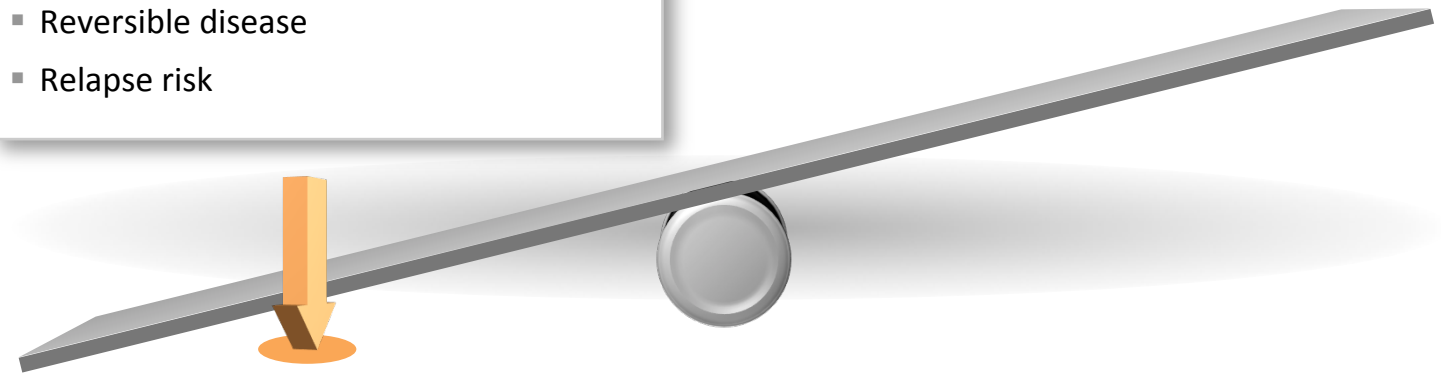
NMDAR antibody encephalitis

Factors favouring observation or no further treatment

- Short and long term side effects of treatment

Factors favouring further treatment

- Severity of acute condition
- Risk of permanent disability
- Reversible disease
- Relapse risk



Treatment

Close surveillance with no treatment

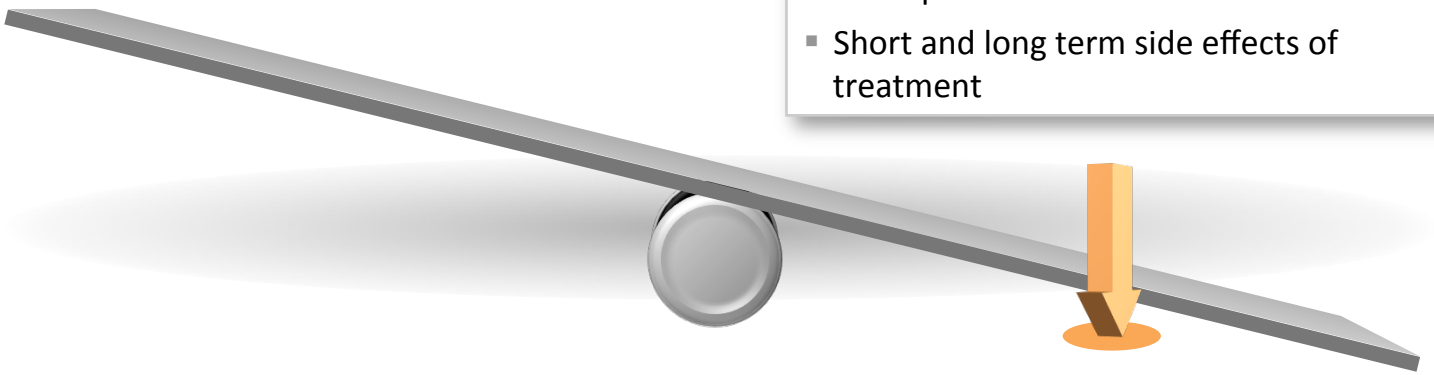
Antibody negative encephalitis

Factors favouring further treatment

- Severity of acute condition
- Risk of permanent disability
- Unclear relapse rate

Factors favouring observation or no further treatment

- Good improvement
- Monophasic illness
- Short and long term side effects of treatment



Treatment

Close surveillance with no treatment

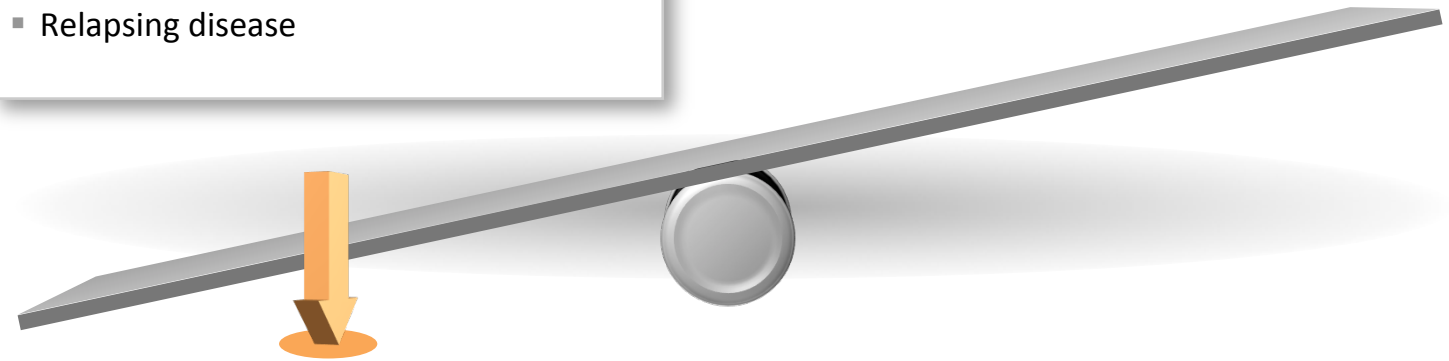
Antibody negative encephalitis

Factors favouring observation or no further treatment

- Good improvement
- Monophasic illness
- Short and long term side effects of treatment

Factors favouring further treatment

- Severity of acute condition
- Risk of permanent disability
- Relapsing disease

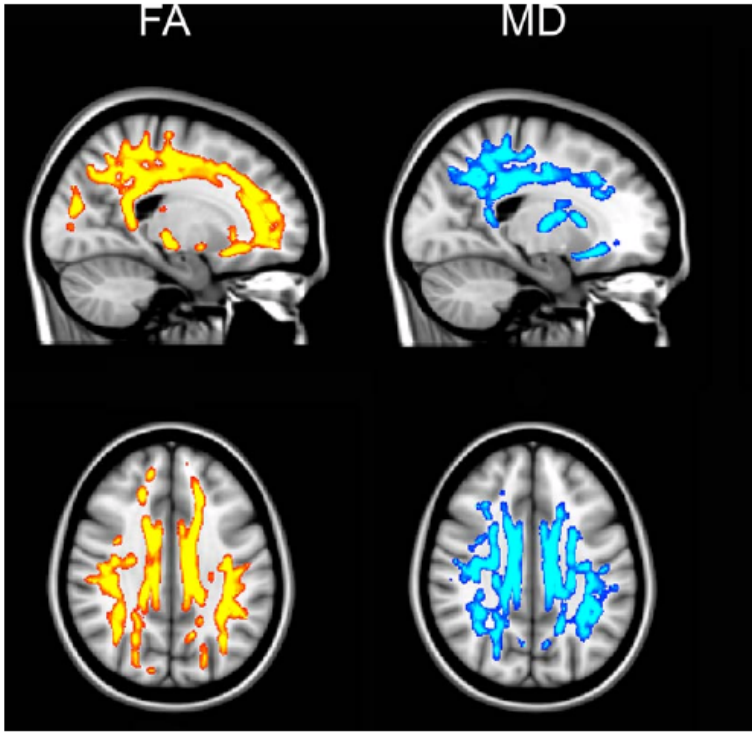


Treatment

Close surveillance with no treatment

Long term sequelae following autoimmune encephalitis

Esseveld et al., 2012
Am J Psychiatry 170 21-2



Finke et al., 2013
Ann Neurol. 74(2):284-96

Symptoms

- Impact of very early onset disease
- Impact of chronic disease during childhood
- Fatigue, headache and painful spasms

Cognition

- Acquisition of core education principles
- Memory, executive function, and sequencing deficits
- Cognitive fatigue

Vocational achievement

- Completing school
- Success in higher academic endeavors
- Impact of disability on vocational selection
- Forced realism

Treatment

- Efficacy and safety treatments
- Long-term effects
- Does early treatment lead to better outcome?

Social independence

- Impact of chronic disease on self and community perception of desirability
- Independence

Reproduction & Parenting

- Ability to parent
- Impact of medication on fertility
- Sexual health

Patients required for RCT in NMDAR to demonstrate improvement in outcome

- Estimate new paediatric cases in the UK/year 20
- From Dale et al 2014 mRS in early vs late treatment 57% vs 80%
- Treated early vs late 1:1. Improve outcome from 60% to 80% (power 80%, 0.05 significance) requires 82 children in each arm (Total 164)

➔ Multicenter European trial

How do we treat autoimmune encephalitis?

