Neurochirurgie guidée par l'image

Emmanuel Mandonnet

Service de Neurochirurgie du Pr Froelich

Hôpital Lariboisière

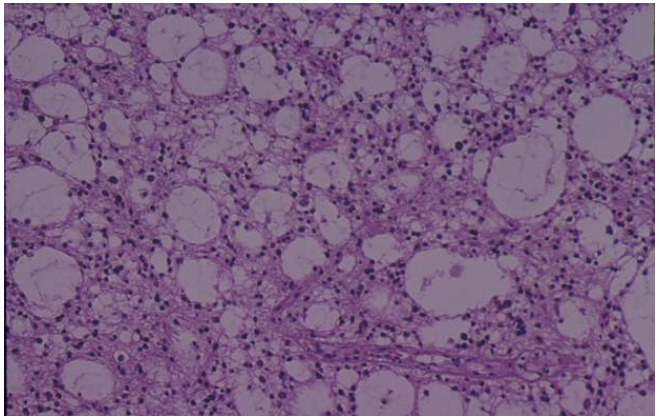
Laboratoire IMNC Paris 7 - UMR 8165

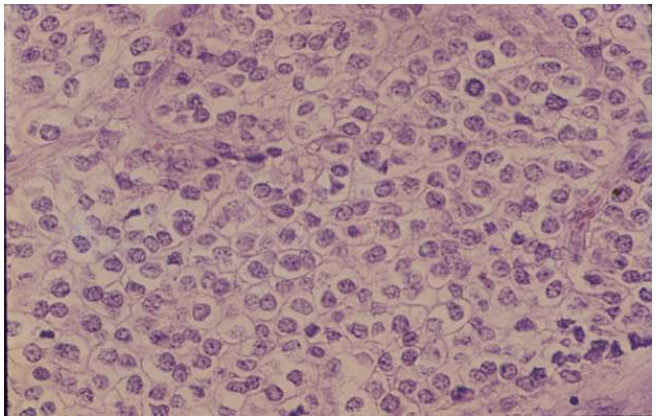
mandonnet@mac.com

27/05/2014

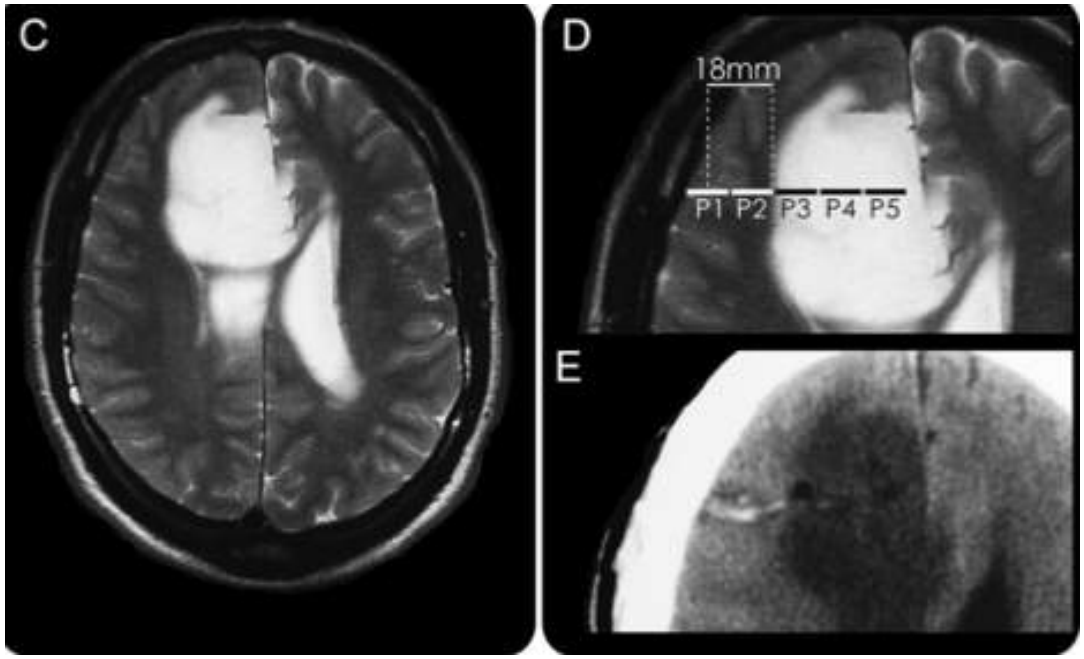
Gliomes diffus de bas grade

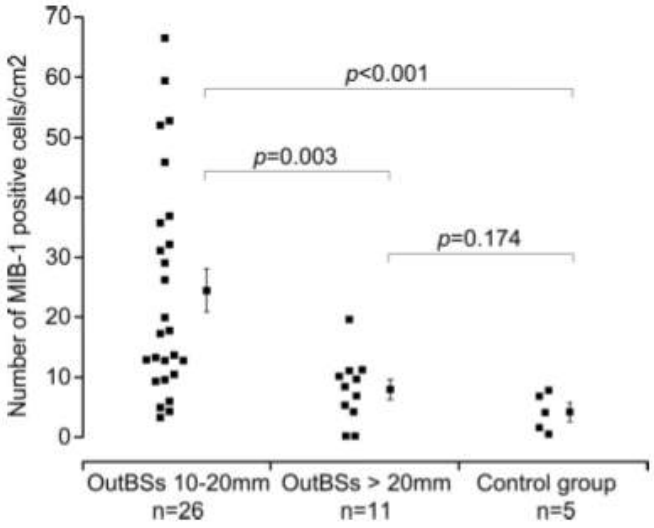
- Grade II de l'OMS
  - astrocytome, oligodendrogliome
  - 10 % des gliomes
  - incidence : 0.55-0.8/100 000/an
  - patients jeunes (30-40 ans)
  - médiane de survie : 10 ans (grande hétérogénéité)





Extension invisible

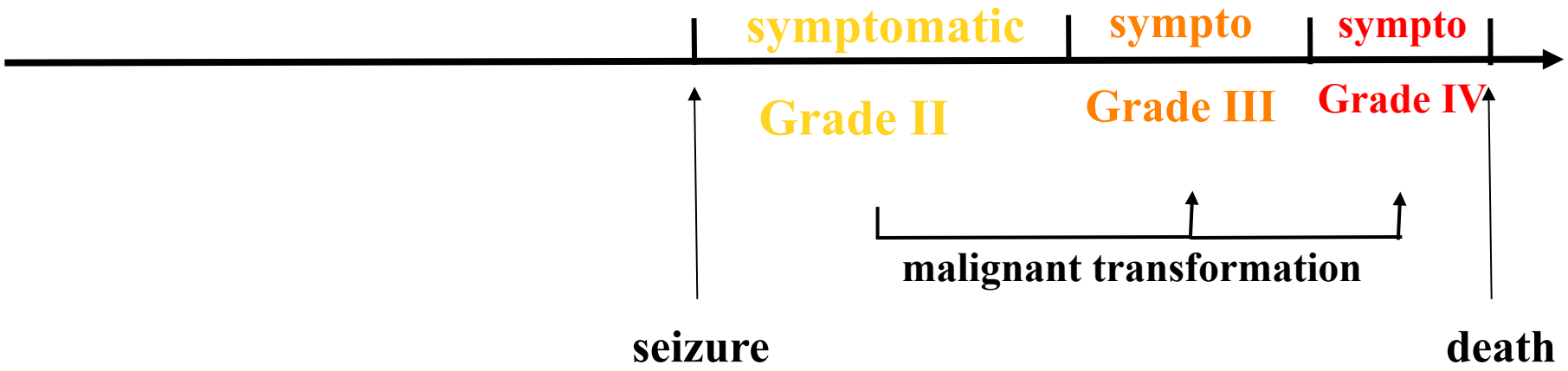




The number of cycling cells is expressed as MIB-1–positive cells per square centimeter, and the distance from MRI-defined abnormalities is expressed in millimeters. OutBS = biopsy sample taken outside MRI-defined abnormalities.

Pallud & al. 2010, *Neurology*

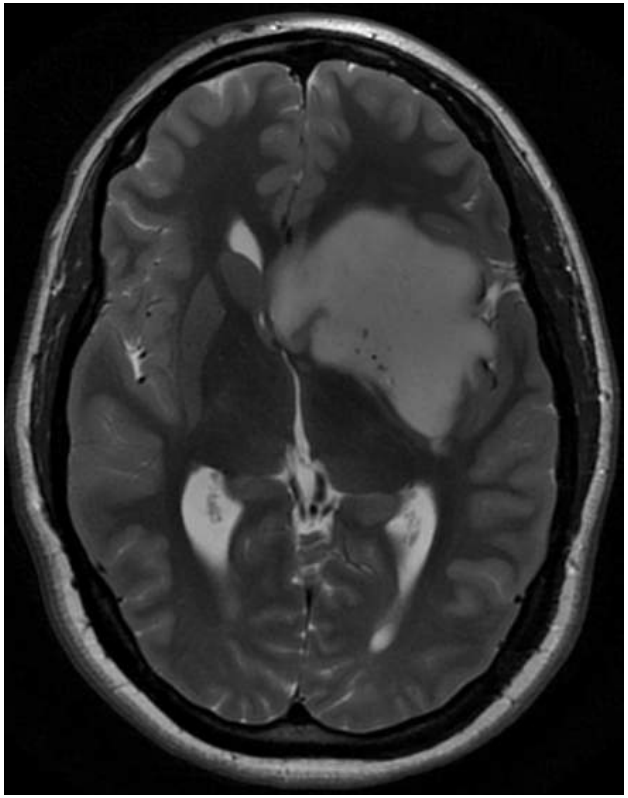
Natural history of a diffuse low-grade glioma



Plasticité cérébrale et cinétique tumorale

- Asymptomatique (90 % des cas) car la lenteur de l'évolution permet la mise en place des phénomènes de plasticité

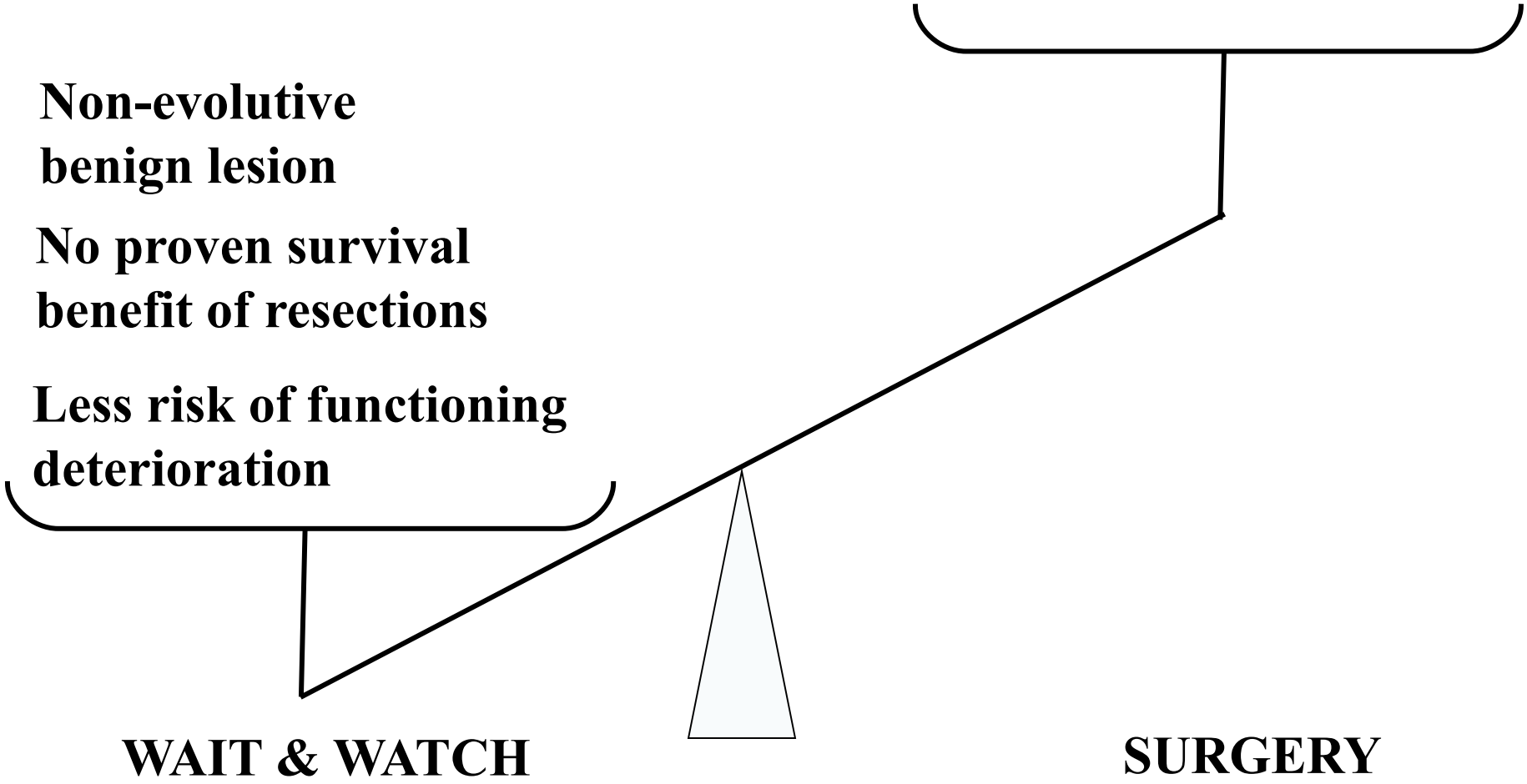
- Asymptomatique mais …
  - déficits aux examens neuropsychologiques
  - déficits aux examens d'orthophonie
  - retentissement socio-professionnel



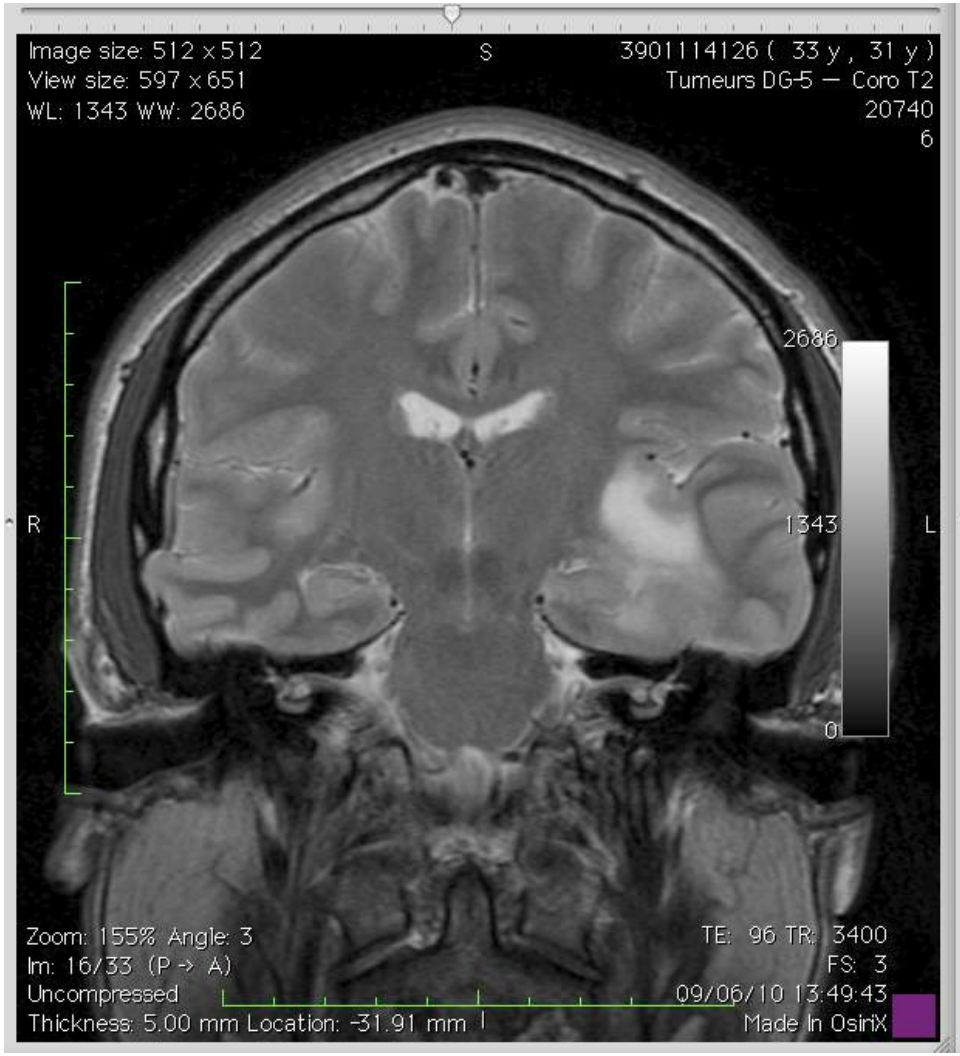
Problématiques du chirurgien

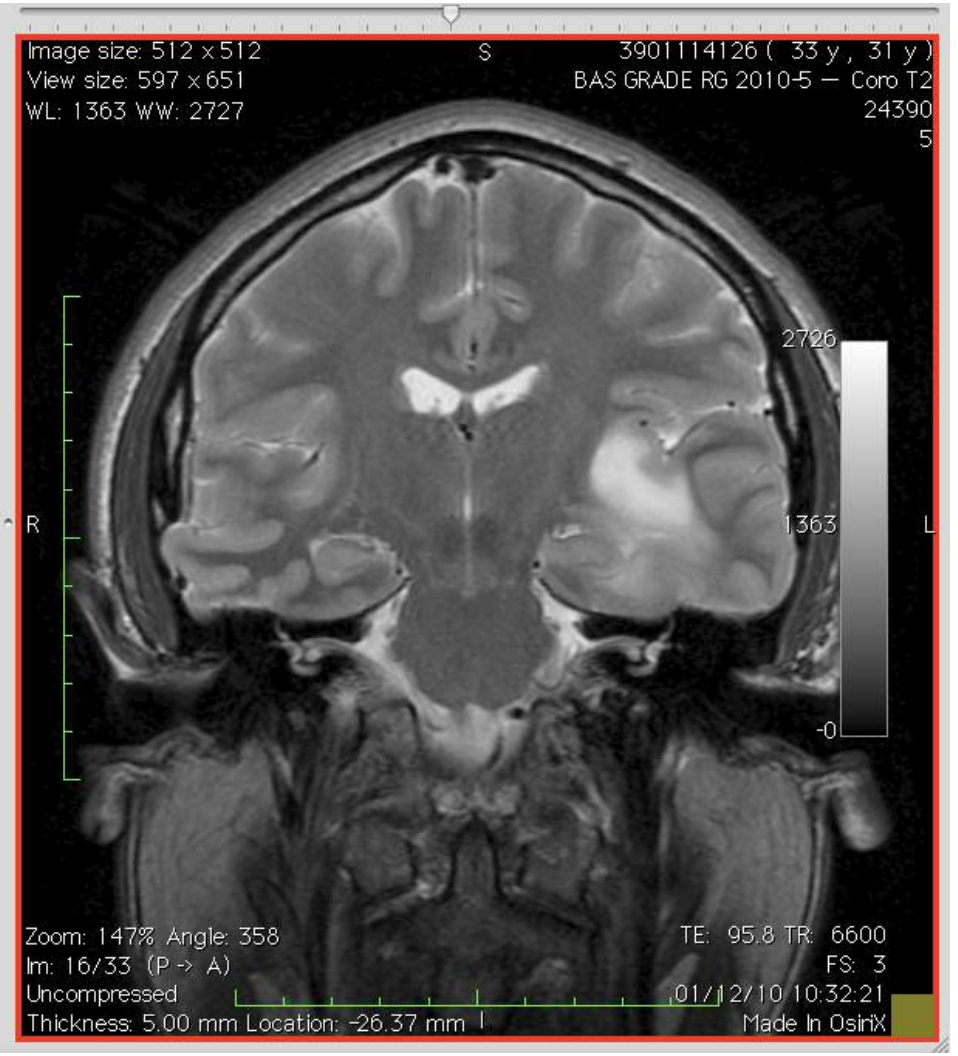
- Faut-il opérer ?
- Comment opérer ?

The pro & cons balance (in the 20th century)

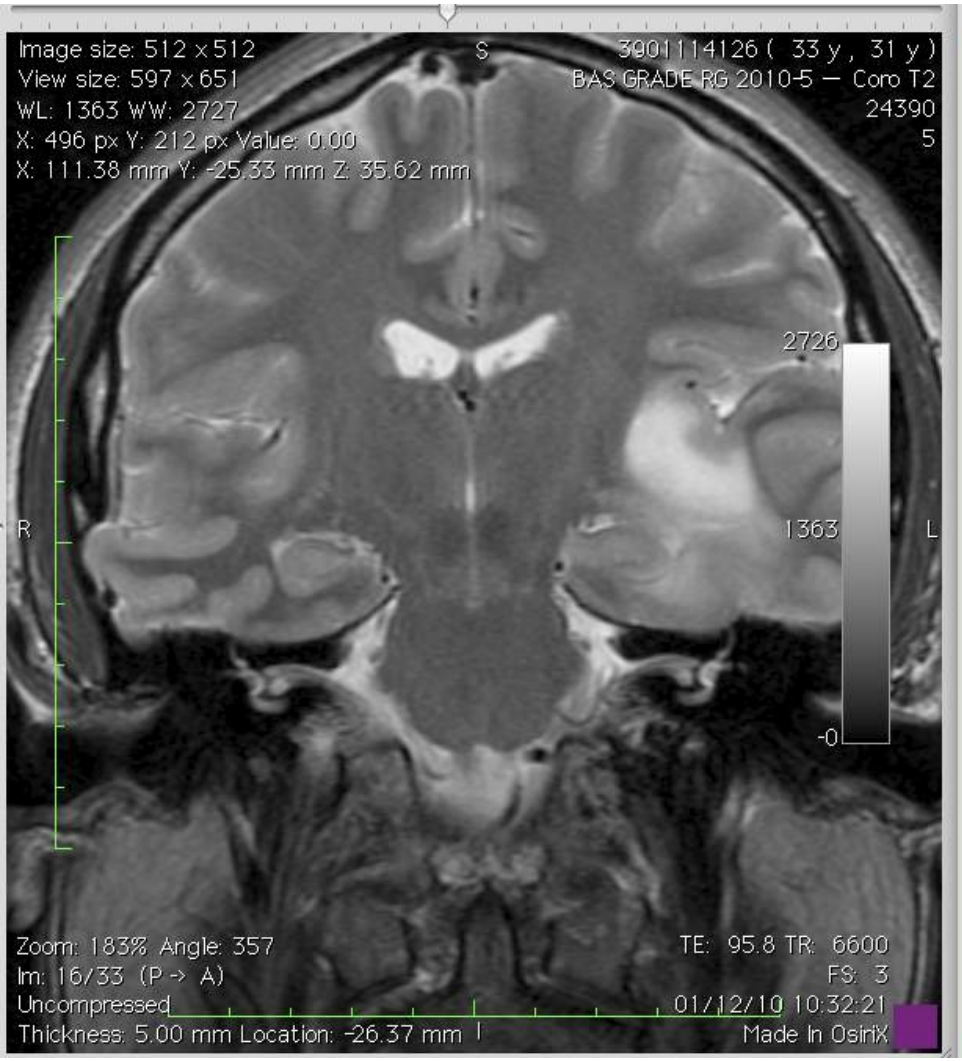


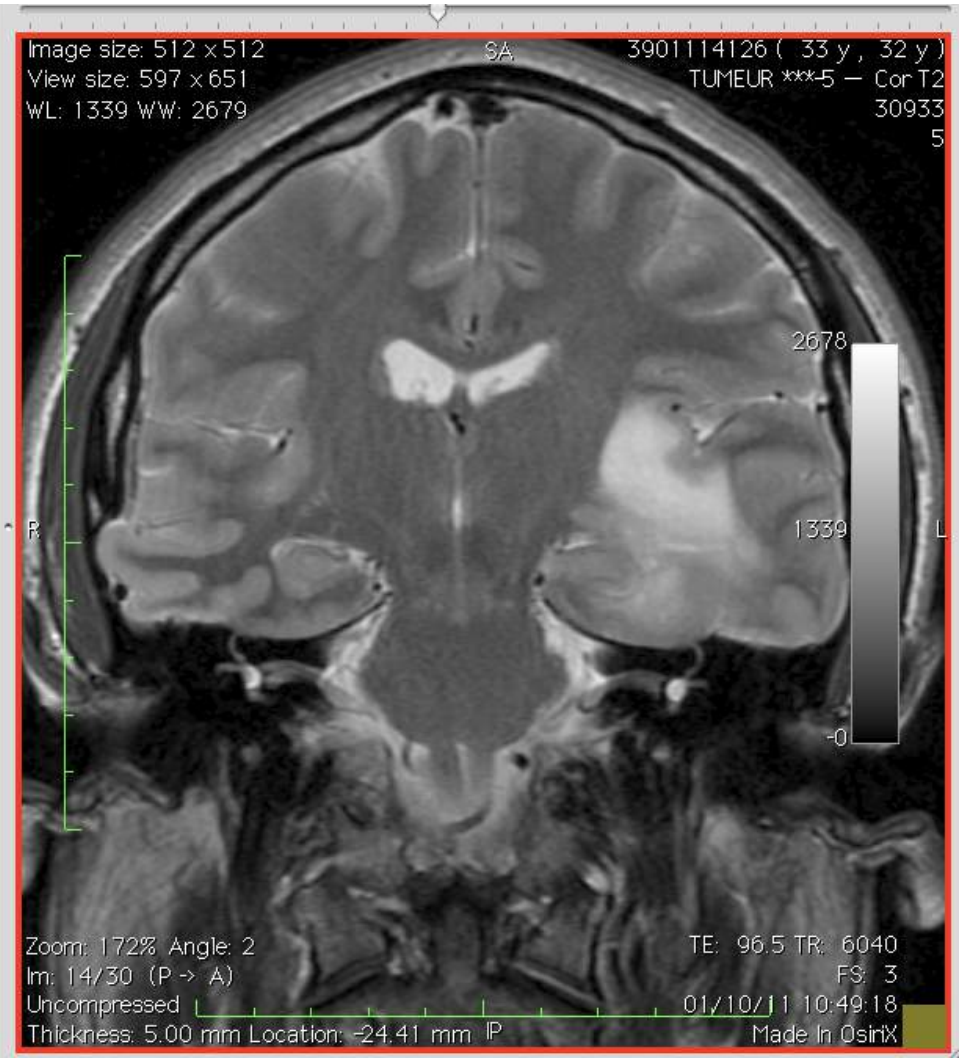
LGG are evolutive tumors, albeit looking stable !



