History, challenges and what we know now

Dr Sue Swedo, Dr Tim Ubhi,
Professor Jennifer Frankovich
and Professor Ming Lim.

A Brief History of PANS & PANDAS

Susan E. Swedo, M.D.
Scientist Emerita
U.S. National Institute of Health

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 “just missed 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!

Historical Links Between Sydenham chorea & OCD

- **1894 -** Sir William Osler described "perseverativeness" of behavior in choreic children; parents reported "changed child"
- **1950's & 60's -** Increased "obsessional neurosis" among children with SC and adults with hx of SC during childhood
- **1989 -** SC pts, (but not carditis pts) have OC symptoms (12/23 vs 0/14) with three SC pts meeting criteria for OCD
- **1994 & 2002 -** Two prospective NIMH studies revealed OC symptoms in 75% of acutely ill pts with SC
- **1998 & 2005 -** Brazil – 25-65% of SC pts had OC symptoms at initial episode (none in RF carditis). Follow-up revealed that **100% of children with multiple episodes had OCD.**

IN ALL SC CASES: Obsessions & compulsions started 2-4 weeks BEFORE chorea began.

OCD in Sydenham chorea = OCD+

cated retroversion. Although some disagree with us in regard to uncomplicated retroversions, really in point of fact I do not think that there is any wide difference. Only 4 per cent. of my cases are classified as uncomplicated. It is possible that as only two of these women were operated on—and I promise never to do it again—possibly some of the eighteen patients had some pathologic condition in the pelvis that I did not recognize. I thought I was reasonably sure that they

PSYCHOSES ASSOCIATED WITH SYDENHAM'S CHOREA *

E. M. HAMMES, M.D.
Associate Professor of Neurology and Psychiatry, University of Minnesota Medical School
ST. PAUL

Mental symptoms may occur at any stage in the course of Sydenham's chorea. In patients with marked muscular twitchings, the psychosis often runs a course parallel with the severity of the choreiform movements. Case 2 is illustrative of this

have periods of depression, crying spells and fear of death. June 1, she developed a Sydenham's chorea which continued for one month. With the onset of the chorea, she became acutely disturbed and excited; she would tear her clothes and threaten suicide. She refused to eat because the food was doped, saying the potatoes were filled with fecal material,

onset of the chorea, she had periods when she became terrified, was afraid to be alone, especially in the dark, had hallucinations of sight, saw mice and moving objects in her room, saw a man climbing through the window, and she would scream with fear. For ten days she had to be tube-fed because she thought the food was poisoned; she became very resistive

Is PANDAS Just Misdiagnosed Sydenham Chorea?

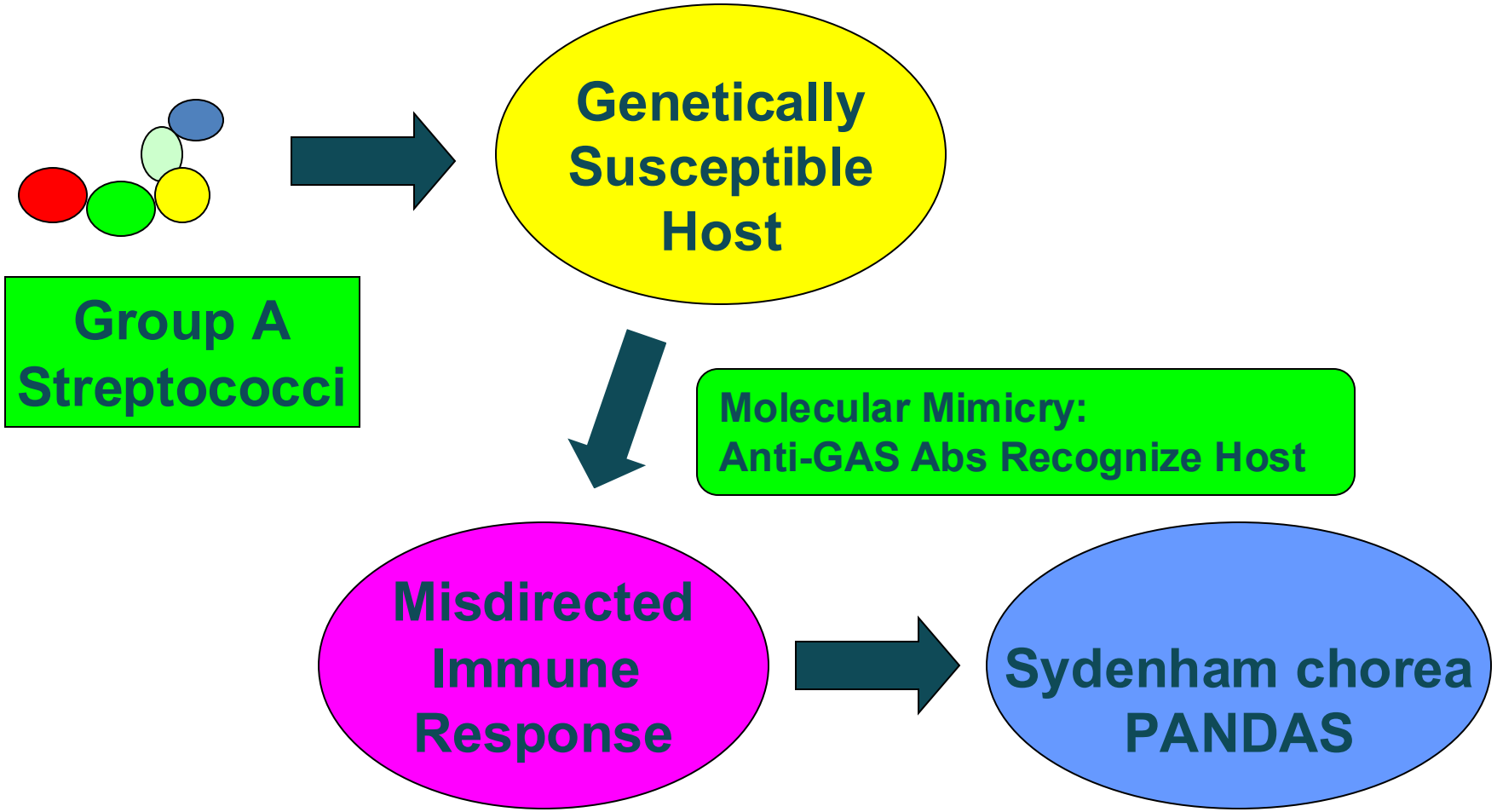
SYDENHAM CHOREA (SC)	PANDAS
Primary symptom: Chorea/adventitious movements (including tics)	Primary symptom: OCD, emotional lability, separation anxiety, personality change, etc
Also see: OCD, emotional lability, separation anxiety, hallucinations.	Also see: Choreiform movements, motor hyperactivity, urinary urgency/frequency, sensory sensitivities
Associated with: Other signs of acute rheumatic fever (ARF): Carditis, arthritis, erythema nodosum	NOT associated with ARF carditis or arthritis. (Have to diagnose SC instead) Do see arthralgias, back pain, sleep disruptions
Onset: Semi-acute onset and 3 – 12 months offset	Onset: Extremely acute onset. Offset depends on symptom severity.
Course: Usually single episode but relapses do occur.	Course: Usually relapsing-remitting but may be single episode

Evidence Supporting PANDAS as a Distinct Entity

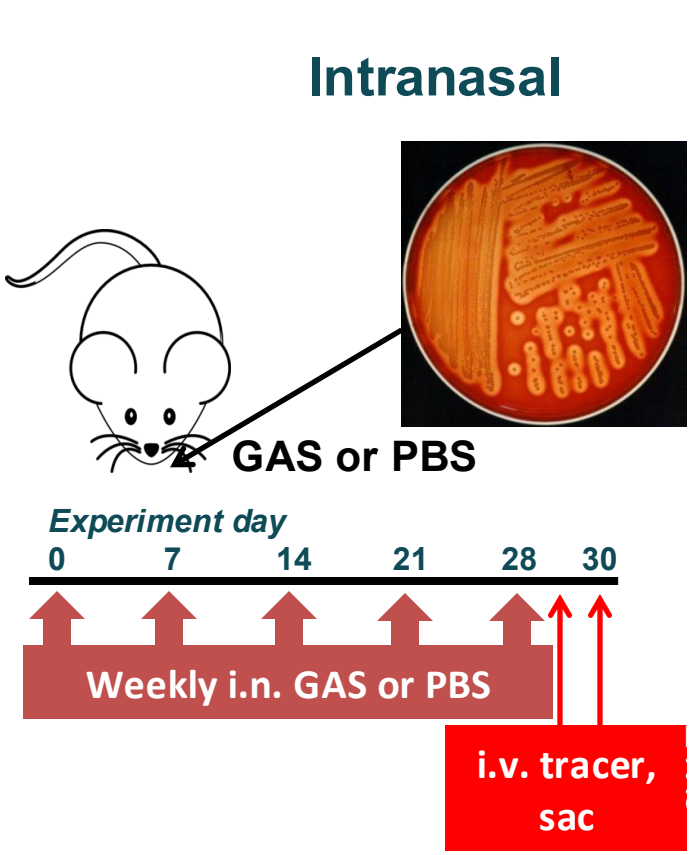
Parallel investigations of Sydenham chorea (SC) and pediatric obsessive compulsive disorder (OCD)

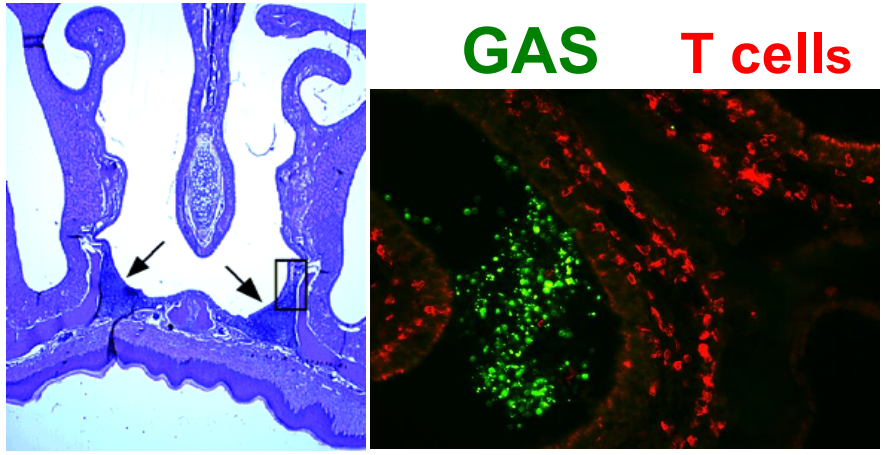
- 1988 – 2/3's of children with SC have OCD which precedes onset of SC by 2 – 4 weeks
- 1992 – ¼ of pediatric OCD patients have Acute onset and Episodic course (accompanied by choreiform movements)
- 1995 – PITANDS – published 5 cases triggered by Group A streptococcal (GAS) infections, varicella and influenza
- 1998 – PANDAS – published first 50 cases of Strep-triggered OCD & tic disorders; clinical characteristics described and research criteria proposed

Model of Etiopathogenesis for Sydenham's chorea and PANDAS

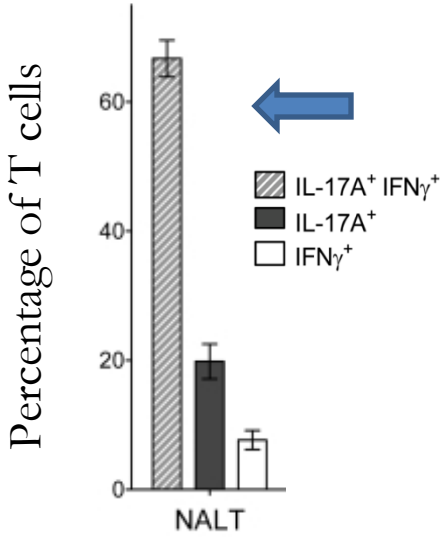


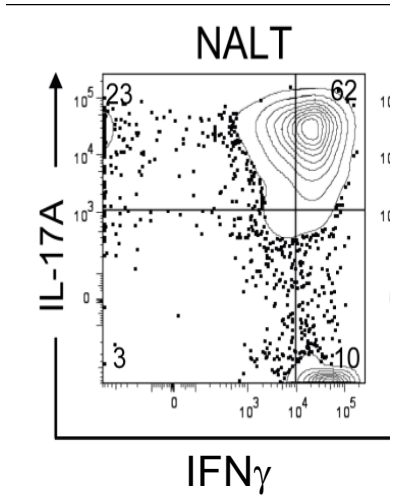
LABORATORY EVIDENCE THAT GROUP A STREPTOCOCCAL INFECTIONS PLAY A CAUSATIVE ROLE IN PANDAS





