

JNI

Clermont-Ferrand, France  
12 au 14 juin 2013

# **Encéphalites autoimmunes**

Pr J. Honnorat

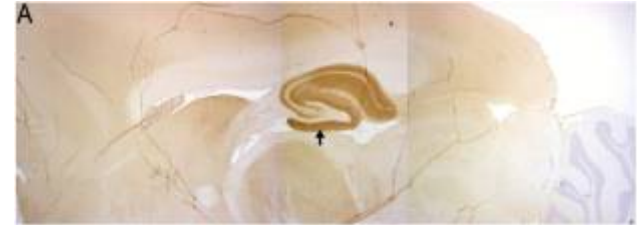
Neuro-Oncology  
Lyon's neurological hospital

Lyon's neuroscience research center  
Team : « Neuro-Oncology and Neuro-Inflammation »  
Inserm 1028 / CNRS 5292  
Lyon, France

# Encéphalites avec anti-NMDA-R

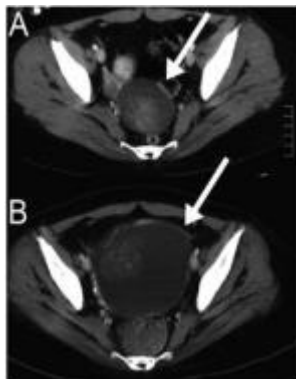
Premiers cas identifiés : jeunes femmes encéphalite et tératome de l'ovaire

Dalmau et al, Ann Neurol 2007

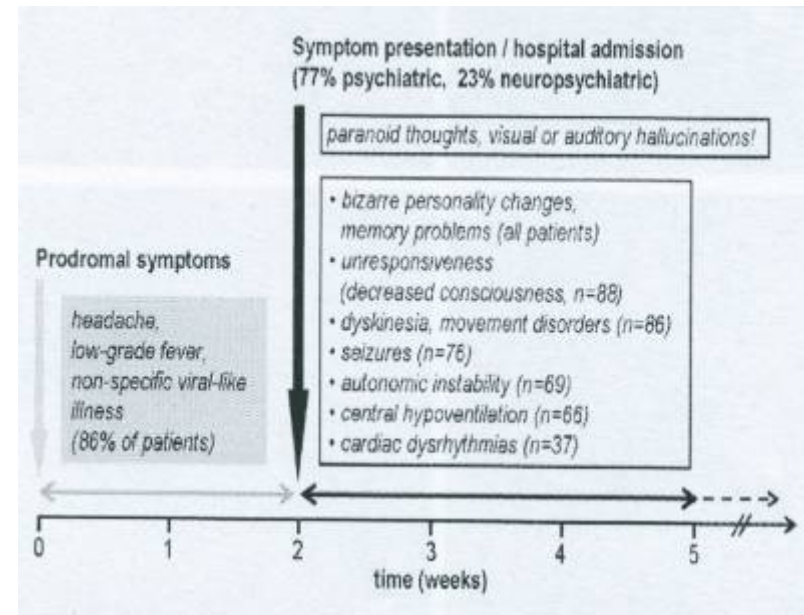


## Dyskinésies bucco-faciales Dysautonomie

Bayreuther et al, Epileptic Disord 2009



Tératomes de l'ovaire



# Les Encéphalites avec anti-NMDA-R



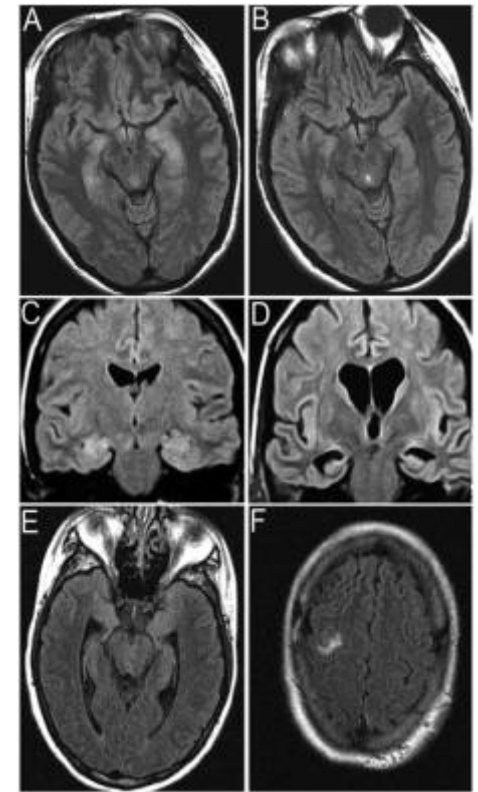
Femme, Mme Y.  
Medeline, Colombie.  
Dr Reiss.



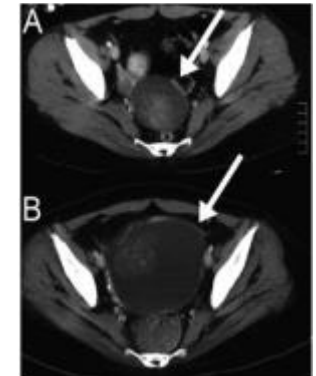
Homme, Mr X.  
Amiens,  
France.  
Dr Bertille.



Enfants,  
Paris, Trousseau



Anomalies IRM non spécifiques



Tératomes non systématiques

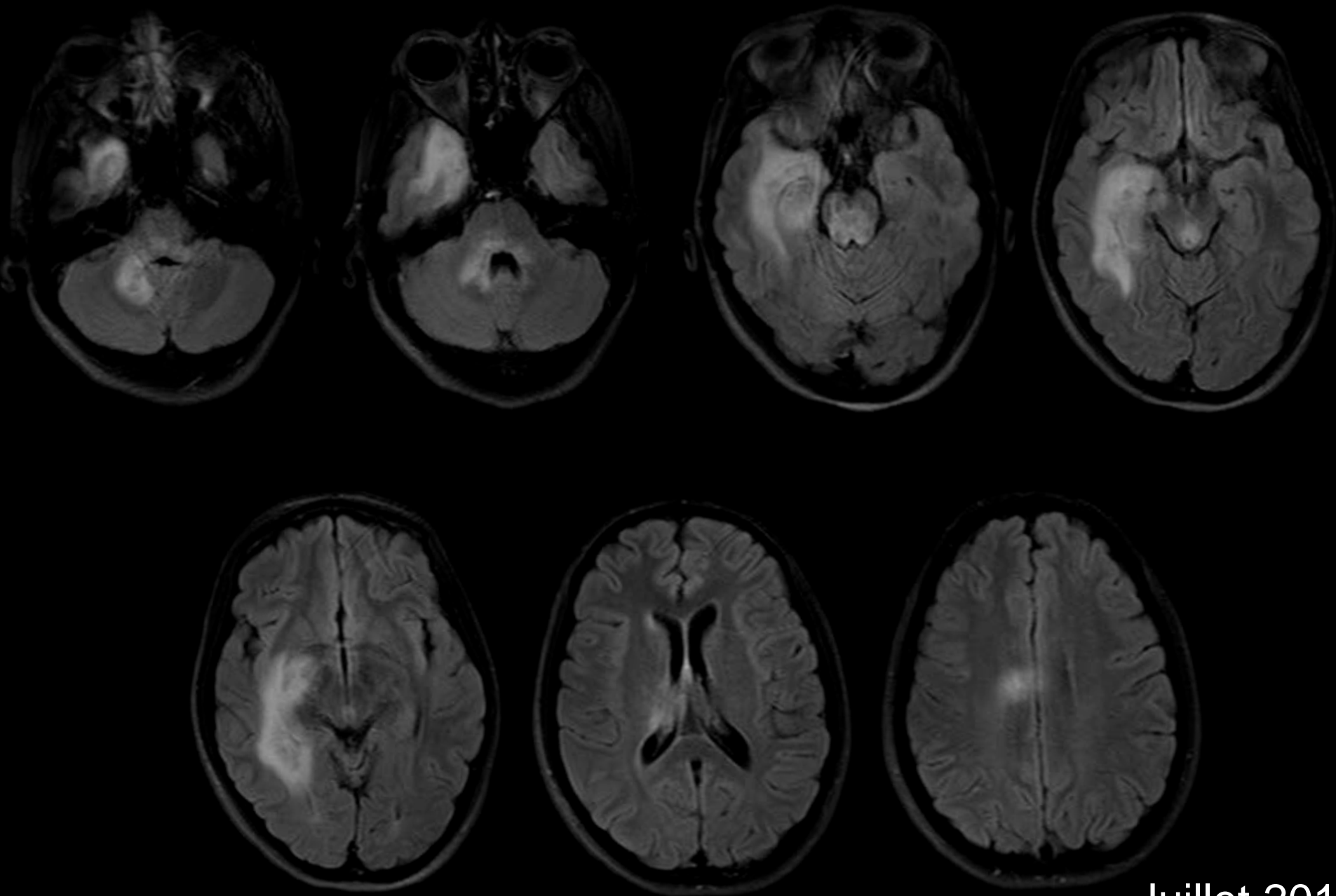
**LCR inflammatoire 91%**  
**EEG anormal 92 %**

