PANS Update 2023
Evidence for PANS as an Inflammatory Disorder

Lucile Packard Children's Hospital Stanford

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Lucile Packard Children's Hospital Stanford

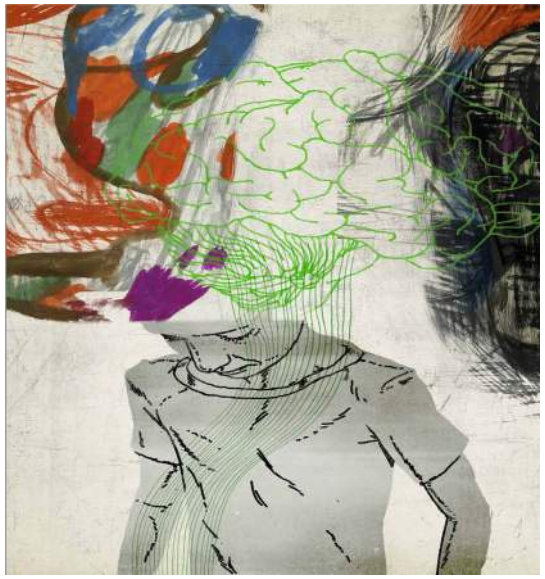
Disclosures / Acknowledgements

Funding for infrastructure of PANS program

Biobank

Imaging research

Basic science research



- U.S. National Institute of Mental Health, Developmental Pediatrics Branch
- Stanford SPARK
- Lucile Packard Foundation for Children's Health
- Stanford Maternal Child Health Research Institute
- Neuroimmune Foundation
- PANS/PANDAs Physician Network (PPN)
- Global Lyme Alliance
- PRAI Kids
- The Dollinger Family Foundation
- Oxnard Foundation
- The Brain Foundation
- The O'Sullivan Foundation
- Caudwell Children's Foundation
- Gracious donors & other community foundations and fundraising efforts

Betsy Mellins

Research grants (unrelated to this presentation)

- GlaxoSmithKline
- Codexis, Inc
- Genentech (completed)

Presentation Outline

1. Review PANS Criteria, Disease trajectories

2. Review key findings regarding evidence for systemic autoimmunity/ inflammation
- Clinical labs & physical exam findings
- Co-morbid arthritis & autoimmune diseases
- Association with anti-basal ganglia autoantibodies

3. New Data on PANS and co-morbid:
- POTS
- Chronic Fatigue
- Pain Amplification

4. Dr. Mellins' slides will review
    1. Correlation of proinflammatory monocytes with PANS flares
    2. Correlation of anti-inflammatory monocytes with improvement
    3. Effects of PANS plasma on brain endothelial cells

Classification Criteria
Pediatric Acute-onset Neuropsychiatric Syndrome (PANS)

Modifying the PANDAS Criteria to Describe PANS (Pediatric Acute onset Neuropsychiatric Syndrome);
Swedo (NIMH), Leckman (Yale), Rose (Hopkins) *Pediatrics & Therapeutics 2012 (2,2)*

I. **Sudden severe-onset of obsessive-compulsive disorder or eating restriction**

II. **Plus 2 co-morbid symptoms (which are also sudden-onset)**

1. **Anxiety** (commonly severe separation anxiety)
2. **Sensory dysregulation** (light, sound, and/or pain dysregulation) **or motor abnormalities** (handwriting deterioration, piano fingers, motoric hyperactivity, tics)
3. **Behavioral (developmental) regression**
4. **Deterioration in cognitive functioning**
5. **Mood disorder:** emotional lability, depression, irritability rage
6. **Urinary symptoms:** polyuria, urge to urinate, secondary enuresis.
7. **Severe sleep disturbances**

Most patients have 5-6 co-morbid symptoms

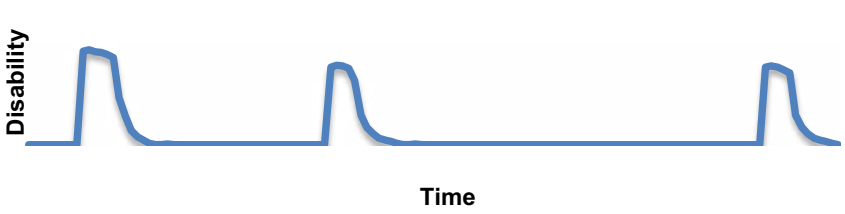


Sue Swedo, James Leckman, Noel Rose

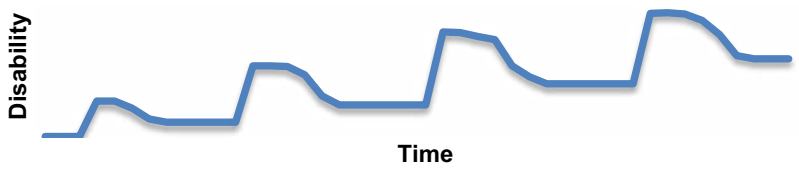
Stanford University

Observed PANS Disease Trajectory

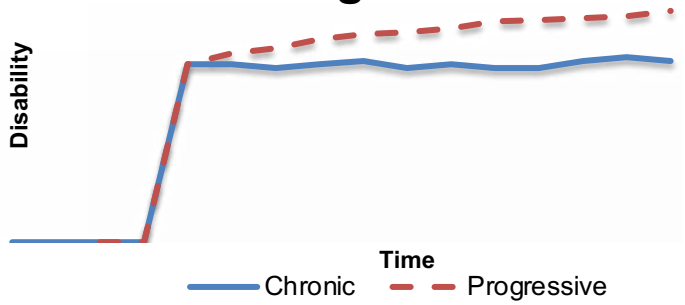
Relapsing and Remitting



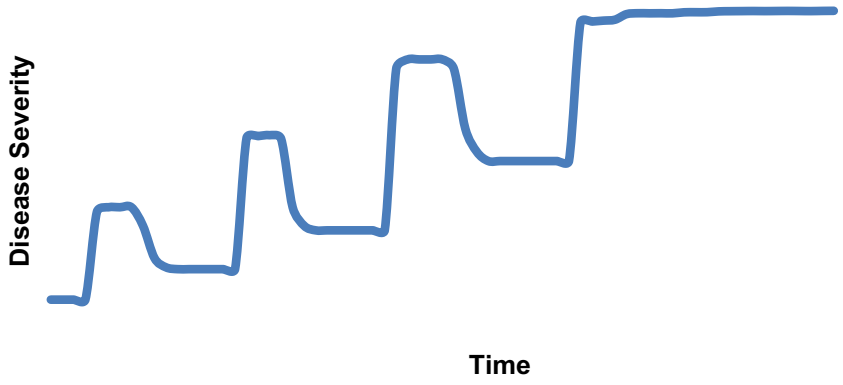
Relapsing Remitting with Worsening Baseline



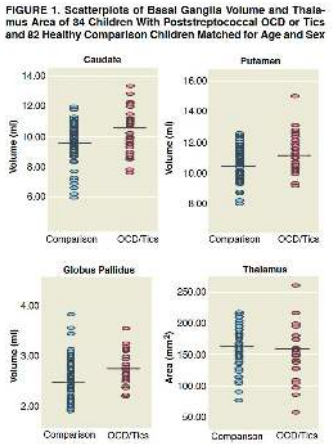
Primary Chronic, Primary Progressive



Secondary Progressive



Imaging & Neurological Signs suggest basal ganglia (BG) inflammation



⬆ BG Volume in the acute stage

Giedd, et al. *AJP* 2000

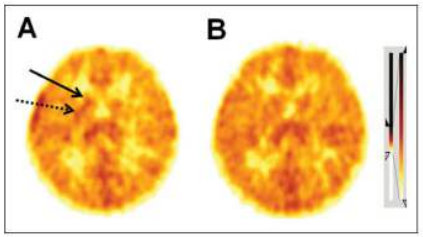
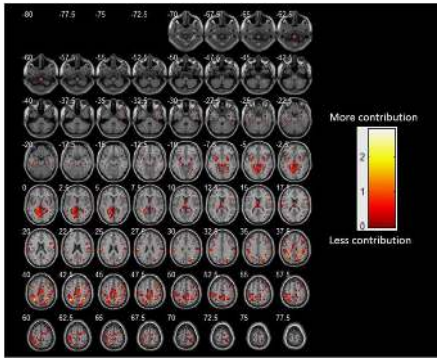


Figure 3. (A) Pre and (B) post (6 months after) immunoglobulin treatment ^{11}C-[R]-PK11195 PET scan, in an 8-year-old male child with pediatric autoimmune neuropsychiatric disorders associated with streptococcal infection (PANDAS), showing reduced tracer binding, suggesting reduced neuroinflammation,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

⬆ Microglia activation in BG

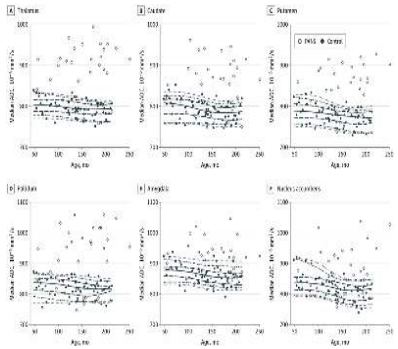
Kumar, et al. *J Child Neuro*. 2015



⬆ Gray matter volume in BG

⬇ White matter Volume in BG

Cabrera et al. *CNS Spectrums*, 2019



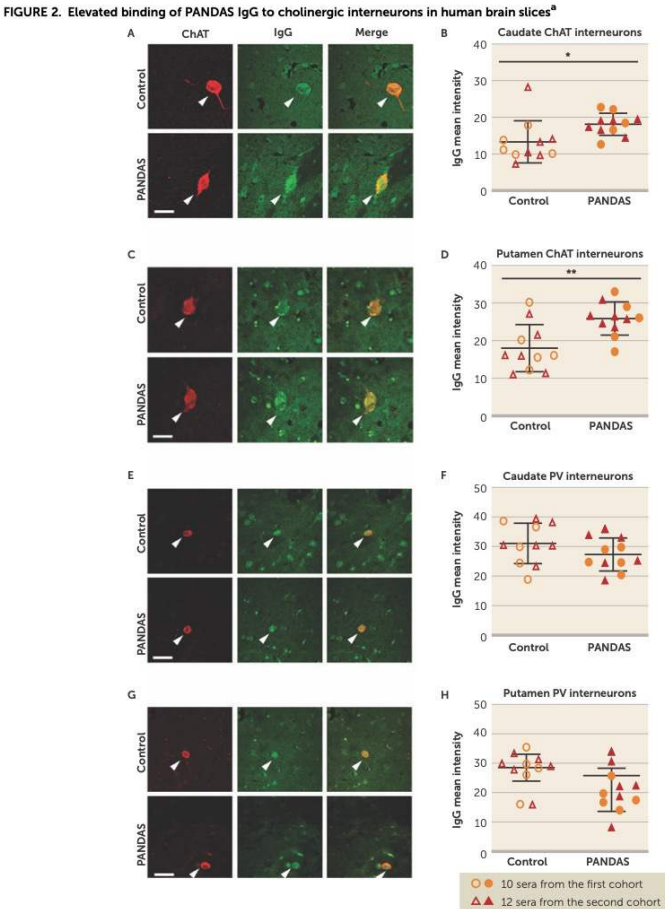
⬆ medium diffusivity all assessed brain regions- most prominent in BG

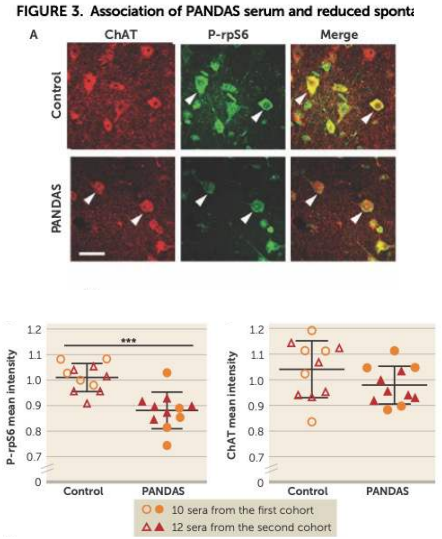
Zheng, et al. *JAMA Netw. Open 2020*

JAMA Network Open

Stanford University

PANDAS Autoantibodies bind to Cholinergic Interneurons in basal ganglia & decrease activity (4 cohorts from NIH)





Autoantibodies- reduce spontaneous neuronal activity…

P-rpS6 is a phosphorylation that is used as a readout of neuronal activity

Xu, et al. *AJP* 2021

Autoantibodies in sera from patients were found to bind cholinergic interneurons in mice and humans.