T cell phenotype after **multiple** intranasal infections

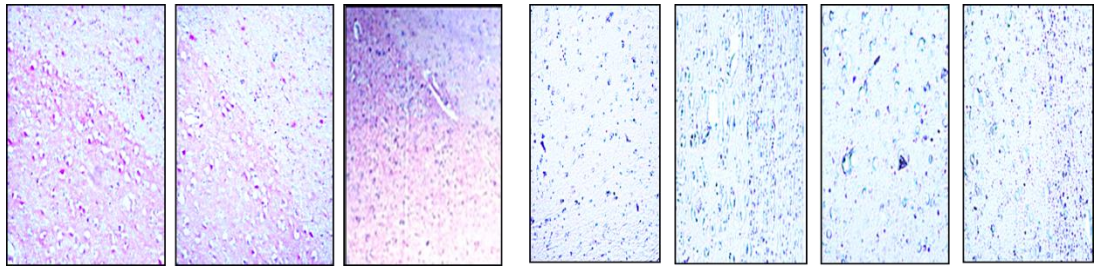


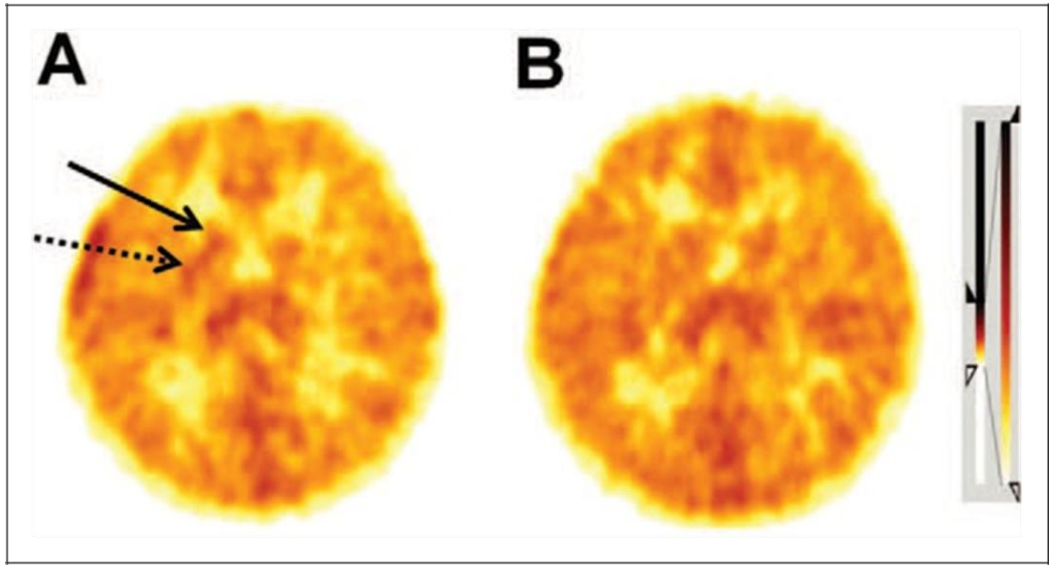


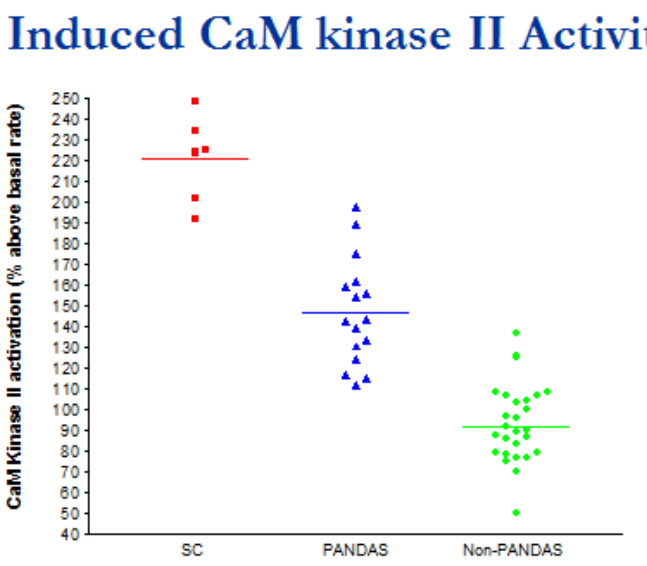
Dileepan T *et al.*, (2011) *PLoS Pathogens*

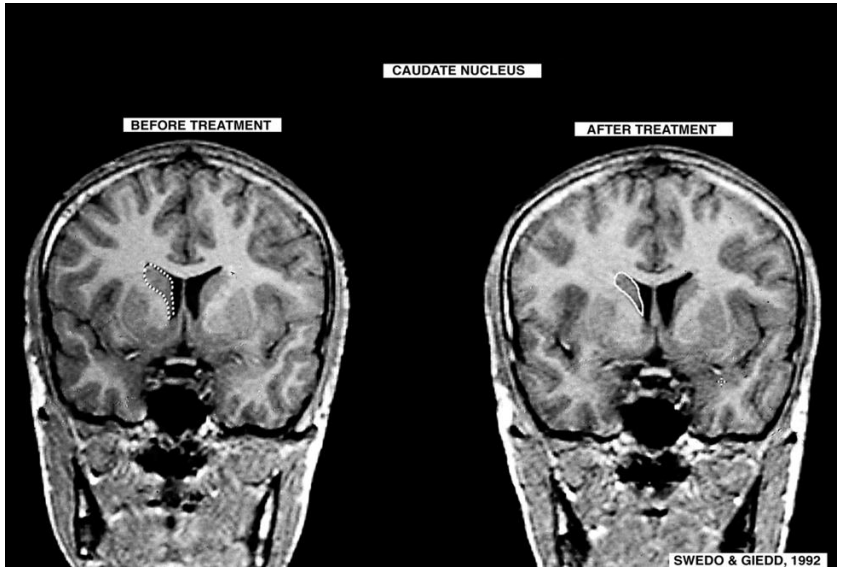
Evidence of Neuroinflammation in PANDAS

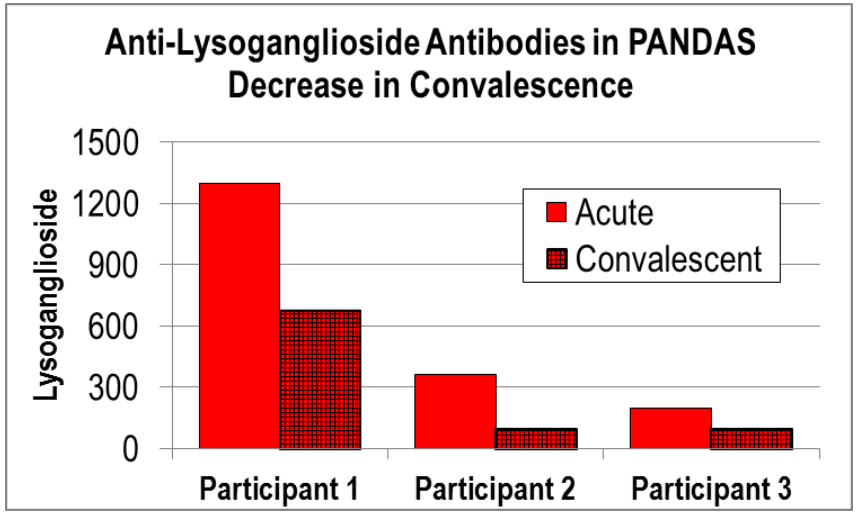
Cross-reactive antibodies correlate with SC & PANDAS severity











Clinical Evidence Supporting PANDAS as a Distinct Entity

- 1998 & 2002 – ANTIBIOTIC PROPHYLAXIS EFFECTIVE IN PANDAS

  Failure to prevent Group A streptococcal (GAS) infections led to neuropsychiatric exacerbations, while Adequate prophylaxis produced sustained remissions

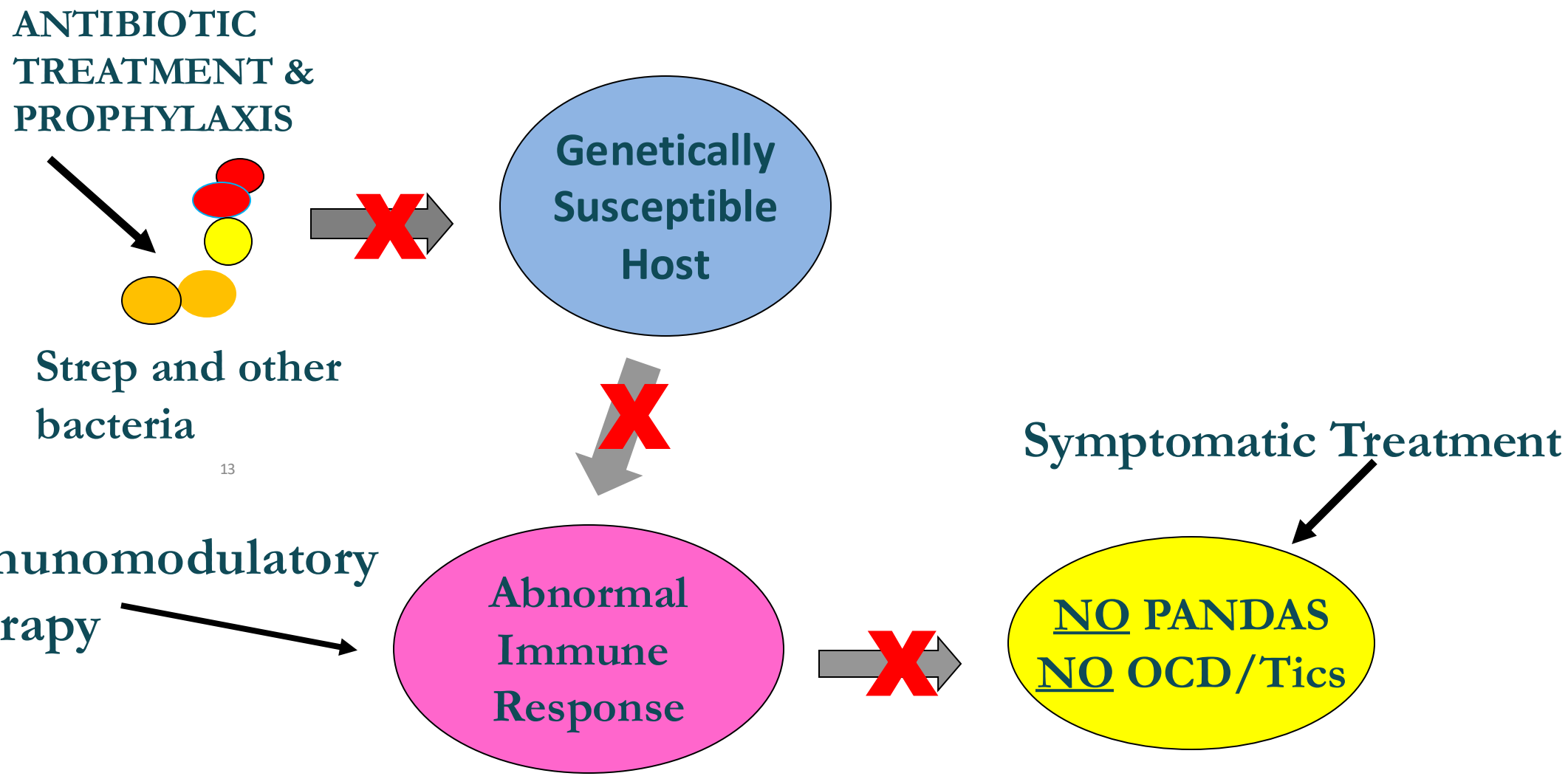
- 1999 – IMMUNOMODULATORY TRIALS

  IVIG and plasmapheresis were superior to placebo for PANDAS

  NOTE: Plasmapheresis failed to help non-PANDAS OCD and tics in a controlled trial. Providing evidence both for an immunologic abnormality in PANDAS,

  AND the importance of making the correct diagnosis.

PANDAS – A Treatable and Preventable Illness



And yet, the Controversy Continued…

PEDIATRICS
OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

Children's Memorial Hospital

"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

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

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

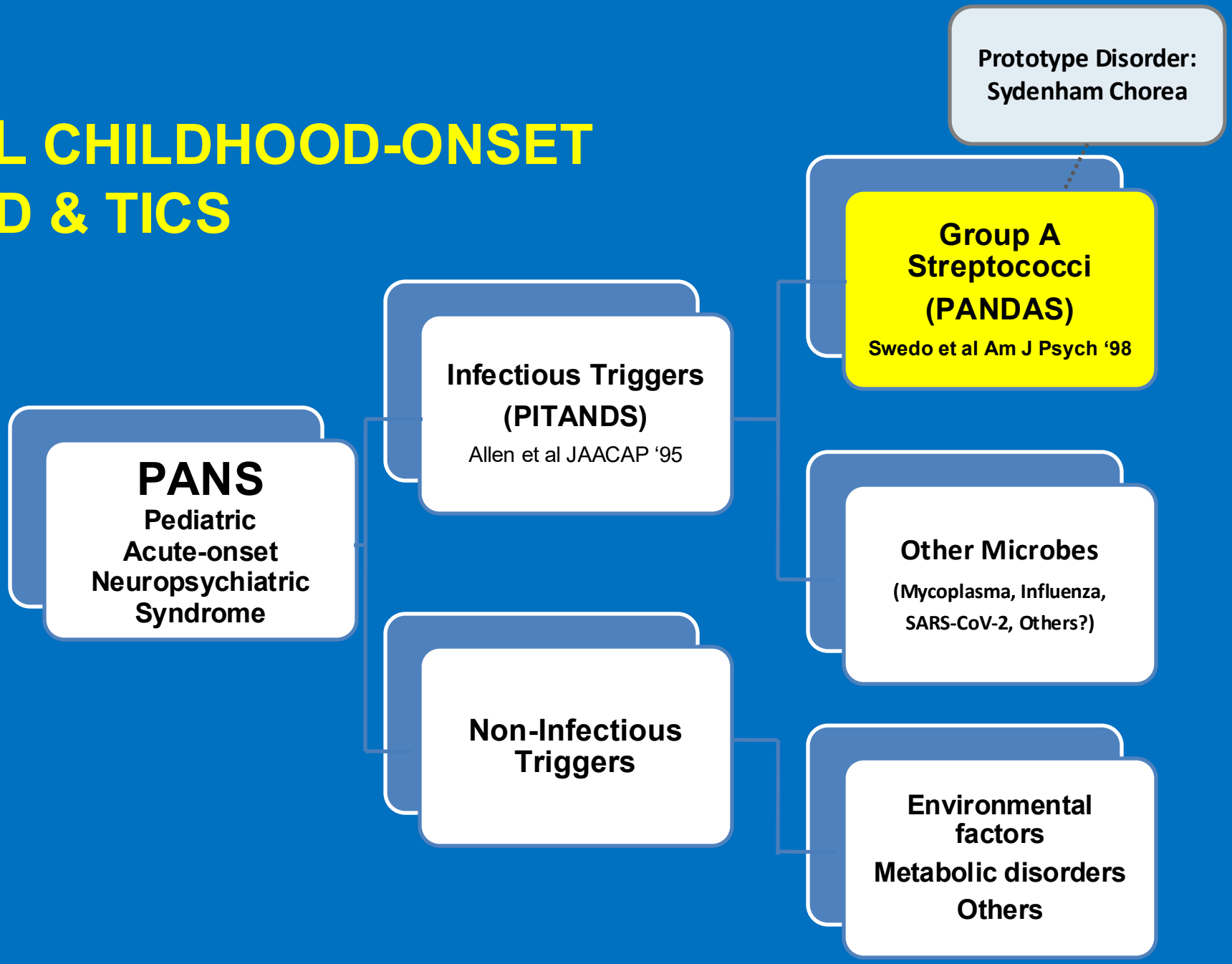
The Need to Move beyond PANDAS

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



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 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.

