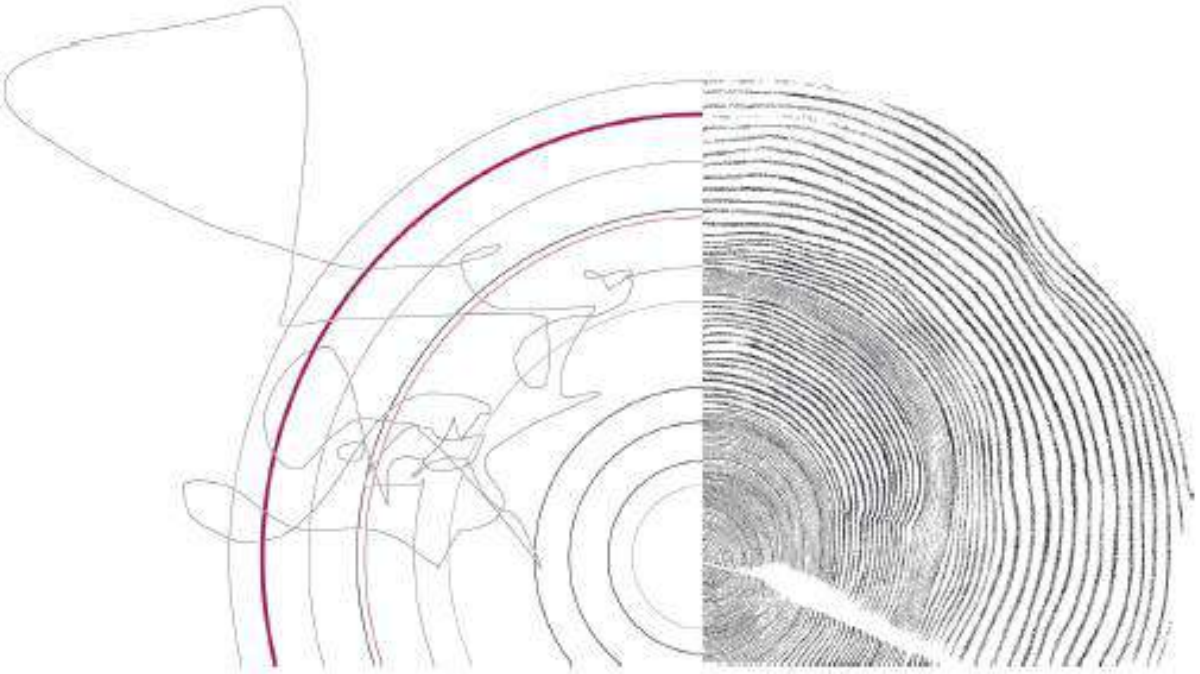


PANS
diagnosis and biomarkers

Eva Hesselmark
BUP OCD, Region Stockholm
Department of Clinical Neuroscience, Karolinska Institutet

The question with PANS and PANDAS

On the one hand…

- Diagnosis is still unclear in clinical practice
- Treatment options are generally poorly examined
- Pathophysiology is still unknown

But on the other…

- Patients with PANS and PANDAS experience that immunomodulatory treatments work
- There is a diagnostic test on the market
- The immunopsychiatry paradigm is gaining ground

The aims of my thesis

I. Describe a Swedish cohort of patients with PANS and PANDAS.

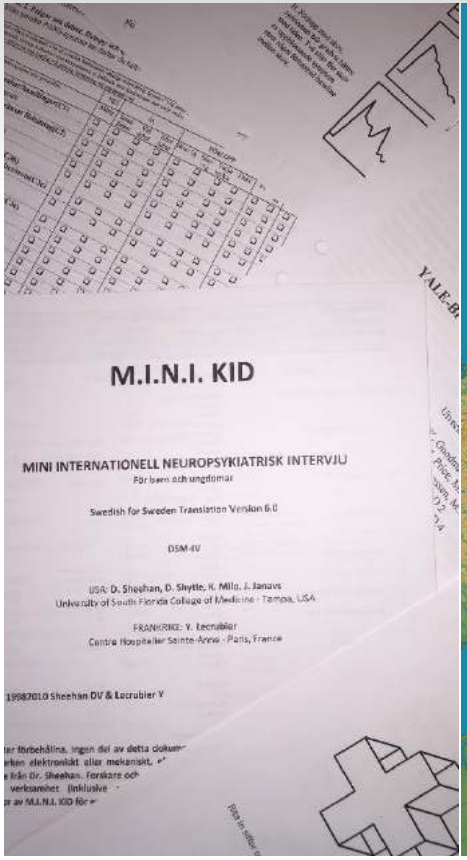
II. Evaluate the diagnostic accuracy of the Cunningham Panel.

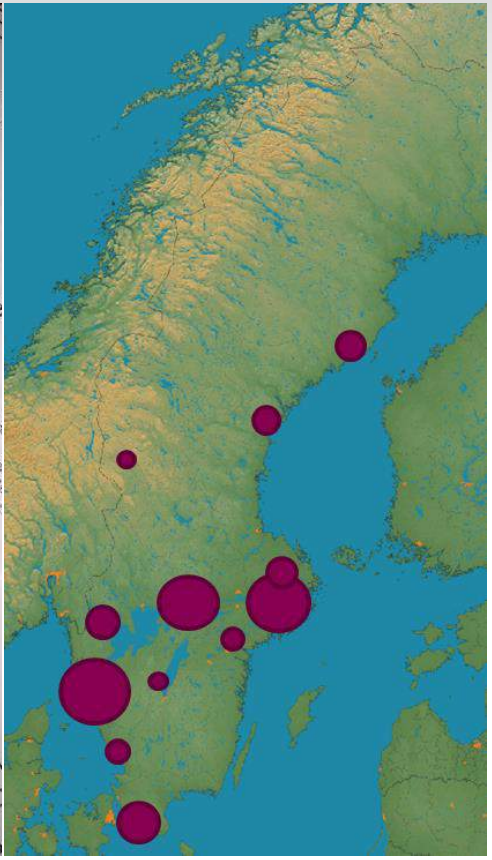
III. Describe the treatments given to a Swedish sample of patients with PANS and PANDAS, and the treatment effects.

IV. Establish if there are currently any evidence-based treatments for PANS or PANDAS.

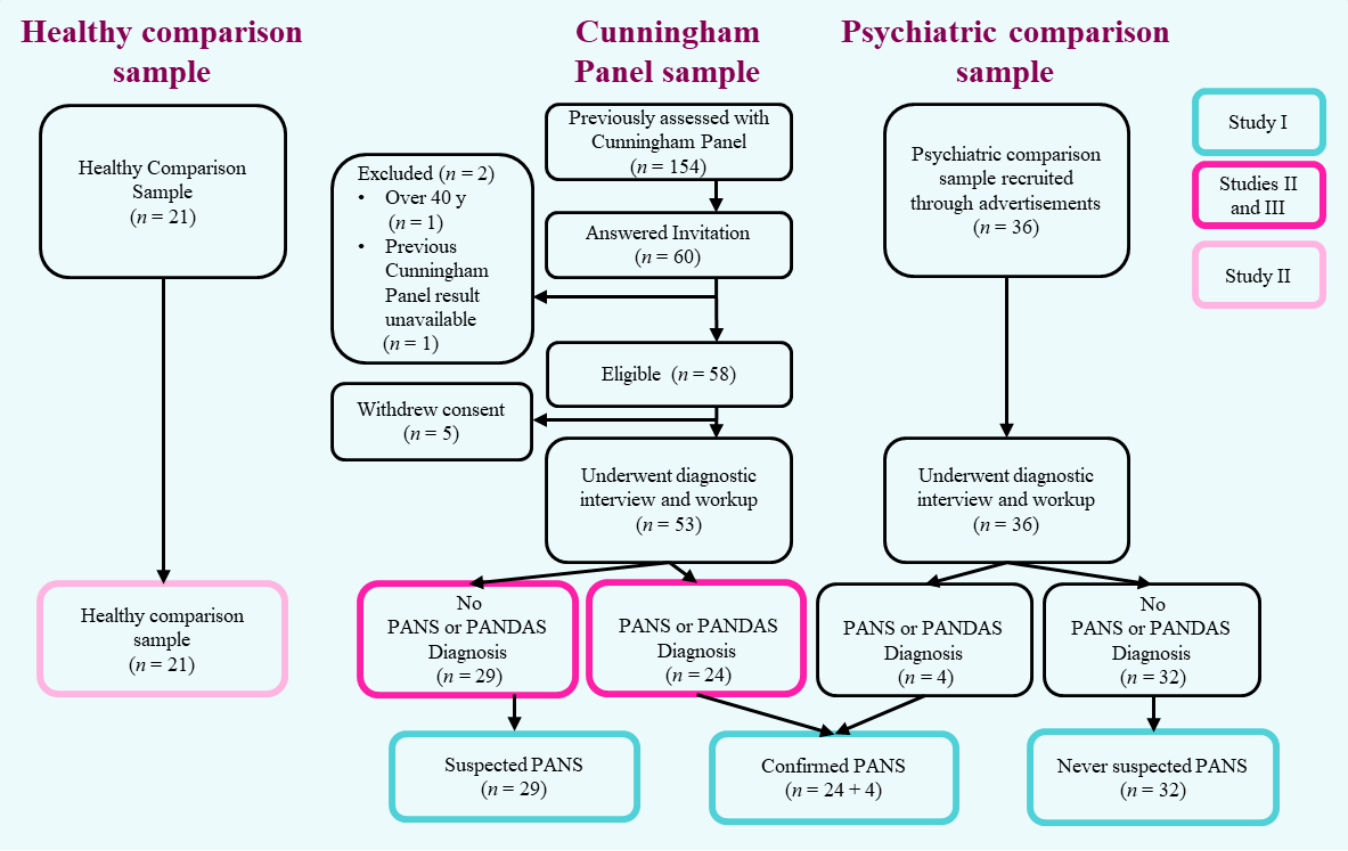
Data collection process

- Psychiatric interviews
  - Standardized
  - Developed to this study
  - Symptoms, onset and course
  - Does each person meet PANS or PANDAS criteria?
- Neuropsychological testing
- Motor testing
- Blood tests
- 3-5 hours





Data collection and study designs



Diagnosis
PANS and PANDAS – clinical features

BJPsych Open (2019)
5, e25, 1–9. doi: 10.1192/bjo.2019.10

Clinical features of paediatric acute-onset neuropsychiatric syndrome: findings from a case– control study

Eva Hesselmark and Susanne Bejerot

Background

Paediatric acute-onset neuropsychiatric syndrome (PANS), an umbrella term that includes PANDAS (paediatric autoimmune neuropsychiatric disorders associated with streptococcal infections) is suggested to be a psychiatric disorder of autoimmune aetiology. PANS is characterised by an acute onset of obsessive–compulsive disorder or restricted eating with multiple comorbid symptoms. The specificity of the PANS criteria is not fully understood.

Aims

To describe a cohort of patients with PANS and to determine if PANS features relating to symptoms, onset and course are more common in PANS than in other psychiatric conditions.

Method

A case–control study comparing patients with interview-confirmed PANS with patients with suspected PANS and patients with a psychiatric condition but with no suspicion of PANS. Validated and non-validated measures of symptoms, onset and episodic course were used.

Results

Patients with interview-confirmed PANS did not present a specific symptom profile.

Conclusions

PANS may be a distinct clinical entity featuring an acute onset, an episodic course and multiple symptoms at onset.

Declaration of interest

None.

Keywords

Pediatric acute-onset neuropsychiatric syndrome; pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections; diagnostic criteria; obsessive-compulsive disorder.

