Autoimmune causes of psychosis: diagnosis and management

Belinda Lennox

Belinda.lennox@psych.ox.ac.uk
@blennox4
www.sinapps.org.uk

Napicu Glasgow 2019

Overview

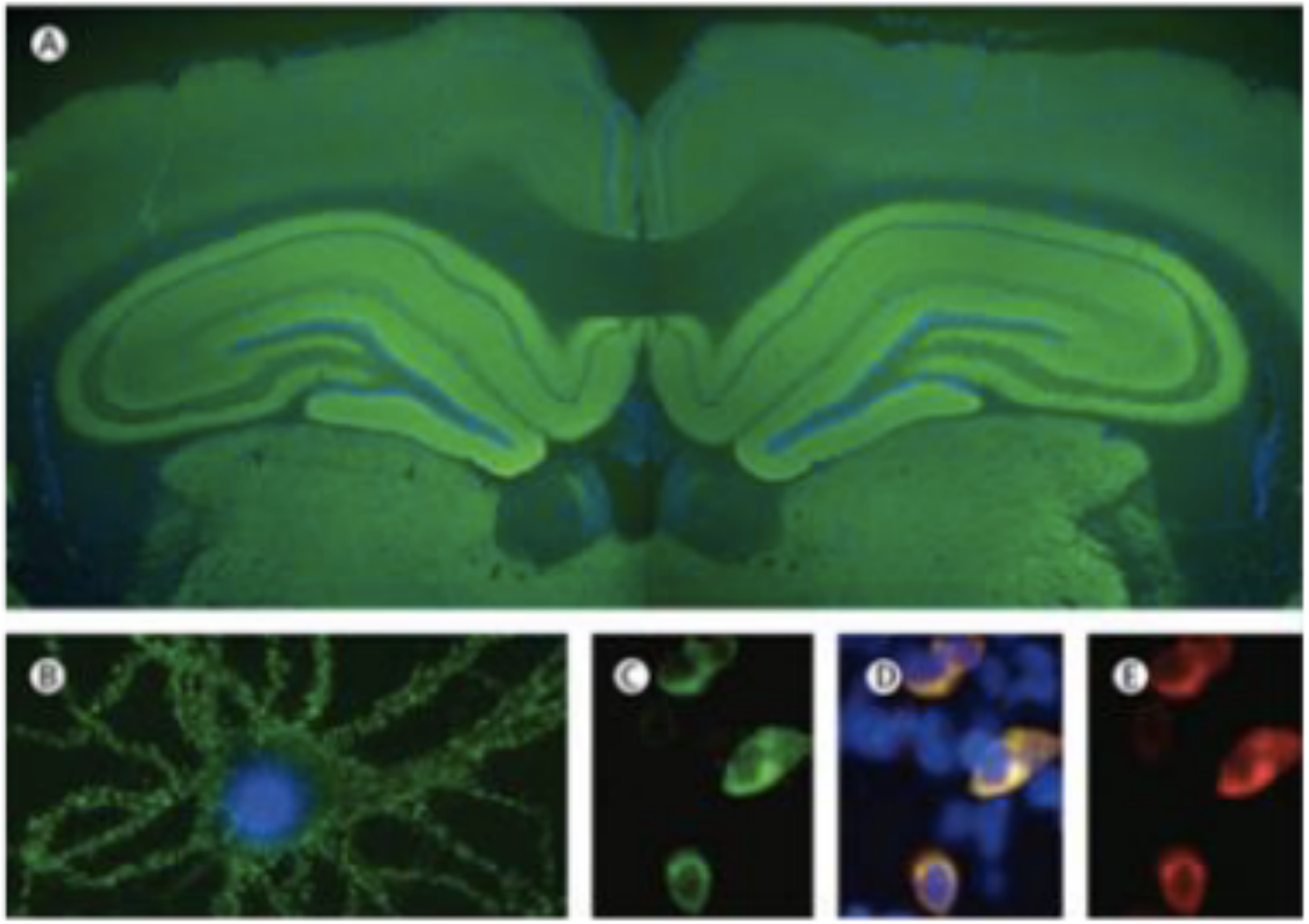
- Autoimmune encephalitis as a disease model for psychosis
- How many patients with psychosis also have antibodies?
- Do patients with psychosis and antibodies have a different type of psychotic illness?
- What should clinicians do now?

