

# **PANDAS: Is It Important?**

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# Round 2





# Twin Studies

## **Monozygotic Twins:**

- Concordance for TS = 55% (53 and 56%)
- Concordance for TS or CTD = 86% (77 and 94%)

## **Dizygotic Twins:**

- Concordance for TS = 10%
- Concordance for TS or CTD = 20%

**MZ twins:** Variable severity of tics despite inheritance of similar genetic material

**Supports importance of genetic factors but suggests non-genetic factors may mediate the form or severity of the phenotype**

Shapiro et al 1978; Price et al 1985; Hyde et al 1992

# **Environmental (non-genetic) Factors**

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- **Exposure to medication/drugs**
- **Factors that influence intrauterine growth**
- **Hyperthermia**
- **Antiphospholipid antibodies**
- **Infection (antineuronal antibodies)**



# Criteria for TS and PANDAS

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**TS** (TS Study Group, 1993)

**PANDAS** (Swedo et al 1998)

**ONSET:** Before age 21

Prepubertal

**TICS:** Multiple motor plus 1 phonic present for more than 1 year

Tic disorder and/or OCD

**COURSE:** Waxing and waning, tics evolve in a progressive manner

Sudden, “explosive” onset of symptoms, course of sudden exacerbations and remissions

**TRIGGER:** No precipitating illness or use of medications that can cause tics

Temporal relationship of onset and exacerbations with GABHS

**OTHER:** Observation by a knowledgeable individual

Choreiform movements, hyperactivity, etc.

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# Challenges for PANDAS – 1

1. Establish direct and etiological link between tics and GABHS
2. Improve diagnostic criteria for PANDAS
  - Similarity to TS: presence of tic disorder, age onset
  - “sudden explosive worsening”
  - “association with GABHS infection”
  - “choreiform” movements
3. Explain why no other features of rheumatic fever:
  - e.g., carditis

# Challenges for PANDAS - 2

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## 4. Clarify 1<sup>st</sup> degree relative studies:

Rates of tic disorders in PANDAS' families similar to TS and OCD families (Lougee et al., 2000)

## 5. Confirm single point ASO and antiDNAseB titer studies in TS patients with longitudinal protocols:

Increased in ADHD, not CTD or OCD (Peterson et al 2000)

Increased in TS (Muller et al., 2000; 2001; Cardona 2001)

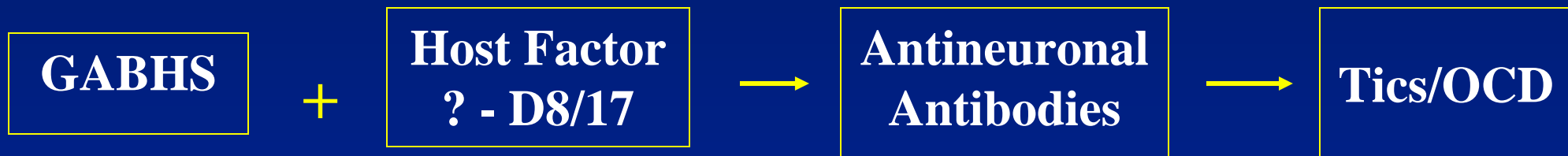
Increased titers of streptococcal M12 and M19 proteins (Muller 2001)

No correlation between strep titers and ANAB (Loiselle 2003)

## 6. Perform interpretable double-blind, cross-over study with oral penicillin: Prior study did not achieve acceptable level of prophylaxis (Garvey et al., 1999)

