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Robotic Arm and Imaging in Neurosurgical Stereotactic Interventions: Oblique Insular Electrodes Implanted in Patients with Epilepsy

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1. Introduction

The human insular lobe was initially described by the anatomist Reil JC (Reil, 1809). This lobe is the first in the cerebral cortex that develops and differentiates in the fetus (Streeter, 1912; Kodam, 1926; Afif et al., 2007). A recent study demonstrates that the formation of insular cortex begins by its inferior region that will later become the limen insula (Afif et al., 2007). This cortical development progresses in parallel with that of the middle cerebral artery (MCA) and its branches in the superior and posterosuperior axis (Afif et al., 2007). The insula consists of three short and two long gyri separated by the central insular sulcus, which defines the anterior and posterior insula (Varnavas & Grand, 1999; Ture et al., 1999; Naidich et al., 2004; Afif & Mertens, 2010). The opercularization is the result of important development of the surrounding insular cortex (frontal, parietal and temporal lobes). Progressive development over the entire surface of the insular cortex encloses the sylvian fissure.

Due to its deep anatomic position and dense surrounding vascular network, few studies involving direct electrical stimulation (ES) of the insular cortex during surgical procedures have been reported (Penfield & Jasper, 1954; Penfield & Faulk, 1955; Oppenheimer et al., 1992; Duffau et al. 2001, 2009).

Immunocytochemistry, functional imaging, direct ES, and lesion studies suggest an important role for the insular cortex. Such roles include language production and grammatical processing (Raichle, 1991; McCarthy et al., 1993; Wise et al., 1999; Price, 2000, 2001; Ackermann & Riecker, 2004; Isnard et al., 2004; Riecker et al., 2005; Friederici et al., 2006; Kato et al., 2007; Afif et al., 2010a), pain modulation (Tarkka & Treede, 1993; Frot & Mauguiere, 1999; Ostrowsky et al., 2000; Peyron et al., 2004; Craig, 2004; Isnard et al., 2005; Brooks et al., 2005 ; Schreckenberger et al., 2005; Mazzola et al., 2006; Henderson et al., 2006, 2007; Afif et al., 2008b), visceral sensory processing (Ostrowsky et al., 2000; Dupont et al., 2003; Isnard et al., 2004), bradycardia (Seeck et al., 2003), dysphagia (Danieles & Foundas, 1997) and auditory processing (Manes et al., 1999; Lewis et al., 2000; Shergill et al., 2000; Bamiou et al., 2003; Afif et al., 2010b).

Until recently the insular cortex has not been investigated using depth electrodes because of its anatomical location in the depth of the sylvian fissure and its close anatomical relationship with segments of the middle cerebral artery constituting a "vascular screen" at the surface of the insula (Ture et al., 1999, 2000; Varnavas & Grand, 1999; Afif & Mertens, 2010).

Recently, however, Stereoelectroencephalographic (SEEG) recordings on epileptic patients with electrodes stereotactically implanted deep in the brain using either the lateral trans-opercula approach (Isnard et al., 2000; Isnard et al., 2004; Isnard and Mauguiere, 2005; Ryvlin et al., 2006) or the oblique approach guided by robotic arm (Afif et al., 2008a), have implicated the insular cortex in seizure generation and initial propagation.

These observations emphasize the need to explore this anatomical structure further during invasive pre-surgical evaluation of epileptic patients. Functional studies of the insula should be treated in terms of its gyral and sulcal anatomy. The oblique approach (trans-frontal or trans-parietal) implantation of the electrodes guided by a robotic arm can explore the different insular regions (sulci and gyri) by avoidance of the sylvian vascular network which prevents access to these regions by the lateral approach.

2. Patient selection criteria

The non-invasive pre-surgical evaluation included in all cases high resolution magnetic resonance imaging (MRI) (with coronal T1-weighted images perpendicular to the hippocampal axis and T2-weighted images parallel to the hippocampal plane), neuropsychological tests, and prolonged electroencephalography (EEG) video monitoring. MRI scans showed unilateral hippocampal sclerosis in 17 patients (56.6%) cortical dysplasia in five patients (16.7%), and a cavernoma in two patients (6.7%). Six patients (20%) were considered cryptogenic (Table 1). Two patients harbored a dysplastic tissue within the insular cortex. The mean duration of epilepsy was 19.4 ± 11 years.

Stereoelectroencephalographic SEEG recordings were judged necessary, in all centers using this technique, when non-invasively obtained data were insufficiently concordant, discordant, inconclusive, and/or suggested an early involvement of highly eloquent areas. SEEG exploration within these patients included deep and superficial structures, including the amygdala, hippocampus, cingulate gyrus, SI, SII areas and temporal cortex, with a total of 12 to 16 electrodes per patient by implanting electrodes using the lateral orthogonal approach (mean 14 electrodes / patient).

Electrode implantation into the insular lobe was justified on clinical grounds in each case, either because patients experienced gustatory hallucinations, laryngeal discomfort or throat tightening, paresthesiae or tonic-clonic movements of the face, unpleasant paresthesiae affecting large somatic territories and hyper salivation (Isnard et al., 2000; Isnard et al., 2004), or because scalp video-EEG data suggested the onset of the first ictal electrical change in the perisylvian opercula area or an early spread to the suprasylvian opercular cortex and insula.

The exploration of the insular cortex was elaborated by deferent hospital centers according to the classical lateral trans-opercula (orthogonal) approach (Isnard et al., 2000; Isnard et al., 2004; Isnard & Mauguiere, 2005). An original oblique approach (trans-frontal or trans-parietal) was elaborated by the center of university hospital of Grenoble (France) to explore the insula (Afif et al., 2008a, 2008b, 2010b).

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P.	Age (y)	Lat. R/L	Sexe	Past history	Age at 1st Seizure	MRI
1	15	R.	f		6 y	HcS
2	28	R.	m	H.T.	20 y	Normal
3	19	R.	f	FC (6 mo)	6 mo	HcS
4	35	R.	f	FC (1 y)	12 y	HcS
5	37	R.	m	H.T. (18 y)	23 y	T. dysplasia
6	11	L.	m		1 y	TP. dysplasia.
7	13	L.	m		6 y	Normal
8	20	R.	f		11 mo	F. dysplasia
9	22	R.	f	H.T. (4 y)	14 y	FP. dysplasia
10	34	R.	f		3 y	Normal
11	38	R.	m	H.T. (14 y)	14 y	HcS
12	41	R.	f	Meningitis (3 y)	12 y	HcS
13	18	R.	m		15 y	HcS
14	44	L.	M	Meningitis (2 y) + FC (3 y)	6 y	HcS
15	42	R.	m		10 y	HcS
16	41	R.	f		13 y	HcS
17	40	R.	m	FC (10 mo)	2 y	HcS
18	18	R.	f	FC (2,5 y)	9 y	HcS
19	42	R.	m		14 y	HcS
20	26	R.	f	FC (18 mo)	18 y	HcS
21	52	R.	m	H. T. (20 y)	20 y	Amygdala Cavernoma
22	18	R.	m	FC (16 mo)	3 y	HcS, F. Cavernoma
23	27	R.	m	H.T. (9 mo)	16 y	HcS
24	26	L.	f	FC (20 mo)	10 y	HcS
25	13	R.	m	West syndrom (10 mo)	18 mo	F. + insular cortical dysplasia
26	9	R.	m		1 y	Orbito-insular cortical dysplasia
27.	37	R.	m	H.T. (3mo) +FC (9 mo)	3 y	HcS
28	53	R.	m	H.T. (5y)	9 y	Normal
29	14	R.	m		5 y	Normal
30	7	R.	f		2.5 y	Normal

Table 1. Patient details P.: patient; MRI: MR imaging; y: year; mo: month; Lat.: hemispheric dominance for language; L.: left; R.: right; m: male; f: female; H.T.: head trauma; FC: febrile convulsion; HcS: hippocampal sclerosis.

