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Perspective

Visceral Influences on Brain and Behavior

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Mental processes and their neural substrates are intimately linked to the homeostatic control of internal bodily state. There are a set of distinct interoceptive pathways that directly and indirectly influence brain functions. The anatomical organization of these pathways and the psychological/behavioral expressions of their influence appear along discrete, evolutionarily conserved dimensions that are tractable to a mechanistic understanding. Here, we review the role of these pathways as sources of biases to perception, cognition, emotion, and behavior and arguably the dynamic basis to the concept of self.

Introduction

The internal state of the body motivates our desire to walk in the shade on a warm summer's day and inhibits the desire to eat or socialize when feeling off-color. Communication from the viscera to brain is continuous and pervasive, yet we rarely give it a second thought. Visceral fluctuations and reactions accessible to introspective appraisal represent only the visible tip of the iceberg. The majority of visceral signals that shape behavior, cognition, and, arguably, emotion go unnoticed. Techniques such as human neuroimaging permit valuable insights into the brain basis of perceptions, thoughts, feelings, and actions, yet these mental functions are for the most part considered in isolation from the physiological state of the body. Nevertheless, experimental information from studies of autonomic psychophysiology, feeding and metabolism, osmoregulation, and psychoneuroimmunology is converging. Identification of the neural circuitry representing internal state paves the way for more comprehensive understanding of how visceral signals shape human cognition and behavior.

The brain is dependent on the physiological state of the body in two ways. First, the brain requires appropriate conditions (physiological context) for efficient biological functioning. Second, the brain receives and responds to continuous dynamic feedback of afferent visceral signals (informational context) that shape its operational functioning. The latter is classical interoception, i.e., the encoding and representation of internal bodily signals reporting the body's physiological state (Craig, 2002). Interoceptive information is conveyed centrally by cranial and spinal nerves and by direct sampling of chemicals carried in the blood within specialized brain structures. This information is comprehensive, encompassing distinct classes of signal with distinct temporal response characteristics (including hormonal, immunological, metabolic, thermal, nociceptive, and visceromotor). These parameters are encoded across a set of brain regions in a way that permits dynamic interaction and integration with descending (top down) expressions of perceptual expectation and volitional control of action.

The concept of homeostasis as a collection of reflexes has biased research on viscera-brain interactions to focus on proximate factors determining stability of physiological state within set ranges. Interoceptive pathways do signal deviation of individual physiological parameters toward the limits of these ranges, but it is behavior that determines the environmental challenges and rate of internal change, e.g., build up of metabolic byproducts. Homeostatic control is well described in terms of local reflexes in individual or groups of organs. Patterned homeostatic autonomic responses are coordinated within brainstem and hypothalamus (Saper, 2002). Efficient internal regulation also requires integration across systems and ultimately at the whole organism level. Internal visceral states drive complex motivational behaviors both implicitly and through cognitive and affective responses, e.g., arousal, sickness behavior, memory, and mood. There is a primacy of interoceptive control to functional health; the fundamental experience and awareness of self is proposed to follow dynamic central representations of physiological state, driven by afferent visceral signaling (e.g., Damasio, 2010). However, empirical neuroscientific data about the extent to which internal bodily state influences behavior have been slow to emerge. Here, we draw together anatomical and experimental information about the representation and influence of visceral state on brain processes to illustrate principles through which human behavior and experience is colored by internal bodily signals.

Interoception and Emotion

Aristotle's attribution of sensation and emotion to the heart contrasted sharply with the Hippocratic recognition of the brain as the source of mental operations and experiences (Gross, 1995). The fundamental association between bodily changes and emotions remains apparent in the universal use of physiological words to describe emotional states. Darwin highlighted the consistency of physiological expression of emotions even across species (Darwin, 1872). Shortly thereafter, James and Lange both argued for an obligatory origin of emotional feelings in bodily physiological changes (Lange, 1885; James, 1894). Lange's conceptualization of specific bodily changes as signatures of individual emotions was in line with Darwin's notion of "basic emotions"; James was more "constructionist," viewing emotions as made up of elements (e.g., bodily arousal) shared by other processes (Gendron and Barrett, 2009). Cannon

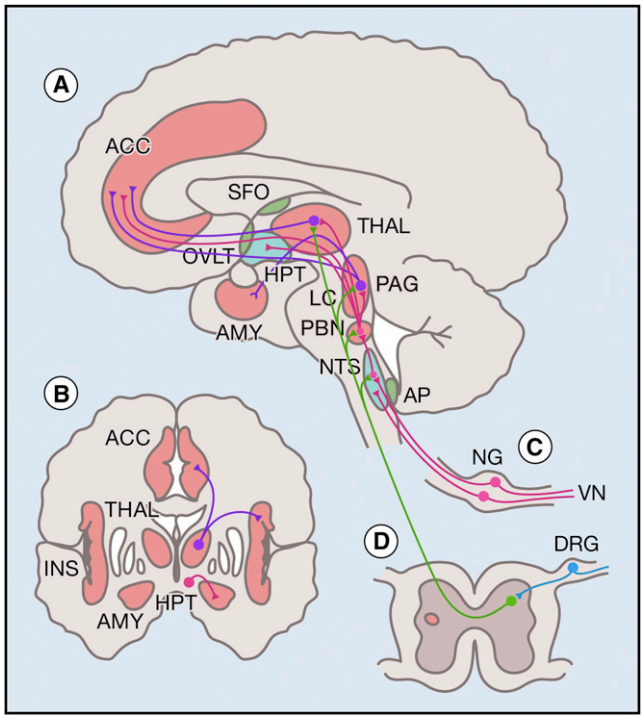

Figure 1. Diagram of Viscerosensory Paths and Centers in the Human Brain

Depicted schematically are (A) parasagittal, (B) coronal brain sections, (C) nodose ganglion of vagus nerve, and (D) section of the spinal cord. These figures illustrate viscerosensory centers and interoceptive neural pathways. Visceral afferent inputs with cell bodies in the dorsal root ganglion (DRG) enter the spinal cord (lamina 1) and ascend in the spinothalamic tract (light green) to terminate in viscerosensory thalamus (THAL) with earlier outputs to the nucleus of the solitary tract (NTS), parabrachial nucleus (PB), and periaqueductal gray matter (PAG). Viscerosensory inputs carried by the vagus nerve (VN) with cell bodies in vagus nerve ganglia (nodose ganglion, NG illustrated) terminate in the NTS and then pass to PB, PAG, and THAL (pink). Information is relayed from THAL, PAG, and PB to hypothalamus (HPT), amygdala (AMY), anterior cingulate cortex (ACC), and insula (INS), the latter being the primary site of viscerosensory cortical representation. Neuromodulatory systems including ascending noradrenergic pathways (originating in the locus coeruleus; LC) are also engaged by visceral afferent inputs. The circumventricular organs (sites of humoral information exchange and sensing of circulatory factors, dark green) include the area postrema (AP), organum vasculosum of lamina terminalae (OVLT) and subfornical organ (SFO). Information from these organs is integrated at a number of sites, notably HPT and NTS.

(1927), meanwhile, argued that physiological changes accompanying emotions were not necessarily specific to emotions. Yet, the idea that emotions are dependent on physiological changes, in conjunction with cognitive evaluation/appraisal of the context, has proved relatively robust (Cantril and Hunt, 1932; Schachter and Singer, 1962). Emotions are now commonly viewed as a class of psychological states that encompass behavioral, experiential, and visceral changes (Gendron and Barrett, 2009).

In parallel with these developments in psychology, knowledge has progressed regarding the representation and control of visceral state above the level of the brainstem. Electrical stimulation in animals and man has demonstrated the coupling of visceral responses to neocortical regions (e.g., Kaada, 1951; Penfield and Faulk, 1955). There is increasing interest in the neural substrates of emotion, triggered in part by evidence-driven arguments for basic emotional states (Ekman et al., 1983; Panksepp, 1998) and emergence of consciousness science. Thus, internal bodily changes are shown to act as covert unconscious influences on "conscious" processes, notably motivational decision making (Bechara et al., 1997). Such effects are linked to the integrity of orbitofrontal, somatosensory, and insular cortices and their putative roles in supporting emotional processes grounded in bodily states. Increasingly detailed understanding of the anatomical projections of interoceptive neural pathways into cortical regions complements functional neuroimaging evidence in humans (Allen et al., 1991, King et al., 1999). The notion that viscerosensory insula cortex supports more general emotional experiences is further highlighted by functional neuroanatomists (Craig, 2002; Saper, 2002). Concepts of emotion continue to be refined, yet distinct theoretical stances typically acknowledge the contribution of physiological changes (Gendron and Barrett, 2009). Experimental research into the mechanisms through which visceral afferent information is represented within the brain will continue to enrich our understanding of emotion, cognition and behavior.

