“The antibody-mediated encephalitis from discovery to new clinical insights and mechanisms”

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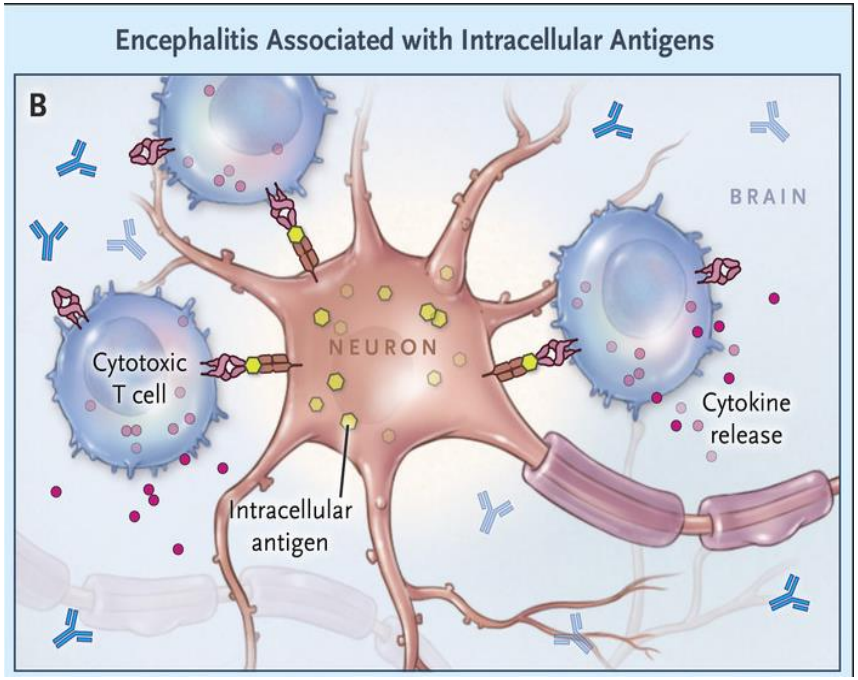
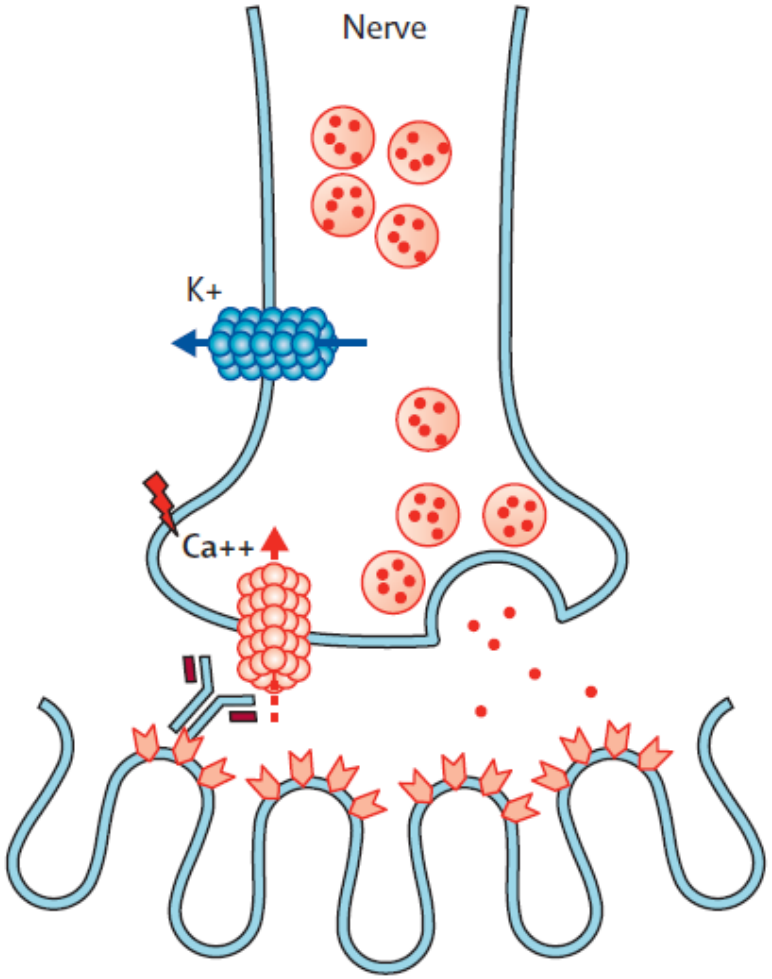
Antibodies to intracellular neuronal proteins (paraneoplastic CNS syndromes)



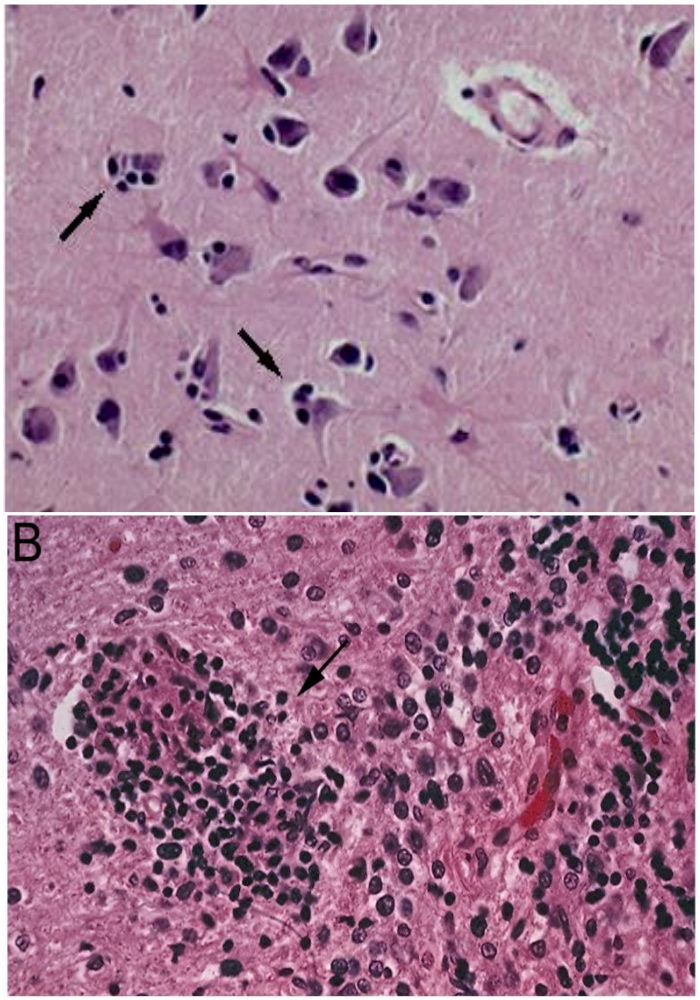
Dalmau and Rosenfeld, Lancet Neurol 2008; 7:327-340

Antibodies to cell surface proteins (Lambert-Eaton; myasthenia gravis)



Titulaer et al., Lancet Neurol 2011;10:1098-107

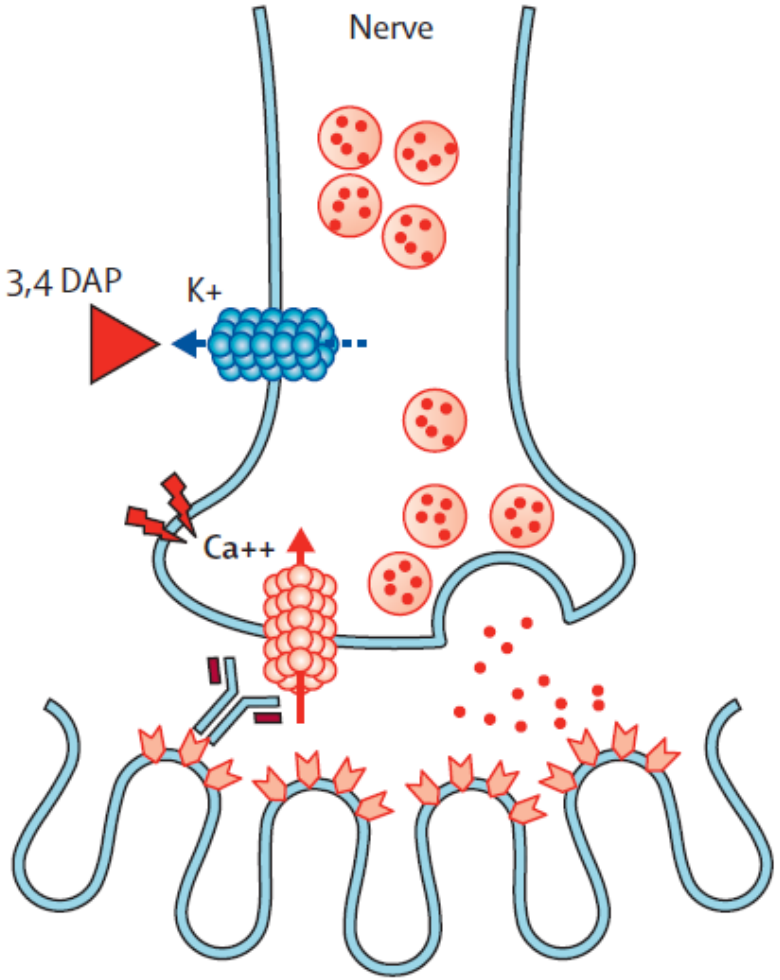
Antibodies to intracellular neuronal proteins (paraneoplastic CNS syndromes)



Irreversible

Dalmau and Rosenfeld, Lancet Neurol 2008; 7:327-340

Antibodies to cell surface proteins (Lambert-Eaton; myasthenia gravis)



Reversible

Titulaer et al., Lancet Neurol 2011;10:1098-107

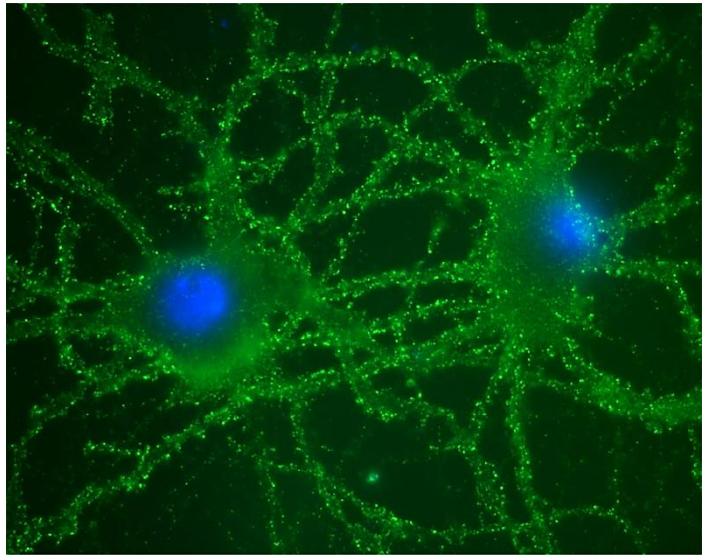
Paraneoplastic Encephalitis, Psychiatric Symptoms, and Hypoventilation in Ovarian Teratoma

Roberta Vitaliani, MD,[1] Warren Mason, MD,[2] Beau Ances, MD, PhD,[1] Theodore Zwerdling, MD,[3]
Zhilong Jiang, PhD,[1] and Josep Dalmau, MD, PhD[1]

Ann Neurol 2005;58:594-604

Four young women (14, 26, 28, 40 years):

- **Psychiatric symptoms:** delusions, hallucinations, disorganized behavior and speech
- **Encephalitis**: Neurologic symptoms including: insomnia, abnormal movements, seizures, autonomic instability, central hypoventilation *and* CSF inflammatory changes
- **Ovarian teratoma**

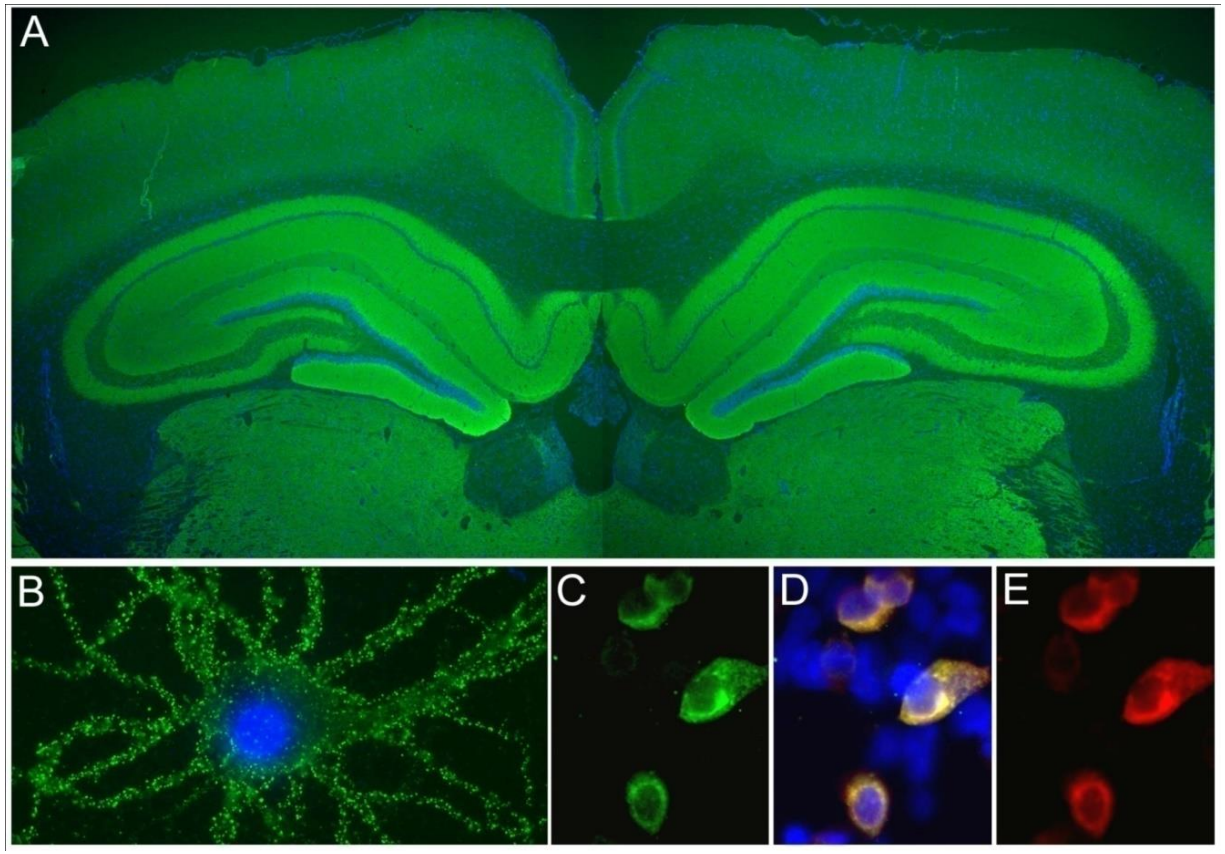


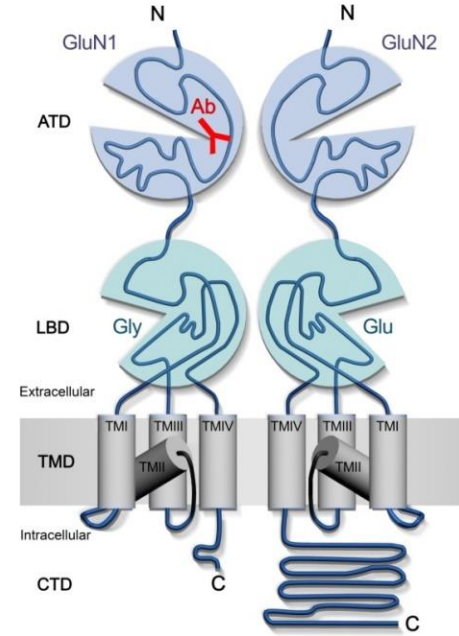
100 patients

Anti-NMDA-receptor encephalitis: case series and analysis of the effects of antibodies

