Anatomy of the insula—functional and clinical correlates

FREDERICK G. FLYNN†*, D. FRANK BENSON‡¶
and ALFREDO ARDILA§

† Madigan Army Medical Center, Washington, USA
‡ University of California at Los Angeles, LA, USA
§ Miami Institute of Psychology, Florida, USA

Abstract

Much information has been acquired on the anatomy and function of the insula over the past two decades. The insula has a dynamic cytoarchitectonic arrangement throughout its length. The anterior insula is comprised of an agranular-allocortical area which functionally is part of the paralimbic belt. Its cortical connections are predominantly with other allocortical areas. Sub-cortical, limbic, and brain stem connections underscore the anterior insula's role in processing and integrating autonomic and visceral information. The posterior insula is comprised of a granular-isocortical area which functionally is linked to somatomotor systems. Its cortical connections are predominantly with other neocortical areas. Insular-cortical and sub-cortical connections, especially with the thalamus and basal ganglia, underscore the posterior insula's role in somatosensory, vestibular, and motor integration. The dysgranular insula lying in between the anterior and posterior insula represents an anatomical and functional transition between these regions. The predominant flow of intra-insular projections from anterior to more posterior regions suggests that the posterior insula also serves as an integrative heteromodal association area for information received by all five senses. The insula plays a role in cardiovascular, gastrointestinal, vestibular, olfactory, gustatory, visual, auditory, somatosensory, and motor modulation. It is also felt to play a role in conditioned aversive learning, affective and motivational components of pain perception, stress induced immunosuppression, mood stability, sleep, and language. Clinical correlation of damage to the insula, and the resultant impairment of the above functions is discussed.

Introduction

The paucity of information concerning the insula in contemporary textbooks of neuroanatomy suggests that little progress has been made since Bonin and Bailey (1947) stated that the insula's 'functions and affinities are totally unknown'. Although much remains to be learned about this mysterious lobe, recent information has been accumulated over the past two decades. Discussion of the development, gross and microscopic morphology, as well as the relationship of the insula to other brain regions will help create a foundation for understanding function and clinical correlation.
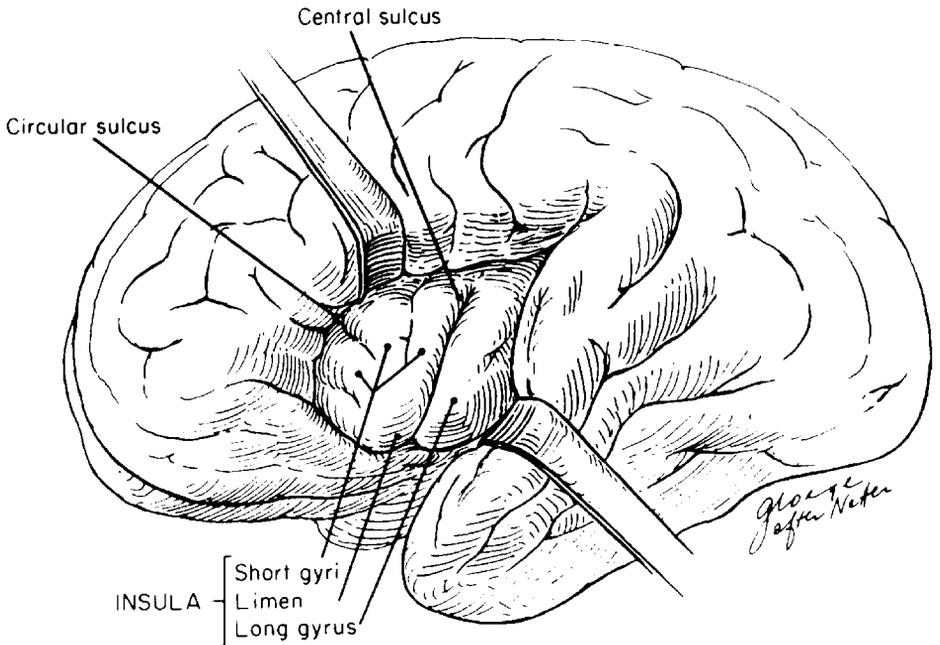
Figure 1.   Artist's rendition of the insula as exposed by retraction of temporal and frontal-parietal opercula. The major gyri and sulci of the insula are labelled.

The insula lies buried in the depth of the lateral sulcus, forming the base of the latter (Reil 1809), and can only be visualized by retraction of the frontal and temporal lobes. The opening leading into this region is often referred to as the limen insula (Carpenter 1985). It is triangular in shape with the apex directed down and forward. The surface of the insula is covered by four to six gyri whose collective direction creates the appearance of a fan (Clark 1896). The circumference of the insula is outlined by the circular sulcus (Augustine 1985), and the anterior and posterior regions are separated by the central insular sulcus in which lies the main branch of the middle cerebral artery (Hefftler 1878, Guldberg 1887, Clark 1896). Three short insular gyri ('gyri breves') can be found in the anterior insula (Carpenter 1985). Ventrally these gyri join at the limen insula. Two long insular gyri ('gyri longus') lie in the posterior insula (Carpenter 1985). The total number of lesser gyri varies from species to species and also from right hemisphere to left within the same species (Clark 1896).

Underlying the insular gyri are the basal nuclei of the brain (Carpenter 1985). The insular region immediately overlying these nuclei is the first to cytologically differentiate (Kodama 1926). Finally, the roof of the insula is formed by the opercula of the inferior frontal gyrus, inferior parietal lobule, and the superior temporal gyrus (Cunningham 1891b).

Embryology

Early in foetal development the primordium of the insula forms on the superolateral surface of the cerebral hemisphere (Lockard 1948). This is followed by an anterior downward shift of the temporal lobe resulting in a depression of the lateral hemispheric surface, and as development continues, the temporal lobe pivots

around the fixed insular surface (Lockard 1948). The surrounding frontal, temporal, and parietal lobes all develop faster than the insula until the latter is covered by these lobes (Clark 1896). The lateral sulcus represents the separation of these three lobes juxtaposing one another over the underlying insula.

The insula surface remains smooth until the 15th week of foetal development when the inferior limiting sulcus forms. (Cunningham 1891a, Lockard 1948). Between 16 and 17 weeks the superior limiting sulcus appears, and shortly thereafter fuses with the inferior sulcus to form the circular insular sulcus which circumscribes its boundary (Lockard 1948, Augustine 1985). By 20 weeks the insula has grown in size and an anterior–posterior differentiation becomes apparent (Augustine 1985). Next, the central insular sulcus appears and is complete prior to the 24th week (Cunningham 1891a, Lockard 1948). Of interest is the perfect alignment of this sulcus with the central sulcus of the cerebral hemisphere. By the 25th–26th week, pre- and post-central insular sulci have formed (Cunningham 1891a). These sulci also have a close anatomic alignment with their respective sulci on the lateral hemisphere.

By 32 weeks all insular sulci are well formed rendering the gross anatomic appearance of the insula at birth identical to that of the adult (Cunningham 1891a, Lockard 1948). The right insula ceases growth earlier than the left and the left insular surface area becomes larger than the right (Cunningham 1891a, Clark 1896). This difference is most apparent in humans with less difference in comparative size in lower primates (Carpenter 1985). Owing to this, it is tempting to speculate that the size difference in humans may underscore a role for the insula in language and related cortical functions. This will be discussed in greater detail later.

