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## FULL-LENGTH ORIGINAL RESEARCH

# Middle short gyrus of the insula implicated in speech production: Intracerebral electric stimulation of patients with epilepsy

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### SUMMARY

**Purpose:** Different lines of evidence have suggested an involvement of the insular cortex in speech production. These have included results from lesion studies, functional imaging techniques, and electrical stimulation of the human insular cortex during invasive evaluation of epileptic patients.

**Methods:** We evaluated 25 patients who had drug refractory focal epilepsy with at least one electrode stereotactically implanted in the insular cortex.

**Results:** Eight responses to insular cortex electrical stimulation were reported by five patients as speech arrest (five responses) and a lowering of voice intensity (three responses).

**Conclusions:** Data from this study implicate the middle short gyrus of the insula in the production of speech and show the importance of intrasular electrode implantation during invasive pre-resection evaluation by stereo-electroencephalography (SEEG) when speech arrest occurs early in seizure semiology.

**KEY WORDS:** Insula, Speech, Epilepsy, SEEG, Electrical stimulation.

First described and named “Island of Reil” by Reil (1809), the insular cortex later became the subject of several anatomic studies (Eberstaller, 1887; Guldberg, 1887; Cunningham, 1891; Clark, 1896). Streeter (1912) and Kodam (1926) identified it as being the first cortex to differentiate and develop in the fetus. In the adult brain the insular cortex is found localized in the depths of the sylvian fissure hidden by other cerebral lobes behind the temporoparietofrontal opercula (Varnavas & Grand, 1999; Ture et al., 2000; Naidich et al., 2004; Afif et al., 2007) and exhibits a trapezoid shape surrounded by four periinsular sulci (anterior, superior, posterior, and inferior) (Afif et al., 2007).

The role of the insular cortex in the processing of speech and in the grammatical construction of a sentence

in humans has been suggested by numerous functional imaging studies (Raichle, 1991; McCarthy et al., 1993; Wise et al., 1999; Price, 2000, 2001; Ackermann & Riecker, 2004; Riecker et al., 2005; Friederici et al., 2006; Kato et al., 2007). Several lesion studies have suggested a role of the anterior insula in coordinating speech articulation (Ferro et al., 1982; Shuren, 1993; Habib et al., 1995; Dronkers, 1996; Nagoa et al., 1999).

Although few, studies performed using direct electrical stimulation (ES) of human cortical brain structures during surgical procedure have suggested that the insula forms part of the language zone (Ojemann & Whitaker, 1978). Recently, observations in epileptic patients submitted to invasive electroencephalography (EEG) recordings from deep brain implanted electrodes have suggested an important role of the insular cortex in seizure onset or during early propagation of the epileptic discharge (Isnard & Mauguire, 2005). In the same way, dysarthria and speech arrest have been observed during routine ES suggesting an insular role in spontaneous speech (Ostrowsky et al., 2000; Isnard et al., 2004). These observations emphasize the need to explore this anatomic structure in more detail

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during invasive presurgical evaluation of epileptic patients. We adjusted a protocol of invasive recordings accordingly by developing an oblique positioning technique of implanting deep brain electrodes coplanar with the insular cortex, enabling a wide and highly specific exploration of the different sulci and gyri. In this way, we have been able to obtain eight responses of speech disturbance, involving speech arrest (five responses) and lowering of voice intensity (three responses), to direct ES. Of these, seven responses (87.5%) were evoked by ES of a small anatomic region localized in the middle short gyrus of the insula. The results of this study are compared to data from other studies, and discussed in terms of anatomic localization in gyral substructures of the insular cortex.

