



# The Neuropsychological Impact of Insular Cortex Lesions

Catherine Louise Jones, Jamie Ward, Hugo D Critchley

## ► To cite this version:

Catherine Louise Jones, Jamie Ward, Hugo D Critchley. The Neuropsychological Impact of Insular Cortex Lesions. *Journal of Neurology, Neurosurgery and Psychiatry*, 2010, 81 (6), pp.611. 10.1136/jnnp.2009.193672 . hal-00557423

**HAL Id: hal-00557423**

**<https://hal.science/hal-00557423>**

Submitted on 19 Jan 2011

**HAL** is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

# **The Neuropsychological Impact of Insular Cortex Lesions**

Catherine L. Jones<sup>1,2,+</sup>, Jamie Ward<sup>2</sup> and Hugo D. Critchley<sup>1</sup>

<sup>1</sup>Dept. of Psychology and <sup>2</sup> Clinical Imaging Sciences Centre, Brighton and Sussex Medical School, University of Sussex, Falmer, UK

+ Corresponding author:

Catherine L. Jones, MSc  
Clinical Imaging Sciences Centre  
University of Sussex  
Eastern Ring Road  
Falmer, Brighton  
BN1 9RR  
+44 1273 876776  
c.l.jones@bsms.ac.uk

**Keywords:** Cognitive Neuropsychology, Limbic System, Stroke, Tumours

**Word count:** approximately 6,500 words

## **Abstract**

Influential models based on an increasing body of neuroimaging evidence propose that insular cortex integrates cognitive, affective, sensory and autonomic information to create a consciously perceived, “feeling state”. To appraise these models and evaluate interpretations of neuroimaging findings, we review evidence pertaining to the psychological and behavioural consequences of insula lesions. We focus on the emotional, perceptual, sensorimotor symptoms and disorders of body awareness associated with insula damage. This comprehensive review is intended to inform existing neuropsychological models of insula function in order to guide future research.

## **Introduction**

Our knowledge regarding the functions of the insula (insular cortex or Island of Reil) are derived from partly convergent evidence from animal experiments, clinical reports, stimulation studies and more recently functional neuroimaging experiments. Located deep within the Sylvian fissure, the human insula is regarded as the “hidden fifth lobe”.

Macroscopically, the structure is divided into anterior and posterior portions by the central insular sulcus. In phylogenetic terms, the insula evolved from a smooth structure, as in the new world monkey, to 5-7 lobes in humans, reflecting increased organisational and thus probably functional complexity. Anatomical and cytoarchitectural studies also suggest subregional specialization within the insula [1, 2]. Post mortem dissections show that the main arterial supply to the insula is the middle cerebral artery (MCA) predominantly the sylvian segment (M2). Isolated insular infarcts are uncommon, occlusion of the MCA results in cerebral infarction which typically affects the insula but will often result in diffuse damage across neighbouring regions including the internal capsule and basal ganglia. The insula can be affected by both high grade and low grade gliomas. Due to its location and functional complexity, resection of insula tumours has traditionally been viewed as hazardous and this procedure is not well documented.

Studies using direct cortical stimulation link the insula to visceral sensation and autonomic regulation. Patients describe gastrointestinal sensations involving nausea and associated chewing, swallowing, salivation and also inhibition of respiration [3] and changes in heart rate [4]. Indeed a number of studies report autonomic dysregulation as a result of damage to the insula [4, 5]. Functional neuroimaging studies reveal insular cortex to be active in a more diverse set of behavioural contexts including language, auditory processing, risk processing, sensorimotor processing, pain processing, taste and flavour perception in addition

to, or in conjunction with, autonomic processing. Enhanced insula activity also appears to be a signature of affective symptoms and neuropsychiatric disturbances including anxiety disorders [6], drug addiction [7] and emotional dysregulation [8]. Thus one challenge in developing a satisfactory neuropsychological model of insula function is to account for its involvement across these different domains which require access across multiple functional circuits. It is thus unclear if a unitary account of insula functioning is feasible or realistic. In the most general terms, one could argue that the insula serves an integrative function. An alternative would be to consider the insula to have a core function (e.g. in visceral control) from which, over the course of evolution, more specialised functions have emerged (e.g. taste perception, disgust, limb awareness, articulation of speech). Craig [9] attempts to explain a wide variety of insula functions within a unitary account. In his model, insular cortex integrates information about changes in bodily, special-sensory and cognitive states to create unitary feelings that encapsulate “emotional now”, “emotional self” or a “global emotional moment”.

Another important consideration is whether different regions of the insula subserve different functions. One apparent anatomical distinction is between the anterior and posterior sections. The more posterior, granular regions of the insula, receive stronger inputs from the sensory thalamus and from parietal, occipital and temporal association cortices. Posterior insula has been ascribed a role in somatosensory, vestibular and motor integration. The more anterior, agranular regions have reciprocal connections to ‘limbic’ regions including anterior cingulate cortex, ventromedial prefrontal cortex, amygdala and ventral striatum. Anterior insula is implicated in the integration of autonomic and visceral information with emotional and motivational functions. A second important anatomical distinction is between possible differences between right and left hemisphere insula functions [10]. Although finer cut

anatomical distinctions are possible [11], at present the neuropsychological literature does not speak to this.

Patients with damage to insular cortex provide privileged means of evaluating the many functions associated with insula engagement. The extensive connections with other subcortical and cortical regions suggest that patients with damage to the insula ought to exhibit widespread neurological and psychological disturbances. The aim of the present review is to appraise and inform current theories of insula function (driven primarily from neuroimaging studies) in the light of neuropsychological studies (which have been featured less prominently). A further goal is to highlight gaps in our present knowledge that could be addressed through studies of neurological patients. An exhaustive search of the empirical literature was performed with keywords: insular cortex, insula, lesion entered as search criteria into the pubmed database. The literature is dispersed between case reports, case series and lesion mapping studies, typically using statistical techniques to compute voxel-level associations between lesion and symptom [12]. Table 1 summarises these studies grouped with reference to these three methodologies. For ease of exposition, the functions that have been attributed to the insula are grouped together below into four general themes. These are; (1) interoception, emotion and emotional decision-making; (2) perceptual functions; (3) speech and sensory-motor integration; and (4) bodily awareness. We also suggest further research approaches for examining neuropsychological effects of insular cortical lesions in order to extend our understanding of how the insula contributes to thinking, feeling and behaviour and to better predict clinical outcomes.