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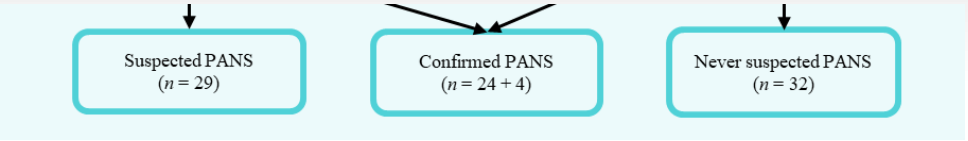
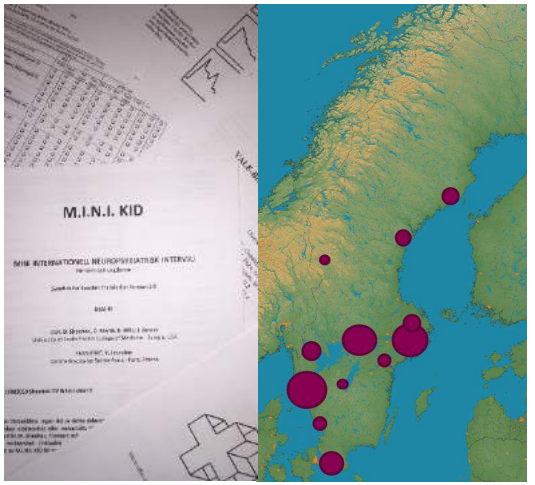
Diagnosis

PANS and PANDAS – clinical features

Methods

- Case-control study
- 3 groups
- Based on the interviews we made





- Symptoms
- Acute onset
- Episodic course

PANDAS

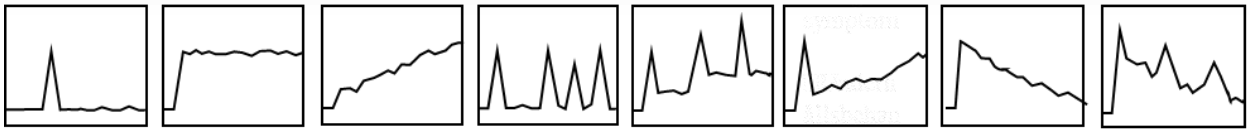
Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal infections (1998)

- OCD and or Tics
  - Pre-pubertal onset
  - Acute onset and dramatic symptom exacerbations
  - Evidence of GABHS infection preceding illness
  - Neurological symptoms

PANS

Pediatric Acute-onset Neuropsychiatric Syndrome (2012)

- Abrupt, dramatic onset of OCD or severely restricted food intake
- Concurrent presence of additional neuropsychiatric symptoms, with similarly severe and acute onset, from at least two of seven categories:
  - Anxiety
  - Emotional lability and/or depression
  - Irritability, aggression and/or severely oppositional behaviors
  - Behavioral (developmental) regression
  - Deterioration in school performance
  - Sensory or motor abnormalities
  - Somatic signs and symptoms, including sleep disturbances, enuresis or urinary frequency
- Not better explained by a known condition


A
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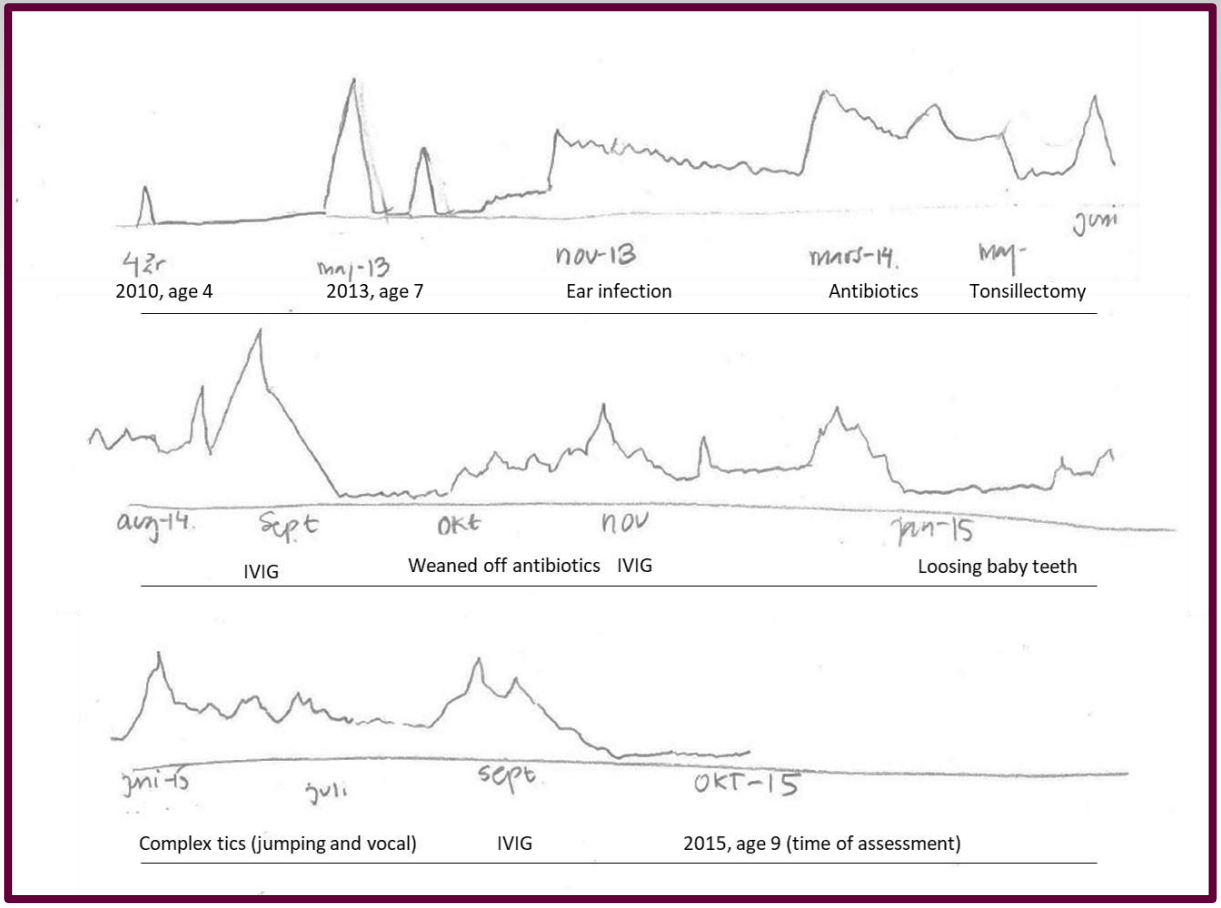

4år
maj-13
nov-13
mars-14
maj-
juni
2010, age 4
2013, age 7
Ear infection
Antibiotics
Tonsillectomy
aug-14
Sept
Okt
nov
jan-15
IVIG
Weaned off antibiotics
IVIG
Loosing baby teeth
juni-15
juli
sept
okt-15
Complex tics (jumping and vocal)
IVIG
2015, age 9 (time of assessment)

The PANS/PANDAS Related Symptom Inventory (PPRSI)

		NO	YES			COURSE				SEVERE SYMPTOM?		NOW?
Symptom (Bold text indicate PANS/PANDAS symptoms and below each symptom are specifiers in non bold text)		Never	Before onset	At onset	After onset	Flare = 1	Flares >1	Every week	Fluctuating	Now	Ever	Now?
a.	**Obsessions or Compulsions**	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑
b.	Hoarding behaviors	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑
c.	**Anorexia or restricted eating**	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑
d.	**Anxiety**	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑
e.	Separation anxiety	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑
f.	**Emotional lability or depression**	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑

The Signs of Severity Questionnaire (SOSQ)

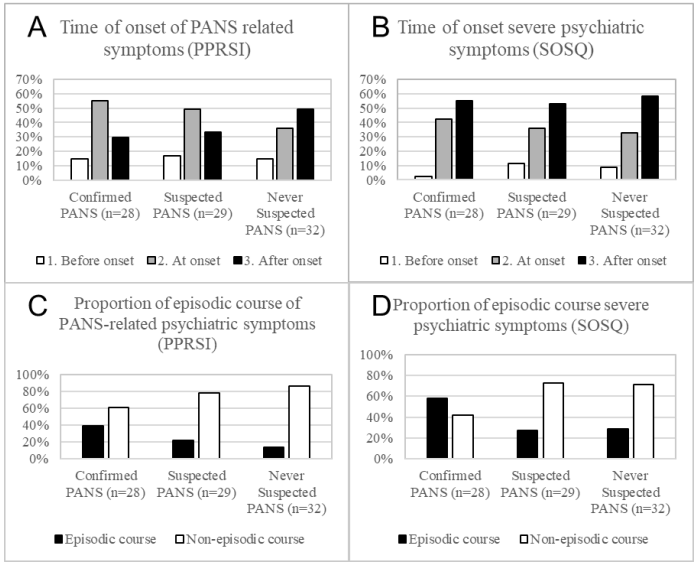
		NO	YES			COURSE				SEVERE SYMPTOM?		NOW?
Symptom		Never	Before onset	At onset	After onset	Flare = 1	Flares >1	Every week	Fluctuating	Now	Ever	Now?
a.	Suicidal ideation	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑
b.	Suicidal gestures	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑
c.	Suicidal intent	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑
d.	Self injury behavior	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑
e.	Homicidal thoughts	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑
f.	Homicidal behaviors	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑

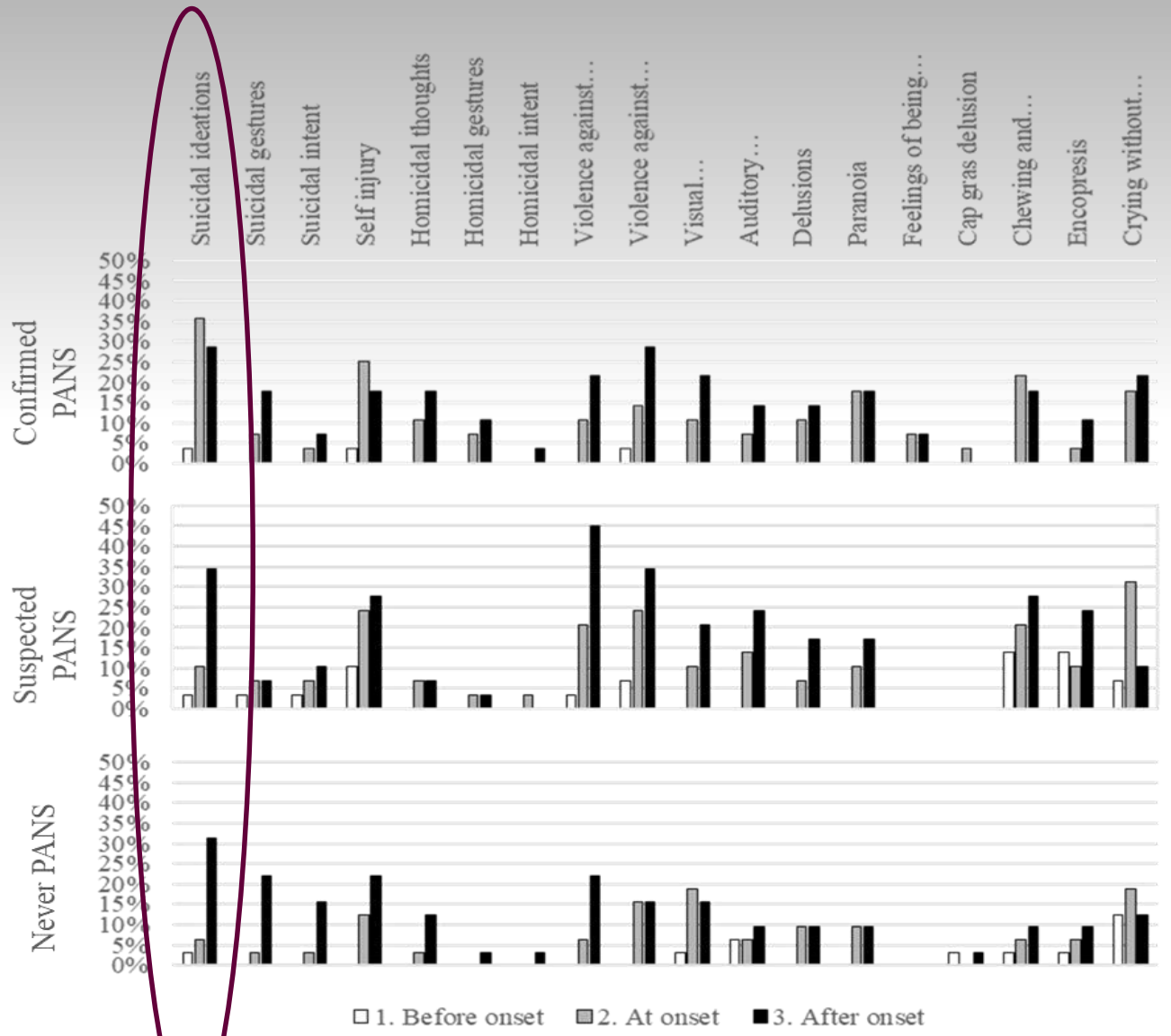
Diagnosis

PANS and PANDAS – clinical features

Results

- Patients with confirmed PANS had
  - Acute onset
  - More symptoms at onset
  - Episodic course
- The three groups had similar symptoms



