



Published in final edited form as:

J Clin Neurophysiol. 2017 July ; 34(4): 300–306. doi:10.1097/WNP.0000000000000377.

Structure and function of the human insula

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Abstract

The insular cortex, or “Island of Reil”, is hidden deep within the lateral sulcus of the brain. Subdivisions within the insula have been identified on the basis of cytoarchitectonics, sulcal landmarks, and connectivity. Depending on the parcellation technique employed, the insula can be divided into anywhere between 2 and 13 distinct subdivisions. The insula subserves a wide variety of functions in humans ranging from sensory and affective processing to high-level cognition. Here we provide a concise summary of known structural and functional features of the human insular cortex with a focus on lesion case studies and recent neuroimaging evidence for considerable functional heterogeneity of this brain region.

Insula structure and connectivity

Location

The insular cortex is located deep within the lateral sulcus of the brain. Also known as the “Island of Reil” based on its initial discovery by Johann Christian Reil in 1809, the insula is a region of cortex not visible from the surface view. Traditionally, the insular cortex has been described as paralimbic or limbic integration cortex¹.

Gyral subdivision and anatomic definitions

The insula is mostly surrounded by the peri-insular sulcus, and is divided in two by the central insular sulcus. Though there is some variability in insular gyri number, the more anterior portion of the insula is typically comprised of the anterior, middle, and posterior short insular gyri, which are separated by the anterior and precentral insular sulcus. The posterior portion of the insula is comprised of the anterior and posterior long insular gyri, separated by the postcentral insular sulcus² (Figure 1).

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Vascularization

Here we provide a brief description of the vascularization of the insula. The insular cortex is hidden under dense arterial and venous blood vessels, making it somewhat difficult to operate on. Arterial supply of the insula is provided by the M2 segment of the middle cerebral artery (MCA) through perforating vessels. These vessels arise at the inferior part of the insula and follow the insular sulci. The superior trunk of the MCA supplies the anterior, middle, and posterior short gyri and the inferior trunk supplies the posterior long gyrus. Venous blood of the insula drains mainly to the deep middle cerebral vein².

Cytoarchitecture, structural and functional connectivity

Some of the earliest work on the human insula provided evidence for a posterior granular area and an anterior dysgranular area separated by the central insular sulcus^{3, 4}. The only study to comprehensively analyze the cytoarchitecture of the human posterior insula using an observer-independent approach points to the existence of three distinct areas therein; two granular areas referred to as Ig1 and Ig2 (“insular lobe granular areas”) found in the dorsal posterior insula, and a dysgranular area labeled Id1 (“d” for dysgranular area) found in the ventral posterior insula⁵. Similarly detailed cytoarchitectonic mapping has not yet been undertaken in the human anterior insula.

Most of the information regarding structural connectivity of the insula is derived from what is known regarding its anatomy in the macaque monkey. Early studies investigating structural connections of the insula in the macaque utilized invasive direct cortical stimulation and ablation techniques. 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, heart beat, blood pressure, and saliva/mucus production⁶. This suggested direct structural connections between the insula and motor cortices and well as with the autonomic nervous system. Ablation techniques identified connections of the insula through neural degeneration related to surgically induced insular lesions. Structural white matter degeneration in response to insula ablations were found in the external and extreme capsules, corona radiata, corpus collosum, anterior commissure, and superior/inferior longitudinal fasciculi; these white matter tracts connect the insula with frontal, parietal, temporal, cingulate, olfactory, and subcortical brain areas such as the hippocampus and amygdala⁶. Later macaque studies utilized tracer techniques to identify structural connections from the insula to the frontal cortex, olfactory cortex, parietal lobe, cingulate cortex, somatosensory cortices, and the temporal lobe⁷. Such tracer studies also 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 while posterior portions had a greater number of connections to cingulate and parietal cortices. Additionally, only the anterior insula had connections to the olfactory cortex.

In humans, *in-vivo* diffusion weighted imaging studies have demonstrated anterior-posterior differences in insular structural connections similar to those found in the macaque. The anterior portion of the insula primarily has connections with the anterior cingulate, frontal, orbitofrontal, and anterior temporal areas while the posterior insula primarily has connections with posterior temporal, parietal, and sensorimotor areas⁸⁻¹¹. Diffusion studies

have also identified a mid-insula “transitional area” that demonstrates structural connections similar to both anterior and posterior insula cortices^{8, 9}.

Functional connectivity (e.g. temporal correlation in blood-oxygen-level-dependent signal)¹² of the human insular cortex has been examined using resting state fMRI, which measures intrinsic, spontaneous correlations among brain areas¹⁵. These functional connectivity studies provide evidence for at least three distinct subdivisions within the human insula. A dorsal anterior insula (dAI) region with connections to frontal, anterior cingulate, and parietal areas is involved in cognitive control processes, a ventral anterior insula (vAI) subdivision has connections with limbic areas and is involved in affective processes, and a mid-posterior insula (PI) subdivision has connections with brain regions for sensorimotor processing¹⁷⁻¹⁹. Using dynamic functional network connectivity (dFNC) analyses to examine time-varying properties of interactions between insular subdivisions and other brain regions, it has been demonstrated that the dAI exhibits more variable connections than the other insular subdivisions²⁰. This is in line with earlier work demonstrating functional “diversity” of the dAI, which is active across multiple task domains¹⁹.

Time-varying dFNC analyses and static analyses have also demonstrated that the three functionally distinct insula subdivisions can also act in concert to integrate information within and across cognitive, affective, visual, and sensorimotor networks during an fMRI scan^{19, 20}. Thus, the three aforementioned insula subdivisions can operate both independently and cooperatively, demonstrating how the insula can be both specialized and integrative. This may help to explain how the insula serves as a network hub that coordinates information across multiple cognitive domains and processes.

