tract to brain, rather than on the descending influences from the brain that lead to heart-rate changes, we do not describe those findings but instead refer the reader to [112–115]. Note that stimulus-driven heart-rate changes are sometimes called the cardiac response (or even the evoked cardiac response) [116], but they should not be confused with the HERs.

Heartbeat Evoked Responses
HERs index the central monitoring of cardiac inputs and can thus be used to experimentally probe the different theoretical hypotheses about the functional role of visceral inputs in emotions, bodily self, and first-person perspective (Figure 1). However, studies on HER historically adopted a simpler stance, testing whether paying attention to cardiac signals might enhance their neural processing.

Heartbeat Evoked Responses and Interoceptive Attention
The first studies on HERs were based on explicit interoceptive tasks (Box 3) in which participants were asked to mentally count their heartbeats [108,117,118]. Those pioneering studies, confirmed by more recent work [119,120], show that paying attention to heartbeats modulates the amplitude of HERs, reflecting a trade-off between internally oriented and externally oriented attention [119]. It has been further proposed that the strength of the HER modulation is related to how accurate participants are at detecting their heartbeats [108,117,118], but measuring explicit interoceptive accuracy has since proved to be a more difficult challenge than expected (Box 3). More recently, it was observed in infants that HERs covary with a new implicit measure of interoception, namely the extent to which infants prefer looking at a stimulus presented asynchronously with heartbeats [121].

Heartbeat Evoked Responses and Emotions
HERs vary with emotions while viewing mood-inducing video clips [122] or while judging the emotional expression of faces [123]. Based on the hypothesis that specific emotions might lead to precise interoceptive predictions [11], the expected repetition of an emotional facial expression leads to a reduction (for angry faces) or increase (for sad or pain faces) in HER amplitude [124,125]. Because emotions are accompanied by changes in bodily parameters, with a linear relationship between heart rate and valence, and between skin conductance and arousal [126], the emotion-related modulations of HERs might reflect either neural responses to changes in bodily state or the cortical mechanisms driving bodily changes [127]. It thus remains to be determined whether HERs drive emotional feelings or are consequences of emotional processing.

Heartbeat Evoked Responses, Bodily Self, and Self-Related Cognition
The experienced bodily self depends on neural responses to heartbeats [128]. In a paradigm using virtual reality to induce full-body illusions [128], the amplitude of responses to heartbeats in mid- to posterior cingulate cortex and supplementary motor area covaried with the degree to which participants identified themselves with an avatar and felt their bodily location displaced towards it (Figure 5A–C). Although this experiment was designed to probe the multisensory integration of HERs in the construction of bodily self, the connection with first-person perspective...
becomes apparent when considering that, in normal situations, the spatial location of our body is also where we identify ourselves to be and the perspective from which we experience the world [30]. The correspondence between body location and first-person perspective is dissolved in patients with derealization/depersonalization disorders. These patients experience the world as unreal and/or experience themselves from outside their body, and notably they do not show the expected increase in HERs when paying attention to their heartbeats [129].

HERs also index the self-relatedness of spontaneous thoughts [130,131] (Figure 5D–F). Self-relatedness was broken down here into two components [132,133]: one related to the explicit self, when one thinks about oneself, as opposed to someone or something else (‘Me’ scale), and the other to the self as an agent, when one says ‘I act/want/feel’ as opposed to ‘It’s raining’ or ‘She is always late’. Participants rated their spontaneous thoughts along these two continuous dimensions. The scores on ‘Me’ scale varied with the amplitude of HERs in ventromedial prefrontal cortex, and the scores on the ‘I’ scale varied with the amplitude of HERs in posterior cingulate cortex. These two midline structures are known core areas for the self [134] and belong to the default network. In this experiment HERs did not vary with the emotional valence of spontaneous thoughts, showing that HERs can covary with aspects of cognition that are not related to emotions. Another study revealed that HERs in medial regions partially overlapping the default network distinguish between self and other [135].

Heartbeat Evoked Responses and Visual Perception
Experiments relating HERs and the different dimensions of the self require explicitly thinking about oneself, and thus might entail a component related to internally directed attention to bodily signals, which is known to increase HERs [108,117–120]. An account that explains HER amplitude solely based on internally directed attention could be ruled out in an experiment on vision at threshold. Indeed, internally directed attention should be detrimental when trying to detect a weak visual input. However, experimental data show that larger responses to heartbeats facilitate the detection of a visual stimulus at threshold [111].

In the experiment depicted in Figure 5G–I, a visual stimulus was presented at low contrast such that participants could detect it in only half of the trials. Whether or not the stimulus was consciously perceived (and thus was reported) depended on the amplitude of prestimulus responses to heartbeats in the ventromedial prefrontal cortex and right inferior parietal lobule. The HER effect was unrelated to changes in arousal or cortical excitability. Interestingly, HERs seemed to behave as sensory evidence, with larger HERs increasing perceptual sensitivity, but did not alter decision criterion. The results are in line with the predictions of the first-person perspective account. When the coordination of different frames of reference (as indexed by HERs) is weak, the visual stimulus fails to be consciously experienced [28,29].

