Oncological and functional results in surgery for insular diffuse low-grade gliomas

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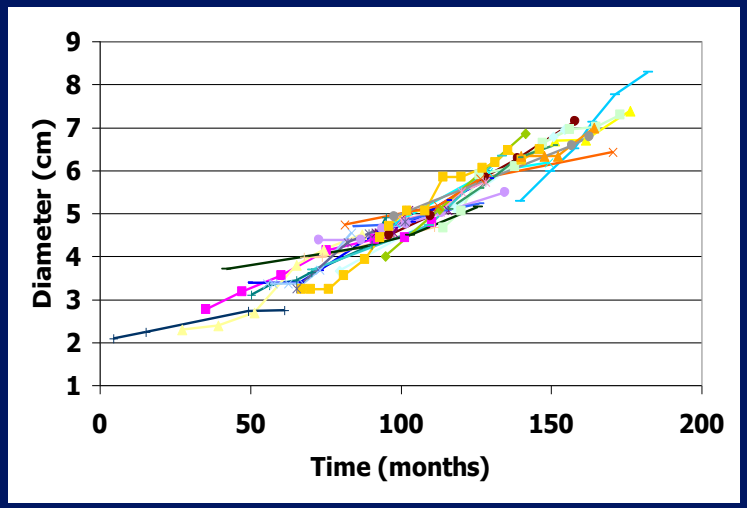
NATURAL HISTORY OF DIFFUSE LOW GRADE GLIOMA

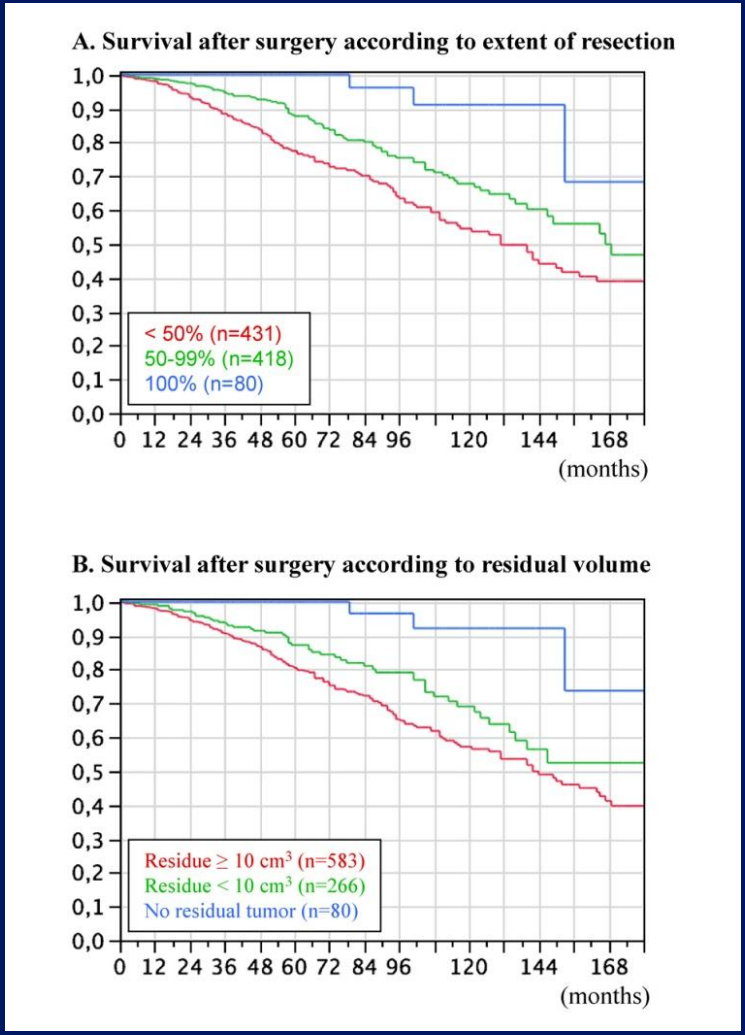
THE END OF THE DOGMAS

- Growing Tumor (4 mm / year) : **NOT STABLE!!!!!**
  - invading the cortico-subcortical functional structures
  - revealed by seizures (90%)
  - young patients with no/slight deficit
- « pre-canecrous » tumor
  - **NOT benign!!!!!**
- Anaplastic transformation
  - Around 50% within 5 to 7 years following the first symptoms
    - Deficit
    - Death (median survival: 5-10 years)



Mandonnet, Ann Neurol 2003
Duffau, J Neuroncol 2006

IMPACT OF SURGERY : SURVIVAL IN RELATION TO THE EXTENT OF RESECTION (n = 1091)



N = 1091

p <0.0001

French Glioma Network, J Neurosurg 2012

IMPACT OF RE-OPERATION

EVEN WITHIN ELOQUENT AREAS (n = 108)

C. Analysis of prognostic factors available at the time of the first recurrence

	Univariate analysis	Multivariate analysis		
Parameters	p-value	p-value	Risk ratio	95% C.I.
Age < 20 yrs				
20-54 yrs	NS	NS		
> 54 yrs	0.0006	0.0025	2.661	1.410-5.020
Location Frontal				
Temporal	0.2306	0.0115	1.650	1.119-2.434
Other sites	<0.0001	<0.0001	2.427	1.729-3.405
Tumoral volume	<0.0001	0.0004	1.003	1.001-1.005
Subsequent chemotherapy	0.0147	NS		
Subsequent resection	0.0048	0.0303	1.603	1.046-2.455

- Prognostic factors (multivariate analysis)

  - postop volume
  - location
  - age < 54 years
  - reoperation +++

French Glioma Network, J Neurosurg 2012;
Martino, Taillandier, Moritz-Gasser, Gatignol and Duffau, Acta Neurochir 2009

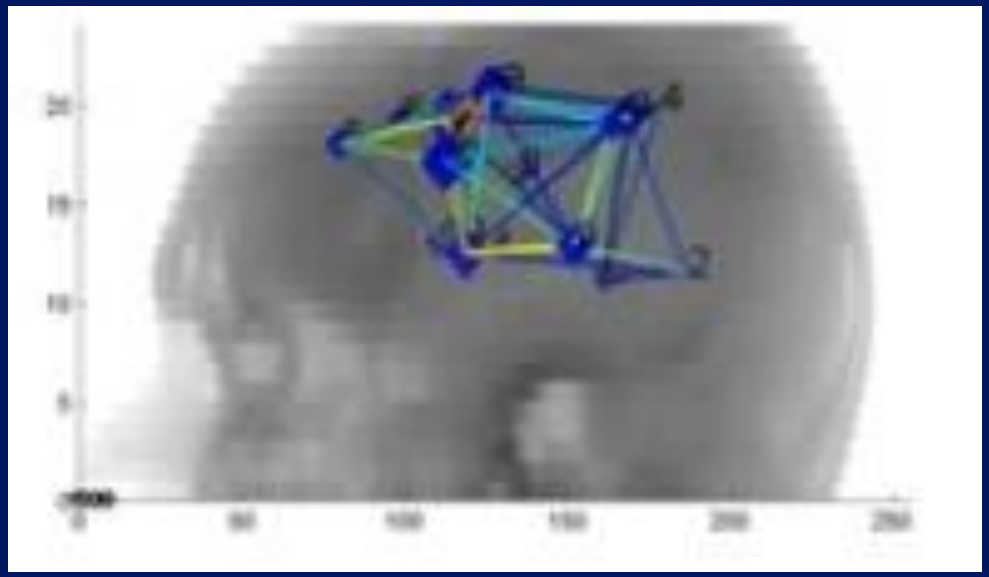
EUROPEAN GUIDELINES – EFNS/EANO TASK FORCE

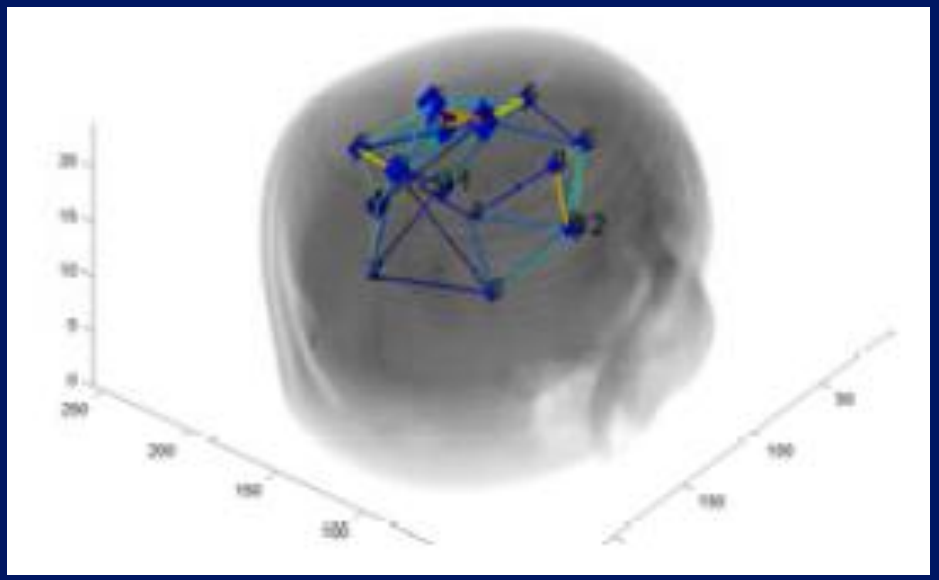
DIFFUSE LOW-GRADE GLIOMAS

« Surgical resection represents the first treatment option, with the goal to maximally resect the tumor mass whenever possible, whilst minimizing the post-operative morbidity »

Soffietti et al., Eur J Neurol, 2010

GRAPH BASED SPATIAL POSITION MAPPING OF DIFFUSE LOW-GRADE GLIOMAS





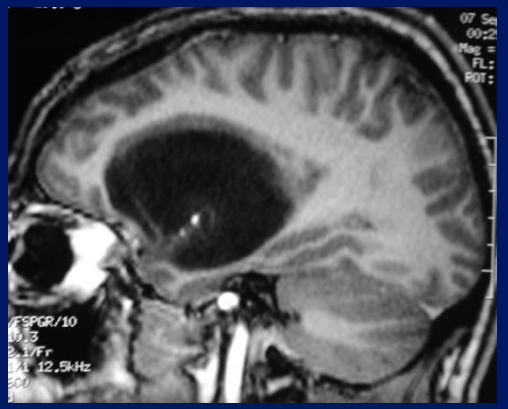
Insular DLGGs are very frequent: 33% +++

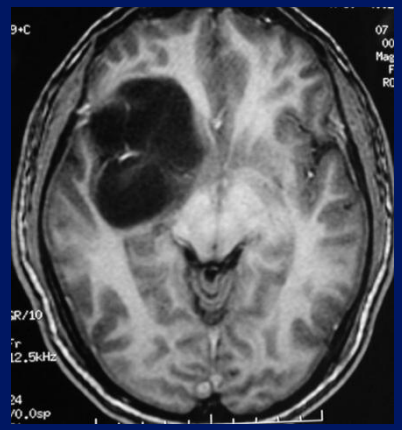
versus

Occipital and prefrontal DLGGs: 7%

Duffau and Capelle, Cancer 2004; Parisot, Duffau, Chemouny and Paragios, MICCAI 2011

RATIONALE IN INSULAR LOW-GRADE GLIOMAS





- Surgery : two antagonist goals
  - Maximal glioma resection
  - BUT
    - **With no permanent deficit!**
    - or even with an improvement of the quality of life (e.g. relief of intractable seizures)

Duffau, Acta Neurochir 2012

PARADIGMATIC SHIFT

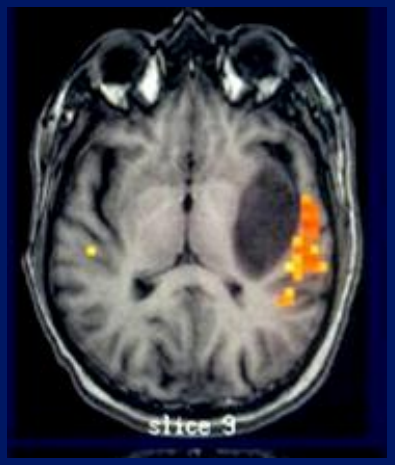
- Early surgery (NO biopsy!)
  - At diagnosis
  - Before any deficit
- Surgery according to functional boundaries and NOT according to « oncological boundaries » - do not exist!
  - Study of the individual functional anatomy
  - Brain connectivity and plasticity: towards hodotopy
- Aim: optimization of BOTH survival and quality of life

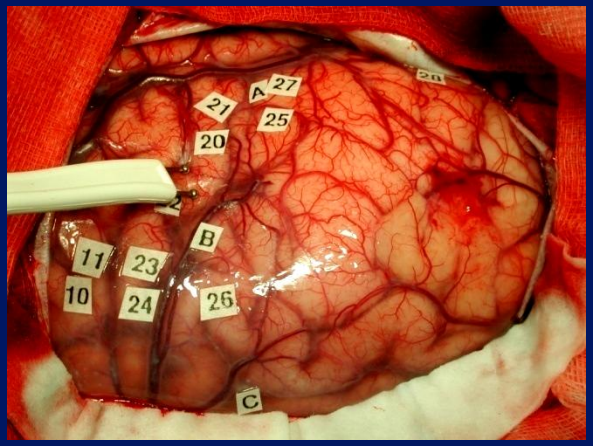
Duffau, Neurosurg Focus 2010, Duffau, Adv Tech Stand Neurosurg 2012

WHY NOT TO OPERATE?

THE FUNCTIONAL RISK OF SURGERY

SOLUTION: MAPPING TECHNIQUES !!!!

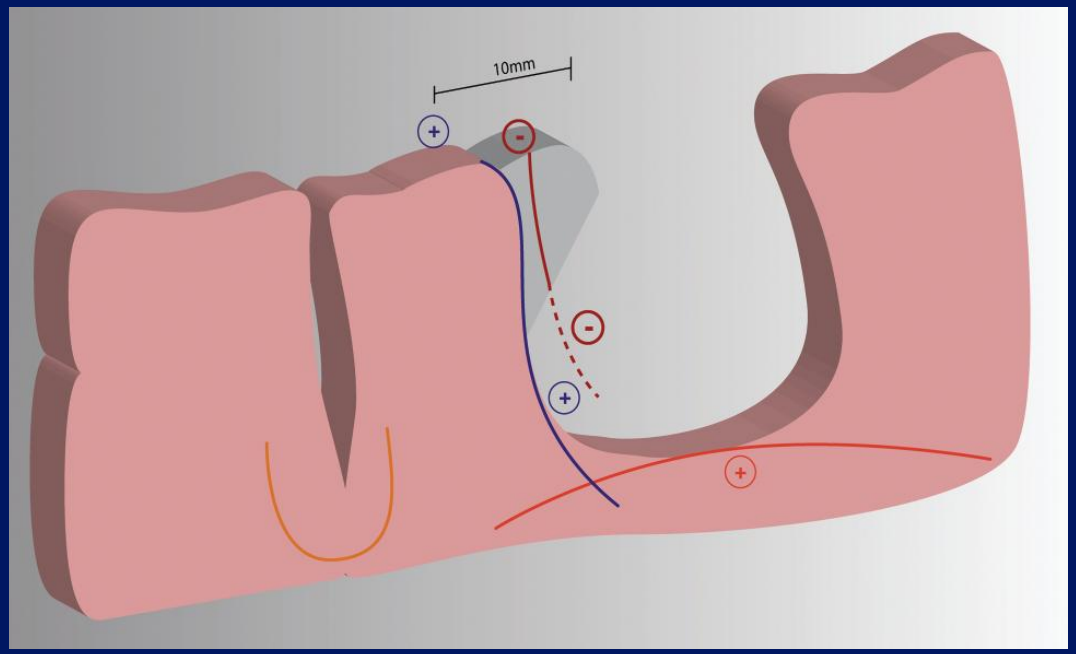




LIMITS OF RESECTION: CORTICAL AND SUBCORTICAL FUNCTIONAL STRUCTURES, WITH NO MARGIN

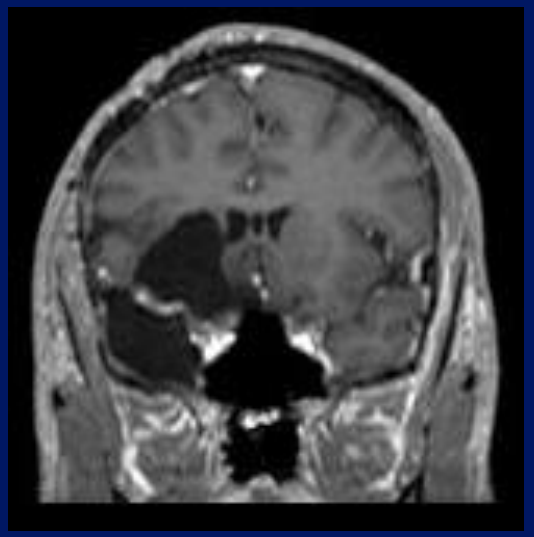
FUNCTIONAL-MAPPED GUIDED RESECTION

BUT NOT IMAGE-GUIDED RESECTION !!!!!!



