TS-school Brussels | training course on Tourette Syndrome

Tuesday 6 June 2023

Royal Museum for Central Africa

How to answer FAQ from patients and families on etiology and pathophysiology of tic disorders

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2023 Brussels

Inheritance

- **Are tic disorders heritable?**
  YES, OF COURSE!! Among the most heritable neuropsychiatric disorders

Not uncommon:

- to «spot» tics in clinic in parents claiming they don't have tics
- to have bilineal transmission
- to detect family history only in relatives beyond the first degree of relatedness
- to detect family history of other neurodevelopmental disorders
- to personalize communication about family history (avoid generating blaming attitude)

Inheritance

- **How much does genetic make-up account for heritability of Tourette syndrome?**

  THE VAST MAJORITY: 77%-92%

Two population-based and genome-wide association studies on almost 5,000 individuals in each [Mataix-Cols et al., 2015; Yu et al., 2019]

- **Is Tourette syndrome more heritable in males than in females?**

  APPROXIMATELY IN EQUAL AMOUNT

Inheritance

- **Is Tourette syndrome more or less heritable than other persistent tic disorders?**

  IN SIMILAR AMOUNT

Another good reason not:

to over-emphasize the «difference» between Tourette syndrome and other persistent tic disorders → both result from a similar genetic background

Inheritance

- **How much of the heritability of TS/PTD is due to narrow-sense heritability (direct additive genetic effect)?**

  VARIABLE ACROSS STUDIES: 25—77%

Narrow-sense heritability of a phenotype: proportion of phenotypic variance attributable to the additive genetic effect (i.e., the combined effect of the two alleles of single genes)

Broad-sense heritability of a phenotype: proportion of phenotypic variance attributable to the total genetic effects (additive + dominant/recessive + epistatic)

[Mahjani et al., 2023]

Inheritance

- **Is maternal inheritance entirely due to narrow-sense heritability (direct additive genetic effect)?**

  NO, MATERNAL GENETIC EFFECT HAS ALSO BEEN DEMONSTRATED.

Maternal effect

effect of the mother's phenotype on the child's phenotype

- Genetic → ***Maternal genetic nurture***
  Mother's genetics → Maternal phenotype → Offspring phenotype
  independent of the offspring's genetics
- Environmental
  Environment → Maternal phenotype → Offspring phenotype

5 major mechanisms of maternal effect

maternal androgen levels – photoperiod (melatonin) – microbiome – immune regulation – milk composition

Direct additive genetic effect from mothers: 61%

Maternal genetic effect (intergenerational transmission of genetic risk): 5%

Inheritance

- **Is a parental history of psychiatric diagnoses a risk factor for Tourette syndrome and/or persistent tic disorders?**

  YES, ESPECIALLY MATERNAL HISTORY. HOWEVER, UNCLEAR IF THIS DIFFERS BETWEEN TS AND PTD RISK.

Any psychiatric diagnosis in either parent increases the risk for TS/PTD by a 2.3-fold factor (*population-based data from Finnish national registers*).

Maternal: personality disorders, anxiety disorders, affective disorders, psychotic disorders, addiction disorders

Paternal: OCD, anxiety disorders

[Leivonen et al., 2023]

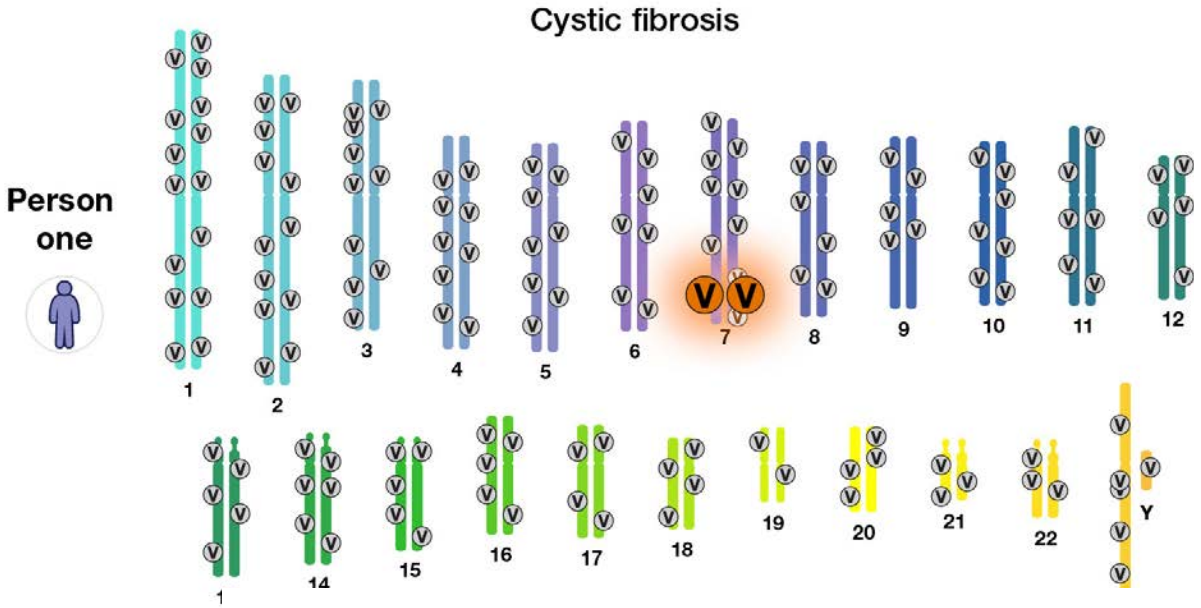
Inheritance

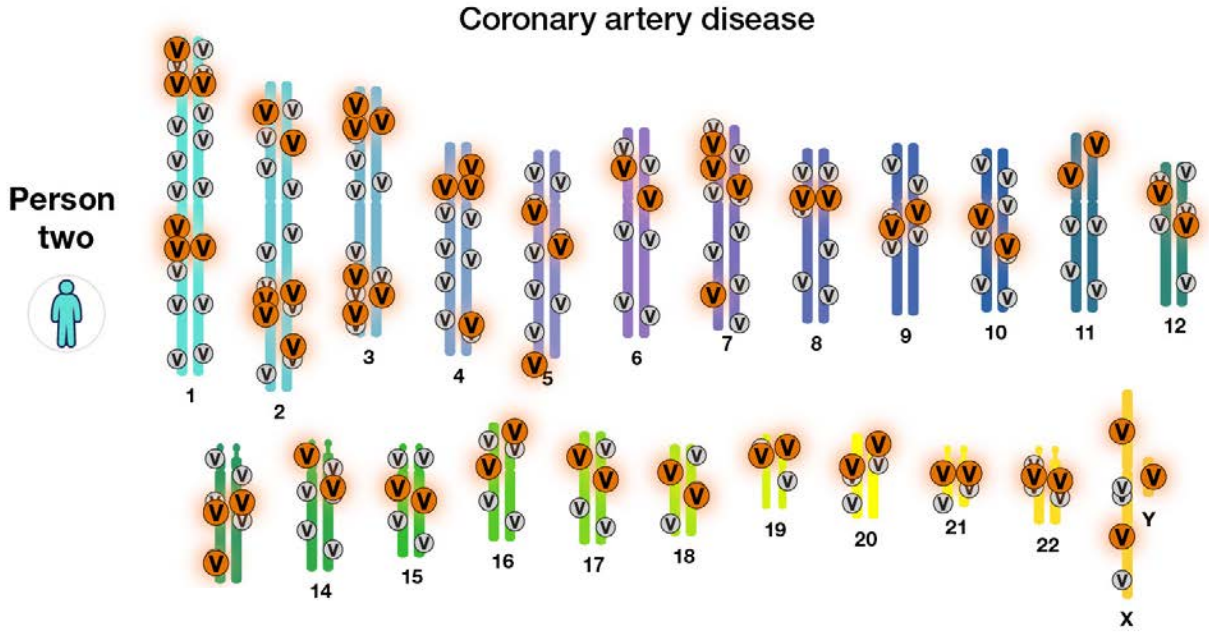
- **Why is a parental history of psychiatric diagnoses a risk factor for Tourette syndrome and/or persistent tic disorders?**

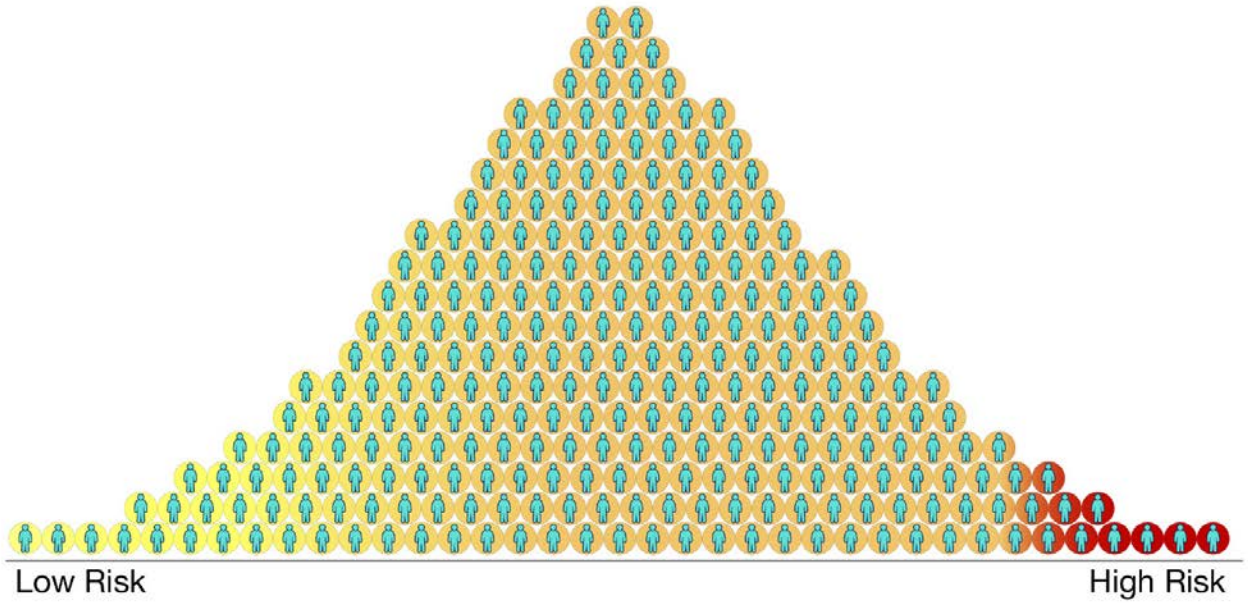
  BECAUSE PSYCHIATRIC DISORDERS SHOW HIGH GENETIC CORRELATION

Important overlap in common gene variants across neurodevelopmental and psychiatric diagnoses

[Anttila et al., 2018; Yang et al., 2021]





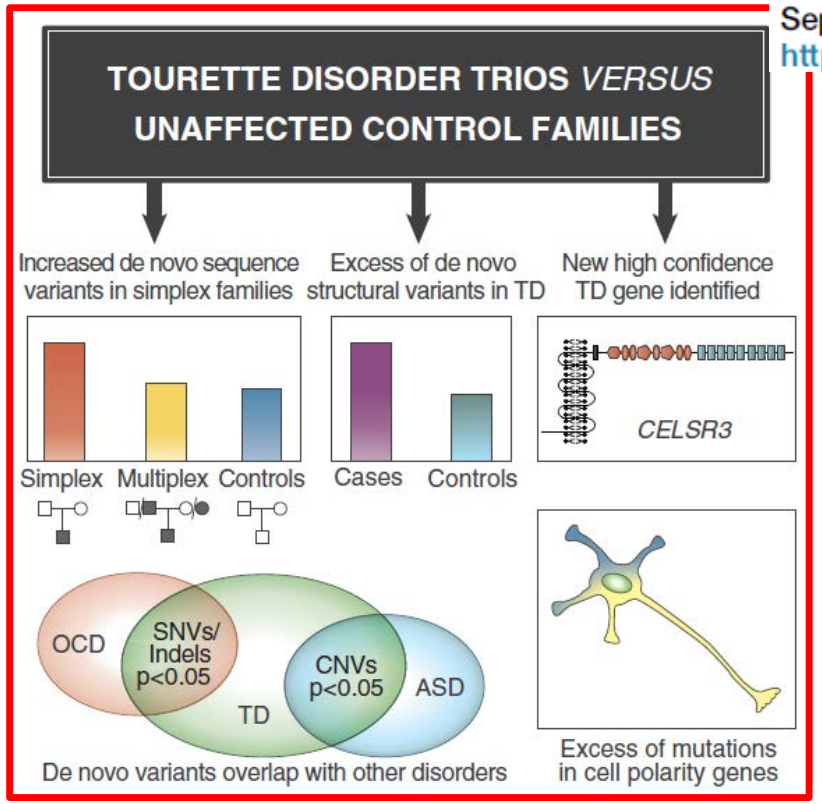


- A polygenic risk score can only explain the **relative** risk for a disease, using data used from large scale genomic studies. These studies find genomic variants by comparing groups with a certain disease to a group without the disease.

