



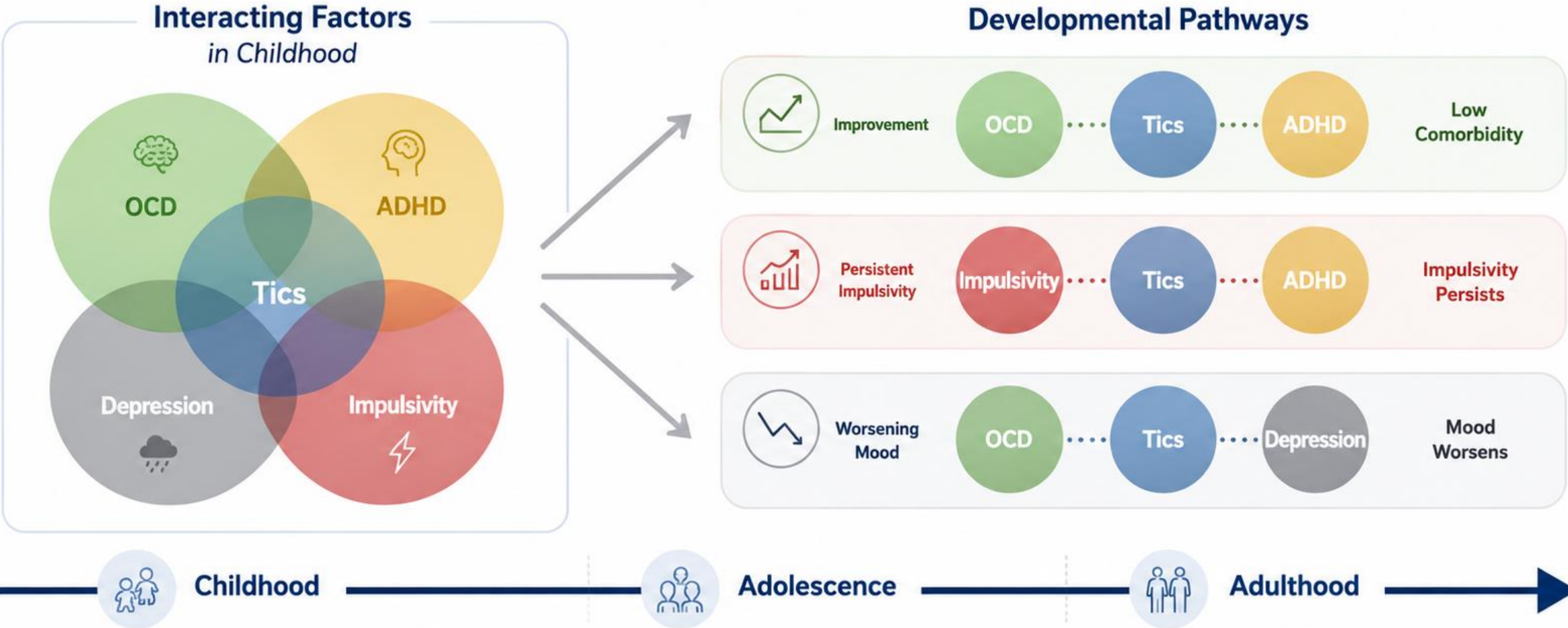
18th International Conference on Tourette Syndrome & Tic Disorders
17–19 June 2026

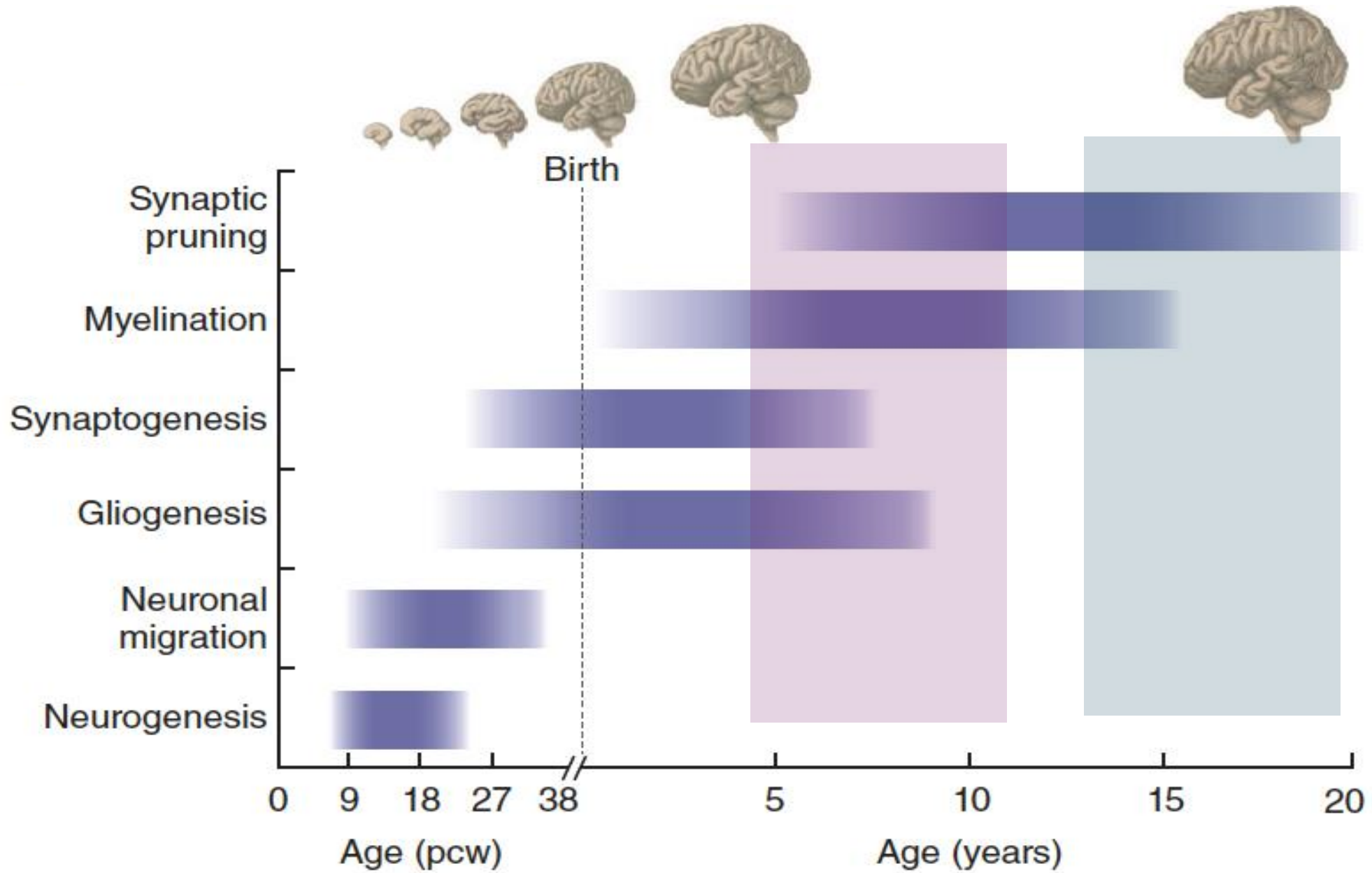
Longitudinal Changes in Cortico-Cerebellar and Striatal Connectivity Track Symptom Evolution in Tourette Syndrome

Yulia Worbe, MD PhD
Sorbonne University, Paris Brain Institute
Paris – France



Variability of clinical trajectories





CADET cohort



KEY SYMPTOM DIMENSIONS ASSESSED



Tics



Obsessive-Compulsive Symptoms



Attention-Deficit / Hyperactivity Disorder



Impulsivity



Depression



- Resting-state fMRI (rs-fMRI)
- Diffusion-weighted imaging (DWI)
- Magnetization transfer (MT)

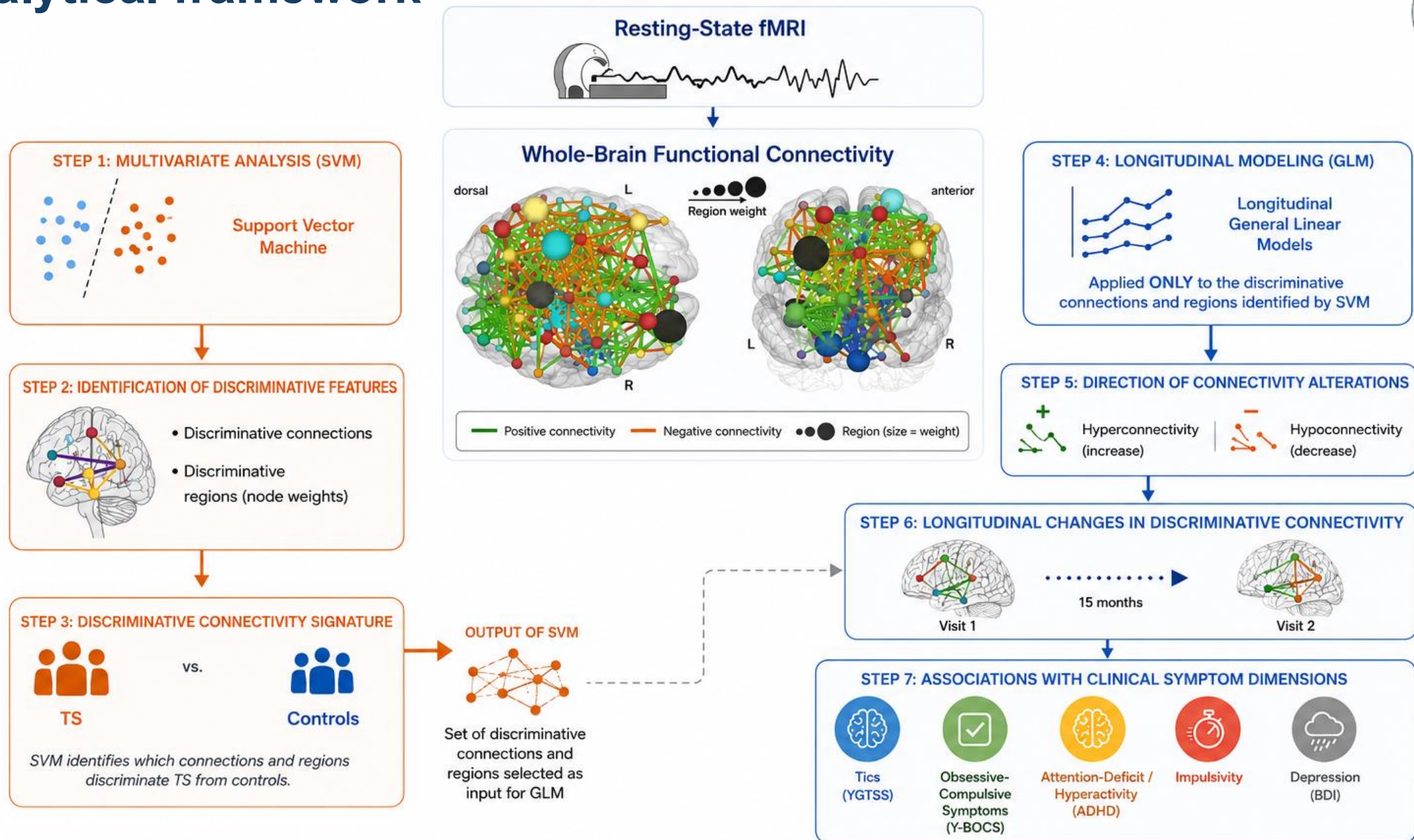


- Motor potential
- Motor resting threshold
- Short-interval intracortical inhibition (SICI)



