# Insular cortex: A hub for saliency, cognitive control, and interoceptive awareness

**Vinod Menon,** Department of Psychiatry and Behavioral Sciences, Department of Neurology and Neurological Sciences, Wu Tsai Neuroscience Institute, Stanford University, Stanford, CA, United States

## Key points

- **Insular cortex structure and connectivity:** Examines the insular cortex's structural and functional heterogeneity, cytoarchitectonic organization, and its extensive network connectivity with other brain regions.
- **Functional roles of insula subdivisions:** Describes the diverse roles of the insula's subdivisions in cognitive control, emotional regulation, and interoception.
- **Cognitive control and executive functions:** Examines insula's involvement in saliency and deviancy detection, inhibitory control, error processing, and adaptive processing under uncertainty, emphasizing its role in cognitive and behavioral regulation.
- **Interoception:** Describes insula's central role in key interoceptive processes such as central autonomic system regulation, visceroception, pain perception, and affective touch.
- **Interoception and emotion processing:** Examination of the insula's pivotal role in interoceptive awareness and its significant impact on emotional experiences and responses.
- **Integrative hub for interoceptive and cognitive-emotional processes:** Discusses how the insula acts as an integrative hub, bridging internal physiological states with external environmental stimuli.
- **Network model of insula function:** Describes insula's role as a key component of the salience network, facilitating network switching and regulating attentional resources by linking saliency, cognitive control and interoception.

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## Abstract

This article provides an overview of the insular cortex's multifaceted role in the human brain. We discuss its structural and functional architecture, and pivotal functions in cognitive control, behavioral regulation, and emotional processing. The review delves into the insula's integral involvement in interoceptive awareness, emphasizing its role in bridging internal physiological states with external stimuli to facilitate adaptive behaviors. We examine how the insula's subdivisions contribute to diverse cognitive and affective processes. The insula emerges as a crucial hub for the dynamic regulation of cognitive and emotional states and the interplay between the mind, body, and environment.

## Introduction

Nestled within the cerebral cortex's folds, the insula (**Fig. 1**), named for its concealed location, plays an outsized role in human brain function (Evrard, 2019; Gogolla, 2017; Nieuwenhuys, 2012; Craig, 2011). Historically viewed as a center for gustatory and chemosensory processing, advances in cognitive and systems neuroscience have revealed the insula's broader role in human cognition, highlighting its involvement in a plethora of functions ranging from attention, cognitive control and interoceptive awareness to central autonomic regulation (Craig, 2009, 2015; Menon and Uddin, 2010; Nieuwenhuys, 2012; Wu et al., 2019; Gu et al., 2013a,b; Wang et al., 2019). Notably, the insula now stands out as one of the most frequently activated regions in human functional neuroimaging research (Menon and Uddin, 2010; Dosenbach et al., 2007, Chang et al., 2013). This paradigm shift reveals the insula as a key player in regulating the influences of both external and Internal stimuli on cognitive and emotional states.

The insula's extensive involvement in a wide range of cognitive and affective domains underscores its pivotal role as a central hub orchestrating cognitive, behavioral, and emotional processes within the human brain (Menon and Uddin, 2010, Menon, 2015;

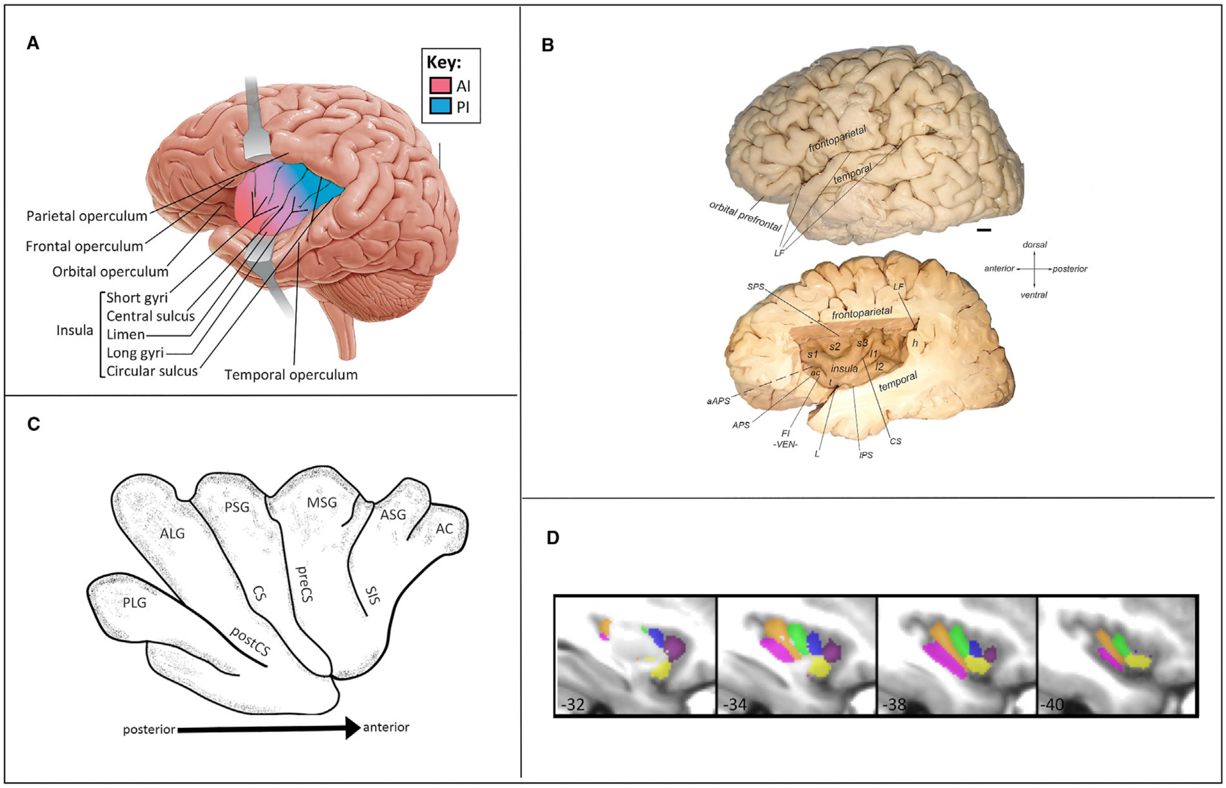


**Fig. 1 Anatomy of the insular cortex.** (A) Surface rendering of human brain highlighting insular cortex nestled in the cerebral folds is divided into dorsal anterior insula (dAI), ventral anterior insula (vAI), and posterior insula (PI), situated bilaterally within the lateral sulcus between the temporal, parietal, and frontal lobes. The circular sulcus outlines its perimeter, and its anterior and posterior parts are demarcated by the central insular sulcus. The anterior insula houses three short gyri, contrasted by two long gyri in the posterior insula. (B) Morphological delineation of the insula and its main structural landmarks in human brain. (a,a') The human insula, shown from the lateral perspective with and without the covering opercula, includes two long posterior gyri (l1 and l2) and three anterior short gyri (s1-3), divided by the central sulcus (CS). The anterior insula features an additional, variable accessory gyrus, overlapping with the FI area, known for its dense von Economo neuron concentration. (C) Macroanatomical structure of the insular cortex modified after Clark (1896). ALG: anterior long gyrus; PLG: posterior long gyrus; PSG: posterior short gyrus; MSG: middle short gyrus; ASG: anterior short gyrus; AC: accessory gryrus; postCS: postcentral sulcus; CS: central sulcus; preCS: precentral sulcus; SIS: short insular sulcus. (D) Insular subdivisions of the probabilistic maps thresholded at 50% superimposed on the average of the 30 MRIs. Pink: Posterior long gyrus; orange: anterior long gyrus; green: posterior short gyrus; blue: middle short gyrus; purple: anterior short gyrus; yellow: anterior inferior cortex. (A) Adapted from Namkung et al. (2017). (B) Adapted from Evrard (2019). (C) Adapted from Quabs et al. (2022). (D) Adapted from Faillenot et al. (2017).

Uddin, 2015). At the heart of the insula's multifaceted functions lies its core capability of interoception—the perception and integration of internal bodily states. This function bridges physiological sensations with emotional experiences, offering key insights into the neural underpinnings of emotions and their regulation. By integrating cognitive processes with bodily sensations, emotions, and autonomic functions, the insula acts as a critical nexus at the interface of the mind, body, and external environment, highlighting its indispensable role in the complex interplay of internal states and external stimuli.

This article delves into the multifaceted roles of the insula, exploring its unique structural characteristics, network connectivity, and pivotal functions in cognitive control, behavioral regulation, and emotional processing. We begin by examining the morphological and cytoarchitectonic organization of the insula, highlighting its unique cellular architecture. We next discuss the insula's complex gyral and sulcal patterns and how these structural aspects contribute to its diverse functions. We then explore the insula's structural connectivity and the extensive network of white matter pathways that link the insula to multiple brain regions. We describe the unique connectivity profiles of different insular subdivisions and their implications for the insula's multifaceted functions, emphasizing the parallel rostro-caudal organization of its connections.

We then shift focus to the insula's intrinsic functional organization. This part of the article examines the functional subdivisions within the insula, as revealed by resting-state functional MRI studies. We discuss the roles of the dorsal anterior, ventral anterior, and posterior insula, integrating these insights with the microstructural properties identified in the earlier sections.

Next, we focus on the functional roles of the insula's subdivisions, guided by meta-analyses of task-related activation. This segment uncovers how different parts of the insula are activated across various cognitive domains and describes task-related coactivation of the insula with distinct brain systems, revealing both segregated and integrative aspects of its functions. We then focus on the insula's central roles in cognitive control, executive functions, and error processing. We examine the insula's role in signaling saliency, as well as its pivotal function in deviancy detection, inhibitory control and error processing. This underscores its essential contribution to adaptive behavior and cognitive flexibility, central to effective decision-making and response adaptation.

In subsequent sections, we delve into interoception, highlighting the insula's vital role in the body's internal sensing system. Our discussion encompasses central autonomic system regulation, where the insula's pivotal function in controlling physiological functions like heart rate and respiratory rate is examined. We examine visceral processing, detailing how the insula integrates various bodily signals to form a cohesive internal state representation. The article then addresses pain perception, emphasizing the insula's ability to discern and process the subjective saliency of painful stimuli. Finally, we examine the insula's involvement in affective touch, illustrating its role in the sensory evaluation of touch and its emotional context. These topics underscore the insula's central contribution to a wide range of interoceptive processes, reflecting its wide-ranging influence in bodily sensation and regulation.

We then present an integrative model of insula function, linking saliency detection, cognitive control, and interoception, building on prior models (Menon and Uddin, 2010; Menon, 2015). This section synthesizes the various roles of the insula, focusing on how it anchors the salience network and facilitates dynamic network switching, thus playing a vital role in the brain's adaptive responses. We conclude with a comprehensive summary that integrates the insights from each section, emphasizing the insula's role as a critical integrative hub in the brain's network architecture. This concluding section highlights the insula's significance in modulating cognitive, emotional, and physiological processes, and its pivotal role in the interplay between mind, body, and the external environment.

## Anatomy and structural connectivity

### Morphological and cytoarchitectonic organization

The insular cortex's distinct morphological and cytoarchitectonic characteristics have been a focal point of neuroanatomical research for over a century (Brodmann, 1909; Mesulam and Mufson, 1985; Augustine, 1996; Von Economo et al., 2008; Allman et al., 2010; Nieuwenhuys, 2012). Stereological analyses have unveiled a cellular architecture in the insula that diverges notably from the typical cortical arrangement seen elsewhere in the brain (Mesulam and Mufson, 1985; Augustine, 1996). Morphologically, the insula is identifiable by its unique gyral and sulcal patterns, which include anterior, middle, and posterior short gyri, as well as anterior and posterior long gyri situated around the central sulcus—a critical landmark demarcating the anterior and posterior divisions of the insula (**Fig. 1**). Faillenot et al. mapped the insula's macro-anatomy by delineating six specific regions on MRI images from 30 healthy individuals. These regions encompass three short gyri in the dorsal aspects of the anterior insula, the anterior ventral insula, and two long gyri in posterior insula. Importantly, they created a probabilistic atlas in MNI152 space, offering a comprehensive reference for the insula's morphology and volume variations (Faillenot et al., 2017).

The insula's cytoarchitectonic organization consists of oblique stripes of agranular, dysgranular, and granular cortex, each with a distinctive arrangement and function (Evrard et al., 2014; Mallela et al., 2023) (**Fig. 2**). The anterior insula is characterized by its predominantly agranular and dysgranular structure, which stands in contrast to the granular nature of the posterior insula (PI). This granular configuration of the PI aligns more closely with the typical architecture prevalent in most other cortical regions. These structural distinctions between the anterior and posterior parts of the insula reflects specialization of functions, with each subsection contributing uniquely to the complex operations of the insular cortex (Evrard, 2019; Mesulam and Mufson, 1982a; Morel et al., 2013; Nieuwenhuys, 2012).