- Diagnose and treat early
- How long do we treat for
  - Why are we treating?
    - Not getting better
    - Preventing relapse
    - Improving long term outcome
- **Understanding biology**

Effects of inflammation in the brain

- **Is inflammation beneficial?**
- Immunobiology versus neurobiology

“Friend and foe”

- Initial response required to remove insult

  Streit 2002 ***Glia*** 40: 133-139

- Overactivation harmful

  Block et al 2007 ***Nat Rev Neurosci*** 8: 57-69

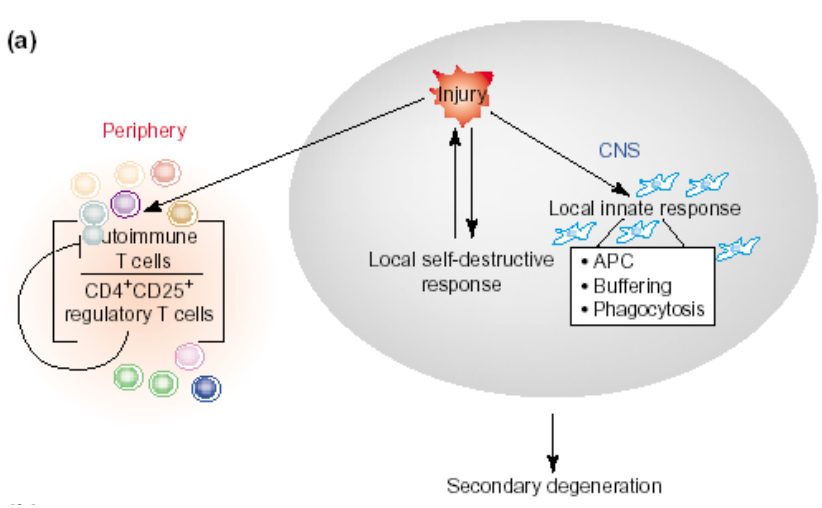
- Chronicity harmful

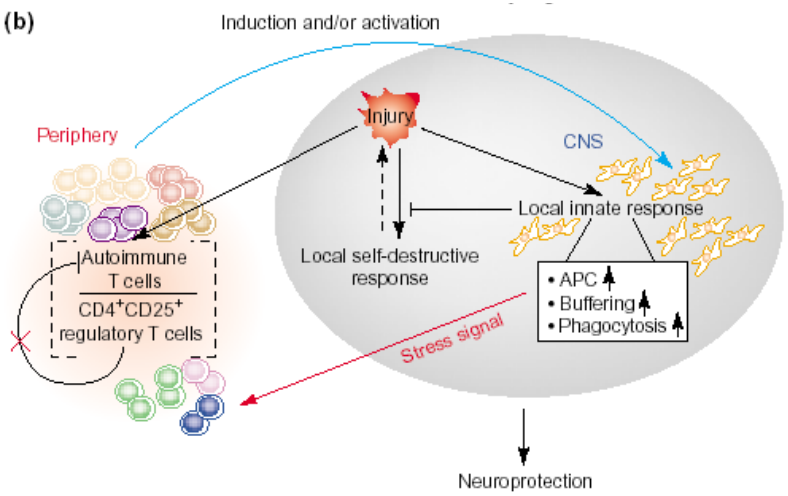
  Aktas et al 2007 ***Arch Neurol*** 64: 185-189

- Senescence of glia

  Streit 2004 ***J Neurosci Res*** 77: 1-8

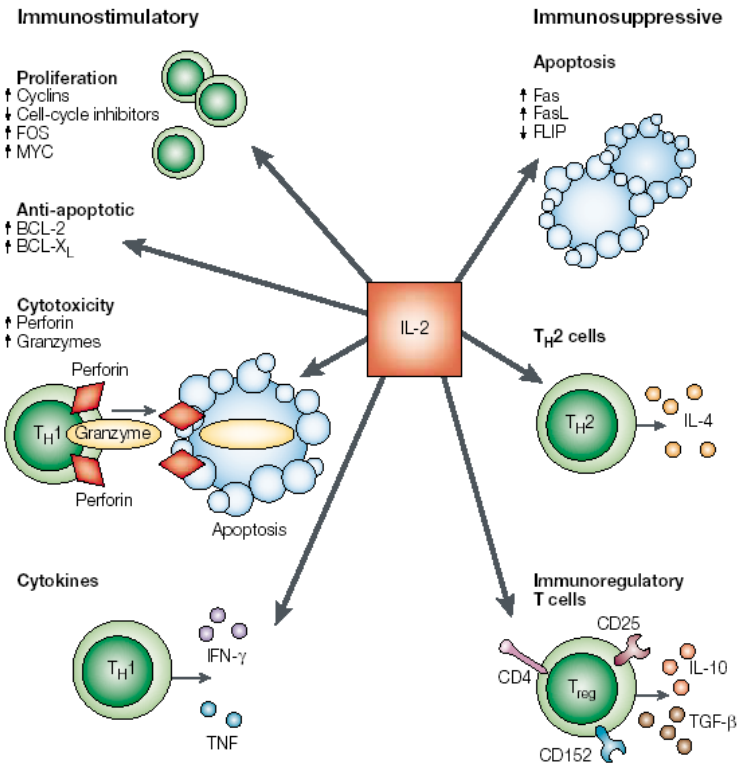
Inflammation has a protective role

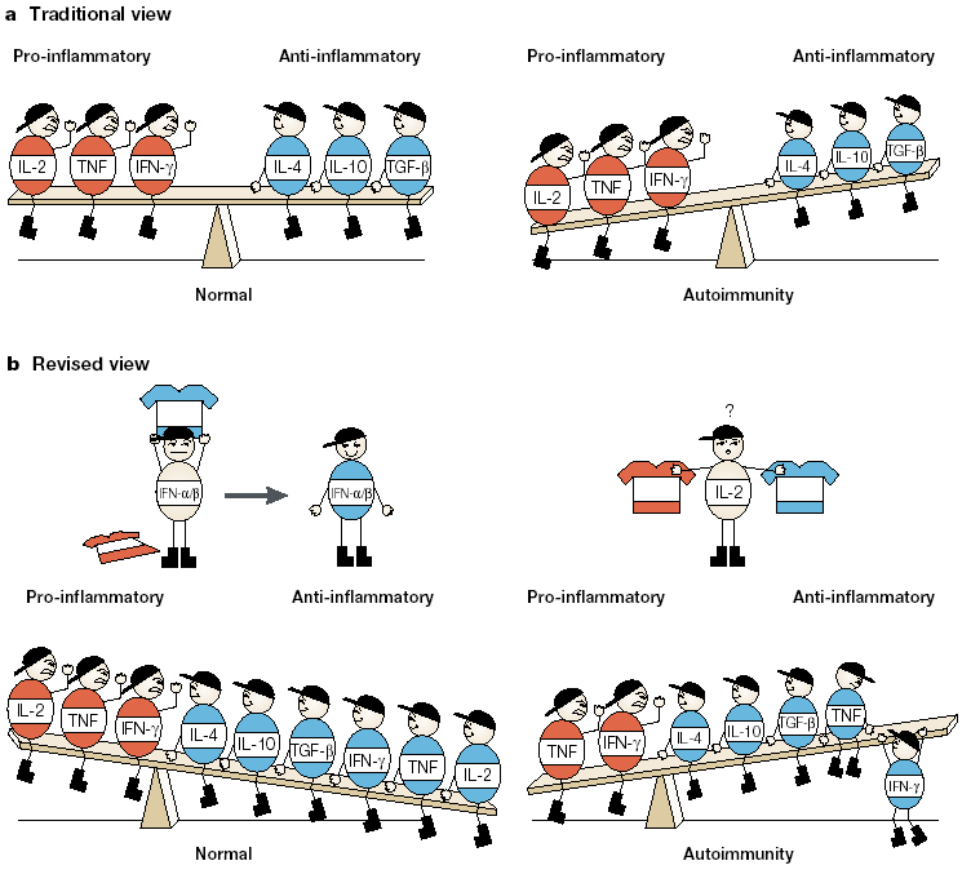




Schwartz & Kipnis 2002 ***Trends Immunol*** 23(11): 530-534

Cytokines can have dual roles





O'Shea et al 2002 ***Nat Rev Immunol*** 2: 37-45

Cells can have dual roles

Table 2. Different activation states of macrophages which by extrapolation may apply to microglia

	M1 (Classic activation)	*M2 (Alternative activation: wound healing)*	*M2 (Alternative activation: regulatory)*
Alternative terms		Tissue repair	Anti-inflammatory
Stimulus	Interferon-γ, TNF-α	IL-4, IL-13, TREM2?	IL-10, glucocorticoids
Source	Natural killer, T helper 1 lymphocytes.	Granulocytes responding to tissue injury, fungi and parasites (chitin), T helper 2 lymphocytes	Macrophage
Macrophage products	Pro-inflammatory cytokines: IL-1β, TNF-α, IL-6, IL-23 Oxygen free radicals	Extracellular matrix components Arginase 1 Chitinase	TGFβ1, IL-10
Cell surface proteins	MHC II?	Mannose receptor (CD206)	
Functions	Kill micro-organisms and other cellular targets. Phagocytosis Present antigen to lymphocytes. May cause collateral damage to host cells.	Tissue repair/wound healing Phagocytosis Increases production/remodelling of extracellular matrix	Inhibits inflammation Phagocytosis

Adapted from Mosser and Edwards (2008) [22]. TNF, tumour necrosis factor; IL, interleukin; TREM2, Triggering Receptor Expressed on Myeloid cells; MHC, major histocompatibility complex.

