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Tourette
OCD
Alberta
Network

Davide Martino

The link between Tourette syndrome/OCD and PANDAS: why does it still divide the scientific community?

Talk outline

1. PANDAS and PANS: what is their clinical definition (and their relationship to Group A Streptococcus)?
2. What is the relationship between Group A Streptococcus (and other pathogens) and ‘classical’ Tourette syndrome and OCD?
3. Are immune mechanisms abnormal in TS, OCD and related disorders?
4. How good are biomarkers to differentiate between PANDAS/PANS and TS/OCD?
5. How does all this influence treatment?

INFECTIONS AND NEURODEVELOPMENTAL DISORDERS (NDD)

- Bacteria, viruses, prions *may* be implicated in many chronic illnesses because immune responses can be implicated in those illnesses
- For example → EBV in MS
- Inflammatory mechanisms can precipitate symptoms of NDD in genetically vulnerable individuals
- Early infections might trigger neuroinflammation
- BUT, a single factor will not explain why an individual develops tics or OCD

1. PANDAS and PANS: what is their clinical definition (and their relationship to Group A Streptococcus)?

Strep and tics: how did it all start?

1890s-1980s: it is all St.Vitus's dance

Mid-1980s-early 1990s: OCS occurs in kids with Sydenham's chorea

Dr. Louise Kiessling

1998: Swedo et al. propose the PANDAS criteria

Dr. Susan Swedo

GAS prior to onset 44%
Pharyngitis prior to onset 28%

GAS & exacerbations 31%
Pharyngitis/URTI & exacerbations 42%

HOW IS PANDAS DIAGNOSED?

- Presence of OCD, a tic disorder, or both
- Pediatric onset of symptoms (i.e., age 3 to puberty)
- Episodic course of symptom severity
- Association with group A Beta-hemolytic strep infection, such as a positive throat culture for strep or history of scarlet fever
- Association with neurological abnormalities, such as physical hyperactivity or unusual, jerky movements that are not in the child's control
- Very abrupt onset or worsening of symptoms

WHAT IS THE LINK BETWEEN STREP AND CLINICAL COURSE IN PANDAS?

- Prospective studies: in kids with already diagnosed with PANDAS, the *exacerbations* of OCD/tics are usually *not related* to new GAS infections (Leckman et al. 2011) → what does it mean?
- GAS infection *might* play a role at the first onset of PANDAS, but not at subsequent fluctuations of symptoms

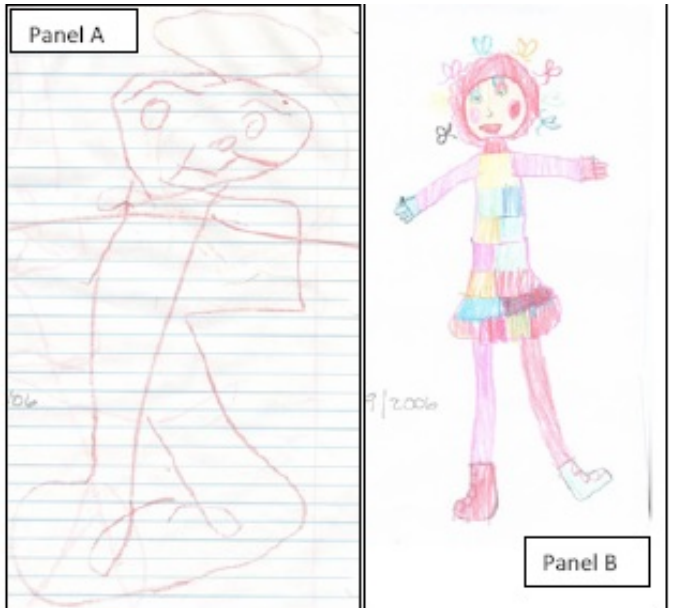
TIME HAS TAUGHT: NOT SO SIMPLE
The «real» face of PANDAS?

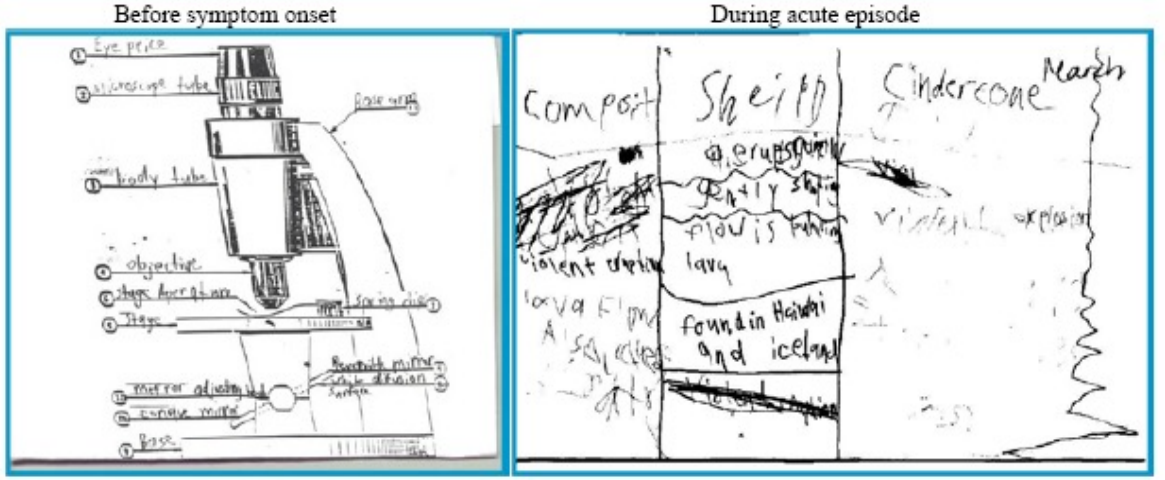
- Very severe and abrupt ('overnight') onset of OCD in a child, with or without tics
- A lot of variability across studies and specialty clinics
  - Not all show GAS at illness onset, let alone at future exacerbations
  - Tic clinics less likely to see possible PANDAS than OCD clinics
  - Acute inflammation may lead to chronic, low-grade inflammation→ blood tests cannot *time-link* infections to symptoms
- Hence, from **PANDAS** to **PANS**
  - **No specific infectious trigger**, no prepubertal onset
  - Tics from primary feature to one of 7 accompanying neuropsychiatric symptom categories

PANS: Psychiatric evaluation

- ❖Hyperalert, unsmiling, anxious aspect
- ❖Memory impairment
- ❖Emotional incontinence and depression (later stages)
- ❖Deterioration handwriting and school performance
- ❖Clumsiness and regression of fine motor skills and speech (baby-talk, mutism, new onset of stuttering)
- ❖Compulsive and frequent urination

