Neuroplasticity in Obsessive-Compulsive Disorder
from lifespan changes to better treatment outcome

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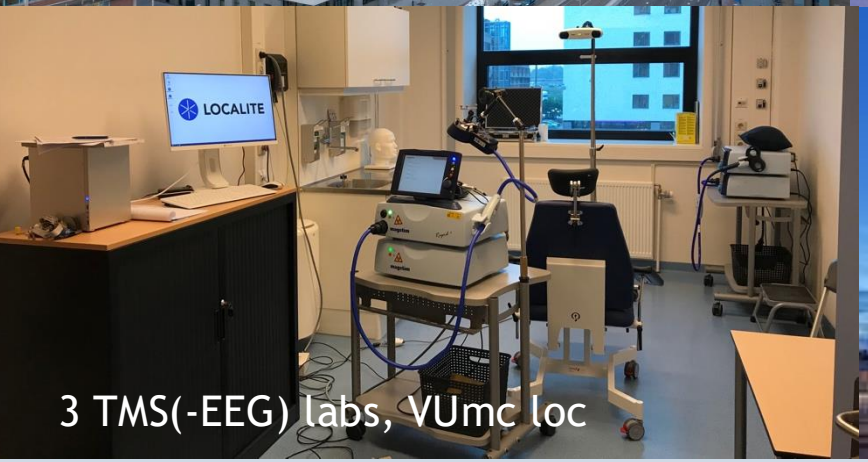
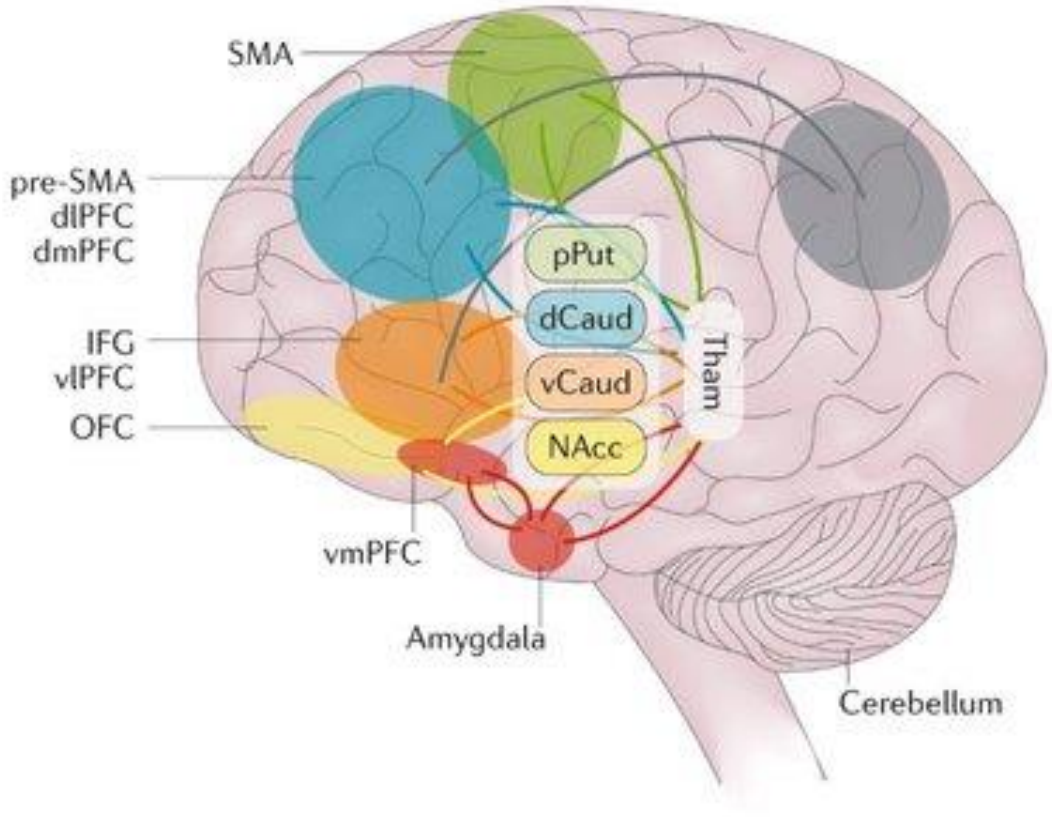
Amsterdam UMC



OCD - Tourette – Parkinson

& cortico-striato-thalamo-cortical (CSTC) circuits



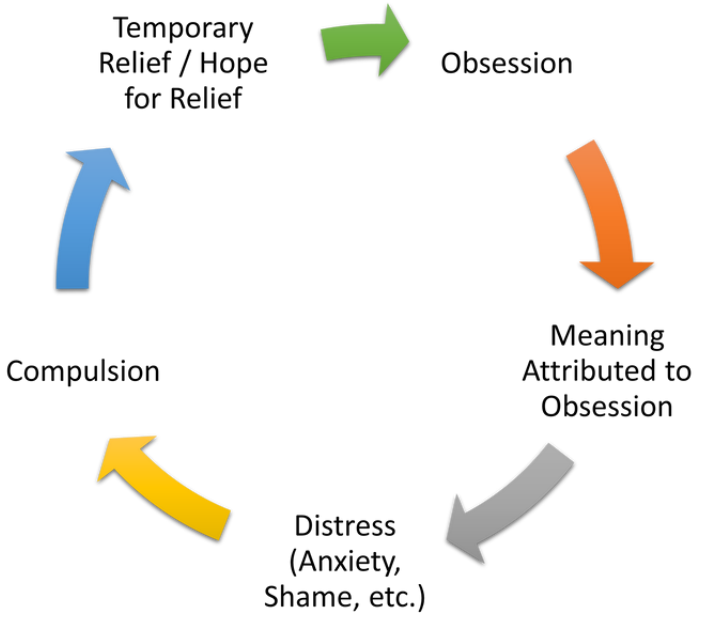
Processes:

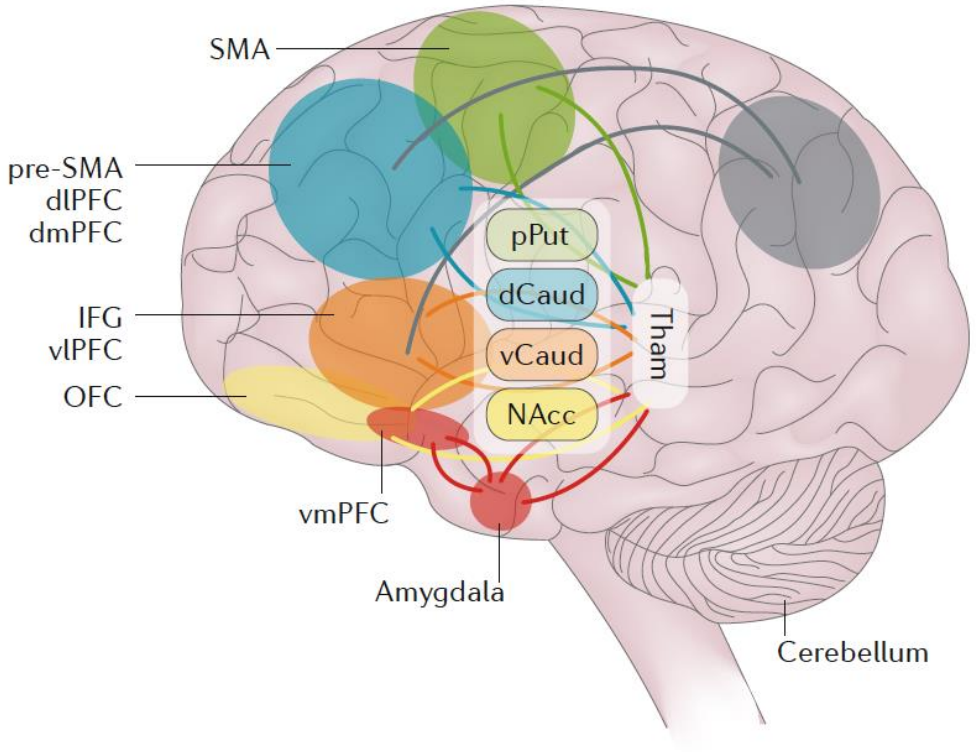
- Sensori-motor function
- Impulsive-compulsive behavior
- Emotion regulation
- Limbic interference on cognition and motor function

Themes:

- Neurodevelopment (Tourette/OCD) to neurodegeneration (Parkinson)
- Hyperdopaminergic (Tourette/OCD) to hypodopaminergic (Parkinson)
- Lifespan neuroplasticity (chronicity / CBT / training / neuromodulation)

Obsessive-Compulsive Disorder





- 'Sensorimotor' CSTC circuit
  - Stimulus-response-based habitual behavior
- 'Dorsal cognitive' CSTC circuit
  - Working memory, planning, emotion regulation
- Frontoparietal network
  - Coordination of cognitive control
- 'Ventral cognitive' CSTC circuit
  - Response inhibition
- 'Ventral motivational' CSTC circuit
  - Stimulus-outcome-based motivational behaviour
- 'Frontolimbic' circuit
  - Fear extinction

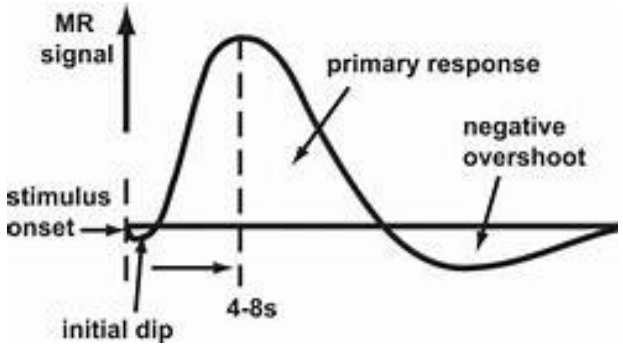
Stein et al. *Nature Reviews Disease Primers* (2019)

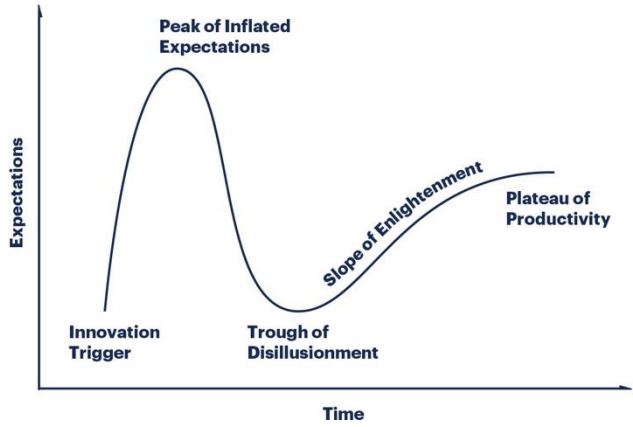
From small samples to big data

1. Lack of reproducibility

2. Slow translation to clinical practice

3. Increase sample sizes by worldwide collaboration
   - Mega-analyses on pooled multi-center data
   - Harmonization of methods worldwide
   - Pre-registrations & open science (e.g., GitHub)

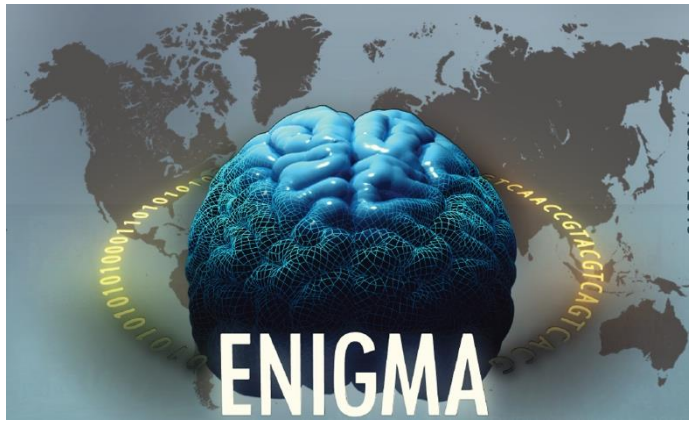




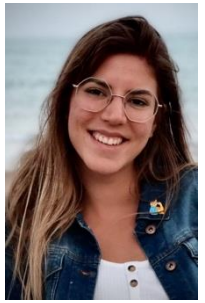
Paul Thompson
director ENIGMA
USC, USA

ENIGMA-OCD working group chairs:
Odile van den Heuvel, Amsterdam, NL
Dan Stein, Cape Town, South Africa (†)

New co-chairs:
Chris Vriend, Amsterdam, NL
Kathrin Koch, Germany



Premika
Boedhoe
(PhD 2015-2019)



Nadza
Dzinalija
(PhD 2021-2026)

Bruno
Moses
RA

ENIGMA-OCD consists of 50 samples
from 38 institutes in 15 countries on 5 continents

Sample sizes differ per project

Total sample of 6,880 (still increasing) with MRI data of:
3,482 OCD patients
- 2,814 adults (>18 yrs)
- 668 adolescents (12–17 yrs) / children (<12 yrs)

3,398 controls
- 3,398 adults
- 654 adolescents / children

[An overview of the first 5 years of the ENIGMA obsessive-compulsive disorder working group: The power of worldwide collaboration.](#)
van den Heuvel OA, Boedhoe PSW, …., Thompson PM, Stein DJ; ENIGMA-OCD working group. **Hum Brain Mapp. 2020**

