History and setting the scene

Dr Susan Swedo
Professor Jennifer Frankovich



PERSPECTIVES
ON PANS

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Scientist Emerita
U.S. National Institutes of Health

Nothing to declare or disclose.

An Abbreviated History of PANDAS

1880 – 1950's Historical Observations of Sydenham chorea, OCD and tics

1972 Husby reports cross-reactive antibodies in Sydenham chorea.
(1990's – Similar antibodies observed in PANDAS patients)

1986 Parallel studies of Sydenham chorea and childhood-onset OCD are begun

1992 – First public critique of post-strep OCD – "Controversy" begins

1994 Publication of five post-infectious cases of OCD (PITANDS)

1998 First 50 cases of PANDAS are described

1995 – 2005 Accumulating evidence supports Group A Strep as cause of PANDAS

2005 – Dueling editorials in *Pediatrics* heighten controversy

So…Why is PANDAS Considered “Controversial”?

Diagnosis is made on clinical/behavioral basis

- PANDAS is dismissed as “missed case of Sydenham chorea”
- Defining course by acuity of onset vs. episodicity
- Consideration of comorbidity and premorbid conditions (autism)
- Have to believe an unbelievable story

Etiologic role of Group A streptococcal (GAS)

- Frequency of GAS in grade-school children
- True-true unrelated or True-true related and etiologic

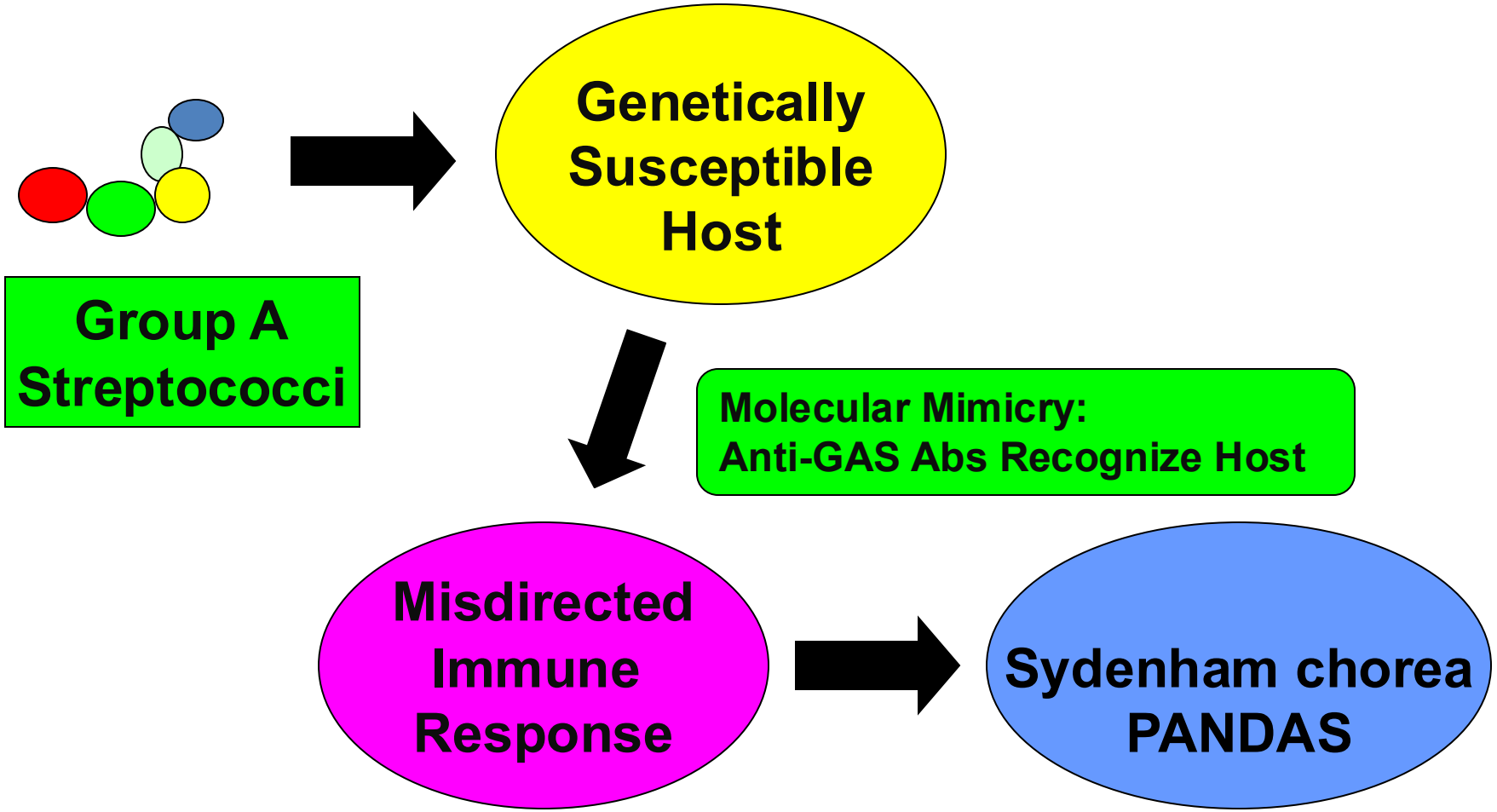
Other!

Evidence Supporting PANDAS as a Strep-Triggered Neuroimmune Disorder

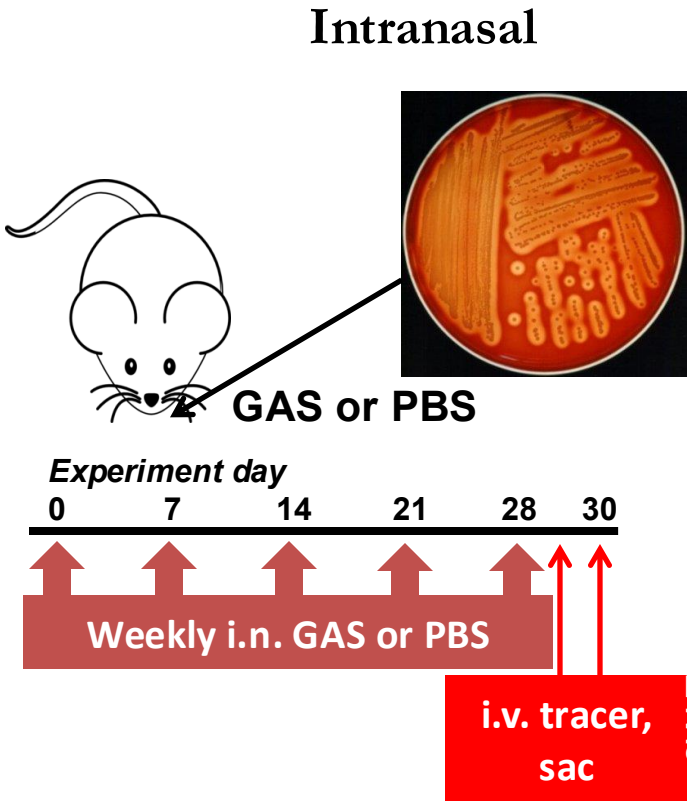
Clinical evidence provided by studies of Sydenham chorea (SC) and pediatric obsessive compulsive disorder (OCD)

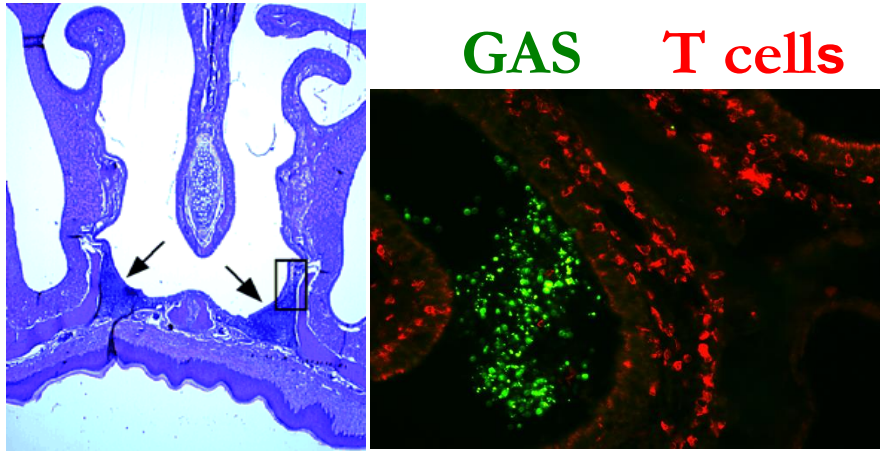
- 1988 – 2/3's of children with SC have OCD which precedes onset of SC by 2 – 4 weeks
- 1992 – ¼ of pediatric OCD patients have Acute onset and Episodic course (accompanied by choreiform movements)
- 1998 - First 50 cases of PANDAS are described
- 1999 - Therapeutic plasma exchange (plasmapheresis) and IVIG are both superior to placebo for treatment of PANDAS symptoms
- 1999 & 2005 – Antibiotic prophylaxis trials show that when Group A strep infections are prevented, so are neuropsychiatric symptom exacerbations

Model of Etiopathogenesis for Sydenham's chorea and PANDAS

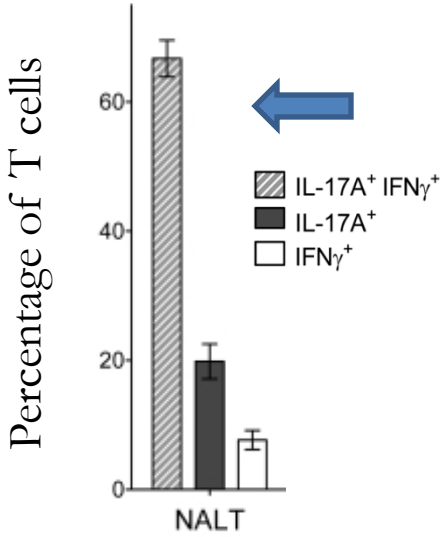


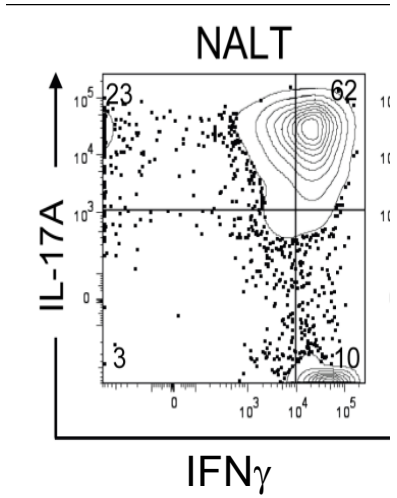
LABORATORY EVIDENCE THAT GROUP A STREPTOCOCCAL INFECTIONS PLAY A CAUSATIVE ROLE IN PANDAS