Heartbeat Evoked Responses: Conclusions
The studies reviewed above show that HERs appear to be functionally relevant not only for emotion but also for basic visual perception and (nonemotional) self-related cognition. The effects were observed in various regions, and at different latencies. The reason for this variety of results is not yet known with certainty, but there are several likely candidates. First, there are multiple mechanisms of transduction of cardiac-related information, with in particular different cardiac mechanoreceptors firing at different phases of the cardiac cycle [51]. Second, the different anatomical pathways involve both fast myelinated fibers and slow unmyelinated fibers, as well as varying numbers of synaptic relays. The combination of those factors is likely to contribute to the emergence of effects at different latencies. Importantly, some of the above-mentioned studies included several physiological measures to verify that the HER effects are not due to changes in cardiac physiological parameters nor to unspecific modulations in arousal state (Box 4).
Temporal Contingencies between External Stimuli and Heartbeats

Another way to investigate the influence of the heart on perception and cognition is to look at how external stimuli are processed depending on their temporal relationship with
heartbeats. Two distinct lines of research have been pursued, one comparing stimuli presented early (systole) versus late (diastole) in the cardiac cycle, in a framework emphasizing bodily arousal and emotions, and the other looking at the effects of temporal synchronization between cardiac contractions and external stimuli, in the framework of multisensory integration.

The Baroreceptor Hypothesis: Systole versus Diastole

The baroreceptor hypothesis [136] inspired a long line of experimental research in humans. As summarized in [137], this hypothesis states that the activation of baroreceptors in the aorta and carotid, that is maximal at systole (when ejected blood distends artery walls), has an inhibitory effect on the CNS [138]. This hypothesis is rooted in the observations that artificial baroreceptor activation can induce sleep, as presented earlier in this review, and predicts that the processing of external sensory information would be dampened at systole. This hypothesis has been experimentally tested by comparing responses with external stimuli presented either at systole or diastole, or by comparing responses with external stimuli presented at systole versus stimuli presented randomly at any point of the cardiac cycle (Figure 4B,C).

Early experiments showed that applying neck suction during systole, a technique that artificially boosts baroreceptors activation, reduces pain sensation [139]. More recent pain studies report congruent results, with reduced pain sensation during normal baroreceptor activation without neck suction [140], and a less-pronounced startle reflex to acoustic stimuli at systole [141]. Although pain seems to be reduced at systole, in line with the baroreceptor hypothesis, other experiments find facilitatory effects for stimuli presented during systole in somatosensory detection [137], visual discrimination [142], and visual search [143] tasks, but not all results are consistent. In the visual modality, some older studies [144] as well as more recent experiments [111] did not observe any modulation of visual detection as a function of the cardiac cycle, and another study [145] found reduced visual awareness and less accuracy for stimuli presented during systole. Interestingly, motor control also seems to be dependent on the phase of the cardiac cycle. Systole is characterized by more frequent microsaccades [146], improved inhibitory motor control [147], and more frequent self-initiated movement [148].

The phasic nature of baroreceptor activity has been also investigated with emotional stimuli ([149] for recent review). The rationale for this line of research is that the physiological state of the body contributes to the experience of emotion: cardiovascular arousal – larger at systole – should therefore influence how emotional stimuli are processed. In agreement with this hypothesis, fearful faces are judged to be of greater emotional intensity and are more easily detected during systole [150]. Emotion perception can sometimes be maladaptive, as for instance in racial stereotypes where threat tends to be associated with Black people. This negative bias is enhanced during systole [151]. In addition to fear and threat, disgust perception is enhanced during late systole [152]. The available evidence thus suggests that fear, threat, and disgust perception are enhanced during systole. Processing emotional stimuli differently at systole and diastole may not convey a specific functional advantage per se, but in a state of high bodily arousal, when the heart is beating rapidly and diastole is shortened, the influence of baroreceptors on the brain would help in prioritizing threatening stimuli.

The results of different studies investigating the modulation of sensory and cognitive processing by cardiac phases are difficult to accommodate within a single account, and numerous questions remain to be answered. Why does baroreceptor activation sometimes facilitate stimulus processing, as for somatosensory detection or threat, and sometimes inhibit it, as for pain? Should all results be interpreted as reflecting baroreceptor activation, or does pulse-related information
mediated by tactile [53] and proprioceptive [54,55] receptors also play a role, with potentially a direct influence on muscle activity.