Boche et al., 2013 ***Neuropathol Appl Neurobiol*** 39(1):3-188

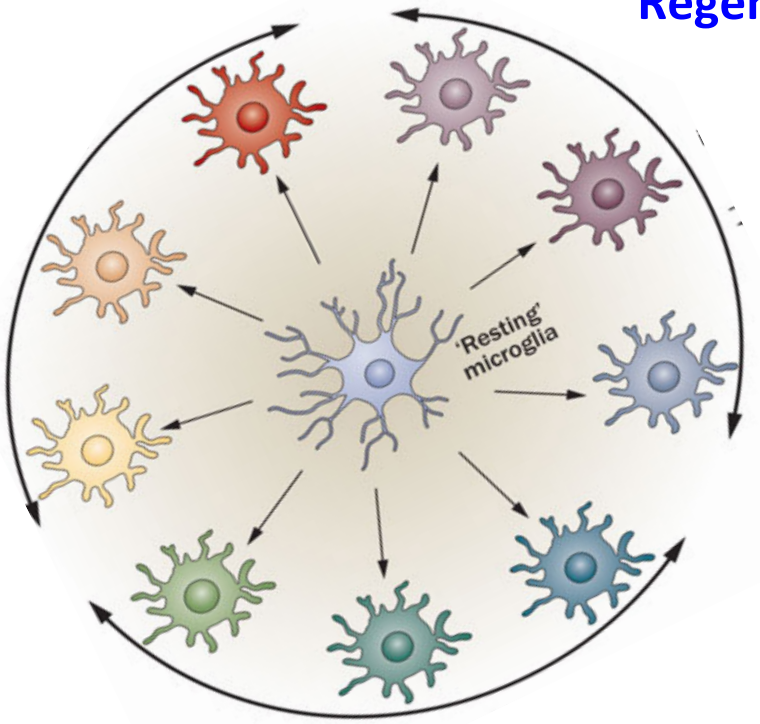
Microglial phenotypes….

M1-Cytotoxic:

COX2
iNOS
IL-6
TNF-a

M2a- Repair and Regeneration:

IGF-1
Gal3
CD206
Arg1



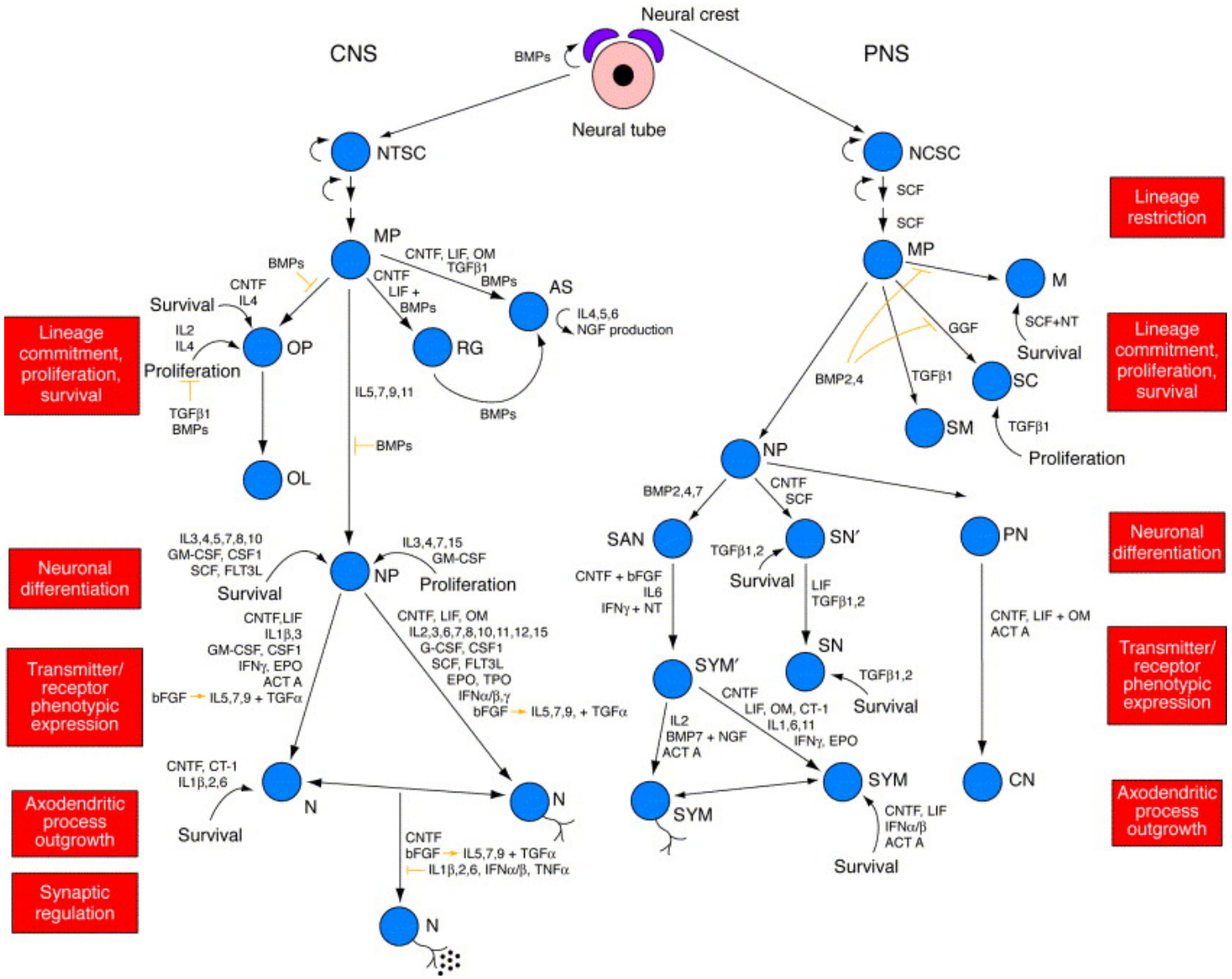
M2b Immunomodulatory:

SOCS3
IL-1Ra
IL-4R
SphK1

Courtesy of **Dr Bobbi Fleiss**
Centre for Brain Development, Kings College Hospital

Effects of inflammation in the brain

- Is inflammation beneficial?
- **Immunobiology versus neurobiology**



Mehler & Kessler 1997 ***TINS*** 20(18): 357-365

Immunity
Review

Chemokines and Chemokine Receptors: Standing at the Crossroads of Immunobiology and Neurobiology

Richard M. Ransohoff[1,*]
[1]Neuroinflammation Research Center (Lerner Research Institute) and Mellen Center for MS Treatment and Research (Neurological Institute), Cleveland Clinic, Mail Code NC30, 9500 Euclid Avenue, Cleveland, OH 44195, USA
*Correspondence: ransohr@ccf.org
DOI 10.1016/j.immuni.2009.09.010

Table 1. Functions of microglia

Function	*Examples*
CNS development	• Phagocytic activity during neuronal/synaptic development likely represents 'pruning' of redundant neurons and connections • Development influenced by secretion of cytokines, neurotrophins and growth factors
Recognition of pathogens (innate immune function)	• Receptors (e.g. Toll-like receptors, TLRs) recognize evolutionarily conserved antigens on surface of pathogens known as pathogen-associated molecular patterns (PAMPs) such as the endotoxin lipopolysaccharide (LPS) • Similar mechanisms possibly also involved in response to extracellular protein accumulations (e.g. amyloid plaques)
Phagocytosis	Ingestion and destruction by digestive enzymes in lysosomes of: • Multiple types of damaged cells (e.g. infarct) • Neurons (e.g. neuronophagia, Wallerian degeneration, tract degeneration) • Micro-organisms (e.g. abscess) • Virally infected cells (e.g. herpes encephalitis) • Erythrocytes and haemoglobin breakdown products (e.g. haemosiderin) following haemorrhage
Antigen presentation	• Presentation of pathogens (e.g. in bacterial, fungal, viral infections) bound to MHC for activation of T lymphocytes • Possibly relevant also in autoimmune disease
Recognition of bound antibody (adaptive immune function)	• Respond to antibodies bound to pathogens (opsonization) • Possibly also relevant to autoimmune disease (e.g. demyelination, paraneoplastic syndromes
Cytotoxicity	• Reactive oxygen species/respiratory burst (H_2O_2, NO) • Cytokines (e.g. IL, TNF, interferons, TGF, CSF) • Secretion of glutamate, aspartate
Extracellular matrix remodelling	• Proteases (MMPs degrade extracellular matrix)
Modulation of inflammation/ immune responses	• Chemokines (attract other inflammatory cells) • CD200 receptor (CD200 secreted by neurons has anti-inflammatory role) • Interferon-γ (promotes further microglial activation)
Repair	• Removal of cell debris facilitates plasticity and synaptogenesis
Stem cells	• Regulation of stem cell proliferation (e.g. granule cell neurons of hippocampus)
Tumours	• Response to neoplastic cells, possible regulation of tumour cell proliferation
Lipid transport	• Secretion of lipoprotein particles which deliver lipids to neurons for maintenance of cell membranes and synapses, facilitating synaptic plasticity
Viral entry into CNS	• CCR5 and CD4 are receptors for entry of HIV into macrophages and hence into CNS
Support mycobacteria	• Permits intracytoplasmic survival of mycobacteria (e.g. tuberculosis)
Demyelination	• Myelin destruction/phagocytosis (e.g. multiple sclerosis)

CNS, central nervous system; MHC, major histocompatibility complex; IL, interleukin; TGF, transforming growth factor; CSF, colony-stimulating factor; MMP, matrix metalloproteinase; HIV, human immunodeficiency virus; CCR5, C–C chemokine receptor 5.

