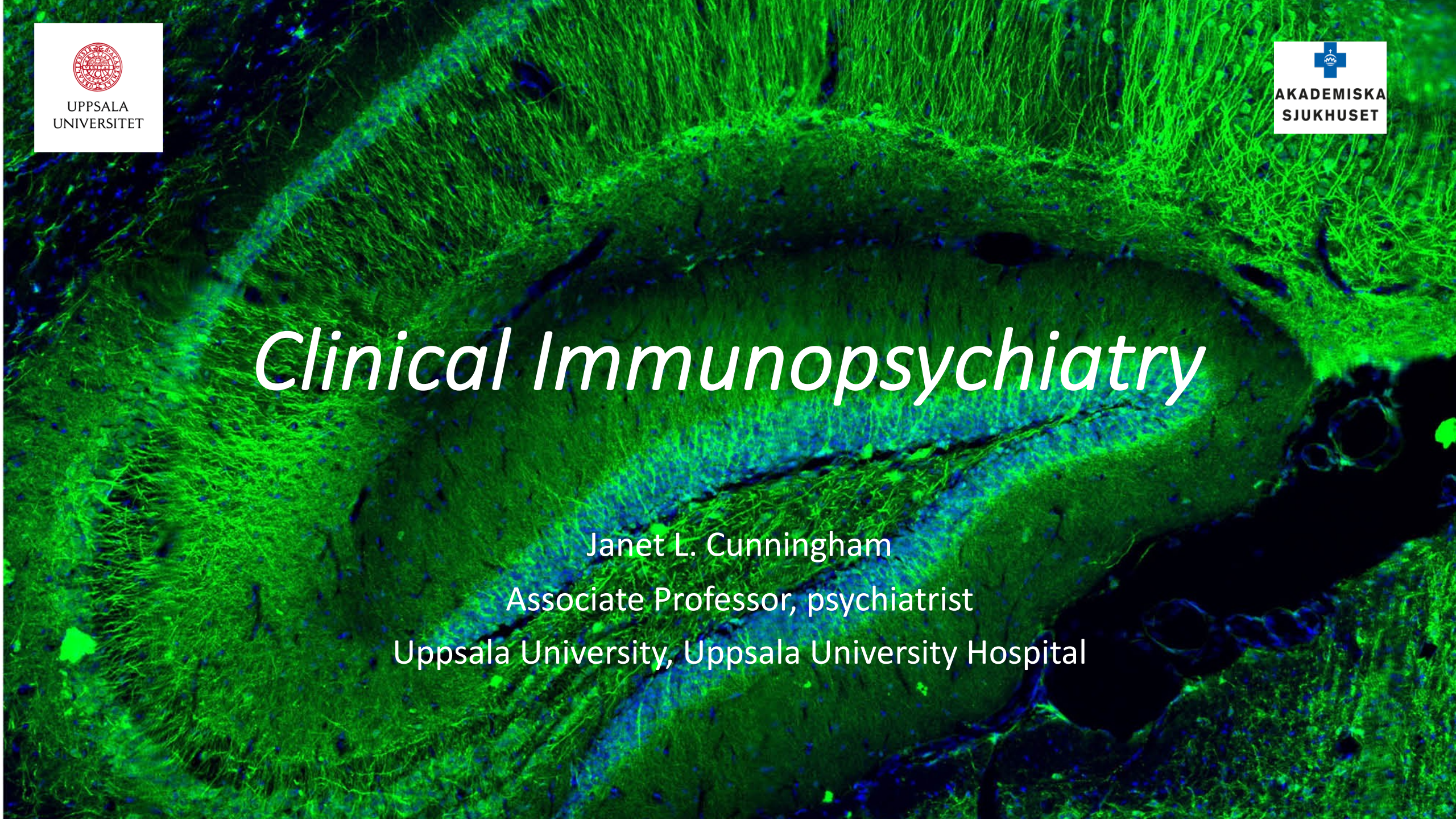


Clinical Immunopsychiatry

Janet L. Cunningham

Associate Professor, psychiatrist

Uppsala University, Uppsala University Hospital

Declarations of interest

I have received lecturing fees from:

- Otsuka Pharma Scandinavia,
- Janssen-Cilag AB
- H. Lundbeck AB

Is Depression an Inflammatory Disorder?

Charles L. Raison and Andrew H. Miller

Depression: an inflammatory illness?

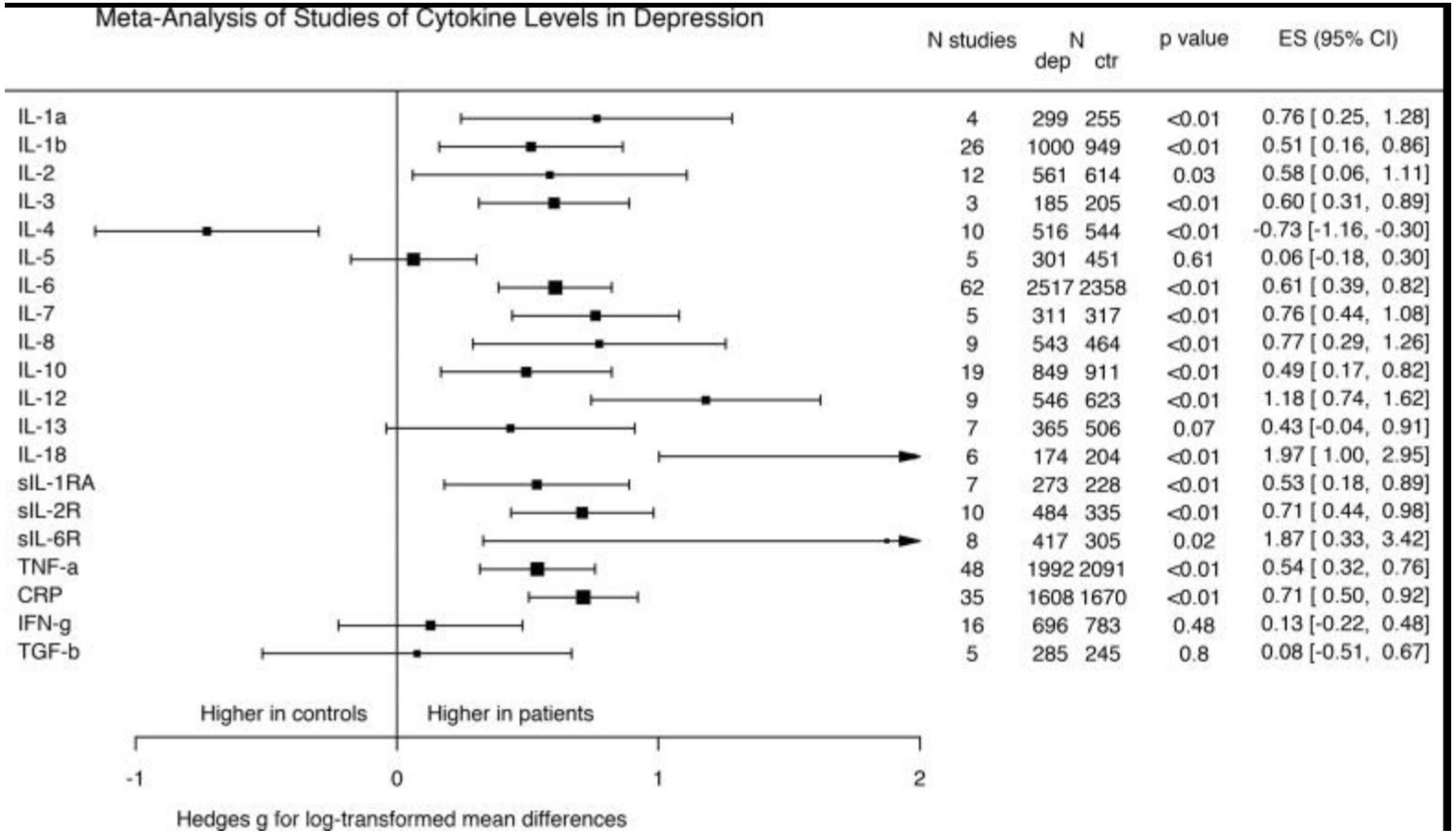
The Role of Inflammation in Depression and Fatigue

Chieh-Hsin Lee[1] and Fabrizio Giuliani[1,2,*]

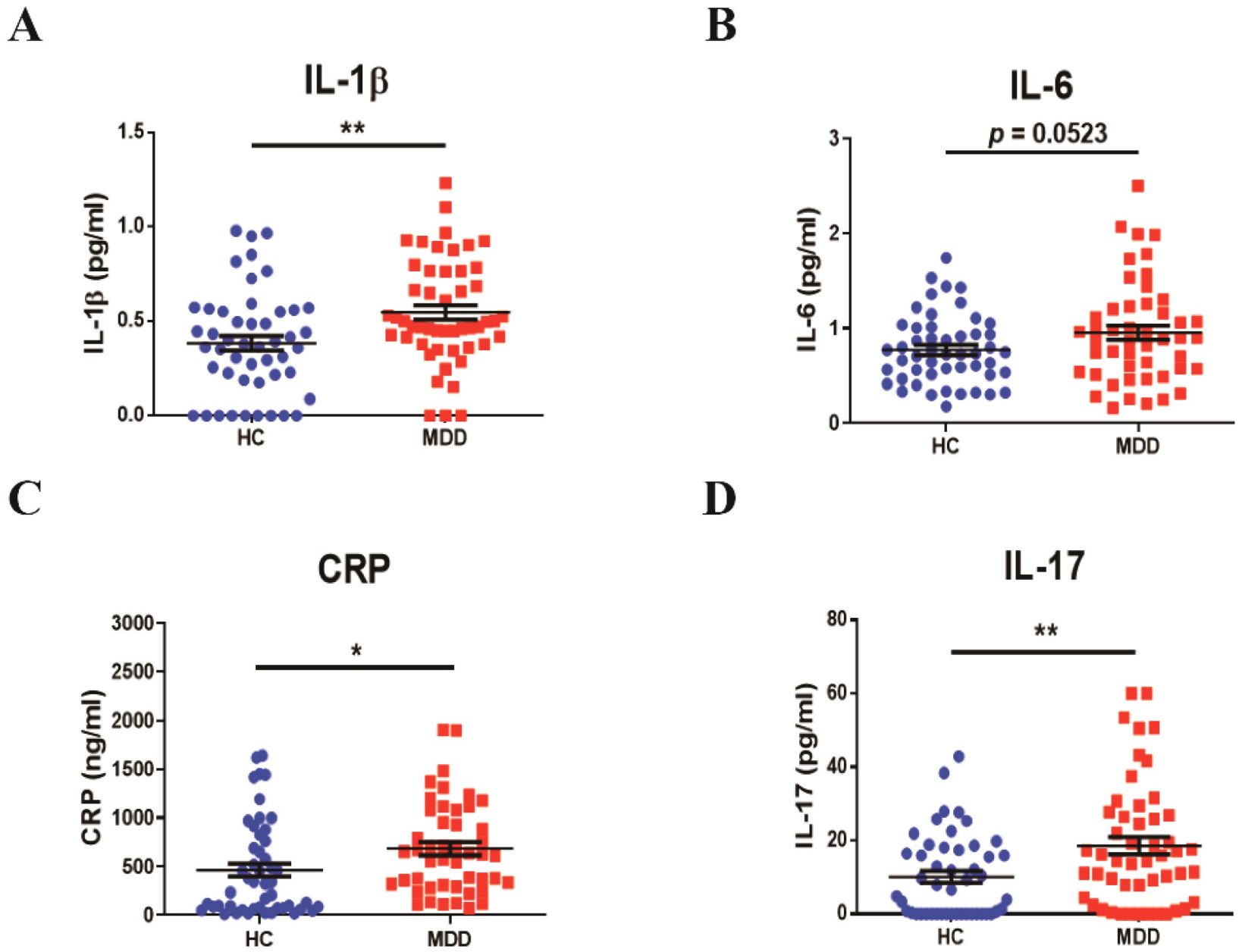
Depression: Not an Inflammatory Disease, but Inflammation Plays a Huge Role