## PATIENTS AND METHODS

### Patients

In this study, 25 epileptic patients with severe drug refractory partial epilepsy were investigated by stereoelectroencephalography (SEEG) at the University Hospital of Grenoble (France) to evaluate the precise location of the zone to be surgically removed (Munari et al., 1994). In each of these patients, at least one electrode was used to explore the insular cortex using an oblique approach (transfrontal or transparietal), and those showing a normal insular region were selected for this retrospective study (Fig. 1). This population included 14

men (56%) and 11 women (44%), aged between 11 and 53 years (mean 29.36 years). The mean duration of epilepsy was  $19.4 \pm 11$  years. Four patients were left-handed (16%) and 21 right-handed (84%). The dominant hemisphere for language was determined by the intracarotid amobarbital test (Wada test). Magnetic resonance imaging (MRI) showed no anatomic lesions or anomalies inside insular structures. None of the 25 patients had previously undergone brain surgery.

In all 25 patients, we hypothesized an early involvement of perisylvian structures in ictal discharge. In addition to the insular electrodes, SEEG exploration in these patients included numerous other brain structures including the amygdala, hippocampus, and the cingulate, SI, SII and temporal cortices, with a total of 12–16 electrodes.

### Stereotactic implantation of electrodes

Targeting of the insular cortex was performed presurgically using a three-dimensional (3D) volume  $T_1$ -weighted MRI scan (imaging parameters were  $T_1$ -3D gradient-echo 20/4.6/30 injected sequence, 1.5 mm thickness, gap 0) with stereotactic software (VoximR, IVS solution, Chemnitz, Germany). Following coagulation of the dural entry point, insular electrodes were implanted through a 2-mm burr hole using an anterior (transfrontal) approach (Fig. 1) with an entry point in the middle frontal gyrus, and/or a posterior (transparietal) approach (Fig. 1) entering the brain at the level of the inferior parietal cortex. Electrodes commonly used (DIXI, Besançon, France) were 0.8 mm in diameter with 10–18 contacts, depending on the length of the electrode. It was thereby possible to sample different insular regions with only one electrode, without passing through the opercula and remaining at a safe distance from any insular or cerebral vessels. Insertion of the electrodes was guided by a robotic arm (Neuro-Mate, ISS, Grenoble, France) connected to the stereotactic frame, and driven by stereotactic planning software (VoximR, IVS solution).

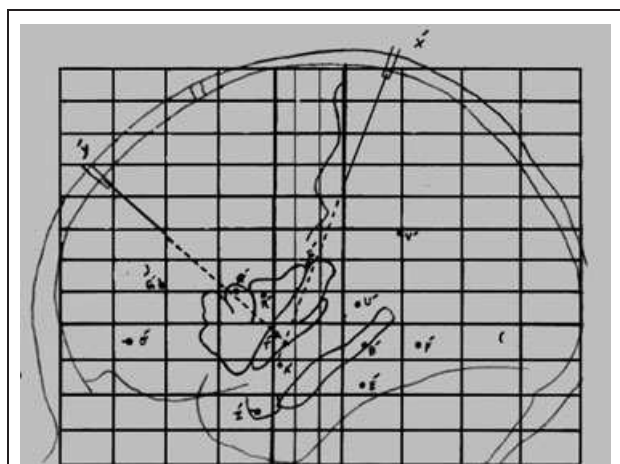
A total number of 29 electrodes were implanted into 27 insulae with 15 electrodes in the right insula (51.7%) and 14 in the left (48.3%). A total of 201 contacts were localized within the different insular gyri (Fig. 2A; Table 1). No morbidity was related to cerebral electrode implantation.

### Anatomic localization of insular contacts

Because of the complex anatomy of the insula, two anatomic localization procedures were retrospectively performed to identify with a high level of accuracy the localization of all electrical contacts within the insular cortex.