Cytoarchitectonics

Most information concerning the cytoarchitectonics of the insula in higher primates has been acquired from the study of this region in the rhesus monkey (Macaca mulatta) (Mesulam and Mufson 1982a). The human insula has a near identical cellular organization, with only rare differences between the species. Mesulam and Mufson (1982a) emphasize the similar cytoarchitectural arrangement of the insula and the lateral orbital cortex and temporal pole, all contiguous with the prepiriform allocortex. Together the insula, temporal pole, and lateral orbital cortex form a paralimbic belt (Mesulam and Mufson 1982a).

The insula is cytoarchitectonically arranged into three contiguous regions of increasingly differentiated cortex (Roberts and Akert 1963, Jones and Burton 1976, Mesulam and Mufson 1982a). The rostroventral portion of the insula consists of agranular cortex while that of the caudal-insula is granular. In between the two regions lies a dysgranular transition zone (Mesulam and Mufson 1982a). Each of the three regions appears to have its own pattern of myelination and acetyl-cholinesterase (AchE) concentration (Mesulam and Mufson 1982a).

Agranular sector

The cortex of the rostroventral insula consists of three cellular strata which contain no aggregates of granule cells. The outer strata, consisting of small pyramidal cells, is directly contiguous with the pyramidal cell layer of the preiriform cortex. The intermediate stratum is occupied by larger hyperchromic pyramidal cells. This stratum is contiguous with layer V of the dysgranular cortex located more dorsally.

The inner stratum consists of polymorphic cells which are contiguous with the deep cell layer of the prepiriform cortex as well as the underlying claustrum.

The quantity of cortical myelin is low with only a limited number of myelinated fibres in layer I. The intermediate and inner strata contain the highest concentration of AchE in the whole insula (Mesulam and Mufson 1982a).

Dysgranular sector

This sector is dorsocaudal to the agranular sector and is continuous with it. In the area bordering agranular cortex, layers II and III are difficult to demarcate. Layer II contains scattered granule cells and remains rudimentary throughout its rostro-caudal distribution. Layer III lacks laminar organization rostro-ventrally, but assumes a columnar arrangement in its more dorsal-caudal regions. Layer IV contains clusters of granule cells rostrally but changes to a continuous lamination of these cells in more dorsal-caudal regions. Layer V is more prominent rostrally and less so in dorsal-caudal areas. Layer VI is difficult to differentiate from both layer V and the white matter below throughout the length of the dysgranular sector.

Myelin content remains relatively low, and that which is present is radially arranged in deeper layers of the cortex. The-zonal layer of myelin readily seen in the agranular sector is no longer discernible and the lines of Baillarger are essentially absent. AchE concentration is present in the infragranular layers, but is in lower quantity than in the agranular sector (Mesulam and Mufson 1982a).

Granular sector

This posterior-dorsal region of the insula demonstrates yet higher degrees of cortical differentiation. Layers II and IV are clearly granular and well defined. Sublamination occurs in layer III and infragranular layers are no longer as well defined. There is a clear demarcation between layers V and VI as well as between layer VI and the underlying white matter.

Myelin is most dense in this cortical sector of the insula. Both inner and outer lines of Baillarger are readily discernible, with persistence of deeper, radially oriented, myelinated fibres. The lowest concentration of cortical AchE in the insula occurs in the loose reticulum of the sparse infragranular layers. The cyto-architecture of the human insula is nearly identical to that of the rhesus monkey with differences limited to a thicker cortex with more depth and larger cells than in the monkey (Major 1877).

In summary, the cytoarchitecture of the insula is rostro-caudally arranged into three sectors, with the least differentiation most rostral, and the greatest differentiation most caudal. The concentration of cortical myelinated fibres parallels this structural format, with the least myelin anteriorly and the most posteriorly. Cortical AchE, on the other hand, has its highest concentration in the anterior agranular regions and lowest in the well differentiated posterior granular sector. The presence of a similar cortical cytoarchitecture in the lateral orbital frontal and temporal pole areas suggests that these two regions and the insula may function as a unit (Sanides 1968, Mesulam and Mufson 1982a). This is supported by the fact that the periallocortical agranular region of all three areas has continuity of their outer stratum with prepiriform cortex, as well as continuum of their inner stratum with the underlying claustrum (Mesulam and Mufson 1982a).

Connections of the insula

Through the use of histochemical and autoradiographic techniques, afferent and efferent connections of the insula have been better discerned. Reciprocal connections between the insula and various cortical locations, basal nuclei, limbic and thalamic areas will be discussed.

Cortical projections of the anterior insula (*figure 2*)

Reciprocal projections of the anterior insula include the prepiriform olfactory area, frontal operculum, orbitofrontal cortex, dorsal and ventral temporal pole, rhinal fissure, supratemporal plane, the anterior and middle cingulate gyrus, and the somatosensory and opercular areas of the parietal lobe. Reciprocal connections with the superior temporal sulcus and inferior temporal gyrus also exist, however the afferent projections are greater than efferents. The lateral entorhinal cortex has an unidirectional input to the anterior insula while the prefrontal cortex receives unidirectional efferents from the insula. There are virtually no projections to the secondary somatosensory cortex and none to the primary and secondary auditory areas (Mesulam and Mufson 1982a, Mufson and Mesulam 1982).

Cortical projections of the middle insula (*figure 3*)

Projections of the middle insula and the frontal lobe are very similar to those of the anterior insula with a few exceptions. There is no prepiriform olfactory input, there is a greater input from prefrontal granular cortex, and there is a prominent projection to premotor cortex. This latter projection is unique in that fibres of insular origin terminating in that specific premotor cortical zone arise exclusively from the middle insula.

The middle insula and the temporal lobe also have similar connections to those of the anterior insula. Some noted exceptions are that there is virtually no input from lateral entorhinal cortex, there are projections to primary and secondary auditory cortex as well as post-auditory and retroinsular cortex, and connections with granular temporal cortex are greater, while those with agranular are less than that seen with the anterior insula. Connections with the cingulate are similar to those of the anterior insula. In addition the middle insula sends projections to the supplementary motor area. Parietal lobe connections with the middle insula are greater and more widely dispersed than those of the anterior insula. These areas include primary and secondary somatosensory cortex, area 5, and the medial and dorsal parietal area as well as the parietal operculum. There is no input to the posterior inferior parietal cortex (Mesulam and Mufson 1982b, Mufson and Mesulam 1982).

Cortical connections of the posterior insula (*figure 4*)

There are far fewer connections of the posterior insula with the frontal lobes and far greater connectivity with the parietal lobe than that seen in anterior and middle insula. Frontal connections are otherwise similar to that of the middle insula with the exception that there is afferent input from the supplementary motor area, and virtually no connections with the frontal opercular cortex.

