28th Annual OCD Conference
San Francisco, CA

July 9, 2023

Craig Shimasaki, PhD, MBA
CEO, Co-founder Moleculera Labs
Adjunct Professor, University of Oklahoma

Autoimmune OCD:
Can Infections Trigger Immune-mediated OCD?

How Can This Be Diagnosed and Treated?

Disclosure Statement

- I am CEO and Co-Founder of Moleculera Labs which performs the Cunningham Panel. Testing data discussed in this presentation will be from published peer-reviewed journal articles and current research.

Disclaimer Statement

- The content is for informational purposes only and is not intended to be medical advice for any individual medical problem, nor a substitute from a qualified healthcare provider.

Topics We Will Cover

1. Challenges Contributing to the Diagnosis and Treatment of Various Neurologic, Psychiatric and Behavioral Disorders

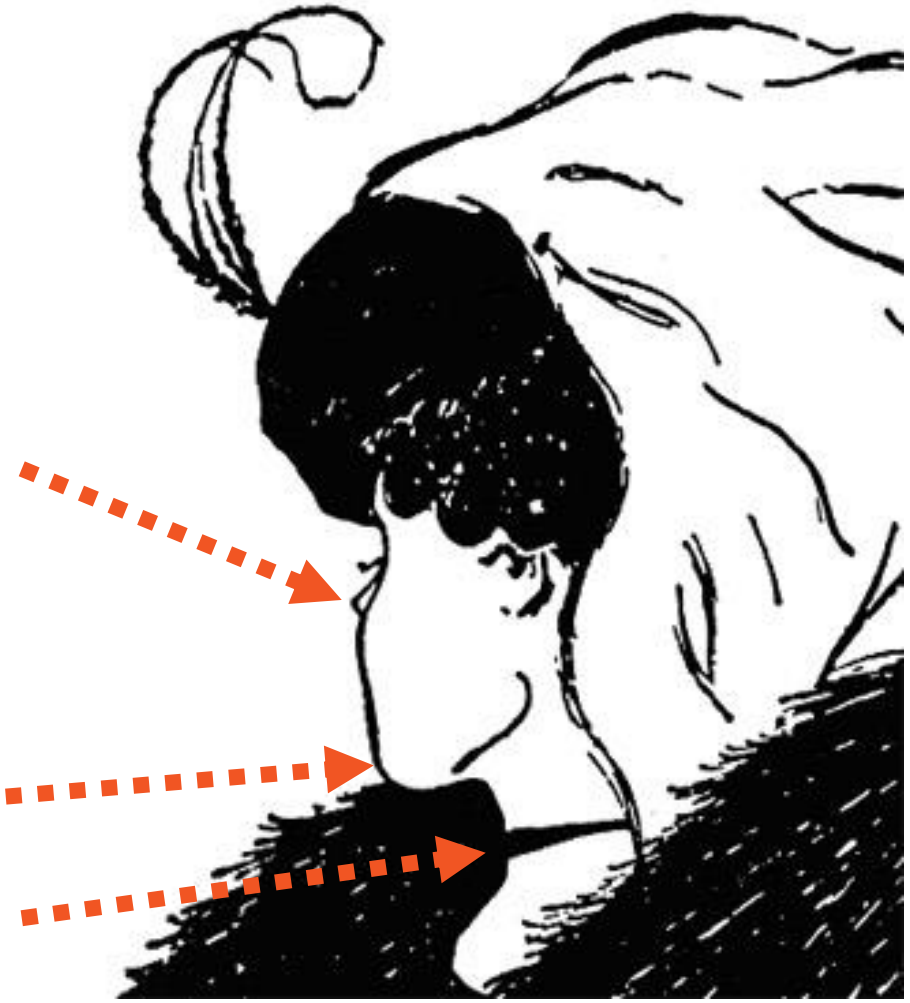
2. Can Infections Trigger Immune System Dysfunction that Leads to Certain Neurologic, Psychiatric, and Behavioral Disorders?

3. What is Molecular Mimicry and How Can this Impact our Immune System: A Medical Model for PANDAS/PANS, Neurologic Lyme, and Long-COVID?

4. Antineuronal Antibodies as an aid in a Clinician's Diagnosis and Treatment of Patients with Autoimmune Neuropsychiatric Disorders Secondary to Infections

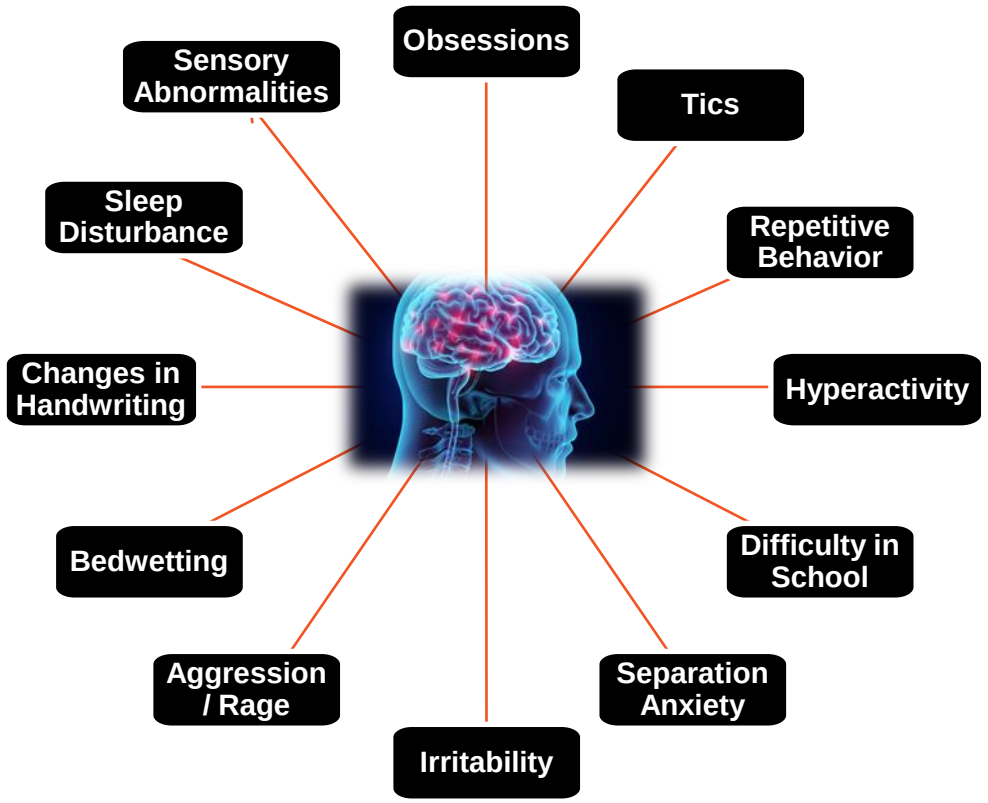
5. Therapeutic Modalities that Have Shown Clinical Effectiveness in Treating Autoimmune Neuropsychiatric Disorders Secondary to Infections

What Do You See?



Most Neurologic, Psychiatric and Behavioral Disorders are Diagnosed and Classified by Symptoms, Not Etiology (Cause)

Symptoms



Diagnoses

- *Bipolar Disorder*
- *Autism Spectrum Disorders (ASD)*
- *Tourette's Syndrome*
- *Psychosis*
- *Attention Deficient Hyperactivity Disorder (ADHD)*
- *Pediatric Autoimmune Neuropsychiatric Disorder Associated with Strep (PANDAS)*
- *Chronic Depression*
- *Obsessive Compulsive Disorder (OCD)*
- *Schizophrenia*
- *Pediatric Acute-Onset Neuropsychiatric Syndrome (PANS)*
- *Asperger's Syndrome*
- *Seizure Disorder*
- *Anxiety Disorder*
- *Seizure Disorders*
- *Epilepsy*
- *Eating Disorder*

<u>Tourette's Syndrome Criteria:</u>

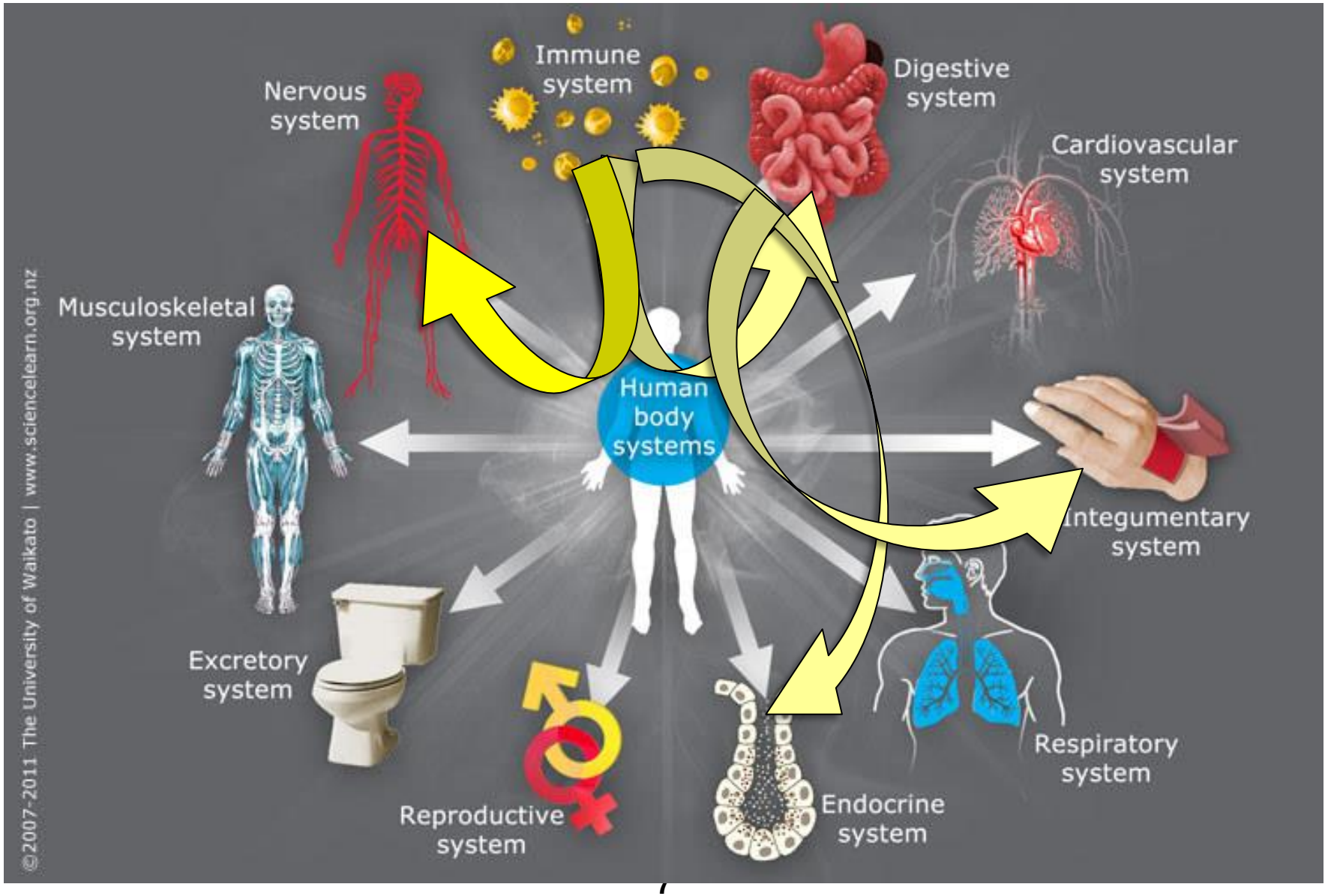
Presence of motor and vocal tics that occur several times a day, every day or intermittently for at least 1 year, begin before age 18 years

Worldwide ~800 Million Individuals* Suffer from Neurologic, Psychiatric and Behavioral Disorders

Neuropsychiatric, behavioral, and mental disorders are diagnosed entirely on clinical presentation *not biology*, yet most often are typically *treated symptomatically* with varied responses to treatment

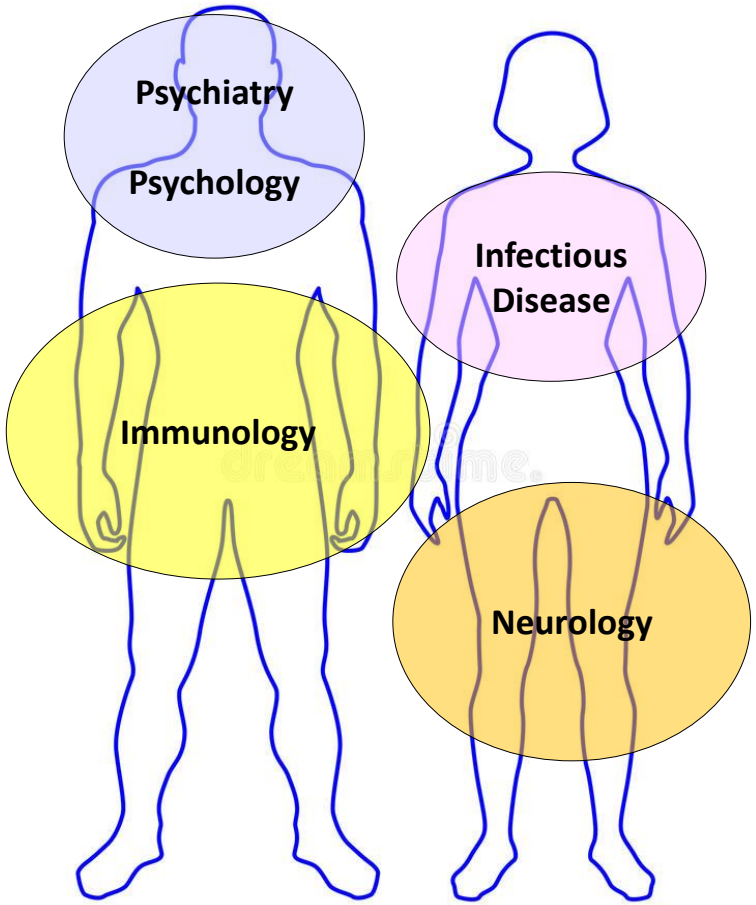
*Hannah Ritchie and Max Roser (2018) - "Mental Health". Published online at OurWorldInData.org.

Our Organ Systems Do Not Operate Independently of Each Other

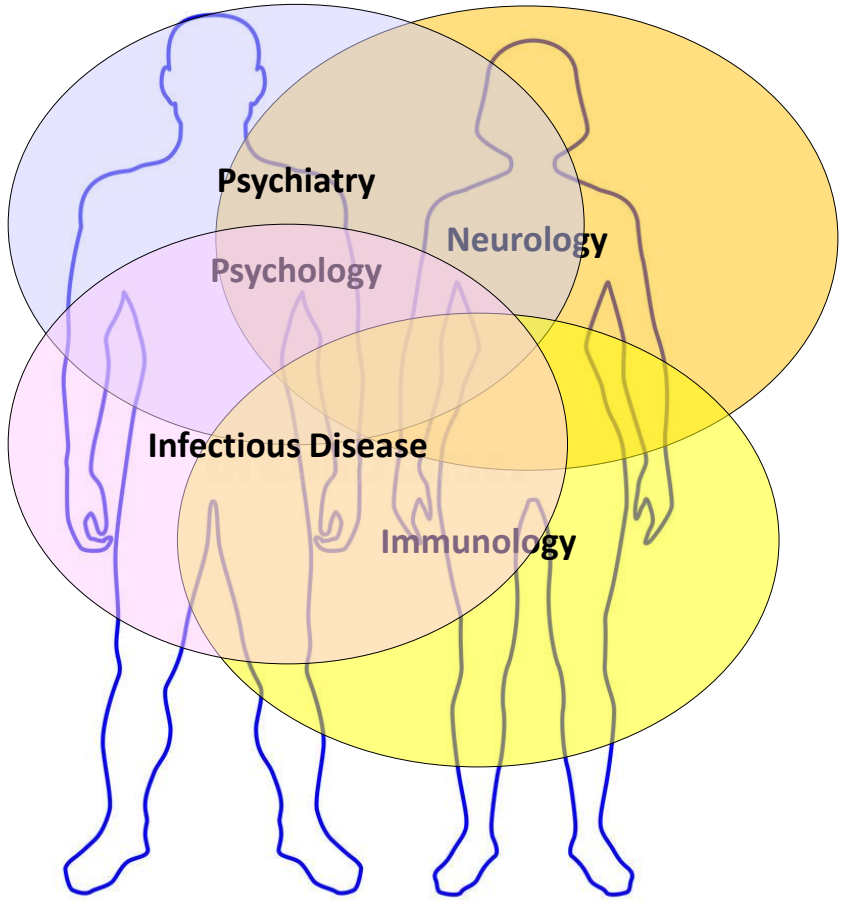


Medical Specialization Unintentionally Contributes to This Challenge

Prevaling Model of Disease Biology

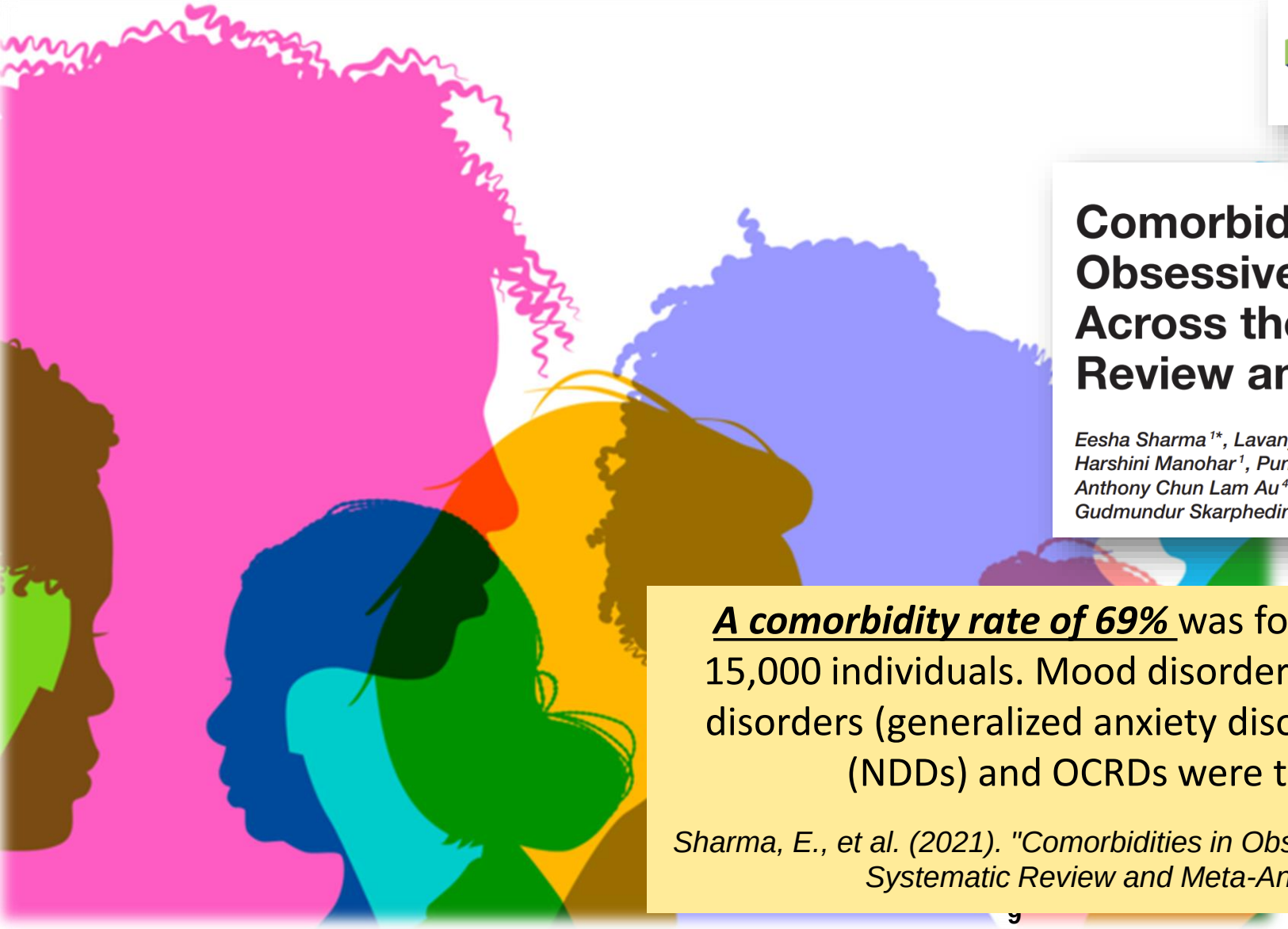


Integrated View of Disease Biology



Cross-disciplinary and Collaborative Medical Care can Accelerate the Diagnosis and Treatment of Chronic Disorders

Comorbidities in Patients with OCD



frontiers in Psychiatry

Comorbidities in Obsessive-Compulsive Disorder Across the Lifespan: A Systematic Review and Meta-Analysis

Eesha Sharma[1], Lavanya P. Sharma[2], Srinivas Balachander[3], Boyee Lin[4], Harshini Manohar[1], Puneet Khanna[1], Cynthia Lu[4], Kabir Garg[5], Tony Lazar Thomas[1], Anthony Chun Lam Au[4], Robert R. Selles[4], Davíð R. M. A. Højgaard[6], Gudmundur Skarphedinsson[7] and S. Evelyn Stewart[4]*

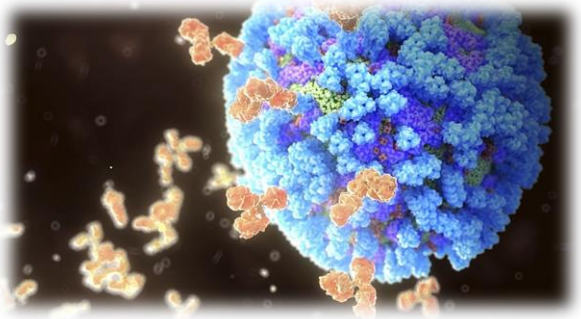
A comorbidity rate of 69% was found in a pooled sample of more than 15,000 individuals. Mood disorders (major depressive disorder), anxiety disorders (generalized anxiety disorder), neurodevelopmental disorders (NDDs) and OCRDs were the commonest comorbidities

*Sharma, E., et al. (2021). "Comorbidities in Obsessive-Compulsive Disorder Across the Lifespan: A Systematic Review and Meta-Analysis." Front Psychiatry **12**: 703701.*

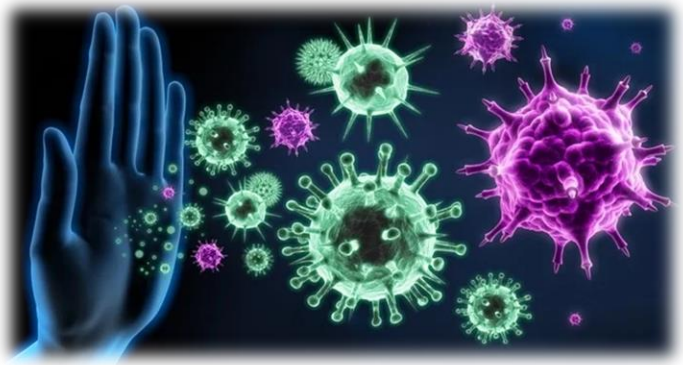
Growing Evidence of a Biological Interconnection

Brain Function
(Neurologic, psychiatric, and behavioral symptoms)

GENETIC PREDISPOSITION — **Axis** — **IMMUNE SYSTEM DYSFUNCTION**



Immune System
(autoimmune antibodies, inflammation, microglia activation, cytokines, mast cell activation)



Infectious/Non-Infectious Triggers
(bacteria, viruses, parasites, microbiome, environmental)

Challenge for Clinicians and Patients With Autoimmune Neuropsychiatric Disorders Secondary to Infections

"Never, ever, think outside the box"

Can Infections Trigger Immune System Dysfunction that Leads to Certain Neurologic, Psychiatric, and Behavioral Disorders?

Can Infections Really Trigger Neuropsychiatric Disorders?

A large portion of neuropsychiatric disorders are caused by an infection-triggered autoimmune dysfunction

March 2019

JAMA Psychiatry: "Harbingers of Mental Disease
Infections Associated With an Increased Risk for Neuropsychiatric Illness in Children"

Danish study of ***1,098,930 individuals birth to 18 year old:***

If ***hospitalized for a severe infection***, the risk of developing mental disorders ***increased by more than 80%*** for diagnosis of:

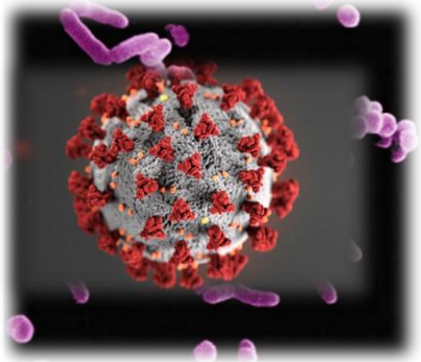
- ***Schizophrenia, autism spectrum disorder, obsessive-compulsive disorders, ADD/ADHD, personality and behavior disorders, ODD/OD and tic disorders***

"How could exposure to infections affect the brain mechanistically to give rise to mental disorders? ***Circulating autoantibodies that enter the brain*** via a compromised blood-brain barrier and ***bind to neurotransmitter receptors*** is a potential explanation, and this mechanism has been proposed in ***PANDAS and other mental disorders***."

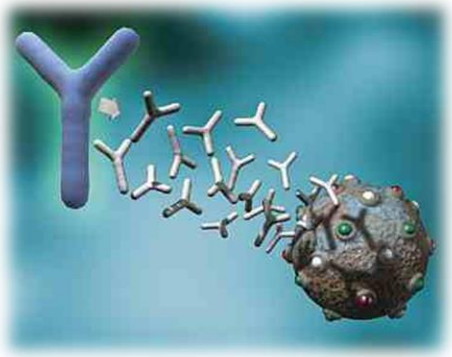
Kohler-Forsberg, O., et al. (2019) *JAMA Psychiatry, 76*(3), 271-279

How Does This Occur Biologically?

Microbial, Viral, Fungal Infection Occurs

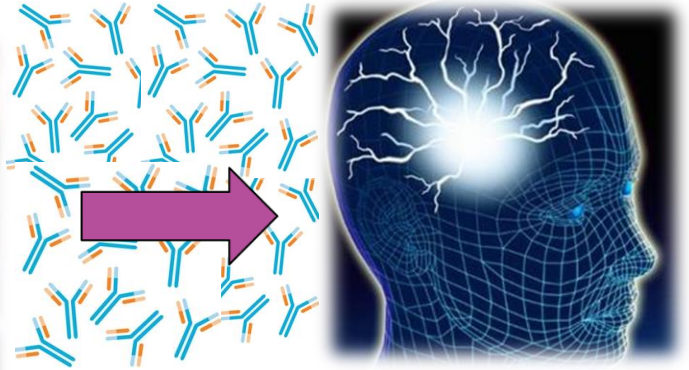


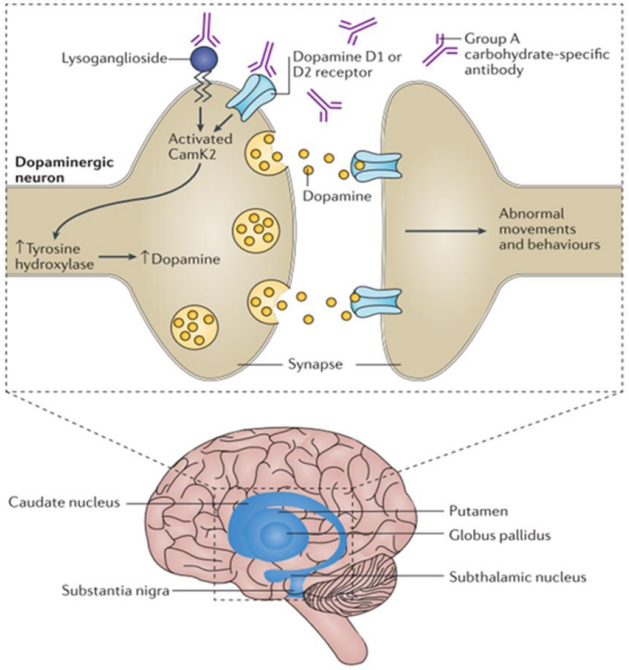
Body Produces Antibodies That Recognize Infectious organism



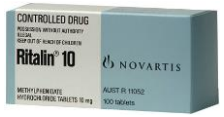
Antibodies Cross-React With Neurologic Receptors (molecular mimicry)

Reaction Disrupts Brain Function (friendly fire)





Autoimmune Neuropsychiatric Symptoms Myocarditis, Cardiovascular, Chronic Fatigue – like Syndrome, MIS-C, Long COVID/PASC



Growing Recognition of the Connection Between Infections, the Immune System and Neurologic, Psychiatric and Behavioral Disorders