More detailed cytoarchitectonic analyses of the primate insula have identified a tripartite organization into the anterior "agranular", intermediate "dysgranular," and posterior "granular," sectors, based on the presence, thickness and distinctiveness of Meynert's granule cell layers 4 and 2 (Evrard, 2019; Nieuwenhuys, 2012). Each of these primary subdivisions can be further divided into more specific sub-regions. Quantitative analysis of layer-specific cellular organization in the human brain has further identified several additional subdivisions: agranular (Ia1, Ia2), dysgranular (Id1-Id7), and granular (Ig1, Ig2, Ig3) (**Fig. 2**). The comprehensive

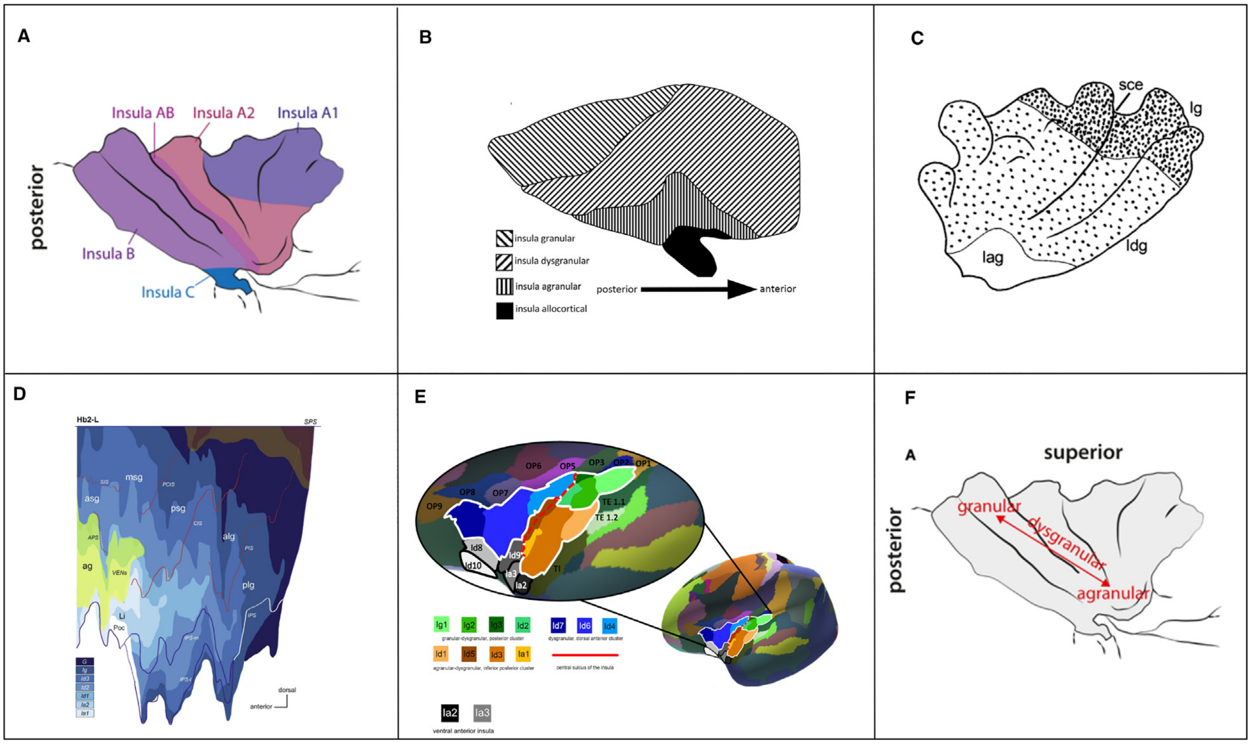


**Fig. 2 Evolving views of insula cytoarchitecture.** (A) Cytoarchitectonic mapping from Von Economo et al. (2008), identifying a lesser granulated area “Insula A1” and more granulated posterior regions, with no agranular areas except a fronto-insular region (not shown here). Notably, they documented a transitional “Insula AB” area between anterior and posterior regions. (B) Mesulam and Mufson’s (1985) microanatomical parcellation presents three radial, wave-like cytoarchitectonic belts encircling an allocortical pole: (i) a granular belt from superior posterior to dorsal anterior insula, (ii) a dysgranular belt spanning the middle posterior to dorsal anterior insula, and (iii) an agranular belt in the inferior posterior to ventral anterior insula. (C) Bonthius et al.’s (2005) subdivision of the human insula into agranular cortex (Iag), dysgranular cortex (Idg), and granular cortex (Ig). (D) An unfolded map of the insula in Hb2-L, showing cytoarchitectonic subdivisions in graded blue hues. Major insular and peri-insular sulci are highlighted. The yellow area marks distribution of VENs. (E) Maximum probability map from the Julich group, revealing new insular areas (Ig3, Ia1, Id2-6) alongside previously identified zones (Ig1, Ig2, Id1, Ia2-3, Id8-10) and ventral AI areas (Ia2, Ia3). (F) Summary cartoon illustrating a cytoarchitectonic gradient in the insula, transitioning from agranular cortex in the anterior inferior region to dysgranular, and finally to granular cortex in the posterior section. (A) Adapted from Klein et al. (2013). (B) Adapted from Quabs et al. (2022). (C) Adapted from Nieuwenhuys (2012). (D) Adapted from Morel et al. (2013). (E) Adapted from Quabs et al. (2022). (F) Adapted from Klein et al. (2013).

cytoarchitectonic mapping of the human insula’s architecture is an ongoing endeavor, with significant advancements anticipated in the coming years as detailed human cellular-level atlases become increasingly sophisticated and accessible (Quabs et al., 2022).

The human insula is distinguished by the presence of von Economo neurons, especially within its ventral anterior agranular region. Characterized by their unique large spindle shape and thick dendrites, these neurons are theorized to facilitate rapid neural communication which is crucial for effective cognitive control and interoception (Evrard, 2019; Nieuwenhuys, 2012) (**Fig. 2**). They are believed to play a pivotal role in the fast implementation of goal-directed behaviors and cognitive control, contributing significantly to complex cognitive, behavioral, and social processes (Craig, 2009; Critchley et al., 2004; Seeley et al., 2007). Notably, von Economo neurons have been reported in only two other brain areas besides the insula: the anterior cingulate cortex (ACC), and dorsolateral prefrontal cortex, areas central to higher-order cognitive and affective functions.

## In vivo MRI-based microstructural organization of the insula

Diffusion MRI (MRI) has significantly advanced our understanding of the insular cortex’s microstructural organization, offering insights beyond what postmortem studies can provide. Notably, non-invasive imaging techniques, coupled with behavioral measures and assessments, are essential for examining individual variations across large populations, providing a comprehensive behavioral context often lacking in postmortem studies. Such in vivo imaging is essential for relating the insula’s structural characteristics with its functional roles and behavioral implications.

Notably, a study utilizing multi-shell diffusion MRI data from 413 participants characterized the human insular cortex’s microstructure in relation to its primary functional subdivisions, overcoming limitations of identifying insular subdivisions based solely on anatomical MRI landmarks (**Fig. 3**). Microstructural properties were assessed using water molecule’s return to the origin probability which provides insights into the density and arrangement of cellular structures within the brain (Menon et al., 2020). Higher

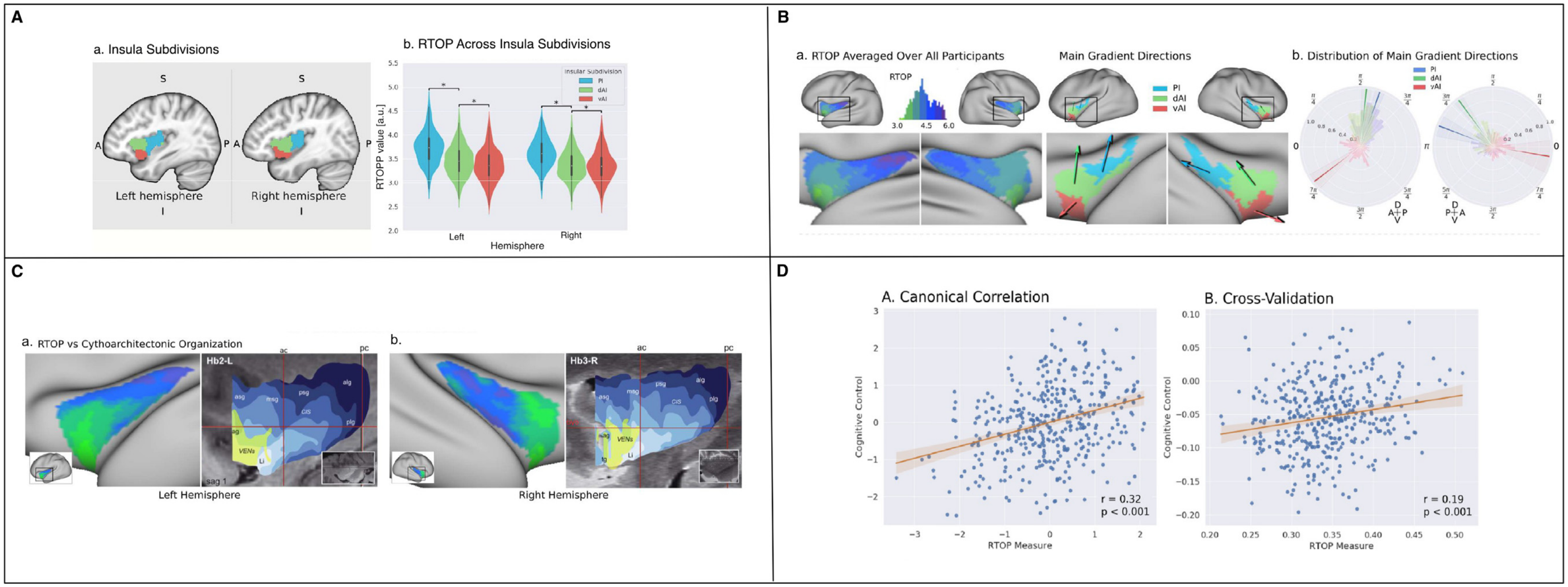


**Fig. 3** **Functional and microstructural characteristics of insular cortex subdivisions.** (A) a. Functional subdivisions across the posterior insula (PI), dorsal AI (dAI), and ventral AI (vAI). b. Significant differences in Return-to-Origin Probability (RTOP) among PI, dAI, and vAI in the left and right hemispheres ($N = 413$). Notably, the right ventral AI exhibits the smallest RTOP values, with statistical significance in all comparisons except when compared to right dorsal AI. (B) Insula microstructure gradients along anterior-posterior and dorsal-ventral axes. a. Microstructural inhomogeneity with a ventral AI peak, and gradients along anterior-posterior and dorsal-ventral axes. A notable gradient extends from the insular pole to the posterior section, with a right hemisphere dominance. b. Main gradient directions using Rayleigh directional statistics in each functional subdivision, showing anterior-to-posterior and inferior-to-superior RTOP organization in the left insula, and an anterior-to-posterior pattern in the right insula. c. Polar plots visualize the distribution of main gradient directions in each subdivision. (C) RTOP isocontours align with insula cytoarchitectonic organization, comparing population-average RTOP isocontours (left) with cytoarchitectonic organization and Von Economo Neurons (VEN) expression from post-mortem brain studies (right, based on Morel et al. (2013)). (D) Insula microstructural predicts cognitive control abilities. (A) Canonical correlation analysis (CCA) identifies a significant link between mean RTOP in each insular subdivision and cognitive control metrics. (B) Cross-validation analysis confirmed that CCA-derived RTOP weights predict cognitive control measures in unseen data. (D) Adapted from Menon et al. (2020).

return to the origin probability values indicate more restricted or hindered diffusion, often found in areas with denser cellular structures like tightly packed neurons or axonal fibers. The ventral AI showed the lowest return to the origin probability values, followed by the dorsal AI, and the highest in the PI. The study further revealed gradients along the anterior-posterior and dorsal-ventral axes with gradient "fingers" extending from the ventral AI along a ventral-dorsal axis, mirroring findings from post-mortem brain studies (Morel et al., 2013). This pattern is also consistent with the distribution of von Economo neurons, mainly found in the agranular insular cortex in dorsal and ventral AI (Morel et al., 2013; Namkung et al., 2017; Nimchinsky et al., 1999).

Moreover, these in vivo diffusion MRI measures also allowed researchers to link insular microstructure to cognitive control (Menon et al., 2020). The insula's microstructural characteristics predicted individual differences in cognitive control abilities, including processing speed, working memory, response inhibition, and cognitive flexibility (**Fig. 3**). This correlation between insular microstructure and cognitive performance highlights the functional significance of the insula's structural properties.

## Structural connectivity

Early work in non-human primates demonstrated that the insula has widespread connections with frontal, temporal, and parietal cortical regions, as well as limbic areas (Mesulam and Mufson, 1982b; Mufson and Mesulam, 1982). These connections include efferent projections to and afferent inputs from key regions such as the amygdala, lateral orbital cortex, olfactory cortex, anterior cingulate cortex, and superior temporal sulcus (**Fig. 4**).

In humans, diffusion MRI studies have revealed widespread white matter pathways linking the insula with the major lobes of the brain and limbic regions (Ghaziri et al., 2017; Jakab et al., 2012; Cloutman et al., 2012; Cerliani et al., 2012). Individual insular subdivisions show distinct connectivity profiles: the AI has connections with the ACC, orbitofrontal cortex, the inferior and superior temporal gyri, the temporal pole, the thalamus, and the amygdala; the middle insular with the superior and inferior frontal gyri, the precentral, postcentral, and supramarginal gyri, the inferior and superior temporal gyri, the orbitofrontal and the parietal cortices, while the PI has connections with the precentral and postcentral gyri, the inferior and superior temporal gyri, the parietal cortex, and the putamen (Ghaziri et al., 2017, 2018). This pattern reflects a parallel rostro-caudal organization of insula-cortical-subcortical connectivity in line with tracing studies in macaques (Nieuwenhuys, 2012; Evrard, 2019).

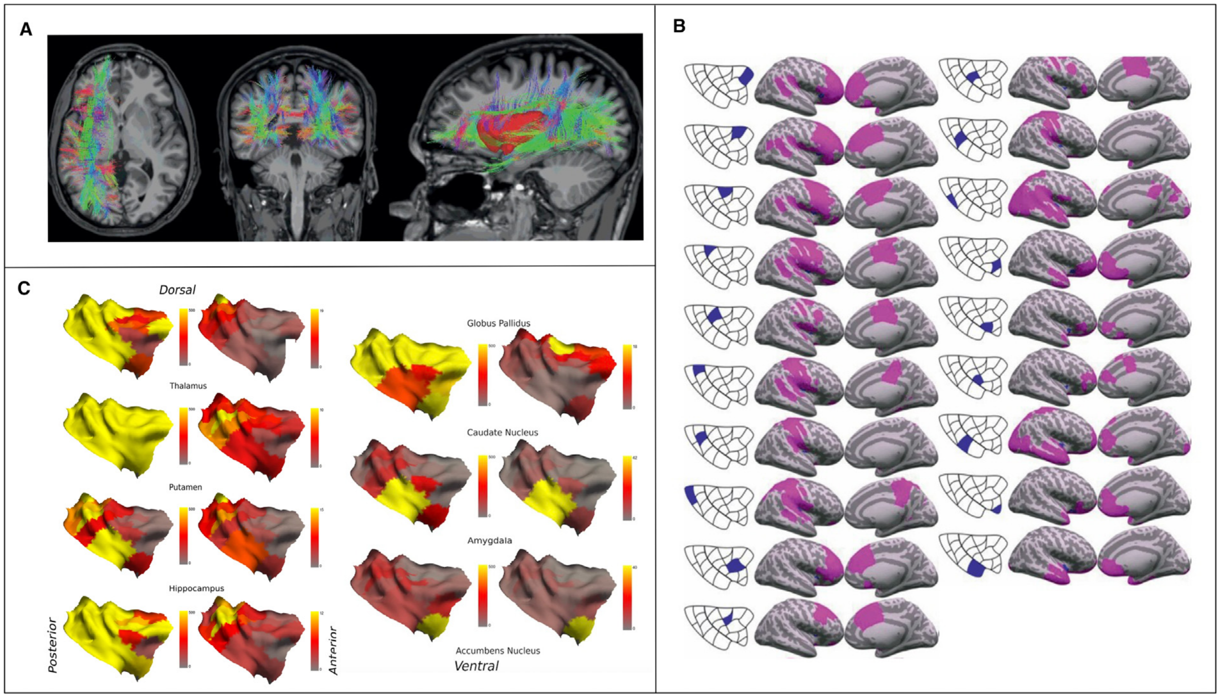


**Fig. 4 Structural connectivity of the human insular cortex.** (A) Tractography-based illustration of the insula's connectivity, showing the extensive network of connections with frontal, parietal, and temporal lobes. (B) Connectivity profile of 19 right insular subregions, revealing extensive connections across all major lobes. The connectivity pattern is characterized by both rostrocaudal and dorsoventral distinctions. Specifically, anterior insular regions are primarily connected to the frontal and temporal lobes' anterior areas, while posterior regions link to the more posterior parts of these lobes and extend to the parietal and occipital lobes. Dorsal insular regions show connections with the frontal and parietal lobes, whereas ventral regions are associated with the temporal lobe. (C) Connectivity between the right and left insula and various subcortical regions: thalamus, putamen, hippocampus, globus pallidus, caudate nucleus, amygdala, and nucleus accumbens. The amygdala predominantly connects to the insula's ventral subdivision, while the hippocampus mainly links to the posterior insula. (A) Adapted from Fei et al. (2022). (B) Adapted from Fei et al. (2022). (C) Adapted from Ghaziri et al. (2018).