Study	Patients (n)	Mean time post onset  (months)	Hemisphere	Insula Region	Observations
-------	-----------------	---	------------	------------------	--------------

### Case Report

Hyman & Tranel, 1989 [67]	1	0	Left	Posterior	Aphasia
Fifer, 1993 [52]	1	-	Right	Undefined	Auditory agnosia
Habib et al., 1995 [53]	1	-	Bilateral	Undefined	Transient mutism, non-verbal auditory agnosia, amusia
Griffiths et al., 1997 [86]	1	4	Right	Posterior	Auditory agnosia
Griffiths, Warren, Dean, & Howard, 2004 [87]	1	12	Left	Anterior	Amusia
Carota et al., 2007 [62]	1	<1	Left	Anterior	Aphasia
Starr et al., 2009 [51]	2	>5years	Left	Undefined	Hypersensitivity to pain

### Case Series

Manes, Spinger, Jorge & Robinson, 1999 [88]	10	1-2	Right (n=4) Left (n=6)	Undefined	Impaired verbal memory (more severe in left lesion patients)
---	----	-----	---------------------------	-----------	--

Pritchard et al., 1999 [48]	6	>1year	Right (n=1) Left (n=5)	Rostradorsal versus non-rostradorsal	Impaired taste recognition and magnitude estimate (taste intensity) in patients with rostradorsal lesions.
Greenspan et al., 1999 [54]	6	-	Right (cases B.B., K.B. and C.M.)  Left (cases M.C., K.H. and J.E.)	Anterior (C.M. and J.E.)  Posterior (M.C.)  Retro (K.H., B.B. and K.B)	Deficits in:  heat pain threshold (M.C. and K.H.)  mechanical pain threshold (M.C., K.H and B.B.)  Cold pain tolerance (M.C. and C.M.)  Innocuous cool threshold M.C., K.H. and B.B)
Cereda et al., 2002 [49]	4	>1	Right (cases 1 and 4)  Left (cases 2 and 3)	Posterior (all)	Sensory deficits including transient pain syndrome and in other modalities (Cases 2 and 4)  Taste recognition deficits (case 2)  Acute pseudovestibular syndrome (cases 1, 2 and 4)  Somatoparaphrenia (case 4)  Aphasia (cases 2 and 3)

---

### Lesion Symptom Mapping

---

Dronkers, 1996 [65]	25	-	Left	Anterior	Apraxia of Speech
Daniels & Foundas, 1997 [89]	4	-	Right (cases 1 and 2)  Left (cases 3 and 4)	Anterior (cases 1, 2 and 3)  Posterior	Dysphagia (cases 1, 2 and 3)



				(cases 2 and 4)	
Manes, Paradiso, Robinson,1999 [90]	9	2	Right (n=4) Left (n=5)	Undefined	Neglect (tactile, auditory and visual) right > left lesions.
Naqvi, Rudrauf, Damasio, & Bechara, 2007 [25]	19	-	Right (n=6) Left (n=13)	Undefined	Disruption of smoking addiction
Clark et al., 2008 [31]	13	>12	Right (n=6) Left (n=7)	Anterior	Impaired risk adjustment
Weller et al., 2009 [32]	10	>3	Right (n=5), Left (n=5)	Undefined	Impaired risk processing (insensitivity to probability)

---

**Voxel based  
lesion-  
symptom  
mapping**

---

Karnath, Baier, & Nagele, 2005 [77]	14	<1	Right	Posterior	Anosognosia for hemiplegia and hemianaesthesia
Borovsky et al ., 2007[91]	50	>12	Left	Anterior	Impaired production of fluent and complex speech
Spinazzola et al., 2008 [80]	4	2	Right	Posterior	Agnosia for hemianaesthesia
Golay et al., 2008[92]	28	2	Right	Posterior	Neglect

---

Table1: Neuropsychological studies of the effects of insula lesions on humans. A summary of human neuropsychological studies that have examined the role of the insula either studying patients with relatively focal lesions, or studying larger groups of patients and inferring the critical lesion site for a given symptom using lesion-symptom mapping methods.

## **1. Interoception, Emotion and Emotional Decision Making**

### ***1.1 Interoception***

The link between interoceptive awareness and emotional cognition has its historical roots in the writings of James, Lange, and even Descartes, who argued that emotions are the perceptions of bodily responses. For example, fear is associated with sweating and hyperventilating and sadness with the physical act of crying. According to these views, emotion necessitates experience of such bodily responses. These accounts fell out of favour with the view that bodily arousal states lack the same degree of differentiation as emotional states [13] and evidence that cognitive schema determine which specific emotion might arise from a change in bodily arousal [14]. However, elements of such peripheral theories of emotion reappear in several contemporary accounts, most notably Damasio's somatic marker hypothesis [15]. The somatic marker hypothesis was developed to account for why patients with focal frontal brain lesions repeatedly manifest problems with social and motivational behaviour, despite awareness of the appropriate behaviour for that context. Somatic markers, i.e. bodily responses (related to emotional feelings) are proposed to bias and shape behaviour rather independently of conscious thought and awareness. Experimentally, this was apparent during performance of the 'Iowa gambling task' where learning and avoidance of risky decisions develops over the course of repeated trials in healthy people who produce normal somatic bodily responses. A full discussion of this theory is beyond the scope of this report (but see [16]). In developments of this model, insular cortex is highlighted as an important neural substrate for representing these emotional markers derived from internal bodily responses, and through which perception of physiological responses may give rise to a conscious 'gut feeling' or urge that guides behaviour and influences future decisions.