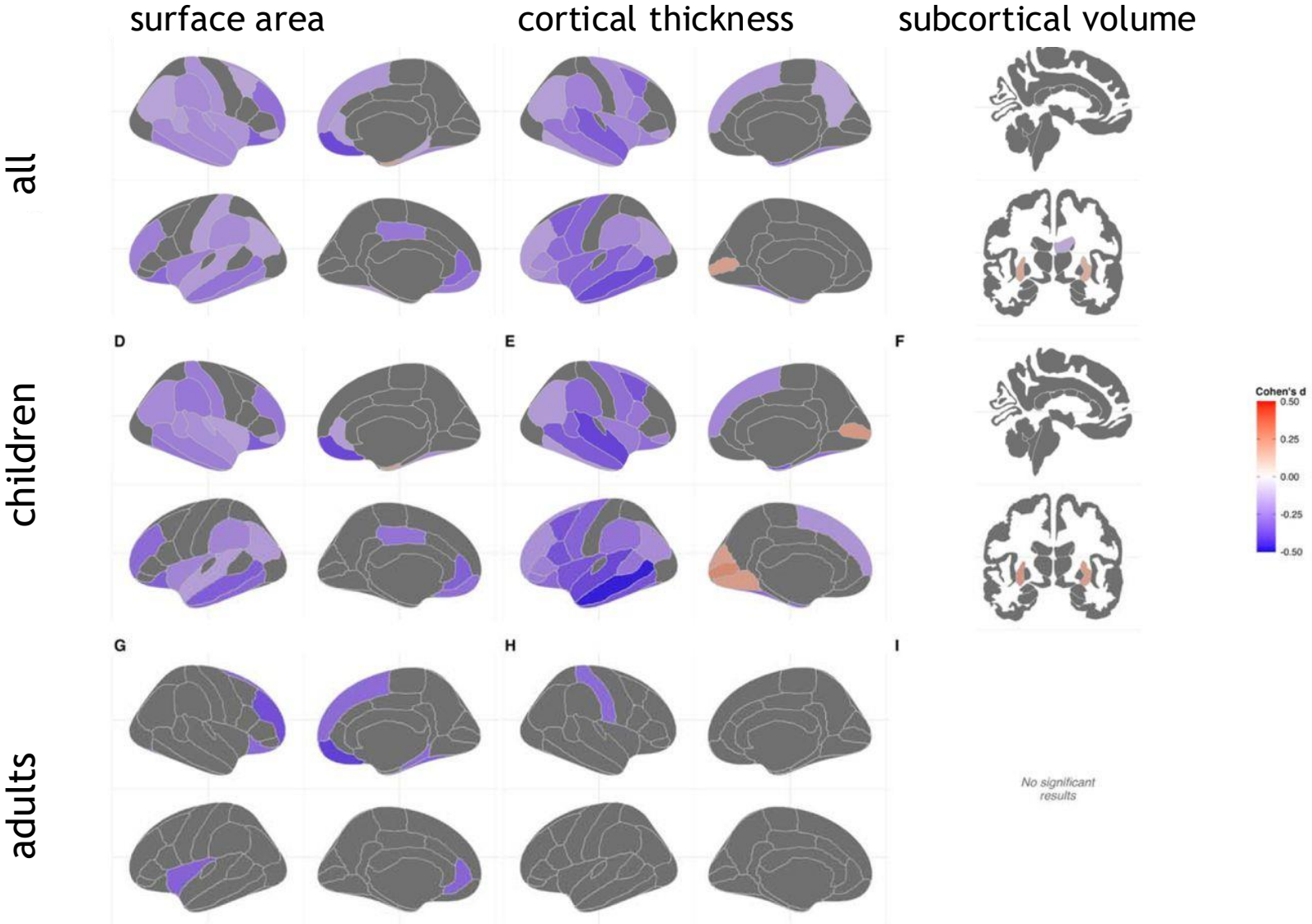
ENIGMA-Tourette

P. Paschou
chair ENIGMA-Tourette

Paschou et al. 2022 Frontiers Psychiatry

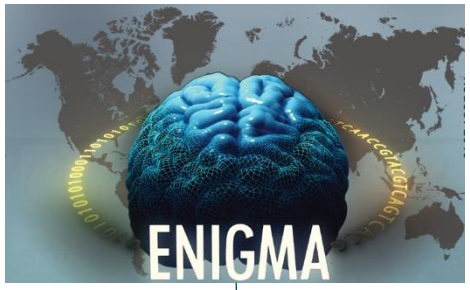
>> Jin et al. 2026 (MedRXiv)
1st paper on brain structure & genetics

745 TS/TD versus 903 controls



Jin et al. *MedRxiv* (2026)

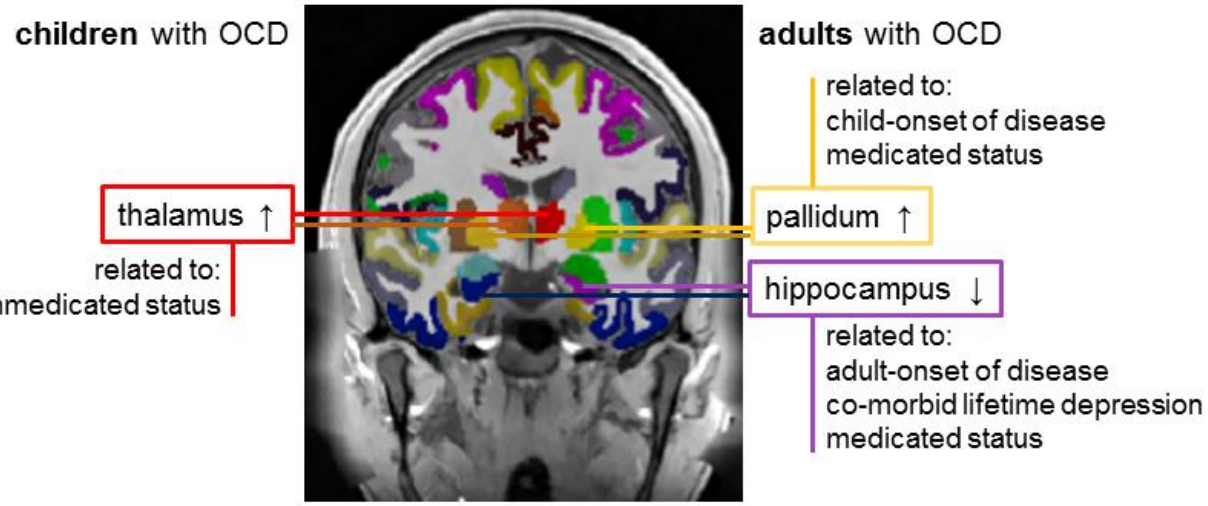
ENIGMA-OCD - Structure



subcortical volume

Effects depend on:

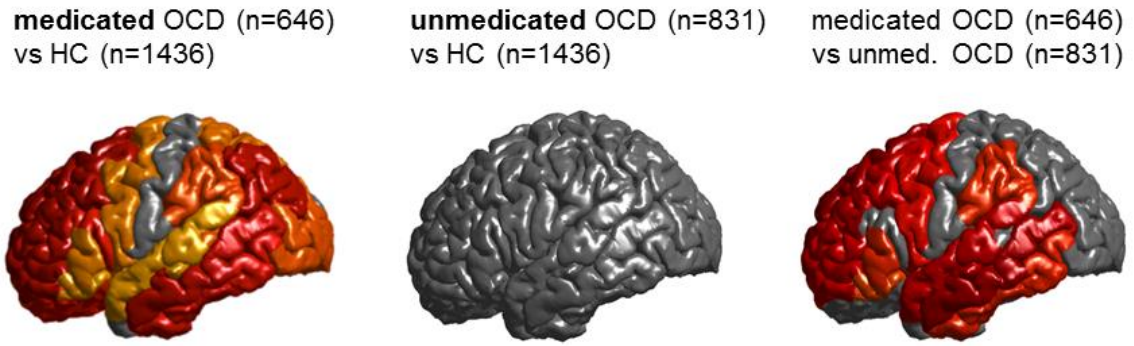
- developmental stage
- age of onset
- medication status
- comorbidity



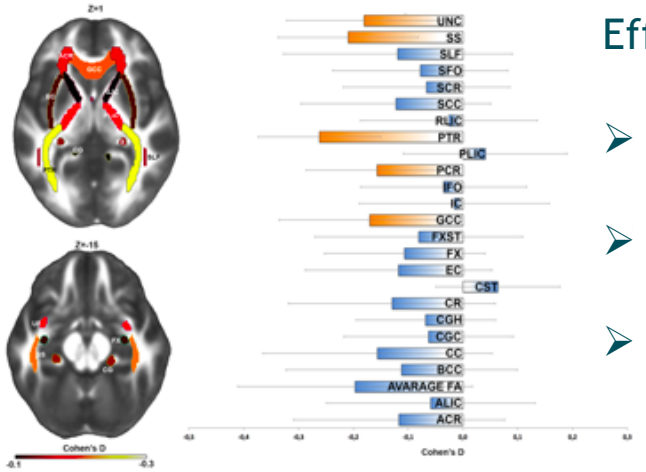
Boedhoe et al. 2017 Am J Psychiatry

cortical thickness & surface area

- Medication effects!



white matter integrity



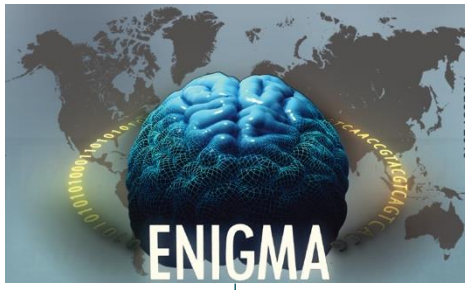
Effects depend on:

- duration of illness (longer is worse)
- age of onset (earlier is worse)
- % of cohort medicated (more=worse)

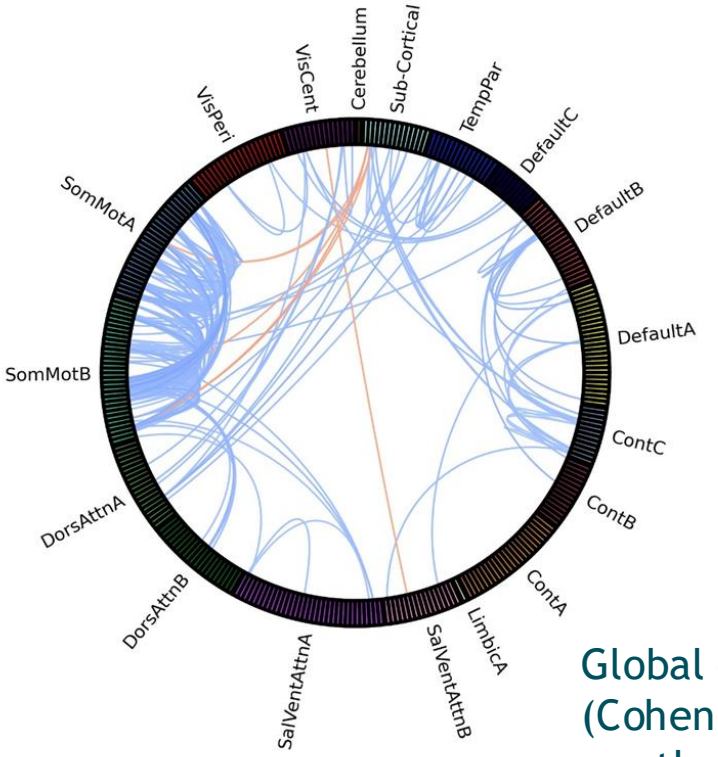
Boedhoe et al. 2018 Am J Psychiatry

Piras et al. 2021 Translational Psychiatry

ENIGMA-OCD - Function



resting state fMRI



Willem Bruin

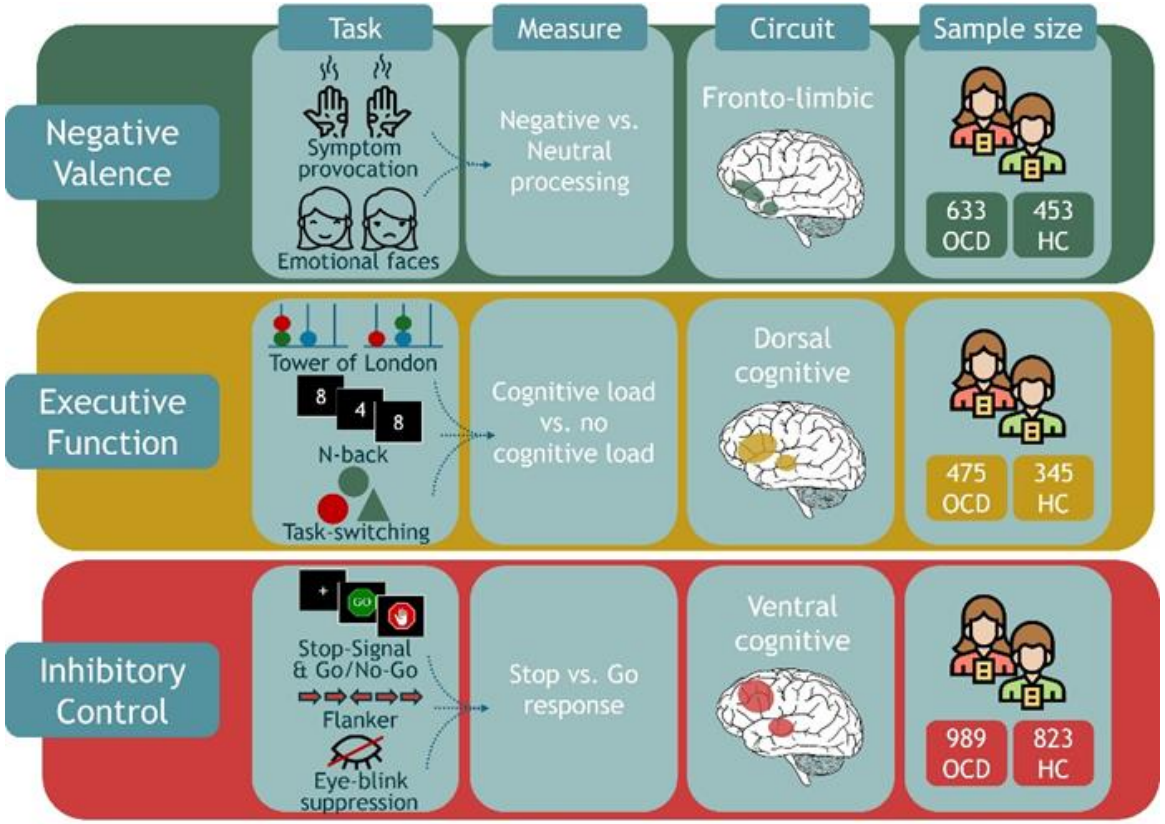
Global cortical hypo-connectivity (Cohen's *d*: -0.27-0.22), mostly located within the sensorimotor network

Few hyper-connections, mainly with the thalamus

Bruin et al. 2023 Molecular Psychiatry

task-based fMRI

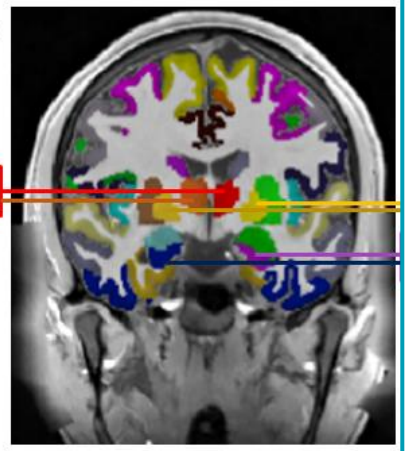
Nadza Dzinalija



Dzinalija et al. 2025 Biol Psych – emotional processing
Dzinalija et al. 2026 Biol Psych CNNI – executive control
Dzinalija et al. Biol Psychiatry (under review) – inhibitory control