Anatomical Organization

Overview

Visceral information reaches the brain through neural and humoral pathways, conveying a richness of ascending visceral information with in-built redundancy. Visceral afferent fibers innervate almost all tissues of the body and fall into two broad groups: First, those that carry motivational information, e.g., hunger, satiety, thirst, nausea, and respiratory sensations, and travel mainly along cranial, e.g., vagus and glossopharyngeal, nerves to terminate within NTS (nucleus of the solitary tract). Second, spinal visceral afferents that project to the dorsal horns of the spinal cord and, via spinal laminar 1, into the spinothalamic tract. These tend to have a more prominent role in signaling tissue damage. Humoral information is processed largely through circumventricular organs, though some, e.g., core temperature, glucose, and insulin, are also sensed directly within other brain regions including hypothalamus. Inflammatory mediators can additionally influence brain function through microglial transduction pathways, resulting in a wave of microglial activation that propagates across the brain (Rivest, 2009; Figure 1).

The Nucleus of the Solitary Tract (NTS)

The NTS is a site of anatomical convergence of visceral inputs (Blessing, 1997). There is a broad rostrocaudal viscerotopic organization, yet neurons that receive input from distinct bodily organs (stomach, renal, heart) and types of visceroceptor (chemoreceptors, baroreceptors thermal) lie in close proximity to each other (Paton et al., 1999). This arrangement suggests early integration of viscerosensory information across modalities that are linked through patterned responses to functional goals. Correspondingly, NTS projects to hypothalamus, ventrolateral medulla and parabrachial nucleus, regions that contribute to coordinated autonomic, hormonal, and even immune outputs (reviewed in Blessing, 1997; Goehler et al., 2000; Saper, 2002).

The NTS is of primary importance to the control of physiological state, a function nicely illustrated by its role in the baroreflex

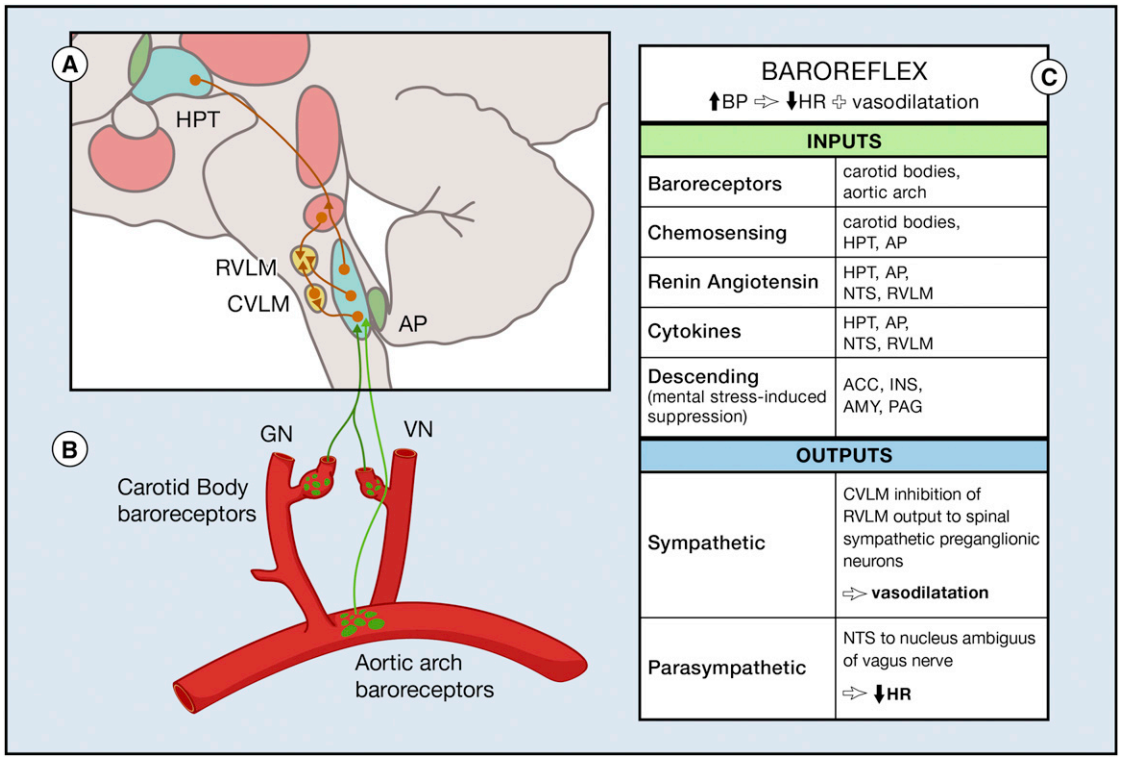

Figure 2. Organizational Arrangements and Influences on Baroreflex

(A) Schematic illustration of viscerosensory brain centers (subsection of Figure 1) and connectivity involved in baroreflex. Rostroventrolateral medulla (RVLM), caudoventrolateral medulla (CVLM), area postrema (AP), hypothalamus (HPT), and nucleus of solitary tract (NTS) located as in Figure 1B.

(B) Illustration of aortic arch and carotid showing location of arterial baroreceptors and cranial nerves (GN, glossopharyngeal nerve; VN, vagus nerve) carrying baroreceptor afferent signal to NTS.

(C) Overview of baroreflex and influences. Baroreceptor firing signals the timing and strength of each heartbeat. Increases in blood pressure to elicit a slowing of subsequent heart beat through dorsal motor nucleus of vagus, increase parasympathetic drive to sinoatrial node, and engender vasodilatation in muscle vascular beds through inhibition of muscle sympathetic nerve traffic via CVLM inhibition of RVLM influence on preganglionic sympathetic neurons in intermediolateral column of spinal cord. Anterior cingulate, insula, amygdala, and periaqueductal gray (PAG) activity is associated with top down suppression of baroreflex induced by stress challenge (Gianaros et al., 2012).

control of circulation (Figure 2). Briefly, stretch-responsive arterial baroreceptors located within the aortic arch and carotid bodies detect the mechanical distortion of vessel walls that occur with each heartbeat. This information is conveyed to the NTS by glossopharyngeal and vagus nerves where an increase in blood pressure triggers a reflex slowing of the next heartbeat and peripheral vasodilatation. Heart beat slowing is achieved by activation of vagus nerve parasympathetic drive to the heart via the nucleus ambiguous. Vasodilation is mediated via NTS projections to inhibitory neurons within caudal ventrolateral medulla (CVLM) that gate efferent muscle sympathetic nerve traffic relaying within the rostral ventrolateral medulla (RVLM). Though the principal function of the baroreflex is to smooth out short-term changes in blood pressure, it is also embedded within a broader system for circulatory control mediated by sympathetic efferents to heart, blood vessels, kidney, and adrenal medulla. The baroreflex is additionally modulated and reset, at the level of second-order NTS neurons that project to CVLM, by ascending (nociceptive and metabolic) (Paton et al., 2001) and descending (top-down) influences via the hypothalamic paraventricular nucleus (Dampney et al., 2001). Together, these allow blood pressure to rise (or fall) in response to changing behavioral needs and mediate responses to stress (Dampney et al., 2001). The NTS also receives neural visceral information conveyed via the spinal cord (notably laminar 1), humoral information via dense projections from the adjacent area postrema and can intrinsically sense specific blood borne factors, e.g., leptin and glucose (Merchenthaler et al., 1999).