- A polygenic risk score tells you how a person's risk compares to others with a different genetic constitution.

Genetic factors

- Are there specific (inherited) genetic variants that co-segregate with TS in families?



Wang et al., 2018, Cell Reports *24*, 3441–3454
September 25, 2018 © 2018 The Author(s).
https://doi.org/10.1016/j.celrep.2018.08.082

DE NOVO, POTENTIALLY PATHOGENIC VARIANTS APPEAR TO CONTRIBUTE MORE

Approximately 12% of TS individuals express these

WES of a large number (>500) trios allowed to detect these

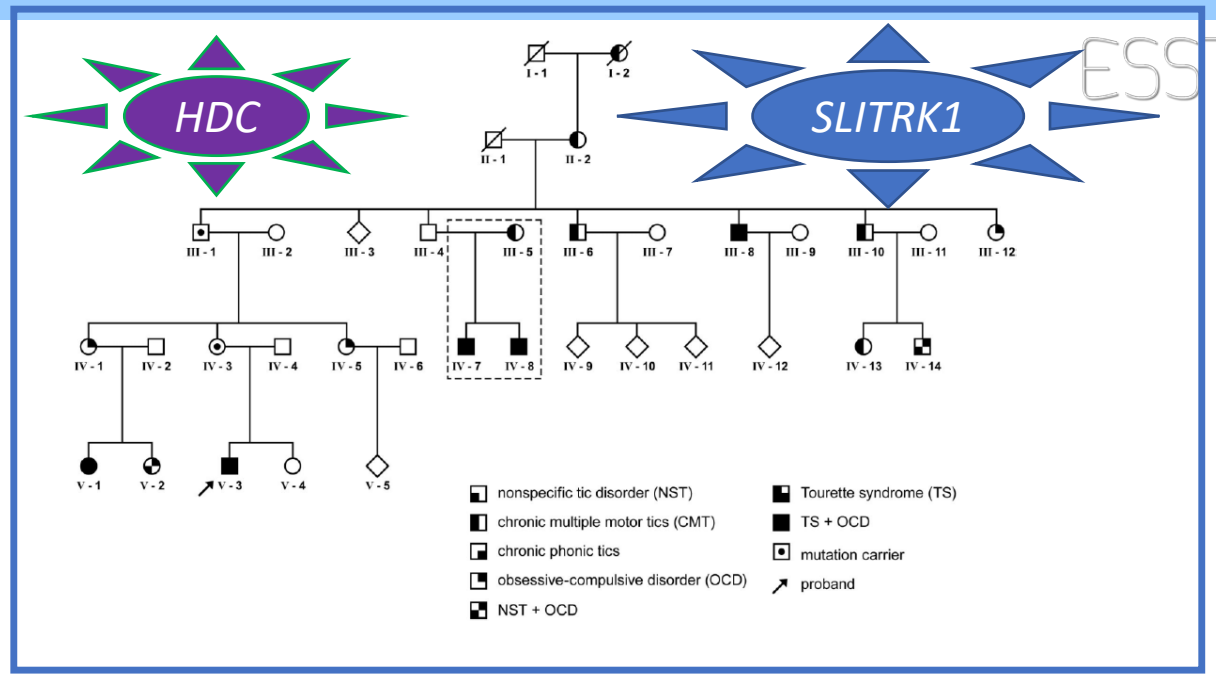
Genetic factors

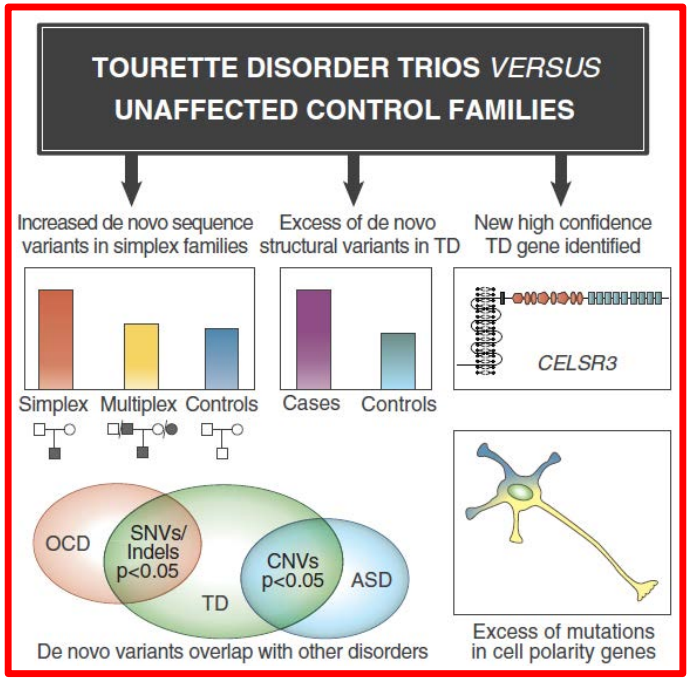
- **Are the same variants also co-segregating with OCD?**

  DE NOVO VARIANTS ARE EVEN MORE IMPORTANT IN OCD THAN IN TS

However, no gene implicated in TS has met the threshold for high-confidence association with both TS and OCD → specific neuronal pathways for these disorders, despite being part of the same impulsivity-compulsivity spectrum

[Cappi et al., 2020; Tsetsos et al., 2020]





Genetic factors

- **Does monogenic TS exist?**

THEY MAY INVOLVE <2% OF PATIENTS → generalization of findings is really difficult

SLITRK 1-6
CELSR3
CNTN6
NRXN1

- Neuronal and dendrite development
- Axonal guidance, cell polarity and migration
- Cellular membrane stability
- Cell adhesion molecules implicated in trans-synaptic signalling

OPRK1
HDC

- Neurotransmitters (GABA, glutamate, opioids, histamine)

FLT3

- Glial-derived neuroimmunity

Genetic factors

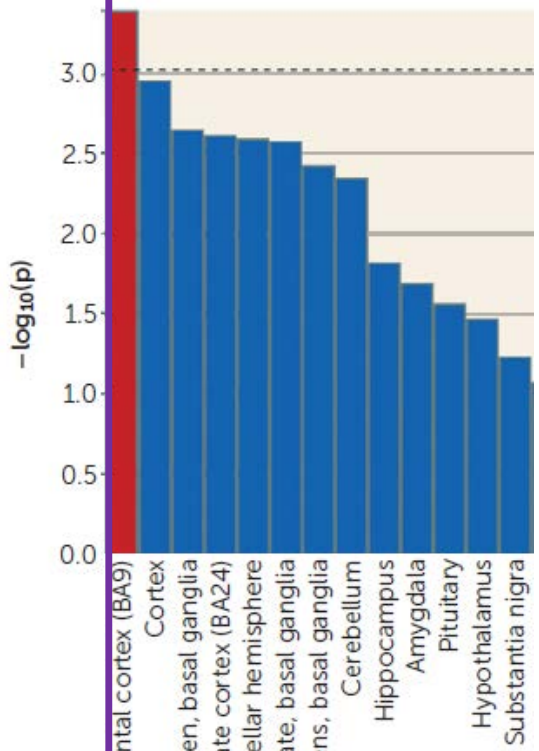
- **How does the genetics of TS relate to the brain networks involved in TS?**

GENES CONTRIBUTING TO THE POLYGENIC RISK OF TS→ specific brain expression profile

- Genome-wide cell and tissue-based enrichment analyses in 714 healthy adult donors (53 human tissues)
- **Cortico-basal ganglia** and **cortico-cerebellar** circuits
- Special emphasis on the DLPFC, followed by other frontal regions, striatum and cerebellum

Interrogating the Genetic Determinants of Tourette's Syndrome and Other Tic Disorders Through Genome-Wide Association Studies

Am J Psychiatry 2019; 176:217–227; doi: 10.1176/appi.ajp.2018.18070857



Genetic factors

GENES CONTRIBUTING TO THE POLYGENIC RISK OF TS→ significant locus on chromosome 5q15

- *NR2F1* gene and associated long noncoding RNA within the locus
- Significant enrichment inbrain tissue histone marks
- Significant association with right and left thalamus volumes and right putamen volume

ESSTS

NR2F1 gene → nuclear hormone receptor and transcriptional regulator → regulates regional progenitor dynamics in neocortex and cortical gyrification

{Bosch-Boonstra-Schaaf optic atrophy syndrome}

Biol Psychiatry. 2023 Feb 2;S0006-3223(23)00051-3. doi: 10.1016/j.biopsych.2023.01.023.
Online ahead of print.

Genome-wide Association Study Points to Novel Locus for Gilles de la Tourette Syndrome

Fotis Tsetsos [1], Apostolia Topaloudi [2], Pritesh Jain [2], Zhiyu Yang [2], Dongmei Yu [3], Petros Kolovos [1], Zeynep Tumer [4], Renata Rizzo [5], Andreas Hartmann [6], Christel Depienne [7], Yulia Worbe [8], Kirsten R Müller-Vahl [9], Danielle C Cath [10], Dorret I Boomsma [11], Tomasz Wolanczyk [12], Cezary Zekanowski [13], Csaba Barta [14], Zsofia Nemoda [14], Zsanett Tarnok [15], Shanmukha S Padmanabhuni [2], Joseph D Buxbaum [16], Dorothy Grice [17], Jeffrey Glennon [18], Hreinn Stefansson [19], Bastian Hengerer [20], Evangelia Yannaki [21], John A Stamatoyannopoulos [22], Noa Benaroya-Milshtein [23], Francesco Cardona [24], Tammy Hedderly [25], Isobel Heyman [26], Chaim Huyser [27], Pablo Mir [28], Astrid Morer [29], Norbert Mueller [30], Alexander Munchau [31], Kerstin J Plessen [32], Cesare Porcelli [33], Veit Roessner [34], Susanne Walitza [35], Anette Schrag [36], Davide Martino [37]; PGC TS Working Group; TSAICG; TSGeneSEE Initiative; EMTICS Collaborative Group; TS-EUROTRAIN Network; TIC Genetics Collaborative Group; Jay A Tischfield [38], Gary A Heiman [38], A Jeremy Willsey [39], Andrea Dietrich [40], Lea K Davis [41], James J Crowley [42], Carol A Mathews [43], Jeremiah M Scharf [44], Marianthi Georgitsi [45], Pieter J Hoekstra [46], Peristera Paschou [47]

Genetic factors

- **Which phenotypic factors are associated with polygenic risk?**

{PHENOME-GENOME LINK}

- 57 traits associated with TS polygenic risk
  - multiple psychosocial factors and mental health conditions → anxiety disorders and depression
  - T2DM (males), heart palpitations (males), respiratory diseases (females)
- Similar associations seen for ADHD and ASD
- Opposite direction of effect for OCD except for mental health factors

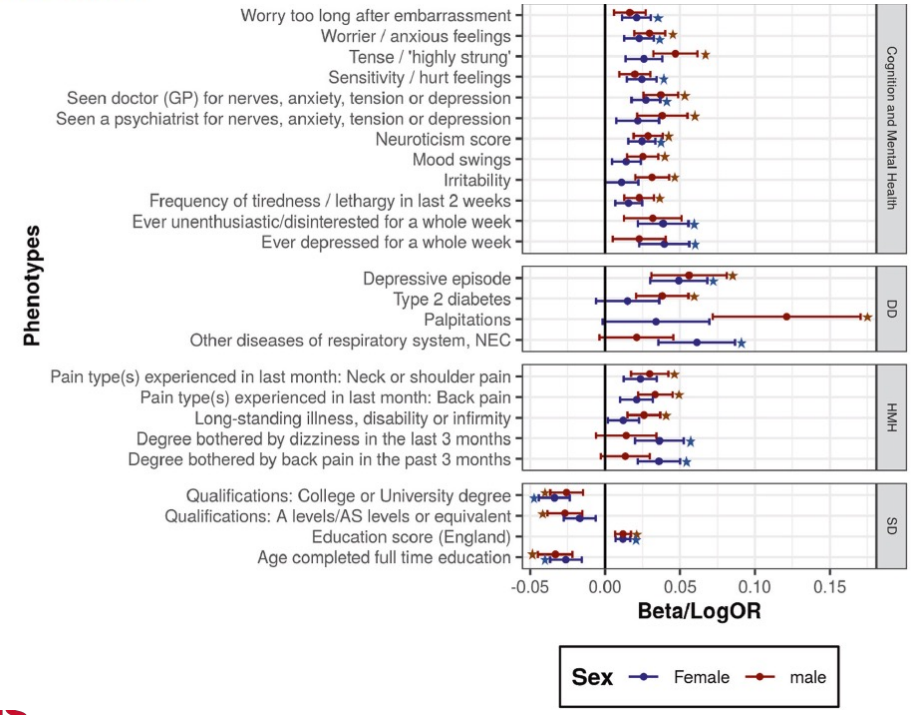
Translational Psychiatry www.nature.com/tp