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%

PANDAS & PANS
Guidelines for a Diagnostic Evaluation

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*

Areas of agreement and disagreement

Dr Tim Ubhi
Paediatrician & PANS PANDAS Specialist
The London PANS Clinic

Relevant Groups & Disclosures

- The London PANS Clinic & Children's e-Hospital
- UK PANS PANDAS Guideline Development Group
- European Research Consortium - PANS PANDAS BGE
- PANS PANDAS UK Steering Group
- Guideline Development Group
- Open University
- Anglia Ruskin University – PANS PANDAS Joint PhD

Areas of Professional Agreement & Disagreement

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“We only know what we know”

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Areas of Professional Agreement

- We want to make sick children better
- We need more research data and evidence to help us treat these children
- A UK guideline would be helpful
- Research funding is needed

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Areas of Professional Disagreement

- *“PANS PANDAS doesn’t exist”* v *“PANS PANDAS does exist”*
- BPNA “Consensus” Statement
- “Reductive inflammation”
- The role of Group A Strep
- Autism
- Functional Neurological Disorder
- Disorder of the mind v the molecule
- Functional Medicine
- We need to put our professional bodies first

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Evidence base

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No conflict of interests.

No disclosures to report.

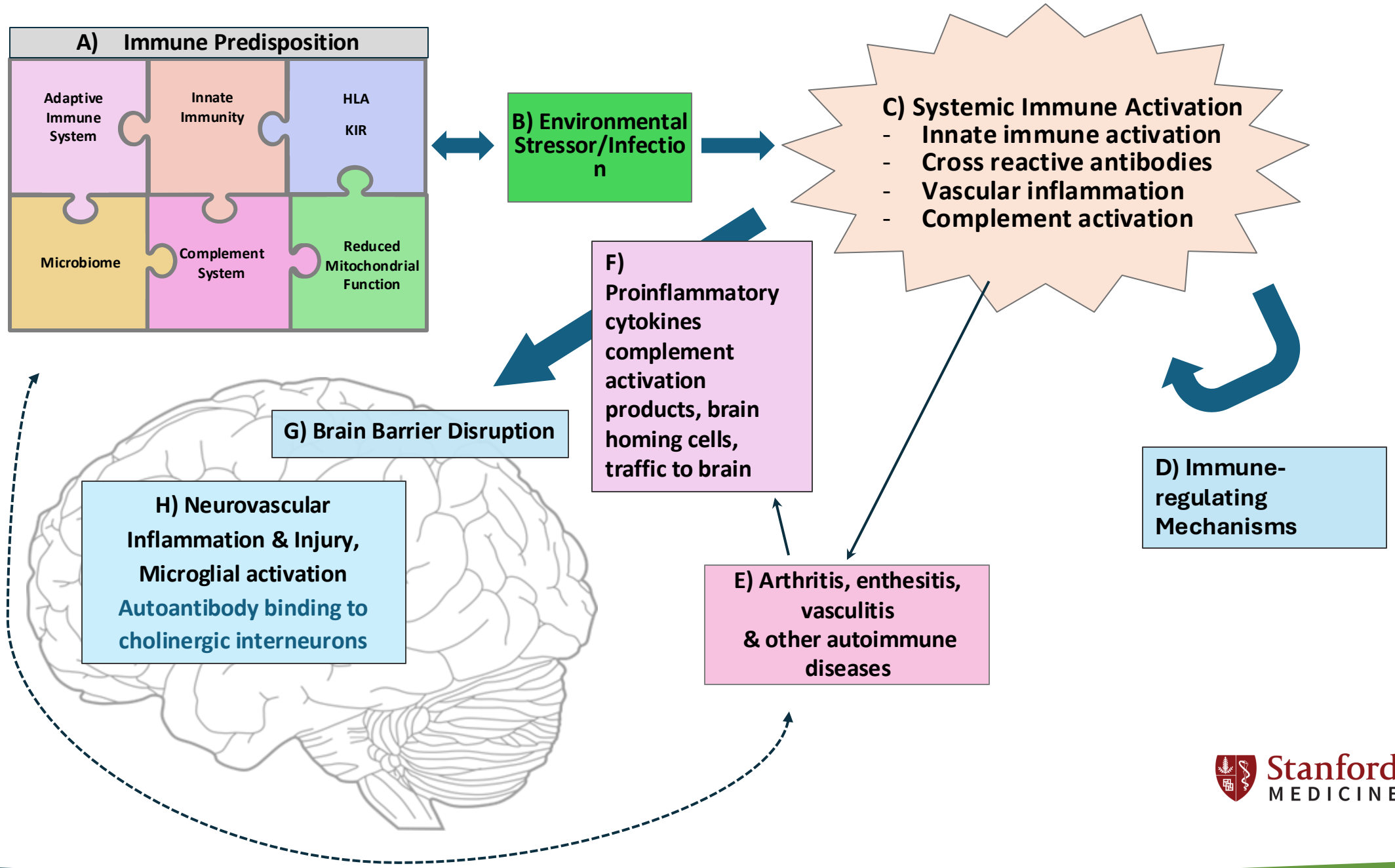
No financial relationship(s) with ineligible companies whose primary business is producing, marketing, selling, re-selling, or distributing healthcare products used by or on patients to disclose.

History, Challenges, & What We Know Now

Current evidence base:

- Brain imaging studies
- REM sleep abnormalities
- Cholinergic Interneuron Antibodies
- Brain Endothelial Disruption
- Immunophenotyping

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

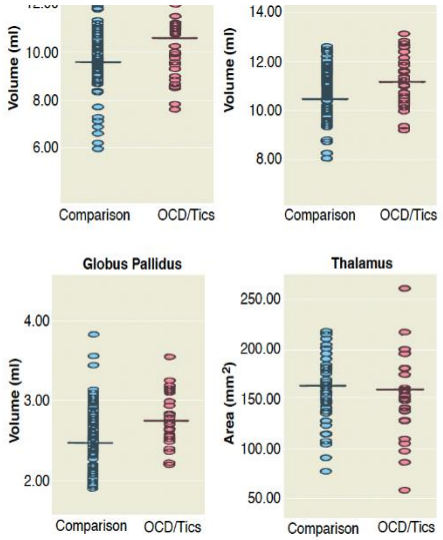


FIGURE 1. Scatterplots of Basal Ganglia Volume and Thalamus Area of 34 Children With Poststreptococcal OCD or Tics and 82 Healthy Comparison Children Matched for Age and Sex

⬆ BG Volume
in the acute stage

Giedd, et al. *AJP* 2000

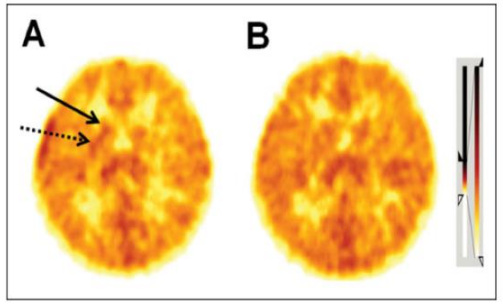
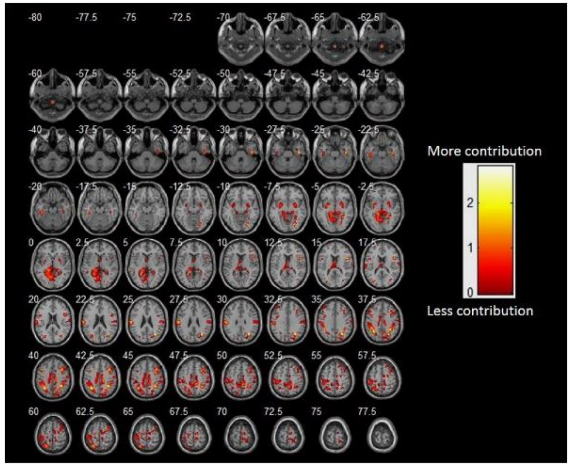


Figure 3. (A) Pre and (B) post (6 months after) immunoglobulin treatment ^{11}C-[R]-PK11195 PET scan, in an 8-year-old male child with pediatric autoimmune neuropsychiatric disorders associated with streptococcal infection (PANDAS), showing reduced tracer binding, suggesting reduced neuroinflammation,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

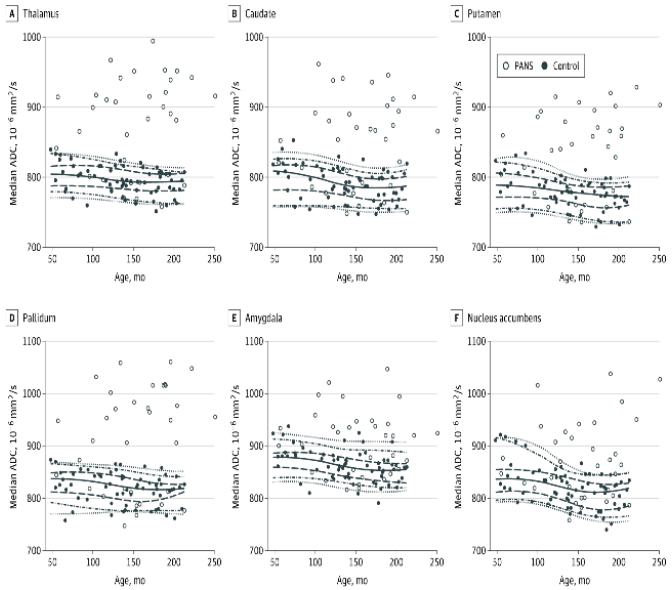
⬆ Microglia activation in BG

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



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

Cabrera et al. *CNS Spectrums*, 2019

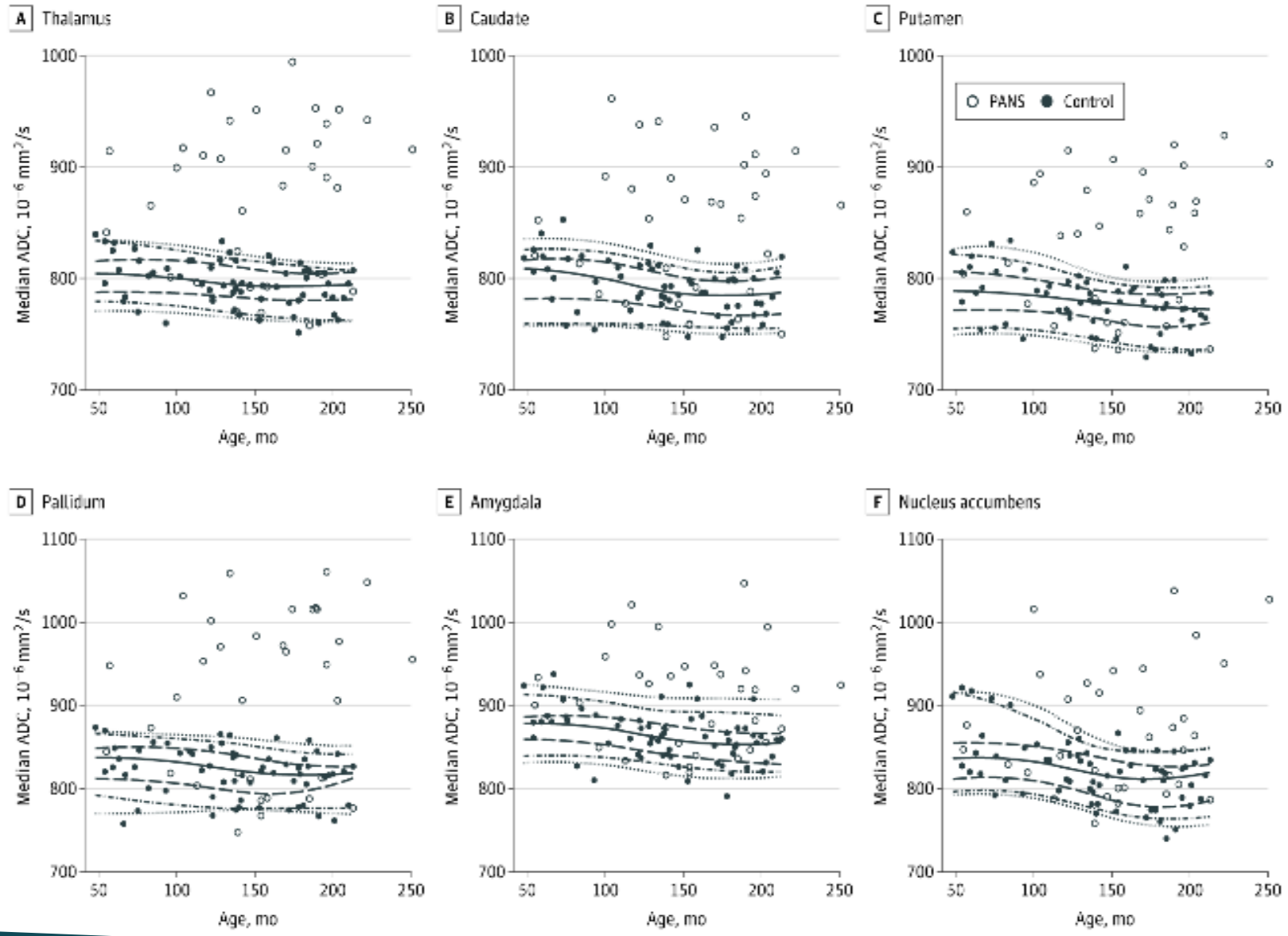


⬆ Medium diffusivity all assessed brain regions—most prominent in BG

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

JAMA Network | Open

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.