New disorders of autoimmune encephalitis

"She had been well until July, 1994, when she developed impairment of recent memory…she gradually lost contact with reality…she became acutely confused and was transferred to a psychiatric unit. On admission, she had a stiff facial expression, incoherent thoughts, and was dismissive; we could not communicate with her at all. On physical examination, a mass was palpated in the lower abdomen. Neurological examination was unremarkable." Okamura et al Lancet 1997

Okamura et al Lancet 1997

Neuronal cell surface antibodies = pathogenic



Antibody immunolabelling on hippocampal slices, hippocampal neuronal cultures, HEK cell based assays (from Dalmau et al 2011)

Breakthrough discovery of neuronal cell surface antibodies causing encephalitis

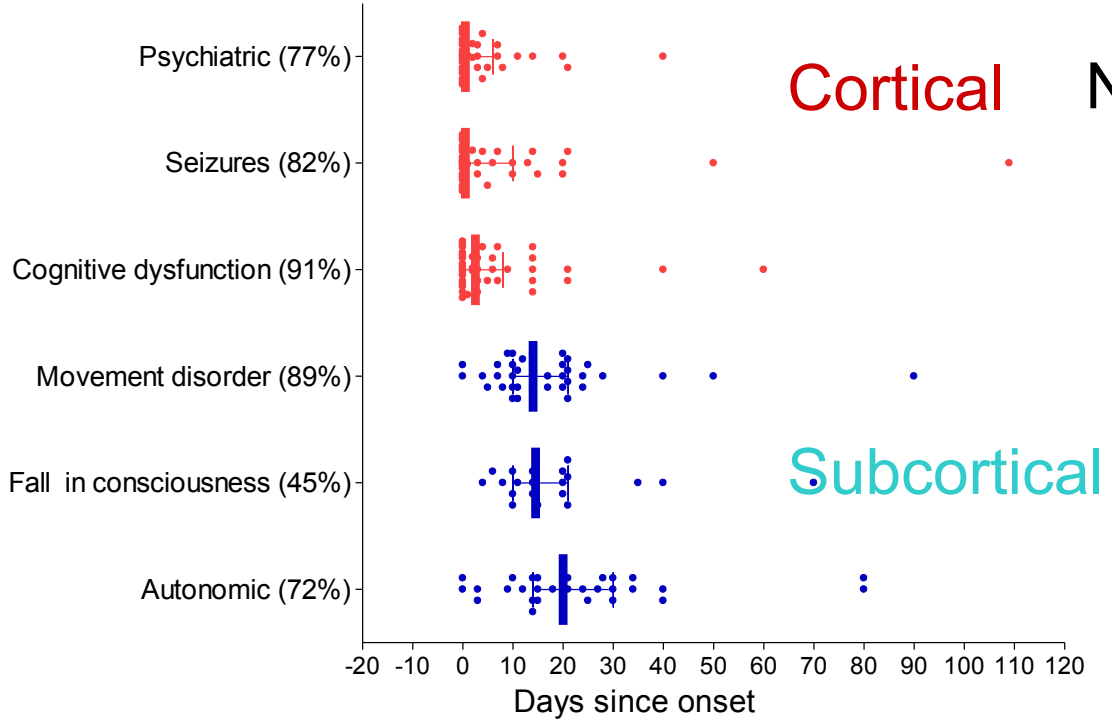
- Voltage Gated Potassium Channel complex (LGI1, CASPR2, contactin-2) 2001, 2010
- **N-Methyl-D-aspartate receptor (NMDA) 2008**
- AMPA receptor 2009
- GABA-B 2010
- mGluR5 2011
- Glycine receptor 2012
- D2 receptor 2013
- DPPX 2013
- Glycine receptor 2014
- IgLON5 2014
- GABA-A receptor 2015
- Neurexin-3-alpha 2016

