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Functional mapping of the human insula: data from electrical stimulations.

Laure Mazzola MD, PhD^{1, 2, 3*}, François Mauguière MD, PhD^{2, 4, 5} and Jean Isnard MD,
PhD^{2, 4, 5}

¹Neurology Department, University Hospital, St-Etienne (France)

²Team ‘Central Integration of Pain’, Lyon Neuroscience Research Center, INSERM U
1028, CNRS UMR 5292 Lyon (France)

³Jean Monnet University St-Etienne (France)

⁴Functional Neurology and Epilepsy Department, Neurological Hospital, Hospices Civils
de Lyon, Lyon (France)

⁵Claude Bernard University Lyon 1 (France)

***Corresponding author:** Laure Mazzola. Neurology Department, University Hospital,
St-Etienne. 42055 cedex 2, France.

Phone : 00 33 (0) 4 77 12 77 33; Fax : 00 33 (0) 4 77 12 77 41

e-mail: lauremazzola@yahoo.fr

Abstract

Electrical stimulations of the insula performed during stereo-electro-encephalography (SEEG) reproduce the ictal symptoms observed during the development of insular seizures and are also a unique opportunity to provide a functional mapping of the insular cortex.

We provide here a functional mapping of the insular cortex obtained by electrical stimulation, based on our previous work and a review of literature. The most frequent responses to insula stimulation were somatosensory sensations followed by visceral responses. Then, in decreasing order of frequency, auditory sensations, vestibular illusions, speech impairment, gustato-olfactory sensations and motor reactions were evoked. A bipolar organization could be evidenced with a posterior part assigned to somatosensory functions and notably to pain perception; and an anterior part assigned to visceral functions. Although some degree of spatial segregation could be evidenced, there was a clear spatial overlap between the representations of the different types of responses.

These data provide a better understanding of physiological insular functions, insula seizures semiology and a prediction of post-surgical deficits. Insula is the only cortical region where stimulations demonstrate such a multi-modal representation, perhaps supporting its integrative functions of polymodal inputs.

Key words: insula; stereotactic electro-encephalography (SEEG); functional anatomy; electrical stimulations.

Introduction

A large body of data produced by various techniques (functional MRI, positron emission tomography) has established a role for the insula in a wide array of functions, including somatosensory, pain, viscerosensory, visceromotor, vestibular, autonomic and motor functions, language, audition, emotions, bodily awareness, self-recognition, attention, empathy, motivation, craving, addiction and time perception (for review, see [1,2]).

One limitation of these neuroimaging studies is that activation paradigms including sensory, motor, emotional, and cognitive tasks, give rise to a combination of effects that are difficult to dissociate from activation linked to the stimulus itself. This also raises the question of whether the observed responses are top down (that is, originating in the insula) or bottom up (that is, insular response to peripheral input). For example, most techniques commonly used to activate the gustatory or olfactory receptors in neuroimaging studies also trigger tactile and thermal stimulation of the mouth or tongue and somatosensory stimulation of the nasal mucosa [3]. One may question to what extent insular activations revealed by these studies are specific to gustatory and olfactory cortical processing since neuroimaging data have shown that the insula is also activated by intra-oral somatosensory sensations [4]. Direct electrical stimulation of the insula, which bypasses these technical interferences, offers a way to infer a direct causal relationship between the evoked sensation and insular functions.

In the 1950s, Penfield and colleagues [5,6] were pioneers in using electrical stimulation to study the function of the human brain. They collected clinical symptoms evoked by electrical stimuli applied to the cortical surface during brain surgery carried out under local anesthesia in awakened patients. The purpose was *i*) to localize the epileptogenic cortex by triggering symptoms mimicking the clinical symptomatology of spontaneous seizures and *ii*) to map individual functions of the cortical regions so post-surgical deficits could be avoided. Thus, Penfield performed an important number of insular stimulations after temporal lobectomies or, more exceptionally, after the outer part of the fronto-parietal operculum had been removed [7]. He found that insular

stimulation evoked a wide range of different symptoms, defining this brain area as singularly polymodal. He noted that some of these symptoms could be close to that usually considered as manifestations of temporal lobe seizures, leading to a risk of confusion between temporal and insular seizures.

