

CNS AUTOIMMUNITY AND INFECTION IN PSYCHOTIC DISORDERS

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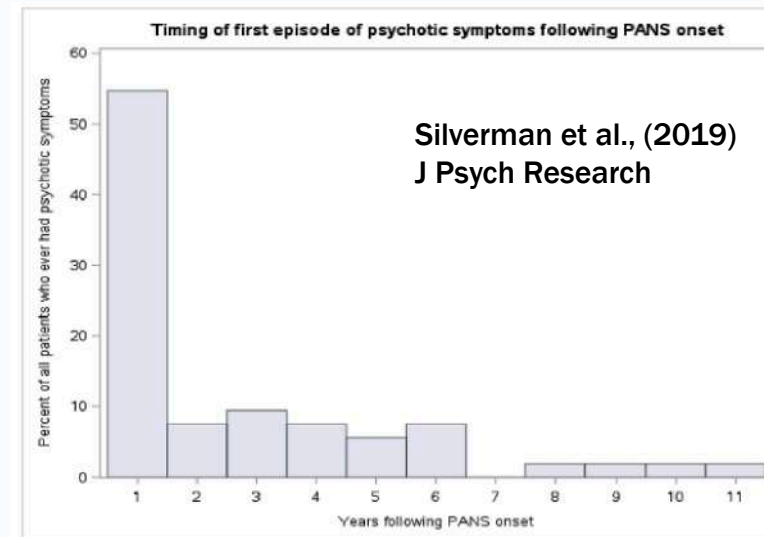
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PSYCHOSIS IN PANS?

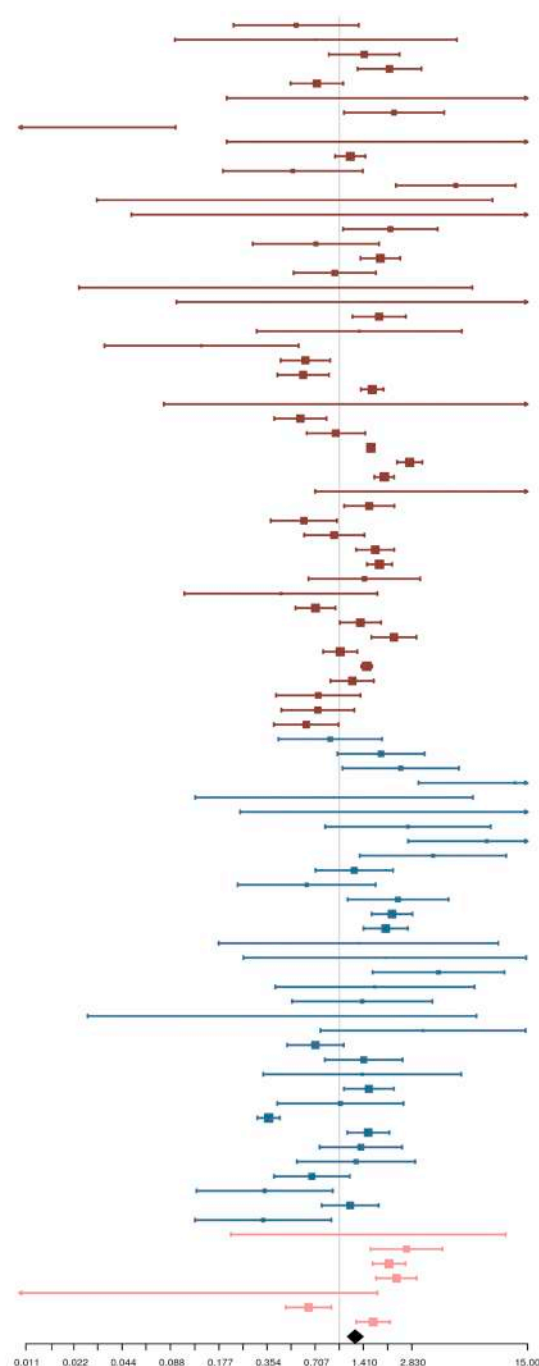
- Not part of diagnostic criteria
- BUT present in 37% (Silverman et al., 2019)
 - Hallucinations (auditory/visual equally common; non-threatening/pejorative)
 - No association with age or sex or time-to-treatment
 - Associated with severity of symptoms, functional impairment and caregiver burden
- Note relative risk of schizophrenia is x9 in Sydenham's chorea (Wilcox and Nasrallah, 1998)

	Prevalence of symptoms (n = 143 patients)
Any Disturbance	53/143 (37%)
Perceptual Disturbance	
Hallucinations	52/143 (36%)
Auditory	37/143 (26%)
Visual	37/143 (26%)
Other (gustatory, olfactory, tactile)	9/143 (7%)
Auditory + visual	24/143 (17%)
Auditory + visual + other	6/143 (4%)
Thought Disturbances	
Delusions	9/143 (6%)
Thought Disorganization	8/143 (6%)