(Bernstein et al., *J Child Adolesc Psychopharmacol* 2010;
Murphy et al., *J Pediatr* 2012)





[Swedo et al., Pediatr Therapeut 2012; 2:2]

The face of PAN(DA)S

- CLUSTER 1 → emotional lability, anxiety, sleep disruption, decline of school performance, behavioural regression [the «TYPICAL» cluster]
- CLUSTER 2 → urinary symptoms, ADHD, handwriting deterioration, sensory problems, simple tics
- CLUSTER 3 → food restriction, pupil dilatation, fatigue, GI problems, depressive symptoms, hallucinations and/or psychotic symptoms, complex tics {lower QoL}

- Other features: REM sleep behavioural problems
- PANS onset related to a recent infection in the vast majority of cases
- Relapsing-remitting course is frequent
- Half with family history of developmental, neuropsychiatric or autoimmune/inflammatory disorders

The face of PAN(DA)S

- CAREGIVER BURDEN

  >50% caregivers of pts with PANS score above threshold used to determine respite need

  Faster assessment in PANS multidisciplinary clinic improves caregiver burden and parent-rated severity of neuropsychiatric symptoms in the following 12 weeks [Frankovich, 2018; Harris, 2021]

- BRAIN IMAGING
  - Abnormal structure and function in the same brain regions controlling ‘motion’ and ‘emotion’ as in chronic neurodevelopmental disorders → not surprising as same type of symptoms (part. OCD)

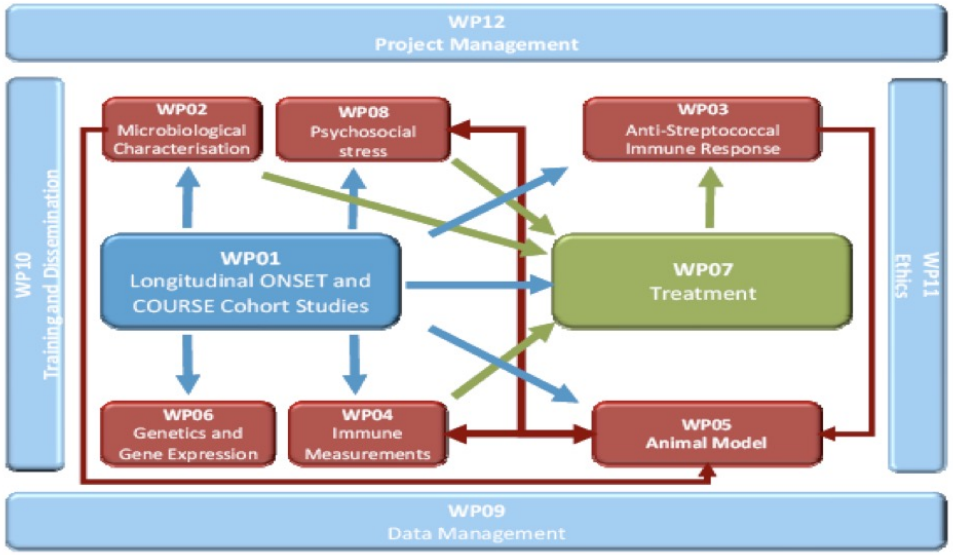
2. What is the relationship between Group A Streptococcus (and other pathogens) and ‘classical’ Tourette syndrome and OCD?

WHAT IS THE LINK BETWEEN STREP AND TS/OCD?

- Cross-sectional studies: serological test → 40%-60% of patients are antibody-positive (ASOT) → what does it mean?
- Prospective studies: kids with chronically elevated anti-strep antibodies are more likely to fluctuate in severity of tics and OCD (Murphy, 2004)

EMTICS
European Multicentre Tics Study

SEVENTH FRAMEWORK PROGRAMME



Lack of Association of Group A Streptococcal Infections and Onset of Tics

European Multicenter Tics in Children Study

Anette-Eleonore Schrag, MD, PhD, Davide Martino, MD, PhD, Hanyuying Wang, PhD, Gareth Ambler, PhD, Noa Benaroya-Milstein, MD, PhD, Maura Buttiglione, PhD, Francesco Cardona, MD, Roberta Creti, PhD, Androulla Efstratiou, PhD, Tammy Hedderly, MD, Isobel Heyman, MBBS, PhD, FRCPsych, Chaim Huyser, MD, PhD, Pablo Mir, MD, PhD, Astrid Morer, MD, PhD, Natalie Moll, MSc, Norbert E. Müller, MD, Kirsten R. Müller-Vahl, MD, Kerstin J. Plessen, MD, Cesare Porcelli, MD, Renata Rizzo, MD, PhD, Veit Roessner, MD, PhD, Markus Schwarz, MD, PhD, Zsanett Tarnok, PhD, Susanne Walitza, MD, MSc, Andrea Dietrich, PhD, and Pieter J. Hoekstra, MD, PhD, on behalf of European Multicentre Tics in Children Study (EMTICS)

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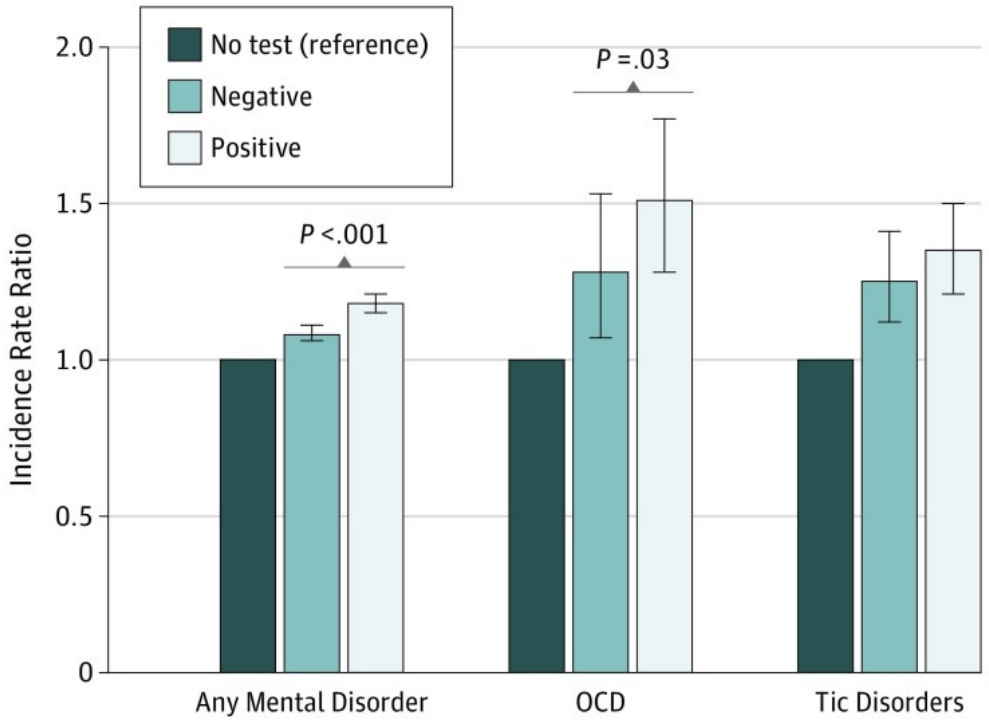
- 259 unaffected sibs in vulnerable age period for 3 years, 11 European sites
- 61 “onset” events captured
- Different definitions of GAS exposure adopted
- No association with tic onset