Thalamus

an early marker of OCD



Cees Weeland

MRI @7.5 yr
n≈1070

MRI @10 yr
n≈4050

MRI @14 yr
n≈4500

probable OCD,n≈164
control children, n≈164

behavior: e.g., OCD symptoms (SOCS score)

pre-, peri-, neonatal

7.5 yrs

10 yrs

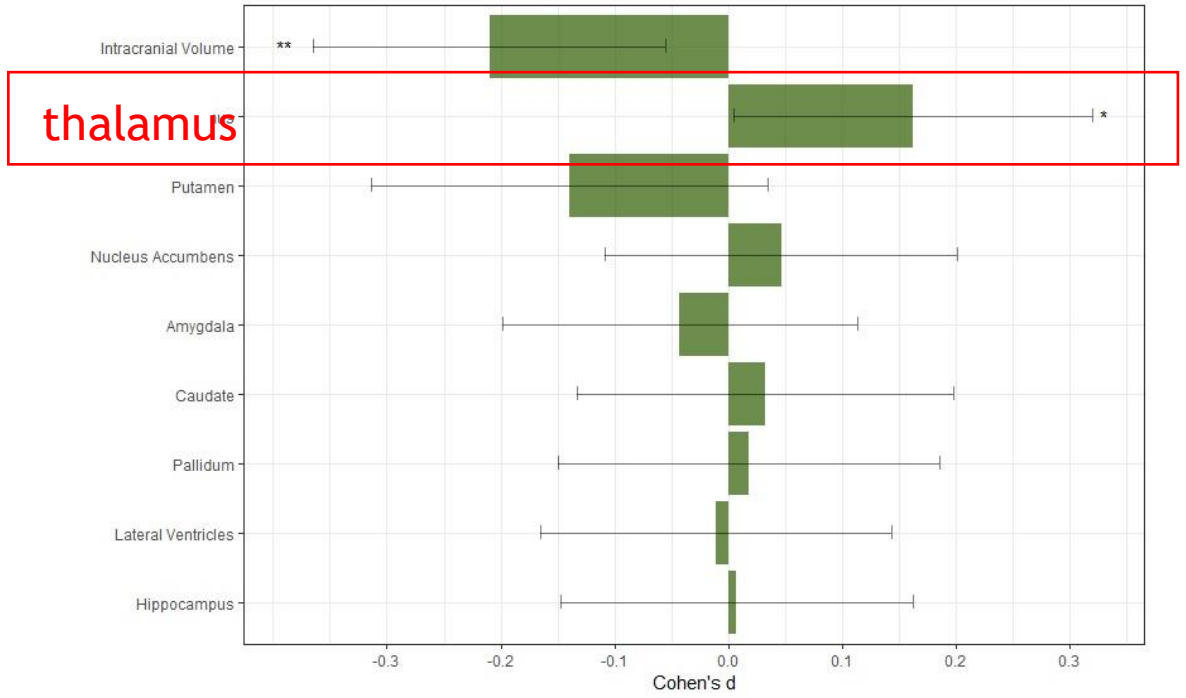
14 yrs

Weeland et al. 2021 JAACAP

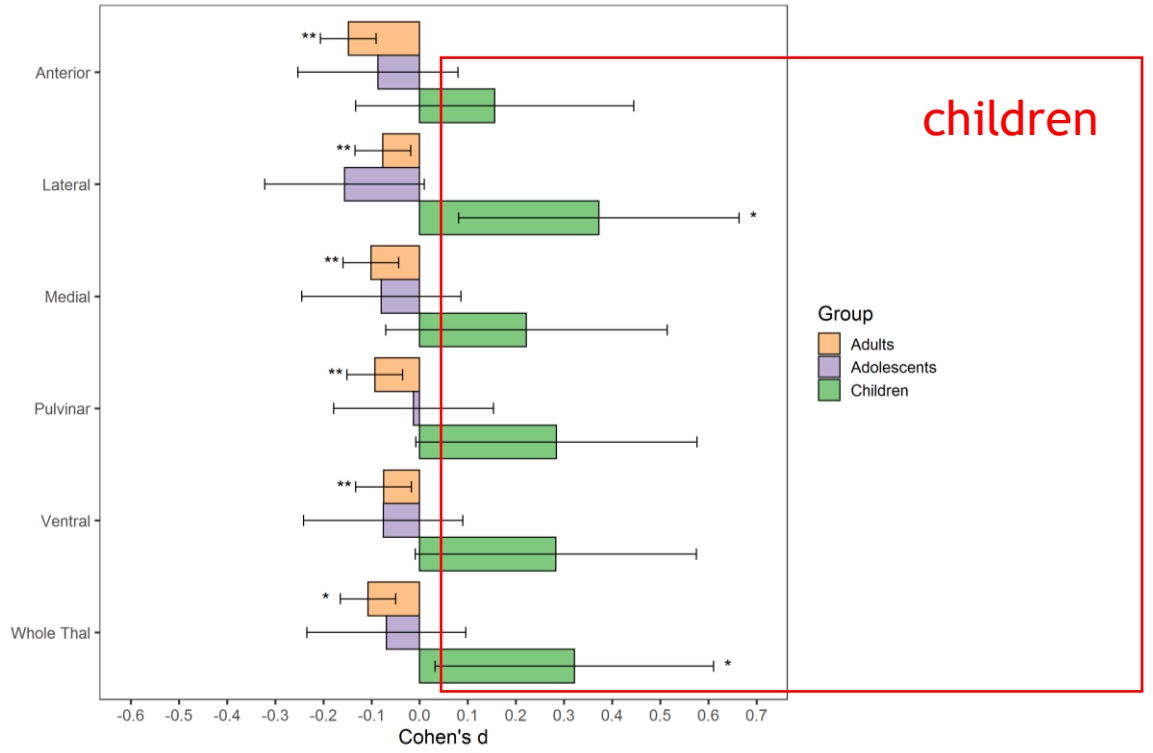
Thalamus

an early marker of OCD

>> bigger thalamus in children aged 10-12 yr
with SOCS-score above cut-off



Bigger thalamus:
>> neurodevelopmental stage
(only kids, not adolesc / adults)
>> medication status
(only in untreated children)



Weeland et al. 2021 JAACAP

Weeland et al. 2022 JAACAP

Thalamus

an early marker of OCD


Willem Bruin

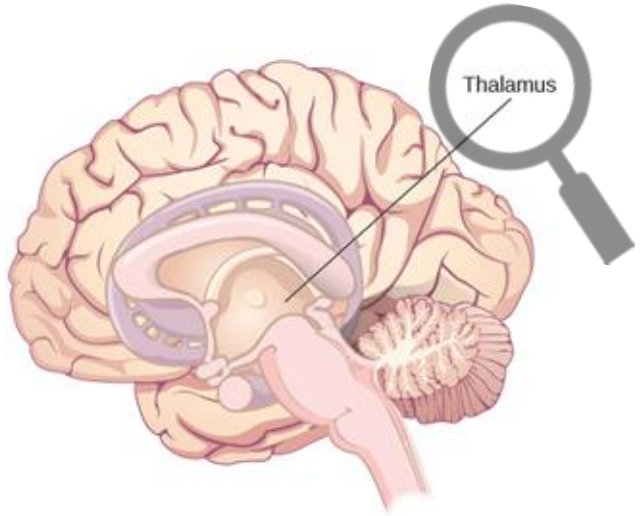

Carol Gaiser


Ryan Muetzel

Bigger thalamus at age 10-12 yr
>> flatter slope of cortical thinning from age 10 to 14
>> preservation of OCD symptoms from age 10 to 14

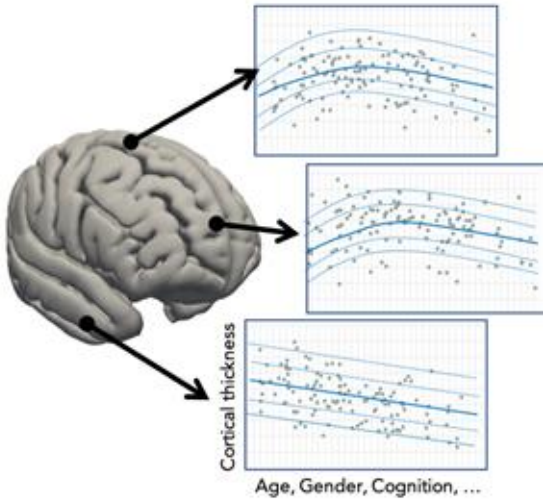
Hypothesis:
maturation of the thalamus drives cortical maturation

Normative modeling



Age,
Gender,
Cognition,
...

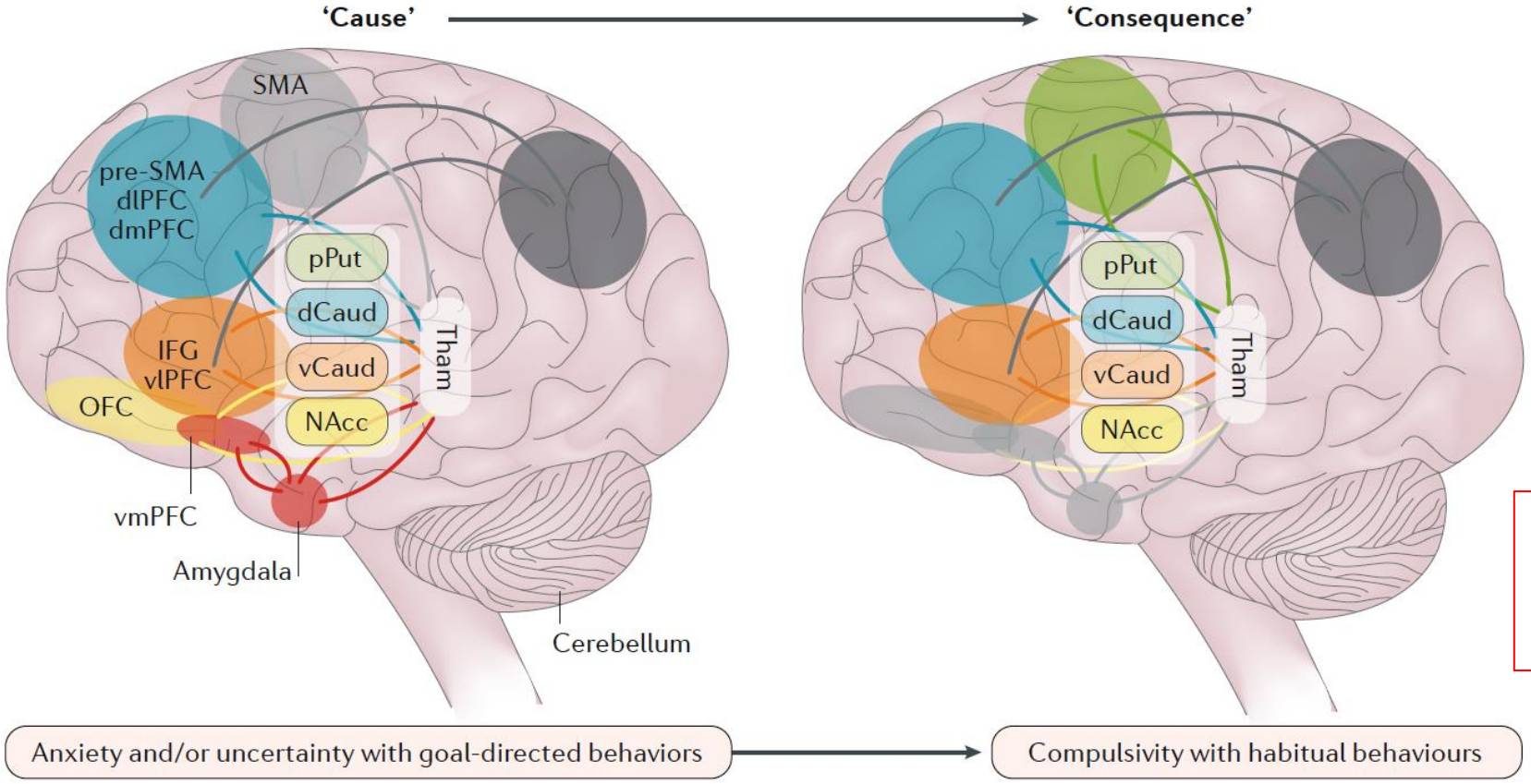
$y = f(x)$



Weeland et al. 2024 JAACAP Open

Lifespan view on OCD

Altered neurodevelopment contributes to the vulnerability to develop OCD (driven by altered maturation of the thalamus)



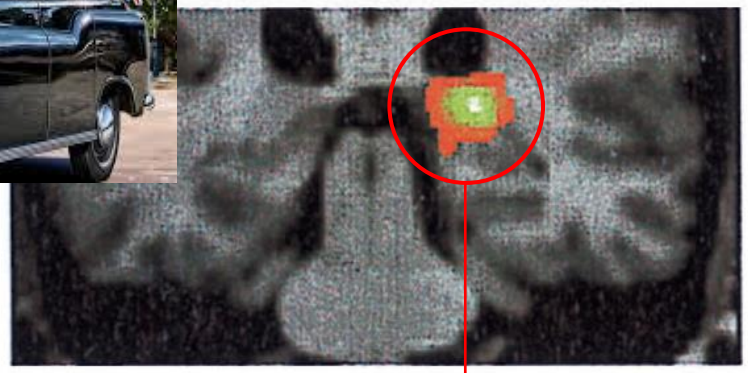
OCD (due to the endless repetitive behaviors), by the power of repetition, 'shapes' the brain

But with treatments we can 'reshape' the brain

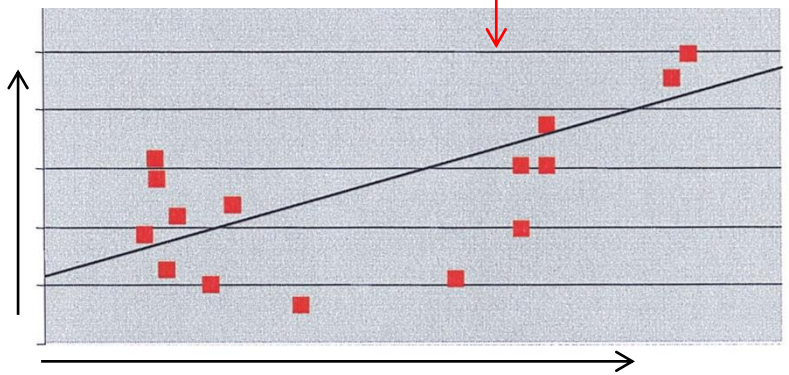
Stein et al. *Nature Reviews Disease Primers* (2019)

Brain plasticity

= the power of repetition

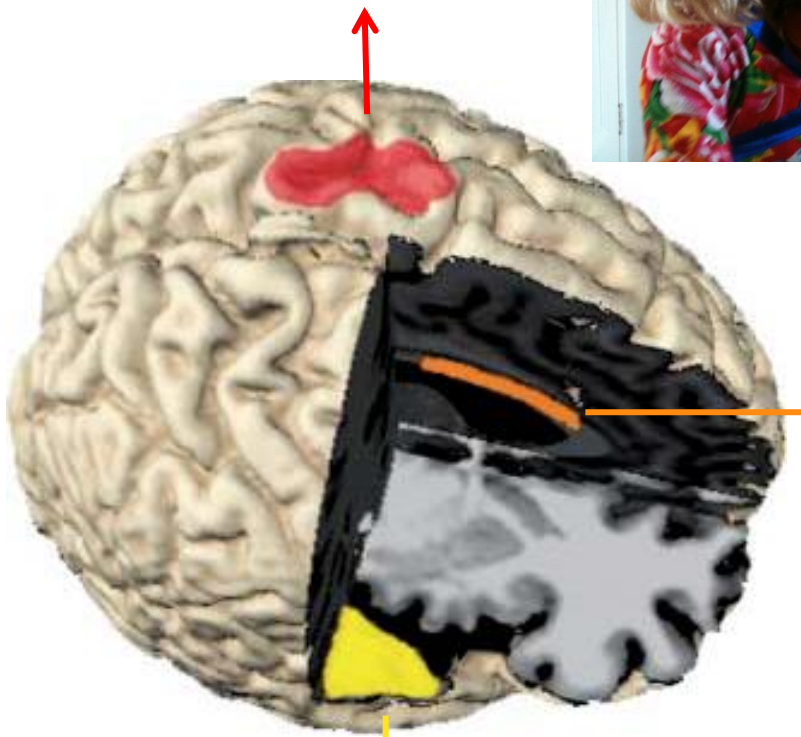


volume
posterior part
hippocampus



Maguire et al. 2000 PNAS

Finger speed
non-dominant hand



communication
between hemispheres

Sensitivity
to tone and timing

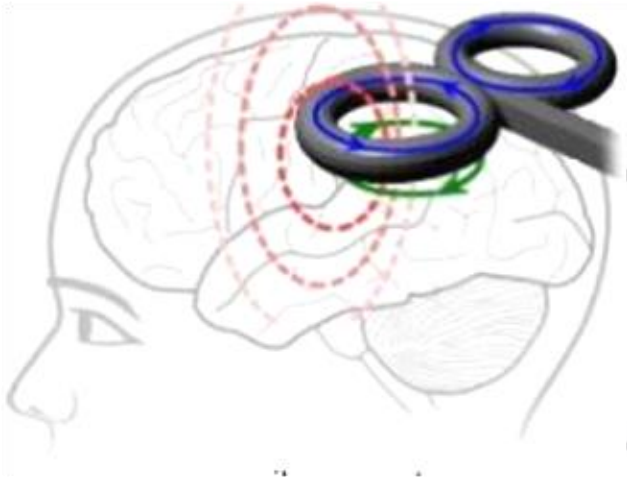
Münte et al. 2002 Nature Rev Neurosci

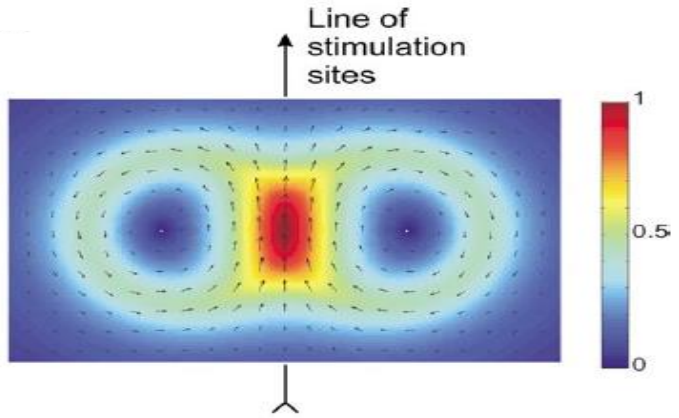
cognitive behavior therapy (ERP) > aims to change longlasting ingrained behavior