AUTOIMMUNITY AS A PSYCHOSIS RISK FACTOR

Author	AI Disorder [Disg]	OR [95% CI]
Chen et al (2012) (8)	Atopic eczema [SZ]	0.54 [0.22-1.32]
Chen et al (2012) (8)	Anaemia [d] [SZ]	0.71 [0.39-1.42]
Chen et al (2012) (8)	Anaemia [d] [SZ]	1.43 [0.88-2.38]
Chen et al (2012) (8)	Anaemia [c] [SZ]	2.06 [1.30-3.25]
Chen et al (2012) (8)	Ankylosing spondylitis [SZ]	0.72 [0.50-1.04]
Chen et al (2012) (8)	Atherosclerosis [SZ]	10.60 [0.20-504.01]
Chen et al (2012) (8)	Celiac disease [SZ]	2.20 [1.07-4.52]
Chen et al (2012) (8)	Crohn's disease [SZ]	0.01 [0.00-0.09]
Chen et al (2012) (8)	Goodpasture syndrome [SZ]	10.60 [0.20-504.01]
Chen et al (2012) (8)	Graves disease [SZ]	1.17 [0.94-1.45]
Chen et al (2012) (8)	Hashimoto's thyroiditis [SZ]	0.51 [0.19-1.45]
Chen et al (2012) (8)	Hypersensitivity vasculitis [SZ]	5.34 [2.26-12.58]
Chen et al (2012) (8)	Kawasaki disease [SZ]	0.53 [0.03-9.04]
Chen et al (2012) (8)	Pemphigoid [SZ]	0.81 [0.05-18.44]
Chen et al (2012) (8)	Polysarthritis nodosa [SZ]	2.08 [1.05-4.12]
Chen et al (2012) (8)	Polymyalgia rheumatica [SZ]	0.71 [0.29-1.77]
Chen et al (2012) (8)	Purpura [SZ]	1.80 [1.36-2.40]
Chen et al (2012) (8)	SLE [SZ]	0.94 [0.52-1.69]
Chen et al (2012) (8)	Systemic sclerosis [SZ]	0.40 [0.02-6.76]
Chen et al (2012) (8)	Thrombocytitis obliterans [SZ]	2.00 [0.10-41.66]
Chen et al (2012) (8)	Type 1 Diabetes [SZ]	1.77 [1.21-2.60]
Chen et al (2012) (8)	Ulcerative colitis [SZ]	1.33 [0.30-5.83]
Chen et al (2012) (8)	Uveitis [SZ]	0.14 [0.03-0.56]
Chu et al (2012) (33)	Atopic eczema [SZ]	0.61 [0.42-0.86]
Cremonesi et al (2017) (34)	Hyperthyroidism [SZ]	0.99 [0.41-2.36]
Cremonesi et al (2017) (34)	Hypothyroidism [SZ]	1.61 [1.36-1.90]
Cremonesi et al (2017) (34)	Polymyalgia rheumatica [SZ]	1.28 [0.08-20.52]
Cremonesi et al (2017) (34)	SLE [SZ]	0.57 [0.39-0.83]
Cremonesi et al (2017) (34)	Type 1 Diabetes [SZ]	0.85 [0.63-1.15]
Guerni et al (2012) (19)	Purpura [PV]	1.57 [1.52-1.64]
Hulaja et al (2016) (36)	Hidradenitis suppurativa [PV]	2.75 [2.30-3.30]
Hulaja et al (2016) (36)	Purpura [PV]	1.91 [1.69-2.25]
Hutchinson et al (1996) (4)	SLE [PV]	13.17 [0.71-245.47]
Kidde et al (2017) (38)	Pemphigoid [SZ]	1.54 [1.07-2.21]
Rehman et al (2017) (43)	Type 1 Diabetes [SZ]	0.80 [0.37-1.72]
Schmitt & Ford (2010) (45)	Purpura [SZ]	0.90 [0.60-1.43]
Toscano et al (2017) (48)	SLE [SZ]	1.68 [1.27-2.20]
Tu et al (2017) (49)	Purpura [SZ]	1.78 [1.49-2.14]
Weber et al (2013) (18)	Anaemia [c] [SZ]	1.43 [0.64-3.20]
Weber et al (2013) (18)	Ankylosing spondylitis [SZ]	0.43 [0.11-1.73]
Weber et al (2013) (18)	Crohn's disease [SZ]	0.71 [0.53-0.95]
Weber et al (2013) (18)	Graves disease [SZ]	1.35 [1.01-1.82]
Weber et al (2013) (18)	Purpura [SZ]	2.19 [1.59-3.03]
Weber et al (2013) (18)	SLE [SZ]	1.01 [0.79-1.30]
Weber et al (2013) (18)	Type 1 Diabetes [SZ]	1.48 [1.37-1.61]
Weber et al (2013) (18)	Ulcerative colitis [SZ]	1.20 [0.88-1.64]
West et al (2006) (50)	Celiac disease [SZ]	0.74 [0.45-1.30]
West et al (2006) (50)	Crohn's disease [SZ]	0.75 [0.43-1.24]
West et al (2006) (50)	Ulcerative colitis [SZ]	0.62 [0.39-0.98]
Butwicki et al (2015) (31)	Type 1 Diabetes [I] [PV]	0.89 [0.42-1.85]
Butwicki et al (2017) (22) Part A	Celiac disease [I] [PV]	1.82 [0.97-3.41]
Eston et al (2008) (9)	Atopic eczema [SZ]	2.42 [1.05-5.60]
Eston et al (2008) (9)	Anaemia [d] [SZ]	12.50 [3.13-50.01]
Eston et al (2008) (9)	Anaemia [e] [SZ]	0.93 [0.13-6.81]
Eston et al (2008) (9)	Anaemia [c] [SZ]	5.00 [0.24-104.15]
Eston et al (2008) (9)	Ankylosing spondylitis [SZ]	2.68 [0.81-8.81]
Eston et al (2008) (9)	Chronic active hepatitis [SZ]	0.34 [0.29-0.39]
Eston et al (2008) (9)	Celiac disease [SZ]	3.85 [1.34-11.03]
Eston et al (2008) (9)	Crohn's disease [SZ]	1.24 [0.71-2.17]
Eston et al (2008) (9)	Endometriosis [SZ]	0.62 [0.23-1.66]
Eston et al (2008) (9)	Graves disease [SZ]	2.33 [1.13-4.80]
Eston et al (2008) (9)	Interstitial cystitis [SZ]	2.13 [1.59-2.86]
Eston et al (2008) (9)	Myositis [SZ]	1.95 [1.42-2.68]
Eston et al (2008) (9)	Other adrenal gland [SZ]	1.32 [0.18-9.83]
Eston et al (2008) (9)	Pemphigoid [SZ]	1.92 [0.25-14.70]
Eston et al (2008) (9)	Polymyalgia rheumatica [SZ]	4.17 [1.62-10.75]
Eston et al (2008) (9)	Purpura [SZ]	1.67 [0.40-6.96]
Eston et al (2008) (9)	Purpura [SZ]	1.39 [0.51-3.80]
Eston et al (2008) (9)	SLE [SZ]	0.44 [0.05-3.18]
Eston et al (2008) (9)	Thyroiditis [SZ]	3.33 [0.76-14.58]
Eston et al (2008) (9)	Type 1 Diabetes [SZ]	0.71 [0.47-1.08]
Eston et al (2008) (9)	Ulcerative colitis [SZ]	1.42 [0.81-2.48]
Eston et al (2008) (9)	Uveitis [SZ]	1.39 [0.33-5.77]
Forst et al (2016) (35) Part A	Pemphigoid [NSP]	1.83 [1.07-3.19]
Forst et al (2016) (35) Part A	Pemphigoid [SZ]	1.02 [0.41-2.51]
Juononen et al (2007) (57)	Type 1 Diabetes [SZ]	0.36 [0.31-0.42]
Ludvigsson et al (2007) (40)	Celiac disease [NSP]	1.52 [1.12-2.05]
Ludvigsson et al (2007) (40)	Celiac disease [SZ]	1.36 [0.75-2.47]
Shen et al (2015) (46)	Ankylosing spondylitis [SZ]	1.27 [0.54-3.06]
Sundquist et al (2008) (47)	Ankylosing spondylitis [NSP]	0.87 [0.39-1.10]
Sundquist et al (2008) (47)	Ankylosing spondylitis [SZ]	0.54 [0.13-2.91]
Sundquist et al (2008) (47)	SLE [NSP]	1.17 [0.78-1.76]
Sundquist et al (2008) (47)	SLE [SZ]	0.33 [0.13-0.89]
Butwicki et al (2017) (22) Part B	Celiac disease [I] [PV]	1.62 [0.21-10.94]
Chen et al (2011) (32)	Pemphigoid [SZ]	2.63 [1.57-4.41]
Forst et al (2016) (35) Part B	Pemphigoid [NSP]	2.05 [1.62-2.58]
Forst et al (2016) (35) Part B	Pemphigoid [SZ]	2.27 [1.70-3.04]
Petrak et al (2003) (42)	Type 1 Diabetes [PV]	0.11 [0.01-1.73]
Solgen et al (2014) (20)	Ankylosing spondylitis [SZ]	0.64 [0.46-0.89]
Yu et al (2017) (51)	Purpura [SZ]	1.82 [1.29-2.61]
Summary		1.26 [1.12-1.41]



Archival Report

Associations Between Non-neurological Autoimmune Disorders and Psychosis: A Meta-analysis

Alexis E. Cullen, Scarlett Holmes, Thomas A. Pollak, Graham Blackman, Dan W. Joyce, Matthew J. Kempton, Robin M. Murray, Philip McGuire, and Valeria Mondelli

Table 2. Results of Meta-analyses Examining Associations Between Non-neurological Autoimmune Disorders and Psychosis

Analysis	Number of Studies (Type)	Number of Effect Sizes (Diagnosis)	N (PSY/NNAI)	OR (95% CI)	p	Q (p)	I ² (95% CI)
Overall ^a	27 (A = 13; B = 8; C = 6)	90 (SZ = 77; BDP = 8; NSP = 5)	641,613/540,349	1.26 (1.12–1.41) ^b	< .001 ^b	< .001 ^b	88.08 (85.94–89.89)
Temporal Relationship^a							
Comorbidity (A)	7 (A = 13)	49 (SZ = 45; BDP = 4)	410,627/328,199	1.20 (1.06–1.35) ^b	.003 ^b	< .001 ^b	84.80 (80.67–88.04)
NNAI precedes PSY (B)	6 (B = 8)	34 (SZ = 28; BDP = 2; NSP = 4)	193,594/176,578	1.43 (1.04–1.95) ^b	.03 ^b	< .001 ^b	88.58 (85.10–91.25)
PSY precedes NNAI (C)	3 (C = 6)	7 (SZ = 4; BDP = 2; NSP = 1)	37,392/35,572	1.55 (1.01–2.38) ^b	.046 ^b	< .001 ^b	87.14 (75.77–93.18)
Psychiatric Diagnosis^a							
Schizophrenia	20 (A = 10; B = 6; C = 4)	77 (SZ = 77)	615,498/290,506	1.21 (1.04–1.40) ^b	.01 ^b	< .001 ^b	87.08 (84.50–89.23)
Psychosis (broadly defined)	7 (A = 3; B = 2; C = 2)	8 (BDP = 8)	14,241/167,104	1.81 (1.39–2.37) ^b	< .001 ^b	< .001 ^b	85.60 (73.58–92.16)
Nonschizophrenia psychosis	4 (B = 3; C = 1)	5 (NSP = 5)	11,874/82,739	1.38 (1.01–1.88) ^b	.046 ^b	.003 ^b	75.34 (39.36–89.97)
Autoimmune Disorder							
Alopecia areata	3 (A = 2; B = 1)	3 (SZ = 3)	18,777/5283	0.90 (0.38–2.10)	.80	.010 ^b	78.26 (29.97–93.25)
Anemia (pernicious)	3 (A = 2; B = 1)	3 (SZ = 3)	32,239/1009	1.91 (1.29–2.84) ^b	.001 ^b	.61	0.00 (0.00–93.12)
Ankylosing spondylitis	6 (A = 2; B = 3; C = 1)	7 (SZ = 6; NSP = 1)	73,967/63,198	0.72 (0.54–0.98) ^b	.04 ^b	.14	37.54 (0.00–73.70)
Celiac disease	6 (A = 2; B = 3; C = 1)	7 (SZ = 4; BDP = 2; NSP = 1)	19,507/54,624	1.53 (1.12–2.10) ^b	.008 ^b	.131	39.08 (0.00–74.38)
Crohn's disease	4 (A = 3; B = 1)	4 (SZ = 4)	32,364/20,907	0.67 (0.34–1.30)	.22	.002 ^b	79.97 (46.98–92.44)
Graves' disease	3 (A = 2; B = 1)	3 (SZ = 3)	32,239/7799	1.33 (1.03–1.72) ^b	.03 ^b	.18	41.19 (0.00–82.07)
Pemphigoid	6 (A = 2; B = 2; C = 2)	8 (SZ = 6; NSP = 2)	20,232/23,585	1.90 (1.62–2.24) ^b	< .001 ^b	.322	13.81 (0.00–56.59)
Polymyalgia rheumatica	3 (A = 2; B = 1)	3 (SZ = 3)	23,354/112	1.63 (0.41–6.48)	.49	.030	71.35 (2.74–91.56)
Psoriasis	6 (A = 6; B = 1; C = 1)	8 (SZ = 6; BDP = 2)	54,578/141,673	1.70 (1.51–1.91) ^b	< .001 ^b	.010 ^b	61.94 (17.82–82.38)
Rheumatoid arthritis	12 (A = 6; B = 4; C = 2)	17 (SZ = 14; BDP = 1; NSP = 2)	244,320/125,090	0.65 (0.50–0.84) ^b	.001 ^b	< .001 ^b	79.28 (67.52–86.79)
SLE	7 (A = 5; B = 2)	8 (SZ = 6; BDP = 1; NSP = 1)	48,140/66,545	0.95 (0.65–1.39)	.80	< .001 ^b	76.91 (54.10–88.39)
Type 1 diabetes	8 (A = 4; B = 3; C = 1)	8 (SZ = 6; BDP = 2)	47,208/132,921	0.79 (0.43–1.46)	.46	< .001 ^b	97.31 (96.10–98.14)
Ulcerative colitis	4 (A = 3; B = 1)	4 (SZ = 4)	32,420/15,526	1.04 (0.69–1.56)	.86	.08	56.20 (0.00–85.48)