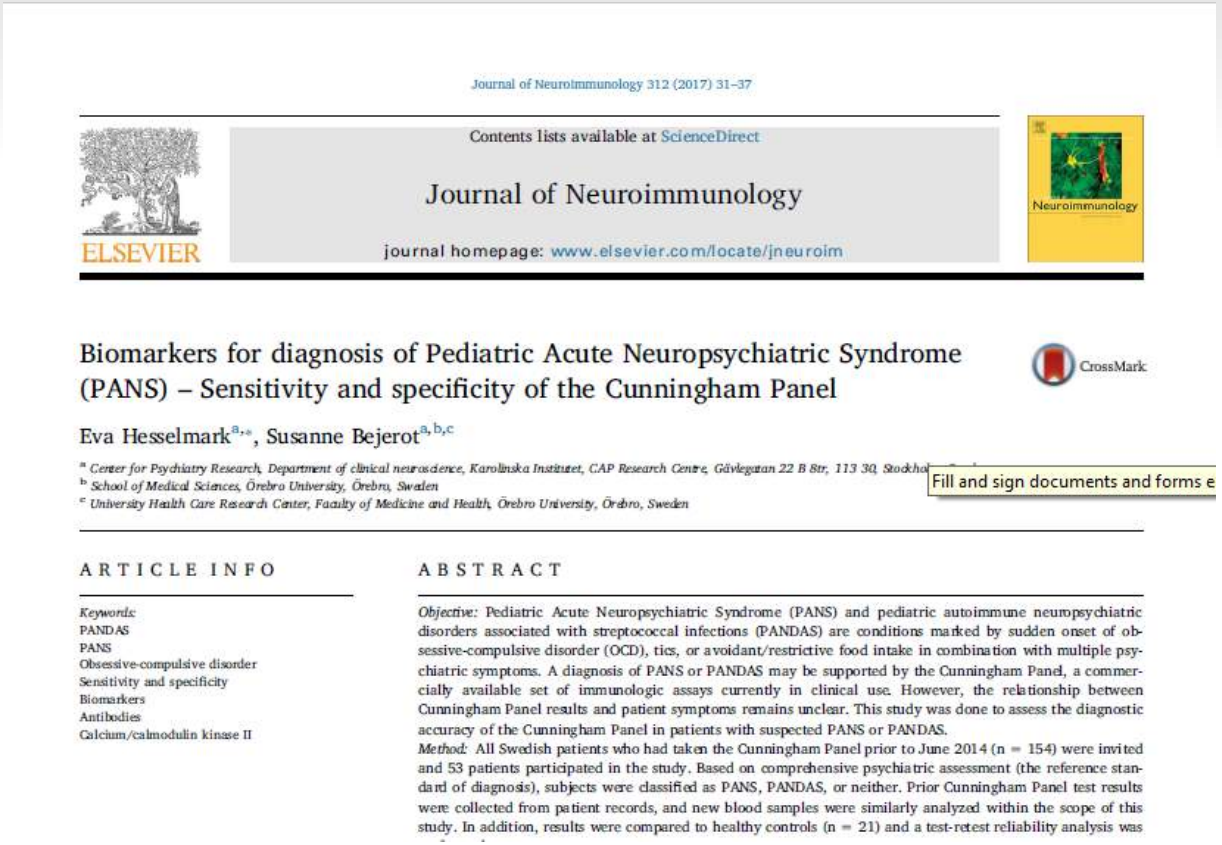

Suicidal ideations
Suicidal gestures
Suicidal intent
Self injury
Homicidal thoughts
Homicidal gestures
Homicidal intent
Violence against…
Violence against…
Visual…
Auditory…
Delusions
Paranoia
Feelings of being…
Cap gras delusion
Chewing and…
Encopresis
Crying without…
Confirmed PANS
Suspected PANS
Never PANS
50%
45%
40%
35%
30%
25%
20%
15%
10%
5%
0%
1. Before onset
2. At onset
3. After onset

Diagnosis
Conclusions

- Acute onset was associated with an episodic course and high symptom load at onset
- Symptom panorama were very similar in the groups with suspected and confirmed PANS
- When assessing and diagnosing PANS, the focus of the psychiatric assessment should be on the onset and course of the disorder, in addition to individual psychiatric symptoms.

Biomarkers

What is the diagnostic value of the Cunningham panel?



Journal of Neuroimmunology 312 (2017) 31–37

Contents lists available at ScienceDirect

Journal of Neuroimmunology

journal homepage: www.elsevier.com/locate/jneuroim

Biomarkers for diagnosis of Pediatric Acute Neuropsychiatric Syndrome (PANS) – Sensitivity and specificity of the Cunningham Panel

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[b] School of Medical Sciences, Örebro University, Örebro, Sweden

[c] University Health Care Research Center, Faculty of Medicine and Health, Örebro University, Örebro, Sweden

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ARTICLE INFO

Keywords:
PANDAS
PANS
Obsessive-compulsive disorder
Sensitivity and specificity
Biomarkers
Antibodies
Calcium/calmodulin kinase II

ABSTRACT

Objective: Pediatric Acute Neuropsychiatric Syndrome (PANS) and pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS) are conditions marked by sudden onset of obsessive-compulsive disorder (OCD), tics, or avoidant/restrictive food intake in combination with multiple psychiatric symptoms. A diagnosis of PANS or PANDAS may be supported by the Cunningham Panel, a commercially available set of immunologic assays currently in clinical use. However, the relationship between Cunningham Panel results and patient symptoms remains unclear. This study was done to assess the diagnostic accuracy of the Cunningham Panel in patients with suspected PANS or PANDAS.

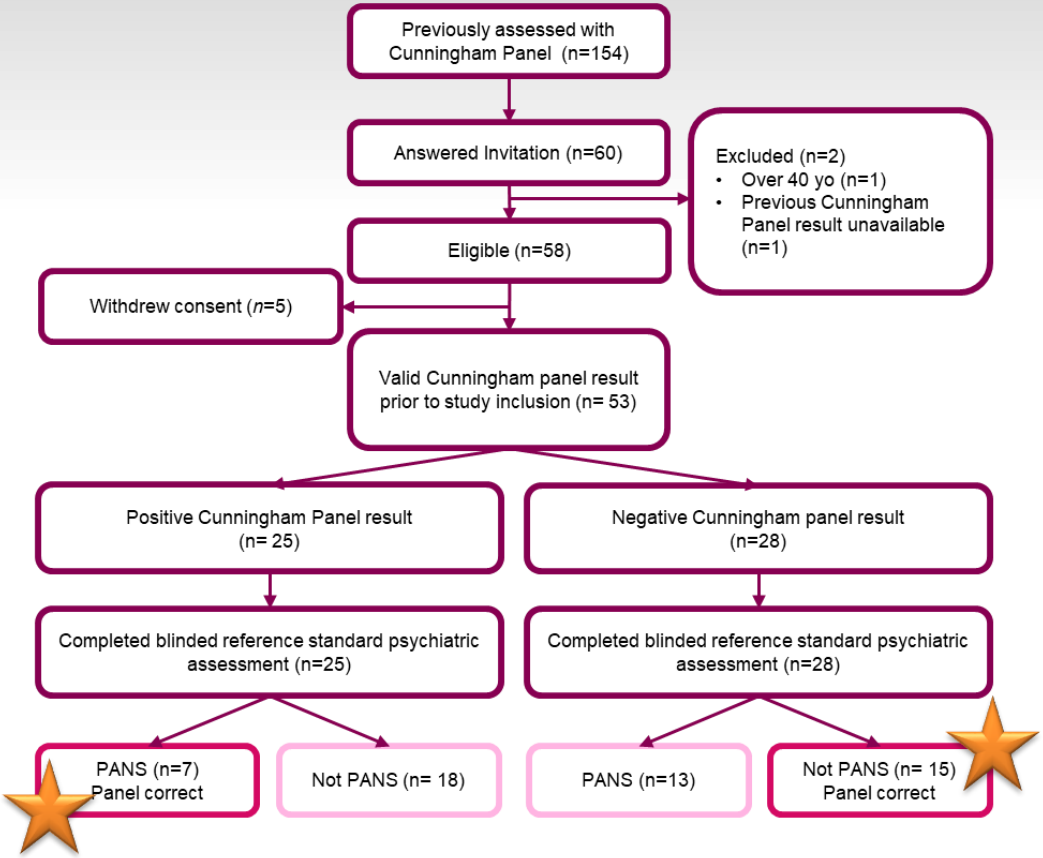
Method: All Swedish patients who had taken the Cunningham Panel prior to June 2014 (n = 154) were invited and 53 patients participated in the study. Based on comprehensive psychiatric assessment (the reference standard of diagnosis), subjects were classified as PANS, PANDAS, or neither. Prior Cunningham Panel test results were collected from patient records, and new blood samples were similarly analyzed within the scope of this study. In addition, results were compared to healthy controls (n = 21) and a test-retest reliability analysis was

What is the diagnostic value of the Cunningham panel?

Cunningham Panel

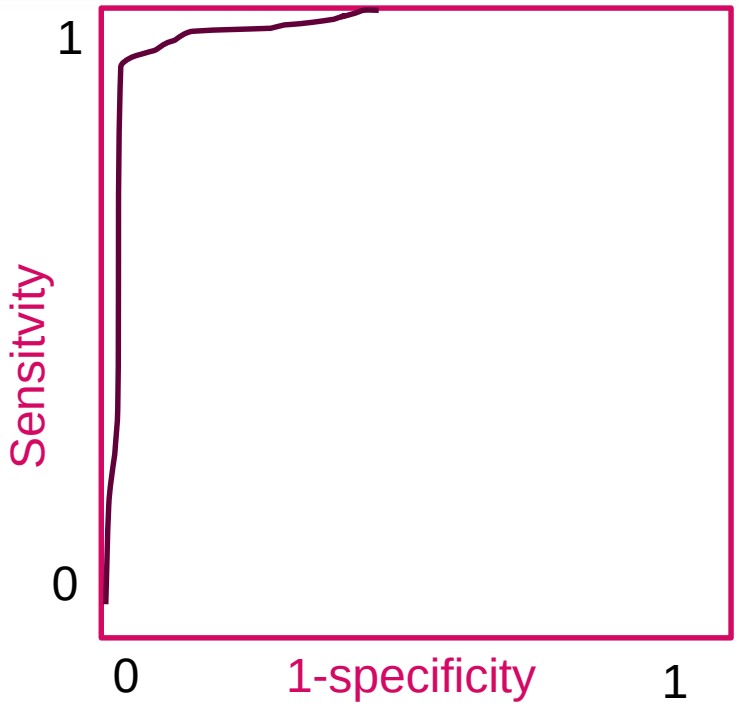
Analysis	
Antibody against Dopamine receptor D1	
Antibody against Dopamine receptor D2	
Antibody against Beta-tubulin	
Antibody against lyso-ganglioside	
Activation of Calcium/Calmodulin dependent kinase II	

What is the diagnostic value of the Cunningham panel?