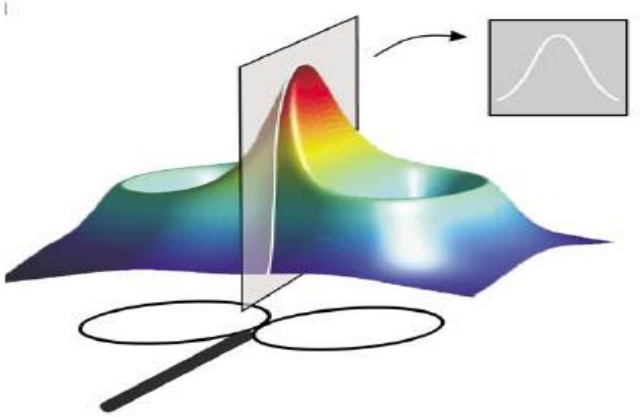
intensive training and repetition of new behavior is needed for longterm impact

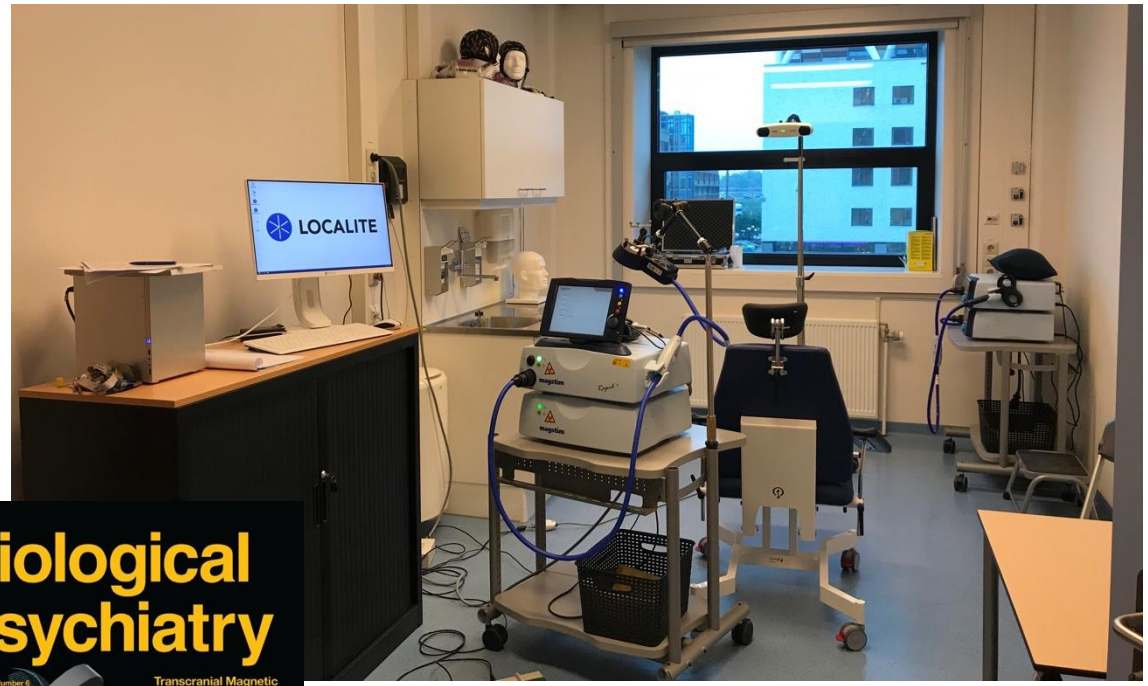
>> Brain plasticity

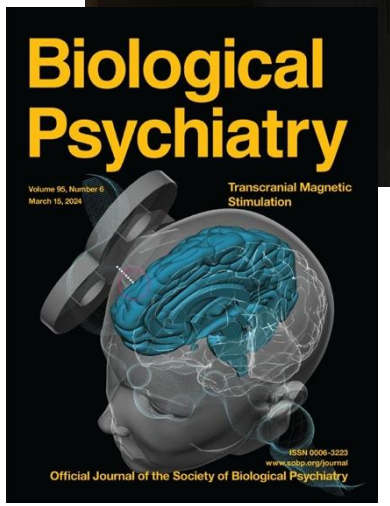
using repetitive Transcranial Magnetic Stimulation (rTMS)











Biological Psychiatry, 2024
Special issue:
TRANSCRANIAL MAGNETIC STIMULATION
Guest Editors:
Odile A. van den Heuvel and Lindsay M. Oberman

25 yr journey

- From task-based fMRI in OCD (& anxiety) to disease model (PhD project 1999-2005)


Stella de Wit

- Experimental single session rTMS-fMRI study in OCD (VENI project 2008-2014)
- Proof-of-concept TIPICCO randomized controlled trial (VIDI project 2018-2023)
  - Prediction rTMS response in OCD
  - Analyses on dosing and targeting


Sophie Fitzsimmons


Tjardo Postma


Milan Houben


Coen Coomans


Hidde Woerdman

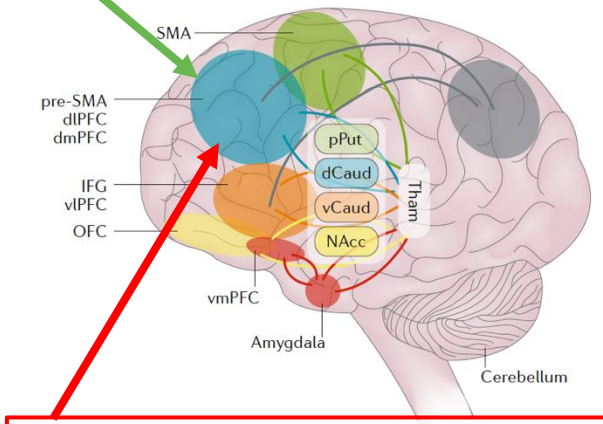

Wianne Schipper


Leonardo Nacci

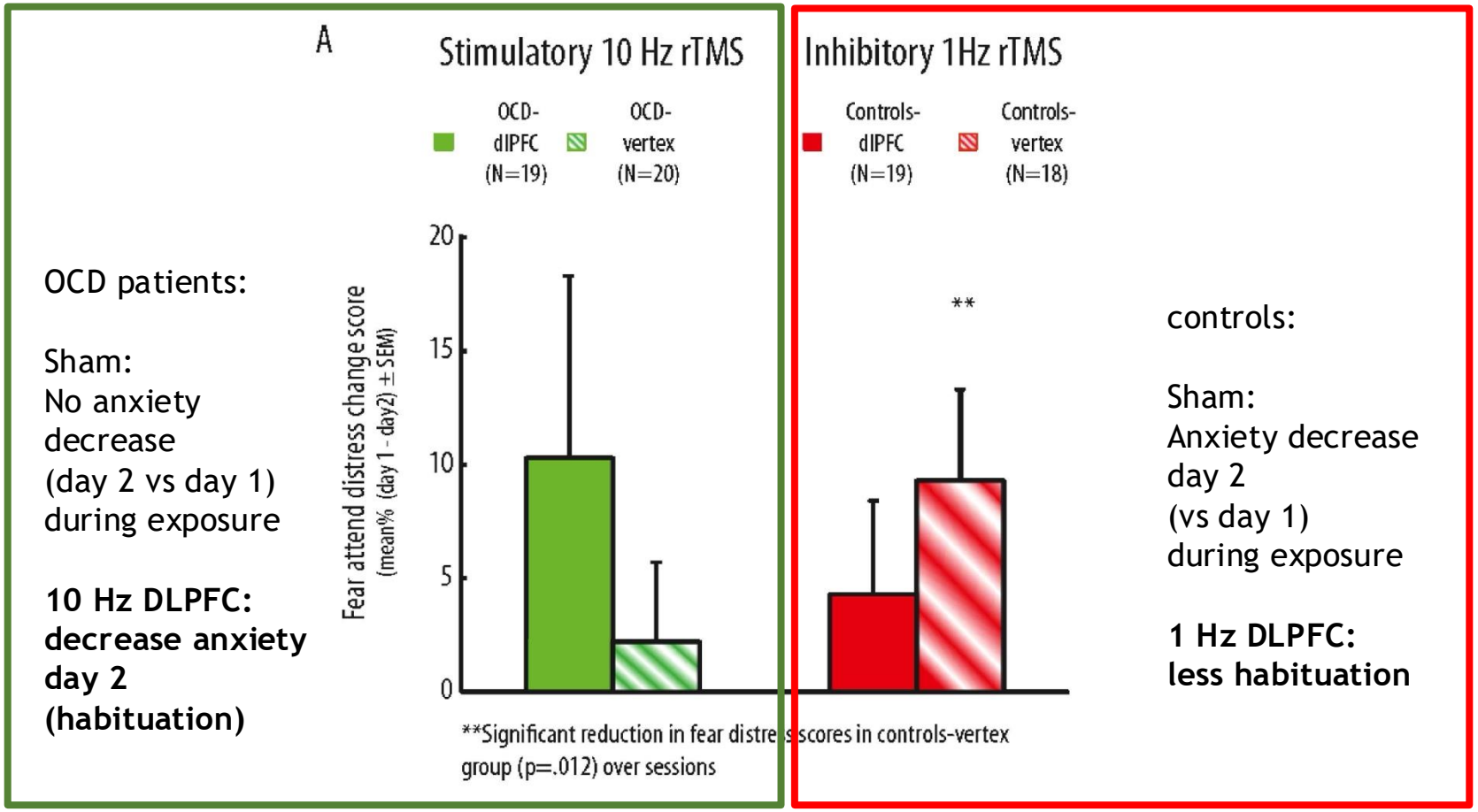
- TETRO trial (cost-effectiveness RCT 2021-2027)
- From biotypes to personalized targeting (VICI project 2025-2030)

Emotion regulation – proof-of-concept

OCD patients (n=43):
High-frequency rTMS vs. sham
(= stimulation of control)



Controls (n=38):
Low-frequency rTMS vs. sham
(= inhibition of control)



OCD patients:

Sham:
No anxiety decrease
(day 2 vs day 1)
during exposure

10 Hz DLPFC:
decrease anxiety day 2
(habituation)

controls:

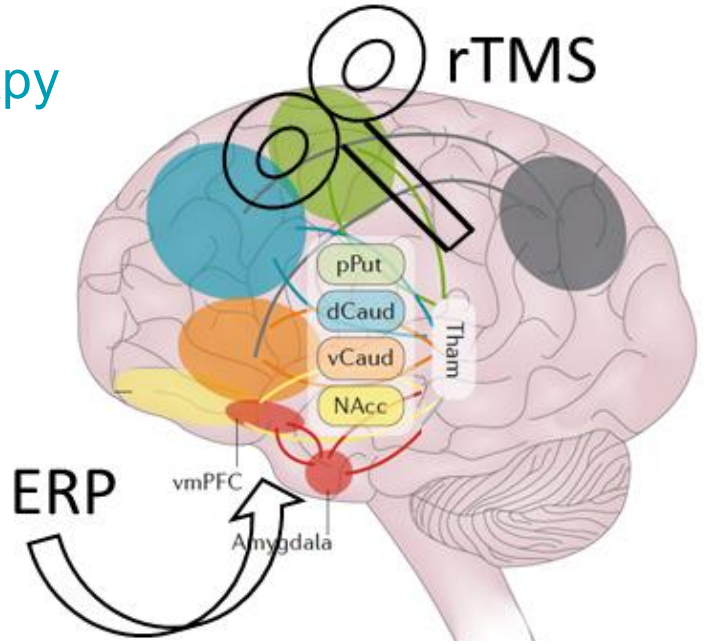
Sham:
Anxiety decrease
day 2
(vs day 1)
during exposure

1 Hz DLPFC:
less habituation

de Wit et al. *Psychological Medicine* (2015)

‘re-shaping’ the brain

by combining TMS & exposure therapy



TIPICCO | TMS-induced plasticity improving cognitive control in OCD

Proof-of-concept RCT in 61 patients

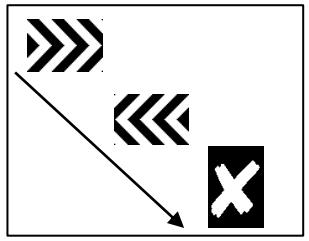
(10 Hz DLPFC, 10 Hz pre-SMA, vertex)

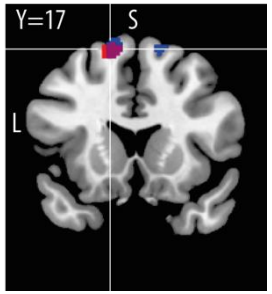
TETRO

TMS for Exposure Therapy-Resistant OCD

Multi-center cost-effectiveness RCT in 250 patients

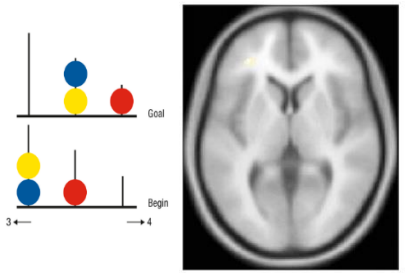
(1 Hz pre-SMA, sham)





