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Research article

Neuropsychological Patterns Following Lesions of the Anterior Insula in a Series of Forty Neurosurgical Patients

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Abstract: In the present study we investigated the effects of lesions affecting mainly the anterior insula in a series of 22 patients with lesions in the left hemisphere (LH), and 18 patients with lesions involving the right hemisphere (RH). The site of the lesion was established by performing an overlap of the probabilistic cytoarchitectonic maps of the posterior insula. Here we report the patients' neuropsychological profile and an analysis of their pre-surgical symptoms. We found that pre-operatory symptoms significantly differed in patients depending on whether the lesion affected the right or left insula and a strict parallelism between the patterns emerged in the pre-surgery symptoms analysis, and the patients' cognitive profile. In particular, we found that LH patients showed cognitive deficits. By contrast, the RH patients, with the exception of one case showing an impaired performance at the visuo-spatial planning test were within the normal range in performing all the tests. In addition, a sub-group of patients underwent to the post-surgery follow-up examination.

Keywords: insula; glioma; neurosurgery; neuropsychology; lesion mapping

1. Introduction

The insula cortex is an integrative area [1–3]. A functional parcelization of the insular sub-regions is indicated by tracer studies in animals [4,5] which represent our primary understanding of structural connections of the insula, and indicate the differentiation of an anterior and a posterior sectors. Except for some DTI studies on humans [3,6–8], parcelization studies about the structural connectivity of the human insula are lacking due to technical problems in reconstructing the pathways passing thought he insula. Tracing studies in non-human primates [9,10] evidenced that the anterior-basal sector, connected with limbic areas, is part of a frontal-entorhinal, piriform and olfactory cortex network, while the mid-dorsal insula receives input from the thalamic taste area [11].

The mid-posterior sector of the insula cortex, instead, is connected with somatosensory areas [12,13].

This reach connectivity confers to the insular cortex the status of a multimodal processing area. A recent quantitative meta-analysis of neuroimaging studies, addressing functional activations found in the insula [3], showed that the anterior-ventral insula and the right central region are activated by emotional-social tasks, the right central region by gustatory-olfactory stimuli, and the anterior-dorsal insula by cognitive tasks. In particular, attention-related tasks activated the anterior-dorsal insula bilaterally, and language-related tasks such as lexical decision or semantic judgments activated the anterior dorsal insula bilaterally, and speech activated the anterior dorsal insula bilaterally. Working memory too activated the anterior dorsal insula bilaterally, while the sensorimotor tasks mainly activated the mid-posterior insula. In the same study [3], a conjunction analysis showed that the portion of the insula cortex shared by social-emotional, gustatory-olfactory and cognitive tasks involved the anterior-dorsal insula.

Despite this functional selectivity found in sub-parts of the insular cortex, selective lesions affecting the insula alone are extremely rare. Therefore exploring which selective deficits are caused by lesions to sub-parts of the insula is not a simple exercise. For instance it has been shown that only 4 out of 4800 examined (0.0008%) patients with stroke had a lesion selectively involving the insula [14]. This indicates that neuropsychological descriptions of insular patients often include lesions extending beyond the insula. Similarly, other authors showed that out of 72 examined patients with lesions to the insular cortex, none had purely isolated infarction of the insula without involvement of surrounding areas [15]. These data are provided in the context of studies including stroke patients. Neurosurgical lesions, such as those due to low or high grade gliomas, are usually more selective than those due to stroke in that the areas involved in the lesion are less diffuse than the damaged areas involved in stroke lesions. However, also for patients with insular neurosurgical lesions, the interpretation of cognitive deficits might be done in the context of the complex interactions between the insula and its adjacent areas. The neurosurgical studies mainly report effects of cortical stimulation or effects of the medial temporal lobe epilepsy. For example, the intraoperative direct stimulation of the anterior insula led to gustatory and olfactory sensations [16]. Some authors [17] observed clinical responses in 10 out of 14 patients, and found a clear topography during stimulation of the insular cortex. In particular, viscerosensitive and visceromotor responses were evoked in the anterior insula, while somesthetic sensations were evoked by posterior insula stimulation. Other authors [18], in a PET study, compared patients with medial temporal lobe epilepsy who experienced visceral or emotional symptoms with those who did not. They found that emotional symptoms were correlated with hypometabolism in the anterior ipsilateral insula while visceral symptoms were correlated with hypometabolism of the posterior insula. In addition it has been shown that insular epilepsy can trigger gustatory hallucinations [19].

Studies reporting the cognitive profile of neurosurgical patients include a retrospective study of a series of 66 cases (19 right insula and 47 left insula) of surgery of insular nonenhancing gliomas indicating that language disorders were reported in the immediate postoperative phase in 11 patients (16.7 articulatory disorders in 1 patient, phonemic paraphasia without comprehension deficit in 8 patients, speech disorders with comprehension deficits in 2 patients). At a three-month follow up examination, speech disorders were reported in 3% of the patients [20]. In addition, it has been argued that the left insula can be removed without inducing definitive aphasia due to a preoperative language reshaping shown by fMRI [21]. In another study with 42 neurosurgical patients with low-grade insular glioma, immediately following resection 10 patients experienced articulatory disorders, while at a three-month post surgery examination there was no evidence of language disorders [22]. No indication as to whether the anterior- vs posterior- subpart of the insula was

involved, can be found. These results however are in contrast with other studies indicating a role of the anterior insula in language processing [23,24]. Deficits in sound detection and auditory temporal processing have been described in insula patients [25], as well as Broca's aphasia [26] apraxia of speech [27], repetition deficit [28] and reduced fluency [29]. The insula has afferent and efferent connections to the temporal lobes. In addition, because of its proximity to other areas involved in language processing its linguistic role should be taken with caution. When lesions were restricted to the left insula [14], aphasic symptoms were inconsistent. It is however unclear which language-related tasks were administered. Thus the exact role of insula in language processing remains unclear. A meta-analysis of expressive language tasks [30] showed that the left insula was involved, among other areas, in the network supporting speech production, and another recent meta-analysis showed that receptive language, expressive language and speech production activated very similar regions of the anterior insula, while activation related to perception of speech activated the left dorsal mid-insula [31].

