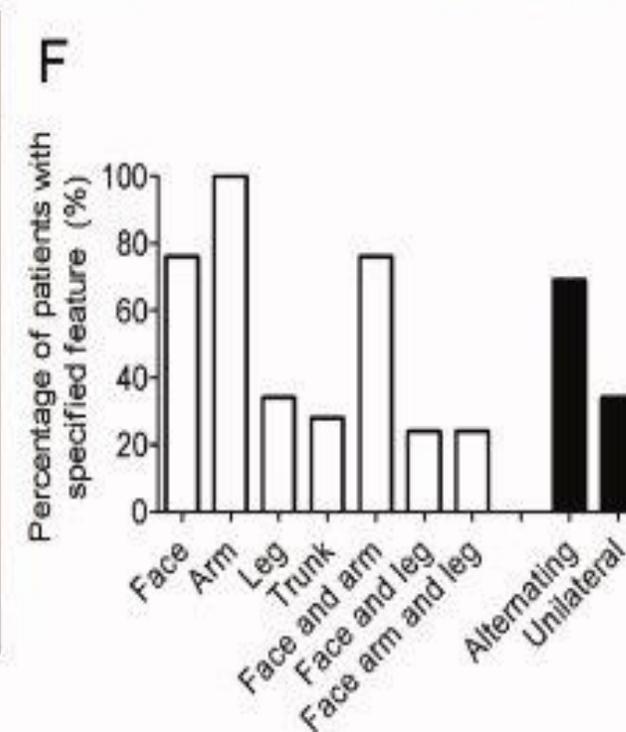
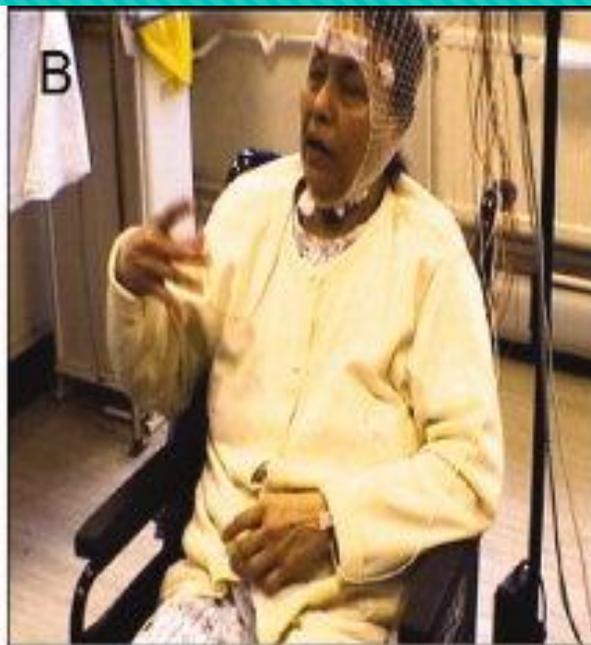


# Autoimmune Antibody Mediated Psychosis

Joab Chapman, Neurology, Sheba MC, TAU.

# Case study: August 2012-March 2013

- 59 year old female academic
- Background: dyslipidemia, arterial hypertension, osteoporosis, hyperthyroidism, obesity.
- Onset of involuntary movements 15-20 daily left face
- Normal brain MRI, Normal EEG
- Severe Bizarre Obsessive Behavior, Memory Erased
- Hyponatremia

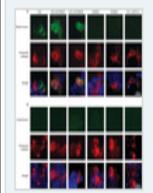
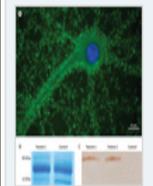


# Differential Diagnosis

- Neurodegenerative disease: Creutzfeldt-Jakob Disease: No specific EEG, MRI or tau in CSF.
- Systemic disease: Normal antibodies to thyroid. No elevated ACE and negative scans, normal reactive bone marrow.
- Autoimmune disease: SLE and similar diseases ruled out by blood antibodies and markers. Paraneoplastic diseases ruled out by blood antibodies.
- POSITIVE antibodies to LGI1 1:2000 in blood, 1:16 in CSF.

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Tel Aviv University

- Show thumbnails in outline
- Summary
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  - Methods
  - Findings
  - Interpretation
  - Funding
- Introduction
- Methods
  - Study population
  - Procedures
  - Role of the funding source
- Results
  - Table



# THE LANCET Neurology

Volume 9, Issue 8, August 2010, Pages 776–785



Fast track — Articles

## Investigation of LGI1 as the antigen in limbic encephalitis previously attributed to potassium channels: a case series

Meizan Lai, MD<sup>a, †</sup>, Maartje GM Huijbers, BS<sup>a, †</sup>, Eric Lancaster, MD<sup>a</sup>, Prof Francesc Graus, MD<sup>c</sup>, Luis Bataller, MD<sup>d</sup>, Prof Rita Balice-Gordon, PhD<sup>b</sup>, Prof John K Cowell, PhD<sup>e</sup>, Prof Josep Dalmau, MD<sup>a, †</sup>