# Encéphalites à auto-anticorps anti-NMDAr

## Importance des troubles psychiatriques initiaux

- Jeune femme de 20 ans
- Tableau psychiatrique progressif depuis avril 2012
- Infantilisation, hallucinations, terreurs, catatonie, comportement inapproprié, mange deux phalanges...

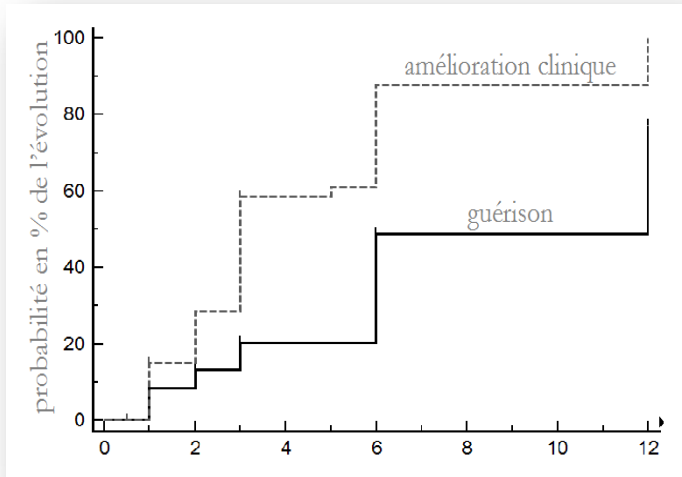
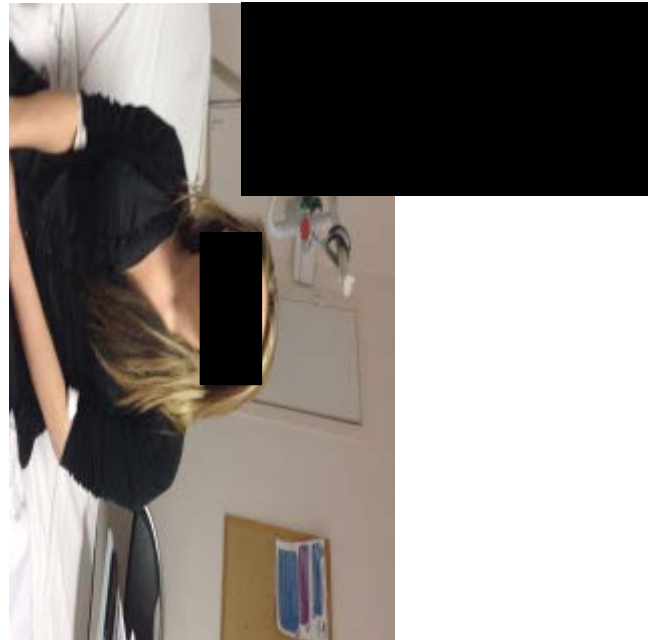


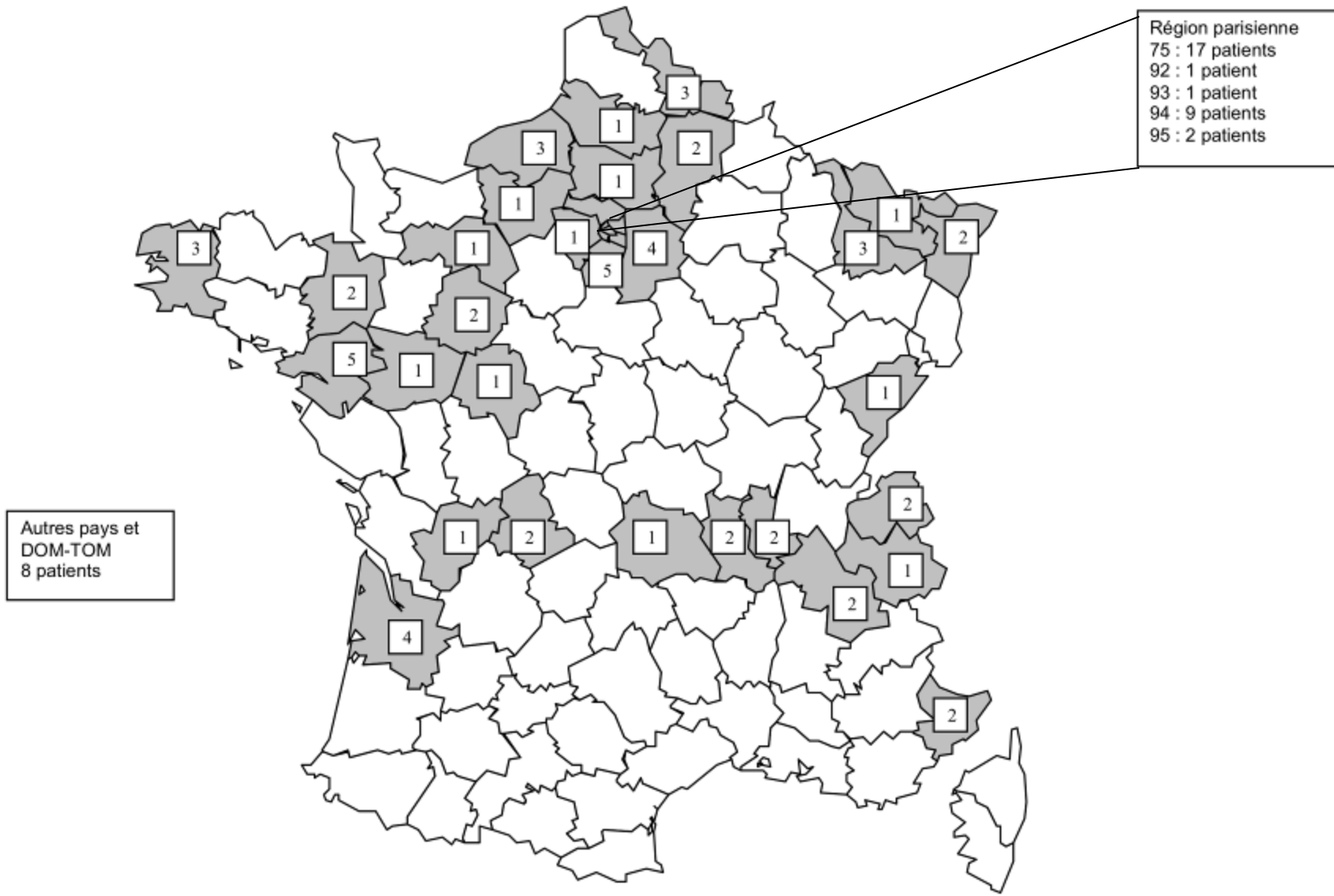


Juillet 2012

# amélioration spectaculaire

sous ivlg et rituximab





**REPARTITION GEOGRAPHIQUE DES 100 PATIENTS NMDA+ DIAGNOSTIQUES ENTRE MAI 2007 ET MAI 2012 PAR LE CENTRE DE REFERENCE DES SYNDROMES NEUROLOGIQUES PARANEOPLASIQUES**