Since that time, the advent of stereo-electro-encephalography (SEEG) has made it possible to stimulate brain regions electrically, in perfectly awake patients, outside the surgery setting [8,9]. Even so, for many years, it was considered too dangerous to implant orthogonal electrodes through peri-sylvian opercular cortices to reach the insular cortex because of the risk of vascular injuries to the dense network of blood vessels in the lateral fissure. By the end of the 1990s, the safety of trans-opercular stereotactic electrode implantation in the insula was demonstrated, so the study of this cortical structure using electrical stimulation could start again [10,11].

We provide here, a function map of the insular cortex obtained by electrical stimulation, based on our previous work and a review of literature.

Clinical responses to insula stimulation

Available studies reporting on insular stimulation have used electrodes inserted orthogonally to the mid-sagittal plane to also explore the opercula [12,13,14] and/or transfrontal or transparietal electrodes inserted obliquely to better sample the insular cortex [13,15,16,17]. The insula was found to be a very eloquent cortical structure as its stimulation evoked a clinical response very frequently (from 55% [17] to 89% [16] of stimulations). Although ‘non-eloquent’ sites were widely distributed, there was a clear antero-posterior gradient, as sites where no clinical sensations were evoked were significantly more anterior than the eloquent ones [14,17].

Many different types of clinical responses can be evoked by insular stimulation, making the insular cortex a singularly poly-modal area. Most of the evoked responses have the common feature of being related to body sensations, usually perceived as neutral or unpleasant and with no clear hemispheric specialization [14].

In all studies, somatosensory sensations were the most frequently reported sensations followed by visceral responses [12-17]. Percentages of each type of evoked

sensations were compared in the different published studies presented in Table 1.

Somatosensory responses

Somatosensory responses represent the most frequently evoked sensations after insular stimulation, from 43% to 70% of clinical responses [12,13,14,16,17] except in the study by Afif and colleagues [15] in which they accounted for only 23% of responses. They consist of paresthesiae in about 40%, thermal sensations in 12% and pain in 10% of stimulations [17]. Although sites where these responses were obtained were widely distributed, there was a clear posterior predominance, particularly for pain responses predominating in the dorsal posterior insula (figure 1A) [18,19].

Non-thermal and non-painful somatosensory sensations are often reported as sensations of slight electric current, tingling or light touch [12,13,14,16,17]. They are obtained from stimulation sites that are largely distributed over the posterior part of insular cortex. Temperature sensations are evoked by stimulation through contacts located in the median part of insula, mostly around the central sulcus [14,16,17]. Warm sensations are more frequently evoked than cold sensations. Painful sensations are described as painful electric shock, stinging, burning, crushing or cramp sensation. Mean pain visual analogic scale scores range from mild to intense pain (from 4/10 to 9/10; mean=6.7/10) [18]. Pain is obtained in the posterior insula [12,14,17], mostly in its postero-superior part where the threshold intensity of pain responses is the lowest [18]. In one study [15] pain was reported after the middle short gyrus stimulation.

Body regions involved by somatosensory manifestations can vary widely, from very small regions (such as nose or finger), to very large areas (for some patients, half body or even the whole body). When sensations involve the face or trunk, they are mostly bilateral (68%) and less frequently contralateral (24%) or ipsilateral (8%) to stimulation. Evoked responses affecting limbs are predominantly contralateral to stimulation (94%) but can also be bilateral (3%) or ipsilateral (3%) [14,20]. The median size of skin territories involved by somatosensory sensations obtained after insular stimulation is larger than after the stimulation of secondary or primary somatosensory areas [20]. Despite large and often bilateral receptive fields, pain representation shows some degree of somatotopic organization in the insula, showing face representation rostral to those of

upper and lower limbs, with an upper limb representation located above that of the lower limb [21].

The involvement of the insular cortex in the processing of painful and non-painful somatosensory inputs is convergent with numerous data including cytoarchitectonic, anatomical and microelectrodes studies in monkeys [22,23,24] showing that only the posterior part of the insula, which corresponds to the granular insular cortex, receives direct thalamic afferents from the posterior thalamic nuclei and is considered as involved in the sensory discriminative processing of pain inputs. This is also congruent with numerous functional imaging studies (for a review see [25] and [2]).

Visceral sensations (fig 1B)

Visceral sensations are the second major group of evoked sensations produced after insular stimulation, representing from 5% to 32% of clinical responses in the different published studies (table 1). They can be classified as *i*) constrictive sensations located in the pharyngo-laryngeal, retrosternal or abdominal region; *ii*) viscerovegetative sensations including nausea, salivation, facial blush or dyspnea; and *iii*) visceropsychic symptoms consisting of visceral sensations with a feeling of anxiety or fear.