**Multisensory Integration: Synchronous versus Asynchronous Conditions**

Multisensory integration depends on temporal contingencies between stimuli, as repeatedly shown for exteroceptive stimuli. Assuming that the same rule holds true for the integration of interoceptive and exteroceptive stimuli, several studies investigated whether external events occurring synchronously (most frequently around the time of R-peak) have a different fate than external events occurring at random phases of the cardiac cycle (Figure 4C). According to the hypothesis that bodily ownership depends on multisensory integration (Figure 1D) [9,26], participants experienced enhanced body ownership of a virtual avatar hand [153] and a virtual avatar body [154,155] when these were illuminated in synchrony with their heartbeats. Participants also identified a face as their own more easily when the face was visually pulsating synchronously with their heartbeats [156].

**Concluding Remarks and Future Perspectives**

Despite the vital roles of the heart and GI tract, there are surprising gaps in our knowledge of brain–viscera interactions, including basic questions regarding transduction mechanisms and anatomical pathways or visceral representations in somatotopically organized cortices. Nevertheless, the recent findings reviewed here show that visceral signals are coupled with, and sometimes drive, spontaneous brain dynamics, indicating that the viscera and the brain form a single complex system. This view could open new leads to understanding the nature of spontaneous brain activity: some of the ‘background noise’ in spontaneous neural firing might be related to relevant brain–viscera interactions [104], and taking into account visceral inputs might prove useful in revisiting the origin and dynamics of RSNs (see Outstanding Questions). Moreover, the importance of visceral signals extends beyond emotions to include emotionless, basic visual perception, self-location, and spontaneous self-related cognition. An interpretative framework that could encompass numerous, but not all, experimental findings is that visceral inputs are useful to coordinate information expressed in different frames of reference, hence generating the unified viewpoint of the first-person perspective. Whether this hypothesis proves to hold true or not, this active field of research offers a unique opportunity to develop new theories that could blur the border between cognition and emotion, between consciousness and cognition, and between mind and body.

**Acknowledgments**

C.T.B. is supported by the European Research Council (ERC) under the EU Horizon 2020 Research and Innovation Program (grant agreement 670325, Advanced grant BRAVIUS), a senior fellowship from the Canadian Institute for Advanced Research (CIFAR) program in Brain, Mind, and Consciousness, as well as by the Agence Nationale de la Recherche (ANR-17-EURE-0017). I.R. is supported by grants from Domaine d’Intérêt Majeur (DIM) Cerveau et Pensée and the Fondation Bettencourt-Schueller. D.A. is supported by a grant from the École des Neurosciences de Paris Ile de France.

**References**

1. Kandel, E.R. et al. (2013) Nerve cells, neural circuitry, and behavior. In Principles of Neural Science 5th edn (Kandel, E.R. et al., eds), pp. 21–38, McGraw-Hill Professional
2. Schultz, W. et al. (1997) A neural substrate of prediction and reward. Science 275, 1500–1509
3. Critchley, H.D. and Harrison, N.A. (2013) Visceral influences on brain and behavior. Neuron 77, 624–638
4. Tort, A.B.L. et al. (2016) Respiration-entrained brain rhythms are global but often overlooked. Trends Neurosci. 41, 189–197
5. Smith, R. et al. (2017) The hierarchical basis of neurovisceral integration. Neurosci. Biobehav. Rev. 75, 274–296
6. Sterling, P. and Eyer, J. (1968) Arousal: a new paradigm to explain arousal pathology. In Handbook of Life Stress, Cognition and Health (Fisher, S. and Reaason, J., eds), pp. 629–649, John Wiley & Sons
7. Ramsey, D.S. and Woods, S.C. (2014) Clarifying the roles of homeostasis and allostatics in physiological regulation. Psychol. Rev. 121, 225–247
8. McEwen, B.S. and Seeman, T. (1999) Protective and damaging effects of mediators of stress. Elaborating and testing the concepts of allostatics and allostatic load. Ann. N. Y. Acad. Sci. 896, 30–47
9. Seth, A.K. (2013) Interoceptive inference, emotion, and the embodied self. Trends Cogn. Sci. 17, 565–573
10. Pezzulo, G. et al. (2015) Active Interoception, homeostatic regulation and adaptive behavioural control. Prog. Neurobiol. 134, 17–35
11. Barrett, L.F. and Simmons, W.K. (2015) Interoceptive predictions in the brain. Nat. Rev. Neurosci. 16, 419–429
12. Marshall, A.C. et al. (2018) The interaction between interoceptive and action states within a framework of predictive coding. Front. Psychol. 9, 180

**Outstanding Questions**

How are the viscera represented? Is there a visceral homunculus, and if yes, how does it map onto the somatomotor homunculus? Is there a primary viscerosensory cortex, as for exteroceptive modalities, or is the visceral sensory system relatively distributed, as is the vestibular system for instance?

Are cardiac and GI tract inputs combined in the brain, and if yes how? Are the heart and GI tract related to different aspects of cognition, with different timescales?

What is the functional role of the link between occipital cortex activity and visceral signals?