# Les encéphalites anti-NMDAR sont elles un diagnostic différentiel des encéphalites infectieuses

Etude de 108 LCR de patients « Encéphalites infectieuses France 2007 »  
(Mailles et al, Clin Infect Dis 2009;49:1838-47)

		N. of cases	%
Virus	HSV	17	15,7
	VZV	7	6,5
	CMV	2	1,8
	Toscana virus	1	0,9
	Influenze A	1	0,9
	Enterovirus	1	0,9
	Bacteria	<i>Mycobacterium tuberculosis</i>	5
<i>Listeria monocytogenes</i>		4	3,7
Undetermined		68	62,9
Auto-immune	Anti NMDAR	2	1,8

**Anti-NMDAR = 3% des causes indéterminées (2/70)**

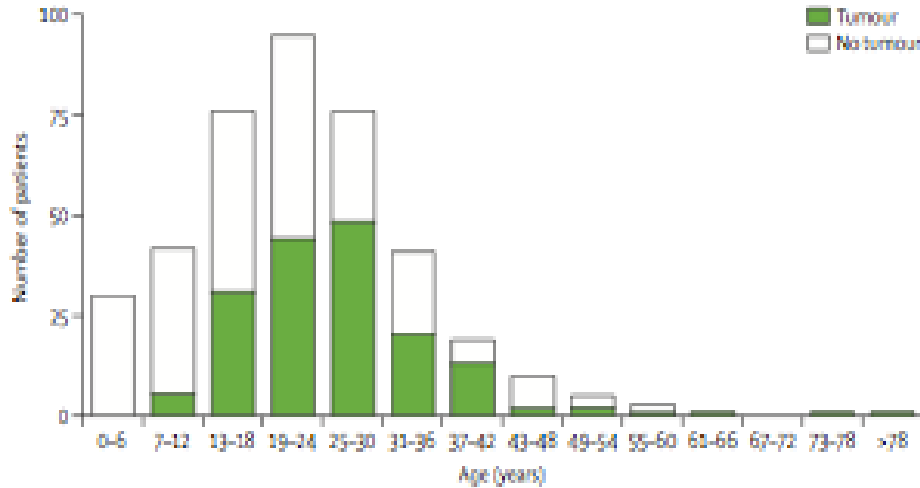


# What we learnt from NMDAR-Ab encephalitis ?

**More than 50% of patients have no tumor**

**Frequency > all onconeural antibodies**

(> 700 patients with NMDAR identified between 2007 and 2011 in the world and 80 in France)

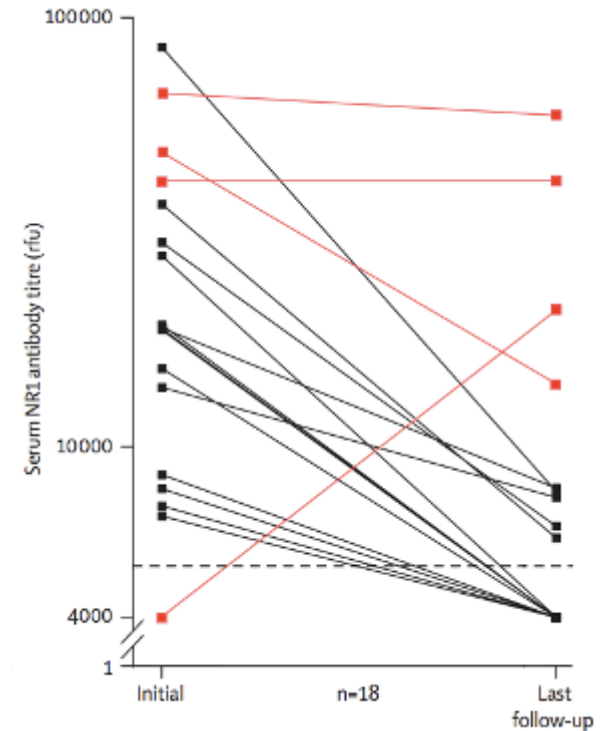


Dalmau et al, Lancet Neurol. 2011

## Tumor frequency in 400 patients

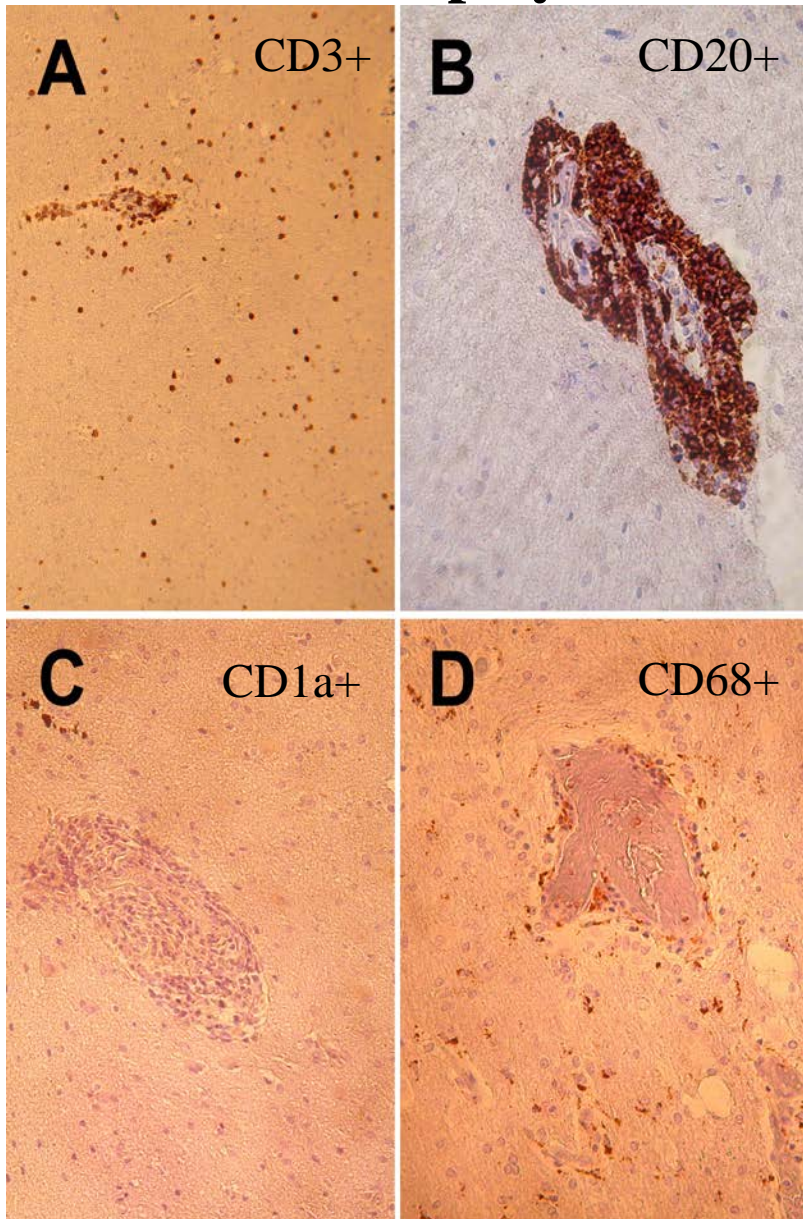
- Women (335 pts) :
- > 18 ans : 58% of tumors (98% ovary teratoma)
  - < 18 ans : 35% of tumors
  - < 14 ans : 15% of tumors
- Hommes (65 pts) :
- > 18 ans : 5% of tumors (testicular seminoma, SCLC)
  - < 18 ans : 0%
  - < 14 ans : 1% Neuroblastoma

**Autoantibodies level decrease with clinical improvement**



Dalmau et al, Lancet Neurol. 2010;10:63-74

# NMDAR-Ab could play a direct role in encephalitis pathophysiology



## Brain immunohistochemical analysis

Few CD3 positive T-cells  
Few CD68 positive macrophages

Prominent perivascular cuffing  
of CD20 positive B-cells.