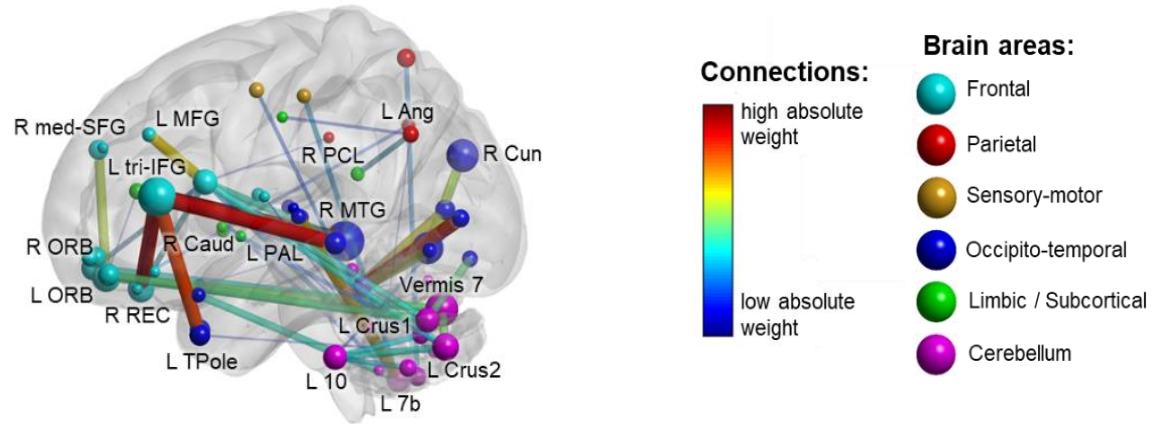
- Motor impulsivity
- Habit formation
- Agency
- Reward sensitivity

Analytical framework

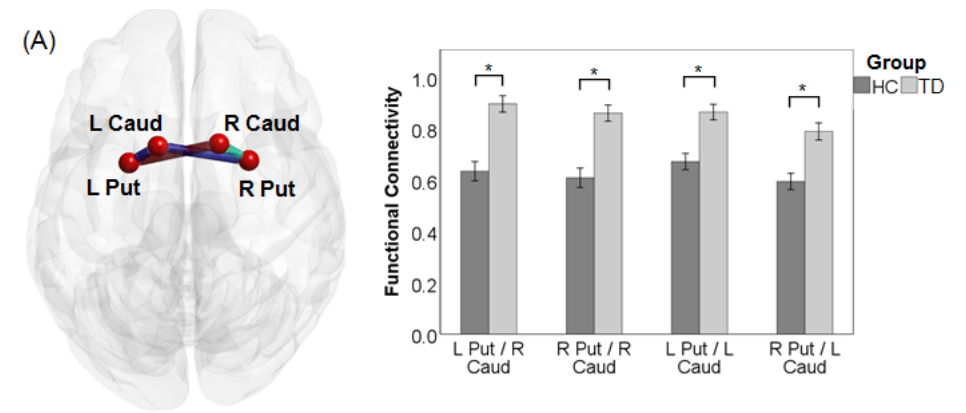
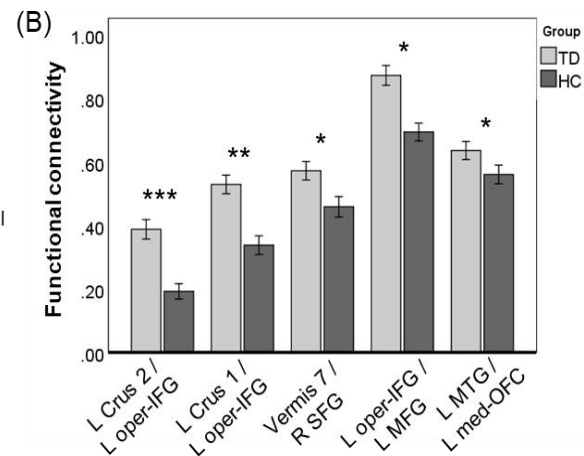
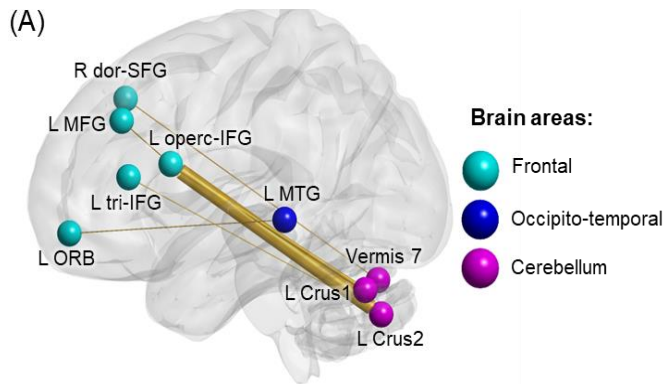
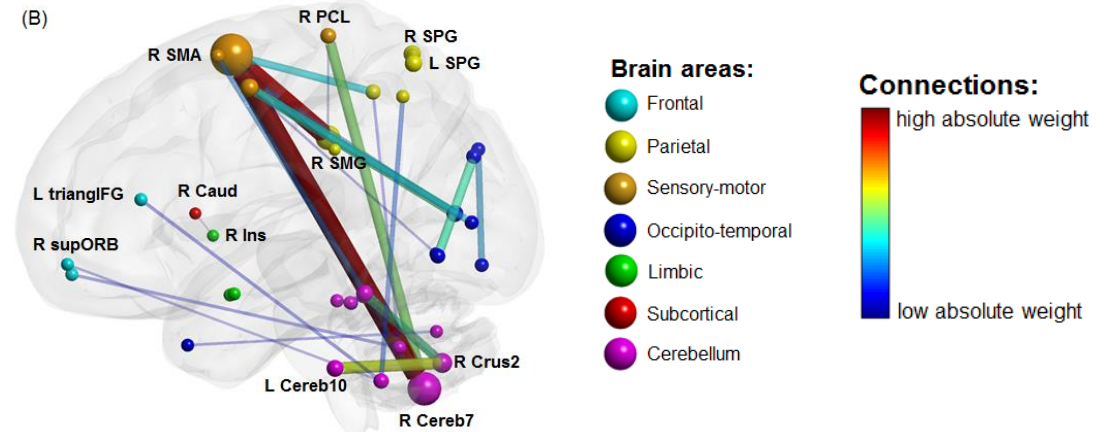




Adolescents : TS Patients > Controls



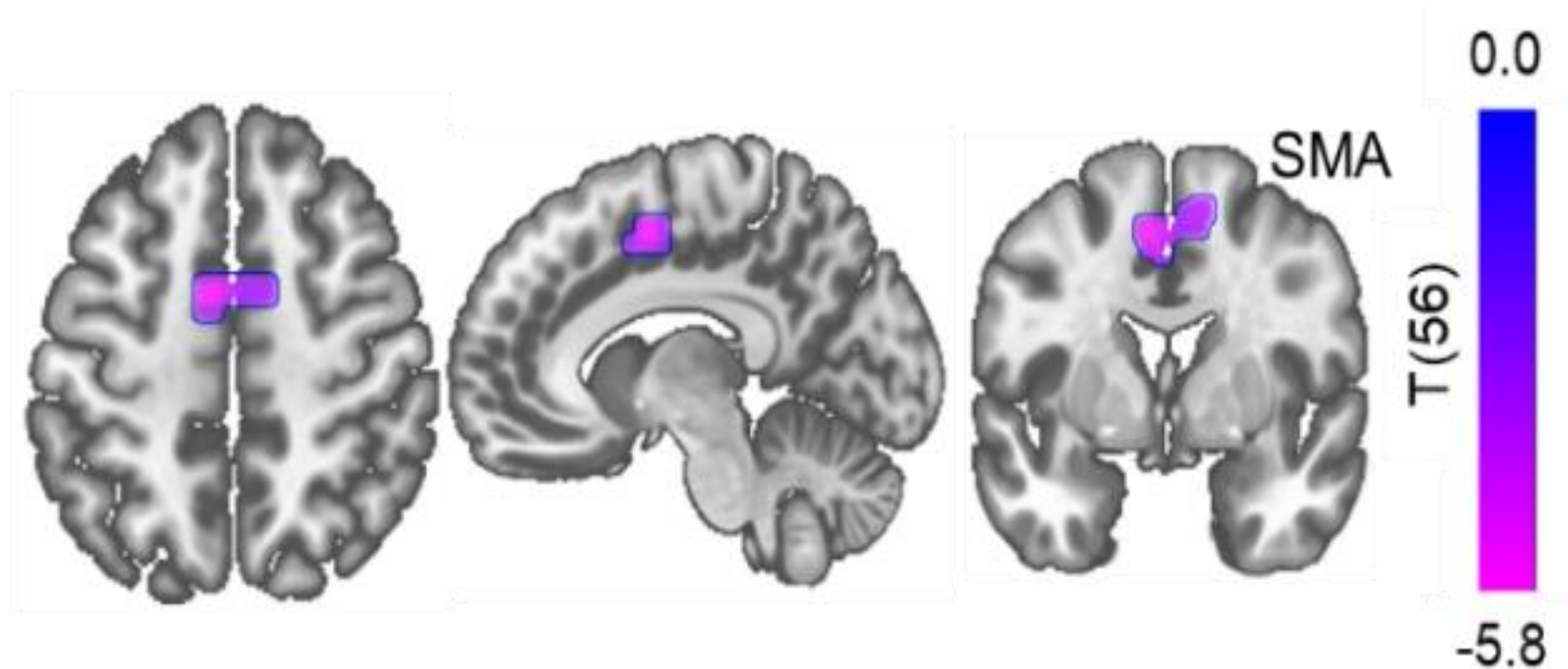
Adults : TS Patients > Controls



Longitudinal Decrease in Cerebellum - Supplementary Motor Area Functional Connectivity