Duffau et al, J Neurosurg 2008; Gil Robles and Duffau, Neurosurg Focus 2010

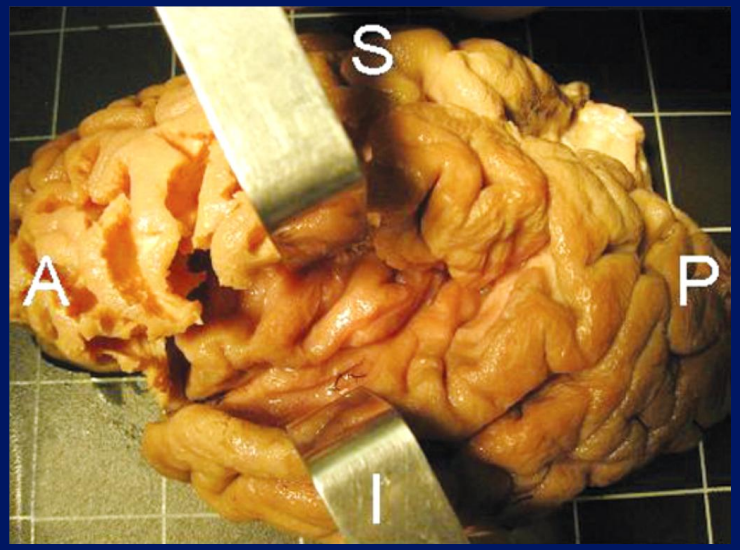
THE INSULAR LOBE

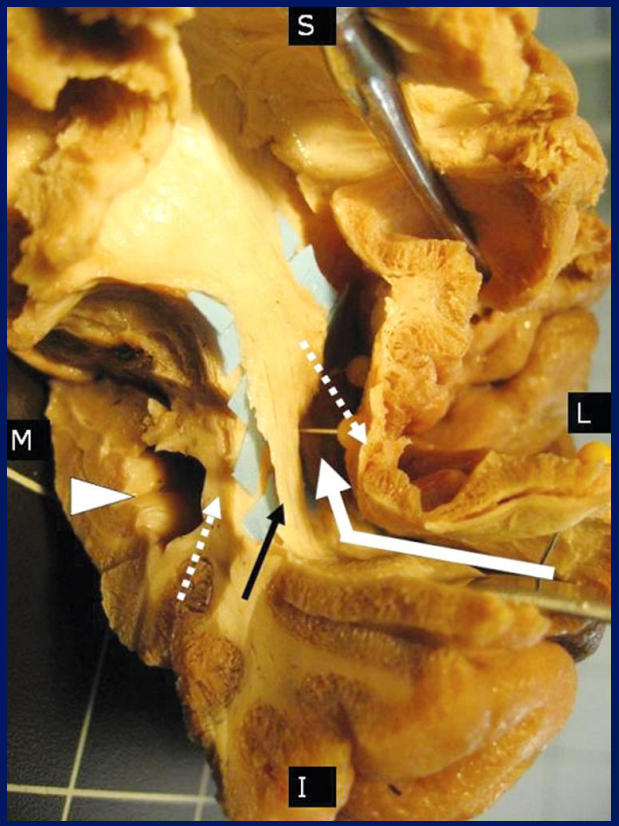


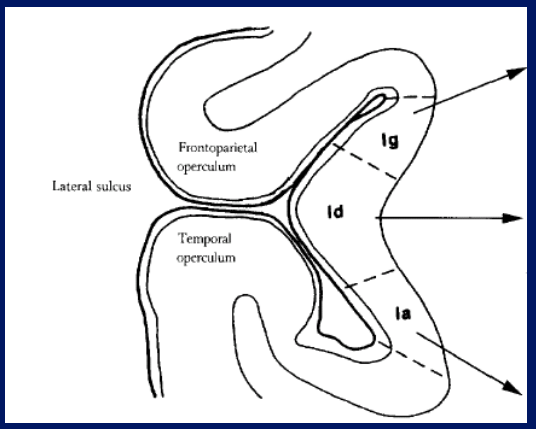
- Fifth lobe (Reil's Island)
- Buried within the sylvian fissure
- Not studied for a long time - deep location
- Part of the paralimbic system with the orbito-frontal and temporo-polar areas
- Strong connections with the other brain cortical and subcortical structures

Duffau et al., Neurosurgery 2000

ANATOMY AND CYTOARCHITECTONY







3 anterior short gyri

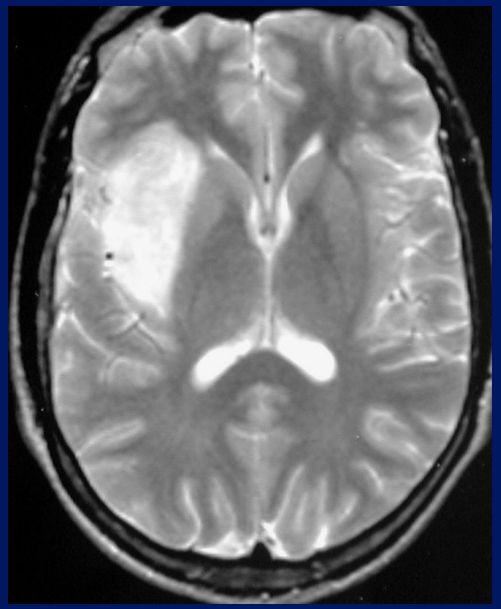
2 posterior long gyri

Cytoarchitectonical gradient

Martino, Vergani, Gil Robles and Duffau, Neurosurgery 2010

FUNCTIONAL ROLE

- Interface between the limbic system and the neocortex
- Plurimodal area
  - **Visceral sensorimotor processing**
  - **Sympathetic control of cardiovascular tone**
  - **Somatosensory function (including pain)**
  - **Motor function**
  - **Volitional swallowing**
  - **Olfacto-gustatory function**
  - **Auditivo-vestibular function**
  - **Emotion**
  - **Language and cognition**

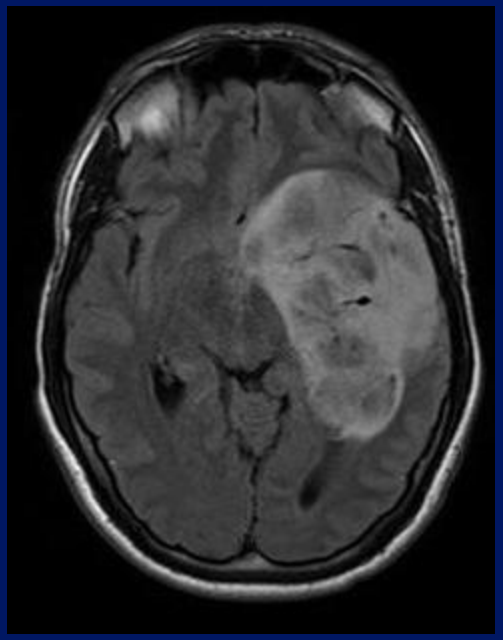


Duffau, J Neurosurg 2009

PREOPERATIVE NEUROPSYCHOLOGICAL ASSESSMENT

NOT A LUXURY!

- Cognitive deficit despite a « normal life » in > 80% of cases
  - Working memory
  - Attention
  - Executive functions (increase reaction time)
  - Emotion
  - Social cognition



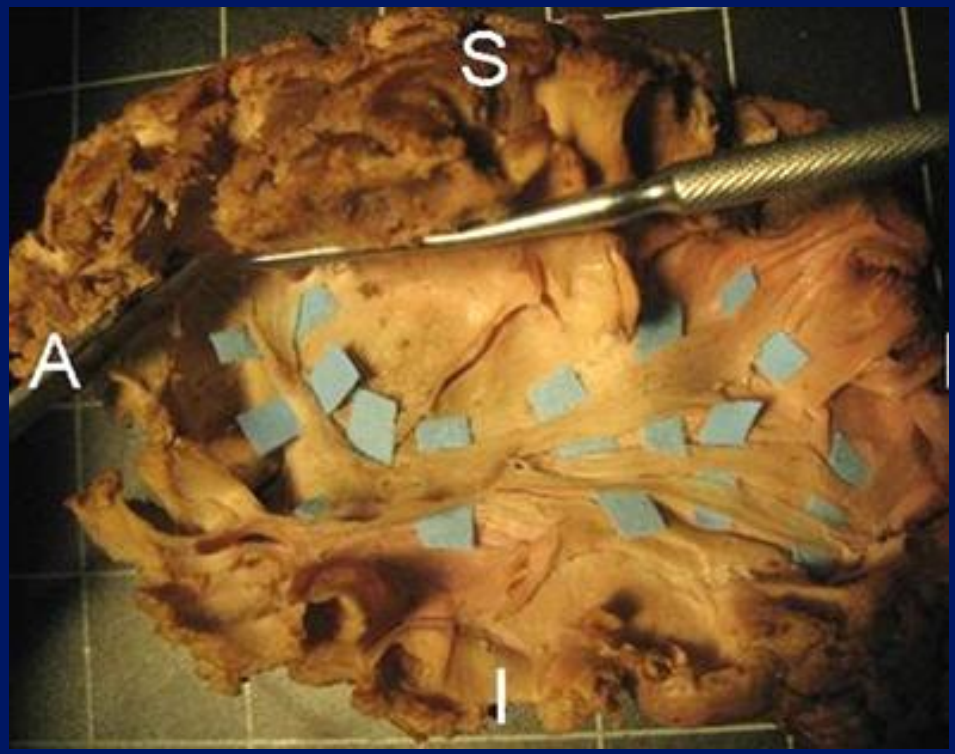
Teixidor et al., J Neurooncol 2006;
Moritz-Gasser et al., J Neurooncol 2012
Klein, Duffau and de Witt, J Neurooncol 2012

SURGERY

BRAIN ANATOMY IS CRUCIAL BUT NOT ENOUGH

Subcortical pathways

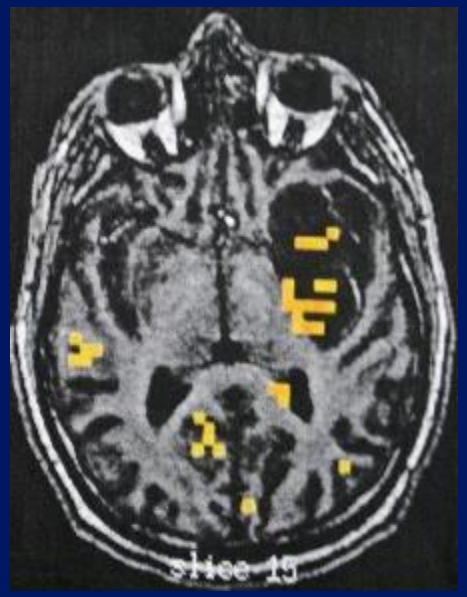
Superior longitudinal fasciculus

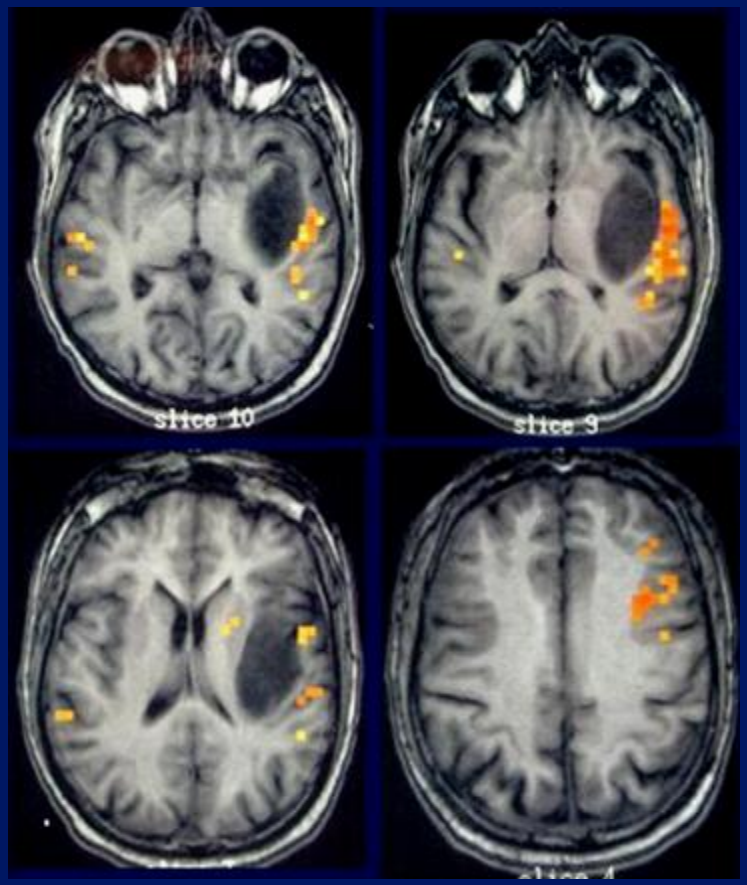


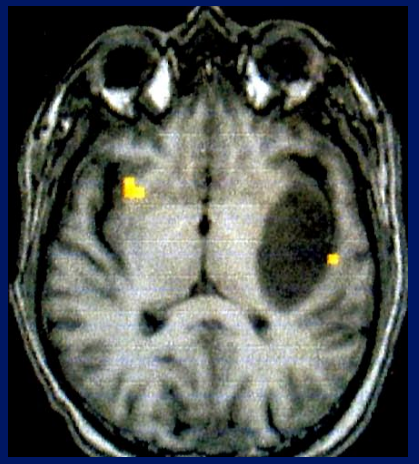
Inferior fronto-occipital fasciculus

Martino, Brogna, Gil Robles, Vergani and Duffau, Cortex 2010

PREOPERATIVE fMRI : STUDY OF THE VARIOUS PATTERNS OF FUNCTIONAL REORGANIZATION



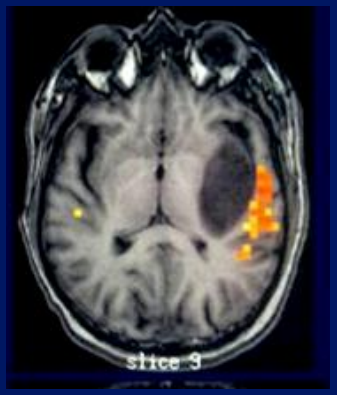




Intralesional **Perilesional** **Contralesional**

Duffau, Lancet Neurol 2005; Duffau, Adv Tech Neurosurg 2008

BUT PREOPERATIVE FUNCTIONAL NEUROIMAGING IS LIMITED !!!!



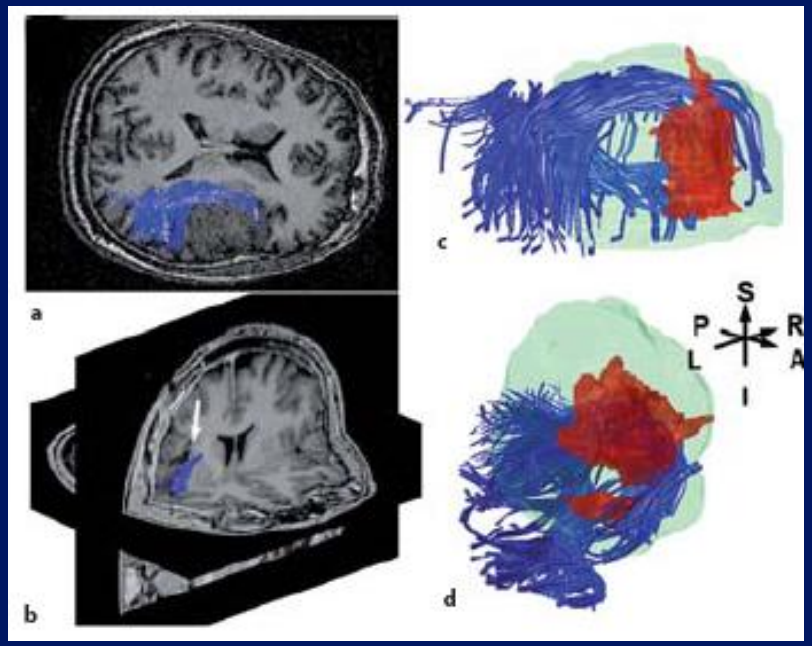
- Advantages
  - Non-invasive
  - Cortical mapping of the whole brain
    - » Hemispheric language lateralization

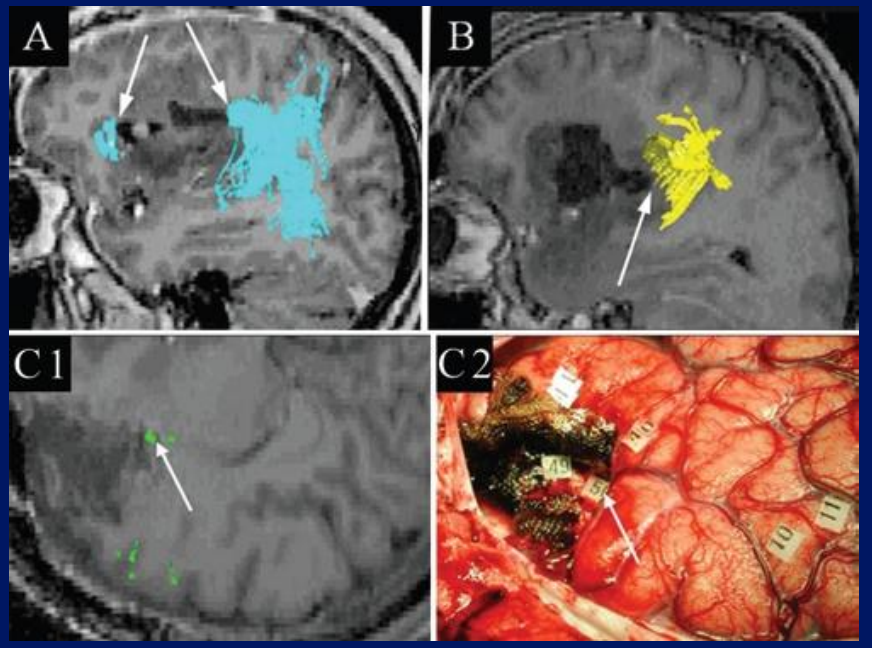
- Limitations
  - No differentiation critical vs compensable areas +++
  - 66% of sensitivity for language : neurovascular decoupling ?
  - NO VALUE at the individual scale!

Duffau, Adv Tech Neurosurg 2012

DIFFUSION TENSOR IMAGING : TRACTOGRAPHY

OF THE ANATOMIC CONNECTIVITY IS LIMITED!!!