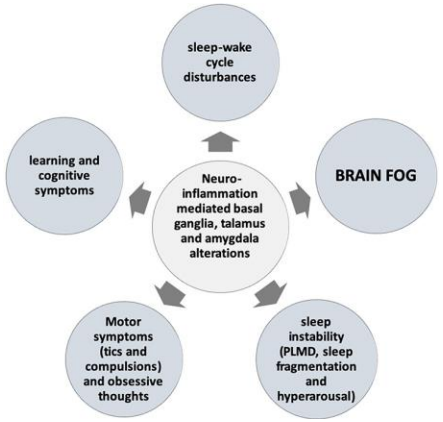
Gaughan, Swedo, et al.
J of Sleep Med. 2016

Stanford PANS Cohort

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

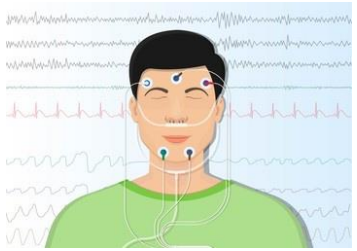
7/9 (78%) movements +/- loss of atonia during REM sleep

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

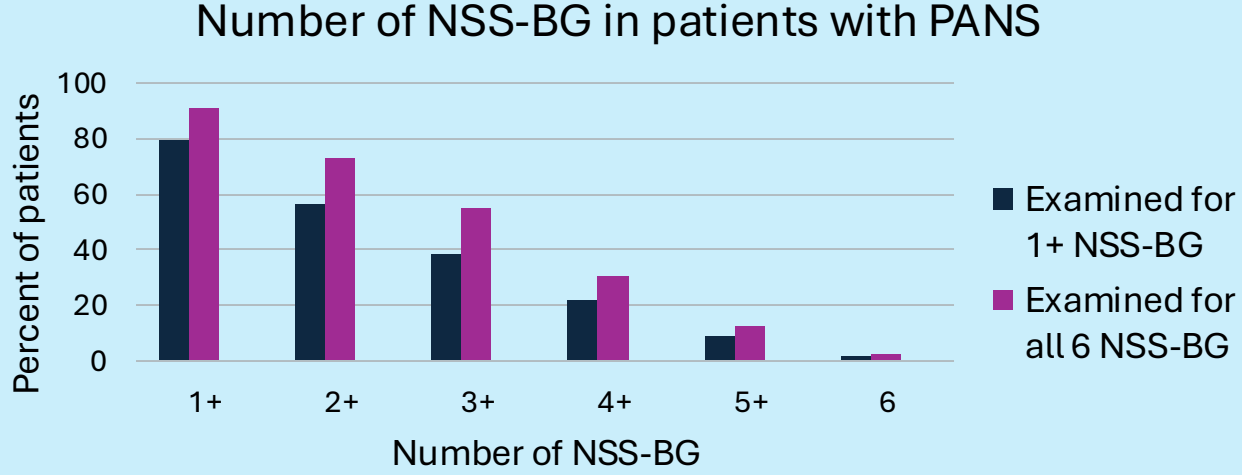
Movements during REM sleep → common in PANS/PANDAS
Movements during REM sleep → are a predictor of Parkinson's & multiple systems atrophy disease in adults.

Neurological signs in PANS/PANDAS

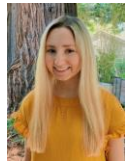
Abnormal finding (NSS-BG) on Exam N=119	Abnormal/ present (%)
Glabellar tap reflex	**22**
Abnormal tongue movements	**31**
Darting tongue	6
Wormian tongue	24
Deviation	8
Milkmaid's grip	**30**
Choreiform movements	**52**
Choreiform leg movements	5
Choreiform arm movements	32
Choreiform finger movements ("piano-playing" finger movements)	40
Spooning	**18**
Overflow movements	**60**
In touchdown position	33
In stressed gait	50

All patients (N=119):
- 80% had ≥1 sign
- Mean=2.1 signs

Patients examined for all 6 signs (N=71):
- 92% had ≥1 NSS-BG
- Mean=2.6 NSS-BG



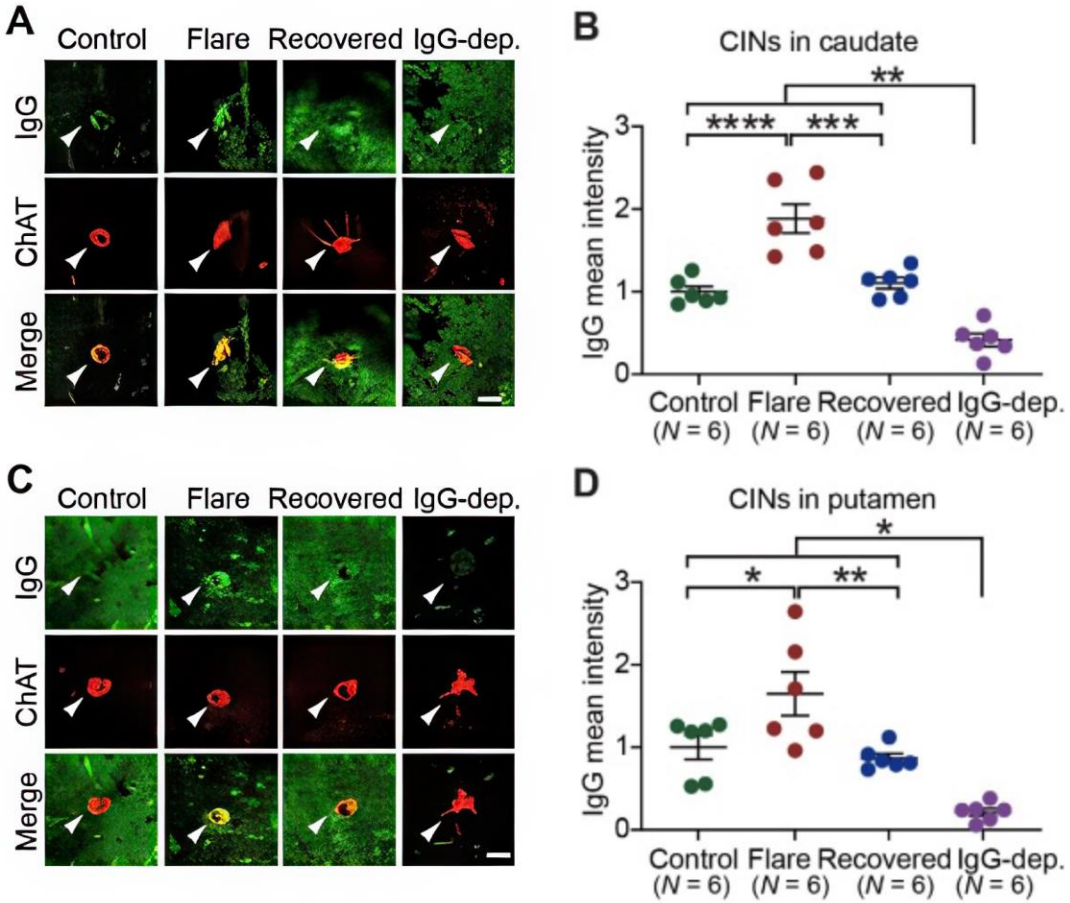
Number of signs was significantly associated with
- Number of PANS symptoms (p=0.002)
- Global Impairment Score (p=0.045) at clinical presentation

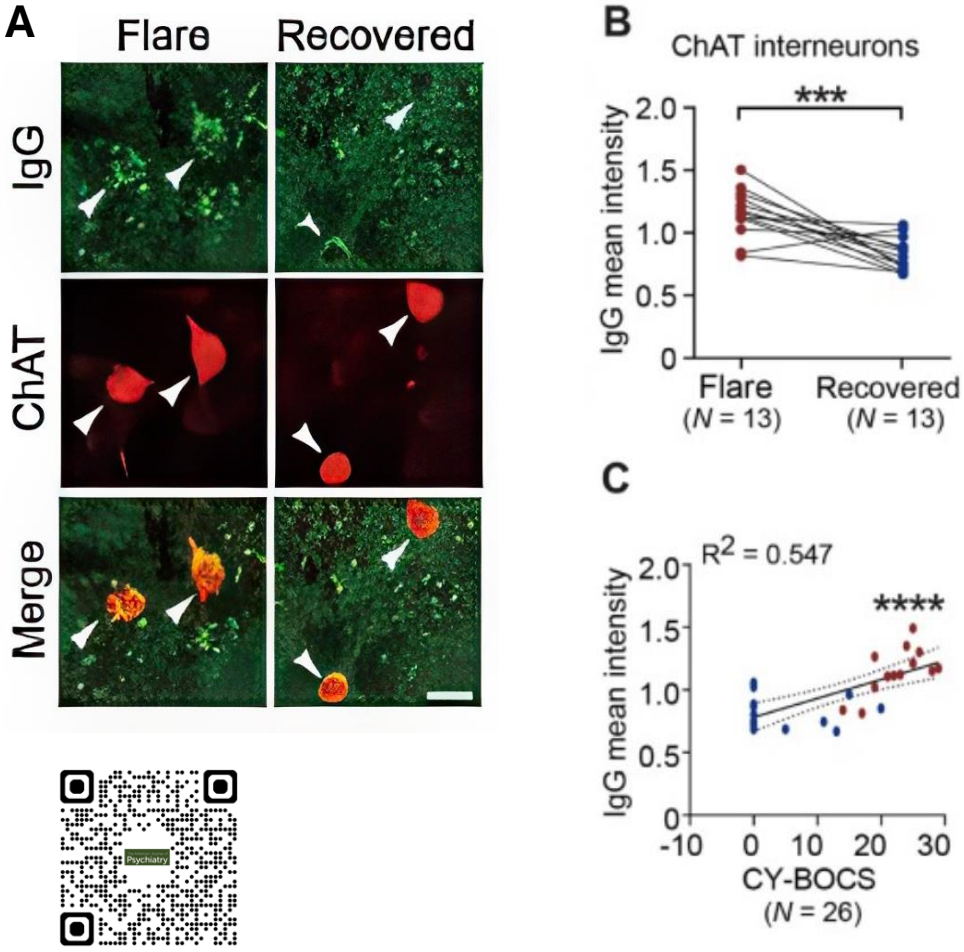


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MD Student c/o 2028, Duke

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





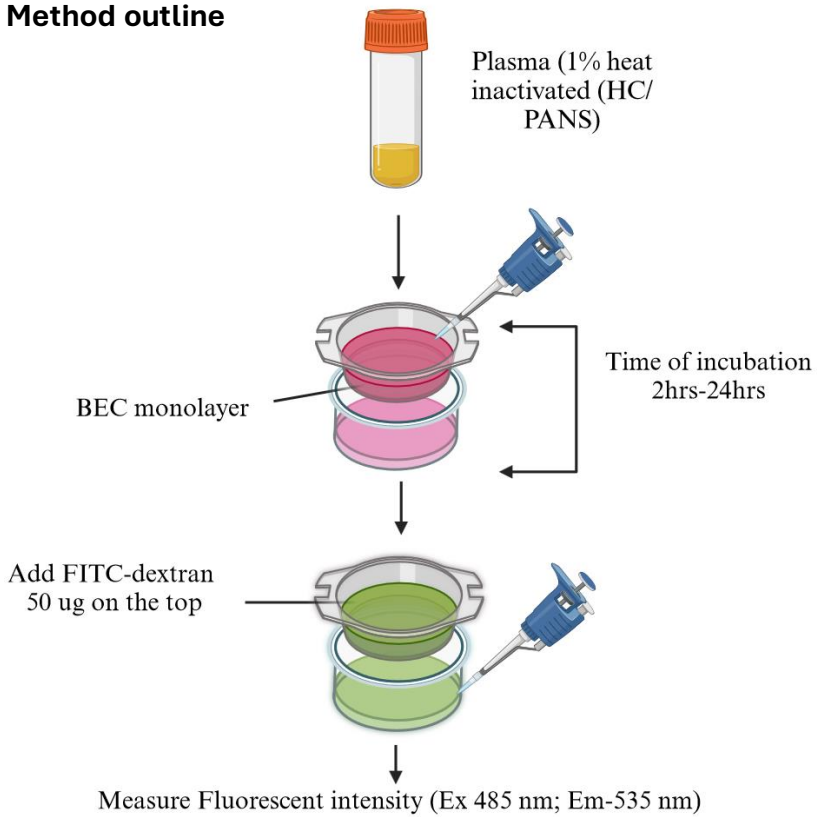


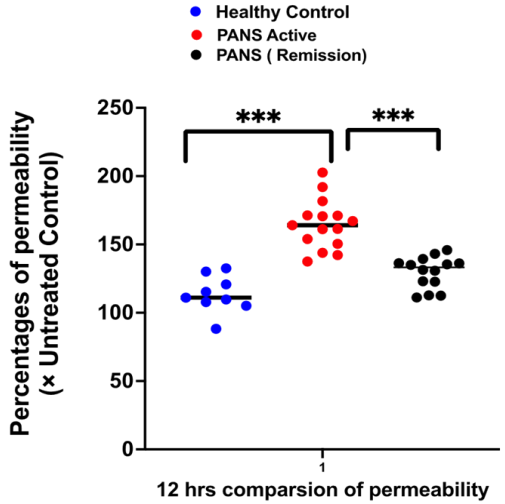
Christopher Pittenger, MD PhD
Director, Yale OCD Research Clinic
Yale University

