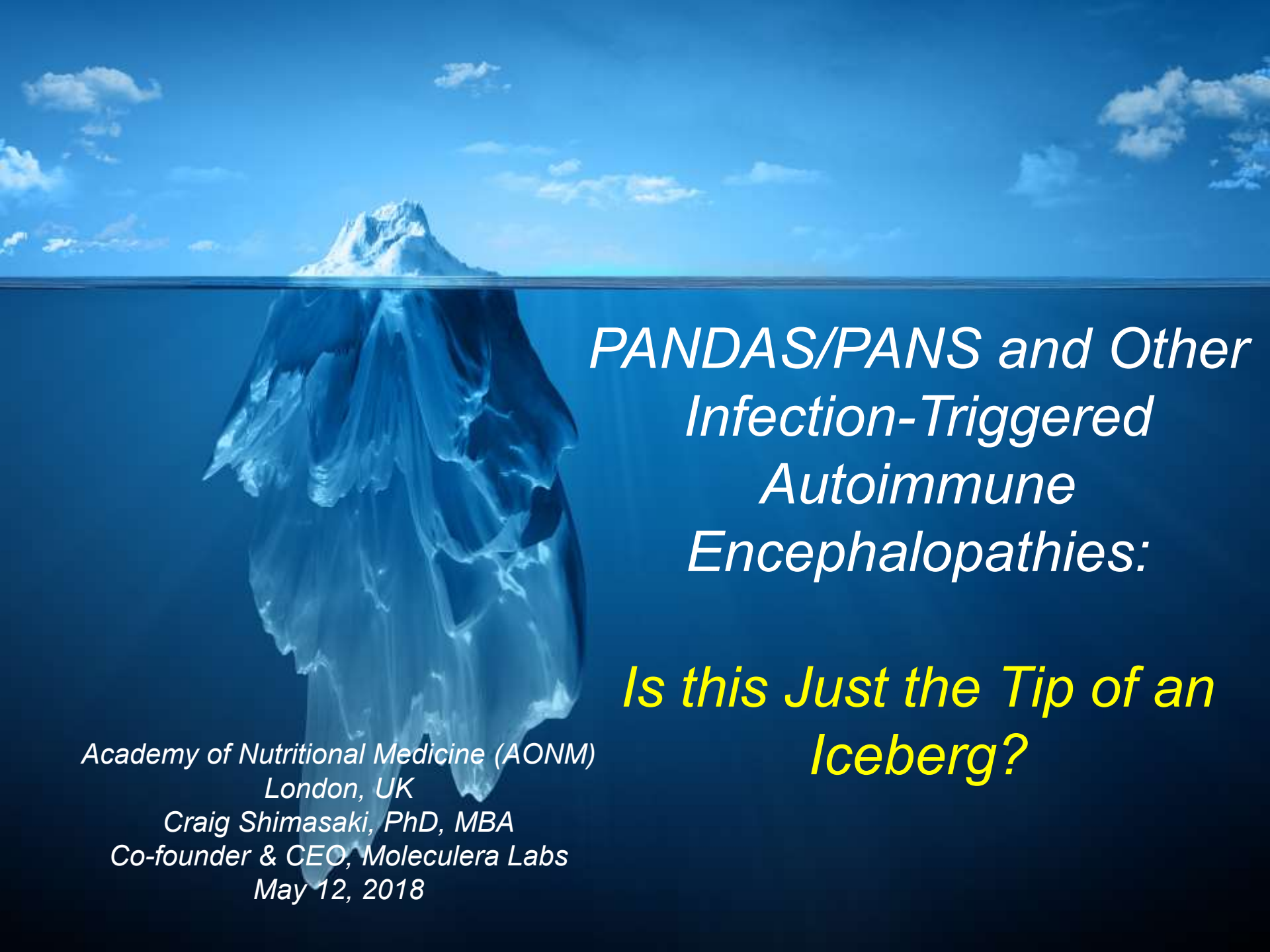


PANDAS/PANS and Other Infection-Triggered Autoimmune Encephalopathies:

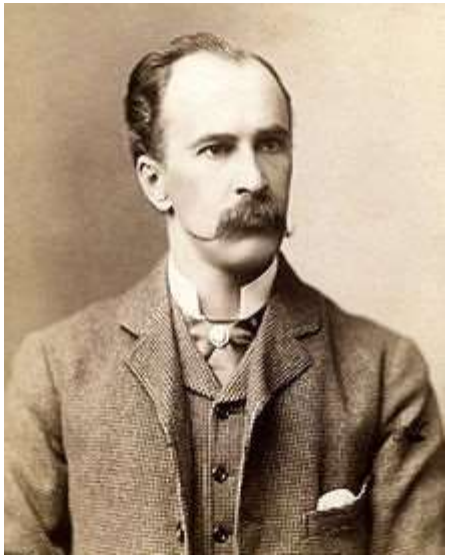
Is this Just the Tip of an Iceberg?

Academy of Nutritional Medicine (AONM)
London, UK
Craig Shimasaki, PhD, MBA
Co-founder & CEO, Moleculera Labs
May 12, 2018

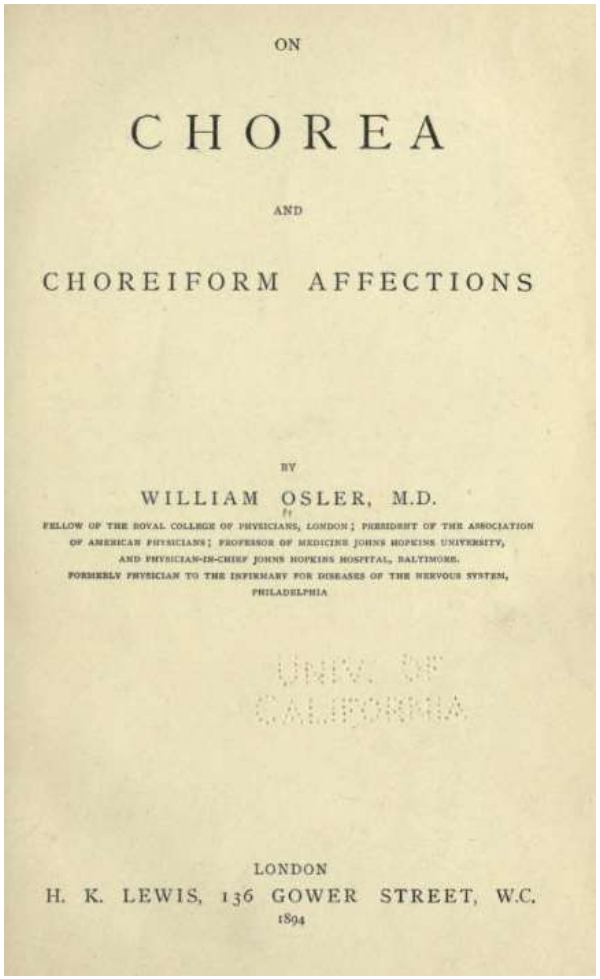
Topics We will Cover

1. **Definition of PANDAS/PANS**
   - Nomenclature and alternative nomenclature
   - Proposed mechanism
   - What is the controversy?
2. **Brief clinical presentation and symptoms associated with PANDAS/PANS**
   - Some common infectious triggers
3. **Molecular mimicry and its role in post-infectious autoimmune disorders of the brain**
4. **Anti-neuronal antibodies in the Cunningham Panel**
   - Biomarker selection
   - Patient population study
   - Swedish study conclusions and issues
5. **Broader-based patient populations outside of PANDAS/PANS, including adults**

What is PANDAS? Sydenham's Chorea is the Model



In 1894, Sir William Osler described "bizarre" and "perseverative behaviors" of children with "chorea minor," and first made the relationship between obsessive-compulsive OCD symptoms and Sydenham's chorea (SC)


ON

CHOREA

AND

CHOREIFORM AFFECTIONS

BY

WILLIAM OSLER, M.D.

FELLOW OF THE ROYAL COLLEGE OF PHYSICIANS, LONDON; PRESIDENT OF THE ASSOCIATION OF AMERICAN PHYSICIANS; PROFESSOR OF MEDICINE JOHNS HOPKINS UNIVERSITY, AND PHYSICIAN-IN-CHIEF JOHNS HOPKINS HOSPITAL, BALTIMORE. FORMERLY PHYSICIAN TO THE INFIRMARY FOR DISEASES OF THE NERVOUS SYSTEM, PHILADELPHIA

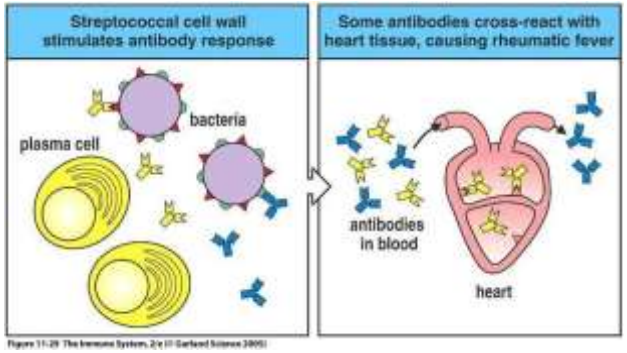
LONDON

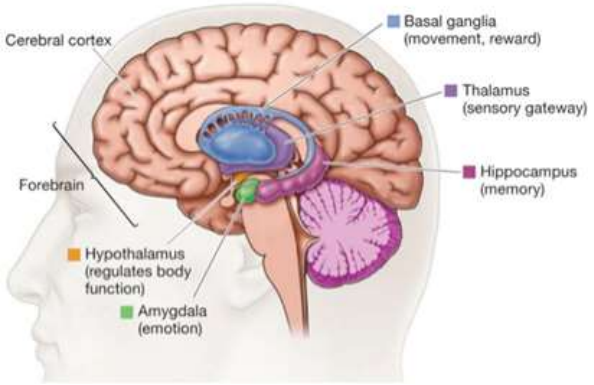
H. K. LEWIS, 136 GOWER STREET, W.C.

1894

Sydenham's Chorea is the Medical Model for PANS/PANDAS

- Chorea: "Dance-like" abnormal movements.
  - Loss of fine-motor control
  - Loss of emotional control
- Sydenham's Chorea is the neurological manifestation of Acute Rheumatic Fever
- Group A Streptococcus-triggered autoimmune reaction involving the brain





What is PANDAS?

Pediatric Autoimmune Neuropsychiatric Disorder Associated with Streptococcal infection

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.

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

THE AMERICAN JOURNAL OF PSYCHIATRY

The PANS Research Consortium (PRC) Immunomodulatory Task Force

Comprised of immunologists, rheumatologists, neurologists, infectious disease experts, general pediatricians, psychiatrists, nurse practitioners, and basic scientists with expertise in neuroimmunology and PANS-related animal models

- Stanford PANS Clinic and Research Program at **Lucile Packard Children's Hospital**, Stanford University School of Medicine, Palo Alto, California.
- Pediatric Allergy, Immunology, and Rheumatology, **Stanford University School of Medicine**, Palo Alto
- Pediatrics and Developmental Neuroscience Branch, **National Institute of Mental Health**, Bethesda, Maryland
- Rothman Center for Pediatric Neuropsychiatry, Pediatrics and Psychiatry, **University of South Florida Morsani College of Medicine**, Tampa, Florida.
- Paediatrics and Child Health, Institute for Neuroscience and Muscle Research, the **Children's Hospital at Westmead, University of Sydney**, Sydney, Australia
- Pathology and Cell Biology (in Neurology and Pharmacology), **Columbia University**, New York, New York
- Pediatric Neuropsychiatry and Immunology Program in the OCD and Related Disorders Program, **Harvard Medical School**, Boston, Massachusetts
- Allergy, Immunology, and Rheumatology, The **University of Arizona College of Medicine**, Tuscon, Arizona
- Epidemiology, Center for Infection and Immunity, **Columbia University Medical Center**, New York, New York
- Pediatric Neurology, **Nemours/Alfred I. duPont Hospital for Children**, Wilmington, Delaware
- Neurology, University of Southern California Pediatric Movement Disorders Center, **Children's Hospital of Los Angeles**, Los Angeles, California
- Pediatric Rheumatology, **Baylor College of Medicine**, Houston, Texas
- Pediatric Infectious Disease, **Harvard Medical School**, Boston, Massachusetts
- Pediatric Infectious Diseases, **University of Missouri School of Medicine**, Columbia, Missouri
- Pediatric Infectious Diseases, **Stanford University School of Medicine**, Stanford, California
- Pediatric Rheumatology, **Tufts University School of Medicine**, Boston, Massachusetts
- Microbiology and Immunology, **College of Medicine, University of Oklahoma Health Sciences Center**, Oklahoma City, Oklahoma
- Child and Adolescent Psychiatry, **University of Minnesota Medical School**, Minneapolis, Minnesota
- Pediatric Rheumatology, **Miami Rheumatology**, LLC, Miami, Florida
- Psychiatry and Behavioral Sciences, Child and Adolescent Psychiatry, **Stanford University School of Medicine**, Palo Alto, California
- Pediatric OCD and Tic Disorder Program, **Harvard Medical School**, Boston, Massachusetts
- Pediatric Neurology, **Georgetown University Hospital**, Washington, District of Columbia
- Child Psychiatry, Psychiatry, Psychology and Pediatrics, **Yale Child Study Center, Yale School of Medicine**, New Haven, Connecticut

Nomenclature and Hierarchy

PANS
Pediatric Acute-onset Neuropsychiatric Syndromes

PITANDS
Pediatric Infection Triggered Autoimmune Neuropsychiatric Disorders

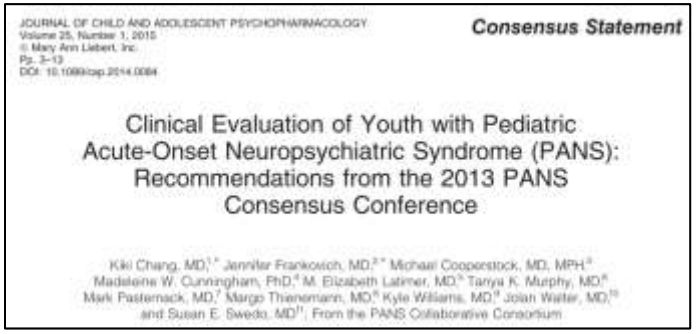
PANDAS
Pediatric Autoimmune Neuropsychiatric Disorder Associated with Streptococcal Infection

Other Microbes
(Lyme, Mycoplasma, others?)

Non-Infectious Triggers

Environmental factors
Metabolic disorders
Others

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

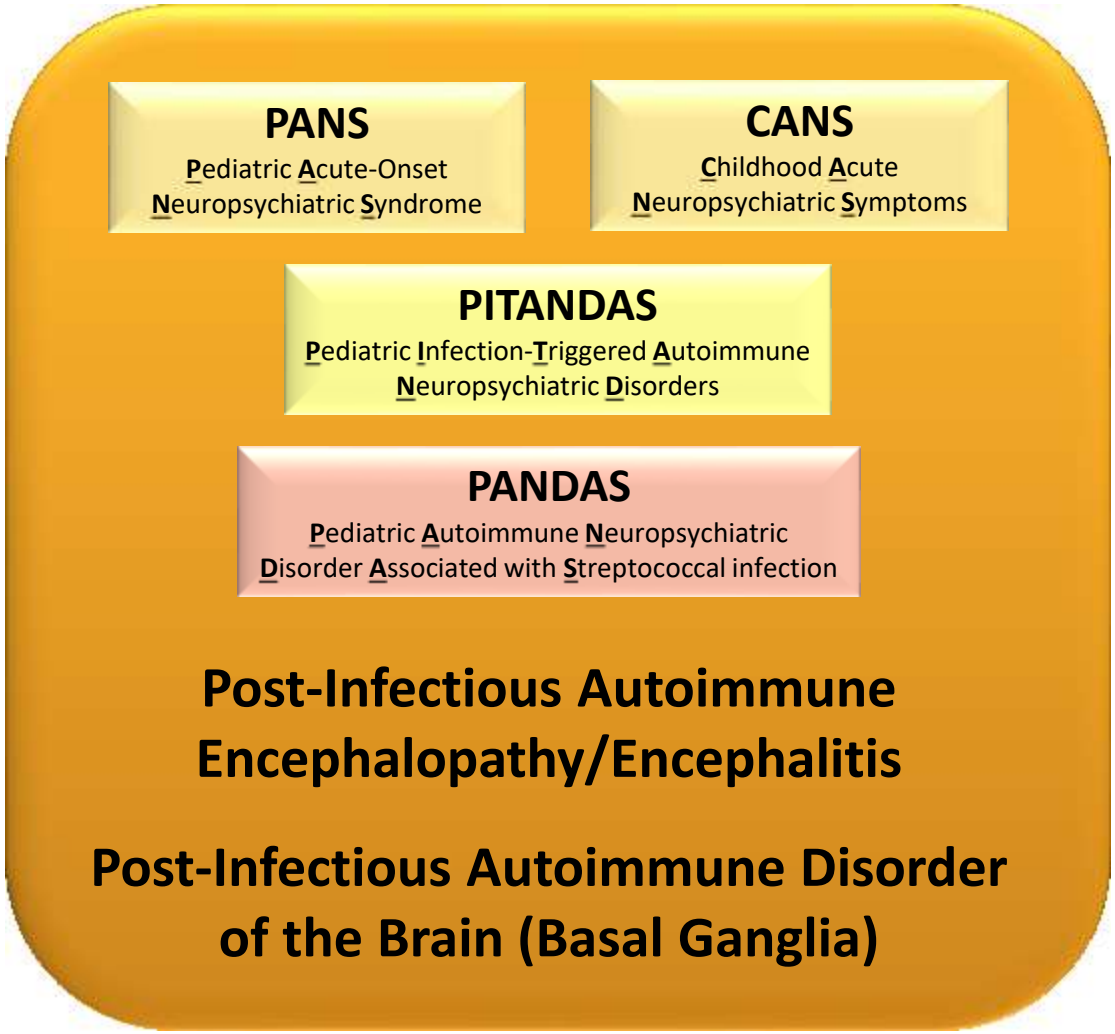

JOURNAL OF CHILD AND ADOLESCENT PSYCHOPHARMACOLOGY
Volume 25, Number 1, 2015
© Mary Ann Liebert, Inc.
Pp. 3–13
DOI: 10.1089/cap.2014.0084

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] Joan Walter, MD,[10] and Susan E. Swedo, MD[11]; From the PANS Collaborative Consortium

PANDAS is a Subset of Broader Related Conditions

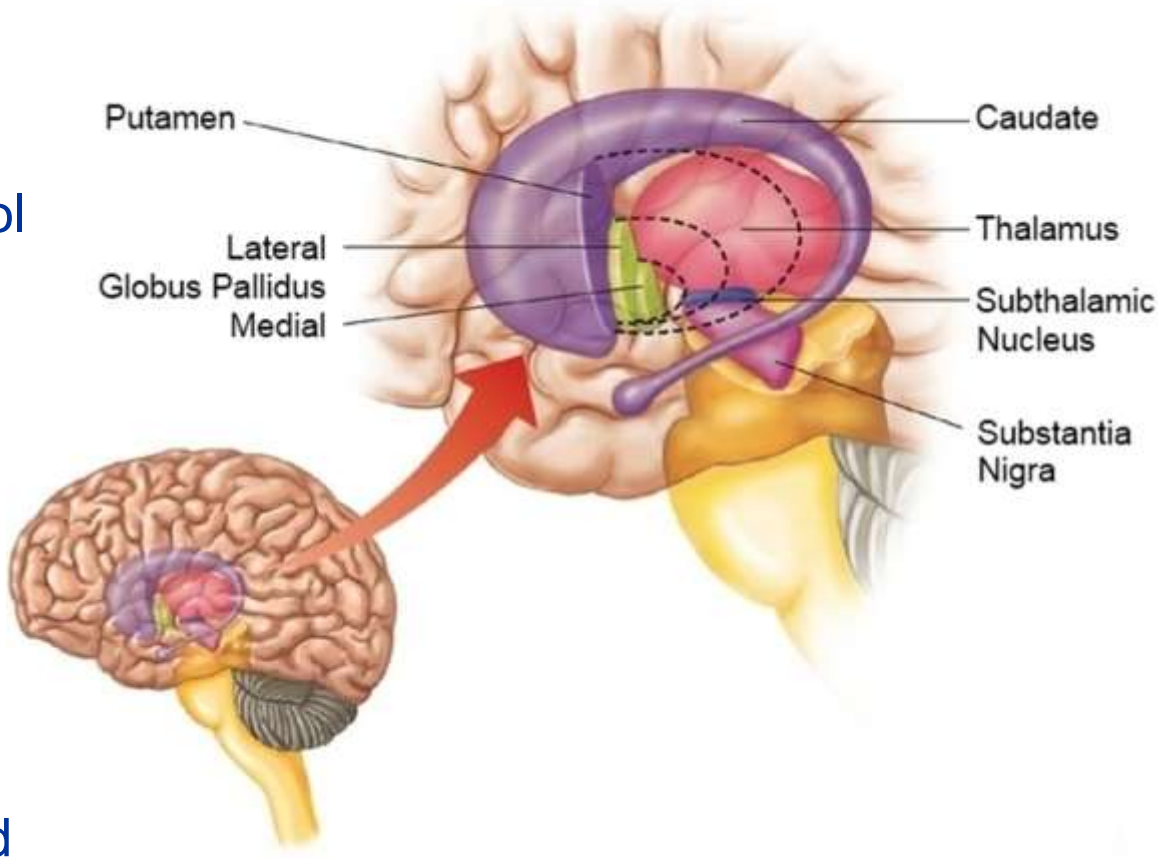


1. **Infection-Triggered**
   - Bacterial, Viral, Parasitic, Fungal or possibly environmental?
2. **Autoimmune**
   - Immune dysfunction or Immune-mediated
3. **Neuropsychiatric Syndrome or Symptoms**
   - Multisymptom
4. **Directed against portions of the brain**
   - Basal ganglia
5. **Acute-Onset**
   - (Criteria for PANDAS/PANS but not observed in all conditions)