Josep Dalmau, *Amy J Gleichman, *Ethan G Hughes, Jeffrey E Rossi, Xiaoyu Peng, Meizan Lai, Scott K Dessain, Myrna R Rosenfeld, Rita Balice-Gordon, David R Lynch

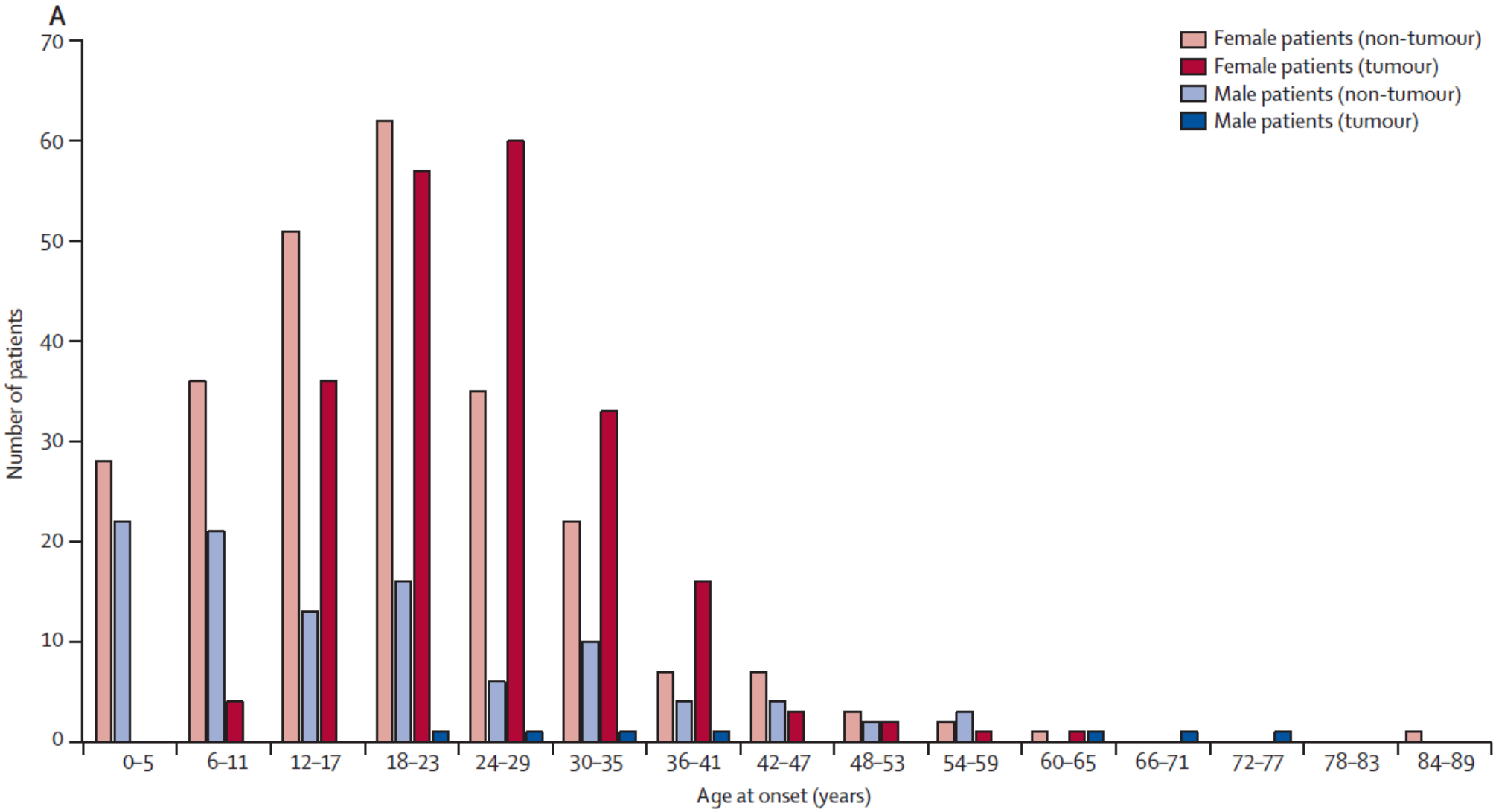
Lancet Neurol 2008;7:1091





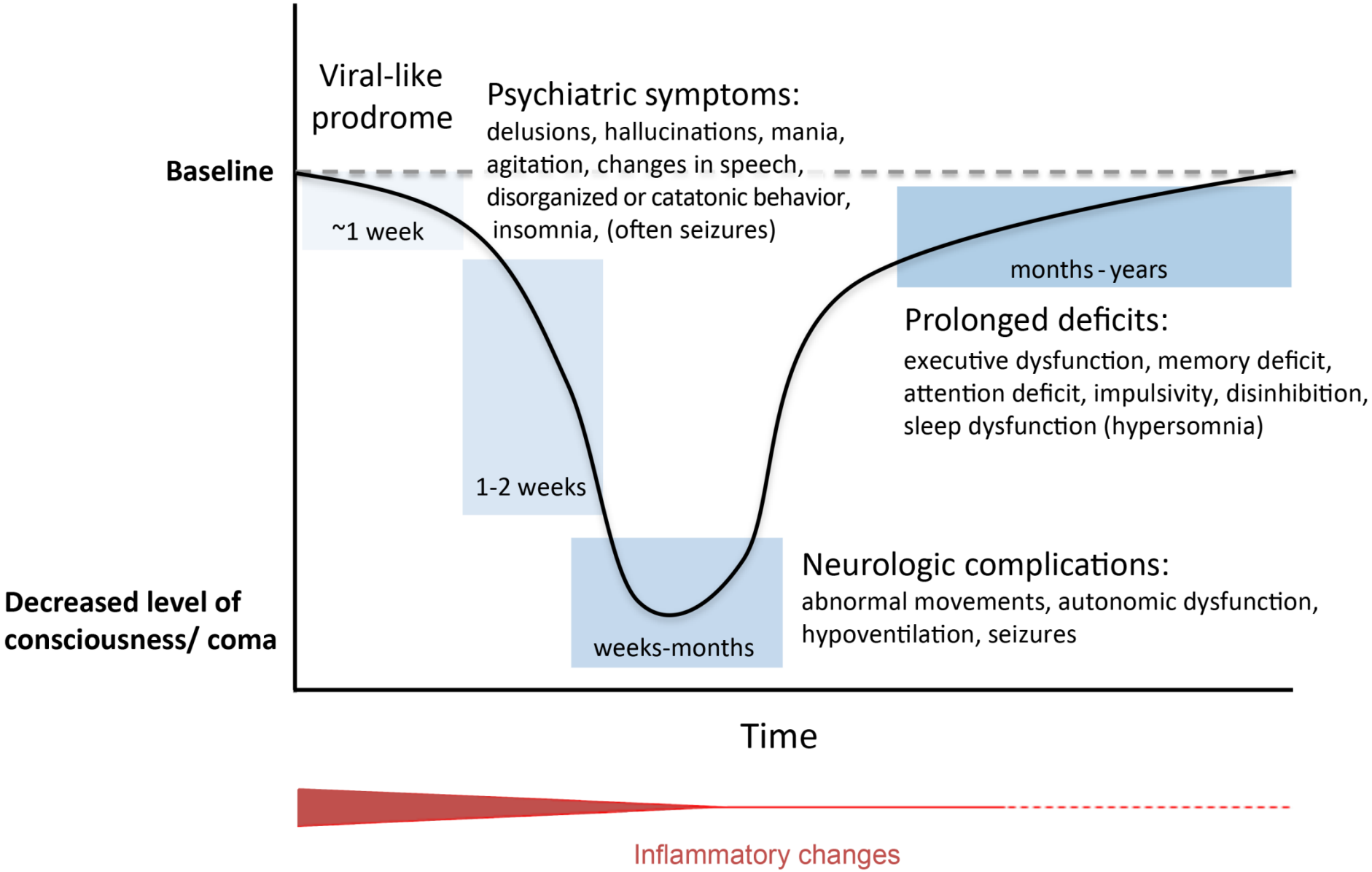
Dalmau, Geis, and Graus.
Physiol Rev 2017;97:839

Anti-NMDAR encephalitis: gender and tumor association in 577 patients

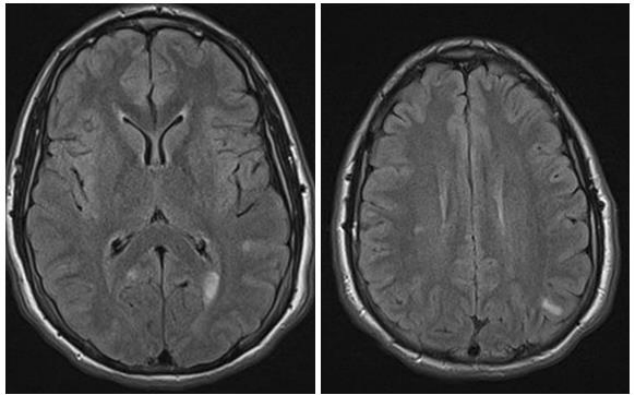


Titulaer et al., Lancet Neurol 2013;12:157

Symptoms and course of anti-NMDAR encephalitis



MRI: 35% non-specific findings



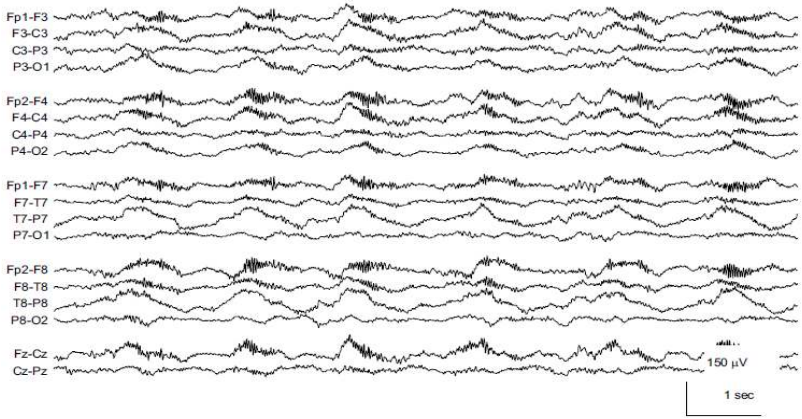
<u>EEG abnormal >95%</u>

Extreme delta brush ~10-30%

<u>CSF: 85% abnormal</u>

- Lymphocytic pleocytosis

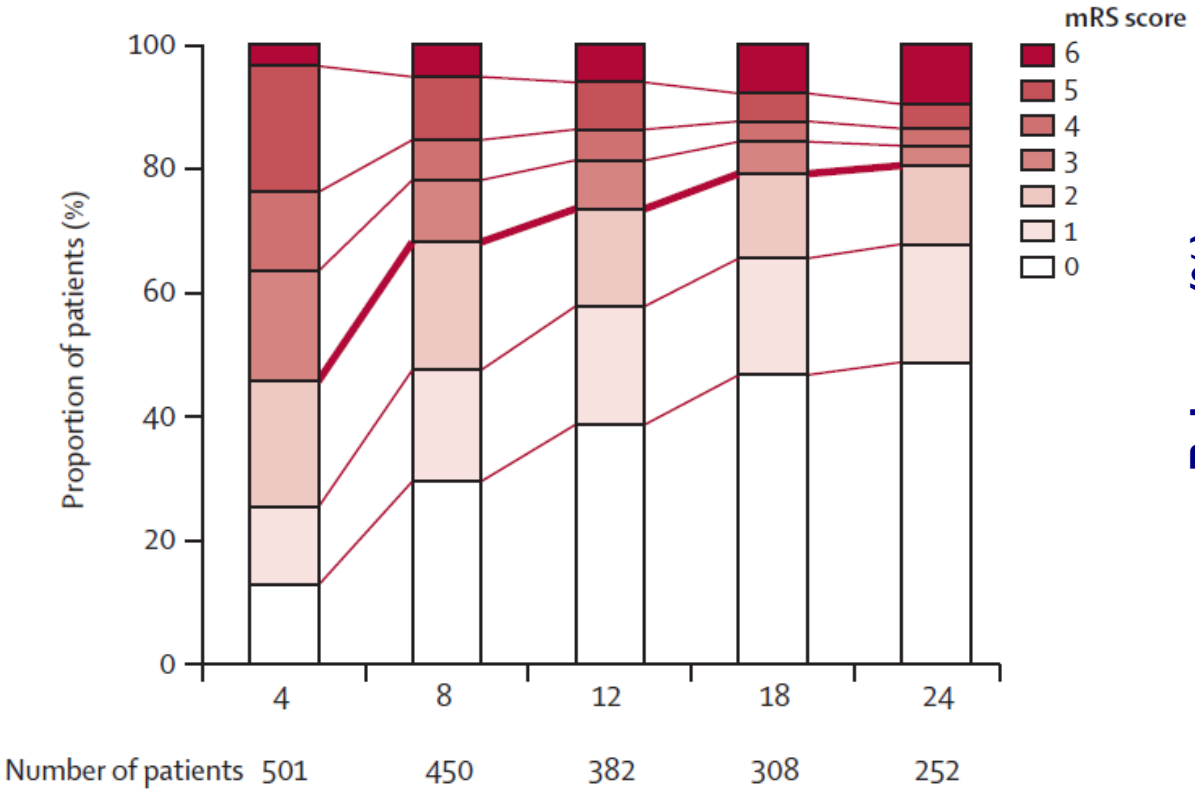
  WBC 32 (5-480) 91%
- Increased proteins 32%
- Oligoclonal bands 67%