T E M P O R A L

●Temporal pole ●Sup. temporal sulcus (anterior) ●Inf. temporal gyrus ●Prepiriform cortex Supratemporal plane

Dorsal (Ag) (Dys)

●Ventral ●Rhinal fissure ●Lat. entorhinal cortex

FRONTAL
●Orbitofrontal lat. ant. lat. caudal
●Frontal operculum
●Prepiriform olfactory
●Prefrontal area 46 & 12

ANT. INSULA (Ag)⇄(Dys)

Mid-insula Post-insula

CINGULATE
●Ant. gyrus (area 24)
●Mid. gyrus
●Cingulate sulcus (lower bank)

PARIETAL
●Area 3,1,2
●Opercular area
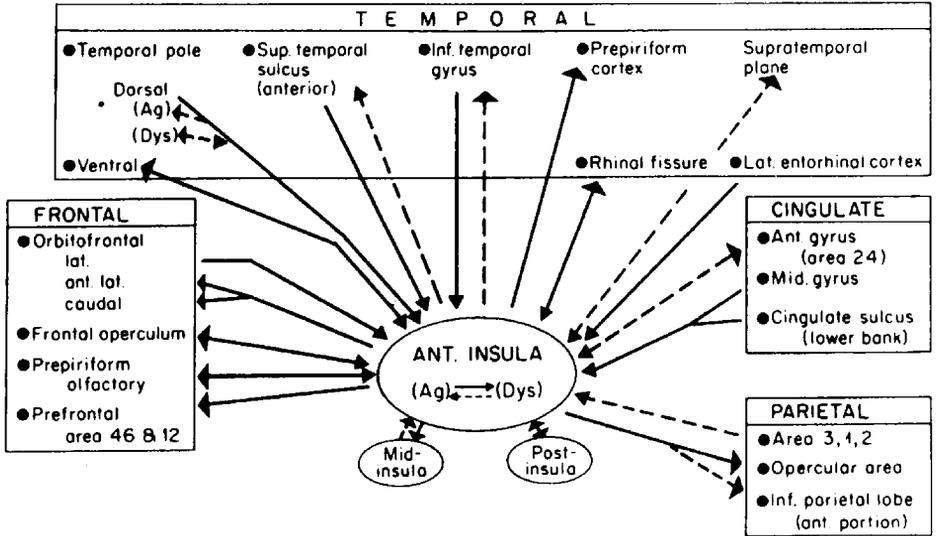●Inf. parietal lobe (ant. portion)

Figure 2. Graphic representation of the major cortical connections of the anterior insula. Heavy lines indicate stronger, dashed lines weaker connections. (Ag = agranular; Dys = dysgranular).

T E M P O R A L

●Auditory area primary secondary posterior
●Retroinsular
●Temporal pole
●Sup. temporal sulcus ant. post.
●Parainsular area
●Inf. temporal gyrus (middle part)
●Rhinal fissure
●Supratemporal plane
●Prepiriform cortex

FRONTAL
●Orbitofrontal lat. areas 11,12,13
●Opercular area precentral
●Premotor
●Prefrontal

MIDDLE INSULA (Dys)

Ant. insula Post insula

CINGULATE
●Ventral ant.
●Dorsal (area 23 & 24)
●SMA

PARIETAL
●Somatosensory primary ant. inf. opercular secondary
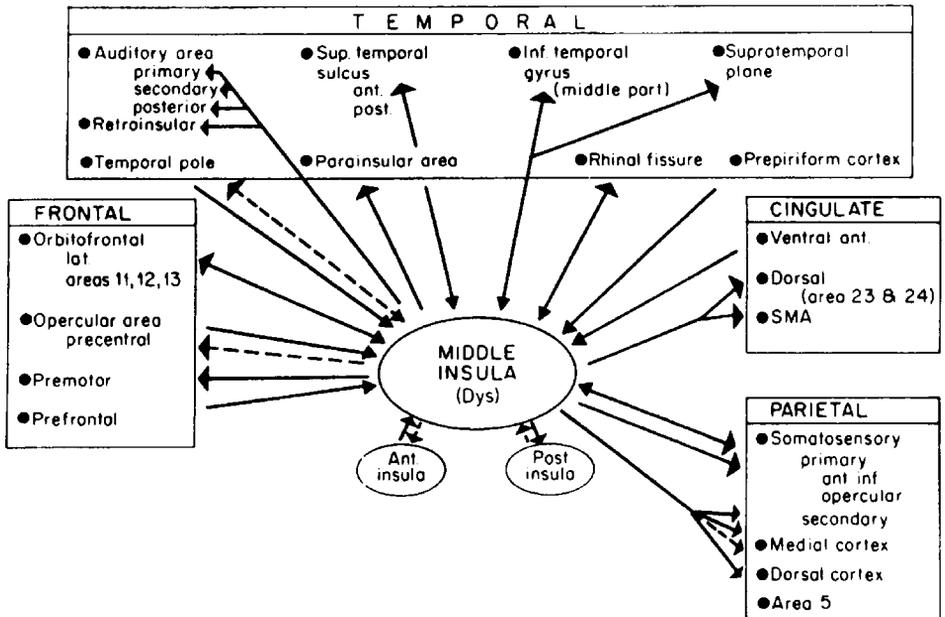●Medial cortex
●Dorsal cortex
●Area 5

Figure 3. Graphic representation of the major cortical connections of the middle portion of the insula. (Dys = dysgranular).

The greatest number of projections between posterior insula and parietal lobe are located in the primary and secondary somatosensory cortex, and the inferior parietal lobule. The superior parietal lobule has slightly less connectivity. Cingulate projections arise predominantly from area 23 and 24 as well as the supplementary motor area. Temporal lobe connections are similar to those of the middle insula with the exception that there is even greater association with the primary,
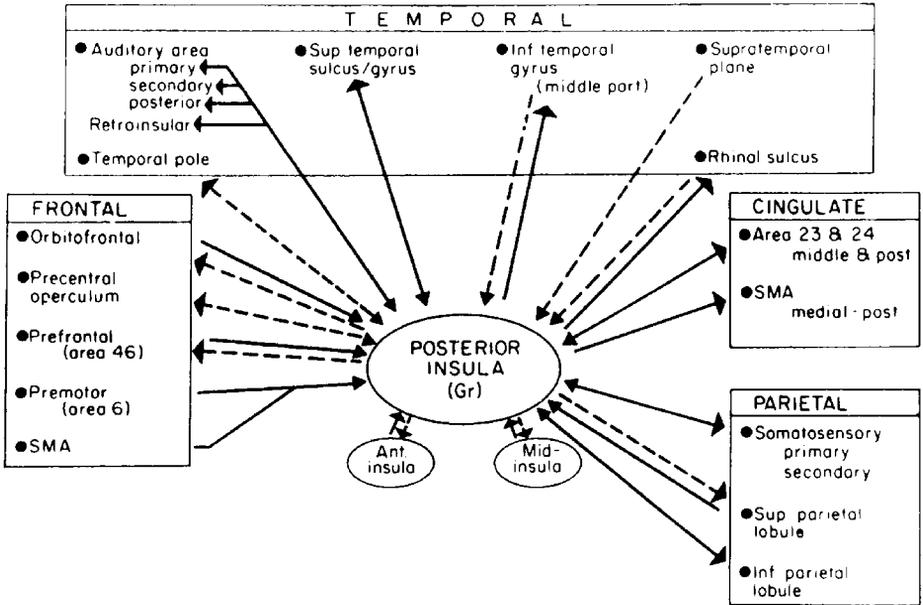
Figure 4.   Graphic representation of the major cortical connections of the posterior insula. (Gr = granular; SMA = supplementary motor area).

secondary, and posterior auditory areas. There is virtually no direct connection between the entorhinal or perpiriform cortex and the posterior insula (Mesulam and Mufson 1982b, Mufson and Mesulam 1982).