Post-infectious Autoimmune Disorders of the Basal Ganglia

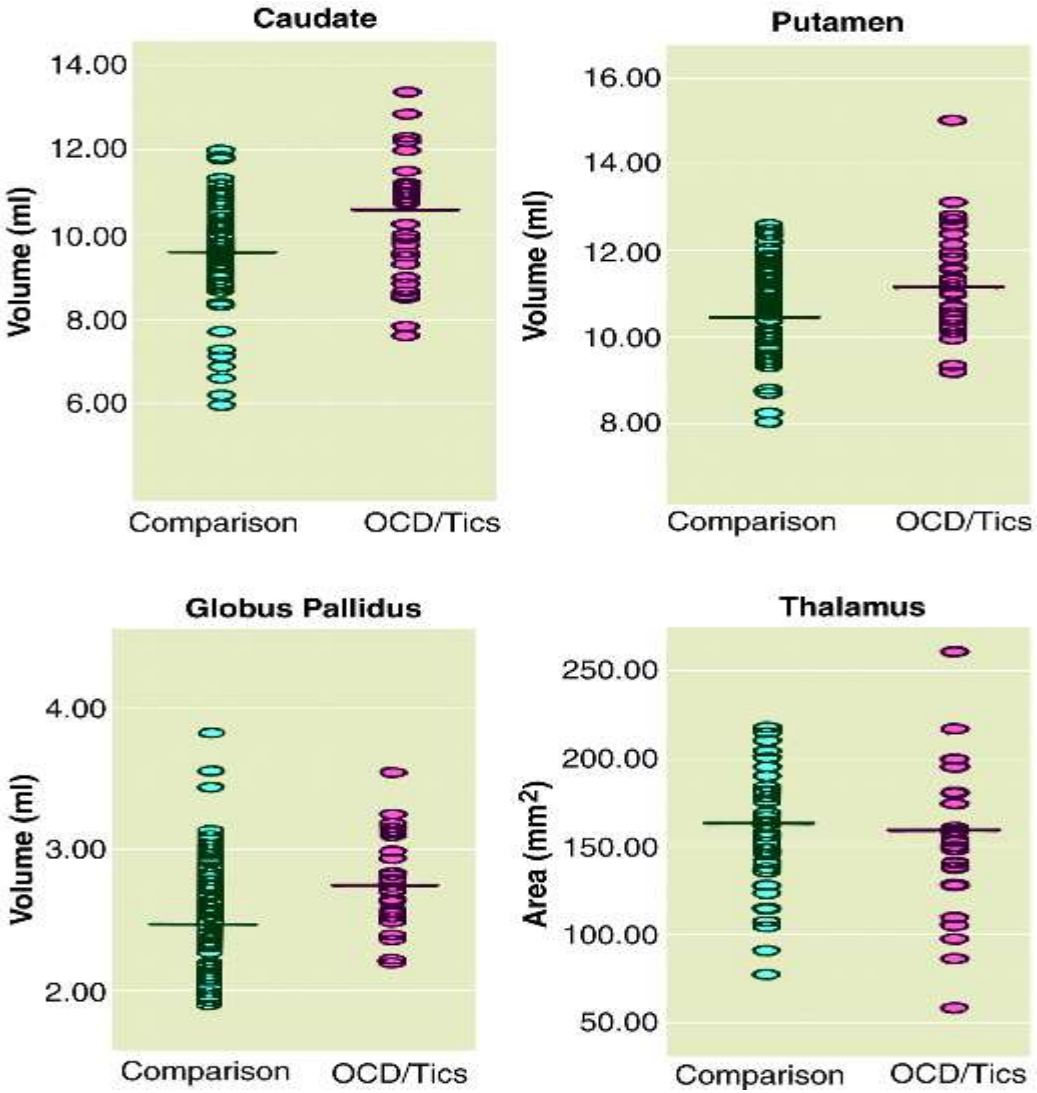
Responsible for:

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



Two disorders of the Basal Ganglia are Parkinson's' Disease and Huntington's Disease

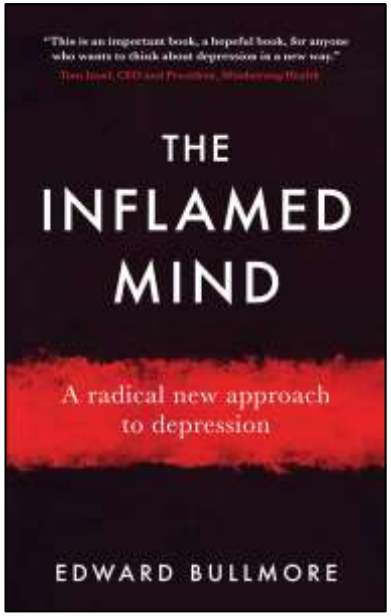
MRI Inflammation in Strep-Associated Children with OCD/Tics compared to Healthy Children



The average size of the Caudate, Putamen, Globus Pallidus was enlarged, but not the Thalamus or total Cerebrum in Strep Associated OCD/Tics children compared to health children

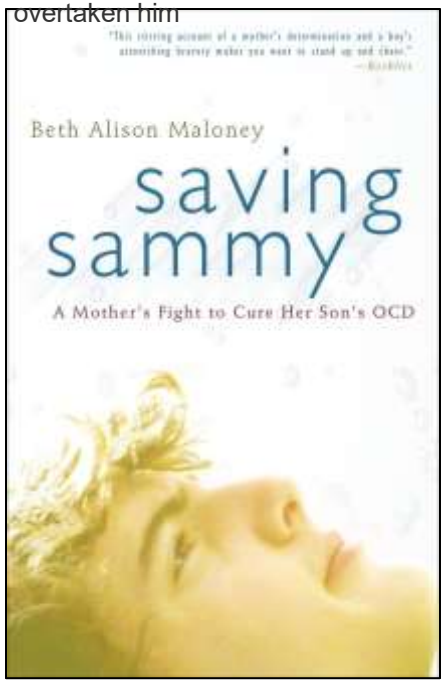
Am J Psychiatry 2000, Giedd et al. 157:281-283

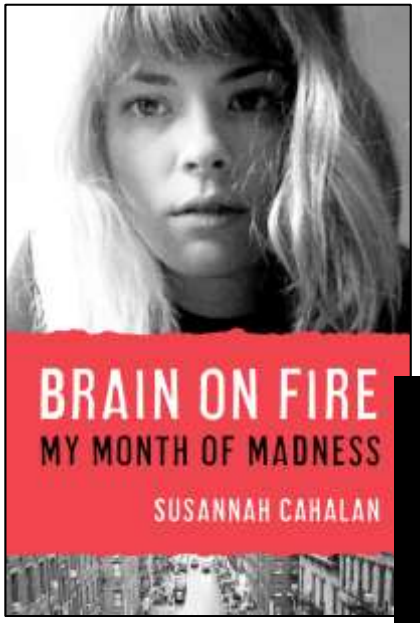
Neuroinflammation, Autoimmunity and the Brain



Released April 2018
Dr. Bullmore is Co-Chair of Cambridge Neuroscience, Scientific Director of the Wolfson Brain Imaging Centre, and Head of the Department of Psychiatry at Cambridge University

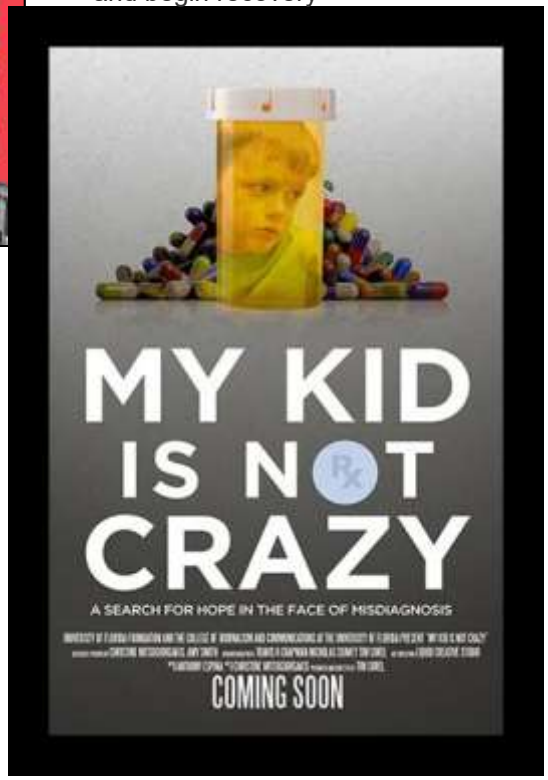
Linking infection to "mental" illness, as strep antibodies are linked to the neurological Tourette's syndrome, has been rejected by many doctors since the rise of psychoanalysis, but Maloney insisted Sammy be tested for strep titers when he became unable to attend school and to walk. He was diagnosed with PANDAS. Antibiotics ended two torturous years for the family, and Sammy's regains came as rapidly as the symptoms had overtaken him





Susannah Cahalan is a news reporter at the *New York Post* who succumbed to an infection then began a painful journey to be diagnosed with an autoimmune disorder attacking her brain, and then the path to recovery after receiving the right treatment.

DVD: Documentary chronicling several families and their children suffering from PANDAS and what they went through to reach a diagnosis and begin recovery



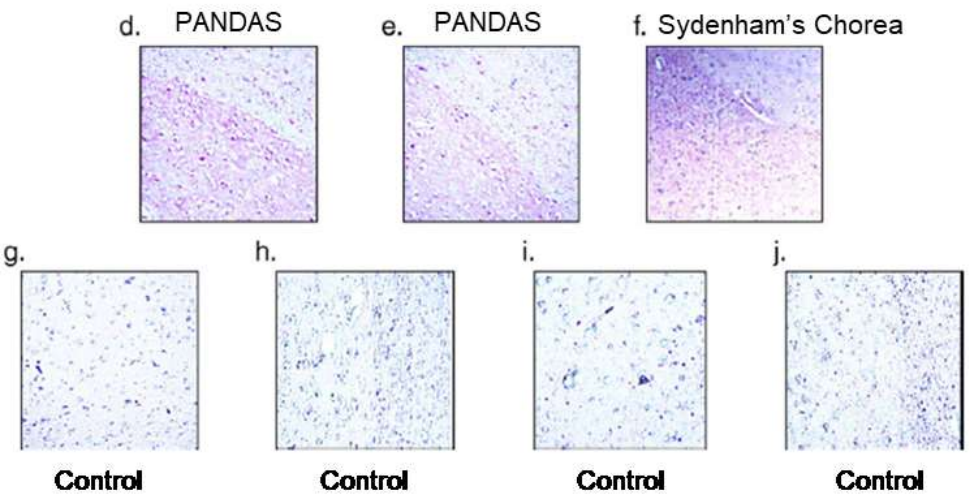
CSF and Serum Autoantibody Binding to the Brain

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

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

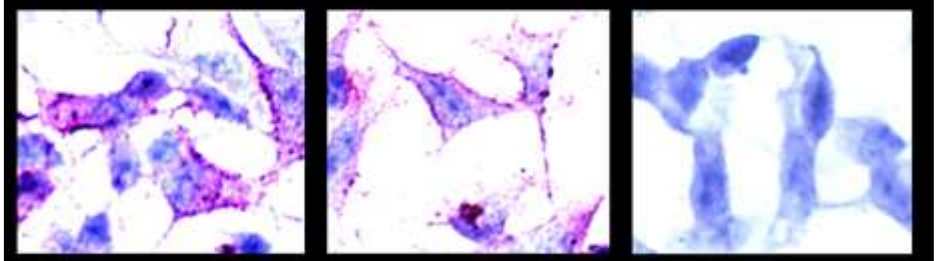
Antibody-Mediated Neuronal Cell Signaling in Behavior and Movement Disorders

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

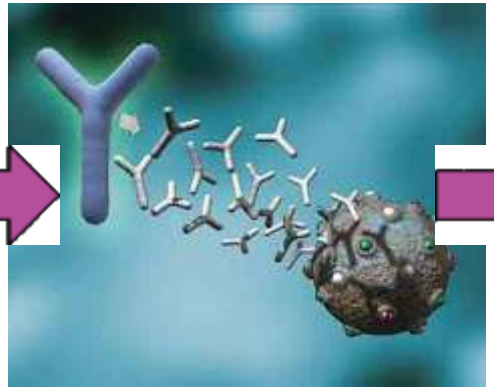


VOLUME 9 | NUMBER 7 | JULY 2003 NATURE MEDICINE

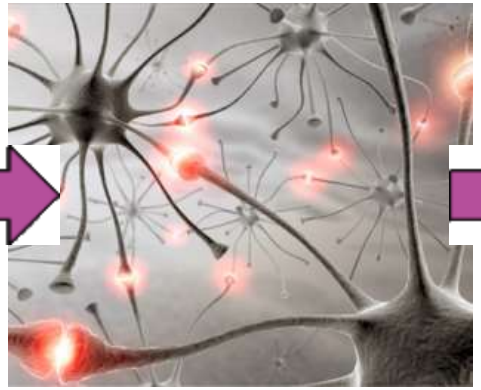
One Mechanism of Infection-Triggered Autoimmune Neuropsychiatric Disorders

Microbial, Viral, Fungal Infection Occurs

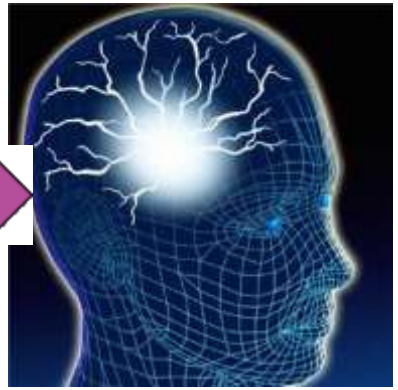
Body Produces Antibodies That Recognize Infectious Agent



Antibodies Cross-React With Neurologic Receptors (molecular mimicry)



Reaction Disrupts Brain Function (friendly fire)



Population-based Studies Linking Infection, the Immune System and Mental Illness

Danish study of ~4,500 individuals revealed a relationship between inflammatory markers and neuropsychiatric disorders[2]

Patients with elevated Interleukin-6 (IL-6) were more likely to be depressed at age 18 years	+55%
Higher IL-6 baseline levels increased the risks of psychotic experiences and psychotic disorder at age 18	+81%

Danish study of 3.6 million individuals revealed an increased risk of mental illness associated with infections[1]

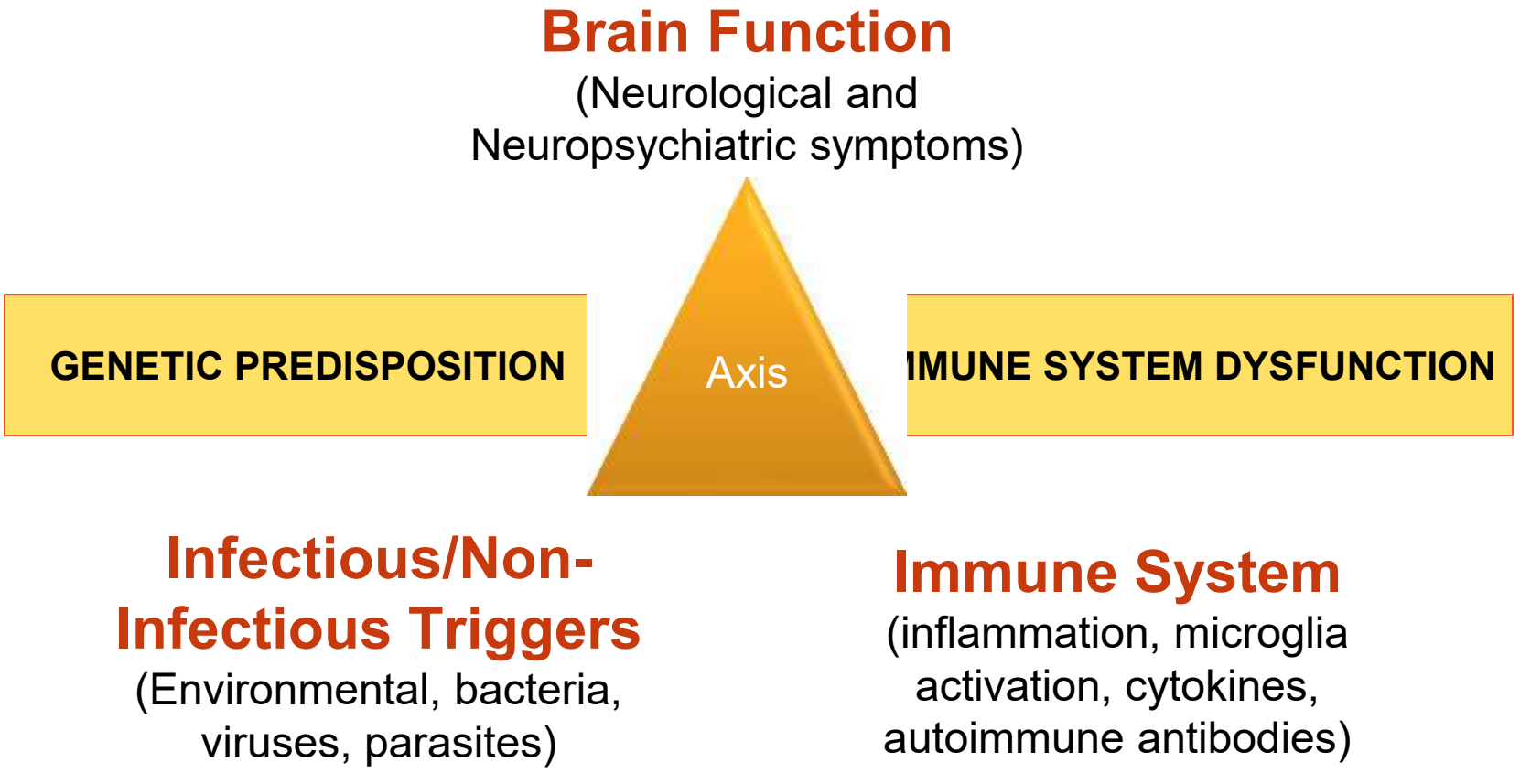
History of hospitalization for infection increased the risk of mood disorders (bipolar affective disorder or depression)	+62%
Hospitalization for autoimmune disease increased the risk of a mood disorder diagnosis	+45%
The two risk factors together increased the risk of subsequent mood disorders	+135%

1. "Autoimmune Diseases and Severe Infections as Risk Factors for Mood Disorders" JAMA Psychiatry. 2013;70(8):812-820
2. "Association of Serum Interleukin 6 and C-Reactive Protein in Childhood With Depression and Psychosis in Young Adult Life" JAMA Psychiatry. 2014;71(10):1121-1128

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

Infection, Immune, Brain Connection to Neuropsychiatric Disorders

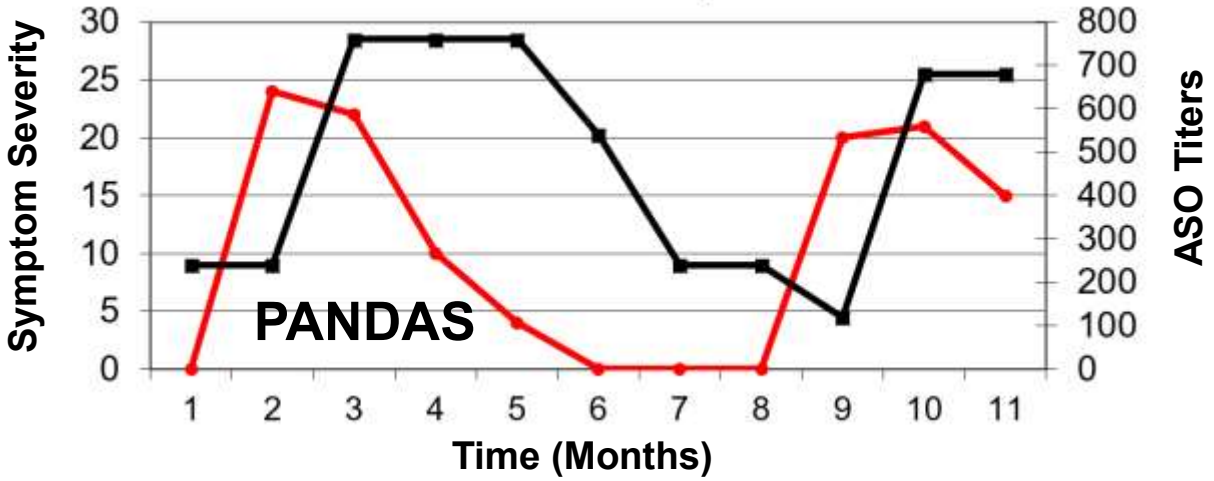


What is the Controversy?