ARTICLE OPEN

Check for updates

Polygenic risk score-based phenome-wide association study identifies novel associations for Tourette syndrome

Pritesh Jain[1], Tyne Miller-Fleming[2,3], Apostolia Topaloudi[1], Dongmei Yu[4,5], Petros Drineas[6], Marianthi Georgitsi[7,8], Zhiyu Yang[1], Renata Rizzo[9], Kirsten R. Müller-Vahl[10], Zeynep Tumer[11,12], Nanette Mol Debes[13], Andreas Hartmann[14], Christel Depienne[15], Yulia Worbe[16,17], Pablo Mir[18,19], Danielle C. Cath[20], Dorret I. Boomsma[21,22], Veit Roessner[23], Tomasz Wolanczyk[24], Piotr Janik[25], Natalia Szejko[25,26], Cezary Zekanowski[27], Csaba Barta[28], Zsofia Nemoda[28], Zsanett Tarnok[29], Joseph D. Buxbaum[30,31,32,33,34,35], Dorothy Grice[30,34,35,36], Jeffrey Glennon[37], Hreinn Stefansson[38], Bastian Hengerer[39], Noa Benaroya-Milshtein[40], Francesco Cardona[41], Tammy Hedderly[42], Isobel Heyman[43], Chaim Huyser[44,45], Astrid Morer[46,47,48], Norbert Mueller[49], Alexander Munchau[50], Kerstin J. Plessen[51,52], Cesare Porcelli[53], Susanne Walitza[54], Anette Schrag[55], Davide Martino[56], The Psychiatric Genomics Consortium Tourette Syndrome Working Group (PGC-TS), The EMTICS collaborative group, Andrea Dietrich[57], The TS-EUROTRAIN Network, Carol A. Mathews[58], Jeremiah M. Scharf[4,5,59], Pieter J. Hoekstra[57], Lea K. Davis[2,3]✉ and Peristera Paschou[1]✉

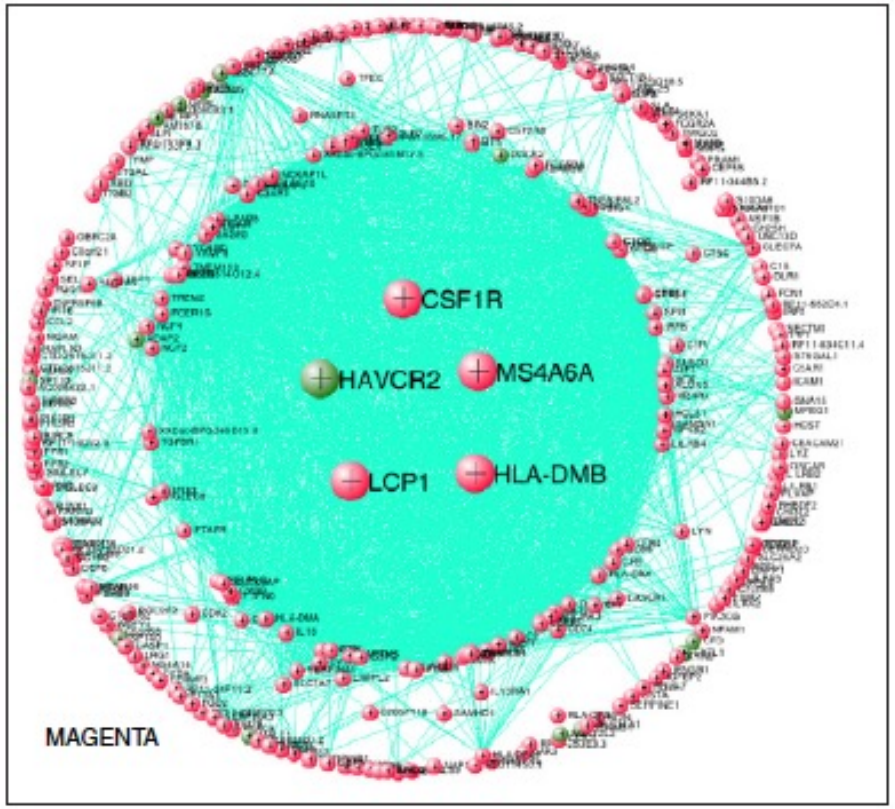


Archival Report

Biological Psychiatry

Transcriptome Analysis of the Human Striatum in Tourette Syndrome

Jessica B. Lennington, Gianfilippo Coppola, Yuko Kataoka-Sasaki, Thomas V. Fernandez, Dean Palejev, Yifan Li, Anita Huttner, Mihovil Pletikos, Nenad Sestan, James F. Leckman, and Flora M. Vaccarino



Basal ganglia transcriptome in caudate/putamen of 9 TS and 9 matched control brains

ESSTS

Genetic factors

- **What is the relationship between genetics and immune response in TS?**

OVER-EXPRESSION OF IMMUNE-RELATED GENE HUBS IN THE STRIATUM OF TS BRAINS

- Up-regulation of transcripts involved in monocyte-macrophage-mediated inflammatory responses
- Potential association with microglial activation in the striatum

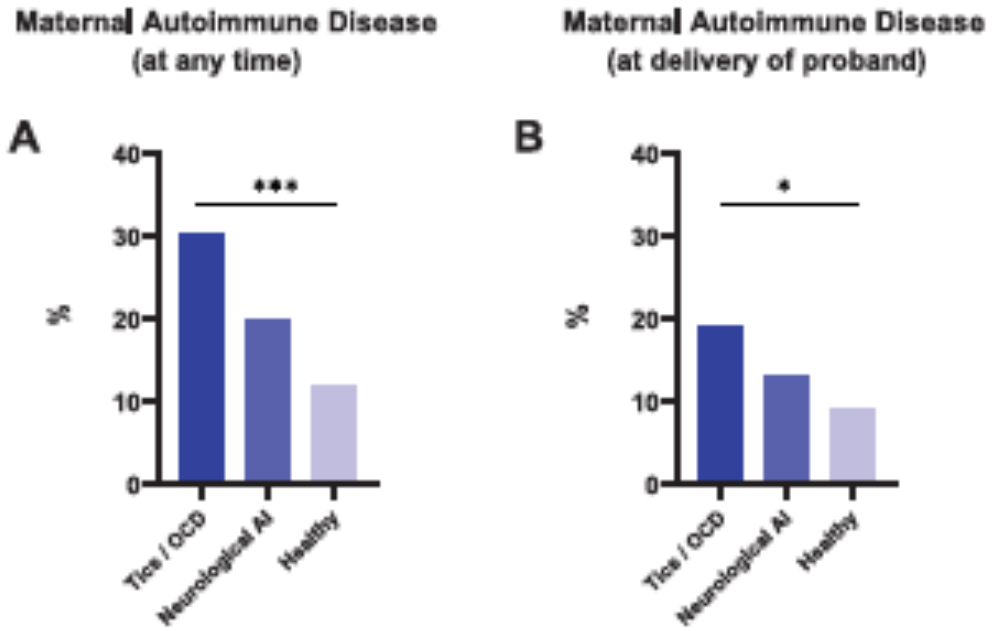
Contents lists available at ScienceDirect

Brain Behavior and Immunity

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

Maternal autoimmunity and inflammation are associated with childhood tics and obsessive-compulsive disorder: Transcriptomic data show common enriched innate immune pathways

Hannah F. Jones[a,b,c], Velda X. Han[a,d], Shrujna Patel[a,c], Brian S. Gloss[e], Nicolette Soler[a,c,f], Alvin Ho[a,g], Suvasini Sharma[a,h], Kavitha Kothur[a,c], Margherita Nosadini[a,i], Louise Wienholt[c,j], Chris Hardwick[f], Elizabeth H. Barnes[k], Jacqueline R. Lim[c], Sarah Alshammery[a,c], Timothy C. Nielsen[l], Melanie Wong[m], Markus J. Hofer[n], Natasha Nassar[l], Wendy Gold[a,o,p], Fabienne Brilot[a,c,q], Shekeeb S. Mohammad[a,c], Russell C. Dale[a,c,q,*]



Genetic factors

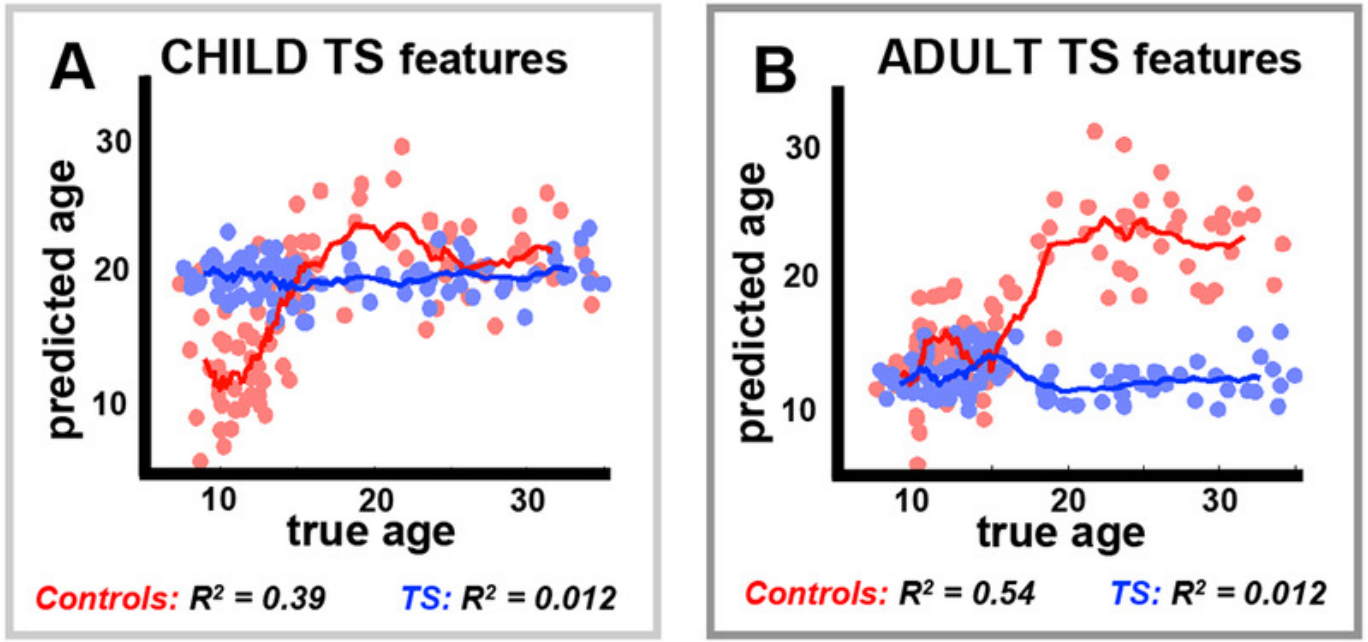
- **What is the relationship between genetics and immune response in TS?**

MOTHERS OF TS PATIENTS EXHIBIT SIMILAR GENE EXPRESSION PROFILES

- Mothers of children with tics/OCD have higher rate of autoimmune disease
- Up-regulation of inflammatory response transcripts in blood of mothers of children with tics/OCD
- Up-regulation of immune-related genes is an important heritable or transmissible pattern in TS