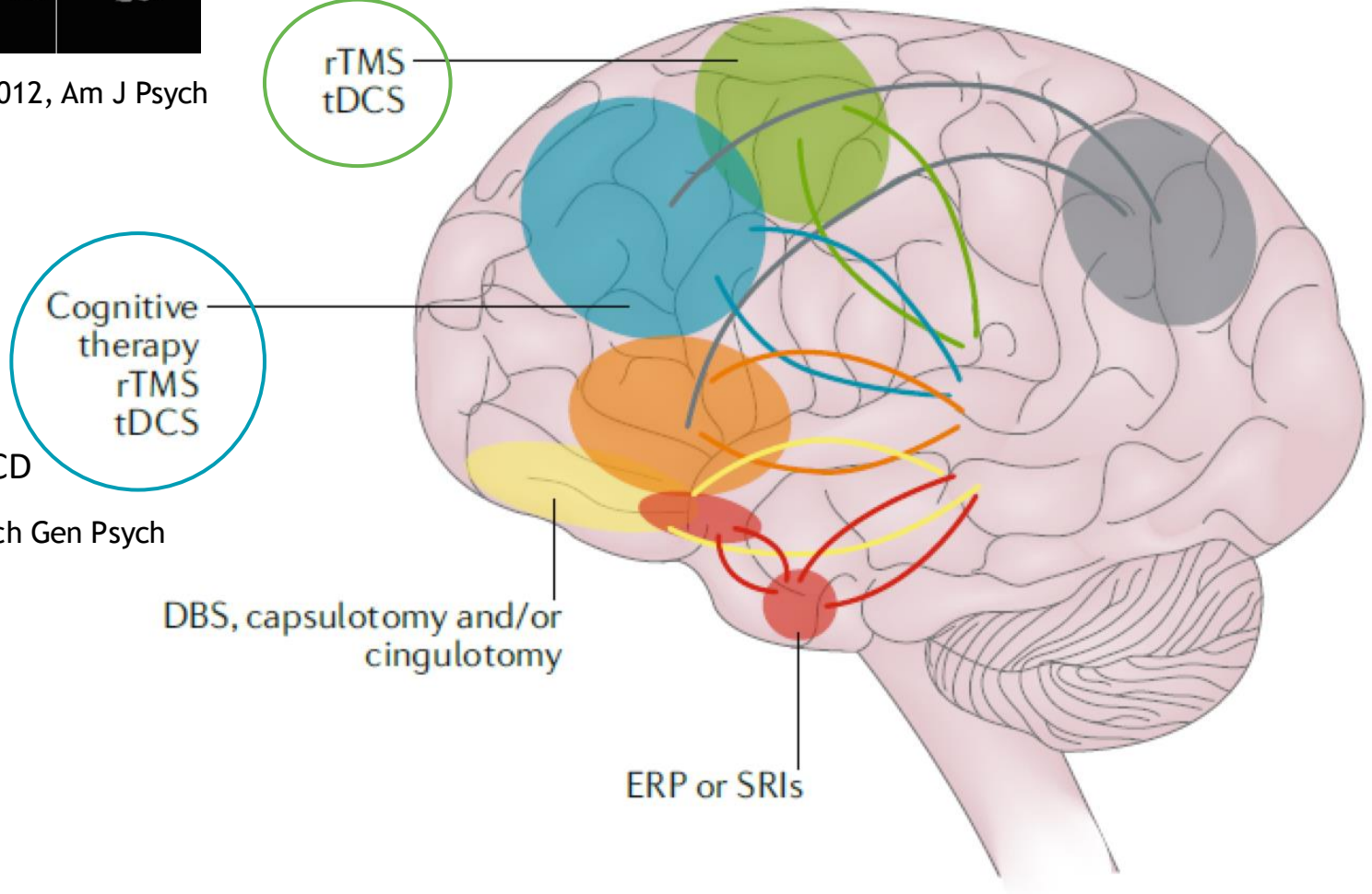
↑ preSMA activity (compensatory) in OCD & siblings

de Wit et al 2012, Am J Psych



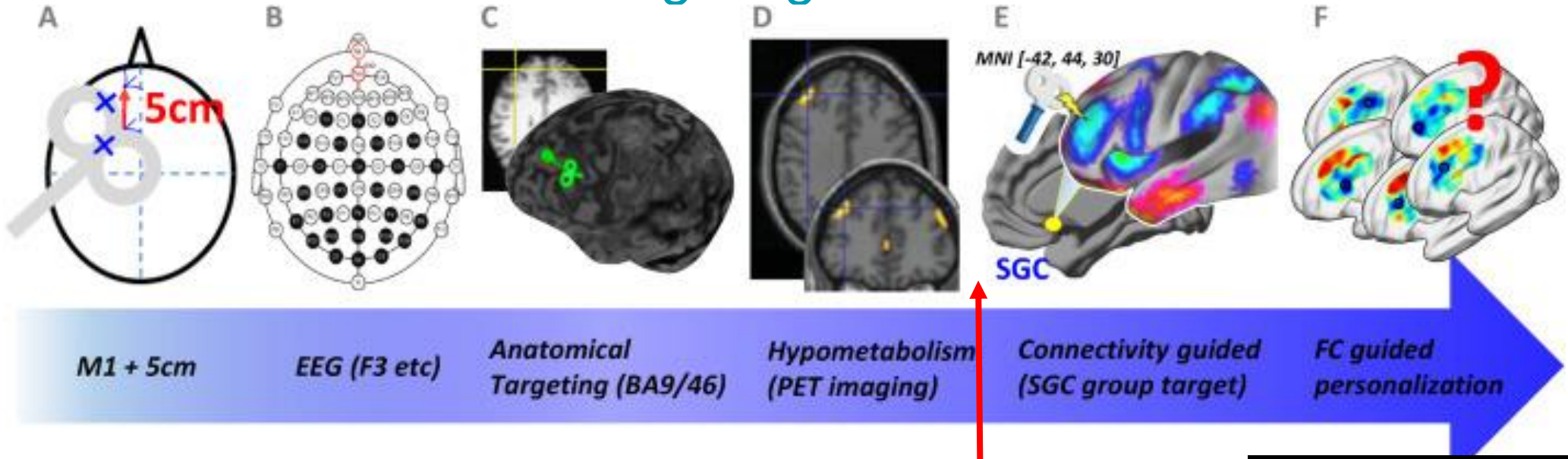
↓DLPFC activation in OCD

Van den Heuvel et al 2005, Arch Gen Psych



Stein et al. 2019; van den Heuvel et al. 2005; de Wit et al. 2012

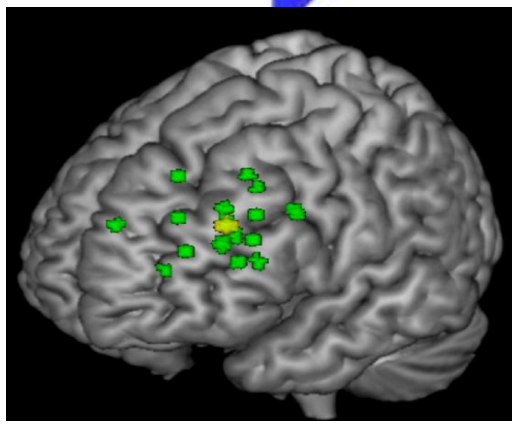
Task-based fMRI for rTMS targeting



Task-fMRI-based targeting

for dorsolateral PFC (DLPFC) rTMS target e.g. emotion regulation task of planning task

for pre-SMA rTMS target e.g. Stop-Signal task



Cash et al, 2021 Biol Psychiatry

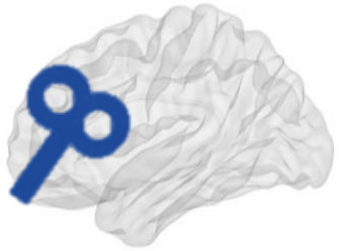
de Wit et al. 2015 Psychol Med

Fitzsimmons et al, 2025 Biol Psychiatry

TIPICCO | TMS-induced plasticity improving cognitive control in OCD

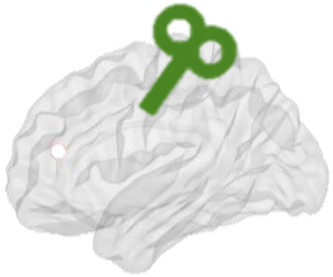
Sophie Fitzsimmons

- 3-arm single-blind RCT
- clinicaltrials.gov (NCT03667807)
- 3 treatment protocols:



10 Hz rTMS L DLPFC
100% RMT
N=19

10 Hz rTMS pre-SMA
100% RMT
N=23



10 Hz rTMS vertex
60% RMT
N=19
('control' condition)

- Treatment:
  - 8 wk (2x/week)
  - 16 x 20-min rTMS + 45 min exposure & response prevention
  - Neuronavigation based on individual functional MRI at baseline

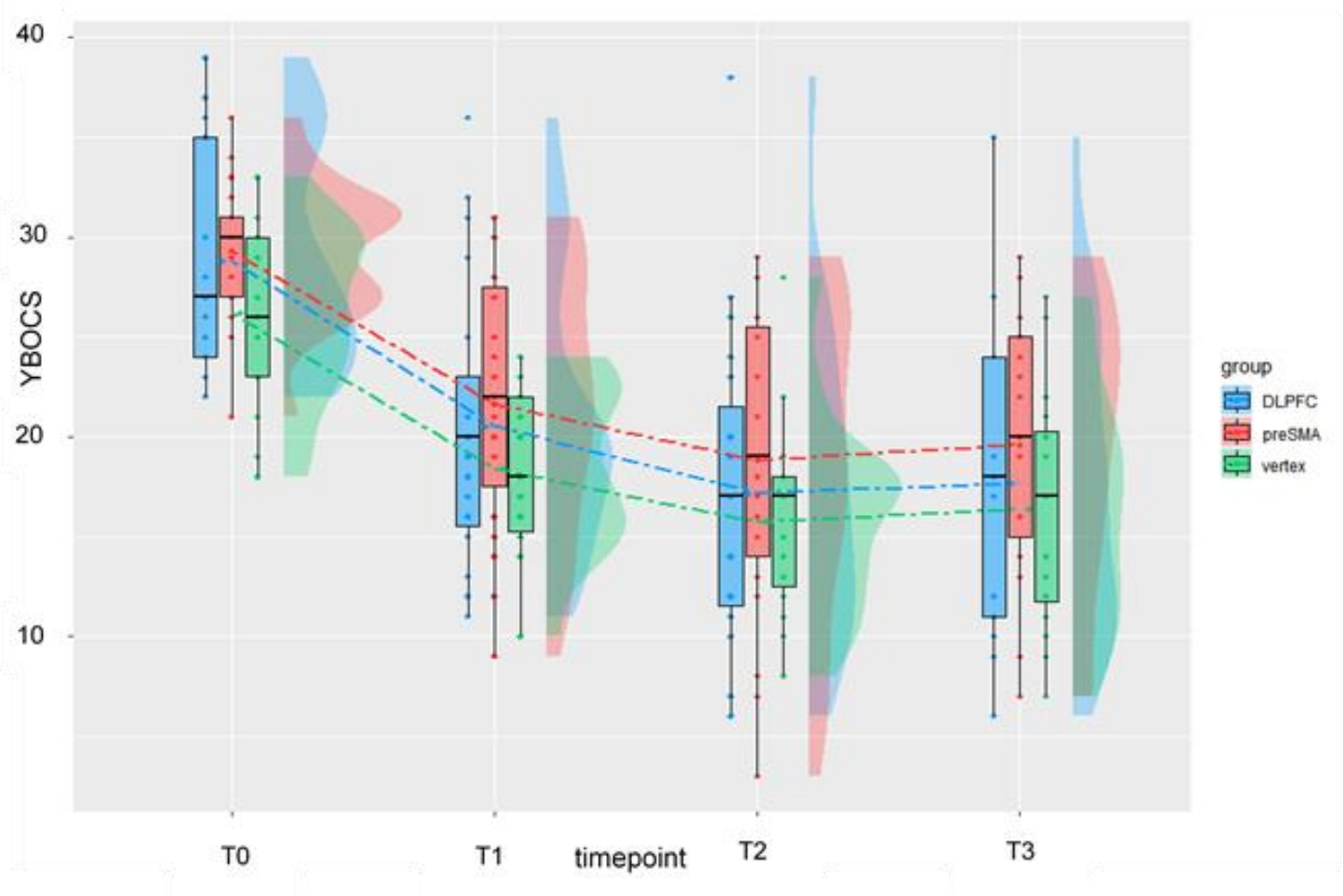
(3000 pulses at 100% RMT, 30 10-s trains, 30s intertrial interval, 20 mins total – based on de Wit et al 2015)

NWO
Netherlands Organisation for Scientific Research

Results

TIPICCO | TMS-induced plasticity improving cognitive control in OCD

symptom change (YBOCS) over time

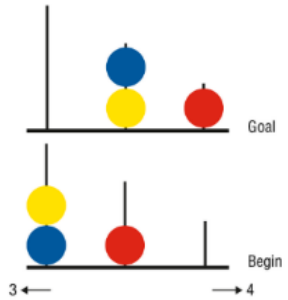


- Significant reduction in OCD symptoms over time ($p<0.001$) in this treatment-resistant sample
- 57,4% response (>35% reduction on YBOCS)
- No difference between groups

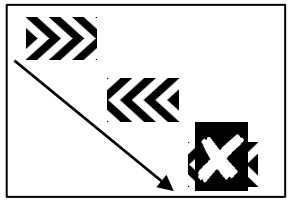
Fitzsimmons et al, *Biological Psychiatry* (2025)

Results

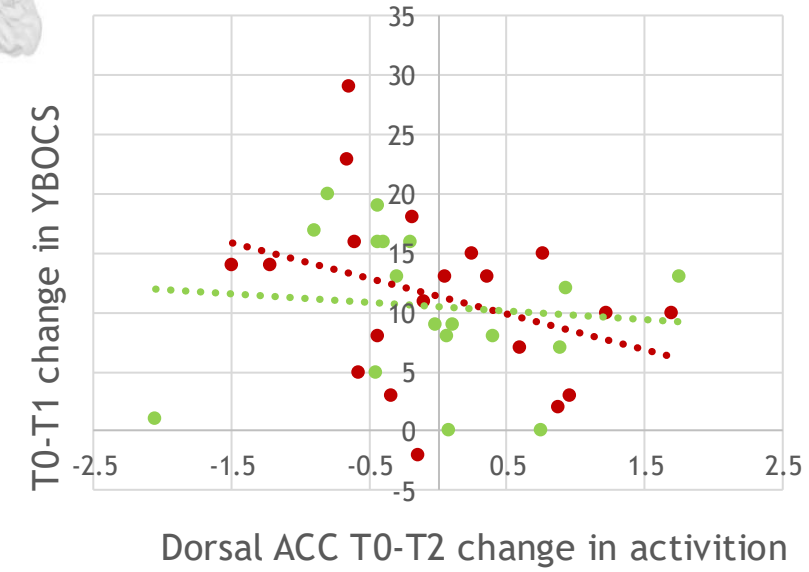
pre-post rTMS - fMRI during tasks



>> After DLPFC rTMS: more reduction in planning-related activity after rTMS associated with better clinical response



>> After pre-SMA rTMS:
Reduction in error-related activity is associated with better clinical response



Fitzsimmons et al, *Biological Psychiatry* (2025)

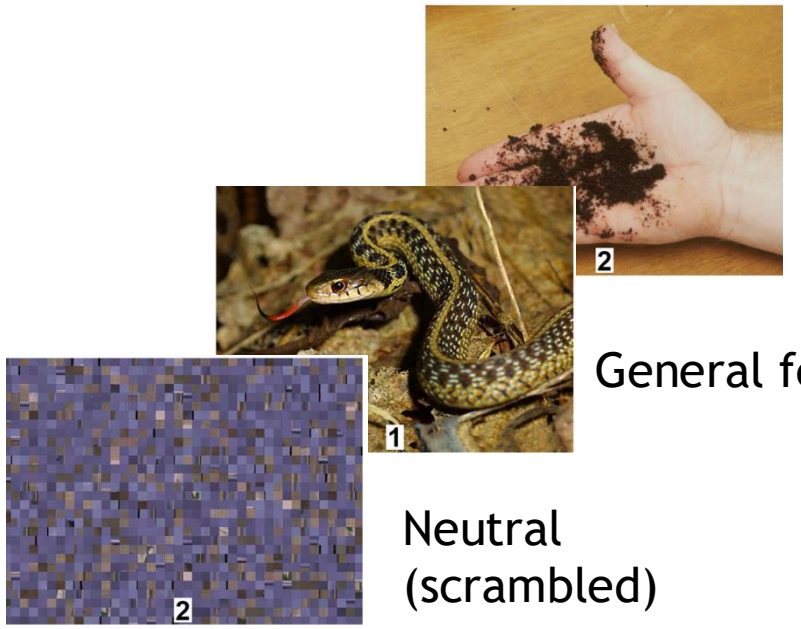
Prediction

rTMS response predicted by baseline fMRI **during symptom provocation**

Milan Houben

>> right amygdala activation during symptom provocation at baseline predicts better treatment response (in all groups)