To what extent will taking into account the constant stream of visceral inputs reaching the brain modify current views on spontaneous, resting-state brain activity? Can mechanistic models of spontaneous brain activity, either at whole-brain or unit level, be improved by including brain coupling with the heart and GI tract? Is the coordination between classical RSNs mediated by visceral inputs?

Could interventions on the heart or GI tract be informative? Several types of interventions can be considered, from invasive GI tract stimulations with inflatable balloons to patients with cardiac pacemakers, to study brain responses to visceral inputs and/or temporal contingencies between visceral and external inputs, or to design more reliable procedures for explicit interoception. It remains to be determined whether these artificial, noneocological stimulations tap onto the same mechanisms as physiological stimuli.

Different theoretical perspectives propose a functional role for ascending signals from the heart and GI tract. Can they be combined into a single account that encompasses emotions, arousal, self, and conscious perception and cognition, or are these different concepts separated by hard borders that cannot and should not be crossed?
69. Shoemaker, J.K. et al. (2012) Cortical circuitry associated with reflex cardiovascular control in humans: does the cortical autonomic network “speak” or “listen” during cardiovascular arousal. Anat. Rec. (Hoboken) 295, 1375–1384.

70. Thayer, J.F. et al. (2012) A meta-analysis of heart rate variability and neuroimaging studies: implications for heart rate variability as a marker of stress and health. Neurosci. Biobehav. Rev. 36, 747–756.

71. Beissner, F. et al. (2013) The autonomic brain: an activation likelihood estimation meta-analysis for central processing of autonomic function. J. Neurosci. 33, 10503–10511.

72. Gianaros, P.J. and Wager, T.D. (2015) Brain-body pathways linking psychological stress and physical health. Curr. Dr. Psychol. Sci. 24, 215–219.

73. Kern, M. et al. (2013) Heart cycle-related effects on event-related potentials, spectral power changes, and connectivity patterns in the human EEG. Neuromage 81C, 175–190.

74. Derbyshire, S.W. (2003) A systematic review of neuroimaging data during visceral stimulation. Am. J. Gastroenterol. 98, 12–20.

75. Lee, I.S. et al. (2016) Functional neuroimaging studies in functional dyspepsia patients: a systematic review. Neurogastroenterol. Motil. 28, 793–805.

76. Kano, M. et al. (2018) Understanding neurogastroenterology from neuroimaging perspective: a comprehensive review of functional and structural brain imaging in functional gastrointestinal disorders. J. Neurogastroenterol. Motil. 24, 512–527.

77. Ladabaum, U. et al. (2001) Gastric distention correlates with activation of multiple cortical and subcortical regions. Gastroenterology 120, 369–376.

78. van Oudenhove, L. et al. (2009) Cortical deactivations during gastric fundus distension in health: visceral pain-specific response or attenuation of “default mode” brain function? A H2(18)O-PET study. Neurogastroenterol. Motil. 21, 259–271.

79. Hobday, D.J. et al. (2001) A study of the cortical processing of ano-rectal sensations using functional MRI. Brain 124, 361–368.

80. Schulz, A. et al. (2017) Gastric modulation of startle eye blink. Biol. Psychol. 127, 25–33.

81. Critchley, H.D. et al. (2004) Neural systems supporting interoceptive awareness. Nat. Neurosci. 7, 189–195.

82. Fox, M.D. and Raichle, M.E. (2007) Spontaneous fluctuations in brain activity observed with functional magnetic resonance imaging. Nat. Rev. Neurosci. 8, 700–711.

83. Chang, C. et al. (2015) Association between heart rate variability and fluctuations in resting-state functional connectivity. Neuronage 68, 93–104.

84. Nikolau, F. et al. (2016) Spontaneous physiological variability modulates dynamic functional connectivity in resting-state functional magnetic resonance imaging. Philos. Transact. A Math. Phys. Eng. Sci. 374, 20150283.

85. Shokri-Kojori, E. et al. (2018) An autonomic network: synchrony between slow rhythms of pulse and brain resting state is associated with personality and emotions. Cereb. Cortex 28, 3356–3371.

86. Glover, G.H. et al. (2000) Image-based method for retrospective correction of physiological motion effects in fMRI: RETROICOR. Magn. Reson. Med. 44, 162–167.

87. Blom, P.M. (2012) The role of physiological noise in resting-state functional connectivity. Neuroimage 62, 864–870.

88. Chang, C. et al. (2016) Brain-heart interactions: challenges and opportunities with functional magnetic resonance imaging at ultra-high field. Philos. Transact. A Math. Phys. Eng. Sci. 374, 20150188.

89. Koch, K.L. and Stern, R.M. (2004) Handbook of Electrogastrography. Oxford University Press.

90. Yin, J. and Chen, J.D. (2013) Electrogastrography: methodology, validation and applications. J. Neurogastroenterol. Motil. 19, 5–17.

91. Rebollo, I. et al. (2018) Stomach-brain synchrony reveals a novel, delayed-connectivity resting-state network in humans. Elife 7, e33231.