MHC II associated CD1a protein is not expressed

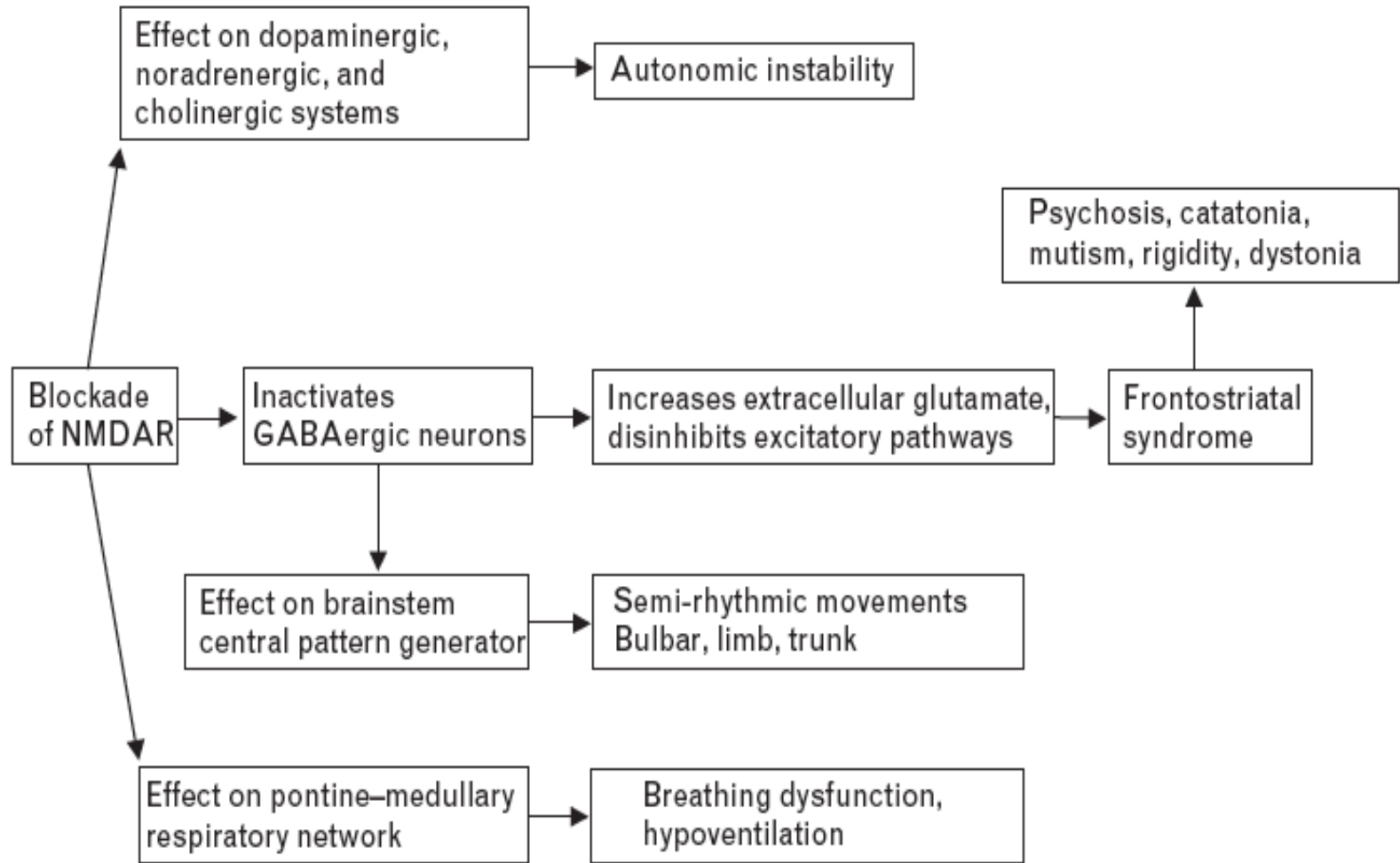
**Totally different than patients with Hu, Yo or CV2-Abs**

*(Camdessanche et al, Eur J Neurol 2010 August Epub)*

14 biopsies and 3 autopsies  
in the litterature with the same result

*(Moscatto et al, Eur J Neurosci 2010;32:298-309)*

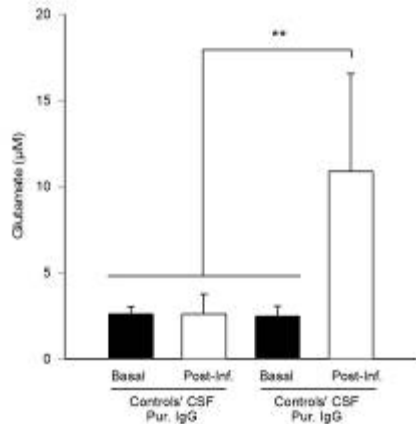
# Clinical presentation of patients with NMDAr-Ab is similar to Pharmacological or genetic inactivation of NMDAr of Gabaergic interneurons



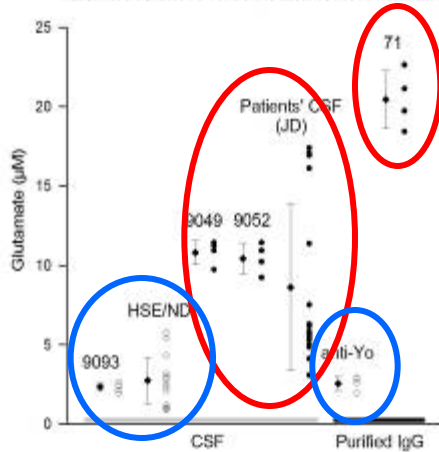
See Florance-Ryan and Dalmau, Curr Opin Pediatr 2010

# In vivo, NMDAR-Ab increase cellular level of glutamate

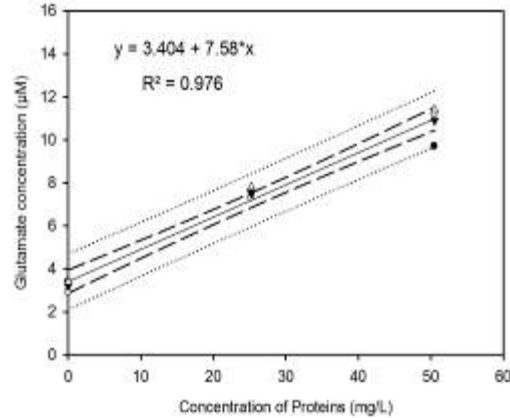
**A** Effects of Patients' CSF/Purified IgG on Extra-Cellular Concentrations of Glutamate



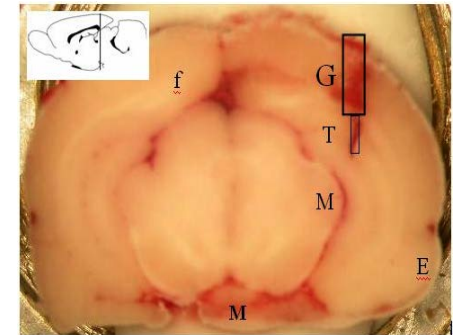
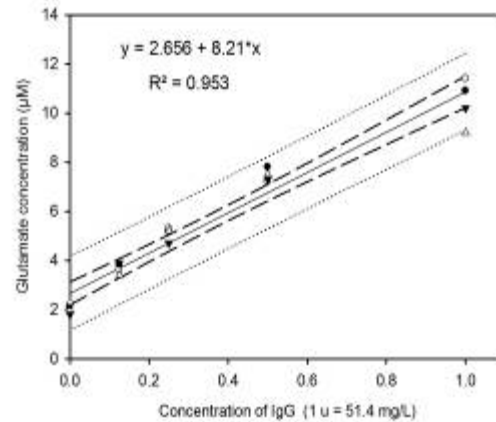
**B** Effects of Patients' CSF/Purified IgG on Extra-Cellular Concentrations of Glutamate



