Anterior insula as a gatekeeper of executive control

Istvan Molnar-Szakacs, Lucina Q. Uddin

Executive control is a complex high-level cognitive function that relies on distributed brain circuitry. We propose that the anterior insular cortex plays an under-appreciated role in executive processes, acting as a gatekeeper to other brain regions and networks by virtue of primacy of action and effective connectivity. The flexible functional profile of the anterior insular subdivision renders it a key hub within the broader midcingulo-insular 'salience network', allowing it to orchestrate and drive activity of other major functional brain networks including the medial frontoparietal 'default mode network' and lateral frontoparietal 'central executive network'. The microanatomy and large-scale connectivity of the insular cortex positions it to play a critical role in triaging and integrating internal and external multisensory stimuli in the service of initiating higher-order control functions. Multiple lines of evidence scaffold the novel hypothesis that, as a key hub for integration and a lever of network switching, the anterior insula serves as a critical gatekeeper to executive control.

1. The insula: a multifaceted brain structure

Executive functions are the mental processes that enable us to plan, focus attention, remember instructions, and juggle multiple tasks successfully. The terms executive control or cognitive control are sometimes used interchangeably in the literature to refer to aspects of executive function (Diamond, 2013). Most influential cognitive neuroscience models of executive function or executive/cognitive control implicate the prefrontal cortex as the primary brain region subserving these high-level processes (Mesulam et al., 2002). Prefrontal cortices are thought to provide the neural substrate for executive functions, which permit flexible, adaptive, goal-directed behaviors (Banich, 2009). The view that the prefrontal cortex plays a critical role in executive control is widely accepted (Miller and Cohen, 2001), and has been further extended to implicate specific brain structures such as lateral prefrontal and dorsal anterior cingulate cortices (Niendam et al., 2012). In a recent review of prefrontal systems involved in executive control, Menon & D’Esposito discuss the role of six prefrontal cortical networks - the cingulo-opercular network, central executive network (CEN), salience network (SN), default mode network (DMN), dorsal attention network (DAN) and ventral attention network (VAN). In their assessment, they assert that executive control is not implemented by one individual network, but rather by dynamic interactions among these networks (Menon and D’Esposito, 2021). Our view is in line with this proposal, and further delineates the mechanisms by which these interactions unfold.

We propose that the anterior insula (AI) plays an under-appreciated role in executive processes. We outline supporting evidence for the hypothesis that the AI, by virtue of primacy of action and effective connectivity, acts as a gatekeeper to frontal and other brain regions that provide the neural substrate for executive functions. The insular cortex is composed of subdivisions that have complex patterns of unique and overlapping functional and structural connections with other cortical and subcortical regions. The flexible functional profile of the AI subdivision renders it a key hub directing activity of major functional brain networks including the midcingulo-insular SN, the medial frontoparietal DMN, and the lateral frontoparietal CEN (Sridharan et al., 2008; Uddin, 2015) (Fig. 1). These lines of evidence converge on a pivotal role for the AI in executive functioning, as a gateway to the frontal cortices, serving as a gatekeeper to executive control.

1.1. Historical notes on the insula

The insula - an ‘island’ of cortex not visible from the surface view of the brain - has a scientific history going back at least to the Middle Ages, when Vesalius (Saunders and O’Malley, 1982) made simplistic sketches of the area, presumably based on his dissections, in ‘de Humani Corporis Fabrica Libri Septem’ (1543). However, the first unmistakable...
neuroimaging investigations have reported that compared with the Sylvian fissure and the corpus striatum (Vicq-d’Azyr, 1786).

It was not until 1809 that Johann Christian Reil, a German psychiatrist and polymath, wrote an important exposition of ‘die Insel’ (German: island) (Binder et al., 2007). In recognition of his work, Henry Gray named this brain region ‘the island of Reil’ in the first edition of Gray’s Anatomy in 1858 (Fusar-Poli et al., 2009). Interestingly, Reil thought that the insula was the seat of mental processes (Clarke and O’Malley, 1996). Although that idea has proven to be overly simplistic, subsequent research has provided evidence that it is indeed important for a number of fundamental aspects of brain function, including its more recently appreciated role in executive functions.

1.2. Unique attributes of the anterior insula for scaffolding executive control

We posit that the seminal role played by the AI in gating executive control is made possible by a set of unique attributes that include its microstructural organization, structural and effective connectivity, and temporal activation profile, along with its unique position at the crossroads of interoceptive and exteroceptive information. Of note, recent network neuroscience investigations have reported that compared with the lateral prefrontal and anterior cingulate cortex (ACC), activation in the AI tends to come online earlier and exert a causal influence on these and other brain structures (Cai et al., 2016; Sridharan et al., 2008). This primacy of activation and causal influence renders the AI unique in the hierarchy of neural machinery giving rise to executive control processes.

1.3. Functional architecture of the insula

What is the function of the insular cortex? The insula is one of the most widely and consistently activated brain regions across human neuroimaging studies (Yeo et al., 2014), and yet, is perhaps one of the least well understood (Menon et al., 2020). This is partly due to its location in the depths of the Sylvian fissure, which makes it difficult to access, and to the very low prevalence of isolated insular lesions (Cereda et al., 2002). Seminal work using electrocortical stimulation by Wilder Penfield provided some of the first insights about the functional role of the human insula in the mid-twentieth century. Removal of the temporal lobe for the treatment of drug-refractory seizures in patients suffering from temporal dementia, and schizophrenia. Finally, we suggest future methodological and clinical directions for this line of research.

Fig. 1. Anterior insular processing of salient inputs and influence on dynamic switching between cortical networks. Ascending interoceptive information travels via the vagus nerve through autonomic afferent nuclei (nucleus of the solitary tract (NST); parabrachial nucleus (PBN)) and the ventromedial thalamus (VMT) to the anterior insula (AI) via the posterior (PI) and mid-insula (midINS). AI together with the anterior cingulate cortex (ACC) comprise the major cortical nodes of the midcingulo-insular salience network (SN, blue), responsible for integrating information necessary to maintain goal-directed behavior. The SN communicates with the hypothalamus (HT), amygdala (AMY) and periaqueductal gray (PAG) that transmits to autonomic efferent nuclei and the vagus nerve. Salient signals integrated in the right dAI causally influence the medial frontoparietal default mode network (DMN, yellow; key nodes in posterior cingulate cortex (PCC); ventromedial prefrontal cortex (vmPFC)) and the lateral frontoparietal central executive network (CEN, green; key nodes in posterior parietal cortex (PPC); dorsolateral prefrontal cortex (dPFC)). This is mechanistically observed as SN-mediated switching between the CEN and DMN. This integration of signals from interoception and visceromotion via the AI guides large scale brain network dynamics underlying adaptive behavior. Modified from (Margulies and Uddin, 2019; Uddin, 2015).
responses, as well as somatic sensory responses, especially in the face, tongue, and upper limbs (Penfield and Faulk, 1955). This stimulation work contributed to the early conception of the insula as a primarily visceral–somatic region. Only later would its more ubiquitous role across cognitive, affective, and sensorimotor domains be recognized (Chang et al., 2013; Uddin et al., 2014).

Non-invasive neuroimaging techniques such as functional magnetic resonance imaging (fMRI) have provided opportunities to investigate in vivo functioning of the insula and have revealed insular activation in response to an expansive range of stimuli and paradigms. An early meta-analysis of nearly 1800 functional neuroimaging experiments defined four functionally distinct subdivisions within the human insula, including: (1) a sensorimotor region located in the mid-posterior insula (PI); (2) a central olfacto-gustatory region; (3) a socioemotional region in the ventral anterior insula (vAI); and (4) a cognitive region in the dorsal anterior insula (dAI) (Kurth et al., 2010). Although these functional subdivisions represent an oversimplification of the functional neuroanatomy of the insula, this broad categorization helps us to parse the main functions attributed to the insula in relation to its connectivity with other brain areas and networks.

The recent development of more sophisticated neuroimaging techniques and analysis methods have permitted researchers to better understand the microstructural organization of the insula, its structural connectivity, as well as the dynamics of its functional relationships with other brain structures. Table 1 includes brief descriptions of some of the advanced neuroimaging approaches that have permitted more nuanced characterization of insular function, and what each has revealed.