T cell phenotype after **multiple** intranasal infections

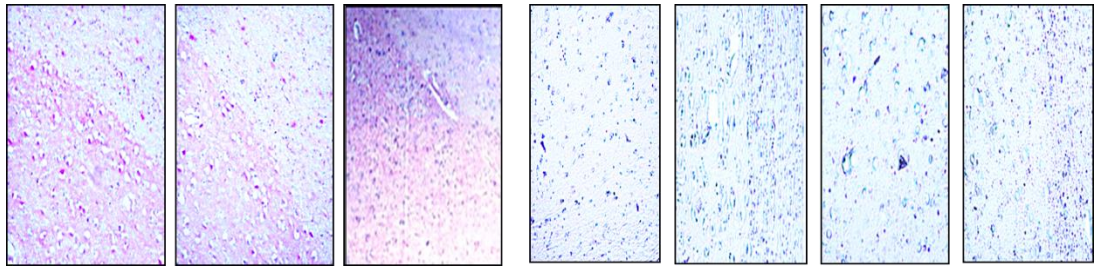


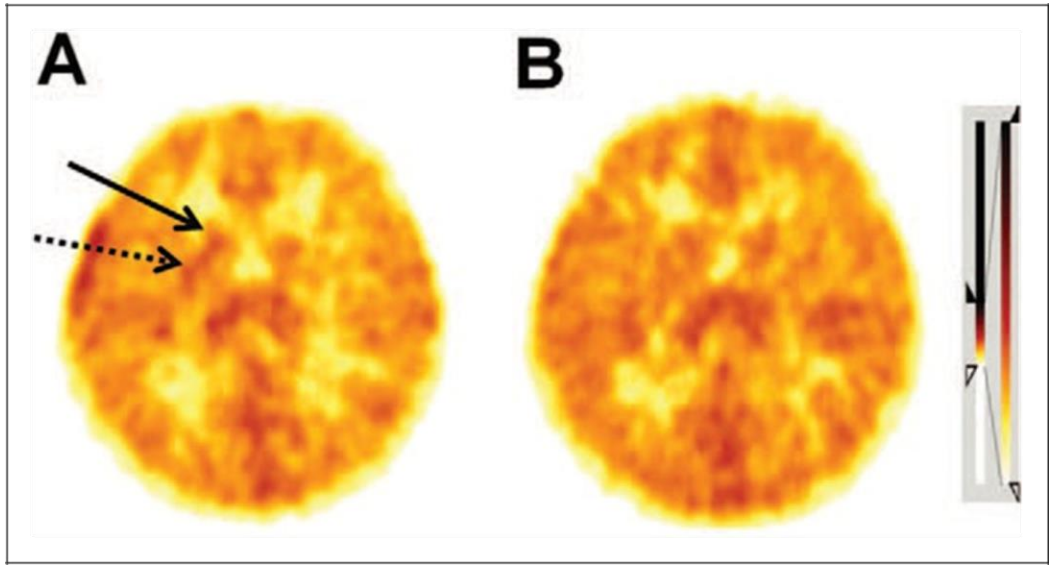


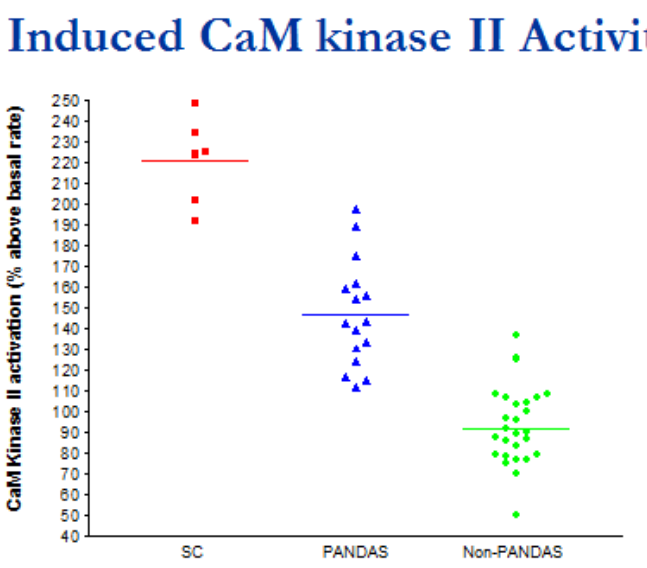
Dileepan T *et al.*, (2011) *PLoS Pathogens*

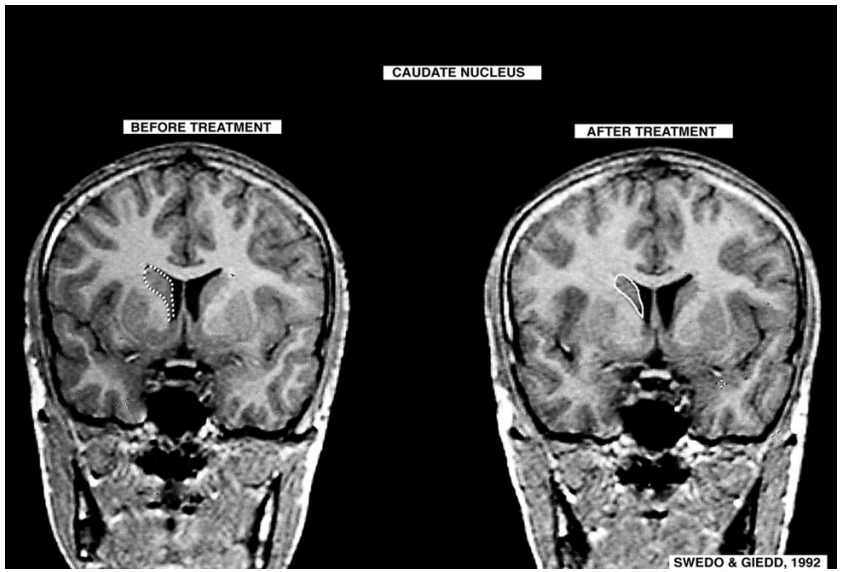
Evidence of Neuroinflammation in PANDAS

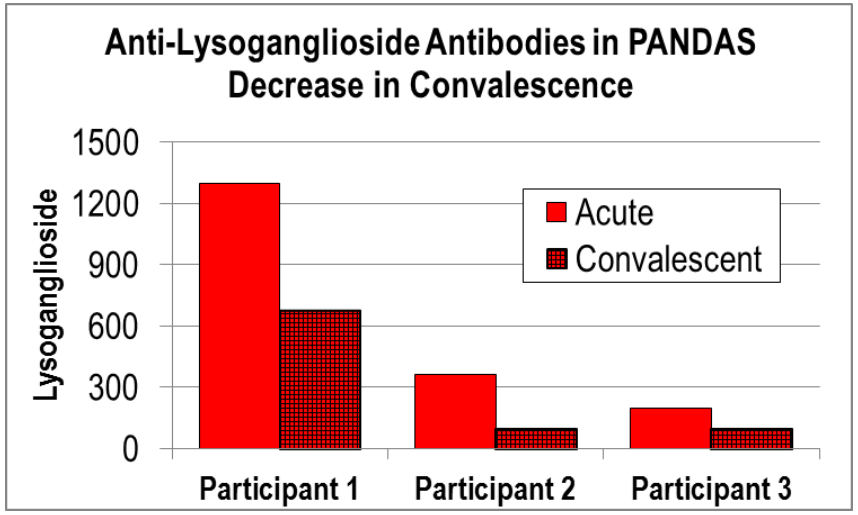
Cross-reactive antibodies correlate with SC & PANDAS severity











And yet, the Controversy Continued…

PEDIATRICS
OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

Children's Memorial Hospital

The Pediatric Autoimmune Neuropsychiatric Disorders Associated With Streptococcal Infection (PANDAS) Etiology for Tics and Obsessive-Compulsive Symptoms: Hypothesis or Entity? Practical Considerations for the Clinician
Roger Kurlan and Edward L. Kaplan
Pediatrics 2004;113;883

"At best, PANDAS is an extremely controversial diagnostic entity. Even if one were to believe in the diagnosis, there is no evidence that prednisone therapy, treatments with intravenous immune globulin, or prolonged antibiotics will alter the course in any way." Dec 2008

Pediatrics

INFECTIOUS DISEASES IN CHILDREN

PANDAS to CANS: Evolution of a controversial disorder

Little consensus exists on role of group A streptococcal infection in autoimmune/neurological phenomenon.

Infectious Diseases in Children, October 2012

THE JOURNAL OF PEDIATRICS • www.jped

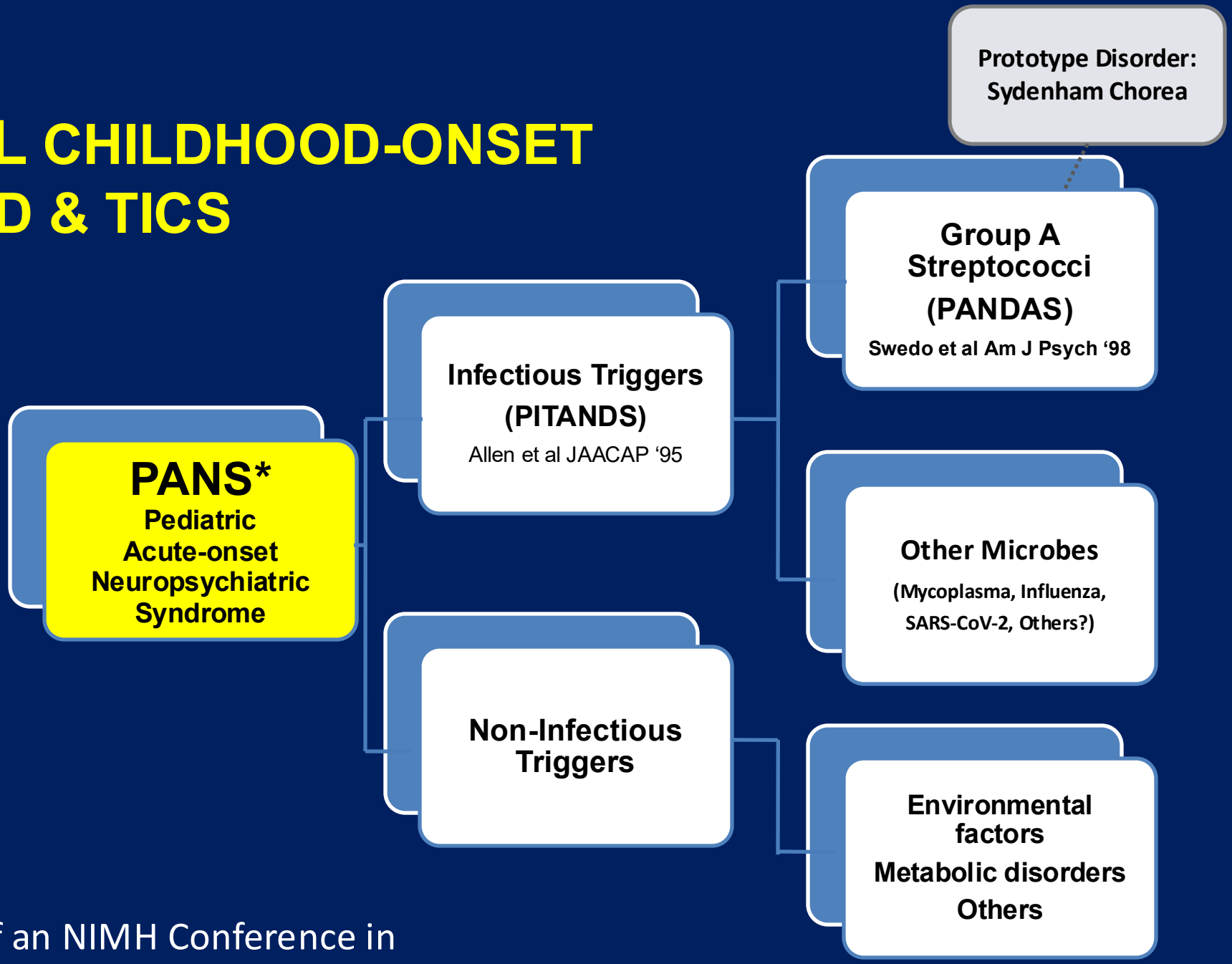
The Need to Move beyond PANDAS

The concept of PANDAS has been the topic of intense debate and controversy for many years.[2-8] Historically, several re-