In accordance with Penfield and Faulk [7] who reported a high frequency of visceral responses to stimulation of the antero-inferior insular quadrant (that they could explore after surgical removal of the temporal operculum), the stimulation sites where visceral sensations are evoked are located anterior to the somatosensory ones, especially around or rostral to the central insular sulcus (Figure 1B) [12,14,15,17]. Studies using only orthogonally implanted electrodes probably underestimate visceral responses, because of the emergence of sylvian vessels that make implantation of electrodes in the anterior part of insula scarcer.

The predominance of visceral sensations in the medium and anterior insula is congruent with the location of the dysgranular cortex [26], with data in monkeys that found interoceptive units mainly in the midinsula [27] and also with functional imaging meta-analysis [2], in which the midinsula is involved in human interoceptive processing.

Auditory sensations (Fig 1C)

Intracranial stimulation studies described auditory manifestations with a variable percentage (from 4% to 10% of total evoked responses) [12-16] except in the work of Stephani and colleagues [17] that did not report any auditory sensation. They were mostly perceived in the contralateral ear to the stimulation side, but could be bilateral and exceptionally ipsilateral.

Auditory sensations are mostly but not exclusively obtained in response to stimulation of the posterior insula [12,15,16] and especially in the mid posterior long gyrus of the insula [14]. This could raise the question of whether the auditory responses should be ascribed not to stimulation of insula proper but rather, to a spread of the electrical current to the contiguous auditory cortex of the Heschl gyrus. However, if the type of auditory evoked sensation can be very similar to that obtained after Heschl stimulation, consisting of elementary sensations such as buzzing, whistling or rhythmic auditory perception, it can also be more complex associating auditory perception with a feeling of vibration, pressure or paresthesiae in the ears. This is in agreement with lesion [28] and functional neuroimaging studies [29] that support the role of the insula in the processing of auditory stimuli.

Vestibular Sensations (Fig 1D)

Vestibular sensations were reported in 3% to 10% of insula stimulations [12,13,14,16,] except in two studies where they were not reported [15,17] (Table 1). Most of the vestibular sensations evoked by electrical stimulations are described as a feeling of body motion (95%) rather than as an illusion that the visual environment is moving (5%). They are more frequently perceived as an illusion of translation (such as feelings of levitation or flying) than as an illusion of rotation. However, in our own study 44% of patients could not classify precisely the vestibular sensation and reported indefinable feelings of “dizziness” or “instability” [30]. In this study vestibular responses were mostly obtained after stimulation of the posterior insula, that is, in the granular insular cortex and the postcentral insular gyrus (fig 1D). There might be a spatial segregation of the responses in the insula, with the rotatory and translational vestibular sensations being evoked at more posterior stimulation sites than other less definable vestibular sensations [30]. The importance of the posterior insula for vestibular processing corroborates recent

meta-analytic definitions of the human vestibular cortex in the operculo-insular complex [31,32], showing convergence of vestibular activations in the posterior insula, parietal opercular and retro-insular regions. Electrophysiological recordings in monkeys also revealed vestibular-responding neurons in the parieto-insular vestibular cortex (PIVC), “within the most posterior and upper part of the insular cortex” [33].

Speech Disturbances (Fig 1E)

Speech disturbances were reported in 2% to 10% of evoked sensations [12-16] except in the study of Stephani and colleagues [17] (table 1). The sites where they were evoked show a widespread distribution, although some studies pointed out their predominance in the short anterior gyrus of the insula [15]. Speech disturbances include slurred speech, lowering of voice intensity or speech arrest and can be evoked in both non-dominant and dominant hemispheres for language. This is in line with data of lesion [34,35] and functional imaging studies [36,37] suggesting a role of the insula in speech production.

Olfacto-Gustatory Sensations (Fig 1F)

Historically, Penfield and Faulk (55) [7] were the first to report five gustatory sensations out of 82 insular stimulations, located in the lower part of the insula, during their intraoperative explorations. In more recent studies, they represented 1% to 13% of insula responses to stimulation [12-17] (Table 1). Most often, taste sensations are described as unpleasant and are not clearly identified, but some patients can further qualify them as “metallic”, “acid” or “salty”. Gustatory sensations are localized in the whole oral cavity, the tongue or the mouth and throat, mostly without lateralization.