For instance, a recent investigation of structure-function associations across the insula found that it is organized along multiple interleaved axes of microstructural differentiation that each reflect a different balance of local and distal connections associated with neural networks supporting different functions (Royer et al., 2020). Patterns within the microstructural organization of the insula appear to reflect features of the neural basis for awareness is the neural

Table 1

| Neuroimaging approaches applied to insula characterization. |
|---------------------------------|-----------------|-------------------------------|-----------------------------|
| Technique/Approach              | Neuroimaging modality | What is measured                               | Main findings                          |
| Static functional connectivity  | Functional MRI      | Computes average temporal correlations between neural systems | Clustering analyses reveal three insula subdivisions exhibiting distinct whole-brain functional connectivity patterns |
| Dynamic functional connectivity (eg. sliding window) | Functional MRI      | Examines dynamic (moment-to-moment) patterns of correlations between neural systems | dAI subdivision exhibits more variable patterns of whole-brain functional connectivity compared with other insula subdivisions |
| Effective connectivity (eg. Granger causal analysis, GCA) | Functional MRI      | Computes the causal influence one neural system exerts over another | Right dAI plays a causal role in switching between CEN and DMN |
| Co-activation meta-analysis (eg. meta-analytic connectivity modeling) | Functional MRI      | Computes co-activation (co-variation) among neural systems, typically during task performance | Right dAI exhibits activity across multiple task domains |
| Diffusion weighted imaging (eg. diffusion tensor imaging, DTI, and multi-shell) | Structural MRI      | Single b-value (‘single shell’) diffusion acquisitions provide image contrast based on differences in the magnitude of diffusion of water molecules within the brain, providing an estimate of structural connectivity; different b-values (‘multi-shell’) systematically varied over an acquisition provide more detailed differential tissue responses than single shell | Bilateral gradients along anterior-posterior and dorsal-ventral axes can be observed in the insula, suggesting that a gradient-based rather than cluster-based conceptualization might better reflect the underlying cytoarchitecture |
| High angular resolution diffusion weighted imaging (HARDI) | Structural MRI      | Requires acquisition of > 50 gradients and high b-values to provide a higher resolution of the 3D patterns of water diffusion within a brain voxel | Structural connections link insula and ACC; insula subdivisions exhibit both overlapping and unique structural connectivity profiles |

I. Molnar-Szakacs and I.Q. Uddin Neuroimaging approaches applied to insula characterization. Table 1 includes brief descriptions of some of the advanced neuroimaging approaches that have permitted more nuanced characterization of insular function, and what each has revealed.

For instance, a recent investigation of structure-function associations across the insula found that it is organized along multiple interleaved axes of microstructural differentiation that each reflect a different balance of local and distal connections associated with neural networks supporting different functions (Royer et al., 2020). Patterns within the microstructural organization of the insula appear to reflect features of the organizational cortex as a whole, which may explain how insular signals can convey information regarding a wide range of functional states, making the insula a pivotal hub for the prioritization of sensory, visceral, autonomic processes and higher-order attentional and executive functions guiding appropriate responses to relevant stimuli (Royer et al., 2020). Independent functional activation and connectivity studies also support these findings, showing that insular subdivisions can behave in either a parallel or a heterogeneous manner, depending on task demands. For example, Uddin and colleagues used co-activation meta-analysis to demonstrate that each of three insular functional subdivisions exhibited some unique task-related activation patterns consistent with a tripartite cognition-emotion-interoception parcellation (Fig. 2). However, they also found evidence for a common functional fingerprint across subdivisions, suggesting that each subdivision participates to varying degrees across a variety of cognitive domains, including language, memory, sensory and emotional processing (Uddin et al., 2014). Similarly, a later study used dynamic functional connectivity analysis applied to resting state fMRI data to examine time-varying patterns of communication between insular subdivisions and the rest of the brain. This study found substantial overlap of insula subdivisions during some (but not all) functional connectivity states, highlighting the ubiquity and functional flexibility of the insula (Nomi et al., 2016).

The multiple sensory functions of the more posterior aspects of the insula have been unified under the concept of interoception (Craig, 2009), or the perception and integration of autonomic, hormonal, visceral, and immunological homeostatic signals that collectively describe the physiological state of the body (Namkung et al., 2017). Nearly twenty years ago, an influential theory of insular function was put forward by Craig, who proposed that the representation and integration of interoceptive feelings by the insula provides a neuronal substrate for subjective feelings, emotions and human self-awareness (Craig, 2002). In his view, “the neural basis for awareness is the neural representation of the physiological condition of the body, and the...
organism to its external environment, which results in loss of behavioral responsiveness (LOBR) that has been used as an observable index of such interruption (Mashour, 2014). While perceptual awareness and thalamocortical processing of sensory stimuli persists after measurable LOBR (Mhuircheartaigh et al., 2013), it appears that waking consciousness and the volition to respond require AI activity. In fact, around LOBR, stimulus-evoked activity including auditory tones, words and noxious stimulation were suppressed in the right dAI (Warnaby et al., 2016). After LOBR, the authors also found reduced functional connectivity of the right dAI with the dorsolateral prefrontal cortex (DLPFC) and inferior parietal lobule (IPL). Thus, by virtue of its structural and functional connectivity and the ability to integrate multisensory inputs from the environment and from within the organism, the dAI is conferred a role of gatekeeper to conscious awareness (Deen et al., 2011; Nomi et al., 2018; Warnaby et al., 2016). We posit a similar gatekeeping function for the AI in the service of executive control. Executive control being a process that requires conscious awareness, we extend findings from the LOBR literature and bring to bear evidence from recent network neuroscience studies to provide, for the first time, a mechanistic account of AI contributions to executive control.

In this theoretical review, we put forward the novel theory that the AI is functionally well positioned to serve as a gateway to association cortices in frontoparietal networks, and act as gatekeeper to executive control. It achieves this through a microstructural organization specifically adapted to receiving inputs about both the external environment and internal conditions of the body, which enables it to initiate switches between large-scale functional brain networks involved in high-level control processes. In support of our theory, we build on early work describing insular function and recent sophisticated connectivity modeling approaches applied to functional neuroimaging data that have permitted us to develop a model of the mechanism by which the AI sits at the apex of executive control.

2. Anterior insular gating of executive control

Although executive functions have often been categorized into the cognitive domains of (i) response inhibition, (ii) switching and updating, and (iii) working memory (Best and Miller, 2010; Diamond, 2002; Fiske and Holmboe, 2019; Miyake et al., 2000) in the psychology literature, these processes ultimately serve a common purpose: the allocation of attention and control over behavior in order to meet adaptive goals (Friedman and Miyake, 2017). Executive function is what allows us to filter distractions, prioritize tasks, set and achieve goals, and control impulses (Diamond, 2013; Wager and Barrett, 2004). In humans, executive functions such as planning and organization, behavioral control and adaptation, and decision-making, rely on an intact prefrontal cortex (Fuster, 1980; Robbins, 1996). The prefrontal cortex in humans is very large, even by primate standards (Rilling and Insel, 1999), and has rich functional connections with the insular cortex (Craig, 2009; Carmichael and Price, 1996; Sridharan et al., 2008). We argue that the AI has the unique capacity to gate executive control due to its integrative functional repertoire, its temporal activation profile, and its widespread connectivity fingerprint. In recent years, network analysis applied to fMRI data has permitted direct tests of this hypothesis.

2.1. Anterior insula as a ’causal outflow hub’

How exactly does the AI influence other brain regions? A prominent neurocognitive model describing interactions among three core large-scale brain networks describes relationships among the midcingulo-insular SN, lateral frontoparietal CEN, and medial frontoparietal DMN (Menon, 2011; Menon and Uddin, 2010; Uddin et al., 2019). The DMN, with nodes in the ventromedial prefrontal cortex (VMPFC) and posterior cingulate cortex (PCC), is an internally directed system that is primarily engaged by self-related cognitions and evaluations, autobiographical memory, and self-referencing (Iacoboni et al., 2004; Molnar-Szakacs and
The CEN, comprising the dorsolateral prefrontal cortex (DLPFC) and posterior parietal cortex (PPC), implements the maintenance and manipulation of information and decision-making in the context of goal-directed behavior (Cole and Schneider, 2007; Dosenbach et al., 2007; Molnar-Szakacs and Uddin, 2013; Sridharan et al., 2008). An antagonistic relationship is often observed between the DMN and the CEN, whereby increased activation of the former leads to decreased activation in the latter (Fox et al., 2005; Greicius et al., 2003). The function of the SN, composed of nodes in the right AI and ACC, is to identify the most homeostatically relevant among multiple competing internal and external stimuli (Uddin, 2015). Thus, the CEN and SN typically show increased activation during stimulus-driven cognitive or affective processing, while the DMN typically shows increased activation during self-referential and stimulus-independent cognitions, such as mind wandering (Kucyi and Davis, 2014).

