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An Update on PANDAS Treatment and Research

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Disclosures

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My spouse/partner and I have the following relevant financial relationship with a commercial interest to disclose:

- **Consulting: Pfizer, USA**
- **Research Funding: Octapharma, USA**

- **I will discuss the off-label use of the following medications/therapies for the treatment of PANS/PANDAS, OCD:**
- **Intravenous Immunoglobulin (IVIG)**
- **Non-Steroidal Anti-inflammatory Drugs (NSAIDs)**
- **Antibiotics**

Introduction

‘It is quite a common thing for children of tender years to be sent to mental institutions, but it is somewhat unusual for mental disorder of such a degree as to require certification to occur in a boy æt. 10 who had previously been of sound mind’

-Encephalitis Lethargica

Obsessive compulsive disorder (OCD)

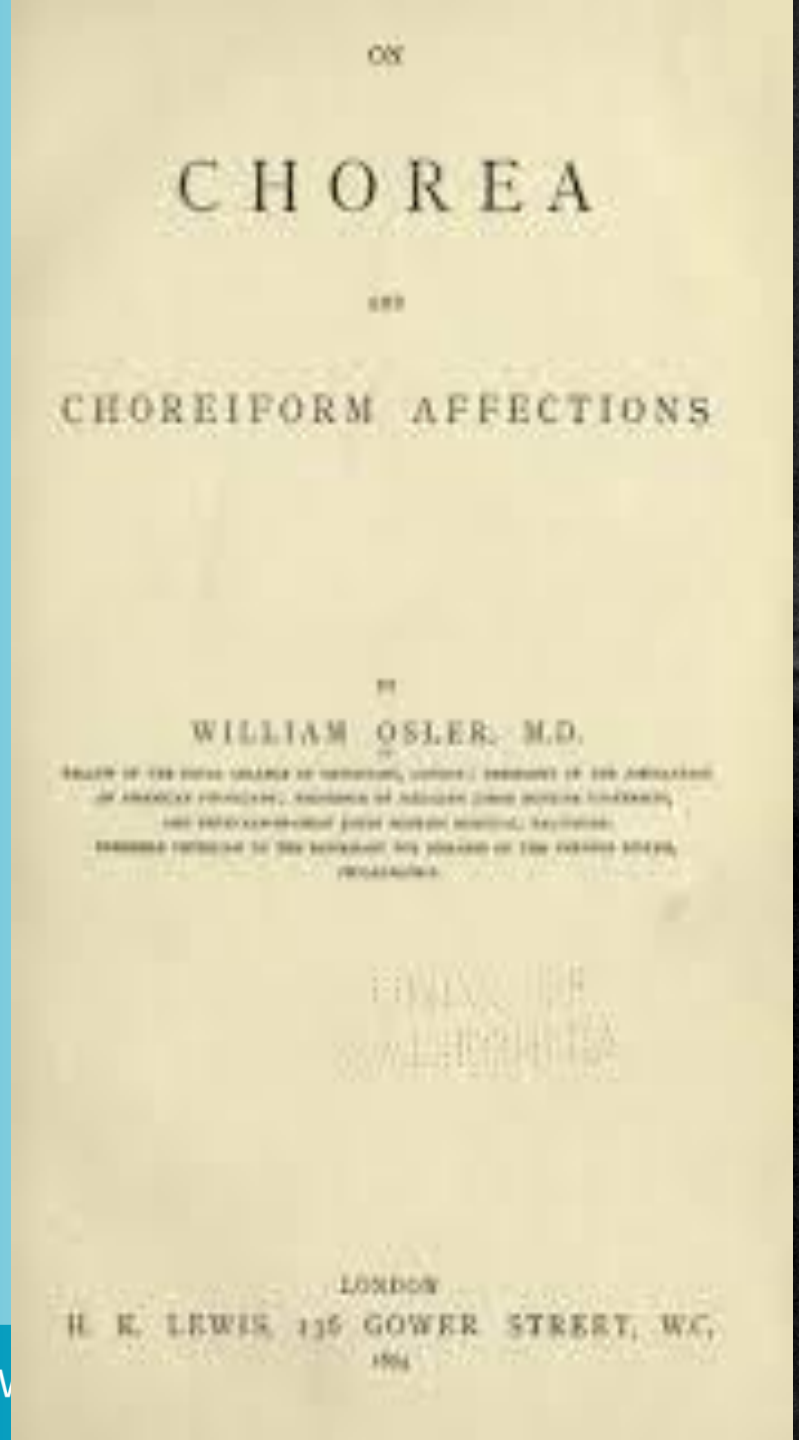
- Common psychiatric disorder in children worldwide (~2%)
- Characterized by repetitive anxious ideation and repeated behaviors to decrease the anxiety
- ~30% of patients fail to respond to standard treatments
- Despite demonstrated heritability, no genetic etiology has been identified
- Increased interest in autoimmunity and inflammation as an etiology for Obsessive Compulsive Disorder and Tourette Syndrome (TS)

How do we get from OCD to PANDAS?

Historical Context

"A frequent complaint heard from the mother is that the character of her child is completely changed"

"A patient may do odd and meaningless acts"


ON

CHOREA

AND

CHOREIFORM AFFECTIONS

BY

WILLIAM OSLER, M.D.

LONDON

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

1894

Sydenham Chorea

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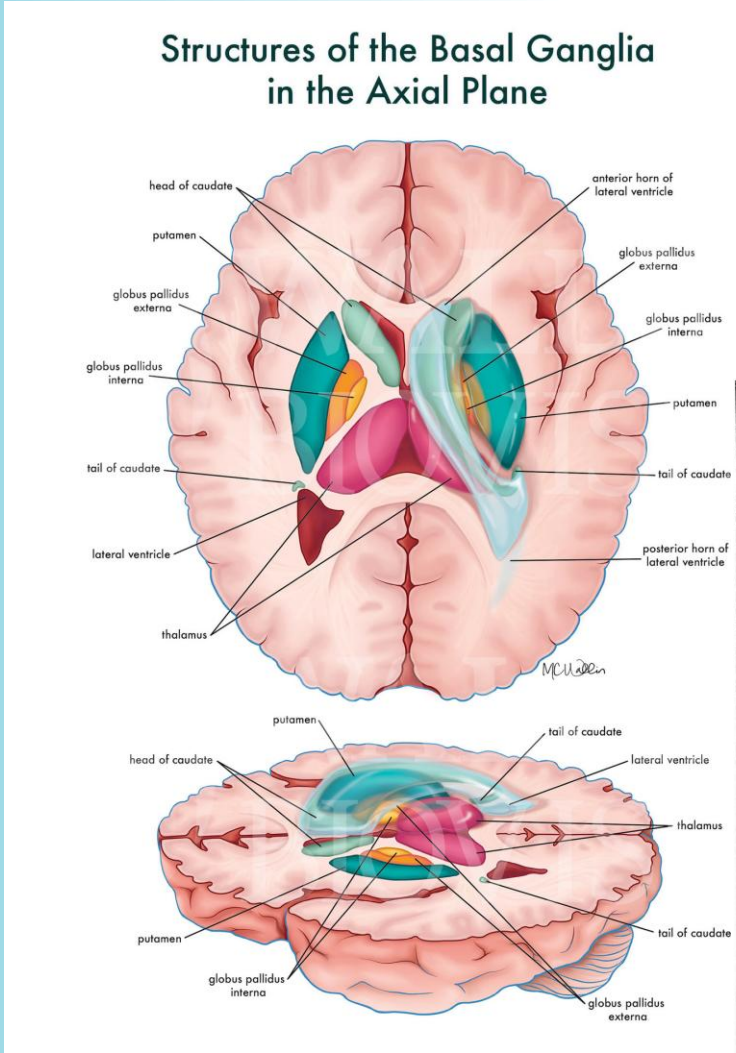
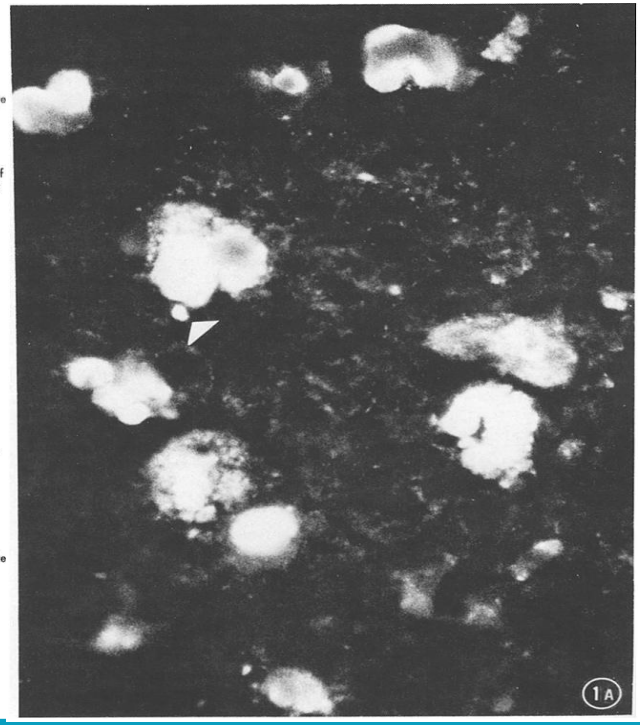
- Hypothesis is derived from Sydenham Chorea (SC)
- SC is a post-streptococcal movement disorder
- Hypothesized to be an induced autoimmune disorder
- Antibodies/inflammation in the basal ganglia are thought to be pathogenic
- High rate of OCD (40-70%) of OCD





Husby, J Exp Med, 1976

PANDAS

Pediatric Autoimmune Disorder Associated with Streptococcal infections

Diagnostic Criteria

- Presence of Obsessive-Compulsive symptoms and/or motor/vocal tics
- Pediatric Onset
- Abrupt symptom onset and/or episodic waxing and waning of symptoms
- Association with Group A Streptococcal infection
- Presence of neurological abnormalities ("choreiform movements", fine motor control deficits)