October 27, 2018

Allison Inserro

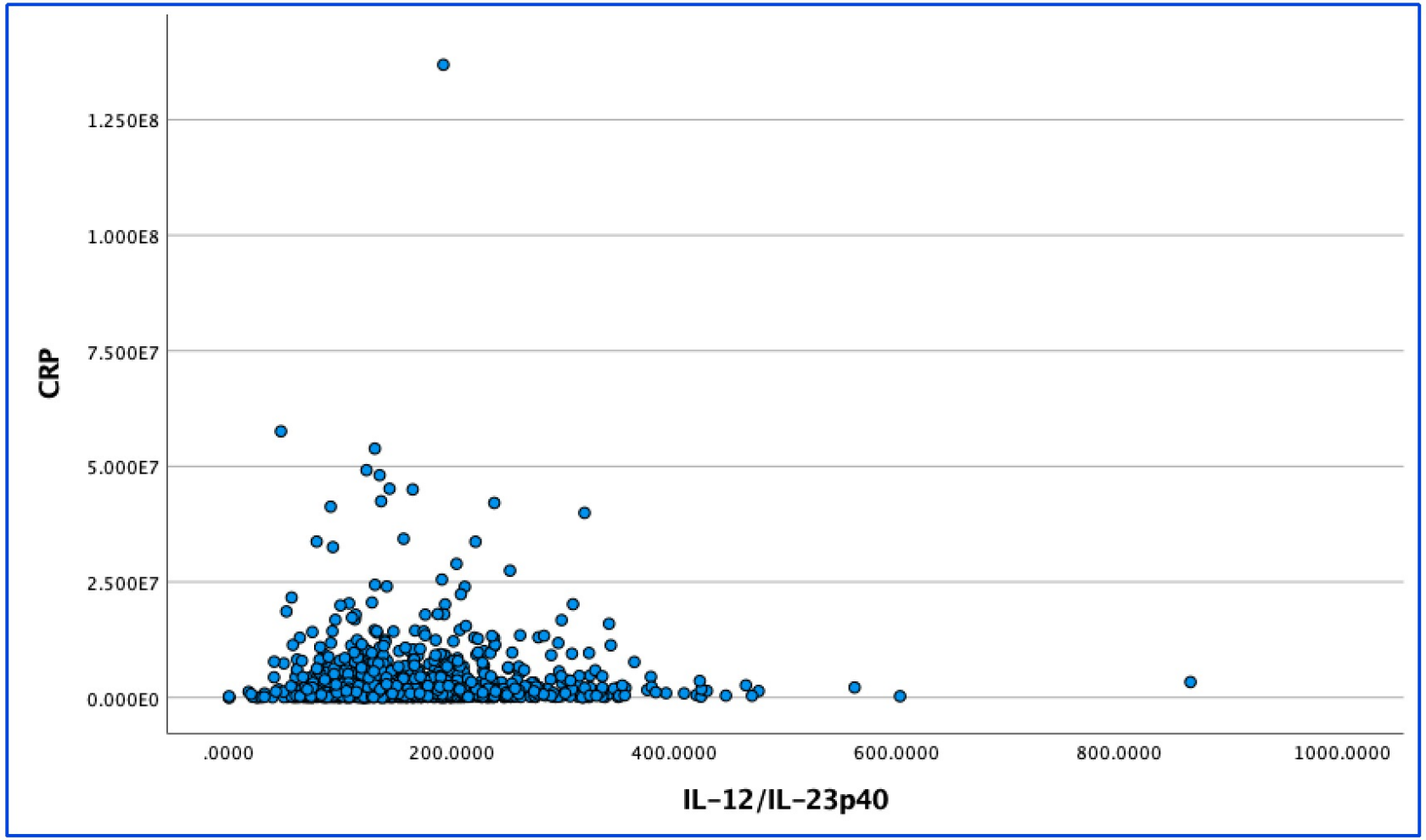


Brain Behav Immun. 2020 Jul;87:901-909.



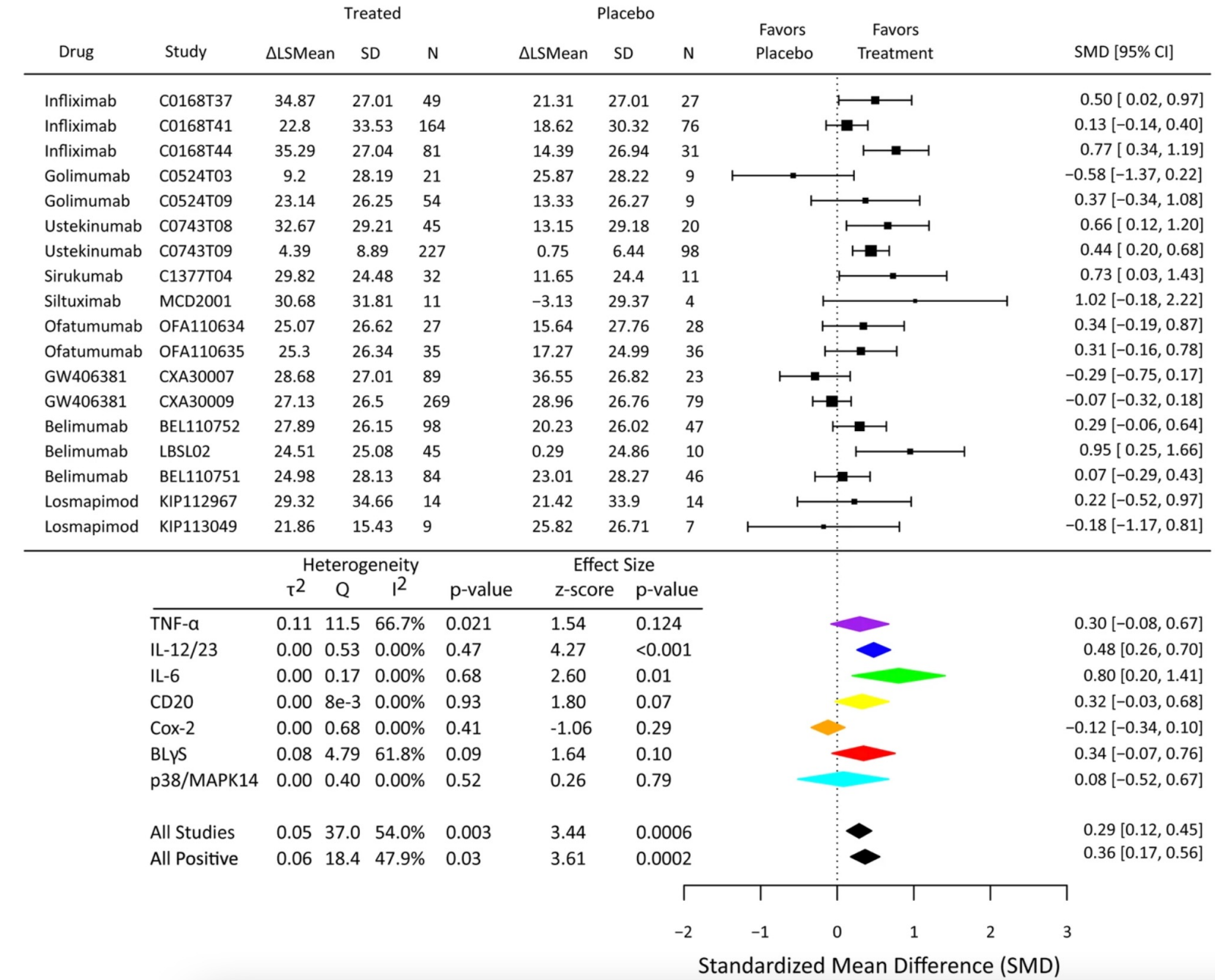
Biomedicines **2021**, *9*(7), 708;

Only weak correlations between inflammatory markers -> different types of inflammation



Unpublished raw data from the UPP: Young Adults cohort
Consecutive general psychiatric outpatients ages 18-25.