2.1 Stereotactic implantation of intra-cerebral electrodes

Targeting of the insular cortex was performed using 3D presurgical T1- MRI images (Imaging parameters included 3D T1 gradient Echo 20/4.6/30 injected sequence, 1.5 mm thickness, gap: 0) computed with stereotactic software (VoximR, IVS solution, Chemnitz, Germany). The

avascular characteristics of each trajectory were systematically evaluated by stereotactic and stereoscopic digital cerebral teleangiography (Pixray; Bioscan system, Geneva, Switzerland), as described elsewhere (Bancaud et al., 1967; Talairach et al., 1988; Kahane et al., 1993). Following coagulation of the dural entry point, insular electrodes were implanted through a 2 mm burr hole using either an anterior (transfrontal) approach (Fig. 1   A,C)
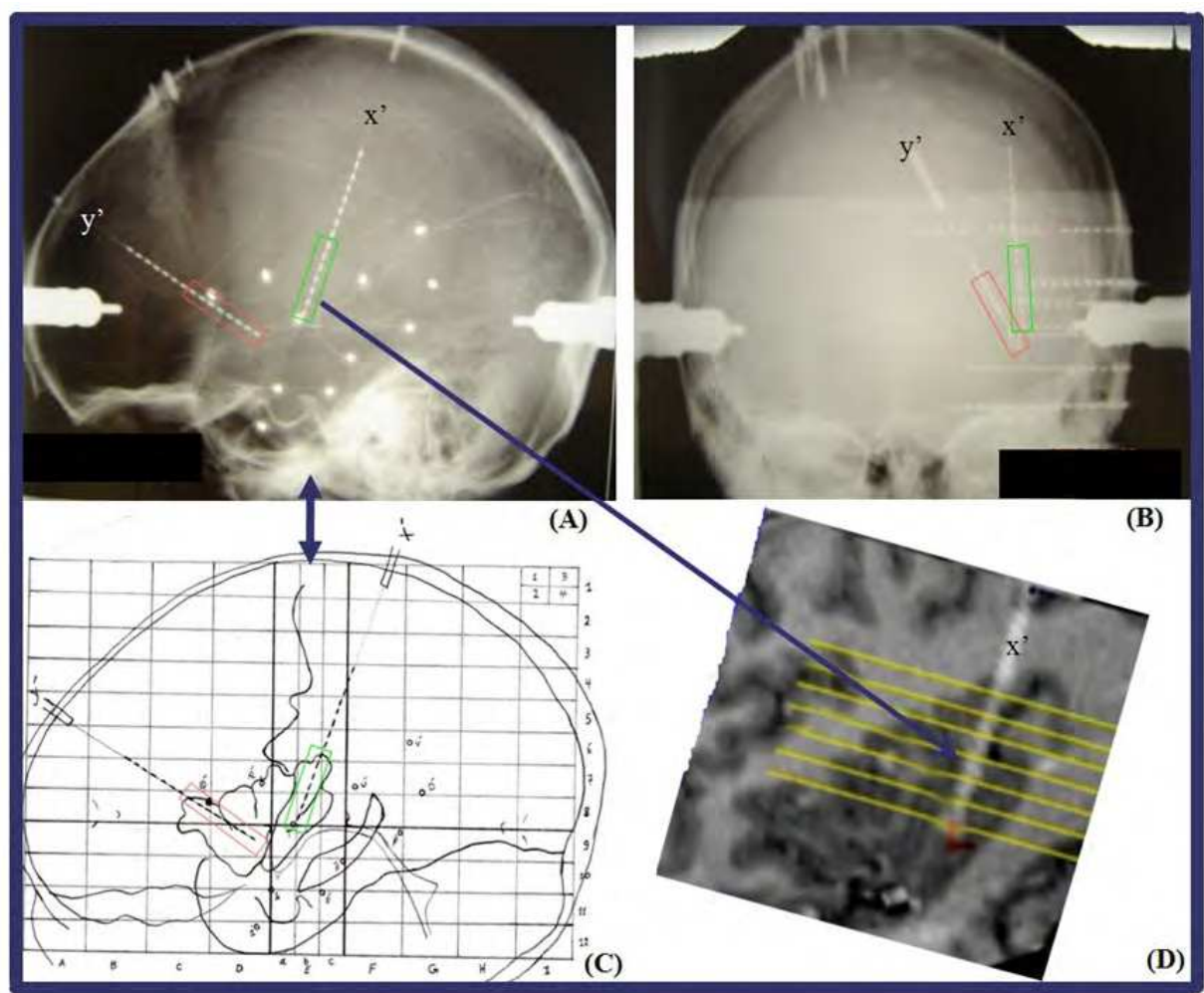

Fig. 1. Locating the insular cortex electrodes: Lateral (A) and frontal (B) X-rays of the patient's head after intracerebral electrode implantation. y': Anterior oblique electrode ("transfrontal") targeting the anterior and middle short gyrus of the insula; x': Posterior oblique electrode ("transparietal") targeting the post-central gyrus of the insula; boxes indicate the electrode's contacts within the insular cortex. (C): corresponding sagittal patient diagram showing intrinsic anatomical insular structures and implanted electrodes (small letters). We constructed an individual diagram for each patient using different slices from pre-surgical T1-MRI images, in the AC-PC reference system. The box around electrode y' represents the contacts within both the anterior and middle short insular gyrus; the box around electrode x' represents the contacts within the post-central insular gyrus. (D): image fusion of the pre-operative 3D MRI and the post-operative contrast-enhanced 3D CT scan, using VOXIM stereotactic software. We could then identify the anatomical position of each electrode with reference to the cortical gyri and sulci. The sagittal slice is co-planar to electrode x'; each perpendicular line on the electrode trajectory pass through one electrode contact.

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with an entry point in the middle frontal gyrus, or a posterior (transparietal) approach (Fig. 1 A, D), entering the brain at the level of the inferior parietal cortex, or both approaches. Similarly to other groups, the lateral orthogonal approach used for all deep brain electrodes (SEEG) stereotactically implanted outside the insular cortex. Electrode insertion was guided by a robotic arm (Neuromate, Renishaw mayfield, Nyon, Switzerland) connected to the stereotactic frame and driven by stereotactic planning software (VoximR, IVS solution, Germany).

In fact, the choice of the oblique approach to explore the insular cortex was decided because the orthogonal approach is less adapted to explore the insula due to several points (Afif et al., 2008b): I) The first one, that the insula lies almost parallel to the sagittal plane in the depth of sylvian fissure behind of the opercula which overlapping irregular folds of the lateral insular surface. II) The second one, that the thickness of the insular cortex is less than the distance covered by two contiguous contacts (up to 5mm), so in SEEG, only one contact of a laterally (trans-opercula) introduced electrode would lie within the insular cortex (Fig. 2). The second contact will be in the mesial part within the extreme capsula or in the lateral part within the opercula. III) The third one, that the dense network of vessels overlying the lateral surface of the insular cortex (Varnavas & Grand, 1999; Ture et al., 1999; Afif & Mertens, 2010) prevents the safely access to this region by a lateral orthogonal approach and only the peripherical region near the periinsular sulci can be reached safely.

Fig. 2. Example of an orthogonal insular electrode (axial slice): Image fusion of the preoperative 3D MRI and the postoperative contrast-enhanced 3D CT scan of the axial slice using VOXIM stereotactic software. E: Orthogonal trans-opercula insular electrode in SEEG, one contact (n°: 1) in the mesial part within the extreme capsula, one contact (n°: 2) within the insular cortex and one contact (n°: 3) in the lateral part within the frontal opercula.

The methodology targeted the insular cortex using an oblique approach, which allowed exploration of a larger surface of the insula by one electrode without passing through the

opercula. Most patients were explored by means of at least one trans-frontal insular electrode, while the choice to use an additional trans-parietal electrode was reserved for patients showing a rapid posterior spread of the ictal electrical discharge on EEG (Afif et al., 2008a). Electrodes (DIXI Besançon, France) were 0.8 mm in diameter, with 10 to 18 contacts, of 2 mm in length and 1.5 mm apart, depending on the length of the electrode (Fig. 3). This allowed to sample different insular regions using only one electrode and to avoid passing through the opercula.
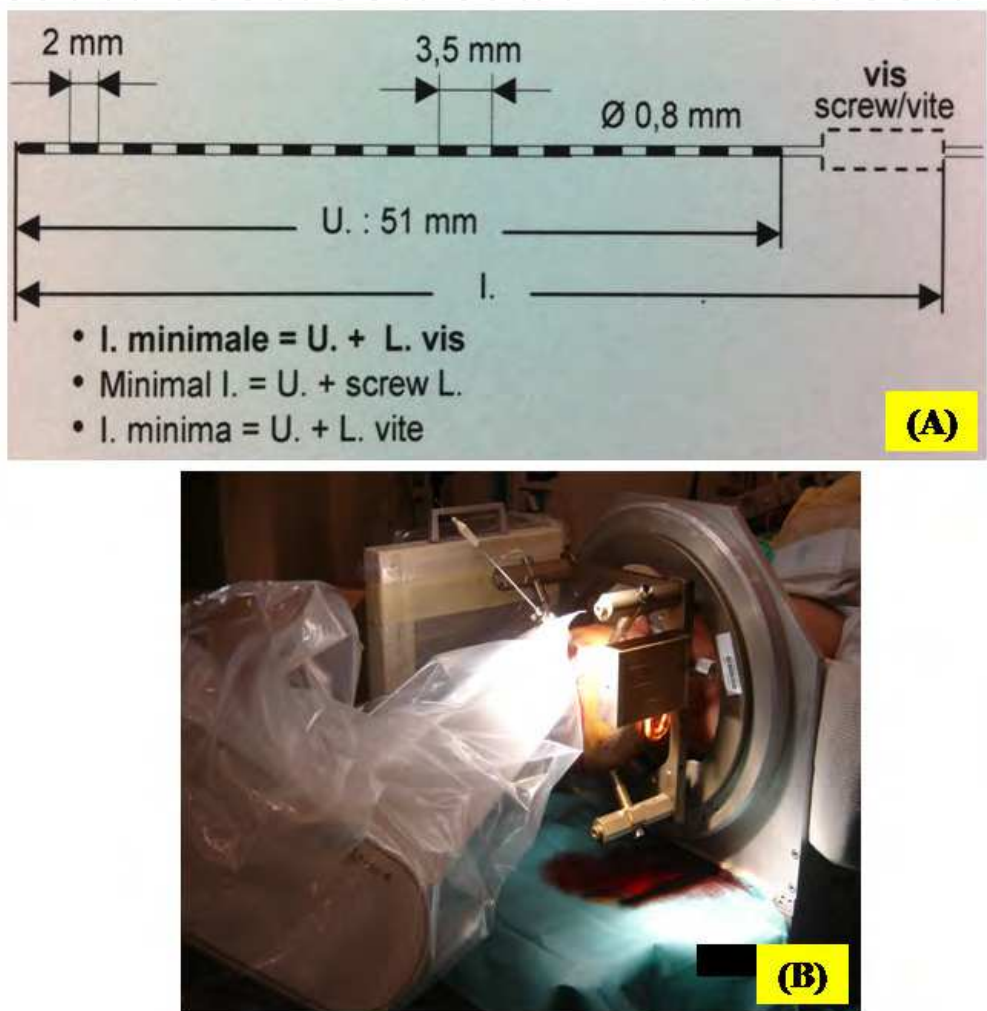
Fig. 3. (A) Drawing of an electrode with 15 contacts: U.: electrode length of 15 contacts = 51 mm, Ø: diameter of the electrode = 0.8 mm, length of each contact = 2 mm, distance between the two contacts = 1.5 mm. (B) Robotic arm: in the position of an anterior (trans opercular) oblique insular electrode trajectory.