EPIDEMIOLOGICAL STUDIES



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PMCID: PMC5710247
PMID: 28538981

Association of Streptococcal Throat Infection With Mental Disorders

Testing Key Aspects of the PANDAS Hypothesis in a Nationwide Study

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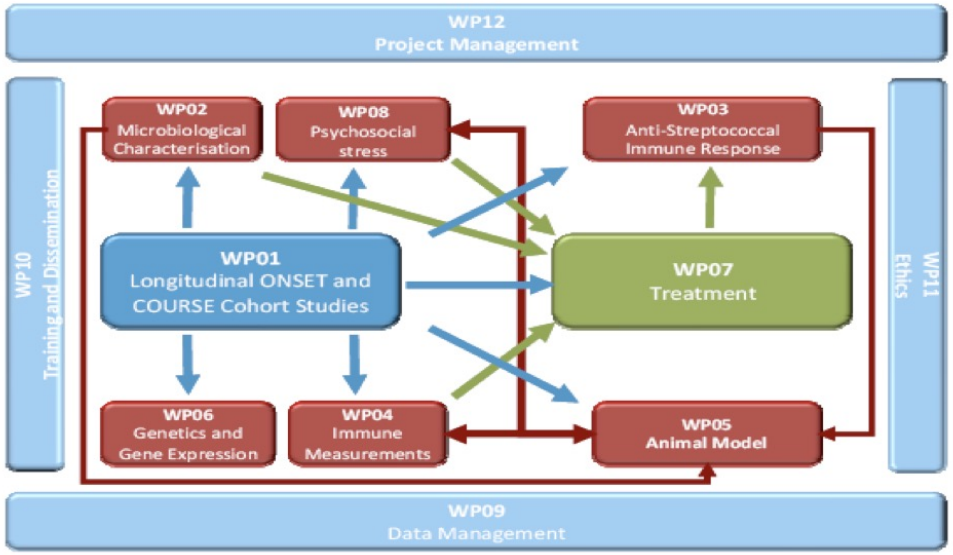
EMTICS
European Multicentre Tics Study

SEVENTH FRAMEWORK PROGRAMME



Association of Group A *Streptococcus* Exposure and Exacerbations of Chronic Tic Disorders

A Multinational Prospective Cohort Study

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- 715 children followed up for 16 months, 11 European sites
- 409 tic “exacerbation” events captured
- Different definitions of GAS exposure adopted

No association with tic changes, but with hyperactive – impulsive symptoms

Mycoplasma pneumoniae IgG positivity is associated with tic severity in chronic tic disorders

Jaana Schnell, Molly Bond, Natalie Moll, Elif Weidinger, Bianka Burger, Rod Bond, Andrea Dietrich, Pieter J. Hoekstra, Anette Schrag, Davide Martino, Markus Schwarz, Ute-Christiane Meier, Norbert Müller

- *M. pneumoniae* IgG positivity was not associated with the presence of CTD
- *M. pneumoniae* IgG positivity was not associated with the first onset of tics
- *M. pneumoniae* IgG positivity was significantly associated with higher tic severity

Independent variable (dependent variable)	*β*	SE	95% CI	*p*
M. pneumoniae IgG				
(YGTSS Total)	2.64	1.15	0.38-4.89	0.02*
(YGTSS Motor)	1.02	0.62	-0.21-2.24	0.10
(YGTSS Vocal)	1.71	0.78	0.18-3.24	0.03*
(CGI-S)	0.17	0.13	-0.09-0.44	0.20