A. Depressive Symptom Score

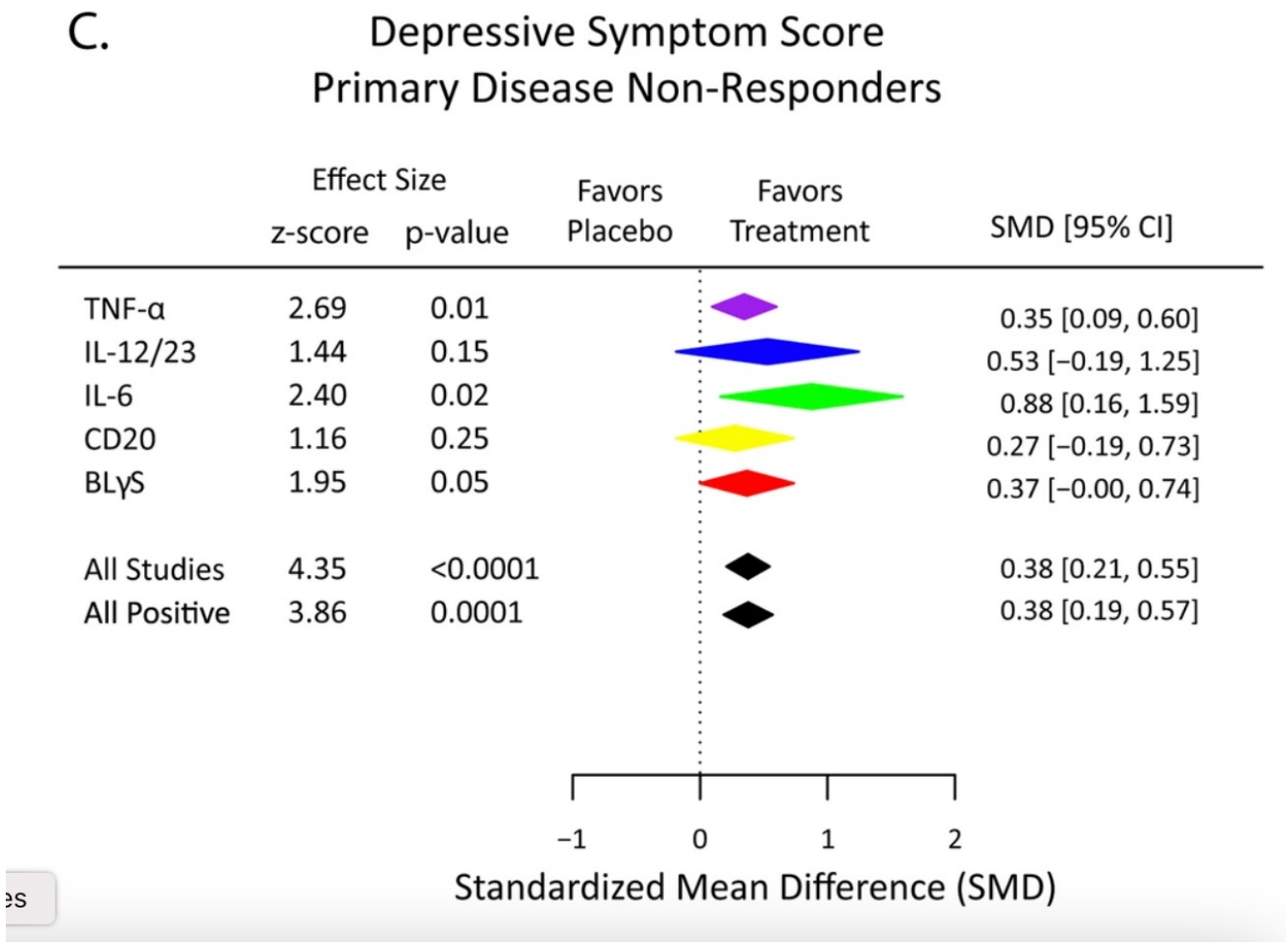


Drug	Study	Treated ΔLSMean	Treated SD	Treated N	Placebo ΔLSMean	Placebo SD	Placebo N	SMD [95% CI]
Infliximab	C0168T37	34.87	27.01	49	21.31	27.01	27	0.50 [0.02, 0.97]
Infliximab	C0168T41	22.8	33.53	164	18.62	30.32	76	0.13 [−0.14, 0.40]
Infliximab	C0168T44	35.29	27.04	81	14.39	26.94	31	0.77 [0.34, 1.19]
Golimumab	C0524T03	9.2	28.19	21	25.87	28.22	9	−0.58 [−1.37, 0.22]
Golimumab	C0524T09	23.14	26.25	54	13.33	26.27	9	0.37 [−0.34, 1.08]
Ustekinumab	C0743T08	32.67	29.21	45	13.15	29.18	20	0.66 [0.12, 1.20]
Ustekinumab	C0743T09	4.39	8.89	227	0.75	6.44	98	0.44 [0.20, 0.68]
Sirukumab	C1377T04	29.82	24.48	32	11.65	24.4	11	0.73 [0.03, 1.43]
Siltuximab	MCD2001	30.68	31.81	11	−3.13	29.37	4	1.02 [−0.18, 2.22]
Ofatumumab	OFA110634	25.07	26.62	27	15.64	27.76	28	0.34 [−0.19, 0.87]
Ofatumumab	OFA110635	25.3	26.34	35	17.27	24.99	36	0.31 [−0.16, 0.78]
GW406381	CXA30007	28.68	27.01	89	36.55	26.82	23	−0.29 [−0.75, 0.17]
GW406381	CXA30009	27.13	26.5	269	28.96	26.76	79	−0.07 [−0.32, 0.18]
Belimumab	BEL110752	27.89	26.15	98	20.23	26.02	47	0.29 [−0.06, 0.64]
Belimumab	LBSL02	24.51	25.08	45	0.29	24.86	10	0.95 [0.25, 1.66]
Belimumab	BEL110751	24.98	28.13	84	23.01	28.27	46	0.07 [−0.29, 0.43]
Losmapimod	KIP112967	29.32	34.66	14	21.42	33.9	14	0.22 [−0.52, 0.97]
Losmapimod	KIP113049	21.86	15.43	9	25.82	26.71	7	−0.18 [−1.17, 0.81]

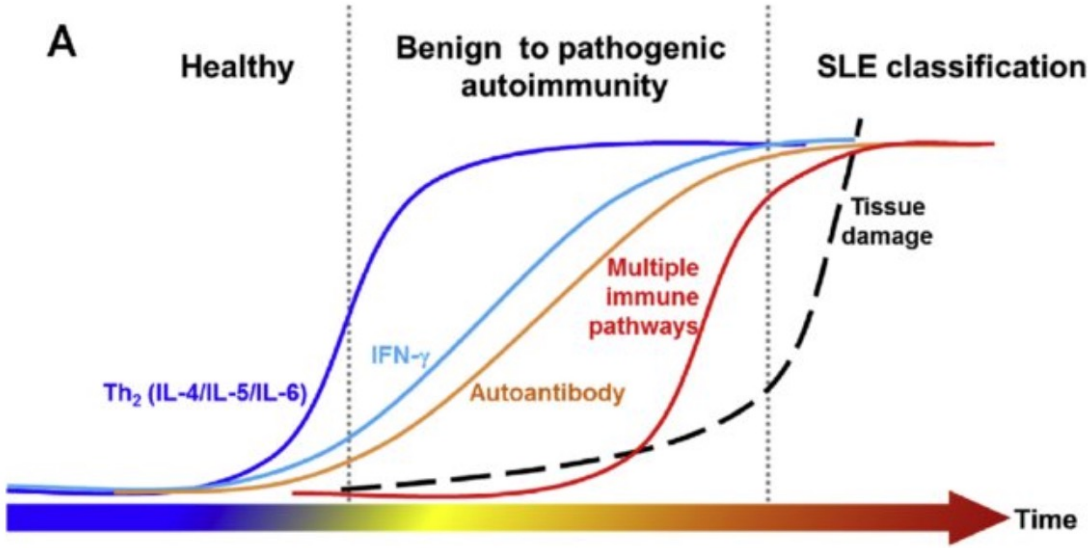
	Heterogeneity τ^2	Q	I^2	p-value	Effect Size z-score	p-value	
TNF-α	0.11	11.5	66.7%	0.021	1.54	0.124	0.30 [−0.08, 0.67]
IL-12/23	0.00	0.53	0.00%	0.47	4.27	<0.001	0.48 [0.26, 0.70]
IL-6	0.00	0.17	0.00%	0.68	2.60	0.01	0.80 [0.20, 1.41]
CD20	0.00	8e-3	0.00%	0.93	1.80	0.07	0.32 [−0.03, 0.68]
Cox-2	0.00	0.68	0.00%	0.41	-1.06	0.29	−0.12 [−0.34, 0.10]
BLyS	0.08	4.79	61.8%	0.09	1.64	0.10	0.34 [−0.07, 0.76]
p38/MAPK14	0.00	0.40	0.00%	0.52	0.26	0.79	0.08 [−0.52, 0.67]
All Studies	0.05	37.0	54.0%	0.003	3.44	0.0006	0.29 [0.12, 0.45]
All Positive	0.06	18.4	47.9%	0.03	3.61	0.0002	0.36 [0.17, 0.56]