The NTS has proximate connections to hypothalamus, parabrachial nucleus and periaqueductal gray. These centers are anatomically (mainly via thalamus) and functionally connected to forebrain regions, including amygdala, insular cortex, rostral and anterior mid cingulate, and orbitomedial prefrontal regions (Blessing, 1997; Figures 1 and 3). Thus, the role of the NTS in sensing and coordinating physiological responses is anatomically linked to perception, cognition, and adaptive behavior. Direct ascending projections are bolstered by projections from neuromodulator systems (particularly monoaminergic) originating in brainstem nuclei (A1/C1 in VLM, A2/C2 in NTS, A6 in locus coeruleus). Many of these monoamine projections are themselves responsive to visceral afferent inputs

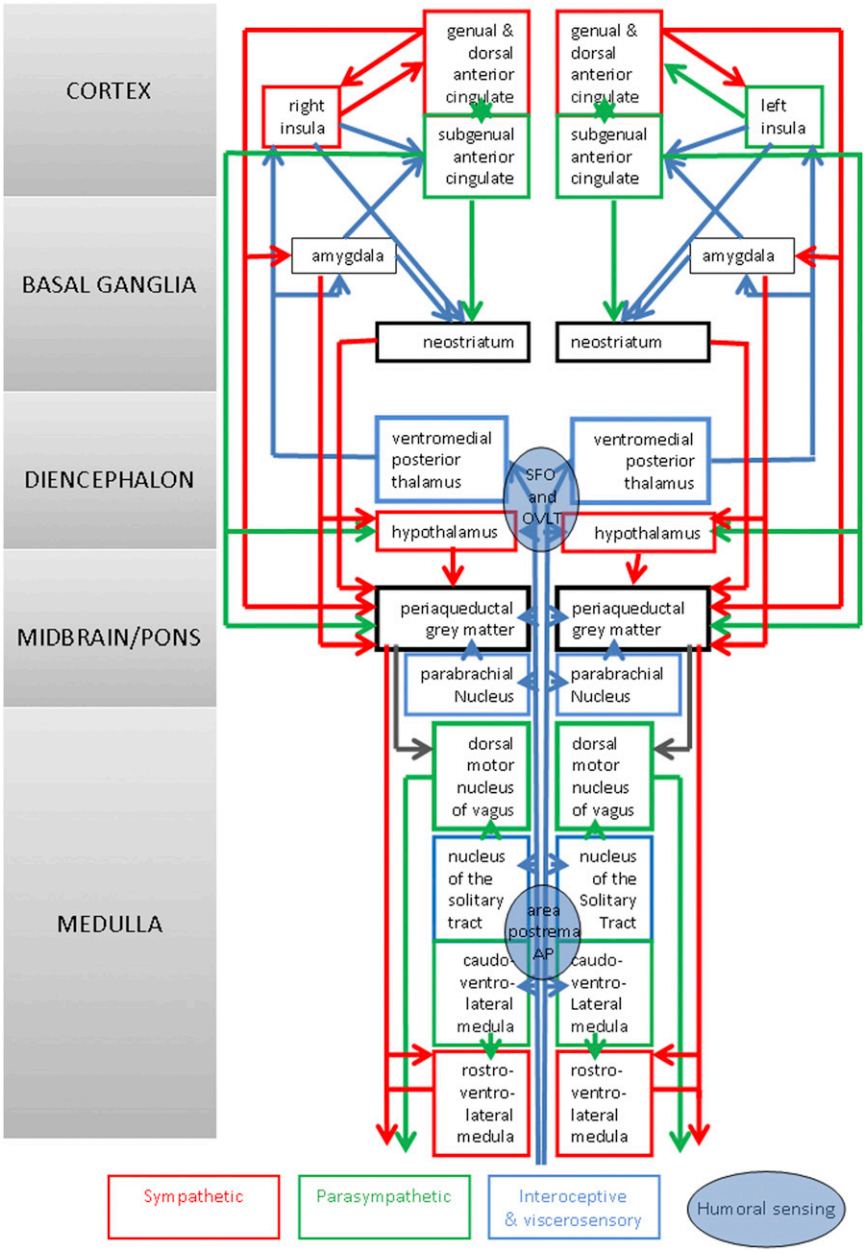

Figure 3. Diagram Illustrating Central Afferent and Efferent Neural Pathways of Interaction Mediating the Central Control of Autonomic Bodily State

The figure links discrete brain regions according to their association with visceral afferent sympathetic and parasympathetic drives (e.g., Critchley, 2009; Critchley et al., 2011). A number of questions arise from this framework, including how hemispheric lateralization relates to autonomic control, and the major sites of humoral influence (e.g., AP connectivity to NTS). While all parts of the neuroaxis are presented in this model, inferred coupling of autonomic control to cognitive functions suggest greater sensitivity of cognitive control (anterior cingulate), hedonic motivation (insula, amygdala, subgenual cingulate) and psychomotor (basal ganglia) processes than mnemonic functions (amygdala, see text) and little impact on early sensory processes. The validity of such inferences needs establishing.

(Elam et al., 1984; Cunningham et al., 1994). Importantly, these connections facilitate early integration of different modalities of viscerosensory information within the NTS.

Visceral Afferents Traveling through the Spinal Cord

The spinal cord receives and carries afferent information about local tissue injury and mechanical changes consequent upon visceromotor activity and organ filling. Autonomic spinal reflexes provide a degree of proximate homeostatic control; however, the consequences of such reflexes may also be systemic, for example in dysreflexic responses to tissue injury or bladder filling in patients with spinal cord transection (Rabchevsky, 2006). Voiding and sexual functions also depend on visceral afferent feedback into spinal reflexes, processes clearly under descending control. The input of spinal Lamina 1 into the dorsal spinothalamic tract, which conveys temperature and pain sensations, has been proposed as a dedicated channel of viscerosensory information and related affectively-laden sensations (Craig, 2003). Lamina 1 receives monosynaptic input from small diameter (unmyelinated) afferent fibers, many of which travel via sympathetic nerves and paravertebral ganglia to spinal cord. Disruption of tissue integrity is signaled by responses to changes in local metabolism (acidic pH, hypoxia, hypercapnia, hypoglycaemia, hypo-osmolarity, lactic acid), cell rupture (ATP, glutamate), cutaneous parasite penetration (histamine), mast cell activation (serotonin, bradykinin, eicosanoids [prostaglandins]), immune and hormonal activity (cytokines, somatostatin), temperature, and mechanical stress (Beyak, 2010). Lamina 1 also carries information experienced as positive feelings, e.g., "sensual touch," originating from unmyelinated fibers within cutaneous or mucosal epithelia evoked by slow, light, repeated mechanical stimuli (Nordin, 1990).

Within the brain, fibers from lamina 1 project into the NTS, parabrachial nucleus, periaqueductal gray, and other brainstem autonomic output nuclei. These are likely to influence patterned changes in bodily state. However, the ventromedial posterior nucleus of the thalamus is the main relay of viscerosensory information within the spinothalamic tract projecting onto insular cortex. The distinct central projection of this laminar 1 "affective" sensory pathway was elegantly illustrated for sensual touch (when compared to classical somatosensory sensation) in a neuroimaging study of patients with loss of classical touch sensation (Olausson et al., 2008; Figures 1 and 3).

Classical Humoral Pathways: Sensory Circumventricular Organs

Circulating substances can access the brain directly via the sensory circumventricular organs—the area postrema (AP), organum vasculosum of the lamina terminalae (OVLT), and subfornical organ (SFO)—located in the walls of the third and fourth ventricles. Specialized loops of fenestrated capillaries surrounded by large perivascular spaces result in a 150-fold increase in surface area/permeability ratio (Gross, 1991). Dense receptor expression enables detection of large circulating molecules that provide information about the systemic milieu, e.g., global metabolic, osmotic, or inflammatory status. Secretory circumventricular organs (pineal gland, subcommissural organ, posterior pituitary, and median eminence) secrete hormones and proteins into the systemic blood stream, in a manner also sensitive to feedback sampling of the blood.

The AP was initially recognized as the site for triggering emetic responses to noxious substances (Borison and Wang, 1953). However, its role extends to include sensing of diverse metabolic, cardiovascular and immune factors (Price et al., 2008). The AP is involved in the control of feeding behavior and expresses receptors for satiety/anorexogenic (hunger suppressing) and orexigenic (hunger stimulating) peptides released from stomach, small bowel, and hypothalamus (Hindmarch et al., 2011). It is closely and reciprocally connected to the NTS and hypothalamus. Within AP, there is functional integration of neuronal viscerosensory and humoral information. AP responses to cholecystokinin are potentiated by gastric distension (transmitted by vagal afferents) (Hayes and Covasa, 2006) and its responses to Angiotensin II impact baroreflex sensitivity (Reid, 1992). Outputs from AP also include the parabrachial nucleus, sympathetic medullary nuclei and the dorsal motor nucleus and nucleus ambiguous of the parasympathetic vagus nerve (Shapiro and Miselis, 1985). Other circumventricular organs, such as the OVLT, appear to play important roles in osmosensation and contain cells with intrinsic osmosensory properties (Ciura et al., 2011). Efferent projections to the hypothalamic supraoptic nucleus (SON) have been proposed to regulate vasopressin release in response to a rise in osmolality, and projections to midline thalamic nuclei, which project to insular and cingulate cortices, are involved in thirst and the desire to drink (Hollis et al., 2008; Bourque, 2008). Of note, the OVLT is embedded within the medial preoptic region, which contains other neurons that may participate in osmoregulation and also project to SON and midline thalamus. The SFO also contributes to osmoregulation, but this region is also sensitive to a range of vasoactive, metabolic, gastrointestinal and gonadal signals (Smith and Ferguson, 2010) demonstrating a broader role in viscerosensing. The extent to which such viscerosensory redundancy is functional (i.e., related to specific neurohumoral response patterns and behaviors) remains to be clarified.