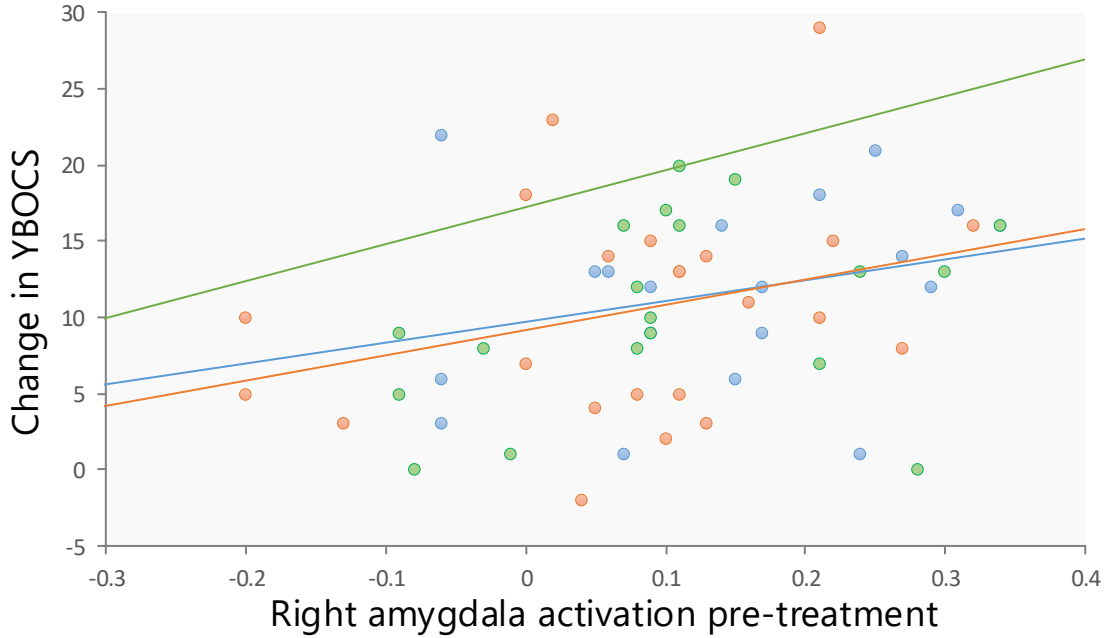
Variable	B	SE B	p
Left dmPFC	19.71	14.84	0.19
Right dmPFC	-12.78	11.71	0.28
Left amygdala	-5.86	7.83	0.46
Right amygdala	17.71	8.13	**0.03**



OCD specific

General fear

Neutral (scrambled)



Houben et al. *Biol Psych CNNI* (2025)

Summary TIPICCO trial

TIPICCO | TMS-induced plasticity improving cognitive control in OCD

- rTMS target specific effects on the brain (during executive and inhibitory control)

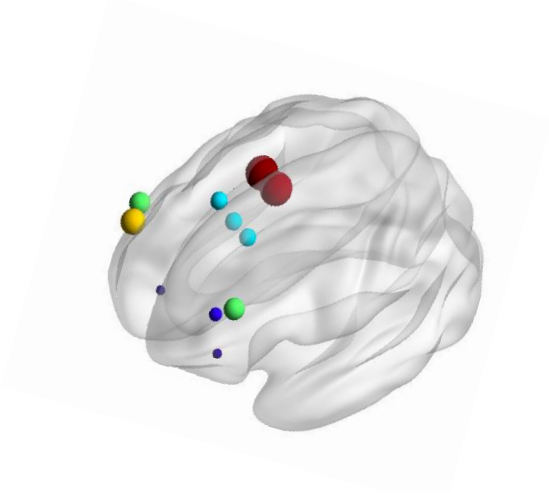
  (Fitzsimmons et al. 2025 Biol Psych)

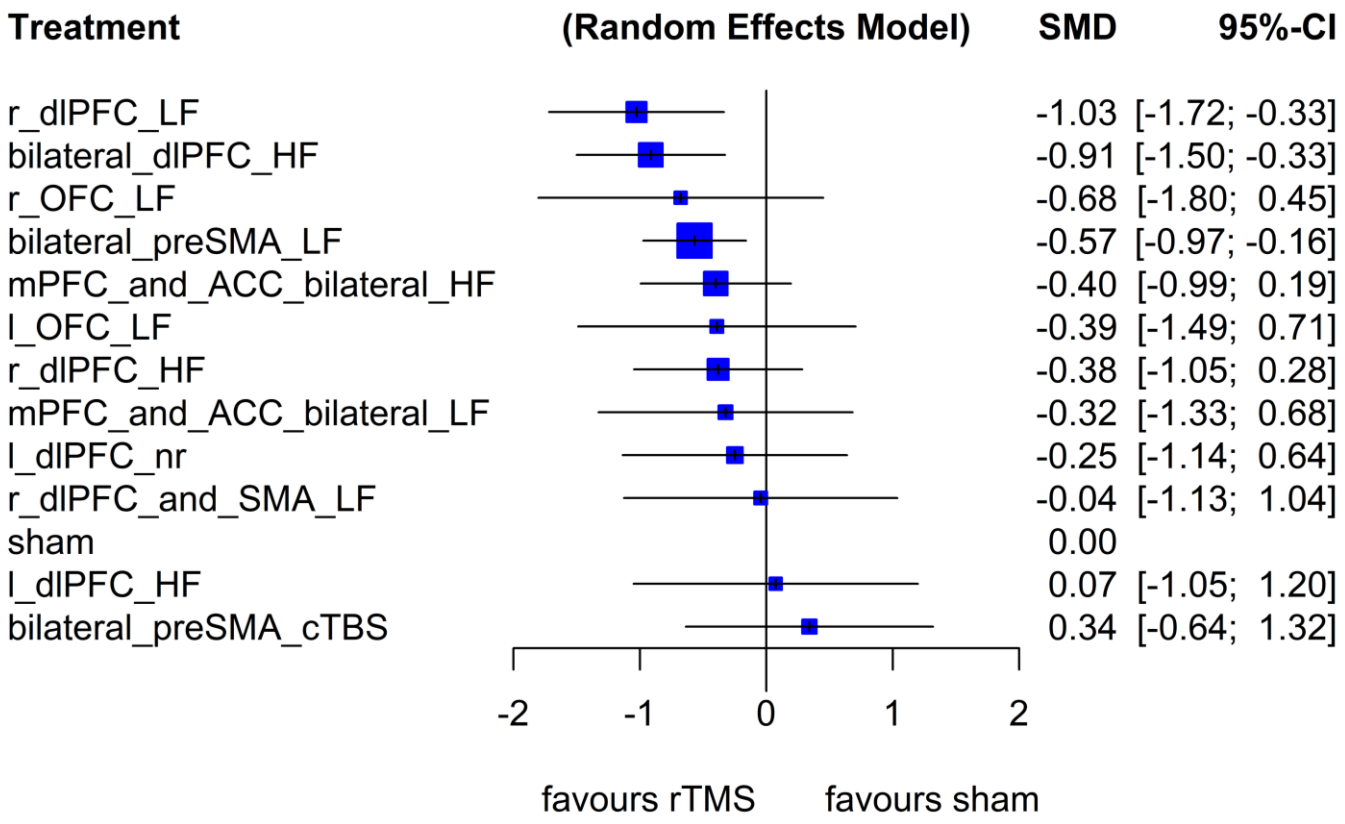
- Variation in treatment response explained by pre-treatment task-fMRI-based activations
  - During **executive and inhibitory control** (Postma et al. 2025 Biol Psych)
  - During **symptom provocation** (Houben et al. 2025 Biol Psych CNNI)

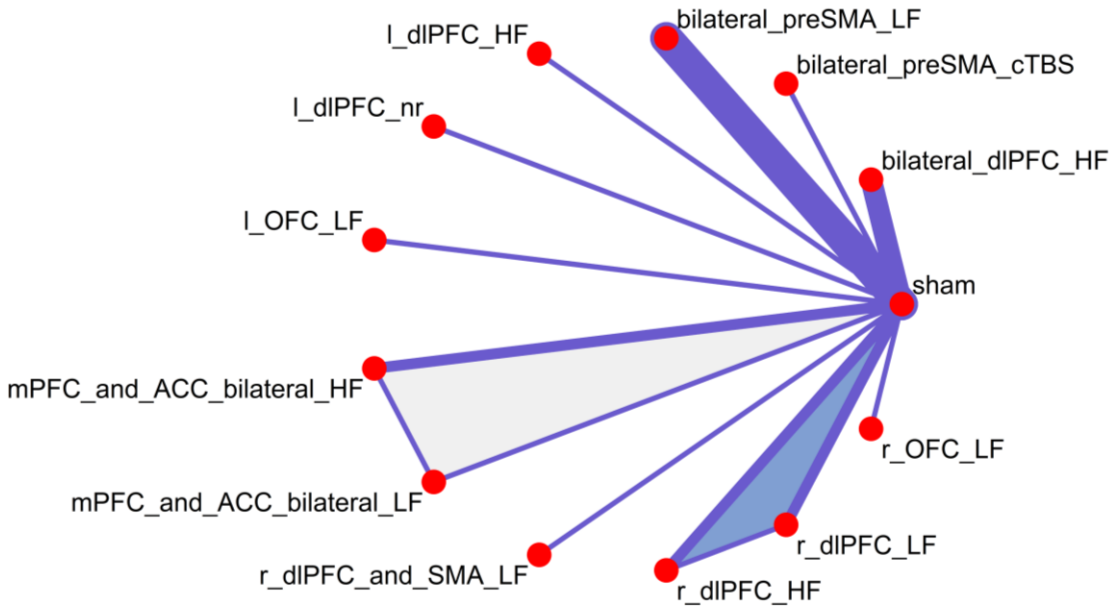
- Variation in treatment response explained by pre-treatment resting state fMRI connectivity between stimulated target and normative network (Coomans et al, under review)

- Variation in dosage (rTMS-induced E-field) (Woerdman et al, under review)

rTMS in OCD
meta- and network analysis





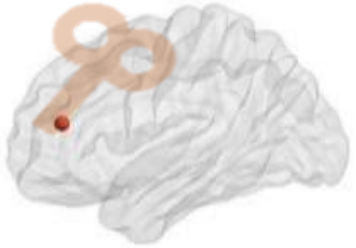


Fitzsimmons et al., *J Aff Disorders* (2022)

https://www.tetro-ocd.nl

TETRO

TMS for Exposure Therapy-Resistant OCD



1500 pulses of 1 Hz rTMS
L pre-SMA N=150
N=167

1500 pulses of 1 Hz sham-rTMS
L pre-SMA N=75
N=83

Tjardo Postma

Placebo-controlled multi-center RCT
250 OCD patients with insufficient response to ERP (with/without medication)
Focus on the added value of 1 Hz pre-SMA rTMS versus sham as adjuvant to intensive ERP
4 sessions/week, for 5-7 weeks
Every rTMS session followed by 90 minutes guided ERP