92. Cizovsky, P. et al. (2010) Topographic representation of the human body in the occipitotemporal cortex. Neuron 68, 586–600.

93. Hashimoto, T. et al. (2015) Neural correlates of electrogastrography: neural activity modulated by signals recorded from the abdominal surface. Neuroscience 299, 1–8.

94. Bragon, A. et al. (1995) Gamma (40–100 Hz) oscillation in the hippocampus of the behaving rat. J. Neurosci. 15, 47–60.

95. Richter, C.G. et al. (2017) Phase-amplitude coupling at the organism level: the amplitude of spontaneous alpha rhythm fluctuations varies with the phase of the infra-slow gastric basal rhythm. Neuroimage 146, 951–960.

96. Lechinger, J. et al. (2015) Heartbeat-related EEG amplitude and phase modulations from wakefulness to deep sleep: interactions with sleep spindles and slow oscillations. Psychophysiology 52, 1441–1450.

97. Koch, E. (1952) Die Irradiation der pressorezeptorischen Kreislaufreflexe. Klin. Wochenschr. 11, 225–227.

98. Bonavall, M. et al. (1954) Tonus sympathique et activity electrique corticale. Electroencephalogr. Clin. Neurophysiol. 6, 1441–1450.

99. Persson, B. and Svensson, T.H. (1981) Control of behaviour and brain noradrenaline neurons by peripheral blood volume receptors. J. Neural Transm. 52, 73–82.

100. Elam, M. et al. (1986) Regulation of locus coeruleus neurons and splanchnic, sympathetic nerves by cardiovascular afferents. Brain Res. 390, 281–287.

101. Kukorelli, T. and Jurjus, G. (1977) Sleep induced by intestinal visceral stimulation in cats. Physiol. Behav. 19, 355–358.

102. Pigeon, L.N. et al. (2013) Cortical visual areas process intestinal information during slow-wave sleep. Neurogastroenterol. Motil. 25, 288–295.

103. Ponce-Alvarez, A. et al. (2013) Resting-state temporal synchronization networks emerge from connectivity topology and heterogeneity. PLoS Comput. Biol. 11, e1004100.

104. Kim, K. et al. (2019) Resting-state neural firing rate is linked to cardiac cycle duration in the human cingulate and parahippocampal cortices. J. Neurosci. Published online March 6, 2019. https://doi.org/10.1523/JNEUROSCI.2291-18.2019.

105. Varna, E.P. and Tranle, D. (2006) Gastric myoelectrical activity as an index of emotional arousal. Int. J. Psychophysiol. 61, 70–76.

106. Harrison, N.A. et al. (2013) The embodiment of emotional feelings in the brain. J. Neurosci. 33, 12079–12084.

107. Bernstein, G.G. et al. (2007) Cardiovascular psychophysiology. In Handbook of Psychophysiology (3rd edn) (Cacioppo, J.T. et al., eds), pp. 182–210, Cambridge University Press.

108. Montoya, P. et al. (1993) Heartbeat evoked potentials (HEP): topography and influence of cardiac awareness and focus of attention. Electroencephalogr. Clin. Neurophysiol. 88, 163–172.

109. Schandry, R. and Montoya, P. (1996) Event-related brain potentials and the processing of cardiac activity. Biol. Psychol. 45, 75–95.

110. Gray, M.A. et al. (2007) A cortical potential reflecting cardiac function. Proc. Natl. Acad. Sci. U. S. A. 104, 6818–6823.

111. Park, H.D. et al. (2014) Spontaneous fluctuations in neural responses to heartbeats predict visual detection. Nat. Neurosci. 17, 612–618.

112. Somers, R.J. et al. (2004) The cardiac cycle time effect revisited: temporal dynamics of the central–skeletal modulation of heart rate in human reaction time tasks. Psychophysiology 41, 941–953.

113. Bradley, M.M. (2009) Natural selective attention: orienting and emotion. Psychophysiology 46, 1–11.

114. Thayer, J.F. et al. (2006) Heart rate variability, prefrontal neural function, and cognitive performance: the neurovisceral integration perspective on self-regulation, adaptation, and health. Ann. Behav. Med. 37, 141–153.

115. Allen, M. et al. (2018) Unexpected arousal modulates the influence of sensory noise on confidence. Elife 5, e18103.

116. Lawrence, C.A. and Barry, R.J. (2010) Cognitive processing effects on auditory event-related potentials and the evoked cardiac response. Int. J. Psychophysiol. 78, 100–106.