PANS

Pediatric Acute Onset Neuropsychiatric Syndrome

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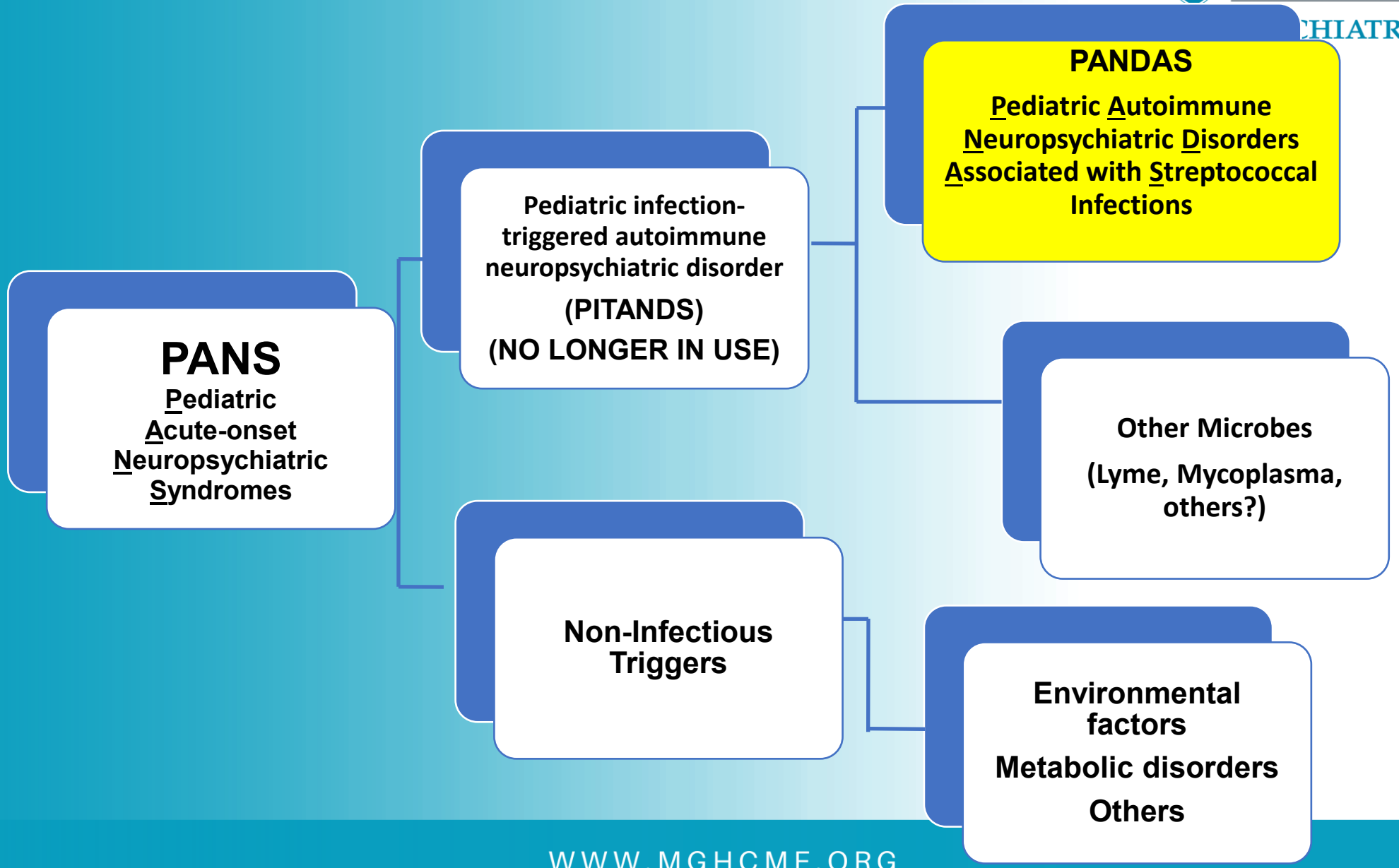
Diagnostic Criteria

- Abrupt onset of Obsessive-Compulsive symptoms, or restrictive eating (**TICS ARE NOT INCLUDED**)
- Concurrent presence of at least two of the following symptoms concurrent with the above symptoms:
  - Anxiety
  - Emotional lability/opposition
  - Behavioral regression
  - Sudden deterioration in school performance
  - Motor sensory abnormalities
  - Sleep disturbance, enuresis, or urinary frequency


PANS
Pediatric
Acute-onset
Neuropsychiatric
Syndromes
Pediatric infection-triggered autoimmune neuropsychiatric disorder
(PITANDS)
(NO LONGER IN USE)
PANDAS
Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal Infections
Other Microbes
(Lyme, Mycoplasma, others?)
Non-Infectious Triggers
Environmental factors
Metabolic disorders
Others

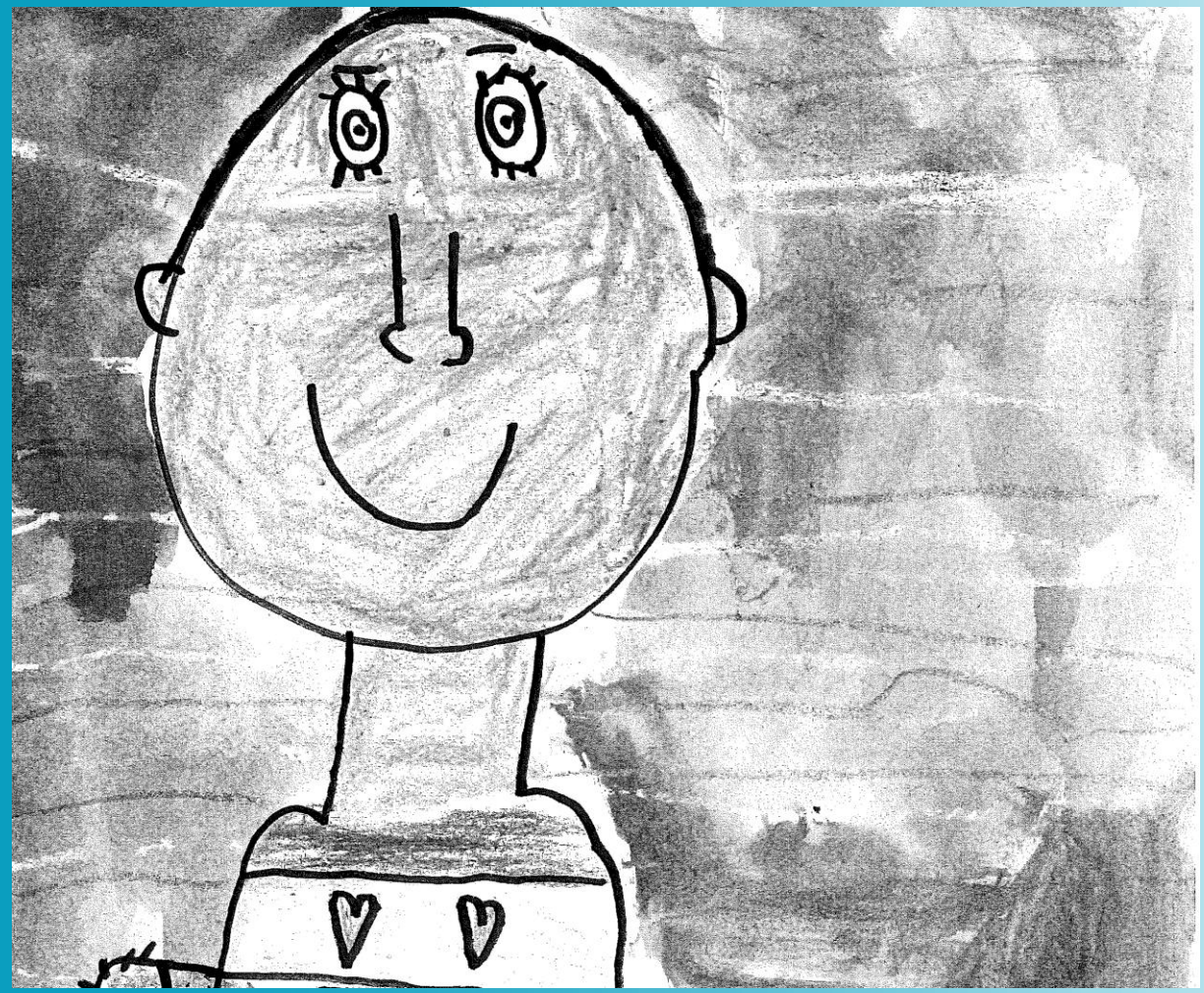
Clinical Case

- *7* y.o. male with no previous history of psychiatric illness, no family hx of OCD/Tics
  - Independent, A student, socially well adjusted
- Feb: School letter advising 6 “Strep throat” infections in pt’s classroom
- Feb: Pt ill with sore-throat, high fever, throat swab positive for *Streptococcus pyogenes* (Group A Strep)
  - Treated with antibiotics; full recovery

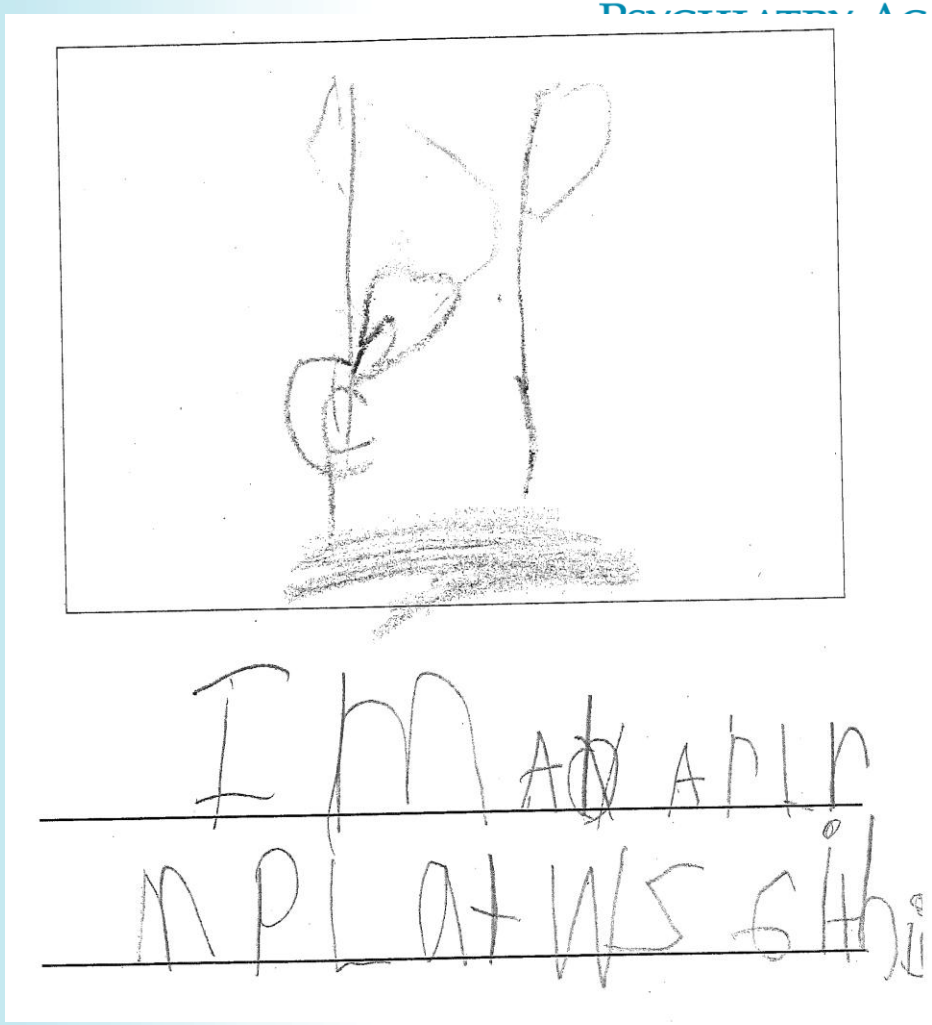
Clinical Case- PANDAS

- March-April: Mother notices severe stuttering not present the day prior, shortly after:
  - Pt expresses fear over not pronouncing words “exactly”
  - New onset frequent hand-washing and showering rituals
  - Extreme avoidance of door-knobs and “dirty surfaces”
  - Pt’s blinking more pronounced, new “grunting” noise
- March-April: Symptoms become disabling, severe disruption at home/school, school performance declines to C’s/D’s
- Acute deterioration in handwriting

Clinical Case-PANDAS



Prior to symptom onset



3 months following onset

PANDAS?