#### *The individual scheme of the insular gyri in a bicommissural reference system*

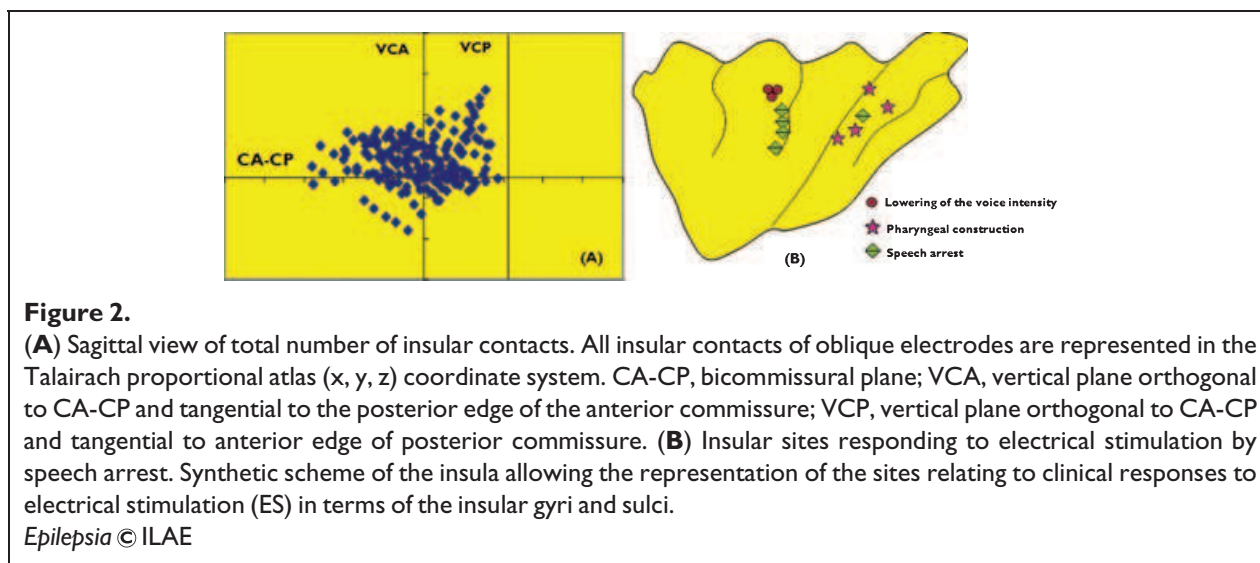
All electrode positions were plotted into the individual scheme where the insular gyri were identified in a



**Figure 1.**

Individual scheme (sagittal view) in Talairach bicommissural referenced system. One of the patients of this study (sagittal view) showing two oblique electrodes:  $y'$ , trans-frontal electrode targeting middle and posterior short gyri and the inferior part of both long insular gyri;  $x'$ , transparietal electrode targeting post-central and posterior gyri. Other letters represent laterally introduced electrodes.

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**Table 1. Anatomic position of contacts and responses in insular structures**

Anatomical position	Nmb. of stim. cont.	Nmb. of pats.	Nmb. of clin. resp.	Resp. versus total, %	Sensory resp.	Motor resp.	Pain resp.	Auditory resp.
Ant. short gyrus	11	8	4	4.8				1
Mid. short gyrus	42	17	27	32.5		1	8	
Precentral gyrus	49	19	13	15.6		1		
Postcentral gyrus	57	20	36	43.3	11	8		2
Post. long gyrus	17	8	3	3.7		1		
Insular pole	3	1	0	0				

