From TS-Pathophysiology to Treatment – and Back: What Neuromodulation Tells Us About Tic Disorders

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University Hospital of Freiburg
Department of Psychiatry and Psychotherapy

19.11.2024

Conflicts of Interests

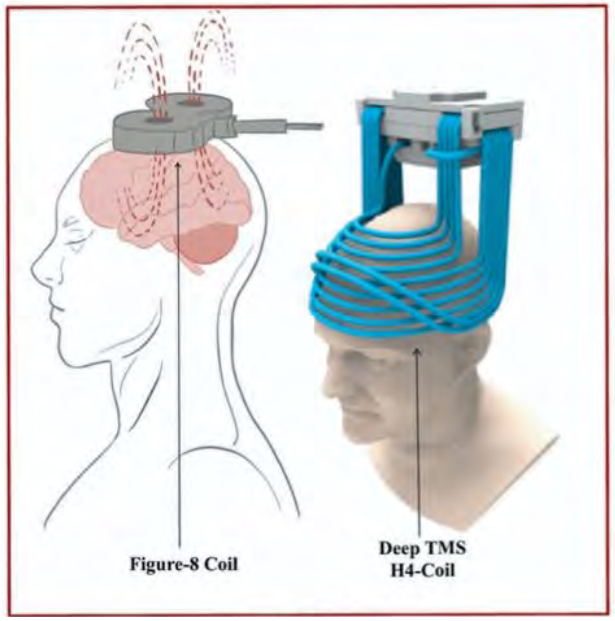
- No Industry Conflicts

Neuromodulation – a Fourth Treatment Pillar in Neuropsychiatry

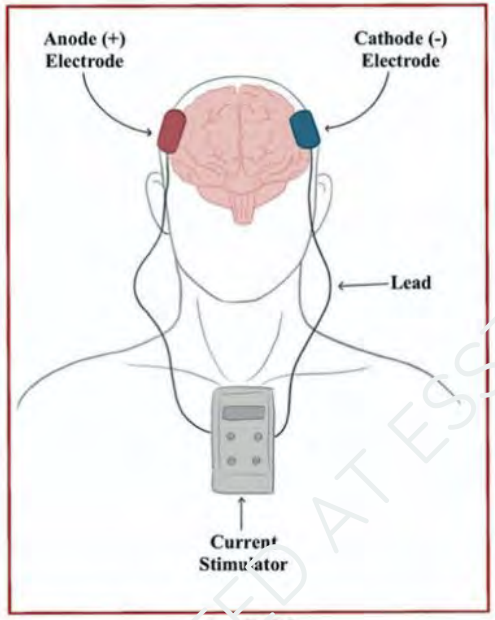
- Psychotherapy
- Pharmacotherapy
- Psychosocial Interventions
- Neuromodulation

Different Ways of Stimulating Brains

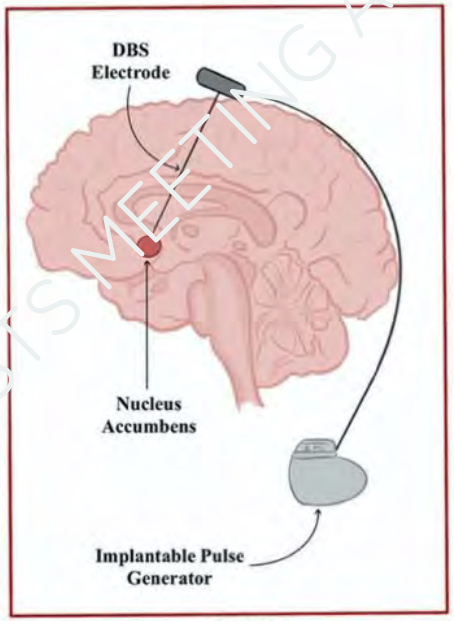
Transcranial Magnetic Stimulation (TMS)