Zorginstituut Nederland

VeZo grant Zorginstituut NL
(PI: van den Heuvel)
Study period: 2021-2027

Amsterdam UMC
Universitair Medische Centra

GGZ inGeest

Radboudumc

Pro Persona
geestelijke gezondheidszorg

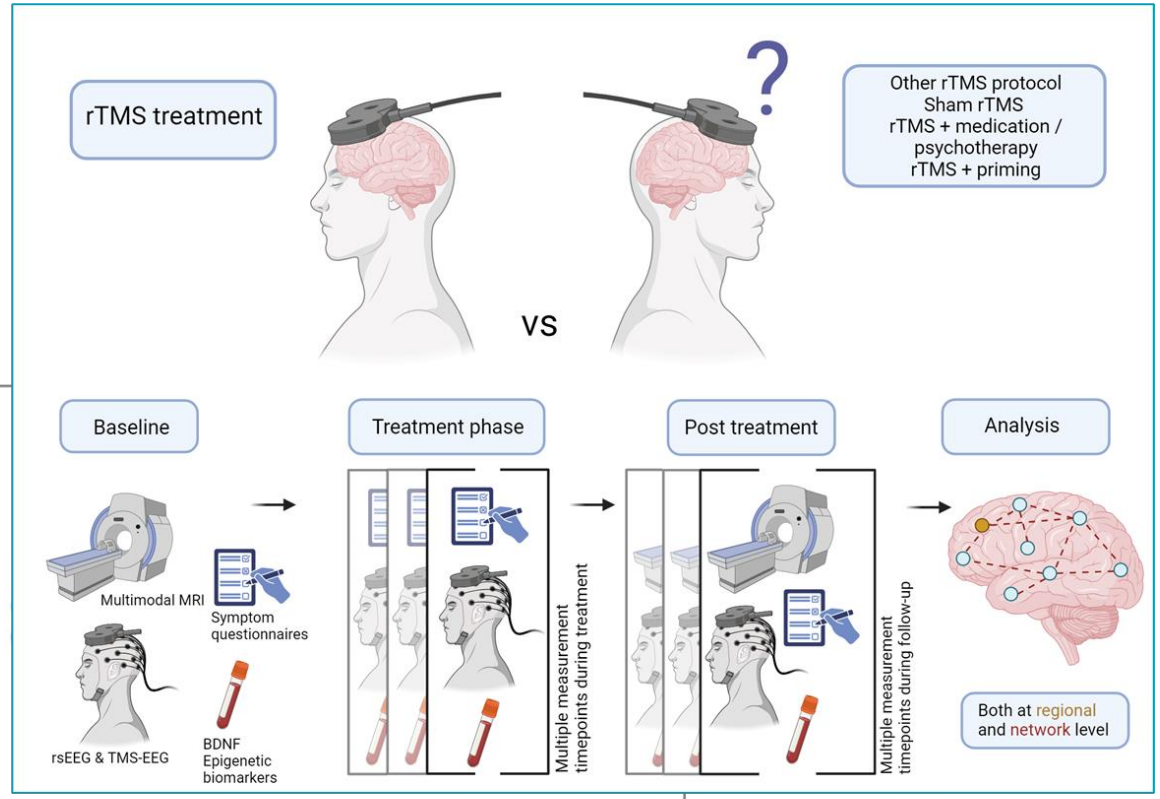
Maastricht UMC+

Mondriaan
voor geestelijke gezondheid

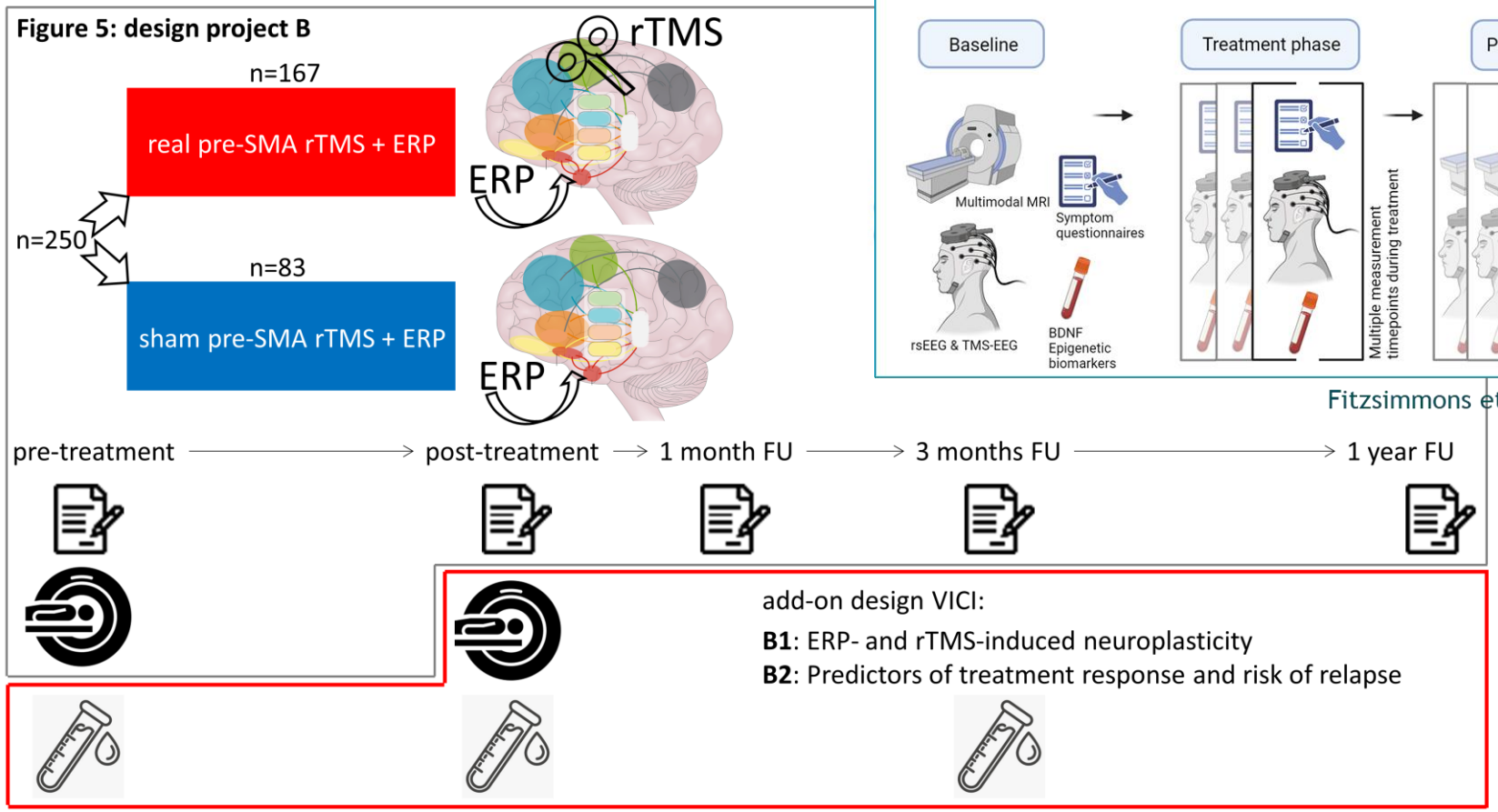
neurocare

adf
stichting

Treatment-induced plasticity



Fitzsimmons et al. *Biological Psychiatry* (2024)

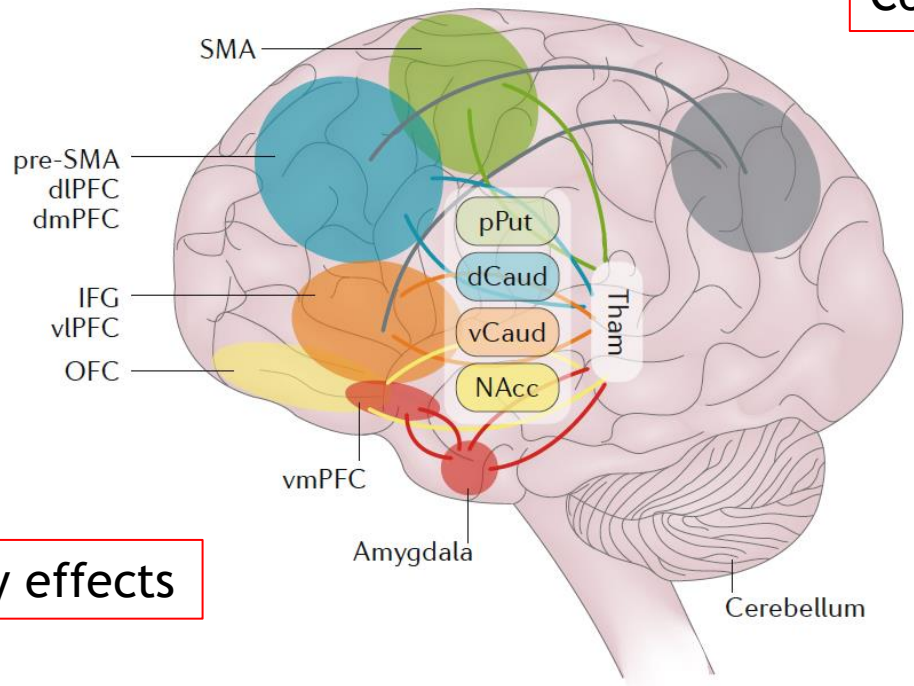


‘The’ OCD brain

Neurodevelopmental effects

Medication effects

Compensatory effects

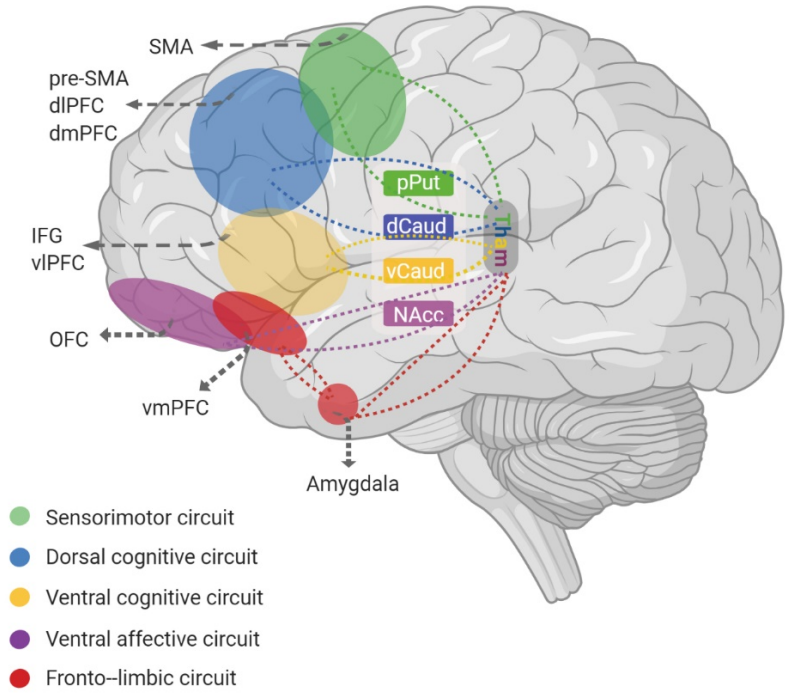


- ‘Sensorimotor’ CSTC circuit
  - Stimulus-response-based habitual behavior
- ‘Dorsal cognitive’ CSTC circuit
  - Working memory, planning, emotion regulation
- Frontoparietal network
  - Coordination of cognitive control
- ‘Ventral cognitive’ CSTC circuit
  - Response inhibition
- ‘Ventral motivational’ CSTC circuit
  - Stimulus-outcome-based motivational behaviour
- ‘Frontolimbic’ circuit
  - Fear extinction

Onset and chronicity effects

Symptom profile dependent

Stein et al. *Nature Reviews Disease Primers* (2019)



1

Fronto-limbic circuit

Clinical profiles:
Dysregulated fear
Intolerance of uncertainty

Treatment approach:
Reduce fronto-limbic hyperactivity
Increase dorsal cognitive top-down control

Potential treatment methods:
CBT / SSRIs
Amygdala/vmPFC fMRI-neurofeedback
dlPFC rTMS
ALIC deep brain stimulation

2

Sensorimotor circuit

Clinical profiles:
Sensory phenomena
Excessive habit-formation

Treatment approach
Reduce sensorimotor circuit overactivity
Regulate insula activity (sensory phenomena only)

Potential treatment methods:
Habit-reversal training
SMA rTMS
H-coil insula rTMS
Ondansetron

3

Ventral cognitive circuit

Clinical profiles:
Impaired response inhibition

Treatment approach:
Increase ventral cognitive circuit hypoactivity

Potential treatment methods:
IFG fMRI-neurofeedback
STN/VS deep brain stimulation

4

Ventral affective circuit

Clinical profiles:
Altered reward responsiveness

Treatment approach:
Restore reward mechanisms

Potential treatment methods:
SSRIs
Dopamine-acting medication (e.g. methylphenidate)
NAcc fMRI-neurofeedback
NAcc deep brain stimulation

5

Dorsal cognitive circuit

Clinical profiles:
Executive dysfunction

Treatment approach:
Increase hypoactive dorsal cognitive circuit function

Potential treatment methods:
CBT
Methylphenidate
dlPFC and pre-SMA rTMS/tDCS

Shephard et al. *Molecular Psychiatry* (2021)

MEGA-OCD

National Institutes of Health



NIMH R01MH138569-02, 2024-2029

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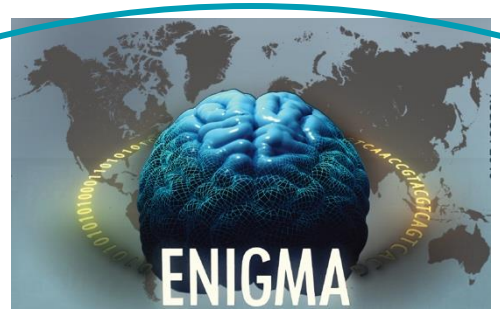
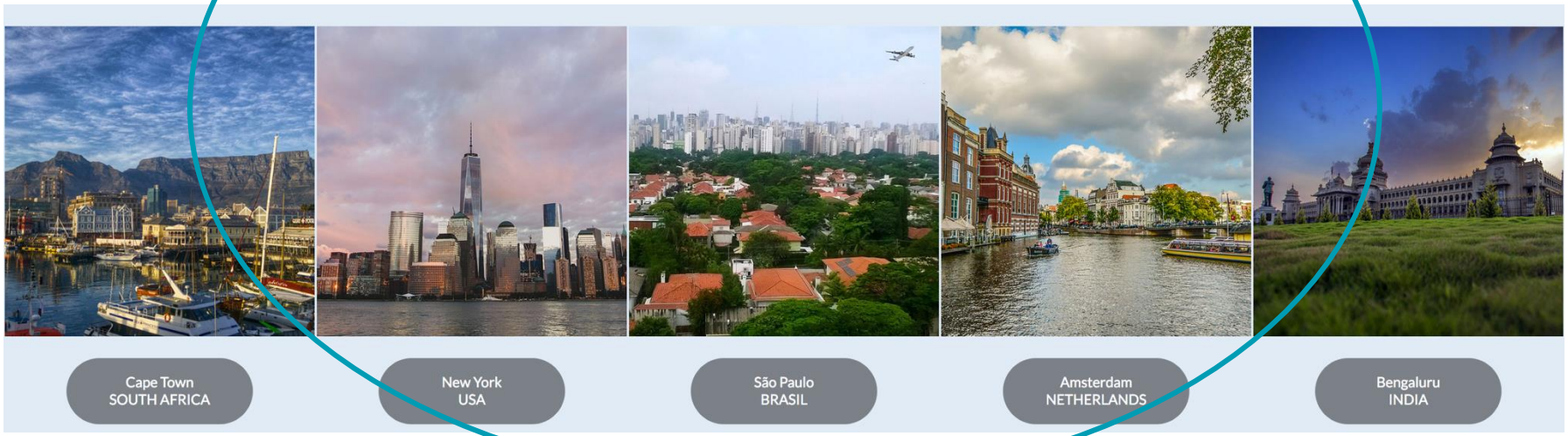




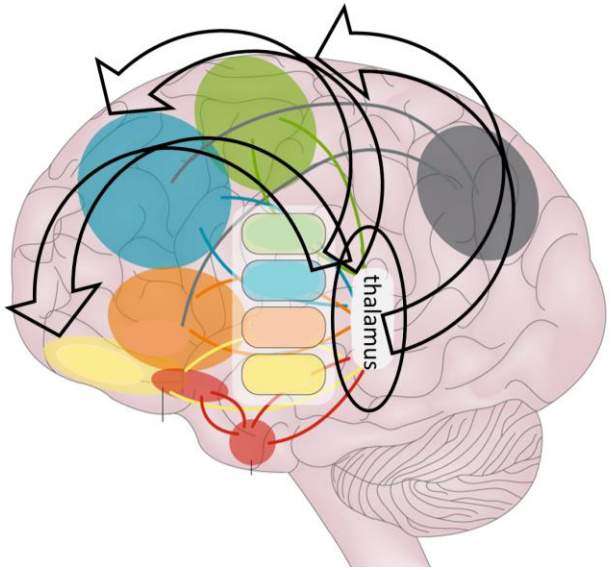
- Multi-modal MRI-based biotypes of OCD

↓

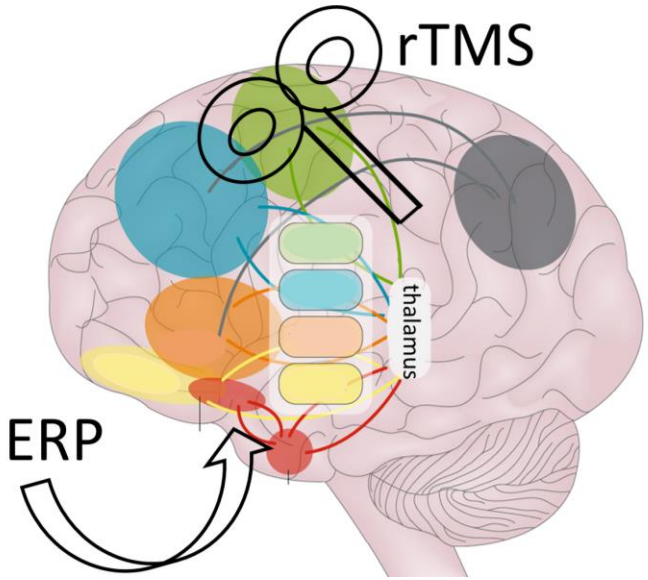
input for
n-of-1 design
rTMS trial on
individualized
targeting