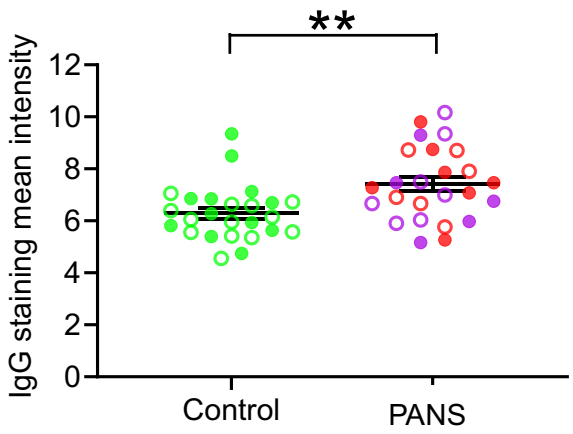
Jian Xu
Yale University

Christopher Pittenger
Yale University

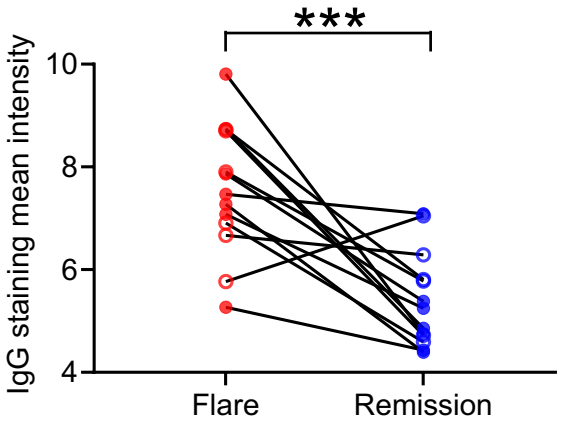
Stanford University

PANS (post-strep) Autoantibodies bind to Cholinergic Interneurons in basal ganglia & decrease activity (Stanford Cohort)

t(48) = 3.229, P = 0.002

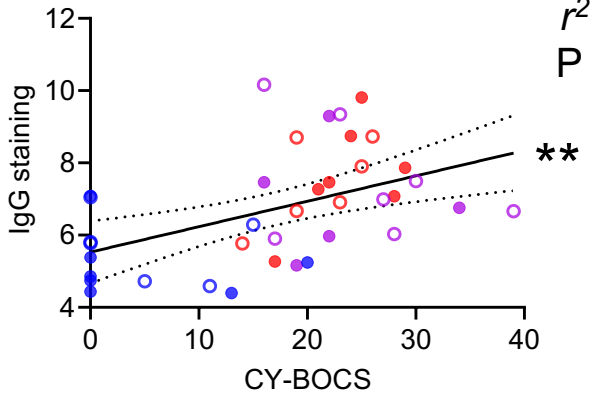


t(12) = 4.455, P = 0.0008



IgG binding to CINs correlates with CY-BOCS among patients with PANS

r^2 = 0.237,
P = 0.0019

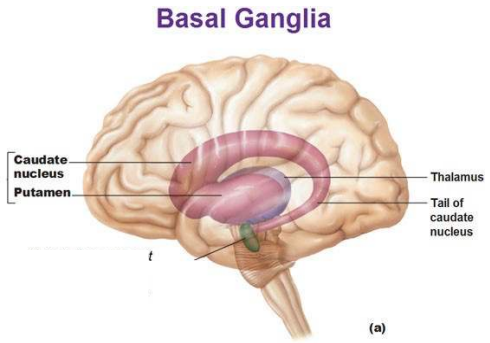


Jian Xu
Yale University

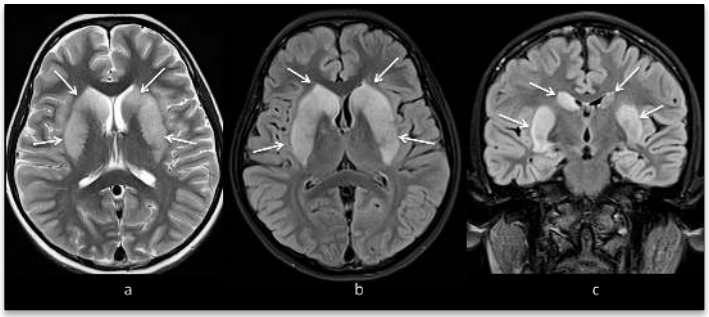
Christopher Pittenger
Yale University

Stanford University

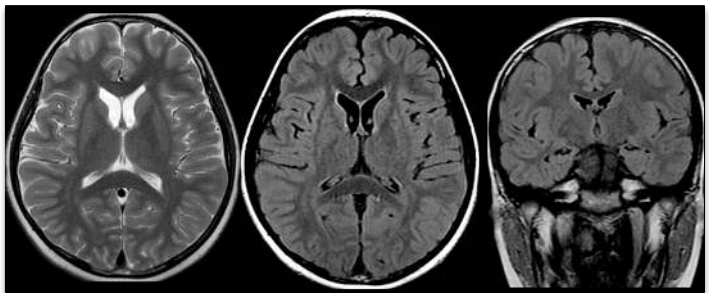
Imaging & Neurological Signs suggest basal ganglia inflammation



MRI with in 3 days of onset



MRI at 6 months



Basal ganglia exerts an inhibitory influence on motor & behaviors systems.

Inflammation/autoantibodies/injury causes disinhibition and thus disrupts the normal role of the BG in governing:

- Movements
- Mood & emotion
- Behavior
- Procedural learning
- Cognition

Symptoms of PANS

Stanford PANS Cohort (n=220)

Obsessions & compulsions: 92%
Eating restriction: 53%

- Anxiety: 97%
- Mood disorder: 92%
- Irritability/aggression: 90%
- Behavioral regression: 73%
- Deterioration in school: 72%
- Sensory amplification: 97%
- Urinary symptoms: 66%
- **Sleep issues: 93%**

Sleep issues:

- Insomnia
- Nightmares
- Restless sleep
- Reverse cycling
- **REM motor disinhibition = REM Behavior Disorder (RBD)**

Gaughan T, Buckley A, Hommer R, Grant P, William K, Leckman JF, Swedo SE. REM sleep abnormalities in children with PANS. J Clin Sleep Med. 2016 Jul 15;12(7):1027-1032

Continued Presence of Period Limb Movements During REM Sleep in Patients With Chronic Static PANS. Journal of clinical slee medicine : JCSM : official publication of the American Academy of Sleep Medicine Santo J. D., Frankovich, J., Bhargava, S. 2018; 14 (7): 1187–92

Gagliano A, Puligheddu M, Ronzano N, Congiu P, Tanca MG, Cursio I, Carucci S, Sotgiu S, Grossi E, Zuddas A. Artificial Neural Networks Analysis of polysomnographic and clinical features in Pediatric Acute-Onset Neuropsychiatric Syndrome (PANS): from sleep alteration to "Brain Fog". Nat Sci Sleep. 2021 Jul 23;13:1209-1224. doi: 10.2147/NSS.S300818. PMID: 34326674; PMCID: PMC8315772.


Margo Thienemann


Bahare Farhadian


Theresa Willett


Mei Ma


Melissa Silverman


Yuhuan Xie


Kiki Chang


Jenny Frankovich

Non-specific signs of Immune dysregulation & Inflammation in consecutive patients with PANS (n=147)

Blood Dyscrasia	
Leukopenia	14%
Lymphopenia	14%
Autoantibodies	
Positive Anti-Nuclear Antibody	26%
High Anti-Histone Antibody	17%
High Anti-Thyroglobulin Antibody	22%
High Thyroid Peroxidase Antibody	15%
Complement Activation	
Elevated C1Q Binding Assay	34%
Low C4	**41%**
Low C3	11%
Elevated C4a	75%

Hypoferritinemia → 27% of patients.

Patients with **hypoferritinemia** (compared to patients with normal ferritin)
→ had worse global impairment
→ more comorbid inflammatory diseases
→ exhibited a chronic course of PANS illness

Prevalence of iron deficiency anemia
→ 1.5-fold higher than age- and sex-matched U.S population (CDC data)

Pediatric Research. 2021 05; 89(6):1477-1484

C4 gene copy number in PANS is not different compared to controls

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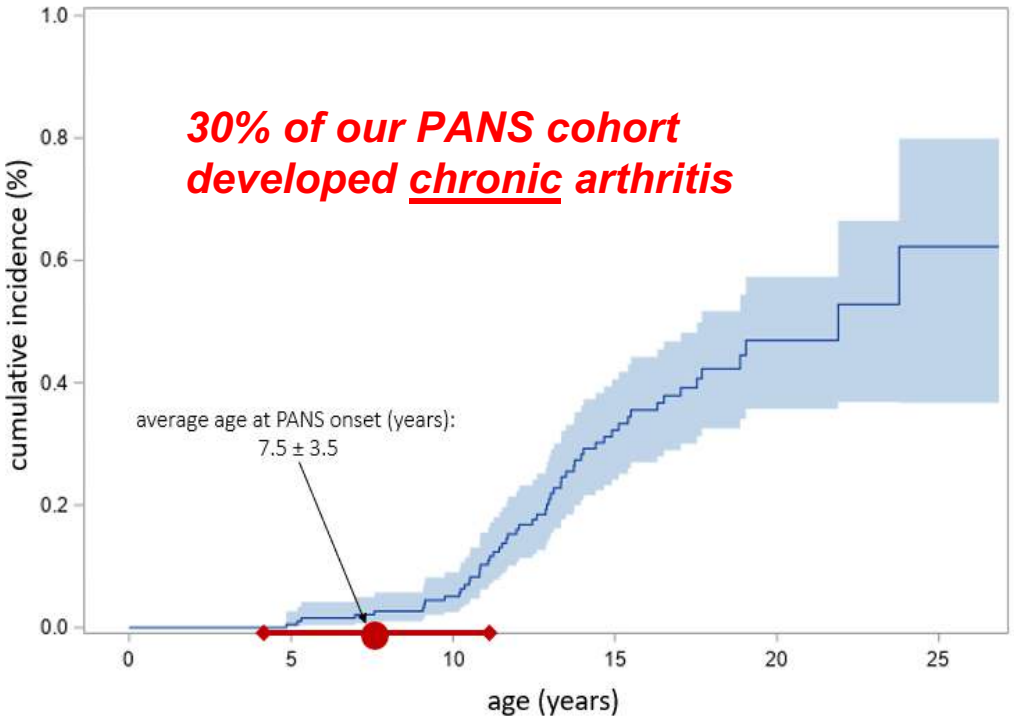
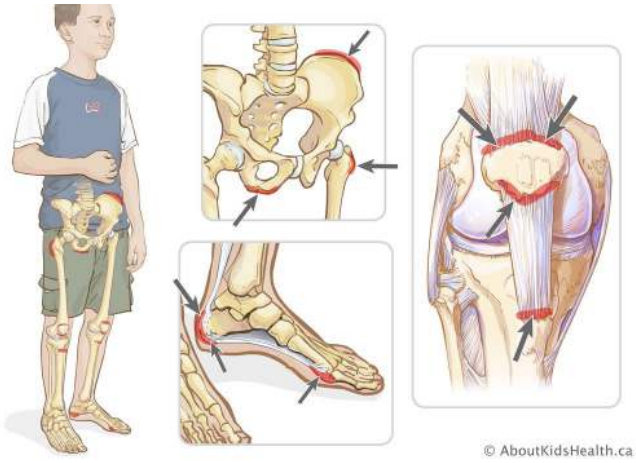
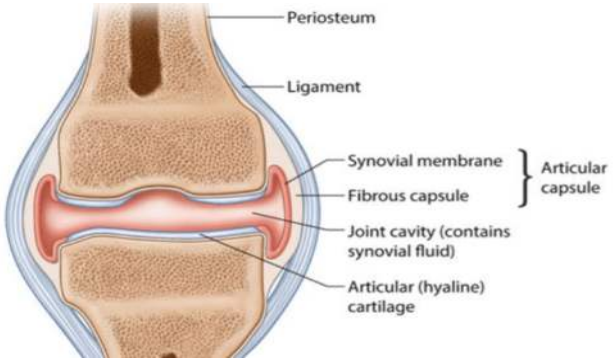
cumulative incidence (95% CI) of juvenile-onset arthritis by age