Moving from PANDAS to CANS

Harvey S. Singer, MD[1], Donald L. Gilbert, MD[2], David S. Wolf, MD, PhD[1], Jonathan W. Mink, MD, PhD[3], and Roger Kurlan, MD[4]

ALL CHILDHOOD-ONSET OCD & TICS



*Construct of an NIMH Conference in 2010

PANDAS Comorbid Symptomatology

- Separation anxiety 98%
- Urinary frequency, urgency, enuresis & “accidents” 90%
- Sleep disorders 80%

  Insomnia, night terrors, restless sleep. REM abnormalities (80%) and other polysomnographic abnormalities
- Behavioral regression 70%

  Baby talk, tantrums
- Hyperactivity, inattentiveness 70%
- Aggressiveness 60%
- Learning difficulties 60%
- Tics 70%
- Terror stricken look (mydriasis) or Hyper-alert appearance 80%
- Handwriting deterioration 90%
- Short-term memory loss 60%
- Sensory hypersensitivity or Insensitivity 40%
- Eating disorder 20%
- Hallucinations 10%

Clinical Criteria Define Both PANDAS & PANS

PANDAS = DISORDER

1) Presence of OCD or tic disorder
2) Prepubertal onset
3) **ACUTE** onset and episodic course
4) Association with neurological abnormalities (choreiform movements)
5) Temporal relationship between symptoms exacerbations and[12] Group A Streptococcal infections (Strep)

PANS = SYNDROME

1) **ACUTE** onset of OCD or Eating restrictions
2) Concurrent onset of at least two of the following:
   1. Anxiety (esp. separation anxiety)
   2. Behavioral/developmental regression
   3. Emotional lability or depression
   4. Irritability, aggression and/or severely oppositional behavior
   5. Deterioration in school performance
   6. Sensory or motor abnormalities
   7. Somatic signs/symptoms, especially insomnia and urinary symptoms
3) Symptoms are not better explained by a known neurologic or medical disorder, such as SC or Tourette.

JOURNAL OF CHILD AND ADOLESCENT PSYCHOPHARMACOLOGY
Volume xx, Number x, 2014
© Mary Ann Liebert, Inc.
Pp. 1–11
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 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

Summary & Diagnostic Flowchart – See *PANDASPPN.org*

Treatment Recommendations

Journal of Child & Adolescent Psychopharmacology, Sep 2017

JOURNAL OF CHILD AND ADOLESCENT PSYCHOPHARMACOLOGY
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

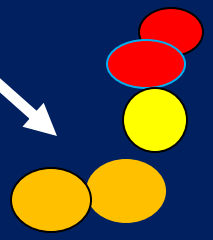
Susan E. Swedo, MD,[1] Jennifer Frankovich, MD, MS,[2,3] and Tanya K. Murphy, MD, MS[4]

ANTIBIOTICS (AS INDICATED)
IMMUNOMODULATORY THERAPY
SYMPTOMATIC TREATMENT



PANDAS – A Treatable and Preventable Illness

ANTIBIOTIC TREATMENT & PROPHYLAXIS



Strep and other bacteria

Genetically Susceptible Host

Symptomatic Treatment

Immunomodulatory Therapy

Abnormal Immune Response

NO PANDAS
NO OCD/Tics

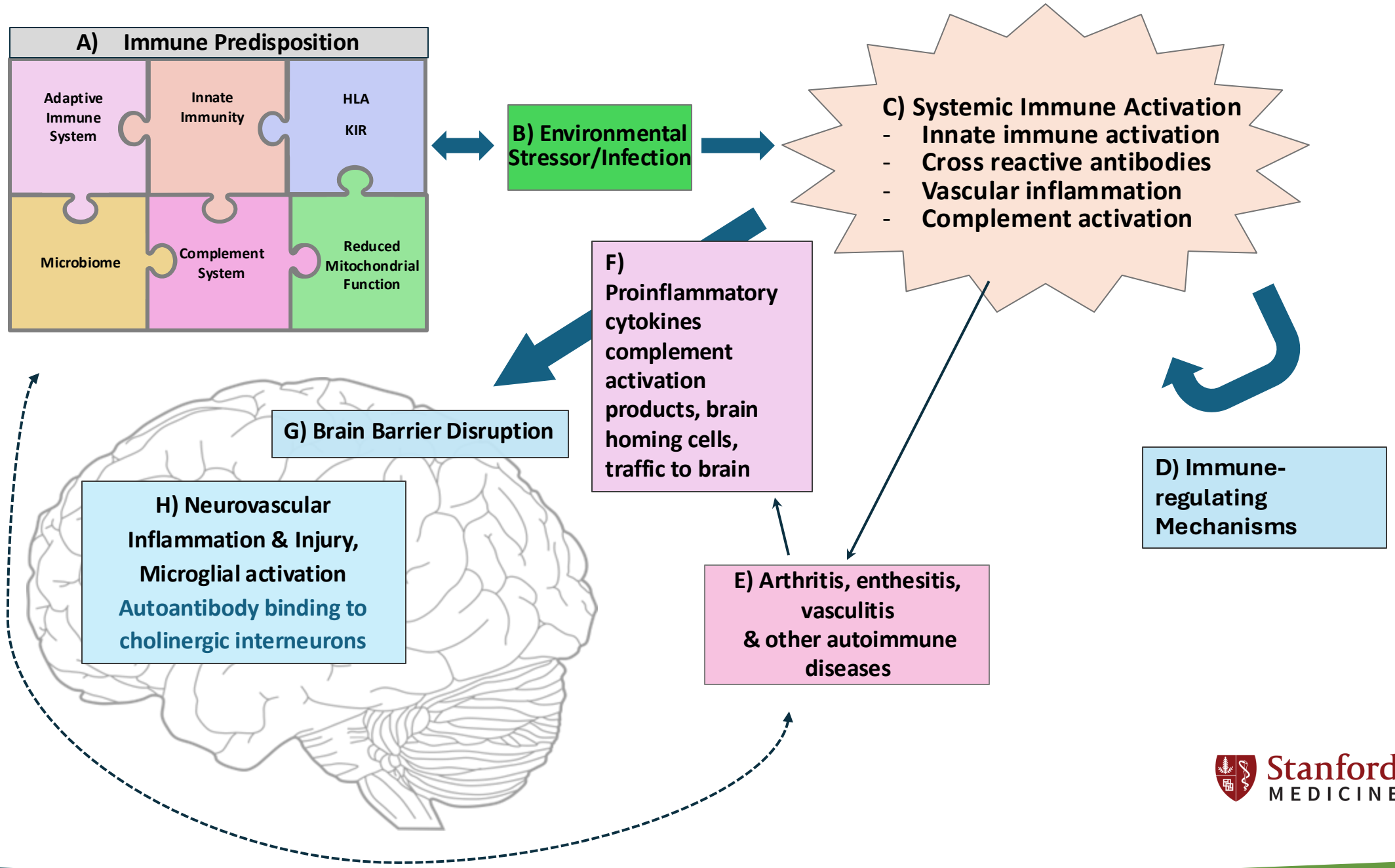
PANS PANDAS UK

Perspectives on PANS

8 - 10 October 2026

PERSPECTIVES ON PANS

Jennifer Frankovich, MD MS
Clinical Professor of Pediatrics & Pediatric Rheumatology
Director, Immune Behavioral Health (IBH) Clinic & Research
Stanford School of Medicine • Stanford Children's Hospital



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4 imaging studies = basal ganglia injury/inflammation in PANS/PANDAS

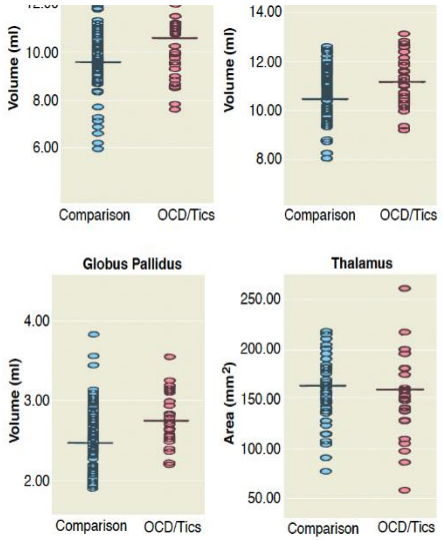


FIGURE 1. Scatterplots of Basal Ganglia Volume and Thalamus Area of 34 Children With Poststreptococcal OCD or Tics and 82 Healthy Comparison Children Matched for Age and Sex

⬆ BG Volume
in the acute stage

Giedd, et al. *AJP* 2000

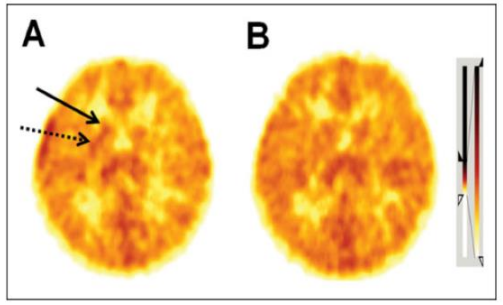
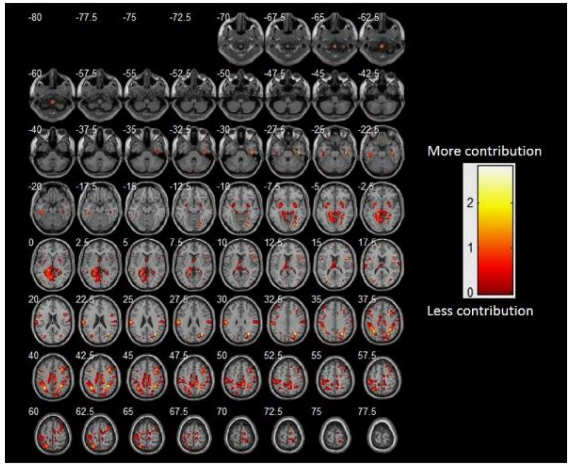


Figure 3. (A) Pre and (B) post (6 months after) immunoglobulin treatment ^{11}C-[R]-PK11195 PET scan, in an 8-year-old male child with pediatric autoimmune neuropsychiatric disorders associated with streptococcal infection (PANDAS), showing reduced tracer binding, suggesting reduced neuroinflammation, in the right caudate (arrow) and right lentiform nucleus (broken arrow) after immunoglobulin therapy.