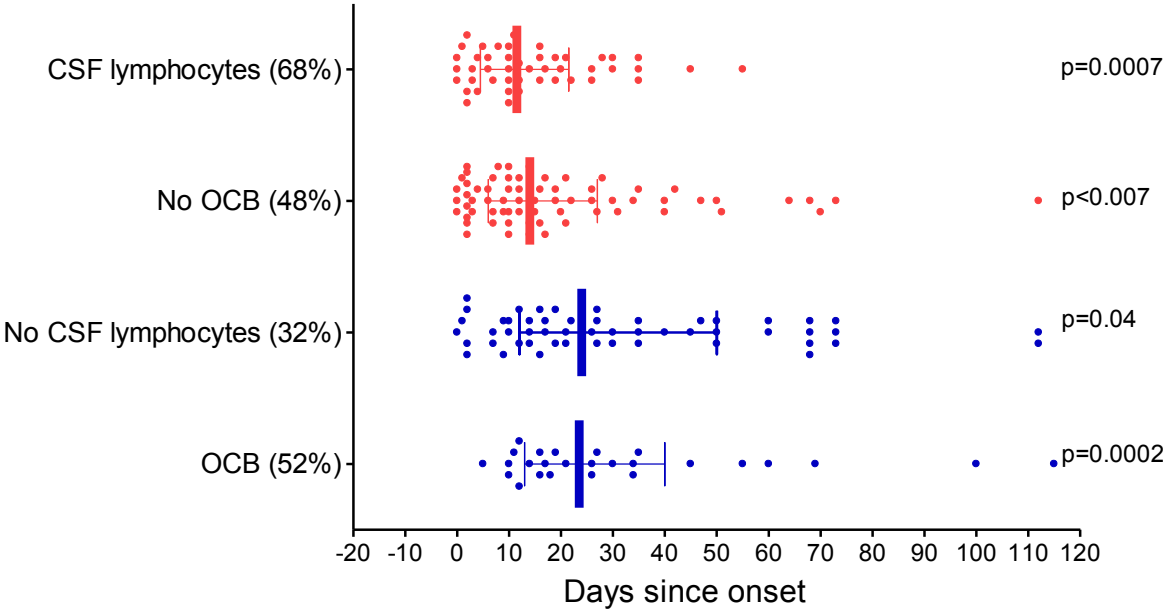
NMDA-receptor encephalitis:

- Progessive life threatening limbic encephalitis,
- seizures, 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)