**C** Patient's CSF 9049 - Dose response



Purified IgG - Dose response



CSF and purified IgGs of patients with NMDAR-Ab

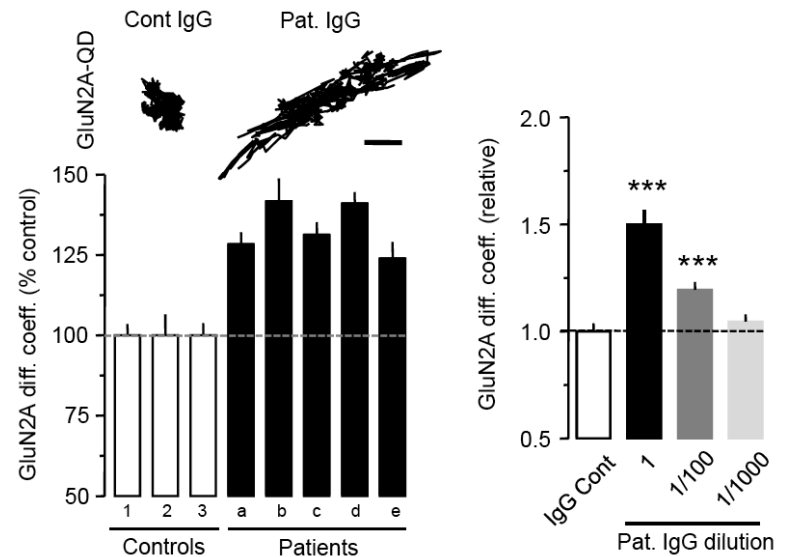
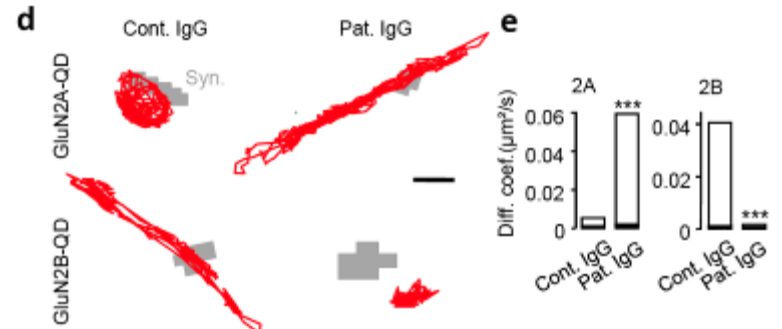
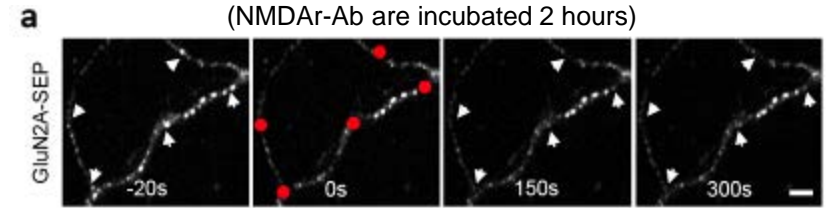
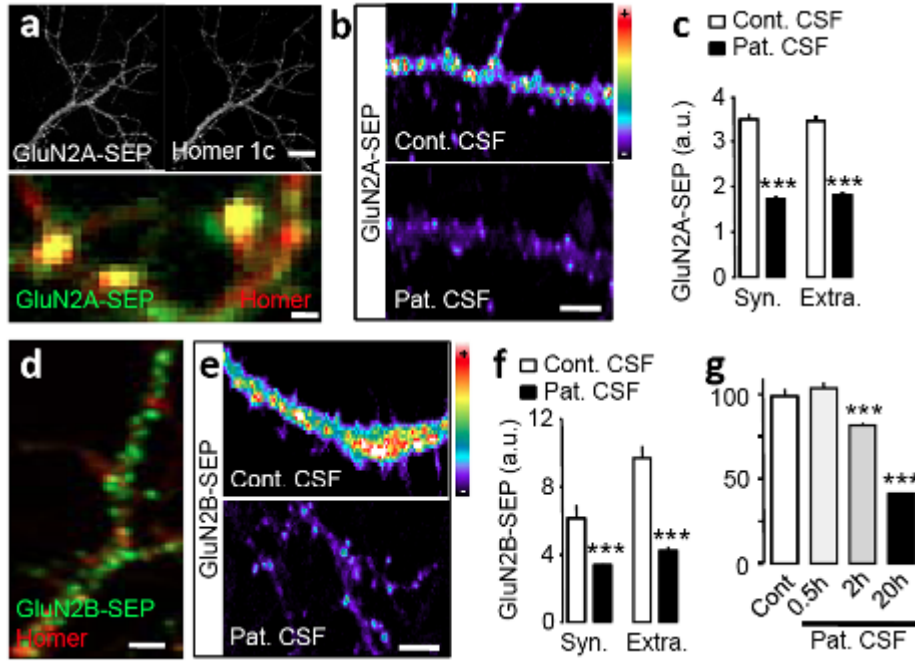
Increase in vivo:

levels of extra-cellular  
Glutamate

# How NMDAr-Ab provoke receptor internalization ?

NMDAr-Ab differentially affects the surface diffusion of NMDAr

NMDAr internalization is significant after 2 hours

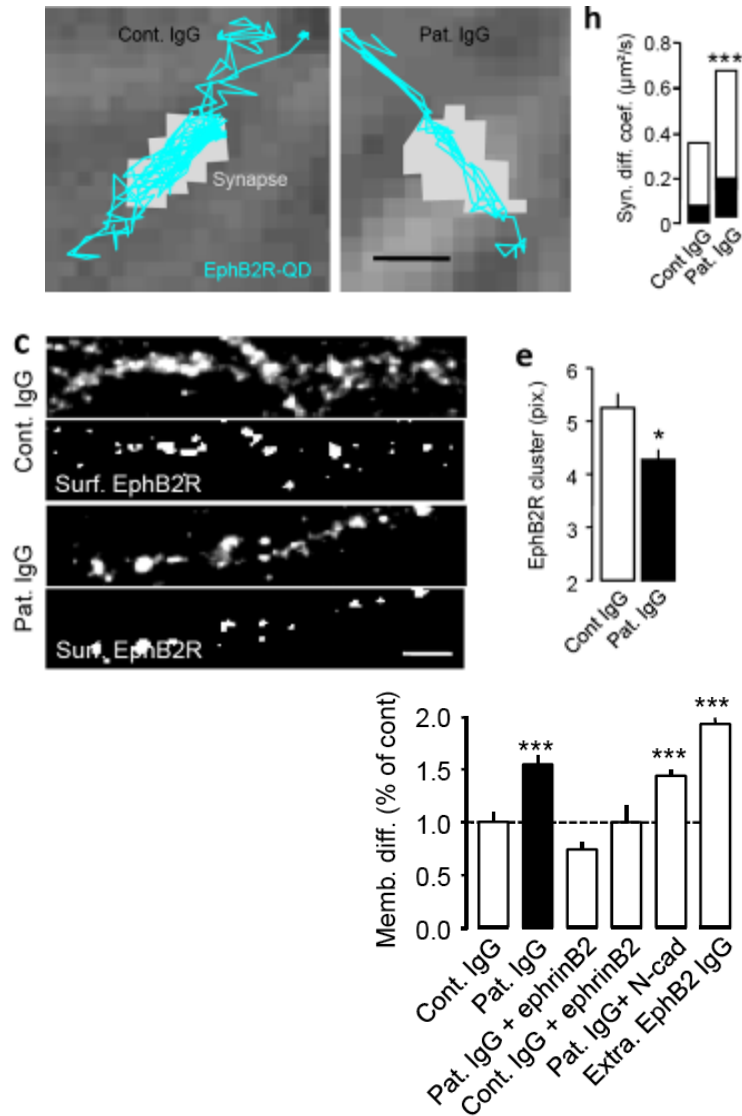


**NMDAr-Ab differentially affects the surface diffusion of NR2A and NR2B subunits**

- dose dependance
- All tested patients have the same effect

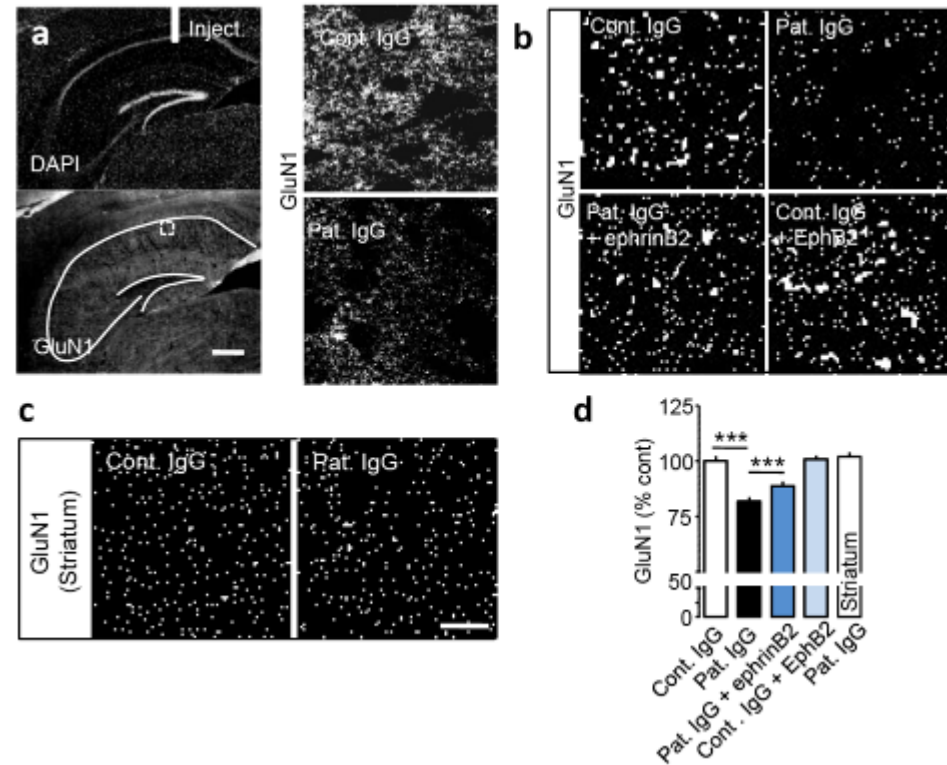
# How NMDAr-Ab provoke receptor internalization ?

NMDAr alters the EPHB2R surface diffusion and disturbs the interaction between surface GluN2A-NMDA receptor and EPHB2R.



Ephrin-B2 ligand-induced activation of EPHB2R reverses the effect of NMDAr in vitro and in vivo

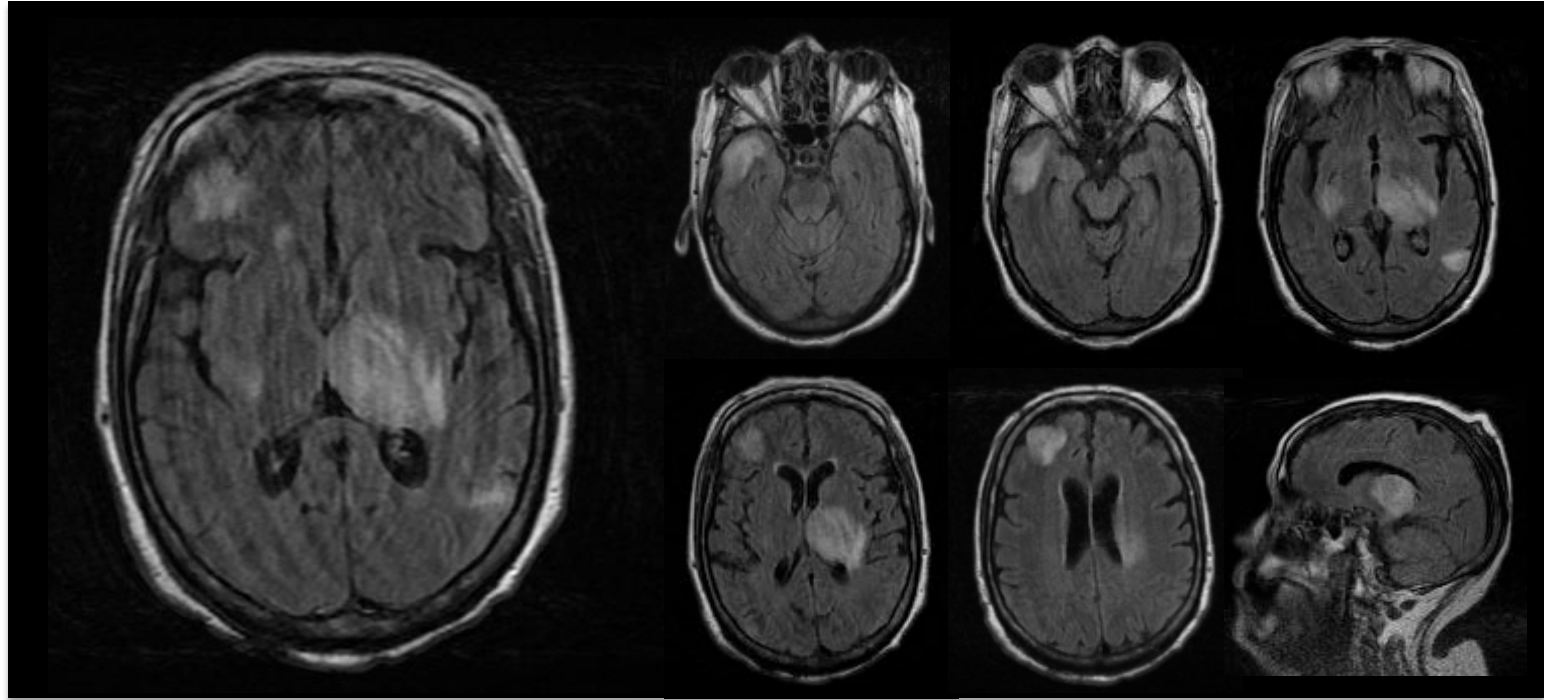
(NMDAr-Ab are injected 5-7h before mice death)



# Other encephalitis with autoantibodies

Man 55 years old. Right facial palsy. Myoclonus for 15 days  
Brutal breath arrest and hypertonic crisis  
Myoclonus, Dysautonomia  
CSF : inflammatory ; MRI normal ; Anti-Glycine réceptors antibodies  
IvIg, Plasma exchange, cyclophosphamide