Features of Arthritis in PANS

- Arthritis is dry
- Spondylitis
- Enthesitis
- Capsular thickening in 30%



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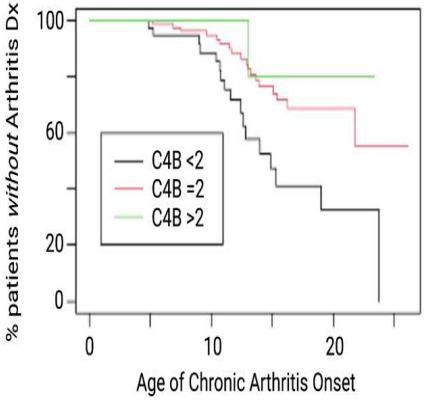


b

CN comparison	Time to Chronic Arthritis Onset			Time to Autoimmune Disease Onset		
	HR	95% CI	p-value	HR	95% CI	p-value
C4A <2 vs. C4A = 2	0.55	0.16 - 1.8	0.32	0.47	0.06 - 3.7	0.48
C4A >2 vs. C4A = 2	0.71	0.32 - 1.6	0.40	0.99	0.32 - 2.9	0.99
C4B <2 vs. C4B = 2	2.7	1.4 - 5.2	**0.004**	2.8	1.0 - 7.7	0.05
C4B >2 vs. C4B = 2	0.57	0.08 - 4.3	0.58	3.8	0.77 - 18	0.10

Agnieszka Kalinowski

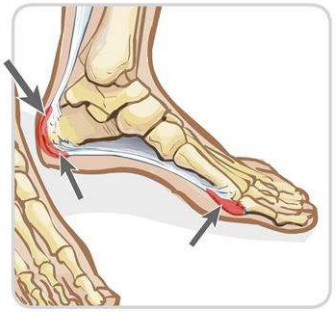
Mei Ma

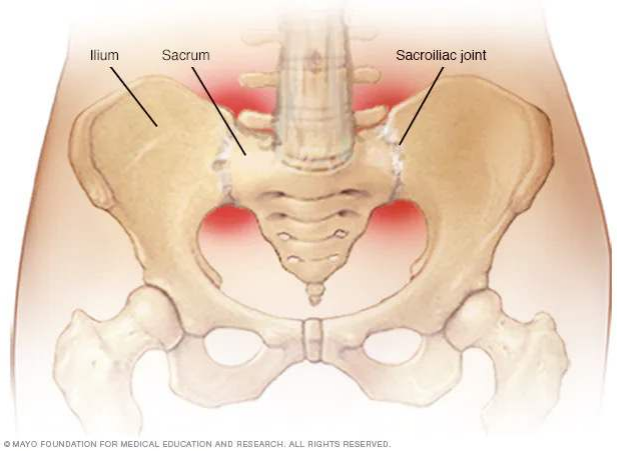
Stanford University

Most common sites of tenderness

193 patients who met strict PANS criteria

Distal Interphalangeal Joints (DIP)	84 (43 %)
Spinous process tenderness	77 (40 %)
Sacroiliac joint tenderness	68 (35 %)
Achilles tendon insertion (heel enthesitis)	50 (26 %)

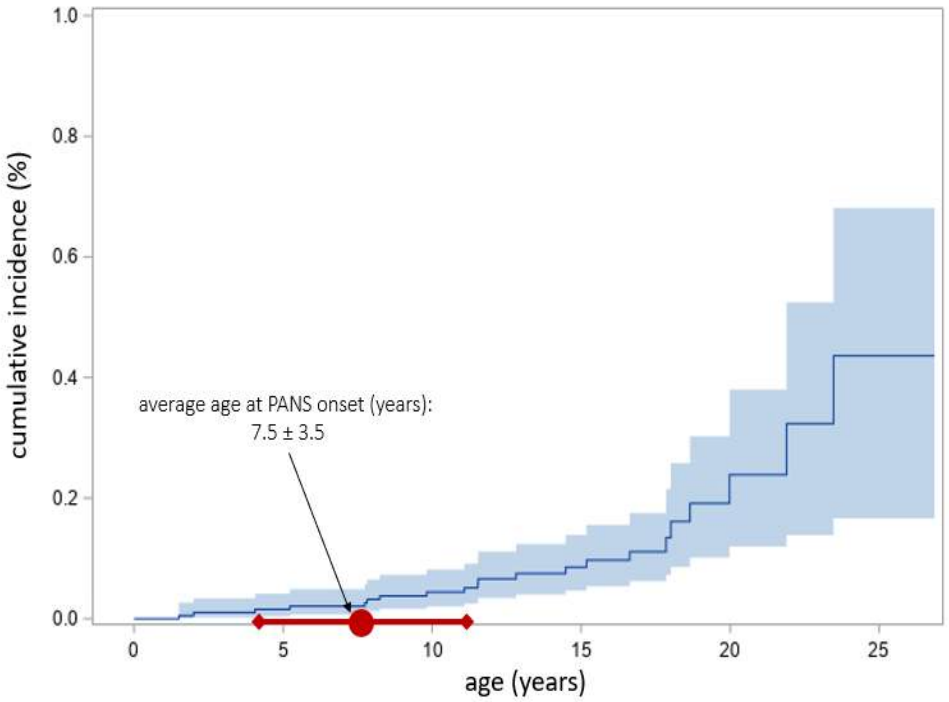




Mei Ma

Stanford University

cumulative incidence (95% CI) of autoimmune/inflammatory diseases (beyond arthritis and PANS) by age



20% of our cohort developed autoimmune disease (thyroiditis, psoriasis, celiac, Behcets, Lupus, etc.) by age 18

EPIDEMIOLOGY studies show association between OCD & Eating Disorders with Autoimmunity

1) A total-population multigenerational family clustering study of autoimmune diseases in obsessive-compulsive disorder and Tourette's/chronic tic disorders

Mataix-Cols, D., Frans, E., Pérez-Vigil, A., Kuja-Halkola, R., Gromark, C., Isomura, K., Fernández de la Cruz, L., Serlachius, E., Leckman, J. F., Crowley, J. J., Rück, C., Almqvist, C., Lichtenstein, P., & Larsson, H. (2018). Molecular psychiatry, 2017

2) Eating Disorders, Autoimmune, & Autoinflammatory Diseases

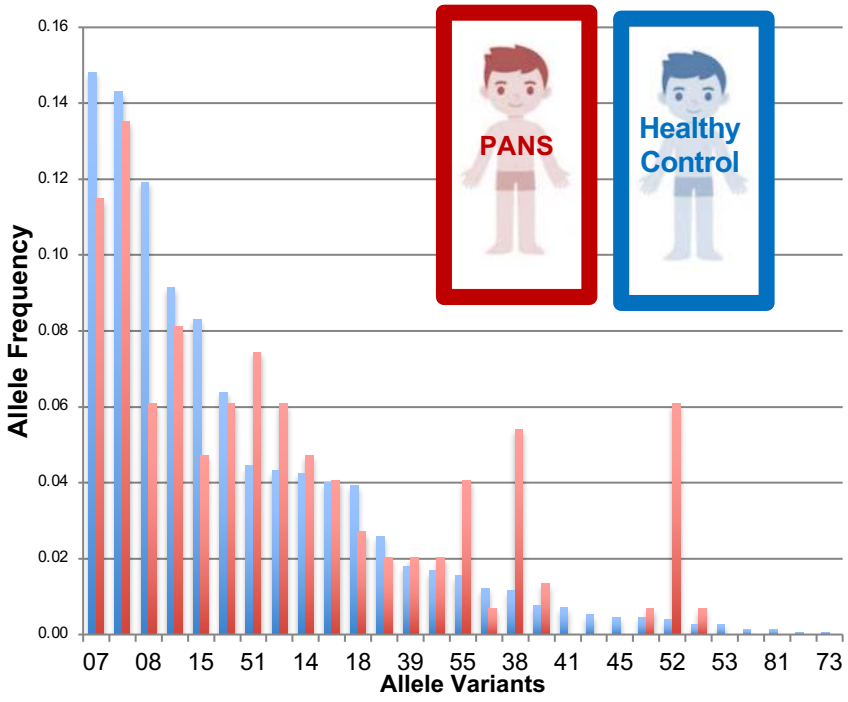
Stephanie Zerwas, PhD et al. PEDIATRICS, 2017

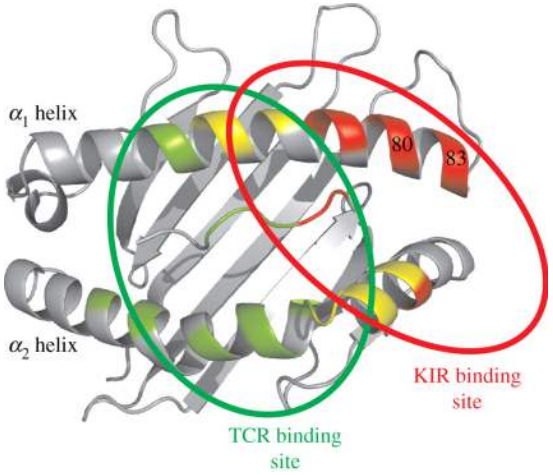
Mei Ma

Jenny Frankovich

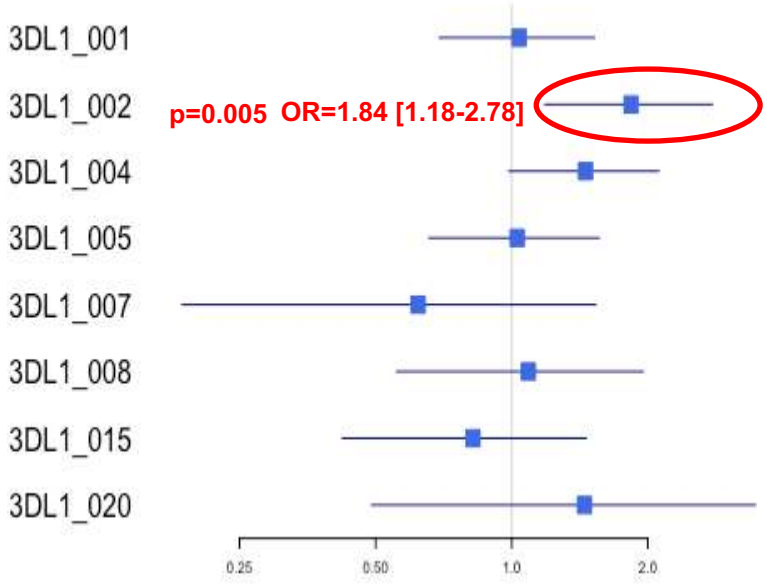
Stanford University

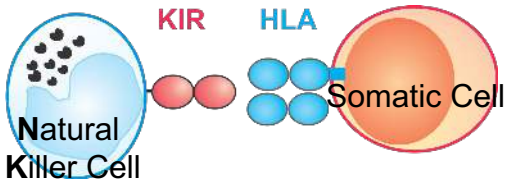
HLA-B allelic variants





KIR3DL1*002 with HLA-Bw4 confers risk for PANS





HLA-Bw4 epitope is defined by positions 80-83

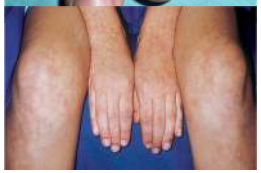
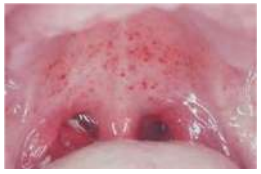
HLA-Bw4 mediates binding to inhibitory receptor KIR3DL1 on surface of NK cells