Boche et al., 2013 ***Neuropathol Appl Neurobiol.*** 39(1):3-188

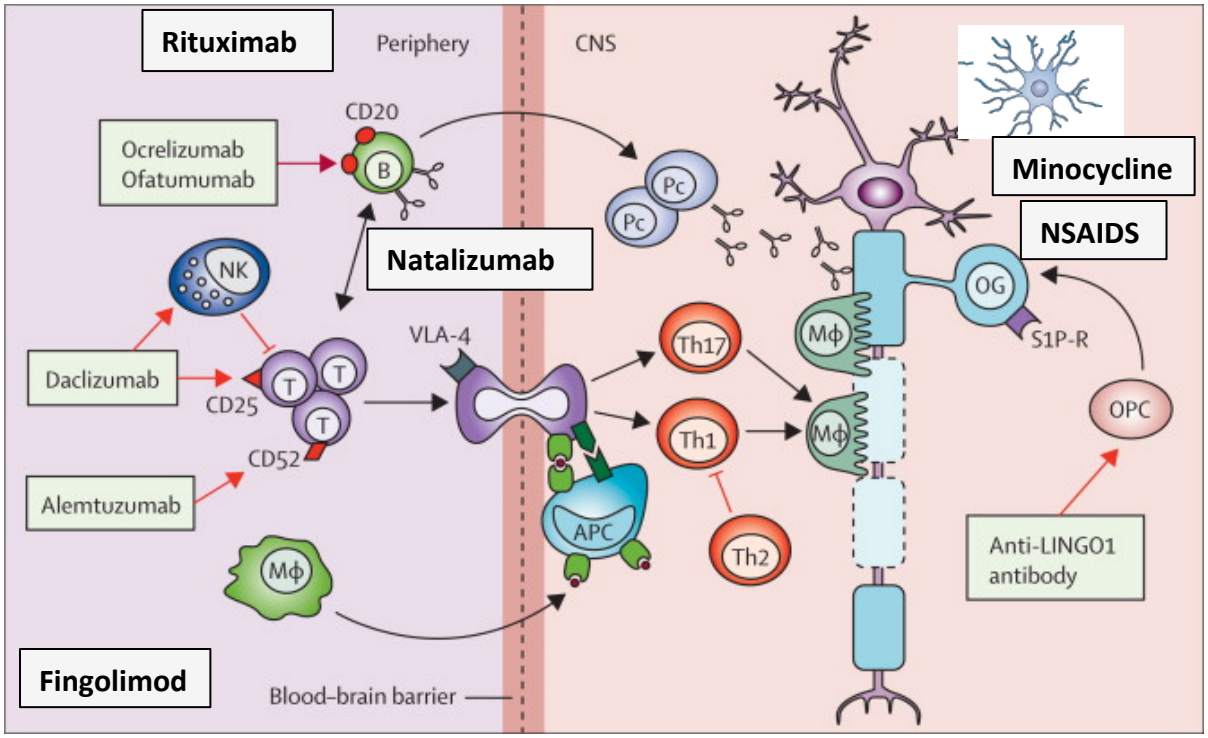
Cellular targets in treating inflammation

B cell targeting

Belimumab	BAFF blockade
Atacicept	BAFF & APRIL blockade
Tabalumab	BAFF blockade
BG9588	CD40L blockade
IDEC-31	CD154–CD40 blockade

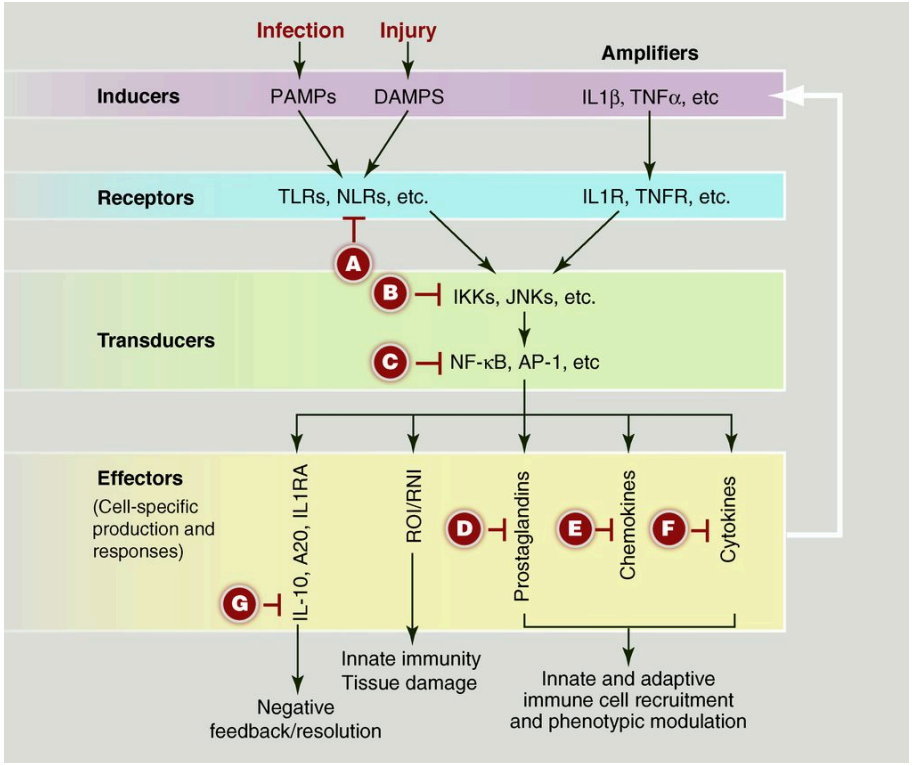
Anti-metabolites

Azathioprine
Mycophenolate
Methotrexate
Teriflunomide



Modified form Jiwon and Calabressi 2013 ***Lancet Neurology;*** 12 (11): 1115 - 1126

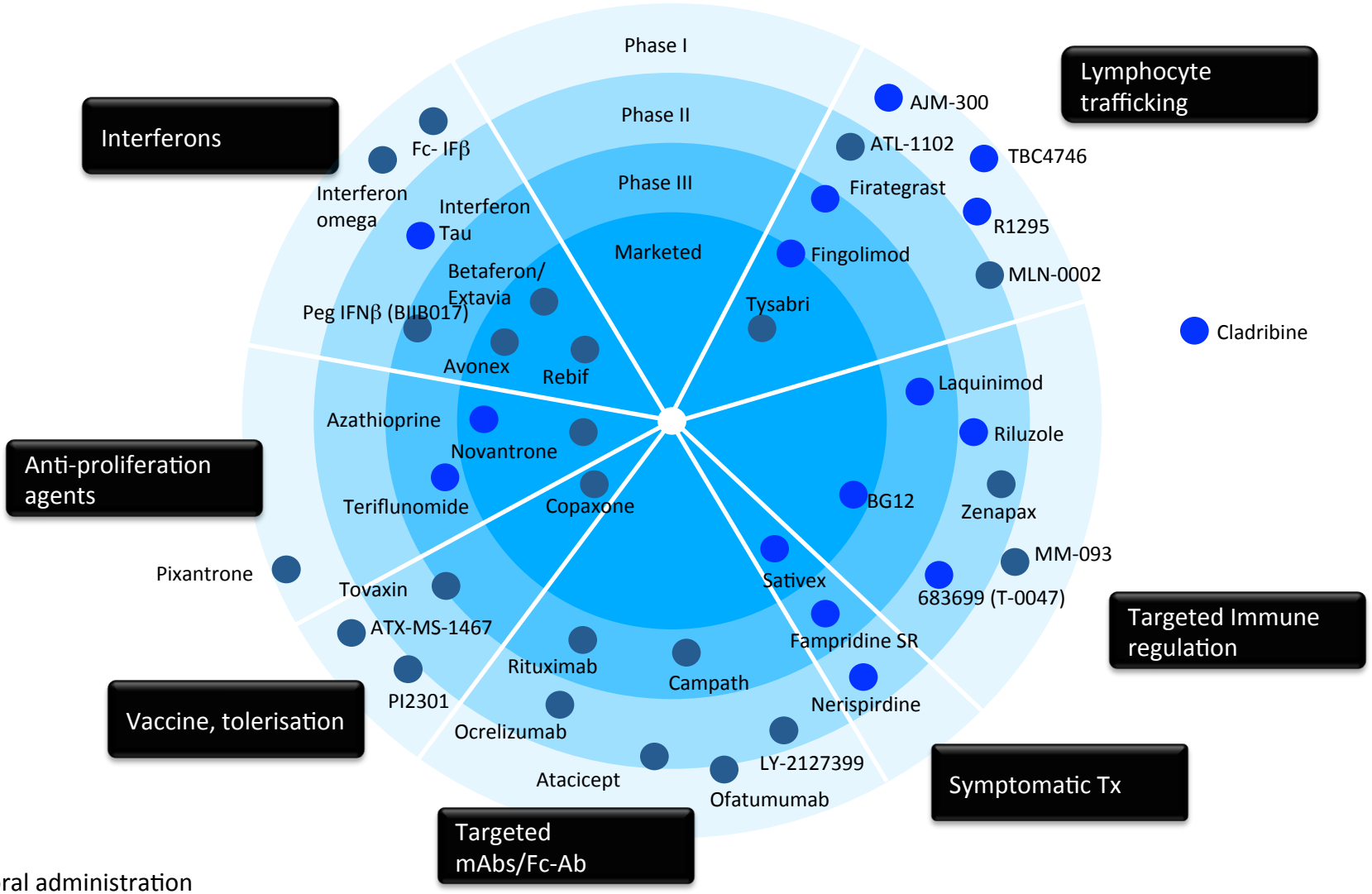
Inflammation at a signalling level and candidate therapeutic targets