- “All kids get Strep throat"
- OCD is a common psychiatric disorder in school age children (~2% pediatric population)
- 1+1=3?

Challenges

- This child meets criteria for PANDAS
- This is a clinical diagnosis with no accepted biomarker or genetic identifier
- No large-scale natural history studies of PANDAS
  - No ability to estimate prevalence
- Mechanism(s) (i.e. autoantibodies/autoimmunity) have yet to be demonstrated
- Do we have a rationale for deviating from standardized OCD therapies for these children?

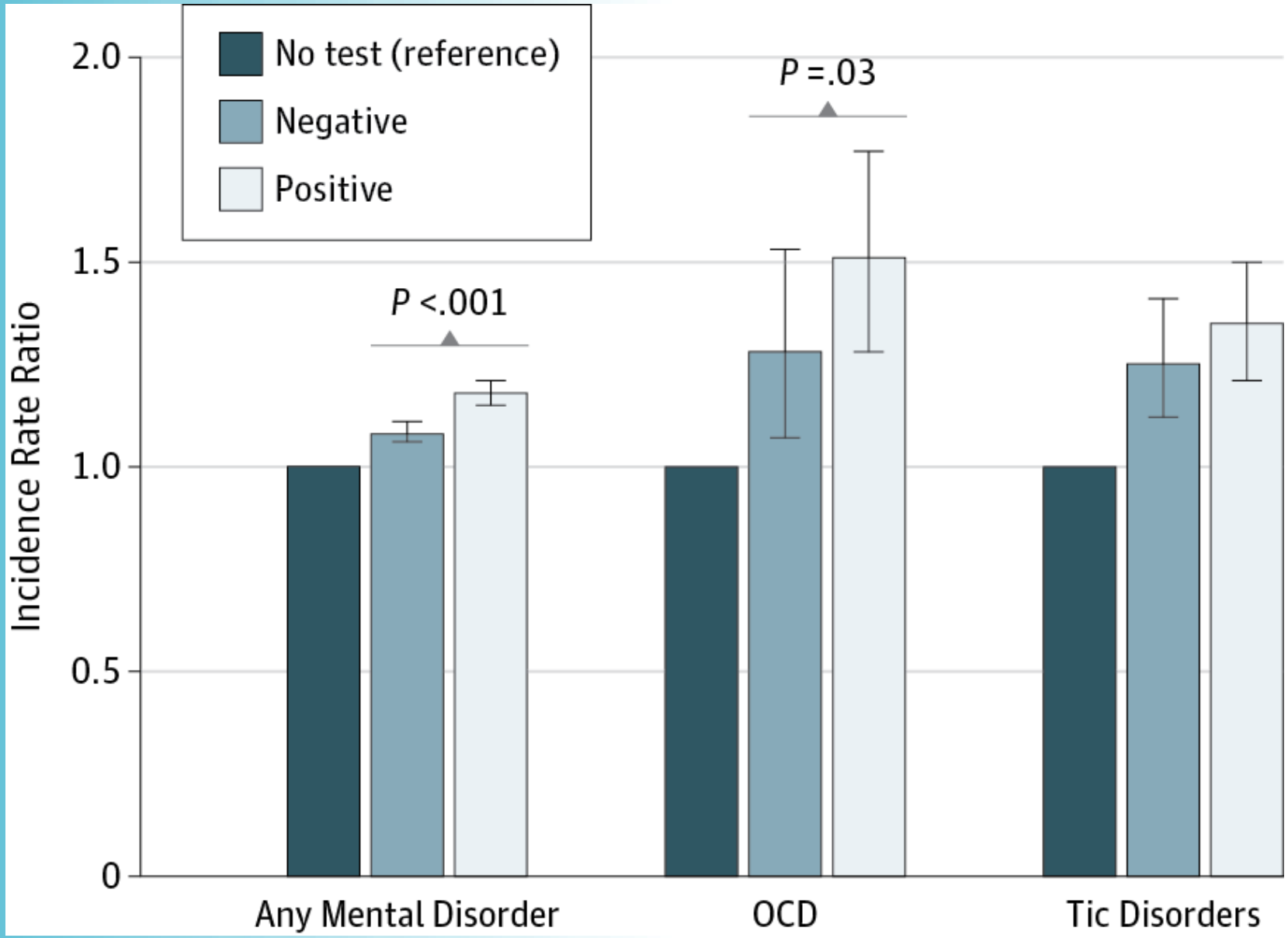
Evidence for Streptococcal Infections as a trigger for OCD/tics

- Danish Health Registry Study analyzing >1 million children in Denmark, followed for up to 17 years
- Analyzed the incidence of new psychiatric diagnoses following testing for Group A Streptococcal infections
    - Positive streptococcal test was inferred from the filling of an antibiotic prescription in the 8 days following a streptococcal test

- Orlovska *et al., JAMA Psych,* 2017

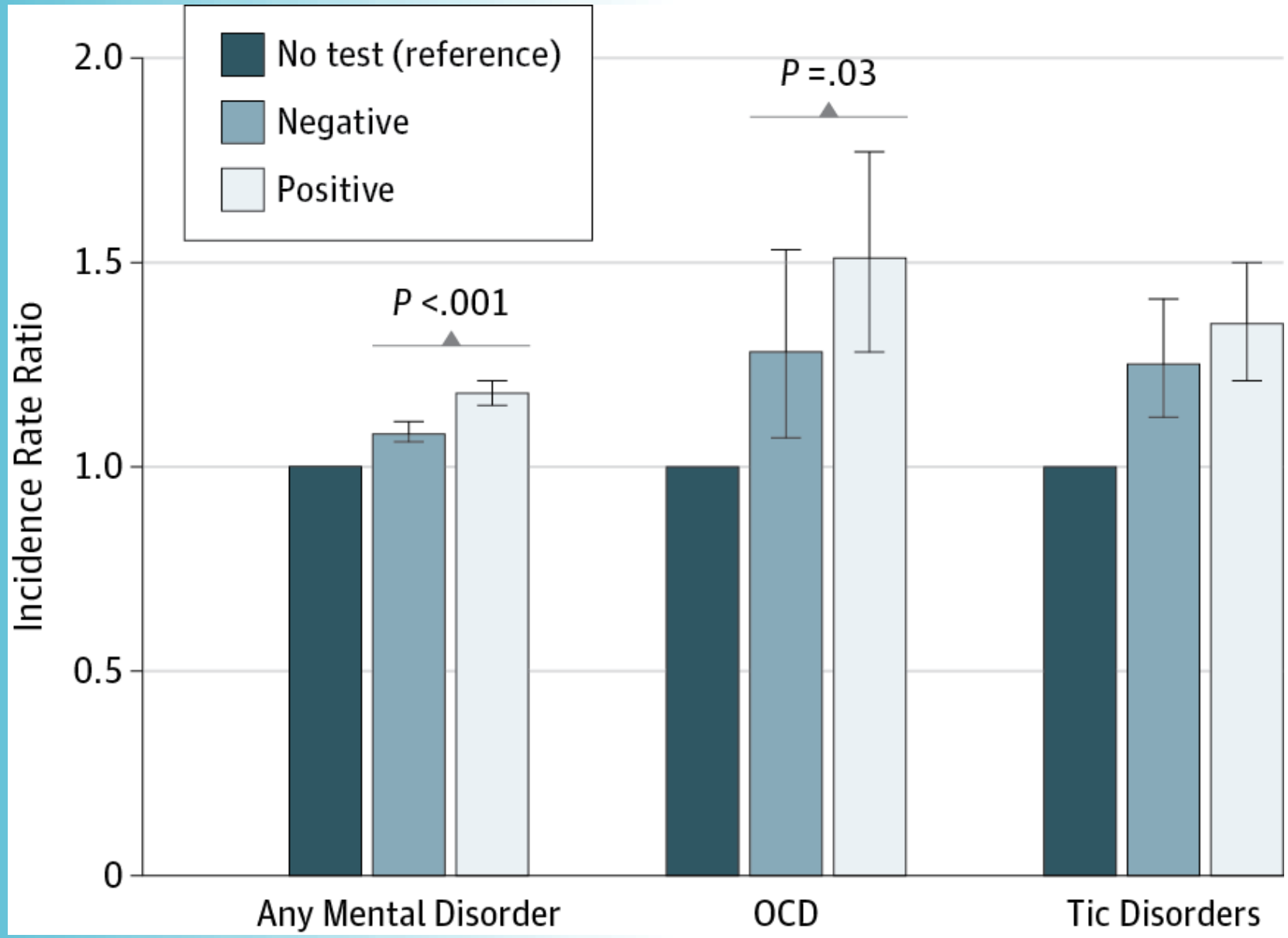
- Children with a positive streptococcal test had an 18% increased rate for **any** psychiatric disorder

- Children with a negative test had a 28% and 25% increased risk for OCD and tics, respectively



Orlovska *et al., JAMA Psych,* 2017

- Children with a positive streptococcal test had an 51% increased rate for **an OCD** diagnosis
- Children with a positive streptococcal test had an 35% increased rate for **a tic disorder** diagnosis
- Sibling pair analysis showed a 94% increased risk for OCD with a positive streptococcal result



Orlovska *et al., JAMA Psych,* 2017

How Prevalent is PANS/PANDAS?

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One Controlled Study: Wald *et al.*, 2023

- Estimated prevalence from 3 primary care clinics using EMR data:
  - Cases defined as children ages 3-12 with one of 5 new diagnoses (using ICD codes): Avoidant/restrictive food intake disorder (ARFID), other specified eating disorder, separation anxiety disorder, Obsessive Compulsive Disorder, or other specified disorder of the immune system
  - Cases reviewed by 2 investigators using PANDAS and PANS diagnostic criteria
  - Of the 95,498 included cases: 357 possible cases of PANS and 13 definite cases identified
  - Estimated annual incidence of PANS/PANDAS was **1/11,765**

Mechanism(s)?