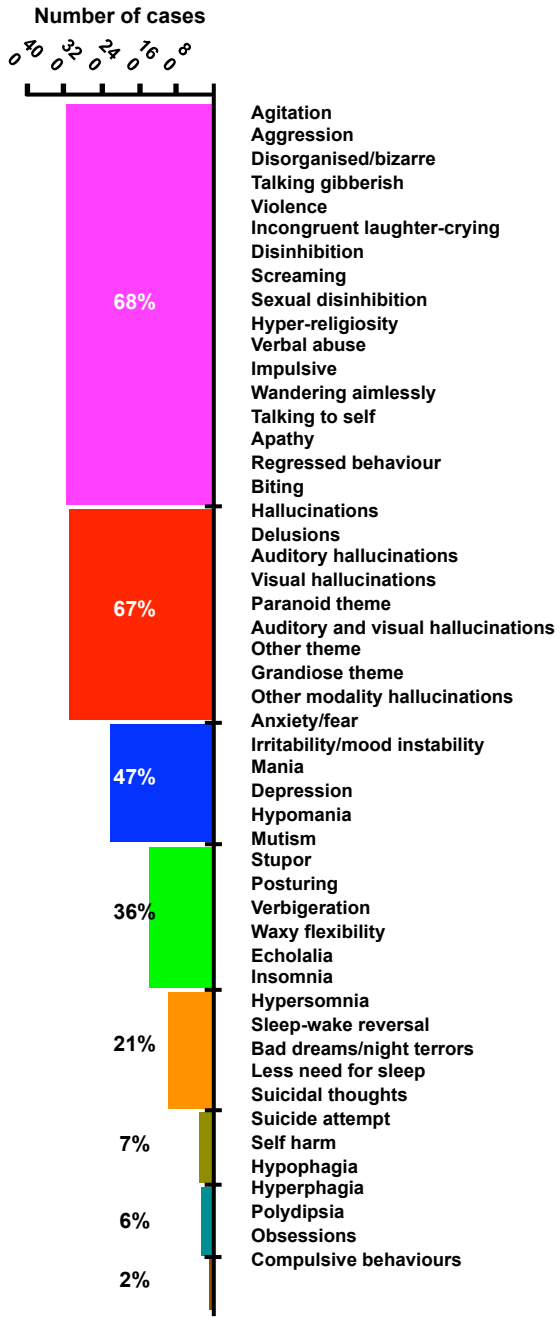
NMDAR encephalitis

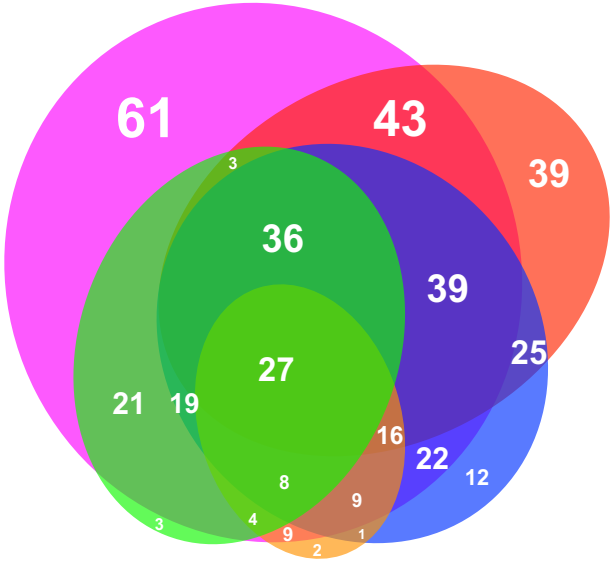


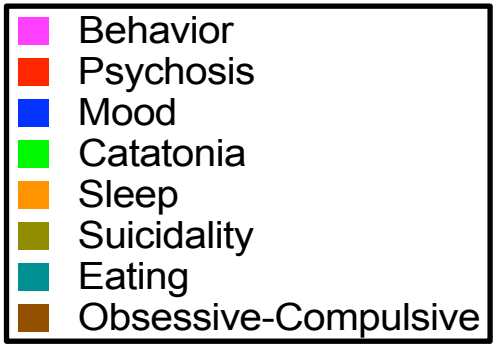


Irani et al *Brain* (2010)