Autoimmune Diseases and Psychotic Disorders

*Rose Jeppesen and Michael Eriksen Benros**

Mental Health Centre Copenhagen, Gentofte Hospital, Copenhagen University Hospital, Hellerup, Denmark

frontiers in Psychiatry

March 2019

OPEN ACCESS

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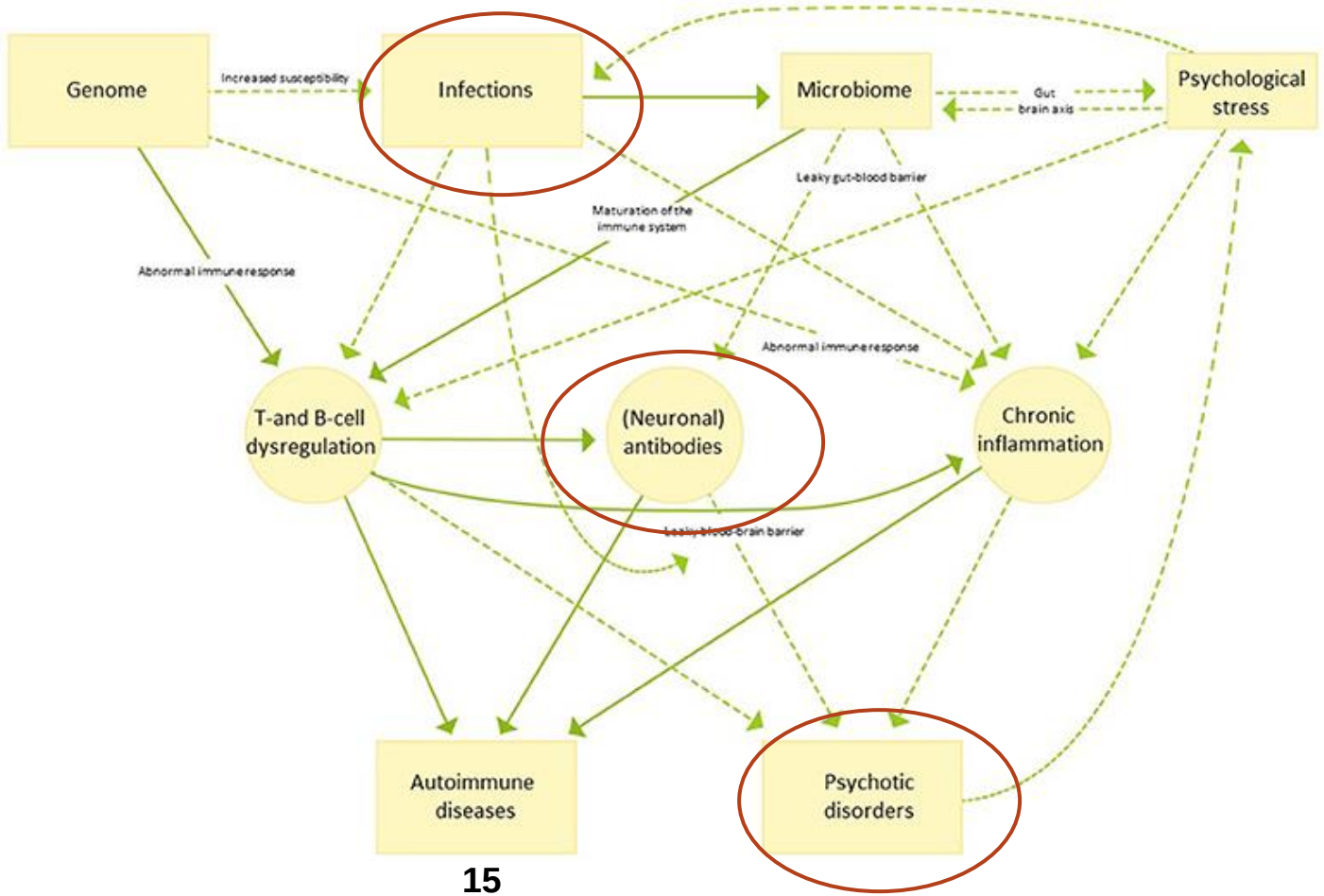
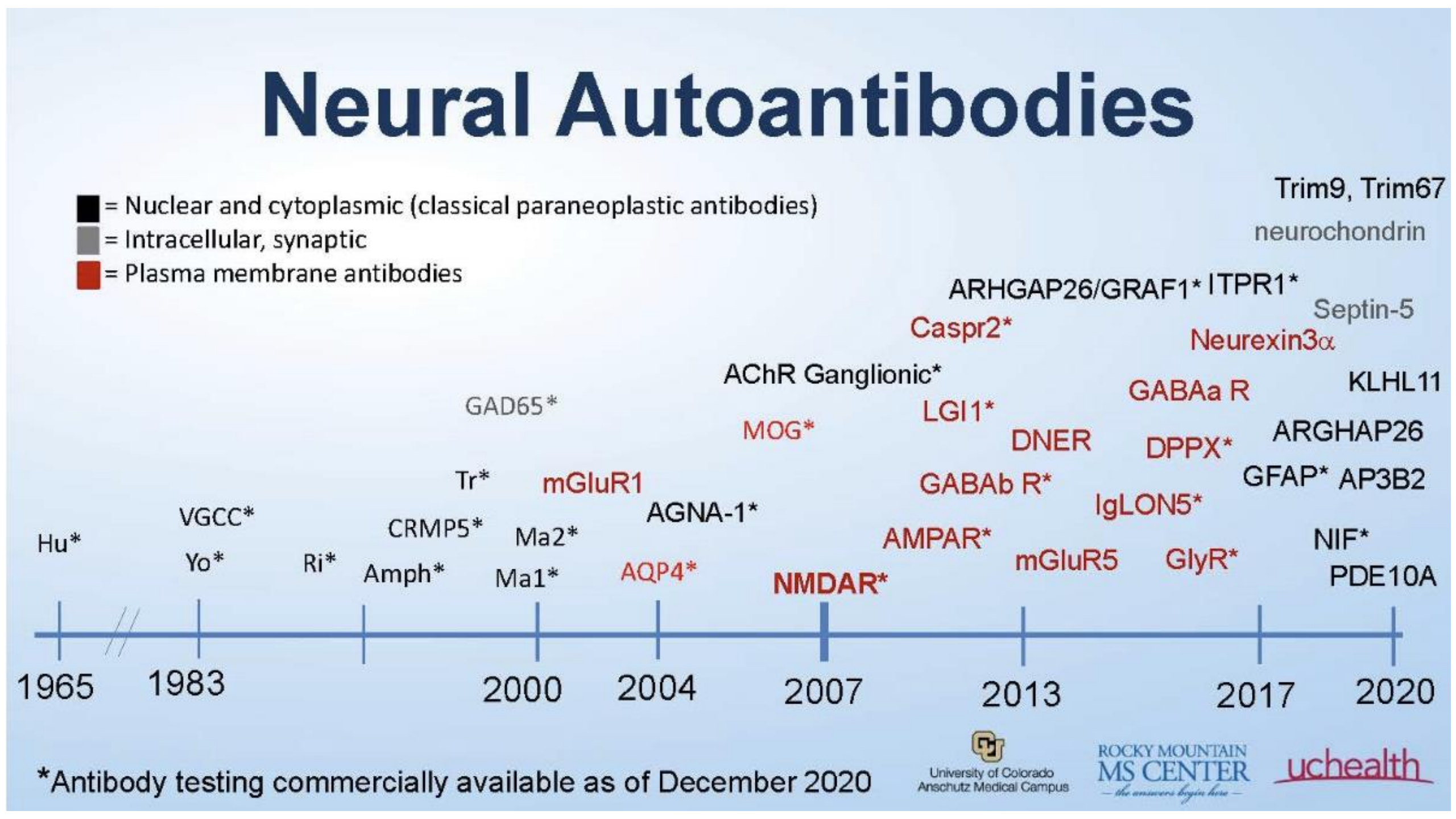


Neural Autoantibodies



*Antibody testing commercially available as of December 2020

University of Colorado Anschutz Medical Campus

ROCKY MOUNTAIN MS CENTER — the answers begin here —

uchealth

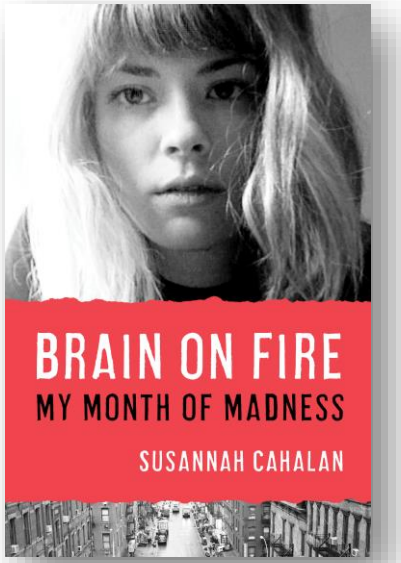
Susannah Cahalan – Brain on Fire "My Month of Madness"

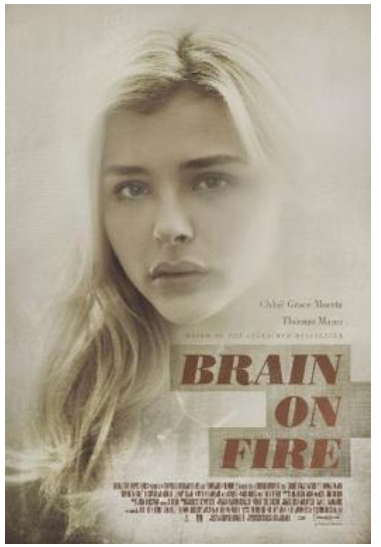
Susannah Cahalan – New York Post Journalist
Suddenly developed psychosis, violence and instability requiring hospitalization

Symptoms of Psychosis, Paranoia, Hallucinations, Seizures, Memory loss, Loss of consciousness

"Symptoms are similar to those that accompany psychotic disorders like schizophrenia and bipolar"

Anti-N-Methyl-D-Aspartate Receptor (NMDAR) Encephalitis
An infection-triggered autoimmune neuropsychiatric disorder that targets receptors in the brain





Translational Psychiatry

Denzel, D., et al. (2023). "Autoantibodies in patients with obsessive-compulsive disorder: a systematic review." Transl Psychiatry 13(1): 241.

SYSTEMATIC REVIEW OPEN

Check for updates

Autoantibodies in patients with obsessive-compulsive disorder: a systematic review

Dominik Denzel[1], Kimon Runge[1], Bernd Feige[1], Benjamin Pankratz[1], Karoline Pitsch[1], Andrea Schlump[1], Kathrin Nickel[1], Ulrich Voderholzer[1,2,3], Ludger Tebartz van Elst[1], Katharina Domschke[1], Miriam A. Schiele[1,4] and Dominique Endres[1,4]✉

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]

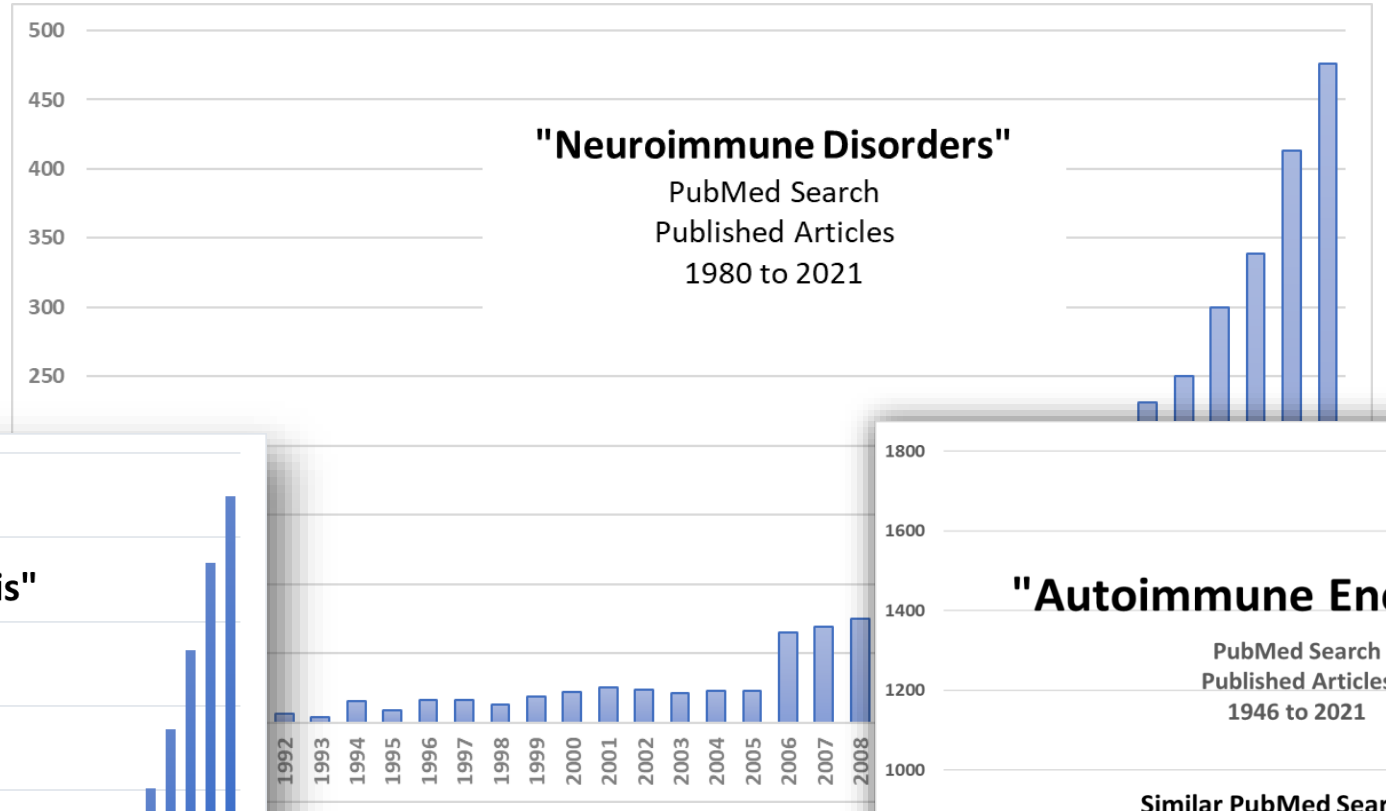
Endres, D., et al. (2022). "Immunological causes of obsessive-compulsive disorder: is it time for the concept of an "autoimmune OCD" subtype?" Transl Psychiatry 12(1): 5

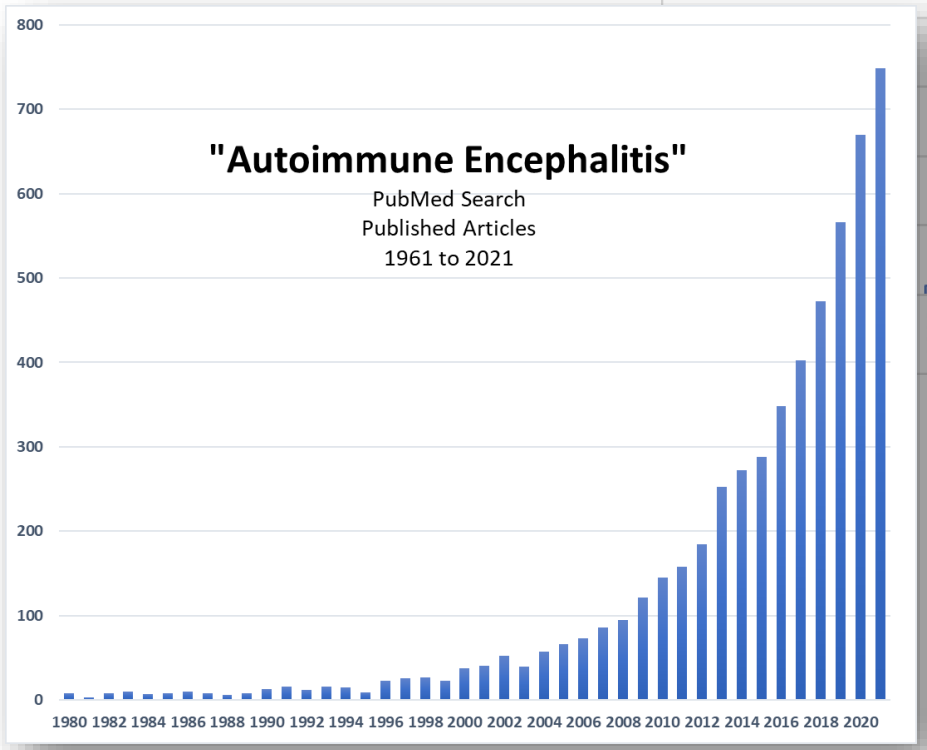
Published Peer-Reviewed Scientific and Medical Literature Precedes Standard Medical Practice and Clinical Adoption

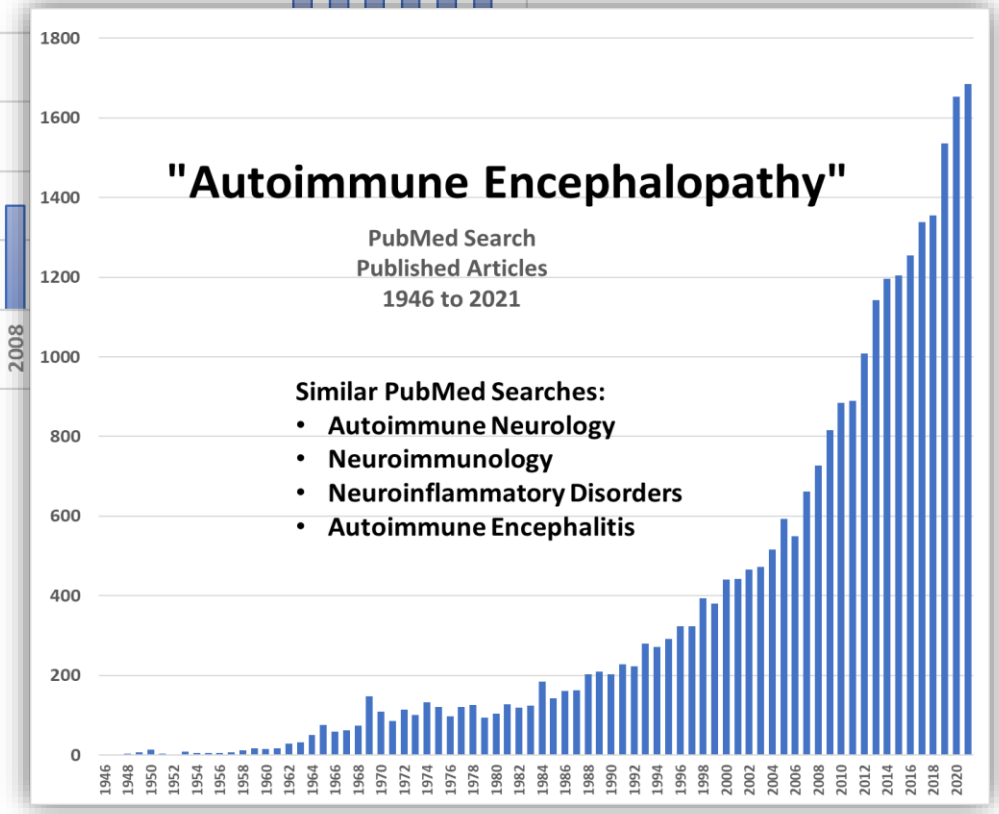
Similar publication growth

"Cancer Immunotherapy"

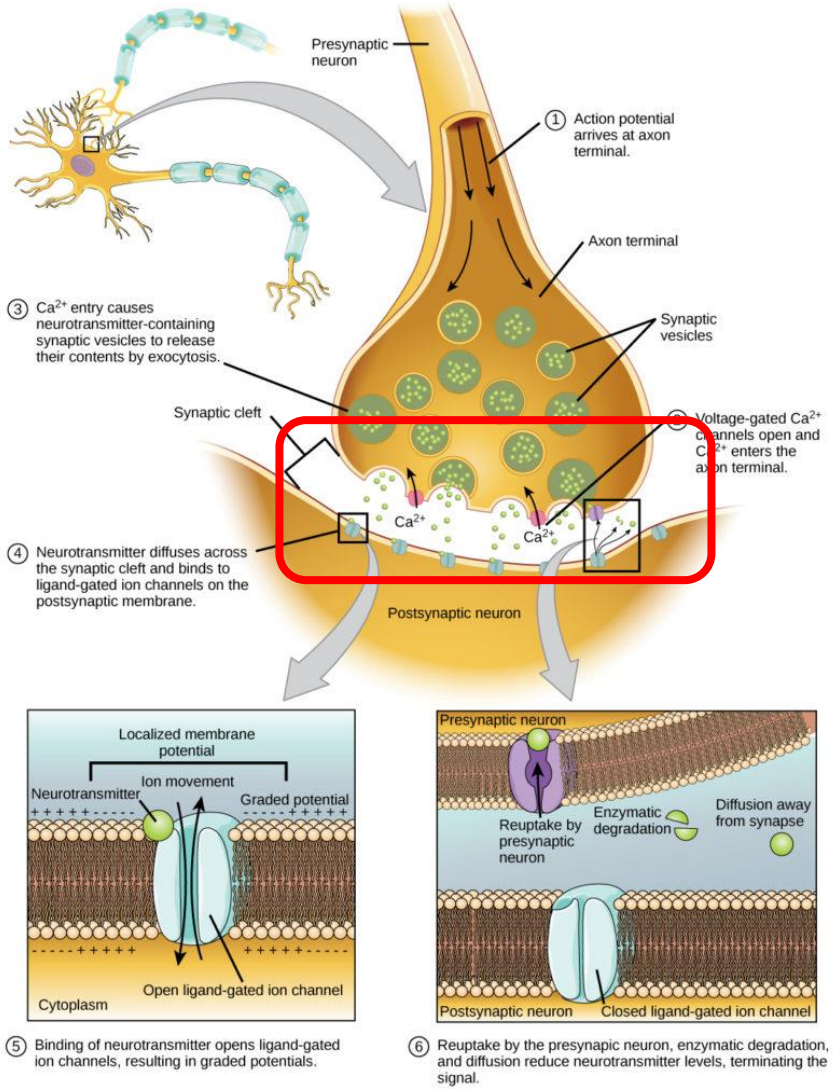
~25 years ago







General Mechanism of Many Anti-Neuronal Antibodies



https://courses.lumenlearning.com/wm-biology2/chapter/chemical-and-electrical-synapses/

frontiers in Immunology

The Role of Brain-Reactive Autoantibodies in Brain Pathology and Cognitive Impairment

*Simone Mader, Lior Brimberg and Betty Diamond**

The Feinstein Institute for Medical Research, The Center for Autoimmune, Musculoskeletal and Hematopoietic Diseases, Northwell Health System, Manhasset, NY, United States

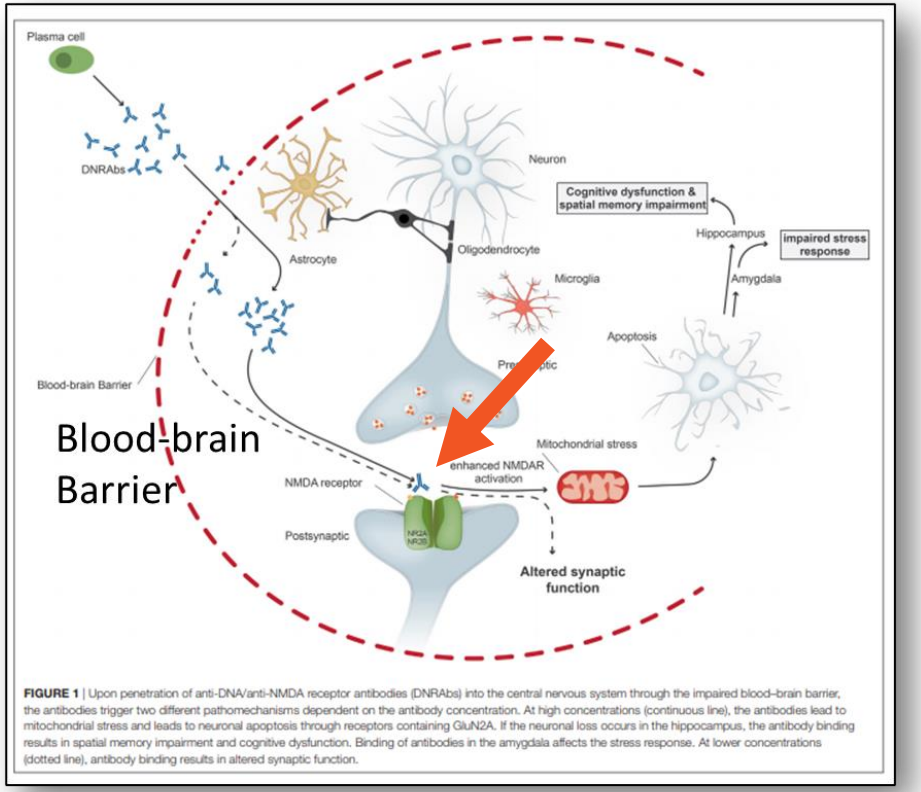
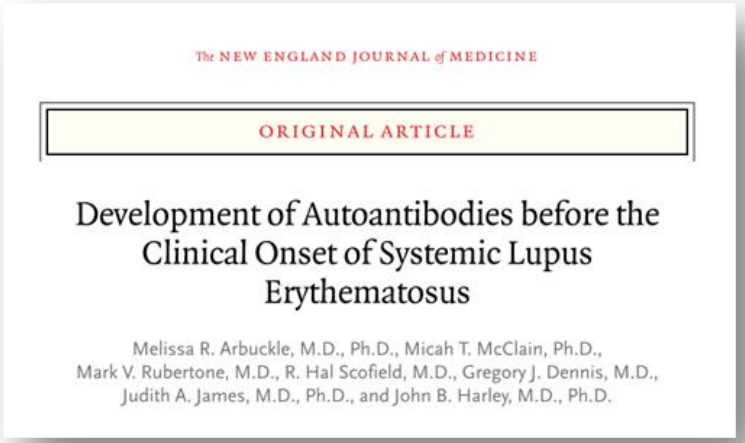


FIGURE 1 | Upon penetration of anti-DNA/anti-NMDA receptor antibodies (DNRAbs) into the central nervous system through the impaired blood–brain barrier, the antibodies trigger two different pathomechanisms dependent on the antibody concentration. At high concentrations (continuous line), the antibodies lead to mitochondrial stress and leads to neuronal apoptosis through receptors containing GluN2A. If the neuronal loss occurs in the hippocampus, the antibody binding results in spatial memory impairment and cognitive dysfunction. Binding of antibodies in the amygdala affects the stress response. At lower concentrations (dotted line), antibody binding results in altered synaptic function.

Mader, S., et al. (2017). "The Role of Brain-Reactive Autoantibodies in Brain Pathology and Cognitive Impairment." Front Immunol 8: 1101

Autoantibodies Precede Manifestation of Clinical Disease in Lupus

"Development of Autoantibodies before the Clinical Onset of Systemic Lupus Erythematosus"

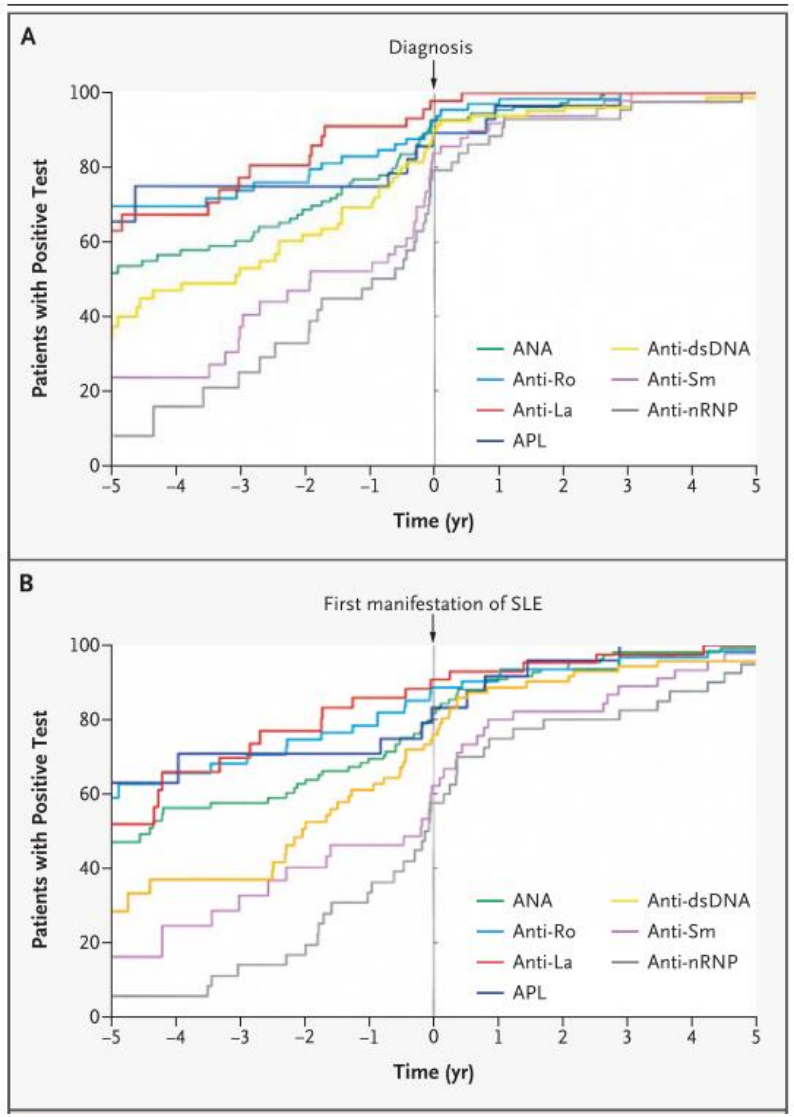


The NEW ENGLAND JOURNAL of MEDICINE

Arbuckle, M. R., et al. (2003). "Development of Autoantibodies before the Clinical Onset of Systemic Lupus Erythematosus." New England Journal of Medicine(349): 1526-1533

*"**88%** of patients (115/130) diagnosed with SLE had at least one SLE autoantibody up to 9.4 years **prior to clinical diagnosis** compared to **3.8%** (5/130) of age-matched controls"*

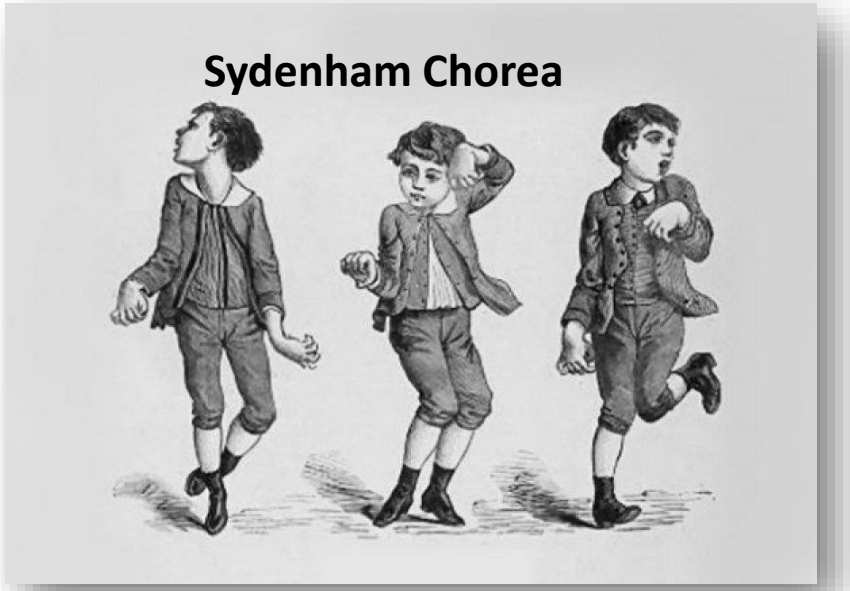
"…the appearance of autoantibodies in patients with SLE tends to follow a predictable course, with a progressive accumulation of specific autoantibodies before the onset of SLE, while patents are still asymptomatic."