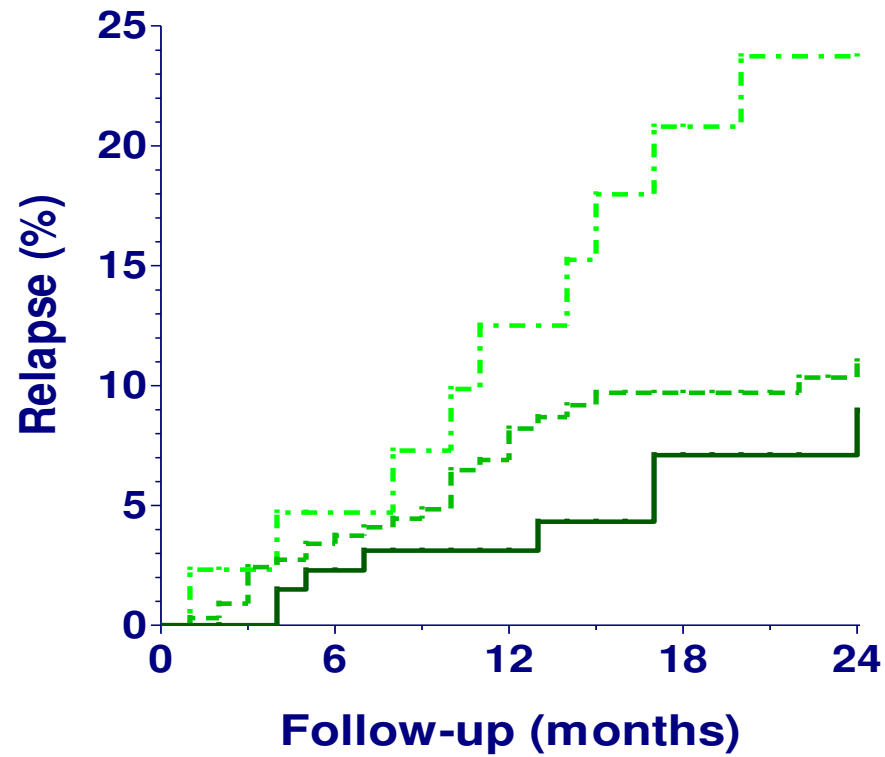


Dalmau et al., Lancet Neurol 2008;7:1091

Schmitt et al., Neurology 2012;79:1094

Anti-NMDAR encephalitis: Outcome and relapses





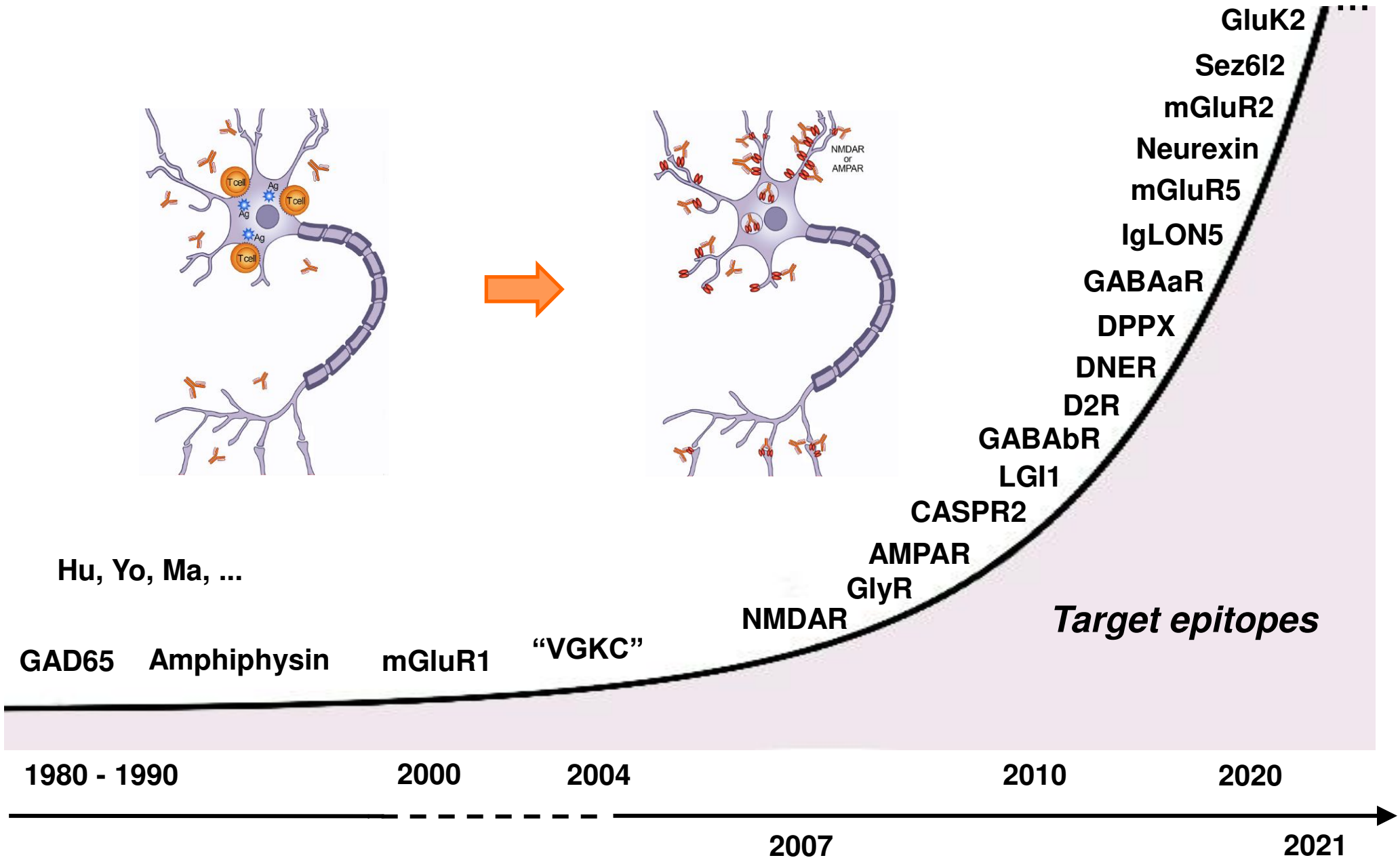
- no treatment
- 1st line treatment (steroids, IVIg, plasma exchange)
- 2st line treatment (rituximab, cyclophosphamide)

Titulaer et al., Lancet Neurol 2013;12:157

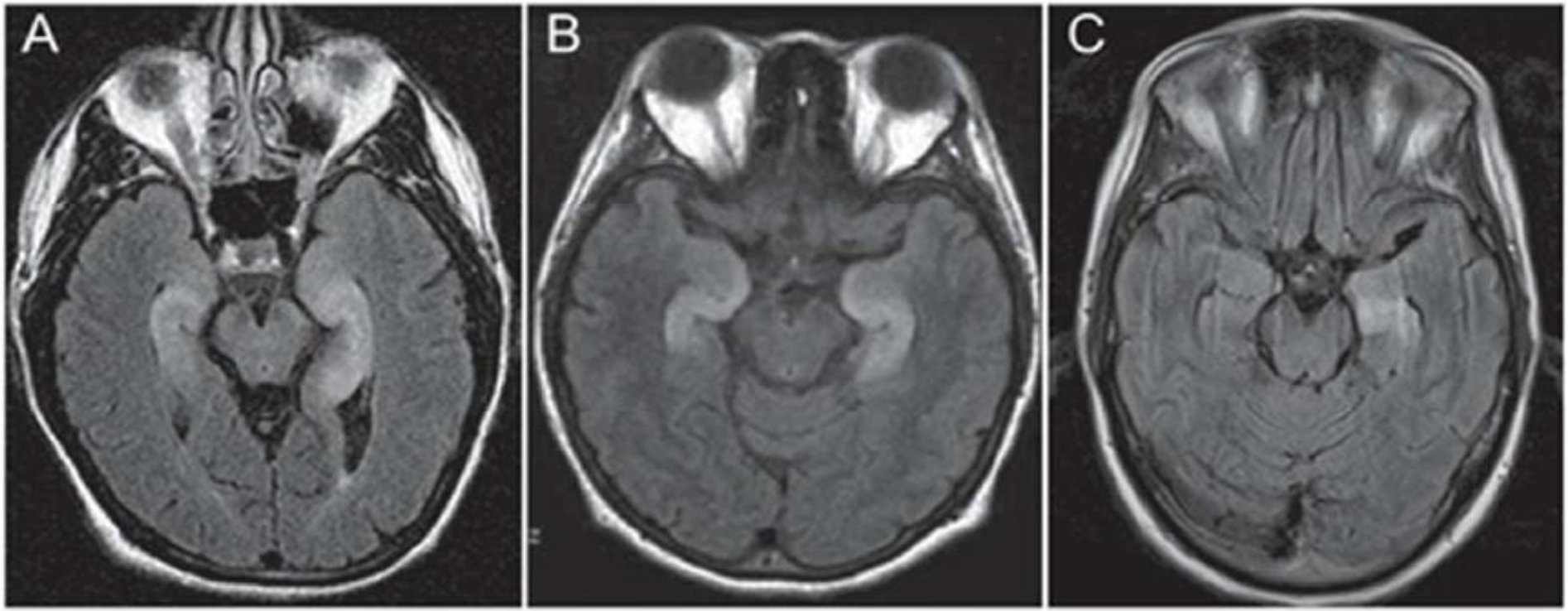
Implications

Neurology
Neuroscience
Psychiatry

New category of antibody-mediated encephalitis



MRI findings in several autoimmune limbic encephalitis



Anti-LGI1

- No cancer
  (<10% thymoma)
- Hyponatremia
- Faciobrachial dystonic seizures

Anti-AMPA-R

- 65% cancer
  (lung, breast, thymoma)
- Concurrent autoimmunities
- Tendency to relapse

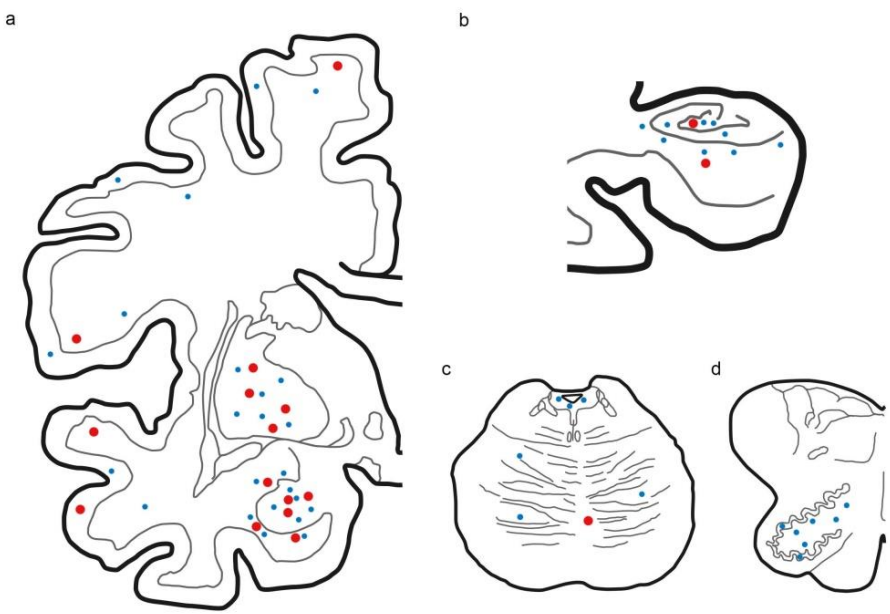
Anti-GABAb-R

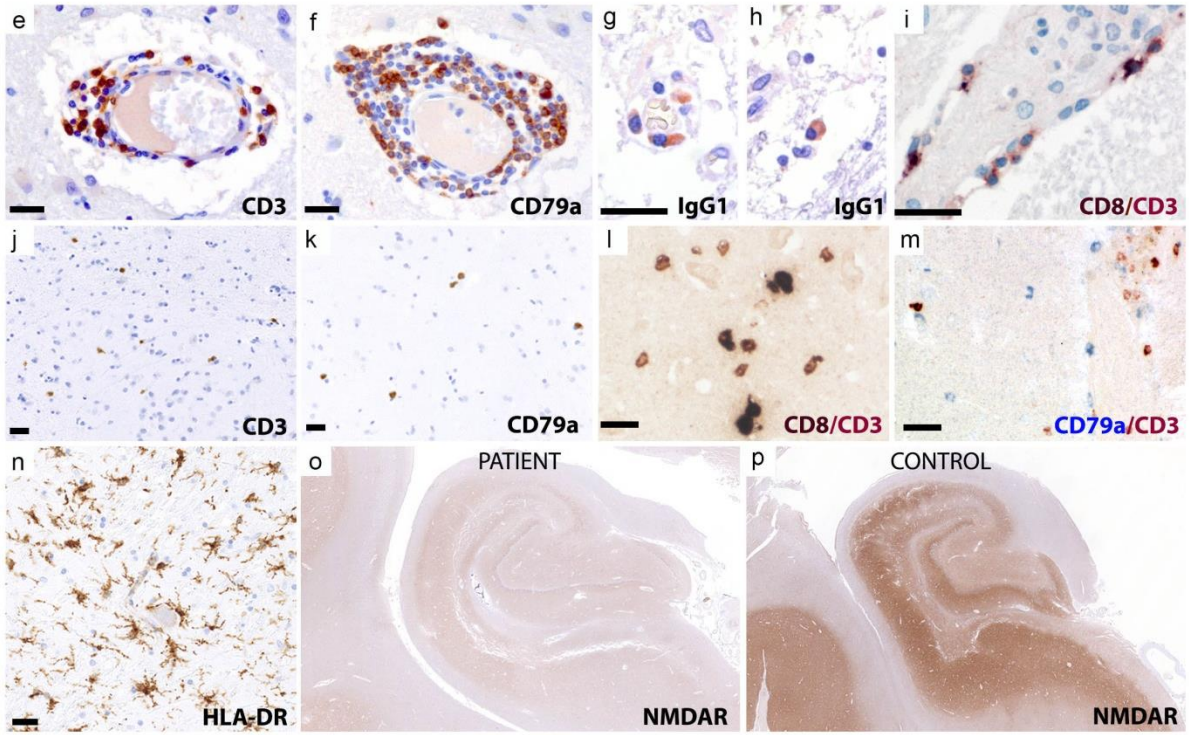
- 50% SCLC
- early and prominent seizures

Adapted from Leypoldt et al., *Ann NY Acad Sci.* 2015;1338:94-114

Neuroscience/Immunology
(pathogenic effects of the antibodies)