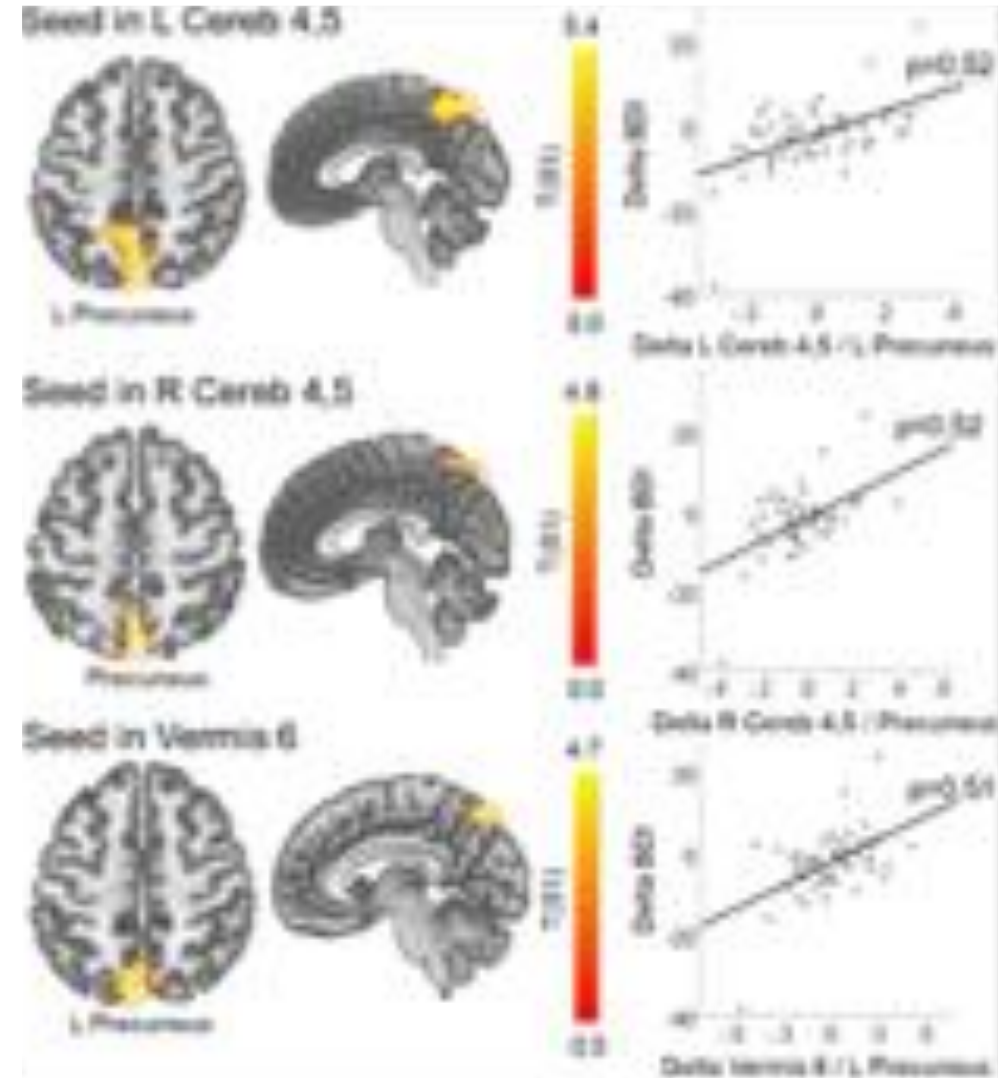
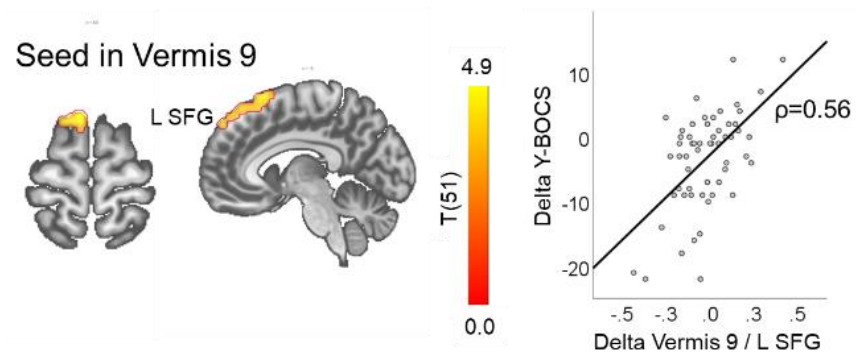
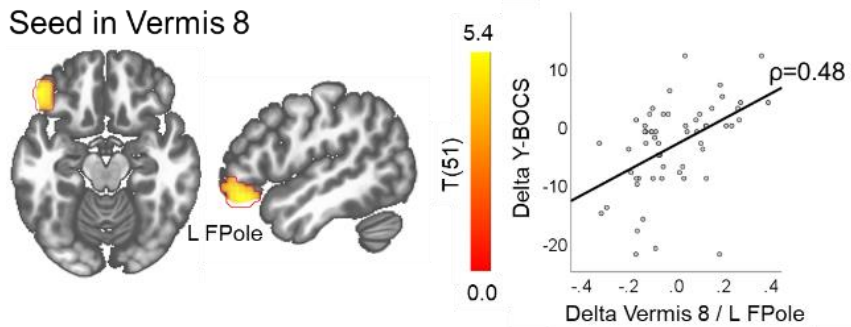
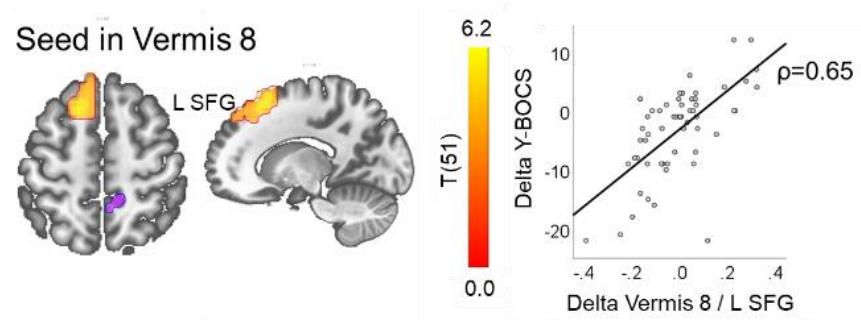


TS : Visit 1 > Visit 2



YGTSS/50 : 10 % decrease, $p < 0.001$

Reduction in cerebello-cortical connectivity and improvement in OCD and depression.



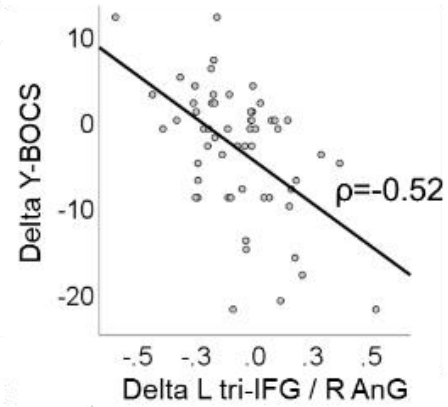
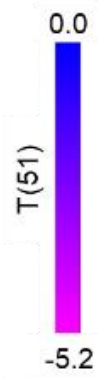
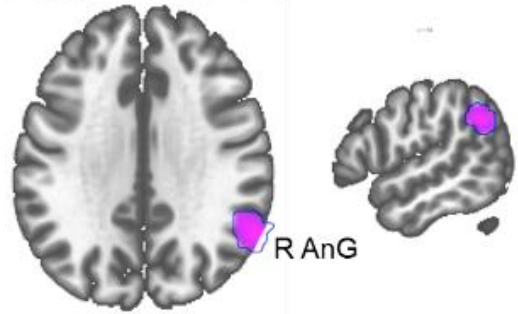
Sustained cortico-cortical connectivity associated with improvement in OCD and tic severity



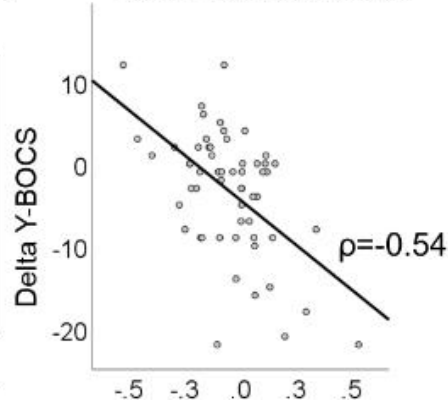
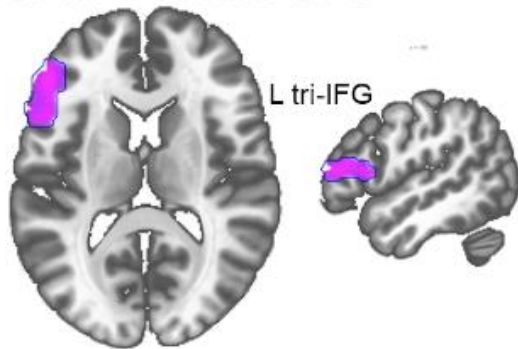
OCD