Jill Hollenbach
UCSF
Neuroimmunology

nford University

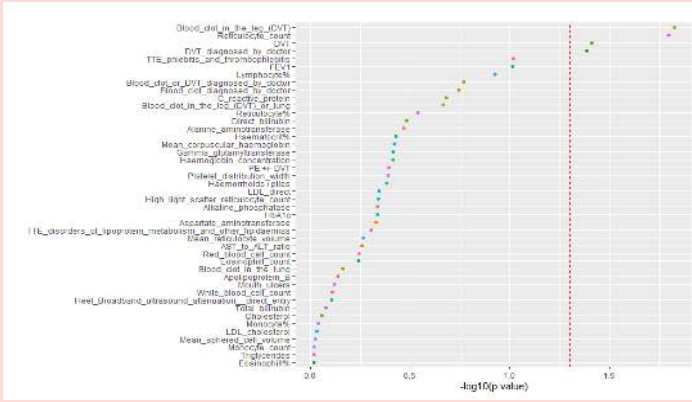
Stanford PANS Cohort

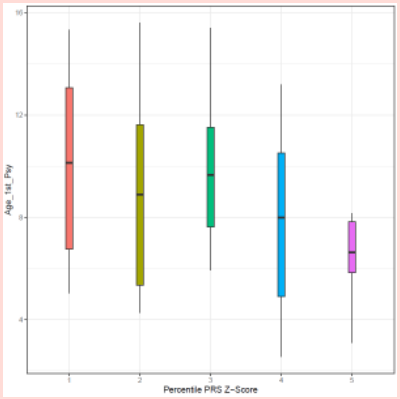
Indirect Signs of Vascular Inflammation and/or Injury at Presentation*

Dermatological Exam		N%
	**Prominent onychodermal band**	33%
	**Periungual redness/swelling**	13%
	**Livedo Reticulitis**	33%
	**Palatal Petechiae**	7%

*At presentation (defined as within four months of symptom onset)

Higher Blood Clot
Polygenic Risk Score (PRS)
previously associated with COVID1
shows a trend towards the association w
younger age 1st psychiatric deteriorati





Percentile PRS for blood clot on PANS patients

1=lower percentile; 5= highest percentile)

Carlos Bustamante, PhD

Stanford MEDICINE

Non-specific signs of Immune dysregulation & Inflammation in consecutive patients with PANS (n=147)

Blood Dyscrasia	
Leukopenia	14%
Lymphopenia	14%
Autoantibodies	
Positive Anti-Nuclear Antibody	26%
High Anti-Histone Antibody	17%
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Prevalence of iron deficiency anemia
→ 1.5-fold higher than age- and sex-matched U.S population (CDC data)

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C4 gene copy number in PANS is not different compared to controls

Stanford University

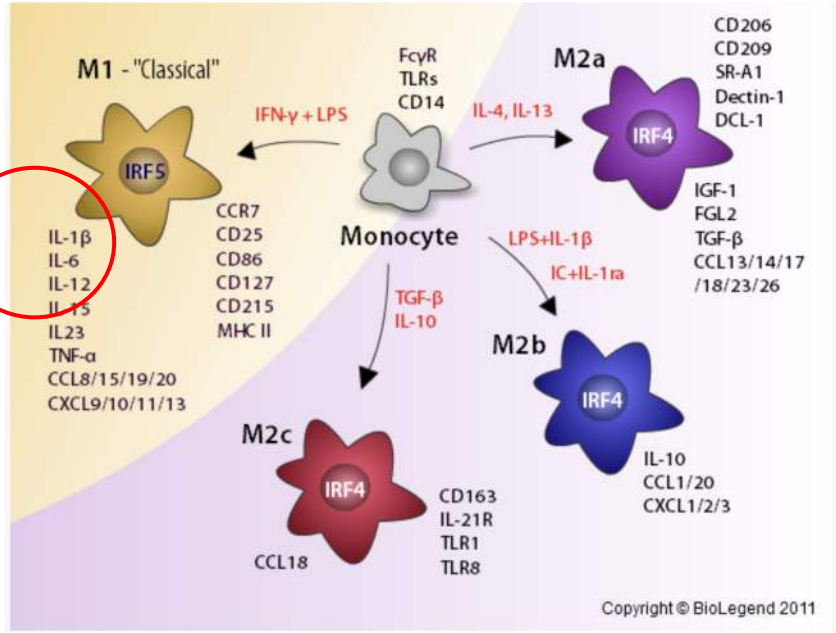
Monocytes in PANS

M1-phenotype (pro-inflammatory):

- induced by IFNg and LPS
- $CD86^{hi}CD206^{lo}$ with high levels of CD64, CD80 and HLA-DR.
- Express inflammatory mediators

M2-phenotypes (anti-inflammatory):

- induced by Th2 cytokines, (TGF-b, IL-10)
- Express $CD206^{hi}$ $CD163^{hi}$
- $CD86^{lo}$ $CD86^{lo}$
- Express anti-inflammatory mediators



Betsy Mellins, MD

Shamma Rahman, PhD

Note: these phenotypes are an over-simplification

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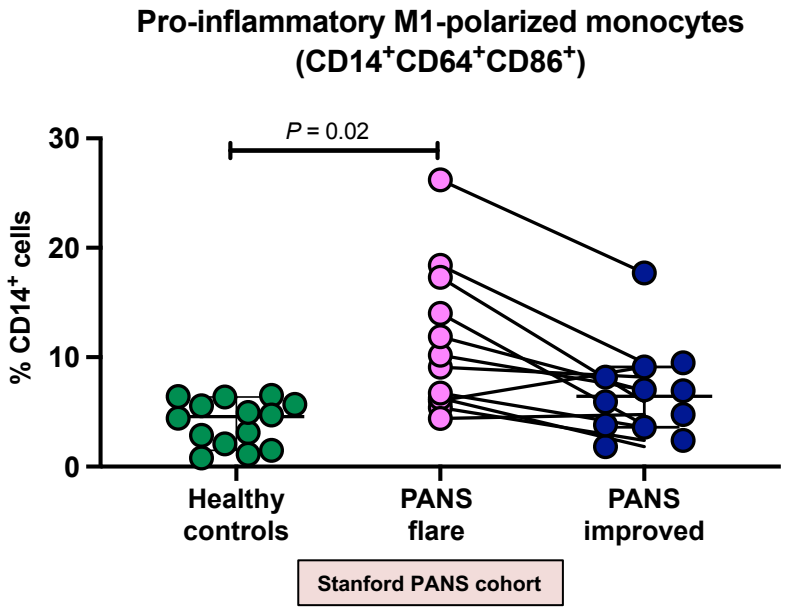
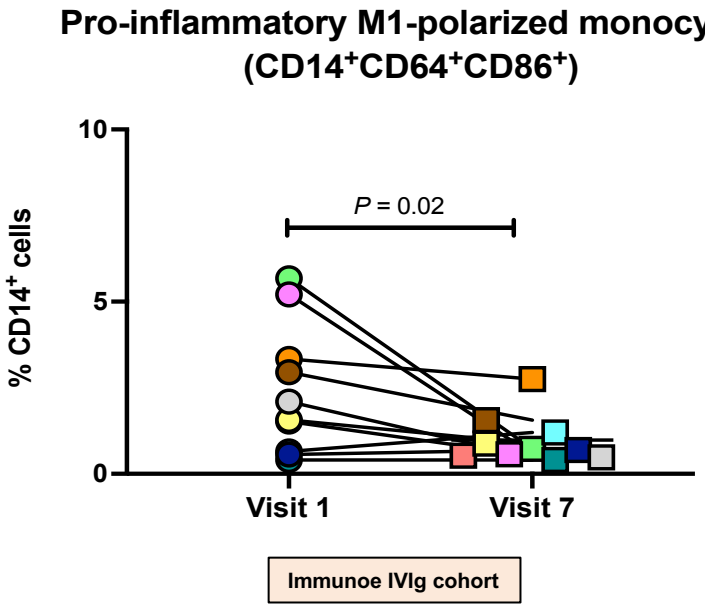
M1-polarized (pro-inflammatory) monocytes elevated in flare and diminish with improved status





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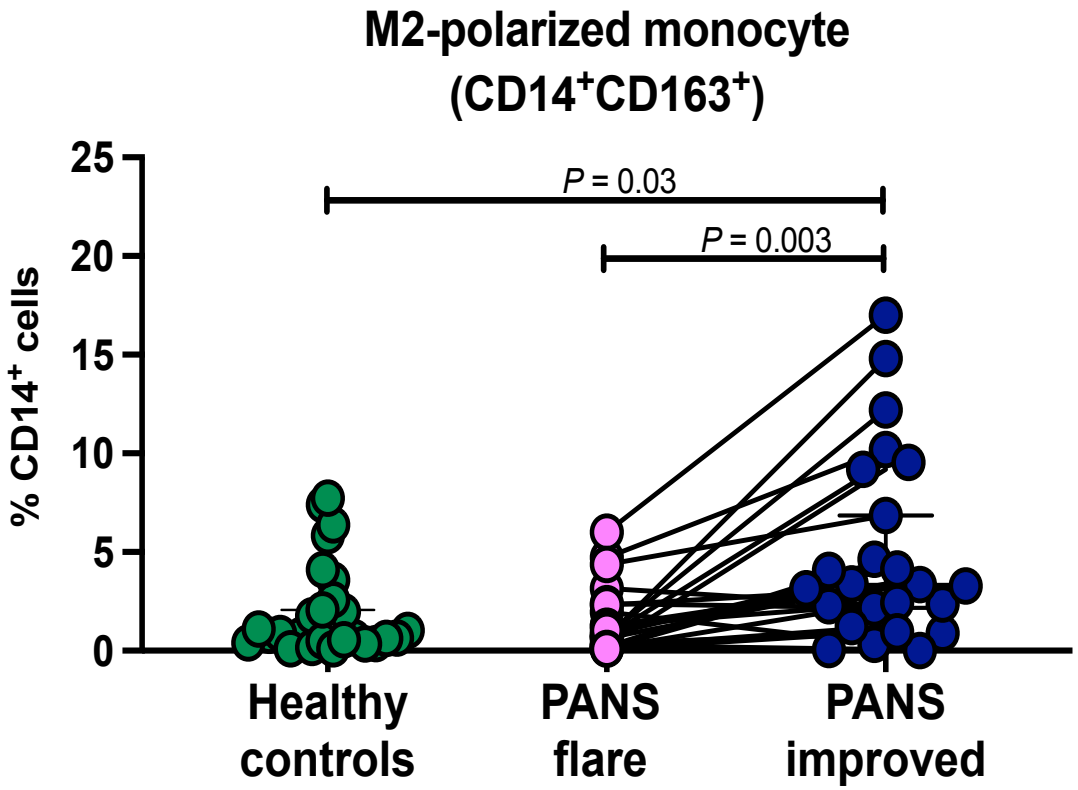
M2-polarized (anti-inflammatory) monocytes are low in flare and elevated in improved state



Stanford PANS cohort

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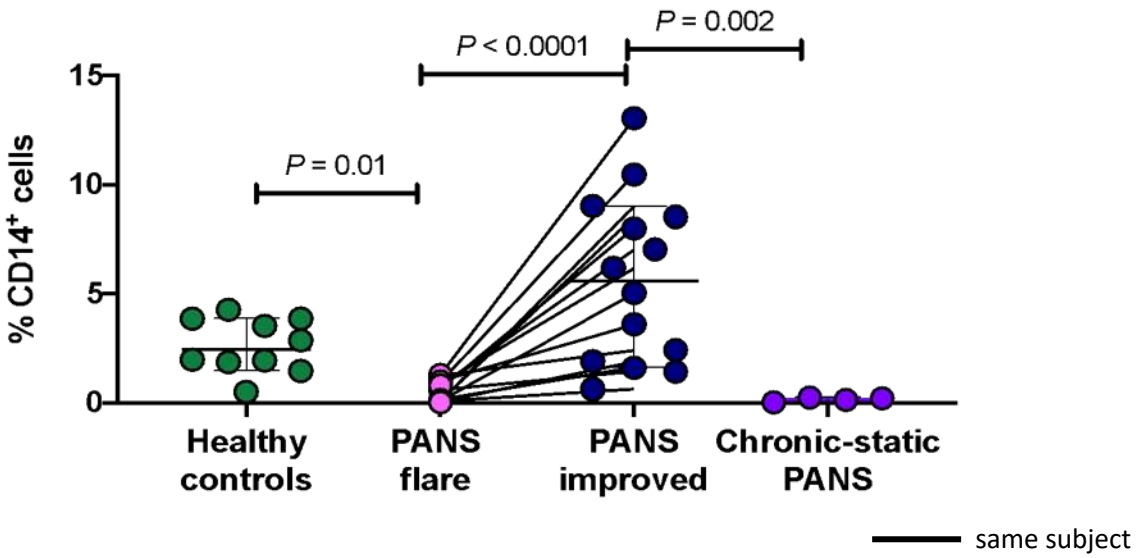
Repairing brain-homing monocyte (a novel candidate monocyte subset)