Neuroimaging studies show enhancement of insula activity when threatening emotional stimuli are perceived consciously in conjunction with bodily arousal [17], and both the level of activity and spatial extent of right insula activity in fMRI predict conscious awareness of one's own physiological processes such as heart beat [18]. Similarly, representations of changes in physiological state in mid and anterior insula appear to underpin consciously experienced fatigue associated with inflammation associated sickness [19]. Interoception may allow for representations of cardiac (baroreceptor) function within the insula [20,21,22] to be integrated with beliefs about one's physiological state (based on false cardiac feedback for example), to guide emotional attributions [23]. Interestingly, bilateral insula activation also commonly accompanies anxiety states associated with enhanced physiological arousal [24]. Naqvi and co-workers [25] showed lesions to the insula (in either hemisphere) diminished addictive behaviours; patients with strokes involving insula reported greater ease in giving up smoking, without relapse or persistent urge to smoke, in contrast to smokers with strokes affecting other areas. This effect may be the result of a reduced ability to detect interoceptive states linked to craving, or a reduction in hedonic feelings induced by smoking cigarettes [26]. This finding is also in line with a Somatic Marker model of addictive behaviour in which exposure to or recollection of an experience associated with a drug can reactivate this 'interoceptive memory' state [7]. Future patient studies will establish how general the effects of insula lesions are on other forms of addiction. Evidence within the animal learning literature highlights the contribution of visceral states and insula cortex to motivational learning [27]. In broad terms, lesions to insular cortex are predicted to compromise the central representation of bodily responses, and thereby impact on social and motivational behaviour. Neuropsychological evidence relating to this idea is discussed in the next two sections.

## ***1.2 Emotional Decision Making***

Humans can appear irrational in their reasoning often relying on fast, intuitive, instinctive reactions to uncertain situations rather than rational deliberation [28]. However lesions affecting insular cortex may disrupt these intuitive processes. Bar-On and co-workers [29] recruited patients with non-focal lesions of the ventromedial prefrontal cortex, amygdala and insular/somatosensory cortices (experimental group) and assessed levels of emotional intelligence, social functioning, decision making and general cognitive ability against patients with focal lesions in brain regions outside limbic and viscerosensory regions (control group). There were no significant differences between the experimental and control group in general cognitive performance. When playing the Iowa gambling task, normal subjects learn over time, through a schedule of rewards and punishments, to choose the one pack associated with the highest overall gain (and least risk) [30]. In the Bar-On study, the experimental group made significantly more disadvantageous than advantageous choices over time resulting in an overall loss compared to the controls. Patients in the experimental group also had significantly impaired social functioning and emotional intelligence compared with control patients. Due to small group sizes in this study, the authors were unable to compare performance between lesion sites of interest e.g. vmPFC, amygdala and insula. Also the lesions extended across other brain regions making it difficult to infer if a specific region or set of regions was responsible for poor task performance. However, the findings do have wider implications for patient recovery in terms of their neuropsychological and neuropsychiatric outcome.

Clark and colleagues [31] compared performance of patients with focal stable ventromedial prefrontal cortex (vmPFC) lesions and focal insula lesions (greatest overlap in anterior portion), to a ‘control lesion’ group (lesions affecting dorsal and lateral PFC) and healthy control subjects on the Cambridge Gambling Task, a paradigm quantifying risky

decision making. Patients with insula lesions differed significantly from other groups in that they consistently betted at a high level, even as the odds became less favourable, thereby showing no evidence of risk adjustment. Paradoxically, another study demonstrates that insula lesion patients were more cautious in their decision-making, displaying significantly reduced risk-taking behaviour when compared to healthy controls even in risk advantageous situations where there is the potential of gaining money [32]. Common to both these observations [31,32] is the observed insensitivity of insula patients to the expected value associated with the outcome which Weller [32] proposes reflects an ‘emotional bluntness toward risk’.

### ***1.3 Emotion: Experience and Recognition***

Neuroimaging studies indicate a role for human insular cortex in representing autonomic information in the context of both negative emotion and positive emotion [33]. Again, the postulated role of the insula is in the ‘feeling states’ of the emotion, in particular, the associated bodily sensations. One prediction is that patients with insula lesions will be able to perceive the emotional nature of stimuli illustrated, for example by accurately categorising fearful and happy faces. However, insular patients would lack the appropriate affective response. Adolphs and colleagues [34] studied 108 patients with focal brain damage and determined the degree of lesion overlap as a function of emotional recognition. Right somatosensory related cortices, insula, anterior supramarginal gyrus along with left frontal opercular lesions were associated with poor performance in categorising facial expressions, consistent with the notion that the representation of bodily reactions (somatosensory and viscerosensory knowledge) contributes to emotional recognition through a simulatory ‘as-if loop’.

In terms of specific emotional deficits following insula damage, neuropsychological evidence is sparse, with the exception of disgust recognition, where integrity of the left anteroventral insula appears important. In a single case report, Patient NK showed highly selective impairments for recognising disgust from facial and vocal cues and diminished subjective experience of disgust following a focal lesion involving the left insula and basal ganglia [35]. Another single case, patient B, had impaired recognition for dynamic facial expressions of disgust resulting from bilateral insula lesions [36]. To further clarify insula involvement in disgust, Kipps and colleagues [37] used voxel based morphometry to investigate how differences in gray matter volume, probably reflecting tissue atrophy, were related to deficits in emotion processing in patients with preclinical Huntington's Disease. Significant correlations were found in volume of grey matter in left anteroventral insula and disgust recognition (this finding did not generalise to other emotions) in HD mutation carriers; this correlation was not present in the control group. It would be useful to establish whether self-reported emotional intensity and autonomic responses to emotional stimuli are normal in such patients. These lesion studies are consistent with neuroimaging data supporting a function of insular cortex in the recognition and experience of disgust, perhaps more so in the left hemisphere [38]. Differential hemispheric sensitivity has been proposed for different emotion types, with the right hemisphere activity associated with negative emotion and left hemisphere activity associated with positive emotion [39]. Some argue this functional asymmetry in emotion processing applies to insular cortex and reflects asymmetrical representation of homeostatic states derived from peripheral autonomic nervous system activity [9, 10]. The lesion data discussed thus far do not fully support this view, in that impairment in disgust processing results particularly from left insula damage. However, insular cortex in both hemispheres is involved in gustatory representation [40, 41] and is an early point of convergence for gustatory, olfactory and autonomic inputs [42]. Left anterior

insular cortex with the frontal operculum dominates in declarative perception of taste (see below). A greater body of patient-based evidence is needed to resolve whether there is topographic or hemispheric insula organisation with respect to negative and positive valenced stimuli and require further tests specifically designed to assess lateralisation differences in patients with unilateral lesions.