2.2 Determining the anatomical location of the insular contacts

Due to the complex anatomy of the insula (its located in the depth of the sylvian fissure and the arteriovenous dense vascular network on the lateral surface of the insula) (Fig. 4) it was necessary to identify with high accuracy the localization of electrical contacts. Two anatomical and one electrophysiological procedure were utilized to accurately establish the location of all contacts clearly located in the insular cortex.

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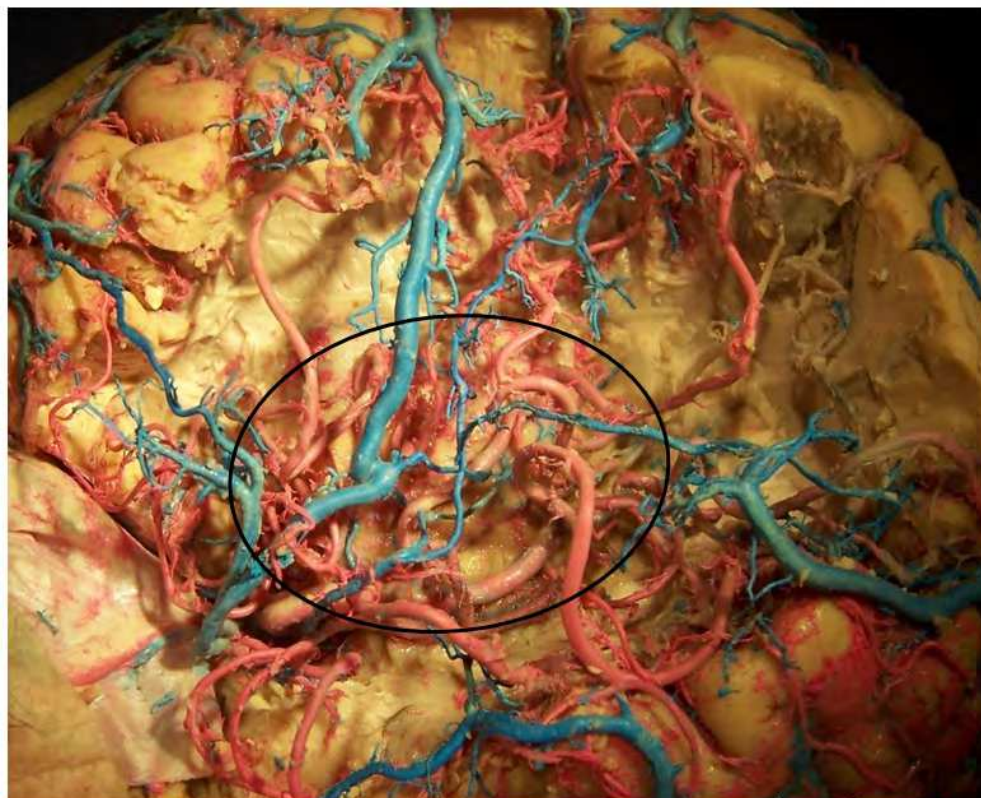Oblique Insular Electrodes Implanted in Patients with Epilepsy
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Fig. 4. View of the left insula, showing the MCA collaterals (insular and opercular arteries) and the sylvian venous system on the lateral surface of the insula (in the interior of the cycle) and the supra-sylvian region.

2.2.1 Anatomy-based procedures

- Individual insular diagrams:

This diagram was constructed for each patient using different sagittal slices of presurgical T1 MRI images referenced to the bicommissural plane (AC-PC) reference system (Fig. 1 C). The electrode contacts localization was identified in reference to insular gyri and sulci in the sagittal diagram (Afif et al., 2008b, 2010b).

- Individual 3D neuro-imaging:

To increase accuracy, a postoperative contrast-enhanced 3D CT scan was performed. All stimulation sites were anatomically located via image fusion between pre-implantation 3D MRI and post-implantation 3D CT scans (Afif et al., 2008b, 2010b). So, the cortical location and anatomical position of each contact were identified in reference to insular gyri in the three dimensions (sagittal, axial and coronal) (Fig. 5). No calculation was needed to reference the anatomical position of the electrical contacts to a standardized system since 3D anatomical localization was obtained by distortion free 3D CT performed immediately after electrode implantation.

In order to represent each stimulation response in a homogeneous manner, a template of the insula, including its sulci and gyri was used. The stimulation sites were located on each patient's individual diagram, before locating it on the insular template with respect to the insular gyri from the individual diagram (Fig. 6).
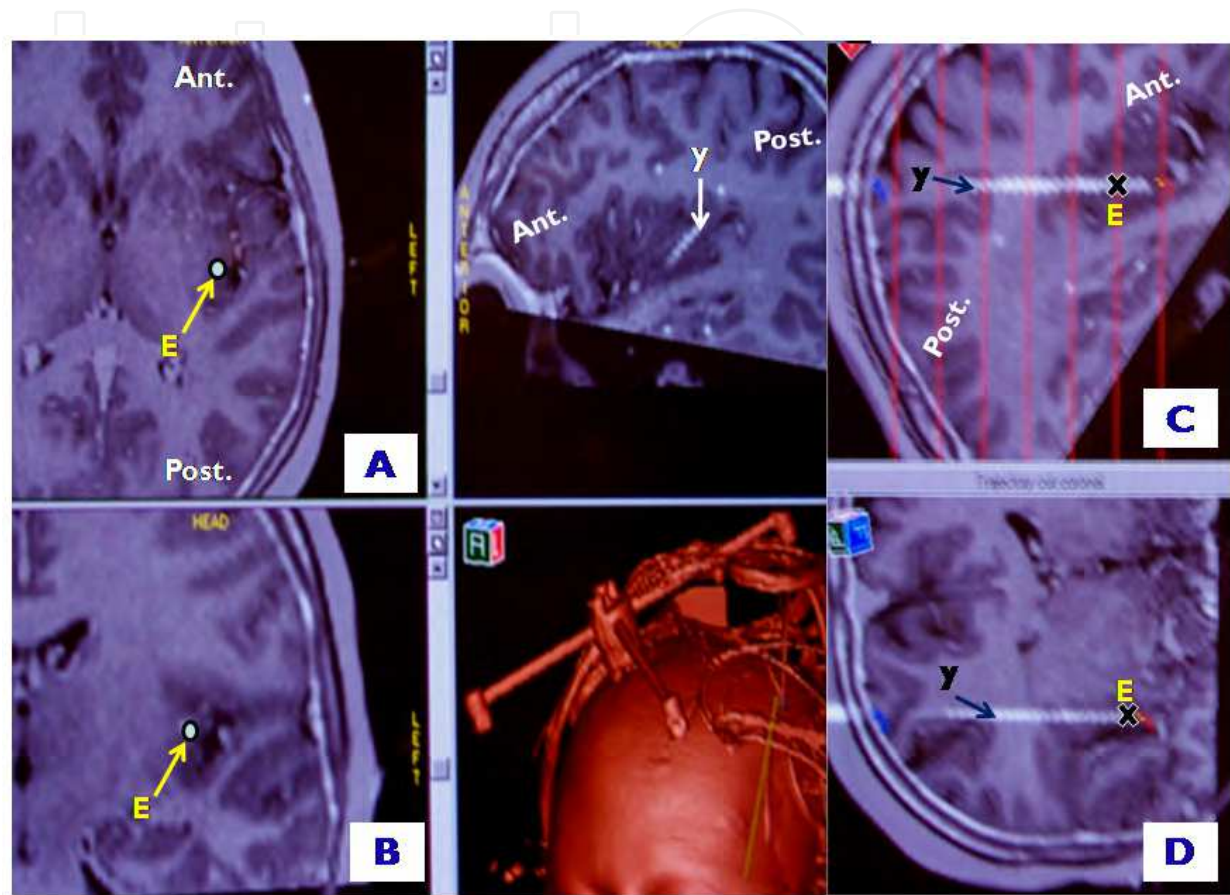
Fig. 5. Example of an oblique insular electrode. Image fusion of preoperative 3D MRI and post-operative contrast-enhanced 3D CT scans using VOXIM stereotactic software. This technique enabled us to identify the contact locations in three dimensions (sagittal, axial and coronal). Axial (A) and frontal (B) section crossing the trajectory of electrode y at the level of the contact E in figures (C) and (D). Lateral (C) and frontal (D) reconstruction of an oblique electrode (y) inserted into the posterior insula using a trans-parietal trajectory. This example clearly demonstrates how oblique implantation enables the exploration of a large part of the posterior insular cortex. E: one contact in the oblique electrode; Ant.: anterior; Post.: posterior.

