# The Isle of Craig: Neuroanatomical and Functional Evidence for a Role of the Insular Cortex in Subjective Feelings

**Henry C. Evrard**

## Contents



**Abstract** At the start of the twenty-first century, Arthur D. (Bud) Craig brought back to the fore the Island of Reil (insular cortex or insula). He did so by following, step by step, with rigor and tenacity, the afferent sensory pathway that informs the

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forebrain about the ongoing physiological status of the organs and tissues of the body. Along with his demonstration of the existence of a primate-specific ascending interoceptive pathway and his subsequent re-interpretation of Sherrington's concept of interoception, Bud Craig's seminal experiments and profound interpretations led him to make the groundbreaking proposals that the dorsal posterior insular cortex provides an ideal substrate for James's concept of emotional embodiment, that the insular cortex contextualizes interoception across a posterior-to-mid-to-anterior integration with multimodal activities, and that the anterior insular cortex has a crucial role in the evolutionary emergence of the awareness of subjective feelings in humans, for the purpose of optimizing metabolic energy usage. Bud Craig's unique work paves the path for further elucidation of the role of the insula and other brain regions in subjective feelings. His discoveries and proposals rest on implacable attention to neuroanatomical and neurophysiological details and a serendipitous quest for the fundamental evolutionary Logic of Life. This chapter provides a detailed description of the ascending interoceptive pathway and the functional and comparative neuroanatomy of the insular cortex in primates. Building on Bud Craig's work, our recent findings suggest that the primary interoceptive cortex serves as a representation of the spino-solitary-parabrachial neuraxis, merging with posterior-to-mid-anterior and dorsal-to-ventral processing streams that form a latticework integration pattern. At the ventral anterior tip of this integration, the von Economo neuron area closes the corticofugal interoceptive-autonomic loop of the sensory-motor homeostatic system through projections to all brainstem nuclei integrating interoceptive afferences.

**Keywords** Awareness · Embodiment · Homeostasis · Interoception · Von Economo neuron

## 1 Introduction

The scientific career of Arthur D. (Bud) Craig (1951–2023) is distinguished by a remarkable series of groundbreaking discoveries, culminating in a major paradigm shift in how we understand pain, subjective feelings, and their evolutionary underpinnings (Blomqvist et al. 2023; Strigo et al. 2024). In this transformative framework, the insular cortex emerges as a crucial cortical hub continuously mapping the ongoing physiological condition of the body – interoception – and integrating it with salient multimodal information to construct a cohesive, embodied sense of self. This integration aligns cognitive appraisal, autonomic regulation, and behavioral outputs with the overarching goal of optimizing metabolic, energetic efficiency (Craig 2002). This dynamic integration underscores how interoception serves not merely as a measure of bodily needs but as the cornerstone of the subjective awareness of any and all feelings across time, making it a prerequisite for embodied consciousness (Craig 2010, 2015).

While most readers of Bud's work find inspiration in his revolutionary theories on interoception and the insula's role in subjective experience, it is essential to realize that these conclusions stem first and foremost from his unrelenting examination of structural and functional details defining the ascending interoceptive pathway and laying the foundation of his model for the insula. Qualified by Bud as a "work in progress," the map of the ascending interoceptive pathway represents over 25 years of mostly single-handed, tenacious, and rigorous neuroanatomical tract-tracing and neurophysiological recording in the macaque monkey (Craig 2015; Blomqvist 2023; Blomqvist and Dostrovsky 2025). The progressive construction of this map is marked by key breakthroughs: *(1)* Lamina 1 (SpL1) spinothalamic tract (STT) neurons – but not spinal lamina 5 wide dynamic range (WDR) neurons – encode the intensity of thermal and nociceptive stimuli along discrete modality-specific "labeled lines," aligning closely with human psychophysical ratings (Craig 2003a, 2004a). *(2)* Small-diameter afferents to SpL1 encode, beyond cutaneous thermoreceptors and nociceptors, a broad diversity of homeostatically relevant activities that continuously inform the brain about the health of bodily tissues (Craig and Kniffki 1985; Craig et al. 1988; Han et al. 1998; Andrew and Craig 2001; Wilson et al. 2002; Craig 2002). *(3)* SpL1 projects to spinal and brainstem autonomic centers, further relating small-diameter afferences to homeostasis (Craig 1992, 1993, 1995a, b; Westlund and Craig 1996). *(4)* In primates, but not other mammals, SpL1 projects directly to a phylogenetically novel nucleus of the thalamus (which Bud named the *posterior part of the ventral medial nucleus*; VMpo) located adjacent to the basal part of the ventral medial nucleus (VMb; also known as VPMpc) that receives visceral inputs from the vagus nerve via the solitary tract nucleus (nTS) and parabrachial nucleus (PB) (Craig et al. 1994; Craig 1995a, 2004a, b, 2006; Blomqvist et al. 2000; Craig and Blomqvist 2002; Craig and Zhang 2006). *(5)* VMpo projects primarily to the posterior dorsal fundus of the insula (IDFP, formerly abbreviated dpIns) (Craig et al. 1995; Craig 2014), next to the projection of VMb to a more anterior portion of the dorsal fundus (Pritchard et al. 1986; Ito and Craig 2008; Strigo and Craig 2016). *(6)* VMpo and IDFP have a posterior-to-anterior bodily map (foot-to-face) that is orthogonal to the classical homunculus of VP and S1 (Craig 2004b, 2014; Hua et al. 2005; Baumgartner et al. 2006).

This body of evidence refutes the long-standing incongruity of the *Gate Control Theory of Pain*, which misclassifies pain and temperature as exteroceptive modalities represented in VP and S1 alongside touch (Melzack and Wall 1965; Craig 2003a). More critically, it led Bud to redefine Sherrington's concept of interoception as the physiological condition of all body tissues – not just the viscera – represented along a phylogenetically novel ascending sensory pathway in primates (Sherrington 1948; Craig 2002, 2003b), serving homeostasis as the ascending counterpart to Langley's autonomic pathway (Langley 1921; Craig 1996) and providing a neurobiological substrate for Weber's "common sensation" (*Gemeingefühl*), Sherrington's "material me," and the "emotional embodiment" underlying subjective feelings as envisioned in the *James-Lange Theory of Emotion* (Weber 1846; Lange 1885; James 1894; Craig 2002) – an undeniable paradigm shift.

Bud's seminal PET study revealed that objective cooling of the right hand correlated primarily with activity in the contralateral IDFP, while subjective ratings of cooling intensity engaged the mid-insula bilaterally and, more prominently, the right anterior insular cortex (AIC) (Craig et al. 2000). This posterior-to-anterior pattern has since been replicated across various interoceptive modalities (Drzezga et al. 2001; Olausson et al. 2002; Wattendorf et al. 2016; Hassanpour et al. 2018), reinforcing the AIC's consistent association with subjective feelings (Craig et al. 2000; Craig 2002, 2009a). From this foundation, Bud formulated his influential model of posterior-to-mid-to-anterior integration: interoceptive signals are first mapped in the dorsal posterior insula (the primary interoceptive cortex) and then progressively enriched in the mid-insula through integration with multisensory, hedonic, and homeostatic information, generating what he termed "homeostatic sentience." This evolving representation culminates in the AIC, where it merges with other salient brain activities into a unified "global emotional moment," encompassing all bodily sensations, social emotions, and cognitive states linked to attention, thought, and introspection (Craig 2009a). Through a "cinemascopic" sequencing of these moments across time, the AIC supports the continuous and embodied sense of self, manifest in our awareness of bodily states, emotional shifts, fluid thoughts, and the passing of time (Craig 2009a, b, 2011, 2015; Engström et al. 2014).