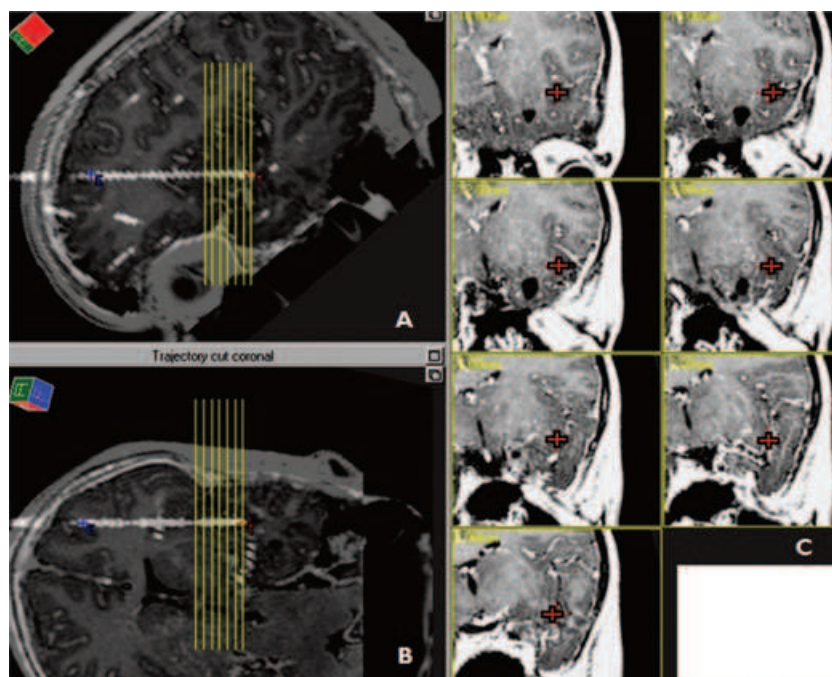
Ant., anterior; mid., middle; post., posterior; nmb. of stim. cont., number of stimulated contacts inside the structure; nmb. of pats., number of patients explored in this structure; nmb. of clin. resp., number of clinical responses in this structure; resp. versus total, percentage of the number of clinical responses obtained by ES of this structure in reference to the total number of responses obtained by ES of insula; sensory resp., number of sensory responses; motor resp., number of motor responses; pain resp., number of pain responses; auditory resp., number of auditory responses.

bicommissural reference system (Bancaud et al., 1967; Talairach & Tournoux, 1988), and each electrode contact referenced by its coordinates in individual space (x, y, z). The x coordinate defined the mediolateral axis, with x = 0 at the sagittal interhemispheric plane; the y coordinate defined the anteroposterior axis, with y = 0 at the vertical plane orthogonal to the bicommissural plane (CA-CP) and tangential to the posterior aspect of the anterior commissure (VAC); and the z coordinate defined the superoinferior axis, with z = 0 at the horizontal plane passing through the anterior and the posterior commissures (AC-PC plane). Each insular contact was plotted into an individual scheme, where the insular gyri and sulci were identified (Fig. 1). This scheme was built up from the different slices of presurgical T1-MRI images referenced to the AC-PC baseline. Imaging parameters were: echo spin, repetition time (TR) = 500 ms, echo time (TE) = 10 ms, section thickness = 4 mm, and intersection gap = 1 mm. It was then possible to identify the position of each of the insular

electrical contacts by the individual x, y, and z coordinates and its gyral localization on the lateral scheme. However, inter-individual variability in insular cortex shape and the position of the corresponding gyri limit the accuracy of this statistical reference system.

#### *The 3D neuroimaging pre- and postoperative fusion*

To increase the anatomic accuracy of localizing each electrode, we performed a postoperative contrast-enhanced 3D computed tomography (CT) scan. This enabled the fusion of the resulting image with the preoperative 3D MRI in the same stereotactic referenced system (Fig. 3). CT scans were chosen in preference to MRI due to the absence of image distortion caused by electrodes. The fusion between the preoperative 3D MRI and the postoperative 3D CT scan enabled us to identify the contact location in three dimensions (sagittal, axial, and coronal). We could then identify its cortical location and anatomic position in reference to the insular gyri.



**Figure 3.**

Example of one insular electrode. Lateral (A) and frontal (B) reconstruction of an insular oblique anterior inserted electrode. This image is obtained after preoperative 3D MRI and postoperative 3D CT scan image fusion using stereotactic software (VOXIM). This particular electrode demonstrates how an oblique way of implantation allows the exploration of a large part of the insular cortex. In this case, the electrode covers the insular cortex from the anterior short gyrus to the posterior insular pole. (C) Represents frontal sections perpendicular to the electrode corresponding for each image to the lines crossing the electrode trajectory in (A) and (B).