In the most comprehensive multi-modal whole-brain parcellation study to date, Glasser and colleagues²¹ delineated 13 insular/frontal operculum subdivisions on the basis of a combination of features derived from resting state fMRI, task fMRI, myelin maps, and cortical thickness. In their parcellation scheme these areas are labeled 52, PI (ParaInsular cortex), Ig (Insula granular), Posterior Insular areas PoI1 and PoI2, Frontal Opercular areas FOP2 and FOP3, a Middle Insular area MI, an Anterior Ventral Insular area AVI, an Anterior Agranular Insular Complex AAIC, the Piriform cortex Pir, and Frontal Opercular areas FOP4 and FOP5 (Figure 2).

Insula function

The insula is one of the least understood brain regions. This is mainly 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 lesions²². Among the first insights about the role of the human insula came from the seminal works by Wilder Penfield using electro-cortical stimulation, in the mid-20th century²³. After removal of the temporal lobe for the treatment of drug-refractory seizures in patients suffering from epilepsy, stimulation of the exposed inferior portion of the insular cortex elicited a variety of visceral sensory and motor responses, as well as somatic sensory responses, especially in the face, tongue, and upper limbs. This contributed to the conception of the insula as a primarily visceral-somatic region. While recent investigations have replicated these findings, other types of sensory and motor

responses were also documented, thanks to a more complete coverage of the insular cortex by intracranial electrodes^{24–26}, suggesting a role beyond visceral-somatic processing.

Interest in the function of the insular cortex has increased drastically since the advent of functional neuroimaging techniques, which revealed insular activation in response to a wide variety of stimuli and paradigms, often unexpectedly. A meta-analysis of nearly 1,800 functional neuroimaging experiments by Kurth and colleagues⁵ suggested the existence of four functionally distinct regions in the human insula: 1) a sensorimotor region located in the mid-posterior insula; 2) a central-olfactogustatory region; 3) a socio-emotional region in the anterior-ventral insula; and 4) a cognitive anterior-dorsal region. Although these functional subdivisions probably represent an oversimplification of the actual functional neuroanatomy of the insula¹⁹, this broad categorization helps understand the main functions attributed to the insula in relation to its connectivity with other brain areas.

Sensorimotor processing

Visceral sensations, autonomic control, and interoception—Early reports of a large proportion of visceral responses elicited by direct electro-cortical stimulation of the insula prompted researchers to dub the insula the ‘visceral brain’²³. In recent years, tract-tracing studies have supported the view of a central viscerosomatosensory role for the insula, which is now known to receive visceral afferent projections conveying interoceptive information from all over the body²⁷. Later studies of direct electro-cortical stimulation confirmed Penfield’s findings^{25, 26, 28}. Visceral sensations were described as unpleasant feelings of constriction ranging from a simple breathing discomfort to painful paresthesia, and motor responses included borborygmi and vomiting. This role in visceral processing has led researchers to posit that the insula could also play an important role in the regulation of autonomic function. This conjecture is supported by reports of heart rate and blood pressure changes following electrical stimulation and focal lesions of the insula^{29, 30}.

Beyond visceral information processing, it has been proposed that the insula plays a broader role in interoception, i.e., the sense of the physiological condition of the body²⁷. Indeed, functional neuroimaging studies have reported heightened insular activation when participants are made aware of their thirst, heartbeat, and distention of the esophagus, stomach, bladder, or rectum^{27, 31}. Congruently, insular lesions have been associated with delayed moment-to-moment awareness of cardiovascular sensations and with anosognosia for hemiplegia/hemiparesis^{32, 33}. Craig³¹ proposed a posterior-to-anterior progression of integration of visceral information in the insula, whereby the primary interoceptive signals are first represented in its posterior portion, then abstracted in the mid and anterior parts, where integrated perceptual maps of the organism state are more refined.

Somatic processing and pain—Somatosensory manifestations represent a large proportion of responses elicited by electrical stimulation of the insular cortex in humans³⁴. These include paresthesia such as tingling, electric, warm, cold, shiver, and constriction sensations, predominantly in the contralateral face and arm regions, although ipsilateral, bilateral, and midline regions may be involved. Painful somatic sensations (e.g., pinprick, burning) are also regularly obtained^{24, 26, 35}. In neuroimaging studies, both non-painful

tactile and painful stimulation lead to insular activation³⁶. The role of the posterior insula in thermosensory function and pain have received considerable attention. In a seminal PET study, Craig and colleagues³⁷ showed that the intensity of graded cooling of the right hand correlated with activity in the dorsal margin of the contralateral middle/posterior insula, but not in the parietal somatosensory regions, suggesting that the thermosensory cortex is located in the insula. This has been supported by isolated deficits in temperature perception following lesions of the posterior insula³⁸. The posterior insula is also thought to play a fundamental role in pain perception, showing consistent activation in response to noxious stimuli in neuroimaging studies, irrelevant of modality or body part^{39, 40}. Interestingly, strokes and cortical resections involving the posterior insula and the innermost parietal operculum have been associated with a central pain syndrome with dissociated contralateral thermoalgesic sensory loss⁴¹, suggesting an intimate relation between the thermal and nociceptive functions of the insula.

Auditory processing—Involvement of the insular cortex in central auditory processing is not surprising given the efferent projections it receives from the primary auditory, auditory association, and post-auditory cortices¹. As such, auditory responses – mostly illusions and distortions – have been reported following electrical stimulation of the lower posterior part of the insula^{24, 25, 28}. Insular activation is also typically observed in functional neuroimaging paradigms involving sound detection, auditory temporal processing, and non-verbal stimuli and phonological processing⁴². Congruently, central auditory deficits following isolated insular lesions are relatively frequent. In a study of eight patients with strokes affecting the insula, all patients were found to have central auditory deficits including temporal resolution and sequencing deficits⁴³. Hyperacusis (i.e., increased sensitivity to sounds), as revealed by decreased loudness discomfort levels, was also documented after isolated insular stroke and following insular resection as part of epilepsy surgery⁴⁴, suggesting a role in auditory intensity processing. More anecdotic auditory impairments that have been reported include unilateral deficits in processing speech sounds⁴⁵ and non-verbal auditory agnosia⁴⁶.