Following Bud's footsteps, this chapter examines the functional neuroanatomy of the macaque insula while identifying possible homologies with the human insula. After reviewing the macroscopic organization of the insula and the refined subdivision of each of its three vast architectonic sectors – granular, dysgranular, agranular – into smaller areas and "stripes," this chapter focuses on the convergence of functional activations of the dorsal fundus with topographic features of the ascending interoceptive pathway to tentatively propose that the primary interoceptive cortex in macaque represents the progressive integration of interoception along the spino-solitary-parabrachial hierarchy. Building on this and the partitioning of the macaque dysgranular insula into integration stripes, this chapter proposes a novel latticework model of insular integration, complementing Bud's framework by adding a dorso-ventral axis and linking the posterior-to-mid-to-anterior progression to a representation of the spino-solitary-parabrachial neuraxis – a new idea that Bud and I discussed in recent years. Finally, new evidence on the von Economo neuron (VEN) is presented, indicating that VEN belongs to a unique architectonic area that projects to brainstem homeostatic centers, hereby closing one of the corticofugal interocepto-autonomic loops sitting atop the interoceptive neuraxis.

## 2 Folds of the Insular Cortex: Evolutionary and Comparative Landmarks

### *2.1 The Dorsal Fundus as an Evolutionary and Development Cortical Anchor*

The insular cortex, named for its location deep within the lateral (Sylvian) fissure, is hidden beneath the orbital prefrontal cortex anteriorly, the frontoparietal operculum dorsally, and the temporal operculum ventrally (Reil 1809; Naidich et al. 2004; Afif and Mertens 2010). Once these opercula are removed, the insula appears, outlined by the anterior, superior, and inferior circular sulci (Fig. 1a, b). Bud identified the dorsal anterior and posterior fundal regions, straddling the superior circular sulcus, as the primary targets of the interoceptive pathway via VMpo and VMb (Craig 2002). Drawing on the tension-based morphogenesis theory (Van Essen 1997, 2020), and noting that other VMpo projections terminate in deep fundi (areas 3a and 24d), Bud proposed that these interoceptive cortices act as tensile anchors, pulling themselves into close proximity to optimize energy-efficient cortico-cortical communication (Craig 2011, 2015), noting also that the dorsal fundus, the last insular feature to emerge evolutionarily, forms first during development (Afif et al. 2007; Butti and Hof 2010; Mallela et al. 2023), suggesting an evolutionary late orchestration of insular functions by the ascending interoceptive pathway (Craig 2015). While most tension-based models emphasize corticocortical tensions (Van Essen 2020), the anchoring might also result from thalamocortical axon tension (Striedter et al. 2015), compensating for the slow conduction of unmyelinated C-fibers during early development when interoceptive inputs already engage the cortex (Evrard 2019).

## 2.2 *Insular Sulci and Dimples: A Quest for Structural Homologies*

Beyond the dorsal fundus, the human insula is divided into anterior and posterior lobules by the central insular sulcus (Fig. 1a). The posterior lobule contains two long gyri, while the anterior typically has three short gyri, flanked anteriorly by the accessory and transverse gyri (Ture et al. 1999; Afif and Mertens 2010), separated from the short gyri by an accessory anterior circular sulcus (Evrard 2019).[1] The accessory and transverse gyri, collectively known as frontoinsula, are distinctively enriched in VENs and their companion bifid fork neurons (FNs) (Von Economo and Koskinas 1925; Ngowyang 1932; Allman et al. 2010). In light of Bud's view of the dorsal fundus as major interoceptive anchor, which tensile anchors create these additional sulci and whether these anchors have precursors in non-hominin monkeys remain to be explored.

[1] Bud taught that the primate brain is like a face, varying in shape but with essential elements always found where expected (Craig 2015, p. 111). At the 2009 SfN meeting, Jack Johnson and colleagues reported that the number and orientation of insular gyri vary markedly between individuals and hemispheres (Johnson et al. 2009; Craig 2010; Wysiadecki et al. 2018). Group fMRI analyses should carefully consider this variability in their registration and normalization procedures. John "Jack" Irwin Johnson was an inspirational functional neuroanatomist at Michigan State University (Prof. Johnson Memorial Source: https://www.youtube.com/watch?v=2CQUjbK7kZc). Bud always credited Jack for opening him the doors to the fields of neuroscience by authorizing him to attend his course in functional neuroanatomy (Craig 2015). They remained in close contact ever since. Jack passed away in 2017.