## **2. Perception**

In this section the impact of insula lesions on representing sensory information to form integrated percepts, specifically in the context of taste, pain and audition, is addressed.

### ***2.1 Taste and Flavour***

The primary taste cortex in primates and humans is located in the rostradorsal insula both anterior and posterior [42, 43] where gustatory, olfactory, and visceral sensory inputs required for taste representation and perception of flavour are integrated. Taste and interoceptive inputs enter distinct parts of the nucleus tractus solitarius forming two pathways, which first come together in the insula [44]. Some patients with insula tumours and resulting epilepsy are reported to experience seizures preceded by a gustatory aura [45] and insular epilepsy can trigger gustatory hallucinations [46]. Further, electrical stimulation of the insula in patients undergoing surgery for epilepsy can elicit nausea, unpleasant tastes and unpleasant throat and stomach sensations [3, 47].

Interestingly, evidence suggests right insula lesions induce ipsilateral perception and recognition deficits, whereas left insula damage results in an ipsilateral deficit in taste perception but a bilateral deficit in taste recognition [48, 49]. This suggests the left insula receives input from both sides of the tongue and relays this information to secondary taste

and appraisal regions accessing language. Insula lesions can disrupt acquisition and expression of conditioned taste aversion and the enhancement or suppression of conditioned immune responses coupled to either taste or olfactory cues, leaving the normal immune functioning unaffected [50]. Damage to the left insula is also associated with difficulties in assigning taste adjectives to smell (e.g. classifying an odour as “sweet”) in the absence of impairments in olfactory processing [51].

## ***2.2 Pain***

The insula is a major site for cortical pain encoding [52]. Nociceptive information is relayed via afferent fibres from the second somatosensory cortex (SII) to the posterior insula and then to the anterior insula. Clinical evidence supports this idea with patients with posterior insula lesions (but not anterior) exhibiting heightened pain thresholds [53] or asymbolia (pain is perceived but its aversive nature has been abolished) [54, 55]. Further, evidence suggests both the posterior and anterior insular cortices are somatotopically organised, supporting graded rerepresentations of pain signals [56].

Reciprocal connections with prefrontal cortex, anterior cingulate cortex, amygdala, parahippocampal gyrus and the SII promote the idea that the insula uses cognitive information to modulate connected brain regions involved in processing sensory-discriminative, affective and cognitive-evaluative components of pain. Therefore, one could postulate that insula lesions would result in a complex pattern of altered sensitivity to pain stimuli. Recently, Starr and colleagues [57] used sensory assessment and fMRI with two patients who had suffered large left MCA ischemic strokes involving insular cortex, to assess pain perception, sensory thresholds and neural correlates of pain experience. Both patients were able to rate the intensity of noxious stimuli of their affected side (right) with no evidence of insula activation in either hemisphere. However, stimulation of the unaffected



side (left) was associated with activation in right insular cortex. Consistent with the previous literature, regions activated in controls related to generation of pain experience included ACC, SMA, SII, insula, DLPFC and cerebellum. Perhaps unexpectedly, both patients rated pain stimuli as significantly *more* intense compared with the healthy control group when their affected side was stimulated. Interestingly, there was no difference in the groups for unpleasantness rating of pain experience suggesting a decoupling of the two dimensions of pain may have occurred. The authors [57] conclude that subjective awareness of noxious stimuli involves multiple, distinct patterns of brain activity where insular cortex is not a prerequisite.

### ***2.3 Auditory Perception***

The role of insular cortex in auditory perception is controversial. There are a number of clinical reports of auditory agnosia on the contralateral side following insula infarction [58, 59]. Bamiou and colleagues [60] describe auditory temporal processing deficits following insula infarction (particularly left hemispheric), in patients who otherwise had preserved cognitive function. Central auditory function in a series of patients with ischemic lesions of the insula and of adjacent cortical and subcortical areas, with and without involvement of other auditory structures, was assessed by means of a validated central auditory test battery.

There is also evidence to suggest insula is part of a functional network supporting sensory integration through processing temporal information about stimuli across different modalities [61]. Assuming the insula does play a role in temporal synchrony detection, it is unclear whether this role is strictly for multisensory events or for two events in the same modality (a recent review of the latter highlights the role of a parietal ‘when’ route [62]).

Important questions remain such as the distinct functions of the posterior and anterior insula in auditory processing, e.g. whether the posterior insula is a primary sensory region

representing basic auditory signals, while the anterior insula reacts to bimodal information and integrates multimodal sensory, cognitive and affective information. It is also of interest how these processes contribute to the emotional experience of music, potentially another important function of the anterior insula [9]. These ideas can be explored by comparing patients with damage affecting posterior insula to patients with anterior insula damage on performance of both pure auditory perception tasks and tasks which require integration of sensory information and the recruitment of higher associative brain regions.

### **3. Speech and sensori-motor integration**

Dronkers [65] used the overlapping lesion method based on CT and MRI scans to show that lesions to the left anterior insula are associated with problems in articulation termed ‘apraxia of speech’, a form of aphasia. This finding is supported by a number of studies [63-65] but is not a universally accepted view. Hillis and colleagues [66] argue that Broca’s area, and not the insula, is associated with articulatory impairments. Detail of tissue damage was acquired using diffusion weighted and perfusion-weighted imaging revealing that apraxia of speech was correlated with damage to Broca’s area and not the insula. The authors conclude that in apraxia of speech the insular is most commonly damaged because it is most vulnerable to disruption of the middle cerebral artery, and therefore this symptom and insular damage may be independent manifestations of large stroke [66]. Other studies have also noted difficulties with speech that are significantly greater in speech repetition (i.e. audio-motor transformation) than in reading aloud or other modes of speech production [67, 68]. Consistent with these findings, Schmid and Ziegler [69] noted that performance in a multi-sensory matching task (involving audio-visual syllables) was predicted by both repetition ability and presence of apraxia for speech. Evidence for functional compensation of the insula in language arises from a study of 42 patients who underwent surgery for insular

low-grade glioma. Intraoperative electrical mapping evoked language, sensory (pain) and vestibular disturbances in some patients. Immediately following resection, 21 patients experienced transient contra-lateral hemiparesis, 10 patients developed articulatory disorders and in 7 cases inertia with loss of interest and affect (abulia) was reported [70]. However, 3 months post surgery there was no evidence of visceral, cardiovascular, sensorimotor, gustatory, auditory-vestibular or language disorders in any of the patients. Research which fully assesses cognitive functioning in tumour patients pre-, intra- and post-operatively will be an important future resource for determining regional functional specificity [e.g. 71].