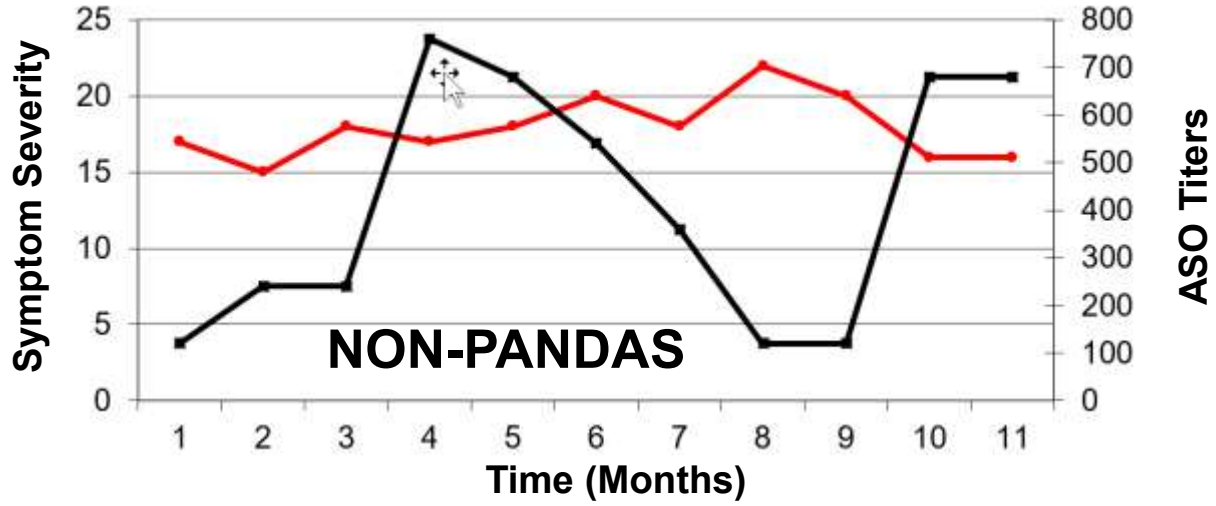
Defining, Diagnosing and Treating a Cross-disciplinary Multi-symptom Neuropsychiatric Disorder

1. **PANDAS**
   - Association with Group A Streptococcus (GAS) but 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 without identifying biological markers**
   - based upon symptoms and often a diagnosis of exclusion

Anti-Streptolysin O Titers and OCD Symptom Severity (Y-BOCS)



ASO TITER ---
Y-BOCS ---

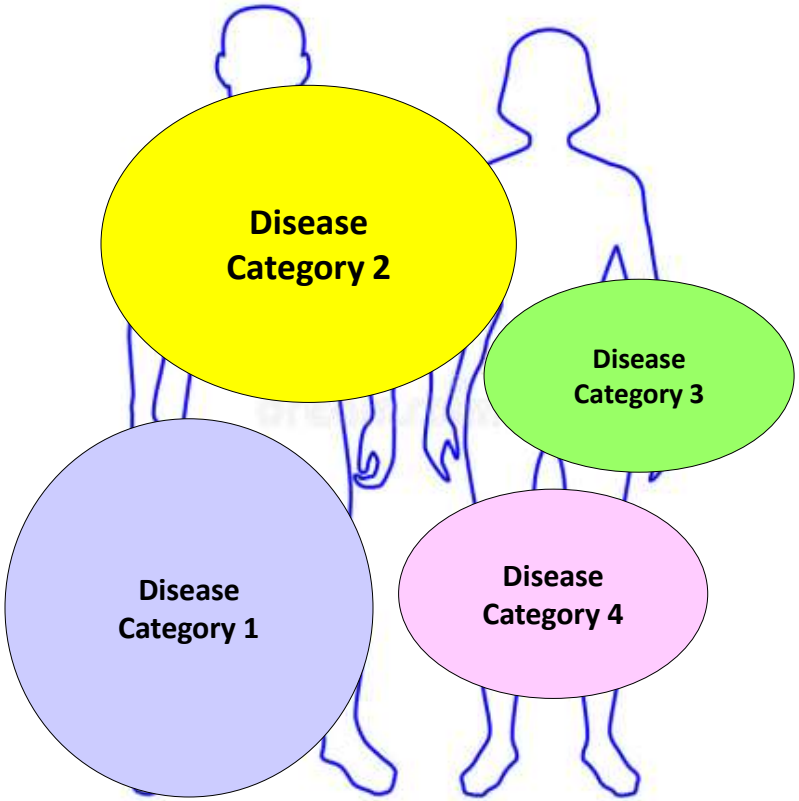


ASO TITER ---
Y-BOCS ---

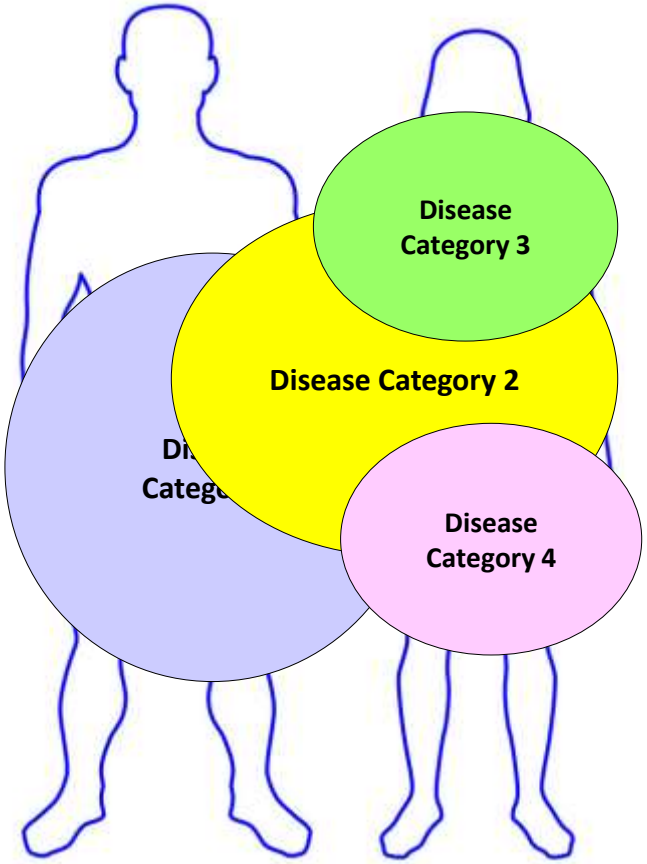
Credits: Dr. Susan Swedo

Challenges when Diagnosing Human Disease and the Impact of Organ System Specialization in Medicine

Artificial View of Disease



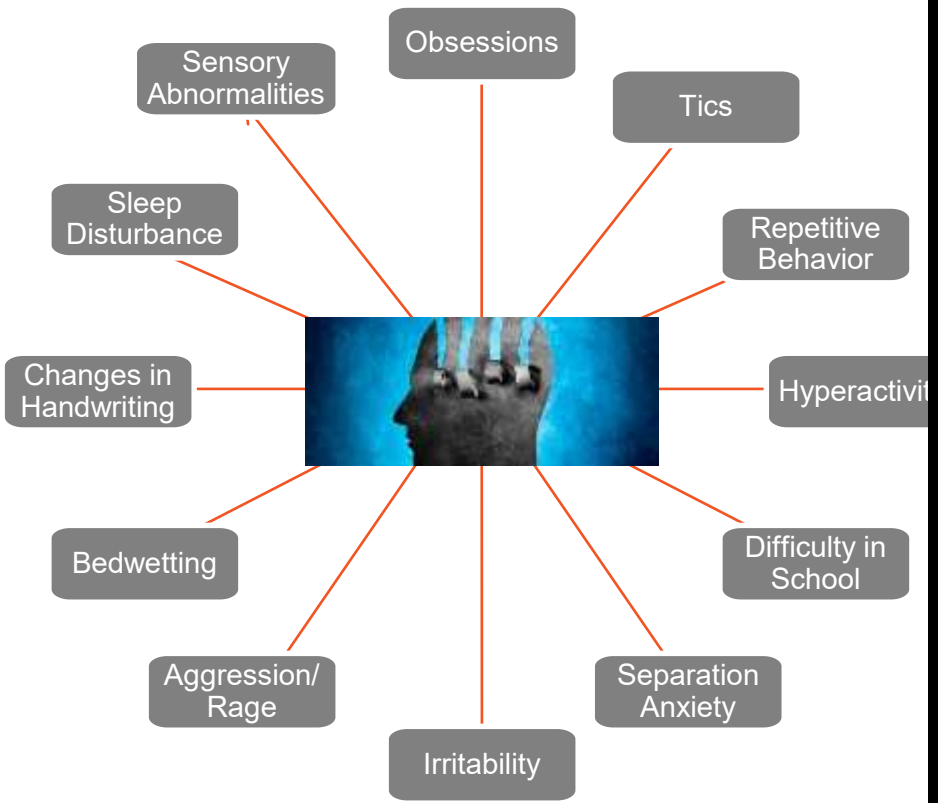
More Practical View of Disease



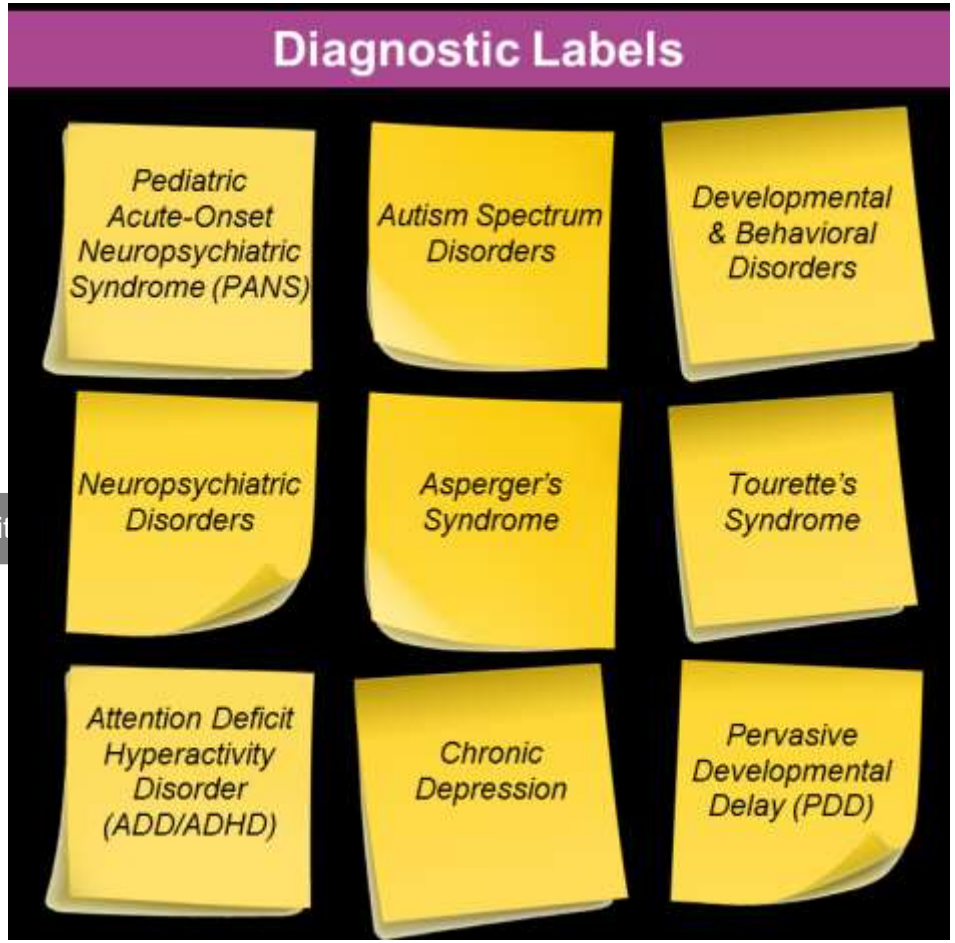
Different etiologies of disease can manifest identical symptoms but resolution is only possible with an understanding of the etiology

Problem: Patients Become Labeled into Symptom-Based Categories

Common Symptoms



Diagnostic Labels



Tack Laws #1 and #2 (Dr. Sydney Baker)

Tack Law #1

- If you are sitting on a tack, the treatment is not two Advil every 3-4 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 ***causes*** for resolution

Correctly diagnosing the root cause for patients with neuropsychiatric symptoms is critical to prescribing the correct treatment

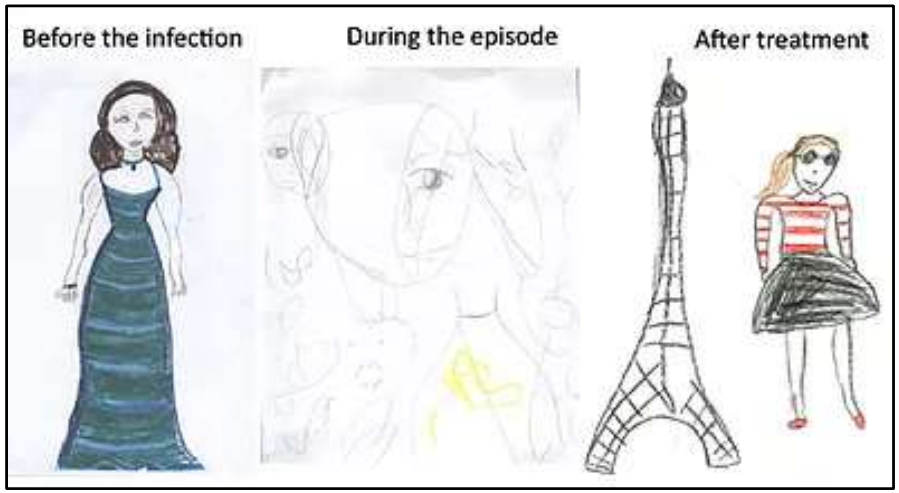
Topics We will Cover

1. **Definition of PANDAS/PANS**
   - Nomenclature and alternative nomenclature
   - Proposed mechanism
   - What is the controversy?
2. **Brief clinical presentation and symptoms associated with PANDAS/PANS**
   - Some common infectious triggers
3. **Molecular mimicry and its role in post-infectious autoimmune disorders of the brain**
4. **Anti-neuronal antibodies in the Cunningham Panel**
   - Biomarker selection
   - Patient population study
   - Swedish study conclusions and issues
5. **Broader-based patient populations outside of PANDAS/PANS, including adults**

Estimated that 1 out of 150 to 250 children have PANS/PANDAS

PANDAS DIAGNOSIS CRITERIA

- Presence of OCD and/or tics, particularly multiple, complex or unusual tics
- Age requirement (Symptoms of the disorder first become evident between 3 years of age and puberty)
- Acute onset and episodic (relapsing-remitting) course
- Association with Group A Streptococcal (GAS) infection
- Association with neurological abnormalities



- Young 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

Symptoms found in National Institute of Mental Health Samples (NIMH) USA

Symptoms During Exacerbations

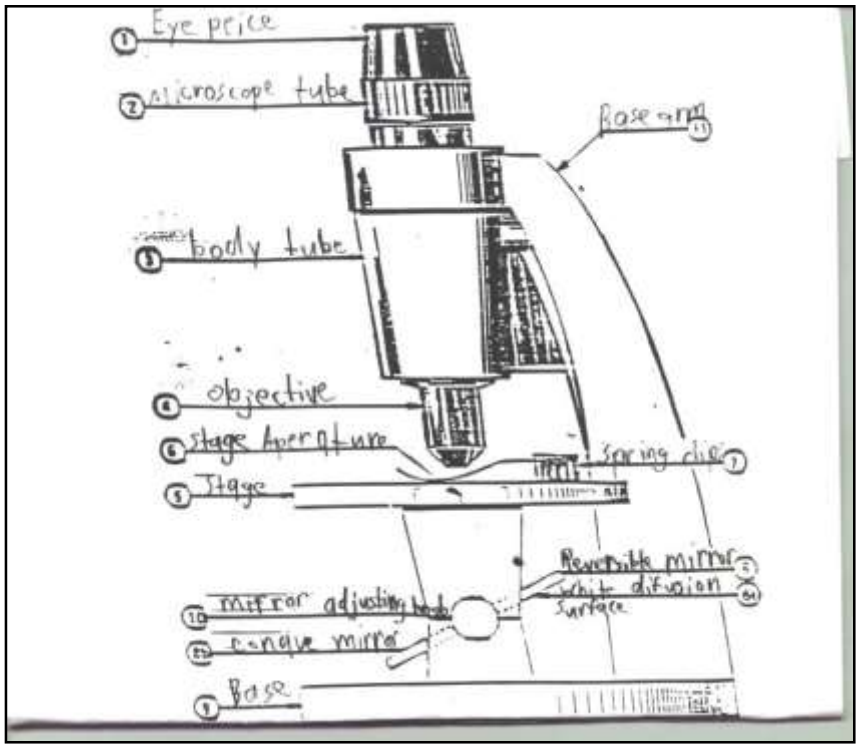
- Choreiform movements 95%
- Emotional lability 66%
- School changes 60%
- Personality changes 54%
- Bedtime fears 50%
- Fidgetiness 50%
- Separation fears 40%
- Sensory defensiveness 40%
- Irritability 40%
- Impulsivity and distraction 38%

Comorbid Diagnoses

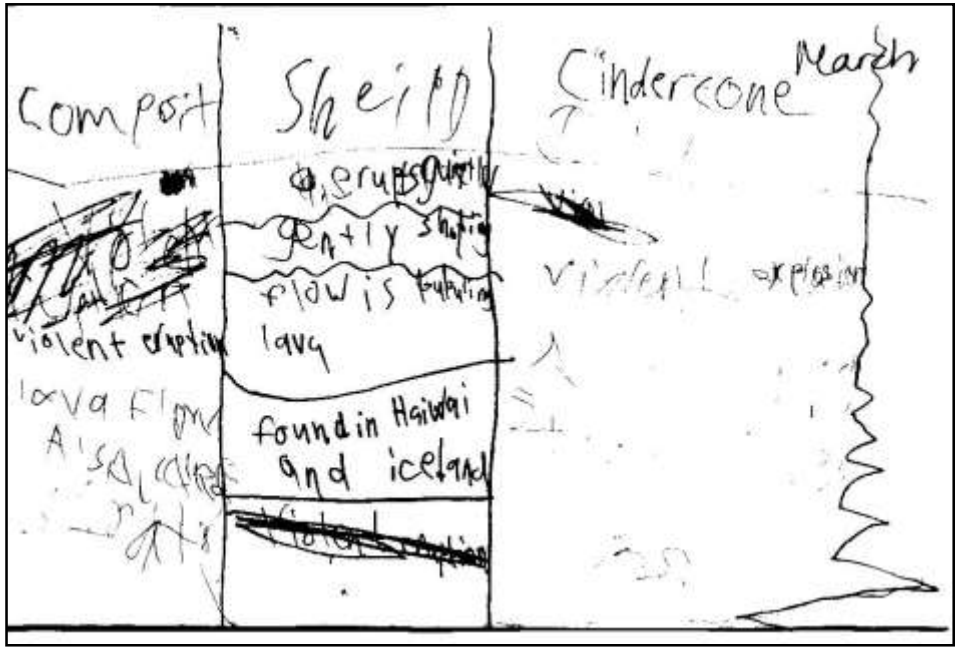
- ADHD 40%
- ADD 40%
- Depression 36%
- Separation anxiety 20%
- Overanxious 28%
- Enuresis 20%
- Anorexia 17%

Dysgraphia is Frequently Observed in Children with These Conditions

Subject 1: Before Observed Motor Tics



Subject 1: After Observed Motor Tics



Before and after pictures illustrate how a child with tics is profoundly impacted

Some Infectious Triggers that are Associated with PANDAS or PANS

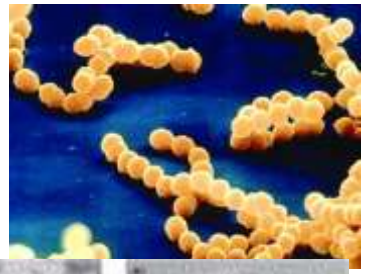
- **Group A streptococci**
- **Influenza A**
- **Varicella (chickenpox)**
- **Mycoplasma**
- **Lyme disease**
- **Babesia**
- **Bartonella**
- **Coxsackie virus**

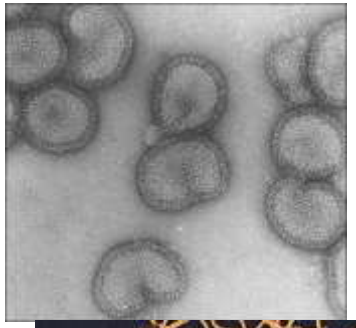

BIOLOGY | HEALTH

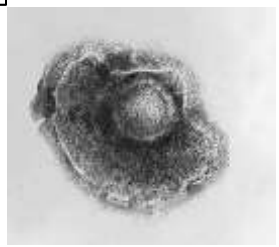
Yes, You Can Catch Insanity

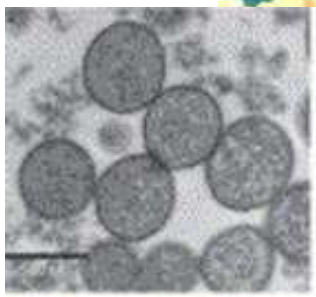
A controversial disease revives the debate about the immune system and mental illness.