# D'autres auto-anticorps sont associés à des tableaux de pseudo-ADEM



59 years old woman

No past medical history

April 2011, brachio-facial myoclonus, hyponatremia

June 2011, myoclonus, sudden falls, confusion

October 2011, dysautonomia, right hemiplegia

MRI : lesions with mass effects

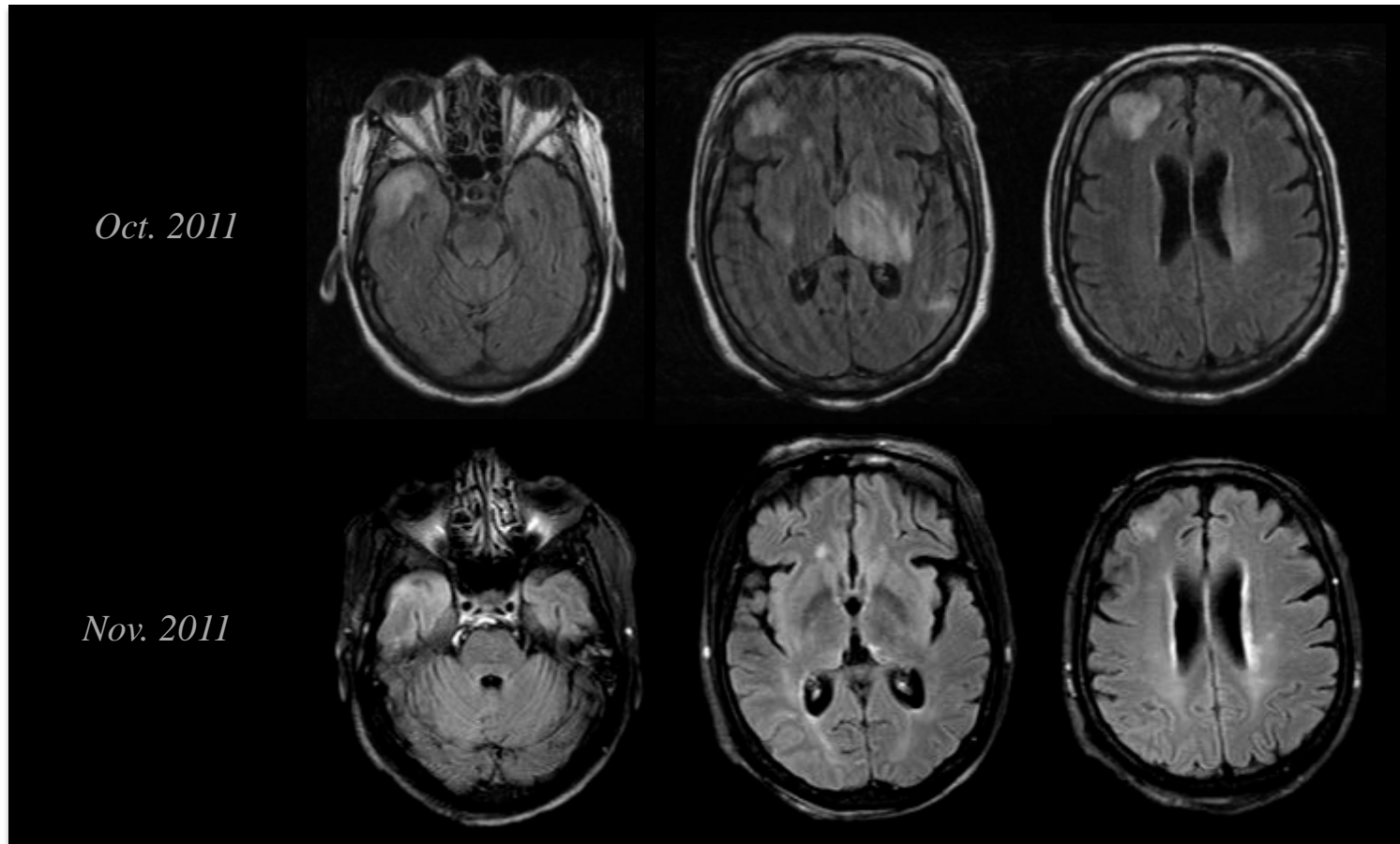
Biopsy : Inflammation +++ discussion of gliomatosis

February 2012 : lung adenocarcinoma



# Anti-Lgi1 auto-antibodies

Pseudo-tumoral lesions



Improvement after immunomodulator treatments  
Reccurence with tumor diagnosis without MRI modifications

## Other autoantibodies associated with encephalitis directed against cell surface antigens

	NMDAr	AMPAr	GABA <sub>BR</sub>	Lgi1	CASPR2	Glycine R	mGluR1	mGluR5	GAD
Number of published cases	>600	12	17	>100	30	6	4	3	>10
Clinical signs	encephalitis	LE	LE	LE	LE myotonia	LE myoclonus	ataxia	LE	Ataxia Stiff LE
Role	antagonist	antagonist	?	?	?	antagonist	agonist	?	?
Paraneoplastic cases	60%	70%	47%	15%	15%	10%	25%	100%	15%
Associated tumors	Ovary teratoma	Thymoma breast SCLC	SCLC	SCLC, thymoma	SCLC, thymoma	Thymoma	Hodgkin	Hodgkin	Lung thymoma

Anti-VGKC = anti-Lgi1 and anti-CASPR 2 +++  
LE = limbic encephalitis

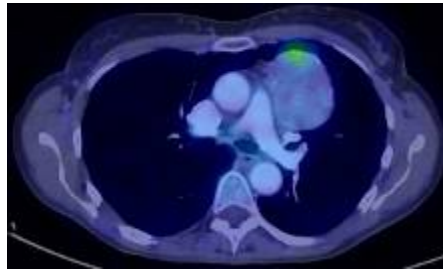
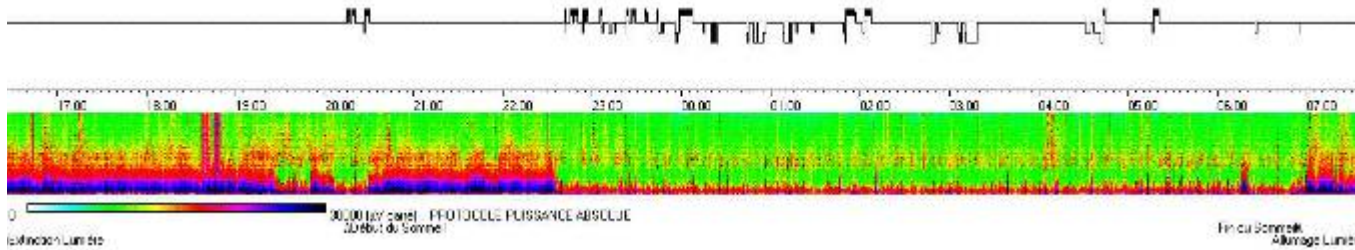
Lai et al, Lancet Neurol 2010;9:776-785  
Irani et al, Brain 2010;133:2734-2748