Tics

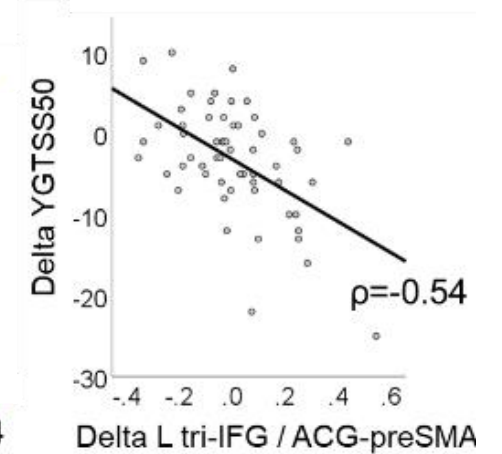
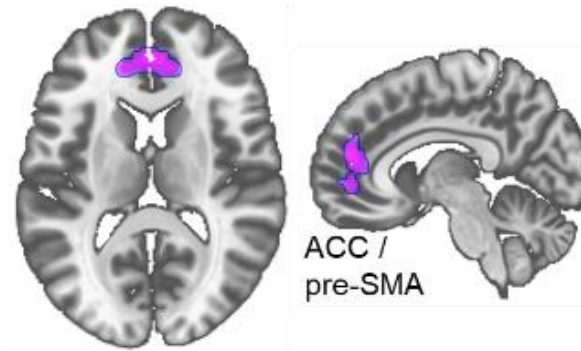
Seed in L tri-IFG



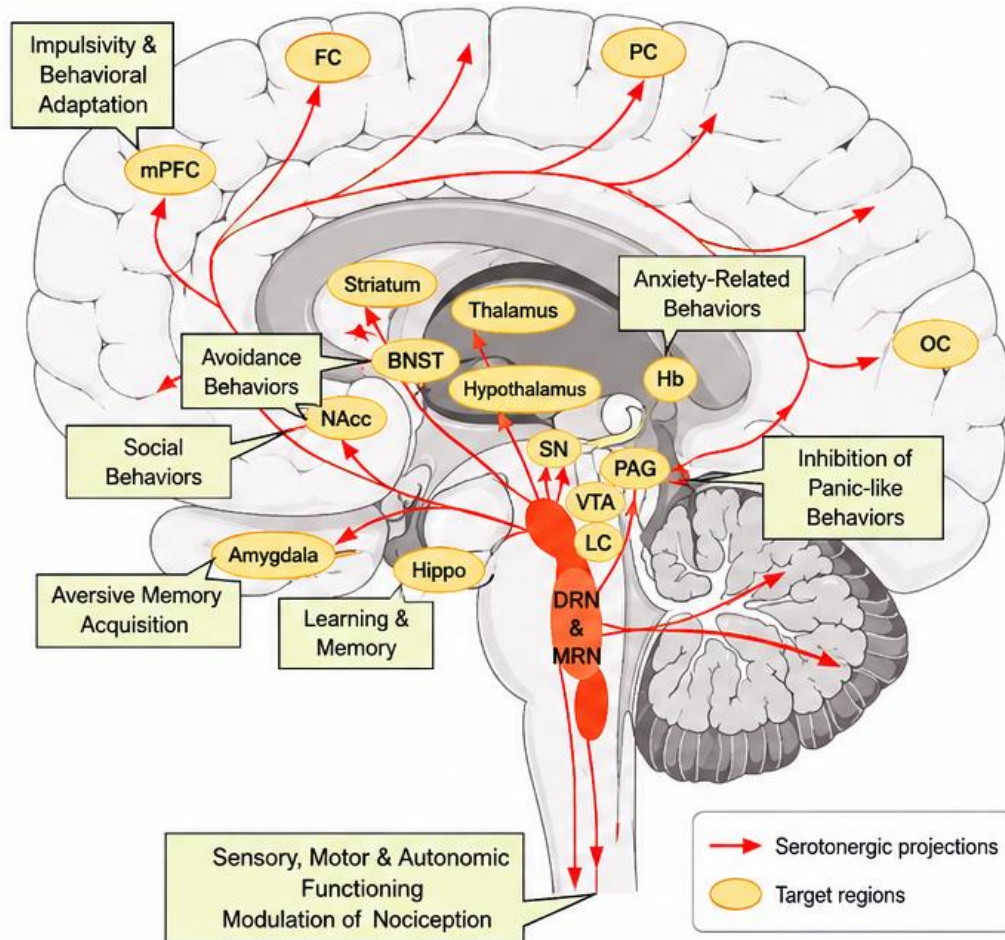
Seed in R med-SFG



Seed in L tri-IFG



SERT : serotonin signaling, dopaminergic modulation and neuroplasticity



WHY SERT?

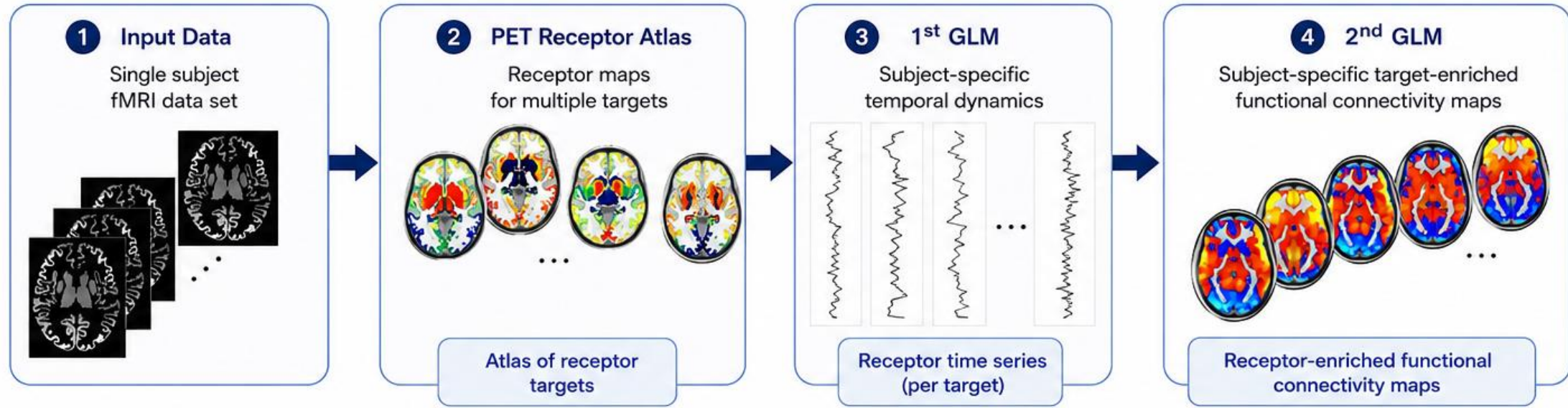
- Regulates serotonin availability (Murphy et al 2008)
- Modulates neurodevelopment and plasticity (Gaspar et al 2003)
- Altered serotonergic markers in adults with TS (Wong et al 2008; Hildonen et al 2021; Muller-Vahl et al 2019)

WHY ADOLESCENCE?

- Peak period of symptom evolution in TS (Bloch & Leckman, 2009)
- Major period of brain reorganization and plasticity (Casey et al 2008; Giedd 2004)

Analytical framework

Receptor-Enriched Analysis of functional Connectivity by Targets



Preprocessed resting-state fMRI data (e.g., motion correction, normalization, smoothing, filtering).



PET-derived receptor maps for multiple neurotransmitter systems (e.g., D2/D3, 5-HT1A, mGluR5, $\alpha 4\beta 2$ -nAChR, etc.).



GLM extracts the average BOLD time series from each receptor map to obtain subject-specific temporal dynamics.



GLM estimates functional connectivity between the target region and all other brain voxels, yielding receptor-enriched connectivity maps.

METHODS SUMMARY

- Receptor maps from post-mortem PET atlases
- Resting-state fMRI data (preprocessed)
- 1st GLM: extraction of receptor-specific time series
- 2nd GLM: voxel-wise functional connectivity for each receptor target
- Outputs: receptor-enriched functional connectivity maps