Pathophysiology

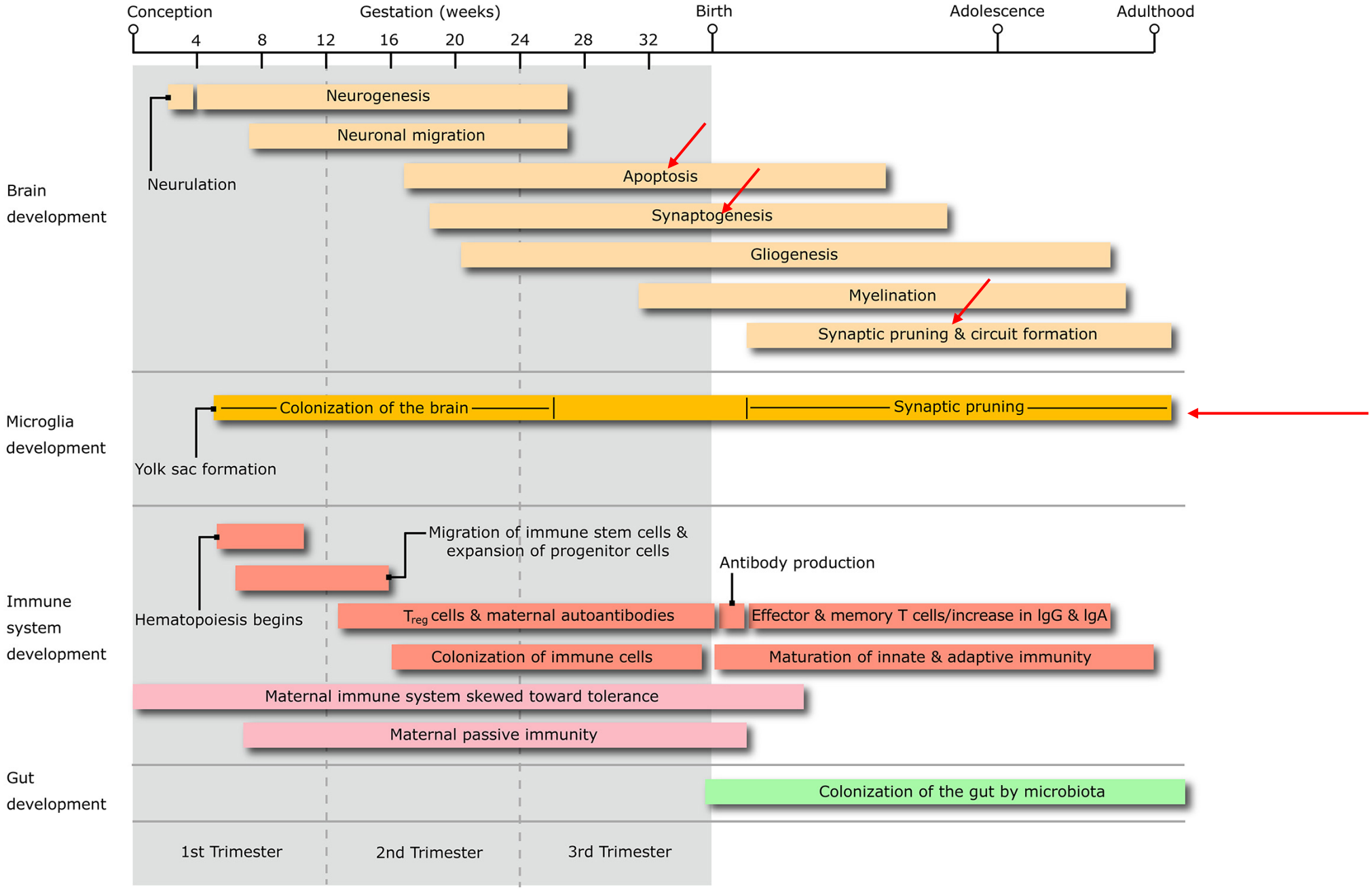
- **«What is going on» in the brain networks of people with Tourette syndrome that leads them to manifest tics?**



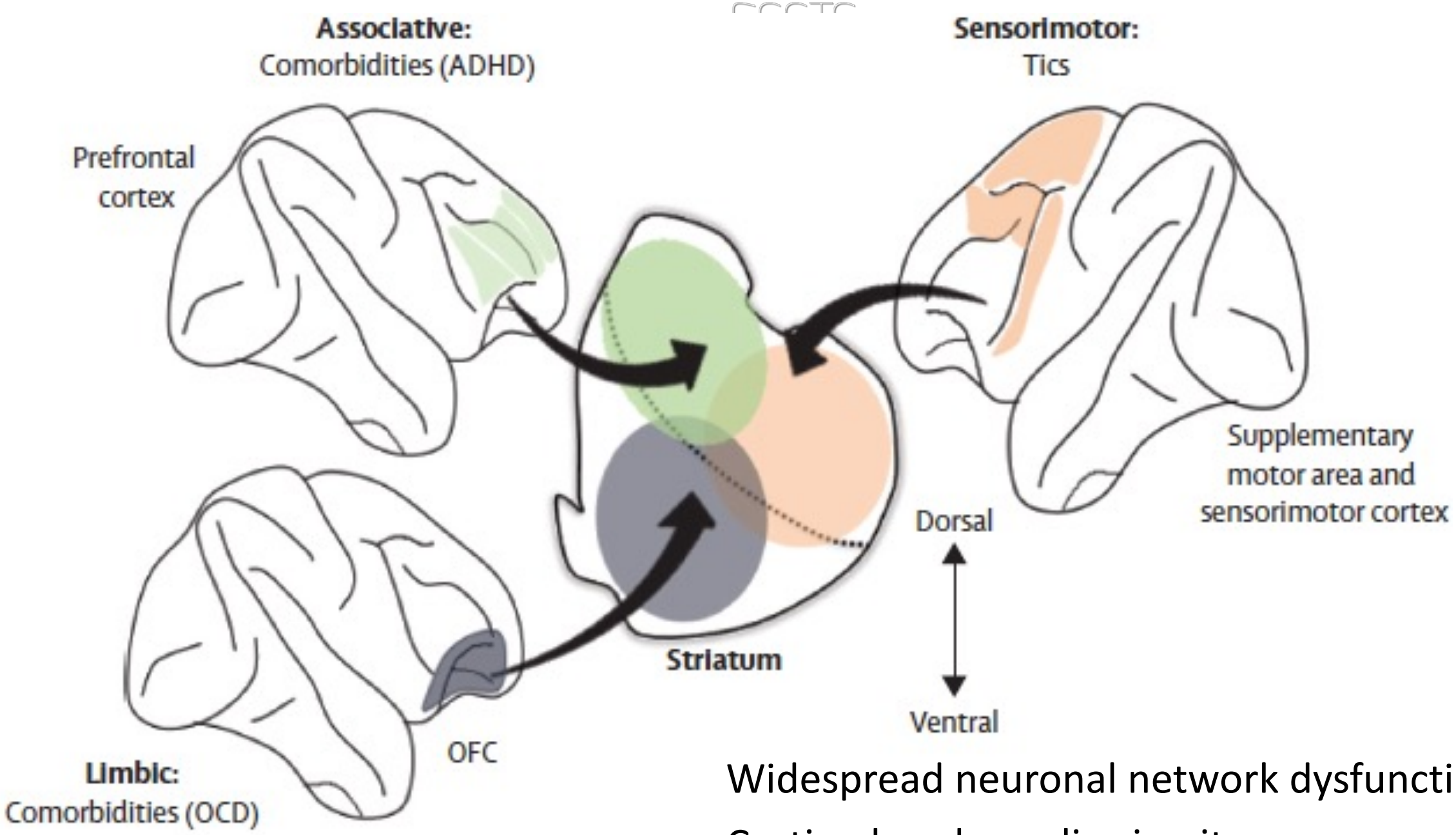
[Nielsen et al., 2020]

NEUROIMAGING STUDIES HELP ANSWERING THIS QUESTION

- Difference in functional brain connectivity (from the 'at-rest' condition) between adults with TS and children with TS
- Children with TS show «older» brain connectivity
- Adults with TS show «younger» brain connectivity