Intrainsular connections (figures 2–4)

Connections between insular areas are relatively rich but are not directionally equal. Mesulam and Mufson (1982b) demonstrated a definite anterior to posterior bias. The anterior insula receives afferents primarily from adjacent agranular and anterior dysgranular—areas with relatively few connections from more posterior insular areas (figure 2). The mid-insula receives afferents from both the anterior and posterior insula and sends efferents in both directions (figure 3). The posterior insula receives afferents from both anterior and mid-insula but sends few efferents to anterior regions (figure 4). Thus, a distinct predilection for intrainsular connections to flow from anterior to posterior is evident, an observation of potential functional significance.

Summary of cortical-insula connectivity

Most cortical connections of the insula are reciprocal (Aggleton *et al*. 1980) and have both topographic and architectonic organization. The connections of the ventral anterior and dorsal caudal insular regions are preferentially distributed. The ventral anterior area has prominent connections with the orbitofrontal and frontal opercular cortex as well as prepiriform olfactory and entorhinal cortex. The posterior dorsal insula has prominent connections with the supplementary motor area, the primary and secondary somatosensory cortex, the primary and secondary auditory cortex, the inferior parietal lobule, and the retroinsular area. All areas of the insula have connections with temporal lobe and cingulate regions.

Most of the connections of the insula demonstrate specific reference to architectonic zones. Virtually all of the afferent and efferent connections of granular insula project to or arise from other areas of granular cortex, while connections associated with the agranular insula have projections to and from other agranular cortical regions. Projections originating and terminating in dysgranular insula have a more heterogeneous architectonic connectivity but a rostral-caudal specificity is evident. The most anterior part of dysgranular insula is more likely to connect with agranular or dysgranular cortical regions while the more posterior dysgranular insula tends to connect with other dysgranular or granular cortical areas (Mesulam and Mufson 1982a, b, Mufson and Mesulam 1982).

Subcortical connections of the insula (figure 5)

Insula—basal ganglia connections

Efferent projections of the insula have been demonstrated terminating in the lentiform nucleus (Showers and Lauer 1961), the ventral (Turner et al. 1980) and caudoventral (Forbes and Moskowitz 1974) putamen, and the tail of the caudate (Turner *et al*. 1980). Projections from less differentiated agranular insula project to the ventral striatum, whereas dorsolateral striatum receives fibres from the more differentiated granular insula. The functional correlate to this anatomic arrangement is that the agranular-ventral striatal projection system represents a limbic integrative circuit primarily related to integrating feeding behaviour with rewards and memory, whereas the granular-dorsal striatal system represents a somatosensorimotor integration area (Chikama *et al*. 1997). Dorsal agranular insular projections to the lateral nucleus accumbers and ventral striatum overlap with parallel projections to these areas from the intermediodorsal thalamus and the magnocellular basal amygdala. This parallel circuitry appears to functionally influence the prefrontal-corticostriatal pathway involved in limbic motor integration (Wright and Groenewegen 1996). Reciprocal projections with the claustrum have also been demonstrated (Berke 1960). The ventral claustrum appears to be a major terminal for posterior insula efferent projections (Turner *et al*. 1980, Mesulam and Mufson 1982b). The areas of cortex sending efferents to the insula have similar efferents to the claustrum (Mufson and Mesulam 1982). Efferent projections from both areas also terminate in similar regions of cortex (Mesulam and Mufson 1982b). Despite the close anatomic relationship of the insula and the claustrum, many more cortical regions project to the claustrum than send projections to the insula (Mufson and Mesulam 1982). This is particularly true with regard to input from the visual system (Olson and Graybiel 1980, LeVay and Sherk 1981). Topographic associations of the insula and claustrum are not well established (Mesulam and Mufson 1982b).

Insula—thalamic connections

Afferent fibres to the insula originate from the centromedial nucleus (CM) (Clark and Russell 1939), the ventral anterior nucleus (VA) (Angevine *et al*. 1962), the parvocellular region of the ventral posterior medial nucleus (VPMpc) (Roberts and Akert 1963), the ventral posterior inferior nucleus (VPI) (Burton and Jones 1945), and the ventral posterior lateral nucleus (VPL) (Guldin and Markowitsch 1984, Augustine 1985). The posterior nuclei along with the suprageniculate nucleus
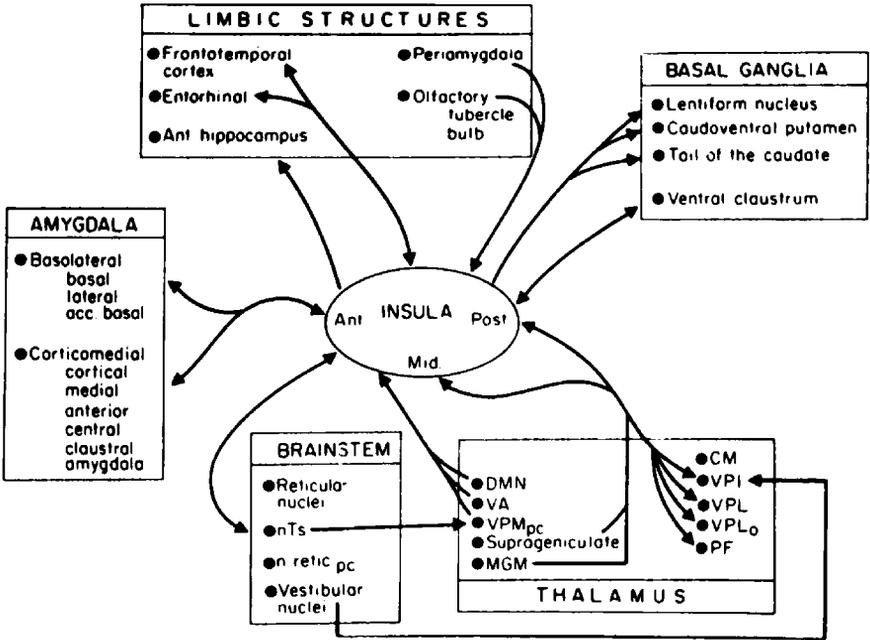
Figure 5. Graphic representation of the major sub-cortical connections of the insula. Specific brainstem and thalamic nuclei are abbreviated, but the full names are presented in the text.

project throughout the insula (Burton and Jones 1976). The VPMpc and CM project predominantly to the anterior insula while-the medial and dorsal parts of the medial geniculate nucleus (MGN) project to the posterior insula (Guldin and Markowitsch 1984). The anterior insula is the only insular region that receives afferents from the mediodorsal nucleus of the thalamus (Guldin and Markowitsch 1984).

Wirth (1973) studied efferent projections from the insula to the thalamus. He found fibres terminating in the VPL nucleus, including the oralis portion (VPLo), VPI, CM, and the parafascicular nucleus in the intralaminar nuclear group. Other investigators have defined connections with the nucleus reuniens, the reticular nucleus, and the oralis and medial areas of the pulvinar (Mufson and Mesulam 1984). Clasca *et al*. (1997) demonstrated architectonic connections with the thalamus from all regions of the insula. They demonstrated that ventral agranular regions sparsely connected with the midline nuclei of the thalamus, while dorsal agranular insula linked to the mediodorsal, ventromedial, parafascicular and midline nuclei. The dysgranular insula connects to the gustatory and viscerosensory portions of the ventroposterior thalamus and ventrolateral nucleus. The granular insular area is connected to the posteriormedial and the VPI of the thalamus, recipients of spino-thalamic input. Functional implications include a wide distribution of architectonically arranged limbic, motor, and sensory integration circuits (Clasca *et al*. 1997). Because of the large input to the medial pulvinar from limbic and polymodal association cortex, this nucleus may serve to integrate multisensory and limbic information (Mufson and Mesulam 1984).