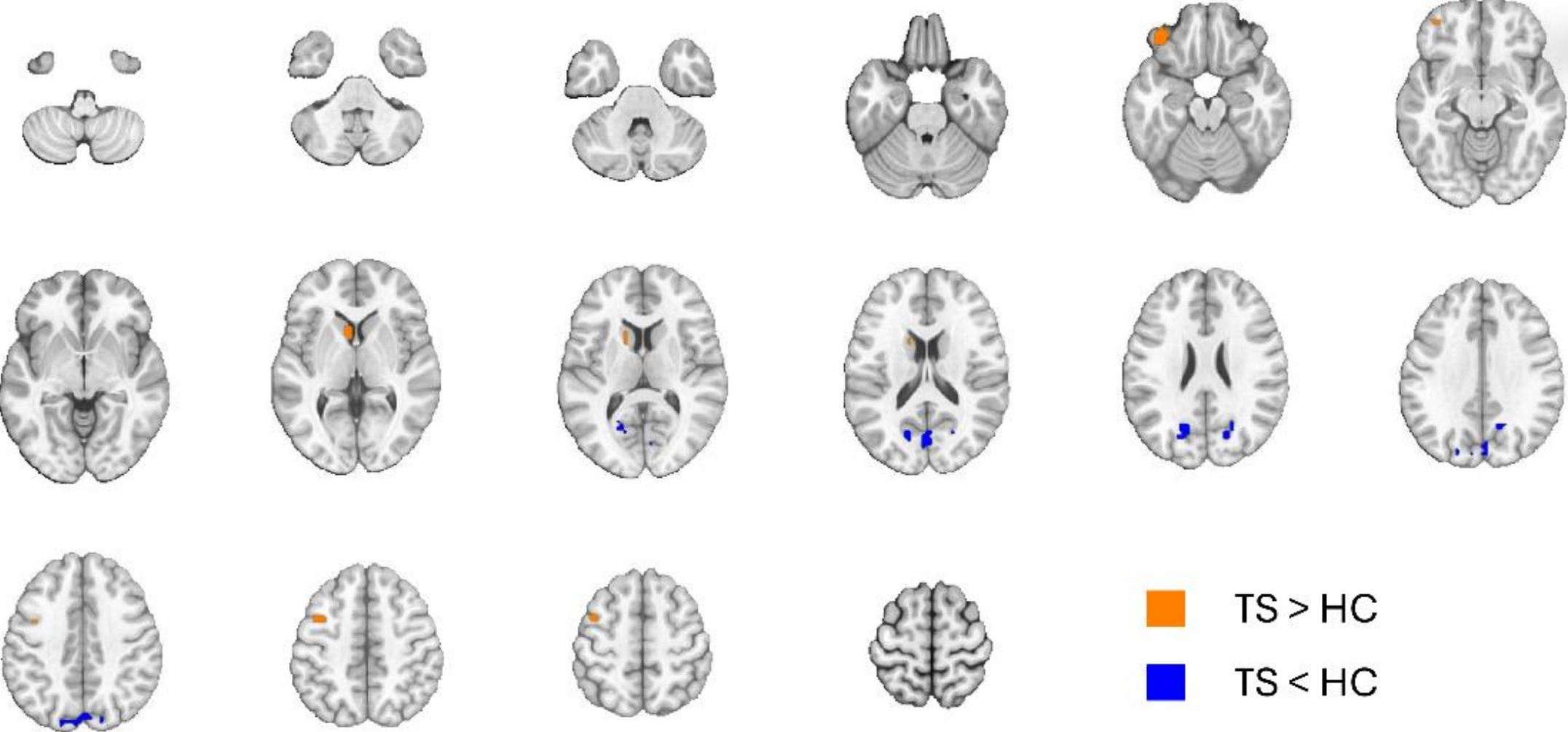
OUTPUT



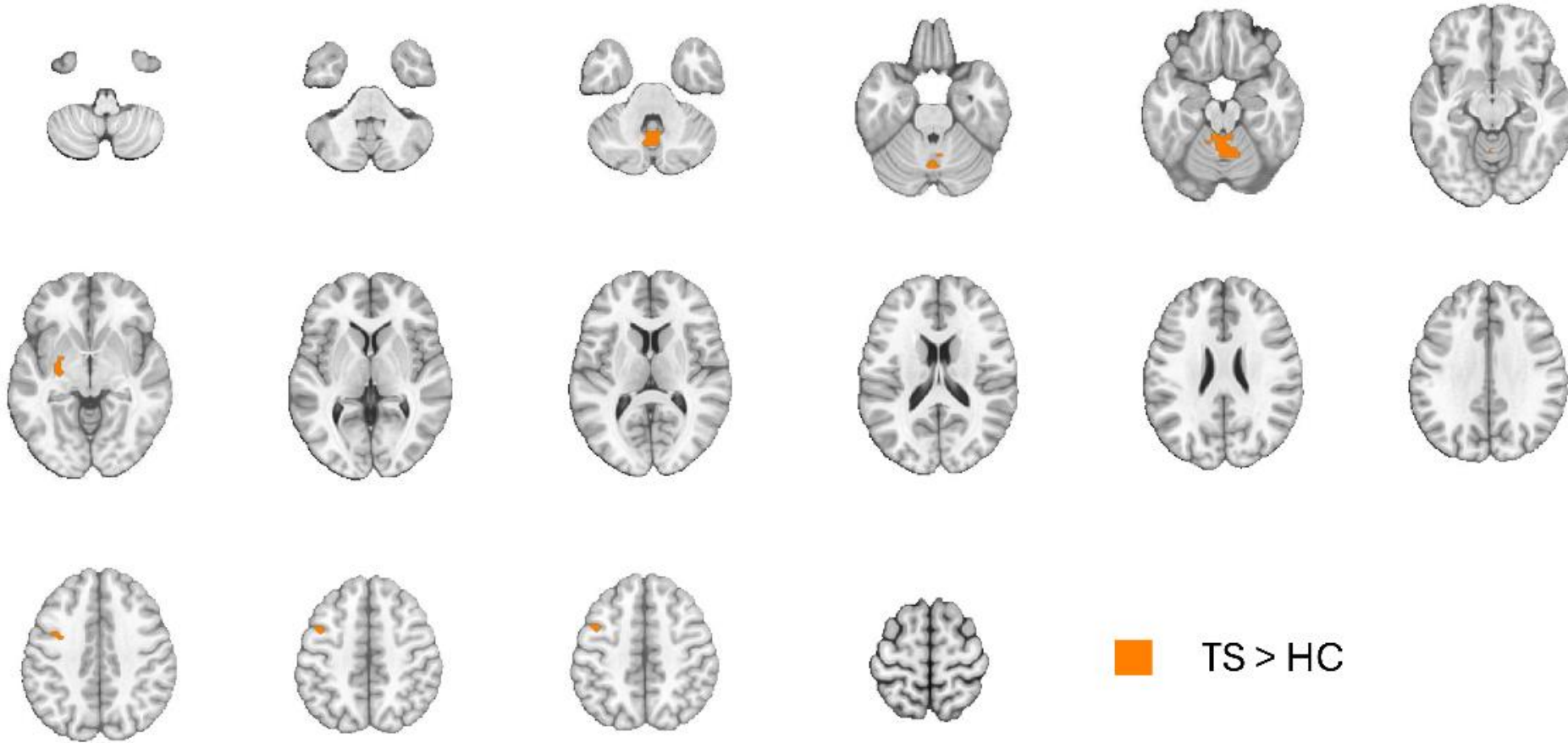
Receptor-enriched Functional Connectivity Maps

- ✓ Target-specific connectivity profiles
- ✓ Subject-specific maps for each receptor system
- ✓ Input for group-level analyses and clinical associations

SERT-Weighted Connectivity: Group Differences at Baseline

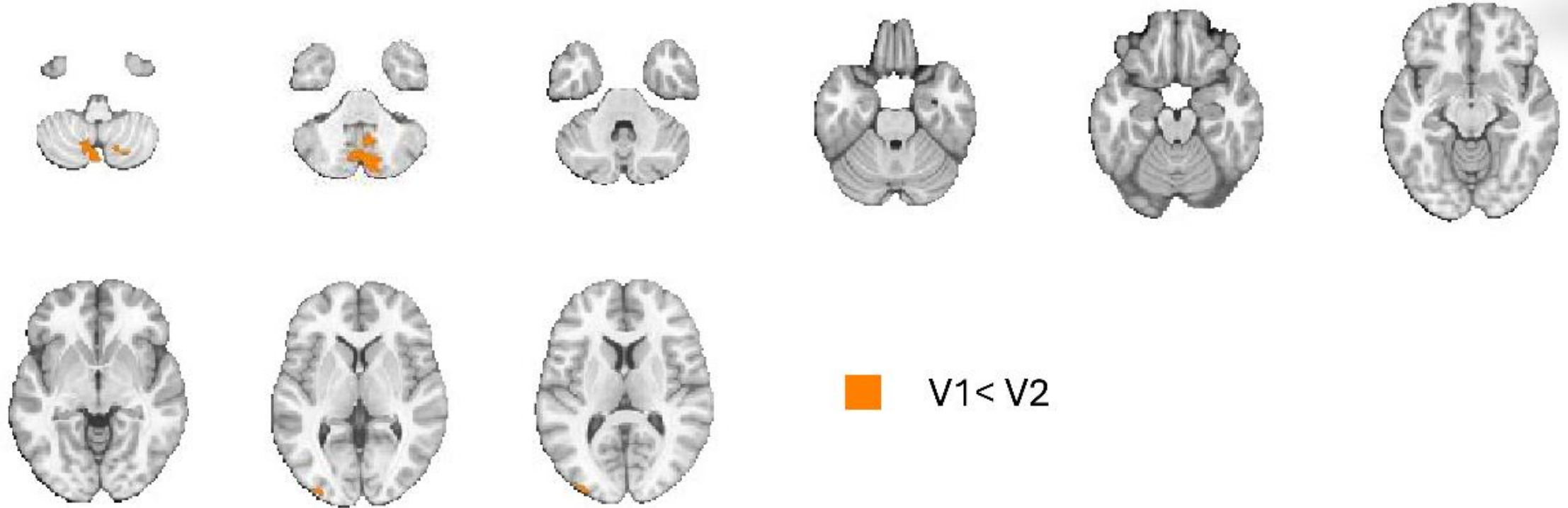


SERT-Weighted Connectivity: Group Differences at follow-up



Sensorimotor cerebellum (III L, IV–V L/R, VI R, VIII L, Vermis III, Vermis VI, Vermis VIII) : 64%
Cognitive cerebellum (Vermis VI, Vermis VII) : 18%
Limbic / affective cerebellum (Vermis VII, Vermis IX) : 6%