Aside language, the clinical effects of insular damage are multiple [32] and involve autonomic, perceptual, somatosensory, vestibular systems, pain processing, stimuli awareness, emotion, mood and willed action, language, and memory processing. Similarly, other authors [33] reviewed the effects of insular lesions by focusing on emotional, perceptual, sensorimotor, and body awareness disorders. Damage to the left insula can cause deficit in assigning taste adjectives to smell in the absence of olfactory processing impairments [34]. Auditory agnosia [35,36] and auditory temporal processing deficits [25] might arise following insular infarction. Right insular lesions can cause neglect [37,38]. Patients with right insular lesions had a greater frequency of subjective anergia, tiredness, depression and other mood disorders [39].

In the present study we investigated the effects of lesions affecting mainly the anterior insula in a series of 22 patients with lesions to the LH and 18 patients with lesions involving the RH. The insula can be affected by both low and high grade gliomas. Due to its location and its functional integration role resection of the insula tumors has traditionally been viewed as hazardous [33]. In particular, their tendency to spread along the intricate network of afferent and efferent connections between the insula itself and the surrounding cortical areas, constitutes a major difficulty in reaching a gross total resection [20]. We studied patients in the pre-operative phase, and reported their neuropsychological profile and an analysis of their pre-surgical symptoms. Besides characterizing the patients' lesions as involving the anterior-posterior insula, we also investigated the effect of lesions involving the left and the right hemisphere. In addition, a sub-group of patients (8 RH patients and 9 LH patients) underwent to the post-surgery follow-up examination.

2. Materials and Method

2.1. Participants

Twenty two right-handed neurosurgical patients (7 female, mean age 47.76 ± 11.71 years, range 32–70 and mean education 13.23 ± 3.50 years, range 5–18), whose tumor involved the left insula, and 18 right-handed neurosurgical patients (7 female) whose tumor involved the right insula (mean age 45 ± 14.54, range 23–71 and mean education 12.05 ± 4.22, range 5–18) participated in the study. They were admitted to the A.O.S. Maria della Misericordia a few days before the beginning of the study. All participants were native Italian speakers, had normal or corrected-to-normal vision and reported no history of psychiatric disease or drug abuse. All the patients participated in the study before surgery. For some of them (8 RH patients and 9 LH patients) a follow-up examination was also included. Conventional T2-weighted MR imaging revealed lesions measuring 95 ± 58.52 cc for

LH patients (volume range: 28–228.3 cc) and 91.95 ± 62.17 cc for RH patients (range 13.90–290.40, see Table 1 for individual volumes) ($P > 0.05$, n.s.). Inclusion criteria were as follows: i) presence of unilateral lesions due to tumors involving the insular cortex; ii) excluded extra-perenchimal lesions as meningioma. The study was approved by the ethical committee and has therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. All participants signed the informed consent.

2.2. Lesion reconstruction

2.2.1. MRI data acquisition

A 3-T Philips Achieva whole-body scanner was used for the patients using a SENSE-Head-8 channel head coil and a custom-built head restrainer to minimize head movements. Magnetic resonance imaging was performed 6-10 days prior to craniotomy. High-resolution T2-weighted and post-gadolinium contrast T1-weighted anatomical MR images were acquired for use with the stereotactic surgical navigation system by using a T1-weighted 3D magnetization-prepared, rapid acquisition gradient-echo fast field echo (T1W_3D_TFE SENSE) pulse sequence (TR = 8.1007 ms, TE = 3.707 ms, FOV = 240.000 mm, 190 sagittal slices of 1 mm thickness, flip angle = 8°, voxel size: 1 × 1 × 1) and a T3-weighted 3D magnetization-prepared, rapid acquisition gradient-echo fast field echo (T2W_3D_TFE SENSE) pulse sequence (TR = 2500 ms, TE = 368.328 ms, FOV = 240.000 mm, 190 sagittal slices of 1 mm thickness, flip angle = 90°, voxel size: 1 × 1 × 1).

2.2.2. ROI overlapping analysis of the lesions

To determine the location of patients' lesions we used the overlap method. MRIcron software http://www.mccauslandcenter.sc.edu/mricro/mricron/index.html) was used to draw the patients' lesions on their T1 and T2 MRI scans, creating 40 ROIs which were normalized to the MNI space using the "Clinical Toolbox" (http://www.mccauslandcenter.sc.edu/CRNL/clinical-toolbox) for SPM8 (http://www.fil.ion.ucl.ac.uk/spm/software/spm8/) (Figure 1). By using MRIcron software we created the overlay plot of all the LH patients and that of RH patients. In Figure 1 the lesion density bar shows that as many as 20/22 of the LH patients and 16/18 RH patients had a lesion involving the anterior insula. By using the probabilistic cytoarchitectonic maps of the posterior insula derived by the anatomy toolbox [40] we created a ROI and we overlapped it (in violet) on the overlay plot of all the LH patients (Figure 1A) and that of RH (Figure 1B) patients. Figure 1 clearly shows that the lesions were anterior to the ROI comprising the posterior part of the insula (as shown bilaterally in violet). Lastly, the anatomical interpretation of the overlay plot of all the LH patients and that of RH patients has been made by using the Anatomy toolbox [40] which revealed that for both the LH and the RH patients the maximum density area overlapped with the insular cortex.