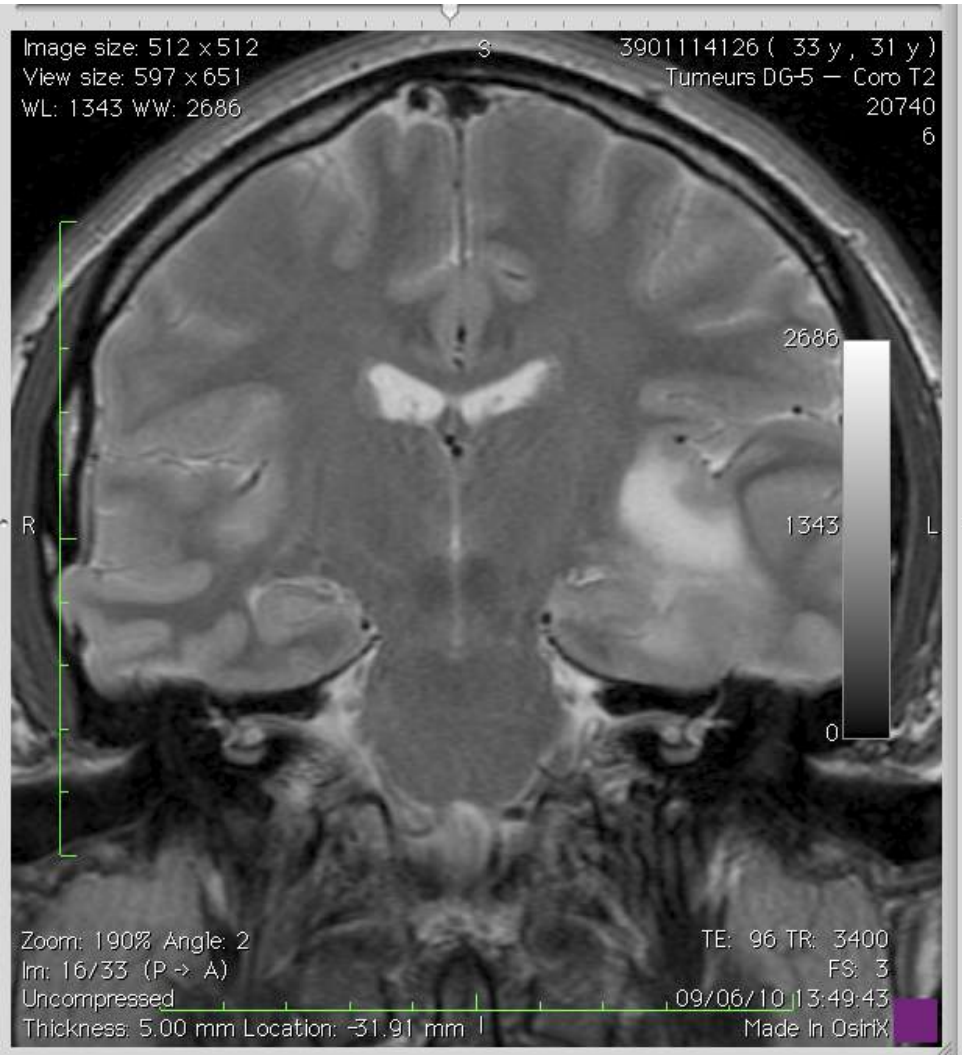


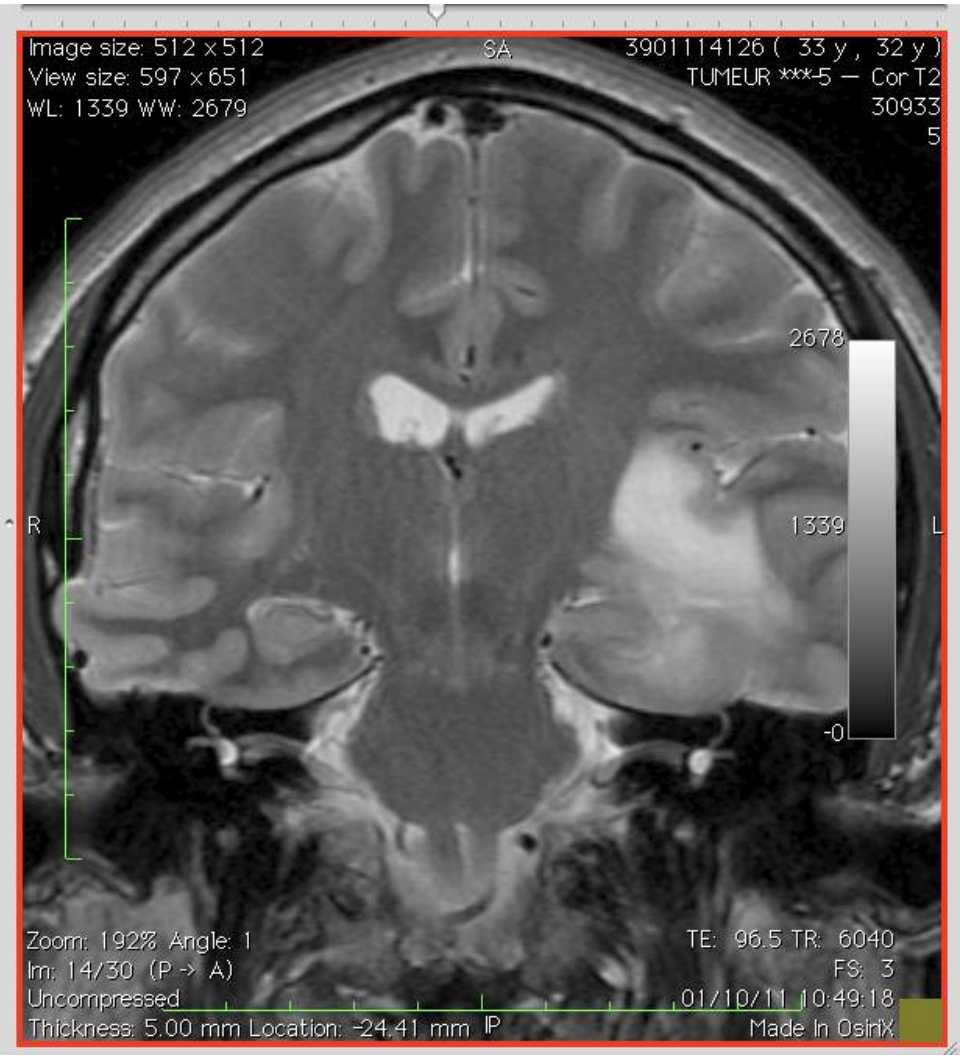
LGG are evolutive tumors, albeit looking stable !



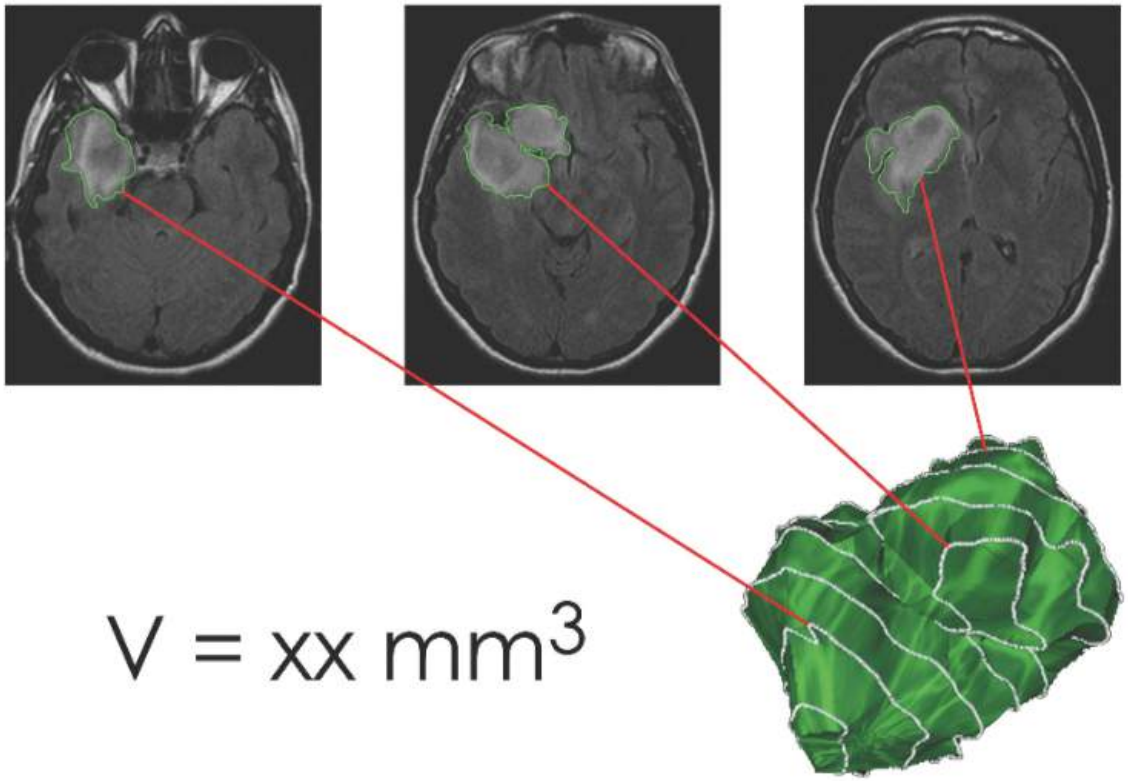


LGG are evolutive tumors





Quantitative morphological MRI follow-up

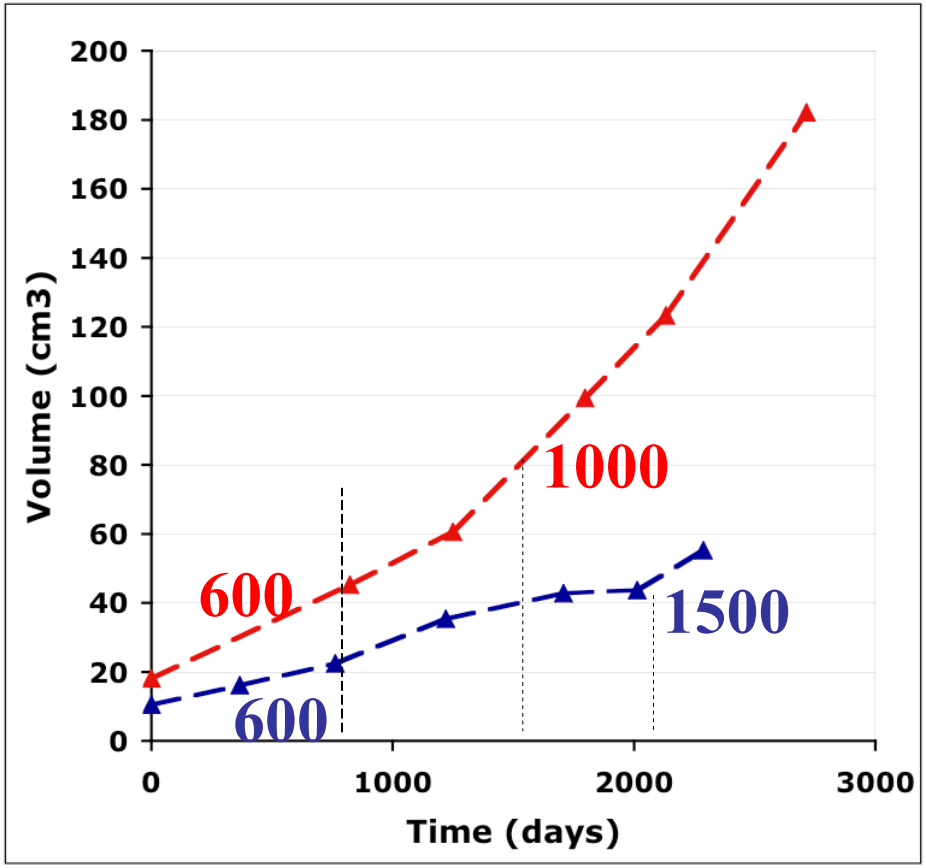


Sorensen & al. 2001, *JCO*

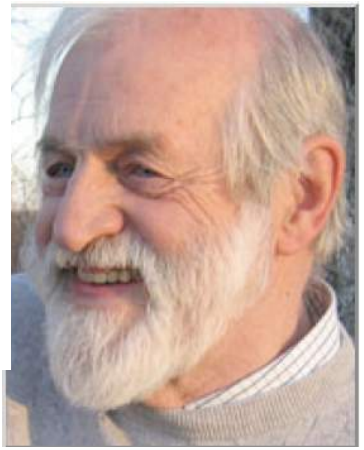
Pallud & al. 2012, *Neurosurgery*

Schmitt & al . 2013, *J Neurooncol*

The begining of the story

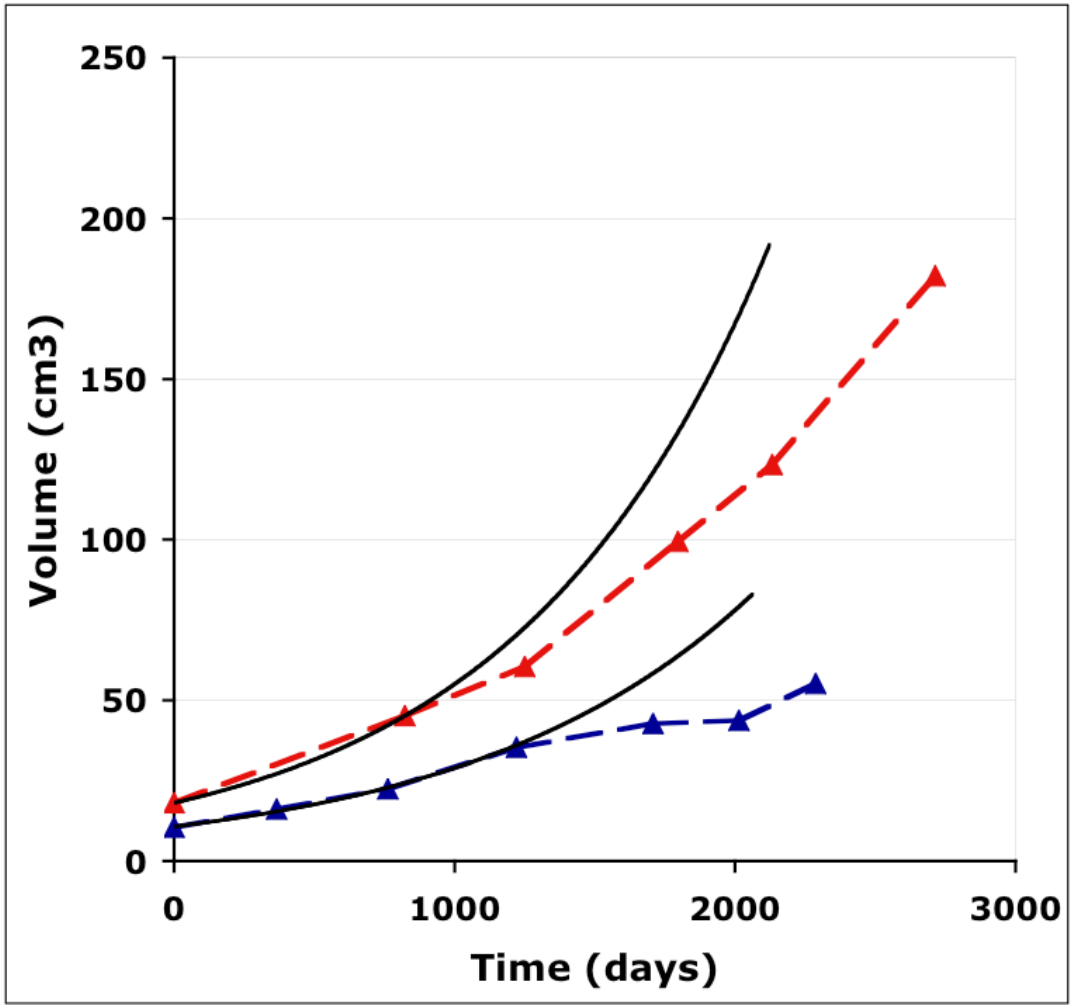


Buster Alvord



James Murray

Is tumor volume growing exponentially ?



In silico glioma growth

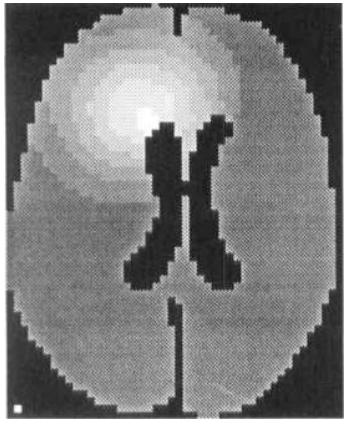
Model equation

$$\frac{\partial c}{\partial t} = \nabla . \left(D \nabla c \right) + \rho c$$

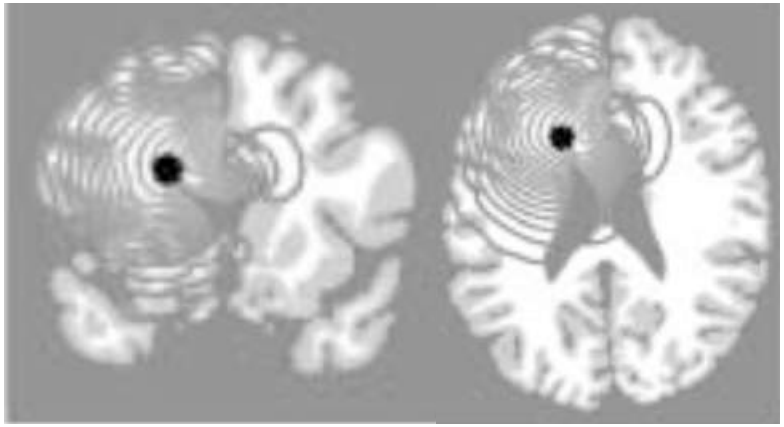
variable : cell density

tunable parameters : D,

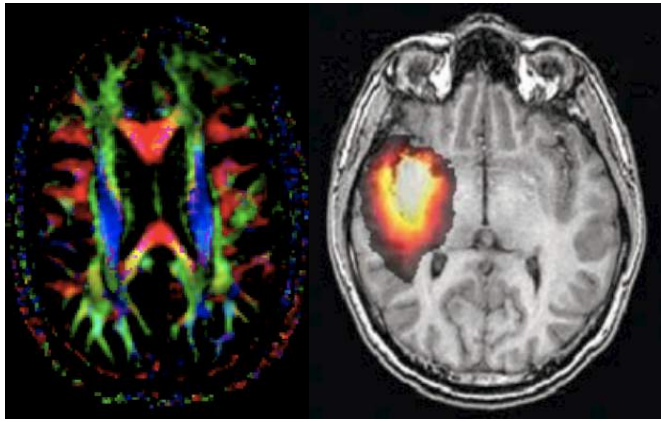
In silico glioma growth : virtual cell density maps



Tracqui & al.
Cell Prolif
1995



Swanson & al.
Cell Prolif
2000



Jbabdi & al.
MRM
2005

In silico glioma growth

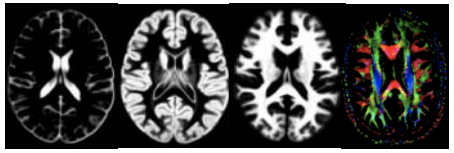
Model equation

$$\frac{\partial c}{\partial t} = \nabla . \left(D \nabla c \right) + \rho c$$

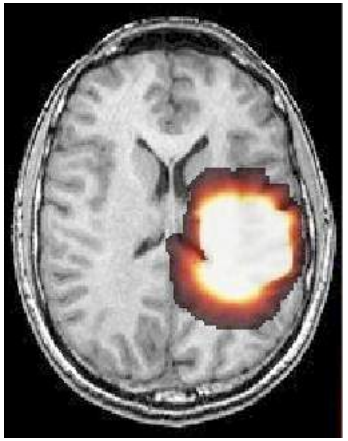
variable : cell density

tunable parameters : D,

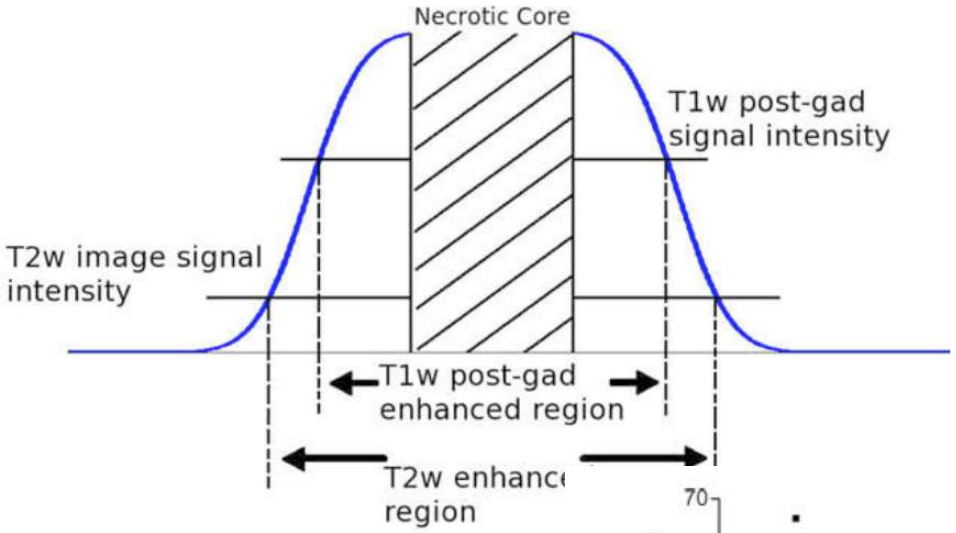
anatomical knowledge



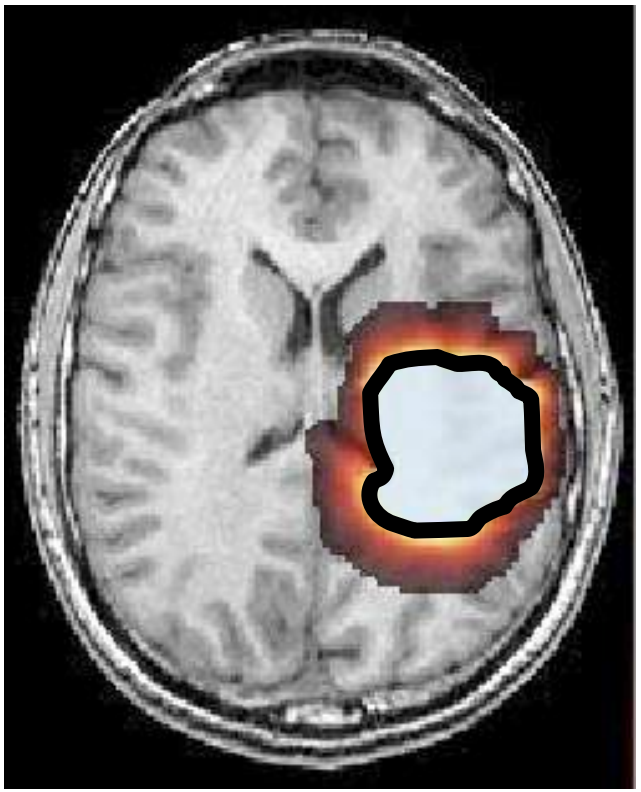
Virtual cell density maps

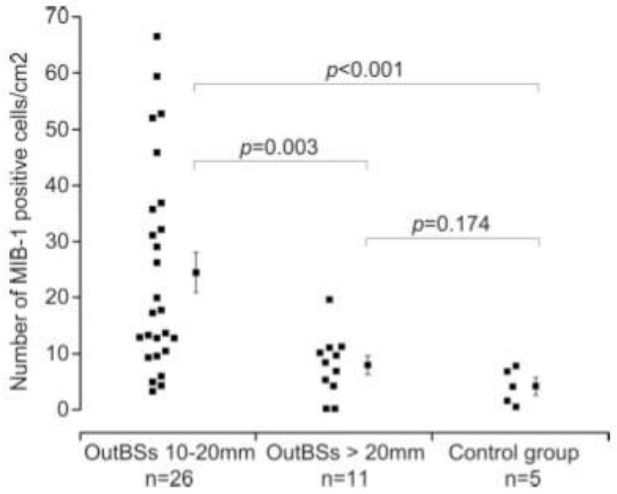


Cell density threshold of visibility



Konukoglu & al. 2011, *MedIA*

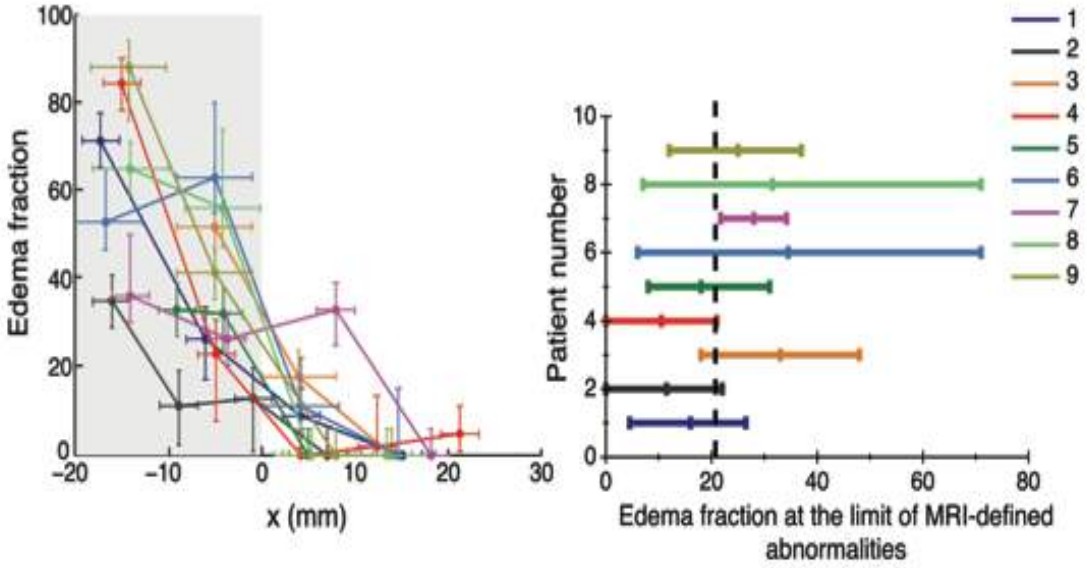


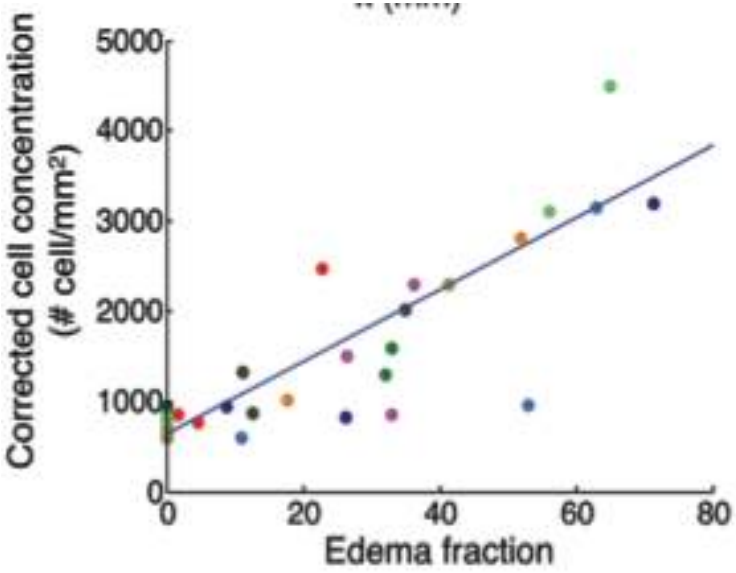


The number of cycling cells is expressed as MIB-1–positive cells per square centimeter, and the distance from MRI-defined abnormalities is expressed in millimeters. OutBS = biopsy sample taken outside MRI-defined abnormalities.