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### Stimulation procedure

After implantation, simultaneous video and EEG recordings were performed enabling a complete online clinical examination of the patient by later analysis. ES was applied to every bipole of contiguous contacts selected for EEG recordings (Munari et al., 1993). According to previous studies (for references see Ranck, 1975), the current spread linked to a stimulation intensity of 3 mA is able to stimulate excitable nervous elements up to a maximum distance of 5 mm. We chose bipolar stimulation known to involve a smaller cortical volume compared to monopolar stimulation, thereby leading to more accurate anatomic localization of within 5 mm around the stimulated bipole (Nathan et al., 1993). To increase this accuracy further by reducing the current spread, we used only bipolar stimulation at current intensities of between 0.2 and 3 mA.

The aim of the stimulation protocol was to reproduce part of, or all, the ictal clinical symptomatology and map functionally eloquent areas, which needed to be avoided during surgery. ES was performed at low frequency (LF) 1 Hz (pulse width = 3 ms) and high frequency (HF) 50 Hz (pulse width = 1 ms) using a constant current, rectangular

pulse generator (Micromed, Treviso, Italy). Stimulations started at intensities ranging from 0.2 to 3.0 mA depending on the area of stimulated cortex, and increased in increments of between 0.2 and 3.0 mA. Stimulations usually lasted for 40 s at 1 Hz (0.2–3 mA), and 5 s at 50 Hz (0.2–1 mA). At these electrical current parameters, the  $50 \mu\text{C}/\text{cm}^2$  charge density per phase avoids tissue injury (Gordon et al., 1990) and the chosen stimulation parameters are commonly used for these types of exploration (Kahane et al., 1993; Ostrowsky et al., 2000, 2002; Isnard et al., 2004). The patients were asked to report any symptoms they felt as soon as possible and were then immediately examined and questioned.

Only those phenomena not associated with electrical afterdischarge were considered (Jefferys & Traub, 1998). The absence of afterdischarge was verified by analyzing the electrical signals obtained during cortical activity recordings on the electrode containing the stimulated bipole as soon as it was reconnected, alongside those obtained on all other deep brain electrodes during and after the stimulation procedure. All stimulation sites were stimulated by both LF and HF protocols, starting with LF.

## RESULTS

A total of 313 ES (191 HF at 50 Hz, and 122 LF at 1 Hz) were performed in 128 insular sites in the 25 patients. Eighty-three responses were evoked in 22 of the 25 patients, and within 24 of the 27 insulae by 67 ES; 50 HF (74.6%), and 17 LF (25.4%) with at least one response by stimulation. These responses were classified as sensory responses, that is, paresthesias and localized warm sensations (11); motor (11), painful (8), auditory (3), or oropharyngeal (8) responses; speech arrest and lowering of voice intensity (8); or neurovegetative, that is, facial rubefaction with general warm sensation, cool sensation, hypogastric sensation, rotation, and nausea (20) phenomena. Three responses could not be classified due to poor description by the patients. In 10 cases the ES reproduced epileptic aura, that is, epigastric block sensation, anxiety, and respiratory trouble. In one case the ES induced a seizure. All these manifestations started immediately after onset of the electrical stimulus and disappeared simultaneously with stimulus offset. The percentage of evoked responses in each insular region is presented in Table 1.

During a counting exercise forming part of our methodologic approach during the ES, five patients reported a total of eight responses (9.6% of total responses) as speech disturbances. Of these, seven responses were evoked in four patients by stimulation in the middle short gyrus (8.4% of total responses, and 25.9% of responses evoked in the middle short gyrus).

Two different types of response were reported in these patients: speech arrest (five responses: four following stimulation in the middle short gyrus “anterior to the precentral insular sulcus” and one following stimulation in the postcentral gyrus), and lowering of voice intensity (three responses in the middle short gyrus) (Fig. 2B and Table 2).