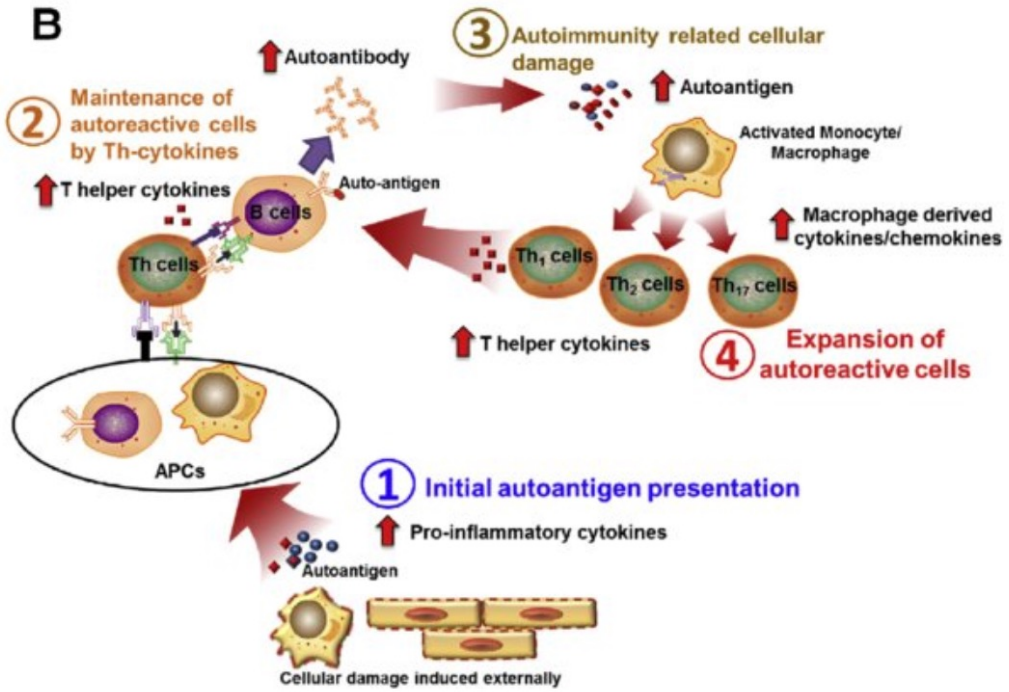
Wittenberg, Mol Psych, 2020

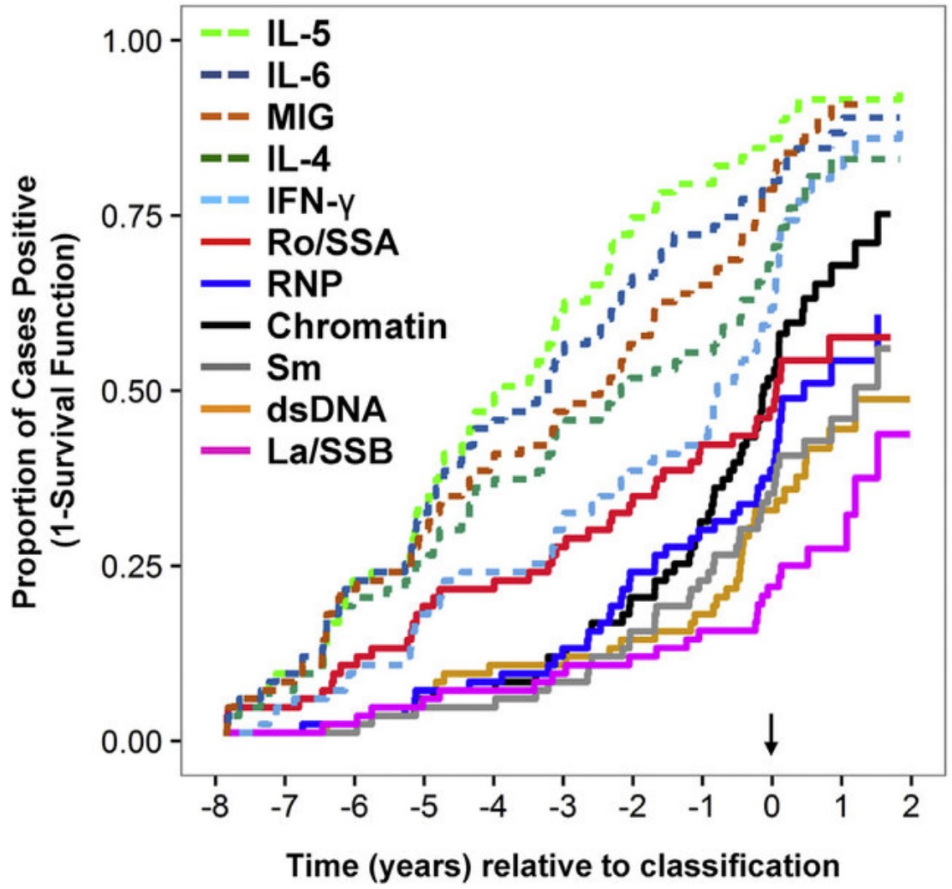
Immunotherapy reduced depressive symptom even when it didn't treat primary disease



Wittenberg, Mol Psych, 2020


A
Healthy
Benign to pathogenic autoimmunity
SLE classification
Tissue damage
Multiple immune pathways
IFN-γ
Autoantibody
Th2 (IL-4/IL-5/IL-6)
Time


B
Autoantibody
3 Autoimmunity related cellular damage
Autoantigen
Activated Monocyte/ Macrophage
2 Maintenance of autoreactive cells by Th-cytokines
T helper cytokines
Auto-antigen
B cells
Th cells
Macrophage derived cytokines/chemokines
Th1 cells
Th2 cells
Th17 cells
T helper cytokines
4 Expansion of autoreactive cells
APCs
1 Initial autoantigen presentation
Pro-inflammatory cytokines
Autoantigen
Cellular damage induced externally


IL-5
IL-6
MIG
IL-4
IFN-γ
Ro/SSA
RNP
Chromatin
Sm
dsDNA
La/SSB
Proportion of Cases Positive (1-Survival Function)
1.00
0.75
0.50
0.25
0.00
-8
-7
-6
-5
-4
-3
-2
-1
0
1
2
Time (years) relative to classification

Networks at a glance

Horizon 2020

Create and join: FAQ

List of ECNP Networks and TWGs >

- ADHD across the Lifespan
- Anxiety Disorders
- Bipolar Disorders
- Child and Adolescent Neuropsychopharmacology
- Digital Health Applied to the Clinical Research of Brain Disorders

Immuno-NeuroPsychiatry Network

Mission statement/aims

Immune-NeuroPsychiatry
ECNP Network

Immune processes are major factors for central nervous system health, as well as for risk or resilience to brain disorders. Exciting scientific insights indicate a highly sensitive and fine-tuned equilibrium of inflammation modulating our cognitive and social abilities. Recent discoveries in neurology and psychiatry are challenging our traditional classification of brain diseases. Among the pathophysiological mechanisms underlying the strong link between psychiatric and neurologic disorders, one of the most relevant refers to the pivotal position of inflammation. New biomarkers to identify homogenous subgroups are required to identify subgroups of patients to pave the way towards precision medicine and in particular to uncover mechanism-based immune treatments. Immune-modulatory therapies are effective options for a range of neurologic and psychiatric diseases. It is of fundamental importance to identify subgroups of psychiatric patients with signs of immune dysregulation to develop individualized therapeutic strategies.

For example, in psychiatric disorders with very early onset, such as Autism Spectrum Disorders, early insults such as maternal infections or maternal auto- antibodies against fetal brain have been repeatedly found to be associated with increased risk of Autism Spectrum Disorders leading to chronic inflammation in the offspring at peripheral, brain and digestive sites.

New autoimmune psychiatric diseases?

THE LANCET
Psychiatry
Volume 7, Issue 1, January 2020, Pages 93-108

Position Paper

Autoimmune psychosis: an international consensus on an approach to the diagnosis and management of psychosis of suspected autoimmune origin

Thomas A Pollak PhD [a], Belinda R Lennox DM [b], Sabine Müller PhD [c], Michael E Benros PhD [d], Harald Prüss MD [e, f], Prof Ludger Tebartz van Elst [g], Hans Klein MD [h, i, j], Prof Johann Steiner MD [k], Prof Thomas Frodl [k], Prof Bernhard Bogerts [k], Li Tian PhD [l, m], Laurent Groc PhD [n], Prof Alkomiet Hasan MD [o], Prof Bernhard T Baune MD [q, r], Dominique Endres MD [g], Ebrahim Haroon MD [s], Prof Robert Yolken MD [t], Francesco Benedetti MD [u, v] … Prc Karl Bechter [ag, †]

Translational Psychiatry www.nature.com/tp

REVIEW ARTICLE OPEN

Check for updates

Immunological causes of obsessive-compulsive disorder: is it time for the concept of an "autoimmune OCD" subtype?

Dominique Endres[1,2]✉, Thomas A. Pollak[3], Karl Bechter[4], Dominik Denzel[2], Karoline Pitsch[2], Kathrin Nickel[1,2], Kimon Runge[1,2], Benjamin Pankratz[2], David Klatzmann[5,6], Ryad Tamouza[7], Luc Mallet[7], Marion Leboyer[7], Harald Prüss[8,9], Ulrich Voderholzer[10,11], Janet L. Cunningham[12], ECNP Network Immuno-NeuroPsychiatry, Katharina Domschke[2,13,14], Ludger Tebartz van Elst[1,2,14] and Miriam A. Schiele[2,14]

Obsessive-compulsive disorder (OCD) is a highly disabling mental illness that can be divided into frequent primary and rarer organic secondary forms. Its association with secondary autoimmune triggers was introduced through the discovery of Pediatric Autoimmune Neuropsychiatric Disorder Associated with Streptococcal infection (PANDAS) and Pediatric Acute onset Neuropsychiatric Syndrome (PANS). Autoimmune encephalitis and systemic autoimmune diseases or other autoimmune brain diseases, such as multiple sclerosis, have also been reported to sometimes present with obsessive-compulsive symptoms (OCS). Subgroups of patients with OCD show elevated proinflammatory cytokines and autoantibodies against targets that include the basal ganglia. In this conceptual review paper, the clinical manifestations, pathophysiological considerations, diagnostic investigations, and treatment approaches of immune-related secondary OCD are summarized. The novel concept of "autoimmune OCD" is proposed for a small subgroup of OCD patients, and clinical signs based on the PANDAS/PANS criteria and from recent experience with autoimmune encephalitis and autoimmune psychosis are suggested. Red flag signs for "autoimmune OCD" could include (sub)acute onset, unusual age of onset, atypical presentation of OCS with neuropsychiatric features (e.g., disproportionate cognitive deficits) or accompanying neurological symptoms (e.g., movement disorders), autonomic dysfunction, treatment resistance, associations of symptom onset with infections such as group A streptococcus, comorbid autoimmune diseases or malignancies. Clinical investigations may also reveal alterations such as increased levels of anti-basal ganglia or dopamine receptor antibodies or inflammatory changes in the basal ganglia in neuroimaging. Based on these red flag signs, the criteria for a possible, probable, and definite autoimmune OCD subtype are proposed.

Translational Psychiatry (2022)12:5 ; https://doi.org/10.1038/s41398-021-01700-4

UPPSALA UNIVERSITET

AKADEMISKA SJUKHUSET

Autoimmune psychosis or OCD

Red flags:
Akut debut *(eller skov)*
Förekomst av autoimmun sjukdom
Tidssamband infektion
Atypisk sjukdomspresentation
Förekomst av tumör
Avvikande rörelsemönster
Katatoni
Onormal reaktion på antipsykotika *(svår/ovanliga biverkningar, terapiresistens)*
Medvetandesänkning, *(extreme fattige)*
Huvudvärk *(ledvärk)*
Kramper
Fokal neurologisk avvikelse
Språkrubbning
Svår eller disproportionell kognitiv dysfunktion
Autonom instabilitet

Pollak T. et al. Autoimmune psychosis: an international consensus on an approach to the diagnosis and management of psychosis of suspected autoimmune origin. 2020. Herken J. and Pruss H. "Red flags: Clinical Signs for Identifying Autoimmune Encephalitis in Psychiatric Patients". 2017.

In press: Guidelines for Autoimmune OCD. Endres et al, Translational psychiatry

Pediatric Rheumatology

CASE REPORT Open Access

Adolescent Sjogren's syndrome presenting as psychosis: a case series

Erin K. Hammett[1*], Cristina Fernandez-Carbonell[2], Courtney Crayne[3], Alexis Boneparth[4], Randy Q. Cron[3] and Suhas M. Radhakrishna[1]