Transcranial Electric Stimulation (TES)



Deep Brain Stimulation (DBS)



Metha et al., Neuropsychopharmacology 2023

Median Nerve Stimulation (MNS)

Henry et al., Neuromodilation 2024

So far, Deep Brain Stimulation is the Only Neuromodulation Strategy in TS-Guidelines

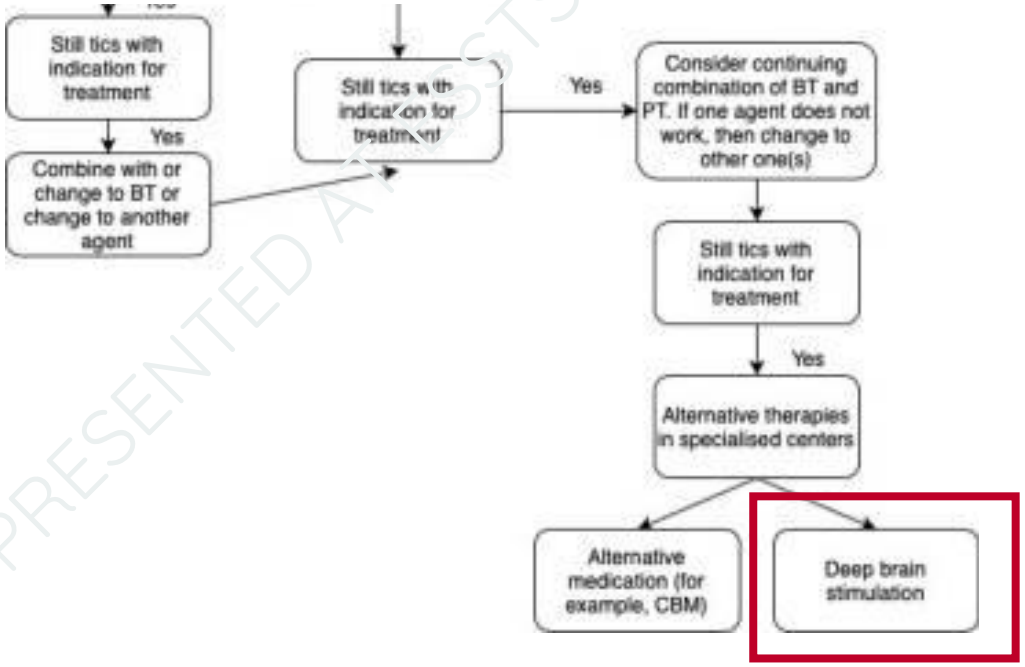
European Child & Adolescent Psychiatry (2022) 31:377–382
https://doi.org/10.1007/s00787-021-01832-4

REVIEW

Check for updates

European clinical guidelines for Tourette syndrome and other tic disorders: summary statement

Kirsten R. Müller-Vahl[1] · Natalia Szejko[2,3,4] · Cara Verdellen[5,11] · Veit Roessner[6] · Pieter J. Hoekstra[7] · Andreas Hartmann[8] · Danielle C. Cath[9,10]



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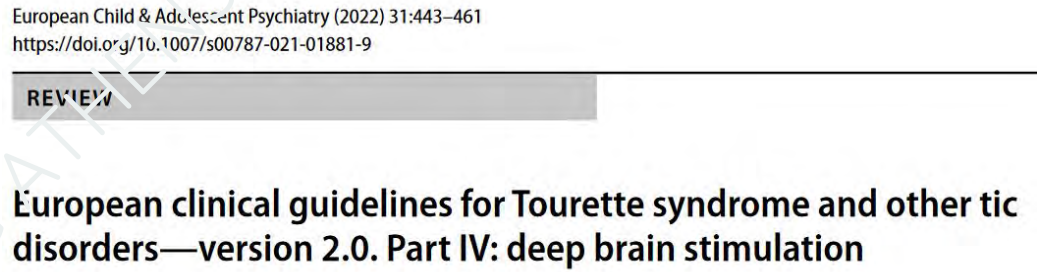
Deep Brain Stimulation

Who qualifies for DBS?