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- <sup>b</sup> Department of Neuroscience, University of Pennsylvania, School of Medicine, Philadelphia, PA, USA
- <sup>c</sup> Service of Neurology, Hospital Clínic, and Institut d'Investigació Biomèdica August Pi i Sunyer (IDIBAPS), Barcelona, Spain
- <sup>d</sup> Department of Neurology, University Hospital La Fe, Valencia, Spain
- <sup>e</sup> Medical College of Georgia Cancer Center, School of Medicine, Medical College of Georgia, Augusta, GA, USA

[http://dx.doi.org/10.1016/S1474-4422\(10\)70137-X](http://dx.doi.org/10.1016/S1474-4422(10)70137-X), How to Cite or Link Using DOI

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**Refers To** Jérôme Honnorat  
**Is autoimmune limbic encephalitis a channelopathy?**  
*The Lancet Neurology, Volume 9, Issue 8, August 2010, Pages 753-755*

PDF (395 K)

- Bibliographic information
- Citing and related articles
  - Related articles
    - Voltage-Gated Potassium Channel Antibody Associ...**  
2011, Biological Psychiatry  
▶ Show more information
    - Voltage-gated potassium channel antibodies associ...**  
2006, Journal of the Neurological Sciences  
▶ Show more information
    - CNS autoimmunity: new findings and pending issues**  
2012, The Lancet Neurology  
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    - Paraneoplastic Syndromes, Immunology**  
2003, Encyclopedia of the Neurological Sciences  
▶ Show more information
    - Neuromuscular Junction (NMJ): Inherited and Acqui...**  
2009, Encyclopedia of Neuroscience
- Applications and tools
- Workspace

# Antibodies to Kv1 potassium channel-complex proteins leucine-rich, glioma inactivated 1 protein and contactin-associated protein-2 in limbic encephalitis, Morvan's syndrome and acquired neuromyotonia

Sarosh R. Irani,<sup>1,\*</sup> Sian Alexander,<sup>1,\*</sup> Patrick Waters,<sup>1,\*</sup> Kleopas A. Kleopa,<sup>2</sup> Philippa Pettingill,<sup>1</sup> Luigi Zuliani,<sup>1</sup> Elior Peles,<sup>3</sup> Camilla Buckley,<sup>1</sup> Bethan Lang<sup>1</sup> and Angela Vincent<sup>1</sup>

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1 Neurosciences Group, Department of Clinical Neurology, University of Oxford, John Radcliffe Hospital, Oxford, OX3 9DS, UK

2 Neurology Clinics and Neuroscience Laboratory, The Cyprus Institute of Neurology and Genetics, 1683 Nicosia, Cyprus

3 Department of Molecular Cell Biology, The Weizmann Institute of Science, Rehovot 76100, Israel

\*These authors contributed equally to this work.