Markers: XXXX. XXXXX. XXXXX. XXXX



Repairing brain homing monocytes

- *Low in blood during flare but **found in spinal fluid of flaring PANS patients who recover** (n=7/7)*
- *These cells are very **low in blood in chronically active PANS** & **not in their spinal fluid (n=5),** suggesting low production*

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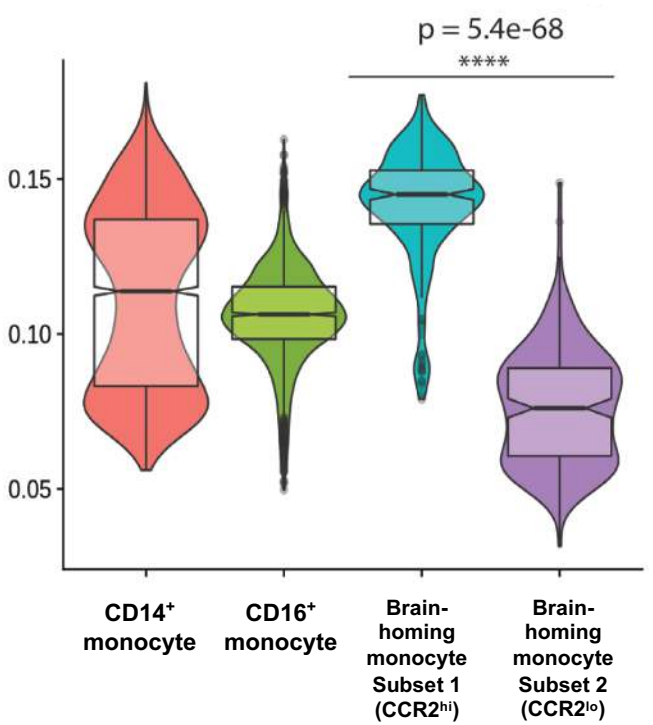
Immunosuppressive/anti-inflammatory gene expression in brain-homing CCR2^{hi} monocytes

MARKER	FUNCTION
CD163	scavenger receptor on alternatively activated (M2) monocyte/macrophages
TGFB	anti-inflammatory cytokine; inhibits proinflammatory activation of macrophages, upregulates CX3CR1
CCR1	chemokine receptor for CCL3, made by astrocytes and activated microglia
VLA-4	promotes extravasation of monocytes into brain
TNFSF13	APRIL; immunomodulatory receptor on M2 macrophages
IL10RA	inhibits synthesis of proinflammatory cytokines
IL-10	anti-inflammatory cytokine; downregulates MHC class II, co-stimulatory molecules on macrophages

Expression of immunosuppressive genes across monocyte subsets



Müller, S *et al.* Single-cell profiling of macrophage ontogeny
Genome Biol **18,** 234 (2017)


Betsy Mellins, MD Achia Khatun, PhD
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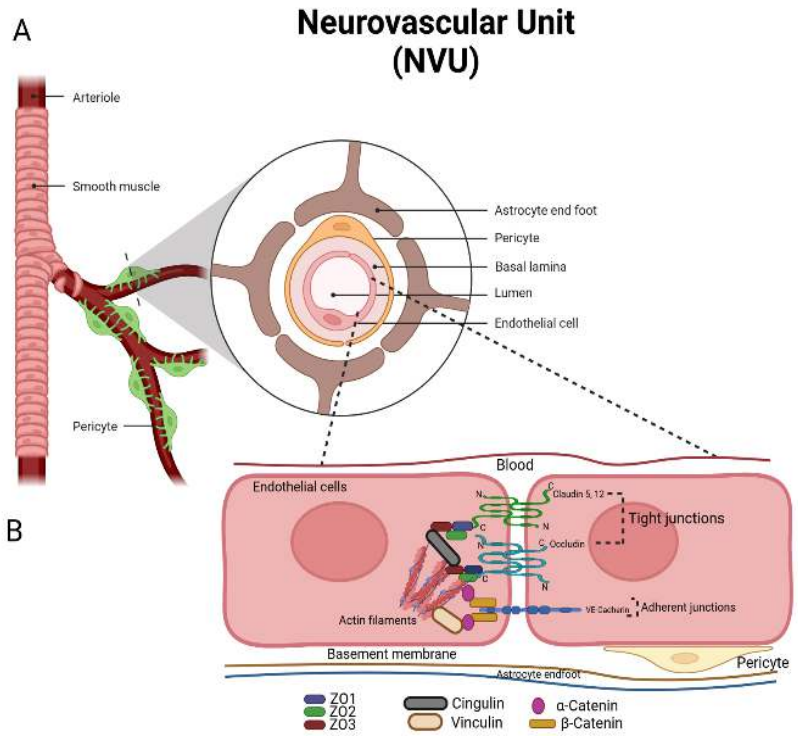
Blood brain barrier



BBB comprised of different cell types.

- **Brain endothelial cells (BEC)**
- Basement membrane (agrin= heparin sulphate)
- Regulated by astrocytes, pericytes

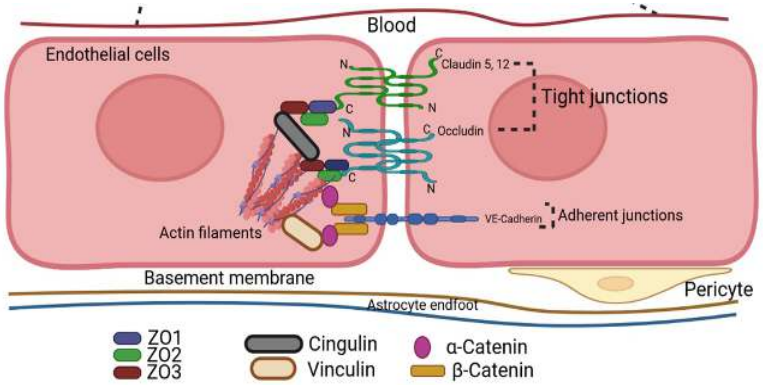
Brain endothelial cells (BEC)

- Express transporters & tight junctions
- Regulate solute movement into the CNS

BBB homeostasis/integrity

- Efflux transporter: **pGp**
- Solute carrier transporters: **GLUT 1, LAT1, MCT1**
- Transferrin receptors
- Tight junction proteins
  - →prevent transport of bacteria, large molecules, and most small molecules into the brain.
  - → only fat soluble <400 Da molecules cross the BBB
- Adherens junction proteins

Blood brain barrier



Tight Junctions (TJs)

Claudins:

- Involved in maintaining paracellular TJs between endothelial cells (EC) and in the maturation of BBB.
- Subtypes 1, 3, 5 and 12 are expressed on EC TJs; Claudin 5 is the major contributor.

Occludin:

- Maintains trans-endothelial resistance at the BBB and aids in assembly of Claudin 5 at TJs.

ZO1:

- Maintains integrity of brain EC, stabilizing claudin 5 and Occludin interactions.

Adherens Junctions

- Located at basolateral end of endothelial cells; Vascular endothelial (VE), neural (N), and epithelial cadherins are present in BEC, but **VE-cadherins** are the most abundant.
- Intracellular domain of **VE-Cadherin interacts with catenins** to maintain junctional stability and also forms homophilic interactions between adjacent endothelial cells.
- **Stabilizes TJs by increasing expression of Claudin 5**

Other Functions of Brain Endothelial Cells (BEC)

- **Cell adhesion molecules** (VCAM1, ICAM1) **on BEC control leukocyte infiltration.**
- **BECs restrict free transport of solutes from circulation by limiting expression of transporters**, such as GLUT1, MCT1, LAT1, and MFSD2a
- Pericytes maintain low level of transcytosis by BEC

BBB Disruption Mechanisms

- Loss of tight junction and adherent junction proteins
- Increase in transcytosis
- Alteration in transporter proteins
- Increased expression of leukocyte adhesion molecules (VCAM, ICAM)

Hypothesis

Plasma from active PANS patients contains factors that alter cellular functions of the BBB

- **Plasma factors, ↑cytokines, ↑chemokines** are associated with neurological disorders and BBB dysfunction.
  - **Albumin**: Cross BBB and triggers neurodegeneration in Alzheimer's disease (PMID: 35363449)
  - **Thrombin**: Causes BBB dysfunction in intracerebral hemorrhage (ICH) and promotes brain damage, including edema, glial activation, and neuronal cell death through PAR-1 activation cascade (PMID: 24323711)
  - **Cytokines and chemokines**:
    - IL 6, TNFa, IL1b, VEGFA, CCL2, GM-CSF
      → impair TJ and adherns junction integrity on ECs.
    - Cytokine effects on ECs stimulate MMP9 activation
      → downregulation of protective hedgehog signaling pathway
      → Disrupts TJ interactions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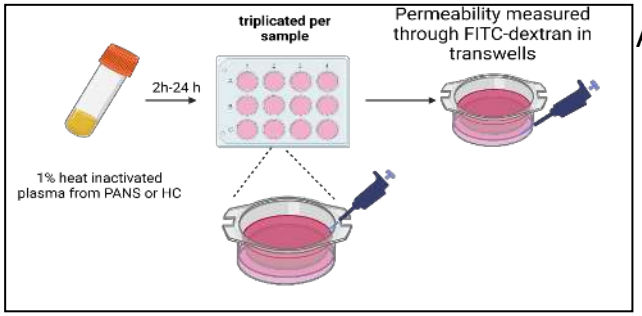
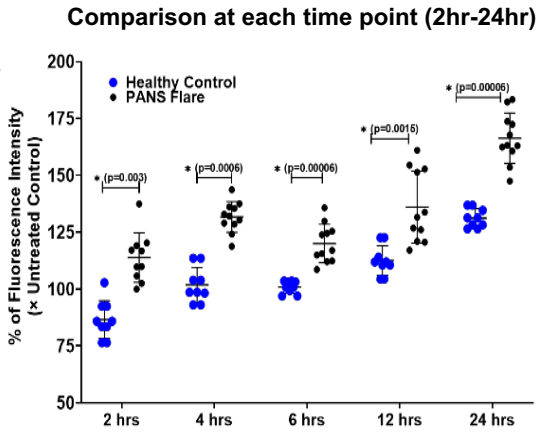
Increased permeability of human BEC monolayer after exposure to PANS plasma vs healthy control plasma



A.



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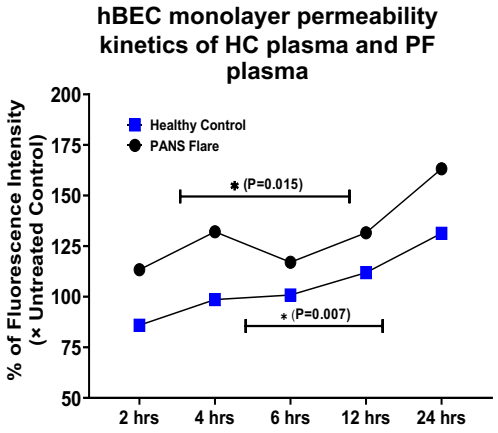

100% refers to no permeability

Summary: Permeability consistently and significantly increased over 2-24 hrs with PANS compared to healthy control plasma.