Insula—amygdala connections

The insula sends efferent fibres to both basolateral and corticomedial amygdala. In the former, fibres specifically terminate in the lateral and basal nuclei (Aggleton *et al*. 1980, Turner *et al*. 1980, Mufson *et al*. 1981). Mufson *et al*. (1981) also described a projection to the accessory basal nucleus. Specific nuclei of the corticomedial portion receiving insula efferents include the medial and cortical nuclei (Mufson *et al*. 1981), the anterior and central amygdaloid nuclei (Turner *et al*. 1980, Mufson *et al*. 1981), and the claustral portion of the amygdaloid body.

Mufson *et al*. (1981) demonstrated reciprocal connections between the amygdala and insula with greatest insular involvement in the anterior agranular-dysgranular cortex.

Insula—limbic connections

Many of these projections have already been discussed in the above sections. In addition, the insula projects to the anterior hippocampus (Pribram and MacLean 1953), the bed nucleus of the stria terminalis (Saper 1982), the limbic ventral striatum (Wright and Groenewegen 1996, Chikama *et al*. 1997) and the lateral nucleus accumbens (Wright and Groenewegen 1996). The insula receives afferents from the periamygdaloid cortex (Pribram *et al*. 1950, Pribram and MacLean 1953), the olfactory tubercle (Pribram *et al*. 1950), and the olfactory bulb (Kaada 1951). Reciprocal connections to the posterior hypothalamus and tuberomammilary nucleus are also present (Saper 1982).

Insula—brainstem connections

Evidence suggests that direct projections to reticular and brainstem autonomic nuclei exist (Ruggiero *et al*. 1987). Midbrain nuclei receiving projections from the insula include the dorsal and superior central raphe (Saper 1982), the ventral tegmental area, and the periaqueductal gray (Neafsey *et al*. 1986). The parabrachial nucleus and locus ceruleus also receive fibres from the insula (Saper 1982). The nucleus of the tractus solitarius (NTS) (Shipley 1982), as well as the nucleus reticularis parvocellulars have been shown to receive insular efferents (Ruggiero *et al*. 1987). The efferents to NTS are arranged in a topographic manner (Shipley 1982). A recent study suggests that some of these insular NTS projection neurons may be glutaminergic (Torrealba and Muller 1996). No conclusive evidence of direct projections to the insula from these nuclei exists but the VPMpc of the thalamus has been shown to serve as a intermediate relay for information ascending from NTS to the anterior insula (Beckstead *et al*. 1980). Electrical stimulation of the chorda tympani results in cellular responses in the anterior insula. Stimulation of the lingual-tonsillar and pharyngeal branches of the glossopharyngeal nerve and the superior laryngeal branch of the vagus nerve activate cells in the posterior insula (Hanamori *et al*. 1997b).

Vestibular information arriving in the posterior insula is thought to be projected from the vestibular nuclei through the VPI of the thalamus (Deecke *et al*. 1974). When considering the functions of the insula it becomes clear that insula-brainstem interaction, whether through direct or multi-synaptic pathways, is considerably more complicated than is presently recognized.

Other insula projections

In addition to the above-mentioned connections, long projections from the insula have been described traversing the internal (Lockard 1948) and external (Berke 1960) capsules, the anterior commissure (Krieg 1965), and the corpus callosum (Hurst 1959) with projections to ipsilateral and contralateral cortical areas as well as brainstem relay nuclei, and spinal cord (Shimada *et al*. 1985).

Functional correlates and clinical aspects of the insula

The cytoarchitectonic changes that occur from the anterior agranular to the granular posterior insular cortex, along with the connections of these regions with respective similar histologic areas of adjacent cortex, establish anatomical substrates for organizational units of function. The anterior insula forms a functional unit with adjacent orbital, frontal opercular, and temporal polar areas. This functional unit appears to serve a prominent role in autonomic and visceral activities. The link of this area with the amygdala and brainstem nuclei serve to establish the functional bridge between visceral and autonomic afferent and efferent connections and cortical-limbic influence. Olfactory and gustatory functional areas are formed in the anterior insula (Tilney and Riley 1938, Bagshaw and Pribram 1953, Penfield and Faulk 1955, Sudakov *et al*. 1971). The insula's role may be to integrate these special visceral senses with behavioural and emotional events (Saper 1982). It may also act as a substrate by which the cortex may influence the processing of this visceral information and provide a role for higher cortical modulation of visceral and autonomic functions (Shipley 1982).

The insula serves a role in learning and memory. Lasiter *et al*. (1985) pointed out that the insula plays a role in odour and taste aversion learning. The conditioned stimulus (exposure to a novel taste) in the conditioned taste aversion (CTA) paradigm has been said to be cholinergically modulated within the insular cortex (Naor and Dudai 1996). However Rosenblum *et al*. (1997) demonstrated that tyrosine phosphorylation of the NMDA 2B receptor subunit is involved in CTA. Furthermore they found that the level of tyrosine phosphorylation was a function of the novelty of the taste and quantity of the taste substance consumed. Nerad *et al*. (1996) demonstrated that the caudal parts of the insula were necessary for spatial learning (water maze test), while the central insula is crucial for both the acquisition of CTA learning and spatial learning. Stimulation of the basolateral amygdala has been shown to induce long term potentiation (LTP) in the insula (Escobar *et al*. 1998). NMDA receptor antagonists inhibit this induction (Escobar *et al*. 1998). Long term retention of aversively motivated training is also felt to be a function of the insula (Bermudez-Rattoni *et al*. 1997). Other forms of learning have also been attributed to the insula. Vestibular memory, a dynamic form of spatial memory (also referred to as 'topokinetic' memory), is impaired in parietal-insula junctional lesions (Berthoz 1997). Petersen *et al*. (1998) noted that novel verbal and motor tasks elicited increased activity in anatomical regions outside of the insula, but this increased functional activity shifted to the insular cortex following practice of the tasks. This was posited by these authors to possibly represent storage of particular associations or capabilities allowing for skilled performance. DeCoteau *et al*. (1997) demonstrated that the agranular insular cortex may play a role in the processing of

affect-laden information. This is felt to take place within a prefrontal short term or working memory system.

The insula appears to play a specific role in learning and memory processing. Visceral aversive learning and its associated motivational-affectual response underscores the insula's integrative role. It appears to process visceral and special sensory input and integrate it with limbic emotional, affectual, and motivational expression. Aversive visceral learning appears to be mediated by LTP through glutaminergic—NMDA receptor interaction (Escobar *et al.* 1998). This type of learning may be the reason why the odour or taste of a food or substance that was previously associated with sickness may evoke the same feelings of illness upon reexposure to sensory stimulus.