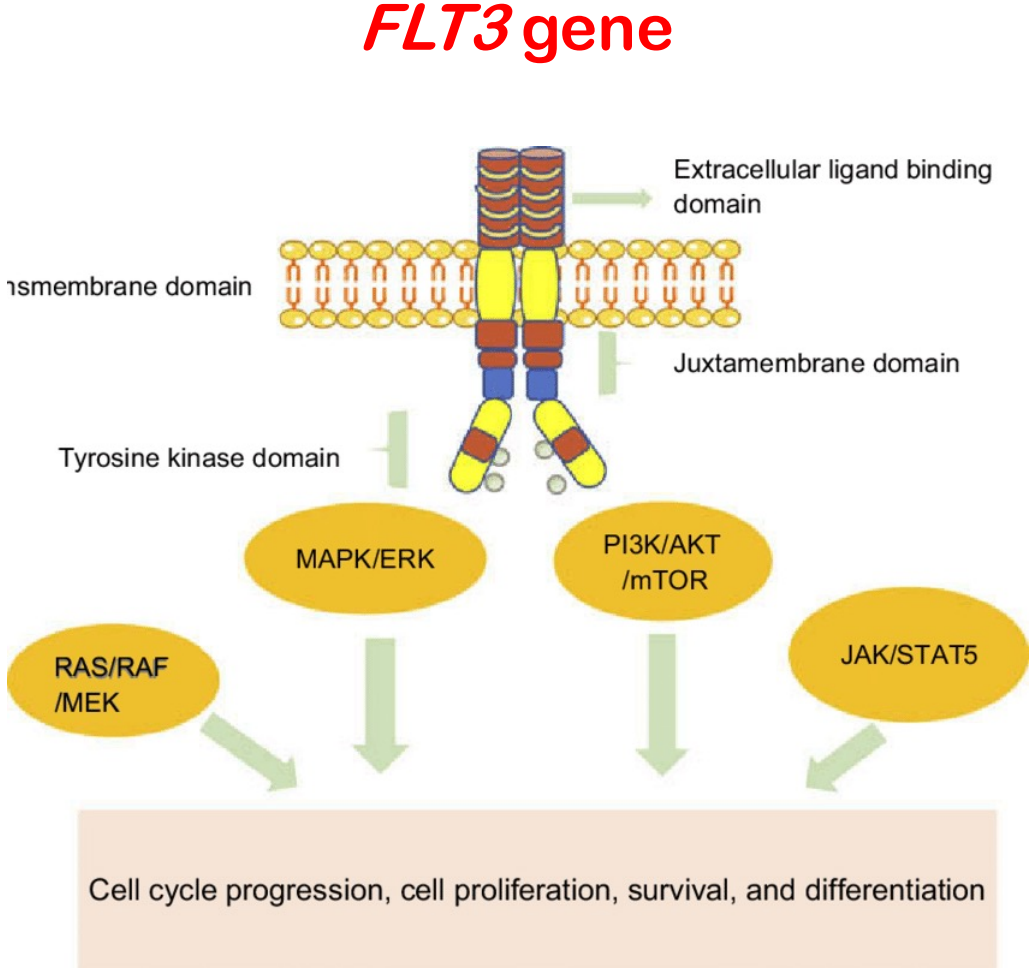
LET'S TALK ABOUT…STRESS

- TS, OCD, ADHD patients are sensitive to psychosocial stress
- Psychosocial stress influences immune and hormonal stress reponses and increases rates of infection (including GAS)
- Small prospective studies [Lin et al., 2010] → GAS infections may cause slight worsening of tics/OCS, but the effect of psychological stress is ***greater***

3. Are immune mechanisms abnormal in TS, OCD and related disorders?

Genetic predisposition to immune dysregulation

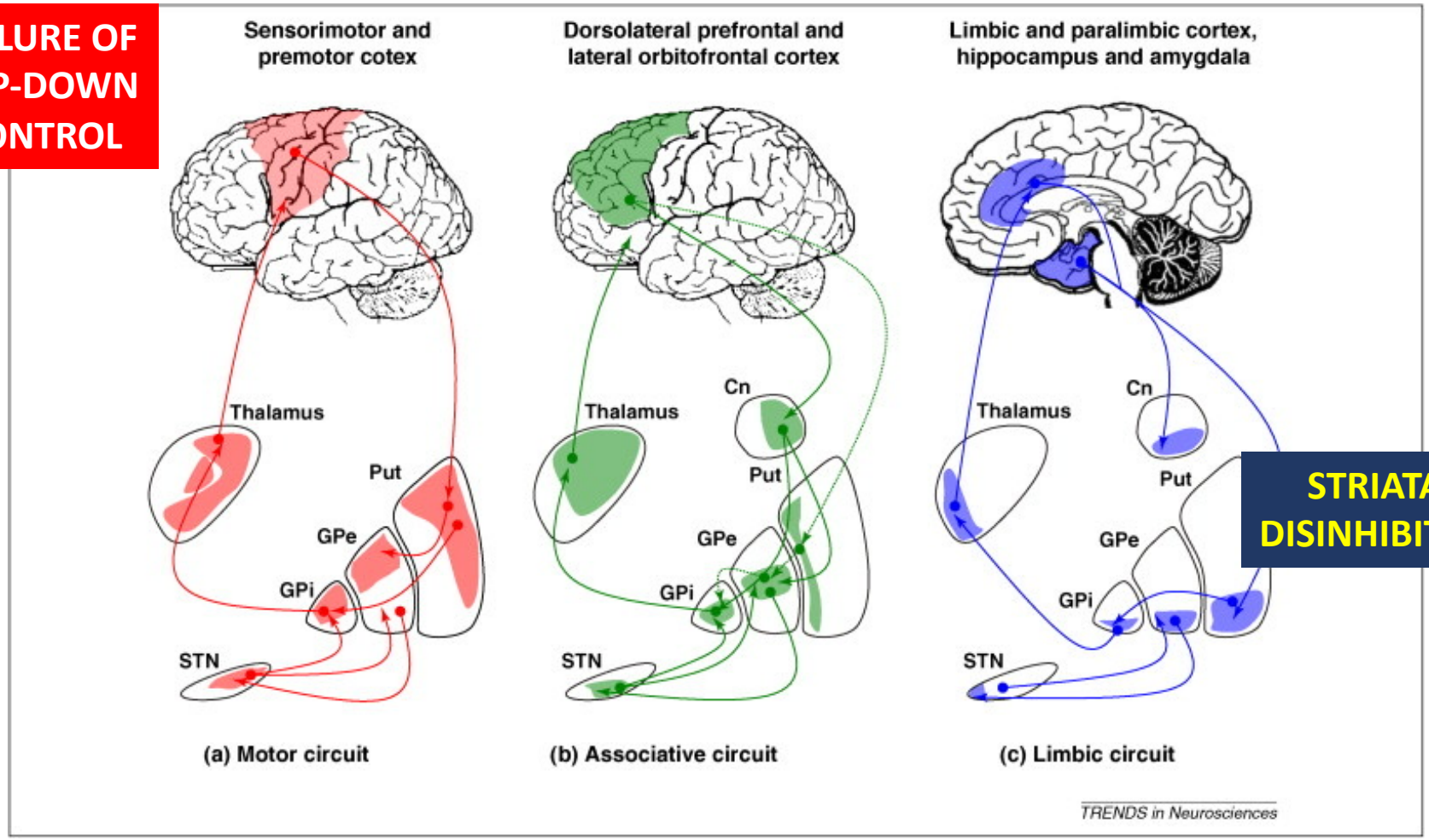
- Polygenic → 'immunological' interactome
- Still poorly understood in TS, OCD and ADHD
- Genome-wide data → TS associated with Lymphocytic gene set
- OCD → TGF-β signalling
- GWASs → genetic correlation with immune-mediated diseases



Brain networks in TS/OCD/ADHD

(Worbe et al., Brain 2012, 2015; Cortex 2012)