BDP, broadly defined psychosis; CI, confidence interval; NNAI, non-neurological autoimmune (disorder); NSP, nonschizophrenia psychosis; OR, odds ratio; PSY, psychiatric disorder; SLE, systemic lupus erythematosus; SZ, schizophrenia.

^aEffect sizes for rheumatoid arthritis excluded from analyses. Temporal relationship group: A, comorbidity of schizophrenia/psychosis and autoimmune; B, autoimmune diagnosis precedes schizophrenia/psychosis; C, schizophrenia/psychosis diagnosis precedes autoimmune.

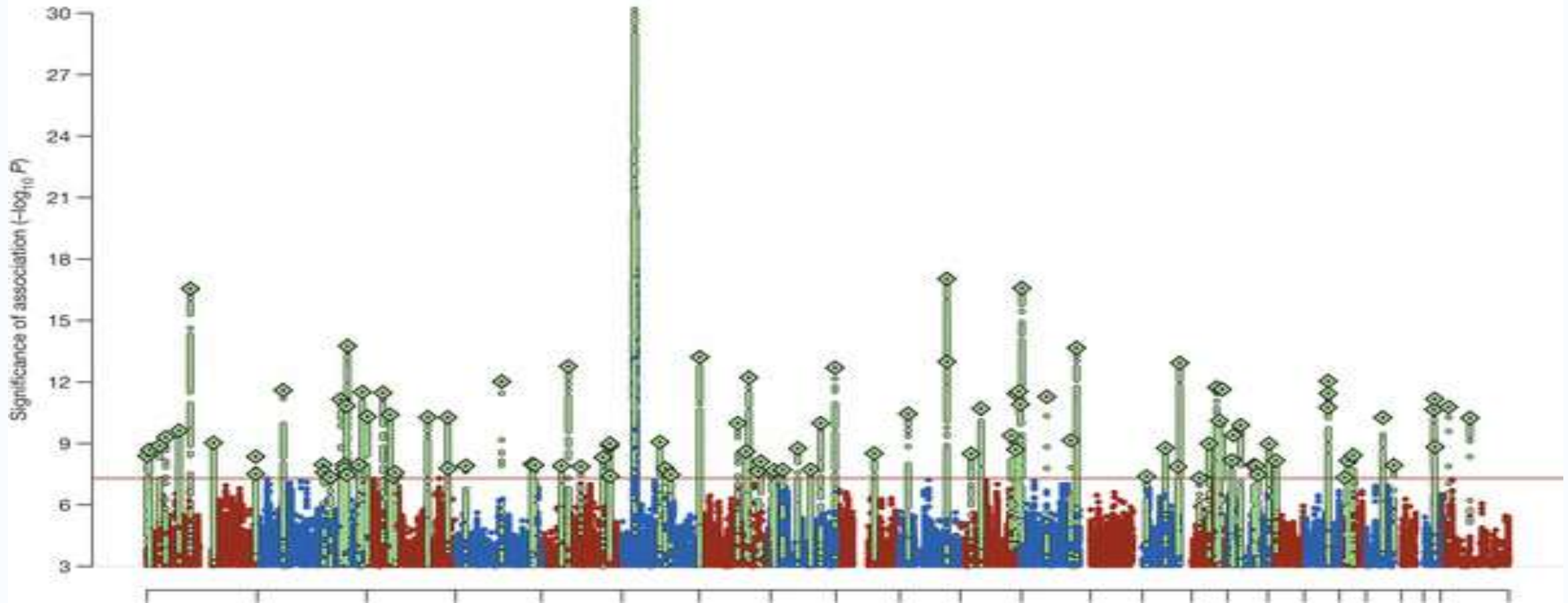
^bStatistical significance at .05 level (two-tailed).

Archival Report

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PSYCHOSIS AND THE (ADAPTIVE) IMMUNE SYSTEM



Schizophrenia Working Group of the Psychiatric Genomics Consortium (2014) *Nature*



BRAIN ON FIRE

MY MONTH OF MADNESS

SUSANNAH CAHALAN



BRAINS ON FIRE: AUTOIMMUNE ENCEPHALITIS

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

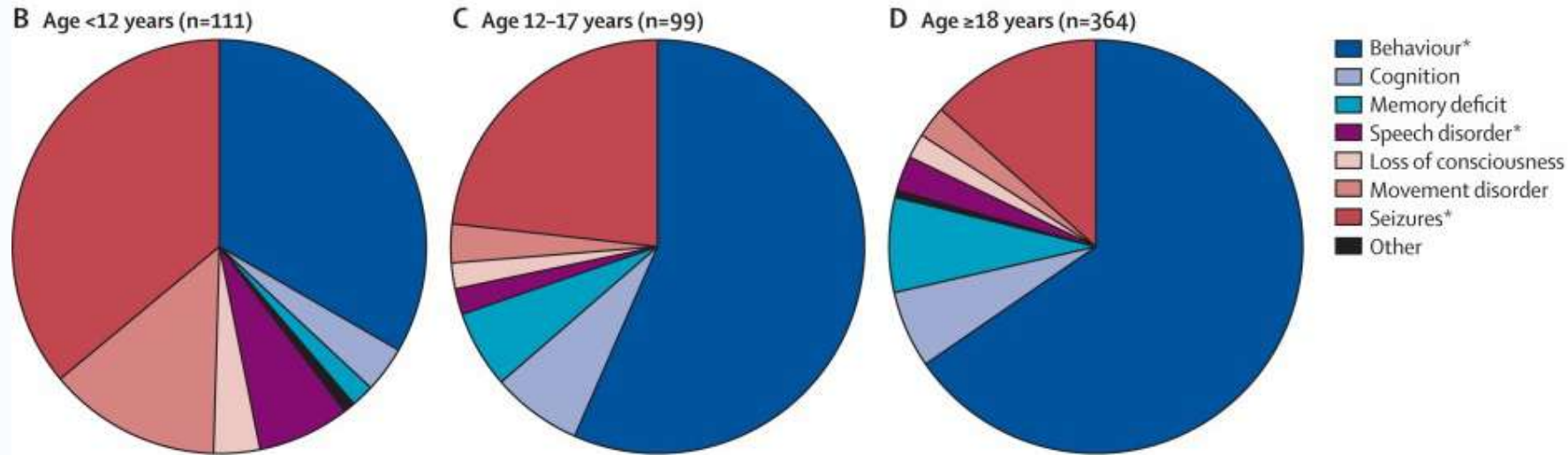
Josep Dalmau, *Amy J Gleichman, *Ethan G Hughes, Jeffrey E Rossi, Xiaoyu Peng, Meizan Lai, Scott K Dessain, Myrna R Rosenfeld, Rita Balice-Gordon, David R Lynch

Lancet Neurol 2008; 7: 1091-98

- Acute encephalopathy with characteristic progression:
 - Prodromal malaise/flu-like symptoms >> psychiatric symptoms (including sleep disturbance) >> movement disorder (catatonia/dyskinesia) >> seizures >> autonomic dysfunction >> coma
 - Associated with ovarian teratoma
- Associated psychiatric symptoms in 100 patient series:
 - Anxiety
 - Agitation
 - Psychosis: Delusions / Paranoia/ Hallucinations
 - Catatonia/echolalia

77% present to psychiatry services before neurological symptoms (mostly seizures / dyskinesias) develop.