Immunopathology: patient with anti-NMDAR encephalitis

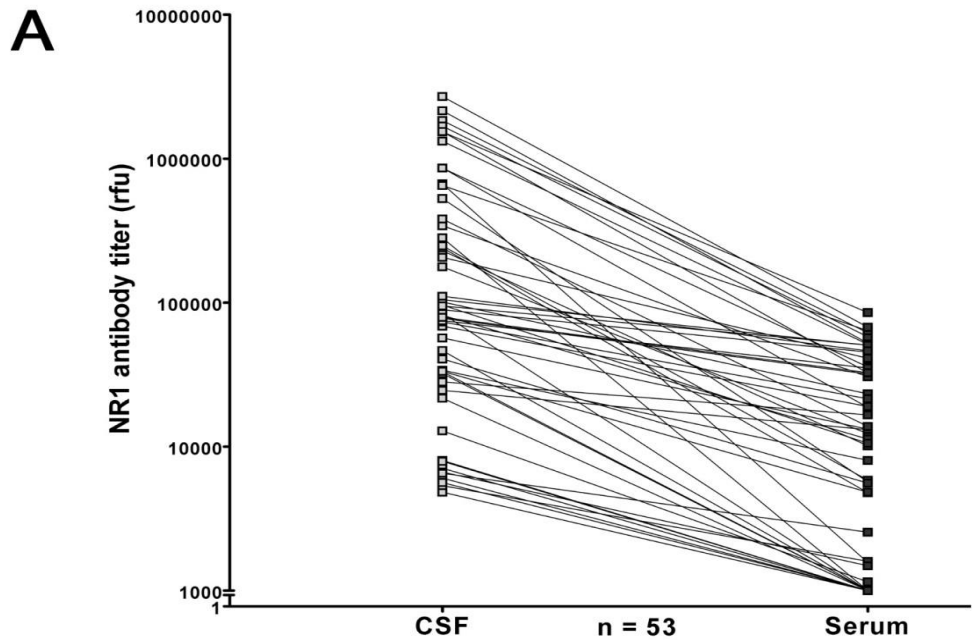




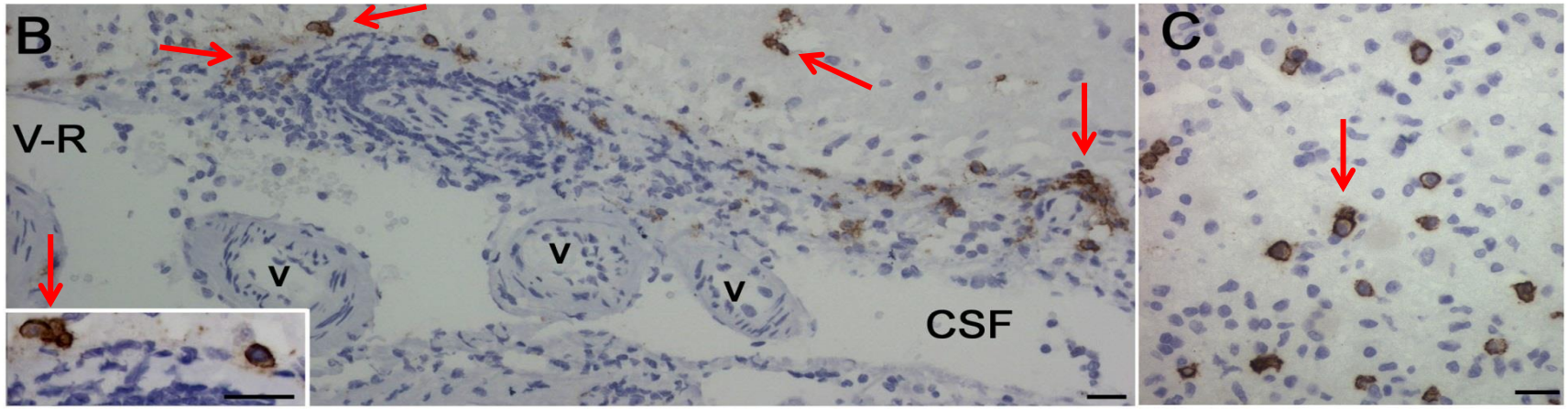
Red dot: CD79a+ (plasma cells)
Blue dot: CD3+ T cells

Zrzavy T. et al., Ann Neurol 2021;90:725-737

Anti-NMDAR encephalitis: Intrathecal synthesis of antibodies and presence of plasma cells in CNS

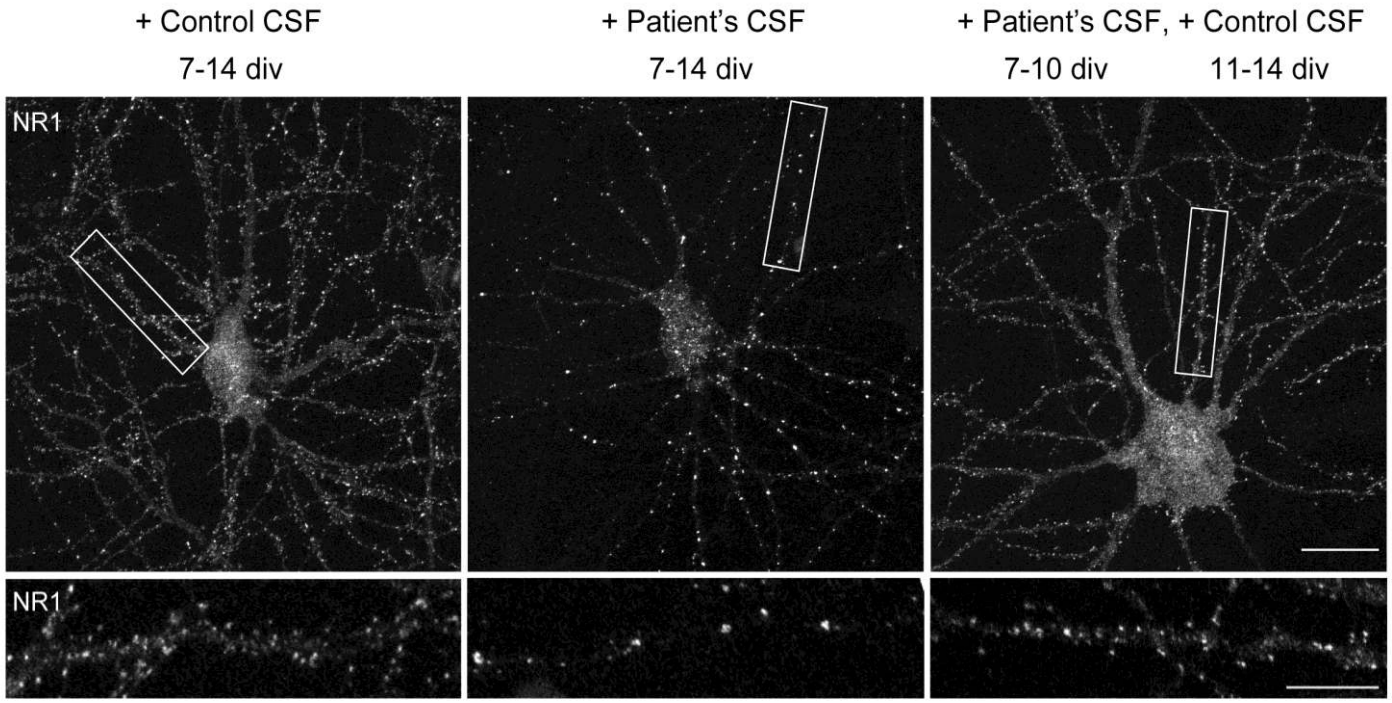


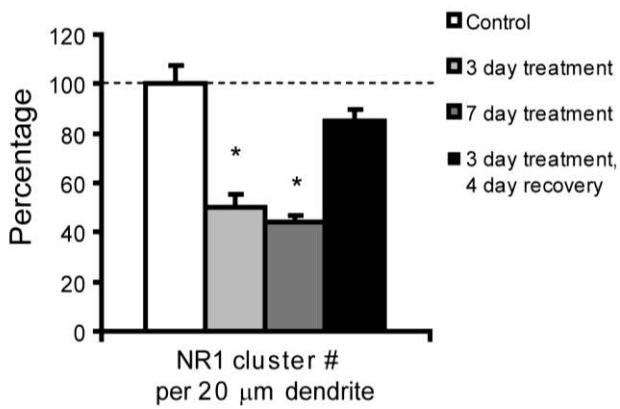
Dalmau et al., Lancet Neurol 2008; 7:1091

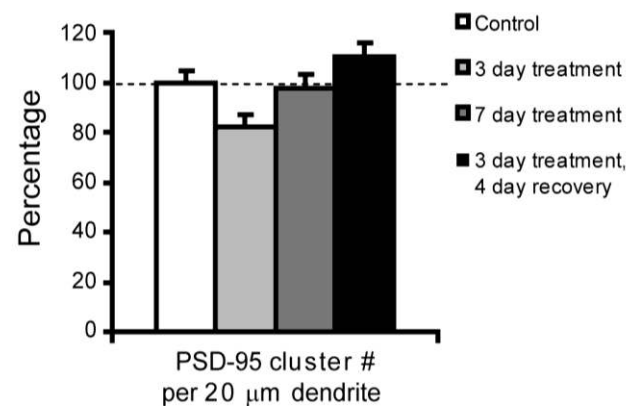


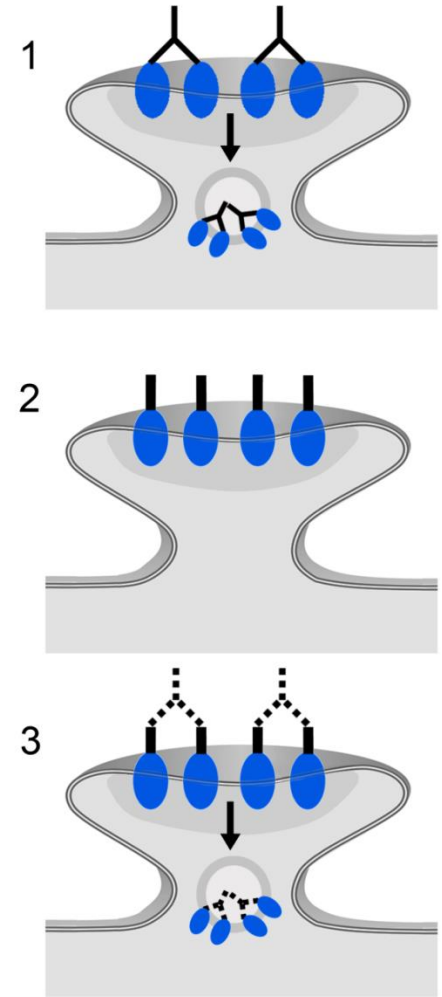
Martinez-Hernandez et al., Neurology 2011;77:589

Patient's antibodies decrease the number of clusters of NMDAR



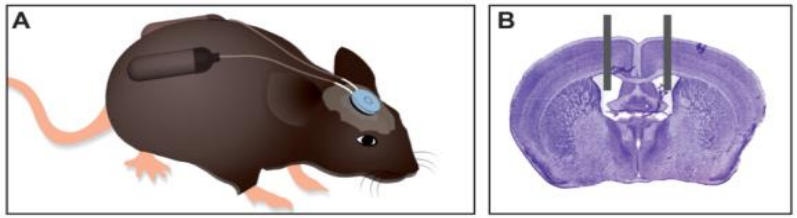


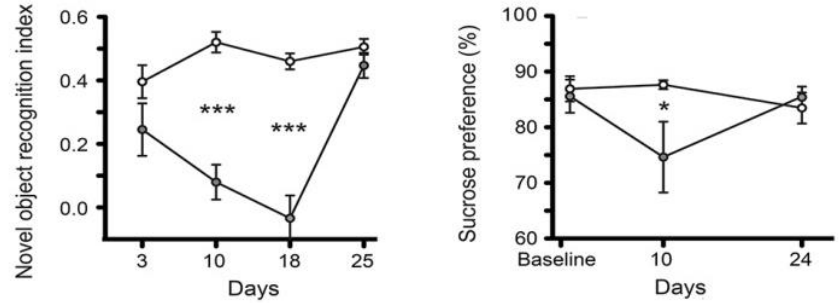




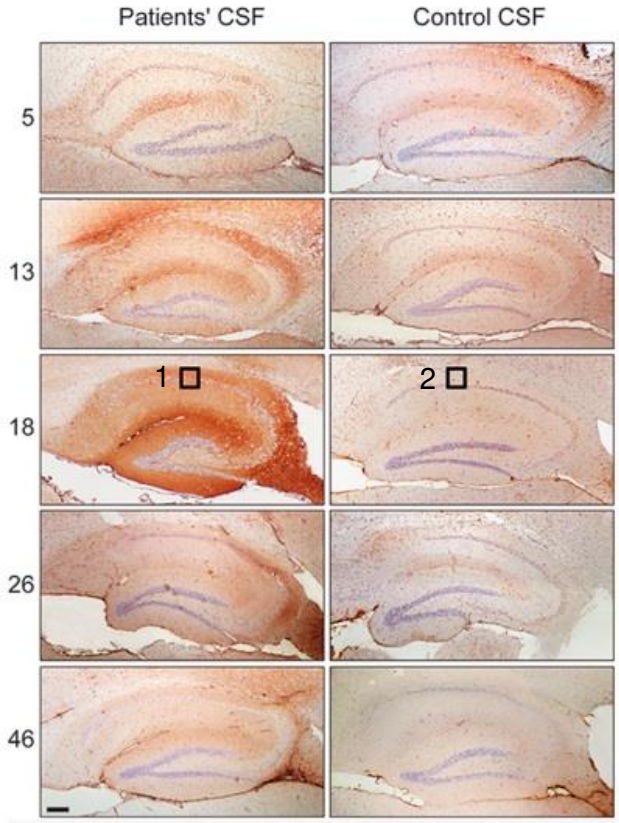
Dalmau et al. Lancet Neurol 2008;7:1091-8

Patients' antibodies alter memory and behavior

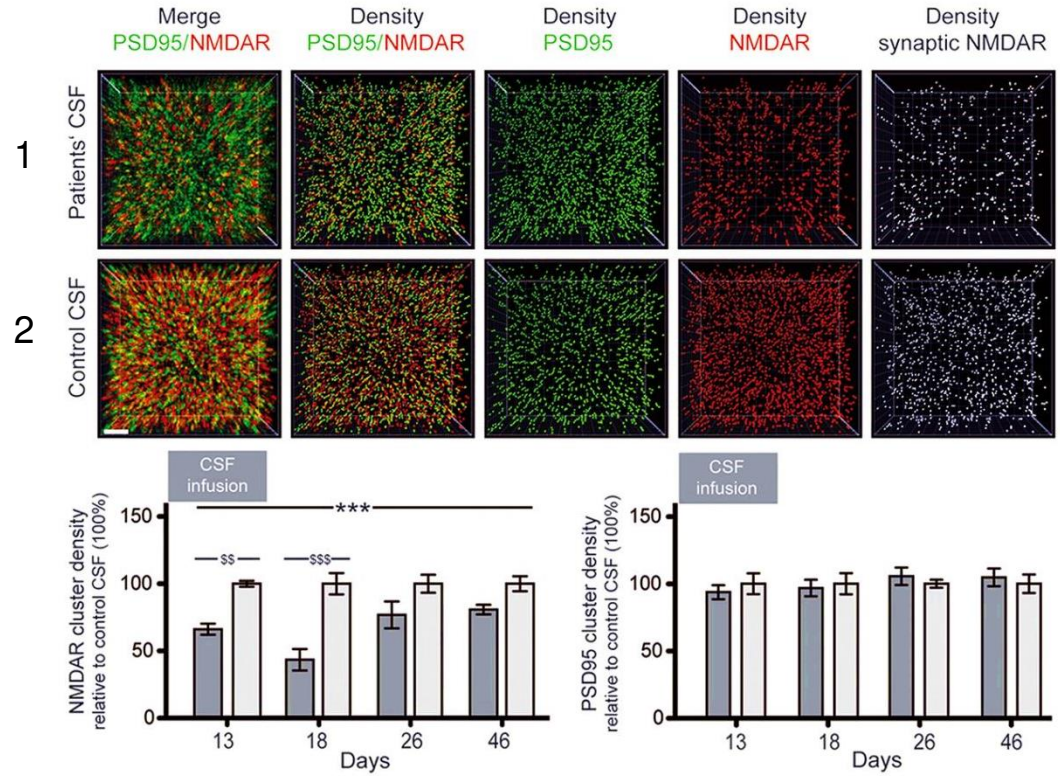




Antibody binding to brain

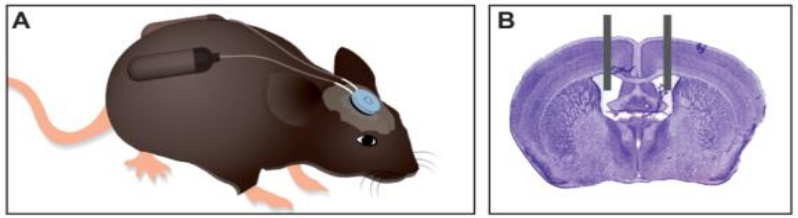


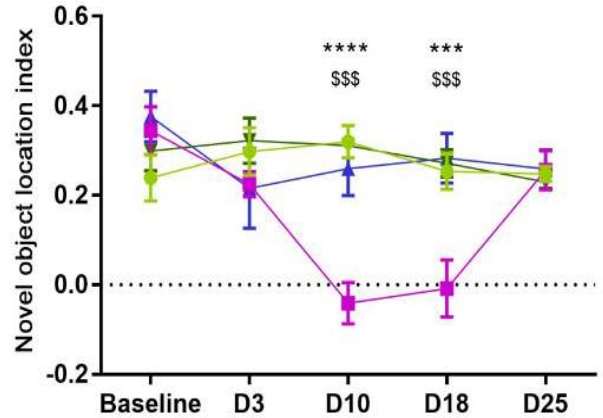
Patients' antibodies specifically decrease of synaptic NMDARs