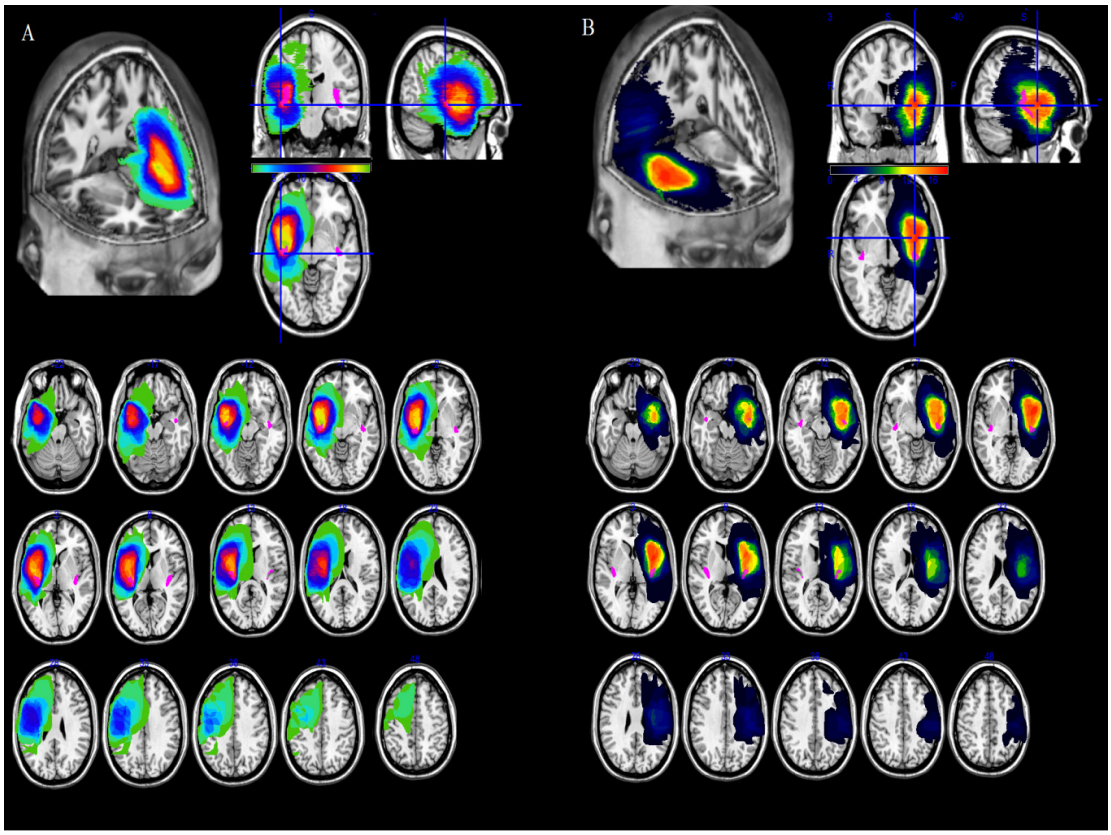

Figure 1. Areas of lesion overlap in LH patients (A) and RH patients (B) on the standard brain. The number of overlapping lesions is illustrated by different colors that code for increasing frequencies. In violet the ROI including the probabilistic cytoarchitectonic maps of the posterior insula obtained using the anatomy toolbox (Eickhoff, Stephan, Mohlberg, Grefkes, Fink, Amunts, and Zilles, 2005) which shows that the lesions were anterior to the posterior part of the insula.

2.3. Pre-surgery symptoms

Particular attention was given to patients' own description of pre-surgery symptoms. In particular the following categories were created: i) anxiety/panic and attacks/fear ii) gastric/nausea, iii) fainting sensations, iv) paresthesia, v) olfactory, vi) gustatory, vii) sweating, viii) auditory, ix) cognitive, x) sensations, and xi) motor. For the LH and RH group we then calculated the percentage of patients reporting symptoms involving the above mentioned categories.

2.4. Neuropsychological testing

Each patient was submitted to a neuropsychological battery before the MRI scanning. The neuropsychological evaluation for our LH patients included tests assessing spatio-temporal orientation, handedness (Edinburgh Handedness Inventory [41], non-verbal intelligence [Raven's Colored Progressive Matrices [42], verbal short-term memory [43], praxis (buccofacial [44] and ideomotor [45], language comprehension (Token test [46]), noun naming and verb naming [47], phonological fluency [48], word and pseudoword reading, repetition and writing [47], phonological discrimination and lexical decision [47]. The neuropsychological evaluation of the RH patients

included tests assessing the spatio-temporal orientation, handedness (Edinburgh Handedness Inventory [41]), non-verbal intelligence [42], spatial short-term memory, constructional apraxia [44], visuospatial planning [49], visuo-spatial ability [50], and attention [51].

3. Results

3.1. Pre-surgery symptoms

We found that 38.88% of the RH patients reported anxiety/fear/panic attacks, 27.77% reported taste sensations (e.g, bitter taste, strange gustatory sensations), 22.22% gastric sensations (e.g, stomach/nausea), 22.22% paresthesia (e.g, leg, arm), 16.66% cognitive changes (e.g, attention, confusion), 11.11% olfactory sensations (e.g, ointment odor), 11.11% auditory sensations (e.g, increased sensibility, confusion) and 5.55% other sensations (e.g, sweating and feeling fainting). None reported motor symptoms or sensations (Figure 2).

The LH patients presented a different pattern. The 63.63% presented cognitive changes (e.g, phonologic paraphasia, speech arrest, anomia), 27.27% motor symptoms (e.g, seizures involving the arm or the leg, or mouth), 18.18% anxiety/fear/panic attacks, 18.18% paresthesia (e.g, hand, arm, face), 9% gastric sensations (e.g, stomach/nausea/cold sensations to the stomach), 4.5% general sensations (e.g, hot air while breathing from the nose) and gustatory sensations (e.g, bitter taste). None reported experience of olfactory, auditory sensation nor feeling fainting or sweating.

By comparing the LH and RH patients we found a significant difference for two categories, namely cognitive ($\chi^2 = 8.93$, $P > 0.005$) and motor symptoms ($\chi^{2y1} = 3.83$, $P > 0.05$) with significantly higher percentage of LH patients reporting changes in the two categories than RH patients. All the others did not differ significantly between LH patients and RH patients (all Yates' *P*-value > 0.05, n.s.) (Figure 2 and Table 1).

3.2. Pre-surgical neuropsychological testing

A tight parallelism was found between the pattern that emerged in the pre-surgery symptoms analysis and the patients' cognitive profile. In particular, we found that LH patients showed more cognitive deficits than RH patients (see Tables 2–3 and Figure 2B). With the exception of one case showing buccofacial apraxia in addition to reading and repetition deficit (P5) and one case showing a mild comprehension deficit at the Token test in addition to lexical decision deficit (P15) and two cases showing a lexical decision deficit (P13 and P17), 31.81% of the LH patients showed a noun naming deficit, the 36.26% showed a verb naming deficit and the 27.27% showed an impaired performance at the phonological fluency test. All the other tests were within the normal range (Table 2 and Figure 2B). By contrast, the RH patients, with the exception of one patient showing an impaired performance at the visuo-spatial planning test (Clock test) (P2), were within the normal range in performing all the tests (Table 3 and Figure 2B). This result fits with the pre-surgery symptoms analysis where the majority of the RH patients did not report changes or symptoms involving the cognitive functions.