Chemosensory functions—The primary gustatory area in nonhuman primates is located in the anterior insula and adjoining frontal operculum, and functional neuroimaging studies suggest that it is located somewhat more caudally in humans, probably in the mid-insula⁴⁷. The insula is thought to be involved in processing the intensity, quality, and affective value of taste stimuli^{47, 48}. However, precise localization of the primary gustatory cortex in the insula is complicated by the fact that the same region is also involved in oral somatosensory processing and in higher order processes related to attention to taste and expectations⁴⁹. The role of the insula in primary processing of taste is further supported by the fact that electrocortical stimulation of the short insular gyri or mid-insular cortex may elicit gustatory hallucinations, such as metallic or bitter taste^{26, 28, 34}. A few case studies have also reported taste deficits following insular damage, including ipsi- and bilateral taste recognition and intensity deficits^{50, 51}.

The insula is also involved in olfaction, although its specific role is less clearly established. In functional neuroimaging studies, the insula is consistently activated by olfactory stimuli, along with other regions including the piriform and orbitofrontal cortex, the amygdala, and

the ventral putamen⁵². Increased contralateral sensitivity to odors and taste has previously been reported following left posterior insular stroke⁵³. Interestingly, odor intensity changes were more pronounced for unpleasant odors. Increased sensitivity to odors has also been reported by an epileptic patient following right insular resection⁴⁴, which may suggest a role in modulating the intensity of olfactory stimuli.

Vestibular function—The involvement of the parietal operculum-insular region in vestibular processing is supported by various findings. Vestibular responses have been elicited by posterior insular stimulation³⁵. Recent activation likelihood estimation meta-analyses identified the posterior parietal operculum and retroinsular region as crucial regions for central vestibular processing^{54, 55}. Whether the posterior insula per se plays an essential role in vestibular processing remains, however, equivocal. To our knowledge, only one case study reported vestibular symptoms (i.e., vertigo and imbalance) following isolated insular damage, and the damage was unexpectedly localized in the anterior portion of the insula⁵⁶. In a study of 10 consecutive cases of acute unilateral stroke restricted to the insula, none of the patients displayed vestibular otolith dysfunction nor vertigo⁵⁷.

Socio-emotional processing

Emotional experience—The James-Lange theory of emotion posits that emotional feelings are activated by bodily changes evoked by emotional stimuli, emphasizing the importance of internal body sensations on the subjective experience of emotions^{58, 59}. As a cortical center of visceral information processing and interoception, the anterior insula is thought to play a crucial role in emotional experience and subjective feelings²⁷. Indeed, inter-individual differences in interoceptive sensitivity correlate with reports of negative emotional experience, both of which are predicted by right anterior insular activation while paying attention to internal bodily processes⁶⁰. Furthermore, functional neuroimaging employing emotionally arousing stimuli such as disgusting, scaring, happy, sad, or sexual pictures, have also consistently reported activation in the insula³¹.

Cerebral damage involving the insula has been associated with a variety of alterations of subjective emotional experience. Calder et al.⁶¹ first described the case of a young adult patient who manifested a specific impairment in the experience and recognition of the emotion of disgust following a left hemisphere infarction involving insula and basal ganglia. Other studies, however, did not find such a specific impairment in disgust experience following insular lesions. Borg and colleagues⁶² reported the fascinating case of a rare patient who reported her emotions as less intense and who developed a new compulsive need to paint following stroke in the left posterior insula-SII territory. Studies using voxel-based lesion-symptom mapping in patients with traumatic brain injury have associated insular lesions with apathy⁶³, and anxiety⁶⁴.

Empathy and social cognition—Empathy is the ability to perceive, understand and experience others' feelings in relation to oneself, implying an emotional and cognitive response⁶⁵. To be processed and felt, this emotion entails interoception and self-awareness to relate to another's feeling, as well as social cognition and the sensorimotor system for subjective feeling and social interaction, all are functions relating to the insula^{31, 65–67}. The

role of the anterior insula in empathy has been supported by numerous neuroimaging studies reporting activation in response to others in pain (e.g. painful physical or thermal heat stimuli) and to expressions of disgust, fear, anxiety, and happiness. In a meta-analysis of fMRI studies on empathy, Fan et al.⁶⁸ found that the right anterior insula was associated with the affective-perceptual form of empathy, while the left insula was associated with both the affective-perceptual and cognitive-evaluative forms of empathy. The role of the insula in empathy and social cognition has been confirmed in lesion studies. In a voxel-based lesion-symptom mapping study conducted in a large group of patients with focal penetrating traumatic brain injury, lesions localized were associated in the left insula difficulties recognizing both unpleasant and pleasant emotions⁶⁹. Contrasting with earlier reports of a specific impairment in disgust recognition⁶¹, a consecutive study of 15 patients who underwent insular resection as part of epilepsy surgery reported significant impairments in recognizing facial expressions of fear, happiness, and surprise, but not disgust⁷⁰. A recent study using intraoperative stimulation in awake patients undergoing neurosurgery for removal of a glioma showed that stimulation of the left insula altered the ability to recognize emotions in facial expressions, which turned out to be statistically significant only for the emotion of disgust⁷¹. Taken together, these studies enlighten the important role of the left anterior insula in social affect, such as empathy, to distinguish primordial emotions like disgust, fear and happiness.