Abstract

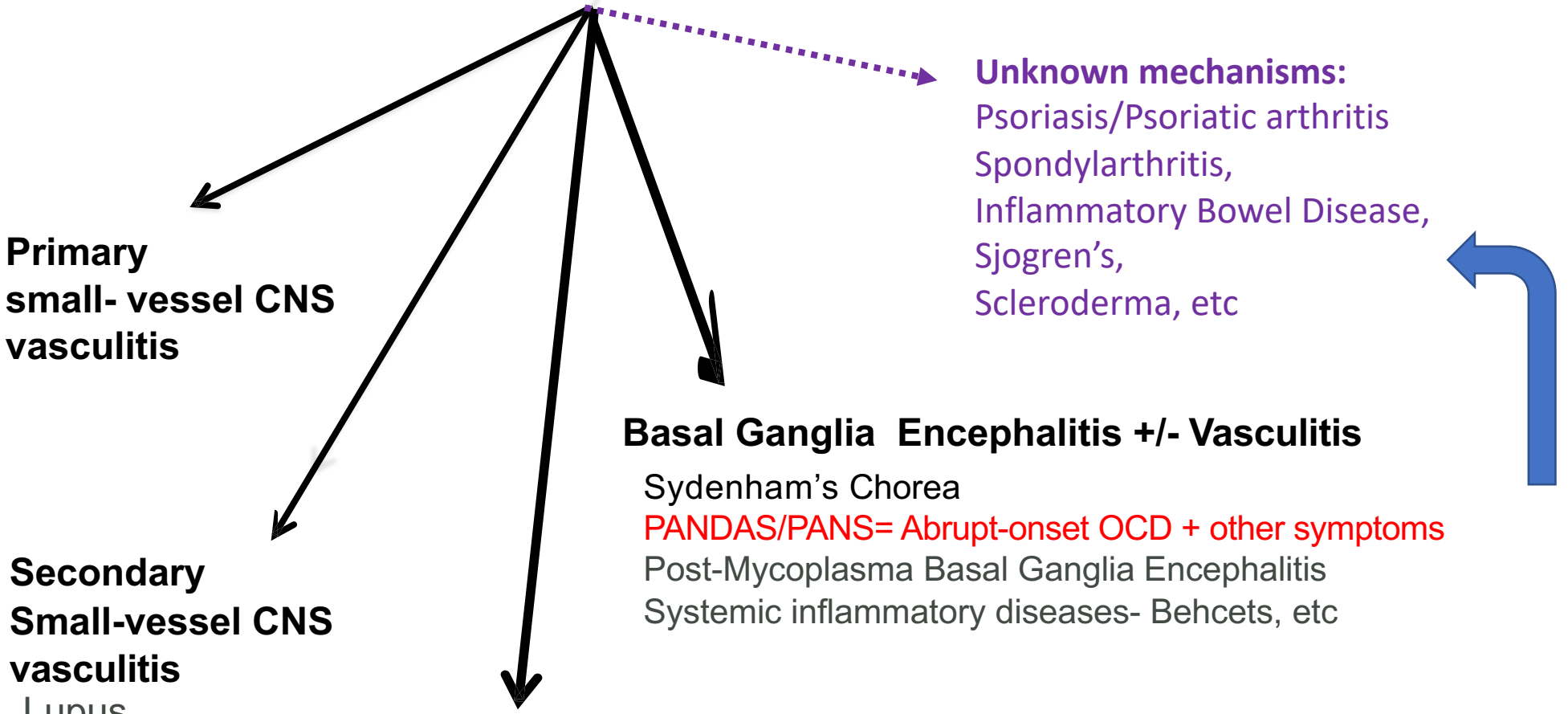
Background: Neurological involvement has been reported in up to 80% of adults with Primary Sjogren's syndrome (pSS) with psychiatric abnormalities including anxiety, depression, and cognitive dysfunction being common. Psychosis due to pSS has been reported in adult patients but has never been previously reported in the adolescent/pediatric literature. Here we describe for the first time four cases of adolescent Sjogren's syndrome that presented with psychotic symptoms. Rituximab treatment was followed by improvement of psychiatric symptoms in all patients.

Case presentation: **1**: 16 year old female without significant past medical history presented to the emergency department with 4 days of abnormal behavior, tremors, insomnia, polyphagia, polyuria, and suicidal ideation.
2: 16 year old female with a 4 year history of severe anxiety, OCD, and tic disorder treated with fluoxetine with partial benefit presented with an abrupt and severe worsening of anxiety, OCD and new auditory hallucinations.
3: 19 year old female without significant past medical history presented with a 3 day history of progressively altered behavior, incoherent speech, insomnia, headache, and tangential thoughts.
4: 17 year old female without significant past medical history presented with new onset suicidal ideation, paranoia, confusion, and emotional lability.

Conclusion: Psychosis is more common in autoimmune disease than previously known. To our knowledge, the four teenage women described above are the first reported patients with adolescent pSS manifesting as psychosis. pSS should be considered in the differential diagnosis of young patients with new psychiatric disorders, even in the absence of sicca symptoms. Psychiatric symptoms improved with rituximab infusions in all 4 of our patients, which suggests rituximab may be an effective treatment option that should be considered early after the diagnosis of pSS-associated psychiatric disturbance.

Keywords: Central nervous system (CNS) Sjogren's syndrome, Pediatric Sjogren's syndrome, Psychosis

Inflammatory diseases with co-morbid psychiatric symptoms



Unknown mechanisms:
Psoriasis/Psoriatic arthritis
Spondylarthritis,
Inflammatory Bowel Disease,
Sjogren's,
Scleroderma, etc

Primary small- vessel CNS vasculitis

Basal Ganglia Encephalitis +/- Vasculitis
Sydenham's Chorea
PANDAS/PANS= Abrupt-onset OCD + other symptoms
Post-Mycoplasma Basal Ganglia Encephalitis
Systemic inflammatory diseases- Behcets, etc

Secondary Small-vessel CNS vasculitis
Lupus
Behcet's

Autoimmune Encephalitis
Diffuse cerebritis
Lupus
Limbic Encephalitis
NMDA Receptor Ab Encephalitis
? Hashimoto's Encephalopathy

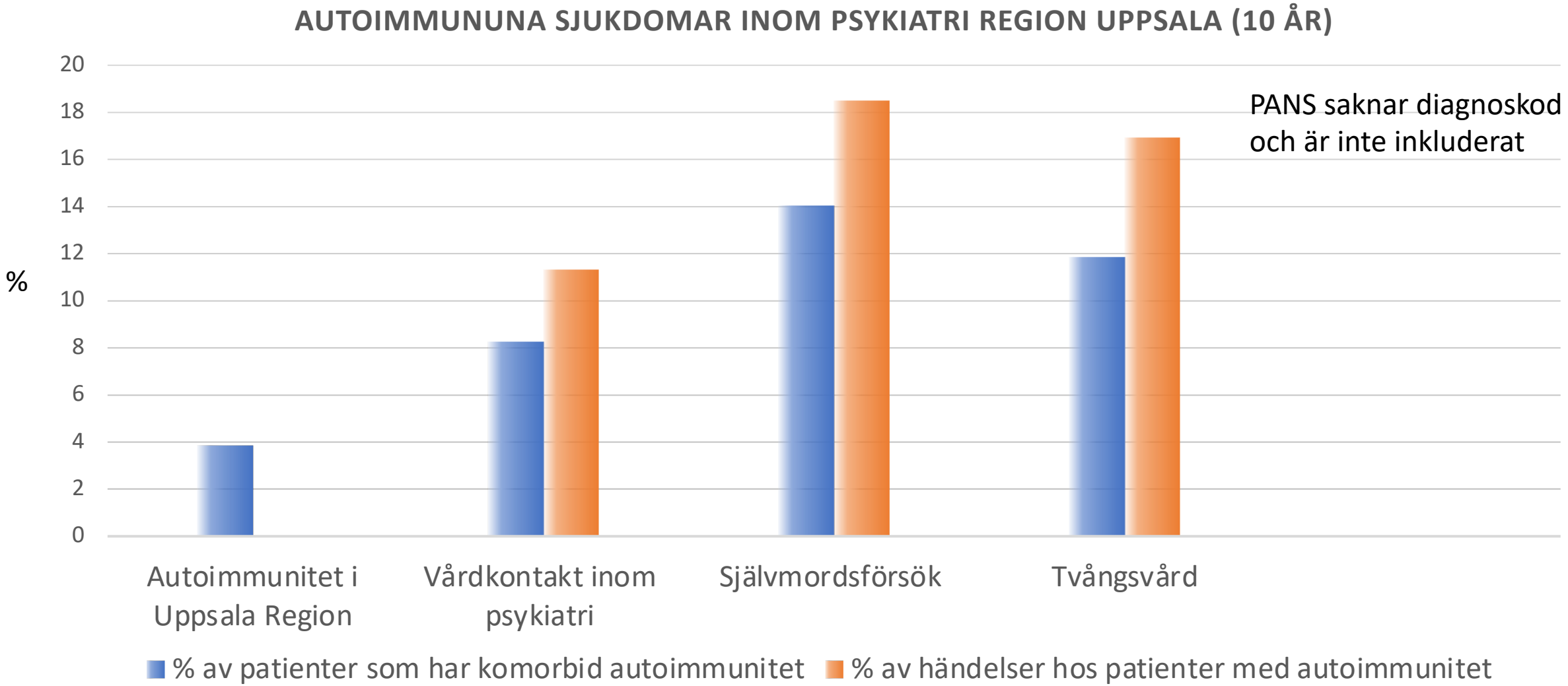
Adapted from J. Frankovich

Komplexa samband

- Det kan ta decennier att diagnostisera en **autoimmun sjukdom.**

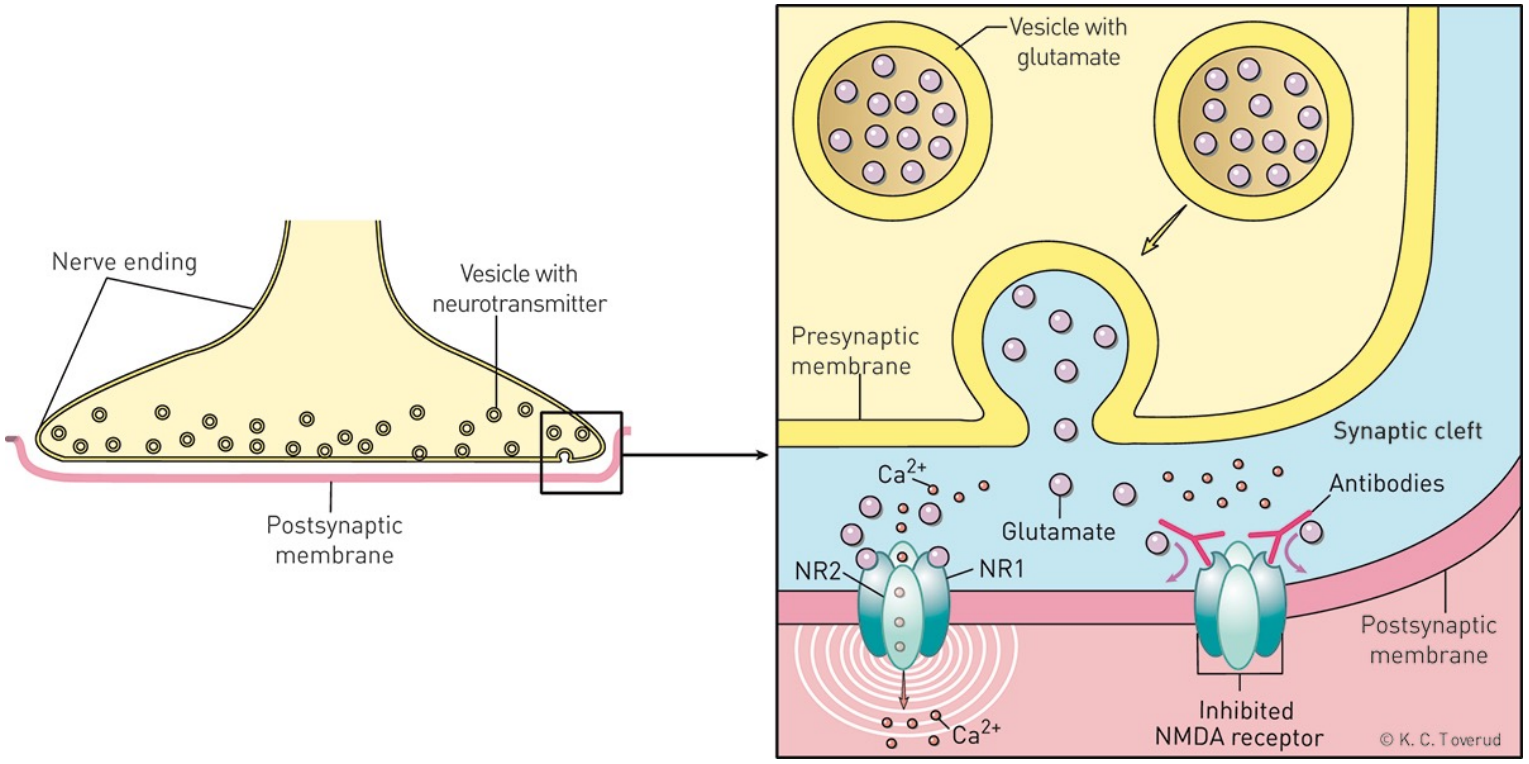
- *”Det är ett observandum att patienten har antikroppar som är associerade med SLE men har inga SLE symptom därmed kan vi inte konstatera ett systemiskt reumatologiskt sjukdom ”*

Det är väl känt att reumatologiska sjukdomar kan ge psykiatriska symptom men psykiatriska symptom ingår inte i de diagnostiska kriterierna.