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

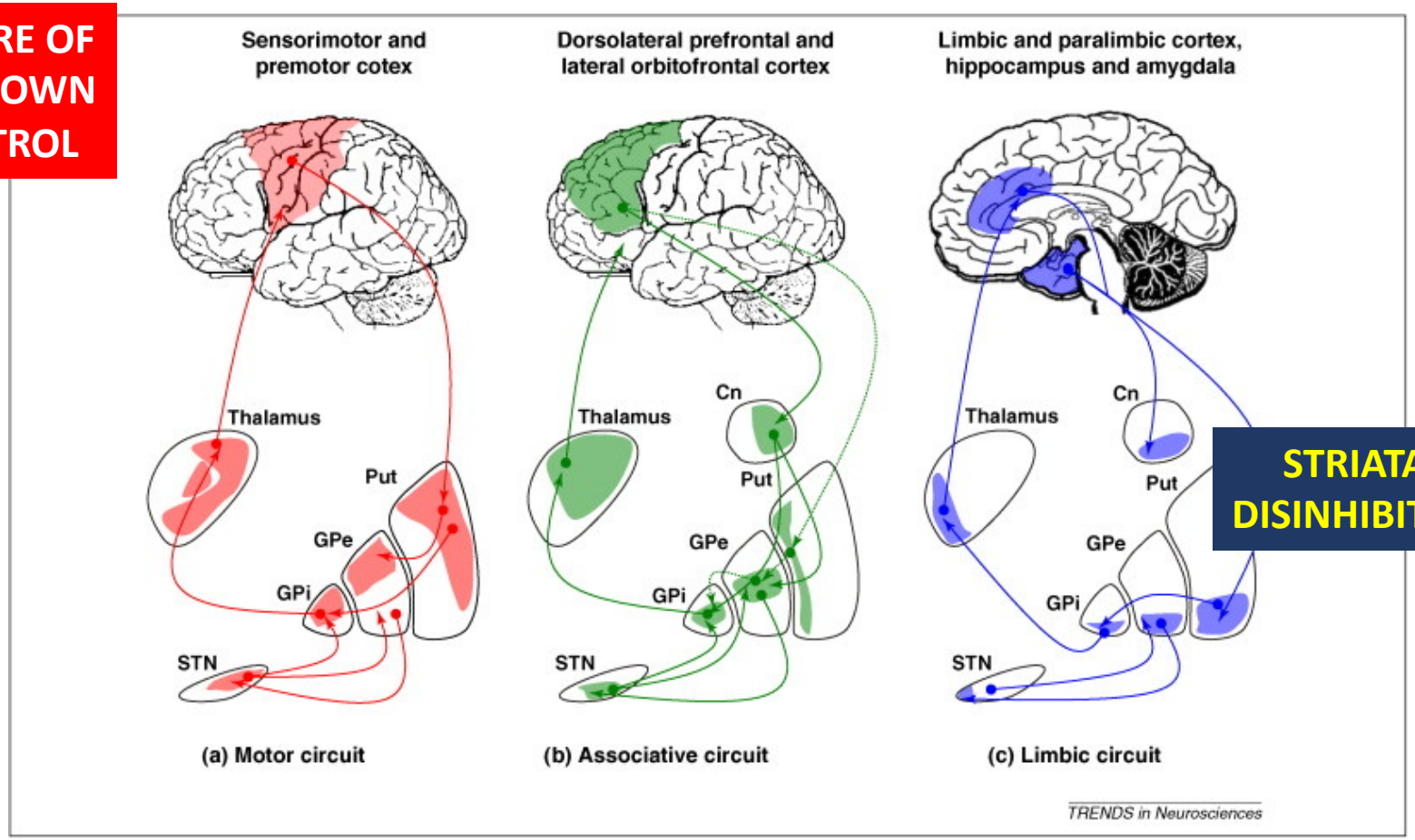


Widespread neuronal network dysfunction

Cortico-basal ganglia circuits

- **Is there a «tic network» in the brain?**

FAILURE OF TOP-DOWN CONTROL



STRIATAL DISINHIBITION

Simple tics

Complex tics

Hyperactivity

Compulsive actions

Impulsive actions

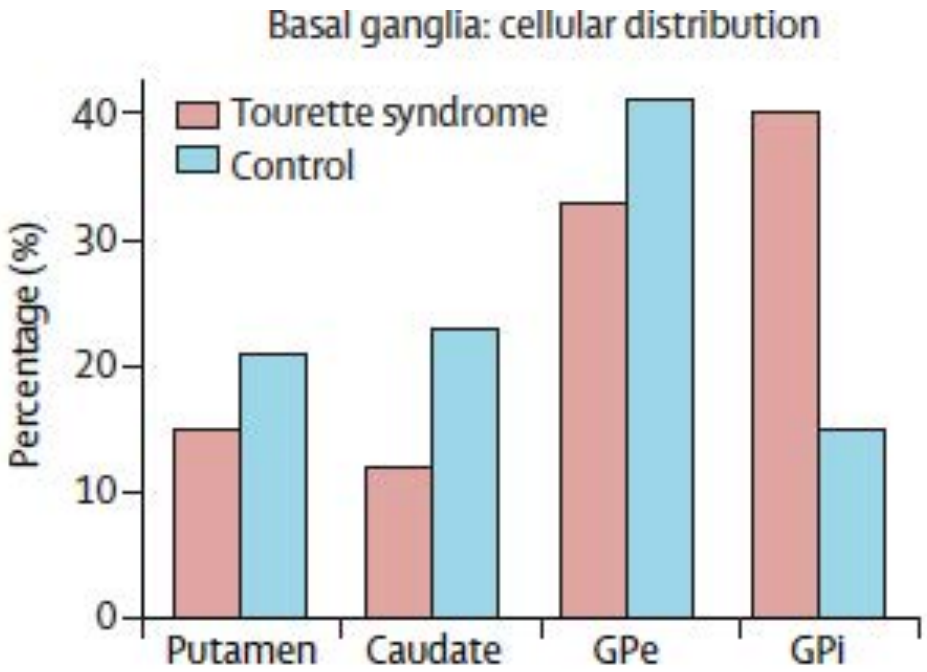
complexity

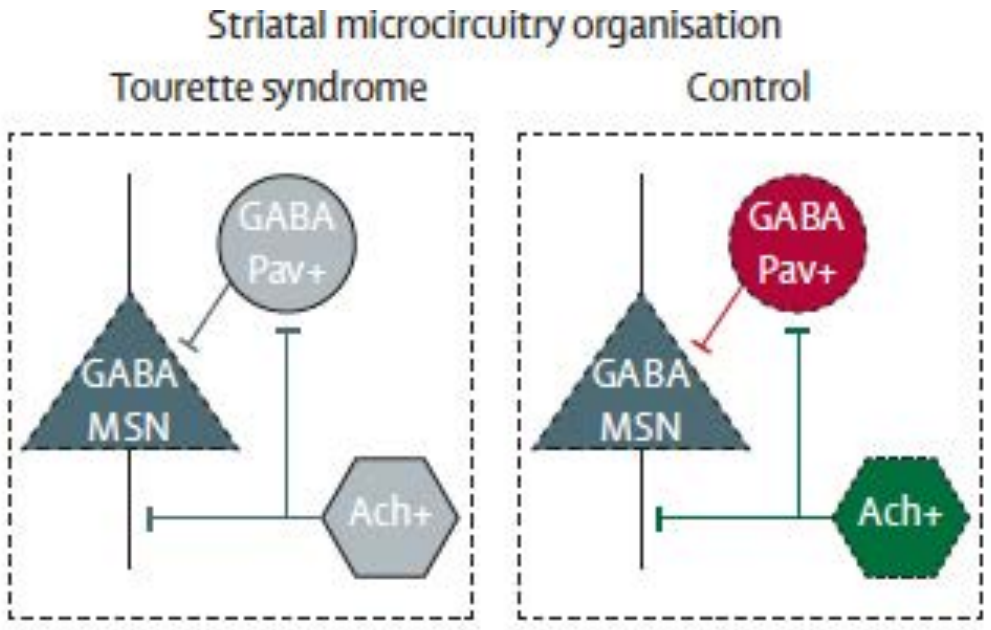
(Worbe et al., *Brain* 2012, 2015; *Cortex* 2012)

- **Are tics related to an abnormality of a specific brain cell type?**

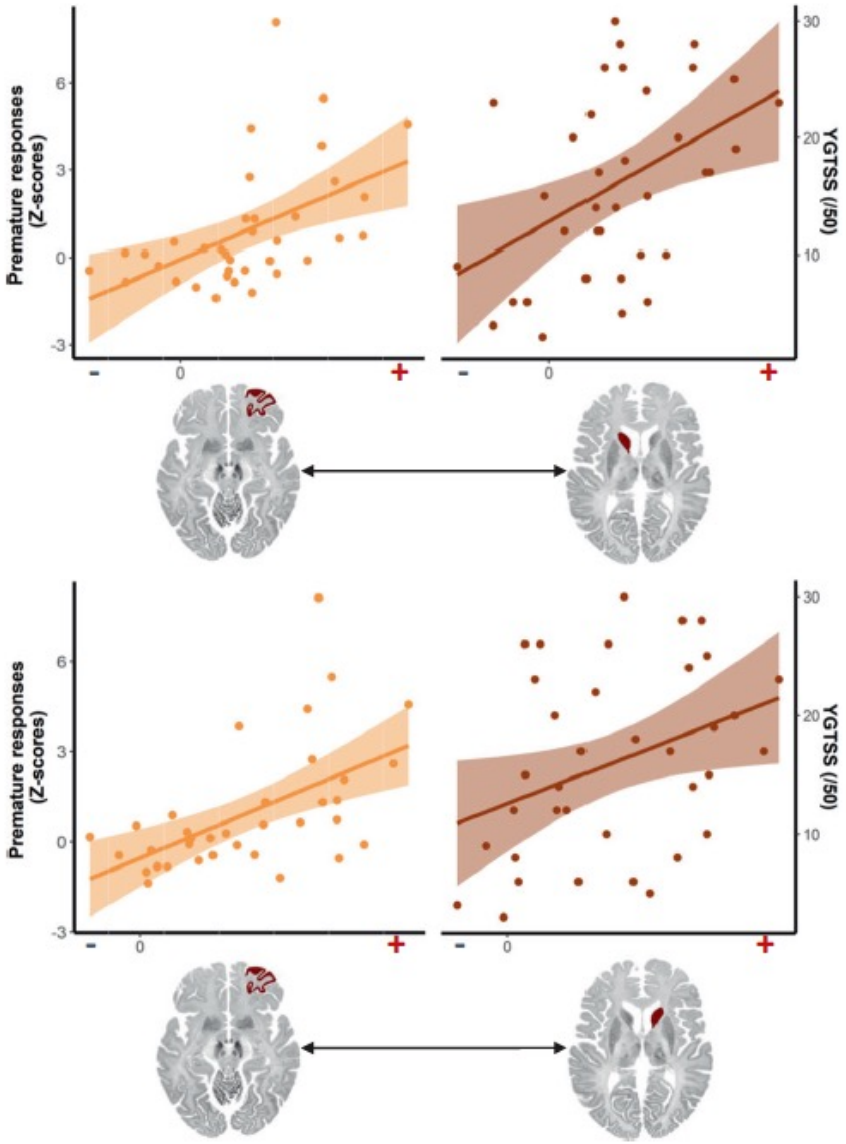
EVIDENCE IS STILL LIMITED, AND MOSTLY COMING FROM SMALL SIZE PATHOLOGY STUDIES AND PRE-CLINICAL MODELS

- Alterations of striatal inhibitory microcircuitry
- Altered automatic inhibition of actions





- **Are tics resulting from a deficit in action inhibition? <u>the DISINHIBITION hypothesis</u>**



Molecular Psychiatry (2021) 26:3548–3557
https://doi.org/10.1038/s41380-020-00890-5

ARTICLE

Impulsive prepotent actions and tics in Tourette disorder underpinned by a common neural network

Cyril Atkinson-Clement[1,2] · Camille-Albane Porte[1,2] · Astrid de Liege[1,3] · Yanica Klein[1,3] · Cecile Delorme[1,3] · Benoit Beranger[4] · Romain Valabregue[4] · Cecile Gallea[1,2] · Trevor W. Robbins[5,6] · Andreas Hartmann[1,2,3] · Yulia Worbe[1,2,3,7]

TIC SEVERITY CORRELATES WITH A **REDUCED ABILITY TO «HOLD IN»** (i.e., DELAY) **AN «AUTOMATIC» ACTION**

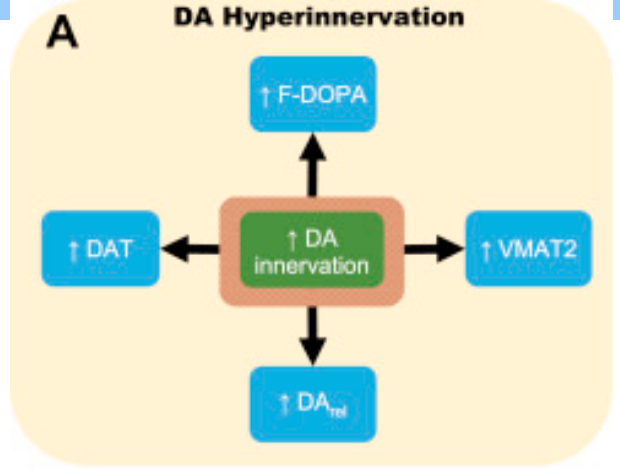
- This deficit is related to changes in functional connectivity between the left middle orbitofrontal gyrus and bilateral caudate

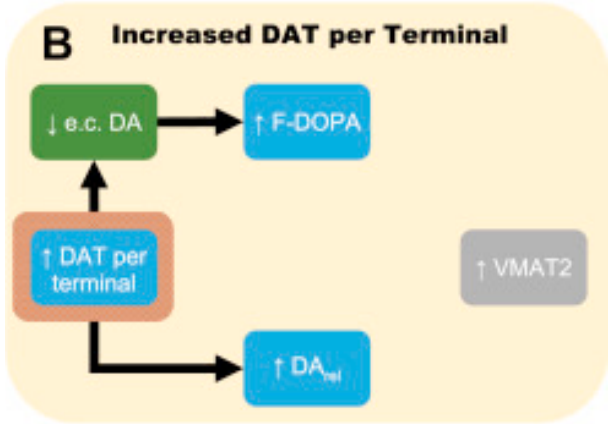
HOWEVER, **THE ABILITY TO INHIBIT AN ALREADY INITIATED ACTION IS NOT ALTERED**, AND RELATES TO THE CAPACITY TO INHIBIT TICS ON DEMAND

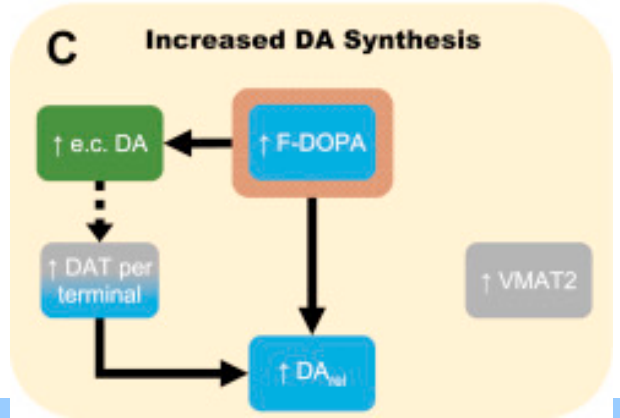
- **What is the link between tics and dopaminergic transmission?**

- This would explain, in part, the large effect of dopamine receptor modulating agents (**antipsychotics**) in the treatment of tics
- The disinhibition hypothesis does not explain waxing and waning of tics and premonitory urges

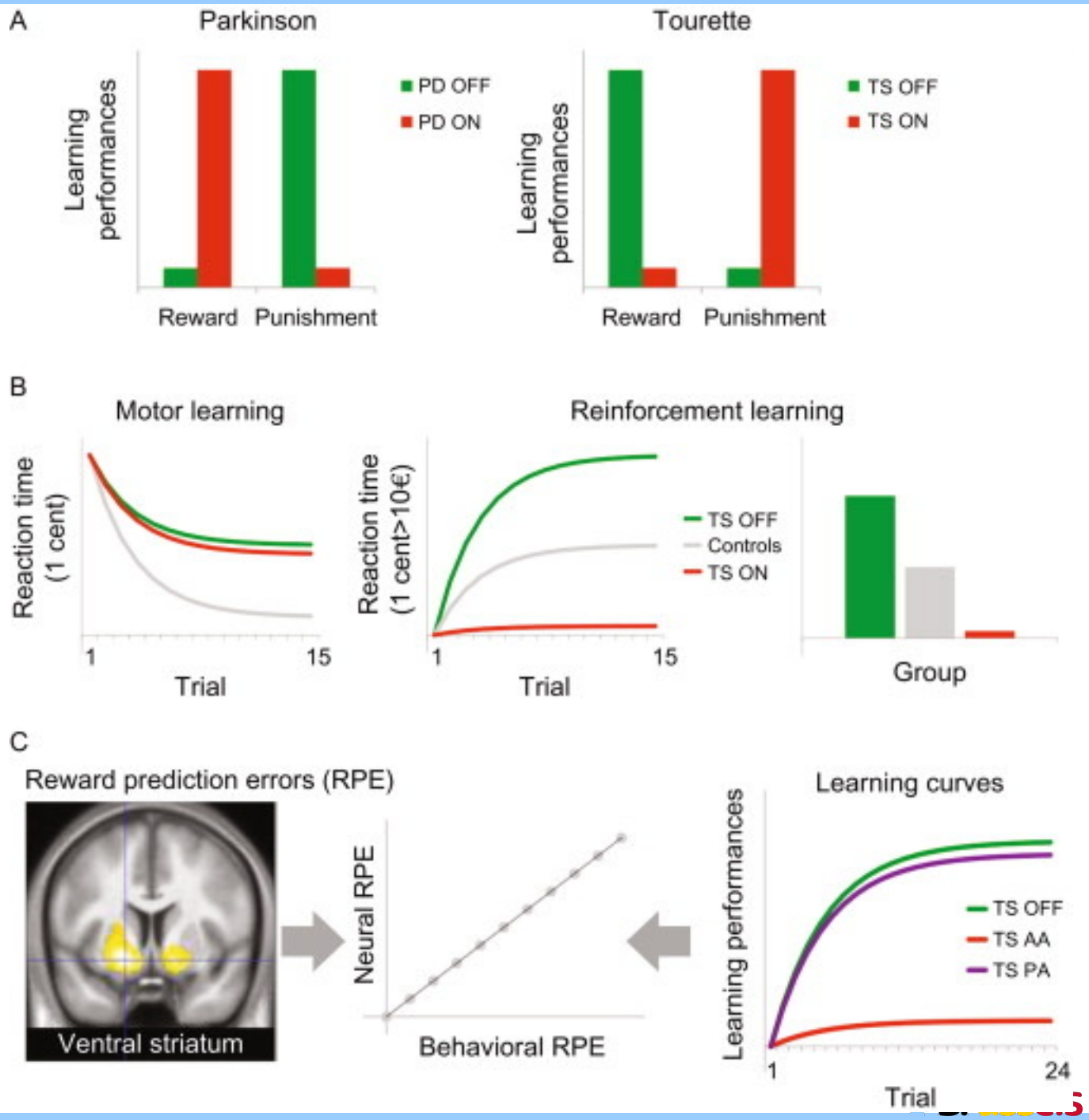
ALTERNATIVELY, TICS COULD BE SEEN AS **PERSISTENT, EXAGGERATED MOTOR HABITS** THAT ARE **REINFORCED BY AN INCREASE IN <u>PHASIC</u> DOPAMINE RELEASE**