# Proposed Mechanism for PANDAS

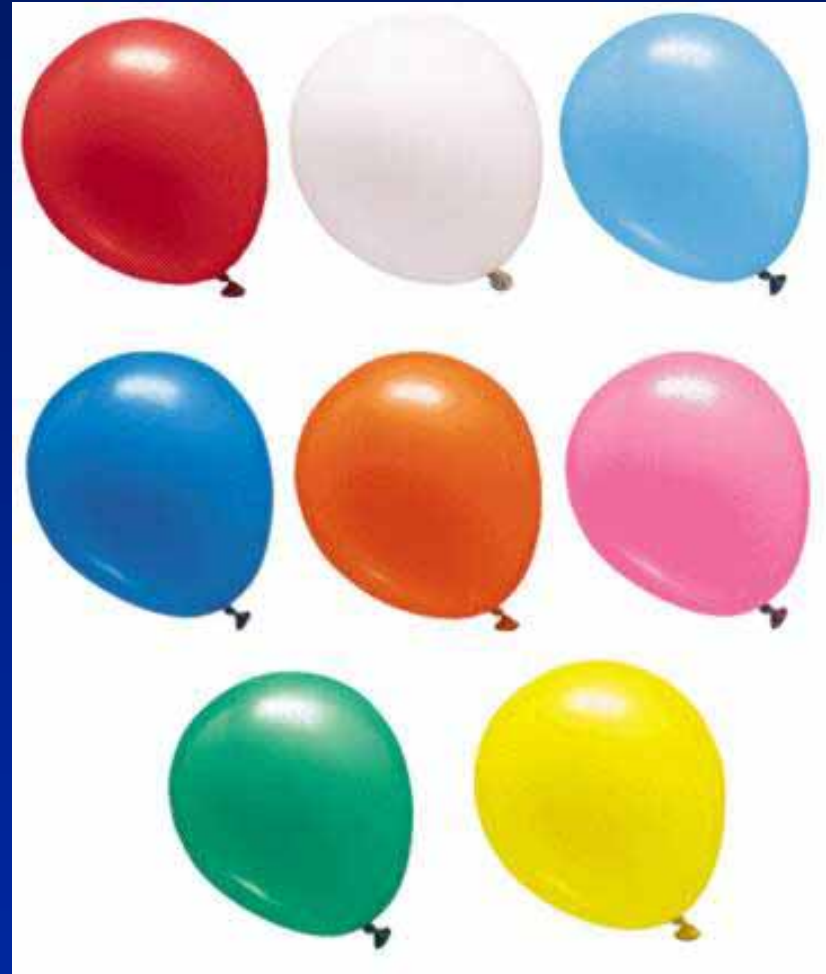
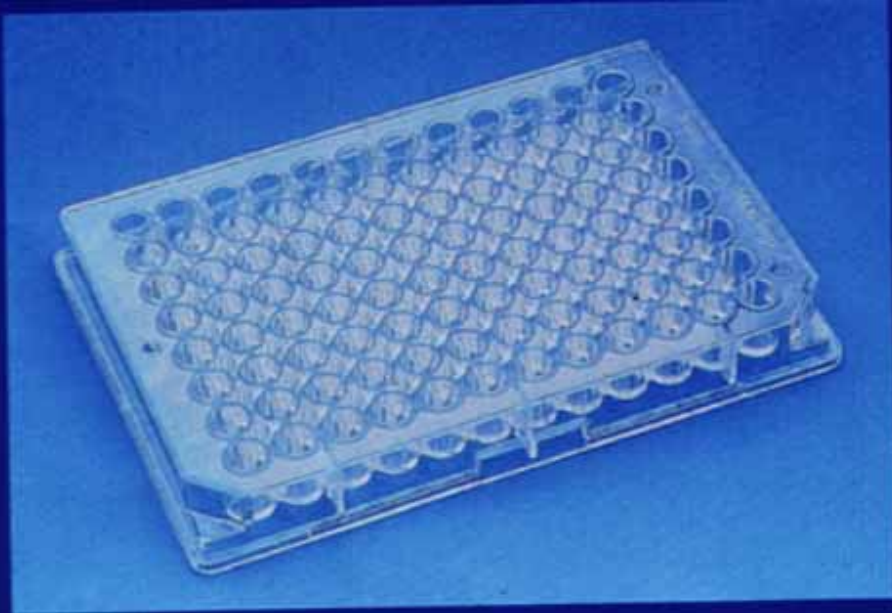
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