Cunningham, opublicerade vårdplanerings data, 2021

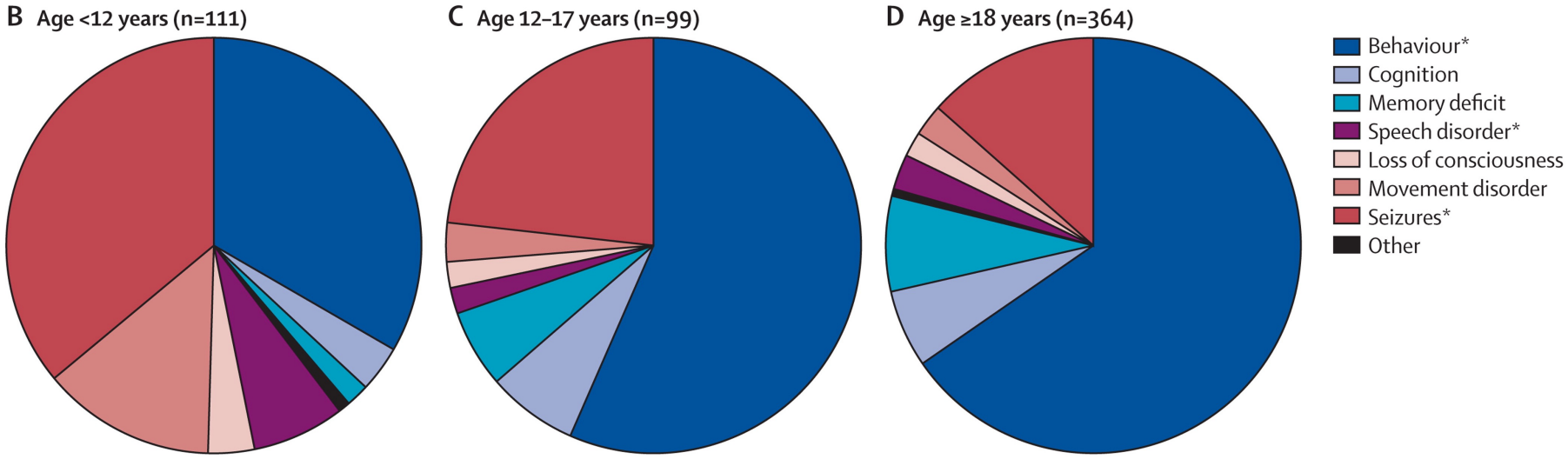
NMDAr Autoantibodies: Mechanism?



Higher prevelance of NMDArAB after:

- Influenza A (Males)
- Influenza B (Males)
- Vaccination (influenza)
- Measles
- Herpes encephalitis (6 weeks after in children)
- SARS-Cov2 (?)
- In women-> look for teratoma!

Age differences in debut symptoms



Titulaer MJ, McCracken L, Gabilondo I, et al. Treatment and prognostic factors for long-term outcome in patients with anti-NMDA receptor encephalitis: an observational cohort study. *Lancet neurology*. 2013; 12: 157-65.

Commercial Tests for NMDAr-Abs with fixed cells have very low sensitivity

	Positive	Weak positive	Total
Live CBA (serum) *Lab A*	8	6	14
Live CBA (serum) *Lab B*	5	4	9
Fixed CBA (serum) *Lab C*	1	1	2
Live CBA (purif. IgG) *Lab A*	5	3	8

http://dx.doi.org/10.1016/j.biopsych.2017.06.015

Translational Psychiatry

Transl Psychiatry. 2020; 10: 401.
Published online 2020 Nov 18. doi: 10.1038/s41398-020-01079-8

PMCID: PMC7676257
PMID: 33208725

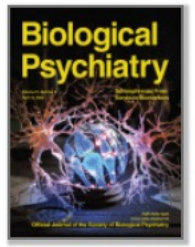
Exploring autoantibody signatures in brain tissue from patients with severe mental illness

David Just,[1,2] Anna Månberg,[1] Nicholas Mitsios,[3] Craig A. Stockmeier,[4] Grazyna Rajkowska,[4] Mathias Uhlén,[1,3] Jan Mulder,[3] Lars Feuk,[5] Janet L. Cunningham,[2] Peter Nilsson,[1] and Eva Lindholm Carlström[5]

Autoimmunity against other NMDAr subunits may be of interest for psychiatric diseases:

"Among the detected autoantigens, **higher IgG reactivity in subjects with schizophrenia, as compared to psychiatrically healthy subjects, was found against the glutamate ionotropic receptor NMDA type subunit 2D (anti-GluN2D).** In a separate cohort with serum samples from 395 young adults with a wider spectrum of psychiatric disorders, higher levels of serum autoantibodies targeting GluN2D were found when compared to 102 control individuals. "

Biological Psychiatry
Available online 19 February 2022
In Press, Journal Pre-proof



Archival Report

Spectrum of novel anti-CNS autoantibodies in the cerebrospinal fluid of 119 patients with schizophreniform and affective disorders

Dominique Endres [1], Katharina von Zedtwitz [1], Isabelle Matteit [1], Isabel Bünger [2, 3], Helle Foverskov-Rasmussen [2, 3], Kimon Runge [1], Bernd Feige [1], Andrea Schlump [1], Simon Maier [1], Kathrin Nickel [1], Benjamin Berger [4], Miriam A. Schiele [1], Janet L. Cunningham [5], Katharina Domschke [1, 6], Harald Prüss [2, 3] *, Ludger Tebartz van Elst [1] *

Show more

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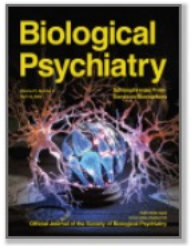
https://doi.org/10.1016/j.biopsych.2022.02.010

Biological Psychiatry
Available online 19 February 2022
In Press, Journal Pre-proof



Archival Report

Spectrum of novel anti-CNS autoantibodies in the cerebrospinal fluid of 119 patients with schizophreniform and affective disorders

Based on the findings from all 119 patients, **anti-CNS IgG autoantibodies against brain tissue were detected in 18% (N=22) of patients (serum 9%, CSF 18%)** following five principal patterns:

1) against **vascular structures,** most likely endothelial cells (serum 3%, CSF 8%);
2) against **granule cells in the cerebellum and/or hippocampus** (serum 4%, CSF 6%);
3) against **myelinated fibers** (serum 2%, CSF 2%);
4) against cerebellar **Purkinje cells** (serum 0%, CSF 2%); and
5) against **astrocytes** (serum 1%, CSF 1%).

The patients with novel anti-CNS autoantibodies showed increased albumin quotients (p=0.026) and white matter changes (p=0.020) more frequent compared to those who tested negative for autoantibodies.

Post-covid psychiatric disease

- EBV rectivation?
- Covid super-antigen and activates latent autoimmunity?
- Persistant infection?
- Anti-brain autoimmunity?
- Premorbid psychiatric vunerability?
- All of the above?

Late regression of autism?

- Obsessive and increased ritualistic behaviours
- Mood and behavioural changes
- Freezing moments
- Getting stuck in the doorways
- New-onset aggression
- Pressured speech
- Overactivity resembling hypomania,
- Echolalia
- Stereotypies
- Impulsive behaviours
- Urine retention

Late regression of autism? Think Catatonia

Catatonia 2

Catatonia and the immune system: a review

Jonathan P Rogers, Thomas A Pollak, Graham Blackman, Anthony S David

Lancet Psychiatry 2019; 6: 620–30

Published Online June 10, 2019 http://dx.doi.org/10.1016/S2215-0366(19)30190-7

See Comment page 554

This is the second in a Series of two papers on catatonia

Department of Psychosis Studies, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, UK (Dr J P Rogers MBBChir, Dr T A Pollak PhD, Dr G Blackman MBBS); **South London and Maudsley National Health Service Foundation Trust, Bethlem Royal Hospital, UK** (Dr J P Rogers, Dr T A Pollak, Dr G Blackman); **and Institute of Mental Health, University College London, London, UK** (Prof A S David FRCPsych)

Correspondence to: Dr Jonathan P Rogers, Department of Psychosis Studies, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, SE5 8AF, UK. **jonathan.rogers@kcl.ac.uk**

See Online for appendix

Catatonia is a psychomotor disorder featuring stupor, posturing, and echophenomena. This Series paper examines the evidence for immune dysregulation in catatonia. Activation of the innate immune system is associated with mutism, withdrawal, and psychomotor retardation, which constitute the neurovegetative features of catatonia. Evidence is sparse and conflicting for acute-phase activation in catatonia, and whether this feature is secondary to immobility is unclear. Various viral, bacterial, and parasitic infections have been associated with catatonia, but it is primarily linked to CNS infections. The most common cause of autoimmune catatonia is N-methyl-D-aspartate receptor (NMDAR) encephalitis, which can account for the full spectrum of catatonic features. Autoimmunity appears to cause catatonia less by systemic inflammation than by the downstream effects of specific actions on extracellular antigens. The specific association with NMDAR encephalitis supports a hypothesis of glutamatergic hypofunction in catatonia.

Introduction

Catatonia is a psychomotor disorder characterised by diverse clinical signs, including mutism, negativism, ambitendency, stereotypy, posturing, waxy flexibility, and echophenomena.[1] The structure and neural mechanisms of the disorder are reviewed elsewhere in this issue of *The Lancet Psychiatry* by Walther and colleagues.[2] Understanding the pathophysiology of this severe disorder is crucial given its high rate of medical complications, including pressure ulcers, infections, and venous thromboembolism.[3] Moreover, such understanding might aid the comprehension of other neuropsychiatric disorders.