Correlation DTI/subcortical stimulation: 82% of reliability (language tracts)

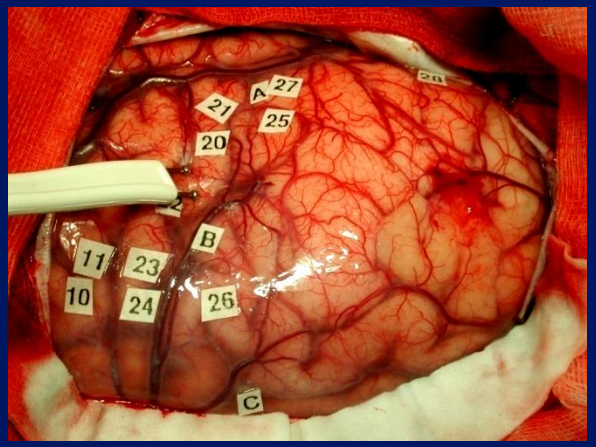
Anatomical tracking but NO FUNCTIONAL mapping of the white matter
Unable to track the fibers to their cortical terminations

Leclerq, Duffau, Delmaire, et al., J Neurosurg 2010

INTRAOPERATIVE AWAKE MAPPING

DIRECT ELECTRICAL STIMULATION

- Advantages
  - Detection of ESSENTIAL areas: « epicenters »
  - Cortical AND subcortical mapping
  - Accurate (5 mm)
  - Reliable
  - On-line
  - Safe

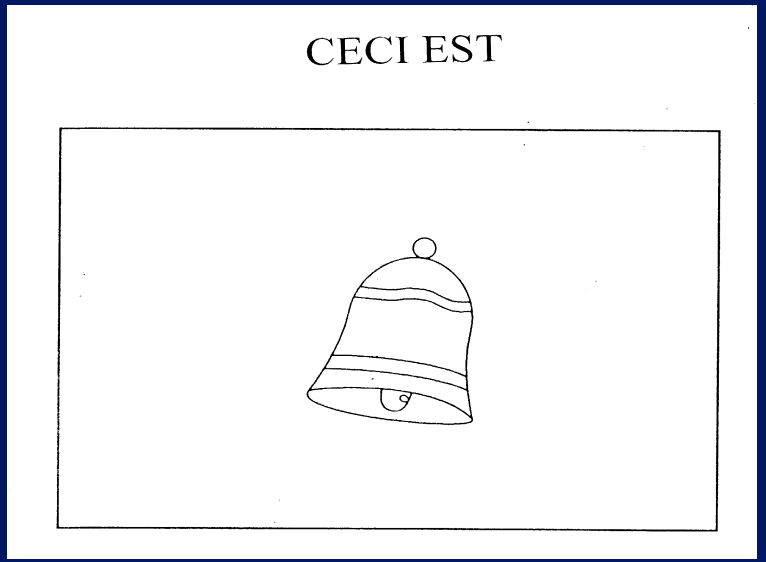


Crucial role of speech therapist in the OR

Duffau et al, J Neurosurg 2003

INTRAOPERATIVE ON-LINE COGNITIVE MONITORING

- Tasks continuously performed througout the resection ++
- Necessity of speech therapist in the operative room ++
  - Detail of the language disorders elicited by stimulation
  - Cortico-subcortical anatomo-functional correlations
  - On-line
- Tasks
  - Counting
  - Object naming
  - Reading
  - Comprehension / Memory
  - Writing / Calculation ...



Duffau et al, J Neurosurg 2008

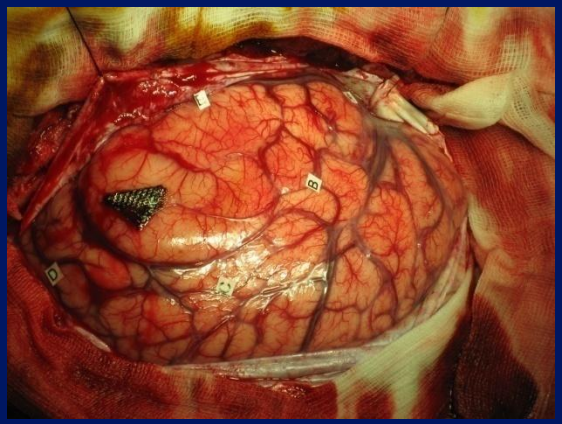
SELECTION OF INTRAOPERATIVE TASKS

- Patient
  - Job, hobby, habits , social activity (e.g. multilingualism…)
- Preoperative clinical and neuropsychological assessment
  - Neurological or cognitive deficit ?
  - Handedness
- Glioma location
  - In relation to the « classical » anatomical landmarks
  - On the lights of functional neuroimaging
    - » Hemispheric lateralization (language)?
    - » Functional network?

Duffau, Neurosurgery 2010

ULTRASONOGRAPHY

LANDMARKS OF THE GLIOMA

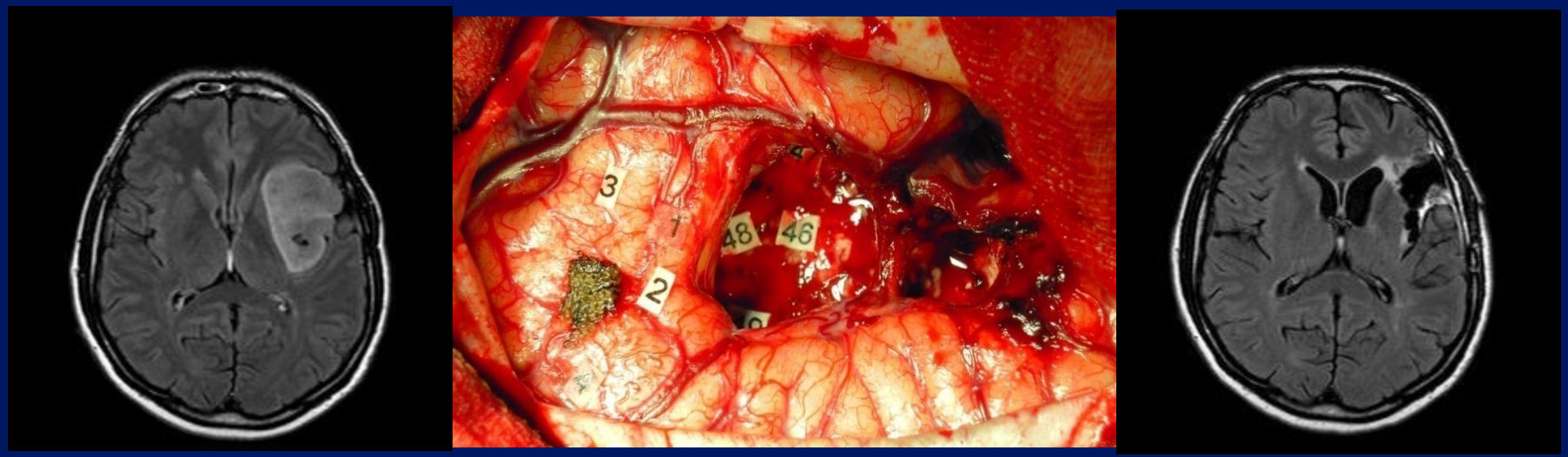


No neuronavigation in insular surgery due to brain shift

Duffau et al, J Neurosurg 2008

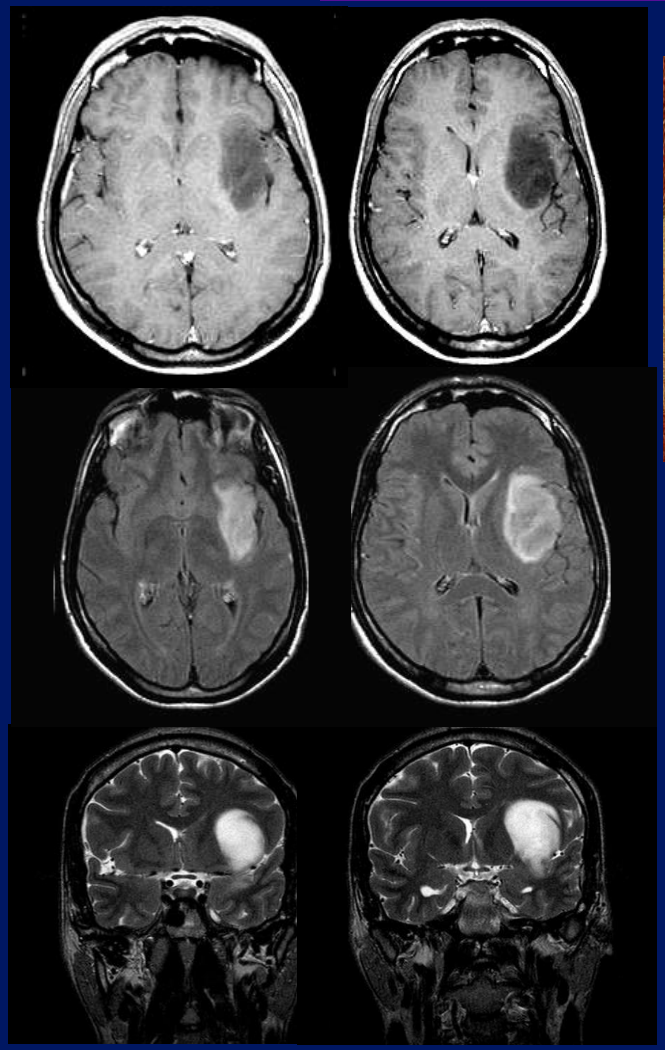
SURGICAL APPROACH

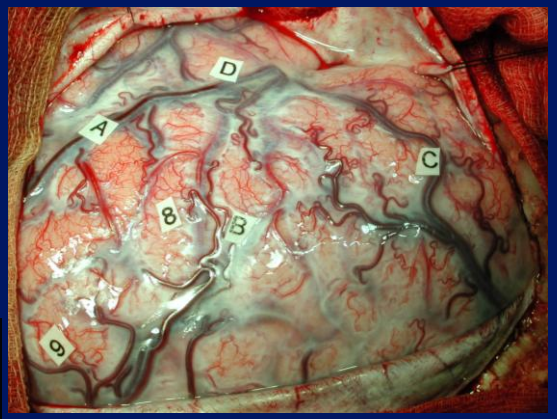
Opening of the sylvian fissure is more dangerous than resection of frontal and/or temporal operculae after individual cortical mapping: no vascular problems thanks to subpial dissection +++

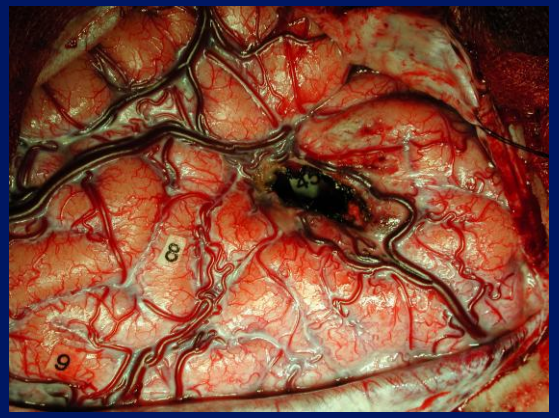


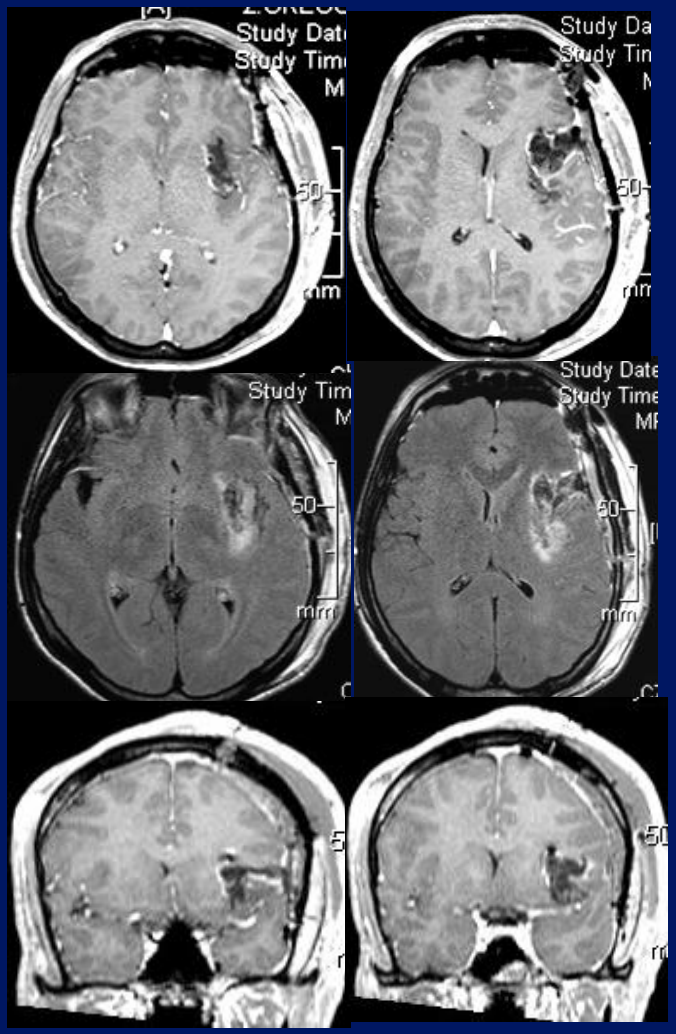
Duffau et al., Clin Neurol Neurosurg 2006

REMOVAL OF LEFT INSULAR GLIOMAS THROUGH THE OPERCULUM NOT INVADED BY THE TUMOR



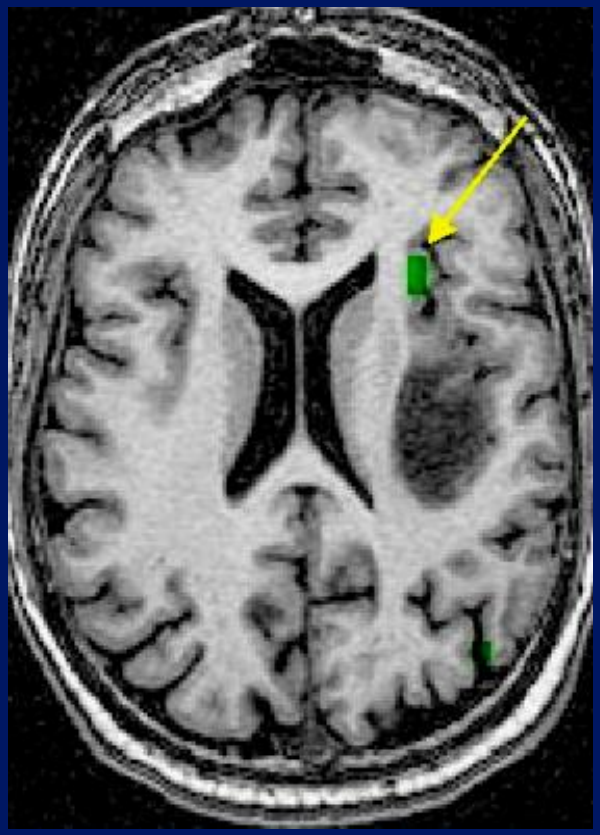


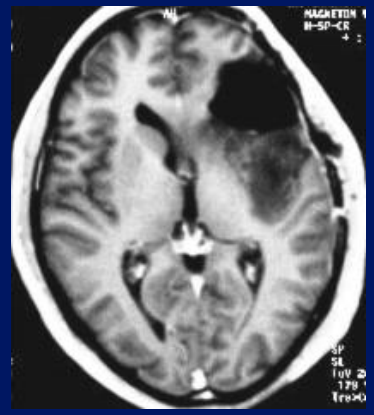




Duffau et al, Neurosurg Focus 2009

MAPPING OF THE INDIVIDUAL FUNCTIONAL ORGANIZATION OF THE INSULAR CORTEX





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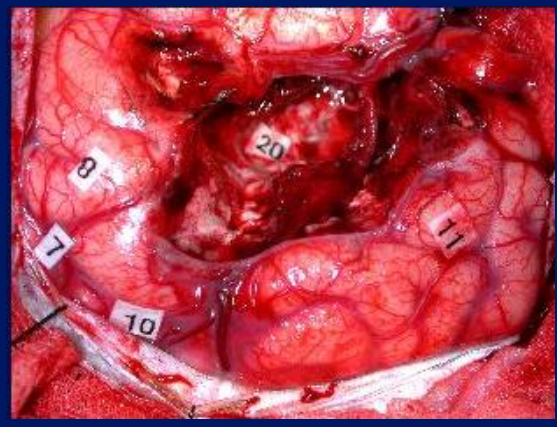


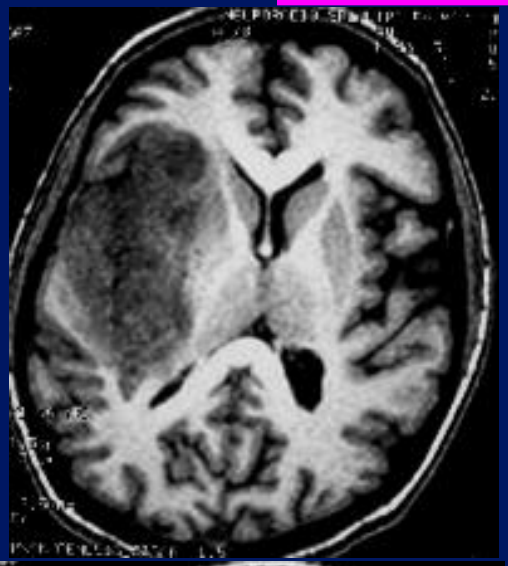
A

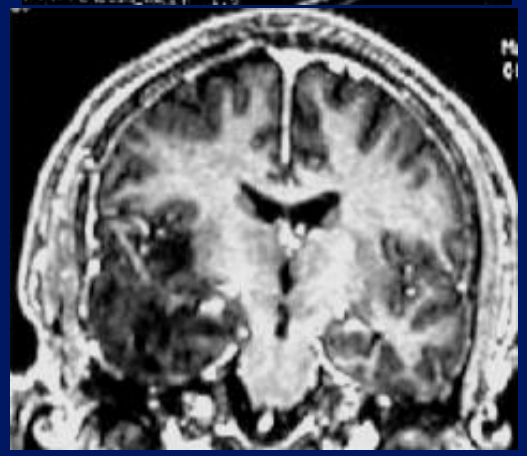
Insular mapping: role of left anterior insula in planning of speech (8%)