The right dAI is a key node of the SN, but also has direct connections to principal nodes of the DMN and the CEN through ipsilateral structural connections in both hemispheres to medial prefrontal cortex (MPFC) and the PPC, respectively (Nomi et al., 2018). Using Granger causal analyses (GCA) to examine effective connectivity among nodes of the SN, DMN and CEN, Sridharan and colleagues first demonstrated that the right AI and ACC play a critical and causal role in activating the CEN and deactivating the DMN across task paradigms and stimulus modalities (Sridharan et al., 2008) (Fig. 3). GCA enables the detection of causal interactions between brain regions by assessing the extent to which fMRI signal changes in one brain region can predict signal changes in another brain region (Goebel et al., 2003). The influence of the AI and ACC nodes of the SN on other brain regions within the DMN and CEN (Cai et al., 2016; Supekar and Menon, 2012) is a finding that has since been replicated across multiple datasets and methods (Uddin, 2015), confirming the role of the right dAI as a causal outflow hub acting to coordinate these major large-scale brain networks.

In addition to demonstrating its predominant causal influence, these studies have also revealed the temporal primacy of dAI activity; that is, the dAI showed an earlier onset of responses compared with other brain regions, including the ACC, across a variety of task and resting state fMRI paradigms (Sridharan et al., 2008). This primacy of activation combined with the ability to causally influence other brain regions renders the AI unique in the hierarchy of neural machinery giving rise to executive control processes.

Although the dAI typically exhibits anticorrelated patterns of activity with DMN nodes (Fox et al., 2005), communication between the SN and the DMN is dynamic, such that functional connections between these nodes fluctuate across timecales of milliseconds to seconds (Fox et al., 2005; Uddin et al., 2007) and can be modulated by experimental factors such as task demand and cognitive load (Sridharan et al., 2008; Sridharan and Molnar-Szakacs, 2011).

**Fig. 3.** Anterior insula is a causal outflow hub. Granger causality analysis (GCA) revealed that the right dAI (also referred to as the fronto-insular cortex (rFIC)) - key node of the salience network (SN; purple) - plays a critical and causal role in switching between the central-executive network (CEN; green) and the default mode network (DMN; yellow) across three different tasks, including (A) auditory event segmentation, (B) visual oddball attention task, and (C) task-free resting state. Right hemisphere results are displayed. The thickness of the connecting arrows between key nodes of the CEN, DMN and SN corresponds to the strength of directed influence between any pair of regions for that task. Only links that showed significant directed connectivity at the group-level (Mann-Whitney U test, $P < 0.01$; Bonferroni corrected for multiple comparisons) are shown (gray arrows); a subset of these links with a dominant directional influence are highlighted in red (Mann-Whitney U test, $P < 0.05$). Reproduced with permission from (Sridharan et al., 2008).
networks can display transient properties. In addition to its causal influence on the activity of DMN nodes (Sridharan et al., 2008), time-varying functional connectivity analysis has shown that the dAI can form transient functional connections with the MPFC node of the DMN (Chang and Glover, 2010; Nomi et al., 2016) (Fig. 4).

As a principal node of the SN, the dAI coordinates network dynamics to enable functional switching between the internally-oriented DMN and the externally-oriented CEN (Uddin, 2015) in ways that support executive functioning. The right dAI node of the SN is thought to be the source of control signals coordinating these brain network dynamics, acting as a causal outflow hub at the junction of these large-scale brain networks (Chen et al., 2013; Goudlen et al., 2014; Sridharan et al., 2008; Supkar and Menon, 2012; Uddin et al., 2011). In tasks requiring greater cognitive control, the dAI exerts stronger causal influence (Cai et al., 2016). Taken together, the body of available empirical work suggests that the dAI prioritizes and integrates external sensory information with internal emotional and bodily state signals to mobilize neural resources for optimal executive control. One of the ways the dAI initiates control is by leveraging its role in salience processing and attention.

2.2. Role of the anterior insula in salience processing and attention

Through its role in the neural integration of internal states with external stimuli, the insula plays an important role in salience processing and attention, which are key cognitive components necessary for implementing executive function (Dajani and Uddin, 2015). We make sense of the multiple internal and external inputs that compete for our attention by determining which ones are salient. Salience processing is not always accessible to conscious awareness; the integration of previous experiences and memories with visceral and autonomic functions, and homeostatic functions of the brain can influence what is perceived to be salient (Critchley and Harrison, 2013; Puglisi-Allegra and Ventura, 2012). In other instances, salience processing can be dependent on top-down attention and cognitive control processes that are focused on the execution of goal-directed behaviors (Corbetta et al., 2008).

A consistent finding with respect to AI function that cuts across sensory modalities is its involvement in the detection of novel stimuli. A prevailing neurobiological model of attention systems in the human brain posits that a dorsal attention network (DAN), with nodes in the frontal eye fields (FEF) and intraparietal sulcus (IPS) mediates goal-directed allocation of attention to specific stimuli, whereas the ventral attention network (VAN) comprised of the temporoparietal junction (TPJ), middle frontal gyrus and AI mediates stimulus-driven, bottom-up control of attention (Corbetta et al., 2008, 2002). Thus, these ventral brain regions seem to interact with nodes of the DAN when moving attention from a current focus towards a new source of information in stimulus-driven reorienting of attention (Shulman and Corbetta, 2012; Sridharan et al., 2007; Wen et al., 2012). In fact, recent work demonstrated anticorrelated patterns of activity between the DAN and the DMN in resting-state fMRI data from pharmacologically anesthetized patients and patients with unresponsive wakefulness syndrome (Huang et al., 2020), similar to the anticorrelated functional dynamics seen in interactions of the CEN and the DMN. The authors showed that conscious awareness is related to a dynamic balance of the brain states enacted by the DAN and DMN, whereas an ‘unresponsive’ state is characterized by fragmented regional brain activity. This fragmentation functionally isolates the networks from one another, and it appears that the AI is the functional switch gating the temporal dynamics between DAN and DMN. The authors posit that the AI, by virtue of its position in the cortical hierarchy, regulates brain network transitions that gate conscious access to sensory information (Huang et al., 2021), providing additional direct evidence for the proposed gatekeeping function of the AI.

Attentional processes have been studied extensively using the oddball paradigm (Picton, 1992; Squires et al., 1975), where an aberrant stimulus is interspersed among a series of the same item. Oddball tasks consistently reveal activation of regions of the SN, including the dACC and AI along with amygdala and other subcortical structures during processing of rarely occurring oddball stimuli (Kim, 2014; Levy and Wagner, 2011). A recent study has made progress towards differentiating the functional contributions of the AI and the dACC of the SN to show that the function of the AI consists in alerting the system for the presence of a behaviorally relevant event, whereas the dACC is primarily involved in shifts of goal-oriented behavior in response to such an event (Han et al., 2019). Specifically, when a salient or task-relevant stimulus is presented, the AI alerts information processing systems to that event. Then, based on the behavioral relevance of the event, it is determined if a response is required. Supporting this response, the dACC is proposed to be involved in switching of attentional set from a distracting, task-irrelevant event to goal-oriented behavior, consistent with the hypothesis that this area is part of a network that promotes switching between internal and externally directed psychological processes (Han et al., 2019; Sridharan et al., 2008). Once again, these findings reinforce the primary and significance of AI function in salience processing at the crossroads of bottom-up and top-down attentional networks.

The CEN and SN have both been implicated in executive control and in stimulus-driven reorienting of attention, suggesting some degree of functional overlap between mechanisms underlying stimulus-driven and top-down control of attention. To better understand if this overlap potentially leads to processing bottlenecks under concurrent attentional demands, Trautwein and colleagues used a task that combines a flanker-target conflict (Eriksen and Eriksen, 1974) with spatial cueing of the target location (Posner, 1980) to test for independent versus shared neural mechanisms. They found that conditions that required both attentional reorienting and executive control in order to resolve a flanker-target conflict resulted in an enhanced response. Specifically, stimulus-driven orienting due to invalidly cued targets induced robust activations in areas of the VAN, SN regions with peaks in bilateral AI and dACC, and in bilateral IPS and superior frontal gyri (Trautwein et al., 2016). Executive control of attention activated areas typically involved in conflict resolution (Nee et al., 2007), including the SN as well as IPS and frontal areas (precentral and middle frontal gyri). Interactions of stimulus-driven reorienting and executive control led to a super-additive increase of activation in the left AI, as well as behavioral response costs, suggesting a common bottleneck for these two cognitive processes under concurrent demands.

The ability to switch attention voluntarily and flexibly from one task or operation to another, or among different stimulus sets, reflects a core aspect of executive control (Miyake et al., 2000). Two meta-analyses of set-switching in healthy participants reported activation of a widespread neural circuitry during set-switching, comprising prefrontal, fronto-parietal and AI regions (Derrfuss et al., 2005; Wagner et al., 2004). Acute stroke patients with localized damage to the left insular cortex performed worse in the set-switching test of the shape-based Trail-Making Test (TMT) analogue compared with patients without such damage (Varjacic et al., 2018). Another combined, multi-center study that mapped TMT set-switching performance on separate indices of grey matter and white matter damage yielded complementary data for the left insular involvement in executive function (Muir et al., 2015). Specifically, the study found that ischemic stroke within the left superior longitudinal fasciculus, a white matter tract traversing peri-insular regions, predicted TMT set-switching deficits in both acute and chronic stroke cohorts. Conversely, stroke involvement with the grey matter regions within the executive network (including lateral and medial PPC, lateral parietal cortex and thalamus) was not associated with TMT set-switching deficits.