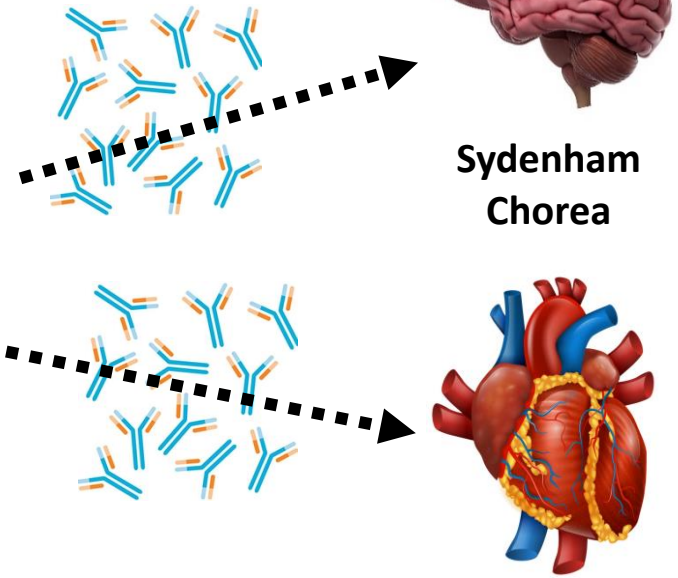
Autoimmune Neuropsychiatric Disorders Triggered by Infections are not "New"

Also known as "St. Vitus' dance"

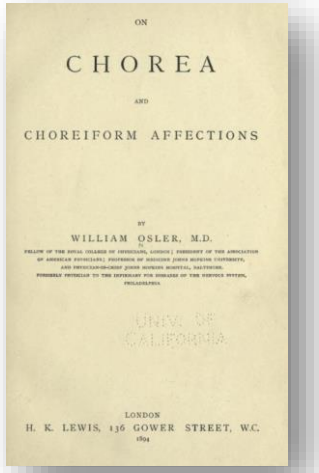
- abnormal movements
- Loss of fine-motor control
- Loss of emotional control

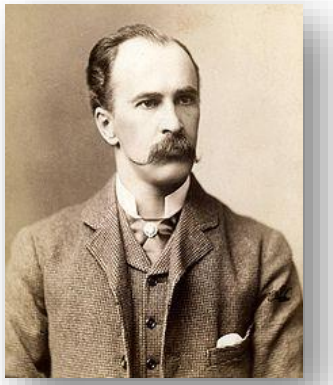


Group A Strep



In 1686, Thomas Sydenham described what he termed "chorea minor"

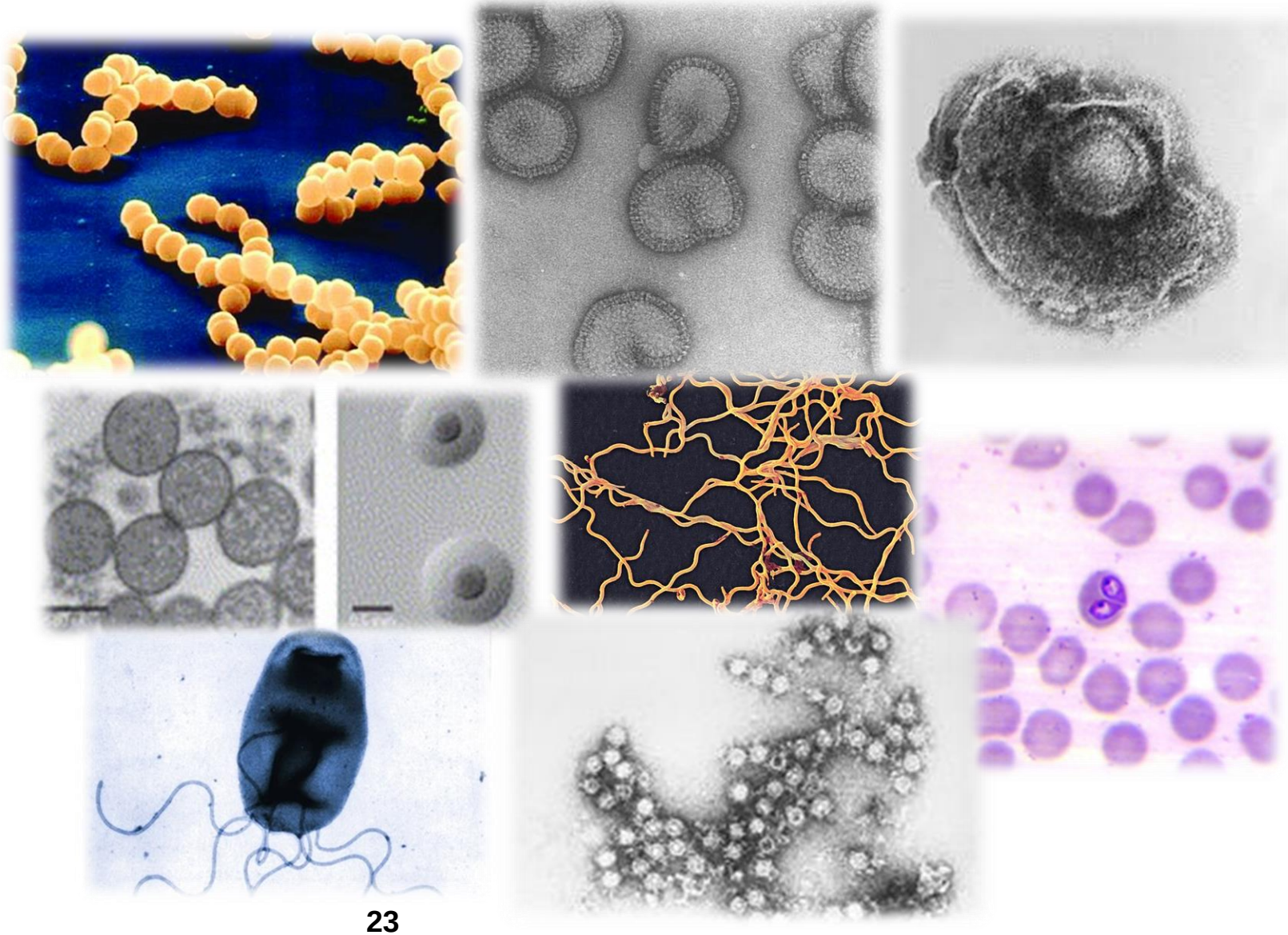




1894: Sir William Osler described ***"bizarre"*** and ***"perseverative behaviors"*** of children with ***"chorea minor,"*** obsessive-compulsive (OCD) symptoms and Sydenham's chorea (SC)

Certain Infections Are More Frequently Associated with Autoimmune Encephalopathies and Neuropsychiatric Symptoms

- Group A streptococci
- Influenza A
- Varicella (chickenpox)
- Mycoplasma
- Lyme disease
- Babesia
- Bartonella
- Coxsackie virus
- Others



COVID-19 Pandemic Impact: Cases of Strep Throat Dramatically Dropped But Resurged Post Pandemic

FIGURE 2

Percentage of Encounters for Strep Throat by Age

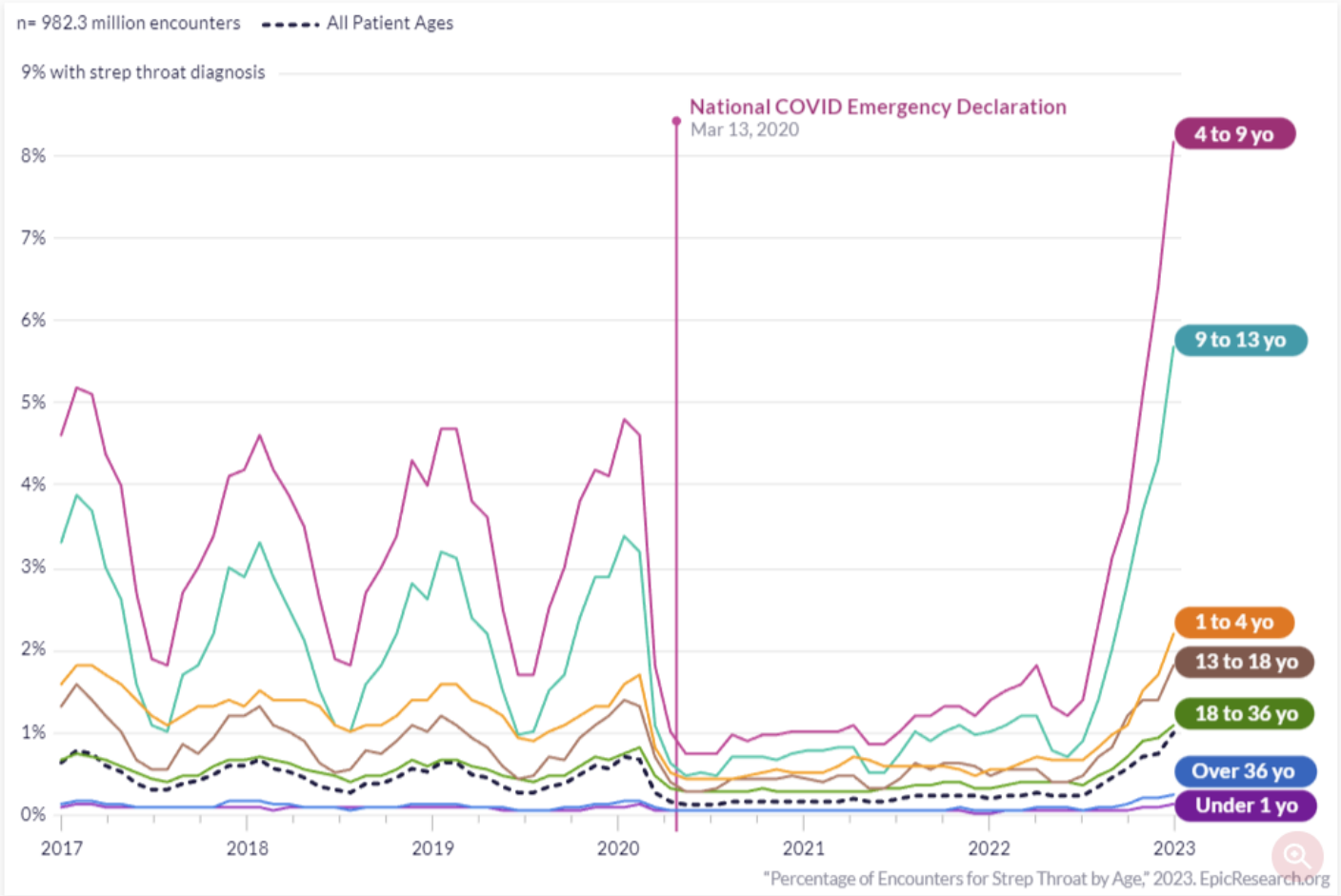


Figure 2. Percentage of office visit and emergency encounters with a strep pharyngitis or strep tonsillitis diagnosis by month from January 2017 to February 2023 stratified by age.

Epic Research

COSMOS STUDY

Strep Throat Infections Up 30% From 2017 Peak After Pandemic Drop

April 19, 2023

Dual Team Study

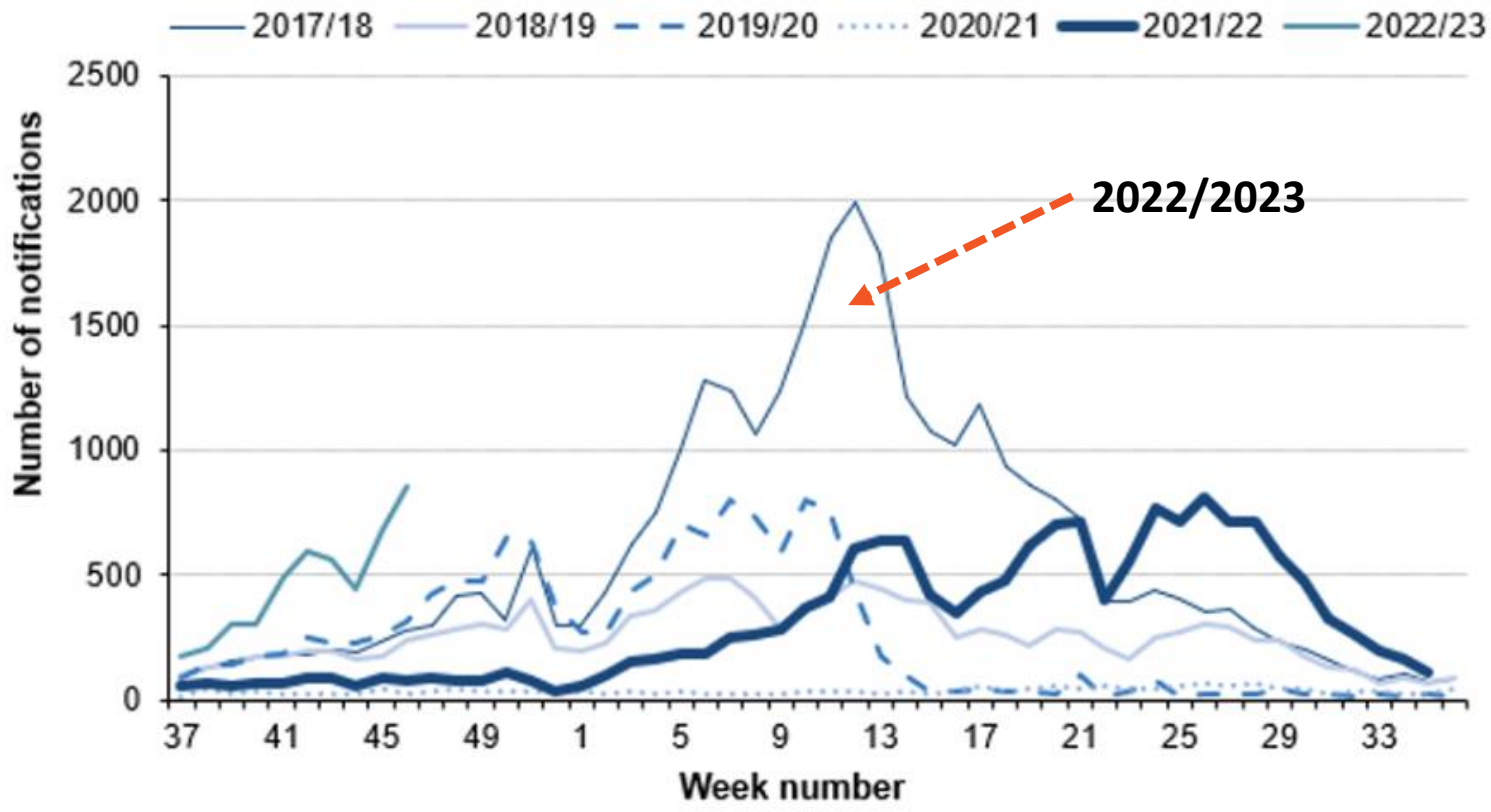
Team A: Kersten Bartelt, RN • Alex Piff

Team B: Christopher Alban, MD • Brendan Joyce

https://epicresearch.org/articles/strep-throat-infections-up-30-from-2017-peak-after-pandemic-drop

Post-COVID Emergence of Scarlet Fever in the UK

Figure 1. Weekly scarlet fever notifications in England, by season, 2017 to 2018 onwards

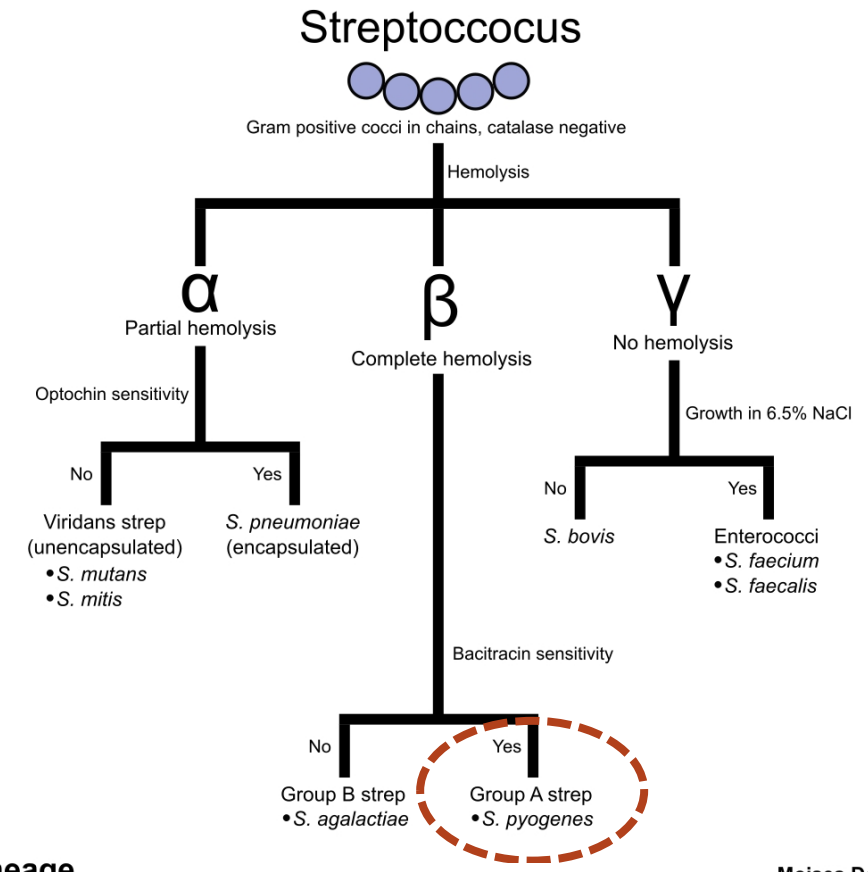


www.gov.uk/government/publications/group-a-streptococcal-infections-activity-during-the-2022-to-2023-season/group-a-streptococcal-infections-report-on-seasonal-activity-in-england-2022-to-2023#fig1

Group A Strep: S. pyogenes

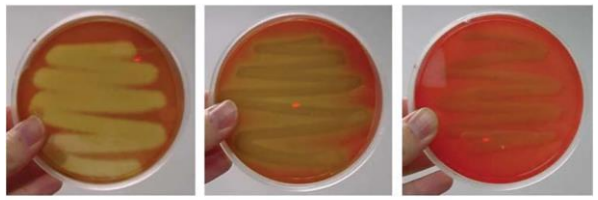
the name 'scarlet fever' came later, when British physician Thomas Sydenham labeled it febris scarlatina in 1676

Streptococcal Subtypes: Group A Strep (GAS) S. *pyogenes*



Moises Dominguez

Hemolysis of Streptococci- Types and Examples



Beta Hemolysis | Alpha Hemolysis | Gamma Hemolysis

<u>Strep is short for Streptococcus</u>, a type of bacteria. There are several types. (A, B, C, G) Two of them cause most of the strep infections in people: group A and group B

Group A strep (GAS) causes:

- Strep throat
- Scarlet fever - an illness that follows strep throat.
- Impetigo - a skin infection
- Toxic shock syndrome
- Cellulitis and necrotizing fasciitis (flesh-eating disease)

Group B strep can cause:

- blood infections, pneumonia and meningitis in newborns
- urinary tract infections
- skin infections and pneumonia in adults

What is Molecular Mimicry and How Can this Impact our Immune System: A Medical Model for PANDAS/PANS, Neurologic Lyme, and Long-COVID?

What is Molecular Mimicry? How is Our Immune System Involved?

Molecular mimicry is a process that occurs when sequence similarities between foreign and self-peptides result in the activation of self-reactive T or B cells

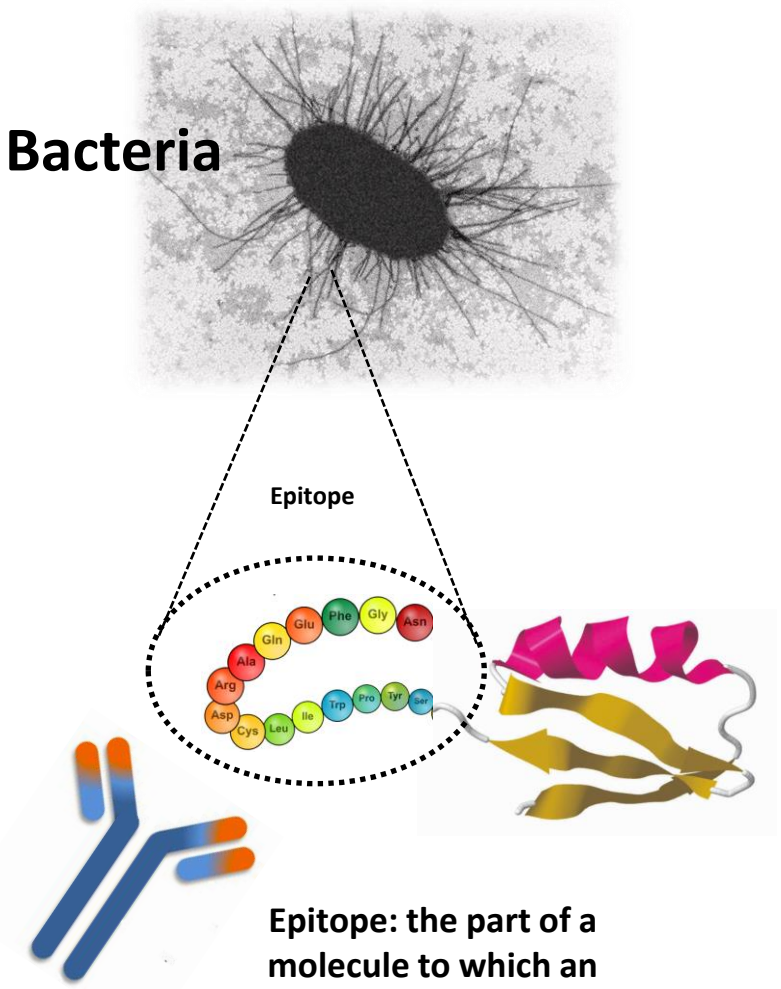
Mimicry in Nature

20 “Letters” of the Protein Alphabet

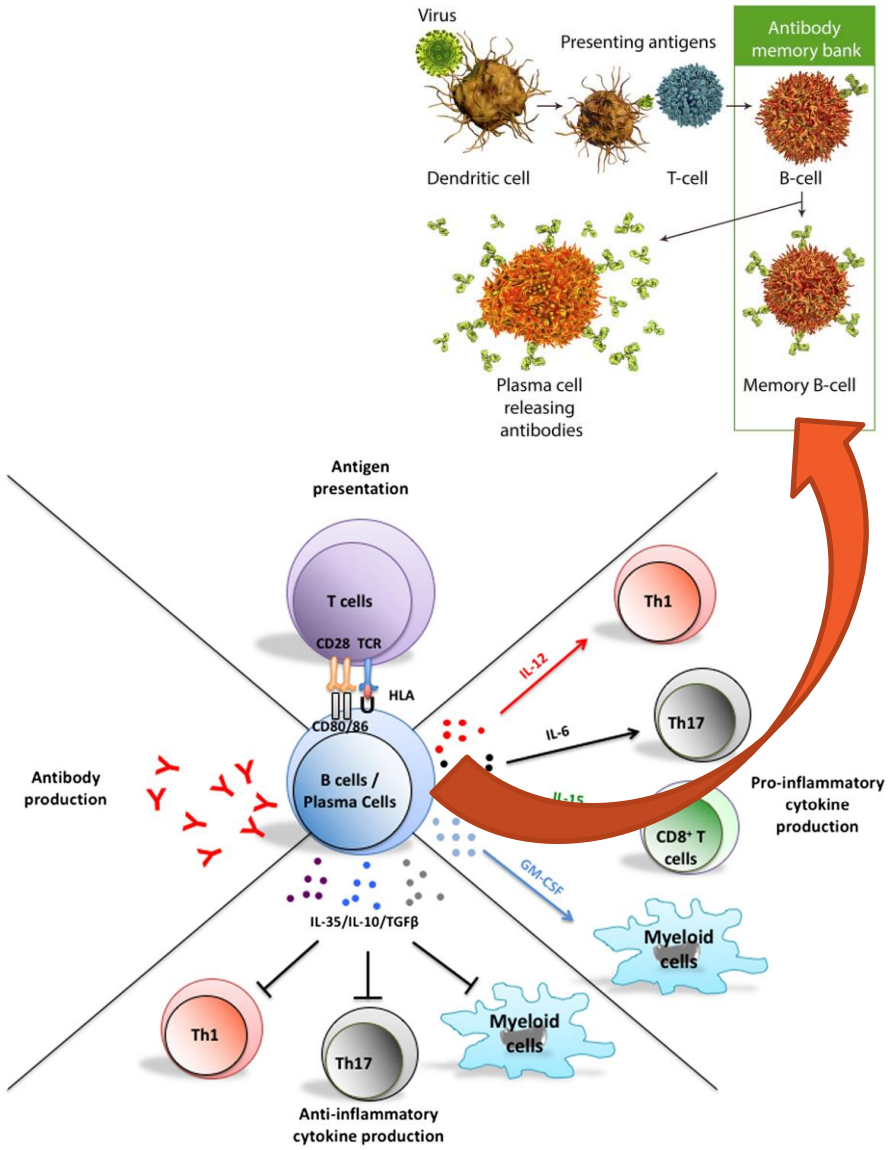
G	Glycine	Gly	**P**	Proline	Pro
A	Alanine	Ala	**V**	Valine	Val
L	Leucine	Leu	**I**	Isoleucine	Ile
M	Methionine	Met	**C**	Cysteine	Cys
F	Phenylalanine	Phe	**Y**	Tyrosine	Tyr
W	Tryptophan	Trp	**H**	Histidine	His
K	Lysine	Lys	**R**	Arginine	Arg
Q	Glutamine	Gln	**N**	Asparagine	Asn
E	Glutamic Acid	Glu	**D**	Aspartic Acid	Asp
S	Serine	Ser	**T**	Threonine	Thr

```
CAA37898.1      ----------MSTLEGRGFTE--EQEALVVKSWSAMKPNAGELGLKFFLKIFEIAPSAQ     47
P68871.2        ----------MVHLTPEEKSA-------VTALWG-KV-NVDEVGGEALGRLLVVYPWTQ     40
CAA77743.1      MHSSIVLATVLFVAIASASHTRELCMKSLEHAKVG-TSKEAKQDGIDLYKHMFEHYPAMK     59
AAA29796.1      MHSSIVLATVLFVAIASASHTRELCMKSLEHAKVG-TSKEAKQDGIDLYKHMFEHYPAMK     59
                          :  :    :             .    :. : * .   :::   *  :

CAA37898.1      KLFSFLKDSNVPL--ERNPKLKSHAMSVFLMTCESAVQLRKAGKVTVRESSLKKLGASHF    105
P68871.2        RFFESFGDLSTPDAVMGNPKVKAHGKKVLG-AFS-------DGL----AHLDNLKGTFAT     88
CAA77743.1      KYFKHRENY-TPADVQKDPFFIKQGQNILL-ACHVLCATY-DDR----ETFDAYVGELMA    112
AAA29796.1      KYFKHRENY-TPADVQKDPFFIKQGQNILL-ACHVLCATY-DDR----ETFDAYVGELMA    112
                : *.   :  .*     :* .  :. .::  :          .           *

CAA37898.1      KHGVAD-------EHFEVTKFALLETIKEAVPETWSPEMKNAWGEAYDKLVAAIKLEMKP    158
P68871.2        LSELHCDKLHVDPENFRLLGNVLVCVLAHHFGKEFTPPVQAAYQKVVAGVANALAHK---    145
CAA77743.1      RHE--RDHVKIPNDVWNHFWEHFIEFLG--SKTTLDEPTKHAWQEIGKEFSHEISHHGRH    168
AAA29796.1      RHE--RDHVKVPNDVWNHFWEHFIEFLG--SKTTLDEPTKHAWQEIGKEFSHEISHHGRH    168
                         : :.     ::  :           : *: :    .   :  .
```

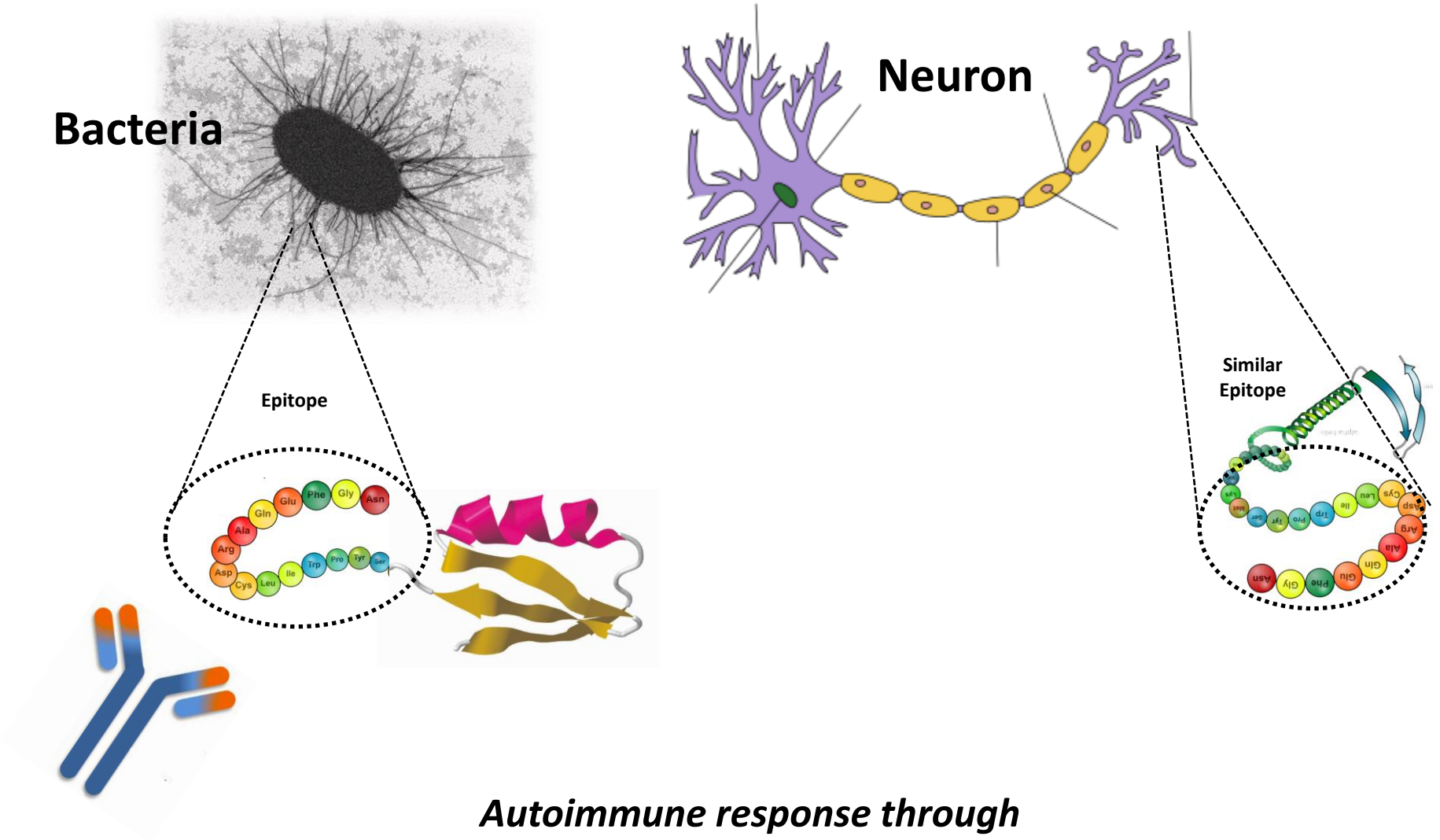
How is Our Immune System Involved: Antibodies Recognize “Epitopes” on Infectious Agents