Functional imaging studies show that both auditory speech perception and speech production activate a region in the left insula [72] and that the bilateral insula responds to both heard mouth sounds [non-speech] and motor execution of the mouth [73]. The generation of the illusory syllable in the McGurk illusion (synchronous presentation auditory /ba/ and visually presented /ga/ gives rise to illusory syllable /da/ [74]), relative to non-illusory audio-visual synchronous syllables, has been linked to activation of motor representations of speech including the insula and Broca's area [75].

In sum, although there is evidence for an audio-visuo-motor representation of speech in the insula, there is presently insufficient evidence to distinguish its functional role (if any) from other speech and motor regions. Clinical findings are inconsistent, perhaps reflecting inadequacies of patient selection criteria, differences in patient assessment and radiology, involvement of neighbouring regions and patients own inherent characteristics pre-lesion onset.

#### **4. Bodily Awareness**

Some patients with right posterior insula lesions deny paralysis (anosognosia for hemiplegia) or may deny lack of tactile sensation (anosognosia for hemianaesthesia). This

condition does not seem to reflect deficits in motor or sensory perception per se but a disturbance in the ‘highest level of organisation’ of a given function [76]. Karnath, Baier and Nagele [77] used lesion overlay plots to show the posterior insula is the structure most commonly damaged in a group of stroke patients with anosognosia for hemiplegia/hemiparesis compared to a group otherwise matched for clinical and demographic variables, where posterior insula damage occurred in half of the patients. Anosognosia for hemiplegia or hemiparesis predominantly originates from damage to the right side of the brain. It is a major neuropsychological disorder frequently observed in neurological patients with failure of recovery and rehabilitation often depending on its presence. Increasing severity of anosognosia is associated with larger lesions, suggesting that the condition may result from damage to or disconnection of a network of cerebral regions, typically frontal and parietal, and not a specific cortical or subcortical region and thus a limitation of the Karnath and co-workers [77] study is that the patients sustained damage to multiple brain structures. However Cereda and co-workers [49] report striking evidence that a focal lesion to the right posterior insula can be sufficient to induce a form of anosognosia – somatoparaphrenia. In this instance, the patient experienced delusions of being touched by a stranger’s hand and she thought of her upper limb as a foreign body. In healthy participants, the right posterior insula is activated in one multi-sensory illusion that distorts body ownership, namely the rubber hand illusion [78]. In this illusion, the location of one’s own arm/hand (hidden from view) is mislocalised to an observed arm/hand when both are stroked in synchrony. A patient group with lesions involving posterior insula, who are generally more resistant to the rubber hand illusion compared to other lesion groups, would be of future experimental interest. A functional imaging study used PET in healthy volunteers to show right posterior insula activation when visually observed movement corresponded to the participants’ executed movements, with activity decreasing with a reduced sense of controlling the movement [79].

Thus the posterior insula seems to be significantly involved in the integration of sensory and motor information with input signals relating to self-awareness and expectations of the functioning of one's body.

In a recent review paper, Spinazzola and colleagues [80] argue that different disorders of unawareness such as varying forms of anosognosia, somatoparaphrenia and neglect are domain specific disorders of consciousness, with the region of brain damage differentially disrupting self-monitoring processes that in normal circumstances act to regulate awareness of our physical and cognitive status. The insula is viewed as a comparator site, detecting mismatch between predicted and actual peripheral feedback and therefore may act as a key structure in self-monitoring.

## **Summary and Conclusion**

Evidence from neuropsychological reports discussed in this paper indicates that insular cortex is active in multiple functional networks. Certain symptoms seem to be more closely associated with lesions involving the anterior insula, including disruption of affective responses e.g. in amusia (impaired ability to appreciate the emotional content of music) but also language functions, especially following left hemisphere damage. In contrast lesions involving the posterior insula are more likely to result in disruption of the representation of interoceptive information e.g. alterations in pain, temperature or tactile perception. While some previous reviews imply that anosognosia for hemiplegia/hemianaesthesia are disorders of emotional awareness that reflect anterior insula damage, evidence suggests the disorder is more closely associated with posterior insula damage.

At present, models of insula function fall short of adequately explaining in detail the range of neuropsychological effects reviewed above. From lesion and neuroimaging data, we

can conclude broadly that the insula supports an integration of body and mind, yet the mechanisms through which these interoceptive signals are perceived, how they are translated into perceptual sensation (“feeling”), and compared to detect disparity between predicted and actual feeling states is less obvious in the presence of marked insula damage. Craig proposes a meta-representational model of integration across insula cortex where primary interoceptive signals are represented in posterior insula and are integrated with affective, sensory and cognitive information to be represented as a ‘global emotional moment’ where awareness of feeling state occurs in the anterior insula [9]. This re-representation does not imply redundancy, but rather the integrated whole may have an important role to play in behaviour and underpin certain subjective states such as those implicated in anxiety [18, 81]. Indeed when interoceptive mismatch is induced experimentally using false physiological feedback, enhanced anterior insula activity correlates with increased emotional salience attributed to previously unthreatening neutral face stimuli [23]. In this sense, a general function of the insula is as a comparator, detecting incongruence in predicted and actual emotional states. These concepts are embodied within an recent integrative model of insula function in which amplitude and variance data regarding internal physiological and external sensory information are represented as concurrent and prediction signals [sensory feeling states] and integrated into a dominant motivational feeling state [82]. Neuroimaging has shown that the anterior insula stores an error representation when the states are mismatched this information can be used in reinforcement learning, to adjust future behaviour [83, 84]. Damage to such a mechanism may for example result in the inability to adjust risk behaviour, as was observed recently [32] which could have significant clinical implications. Establishing the precise role of the insula in decision making under uncertainty is possible with tasks designed to probe specific questions e.g. whether the insula is chiefly involved in risk prediction learning or if it is also active in reward prediction learning.