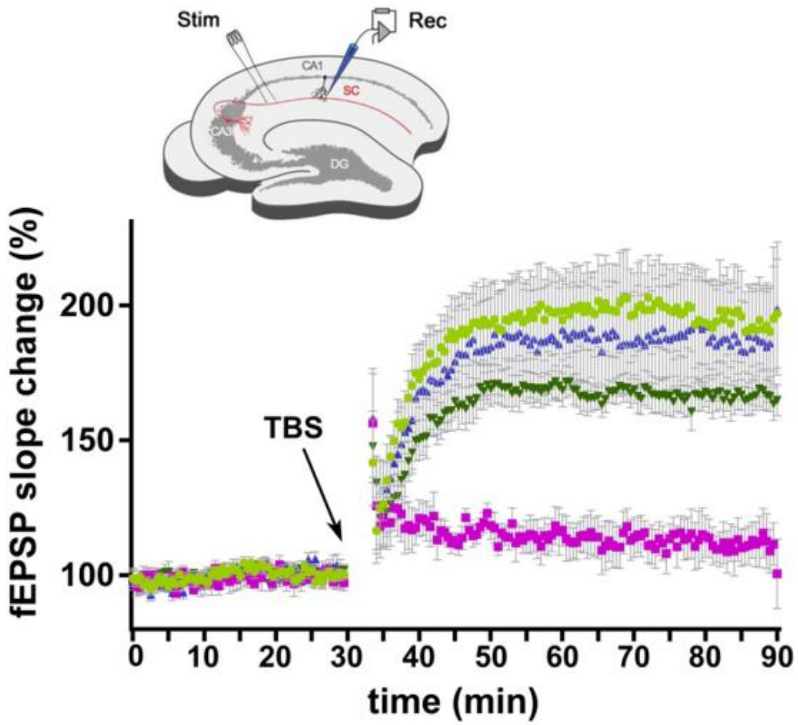


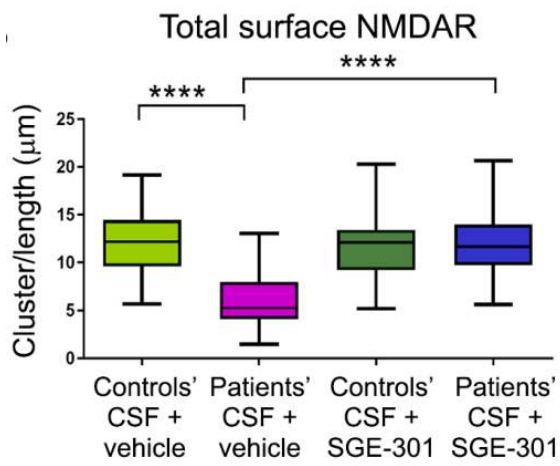
Planagumà J, et al. Brain 2015; 138:94-109

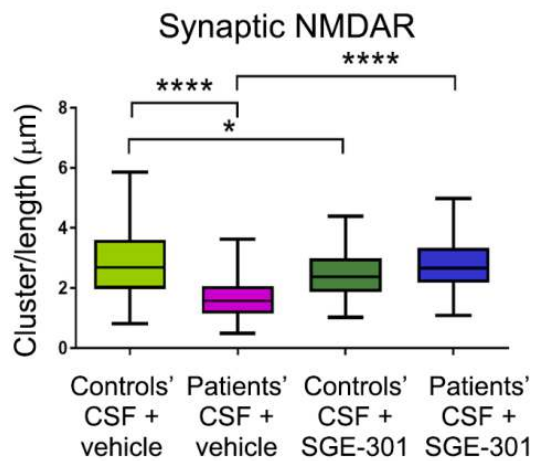
A lipophilic allosteric modulator of NMDAR prevents the pathogenic effects of patients antibodies





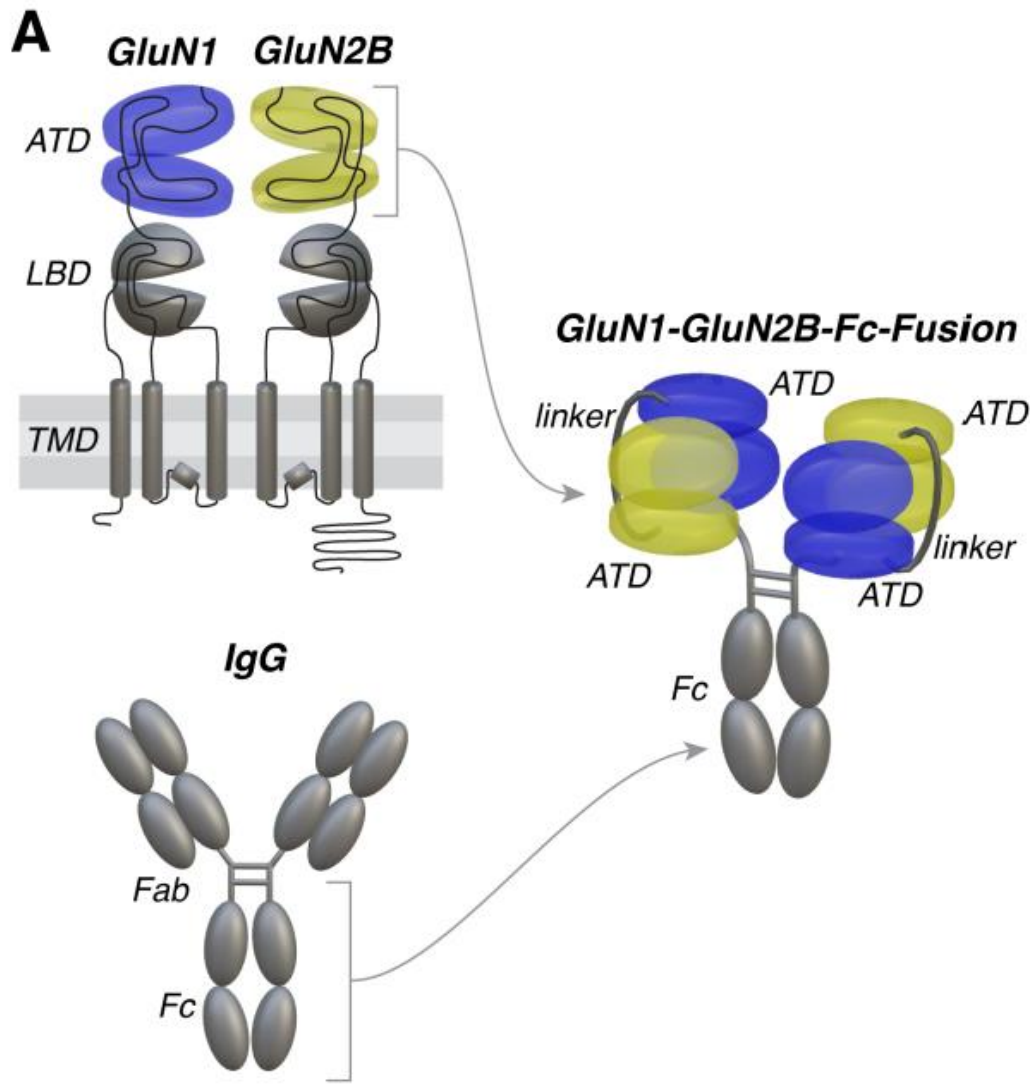






Mannara et al., Brain 2020;143:2709-2720.

An NMDAR-Fc-fusion construct neutralizes the pathogenic effect of patients' NMDAR antibodies



Steinke S et al., Brain 2023, Mar 3;awac497. doi: 10.1093/brain/awac497

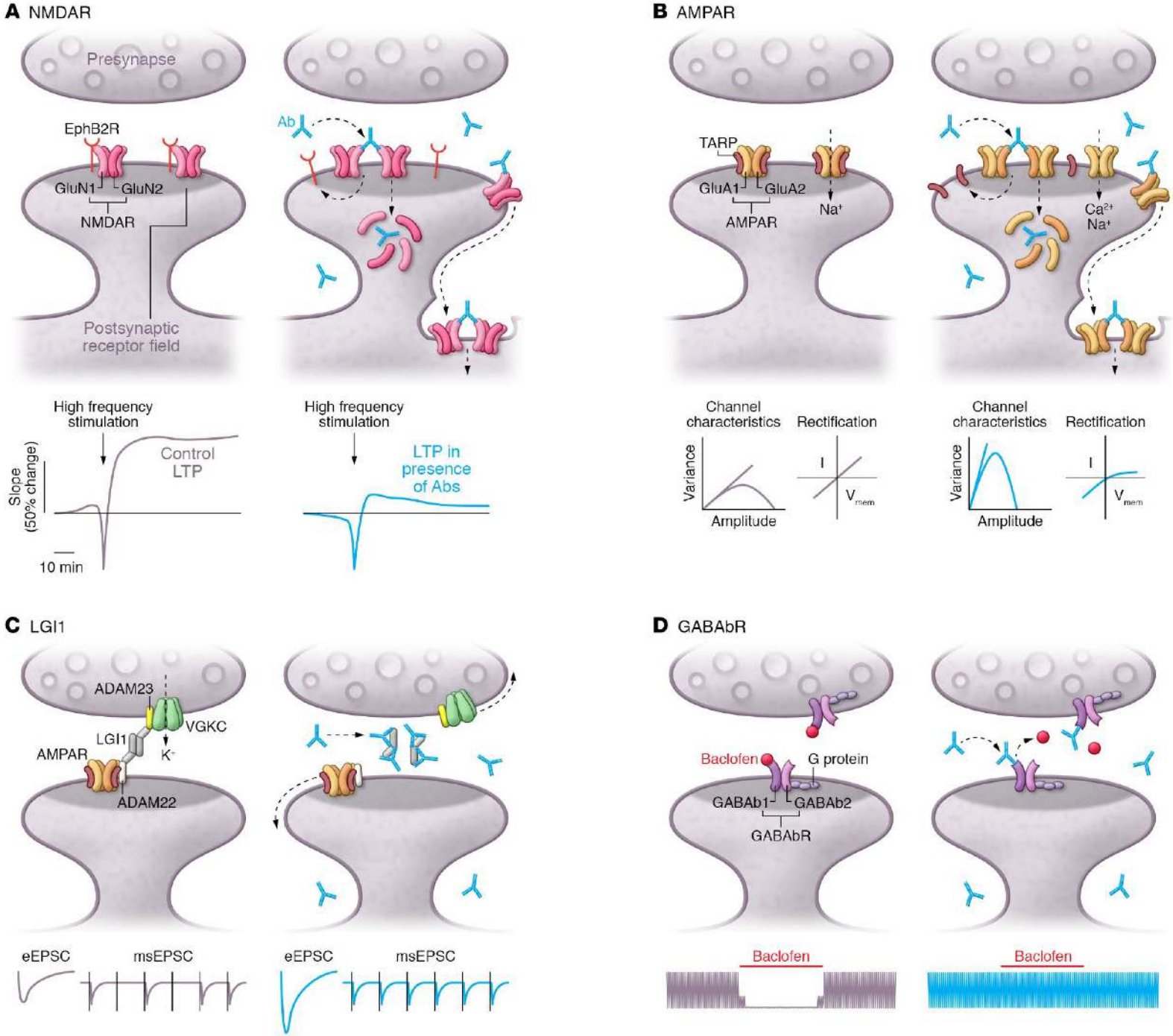
Antibody-mediated mechanisms

Haselmann et al. Neuron 2018;100:91-105

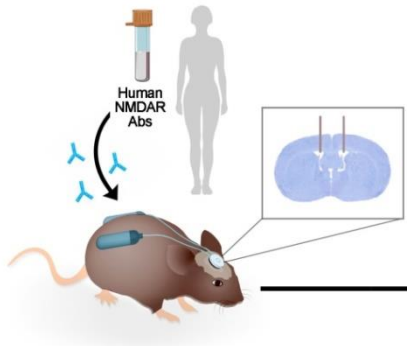
Geis et al., J Clin Invest 2019;129:926-940

Petit-Pedrol M, et al., Brain 2018;141:3144-3159

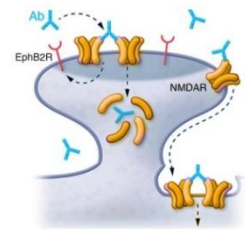
Courtesy of Lancaster E. et al;