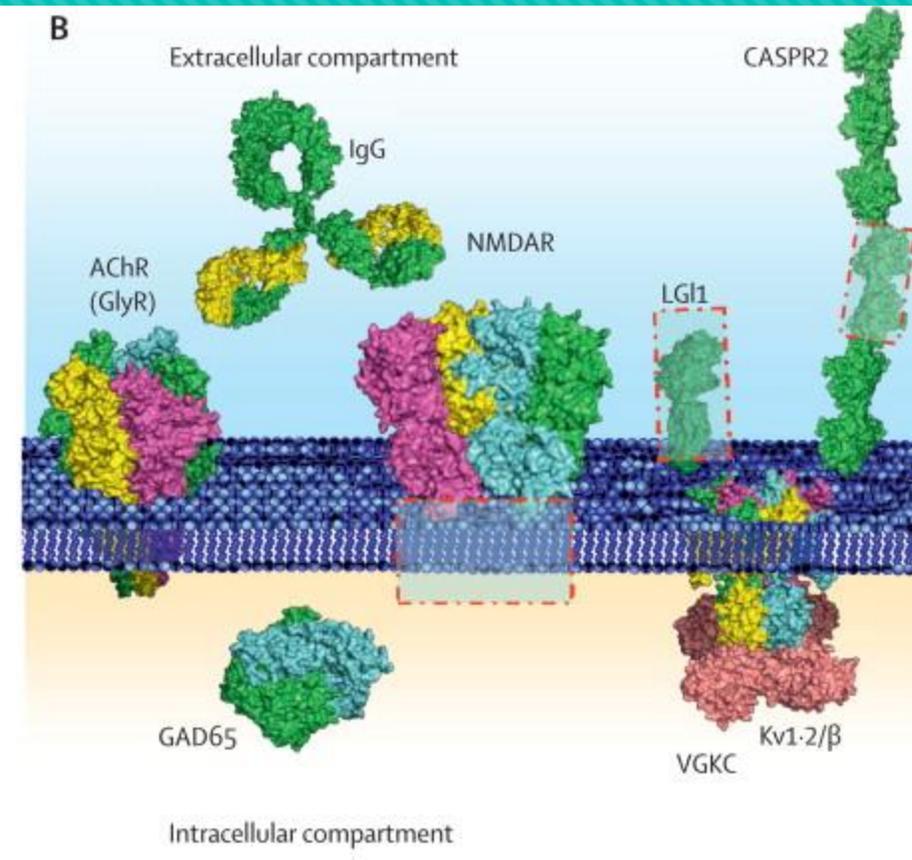
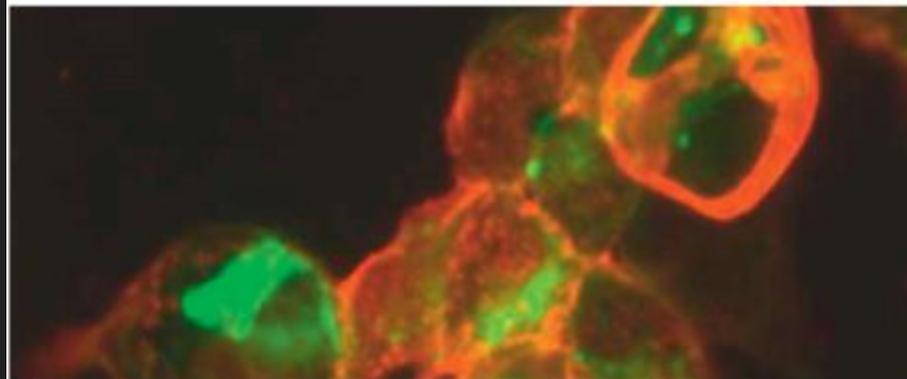
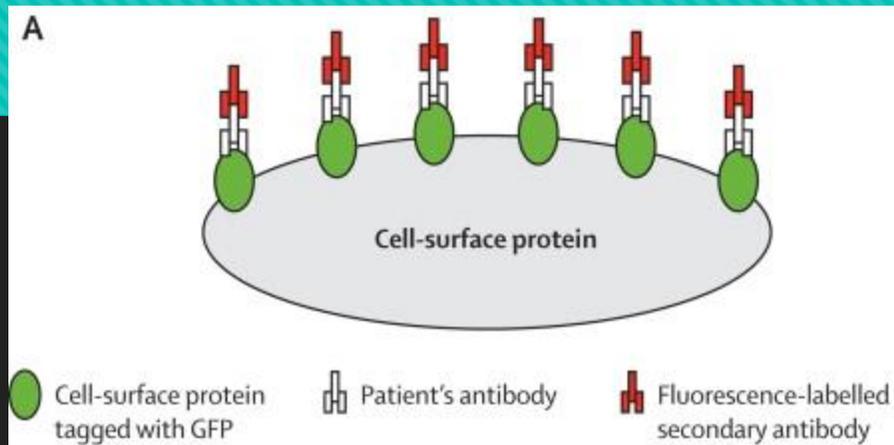
# Clinical Features

- Seizures: Faciobrachial dystonic seizures with poor response to antiepileptic medication and with temporal lobe activity.
- Cognitive and behavioral dysfunction.
- REM sleep behavior disorder.
- Hyponatremia in 60%.

# Treatment

- Treated with steroids, plasma exchange and azathioprine.
- Immediate beneficial effect on movements.
- Near normalization of cognition and behavior over 2 years.

# From Vincent et al., Lancet Neurology 2011



# New Antibody Mediated Encephalopathies

- Voltage Gated Potassium Channel complex (LGI1, CASPR2, contactin-2) 2001
- N-Methyl-D-aspartate receptor (NMDA) 2008
- AMPA receptor 2009
- GABA-B 2008
- Glycine receptor 2012
- D2 receptor 2013
- GABA-A receptor 2014

# Case Study 2

- 22 year old ♀
- Trip to Berlin... Confusion, Agitation
- 2 ERs → Psychiatry .... Loss of consciousness, Seizures
- Neurology: LP, CT, MRI all Normal.