Longitudinal differences for TS for SERT-weighted REACT

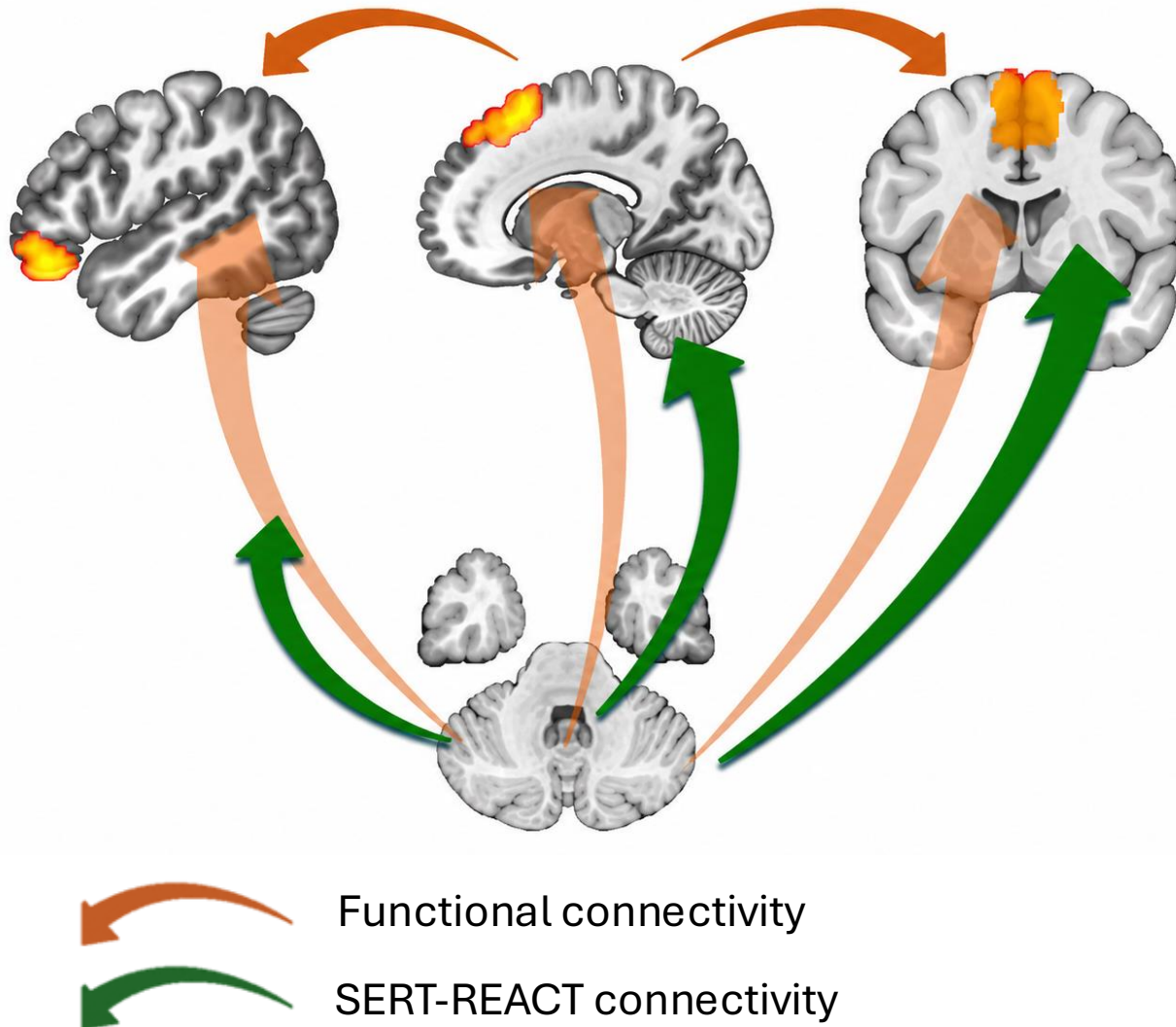


Sensorimotor processing (VIII L&R , Vermis VIII) : 45 %

Higher-order cognitive control (VIIb L&R) : 17%

Default-mode and limbic-related processes (Vermis IX) : 2%

Take home message



- Connectivity patterns distinguishing TS from HC are predominantly localized within cerebellar networks in adolescents
- Developmental shift in connectivity patterns differentiating TS from HC: predominant cortico-cerebellar involvement in adolescents, compared with predominant striatal involvement in adults
- Longitudinal changes are dominated by increased SERT-weighted connectivity within mostly sensorimotor cerebellar networks in adolescents
- Favorable clinical evolution is associated with reduced cerebellar–frontal and increased cortico-cortical connectivity in adolescents

CADET cohort



KEY SYMPTOM DIMENSIONS ASSESSED



Tics



Obsessive-Compulsive Symptoms



Attention-Deficit / Hyperactivity Disorder



Impulsivity



Depression



- Resting-state fMRI (rs-fMRI)
- Diffusion-weighted imaging (DWI)
- Magnetization transfer (MT)

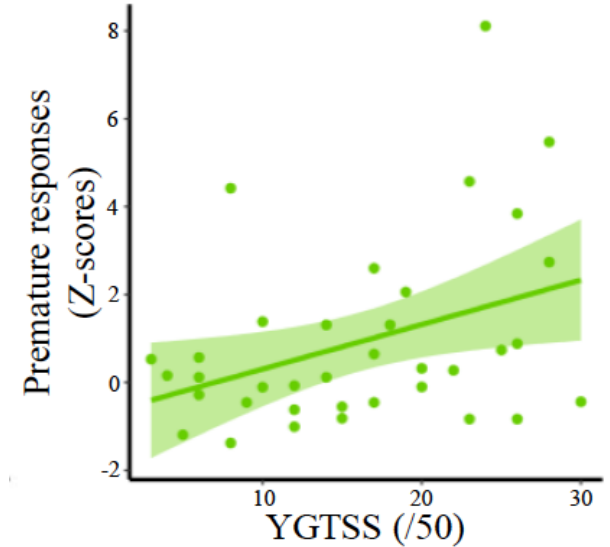
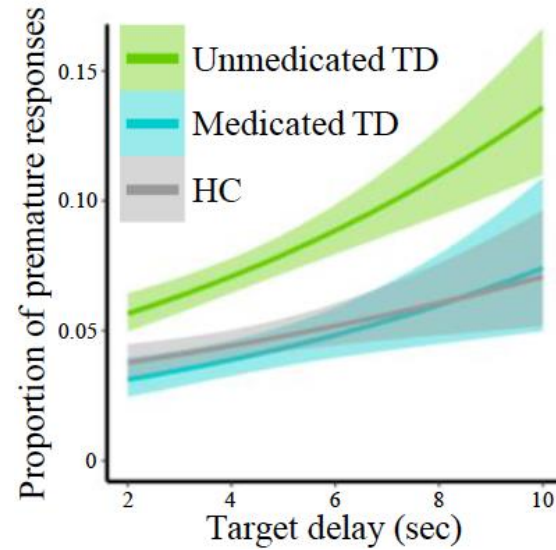
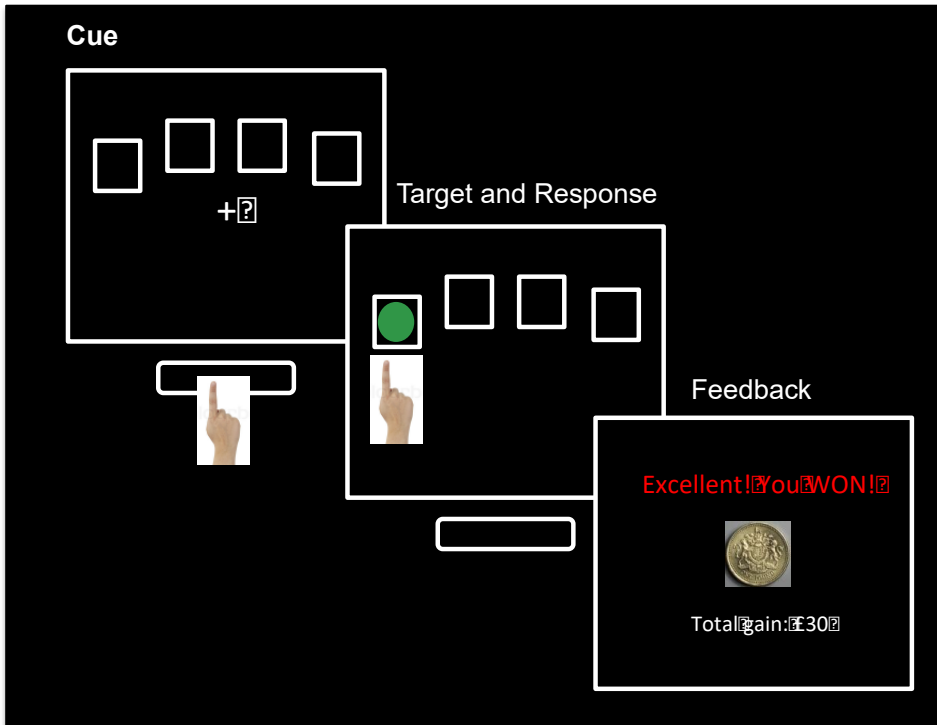


- Motor potential
- Motor resting threshold
- Short-interval intracortical inhibition (SICI)



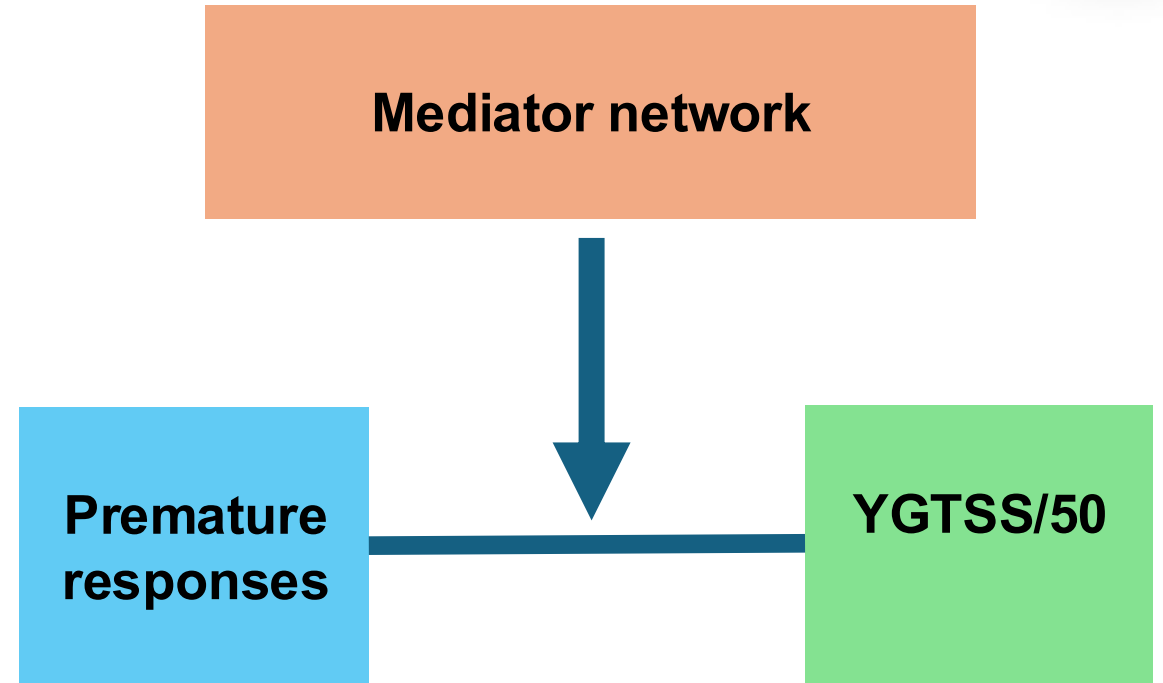
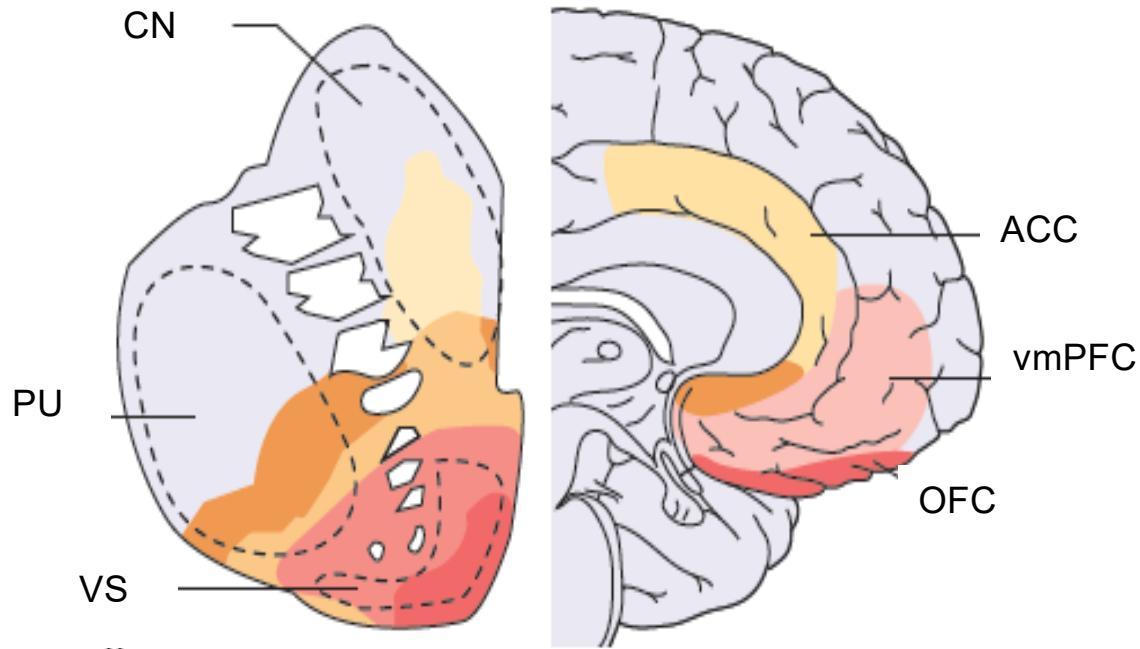
- Motor impulsivity
- Habit formation
- Agency
- Reward sensitivity