Nonclassical Humoral Pathways: Direct Actions on Sensitive Brain Regions

While the circumventricular organs are specialized for the central detection of low concentrations of circulating humoral factors, many circulating molecules are also able to cross the blood brain barrier (either actively or passively) to exert direct functional effects on discrete brain systems. Many NTS neurons express receptors for Angiotensin II and the satiety factor GLP-1 (Merchenthaler et al., 1999) while hypothalamic nuclei are broadly sensitive to metabolic and reproductive hormones and vascular and immune mediators. Regions of hypothalamus also respond to changes in osmolarity, temperature, and glucose concentration. Glucose is actively transported across the blood-brain barrier and hypothalamic glucose-sensing is linked to the control of feeding (lateral arcuate nucleus) and satiety (ventromedial hypothalamus) (Oomura et al., 1969). Interconnectivity between hypothalamus and NTS embeds neural viscerosensory encoding within the broader context of glucose sensing. A number of other brain regions are directly sensitive to glucose level, such as the medial amygdala nucleus (Karnani and Burdakov, 2011; Dunn-Meynell et al., 1998). In neuromodulator pathways, monoaminergic (dopamine and noradrenaline) neurons express ATP-sensitive potassium channels that are modulated by glucose level (Dunn-Meynell et al., 1998). Interestingly, abnormal systemic glucose regulation (i.e., insulin resistance) can also influence the interaction between ventral striatum, interoceptive insula and cingulate cortex to predict depressed mood (Ryan et al., 2012), an observation that extends the link between glucose sensing and motivational behavior beyond the regulation of food intake to affective processes supported in part by monoamine systems.

Extraneuronal Humoral Mechanisms: Microglia

Another mechanism through which internal bodily state affects brain and behavior involves microglia (brain immune cells). In health, microglia show remarkably dynamic behavior, continuously sampling the extracellular space via ramified processes (Nimmerjahn et al., 2005). This behavior may be involved in synaptic pruning (Schafer et al., 2012), a process critical to neural plasticity and learning. Microglia express Toll-like receptors (TLRs) (Laflamme and Rivest, 2001) enabling them to detect pathogens and tissue damage. Following peripheral infection and/or inflammation, microglia in the circumventricular organs, leptomeninges, and choroid plexus rapidly activate and undergo morphological and functional transformations (Laflamme and Rivest, 2001). This may occur in response to direct sensing of circulating cytokines (Rivest, 2009) or prostaglandin E2 produced by perivascular and endothelial cells (Saper et al., 2012). Activated microglia release tumor necrosis factor (TNF) (Nadeau and Rivest, 2000), which acts on adjacent cells, resulting in a cascade of microglia activation across the brain parenchyma. Recognition of this brain response to systemic infection challenges the concept of the central nervous system as an immune-privileged site and highlights a channel through which changes in peripheral physiological state are communicated to the brain.

Integration and Influence of Interoceptive Information

Viscerosensory Integration

The interoceptive channels described above convey motivationally salient information about the functional state of bodily organs, circulating environment and the presence of threats to the biological integrity of the individual. The same channels carry signals that evoke appetitive and positive hedonic responses (e.g., pleasant taste, satiety and sensual touch). Integration of visceral information begins in the periphery, where prespinal

and spinal reflexes provide initial adaptive responses. At the brainstem, the capacity to integrate viscerosensory information and orchestrate patterned responses increases.

The partial specialization between, and even within, viscerosensory hubs suggests an underlying representational architecture for integration, yet interaction between humoral and neural signals within NTS, AP and hypothalamus blurs such boundaries. The notion of a hierarchy of viscerosensory representation is countered by the extent of crosstalk between levels, including the top-down cortical/behavioral influences to brainstem and spinal centers. The integration of viscerosensory signals may result in a global representation of physiological integrity (Craig, 2003; Singer et al., 2009). This could translate to a one-dimensional hedonic state (Ramirez and Cabanac, 2003), serve as a descending predictive model to shape processing of ascending afferent information (Seth et al., 2011) or translate into a subcortical neuromodulatory signal (e.g., dopamine; Schultz, 2010) that mediates influence of motivational value. It is plausible that integration of viscerosensory information results in representations similar to those observed in the related gustatory system. Taste phenomenology may therefore usefully inform our understanding of less consciously accessible interoceptive information. Advances in the anatomical characterization of interoceptive regions, including insula cortex, will undoubtedly provide major insights into the neural coding and integration of visceral state with behavior (Evrard et al., 2012).

Autonomic and Respiratory Influences on Cerebrovasculature

At the most basic level, physiological health dictates the environment for efficient brain function. Neural and humoral control of internal bodily state broadly constrains cognitive and affective processes. Microglial communication of inflammation represents one expression of this. Autonomic innervation of the cerebrovasculature is another, wherein regional cerebral blood flow is partially under direct autonomic control. Autonomic nerves, predominantly from the superior cervical and sphenopalatine ganglia, densely innervate cortical blood vessels. While autonomic activity is generally assumed to exert global effects on neurovascular coupling (e.g., during extreme physiological challenges) this is not empirically established, particularly in humans. Animal studies indicate that sympathetic activation blunts cerebral blood flow responses to hypoxia, hypercapnia, and hypertension (López de Pablo et al., 1982; Busija, 1984). Sympathetic activation can also impair neurovascular responses evoked by somatosensory stimulation (Tsubokawa et al., 1980), and in humans reduced sympathetic activity (following experimental autonomic ganglion blockade) disrupts dynamic beat-to-beat autoregulation of cerebral blood flow in response to changes in systemic blood pressure (Zhang et al., 2002). These findings suggest that cortical blood flow is influenced by peripheral bodily state independent of local neuronal activity and metabolic demand (Sato and Sato, 1992; Drake and Iadecola, 2007). Remote vascular effects can also be mediated by the action of neuromodulatory systems (monoaminergic and cholinergic neurons from basal forebrain, raphé, ventral tegmental area, and locus coeruleus) that are themselves sensitive to interoceptive information. Oxygen-sensing neurons within the RVLM (noted above as a sympathetic relay contributing to the baroreflex), in conjunction with those in the subthalamic region, are implicated in the systemic sympathetic response to hypoxia and intrinsic changes in cerebral blood flow (Golanov et al., 2001; Reis et al., 2006). These effects on brain vascular responses are perhaps not as marked as the modulation of cerebral perfusion by CO_2 levels, an effect that, even at resting physiological ranges produces fluctuations in hemodynamic signals used to infer neural activity in neuroimaging studies (Wise et al., 2004). Yet direct CO_2 effects are not global in their expression and are accompanied by shifts in regional activity within affective and motivational brain centers (Corfield et al., 1995). The close coupling of ventilation to other interoceptive processes (pH balance, cardiovascular function, inflammatory states) and motoric and affective behavior, suggests that respiration via CO_2 is a major bodily influence on brain processes.

Modes of Influence of Interoceptive Information Processing

The respiratory and vascular effects mentioned above are distinct from the neural signaling and representation of interoceptive information within the brain. The central representation of internal physiological state may emerge as a foreground sensory experience (e.g., visceral pain or nausea) that can grab and dominate one's attention, interrupt ongoing thoughts and feelings and compete with other cognitive and sensory processes. Given the intrinsic motivational meaning of such foreground visceral sensations (often affectively negative), a constellation of associated cognitions and behaviors may be engendered. Alternatively, viscerosensory information may be fully integrated with other perceptions and cognitions through temporal congruence, directly coloring them with value and motivational significance, thereby enhancing their emotional salience and facilitating encoding into memory (Cahill and McGaugh, 1998). Bodily state may also act as a variable context or "occasion setter" for emotional and cognitive processes; Information learned in low arousal is best recalled in low arousal. One's exteroceptive perception of bodily state may also affect behavior. This can include seeing the pallor of one's face in the mirror, internalizing the perceived physiological state of others, or perceiving the reactions of others to one's own apparent physiological or emotional state. Simulation (mirroring) of emotional state through physiological embodiment of the corresponding bodily responses is linked to empathy (Harrison et al., 2010; Singer et al., 2009).