Gastrointestinal sensory and motility changes have been well documented with both stimulation and ablations in animals and humans alike (Kaada 1951, Hoffman and Rasmussen 1953, Daly 1953, Penfield and Faulk 1955, Showers and Lauer 1961, Augustine 1985). Penfield and Faulk (1955) with insular stimulation experiments in humans demonstrated that this area was associated with feeding patterns involving mastication, salivation, swallowing, oesophageal contraction and inhibition of the pylorus. Dysphagia has been described with discrete lesions of the anterior insula (Daniels and Fourdas 1997). In some cases stimulation within the same area of the cortex may cause decreased amplitude or inhibition of gastric activity whereas stimulation of adjacent cells produce an increase in rate and amplitude of gastric activity. Ablation of this region of insular cortex causes sudden and complete inhibition of gastic and pyloric contractions. Viscral sensory phenomena experienced by patients stimulated in the anterior insula included discomfort in the xiphoid, epigastrium, and umbiliculus as well as feelings of gastrointestinal 'gurgling', 'rolling', pain, nausea and 'scratching'. Visceral motor phenomena included borborygmus, belching and vomiting (Penfield and Faulk 1955). Specific cell groups in the agranular and dysgranular insula project to a bulbar gastric centre of the dorsal vagal complex. This plays a role in regulating gastrointestinal function (Aleksandrov *et al.* 1996). Daly (1953) reported a patient with an anterior insular tumour who manifested seizures consisting of light-headedness, nausea, retching, and vomiting. Another patient with an insular tumour had chronic episodic alternating diarrhoea and constipation (Pool 1954).

Cardiovascular and blood pressure changes have been associated with anterior insular function (Kaada *et al.* 1949, Wall and Davis 1951, Hoffman and Rasmussen 1953, Showers and Lauer 1961, Ruggiero *et al.* 1987). Stimulation of this area has been shown to increase blood pressure and heart rate (Ruggiero *et al.* 1987), as well as show the paradoxical response of lowering blood pressure when specific insular sites are stimulated (Penfield 1955). Insular projections to the NTS overlie baroreceptor afferent fields in the brainstem creating a possible mechanism for cortical control of cardiovascular and blood pressure changes (Ruggiero *et al.* 1987). Experiments conducted by Smith *et al.* (1986) demonstrated that cats subjected to middle cerebral artery occlusion had significantly elevated norepine-phrine, epinephrine, and dopamine plasma levels, but only if the infarct involved the insula. They concluded that the infarct caused loss of descending inhibitory input to brainstem cardiovascular regulating centres resulting in increased sympathoadrenal function.

Recent studies have elucidated the insula's role in cardiovascular modulation and have demonstrated some degree of lateralized function (Verberne *et al.* 1998). Cells

of the insula found to be responsive to baroreceptor stimulation with phenyl-epherine and sodium nitroprusside are predominantly sympatho-excitatory and found diffusely throughout the insula (Zhang and Oppenheimer 1997). Insular cells responding specificaly to blood pressure changes are predominantly located in the right posterior areas (Zhang and Oppenheimer 1997). Oppenheimer and Kedem (1996) demonstrated that the left insula is predominantly responsible for parasympathetic cardiovascular effects. This was also demonstrated to be the site of cortical regulatory cardiac parasympathetic activity during dynamic exercise (Williamson *et al*. 1997). It is postulated that damage in this area could result in increased sympathetic tone leading to a pro-arrhythmic state. It is posited that this pathophysiology may underlie increased cardiac mortality following stroke (Oppenheimer *et al*. 1996). Subsequent to insular infarction there is a pathological activation of the sympathetic nervous system. The percentage of circadian blood pressure variation is proportional to the extent of insular infarction. This circadian blood pressure variation is diminished in right sided insular infarcts, and the subsequent cardiovascular instability after stroke is the result of disinhibition of insular cortex leading to sympathetic activation (Klingelhofer and Sander 1997). In experimental middle cerebral artery occlusion the autonomic changes seen after insular infarction are exaccerbated by right sided lesions and advancing age (Cechetto and Hachiaski 1997). The time course of the most prominent response to stress after middle cerebral artery occlusion is between 3–5 days. This correlates with a measured increase in dynorphin from the central nucleus of the amygdala after an insula lesion (Cechetto and Hachinski 1997).

Alteration of respiration can also be seen as a function of the anterior insular (Sugar *et al*. 1948, Kaada *et al*. 1949, Kaada 1951, Hoffman and Rasmussen 1953, Frontera 1956, Showers and Lauer 1961). These authors showed that stimulation of the insula may result in respiratory slowing in either inspiration or expiration as well as frank respiratory arrest. Other visceral-autonomic functions in which the insula may serve a role include pupillary-dilatation (Kaada *et al*. 1951), shivering (Frontera 1956) and oral secretion (Frontera 1956, Showers and Lauer 1961). Because of the varieties of general and special visceral afferent input to the anterior insula, as well as its role in autonomic function, it has been suggested that this region serves as a multi-modal association area for visceral-autonomic function, (Mesulam and Mufson 1982b). These authors also propose that through the anterior insula's connections with the amygdala a visceral-limbic functional unit is established. Therefore the anterior insula may serve in the expression of various complex autonomic and visceral behaviours in response to affective tone (Mesulam and Mufson 1982b). A recent study has also suggested that the posterior insula also serves as a convergent receptor site for inputs from baroreceptors, chemoreceptors, and oropharyngolaryngeal brainstem nuclei. This suggests that this insular area is involved in the integration of a variety of visceral-autonomic input (Hanamori *et al*. 1997a).

The middle and posterior insula appear to be involved in vestibular sensory (Augustine 1985) and paramotor activity (Sugar *et al*. 1948, Frontera 1956, Showers and Lauer 1961, Crosby and Augustine 1976, Augustine and Crosby 1977). Temporal insular regions are involved in the temporal sequencing of multiple sensory modality inputs to the insula (Colavita *et al*. 1974, Layton *et al*. 1979). The posterior insula appears to be involved in somesthetic (Sudakov *et al*. 1971, Robinson and Burton 1980, Mufson *et al*. 1981, Mufson and Mesulam 1982),

auditory (Sudakov *et al*. 1971), visual (Maire-Lepoivre *et al*. 1986) and auditory-visual integration (Fallon *et al*. 1978, Loe and Benevento 1969).

Vestibular information is thought to be blended with somatic proprioceptive input at the thalamic level, in particular the VPI (Deecke *et al*. 1974), before being processed by the posterior insula (Rivier and Clarke 1997). Augustine (1985) suggests that the posterior insula may contribute a visceral component to vestibular consciousness and posits that the subjective visceral experiences of vertigo, such as nausea, require insula function.

Stimulation of the posterior insula has been shown to elicit gross skeletal muscle movements (Showers and Laucer 1961) as well as restricted movements of single muscles or small groups of muscles including contralateral ocular conjugate gaze and ipsilateral rotational movements (Sugar *et al*. 1948, Augustine and Crosby 1977). These movements may occur following stimulation of the posterior insula even in the absence of the primary motor area (Sugar *et al*. 1948). The insula is also one of a number of cortical areas involved in manual dexterity (Darian-Smith *et al*. 1996). Schneider *et al*. (1971), reported five seizure patients with circling and rotational movements as part of their ictus. In one case a middle cerebral artery aneurysm was found overlying the insula. Researches have suggested a crude rostral-caudal motor homunculus in the posterior insula (Frontera 1956, Showers and Lauer 1961) as well as in the region of the central insular sulcus (Crosby and Augustine 1976, Augustine and Crosby 1977). Because of its role in movement, Augustine (1985) has classed the posterior insula as a supplementary motor area.

Colavita *et al*. (1974) suggested that the insular-temporal region is critical for the ability to discriminate changes in the temporal sequencing of sensory stimuli. They felt this is true whether the task calls for differentiating auditory changes in frequency, or change in visual or tactile intensity. Layton *et al*. (1979) in another study demonstrated that ablation of this insula region caused an inability to re-learn temporal pattern discrimination tasks. It is felt that the insular temporal cortex is a multi-modal area concerned with the perception of temporal sequencing of sensory stimuli (Colavita *et al*. 1974).