Risky decision making—Decisions under uncertainty are the result of both rational and emotional drives, which is illustrated by the influence of affective states and of judgement biases on decision making^{72, 73}. The ‘somatic marker’ hypothesis posits that emotions influence the decision process through internal sensations, visceral, and musculoskeletal physiologic changes which are associated with reinforcing stimuli⁷⁴. Given its role in viscerosensory processing and its connexions with the orbitofrontal cortex – a key structure in the decision-making circuitry – the insula is likely to play a critical role in risky decisions. This is supported by robust insular activation revealed by neuroimaging during gambling tasks, in which decisions must be made between options associated with uncertain outcomes (e.g.,^{75, 76}). In an fMRI experiment, anterior insular activation has been found to mediate the relationship between mood state and decision bias⁷⁷. Despite limited by small sample size and heterogeneity in the extent of cerebral damage, a growing number of studies using gambling tasks in patients with insular lesions have reported decision making deficits. The gambler’s fallacy and near-miss effects, two types of cognitive biases affecting decision making in healthy individuals, were found to be absent in stroke patients with insular damage⁷⁸. In a group of patients who underwent selective operculo-insular resection for drug-resistant epileptic seizures, sensitivity to expected value when making risky vs. safe decisions was found to be selectively impaired when facing a potential loss⁷⁹, consistent with a role in loss aversion⁸⁰. Taken together, these findings suggest that the insula is actively involved in the emotional aspects of risky decision making.

Cognitive functions

Attention and salience processing—The insula is one of the most popular brain regions in cognitive neuroscience, with a high likelihood of activation across various states⁸¹. One of the most consistent findings with respect to insula function is its

involvement in detection of novel stimuli across sensory modalities. Insula activation, along with dorsal anterior cingulate (dACC), is observed in response to “oddball” stimuli interspersed among a series of the same item^{82, 83}. Together, the insula and dACC, amygdala, and other subcortical structures are often referred to as the “salience network”, the function of which is to identify the most homeostatically relevant among multiple competing internal and external stimuli⁸⁴. Analysis of effective or causal connectivity across auditory, visual, and task-free conditions demonstrate that the dorsal anterior insula causally influences other large-scale brain networks including the default mode network (DMN, underlying self-related and social cognitive processes) and central executive network (CEN, which implements the maintenance and manipulation of information and decision-making)⁸⁵. In tasks requiring greater cognitive control, the dAI exerts stronger causal influence⁸⁶. Taken together, the body of available empirical work suggests that the dAI is in a position to integrate external sensory information with internal emotional and bodily state signals to coordinate brain network dynamics and to initiate switches between the DMN and CEN⁸⁷.

Speech—Although the contribution of Broca’s area to language production is undisputed, there is considerable evidence suggesting that the insular cortex is also involved in speech, although controversy remains concerning the nature of its contribution(s). Dronkers⁸⁸ found that the left precentral insular gyrus was damaged in all of her stroke patients suffering from apraxia of speech, suggesting a role in the motor planning of speech. This was supported later by a voxel-based lesion symptom mapping study which showed that performance on an articulation task was dependent on the left precentral insular gyrus⁸⁹. However, although speech deficits have been reported following isolated left insular strokes and resections, patients most often fully recover in days or weeks following lesion^{22, 90}, which questions the critical role of the left insula in speech production. Furthermore, the contribution of the insula to speech may not be confined to the dominant hemisphere, as right posterior insula damage has also been related to dysarthria⁹¹. Congruently, electric stimulation of the insular cortex from both hemispheres has also been associated with speech arrest, dysarthria, and reduced voice intensity^{24, 25, 34}. In their study of 10 patients with isolated insular stroke, Baier et al.⁵⁷ reported that only those with left hemisphere damage showed aphasia during the acute period, while damage to either of the hemispheres displayed dysarthria. In a group of 18 epileptic patients who underwent insulectomy, although expressive aphasia was observed in the post-surgery period in patients with left hemisphere resections, the only statistically significant long-lasting (> 6 months) deterioration on a standard neuropsychological assessment battery was a slight delay in oro-motor speed, and this effect was also present when analyses were restricted to right-hemisphere surgeries⁷⁰. In conclusion, the insula appears to be involved in speech production, but whether this role is critical or secondary (e.g., through higher-order articulatory processes), remains unclear⁹².

Summary

Though hidden from view, the insula contributes to multiple functions critical for human cognition and behavior. The summary of human insular cortex structure and function provided here suggests a need to go beyond the initial characterization of the insula as

limbic cortex to include a variety of other functions ranging from sensorimotor, pain, and socio-emotional processes to high-level attention and decision making.

Acknowledgments

This work was supported by R01MH107549 from the National Institute of Mental Health and a NARSAD Young Investigator Grant to LQU. We thank Dr. Tram Nguyen for providing the insula illustration in Figure 1.