- EEG generalized slowing=encephalopathy
- Abdominal CT .... Mature Teratoma of Ovary
- Rx Plasma Exchange and anti-epileptic

## Synopsis (Wikipedia)

The book narrates Cahalan's issues with anti-NMDA receptor encephalitis and the process by which she was diagnosed with this form of encephalitis. She wakes up in a hospital with no memory of the events of the previous month, during which time she would have violent episodes and delusions. Her eventual diagnosis is made more difficult by various physicians misdiagnosing her with several theories such as "partying too much" and schizoaffective disorder.



# BRAIN ON FIRE

MY MONTH OF MADNESS

SUSANNAH CAHALAN

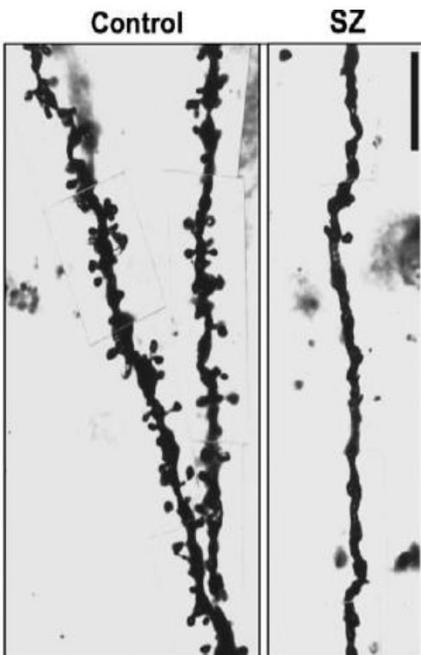
# NMDA antibody related Encephalitis

- Progressive life threatening limbic encephalitis,
- Fits, cognitive impairment, autonomic instability, coma and dystonic movement disorder
- 20-50% paraneoplastic (ovarian teratomas)
- 66-80% women, age 5-80 (mean 23)
- 1% all admissions to ITU