The anatomical and functional evidence reviewed thus far suggests that there are several factors that contribute to the AI being an ideal gatekeeper of executive control, including (i) its structural and functional connectivity within the neural hierarchy that includes cortical and subcortical inputs of multisensory information from both internal and external environments; (ii) its microstructural organization that...
State 1 (24%)  
\[ n = 31 \]

State 2 (5%)  
\[ n = 9 \]

State 3 (38%)  
\[ n = 31 \]

State 4 (13%)  
\[ n = 26 \]

State 5 (20%)  
\[ n = 30 \]
allows the prioritization of sensory, visceral, autonomic processes, and higher-order attentional and executive functions; (iii) its network location as a causal outflow hub within the SN that permits control of network dynamics through direct links to key nodes within major networks, including the CEN, DMN, DAN and VAN. 

2.3. Role of the mid- and posterior insula in interoception & self-awareness 

Alongside salience processing and attention, the insula plays a key role in interoception & self-awareness. There are generally two major ascending peripheral neural or afferent pathways that transmit interoceptive signals to the brain (Chen et al., 2021; Craig, 2002). Parasympathetic afferents travel along cranial nerves, including the vagus, and sympathetic afferents travel through the dorsal column of the spinal cord (Mei, 1983). While vagal afferents are thought to carry primarily mechanoreceptor and chemosensory signals; spinal afferents carry signals related to temperature, pain, and tissue injury (Saper, 2002). Ascending interoceptive information is first processed in subcortical structures of the brain such as the medial solitary nucleus, the parabrachial nucleus, and the ventromedial nucleus of the thalamus (Janig, 1996; Suarez et al., 2018). Higher-level integration and interpretation of interoceptive information may occur in higher brain regions including the hypothalamus, somatosensory cortex, ACC, and insula (Iwai et al., 2015; Wang et al., 2019). Indeed, the insula participates in visceral and somatic sensory processing, contributes to autonomic regulation of the gastrointestinal tract and heart, and is a motor association area (Augustine, 1996; Craig, 2002; Critchley and Harrison, 2013). Fig. 1 depicts a potential mechanism by which the right dAI implements its network control function at the intersection of interoceptive signals and external stimuli. Ascending interoceptive information travels via the vagus nerve through autonomic afferent nuclei and the thalamus to the AI via the P1 and mid-insula. The AI together with the ACC comprise the major cortical nodes of the SN, which communicates with hypothalamus, amygdala and PAG that transmits to autonomic efferent nuclei and the vagus nerve. Salient external signals integrated in the AI causally influence the DMN and the CEN, mechanistically observed as SN-mediated switching between the CEN and DMN. This integration of signals from interoception and visceromotion via the AI guides large scale brain network dynamics underlying adaptive behavior, creating a causal pathway for access to executive control. 

A recent integrative model based on tract-tracing data and functional studies in the macaque monkey led to the proposal of the flow of interoceptive information processing from the dorsal granular insula to the intermediate dysgranular insula and finally to the anterior agranular insula (Evrard, 2019). This posterior-to-anterior progression of interoception through the insula has also been proposed in humans (Craig, 2009; Craig, 2002). First, objective interoceptive signals arrive via spino-thalamo-cortical pathways in the P1, where low-level sensory features are processed. Then, this information is passed to the AI where the interoceptive signals are integrated with emotional, cognitive, and motivational signals collected from other cortical and subcortical regions, such as the amygdala, the ACC, the DLPFC, and the ventral striatum (Critchley and Harrison, 2013; Harrison et al., 2010). In particular, the right AI mediates the incorporation of autonomic nervous signals with conscious thought processing to represent an individual’s subjective and conscious emotional state, as well as the emotive value of external stimuli - such as feeling disgust (Craig, 2002; Critchley, 2004; Critchley et al., 2002; Gray and Critchley, 2007; Nguyen et al., 2016). 

An incredibly broad array of responses beyond visceral-somatic processing, including sensory (paresthesias and localized warm sensations), motor, pain, auditory, oropharyngeal, speech disturbances that included speech arrest and reduced voice intensity, or neurovegetative phenomena, such as facial reddening, generalized sensations of warmth or cold, hypogastic sensations, anxiety attacks, respiratory accelerations, and sensations of rotation and nausea (Afif et al., 2010; Isnard et al., 2004; Stephani et al., 2011) have been documented by studies involving direct electrical stimulation of the insular cortex during surgical procedures for epilepsy, functional imaging techniques, and lesion studies. Interestingly, in a study of a large sample of brain-injured patients, it was found that damage to AI, but not to ACC or to the whole brain in general, was predictive of acquired alexithymia, a subclinical condition characterized by impaired awareness of one’s emotional states (Hogeveen et al., 2016). Such impairment in emotional awareness could be explained as a direct result of the breakdown of the integration of multisensory information from interoceptive and exteroceptive domains at the level of the AI, reflecting a dis-integration of the experience of selfhood as supported by the AI (Seth, 2013). The inability to accurately interpret and describe internal affective states, as occurs in alexithymia characterizes a number of related psychiatric disorders with insular involvement (Bird et al., 2010; Molnar-Szakacs and Heaton, 2012; Valdespino et al., 2017). 

The perception and regulation of interoceptive signals are important components of self-awareness and executive control. It has been theorized that the insula may provide the neural substrate for interoceptive inference, in which predictions regarding interoceptive signals are compared with actual sensory and interoceptive afferent inputs (Apps and Tsakiris, 2014; Critchley and Seth, 2012; Seth, 2013). According to Bayesian inference models of interoceptive predictive coding (Barrett and Kyle Simmons, 2015; Seth and Critchley, 2013; Seth and Friston, 2016), current interoceptive experience largely reflects predictions about the expected state of the body based on previous experiences. Interoceptive predictors engage descending signals that elicit autonomic responses that provide a homeostatic set point against which present interoceptive inputs can be compared. In this model, expected and actual sensation would be compared in the P1, generating an error signal that is propagated back to visceromotor regions (Barrett and Kyle Simmons, 2015). The AI and ACC can contribute to reducing this error signal through their involvement in orchestrating executive control and attention networks (Fox et al., 2005; Seeley et al., 2007; Yeo et al., 2011). 

In an interesting set of experiments, Salomon and colleagues demonstrated the impact of interoceptive signals on visual awareness, whereby visual targets presented in synchrony with one’s cardiac frequency required more time and were more difficult to discriminate than the same stimuli presented asynchronously to the heartbeat (Salomon...
feedback. Activity in the PI was unrelated to age. These findings show developmental trajectories and are subserved by distinct subdivisions in generated here to guide regulation in the absence of exteroceptive awareness. In a follow-up study of lesion patients and controls, the authors also found that the two patients with lesions in the AI - but not other regions - did not show this cardio-visual suppression effect, providing causal evidence for the role of the AI in the integration of interoceptive signals and external visual stimuli (Salomon et al., 2018).

2.4. Developmental considerations

When does insular function typically mature to adult levels? The development of interoceptive regulation was investigated in female adolescents with a mean age of 15 years by inducing gut activity using a virtual rollercoaster paradigm, and asking participants to regulate that gut feeling with or without biofeedback (Li et al., 2017). The fMRI data revealed that dorsal and ventral sub-regions of the AI showed distinct functional contributions and developmental profiles. The activation profile of the dAI, involved in executive control processes, showed a linear relationship with age, during both induction and regulation of gut activity. In the vAI, predominantly involved in affective processing (Chang et al., 2013), activity peaked in mid adolescence during the induction phase (Li et al., 2017). Interestingly, the no-biofeedback condition elicited more activation in the bilateral PI compared to the biofeedback condition. Given that interoceptive inputs arrive first in the PI (Craig, 2002), higher activation in the no-biofeedback condition suggests that the participants relied more on the interoceptive markers generated here to guide regulation in the absence of exteroceptive feedback. Activity in the PI was unrelated to age. These findings show that various aspects of interoception are associated with different developmental trajectories and are subserved by distinct subdivisions in the insular cortex. They also further confirm the specific involvement of the dAI in the regulation of interoceptive processes.