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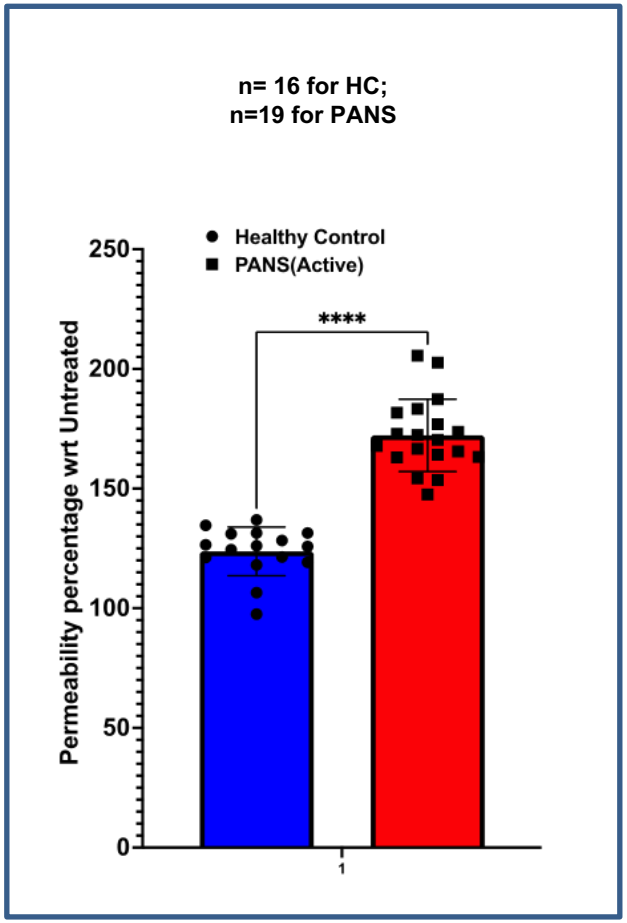
Permeability of human BEC monolayer after exposure to PANS plasma vs healthy control plasma



100% = no permeability

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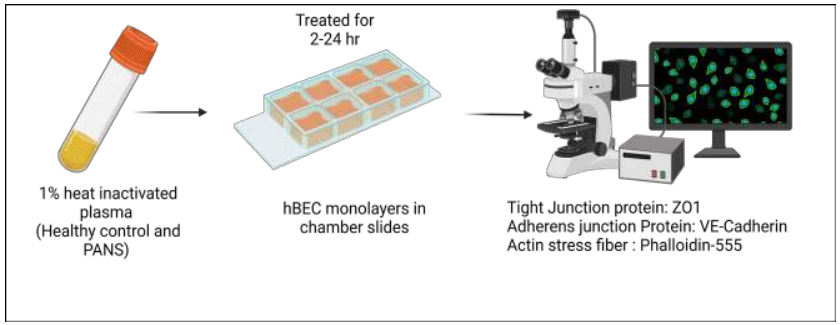
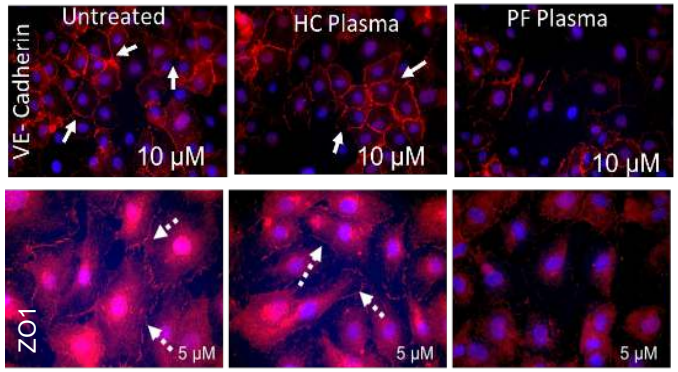
PANS plasma alters the physiology of Brain Endothelial Cells (BEC)

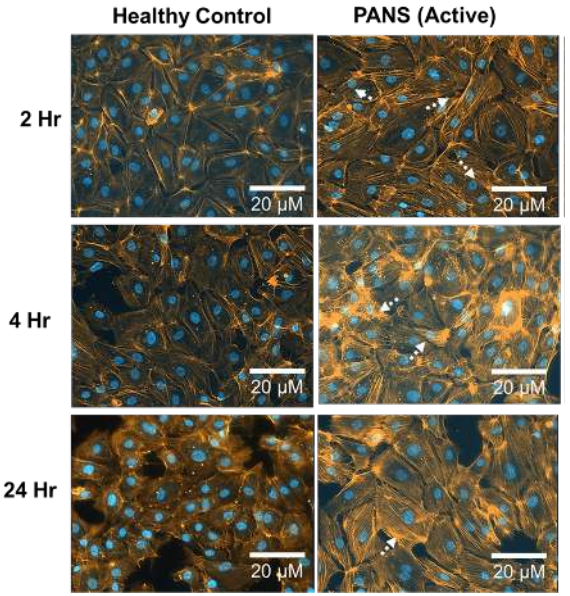




PANS plasma caused:

- Disruption of adherens junction protein (VE-cadherin)
- Disruption of TJ protein (ZO1)

Actin stress fiber formation



Phalloidin to mark F-actin in BEC after plasma exposure at different time points.
Dense yellow stain represents actin stress fiber
→Stress fiber formation increased with plasma from active disease with increasing time.

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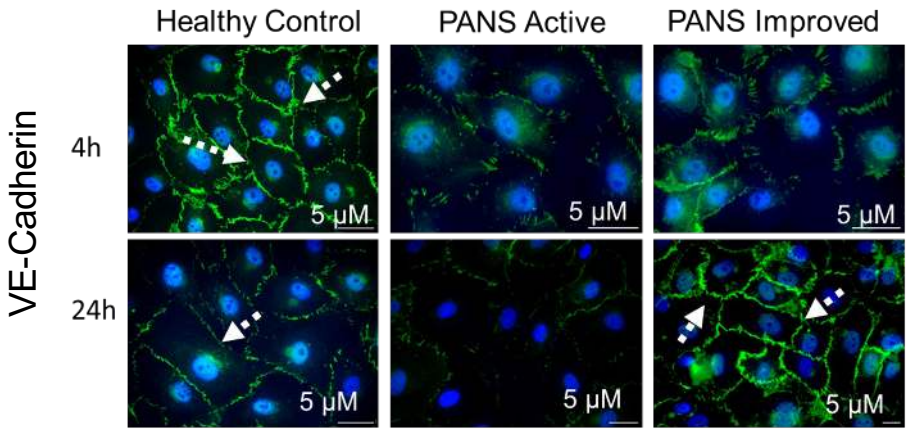
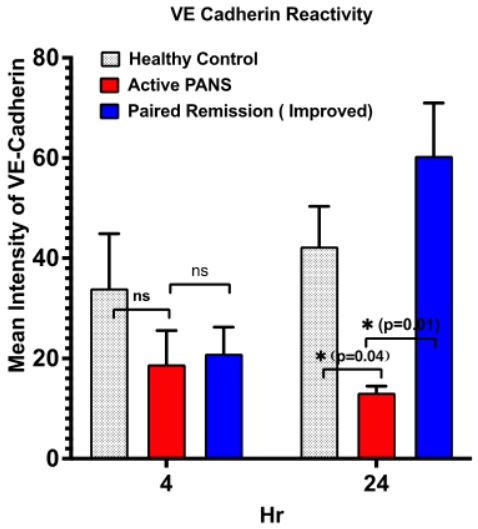
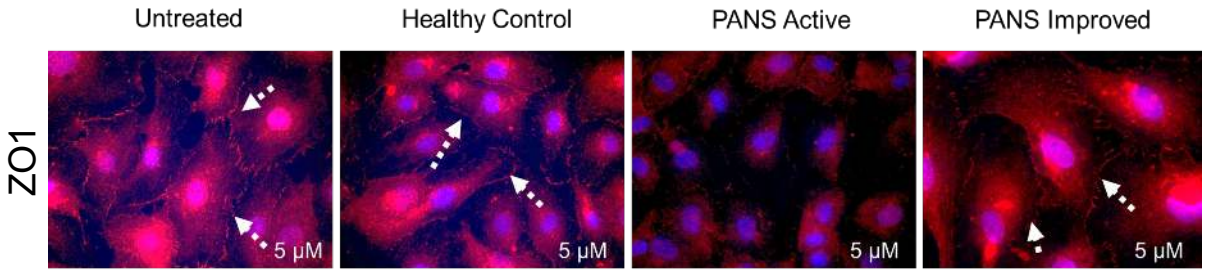
Plasma from the patients after clinical improvement maintained junctional integrity at 24 hrs







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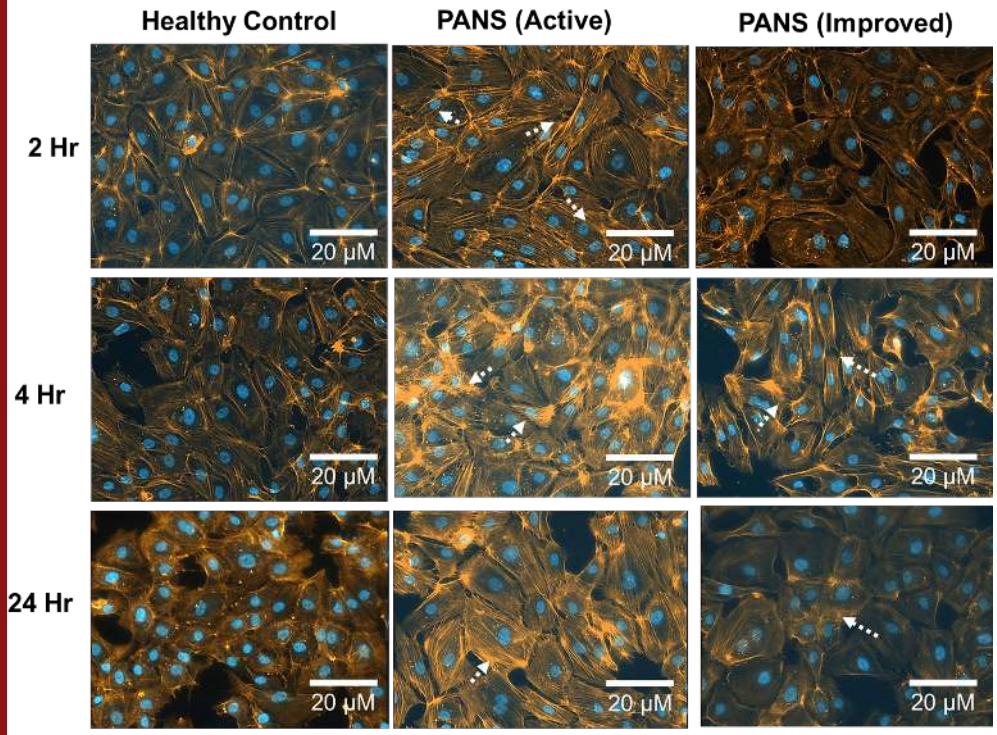
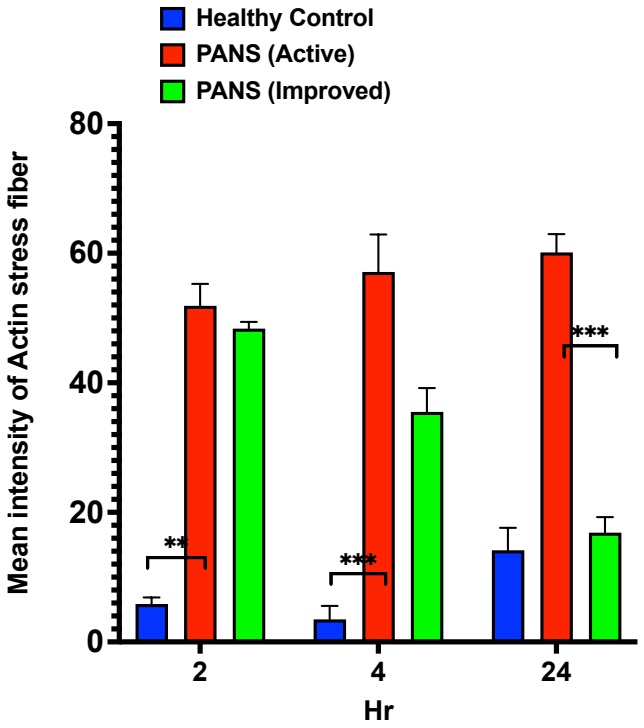
Reduced actin stress fiber with PANS plasma after clinical improvement in 24 hr



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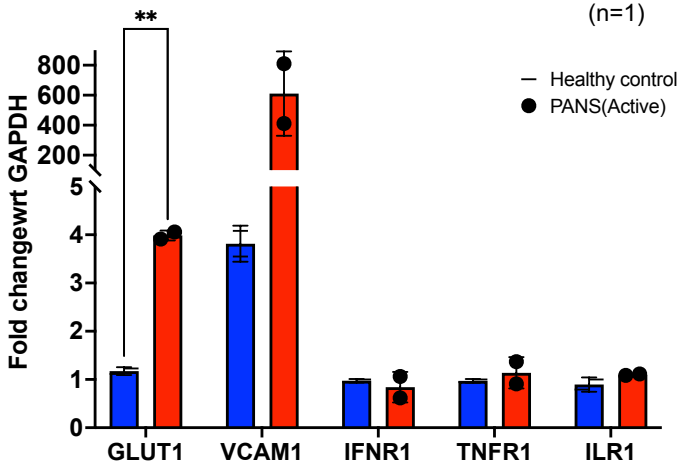
Gene expression study in BEC following treatment with plasma from PANS plasma & Healthy control plasma