Visual association information, although limited, arrives in the posterior insula via projections from the middle inferior temporal gyrus (Mufson and Mesulam 1982). Auditory input from primary and secondary sensory receptive areas are directly integrated with other sensory modalities in the posterior insula. Fallon *et al*. (1978) identified multi-modal cells of the insula responding both to auditory and visual input. The largest class of these neurons was felt to serve an inhibitory function for auditory tones. This was felt to be carried out through a descending auditory system which modified incoming auditory tones (Loe and Benevento 1969). The known anatomic connection between the medial geniculate body and the insular cortex more than likely plays a role in this descending system. What is most intriguing is that this system is activated greatest when both visual and auditory cues are present, rather than auditory alone (Loe and Benevento 1969). This may represent a mechanism for selected attention to specific auditory stimuli when associated with a visual correlate, while filtering out 'background noise' from other unrelated sources. Marie-Lepoivre *et al*. (1986) also demonstrated that cats with insular lesions had considerable difficulty attending and fixating on objects as well as problems with visually guided behaviour.

The posterior insula is also involved—with processing and integrating somesthetic input. Mishkin (1979) postulated that the most important region for

this input was in the secondary somatosensory cortex (SII). Damage to this region is thought to impair learning dependent upon somesthetic discrimination (Murray *et al*. 1980). Biemond (1956) also felt that conscious pain appreciation required SII to be intact. This was based upon his description of a patient with a dramatic loss of pain perception after a posterior insular lesion, even though the primary sensory cortex and thalamus were unaffected. Robinson and Burton (1980) however found that although some pain responding neurons were located in SII the adjacent posterior granular insula and area 7b of the parietal operculum contained numerous neurons far more sensitive to noxious stimuli. More recent evidence helps to corroborate the greater role of the posterior insula and parietal operculum than SII in the conscious response to painful stimuli. Berthier *et al*. (1988) described six patients with asymbolia for pain. These patients showed a lack of withdrawal to painful stimuli and decreased or absent emotional response to the same over both sides of their bodies, despite unilateral lesions which spared primary sensory and thalamic areas. All of their patients had posterior insular and parietal opercular damage, but in two patients SII was spared. Geschwind (1965) was one of the first to speculate that asymbolia for pain may be due to disruption of sensory-limbic connections. Mesulam and Mufson (1985) suggest that posterior insular damage may impair the processing of noxious stimuli through the disruption of insula-amygdala pathways. This pathway is felt to be necessary if an affective and motivational quality is to be linked with the sensory stimulus to create a perceptional experience and appropriate motor response. This postulate is supported by Cesaro and Ollath (1997) who noted that the medial thalamic nuclei encode nociceptive stimuli during attention-directed tasks. The cortical projections from the medial thalamus to the anterior cingulate and insula underscore the affective-motivational dimension of pain. Berthier *et al*. (1988) suggest that disconnection between the limbic system and the neocortex may prevent appropriate cognitive as well as behavioural reactions to pain.

A related but functionally paradoxical clinical disorder, the pseudothalamic pain syndrome (Benson 1979), was reported in a patient with consistent focal dysesthesia and conduction aphasia. There was involvement of the insula, however, in this case there appears to be an up-regulation in somatosensory limbic processing resulting in increased attention and affect to somesthetic stimuli.

An important clinical correlation of insular pathology and somesthetic dysfunction is the tendency to observe contralateral, bilateral (Penfield and Faulk 1955, Berthier *et al*. 1988) or ipsilateral (Penfield and Faulk 1955, Schneider and Crosby 1983) sensory deficits with a unilateral lesion. A regional cerebral blood flow study of normal volunteers receiving noxious stimuli compared to baseine demonstrated increased activity in the ipsilateral anterior insula (Andersson *et al*. 1997). This region of the insula along with ipsilateral prefrontal and contralateral anterior cingulate are felt to be involved in the spatial discrimination of acute cutaneous pain (Andersson *et al*. 1997). However, a study by Svensson *et al*. (1997) demonstrated that regional cerebral blood flow was increased in the contralateral anterior insula in response to both noxious cutaneous and intramuscular stimuli. This has significant implications in the evaluation of patients with insular pathology because there is often the tendency to think of the patient as being hysterical if they present with 'unconventional' neurologic symptoms.

Neuropeptides and endogenous opioids provide a neurochemical correlate of insular pathophysiology. Delta opioid receptors and met-enkephalin have been

shown to have a wide distribution throughout the insular cortex (Svingos *et al*. 1995). The rostral agranular insular cortex contributes to opioid-receptor mediated antinociception after local or systemic morphine administration (Burkey *et al*. 1996). This antinociception effect is felt to be associated with increased descending inhibition of dorsal horn neurons. When excitotoxic damage occurs in the insular cortex, immunoreactive changes in neuropeptides occur in the ipsilateral amygdala. The basolateral amygdala demonstrates increases in neuropeptide Y, while increases in leuenkephalin, dynorphin, and neurotensin are demonstrated in the central nucleus of the amygdala. These neurochemical changes in the ipsilateral amygdala are dependent on damage to the insular cortex.

The discussion of the role of the posterior insula in sensory processing would be incomplete without emphasis on its function as a multi-modal sensory cortex area. In this regard one of the more interesting aspects in the cases of pain asymbolia previously discussed (Berthier *et al*. 1988) is that the patients also failed to elicit any emotional affective, or motivational response to threatening visual and auditory stimuli. This was despite retention of the ability to describe the stimulus no matter what the modality. The work of Robinson and Burton (1980) identified neurons in area 7b which responded specifically to visually threatening stimuli. The presence of auditory responsive cells within the same general area (Fallon *et al*. 1978) corroborates the concept of a multi-modal sensory cortical area. Although olfactory and gustatory functions are predominantly associated with the anterior insula it is tempting to speculate that had Berthier and colleagues tested their patients with noxious olfactory or gustatory stimuli they might have experienced the same phlegmatic response that was derived with visual and auditory stimuli. As previously described, intrainsular anatomy strongly suggests a greater directional bias from anterior to posterior (Mesulam and Mufson 1982b). Therefore, although olfactory and gustatory information is processed in the anterior insula, there is evidence to suggest that this sensory information is also relayed to the posterior insula for incorporation with other multi-modal inputs. Indeed Mesulam and Mufson (1982b) note the uniqueness of the posterior insula as possibly the only cortical area in which input from all five senses converge to form a multi-modal association area.

The insula appears to play a role in emotional affectual response, and emotional components of recall. The anterior insula has been shown to be involved in the neural response to strong and mild expression of disgust (Phillips *et al*. 1997). This is the same area of the insula known to be involved in conditioned taste aversion. Phillips *et al*. (1997) posits that this area of the insula is involved with the appraisal of distateful stimuli. The recall generated emotion of sadness has been linked to increased activity in the anterior insula on positron emission tomography. It has been suggested that this region participates in the emotional response to potentially distressing cognitive or interoceptive sensory stimuli (Reiman *et al*. 1997).