A variety of cognitive, attentional and executive function tasks require the temporally coordinated activity of the CEN (Crittenden et al., 2016; Niendam et al., 2012; Owen et al., 2005), and the SN (Dosenbach et al., 2008, 2006; Menon and Uddin, 2010) in adults. Developmentally, it has been shown that children and early adolescents (3rd to 8th grade) also engaged regions comprising the CEN and SN during switching, updating and inhibition tasks, as has been described in adults. A core set of regions engaged during more difficult task demands include the dACC and right AI, as well as right FEF, left inferior frontal sulcus, and left IPL (Engelhardt et al., 2019). These findings suggest that the common neural architecture of executive functions seen in adulthood is present by middle childhood (Supkar and Menon, 2012). A recent meta-analysis of neurodevelopmental studies of stop-signal tasks found that children and adults showed similar global activation patterns associated with inhibitory control, whereby the SN and the CEN showed the greatest activation during stopping, while the DMN showed the greatest deactivation or the least activation (Cai et al., 2019). Furthermore, the strength of task-modulated connectivity between the right AI and right subthalamic nucleus (STN) was correlated with inhibitory control abilities in children, providing functional significance to the important role of the hyperdirect structural link between the STN of the basal ganglia and insular cortex (Cauda et al., 2011; Lambert et al., 2012) in the development of mature inhibitory control. Directly linking the STN with cortex, this pathway bypasses the striatum and allows for the rapid stopping of previously initiated actions (Nambu, 2004; Schmidt and Berke, 2017). The authors also found that the right AI was the most strongly activated among all nodes of the inhibitory control network in both adults and children (Cai et al., 2019). Such a role for the AI is not surprising given that it is the most strongly and consistently activated brain region during inhibitory control in adults (Cai et al., 2014) and is important for detection of salient cues that signal the need for inhibitory control (Cai et al., 2017, 2016). Taken together, these findings suggest that the stage is set relatively early in development for the gatekeeping functions of the insula to fully mature in adulthood.

3. Insular anatomy supports its gatekeeping function

Having described the evidence that the AI is a functional hub exerting an early and causal influence among key neural networks to support executive control, we turn now to a discussion of how its unique anatomy scaffolds this role. The human insular cortex is delimited from the frontal, parietal, and temporal opercula by the perinsular sulcus and is divided into posterior and anterior lobules by the central insular sulcus (Wysidecki et al., 2018). Although there is some variability in the number of insular gyri, the more anterior portion of the insula is typically composed of the anterior, middle, and posterior short insular gyri, which are separated by the anterior and precentral insular sulci. The posterior portion of the insula is composed of the anterior and posterior long insular gyri, separated by the postcentral insular sulcus (Mavridis, 2014; Morel et al., 2013). The orientation, size of the gyri, and exact number of short gyri can vary across individuals and cerebral hemispheres (Wysidecki et al., 2018).

The architectonic organization of the human insula consists of concentric layers of cell structures that radiate outward from the ventral anterior portion of the insula to the dorsal posterior portion of the insula. These concentric layers of granularity cut across the insular gyri, as their arrangement orient them in different directions. It was Brodmann’s work on the human insula that first provided evidence for a posterior granular area and an anterior dysgranular area separated by the central insular sulcus. Brodmann areas 13–16 represent the human insular lobe. A dorsocaudal granular field is designated as area 13, while a ventro-lateral agranular field is assigned to areas 14–16 (Brodmann, 1909).

Based on cytoarchitectonic analyses of the presence and density of cortical granular cell layer 4, further work has subdivided the insula into posterior granular, intermediate dysgranular, and anterior agranular sectors (Craig, 2011; Morel et al., 2013; Nieuwenhuyis, 2012). Alongside these delineations of insular subdivisions, models of insular heterogeneity without discrete boundaries have been suggested by Cerliani and colleagues (Cerliani et al., 2012), quoting Brodmann, who already over 100 years ago had written that “there are great difficulties in dividing [the insula] into individual fields” (Brodmann, 1909). Indeed, macaque studies suggest that insula cytoarchitecture and connectivity vary gradually and continuously, arranged topographically along a rostrocaudal axis, with the agranular and granular insula portions separated by a transitional dysgranular zone (Mesulam and Mufson, 1982a, 1982b).

Cytoarchitectonic analysis of the human PI using an observer-independent approach provides evidence of two granular areas referred to as insular lobe granular areas 1 and 2 (Ig1 and Ig2) in the dorsal PI, and a dysgranular area labeled as Id1 in the ventral PI (Kurth et al., 2010). Similarly detailed cytoarchitectonic mapping has not yet been undertaken in the human AI, however, this portion of the insula displays an intermediate dysgranular profile (Mesulam and Mufson, 1985, 1982a; Morel et al., 2013) in the dAI and an agranular structure characterized by undifferentiated layers II/III in the vAI. These are both distinct from the fully developed granular neocortex with a canonical 6-layer architecture (Menon et al., 2020; Uddin et al., 2017). While agranular cortex has no granule cells, dysgranular cortex has fewer granule cells, which are grouped in a single layer or as distinct clusters (Mesulam and Mufson, 1982b).

Recently, Menon and colleagues leveraged advances in multi-shell diffusion MRI acquisition protocols and signal reconstruction techniques to study the microstructural features of the insular cortex (Menon et al., 2020). There is a similar microstructural organization in the ACC and within the three insular subdivisions with which it is differentially connected. They were also able to show bilateral gradients along the anterior-posterior as well as dorsal-ventral axes in the insula, that are
consistent with known cytoarchitectonic differences derived from studies of post-mortem human brains (Ding et al., 2016; Morel et al., 2013). This finding led the authors to propose that a gradient-based rather than cluster based conceptualization might better reflect the underlying cytoarchitecture of the insula and its connectivity (Menon et al., 2020), a view that mirrors evidence of a continuum of gradual changes in functional connectivity across this brain region (Tian and Zalesky, 2018).

Interestingly, the agranular portion of the human AI has grown disproportionately more than the rest of the insula compared with all other primate species (Bauernfeind et al., 2013), and harbors von Economo neurons (VENs) and fork neurons, which are morphologically specialized cortical projection neurons (Allman et al., 2011b, 2005) (Fig. 5). VENs differ from the typical pyramidal neurons by virtue of their large spine shape and thick basal and apical dendrites which allow for speeded communication with other brain areas (Seeley et al., 2012; Von Economo, 1926). When they were initially found only in humans and great apes, VENs were viewed as a cellular contributor to the evolutionary emergence of self-consciousness and social awareness (Craig, 2009; Critchley and Seth, 2012). However, this type of neuron has since been identified in lesser apes, elephants, dolphins, whales and more recently in many other species (Evrard, 2019). In humans, VENs have been predominantly described in layer Vb of the ACC and in the AI (Allman et al., 2011a; Nimchinsky et al., 1995). More recently, VENs have been described in the medial prefrontal cortex, 5 mm from the dorsomedial convexity, a region corresponding to Brodmann’s area 9 (BA9; Fajardo et al., 2008). There appears to be a rightward asymmetry in VENs, with stereological evidence showing higher numbers of VENs in the right hemisphere than the left except in the very young (Allman et al., 2011a). This right > left asymmetry is also supported by MRI findings (Shaw et al., 2009; Watkins et al., 2001). VENs project to the contralateral AI cortex, ipsilateral ACC, and particularly target brainstem nuclei involved in visceral sensation and autonomic control, including the periaqueuductual gray (PAG) and parabrachial nucleus (Evrard, 2019). VENs are particularly vulnerable in neuropsychiatric conditions characterized by deficits in social and emotional functioning, autonomic control and decision making, which, when considered in the context of the functional role of the cortical regions that host them, points to a likely role in executive functioning (Allman et al., 2011a; Butti et al., 2013).

3.1 Structural connectivity of the insula

Most of the information regarding structural connectivity of the insula is derived from what is known regarding its anatomy in the macaque monkey (Mesulam and Mufson, 1982b). Early studies using direct cortical stimulation of the insula produced motor movements in the face, body, and tail of the macaque monkey and also resulted in changes to respiration, heartbeat, blood pressure, and saliva/mucus production (Showers and Lauer, 1961). This suggested direct structural connections between the insula and motor cortices as well as with the autonomic nervous system.

Ablation techniques identified connections of the insula through neural degeneration related to surgically induced lesions. Structural white matter degeneration in response to insula ablations was found in the external and extreme capsules, corpus callosum, anterior commissure, and superior/inferior longitudinal fasciculi. These white matter tracts connect the insula with frontal, parietal, temporal, cingular, olfactory, and subcortical brain areas such as the hippocampus and amygdala (Showers and Lauer, 1961).

Later macaque studies used tracer techniques to identify structural connections from the insula to the frontal cortex, olfactory cortex, parietal lobe, cingulate cortex, somatosensory cortices, and the temporal lobe (Mufson and Mesulam, 1982). Such tracer studies identified an anterior–posterior difference for insular structural connections, where more anterior portions of the insula had a greater number of connections to the frontal cortex, whereas posterior portions had a greater number of connections to cingulate and parietal cortices. In addition, only the AI had connections to the olfactory cortex.