Neuroimmune Dysregulation and OCD Behaviors

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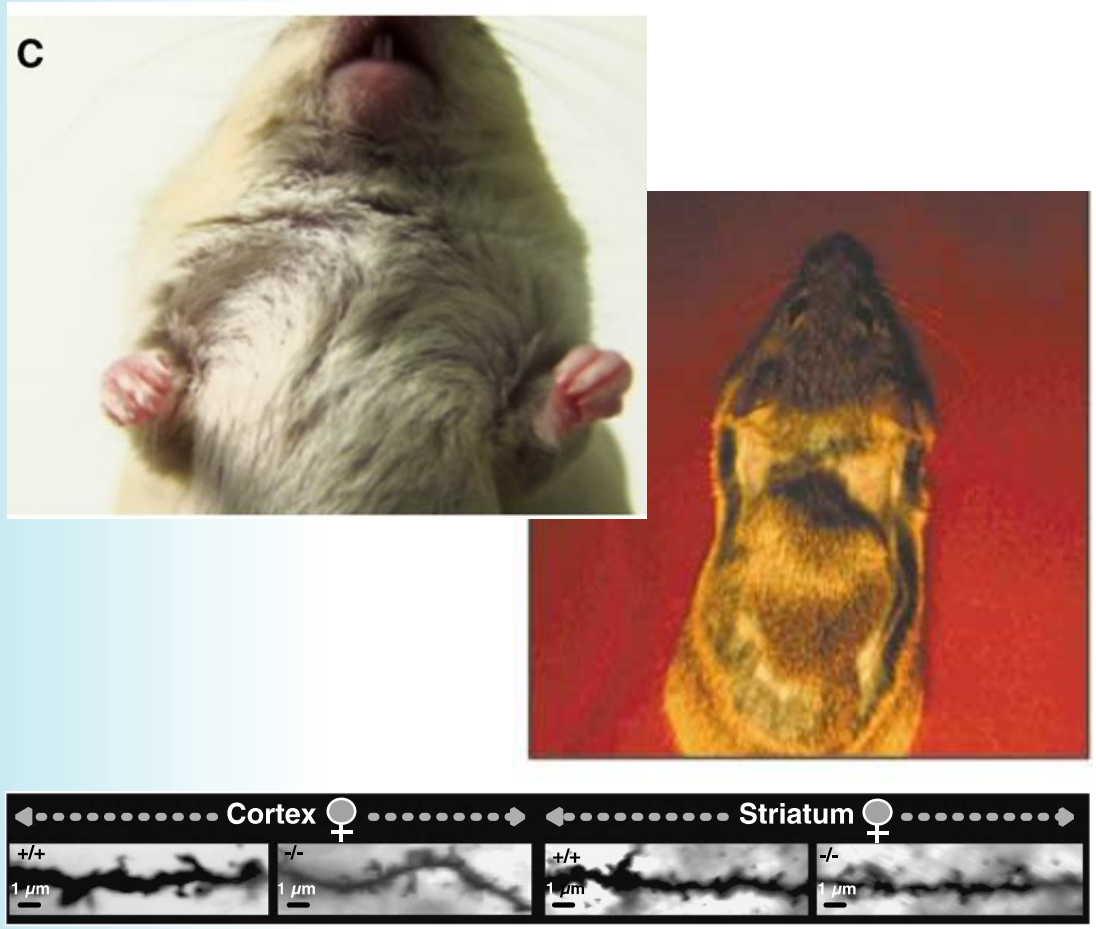
- *Hoxb8*$^{-/-}$ mice display a severe, repetitive grooming phenotype (Greer & Capecchi, 2002)
- This is the result of the lack of hematopoietic-derived microglia in the CNS (Chen *et al*, 2010), and abnormal corticostriatal synapse development (Nagarajan, 2017)
- This phenotype can be reversed through chronic fluoxetine treatment (Nagarajan, 2017), or a WT bone-marrow transplant (Chen *et al*, 2010)



MICROGLIA DYSFUNCTION IN HUMANS WITH OCD?

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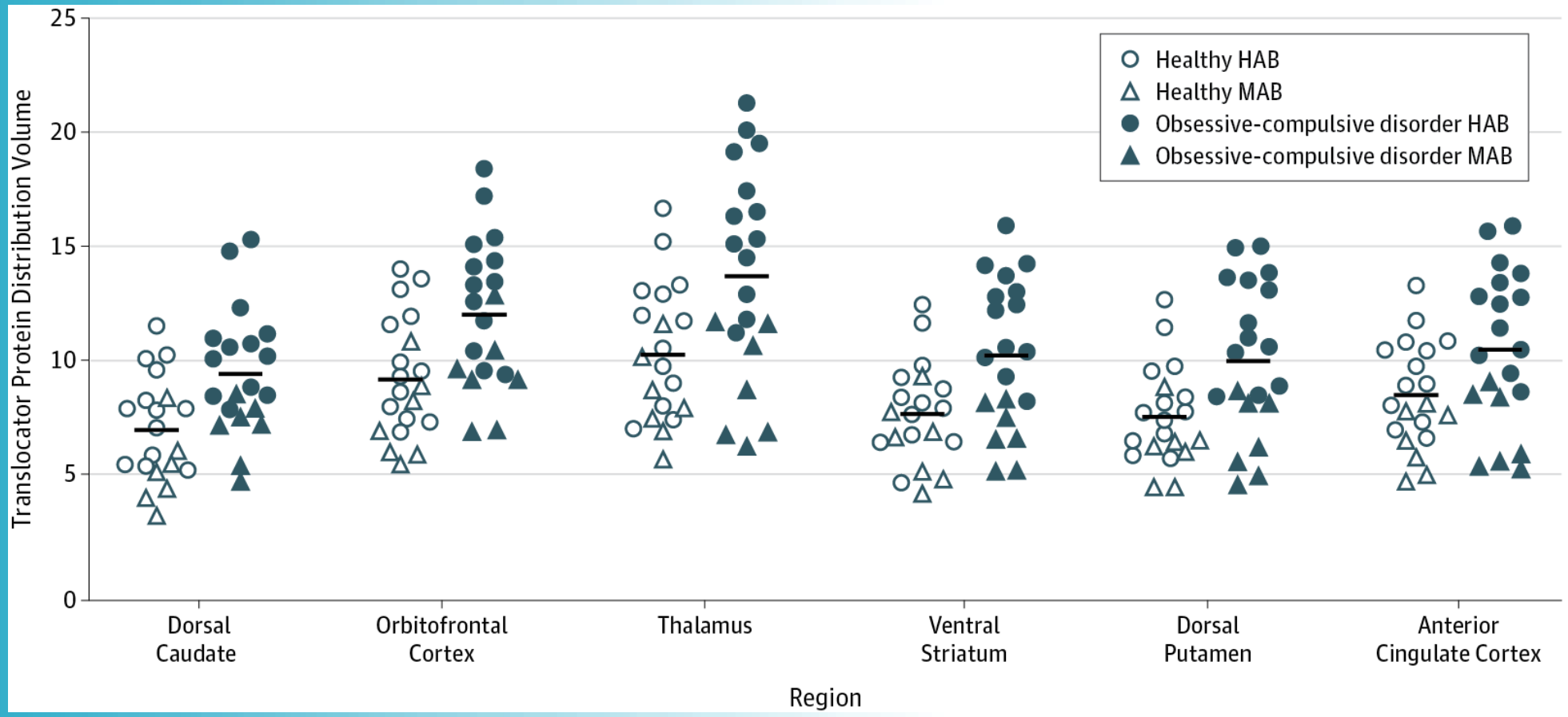
- PET study investigating inflammation in adults with OCD compared to healthy controls
- Significantly higher levels of TSPO binding in adult OCD patients



Attwells *et al*., *JAMA Psych*, 2017

MGH PET STUDY OF TSPO IN OCD

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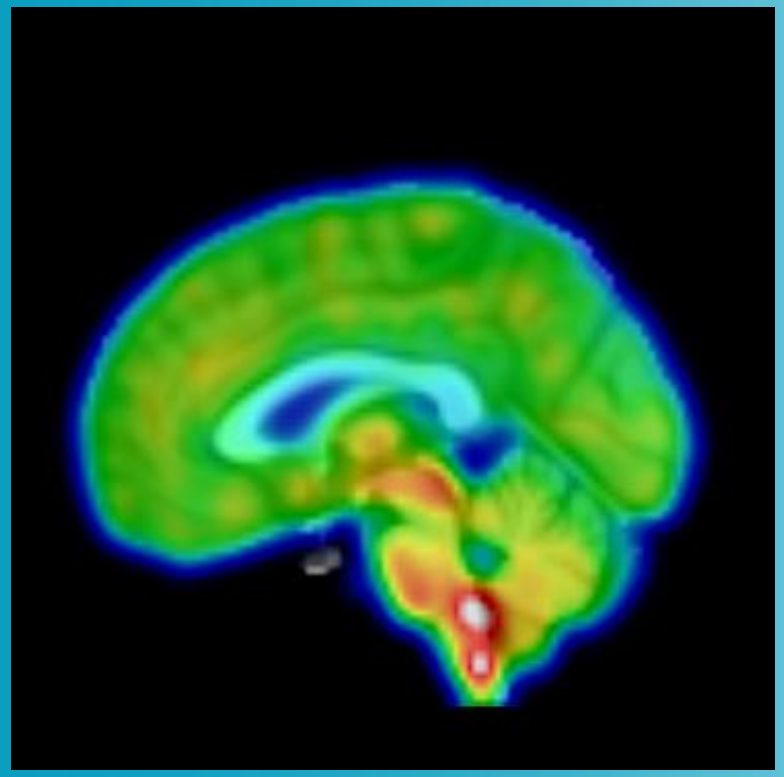

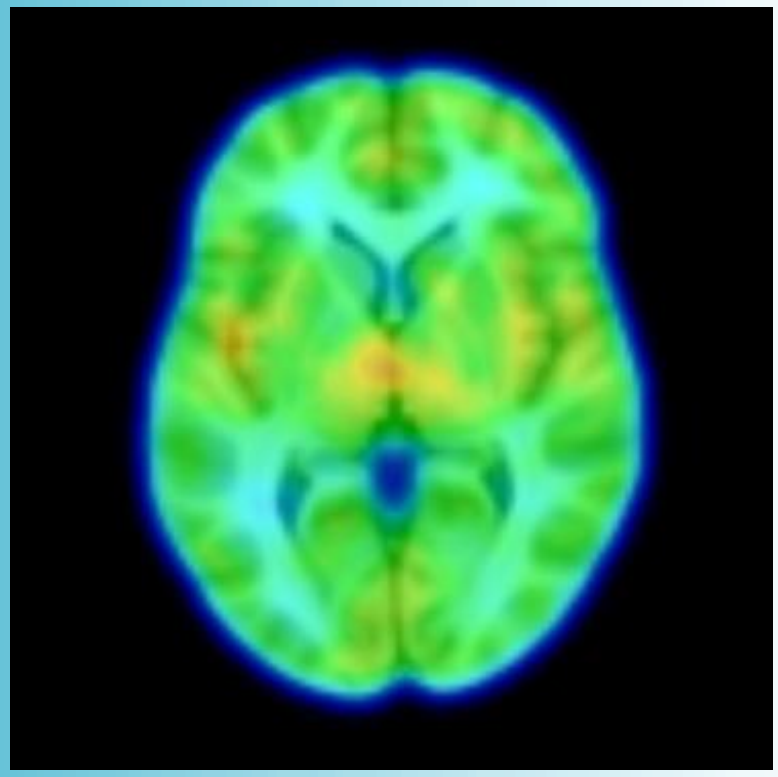

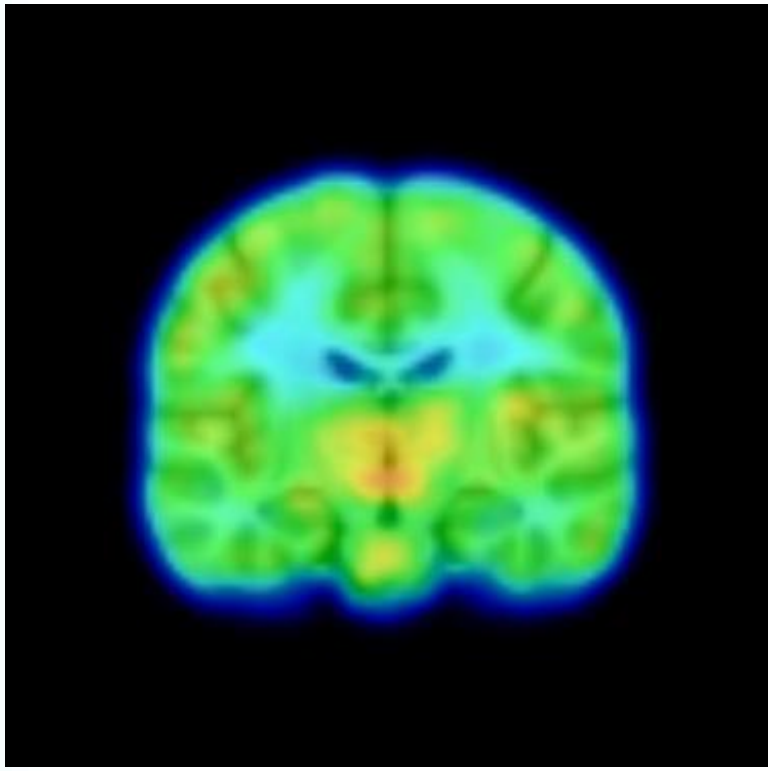

[^{11}C]PBR28 SUVRwb $_{60\text{-}90}$

ARE MICROGLIA ABNORMAL IN HUMANS WITH PANDAS?