117. Schandry, R. et al. (1986) From the heart to the brain: a study of heartbeat contingent scalp potentials. Int. J. Neurosci. 30, 261–275.
118. Polatios, O. and Schendy, R. (2004) Accuracy of heartbeat perception is reflected in the amplitude of the heartbeat-evoked brain potential. Psychophysiology 41, 476–482
119. Villena-Gonzalez, M. et al. (2017) Attending to the heart is associated with posterior alpha band increase and a reduction in sensitivity to concurrent visual stimuli. Psychophysiology 54, 1483–1497
120. Petzschner, F.H. et al. (2018) Focus of attention modulates the heartbeat evoked potential. Neuroimage 180, 595–606
121. Maister, L. et al. (2017) Neurobehavioral evidence of interoceptive sensitivity in early infancy. Elfe 6, e05318
122. Couto, B. et al. (2015) Heart evoked potential triggers brain responses to natural affective scenes: a preliminary study. Auton. Neurosci. 193, 132–137
123. Fukushima, H. et al. (2009) What is self-specification? Trends Cogn. Sci. 13, 657–660
124. Qin, P. and Northoff, G. (2011) How is our self related to midline heartbeat evoked potential. Biol. Psychol. 84, 100–115
125. Luft, C.D. and Bhattacharya, J. (2015) Aroused with heart: Modulation of heartbeat evoked potential by arousal induction and its oscillatory correlates. Sci. Rep. 5, 15717
126. Park, H.D. et al. (2016) Transient modulations of neural responses to heartbeats covary with bodily self-consciousness. J. Neurosci. 36, 8453–8460
127. Schulz, A. et al. (2015) Altered patterns of heartbeat-evoked potentials in depersonalization/derealization disorder: neuro-physiological evidence for impaired cortical representation of bodily signals. Psychosom. Med. 77, 506–516
128. Luft, C.D. and Babo-Rebelo, M. et al. (2016) Neural responses to heartbeats in the default network encode the self in spontaneous thoughts. J. Neurosci. 36, 7829–7840
129. Park, H.D. et al. (2016) Is the cardiac monitoring function related to the self in both the default network and right anterior insula? Philos. Trans. R. Soc. Lond. Ser. B Biol. Sci. 371
130. Legrand, D. and Ruby, P. (2009) What is self-specific? Theoretical investigation and critical review of neuroimaging results. Psychol. Rev. 116, 252–282
131. Christoff, K. et al. (2011) Spontaneity for the self for cognitive neuroscience. Trends Cogn. Sci. 15, 104–112
132. Qin, P. and Northoff, G. (2011) How is our self related to midline regions and the default-mode network? Neuroimage 57, 1221–1233
133. Babo-Rebelo, M. et al. (2019) Neural responses to heartbeats distinguish self from other during imagination. Neuroimage 191, 10–20
134. Lacey, J.J. (1967) Somatic response patterning and stress: some revisions of activation theory. In Psychological stress: Issues in Research (Appley, M.H. and Trumbull, R., eds), pp. 14–42, Appleton-Century-Crofts
135. Edwards, L. et al. (2009) Sensory detection thresholds are modulated across the cardiac cycle: evidence that cutaneous sensitivity is greatest for systolic stimulation. Psychophysiology 46, 252–256
136. Rau, H. et al. (1993) Baroreceptor stimulation alters cortical activity. Psychophysiology 30, 322–325
137. Dworkin, B.R. et al. (1994) Central effects of baroreceptor activation in humans: attenuation of skeletal reflexes and pain perception. Proc. Natl. Acad. Sci. U.S.A. 91, 6239–6233
138. Wilkinson, M. et al. (2015) Electrocortical pain thresholds are higher during systole than diastole. Biol. Psychol. 94, 71–73
139. Scholz, A. et al. (2009) Cardiac modulation of startle eye blink. Psychophysiology 46, 234–240
140. Pramme, L. et al. (2014) Cardiac cycle time effects on mask inhibition. Biol. Psychol. 100, 115–121
141. Scholz, A. et al. (2018) Cardiac cycle time effects on selection efficiency in vision. Psychophysiology 53, 1702–1711
142. Elliott, P. and Graf, V. (1972) Visual sensitivity as a function of phase of cardiac cycle. Psychophysiology 9, 307–381