Diffusion MRI studies in humans have also attempted to map structural connections of the insula. However, it should be noted that diffusion MRI suffers from both false positives and negatives and poorly captures connection weight or strength (Donahue et al., 2016). As such, it is prudent to be very cautious in interpreting human tractography results in the absence of verification of findings in other modalities and species. Nevertheless, diffusion MRI studies in humans over the past decade have attempted to map the whole-brain structural connections of the insula (Cerliani et al., 2012; Cloutman et al., 2012; Dennis et al., 2014; Jakab et al., 2012), suggesting that afferents from sensory, limbic, autonomic and frontal brain regions converge on the insula (Gogolla, 2017). Ghaziri and colleagues used a deterministic algorithm applied to high angular resolution diffusion-weighted imaging (HARDI) data to demonstrate an anterior–posterior organization in accord with previous structural work, as well as identifying connections between the insula and the ACC (Ghaziri et al., 2017; Sotiropoulos et al., 2013; van den Heuvel et al., 2009; Wiech et al., 2014).

Also using a HARDI dataset, Nomi and colleagues demonstrated overlapping structural connections across insular subdivisions to frontal, temporal, parietal, occipital, and subcortical brain areas. This common set of fiber pathways could facilitate coordinated activity across insular subdivisions, allowing them to act in concert in certain circumstances. Unique connections for the dAI were found bilaterally for MPFC, frontal inferior operculum (FIO), and thalamus (Nomi et al., 2018). These unique structural connections are in line with a functional...
framework demonstrating interactions between the dAI and frontal areas involved in higher-level cognitive processes (Uddin, 2015).

3.2. Hemispheric asymmetry of the insula

We have noted that the right AI appears to drive the gatekeeping of executive control. Structural and functional hemispheric asymmetries may provide insight into why this is the case. A study using voxel-based analyses of gray matter to examine structural asymmetries throughout the whole brain in a population of 142 healthy adults found that the inferior portion of the AI showed a highly significant right > left asymmetry, whereas a more superior portion of the AI showed the opposite left > right asymmetry (Watkins et al., 2001). Hemispheric asymmetry in microstructural organization of the insula, and its putative links with differential expression of VENs, are consistent with reports of a left-right functional asymmetry in the insula (Craig, 2005).

The proposal has been made that leftward asymmetries are most likely related to the involvement of the insula in language and gesture (Bidula and Krolczak, 2015; Chiarello et al., 2013). Left insular activation has been found in neuroimaging paradigms of speech production, phonological working memory, rhyme detection, sublexical phonological coding during reading and comprehension of actions (Ackermann and Riecker, 2010; Borowski et al., 2006; Chee et al., 2004; Eickhoff et al., 2009; Hurschler et al., 2013; Marvel and Desmond, 2012; Price, 2012; Saygin et al., 2004). Furthermore, patients with left AI lesions may have deficits in speech planning and/or execution (Baldo et al., 2011; Dronkers, 1996; Ogar et al., 2006). One study reported that insular volume asymmetry predicts functional language dominance, and that a larger insula predicts functional lateralization to the same hemispheric side for the majority of subjects (Keller et al., 2011).

Menon and colleagues suggest that the hemispheric asymmetry in microstructural organization of the insula may contribute to lateralization of function, and in particular the differential role of the right insula in monitoring internal bodily states and subjective awareness across a wide range of cognitive and affective processing tasks (Menon et al., 2020). For instance, it has been found that homeostatic afferents, including hot and cold, pain, muscle and visceral pain, sensual touch and sexual arousal all produce strong right lateralized activation in the AI (Craig, 2002). The right AI mediates the incorporation of autonomic signals into higher order cognitive processing, to represent an individual’s conscious emotional state, as well as the subjective emotive value of external stimuli - such as feeling disgust (Craig, 2002; Critchley, 2004; Critchley et al., 2002; Gray and Critchley, 2007; Nguyen et al., 2016).

It is notable that the right AI plays a prominent role in subjective awareness and salience detection models (Craig, 2009; Menon and Uddin, 2010) and is also considered part of the VAN (Corbetta et al., 2008). The right AI has been shown to exert significant causal influences on multiple other brain areas in a wide range of cognitive and emotion control tasks such as the Go-No-Go, Stop Signal and Emotional Stroop tasks (Cai et al., 2019, 2016, 2014; Ham et al., 2013) and lesions to this region are known to impair cognitive control (Ding et al., 2016). Consistent with these high-level functions, there is some evidence from both structural (Cerfiani et al., 2012) and functional connectivity studies (Cauda et al., 2011) that the right insula communicates with a more diverse array of structures than the left (but see also Jakab et al., 2012). Further work examining unique lateralized connections of the insula subdivisions are needed.

Kann and colleagues examined lateralization of the resting-state functional connectivity of the AI in a dataset of 250 healthy adults by computing a laterality index of connectivity with 54 different brain regions (Kann et al., 2016). They found that the AI is left lateralized in connectivity with the dorsomedial prefrontal cortex, superior frontal gyrus, inferior frontal cortex, and posterior orbital gyrus and right lateralized in connectivity with the postcentral gyrus, supramarginal gyrus, and superior parietal lobule. The authors concluded that this pattern of lateralized functional connectivity reflects the role of the right insula in salience detection, attention orientation, interoception, and physiological arousal (Schott et al., 2011; Sturm et al., 1999), and a role of the left insula in cognitive and affective control, as well as perspective taking (Barber et al., 2011; Ham et al., 2013). Indeed, interactions of stimulus-driven reorienting and executive control of attention led to a super-additive increase of activation in the left AI, paralleled by behavioral response costs, suggesting a bottleneck for these two cognitive processes (Trautwein et al., 2016). The interference resulting from situations of concurrent task demands provides further evidence for the role of the AI as a functional switch (Huang et al., 2021) at the intersection of major brain networks whose temporally coordinated dynamics give rise to our conscious experience of the world.

Taken together, the pattern of functional lateralization of the insula appears to generally accord with the role of the right and left AI in sympathetic and parasympathetic autonomic responses, respectively (Craig, 2005) as well as hemispheric lateralization of neural networks to support bottom-up and top-down processing (Gotts et al., 2013). However, the precise contributions of the left and right AI to executive control still need to be clearly defined and refined. With current non-invasive neuroimaging technologies and analysis techniques, it is becoming possible to develop and test increasingly precise hypotheses about structure-function relationships in the brain to further resolve the hemispheric asymmetries observed. For example, the right AI is predominantly activated by salient stimuli (Craig, 2002; Sridharan et al., 2008) and provides input into the SN (Ham et al., 2013). Furthermore, Zhang and colleagues confirmed a significantly right-sided laterality in both functional and structural connectivity between the AI and dACC, core nodes of the SN (Zhang et al., 2019), supporting earlier evidence that the intrinsic functional coupling of the SN nodes is stronger and broader in the right than the left hemisphere (Cauda et al., 2011; Seeley et al., 2007). In future studies, it will be important to understand how this asymmetry relates both structurally and functionally to higher rightward density of VENs seen in both apes and humans (Evrad et al., 2012).

3.3. Interim summary

The evidence reviewed thus far supports a network view of executive functioning that is scaffolded by major functional brain networks including the midcingulo-insular SN, the medial frontoparietal DMN, lateral frontoparietal CEN, as well as the VAN and DAN. We have proposed and aimed to provide evidence for the right AI as a seminal component of this system, contributing to executive functioning through network coordination via its neural gating mechanisms. The AI is a region that has the ideal set of functional and anatomical characteristics to subserve this role, including its gradient-based microstructural organization that supports the integration of interoceptive and exteroceptive information, and mirrors its functional connectivity at the crossroads of bottom-up and top-down attentional networks. This functional connectivity confers the AI the ability to act as a causal outflow hub to coordinate the major large-scale brain networks implementing executive functions. In our model, the AI takes as input interoceptive information and the neural activation states of the major neural networks and through its primacy of action and gating function, yields as output coordinated information flow among the networks to achieve executive control.

4. Comparison with other cognitive neuroscience models of executive control

As discussed at the outset, it is widely accepted that the prefrontal cortex is the neural substrate of executive control (Miller and Cohen, 2001). The model we put forth highlights a primary role for the AI in this process, while acknowledging, complementing, expanding on (and in some cases diverging from) prior models of executive control. We next
discuss these relevant models and points of convergence and divergence with our proposal.