Most of the sites where stimulation produced gustatory sensations are located in the mid-dorsal insula, especially in posterior and median short gyri [13,14,16,17,38] (Figure 1F). Converging data indicate that the insular taste cortex is located more caudally in humans than in monkeys, suggesting that the location of the taste cortex in humans “migrated” during evolution [3,39]. Meta-analysis of neuroimaging data indicates that gustatory inputs activate both the anterior and the mid dorsal insula [40] whereas gustatory sensations are rarely obtained by stimulating the anterior insula, which may be

due to the low sampling in the very anterior part of insula.

Olfactory sensations

Olfactory sensations were rarely reported (1%). Although the implication of the insula in olfactory processing is supported by numerous functional neuro-imaging data [41,42] none of recent insular stimulation studies [13,16,17] reported olfactory sensations except our recent work [14,38], which was the largest in terms of the number of stimulations. Patients described odors as unpleasant or as indefinable. Some patients identified them as “ether”, “metallic” or “chlorine” odor. Olfactory sensations were located in the nasal cavity and were not lateralized. Spatial distribution of stimulation sites producing olfactory sensations is illustrated in Figure 1F. Except for one, olfactory stimulation sites were all located around the central sulcus of the insula, just ventral to gustatory stimulation sites or partially overlapping with them.

Motor responses

Motor responses were inconsistently reported. Whereas some studies described motor responses in 7% to 13% of responses to insula stimulation [13,15,16], others reported none [12,14,17]. They consist of myoclonic phenomena, tremor or involuntary movements (including ocular movements) contralateral to the stimulation side, and are mainly obtained in the mid-posterior insula [13,15,16]. The fact that some authors never obtained motor responses in spite of a large number of stimulations may be due to methodological differences, since some authors used oblique transfrontal or transparietal electrodes and high maximal stimulation intensities (up to 5 mA for Pugnaghi et al. [13]), whereas others used only electrodes implanted orthogonally to the mid-sagittal plane and lower stimulus intensities.

Discussion

Functional Mapping

A bipolar organization

A bipolar organization of major insular functions can be evidenced through direct cortical stimulations: a posterior part assigned to somatosensory functions, and

noteworthy to pain perception; and an anterior part assigned to visceral sensitivity and visceromotor functions. These data are congruent with cytoarchitectonic studies, in which the insular cortices of human and nonhuman primates show an antero-posterior gradient that include posterior granular, middle transitional dysgranular, and anterior agranular areas, that may underlie this functional segregation [43-45].

The involvement of the insula in two distinct neural networks is also supported by numerous connectivity studies [43,46,47] showing that the posterior insula is predominantly connected with sensory cortices (auditory, visual, and sensorimotor cortex), whereas the anterior insula is predominantly connected with the frontal cortex, the cingulate cortex and the amygdala. Such a connectivity pattern is also congruent with the functional differences between these two regions of the insula.

Interestingly, although the insula can be considered as a very ‘eloquent’ cortical structure since about 80% of electrical stimulations elicited a clinical response, sites where no clinical response could be evoked were located mostly in the anterior part of the insula. This may be due to the fact that this part of the insula has been assigned to cognitive [48,49] and emotional functions [50,2] that may not be apparent during electrical stimulations carried out without specific protocols testing cognitive or emotional responses.

Spatial overlap, substratum of functional integration?

Although responses to stimulation showed some functional segregation in the insula, there is a clear spatial overlap between the representations of the different types of responses. This spatial overlap may be the anatomical substratum for functional integration of multiple physiological functions. For example, we showed in a previous work [38] that there is a spatial overlap in the mid-dorsal insula of stimulation sites evoking gustatory, olfactory and somatosensory sensation in the mouth, nose and throat. This co-localization of oral and peri-oral somatosensory and olfacto-gustatory responses to insular stimulation is not surprising knowing that the trigeminal system contributes to the processing of chemosensory inputs. Flavor being defined as the unitary percept that results from the integration of oral somatosensation, gustation, retronasal olfaction during eating or drinking, the mid-dorsal insula may be an integrated oral sensory region playing

a key role in flavor perception. In accordance with this is the recent discovery of a convergence of visceral interoceptive and taste perception representation within the neurons of the human dorsal mid-insula, suggesting the existence of a neural pathway by which visceral signals from the periphery can modulate the activity of brain regions involved in feeding behavior [51].