Cortical Centers for Autonomic Integration

Following the theoretical models of emotion that incorporate a central role for internal bodily states (e.g., James, 1894; Schachter and Singer, 1962), particular brain regions have been implicated in the representation and integration of viscerosensory information with emotions, feelings, cognition, and behavior mental functions. This area of study is guided by inferences from neuroanatomical studies (Craig, 2002, 2003) and explored directly using functional neuroimaging. The combination of human neuroimaging and clinical research has provided insight into mechanisms underlying the central generation of internal bodily responses and their feedback representation to influence mental processes (e.g., King et al., 1999; Critchley, 2009; Harrison et al., 2010; Critchley et al., 2011). There is evidence within forebrain regions of a medial generator system,

wherein rostrodorsal anterior cingulate cortex drives sympathetic arousal during emotive and effortful behaviors, typically in association with dorsal pons and (although less consistently observed) with hypothalamic and/or amygdala activity. Human neuroimaging evidence indicates a partial segregation of autonomic control within dorsal anterior and mid cingulate (blood pressure, pupil size, heart rate, electrodermal activity) (Critchley, 2009) Similarly, subgenual cingulate, with ventromedial prefrontal cortex (VMPFC) appears antisympathetic (and parasympathetic) (Critchley, 2009; Critchley et al., 2011; Nagai et al., 2004; Wager et al., 2009).

Neuroimaging studies implicate insular cortex in the cortical representation of autonomic responses and changes in visceral state (e.g., King et al., 1999); right anterior insula supports integration of visceral arousal with conscious processing (Craig, 2002; Critchley et al., 2002, 2004). Insula activity, often with amygdala, encodes both subjective emotional state and the emotive value of external stimuli (Critchley et al., 2004; Gray et al., 2007). Interestingly, the representation of different bodily states (i.e., axes of interoceptive information) maps onto subregions of insula and gives rise to dissociable emotional feeling states (e.g., heart and stomach responses during disgust-associated nausea or light-headedness [Harrison et al., 2010]).

Metabolism and Feeding

Taste is powerfully linked to motivational behavior; evident in the impact that nutritional and metabolic status has on dietary selection. Sodium-deficient rats seek salty drinking water, whereas thiamine-deficient rats broaden intake of novel foods, increasing their chance of ingesting thiamine (Rodgers and Rozin, 1966). Mesolimbic projections to ventral pallidum (including signals from the ventral tegmentum) may underpin the ''wanting'' of specific nutrients (Tindell et al., 2009),while brainstem and hypothalamic projections to insula likely support conditioned taste aversions, the learned associations between taste and sickness (Dunn and Everitt, 1988). Vagus nerve projections to the NTS and parabrachial nucleus also signal satiety through mechanoreceptive (gastric distension) and chemical signaling (cholecystokinin CCK and 5-hydroxytryptamine 5HT) (Hayes and Covasa, 2006; Mazda et al., 2004).

Satiation and satiety signaling when eating food involves integration of gastric and intestinal feedback with information about the sensory qualities (including taste) of the food (Rolls, 2011). Gastric satiation signals occur almost exclusively in response to volumetric distension of the stomach (Powley and Phillips, 2004) and do not directly result from nutritive or chemical properties. Conversely, satiety signaling arising from the intestine results from nutrient detection and release of various anorectic gut peptides and neurotransmitters (Ritter, 2004). Many of these intestinally derived anorectic signals stimulate vago-vagal reflexes, reduce gastric emptying, and result in gastric retention. Meal termination is postulated to occur principally in response to neuronal integration of gastric and intestinal negative feedback signaling (Powley and Phillips, 2004; Ritter, 2004). One site of neuronal integration between gastric and intestinal anorectic signals is the dorsal vagal complex (DVC), which receives and relays neuronal signals from the gastrointestinal tract and regions of the forebrain (Mazda et al., 2004; Ricardo and Koh, 1978). Not every brain region expresses the same type of viscerosensory integration. While taste response neurons within primate NTS, taste thalamus and primary taste cortex do not typically change their responses after feeding to satiety, taste-responsive neurons within orbitofrontal cortex and lateral hypothalamus reflect motivation state by responding only when hungry (Rolls, 2011).

Sickness Behaviors

The immune system operates as a diffuse chemosensory system, signaling the presence of infective agents (though detection of PAMPs, such as lipopolysaccharide, flagellin, or CpG-containing DNA) or alteration to the integrity of tissues (tissue DAMPs, such as heat shock proteins or uric acid). Activated immune cells release immune and inflammatory mediators, notably cytokines, that activate vagus afferent neurons projecting to the NTS and, via humoral sensing, activate cells within the SFO. Interestingly, immunosensitive vagus afferent neurons exhibit sensitization, present elsewhere in the immune system; the number of vagus nerve afferents responding to antigen exposure rises dramatically (from 20% to 85%) after a second re-exposure (Weinreich et al., 1997). NTS and AP responses initiate cardiovascular and gastrointestinal reflexes, regulate peripheral immune responses (Tracey, 2009), and evoke a stereotyped constellation of responses known as sickness behaviors including fever, lassitude or fatigue, social isolation, and reduced food and water intake (Dantzer et al., 2008). These responses are proposed to support host defense. CNS sensing of inflammation, particularly within NTS, also plays a critical role in regulating the magnitude of innate immune response to infection, injury or ischemia (Tracey, 2009).

Animal studies link distinct pathways from the NTS (to hypothalamus, extended amygdala, thalamus, and insula) to specific components of coherent sickness response (including changes in emotional state and altered taste perception during illness) (Goehler et al., 2000). Human functional imaging studies demonstrate activation of a neurally mediated interoceptive pathway (including basal and posterior ventromedial thalamus and dorsal mid/posterior insula) within 3 hr of inflammatory challenge (Harrison et al., 2009a; Figure 4). In humans, inflammation-induced responses within discrete brain regions appear to underpin individual components of sickness behavior: altered mid-insula activity predicts subjective fatigue (Harrison et al., 2009a), while altered substantia nigra reactivity predicts psychomotor slowing (Brydon et al., 2008). Similarly, altered subgenual cingulate reactivity is associated with mood changes evoked by sickness, with changes in connectivity to discrete amygdala and ventral striatum (Harrison et al., 2009b; Figure 4). These centers are critical for emotion and motivation and are implicated in the etiology of idiopathic depression (Ressler and Mayberg, 2007). Inflammatory effects on discrete mood symptoms, notably anhedonia, are further linked to suppressed ventral striatal responses to reward (Eisenberger et al., 2010). Human functional imaging studies of inflammatory responses and sickness behaviors have typically not evoked pyrexia, a sickness response closely associated with the humoral release of prostaglandins (Saper et al., 2012), reflecting instead patterns of response putatively mediated by vagus nerve afferents (Luheshi et al., 2000). This is clearly a rich area of research to pursue.