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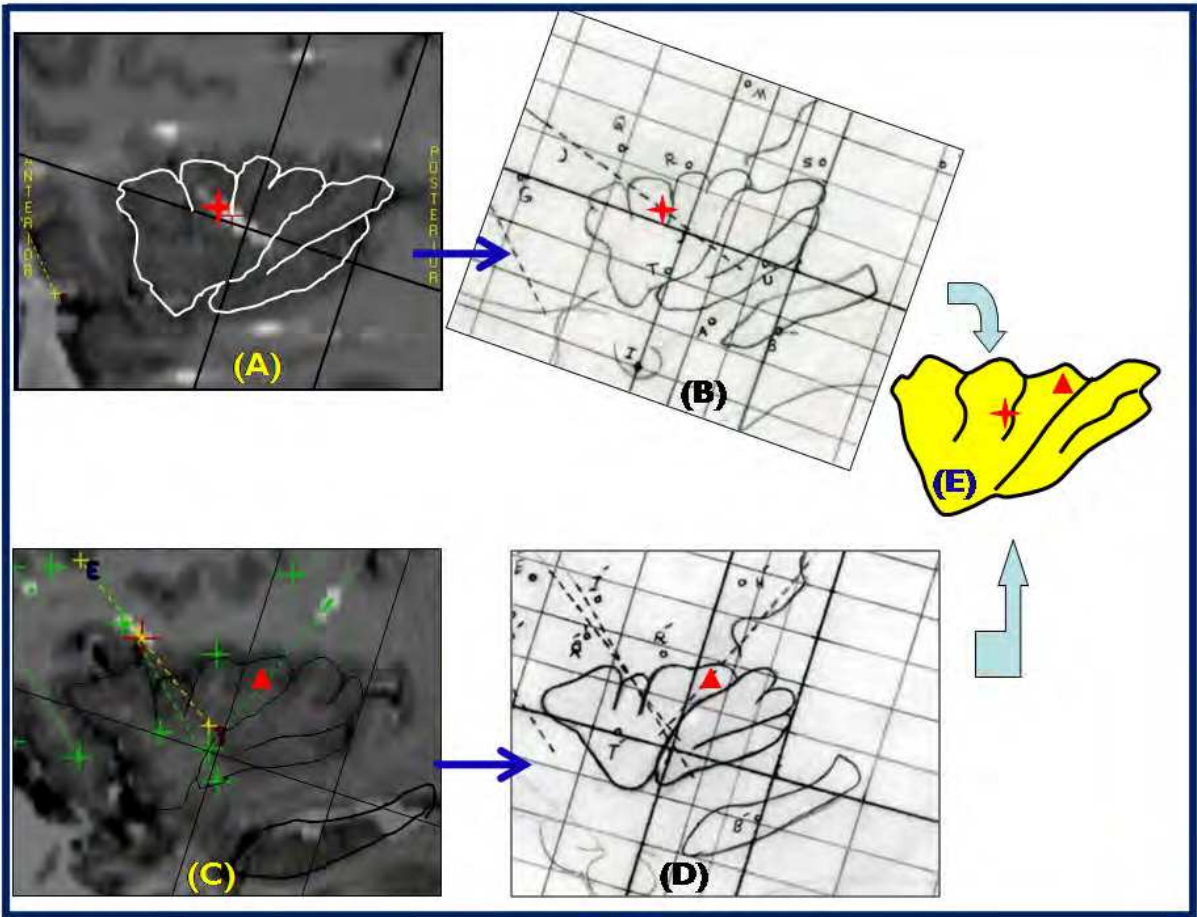
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Fig. 6. Our strategy to present the electrical stimulation data. Lateral (A) and (C) individual insula reconstruction in bi-commissural references of 2 patients with the stimulation sites " ✚ in figure (A) and ▲ in figure (C)". (B) and (D) individual insular diagram (sagittal view) with the stimulation sites between the two contacts stimulated of the 2 patients in figures A and C. (E) template of the insula, including its sulci and gyri, the stimulation sites were located on the insular template with respect to the insular gyri from the individual diagram.

2.2.2 Electrophysiological identification

The localization protocol was based on electrophysiological data enabling us to distinguish between gray and white matter since electrical activity (both voltage and rhythm) decreases significantly in white matter (Fig. 7). All contacts were individually checked by bipolar recording their spontaneous electrical activity.

Fig. 7. Bipolar EEG recordings from a right oblique insular electrode. Right oblique insular electrode (y) is shown on a patient's individual diagram. Contact n°: 1 (the deepest) and contact n°: 15 (the most superficial). Test recordings were performed on contiguous bipolar electrodes from y = 1-2 to y = 14-15. Electrical activity shows typical cortical voltage and rhythms from bipolar electrodes y = 1-2 to y = 9-10. Activity drops to typical white substance levels from bipolar electrodes y = 10-11 to y = 14-15. Analysis of this EEG activity identifies contact y = 9 as the last one exploring the insular cortex.

3. Stimulation procedure

After implantation, EEG recordings were obtained for several hours per day to monitor interictal and ictal activity. Simultaneous video and EEG recordings were performed enabling a complete online clinical examination of the patient by later analysis.

Following the previously described clinical protocol, ES was applied to every bipole of contiguous contacts selected for EEG recordings (Munari et al., 1993). According to previous studies (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, thus leading to more accurate anatomical localization of less than 5 mm around the stimulated bipole (Nathan et al., 1993). To increase this accuracy by diminishing the current spread, we used only current intensities of bipolar stimulation between 0.2 and 3 mA (Afif et al., 2008b).

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

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frequency (HF) 50Hz (pulse width = 1 ms) using a constant current, rectangular pulse generator (Micromed Treviso, Italy). Stimulations were performed after confirming a normal baseline activity of depth EEG recording. During stimulation the electrode containing the stimulated bipole was disconnected from recording amplifiers; electrical activity recordings continued on the other deep brain electrodes. ES was performed at both low frequency (LF; 1Hz; pulse width= 3 ms) and high frequency (HF;50Hz; pulse width= 1 ms). Stimulations usually lasted for 40 s at 1Hz, and 5 s at 50Hz. The patients were asked to report any symptoms they felt as soon as possible and were then immediately examined and questioned. Data on stimulation-evoked phenomena (Kahane et al., 1993; Afif et al., 2008b), only those phenomena not associated with electrical after-discharge and clearly not due to current spread out of insula were considered (Jefferys & Traub, 1998). Verification of the absence of afterdischarge could be obtained by analyzing the electrical signals obtained during cortical activity recordings on the electrode containing the stimulated bipole as soon as it was reconnected, and 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 (Afif et al., 2008b).

4. SEEG data

Three groups of patients were identified according to insular involvement during SEEG-recorded seizures (Table 2). Group 1 showed no insula involvement during seizures (Fig. 8a) including patients with temporal lobe epilepsy (TE) and/or with frontal lobe epilepsy (FE). Group 2 showed no insular involvement at seizure onset but involvement after a short delay during seizure evolution (Fig. 8b) including patients suffered from TE and from temporo-frontal lobe epilepsy (TFE). Group 3 showed insular involvement at seizure onset (Fig. 8c). Seizures arose either from the insula alone or from both the insula and the frontal operculum.

Compared to the initial hypothesis, SEEG changed the final location of the diagnosed epileptogenic zone in 43.3% (Afif et al., 2008a). In this study, three patients out of six with an initial hypothesis as suffering from FE were finally considered as having insulo-frontal epilepsy (IFE). Ten out of 14 patients with an initial hypothesis of TFE were finally considered as TE in seven patients, FE with secondary propagation to insula in one patient, and insulo-temporo-frontal epilepsy (ITFE) in the remaining two patients. Thus the SEEG data reduced the proposed surgical resection or disconnection zone in 57.1% in whom the initial hypothesis was TFE (Table 2).