Psychiatric symptomatology in NMDAR encephalitis n=464





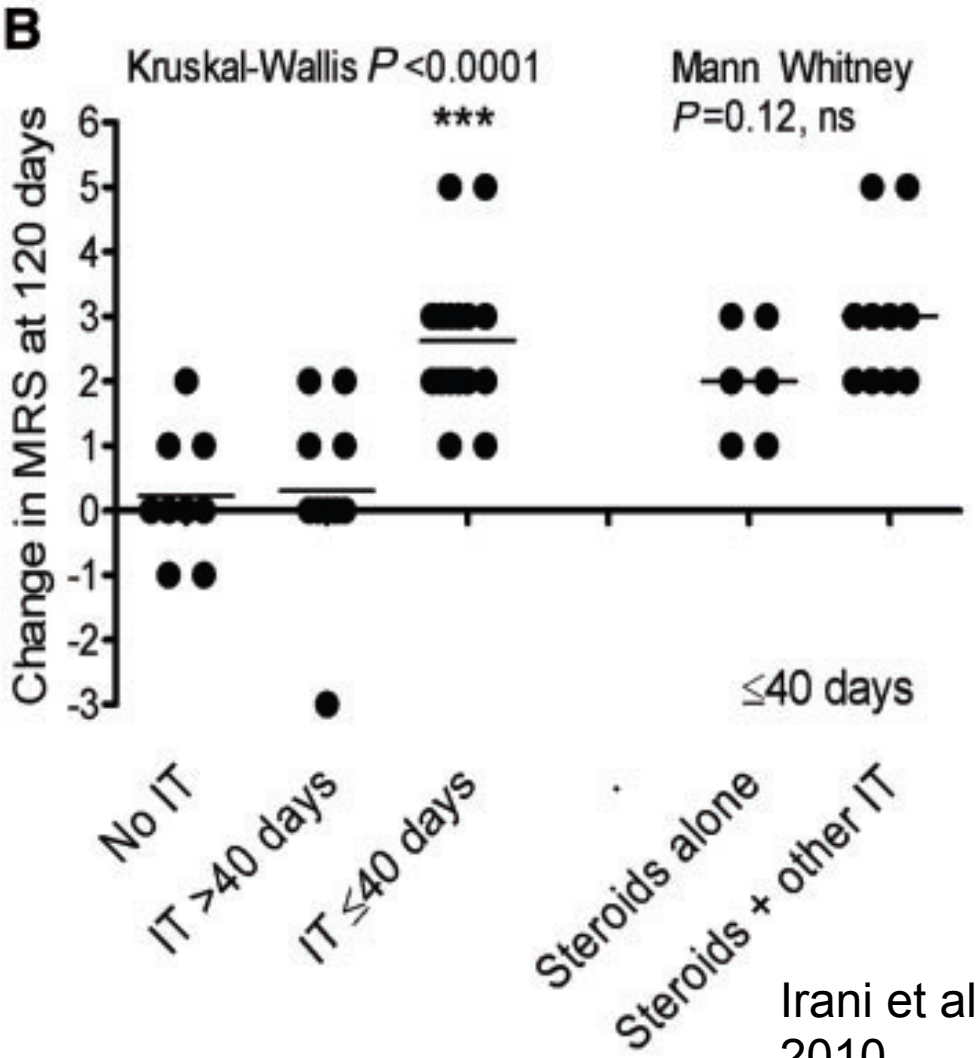


Al-Diwani et al The Lancet Psychiatry 2018

All symptoms and signs of AE also seen in schizophrenia

	Occurrence in schizophrenia
Seizures	OR 11.1 (Makikyro, et al., 1998)
Cognitive dysfunction	Current iQ, category fluency, verbal memory, sustained attention, response inhibition – effect size 1.0-1.5
Movement disorders	9% spontaneous dyskinesias; 17% spontaneous parkinsonism (Pappa and Dazzan, 2009), 7.6-38% catatonia (Taylor and Fink 2003)
Autonomic dysfunction	Neuroleptic malignant syndrome in 0.07 to 2.2%.
CSF inflammation	CSF lymphocytes 3.4%, OCB in 7.2% (Endres et al 2015)
Sleep dysfunction	30 to 80% of patients with schizophrenia (Cohr, 2008). Al-Diwani et al Frontiers 2017

NMDAR encephalitis responsive to early immunotherapy



Irani et al Brain 2010

How many patients with psychosis without other features of encephalitis also have NMDAR antibodies?

MRC PPiP study

Prevalence of Pathogenic Autoantibodies In Psychosis

Patients

- 37 sites across England Mental Health Trusts 2012-2014
- First episode psychotic illness
- Aged 14-35 years
- < 6 weeks medication

Controls

- General population (Cambridge) - Opportunity sample
- No personal or family history of mental illness
- Age, gender and ethnicity matched to a FEP population

Neuronal cell surface antibodies in psychosis

Live cell-based assay	Titres	FEP Patients (n=228)	Controls (n=105)	Odds ratio (95% CI)
NMDAR antibodies	1:30 - 1:150	7 (3·1%)	0	5.4 (p=0.02)*
LGI1 antibodies	1:20 - 1:100	3 (1·3%)	0	2.3 (p=0.13)*
CASPR2 antibodies	1:100 - 1:250	2 (0·9%)	3 (2·9%)	0·3 (0·1 - 1·8)
GABA-AR antibodies	1:50 - 1:100	8 (3·5%)	1 (1%)	3·8 (0·5 - 30·7)
AMPAR antibodies	-	0	0	
Prevalence any neuronal cell surface antibody		20 (8·8%)	4 (3·8%)	2·4 (0·8 - 7·3)