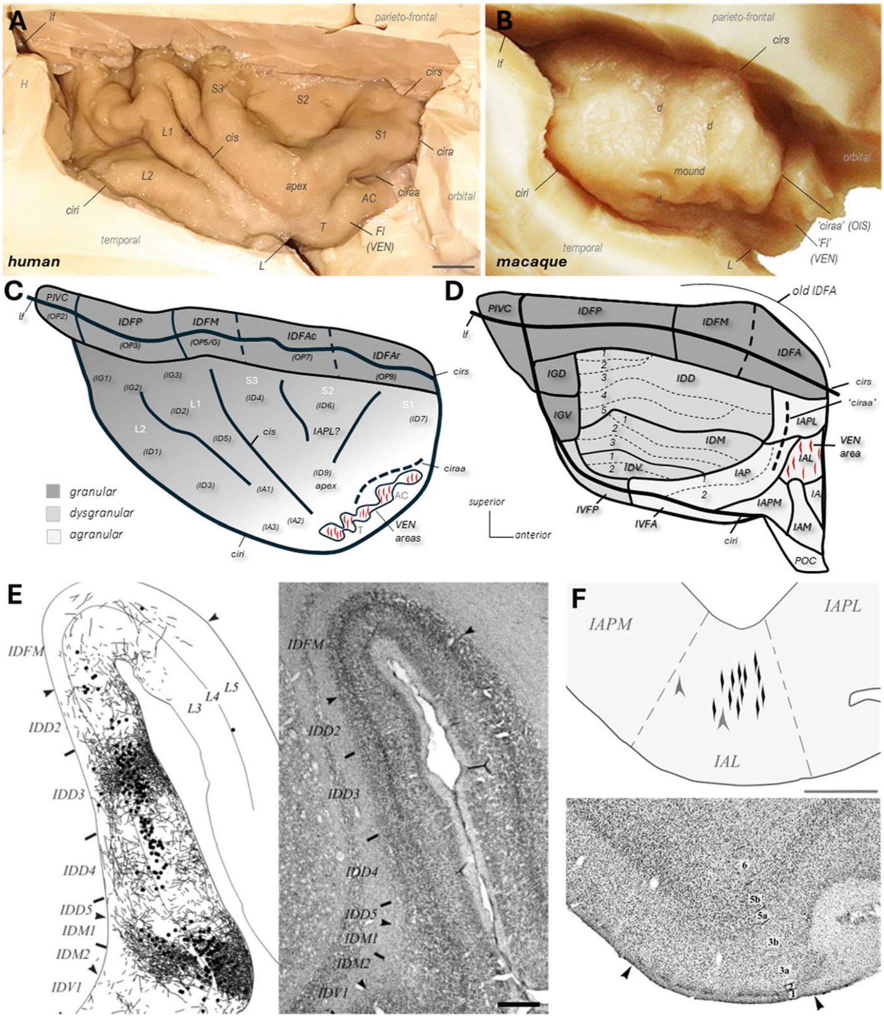


**Fig. 1** (**a**, **b**): Lateral views of the human (**a**) and cynomolgus macaque monkey (**b**) insula exposed after excision of the frontoparietal and temporal opercula. (**c**, **d**): Flat map views of the architectonic parcellation of the human (**c**) and cynomolgus macaque monkey (**d**) insula. (**e**): Comparison of the distribution of anterograde (lines) and retrograde (dots) labeling (left panel) with the Nissl stain-based cytoarchitectonic parcellation (right panel) in the insula in case OM85 with an injection of lucifer yellow in area 24 of the cingulate cortex. Adapted from Krockenberger et al. (2023) with permission. (**f**): Comparison of the distribution of spindle-shaped von Economo neurons (elongated rhombi) and bifid fork (Y-shaped symbols) neurons (top panel) with the Nissl stain-based cytoarchitectonic parcellation (bottom panel) in the ventral anterior insula in one macaque monkey. Adapted from Horn (2020) with permission. *Abbreviations*: *aals* accessory anterior limiting sulcus (human), *AC* accessory gyrus, *cis* central insular sulcus, *cira* circular sulcus, anterior branch, *ciraa* circular sulcus, accessory anterior branch, *ciri* circular sulcus, inferior branch, *cirs* circular sulcus, superior branch, *d* dimple, *IAL* lateral agranular area of the insula, *IAPL* posterior lateral agranular area of the insula, *IAPM* posterior median agranular area of the insula, *IDD1–5* dorsal dysgranular area stripes 1–5 of the insula, *IDFM* middle dorsal fundus area of the insula, *IDM1–3* mound

The macaque insula is largely lissencephalic, complicating the direct application of Bud's posterior-to-mid-to-anterior model to macaque data. It features a rudimentary ventral horizontal gyrus – the "mound" (Fig. 1b) – which is dysgranular, receives VMpo projections (Craig 2014), and lacks a clear human counterpart. Additionally, a distinct anterior vertical groove, previously termed the "orbitoinsular sulcus" (Mesulam and Mufson 1985; Mufson et al. 1997) borders an elevated region rich in VENs and FNs (Evrard et al. 2012), suggesting homology with the human frontoinsula and accessory anterior circular sulcus (Evrard 2019). The macaque insula also shows subtle dimples that may represent precursors of human insular sulci, as suggested by recent findings on prefrontal dimples (Amiez et al. 2023). In fact, species close to macaques, such as baboons, display an incipient central insular sulcus (Mufson et al. 1997).

## 3 Architectonic Parcellation: The Highly Organized Brain

### *3.1 IDFP: Another Region Discovered by Bud, as Important as VMpo*

Since the dorsal posterior fundus is the main target of VMpo projections, Bud sought to examine its cellular organization using classical cyto- and myelo-architectonics. At the time, the insula was broadly divided into posterior granular, middle dysgranular, and anterior agranular sectors, with the border to secondary somatosensory cortex (S2) variably placed around the superior circular sulcus (Roberts and Akert 1963; Sanides 1968; Burton and Jones 1976; Mesulam and Mufson 1982). Bud's anterograde labeling from VMpo injections consistently straddled the fundus (Craig 1995a, 2014; Craig et al. 1995), similar to VMb projections to the dorsal anterior fundus (Pritchard et al. 1986; Strigo and Craig 2016). In my very first hour in Bud's lab in Phoenix, AZ, Bud placed under the stereomicroscope a thin section of the macaque insula histologically stained to reveal myelinated fibers. Pointing to the dorsal posterior fundus, he asked with excitement: "Isn't that obvious?" Yes, it was obvious: the dorsal posterior fundus forms a single area – which we named the *dorsal fundal posterior area of the insula* (IDFP; Fig. 1d) – with sharp medial and lateral boundaries, coinciding precisely with the projection field (Craig 2014; Evrard et al. 2014). At the fundus midpoint, a boundary marked the transition from VMpo to

**Fig. 1** (continued) dysgranular area stripes 1–3 of the insula, *IDV1–2* ventral dysgranular area stripes 1–2 of the insula, *FI* frontoinsula, *H* Heschl gyrus, *L* limen insula, *L1–2* posterior long gyri 1–2, *lf* fundus of the lateral fissure (denotes the fundus posterior to the insula and circular sulcus), *PIVC* posterior insular vestibular cortex, *POC* piriform cortex, *S1–3* anterior short gyri 1–3, *T* transverse gyrus, *VEN* von Economo neuron, *(IA1–3)* Jülich agranular areas 1–3, *(ID1–9)* Jülich dysgranular areas 1–9, *(IG1–3)* Jülich granular areas 1–3. *Scale bars*: 2 mm in **a**–**D**, 500 μm in **e**–**f**

VMb projections. We initially designated the VMb-recipient region as the *dorsal fundal anterior area* (IDFA) and considered it the macaque's gustatory cortex (Kadohisa et al. 2005; Evrard et al. 2014). Later, this "old IDFA" was subdivided into IDFA and IDFM (Fig. 1d) to reflect fMRI evidence that the primary gustatory cortex lies in the fundus' mid-portion (IDFM), possibly like in humans (Hartig 2019; Evrard 2021; Hartig et al. 2023) (see Sect. 4).

## 3.2 The Macaque Insula Contains Numerous Sharply Delimited and Highly Reproducible Areas

How is the rest of the insula organized? Inspired by Joel Price's re-examination of the prefrontal cortex (Carmichael and Price 1994; Ongur et al. 2003), Bud and I went through several iterations of the macaque insula's architectonic map. My first map, drawn in Phoenix, identified 21 areas – a number we worked hard to reduce a more "realistic" value. Yet, when revisiting the project together at the *Max Planck Institute for Biological Cybernetics* in Tübingen, where I had taken a position, we concluded that the insula is indeed highly organized, revealing up to 24 sharply defined areas (Fig. 1d). To satisfy reviewers, we consolidated this into 15 areas: 2 fundal granular areas (IDFP and IDFA, later joined by IDFM), 2 posterior granular areas (IGD and IGV), 4 dysgranular areas – dorsal (IDD), mound (IDM), ventral (IDV), and posterior fundal (IVFP), and 7 agranular areas, including 5 pre-limen (IAI, IAM, IAL, IAPL, IAPM) and 2 post-limen areas (IAP, IVFA), as initially recognized by Carmichael and Price (1994). We also suggested that 3 dysgranular areas (IDD, IDM, IDV) may each contain 2 to 5 subtle subareas, which we termed "stripes" (Evrard et al. 2014).