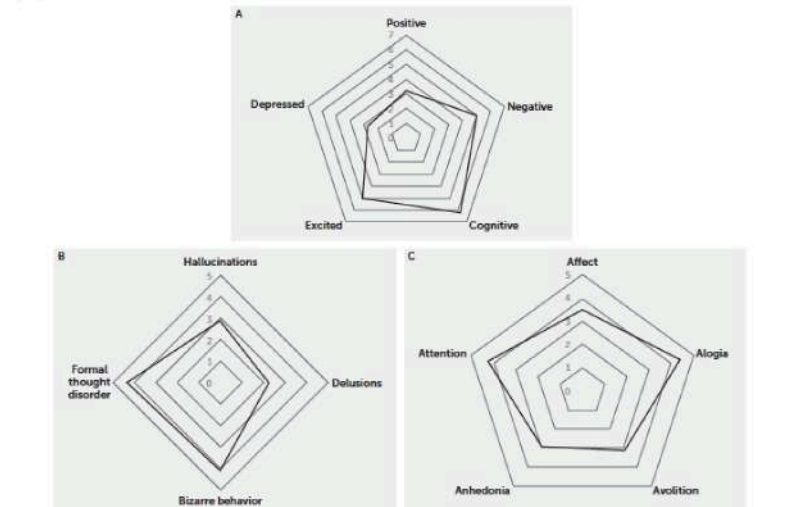
PSYCHIATRIC FEATURES PREDOMINATE IN AUTOIMMUNE ENCEPHALITIS



- Distribution by age of initial symptoms in anti-NMDA receptor encephalitis (Titulaer et al., 2013)
- **Kayser et al (2013): 4% of patients with NMDAR encephalitis had isolated psychotic episodes either at presentation or relapse.**

APPLES AND ORANGES?

FIGURE 2. Mean Scores for the Positive and Negative Symptom Scale (PANSS) and the Scale for the Assessment of Negative Symptoms (SANS)^a

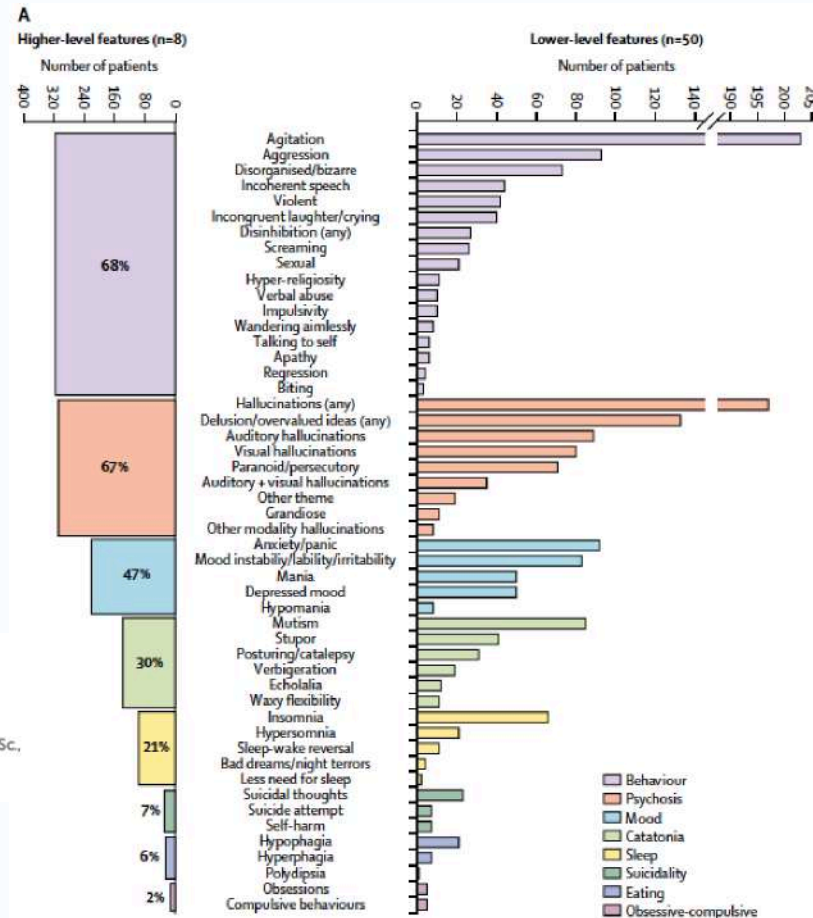


^a Panel A shows the mean scores on the Wallwork domains of PANSS. Panel B shows the mean global symptom scores on the Scale for the Assessment of Positive Symptoms. Panel C shows the mean global symptom scores for SANS.

The Psychiatric Phenotype of Anti-NMDA Receptor Encephalitis

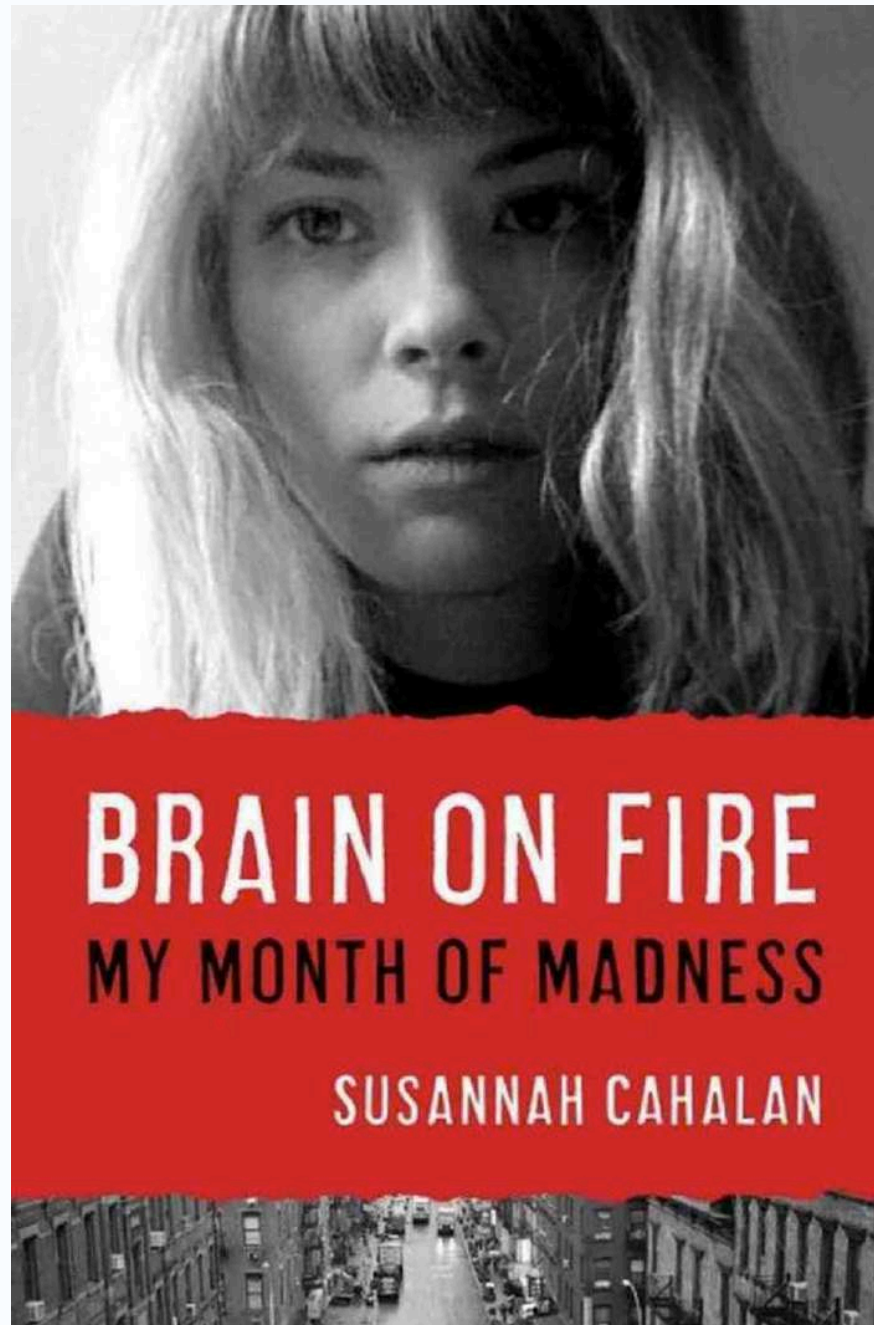
Lucy L. Gibson, M.B.B.S., Thomas A. Pollak, M.B.B.S., M.Sc., Graham Blackman, M.B.Ch.B., Mary Thornton, M.B.Ch.B., M.Sc., Nicholas Moran, M.R.C.P., M.Sc., Anthony S. David, M.D., F.R.C.Psych.