4.1. Models highlighting the role of anterior cingulate cortex

Traditionally, it is the ACC rather than the insula that has been highlighted for its role in response selection, cognitive processing, interactions with motor systems, and affective behaviors as related to executive functioning (Carter et al., 1999; Devinsky et al., 1995). The ACC is often discussed as being at the interface of motor control, motivation, and cognition (Paus, 2001) or as being a region for integration of negative affect, pain and cognitive control (Shackman et al., 2011). Indeed, the ACC serves as an effective network convergence zone, participating in multiple regulatory and control behaviors (Margulies and Uddin, 2019). Somewhat surprisingly, many of the earlier theories positing a role for the ACC in executive control neglect the insula entirely, despite strong evidence that the AI and ACC are functionally linked, exhibiting correlated activity levels as part of the SN (Woolley et al., 2007). Our model differs from these prior models focused on the ACC by positing a unique and predominant role for the AI in executive control. We emphasize the primacy and causal influence the AI exerts on ACC and other fronto-parietal brain regions.

4.2. Model of embodied predictive interoceptive coding

Our proposed model of the AI as a gatekeeper of executive control is consistent with the Embodied Predictive Interoceptive Coding (EPIC) model put forth by Feldman Barrett and Simmons, proposing that interoceptive predictions play a role in dynamic coordination of brain activity (Barrett and Kyle Simmons, 2015). While the EPIC model is focused on the role of interoceptive predictions and does not explicitly discuss how executive control emerges, it draws on similar lines of evidence for the role of the insula in estimating the balance between autonomy, metabolic, and other predicted requirements of the body.

4.3. Models emphasizing large-scale network interactions

It is increasingly recognized that executive functions are not strictly top-down processes, nor can they be localized to specific brain correlates, but rather that they emerge through communication within a broad network of spatially dispersed brain regions that integrate different aspects of executive functions (Zink et al., 2021). While some argue that this empirical observation suggests that executive control is an emergent property of a distributed system rather than the outcome of a sequence of hierarchical processes, we argue that the temporal precedence and causal influence of the dAI is consistent with the view that this brain region functions as a gatekeeper, serving a control function that is germane to both distributed and hierarchical processes. As such, our model diverges from other models of executive control in attributing special significance to the role of the AI.

For instance, Menon & D’Esposito recently reviewed the role of six prefrontal cortical networks - the cingulo-opercular network, CEN, SN, DMN, DAN and VAN - in executive control. They assert that executive control is not implemented by one individual network, but rather by dynamic interactions among these networks (Menon and D’Esposito, 2021). The model we put forth here is largely in agreement with these proposals, but diverges in positing that the AI plays a more prominent role in cognitive control by serving as a gatekeeper to executive functions through its role as a causal outflow hub coordinating these networks.

5. Dysfunctional gatekeeping and consequences for executive control

As the AI plays a critical role in gatekeeping of executive control, it is no surprise that clinical conditions in which executive functions are impaired are often characterized by dysfunction of this brain region. Several theoretical accounts and comprehensive reviews have linked AI dysfunction to autism spectrum disorder (ASD), fronto-temporal dementia (FTD), and schizophrenia, positing that this dysfunction contributes transdiagnostically to deficits in executive functioning (Goodkind et al., 2015; Uddin, 2015). Here we will use these three clinical examples to illustrate how dysfunctional AI gatekeeping contributes to deficits in executive control.

5.1. Autism spectrum disorder

Executive function, which has a protracted development into adolescence and reflects the integration of multiple widely distributed brain networks (Uddin, 2021), is affected in individuals diagnosed with ASD, although there is considerable heterogeneity in executive function profiles in this population (Dajani et al., 2016). Uddin & Menon were the first to suggest that dysfunctional AI connectivity plays an important role in autism symptomatology (Uddin and Menon, 2009). In a recent review we highlighted how evidence has accumulated implicating atypical AI activity with executive dysfunction in ASD, particularly in younger individuals. The gatekeeping role of the AI that we propose accounts for how individuals with ASD might exhibit altered orientation towards salient information and subsequent SN dysfunction, leading to an inability to engage the CEN (Nomi et al., 2019). Additional empirical support for this model comes from findings demonstrating that neural signals derived from the AI during an attention task requiring executive control may be a potential biomarker that can discriminate ASD from typical development (Odriozola et al., 2016).

5.2. Frontotemporal dementia

Individuals with FTD experience neurodegeneration of the AI and ACC and have difficulties with problem solving and self-control (Miller et al., 1993). Strong links between AI functional connectivity and clinical severity in FTD have been documented (Day et al., 2013; Zhou et al., 2010). VENs appear to be selectively vulnerable in FTD, as documented in post-mortem quantitative neuroanatomical studies (Kim et al., 2012). In FTD, reduction in the volume of insular gray matter correlates with reduced expressive suppression ability, or the ability to conceal the outward expression of emotion that is already underway. This suggests that insular dysfunction in FTD underlies difficulties in executive control - particularly in the emotional domain (Muhtadie et al., 2021).

5.3. Schizophrenia

Schizophrenia, characterized by delusions and hallucinations that can be thought of as a loss of executive control, is consistently found to be associated with reduced gray matter in the insular cortex (Glahn et al., 2005). Recent studies investigating insular functional connectivity in individuals with schizophrenia also found an overall reduction in insula functional connectivity as well as reduced differentiation in connectivity profiles between insular subregions that was related to variability in clinical symptoms (Tian et al., 2019). Several studies using GCA to examine effective connectivity among brain regions in schizophrenia have reported that diagnosed individuals exhibit reduced strength of causal influence from the AI to the CEN and DMN (Moran et al., 2013; Palaniyappan et al., 2013).

These findings illustrate how dysfunction and/or disconnection of a critical gatekeeper in the AI can affect executive control across a range of clinical conditions. We suspect that similar insights regarding the crucial role of the AI to executive functioning will emerge from examination of other clinical populations in which executive control is compromised.

6. Future directions

The theory that the AI serves as a gatekeeper to executive control
permits the development of a novel framework guiding future basic cognitive neuroscience and clinical translational research. First, to further validate and support this claim, there is a role for direct recordings from the human cortex (intracranial electroencephalography, iEEG) in measuring the primacy of signals from the AI and the causal influence this brain region exerts on other frontoparietal networks for executive control. There is already emerging evidence from patients who are undergoing iEEG for monitoring epilepsy that AI activation occurs very early in the chain of events (Citherlet et al., 2020; Das and Menon, 2020). Future directions for the field include collecting and analyzing iEEG data using depth electrodes placed specifically within the AI (Bottan et al., 2020) to permit further validation of the anatomical specificity of our claim.

In the clinical transnational realm, the AI gatekeeping theory has implications for treatment of executive control deficits across a range of psychopathologies involving AI dysfunction. One can imagine that neurofeedback, transcranial magnetic stimulation, or ultrasound to target AI function might conceivably be conducted in clinical trials to assess the effects of altering activity in this brain region on executive control processes in these populations. It has previously been suggested that novel clinical insights will be gleaned from future work using neural signals derived from the insula to parse heterogeneity in complex neuropsychiatric conditions (Uddin, 2015). Considering the trans-diagnostic nature of AI dysfunction that results in deficits within the realm of executive functioning in ASD, FTD and schizophrenia, future studies should consider how to leverage this as a possible early biomarker of these, and other clinical conditions. Finally, tracking AI function and dysfunction may be relevant as well as for the study of resilience, a dynamic process of adaptation influenced by genetic and environmental factors (Molnar-Szakacs et al., 2020).

7. Conclusion
Buried within the lateral sulcus of the human brain and hidden from view, the insula has a unique functional profile at the intersection of the internal and external environment, at the crossroads of cortical and subcortical neural hierarchies, and as a functional lever at the juncture of the major large-scale functional brain networks. The insula receives sensory inputs from both inside and outside the body, and while some topographical localization of sensory regions is possible, all parts of the insula receive heavy cross-modal afferents and are best thought of as multimodal integration sites. The insula also has connections to the limbic system, the reward system, and frontal cortex implicated in cognitive, emotional, and executive functions, establishing a basis for cross-modal and cross-functional association that is reflected in the microstructural organization of the brain region itself. The widespread short- and long-range connections of the anterior subdivision of the insula with an extensive network of cortical and subcortical brain regions make it an ideal hub to coordinate the broad scope of sensory, emotional, motivational, and cognitive functions attributed to it. We have proposed that its role as a functional switch gating the temporal dynamics within large-scale neural networks makes the AI an effective regulatory convergence zone and critical gatekeeper to executive control. We have outlined supporting evidence to show how insular anatomy, microstructure and connectivity underpin the role of this unique island of cortex in integrating and prioritizing internal and external signals to guide and maintain adaptive behaviors. Demonstrating a temporal activation profile consistent with the role of a causal outflow hub coordinating temporal dynamics of activity across frontoparietal association cortices comprising executive control networks of the brain, the AI serves as gatekeeper of executive control.

Data Availability
No data was used for the research described in the article.

Acknowledgments
LQU is supported by the National Institute on Drug Abuse, USA (U01DA050987).