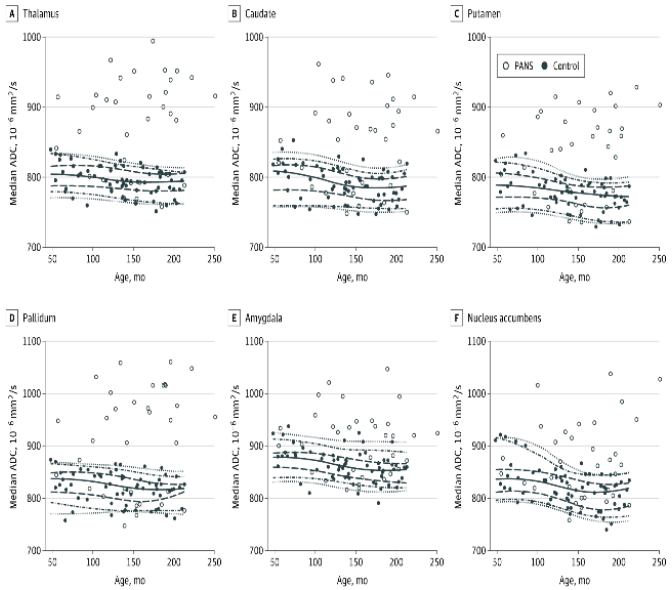
⬆ Microglia activation in BG

Kumar, et al. *J Child Neuro*. 2015



⬆ Gray matter volume in BG
⬇ White matter volume in BG

Cabrera et al. *CNS Spectrums*, 2019

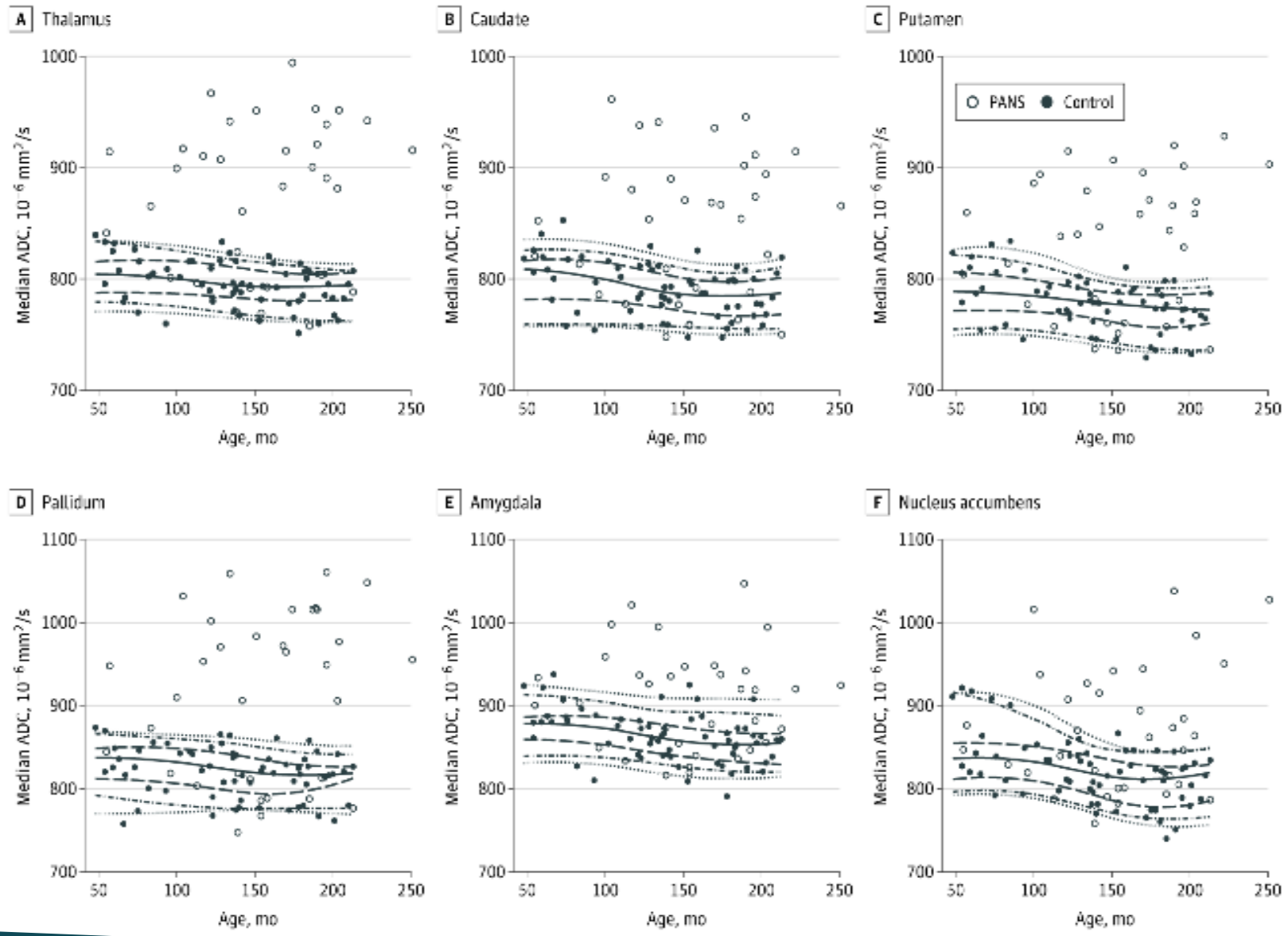


⬆ Medium diffusivity all assessed brain regions—most prominent in BG

Zheng, et al. *JAMA Netw. Open* 2020

JAMA Network | Open

DWI: Medium diffusivity ↑ in all assessed brain regions



Thalamus:
brain's "relay station," alterations here are linked to the sensory sensitivities and sleep disturbances common in PANS

Caudate, **putamen**, and **pallidum**.
aligns with the motor symptoms, altered behavior, OCD, learning

Amygdala:
fear-based symptoms, extreme separation anxiety and emotional lability

Pallidum
satisfaction center

Nucleus accumbuns
motivation center

JAMA Network Open

Sleep studies = basal ganglia (BG) dysfunction in PANS/PANDAS

REM sleep = **dream sleep** (normal = paralyzed)
Abnormal if → movements, laughing, moaning, hand stereopathies, or loss of atonia during REM sleep.



NIH Swedo Cohort

New-onset patients (~6 months of PANS)

12/15 (80%) had movements during REM sleep.

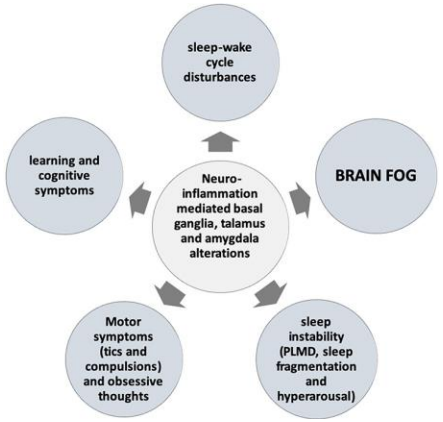
Gaughan, Swedo, et al.
J of Sleep Med. 2016

Stanford PANS Cohort

Patient with chronic symptoms (~4 years of PANS symptoms)

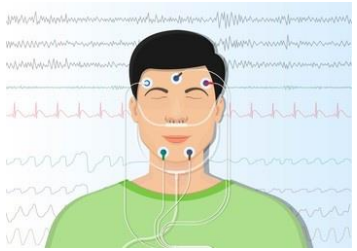
7/9 (78%) movements +/- loss of atonia during REM sleep

Santoro, Frankovich, et al.
Journal of Sleep Med. 2018



11/17 (65%) had movements +/- loss of atonia during REM sleep

Gagliano, et al.
Nat Sci Sleep. 2021



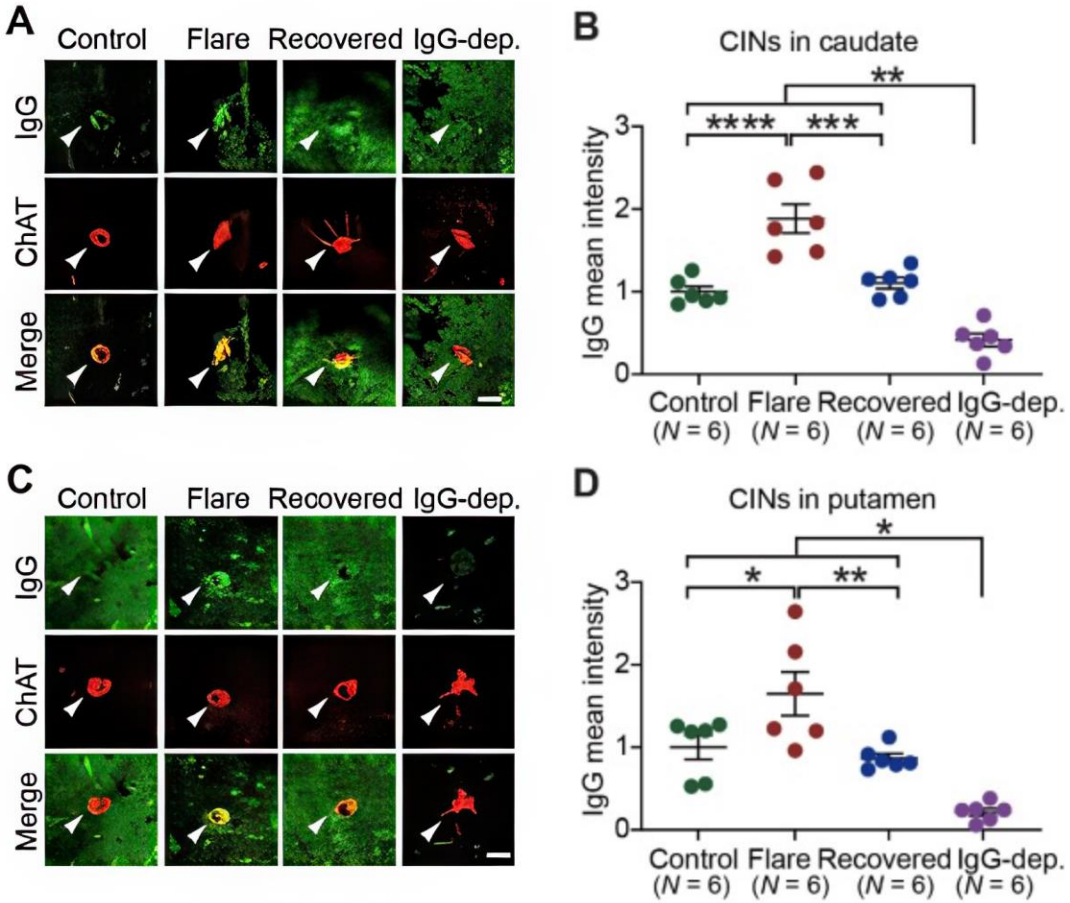
25/57 (21%) had **REM atonia index below age/sex normal limits**