JNCN (2018)



Al-Diwani et al., *Lancet Psychiatry* (2019)





“how many people currently are in psychiatric wards and nursing homes denied the relatively simple cure of steroids, plasma exchange, [or] more intense immunotherapy...?”

(Cahalan, 2012).

HOW COMMON IS AUTOANTIBODY-MEDIATED

Psychological Medicine, Page 1 of 13. © Cambridge University Press 2013
doi:10.1017/S003329171300295X

REVIEW ARTICLE

Prevalence of anti-*N*-methyl-D-aspartate (NMDA) antibodies in patients with schizophrenia and related psychoses: a systematic review and meta-analysis

T. A. Pollak^{1,2*}, R. McCormack^{1,2}, M. Peakman^{3,4}, T. R. Nicholson² and A. S. David²

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⁴Biomedical Research Centre at Guy's and St Thomas' NHS Trust and King's College London, UK

Belinda R. Lennox

46 patients with

- 3 anti-NMDA (1 got better, 1 VGKC A)

- Positive pa



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Meta-analysis of the association between *N*-methyl-D-aspartate receptor antibodies and schizophrenia, schizoaffective disorder, bipolar disorder, and major depressive disorder

Daniel M. Pearlman^{a,b,1}, Souhel Najjar^{a,*,1}

AUTOIMMUNE ENCEPHALITIS IN PSYCHIATRY – SHOULD WE BELIEVE EVERYTHING WE READ?

Eur Child Adolesc Psychiatry (2015) 24:1321–1324
DOI 10.1007/s00787-015-0682-8



ORIGINAL CONTRIBUTION

Anti-NMDA receptor encephalitis presenting as atypical anorexia nervosa: an adolescent case report

David Mechelhoff · Betteke Maria van Noort ·
Bernhard Weschke · Christian J. Bachmann ·
Christiane Wagner · Ernst Pfeiffer · Sibylle Winter



Contents lists available at ScienceDirect

Journal of Neuroimmunology

journal homepage: www.elsevier.com/locate/jneuroim

Short communication

A case of treatable dementia with Lewy bodies remarkably improved by immunotherapy

Kie Abe, Yuhei Chiba*

Psychological Medicine

cambridge.org/psm

NMDA receptor autoimmunity in mania following HSV encephalitis

Graham Blackman¹, Nicholas Moran^{2,3}, Eli Silber², Christopher Symeon¹,
Franz Brunnhuber⁴, Asif Mazumder^{5,6}, Fatima Jaffer² and Thomas Pollak¹

Correspondence

CASE REPORT

Open Access



Steroid responsive encephalopathy associated with autoimmune thyroiditis (SREAT) presenting as major depression

Dominique Endres¹, Evgeniy Perlov¹, Oliver Stich² and Ludger Tebartz van Elst^{1*}

DEVELOPMENTAL MEDICINE & CHILD NEUROLOGY

CASE REPORT

N-methyl-D-aspartate (NMDA) receptor antibodies encephalitis mimicking an autistic regression

Yael Hachon^{1,2*} | Sukhvir Wright^{1,3*} | Jonathan Gadian² | Angela Vincent¹ | Ming Lim^{2*} |
Evangeline Wassmer³ | Jean-Pierre Lin²

Schizophrenia

AUSTRALASIAN PSYCHIATRY

LGI1 antibody encephalitis and psychosis

Australasian Psychiatry
2018, Vol 26(6) 612–614
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DOI: 10.1177/1039856218771513
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ARCHIVAL REPORT

Antibodies to Surface Dopamine-2 Receptor and N-Methyl-D-Aspartate Receptor in the First Episode of Acute Psychosis in Children

Karnan Pathmanandavel, Jean Starling, Vera Merheb, Sudarshini Ramanathan, Nese Sinmaz, Russell C. Dale, and Fabienne Brilot

Anti-NMDA-receptor encephalitis presenting with catatonia and neuroleptic malignant syndrome in patients with intellectual disability and autism

Reza Kiani^{1,2} Mark Lawden³ Penelope Eames³ Peter Critchley³ Sabyasachi Bhaumik^{1,4}
Sunita Odedra⁴ Rohit Gumber¹

THE DANGERS OF RELYING ON BLOOD TESTS

Seroprevalence of Autoantibodies against Brain Antigens in Health and Disease

Liane Dahm, PhD,^{1*} Christoph Ott, MSc,^{1*} Johann Steiner, MD,^{2,3*}
Beata Stepniak, MSc,¹ Bianca Teegen, PhD,⁴ Sandra Saschenbrecker, PhD,⁴
Christian Hammer, PhD,¹ Kathrin Borowski,⁴ Martin Begemann, MD,¹
Sandra Lemke,⁴ Kristin Rentzsch,⁴ Christian Probst, PhD,⁴ Henrik Martens, PhD,⁵
Jürgen Wienands, PhD,⁶ Gianfranco Spalletta, MD, PhD,⁷
Karin Weissenborn, MD,⁸ Winfried Stöcker, MD,⁴ and
Hannelore Ehrenreich, MD, DVM^{1,9}

Objective: We previously reported an unexpectedly high seroprevalence (~10%) of N-methyl-D-aspartate-receptor subunit-NR1 (NMDAR1) autoantibodies (AB) in healthy and neuropsychiatrically ill subjects (N = 2,817). This finding challenges an unambiguous causal relationship of serum AB with brain disease. To test whether similar results would be obtained for other brain antigen-directed AB previously connected with pathological conditions, we systematically screened serum samples of 4,236 individuals.

Methods: Serum samples of healthy (n = 1,703) versus neuropsychiatrically ill subjects (schizophrenia, affective disorders, stroke, Parkinson disease, amyotrophic lateral sclerosis, personality disorder; total n = 2,533) were tested. For analysis based on indirect immunofluorescence, we used biochip mosaics of frozen brain sections (rat, monkey) and transfected HEK293 cells expressing respective recombinant target antigens.

Results: Seroprevalence of all screened AB was comparable in healthy and ill individuals. None of them, however, reached the abundance of NMDAR1 AB (again ~10%; immunoglobulin [Ig] G ~1%). Appreciable frequency was noted for AB against amphiphysin (2.0%), ARHGAP26 (1.3%), CASPR2 (0.9%), MOG (0.8%), GAD65 (0.5%), Ma2 (0.5%), Yo (0.4%), and Ma1 (0.4%), with titers and Ig class distribution similar among groups. All other AB were found in ≤0.1% of individuals (anti-AMPA-1/2, AQP4, CV2, Tr/DNER, DPPX-IF1, GABAR-B1/B2, GAD67, GLRA1b, GRM1, GRM5, Hu, LGI1, recoverin, Ri, ZIC4). The predominant Ig class depended on antigen location, with intracellular epitopes predisposing to IgG (chi-square = 218.91, $p = 2.8 \times 10^{-48}$).

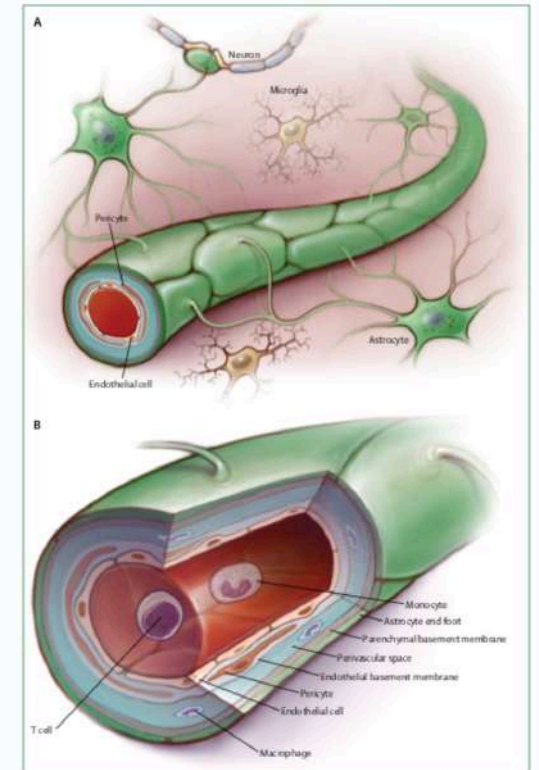
Interpretation: To conclude, the brain antigen-directed AB tested here are comparably detectable in healthy subjects and the disease groups studied here, thus questioning an upfront pathological role of these serum AB.