Craig [52] proposed a posterior-to-anterior functional gradient within the insula, from primarily interoceptive representations in the posterior insula to higher subjective awareness representations in the anterior insula. Using intracranial electroencephalography and electrical cortical stimulation to investigate the causal roles of subdivisions of the insula in auditory emotion perception in epileptic patients, Zhang et al. [47] showed distinct response properties to auditory emotional stimuli in the posterior and anterior insula. The posterior insula showed auditory responses that resemble those observed in Heschl's gyrus, whereas the anterior insula responded to the emotional contents of the auditory stimuli in a similar way as observed in the amygdala. Furthermore, the degree of the differentiation between various emotion types increased from the posterior to the anterior insula. These findings suggest different roles played by the two regions of the human insula and a transformation from sensory to affective representations in auditory modality along the posterior-to-anterior axis.

Electrical stimulations versus neuroimaging activation studies: are they redundant or complementary in the functional evaluation of the insula cortex?

Another question is what are the differences in the meaning of neuroimaging activations during a task or a stimulus compared to sensations evoked by direct electrical stimulations of cortical regions? Activation studies based on functional magnetic resonance imaging provide a complete map of the network implicated in the processing of the task under study, but it is often difficult to disentangle the role of each area from the activated network in the completion of the task. Moreover, this activation is not necessarily predictive of a post-operative deficit. We studied 4160 cortical stimulations using intracerebral electrodes implanted in all cortical lobes [18]. Pain responses were scarce (1.4%) and concentrated in the medial part of the parietal operculum and the posterior insula. We obtained no pain response anywhere else in the cortex, including in

regions consistently activated by pain in most functional imaging studies, referred to as the ‘pain matrix’, i.e. the first somatosensory area, the lateral part of the secondary somatosensory area, anterior and mid-cingulate cortex, and anterior frontal, posterior parietal and supplementary motor areas [25,53]. The medial posterior insula and parietal medial operculum are thus the only areas where electrical stimulation is able to trigger activation of the pain cortical network and thus the experience of somatic pain. This dissociation between activation by pain in functional imaging studies and absence of pain response to direct stimulation is not an exception but is the rule in all cortical areas involved in building the ‘experience of pain’, except for the posterior insular cortex and the deep part of the parietal operculum. Interestingly, among the cortical pain matrix areas, only the posterior insula and the medial operculum cortex were able to trigger the “experience of pain” during a seizure [54]. Likely this is the only region in which a cortical lesion or post-surgery deficit can provoke a central pain syndrome with a thermo-nociceptive deficit [55,56].

Thus, direct electrical stimulation of the cortex is complementary to functional imaging studies and may be better predictor of the semiology of partial seizures and of post-surgery potential deficit.

Conclusion

The insula is the only cortical region where stimulations demonstrate such a multi-modal representation. A bipolar organization can be evidenced with a posterior part assigned to somatosensory functions and notably to pain perception; and an anterior part assigned to visceral functions. Although some degree of spatial segregation can be evidenced, there is a clear spatial overlap between the representations of the different types of responses that may support insular integrative function of polymodal inputs.

Conflicts of interest

None of the authors has any conflict of interest to disclose.

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Figures legends

Figure 1: Distribution of contacts where electrical stimulation elicited (adapted from Mazzola et al, 17): (A) Somatosensory responses (n=335): somatosensory non-painful non-thermal sensations are represented in light blue, thermal sensations in deep blue and painful sensations in black; (B) Visceral sensations (n=82): constrictive sensations are represented in light pink, viscerovegetative sensations in deep pink and visceropsychic symptoms in old pink; (C) Auditory sensations (green circles, n=44); (D) Vestibular sensations (orange circles, n=41); (E) Speech disturbances (purple circles, n=27); (F) Gustato-olfactory sensations (red circle for taste (n=15), yellow circles for smell sensations (n=6)). Bold circles represent sites where several stimulations were performed.

Study	Number of stimulations	Type of responses (percentage of total eloquent stimulations)						
		Somatosensory (%)	Visceral (%)	Auditory (%)	Vestibular (%)	Speech (%)	Motor (%)	Gustatory (%)
Isnard (2004)	139	43	24	10	4	6	0	2
Nguyen et al. (2009)	34	62	6	9	3	3	12	6
Afif et al. (2010)	83	23	24	4	0	10	13	0
Stephani et al. (2010)	54	55	32	0	0	0	0	13
Pugnaghi et al. (2011)	193	70	5	8	10	2	7	1
Mazzola et al. (2017)	550	61	15	8	8	5	0	3

Table 1: Clinical responses obtained after insular stimulation: a comparison of published studies.