Although catatonia has numerous possible symptom combinations,[4] compelling reasons to study it as a single entity exist. Clinical and demographic factors can distinguish catatonia from other psychotic and affective disorders.[5] Different forms of catatonia (retarded catatonia, malignant catatonia, and neuroleptic malignant syndrome) are highly comorbid.[1] In terms of treatment, response rates to benzodiazepines and electroconvulsive therapy (ECT) are high, regardless of the cause of the catatonia.[6] Moreover, catatonia is not a common disorder, so pragmatically, cause catatonia (tables 1, 2). We address whether the immune system has a role in catatonia, using some direct and some more circumstantial evidence, and endeavour to establish specific models. We consider immunity in terms of innate and adaptive systems for the purposes of clarity, while acknowledging that strictly demarcating the two is not always possible.

Innate immune system

Catatonia due to infection

A systematic review reported that 20% of catatonia has a general medical cause, of which CNS inflammation (comprising both infective and immune causes) accounts for 29%.[9] Numerous infectious diseases have been reported to cause catatonia. Here, we present the results of a new systematic search of the literature (table 1; appendix). We identified 124 cases, the majority of which were published as case reports, with the remaining reported as case series. Laboratory evidence of infection (such as isolation of the organism in the serum, or viral DNA in the cerebrospinal fluid [CSF]) was reported in 85 of the cases (69%). A robust temporal association between the infection and catatonia was

Animal Models for PANDAS

Three animal models have been utilized to demonstrate autoantibody-mediated neuropsychiatric changes

- after crude GAS immunization of mice or rats (Hoffman et al. 2004; Brimberg et al. 2012),
- after passive transfer of IgG intravenously from GAS-immunized mice (Yaddanapudi et al. 2010)
- after transfer of IgG into the striatum of naïve rats (Lotan et al. 2014).
- In a recent fourth animal model, it was demonstrated that repeated nasopharyngeal GAS infections resulted in trans-olfactory sterile central nervous system inflammation mediated by Th17 lymphocytes (Dileepan et al. 2016).

Antibodies From Children With PANDAS Bind Specifically to Striatal Cholinergic Interneurons and Alter Their Activity

Jian Xu, Ph.D., Rong-Jian Liu, Ph.D., Shaylyn Fahey, B.S., Luciana Frick, Ph.D., James Leckman, M.D., Ph.D., Flora Vaccarino, M.D., Ronald S. Duman, Ph.D., Kyle Williams, M.D., Ph.D., Susan Swedo, M.D., Christopher Pittenger, M.D., Ph.D.

Striatal Cholinergic Interneurons (CINs)

- regulate motor function
- are depleted in post-mortem brains of patients with Tourrettes
- depletion in mice → repetitive behaviors

3 findings of this study:

1) Increased binding of antibodies to striatal CINs (patients vs controls)
2) IgG binding CINs reduced signaling
3) Electrophysiological data supports reduced responsiveness CINs

children and adolescents in the United States, and a comparable fraction worldwide (1, 2). In a subset of pediatric OCD cases, onset of neuropsychiatric symptoms is strikingly abrupt; this has been termed pediatric acute-onset neuropsychiatric syndrome, or PANS (3, 4). In some children, symptom onset is temporally associated with an infectious illness, often with

PANS have been the focus of considerable research, and some controversy, over three decades (5–7).

It has been suggested that PANDAS results from the postinfectious production of antibodies that target the basal ganglia, perhaps through the phenomenon of molecular mimicry (8, 9). This hypothesis draws an analogy to Sydenham

Important differential diagnostics!

Parkinsonism and Related Disorders 85 (2021) 124–132

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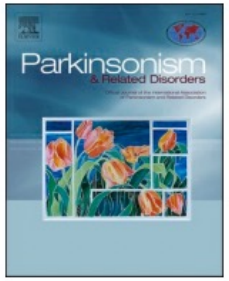
journal homepage: www.elsevier.com/locate/parkreldis



Review article

How to detect late-onset inborn errors of metabolism in patients with movement disorders – A modern diagnostic approach☆

Lisette H. Koens [a,b], Jeroen J. de Vries [a,b], Fleur Vansenne [b,c], Tom J. de Koning [b,c,d,1], Marina A. J. Tijssen [a,b,*,1]

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Journal of
Clinical Medicine

MDPI

Review

Autoimmunity in Primary Immunodeficiency Disorders: An Updated Review on Pathogenic and Clinical Implications

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† Equally contributed to this paper.

Abstract: During the last years, studies investigating the intriguing association between immunodeficiency and autoimmunity led to the discovery of new monogenic disorders, the improvement in the knowledge of the pathogenesis of autoimmunity, and the introduction of targeted treatments. Autoimmunity is observed with particular frequency in patients with primary antibody deficiencies, such as common variable immunodeficiency (CVID) and selective IgA deficiency, but combined immunodeficiency disorders (CIDs) and disorders of innate immunity have also been associated with autoimmunity. Among CIDs, the highest incidence of autoimmunity is described in patients with autoimmune polyendocrine syndrome 1, LRBA, and CTLA-4 deficiency, and in patients with STAT-related disorders. The pathogenesis of autoimmunity in patients with immunodeficiency is far to be fully elucidated. However, altered germ center reactions, impaired central and peripheral lymphocyte negative selection, uncontrolled lymphocyte proliferation, ineffective cytoskeletal function, innate immune defects, and defective clearance of the infectious agents play an important role. In this paper, we review the main immunodeficiencies associated with autoimmunity, focusing on the pathogenic mechanisms responsible for autoimmunity in each condition and on the therapeu-

Citation: Costagliola, G.; Cappelli, S.; Consolini, R. Autoimmunity in

Utredning kräver multidiciplinär samarbete!

Mycket begränsad tillgång för psykiater

- Tidslinje!
- Omfattande psykiatriskt anamnes
- Reumatologiskt anamnes
- Gastroenterologiskt anamnes
- Neurologiskt anamnes
- Infektions anamnes

Kompliceras av kognitiva symptom, desorginaserat beteende, känslor och tankar.

- Blodprov: inflammation, metabol och reumatologiskt screening
- Likvor analys: Neuroinflammation, hjärnskadamärkörer, autoimmna antikroppar. *(Saknas i Sverige: Indirket-immunohistokemi, Live-cell assays)*
- MRI, EEG, Ibland 18-FDG-PET


10

The Uppsala Immunopsychiatry Clinic

- Started Fall 2015
- An interdisciplinary center for further investigation and possibly treatment of psychiatric syndromes with suspected (auto)immune pathogenesis. We evaluate patients referred from all over Sweden, presenting with **acute or atypical debut of psychiatric symptoms in conjunction with infections, autoimmunity or risk for autoimmunity.**
- >250 patients are now evaluated

Psychiatry

Janet Cunningham

Neurology

Joachim Burman

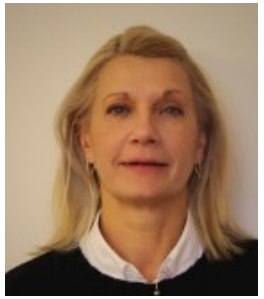
Reumatology

Gunnel Nordmark

Elisabeth Skoglund

Clinical Immunology

Johan Rönnelid



Barbra Persson

Neuroradiology

David Fällmar

Autoimmunity and cerebral folate deficiency in autism spectra disorders

- Antibodies against glutathione and folate receptor-α autoantibody (FRAA) elevated in AST (>40%) linked to cerebral folate deficiency
- High dose folate (50mg) improves symptoms is AST with FRAA
- Mothers with FRAA have higher risk for children with FRAA
- Test not available yet in Sweden.

Frye, Front. Neurosci., 09 March 2016 , J Pers Med. 2021 Aug; 11(8): 710.

WMA DECLARATION OF HELSINKI

- **Unproven Interventions in Clinical Practice**
- 37. In the treatment of an individual patient, where proven interventions do not exist or other known interventions have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorised representative, may use an unproven intervention if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. This intervention should subsequently be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information must be recorded and, where appropriate, made publicly available.

Behandlingsmöjligheter – Vem kan ta ansvar?

- Diet
- Antibiotika
- NSAIDs (anti-inflamatoriska)
- Steroider
- IVIG (i.v. immunoglobuliner)
- Plasmafores, cytostatika och Immunoterapi

Stor motstånd:

- “Dessa behandlingar ingår inte i vårt uppdrag eller budget”
- “Det saknas evidens” –> Men patienterna har redan provat evidence baserad terapi utan att det hjälper.
- “Vi kan inte ta ansvar för en behandling där vi inte kan utvärdera symptom och behandlingssvar”

Optimera psykiatriska läkemedel -> Många psykiatriska behandlingar har immunologisk påverkan

KBT, SSRIs, Anti-histaminer, Melatonin, (benzodiazipiner), ECT, Lithium, Clozapine..

Problems to solve

- We need to rework our definition of psychiatric disease to incorporate new knowledge and multidisciplinary collaborations

“The symptoms are not attributable to another medical condition”

- Incorrect interpretation of “evidence-based medicine”
- Less and less resources for the most severe patients
- Increasing division of clinic and research creates huge bias in the data
- Underfunding of psychiatric and transdiagnostic research
- The enormous burden on relatives – patients are outside many support systems – parents alone in trying to navigate impenetrable medical care

What can we do?