### Speech arrest

Five patients reported five responses of speech arrest induced by HF stimulations. All of these responses were

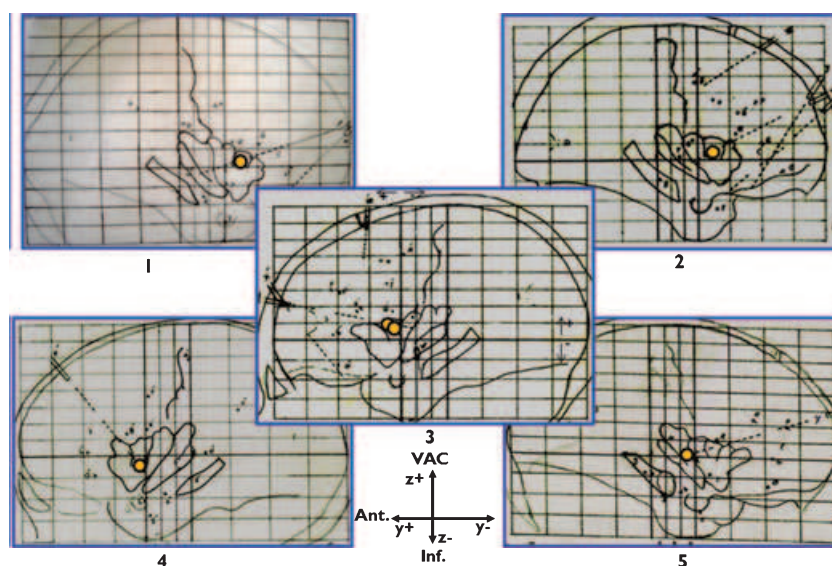
evoked during a counting exercise. Following stimulus offset, patients reported an inability to continue counting or speaking (Table 2) during the ES without other associated phenomena such as pharyngeal construction, memory deficits, trouble in the articulatory movements, panic, or asphyxial sensation. Patient 1, a 38-year-old right-handed man, was unable to continue counting and speaking in response to a 2-mA ES of the right insular site (−39, 5.5, 2.5). Patient 2, a 34-year-old right-handed woman, was unable to continue counting and speaking in response to a 2.4-mA ES of the right insular site (−37, 5.5, 3). The patient described, following stimulus offset, a highly unpleasant headache during this stimulation. She was unable to describe this sensation during the ES due to associated speech arrest. Patient 3, a 14-year-old right-handed boy, was unable to continue counting and speaking during ES at 1.6 mA of the left insular site (38, 0, 7.5). Following stimulus offset, he described a superficial pain in the head during this stimulation. Patient 4, a 11-year-old left-handed boy, was unable to continue counting and speaking during ES at 2.4 mA of the left insular site (38, 1.5, −8). No response was evoked from these sites by LF stimulation. All of these four responses of speech arrest were found in the middle short gyrus and restricted to the anterior edge of the precentral insular sulcus (see Fig. 4).

Patient 5, a 27-year-old right-handed man, was unable to continue counting and speaking (the fifth response) during HF stimulation at 1 mA of the right insular site (−35, −4.5, 0.5) in the postcentral insular gyrus. The patient described, following stimulus offset, as no painful paresthesias “pins and needles” in the left lower limb during this stimulation. He was unable to describe this sensation during the ES due to associated speech arrest. No response was evoked from this site by LF stimulation. The site of this response was located in the same insular region as the oropharyngeal responses induced by other ES (pharyngeal construction) in this study (Fig. 4). All the pharyngeal construction responses were evoked during HF stimulation of between 1 and 2 mA.

**Table 2. Summary of all speech disturbances responses to ES of insular contacts**

Response	P	Age (year)	Handedness	Side	ES		Ind. coord. (x, y, z)	Insular region
					F	mA		
Speech arrest	1	38	Right	R.	HF	2.0	−39, 5.5, 2.5	Middle short gyrus
	2	34	Right	R.	HF	2.4	−37, 5.5, 3	Middle short gyrus
	3	14	Right	L.	HF	1.6	38, 0, 7.5	Middle short gyrus
	4	11	Left	L.	HF	2.4	38, 1.5, −8	Middle short gyrus
	5	27	Right	R.	HF	1.0	−35, −4.5, 0.5	Postcentral gyrus
Lowering of the voice intensity	3			L.	HF	(2.0, 2.6, 3)	37.5, 2.5, 8	Middle short gyrus

P, patient; column 2, patients are referenced by number from 1 to 5; column 5, side of exploration; L, left; R, right; ES, electrical stimulation; column 6, type of ES; HF, high frequency; mA, intensity of the ES; Column 7, ind. coord., coordinates of individual bipolar stimulation sites in (x, y, z) reference of Talairach and Tournoux proportional atlas; column 8, Insular region of the speech disturbance evoked by each stimulation.