ANN NEUROL 2014;76:82-94

The blood-brain barrier in psychosis

Thomas A Pollak, Svetlana Drndarski, James M Stone, Anthony S David, Philip McGuire, NJoan Abbott

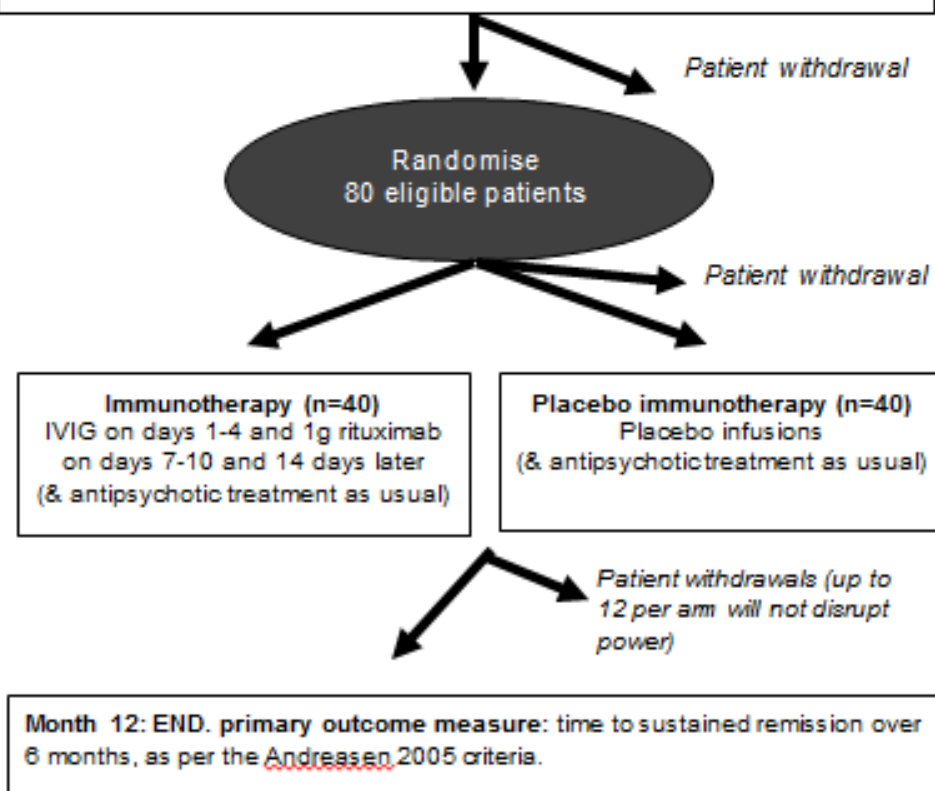
Lancet Psychiatry 2018



Randomised placebo-controlled double-blind trial of immunotherapy in acute psychosis with anti-membrane antibodies (SINAPPS2)

Screening of people with acute psychosis for antibodies (n=c. 2461). First Consent: clinical assessment & venepuncture. Stop when 160 antibody positive cases identified, 80 patients randomised or 1^o endpoint reached.

Screening of c. 160 antibody-positive people with acute psychosis for eligibility to trial. Second Consent: to participate in a blinded trial of immunotherapy. (Any antipsychotic treatment continues). Stop when 80 patients randomised or 1^o endpoint reached.



SINAPPS



Study of ImmuNotherapy in
Autoantibody Positive Psychosis



THE STANLEY MEDICAL
RESEARCH INSTITUTE

TIME FOR A CHANGE OF PRACTICE?



BJPsych Open (2018)
4, 69–74. doi: 10.1192/bjo.2018.8

The prevalence and treatment outcomes of antineuronal antibody-positive patients admitted with first episode of psychosis

James G. Scott, David Gillis, Alex E. Ryan, Hethal Hargovan, Nagaraj Gundarpi, Gemma McKeon, Sean Hatherill, Martin P. Newman, Peter Parry, Kerri Prain, Sue Patterson, Richard C. W. Wong, Robert J. Wilson and Stefan Blum

Editorial

Time for a change of practice: the real-world value of testing for neuronal autoantibodies in acute first-episode psychosis[†]

Thomas A. Pollak and Belinda R. Lennox



Summary

It is time that all patients with acute-onset psychosis are screened for autoimmune encephalitis, that lumbar puncture becomes a routine psychiatric investigation and that immunotherapy is available in indicated cases. We call for a culture change in the management of psychosis by psychiatry.

Declaration of interest

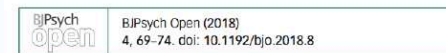
None.

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SCOTT ET AL. (2018)

- Participants (age 12 – 50) were recruited from six mental health units in Queensland, Australia.
- Participants were prospectively tested for serum anti-neuronal antibodies
 - NMDAR
 - VGKC
 - GAD
 - onconeural antibodies (anti-Yo, PCA-2, anti-Hu, anti-Ri, anti-Ma)
- Of 113 consenting participants, **six had anti-neuronal antibodies**
 - NMDAR = 4
 - VGKC = 1
 - antibodies against uncharacterised antigen = 1.
- Seropositive patients had lumbar puncture



The prevalence and treatment outcomes of antineuronal antibody-positive patients admitted with first episode of psychosis

James G. Scott, David Gillis, Alex E. Ryan, Hethal Hargovan, Nagaraj Gundarpi, Gemma McKeon, Sean Hatherill, Martin P. Newman, Peter Parry, Kerri Prain, Sue Patterson, Richard C. W. Wong, Robert J. Wilson and Stefan Blum

PATIENT PROFILES

Table 2 Overview of clinical and paraclinical characteristics of antibody-positive participants

Participant No. Age/ Gender	Initial Diagnosis ICD-10 ³¹	Duration of Untreated Psychosis (Days)	Symptoms	Antibody	Seizure	CSF	Initial EEG	MRI
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	NMDAR	Yes	WCC 50, Prot 360, NMDAR+	Normal	Normal
2. 16, F	Acute and transient psychotic disorder	5	Agitation, confusion, seizures, encephalopathy with seizures 9 days after onset of first symptoms	NMDAR	Yes	WCC 15, Prot 370, OCB+, NMDAR+	Fast background, right temporal slow	Normal
3. 13, M	Schizophreniform disorder	70	Irritable, confusion, labile mood, hallucinations	NMDAR	No	WCC 1, Prot 160, OCB+, NMDA low+	ND	Normal
4. 33, M	Bipolar affective disorder	2	Suicidal thoughts, delusional thoughts, hallucinations, depressed mood	NMDAR	No	WCC 35, Prot 450, OCB-, NMDA-	Normal	Normal
5. 16, M	First episode of psychosis	2	Bizarre behaviour, thought disorder	VGKC	No	WCC 2, Prot 340, OCB-, NMDA-	Diffuse slowing of background	Normal
6. 23, M	First episode of psychosis	7	Mania, psychosis	Unknown	No	ND	Normal	ND, Head computed tomography scan normal

CSF, cerebrospinal fluid; EEG, electroencephalogram; F, female; M, male; MRI, magnetic resonance imaging; ND, not done; NMDAR, N-methyl-D-aspartate receptor antibody; OCB, oligoclonal bands; Prot, protein; VGKC, voltage-gated potassium channel antibody; WCC, white cell count.

TREATMENT RESPONSE

Table 3 Overview of antipsychotic and immunotherapy and treatment response

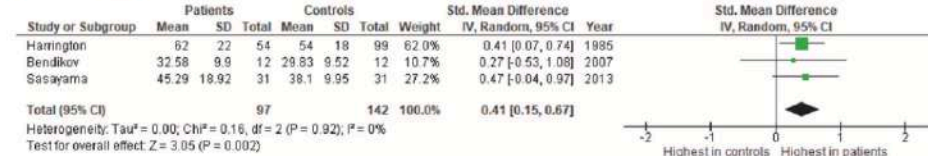
Patient No. Age/Gender	Initial Psychotropic Therapy and Response	Time of Initiation of Immunotherapy	Duration of Follow-Up and Treatment Response
1. 28, F	Olanzapine and diazepam for 6 days. No improvement with medications. Some sedation with fluctuation in mental state	Immunotherapy commenced 6 days after admission for psychosis. Teratoma removal, IVMP, IVIg, RTX.	3 years and 9 months: no psychosis. Some symptoms of depression and anxiety. Working full time
2. 16, F	Olanzapine and diazepam for 4 days. Some reduction in agitation with psychotropic medication	Immunotherapy commenced 4 days after admission for psychosis. Teratoma removal, IVMP, IVIg, RTX	2 years and 9 months: no psychosis. Some social difficulties following illness. Attending university
3. 13, M	Olanzapine for 7 days with no improvement	Immunotherapy commenced 7 days after admission. IVMP, IVIg	2 years and 6 months: no psychosis. Sleep problems and fluctuating mood. Unemployed
4. 33, M	Initially risperidone and mirtazapine. Akathisia experienced, and risperidone ceased. Commenced on quetiapine. No response after 6 days	Immunotherapy commenced 6 days after admission to hospital. IVMP, IVIg, AZA	1 year and 6 months: no psychosis. Persistent symptoms of depression and anxiety. Working full time
5. 16, M	Risperidone with minimal improvement after 22 days	Immunotherapy commenced 22 days after admission to hospital. IVIg, IVMP	2 year and 6 months: good response to IVMP. Relapsing course. Remains on olanzapine. Attending school full time
6. 23, M	Risperidone	No immunotherapy	1 month: remission from psychosis

AZA, azathioprine; IVIg, intravenous immunoglobulins; IVMP, intravenous methylprednisolone; RTX, rituximab.