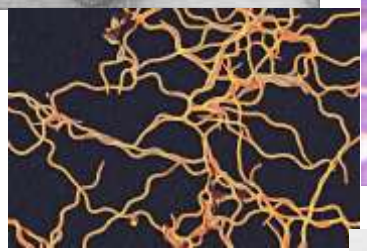
BY ANDREW CURRY
ILLUSTRATION BY HADLEY HOOPER
APRIL 16, 2015

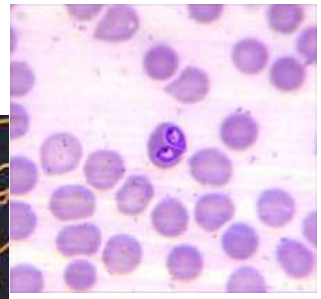


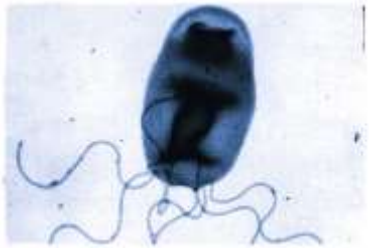


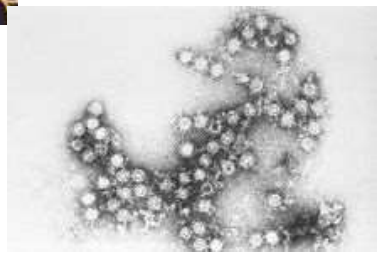






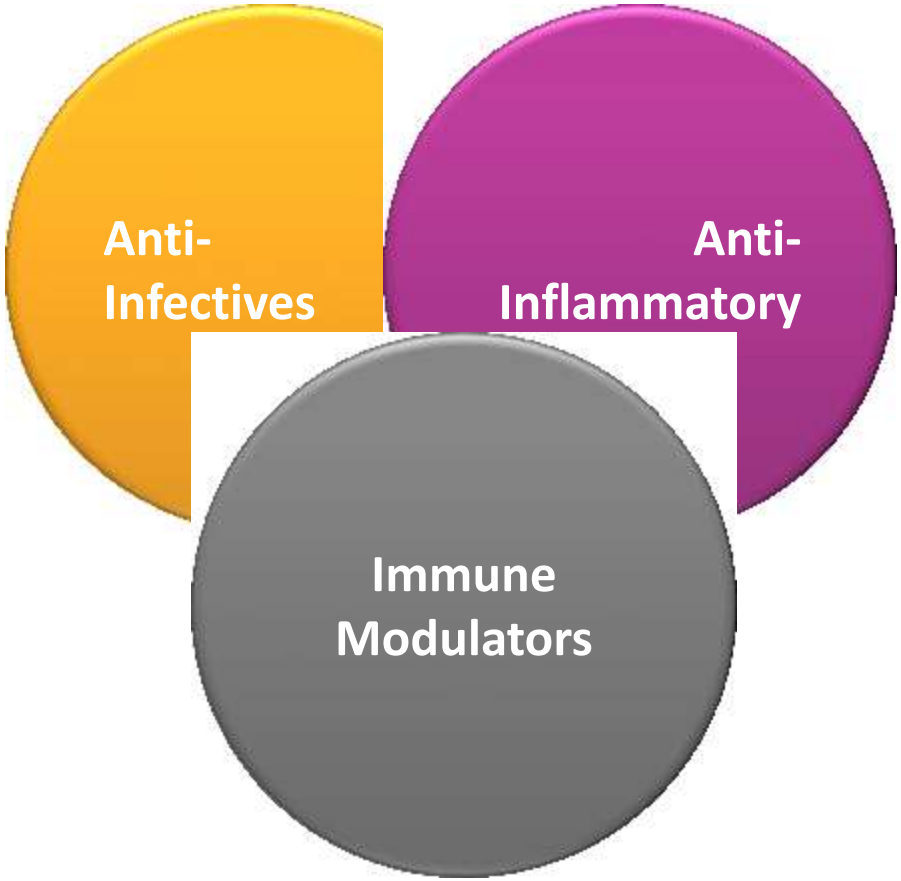






Patients often have more than one infection, and can be subclinical

Treatment Categories for Post-Infectious Autoimmune Neuropsychiatric Disorders of the Brain



- Anti-microbials
- Steroids and NSAIDs
- Plasmapheresis (Plasma exchange)
- Intravenous Immunoglobulins (IVIG)
- Immune modulating medications
- Symptomatic Treatment
  - Cognitive Behavioral Therapy
  - SSRIs

Effective allopathic, integrative or natural treatments tend to fall into these categories

Topics We will Cover

1. **Definition of PANDAS/PANS**
   - Nomenclature and alternative nomenclature
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3. **Molecular mimicry and its role in post-infectious autoimmune disorders of the brain**
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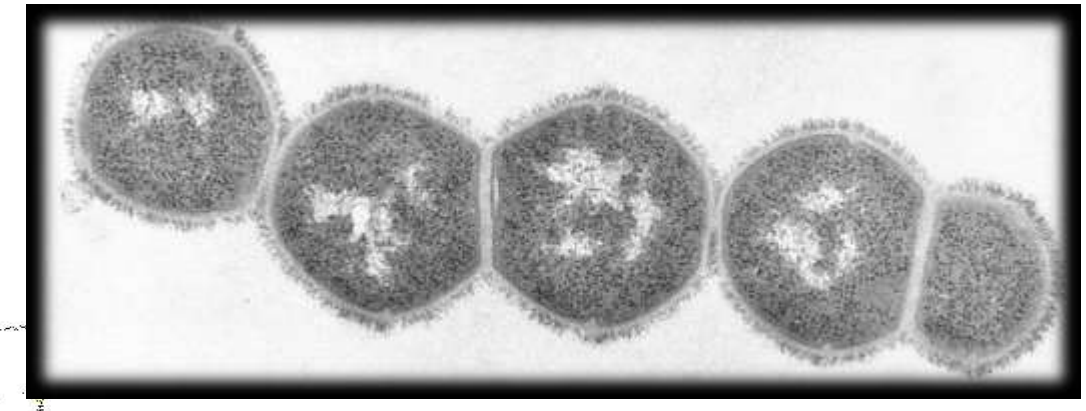
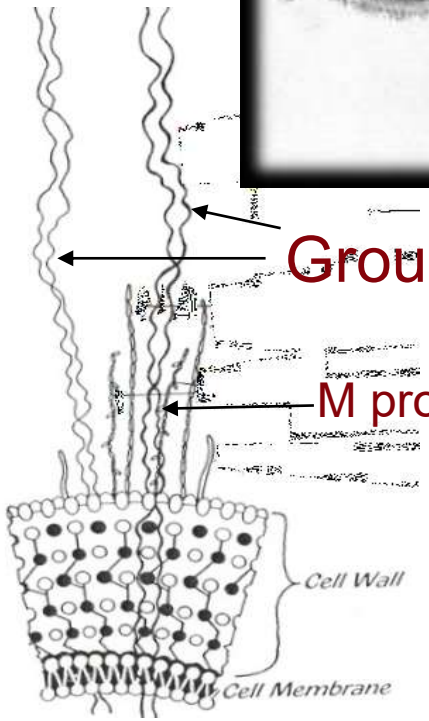
   - Biomarker selection
   - Patient population study
   - Swedish study conclusions and issues
5. **Broader-based patient populations outside of PANDAS/PANS, including adults**

Molecular Mimicry Between Strep and Self-Antigens

Similar antigenic determinants between host and infecting microorganisms





Molecular Mimicry

Heart (carditis)
[cardiac myosin/laminin]
Joint (arthritis)
Brain (chorea)
[lysoganglioside/tubulin]

Streptococcal Cell Wall

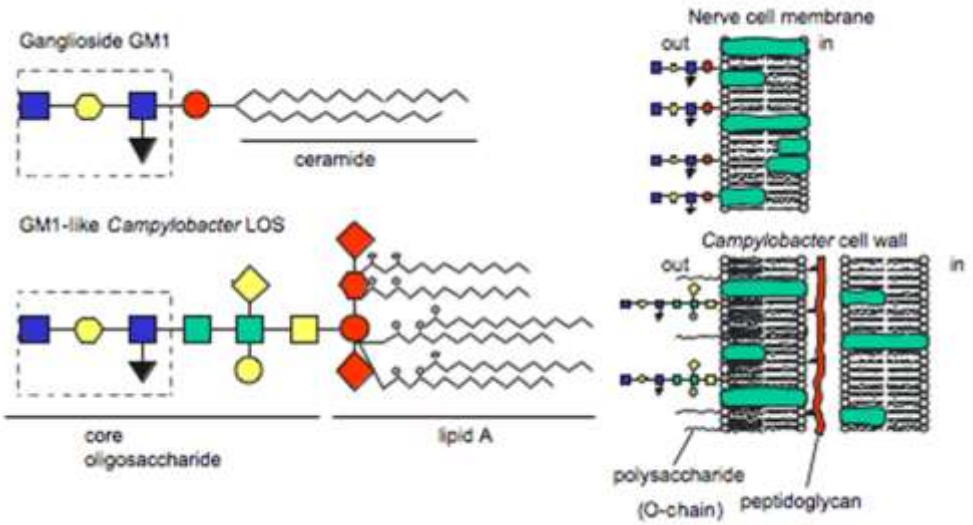
Molecular Mimicry in Guillain-Barré Syndrome

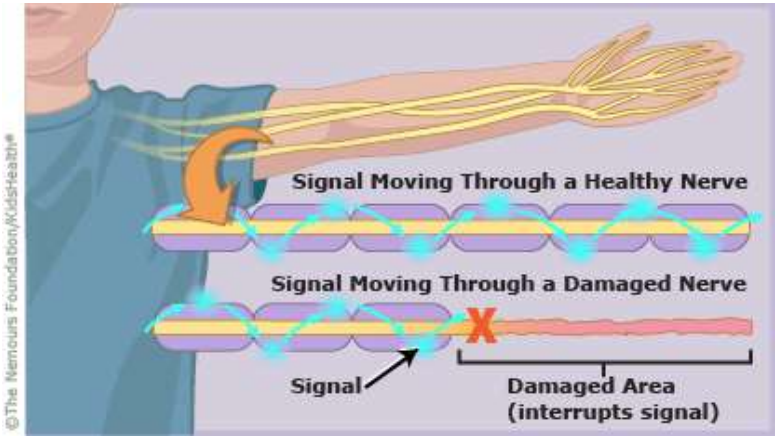
Most often preceded by gastrointestinal or respiratory infections:

- ***Campylobacter jejuni***
- *Mycoplasma*
- *Cytomegalovirus (CMV)*
- *Epstein-Barr virus (EBV)*
- *Varicella-zoster virus*
- *Influenza*

Infection-triggered autoimmune reaction against the peripheral nervous system (the myelin sheath)

Robert K. Yu et al. Infect. Immun. 2006;74:6517-6527





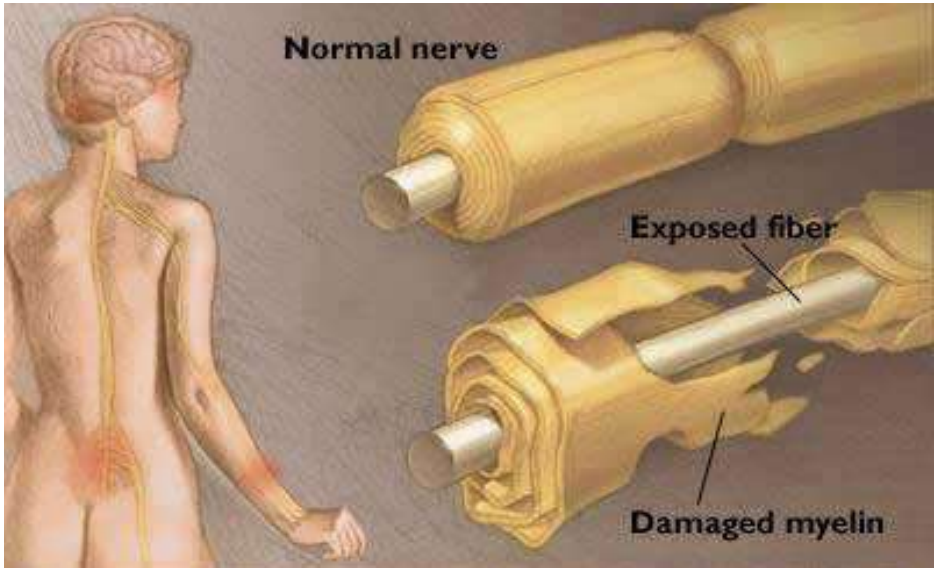
Molecular Mimicry is a Well-Established Mechanism of Autoimmune Dysfunction

Many conditions are believed to have mimicry at the core[(1)]

Guillain-Barré Syndrome occurs after a gut or respiratory infection and involves antibody attack on nerve tissue[(2)]

Neurologic or CNS Conditions	
Guillain-Barré Syndrome	Sydenham Chorea
Multiple Sclerosis	Myasthenia Gravis
Anti-NMDA Receptor Encephalitis	Schizophrenia and Portions of Autism

Conditions Affecting Other Systems	
Lupus	Rheumatic Fever
Myocarditis	Crohn's Disease
Lyme Arthritis	Type 1 Diabetes
Inflammatory Bowel Disease	Rheumatoid Arthritis



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

2. Ref: mayoclinc.org

Inflammation and destruction of tissues and organs impacts over 100 million people afflicted with more than 80 different autoimmune diseases[1]

Infection-Triggered Autoimmune Response through Molecular Mimicry*

Infection Triggers that affect the CNS and other Systems

- **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 as a Basis for Chronic Disorders of the Brain and other Diseases

NIH Public Access
Author Manuscript

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Molecular Mimicry as a Mechanism of Autoimmune Disease

Matthew F. Cusick, PhD, **Jane E. Libbey, MS**, and **Robert S. Fujinami, PhD**[1]
Department of Pathology University of Utah 30 North 1900 East, 3R330 SOM Salt Lake City, UT 84132

Immunological Reviews

Emily M. L. Chastain
Stephen D. Miller

Molecular mimicry as an inducing trigger for CNS autoimmune demyelinating disease

nature medicine ARTICLES

Autoimmunity due to molecular mimicry as a cause of neurological disease

Michael C. Levin[1,2], Song Mei Lee[1,2], Franck Kalume[3,4], Yvette Morcos[1,2], F. Curtis Dohan Jr[5], Karen A. Hasty[3,4,6], Joseph C. Callaway[3,4], Joseph Zuvic[1], Dominic M. Dwyer[1,2] & John M. Stuart[3,6]

INFECTION AND IMMUNITY, Dec. 2000, p. 6517–6527 Vol. 74, No. 12
0019-9567/00/$00.00+0 doi:10.1128/IAI.00967-00
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MINIREVIEW

Ganglioside Molecular Mimicry and Its Pathological Roles in Guillain-Barré Syndrome and Related Diseases[▽]

Robert K. Yu,* Seigo Usuki, and Toshio Ariga
Institute of Molecular Medicine and Genetics and Institute of Neuroscience, Medical College of Georgia, Augusta, Georgia 30912

Rev Endocr Metab Disord (2016) 17:485–498
DOI 10.1007/s11154-016-9343-2

Molecular mimicry and autoimmune thyroid disease

Salvatore Benvenga[1,2,3] · Fabrizio Guarneri[4]

Diabetologia (1998) 41: 40–46

Diabetologia
© Springer-Verlag 1998

Molecular mimicry in diabetes mellitus: the homologous domain in coxsackie B virus protein 2C and islet autoantigen GAD_{65} is highly conserved in the coxsackie B-like enteroviruses and binds to the diabetes associated HLA-DR3 molecule

G. R. Vreugdenhil[1], A. Geluk[2], T. H. M. Ottenhoff[2], W. J. G. Melchers[1], B. O. Roep[2], J. M. D. Galama[1]
[1] University of Nijmegen, Department of Medical Microbiology, Nijmegen, The Netherlands
[2] University of Leiden, Department of Immunohematology and Blood Bank, Leiden, The Netherlands

CLINICAL MICROBIOLOGY REVIEWS, Jan. 2006, p. 80–94 Vol. 19, No. 1
0893-8512/06/$08.00+0 doi:10.1128/CMR.19.1.80–94.2006
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Molecular Mimicry, Bystander Activation, or Viral Persistence: Infections and Autoimmune Disease

Robert S. Fujinami,[1]* Matthias G. von Herrath,[2] Urs Christen,[2] and J. Lindsay Whitton[3]
Department of Neurology, University of Utah School of Medicine, Salt Lake City, Utah 84132-2305[1]; Division of Immune Regulation, La Jolla Institute for Allergy and Immunology, San Diego, California 92121[2]; and Department of Neuropharmacology, The Scripps Research Institute, La Jolla, California 92037[3]

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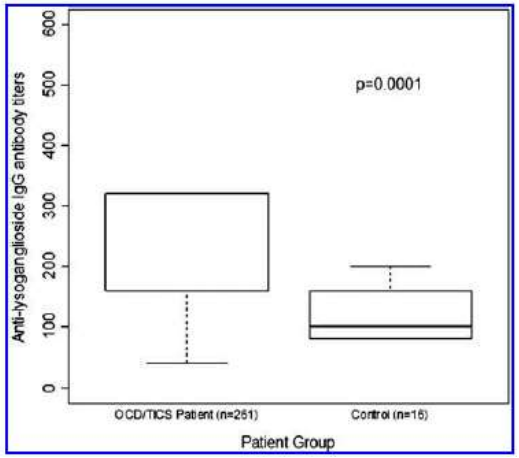
Antineuronal Antibodies in Children with Motor Tics and OCD

JOURNAL OF CHILD AND ADOLESCENT PSYCHOPHARMACOLOGY
Volume 25, Number 1, 2015

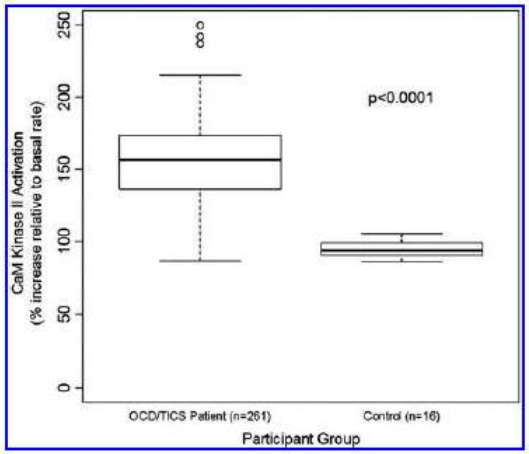
Antineuronal Antibodies in a Heterogeneous Group of Youth and Young Adults with Tics and Obsessive-Compulsive Disorder

Carol J. Cox, PhD,[1*] Amir J. Zuccolo, PhD,[1*] Erica V. Edwards, BS,[1] Adita Mascaro-Blanco, BS,[1] Kathy Alvarez, BS,[1] Julie Stoner, PhD,[2] Kiki Chang, MD,[3] and Madeleine W. Cunningham, PhD[1]

OCD + Tics Association with Anti-Lysoganglioside Antibodies



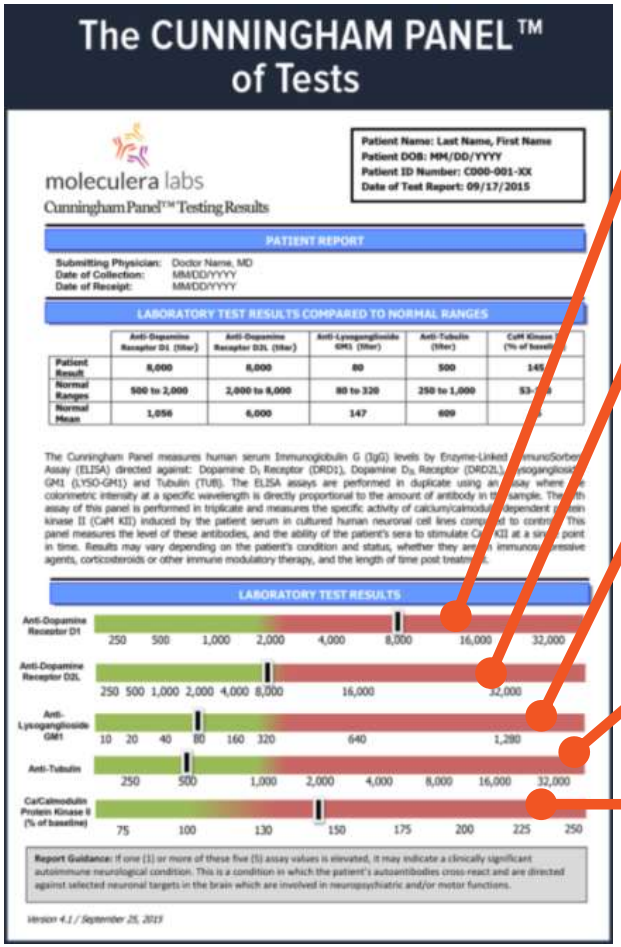
OCD + Tics Association with CaMKII Activity