FAILURE OF TOP-DOWN CONTROL

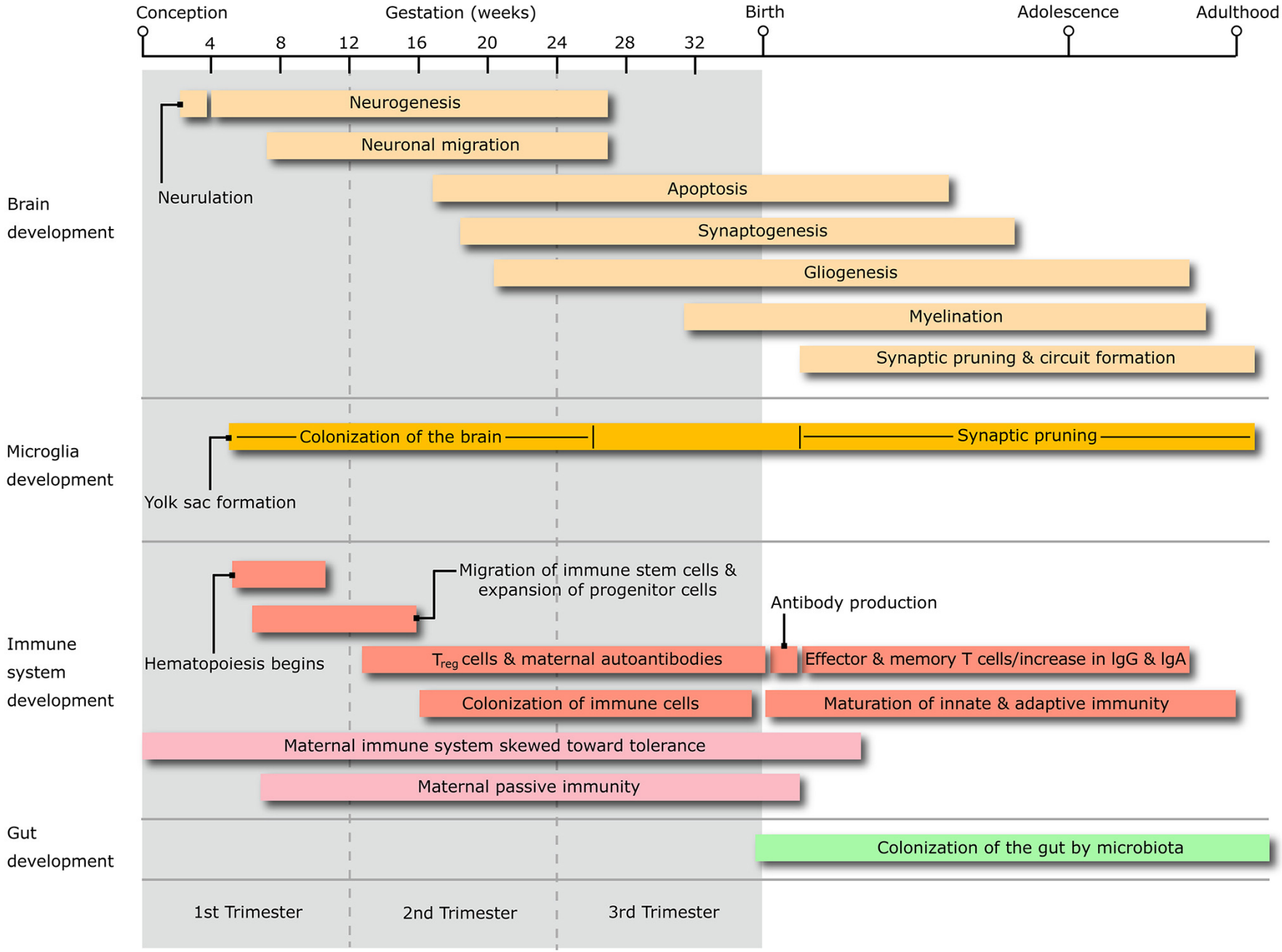


STRIATAL DISINHIBITION

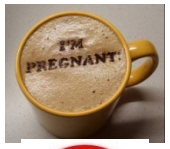
Simple tics **Hyperactivity** **Compulsive actions**