Detailed analysis of high resolution diffusion MRI data has highlighted four main patterns of insular connectivity: (1) AI is primarily connected to anterior regions of the frontal and temporal lobes, (2) PI is connected to posterior regions of the frontal and temporal lobes, extending to the parietal and occipital lobes, (3) dorsal insula is linked with the frontal and parietal lobes, and (4) ventral portions of the insula show pronounced connections to the temporal lobe. This profile reveals a connectivity gradient: the rostrodorsal regions of the insula are predominantly connected to the prefrontal cortex, with a posterior progression showing connections to the premotor cortex, supplementary motor area, sensorimotor regions, and extending to the precuneus. In contrast, more ventral insular areas show diminishing connections to the frontal lobe but increased connections to the temporal lobe (Ghaziri et al., 2017, 2018; Fei et al., 2022). Significantly, Ghaziri et al. (2018) also identified connections from the insula to the cingulate gyrus, with the AI mainly connecting to the ACC and the PI to the posterior cingulate cortex. Additionally, analysis of subcortical structural connectivity has highlighted links with the putamen, globus pallidus, caudate nucleus, nucleus accumbens, and thalamus, delineating a comprehensive map of the insula's cortical and subcortical connectivity.

In addition to these cortical and cortico-subcortical tracts, seminal work by Craig, Evrard and others has identified ascending pathways from the spinal cord that target the insula and anterior cingulate cortex, a "homeostatic afferent pathway" in non-human primates (Craig, 2002, 2003) (**Fig. 5**). This pathway carries information about the physiological status of body organs, and originates from lamina I neurons in the spinal cord that give rise to the lateral spinothalamic tract. This tract first synapses in the ventromedial and mediodorsal nuclei of the thalamus. These thalamic nuclei project topographically to the mid/posterior dorsal insula, which in turn projects to AI. Descending pathways from the dorsal PI have been described which terminate in the periaqueductal gray area of the brainstem, constituting a mechanism for cortical control of brainstem homeostatic systems (Craig, 2002; Flook et al., 2020).

Cell-type-specific monosynaptic rabies virus tracing has led to the characterization of afferent connections onto excitatory or inhibitory insular neurons (Gogolla, 2017). These studies confirm the insula's reciprocal connections with systems involved in sensory processing, emotion, motivation, and cognition (Gehrlach et al., 2020). The insula exhibits bidirectional connectivity with cortical regions, and typically unidirectional connections with subcortical structures. The AI is reciprocally connected to frontal and association areas, the mid insula to somatosensory regions, and the PI to brainstem nuclei. Additionally, the insula receives diverse neuromodulatory input, including cholinergic afferents from the basal nucleus, dopaminergic from the ventral tegmental area, serotonergic from the raphe nuclei, and adrenergic from the locus coeruleus (Gehrlach et al., 2020; Coletta et al., 2020) (**Fig. 6**).

Thus, the insula emerges as a convergence zone at the intersection of multiple cortical and subcortical pathways and networks integral to both cognitive functions and autonomic processing. Its unique position in the brain's structural framework enables the

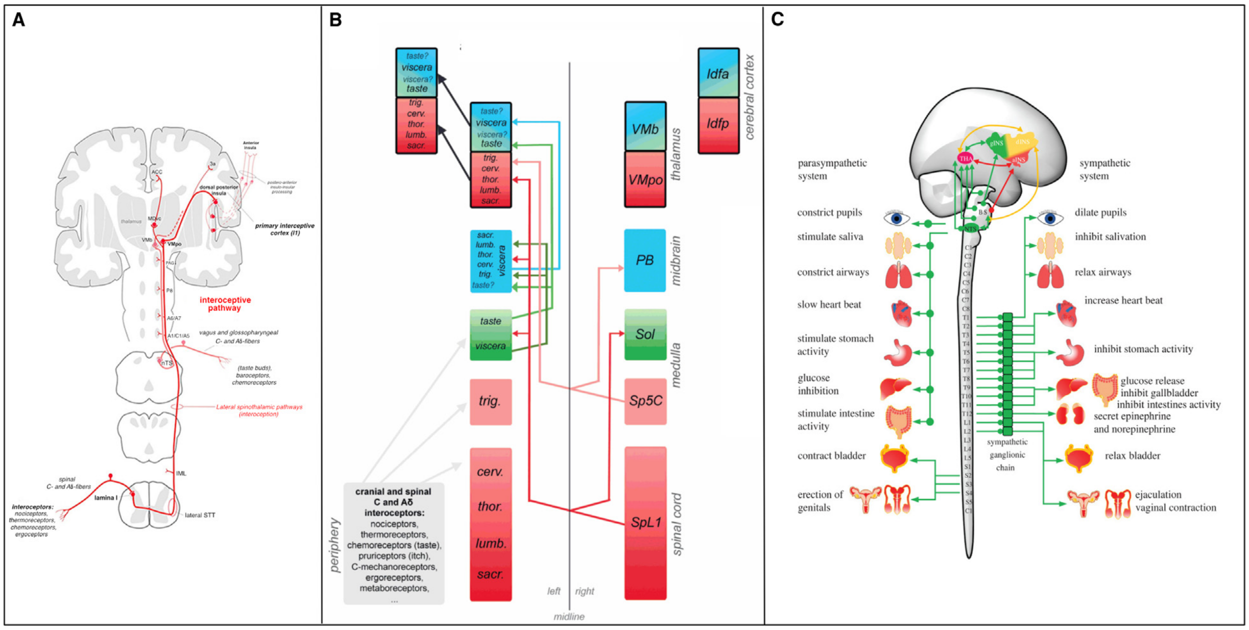


**Fig. 5 Ascending pathways targeting the insula.** (A) Schematic representation of the ascending interoceptive pathway in primates that target the insula and anterior cingulate cortex. (B) Schematic drawing of the primate ascending interoceptive pathway with its three main components (spinal in red, solitary in pink and parabrachial in blue). Simplified schematic representation of the topographic organization of the spinal (SpL1), trigeminal (Sp5C), solitary (Sol), and parabrachial nucleus (PB) projections to the posterior (VMpo) and basal (VMb) parts of the ventral median thalamus. (C) Basic organization of neural pathways linking the parasympathetic and sympathetic branches of the autonomic nervous systems to the insular cortex and their effects on visceral functions. (A) Adapted from Evrard (2019). (B) Adapted from Evrard (2022). (C) Adapted from Fermin et al. (2022).

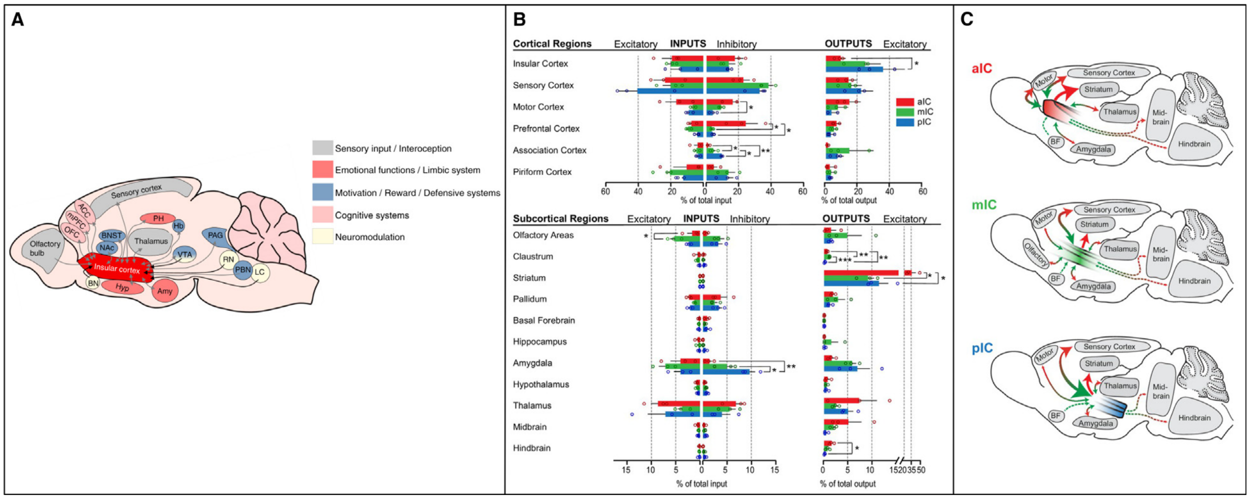


**Fig. 6 Structural connectivity in the rodent insula.** (A) Simplified schematic of insula connectivity in the rodent brain, showing reciprocal connections (gray arrows) between the insula and various sensory, emotional, motivational, and cognitive systems. Additionally, the insula receives strong neuromodulatory inputs (black arrows) from several key regions: cholinergic afferents from the basal nucleus (BN), dopaminergic input from the ventral tegmental area (VTA), serotonergic input from the raphe nuclei (RN), and adrenergic input from the locus coeruleus (LC). Key connected regions include the anterior cingulate cortex (ACC), amygdala (Amy), bed nucleus of the stria terminalis (BNST), habenula (Hb), hypothalamus (Hyp), medial prefrontal cortex (mPFC), nucleus accumbens (NAc), orbitofrontal cortex (OFC), periaqueductal gray (PAG), parabrachial nucleus (PBN), and parahippocampus (PH). (B) Whole-brain insular cortex (IC) connectivity map across three IC subregions (anterior IC (aIC) in red, medial IC (mIC) in green, posterior IC (pIC) in blue) with 17 major brain regions. Inputs to excitatory and inhibitory IC neurons are on the left, while outputs of excitatory IC neurons are on the right. Regional values are expressed as a percentage of total cells (RV) or of total pixels (AAV). The top panel highlights cortical connectivity, while the bottom panel focuses on subcortical connections. (C) Input-output maps for the three IC subdivisions, emphasizing selected brain regions. Weight of arrowhead and thickness of arrow shaft indicate strength of connection. Green arrowheads indicate inputs, red arrowheads indicate outputs. (A) Adapted from Gogolla (2017). (B) Adapted from Gehrlach et al. (2020). (C) Adapted from Gehrlach et al. (2020).

insula to integrate and coordinate activities across these diverse systems, thereby playing a pivotal role in linking cognitive processes with physiological states.

## Intrinsic functional organization of the insula

### Functional subdivisions

Resting-state functional MRI, a powerful tool measuring spontaneous brain activity, has been fundamental in uncovering the insular cortex's functional heterogeneity and subdivisions. By employing cluster analysis based on gradients of connectivity, which involves grouping similar patterns of brain activity to identify distinct functional areas, researchers have significantly advanced our understanding of the insula's diverse roles (Deen et al., 2011; Jakab et al., 2012; Cauda et al., 2012; Kelly et al., 2012; Chang et al., 2013; Ryali et al., 2013) (**Fig. 7**). Depending on the clustering methodologies, studies have identified three to six functional subdivisions within the insula, reflecting variability in parcellation techniques. Broadly, the various solutions represent successive refinement of a tripartite organization comprising the dorsal AI, ventral AI, and PI. More precise quantitative analysis based on both the orientation and strength of connectivity patterns has identified an additional ventral mid insula subdivision that aligns well with prior analysis using multimodal imaging techniques (Kelly et al., 2012; Kurth et al., 2010a,b).

A key challenge in this area of research is the determination of the optimal number of insular clusters. An alternative perspective considers the insula's connectivity along a continuum, with two primary gradients from the dorsal-posterior to ventral-anterior axes (Tian and Zalesky, 2018). This continuum model aligns with the gradients in the insula's microstructural properties as previously discussed (Menon et al., 2020) (**Fig. 3**), and avoids the arbitrariness of defining a specific number of subdivisions.

Despite these different perspectives, the tripartite organization comprising the dorsal AI, ventral AI, and PI has emerged as the more prominent and widely used model, showing broad consistency with anatomical data. However, it is important to recognize that this model is an approximation, useful for theoretical purposes. Further refinements and understanding of finer details will enhance insights into the insula's integrative role, particularly how it processes and combines multiple signals from the central nervous system and viscera.

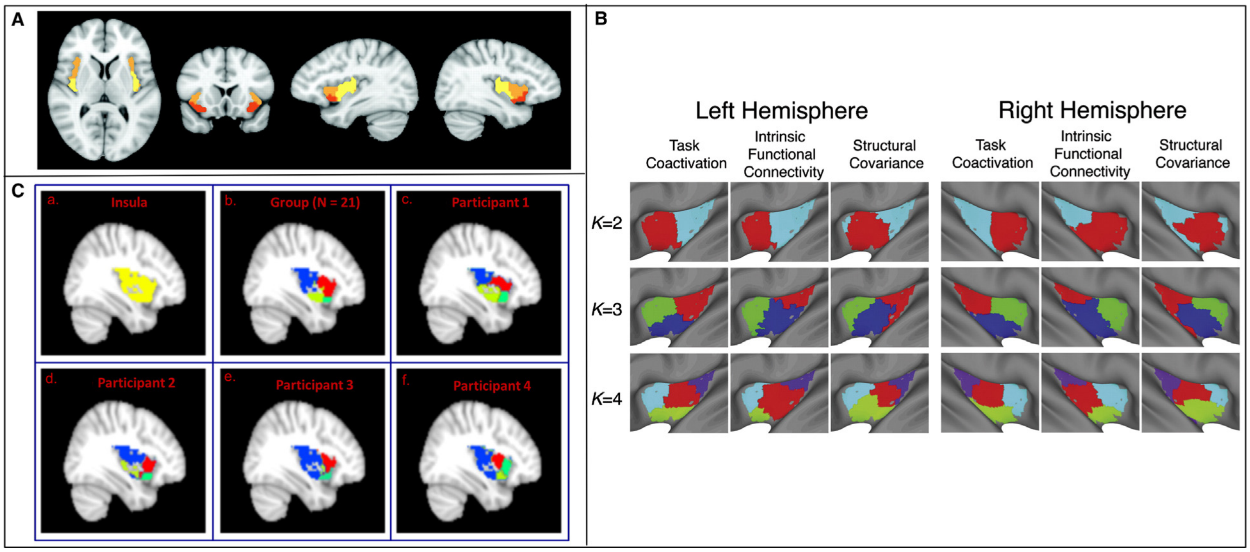


**Fig. 7** **Functional parcellation of the insula.** (A) Three distinct subregions of the insula identified through cluster analysis: dorsal AI (orange), ventral AI (red) and posterior insula (PI, yellow). (B) Consensus and multi-site cluster solutions ranging from $K = 2$ to $K = 4$. These solutions are derived from intrinsic functional connectivity (iFC), task-based coactivation data, and structural covariance. (C) VMF–MRF segmentation process applied to the insula: (a) Insula region of interest. (b) Four clusters identified through group analysis. (c–f) Variability across four individual participants. (A) Adapted from Deen et al. (2011). (B) Adapted from Kelly et al. (2012). (C) Adapted from Ryali et al. (2013).