OCD / motor tics are associated with the presence of antineuronal antibodies and correlation with CaMKII activity

The Cunningham Panel™ Biomarker Components

The 5 biomarkers were originally identified from patients with Sydenham Chorea and PANDAS/PANS children



1) Anti-Dopamine D1

Often positive with psychiatric symptoms including psychosis(1)

2) Anti-Dopamine D2L

Often positive with movement disorders and impulsivity(1)

3) Anti-Lysoganglioside GM1

Often positive with neuropathic symptoms including tics(1)

4) Anti-Tubulin

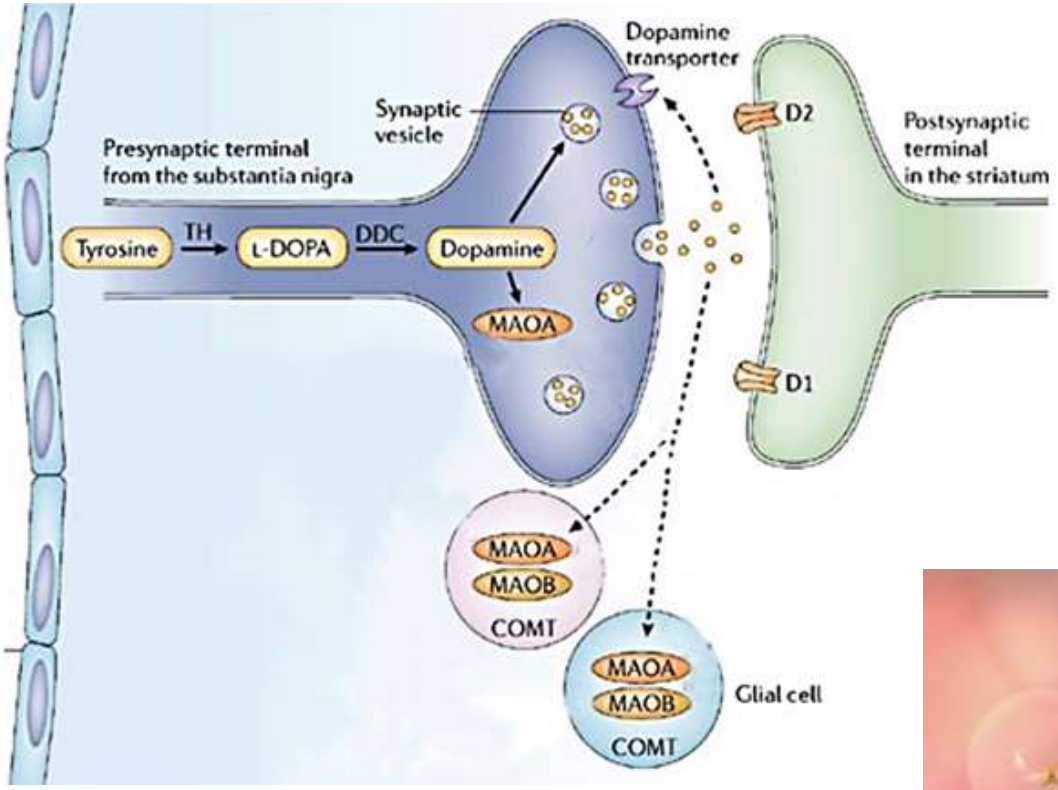
Often positive with cognitive complaints, OCD and brain fog(1)

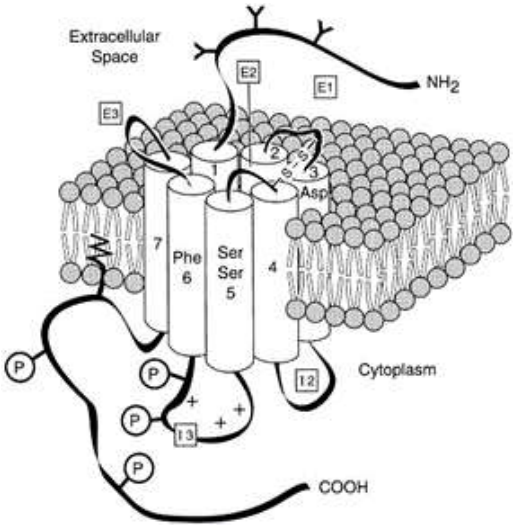
5) CaM KII Activity

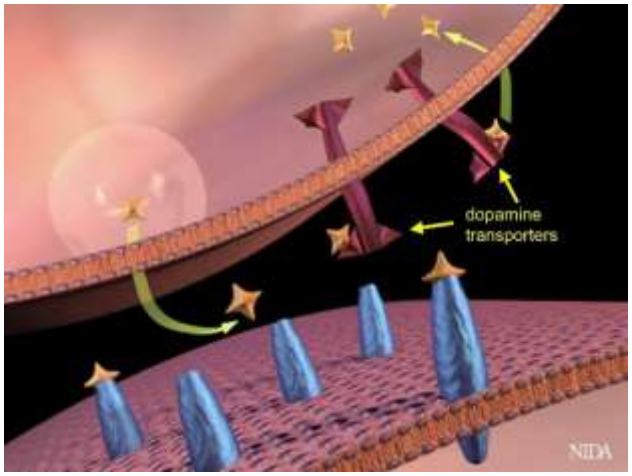
Often positive with involuntary movements and any symptom of adrenergic activation (1)

Ref: (1) Reported by Dr. Amirm Katz base upon his 112 patients studied and our patient responses

Anti-Human Dopamine D1 and D2L Receptors

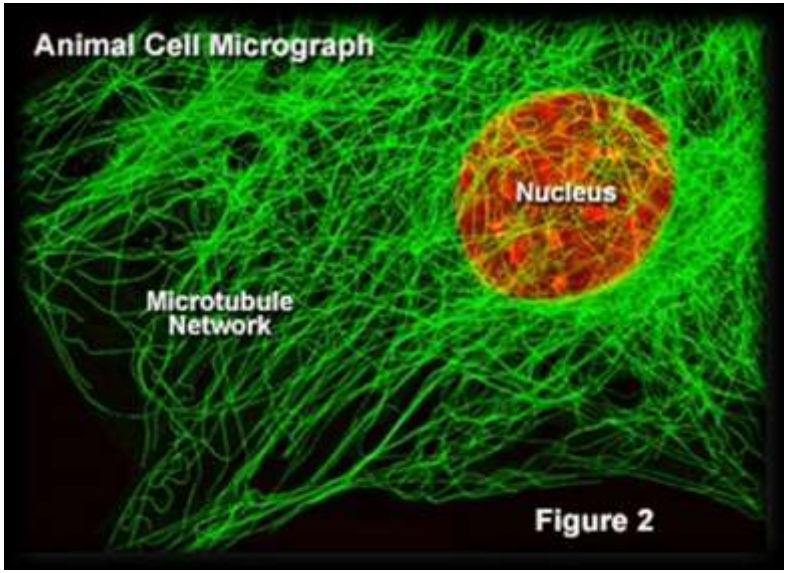




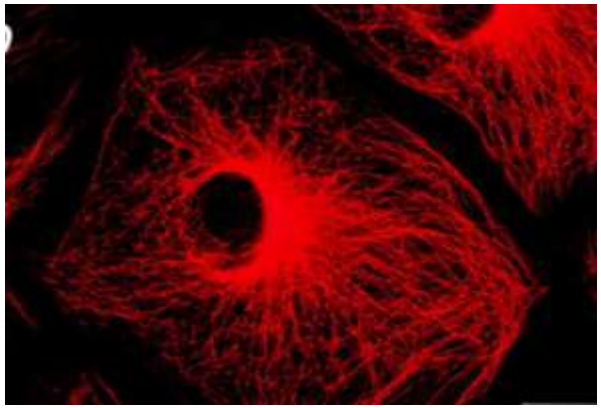


Anti-βTubulin

- Microtubules (tubulin) form part of the cytoskeleton that gives structure and shape to a cell, and also serve to move other organelles throughout the cytoplasm



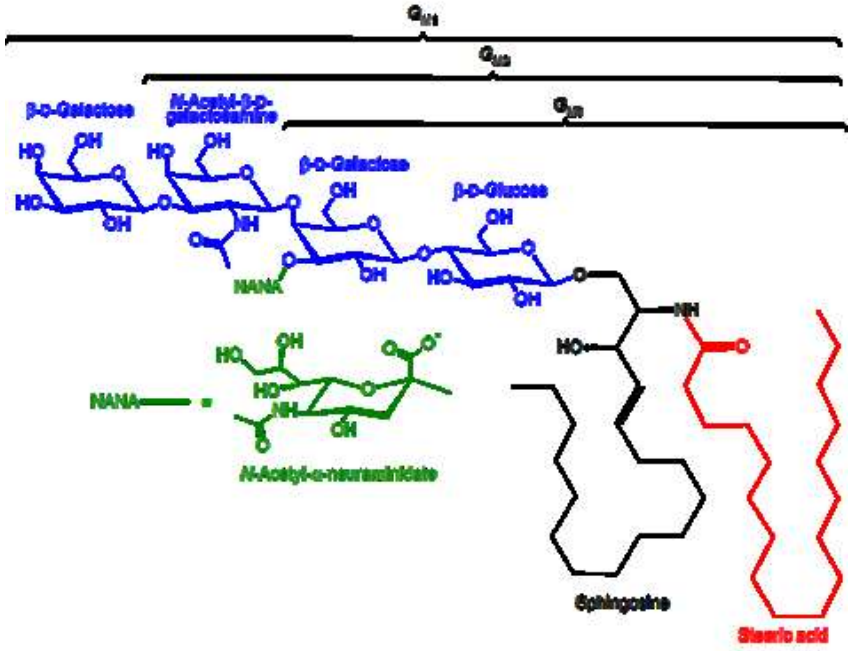
http://quasargroupconsulting.com/genetics/Microtubules.php

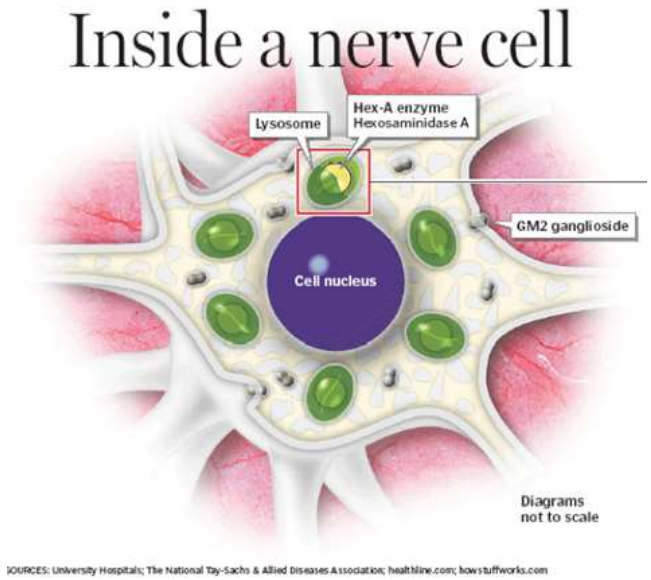


The Journal of biological chemistry.
Karki S, Tokito MK, Holzbaur EL 2000 Feb 18

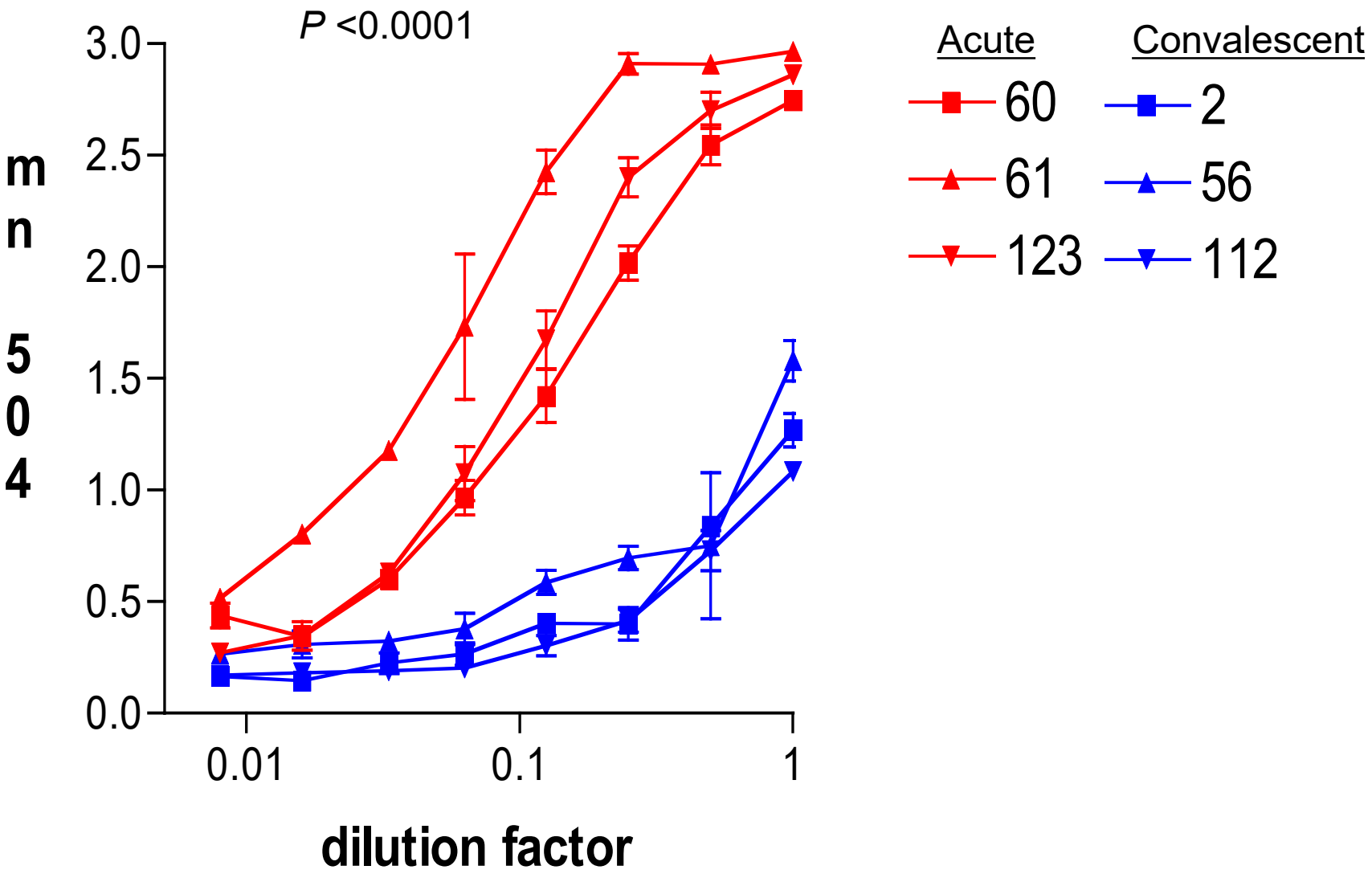
Anti-Lysoganglioside GM1

Gangliosides are lipid components of neuronal cell membranes



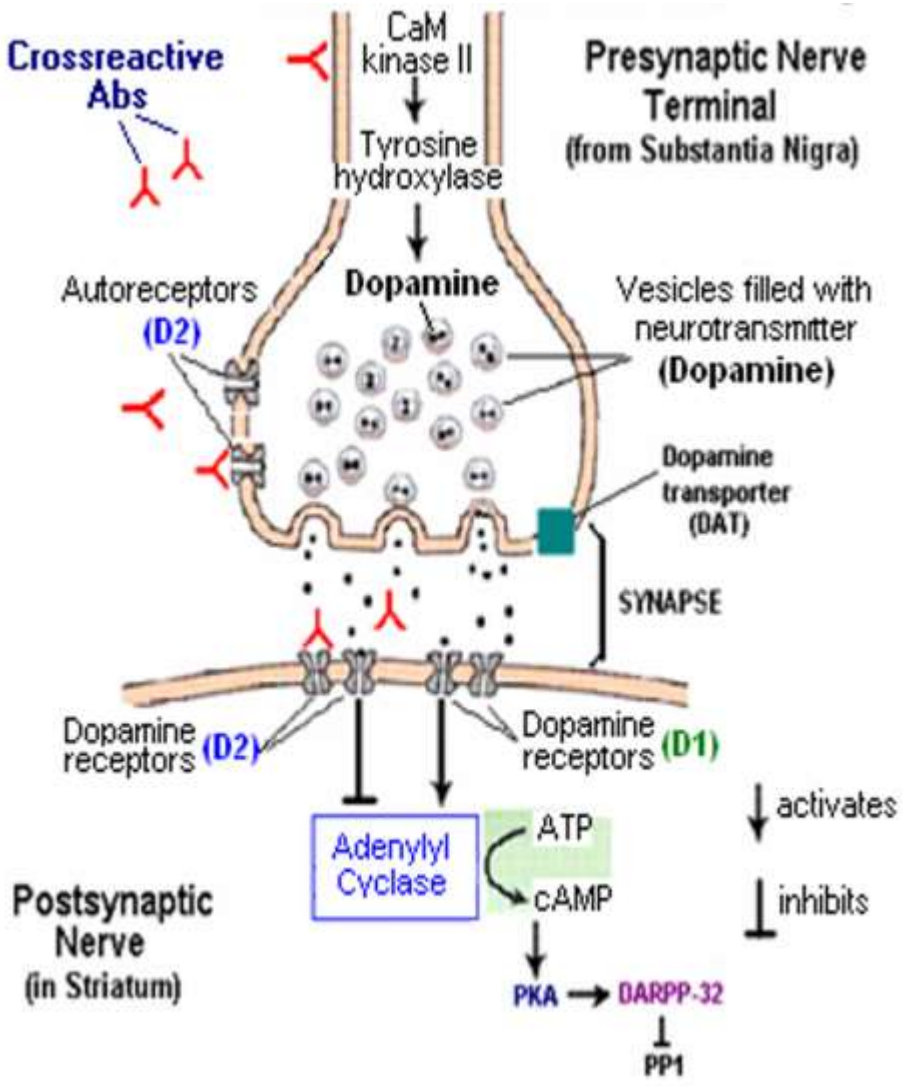


Sydenham Chorea Sera Reacted with Lysoganglioside



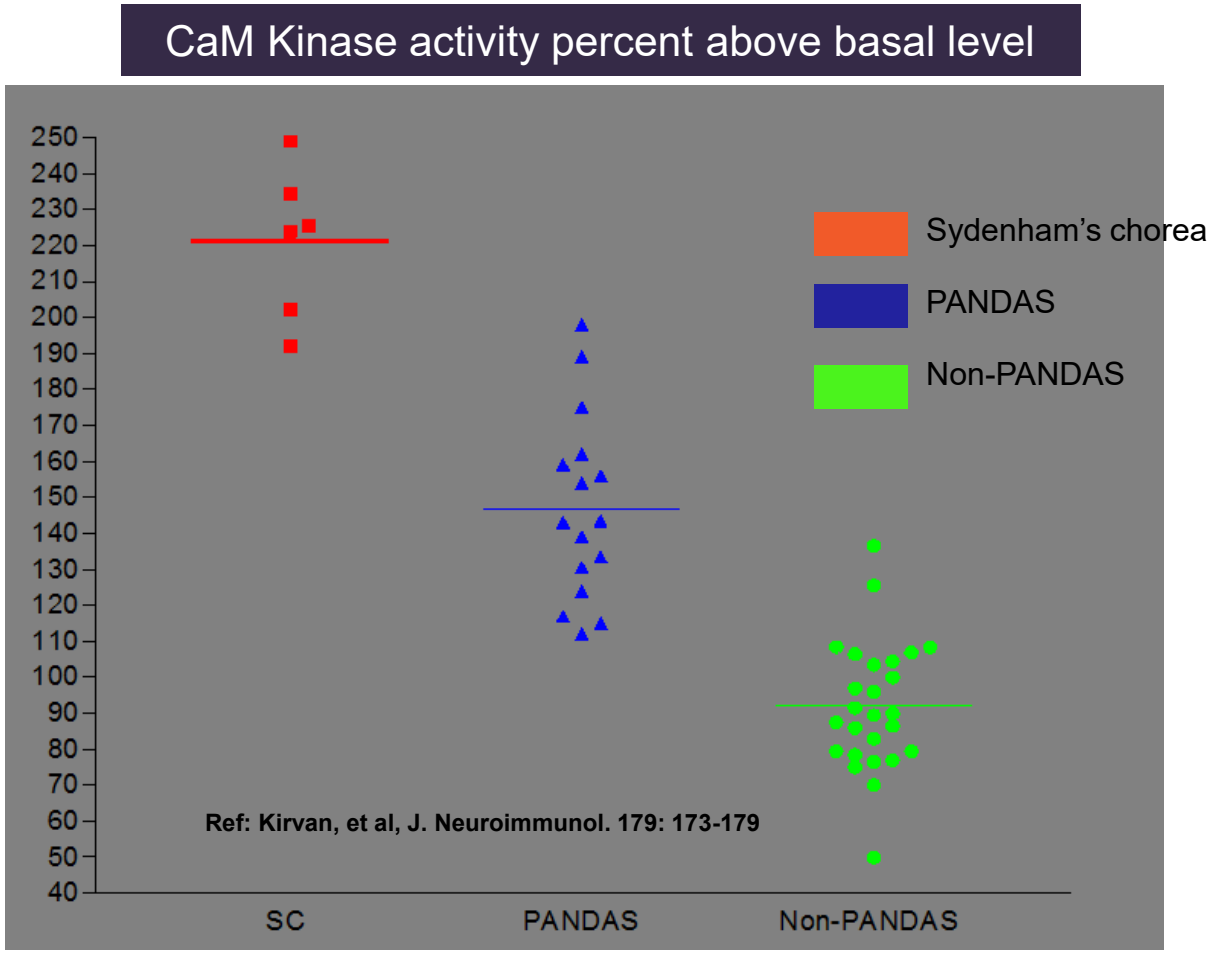
Kirvan et al. 2003. Nature Medicine 9:914-920