## 3.3 Dysgranular Stripes: Overlap Between Architectonics and Tract-Tracing

While training my eye for neuroanatomical details, Bud taught me to trust the subjective impression of consistent structural patterns. Although we initially presented the dysgranular stripes as hypothetical (Evrard et al. 2014), subsequent tract-tracing studies confirmed their reality. Labeling from tracer injections in other cortical areas consistently aligned with the architectonic stripes, showing distinct patterns between adjacent stripes (Krockenberger et al. 2023). For instance, a dual anterograde and retrograde tracer injection in area 24b' of the middle cingulate cortex produced dense labeling precisely matching the independently defined third IDD and second IDM stripes (Fig. 1e). This striped subdivision of the dysgranular insula, parallel to the dorsal fundus, suggests a re-representation of the primary interoceptive map into multiple secondary dysgranular maps, each integrating distinct high-order brain activities (Evrard et al. 2014; Krockenberger et al. 2023) (see Sect. 5).

## 3.4 *Von Economo Neuron Area: Novel Elemental Localization in the Primate Cortex*

VENs (and co-mingled FNs[2]) are found predominantly in the anterior insular cortex (AIC) and anterior cingulate cortex (ACC) of humans and great apes (Nimchinsky et al. 1999; Allman et al. 2010) as well as in non-hominin primates like macaques (Evrard et al. 2012; Steiner et al. 2024) and a few large-brained non-primates (Hakeem et al. 2009; Butti et al. 2011; Raghanti et al. 2015). We first identified the macaque VEN and FN prior to developing the insular architectonic map (Evrard et al. 2012) consistently observing a small cluster within the agranular insula. This cluster precisely matches the lateral agranular area (IAL), now also called the VEN area (Horn et al. 2017; Horn 2020) (Fig. 1f). Its strict confinement, what Brodmann would have termed an "elemental" localization (Brodmann 1909), provides a valuable entry point to explore the developmental, evolutionary, and functional roles of the VEN and its host area (Evrard 2018). Alongside the dysgranular stripes, this elemental VEN localization underscores the macaque insula's fine-grained organization, suggesting an equal or even higher differentiation in humans.

## 3.5 *Architectonic Parcellation of the Human Insular Cortex*

Figure 1c shows my interpretative transposition of the Jülich-Brain Project parcellation of the human posterior lobule and part of the anterior insula (Kurth et al. 2010; Amunts et al. 2020; Duong et al. 2023). This parcellation identifies 5 granular opercular[3] areas (OP2, 3, 5, 7, and 9), 3 posterior granular areas (IG1–3), 10 dysgranular areas, and 3 small agranular areas (IA1–3) at the limen base, resembling Brockhaus' early map (Brockhaus 1940) but differing from maps recognizing 5 agranular areas as in macaques (Carmichael and Price 1994; Ongur et al. 2003). We previously suggested that OP2, OP3, and OP5 correspond to the macaque PIVC, IDFP, and IDFM, respectively (Eickhoff et al. 2006a, b; Evrard et al. 2014;

[2]The literature emphasizes VENs over FNs, due to the lower number of FNs compared to VENs. The two neurons are co-mingled. They express the same immunohistochemical and gene markers (e.g., theta subunit of the GAB receptor) and have the same projections. While their morphology is distinct, whether they have distinct functions is not known (Dijkstra et al. 2016).

[3]The Jülich Brain Project uses an opercular (OP) nomenclature for their dorsal fundus areas. Recognizing that the dorsal fundus belongs to the insular cortex and is distinct from the secondary somatosensory cortex (S2), Bud and I prefer using an insular nomenclature (e.g., IDFP instead of OP3) (Evrard et al. 2014).

Evrard 2019), while OP7 and OP9 may represent an expanded and subdivided IDFA, with OP9 possibly being hominin-specific. The comparison between the other human areas (IGs, IDs, and IAs) with the macaque areas remains to be determined. The human insulas Bud and I collected are now under comparative analysis. Preliminary observations confirm, as in macaques and the Jülich map, multiple sharply delimited areas (Fig. 2a). We expect a more differentiated anterior insula in humans, reflecting its hyperallometric expansion (Bauernfeind et al. 2013). Our ongoing examination suggests that the VEN and FN in humans occur in several distinct frontoinsular areas, unlike the single VEN area in macaques (Fig. 2b) (Horn et al. 2017; Horn 2020).

## 4 Primary Interoceptive Cortex: A Representation of the Interoceptive Neuraxis

In our earlier model, the macaque dorsal fundus was divided into two domains: IDFP and the "old" IDFA, interpreted primarily as gustatory based on earlier macaque recordings (Ogawa et al. 1989; Yaxley et al. 1990; Rolls 2005; Evrard 2015). In contrast, the human dorsal fundus is partitioned into at least three domains – IDFP, IDFM, and IDFA – with human IDFP (OP3) and IDFM (OP5) homologous to macaque IDFP and old IDFA, respectively, and with human IDFA, absent in macaques, being associated with higher-order integrations supporting "homeostatic sentience" and "global emotional moments."

However, in a recent fMRI study using comparable paradigms in anesthetized macaques and humans, my colleague Renée Hartig and I found robust taste-evoked BOLD responses in a middle fundus region (IDFM) and, more variably, at the anterior tip (Fig. 3a) (Hartig et al. 2017, 2023; Hartig 2019). Similar clusters were found in awake macaques (Kaskan et al. 2019); where the anterior cluster, modulated by thirst, likely encodes taste value or expectation as well (Veldhuizen et al. 2011). These findings led us to revise the macaque model, splitting old IDFA into a middle gustatory area (IDFM), similar to human IDFM, and a smaller anterior IDFA, possibly a primordial form of the expanded human IDFA representing homeostatic value (Fig. 1c) (Evrard 2021).

This updated IDFP–IDFM–IDFA sequence in macaques may reflect a cortical map of hierarchical interoceptive integration following the SpL1–nTS–PB sequence. Whether the "primary interoceptive cortex" should be limited to IDFP and IDFM (posterior fundus) or extended to the full posteroanterior fundus in both species remains an open question, though a conservative approach favors restricting it to regions with di-synaptic ascending projections. Importantly, the SpL1–nTS–PB representation could mirror Bud's posterior-to-mid-to-anterior insular integration model (Craig 2009a, b), where each insular stage reflects a corresponding step in the subcortical interoceptive hierarchy. Supporting evidence lies in the topography of SpL1, nTS, and PB projections to VMpo and VMb, and homotopic projections to