Pallud & al. 2010, *Neurology*

Cell density threshold of visibility





Gerin & al. 2013, *Neurooncol*

In silico glioma growth

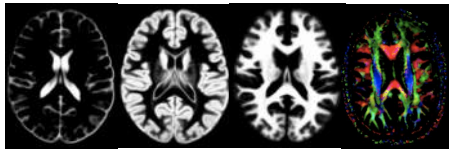
Model equation

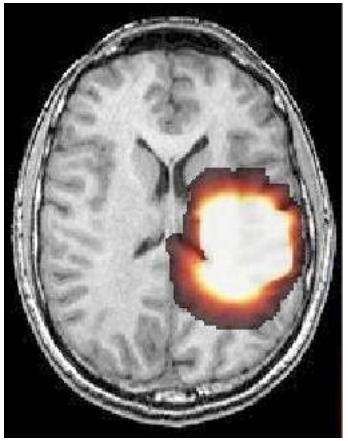
$$\frac{\partial c}{\partial t} = \nabla . \left(D \nabla c \right) + \rho c$$

variable : cell density

tunable parameters : D,

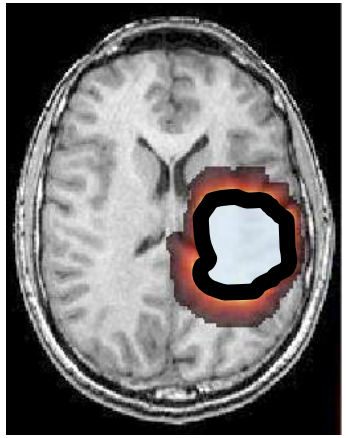
anatomical knowledge





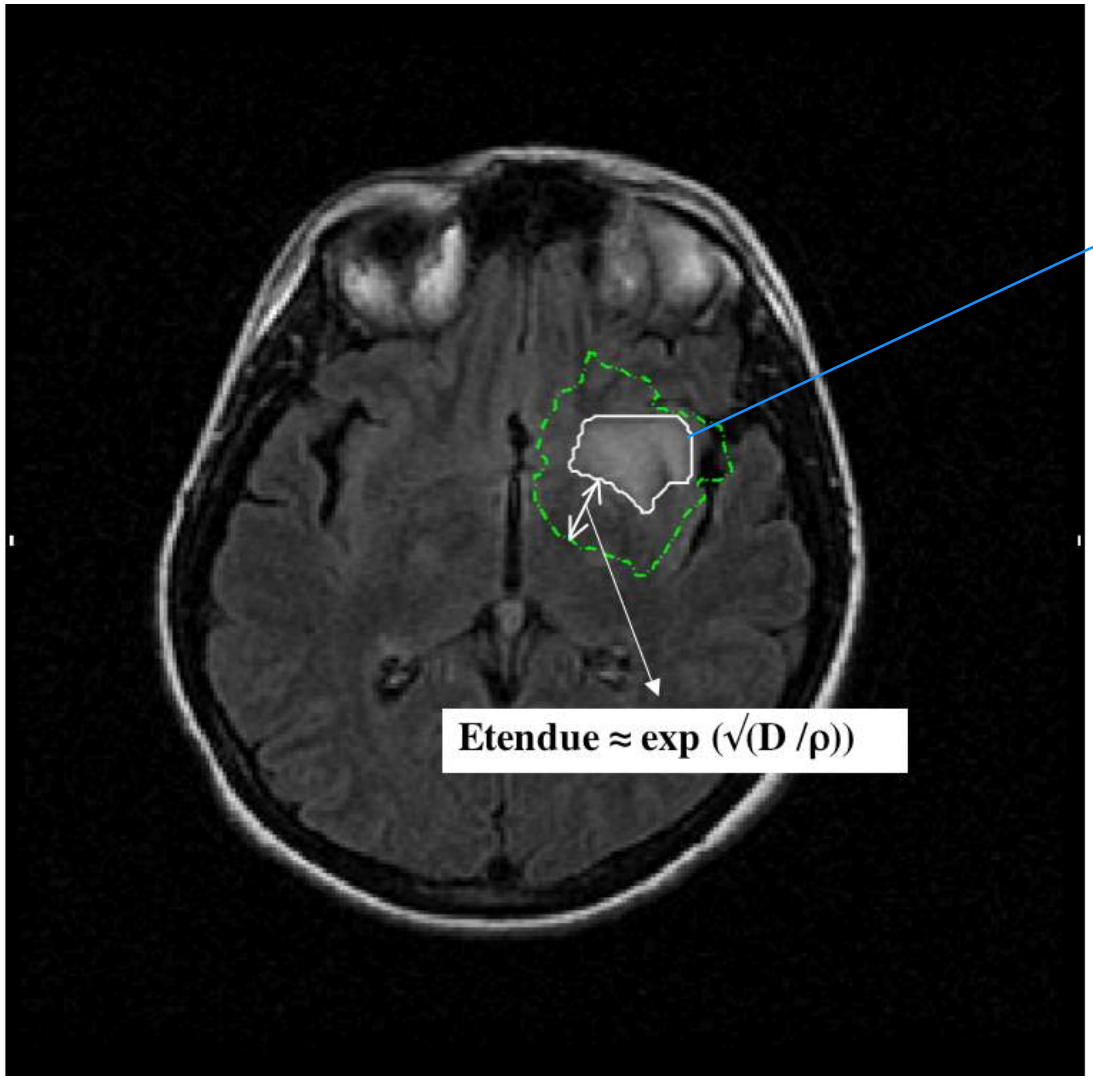
Virtual cell density maps

visibility threshold



Virtual longitudinal MRIs

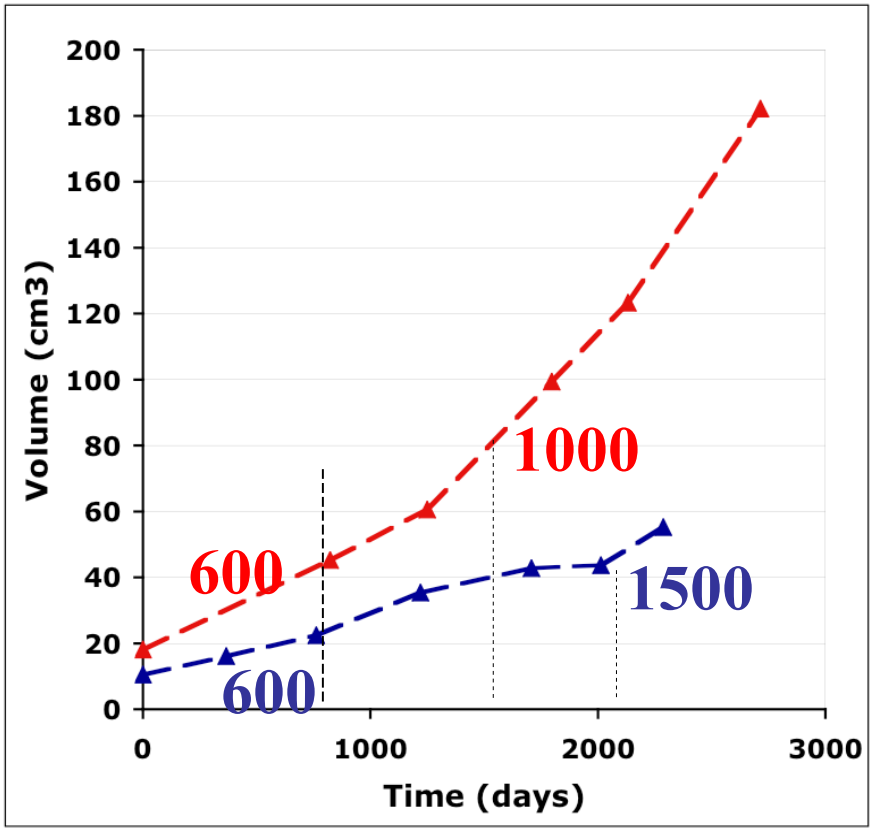
A simplified version of the model …

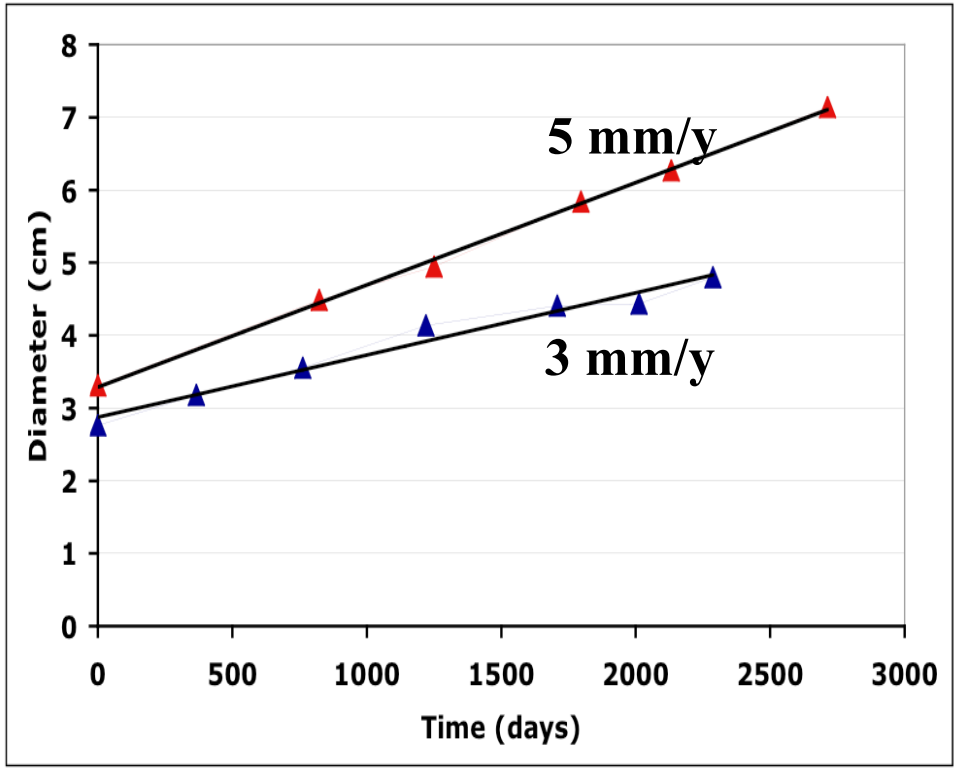


velocity
= 2√(D)