Autoantibodies that stimulate CAMKII in Children with neuropsychiatric syndromes



Children who demonstrate CaMKII neuronal cell stimulation positive tests respond to immunotherapy and their neuropsychiatric symptoms resolve

Calmodulin Calcium-Dependent Kinase II Triggering by Autoantibodies against Neuronal Cell Receptors



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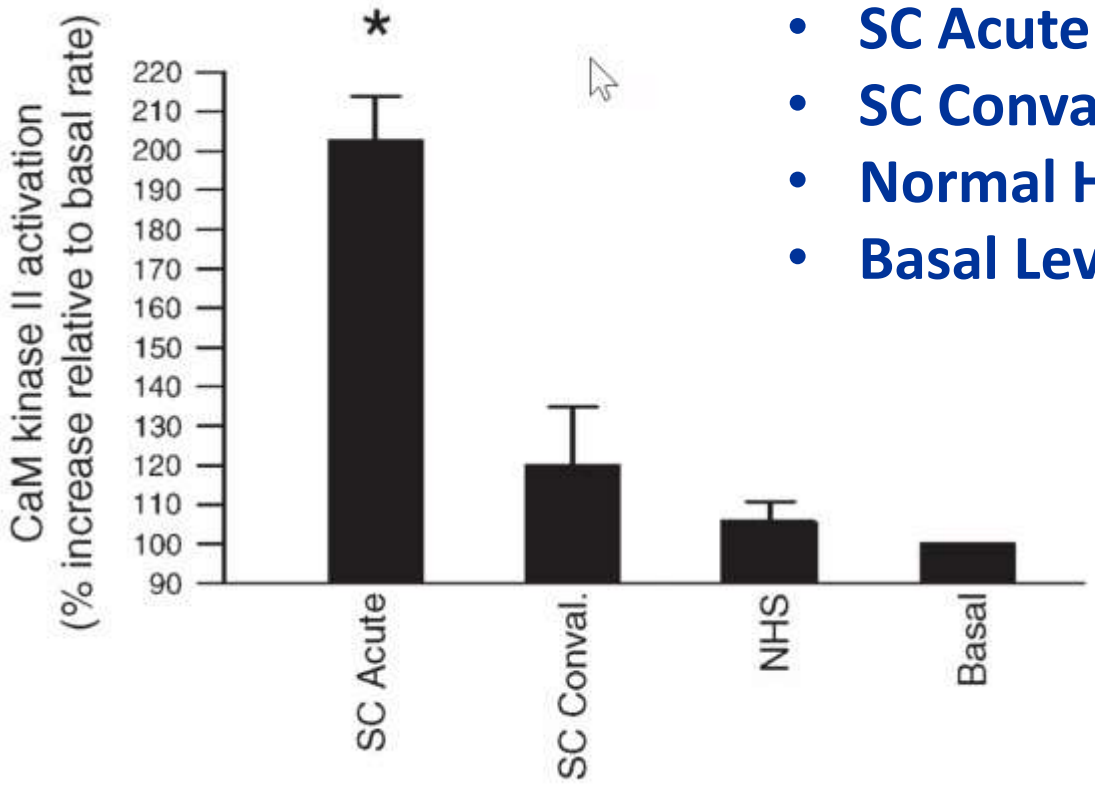
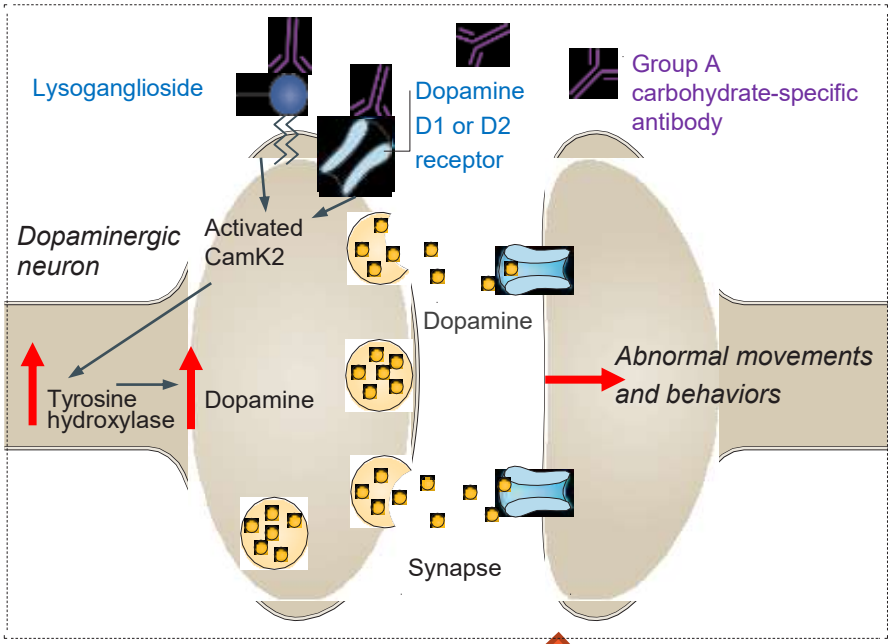


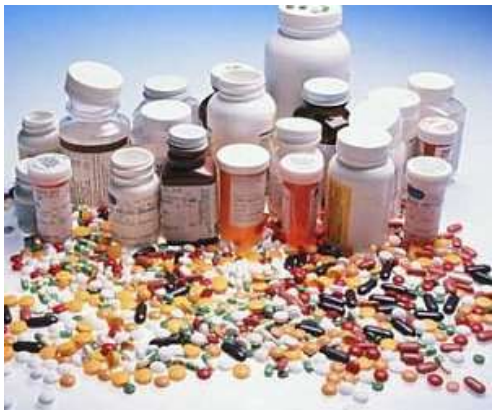
Sydenham's Chorea (SC)

- **SC Acute**
- **SC Convalescent**
- **Normal Human Sera (NHS)**
- **Basal Level of CaMKII Activity**

Kirvan et al., Nature Med, 2003

Connecting Autoimmune Neurologic Antibodies and Neuropsychiatric Symptoms





Resulting in

Symptom treatment

Neuropsychiatric Symptoms Including Anxiety, Aggression, Rage, OCD, Tics, Depression, Hyperactivity, Insomnia, Phobias

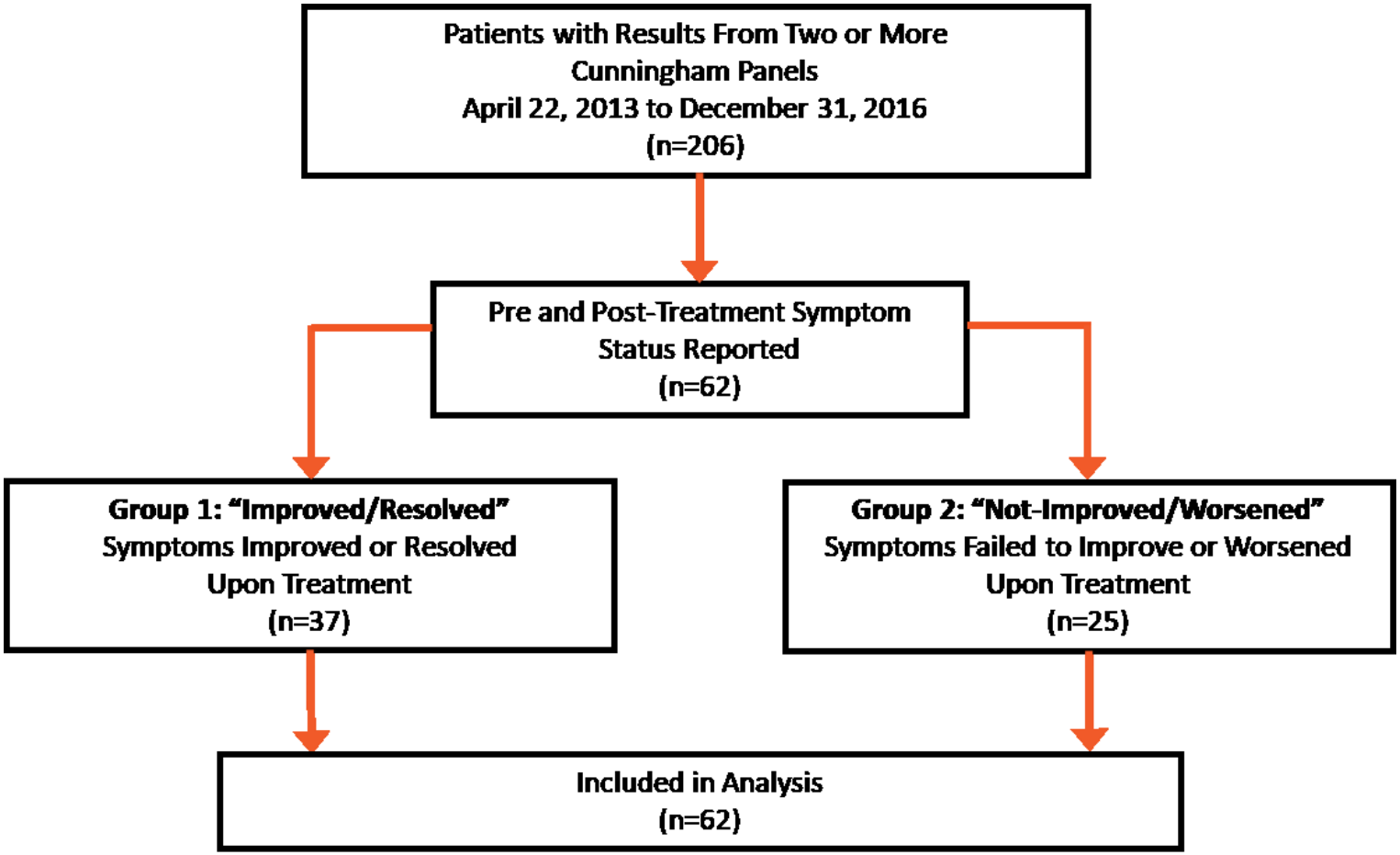
Individual Assay Normal Ranges

Anti-Neuronal Antibody Titer	Normal Ranges (MEAN)
Anti-Dopamine D1	500 to 2,000 (1056)
Anti-Dopamine D2L	2,000 to 8,000 (6000)
Anti-Lysoganglioside-GM1	80 to 320 (147)
Anti-Tubulin	250 to 1,000 (609)
CAMKII	53 to 130 (95)

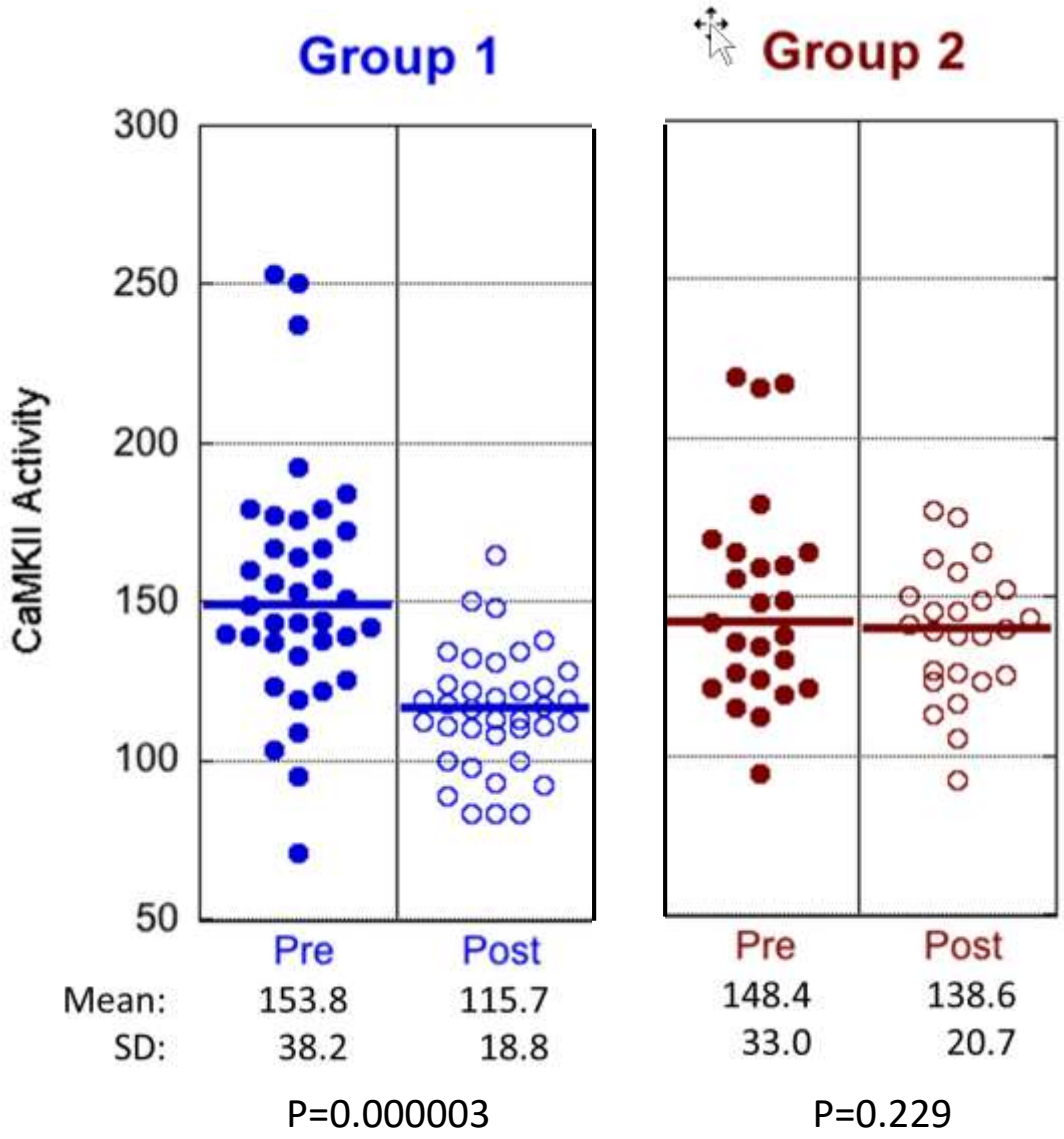
Normal ranges based upon 50 pediatric patients

- Lifetime history of no neuropsychiatric disorders or symptoms
- No first-degree relative with neuropsychiatric disorders
- No patient history of autoimmune diseases
- No active infections or symptoms

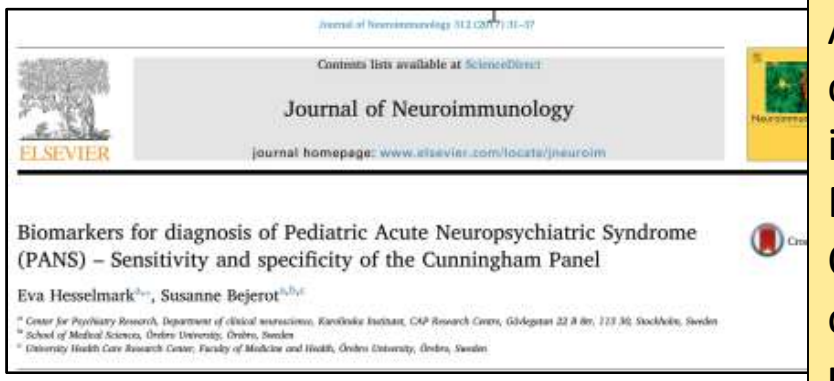
Retrospective Case Study: Autoantibodies Correlation with Treatment/Symptom Resolution



CaMKII Stimulation Assay Results



Swedish Study of Cunningham Panel

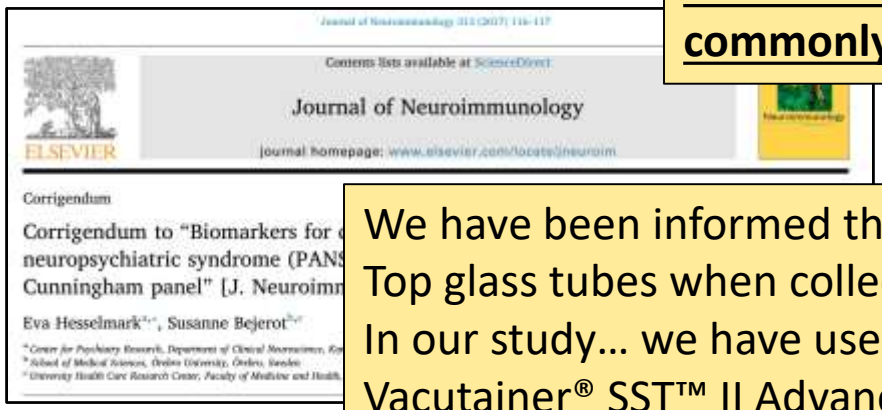


Journal of Neuroimmunology

Biomarkers for diagnosis of Pediatric Acute Neuropsychiatric Syndrome (PANS) – Sensitivity and specificity of the Cunningham Panel

Eva Hesselmark, Susanne Bejerot

Although our findings identified a moderate correlation between change in CaMKII and change in symptom severity in individuals with PANS or PANDAS, there was no indication that the Cunningham Panel can be used to diagnose PANS or PANDAS. Our results also suggest that **test-retest reliability of CaMKII may be insufficient, and that Cunningham Panel results are commonly elevated in healthy controls.**



Journal of Neuroimmunology

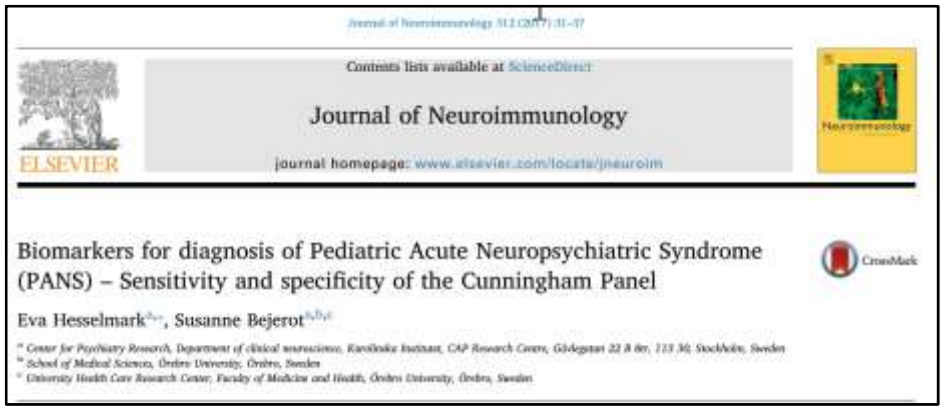
Corrigendum

Corrigendum to "Biomarkers for … neuropsychiatric syndrome (PANS … Cunningham panel" [J. Neuroimm…

Eva Hesselmark, Susanne Bejerot

We have been informed that Moleculera Labs recommend Red Top glass tubes when collecting blood for the Cunningham panel. In our study… we have used serum sampling tubes (BD Vacutainer® SST™ II Advance tubes, Gold Top) but erroneously reported sampling in "serum sampling tube (BD Vacutainer, yellow top)"... **The use of another blood collection tube than the one recommended by Moleculera could be viewed as a limitation in our study.**

Swedish Study of Cunningham Panel



Contents lists available at ScienceDirect

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

Biomarkers for diagnosis of Pediatric Acute Neuropsychiatric Syndrome (PANS) – Sensitivity and specificity of the Cunningham Panel

Eva Hesselmark, Susanne Bejerot

Swedish Study Conclusions of Cunningham Panel

1. "…test-retest reliability of CaMKII may be insufficient"
2. "…results are commonly elevated in healthy controls"