Example Target(s)	Example Drug(s)
A TLRs, inflammasome	Neutralizing Ab (TLRs), Caspase I inhibitor
B IKK, JNK, JAK, MAPK, etc	Small molecule kinase inhibitors
C NFκB, AP-1, 'Epigenome'	GR ligands, HMT/HDM inhibitors
D Cox2	NSAIDs
E MCP-1/Ccr2	Neutralizing Abs, small molecule inhibitors
F TNFα, IL1β	Neutralizing Abs
G Negative feedback/ resolution	Resolution enhancers (e.g., resolvins)

Tabas & Glass 2013 ***Science***;339:166-172

The pipeline of MS therapy



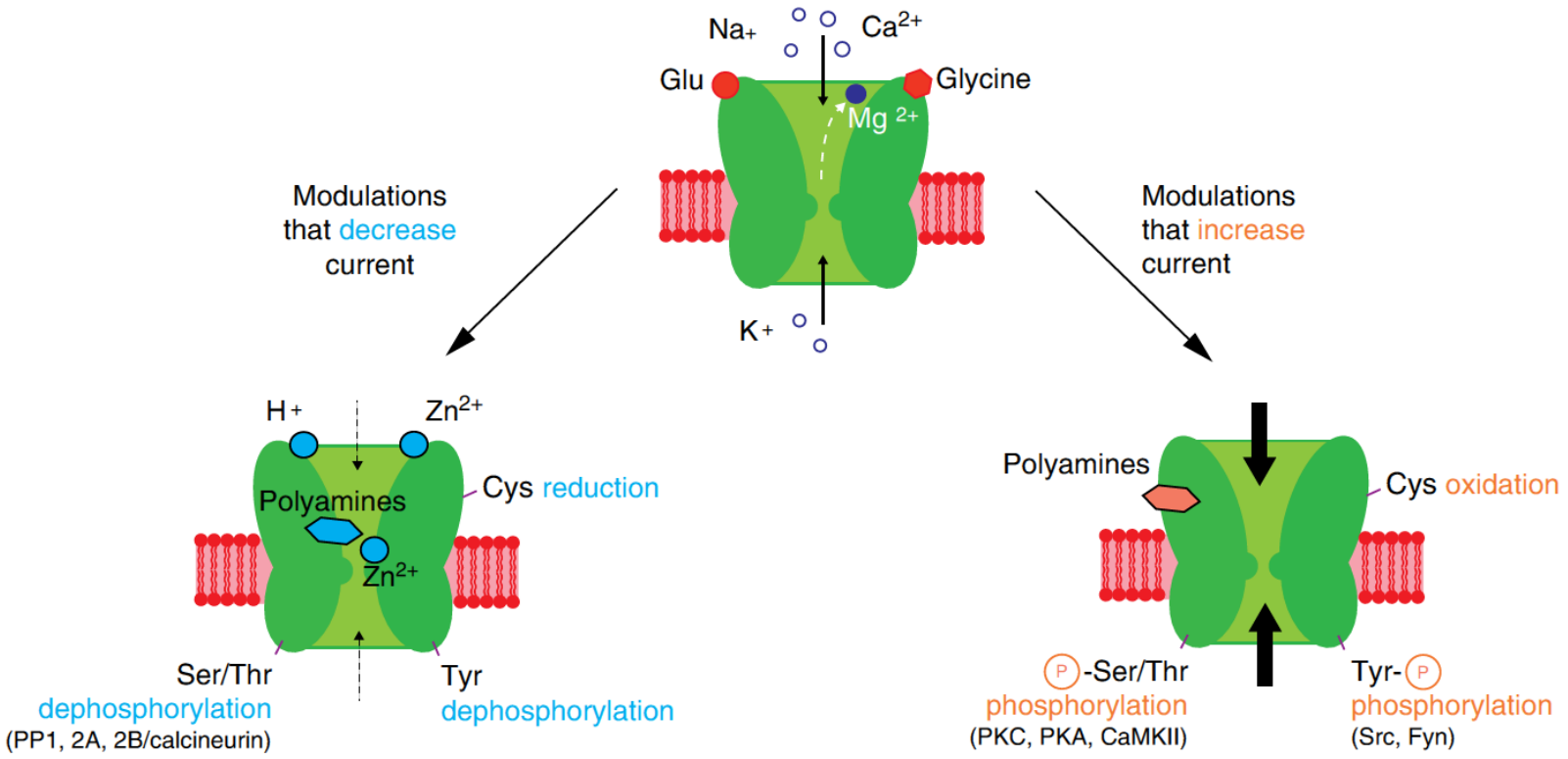
= oral administration

= injectable

Courtesy G Giovannoni

PhI-III are investigational compounds and are not licenced.

The role of immunotherapy maybe beyond immune suppression

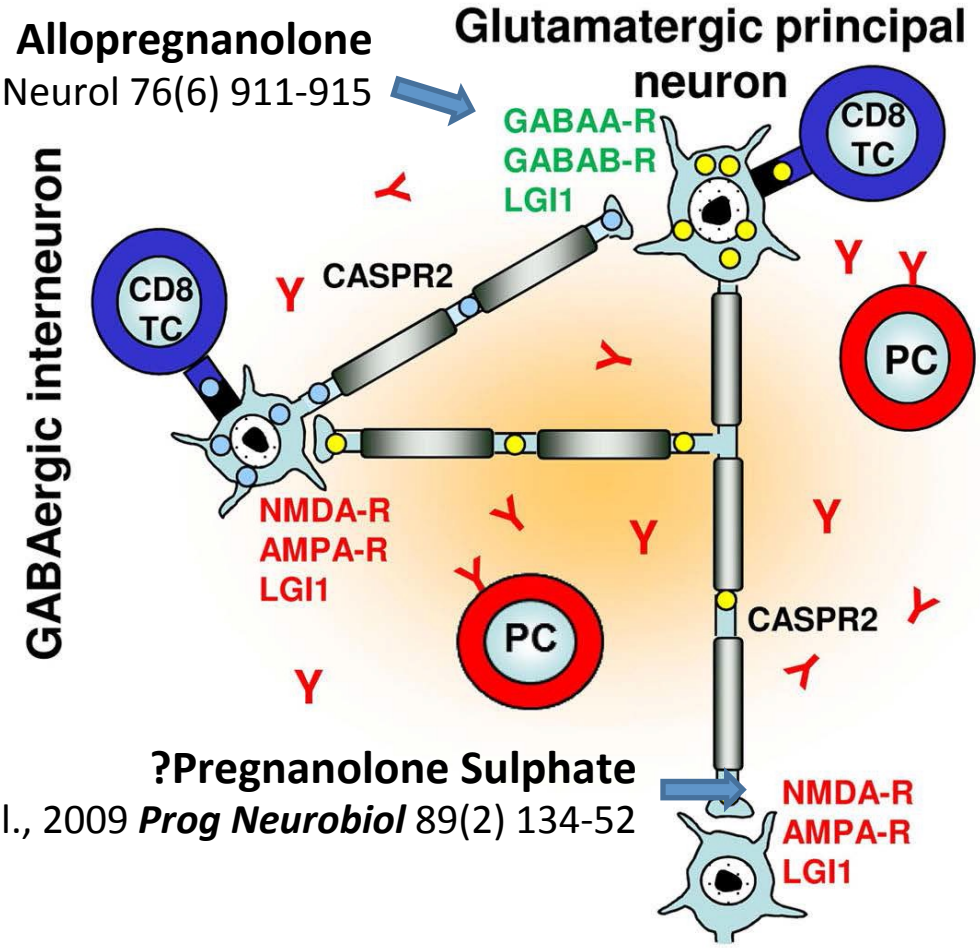


Zito and Scheuss 2009

Impaired inhibitory neurotransmission
→ Hyperexcitability and -function of principal neurons