Another study (Afif et al., 2010a) has shown the importance of SEEG data obtained by recordings and ES of intra-insular oblique electrodes insertions guided by a robotic arm during invasive pre-resection evaluation of epilepsy to identify the insular origin of the evoked clinical responses. This study suggests relationships between insular seizure semiology and evoked clinical responses by ES of insular contacts i.e., the patients with insular involvement at seizure onset or after a short delay during seizure evolution present speech disturbances such as speech arrest, dysarthria, crying and verbal automatism (chic, chic,..) after seizures. These patients reported a speech arrest induced by intra insular HF stimulations during a counting exercise. However, the patients show no insular involvement during seizures. No speech disturbances were described during or after seizures. These patients reported no speech arrest induced by intra insular ES.

P.	E.Z. hypothesis	E.Z. after SEEG	Group	Surgery	Outcome
1	R. T.(i)	R. T.	1	T. Discon.	Ia
2	R. T.(i)	R. T.	1	T. Discon.	Ia
3	L. T.(i)	L. T.	1	T. Lobect	Ia
4	L. T.(i)	L. T.	1	T. Lobect.	Ib
5	R. T.(i)	R. T.	1	T. Lobect.	Ic
6	L. T.F.(i)	L. T.	1	T..Lobect.	III
7	L. T.F.(i)	L. F.	1	F. Lobect.	Ia
8	L. F.(i)	L. F.	1	F. Lobect.	Ia
9	R. F.(i)	R. F.	1	F. Lobect.	Ia
10	R. F.(i)	R. F.	1	F. Lobect.	IV
11	R. T.(i)	R. T.(I*)	2	T. Discon.	Ia
12	R. T.(i)	R. T.(I*)	2	T. Discon.	Ia
13	L. T.(i)	L. T.(I*)	2	T. Lobect.	Ia
14	L. T.F.(i)	L. T.(I*)	2	T. Discon.	Ia
15	R. T.F.(i)	R. T.(I*)	2	T. Discon.	Ia
16	R. T.F.(i)	R. T.(I*)	2	T. Lobect.	Ia
17	L. T.F.(i)	L. T.(I*)	2	T. Lobect.	Ia
18	R. T.(i)	R. T.(I*)	2	T. Lobect.	Ib
19	L. T.F.(i)	L. T.(I*)	2	T. Lobect.	IIb
20	L. T.F.(i)	L. T.(I*)	2	T. Lobect.	IIb
21	L. T.(i)	L. T.(I*)	2	T. Lobect.	IId
22	R. T.F.(i)	R. T.F.(I*)	2	T. Lobect. + F. Lesionect.	Ia
23	R. T.F.(i)	R. T.F.(I*)	2	F. T. Lobect.	Ia
24	R. T.F.(i)	R. T.F.(I*)	2	T. Lobect+ F. Discon.	Ia
25	R. T.F.(i)	R. T.F.(I*)	2	T.+F.+ Insula Lobect.	Ia
26	R. T.F.(i)	R. I.T.F.	3	T.+F.+ ant. Insula Lobect.	III
27.	R. T.F.(i)	R. I.T.F.	3	T.+F.+ ant. Insula Lobect.	IV
28	L. F.(i)	L. I.F.	3	No surgery	NA
29	L. F.(i)	L. I.F.	3	No surgery	NA
30	R. F.(i)	R. I.F.	3	No surgery	NA

Table 2. Summary of the localization of the epileptogenic zone before and after SEEG and case grouping relative to insular involvement and the surgical outcome. TP: temporo-polar; FP: fronto-polar; F: frontal; T: temporal; (i): insular involvement was suspected during seizures prior to SEEG; (I*): secondary insular involvement demonstrated after SEEG evaluation; T.F.: temporo-frontal; I.T.F.: insulo- temporo-frontal; I.F.: insulo-frontal; Discon.: disconnection; Lobect.: lobectomy; Lesionect.: lesionectomy; Outcome according to Engel's classification with at least two year follow-up.
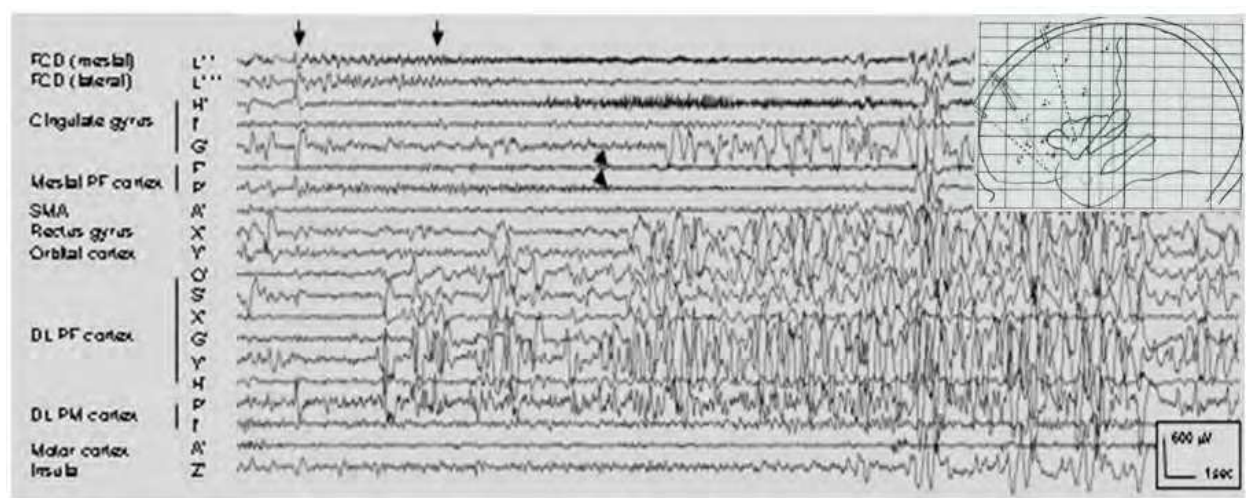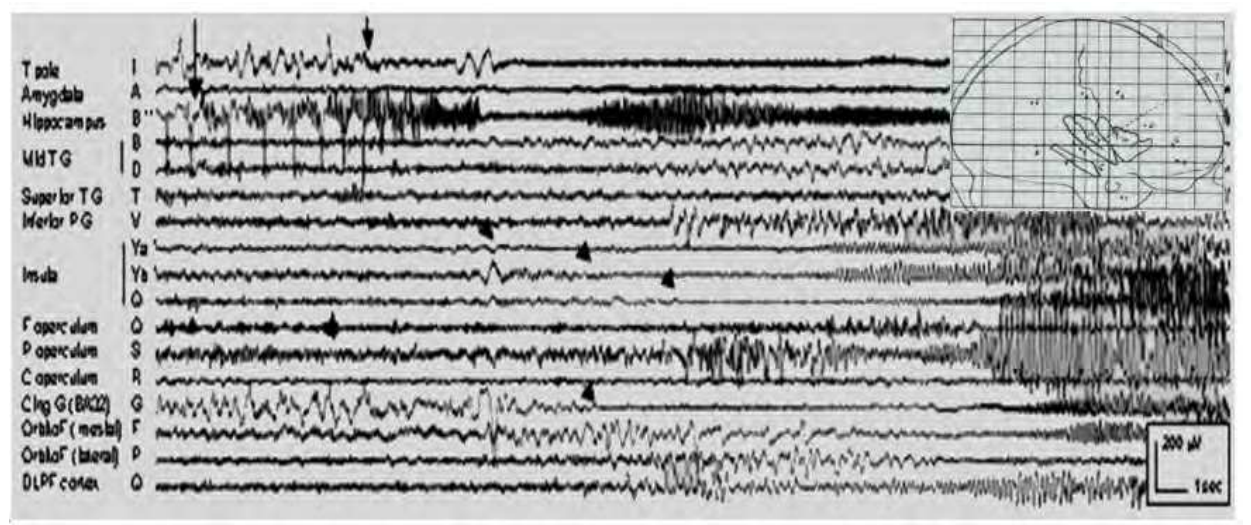
Fig. 8a. No insular involvement during seizure (Group 1) (SEEG trace and individual implantation lateral diagram with an oblique insular electrode). The ictal discharge (fast activity) begins (first arrow) in the lesion FCD (frontal cortical dysplasia) (L') and the anterior cingulate gyrus (H') and then (second arrow) becoming more evident later. later (arrowheads) the ictal discharge propagates to the mesial prefrontal cortex (P' and F'). Other regions are less involved with no involvement of the insular cortex. SMA: supplementary motor area, DLPF: dorsolateral prefrontal, DLPM: dorsolateral premotor.