- Recognize red flags, atypical trajectories, neurological soft signs and signs of excited catatonia.
- Complete history (inclusive family history, trajectory, specific questions about rheumatological symptoms, infections, extended examination)
- Treat mental health symptoms
- Treat ongoing verified infections (in some cases prophylactically)
- Treat a suspected inflammation. However, note that if clinical work-up reveals significant CNS inflammation, differential diagnoses should be considered and expanded diagnostic work-up.
- *Practice humility. There is so much we still don't understand.*

Uppsala Immunopsykiatri

UPPSALA UNIVERSITET

AKADEMISKA SJUKHUSET

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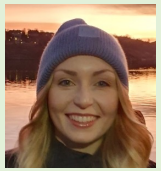

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M och N Nasvells stiftelse

BBW Bissen Brainwalk
Till förmån för forskningen som räddade mitt liv

Svenska Läkaresällskapet

ÅKE WIBERGS STIFTELSE

EKHAGASTIFTELSEN

Vetenskapsrådet

UCR UPPSALA CLINICAL RESEARCH CENTER

Uppsala Biobank

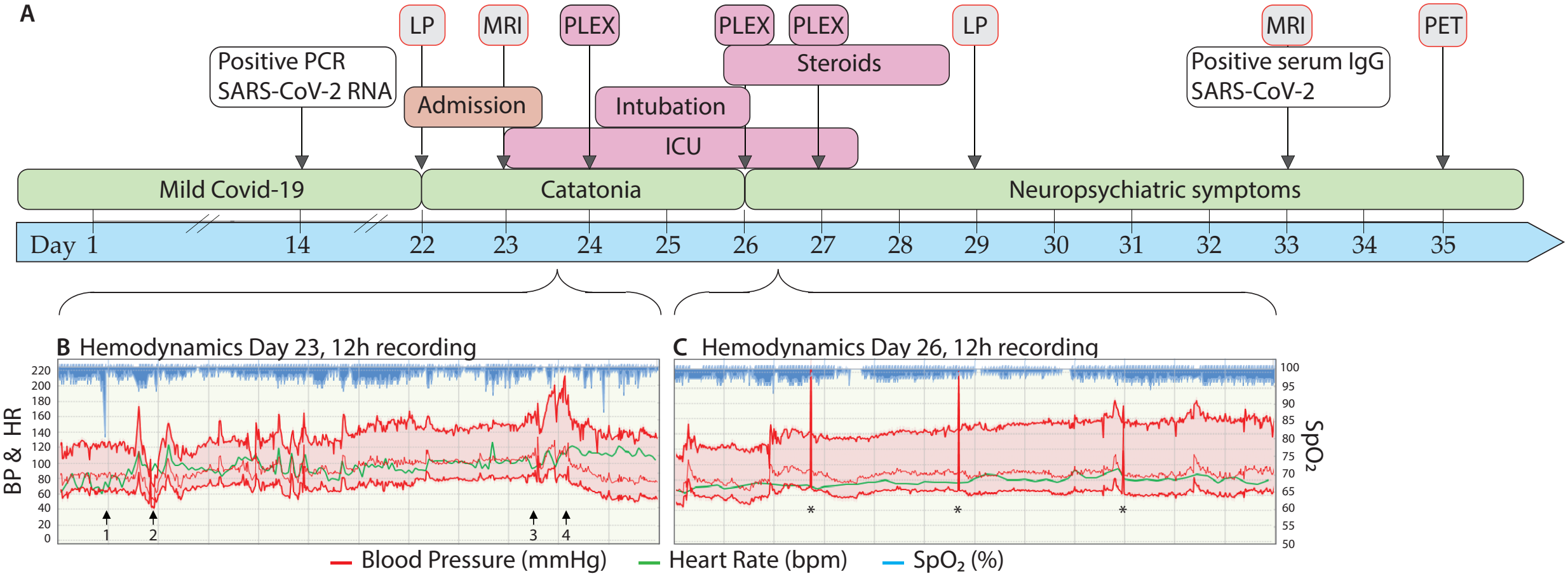
SciLifeLab

NBIS

EU resurser

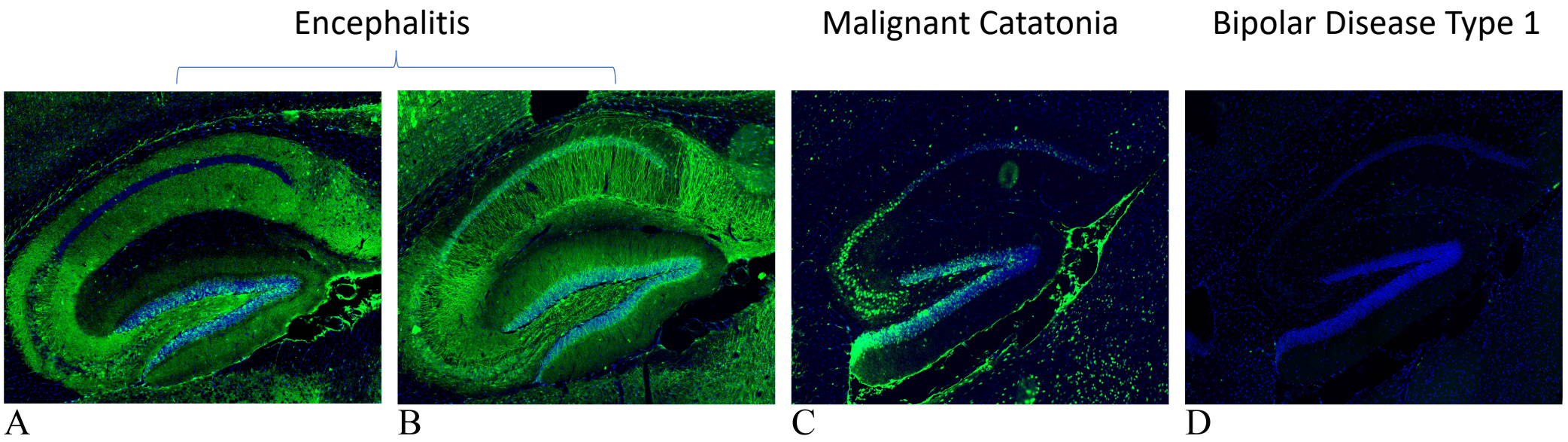
- https://www.ecnp.eu/research-innovation/ECNP-networks/List-ECNP-Networks/Immuno-NeuroPsychiatry
- https://www.expand.care/
- Guidelines för “autoimmune OCD” https://www.nature.com/articles/s41398-021-01700-4
- Guidelines för “autoimmune psykos” https://pubmed.ncbi.nlm.nih.gov/31669058/

Autoimmune Encephalitis Presenting with Malignant Catatonia in a 40-Year-Old Male Patient with Covid-19



Mulder *et al* 2020, Am J Psychiatry, June 2021

Antibodies against hippocampus in patient CSF after COVID-19



1) Mulder et al Manuscript 2021, **2)** Mulder J, et al **,** Autoimmune Encephalitis Presenting with Malignant Catatonia in a 40-Year-Old Male Patient with Covid-19. Am J of Psychiatry, 2020, In press (in press), **3)** Virhammar J, et al Acute necrotizing encephalopathy with SARS-CoV-2 RNA confirmed in CSF. Neurology 2020;95(10):445-9.

Table 4. Preliminary criteria of possible, probable, and definite autoimmune obsessive-compulsive disorders suggested by the authors.

Possible autoimmune OCD*	**Probable autoimmune OCD***	**Definite autoimmune OCD***
(Sub)acute onset of OCD symptoms (< 3 months) AND/OR treatment resistance despite guideline-based therapy in combination with at least one of the following signs:	Combination of *possible autoimmune OCD* AND	*Probable autoimmune OCD* (suspected clinical and diagnostic findings) AND
• Atypical age of onset (early childhood or later adulthood)	at least two suspicious alterations in diagnostic investigations:	• Evidence for IgG neuronal antibodies in CSF and/or
• Atypical presentation of obsessive-compulsive symptoms (e.g., combination with severe hypersomnia or loss of function due to disproportionate cognitive deficits)	• Serum: Neuronal autoantibodies, "potentially neuronal" antibodies (e.g., ANAs against dsDNA), streptococcal antibodies	• Successful immunotherapy
• Accompanying neurological signs (movement disorder, focal neurological deficits, new seizures or headache)	• EEG: Signs of encephalopathy such as spike-wave activity or intermittent slowing	
• Autonomic dysfunction	• MRI: Basal ganglia/mesiotemporal hyperintensities, inflammatory lesions	
• Adverse response to antipsychotics (malignant neuroleptic syndrome)	• FDG-PET: Encephalitic patterns with disturbed metabolism in basal-ganglia, cortical or in temporal regions	
• Association of OCD onset with infections	• CSF: CSF-pleocytosis, CSF-specific oligoclonal bands, detection of (neuronal) autoantibodies, increased antibody indices	
• Comorbid autoimmune diseases (with potential brain involvement)		
• Comorbid malignancies		

ANA antinuclear antibodies, *OCD* obsessive-compulsive disorder, *dsDNA* double strand deoxyribonucleic acid, *EEG* electroencephalography, *MRI* magnetic resonance imaging, *FDG-PET* [18F]fluorodeoxyglucose positron emission tomography, *CSF* cerebrospinal fluid, *IgG* immunoglobulin G.
The criteria are inspired by the concept of autoimmune psychosis by Pollak et al., 2020 [75]. These criteria should be evaluated and refined over time.
*Classification as possible, probable, or definite autoimmune OCD requires exclusion of more likely alternative differential diagnoses (e.g., infectious, metabolic, toxic, "syndromal genetic" forms).

Endres 2022, Translational Psychiatry

Rituximab

Risk of depression in multiple sclerosis across disease-modifying therapies - PMC (nih.gov)

	Model 1 [a]	**Model 2** [a]	**Model 3** [a]
	HR (95% CI)	**HR (95% CI)**	**HR (95% CI)**
Interferons	Ref.	Ref.	Ref.
Dimethyl fumarate	0.80 (0.60–1.06)	0.79 (0.59–1.05)	0.85 (0.62–1.15)
Fingolimod	0.74 (0.51–1.09)	0.75 (0.51–1.11)	0.75 (0.50–1.14)
Glatiramer acetate	1.11 (0.77–1.61)	1.12 (0.77–1.61)	0.79 (0.52–1.19)
Natalizumab	1.13 (0.88–1.47)	1.12 (0.87–1.45)	0.97 (0.73–1.28)
Rituximab	0.78 (0.61–1.00)	**0.77 (0.60–0.99)***	**0.72 (0.54–0.96)****

Longinetti et al., Mult Scler. 2022 Apr; 28(4): 632–641.
Published online 2021 Jul 15. doi: 10.1177/1352458521031128

Possible autoimmune psychosis

The patient must have current psychotic symptoms of abrupt onset (rapid progression of <3 months) with at least one of the following:

- Currently or recently diagnosed with a tumour
- Movement disorder (catatonia or dyskinesia)
- Adverse response to antipsychotics, raising suspicion of neuroleptic malignant syndrome (rigidity, hyperthermia, or raised creatine kinase)
- Severe or disproportionate cognitive dysfunction
- A decreased level of consciousness
- The occurrence of seizures that are not explained by a previously known seizure disorder
- A clinically significant autonomic dysfunction (abnormal or unexpectedly fluctuant blood pressure, temperature, or heart rate)

Pollak et al, Lancet Psychiatry 2020;7: 93–108

For a diagnosis of probable autoimmune psychosis:

After exclusion of alternative diagnoses...

Current psychotic symptoms of abrupt onset (rapid progression of <3 months) with at least one of the seven clinical criteria listed above for possible

autoimmune psychosis and

at least one of the following:

- CSF pleocytosis of >5 white blood cells per µL
- Bilateral brain abnormalities on T2-weighted fluid-attenuated inversion recovery MRI highly restricted to the medial temporal lobes

Or **two** of the following:

- Electroencephalogram encephalopathic changes (ie, spikes, spike-wave activity, or rhythmic slowing [intermittent rhythmic delta or theta activity] focal changes, or *extreme delta brush* (har aldrig sett hos patient med bara psykiatrisk presentation)
- CSF oligoclonal bands or increased IgG index
- serum anti-neuronal antibody detected by cell-based assay

For a diagnosis of definite autoimmune psychosis: + IgG class anti-neuronal antibodies in CSF.

Pollak et al, Lancet Psychiatry 2020;7: 93–108