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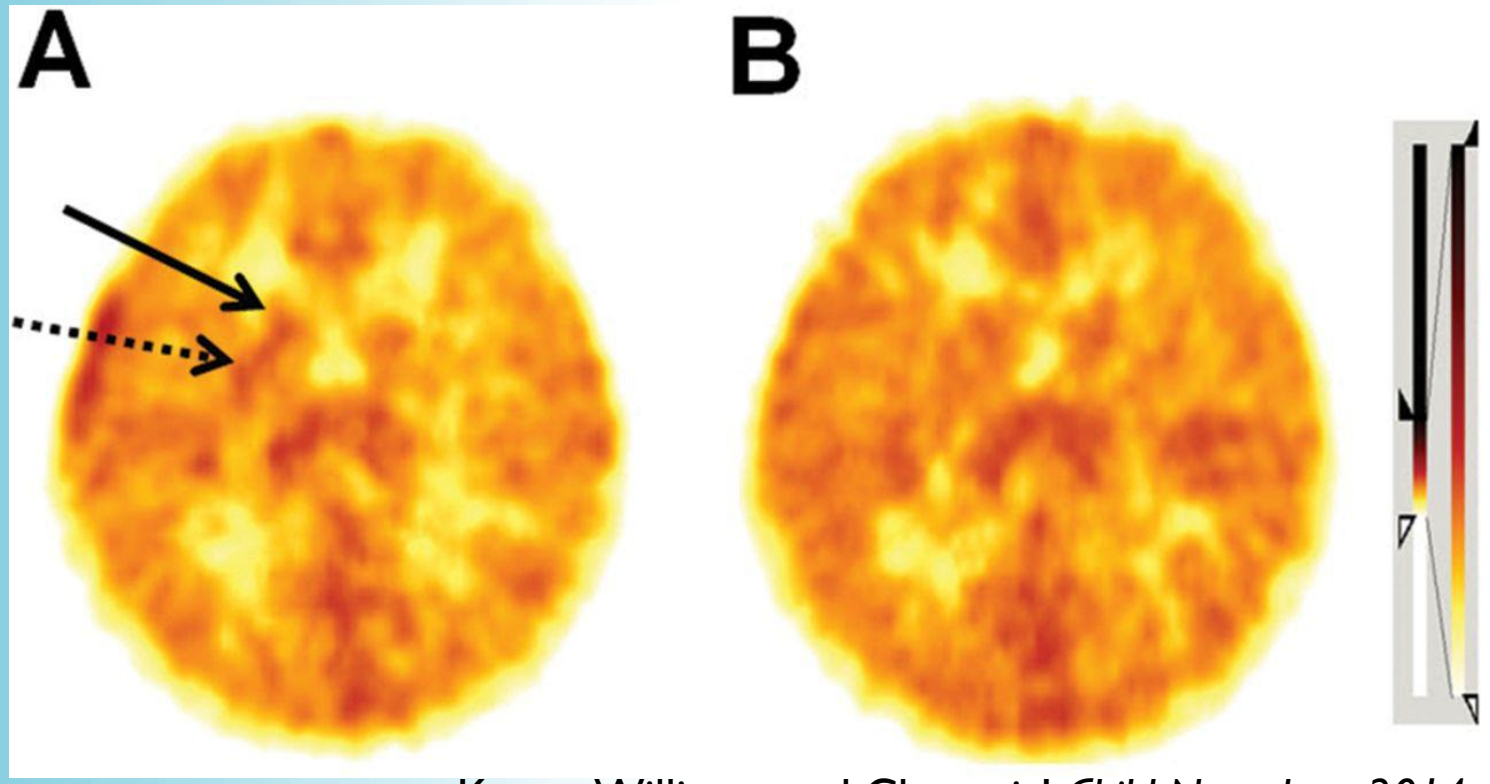
- PET study using TSPO in children with PANDAS and healthy adult controls
- Significantly higher TSPO binding in the caudate in PANDAS subjects compared to controls
- Caudate TSPO binding decreased in one subject treated with intravenous immunoglobulin (IVIG)



Kumar, Williams, and Chugani, J *Child Neurology, 2014*

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- Collaboration with Josef Isung MD, PhD and David Mataix-Cols, PhD, Karolinska Institute
- Analyzed the health records of over 17 million persons in the Swedish population in investigate the co-occurrence of immune deficiencies, psychiatric disorders, and suicide

Table 2. Associations Between Exposure to PID and Psychiatric Disorders and Suicidal Behavior in the Population Cohort and in the Full-Siblings Subcohort

	Population cohort				Full-siblings cohort			
	No. (%)		OR (95% CI)		No. (%)		OR (95% CI)	
Disorder[a]	PID exposed (n = 8378)	PID unexposed (n = 14 297 937)	Minimally adjusted[b]	Fully adjusted[c]	PID exposed (n = 4828)	PID unexposed (n = 8584)	Minimally adjusted[d]	Fully adjusted[c]
Any psychiatric disorder	1720 (20.5)	1 524 737 (10.7)	2.16 (2.05-2.28)[e]	1.91 (1.81-2.01)[e]	1027 (21.3)	1228 (14.3)	1.71 (1.54-1.89)[e]	1.64 (1.48-1.83)[e]
Autism spectrum disorders	89 (1.1)	53 868 (0.4)	3.50 (2.84-4.32)[e]	2.99 (2.42-3.70)[e]	63 (1.3)	49 (0.6)	2.25 (1.45-3.49)[e]	2.29 (1.43-3.66)[e]
Attention-deficit/ hyperactivity disorder	126 (1.5)	114 713 (0.8)	2.31 (1.93-2.76)[e]	1.99 (1.67-2.38)[e]	82 (1.7)	97 (1.1)	1.46 (1.04-2.06)[f]	1.47 (1.03-2.11)[f]
Obsessive-compulsive disorder	54 (0.6)	37 734 (0.3)	2.49 (1.91-3.26)[e]	2.19 (1.68-2.86)[e]	35 (0.7)	40 (0.5)	1.55 (0.94-2.54)	1.55 (0.94-2.56)
Eating disorders	70 (0.8)	40 271 (0.3)	3.03 (2.39-3.84)[e]	2.54 (2.00-3.21)[e]	48 (1.0)	36 (0.4)	1.68 (0.99-2.83)	1.52 (0.86-2.68)
Schizophrenia and other psychotic disorders	204 (2.4)	270 729 (1.9)	1.42 (1.24-1.63)[e]	1.34 (1.17-1.54)[e]	106 (2.2)	171 (2.0)	1.23 (0.94-1.61)	1.23 (0.93-1.63)
Bipolar disorder	100 (1.2)	88 994 (0.6)	1.86 (1.53-2.26)[e]	1.65 (1.35-2.01)[e]	53 (1.1)	80 (0.9)	1.16 (0.80-1.68)	1.08 (0.73-1.59)
Anxiety disorders	777 (9.3)	522 924 (3.7)	2.62 (2.44-2.83)[e]	2.25 (2.09-2.42)[e]	503 (10.4)	519 (6.0)	1.65 (1.43-1.91)[e]	1.61 (1.39-1.87)[e]

L

EMY

Immune deficiency is associated with increased O.R. of Autism, OCD, Eating disorders and suicide

Isung et al., *Am J Psych*, 2021

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PANDAS Treatment

PANDAS Treatment

- **Antibiotic Therapy:**
  - 3 controlled trials of antibiotic therapy for PANS/PANDAS
  - 2 trials failed

  - 3rd Trial: Placebo-controlled trial of Azithromycin in PANS
    - No significant difference in OCD symptoms based on CYBOCS
    - Significant improvement in OCD symptoms based on CGI-S for OCD
    - No significant difference in tic symptoms (Murphy *et al.*, 2017)

PANDAS Treatment

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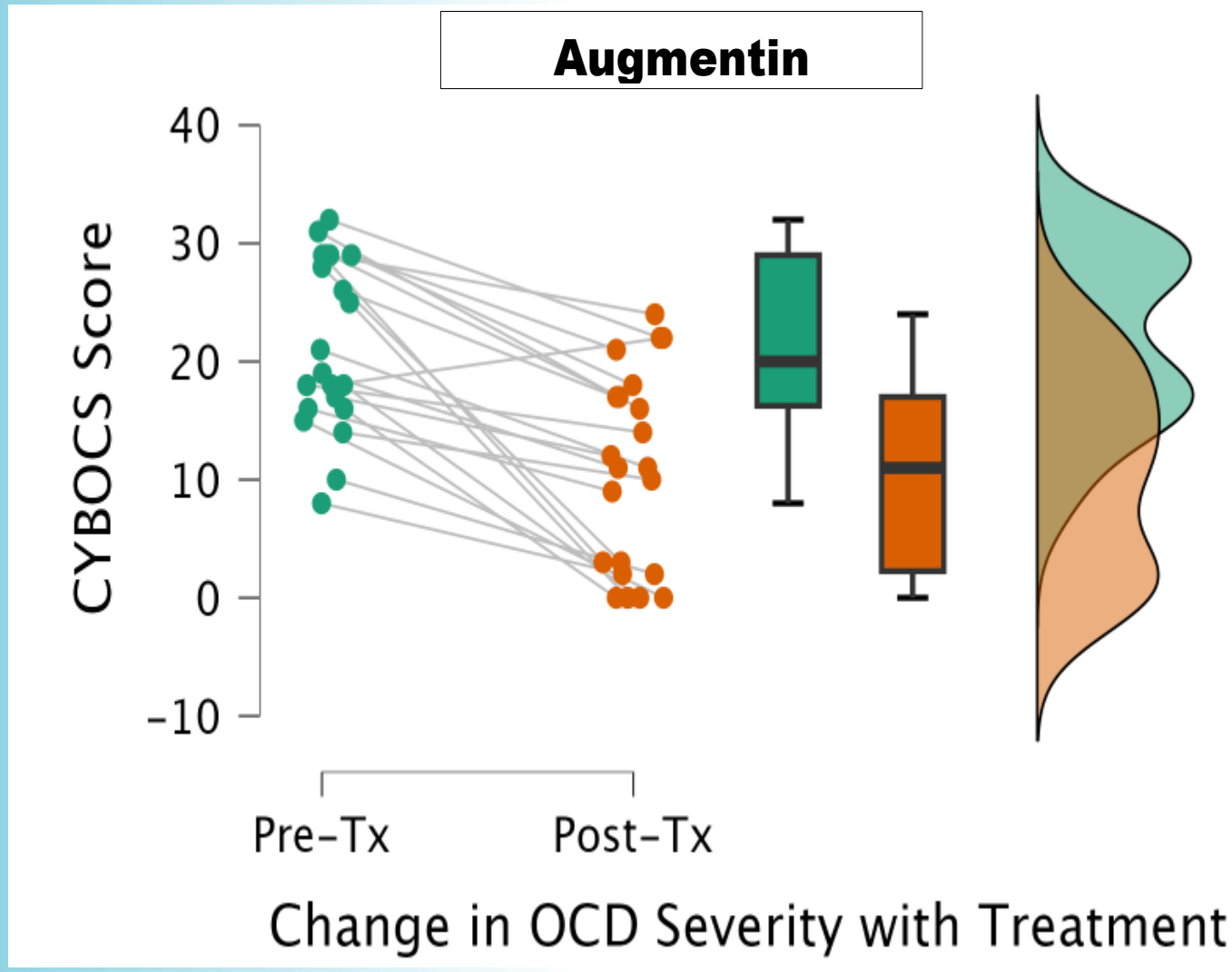
- Pilot Data from MGH Clinic
- 22 PANS/PANDAS subjects
- Treated with prophylactic Augmentin (various doses)
  - 27% Decrease in OCD Severity