References

1. Augustine JR. Circuitry and functional aspects of the insular lobe in primates including humans. *Brain Res Rev.* 1996; 22:229–244. [PubMed: 8957561]
2. Mavridis, IN. *Insula: Neuroanatomy, Functions and Clinical Disorders.* Nova Science Publishers; New York, NY: 2014. Gross, functional and neurosurgical anatomy of the human insula: From basic science to clinical practice.
3. Brodmann, K. *Vergleichende Lokalisationslehre der Grosshirnrinde (in German).* Leipzig: Johann Ambrosius Barth; 1909.
4. Economo, C., Koskinas, GN. *Die Cytoarchitektonik der Hirnrinde des erwachsenen Menschen (in German).* Wien & Berlin: Springer; 1925.
5. Kurth F, Zilles K, Fox PT, Laird AR, Eickhoff SB. A link between the systems: functional differentiation and integration within the human insula revealed by meta-analysis. *Brain Struct Funct.* 2010; 214:519–537. 2010. [PubMed: 20512376]
6. Showers MJC, Lauer EW. Somatovisceral motor patterns in the insula. *J Comp Neurol.* 1961; 117:107–115. [PubMed: 13912292]
7. Mufson EJ, Mesulam M. Insula of the old world monkey. II: Afferent cortical input and comments on the claustrum. *J Comp Neurol.* 1982; 212:23–37. [PubMed: 7174906]
8. Cerliani L, Thomas RM, Jbabdi S, Siero JC, Nanetti L, Crippa A, Gazzola V, D’Arceuil H, Keysers C. Probabilistic tractography recovers a rostrocaudal trajectory of connectivity variability in the human insular cortex. *Hum Brain Mapp.* 2012; 33:2005–2034. [PubMed: 21761507]
9. Cloutman LL, Binney RJ, Drakesmith M, Parker GJ, Lambon Ralph MA. The variation of function across the human insula mirrors its patterns of structural connectivity: evidence from in vivo probabilistic tractography. *Neuroimage.* 2012; 59:3514–3521. [PubMed: 22100771]
10. Ghaziri J, Tucholka A, Girard G, et al. The corticocortical structural connectivity of the human insula. *Cereb Cortex.* Epub 2015 Dec 18.
11. Uddin LQ, Supekar KS, Ryali S, Menon V. Dynamic reconfiguration of structural and functional connectivity across core neurocognitive brain networks with development. *J Neurosci.* 2011; 31:18578–18589. [PubMed: 22171056]
12. Friston KJ, Holmes AP, Worsley KJ, Poline JP, Frith CD, Frackowiak RS. Statistical parametric maps in functional imaging: a general linear approach. *Hum brain mapp.* 1994:189–210.
13. Biswal B, Yetkin FZ, Haughton VM, Hyde JS. Functional connectivity in the motor cortex of resting human brain using echo-planar MRI. *Magnetic resonance in medicine: official journal of the Society of Magnetic Resonance in Medicine/Society of Magnetic Resonance in Medicine.* 1995; 34:537–541.
14. Chang LJ, Yarkoni T, Khaw MW, Sanfey AG. Decoding the role of the insula in human cognition: functional parcellation and large-scale reverse inference. *Cereb Cortex.* 2013; 23:739–749. [PubMed: 22437053]
15. Deen B, Pitskel NB, Pelphrey KA. Three systems of insular functional connectivity identified with cluster analysis. *Cereb Cortex.* 2011; 21:1498–1506. [PubMed: 21097516]
16. Uddin LQ, Kinnison J, Pessoa L, Anderson ML. Beyond the tripartite cognition-emotion-interoception model of the human insular cortex. *J Cogn Neurosci.* 2014; 26:16–27. [PubMed: 23937691]

17. Nomi JS, Farrant K, Damaraju E, Rachakonda S, Calhoun VD, Uddin LQ. Dynamic functional network connectivity reveals unique and overlapping profiles of insula subdivisions. *Hum Brain Mapp.* 2016; 37:1770–1787. [PubMed: 26880689]
18. Glasser MF, Coalson TS, Robinson EC, Hacker CD, Harwell J, Yacoub E, Ugurbil K, Andersson J, Beckmann CF, Jenkinson M, Smith SM, Van Essen DC. A multi-modal parcellation of the human cerebral cortex. *Nature.* 2016; 536(7615):171–178. [PubMed: 27437579]
19. Cereda C, Ghika J, Maeder P, Bogousslavsky J. Strokes restricted to the insular cortex. *Neurology.* 2002; 59:1950–1955. [PubMed: 12499489]
20. Penfield W, Faulk ME. The insula. Further observations on its function. *Brain.* 1955; 78:445–470. [PubMed: 13293263]
21. Afif A, Minotti L, Kahane P, Hoffmann D. Anatomofunctional organization of the insular cortex: a study using intracerebral electrical stimulation in epileptic patients. *Epilepsia.* 2010; 51:2305–2315. [PubMed: 20946128]
22. Isnard J, Guénot M, Sindou M, Mauguière F. Clinical manifestations of insular lobe seizures: a stereo-electroencephalographic study. *Epilepsia.* 2004; 45:1079–1090. [PubMed: 15329073]
23. Stephani C, Fernandez-Baca Vaca G, Maciunas R, Koubeissi M, Lüders HO. Functional neuroanatomy of the insular lobe. *Brain Struct Funct.* 2011; 216:137–149. [PubMed: 21153903]
24. Craig AD. How do you feel? Interoception: the sense of the physiological condition of the body. *Nat Rev Neurosci.* 2002; 3:655–666. [PubMed: 12154366]
25. Nguyen DK, Nguyen DB, Malak R, et al. Revisiting the role of the insula in refractory partial epilepsy. *Epilepsia.* 2009; 50:510–520. [PubMed: 18717706]
26. Oppenheimer SM, Gelb A, Girvin JP, Hachinski VC. Cardiovascular effects of human insular cortex stimulation. *Neurology.* 1992; 42:1727–1732. [PubMed: 1513461]
27. Tayah T, Savard M, Desbiens R, Nguyen DK. Ictal bradycardia and asystole in an adult with a focal left insular lesion. *Clin Neurol Neurosurg.* 2013; 115:1885–1887. [PubMed: 23643181]
28. Craig AD. How do you feel — now? The anterior insula and human awareness. *Nat Rev Neurosci.* 2009; 10:59–70. [PubMed: 19096369]
29. Karnath HO, Baier B, Nagele T. Awareness of the functioning of one's own limbs mediated by the insular cortex? *J Neurosci.* 2005; 25:7134–7138. [PubMed: 16079395]
30. Khalsa SS, Rudrauf D, Feinstein JS, Tranel D. The pathways of interoceptive awareness. *Nat Neurosci.* 2009; 12:1494–1496. [PubMed: 19881506]
31. Pugnaghi M, Meletti S, Castana L, et al. Features of somatosensory manifestations induced by intracranial electrical stimulations of the human insula. *Clin Neurophysiol.* 2011; 122:2049–2058. [PubMed: 21493128]
32. Mazzola L, Isnard J, Peyron R, Guénot M, Mauguière F. Somatotopic organization of pain responses to direct electric stimulation of the human insular cortex. *Pain.* 2009; 146:99–104. [PubMed: 19665303]
33. zu Eulenburg P, Baumgärtner U, Treede RD, Dieterich M. Interoceptive and multimodal functions of the operculo-insular cortex: tactile, nociceptive and vestibular representations. *Neuroimage.* 2013; 83:75–86. [PubMed: 23800791]
34. Craig AD, Chen K, Bandy D, Reiman EM. Thermosensory activation of insular cortex. *Nat Neurosci.* 2000; 3:184–190. [PubMed: 10649575]
35. Baier B, zu Eulenburg P, Geber C, et al. Insula and sensory insular cortex and somatosensory control in patients with insular stroke. *Eur J Pain.* 2014; 18:1385–1393. [PubMed: 24687886]
36. Jensen KB, Regenbogen C, Ohse MC, Frasnelli J, Freiherr J, Lundström JN. Brain activations during pain: a neuroimaging meta-analysis of patients with pain and healthy controls. *Pain.* 2016; 157:1279–1286. 2016. [PubMed: 26871535]
37. Segerdahl AR, Mezue M, Okell TW, Farrar JT, Tracey I. The dorsal posterior insula subserves a fundamental role in human pain. *Nat Neurosci.* 2015; 18:499–500. [PubMed: 25751532]
38. Garcia-Larrea L, Perchet C, Creac'h C, et al. Operculo-insular pain (parasylyvian pain): a distinct central pain syndrome. *Brain.* 2010; 133:2528–2539. [PubMed: 20724291]
39. Bamiou DE, Musked FE, Luxon LM. The insula (Island of Reil) and its role in auditory processing. Literature review. *Brain Res Rev.* 2003; 42:143–154. [PubMed: 12738055]