Duffau and Fontaine, Acta Neurochir 2005

DEEP BOUNDARIES OF RESECTION

SUBCORTICAL SENSORI-MOTOR PATHWAYS





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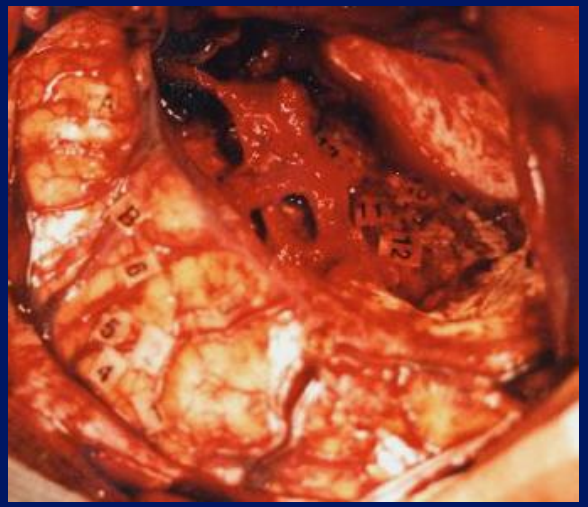

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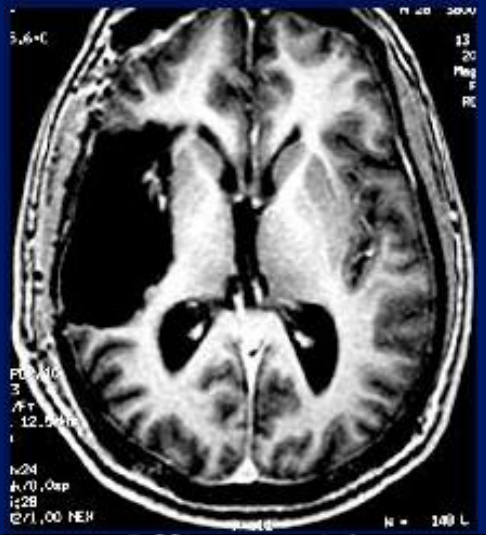
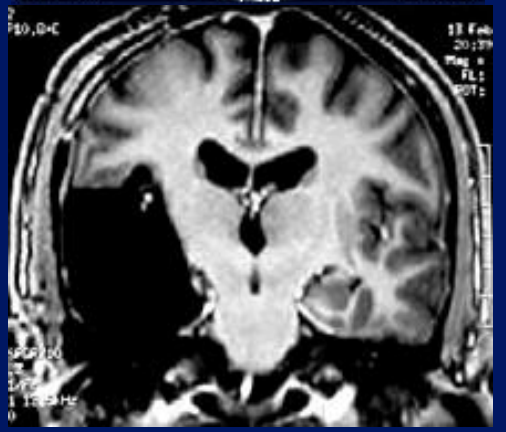
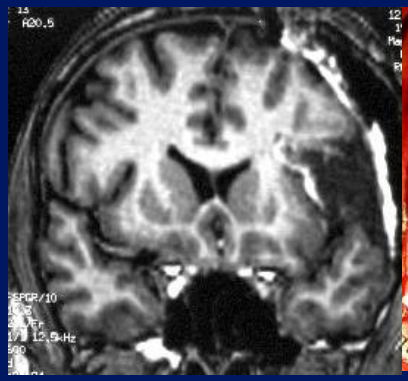


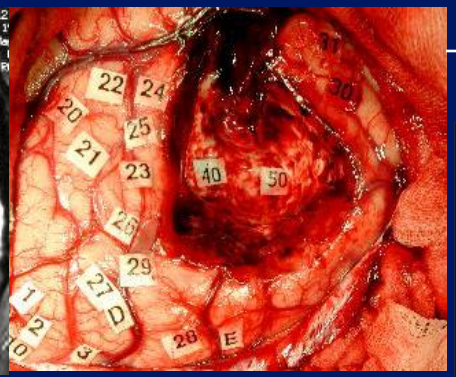


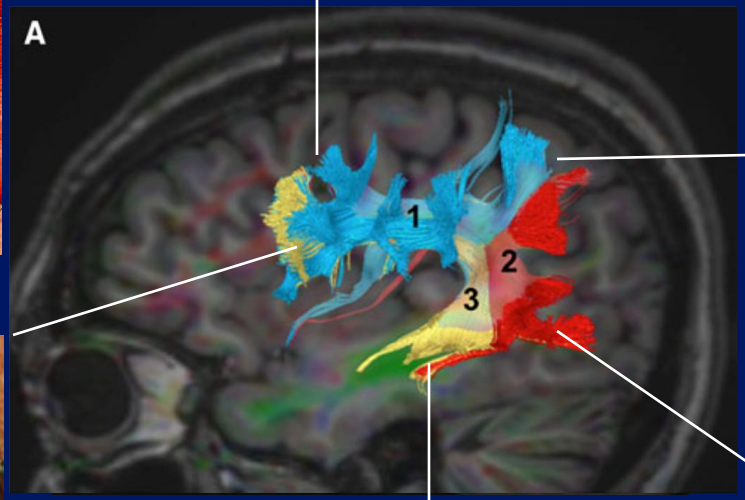
Duffau, J Neurosurg 2009

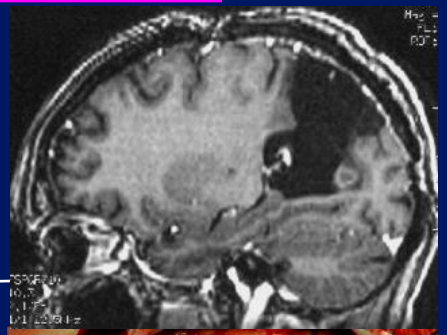
DEEP BOUNDARIES OF RESECTION: LANGUAGE

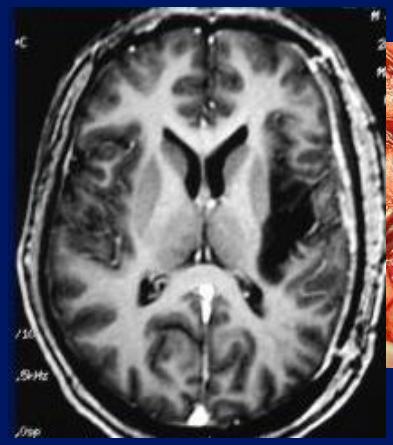
DORSAL PHONOLOGICAL STREAM

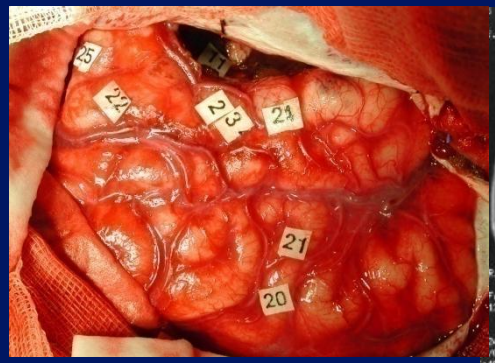


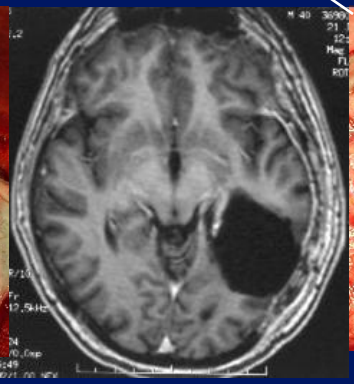


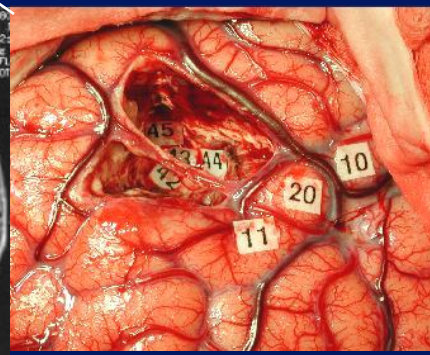










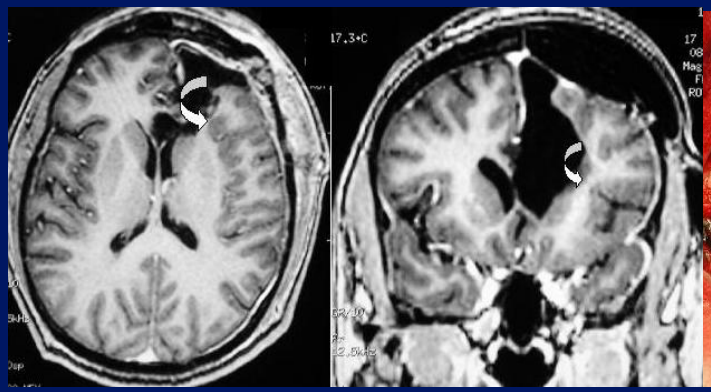


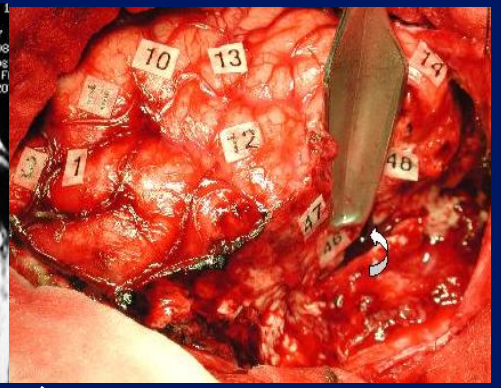
Superior longitudinal fascicle

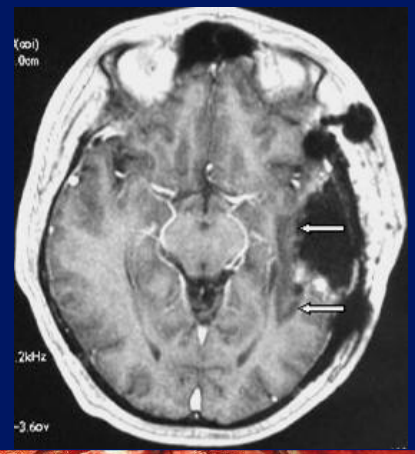
Duffau et al, Brain 2002; Duffau et al., NeuroReport 2004; Maldonado et al, Brain Struct Funct 2011

DEEP BOUNDARIES OF RESECTION: LANGUAGE

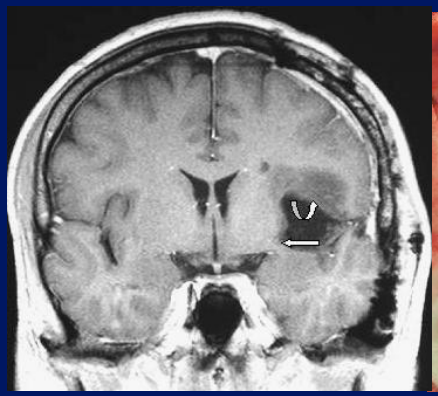
VENTRAL SEMANTIC STREAM

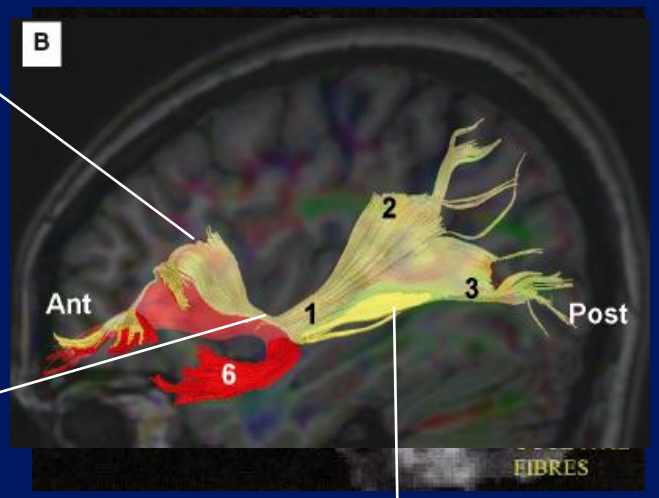


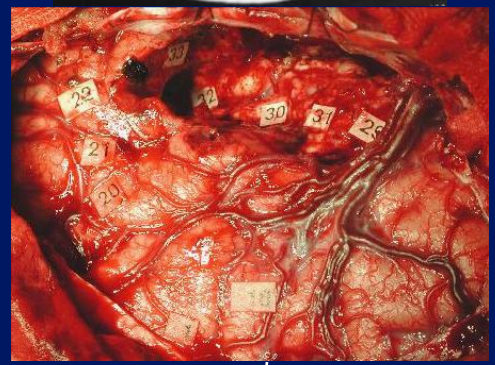




Inferior fronto-occipital fascicle

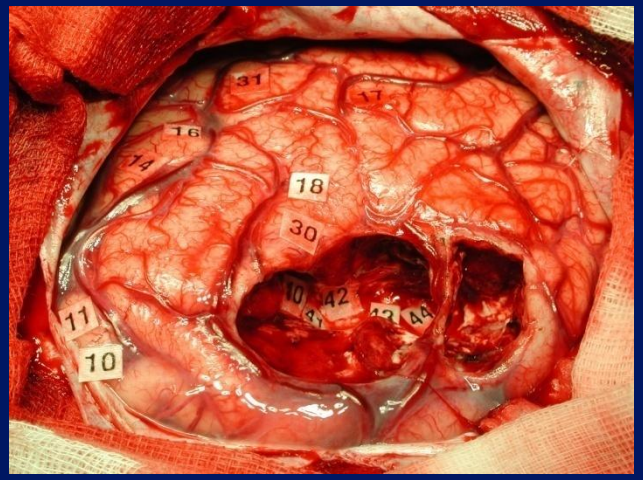


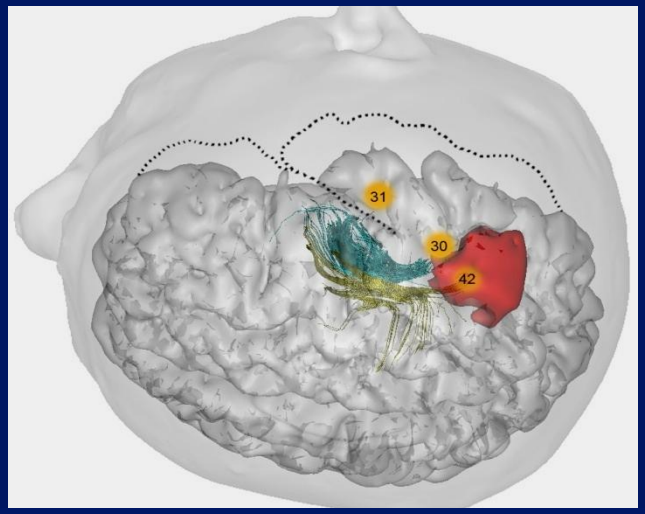




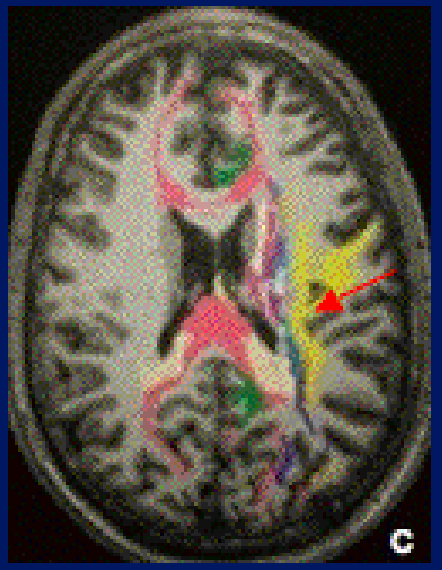
Duffau et al, Brain 2005; Martino et al., J Anat 2011