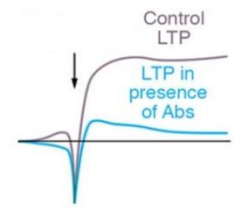


Passive immunization

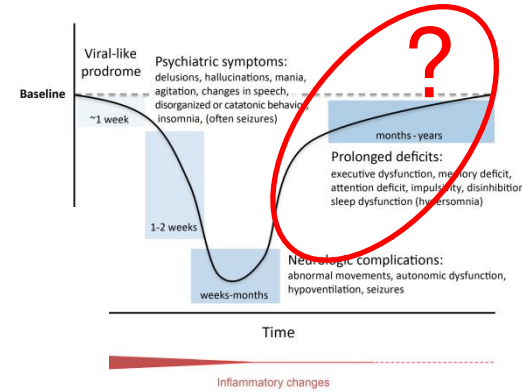


Brain

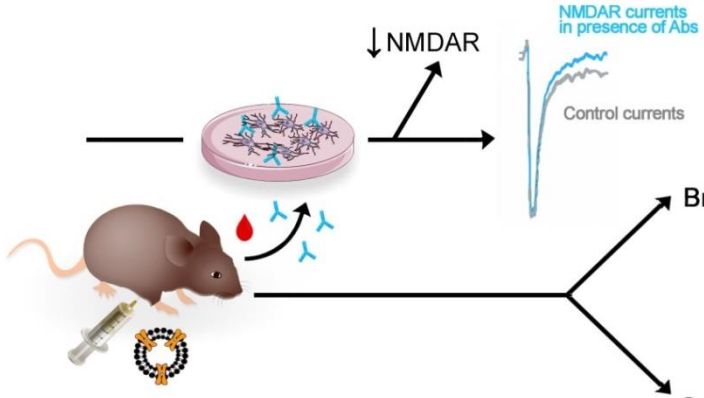




Symptoms
- Memory deficit
- Anhedonia
- Depressive-like behaviour



Active immunization

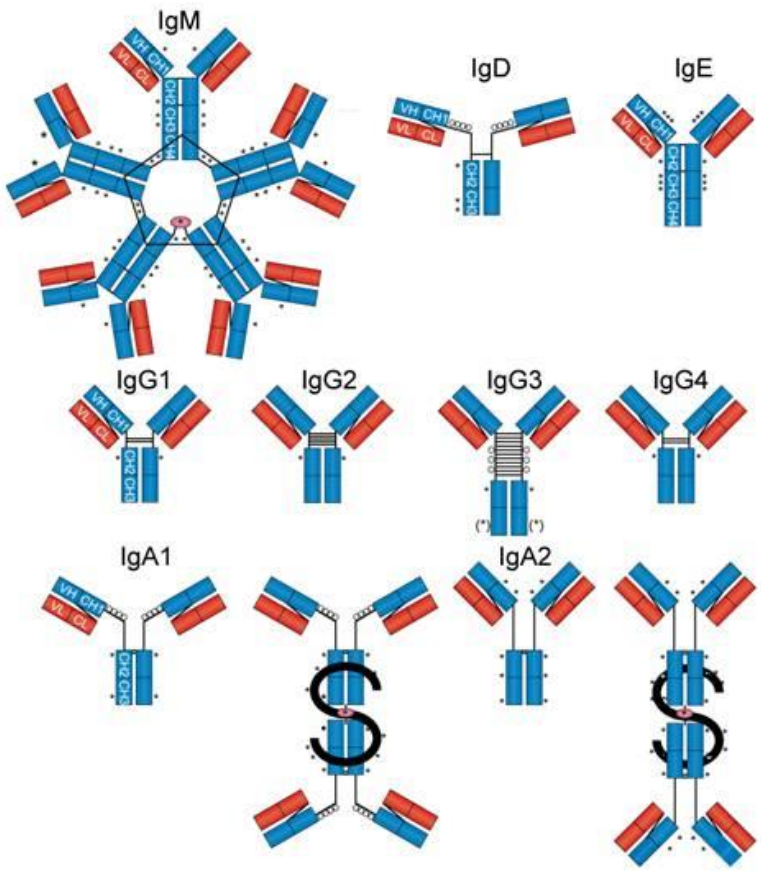


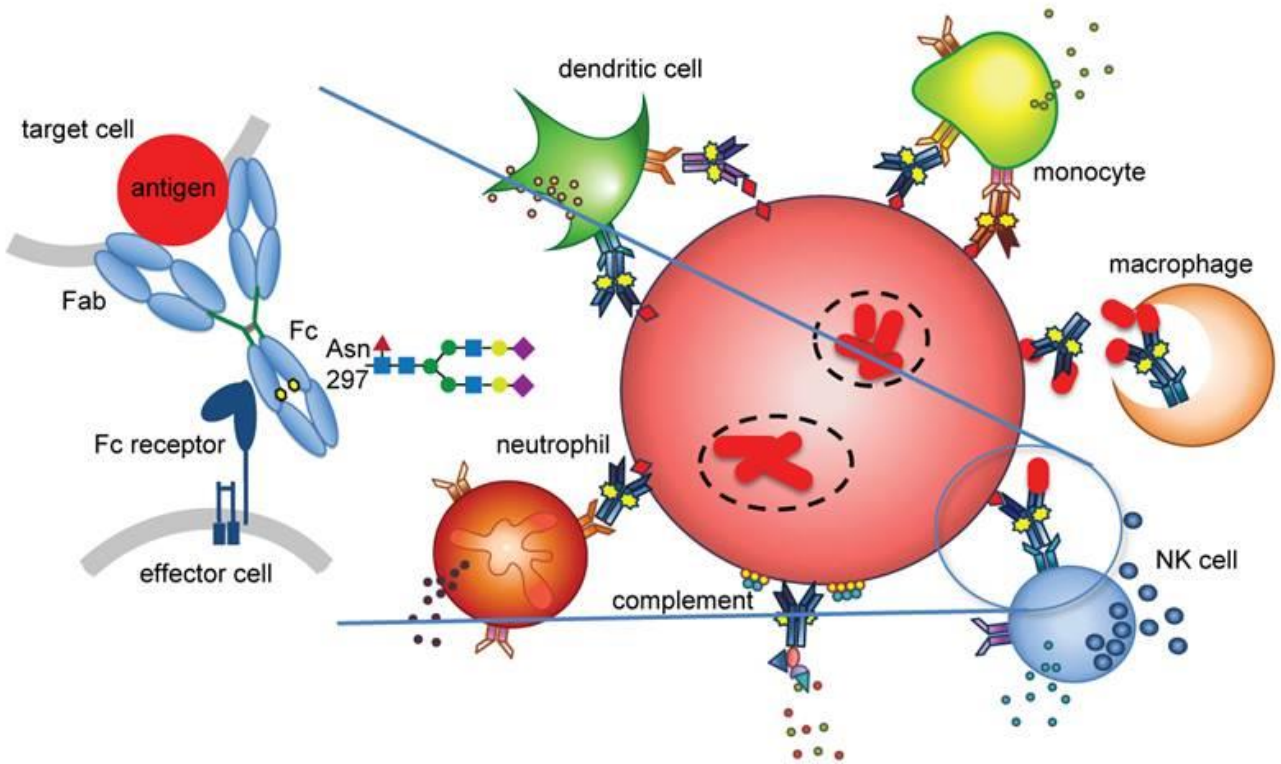
Brain
- NMDAR Abs
- B cell, plasma cells
- T cells (CD4+>>CD8+)
- microglial activation, neuronal loss

Symptoms
- Hyperactivity
- Seizures
- Tight circling
- Hunched back/lethargy

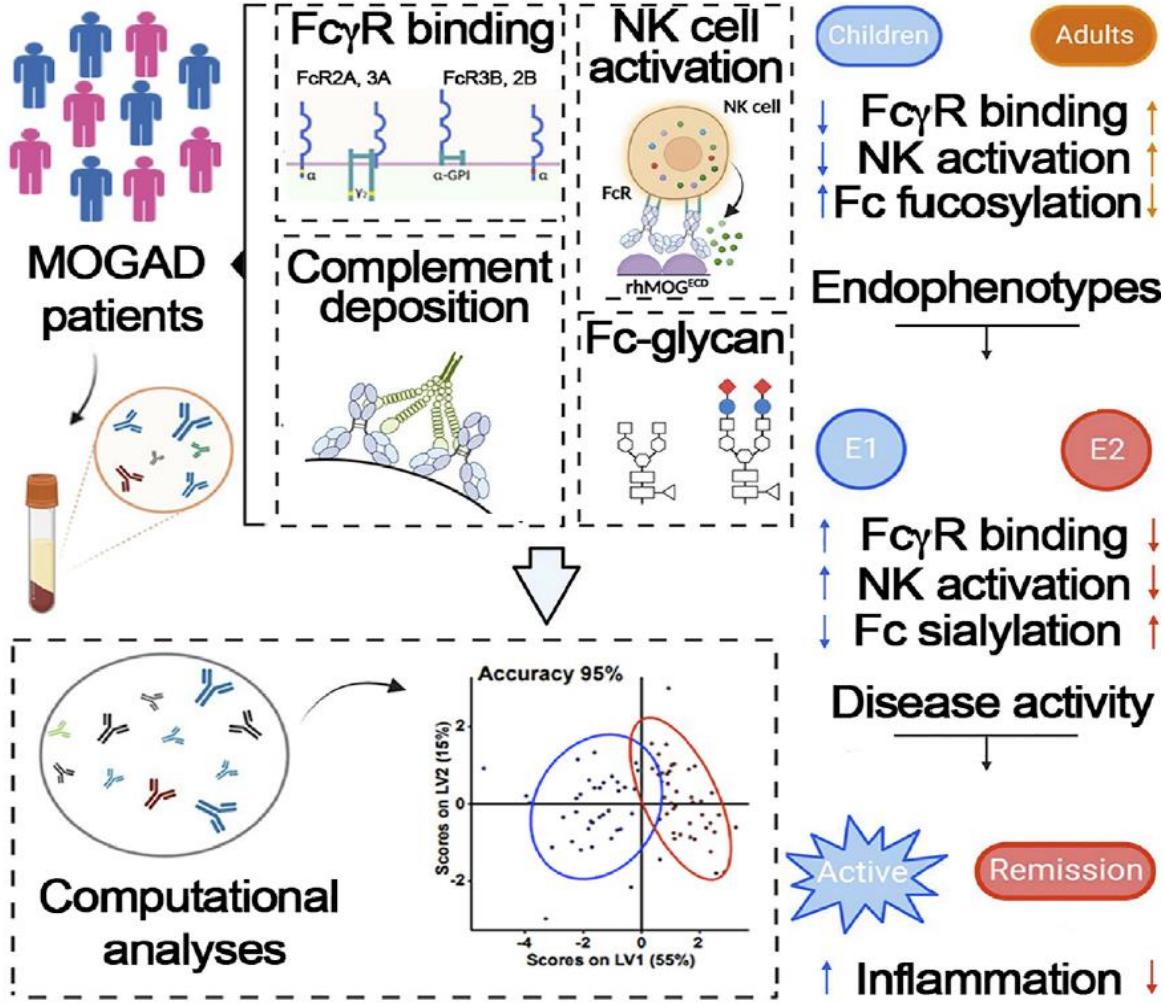
Planagumà et al., J Brain 2015;138:94; Mannara et al., Brain 2020;143:2709; Wright et al., Brain 2015;138:3159-3167
Jones et al., Sci Transl Med 2019;11eaaw0044; Wagnon et al., Brain 2020;143:2957; Ding et al., J Neuroinflamm 2021;18:53

Antibodies at the interface of host and microbes





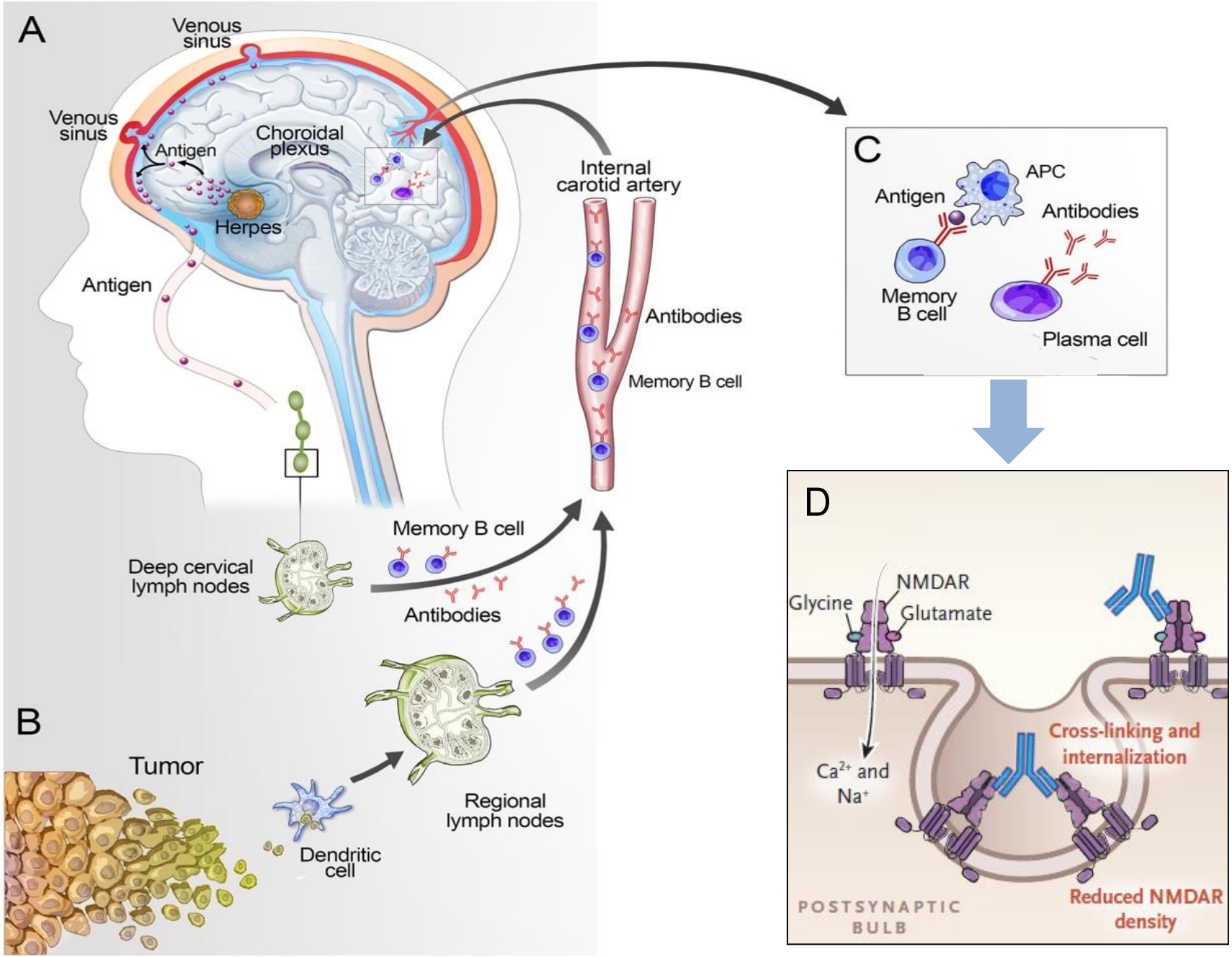
Humoral signatures of MOG-antibody-associated disease track with age and disease activity



Spatola et al., Cell Reports Medicine. Feb 2023

Triggers and predisposing factors

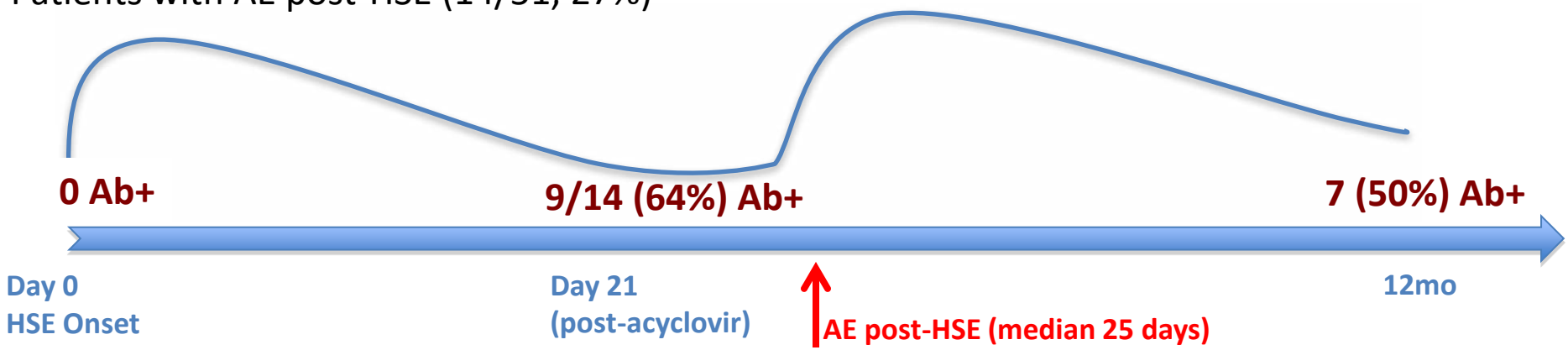
Tumors
Viral infections
HLA


A
Venous sinus
Venous sinus
Antigen
Choroidal plexus
Herpes
Antigen
Internal carotid artery
Antibodies
Memory B cell
Memory B cell
Deep cervical lymph nodes
Antibodies
B
Tumor
Dendritic cell
Regional lymph nodes
C
APC
Antigen
Antibodies
Memory B cell
Plasma cell
D
NMDAR
Glycine
Glutamate
Cross-linking and internalization
Ca2+ and Na+
POSTSYNAPTIC BULB
Reduced NMDAR density