40. Bamiou DE, Musiek FE, Stow I, et al. Auditory temporal processing deficits in patients with insular stroke. *Neurology*. 2006; 67:614–619. [PubMed: 16924014]
41. Boucher O, Turgeon C, Champoux S, et al. Hyperacusis following unilateral damage to the insular cortex: a three-case report. *Brain Res*. 2015; 1606:102–112. [PubMed: 25721796]
42. Fifer RC. Insular stroke causing unilateral auditory processing disorder: case report. *J Am Acad Audiol*. 1993; 4:364–369. [PubMed: 8298171]
43. Spreen O, Benton AL, Fincham RW. Auditory agnosia without aphasia. *Arch Neurol*. 1965; 13:84–92. [PubMed: 14314279]
44. Small DM. Taste representation in the human insula. *Brain Struct Func*. 2010; 214:551–561.
45. Small DM, Gregory MD, Mak YE, Gitelman D, Mesulam MM, Parrish T. Dissociation of neural representation of intensity and affective valuation in human gustation. *Neuron*. 2003; 39:701–711. [PubMed: 12925283]
46. Rolls ET. Functions of the anterior insula in taste, autonomic, and related functions. *Brain Cogn*. Epub 2015 Aug 12.
47. Pritchard TC, Macaluso DA, Eslinger PJ. Taste perception in patients with insular cortex lesions. *Behav Neurosci*. 1999; 113:663–671. 1999. [PubMed: 10495075]
48. Stevenson RJ, Miller LA, McGrillen K. Perception of odor-induced tastes following insular cortex lesion. *Neurocase*. 2015; 21:33–43. [PubMed: 24308589]
49. Seubert J, Freiherr J, Djordjevic J, Lundström JN. Statistical localization of human olfactory cortex. *Neuroimage*. 2013; 66:333–342. [PubMed: 23103688]
50. Mak YE, Simmons KB, Gitelman DR, Small DM. Taste and olfactory intensity perception changes following left insular stroke. *Behav Neurosci*. 2005; 119:1693–1700. [PubMed: 16420174]
51. Lopez C, Blanke O, Mast FW. The human vestibular cortex revealed by coordinate-based activation likelihood estimation meta-analysis. *Neuroscience*. 2012; 212:159–79. [PubMed: 22516007]
52. zu Eulenburg P, Caspers S, Roski C, Eickhoff SB. Meta-analytical definition and functional connectivity of the human vestibular cortex. *Neuroimage*. 2012; 60:162–169. [PubMed: 22209784]
53. Papathanasiou ES, Papacostas SS, Charalambous M, Eracleous E, Thodi C, Pantzaris M. Vertigo and imbalance caused by a small lesion in the anterior insula. *Electromyogr Clin Neurophysiol*. 2005; 46:185–192.
54. Baier B, Conrad J, zu Eulenburg P, et al. Insular strokes cause no vestibular deficits. *Stroke*. 2013; 44:2604–2606. 2013. [PubMed: 23868267]
55. James W. Physical basis of emotion. *Psychol Rev*. 1894; 1:516–529. reprinted in *Psychol Rev*. 1994; 101: 205–210.
56. Lange, CG. The mechanism of emotions. In: Rand, B., editor. *The Classical Psychologist*. Boston: Houghton Mifflin; 1885. p. 672-685.
57. Critchley HD, Wiens S, Rotshtein P, Öhman A, Dolan RJ. Neural systems supporting interoceptive awareness. *Nat Neurosci*. 2004; 7:189–195. 2004. [PubMed: 14730305]
58. Calder AJ, Keane J, Manes F, Antoun N, Young AW. Impaired recognition and experience of disgust following brain injury. *Nat Neurosci*. 2000; 3:1077–1078. [PubMed: 11036262]
59. Borg C, Bedoin N, Peyron R, Bogey S, Laurent B, Thomas-Antérion C. Impaired emotional processing in a patient with a left posterior insula-SII lesion. *Neurocase*. 2013; 19:592–603. [PubMed: 22934884]
60. Knutson KM, Rakowsky ST, Solomon J, et al. Injured brain regions associated with anxiety in Vietnam veterans. *Neuropsychologia*. 2013; 51:686–694. [PubMed: 23328629]
61. Knutson KM, Monte OD, Raymont V, Wassermann EM, Krueger F, Grafman J. Neural correlates of apathy revealed by lesion mapping in participants with traumatic brain injuries. *Hum Brain Mapp*. 2014; 35:943–953. [PubMed: 23404730]
62. Mutschler I, Reinbold C, Wankerl J, Seifritz E, Ball T. Structural basis of empathy and the domain general region in the anterior insular cortex. *Front Hum Neurosci*. 2013; 7:177. [PubMed: 23675334]