Targeted evaluation (hypothesis testing) of the cognitive and emotional status of patients with insular lesions can be achieved using neuropsychological measures adapted to detect changes in functional integration, for example cross-modal integration in speech. Neuropsychological assessments administered at different stages post-lesion onset will aid the discovery of independent predictor variables linked with ongoing cognitive dysfunction and functional outcome. This approach will help to address the many outstanding questions concerning the complex behavioural specialisations of insular cortex: its precise role in interoception, emotional awareness, self recognition, risk prediction and anticipation, time perception and performance monitoring. It also worth noting that few studies have used functional neuroimaging in insular lesion patients, a powerful tool for detecting remaining functionality or functional reorganisation associated with normal task performance [85]. This is an important next step in research and is especially relevant to preoperative and postoperative functional imaging where insights can be gained into brain plasticity. The possibility of other brain regions compensating for damage to this multimodal area will have important implications, in terms of better understanding the pathophysiological role of this structure and its relationship with other brain regions. It is also important from a clinical perspective in tumoural surgery, due to the frequent location of gliomas in the insula; and in degenerative diseases such as Huntington's and Alzheimer's disease, where insula changes may be associated with early stage symptomatology.

## **Acknowledgements**

CLJ is supported by the Medical Research Council and the Brighton and Sussex Medical School. HDC is supported by a programme grant from the Wellcome Trust. HDC and JW

made an equal contribution in the production of this article. The Corresponding Author has the right to grant on behalf of all authors and does grant on behalf of all authors, an exclusive licence (or non exclusive for government employees) on a worldwide basis to the BMJ Publishing Group Ltd and its Licensees to permit this article (if accepted) to be published in the Journal of Neurology, Neurosurgery & Psychiatry editions and any other BMJ PGL products to exploit all subsidiary rights, as set out in our licence (<http://jnnp.bmjournals.com/ifora/licence.pdf>).

Competing Interest: None declared.

## REFERENCE LIST

1. Augustine JR. Circuitry and functional aspects of the insular lobe in primates including humans. *Brain Res Brain Res Rev* 1996;22:229-244
2. Naidich TP, Kang E, Fatterpekar GM, et al. The insula: anatomic study and MR imaging display at 1.5 T. *Ajnr* 2004;25:222-232
3. Penfield W, Faulk ME, Jr. The insula; further observations on its function. *Brain* 1955;78:445-470
4. Oppenheimer SM, Gelb A, Girvin JP, Hachinski VC. Cardiovascular effects of human insular cortex stimulation. *Neurology* 1992;42:1727-1732
5. Meyer S, Strittmatter M, Fischer C, Georg T, Schmitz B. Lateralization in autonomic dysfunction in ischemic stroke involving the insular cortex. *Neuroreport* 2004;15:357-361
6. Paulus MP, Stein MB. An insular view of anxiety. *Biological psychiatry* 2006;60:383-387
7. Naqvi NH, Bechara A. The hidden island of addiction: the insula. *Trends in neurosciences* 2009;32:56-67
8. Crespo-Facorro B, Kim J-J, Andreasen NC, O'Leary DS, Bockholt HJ, Magnotta V. Insular cortex abnormalities in schizophrenia: a structural magnetic resonance imaging study of first-episode patients. *Schizophrenia Research* 2000;46:35-43
9. Craig AD. How do you feel--now? The anterior insula and human awareness. *Nature reviews* 2009;10:59-70
10. Craig AD. Forebrain emotional asymmetry: a neuroanatomical basis? *Trends Cogn Sci* 2005;9:566-571
11. Mutschler I, Wieckhorst B, Kowalevski S, et al. Functional organization of the human anterior insular cortex. *Neuroscience Letters* 2009;457:66-70