Fig. 8b. Earlier insular involvement during seizure (Group 2) (SEEG trace and individual implantation lateral diagram with an oblique insular electrode). The ictal discharge (fast spikes) begins in the hippocampus (first arrow) then involves the temporal pole and the amygdala (fast activity). The insula becomes involved 3 sec later; the cingulate gyrus 2 sec later (arrowheads). Different parts of the insula are successively involved. Note how the insular discharge is firstly recorded at different levels along the axis of the insular oblique electrode (Ya and Yb) before becoming visible over the recording contacts of the perpendicular insular electrode (Q). T: temporal, P: parietal, F: frontal, C: central, Cing: cingulate, DLPF: dorsolateral prefrontal. Letters refer to the recording electrodes.
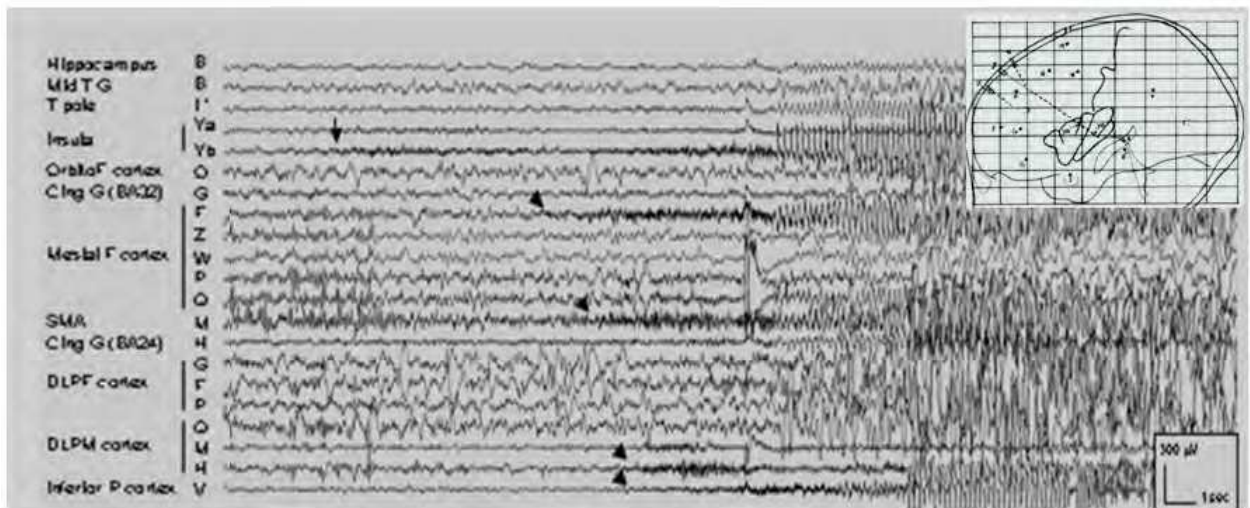
Fig. 8c. Insular involvement at seizure onset (Group 3) (SEEG trace and individual implantation lateral diagram with an oblique insular electrode). The ictal discharge (fast activity) begins in the insula (arrow), involving part of the mesial frontal cortex a few seconds later followed by the dorsolateral frontal cortex and the parietal cortex (arrowheads). Note that only the anterosuperior portion of the insula is involved at seizure onset. T: temporal, F: frontal, P: parietal, Cing: cingulate, SMA: supplementary motor area, DLPF: dorsolateral prefrontal, DLPM: dorsolateral premotor, G: gyrus. Letters refer to the recording electrodes.

5. Surgical treatment and outcome

On the basis of SEEG data analysis, 27 patients underwent a tailored surgical resection or disconnection (Afif et al., 2008a). Temporal lobe surgery was performed in 17 cases, frontal lobe surgery in 4 cases, temporo-frontal resection in 3 cases, temporo-frontal resection associated with removal of the anterior part of the insula in 2 cases, and total insulectomy in one patient who was seizure free (Engel's class I) (Engel et al., 1993).

Overall, (Table 2) 20 of the 27 operated patients (74 %) were seizure free (Engel's class I) following surgery, three had rare seizures (Engel's class II), two had a worthwhile improvement (Engel's class III), and two showed no improvement. With respect to insular involvement, eight of the ten operated patients in Group 1 were seizure free (80%), one was classified in Engel's class III, and one in Engel's class IV. In Group 2, surgery relieved seizures in 12 out of 15 patients (80%) while the remaining three patients suffered rare seizures. Surgery was unsuccessful in those patients in Group 3 who underwent surgery (one in Engel's class III, one in Engel's class IV).

With respect to the epileptogenic zone assessed by SEEG, 13 patients out of 17 were seizure free in TE, three were classified as Engel's class II and one as Engel's class III. In FE, three out of four patients were classified as Engel's class I and one as Engel's class IV. In TFE, all four patients were classified as Engel's class I. Neither of the two patients with initial insular involvement became seizure free following operation (Table 2).

The data strongly suggest the usefulness of insular recording to better predict the postoperative outcome and reduced the proposed surgical resection or disconnection zone in the epilepsy.

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6. Functional data

Only clinical responses evoked by ES in the absence of after discharge were analyzed (Afif et al., 2008b, 2010a, b). These studies are the first to report clinical responses evoked by ES of the insular cortex in terms of gyral and sulcal anatomy and to propose an anatomofunctional organization scheme of this cortex. The image fusion between the postoperative 3D CT scan with all electrodes still in place and the preoperative 3D MRI enabled us to localize the stimulated sites in three dimensions with respect to the individual gyri and sulci.

All the insular structures present responses by the ES. The relative lack of response to direct ES observed in the anterior short gyrus and pole could be due to under-exploration of these areas (5.4% and 1.49% respectively, Table 3) (Afif et al., 2010b).

Anatomical position	Nmb. of Stim. Cont.	Nmb. of Pats.	Nmb. Of Clin. Resp.	Stim. Cont. versus total	Nmb. of Pats. with Resp.	Resp. versus total
Ant. short gyrus	11	8	4	5.4 %	1	4.8 %
Mid. short gyrus	42	17	27	20.89 %	10	32.5 %
Pre central gyrus	49	19	13	23.88%	10	15.6%
Post central gyrus	57	20	36	28.3%	13	43.3%
Post. Long gyrus	17	8	3	8.4 %	3	3.7 %
Insular pole	3	1	0	1.49 %	0	0 %

Table 3. Anatomical positions of electrode contacts and observed responses in insular structures. Ant.: anterior. Mid.: middle. Post.: posterior. *Nmb. Of Stim. Cont.:* number of stimulated contacts inside the structure. *Nmb. of Pats.:* number of patients undergoing stimulation to this structure. *Nmb. of Clin. Resp.:* number of clinical responses in this structure. *Stim. Cont. versus total:* the number of stimulated contacts in this structure as a percentage of the total number of contacts inside the insular cortex. *Nmb. of Pats. with Resp.:* number of patients with clinical responses in this structure. *Resp. versus total:* the number of clinical responses to ES in a structure as a percentage of the total number of responses.

The main responses evoked in this study were classified as sensory (paresthesiae and localized warm sensations), motor, pain, auditory, oropharyngeal, speech disturbances, or neuro-vegetative phenomena. All these responses started immediately after the onset of the electrical stimulus and disappearing with the termination of the stimulus. Table 3 presents the percentage of evoked responses for each insular region.