PANDAS Treatment

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- **Anti-inflammatory Therapies**
  - Non-Steroidal Anti-Inflammatory Drugs (NSAIDs):
    - Open-Label Studies, case reports *only:*
      - 52 clinic patients from a clinical sample
      - After addition of NSAIDs, 31% reported improved neuropsychiatric symptoms
      - 39% reported side effects, typically mild GI symptoms (Spartz *et al.,* 2017)
      - NSIAD use was associated with significantly shorter duration of psychiatric symptom exacerbation (avg 2.6 week shorter) (Brown *et al.,* 2017)
  - Oral Corticosteroid Therapy:
    - Corticosteroid use was associated with significantly shorter duration of psychiatric symptom exacerbation (avg 6 week shorter) (Brown *et al.,* 2017)

PANDAS Treatment

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- Pilot Data from MGH Clinic
- Naproxen Sodium 10mg/kg BID
- 40% reduction in OCD severity
- 68% "treatment responders"
  - Defined as >25% reduction in OCD sx

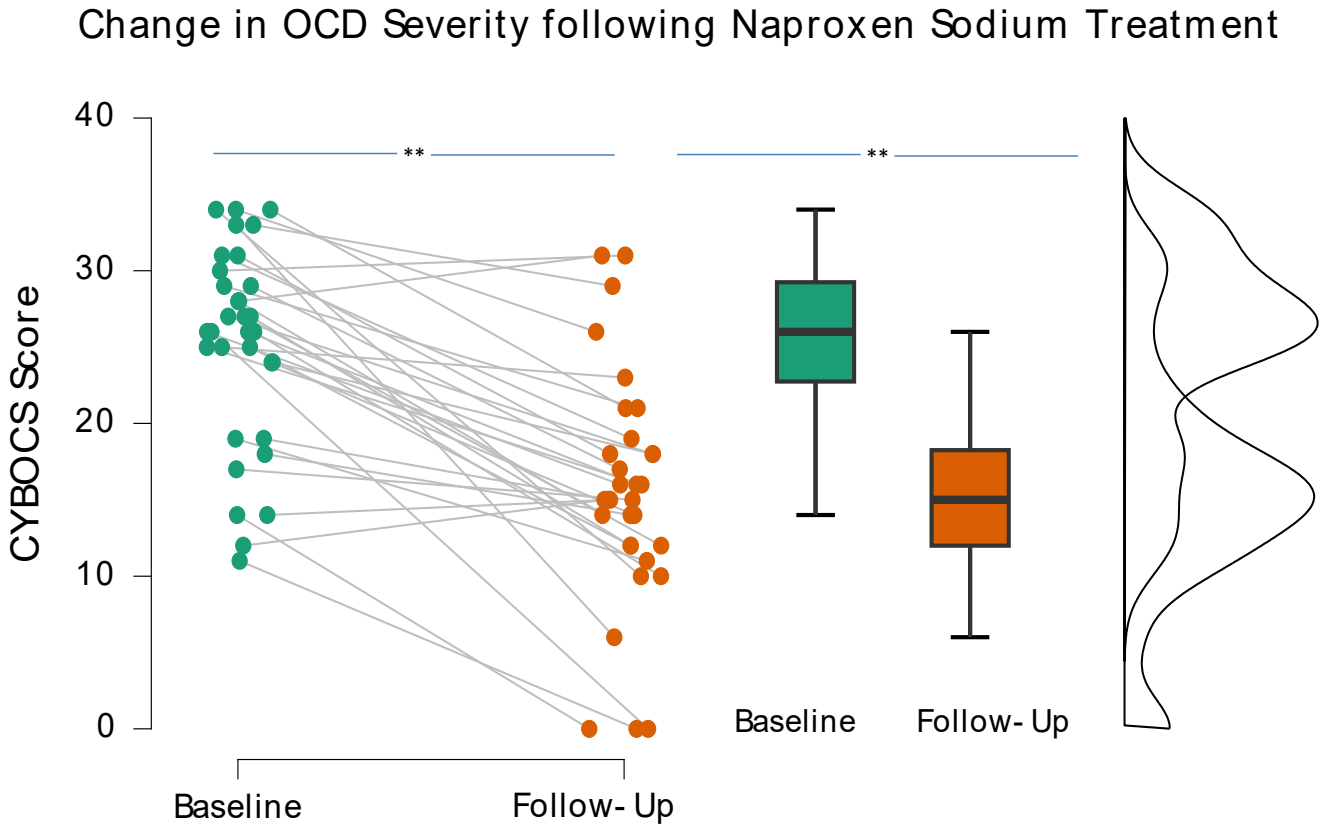

Figure 1: Individual and Average OCD Severity Scores in children treated with Naproxen Sodium. Pre and post treatment OCD severity was significantly reduced following naproxen sodium treatment p<.001, paired two-way T-test, error bars= CI)

PANDAS Treatment

- Immunomodulatory treatments
  - *Hypothesis: If PANDAS is an autoimmune disorder, can the psychiatric symptoms of PANDAS be treated through immunomodulatory therapies?*

  - Intravenous Immunoglobulin (IVIG)
  - Plasma Exchange Therapy (PEX)

IVIG vs. Plasma Exchange vs. Placebo

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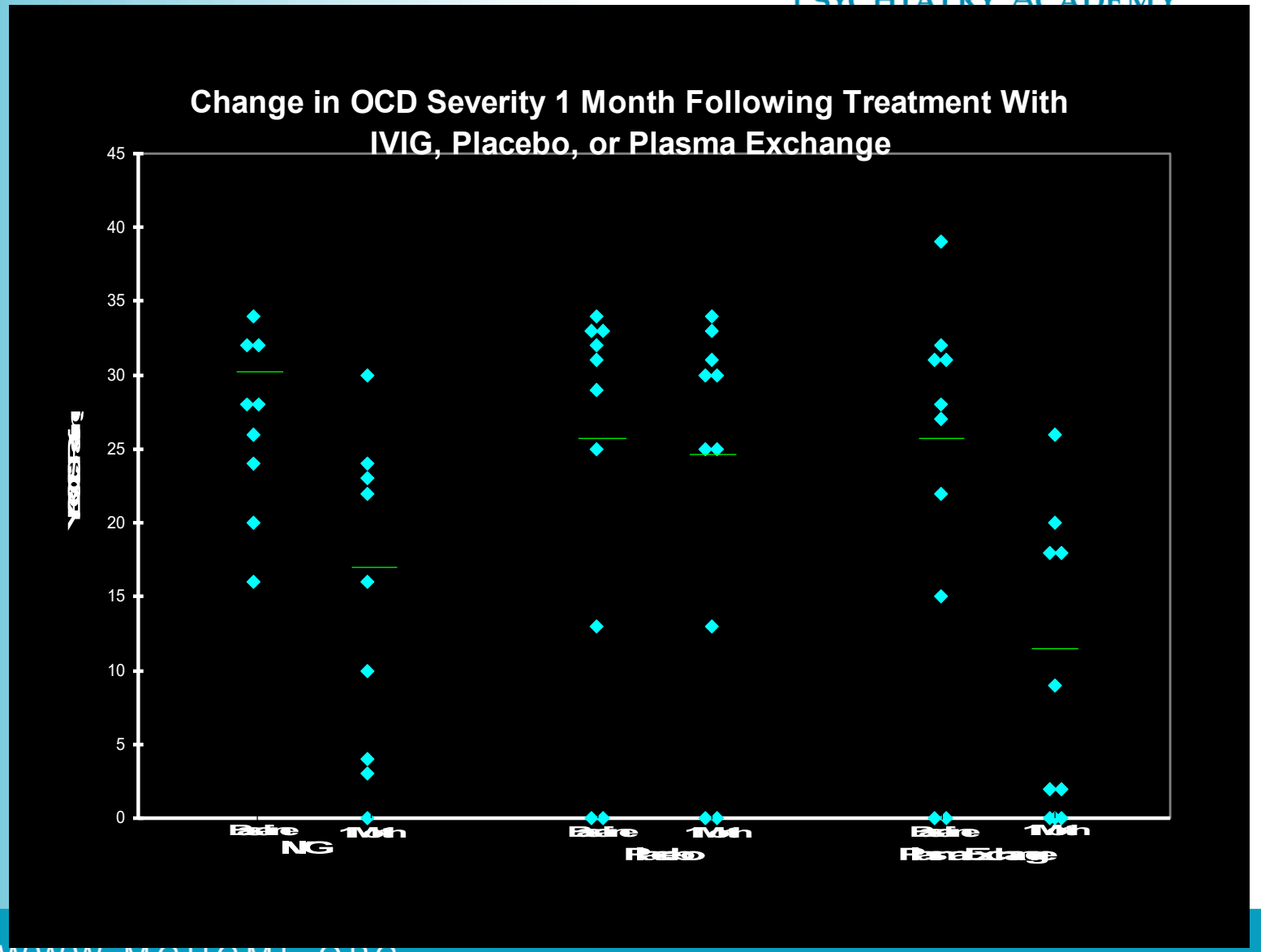
- IVIG group (1 month):
  - 45% decrease in obsessive compulsive symptoms
  - 19% decrease in tic severity
- PEX Group (1 month):
  - 58% decrease in obsessive compulsive symptoms
  - 49% decrease in tic severity
- Placebo Group (1 month):
  - 3% decrease in obsessive compulsive symptoms
  - 12% decrease in tic severity