Epitope: the part of a molecule to which an antibody attaches itself

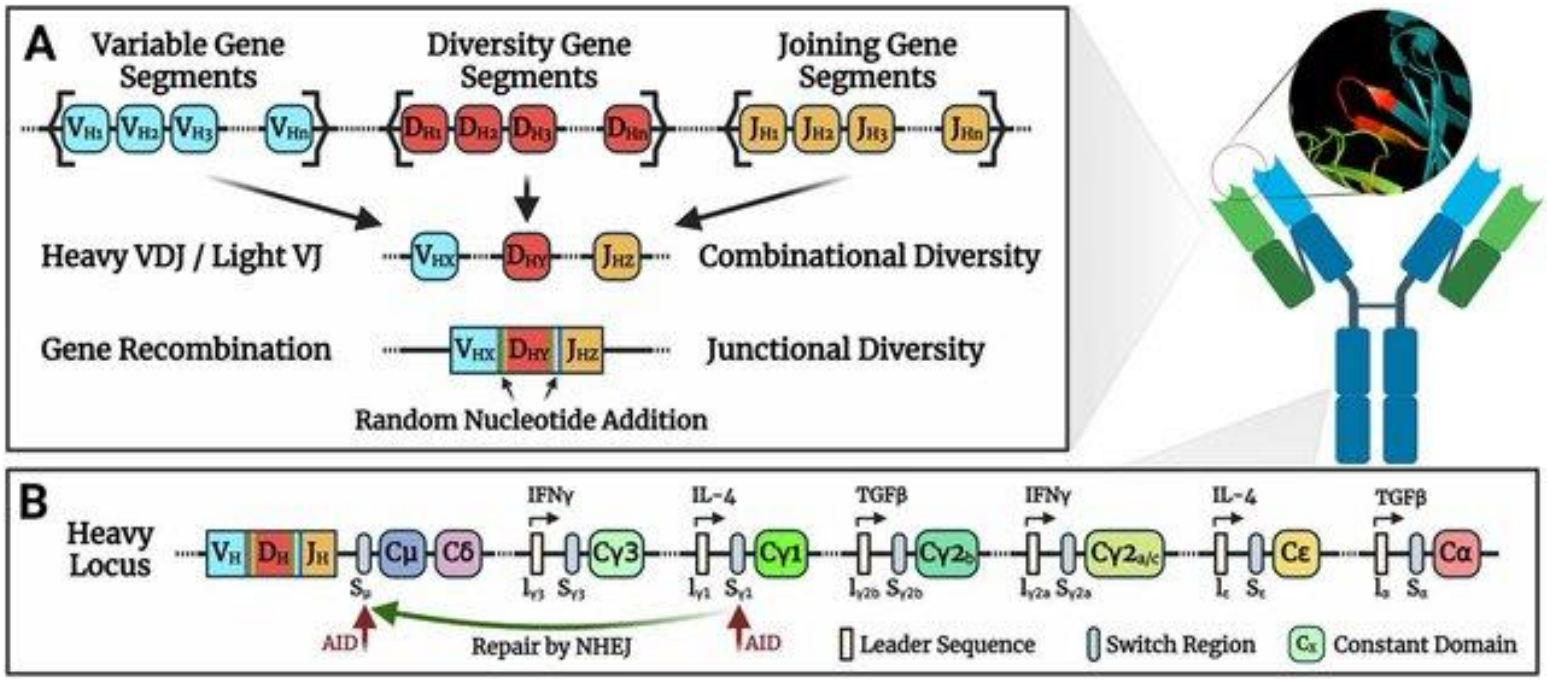


Autoimmunity Occurs when Antibodies Recognize Self Proteins as Foreign



Autoimmune response through
"Molecular Mimicry"

Our Immune System Preemptively Recognizes Over 50,000,000,000,000 (5×10^{13}) Unique Antigens



Our immune system is PREPROGRAMED to recognize ANY antigen it sees presently or in the future

Antibody diversity comes from combination of variable and constant domain gene elements. The B Cell locus is composed of multiple individual **Variable, Diversity, and Joining gene segments** which are randomly assembled into a functional gene exon through **V(D)J recombination**

This also means *self-reactive lymphocytes are generated in the process*

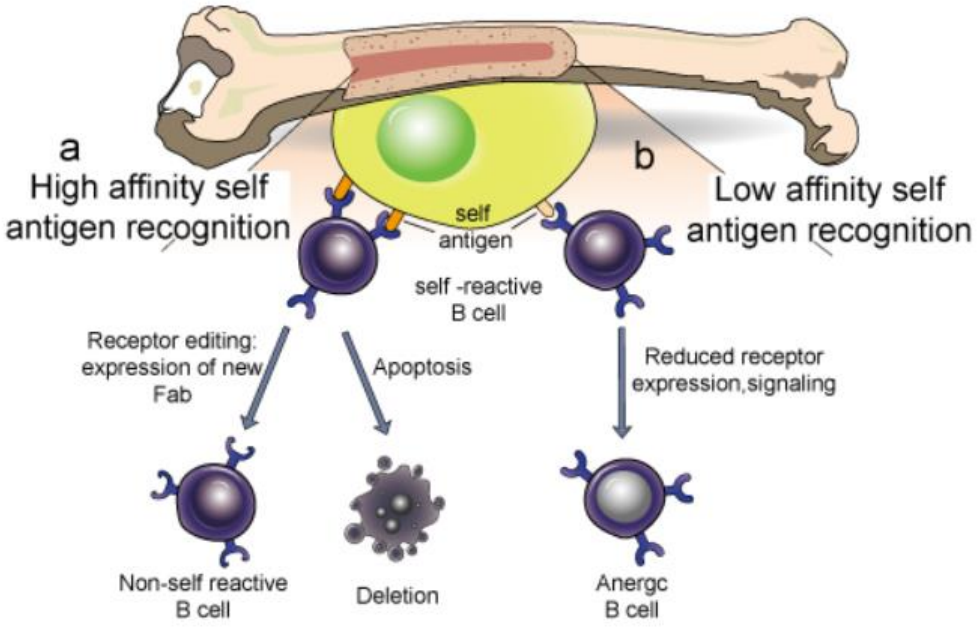
Taylor, Joshua & Hutchinson, Mark & Gearhart, Patricia & Maul, Robert. (2022). Antibodies in action: the role of humoral immunity in the fight against atherosclerosis. Immunity & Ageing. 19. 10.1186/s12979-022-00316-6.

How Does Our Body Eliminate Self-Reactive Immune Cells?
Self/Non-Self Discrimination

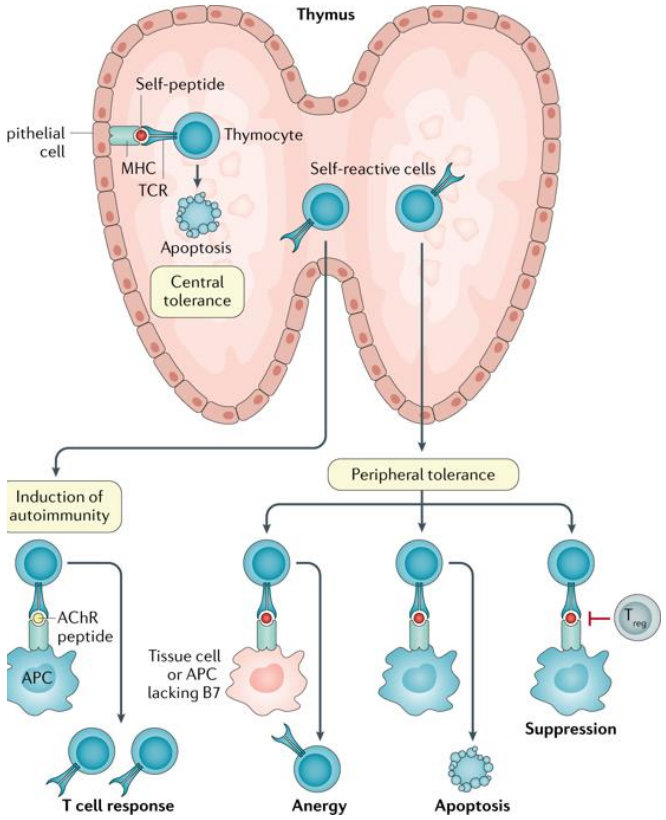
"Central Tolerance"
where most self-reactive, early lymphocytes are eliminated

"Peripheral Tolerance"
T and B cells that escape central tolerance are prevented from maturing

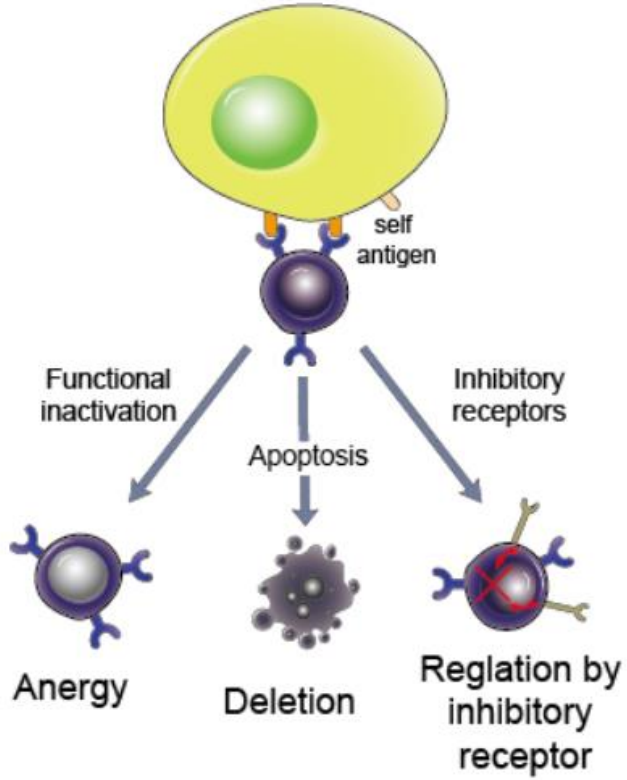
Bone Marrow



Thymus



Spleen and Lymph



https://www.creative-diagnostics.com/Autoimmunity.htm

Autoimmunity is a Breakdown of Self/Non-Self Discrimination

Molecular Mimicry
"Friendly Fire"

The most relevant genetic factors for autoimmune diseases located in the

- ***Major Histocompatibility Complex (MHC)*** and loci from
- ***Human Leukocyte Antigen (HLA) class I and class II***

A family history of autoimmune dysfunction is typically found in patients with immune-mediated neuropsychiatric disorders

Molecular Mimicry

- “Friendly Fire”
- Mechanism of action that is implicated in many chronic debilitating diseases
- Infections that lead to autoimmune responses with debilitating symptoms including neuropsychiatric

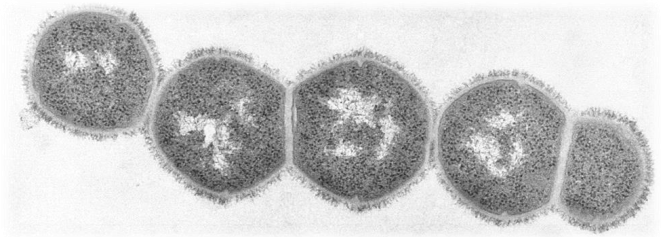
Other Autoimmune Disorders Associated with Infections through Molecular Mimicry*

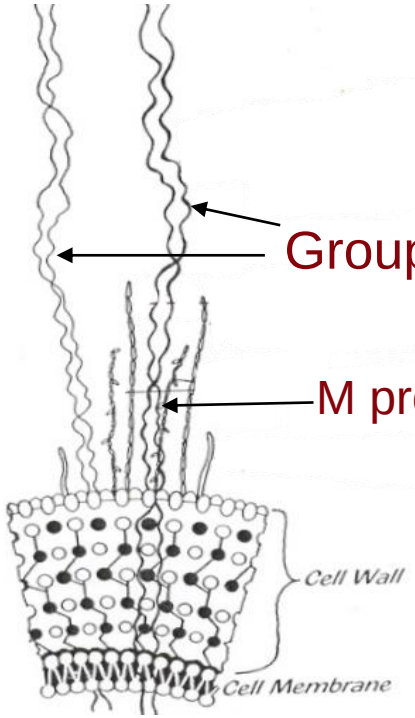
- **Guillain-Barré Syndrome**
  - Campylobacter jejuni
- **Sydenham Chorea**
  - Group A Streptococcus
- **Systemic Lupus Erythematosus (Lupus)**
  - Epstein-Barr virus (EBV nuclear antigen -1)
- **Multiple Sclerosis**
  - EBV, measles and HHV-6
- **Myasthenia Gravis**
  - Herpes Simplex Virus Type 1 (gpD)
- **Cardiomyopathy (myocarditis)**
  - Coxsackie virus, Group A Streptococcus
- **Crohn's Disease**
  - Gram-positive bacterial peptidoglycans
- **Diabetes Type 1**
  - Coxsackie B virus, rubella, herpesvirus, rotavirus
- **Psoriasis**
  - Streptococcus pyogenes (Streptococcal M Protein)

M.F. Cusick, et. al., Clin Rev Allergy Immunol. 2012 February, 42(1): 102-111

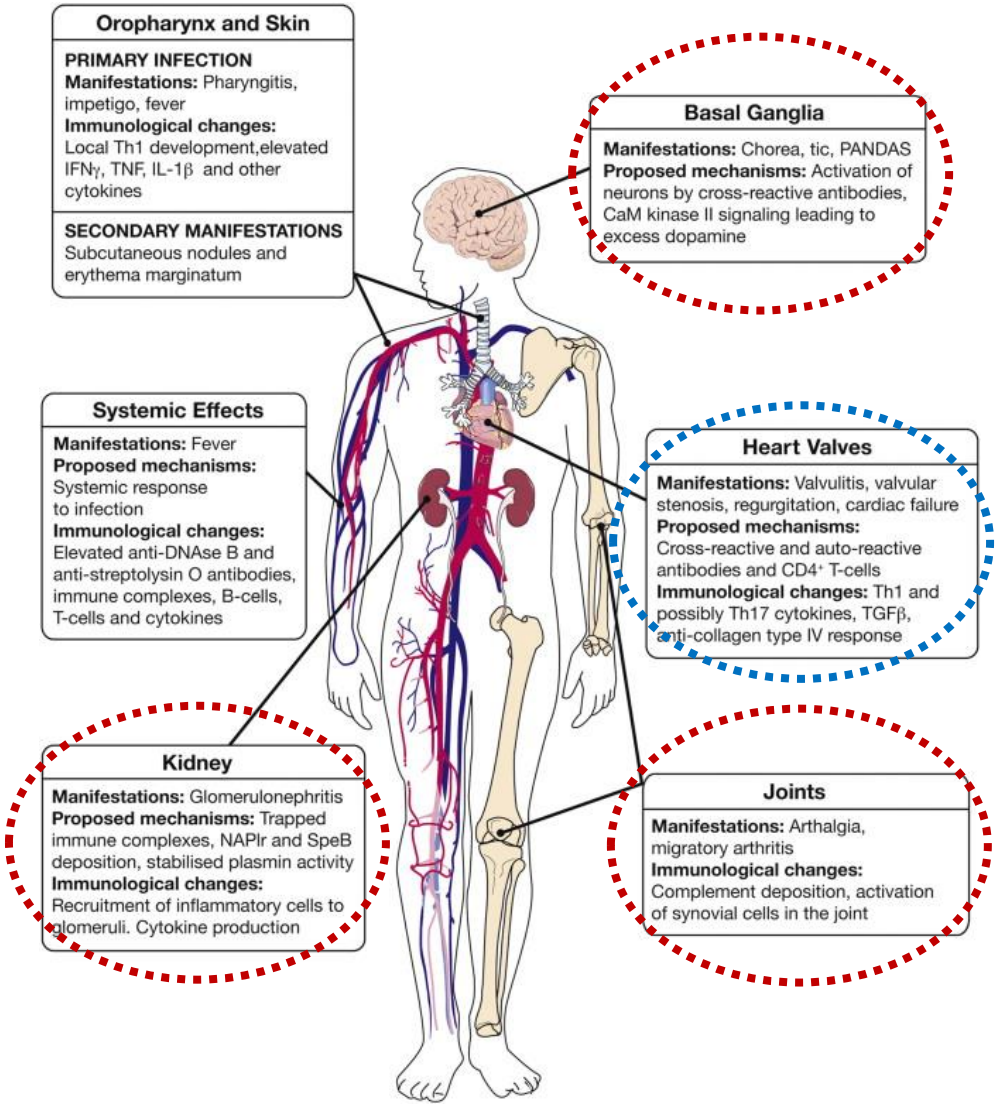
Molecular Mimicry Between Strep (Group A Strep) and Self-Antigens

Similar antigenic determinants between host and infecting microorganisms





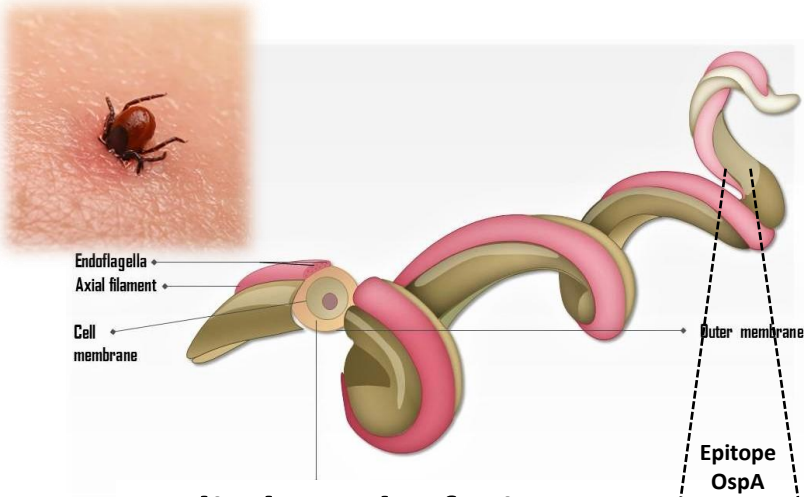
Molecular Mimicry



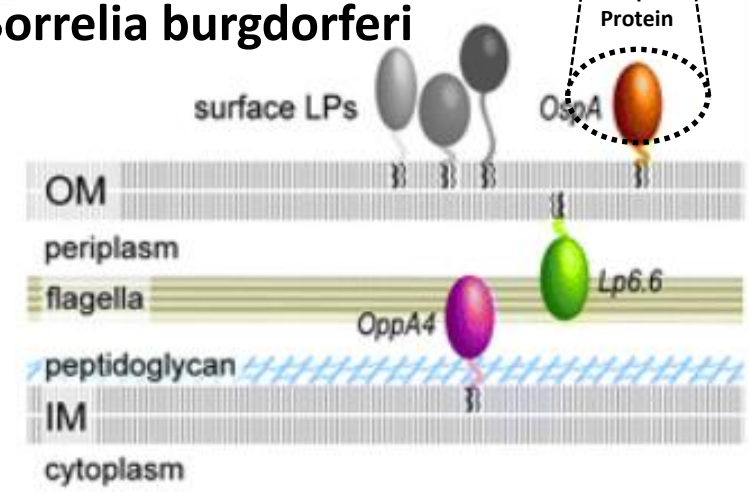
Group A Beta-Hemolytic Streptococcal Cell Wall

Martin, W. J., Steer, A. C., Smeesters, P. R., Keeble, J., Inouye, M., Carapetis, J., & Wicks, I. P. (2015). Post-infectious group A streptococcal autoimmune syndromes and the heart. Autoimmunity Reviews, 14(8), 710-725

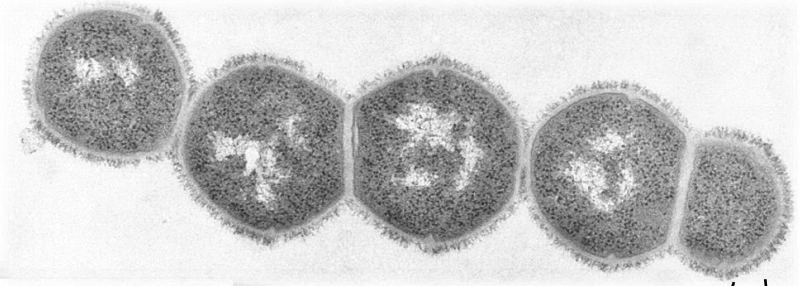
Molecular Mimicry Between *Borrelia burgdorferi* (Lyme) and Streptococcus



Borrelia burgdorferi



Streptococcus pyogenes



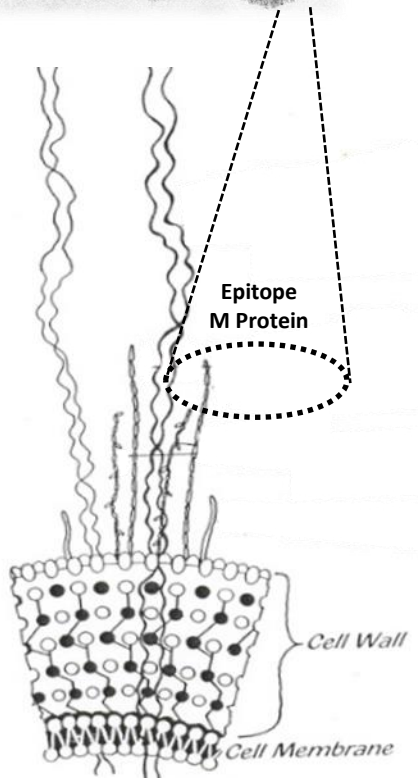
JOURNAL OF CLINICAL MICROBIOLOGY, Feb. 2005, p. 850–856 Vol. 43, No. 2
0095-1137/05/$08.00+0 doi:10.1128/JCM.43.2.850–856.2005

Evidence of *Borrelia* Autoimmunity-Induced Component of Lyme Carditis and Arthritis

Elizabeth S. Raveche,[1] Steven E. Schutzer,[1]* Helen Fernandes,[1] Helen Bateman,[1] Brian A. McCarthy,[1] Steven P. Nickell,[2] and Madeleine W. Cunningham[3]

Departments of Pathology and Medicine, New Jersey Medical School, University of Medicine and Dentistry of New Jersey, Newark, New Jersey[1]; Department of Molecular Genetics and Microbiology, University of New Mexico, Albuquerque, New Mexico[2]; and University of Oklahoma Health Sciences Center, Oklahoma City, Oklahoma[3]

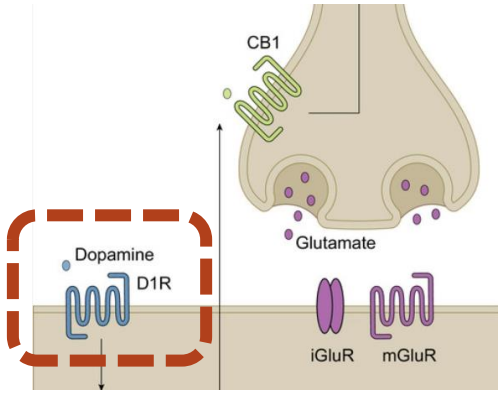
Received 2 January 2004/Returned for modification 29 March 2004/Accepted 5 September 2004



"Sequence similarity between the *B. burgdorferi protein* ***OspA*** and the *S. pyogenes* ***M5 protein***"

"The IgM anti-B. burgdorferi … cross-reacted with S. pyogenes M and myosin, both of which share sequence homology with B. burgdorferi OspA, ***suggesting a role for molecular mimicry in the generation of these Ab reactivities***

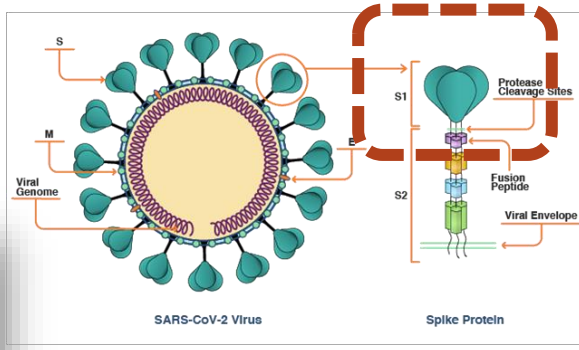
Sequence Homology Between Human Dopamine Receptors and SARS-CoV-2 Spike Protein



Sequence Homology

DRD2 Loop #1	aa start	MD--PLN-LSWYD-DDLE--RQNWSRPFN------GSD-GKADRPHYNYY
SARS-CoV-2 ORF1ab polyprotein	4604	LN-GNWYDFGDL
	4116	MDNSP-N-LAW
	3290	LNGL-WLDD
	4837	D-GNAAISDYDYY
Influenza A neuraminidase	243	D------GSASGKAD
	185	D-GKA
Coxsackievirus A10 capsid protein VP1	142	D-GKA-RP
Varicella zoster tegment serine/threonine protein kinase	391	PHYHYY
	161	SRVFN
Borreliella burgdorferi DUF1073 domain-containing protein	4	RSFNEQAKGLGND-GKGDRS--NYY
B. microti SNARE protein SYN6	2	MD--SL---W-D-DDLQ
M. pneumoniae DNA polymerase IIIb	168	FN------GSN-GK
M. pneumoniae membrane protein	296	DWSRP
S. pyogenes 1,4-alpha-glucan branching enzyme	473	LEWKYDDQLE--WQN

DRD2 Loop #2	aa start	LEVVGEWKFSRIHCD
SARS-CoV-2 ORF1ab poyprotein	192	EWKF
	1514	EVVGD
	438	VVGE
	2809	KFVRIQ
Influenza A H1N1 putative PB1-F2 protein	22	QWKFSR
Coxsackievirus A16 polyprotein	1130	EWIFSKI
	1980	LEVV
Varicella zoster tegment protein	826	LSVVGE
B. burgdorferi multidrug efflux transporter	62	DIVGAWVFRRI
B. microti uncharacterized membrane protein YFL034W	668	EWKFS
B. henselae ShlB/FhaC/HecB family hemolysin secretion/activation protein	458	VGEWNF
M. pneumoniae MPN647 family lipoprotein	16	WKFS
	169	LEMVG
S. pyogenes Kup system potassium uptake protein	195	GIWKFSR



Long-COVID Patients Diagnosed with Neuropsychiatric Conditions

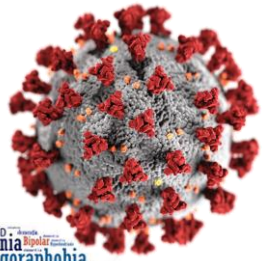
THE LANCET Psychiatry

Published Online April 6, 2021

6-month neurological and psychiatric outcomes in 236 379 survivors of COVID-19: a retrospective cohort study using electronic health records

Maxime Taquet, John R Geddes, Masud Husain, Sierra Luciano, Paul J Harrison

Taquet, M., et al. (2021). "6-month neurological and psychiatric outcomes in 236 379 survivors of COVI retrospective cohort study using electronic health records." The Lancet Psychiatry



Medscape

News > Medscape Medical News > Neurology News

COVID-19: First Data Confirm Neurologic Symptoms Common

Batya Swift Yasgur, MA, LSW

April 16, 2020

11 Read Comments

JAMA Neurology

Original Investigation ONLINE FIRST FREE

April 10, 2020

Neurologic Manifestations of Hospitalized Patients With Coronavirus Disease 2019 in Wuhan, China

Ling Mao[1]; Huijuan Jin[1]; Mengdie Wang[1]; et al

Author Affiliations | Article Information

JAMA Neurol. Published online April 10, 2020. doi:10.1001/jamaneurol.2020.1127

THE LANCET Psychiatry

Psychiatric and neuropsychiatric presentations associated with severe coronavirus infections: a systematic review and meta-analysis with comparison to the COVID-19 pandemic

Jonathan P Rogers, MRCPsych † • Edward Chesney, MRCPsych † • Dominic Oliver, MSc • Thomas A Pollak, PhD • Prof Philip McGuire, FMedSci • Paolo Fusar-Poli, PhD • et al. Show all authors •

frontiers in Psychology

Neuropsychiatric and Cognitive Sequelae of COVID-19

Sanjay Kumar[1*], Alfred Veldhuis[1] and Tina Malhotra[2]

[1]Department of Psychology, Oxford Brookes University, Oxford, United Kingdom
[2]Oxford Health Foundation NHS Trust, Oxford, United Kingdom

Molecular Mimicry in Practical Matters

A Similar Mechanism in PANDAS/PANS, Neurologic Lyme, and Long-COVID

What is PANDAS? A Medical Model for Immune-Mediated Neurologic, Psychiatric and Behavioral Disorders

Pediatric Autoimmune Neuropsychiatric Disorder Associated with Streptococcal infection

(1998) Am J Psychiatry **155**(2): 264-271.

THE AMERICAN JOURNAL OF PSYCHIATRY

Pediatric Autoimmune Neuropsychiatric Disorders Associated With Streptococcal Infections: Clinical Description of the First 50 Cases

Susan E. Swedo, M.D., Henrietta L. Leonard, M.D., Marjorie Garvey, M.D., Barbara Mittleman, M.D., Albert J. Allen, M.D., Ph.D., Susan Perlmutter, M.D., Lorraine Lougee, L.C.S.W., Sara Dow, B.A., Jason Zamkoff, B.A., and Billinda K. Dubbert, M.S.N.

NIH National Institute of Mental Health

In 1990s, Dr. Susan Swedo and team studied children with sudden onset obsessive-compulsive disorder (OCD) and behavioral changes after strep infection

PANDAS/PANS Diagnostic Criteria: Estimated that 1 out of 150 to 200 children have PANS/PANDAS

PANDAS Diagnostic Criteria

All five diagnostic criteria must be met:

1) Presence of obsessive-compulsive disorder (OCD) or a tic disorder

2) Prepubertal symptom onset

3) Acute symptom onset and episodic (relapsing-remitting) course

4) Temporal association between Group A streptococcal infection and symptom onset/exacerbations

5) Associated with neurological abnormalities, (particularly motoric hyperactivity and choreiform movements)

Table 1: PANDAS Diagnostic Criteria.

PANS Diagnostic Criteria

Criterion	Description
I.	Abrupt, dramatic onset of obsessive-compulsive disorder or severely restricted food intake
II.	Concurrent presence of additional neuropsychiatric symptoms, with similarly severe and acute onset, from at least two of the following seven categories (see text for full description):
	1. Anxiety
	2. Emotional lability and/or depression
	3. Irritability, aggression and/or severely oppositional behaviors
	4. Behavioral (developmental) regression
	5. Deterioration in school performance
	6. Sensory or motor abnormalities
	7. Somatic signs and symptoms, including sleep disturbances, enuresis or urinary frequency
III.	Symptoms are not better explained by a known neurologic or medical disorder, such as Sydenham chorea, systemic lupus erythematosus, Tourette disorder or others.
	Note: The diagnostic work-up of patients suspected of PANS must be comprehensive enough to rule out these and other relevant disorders. The nature of the co-occurring symptoms will dictate the necessary assessments, which may include MRI scan, lumbar puncture, electroencephalogram or other diagnostic tests.

Table 2: Diagnostic Criteria Proposed for Pediatric Acute-onset Neuropsychiatric Syndrome (PANS).