Allopregnanolone

Broomall et al., 2014 Ann Neurol 76(6) 911-915



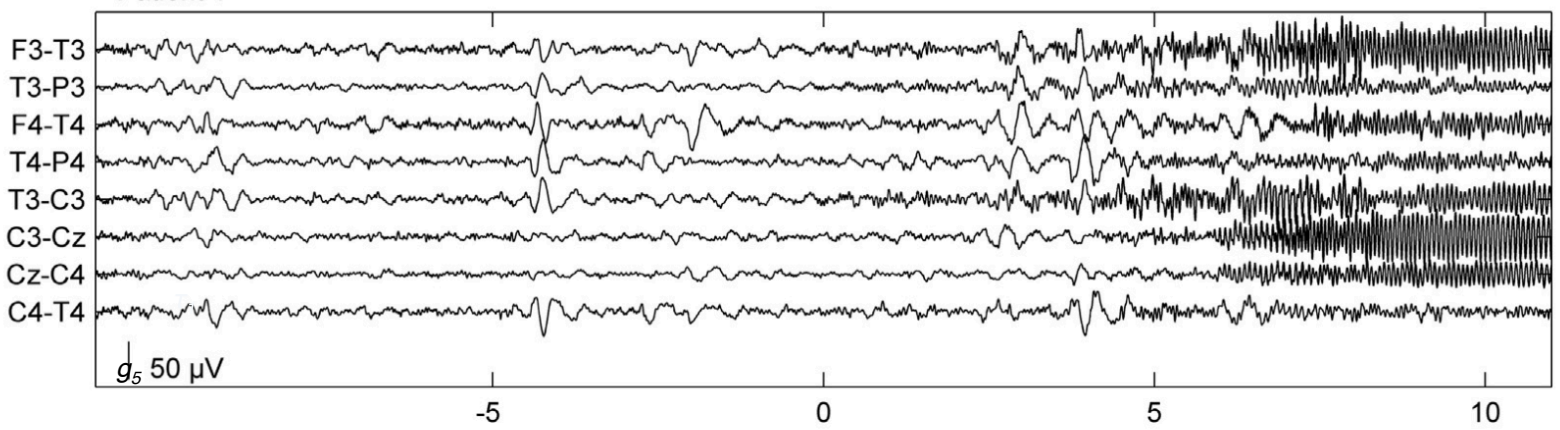
?Pregnanolone Sulphate

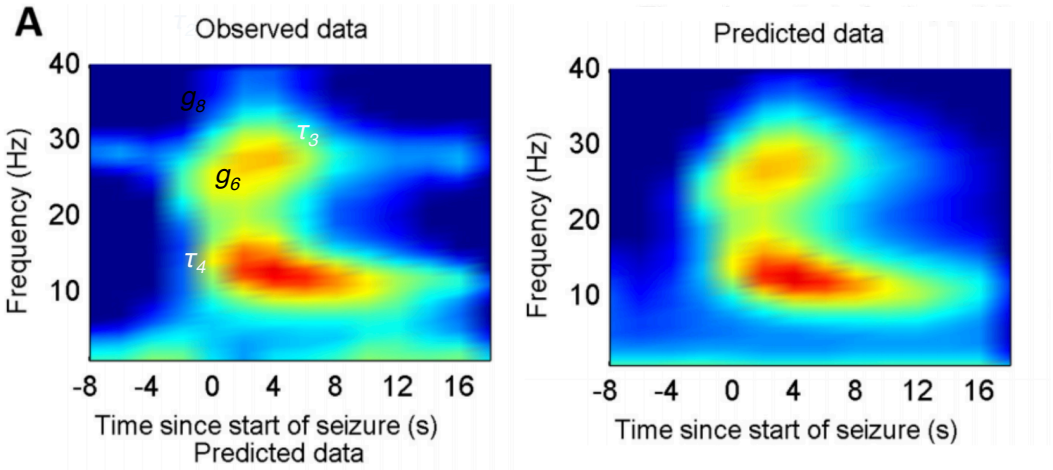
Zheng et al., 2009 ***Prog Neurobiol*** 89(2) 134-52

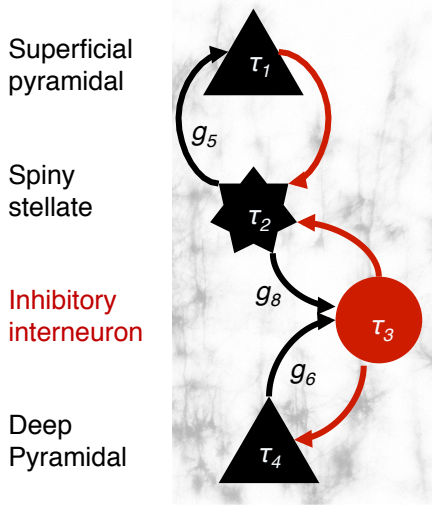
Impaired excitatory neurotransmission
→ Hypoexcitability and -function of principal neurons

Modified from Meltzer et al., 2015 ***Front Neurol*** 6:171

DCM can model complex real EEG data





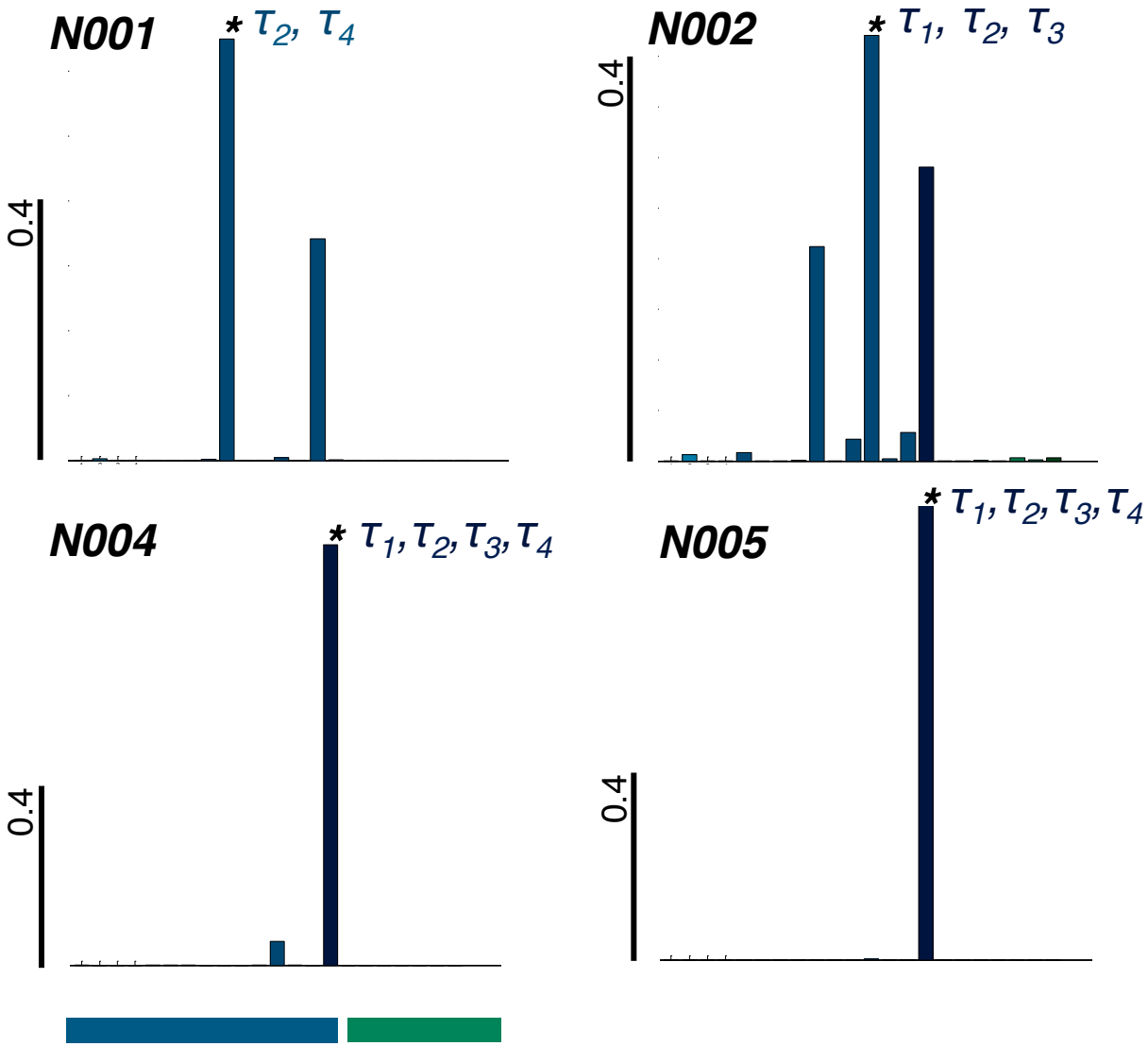


Richard Rosch

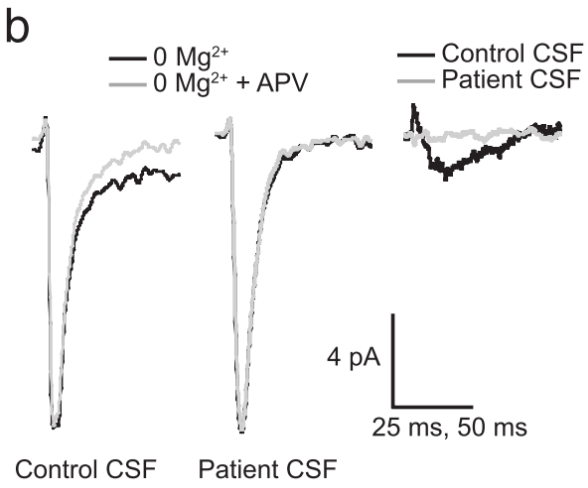
Wellcome Trust Centre for Neuroimaging &
Centre for Developmental Cognitive Neuroscience