Mandonnet & al. 2008,
Neurosurg Rev

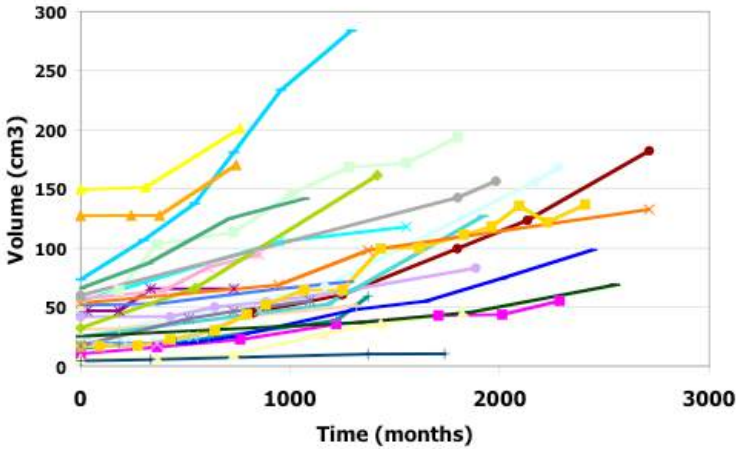
Converting volumes to diameters

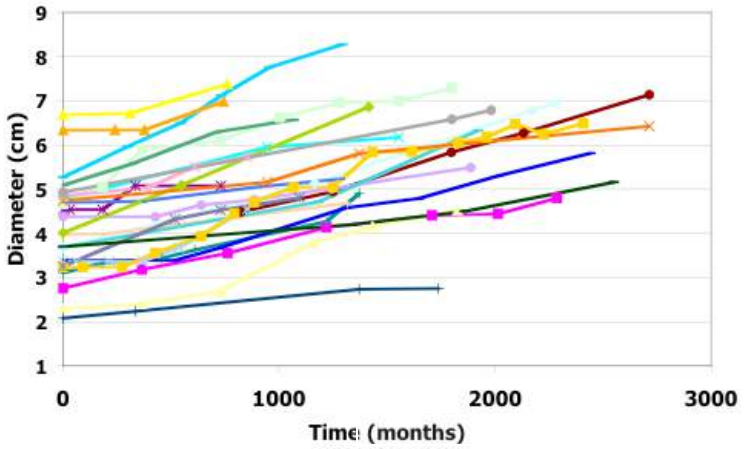


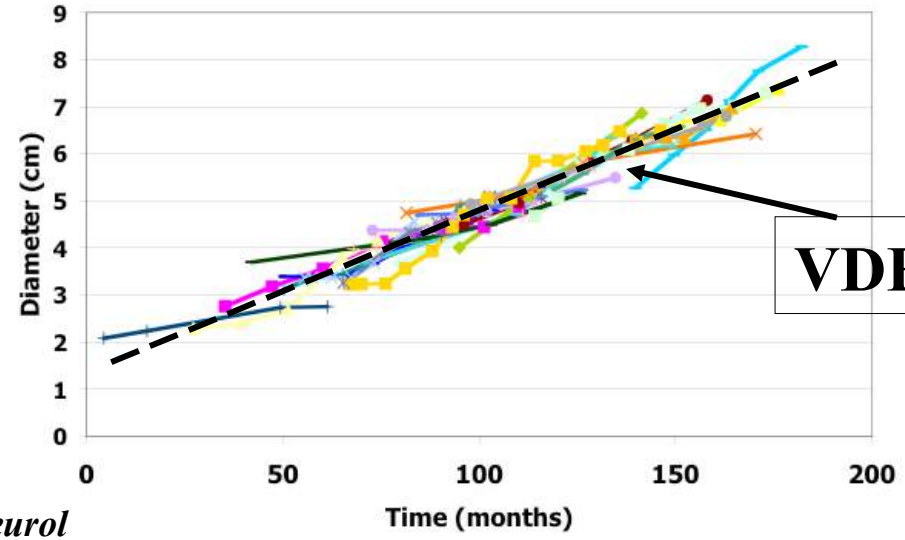


$$D=(2V)^{1/3}$$

VDE of Grade II Gliomas before treatment



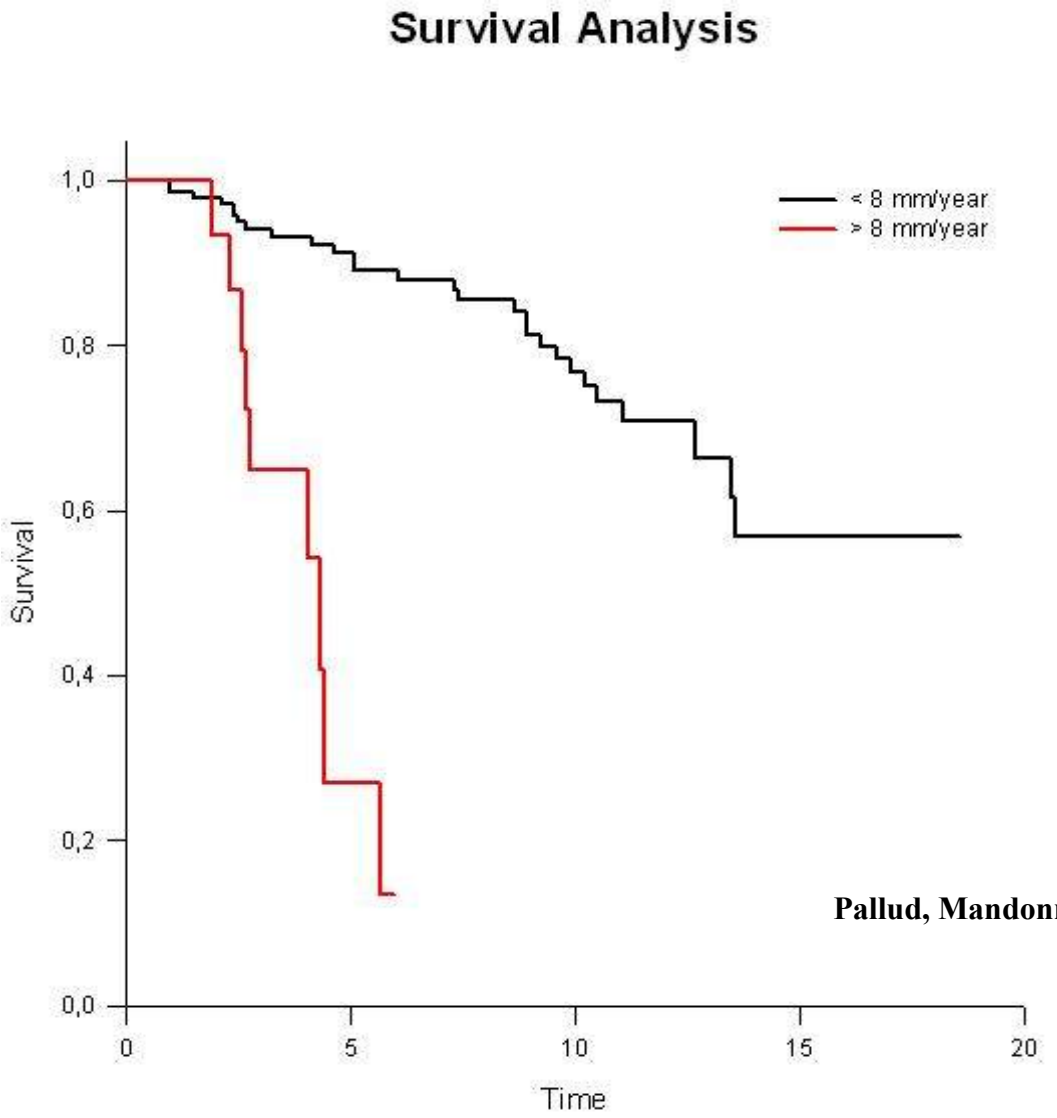




VDE = 4 mm/year

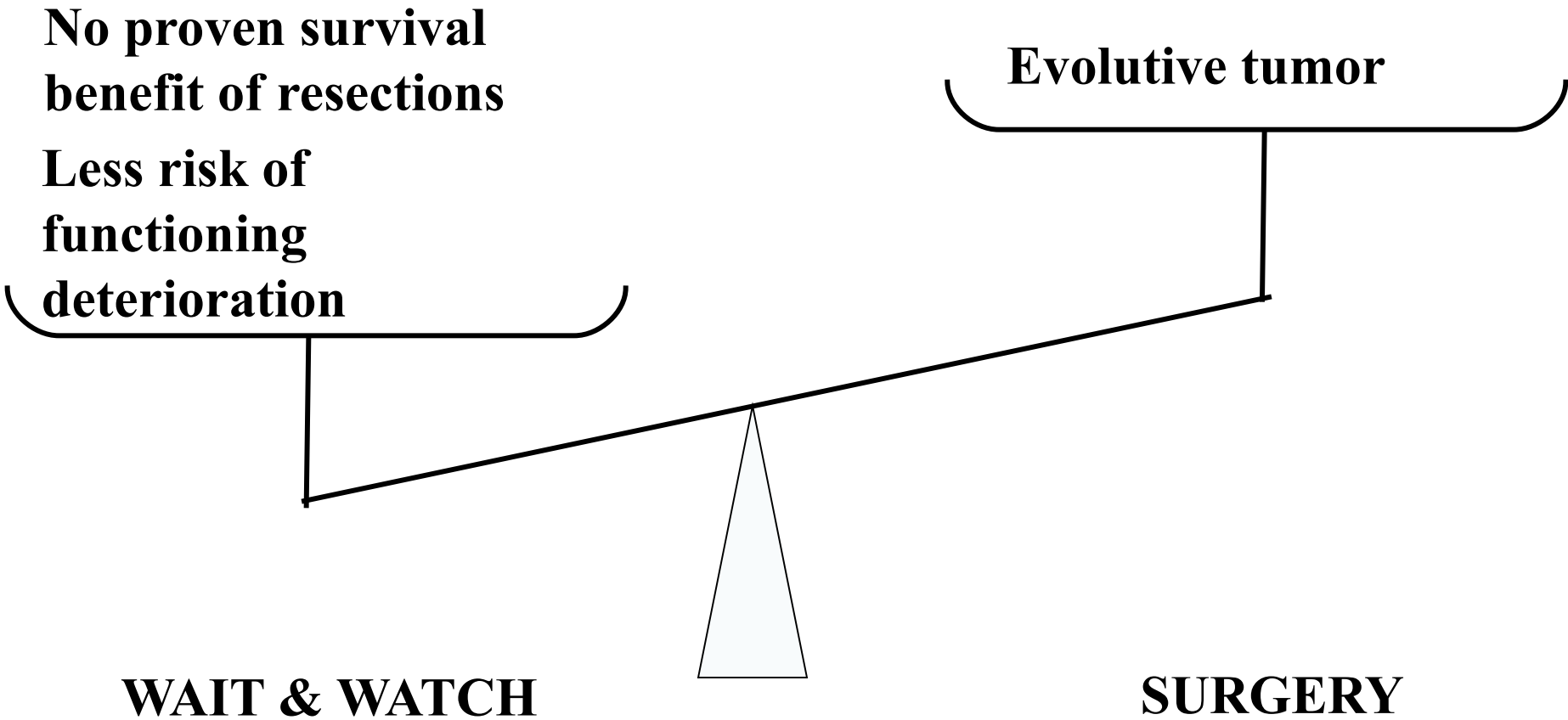
Mandonnet & al. 2003, *Ann Neurol*

Intérêt pronostique

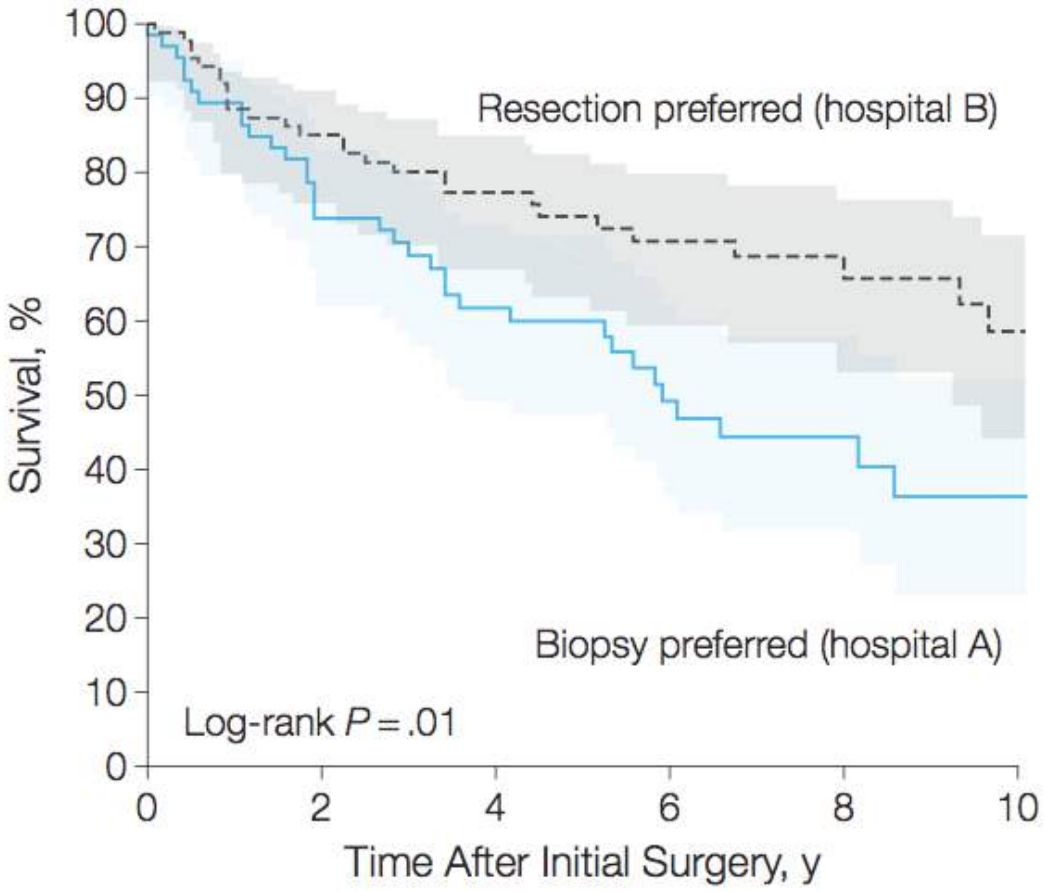


Pallud, Mandonnet & al. 2006, *Ann Neurol*

The pro & cons balance



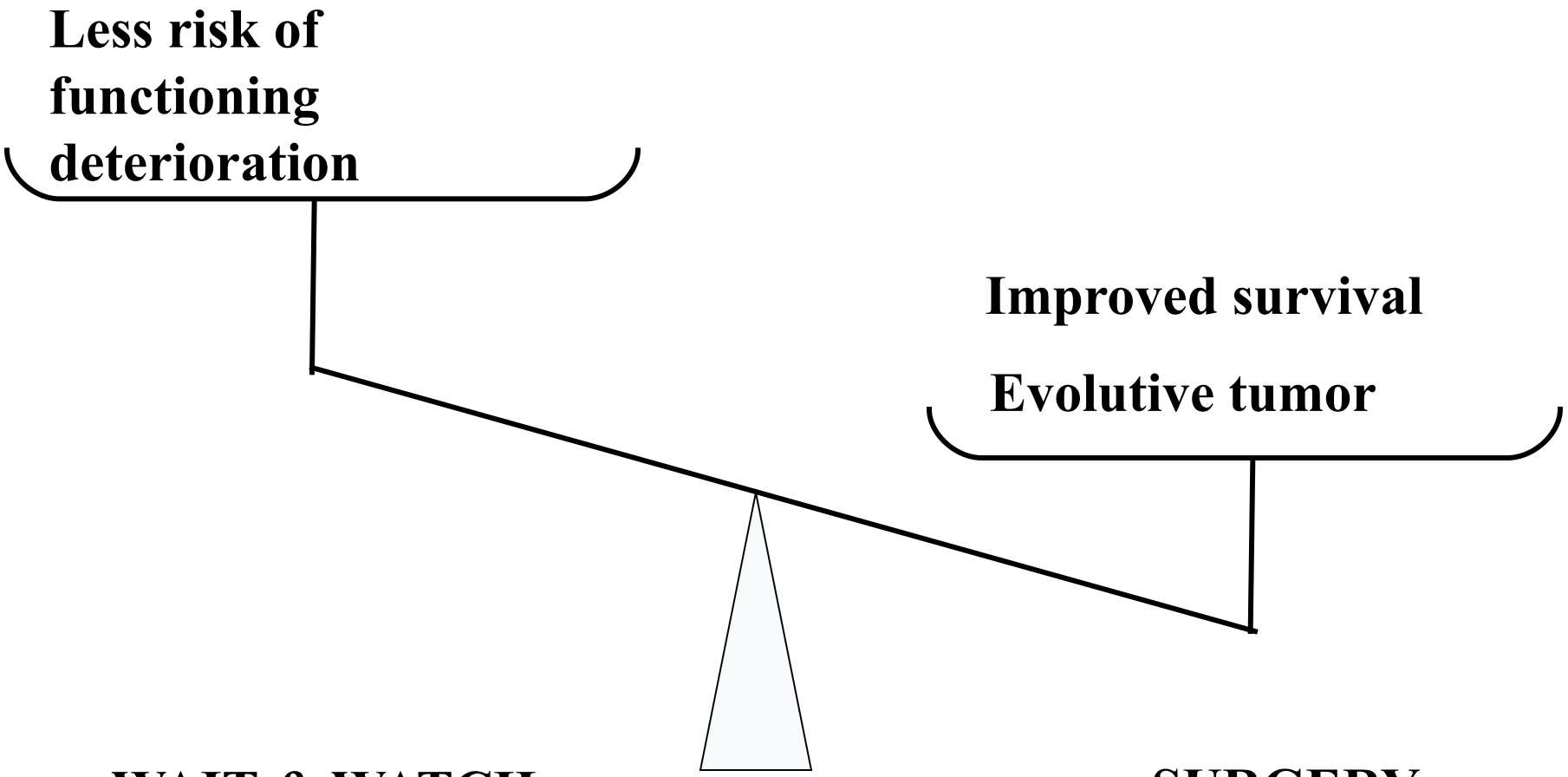
Survival benefit of surgical resection



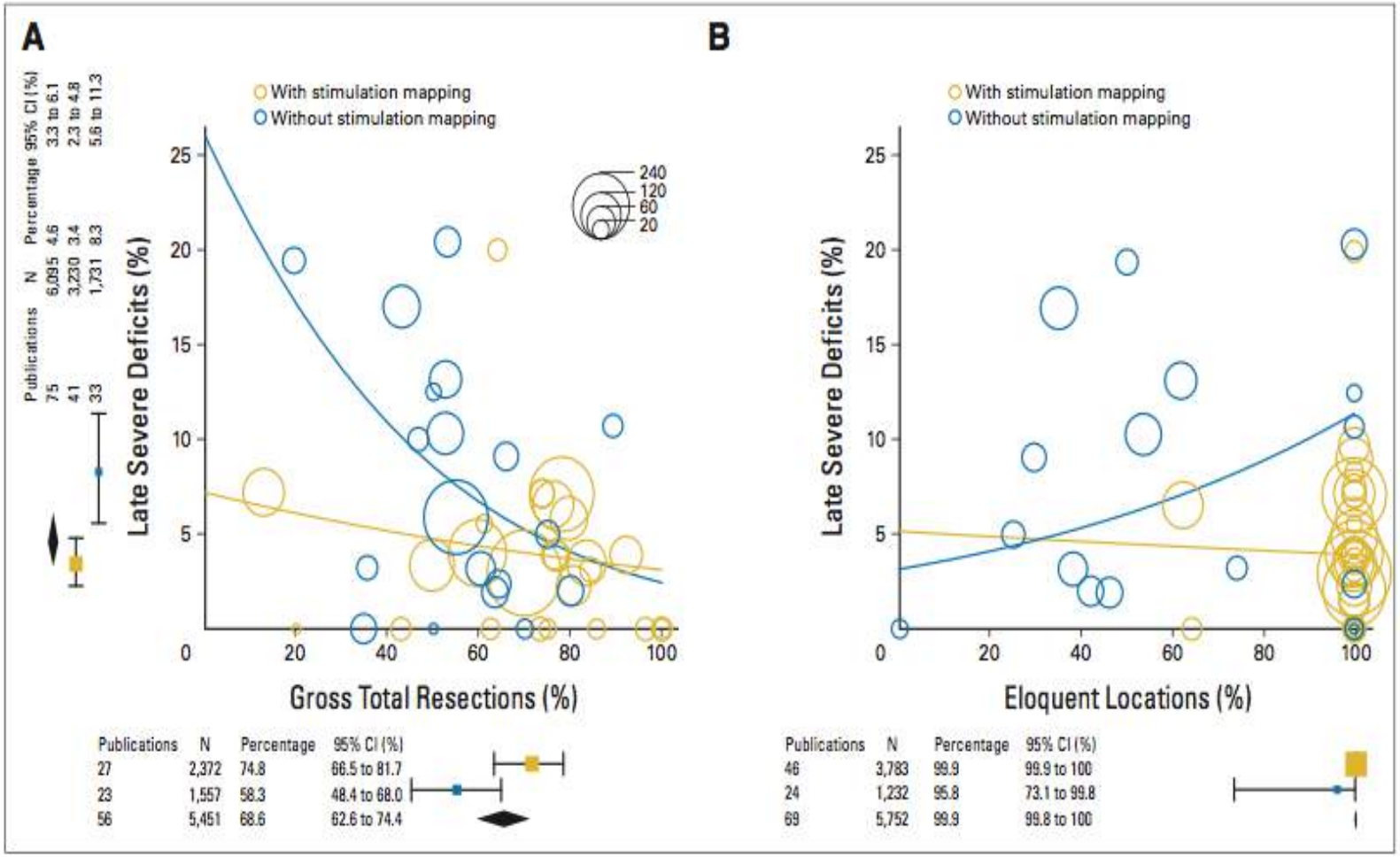
No. of patients at risk						
Biopsy preferred	66	46	36	21	11	6
Resection preferred	87	71	50	40	23	13

Jakola & al., 2012 *JAMA*

The pro & cons balance

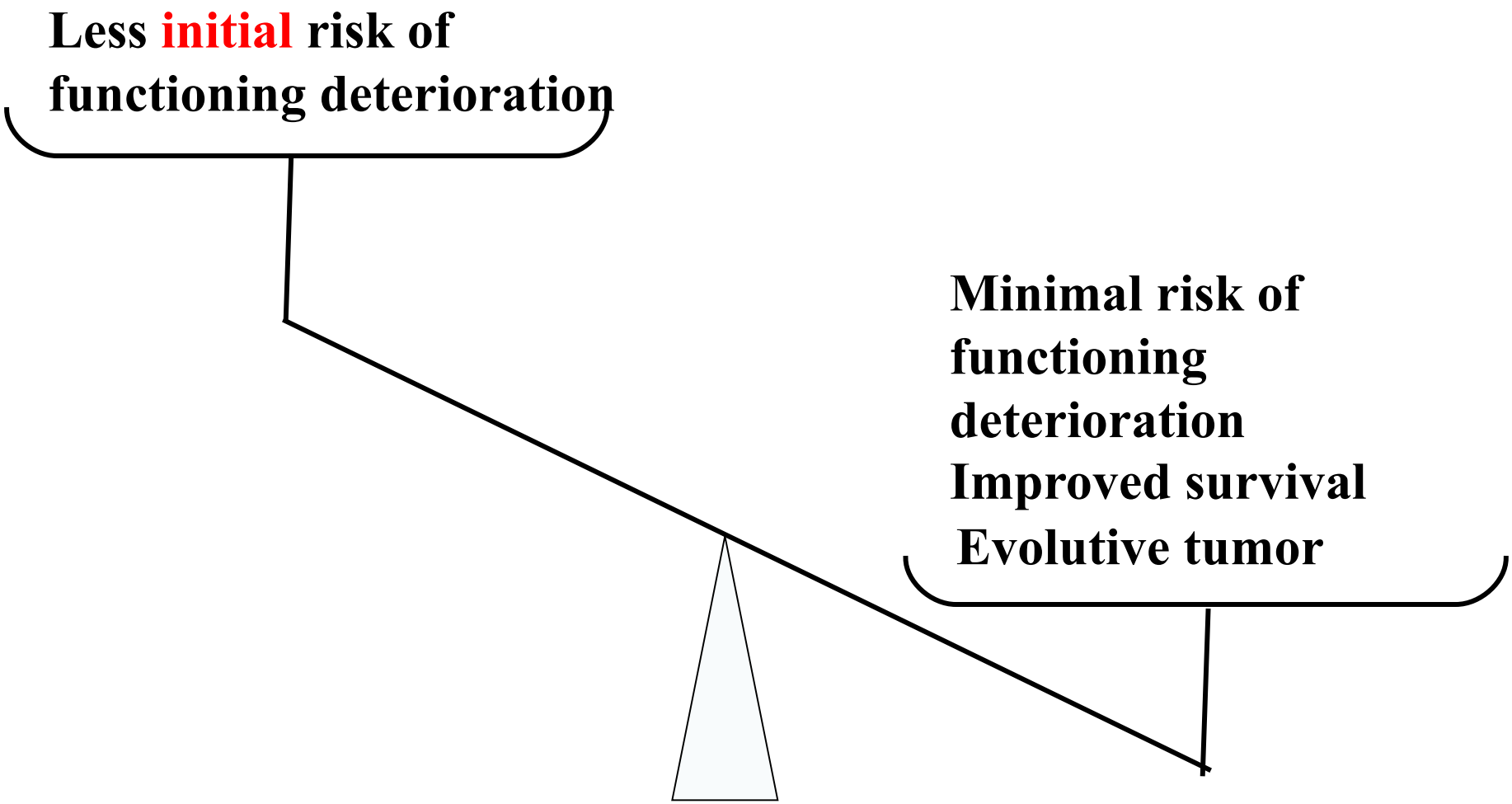


Awake surgery with brain mapping



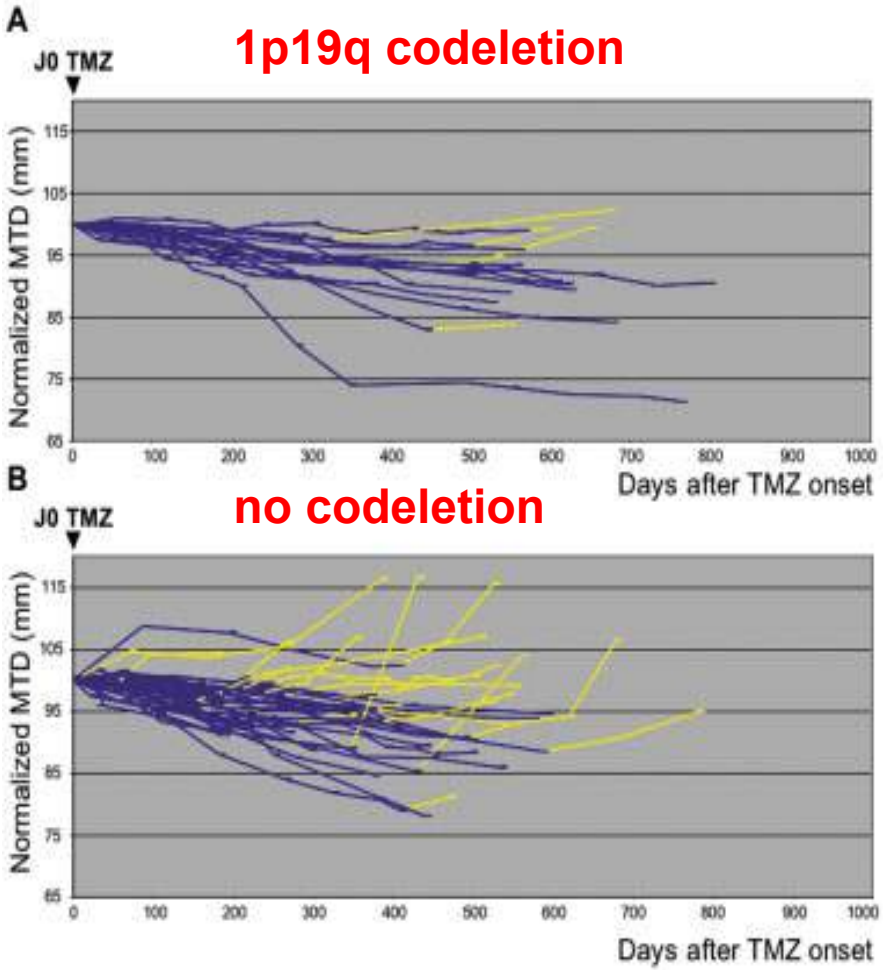
De Witt Hamer & al. 2012, *JCO*

The pro & cons balance

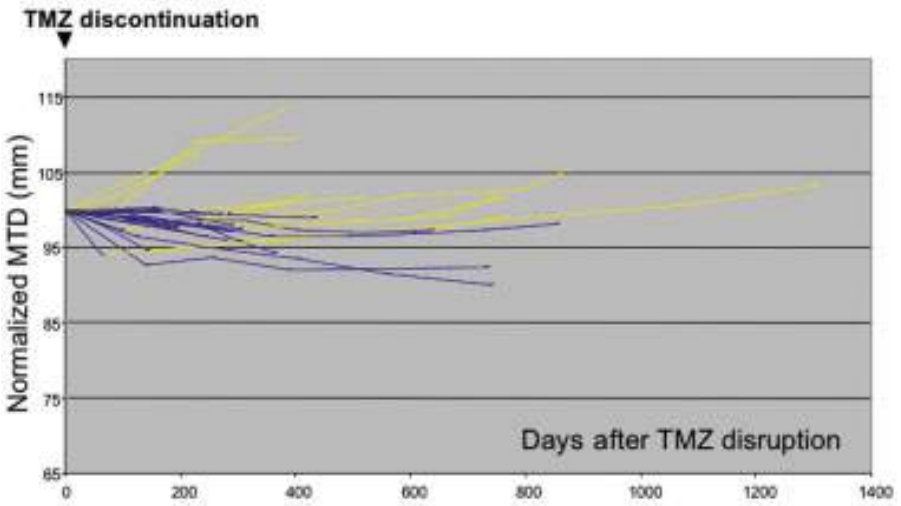


Suivi sous Temozolomide

After TMZ onset



After TMZ disruption



Ricard & al. 2007, *Annals of Neurology*

La radiothérapie

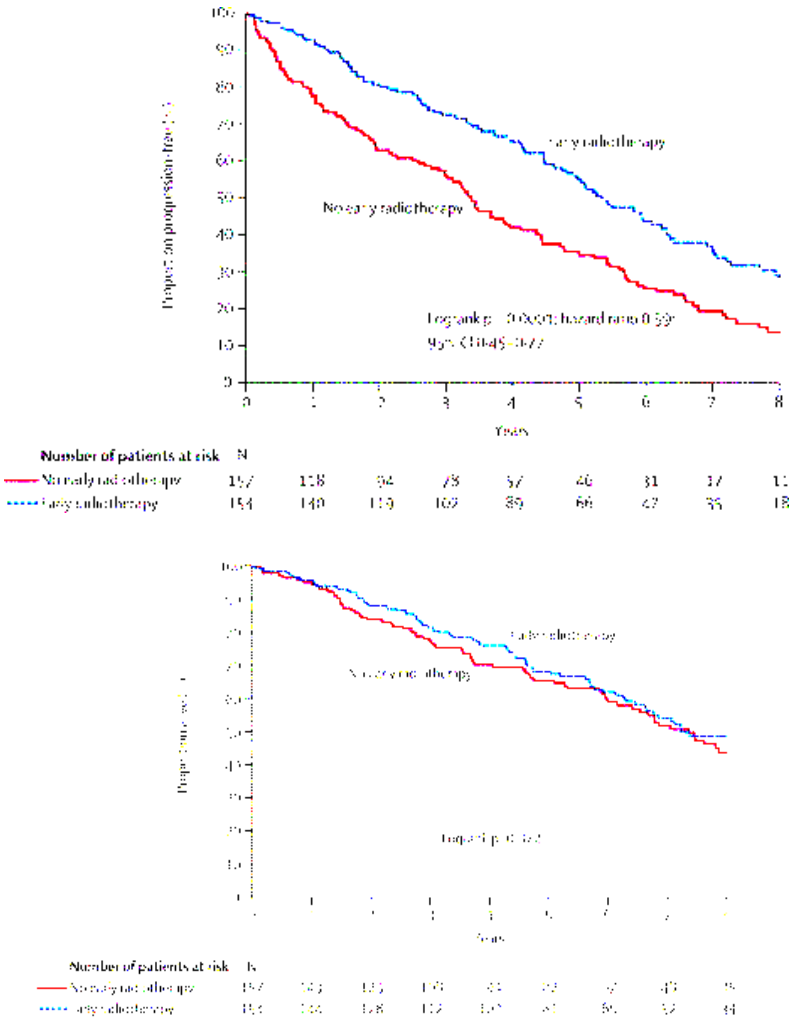
Pas d'effet dose (64 vs 50 vs 45 Gy)

Irradiation précoce

- impact PFS
- pas de bénéfice sur la survie globale

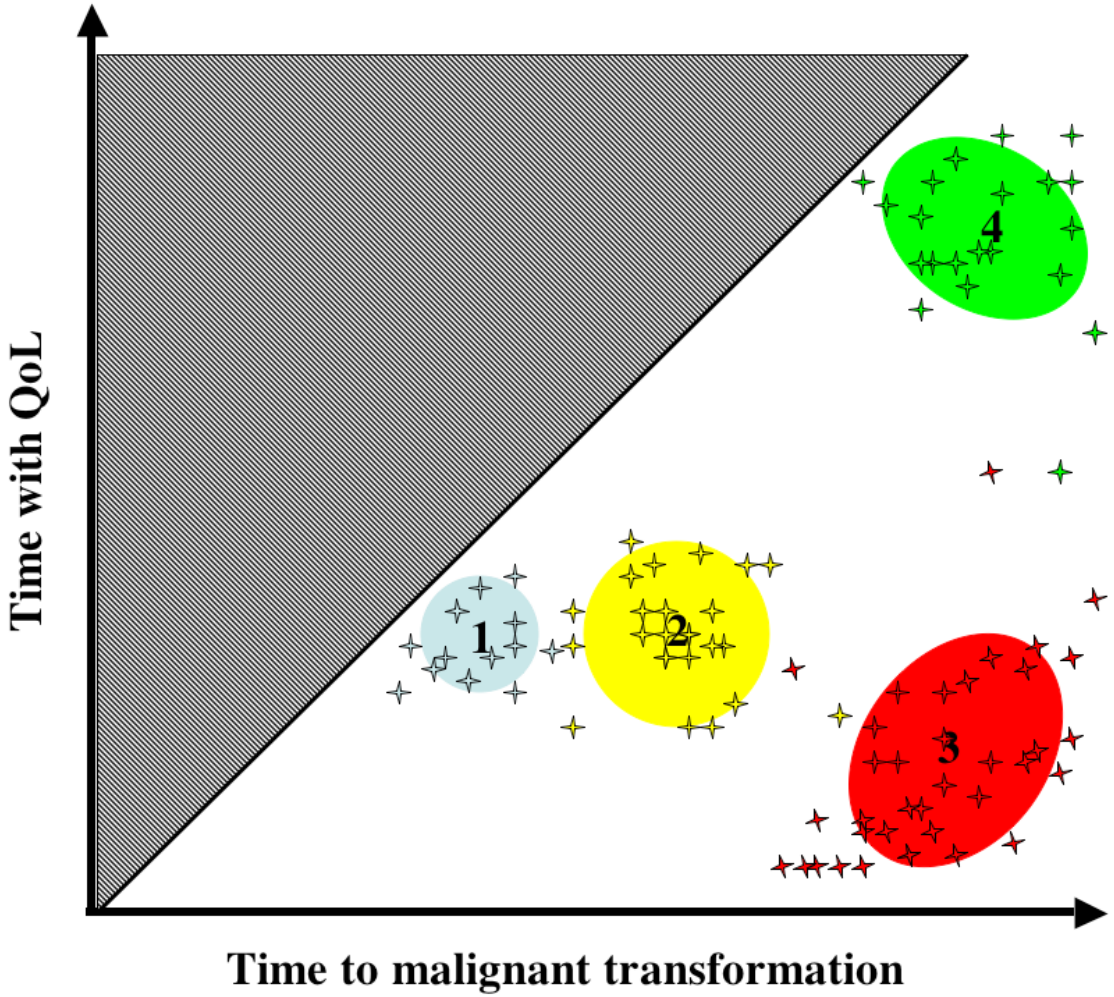
Cliniquement

- effet bénéfique sur les crises
- déficits cognitifs à long terme



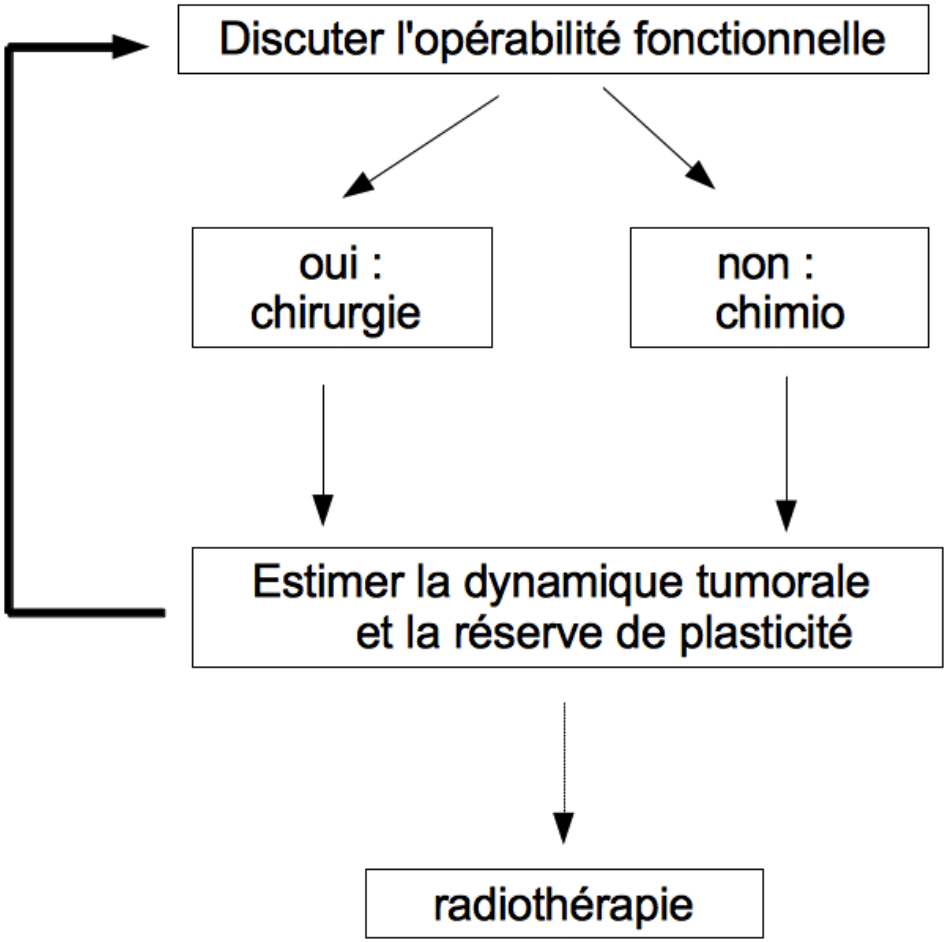
(van den Bent & al. 2005, *Lancet*)

But d'un traitement oncologique



Mandonnet & al. 2011, *J Neurooncol*

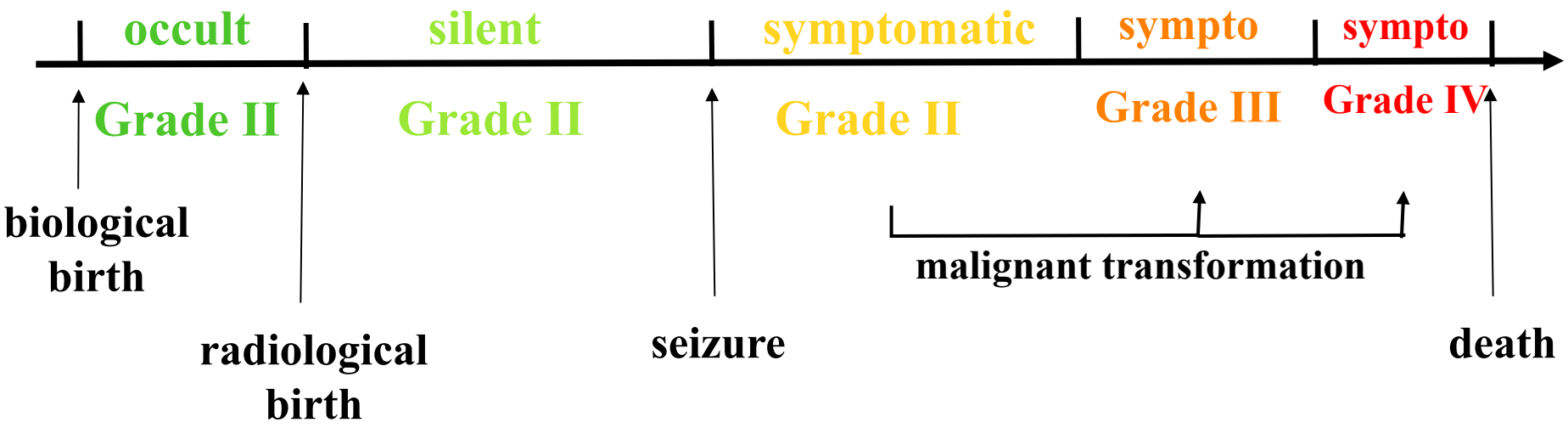
Principes du traitement



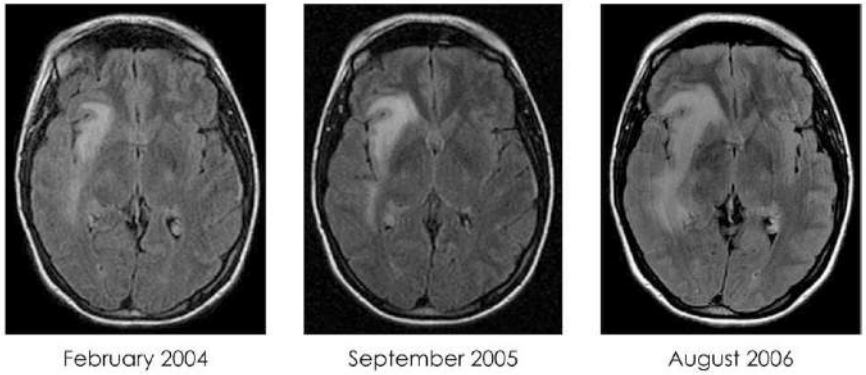
Problématiques du chirurgien

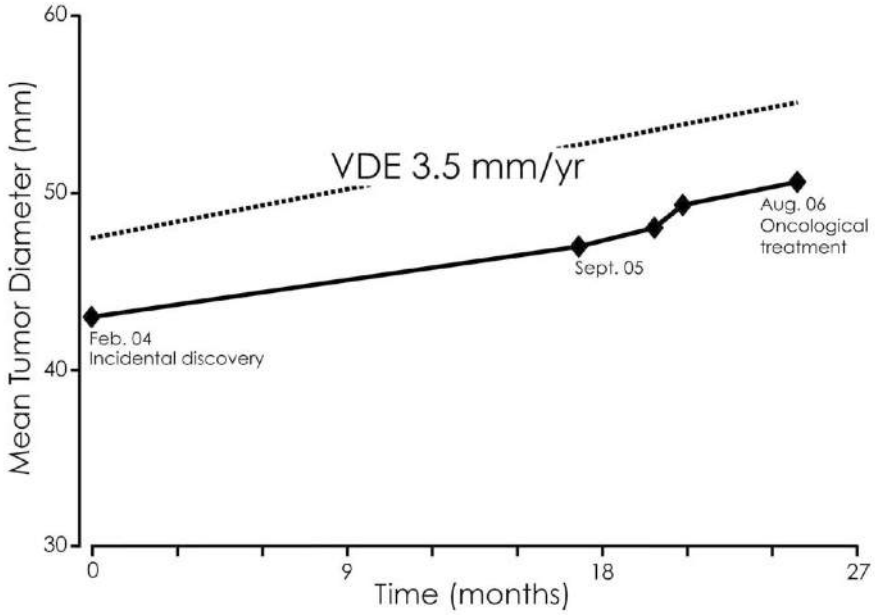
- **Quand** faut-il opérer **ce patient** ?
- Comment opérer ?