### Intrinsic functional connectivity

Intrinsic functional connectivity, assessed primarily using resting-state fMRI, refers to the synchronous coupling of neural activity across different brain regions. It provides a useful approach for understanding the underlying architecture and functionality of brain circuits without the confounding influences and variations induced by various tasks. This approach has proven particularly useful for investigating differences in functional circuity associated with insula subdivisions, and deriving insights into its diverse roles in processing and integrating a range of cognitive, emotional, and sensory information (Fig. 8).

Insula circuitry has been extensively explored within the framework of its tripartite subdivisions (Menon et al., 2020; Cauda et al., 2012; Deen et al., 2011; Nomi et al., 2016; Chang et al., 2013; Kurth et al., 2010b; Ryali et al., 2013). These studies reveal that the dorsal AI primarily connects with regions pivotal in high-level cognitive processing and executive functions. These include the dorsal ACC, pre-supplementary motor area, inferior frontal gyrus, dorsolateral prefrontal cortex, and posterior parietal cortex. In contrast, the ventral AI exhibits stronger functional connections with limbic regions integral to reward processing, emotion, and homeostatic regulation. This includes the ventral anterior cingulate cortex, pregenual cingulate cortex, amygdala, ventral striatum, and hypothalamus, consistent with the insula's hypothesized role in emotional processing and affective responses. The PI, conversely, demonstrates robust connections with primary and secondary somatosensory cortices, and the supplementary motor area. Additionally, connectivity with premotor, sensorimotor, supplementary motor, and middle-posterior cingulate cortices is observed in a middle-posterior insula cluster.

These connectivity patterns, unique to each insular subdivision and overlapping across them, elucidate the insula's dual roles of functional specialization and integration. The insula's unique patterns align with specific functions like sensory processing or emotional regulation, while also integrating these functions within broader cognitive and emotional contexts. Time-varying connectivity analyses further reveal the dynamic nature of insular circuitry, with the dorsal AI alternating between a wide range of functional brain circuits (Nomi et al., 2016). This versatility is underpinned by its differential associations with large-scale networks, aligning the dorsal AI with the salience/ventral attention network, the ventral AI with the frontoparietal network, and the PI with the sensorimotor network (Klugah-Brown et al., 2023). More generally, the insula's diverse connectivity patterns underpin its function as an integrative hub and underscores the insula's pivotal function in coordinating multiple cognitive, emotional, and sensory processes within large-scale brain networks.

## Functional roles of insula subdivisions

### Meta-analysis of task-related activation

Meta-analyses of task-based fMRI studies have greatly expanded our understanding of the insula's multifaceted role in brain functions, revealing it as region involved in a wide range of cognitive tasks, including attention, decision-making, reasoning, emotion, and memory (Fig. 9). Focusing on meta-analyses allows for a more comprehensive and integrated view, synthesizing findings from individual studies to offer a broader perspective on the insula's complex roles and interactions within the brain.

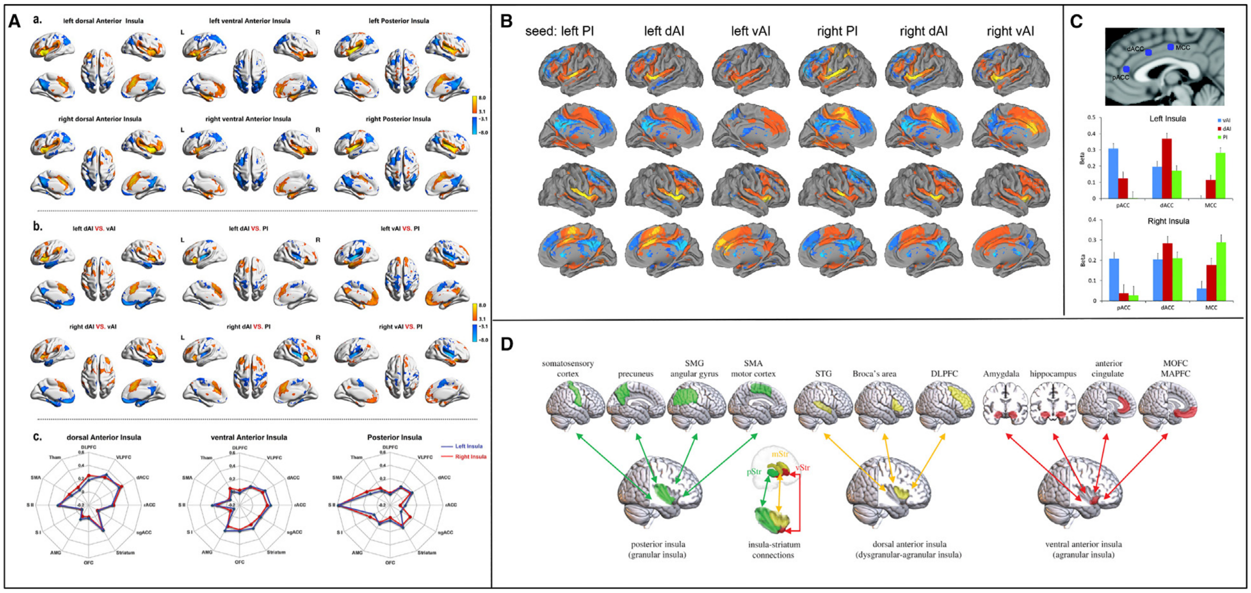


**Fig. 8 Intrinsic functional connectivity of the insula.** (A) a. Functional connectivity patterns of insular subdivisions. Orange represents positive functional connectivity with the insular subregion, while blue indicates negative connectivity. b. Comparison of functional connectivity between insular subdivisions. c. Differential functional connectivity of insular subdivisions with components of the cognitive control network. The dorsal AI (dAI) primarily connects with regions associated with higher cognition and executive control (DLPFC, VLPFC, dorsal STM, dACC), the ventral AI (vAI) with social-emotional processing and autonomic functions (AMG, OFC, ventral STM, rACC, sgACC), and the posterior insula (PI) with sensorimotor regions (SI, SII, SMA). (B) Whole-brain functional connectivity analyses of insula subdivisions showing lateral and medial views. (C) Differential connectivity strength between three insula subregions and three regions of interest along the middle to anterior cingulate cortex (pregenual anterior cingulate cortex (pACC), dorsal anterior cingulate cortex (dACC), and middle cingulate cortex (MCC)). (D) Schematic representation of the differential connectivity of insula subdivisions with various cortical and subcortical regions. (A) Adapted from Zhao et al. (2023). (B) Adapted from Menon et al. (2020). (C) Adapted from Deen et al. (2011). (D) Adapted from Fermin et al. (2022).

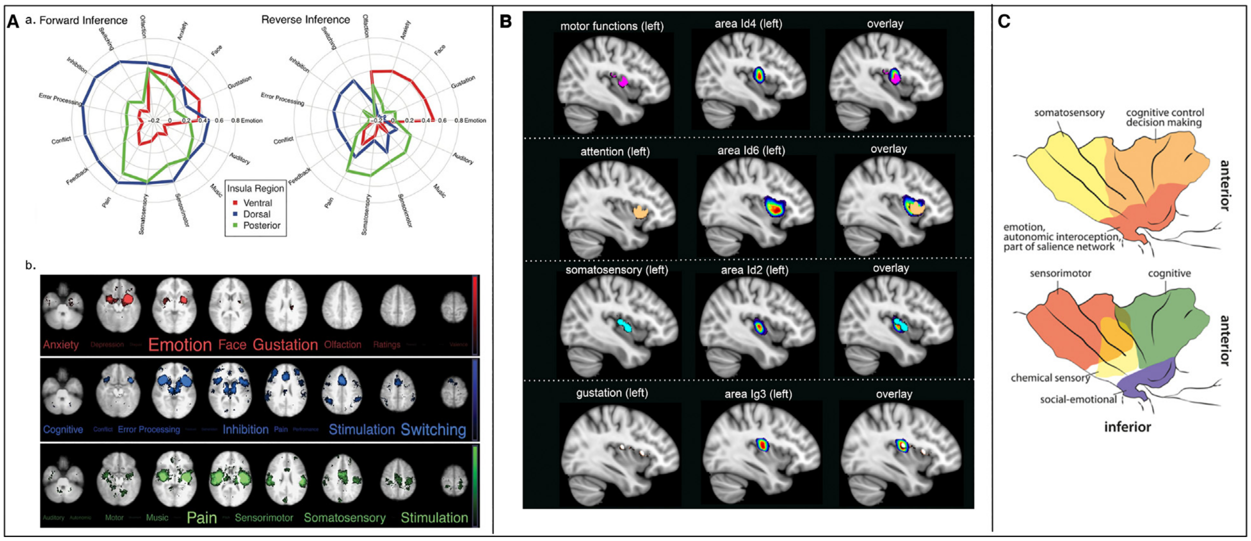


**Fig. 9 Meta-analysis-based cognitive topic mapping.** (A) Meta-analysis of cognitive topics associated with insula subdivisions showing results of forward and reverse inference. (B) Functional rankings of coactivation maps, as depicted in the results of the decoding analysis. The top 15 topics from the reverse inference analysis associated with each Meta-Analytic Functional Coactivation Analysis network map. Networks associated with ventral AI, dorsal AI and PI are shown in red, blue and green, respectively. (C) Cognitive topics associated with four cytoarchitectonic subdivisions of the insula: Area Id6 is associated with cognitive functions such as attention; Id4 with motor function; Area Ig3 with gustatory perception; and Id2 with response to somatosensory stimuli. (D) Schematic illustration of major functional divisions based on (a) tripartite Deen et al. (2011) parcellation, and (b) 4-cluster parcellation according to Kurth et al. (2010a,b) and Ryali et al., (2013). (A) Adapted from Chang et al. (2013). (B) Adapted from Chang et al. (2013). (C) Adapted from Quabs et al. (2022). (D) Adapted from Klein et al. (2013).

Several meta-analyses have revealed that the insula is consistently activated in a wide range of experimental paradigms, underscoring its significance in human brain function (Menon and Uddin, 2010; Chang et al., 2013; Dosenbach et al., 2007; Cai et al., 2017; Swick et al., 2011). Meta-analyses have also highlighted the differential engagement of insula subdivisions to different task demands (Deen et al., 2011; Jakab et al., 2012; Cauda et al., 2012; Kelly et al., 2012; Chang et al., 2013; Craig, 2009; Menon and Uddin, 2010): The dorsal AI is essential for goal-directed cognition, attention, decision-making, error detection, and uncertainty response, emphasizing its role in adaptive behavior and cognitive flexibility (Menon and Uddin, 2010; Eckert et al., 2009) (**Fig. 9**). Remarkably, the dorsal AI is consistently activated across a wide range of experimental paradigms, leading researchers to argue for its crucial role in regulating higher-level cognitive functions (Kurth et al., 2010b; Dosenbach et al., 2007; Menon and Uddin, 2010; Molnar-Szakacs and Uddin, 2022; Menon and D'Esposito, 2022). In contrast, the ventral AI encodes emotional and affective information, playing a key role in empathy and emotional regulation (Kurth et al., 2010b; Singer et al., 2009). Its strong links to limbic structures suggest its importance in integrating emotional information with physiological signals. The PI specializes in sensory processing, significantly contributing to the perception of bodily sensations like pain, temperature, and visceral states (Critchley and Harrison, 2013; Craig, 2002). The middle insula, though less studied, is implicated in olfactory and gustatory processing (Kurth et al., 2010b) and interoception (Kelly et al., 2012; Simmons et al., 2013).

### Meta-analysis of task co-activation

Meta-analysis of co-activation patterns provides insights into the functional networks consistently engaged during a broad range of tasks. This analysis involves examining the simultaneous activation of brain areas across multiple studies to identify networks that are consistently engaged together. It is particularly relevant for studying the insula's functions because it helps unravel the complex interplay between this region and other parts of the brain during various cognitive and emotional tasks (Chang et al., 2013; Quabs et al., 2022) (**Fig. 9**).

Meta-analyses have revealed that the dorsal AI is co-activated with regions involved in high-level cognitive processing and executive functions. This includes bilateral dorsal ACC, dorsolateral prefrontal cortex, and dorsal striatum. This pattern indicates the dorsal AI's role in complex cognitive tasks requiring attention, decision-making, and executive control. In contrast, the ventral AI is co-activated with limbic areas, including bilateral amygdala, ventral striatum, ventral tegmental areas, temporal pole, orbitofrontal cortex, and medial prefrontal cortex, reflecting its role in emotional and affective processing. The PI is typically co-activated with primary and secondary somatosensory cortices, and regions involved in regulating sensorimotor processing such as the supplementary motor area and mid-cingulate cortex. This suggests its primary role in integrating and regulating sensorimotor information.

Task-related co-activation networks exhibit significant overlap with resting-state networks and anatomical pathways, suggesting a fundamental continuity in the insula's functional architecture. This overlap not only highlights the existence of dedicated insular circuits but also emphasizes their adaptability to diverse cognitive and emotional contexts (**Figs. 9** and **10**).

### Forward inference analysis and functional specificity

Forward and reverse inference analyses are critical methodologies in neuroimaging that provide distinct but complementary insights into brain function (**Fig. 9**). Forward inference analysis examines the likelihood of activation in each brain area in response to specific cognitive tasks or processes. This analysis has demonstrated the consistent activation of the dorsal AI and its interconnected network across a wide range of cognitive topics, including attention, cognitive and response inhibition, decision-making, and working memory (Chang et al., 2013). Such evidence solidifies evidence for the dorsal AI's role in goal-directed cognition and underscores its involvement in executive functions (Menon and Uddin, 2010).

On the other hand, reverse inference analysis aims to infer cognitive or mental states based on patterns of brain activation. This approach decodes the brain's activity to understand which mental processes are likely to be occurring during specific patterns of activation. In the insula, reverse inference meta-analysis maps have provided valuable insights into the distinct functions of its subdivisions: the dorsal AI as highlighted in forward inference analyses, is linked with higher cognitive tasks and executive control functions; the ventral AI is primarily associated with processing emotions, chemosensation, and autonomic functions; and the PI is implicated in processing pain, and regulating sensorimotor functions (Quabs et al., 2022).