Maia TV, Conceição VA, *Biol Psychiatry* 2018



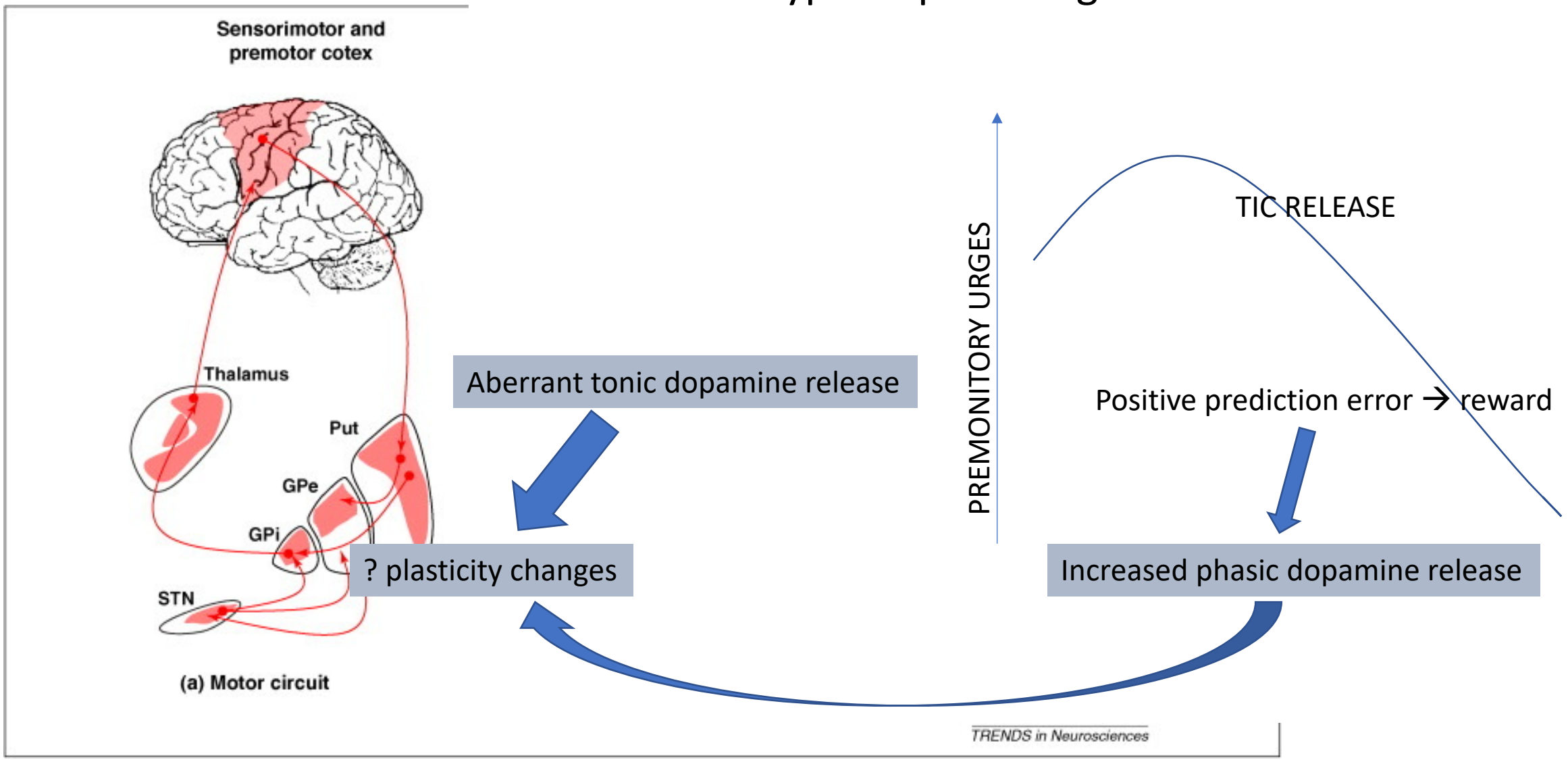
- Hyperdopaminergic tone in TS

EVIDENCE IN FAVOUR OF THIS COMES FROM THE OBSERVATION THAT **DOPAMINE-ASSOCIATED REWARD-GUIDED LEARNING** IS **ENHANCED** IN TS

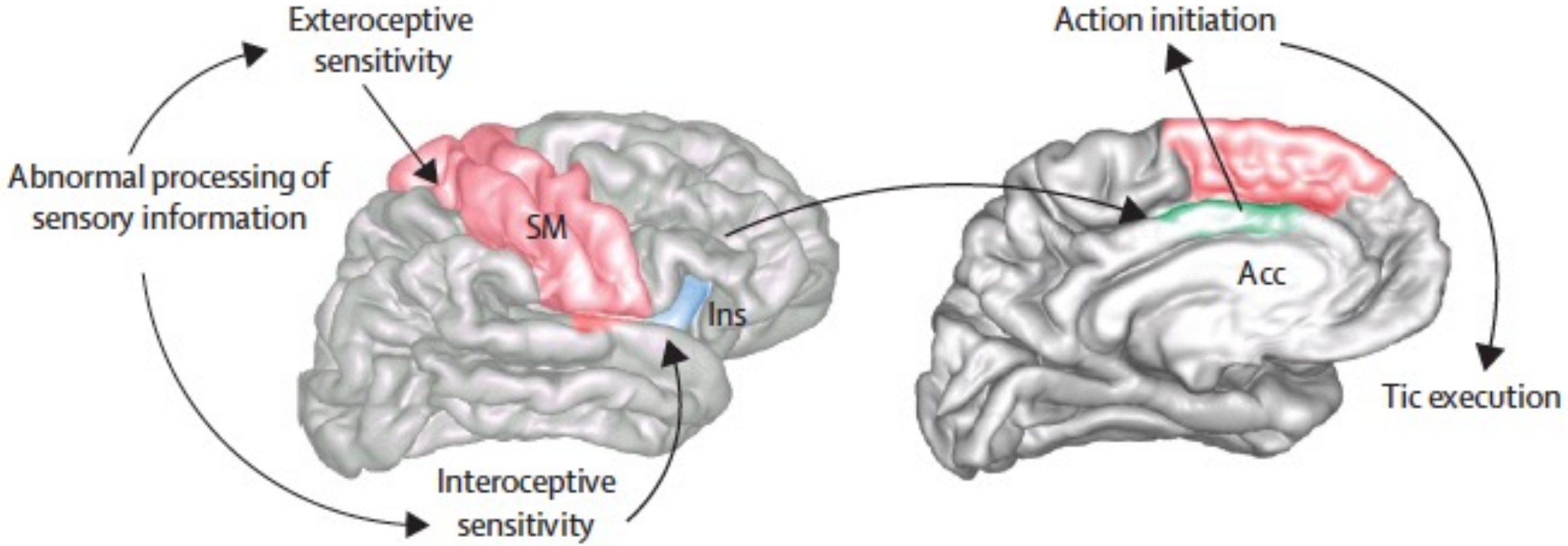
- People with TS who are not treated or medicated → greater strength of habits

Palminteri S, Pessiglione M, *Int Rev Neurobiol* 2013

Hyperdopaminergic tone in TS



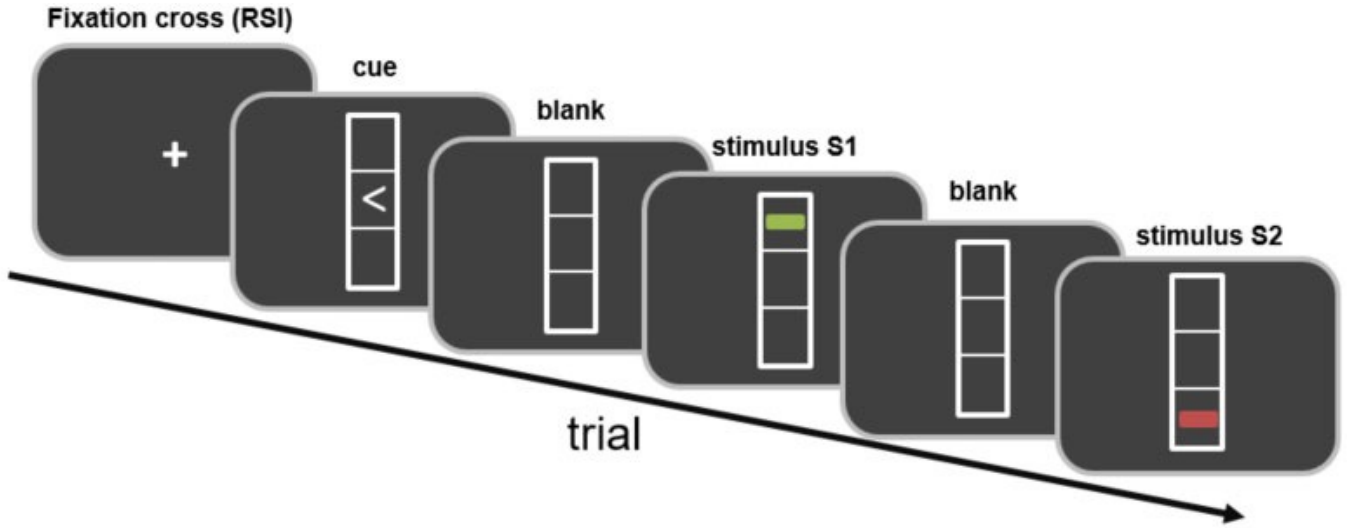
- **What is the link between perception and action in tic disorders?**

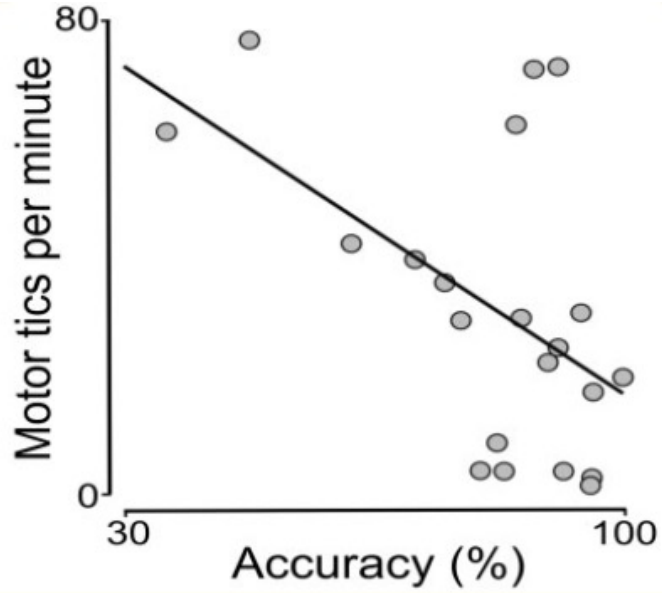


- Processes linking perception and action appear affected in tic disorders (**Perception-Action Binding – Theory of Event Coding**)