143. Salomon, R. et al. (2016) The insula mediates access to awareness of visual stimuli presented synchronously to the heartbeat. J. Neurosci. 36, 5155–5167
144. Oht, S. et al. (2018) Microsaccades are coupled to heartbeat. J. Neurosci. 36, 1237–1241
145. Ral, C.L. et al. (2018) Response inhibition on the stop signal task improves during cardiac contraction. Sci. Rep. 8, 9138
146. Kunzendorf, S. et al. (2019) Active information sampling varies across the cardiac cycle. Psychophysiology 56, e13322
147. Garfinkel, S.N. and Cichy, H.D. (2016) Threat and the body: how the heart supports fear processing. Trends Cogn. Sci. 20, 34–46
148. Garfinkel, S.N. et al. (2014) Fear from the heart: sensitivity to fear stimuli depends on individual heartbeats. J. Neurosci. 34, 608–618
149. Azevedo, R.T. et al. (2017) Cardiac afferent activity modulates the expression of facial stereotypes. Nat. Commun. 8, 13854
150. Gray, M.A. et al. (2012) Emotional appraisal is influenced by cardiac afferent information. Emotion 12, 190–191
151. Suzuki, K. et al. (2013) Multisensory integration across exteroceptive and interoceptive domains modulates self-experience in the rubber-hand illusion. Neuropsychologia 51, 2909–2917
152. Apelt, J.E. et al. (2013) Turning body and self inside out: visceralized heartbeats alter bodily self-consciousness and tactile perception. Psychol. Sci. 24, 2445–2453
153. Heydrich, L. et al. (2018) Cardio-visual full body illusion alters bodily self-consciousness and tactile processing in somatosensory cortex. Sci. Rep. 8, 9230
154. Sel, A. et al. (2017) Heartfelt self: cardio-visual integration affects self-face recognition and interoceptive cortical processing. Cereb. Cortex 27, 5144–5155
155. Agostoni, E. et al. (1957) Functional and histological studies of the vagus nerve and its branches to the heart, lungs and abdominal viscera in the cat. J. Physiol. 135, 192–205
156. Cervero, F. and Tattersall, J.E. (1987) Somasic and visceral inputs to the thoracic spinal cord of the cat: marginal zone (lamina I) of the dorsal horn. J. Physiol. 398, 383–395
157. Arnasian, V.E. (1951) Cortical representation of visceral afferents. J. Neurophysiol. 14, 433–444
158. Downman, C.B. (1951) Cerebral destination of splanchic afferent impulses. J. Physiol. 113, 434–441
159. Cechetto, D.F. and Saper, C.B. (1987) Evidence for a viscerosensory representation in the cortex and thalamus in the rat. J. Comp. Neurol. 262, 27–45
160. Vogt, B.A. and Derbyshire, S.W.G. (2009) Visceral circuits and circulate-mediated autonomic functions. In Circulate Neurobiology and Disease (Vogt, B.A., ed.), pp. 220–235, Oxford University Press
161. Durn, R.P. et al. (2009) The spinothalamic system targets motor and sensory areas in the cerebral cortex of monkeys. J. Neurosci. 29, 14223–14235
162. Castle, M. et al. (2005) Autonomic brainstem nuclei are linked to the hippocampus. Neuroscience 134, 657–669
163. Willis Jr., W.D. et al. (2002) A critical review of the role of the nucleus paraventricularis in pain. J. Pain 3, 79–94
164. Kleitman, I.R. et al. (2017) Evidence for a large-scale brain system supporting allosostasis and interoception in humans. Nat. Hum. Behav. 1, 0069
165. Autsch, S.M. et al. (1989) Viscerotopic representation of the upper alimentary tract in the rat: sensory ganglia and nuclei of the solitary and spinal trigeminal tracts. J. Comp. Neurol. 283, 248–268
166. Schwemmler, J. et al. (1997) Viscero-somatic neurons in the primary somatosensory cortex (SI) of the squirrel monkey. Brain Res. 750, 297–300
167. Ito, S. (2002) Visceral region in the rat primary somatosensory cortex identified by vagal evoked potential. J. Comp. Neurol. 444, 10–24
168. Shipley, M.T. and Sanders, M.S. (1982) Special senses are really special: evidence for a reciprocal, bilateral pathway between insular cortex and nucleus parabrachialis. Brain Res. Bull. 8, 493–501
Trends in Cognitive Sciences