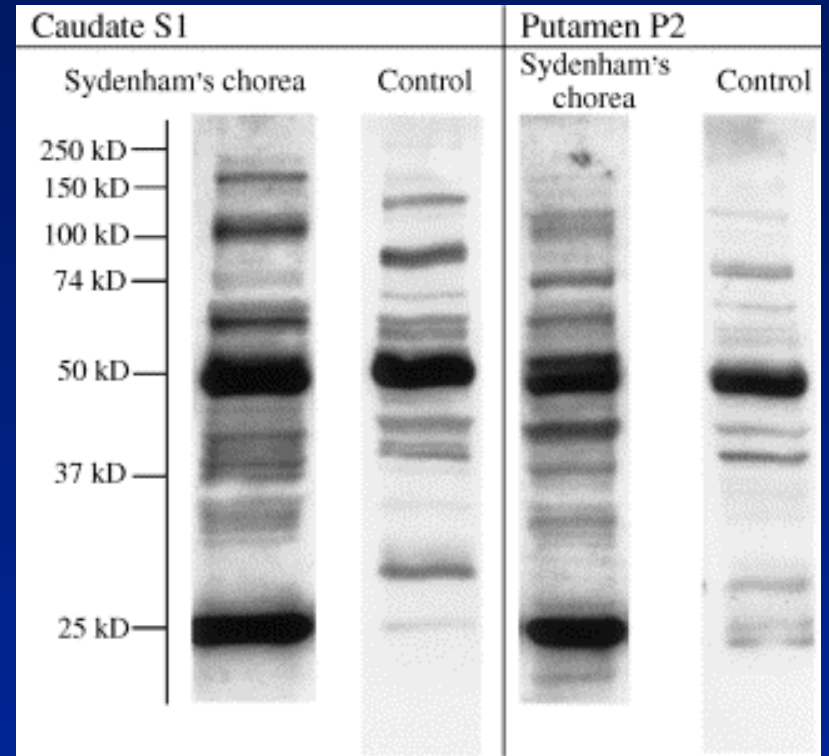
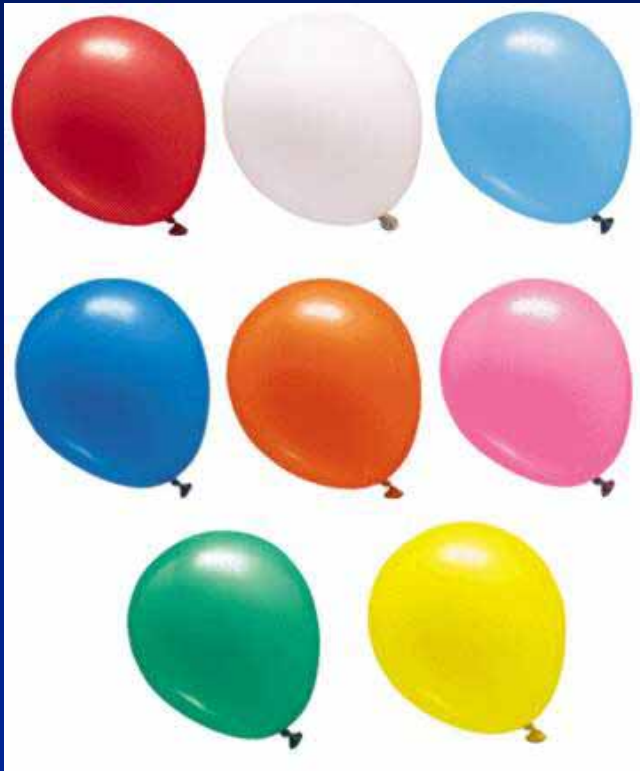
## Confirmation of the ANAb hypothesis