THE ACCURACY OF BINDING PERCEPTS TO BEHAVIOURAL RESPONSES CORRELATES WITH TIC SEVERITY

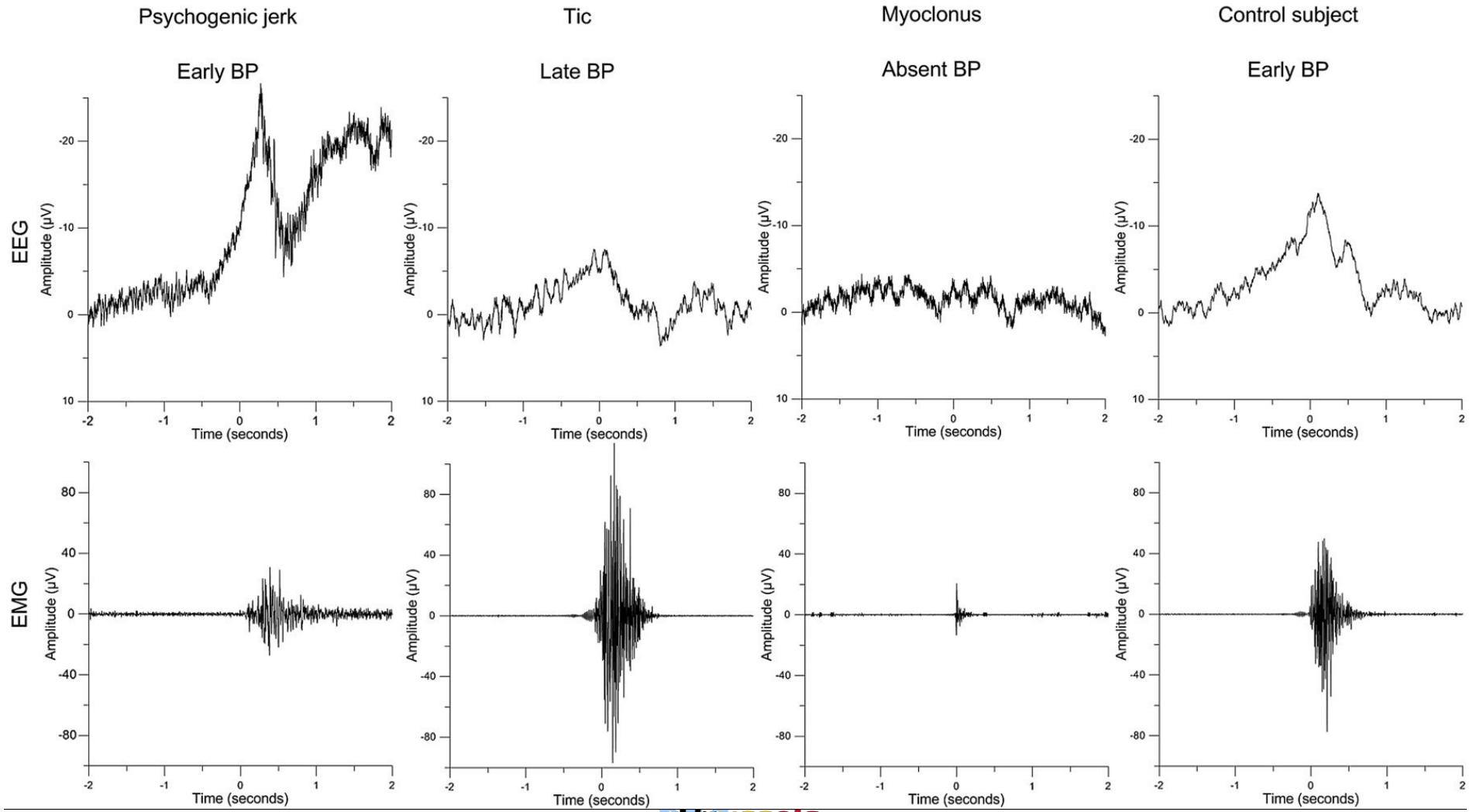
THIS IS COUPLED TO INCREASED ACTIVITY OF INFERIOR PARIETAL CORTEX, where processes linking perception to action localize (but not simple perceptual or motor processes)





- **How ‘voluntary’ are tics?**

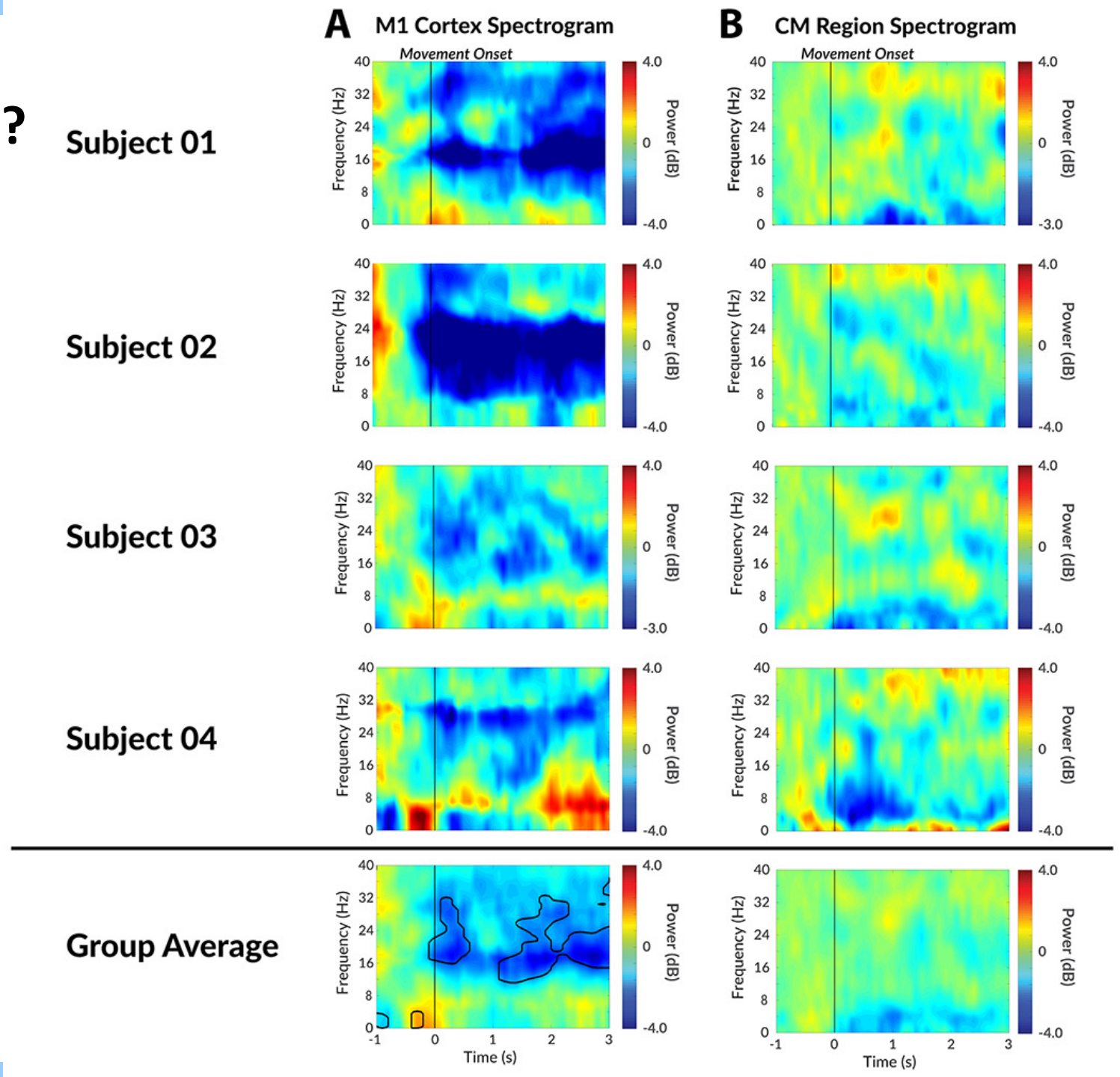
van der Salm SMA, Tijssen MAJ, Koelman JHTM, et al
The bereitschaftspotential in jerky movement disorders
Journal of Neurology, Neurosurgery & Psychiatry 2012;83:1162-1167.



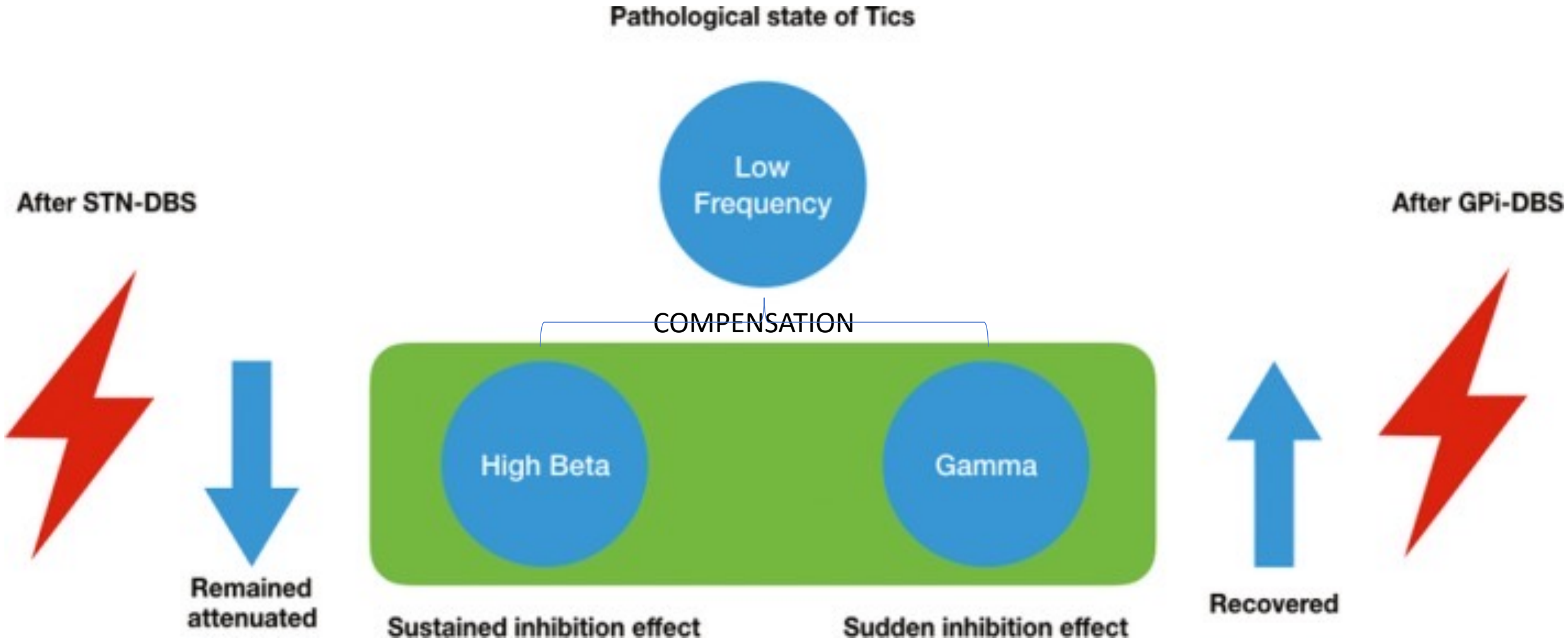
- **Do we have biomarkers for tics?**

- Neurophysiology: externalised lead studies, neurostimulators recording neural activity

- INCREASED ACTIVITY IN LOW-FREQUENCY POWER (1-10 HZ) IN THE CENTROMEDIAN THALAMIC REGION ASSOCIATED WITH TICS IN PEOPLE WITH TS