Perlmutter *et al.*, Lancet, 1999

IVIG Trial in PANDAS

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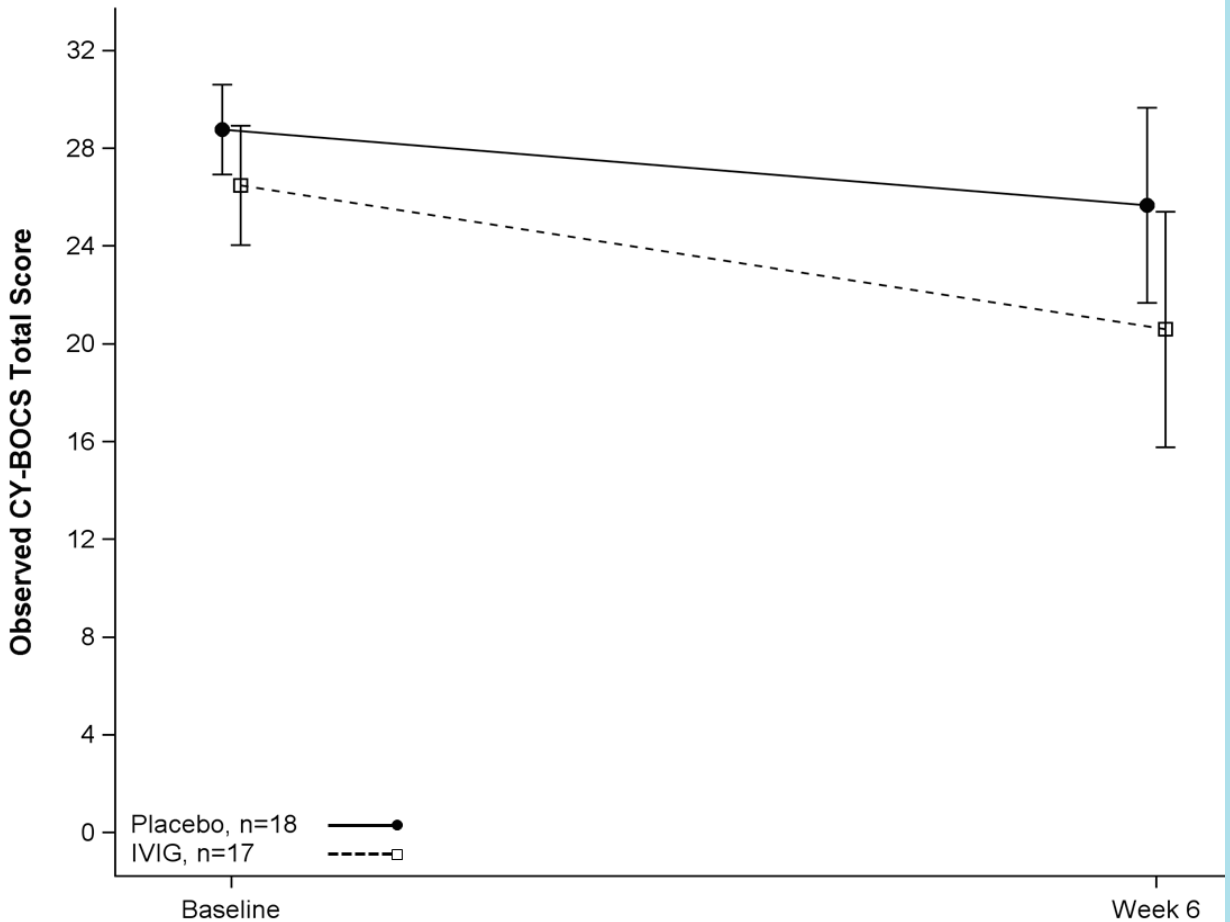
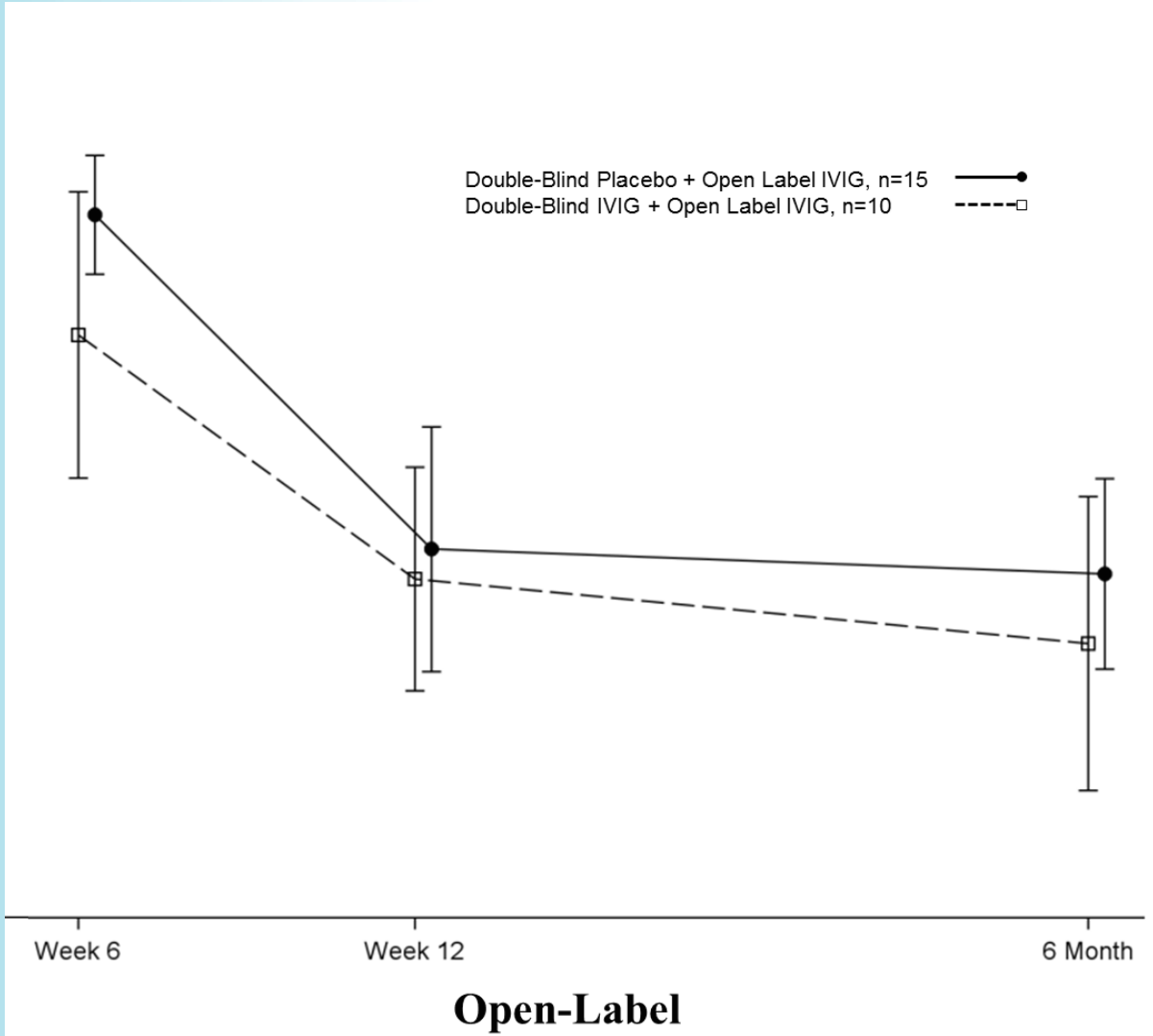
- 36 children who met PANDAS criteria, <1 year of illness
  - Screened from >1100 referrals
  - 18 Received Saline
  - 17 Received IVIG (2gm/kg), blinded (1 child withdrew)
  - Assessed for OCD severity at baseline and 6 weeks following infusion

  - Following the 6-week time-point, those subjects who did not achieve a 30% reduction in OCD severity were offered an open label IVIG infusion
    - OCD severity assessed 6 weeks following open-label infusion