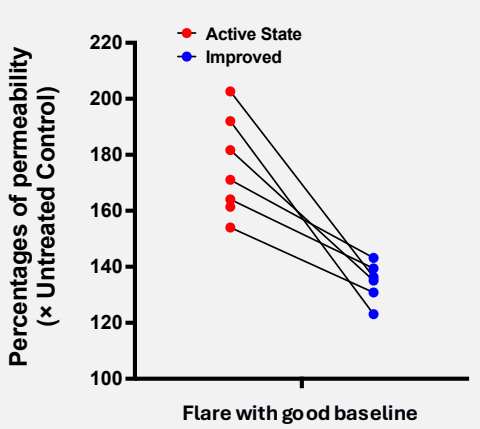
Xu , Frankovich ,et al. Elevated antibody binding to striatal cholinergic interneurons in patients with PANS. Brain Behav Immun. 2024 PMID: 39084540.

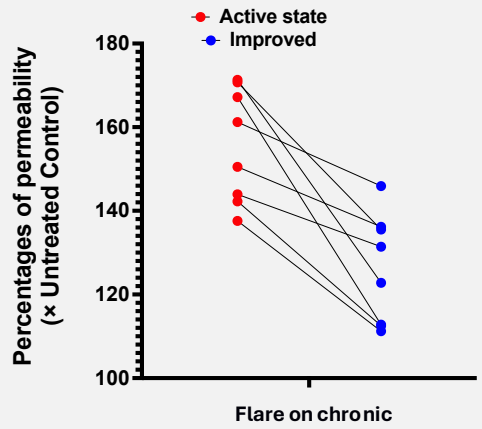
Plasma from PANS (Active) increases Brain Endothelial Cell (BEC) monolayer permeability

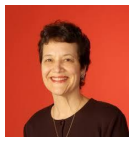
Method outline









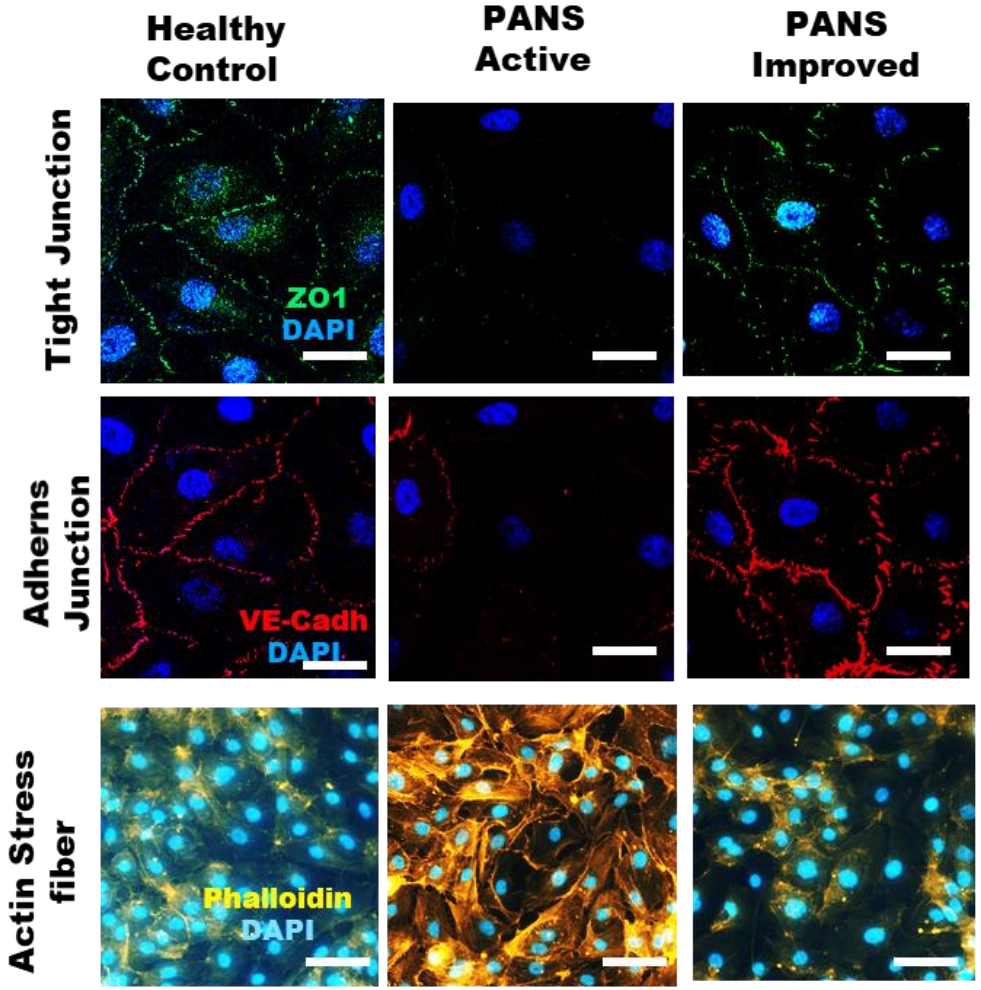


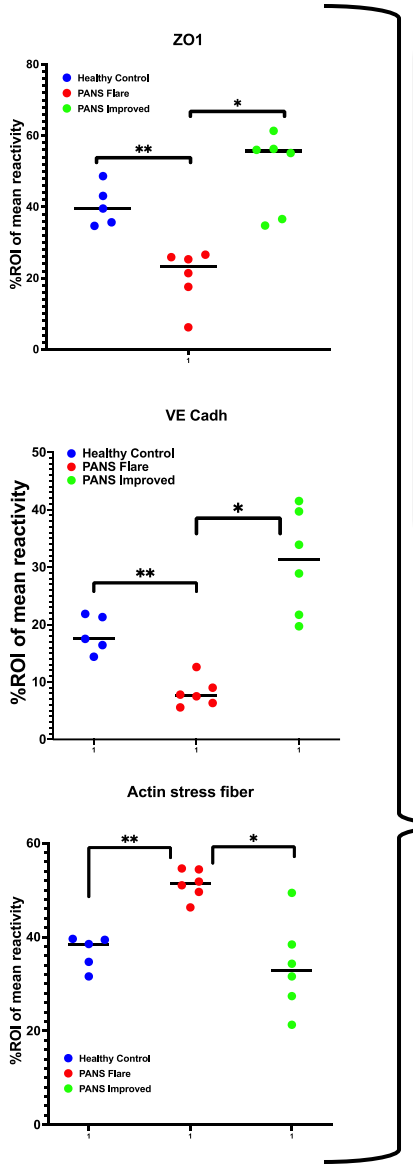


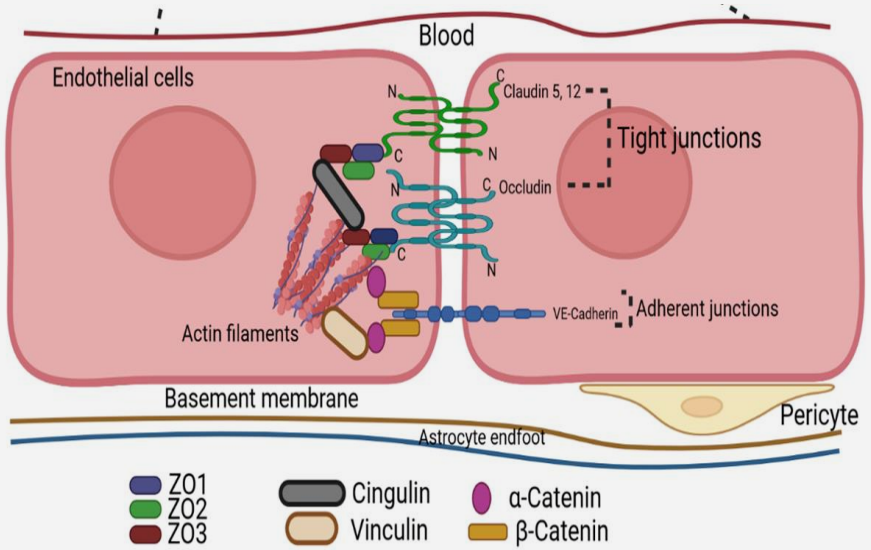
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Betsy Mellins MD & Ayan Mandal, PhD
Stanford Rheumatology/ Human Gene Therapy

Brain Endothelial Cell structural changes in 12 hours with plasma







Unpaired t–test (HC vs PANS Flare)

Paired t-test (Flare vs Recovery)