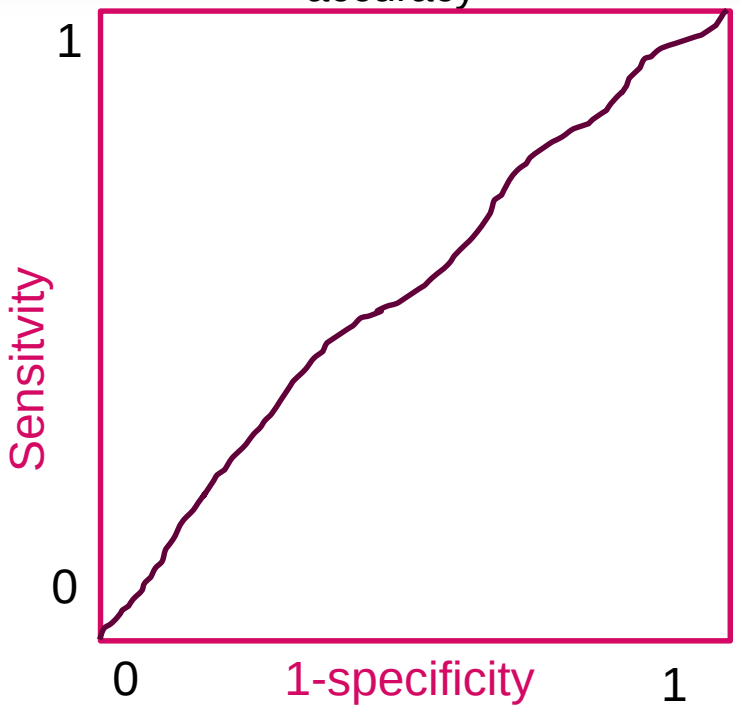


What is the diagnostic value of the Cunningham panel

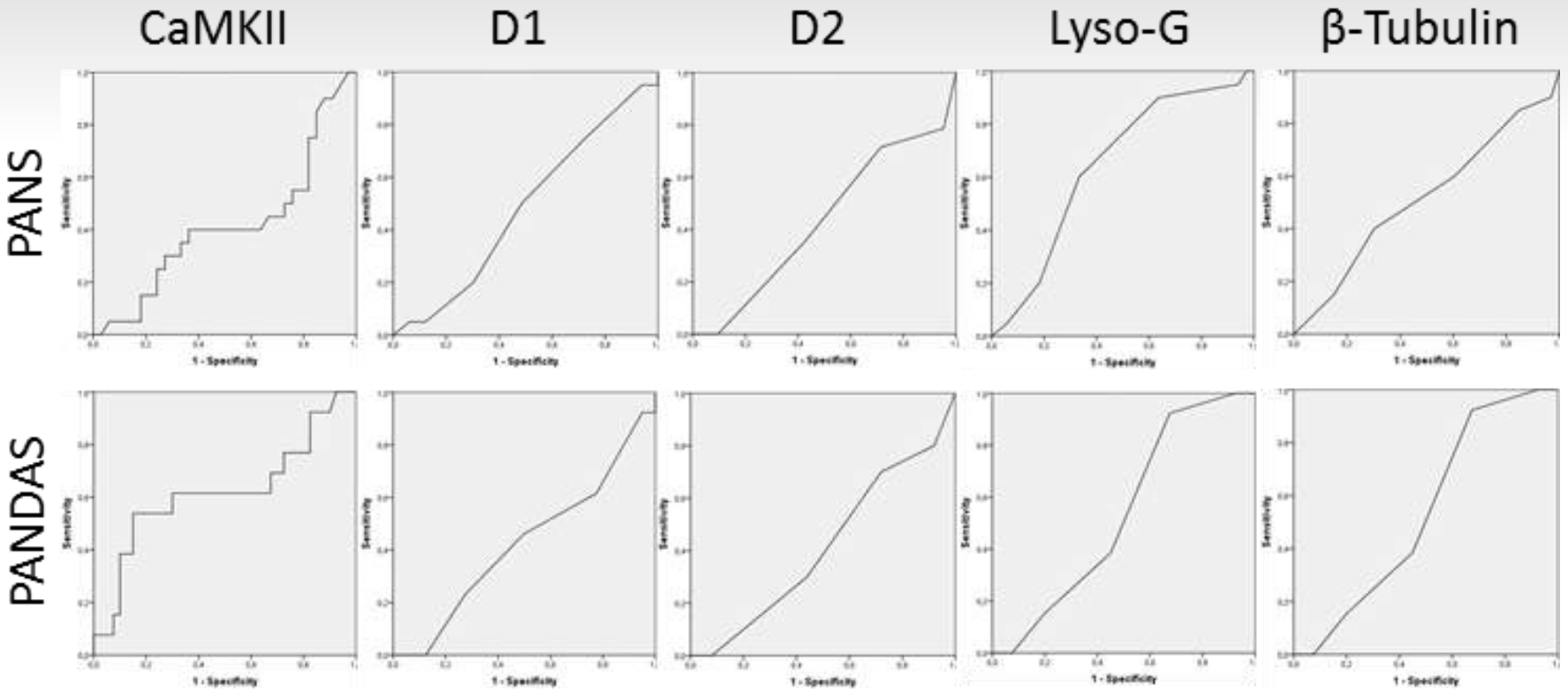
A ROC-curve showing high diagnostic accuracy



A ROC-curve showing low diagnostic accuracy



What is the diagnostic value of the Cunningham panel



What is the diagnostic value of the Cunningham panel

Healthy controls often had elevated levels

- 47% positive CamKII
- 81% positive antibody
- 85% positive in at least one analyte

Bejerot et al. *Translational Psychiatry* (2019)9:224
https://doi.org/10.1038/s41398-019-0562-y

Translational Psychiatry

CORRESPONDENCE Open Access

The Cunningham Panel: concerns remain

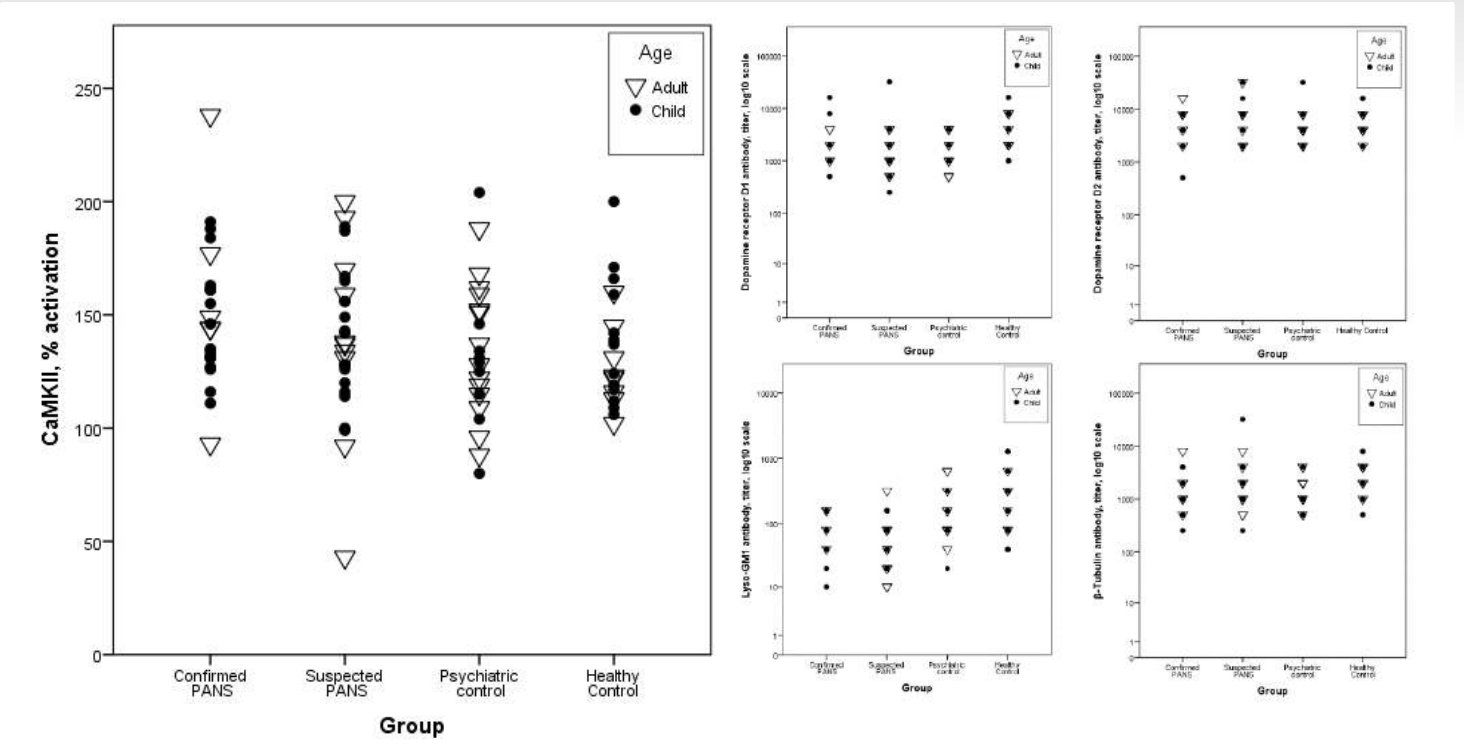
Susanne Bejerot[1,2,3], Albin Klang[1] and Eva Hesselmark[3,4]

Dear Editor,

We thank the authors of the Connery paper[1] for their response[2] on the reliability of the Cunningham Panel[3]. The panel is developed and marketed by Moleculera Labs as a diagnostic test for pediatric acute-onset neuropsychiatric syndrome (PANS) and pediatric autoimmune neuropsychiatric disorder associated with streptococcus (PANDAS). Here we address some misconceptions raised by the authors and present new data.

First, the 21 healthy controls (median age 15 years) tested with the Cunningham Panel in our study were followed Wieslab's instructions, which included plastic tubes and gold top tubes[4].

Although the Cunningham Panel may predict response to intravenous immunoglobulin (IVIG), this was not the case among our participants[4,6,7]. We have made a post hoc analysis including 12 patients from our dataset who had been tested with the panel prior to treatment with IVIG (2 adults, 10 children)[6]. Five had confirmed PANS and 7 suspected but not confirmed PANS. All had elevated Ca^{2+}/calmodulin-dependent protein kinase II (CaMKII) values. Dopamine receptor D2 antibody results


CaMKII, % activation
Age
Adult
Child
Confirmed PANS
Suspected PANS
Psychiatric control
Healthy Control
Group
Dopamine receptor D1 antibody, titer, log10 scale
Dopamine receptor D2 antibody, titer, log10 scale
Lyso-GM1 antibody, titer, log10 scale
β-Tubulin antibody, titer, log10 scale

Conclusions

- Course, acute onset and high symptom load at onset are better specifiers of PANS than presence of specific symptoms.
- The Cunningham Panel was not clinically useful as a diagnostic measure for PANS.