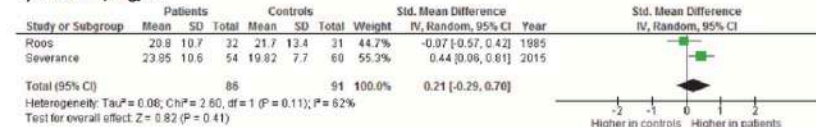
CSF MARKERS OF INFLAMMATION AND INFECTIONS IN SCHIZOPHRENIA

Schizophrenia spectrum disorders vs. healthy controls:

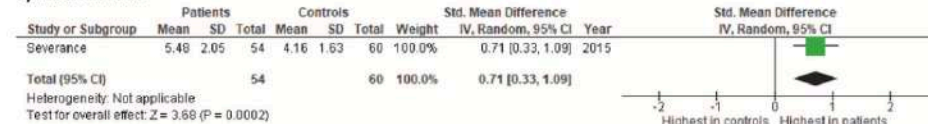
1) Total protein, mg/dL



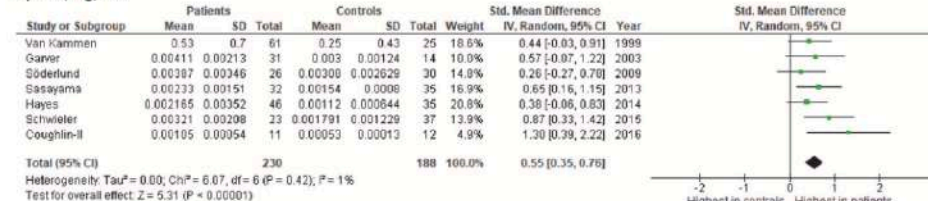
2) Albumin, mg/dL



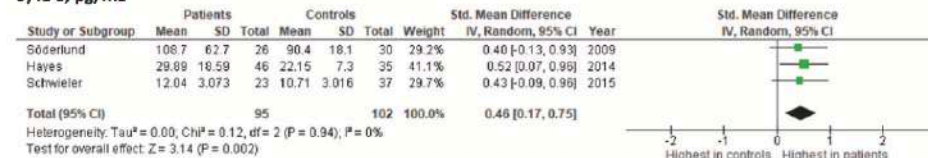
3) Albumin ratio



4) IL-6, ng/mL



5) IL-8, pg/mL



Orlovska-Waast et al. (2018) Mol Psych

Two studies reported a change of diagnosis/management, in 3.2% and 6% of patients.

One study reported rates of adverse events after LP:

- Mild to moderate 10.3% (headache, local pain)
- Severe post-LP headache with nausea 1.3%

SHOULD WE BE DOING LPS IN OUR PATIENTS WITH PSYCHOSIS?

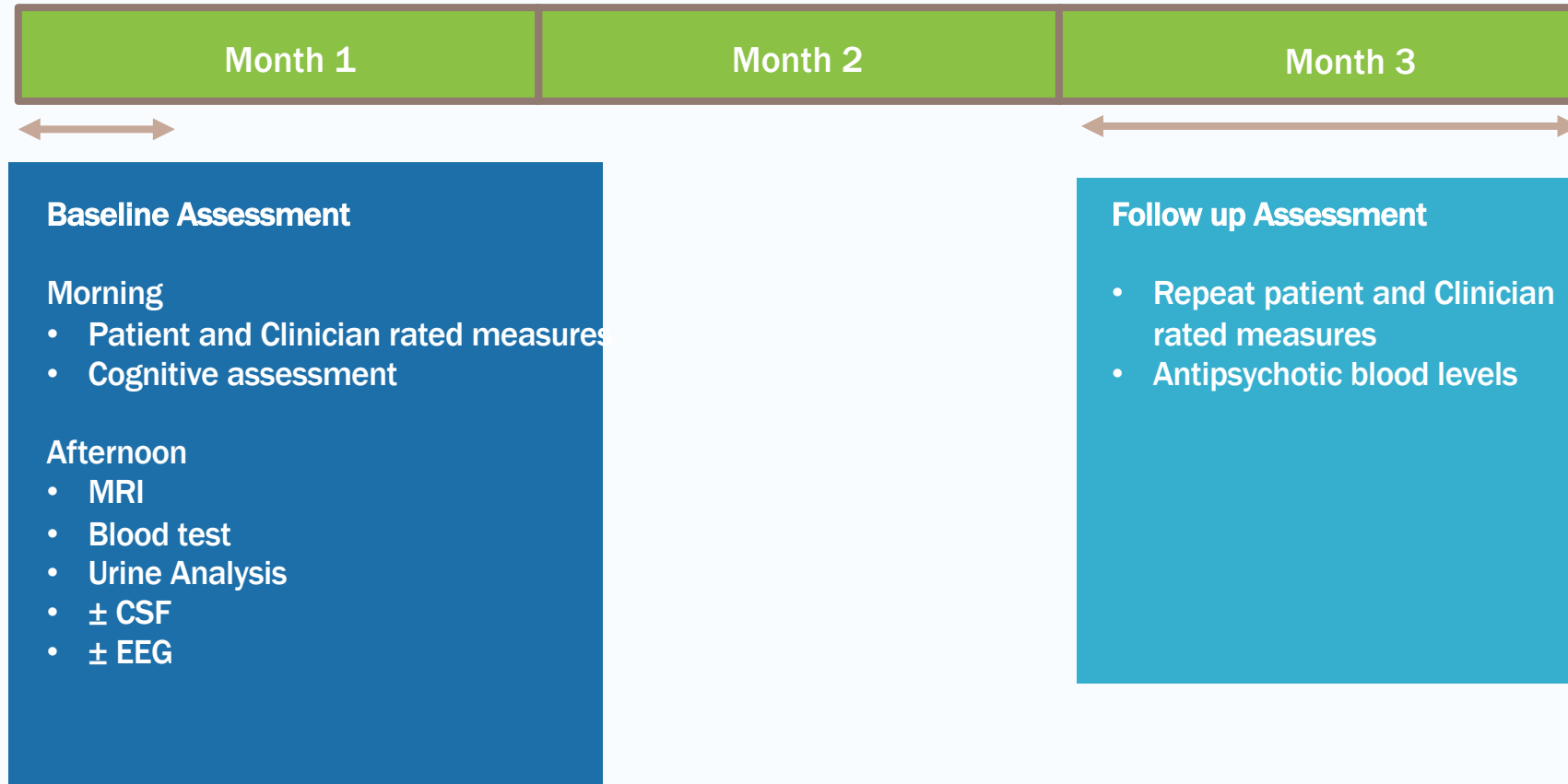
PRO

- Pickup of potentially management-changing abnormalities
- Higher pickup than common investigations e.g. MRI
- Parity between MH and PH