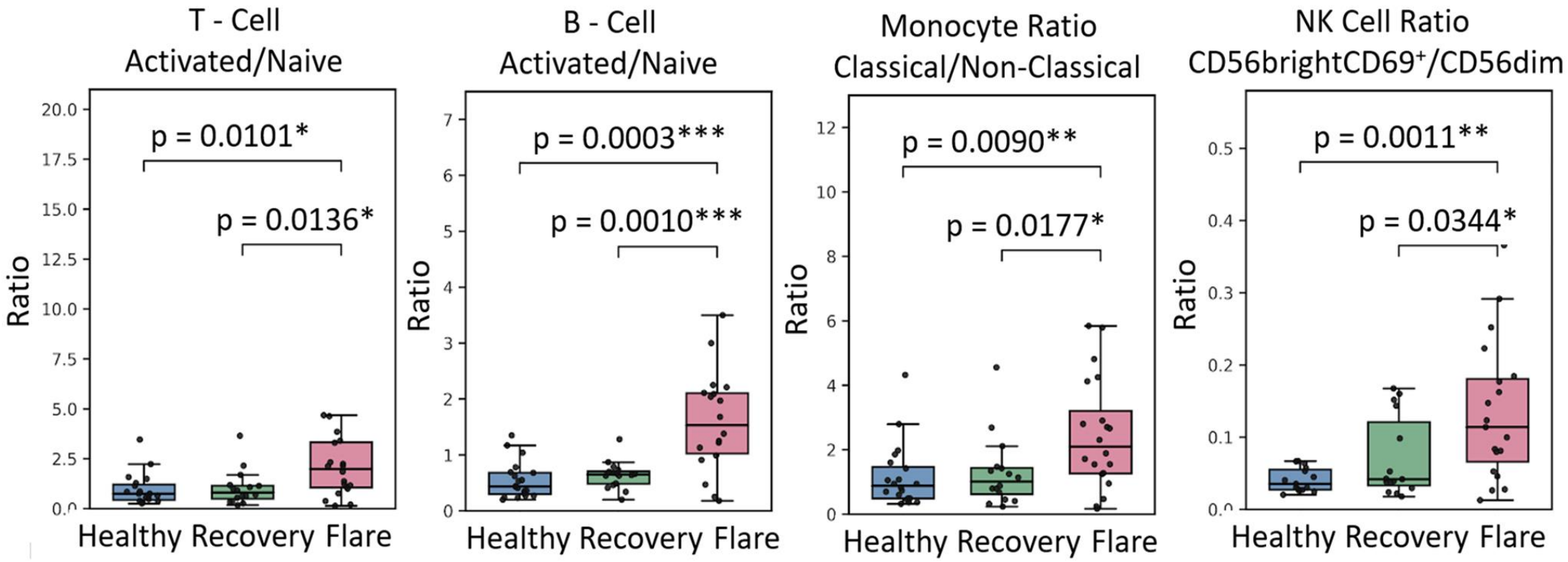


Betsy Mellins MD & Ayan Mandal, PhD
Stanford Rheumatology/ Human Gene Therapy

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



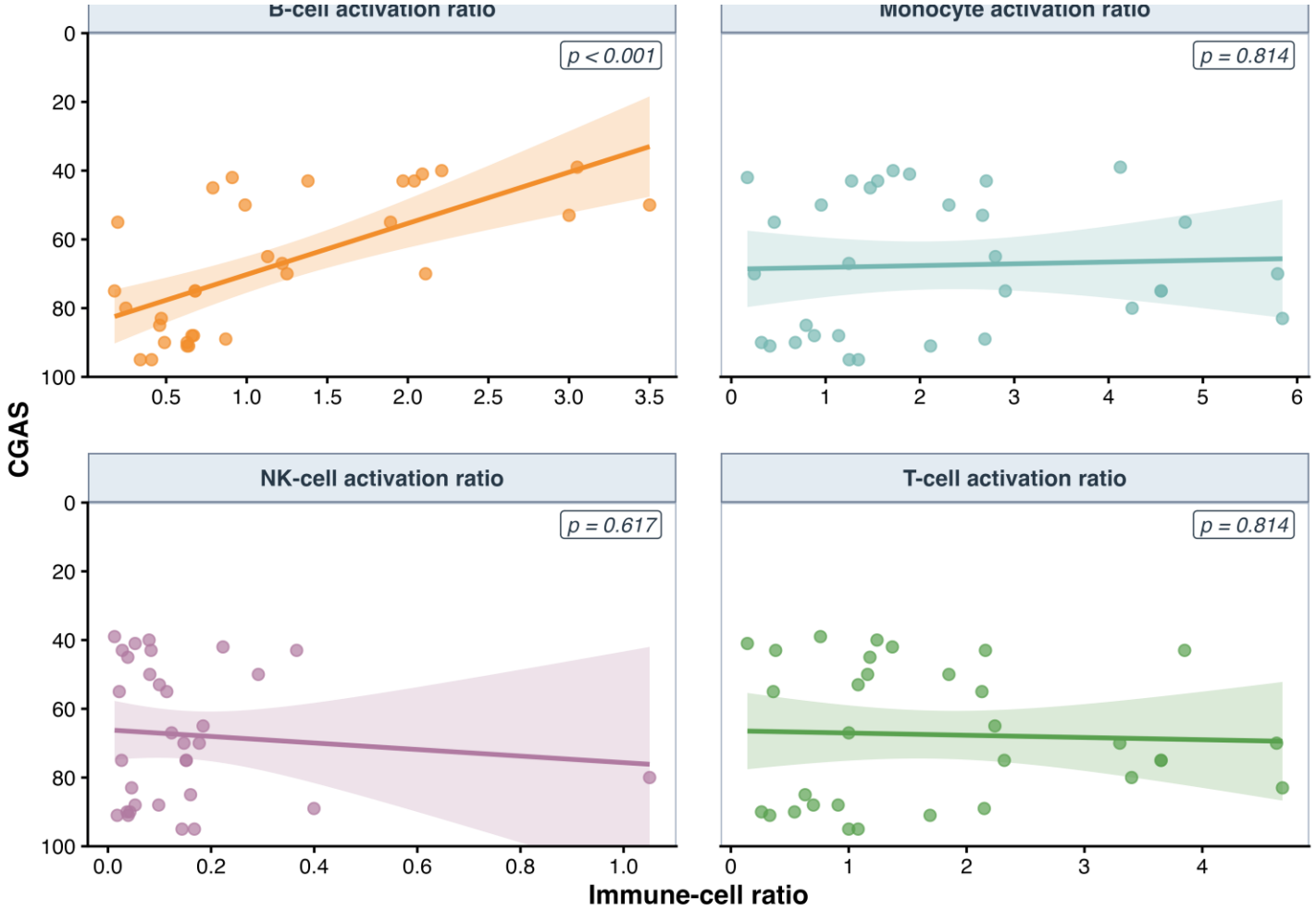
Imran Khan
Immunology Scientist
PANS Research Program

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

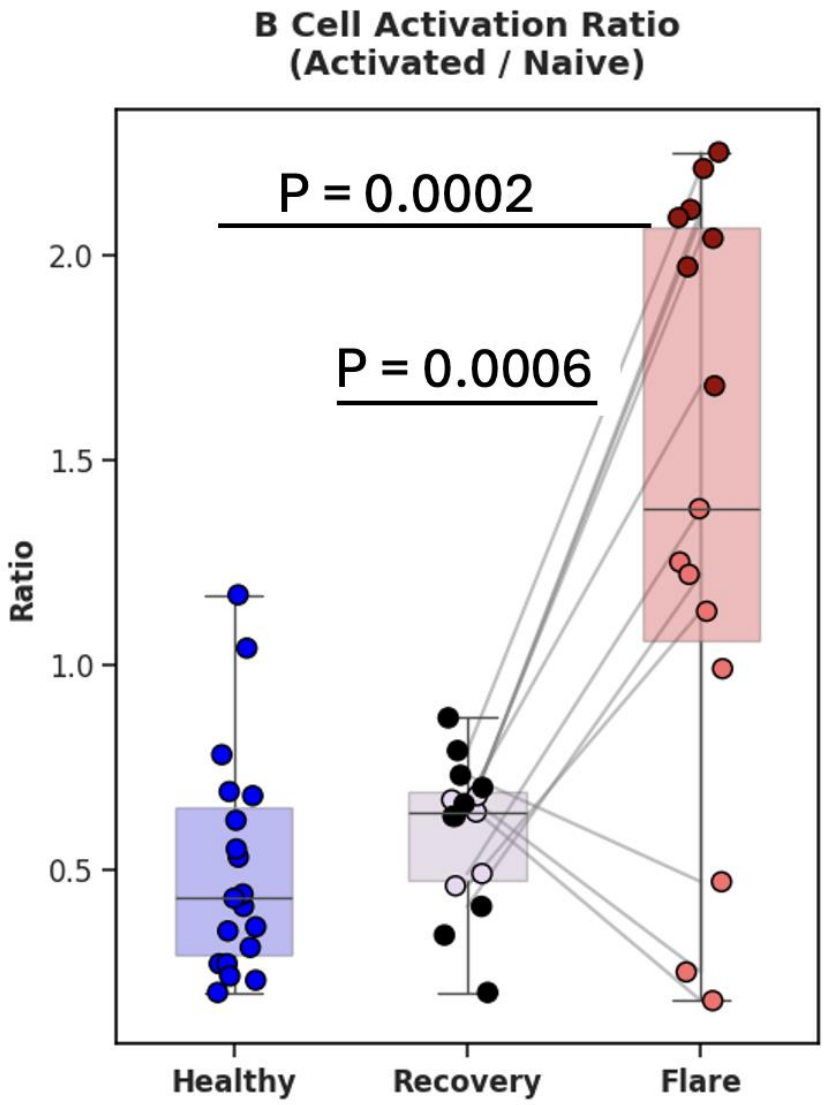
Effect estimates represent the expected change in CGAS associated with a one-unit increase in the corresponding immune-cell ratio.

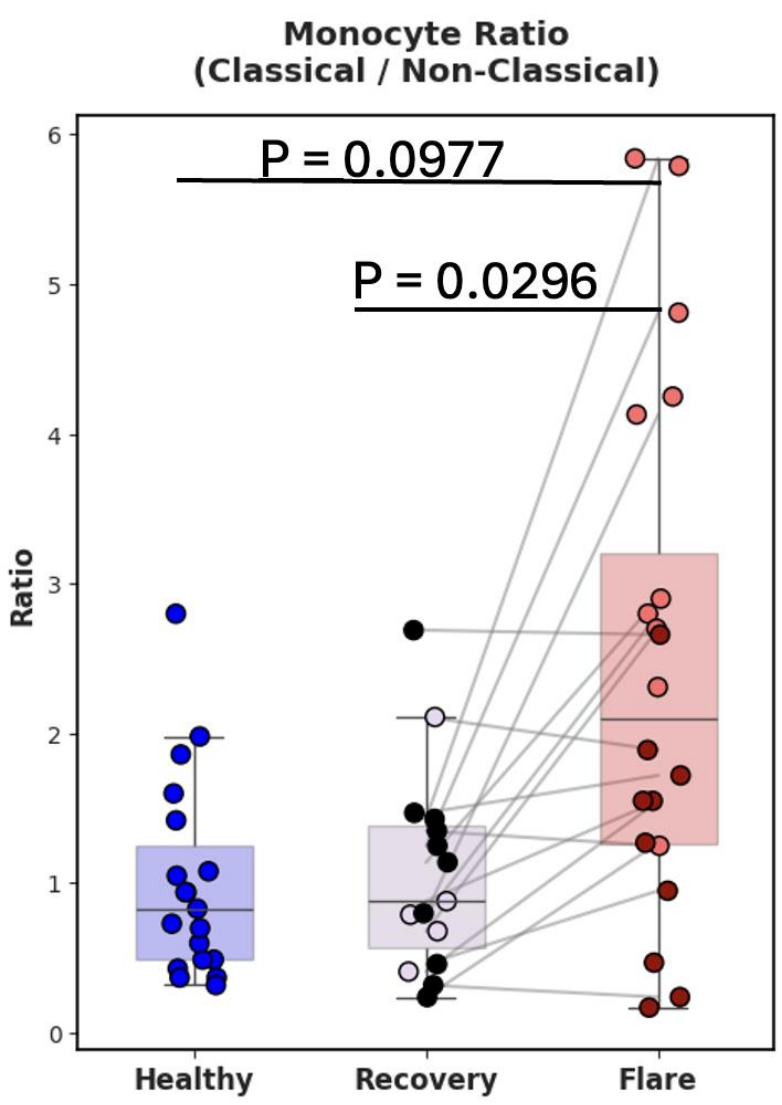




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Samantha Leonard
Clinical Research Epidemiologist
PANS Research Program









Holden Terry Maecker
Professor-Research
Microbiology and Immunology



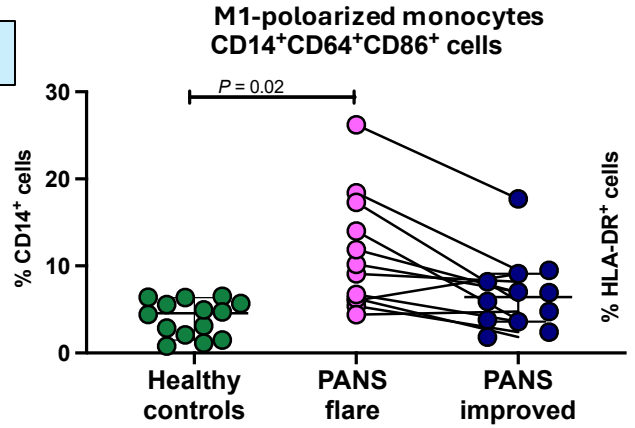
Imran Khan
Immunology Scientist
PANS Research Program

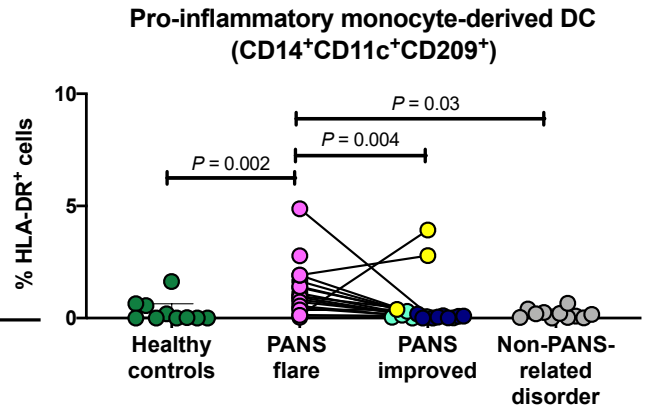
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PANS: M1-polarized (pro-inflammatory) monocytes high in flare & low in recovery

Stanford PANS cohort

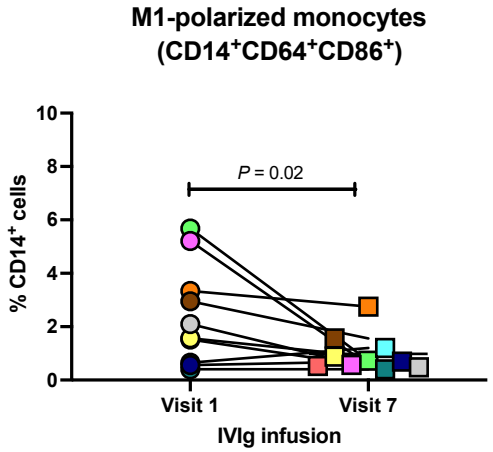
Samples: Unstimulated fixed whole blood.

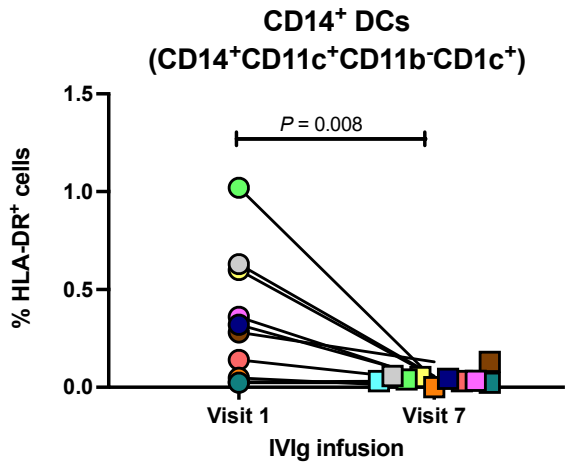




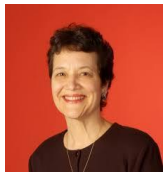
PANS IVIg cohort

Samples: fixed whole blood collected before and after IVIg infusion.