6.1 Speech disturbances

Two different types of speech disturbances were reported (Fig. 9 a): i) speech arrest evoked by HF stimulation of the middle short gyrus (four responses) and one response occurred after stimulating the post-central insular gyrus. ii) episodes of reduced voice intensity in one patient evoked by HF stimulation from a bipolar electrode in the left insula (dominant hemisphere), just superior to the site that induced speech arrest. LF stimulation at this site did not evoke a response (Afif et al., 2010a, 2010b).
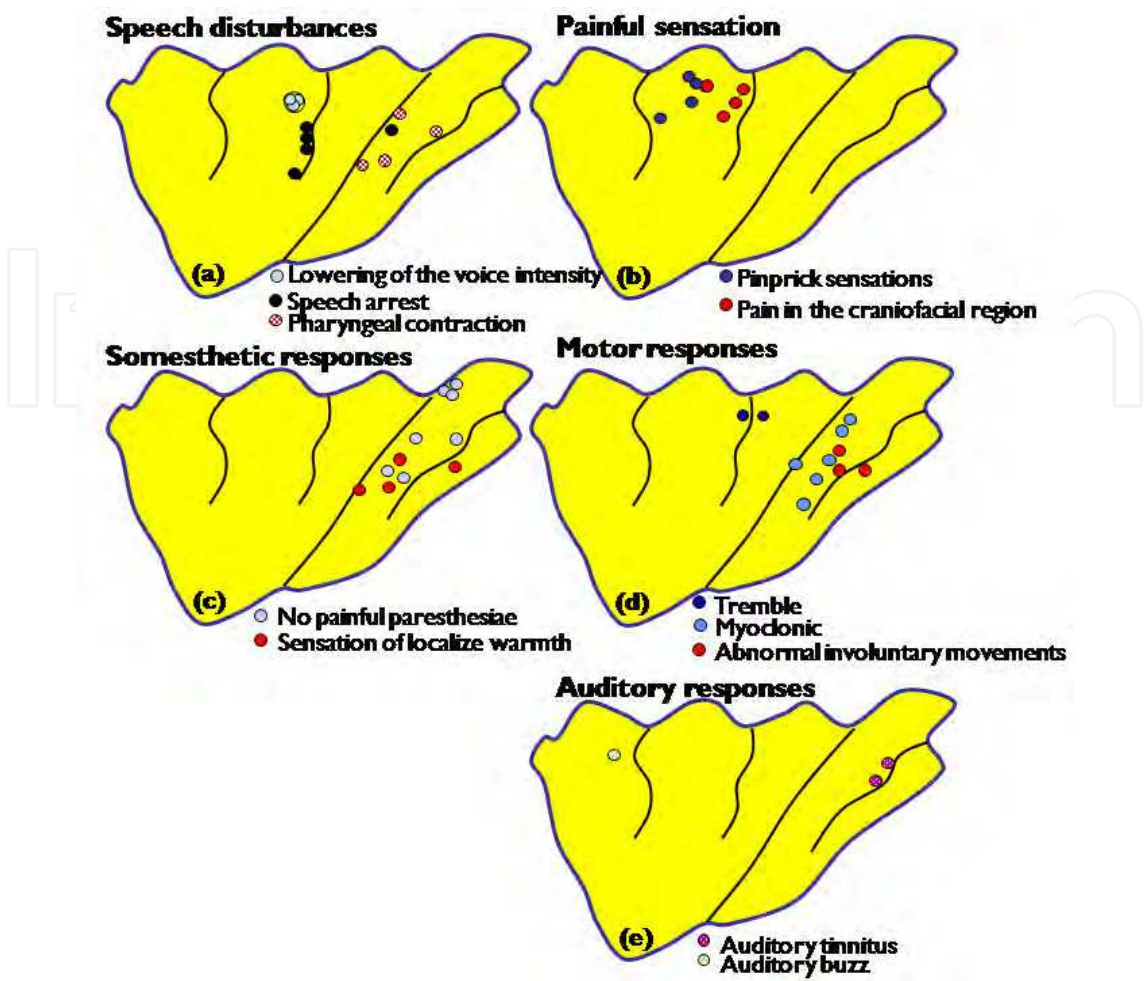
Fig. 9. Insular sites responding to electrical stimulation. The sites corresponding to clinical responses were first located on each patient's individual diagram before being transferred onto the insular template with respect to the insular gyri from the individual diagram. (a): Speech disturbances; (b): Pain; (c): Somesthetic responses; (d): Motor responses; (e): Auditory responses.

The term "speech arrest" used in this study refers to those patients unable to continue counting and speaking during stimulation. The patients later described an inability to continue counting because of an inability to speak (speech arrest) without other associated phenomena, such as pharyngeal constriction, memory deficits, difficulties in performing the movements required for speech, panic or a sensation of asphyxia. 80% of speech arrest responses involved stimulation of the non-dominant hemispheres, thus suggesting that the dominant cerebral hemisphere may function independently the dominant insula.

One of the patients presented a lowering of the voice intensity responses following stimulation of the bipole situated above and adjacent to the one in which stimulation evoked speech arrest in the middle short gyrus. It is possible that these responses could be the consequence of a disturbance in motor control (pharyngeal construction and breathlessness sensation) or due to current spread to the adjacent area producing speech arrest. 87.5% of the speech disturbances resulted from stimulating the middle short gyrus of the anterior insula at the anterior edge of the pre-central insular sulcus in both dominant and non-dominant hemispheres (Afif et al., 2010a). The one remaining response (12.5%) was induced

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by stimulating the post-central insular gyrus, in the same region which also precipitated pharyngeal constriction (Fig. 9 a).

The present study suggests the high restriction of the speech activity (articulation, phonation, etc) to the middle short gyrus of the anterior insula. In this study, all patients with insular involvement at seizure onset or after a short delay during seizure evolution present speech disturbances after seizures and after intra insular HF stimulations during a counting exercise (Afif et al., 2010a).

A few studies have been published that used stereotactically implanted deep brain electrodes (SEEG), inserted in a lateral orthogonal way, to stimulate the human insula directly (Ostrowsky et al., 2000; Isnard & Mauguière, 2005). These studies suggest that the insula is involved in speech disturbances, but localization information for specific gyral or sulcal involvement was not provided. The functional imaging studies have demonstrated the activation of the insula during language-based tasks and grammar exercises (Raichle, 1991; McCarthy et al., 1993; Wise et al., 1999; Riecker et al., 2000, 2005; Friederici et al., 2006). Lesion studies reported speech disturbances relating to the infarctions of the insular cortex (Ferro et al., 1982; Shuren, 1993; Dronkers, 1996; Nagoa et al., 1999)

6.2 Pain

Two different types of painful responses were reported (Afif et al., 2008b): I) Pain in the craniofacial region evoked by HF stimulation either as a highly unpleasant headache or a bilateral throat pain that spread to the mouth and was accompanied by a highly unpleasant sensation of suffocation. All sites had been previously stimulated at LF without inducing pain, except for one patient who reported a pinprick sensation, as described further below. II) Pinprick sensations described occurring either bilaterally or ipsilaterally during LF and HF stimulations. These responses were reported in the upper limbs, the neck and abdomen, spreading to the chest and shoulders. All pain-inducing sites were located in the superior part of the middle short gyrus, in both dominant and non-dominant hemispheres (Fig 9 b). No similar responses were reported from other sites within the insular cortex. These findings cannot be due to under-exploration of other insular areas since contacts located in the middle short gyrus only represented 27.2% of all the insular contacts. Indeed, the post-central gyrus and posterior long gyrus represented 36.7 % of all insular contacts and, furthermore, stimulation here induced 47% of all observed phenomena (Table 3) (Afif et al., 2008b, 2010b). These present studies are the first to report human painful responses evoked by ES of the insular cortex in terms of gyral and sulcal anatomy and suggest a pain somatotopy within the middle short gyrus of the anterior insula, with a posterior representation of the head and a more anterior representation of the upper limbs and trunk (Fig. 10 A).

Few studies have been published using ES of human insular cortex. The present data complement those observed by Penfield and Faulk (1955) which reported a tingling feeling in the upper extremity (arm, hand and fingers) induced by direct stimulation of the anterior insula. No specific location in reference to gyri and sulci was given. Other studies (Ostrowsky et al., 2000; Ostrowsky et al., 2002; Isnard & Mauguière, 2005), used stereotactically implanted deep brain electrodes (SEEG) inserted orthogonal (trans opercula) to the mid-sagittal plane. These studies suggest that the posterior insula processes both painful and painless somesthetic sensations. Recently, Mazzola et al. (2009) suggested the involvement of the posterior two thirds of the insula in processing pain. Using the insular
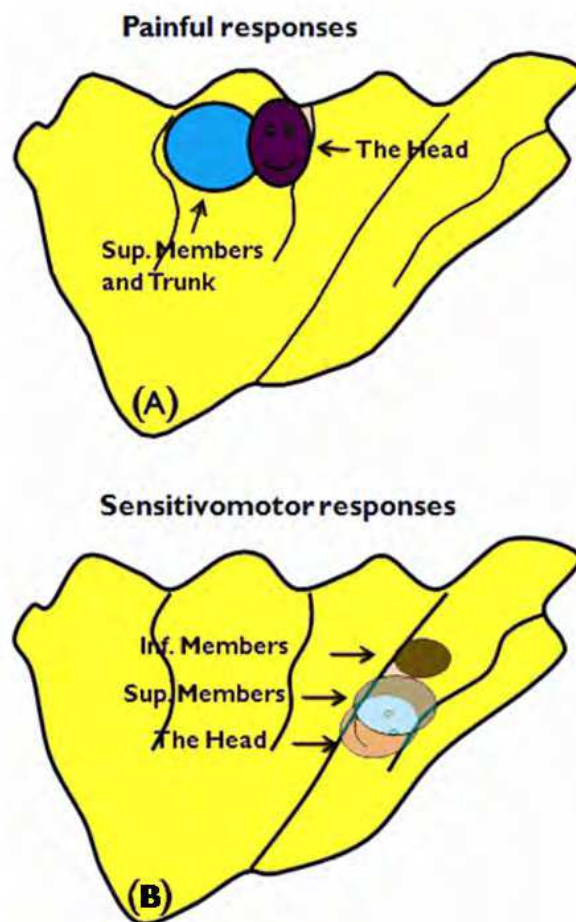
Fig. 10. Somatotopic organization of pain and sensorimotor responses. (A): pain results from stimulating the middle short gyrus of the insula, with a posterior representation of the head and a more anterior representation of the upper limbs and trunk. (B): sensorimotor responses from stimulating the post-central insular gyrus, showing an inferior representation of the head and a more superior representation of the upper and lower limbs.

orthogonal approach exploration, it would be more appropriate to describe the phenomena induced by ES as operculo-insular phenomena (the thickness of the insular cortex is less than the distance covered by two contiguous contacts (Fig. 2), so the bipolar ES will stimulate the overlapping adjacent structures "opercula" of the insula). Moreover, due to the dense network of vessels overlying the insular cortex (Fig. 4), only the peripheral region, near the peri-insular sulci can safely be reached by a lateral orthogonal approach (Afif et al., 2008b, 2010b).