**Figure 4.**

The five individual schemes in the bicommissural reference. The five stereotactic schemes of the patients where speech disturbances were induced by electrical stimulation (ES) of the insular cortex. Ant., anterior; Inf., inferior; VAC, vertical plane orthogonal to the bicommissural plane (CA-CP) and tangential to the posterior edge of anterior commissure; y, the coordinate defining the anteroposterior axis,  $y = 0$  at the VAC; z, the coordinate defining the superoinferior axis,  $z = 0$  at the horizontal plane passing through the anterior and the posterior commissures (AC-PC plane). ●: speech arrest and lowering of voice intensity.

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### Lowering of voice intensity

Patient 3 reported, on three separate occasions, a lowering of voice intensity associated at intensities of 2, 2.6, and 3 mA of HF stimulation of the bipole situated at the left insular site (37.5, 2.5, 8) just above the site at which he reported the speech arrest in response to ES (Table 2 and Fig. 4). The patient described an unpleasant sensation of breathlessness and choking in the same insular site during less intensities (0.6 and 0.8 mA) of HF stimulation.

### SEEG data of these five patients

The five patients were classified in three groups according to insular involvement during SEEG-recorded seizures. Group 1 comprised two patients (patients 2 and 4) showing no insular involvement during seizures. No speech disturbances were described by these two patients during or after seizures. Group 2 comprised two patients (patients 1 and 5) with no insular involvement at seizure onset, but involvement after a short delay during seizure evolution. These patients presented speech disturbances, that is, speech arrest or verbal automatism (chic, chic,...) after seizures. Group 3 comprised one patient (patient 3) with insular involvement at seizure onset. This patient presented speech disturbances, that is, dysarthria and crying after seizures.

## DISCUSSION

The data of the present study provide evidence of a restricted area within the insular cortex inducing speech disturbances in response to direct ES. All areas of the anterior and posterior insula were subjected to a total of 313 electrical stimulations. Twenty-seven responses (6 at LF and 21 at HF stimulation) including speech disturbance, oropharyngeal, neurovegetative, and motor responses and painful sensations were evoked by ES in the middle short gyrus (Table 1). To our knowledge the present study is the first to report responses related to speech disturbance evoked by ES of the insular cortex in terms of gyral and sulcal anatomy. It should be noted that speech disturbance was also observed by ES within many other areas of the brain.

Eight speech arrest and lowering of voice intensity responses represented 9.6% of the total phenomena evoked by ES of insular cortex. Seven of these responses were evoked in sites localized in the middle short gyrus and restricted to the anterior edge of the precentral insular sulcus, in both minor and dominant hemispheres. The term “speech arrest” used in this study refers to those patients unable to continue counting and speaking, thus experiencing trouble with speech production. Our patients described

an inability to continue counting and speaking (speech arrest) with no associated other phenomena, that is, pharyngeal constriction, memory deficits, trouble in the articulatory movements, panic, or asphyxial sensation. The patients with insular involvement during or at seizures onset (Group 2 and Group 3) present speech disturbances after seizures. Four of the five speech arrest responses in four patients were induced in four sites located in the middle short gyrus of the insula and restricted to the anterior edge of the precentral insular sulcus. These responses, present on both the right (three times) and left (two times) sides, concerned the nondominant side four times out of five. The four patients reporting speech arrest and lowering of voice intensity by ES of the middle short gyrus represented 40% of the patients responding to ES of this gyrus. The one remaining speech arrest response was induced by ES localized in the postcentral insular gyrus, in the same region that represented the location of pharyngeal constriction. This response agrees with data reported by Ojemann & Whitaker in 1978 following induction by direct ES of the posterior insula without specific location in reference to gyri and sulci. This response could be the consequence of a disturbance in oropharyngeal motor control or due to current spreading outside the postcentral insular gyrus. Despite the bipolar stimulation and lower intensities of current used in the present study, we cannot entirely rule out the possibility that in some cases the stimulation-evoked responses were due to current spread to fibers outside the postcentral insular gyrus of the insula.