Autoimmune encephalitis triggered by herpes simplex encephalitis (HSE)

OR 11.5, 95% CI 2.7-48.8; p<0.001

Patients with AE post-HSE (14/51, 27%)



Armangue et al., Lancet Neurol 2018;17:760-772
Armangue et al., unpublished

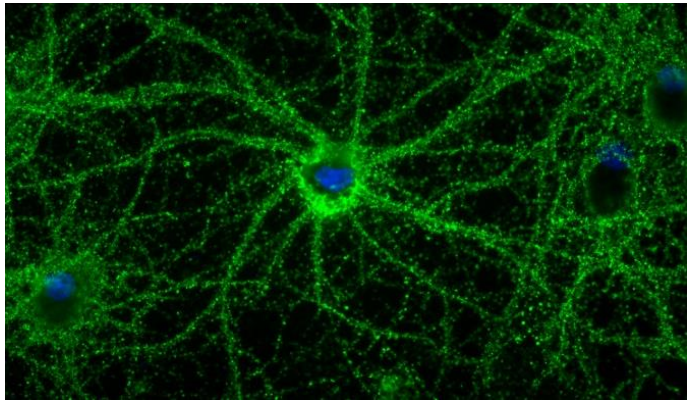
Neuronal surface antibody associated disorders, HLA association

Antibody	IgG subclass	Frequency of tumor association, and main types of tumors	HLA associations
IgLON5	IgG4 with-without: IgG1	0%	DRB1*10:01 and DQB1*05:01[6, 7]
LGI1	IgG4 with-without: IgG1 or IgG2	<10% (thymoma)	DRB1*07:01; DQA1*02:01 and DQB1*02:02[1, 3-5]
CASPR2	IgG4 with-without: IgG1	~20% of all cases have thymoma. Thymoma more frequent in Morvan syndrome (~40%).	DRB1*11:01[5]
NMDAR	IgG1, IgG3	Varies with age and sex; 56% of women 18-45 years old have ovarian teratoma	Unclear; suggested associations with B*07:02,[1] DRB1*16:02[2]

Sabater et al., Lancet Neurol 2014;13:575-86; Mueller et al., Ann Neurol 2018;83:863-9; Shu et al., J Neurol Neurosurg Psychiatry 2019;90:652-8; Van Sonderen et al., Ann Neurol 2017;81:193-8; Kim et al., Ann Neurol 2017;81:183-192; Binks et al., Brain 2018;141:2263-71

Autoimmunity *vs* Neurodegeneration

Anti-IgLON5 disease: REM sleep disorder and non-REM parasomnia

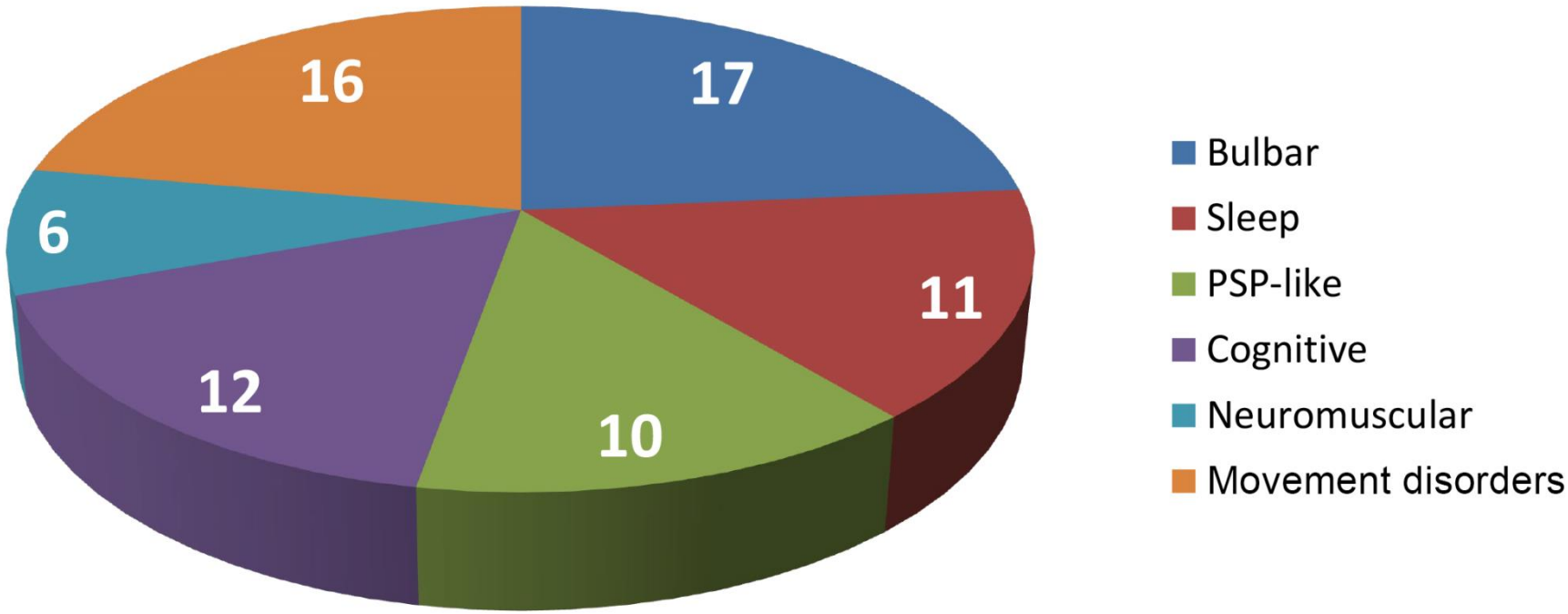


HLA genotyping:

DRB1*1001 and DQB1*0501 (in normal population 1.6% and 14.4%)

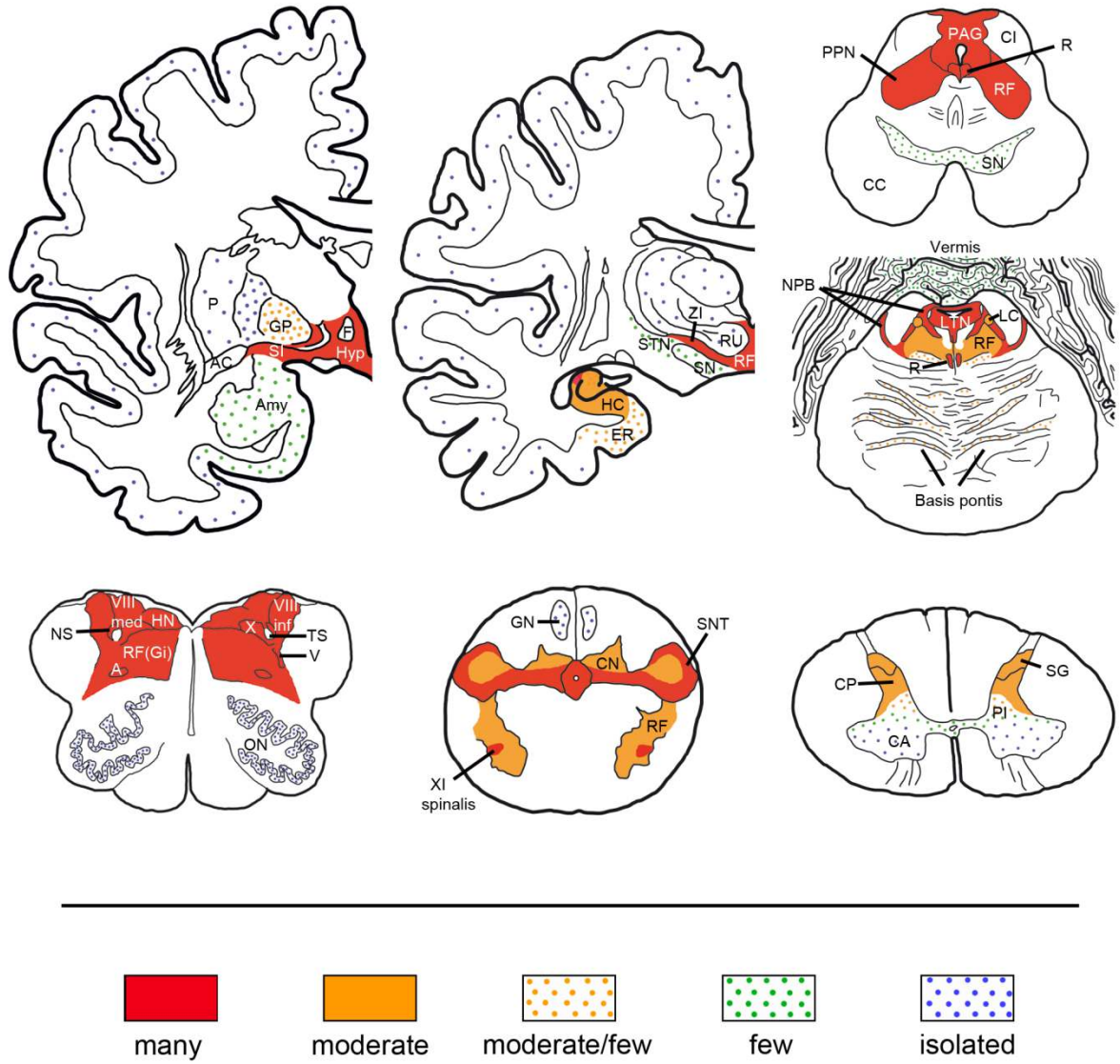
Sabater et al., Lancet Neurol 2014;13:575-86

Anti-IgLON5 phenotypes in 72 patients



Gaig et al., Neurology 2017;88:1736-1743.
Gaig et al., Neurology 2021;97:e1367-e1381
Grüter T et al., Brain 2022 doi: 10.1093/brain/awac090

Schematic distribution of tau pathology in anti-IgLON5 related tauopathy



Gelpi et al., Acta Neuropathol 2016;132:531-543

What is first?

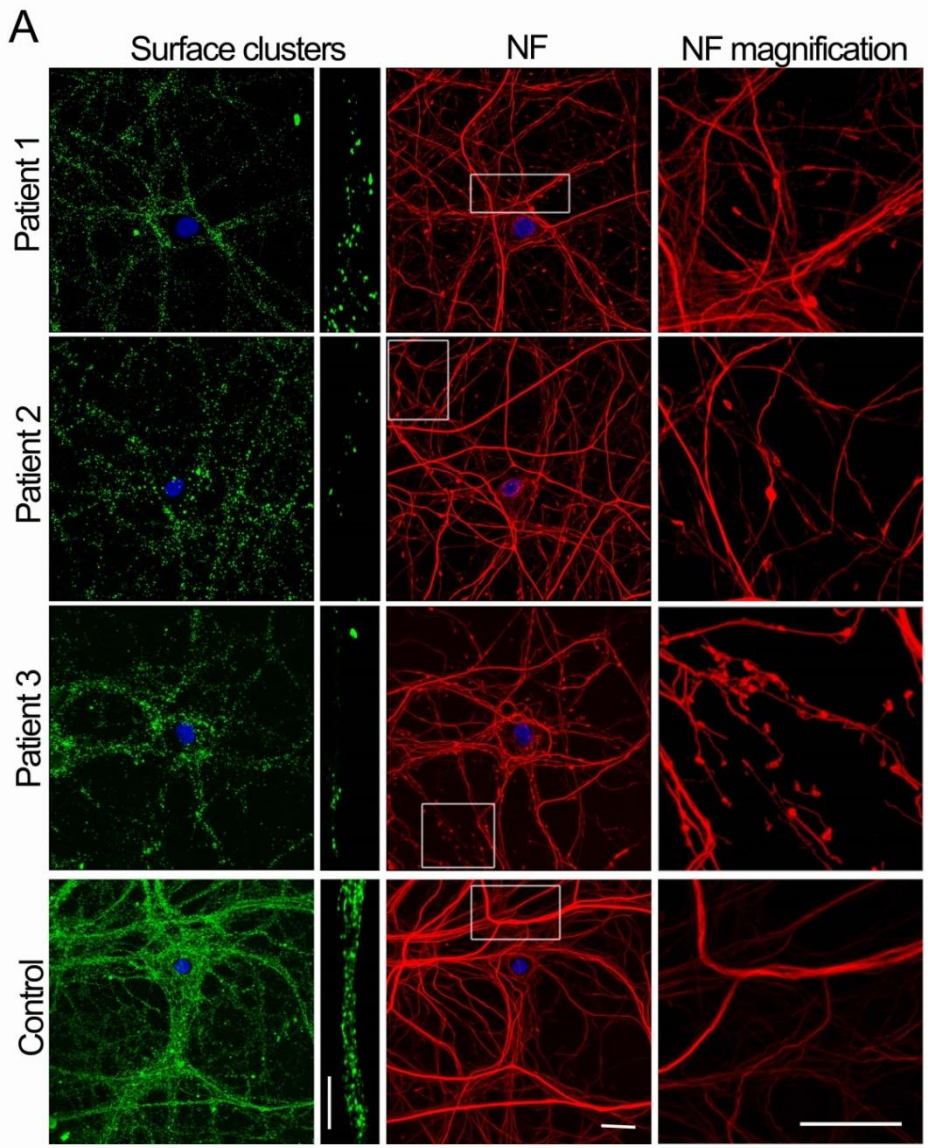
Autoimmunity

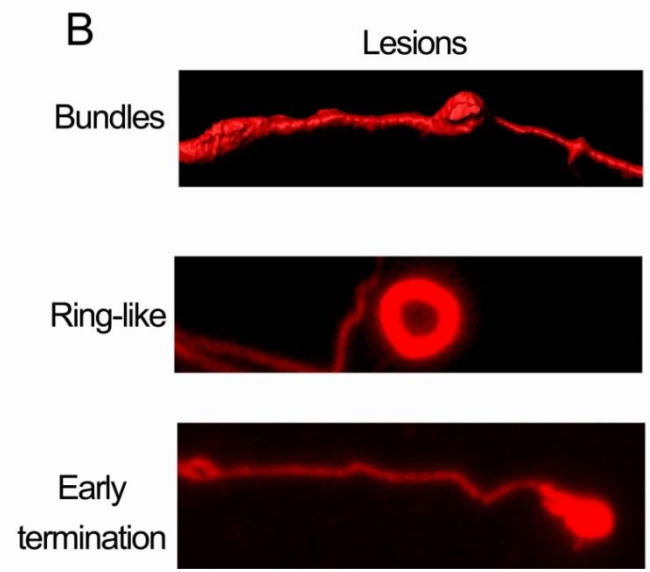
- Highly specific antibodies
- Strong HLA association haplotype DRB1*10:01-DQB1*05:01)