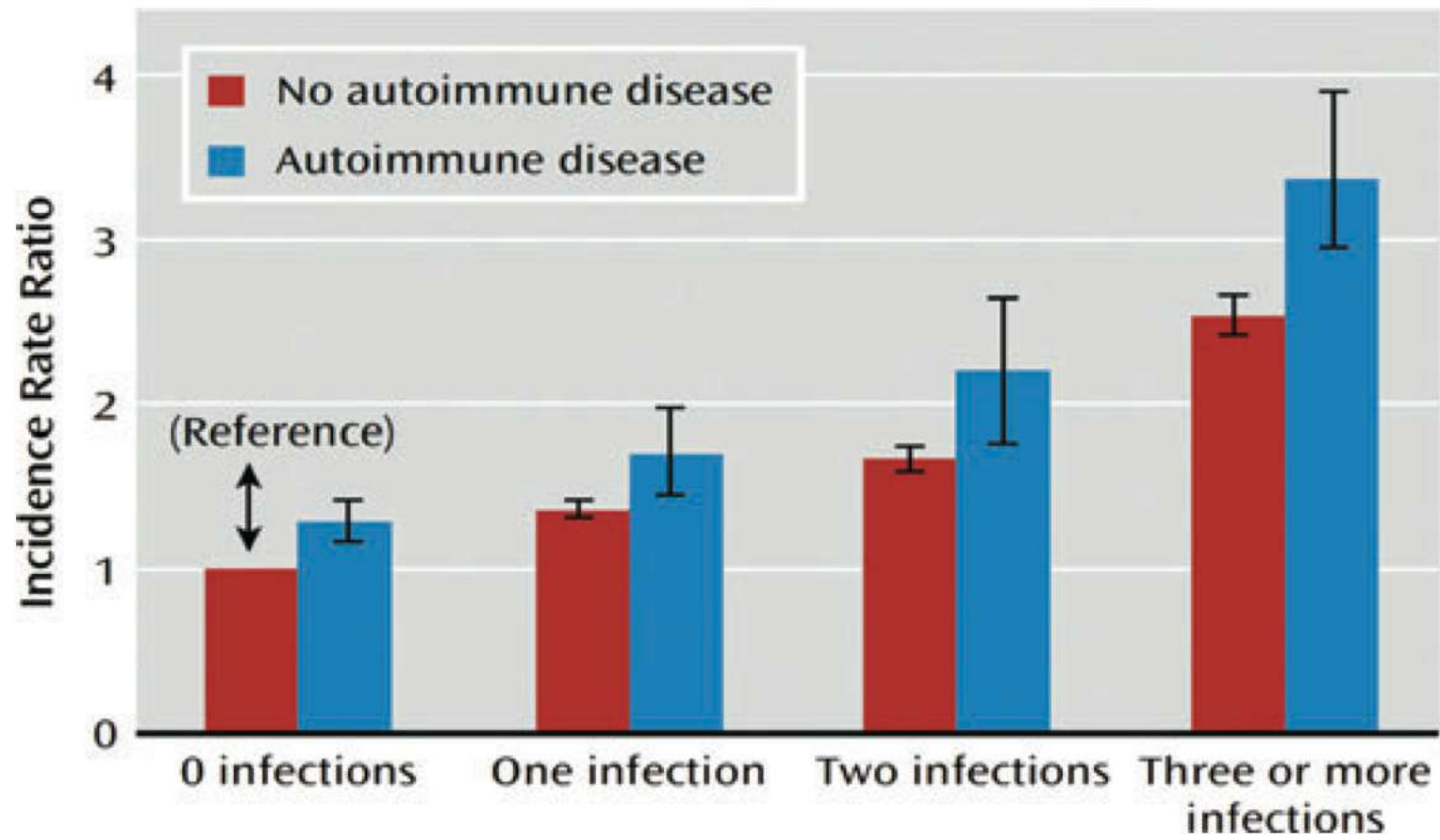
CON

- Adverse events
- Increasing patient anxiety
- Gives patient false hope/reinforces antipsychiatry stigma
- Outside of psychiatrists' expertise

THE BASELINE BIOMARKER CHECK (BBC) STUDY



PI: Philip McGuire (KCL); lead: Graham Blackman



Benros et al. (2012)

INFECTIONS IN PSYCHIATRY: FROM THEN TO NOW

- Syphilis, GPI and the asylums
 - Wagner-Jauregg: first psychiatrist (of 3, ever) to win a Nobel prize, for malarial therapy in treating dementia paralytica, in 1927
 - Broke through the therapeutic nihilism of Kraepelin et al
 - Start of immunopsychiatry?
- Encephalitis lethargica
- Winter birth in schizophrenia
 - Mednick et al., 1988: maternal influenza infections increase risk
- Today: multiple organisms implicated in schizophrenia, bipolar, autism, OCD
 - Herpes viruses (HSV, CMV, EBV)
 - Influenza
 - Toxoplasma
 - Many more
- Emerging role for the microbiome

TOXOPLASMA GONDII

- Devastating infection in neonates and immunosuppressed

people (

- Infection
cats!

- Appea
■ Increa

- Infectio
and per

- Associa
other ps

- Eviden
addictions

- Is cat ownership associated with increased risk of psychosis?



ELSEVIER

Contents lists available at [ScienceDirect](#)

Schizophrenia Research

journal homepage: www.elsevier.com/locate/schres

Is childhood cat ownership a risk factor for schizophrenia later in life?

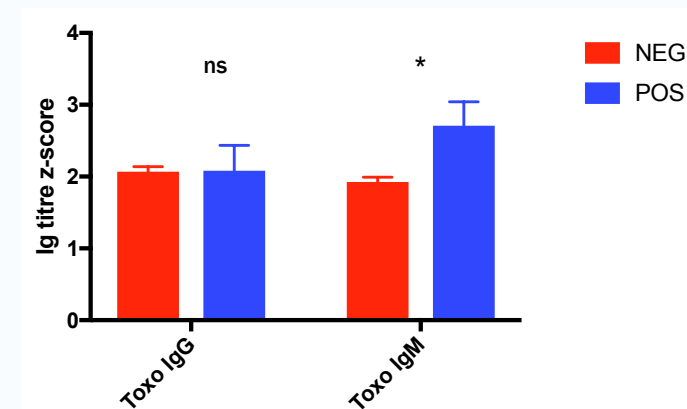
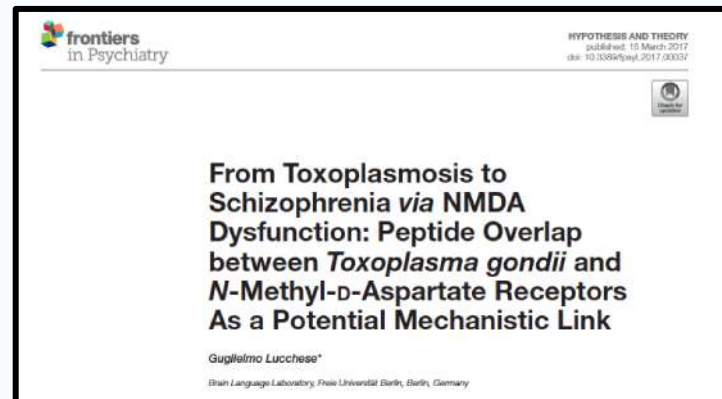
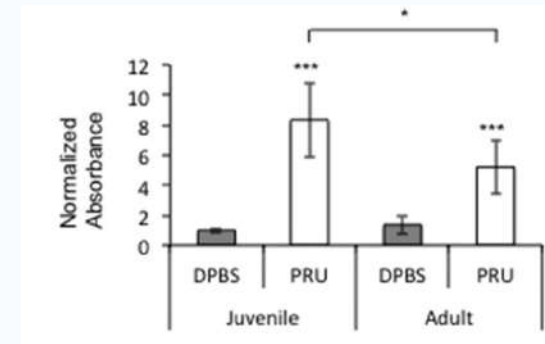
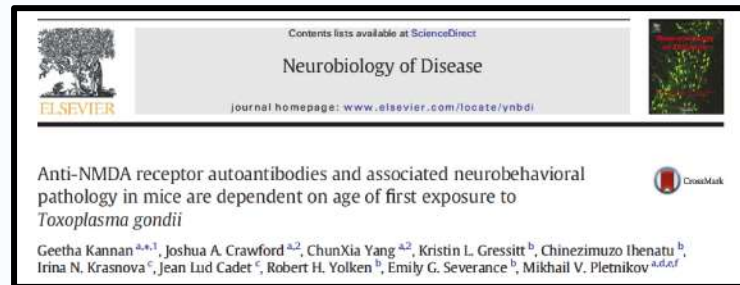
E. Fuller Torrey^{a,*}, Wendy Simmons^a, Robert H. Yolken^b

^a Stanley Medical Research Institute, United States

^b Stanley Laboratory of Developmental Neurovirology, Johns Hopkins University, School of Medicine, United States



INFECTION-INDUCED BRAIN AUTOIMMUNITY?



CONCLUSIONS

- Autoimmunity is a risk factor for psychosis, and vice-versa
- Autoimmune psychosis exists, but requires a high burden of paraclinical evidence beyond blood tests
- Lumbar puncture should become part of the routine assessment of patients with psychosis
- Infections are a risk factor for psychosis in the population
 - but usually impossible to ascribe causality in individual cases
 - ? role for microbiome
- Infection-induced CNS autoimmunity is a promising potential mechanism

ACKNOWLEDGEMENTS

Many, many thanks to:

The EUGEI High Risk Study

Prof Philip McGuire (KCL)

Prof Anthony David (KCL)

Prof Robin Murray (KCL)

Dr James Stone (KCL)

Dr Matthew Kempton (KCL)

Dr Tim Nicholson (KCL)

Dr Conrad Iyegbe (KCL)

Dr Ester Coutinho (KCL)

Dr Graham Blackman (KCL)

Dr Jonathan Rogers (KCL)

Dr Lucy Gibson (KCL)

Dr Bob Yolken (Johns Hopkins)

Dr Fuller Torrey (Stanley MRI)

Prof Angela Vincent (Oxford)

Dr Belinda Lennox (Oxford)

Dr Sarosh Irani (Oxford)

Dr Adam Al-Diwani (Oxford)

Dr Leslie Jacobson (Oxford)

Dr David Menassa (Southampton)

Dr Winfried Stöcker (Euroimmun AG)

Dr Laurent Groc (Bordeaux)

Dr Jerome Honnorat (Lyon)

Prof Marion Leboyer (Paris)