[1] Yates' chi-square and Yates' *p*-value

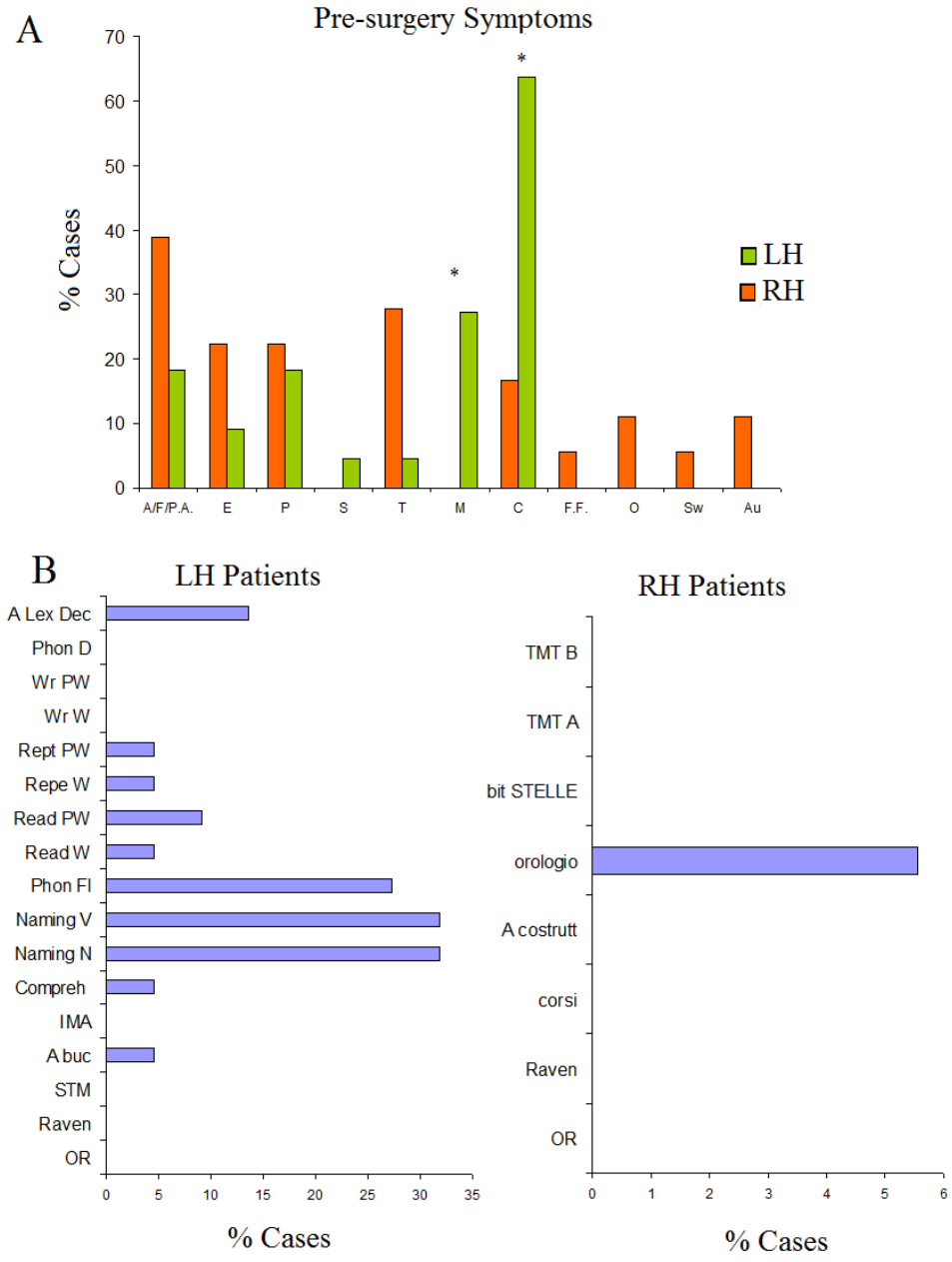

Figure 2. (A) Pre-surgery symptoms of LH and RH patients. Asterisks denote significant differences between the two group pf patients. (B) Pre-surgical cognitive profile of LH and RH patients. Bars show the percentage of patients presenting an impaired performance. RH = Right hemisphere; LH = left hemisphere; A/F/P.A. = anxiety/fear/panic attack; E = epigastric: stomach/nausea; F.F = feeling fainting; P = paresthesia; O = olfaction; Sw = sweating; T = taste; Au = auditory; C = cognitive; S = sensations; M = motor; A lex dec = auditory lexical decision; Phon D = phonological discrimination; Wr = writing; PW = pseudowords; W = words; repe = repetition; OR = orientation; hans = handedness; naming V = naming verbs; naming N = naming nouns; compreh = language comprehension; IMA = ideomotor apraxia; A buc = buccofacial apraxia; STM = Short term memory; OR = orientation; TMT = trial making test; bit = behavioural attention test; Corsi = Spatial short term memory.

Table 1. Right hemisphere (RH) and left hemisphere (LH) patients' presurgical sympthoms.