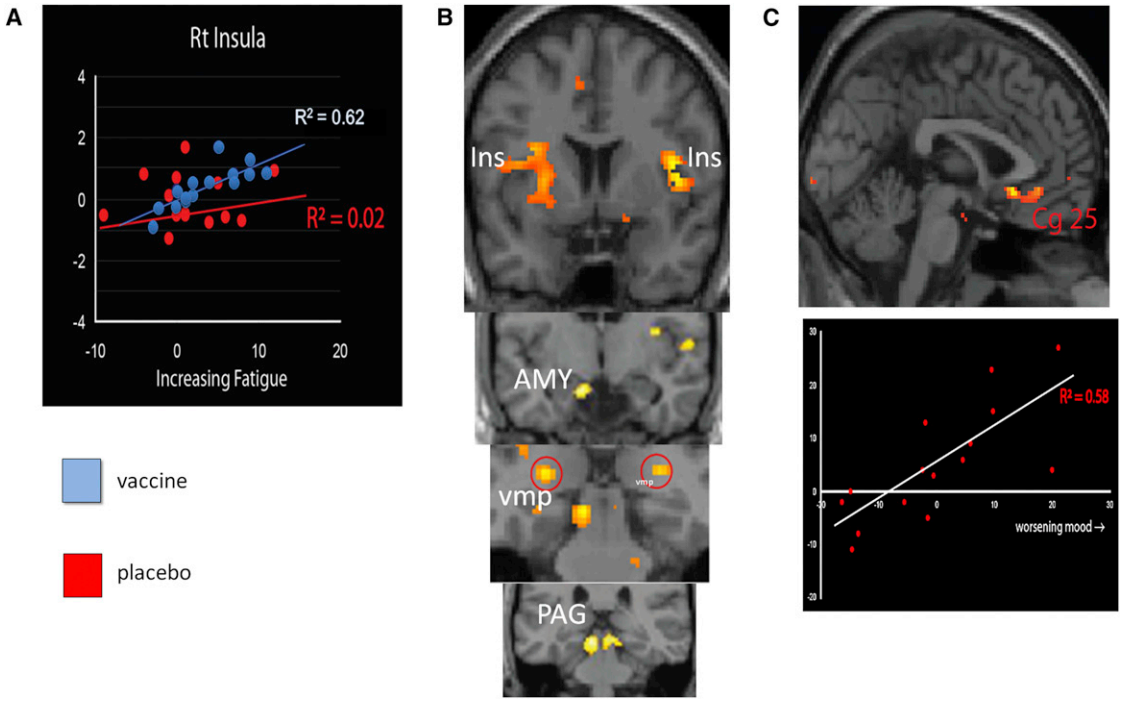

Figure 4. Impact of Peripheral Inflammation on Human Brain Activity, Cognition, and Emotion

Group neuroimaging results are shown from fMRI experiments in which participants were scanned during states of (typhoid vaccine) induced peripheral inflammation or after placebo injection.

(A) Reactivity of right insula cortex to (Stroop task) stimuli; predicted inflammation (not placebo) induced fatigue over the course of the experiment (Harrison et al., 2009a).

(B) Following induced inflammation, brain regions showing greater reactivity map onto known central visceral afferent pathways: dorsal pons and periaqueductal gray matter (PAG); ventromedial pallidum (vmp), amygdala (AMY), and insula (Harrison et al., 2009b).

(C) Inflammation-induced enhanced reactivity within subgenual cingulate cortex (cg25) to emotional face stimuli predicts inflammation-induced worsening of mood. Dysfunction of this region is implicated in pathoetiology of clinical depression. This finding (and other changes in functional connectivity) suggests depression hijacks mechanisms for the expression of social withdrawal and motivational blunting in adaptive sickness behaviors.

Influence of Internal Bodily Signaling on Memory

Increased emotional and physiological arousal enhances memory encoding and facilitates recall (Cahill and McGaugh, 1998). Central noradrenergic and glucocorticoid mechanisms influence hippocampal encoding and amygdalo-hippocampal connectivity. Autonomic and neurohumoral responses, including sympathetic adrenaline release, act directly or via vagus afferent relays on amygdala and associated memory-related forebrain regions. Moreover, later memory can be predicted by autonomic responses (e.g., heart rate response and electrodermal activity). Pharmacological agents that enhance peripheral and/or central sympathetic action can enhance memory (Cahill and McGaugh, 1998) while β-adrenergic antagonists that attenuate sympathetic activity impair memory particularly of emotional material (Cahill and McGaugh, 1998; van Stegeren et al., 1998). Memories grounded upon familiarity (in the absence of accurate recollection) are also marked by increased autonomic activity, as indexed by electrodermal activity (Morris et al., 2008) or pupillometric change (Heaver and Hutton, 2011), suggesting that accompanying bodily changes may mediate the feeling of "knowing" ascribed to such memories (Morris et al., 2008). Subjective memory impairment is common in people with peripheral autonomic failure (Bradbury-Egglestone syndrome) (Heims et al., 2006) and perturbation of afferent visceral information (e.g., via vagus nerve stimulation) influences memory. In depressed patients, vagus nerve stimulation can attenuate encoding of negative information, an effect associated with engagement of ventromedial prefrontal cortex, insula and dorsal pons (Critchley et al., 2007).

Humoral factors associated with emotional and physiological stress (e.g., circulating glucocorticoids) impact memory, but this is complex. Cortisol elevation during stress (or experimental administration) interferes with declarative memory (Kirschbaum et al., 1996) yet the direction (increase or decrease) is sensitive to diurnal fluctuations in physiological state. Cortisol administration interferes with memory most reliably at the time of retrieval (de Quervain et al., 2000). Cortisol elevation at encoding is more likely to facilitate memory in the afternoon (Het et al., 2005). Hippocampal function is also sensitive to a range of dietary and feeding factors. Ghrelin modulates hippocampal synapse density (Diano et al., 2006) and a high-fat meal is associated with spatial memory impairment within 72 hr (Kanoski and Davidson, 2010). Inflammatory cytokines also have complex actions on spatial memory; facilitation occurs at low doses and impairment at higher doses. Cytokines are even implicated in healthy hippocampus-dependent memory function (Yirmiya and Goshen, 2011). Inflammatory cytokines administered to healthy people enhance sleep-associated consolidation of

emotional memories (Benedict et al., 2009), though basal cytokine levels predict a worsening of memory (e.g., Marsland et al., 2006).

The influence of visceral state on memory is also suggested by individual differences in sensitivity to internal bodily state. Individuals with greater interoceptive sensitivity perform better on specific memory tests and show enhanced recognition memory for emotional pictures (Pollatos and Schandry, 2008) and words (Werner et al., 2010). These observations suggest that a greater autonomic response and/or enhanced access to bodily information provide facilitating cues for memory retrieval.

Autonomic Integration with Emotion

Although strongly linked, the precise contribution of physiological response to emotion still remains controversial (Gendron and Barrett, 2009). Emotional response patterning may be consistent within individuals, with internal states of arousal influencing the experience and intensity of emotion. Observed heterogeneity in physiological responses evoked by emotive stimuli argues against unique autonomic signatures of different emotions (Cacioppo et al., 2000; Barrett, 2006). Yet there is also evidence for emotion-specific patterning of autonomic responses (Rainville et al., 2006; Kreibig, 2010). The skepticism regarding association of discrete emotions to discrete physiological states originates, in part, with Walter Cannon who argued that bodily arousal responses are too undifferentiated to account for the variety of distinct emotional feeling states (Cannon, 1927). However ''constructionist'' approaches do not require a specific bodily response for each type of emotion (Gendron and Barrett, 2009). Bodily arousal may initiate and intensify the experience of an emotion, the quality of which is determined by cognitive appraisal of the likely cause of the arousal (Schachter and Singer, 1962). Similar notions exist within the somatic marker hypothesis (Damasio et al., 1991).

Interoceptive Sensitivity

One prediction of ''peripheral models'' of emotion is that the expressions and intensity of emotional experience will differ between individuals according to their sensitivity to internal bodily sensations. There is a revival of interest in the measurement of individual differences in interoceptive sensitivity, proposed to be a consistent trait-like characteristic that underlies emotional style (Cameron, 2001). Interoceptive sensitivity can be quantified using questionnaires or experimental tasks. Questionnaire measures, such as the autonomic perception questionnaire (APQ; Mandler et al., 1958), require participants to rate their awareness of a range of bodily sensations including cardiovascular, digestive, and excretory processes. Some questionnaires also add interpretative elements, probing the perceived meaning of the sensations (e.g., Butler and Mathews, 1983). Experimental tasks have gravitated toward testing how accurately a participant can gauge their heart beating at rest. Most now use the methods of Whitehead et al. (1977) or Schandry (1981). In the former, a series of lights or tones are presented and participants are asked to judge whether they are synchronous or delayed relative to their own heartbeat. Schandry's approach uses a mental tracking task, in which participants silently count their own heartbeats over a set time interval. Both tasks give an accuracy measure of cardiac sensitivity, though neither is free from psychometric issues. Nevertheless, these approaches can predict vulnerability to affective symptoms (notably anxiety; Schandry, 1981), performance on implicit tasks that can be steered by internal arousal responses (e.g., trace fear conditioning; Katkin et al., 2001) and other measures of emotional reactivity (e.g., Wiens et al., 2000).