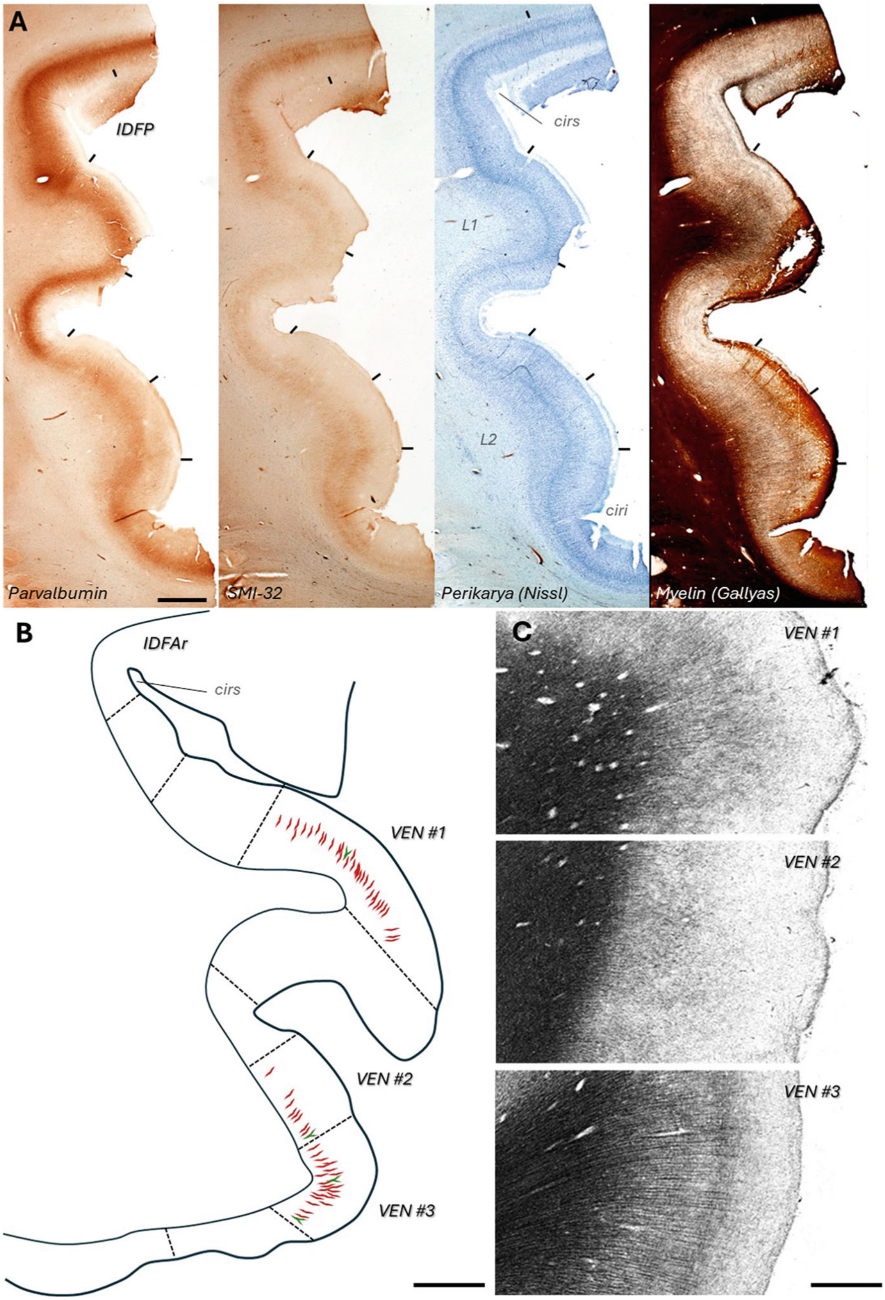


**Fig. 2** (**a**) Photomicrographs of a consecutive series of coronal sections of a human posterior insula stained with four distinct methods. The tick marks indicate architectonic boundaries. In the preliminary view, only IDFP is named. The photomicrographs and the figure panel were originally prepared by A.D. (Bud) Craig and later completed by HCE. (**b**) Chart of the distribution of von Economo neurons (red) and fork neurons (green) and of the position of architectonic boundaries in a coronal section of the anterior insula in one human subject. (**c**) Photomicrographs of subregions of a

IDFP, IDFM, and IDFA (Fig. 3b), as well as in convergent electrophysiological and neuroimaging patterns in monkeys and humans.

### 4.1 SpL1 → VMPo → IDFP

Bud's tract-tracing and electrophysiological studies in macaques established that SpL1 and its trigeminal extension (Sp5C) project contralaterally to VMpo, which in turn projects ipsilaterally to IDFP (Craig et al. 1994; Craig 1996, 2004b, 2014; Craig and Zhang 2006). (In Fig. 3, follow the dark red and light red arrows from SpL1 and Sp5c, respectively, to VMpo and then from VMpo to IDFP.) In both VMpo and IDFP, lumbosacral inputs map posteriorly, while cervical and trigeminal inputs terminate anteriorly (Craig 2004b, 2014; Baumgartner et al. 2006; Hartig 2019; Hartig et al. 2019) (Fig. 3b, c). Neurons in SpL1, Sp5C, VMpo, and IDFP respond selectively to distinct thermal and nociceptive stimuli,[4] preserving the high-resolution "labeled lines" of modality-specific small-diameter fibers, crucial for generating discrete bodily sensations (Han et al. 1998; Andrew and Craig 2001; Craig 2002, 2004a; Hartig 2019; Hartig et al. 2019).

In humans, the existence of VMpo and IDFP has been confirmed via electrophysiology, microstimulation, and imaging (Craig et al. 2000; Blomqvist et al. 2000; Iannetti et al. 2005; Segerdahl et al. 2015; Chien et al. 2017).[5] IDFP, localized in the dorsal fundus capping the posterior insular gyri (Fig. 3d), displays the same posterior-to-anterior somatotopy as in monkeys (Olausson et al. 2002; Hua et al. 2005; Brooks et al. 2005; Mazzola et al. 2009). VMpo is disproportionately larger in

**Fig. 2** (continued) myelin-stained section adjacent to the section shown in panel B, illustrating the myelination pattern in each of the three VEN areas illustrated in panel B. *Abbreviations*: *cirs* superior circular sulcus, *IDFAr* rostral portion of the anterior dorsal fundus area of the insula, *IDFP* posterior dorsal fundus area of the insula, *L1–2* posterior long gyri 1–2, *VEN #1–3* von Economo neuron areas #1–3. *Scale bars*: 1 mm in **a**–**b**, 300 μm in **c**

[4] COOL, HPC, and NS SpL1 STT cells account for ~90% of all SpL1 STT cells in macaque, with the remaining 10% including WARM, histamine-selective (itch), mustard oil-selective cells and a small fraction of "unidentified" cells (Andrew and Craig 2001). Most other projecting SpL1 cells are spinobulbar, including COOL, HPC, and NS cells distinct from the STT cells, cells receiving muscle afferents, and most likely cells receiving visceral afferents that remain to be explored in monkeys (Craig 2015). In rodents, the vagus nerve is the main source of visceral afferences, with the spinal cord contributing about 10% (Janig 2022).

[5] In a fraction of the human literature, VMpo remains either ignored (Blomqvist and Evrard 2024; Mandonnet et al. 2024), or misinterpreted as being indistinct from VP (Lenz et al. 2024; Evrard and Blomqvist 2025) or the anterior pulvinar nucleus (Vartiainen et al. 2016), which does not receive SpL1 projections (Craig 2004b; Dum et al. 2009).