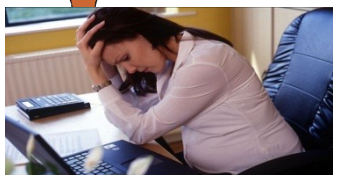
Complex tics **Impulsive actions**

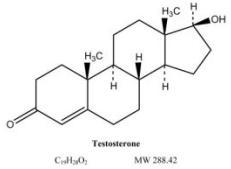
complexity →



Martino D, Johnson IA, Leckman JF, *Front Neurosci* 2020

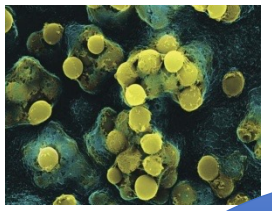






complications

Psychosocial stress



Biological stressors, e.g. infections

PERIPHERAL-CENTRAL IMMUNE CROSSTALK
SECOND 'IMMUNE HITS'→ CHRONIC INFLAMMATION

TRANSPLACENTAL IMMUNE MODULATION

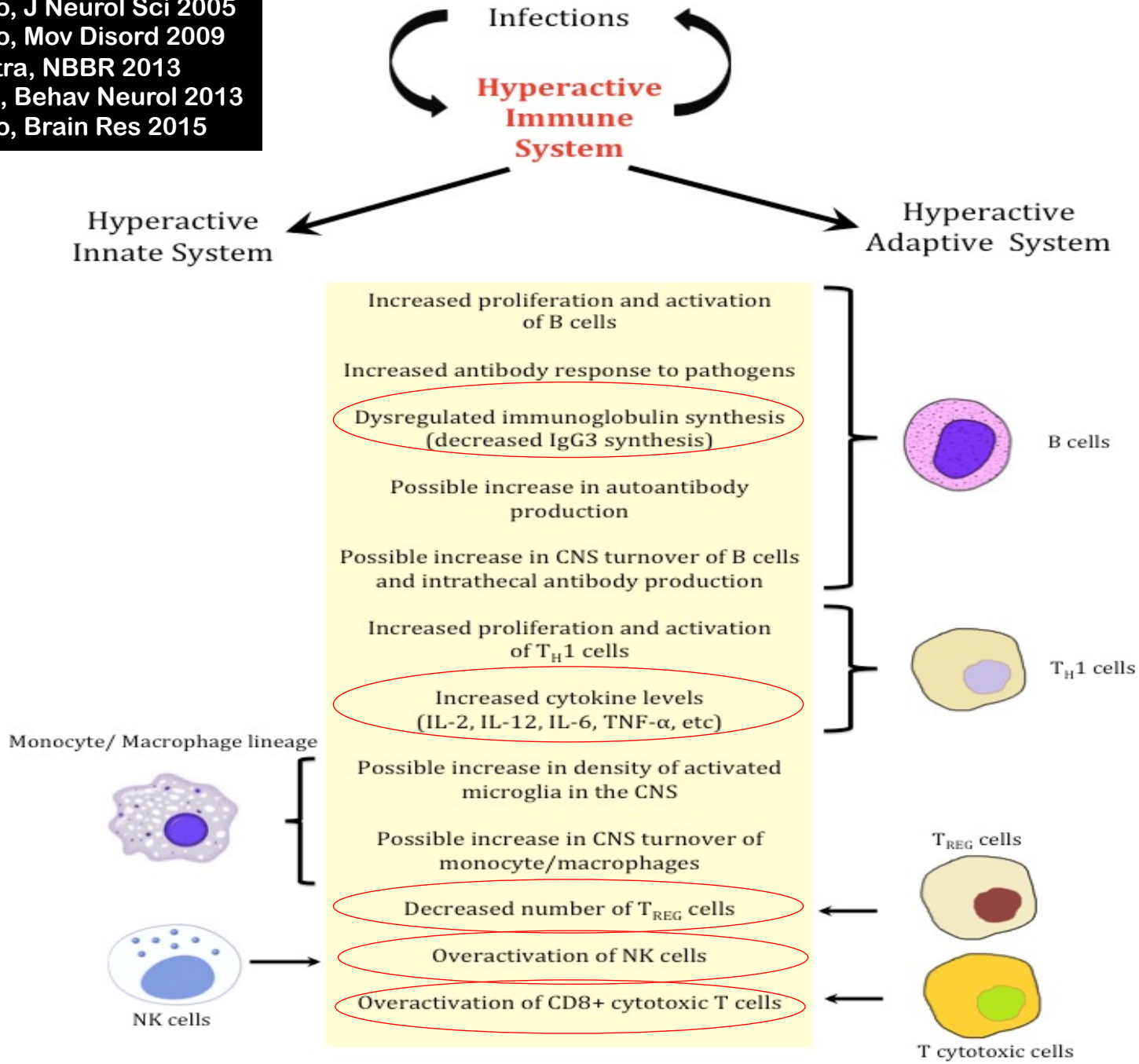
Puberty Adolescence Adulthood

Waxing and waning --- Waxing and waning --- Waxing and waning ---

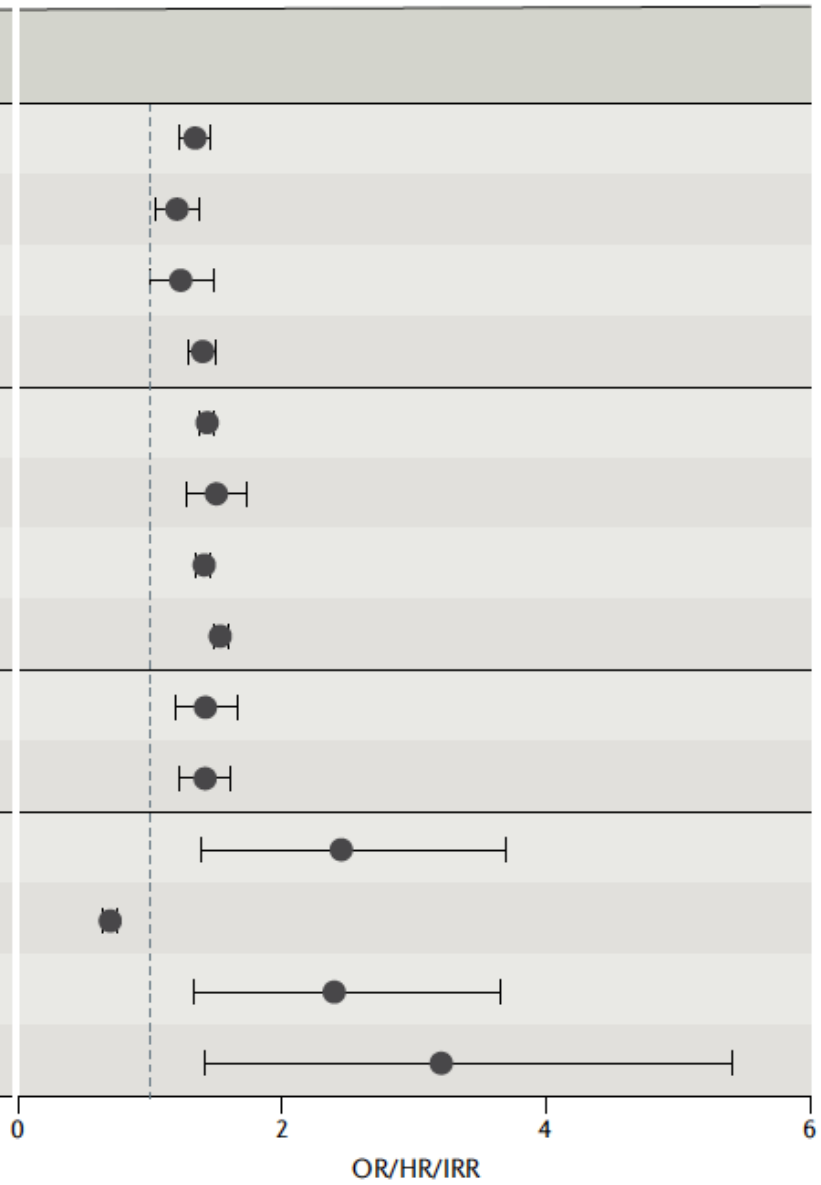
Onset **Peak of severity** **Exacerbations**

(Hoekstra PJ…Martino D, *Neurosci Biobehav Rev* 2013)

Martino, J Neurol Sci 2005
Martino, Mov Disord 2009
Hoekstra, NBBR 2013
Elamin, Behav Neurol 2013
Martino, Brain Res 2015