(Dalmau et al Lancet Neurology 2008, Irani et al Brain 2010 )

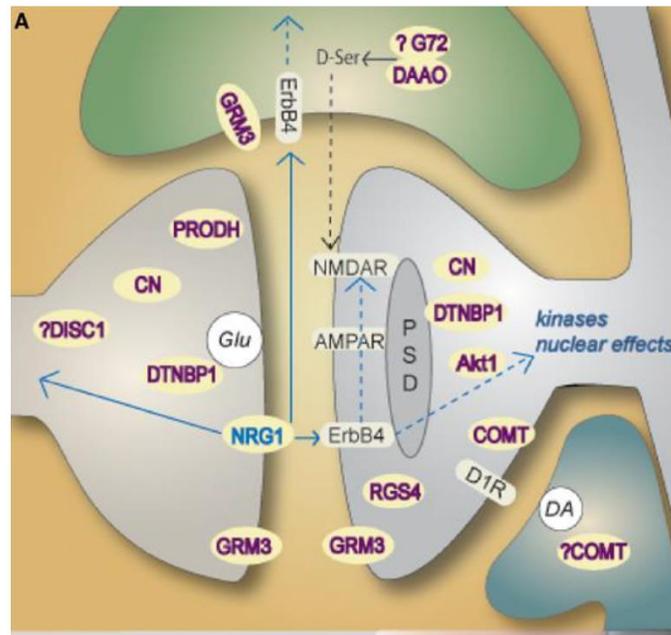
# NMDA linked to models of schizophrenia

## Pathology



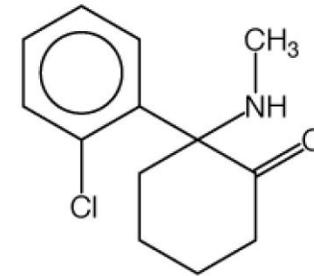
Glantz and Lewis  
Arch Gen Psych 2000

## Genes



Harrison and Weinberger Mol  
Psych 2005

## ketamine



# Systemic autoimmune diseases directly causing neurological disease

- Systemic Lupus Erythematosus
- Antiphospholipid Syndrome
- Sjogren Syndrome
- Rheumatoid Arthritis
- Vasculitis

# Systemic manifestation of APS in mice immunized with $\beta_2$ -GPI

$\beta_2$ GPI



BALB/C

## Serology

anti-CL / anti-PS  
anti-b2GPI



## Obstetrics

Elevated fetal resorptions  
Low placental weight  
Low embryos weight  
Low fecundity