The insula also most likely plays a role in language. It is perhaps the most difficult function to prove because there is no animal model. As mentioned previously the left insular region is larger than the right suggesting a functional substrate for language. Electrical stimulation of the insula has proved difficult to interpret and observations from naturally occurring structural lesions have rendered little hard data concerning language. As early as 1877 Major suggested that the insula played a role in language and in 1890 Pascal reported that motor aphasia could develop from a left insular lesion alone. Others suggested that motor aphasia could arise

after anterior, and sensory aphasia after posterior lesions of the insula, but proof was never established (Monakow 1897). Some reports have suggested that in cases of persistent Broca's aphasia the anterior insula is always involved (Mazzocchi and Vignolo 1979, Murdoch *et al*. 1986, Alexander *et al*. 1989). Wernicke (1874) was one of the first investigators to propose that the crucial lesion in the development of conduction aphasia was in the insula. Goldstein (1911) further suggested that in disorders of language repetition the insula was invariably damaged. Contemporary clinical reports suggest that involvement of the insula is not always necessary in cases of conduction aphasia, but many reported cases did have some degree of insular involvement (Benson 1979, Damasio and Damasio 1983, Ardila *et al*. 1997). Marshall *et al*. (1996) reported a patient with conduction aphasia manifested predominantly with semantic paraphasic errors. These authors suggested that cortical diaschisis with hypoperfusion in the posterior insular-intrasylvian parietal opercular area was responsible for this. In many of these cases insular projections through the extreme capsule may be involved (Damasio and Damasio 1980). Ojemanna and Whitaker (1978) produced transient anomia through electrical stimulation of the posterior insula. Naming errors occurred every time this posterior insula area was stimulated. Wernicke's aphasia, especially when persistent (Mazzocchi and Vignolo 1979, Ardila *et al*. 1997), pure word deafness (Kertesz 1983, Liepmann and Storch 1902), and neologistic jargon (Kertesz and Benson 1970, Kertesz 1983), have all been associated with posterior insular lesions. Cappa *et al*. (1983) suggest that insular involvement may be responsible for the aphasic features seen with subcortical lesions. Although the insula is involved in many aphasic syndromes its exact role in language remains nebulous because other surrounding cortical and subcortical areas are invariably involved. There is strong evidence to suggest that when aphasia, whether anterior or posterior, is persistent there is more likely involvement of the insula than in those patients who manifest more transient symptoms (Ardila *et al*. 1997). Habib *et al*. (1995) reported a patient with transient mutism and persistent auditory agnosia which involved bilateral insula lesions. After language competences returned, an auditory agnosia for non-verbal sounds persisted.

Considering the previously discussed anatomic arrangement of the insula and its functions it is tempting to speculate on the role of language in this schema. The insula may serve as a language area for both propositional comprehension of emotionally charged sensory input (posterior insula) as well as an area for emotionally intoned and motivationally charged verbal output (anterior insula). Like other sensory, visceral and autonomic functions of the insula there may also be an associated language-limbic link which serves to attach an emotional value to incoming verbal information as well as a motivational and affective quality to verbal expression. The paramotor and supplementary motor regions of the insula may even serve to initiate motor responses to the language-limbic drive mechanism. The insula may possibly serve a role in the production of expletive output in response to emotionally charged internal or external stimuli. Most people have had the experience of shouting a four letter expletive in response to a sudden painful stimulus before they have had time to think about it. The limbic charge in response to the somatosensory stimulus might possibly activate speech production in the anterior insula as a result of this. It would be interesting to study non-fluent aphasic patients with regard to insular involvement and correlate those who retain expletive speech and those who do not. Although little is known of the

pathophysiologic mechanism behind the guttural and visceral sounds, throat clearing, and sometimes coprolalia seen with Gilles de la Tourette syndrome, it is tempting to suggest that the insula or its connections may be involved.

It is also of interest that persistently aphasic patients usually have insular involvement. Could the lack of language recovery be related to an impairment in limbic-motivational drive? The indifference to pain as well as threatening visual and auditory stimuli seen with insular lesions may also parallel an indifference to language recovery. Berthier (1987) reported a case of a patient with a right insular lesion in which there was not only multi-modal sensory neglect but also mutism. Although this was described as a case of crossed aphasia the patient was able to comprehend written language and write, similar to the aphemia often seen with left sided insular lesions. One may argue that this is not a true language disorder, but rather a limbic language dissociation depriving the patient of the motivational drive to speak. Further detailed evaluation of patients with insular damage and language disturbance is warranted. For a more detailed description of the insula's role in language please see Ardila *et al*. (1997).

Clinically, the insula may also serve a major role in disease states which present with non-specific somatosensory, visceral, or autonomic symptoms. Patients presenting with these complaints are often very perplexing and lead many physicians to suspect malingering or conversion reactions. Considering the other side of this concept, the insula may also serve as an integrator of neocortical, limbic and autonomic input. The effects of this would be most manifest in normal individuals under emotional stress. Response may result in alteration of gas-trointestinal, cardiovascular, blood pressure, and respiratory functions. This may be a mechanism for 'psychosomatic' illness and a possible cause of stress induced illness such as peptic ulcer or cardiovascular disease. Considering the alterations seen in blood pressure with stimulation of the insula it may even serve a role in the development of essential hypertension.

Ramirez-Amaya *et al*. (1996) demonstrated that the insula is necessary for conditioned immunosuppression. In an interesting experiment investigators demonstrated that rats exposed to a specific taste coupled with coadministration of an immunosuppressive drug developed conditioned immunosuppression. Hence re-exposure to the taste without the drug resulted in an immunosuppressive response. This conditioned immunosuppression was ablated with insular cortex lesions, yet insular lesions did not affect the normal immune response (Ramirez-Amaya *et al*. 1996). The role of the insula in stress induced immunosuppression remains to be elucidated.

Depressed patients have been shown to have decreased uptake of the ligand [18F] altanserin (a select type-2 serotonin receptor binder) within the right anterior insular cortex (Biver *et al*. 1997). This suggests that the insula does play a role in mood regulation. Clinical correlates of insular functions however continue to remain a mystery, and an area for future research. One of the areas for future research includes the role of the insula in sleep. The insula is one of a number of paralimbic regions that is activated during REM sleep (Nofzinger *et al*. 1997). The exact impact of insular lesions on alteration of REM sleep is unknown.

Summary

The insula is a heterogenous area of cortex that architectonically consists of an anterior agranular allocortical region, a posterior granular isocortex, and a middle

dysgranular transition zone. Connections to and from the insula link respective allocortical paralimbic regions and granular-isocortical areas as well as amygdala, thalamus, basal ganglia, and brainstem. Functionally the insula acts as a processing area for all modalities of sensory input. The anterior insula is more involved in processing autonomic and visceral information for maintenance of the internal milieu while the posterior insula is more concerned with integrating extrapersonal sensory stimuli (Mesulam and Mufson 1982b). Somatosensory and visceral autonomic information is integrated in the insula through its connections with other brain regions. The posterior insula also serves the function of a vestibular and supplementary motor area. This may act as a zone for initiation of motor responses to both internal and external stimuli. It appears possible that the insula integrates language functions with the limbic system, thus allowing an appropriate emotional, autonomic, and motivational response to language stimuli and, influencing both the effectual and the prosodic components of language output. Neurological degenerative diseases such as Alzheimer's demonstrate atrophy of insular regions. The cognitive, emotional, and behavioural sequelae of this pathology can better be understood when the functions of multi-modal sensory- motor-limbic integration is considered (Augustine 1996).

In order to better understand insular functions it will be important to utilize the knowledge gained from basic neuroscience research, and modern brain imaging techniques. It will also be clinically important to identify patients with lesions restricted to the insula, and correlate these findings behaviourally.

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