Cooray et al. (2015)
NeuroImage: *Epub*

Paroxysms best explained by time constant changes



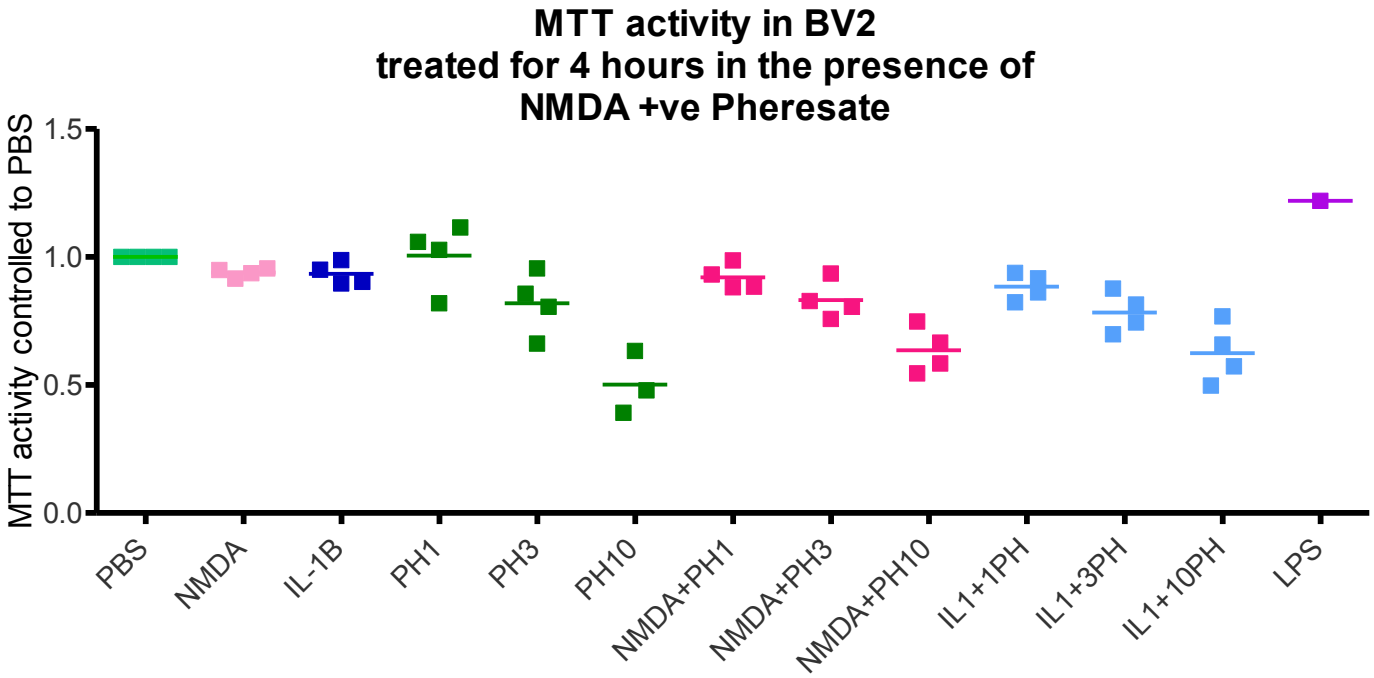
time constants (τ)



The effects of antibodies on immune system

- Activation of microglial N-Methyl-D aspartate receptors triggers inflammation and neuronal cell death
  - Kaindl et al., 2012 ***Ann Neurol*** 72:536–549
- N-methyl-D-aspartate receptor (and other) antibodies interacts with microglia?

N-methyl-D-aspartate receptor antibodies interacts with microglia in-vitro

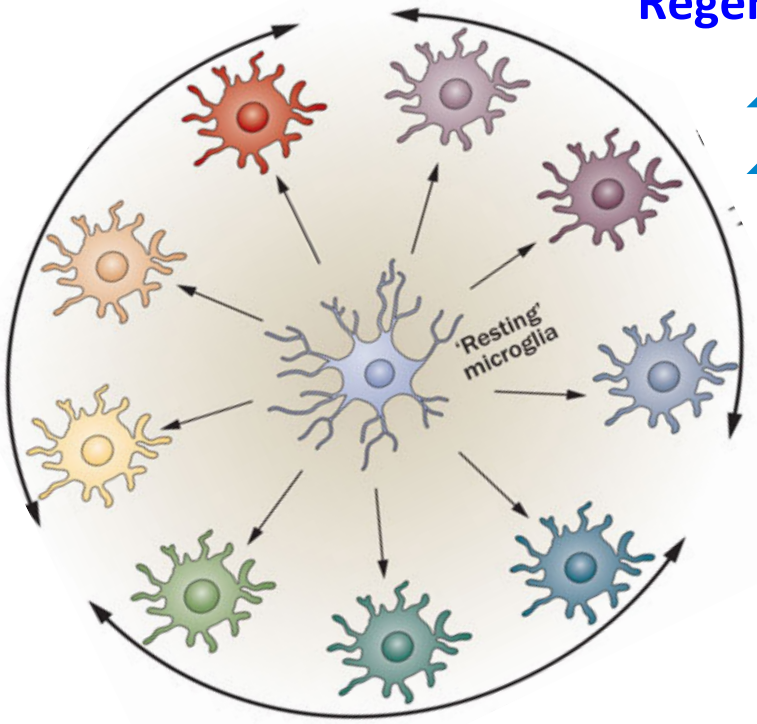


Gadian, Lim, Fleiss and Gressen (Unpublished observations)

N-methyl-D-aspartate receptor antibodies upregulates the regenerative M2a phenotype?