European Child & Adolescent Psychiatry (2022) 31:443–461
https://doi.org/10.1007/s00787-021-01881-9

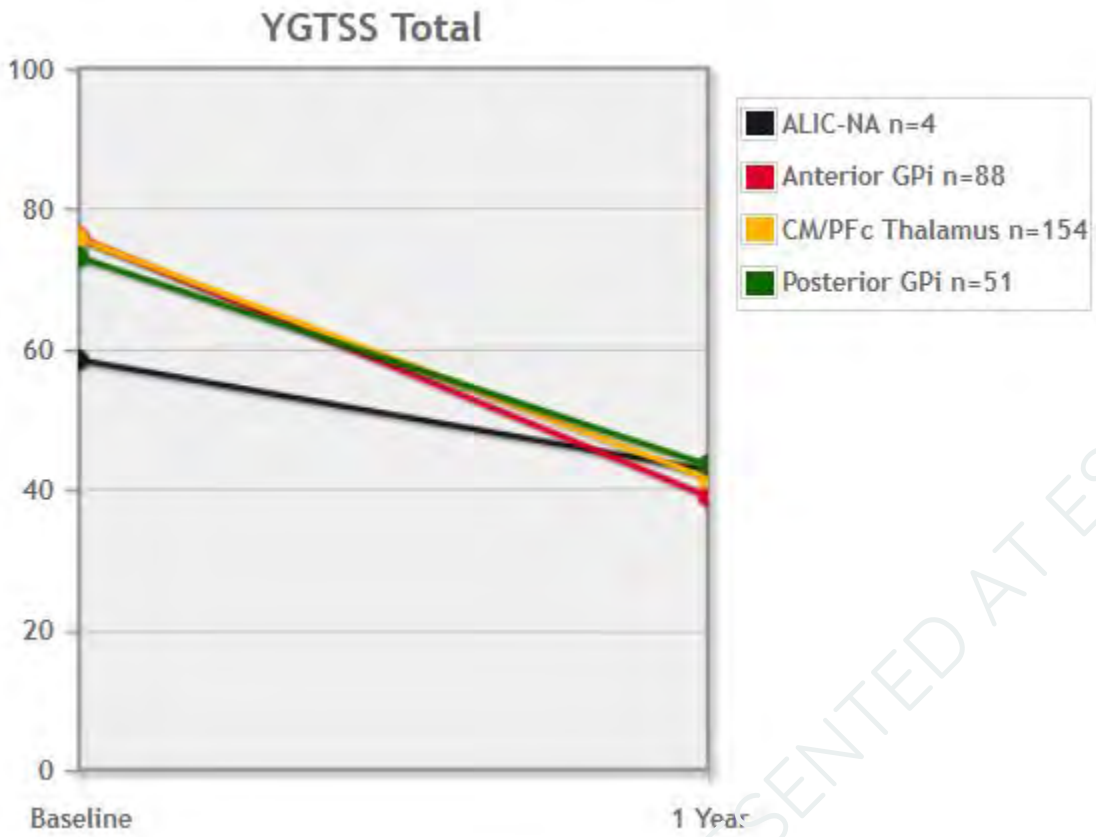
REVIEW

European clinical guidelines for Tourette syndrome and other tic disorders—version 2.0. Part IV: deep brain stimulation

1. Primary tic disorder
2. A functional tic-like disorder must be excluded
3. Primary goal: tic reduction
4. Significant impairment of quality of life (e.g. severe, self-injurious tics)
5. Resistant to established conservative treatments (CBT and pharmacotherapy)
6. No age minimum, but spontaneous remission must be considered
7. Multidisplinary center including psychiatry & neurology