63. Lamm C, Singer T. The role of anterior insular cortex in social emotions. *Brain Struct Funct.* 2010; 214:579–591. [PubMed: 20428887]
64. Singer T, Critchley HD, Preuschoff K. A common role of insula in feelings, empathy and uncertainty. *Trends Cogn Sci.* 2009; 13:334–340. [PubMed: 19643659]
65. Fan Y, Duncan NW, de Greck M, Northoff G. Is there a core neural network in empathy? An fMRI based quantitative meta-analysis. *Neurosci Biobehav Rev.* 2011; 35:903–911. [PubMed: 20974173]
66. Dal Monte O, Krueger F, Solomon JM, et al. A voxel-based lesion study on facial emotion recognition after penetrating brain injury. *Soc Cogn Affect Neurosci.* 2013; 8:632–639. [PubMed: 22496440]
67. Boucher O, Rouleau I, Lassonde M, Lepore F, Bouthillier A, Nguyen DK. Social information processing following resection of the insular cortex. *Neuropsychologia.* 2015; 71:1–10. [PubMed: 25770480]
68. Papagno C, Pisoni A, Mattavelli G, et al. Specific disgust processing in the left insula: New evidence from direct electrical stimulation. *Neuropsychologia.* 2016; 84:29–35. [PubMed: 26836143]
69. Lerner JS, Li Y, Valdesolo P, Kassam KS. Emotion and decision making. *Annu Rev Psychol.* 2015; 66:799–823. [PubMed: 25251484]
70. Tversky A, Kahneman D. The framing of decisions and the psychology of choice. *Science.* 1981; 211:453–458. [PubMed: 7455683]
71. Damasio, AR. *Descartes' Error: Emotion, Reason, and the Human Brain.* New York: Grosset/ Putnam; 1994.
72. Canessa N, Crespi C, Motterlini M, et al. The functional and structural neural basis of individual differences in loss aversion. *J Neurosci.* 2013; 33:14307–14317. [PubMed: 24005284]
73. Levin IP, Xue G, Weller JA, Reinmann M, Lauriola M, Bechara A. A neuropsychological approach to understanding risk-taking for potential gains and losses. *Front Neurosci.* 2012; 6:15. [PubMed: 22347161]
74. Harlé KM, Chang LJ, van 't Wout M, Sanfey AG. The neural mechanisms of affect infusion in social economic decision-making: a mediating role of the anterior insula. *Neuroimage.* 2012; 61:32–40. [PubMed: 22374480]
75. Clark L, Studer B, Bruss J, Tranel D, Bechara A. Damage to insula abolishes cognitive distortions during simulated gambling. *Proc Natl Acad Sci USA.* 2014; 111:6098–6103. [PubMed: 24711387]
76. Von Siebenthal Z, Boucher O, Rouleau I, Lassonde M, Lepore F, Nguyen DK. Decision making impairments following insular and medial temporal lobe resection for drug-resistant epilepsy. *Soc Cogn Affect Neurosci.* 2016 Oct 19.
77. Markett S, Heeren G, Montag C, Weber B, Reuter M. Loss aversion is associated with bilateral insula volume. A voxel based morphometry study. *Neurosci Lett.* 619:172–176.
78. Yeo BT, Krienen FM, Eickhoff SB, et al. Functional specialization in Human Association Cortex. *Cerebral Cortex.* 2015; 10:3654–3672.
79. Kim H. Involvement of the dorsal and ventral attention networks in oddball stimulus processing: a meta-analysis. *Hum Brain Mapp.* 2014; 35:2265–84. [PubMed: 23900833]
80. Levy BJ, Wagner AD. Cognitive control and right ventrolateral prefrontal cortex: reflexive reorienting, motor inhibition, and action updating. *Ann N Y Acad Sci.* 2011; 1224:40–62. [PubMed: 21486295]
81. Seeley WW, Menon V, Schatzberg AF, Keller J, Glover GH, Kenna H, et al. Dissociable intrinsic connectivity networks for salience processing and executive control. *J Neurosci.* 2007; 27(9): 2349–2356. 2007. [PubMed: 17329432]
82. Sridharan D, Levitin DJ, Menon V. A critical role for the right fronto-insular cortex in switching between central-executive and default-mode networks. *Proc Natl Acad Sci U S A.* 2008; 105(34): 12569–12574. [PubMed: 18723676]
83. Cai W, Chen T, Ryali S, Kochalka J, Li CS, Menon V. Causal Interactions Within a Frontal-Cingulate-Parietal Network During Cognitive Control: Convergent Evidence from a Multisite-Multitask Investigation. *Cereb Cortex.* 2016; 26(5):2140–2153. [PubMed: 25778346]