Natural history of a diffuse low-grade glioma



DLGG of incidental discovery





Two series

- **47 patients**
- **35 patients**

Small tumors

(3cm versus 5cm)

But same growth rates !!!

Pallud & al. 2010, *Annals of Neurology*

Potts & al. 2012, *JNS*

Pallud & Mandonnet 2013, *JNS*

When diagnosed, the glioma is already old …

Δt = duration of silent period = $D_{initial} / v_{initiale}$

Retrospective series of 148 patients

Δt = 15 years !!!

Pallud & al. , 2013. ***Acta Neurochir***

Silent period : is it when we missed the action ?

During these 15 years of silent evolution :

- microscopic cellular invasion (undetectable on MRI)
→ no surgical cure

- acquisition and accumulation of genomic mutations
→ chemoresistance

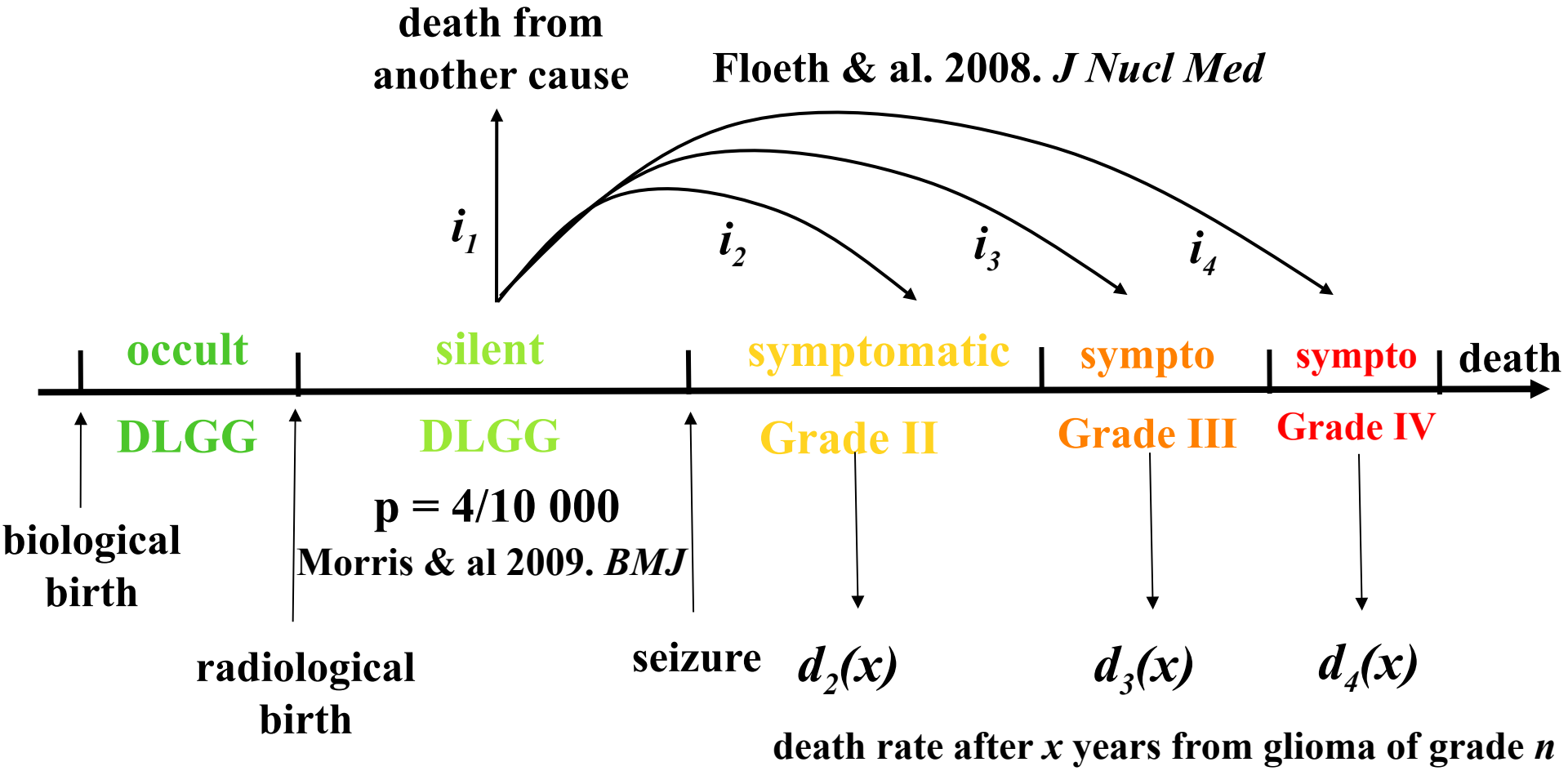
Should we set a screening policy ?

Figure 6: Mobile MRI unit at the reflecting pool in Washington, DC offering scans to members of the U.S Congress and their staffs. Results? Classified.

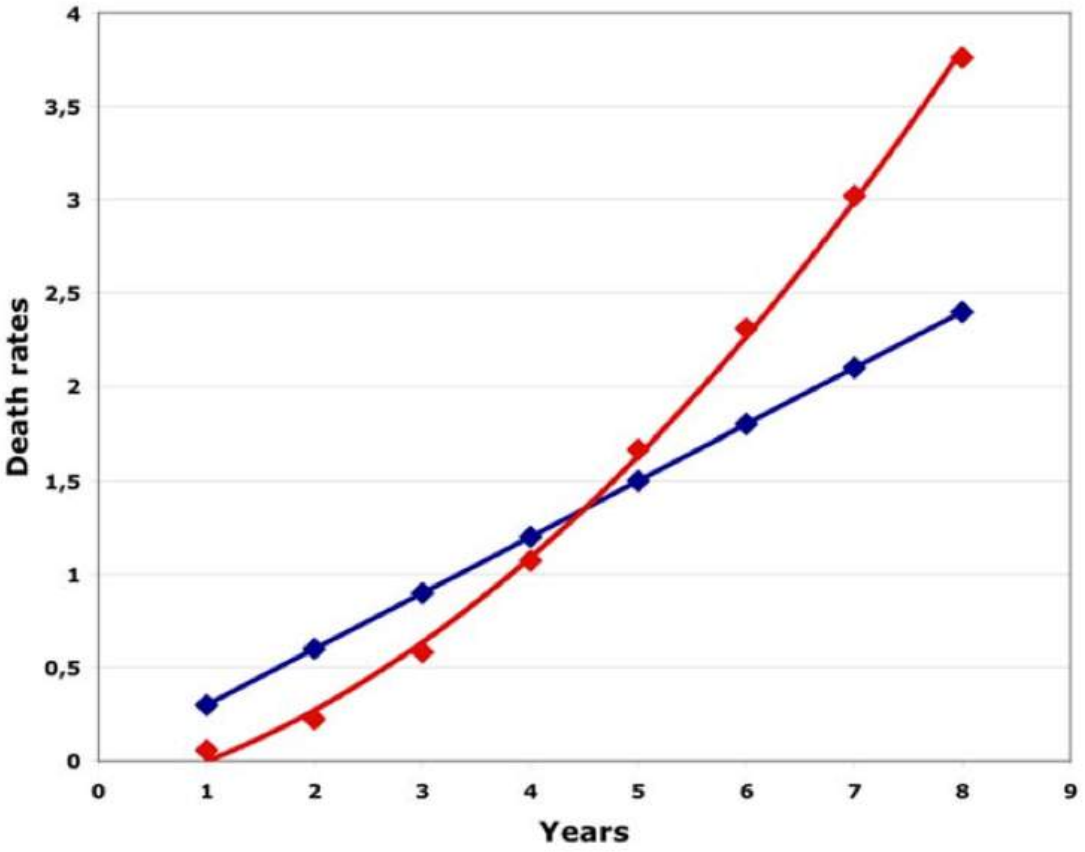
Kelly P. 2010, *Surgical Neurology International*

What about overdiagnosis (and overtreatment) ?

Natural history of silent diffuse low-grade glioma



Dying *from* versus *with* a silent diffuse low-grade glioma

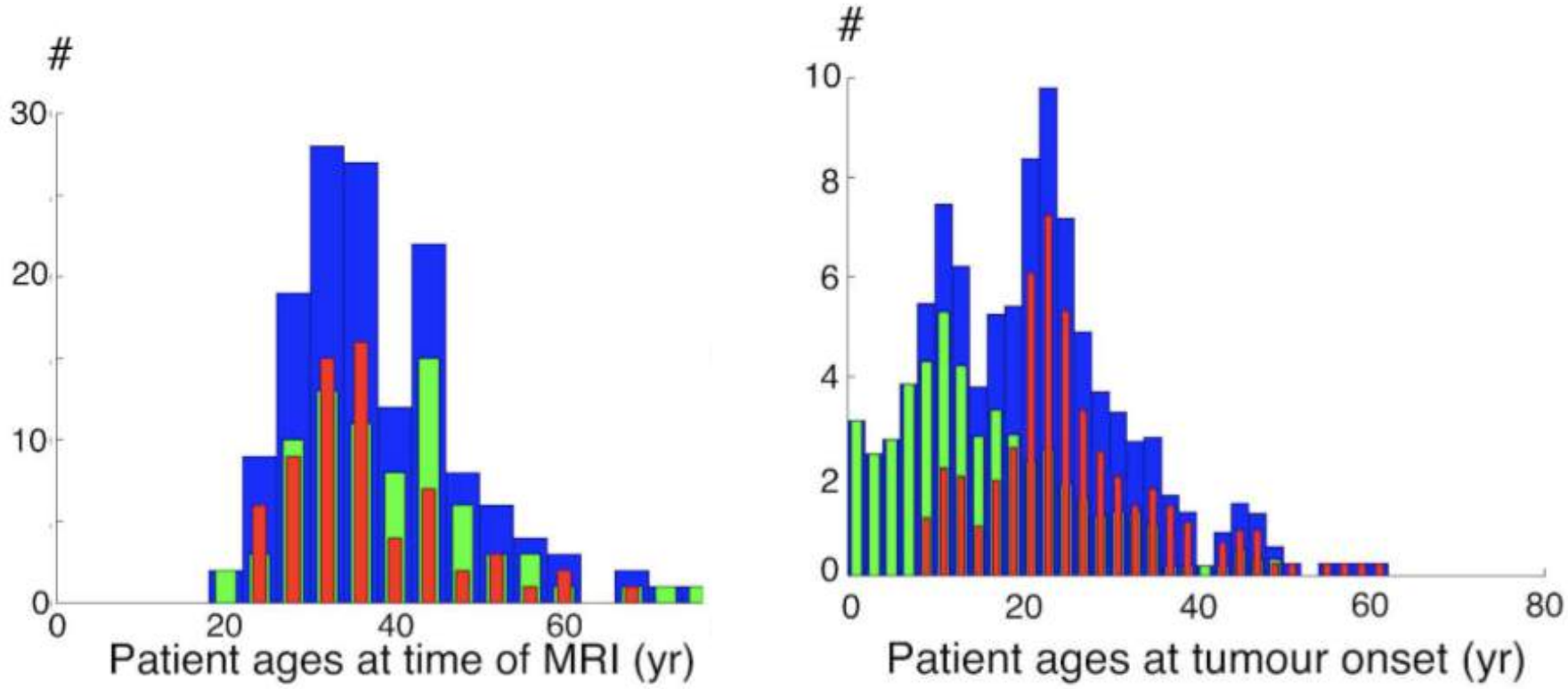


Mandonnet & al. 2014
Cancer

Cost-effectiveness analysis

- **Cost for one MRI (single flair sequence) : $ 150**
- **For 10 000 people : $ 1 500 000**
- **Among these : 4 people with a silent DLGG**
- **Cost of a person-year : $ 120 000**
- **Balance reached if early treatment saves 3 years of active life**

Using the time-machine



Gerin & al. 2011, *Cell Prolif*

Automated tools of MRI analysis

- **Class of age : about 750 000 people in France**
  - 750 000 MRIs = 250 full time neuroradiologists

- **Need of computational algorithms**
  - evaluate their sensitivity and specificity
  - assume a sensitivity of 100 % :
    - A specificity as low as 10 % : 4 x 75 x 10 to be interpreted by an expert (= 1 neuroradiologist full time)

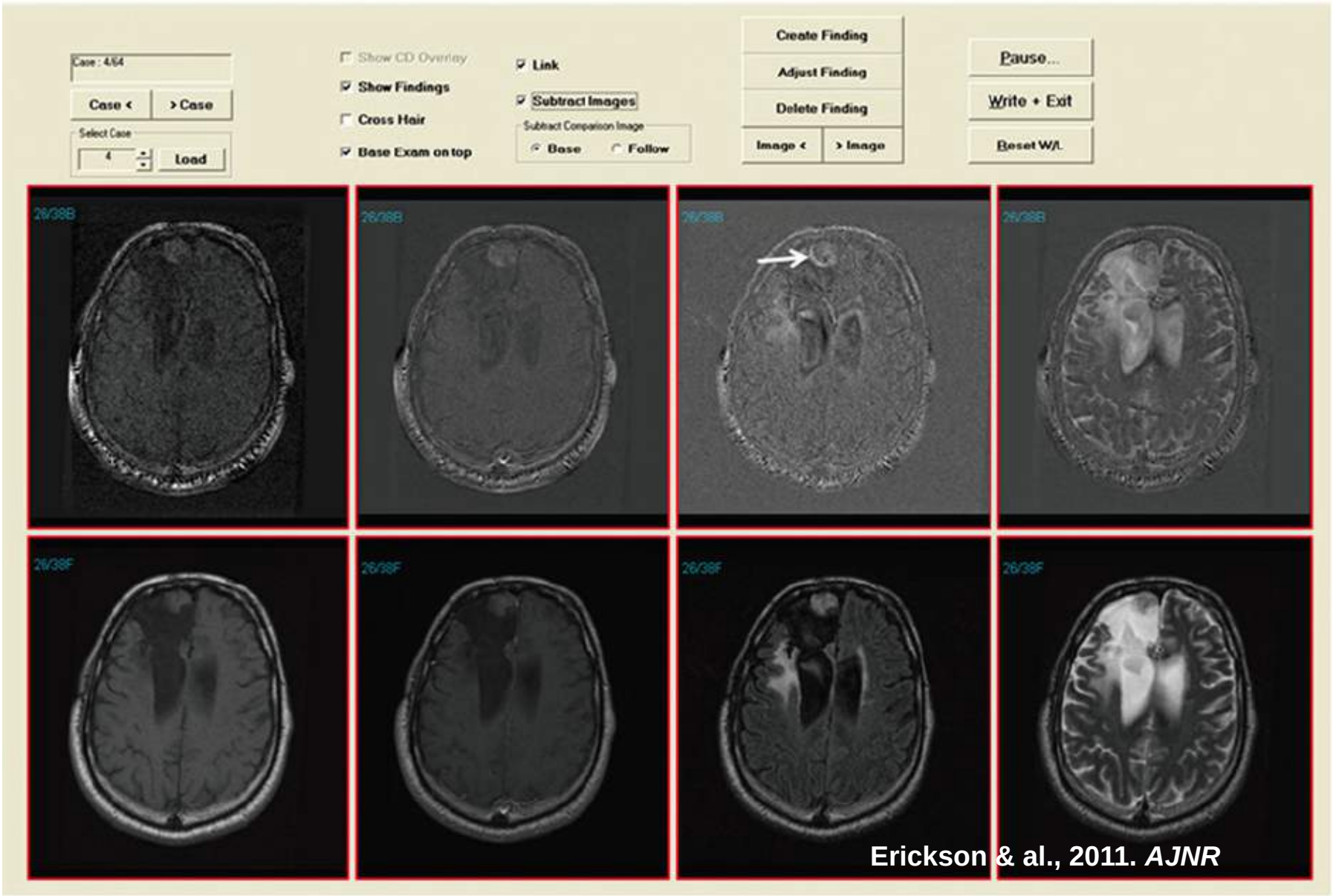
Quand opérer ce patient ?

Quand on espère pouvoir améliorer sa survie
(tout en conservant ou améliorant sa qualité de vie)

Modifier l'histoire naturelle

- quelle est la dynamique du patient ?

  → vitesse d'évolution


Case : 4/64
Case <
> Case
Select Case
4
Load
Show CD Overlay
Show Findings
Cross Hair
Base Exam on top
Link
Subtract Images
Subtract Comparison Image
Base
Follow
Create Finding
Adjust Finding
Delete Finding
Image <
> Image
Pause...
Write + Exit
Reset W/L
26/38B
26/38F
Erickson & al., 2011. *AJNR*

How to match contrast between two images ?

$$H_{midway} = \left(\sqrt{H_{I_1}^{-1} H_{I_2}^{-1}} \right)^{-1}$$

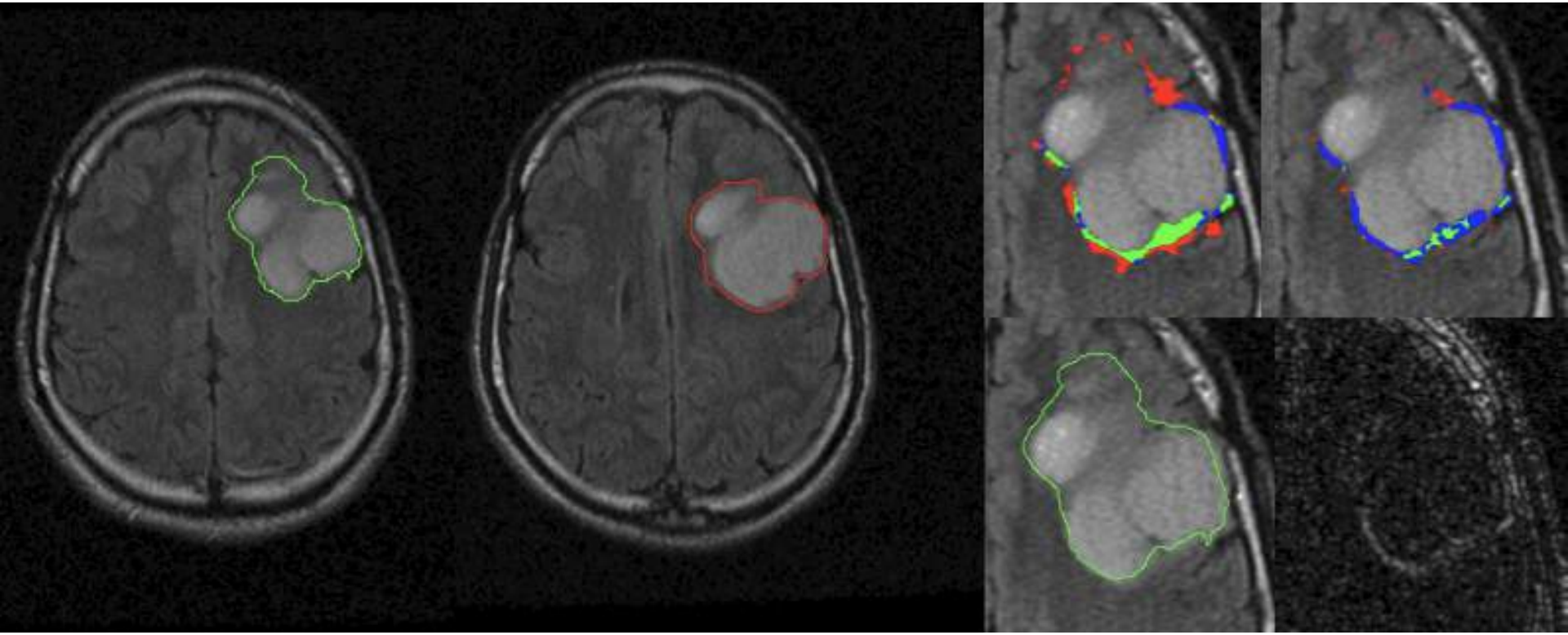
$$I_{midway1} = H_{midway}^{-1} \circ H_{I_1}(I_1) = \sqrt{I_1 \times H_{I_2}^{-1} \circ H_{I_1}(I_1)}$$

$$I_{midway2} = H_{midway}^{-1} \circ H_{I_2}(I_2) = \sqrt{I_2 \times H_{I_1}^{-1} \circ H_{I_2}(I_2)}$$

Angelini & al., 2012, *MedIA*

Delon J. 2004. *Journal of Mathematical Imaging and Vision*

Computational methods of change detection



Angelini & al. 2011, *MedIA*

Quand opérer ce patient ?

Quand on espère pouvoir améliorer la survie
tout en conservant ou améliorant sa qualité de vie

Modifier l'histoire naturelle

- quelle est la dynamique ?

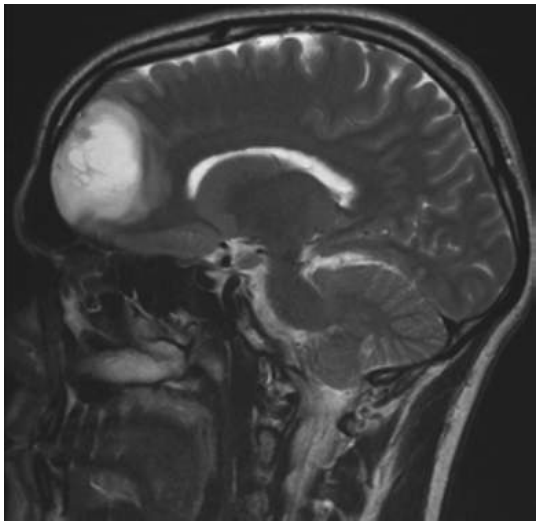
  → vitesse d'évolution

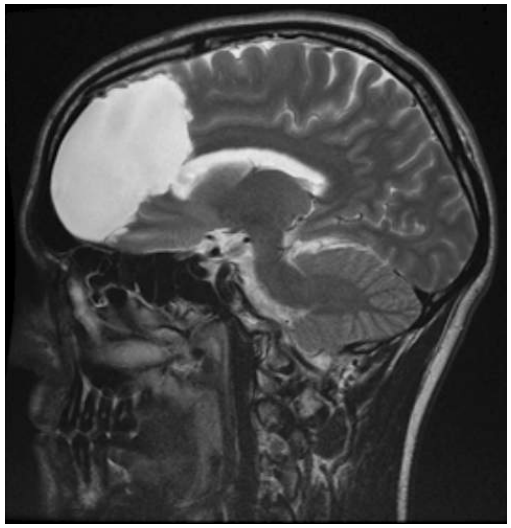
  → invasivité

Effect of surgery

Swanson & al. 2003, *J Neurol Sc*

Grade	ρ (1/day)	D (cm^2/day)	Gross Total % Resected	Survival Time (days)	Extensive % Resected	Survival Time (days)
HH	0.012	0.0013	36.9	127	86.7	254
HL	0.012	0.00013	95.5	421	99.9	869
LH	0.0012	0.0013	12.5	130	55.7	1079
LL	0.0012	0.00013	36.9	1273	86.7	2537





Yordanova & al. 2011, *JNS*

The « inverse » problem

D, : tunable parameters

How to determine their values for a specific patient ?

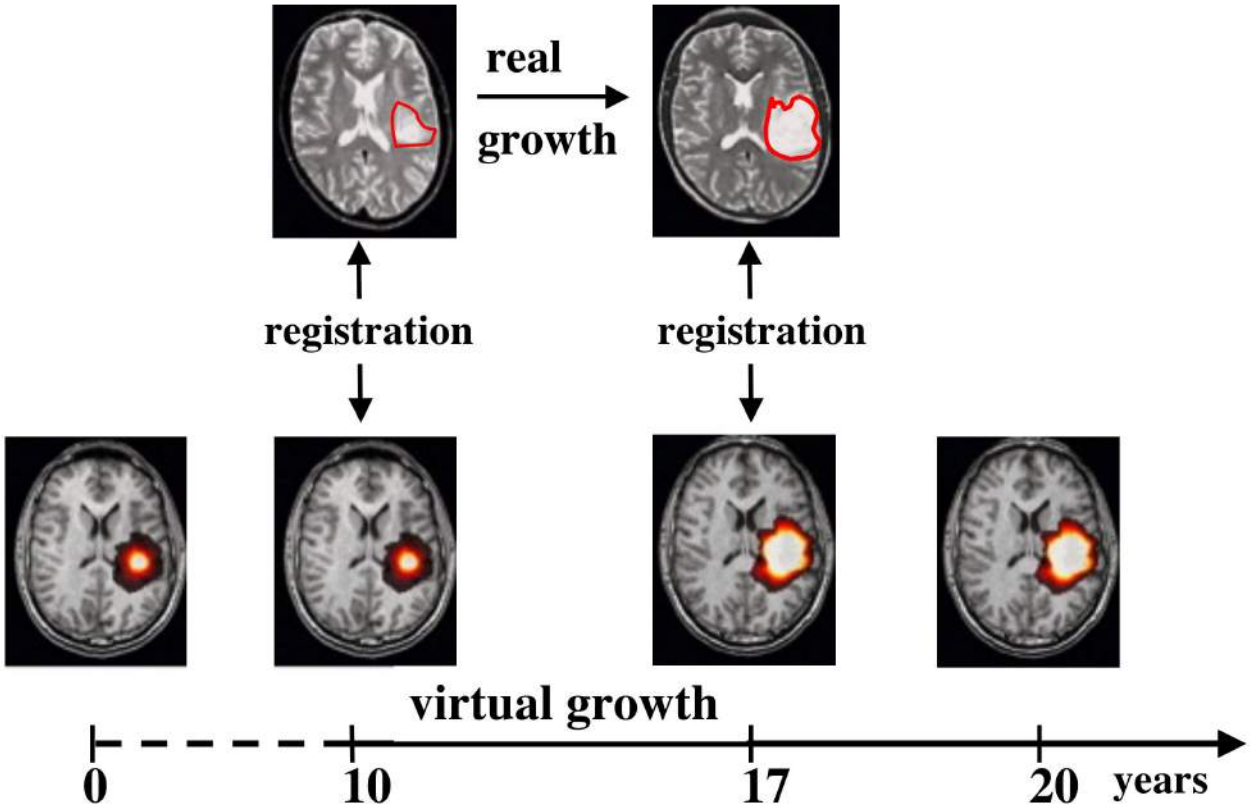
1. Cell biology measurements

- : MIB-1, cell cycle time ?