Szeljko et al., Europ Child & Adol Psych 2022

Registry, Long-Term Data and RCTs support efficacy of DBS for Tourette Syndrome



https://tourettedeepbrainstimulationregistry.ese.ufhealth.org/

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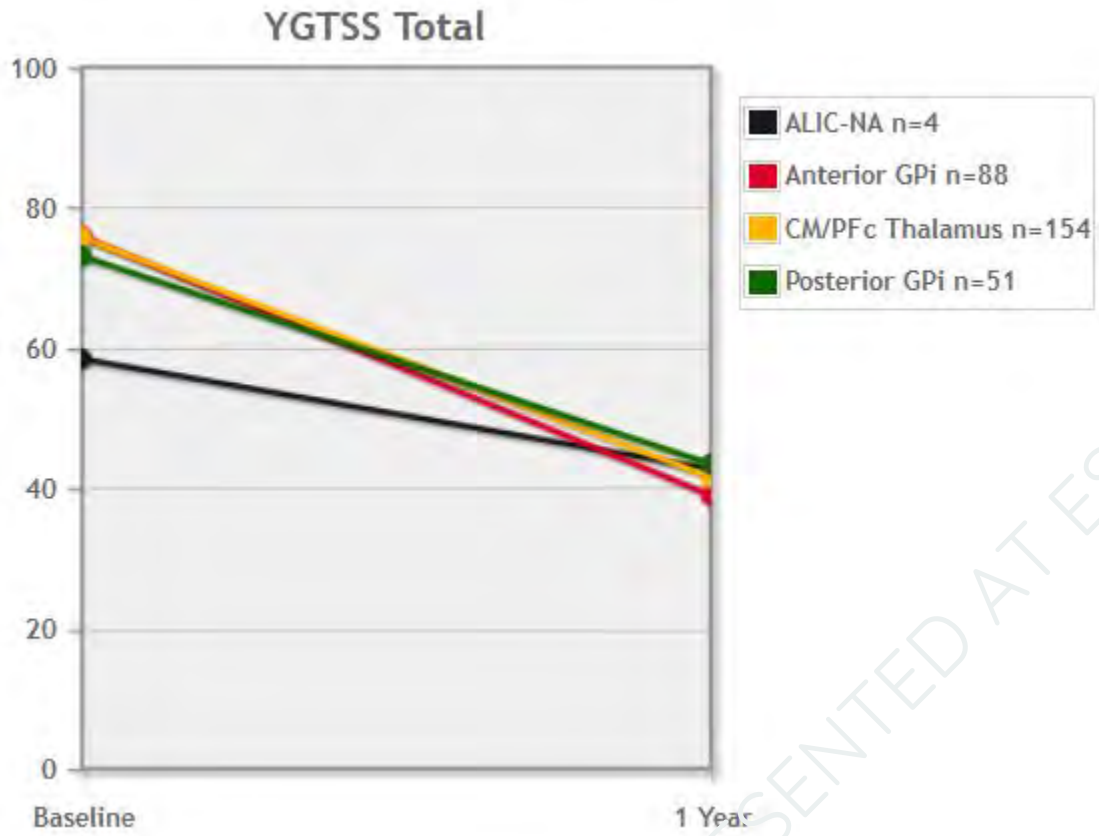