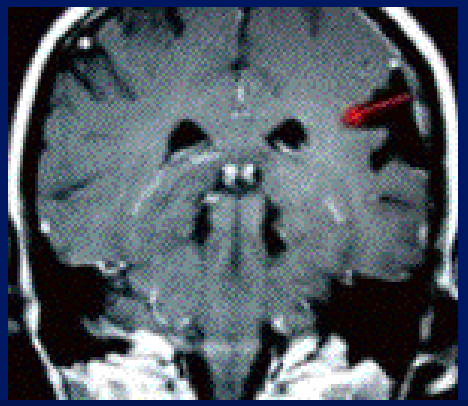
SUBCORTICAL PATHWAYS SUBSERVING VISUO-VESTIBULO-SPATIAL AWARENESS





Thiébaut, Urbanski, Duffau et al, Science 2005

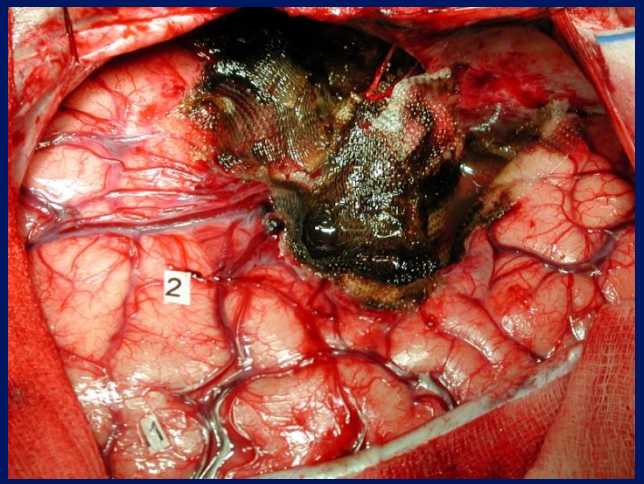


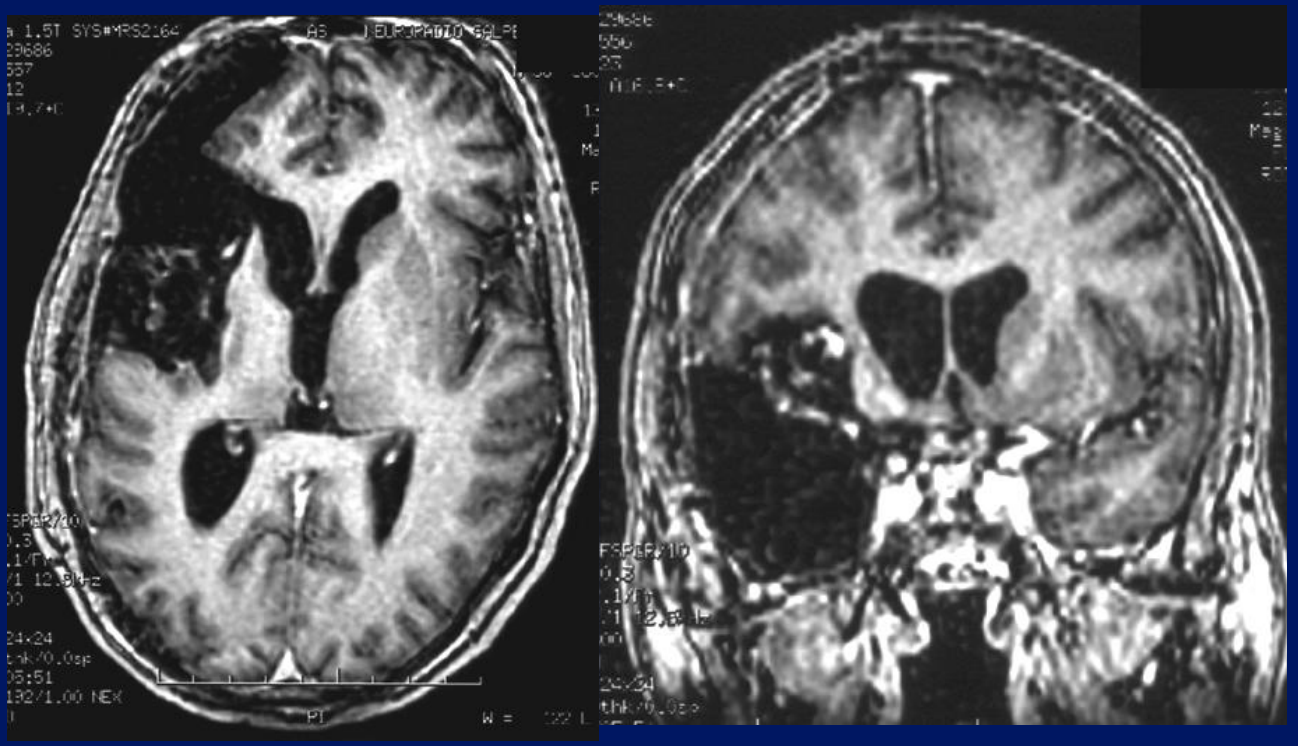


Spena et al., Neuroreport 2006

RESECTION OF CLAUSTRUM

POSSIBLE FUNCTIONAL COMPENSATION

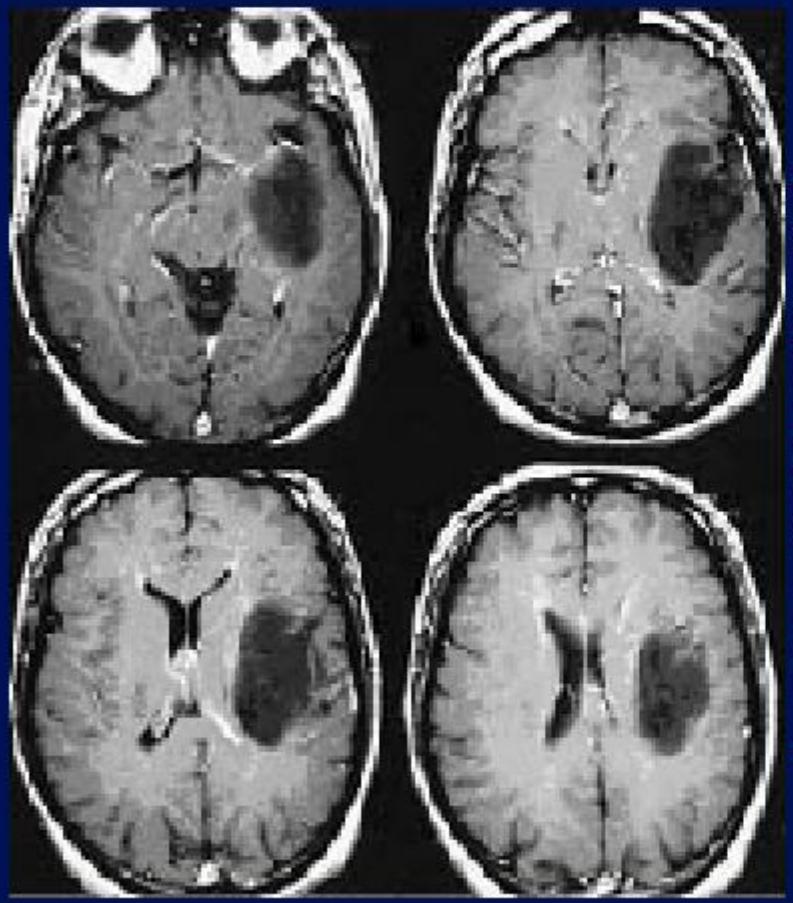




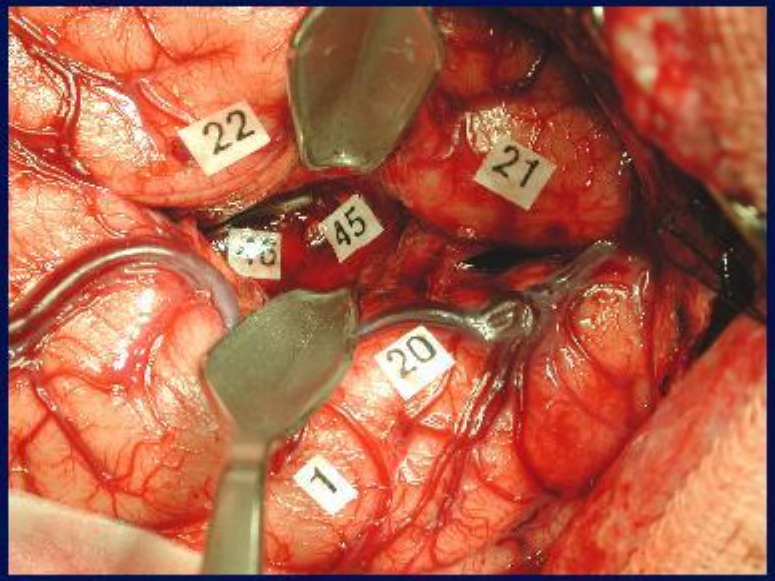
Duffau et al, J Neurooncol 2007

LEFT LENTIFORM NUCLEUS

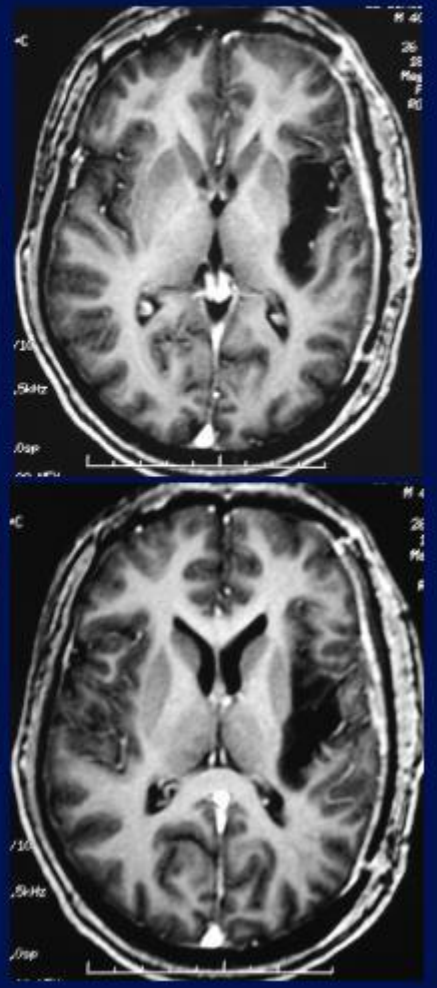
ESSENTIAL ROLE IN ARTICULATION



Temporal Lobe



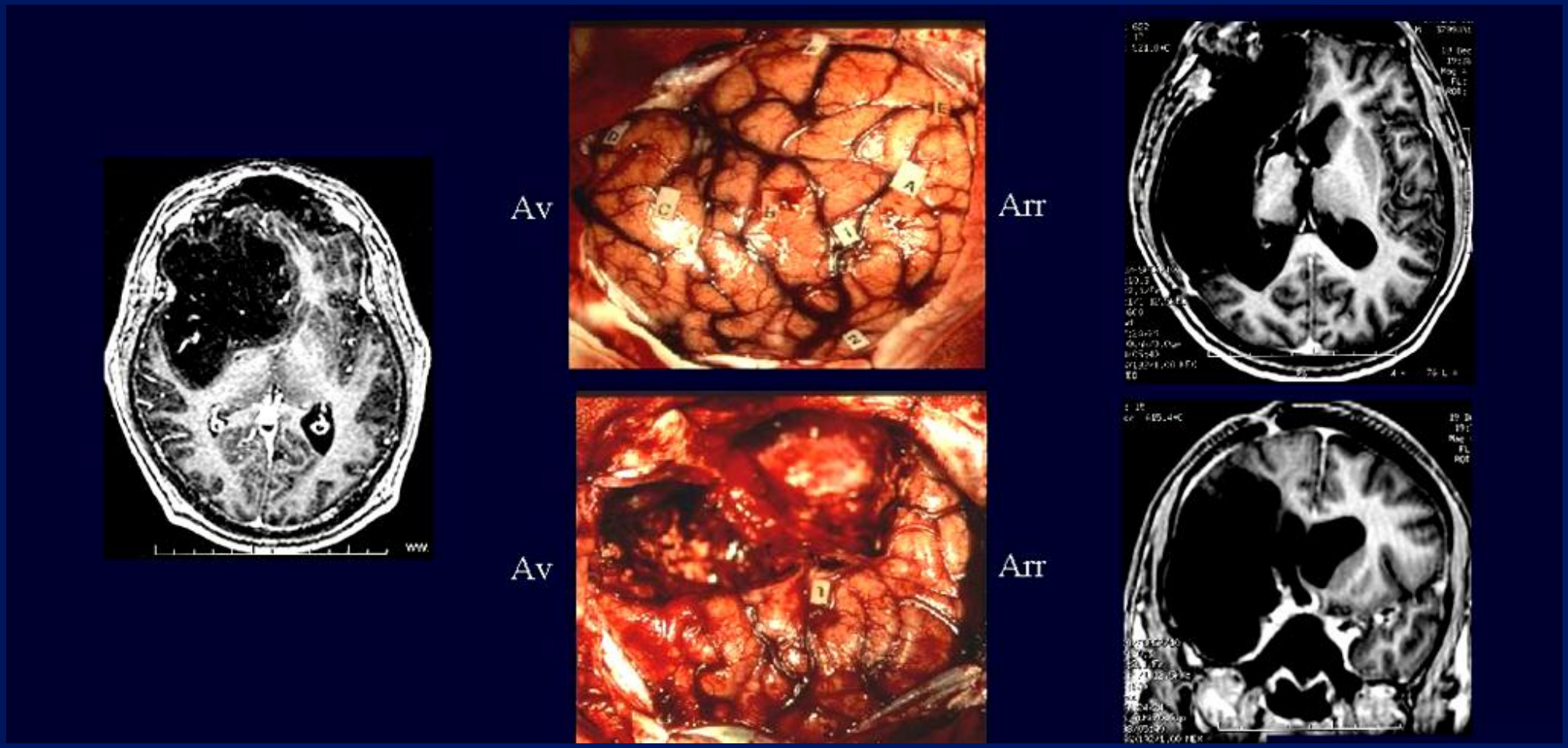
Frontal Lobe



Duffau et al, NeuroReport 2001; Gil Robles et al, JNNP 2005

RESECTION OF RIGHT STRIATUM WHEN INVADED

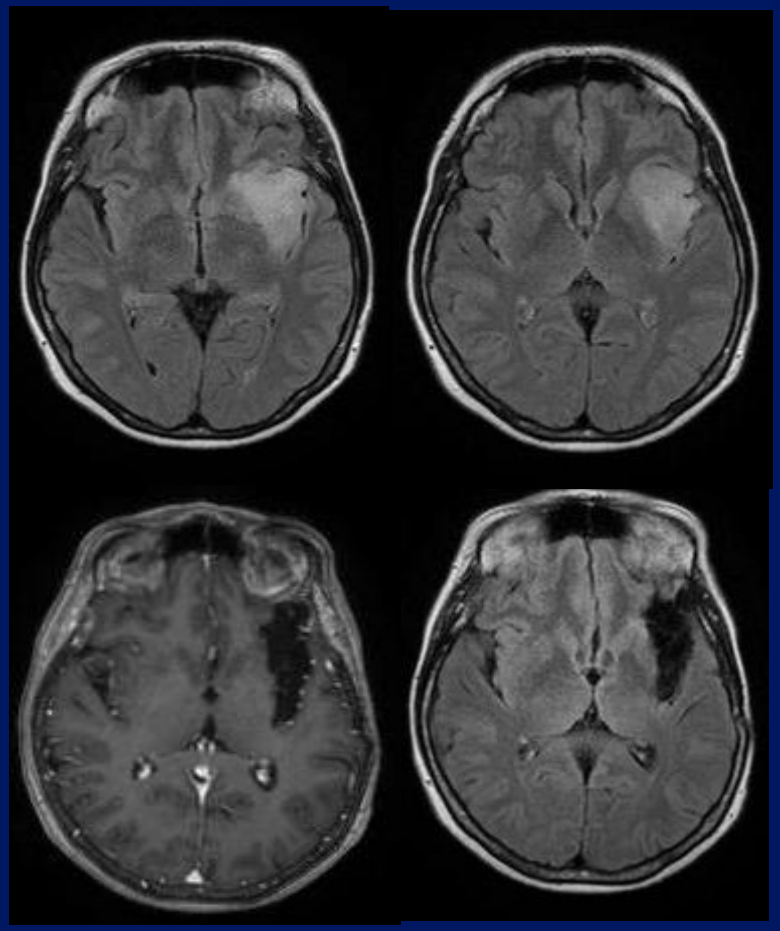
POSSIBLE FUNCTIONAL COMPENSATION

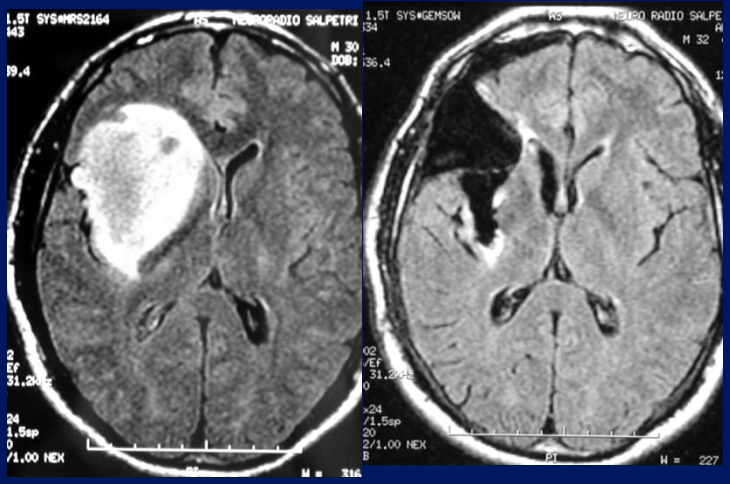


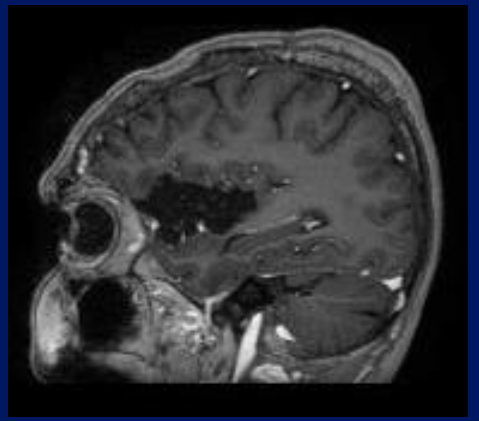
Be careful: perforating arteries !!!