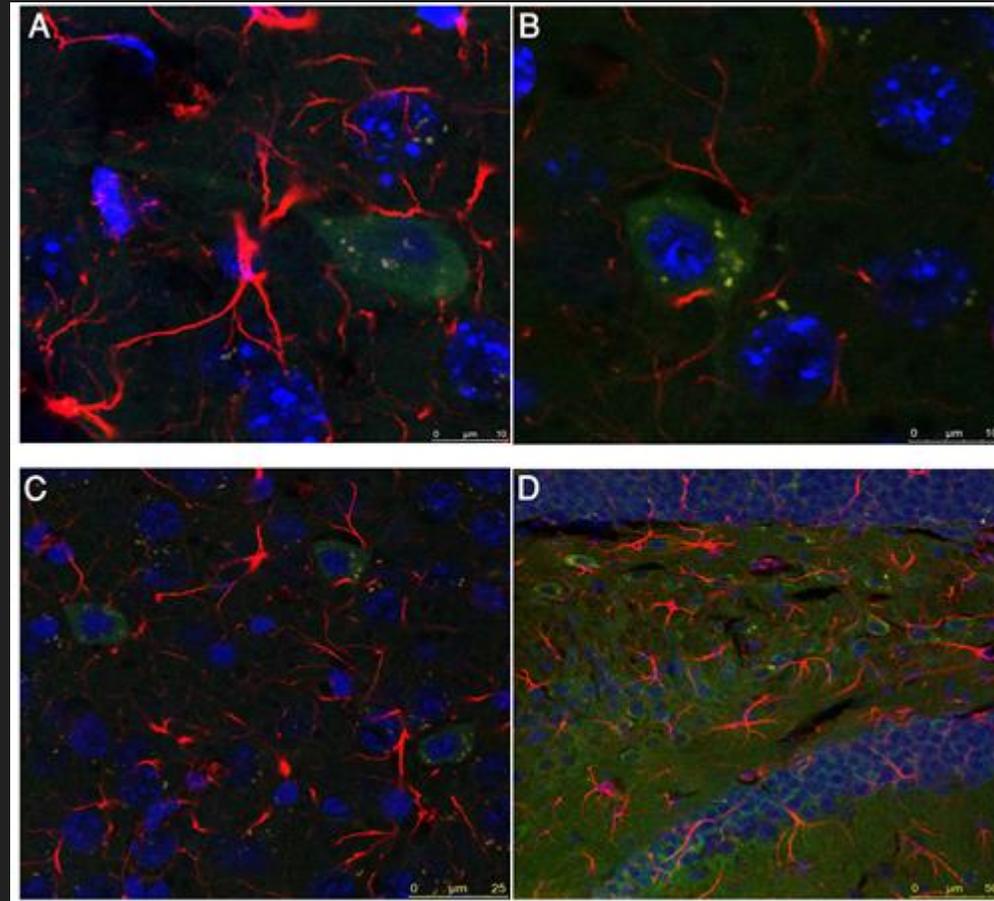
## Thrombocytopenia

## Prolonged aPTT

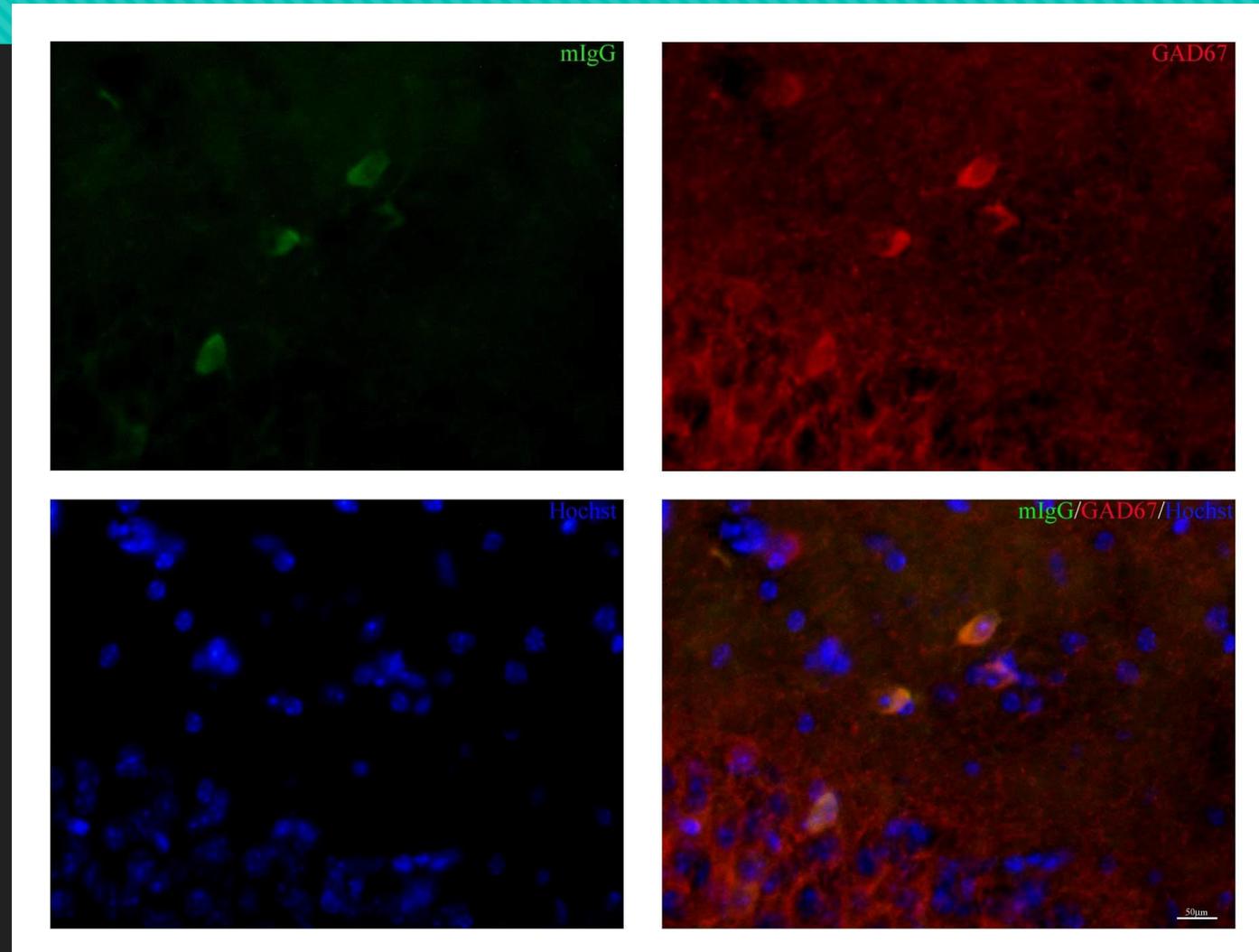
# CNS involvement

# IgG (green) in Inhibitory Neurons in eAPS

J Autoimmun. 2014 Dec;55:86-93.