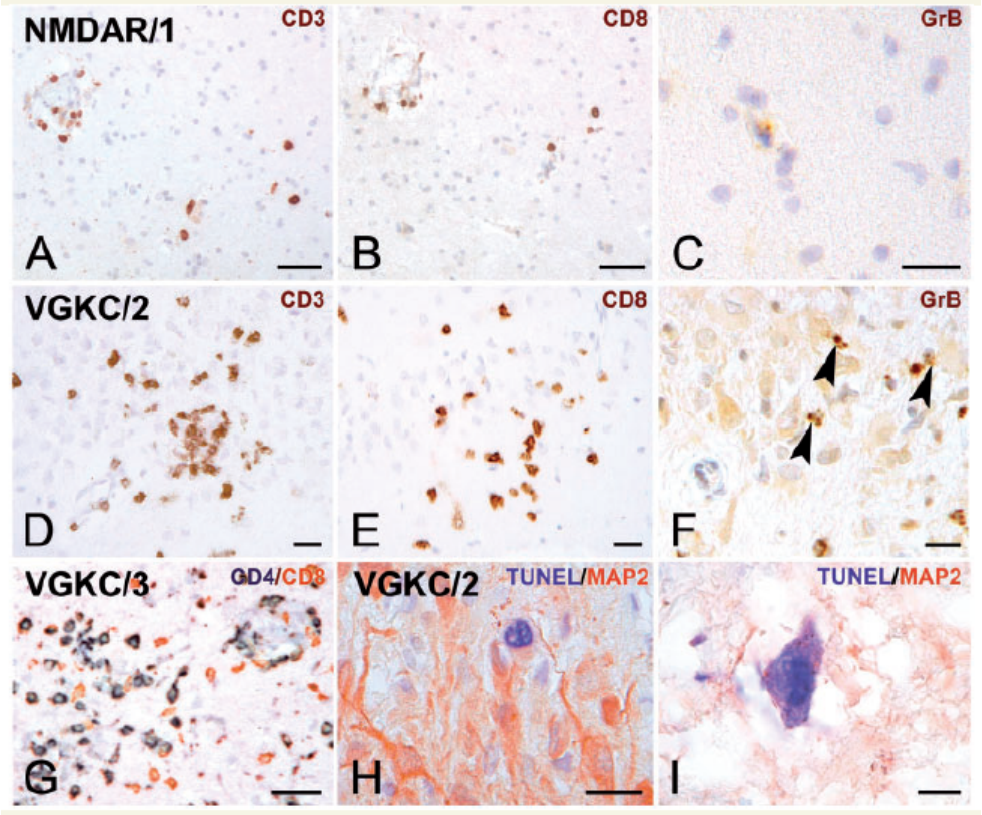
M1-Cytotoxic: ⇔ COX2, ⇔ iNOS

M2a- Repair and Regeneration: ⇑ CD206, ⇑ Arg1



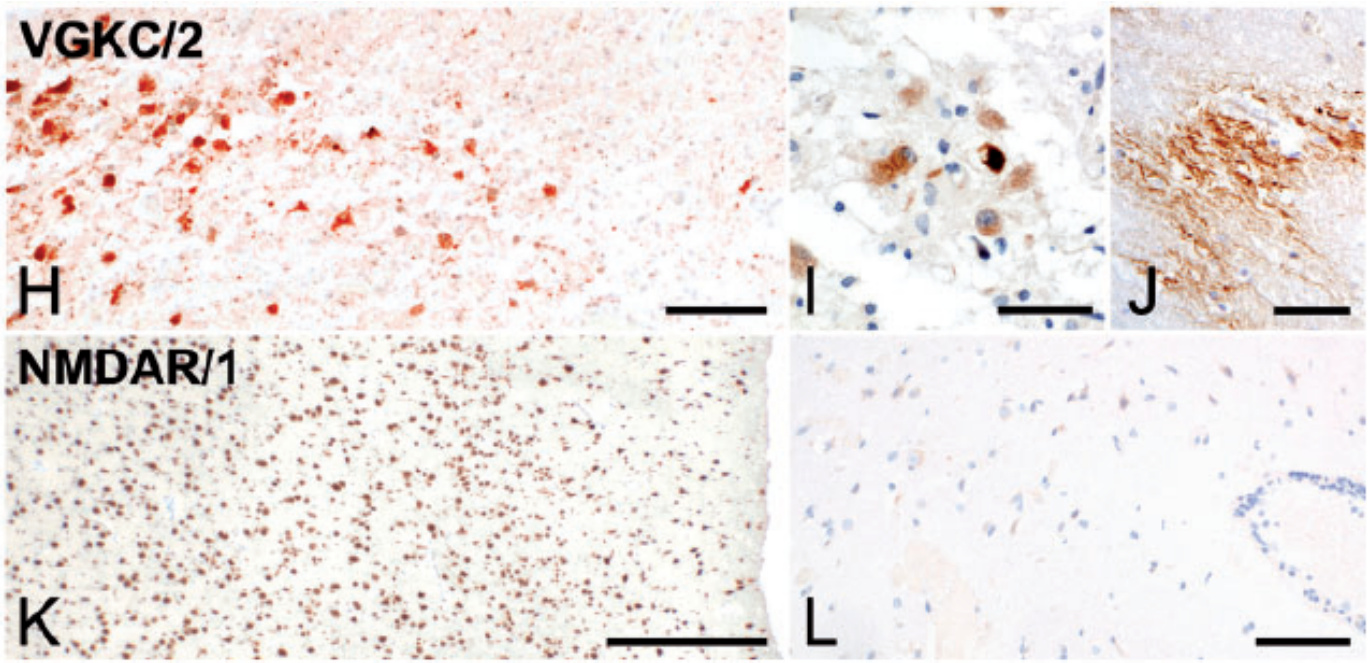
M2b Immunomodulatory: ⇓ SOCS3

Gadian, Lim, Fleiss and Gressen (Unpublished observations)



NMDAR antibodies associated with minimal T cells
VGKC-complex antibodies associated with CD8 T cell infiltrates and perforin release

Bien et al., 2012 ***Brain***135(Pt 5):1622-38.



VGKC-complex antibodies associated with neuronal loss and APP deposits.
NMDAR antibodies associated with no neuronal loss or deposits

Bien et al., 2012 ***Brain*** 135(Pt 5):1622-38.

Conclusion

Antibody-mediated CNS diseases are important to recognise

Several CNS receptors and ion channels have been identified as targets

Presentations include amnesia,
epilepsy, startle, psychosis, sleep, autonomic
and movement disorders

The patients can get considerably better when treated aggressively with steroids, plasma exchange etc.

Long way from optimally managing these children

Kumaran Deiva
Marc Tardieu

Service de neurologie pédiatrique, Hôpitaux Universitaires Paris Sud, Le Kremlin Bicêtre

M Absoud, W.K Chong, C. De Goede , K. Foster, R. Gunny, C. Hemingway, P. Jardine, R. Kneen, M. Likeman, M.J Lim, K. Nischal, M. Pike, N. Sibtain, W. Whitehouse, C Cummins, E Wassmer

UK & Ireland Childhood CNS Inflammatory Demyelination Working Group

Brain and Spine Inflammation
Hock Sin Heng
Yaiza Hernandez
Rahul Singh
John Gadian
Ani Almoyan

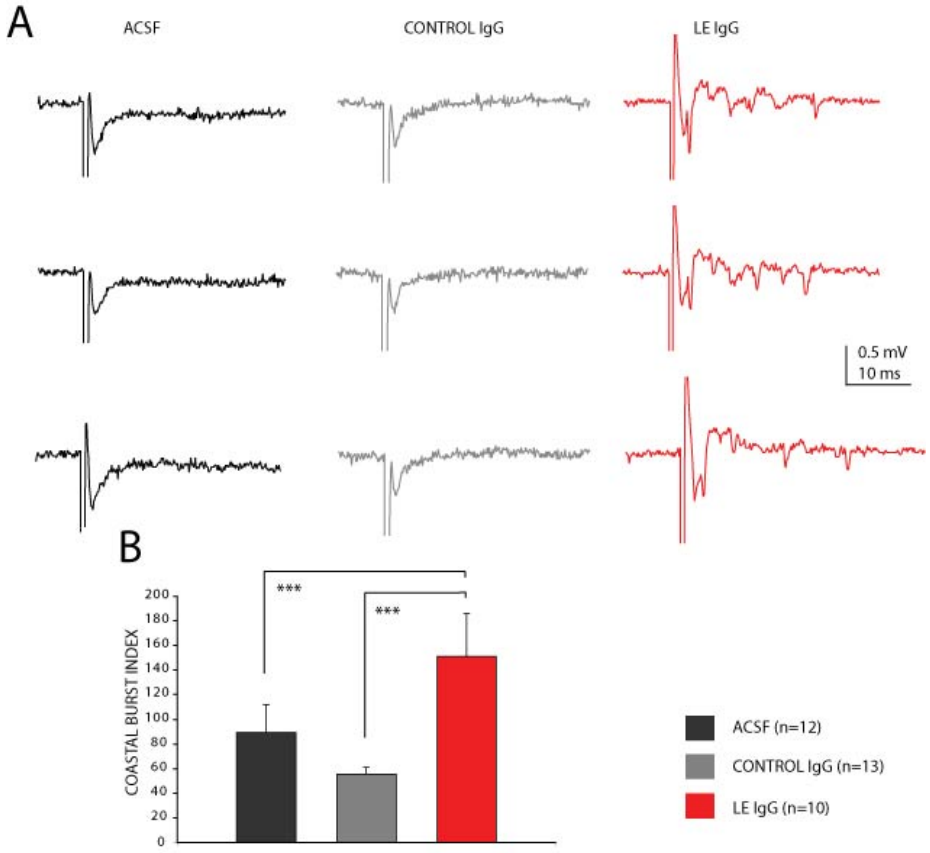
Jean Pierre Lin

Angela Vincent
Bethan Lang
Patrick Waters
C Buckley
M Leite
Yael Hacohen
Sukhvir Wright
M Woodhall
L Jacobs
Linda Gardiner

The British Ophthalmological Surveillance Unit

VGKC/LGI1 Ab IgG elicits epileptiform activity in the CA3 area of hippocampus in brain slices

Extracellular potentials recorded in the stratum lucidum of CA3 pyramidal cell layer with extracellular stimulation of mossy fibres



VGKC/Lgi1 IgG increases burst activity in CA3

Reduces no of failures to stimulation

Effects similar to dendrotoxin

Lalic et al., 2011 ***Epilepsia*** 52(1):121-31

Febrile infection-related epilepsy syndrome (FIRES)

Baalen et al., 2010 ***Epilepsia*** 51(7); 1323-1328

- Idiopathic catastrophic
  Baxter et al., 2003 ***Seizure*** 12; 379-87
- Devastating epileptic encephalopathy in school age children (DESC)
  Mikaeloff et al., 2006 ***Epilepsy Res*** 69; 67-69
- Acute encephalitis with refractory, repetitive partial seizures (AERRPS)
  Sakuma et al., 2010 ***Acta Neurol Scand*** 121(4); 251-6
- New Onset Refractory Status Epilepticus
  Costello et al., 2009 ***J Neurol Sci.*** 15;277(1-2); 26-31

Previously well
Febrile prodrome followed by encephalopathy and fulminant seizures
Refractory seizures (not invariable)

Acute encephalopathy with inflammation-mediated status epilepticus

Nabbout et al., 2011 ***Lancet Neurol.*** 10(1); 99-108
Nabbout 2012 ***Epilepsia*** 2012 53 Suppl 4; 58-62

Rasmussen Encephalitis

- Localised form of inflammation and focal refractory seizures
- Glial activation and cytotoxic T cells infiltration
- Immunomodulation and epilepsy surgery
  - Tacrolimus improves motor and cognition but no effect in seizures

Bien et al., 2005 ***Brain*** 128(3): 454-71

Varadkhar et al., 2014 ***Lancet Neurol.*** 13(2):195-205