84. Uddin LQ. Salience processing and insular cortical function and dysfunction. *Nat Rev Neurosci*. 2015; 16(1):55–61. [PubMed: 25406711]
85. Dronkers NF. A new brain region for coordinating speech articulation. *Nature*. 1996; 384:159–61. [PubMed: 8906789]
86. Baldo JV, Wilkins DP, Ogar J, Willock S, Dronkers NF. Role of the precentral gyrus of the insula in complex articulation. *Cortex*. 2011; 47:800–807. [PubMed: 20691968]
87. Duffau H, Taillandier L, Gatignol P, Capelle L. The insular lobe and brain plasticity: lessons from tumor surgery. *Clin Neurol Neurosurg*. 2006; 108:543–548. [PubMed: 16213653]
88. Baier B, zu Eulenburg P, Glassl O, Dieterich M. Lesions to the posterior insular cortex cause dysarthria. *Eur J Neurol*. 2011; 18:1429–1431. [PubMed: 21771200]
89. Ackermann H, Riecker A. The contribution(s) of the insula to speech production: a review of the clinical and functional imaging literature. *Brain Struct Funct*. 2010; 214:419–433.

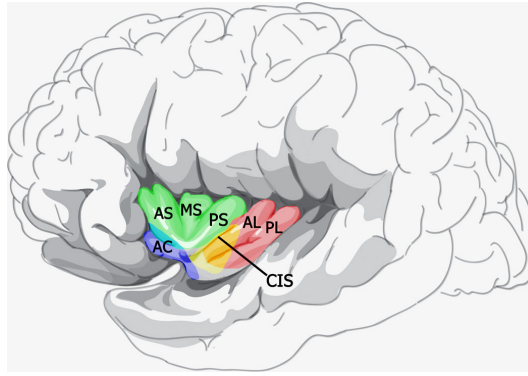


Figure 1. Illustration of the human insular cortex with its broad functional differentiation. AC, accessory gyrus; AS, anterior short insular gyrus; MS, middle short insular gyrus; PS, posterior short insular gyrus; AL, anterior long insular gyrus; PL, posterior long insular gyrus; CIS, central insular sulcus. Estimated functional differentiation was inspired from Kurth et al. (2010)'s meta-analysis on functional neuroimaging experiments: red = sensorimotor; yellow = chemosensory; blue = social-emotional; green = cognitive. Illustration of the insular cortex offered by Dr. Tram Nguyen.

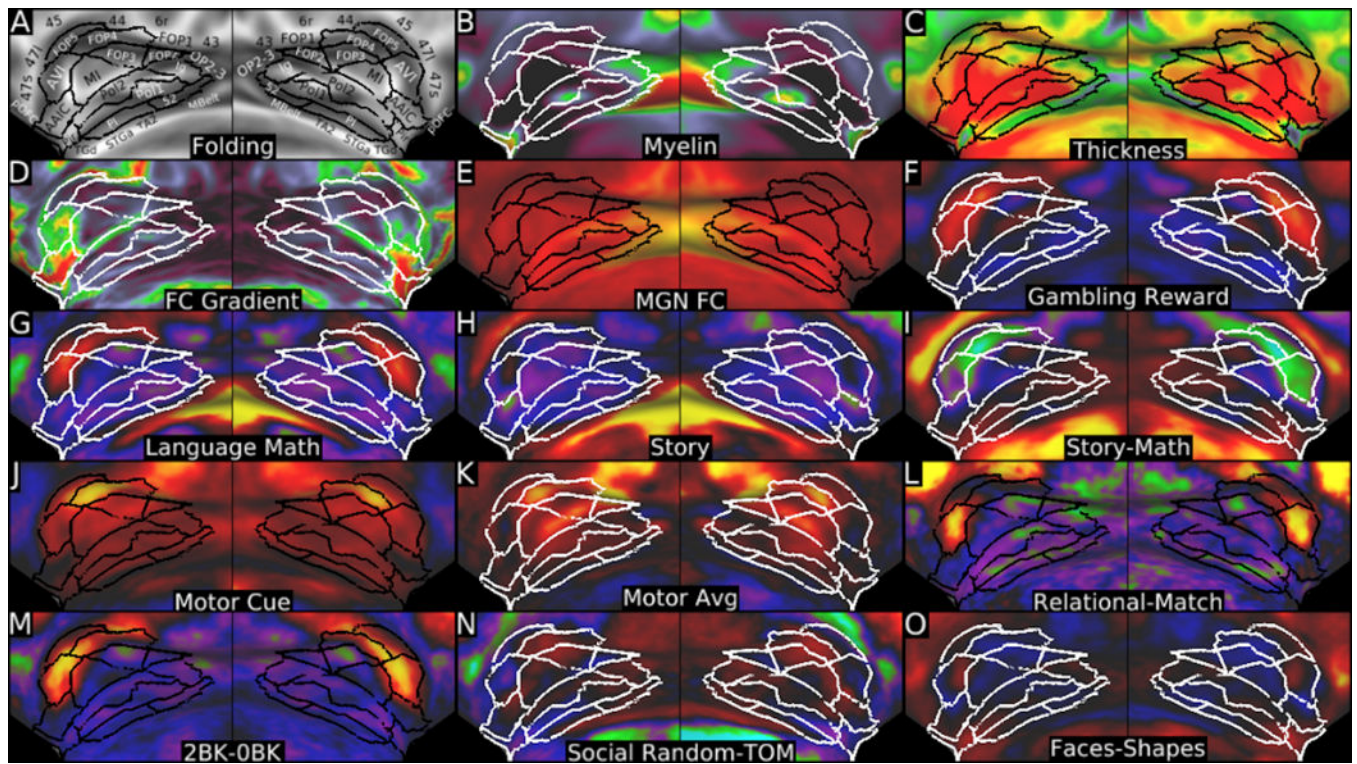


Figure 2. Multi-modal parcellation of the human insular cortex

Thirteen areas in the insula have been identified based on cortical architecture, functional activation, connectivity, and/or topography. Reproduced with permission from Glasser et al. 2016.