anxiety/fear/panic attacks (p.a.)	epigastric: stomach/nausea	Fainting sensation	paresthesia	olfactory	sweating	sensation	gustatory	auditory	motor	cognitive
RH Patients										
P1 anxiety, fear, p.a.	P2 stomach nausea,	P1	P2 leg	P18 strange sensation	P5		P9 difficulty in recognizing taste	P17 confusion		P6 distraction
P2 anxiety	P3 stomach		P8 arm, face	P11 ointment odor			P10 bitter taste	P9 > sensibility to sounds		P11 confusion
P4 p.a.	P7 epigastric		P12 arm, face				P15 gustatory hallucinations			P16 prosopoagnosia
P5 p.a, anxiety depression	P12 stomach		P15 left side of the body				P18 strange taste			
P6 anxiety							P4 strange taste			
P12 pleasure and anxiety										
P15 anxiety										
LH patients										
P1 p.a.	P6 senso di vomito	-	P10 hand, leg and head	-	-	P1 strong breaths from the nose as hot air	P16 bitter taste	-	P2 leg stiffening	P1 Phon par
P10 anxiety	P9 intenso freddo allo stomaco		P16 right side of the body						P3 seizure arm and leg	P2 confusion
P11 p.a.			P18 hand, leg						P5 seizure arm and face	P3 speech arrest
P14 unpleasent			P22 hand						P13 face	P4 anomia

sensations, anxiety	and cheeck		
		P18 hand stiffening	P5 diff to speak phon paraf
		P19 leg stiffening	P7 confusion
			P8 anomia
			P13 diff speak
			P14 anomia
			P15 verbal paraphasia
			P17 diff to speak
			P18 articulation and anomia
			P19 anomia and stm
			P20anomia phon paraph

Table 2. Left hemisphere (LH) patients' neuropsychological screening.

	LH patients																			
Case N#	**Age**	**E**	**loc**	**V (cc)**	**OR**	**hand**	**Raven**	**STM**	**A buc**	**IMA**	**Comp reh**	**Naming N**	**Naming V**	**Phon Fl**	**Read W**	**Read PW**	**Repe W**	**Repe PW**	**Wr W**	**Wr PW**	**Phon D**	**A Lex Dec**
P1	44	13	F i P	91.9	v	100		ne	20	72	35.5	29*	27	***16***	ne	ne	ne	ne	ne	ne	ne	ne
P2	56	13	TF i	105.9	V	83.3	33/36	ne	20	72	34	30*	28		45/45	45/45	30/30	30/30	45/45	25/25	ne	ne
P3	63	5	F i	115.3	v	100	25/36	5	20	71	35	30*	27	35	45/45	45/45	30/30	30/30	45/45	25/25	ne	ne
P4	29	13	F i	143.1	V	100	36/36	ne	19	72	34	***24****	***24***	***6***	45/45	45/45	30/30	30/30	45/45	25/25	30/30	40/40
P5	54	18	F i	79.1	V	100	33/36	ne	***13***	72	34	30*	***24***	34	***42/45***	*37/45*	*40/45*	***28/35***	45/45	24/25	59/60	80/80
P6	56	13	i	104.9	v	100	33/36	6	20	72	35	30*	26	27	45/45	45/45	45/45	35/35	45/45	25/25	ne	ne
P7	49	8	T i	65.3	v	100		5	20	72	28	29*	***25***	22	43/45	***41/45***	30/30	30/30	45/45	24/25	ne	ne
P8	70	18	FT i	46.1	v	100	36/36	ne	20	72	35	29*	26	19	ne	ne	ne	ne	ne	ne	ne	ne
P9	44	13	T iF	66	v	100	30/36	5	20	72	26	***18****	***23***	***16***	ne	ne	ne	ne	ne	ne	ne	ne
P10	44	13	T i	96.9	v	100	30/36	6	20	72	36	***27****	27	38	ne	ne	ne	ne	ne	ne	ne	ne

P11	38	13	T i	43.3	v	83.3	30/36	6	20	70	35	30*	28	54	45/45	44/45	45/45	35/35	45/45	24/25	60/60	80/80
P12	33	18	FT i	28	v	50	34/36	5	20	72	36	30*	28	53	45/45	45/45	45/45	35/35	45/45	25/25	60/60	80/80
P13	52	13	FT i	49.4	v	83,3	24/36	5	20	72	35	***26****	27	***15***	45/45	43/45	45/45	35/35	44/45	25/25	60/60	79/80
P14	37	18	f t i	130	v	100	34/36	6	20	70	34	29*	***23***	21	44/45	45/45	45/45	35/35	45/45	25/25	60/60	***74/80***
P15	49	13		228.3	v	100	29/36	6	20	63	***28***	***27****	***21***	***11***	43/45	44/45	45/45	35/35	45/45	25/25	30/30	***72/80***
P16	32	13	T i	115.1	v	100		6	20	72	36	30*	28	28	45/45	45/45	45/45	35/35	44/45	25/25	60/60	78/80
P17	62	10	T i	154.8	v	100	29/36	6	20	66	32	***26****	***23***	18	45/45	43/45	45/45	34/35	45/45	25/25	60/60	***63/80***
P18	66	8	i	14.3	v	100	ne	4	20	72	35	L 15/15 nl 17/20 ^ L 12/15 nl		***11***	ne	ne	ne	ne	ne	ne	ne	ne
P19	45	13	i	196.4	v	41	ne	5	20	72	36	17/20^ L 10/15 ***nl***			ne	ne	ne	ne	ne	ne	ne	ne
P20	67	13	T P i	166.1	v	100	ne	5	20	72	31	***16/20***^ L 15/15 nl			ne	ne	ne	ne	ne	ne	ne	ne
P21	44	13	F T ins	156	v	100	ne	6	20	72	36	20/20^ L 15/15 nl			ne	ne	ne	ne	ne	ne	ne	ne
P22	44	8	ins	66.9	v	33	ne	5	20	72	36	20/20^			ne	ne	ne	ne	ne	ne	ne	ne
Cutoff	**-**	**-**	**-**		**99**	**-**	**18**	**4**	**16**	**53**	**29**	**28*; L 8 nl 17^**	**26**	**17**	**43**	**43**	**45**	**35**	**43**	**23**	**58**	**78**

*From BADA ^ From BORE = education; loc = localization; F = frontal; i = insular; P = parietal; T = temporal; V = lesion volume (cc); OR = orientation; hans = handedness; STM = Short term memory; A buc = buccofacial apraxia; IMA = ideomotor apraxia; compreh = language comprehension; naming N = naming nouns; naming V = naming verbs; Phon flu = phonological fluency; W = words; PW = pseudowords; repe = repetition; Wr = writing; Phon D = phonological discrimination; A lex dec = auditory lexical decision.

Table 3. Right hemisphere (RH) patients' neuropsychological screening.