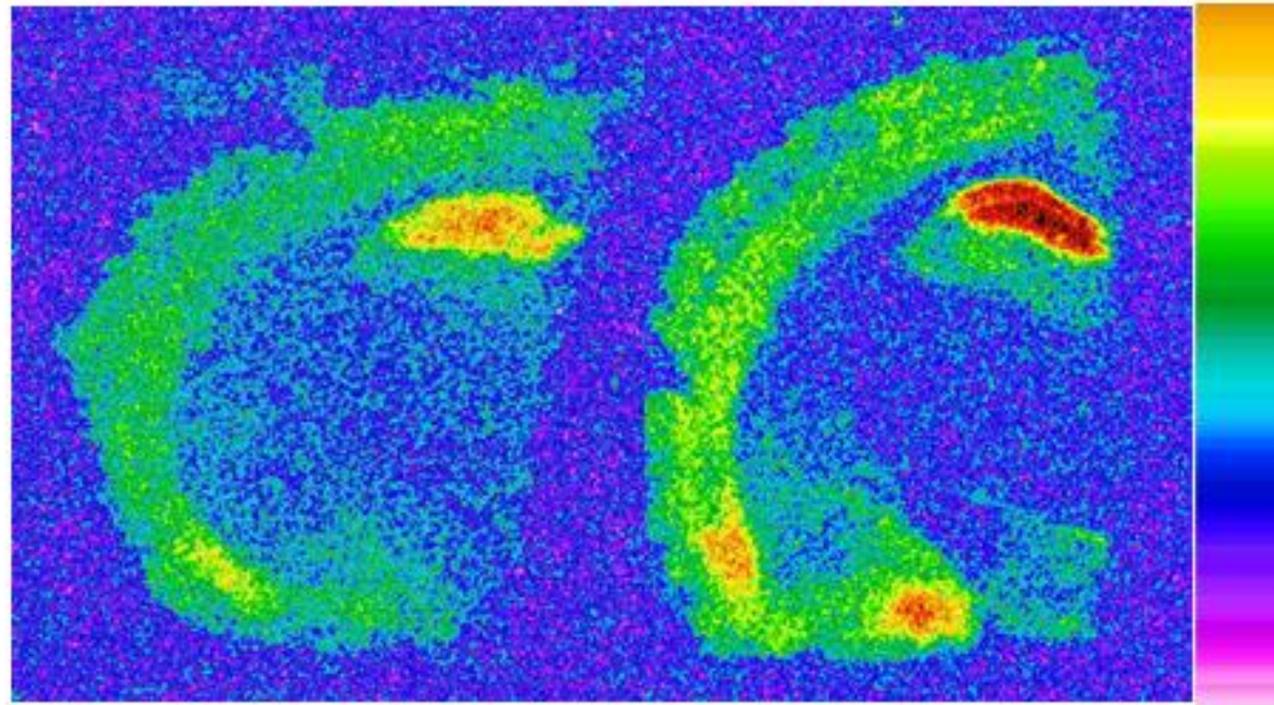


# *In vivo* IgG staining of GABAergic neurons



# 5HT(1A) changes autoradiography

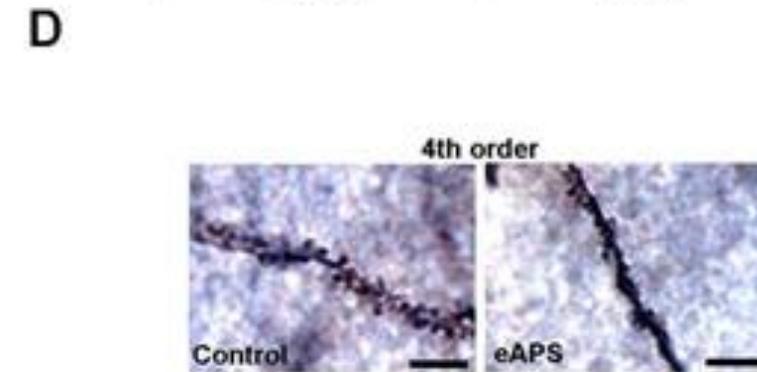
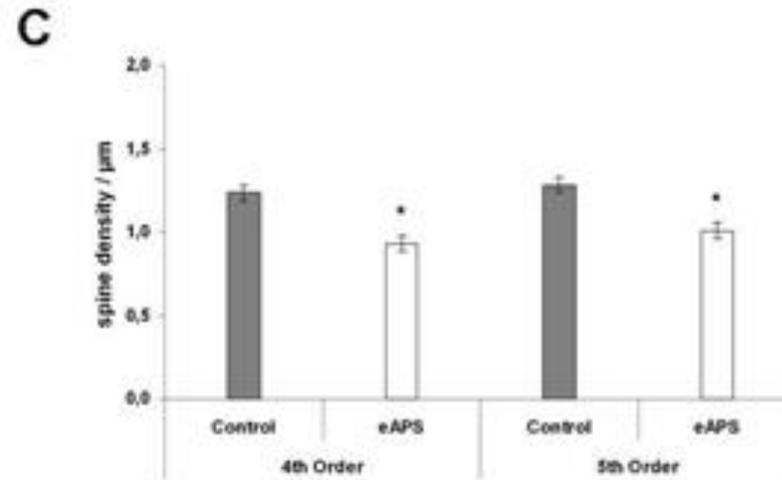
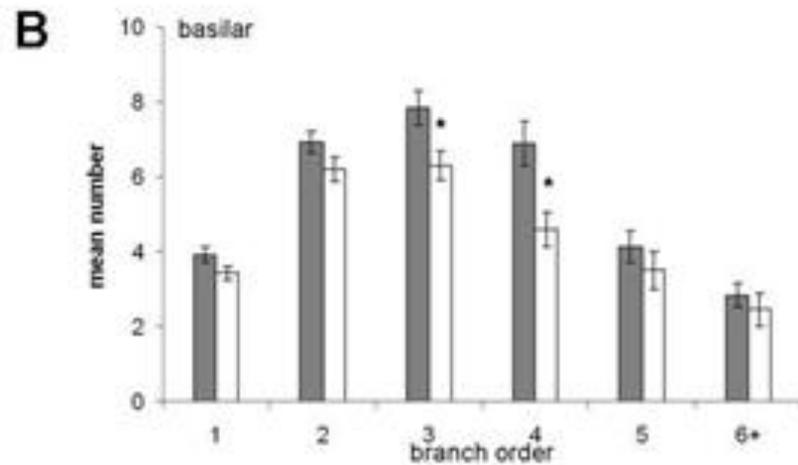
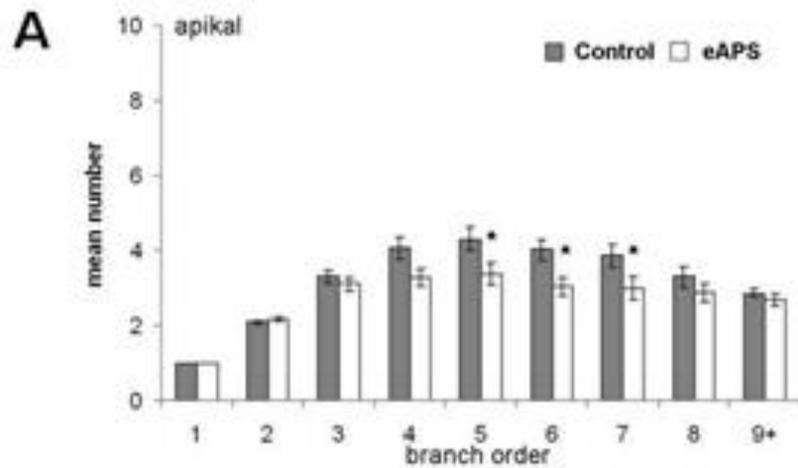
**[<sup>3</sup>H]8-OH-DPAT ligand binding**