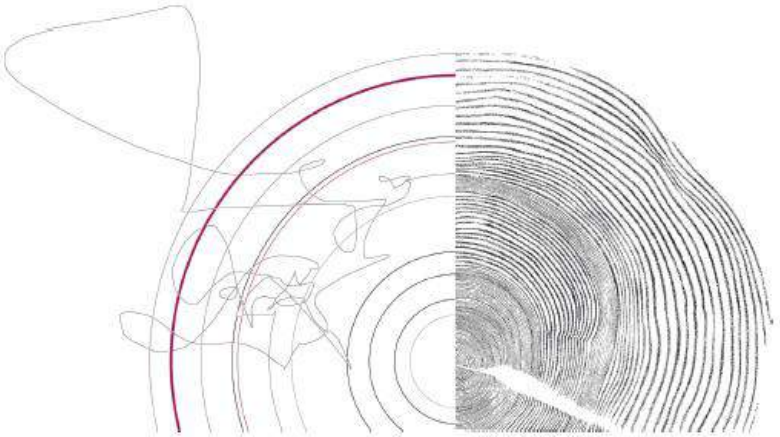
Acknowledgements

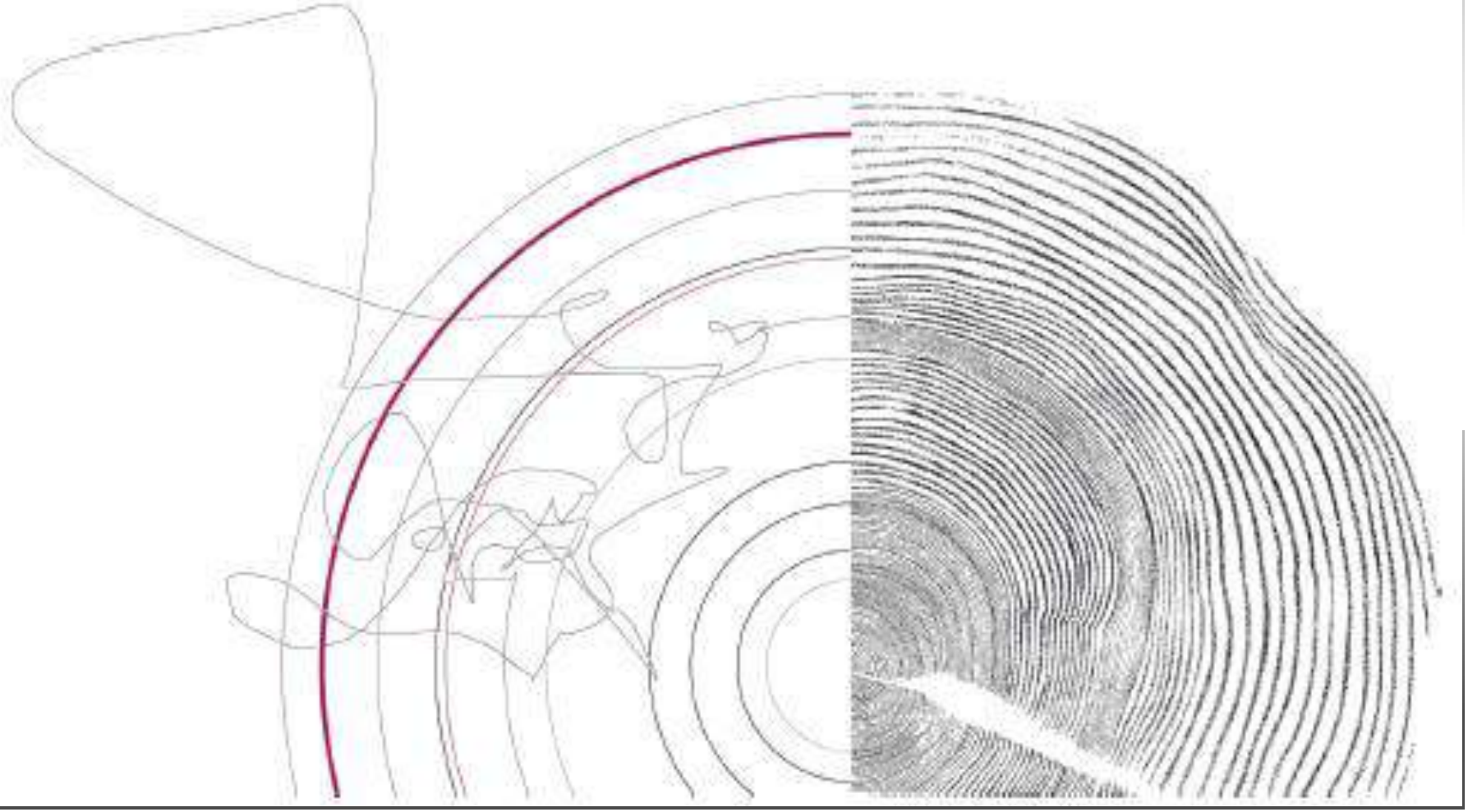
A special thanks to

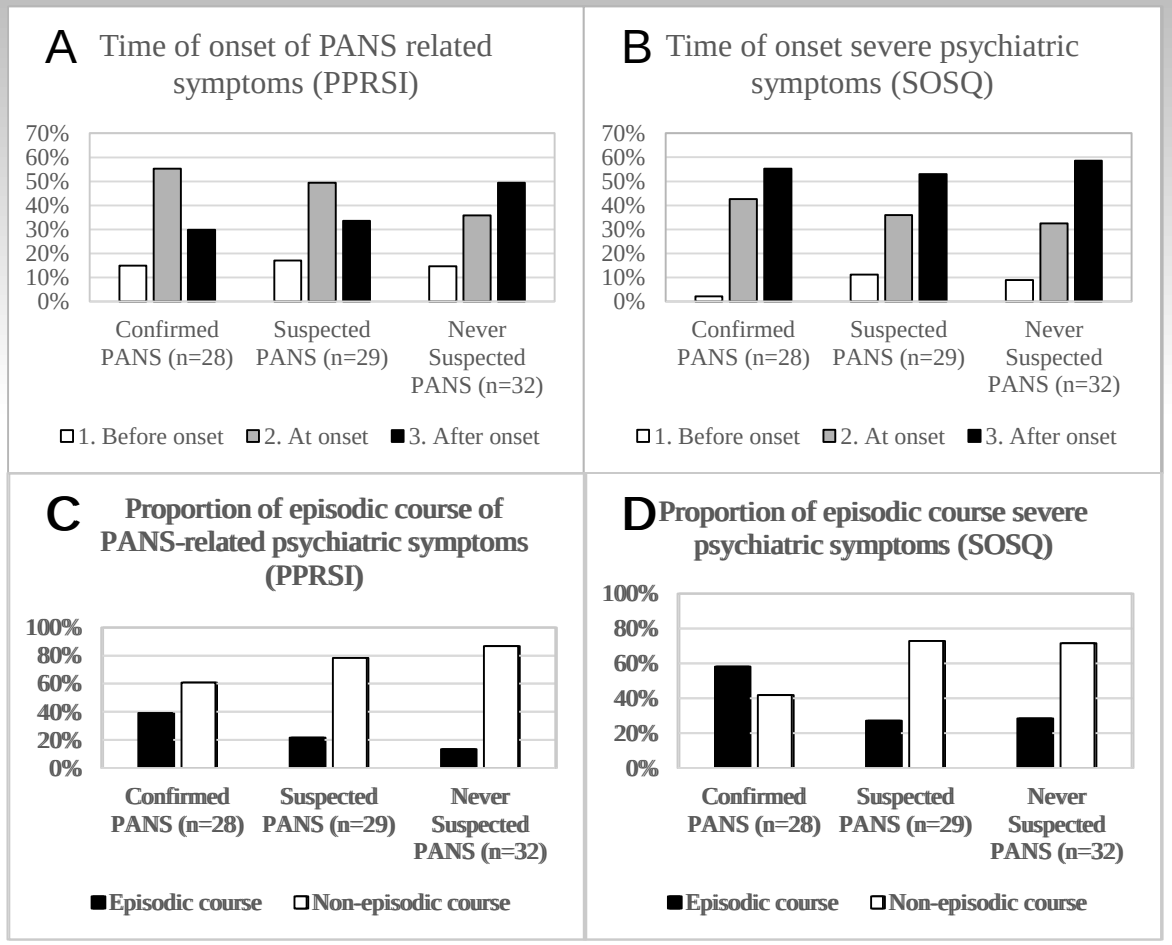
- All the participants in the study, and their families
- Supervisor Susanne Bejerot and co-supervisor Gustav Nilsonne
- Sara Ekman, Jasmina Popaja, Machi Cleanthous, Albin Klang

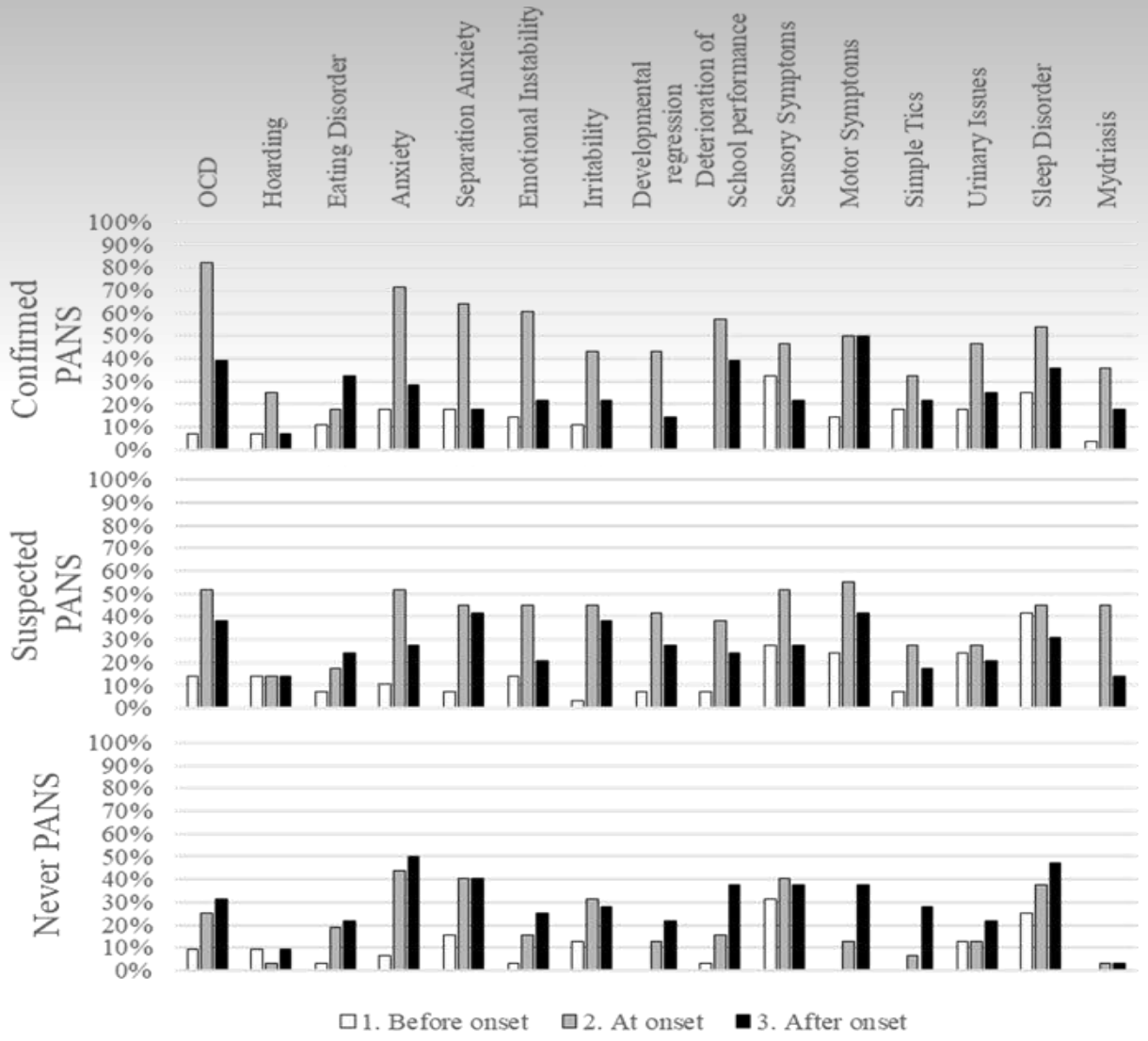
And for Financial Support:

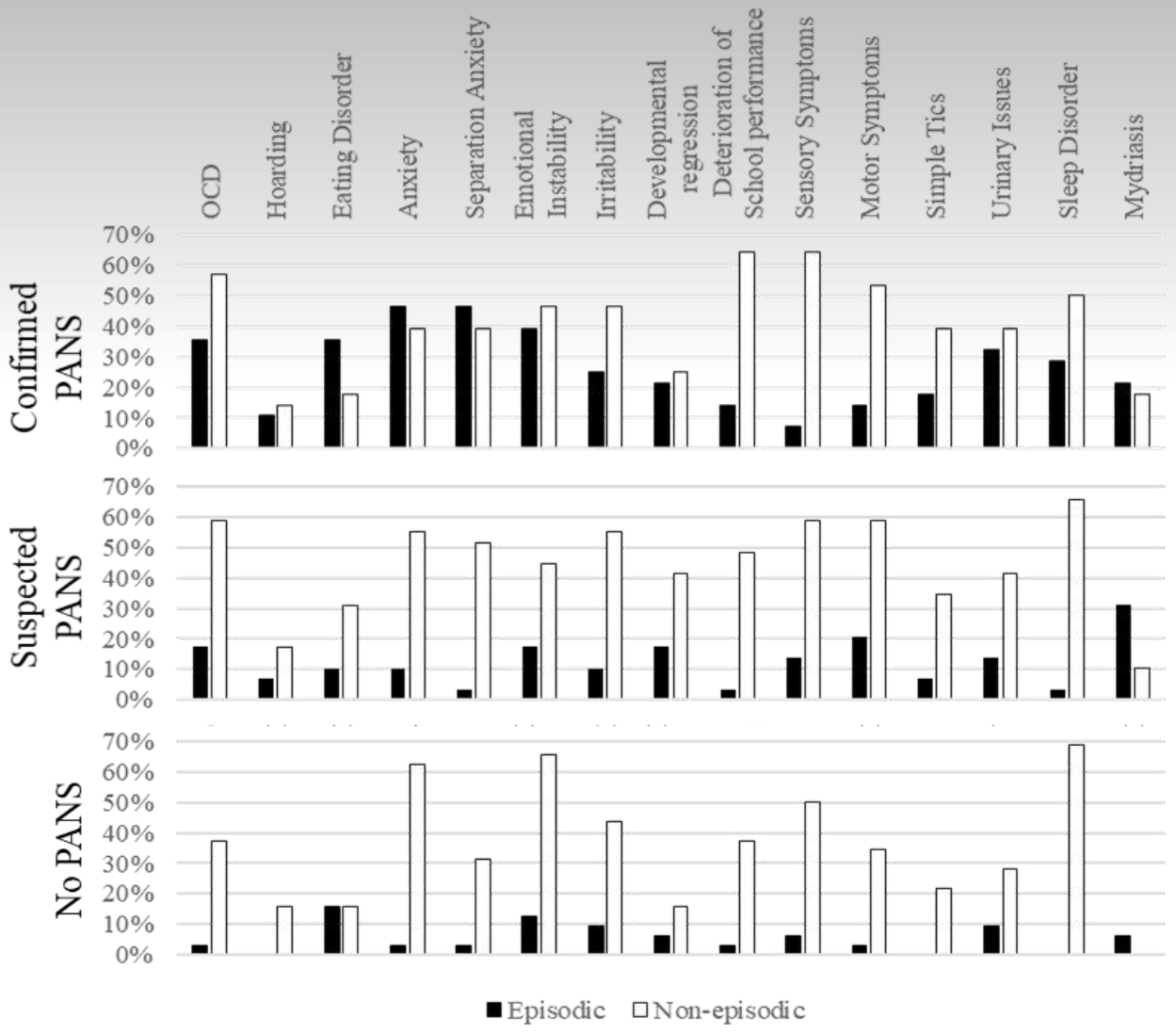
- Swedish Research Council
- Hjärnfonden
- Stockholm County Council (PPG project).
- Bror Gadelius Minnesfond
- Psykiatrifonden