Case N#	Age	E	loc	OR	hand	Raven	corsi	Costr A	Clock	bit star	TMT A	TMT B
P1	64	5	FT i	v	100	n.e.	n.e.	12	9	n.e.	38,0e	146,1e
P2	35	8	i T	v	100	22/36	n.e.	11	8	52		
P3	69	5	i	v	83.33	n.e.	4	11	n.e.	52	25,0e	57,0e
P4	30	18	FT i	v	100	34/36	n.e.	14	n.e.	53		
P5	47	13	T i	v	100		n.e.	14	n.e.	54	18,0e	53,0e
P6	42	18	FT i	v	100	36/36	5	14	10	54		
P7	37	13	FP i	v	100	30/36	n.e.	14	n.e.	54	39,0e	95,0e
P8	62	13	T i	v	100	34/36	5	14	9.5	54	26,0e	96,1e
P9	23	8	T i F	v	100	n.e.	5	14	10	54	26,0e	104,2e
P10	43	13	i	v	100	33/36	n.e.	14	9,5	53		167,0e
P11	71	13	FT i	v	100	34/36	5	14	10	54	25,0e	101,0e
P12	33	17	i	v	100	33/36	6	14	10	54	30,0e	70,0e
P13	35	13	i	v	100	n.e.	5	14	n.e.	16*	30,0e	138,0e
P14	34	13	FT i	v	100	n.e.	4	14	n.e.	16*	n.e.	n.e.
P15	35	18	i FT	v	60	n.e.	6	13	n.e.	22*	n.e.	n.e.
P16	54	8	T i	v	100	n.e.	4	14	n.e.	22*	n.e.	n.e.
P17	59	8	i	v	50	n.e.	n.e.	n.e.	n.e.	20*	n.e.	n.e.
P18	37	13	i	v	50	n.e.	n.e.	n.e.	n.e.	20*	n.e.	n.e.
Cutoff	-	-	-	99	-	18	3.75	8	8.8	51; * balloon test< 16	> 94	> 283

E = education; loc = lesion localization; F = frontal; i = insula; T = temporal; OR = orientation; Corsi = Spatial short term memory; Costr A = constructional apraxia; bit = behavioural attention test; TMT = trial making test.

3.3. Neuropsychological follow-up

Out of our 40 patients, some (N = 9 LH patients and N = 8 RH patients) also performed a follow up examination. In particular, we found that 44.44% of the LH patients who performed the follow up examination showed a comprehension deficit (Token test), 66.66% showed a noun naming deficit, 77.77% showed a verb naming deficit, 55.55% showed a phonological fluency impairment, 66.66% showed a word and pseudoword reading deficit. Other showed a repetition impairment (P1, P6 and P13), a writing deficit (P1 and P13) and a phonological discrimination deficit (P1). All the other tests were within the normal range (Table 4). To date these impaired patients (P2, P4, P6, P7 and P13) had lesions involving as shown by Figure 3 other regions in addition to the anterior insula (e.g, inferior frontal gyrus, premotor cortex; superior temporal gyrus), thus a direct causal relation between the deficit and the presence of a lesion involving the anterior insula cannot be proved unless a VLSM analysis is done; our sample size is too limited for performing such analysis. By contrast, the RH patients, with the exception of two of them who performed poorly on the visuo-spatial planning test (Clock test) (P2 and P12), performed within the normal range on all the tests (Table 4).

Table 4. Left hemisphere (LH) and right hemisphere (RH) patients' neuropsychological follow-up.

LH Patients Follow Up examination

Case N#	OR	STM	A buc	IMA	Compreh	Naming N	Naming V	Phon Flu	Read W	Read PW	Repe W	Rept PW	Wr W	Wr PW	Phon D	A Lex Dec
P2	v	5	16	55	20	17	20	15	34/45	28/35	43/45	27/35	7/15	20/25	54/60	ne
P3	V	ne	20	72	30	5	6	8	ne	ne	ne	ne	ne	ne	ne	
P4	v	5	20	71	26	24	26	10	45/45	45/45	30/30	30/30	45/45	25/25	60/60	80/80
P6	V	ne	20	72	18	6	5	8	35/45	30/45	45/45	30/35	ne	ne	ne	ne
P7	V	5	20	72	23	26	23	20	43/45	41/45	30/30	30/30	45/45	24/25	ne	ne
P11	v	6	20	70	35	30	28	45	45/45	44/45	45/45	35/35	45/45	25/25	60/60	80/80
P12	v	7	20	71	36	29	28	37	45/45	45/45	45/45	35/35	45/45	25/25	60/60	80/80
P13	v	5	13	62	32	27	22	12	88/92	24/45	45/45	34/35	35/45	22/25	60/60	79/80
P16	v	6	20	72	35	28	25	34	44/45	44/45	45/45	35/35	44/45	24/25	60/60	80/80
Cut-off	-	4	16	53	29	28	26	17	43	43	45	35	43	23	58	78

RH Patients Follow Up examination

Case N#	OR	STM Spatial	Constructional Apraxia	Clock test	bit STAR		TMT A	TMT B
P6	v	ne	11	9,5		52	25,0e	51,0e
P7	v	5	14	0		54	33,0e	106,1e
P8	v	ne	12	10		34	70,0e	111,0e
P9	v	6	14	10		54	31,0e	108,1e
P10	v	4	14	10		54	30,0e	76,0e
P12	v	5	14	6.5		54	25,0e	80, 0e
P13	v	4	14	ne		53	ne	ne
P14	v	4	14	ne	ne		ne	ne
Cut-off	-	3.75	8	8.8	51		> 94	> 283