Neuroimaging studies link interoception, and performance on tests of interoceptive sensitivity, to activation of anterior cingulate and insular cortices (Pollatos et al., 2005; Critchley et al., 2004), strengthening evidence for the contribution of these regions in autonomic control. The size and reactivity of anterior insular regions predicts both interoceptive sensitivity and the potential to experience emotions, particularly anxiety (Critchley et al., 2004; Paulus and Stein, 2006). Such evidence reinforces the proposal that right anterior insular cortex is an important site of conscious readout of visceral sensations and their expression as emotional feeling states (Craig, 2002, 2003). This role of insular cortex is further highlighted by a study of disgust. Combining electrocardiography, electrogastrography, and functional magnetic resonance imaging, the physiological effects of core (nauseating) disgust and body boundary violation disgust (engendering feelings of light-headedness) on gastric and cardiac activity were mapped to discrete subregions of insular cortex that also predicted the magnitude of disgust experienced by the observer (Harrison et al., 2010).

Perturbation and Experimental Manipulation of Visceral Afferent Information

The neural architecture supporting the representation of visceral state is also revealed in studies using direct visceral stimulation (e.g., King et al., 1999). Direct gastrointestinal stimulation of esophagus or large bowel activates insula and cingulate cortices, even in the absence of pain (Hobday et al., 2001). Viscerosensory sensation is distinguishable from somatosensory inputs; bilateral insula and dorsal anterior cingulate cortex are activated by rectal (but not anal) stimulation (Eickhoff et al., 2006; Hobday et al., 2001). The ventromedial prefrontal cortex is also implicated in perturbations of visceral afferent information. Observations in patients with spinal cord lesions, and a single patient treated with vagus nerve stimulation for depression, highlight this region's involvement in afferent viscerosensory representation (Critchley et al., 2007; Nicotra et al., 2006).

In human neuroimaging studies, task-induced fluctuations of autonomic state modulate activity within similar brain areas to direct visceral stimulation (i.e., including areas involved in emotion) (e.g., Critchley, 2009; Critchley et al., 2011). Typically evoked changes occur across multiple axes of autonomic response (e.g., pupil, electrodermal, heart), yet with cardiovascular arousal one can be more specific about the afferent channel signaling changes in body state. The phasic discharge of arterial baroreceptors occurring at each cardiac systole signals the timing and strength of individual heartbeats. This information, conveyed via vagus and glossopharyngeal nerves to the NTS, drives the baroreflex control of blood pressure. One can tap into this channel of viscerosensory information by timing brief stimulus presentations to baroreceptor active (systole) and quiescent (diastole) periods. Baroreceptor discharge can thus influence processing of painful and strong unexpected somatosensory stimuli (cutaneous shock), modifying cortical, reflexive, and autonomic responses (Donadio et al.,

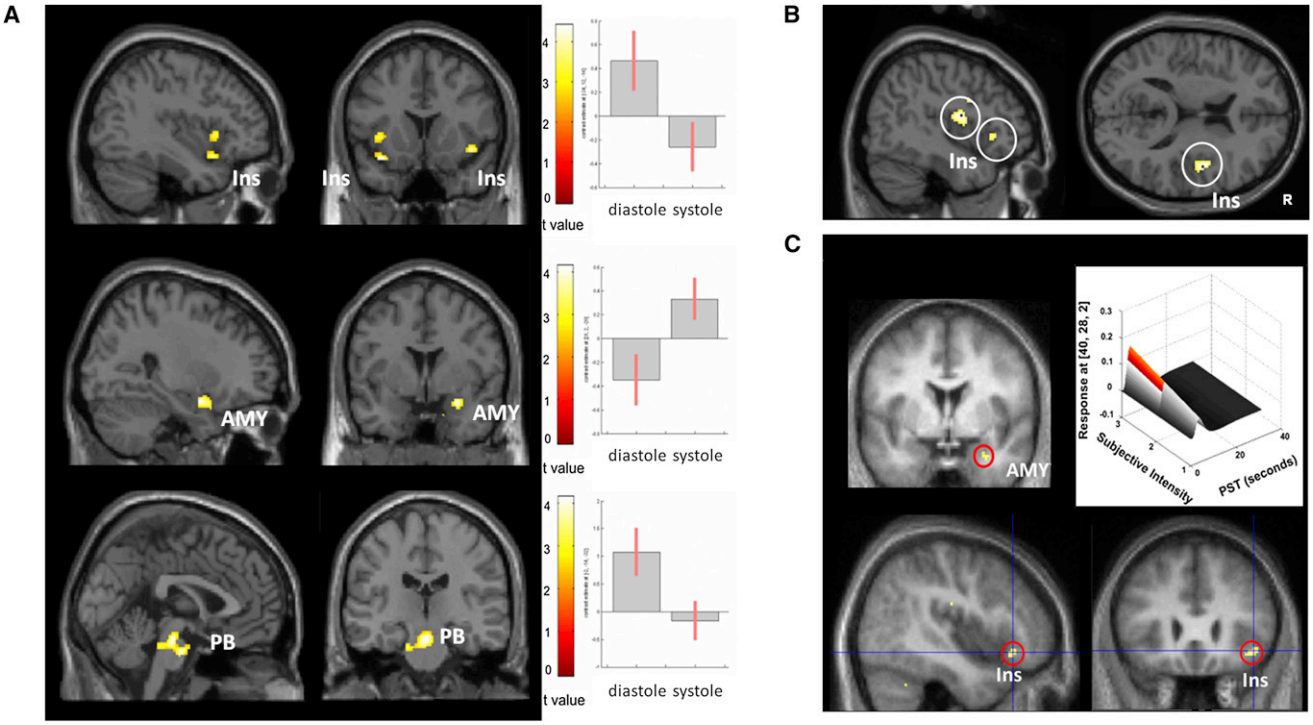

Figure 5. Neuroimaging Studies of Visceral Afferent Interactions with Sensory, Cognitive, and Affective Processes

The panels plot three examples of neuroimaging experiments, plotted on normalized template brains to indicate regional anatomy.

(A) Brain activity predicting the effect of concurrent baroreceptor activation on processing of electrocutaneous shock (Gray et al., 2009). Functional MRI was used to index regional changes in brain activity during a task in which delivery of surprising shocks to the skin was time-locked to different phases of the cardiac cycle: systole (during baroreceptor activation) and diastole (baroreceptor quiescence). Simultaneous beat-to-beat blood pressure recording demonstrated a significant attenuation of autonomic blood pressure responses to shocks delivered at systole compared to diastole. The figure demonstrates regional brain activity changes within bilateral insula (Ins), amygdala (AMY), and pontine regions (parabrachial nucleus, PN) that expressed this interaction.

(B) Right insula activity reflecting interaction between peripheral autonomic response and conscious processing of threat (Critchley et al., 2002). Patients with pure autonomic failure (PAF), a progressive peripheral denervation of autonomic effectors, are unable to generate changes in autonomic state to threat stimuli. PAF patients and controls were scanned during a fear-conditioning task in which the association between face stimuli and an aversive white noise burst was learned over repeated presentations. Backward-masking was used on some presentations to block conscious awareness of threat stimuli. Activity within mid and anterior regions of right insula reflected three-way interaction between presence of threat, conscious awareness of threat stimuli (unmasked v. masked) and presence/absence of autonomic response (PAF v. controls). These findings suggest right insula as a substrate for integration of physiological arousal with conscious appraisal, a basis for subjective emotion states proposed by Schachter and Singer (1962) two-stage model.

(C) Brain activity with right insula and amygdala reflecting the change in intensity ratings of neutral face stimuli in the context of false physiological feedback of increased heart rate. Participants underwent fMRI while performing a task rating face stimuli during isometric exercise and no-exercise conditions. Participants were played auditory tones, which they were told were triggered by their heartbeats. For the most part this was true, but when tones were played back from exercise blocks during no-exercise blocks, this resulted in an elevation in subjective emotional ratings of ambiguous neutral face stimuli. Activity of right anterior insula and amygdala correlated with this effect, with implications for the predictive representations of bodily state and relevance to generation of anxiety and related symptoms.

2002; Edwards et al., 2003; Wallin, 2007). Patients with blood phobia and syncope show exaggeration of such effects, suggesting that baroreceptor afferent mechanisms influence emotional traits and reactivity (Donadio et al., 2007). Neuroimaging observations (Gray et al., 2009) show the interaction between shock stimuli and baroreceptor activation is mediated by differential engagement of brainstem (pons, PAG), amygdala, and insula (Figure 5).