Several functional imaging studies suggest that the posterior operculo-insular complex has a role in pain discrimination and localization (Hua et al., 2005; Baumgärtner et al., 2006). Other studies have identified a region in the anterior insula that becomes activated by noxious stimuli (Brooks et al., 2002, 2005; Henderson et al., 2007). It is interesting to note that the clinical responses evoked by ES within the anterior insular part are usually ipsi- or bilateral to the original peripheral stimulus (Tarkka & Treede, 1993; Henderson et al., 2006; Afif et al., 2008b).

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6.3 Somesthetic responses

Sensory responses (28.2% of responses evoked by stimulation sites within the posterior insula) were described as pins and needles or localized warmth contralateral to the ES sites (Fig. 9 c) (Afif et al., 2010b). All these responses were evoked by HF stimulation. Two different types were distinguished: i) Painless paresthesiae or "pins and needles" were reported in the upper limbs, lower limbs and the neck. 71.4% of these responses were evoked by ES in the non-dominant hemisphere. All responses resulted from electrode contacts stimulated in the post-central insular gyrus. However, paresthesiae in the upper and lower limbs occurred with stimulation in the superior portion of this gyrus. ii) Painless sensations of localized warmth were reported as occurring in the cranial region, contralateral, limbs and in the elbow, evoked by HF stimulation. All these responses were evoked by ES to the middle part of both post-central and posterior insular gyrus. Oppenheimer et al. (1992) noted reports of sensations of warmth when applying ES to the insular cortex, although the precise anatomical site was unknown.

6.4 Motor responses

Motor responses (28.2% of responses evoked by stimulation sites within the posterior insula) were observed in the patients contralateral to the stimulated side (8 responses induced by LF and 3 responses by HF) (Afif et al., 2010b). Three different types were distinguished (Fig. 9 d): i) Myoclonic phenomena in the upper and lower limbs, evoked by LF stimulation to the post-central insular gyrus. ii) Involuntary movements involved the upper and lower limbs. All of these responses resulted from stimulation to the non-dominant hemisphere, (from the post-central and posterior insular gyrus). iii) Upper limb tremors were evoked by stimulating the anterior and posterior edges of the pre-central insular sulcus in the dominant hemisphere.

In our study the majority of the sensorimotor responses (85.3% of cases) resulted from ES in the peri-central area of the insula, especially the post-central insular gyrus. The sites that induced motor responses also overlapped with those eliciting sensory responses. A new finding which has emerged from our data is that both types (motor and sensory responses) indicated a somatotopic organization in the post-central insular gyrus similar to the peri-Rolandic cortex, with an inferior representation of the head and a more superior representation of the arms and legs (Fig. 10 B). It is difficult to determine whether spatial discrimination exists between motor and sensory sites, or whether it results from different motor and sensory neuron densities (neuronal population maps, Roland & Zilles, 1998), as in the supplementary motor area (Lim et al., 1994). In our study, HF stimulation evoked sensory responses, whereas LF evoked motor responses. Our data complement previous studies that suggest that stimulating the posterior insula can evoke somesthetic sensations (Ostrowsky et al., 2000; Isnard et al., 2004).

6.5 Oropharyngeal responses

Eight responses were evoked in 4 patients by HF (0.8 to 2.6 mA) stimulation to the peri-central insular cortex and post-central insular gyrus (Fig. 4 E). Four of these responses were described as a pharyngeal constriction and one as a swallowing sensation associated with mastication. The three remaining responses occurred while stimulating the upper part of the middle short gyrus in one patient, who described a feeling of suffocation in the throat.

6.6 Auditory responses

Two types of responses were observed (Fig. 9 e): i) bilateral auditory tinnitus evoked by ES within the upper part of the post-central insular gyrus in the non-dominant side. These responses were different from those known to occur when stimulating the Heschl gyrus, which are contra lateral hallucinations ii) predominantly contra lateral auditory buzz evoked by stimulating the anterior short gyrus. Auditory buzz might be mediated by a distributed network of the anterior insula with the other structures as the anterior cingulate gyrus, hippocampus, parahippocampal gyrus and the thalamus. The data obtained by stimulating the anterior short gyrus complement those from functional imaging studies (Bamiou et al., 2003; Lewis et al., 2000). Another study suggests the activation associated with auditory buzz in the anterior cingulated gyrus, insula, inferior frontal gyrus, middle temporal gyrus, thalamus, left hippocampus and parahippocampal gyrus (Shergill et al., 2000).

7. Advantages and complications of oblique versus lateral trajectory for placement of insular electrodes

The insula represents a thin layer of grey matter with a width usually less than 5mm and lies almost parallel to the sagittal plane, which consequently allows the placement of a less of two contacts for each electrode implanted orthogonally (Fig. 2) compared to a mean of 7.5 contacts for each electrode implanted with an oblique approach (Afif et al., 2008a).

Firstly, our methodology to target the insula using an oblique approach guided by a robotic arm allows the electrode to cover a larger surface of insula and thus explore the different anatomical parts of the insular cortex without limits in contrast to an orthogonal trans-opercular approach (Afif et al., 2008a). Secondly, the orthogonal approach may distort any data collected due to anatomical limitations not permitting access to the greatest part of the insula largely covered by the sylvian vascular branches (Fig. 4) (Ture et al., 1999; Varnavas & Grand, 1999; Afif & Mertens, 2010). Thirdly, our trajectory enabled the exploration of between two and three distinct insular gyri or even the anterior and posterior insula with one single electrode. This should prove useful when delineating the epileptogenic zone and enable precise tailoring of resection when necessary.

This study provides new arguments in favor of the use of a stereotactic procedure to insert depth recording electrodes in difficult to reach areas such as the insula.

The safety of stereotactic depth electrode implantation has been addressed in numerous studies with severe morbidity with permanent deficit related to electrode implantation ranging from 1 % to 2 % in these series (Binnie et al., 1994; Guenot et al., 2001; Sindou et al., 2006; Tassi et al., 2005). Recently, De Almeida et al. (2006) reported a higher risk of hematoma (2.9 % per hemisphere) in cases where SEEG was performed in frontal epilepsy and when four or more electrodes were implanted. Cossu et al. recently reported the oblique implantation of electrodes in stereotactic conditions in adults (Cossu et al., 2005a) and in children (Cossu et al., 2005b). For these authors, this procedure was mandatory in targeting the frontal or parietal mesial regions, the orbito-basal region, the amygdala and the hippocampus. The oblique approach has also been used to record epileptic activity (Rektor et al., 2002, 2003) from the basal ganglia. In our institution we believe that a safe implantation of electrodes within the insula can be achieved using an oblique stereotactic approach guided by a robotic arm, coupled with preoperative MRI and stereotactic

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angiography. In our study, we observed no morbidity related to the surgical implantation of the oblique insular electrodes.

8. Conclusion

Oblique electrodes implanted using a robotic arm in the insular cortex permit the safe exploration of different insular regions and limit potential electrical contamination from adjacent areas, especially the opercular cortex. Insular recordings provide additional pre-surgical information to allow a tailored surgical approach when necessary and avoid surgery in cases of insular seizure where the insula cannot be removed.

We are not yet able to target one specific part of the insular cortex related to associate clinical phenomena of the epilepsy seizures. The previous results of the insular stimulation studies were not provided in reference to gyral and sulcal anatomy. Consequently, wider sampling of the different sulci and convolutions of insular lobe seems necessary to gather enough information to either exonerate or implicate the insula in a patient's epileptic network. The association of lateral electrodes in the temporal or frontal lobe and oblique electrodes in the insular cortex seems at present to be a good compromise to study multi lobar epilepsy.

The broad sampling of this area by oblique electrodes implanted within the insular cortex has allowed us to construct an original representation that links function to anatomy, according to insular gyri and sulci. The data of this study maybe permeates to target a specific structure of the insular cortex related to the epilepsy seizures manifestations using a functional organization of the insular gyri.

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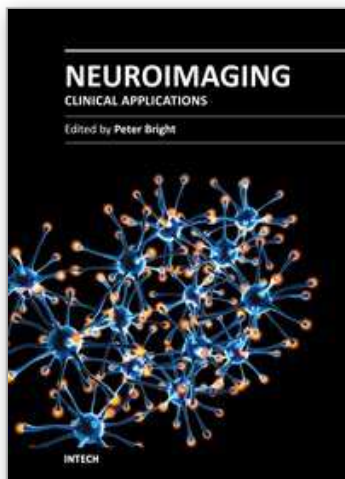
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Modern neuroimaging tools allow unprecedented opportunities for understanding brain neuroanatomy and function in health and disease. Each available technique carries with it a particular balance of strengths and limitations, such that converging evidence based on multiple methods provides the most powerful approach for advancing our knowledge in the fields of clinical and cognitive neuroscience. The scope of this book is not to provide a comprehensive overview of methods and their clinical applications but to provide a "snapshot" of current approaches using well established and newly emerging techniques.

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