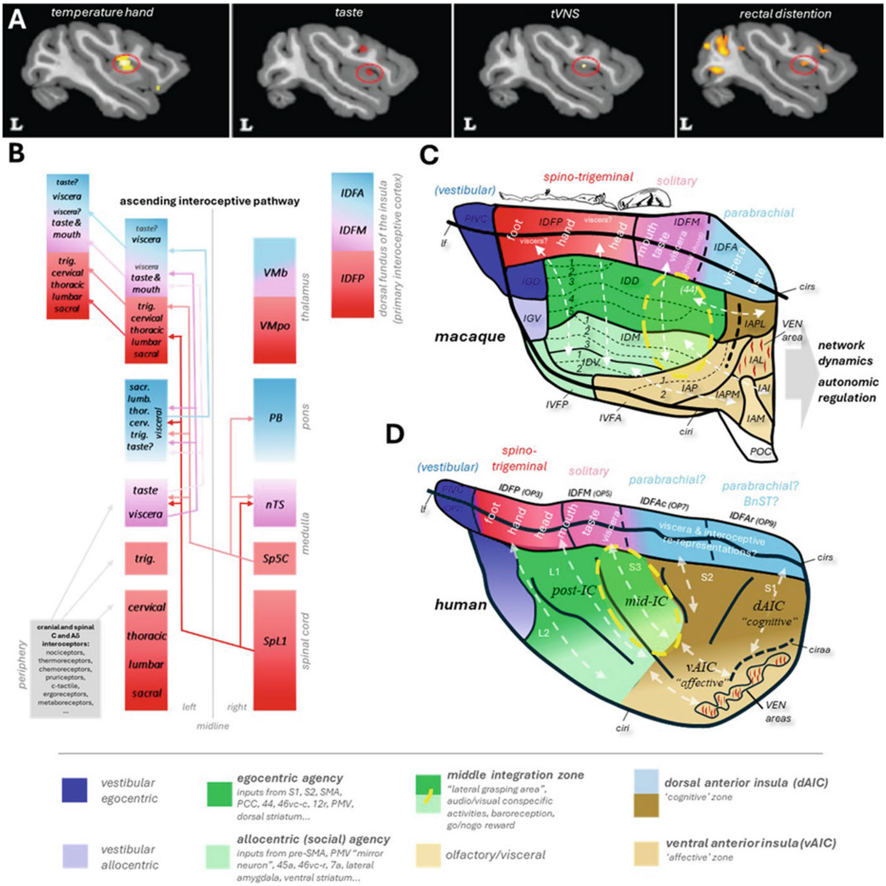

**Fig. 3** (**a**) Distribution of BOLD signal responses to distinct interoceptive stimuli in one representative macaque brain ($p < 0.05$ uncorrected). (**b**) Schematic of the topography of projections in the macaque ascending interoceptive pathway. Each box represents one level of the neuraxis, from the spinal cord to the cerebral cortex. The left and right sides are shown to illustrate also projections crossing the midline. The name of the structures is shown in the boxes on the right side (e.g., SpL1) and the topographic organization within each structure is shown in boxes on the left side (e.g., sacral to cervical, from posterior to anterior SpL1). Lines with arrows indicate projections ascending from a caudal level (e.g., SpL1) to a more rostral level (e.g., nTS). To avoid cluttering, projections are shown mainly from/to one side, chosen arbitrarily. There is no known asymmetry in the overall organization of the ascending pathway. The color code is kept consistent to represent the overall representation of neuraxis level in the thalamus and in cortex. The figure highlights three main projection streams: In dark red, SpL1 projects bilaterally throughout nTS, contralaterally to PB (with an inverted topography, foot/lumbar anterior to hand/cervical posterior) and contralaterally to VMpo (foot/lumbar posterior to hand/cervical anterior). In lighter red, Sp5C projects bilaterally to nTS and PB (posterior to SpL1's cervical representation), contralaterally to VMpo (anterior to SpL1's cervical representation). The SpL1 and Sp5C representations in VMpo project homotopically to the SpL1 and Sp5C representations of ipsilateral IDFP. In light pink, the rostral gustatory portion of nTS projects ipsilaterally mainly to caudolateral VMb and sparsely to PB. The caudolateral region of VMb receiving direct inputs from nTS projects to IDFM. In dark pink, the caudal visceral portion of nTS projects ipsilaterally to PB; and, in blue, PB mainly projects to the rostromedial portion of VMb, which projects to IDFA. **C-D:** Flat map models of the functional organization of the macaque (**c**) and human (**d**) insula. The color code in the dorsal fundus areas

humans (Strigo and Craig 2016), likely reflecting a broader range of interoceptive modalities activating IDFP, thereby enabling a more refined sense of the "material me" and contributing to richer subjective experience (Drzezga et al. 2001; Henderson et al. 2007; Bjornsdotter et al. 2009; Spetter et al. 2014; Craig 2015; Wattendorf et al. 2016).

### 4.2 nTS → VMb → IDFM

The nucleus of the solitary tract (nTS) is a phylogenetically ancient brainstem structure integrating sensory homeostatic inputs. Its rostral third receives topographically organized gustatory inputs from facial, glossopharyngeal, and vagal innervations of the tongue (dark pink in Fig. 3b) (Norgren and Leonard 1973; Beckstead et al. 1980), while its caudal two-thirds process viscerotopic inputs from thoracic and abdominal organs (light pink in Fig. 3b) (Beckstead et al. 1980; Altschuler et al. 1989; Ran et al. 2022). Despite this division, overlapping activity is common; SpL1 and Sp5c project bilaterally across nTS (follow red arrow from SpL1 and Sp5c to nTS), without a clear topography, likely contributing nociceptive and metaboreceptive signals supporting viscerosomatic integration (Burton et al. 1979; Craig 1995a; Boscan et al. 2002; Janig 2022). Visceral inputs also modulate to some extent gustatory responses in rostral nTS (Huang et al. 2009; Contreras et al. 1982). Forming a primitive substrate for computing homeostatic needs and linking sensory inputs with autonomic control (Blessing 1997; Saper 2002; Craig 2002; Janig 2022), nTS could serve as a foundational hub for the mid-insula's "homeostatic sentience."

Rostral nTS projects mainly to the caudolateral VMb and sparsely to the caudal PB, while caudal nTS targets PB and a distinct posterolateral VMb zone (follow dark pink arrow from nTS to VMb) (Fig. 3b) (Beckstead et al. 1980; Ito and Craig 2008; Strigo and Craig 2016). In primates, taste signals reach VMb mostly monosynaptically, while visceral inputs are relayed via PB, though partial overlap exists. Taste