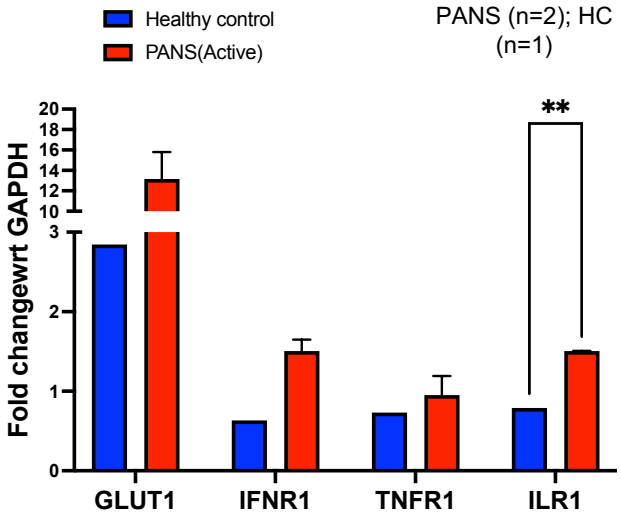
Treatment was done with 8 PANS plasma and 8 age and sex matched HC

12 hrs



Glut1 and VCAM1 expression significantly increased in 12h

24 hrs



Glut1, IFNR1, ILR1 expression significantly increased in 24h

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Summary of BBB Results

Plasma (heat inactivated; 1% treatment volume) from **active PANS plasma** significantly **increased BEC monolayer permeability** at 6-12 hrs.

PANS improved plasma maintained junctional integrity & reduced actin stress fiber formation in 24 hrs compared **to active PANS plasma**


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Care Giver Burden in **PANS higher**
→ than caring for a parent with **Dementia.**

Severe psych symptoms at flare, tends **overshadows all other symptoms** (POTs symptoms , sensory amplification, fatigue, arthritis symptoms, etc).

After there is improvement in psych symptoms, patients develop
- Achiness from arthritis
- Pain syndromes
- Fatigue
- POTS

Most patients have **prolonged periods of inability to attend school, sports,** and **extracurricular activities.**

Families have more than one child affected by this spectrum of problems.

Families are exhausted, appear dysfunctional, and often do not have access to care (even for traditional psychiatry) and frequently pay out of pocket for care by alternative clinics.

Frankovich J, Leibold CM, Farmer C, Sainani K, Kamalani G, Farhadian B, Willett T, Park JM, Sidell D, Ahmed S, Thienemann M. The Burden of Caring for a Child or Adolescent With Pediatric Acute-Onset Neuropsychiatric Syndrome (PANS): An Observational Longitudinal Study. J Clin Psychiatry. 2018 Dec 11;80(1) PMID: 30549499 doi: 10.4088/JCP.17m12091

Farmer C, Thienemann M, Leibold C, Kamalani G, Sauls B, Frankovich J. Psychometric Evaluation of the Caregiver Burden Inventory in Children and Adolescents With PANS. J Pediatr Psychol. March 2018. doi:10.1093/jpepsy/jsy014.

Calaprice D, Tona J, Parker-Athill EC, Murphy TK. A Survey of Pediatric Acute-Onset Neuropsychiatric Syndrome Characteristics and Course. J Child Adolesc Psychopharmacol. 2017 Sep;27(7):607-618. doi: 10.1089/cap.2016.0105. Epub 2017 Jan 31. PMID: 28140619.

PAIN & PANS

Prevalence rates of pain (not due to injury) 109 consecutive patients with PANS

	Symptoms present at least one time point n (%)	Symptoms present for > 3 consecutive months n (%)
Pain episode not due to injury or arthritis	98 (90%)	73 (67%)
Clinician's diagnosis of pain amplification	47 (43%)	39 (36%)
Clinician's diagnosis of fibromyalgia	NA	13 (12%)
Fibromyalgia criteria met (using ACR-tool)[d]	NA	16 (15%)

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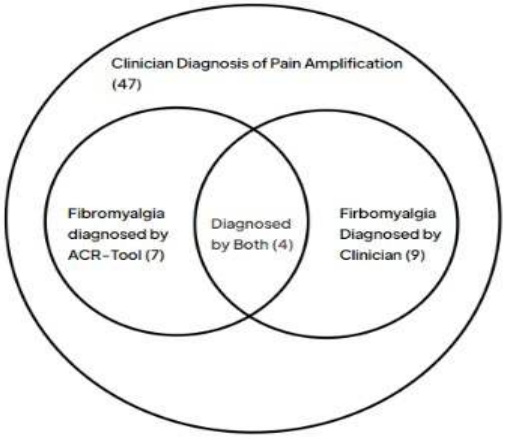

PAIN & PANS

Sensory disturbance/amplification 109 consecutive patients with PANS

	Symptoms present at least one time point n (%)	Symptoms present for > 3 months n (%)
Sensory disturbances, N (%)	69 (65%)	48 (45%)
Cold intolerance	36 (34%)	10 (9%)
Heat intolerance	38 (36%)	16 (15%)
Noise sensitivity	76 (71%)	39 (36%)
Light sensitivity	71 (66%)	35 (33%)
Smell/taste sensitivity	64 (60%)	28 (26%)
Touch/texture sensitivity	66 (62%)	28 (26%)
Shooting or burning pain	33 (31%)	8 (7%)
Numbness	17 (16%)	1 (1%)

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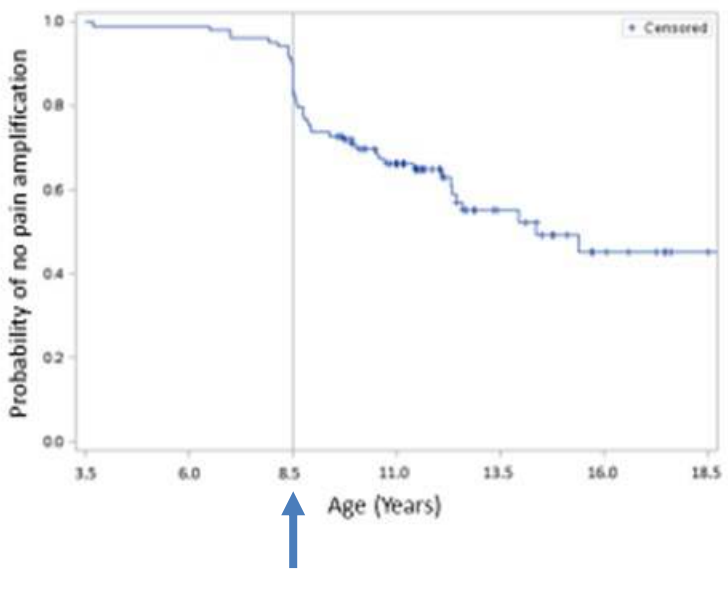
PAIN & PANS

Time-dependent risk of developing pain amplification In 109 consecutive patients with PANS



Pain amplification

- Diagnosed in 47/109 (**43%**) patients with PANS.
- Risk was highest at time of PANS onset
- 8 patients diagnosed w/ pain amp prior to PANS
- 39/47 (83%) had it for more than 3 months

Patients with Pain Amp were more likely to have:

→ **Arthritis**
→ **Period of chronic psychiatric illness**
→ **Higher global impairment & caregiver burden at clinic entry**
→ Higher peak myofascial points (9 vs 2)

compared to those without pain amp ($p < 0.01$).

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PAIN & PANS

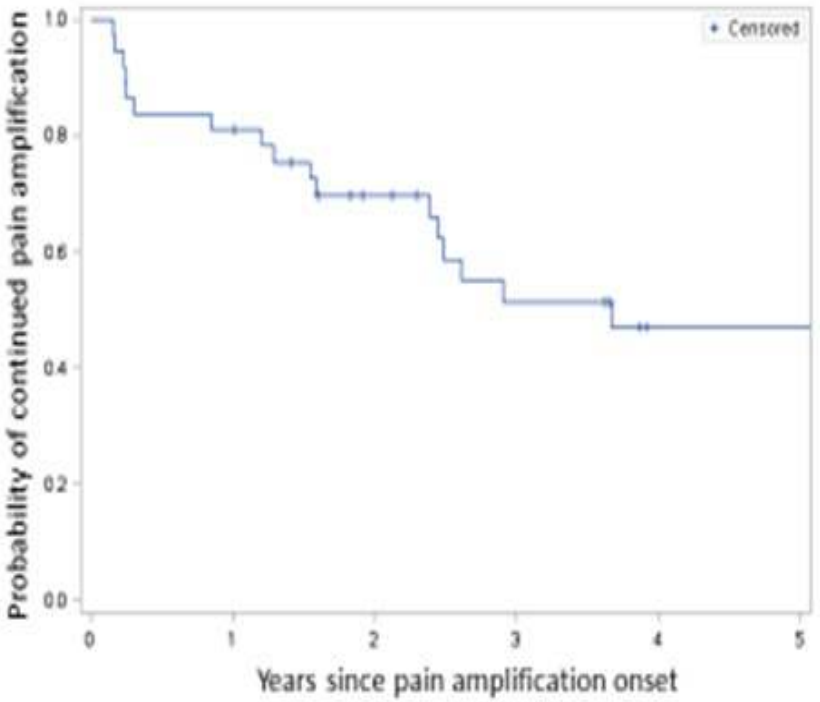
47 patients diagnosed with pain amplification

Definition of pain amplification:
Pain is out of proportion to physical exam findings.

Characteristic	Number (%)
Prominent location of amplified pain[a]	
Widespread body pain	30 (64%)
Localized limb or back pain	11 (23%)
Chronic, recurring headaches	12 (26%)
Abdominal pain	15 (32%)
Functional impairment due to pain	
Reduced or stopped school	18 (38%)
Reduced or stopped sport	17 (36%)
Referral	
Neurology for headaches	24 (51%)
Gastroenterology for abdominal pain	21 (45%)
Pain team	11 (23%)
Physical therapy	34 (72%)
Cognitive behavioral therapy	46 (98%)
Biofeedback	22 (47%)
Treatments offered that may help with pain	
Gabapentin	28 (60%)
Tricyclic antidepressant (Amitriptyline)	8 (17%)
Duloxetine	5 (11%)
Low dose Naltrexone[c]	16 (34%)
Graded exercise teaching	36 (77%)

PAIN

Time-dependent remittance of pain amplification



18/47 (38%) eventually remitted.

Remittance from pain amplification was rapid in the weeks following initial diagnosis
* after 3 months, rate of remittance slowed.

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PANS & Fatigue

182 consecutive patients with PANS

	n=182
1. **Daytime fatigue**	
a. Reported in at least one encounter	
Moderate	65 (36%)
Severe	73 (40%)
b. Reported for ≥ 6 months continuously	
Moderate	47 (26%)
Severe	20 (11%)
2. **Waking unrefreshed**	
a. Reported in at least one encounter	
Moderate	63 (35%)
Severe	72 (40%)
b. Reported for ≥ 6 months continuously	
Moderate	39 (21%)
Severe	27 (15%)
3. **Exercise intolerance/post-exertional fatigue**	
a. Reported in at least one encounter	119 (65%)
b. Reported for ≥ 6 months continuously	44 (24%)
4. **Cognitive difficulties**	
a. Reported in at least one encounter	
Moderate	62 (34%)
Severe	65 (36%)
b. Reported for ≥ 6 months continuously	
Moderate	39 (21%)
Severe	13 (7%)
Meets 2015 IOM criteria for ME/CFS	53 (29%)

2015 Institute of Medicine (IOM) diagnostic criteria of myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS):

1. A substantial **reduction or impairment in the ability to engage in pre-illness levels of activity**
2. **Post-exertional malaise** (PEM)
3. **Unrefreshing sleep**

And **at least one** of the following two **additional manifestations** must be present:

1. Cognitive impairment
2. Orthostatic intolerance

Moderate
- Considerable problem often present at a moderate level.