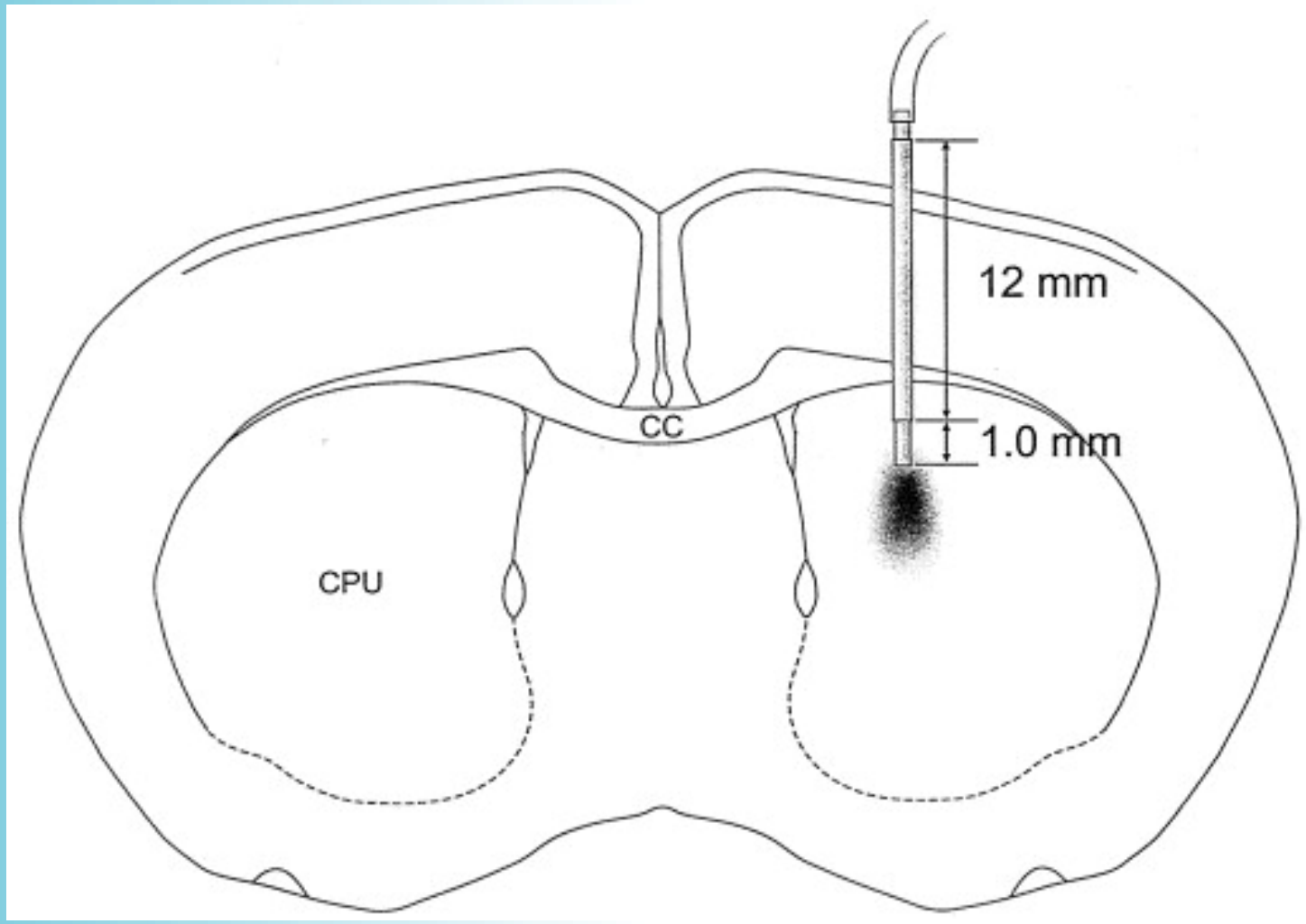
Williams, *et al.*, JAACAP, 2016





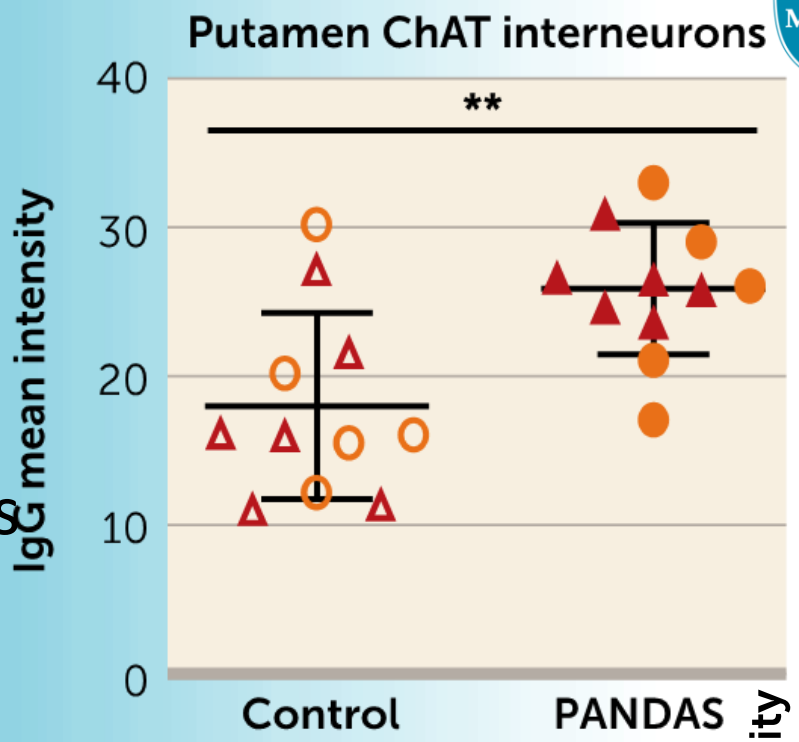
- No significant observed effect of IVIG vs placebo in the blinded phase
- 10% Mean decrease in OCD severity for placebo group
- 23% Mean decrease in OCD severity for IVIG group

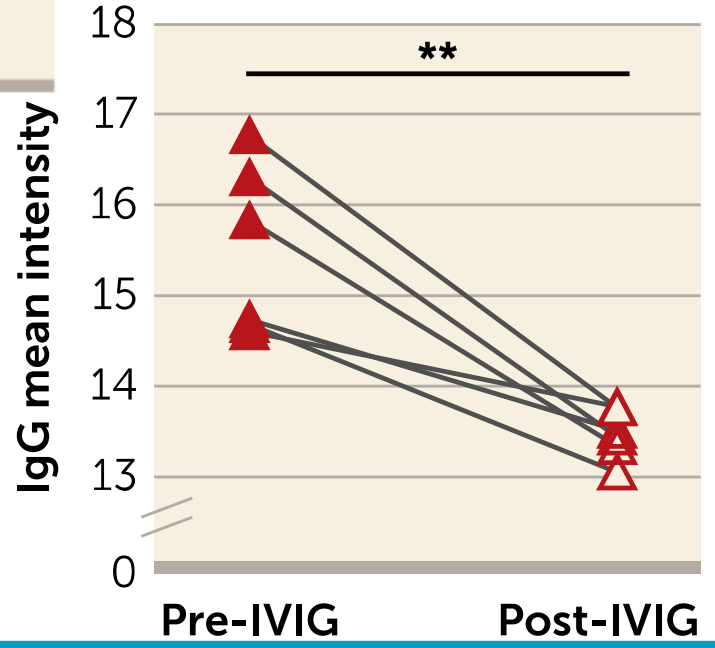
- Serum from 5 PANDAS subjects and 5 age matched healthy controls infused into the striatum of C57/BL6 mice
- 0.5μl serum infused each day for 5 consecutive days, mice sacrificed 5d following last infusion
- 2 mice per serum sample



Autoantibodies in PANDAS

- Blood samples from PANDAS participants involved in an IVIG clinical trial at NIMH/Yale
- These samples contain antibodies that bind to Cholinergic interneurons in the brain of mice (ChAT)
- Also bind to the same neurons in post-mortem human brain
- Following IVIG, these antibodies decrease in binding intensity





Xu et al., *Am J Psych*, 2020

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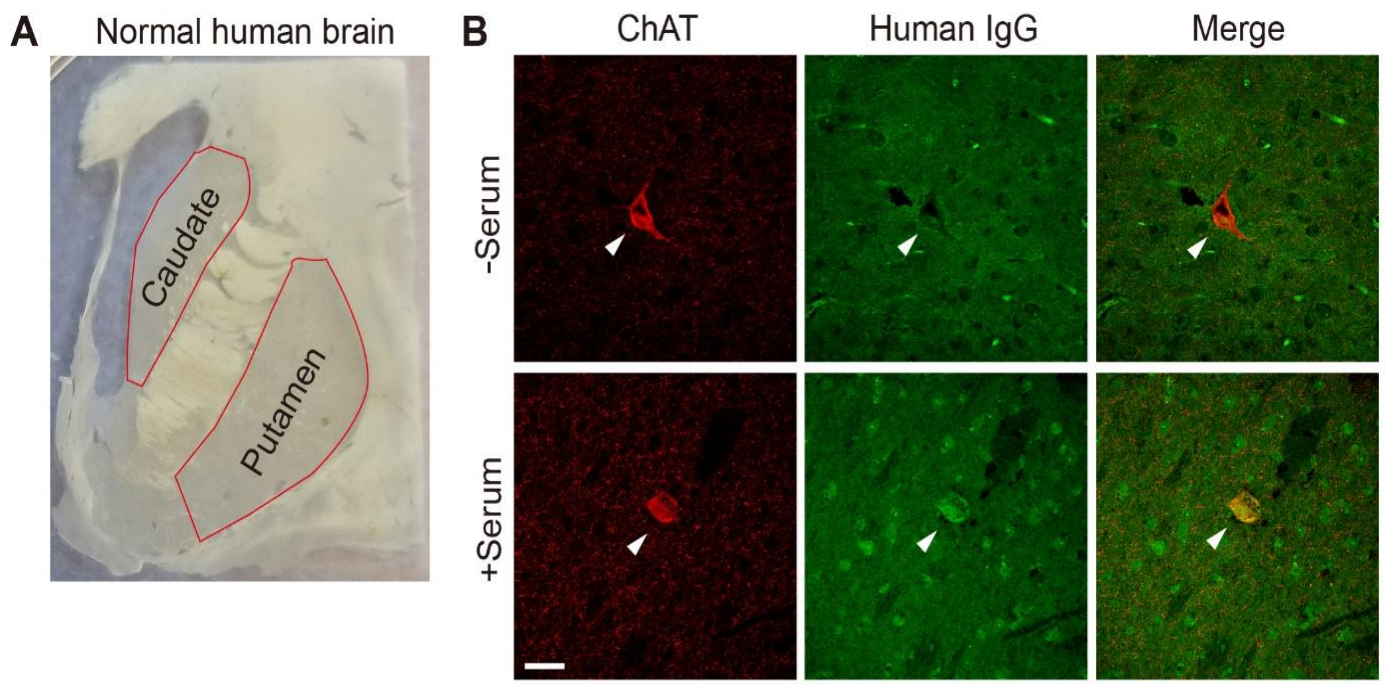

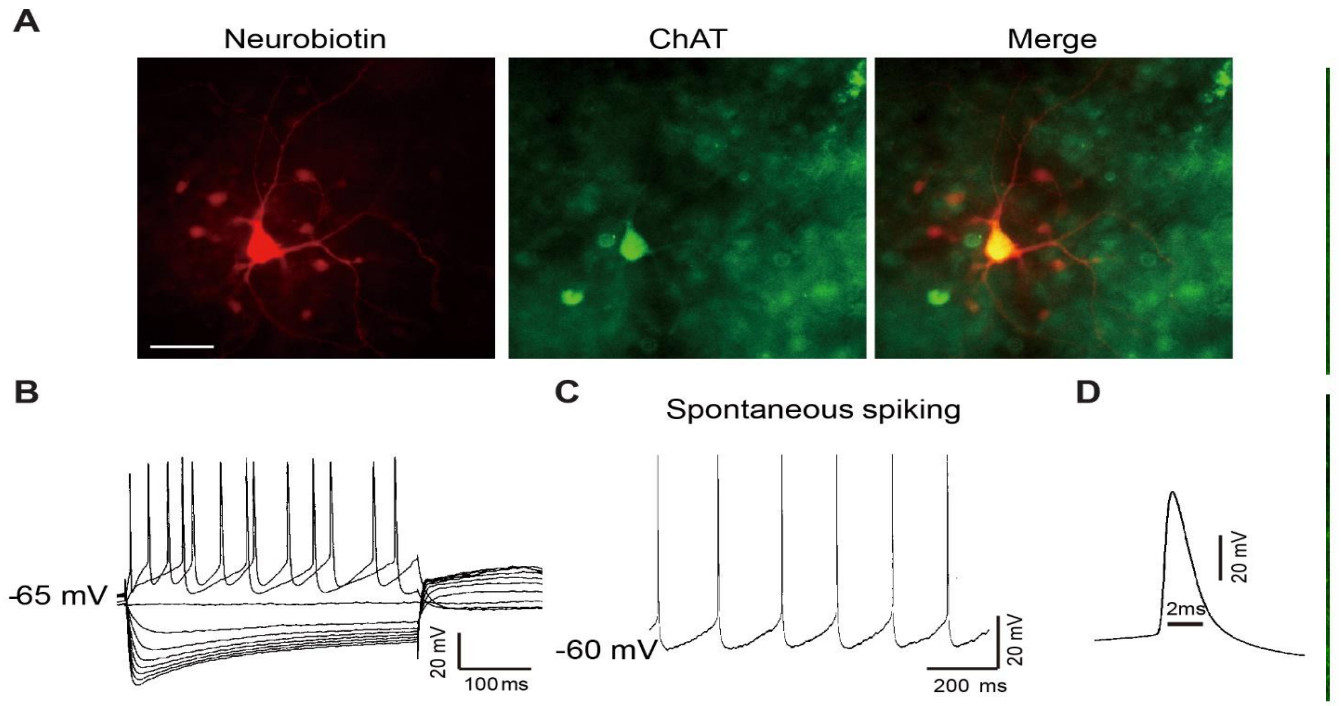

Xu et al., *Am J Psych*, 2020

What would be the “smoking gun”?

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- Genetic tests which enhance discriminatory application of diagnoses (OCD vs. PANDAS/PANS)
- Identification and verification of autoimmune antibodies in clinical populations (OCD vs. PANDAS/PANS)
- Significant divergence in treatment response in *a priori* identified clinical populations (OCD vs. PANDAS/PANS)

Resources:

Journal of Child and Adolescent Psychopharmacology, Vol 27(7), 2017

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

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

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Thank You!

Questions?