Average age at onset

- 6.5 +/- 3.0 years for tics
- 7.4 +/- 2.7 years for OCD

- Boys out number girls 2.6 to 1

www.pandasppn.org/seeingyourfirstchild/

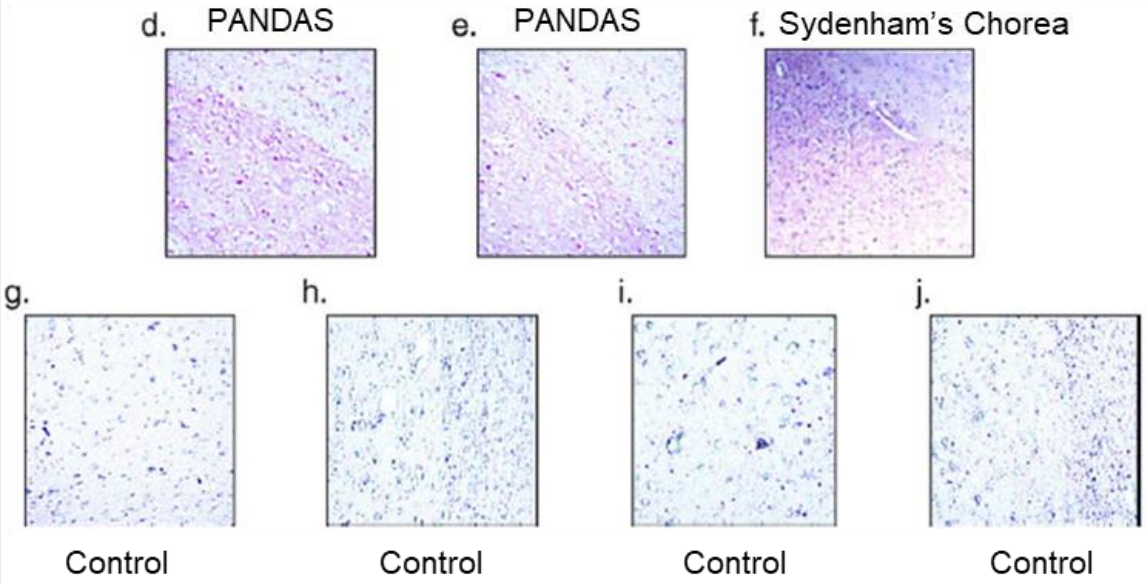
Autoantibodies in Cerebral Spinal Fluid and Serum Bind to Basal Ganglia Brain Tissue

Autoantibodies in CSF bind to Human Brain Caudate-Putamen in Children with Movement Disorders

Journal of Neuroimmunology 2006 Oct;179(1-2):173-9

Antibody-Mediated Neuronal Cell Signaling in Behavior and Movement Disorders

Christine A. Kirvan[a], Susan E. Swedo[b], Lisa A Snider[b], Madeline W. Cunningham

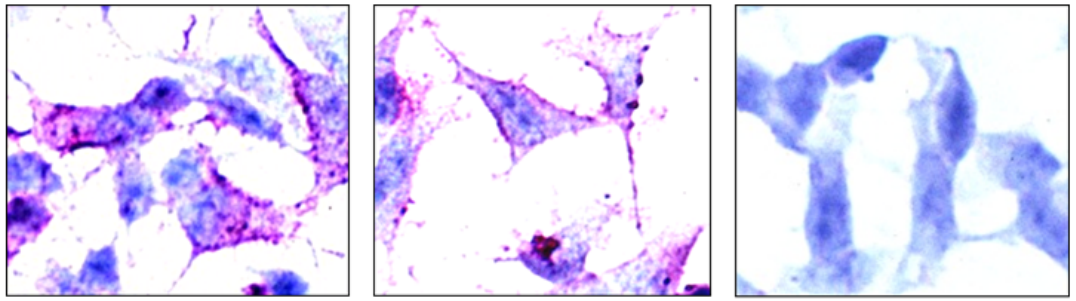


Sydenham Chorea Autoantibodies Bind and Stimulate calmodulin-dependent protein kinase (CaMKII)

nature medicine

Mimicry and Autoantibody-Mediated Neuronal Cell Signaling on Sydenham Chorea

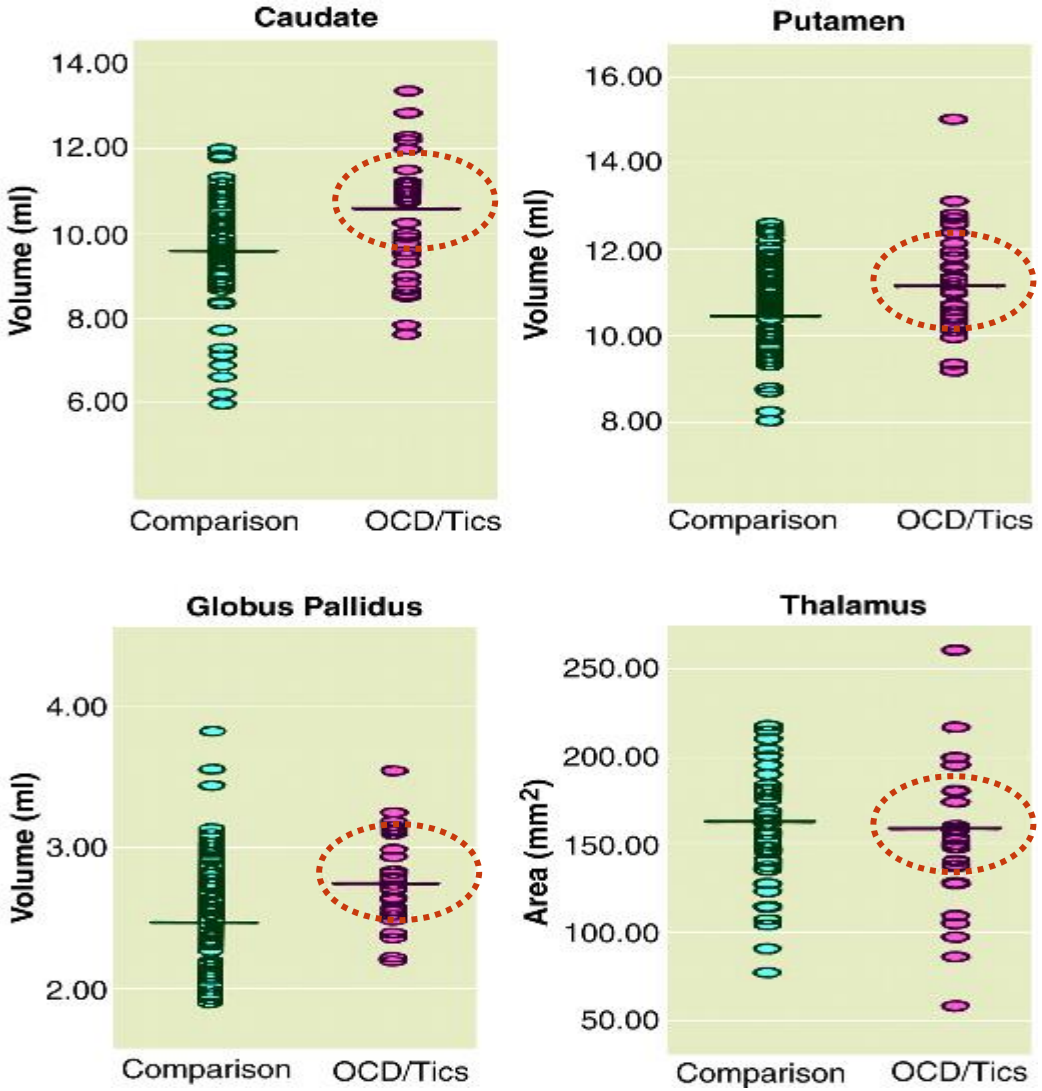
Christine A. Kirvan[1], Susan E. Swedo[2], Janet S Heuser[1], Madeline W. Cunningham[1]



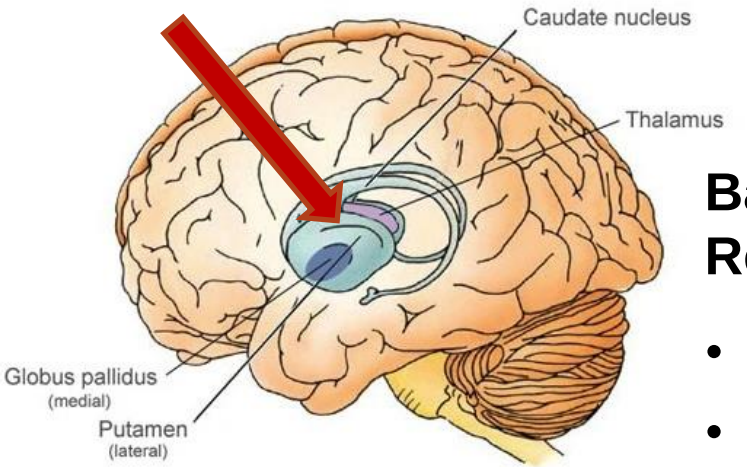
SC mAb 24.3.1 | Anti- ganglioside mAb (commercial) | Isotype

VOLUME 9 | NUMBER 7 | JULY 2003 NATURE MEDICINE

Study of Children with OCD/Tics Associated with Streptococcal Infection Brain Inflammation in MRI



The average size of the caudate and putamen and globus pallidus were enlarged, but not the thalamus or total cerebrum compared to healthy children

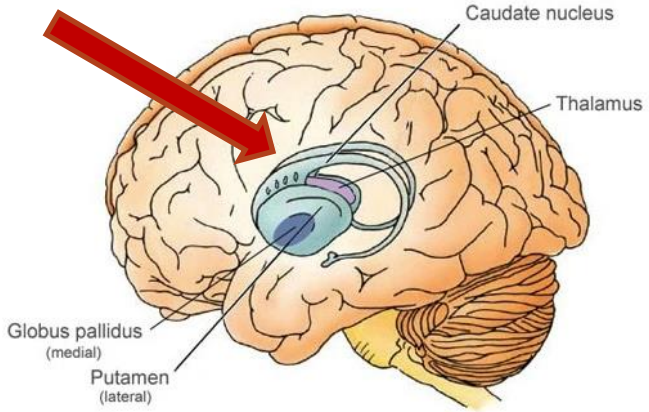


Basal Ganglia is Responsible for:

- Voluntary motor control
- Procedural learning
- Cognitive functions
- Emotional functions
- Eye movement

Am J Psychiatry 2000, Giedd et al. 157:281-283

Basal Ganglia Functions and PANS Criteria Connection



Basal Ganglia is Responsible for:

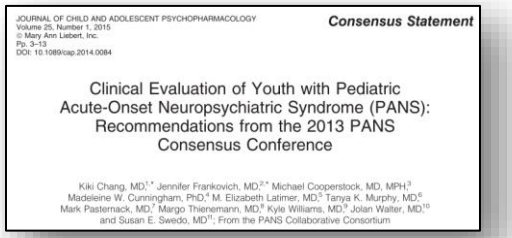
- Emotional functions
- Cognitive functions
- Procedural learning
- Voluntary motor control
- Eye movement

Correlate to interference of normal biological function of basal ganglia

PANS Criteria

1. Abrupt onset of OCD or severely restricted food intake
2. Concurrent presence of additional neuropsychiatric symptoms, with similarly severe and acute onset, from at least two of the following seven categories:
   - anxiety
   - emotional lability or depression
   - irritability, aggression, or severely oppositional behaviors
   - behavioral (developmental) regression
   - deterioration in school performance
   - sensory or motor abnormalities
   - somatic signs and symptoms, including sleep disturbances, enuresis, or increased urinary frequency
3. Symptoms which could not be explained by known neurological or medical disorder such as Sydenham chorea

Nomenclature is Important


JOURNAL OF CHILD AND ADOLESCENT PSYCHOPHARMACOLOGY
Volume 25, Number 1, 2015
© Mary Ann Liebert, Inc.
Pp. 3–13
DOI: 10.1089/cap.2014.0084

Consensus Statement

Clinical Evaluation of Youth with Pediatric Acute-Onset Neuropsychiatric Syndrome (PANS): Recommendations from the 2013 PANS Consensus Conference

Kiki Chang, MD,[1,*] Jennifer Frankovich, MD,[2,*] Michael Cooperstock, MD, MPH,[3] Madeleine W. Cunningham, PhD,[4] M. Elizabeth Latimer, MD,[5] Tanya K. Murphy, MD,[6] Mark Pasternack, MD,[7] Margo Thienemann, MD,[8] Kyle Williams, MD,[9] Jolan Walter, MD,[10] and Susan E. Swedo, MD[11]; From the PANS Collaborative Consortium

2015 Chang, K. et al. J Child Adolesc Psychopharmacol **25**(1): 3-13.

AE
Autoimmune Encephalopathy Secondary to Infection

BGE
Immune-mediated Basal Ganglia Encephalitis

PANS
Pediatric Acute-onset Neuropsychiatric Syndrome

ANDAL
Autoimmune Neuropsychiatric Disorder Associated with Lyme (In Adults)

Infectious Triggers

Non-Infectious Triggers

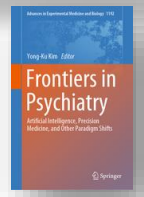
PANDAS
Pediatric Autoimmune Neuropsychiatric Disorder Associated with Streptococcal Infection

Other Microbes
(Lyme, Mycoplasma, Babesia, Bartonella, viruses)

Environmental and other biological factors


Autoantibody Biomarkers for Basal Ganglia Encephalitis in Sydenham Chorea and Pediatric Autoimmune Neuropsychiatric Disorder Associated With Streptococcal Infections

Jennifer L. Chain[1], Kathy Alvarez[1], Adita Mascaro-Blanco[1], Sean Reim[1], Rebecca Bentley[1], Rebecca Hommer[2], Paul Grant[2], James F. Leckman[3], Ivana Kawikova[4], Kyle Williams[5], Julie A. Stoner[6], Susan E. Swedo[2] and Madeleine W. Cunningham[1]*



June 2020 Chain, J… Cunningham, M. W., *Autoantibody Biomarkers for Basal Ganglia Encephalitis in Sydenham Chorea and Pediatric Autoimmune Neuropsychiatric Disorder Associated With Streptococcal Infections.* Frontiers in Psychiatry, Volume 11, Article 564

Immune-Mediated Neuropsychiatric Disorder Have a Enormous Financial Impact on Families

Some comments from a survey of >1,000 Parents

Exhaust savings

Borrow against 401K; burn through my deceased husband's life insurance money because I can't work full-time and barely have been able to hold onto my part-time job.

Brink of bankruptcy

savings exhausted

pre divorce!

job

Extreme credit ca

sold house

We did not lose

I pray it doesn't hav

allow the child to suffer.

Go fund me, fu

rain savings

bought older cars

impacted retirement

nd job

Borrow against life insurance policies

maxed out two credit cards (>$50,000)

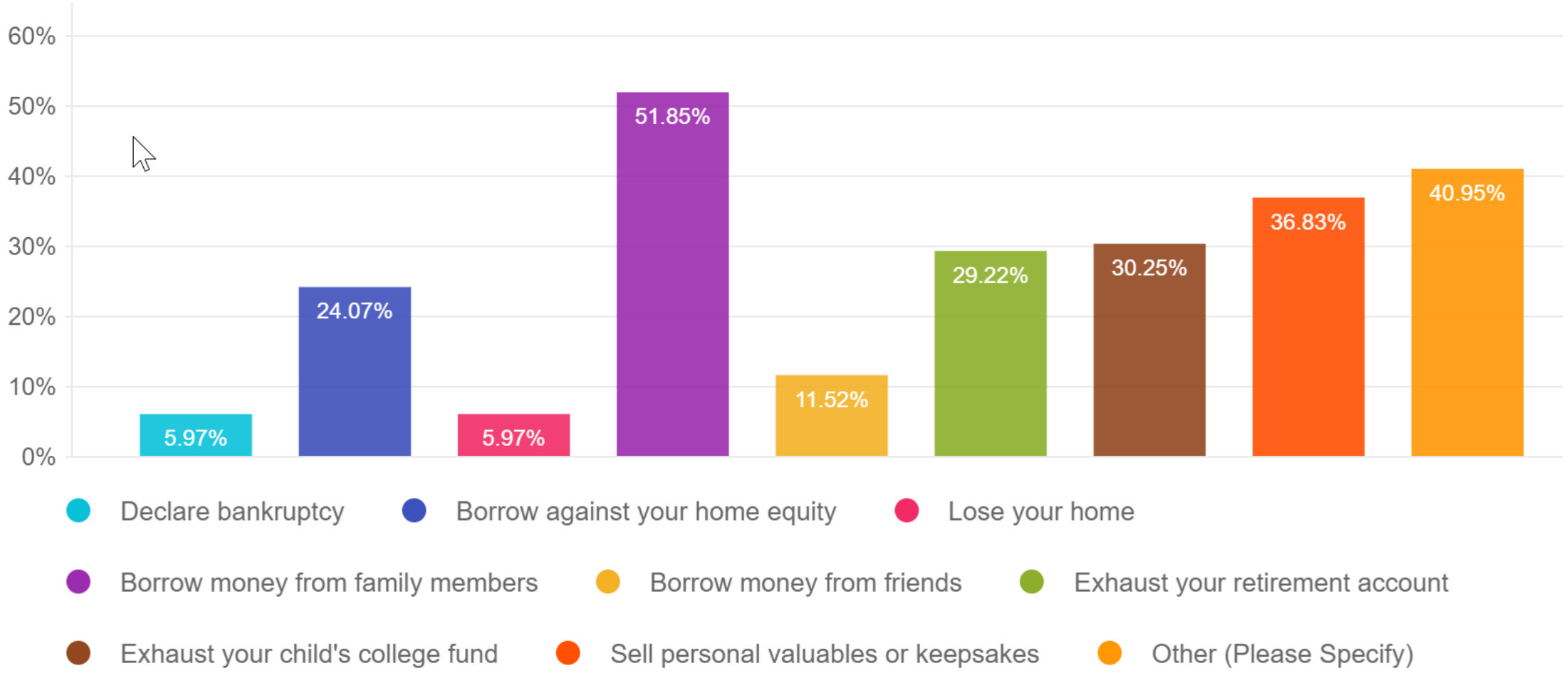
Borrowed $140,000.00 from family and received gifts of $26,000.00 not kidding

Find a part time job in addition to my full time job

- **In our clinical laboratory we have tested over 15,000 patients for autoimmune neuropsychiatric disorders secondary to infections**
- **Patients have visited between 5 to 15 doctors before receiving a proper diagnosis**
- **Length of time from symptom onset to diagnosis is 3 to 5 years, then about 3 to 18 additional months before receiving effective treatment**

Survey of PANDAS/PANS Parents

Has the financial impact of your child's PANDAS/PANS or autoimmune encephalopathy diagnosis or symptoms caused you to do any of the following? Please indicate all that apply.



Grace's Story – Representative of Many we Have Tested with Similar Stories

https://www.moleculeralabs.com/pans-pandas-grace-story/

Amazing Patient Recoveries When Properly Diagnosed and Treated

Grace's Mother recently sent this picture of her on the Cheer Team, back to a normal life and completely well

What is the PANDAS Controversy?

1. PANDAS

– Association with Group A Streptococcus (GAS). Whereas most all children get Strep

2. Heterogeneous symptoms

– Patients present with multiple, and often different neurological and psychiatric symptoms

3. Crosses multiple medical specialties

– Infectious Disease, Immunology/Rheumatology, Neurology, Psychiatry

4. A clinically-defined disorder

– based upon symptoms and often a diagnosis of exclusion

Is There a Controversy that Smoking Causes Lung Cancer?

For those diagnosed with lung cancer over 90% are smokers

Only ~10% to 20% of smokers succumb to lung cancer*

**Center for Disease Control and Prevention (CDC)*

Why do only "some" people get lung cancer?

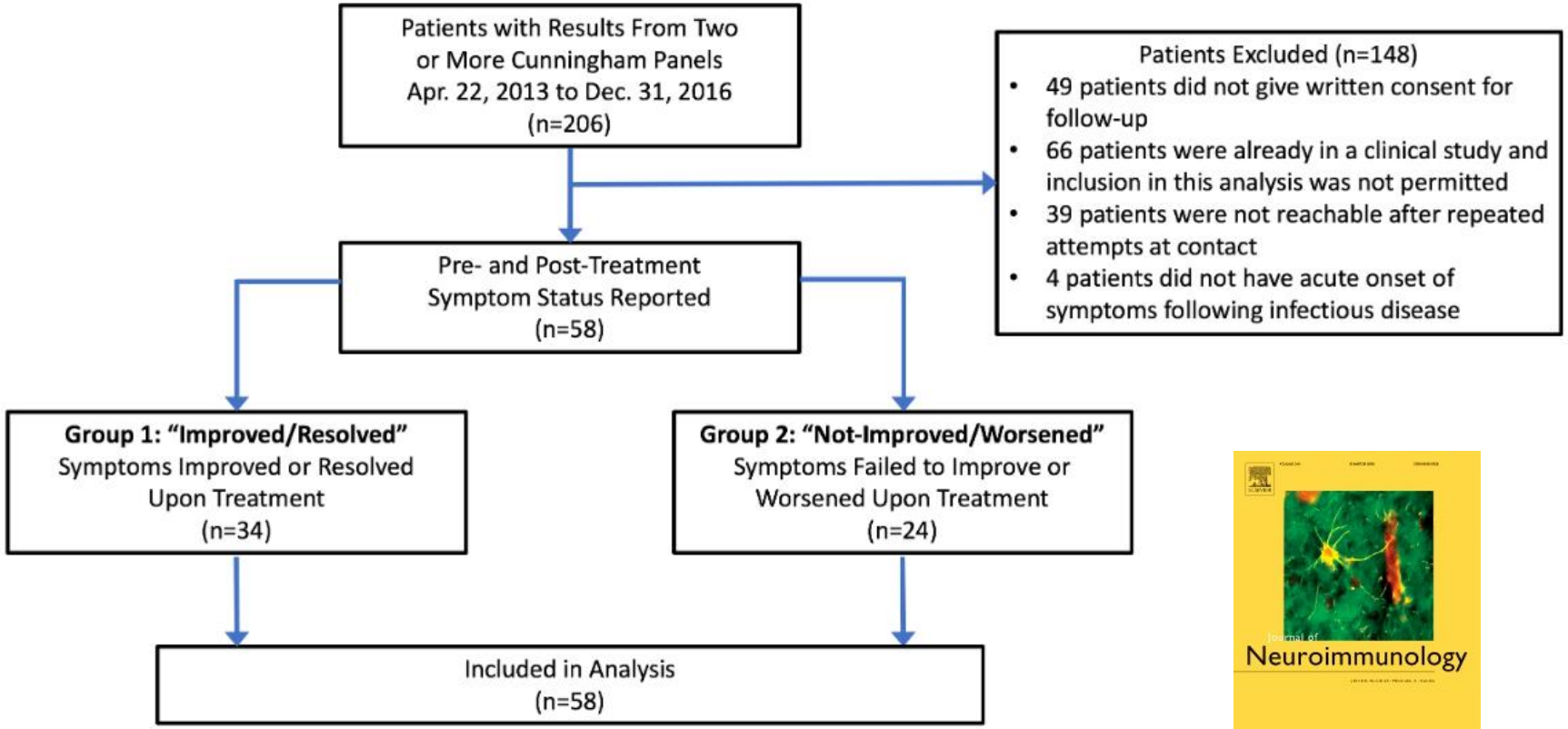
<u>Differences in Genes that Control</u>

- Cell cycle
- DNA repair
- Carcinogen metabolism
- Other genetics

A combination of Genetic Susceptibility and External Factors

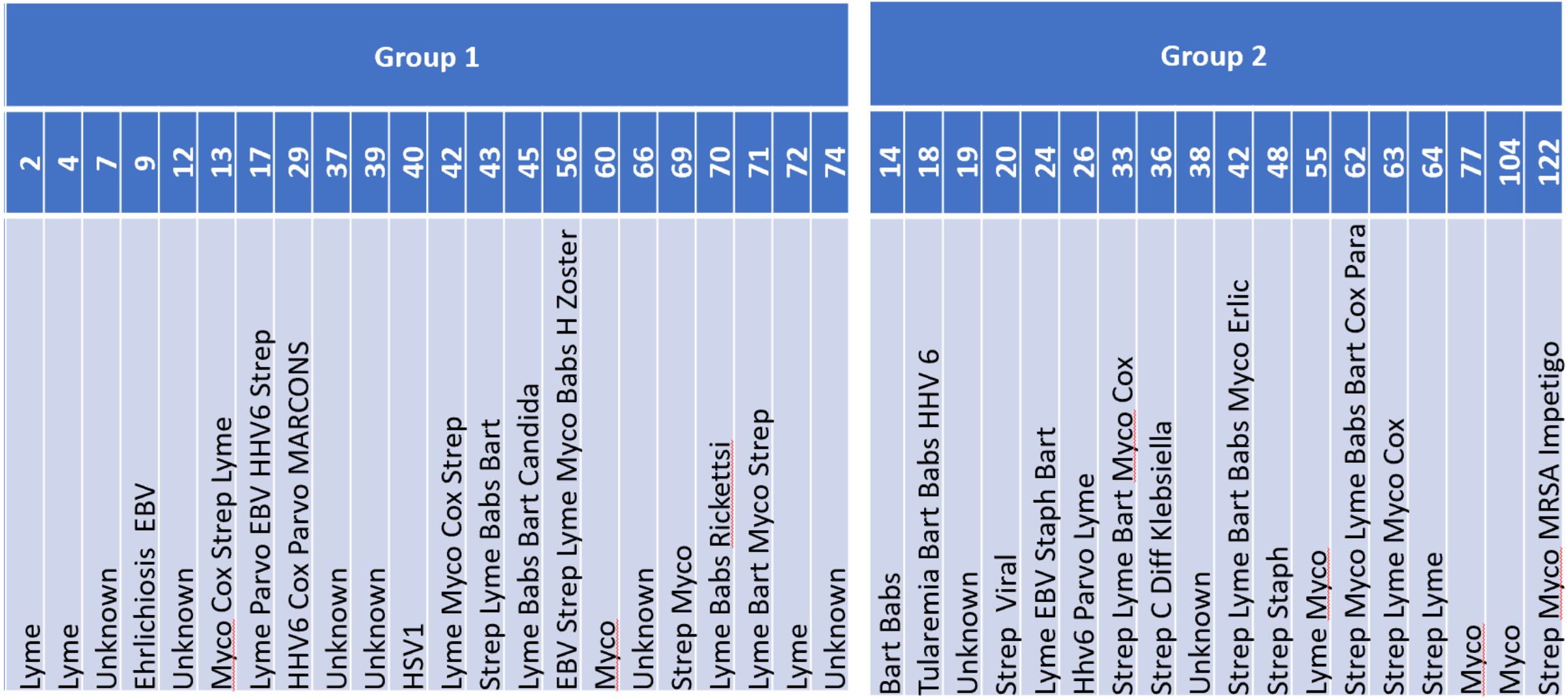
Antineuronal Antibodies as an aid in a Clinician's Diagnosis and Treatment of Patients with Autoimmune Neuropsychiatric Disorders Secondary to Infections

Evaluation of the Cunningham Panel Showing Correlation of Antineuronal Antibodieswith Symptoms Before and after Treatment



Volume 339, 15 February 2020, 577138, Shimasaki et al.
https://www.sciencedirect.com/science/article/pii/S0165572819303522

All Patients Had Various and Multiple Infections



Group 1	
2	Lyme
4	Lyme
7	Unknown
9	Ehrlichiosis EBV
12	Unknown
13	Myco Cox Strep Lyme
17	Lyme Parvo EBV HHV6 Strep
29	HHV6 Cox Parvo MARCONS
37	Unknown
39	Unknown
40	HSV1
42	Lyme Myco Cox Strep
43	Strep Lyme Babs Bart
45	Lyme Babs Bart Candida
56	EBV Strep Lyme Myco Babs H Zoster
60	Myco
66	Unknown
69	Strep Myco
70	Lyme Babs Rickettsi
71	Lyme Bart Myco Strep
72	Lyme
74	Unknown

Group 2	
14	Bart Babs
18	Tularemia Bart Babs HHV 6
19	Unknown
20	Strep Viral
24	Lyme EBV Staph Bart
26	Hhv6 Parvo Lyme
33	Strep Lyme Bart Myco Cox
36	Strep C Diff Klebsiella
38	Unknown
42	Strep Lyme Bart Babs Myco Erlic
48	Strep Staph
55	Lyme Myco
62	Strep Myco Lyme Babs Bart Cox Para
63	Strep Lyme Myco Cox
64	Strep Lyme
77	Myco
104	Myco
122	Strep Myco MRSA Impetigo

All others had Strep Infections

Common Frequency of Symptoms in Group 1 and Group 2

	Group 1 Improved/Resolved		Group 2 Not Improved/Worsened		Combined All Patients	
Symptom	Count (N=34)	Percent	Count (N=24)	Percent	Count (N=58)	Percent
Decreased concentration	31	91%	22	92%	53	91%
OCD	34	100%	18	75%	52	90%
Emotional lability or depression	30	88%	19	79%	49	85%
Sensory symptoms	26	77%	22	92%	48	83%
Anxiety: General and/or Separation	26	77%	22	92%	48	83%
Sleep disorders	29	85%	15	63%	44	76%
Aggressiveness	27	79%	17	71%	44	76%
Tics	22	65%	21	88%	43	74%
Motor symptoms	19	56%	23	96%	42	72%
Developmental regression	23	68%	19	79%	42	72%
Dysgraphia	22	65%	18	24%	40	69%
Urinary urgency or frequency	15	44%	11	46%	26	45%
Chorea/choreiform movements	12	35%	13	54%	25	43%
Behavioral regression	8	24%	1	4%	9	16%
Anorexia or ARFID	3	9%	3	13%	6	10%
Psychosis	4	12%	1	4%	5	9%

Summary of Symptoms of PANS/PANDAS Patients Included in this Study by Individual Patients in Group 1: Improved/Resolved. In Group 2: Not Improved/Worsened

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https://www.sciencedirect.com/science/article/pii/S0165572819303522

No Difference in Age and Gender and Time Between the First and Second Cunningham Panels in Both Groups

Group	# Subjects	Age Range (years)	Mean Age (years)	Females	Males	Time Between First and Second Test (Weeks)	
						Mean	Median
1	34	5-21	12.2 (SD=4.02)	13 (38%)	21 (62%)	68.1	48
2	24	2-23	12.1 (SD=5.1)	9 (38%)	15 (62%)	66.2	62
All Patients	58	2-23	12.2 (SD=4.5)	22 (38%)	36 (62%)	67.3	50

No statistical differences between Group 1 and Group 2 in age or gender distribution No statistical differences between Group 1 and Group 2 in the time between tests

Group 1: Patients who Improved/Resolved (n=34)

Pre-Treatment Results

Case #	Pretreatment				
	D1R	D2R	Tubulin	lyso-ganglioside G_{M1}	CaMKII
6	4000	8000	1000	160	125
72	2000	2000	500	320	137
55	1000	2000	500	80	138
1	1000	2000	500	160	142
30	1000	4000	500	20	143
3	500	1000	250	40	157
42	2000	4000	1000	40	167
7	2000	4000	500	80	172
29	500	4000	1000	80	184
26	1000	1000	250	40	271
5	2000	2000	2000	640	95
12	2000	8000	4000	320	149
37	4000	1000	1000	320	164
39	8000	500	1000	640	123
40	4000	4000	4000	320	122
74	2000	8000	4000	40	133
41	8000	500	1000	320	177
16	2000	2000	2000	320	237
19	1000	2000	4000	20	151
43	16000	2000	8000	160	71
71	1000	4000	2000	20	179
66	8000	2000	2000	160	103
4	8000	32000	4000	320	119
34	4000	16000	500	320	160
54	8000	4000	4000	160	156
35	4000	2000	16000	320	192
2	2000	32000	4000	320	253
45	8000	8000	4000	1280	143
9	32000	4000	8000	640	153
13	8000	8000	4000	640	176
17	8000	2000	4000	640	139
23	4000	16000	2000	320	139
60	8000	16000	2000	80	179
79	4000	16000	2000	160	167