One of the five patients ( $n = 3$ ), presented a lowering of the voice intensity on three occasions following stimulation of the bipole situated above and adjacent to the one in which stimulation evoked speech arrest. In terms of anatomic localization, the stimulated site was also in the middle short gyrus. Responses relating to a lowering of voice intensity were evoked by stimulation between 2 and 3 mA. It is possible that these responses could be the consequence of a disturbance in motor control (pharyngeal constriction and breathlessness sensation) or due to current spread to the adjacent area producing speech arrest. At these intensities the theoretical current spread may reach anatomic structures situated up to 5 mm in distance, which is the case for the site where speech arrest was induced in the same patient.

Few studies exist relating to ES of human cortical brain structures (Ostrowsky et al., 2000; Isnard & Mauguier, 2005) using semichronic stereotactically implanted deep brain electrodes (SEEG) inserted in a lateral orthogonal manner. These studies suggest the involvement of the insula in speech disturbance involving slurred speech or speech arrest. No specific location in reference to gyri and sulci was given.

Numerous functional imaging studies have demonstrated the activation of the anterior insula during language-based tasks. McCarthy et al. (1993) suggest an

activation of the anterior insula during language-based tasks. Riecker et al. (2000, 2005) assume an important role of the anterior insula in speech motor control. Friederici et al. (2006) suggest an activation bilateral of the insula for the phrase structure grammar. Price (2000, 2001) proposed extending the role of Broca's area to the anterior insula in suggesting that articulatory planning activates the left anterior insula or an adjacent region in the frontal operculum. Positron emission tomography (PET) studies show a simultaneous increase in metabolism in the supplementary motor area, the primary sensory cortex, and anterior insular cortex relating to articulation (Raichle, 1991; Wise et al., 1999). Using a magnetoencephalography (MEG) technique, Kato et al. (2007) suggested that the motor control of speech proceeds from insular regions. No specific location in reference to gyri and sulci was given by these studies.

Cases in the literature relating to infarctions in the insular cortex show similarities with the data in the present study. Right striatoinular infarction has previously been associated with speech disturbance (Ferro et al., 1982), and other cases of infarction of the anterior insular area have presented with articulatory disorders or apraxia (Shuren, 1993; Dronkers, 1996). Nagoa et al. (1999) reported a case of apraxia resulting from infarction of the left precentral gyrus of the insula. This finding could corroborate the data of this study. Indeed, the supply of the two edges of each sulcus arises from the same artery (Ture et al., 2000). So, the infarction due to the artery of the precentral insular sulcus occlusions can include the anterior part of the precentral insular gyrus and the posterior part of the middle short gyrus (the two edges of the precentral insular sulcus). Habib et al. (1995) reported a case of mutism and auditory agnosia resulting from bilateral infarction involving the insular cortex on both hemispheres.

In the present study, we performed a postoperative 3D CT scan with the electrodes in place, and fused this with the preoperative 3D MRI. This method of anatomic positioning enabled us to localize the stimulated sites in terms of individual gyri. The high restriction of the speech arrest responses to the middle short gyrus revealed in this study demonstrate the need for anatomic precision during functional studies of the insula in terms of the gyri and sulci.

## CONCLUSIONS

This study provides evidence that the middle short gyrus of the insula in both hemispheres responds to ES producing speech disturbances. These data show the importance of intrasulcal electrode implantation during invasive pre-resection evaluation by SEEG when speech arrest occurs early in seizure semiology. Functional studies of the insula should be treated in terms of its gyral and sulcal anatomy.



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We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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