1/43 (2%) of healthy controls had REM atonia index below age/sex normal limits

Congiu, Gagliano, et al.
Journal of Sleep Med. 2024

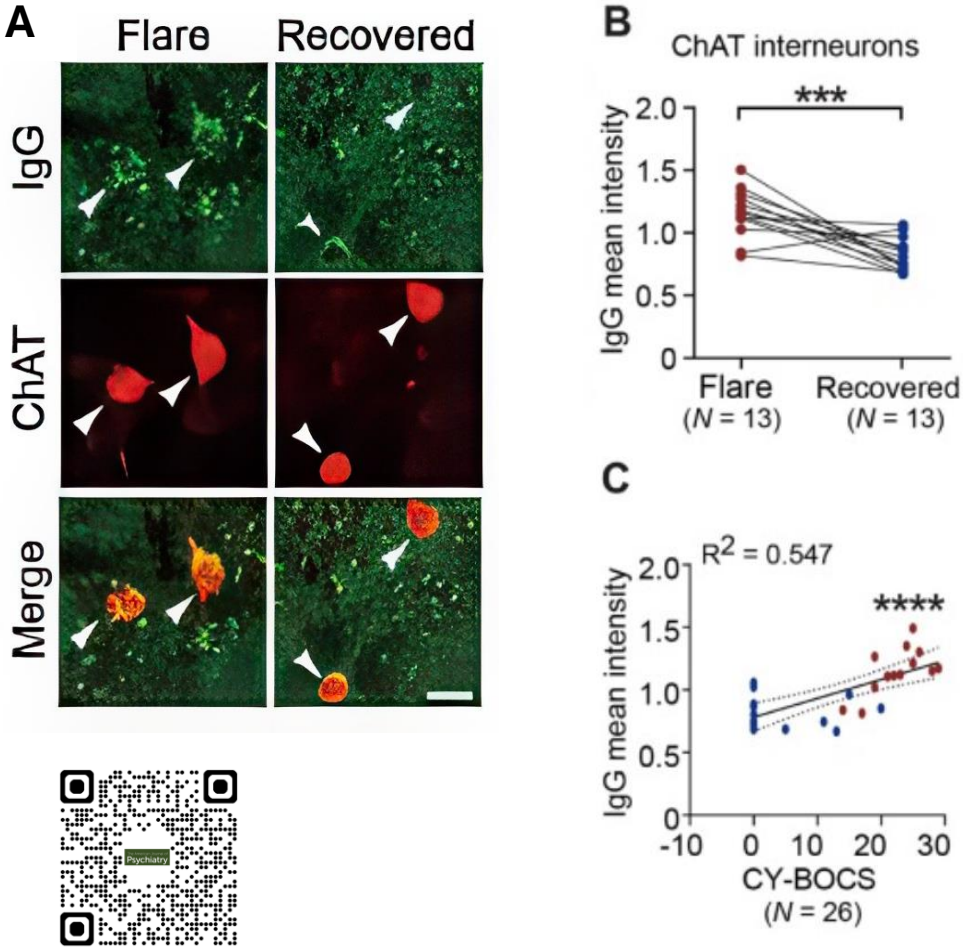
Movements during REM sleep → common in PANS/PANDAS
Movements during REM sleep → are a predictor of Parkinson's & multiple systems atrophy disease in adults.

Autoantibodies bind to Cholinergic Interneurons (CINs) in Basal Ganglia & Alters activity of cholinergic interneurons (CINs)



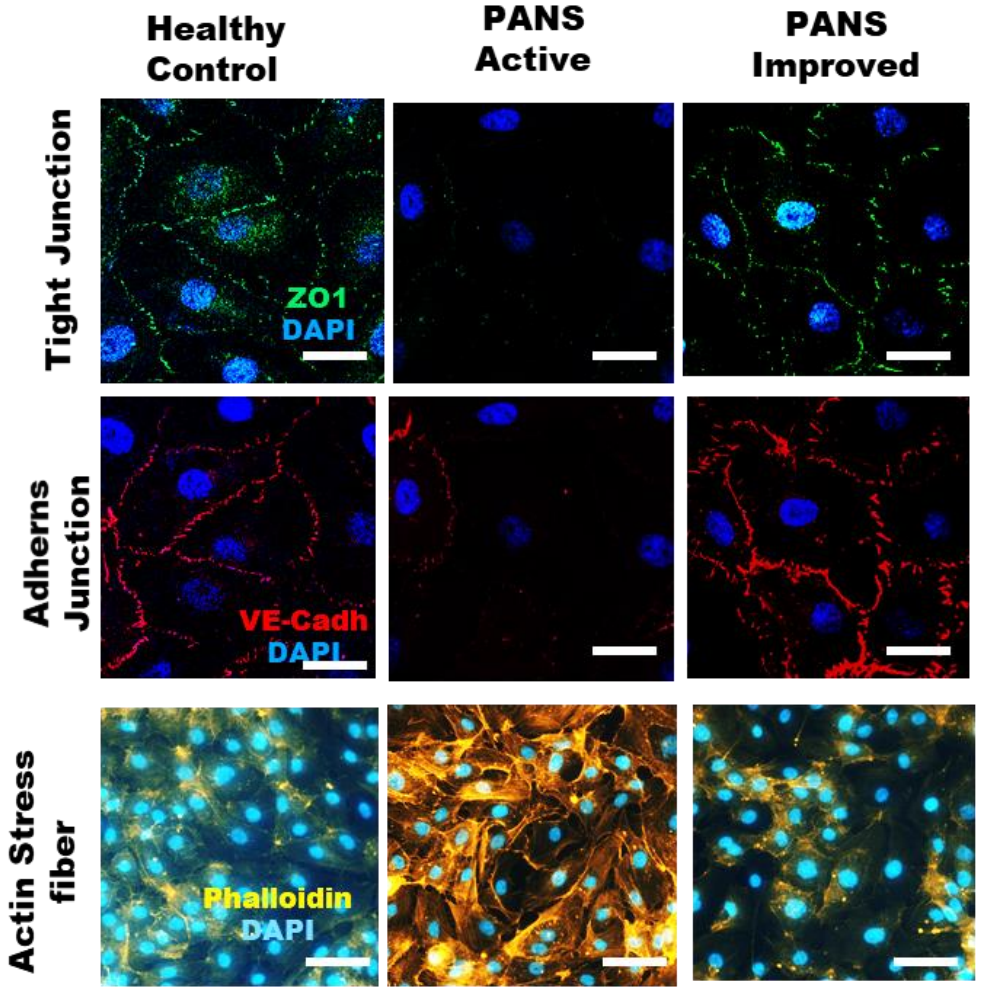


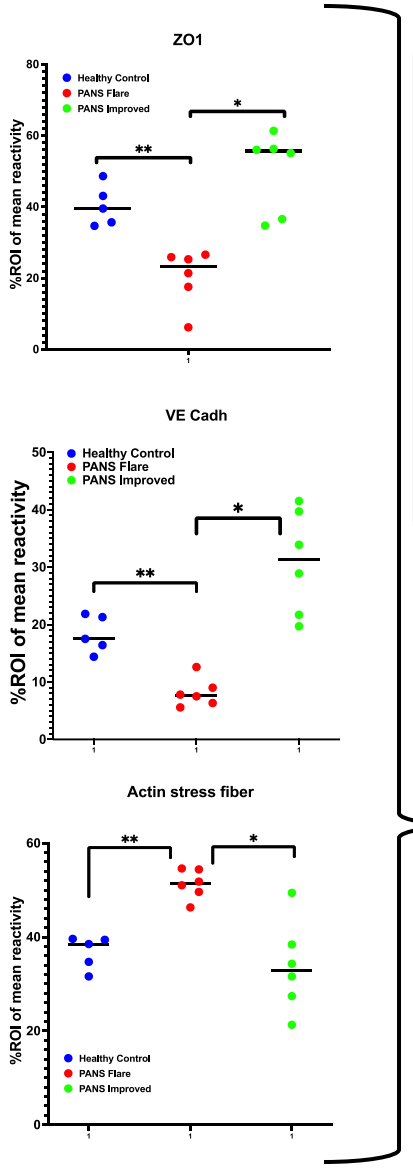
Christopher Pittenger, MD PhD
Director, Yale OCD Research Clinic
Yale University

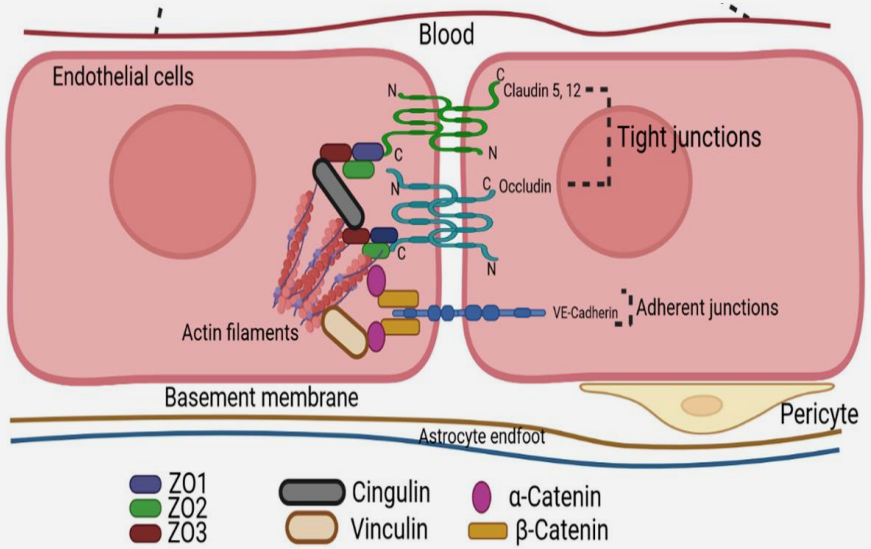


Xu , Frankovich ,et al. Elevated antibody binding to striatal cholinergic interneurons in patients with PANS. Brain Behav Immun. 2024 PMID: 39084540.

Brain Endothelial Cell structural changes in 12 hours with plasma







Unpaired t–test (HC vs PANS Flare)

Paired t-test (Flare vs Recovery)

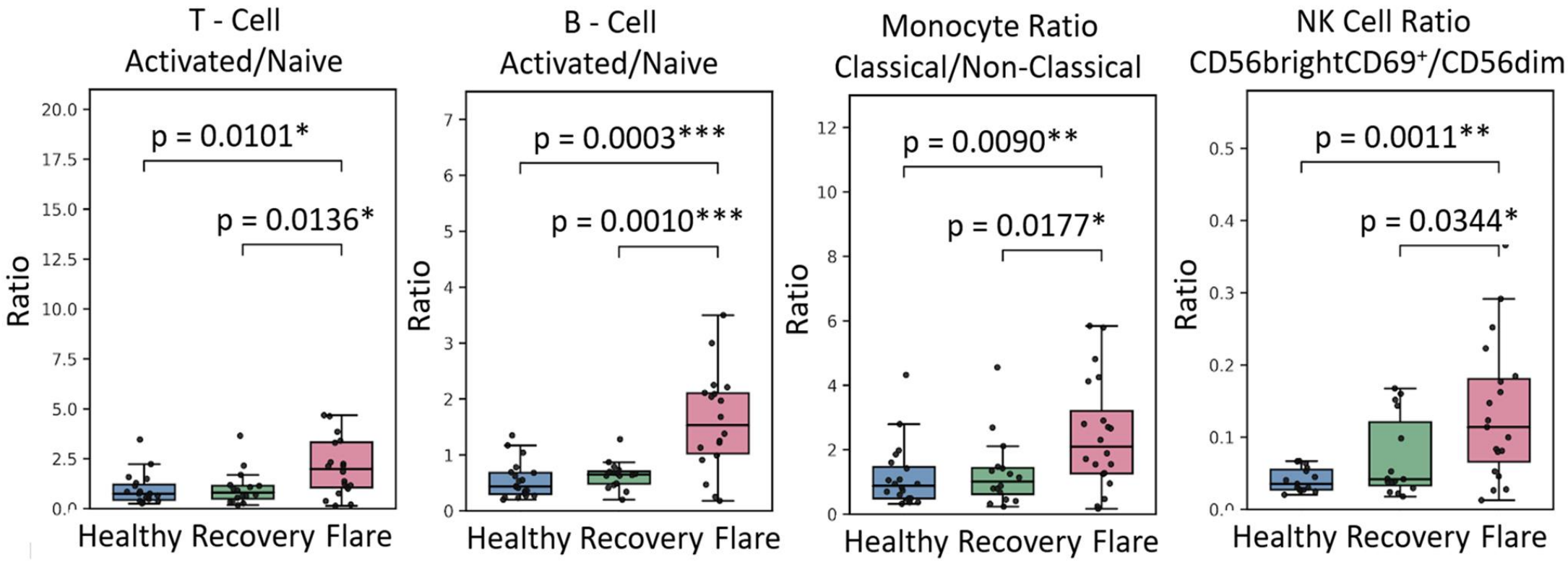


Betsy Mellins MD & Ayan Mandal, PhD
Stanford Rheumatology/ Human Gene Therapy

Bar- 10 um for ZO1 and VE Cadh
Bar-20um for Phalloidin (Actin stress fiber

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Immune Activation Ratios
PANS Flare vs Recovery vs Healthy