Post-Treatment Results

Post treatment				
D1R	D2R	Tubulin	lyso-ganglioside G_{M1}	CaMKII
2000	4000	1000	80	110
500	1000	250	80	117
1000	1000	250	10	93
2000	4000	1000	320	83
1000	2000	1000	80	98
1000	2000	500	80	83
1000	4000	1000	80	123
500	4000	1000	80	112
2000	4000	1000	80	113
1000	1000	250	40	134
500	2000	250	40	112
1000	8000	1000	20	113
500	1000	250	40	92
1000	4000	1000	160	111
250	2000	500	20	122
1000	4000	500	160	116
2000	1000	250	20	83
2000	8000	1000	320	132
2000	4000	2000	80	128
1000	4000	1000	80	148
1000	4000	2000	320	131
2000	8000	2000	320	138
1000	8000	500	40	108
500	2000	500	40	118
500	2000	500	10	89
2000	4000	1000	80	119
8000	16000	4000	320	120
2000	2000	1000	80	100
2000	4000	1000	80	150
1000	2000	2000	80	100
500	2000	250	20	134
4000	8000	1000	320	119
1000	4000	500	80	165
2000	16000	1000	160	110

of Positive Tests/Pt

Number Elevated Markers	
Pretreatment	Post Treatment
1	0
1	0
1	0
1	0
1	0
1	0
1	0
1	0
1	0
1	1
2	0
2	0
2	0
2	0
2	0
2	0
2	0
2	0
2	1
2	1
2	1
2	2
2	2
3	0
3	0
3	0
3	0
3	3
4	0
4	1
4	1
4	1
4	1
4	1
4	1

Group 2: Patients Not Improved/Worsened (n=24)

Pre-Treatment Results

Case #	Pretreatment				
	D1R	D2R	Tubulin	lyso-ganglioside G_{M1}	CaMKII
24	1000	8000	500	80	119
16	1000	4000	1000	20	124
18	1000	2000	250	20	121
19	1000	250	250	160	115
34	2000	2000	500	320	121
77	500	2000	1000	20	126
29	1000	2000	500	80	138
62	2000	4000	1000	80	216
64	500	2000	250	320	134
104	2000	4000	1000	40	149
45	2000	4000	500	80	217
8	1000	8000	1000	40	219
38	1000	1000	1000	160	179
48	1000	2000	2000	80	156
36	2000	16000	1000	160	164
122	500	8000	1000	640	136
20	2000	2000	2000	40	164
42	32000	4000	2000	80	112
55	2000	8000	2000	320	160
39	8000	250	2000	160	159
26	4000	32000	8000	320	94
14	8000	4000	2000	640	148
63	8000	32000	2000	320	142
35	4000	32000	4000	160	130

Post-Treatment Results

Post treatment				
D1R	D2R	Tubulin	lyso-ganglioside G_{M1}	CaMKII
2000	8000	250	320	105
2000	4000	1000	80	138
1000	1000	500	80	138
2000	4000	2000	40	116
2000	8000	1000	20	145
1000	2000	2000	40	141
1000	2000	250	160	127
2000	2000	500	80	123
1000	4000	2000	80	125
2000	4000	1000	40	175
4000	4000	2000	80	158
4000	16000	1000	320	139
8000	8000	4000	1280	140
2000	8000	1000	160	145
8000	8000	4000	160	123
2000	4000	4000	320	143
4000	16000	8000	160	150
4000	16000	2000	160	164
4000	16000	8000	80	152
2000	16000	4000	80	162
8000	16000	8000	1280	177
8000	16000	16000	40	92
32000	32000	8000	640	113
8000	32000	4000	1280	149

of Positive Tests/Pt

Number Elevated Markers	
Pretreatment	Post Treatment
0	0
0	1
0	1
0	1
0	1
0	2
1	0
1	0
1	1
1	1
1	3
1	3
1	4
2	1
2	2
2	2
2	4
2	4
2	4
3	3
3	5
4	3
4	4
4	5

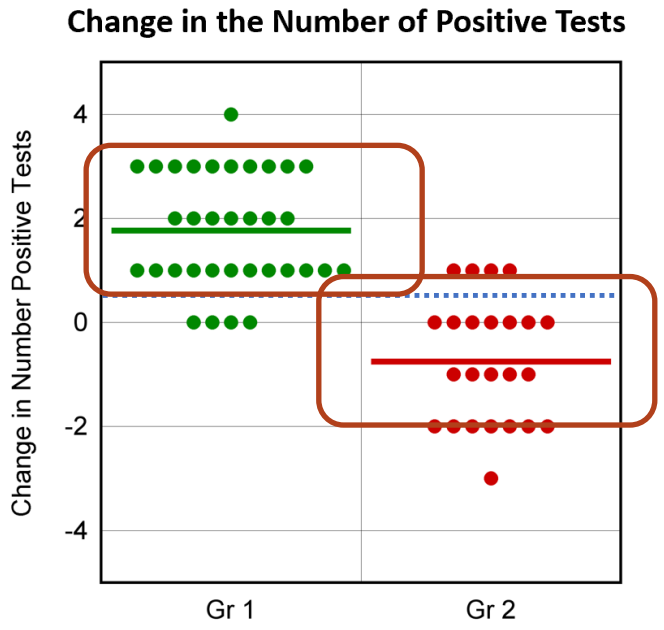
Anti-Neuronal Antibody Targets Associated with the Presence/Absence of Neuropsychiatric Symptoms Pre and Post Treatment

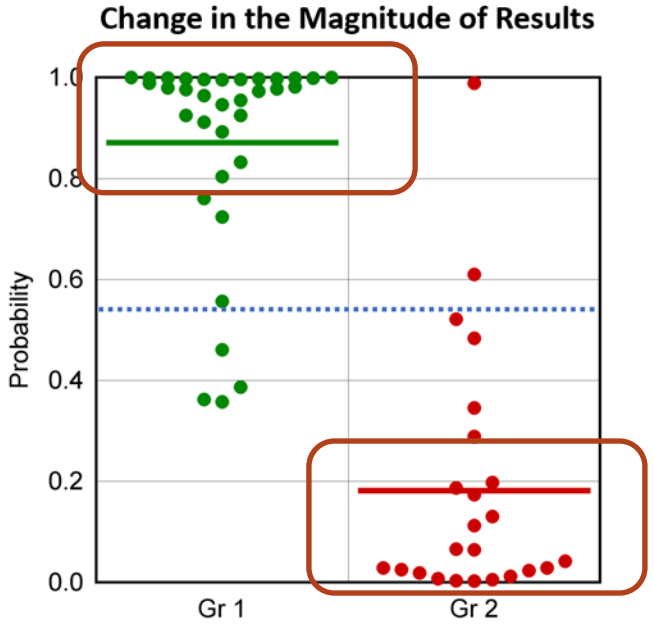
Sensitivity/Specificity Based Upon Positive Tests Compared to Symptoms

		Symptoms Improved			
		Yes (Gr 1)	No (Gr 2)	**Sensitivity**	88%
Predicted in Group 1	Yes	30	4	**Specificity**	83%
	No	4	20		
				Accuracy	86%

Sensitivity/Specificity based upon the Magnitude of Change in the Results (Logistic Regression Analysis)

		Symptoms Improved			
		Yes (Gr 1)	No (Gr 2)	**Sensitivity**	88%
Predicted in Group 1	Yes	30	2	**Specificity**	92%
	No	4	22		
				Accuracy	90%





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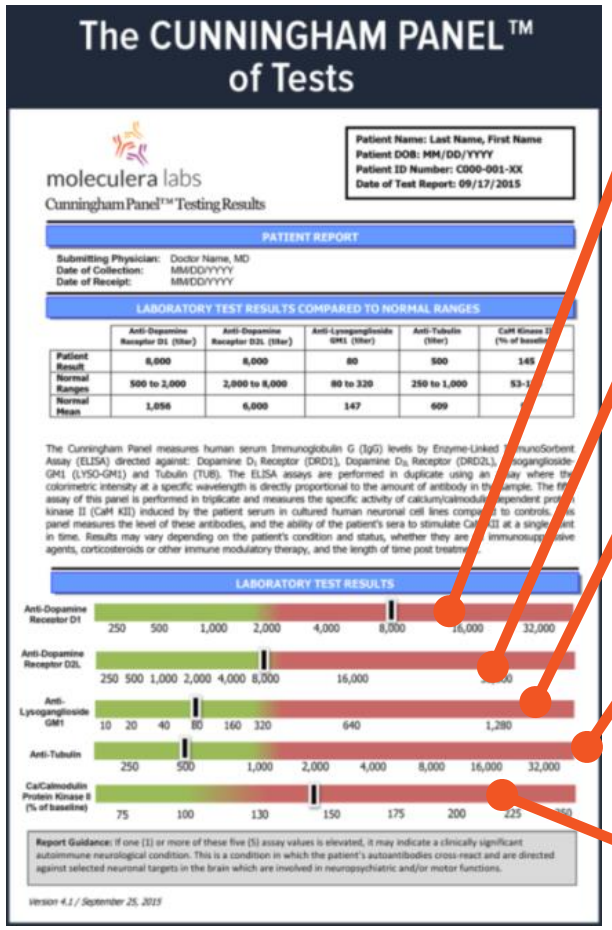
https://www.sciencedirect.com/science/article/pii/S0165572819303522

Years of Sydenham Chorea Research Led to the Identification of Biomarkers Targets and a Cell Stimulatory Assay for Immune-mediated Basal Ganglia Encephalitis


The CUNNINGHAM PANEL™ of Tests

moleculera labs

Cunningham Panel™ Testing Results

Patient Name: Last Name, First Name
Patient DOB: MM/DD/YYYY
Patient ID Number: C000-001-XX
Date of Test Report: 09/17/2015

PATIENT REPORT

Submitting Physician: Doctor Name, MD
Date of Collection: MM/DD/YYYY
Date of Receipt: MM/DD/YYYY

LABORATORY TEST RESULTS COMPARED TO NORMAL RANGES

	Anti-Dopamine Receptor D1 (titer)	Anti-Dopamine Receptor D2L (titer)	Anti-Lysoganglioside GM1 (titer)	Anti-Tubulin (titer)	CaM Kinase II (% of baseline)
Patient Result	8,000	8,000	80	500	145
Normal Ranges	500 to 2,000	2,000 to 8,000	80 to 320	250 to 1,000	53-1
Normal Mean	1,056	6,000	147	609	

The Cunningham Panel measures human serum Immunoglobulin G (IgG) levels by Enzyme-Linked ImmunoSorbent Assay (ELISA) directed against: Dopamine D_1 Receptor (DRD1), Dopamine D_{2L} Receptor (DRD2L), Lysoganglioside GM1 (LYSO-GM1) and Tubulin (TUB). The ELISA assays are performed in duplicate using an assay where the colorimetric intensity at a specific wavelength is directly proportional to the amount of antibody in the sample. The fifth assay of this panel is performed in triplicate and measures the specific activity of calcium/calmodulin dependent protein kinase II (CaM KII) induced by the patient serum in cultured human neuronal cell lines compared to controls. This panel measures the level of these antibodies, and the ability of the patient's sera to stimulate CaM KII at a single point in time. Results may vary depending on the patient's condition and status, whether they are on immunosuppressive agents, corticosteroids or other immune modulatory therapy, and the length of time post treatment.

LABORATORY TEST RESULTS

Anti-Dopamine Receptor D1: 250 500 1,000 2,000 4,000 8,000 16,000 32,000

Anti-Dopamine Receptor D2L: 250 500 1,000 2,000 4,000 8,000 16,000

Anti-Lysoganglioside GM1: 10 20 40 80 160 320 640 1,280

Anti-Tubulin: 250 500 1,000 2,000 4,000 8,000 16,000 32,000

Ca/Calmodulin Protein Kinase II (% of baseline): 75 100 130 150 175 200 225

Report Guidance: If one (1) or more of these five (5) assay values is elevated, it may indicate a clinically significant autoimmune neurological condition. This is a condition in which the patient's autoantibodies cross-react and are directed against selected neuronal targets in the brain which are involved in neuropsychiatric and/or motor functions.

Version 4.1 / September 25, 2015

Based upon over 15,000 patients tested along with reports from Dr. Amiram Katz based upon over 200 patients he studied

1) Anti-Dopamine D1 Receptor

Referred to as **psychiatric cluster.** Patients frequently present with **psychiatric** symptoms, **mood** swings, **depression**, anxiety, irritability, aggression, **delusions**, **psychosis**

2) Anti-Dopamine D2L Receptor

Referred to as **movement clusters**. Patients frequently have some level of **movement disorders**, **chorea**, previous diagnosis of ADHD (could not hold still), possibly Parkinson.

3) Anti-Lysoganglioside GM1

Referred to as **tic cluster**. Patients frequently complain of **joint/connective** tissue pain.

4) Anti-Tubulin

Referred to as **OCD cluster**. Patients frequently present with **obsessions/compulsions** often around **food phobia**, clothing, **intrusive thoughts**, and **brain fog.**

5) CaM KII Activity

Referred to as the **sympathetic nervous system cluster**. When positive patients typically present with any sympathetic nervous system activation symptoms, **fight or flight behavior**, **separation anxiety**, **urinary problems**, bed wetting, sensory sensitivities, **easily startled**, and **mydriasis**. When elevated, suggests that there is still **active infection(s).** Often, we see in an untreated patient, that over time the CaMKII will return to baseline, and the other autoimmune targets tend to increase in elevation.

Calcium Dependent Calmodulin Kinase II (CaMKII) Interacts With Many Neurologic Receptors in Autoimmune Encephalitis

Review

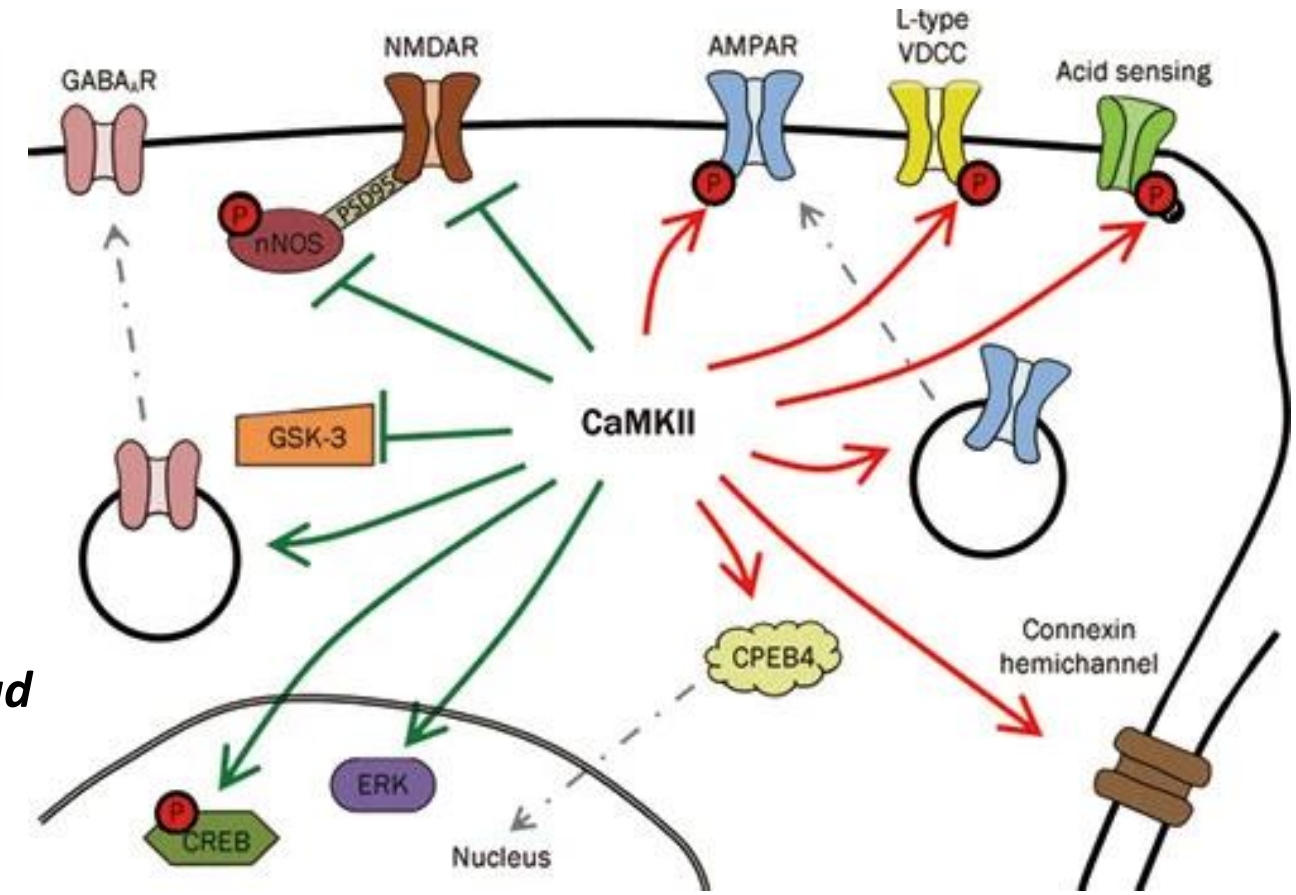
CellPress

Emerging role of CaMKII in neuropsychiatric disease

A.J. Robison

Department of Physiology, Michigan State University, Lansing, MI 48824, USA

Trends in Neurosciences November 2014, Vol. 37, No. 11



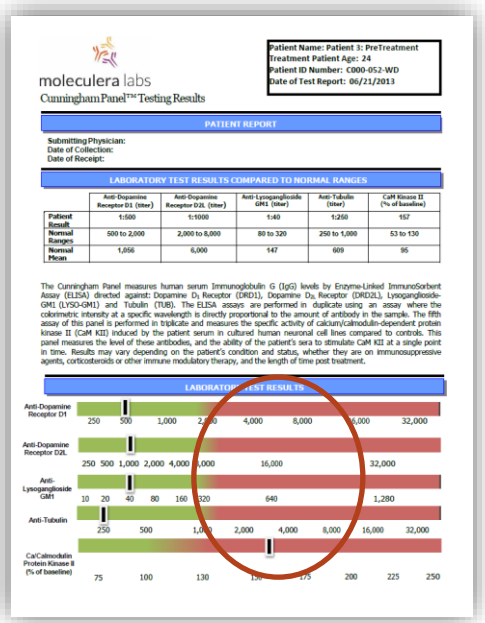
"A series of recent studies suggest that ***CaMKII dysfunction throughout the brain may underlie myriad neuropsychiatric disorders***, **including drug addiction, schizophrenia, depression, epilepsy, and multiple neurodevelopmental disorders**, perhaps through ***maladaptations in glutamate signaling and neuroplasticity***."

Coultrap, S. J., et al. (2011). "CaMKII in cerebral ischemia." Acta Pharmacol Sin 32(7): 861-872.

Case Studies Before and After Treatment

Case Study #1

24 y/o Male: Presenting symptoms: OCD, tics, decreased appetite with 30 pound weight loss, inability to concentrate, sensory abnormalities, emotional lability, behavioral regression, separation anxiety.


moleculera labs
Cunningham Panel™ Testing Results

Patient Name: Patient 3: PreTreatment
Treatment Patient Age: 24
Patient ID Number: C000-052-WD
Date of Test Report: 06/21/2013

PATIENT REPORT

Submitting Physician:
Date of Collection:
Date of Receipt:

LABORATORY TEST RESULTS COMPARED TO NORMAL RANGES

	Anti-Dopamine Receptor D1 (titer)	Anti-Dopamine Receptor D2L (titer)	Anti-Lysoganglioside GM1 (titer)	Anti-Tubulin (titer)	CaM Kinase II (% of baseline)
Patient Result	1:500	1:1000	1:40	1:250	157
Normal Ranges	500 to 2,000	2,000 to 8,000	80 to 320	250 to 1,000	53 to 130
Normal Mean	1,056	6,000	147	609	95

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Anti-Lysoganglioside GM1: 10 20 40 80 160 320 640 1,280
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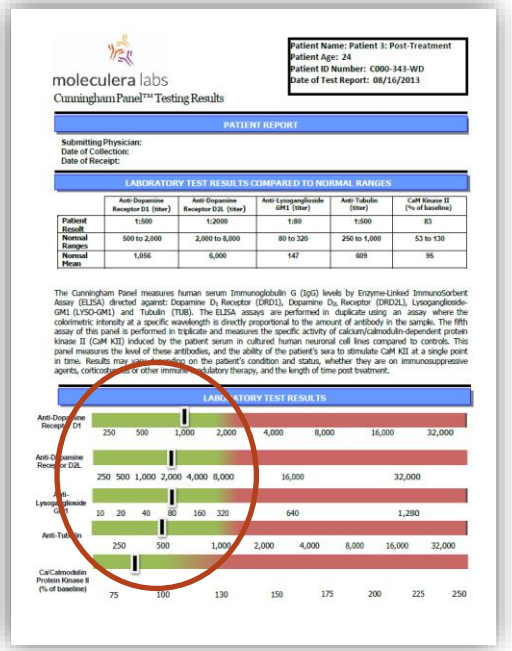
Ca/Calmodulin Protein Kinase II (% of baseline): 75 100 130 150 175 200 225 250


moleculera labs
Cunningham Panel™ Testing Results

Patient Name: Patient 3: Post-Treatment
Patient Age: 24
Patient ID Number: C000-343-WD
Date of Test Report: 08/16/2013

PATIENT REPORT

Submitting Physician:
Date of Collection:
Date of Receipt:

LABORATORY TEST RESULTS COMPARED TO NORMAL RANGES

	Anti-Dopamine Receptor D1 (titer)	Anti-Dopamine Receptor D2L (titer)	Anti-Lysoganglioside GM1 (titer)	Anti-Tubulin (titer)	CaM Kinase II (% of baseline)
Patient Result	1:500	1:2000	1:80	1:500	83
Normal Ranges	500 to 2,000	2,000 to 8,000	80 to 320	250 to 1,000	53 to 130
Normal Mean	1,056	6,000	147	609	95

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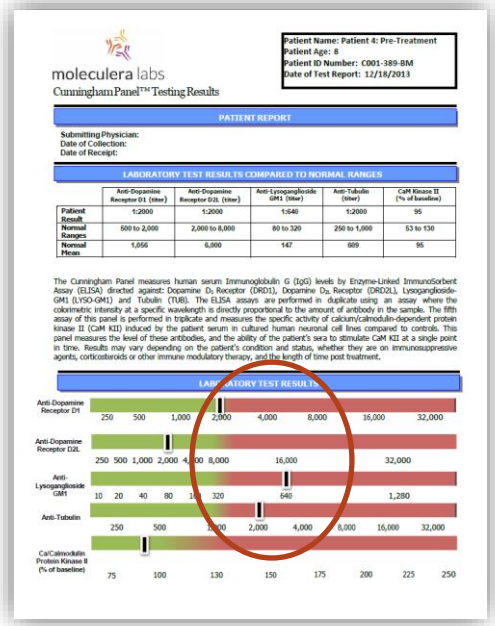
Anti-Tubulin: 250 500 1,000 2,000 4,000 8,000 16,000 32,000
Ca/Calmodulin Protein Kinase II (% of baseline): 75 100 130 150 175 200 225 250

Treatment: Patient treated with IVIG and plasmapheresis resulted in symptom reduction

Case Study #2

9 y/o Female: obsessive-compulsive behaviors, verbal tics and “stimming”, inability to concentrate, sensory and motor abnormalities, emotional lability, behavioral regression, urinary and sleep problems, dysgraphia, and aggressiveness, relapsing and remitting in nature


moleculera labs
Cunningham Panel™ Testing Results

Patient Name: Patient 4: Pre-Treatment
Patient Age: 8
Patient ID Number: C001-389-BM
Date of Test Report: 12/18/2013

PATIENT REPORT

Submitting Physician:
Date of Collection:
Date of Receipt:

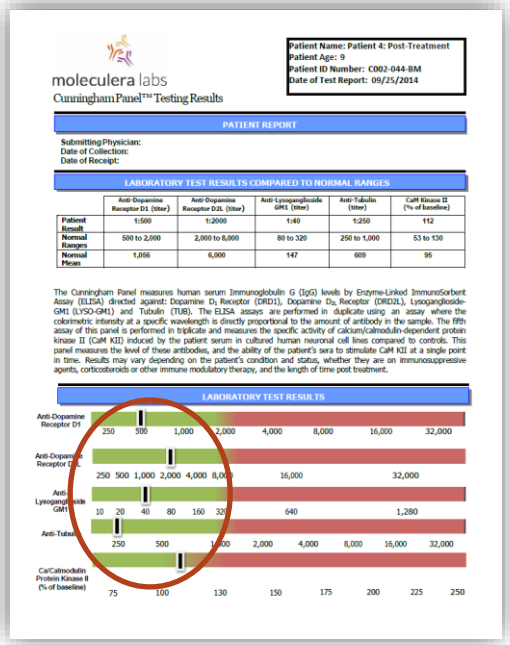
LABORATORY TEST RESULTS COMPARED TO NORMAL RANGES

	Anti-Dopamine Receptor D1 (titer)	Anti-Dopamine Receptor D2L (titer)	Anti-Lysoganglioside GM1 (titer)	Anti-Tubulin (titer)	CaM Kinase II (% of baseline)
Patient Result	1:2000	1:2000	1:640	1:2000	95
Normal Ranges	500 to 2,000	2,000 to 8,000	80 to 320	250 to 1,000	53 to 130
Normal Mean	1,056	6,000	147	609	95

The Cunningham Panel measures human serum Immunoglobulin G (IgG) levels by Enzyme-Linked ImmunoSorbent Assay (ELISA) directed against: Dopamine D_1 Receptor (DRD1), Dopamine D_{2L} Receptor (DRD2L), Lysoganglioside-GM1 (LYSO-GM1) and Tubulin (TUB). The ELISA assays are performed in duplicate using an assay where the colorimetric intensity at a specific wavelength is directly proportional to the amount of antibody in the sample. The fifth assay of this panel is performed in triplicate and measures the specific activity of calcium/calmodulin-dependent protein kinase II (CaM KII) induced by the patient serum in cultured human neuronal cell lines compared to controls. This panel measures the level of these antibodies, and the ability of the patient's sera to stimulate CaM KII at a single point in time. Results may vary depending on the patient's condition and status, whether they are on immunosuppressive agents, corticosteroids or other immune modulatory therapy, and the length of time post treatment.

LABORATORY TEST RESULTS

Anti-Dopamine Receptor D1: 250 500 1,000 2,000 4,000 8,000 16,000 32,000
Anti-Dopamine Receptor D2L: 250 500 1,000 2,000 4,000 8,000 16,000 32,000
Anti-Lysoganglioside GM1: 10 20 40 80 160 320 640 1,280
Anti-Tubulin: 250 500 1,000 2,000 4,000 8,000 16,000 32,000
Ca/Calmodulin Protein Kinase II (% of baseline): 75 100 130 150 175 200 225 250


moleculera labs
Cunningham Panel™ Testing Results

Patient Name: Patient 4: Post-Treatment
Patient Age: 9
Patient ID Number: C002-044-BM
Date of Test Report: 09/25/2014

PATIENT REPORT

Submitting Physician:
Date of Collection:
Date of Receipt:

LABORATORY TEST RESULTS COMPARED TO NORMAL RANGES

	Anti-Dopamine Receptor D1 (titer)	Anti-Dopamine Receptor D2L (titer)	Anti-Lysoganglioside GM1 (titer)	Anti-Tubulin (titer)	CaM Kinase II (% of baseline)
Patient Result	1:500	1:2000	1:40	1:250	112
Normal Ranges	500 to 2,000	2,000 to 8,000	80 to 320	250 to 1,000	53 to 130
Normal Mean	1,056	6,000	147	609	95

The Cunningham Panel measures human serum Immunoglobulin G (IgG) levels by Enzyme-Linked ImmunoSorbent Assay (ELISA) directed against: Dopamine D_1 Receptor (DRD1), Dopamine D_{2L} Receptor (DRD2L), Lysoganglioside-GM1 (LYSO-GM1) and Tubulin (TUB). The ELISA assays are performed in duplicate using an assay where the colorimetric intensity at a specific wavelength is directly proportional to the amount of antibody in the sample. The fifth assay of this panel is performed in triplicate and measures the specific activity of calcium/calmodulin-dependent protein kinase II (CaM KII) induced by the patient serum in cultured human neuronal cell lines compared to controls. This panel measures the level of these antibodies, and the ability of the patient's sera to stimulate CaM KII at a single point in time. Results may vary depending on the patient's condition and status, whether they are on immunosuppressive agents, corticosteroids or other immune modulatory therapy, and the length of time post treatment.

LABORATORY TEST RESULTS

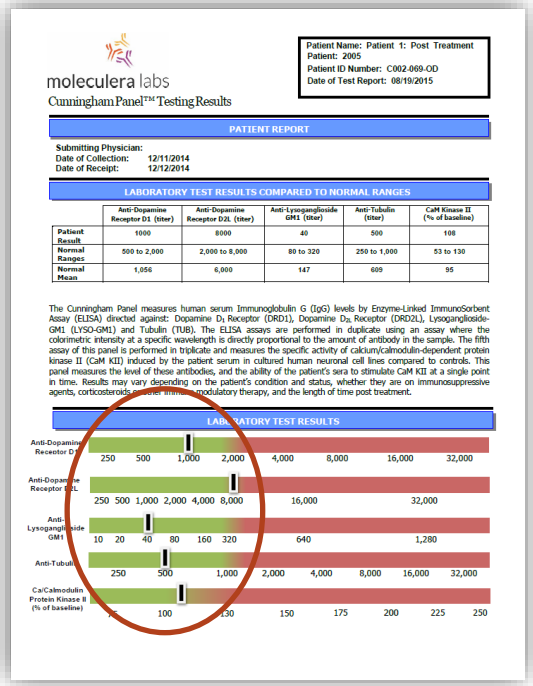
Anti-Dopamine Receptor D1: 250 500 1,000 2,000 4,000 8,000 16,000 32,000
Anti-Dopamine Receptor D2L: 250 500 1,000 2,000 4,000 8,000 16,000 32,000
Anti-Lysoganglioside GM1: 10 20 40 80 160 320 640 1,280
Anti-Tubulin: 250 500 1,000 2,000 4,000 8,000 16,000 32,000
Ca/Calmodulin Protein Kinase II (% of baseline): 75 100 130 150 175 200 225 250

Treatment: Patient was treated with azithromycin with rapid improvement in symptoms

Cunningham Panel Case Studies Before and After Treatment

Case Study #3

9 y/o Female: Presenting with unknown origin of neuropsychiatric symptoms. Lyme disease positive by Western Blot, Child said during a bout of strep, ***"Mom, something happened to my brain"***


moleculera labs
Cunningham Panel™ Testing Results

Patient Name: Patient 1: Post Treatment
Patient: 2005
Patient ID Number: C002-069-OD
Date of Test Report: 08/19/2015

PATIENT REPORT

Submitting Physician:
Date of Collection: 12/11/2014
Date of Receipt: 12/12/2014

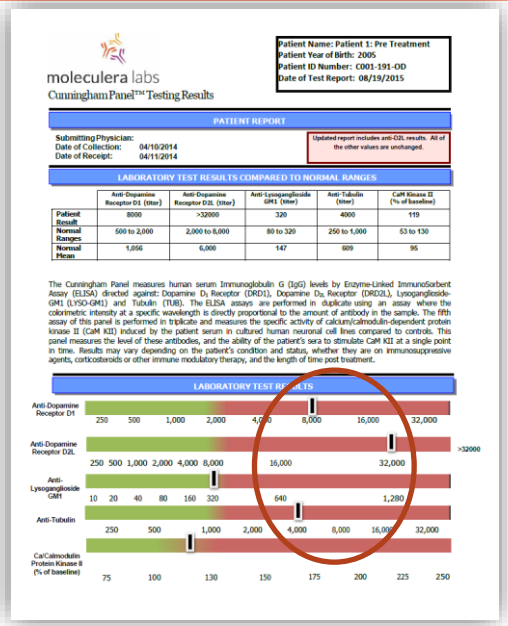
LABORATORY TEST RESULTS COMPARED TO NORMAL RANGES

	Anti-Dopamine Receptor D1 (titer)	Anti-Dopamine Receptor D2L (titer)	Anti-Lysoganglioside GM1 (titer)	Anti-Tubulin (titer)	CaM Kinase II (% of baseline)
Patient Result	1000	8000	40	500	108
Normal Ranges	500 to 2,000	2,000 to 8,000	80 to 320	250 to 1,000	53 to 130
Normal Mean	1,056	6,000	147	609	95

The Cunningham Panel measures human serum Immunoglobulin G (IgG) levels by Enzyme-Linked ImmunoSorbent Assay (ELISA) directed against: Dopamine D_1 Receptor (DRD1), Dopamine D_{2L} Receptor (DRD2L), Lysoganglioside-GM1 (LYSO-GM1) and Tubulin (TUB). The ELISA assays are performed in duplicate using an assay where the colorimetric intensity at a specific wavelength is directly proportional to the amount of antibody in the sample. The fifth assay of this panel is performed in triplicate and measures the specific activity of calcium/calmodulin-dependent protein kinase II (CaM KII) induced by the patient serum in cultured human neuronal cell lines compared to controls. This panel measures the level of these antibodies, and the ability of the patient's sera to stimulate CaM KII at a single point in time. Results may vary depending on the patient's condition and status, whether they are on immunosuppressive agents, corticosteroids or other immune modulatory therapy, and the length of time post treatment.