**Fig. 3** (continued) (IDFP, IDFM, and IDFA) uses the same color code as in Fig. 3a. In monkeys, IDFP receiving inputs from SpL1 and Sp5c via VMpo, with a posterior (foot/lumbar) to anterior (trigeminal/face) somatotopy. Sparse visceral inputs from the spinal cord may reach IDFP, although most SpL1 visceral afferences in monkeys stop in PB. IDFM receives inputs from nTS, mainly from the rostral gustatory nTS, with possibly some visceral inputs as well; whether these inputs are co-mingled or separated along a gradient remains to be explored. In monkeys, IDFA receives inputs from PB via VMb. Whether IDFA in humans also receives inputs from PB via VMb as well as possibly other inputs remains hypothetical. For the rest of the insula, see the color code at the bottom of the figure and see the text. *Abbreviations*: *IDFA, IDFM, IDFP* anterior, middle, and posterior dorsal fundus area of the insula, respectively, *nTS* solitary tract nucleus, *PB* parabrachial nucleus, *Sp5c* trigeminal lamina 1, *SpL1* spinal lamina 1, *VMb* ventral medial nucleus of the thalamus, basal part, *VMpo* ventral medial nucleus of the thalamus, posterior part. For other abbreviations, see the legend of Fig. 1. (Panels **b**–**d** were adapted from similar figures in Evrard (2021), with permission) activity is well documented in VMb of both monkeys (VPMpc) and humans (ventral caudal parvicellular interne; Vcpci) (Pritchard et al. 1989; Lenz et al. 1997). Posterolateral VMb neurons selectively encode gustatory, thermal, and mechanical oral stimuli, with sparse anticipatory modulation (Yaxley et al. 1990; Verhagen et al. 2004; Rolls 2005), and project to IDFM, putatively forming a gusto-visceral gradient (Fig. 3b, c). IDFM itself responds robustly to oral and taste stimuli in macaques and humans (Ogawa et al. 1989; Jantsch et al. 2005; Ifuku et al. 2006; Small 2010; Trulsson et al. 2010; Nakamura et al. 2011; Hartig 2019; Avery et al. 2019; Hartig et al. 2023), while also displaying overlapping or nearby responses to vagal and rectal stimuli in macaques (Fig. 3a) (Hartig et al. 2017; Hartig 2019) and attention to heartbeat in humans (Avery et al. 2017). Gustatory and visceral activations consistently localize to the middle of the dorsal fundus, aligning with Bud's mid-insular integration stage (Fig. 3d) (Craig 2009a, 2015). This region is further implicated in processes such as craving (DelParigi et al. 2005), thirst (Becker et al. 2017), pain unpleasantness (Schreckenberger et al. 2005), uncertainty (Rubio et al. 2015), vividness (Todd et al. 2012), emotional processing (Duerden et al. 2013), repetition suppression (Zweynert et al. 2011), and encoding of time intervals (Wittmann et al. 2010). While the boundary between gustatory and visceral representations remains to be fully resolved, the evidence suggests that IDFM, in addition to purely gustatory signals, could embody homeostatic needs pre-processed in nTS and supports the construction of homeostatic sentience. Bilateral SpL1 projections to nTS (Craig 1995a) and transcallosal communication (Craig 2009a, b) could contribute to the bilateral mid-insular activation commonly observed.

## *4.3 PB → VMb → IDFA*

The parabrachial nucleus (PB) integrates homeostatic, interoceptive, and affective information (Saper 2002), receiving dense inputs from SpL1 (and Sp5c) and nTS, including nociceptive, visceral, and chemosensory signals (Fig. 3b) (Saper 2002; Craig 1995b, 2015; Beckstead et al. 1980; Kitamura et al. 2001). SpL1 projects contralaterally along the rostrocaudal extent of PB with an inverted anteroposterior somatotopy relative to VMpo (Craig 1995b, 2015). Rostral nTS projects sparsely to caudal PB, while caudal nTS densely innervates the entire ipsilateral PB, mainly in lateral PB, with possible separation from SpL1 afferences that also terminate in lateral PB (Beckstead et al. 1980; Herbert et al. 1990; Craig 1995a; Feil and Herbert 1995; Hermanson and Blomqvist 1996, 1997). PB, in turn, projects to the rostromedial VMb, which encodes vagal and cardiorespiratory signals and projects predominantly to IDFA, with moderate input to IDFM (Pritchard et al. 2000; Ito and Craig 2008; Strigo and Craig 2016). PB's inverted somatotopy may account for secondary gustatory activation at the rostral tip of VMb and IDFA, distinct from the main taste zone in VMb and IDFM (Fig. 3b, c) (Craig 2015, 2018; Strigo and Craig 2016; A.D. Craig personal communication).

PB serves as a dynamic integrator, amplifying salient interoceptive signals to prioritize bodily urgency and link physiological states to motivational and affective processes (Saper 2002; Craig 2003b; Palmiter 2018). It likely achieves this through integrating ascending afferents with descending inputs from AIC, ACC, amygdala, BnST, and hypothalamus (Moga et al. 1990; Chiba et al. 2001; Evrard 2018; Grady et al. 2020). This has been proposed to provide PB with real-time monitoring of global brain states and to enable it to influence network dynamics (e.g., sleep-wake transitions) underlying cortical arousal and internally driven cognitive processes (Munk et al. 1996; Parvizi and Damasio 2003; Fuller et al. 2011; Ramirez-Villegas et al. 2020).

In humans, IDFA – often considered part of the dAIC – is consistently activated during bodily, emotional, and cognitive feelings, giving rise to "global emotional moments" through the sequential "cinemascopic" registration of such moments across time (Craig 2009a, 2015; Harrison et al. 2010; Zaki et al. 2012; Terasawa et al. 2013). The AIC contributes to global brain dynamics by switching functional networks to optimize cognitive control and metabolic efficiency (Menon and Uddin 2010; Ham et al. 2013). More recently, dAIC has been proposed to gate the access of sensory information to consciousness by weighing on subsequent prefrontal activation bound to perception (Warnaby et al. 2016; Wu et al. 2019; Huang et al. 2021; Molnar-Szakacs and Uddin 2022), a critical step anticipated by Bud's model.

The role of PB as a salience amplifier aligns with the salience detection and gating function of human IDFA (and dAIC). Although the presence of a dorsal salience network in macaques is debated (Touroutoglou et al. 2016), monkey IDFA is recruited during both internal state processing and cognitive appraisal (Wang et al. 2015; Kaskan et al. 2019; Yang et al. 2022), suggesting it may represent a precursor of the hyperallometrically expanded human IDFA (Bauernfeind et al. 2013). In our model, the human IDFA caps the dorsal fundus, encompassing the anterior and middle short gyri, the frontoinsula, and possibly part of the posterior short gyrus (Fig. 3d). The presence of VENs in the ventral AIC in both macaques and humans (Fig. 3c, d) suggests that the anterior insula expanded rostrally in a fan-like manner with the VEN region as a pivot, which itself may have expanded (Figs. 1e and 2b). A systematic analysis of the dAIC is needed to identify potential functional and connectional loci unique to humans, possibly involving additional subcortical representations anterior to the putative PB-recipient zone of monkey IDFA – one of which, as Bud highlighted, could be the BnST (Craig 2018).

## 5 Latticework Model of Insular Integration

The "latticework" model of insular integration extends Bud's posterior-to-mid-to-anterior model by incorporating two key hypotheses: first, that the dorsal fundus, or primary interoceptive cortex, maps the hierarchical interoceptive neuraxis; and second, that a serial re-representation occurs across the dorsoventrally stacked dysgranular stripes (Evrard 2021). Figure 3c, d illustrates this model on flat maps of the macaque and human insula, respectively, with dorsal fundus subdivisions color-coded as in Fig. 3b. The ascending interoceptive pathway and the dorsal fundus, as detailed earlier, provide the organizational foundation for the entire insular cortex.