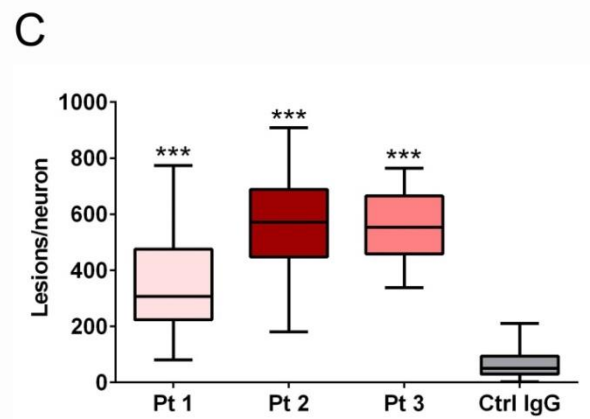
Neurodegeneration

- Chronic course
- Deposits of phosphorylated tau
- Absent pleocytosis

Effects of IgLON5 antibodies on the cytoskeleton of neurons





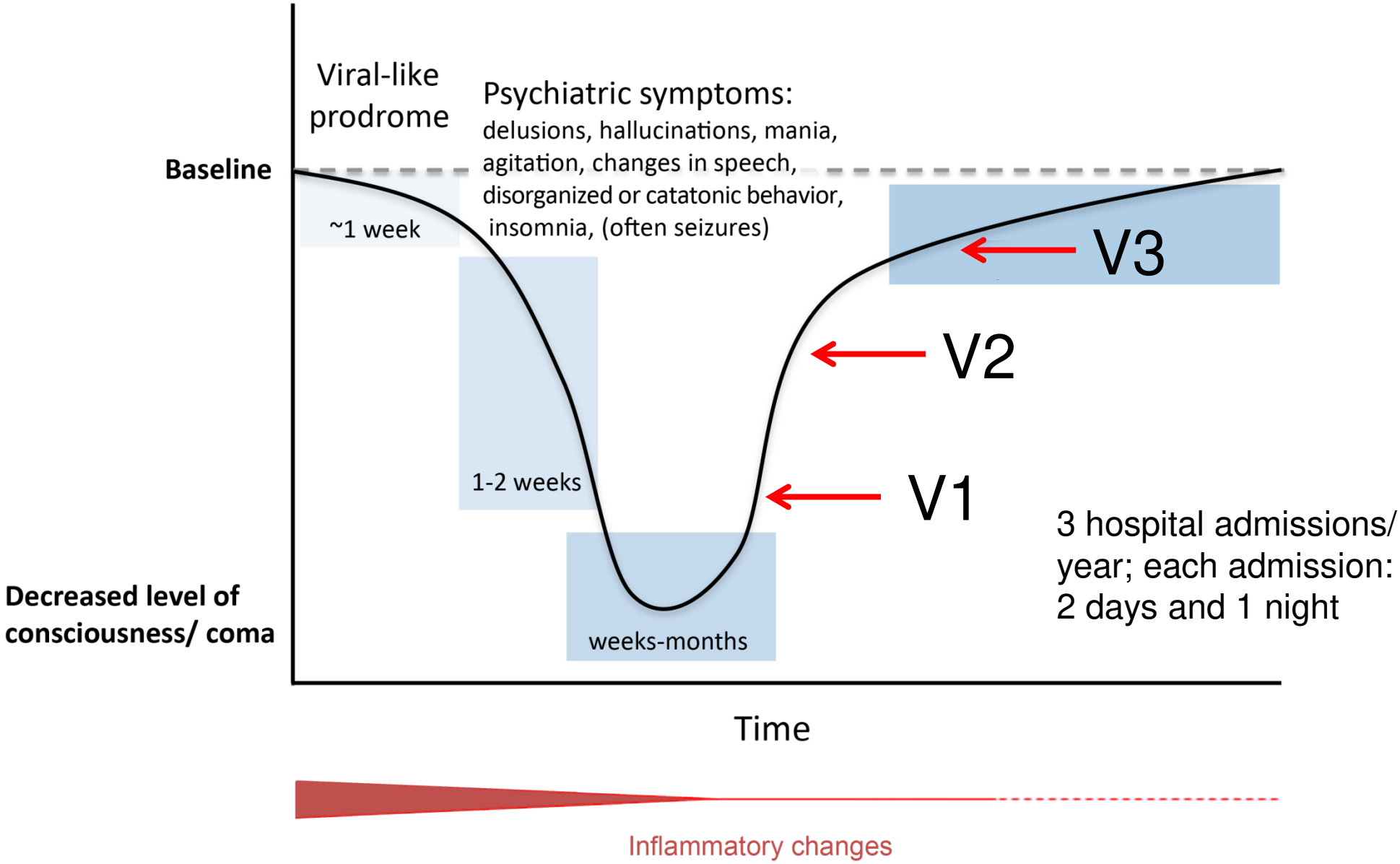


Landa et al., Ann Neurol 2020;88:1023-7
Ryding et al., Cells 2021;10:837

What’s next?

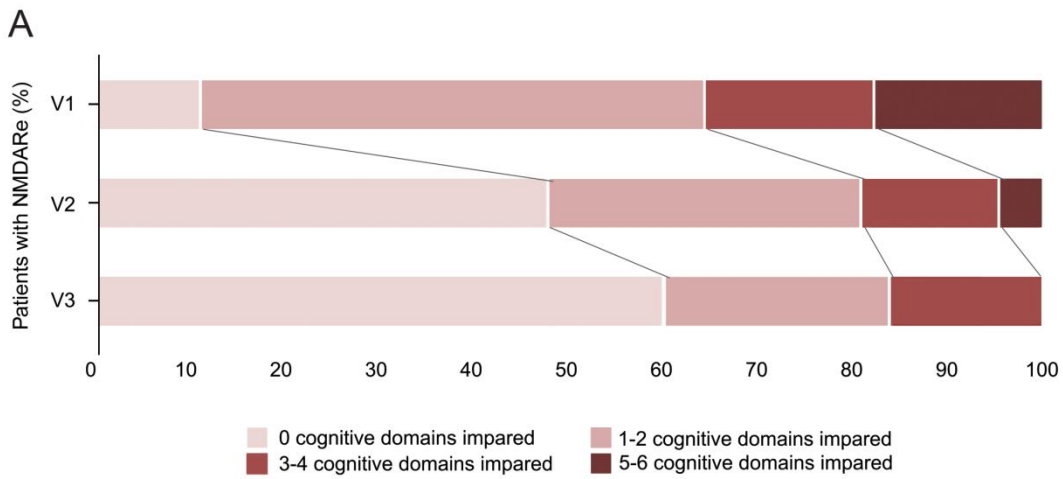
Improve clinical knowledge
(decrease misdiagnoses)
Biomarkers and models
Clinical trials

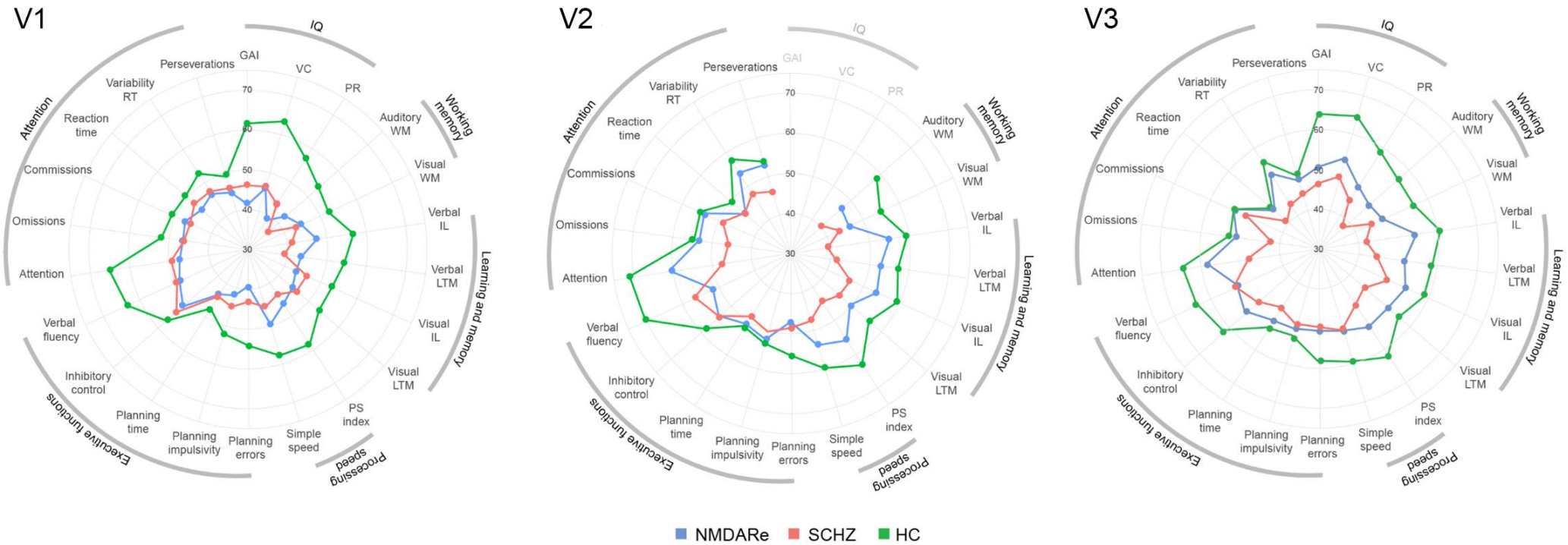
Disease stages and treatment approaches



Guasp et al., Lancet Neurol 2022;21:899-910

Follow-up of cognitive domains in the post-acute stage of NMDARe

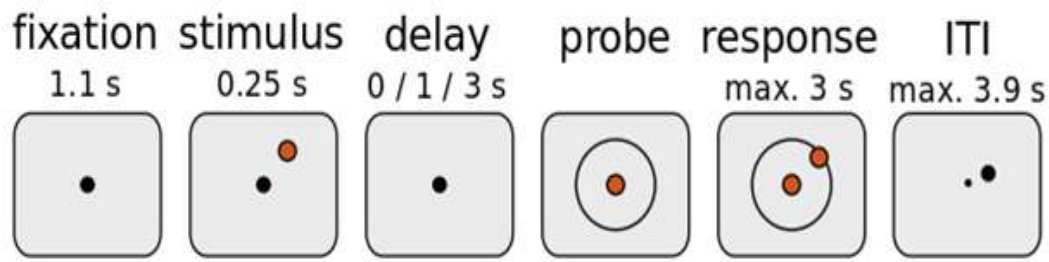




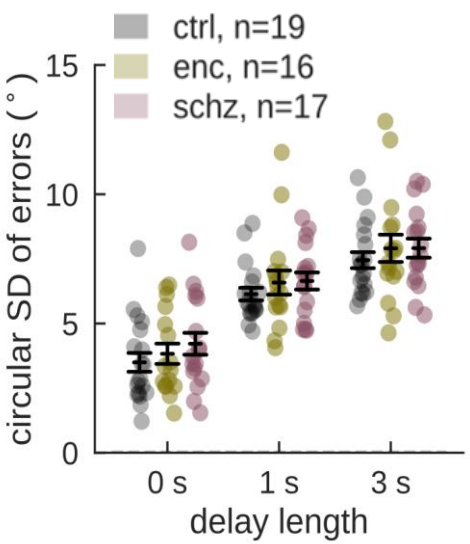
Guasp et al., Lancet Neurol 2022;21:899-910

Working memory-related serial dependence in anti-NMDAR encephalitis and schizophrenia

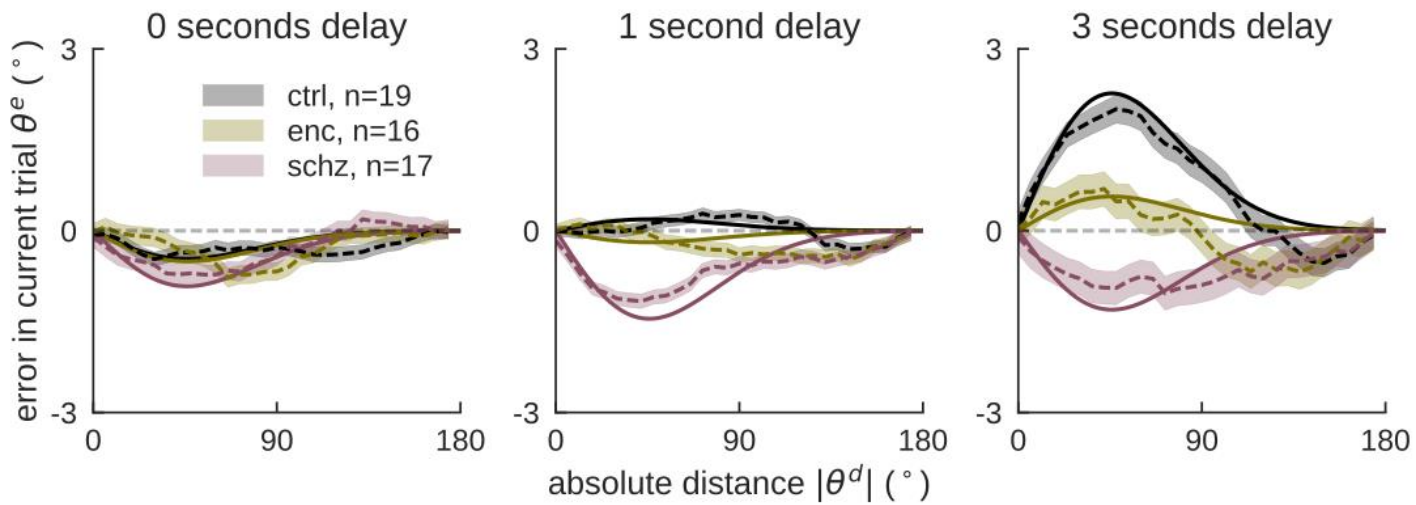
WM: Visuospatial delayed response task (2 temporal scales)



Single trial WM accuracy (active memory maintenance during delays



Serial dependence of responses on previously memorized stimuli (passive memory maintenance across trials)



Stein et al., Nat Commun. 2020;11(1):4250

THE EXTINGUISH
NMDAR ENCEPHALITIS TRIAL

A PHASE-2B, DOUBLE-BLIND, RANDOMIZED CONTROLLED TRIAL TO EVALUATE THE ACTIVITY AND SAFETY OF INEBILIZUMAB IN ANTI-NMDA RECEPTOR ENCEPHALITIS AND ASSESS MARKERS OF DISEASE

Summary

- There is an exponential growth in the number of encephalitis mediated by antibodies against neuronal surface antigens.
- It is critical to know the disease and mechanisms in order to treat them and understand the clinical course and outcome.
- Neuronal surface antibodies alter the structure and function of the target receptors leading to symptoms. Knowing the mechanisms may lead to new treatment strategies.
- Future studies should focus in defining better the syndromes, immune-mechanisms, biomarkers of outcome, and disease models.

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