Thus, forward inference analysis confirms the involvement of insular regions in specific cognitive processes, while reverse inference provides an understanding of the cognitive and affective processes associated with activation in these regions. Together, these methods enrich our understanding of the functional specificity of the insular cortex and its subdivisions, highlighting its complex and integral role in coordinating a range of cognitive, emotional, and sensory processes.

## Cognitive control and executive functions

### Detection of deviant stimuli

The AI is instrumental in detecting behaviorally salient events, a fundamental aspect of flexible cognitive control (Corbetta and Shulman, 2002; Petersen and Posner, 2012). For instance, in the "oddball" task, which elicits the well-known P300 response studied through EEG, the AI, together with the dorsal anterior cingulate cortex, shows strong activation, in response to unexpected stimuli

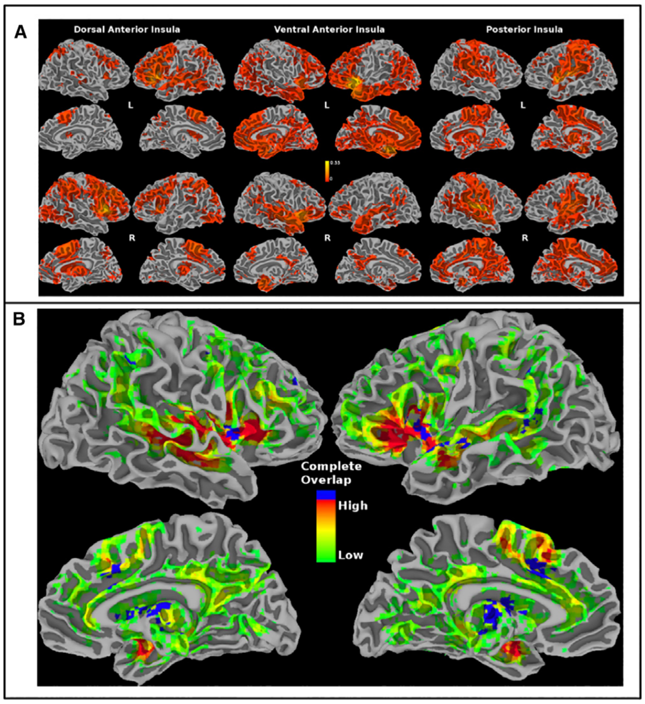


**Fig. 10 Meta-analysis based coactivation maps and overlap across insula subdivisions.** (A) Coactivation of insula subdivisions, demonstrating how different insular regions are functionally interconnected during task performance. The color bar reflects the partial correlation value with a specific insular subregion "seed," while accounting for the influence of other subdivisions, in the dorsal AI, ventral AI and PI. (B) Overlap in co-activation maps across the three insular subdivisions showing brain areas of high and low overlap. Voxels shown in green-to-red colors were coactive with two of the three subregions (the color bar indicates the strength of overlap, specifically, the smallest value of the two strongest partial correlations). Voxels in blue were coactive across all three subdivisions. Dorsomedial prefrontal cortex, thalamus and basal ganglia show the largest overlap. Adapted from Uddin et al. (2014).

(Crottaz-Herbette and Menon, 2006). Notably, right AI activation is enhanced in response to deviant stimuli embedded within a stream of standard events regardless of stimulus modality (Sridharan et al., 2008; Citherlet et al., 2019).

## Signaling saliency

The AI plays a critical role in signaling saliency, an essential aspect of cognitive processing and decision-making. This function involves discerning the behavioral relevance of external stimuli, including both appetitive and aversive elements such as thirst, hunger, and pain. Studies have shown that the AI encodes the salience of these stimuli, integrating both their inherent value and any deviations from expected outcomes (Preuschoff et al., 2008; Fazeli and Buchel, 2018; Geuter et al., 2017; Wiech et al., 2010). The AI exhibits a U-shaped response pattern as a function of stimulus valence, where stimuli perceived as either positive or negative elicit stronger neural responses compared to neutral cues (Litt et al., 2011; Bartra et al., 2013).

Neurophysiological studies employing intracranial EEG have provided deeper insights into the neural mechanisms at play, particularly in the context of how the brain processes salient stimuli. These studies demonstrate that salient outcomes—those that are notable due to their positive, negative, or unexpected nature—trigger more pronounced beta oscillations in the AI. This neural response is not uniform; the amplitude of these beta bursts varies in accordance with the stimulus's salience. Specifically, neutral outcomes elicit lower beta burst amplitudes compared to those outcomes that carry high positive or negative emotional weight (Haufler et al., 2022).

Thus, both fMRI and intracranial EEG studies underscore the AI's crucial role in attentional orientation. By differentiating the intensity of neural responses based on the salience of stimuli, the AI effectively guides attention to more significant events, thereby facilitating adaptive cognitive processing.

## Inhibitory control

The AI, especially its right hemisphere division, is central to inhibitory control, evidenced by studies of the Go/NoGo, Stop-Signal, and Flanker tasks (Fig. 11). Comprehensive meta-analysis of studies specifically focused on inhibitory control have revealed that the AI has a role distinct from the adjoining inferior frontal cortex (Cai et al., 2014). Additionally, the right AI exhibits stronger functional connectivity with the ACC, whereas the inferior frontal cortex is more strongly connected with lateral prefrontal and posterior

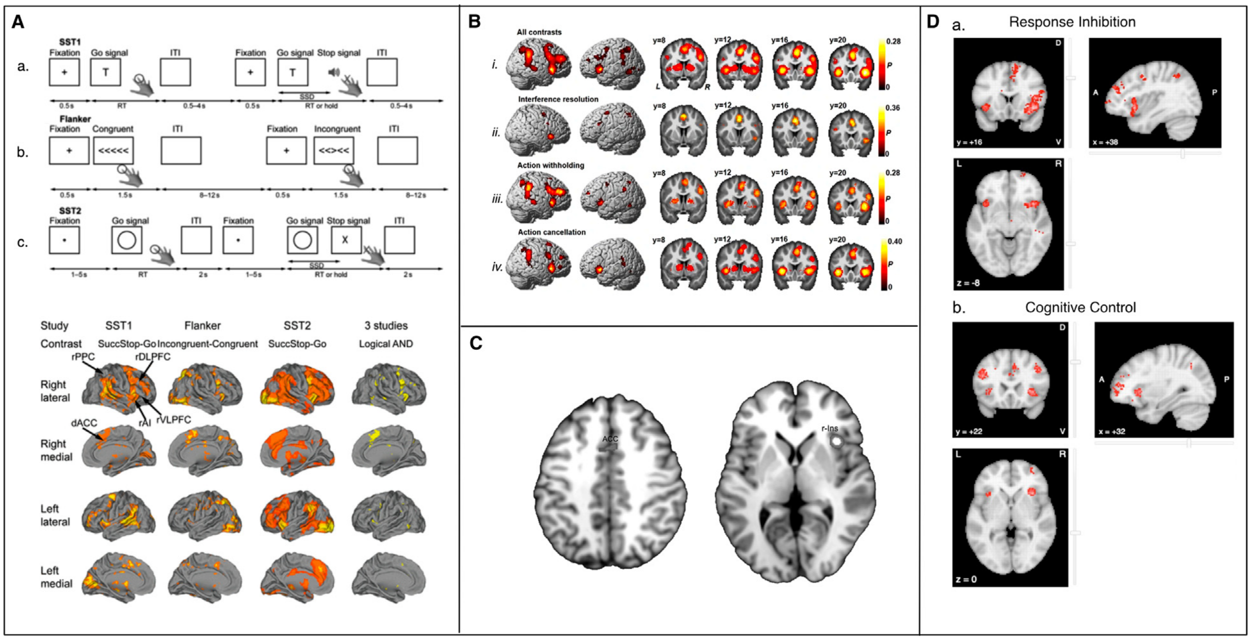


**Fig. 11 Insula involvement in cognitive control.** (A) Canonical stop signal task (SST) and Flanker task used to study response inhibition in cognitive control. In the SST participants make left/right button presses, with an instruction to stop responding on certain trials. In the Flanker task, participants respond to the direction of the central arrow among flanker arrows, testing interference resolution. The insula and dorsal anterior cingulate cortex (ACC)/dorsomedial prefrontal cortex show common patterns of activation during these cognitive control tasks, revealing shared neural substrates across different cognitive control tasks. (B) Results from meta-analysis of cognitive control tasks reveals consistent activation of the right AI, along with the inferior frontal gyrus, anterior and mid cingulate cortex, and posterior parietal cortex across various cognitive processes including interference resolution, action withholding, and action cancellation. (C) Coactivation of the insula and anterior cingulate cortex (ACC) in both proactive and reactive inhibitory processes. (D) Neurosynth-based meta-analysis, demonstrating activation of the anterior insula and ACC across a wide range of tasks associated with a. response inhibition and b. cognitive control. (A) Adapted from Cai et al. (2016). (B) Adapted from Zhang et al. (2017). (C) Adapted from Gavazzi et al. (2021).

parietal cortices. Cai et al. (2016) further demonstrated that the right AI is a key causal hub in a frontal-cingulate-parietal network central to cognitive control (Cai et al., 2016). Their findings, derived from multiple tasks, highlight significant causal influences from the AI to the dorsal ACC, stressing the AI's pivotal role in cognitive control dynamics (Fig. 12). Importantly, these influences are pronounced during trials demanding greater cognitive control, correlating with individual cognitive control abilities.

Notably, this function of the right AI in inhibitory control is intricately linked with its ability to detect salient cues, such as the infrequent behaviorally relevant stimuli in stop signal and no-go tasks. Thus, cognitive control ability, to a certain extent, can be understood as an extension of salient cue detection ability. The right AI emerges as a key node for identifying behaviorally relevant stimuli, signaling the need for cognitive control, and bridging the gap between sensory detection and higher-order cognitive processes. This interplay of cognitive control and salience detection underscores the AI's multifaceted role in orchestrating complex cognitive functions.

## Error processing

The AI is integral to error processing, managing complex signals like reward prediction errors, risk assessment, and cognitive control, which are essential for adaptive behavior and learning (Ullsperger et al., 2010; Preuschoff et al., 2008; Bossaerts, 2010). Research has demonstrated that the AI's involvement in conscious error perception is essential for strategic behavioral adjustments (Klein et al., 2013). The AI rapidly detects errors and conveys feedforward signals to the dorsomedial prefrontal cortex as part of the error-monitoring network (Bastin et al., 2016; Billeke et al., 2020). Additionally, the AI's role in integrating pain intensity with expectations and encoding pain-related prediction errors further underscores its role in error processing (Fazeli and Buchel, 2018). This heightened activity reflects the AI's integral role in the detection and processing of errors, as well as its involvement in coordinating the body's physiological responses to cognitively detected discrepancies (Harsay et al., 2018).

In tasks requiring inhibitory control, the AI is actively engaged in monitoring and processing task performance, especially in the context of unexpected challenges (Bastin et al., 2016; Ide et al., 2013). This is evident in situations involving stop-signal tasks, where the AI shows increased activation during unsuccessful attempts at response inhibition. The AI demonstrates enhanced activation and connectivity correlated with elevated autonomic reactivity when errors are consciously recognized (Harsay et al., 2018; Ullsperger et al., 2010).

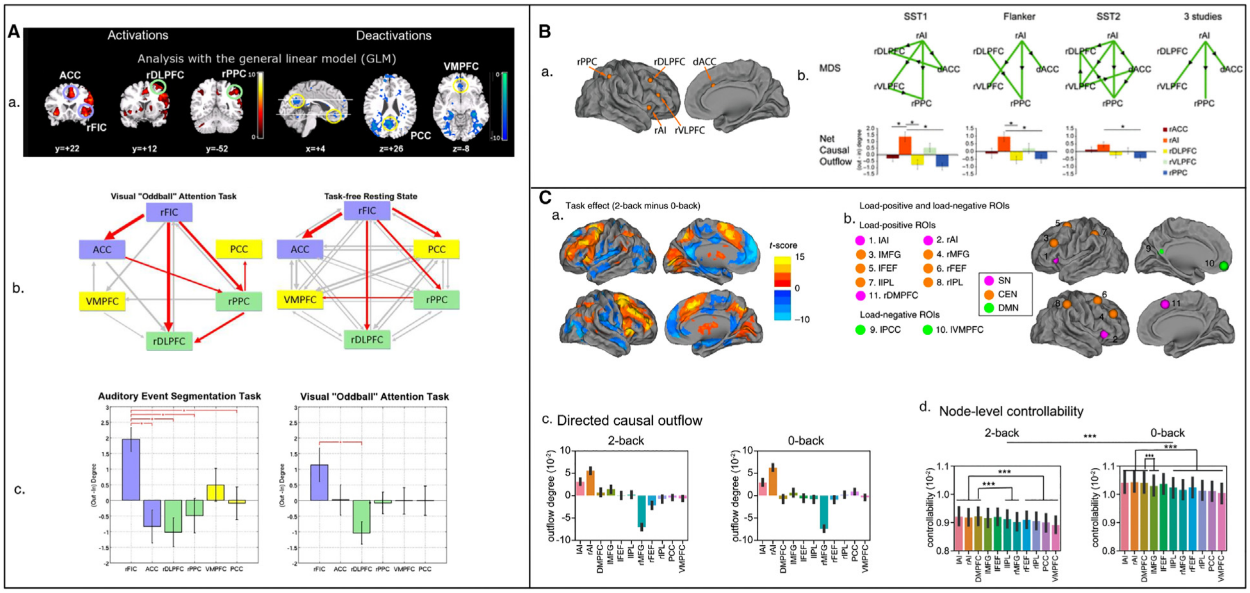


**Fig. 12 Anterior insula as a causal hub in brain networks.** (A) a. Insula and ACC activation, along with lateral fronto-parietal cortical regions, and deactivations in the default-mode network during auditory event transitions. b. Causal interactions among six key nodes of the salience, front-parietal (central-executive), and default-mode networks across tasks. The thickness of connecting arrows between regions corresponds to the strength of directed connections. Significant causal outflow from the right AI and adjoining inferior frontal cortex (FIC) is highlighted across different tasks and stimulus modalities. c. The right FIC shows a higher net causal outflow compared to other regions in these networks. (B) a. Anatomical locations of five regions of interest in the right hemisphere, based on the salience and front-parietal (central-executive) networks. b. Causal interactions in three cognitive control tasks. The right anterior insula (AI) exerts significant causal influence on the dorsal anterior cingulate cortex (dACC) and right posterior parietal cortex (PPC) across all three tasks. The right AI has the highest net causal outflow, compared to other nodes. (C) a. Activation of salience network, frontal-parietal, and default mode network nodes: AI, dorsomedial prefrontal cortex, middle frontal gyrus, frontal eye fields, intraparietal sulcus, posterior cingulate cortex, and ventromedial prefrontal cortex, during an n-back working memory task. b. The anterior insula shows the highest directed causal outflow between all network nodes. c. Functional network controllability in each brain node, with a particular focus on the anterior insula and dorsomedial prefrontal cortex, which exhibit higher controllability compared to FPN and DMN nodes during working memory. Results from $n = 737$ participants. (A) Adapted from Sridharan et al. (2008). (B) Adapted from Cai et al. (2016). (C) Adapted from Cai et al. (2021).