LABORATORY TEST RESULTS

Anti-Dopamine Receptor D1: 250 500 1,000 2,000 4,000 8,000 16,000 32,000
Anti-Dopamine Receptor D2L: 250 500 1,000 2,000 4,000 8,000 16,000 32,000
Anti-Lysoganglioside GM1: 10 20 40 80 160 320 640 1,280
Anti-Tubulin: 250 500 1,000 2,000 4,000 8,000 16,000 32,000
Ca/Calmodulin Protein Kinase II (% of baseline): 75 100 130 150 175 200 225 250


moleculera labs
Cunningham Panel™ Testing Results

Patient Name: Patient 1: Pre Treatment
Patient Year of Birth: 2005
Patient ID Number: C001-191-OD
Date of Test Report: 08/19/2015

PATIENT REPORT

Submitting Physician:
Date of Collection: 04/10/2014
Date of Receipt: 04/11/2014

Updated report includes anti-D2L results. All of the other values are unchanged.

LABORATORY TEST RESULTS COMPARED TO NORMAL RANGES

	Anti-Dopamine Receptor D1 (titer)	Anti-Dopamine Receptor D2L (titer)	Anti-Lysoganglioside GM1 (titer)	Anti-Tubulin (titer)	CaM Kinase II (% of baseline)
Patient Result	8000	>32000	320	4000	119
Normal Ranges	500 to 2,000	2,000 to 8,000	80 to 320	250 to 1,000	53 to 130
Normal Mean	1,056	6,000	147	609	95

The Cunningham Panel measures human serum Immunoglobulin G (IgG) levels by Enzyme-Linked ImmunoSorbent Assay (ELISA) directed against: Dopamine D_1 Receptor (DRD1), Dopamine D_{2L} Receptor (DRD2L), Lysoganglioside-GM1 (LYSO-GM1) and Tubulin (TUB). The ELISA assays are performed in duplicate using an assay where the colorimetric intensity at a specific wavelength is directly proportional to the amount of antibody in the sample. The fifth assay of this panel is performed in triplicate and measures the specific activity of calcium/calmodulin-dependent protein kinase II (CaM KII) induced by the patient serum in cultured human neuronal cell lines compared to controls. This panel measures the level of these antibodies, and the ability of the patient's sera to stimulate CaM KII at a single point in time. Results may vary depending on the patient's condition and status, whether they are on immunosuppressive agents, corticosteroids or other immune modulatory therapy, and the length of time post treatment.

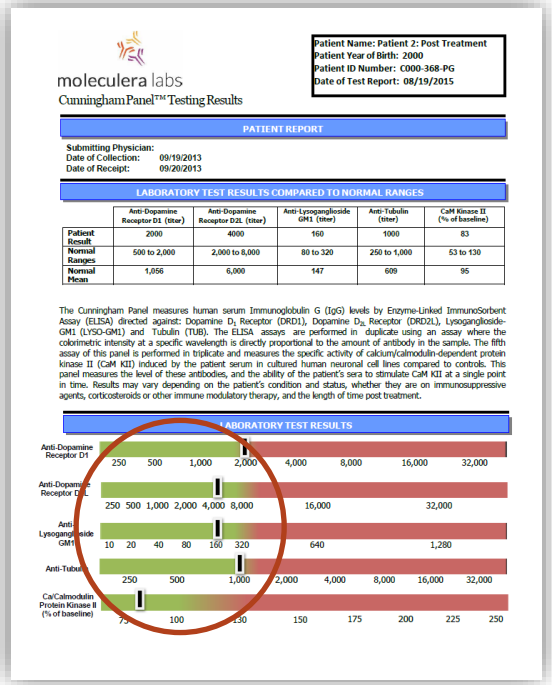
LABORATORY TEST RESULTS

Anti-Dopamine Receptor D1: 250 500 1,000 2,000 4,000 8,000 16,000 32,000
Anti-Dopamine Receptor D2L: 250 500 1,000 2,000 4,000 8,000 16,000 >32000
Anti-Lysoganglioside GM1: 10 20 40 80 160 320 640 1,280
Anti-Tubulin: 250 500 1,000 2,000 4,000 8,000 16,000 32,000
Ca/Calmodulin Protein Kinase II (% of baseline): 75 100 130 150 175 200 225 250

Treatment: azithromax, naproxen, omnicef, and Bactrim, Tindamax (anti parasitic) 3 IVIG treatments; complete symptom regression

Case Study #4

9 y/o Male: Presenting 30 days post confirmed strep infection with OCD, Tics, inability to concentrate, sensory abnormalities, emotional lability, separation anxiety, developmental regression, urinary frequency and urgency, sleep disturbance, dysgraphia, aggressiveness, choreiform movements, relapsing and remitting symptoms.


moleculera labs
Cunningham Panel™ Testing Results

Patient Name: Patient 2: Post Treatment
Patient Year of Birth: 2000
Patient ID Number: C000-368-PG
Date of Test Report: 08/19/2015

PATIENT REPORT

Submitting Physician:
Date of Collection: 09/19/2013
Date of Receipt: 09/20/2013

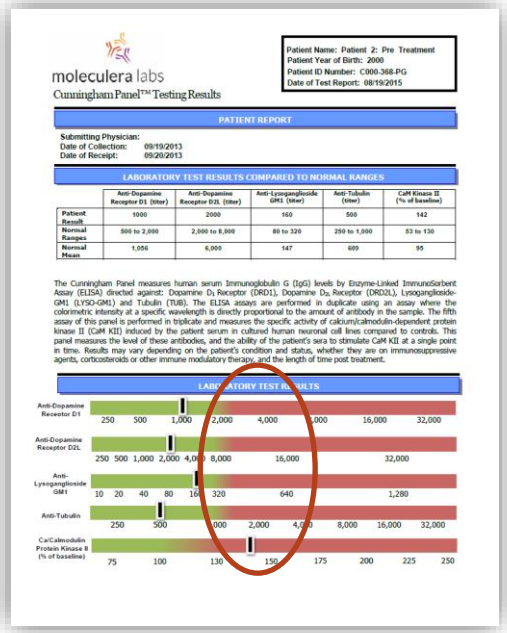
LABORATORY TEST RESULTS COMPARED TO NORMAL RANGES

	Anti-Dopamine Receptor D1 (titer)	Anti-Dopamine Receptor D2L (titer)	Anti-Lysoganglioside GM1 (titer)	Anti-Tubulin (titer)	CaM Kinase II (% of baseline)
Patient Result	2000	4000	160	1000	83
Normal Ranges	500 to 2,000	2,000 to 8,000	80 to 320	250 to 1,000	53 to 130
Normal Mean	1,056	6,000	147	609	95

The Cunningham Panel measures human serum Immunoglobulin G (IgG) levels by Enzyme-Linked ImmunoSorbent Assay (ELISA) directed against: Dopamine D_1 Receptor (DRD1), Dopamine D_{2L} Receptor (DRD2L), Lysoganglioside-GM1 (LYSO-GM1) and Tubulin (TUB). The ELISA assays are performed in duplicate using an assay where the colorimetric intensity at a specific wavelength is directly proportional to the amount of antibody in the sample. The fifth assay of this panel is performed in triplicate and measures the specific activity of calcium/calmodulin-dependent protein kinase II (CaM KII) induced by the patient serum in cultured human neuronal cell lines compared to controls. This panel measures the level of these antibodies, and the ability of the patient's sera to stimulate CaM KII at a single point in time. Results may vary depending on the patient's condition and status, whether they are on immunosuppressive agents, corticosteroids or other immune modulatory therapy, and the length of time post treatment.

LABORATORY TEST RESULTS

Anti-Dopamine Receptor D1: 250 500 1,000 2,000 4,000 8,000 16,000 32,000
Anti-Dopamine Receptor D2L: 250 500 1,000 2,000 4,000 8,000 16,000 32,000
Anti-Lysoganglioside GM1: 10 20 40 80 160 320 640 1,280
Anti-Tubulin: 250 500 1,000 2,000 4,000 8,000 16,000 32,000
Ca/Calmodulin Protein Kinase II (% of baseline): 75 100 130 150 175 200 225 250


moleculera labs
Cunningham Panel™ Testing Results

Patient Name: Patient 2: Pre Treatment
Patient Year of Birth: 2000
Patient ID Number: C000-368-PG
Date of Test Report: 08/19/2015

PATIENT REPORT

Submitting Physician:
Date of Collection: 09/19/2013
Date of Receipt: 09/20/2013

LABORATORY TEST RESULTS COMPARED TO NORMAL RANGES

	Anti-Dopamine Receptor D1 (titer)	Anti-Dopamine Receptor D2L (titer)	Anti-Lysoganglioside GM1 (titer)	Anti-Tubulin (titer)	CaM Kinase II (% of baseline)
Patient Result	1000	2000	160	500	142
Normal Ranges	500 to 2,000	2,000 to 8,000	80 to 320	250 to 1,000	53 to 130
Normal Mean	1,056	6,000	147	609	95

The Cunningham Panel measures human serum Immunoglobulin G (IgG) levels by Enzyme-Linked ImmunoSorbent Assay (ELISA) directed against: Dopamine D_1 Receptor (DRD1), Dopamine D_{2L} Receptor (DRD2L), Lysoganglioside-GM1 (LYSO-GM1) and Tubulin (TUB). The ELISA assays are performed in duplicate using an assay where the colorimetric intensity at a specific wavelength is directly proportional to the amount of antibody in the sample. The fifth assay of this panel is performed in triplicate and measures the specific activity of calcium/calmodulin-dependent protein kinase II (CaM KII) induced by the patient serum in cultured human neuronal cell lines compared to controls. This panel measures the level of these antibodies, and the ability of the patient's sera to stimulate CaM KII at a single point in time. Results may vary depending on the patient's condition and status, whether they are on immunosuppressive agents, corticosteroids or other immune modulatory therapy, and the length of time post treatment.

LABORATORY TEST RESULTS

Anti-Dopamine Receptor D1: 250 500 1,000 2,000 4,000 8,000 16,000 32,000
Anti-Dopamine Receptor D2L: 250 500 1,000 2,000 4,000 8,000 16,000 32,000
Anti-Lysoganglioside GM1: 10 20 40 80 160 320 640 1,280
Anti-Tubulin: 250 500 1,000 2,000 4,000 8,000 16,000 32,000
Ca/Calmodulin Protein Kinase II (% of baseline): 75 100 130 150 175 200 225 250

Treatment: Patient had IVIG within one month of diagnosis with complete symptom elimination.

Passive Transfer of Strep-Induced Antibodies Reproduces Behavioral Disorders in Mouse Model

Molecular Psychiatry (2009), 1–15
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www.nature.com/mp

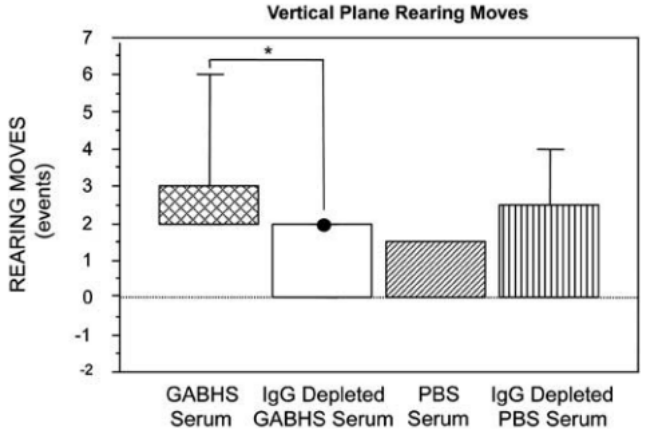
ORIGINAL ARTICLE

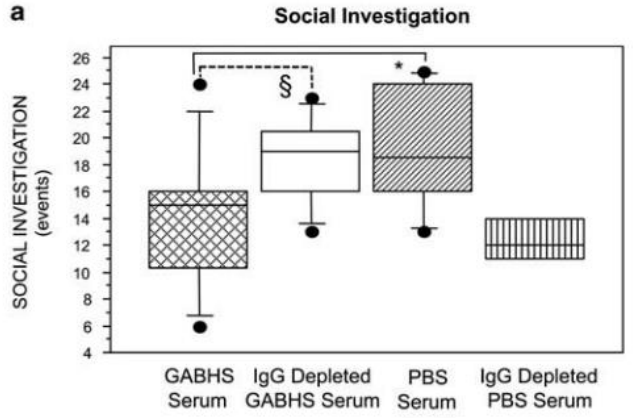
Passive transfer of streptococcus-induced antibodies reproduces behavioral disturbances in a mouse model of pediatric autoimmune neuropsychiatric disorders associated with streptococcal infection

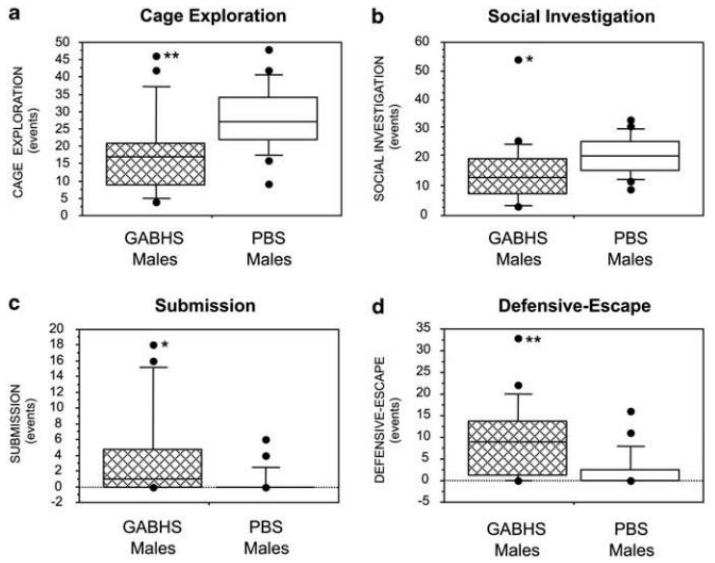
K Yaddanapudi[1], M Hornig[1], R Serge, J De Miranda, A Baghban, G Villar and WI Lipkin

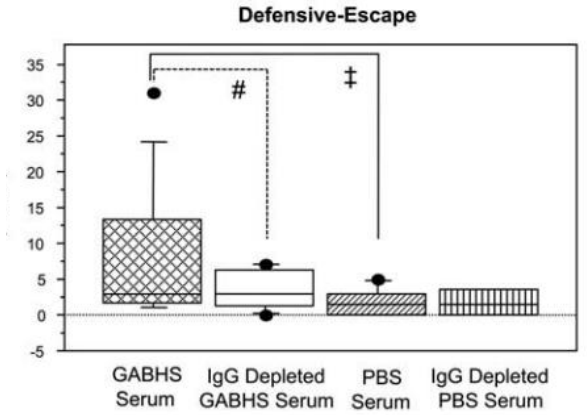
Center for Infection and Immunity and Department of Epidemiology, Mailman School of Public Health, Columbia University, New York, NY, USA

These antibodies are directed against group A b-hemolytic streptococcus matrix (M) protein and cross-react with molecular targets complement C4 protein and a-2-macroglobulin in brain. Here we show additional deficits in motor coordination, learning/memory and social interaction in PANDAS mice, replicating more complex aspects of human disease. Furthermore, we demonstrate for the first time that humoral immunity is necessary and sufficient to induce the syndrome through experiments wherein naive mice are transfused with immunoglobulin G (IgG) from PANDAS mice. Depletion of IgG from donor sera abrogates behavior changes.

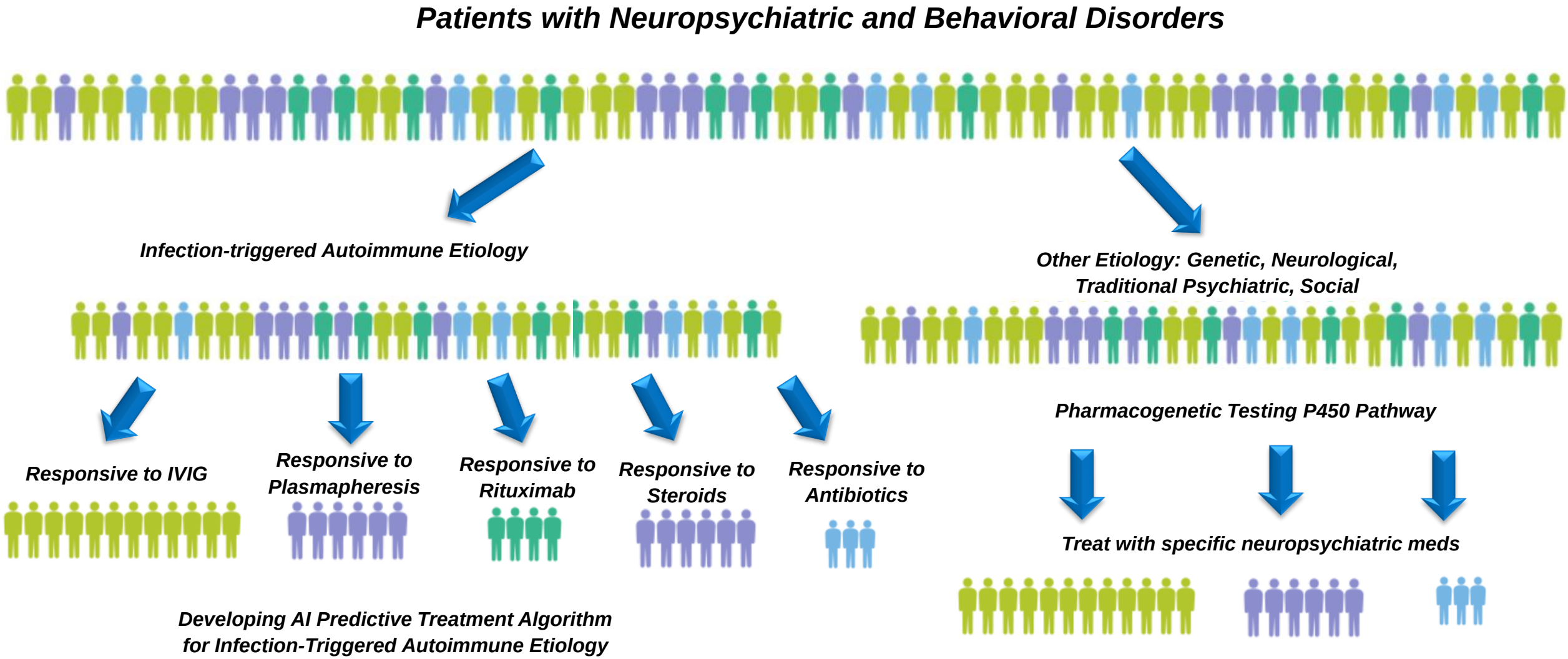




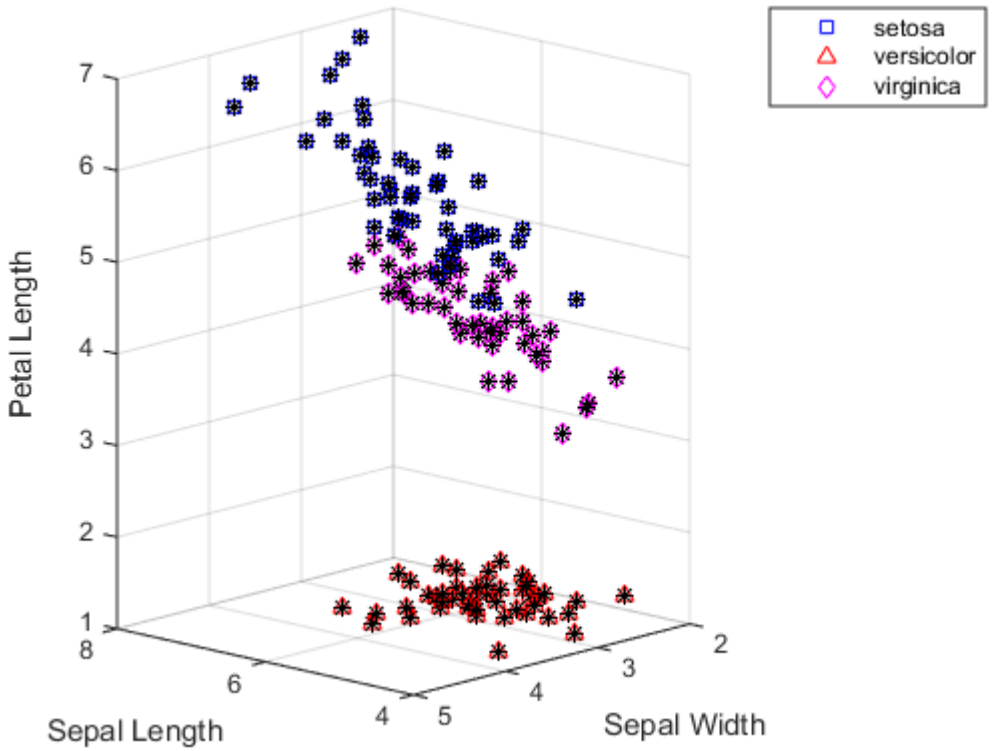




The Goal of Precision Medicine to Identify Patients Who Would Predictively Respond to Anti-inflammatory, Immune Modulatory, or Anti-infective Therapy



Hierarchal Clustering for Patient Stratification

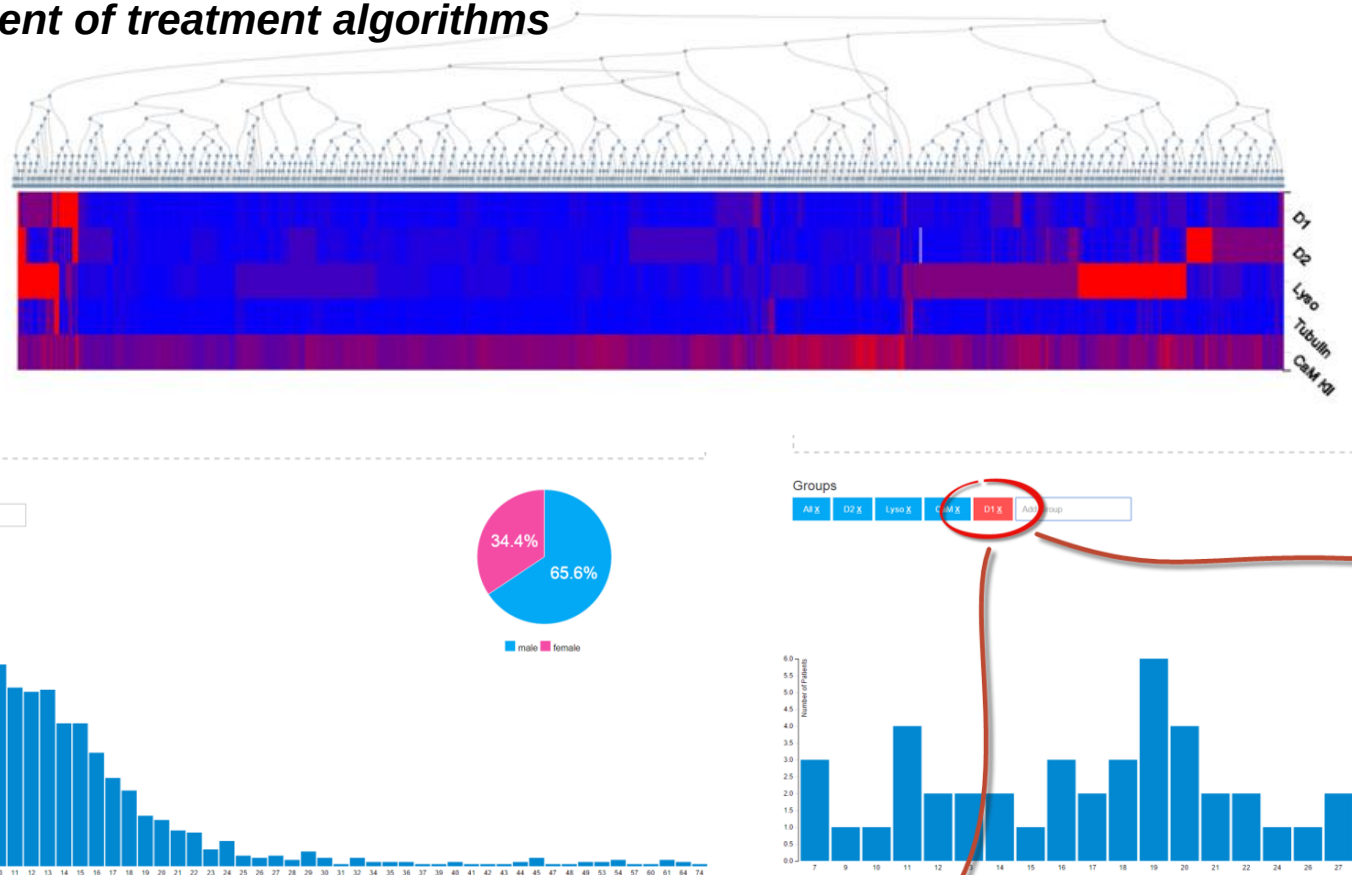


Hierarchal clustering analyzes the distance between points in n-dimensional space in order to identify cohorts.

A 3-dimensional example dataset is shown on the left, but this technique scales to any number of dimensions.

Demonstration of Patient Stratification for Development of Treatment Prediction Algorithm

A heat map of Moleculera proprietary data reveals clustering of patient symptoms, enabling development of treatment algorithms

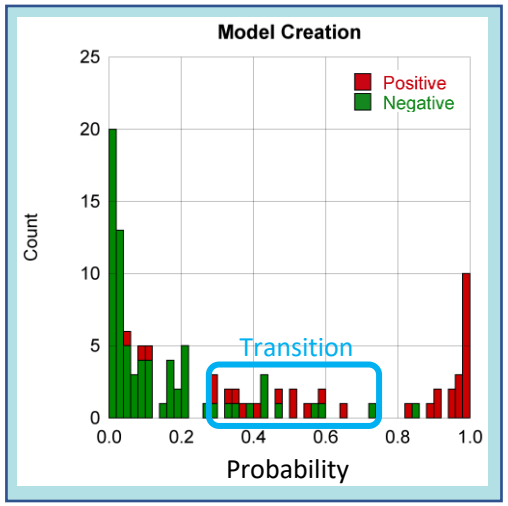


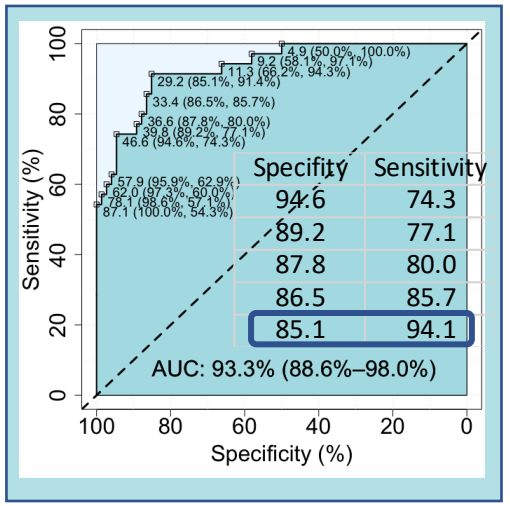
Example of patient stratification by results, age and gender with informed consent and IRB approval covering 3,000 patient specimens demonstrates the basis for algorithm development

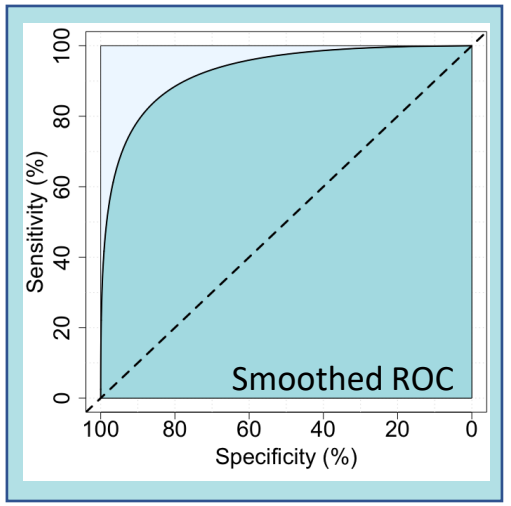
Demonstration of Logistic Regression Model Development for Treatment Prediction

MODEL A
- All subjects
- All assays

MODEL CREATION





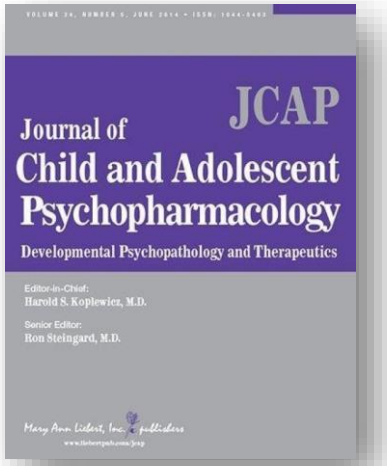


Coefficient	Description	Estimate	Std. Error	z value	Pr(>|z|)	P Group
c_0	(Intercept)	-7.36758	3.88457	-1.897	0.058	.
c_1	LogD1R	2.59815	1.30228	1.995	0.046	*
c_2	LogD2R	-0.11376	1.33203	-0.085	0.932	
c_3	LogLyso	2.43961	1.27585	1.912	0.056	.
c_4	LogTubulin	-5.67302	1.70016	-3.337	0.00085	***
c_5	CaMKII	0.07824	0.01785	4.384	0.000012	***

Signif.	Symbol
< 0.001	***
< 0.01	**
< 0.05	*
< 0.1	.