- Immunotherapy
- Quantify/Qualify ANAb
  - ELISA
  - Western blot
  - Immunohistochemistry
- Striatal microinfusions

# ELISA



# Western blot



# ELISA Studies in PANDAS

## London

**INCREASED** in pooled group

### Tissue

Frozen (?) caudate and putamen

### Subjects

20 SC, 16 PANDAS, 4 other (all post-streptococcal infections)

### ELISA Results

Elevated ELISA assay in patients:  
Patients: 0.396 OD ( $p < 0.001$ )  
Control groups (3): 0.19 – 0.251 OD

## Baltimore Study 1

**NOT INCREASED** in PANDAS vs. Control

Assayed separately on fresh caudate, putamen, and GP S1, P2, and synaptosomal fractions

15 PANDAS and 15 controls

No difference between patient and control groups for all assays

Church et al. 2004

Singer et al. 2004

# ELISA Studies in PANDAS

## Baltimore Study 2

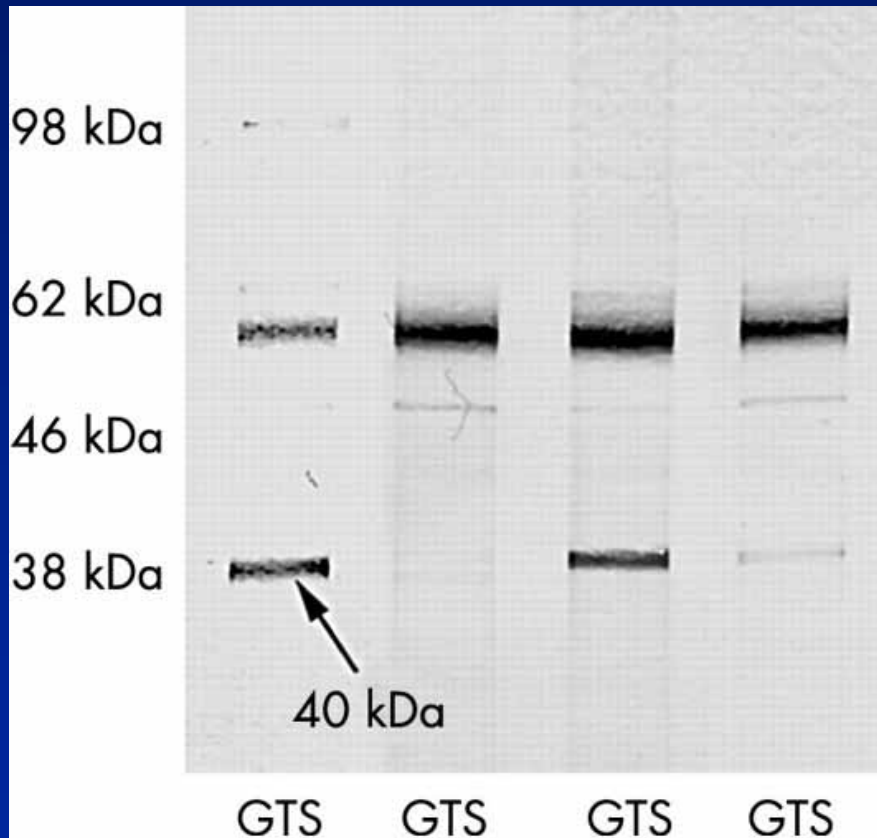
**NOT INCREASED in PANDAS  
vs. TS**

<b>Tissue</b>	Fresh caudate supernatant fraction
<b>Subjects</b>	48 PANDAS and 46 TS
<b>ELISA Results</b>	No difference between patient groups