Holden Terry Maecker
Professor-Research
Microbiology and Immunology



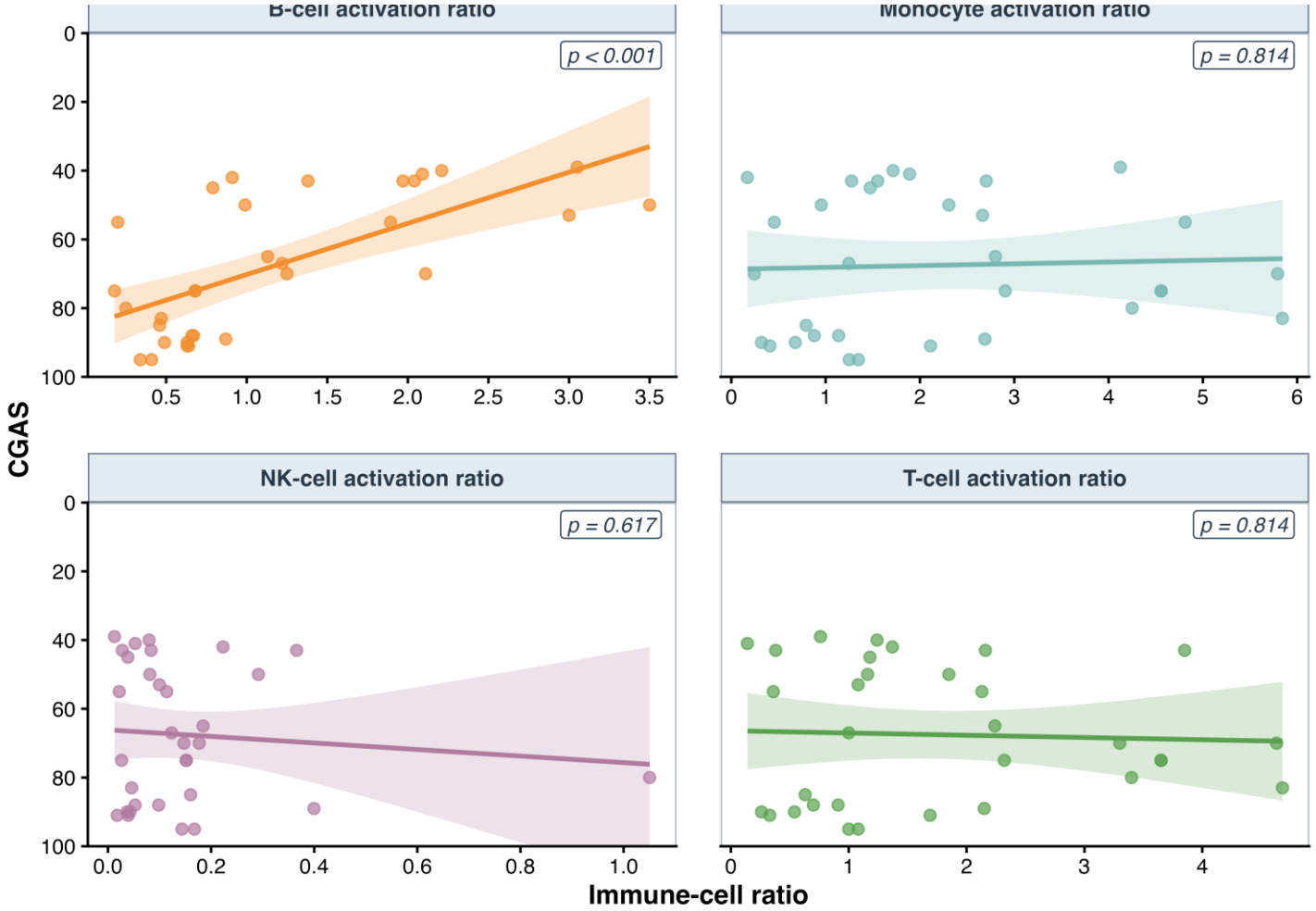
Imran Khan
Immunology Scientist
PANS Research Program

Associations between immune-cell ratios & CGAS (Children's Global Assessment Scale)

Linear mixed-effects models with a random intercept for participant

Immune-cell ratio	Effect estimate	95% CI	p value
B-cell ratio	-14.891	-20.772 to -9.010	<0.001
Monocyte ratio	-0.519	-4.807 to 3.768	0.814
NK-cell ratio	9.531	-27.469 to 46.530	0.617
T-cell ratio	0.651	-4.723 to 6.025	0.814

Effect estimates represent the expected change in CGAS associated with a one-unit increase in the corresponding immune-cell ratio.

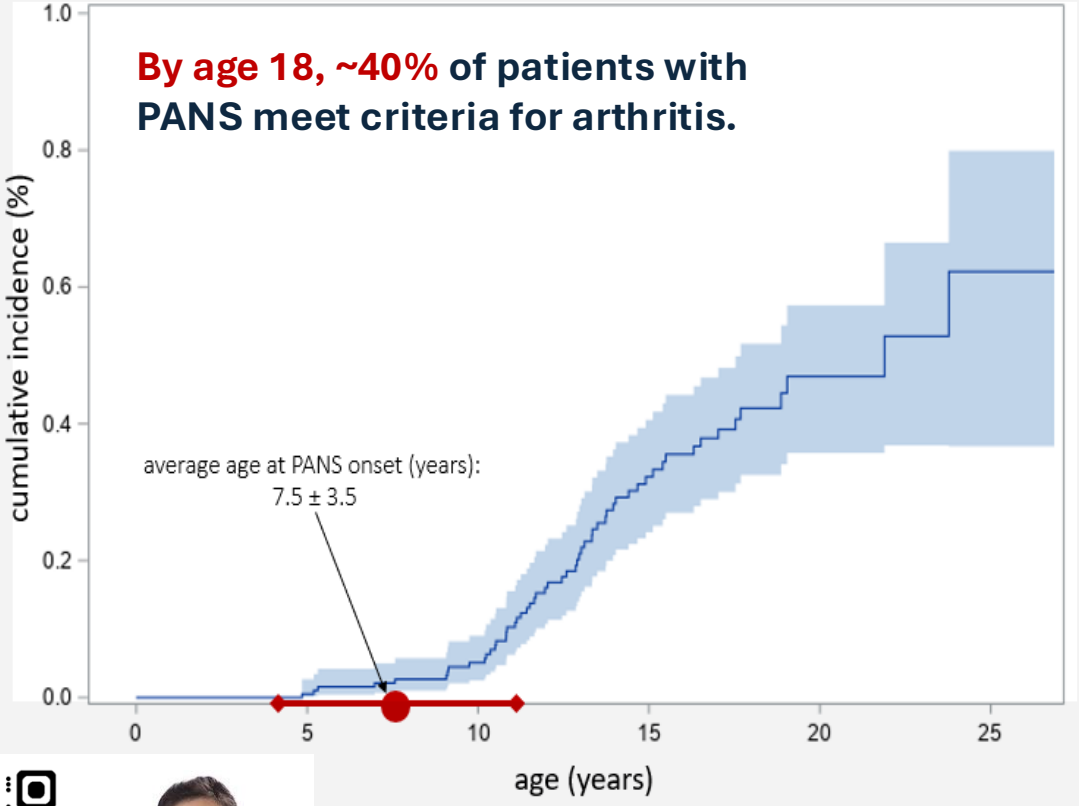


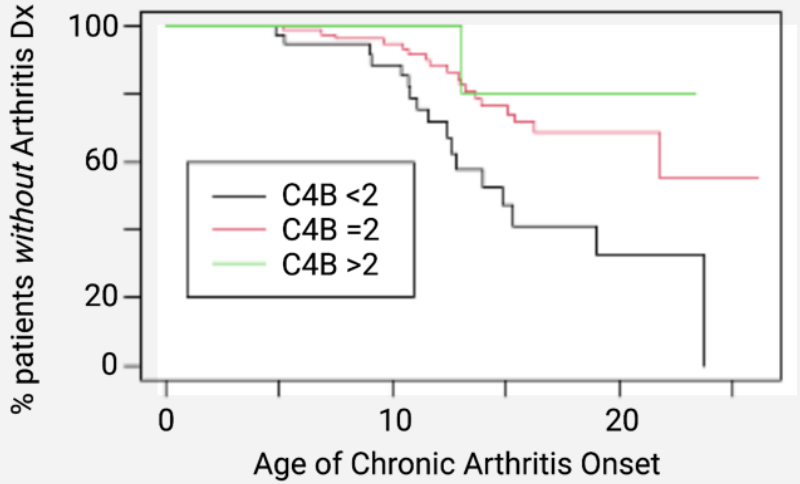


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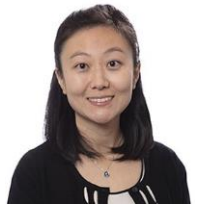
Samantha Leonard
Clinical Research Epidemiologist
PANS Research Program

Cumulative incidence (95% CI) of Arthritis (Joint inflammation)