- D : *in vitro* cell migration experiments

2. Image-based determination

Making the model patient-specific



Angelini & al. 2007, *Current Medical Imaging Reviews*

Towards patient-specific modeling

(a) First Image

(b) 2^{nd} image taken 39 days after the first one

(c) 3^{rd} image taken 121 days after the first one

(d) 4^{th} image taken 210 days after the first one

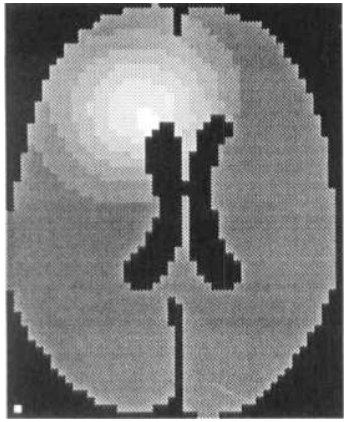
(e) Final image taken 390 days after the first one

(f) Another slice of the final image

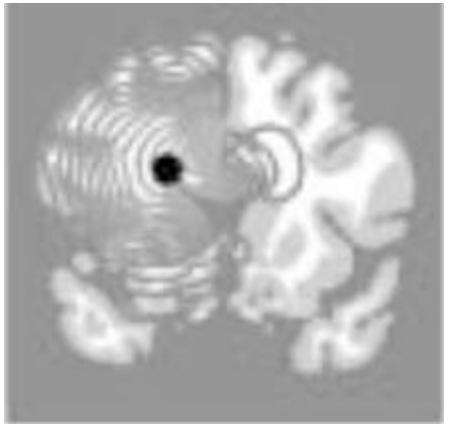
ρ(set)	d_w	d_g
0.008 $1/day$	0.15 mm^2/day	5x10^{-4} mm^2/day

Konukoglu & al. 2010, *IEEE*

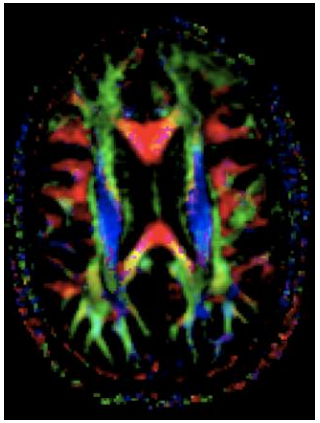
In silico glioma growth : virtual cell density maps



Tracqui & al.
Cell Prolif
1995



Swanson & al.
Cell Prolif
2000



Jbabdi & al.
MRM
2005

?

cell
density
estimation

?

2015

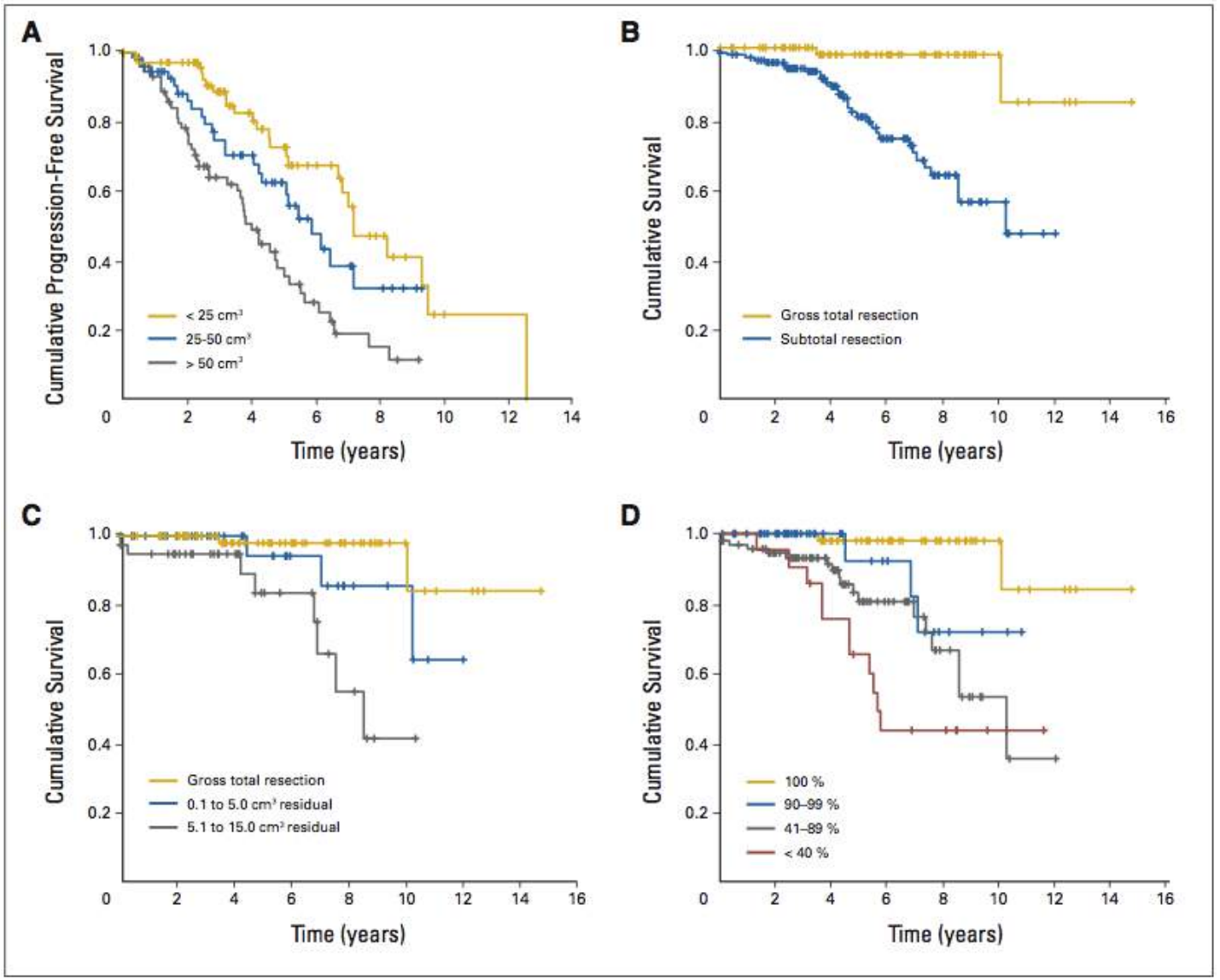
Quand opérer ce patient ?

Quand on espère améliorer la survie
(tout en conservant ou améliorant sa qualité de vie)

Modifier l'histoire naturelle

- quelle est la dynamique ?
  - → vitesse d'évolution
  - → invasivité
- quelle sera l'étendue de l'exérèse en allant jusqu'aux limites fonctionnelles ?

Survival benefit of surgical resection



Smith & al., 2008 *JCO*

Quand opérer ce patient ?

Quand on espère améliorer la survie
tout en conservant ou améliorant sa qualité de vie

Modifier l'histoire naturelle

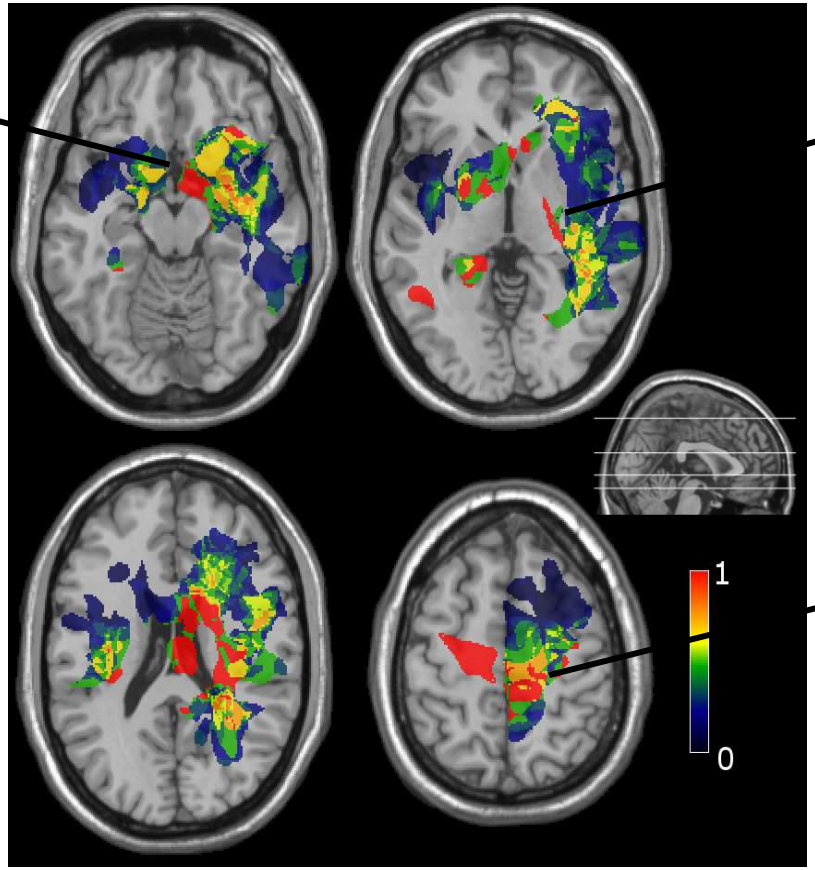
- quelle est la dynamique ?

  → vitesse d'évolution

  → invasivité

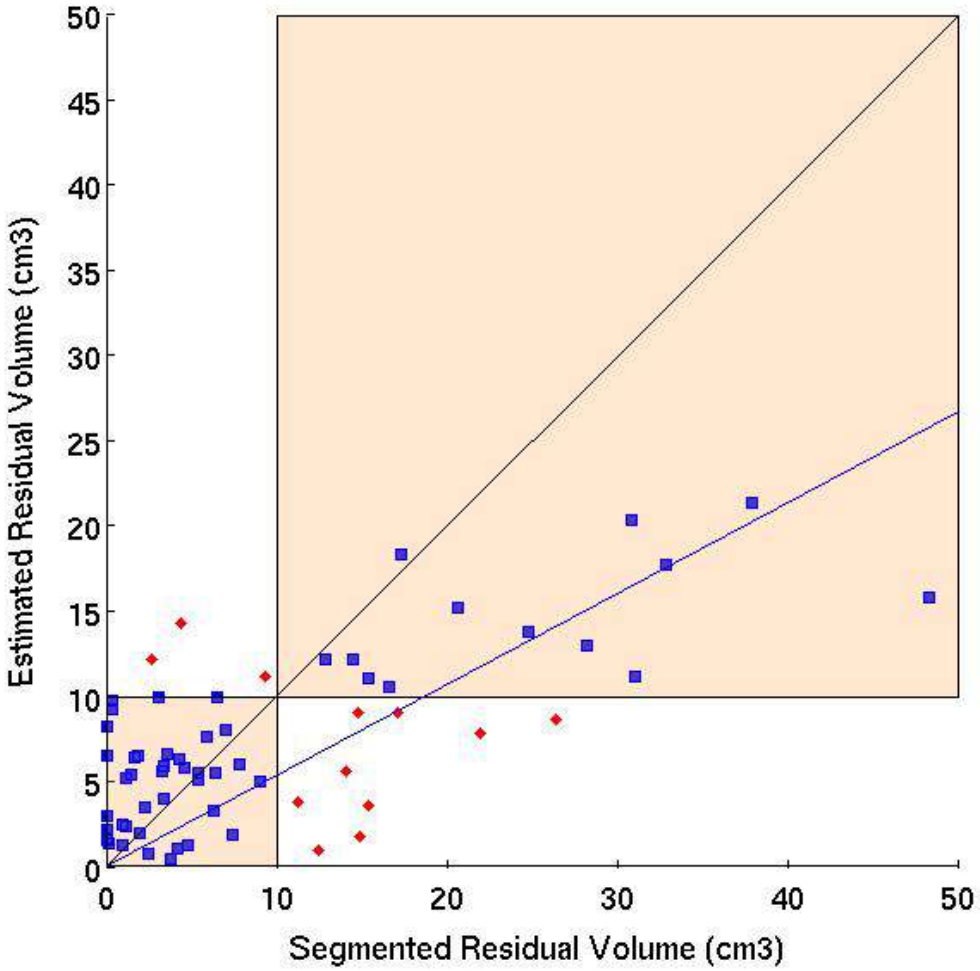
- quelle sera l'étendue de l'exérèse en allant jusqu'aux limites fonctionnelles?
  - **supratotale / totale / subtotale** / partielle

Probabilistic atlas of functional resectability



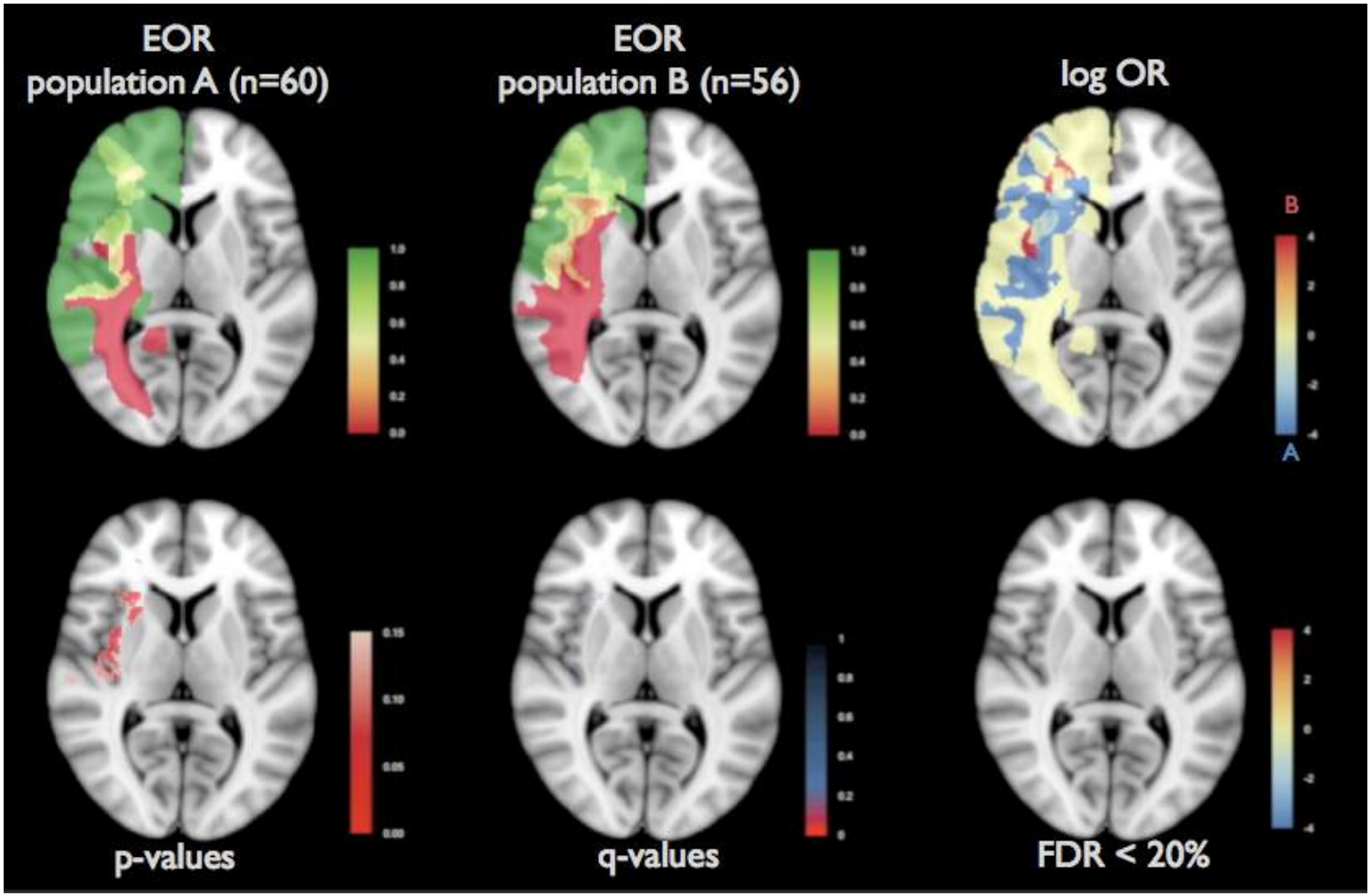
Mandonnet, Jbabdi & al. 2007, *Neuro-oncology*

Pre-operative estimation of residual volume



Mandonnet, Jbabdi & al. 2007, *Neuro-oncology*

Validating the reproductibility of a surgical technique



De Witt Hamer & al. 2013, *Plos One*

Problématiques du chirurgien

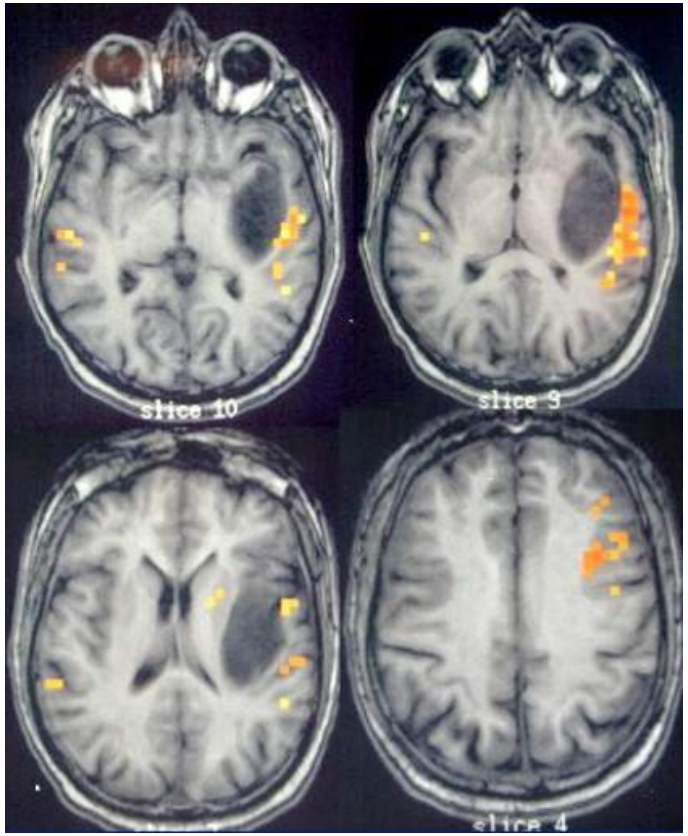
- Quand faut-il opérer ce patient ?
- **Comment opérer ?**

Planning pré-chirurgical : IRMf

Principe
- effet BOLD

Avantages
- non invasif

Inconvénients
- aires activées mais non essentielles
- Sensibilité et spécificité limitées par la tumeur, qui perturbe l'hémodynamique



Planning pré-chirurgical : DTI

Principe

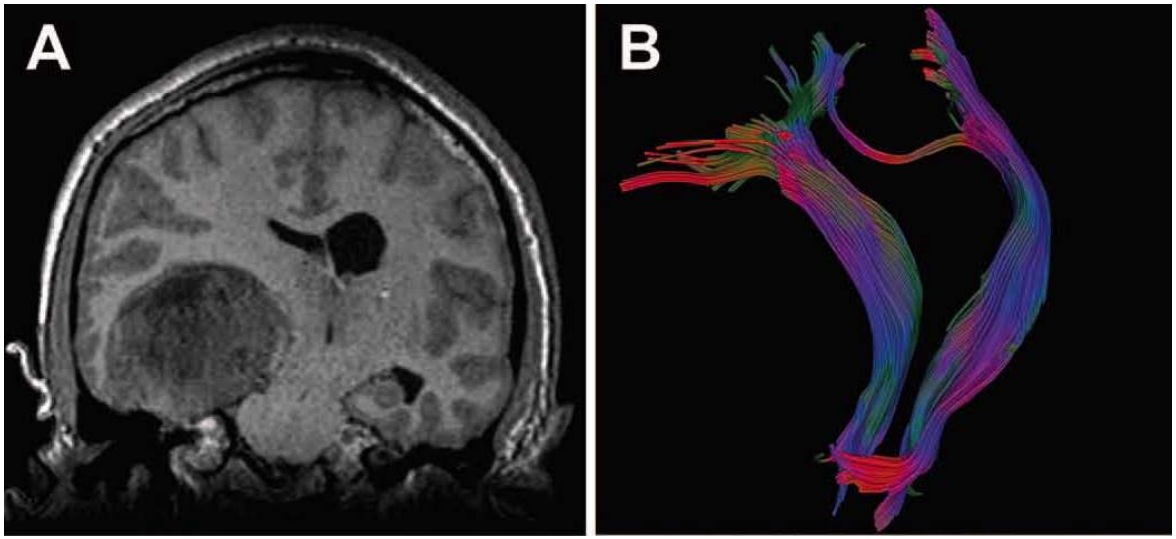
- tenseur de diffusion de l'eau
- puis algorithme de tracking à partir d'un ou plusieurs ROI

Avantages

- non invasif

Inconvénients

- tracking
- fonction ?



En per-opératoire : navigation anatomique

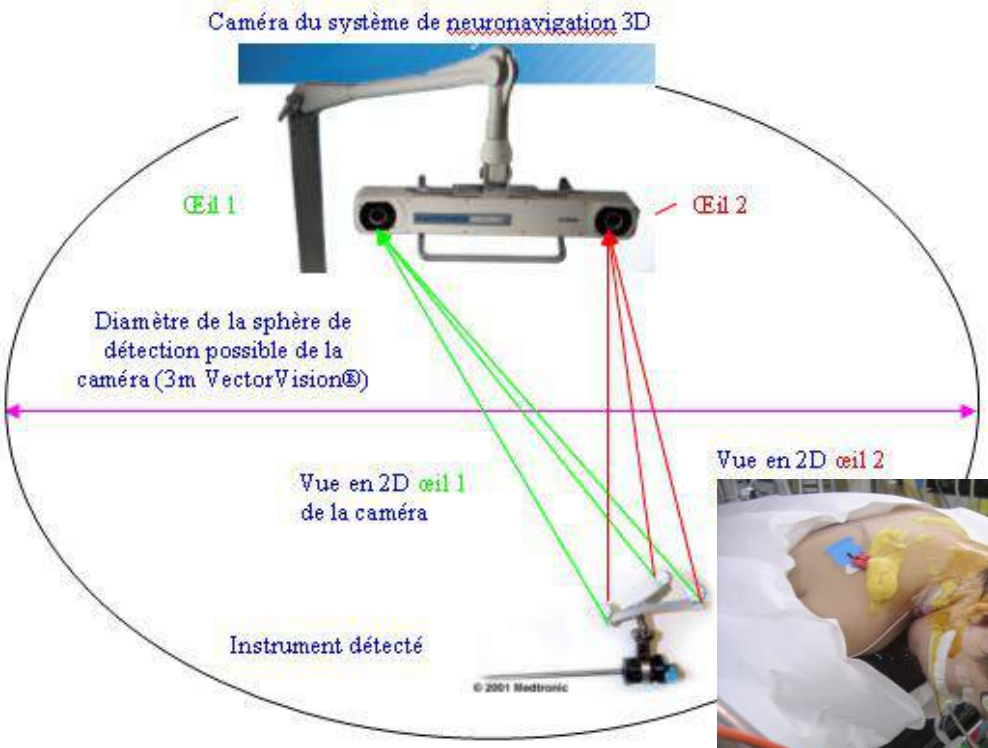
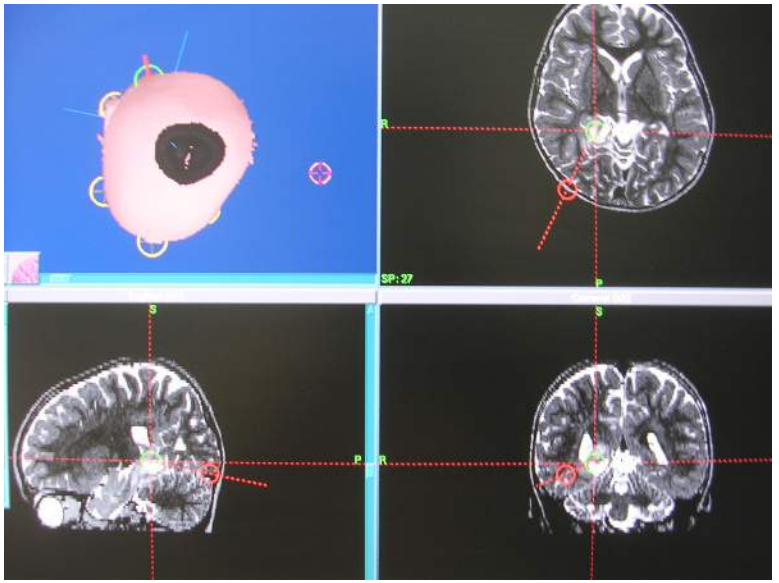


Figure 15 : Principe de triangulation des systèmes de repéra



Vue en 2D œil 2

Neuronavigation anatomique (2)