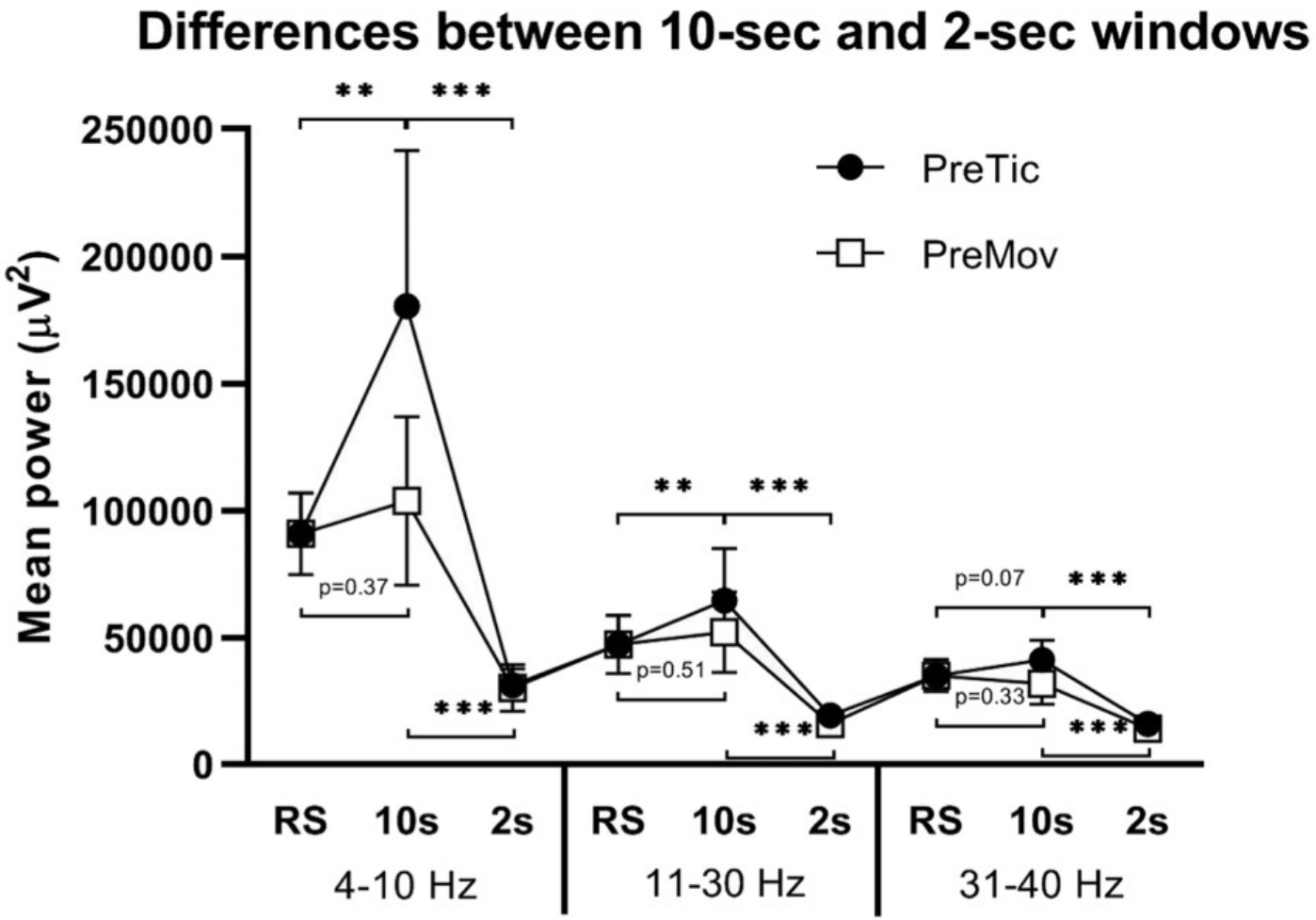
Cagle JN, Okun MS, Opri E, et al
Differentiating tic electrophysiology from voluntary movement in the human thalamocortical circuit
Journal of Neurology, Neurosurgery & Psychiatry 2020;91:533-539.



Zhu, G-Y, Geng, X-Y, Zhang, R-L, et al. Deep brain stimulation modulates pallidal and subthalamic neural oscillations in Tourette's syndrome. *Brain Behav*. 2019; 9:e01450.

- **Do we have biomarkers for urges?**

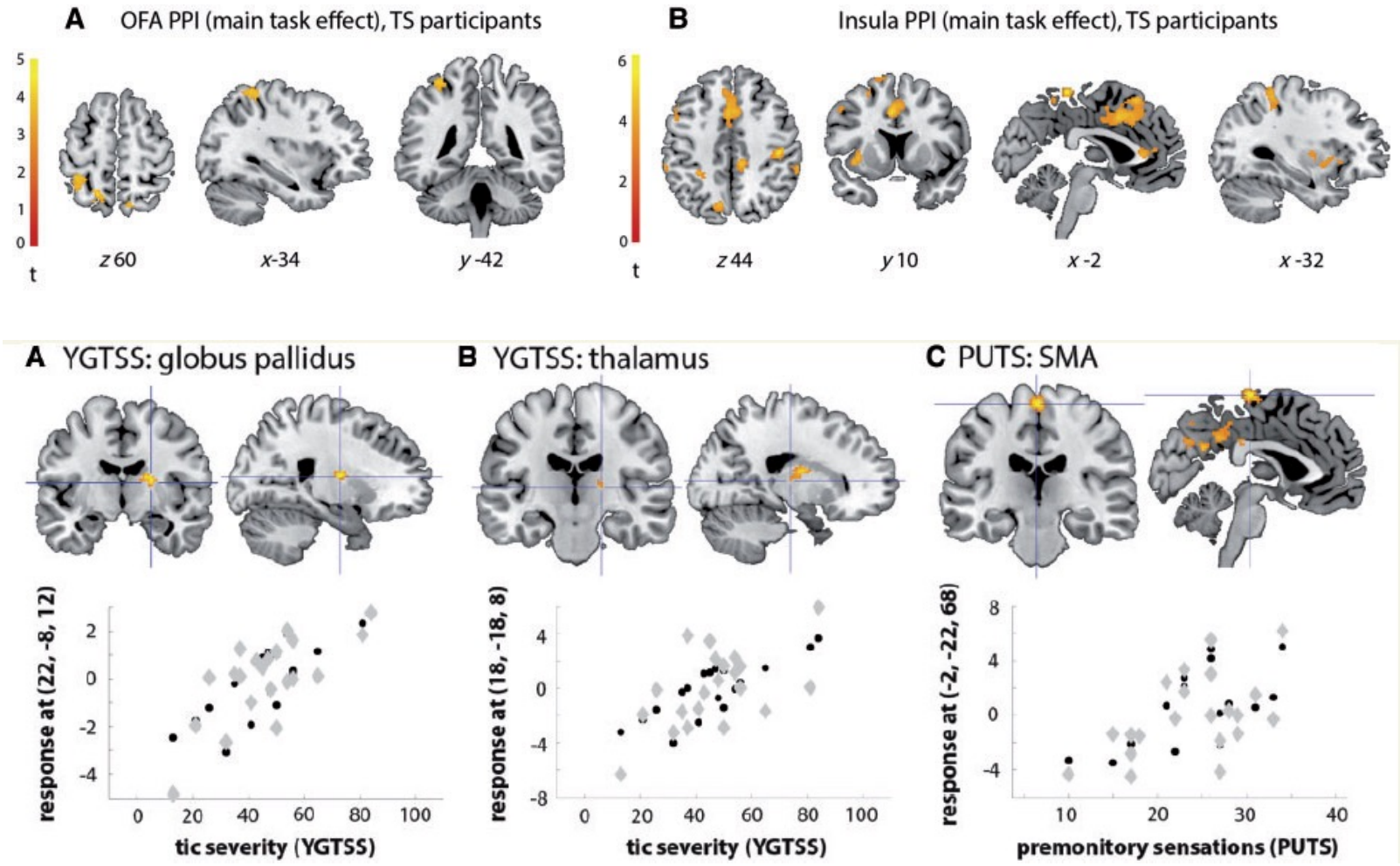
- INCREASED ACTIVITY IN LOW-FREQUENCY POWER (1-10 HZ) IN THE ANTERIOR PALLIDUM REGION ASSOCIATED WITH URGES IN PEOPLE WITH TS



Wilken, M., Cerquetti, D., Rossi, M., Obeso, J.A. and Merello, M. (2021), Low-Frequency Oscillations at The Limbic Globus Pallidus Internus Seem to Be Associated With Premonitory Urges in Tourette's Syndrome. Mov Disord, 36: 2966-2967.

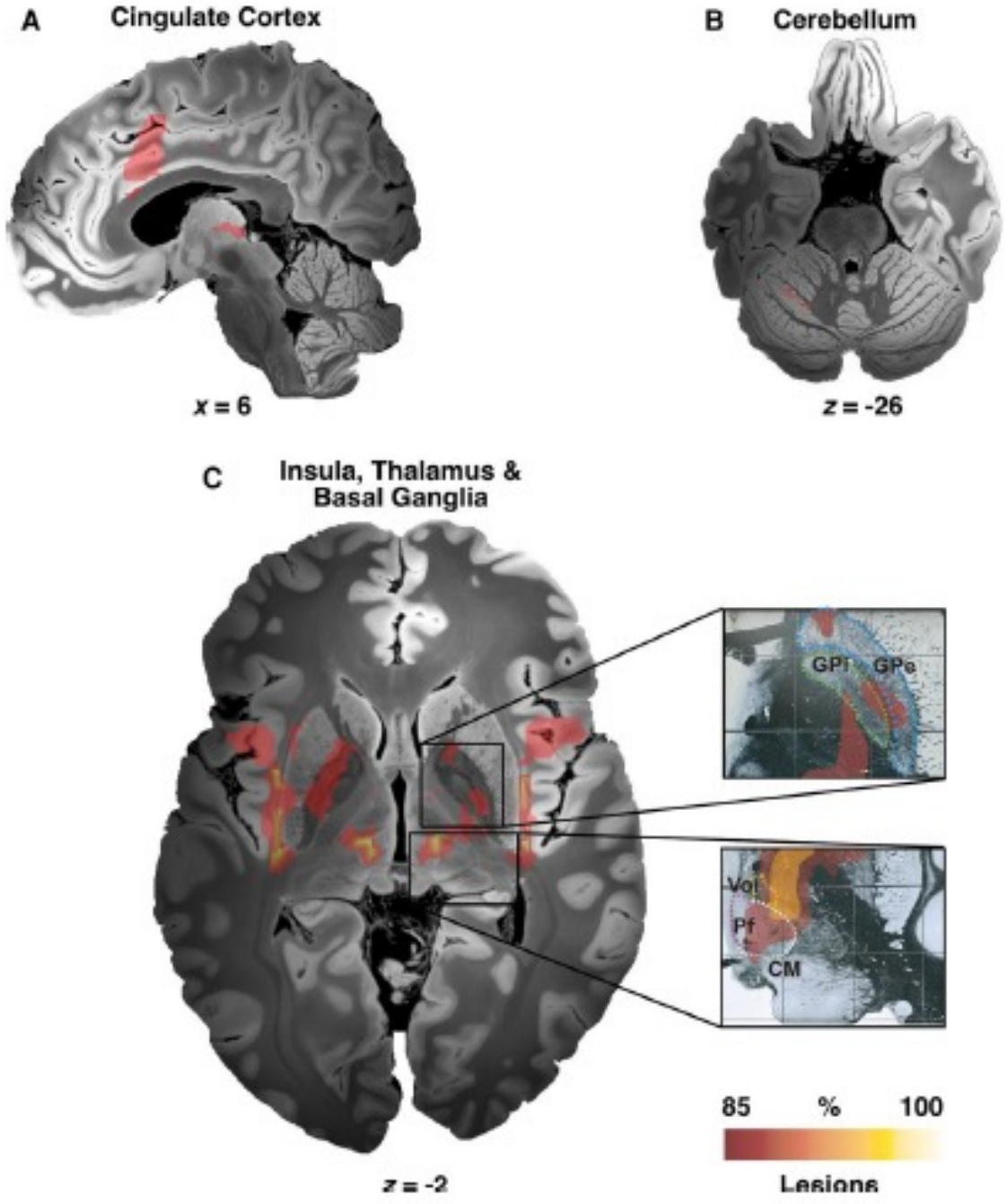
- **Link between social behaviour and tic generation**

- Emotional facial recognition task
- INCREASED ACTIVITY IN AREAS INVOLVED IN EMBODIMENT OF AFFECTIVE SOCIAL INFORMATION → insula
- Functional connectivity between insula and networks of tic generation correlates with severity of tics and urges



Rae et al., *Brain* 2018; *Brain Comm* 2020

Ganos et al., *Brain* 2022



LESION NETWORK MAPPING OF TICS

- Applied to 22 cases of tics attributed to brain lesions identified by systematic literature review
- Contrasted tic-lesion connectivity maps to those seeding from >700 lesions associated with wide array of neurological and psychiatric symptoms

- MAP: insula, cingulate gyrus, striatum, globus pallidus internus, thalamus, cerebellum
- Anterior striatum the most specific seed for tic-inducing lesions
- Connectivity between DBS electrodes and the lesion network map → predictive of tic improvement with DBS