Mei Ma et al., 2024
JAMA Netw



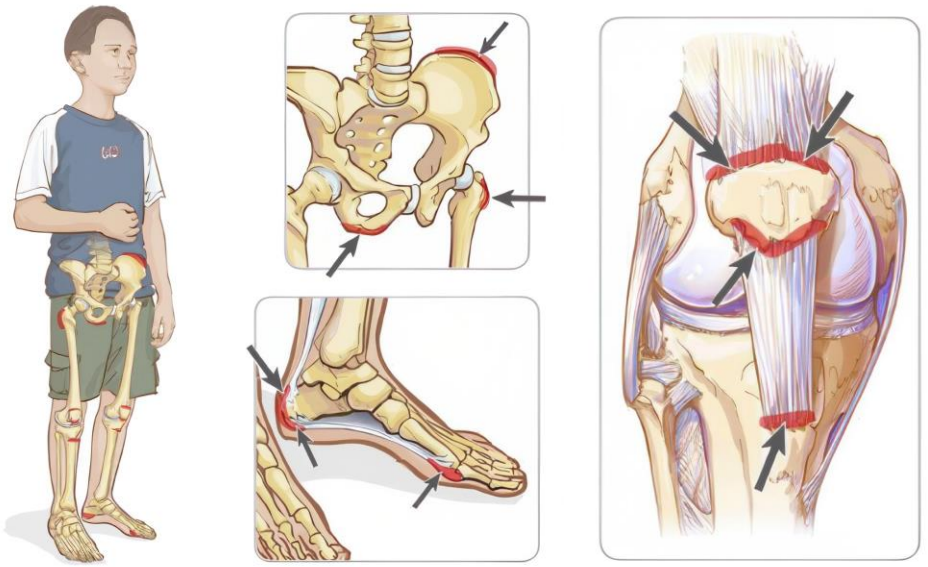


Evaluation of C4 Gene Copy Number in PANS *Dev Neurosci* 2023

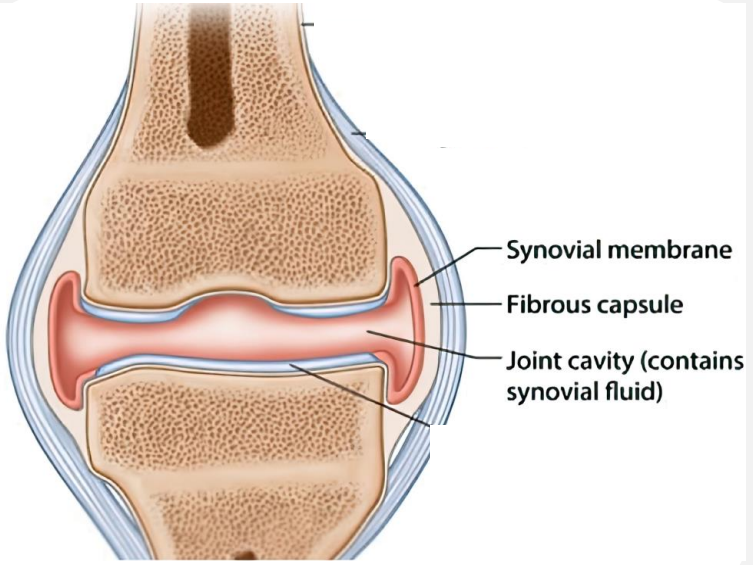
Agnieszka Kalinowski, MD PhD

Arthritis in PANS/PANDAS

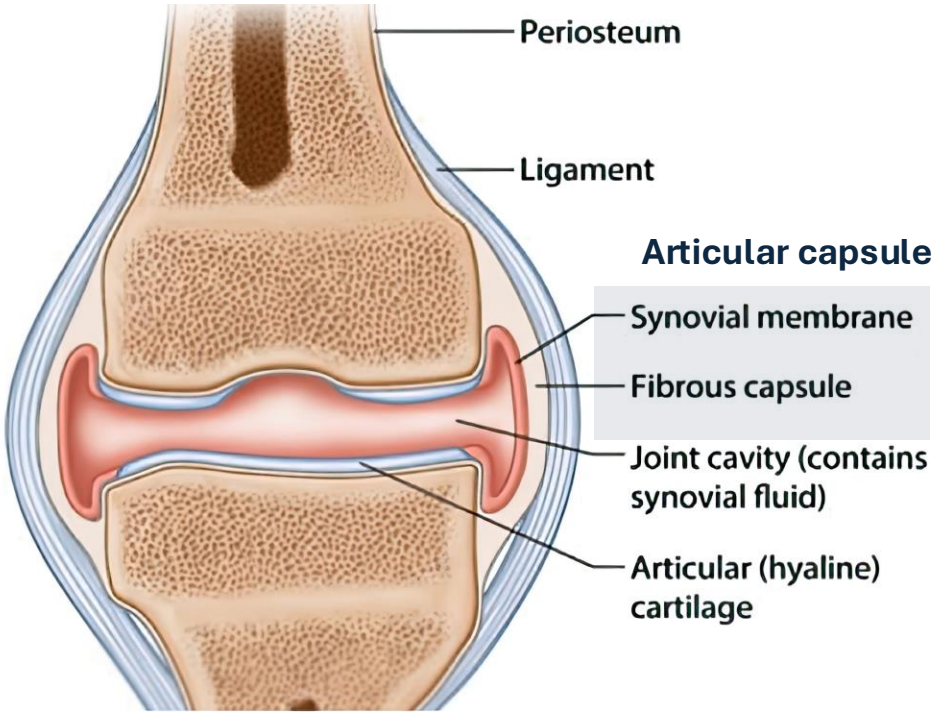
- **Enthesitis Related Arthritis**
  - ~50% inflammatory back pain
  - ~ 10 % psoriatic arthritis
- **Arthritis is “dry”**
- **Capsular thickening**
- **Enthesitis**
  - inflammation where tendons & ligaments insert on to bone
- Psych symptoms overshadow joint symptoms



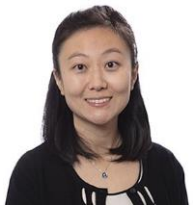
JAMA Netw Open. 2024



Consecutive Joint Ultrasounds in patients with PANS (N=67)



Joint Ultrasound Read by MSK Radiologist	Met arthritis criteria (n=40)	Did not meet arthritis criteria (n=27)
Abnormal	**37 (93%)**	11 (40%)
Joint effusion	**31 (78%)**	8 (30%)
Capsular thickening (capsulitis)	**22 (55%)**	0
Synovial thickening (synovitis)	**2 (5%)**	4 (15%)



Ma et al., 2024
JAMA Netw

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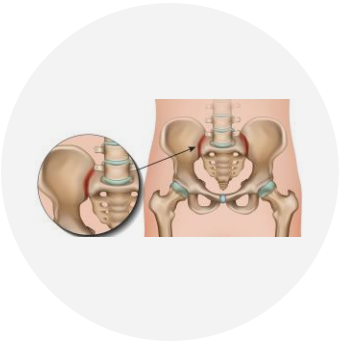
Common sites of tenderness in PANS

193 consecutive patients who met strict PANS criteria (meets JIA criteria in red)



Distal Interphalangeal Joints (DIP joint)

43% / 82%



Sacroiliac joint tenderness

35% / 69%



Spinous process tenderness (enthesitis)

40% / 80%



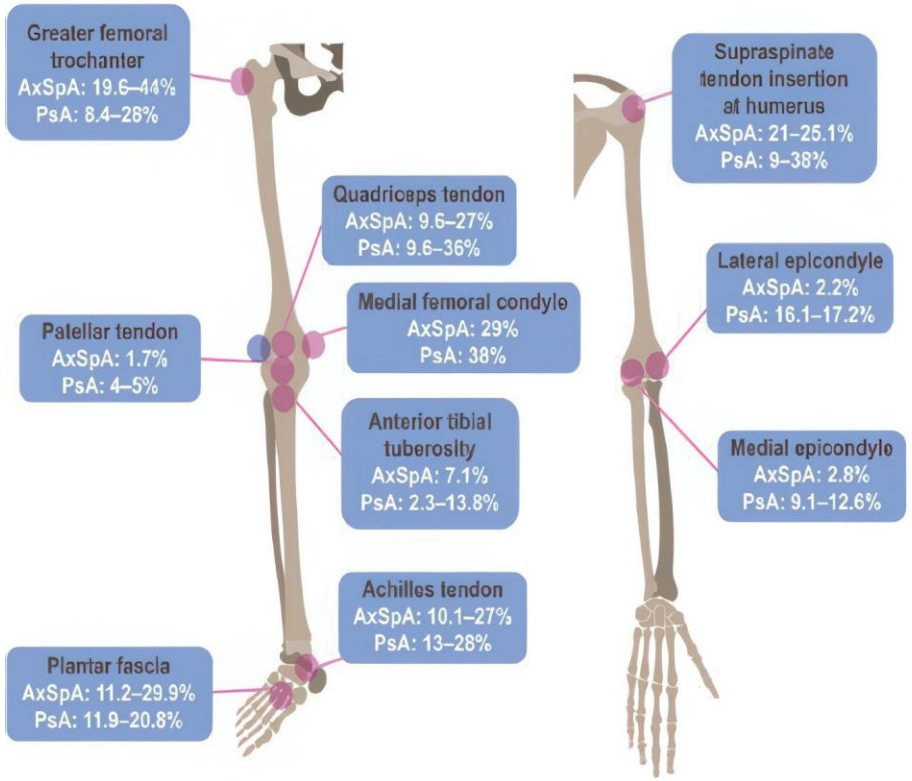
Achilles tendon insertion (enthesitis)