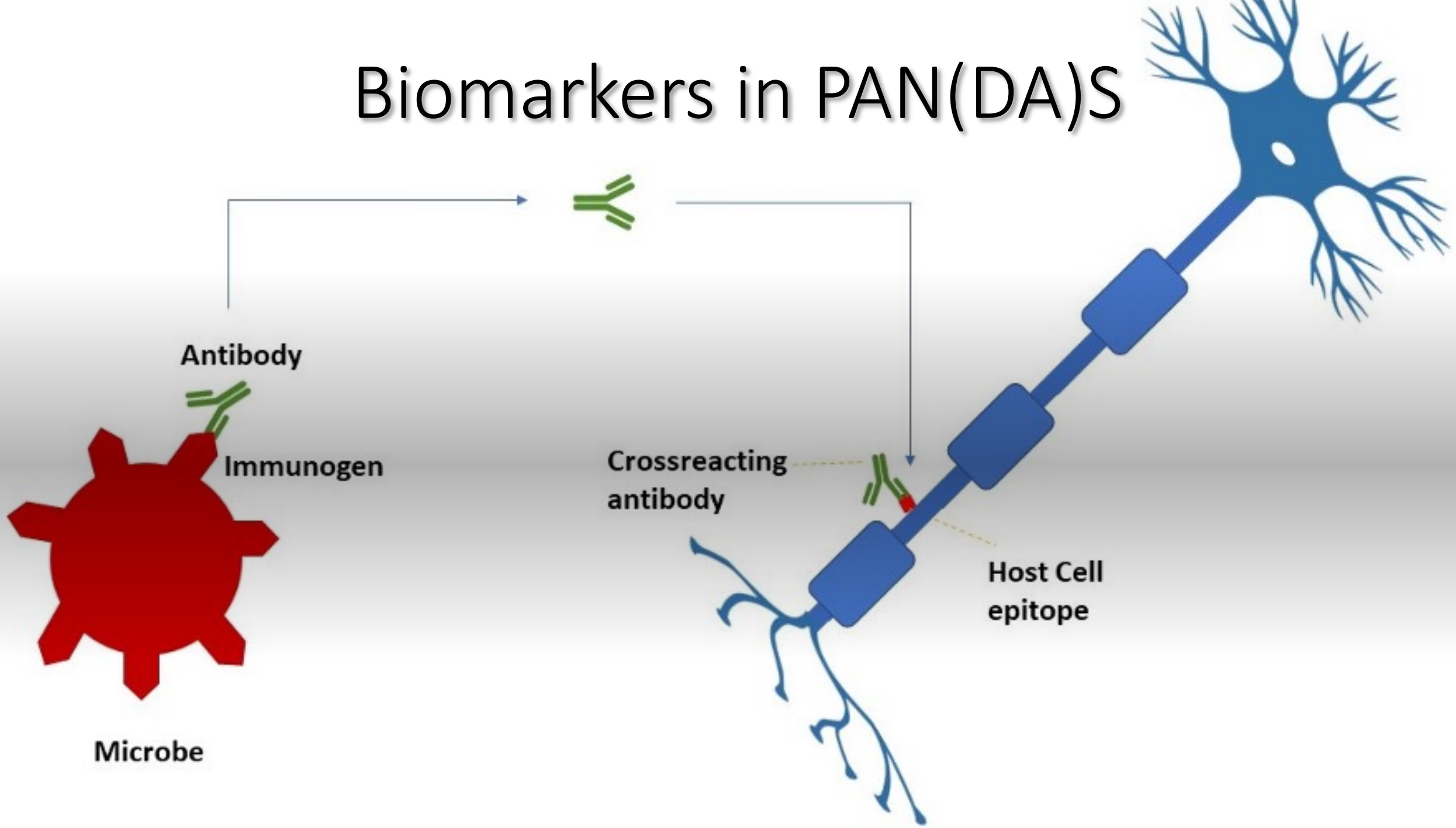
Risk factor	Author (year)	Developmental disorder	Effect estimate (95% CI)
Autoimmune disease	Chen et al. (2016)[44]	ASD	OR 1.34 (1.23–1.46)
	Nielsen et al. (2021)[43]	ADHD	OR 1.20 (1.04–1.38)
	Dalsgaard et al. (2015)[42]	TS	IRR 1.22 (1.01–1.48)
	Mataix-Cols et al. (2018)[45]	TS	OR 1.40 (1.30–1.51)
Asthma	Gong et al. (2019)[46]	ASD	OR 1.43 (1.38–1.49)
	Hisle-Gorman et al. (2018)[47]	ASD	OR 1.49 (1.29–1.74)
	Liu et al. (2019)[48]	ADHD	OR 1.41 (1.36–1.46)
	Instanes et al. (2017)[49]	ADHD	OR 1.50 (1.50–1.60)
Obesity	Lei et al. (2019)[208]	ASD	OR 1.41 (1.19–1.67)
	Jenabi et al. (2019)[209]	ADHD	OR 1.42 (1.23–1.61)
Low SES	He et al. (2018)[210]	ASD	Low:high tertile 2.27 (1.39–3.70)
	Durkin et al. (2010)[211]	ASD	Low:medium PR 0.70 (0.64–0.76)
	Russell et al. (2016)[52]	ADHD	OR 2.21 (1.33–3.66)
	Miller et al. (2014)[53]	TS	OR 2.78 (1.42–5.43)