Duffau et al, J Neurosurg 2002

RESULTS



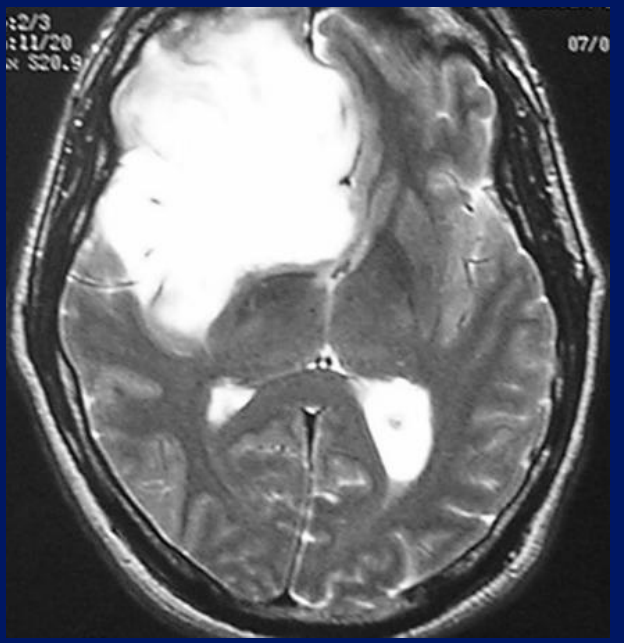

1.5T SYS*MRS2164
1.5T SYS*GEMSOW
RADIO SALPETRI
RADIO SALPE
M 30
M 32
/1.5ep
2/1.00 NEX



PATIENTS

A personal series of 144 patients with insular LGG (1997-2012)

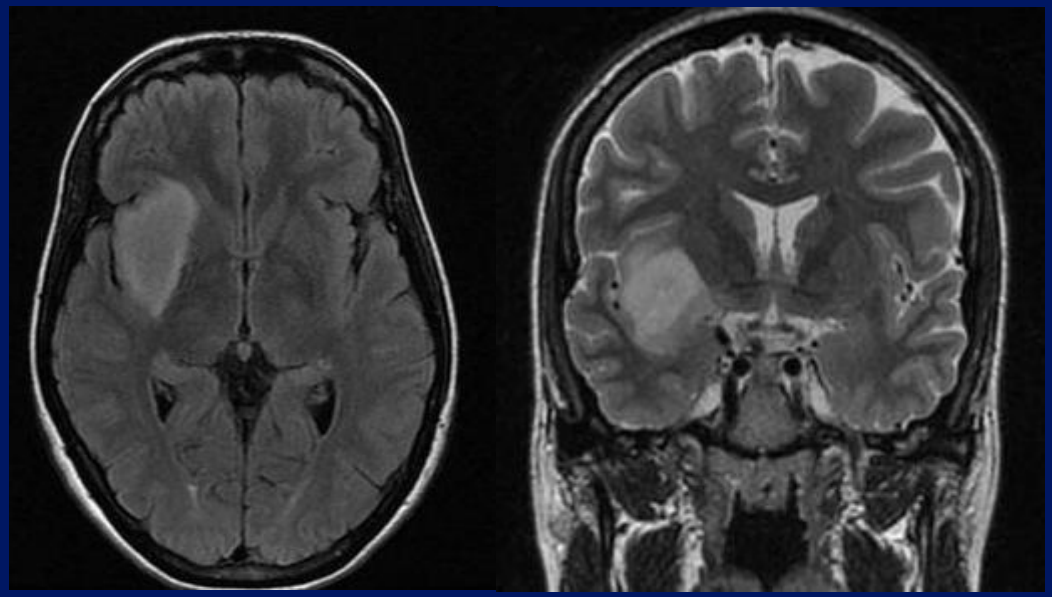
- 74 M / 70 F (mean age of 36 years)
- All right-handed except 6
- Revealed by seizures in all cases
- 37% pharmaco-resistant epilepsy
- Neurological examination
  - Normal in 134 patients (KPS 90 or 100)
  - Mild dysarthria in 10 patients (KPS 80)

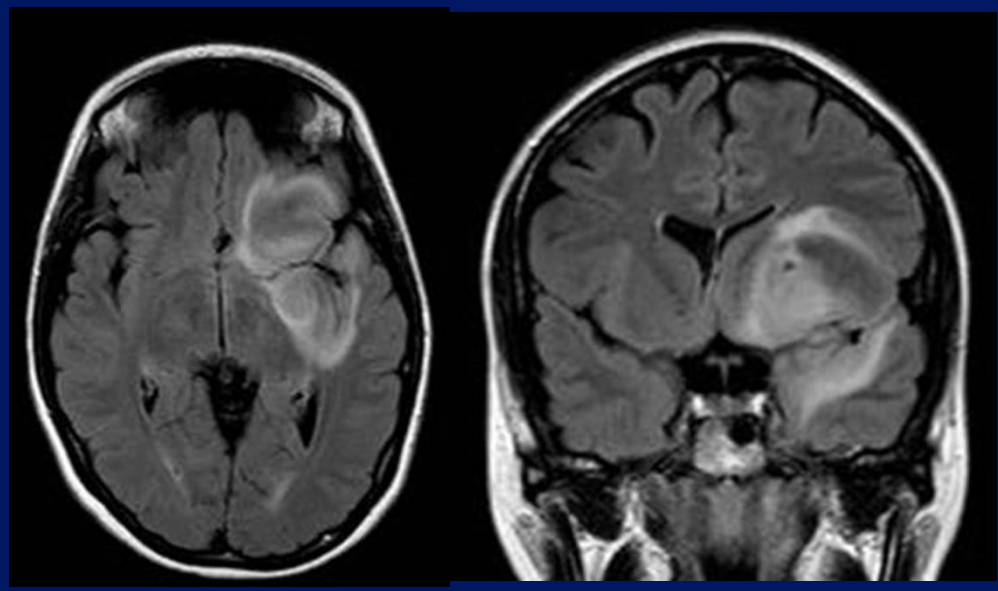


Duffau, J Neurosurg 2009

PREOPERATIVE MRI : GLIOMA LOCATIONS

(70 RIGHT and 74 LEFT LGG)



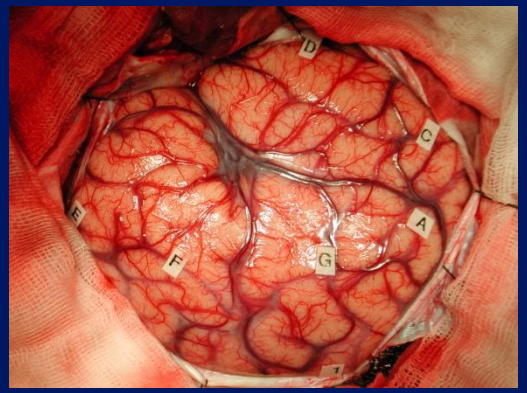


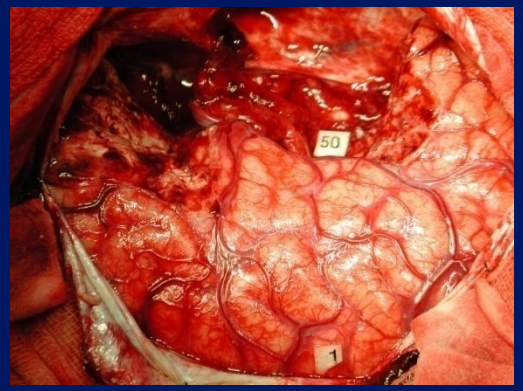
17% pure insular LGG

83% paralimbic LGG

INTRAOPERATIVE FUNCTIONAL MAPPING

- 49 patients operated under general anesthesia (first period)
  - **No response during stimulation of the insular cortex**
  - **Pyramidal fibers systematically detected and preserved**
- 95 patients operated on whilst awake (second period)
  - **Dysarthria induced by insular stimulation in 8 cases**
  - **No other functional disturbance elicited during cortical mapping**
  - **Language pathways/deep grey nuclei detected and preserved in all cases**



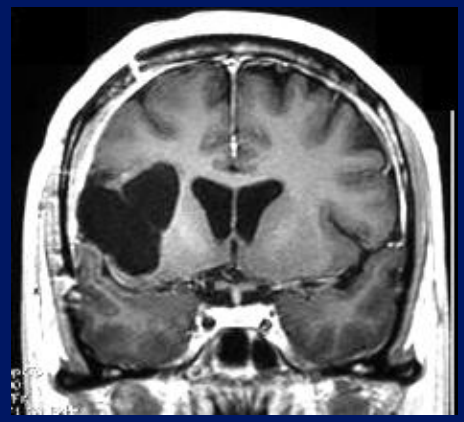


Opercular

resection in 130 cases

POST-OPERATIVE FUNCTIONAL RESULTS

- Postoperative rehabilitation adapted to each patient
- Delayed postsurgical results
  - 142 patients recovered a normal examination
  - 40 improved relative to their preoperative status
  - KPS 90 or 100 in 142/144 cases
  - Normal socio-professional life in 142 cases
  - 2 permanent hemiparesis due to a deep stroke (0 in awake patients+++)

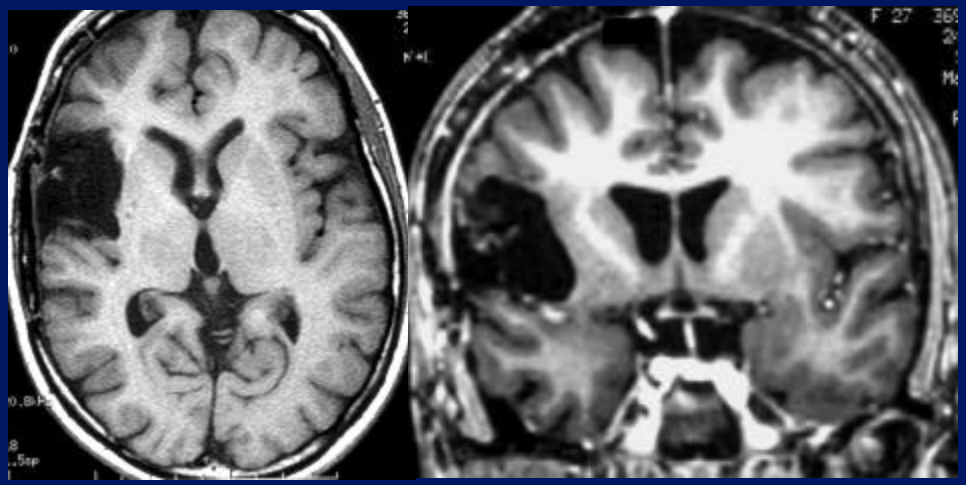


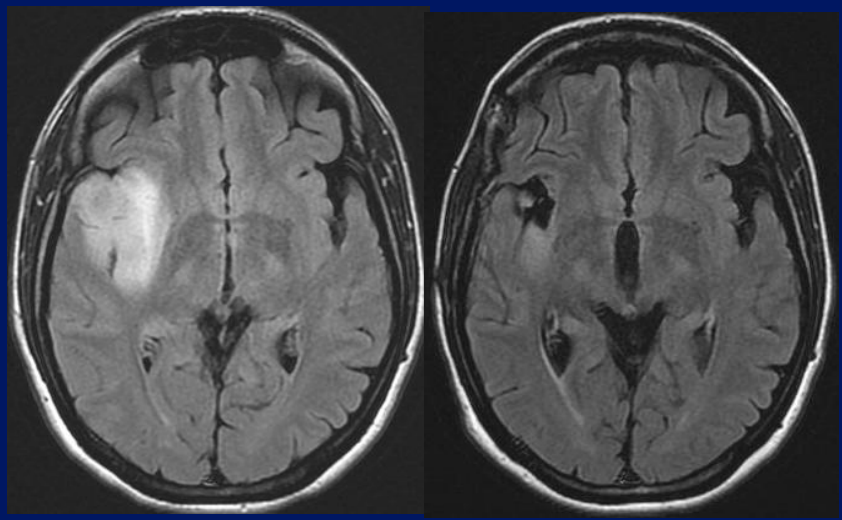
- 98.6% of favorable functional results in insular surgery

Duffau, J Neurosurg 2009; Duffau et al., Neurosurgical Focus 2009

POST-OPERATIVE EPILEPTOLOGICAL RESULTS

- Relief of intractable epilepsia
  - 81% of patients in Engel Class I
  - With dramatic improvement of the quality of life
  - But still under antiepileptic drugs (except in 20% of cases)

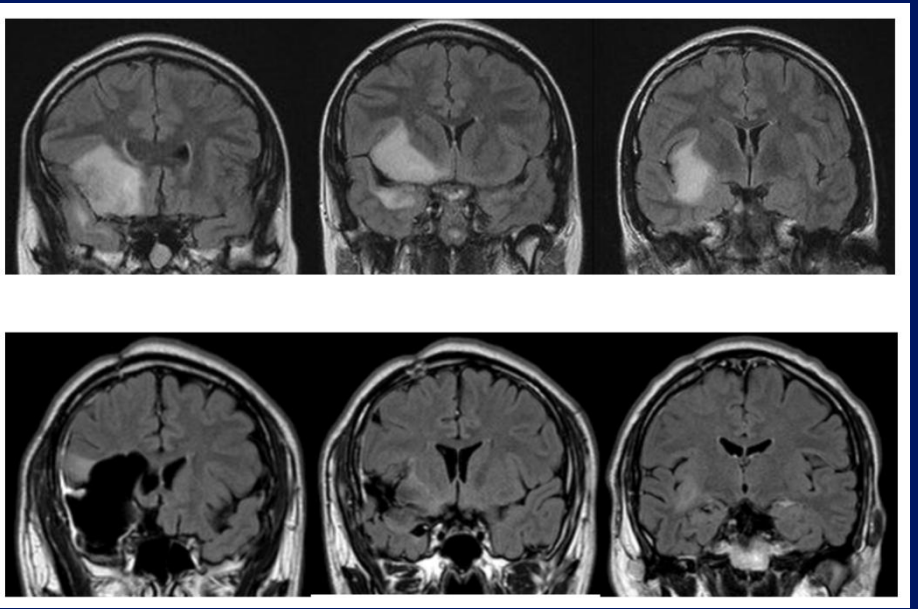




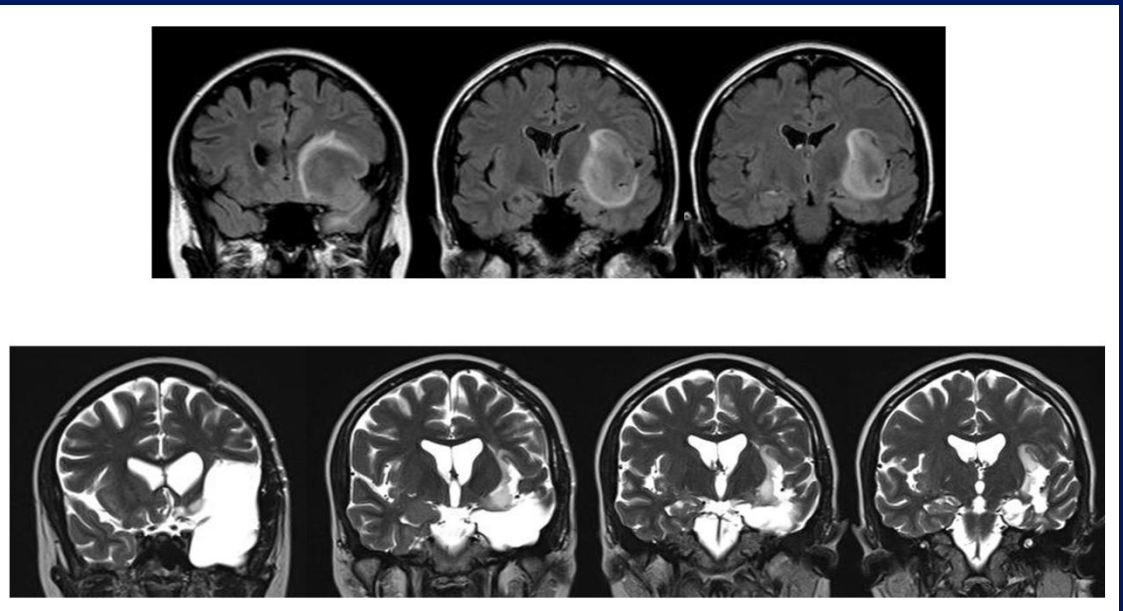
Duffau et al, Acta Neurochir 2002

IMPACT OF RESECTION OF THE HIPPOCAMPUS NOT INVADED BY THE TUMOR IN PARALIMBIC LGG

15 patients with a (fronto-)temporo-insular LGG eliciting intractable epilepsy



LGG resection with no hippocampectomy
N = 8; 4 Engel's II and 4 Engel's III



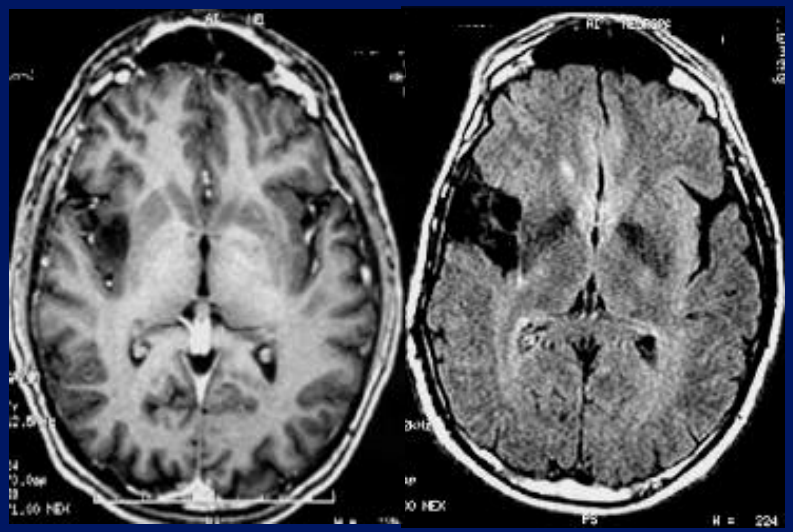
LGG resection with hippocampectomy
N = 7; 7 Engel's I

p = 0.0001

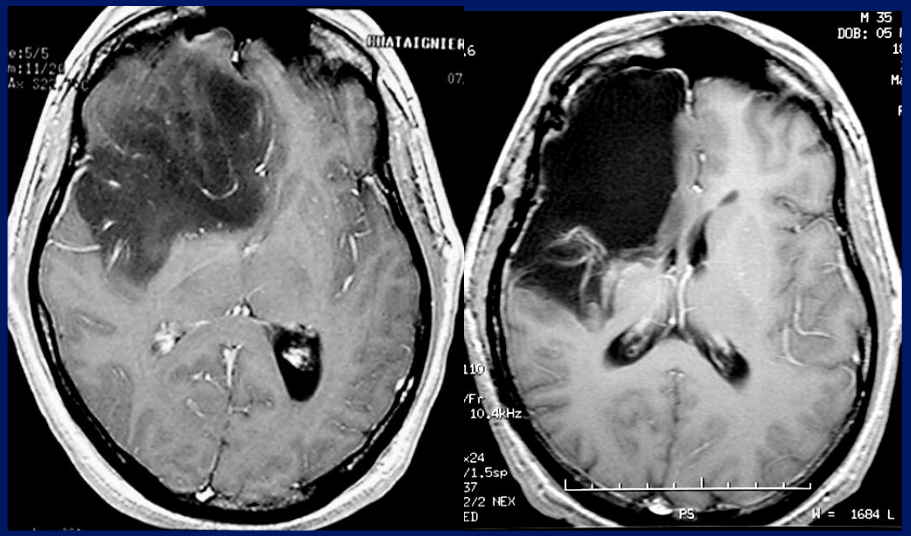
Ghareeb and Duffau, J Neurosurg 2012

RESULTS : EXTENT OF RESECTION

- Total or subtotal in 82% of patients
  - Whatever the Type
  - Verified on MRI +++