Neuroplasticity in OCD

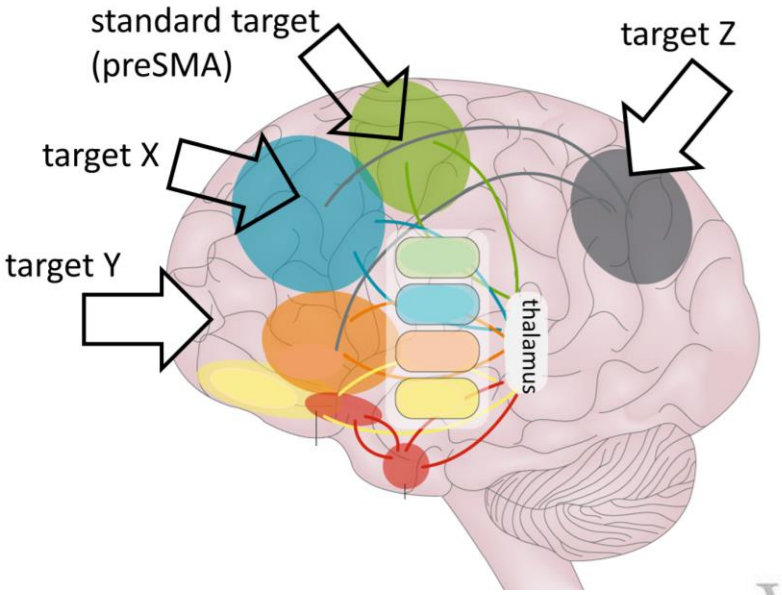
Project A
Neurodevelopment



Project B
ERP / rTMS induced neuroplasticity



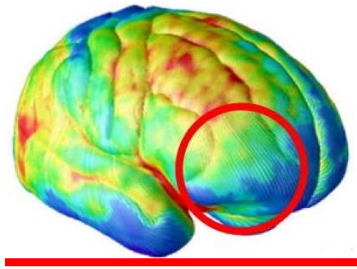
Project C
Personalized treatment



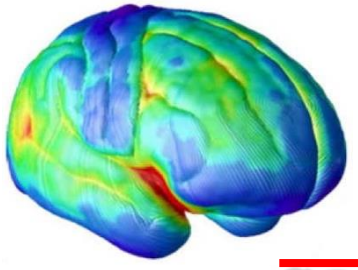
VENI
VIDI
VICI

Lifespan view on OCD

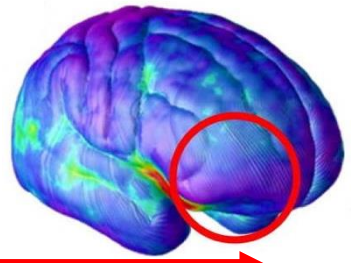
‘cause’



disease onset

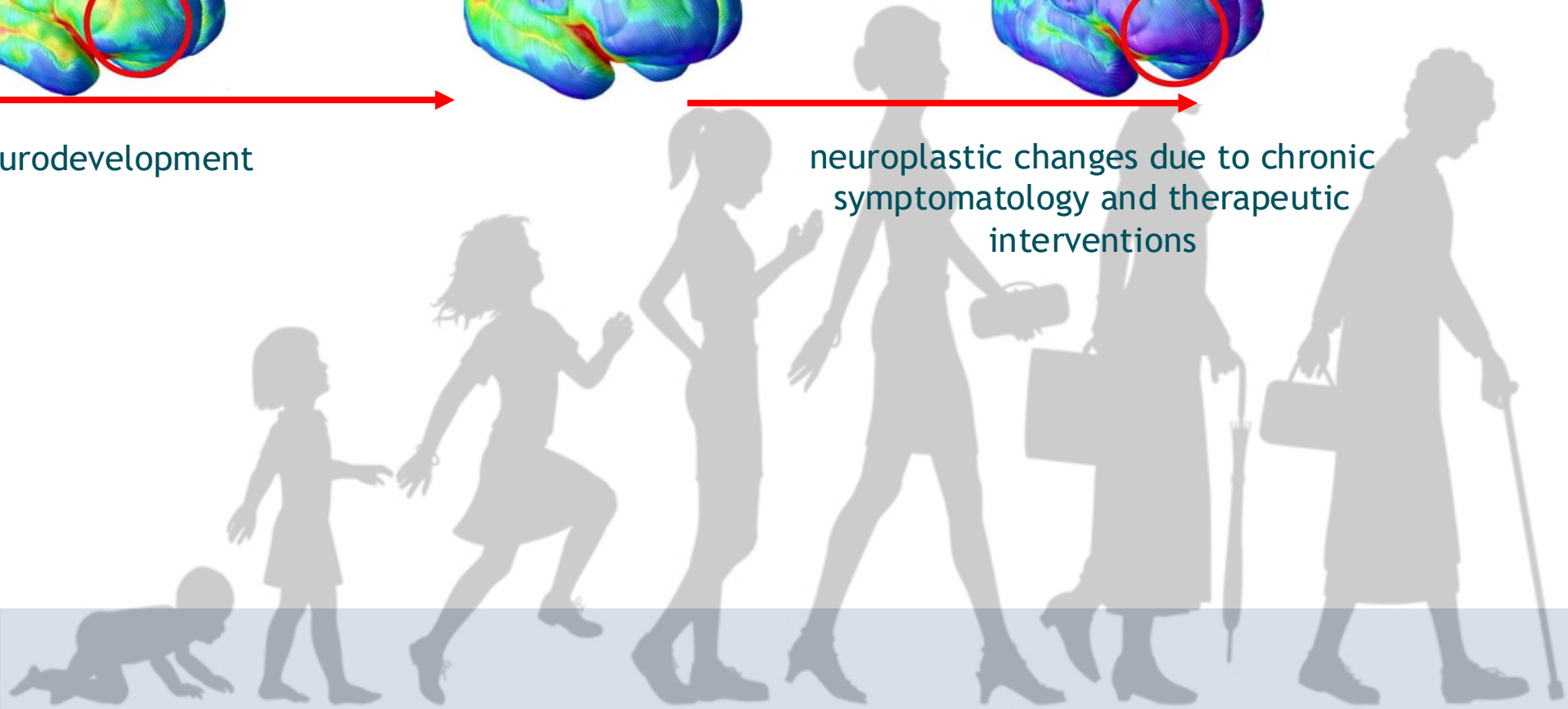


‘consequence’



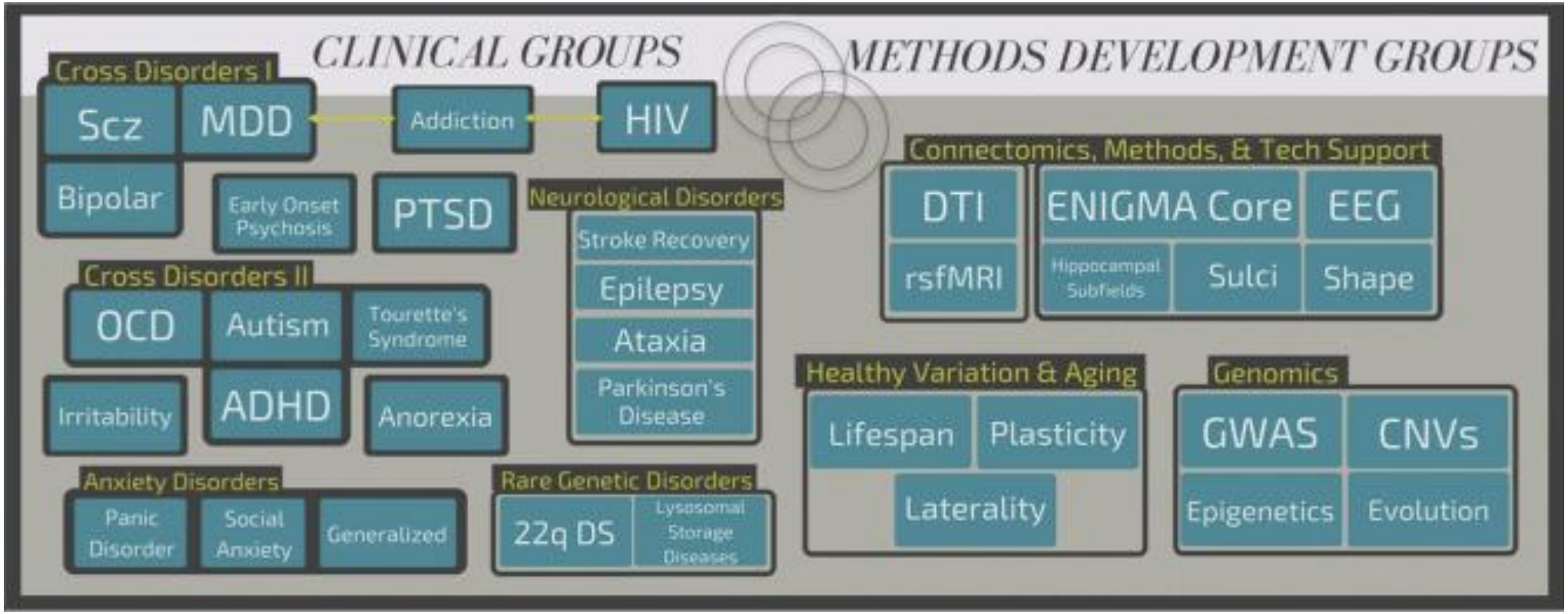
early neurodevelopment

neuroplastic changes due to chronic symptomatology and therapeutic interventions

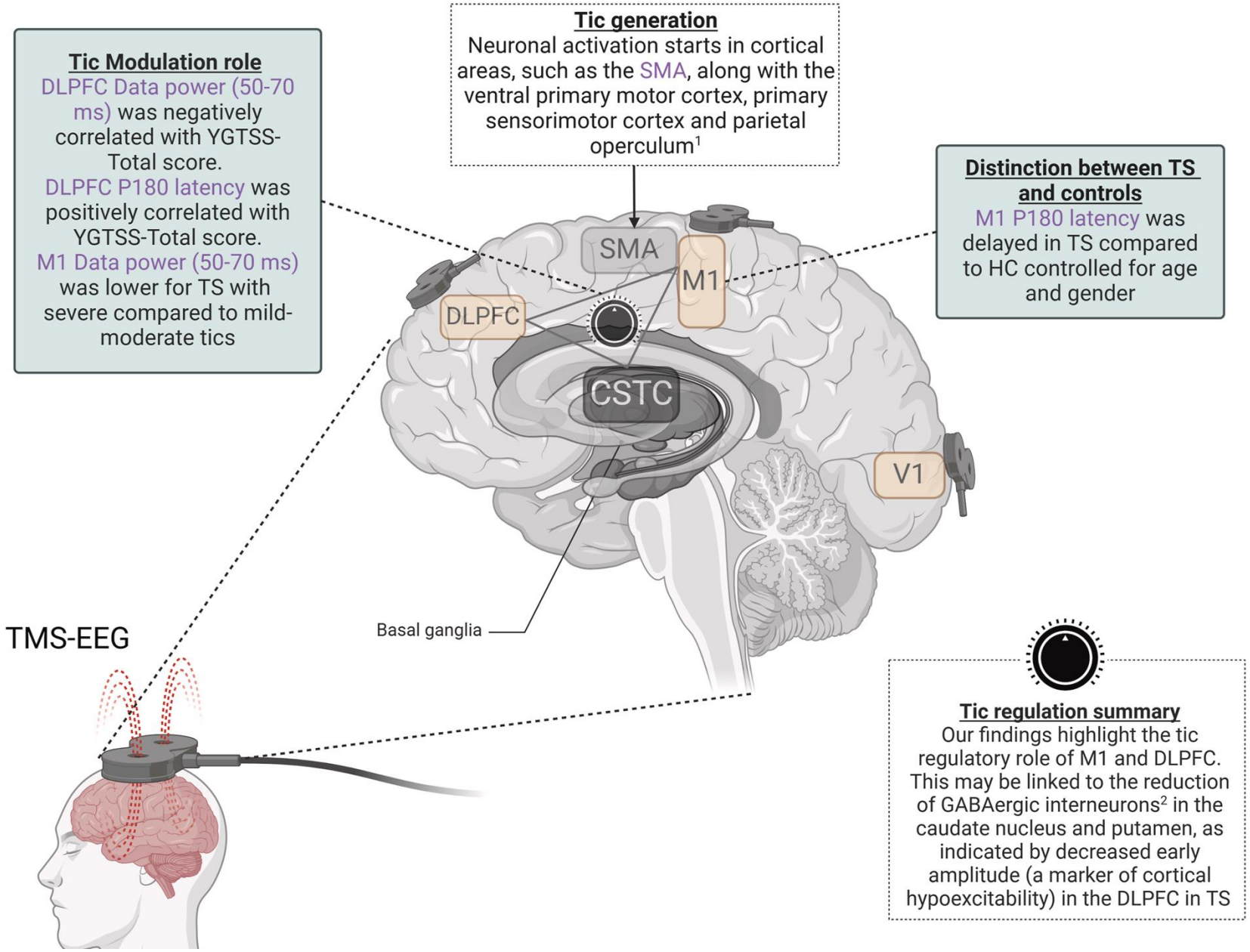


Tourette

and the overlap with other neurodevelopmental disorders



TMS in Tourette

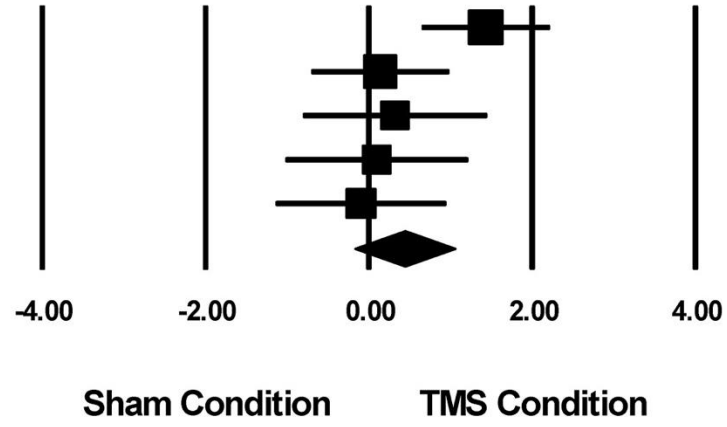


Lassman et al. *Parkinson Rel Dis* (2025)

rTMS in Tourette

0,5 Hz rTMS parietal
1 Hz rTMS SMA
1 Hz rTMS pre-motor
30 Hz cTBS SMA

	Hedges's g	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Fu et al. 2021	1.432	0.401	0.160	0.647	2.217	3.576	0.000
Landeros-Weisenberger et al. 2014	0.142	0.431	0.186	-0.703	0.987	0.330	0.741
Orth et al. 2005a	0.322	0.576	0.332	-0.806	1.451	0.560	0.575
Orth et al. 2005b	0.099	0.572	0.327	-1.022	1.219	0.173	0.863
Wu et al. 2014	-0.094	0.533	0.284	-1.139	0.952	-0.176	0.861
Pooled	0.436	0.311	0.097	-0.174	1.046	1.400	0.162



Steuber et al. 2024 J Psych Res

Take home message

- The brain adapt to our behavior during life
- The thalamus plays an important role in neurodevelopment and OCD
- More transdiagnostic work needed to understand lifespan changes in neurodevelopmental disorders
- With treatment we can ‘re-shape’ the brain
- rTMS might potentiate the response to behavioral therapy
- The optimal rTMS target is probably developmental stage and biotype-dependent
- Due to chronic disease vulnerability durable care remains a challenge

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adf stichting

TETRO
TMS for Exposure Therapy-Resistant OCD

ENIGMA-OCD & Global OCD consortium

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Christine Lochner
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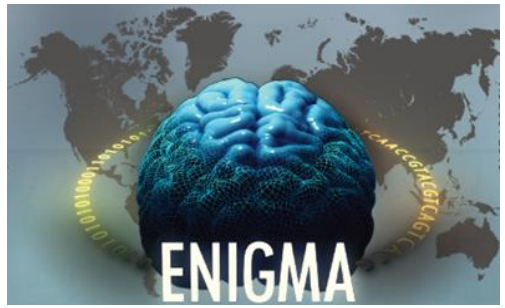
and consortium members



NIMH National Institute of Mental Health

International OCD Foundation

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Erasmus MC

Neuromodulation
ECNP Network

ecnp Neuroscience applied

NWO

VENI (2008-2012)
VIDI (2018-2023)
VICI (2025-2030)

ZonMw