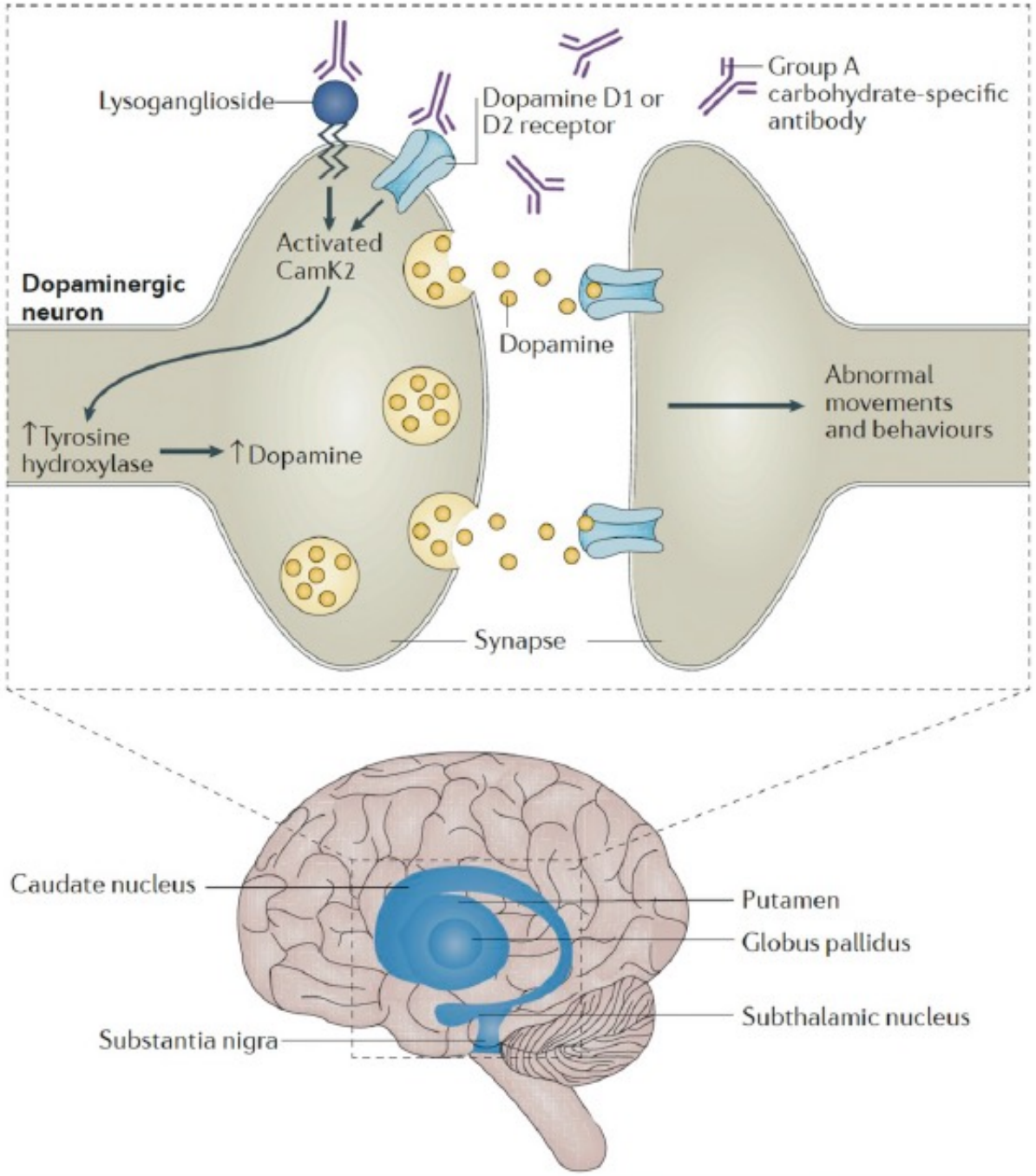
Han VX...Dale RC, 2021

4. How good are immune biomarkers in differentiating between PANDAS/PANS and TS/OCD?

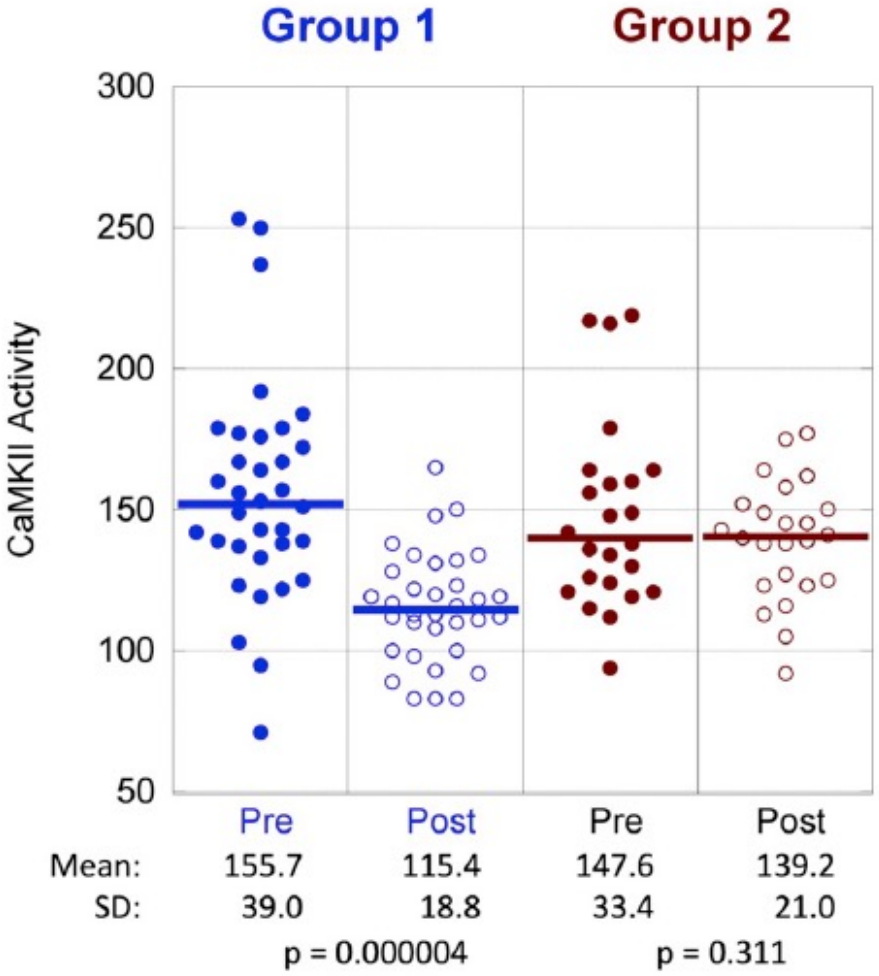
Biomarkers in PAN(DA)S



The Cunningham Panel™



Shimasaki et al., 2020



The Cunningham Panel™

- Hesselmark & Bejerot, 2017
- 53 patients with or without PANS/PANDAS + 21 HC, all tested with the panel
- Individual markers in the panel:
  - Sensitivity 15-60%
  - Specificity 28-92%
  - PPV 17-40%
  - NPV 44-74%
- Definitely sub-optimal accuracy in discriminating between subjects with and without PANS/PANDAS
- Insufficient test-retest reliability

5. How does all this influence treatment?

TREATMENT of PANS/PANDAS: we can't neglect the uncertainty of evidence

- Current treatment continues to be the same of standard of care practices for pts with TS/OCD
- Early trials of **antibiotics** are inconclusive due to design issues
- New studies need to establish efficacy of individual antibiotics
- Many mechanisms potentially at play
  - Decrease antigenic load from undetected, asymptomatic intracellular GAS
  - Cytokine modulation → reduce IFNγ activity (also an effect of SSRIs)
  - Reduce tryptophan (precursor of serotonin) degradation
  - Promote expression of glutamate transporter GLT1 (neuroprotection)

TREATMENT of PANS/PANDAS: we can't neglect the uncertainty of evidence

- Adenotonsillectomy: no evidence that it helps clinical progression, antibody status or severity of neuropsychiatric symptoms

- Superiority to placebo of IVIG in the treatment of OCS in the context of PANS/PANDAS remains undemonstrated → negative RCT

- Problems with reports of immune-modulatory treatments in PANS/PANDAS
  - Use of combination therapy
  - Ascertainment bias
  - Fluctuating course of symptoms

KEY POINTS

- Several associations between patients with infections, particularly group A streptococcal (GAS) infections, and subsequent TS and OCD symptoms have been established in population-based studies, suggesting at least a nonspecific role of infections in a subgroup of patients with tics.
- In the late 1990's, researchers from the National Institute of Mental Health (NIMH) characterized an entity they called "Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcus," or PANDAS.
- Subsequently, a broader spectrum named Pediatric Acute-Onset Neuropsychiatric Syndromes (PANS) has been proposed, which encompasses phenotypes dominated by obsessive-compulsive symptoms or eating behavior abnormalities and includes tics as accompanying features. PANS are defined by the temporal course but are not limited to post-infectious etiologies.

KEY POINTS

- Children with PANDAS/PANS by definition have dramatic onset, or “overnight” neuropsychiatric symptoms.
- GAS infections do not seem to be a major determinant of tic exacerbations or onset in TS, although a potential interactive effect with psychosocial stress cannot be excluded. The role of other pathogens in influencing course and onset of tic disorders remains uncertain.
- The complex interaction of patient specific attributes (neurochemical and immune vulnerability genes leading to maladaptive neuropsychiatric or immune function), with environmental attributes (psychosocial stress, injuries, substance exposures and pathogen specific properties) creates an interesting and ongoing research challenge.