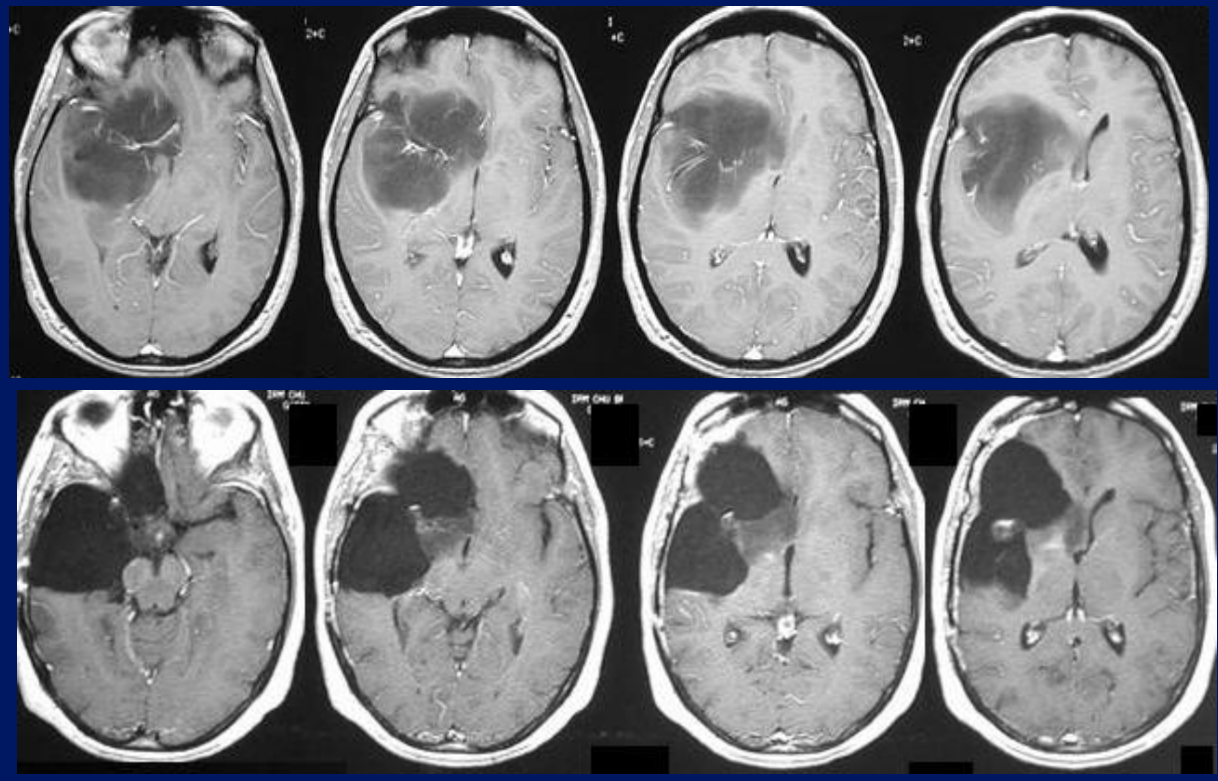
Pure insular



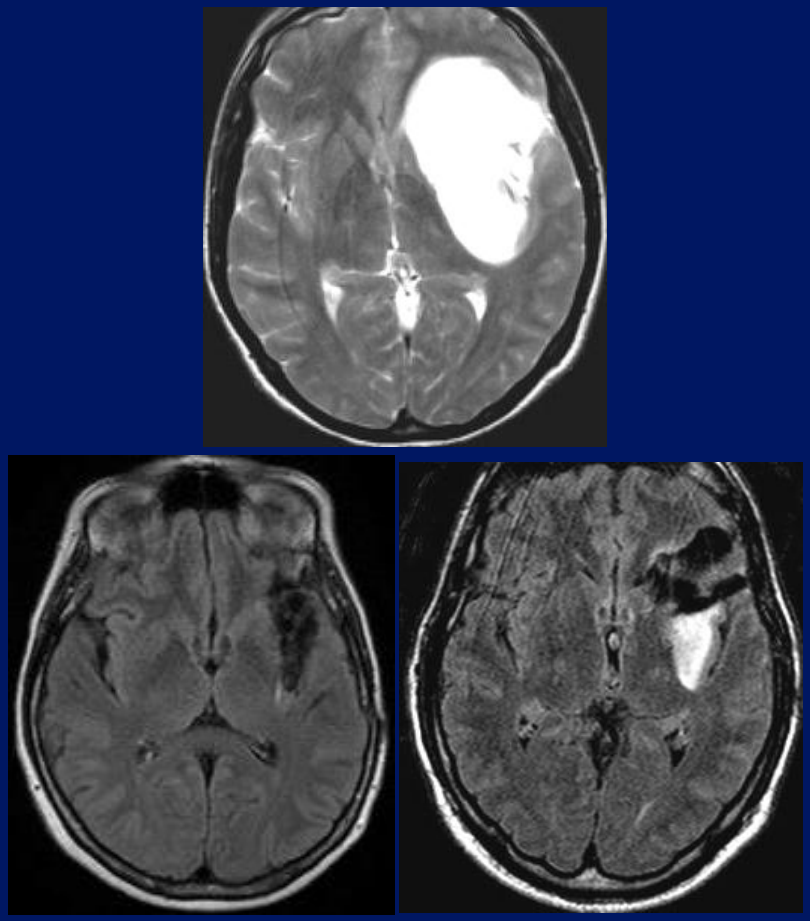
Fronto-temporo-insular

- Partial in 18% of patients

LIMITATIONS

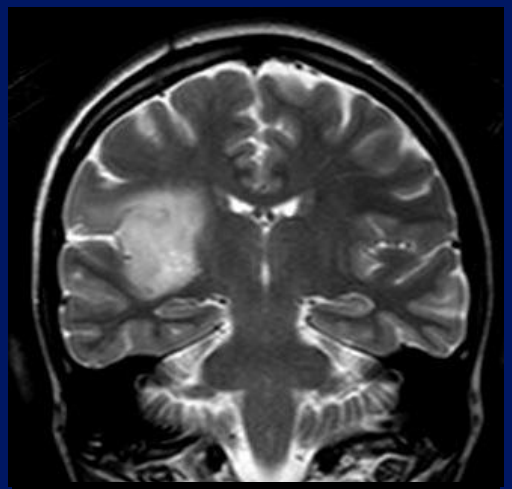


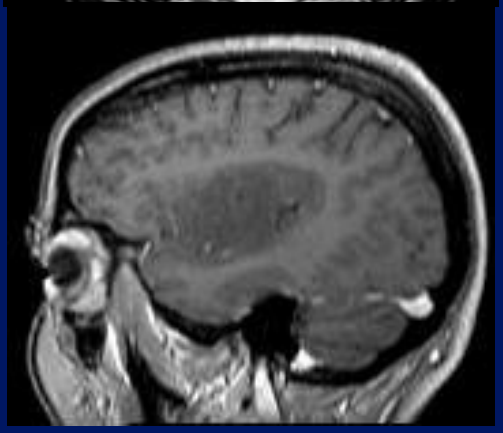
Anterior perforating substance

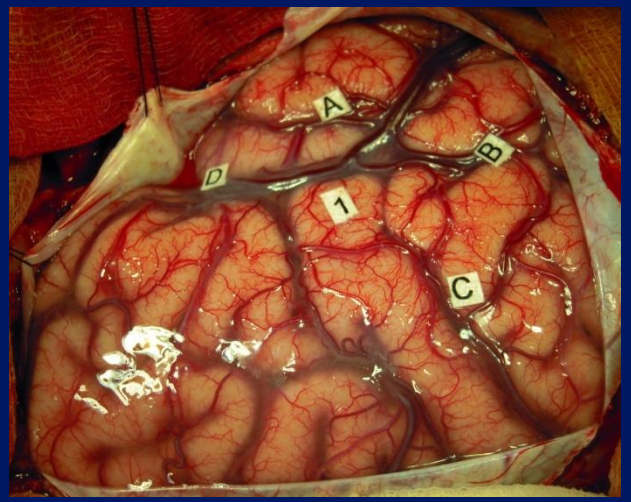


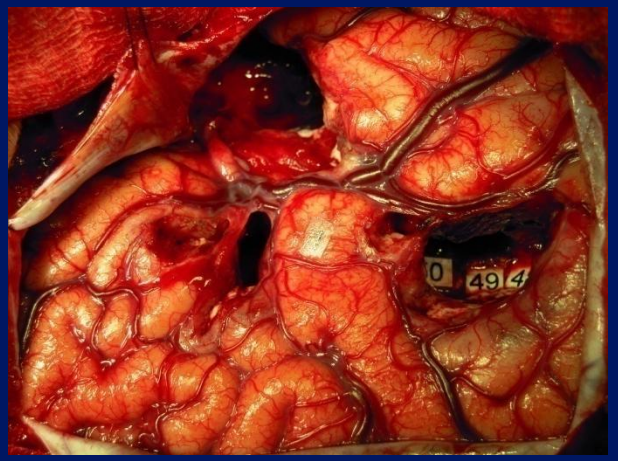
Left dominant
postero-superior insula

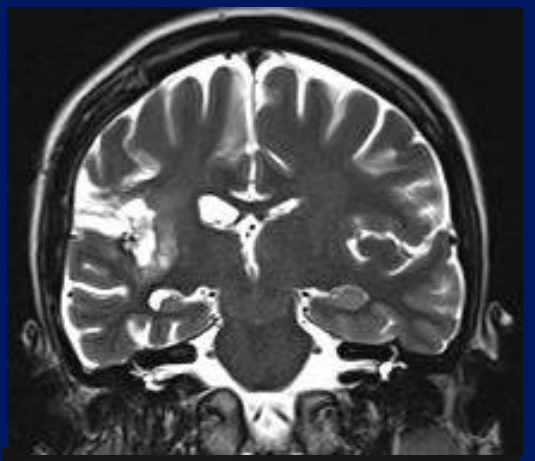
SOLUTION ?

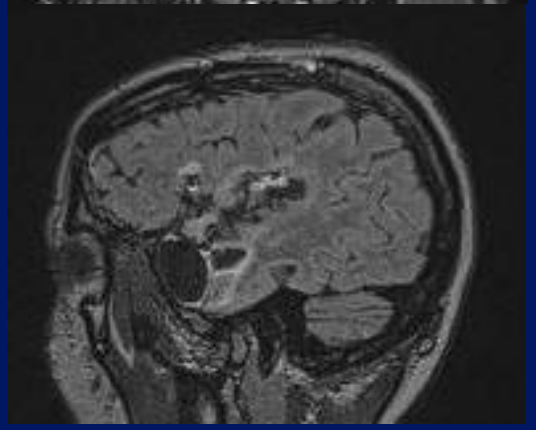








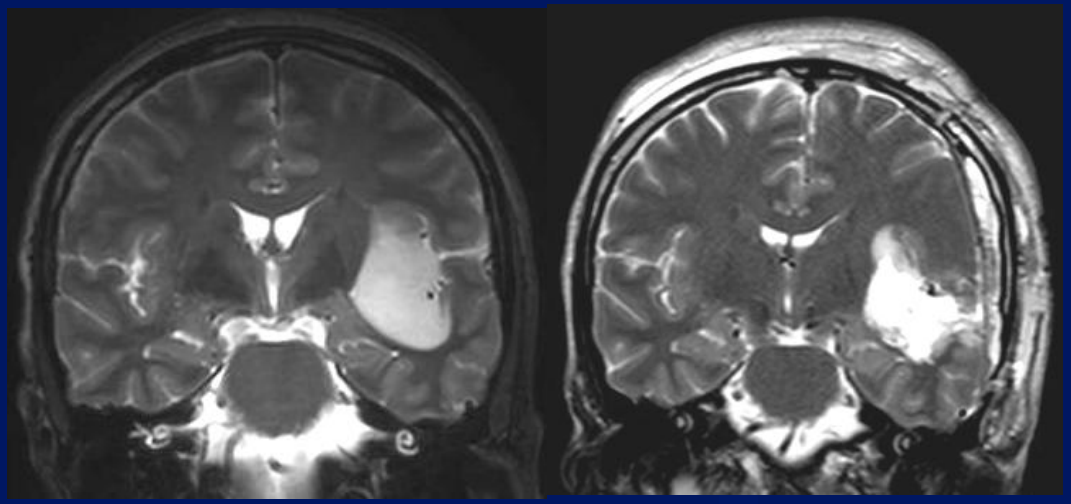




Surgical approach through the parietal operculum (example of left-hander)

RESULTS : RE-OPERATION AFTER TUMOR REGROWTH

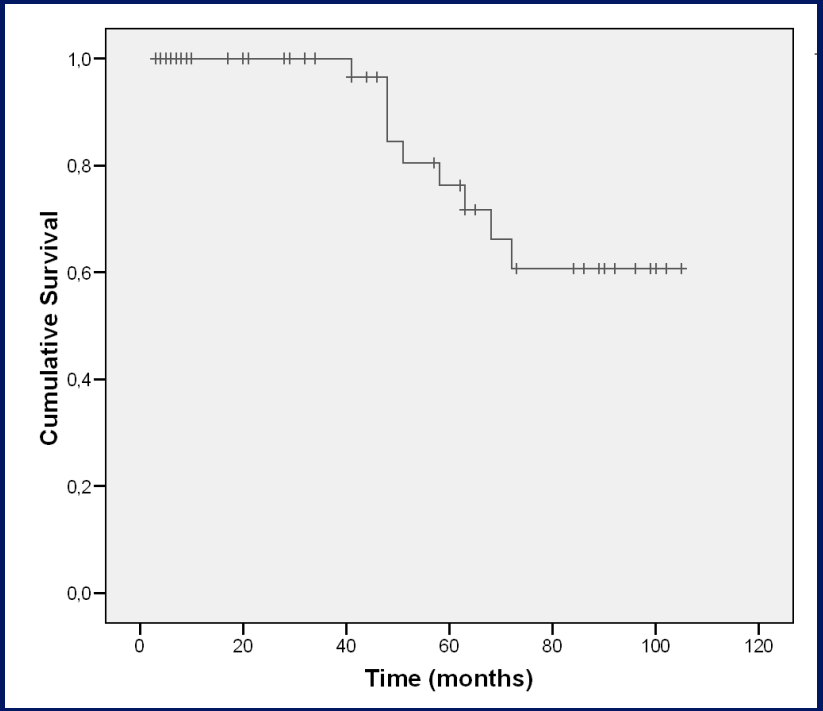
- Twenty patients underwent a second surgery
- Four patients underwent a third surgery
- With no additional permanent deficit
- With improvement of the extent of resection in all cases



FOLLOW-UP

- Median FU: 74 (3-148) months since the first surgery
- Median FU: 90 (6-260) months since the first symptom
- Ten patients died (15%)
- 85% of patients are still alive

Survival after the first surgery

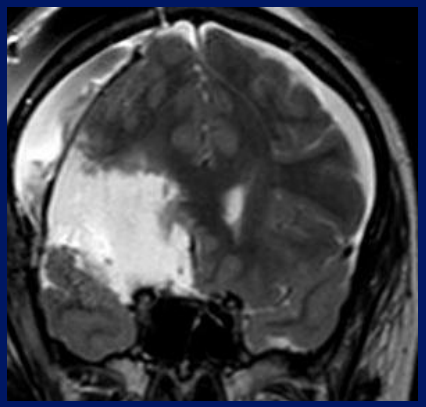


Duffau, J Neurosurg 2009

CONCLUSIONS

SURGERY FOR INSULAR GLIOMAS

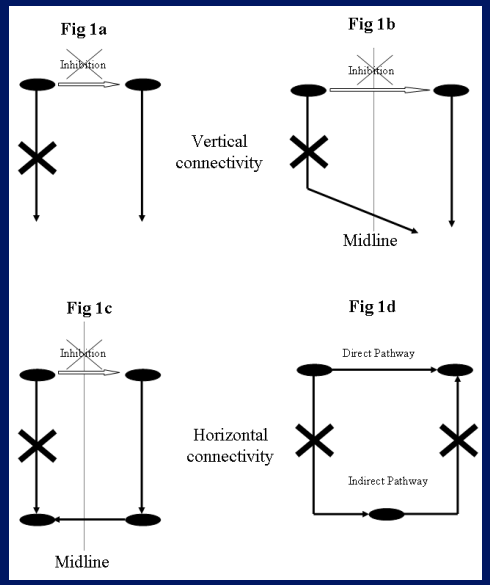
- Integration of new concepts in the surgical strategy
  - Better knowledge of the role of the insular lobe
  - Study of the individual functional anatomy