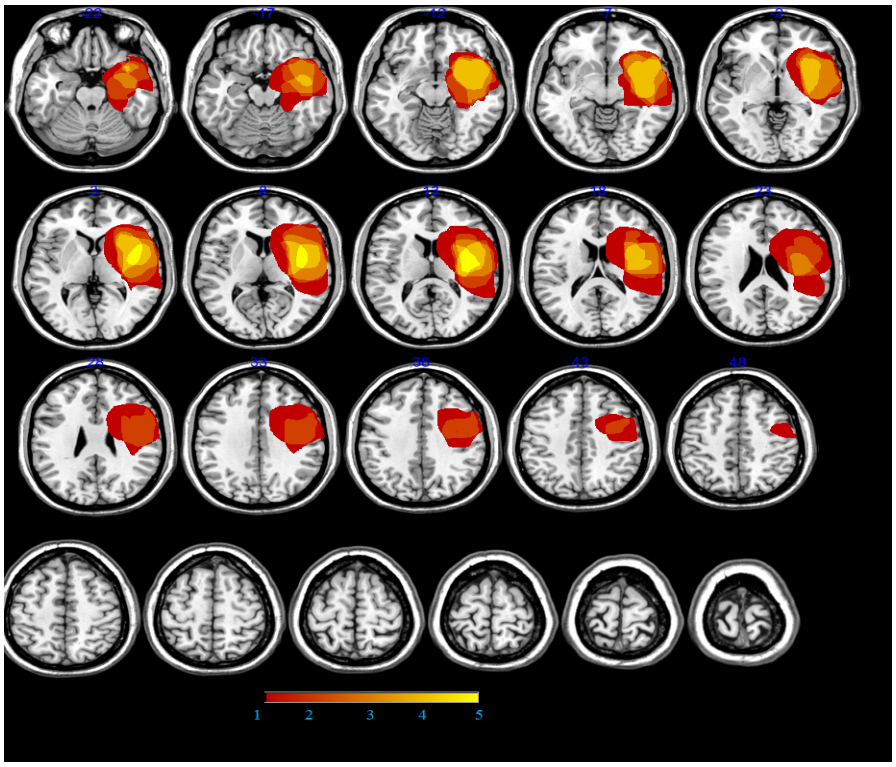

Figure 3 Lesion reconstruction of a subgroup of LH patients who performed the follow-up testing (*N* = 9)

4. Discussion

We investigated the cognitive effects of neurosurgical lesions involving the insular cortex in a series of 22 patients with lesions involving the LH and 18 patients with lesions involving the RH. Different cognitive tests were administered to LH and RH patients. The involvement of the insula was ensured by performing a lesion overlapping analysis. The patients' lesions were manually traced, normalized, and overlapped on a standard template. The maximum overlap of lesions involved the insula. In particular, the lesions involved the anterior insula as indicated by the overlapping of the probabilistic cytoarchitectonic maps of the posterior insula obtained using the anatomy toolbox [40]. We created a ROI and we overlapped it (in violet) on the overlay plot of all the LH patients and that of RH patients. The lesions were anterior to the ROI comprising the posterior part of the insula. It is known that lesions involving the insula typically include and spread also to other surrounding areas and that patients with isolated insular lesions are very rare [14]. Also in the present study, the patients we included had a lesion involving in addition to the insula also the surrounding areas, however the lesion overlapping analysis showed that the maximum overlapping lesioned area involved the insula (mainly anterior) itself. Thus the interpretation of cognitive deficits in patients with insular neurosurgical lesions might be interpreted in the context of the complex interactions between the insula and its adjacent areas. Indeed the insula is located closely to the white matter pathways: the corticospinal tract runs in the superior posterior sector of the insula, the inferior fronto-occipital fasciculus runs medially to the insula and the arcuate fasciculus runs more superiorly and could be very close to insular tumors [20]. Indeed the tendency of tumors to spread along the intricate network

of afferent and efferent connections between the insula itself and surrounding cortical areas, constitute a major difficulty in reaching a gross total resection [20]. Thus, given that the insula is an integrative area linking information from different functional systems, i.e, cognitive, sensorimotor, social-emotional, and olfacto-gustatory [1–3], it is not surprising that the insular cortex is considered a multimodal processing area [3].

4.1. Pre-surgery symptoms profile

We found that pre-operatory symptoms significantly differed between patients with left and right insular lesions. In particular, a significant difference between cognitive and motor symptoms was observed, particularly in the case of LH patients, relative to RH patients. All the other categories of symptoms did not differ significantly between LH and RH patients.

The 38.88 of the RH patients and 18.18% of the LH patients reported anxiety/fear/panic attacks. This result is consistent with previous studies showing that patients with right insular lesions had a greater frequency of depressive and other mood disorders [39]. These effects might be related to disconnection between the insula and the frontal lobe or the anterior cingulate cortex, structures that have been associated with willed action and motor behaviour. The insula is an important neural substrate for representing emotional markers derived from internal states and through which perception of physiological responses may give raise to a conscious feedback on the internal state that guide behaviour [52]. In the model proposed by Craigh [53] the insula integrates the information about changes in bodily and cognitive states to create unitary feelings that encapsulate the "emotional now" or the "emotional self" [33]. Grey matter volume reduction of the left insula has been related to major depression [54,55] and bilateral reductions have been reported in posttraumatic stress disorder [56]. Similarly increased blow flow and metabolism have been reported in the insula of patients with major depression [57] and social anxiety disorders [58]. It has been proposed that patients with anxiety or depressive disorders interpret interoceptive states as threatening or negative states, which in turn cause hyper activity of the insula [59]. We add that RH more than LH patients seem to show anxiety/fear/panic attacks as pre-surgical symptoms.

We found that 27.77% of the RH patients and 4.5% of the LH patients reported taste sensations (e.g, bitter taste, strange gustatory sensations) in addition to 11.11% of the RH patients and none of the LH patients reported olfactory sensations (e.g, ointment odour). This is in line with fMRI results showing an insular activation in olfactory and gustatory tasks [60–62] and with intraoperative direct stimulation of the anterior insula studies reporting gustatory and olfactory sensations [16]. In particular, stimulation of the anterior part elicited "bad taste" or feelings of fear and stimulation of the posterior part elicited sensation in the mouth, salivation, increased gastric motility. Similarly our patients reported "bad taste" sensations as pre-operative symptoms. Patients' studies have shown that lesions to insula might cause deficits in gustatory perception [14,63] or olfactory functions [34,64]. Insular epilepsy can trigger gustatory hallucinations [19]. Lesions to the right insula cause ipsilateral perception and recognition deficits, whereas lesion to the left insula cause ipsilateral deficit in taste perception and bilateral deficit in taste recognition [14,63]. Damage to the left insula can cause deficit in assigning taste adjectives to smell in the absence of olfactory processing impairments [34]. None of our RH patients showed olfactory symptoms, whereas there was a preponderance of RH patients, compared to LH patients, reporting gustatory sensations.