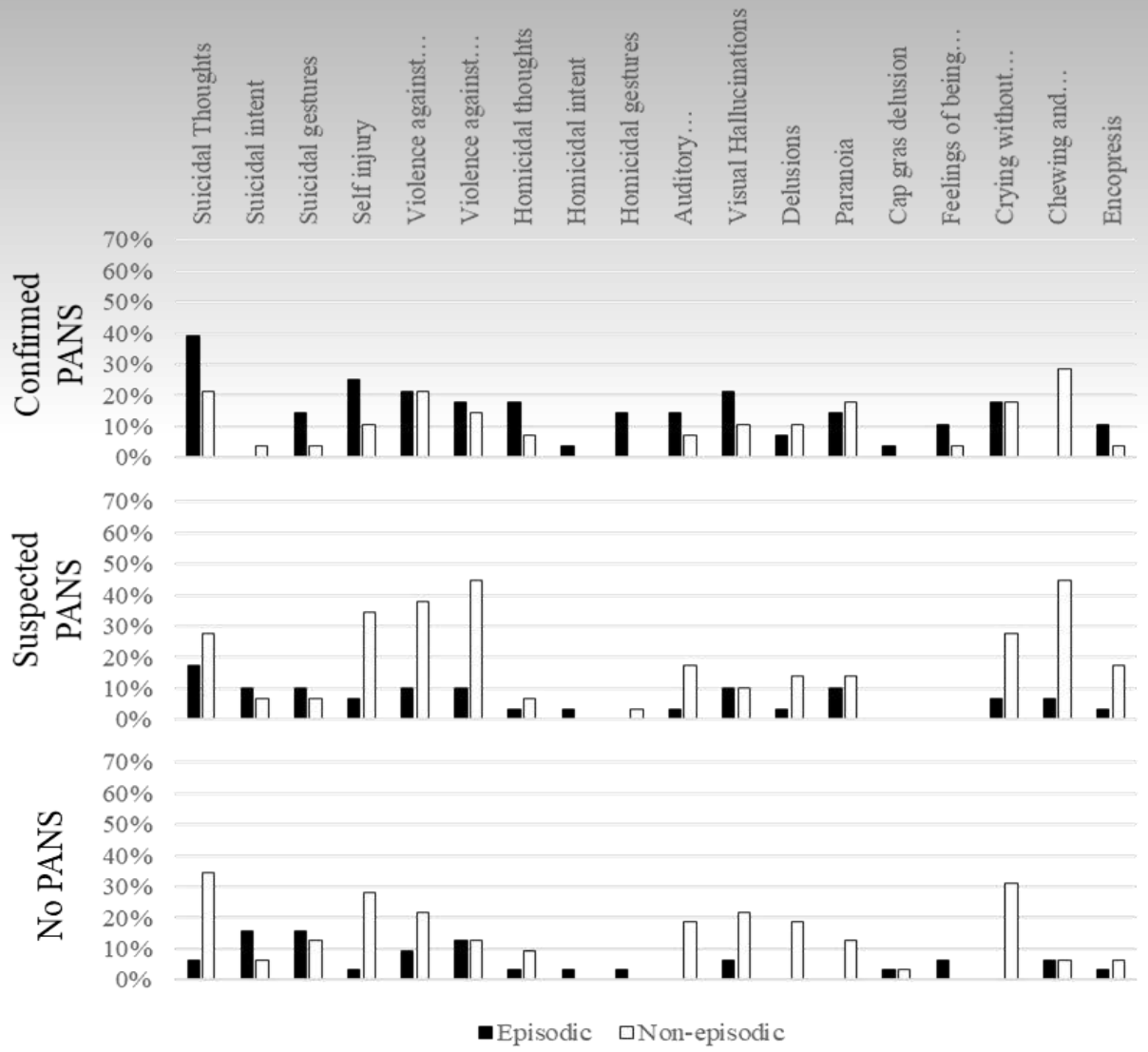


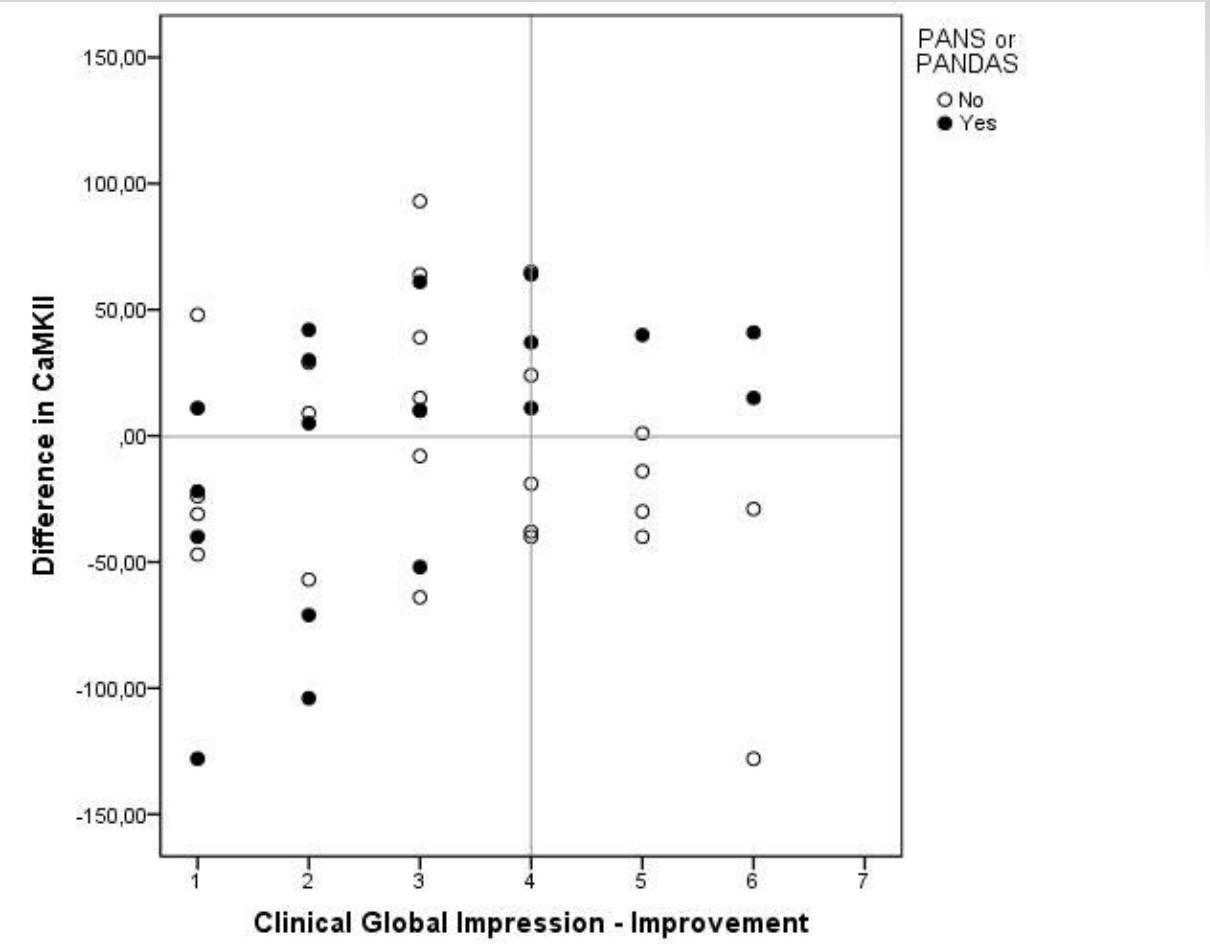


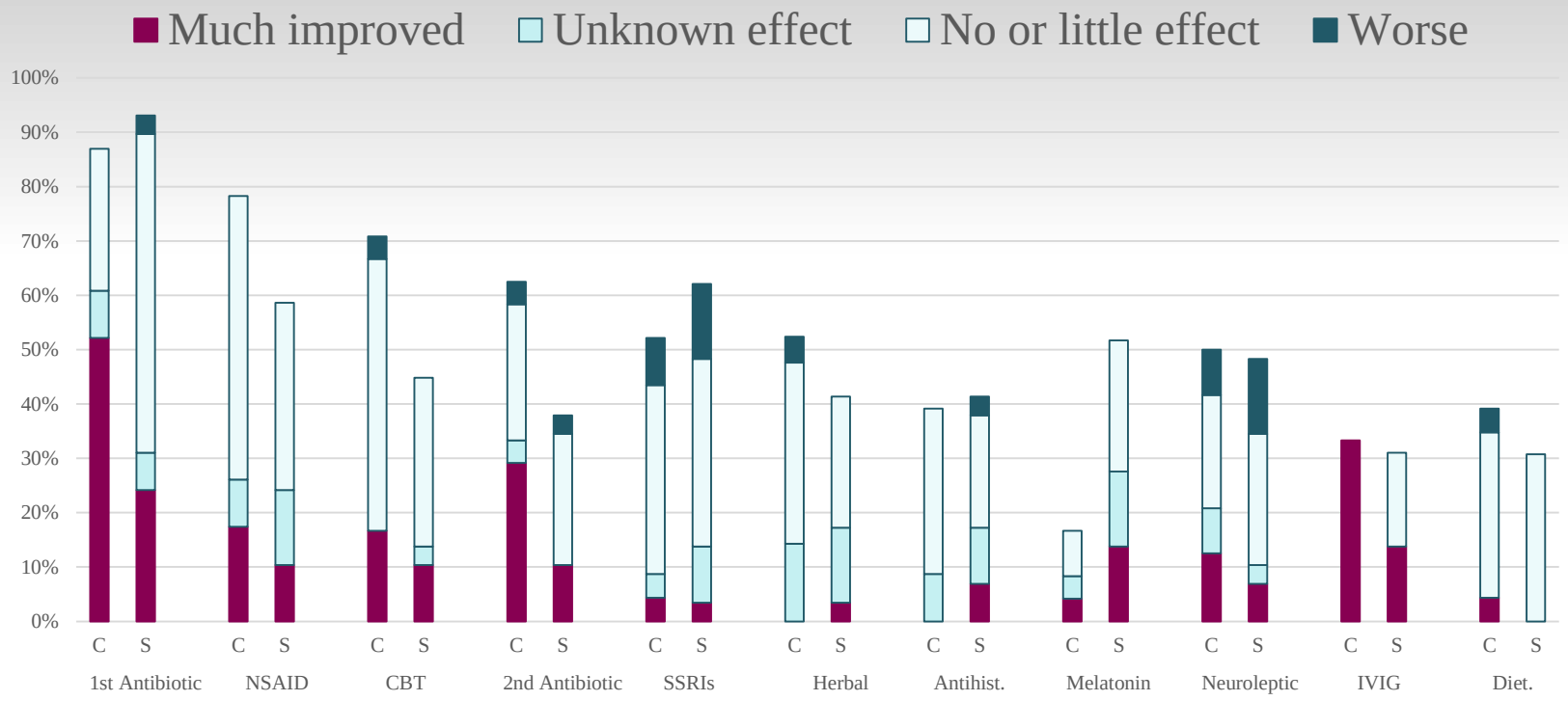

A
Time of onset of PANS related symptoms (PPRSI)
70%
60%
50%
40%
30%
20%
10%
0%
Confirmed PANS (n=28)
Suspected PANS (n=29)
Never Suspected PANS (n=32)
1. Before onset
2. At onset
3. After onset
B
Time of onset severe psychiatric symptoms (SOSQ)
70%
60%
50%
40%
30%
20%
10%
0%
Confirmed PANS (n=28)
Suspected PANS (n=29)
Never Suspected PANS (n=32)
1. Before onset
2. At onset
3. After onset
C
Proportion of episodic course of PANS-related psychiatric symptoms (PPRSI)
100%
80%
60%
40%
20%
0%
Confirmed PANS (n=28)
Suspected PANS (n=29)
Never Suspected PANS (n=32)
Episodic course
Non-episodic course
D
Proportion of episodic course severe psychiatric symptoms (SOSQ)
100%
80%
60%
40%
20%
0%
Confirmed PANS (n=28)
Suspected PANS (n=29)
Never Suspected PANS (n=32)
Episodic course
Non-episodic course

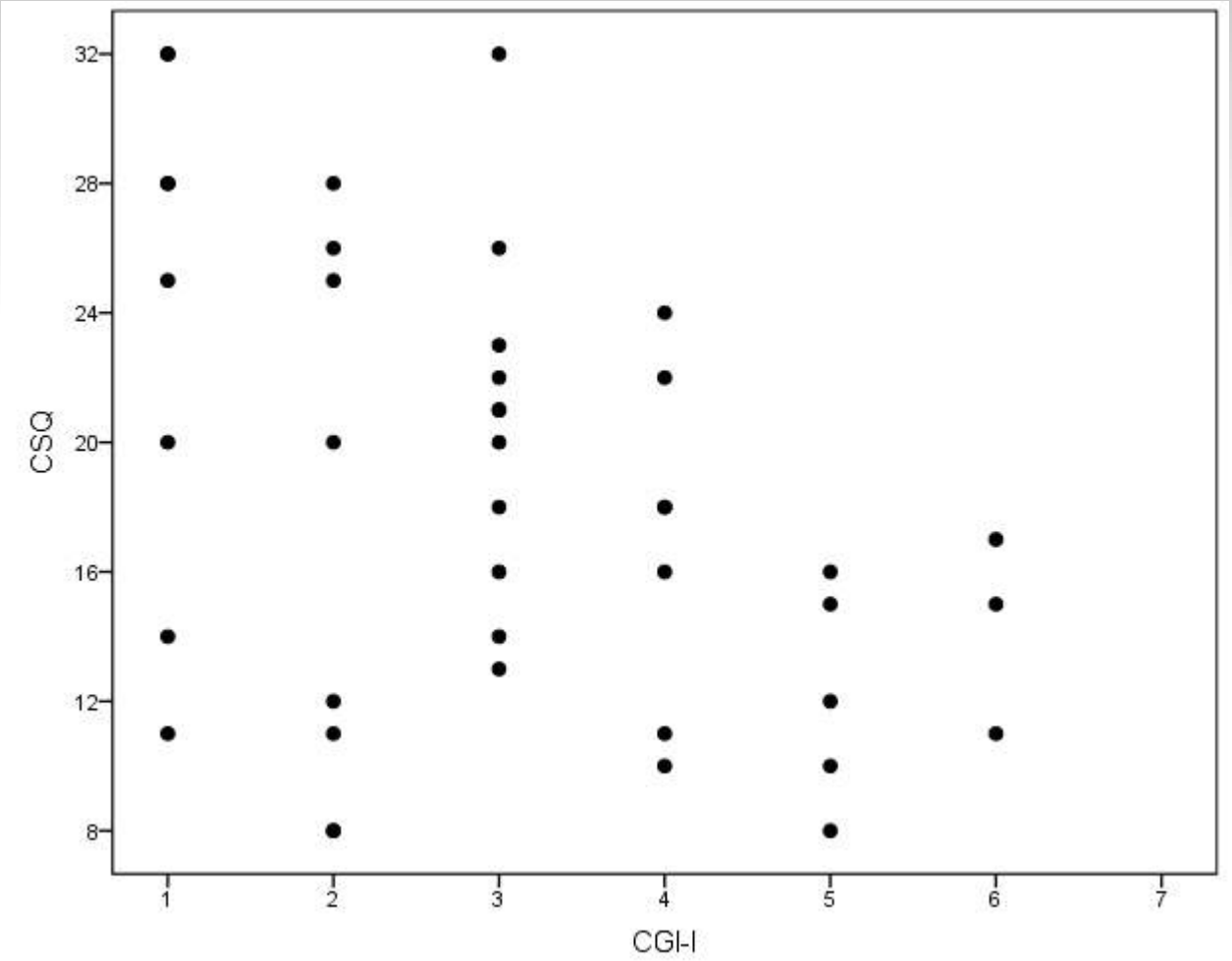

OCD
Hoarding
Eating Disorder
Anxiety
Separation Anxiety
Emotional Instability
Irritability
Developmental regression
Deterioration of School performance
Sensory Symptoms
Motor Symptoms
Simple Tics
Urinary Issues
Sleep Disorder
Mydriasis
Confirmed PANS
Suspected PANS
Never PANS
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
1. Before onset
2. At onset
3. After onset


OCD
Hoarding
Eating Disorder
Anxiety
Separation Anxiety
Emotional Instability
Irritability
Developmental regression
Deterioration of School performance
Sensory Symptoms
Motor Symptoms
Simple Tics
Urinary Issues
Sleep Disorder
Mydriasis
Confirmed PANS
Suspected PANS
No PANS
70%
60%
50%
40%
30%
20%
10%
0%
Episodic
Non-episodic


Suicidal Thoughts
Suicidal intent
Suicidal gestures
Self injury
Violence against…
Violence against…
Homicidal thoughts
Homicidal intent
Homicidal gestures
Auditory…
Visual Hallucinations
Delusions
Paranoia
Cap gras delusion
Feelings of being…
Crying without…
Chewing and…
Encopresis
Confirmed PANS
Suspected PANS
No PANS
70%
60%
50%
40%
30%
20%
10%
0%
Episodic
Non-episodic