171. Pritchard, T.C. et al. (2000) Projections of the parabrachial nucleus in the old world monkey. Exp. Neurol. 165, 101–117
172. Saper, C.B. (2002) The central autonomic nervous system: conscious visceral perception and autonomic pattern generation. Annu. Rev. Neurosci. 25, 433–469
173. Ruch, T.C. et al. (1992) Topographical and functional determinants of cortical localization patterns. Res. Publ. Assoc. Res. Nerv. Ment. Dis. 30, 403–429
174. Schulte, S.M. (2016) Neural correlates of heart-focused interoception: a functional magnetic resonance imaging meta-analysis. Philos. Trans. R. Soc. Lond. Ser. B Biol. Sci. 371
175. Khalsa, S.S. et al. (2009) The pathways of interoceptive awareness. Nat. Neurosci. 12, 1494–1496
176. Ronchi, R. et al. (2011) Right insular damage decreases heartbeat awareness and alters cardiac–visual effects on bodily self-consciousness. Neuropsychologia 70, 11–20
177. Deen, B. (2011) Three systems of insular functional connectivity identified with cluster analysis. Cereb. Cortex 21, 1498–1506
178. Chang, L.J. et al. (2013) Decoding the role of the insula in human cognition: functional parcellation and large-scale reverse inference. Cereb. Cortex 23, 739–749
179. Evard, H.C. (2018) von Economo and thalamus in the monkey brain: implications for evolution of cognition. Curr. Opin. Behav. Sci. 21, 182–190
180. Nomi, J.S. et al. (2019) Structural connections of functionally defined human insular subdivisions. Cereb. Cortex 29, 3445–3456
181. Yarkoni, T. et al. (2011) Large-scale automated synthesis of human functional neuroimaging data. Nat. Methods 8, 665–670
182. Behrens, T.E. et al. (2013) What is the most interesting part of the brain? Trends Cogn. Sci. 17, 2–4
183. Menon, V. and Uddin, L.Q. (2010) Saliency, switching, attention and control: a network model of insula function. Brain Struct. Funct. 214, 655–687
184. Gu, X. and FlitGerald, T.H. (2014) Interoceptive inference: homeostasis and decision-making. Trends Cogn. Sci. 18, 269–270
185. Mandler, G. (1952) Topographical and functional parcellation of the brain. Annu. Rev. Neurosci. 25, 433–469
186. Mehling, W.E. et al. (2012) The multidimensional assessment of interoceptive awareness (MAIA). PLoS One 7, e48230
187. Khalsa, S.S. et al. (2018) Interoception and mental health: a roadmap. Biol. Psychiatry Cogn. Neurosci. Neuroimaging 3, 501–513
188. Quadri, L. et al. (2018) The neurobiology of interoception in health and disease. Annu. N. Y. Acad. Sci. 1428, 112–128
189. Paulus, M.P. and Stein, M.B. (2010) Interoception in anxiety and depression. Brain Struct. Funct. 214, 451–463
190. Garfinkel, S.N. et al. (2018) Discrepancies between dimensions of interoception in autism: implications for emotion and anxiety. Biol. Psychiatry 114, 117–126
191. Schandy, R. (1981) Heart beat perception and emotional experience. Psychophysiology 18, 483–488
192. Zamaro, G. et al. (2018) Interoceptive accuracy scores from the heartbeat counting task are problematic: evidence from simple bivariate correlations. Biol. Psychol. 137, 12–17
193. Ring, C. et al. (2015) Effects of heartbeat feedback on beliefs about heart rate and heartbeat counting: a cautionary tale about interoceptive awareness. Biol. Psychol. 104, 193–198
194. Desmedt, O. et al. (2018) The heartbeat counting task largely involves non-interoceptive processes: evidence from both the original and an adapted counting task. Biol. Psychol. 138, 185–189
195. Brener, J. and Ring, C. (2016) A psychophysiology of interoceptive processes: the measurement of heartbeat detection. Philos. Trans. R. Soc. Lond. Ser. B Biol. Sci. 371, 20160015
196. Whitehead, W.E. et al. (1977) Relation of heart rate control to heartbeat perception. Biofeedback Self Regul. 2, 317–392
197. Brener, J. and Kluvitse, C. (1988) Heartbeat detection: judgments of the simultaneity of external stimuli and heartbeats. Psychophysiology 25, 554–561
198. Ring, C. and Brener, J. (2018) Heartbeat counting is unrelated to heartbeat detection: a comparison of methods to quantify interoception. Psychophysiology 55, e13084
199. Garfinkel, S.N. et al. (2015) Knowing your own heart: distinguishing interoceptive accuracy from interoceptive awareness. Biol. Psychol. 104, 65–74
200. Khalsa, S.S. et al. (2008) Interoceptive awareness in experienced meditators. Psychophysiology 45, 671–677
201. Melloni, M. et al. (2013) Preliminary evidence about the effects of meditation on interoceptive sensitivity and social cognition. Behav. Brain Funct. 9, 47
202. Parkin, L. et al. (2014) Exploring the relationship between mindfulness and cardiac perception. Mindfulness 5, 298–313
203. Dirlich, G. et al. (1997) Cardiac field effects on the EEG. Electroencephalogr. Clin. Neurophysiol. 102, 307–315
204. Joussamai, V. and Hari, R. (1996) Cardiac artifacts in magnetoencephalograms. J. Clin. Neurophysiol. 13, 172–176
205. Makeg, S. et al. (2002) Dynamic brain sources of visual evoked responses. Science 295, 690–694
206. Dirlich, G. et al. (1996) Topography and morphology of heart action-related EEG potentials. Electroencephalogr. Clin. Neurophysiol. 106, 299–305
207. Perez, J.J. et al. (2005) Suppression of the cardiac electric field artifact from the heart action-evoked potential. Med. Biol. Eng. Comput. 43, 572–581
208. Park, H.D. et al. (2018) Neural sources and underlying mechanisms of neural responses to heartbeats, and their role in bodily self-consciousness: an intracranial EEG study. Cereb. Cortex 28, 2351–2364
209. Walker, B.B. and Sandman, C.A. (1982) Visual evoked potentials change as heart rate and cardiac pressure change. Psychophysiology 19, 520–527
210. Edwards, L. et al. (2008) Pain-related evoked potentials are modulated across the cardiac cycle. Pain 137, 488–494