SST Gold Top Blood Collection Tube

Red Top Glass Blood Collection Tube

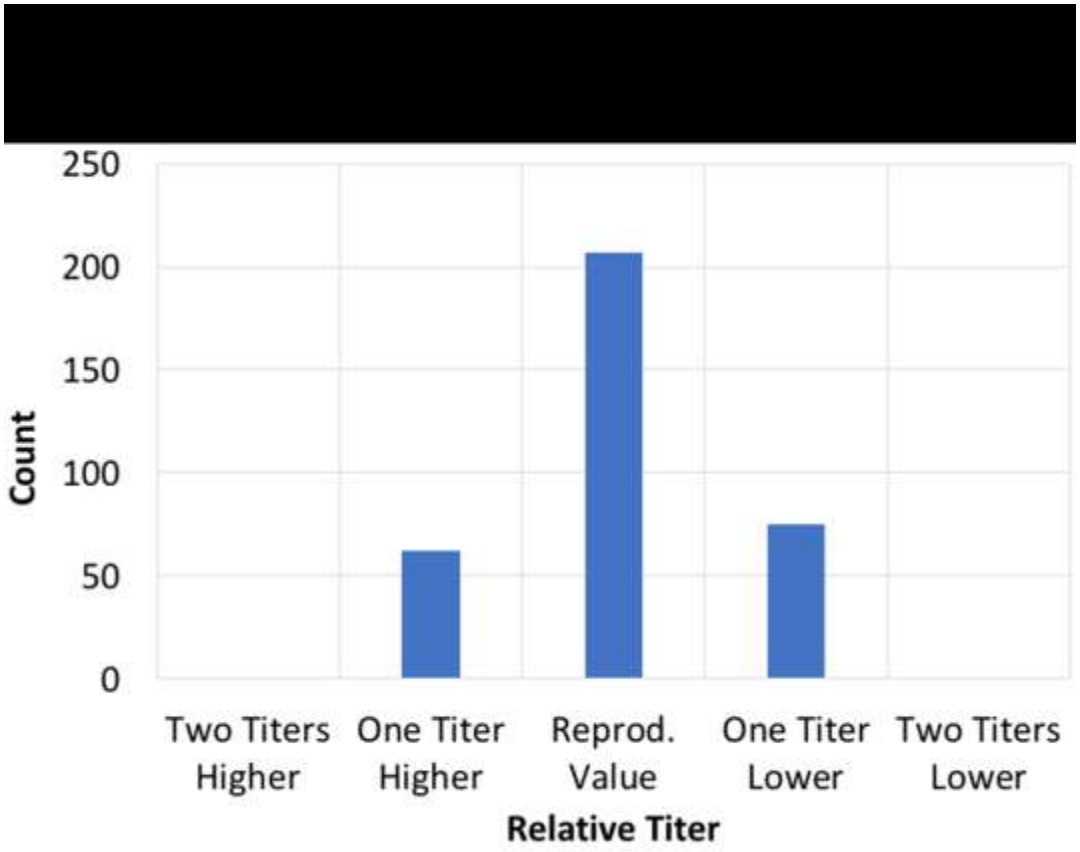
Invalid Blood Collection Tube

- Polymer Gel for serum separation
- **Interferes with assay results**

Only validated Blood Collection Tube

- No Polymer Gel

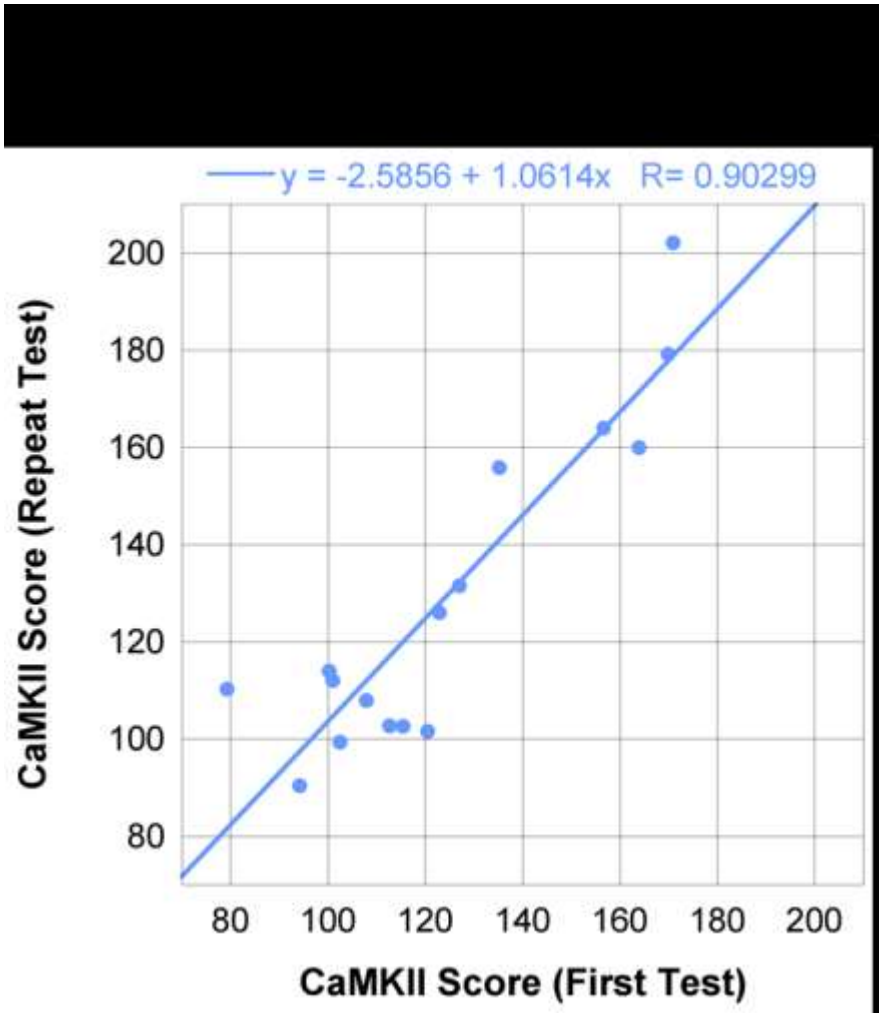
Anti-Dopamine D1R Test-Retest Reproducibility in Tubes w/o Additives



Results of 344 individual repeated tests on 7 individual patients over several months

Seven patient samples collected in validated glass tubes with no additives (Red Top glass tubes) tested at **random intervals** over a period of **several months for 344 individual tests**. We observed 62 readings at one dilution higher, 207 readings at the most commonly observed dilution, and 75 readings at one dilution lower

CaMKII Test-Retest Reproducibility in Tubes w/o Additives



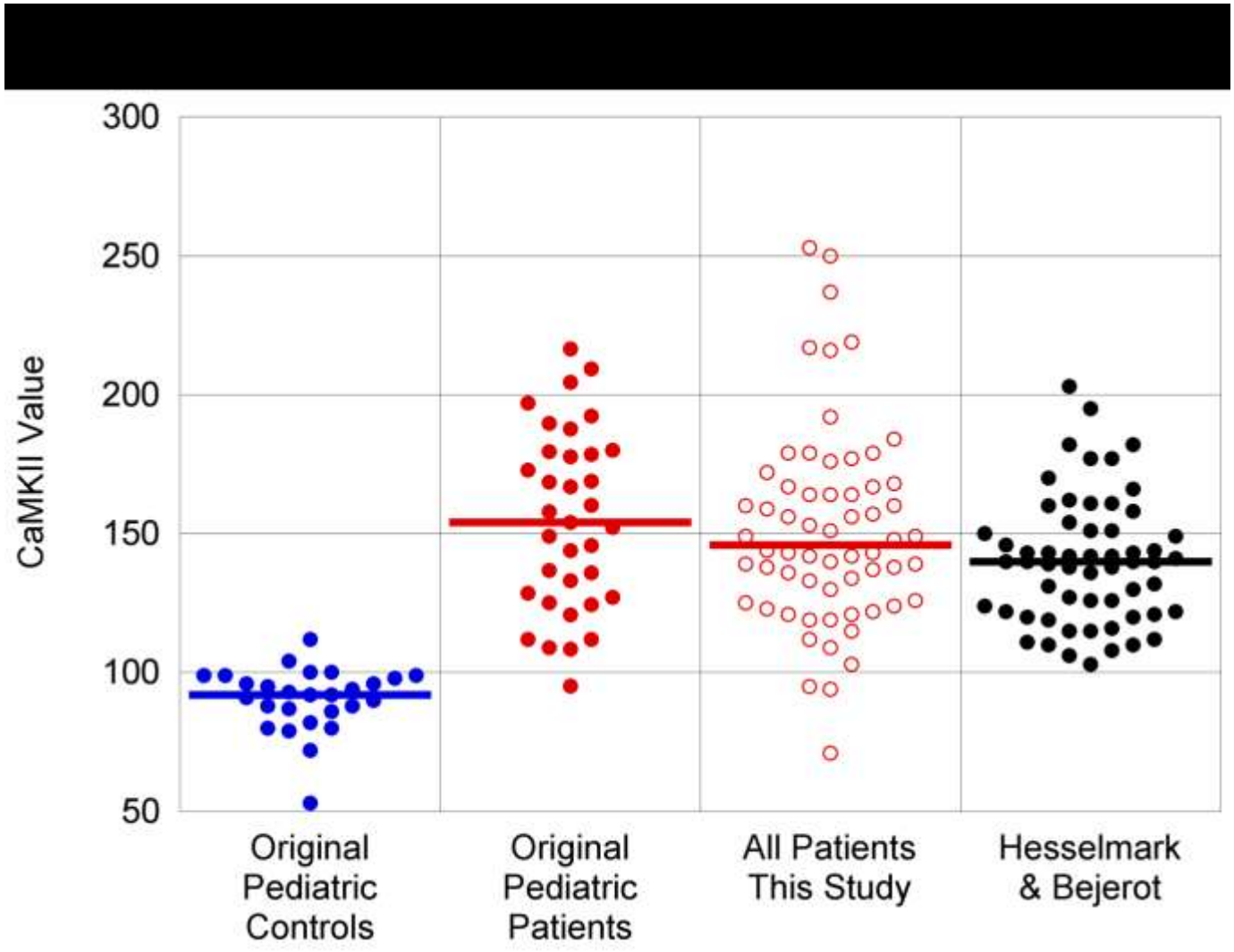
Multiple Test-retesting of samples collected in Red Top Glass Tubes (No additives)

- **First test on the X axis**
- **Repeat test on the Y axis**
- **R=0.90299**

Impact of Control Population Selection
CaMKII Results in Study Populations of Diseased Children

Normal ranges based upon 50 pediatric patients

- No Lifetime history of neuropsychiatric disorders
- No first degree relative with neuropsychiatric disorders
- No patient history of autoimmune diseases
- No active infections or symptoms



Cunningham Panel Performance Conclusions

1. **Results are variable and uncertain when blood is collected in non-valid tubes**, working on finding if other collection tubes can be validated

2. **Assay test-retest reproducibility is robust and highly reproducible**, especially considering this is a biological assay

3. **Selection of control population for these patients and in this Panel is critical** to understanding the differences in diseased and “healthy patients”

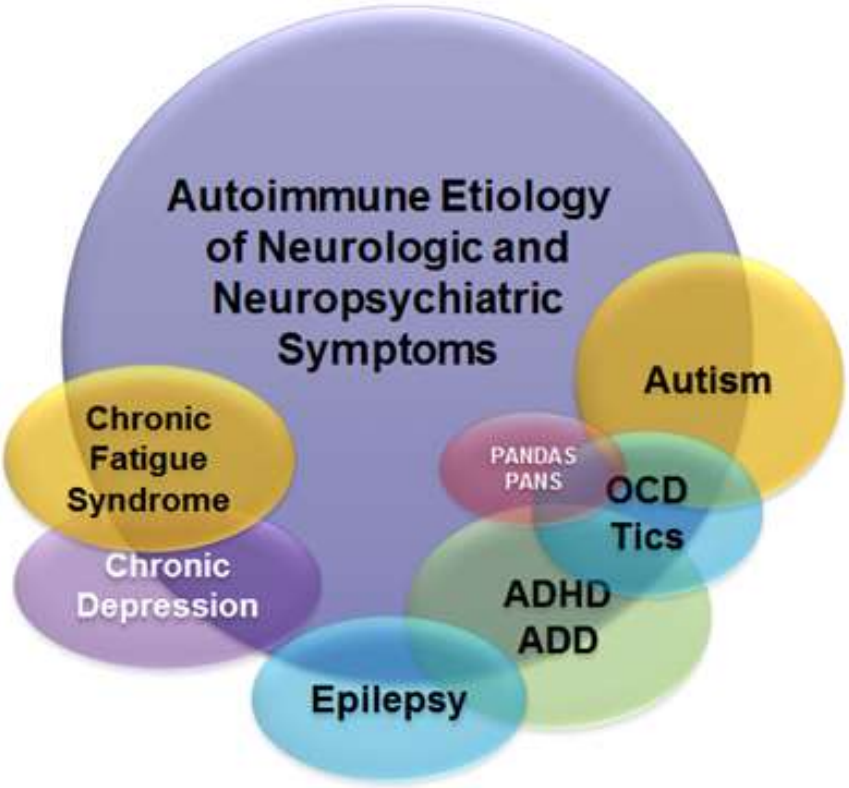
4. **More studies are needed** to better understand the biology and other potential biomarkers in PANS/PANDAS patients

Topics We will Cover

1. **Definition of PANDAS/PANS**
   - Nomenclature and alternative nomenclature
   - Proposed mechanism
   - What is the controversy?
2. **Brief clinical presentation and symptoms associated with PANDAS/PANS**
   - Some common infectious triggers
3. **Molecular mimicry and its role in post-infectious autoimmune disorders of the brain**
4. **Anti-neuronal antibodies in the Cunningham Panel**
   - Biomarker selection
   - Patient population study
   - Swedish study conclusions and issues
5. **Broader-based patient populations outside of PANDAS/PANS, including adults**

Challenges with Organ System Specialization in Medicine

Medical system rewards treatment (and retreatment) of symptoms rather than identification of etiology and resolution of underlying cause



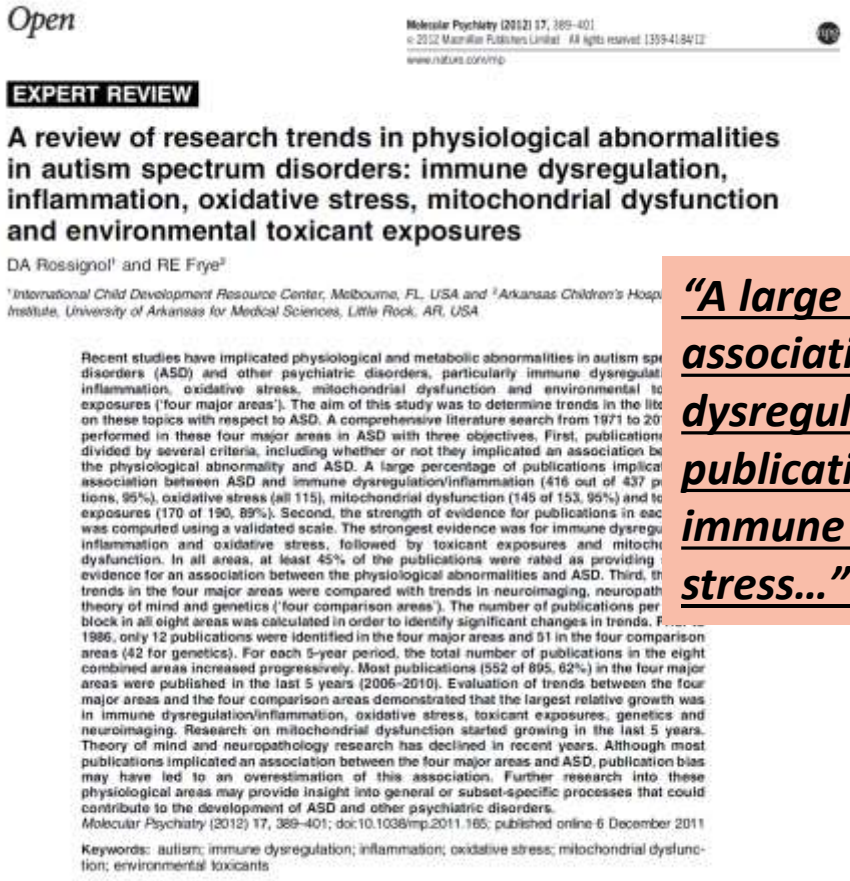
Distinctly different etiologies of disease can manifest identical symptoms but resolution is only possible with an understanding of the etiology

Autoantibody Etiology for Multiple Neuropsychiatric Disorders Detected by These 5 Biomarkers

- PANDAS/PANS
- Autism Spectrum Disorder (ASD)
- ADHD
- Tourette's
- Anxiety
- Obsessive Compulsive Disorder
- Chronic Depression
- Bipolar Disorder
- Epilepsy
- Eating Disorders

Physicians have been utilizing the panel for many of these disorders with positive results when using similar therapy. Case studies are being generated and working manuscripts.

Portions of Autism Spectrum Disorder are being linked to Immune Dysfunction



Open

Molecular Psychiatry (2012) 17, 389–401

www.nature.com/mp

EXPERT REVIEW

A review of research trends in physiological abnormalities in autism spectrum disorders: immune dysregulation, inflammation, oxidative stress, mitochondrial dysfunction and environmental toxicant exposures

DA Rossignol[1] and RE Frye[2]

[1]International Child Development Resource Center, Melbourne, FL, USA and [2]Arkansas Children's Hosp... Institute, University of Arkansas for Medical Sciences, Little Rock, AR, USA

Recent studies have implicated physiological and metabolic abnormalities in autism sp... disorders (ASD) and other psychiatric disorders, particularly immune dysregulat... inflammation, oxidative stress, mitochondrial dysfunction and environmental t... exposures ('four major areas'). The aim of this study was to determine trends in the lit... on these topics with respect to ASD. A comprehensive literature search from 1971 to 20... performed in these four major areas in ASD with three objectives. First, publication... divided by several criteria, including whether or not they implicated an association b... the physiological abnormality and ASD. A large percentage of publications implica... association between ASD and immune dysregulation/inflammation (416 out of 437 p... tions, 95%), oxidative stress (all 115), mitochondrial dysfunction (145 of 153, 95%) and t... exposures (170 of 190, 89%). Second, the strength of evidence for publications in eac... was computed using a validated scale. The strongest evidence was for immune dysregu... inflammation and oxidative stress, followed by toxicant exposures and mitoch... dysfunction. In all areas, at least 45% of the publications were rated as providing ... evidence for an association between the physiological abnormalities and ASD. Third, t... trends in the four major areas were compared with trends in neuroimaging, neuropath... theory of mind and genetics ('four comparison areas'). The number of publications per... block in all eight areas was calculated in order to identify significant changes in trends. F... 1986, only 12 publications were identified in the four major areas and 51 in the four comparison areas (42 for genetics). For each 5-year period, the total number of publications in the eight combined areas increased progressively. Most publications (552 of 895, 62%) in the four major areas were published in the last 5 years (2006–2010). Evaluation of trends between the four major areas and the four comparison areas demonstrated that the largest relative growth was in immune dysregulation/inflammation, oxidative stress, toxicant exposures, genetics and neuroimaging. Research on mitochondrial dysfunction started growing in the last 5 years. Theory of mind and neuropathology research has declined in recent years. Although most publications implicated an association between the four major areas and ASD, publication bias may have led to an overestimation of this association. Further research into these physiological areas may provide insight into general or subset-specific processes that could contribute to the development of ASD and other psychiatric disorders.
Molecular Psychiatry (2012) 17, 389–401; doi:10.1038/mp.2011.165; published online 6 December 2011

Keywords: autism; immune dysregulation; inflammation; oxidative stress; mitochondrial dysfunction; environmental toxicants

"A large percentage of publications implicated an association between ASD and immune dysregulation/inflammation (416 out of 437 publications, 95%)…The strongest evidence was for immune dysregulation /inflammation and oxidative stress…"

Portions of OCD and Tourette's are Associated with Immune Dysfunction

JOURNAL OF CHILD AND ADOLESCENT PSYCHOPHARMACOLOGY
Volume 20, Number 4, 2010

Pp. 317–331
DOI: 10.1089/cap.2010.0043

The Immunobiology of Tourette's Disorder, Pediatric Autoimmune Neuropsychiatric Disorders Associated with *Streptococcus*, and Related Disorders: A Way Forward

Tanya K. Murphy, M.D.,[1] Roger Kurlan, M.D.,[2] and James Leckman, M.D.[3]

Abstract

Obsessive-compulsive disorder (OCD) and relate
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through searches of the PsycINFO and MedLine
Sydenham chorea, Tourette's disorder Group A *Streptococcus*. Articles were also identified through reference lists from research articles and other materials on childhood OCD, PANDAS, and TD between 1966 and December 2010. Considering the overlap of clinical and neuroanatomic findings among these disorders, this review explores evidence regarding the immunobiology as well as the relevant clinical and therapeutic aspects of TD, OCD, and PANDAS.