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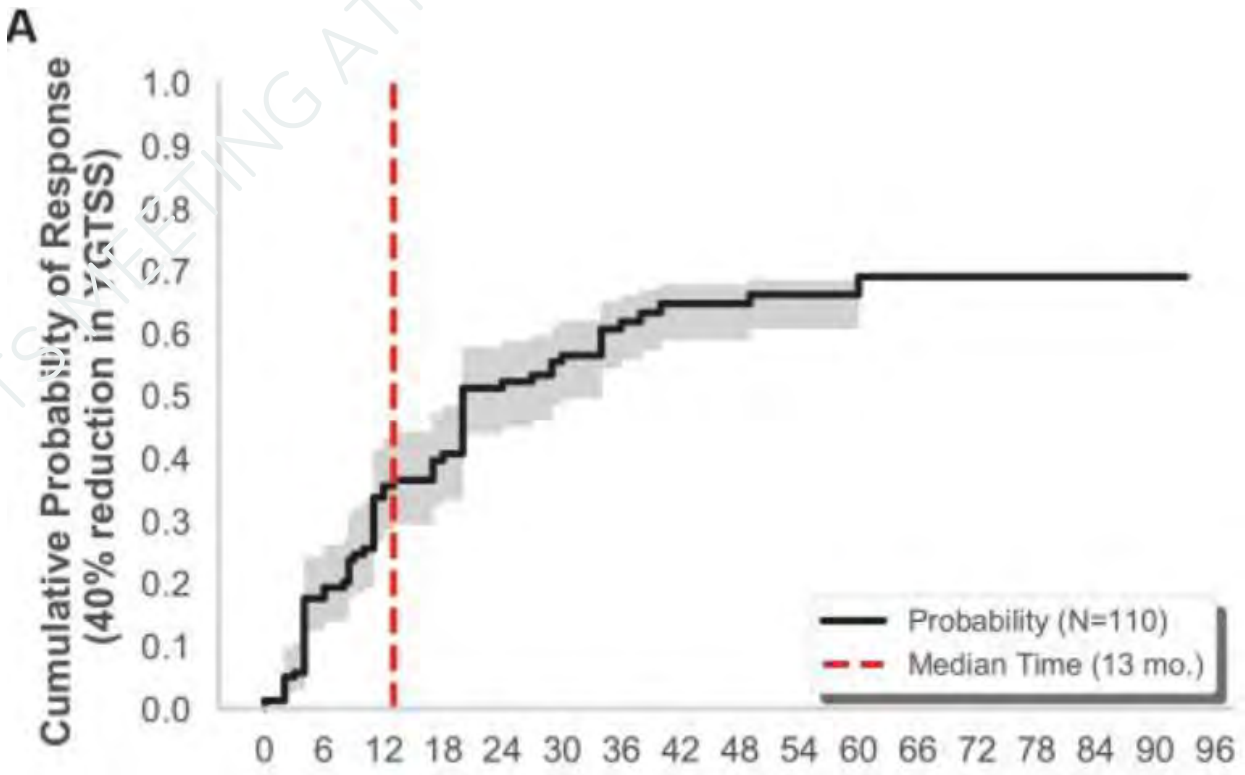

Johnson et al., JNNP 2019

Long-Term Data and RCTs support efficacy of DBS for Tourette Syndrome

Dr. Laura Wehmeyer PhD

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI	Year
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Ackermans et al. (Tha)	25.6	12.8	6	41.1	5.4	6	9.5%	-1.46 [-2.79, -0.12]	2011
Kefalopoulou et al. (Gpi)	34.4	8.5	13	40	5.7	13	22.3%	-0.75 [-1.55, 0.05]	2015
Welter et al. (Gpi)	32	7.13	7	39	4.13	9	13.5%	-1.18 [-2.27, -0.08]	2017
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Müller-Vahl et al. (Gpi)	33.33	9.49	9	34.78	10.6	8	16.9%	-0.14 [-1.09, 0.82]	2021
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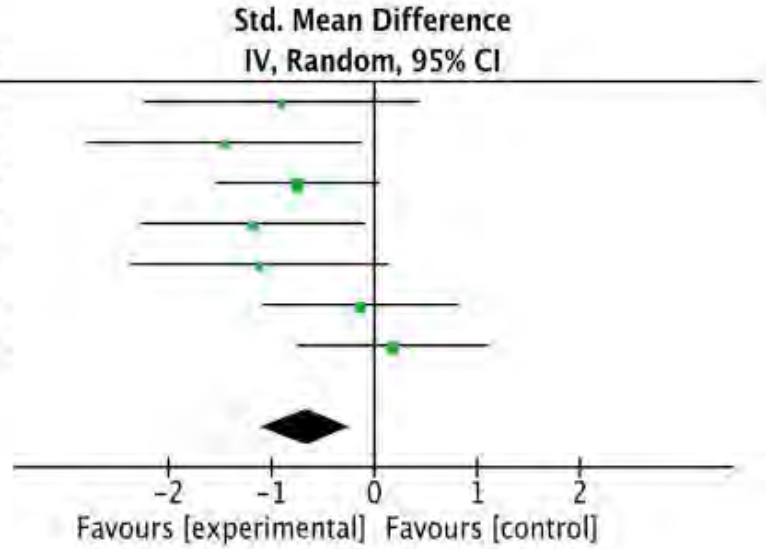
Total (95% CI)			**56**			**55**	**100.0%**	**-0.66 [-1.10, -0.22]**	