### 5.1 Posterior Insula

In monkeys, the dysgranular stripes form two integration domains (Fig. 3c). The dorsal “egocentric” domain (dark green) at the level of IDFP receives somatotopically aligned projections from somatosensory and higher-order proprioceptive cortices, supporting interoceptive-propriomotor integration (Evrard 2019). The ventral “allocentric” domain (light green) connects with audio- and visuo-motor regions, likely processing environmental and social cues (Evrard 2019). This dorsal-ventral dichotomy parallels the body- vs. world-centered integration seen in the IGD and IGV granular areas. In humans, microstimulation and recordings reveal a similar posteroanterior gradient of vestibular and somatic activities across the posterior long gyri, roughly preserved along the dorsoventral axis (Stephani et al. 2011; Mazzola et al. 2019; Duong et al. 2023) (Fig. 3d).

### 5.2 Middle Insula

Ventral to IDFM, the dorsal “egocentric” region hosts a “lateral grasping network” that integrates homeostatic states and motor execution into vitality forms proposed to reflect internal feelings (Borra et al. 2017; Di Cesare et al. 2020, 2021). A similar representation is found at the junction of the third short gyrus in humans, ventral to IDFM (Di Cesare et al. 2021) (Fig. 3d). In monkeys, the ventral middle dysgranular region supports affective audio-visual communication, such as lip-smacking, and its gray matter volume correlates with social network size (Remedios et al. 2009; Caruana et al. 2011; Ku et al. 2011; Testard et al. 2022; Simone et al. 2025). This region also responds to convergent baroreceptive and somatosensory inputs and during reward-based go/no-go tasks (Zhang et al. 1998; Asahi et al. 2006). Collectively, these findings suggest that the middle insula integrates self- and world-centered actions with homeostatic needs, processed via nTS and relayed through VMb to IDFM. In humans, taste and vitality-related activities overlap along the central insular sulcus, with the taste axis likely positioned slightly posterior to the vitality axis (Porcu et al. 2020; Avery et al. 2021; Di Cesare et al. 2021).

## 5.3 Anterior Insula

***Dorsal Anterior Insula*** Human dAIC activity is associated with attention to emotion and interoception, integration of bodily feelings, emotions, and thoughts, self-reflection, feeling-of-knowing, error detection, word processing, visual awareness, and decision-making (Craig 2015). It also contributes to managing cognitive and multiple-demand networks (Sridharan et al. 2008; Duncan 2010), regulating information capacity and timing (Wilk et al. 2012; Wu et al. 2019), with possible implications in salience gating (Smith et al. 2015; Warnaby et al. 2016; Huang et al. 2021), aligning with the role of PB in gating interoceptive inputs to the forebrain. In macaques, neuroimaging and electrophysiology implicate dAIC in cognition (Wang et al. 2015; Yang et al. 2022) and in a multiple-demand network (Mitchell et al. 2016); its involvement in cognitive appraisal predates humans, consistent with the notion that cognition evolved around the representation of homeostatic and metabolic needs (Evrard 2018).

***Ventral Anterior Insula*** Human vAIC is primarily linked to emotional intensity and perception, social empathy, self-other distinction, and the prediction and adaptation of affective bodily states (Harrison et al. 2010; Critchley and Seth 2012; Zaki et al. 2012; Craig 2015). The presence of VENs and a ventral salience network in both human and macaque vAIC, combined with the induction of autonomic and emotional motor responses by electrical stimulation (Kaada 1951; Caruana et al. 2011; Evrard et al. 2012; Touroutoglou et al. 2016), suggests evolutionary continuity, despite the conspicuous expansion of the human AIC and its likely greater number of VEN areas compared to the smaller macaque IDFA and AIC.

In macaques, VENs and FNs in vAIC and ACC project massively to PAG, PB, and nTS (Evrard 2018; Chavez et al. 2023), hereby partly closing the highest hierarchical loop of the sensorimotor homeostatic system formed by ascending interoceptive and descending autonomic pathways. Other insular or cortical projections likely regulate spinal sympathetic efferences as well, in line with the idea that the insula is divided along a spino-medullar axis in which dorsal “sensory” fundi feed integrated output to the ventral “motor” or regulatory mound and VEN area protuberance (Evrard 2019). From a predictive coding perspective, vAIC projections may provide PB with real-time cortical state monitoring for top-down autonomic regulation, attenuating interoceptive prediction errors and reducing free-energy (Parvizi and Damasio 2003; Seth and Friston 2016; Ramirez-Villegas et al. 2020). Notably, dAIC is the last cortical region active before anesthesia-induced unresponsiveness (Warnaby et al. 2016; Huang et al. 2021), while vAIC and PB are functionally connected in healthy humans but disconnected in coma (Fischer et al. 2016). This pattern suggests that AIC operates much like a homeostatically-governed waterwheel system: driven by ascending interoceptive salience while simultaneously gating the propagation of interoceptive afferences along the neuraxis – including, crucially, PB – and forward perceptual representations in prefrontal cortex. This dual role would ensure the continuous and adaptive construction of subjective awareness.

## 6 Conclusion

This chapter proposes a refinement of our model of the primate insula, grounded in neuroanatomical and neurophysiological details that reveal both shared features between the human and macaque insula and the remarkable expansion of the human insula – likely supporting uniquely human cognitive and perceptual capacities. The prospect of a small, primal IDFA in macaques – if confirmed – may provide a precious opportunity to probe the roots of interoceptive integration, which in humans becomes the very substrate of feelings.

Bud's work was never about accumulating facts for their own sake or merely extending existing models. Instead, it charted a bold trajectory, providing deeply insightful evidence that systematically challenged dogma and led to a paradigm shift with profound implications for understanding the human condition. His contributions extend and refine the foundational works of Weber, Langley, James, and Sherrington, and I fully concur with my colleague that his legacy rivals, if not surpasses, that of the seminal discoveries on the molecular basis of interoception (Blomqvist 2023). More than two decades after his landmark *Nature Reviews Neuroscience* paper, Bud's scientific and intellectual legacy continues to shape the field, guiding the community's deepening engagement with interoception. His work will inspire for decades, with certainly still much to "digest" and appreciate in his writings, beyond the principal tenets of his theories.

While some of Bud's proposals may have appeared to be rather non-compromising, he was well aware that much remains to be done to further elucidate interoception, the insular cortex, and the nature of the self. While strongly advocating – after having provided implacable evidence – for the inclusion of pain and temperature in an expanded definition of interoception and for the role of interoception and the insula in the emergence of subjective feelings, Bud was not dogmatic; he would readily accept rigorous scientific evidence from others and adapt his thinking and interpretations. While recognizing his models as "work in progress," Bud had the merit to stick his neck out with challenging but lucid proposals that can be tested in the laboratory. His models continue to be supported by an increasing amount of new data, which hopefully will also lead to refined concepts that Bud would have gladly embraced if supported by strong and unflawed evidence. In his book, he listed many questions that remain to be addressed, for example, regarding the fine topographic organization the primary interoceptive cortex beyond what is currently known from tract-tracing and functional data; or regarding the overlap or separation of functional loci in dAIC and vAIC, which are known to contain multiple architectonic areas; or regarding how the two different sides of the insula interacts to contribute to a unified sense of self; and whether every feeling and thought must have an autonomic correlate and homeostatic value.

In recent years, Bud and I continued our discussions, too rarely, with the shared goal of publishing a remarkable collection of unpublished neuroanatomical and neurophysiological data. This effort is ongoing, with the hope that further characterization of these pathways will continue to illuminate "what goes on in these amazing bodies and in our remarkable brains" (Craig 2015).

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