# Probably many other autoantibodies are unknown

62 years old woman without medical past history

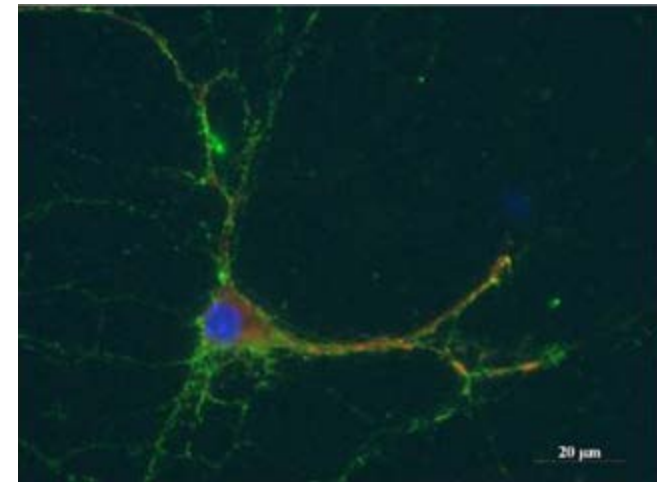
Sudden seizures, confusion

**Abnormal polysomnography** – Drastic reduction of total sleep time  
Complete loss of REM sleep

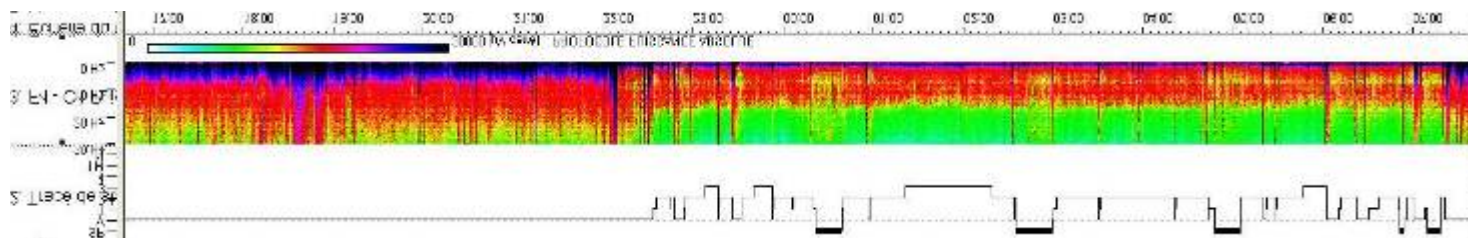


Malignant Thymoma  
Surgery

## Unknown circulating antibody



## Total recovery after surgery and immunoglobulines

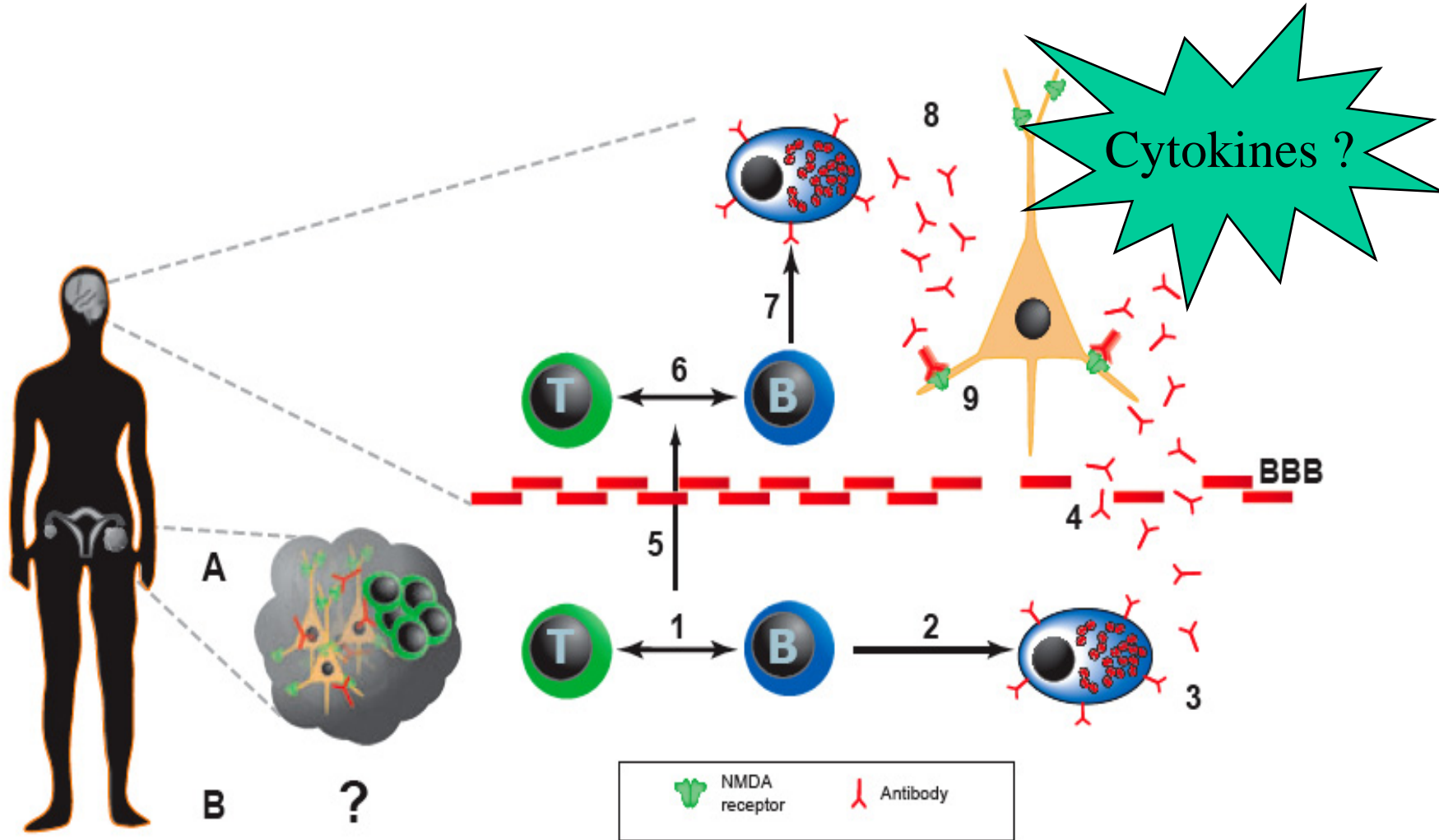


**BILAN DES ANTICORPS DETECTES ENTRE MAI 2007 ET  
OCTOBRE 2012 PAR LE CENTRE DE REFERENCE**

Anticorps ou groupe d'anticorps détecté	2008	2009	2010	2011	01/2012 à 10/2012
HU	35	27	33	31	37
NMDAr	6	20	22	35	42
Atypique	3	5	14	21	8
YO	12	3	7	5	11
MA2/MA1	5	1	4	4	2
CV2	7	2	3	4	7
RI	4	1	3	3	5
GAD	2	-	5	7	5
Amphiphysine	3	1	2	5	-
LG11	-	-	3	13	7
Sox-1	-	2	1	1	-
CASPR2	-	-	-	5	3
VGKC	-	1	1	-	-
TR	3	1	-	-	1
GABA <sub>B</sub>	-	-	-	1	2
AMPAr	-	-	-	2	3
HU/CV2	2	-	1	-	-
HU/RI	1	-	-	1	-
Nucléaire	-	-	1	-	-
Glycine-récepteur	-	1	-	-	-
VGCC	1	-	-	-	-
Anti-MAG	-	-	1	-	-
RNP	-	1	-	-	-
CV2/VGCC	-	-	1	-	-
HU/Amphiphysine	-	-	1	-	-
VGKC/AMPAr	-	-	1	-	-
MA/TA/VGCC	-	-	-	-	-
YO/Atypique	1	-	-	-	-
CRMP5	-	-	-	-	2
GAD+Neuropile	-	-	-	-	1
<b>Total anticorps détectés</b>	<b>85</b>	<b>66</b>	<b>106</b>	<b>138</b>	<b>136</b>

	2008	2009	2010	2011	01/2012 à 05/2012
Patients Anti-NMO+	42	54	102 dont 15 déjà connus	103	54

# Pathophysiology of encephalitis with autoantibodies ?



## **Conclusion :**

- Concept d'encéphalite autoimmune avec autoanticorps clairement établi
- Les autoanticorps dirigés contre un antigène membranaire jouent un rôle direct
- Existence très probable de formes frustes ou modérées
- La fréquence des formes idiopathiques est supérieure aux paranéoplasiques
- Les tumeurs sont probablement un élément déclencheur parmi d'autres
- Aucun guideline de traitement
- Physiopathologie exacte non élucidée

Thanks to

*Members of  
Paraneoplastic neurological syndrome reference center  
Lyon, Paris, St-Etienne*



Lyon's neuroscience research center  
Team : « Neuro-Oncology and Neuro-  
Inflammation »  
Inserm 1028 / CNRS 5292  
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