* Likelihood ratio

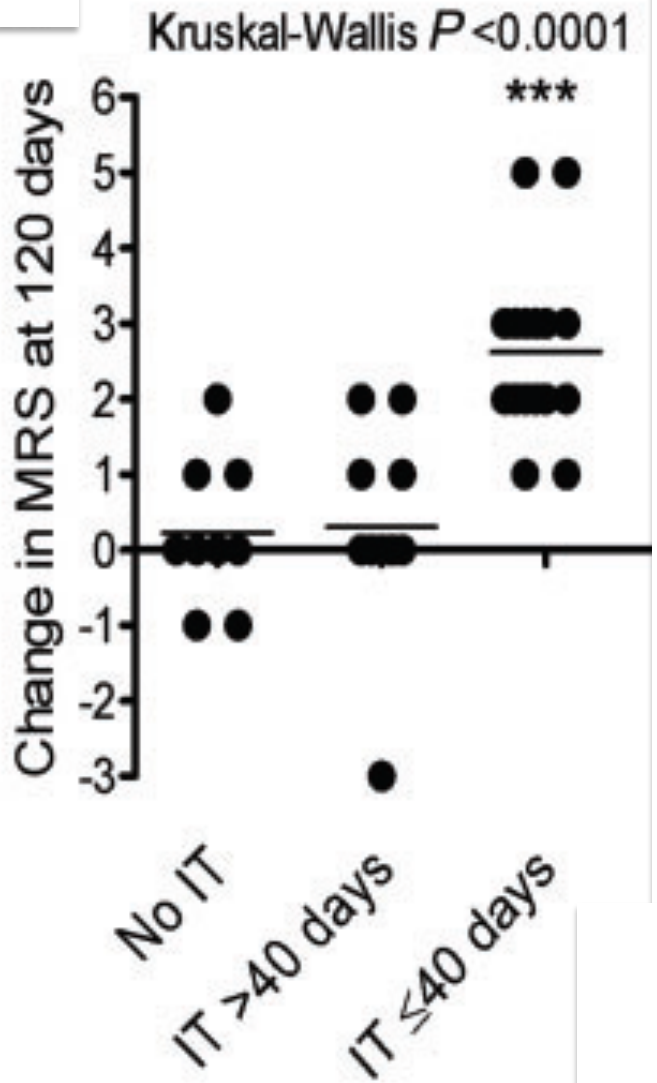
Lennox et al The Lancet Psychiatry 2016

So What?

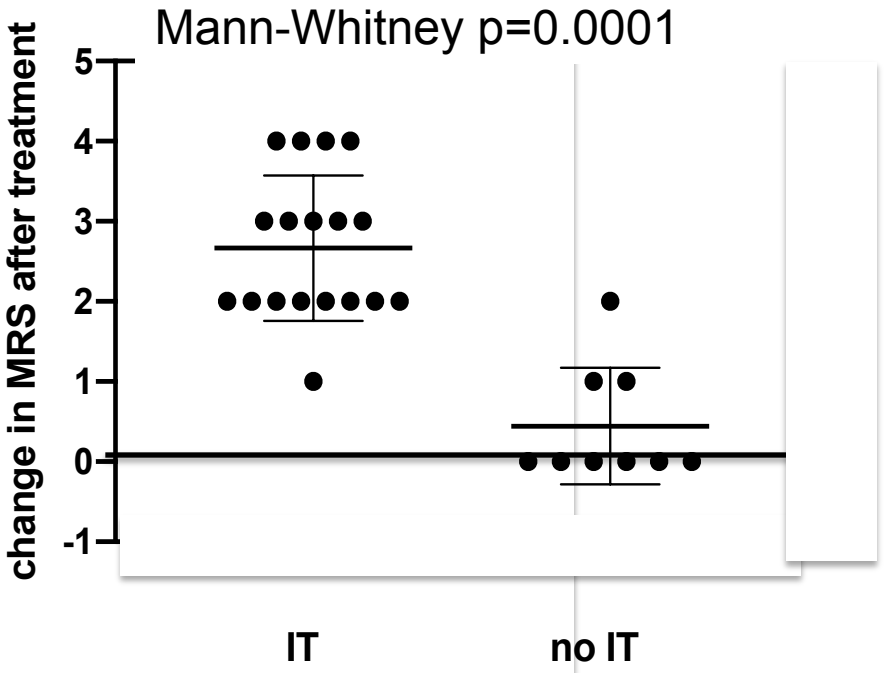
Do patients with psychiatric presentations and NMDAR antibodies get better with immunotherapy in the same way as those with encephalitis?