26% / 31%

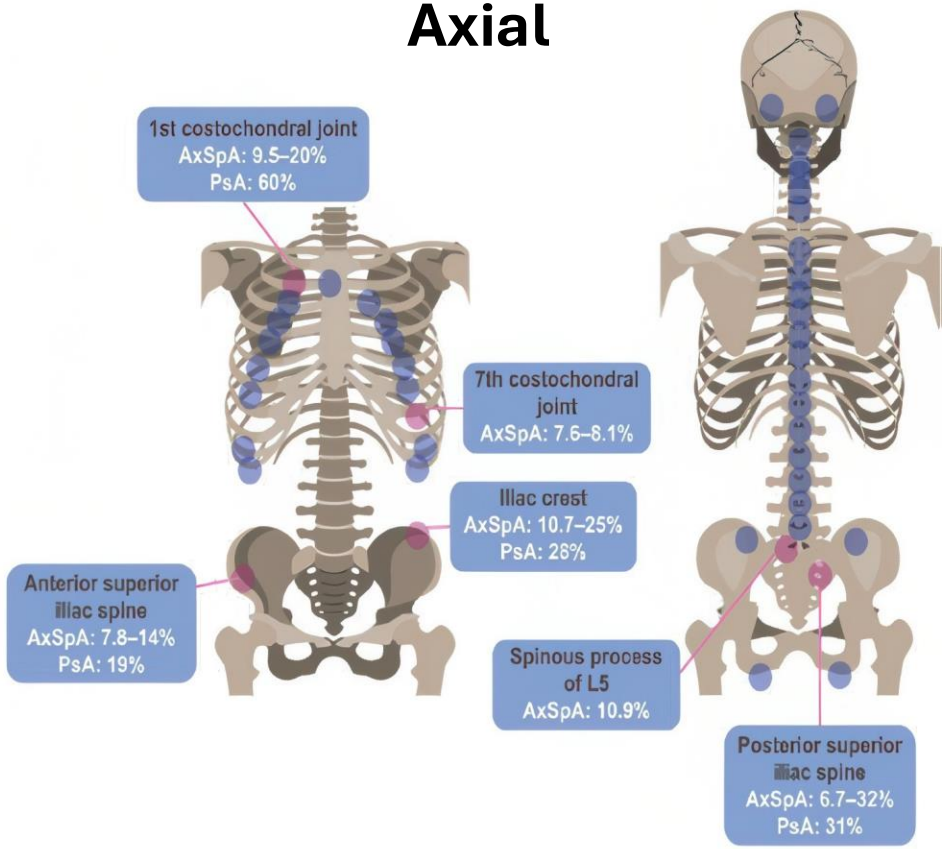
Ma et al., 2024 JAMA Netw

Enthesitis Evaluation

Peripheral



Axial

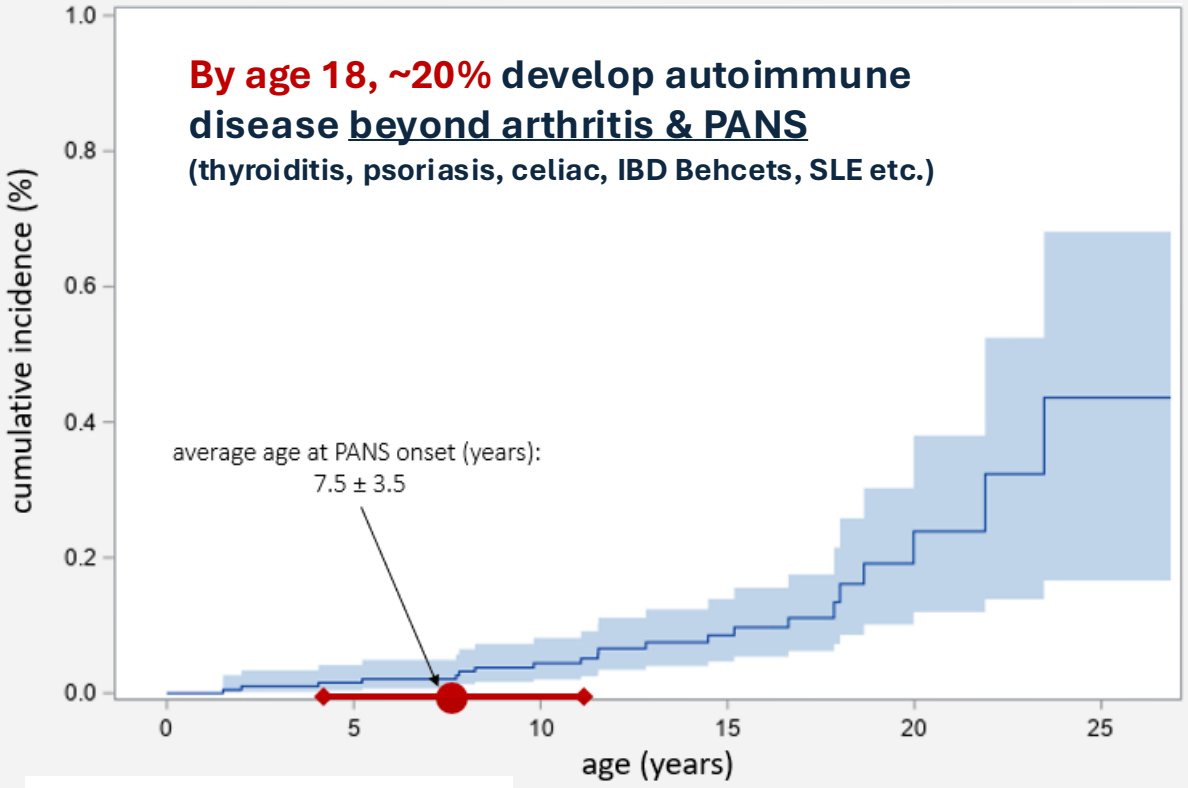


Hidden in plain sight: crucial role for enthesitis assessment in the treatment and monitoring.
McGonagle [et al] https://doi.org/10.1016/j.semarthrit.2021.07.011

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Cumulative incidence (95% CI) of *autoimmune*/inflammatory diseases (beyond arthritis and PANS)





Ma et al., 2024
JAMA Netw

EPIDEMIOLOGY studies show association between OCD & Eating Disorders with Autoimmunity

Link between autoimmune diseases and OCD & tic disorders.
Pérez-Vigil, *Neuroscience & Biobehavioral Reviews, 2016*

Family clustering- autoimmune diseases in OCD & tic disorders
Mataix-Cols, Molecular psychiatry, 2018

Eating disorders, autoimmune, and autoinflammatory disease.
Zerwas, Pediatrics, 2017

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Blood Vessel Inflammation in PANS

Palatal petechiae



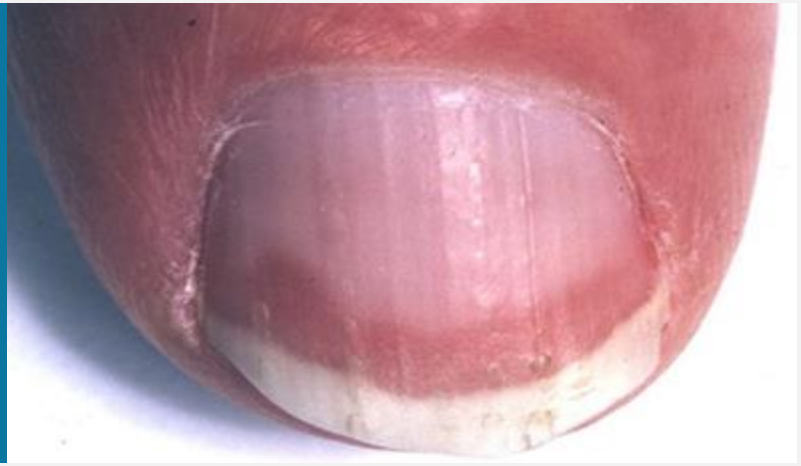
Periungual redness



Livedo reticularis



Prominent Onychodermal band





Ma et al., 2024
JAMA Netw

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Postural Orthostatic Tachycardia Syndrome (POTS)

- Autonomic nervous system disorder
- Racing heart and sometimes fall in blood pressure when patient laying/sitting → standing up
- Symptoms: lightheadedness, fainting, palpitations, brain fog, fatigue

Patient with PANS:
9% develop POTS*

General Population:
1% may develop POTS*

POTS Symptoms worsen with PANS flares

Fibromyalgia (FM)

- Widespread musculoskeletal pain > 3 months
- Pain processing problem
- Symptoms: pain, fatigue, sleep disturbance, brain fog, +/- mood issues, +/- abdominal pain, +/- headaches

Myalgic Encephalomyelitis / Chronic Fatigue Syndrome (ME/CFS)

- Profound, persistent fatigue
- Key: **post-exertional malaise (PEM)**
- Symptoms: fatigue, unrefreshing sleep, brain fog, pain, autonomic issues

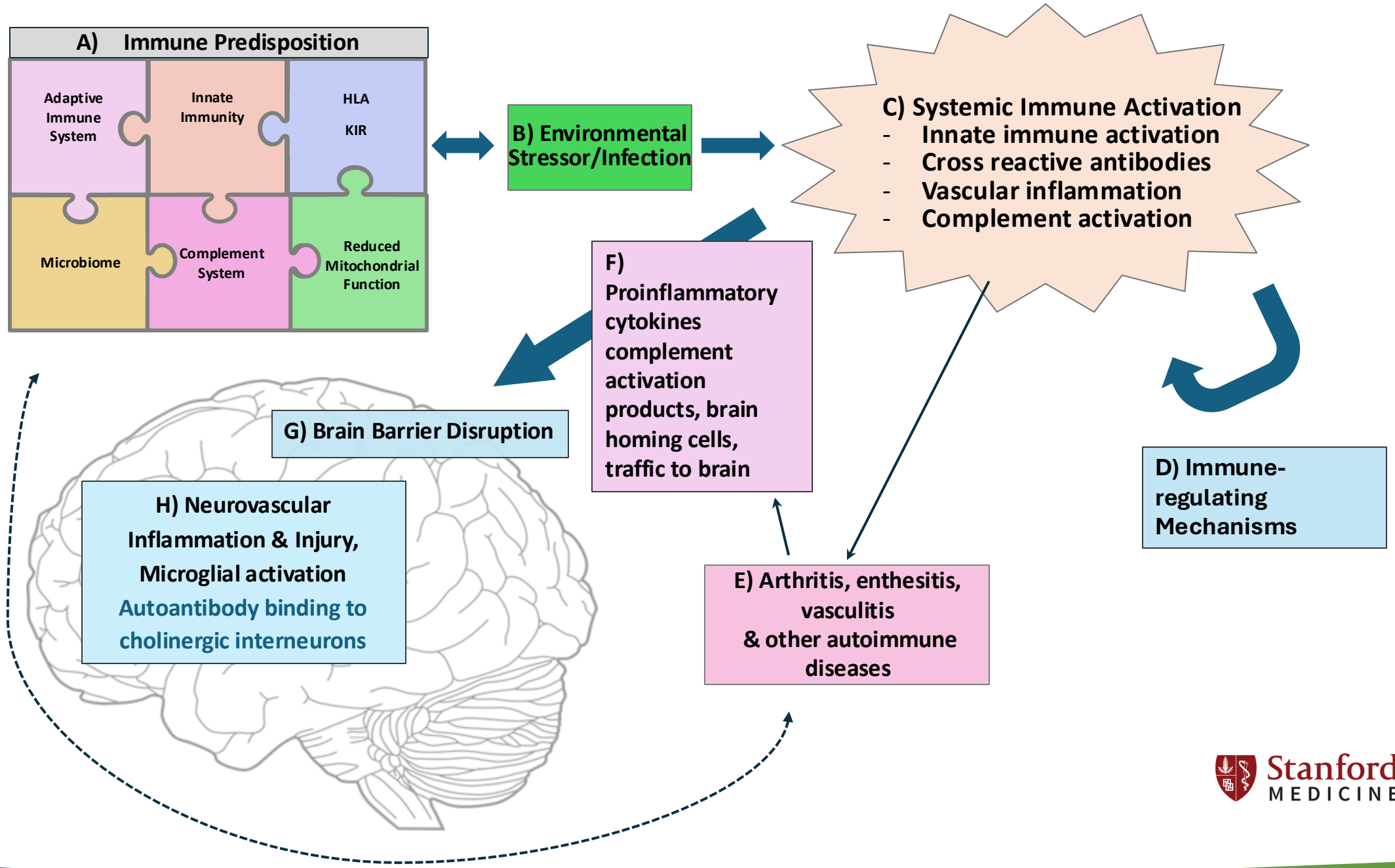
Patients with PANS:
40% fibromyalgia thresh scores
13% full criteria fibromyalgia

If meet full fibromyalgia criteria→
~70% also meet ME/CFS criteria

General Population:
2-4% develop FM

<1% develop ME /CFS

* Chan et al. (2022)



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Acknowledgements and Recognition

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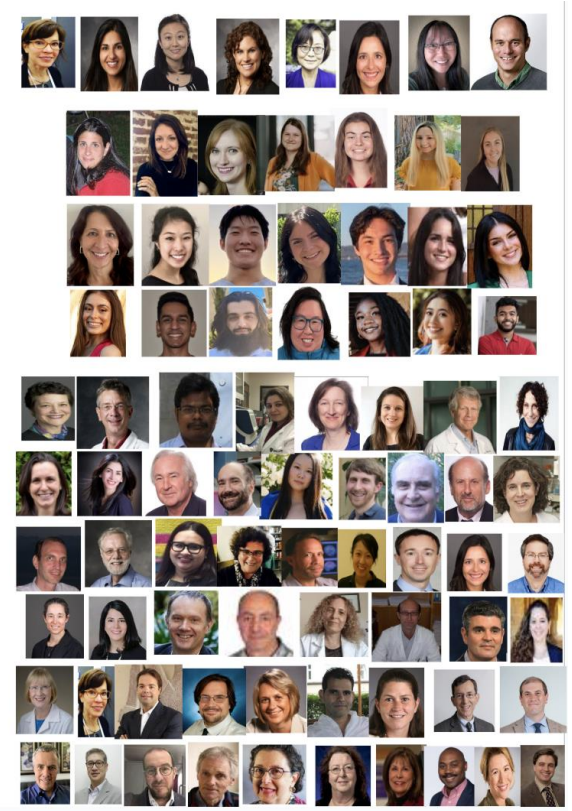
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