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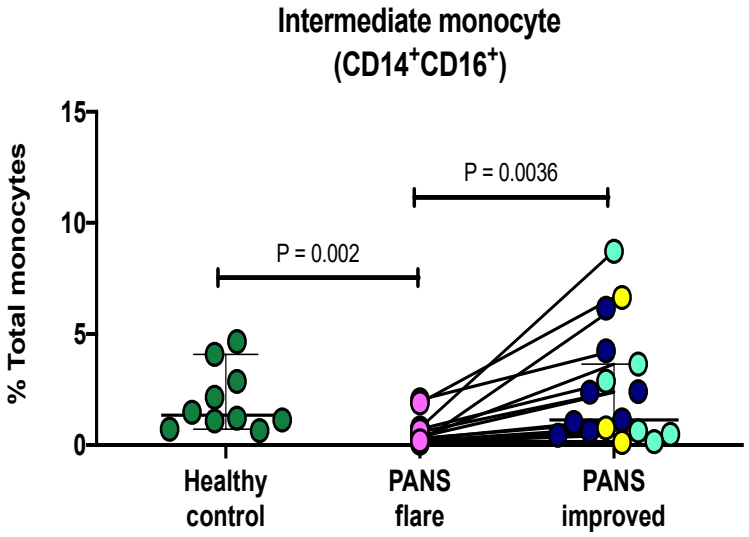


Betsy Mellins MD & Shamma Rahman, PhD

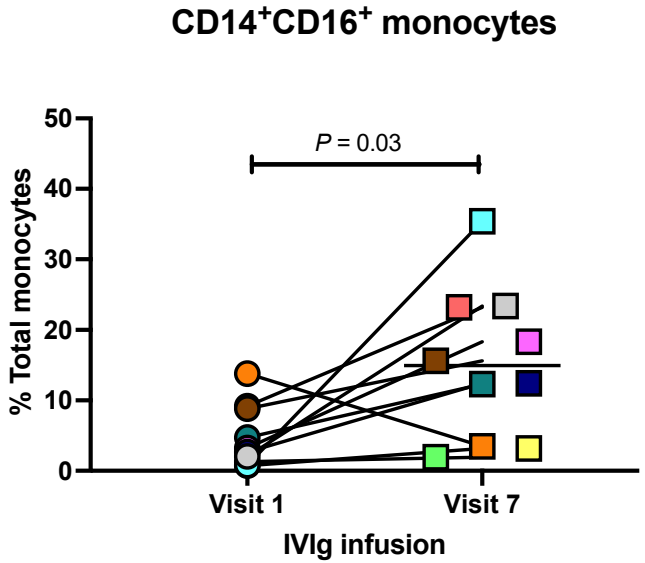
IVIG response in PANS correlates with reduction in pro-inflammatory monocytes and neuropsychiatric measures. 2024

PANS: M2-polarized (anti-inflammatory) monocytes are low in flare & high in recovery

Stanford PANS cohort



PANS IVIg cohort







Betsy Mellins, MD Shamma Rahman, PhD

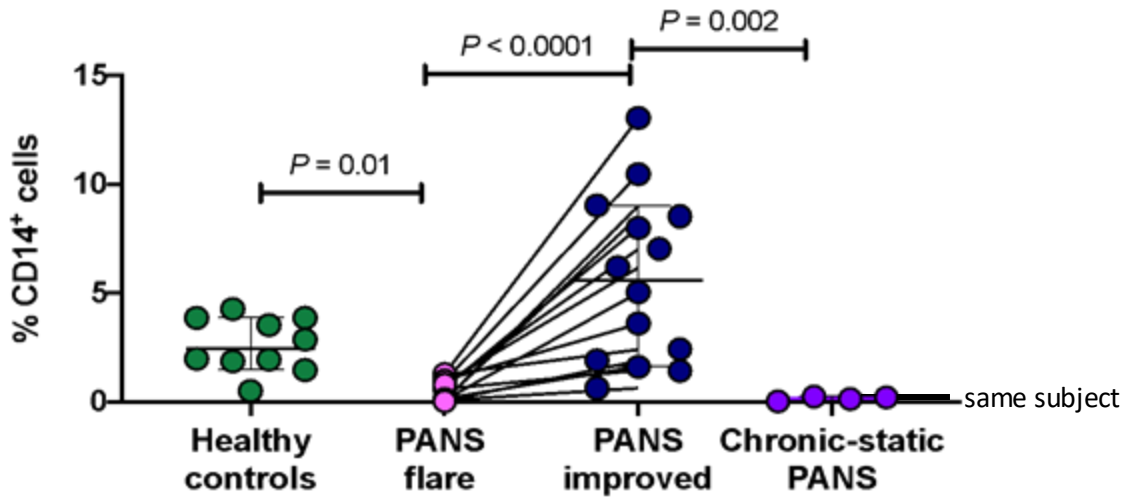
Stanford MEDICINE

Rahman & Mellins. *IVIG response in PANS correlates with reduction in pro-inflammatory monocytes and neuropsychiatric measures.* 2024

PANS: CSF-homing Repairing monocyte

"Repairing " monocytes

HLA-DR, CD14, CCR2, CX3CR1, VLA-4, CD166



Rahman & Mellins. *IVIG response in PANS correlates with reduction in pro-inflammatory monocytes and neuropsychiatric measures.* 2024





Betsy Mellins, MD Shamma Rahman, PhD

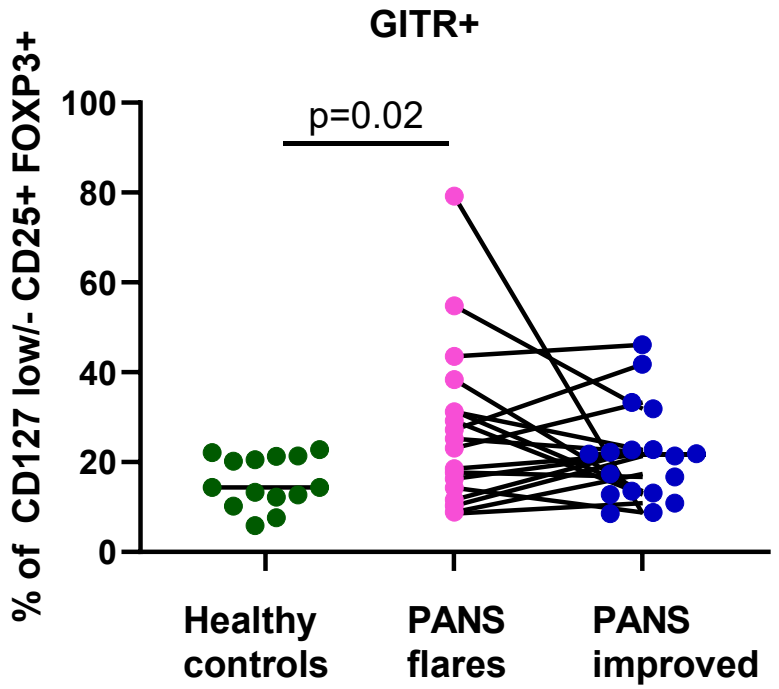
Repairing brain homing monocytes

- ***Recovered patients:*** *Low in blood during flare but* ***found in CSF (n=7)***
- ***Chronic patients:*** *low in blood in chronically active PANS* & *NOT in CSF (n=5)* → *low production*

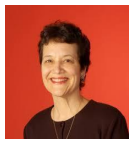
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Highly activated Treg subsets are

Increased in PANS Flare vs Controls vs Recovery



Glucocorticoid-induced TNF-R-related (GITR) expressed at high levels on activated Tregs




Betsy Mellins MD & Noor Hussein, PhD
Stanford Rheumatology/ Human Gene Therapy

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Conclusion- what we know now

Current evidence base:

- **Brain imaging studies** x 4 studies
- **REM sleep** abnormalities x 4 studies
- **Basal ganglia signs** x 1 study
- **Cholinergic Interneuron Autoantibodies** x 4
- **Brain Endothelial Disruption** x 2 lines
- **Immunophenotyping**
  - All immune cell subsets skew towards pro-inflammatory state in flare
  - **B-cell** activation correlates with **psych symptoms**

Acknowledgements and Thanks!

IBH Clinical Team

Bahare Farhadian, Mei Ma, Melissa Silverman, Yuhan Xie, Allison Vreeland, Kevin Hoffman, Angela Tang, Joseph Hernandez, and our past and present COMET, clinic staff, volunteers and past co-founders Margo Thienemann and Kiki Chang

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Basic Science Team

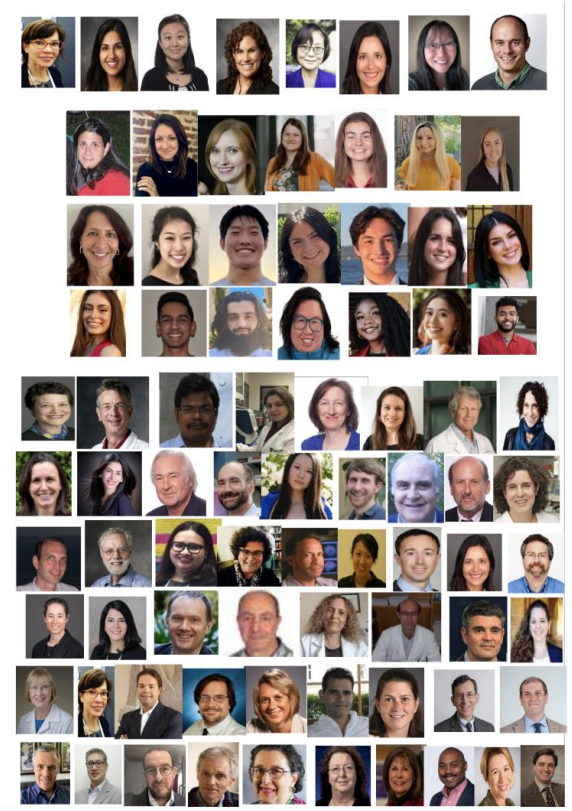
Mellins Lab (Shamma Rahman, Ayon Mondal, Noor Hussein), **David Lewis,** Holden Maecker, Marcelo Fernández-Viña, Agnes Kalinowski, Alex Urban, Fereshteh Jahaniani**, PJ Utz** (Tyler Prestwood & Xihui Yin), Catherine Blish, **David Stevenson**, Ron Davis

Imaging Team

Jesse Sandberg, Stanford MSK and NEURORADIOLOGY teams

Other Key Collaborators

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Lucile Packard Foundation
Children's Health

the brain foundation

NEUROIMMUNE FOUNDATION

TARA & DAVE DOLLINGER FOUNDATION

The O'Sullivan Foundation

The Louisa Adelynn Johnson Fund
for Complex Disease

Brain Inflammation Collaborative

CAUDWELL Children

Oxnard Foundation

PANDAS PHYSICIANS NETWORK
PPN
A DIVISION OF THE FOUNDATION FOR BRAIN SCIENCE AND IMMUNOLOGY

NIH National Institute of Mental Health

STANFORD MATERNAL & CHILD HEALTH RESEARCH INSTITUTE

SPARK AT STANFORD

Gracious donors & other community foundations!

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Acknowledgements and Recognition

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We are endlessly **grateful** for all the **children, their families, and students** who participate in our **program, research & fundraising** efforts.

Our clinical insights would not be possible without your time and contributions!

Thank you!





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Where do we go next?