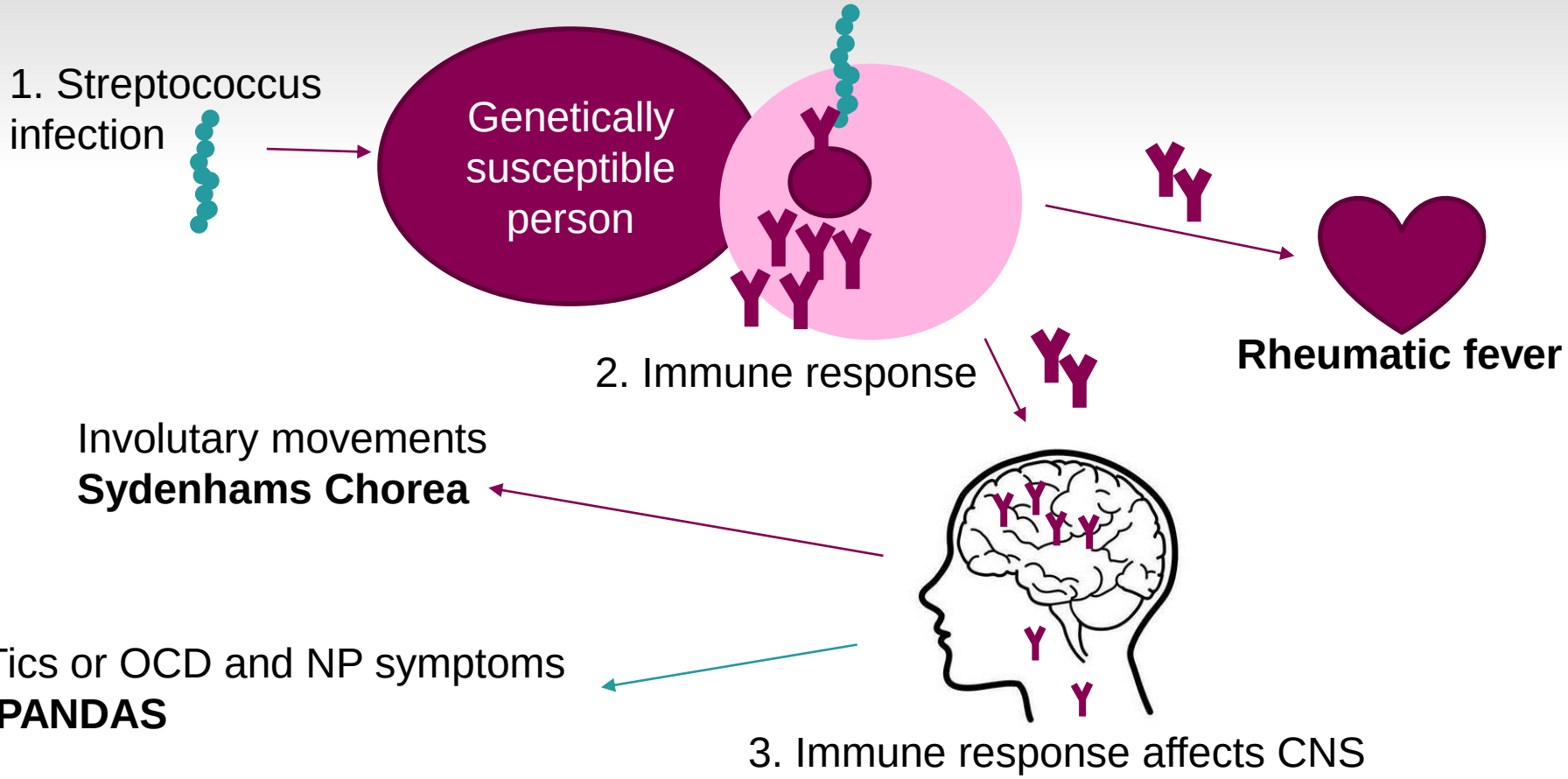

PANS or PANDAS
No
Yes
150,00
100,00
50,00
,00
-50,00
-100,00
-150,00
Difference in CaMKII
1
2
3
4
5
6
7
Clinical Global Impression - Improvement


Much improved
Unknown effect
No or little effect
Worse
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
C S
1st Antibiotic
NSAID
CBT
2nd Antibiotic
SSRIs
Herbal
Antihist.
Melatonin
Neuroleptic
IVIG
Diet.

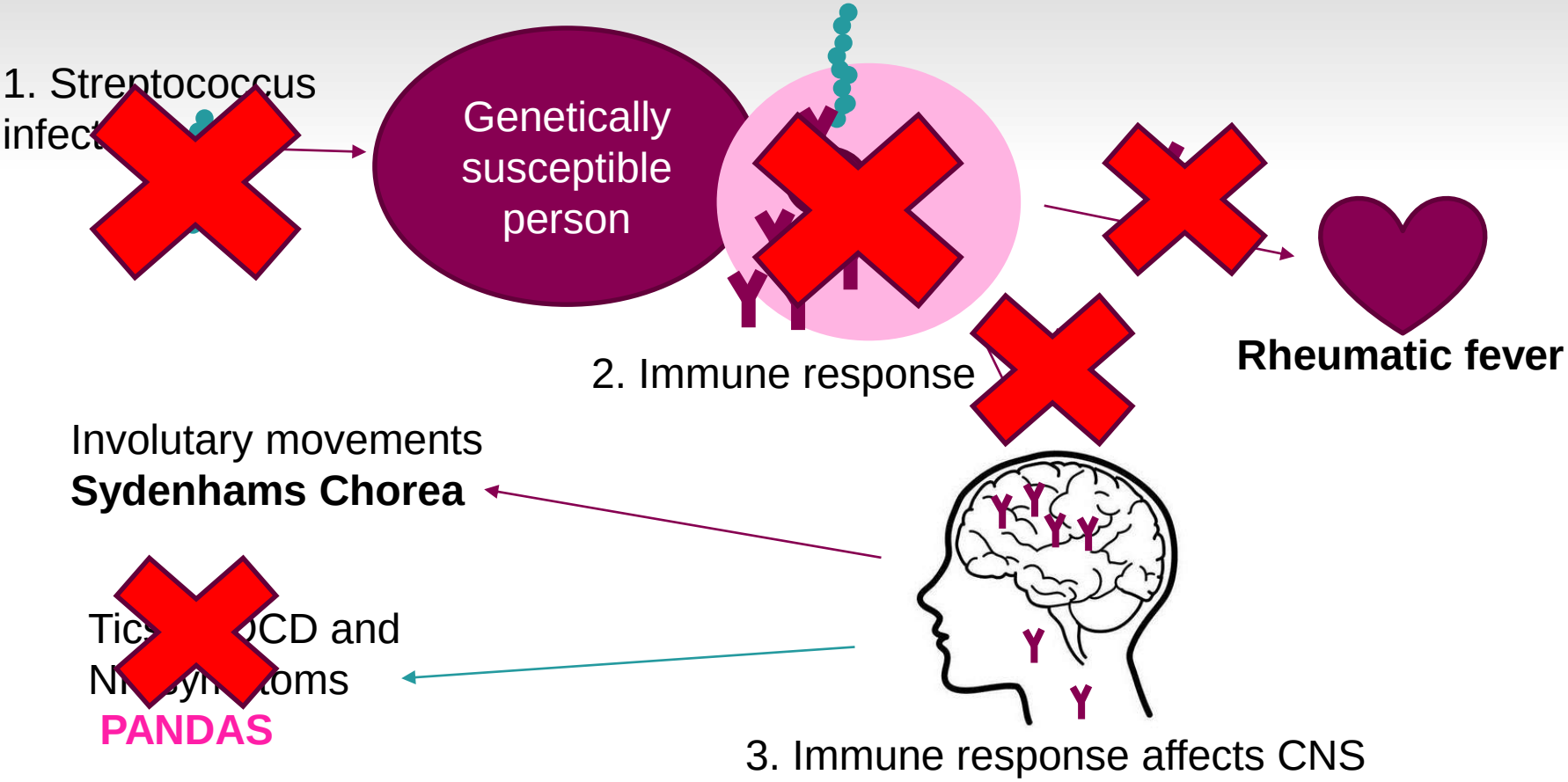

CSQ
32
28
24
20
16
12
8
1
2
3
4
5
6
7
CGI-I

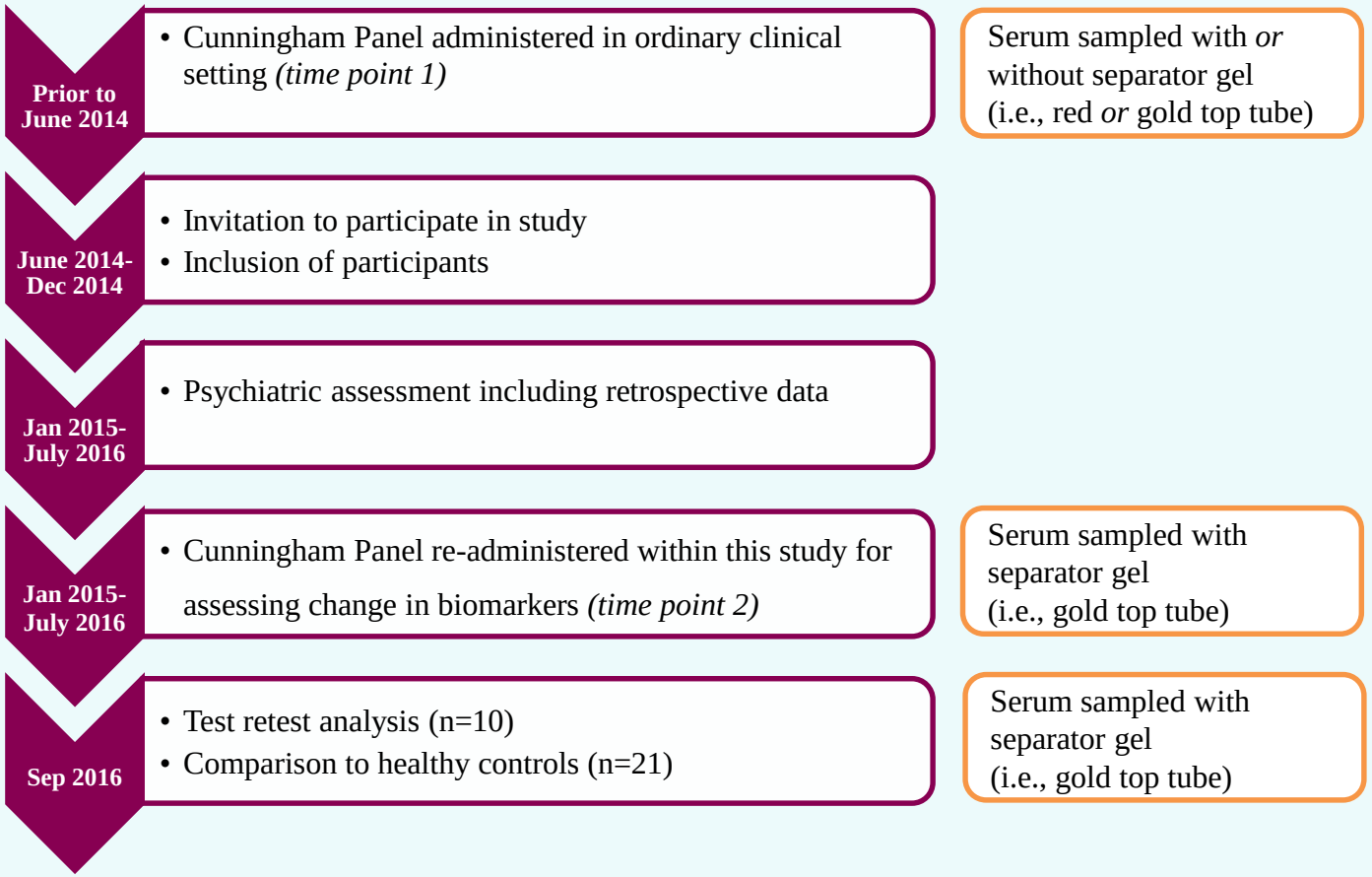
?

Proposed pathofysiology of PANDAS



Treatment options




Prior to June 2014
• Cunningham Panel administered in ordinary clinical setting *(time point 1)*
Serum sampled with *or* without separator gel (i.e., red *or* gold top tube)
June 2014-Dec 2014
• Invitation to participate in study
• Inclusion of participants
Jan 2015-July 2016
• Psychiatric assessment including retrospective data
Jan 2015-July 2016
• Cunningham Panel re-administered within this study for assessing change in biomarkers *(time point 2)*
Serum sampled with separator gel (i.e., gold top tube)
Sep 2016
• Test retest analysis (n=10)
• Comparison to healthy controls (n=21)
Serum sampled with separator gel (i.e., gold top tube)