Waiting Impulsivity in TS: Background and Rationale



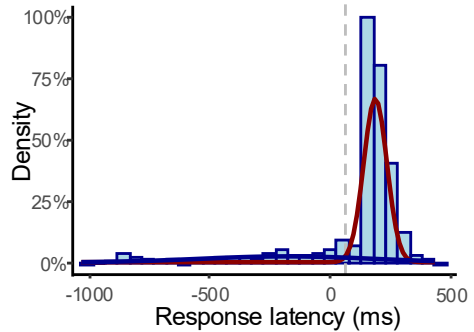
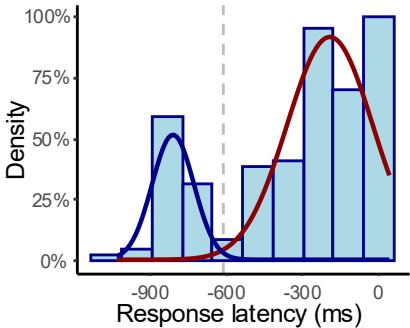
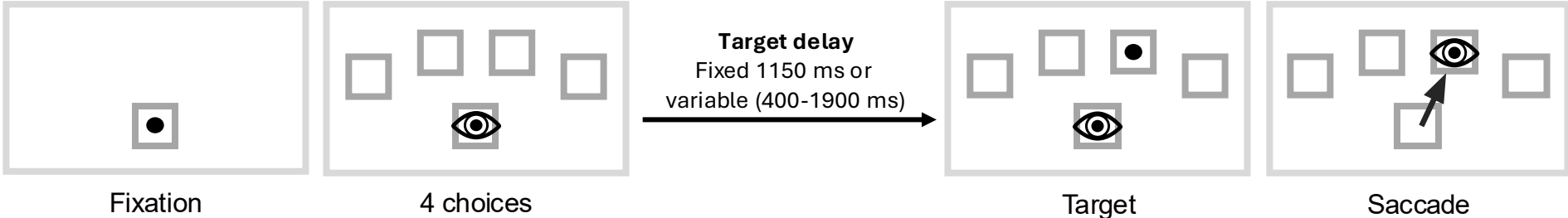
Waiting impulsivity: type of motor impulsivity – action temporality

Waiting Impulsivity in TS: Background and Rationale



Waiting impulsivity: type of motor impulsivity – action temporality

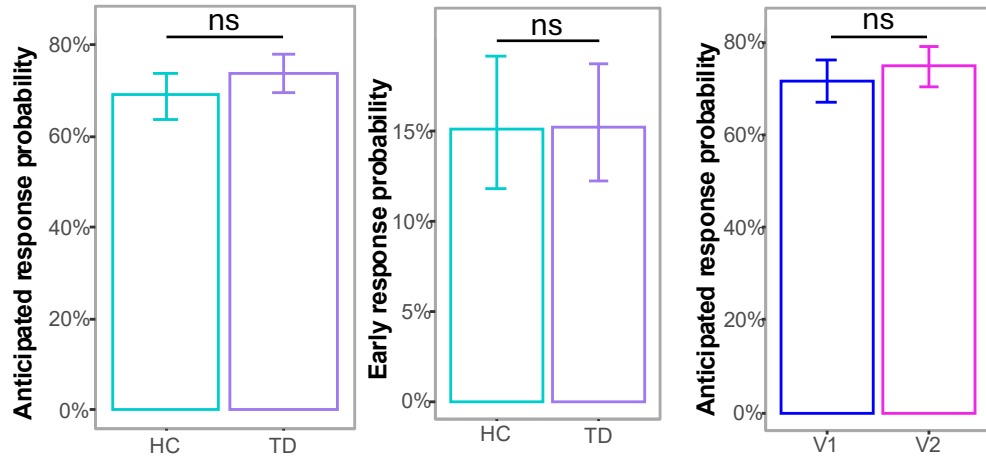
Waiting impulsivity task



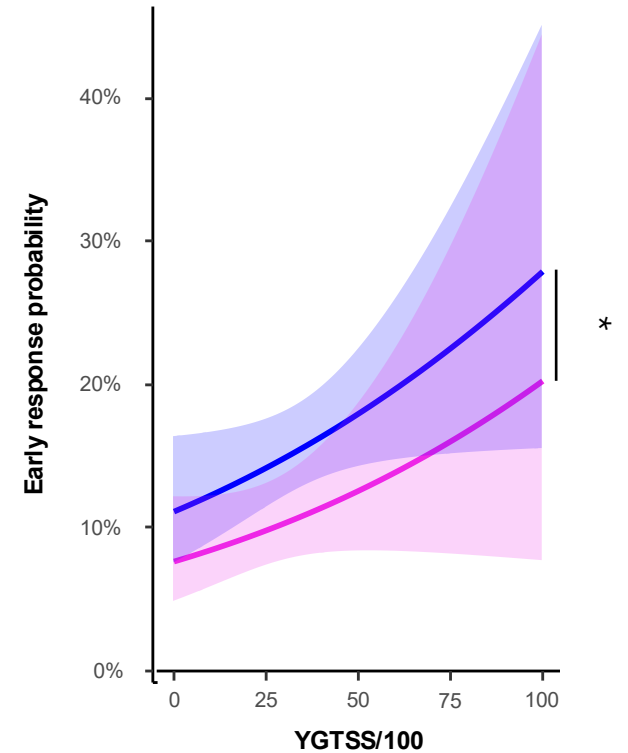
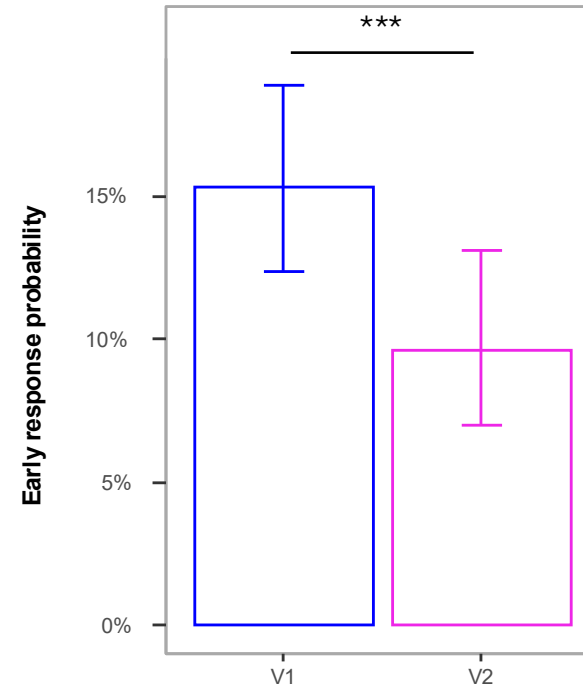
Waiting impulsivity task: behavioural results