Additionally, intracranial EEG studies have reported a significant correlation between beta bursts in the AI and unsigned prediction errors (Haufler et al., 2022). This connection suggests that the AI is actively involved in processing prediction errors regardless of their positive or negative valence. Complementing this, insula responses often precede that of other brain regions in conveying reward prediction errors (Hoy et al., 2022). This temporal precedence indicates a potentially central role for the AI in the initial detection and processing of discrepancies between expected and received rewards, acting as an early signaler in the neural circuitry responsible for error detection and adaptive learning.

## Dynamic anticipation and adjustment of cognitive control

The AI's crucial role extends to dynamic anticipation and adjustment within executive control systems, influencing cognitive strategies and learning mechanisms (Ide et al., 2013; Cai et al., 2017). In particular, the right AI exhibits heightened activation in tasks requiring inhibitory control, particularly when anticipatory cues are low (Cai et al., 2011; Verbruggen and Logan, 2009). This points to its vital role in detecting unexpected events and orchestrating reactive inhibitory control. In scenarios demanding a balance between reactive and proactive responses, the AI exhibits a complex balance of bottom-up and top-down processes, acting as a switch for salient cues and influencing the cognitive control network (Cai et al., 2011, 2017; Verbruggen and Logan, 2009).

When anticipatory cues are low, the right AI serves as a switch for unexpected salient cues, triggering the cognitive control network to engage reactively (Cai et al., 2014). Conversely, when anticipatory cues for control are high, the lateral prefrontal cortex exerts a modulating influence on the right AI, promoting a more proactive control approach. This dynamic interplay underscores the AI's multifaceted role in executive control, adapting to varying cognitive demands through a balance of proactive and reactive mechanisms.

The role of the AI in dynamic anticipation and adjustment of control is further highlighted across various studies involving emotion and risk. AI responses are enhanced during anticipation of emotional (Denny et al., 2014) and rewarding outcomes (Knutson and Greer, 2008). Similarly, the AI signals risk prediction during decision-making under uncertainty (Bossaerts, 2010, 2018).

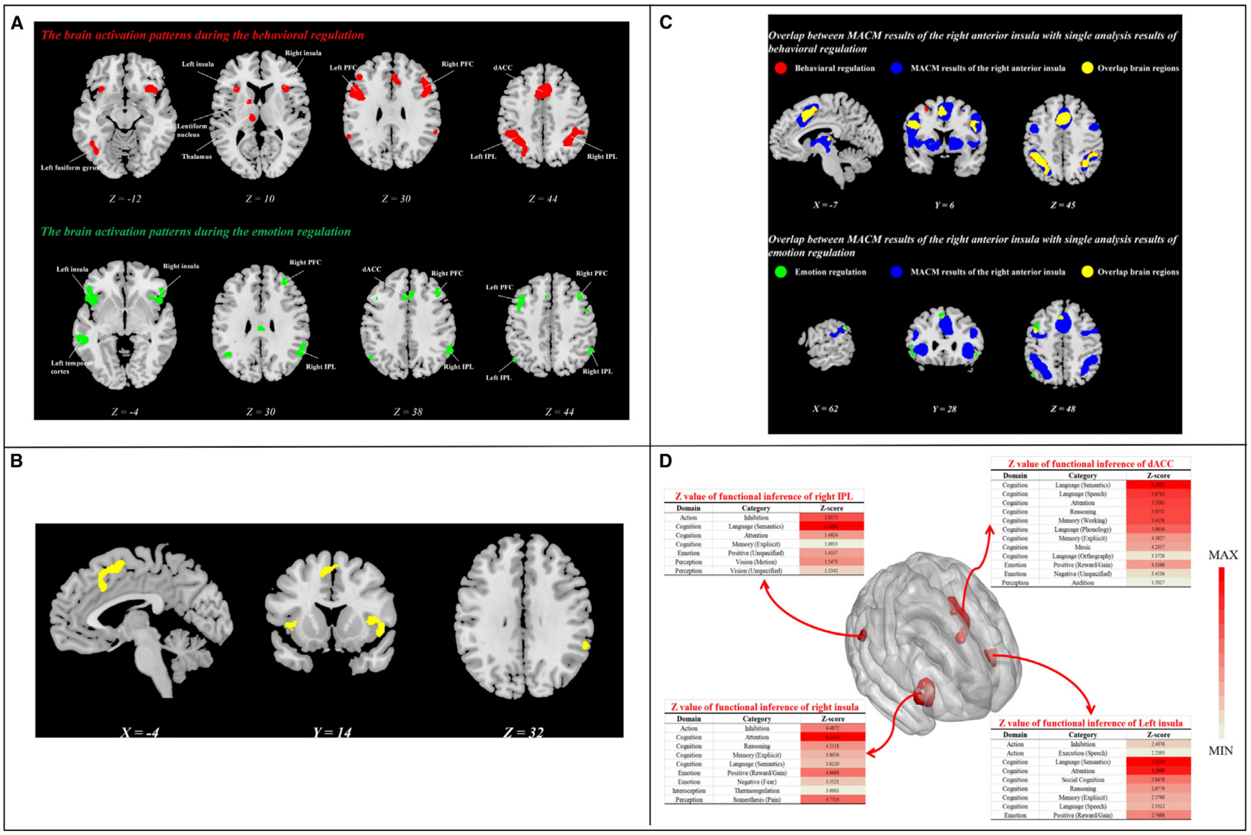
This aspect is underscored by its identification as a key element in the brain's "risk matrix" for risk assessment (Knutson and Huettel, 2015).

The AI also anticipates impending stimulus significance (Lovero et al., 2009) and mediates flexible cognitive control by adaptively predicting changing control demands (Jiang et al., 2015). Recent studies have shown that the AI encodes stimulus and contextual state uncertainty, contrasting with the dorsolateral prefrontal cortex's encoding of outcome uncertainty (Alexander et al., 2023). Together, these studies demonstrate that the AI plays a dynamic role in adaptive control mechanisms associated with anticipation of sensory cues, affective context, and cognitive demands.

## Broader role in behavioral and emotional regulation

Beyond its role in cognitive control tasks the AI's is also consistently involved in a wide range of tasks involving behavioral and emotional regulation (Zhang and Peng, 2023). This is substantiated by meta-analyses of brain imaging studies, which pinpoint the bilateral AI and dorsal ACC as pivotal regions consistently engaged in both emotional and behavioral regulation tasks (**Fig. 13**). This engagement underscores their critical contribution to diverse self-regulatory processes. Further, meta-analytic connectivity modeling reveals that the coactivation patterns between the bilateral AI and dorsal ACC are closely aligned with neural networks implicated in these regulatory domains, reinforcing their interconnected role in self-regulation.

In summary, these findings highlight the importance of the AI, especially its right subdivision, as a neural hub for processing and integrating emotional, sensory, and cognitive signals. Its ability to signal saliency, integrating affective value and expectancy, underlines its role in adaptive behavior and efficient decision-making. Additionally, its contribution to error processing is vital for adaptive behavior, cognitive control, and learning. The AI's involvement in anticipatory and adaptive control is essential for regulating complex human behaviors and cognitive processes.



Z value of functional inference of right IPL

| Domain | Category | Z-score |
|---|---|---|
| Action | Inhibition | 1.8175 |
| Cognition | Language (Semantics) | 2.1890 |
| Cognition | Attention | 1.4924 |
| Cognition | Memory (Expliicit) | 1.0933 |
| Emotion | Positive (Unspecified) | 1.4537 |
| Perception | Vision (Motion) | 1.5473 |
| Perception | Vision (Unspecified) | 1.2342 |

Z value of functional inference of dACC

| Domain | Category | Z-score |
|---|---|---|
| Cognition | Language (Semantics) | 6.3801 |
| Cognition | Language (Speech) | 5.6711 |
| Cognition | Attention | 5.5181 |
| Cognition | Reasoning | 5.4551 |
| Cognition | Memory (Working) | 5.4158 |
| Cognition | Language (Phonology) | 5.0656 |
| Cognition | Memory (Expliicit) | 4.3827 |
| Cognition | Music | 4.2357 |
| Cognition | Language (Orthography) | 3.3726 |
| Emotion | Positive (Reward/Gain) | 4.3386 |
| Emotion | Negative (Unspecified) | 3.4536 |
| Perception | Audition | 3.2027 |

Z value of functional inference of right insula

| Domain | Category | Z-score |
|---|---|---|
| Action | Inhibition | 4.4872 |
| Cognition | Attention | 6.1414 |
| Cognition | Reasoning | 4.2118 |
| Cognition | Memory (Expliicit) | 3.8056 |
| Cognition | Language (Semantics) | 3.6120 |
| Emotion | Positive (Reward/Gain) | 4.6688 |
| Emotion | Negative (Fear) | 3.5521 |
| Interoception | Thermoregulation | 3.0003 |
| Perception | Somesthesis (Pain) | 4.7514 |

Z value of functional inference of Left insula

| Domain | Category | Z-score |
|---|---|---|
| Action | Inhibition | 2.4076 |
| Action | Execution (Speech) | 2.2393 |
| Cognition | Language (Semantics) | 3.4204 |
| Cognition | Attention | 3.2999 |
| Cognition | Social Cognition | 2.8478 |
| Cognition | Reasoning | 2.6779 |
| Cognition | Memory (Expliicit) | 2.5790 |
| Cognition | Language (Speech) | 2.5312 |
| Emotion | Positive (Reward/Gain) | 2.7688 |

**Fig. 13 Meta-analysis-based task activation and coactivation in behavioral and emotion regulation.** (A) a. Meta-analysis of behavioral regulation across 155 experiments examining behavioral regulation (1884 foci and 3852 subjects). b. Meta-analysis of emotion regulation across 59 experiments (560 foci and 1657 subjects). (B) Conjunction map showing overlap between behavioral and emotion regulation in insula and ACC/ dorsomedial prefrontal cortex. (C) Results from meta-analytic connectivity mapping for the right AI showing overlap with brain areas involved in behavioral and emotion regulation. (D) Reverse-inference reveals that topics associated with cognition, emotion, interoception and somatic sensation are highly represented in both the right and left AI. Adapted from Zhang and Peng (2023).

## Interoception

### Central autonomic system regulation

The insula is central to the central autonomic network which regulates the body's autonomic processes such as heart rate, digestion, respiratory rate, and blood pressure (Sklerov et al., 2019). The insula is also implicated in both sympathetic and parasympathetic responses, playing a pivotal role in homeostatic regulation (**Fig. 14**). Findings such as the right mid-insula's heightened responsiveness during peaks of sympathetic arousal and cardiorespiratory sensation underscore its dynamic role in processing changes in the body's internal state (Hassanpour et al., 2018; Ferraro et al., 2022).

Metanalyses have pointed to the bilateral dorsal AI's involvement in the central autonomic network (Oppenheimer et al., 1996; Ferraro et al., 2022). The dorsal AI plays a role in both sympathetic and parasympathetic responses, which is crucial for homeostatic regulation (Seeley, 2019). Recent research further elucidates the insula's role in autonomic regulation (Sturm et al., 2018): lower baseline respiratory sinus arrhythmia correlated with a smaller volume in the left ventral AI. Additionally, this was linked with weaker connectivity between bilateral ventral AI and the ACC. Conversely, a lower baseline skin conductance level was associated with smaller volumes in dorsal mid-insula and stronger connectivity between bilateral dorsal AI and periaqueductal gray. Thus, the insula and its network connections, particularly within the salience network, are crucial in maintaining homeostasis and regulating the autonomic nervous system's activity (**Fig. 14**).

### Visceral processing

The insula's importance in processing visceral sensations was highlighted by Penfield's neurosurgical experiments (Penfield and Faulk Jr, 1955). Recent investigations have revealed a viscerotopic organization within the insula, arranged in a posterior-to-anterior gradient. Specifically, the PI, with inputs from the ventromedial nucleus of the thalamus, aggregates signals from various body

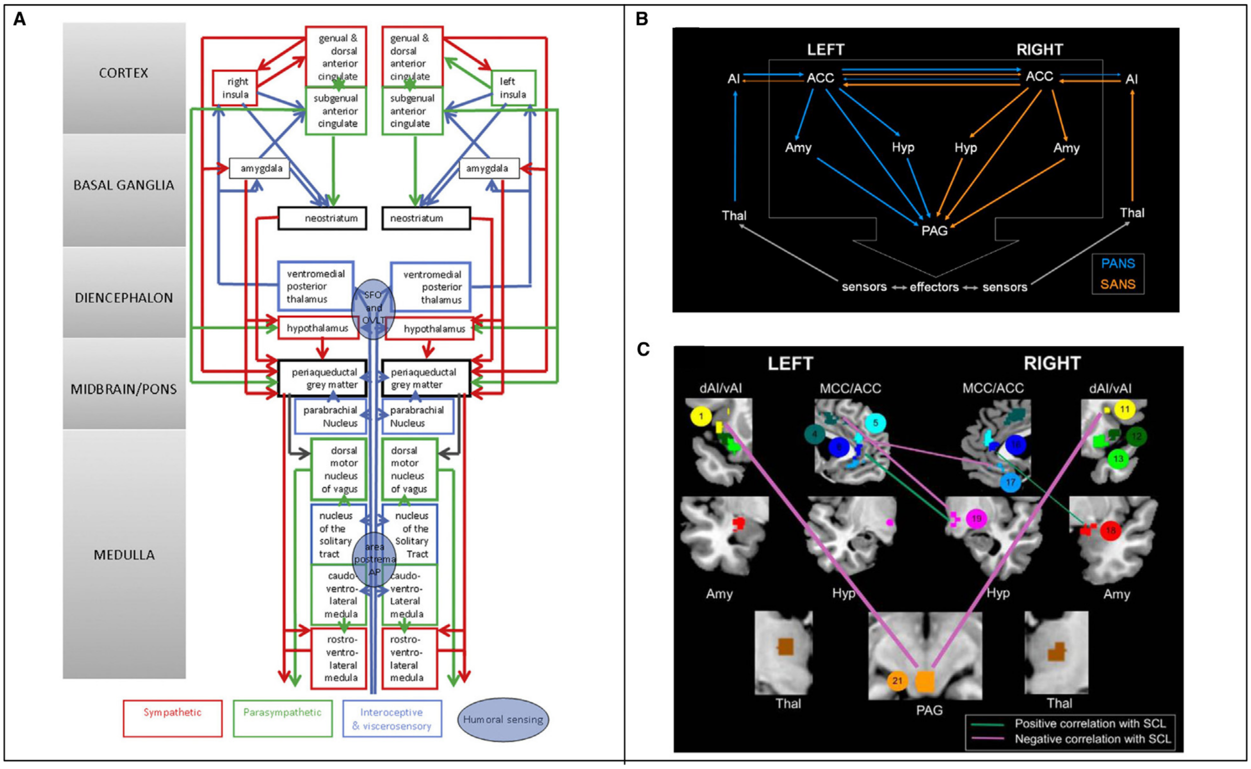


**Fig. 14** **Neural pathways in autonomic bodily state control converge on the insula.** (A) Diagram of central afferent and efferent neural pathways: This diagram links key brain regions in the context of their roles in visceral afferent sympathetic and parasympathetic drives. While encompassing the entire neuroaxis, the model suggests a closer connection of autonomic control with cognitive control (insula, anterior cingulate), motivation (insula, amygdala, subgenual cingulate), and psychomotor processes (basal ganglia). (B) Hemispheric differences in insula afferent pathways for parasympathetic (PANS) and sympathetic (SANS) nervous system functioning, anchored by the salience network with hubs in the anterior insula (AI) and anterior cingulate cortex (ACC). This network is tightly connected to the amygdala, hypothalamus (Hpy), and periaqueductal gray (PAG). (C) Lower baseline PANS activity is associated with lower vFI-ACC connectivity and higher connectivity primarily in ACC-hypothalamus/amygdala. c. Lower SANS is associated with lower connectivity in right amygdala/hypothalamus edges and higher connectivity primarily in bilateral dAI-PAG edges. (A) Adapted from Critchley and Harrison (2013). (B,C) Adapted from Sturm et al. (2018).

systems, forming a neural representation of the body's internal state. fMRI studies have also revealed widespread viscera—brain coupling with a key role for the insula (King et al., 1999; Azzalini et al., 2019; Chen et al., 2021; Kleckner et al., 2017).