"Obsessive-compulsive disorder (OCD) and related conditions including Tourette's disorder (TD) are chronic, relapsing disorders of unknown etiology… <u>Associated immune dysfunction has been reported and debated in the literature since the late 80s.</u>"

Portions of Autism Spectrum Disorder are being linked to Immune Dysregulation

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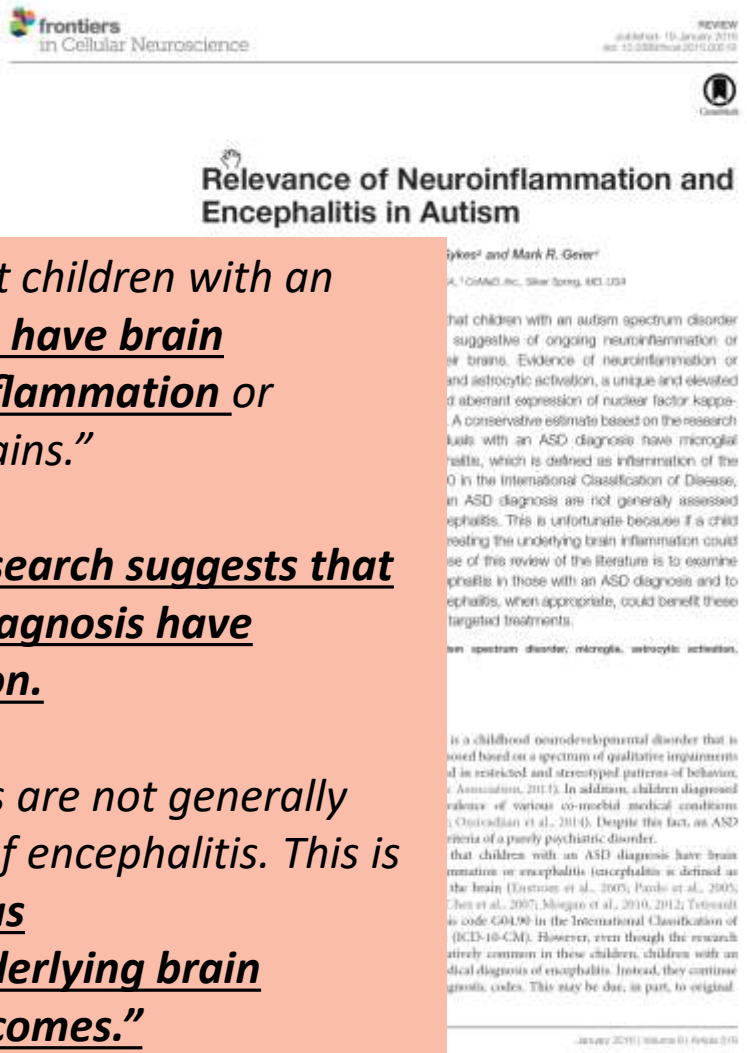
frontiers in Cellular Neuroscience

REVIEW

Relevance of Neuroinflammation and Encephalitis in Autism

"In recent years, many studies indicate that children with an ***autism spectrum disorder (ASD) diagnosis have brain pathology suggestive of ongoing neuroinflammation*** *or encephalitis in different regions of their brains."*

"A conservative estimate based on the research suggests that at least 69% of individuals with an ASD diagnosis have microglial activation or neuroinflammation.

"…however, children with an ASD diagnosis are not generally assessed for a possible medical diagnosis of encephalitis. This is unfortunate because ***if a child with ASD has neuroinflammation, then treating the underlying brain inflammation could lead to improved outcomes."***

Portions of OCD and Tourette's are Associated with Immune Dysfunction

JOURNAL OF CHILD AND ADOLESCENT PSYCHOPHARMACOLOGY
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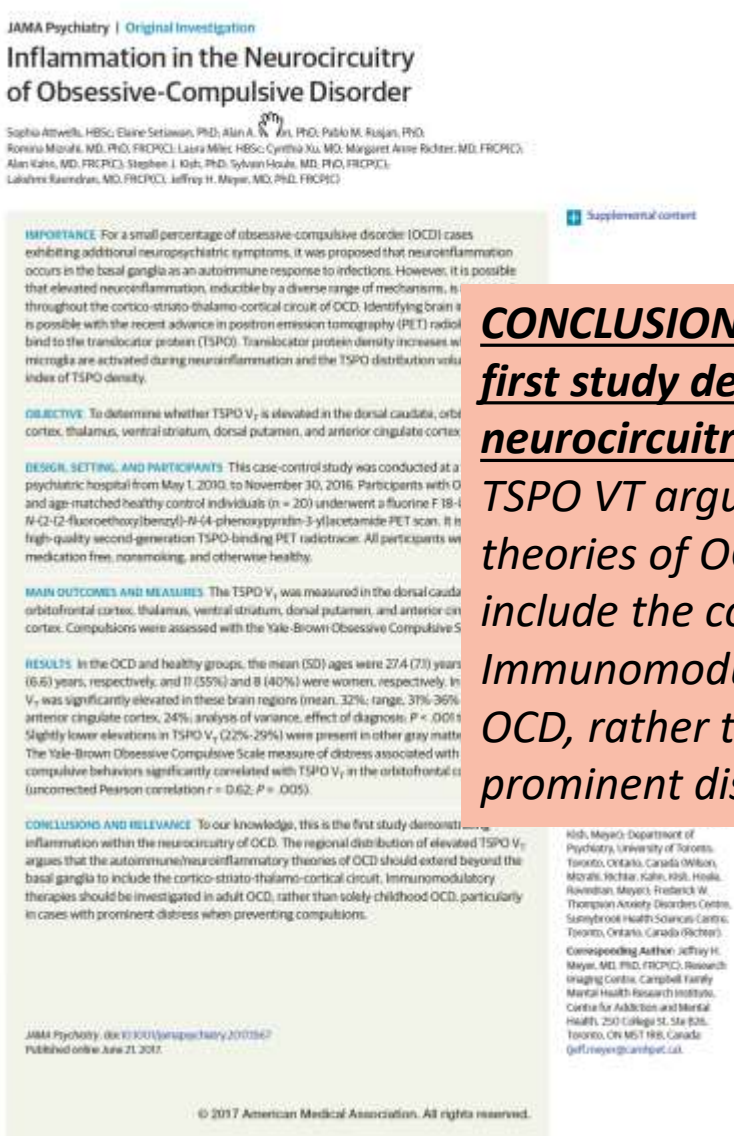
Portions of OCD are Associated with Basal Ganglia Neuroinflammation



JAMA Psychiatry | Original Investigation

Inflammation in the Neurocircuitry of Obsessive-Compulsive Disorder

Sophia Attwells, HBSc; Elaine Setiawan, PhD; Alan A. Wilson, PhD; Pablo M. Rusjan, PhD; Romina Mizrahi, MD, PhD, FRCP(C); Laura Miler, HBSc; Cynthia Xu, MD; Margaret Anne Richter, MD, FRCP(C); Alan Kahn, MD, FRCP(C); Stephen J. Kish, PhD; Sylvain Houle, MD, PhD, FRCP(C); Lakshmi Ravindran, MD, FRCP(C); Jeffrey H. Meyer, MD, PhD, FRCP(C)

Supplemental content

IMPORTANCE For a small percentage of obsessive-compulsive disorder (OCD) cases exhibiting additional neuropsychiatric symptoms, it was proposed that neuroinflammation occurs in the basal ganglia as an autoimmune response to infections. However, it is possible that elevated neuroinflammation, inducible by a diverse range of mechanisms, is throughout the cortico-striato-thalamo-cortical circuit of OCD. Identifying brain is possible with the recent advance in positron emission tomography (PET) radio bind to the translocator protein (TSPO). Translocator protein density increases w microglia are activated during neuroinflammation and the TSPO distribution volu index of TSPO density.

OBJECTIVE To determine whether TSPO V_T is elevated in the dorsal caudate, orbe cortex, thalamus, ventral striatum, dorsal putamen, and anterior cingulate cortex

DESIGN, SETTING, AND PARTICIPANTS This case-control study was conducted at a psychiatric hospital from May 1, 2010, to November 30, 2016. Participants with O and age-matched healthy control individuals (n = 20) underwent a fluorine F 18-(*N*-(2-(2-fluoroethoxy)benzyl)-*N*-(4-phenoxypyridin-3-yl)acetamide PET scan. It i high-quality second-generation TSPO-binding PET radiotracer. All participants w medication free, nonsmoking, and otherwise healthy.

MAIN OUTCOMES AND MEASURES The TSPO V_T was measured in the dorsal cauda orbitofrontal cortex, thalamus, ventral striatum, dorsal putamen, and anterior cin cortex. Compulsions were assessed with the Yale-Brown Obsessive Compulsive S

RESULTS In the OCD and healthy groups, the mean (SD) ages were 27.4 (7.1) years (6.6) years, respectively, and 11 (55%) and 8 (40%) were women, respectively. In V_T was significantly elevated in these brain regions (mean, 32%; range, 31%-36% anterior cingulate cortex, 24%; analysis of variance, effect of diagnosis: $P < .001$ Slightly lower elevations in TSPO V_T (22%-29%) were present in other gray matte The Yale-Brown Obsessive Compulsive Scale measure of distress associated with compulsive behaviors significantly correlated with TSPO V_T in the orbitofrontal c (uncorrected Pearson correlation $r = 0.62$; $P = .005$).

CONCLUSIONS AND RELEVANCE To our knowledge, this is the first study demonstrat inflammation within the neurocircuitry of OCD. The regional distribution of elevated TSPO V_T argues that the autoimmune/neuroinflammatory theories of OCD should extend beyond the basal ganglia to include the cortico-striato-thalamo-cortical circuit. Immunomodulatory therapies should be investigated in adult OCD, rather than solely childhood OCD, particularly in cases with prominent distress when preventing compulsions.

JAMA Psychiatry. doi:10.1001/jamapsychiatry.2017.0547
Published online June 21, 2017.

Kish, Meyer): Department of Psychiatry, University of Toronto, Toronto, Ontario, Canada (Wilson, Mizrahi, Richter, Kahn, Kish, Houle, Ravindran, Meyer); Frederick W. Thompson Anxiety Disorders Centre, Sunnybrook Health Sciences Centre, Toronto, Ontario, Canada (Richter).

Corresponding Author: Jeffrey H. Meyer, MD, PhD, FRCP(C), Research Imaging Centre, Campbell Family Mental Health Research Institute, Centre for Addiction and Mental Health, 250 College St, Ste 836, Toronto, ON M5T 1R8, Canada (jeff.meyer@camhpet.ca).

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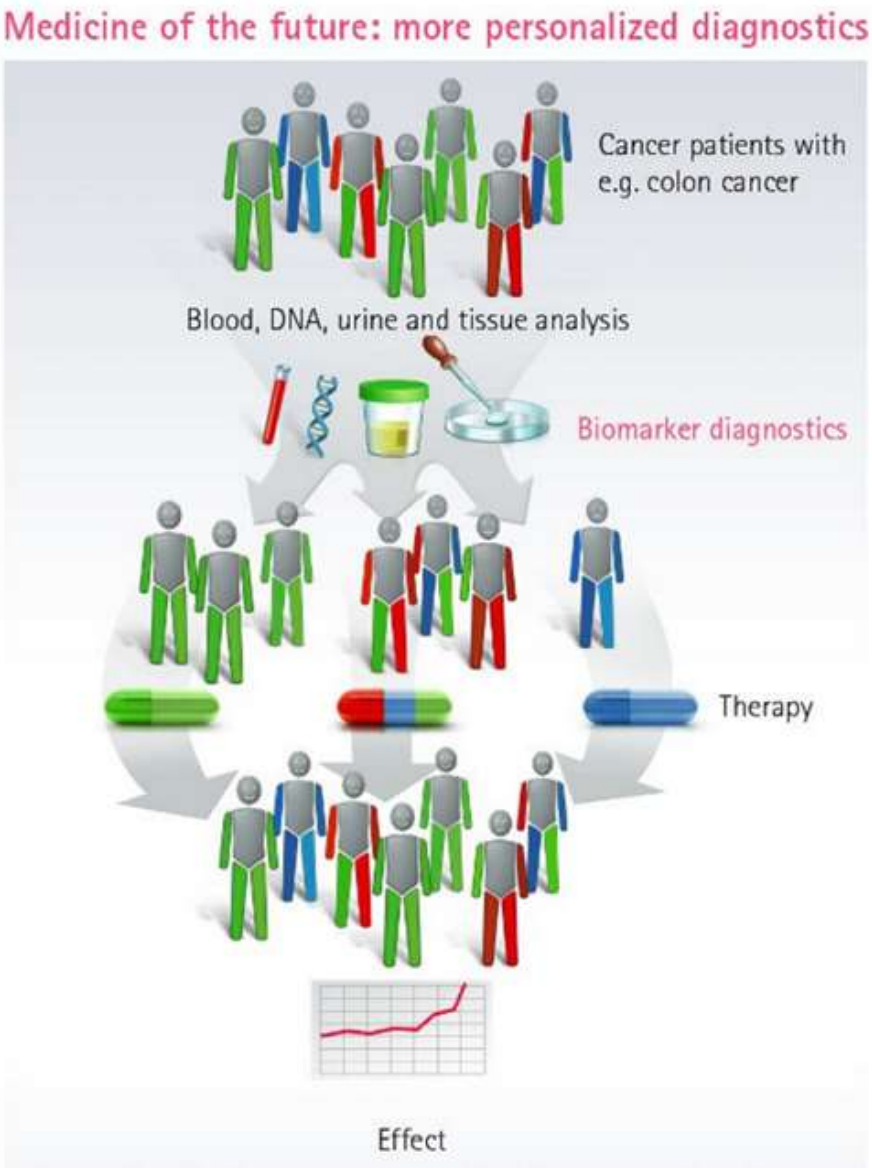
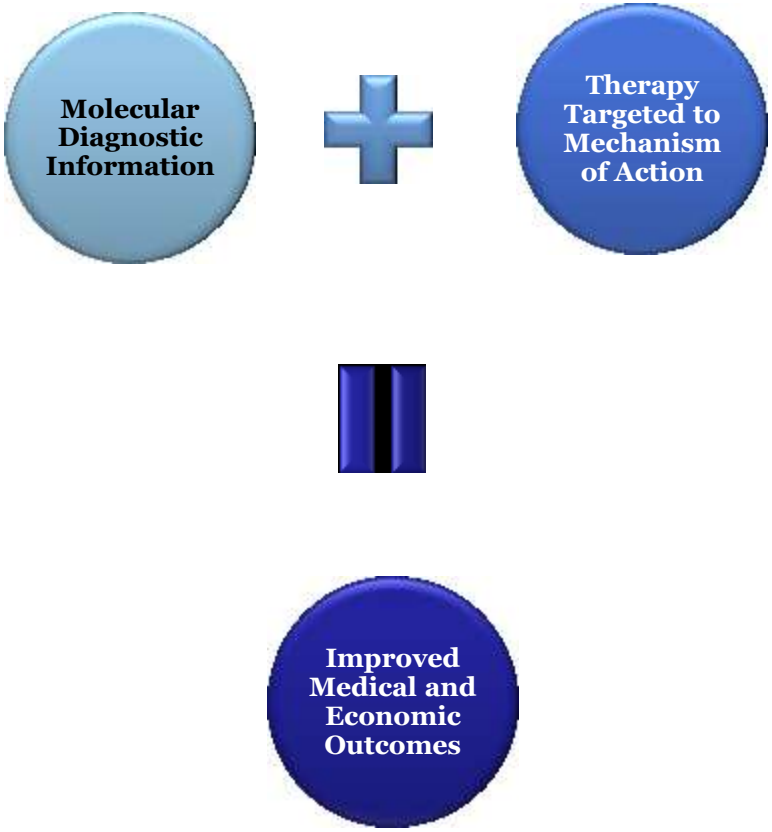
The Goal of Precision Medicine





Additional Information Sources

PANDAS PHYSICIANS NETWORK

P P N

A DIVISION OF THE FOUNDATION FOR BRAIN SCIENCE AND IMMUNOLOGY

www.pandasppn.org

PANDAS NETWORK

Pediatric Autoimmune Neuropsychiatric Disorders

www.pandasnetwork.org

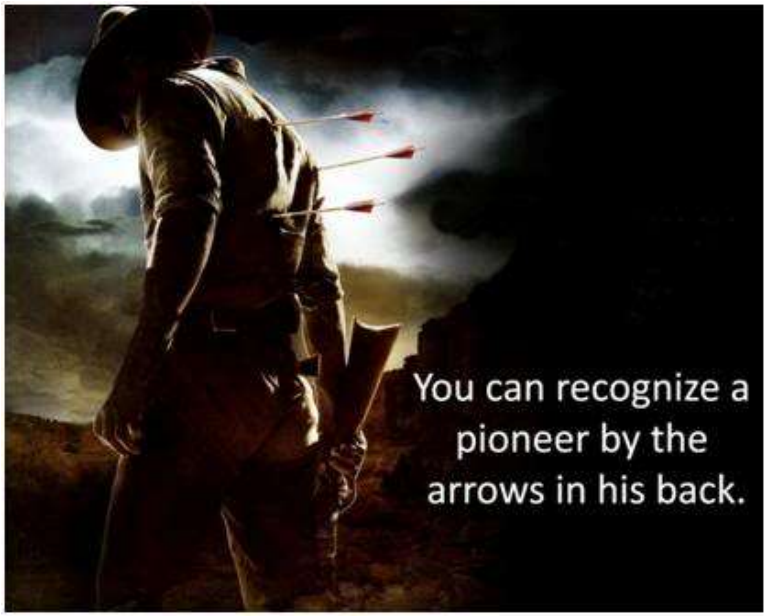
moleculera labs

www.moleculeralabs.com

NIH National Institute of Mental Health

www.nimh.nih.gov

When Working with These Patients you Become Pioneers

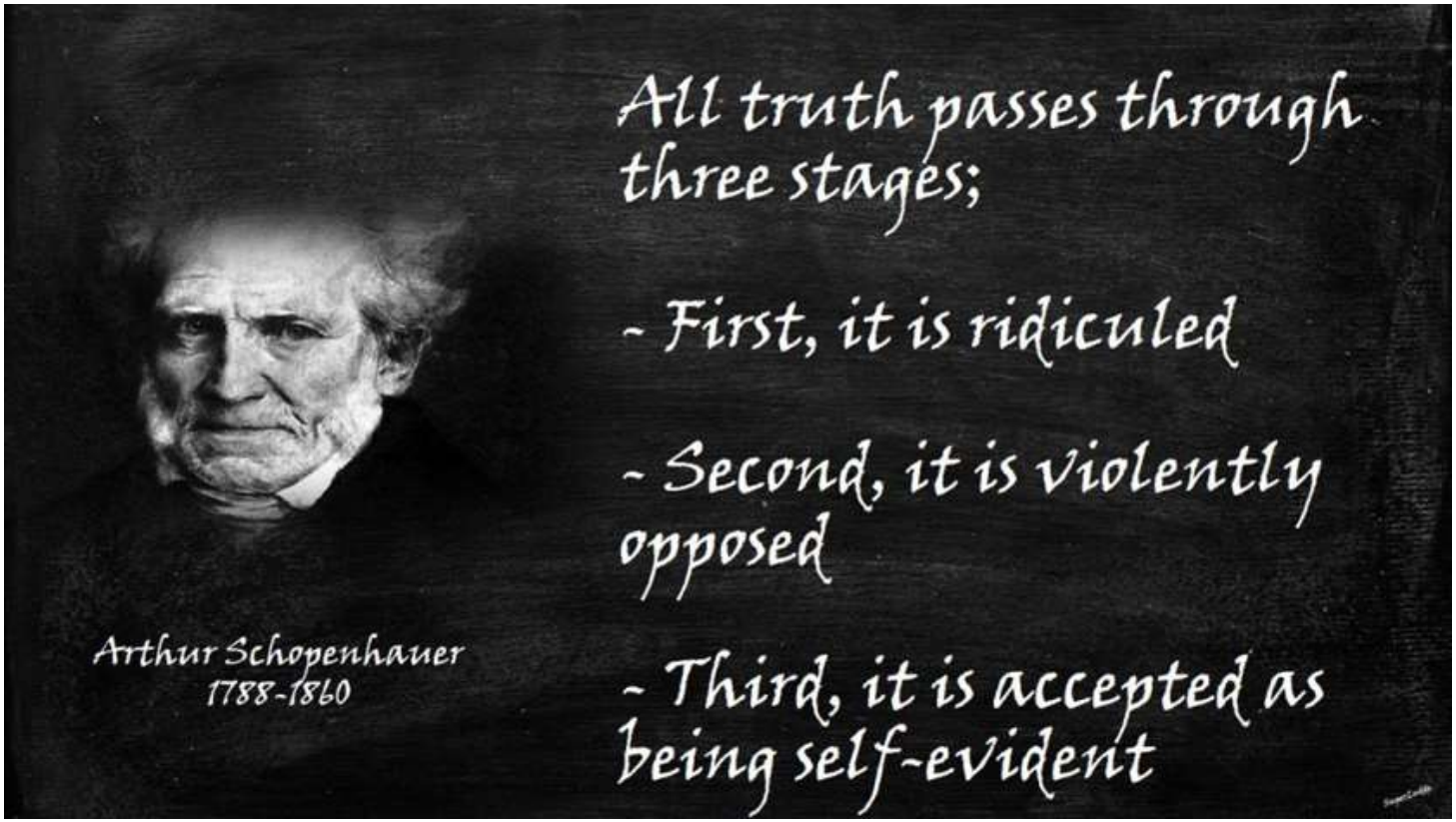


pi·o·neer

Noun: a person who is among the first to explore or settle a new country or area.

Verb: develop or be the first to use or apply (a new method, area of knowledge, or activity)

When Working with These Patients you Become Pioneers



Grace's Story – One of Thousands we Have Tested

Our Mission is to Help Change How Medicine is Practiced for Neuropsychiatric Disorders

Thank you for helping those suffering with this disorder, to gain hope and get well!

For More Information Contact:
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