Cardiac cycle and baroreceptor activation also influences the processing of emotional facial expressions (Gray et al., 2012). Systole is associated with increased intensity ratings of expressions of disgust and an attenuation of evoked cardiac responses to both happy and disgusted faces. These effects were linked to changes in activity within dorsal brainstem and orbitofrontal cortices. This is in contrast to other emotions (anger, sadness) where responses were not modified by cardiac cycle. These findings point to an integrative role of orbitofrontal cortex in combining perceptual representations with motivationally salient physiological information. The impact of baroreceptor afferent formation is also observed on memory for words, an effect modulated by interoceptive sensitivity (S.N. Garfinkel, A. Barrett, L. Minati, R.J. Dolan, A.K. Seth, and H.D.C., unpublished data).

Autonomic Communication and Empathy

The integration of cognitive, affective and autonomic responses is proposed to guide adaptive social behavior (Damasio et al., 1991; Damasio, 1994, 1999). Simulation models of emotion suggest that we understand emotions of others if we experience similar changes in our visceral state, i.e., if we mirror and feel the internal state of the perceived emotion. The degree to which individuals are susceptible to this "emotion contagion" predicts

individual differences in empathy ratings (Sonnby-Borgström, 2002). Patients who cannot generate autonomic responses reported reduced empathetic experience on such questionnaires (Chauhan et al., 2008).

Reciprocation is visibly evident in the contagion of fear (including facial pallor) and anger responses (facial flushing), but often the exchange is subtle and the signals covert. This is evident in the mirroring of pupillary signals (Harrison et al., 2006, 2007). When asked to rate pictures of emotional faces, healthy volunteers implicitly perceived sad faces to be more negatively intense if the pupil size was smaller (the size of the stimuli pupils was digitally manipulated across a biologically plausible range). This replicated effect was not seen for other emotional expressions and refuted an initial prediction that enlarged pupils would increase intensity ratings. The sensitivity of these individuals to pupil size also correlated with empathy ratings. A parallel pupillometry/neuroimaging study using the same stimuli showed that the observer's own pupil size mirrored the observed pupil size when processing sad faces. This effect was associated with activity changes in amygdala, insula, and superior temporal sulcus and also in dorsal brainstem within an region encompassing the Edinger-Westphal nucleus (responsible for autonomic pupillary control) and locus coeruleus. Independently, this specific link between sadness and pupil size is noted in Holmes-Adie syndrome (del Valle Loarte and Garcia Ruiz, 2009).

Contagion of emotion is linked to mirroring of bodily state to amplify corresponding emotional feelings (Critchley, 2009). Individuals with enhanced interoceptive sensitivity thus may manifest increased empathy. This link has been made in healthy volunteers in whom the amplitude of heartbeat-evoked potentials, thought to reflect cortical representation of afferent cardiac signals, correlates with self-rated empathy scores (Fukushima et al., 2011).

Viscerosensory Integration in Self-Representation

There is a longstanding notion that the mental representation of self is ultimately grounded in the representation of the body. The internal body ultimately may provide the primary reference, a material self, for interaction with the environment. This supposes stability in viscerosensory representation and while homeostasis constrains the milieu interieur within broad limits, internal state fluctuates and is controlled through interacting physiological and behavioral (allostatic) mechanisms. Nevertheless, adaptive control of internal state requires a fairly stable model, that may represent a consistent factor for self-reference. Within the brain, adaptive control is achieved through forward models, efference copies and prediction errors wherein viscerosensory data is continuously compared against expected bodily state to evoke physiological and mental reactions. The integrity of self-representation therefore depends on the quality and fidelity of viscerosensory information to generate accurate predictions and prospectively tune these through prediction errors. Feeling states can be viewed as the expression of such predictions. Uncoupling efferent visceral control from internal feedback might, if transient, provoke a sense of unease, requiring behavioral or psychological adjustment. More persistent or profound uncoupling may destabilize established cognitive and emotional processes and fundamentally compromise self-representation (Seth et al., 2011).

There are few clear instances of this. Patients with acquired (typically traumatic) high spinal cord transection experience a major uncoupling of part of their internal and external bodily control. However, there is little compelling evidence that basic self-representation is compromised (Nicotra et al., 2006). People with spinal transection are vulnerable to depression and chronic pain occurring in the context of a need to adjust psychologically to paralysis and potential loss of independence. These experiences can enhance self-referential thoughts. Moreover, intact cranial nerves, including the vagus, may provide sufficient visceral control and feedback to sustain affective mental reactivity. Another potential lesion/deficit model is represented by patients with pure autonomic failure (PAF) in whom there is a gradual deterioration of autonomic effector function. Visceral afferents are presumed intact. Emotional reactivity is broadly normal; the apparent pragmatism of PAF patients is often noteworthy. (Heims et al., 2006). In everyday situations, behavioral strategies help regulate fluctuations in viscerosensory state (particularly blood pressure), arguably preserving the contribution of viscerosensory feedback to self-representation.

Mismatch and misattribution of interoceptive cues appears key to psychological disorders affecting self-representation. In a "comparator model" of schizophrenia, it is proposed that disturbances of self (e.g., delusions of control) arise as a consequence of problems in predictive coding, reflecting confusion between evaluation of changes in sensations caused by the self or by external causes (Frith, 2011). The generation of exaggerated internal bodily prediction errors is implicated in anxiety, mediated by interoceptive insular cortex (Paulus and Stein, 2006). Highly anxious individuals show increased anterior insular cortex activity during emotion processing. Inducing mismatch between predicted and actual interoceptive signals via false physiological feedback further endorses this role of insular cortex (Gray et al., 2007). In schizophrenia and primary dissociative disorders (e.g., depersonalization and derealization disorder), the concept of self is disturbed. Psychotic or dissociated patients show misattribution of interoceptive cues, where pain signals are dulled and their origin misattributed, with corresponding autonomic disturbances (Koponen et al., 2008; Griffin et al., 1997; Latalova et al., 2010).

Illusions of body ownership, e.g., the Rubber Hand Illusion, in which synchronous tactile and visual stimulation can lead individuals to experience a false hand as their own, can be used to probe mechanisms underlying the integrity of self-representation. Susceptibility to the Rubber Hand Illusion is increased by dissociative drugs such as Ketamine (Morgan et al., 2011), and schizophrenia patients are more prone to this type of illusion (Peled et al., 2000). Interestingly, people with enhanced interoceptive sensitivity are less susceptible (Tsakiris et al., 2011). This reinforces the link between representation of internal bodily state and the integrity of selfhood and its malleability by exteroceptive perceptions. There is increasing weight behind the notion that interoception, and interoceptive predictive coding, is at the heart of a neural representation of self critical to emotional and motivational feelings and the continuity of conscious experience (Singer et al., 2009; Craig, 2003; Damasio, 2010; Seth et al., 2011).

Conclusions

Internal bodily state exerts pervasive influences on brain function and mental activity. There is a primacy to these representations. Interoceptive signals inform central control processes necessary to maintain life, a role that naturally emerges prior to maturation of the exteroceptive senses and which is usually uninterrupted thereafter. Adaptive behavior is motivated by the need to ensure immediate and prospective integrity of internal physiology, from which emerges motivational states and emotions of increasing complexity. The integration of rich humoral and neural viscerosensory information is supported by a relatively small set of interacting brain areas linked to low-level homeostatic reflexes, but these are able to draw on both instinctive and volitional behavioral repertoires when functionally challenged. It is likely that predictive coding underlies the operational architecture of viscerosensory control, including consciously accessible feeling states, influencing motivational behaviors and directing cognitive processes including memory. Interoceptive representations are also engaged, perhaps symbolically, in the exchange of social emotions. Perturbation of viscerosensory representation is anticipated to impact multiple levels of functioning, yet clinically there appears to be redundancy and a robustness that mitigates major decompensation. Affective, dissociative, and psychotic phenomena suggest uncoupling of a usually integrated physiological and cognitive representation of self. A comprehensive understanding of the integration of internal bodily signals in health is ultimately required for effective management of physical and psychological symptoms in illness. Such a goal can only be achieved through coordinated experimental approaches and perhaps a move away from treating physiological changes as irrelevant confounds in neuropsychological experiments. Together, these observations make "us realize more deeply than ever how much of our mental life is knit up in our corporeal frame" (James, 1890).

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