Response to immunotherapy in patients with NMDAR abs

1) AE (Irani et al 2010)



2) psychosis (n=27, Zandi et al 2014, Lennox et al 2018)



Prospective screening 113 inpatients in Queensland

Participant No. Age/ Gender	Initial Diagnosis ICD-10[31]	Duration of Untreated Psychosis (Days)	Symptoms
1. 28, F	Substance-induced psychosis (cannabis)	7	Acute confusion, headaches, hallucinations, agitation, catatonia, encephalopathy with reduction in level of consciousness 8 days after psychosis onset
2. 16, F	Acute and transient psychotic disorder	5	Agitation, confusion, seizures, encephalopathy with seizures 9 days after onset of first symptoms
3. 13, M	Schizophreniform disorder	70	Irritable, confusion, labile mood, hallucinations
4. 33, M	Bipolar affective disorder	2	Suicidal thoughts, delusional thoughts, hallucinations, depressed mood
5. 16, M	First episode of psychosis	2	Bizarre behaviour, thought disorder
6. 23, M	First episode of psychosis	7	Mania, psychosis

CSF, cerebrospinal fluid; EEG, electroencephalogram; F, female; M, male; MRI, magnetic resonance imaging; ND, not done; NMDAR, *N*-methyl-D
cell count.

Scott et al BJPO 2018

Lumbar puncture and EEG helpful

Participant No. Age/ Gender	Antibody	Seizure	CSF	Initial EEG	MRI
1. 28, F	NMDAR	Yes	WCC 50, Prot 360, NMDAR+	Normal	Normal
2. 16, F	NMDAR	Yes	WCC 15, Prot 370, OCB+, NMDAR+	Fast background, right temporal slow	Normal
3. 13, M	NMDAR	No	WCC 1, Prot 160, OCB+, NMDA low+	ND	Normal
4. 33, M	NMDAR	No	WCC 35, Prot 450, OCB–, NMDA–	Normal	Normal
5. 16, M	VGKC	No	WCC 2, Prot 340, OCB–, NMDA–	Diffuse slowing of background	Normal
6. 23, M	Unknown	No	ND	Normal	ND, Head computed tomography scan normal

/l-D-aspartate receptor antibody; OCB, oligoclonal bands; Prot, protein; VGKC, voltage-gated potassium channel antibody; WCC, white

Scott et al BJPO 2018

Treatment and outcome

Subject	Treatment	Outcome
1 NMDAR	Teratoma removed, steroids, IVIG, rituximab	No psychosis, working full time
2 NMDAR	Teratoma removed, steroids, IVIG, rituximab	No psychosis, at university
3 NMDAR	Steroids IVIG	No psychosis, unemployed
4 NMDAR	Steroids, IVIG, azathioprine	No psychosis, working full time
5 VGKCC	Steroids IVIG	Relapsing course, return to school, on olanzapine
6 unknown	No immunotherapy	

Scott et al BJPO 2018

Suggested Clinical pathway

Acute psychosis (FEP or relapse)

Serum NMDAR (live assay) LGI1

\+ Investigations EEG/CSF/MRI

+ve   -ve

Encephalopathy
Urgent treatment

???

Summary

- There is an overlap in clinical phenotype between encephalitis and schizophrenia
- 5-9% patients with psychosis have antibodies against a neuronal cell surface target
- Patients with psychosis and antibodies have an abrupt onset to illness, but do not have a distinct clinical phenotype
- Patients with psychosis and antibodies may respond to treatment with immunotherapy rather than antipsychotics
- Psychiatry needs to reclaim the brain

Acknowledgements

- Angela Vincent, Camilla Buckley, M. Isabel Leite, Sarosh Irani, Paddy Waters, Leslie Jacobsen Neuroimmunology Group, NDCN, University of Oxford
- Adam Al-Diwani, Paul Harrison, Ksenija Yeeles, Amy Kao, Phil Burnet, SINAPPS team Department of Psychiatry, University of Oxford
- Alasdair Coles, Therapeutic Immunology Group, University of Cambridge
- Peter Jones, Department of Psychiatry, University of Cambridge
- Mike Zandi, National Hospital, UCL
- Tom Pollak, Ester Coutinho KCL

- 37 PIs and NIHR CRN: Mental Health staff across England
- Funding: MRC, Stanley Medical Research Institute, Wellcome Trust, NIHR