Severe
- Severe, pervasive, continuous, life-disturbing problem

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Chronic Fatigue (ME/CSF) & PANS

Comparison between patients with and without ME/CFS

	Meet ME/CFS criteria (N=53)	Do not meet ME/CFS criteria (N=129)	P-value[a]
Demographics			
Age of PANS onset (years), mean ± SD	9.2 ± 3.5	8.3 ± 3.6	0.13
Follow-up time (years), mean ± SD	3.8 ± 1.7	2.9 ± 1.6	<0.01
Male gender	33 (63%)	79 (61%)	0.90
Non-Hispanic White	46 (87%)	101 (78%)	0.19
Comorbidities			
Fibromyalgia diagnosed by clinicians	12 (23%)	6 (5%)	<0.001
Pain amplification syndrome[b]	23 (43%)	11 (9%)	<0.001
Joint hypermobility	2 (4%)	8 (6%)	0.73
Depression/depressive symptoms	35 (66%)	54 (42%)	<0.01
Family history			
Chronic fatigue syndrome	2 (4%)	5 (4%)	1.00
Fibromyalgia	11 (21%)	11 (9%)	0.02
Obsessive compulsive disorder	13 (25%)	16 (12%)	0.04
Depression	37 (29%)	17 (32%)	0.65

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Chronic Fatigue & PANS

Time-dependent predictors of ME/CSF on Cox regression models.

	Unadjusted hazard ratio (95% confidence interval)	Adjusted hazard ratio (95% confidence interval)[a]
Malaise/fatigue score (at initial clinic visit)	1.32 (1.21-1.43)	1.20 (1.10-1.31)
Global impairment (at initial clinic visit)	1.02 (1.01-1.04)	1.02 (1.01-1.03)
Use of immunosuppressants [b] (prior to ME/CFS if present, or by the end of study period)	2.17 (1.24-3.79)	2.72 (1.45-5.10)
Use of high IVIG (prior to ME/CFS if present, or by the end of study period)	1.90 (1.08-3.23)	2.29 (1.24-4.26)
Competitive athletic training (prior to ME/CFS if present, or by the end of study period)	0.50 (0.28-0.87)	0.85 (0.43-1.69)

[A] Adjusted for gender, age of PANS onset, follow-up time, and global impairment score except malaise score and global impairment where the independent score was not added to the adjusted model due to strong correlations between the scores.

[B] Immosuppresants include pulses of methylprednisolone, oral steroids for >2 months, rituximab, methotrexate, and mycophenolate mofetil, prior to ME/CFS if present, or by the end of the study period in patients without ME/CFS.

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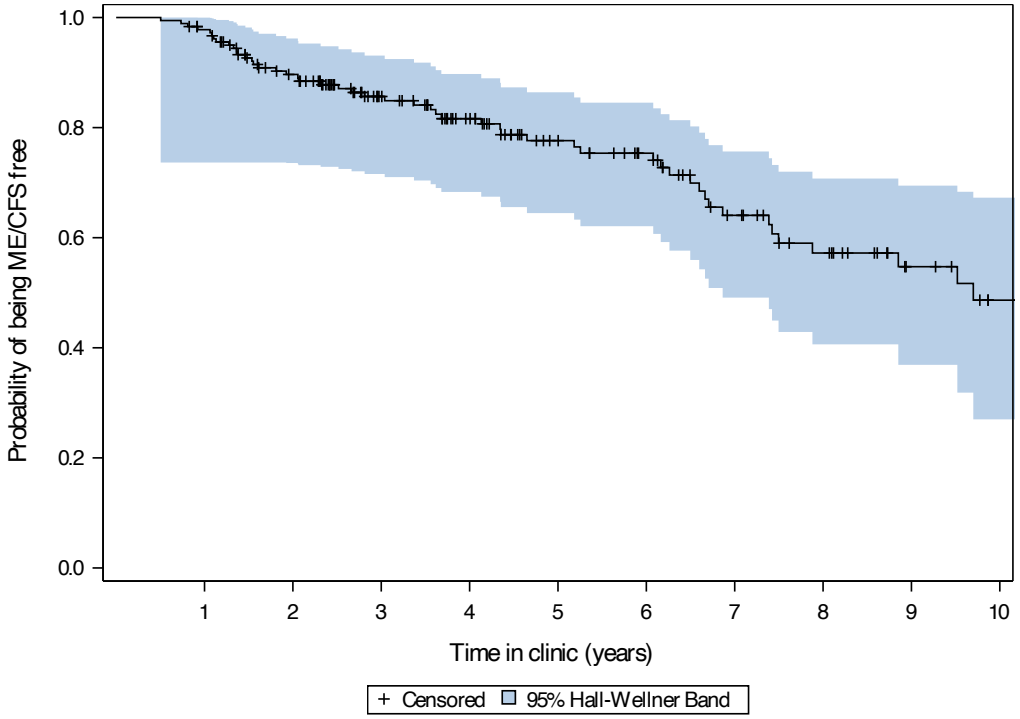
Chronic Fatigue

Time-dependent risk of developing myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS)



*Patients were censored at the last clinic visit.

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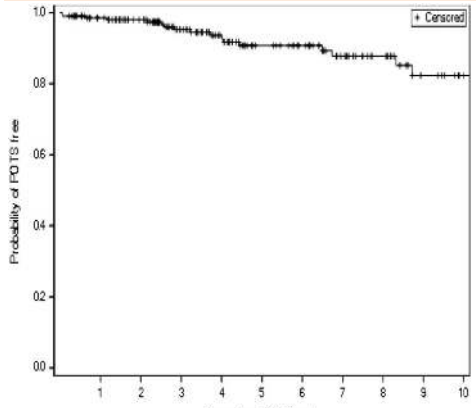
POTS & PANS

We screened 103 patients for POTS (fatigue, dizziness, palpitations, etc):

18% met criteria

POTS criteria:

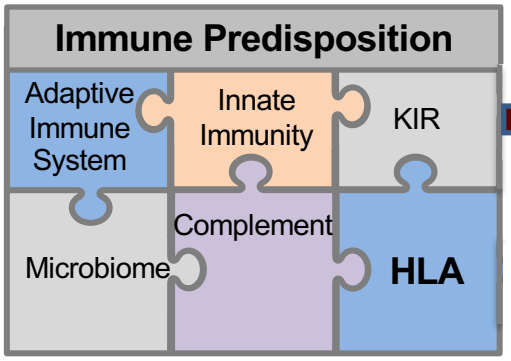
- **Presence of orthostatic intolerance symptoms (lightheadedness or palpitations)**
- **Frequent occurrence of symptoms when assuming upright position**
- **Exaggerated heart rate increase associated with postural change from lying to standing.**



Time-dependent risk of developing POTS in 204 consecutive patients PANS[a].

	POTS (N=19)	No POTS (N=84)	P value [a]
Age (years) at first clinic visit, mean ± SD	12.4 ± 4.1	10.3 ± 4.1	0.07
Male gender, N (%)	15 (79%)	46 (55%)	0.05
BMI at initial clinic visit median ± IQR	19.0 ± 9.1	19.3 ± 4.4	0.98
Weight loss 3 months leading up to fist clinic visit [b]	13 (68%)	43 (51%)	0.17
Comorbidities[c]			
Joint hypermobility	12 (63%)	31 (37%)	0.04
Headache	11 (58%)	39 (46%)	0.28
Gastrointestinal symptoms	10 (53%)	46 (55%)	0.99
Depression	10 (53%)	40 (48%)	0.57
Anxiety	7 (37%)	57 (68%)	0.02
Sleep problems	6 (32%)	43 (51%)	0.16
Chronic fatigue	8 (42%)	15 (18%)	0.03
Cognitive impairment	11 (58%)	44 (52%)	0.53
Family history, N (%)			
Chronic fatigue	1 (5%)	3 (4%)	0.56
POTS	3 (16%)	3 (4%)	0.07
Palpitations or syncope	2 (11%)	0	0.03

Chan A, et al. Children With PANS May Manifest POTS. *Front Neurol*. 2022;13:819636. doi:10.3389/fneur.2022.819636



Infections

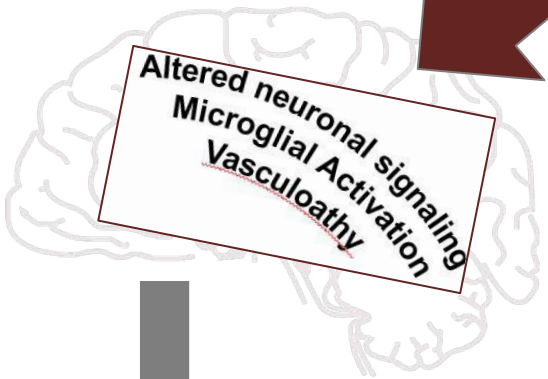
- Group A Strep
- Mycoplasma
- Other (COVID, etc)

Systemic Inflammaion
Vascular inflammation
Complement Activation

Autoantibodies, Monocytes, +/- Cytokines +/- other immune mediators

Disruption of Blood BBB

Data → guide treatments



Arthritis & Autoimmune Disease

PANS & associated symptoms (POTS, fatigue, pain amp)

Stanford University

PANS-Illuminate-Project

Shedding a light on systems-level biology of a rare disease

Infection Triggered Sequelae Collaboration
PANS/PASC/POTS/Dementia

Stanford PANS Dollinger Biomarker Discovery Core

Jennifer Frankovich
& Collaborators

First Flare
Best Remission
Most Recent Flare
Healthy Control

Total Patients= 251
(PANS= 170)
Total Controls= 95

- Autoantibody arrays
  - REAP-Exoproteome (Aaron Ring, Fred Hutch)
  - Connective Tissue array (Utz/Preston, Stanford)
  - Viral antigen array (Utz/Preston, Stanford)
  - GPCR beads (Utz/Preston/Kobilka, Stanford)
  - Epitope mapping (Serimumme)
- MHC/HLA (Hollenbach, UCSF)(Vina-Fernandez, Stanford)
- Proteomics
  - SomaLogics
  - Mass Spec (Zetterberg, U of Gothenburg, UK Dementia Research Institute)
- Metabolomics
  - Clary Clish (Broad Institute, Harvard)
- Human Genetics
  - Bulk RNA sequencing
  - Exomes/GWAS/Invitae
  - Methylation/Epigenetics

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Lucile Packard Children's Hospital Stanford

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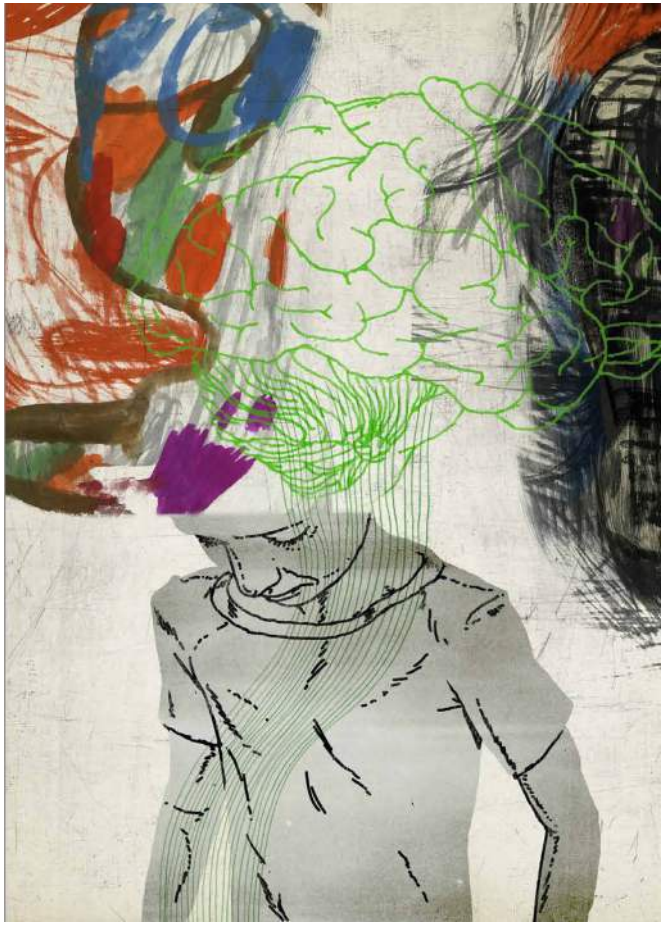

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