References
Ackermann, H., Riecker, A., 2010. The contribution (s) of the insula to speech production: a review of the clinical and functional imaging literature. Brain Struct. Funct. 214, 419-433.
Afif, Afi, A., Minotti, L., Kahane, P., Hoffmann, D., 2010. Anatomofunctional organization of the insular cortex: a study using intracerebral: electrical stimulation in epileptic patients. Epilepsia. https://doi.org/10.1111/j.1528-1167.2010.02755.x.
Allen, E.A., DamaraJu, E., Plii, S.M., Erhardt, E.B., Eichele, T., Calhoun, V.D., 2014. Tracking whole-brain connectivity dynamics in the resting state. Cereb Cortex 24, 2822-2832.
Allman, J.M., Watson, K.K., Tetreault, N.A., Hakeem, A.Y., 2005. Intuition and autism: a possible role for Von Economo neurons. Trends Cogn. Sci. 9, 367-373.
Allman, J.M., Tetreault, N.A., Hakeem, A.Y., Park, S., 2011b. The Von Economo neurons in apes and humans. Am. J. Hum. Biol. 23, 5-21.
Allman, J.M., Tetreault, N.A., Hakeem, A.Y., Manaye, K.F., Semendeferi, K., Erwin, J.M., Park, S., Goubert, H., Von, P.R., 2011a. The Von Economo neurons in the frontoinsular and anterior cingulate cortex. Ann. N. Y. Acad. Sci. 1225, 59-71.
Apps, M.A.J., Tsakiris, M., 2014. The free-energy self: a predictive coding account of self-recognition. Neurosci. Biobehav. Rev. 41, 85-97.
Augustine, J.R., 1996. Circuitry and functional aspects of the insular lobe in primates including humans. Brain Res. Brain Res. Rev. 22, 229-244.
Baldwin, J.V., Wilkins, D.P., Ogir, J., Willock, S., Drnȩk, N.F., 2011. Role of the precentral gyrus of the insula in complex articulation. Cortex 47, 800-807.
Banci, M.T., 2009. Executive function: the search for an integrated account. Curr. Dir. Psychol. Sci. 18, 89-94.
Barber, A.D., Smivaanra, P., Joel, S.E., Cafo, B.S., Pơkar, J.J., Monfoşky, S., 2011. Motor “dexterity”?: evidence that left hemisphere laterialization of motor circuit connectivity is associated with better motor performance in children. Cereb Cortex 22, 51-59.
Barrett, L.F., Kyle Simmons, W., 2015. Interoceptive predictions in the brain. Nat. Rev. Neurosci. https://doi.org/10.1038/nrnn9595.
Bartholini, C., 1645. Institutiones anatomicae, novis recentiorum opinionibus assortata. Acad. Fennicae Helvetica. Apud Francom Hacken.
Cereda, C., Ghika, J., Maeder, P., Bogousslavsky, J., 2002. Strokes restricted to the insular cortex. Neurology. https://doi.org/10.1212/01.wnl.0000038965.75660.bd.

Cerliani, L., Thompson, D., Sabo, S., Siero, J.C., Nakayama, H., Gazzolo, V., D’Arceuil, H., Keysers, C., 2012. Probabilistic tractography recovers a rostrocaudal trajectory of connectivity variability in the human insular cortex. Hum Brain Mapp. 33, 2005-2013.

Chang, C., Glover, G.H., 2010. Time-frequency dynamics of rest-state brain connectivity measured with fMRI. Neuroimage 50, 81–98.

Chang, L.J., Yarkoni, T., kwah, M.W., Saney, A.G., 2013. Decoding the role of the insula in human cognition: functional parcellation and large-scale reverse inference. Cereb. Cortex 23, 793-797.

Chee, M.W.L., Soon, C.S., Lee, H.L., Pallier, C., 2004. Left insula activation: a marker for language attainment in bilinguals. Proc Natl Acad Sci. https://doi.org/10.1073/pnas.1047361139.

Chee, M.W.L., Soon, C.S., Lee, H.L., Pallier, C., 2004. Left insula activation: a marker for language attainment in bilinguals. Proc Natl Acad Sci. https://doi.org/10.1073/pnas.1047361139.

Cheong, C.A., Oates, D.J., Chang, C., Bradley, T., Zhou, Z.-W., Williams, L.M., Glover, G.H., Deisseroth, K., Etkin, A., 2013. Causal interactions between fronto-parietal cental executive and default-mode networks in humans. Proc. Natl Acad. Sci. U.S.A 110, 19944-19949.

Clark, E., O’Malley, C.D., 1996. The Human Brain and Spinal Cord: A Historical Study Illustrated by Writings from Antiquity to the Twentieth Century. Norman Publishing.

Clarke, N., Ayikian, A., Martino, J., Davis, N.J., Hink, N.M., Kenworthy, L., 2016. Surface anatomy of the human insula and its patterns of structural connectivity: evidence from in vivo probabilistic tractography. Neuroimage 59, 3514–3521.

Cole, M.W., Schneider, W., 2007. The cognitive control network: integrated cortical regions with dissociable functions. Neuroimage 37, 434–436.

Corbetta, M., Kincade, J.M., Shulman, G.L., 2002. Neural systems for visual orienting and their relationships to spatial working memory. J. Cogn. Neurosci. 14, 508–523.

Corbetta, M., Patel, G., Shulman, G.L., 2008. The reorienting system of the human brain: from environment to theory of mind. Neurol. 58, 306–324.

Craig, A.D., 2005. Forebrain emotional asymmetry: a neuroanatomical basis? Trends Cogn. Sci. 9, 566–571.

Craig, A.D., 2009. How do you feel - now? The anterior insula and human awareness. Trends Neurosci. 32, 151–158.

Craig, A.D., 2011. Significance of the insula for the evolution of human awareness of feelings from the body. Nat. Rev. Neurosci. 12, 571.

Craig, A.D., 2009. How do you feel - now? The anterior insula and human awareness. Trends Neurosci. 32, 151–158.

Critchley, H.D., 2004. The human cortex responds to an interoceptive challenge. Proc. Natl Acad. Sci. U.S.A 101 (17), 6333-6338.

Critchley, H.D., Harrison, N.A., 2013. Visceral influences on brain and behavior. Neuron 79, 624-638.

Critchley, H.D., McCullagh, J., Dartnall, S., Dolan, R.J., 2003. The human insula cortex responds to an interoceptive challenge. J. Neurosci. 23, 186-204.

Critchley, H.D., McCullagh, J., Dartnall, S., Dolan, R.J., 2003. The human insula cortex responds to an interoceptive challenge. J. Neurosci. 23, 186-204.

Critchley, H.D., Melmed, R.N., Dragojevic, S., Dolan, R.J., 2009. Volitional control of autonomic arousal: a functional magnetic resonance study. Neuroimage 19, 1099-1109.

Critchley, H.D., Harrison, N.A., 2013. Visceral influences on brain and behavior. Neuron 77, 624-638.

Critchley, H.D., McCullagh, J., Dartnall, S., Dolan, R.J., 2003. The human insula cortex responds to an interoceptive challenge. J. Neurosci. 23, 186-204.

Critchley, H.D., McCullagh, J., Dartnall, S., Dolan, R.J., 2003. The human insula cortex responds to an interoceptive challenge. J. Neurosci. 23, 186-204.

Critchley, H.D., McCullagh, J., Dartnall, S., Dolan, R.J., 2003. The human insula cortex responds to an interoceptive challenge. J. Neurosci. 23, 186-204.

Critchley, H.D., McCullagh, J., Dartnall, S., Dolan, R.J., 2003. The human insula cortex responds to an interoceptive challenge. J. Neurosci. 23, 186-204.

Critchley, H.D., McCullagh, J., Dartnall, S., Dolan, R.J., 2003. The human insula cortex responds to an interoceptive challenge. J. Neurosci. 23, 186-204.

Critchley, H.D., McCullagh, J., Dartnall, S., Dolan, R.J., 2003. The human insula cortex responds to an interoceptive challenge. J. Neurosci. 23, 186-204.

Critchley, H.D., McCullagh, J., Dartnall, S., Dolan, R.J., 2003. The human insula cortex responds to an interoceptive challenge. J. Neurosci. 23, 186-204.

Critchley, H.D., McCullagh, J., Dartnall, S., Dolan, R.J., 2003. The human insula cortex responds to an interoceptive challenge. J. Neurosci. 23, 186-204.

Critchley, H.D., McCullagh, J., Dartnall, S., Dolan, R.J., 2003. The human insula cortex responds to an interoceptive challenge. J. Neurosci. 23, 186-204.

Critchley, H.D., McCullagh, J., Dartnall, S., Dolan, R.J., 2003. The human insula cortex responds to an interoceptive challenge. J. Neurosci. 23, 186-204.