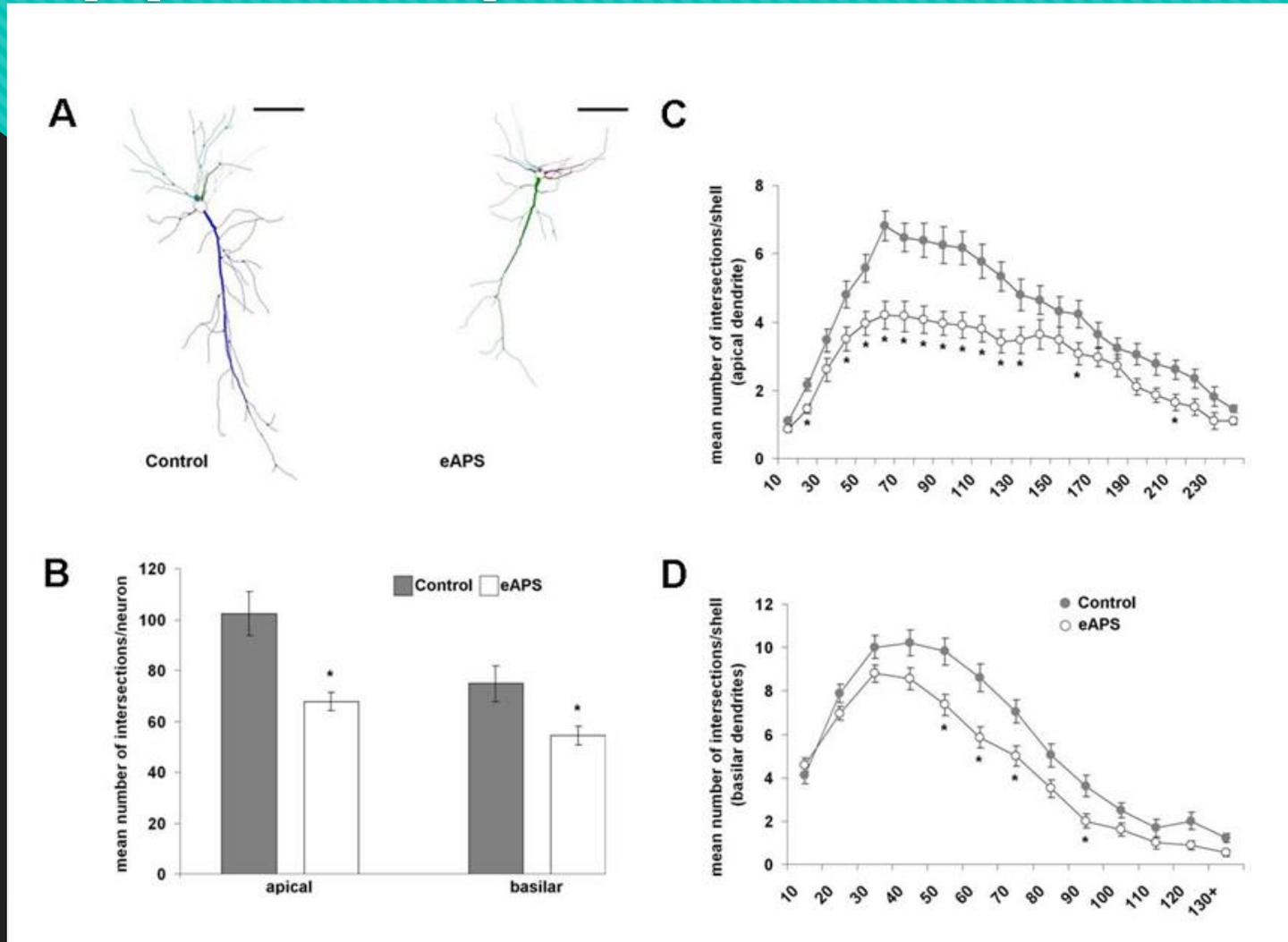
CFA control

eAPS

# Branch analysis and dendritic spine density



# Golgi Cox-impregnated neurons in hippocampal CA1



# Brains on Fire – Autoimmune causes of psychosis

Dr Belinda Lennox  
Department of Psychiatry,  
University of Oxford  
Belinda.lennox@psych.ox.ac.uk



RCPsych Brighton 16<sup>th</sup>  
October 2014

# Prevalence of pathogenic antibodies in first episode psychosis. Deakin J, Lennox BR, Zandi MS.

Biol Psychiatry. 2014;75:284-91

- 3 of 46 patients with first episode psychosis had pathogenic antibodies, prevalence 6.3% (1.9-16.5) ( )
- 2 had NMDAR antibodies (score 2, score 1.5). 1 had VGKC-complex antibodies (1435 pM; normal <100).
- All three of the patients have DSMIV schizophrenia.
- None of the group as a whole developed typical autoimmune encephalitis or other neurological diagnosis.



# Prevalence and clinical characteristics of serum neuronal cell surface antibodies in first-episode psychosis: a case-control study

*Belinda R Lennox, Emma C Palmer-Cooper, Thomas Pollak, Jane Hainsworth, Jacqui Marks, Leslie Jacobson, Bethan Lang, Hannah Fox, Berne Ferry, Linda Scoriels, Hannah Crowley, Peter B Jones, Paul J Harrison, Angela Vincent, on behalf of the PPIP study team\**

## Summary

**Background** Psychosis is a common presenting feature in antibody-mediated encephalitis, for which prompt recognition and treatment usually leads to remission. We aimed to investigate whether people with circumscribed schizophrenia-like illnesses have such antibodies—especially antibodies against the N-methyl-D-aspartate receptor (NMDAR)—more commonly than do healthy controls.

*Lancet Psychiatry* 2017;  
4: 42–48

Published Online  
December 7, 2016

<http://dx.doi.org/10.1016/>

# Major Finding in Lennox Lancet Psychiatry 2017

	Titres	Patients with first-episode psychosis (n=228)	Controls (n=105)	Odds ratio (95% CI)	Adjusted odds ratio* (95% CI)
NMDAR antibodies	1:30-1:150	7 (3%)	0	5.4 (p=0.0204)†	..
LGI1 antibodies	1:20-1:100	3 (1%)	0	2.3 (p=0.1298)†	..
CASPR2 antibodies	1:100-1:250	2 (1%)	3 (3%)	0.3 (0.1-1.8)	2.2 (0.3-17.1)
GABA <sub>A</sub> R antibodies	1:50-1:100	8 (4%)	1 (1%)	3.8 (0.5-30.7)	0.4 (0.3-3.6)
AMPA antibodies	..	0	0	..	..
Any neuronal cell surface antibody	..	20 (9%)	4 (4%)	2.4 (0.8-7.3)	0.5 (0.1-1.7)
Other antibodies					
VGKC-complex antibodies >150 pM‡	..	11 (5%)	3 (3%)	1.7 (0.5-6.3)	0.8 (0.2-3.2)
Antinuclear antibodies >1/160	..	7 (3%)	9 (9%)	0.5 (0.2-1.4)	3.6 (1.0-13.6)

# Antibody Induced Brain Dysfunction

- Underdiagnosed.
- Treatable.
- Needs better methods for screening
- Needs better understanding of pathogenesis



Thank you