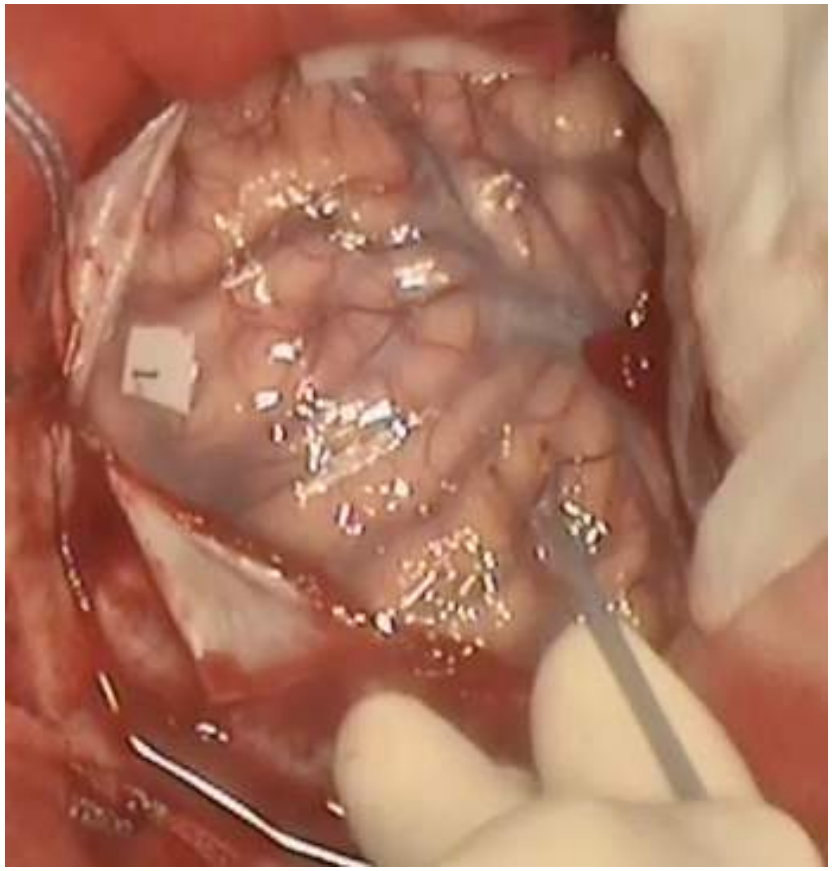
Avantages

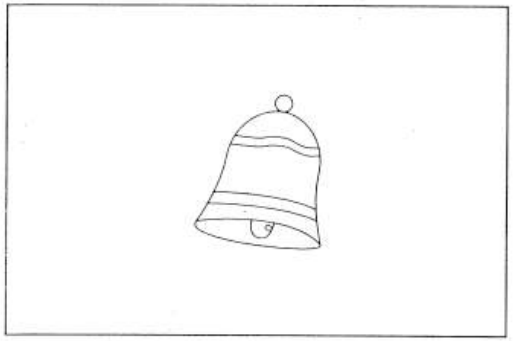
- aide précieuse à la localisation 3D
- possibilité d'intégrer le planning préchirurgical fMRI et DTI

Inconvénients

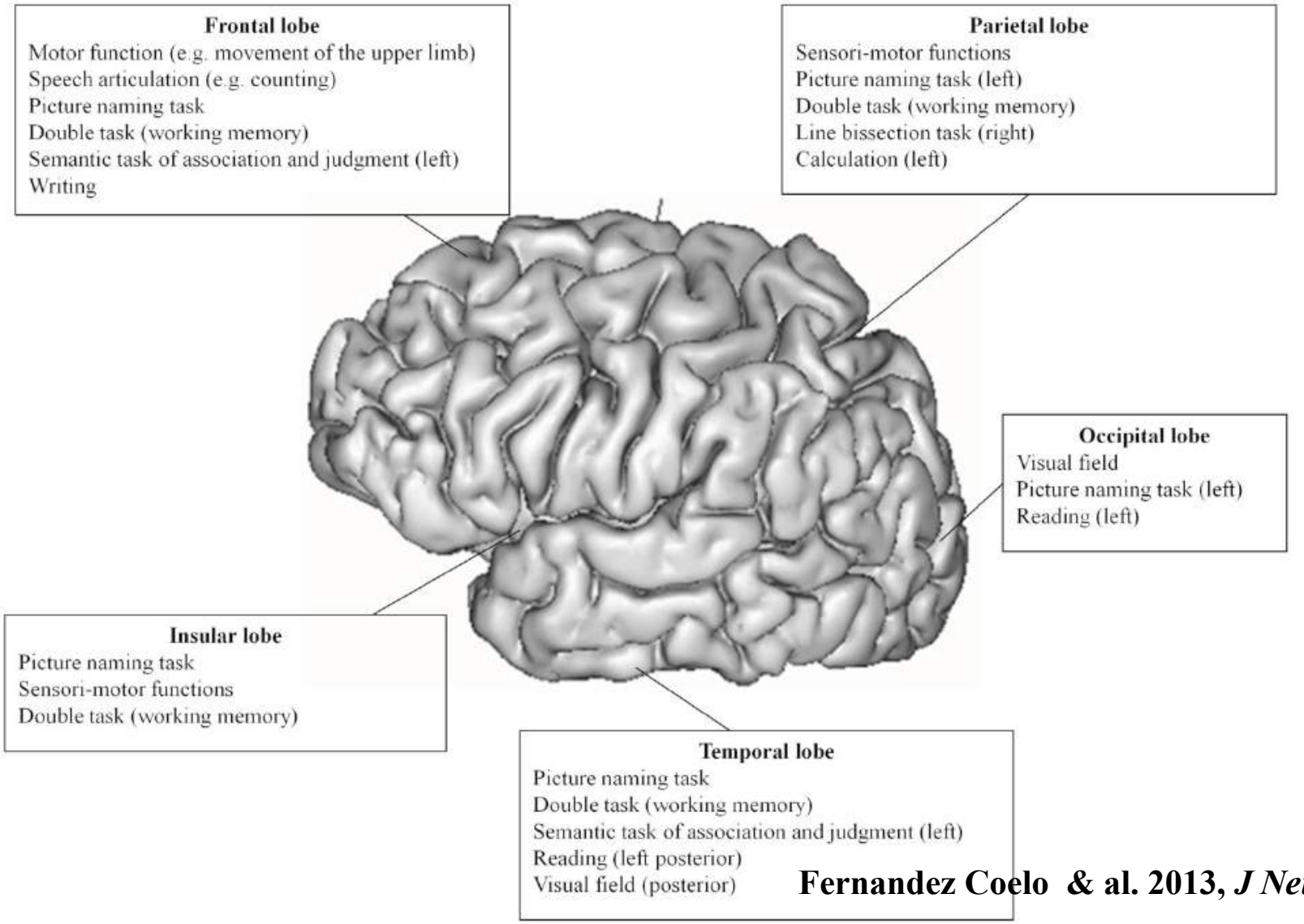
- **« brain shift »**
- limites de l'imagerie fonctionnelle
  - fMRI = aires activées mais non essentielles
  - DTI = aucune information fonctionnelle

Cartographie corticale et axonale per-opératoire



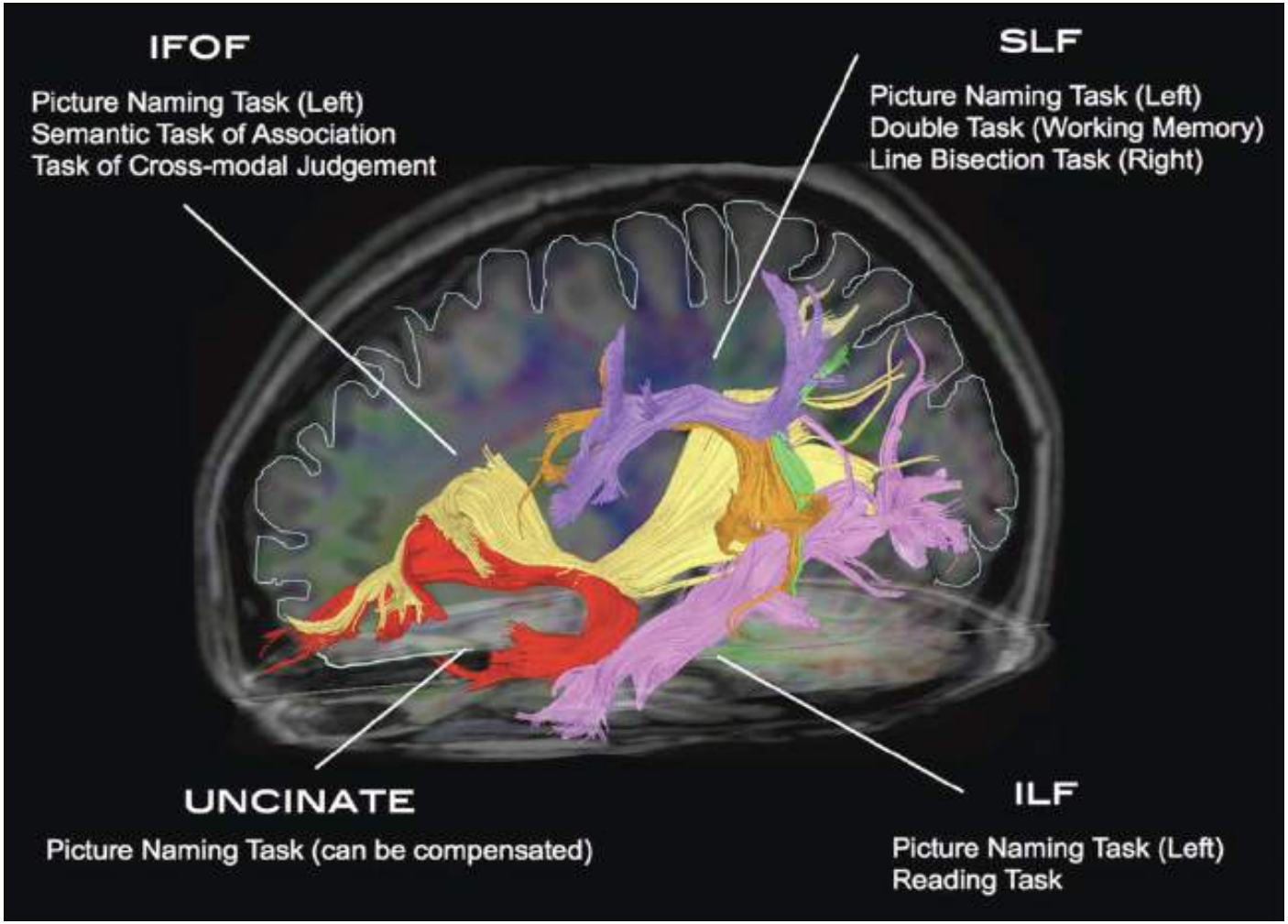


The problem of task selection

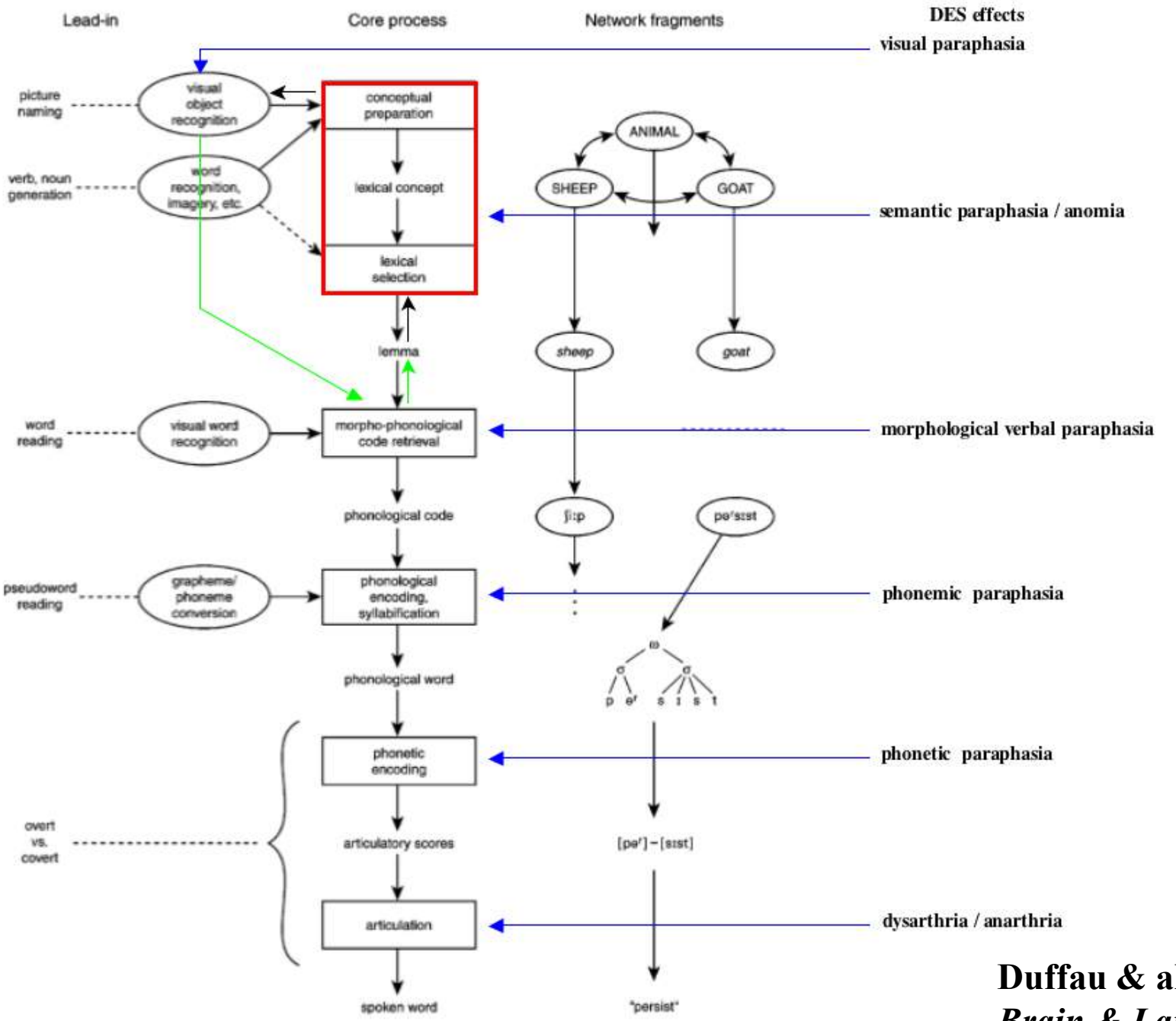


Fernandez Coelo & al. 2013, *J Neurosurg*

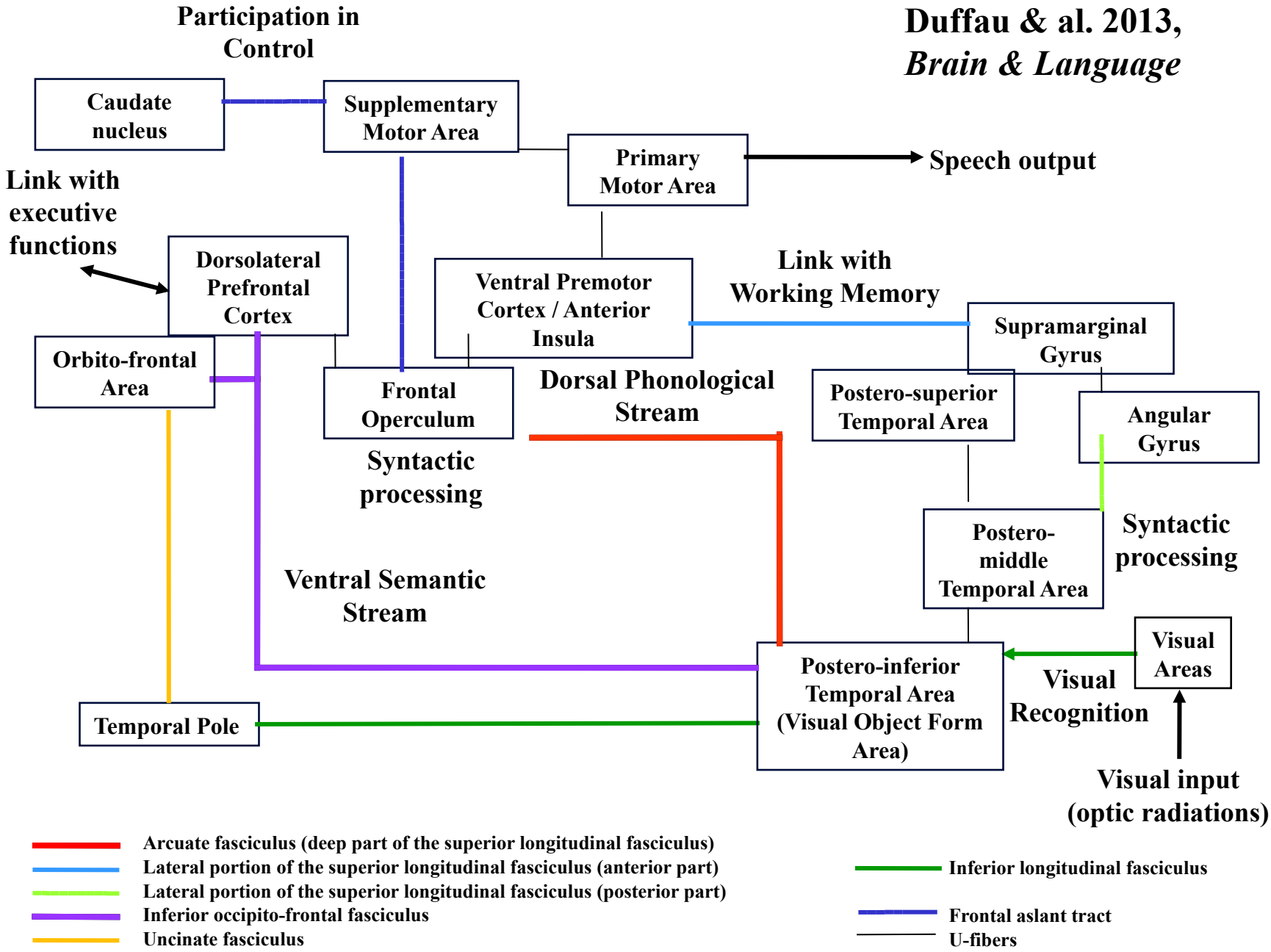
The problem of task selection



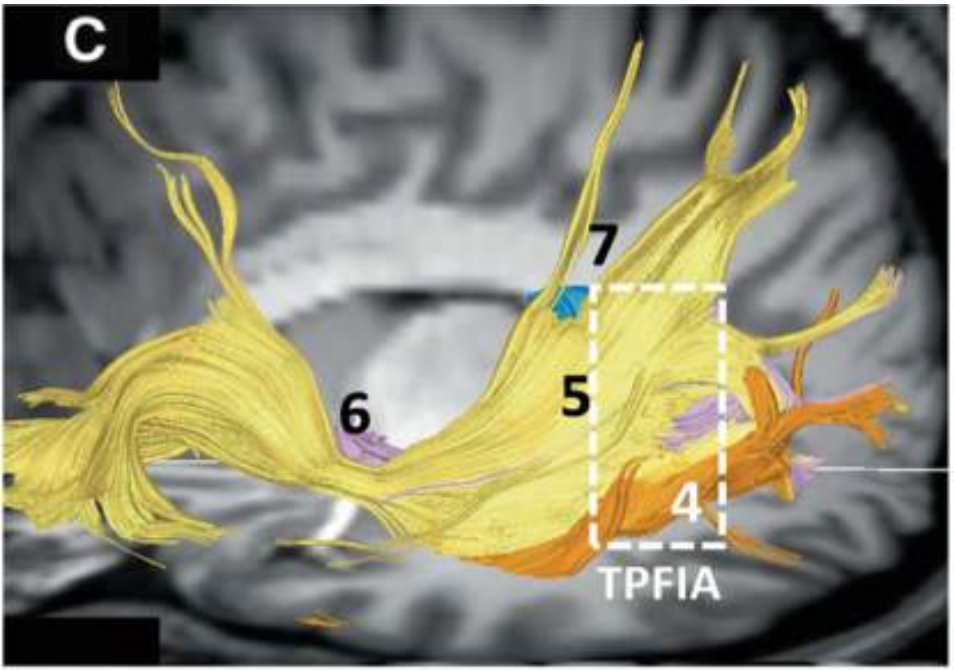
Fernandez Coelo & al. 2013, *J Neurosurg*

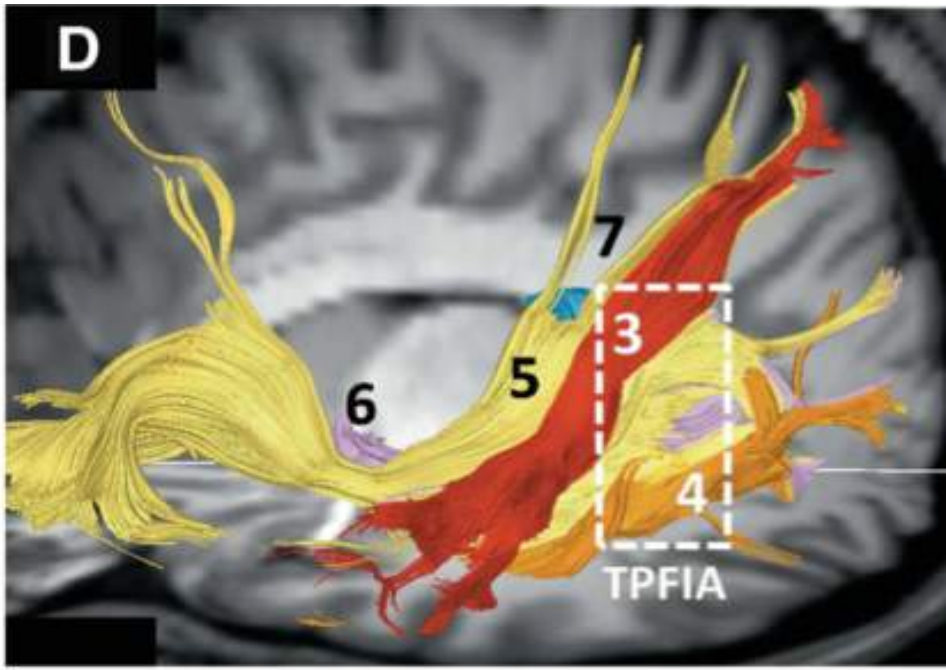


Duffau & al. 2013,
Brain & Language


Participation in Control
Duffau & al. 2013,
Brain & Language
Caudate nucleus
Supplementary Motor Area
Primary Motor Area
Speech output
Link with executive functions
Dorsolateral Prefrontal Cortex
Ventral Premotor Cortex / Anterior Insula
Link with Working Memory
Supramarginal Gyrus
Orbito-frontal Area
Frontal Operculum
Dorsal Phonological Stream
Postero-superior Temporal Area
Angular Gyrus
Syntactic processing
Postero-middle Temporal Area
Syntactic processing
Ventral Semantic Stream
Visual Areas
Postero-inferior Temporal Area (Visual Object Form Area)
Visual Recognition
Temporal Pole
Visual input (optic radiations)
Arcuate fasciculus (deep part of the superior longitudinal fasciculus)
Lateral portion of the superior longitudinal fasciculus (anterior part)
Lateral portion of the superior longitudinal fasciculus (posterior part)
Inferior occipito-frontal fasciculus
Uncinate fasciculus
Inferior longitudinal fasciculus
Frontal aslant tract
U-fibers

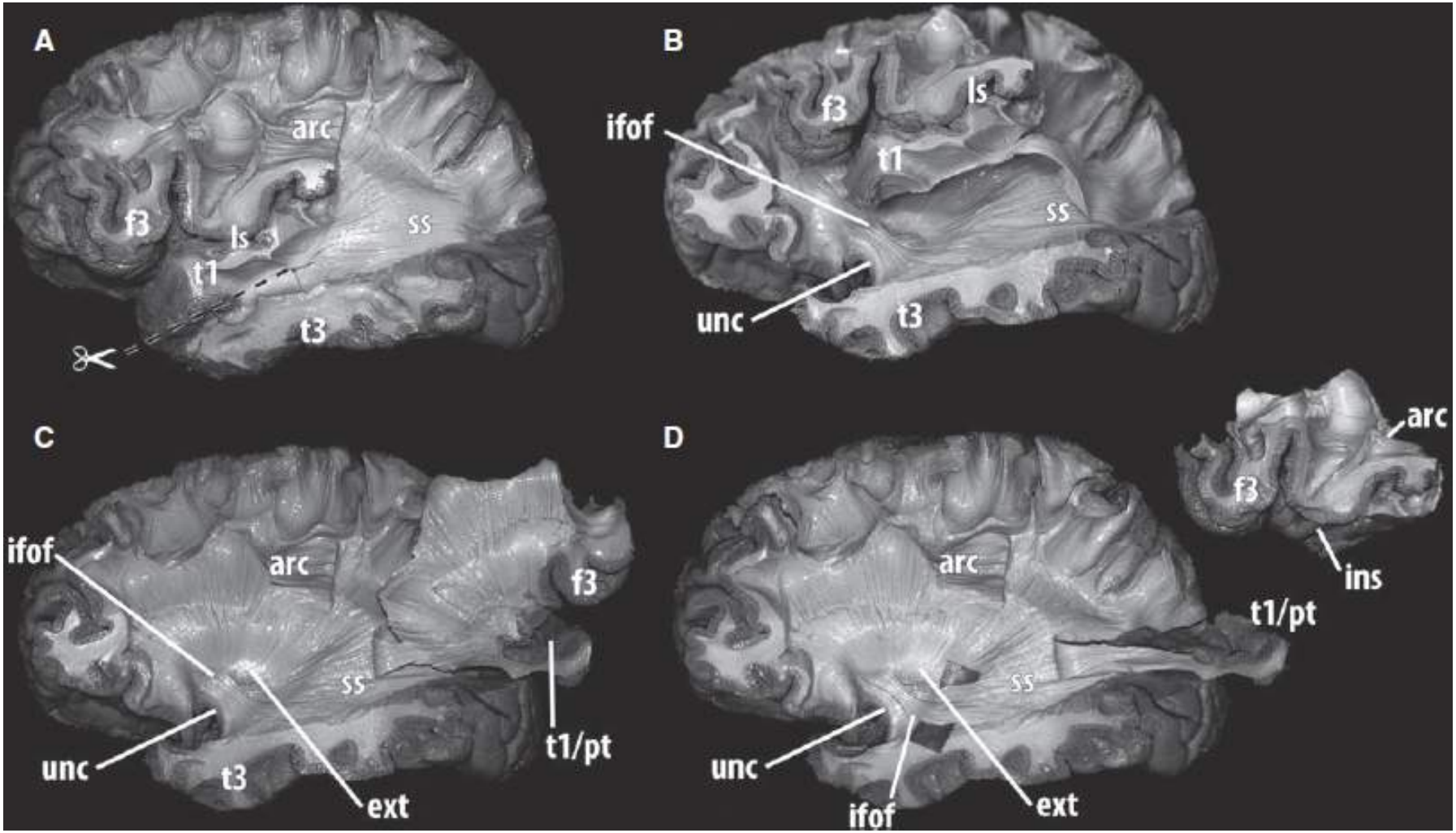
Terminaisons corticales ?