Singer et al. unpublished

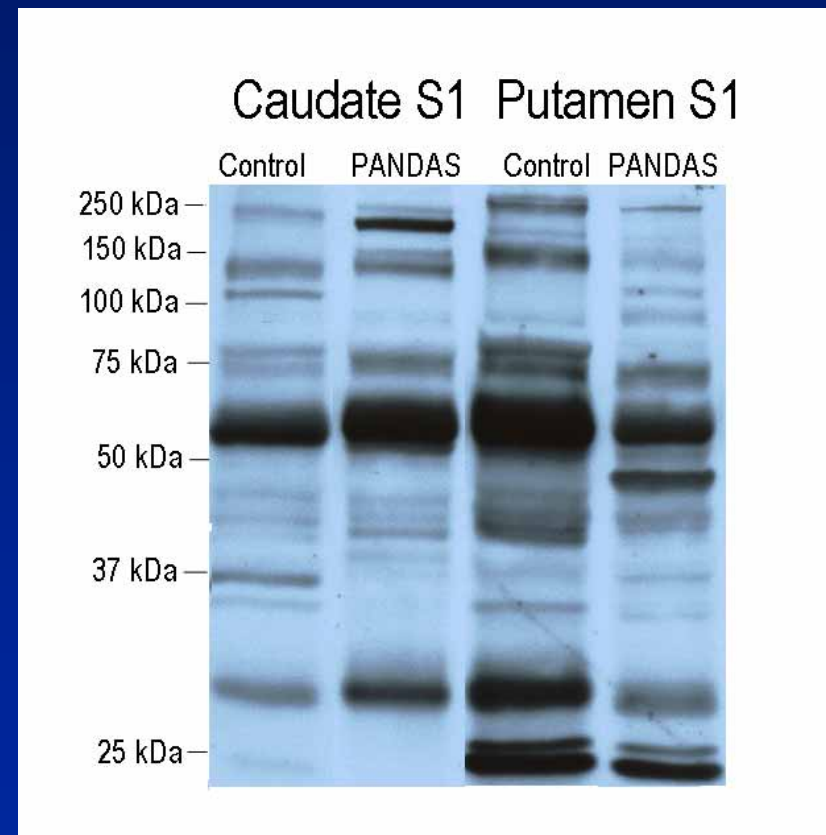
# Western blot studies in PANDAS

## London



WB from TS  
Church et al 2003

## Baltimore Study 1



Singer et al 2004

# Western blot analyses in PANDAS

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## London

Conserved group of autoantigens

**Pooled group** (SC, PANDAS, other):

60 kDa (42.5%), 45 (40%), 40 (47.5%)

**Other groups:**

**SC:** 60 kDa (44%), 45 (42%), 40 (42%)

Church et al 2002

**TS:** 60 kDa (11%), 45 (5%), 40 (7%)

Church et al 2003

## Baltimore Study 1

No major differences

Number of bands not different

Total band density not different

Significant difference did exist in mean binding patterns (discriminant analysis), but only in the caudate S1 preparation (antigen at 183 kDa was the largest contributor to differences)

Singer et al 2004

# Western blot analyses in PANDAS

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## Baltimore Study 2

PANDAS (n=48) vs. TS (n=46) vs. Control (n=43)

Regions studied: Caudate, Putamen, and BA10

- I. Within any given brain region, clinical groups do not differ from controls in:
  - a) average number of bands per blot
  - b) mean area under the curves per blot

# Rodent striatal microinfusion model



# Rodent Infusion Model

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## Rat Striatal Microinfusion Studies:

**YES** Hallett et al 2000; 5 TS sera, titers against neuroblastoma membrane, ventral striatum. **Results** = increased stereotypic behaviors (licks and forepaw shakes) and episodic utterances.

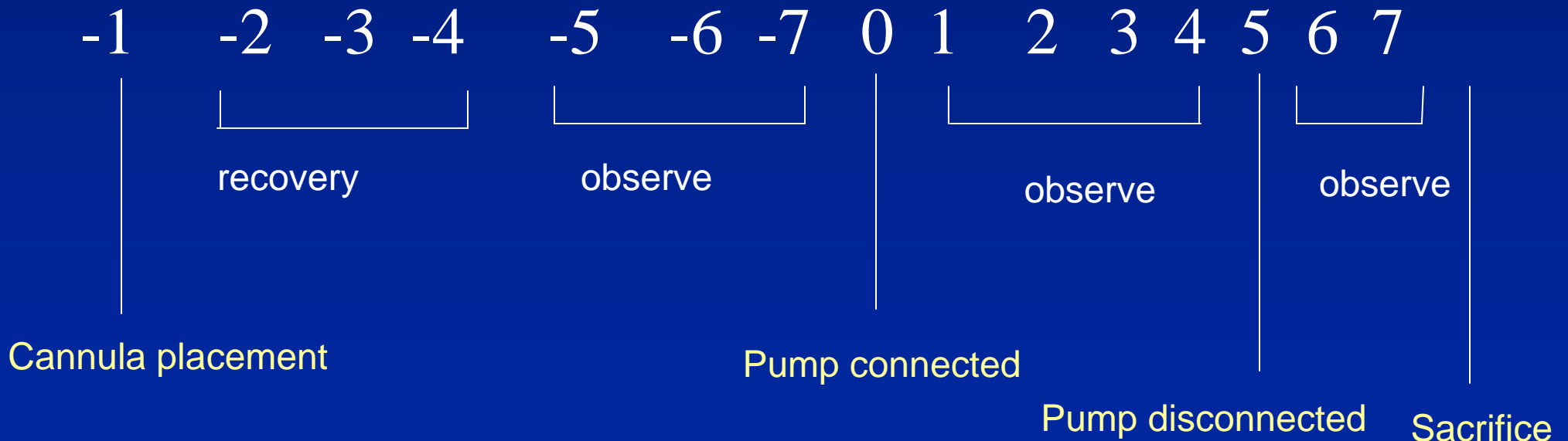
Taylor et al 2002; 12 TS sera, titers against rat striatum. Ventrolateral striatum. **Results** = increased oral stereotypies.