12. Rorden C, Karnath HO. Using human brain lesions to infer function: a relic from a past era in the fMRI age? *Nature reviews* 2004;5:813-819
13. Cannon WB. The James-Lange theory of emotions: a critical examination and an alternative theory. By Walter B. Cannon, 1927. *The American journal of psychology* 1987;100:567-586
14. Schachter S, Singer JE. Cognitive, social, and physiological determinants of emotional state. *Psychological review* 1962;69:379-399
15. Damasio A. The somatic marker hypothesis and the possible functions of the prefrontal cortex. *Philosophical transactions of the Royal Society of London* 1996;351:1413-1420
16. Bechara A, Damasio A. The Somatic Marker Hypothesis: A neural theory of economic decision. *Games and Economic Behavior* 2005;52:336 - 372
17. Critchley HD, Mathias CJ, Dolan RJ. Fear conditioning in humans: the influence of awareness and autonomic arousal on functional neuroanatomy. *Neuron* 2002;33:653-663
18. Critchley HD, Wiens S, Rotshtein P, Ohman A, Dolan RJ. Neural systems supporting interoceptive awareness. *Nature Neuroscience* 2004;7:189-195
19. Harrison NA, Brydon L, Walker C, Gray MA, Steptoe A, Dolan RJ, Critchley HD. Neural origins of human sickness in interoceptive responses to inflammation, *Biological Psychiatry* 2009;66:415-422
20. Gray MA, Rylander K, Harrison NA, Wallin BG, Critchley HD. Following one's heart: cardiac rhythms gate central initiation of sympathetic reflexes. *Journal of Neurosci* 2009; 29:1817-1825
21. Gray MA, Taggart P, Sutton PM, Groves D, Holdright DR, Bradbury D, Brull D, Critchley HD. A cortical potential reflecting cardiac function. *Proc Natl Acad Sci U S A*. 2007a; 104:6818-6823.
22. Zhang Z, Oppenheimer SM. Characterization, distribution and lateralization of baroreceptor-related neurons in the rat insular cortex. *Brain Res*. 1997; 760:243-250.
23. Gray MA, Harrison NA, Wiens S, Critchley HD. Modulation of emotional appraisal by false physiological feedback during fMRI. *PLoS ONE* 2007;2:e546
24. Mobbs D, Marchant JL, Hassabis D, Seymour B, Tan G, Gray M, Petrovic P, Dolan RJ, Frith CD. From threat to fear: the neural organization of defensive fear systems in humans. *J Neurosci*. 2009;29:12236-12243
25. Naqvi NH, Rudrauf D, Damasio H, Bechara A. Damage to the insula disrupts addiction to cigarette smoking. *Science [New York, NY]* 2007;315:531-534
26. Gray MA, Critchley HD. Interoceptive basis to craving. *Neuron*. 2007c;54:183-186.
27. Balleine BW, Dickinson A. The effect of lesions of the insular cortex on instrumental conditioning: evidence for a role in incentive memory. *J Neurosci* 2000;20:8954-8964
28. Sutherland S. *Irrationality*. Pinter & Martin Ltd; 2007
29. Bar-On R, Tranel D, Denburg NL, Bechara A. Exploring the neurological substrate of emotional and social intelligence. *Brain* 2003;126:1790-1800
30. Bechara A, Damasio AR, Damasio H, Anderson SW. Insensitivity to future consequences following damage to human prefrontal cortex. *Cognition* 1994;50:7-15
31. Clark L, Bechara A, Damasio H, Aitken MR, Sahakian BJ, Robbins TW. Differential effects of insular and ventromedial prefrontal cortex lesions on risky decision-making. *Brain* 2008;131:1311-1322
32. Weller JA, Levin IP, Shiv B, Bechara A. The effects of insula damage on decision-making for risky gains and losses. *Social neuroscience* 2009:1-12
33. Damasio A, Grabowski TJ, Bechara A, et al. Subcortical and cortical brain activity during the feeling of self-generated emotions. *Nat Neurosci* 2000;3:1049-1056

34. Damasio A. *Descartes Error: Emotion, reason and the human brain*. Putnam Publishing; 1994
35. 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
36. Adolphs R, Tranel D, Koenigs M, Damasio AR. Preferring one taste over another without recognizing either. *Nature neuroscience* 2005;8:860-861
37. Kipps CM, Duggins AJ, McCusker EA, Calder AJ. Disgust and happiness recognition correlate with anteroventral insula and amygdala volume respectively in preclinical Huntington's disease. *Journal of cognitive neuroscience* 2007;19:1206-1217
38. Phillips ML, Young AW, Senior C, et al. A specific neural substrate for perceiving facial expressions of disgust. *Nature* 1997;389:495-498
39. Davidson RJ, Shackman AJ, Maxwell JS. Asymmetries in face and brain related to emotion. *Trends Cogn Sci* 2004;8:389-391
40. 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
41. Jabbi M, Swart M, Keysers C. Empathy for positive and negative emotions in the gustatory cortex. *Neuroimage* 2007;34:1744-1753
42. Mesulam MM, Mufson EJ. Insula of the old world monkey. III: Efferent cortical output and comments on function. *The Journal of comparative neurology* 1982;212:38-52
43. Small DM, Zald DH, Jones-Gotman M, et al. Human cortical gustatory areas: a review of functional neuroimaging data. *Neuroreport* 1999;10:7-14
44. Toronchuk J. Disgust: Sensory affect or primary emotional system? *Cognition and emotion* 2007;21:1799-1818
45. Penfield W, Jasper H. *Epilepsy and the functional anatomy of the brain*. Boston: Little, Brown; 1954
46. Hauser-Hauw C, J B. Gustatory hallucinations in epileptic seizures, electrophysiological, clinical and anatomical correlates. *Brain* 1987;20
47. Krolak-Salmon P, Henaff MA, Isnard J, et al. An attention modulated response to disgust in human ventral anterior insula. *Annals of neurology* 2003;53:446-453
48. Pritchard TC, Macaluso DA, Eslinger PJ. Taste perception in patients with insular cortex lesions. *Behavioral Neuroscience* 1999;113:663-671
49. Cereda C, Ghika J, Maeder P, Bogousslavsky J. Strokes restricted to the insular cortex. *Neurology* 2002;59:1950-1955
50. Ramirez-Amaya V, Alvarez-Borda B, Bermudez-Rattoni F. Differential effects of NMDA-induced lesions into the insular cortex and amygdala on the acquisition and evocation of conditioned immunosuppression. *Brain, behavior, and immunity* 1998;12:149-160
51. Stevenson RJ, Miller LA, Thayer ZC. Impairments in the perception of odor-induced tastes and their relationship to impairments in taste perception. *Journal of experimental psychology* 2008;34:1183-1197
52. Peyron R, Frot M, Schneider F, et al. Role of operculoinsular cortices in human pain processing: converging evidence from PET, fMRI, dipole modeling, and intracerebral recordings of evoked potentials. *Neuroimage* 2002;17:1336-1346
53. Greenspan JD, Winfield JA. Reversible pain and tactile deficits associated with a cerebral tumor compressing the posterior insula and parietal operculum. *Pain* 1992;50:29-39
54. Greenspan JD, Lee RR, Lenz FA. Pain sensitivity alterations as a function of lesion location in the parasyllvian cortex. *Pain* 1999;81:273-282
55. Berthier M, Starkstein S, Leiguarda R. Asymbolia for pain: a sensory-limbic disconnection syndrome. *Annals of neurology* 1988;24:41-49