The insula is also intricately involved in hunger signaling, playing a key role in the regulation of appetite and satiety and for interpreting signals from the gastrointestinal system and integrating them with other sensory information (Tataranni et al., 1999). In conjunction with the hypothalamus, the insula forms a network responsible for maintaining energy balance. This circuit regulates eating behaviors and signals the initiation of feeding when energy is low and prompting cessation or diversion of attention from food upon reaching satiety (Wright et al., 2016; Livneh et al., 2017). These functions underscore the insula's integral role not just in the sensory aspect of visceral processing but also in the complex regulation of hunger and satiety, aligning physiological needs with cognitive control and behavior.

### Pain perception

The insula is a critical player in pain perception, particularly in assessing the salience of painful stimuli. It goes beyond merely processing nociceptive signals; the insula evaluates their subjective significance, which is crucial for the appropriate allocation of cognitive and emotional resources in response to pain (Ploner et al., 2017). Specifically, the AI is sensitive to the acute aspects of pain, such as its onset and intensity, highlighting its role in responding to the immediate, salient features of pain experiences. In contrast, the PI is more involved in processing sustained or chronic pain, indicative of its role in ongoing pain perception (Wiech et al., 2010; Wager et al., 2013).

The insula's role in pain perception is multifaceted, extending beyond sensory processing to include the integration of emotional and cognitive dimensions of pain. This encompasses modulation by attention, expectation, and fear, emphasizing the insula's involvement in the affective-motivational dimension of pain and its impact on emotional responses to pain (Ploghaus et al., 1999; Sawamoto et al., 2000; Geuter et al., 2017; Horing and Büchel, 2022). The AI integrates information about the salience of pain into perceptual decisions, while also processing pain-related expectation and prediction error signals that are not directly related to the pain intensity (Fazeli and Buchel, 2018; Geuter et al., 2017; Wiech et al., 2010).

Extensive connectivity of the insula with other pain-relevant regions like the thalamus and somatosensory cortex allows it to effectively modulate pain perception. This regulatory capacity, whether to amplify or attenuate pain sensations, positions the insula as a potential target in pain management strategies (Mouraux et al., 2011). Furthermore, variations in the structure and function of the insula among individuals have been associated with differences in pain sensitivity and tolerance, confirming its pivotal role in the pain matrix (Woo et al., 2017).

### Affective touch

Touch plays a fundamental role in human perception, serving as a vital interface between our internal bodily states and the external environment. The insula is involved in the differential processing of touch, demonstrating unique responses depending on the source of the tactile stimulus. The insula exhibits greater activation during touch by others, suggesting its role in processing socially relevant tactile information, and shows deactivation during self-generated touch, indicating a distinct neural processing pathway for self-touch (Boehme et al., 2019). This differential response is crucial for distinguishing self from others and for fostering social bonding.

Further emphasizing the insula's role in tactile perception, studies on right hemisphere stroke patients have shown that lesions in the right AI and PI diminish the perceived pleasantness of C-tactile touch, a specialized system for processing emotionally relevant touch (Kirsch et al., 2020). This finding suggests that the insula contributes significantly to the affective dimension of tactile experiences.

Neuroimaging studies have further delineated functional segregation within the somatosensory system, with primary and secondary somatosensory cortices primarily engaged in discriminatory touch processing, mediated by A-beta sensory fibers. In contrast, the PI is implicated in the processing of tactile pleasantness, mediated by C-tactile fibers, highlighting its involvement in the emotional aspect of touch (Björnsdotter et al., 2009; Morrison, 2016).

## Integrative hub for cognitive-emotional and interoceptive processes

### Convergence zone and integrative hub

Building upon the insights gleaned from the preceding sections, it becomes evident that the insula is not merely a passive recipient of sensory data but rather a dynamic integrator of complex information. Its emergent role as an integrative hub in the human brain is highlighted by its capacity to bridge internal interoceptive signals with external stimuli (Chen et al., 2021; Craig, 2015). This function is pivotal for various cognitive processes, extending beyond mere cognitive control and adaptation to external stimuli to include interoception—the sensing of the body's internal states. In this capacity, the insula is instrumental in processing, interpreting, and integrating internal bodily signals. This integration does not take place in isolation, but rather as a process involving the contextualization of bodily sensations within the context of cognitive and affective functions and mental states. This intricate interplay allows for a more dynamic response to both internal body states and external environmental demands. Consistent with this view, anomalies in insular function have been associated with disturbances in interoceptive processes, as well as a broader dysregulation of behavioral, cognitive, and affective processes. These disturbances can manifest across both conscious and subconscious levels of processing, highlighting the insula's comprehensive influence on a wide range of human functions (Gasquoine, 2014; Berntson and Khalsa, 2021).

Interoceptive signals originating from the humoral, lymphatic, and peripheral nervous systems undergo initial processing in various subcortical structures. Key among these are the medial nucleus tractus solitarius, parabrachial nucleus, and ventromedial nucleus of the thalamus (**Fig. 5**). These signals are then projected to the insula for integration with multiplexed brain circuits. Beyond its role in integrating visceral afference, the insula is distinguished by its extensive connections with key cortical and subcortical regions involved in cognition, emotion, and motivation. They include the ACC, dorsomedial and dorsolateral prefrontal cortex, amygdala, and ventral striatum (Nieuwenhuys, 2012; Oppenheimer and Cechetto, 2011; Tsakiris and Critchley, 2016). This extensive functional circuitry underpins the insula's integral role in the brain's broader functional architecture.

Meta-analytic studies of interoception and behavioral control further suggest that the integration of internal and external signals by the insula occurs within shared cognitive and emotional processing networks (Tsakiris and Preester, 2022; Tan et al., 2022) (**Figs. 15** and **16**). This places the insula at a crucial nexus, not only for processing visceral sensations but also for mediating a wide array of cognitive-emotional processes. The insula's role in this regard is multifaceted: it extends beyond the mere perception of visceroceptive information to actively influence the emotional and cognitive outcomes that emerge from, and in turn, regulate internal bodily states (Berntson and Khalsa, 2021; Critchley and Harrison, 2013).

In summary, the insula's circuitry and connectivity facilitate a dynamic interplay between the internal physiological state and external cognitive-emotional responses. This underscores its pivotal role in maintaining homeostasis and adapting behavior to internal and external stimuli.

## Interoceptive awareness

The insula has also been implicated in interoceptive awareness, the conscious perception of internal bodily states which plays a vital role in shaping our sense of self (Craig, 2015; Sklerov et al., 2019). This awareness, especially evident in heartbeat detection, tracking

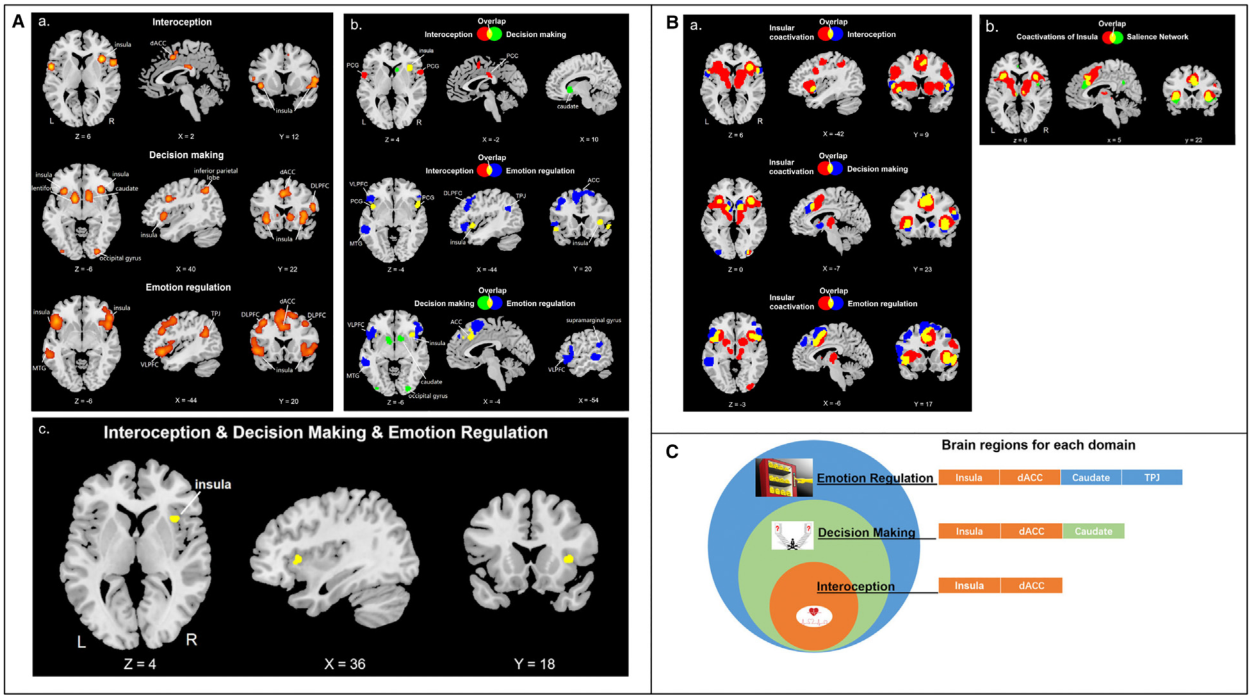


**Fig. 15 Integration of interoceptive processing in decision-making and emotional regulation pathways.** (A) a. Meta-analysis results for three distinct domains: interoception, decision-making, and emotion regulation. Key areas include the AI, dorsal ACC (dACC), dorsolateral prefrontal cortex (DLPFC), middle temporal gyrus (MTG), ventral lateral prefrontal gyrus (VLPFC), and the temporal parietal junction (TPJ). b. Pairwise conjunction analysis highlighting neural overlap and distinctions between interoception and emotion regulation, interoception and decision making, and emotion regulation and decision making. c. Overlap in the of interoception, decision making, and emotion regulation pathways. (B) a. Results from meta-analytic connectivity mapping (MACM) for the right anterior insula, demonstrating the overlap between MACM results and the salience network. (B) Overlap between MACM results and task-metanalysis in the three domains. Right AI's task connectivity patterns intersect with all three domains. (C) Schematic illustration of overlap in intero-exteroceptive integration in decision making and emotion regulation, highlighting the role of the AI and dACC. Thus, interoceptive processing is intricately linked with brain networks involved in decision making and emotion regulation. Adapted from Qin et al. (2020).

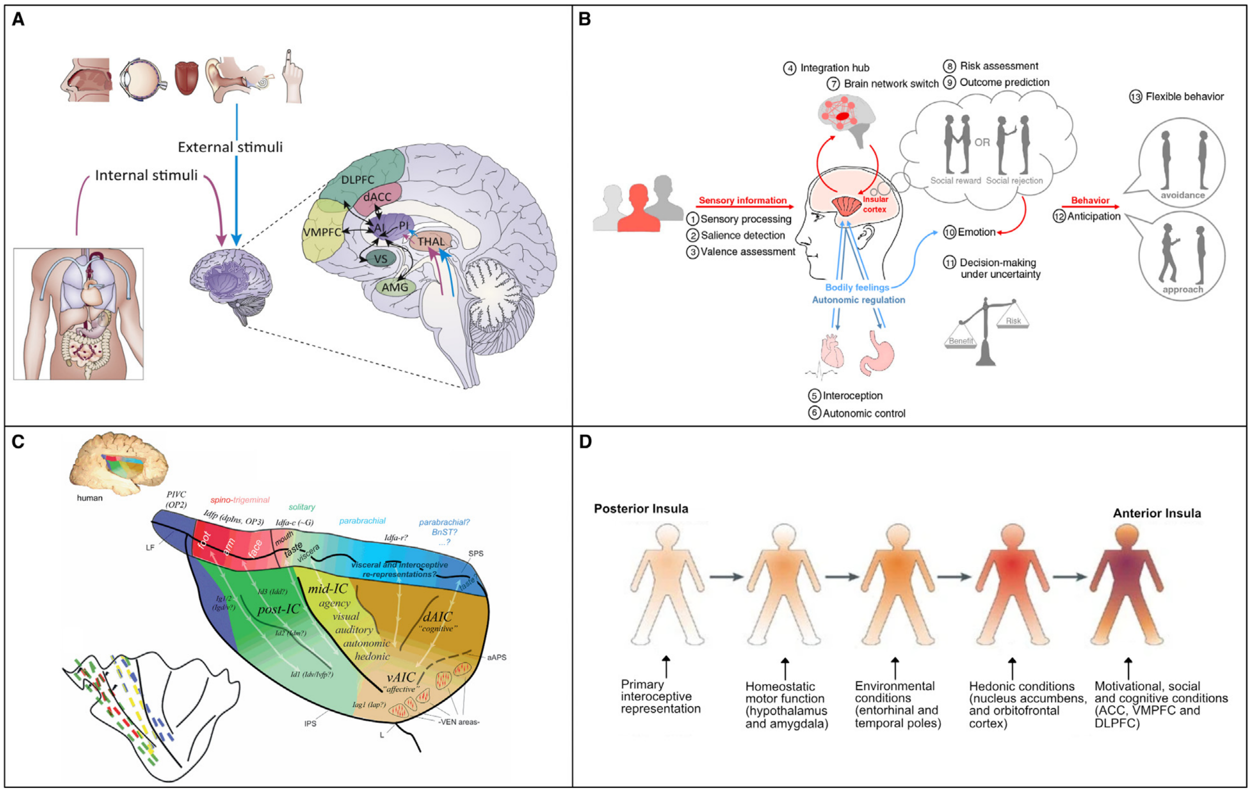


**Fig. 16 Integration of exteroceptive and interoceptive signals in the insula.** (A) Illustration of insula's crucial role in integrating external and internal signals to maintain emotional balance and guide behavioral responses. Key regions involved include the anterior insula (AI), amygdala (AMG), dorsal anterior cingulate cortex (dACC), dorsolateral prefrontal cortex (DLPFC), posterior insula (PI), thalamus (THAL), ventromedial prefrontal cortex (VMPFC), and ventral striatum (VS). (B) A schematic integrated model of diverse insular functions. Model captures the insula's role in receiving multisensory information, processing stimulus salience and valence, integrating emotional and cognitive inputs, perceiving bodily feelings, and contributing to physical reactions in social encounters. The model further explores the insula's involvement in risk assessment, outcome prediction, and decision-making in social interactions. (C) Insula subdivisions for segregation and integration of external and internal signals. (D) Model of posterior-to-middle-to-anterior interoceptive integration in the human insula. The posterior insula receives interoceptive information about bodily states via sensory pathways and thalamic relays. This information is then conveyed to the anterior insula, where it merges with emotional, cognitive, and motivational signals from various brain regions. The anterior insula, positioned at the nexus of these pathways, influences subjective feelings, as well as cognitive and motivational processes. (A) Adapted from Namkung et al. (2017). (B) Adapted from Gogolla (2017). (C) Adapted from Evrard (2022). (D) Adapted from Craig (2015).