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Ming.lim3@nhs.net

PANS PANDAS STEERING GROUP

RCPCH Royal College of Paediatrics and Child Health — Leading the way in Children's Health

PANS PANDAS UK

RCOT Royal College of Occupational Therapists

BPAIIG British Paediatric Allergy Immunity & Infection Group

RC PSYCH Royal College of Psychiatrists

Royal College of Nursing — The voice of nursing

BPNA British Paediatric Neurology Association

BASW — The professional association for social work and social workers



Consensus Working Group

Working towards a true multi-stakeholder consensus regarding treatment options in the NHS

Group convened (*September 2026 delivery*)



Research Working Group

In collaboration with NHS England, BPSU, BPNSU and CAPPS, a nationwide surveillance study application is being made to determine prevalence

November 2026 Stage 2 application



Pathway Working Group

This group will aim to identify specialist services or other enhanced clinical pathways for MDT management of affected children and young adults

To convene as consensus near completion



Education Working Group

Development of a position statement encompassing health and education information to distribute to Local Authorities

See https://panspandasuk.org/ for outputs

M1: Establishing a UK incidence and prevalence



Prevalence 1:60,155

Goren et al, 2024 ***Paediatr Child Health*** 30(3) 157-63

Estimate of the incidence of PANDAS and PANS in 3 primary care populations

Ellen R. Wald[1*], Jens Eickhoff[2], Grace E. Flood[3], Michael V. Heinz[4], Daniel Liu[5], Alisha Agrawal[4], Richard P. Morse[6], Veronica M. Raney[7], Aravindhan Veerapandiyan[5] and Juliette C. Madan[4,8,9]

1:12,000

Wald et al., 2023
Front Pediatr S11:1170379

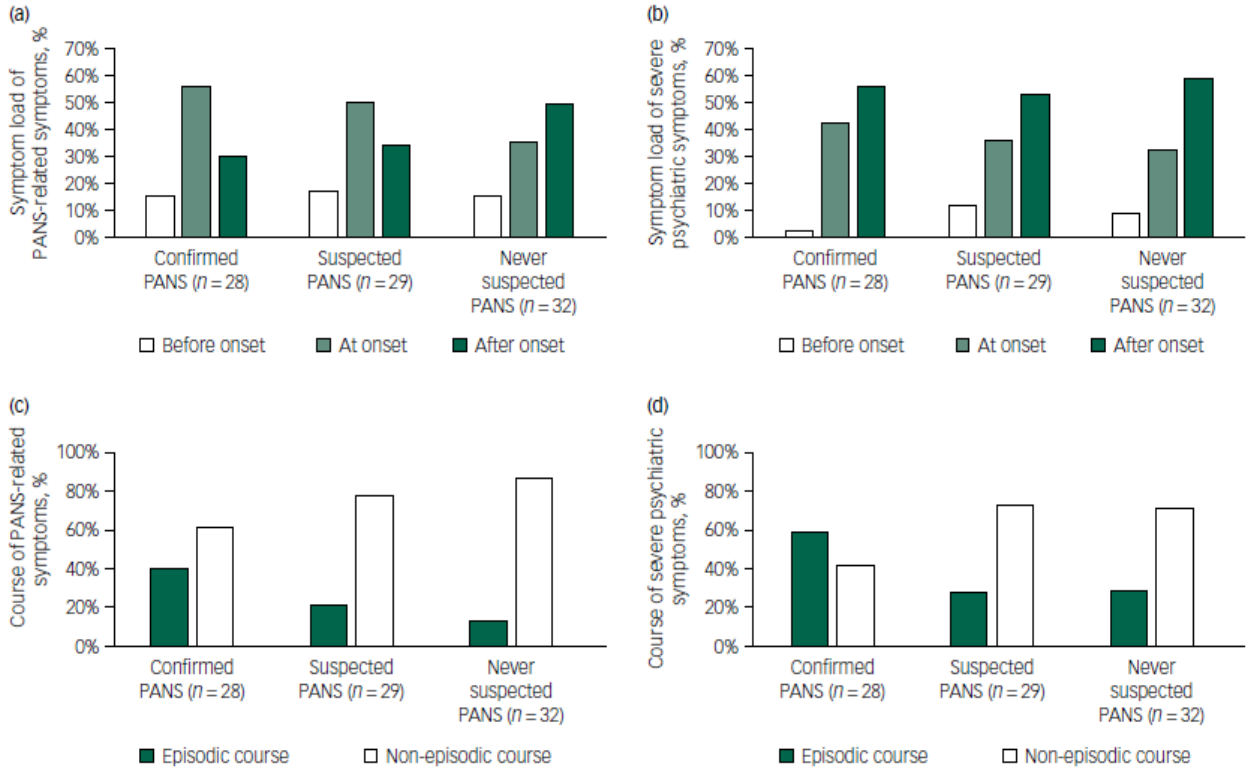
1:200
PANDAS network
https://pandasnetwork.org/

PANS PANDAS UK

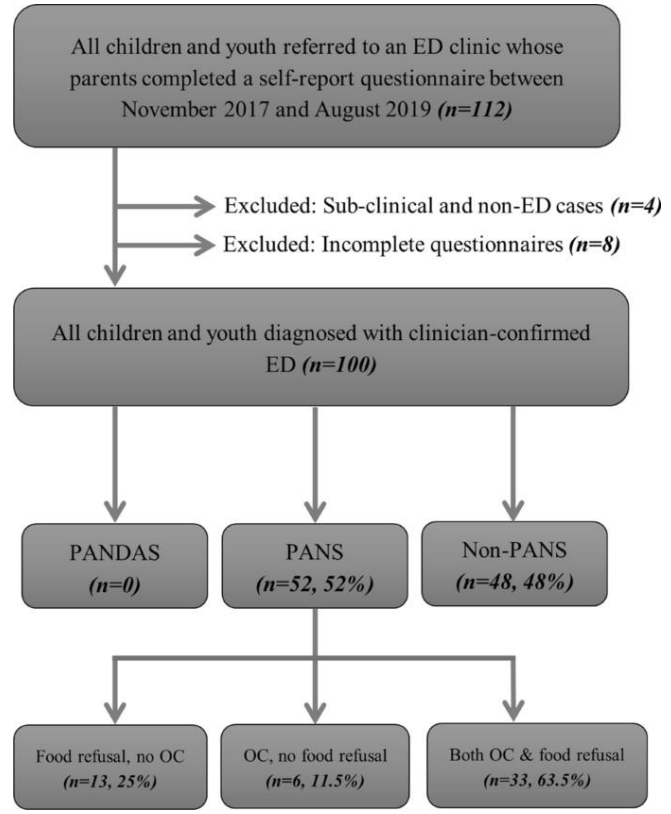
Represent **over 6000** families, all experiencing similar symptoms and looking for answers

UK Surveillance study - Ashley Liew

M2: Is this a variant of a psychiatric condition?



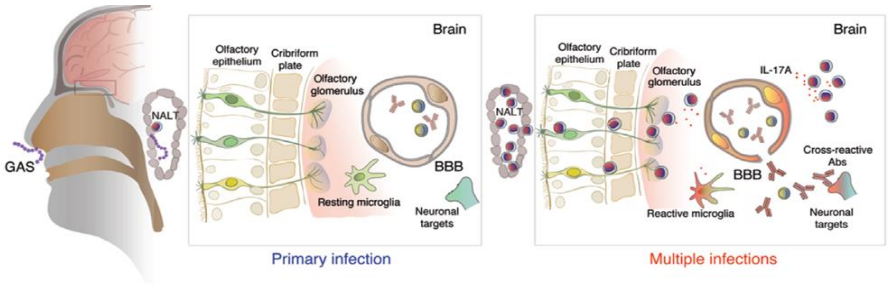
Hesselmark and Bejerot 2019 ***BJPsych Open*** 5, e25; 109



Aman et al., 2022 ***J Eat Disord*** 10(1):194

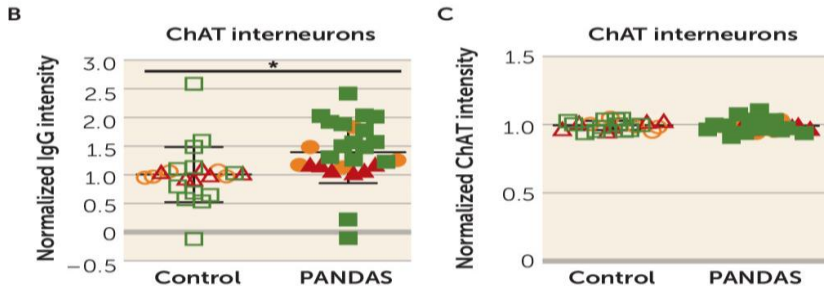
M3: Unravelling the immune and other biological mechanisms

Autoimmunity induction in an animal model

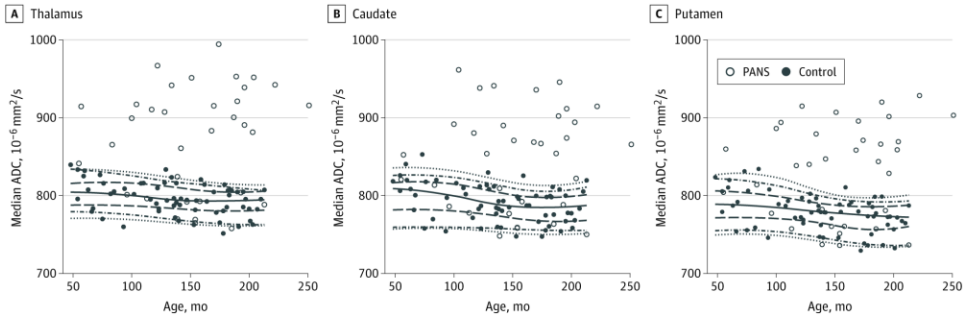


Dileepan et al 2016 ***J Clin Invest.*** 126(1):303-17

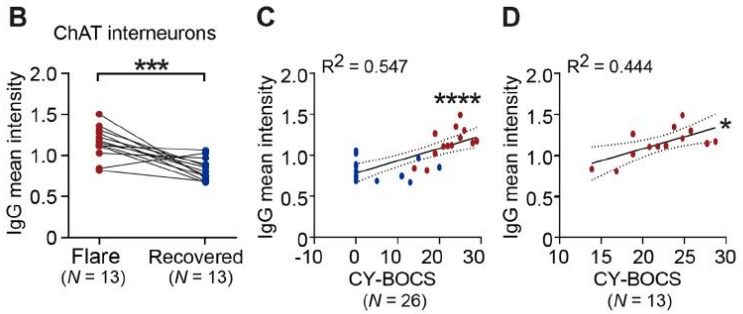
PANS and PANDAS patient sera bind specifically to striatal cholinergic interneurons and alter their activity



All assessed brain regions had statistically significantly increased median diffusivity showing microstructural differences



Zheng et al., 2020 ***JAMA Netw Open. 3(5)***:e204063



Xu et al., 2021 ***Am J Psychiatry*** 178(1):48-64

Xu et al., 2024 ***Brain Behav Immun*** 122:241-255

M3: Unravelling the immune and other biological mechanisms



Upregulated pathways in ribosomal biogenesis and RNA methyltransferases, and downregulated pathways in diverse cellular functions such as mitochondrial activity, cell signalling, endocytosis, and immune responses in PANS

Han et al., 2025 ***Mol Psychiatry*** doi: 10.1038/s41380-025-03127-5

Han et al., 2025 ***Neurol Neuroimmunol Neuroinflamm***. 12(6):e200467

M4: Getting robust natural history and outcome data

Study	Sample	Design / follow-up	Long-term outcome
Silverman et al., 2019 PMID 30605785	**143** PANS S	Retrospective cohort review Follow-up N/D	 Mono 7% · **RR 70%** · C/S 23%
Lepri et al., 2019 PMID 31140830	**345 + 26** PANDAS + PANS	Retrospective 7-year follow-up	75% of PANDAS improved within 3–5 months; 88.4% of PANS after 6–12 months
Visscher et al., 2021 PMID 34607588	**34** PANS	Prospective observational	Mainly a disease-outcome methodology study
O'Dor et al., 2022 PMID 36383096	**490** PANS/PANDAS	Survey	High psychiatric morbidity across the board
Gromark et al., 2022 PMID 33559023	**34** PANS	Prospective observational 2–5 year follow-up	 Mono 6% · **RR 60%** · C/S 35%
Calaprice-Whitty et al., 2023 PMID 37902971	**646** PANS	Survey-based questionnaire	More pervasive symptoms and lack of IVIG response predicted a refractory course
Ma et al., 2024 PMID 39078633	**193** PANS	Retrospective cohort Stanford IBH clinic	Arthritis in **28.3%** by age 14; raised risk of autoimmune disease
Masterson et al., 2025 PMID 40188825	**264** PANS	Retrospective cohort Stanford IBH, 2012–2023	**RR 74%** · persistent course 43% · **77% ultimately recovered**

Mono = monophasic · RR = relapsing–remitting · C/S = chronic/static · N/D = not defined

M5: Robust data on how to treat and manage

- very low certainty of evidence of beneficial effects
- moderate certainty of evidence of adverse effects, of anti-inflammatory, antibacterial or immuno- modulating treatments in patients with PANS
- **available evidence neither supports nor excludes potential beneficial effects but supports that such treatment can result in adverse effects**.

Sigra et al., 2018 ***Neurosci Biobehav Rev*** 2018 86:51-65

Johnson et al. 2021 ***PLoS ONE*** 16(7): e0253844

Overview of evidence synthesis – PANS PANDAS unveiled

Drs Michael Nunns and Sam Febrey
Isca (Dumnoniorum) Evidence Synthesis team, University of Exeter

Childhood Neurological Conditions Priority Setting Partnership

James Lind Alliance
Priority Setting Partnerships

BPNA
British Paediatric Neurology Association

Top 10 research priority

01 Can early therapy interventions improve functional and developmental outcomes in babies experiencing brain injury during pregnancy or infancy?

02 What are the most effective interventions to support sleep in children and young people with neurological conditions?

03 How should we best manage emotional well-being in children and young people with neurological conditions?

04 What are the most effective strategies to support communication in children and young people with neurological conditions? (e.g. use of high and low technology augmentative alternative communication (AAC) and to improve speech intelligibility.)

05 What are the most effective medicinal and non-medicinal treatments to manage distressing symptoms (e.g. pain, irritability) in children and young people suffering life limiting neurological conditions?

06 What are the safest and most effective anti-seizure medications for seizures in new-born babies less than 28 days old?

07 Which medications should be used, and in what sequence, in the management of muscle stiffness (hypertonia) in children and young people?

08 Are medications (e.g. antibiotics and/or immune treatments) effective in the management of PANS/PANDAS? (Paediatric Acute-onset Neuropsychiatric Syndrome/Paediatric Acute-onset Neuropsychiatric Disorders Associated with Streptococcal infection)

09 Which psychological interventions are most effective in children and young people who have functional neurological disorders?

10 What are the best non-medicinal interventions (including therapies, orthotics e.g. splints, high and low technology supports) for children and young people with motor disorders?

Dev Med Child Neurol. 2024 Dec;66(12):1590-1599

Round up

Professor Rajat Gupta