56. Henderson LA, Gandevia SC, Macefield VG. Somatotopic organization of the processing of muscle and cutaneous pain in the left and right insula cortex: a single-trial fMRI study. *Pain* 2007;128:20-30
57. Starr CJ, Sawaki L, Wittenberg GF, et al. Roles of the insular cortex in the modulation of pain: insights from brain lesions. *J Neuroscience* 2009;29:2684-2694
58. Fifer RC. Insular stroke causing unilateral auditory processing disorder: case report. *Journal of the American Academy of Audiology* 1993;4:364-369
59. Habib M, Daquin G, Milandre L, et al. Mutism and auditory agnosia due to bilateral insular damage--Role of the insula in human communication. *Neuropsychologia* 1995;33:327-339
60. Bamiou DE, Musiek FE, Luxon LM. The insula [Island of Reil] and its role in auditory processing. Literature review. *Brain research* 2003;42:143-154
61. Bushara KO, Grafman J, Hallett M. Neural correlates of auditory-visual stimulus onset asynchrony detection. *J Neurosci* 2001;21:300-304
62. Battelli L, Walsh V, Pascual-Leone A, Cavanagh P. The 'when' parietal pathway explored by lesion studies. *Current opinion in neurobiology* 2008
63. Donnan GA, Darby DG, Saling MM. Identification of brain region for coordinating speech articulation. *Lancet* 1997;349:221-222
64. Nestor PJ, Graham NL, Fryer TD, Williams GB, Patterson K, Hodges JR. Progressive non-fluent aphasia is associated with hypometabolism centred on the left anterior insula. *Brain* 2003;126:2406-2418
65. Dronkers NF. A new brain region for coordinating speech articulation. *Nature* 1996;384:159-161
66. Hillis AE, Work M, Barker PB, Jacobs MA, Breese EL, Maurer K. Re-examining the brain regions crucial for orchestrating speech articulation. *Brain* 2004;127:1479-1487
67. Hyman BT, Tranel D. Hemianesthesia and aphasia. An anatomical and behavioral study. *Archives of neurology* 1989;46:816-819
68. Carota A, Annoni JM, Marangolo P. Repeating through the insula: evidence from two consecutive strokes. *Neuroreport* 2007;18:1367-1370
69. Schmid G, Ziegler W. Audio-visual matching of speech and non-speech oral gestures in patients with aphasia and apraxia of speech. *Neuropsychologia* 2006;44:546-555
70. Duffau H, Taillandier L, Gatignol P, Capelle L. The insular lobe and brain plasticity: Lessons from tumor surgery. *Clinical neurology and neurosurgery* 2006;108:543-548
71. Duffau H, Moritz-Gasser S, Gatignol P. Functional outcome after language mapping for insular World Health Organization grade II gliomas in the dominant hemisphere: experience with 24 patients. *Neurosurg Focus* 2009;27:E7
72. Toyomura A, Koyama S, Miyamaoto T, et al. Neural correlates of auditory feedback control in human. *Neuroscience* 2007;146:499-503
73. Gazzola V, Aziz-Zadeh L, Keysers C. Empathy and the somatotopic auditory mirror system in humans. *Curr Biol* 2006;16:1824-1829
74. McGurk H, MacDonald J. Hearing lips and seeing voices. *Nature* 1976;264:746-748
75. Skipper JJ, van Wassenhove V, Nusbaum HC, Small SL. Hearing lips and seeing voices: how cortical areas supporting speech production mediate audiovisual speech perception. *Cereb Cortex* 2007;17:2387-2399
76. Bisiach E, Vallar G, Perani D, Papagno C, Berti A. Unawareness of disease following lesions of the right hemisphere: anosognosia for hemiplegia and anosognosia for hemianopia. *Neuropsychologia* 1986;24:471-482
77. 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

78. Tsakiris M, Hesse MD, Boy C, Haggard P, Fink GR. Neural signatures of body ownership: a sensory network for bodily self-consciousness. *Cereb Cortex* 2007;17:2235-2244
79. Farrer C, Franck N, Georgieff N, Frith CD, Decety J, Jeannerod M. Modulating the experience of agency: a positron emission tomography study. *Neuroimage* 2003;18:324-333
80. Spinazzola L, Pia L, Folegatti A, Marchetti C, Berti A. Modular structure of awareness for sensorimotor disorders: evidence from anosognosia for hemiplegia and anosognosia for hemianaesthesia. *Neuropsychologia* 2008;46:915-926
81. Paulus MP, Rogalsky C, Simmons A, Feinstein JS, Stein MB. Increased activation in the right insula during risk-taking decision making is related to harm avoidance and neuroticism. *Neuroimage* 2003;19:1439-1448
82. Singer T, Critchley HD, Preuschoff K. A common role of insula in feelings, empathy and uncertainty. *Trends in Cognitive Neuroscience* 2009;13:334-340
83. Preuschoff K, Quartz SR, Bossaerts P. Human insula activation reflects risk prediction errors as well as risk. *J Neurosci* 2008;28:2745-2752
84. Pessiglione M, Seymour B, Flandin G, Dolan RJ, Frith CD. Dopamine-dependent prediction errors underpin reward-seeking behaviour in humans. *Nature* 2006;442:1042-1045
85. Price CJ, Friston KJ. Functional imaging studies of neuropsychological patients: applications and limitations. *Neurocase* 2002;8:345-354
86. Griffiths TD, Rees A, Witton C, Cross PM, Shakir RA, Green GG. Spatial and temporal auditory processing deficits following right hemisphere infarction . A psychophysical study *Brain* 1997;120:785-794
87. Griffiths TD, Warren JD, Dean JL, Howard D “When the feeling’s gone”: a selective loss of musical emotion. *Journal of Neurol Neurosurg & Psychiatry* 2004;75:344-345
88. Manes F, Springer J, Jorge R, Robinson RG. Verbal memory impairment after left insular cortex infarction.
89. Daniels SK, Foundas AL. The role of the insular cortex in dysphagia. *Dysphagia* 1997; 12:146-156
90. Manes F, Paradiso S, Springer JA, Lamberty, Robinson RG Neglect after right insular cortex infarction. *Stroke* 1999;30:946-948
91. Borovsky A, Saygin AP, Bates E, Dronkers N. Lesion correlates of conversational speech production deficits. *Neuropsychologica* 2007;45:2525-2533
92. Golay L, Schnider A, Ptak R. Cortical and subcortical anatomy of chronic spatial neglect following vascular damage. *Behav Brain Funct* 2008;4:43