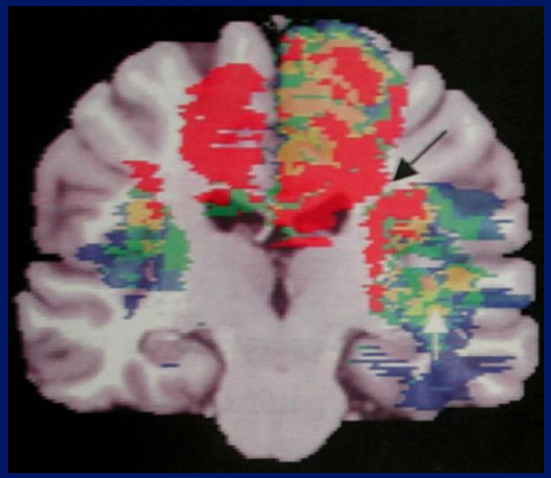


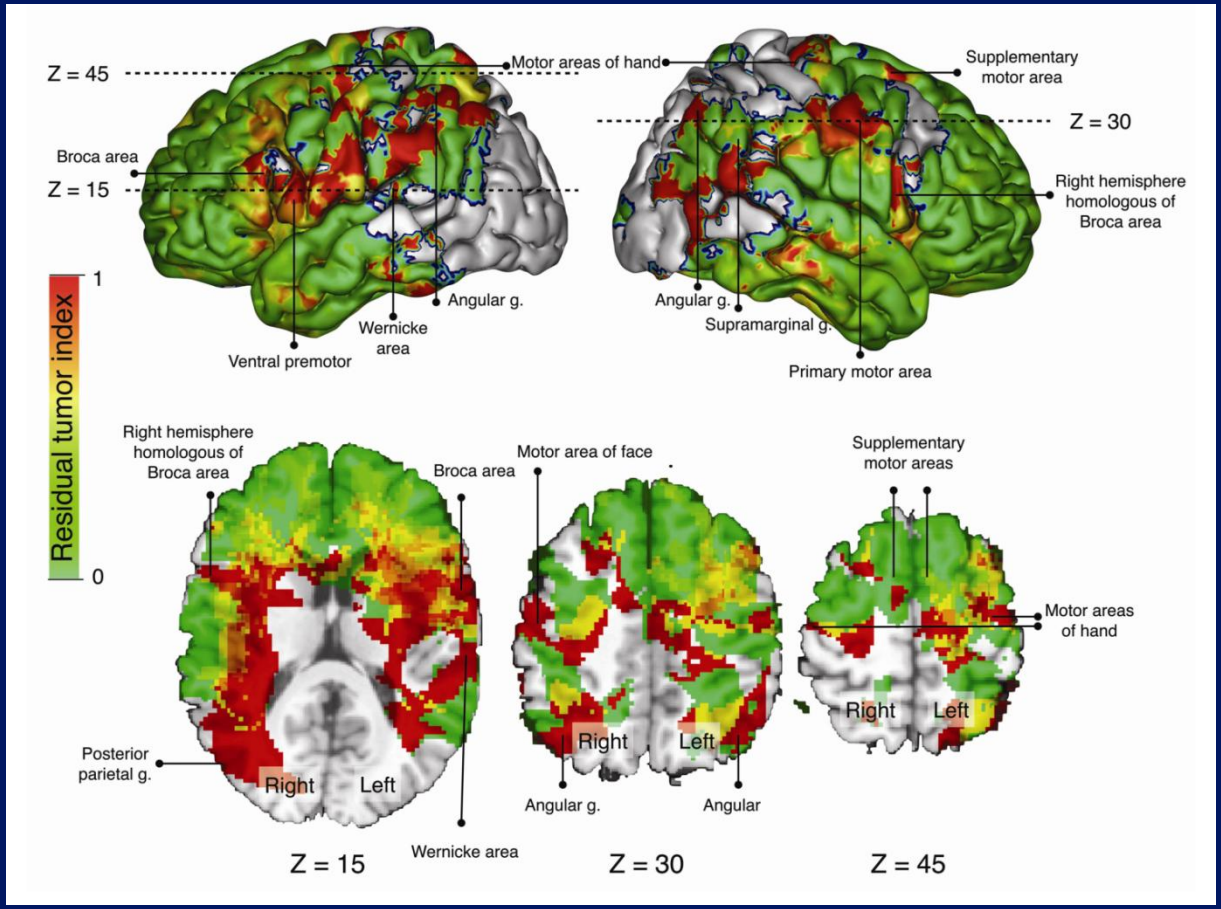
- Optimization of Benefit/Risk Ratio of surgery
  - Extension of surgical indications within the insula, since a functional compensation is possible
  - Improvement of the extent of resection
  - Minimization of the risk of permanent deficit (1.5%)
  - Improvement of the quality of life in intractable epilepsy

LIMITATION : SUBCORTICAL CONNECTIVITY !!

« MINIMAL COMMON BRAIN »



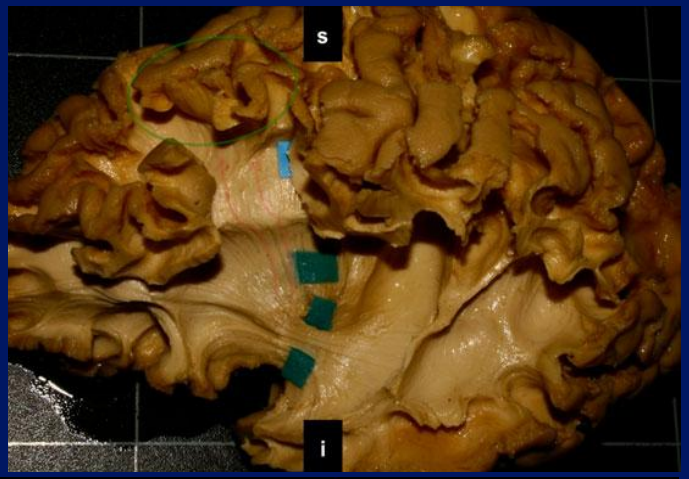


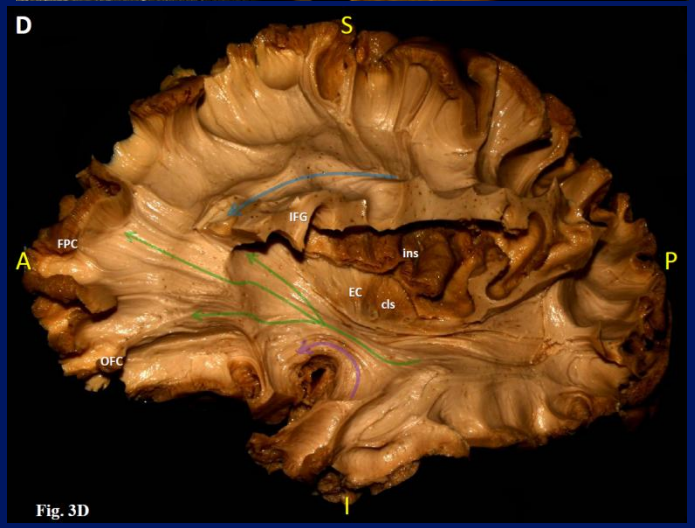


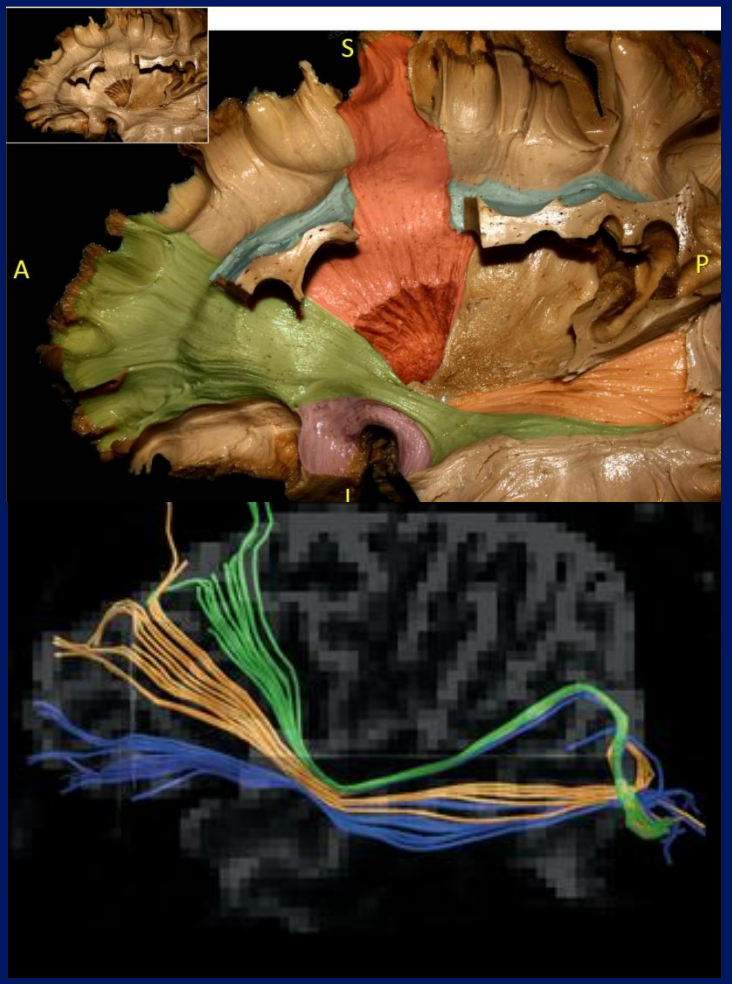
Mandonnet et al., Neurooncology 2006; Duffau, Neurosci Res 2009; Ius et al., Neuroimage 2011

PERSPECTIVES : NEW ANATOMIC STUDIES

OF THE TEMPORAL STEM WITH DISSECTION AND DTI



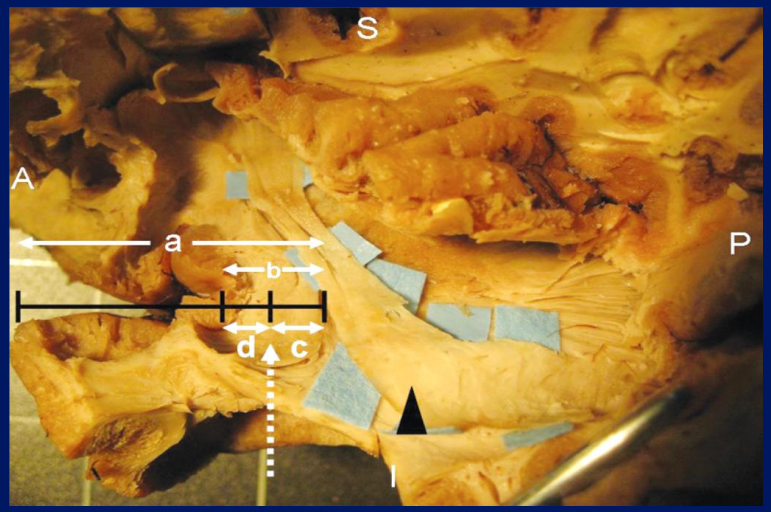


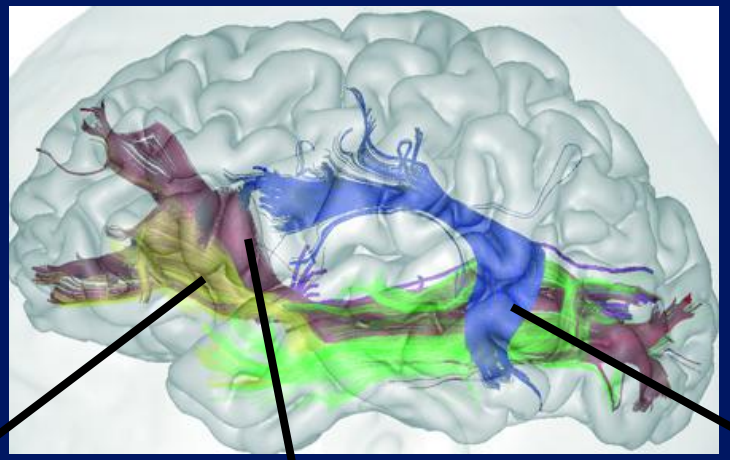


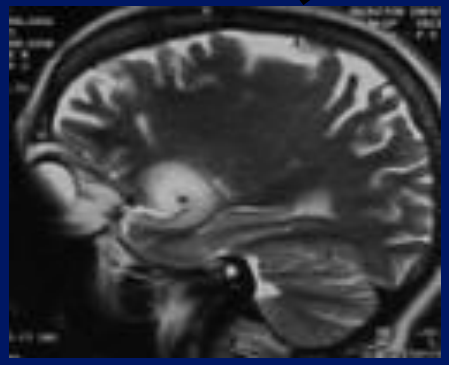
Martino et al., Neurosurgery 2010; De Benedictis, Sarubbo and Duffau, J Neurosurg 2012

PERSPECTIVES : TOWARDS A KINETIC CLASSIFICATION

BASED ON WHITE MATTER INVASION PATTERNS

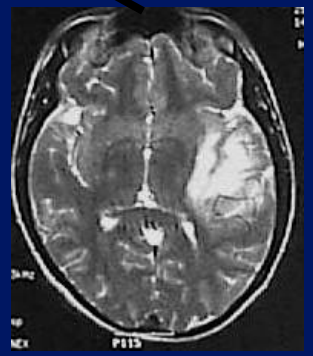






Uncinate fasciculus

Inferior occipitofrontal fasciculus



Arcuate fasciculus

Mandonnet et al, J Neurooncol 2007; Duffau et al. JNNP 2008; Martino et al., Cortex 2010

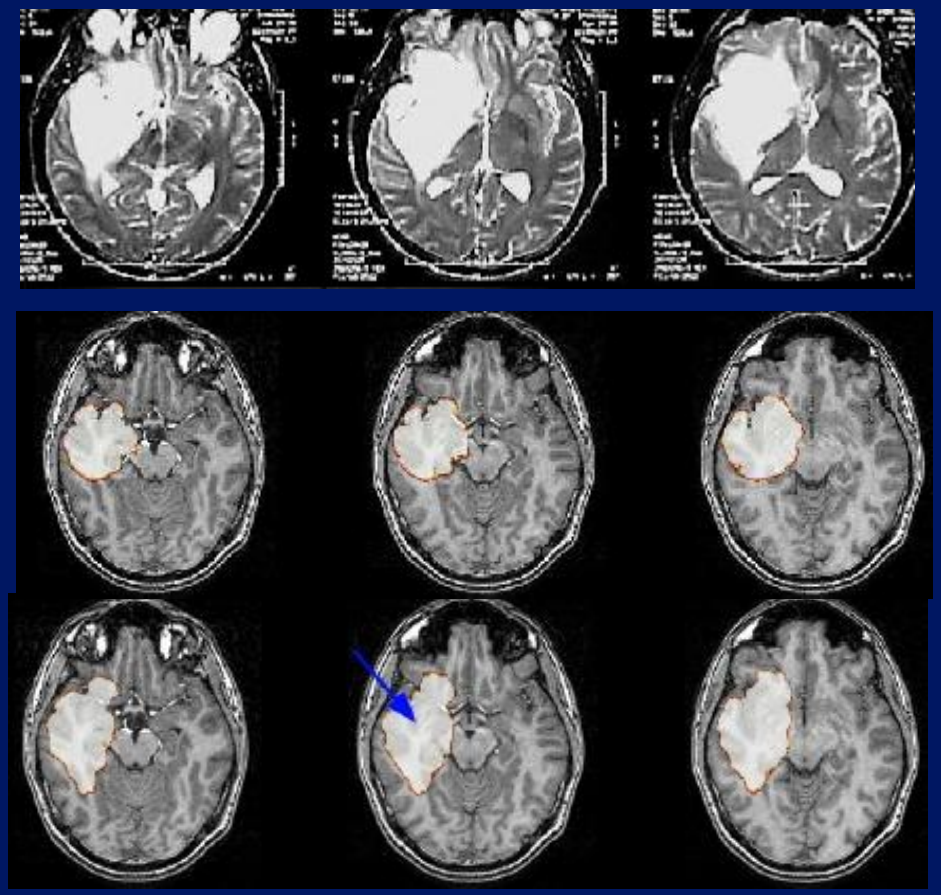
PERSPECTIVES : PREDICTION OF THE EXTENSION OF INSULAR LOW-GRADE GLIOMAS

- Use of the DTI

Tumoral Invasion

Isotropic Model

Anisotropic Model

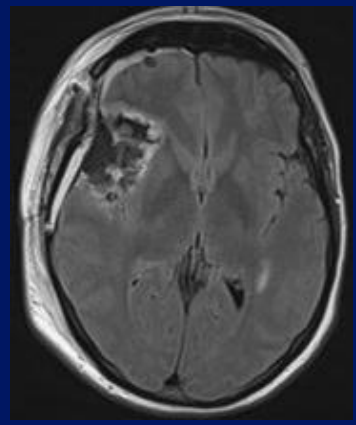


Calculation of a Cellular Tensor Diffusion

Jbabdi et al., MRM 2006

PERSPECTIVES: TOWARDS A BETTER UNDERSTANDING OF THE MOLECULAR BIOLOGY OF INSULAR LGG

- Molecular analysis in the 47 last patients
  - only 15% of 1p19q co-deletion
  - IDH1/2 mutation in all pure insular LGG
  - only 55% mutated in paralimbic LGG (p=0.008)



- Markor of worse prognosis in paralimbic LGG?
- Markor of a lower chemosensitivity?
- Supporting a more surgical attitude / Multiple resections

Goze et al, J Neurooncol 2008; Goze et al., J Neurosurg, in press

TAKE HOME MESSAGE

Although the knowledge of the gray and white matter anatomy is mandatory,

it is NOT ENOUGH

Functional aspects are CRUCIAL!!!