Therapeutic Modalities that Have Clinical Effectiveness in Treating Autoimmune Neuropsychiatric Disorders Secondary to Infections

Download Journal of Child and Adolescent Psychopharmacology Treatment Guidelines for PANDAS/PANS



Volume 27, Number 7 (2017)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Volume 27, Number 7, 2017
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Pp. 1–4
DOI: 10.1089/cap.2017.0042

Introduction

Overview of Treatment of Pediatric Acute-Onset Neuropsychiatric Syndrome

Susan E. Swedo, MD,[1] Jennifer Frankovich, MD, MS,[2,3] and Tanya K. Murphy, MD, MS[4]


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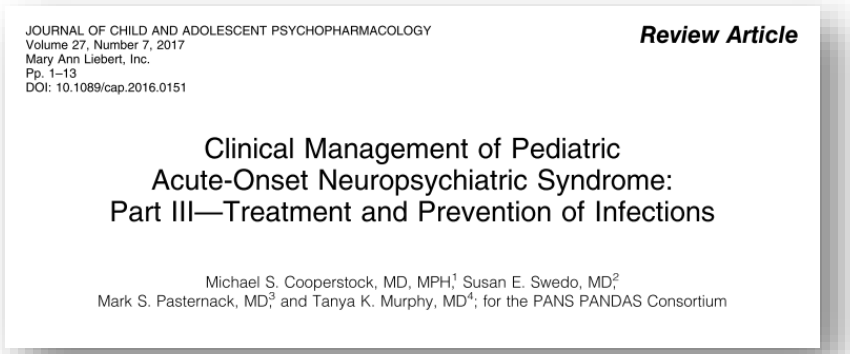
Pp. 1–8
DOI: 10.1089/cap.2016.0145

Review-Article

Clinical Management of Pediatric Acute-Onset Neuropsychiatric Syndrome: Part I–Psychiatric and Behavioral Interventions

Margo Thienemann, MD,[1] Tanya Murphy, MD,[2] James Leckman, MD,[3] Richard Shaw, MD, PhD,[1] Kyle Williams, MD,[4] Cynthia Kapphahn, MD, MPH,[1] Jennifer Frankovich, MD, MPH,[1] Daniel Geller, MD,[5] Gail Bernstein, MD,[6] Kiki Chang, MD,[1] Josephine Elia, MD,[7] and Susan Swedo, MD[8]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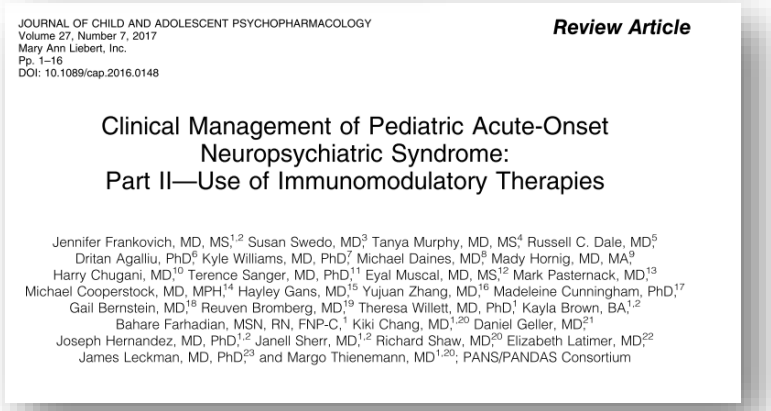
Volume 27, Number 7, 2017
Mary Ann Liebert, Inc.
Pp. 1–13
DOI: 10.1089/cap.2016.0151

Review Article

Clinical Management of Pediatric Acute-Onset Neuropsychiatric Syndrome: Part III—Treatment and Prevention of Infections

Michael S. Cooperstock, MD, MPH,[1] Susan E. Swedo, MD,[2] Mark S. Pasternack, MD,[3] and Tanya K. Murphy, MD[4]; for the PANS PANDAS Consortium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Mary Ann Liebert, Inc.
Pp. 1–16
DOI: 10.1089/cap.2016.0148

Review Article

Clinical Management of Pediatric Acute-Onset Neuropsychiatric Syndrome: Part II—Use of Immunomodulatory Therapies

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PANDAS PHYSICIANS NETWORK

PPN

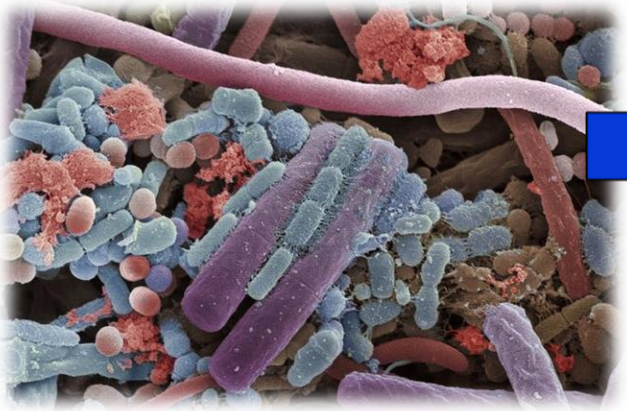
A DIVISION OF THE FOUNDATION FOR BRAIN SCIENCE AND IMMUNOLOGY

Diagnosis and Treatment Guidelines for Clinicians

www.pandasppn.org in the Exhibit Hall

Overview of Guidelines for PANDAS/PANS Treatment

Rule out Other Causes, Establish a Correct Diagnosis



Identify and Treat All Infections

- *Viral, Bacterial, Fungal, etc.*
- *Patients tend to have multiple infections, and many of these may be subclinical*
- *They are a stimulus of autoantibody production*

Treat the Inflammatory Pathway

Provide Symptomatic Relief as Necessary

Treat any Immune Dysregulation/Dysfunction

Effective Treatments Fall Into These Therapeutic Categories

Anti-Infectives

- Anti-microbials, Antivirals, Antifungals

Anti-Inflammatory

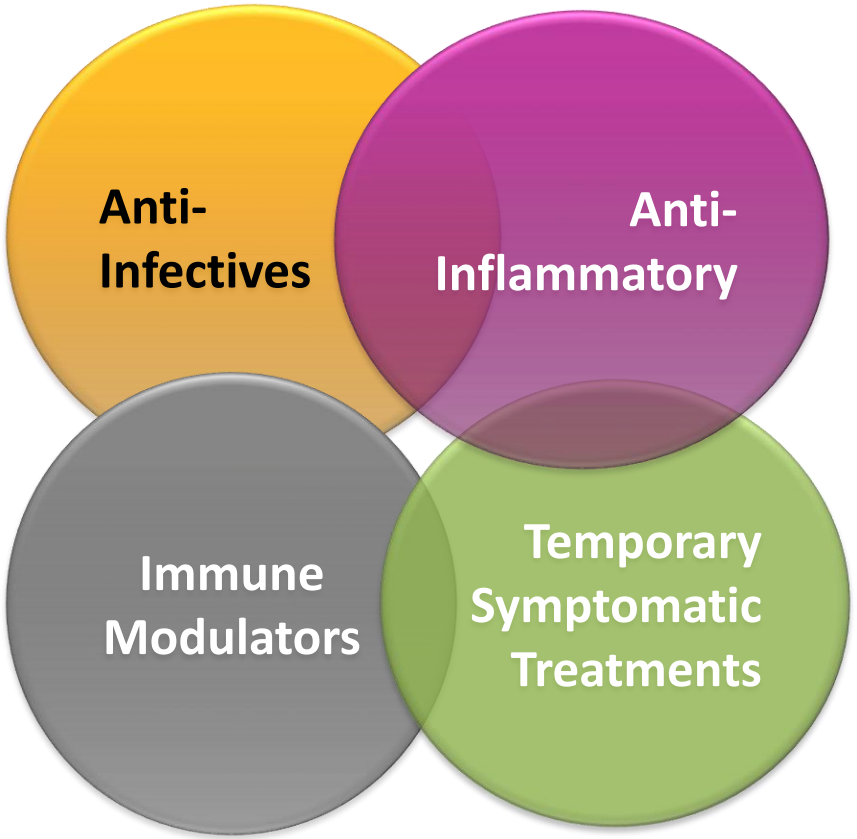
- Steroids
- NSAIDs

Immune modulating Therapies

- Plasmapheresis (Plasma exchange)
- Intravenous Immunoglobulins (IVIG)
- Rituximab

Temporary Symptomatic Treatment

- Cognitive Behavioral Therapy, E&RP
- Low-dose SSRIs

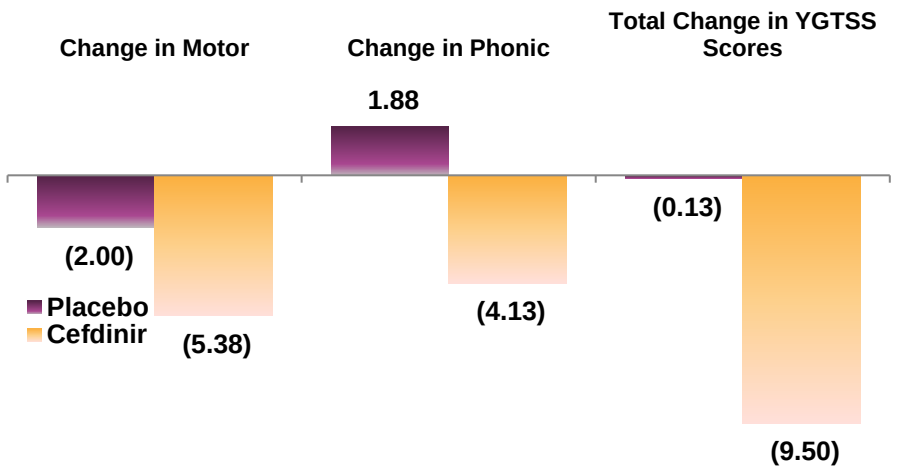


Clinical effectiveness has been demonstrated when there is biological evidence of autoimmune neuroinflammation

Anti-Infective and Immune Treatment Result in Improvements of Tics and OCD in these Patients

Change in motor tics after 30-day treatment

Treatment of Infection/Inflammation(1)



Average change in Yale Global Tic Severity Scale (YGTSS) scores. Scores represent changes in YGTSS taken at baseline and end of study.

30-day study showed positive results for treatment, 20 subjects were randomized to receive placebo or the antibiotic cefdinir for the treatment of recent-onset OCD and/or tics

Murphy, T. K., et al. (2015). "Cefdinir for recent-onset pediatric neuropsychiatric disorders: a pilot randomized trial." J Child Adolesc Psychopharmacol 25(1): 57-64.

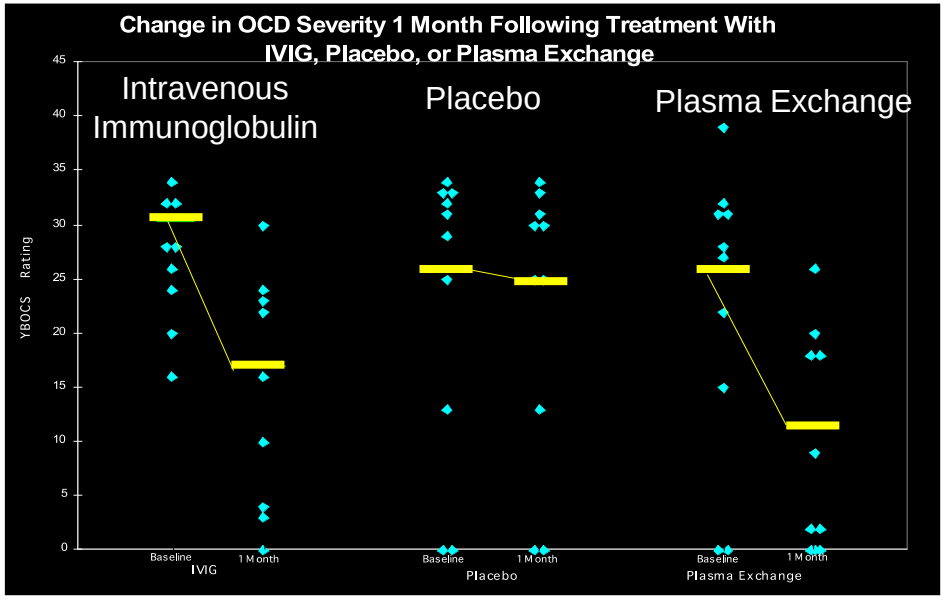
THE LANCET

Therapeutic plasma exchange and intravenous immunoglobulin for obsessive-compulsive disorder and tic disorders in childhood

Perlmutter, S. J., et al. (1999). "Therapeutic plasma exchange and intravenous immunoglobulin for obsessive-compulsive disorder and tic disorders in childhood." The Lancet 354(9185): 1153-1158.

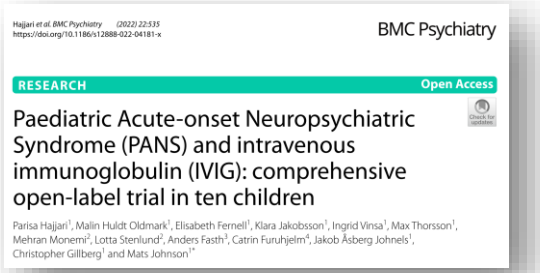
Change in OCD after one treatment

Treatment of Immune System(2)



The NIMH study showed that treatment with IVIG or plasma exchange experienced marked reduction of neuropsychiatric symptoms

Open Label Prospective IVIG Treatment in 10 PANS Patients (2022)


Hajjari et al. BMC Psychiatry (2022) 22:535
https://doi.org/10.1186/s12888-022-04181-x

BMC Psychiatry

RESEARCH Open Access

Paediatric Acute-onset Neuropsychiatric Syndrome (PANS) and intravenous immunoglobulin (IVIG): comprehensive open-label trial in ten children

Parisa Hajjari[1], Malin Huldt Oldmark[1], Elisabeth Fernell[1], Klara Jakobsson[1], Ingrid Vinsa[1], Max Thorsson[1], Mehran Monemi[2], Lotta Stenlund[2], Anders Fasth[3], Catrin Furuhjelm[4], Jakob Åsberg Johnels[1], Christopher Gillberg[1] and Mats Johnson[1*]

- Open-label prospective in-depth trial including ten children (median age 10.3 years) with PANS, who received IVIG treatment 2 g/kg monthly for three months

- This open-label prospective IVIG treatment trial demonstrated substantial improvements in PANS symptom severity and impairment (including OCD symptoms), global functioning and school attendance after 3 monthly IVIG treatments. From severe illness at baseline, 9 patients were clinical responders with > 30% improvement, and 7 patients improved to mild illness or remission

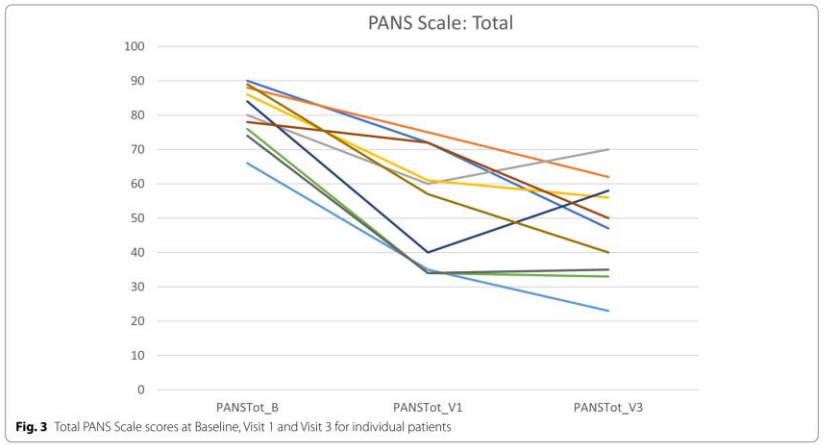


Fig. 3 Total PANS Scale scores at Baseline, Visit 1 and Visit 3 for individual patients

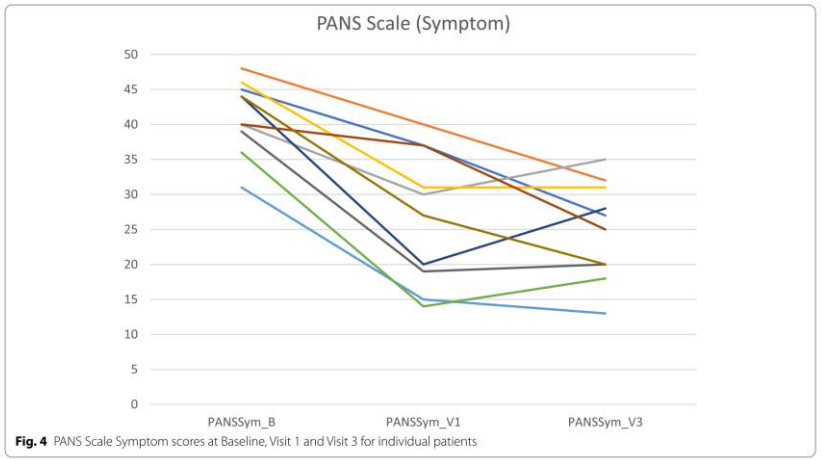


Fig. 4 PANS Scale Symptom scores at Baseline, Visit 1 and Visit 3 for individual patients

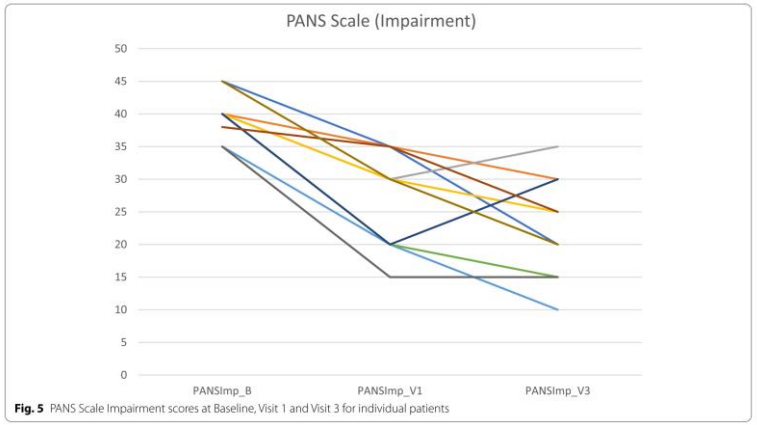


Fig. 5 PANS Scale Impairment scores at Baseline, Visit 1 and Visit 3 for individual patients

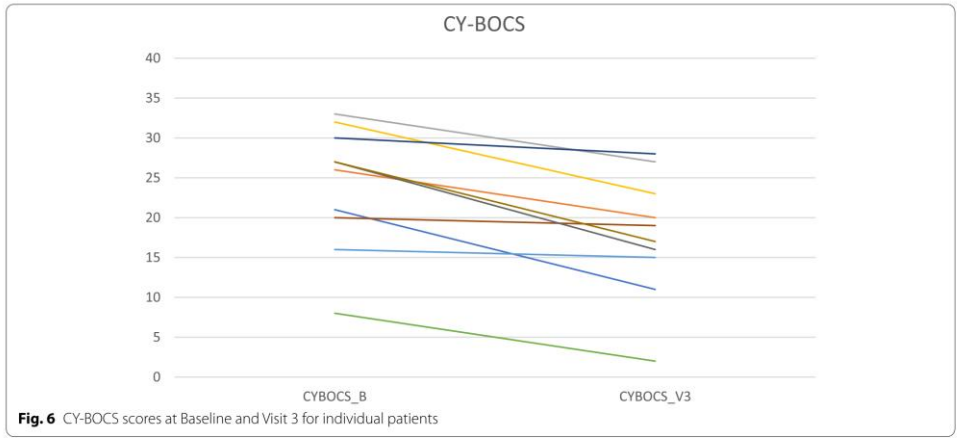
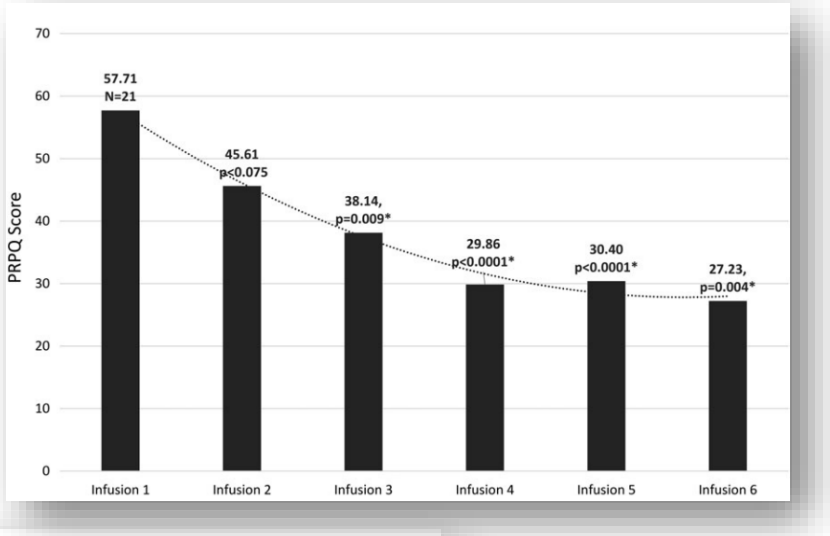
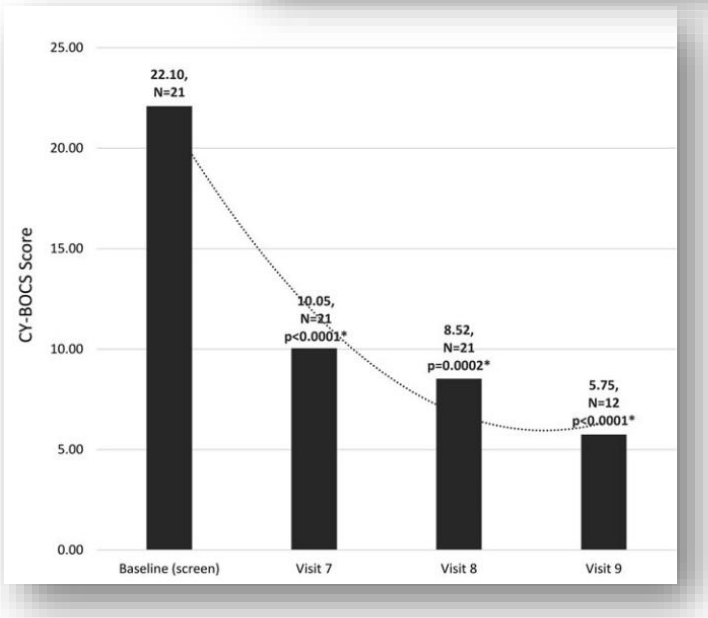


Fig. 6 CY-BOCS scores at Baseline and Visit 3 for individual patients

IVIG Treatment in 21 PANS Patients at 3 Independent Sites (2020)

- Enrolled **21 PANS patients** at **3** independent sites (**7 patients/site**)
- Administered IVIG (Octagam 5) at **1 g/kg** every **21 days** for a total of six infusions (cycles) over a period of 18 weeks.
- Evaluated for psychometric assessments
  - **CY-BOCS** (Children's Yale-Brown Obsessive-Compulsive Scale)
  - **CGI-S** (Clinical Global Impressions Scale)
  - **YGTSS** (Yale Global Tic Severity Scale)
  - **ADIS** (Anxiety and Related Disorders Interview Schedule)
  - **PRPQ** (Parent-Rated PANS Questionnaire)
- >50% improvement for at least 8 weeks, and up to 46 weeks in a subset of subjects





Melamed, I., et al. (2021). "Evaluation of Intravenous Immunoglobulin in Pediatric Acute-Onset Neuropsychiatric Syndrome." J Child Adolesc Psychopharmacol 31(2): 118-128.

Identifying the Root of a Disorder is Critical to Effective Treatment and Outcomes

Tack Law #1

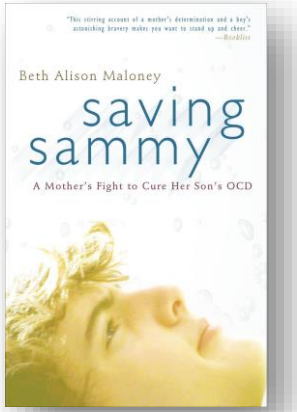
Adapted from Dr. Sidney Baker

- If you are sitting on a tack, the treatment is not two Advil every 3 to 4 hours
- The treatment for **“tack sitting”** is **“tack removal”**
- Search for the root and treat the ***cause*** rather than the symptoms

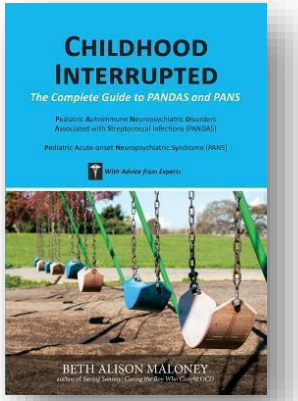
Tack Law #2

- If you are sitting on two tacks, removing one tack does not eliminate 50% of the symptoms
- Complex conditions are “complex”
- To be effective, address all the underlying ***issues*** for resolution

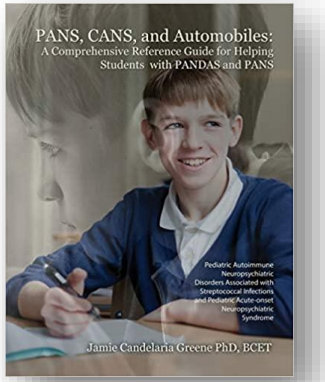
References for Autoimmune Encephalopathies, Basal Ganglia Encephalitis, Post-Treatment Lyme, and PANDAS and PANS



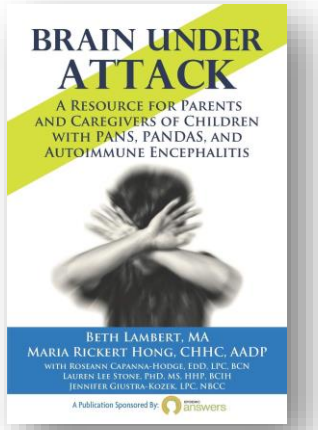
Saving Sammy: A Mother's Fight to Cure Her Son's OCD
By: Beth Alison Maloney



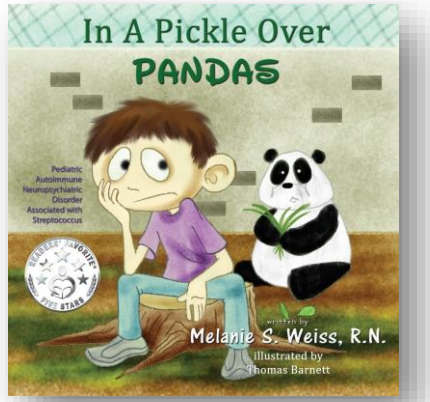
Childhood Interrupted: The Complete Guide to PANDAS and PANS
By: Beth Alison Maloney



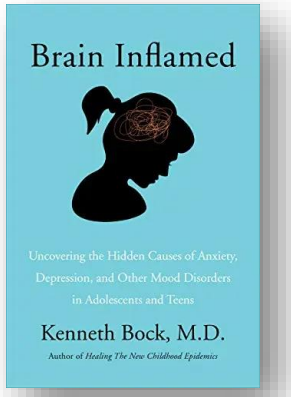
PANS, CANS, and Automobiles: A Comprehensive Reference Guide for Helping Students with PANDAS and PANS
By: Jamie Candelaria Greene



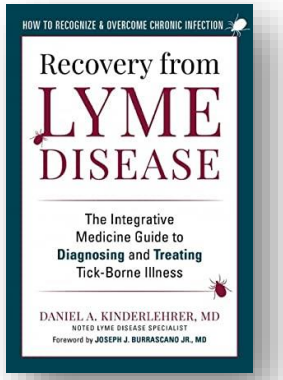
Brain Under Attack: A Resource for Parents and Caregivers of Children with PANS, PANDAS, and Autoimmune Encephalitis
By: Beth Lambert & Maria Rickert Hong



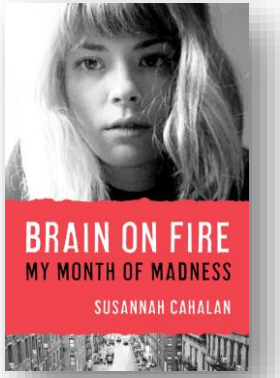
In A Pickle Over PANDAS
By: Melanie S. Weiss



Brain Inflamed: Uncovering the Hidden Causes of Anxiety, Depression, and Other Mood Disorders in Adolescents and Teens
By: Kenneth Bock, M.D.

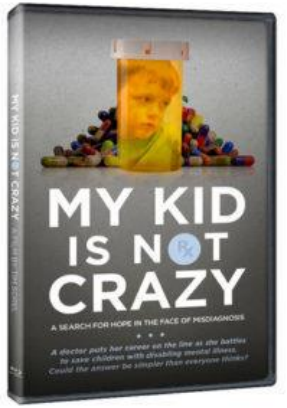


Recovery from Lyme Disease : The Integrative Medicine Guide to Diagnosing and Treating Tick-borne Illness
By: Daniel A. Kinderlehrer, M.D.



Brain on Fire: My Month of Madness
By: Susannah Cahalan

The Parent's Survival Guide to PANDAS/PANS: A Handbook to Manage Neuroimmune Disorders in Your Child Without Losing Your Mind
By: Deborah Marcus



DVD/Video/YouTube
My Kid is Not Crazy: A Search for Hope in the Face of Misdiagnosis
By: Tim Sorel

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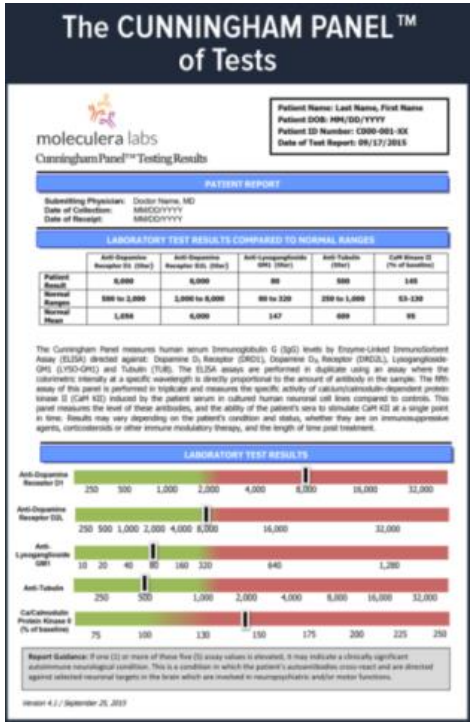

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Our mission is to bring hope and healing to those suffering with autoimmune neuropsychiatric disorders

Thank you for helping those suffering with these disorders, to gain hope and get well!

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- Scientists, clinical, laboratory and support staff
- Scientific and medical advisors

- Over 15,000 patients tested and treated
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Department of Microbiology & Immunology
University of Oklahoma Health Sciences Center

- Dr. Madeleine Cunningham's laboratory
- Post-docs and laboratory staff