Group comparisons



TS visits comparisons

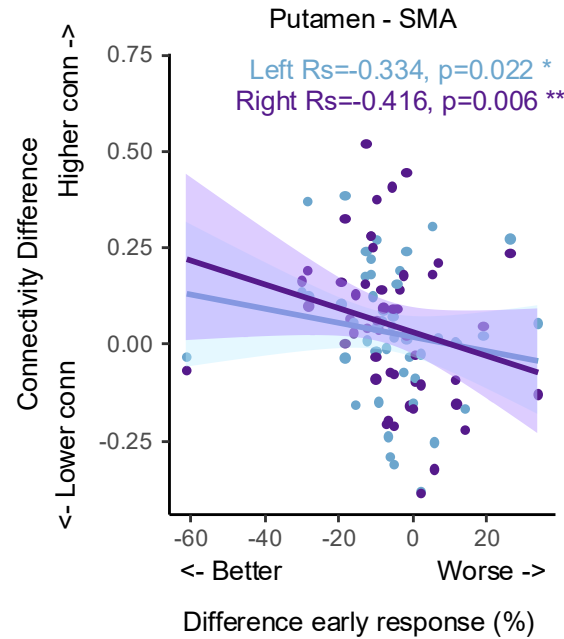
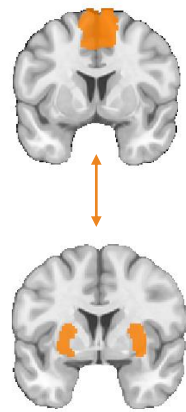
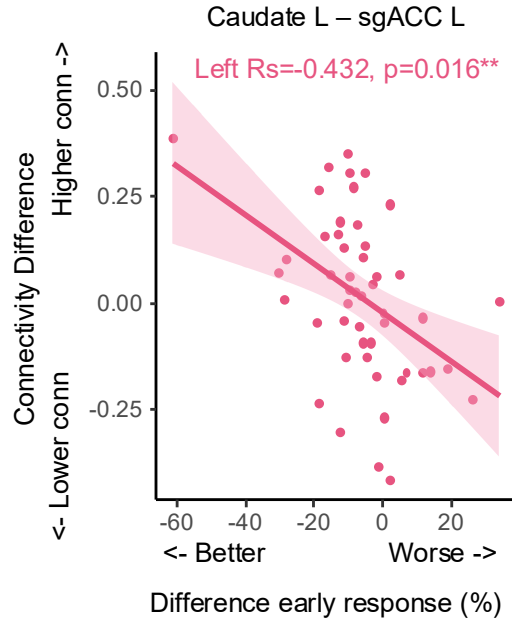
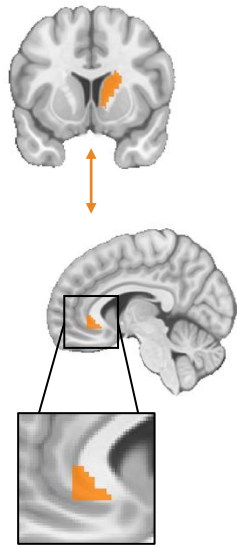


- Behavioral performance comparable to healthy controls
- Significant reduction in premature responses between the two visits
- Premature responses were more frequent in patients with more severe tics

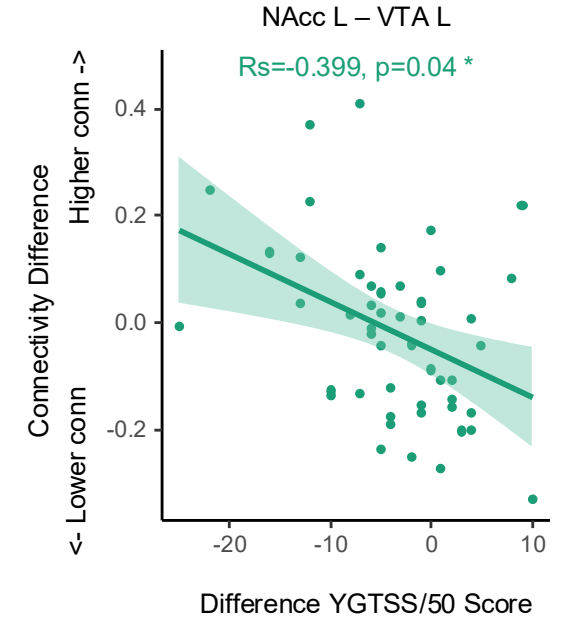
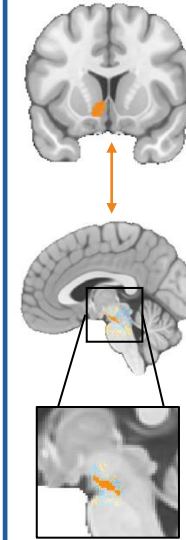
Neuronal networks associated with waiting impulsivity and tic severity changes



Premature responses



Tic severity



Receptor-Enriched Analysis of functional Connectivity by Targets (REACT) : DAT and 5-HT1B receptors



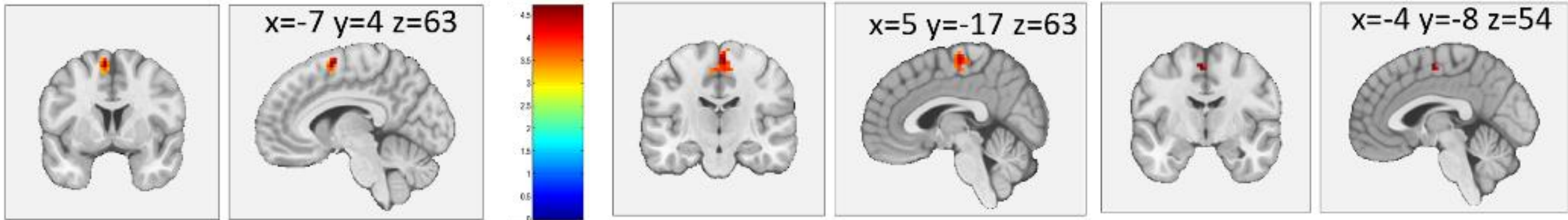
DAT Striatum-SMA :

5-HT1B N Raphe-SMA :

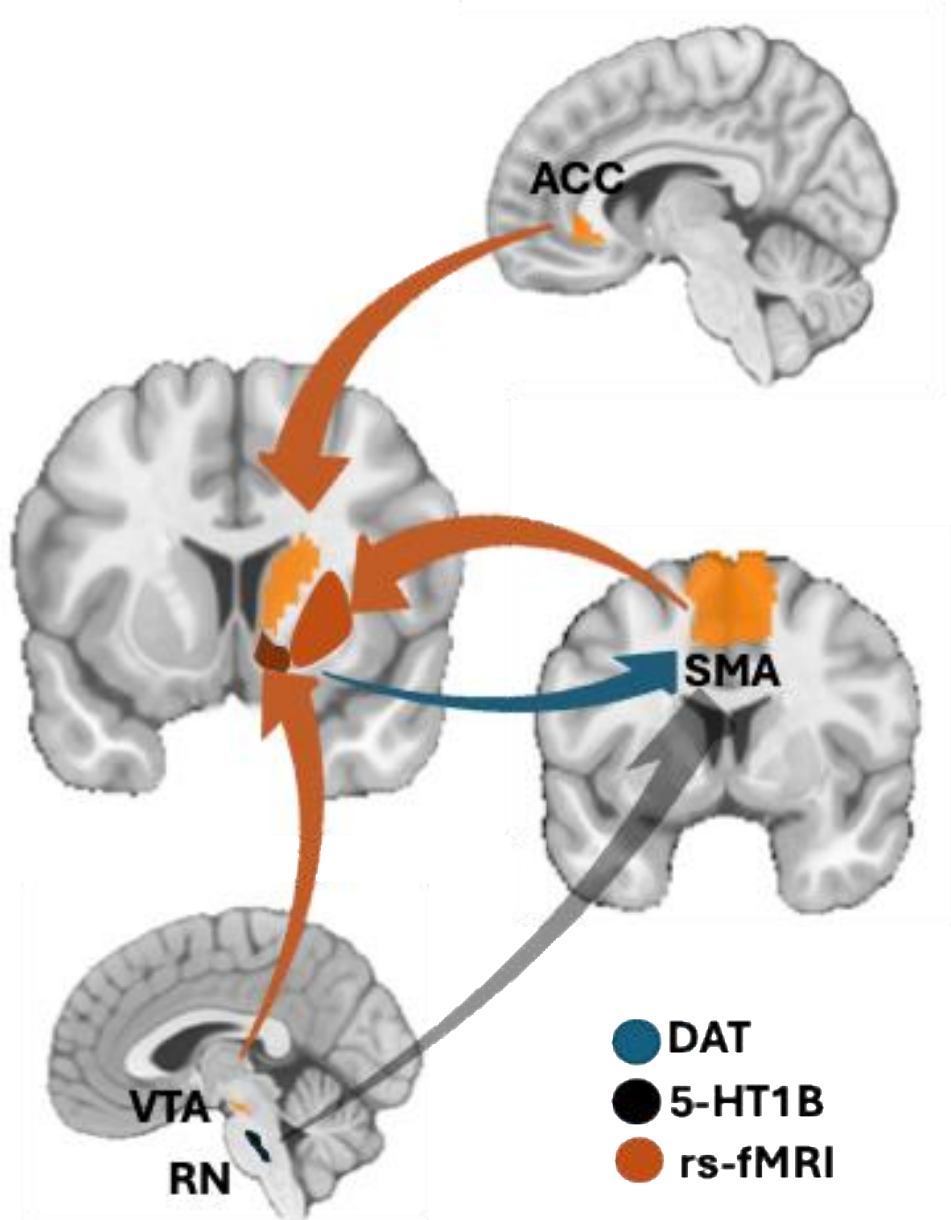
TS V1 > Controls , V1 = V2

TS V1 > Controls

TS V1 > V2



Take home message



- Waiting impulsivity tracks tic severity
- Tics and waiting impulsivity improve longitudinally
- Improvement associated with \uparrow striatal–SMA/ACC/VTA connectivity
- In TS: \uparrow DAT (NAcc–SMA) and 5-HT1B (raphe–SMA) connectivity
- Follow-up in TS: \downarrow 5-HT1B connectivity; DAT stable



- **TS is associated with alterations in distributed cortico-striatal and cortico-cerebellar networks**
- **These networks show age-dependent patterns of involvement**
- **Longitudinal changes in network connectivity accompany clinical improvement**
- **Serotonergic-weighted imaging highlights distinct but complementary neural substrates of symptom evolution**

ICM – Sorbonne, Paris

Cyril Atkinson-Clement, PhD
Giuseppe Zito, PhD
Joanna Loayza, PhD
Charly Lecompte, PhD
Clément Tarrano, MD, PhD

Thérèse-Marie Sartoris, PhD
Emma Benech, MS

Pierre Pouget, PhD
Cecile Gallea, PhD
Martina Bracco, PhD

National Reference Tourette Center

Virginie Czernecki, PhD
Andreas Hartmann, MD
Julie Moulin
Tiphonie Priou



THANK YOU !



yulia.worbe@icm-institute.org