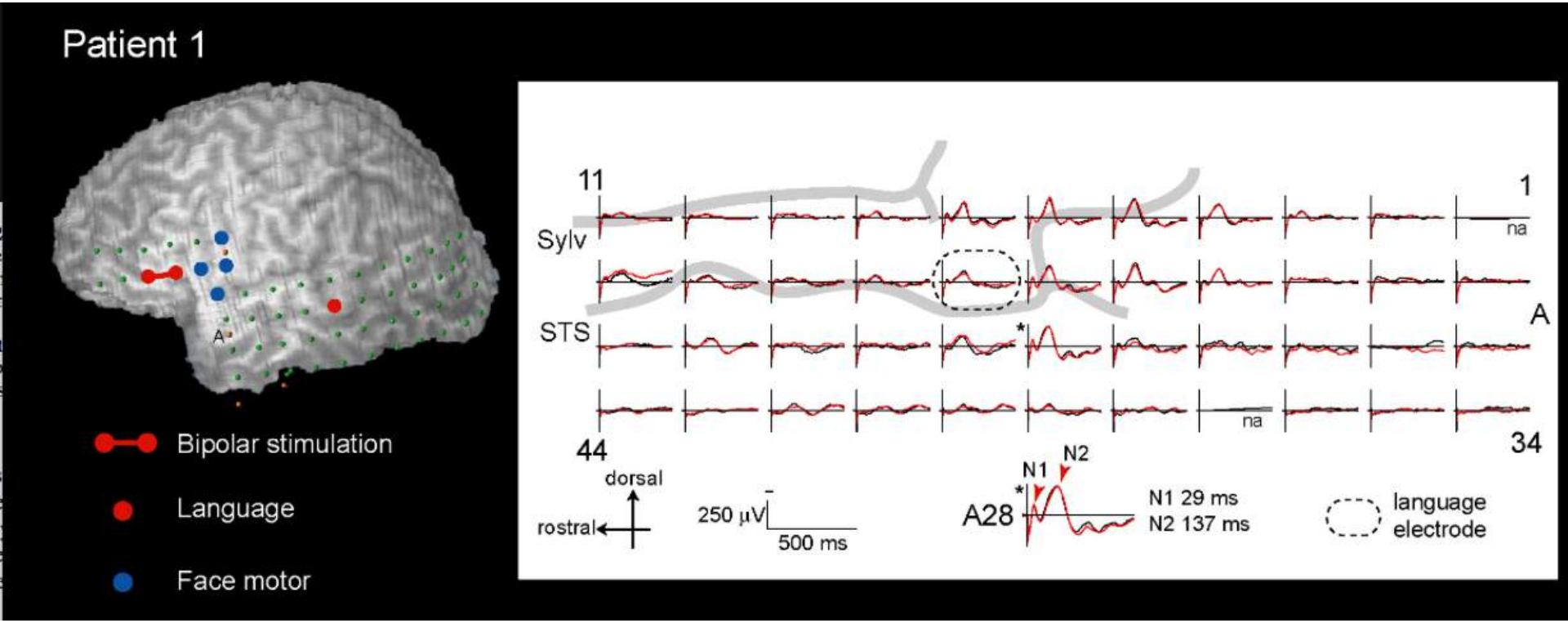
Martino & al. 2014, *Neurosurgery*

Klinger's dissections : terminaisons ?



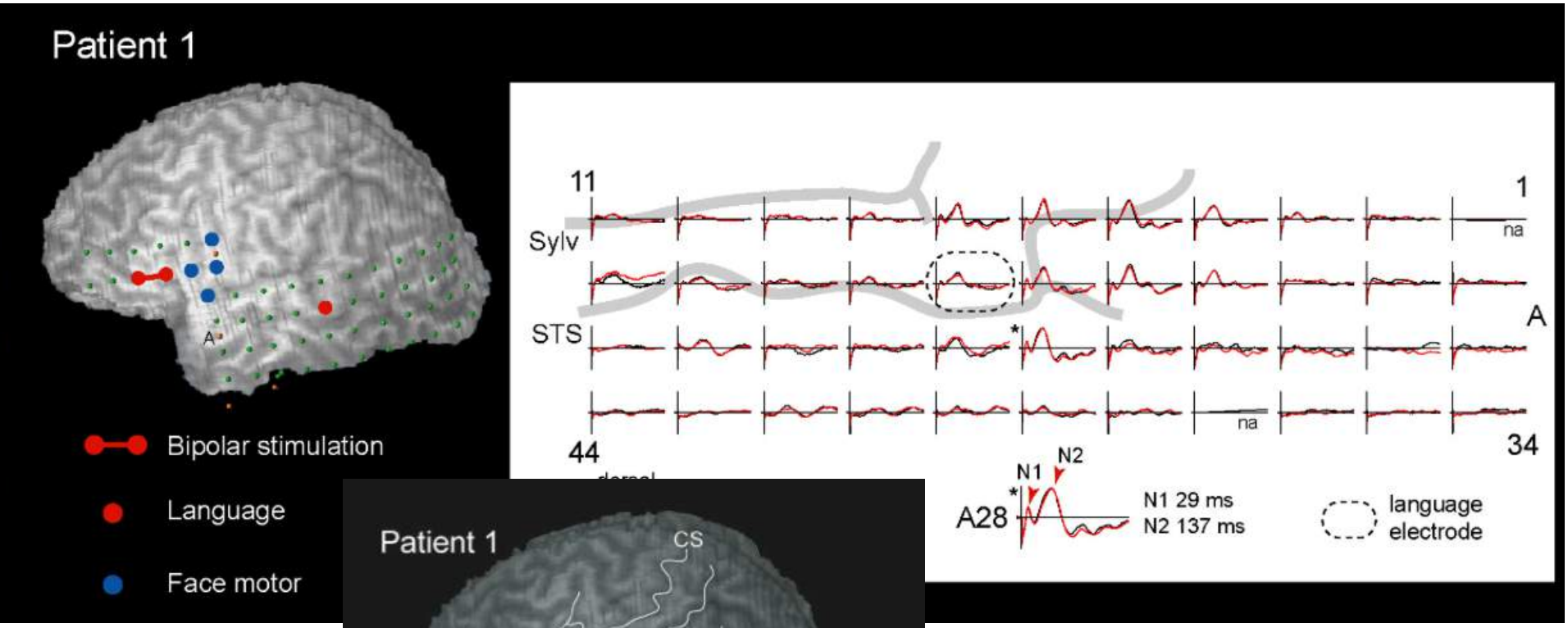
Maldonado & al. 2013, *Journal of Anatomy*

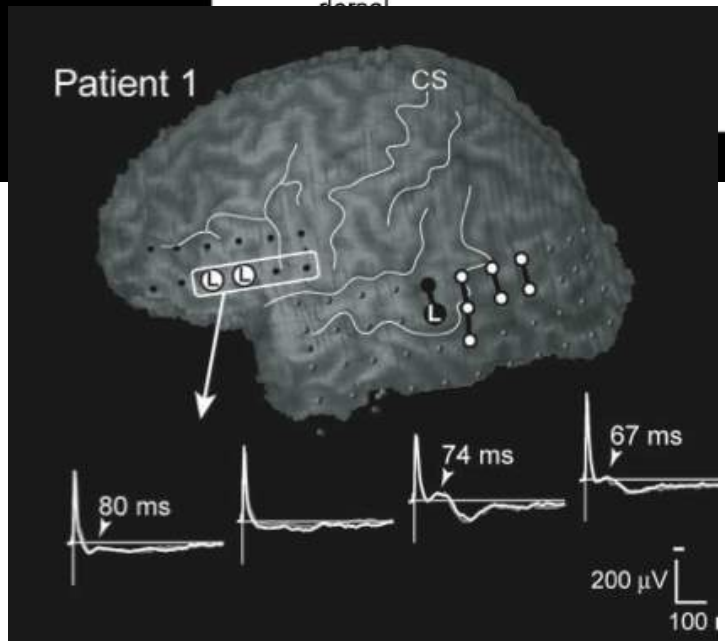
Potentiels évoqués cortico-corticaux



Matsumoto R. *Brain* 2004

PECC : lien bidirectionnel, non bijectif

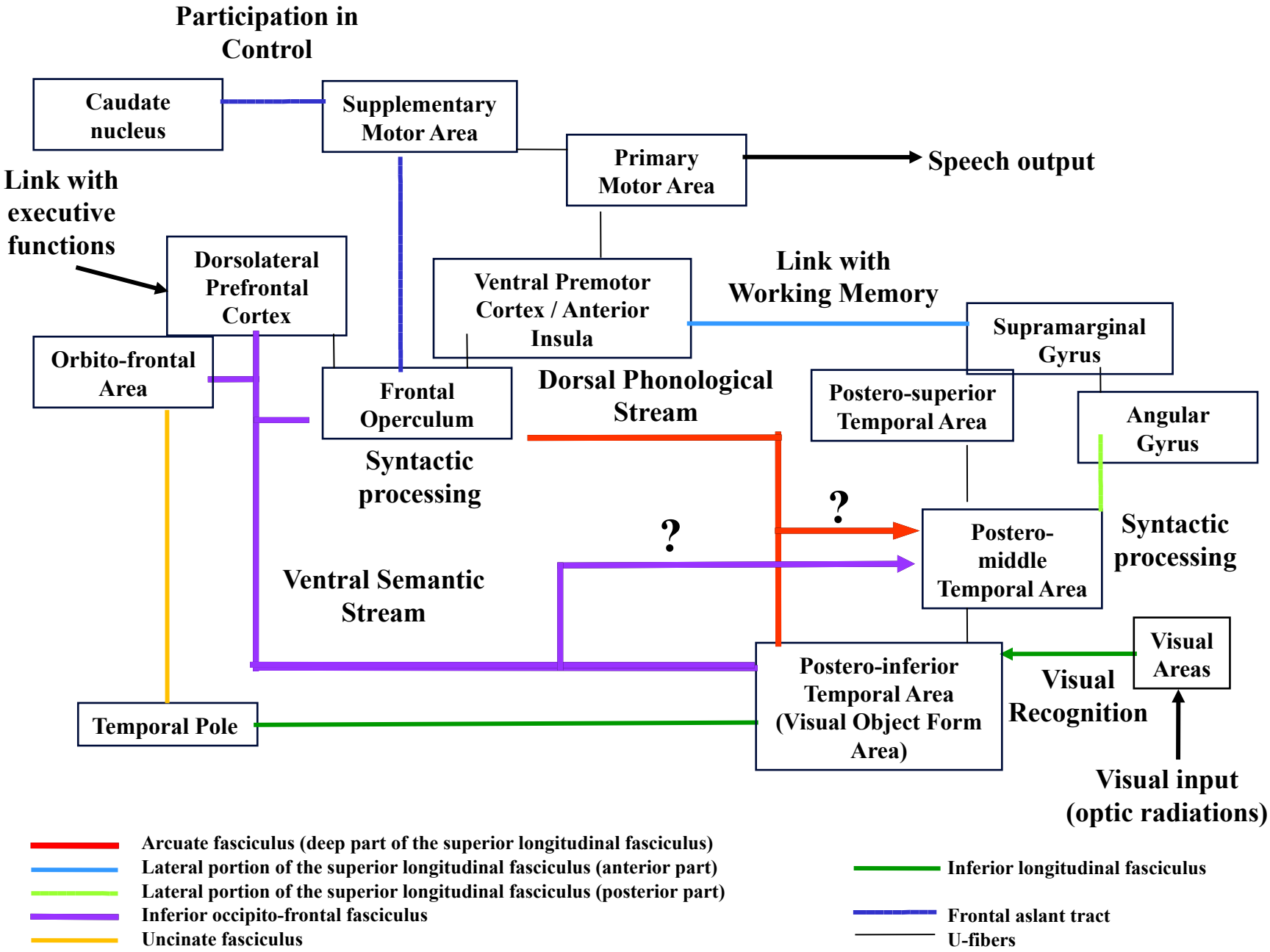




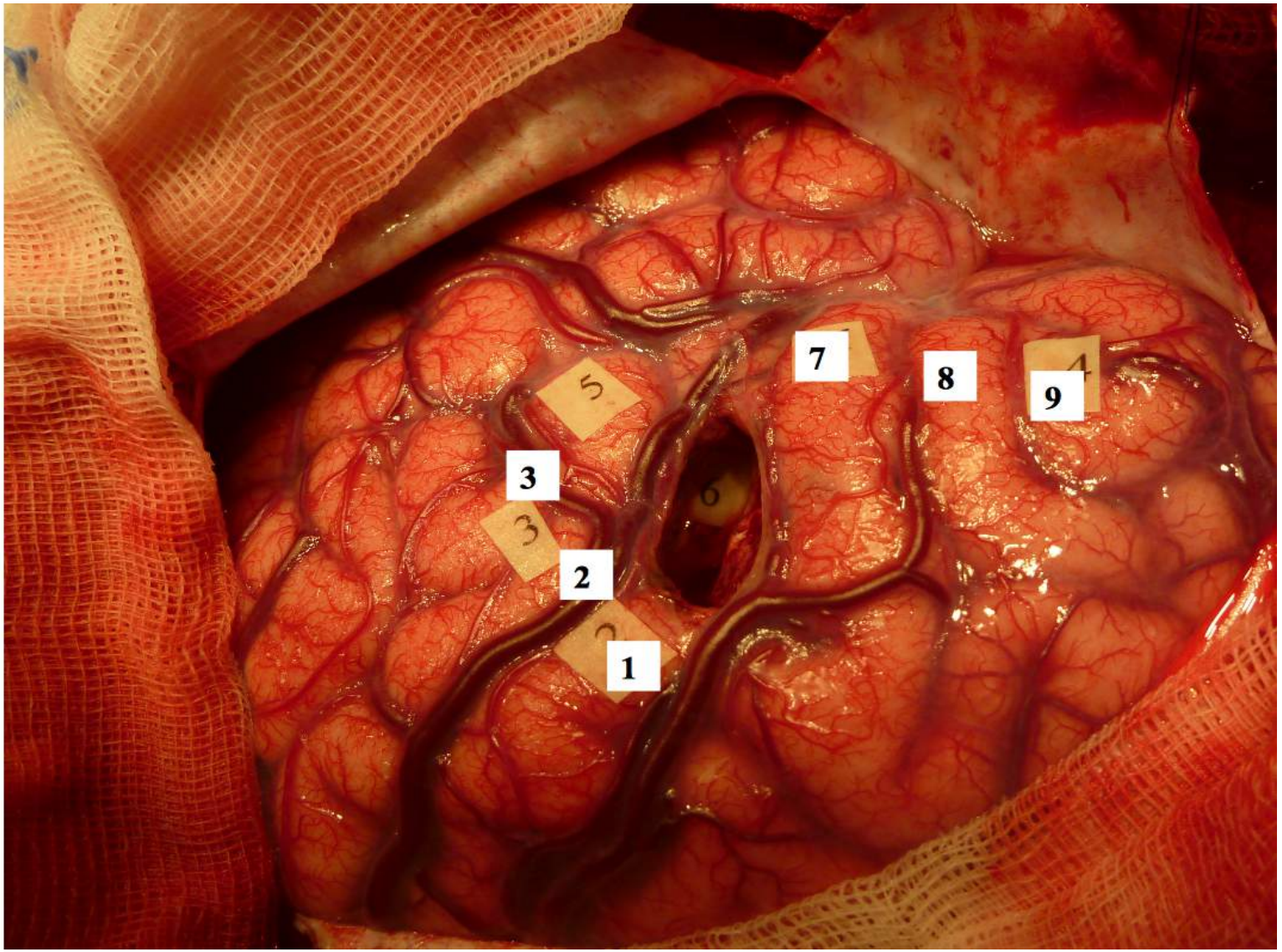
pair of stimulation

with $CCEP_{PL \rightarrow AL}$

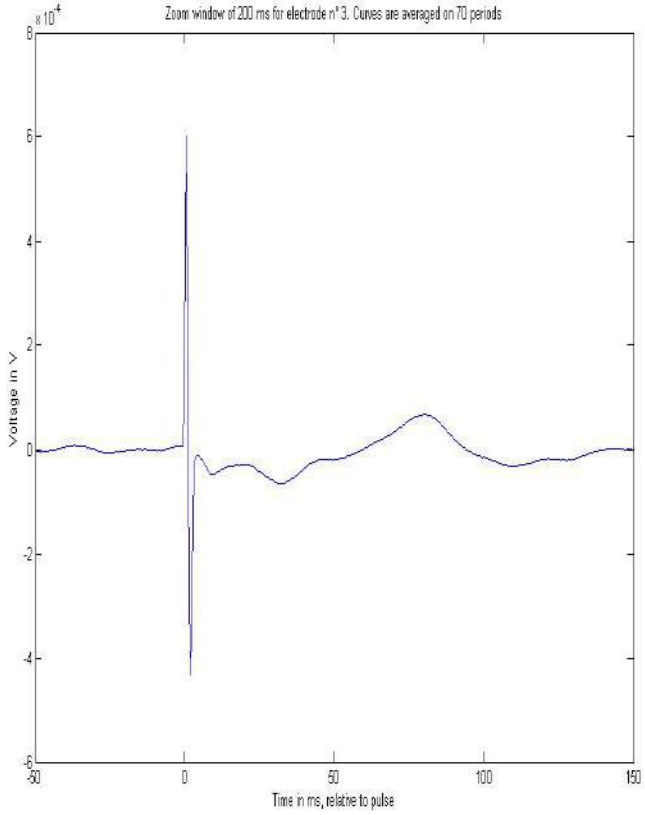
without $CCEP_{PL \rightarrow AL}$

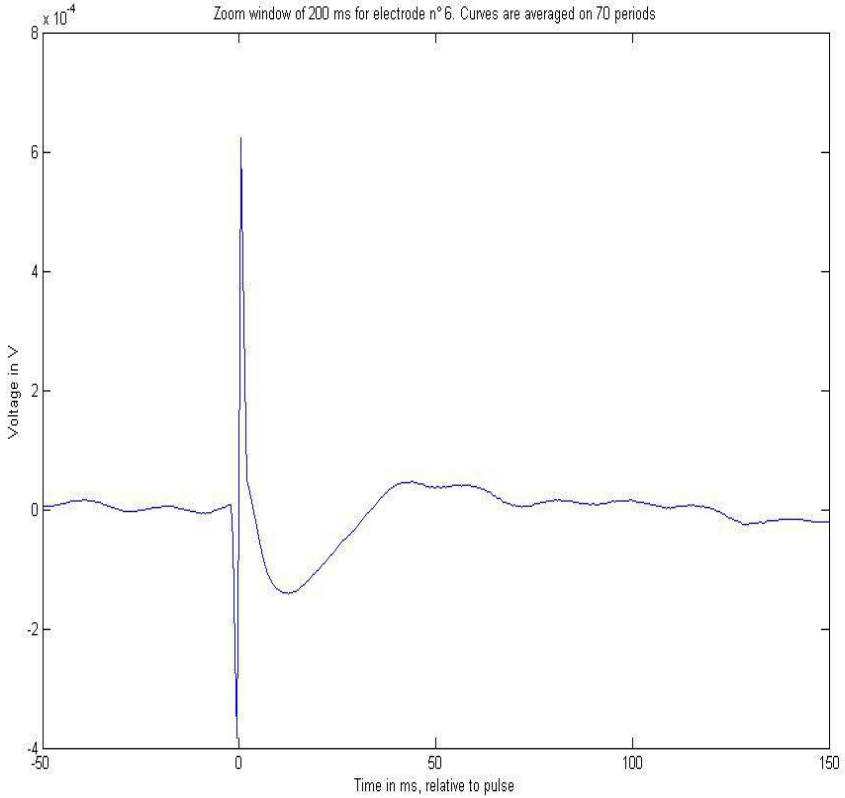

Participation in Control
Caudate nucleus
Supplementary Motor Area
Primary Motor Area
Speech output
Link with executive functions
Dorsolateral Prefrontal Cortex
Ventral Premotor Cortex / Anterior Insula
Link with Working Memory
Supramarginal Gyrus
Orbito-frontal Area
Frontal Operculum
Dorsal Phonological Stream
Postero-superior Temporal Area
Angular Gyrus
Syntactic processing
?
?
Postero-middle Temporal Area
Syntactic processing
Ventral Semantic Stream
Visual Areas
Postero-inferior Temporal Area (Visual Object Form Area)
Visual Recognition
Temporal Pole
Visual input (optic radiations)
Arcuate fasciculus (deep part of the superior longitudinal fasciculus)
Lateral portion of the superior longitudinal fasciculus (anterior part)
Lateral portion of the superior longitudinal fasciculus (posterior part)
Inferior occipito-frontal fasciculus
Uncinate fasciculus
Inferior longitudinal fasciculus
Frontal aslant tract
U-fibers

Protocole PEAC



Protocole PEAC

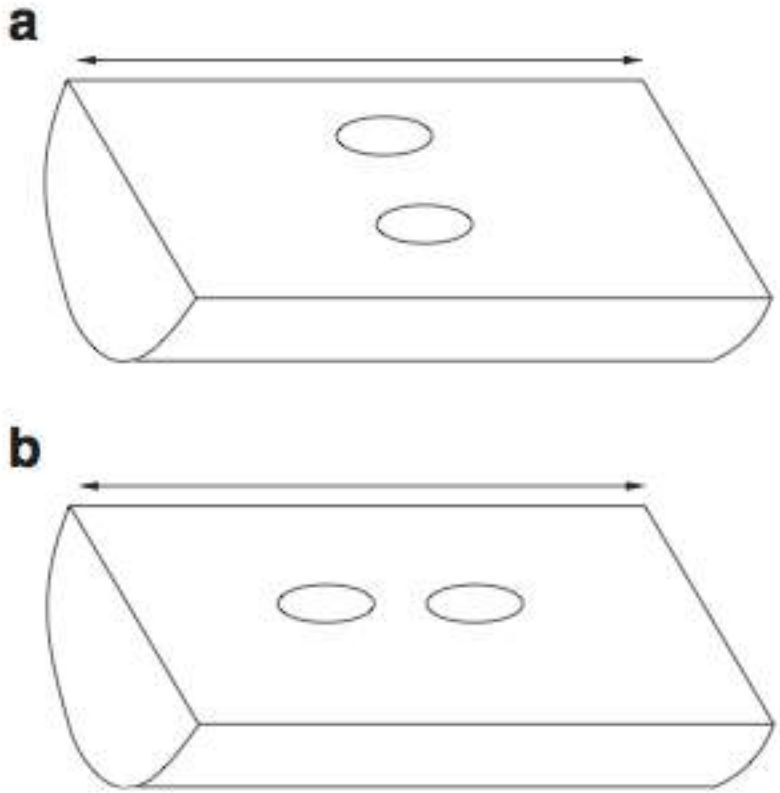




Interpréter les PEAC : un défi pour les neurosciences

- Modélisation des PEAC
  - modélisation locale

Modélisation bi-domaine des stimulations axonales



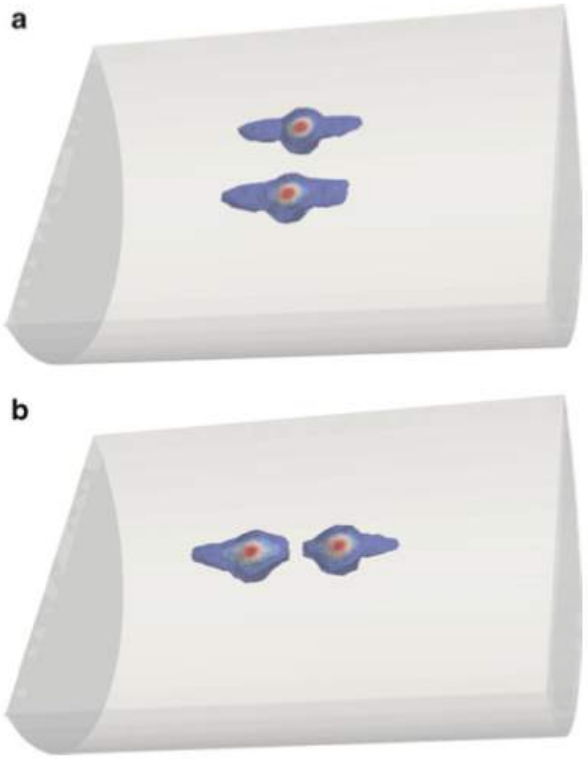


Fig. 5 Activated areas at a stimulation intensity of 5 mA. **a** Orthogonal setting. **b** Parallel setting

Mandonnet & Pantz. 2011, *Acta Neurochir*

Interpréter les PEAC : un défi pour les neurosciences

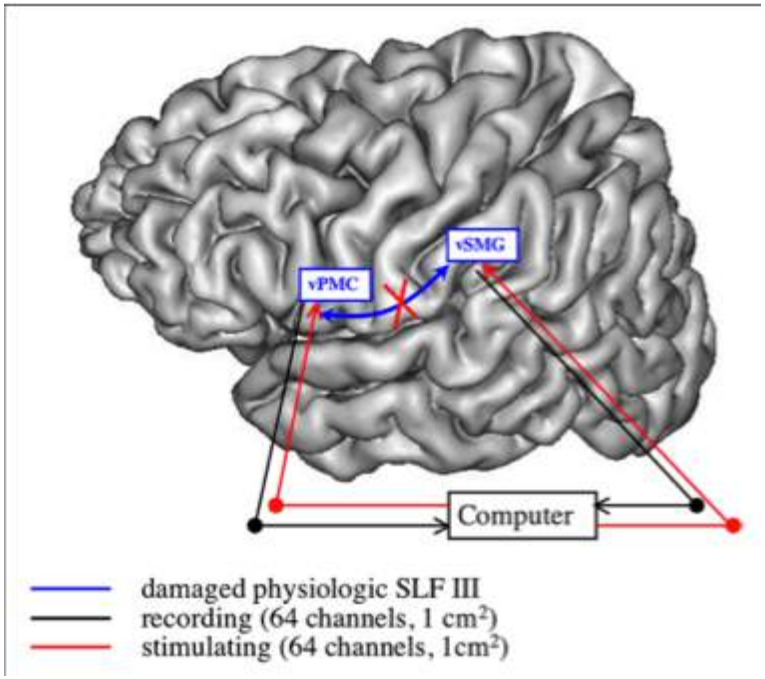
- Modélisation des PEAC
  - modélisation locale
  - repérage du point stimulé en per-op dans l'IRM
    = développer des algo de correction du brainshift
    → modèle anatomique des connections à partir du DTI
  - modélisation des sites corticaux
    → simulation du PE à partir d'un modèle des couches corticales

Conclusion

- Images qui guident le chirurgien :
  - images de la tumeur
  - images du cerveau

- L'interprétation de ces images fait appel à des modèles biophysiques

- Le but ultime de ces modèles :
  - tumeur virtuelle patient-spécifique
    → guider la décision
  - cerveau virtuel patient-spécifique
    → guider le geste et la réparation



Mandonnet, Duffau. 2014. *Front Syst Neurosci*