and regulation, is closely linked to emotional processing and self-awareness, highlighting the insula's role in these domains (Critchley et al., 2004; Tsakiris and Critchley, 2016; Chen et al., 2021). Notably, the insula is a key region within the human central autonomic network. The insula's connections with the central autonomic network, which includes the midcingulate cortex, thalamus, and various brainstem nuclei, facilitate its role in regulating autonomic responses (Sklerov et al., 2019). These connections enable the insula to integrate conscious awareness with regulation of bodily functions (Ferraro et al., 2022). The insula also serves as a neural crossroad for harmonizing signals across homeostatic functions such as temperature, pain, touch, and autonomic responses.

It should be noted that not all interoceptive signals necessitate conscious and higher cortical processing. However, the insula and in particular AI, activation appears central when individuals consciously attend to their interoceptive states and engage in higher-order processing at either the perceptual, cognitive, and affective levels (Sklerov et al., 2019; Berntson and Khalsa, 2021).

## Interoception and emotion

The insula plays a pivotal role in the processing of both affective and bodily signals. This dual role significantly influences emotional responses, highlighting the intrinsic connection between interoception—the awareness of internal bodily states—and emotion (Gu et al., 2013a; Wang et al., 2019). Emotions often manifest alongside physical sensations, such as a racing heartbeat with anxiety. Individuals with heightened interoceptive awareness tend to experience more intense emotional reactions, as they are more attuned to the physical manifestations of their emotions (Critchley and Garfinkel, 2017; Terasawa et al., 2013, 2014).

Furthermore, effective emotion regulation is often contingent upon an accurate perception of one's bodily states, as argued by Critchley and Harrison (2013). This concept is encapsulated in the idea of embodied emotion, which posits that the integration of interoceptive signals with emotional states is fundamental to the subjective experience of emotions (Critchley and Harrison, 2013). The insula, by virtue of efferent visceral signals and bodily sensations, forms a crucial nexus between our physical states and emotional regulation. This interplay is particularly salient in the context of mood disorders, where disruptions in insular functioning has been linked to impaired processing of bodily and emotional signals (Critchley and Garfinkel, 2017; Khalsa et al., 2018). The insula's neural connections with limbic structures are essential for merging bodily sensations with emotional states, enabling it to contribute significantly to the subjective experience of emotions (Critchley et al., 2004; Critchley and Harrison, 2013). Furthermore, research has also highlighted the fundamental link between internal bodily awareness and emotional experiences, further emphasizing the insula's crucial role in shaping mind-body connections (Petzschner et al., 2021).

## Integrative network model of insula function: Linking saliency, cognitive control and interoception

Systems neuroscience approaches have greatly enhanced our understanding of the brain's large-scale organization (Menon and D'Esposito, 2022; Bressler and Menon, 2010), offering deeper insights into the integrative functions of the insula (Menon and Uddin, 2010). These developments underscore that the insula does not function in isolation but is a critical component within a broader network context. Network models have become increasingly pivotal in constructing theories about the insula's multifaceted roles in processing and integrating various types of information.

Central to this understanding is the salience network, a prominent large-scale brain network in which the insula, especially the AI, plays a key role. Alongside the AI, the dorsal ACC forms a crucial node of this network. This network also includes significant subcortical structures such as the amygdala, substantia nigra, ventral tegmental area, dorsomedial thalamus, hypothalamus, and periaqueductal gray. These interconnected nodes highlight the AI's critical association with the dorsal ACC in cognitive and affective control processes. This relationship is emphasized by the consistent coactivation of these nodes across various cognitive and emotional tasks, illustrating their joint contribution to the brain's adaptive responses and regulatory mechanisms.

The insula's role extends beyond individual processing centers to involve dynamic interactions with other brain networks. An integrated network perspective provides a comprehensive framework for understanding the insula's complex contributions to brain function, particularly with respect to its role in mediating saliency detection, cognitive control, and interoceptive processing. Such an understanding is pivotal for deciphering how the brain navigates and responds to the multitude of stimuli and challenges presented by both internal states and the external environment.

The Triple Network Model of cognitive control offers a theoretical and empirical framework for elucidating the insula's role within the broader neural landscape. This model posits three critical brain networks—the salience network, the fronto-parietal central executive network (CEN), and the default mode network (DMN)—as key components interacting to shape human cognition and emotion (Menon, 2011). The AI, as an integral part of the salience network, plays a pivotal role in this interactive network, influencing both cognitive and emotional processes through its ability to detect salient events, both internally within the body and externally in the environment. This network model underscores the AI's function in facilitating the dynamic allocation of attention and working memory resources, crucial for adapting to sensory inputs and shifting cognitive and physiological states (Menon and Uddin, 2010). The proposed integrative model of the insula function emphasizes its pivotal role in linking saliency detection, cognitive control, and interoceptive awareness. Key aspects of the model include (Fig. 17):

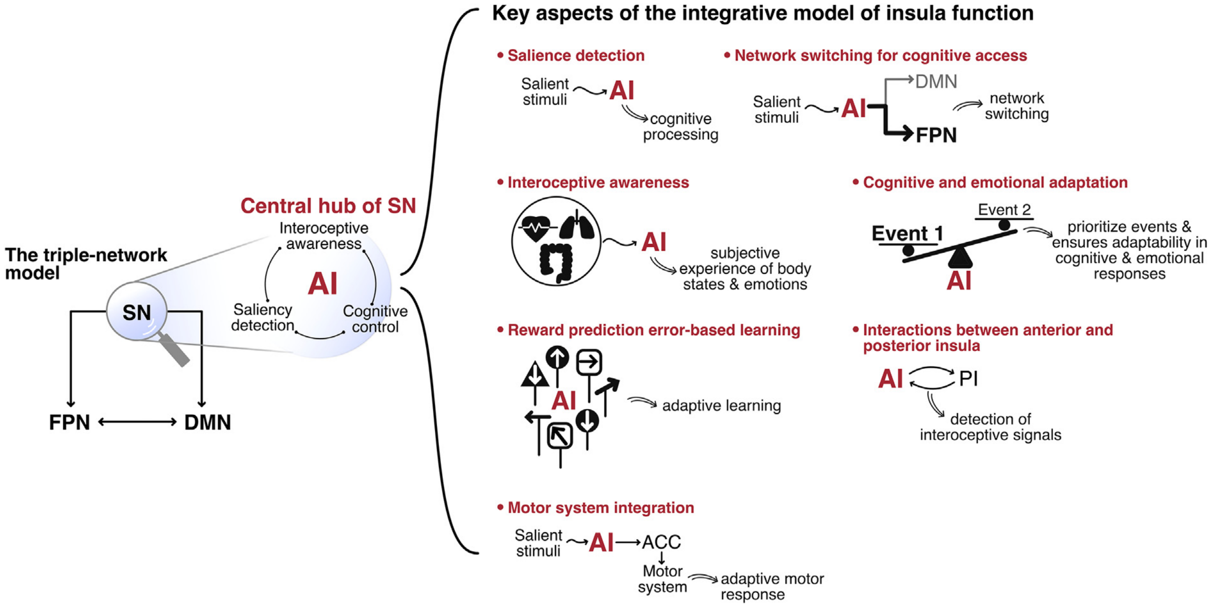


**Fig. 17 Triple network model.** Schematic representation of the triple network model of cognitive control, showing the interactions between the default mode network, central executive network, and salience network, with a focus on the role of the anterior insula, and integration of external and internal signals.

1. **Salience detection**: The AI, as a core node in the salience network and is pivotal in detecting and responding to salient stimuli. It is uniquely positioned to detect both internal (interoceptive) and external stimuli, and gate signals which should receive cognitive processing priority.
2. **Network switching for cognitive access**: The AI facilitates shifts between large-scale networks to allocate attentional and working memory resources during salient event processing. This ability allows the AI to play a crucial role in directing attentional resources and facilitating the switch between different cognitive states and networks. By detecting salient events, the AI can signal the need to disengage from the default mode network processes (e.g., daydreaming or mind-wandering) and engage the frontoparietal/central executive network for active, task-related processes. This dynamic network switching is fundamental for effective cognitive control and adaptive behavioral responses.
3. **Interoceptive awareness**: Insula involvement in processing internal bodily states—such as heart rate, respiratory patterns, and visceral sensations—gives it a significant role in interoceptive experiences. By integrating interoceptive awareness with cognitive processing, the AI contributes to the subjective experience of body states and emotions, influencing cognition and how emotions are perceived, processed, and regulated.
4. **Cognitive and emotional adaptation**: The AI's ability to detect and prioritize salient and unexpected events, whether it is an external stimulus requiring immediate action or an internal physiological change, ensures adaptability and flexibility in cognitive and emotional responses. This adaptability is crucial in environments where rapid changes or uncertain situations demand quick recalibration of perceptions and responses.
5. **Reward prediction error-based learning:** The insula's, and in particular the AI's, sensitivity to reward prediction errors forms a crucial component of its functionality, particularly in the context of learning and adaptation. Reward prediction error, a concept central to reinforcement learning, involves the difference between expected and actual outcomes. The responsiveness of the AI, and its associated ACC circuity, to these prediction errors enables it to contribute significantly to adaptive learning processes.
6. **Interactions between anterior and posterior insula**: This aspect emphasizes the interactions between the anterior and posterior insula in integrating physiological responses with cognitive-affective processes. This interaction significantly influences detection of interoceptive signals, and how the body's reactions to environmental cues and internal states are monitored and attended to.
7. **Motor system integration**: The AI's functional coupling with the ACC provides a dedicated circuit for mapping salient stimuli with adaptive motor responses. This connection illustrates the AI and salience network's integral role in translating cognitive and affective stimuli into appropriate motor actions.

A pivotal aspect of the AI's dynamic function is its role as a central signaling hub, crucial for coordinating cognitive control processes (Cai et al., 2021; Menon and D'Esposito, 2022). This function is particularly prominent in the right AI, which exerts substantial influence on multiple regions within the cognitive control network. The intensity of this influence varies with cognitive load, emphasizing the AI's central role in modulating signals within these circuits (Cai et al., 2014, 2016; Ham et al., 2013; Chen et al., 2015; Taghia et al., 2018). Research across various cognitive and affective tasks has shown that the AI acts as a causal hub, actively engaging the lateral frontoparietal cortex—a key area involved in attention, response inhibition, and working memory—while concurrently disengaging the default mode network during task-focused activities (Menon, 2023). Furthermore, the AI stands out as a control hub with high functional network controllability, suggesting a significant potential to steer global brain dynamics (Cai et al., 2021) (**Fig. 12**). Such capabilities position the AI as a key orchestrator of a broad range of cognitive processes, underscoring its integral role within the broader landscape of brain network functions.

In summary, this model encapsulates the insula's comprehensive and integrative role within the brain's network architecture, highlighting its importance in modulating a wide range of cognitive, emotional, and physiological processes. Key to this model is the AI's function as a central signaling hub, enabling it to detect salient events and facilitate network switching. This pivotal function allows the AI to bridge physiological sensations with higher cognitive functions, involving a network that includes the anterior cingulate cortex and subcortical regions integral for affect, reward, and motivation. Its capacity to link internal and external stimuli is essential for adapting to changing sensory inputs and modulating cognitive and physiological states. The AI's integrative role in linking saliency, interoception, and cognitive control is captured by network models, highlighting its influence across a spectrum of cognitive processes. This model underscores the insula's significance in both attention mechanisms and in orchestrating complex cognitive-affective interactions.

## Conclusion

The insular cortex, nestled within the cerebral folds, is a vital and multifaceted brain region, intricately involved in a wide array of human cognitive, emotional, and physiological processes. This article has highlighted its unique cytoarchitectonic features and its integral role as a hub within the salience network, emphasizing its crucial function in detecting and responding to both internal and external salient stimuli. The insula's tripartite division into cognitive, affective-chemosensory, and sensorimotor domains underscores its versatility and capacity for integrating diverse neural processes. The AI, in particular, emerges as a pivotal area in cognitive control and attentional modulation, causally involved in dynamic network switching and facilitating effective adaptive cognitive and emotional responses.

This comprehensive overview of the insula's functions, from its involvement in interoceptive awareness to its critical role in emotional regulation and cognitive flexibility, underscores its significance in maintaining a balance between internal physiological states and external environmental demands. By bridging the gap between somatic sensations and higher-order cognitive functions, the insula plays a fundamental role in shaping our perception, decision-making, and emotional experiences. Ongoing advances in neuroscience research continue to unravel the complexities of the insular cortex, promising further insights into its multifunctional roles and its pivotal place in the brain's intricate architecture. Future investigations employing causal manipulations and computational models are essential to elucidate the mechanisms underlying the integration of interoceptive and exteroceptive processes. Such studies will be pivotal in determining how the nervous system perceives, interprets, processes, and regulates both internal states and external environments (Petzschner et al., 2021; Chen et al., 2021). This deeper understanding holds immense potential not only for advancing our knowledge of brain function but also for informing clinical approaches in addressing a range of neurological and psychiatric disorders.

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