The 22.22% of the RH patients and 9% of the LH patients reported gastric sensations (e.g, stomach/nausea/cold sensations to the stomach). This result is consistent with stimulation studies reporting gastric sensations following stimulation of the insular cortex [17] and changes in gastric

motility [16]. Similarly a PET study [18] comparing patients with medial temporal lobe epilepsy who experienced visceral or emotional symptoms and those who did not, reported that visceral symptoms were correlated with hypometabolism of the posterior insula. In addition an fMRI study have shown that the insular cortex is activated during oesophageal distension [65]. Again, we found that there was a preponderance of RH patients compared to LH patients who showed gastric sensations.

In addition the 11.11% of the RH patients and none of the LH patients reported auditory sensations (e.g, increased sensibility, confusion). For example other authors found hypoacusia in the contralateral ear following stimulation of the isular cortex [17], auditory agnosia [35,36] and auditory temporal processing deficits [25] following insular infarction. Our data further confirm the crucial role of the right insula in auditory processing due to its functional role itself or to its connections to the auditory cortex.

As mentioned above, there was a significant dissociation between RH and LH patients as to the cognitive and motor symptoms. The 22.22% of the RH patients reported paresthesia (e.g, leg, arm) and none reported motor symptoms whereas the 27.27% of the LH patients reported motor symptoms (e.g, seizures involving the arm or the leg, or mouth). These results are consistent with the role of the insula as a multisensory and motor association area which maintains multiple connections to sensory and motor-relevant areas. In humans the insula and the ventral opercular premotor area contain somatotopically organized motor maps [66]. Somesthetic response (described as a sensation in the contralateral or both superior limbs) has been reported after left insular cortex stimulation [67]. Lastly, RH and LH patients significantly differed for cognitive symptoms. The 16.66% of the RH patients reported cognitive changes (e.g, attention, confusion) whereas the 63.63% of the LH patients presented cognitive changes (e.g, phonologic paraphasia, speech arrest, anomia). This aspect will be discussed in the next section addressing patients' neuropsychological profiles.

4.2. Pre-surgical neuropsychological testing

In a recent review on the clinical effects of insular damage [32] multiple deficits arising following insular lesions have been reported involving autonomic, perceptual, somatosensory, vestibular systems, pain processing, stimuli awareness, emotion, mood and willed action, language, and memory processing. Similarly, other authors [33] reviewed the effects of insular lesions by focusing on emotional, perceptual, sensorimotor, and body awareness disorders. We found a strict parallelism between the pattern emerged in the pre-surgery symptoms analysis, and the patients' cognitive profile. In particular, we found that LH patients showed more cognitive deficits than RH patients. A recent meta-analysis study of neuroimaging results [3] showed that the anterior-dorsal insula is activated by cognitive tasks. Consistent with this view we found that the 31.81% of the LH patients showed a noun naming deficit, the 36.26% showed a verb naming deficit and the 27.27% showed an impaired performance at the phonological fluency test. All the other tests were within the normal range. By contrast, the RH patients, with the exception of one case showing an impaired performance at the visuo-spatial planning test were within the normal range in performing all the tests. Right insular lesions can cause neglect [37,38]. This result fits with the pre-surgery symptoms analysis where the majority of the RH patients did not report changes or symptoms involving the cognitive functions. This result adds also a further indication about the role of the left insula cortex in language processing. We found language-related deficits in left insular patients, due to its functional role itself or to its connections to the language areas. Our results are not in line with previous neurosurgical studies reporting that the left insula can be removed without inducing definitive aphasia due to a preoperative language reshaping shown by fMRI [21]. Similarly, in another study of

42 neurosurgical patients with low-grade insular glioma, it has been shown that immediately following resection 10 patients experienced articulatory disorders while three moths post surgery there was no evidence of language disorders [22].

In addition there are other studies showing that deficit in sound detection and auditory temporal processing have been described in insula patients [25] but the lesions extended to adjacent areas involved in auditory processing. Broca's aphasia [26] and apraxia of speech [27] have been related to insula lesions as well as repetition deficit [28]. A voxel-based lesion-symptom mapping study showed that the verbal fluency was the most affected task by lesions in the insula [29]. Similarly our patients were pathological at the verbal fluency test. A meta-analysis of expressive language tasks showed that the left insula was involved among other areas in the network supporting speech production [30]. Another recent meta-analysis shown that receptive language, expressive language and speech production activate very similar regions of the anterior insula while activation related to perception of speech activates the left dorsal mid-insula [31]. Taken together our results suggest that language disorders can be reported in patients with left insula lesions and are consistent with a previous retrospective study of a series of 66 cases (19 right insula and 47 left insula) of surgery of insular nonenhancing gliomas [20] reporting that language disorders were found in the immediate postoperative phase in 11 patients (articulatory disorders in 1 patient, phonemic paraphasia without comprehension deficit in 8 patients, speech disorders with comprehension deficits in 2 patients). Our follow-up study evidenced that the examined patients, although being a small sample (N = 9 LH patients and N = 8 RH patients), still are pathological post-surgery. However, further studies are necessary to clarify whether selective lesions affecting the insula alone cause language related deficits or whether the pattern of results we found is rather due to the spreading of the lesions to surrounding areas (e.g, premotor cortex, temporal lobe). The insula has efferent and afferent connections to the temporal lobes. It has also been suggested that the critical areas in Broca's region involved in speech production is the insula [24,68] whereas other authors argued that Broca's area and not the insula is associated with articulatory impairments [69]. Indeed it has been shown that when lesions were restricted to the left insula [14] symptoms of aphasia were inconsistent. It is however unclear which language-related tasks have been administered. Thus the exact role of insula in language processing remains unclear. Interestingly, our data further indicate that the left insula might be involved in noun and verbs processing. Some authors [70] found that verb impairment emerged in four patients as a consequence of sub-cortical and insular damage in four of the patients belonging to a large sample of verb- and noun-impaired aphasic patients studied. In another study, the same group [71] showed that the left inferior frontal gyrus, the left insula, and the middle temporal gyrus are responsible for both noun and verb processing. A meta-analysis of action verbs processing found that the left insula was included in the network of areas consistently activated by action verbs [72].

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Conflict of Interest

We disclose any potential sources of conflict of interest.

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