**NO** Loiselle et al 2004; 9 TS sera, titers against human putamen, 8 with PANDAS, rabbit sera with M5 streptococcal AB. Ventral and ventrolateral striatum. **Results** = no changes

# Immune Factors in TS (Hallett, Lombroso, Singer)

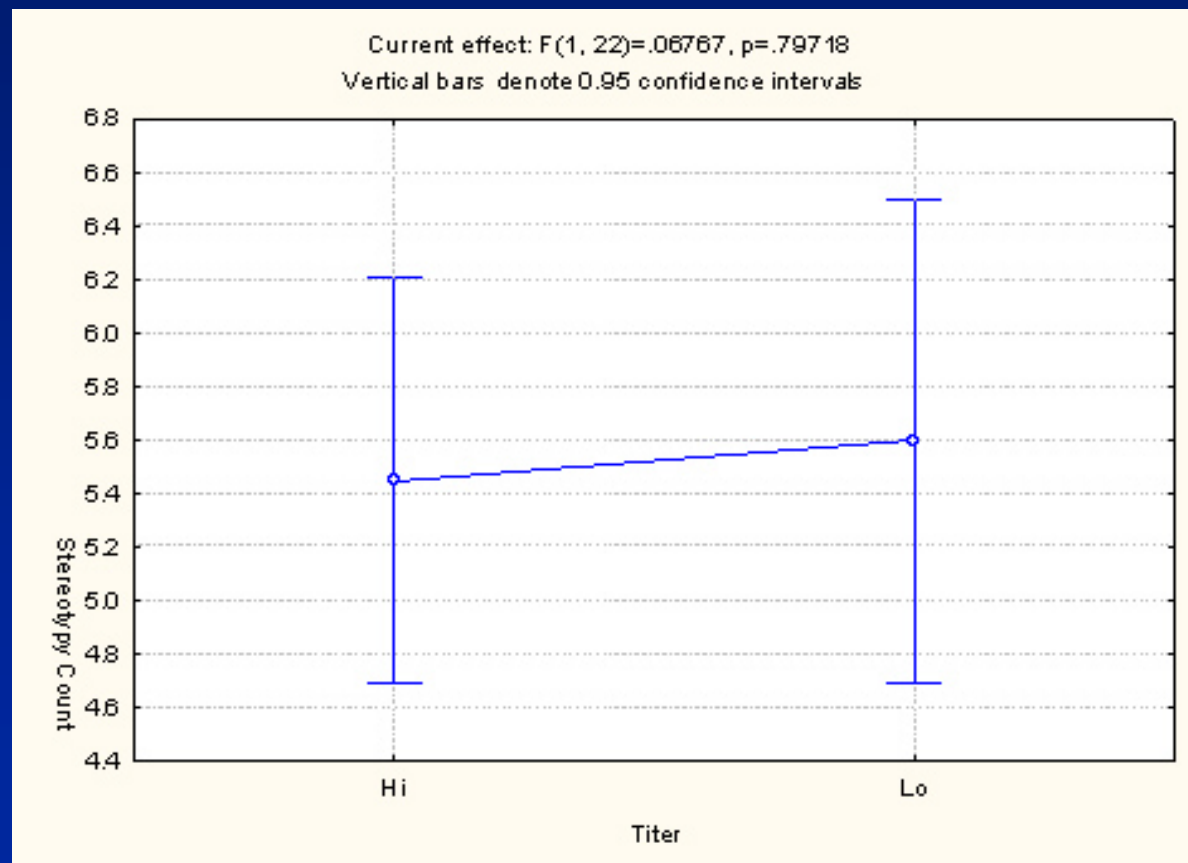
**Question:** Will sera containing high titers of ANAb infused into rodent striatum reliably produce greater levels of stereotypies compared to sera containing low titers?

Timeline:

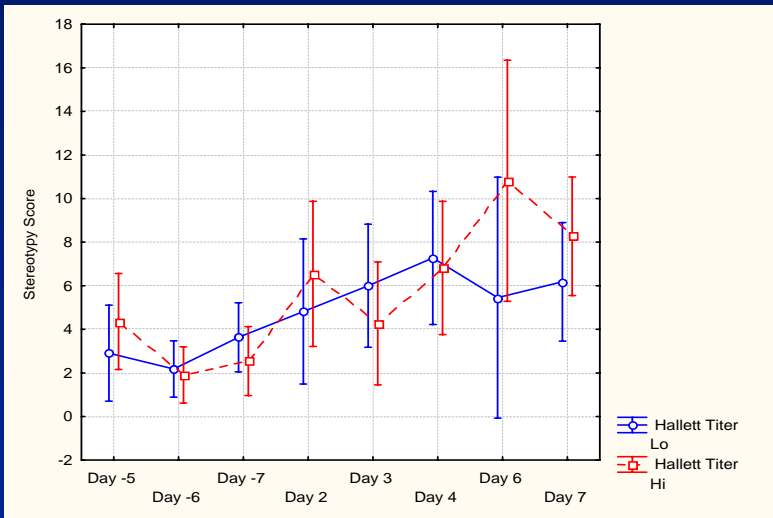


# Is there an effect of titer on stereotypy counts? **NO**

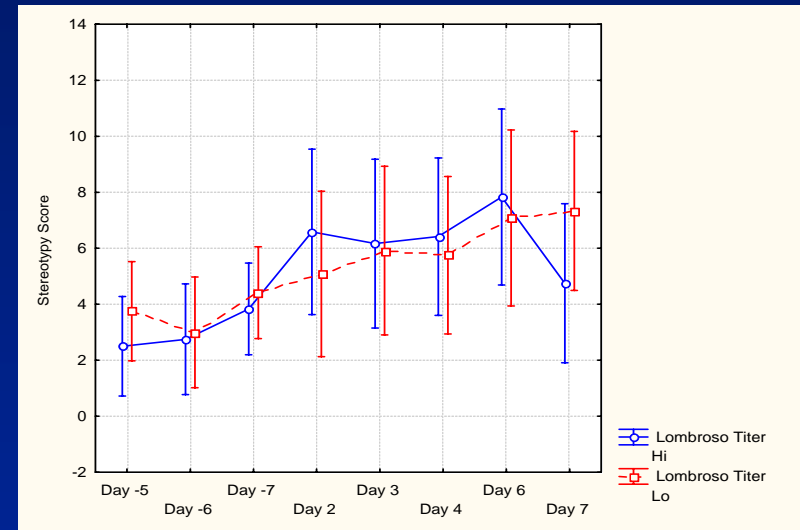
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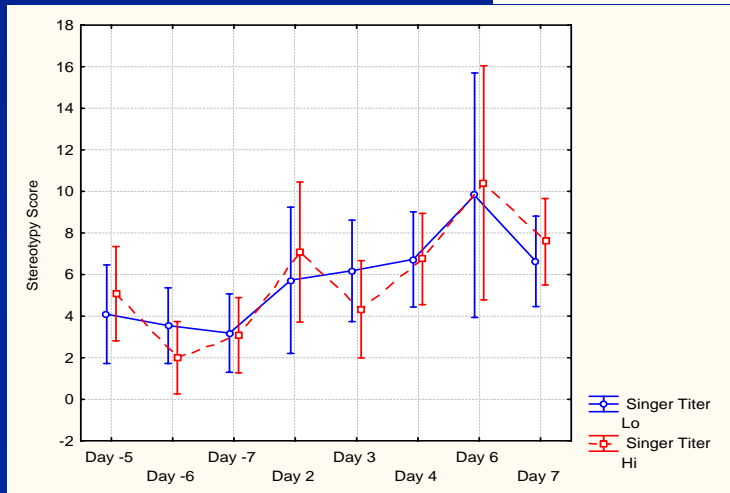
# Is there a difference between high and low titers and stereotypy scores at each center? **NO**



Hallett



Lombroso



Singer

## In Summary

PANDAS is a compelling hypothesis that deserves further study, but final conclusions are still premature.

Investigators on both sides of the “pond” should consider participation in a double-blind protocol.

“Now this is not the end. It is not even the beginning of the end. But it is, perhaps, the end of the beginning.”

(Sir Winston Churchill, Speech in November 1942)

# Recommendations

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1. Careful history:
2. If fulfill criteria:
  - Throat culture, ASO, AntiDNaseB, (if appropriate, repeat titers in 1 month)
3. If Suspect PANDAS:
  - Enter into study
  - “Confirm” with longitudinal evaluations
4. Treatment:
  - a) Penicillin
    - to treat positive throat culture – YES
    - as prophylaxis – NO
  - b) Standard pharmacologic and behavioral therapies for tics/OCD
  - c) Immunomodulatory therapy – NO