Heterogeneity: $Tau^2 = 0.06$; $Chi^2 = 7.15$, df = 6 (P = 0.31); $I^2 = 16\%$

Test for overall effect: Z = 2.97 (P = 0.003)



Wehmeyer et al. Front Neurol 2021

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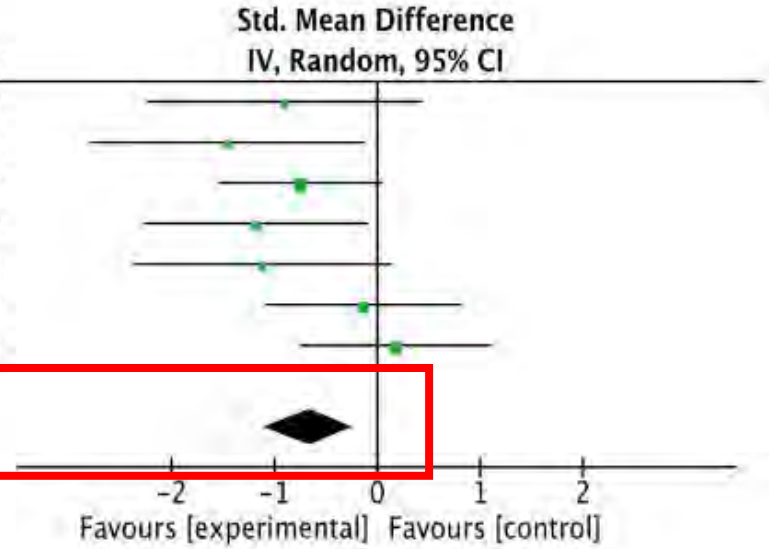

Wehmeyer et al. Front Neurol 2021

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What Can Neuromodulation Tell Us About Pathophysiology?

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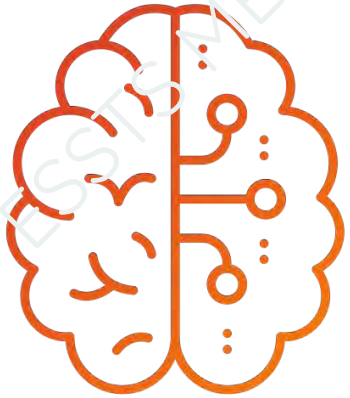
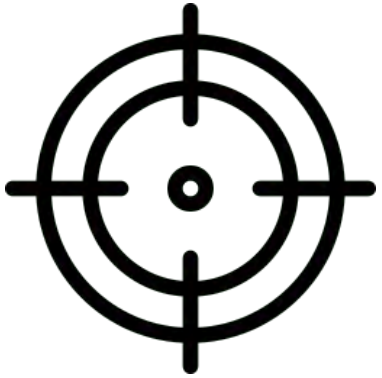
Symptom

Pathophysiology



Neuromodulation Target



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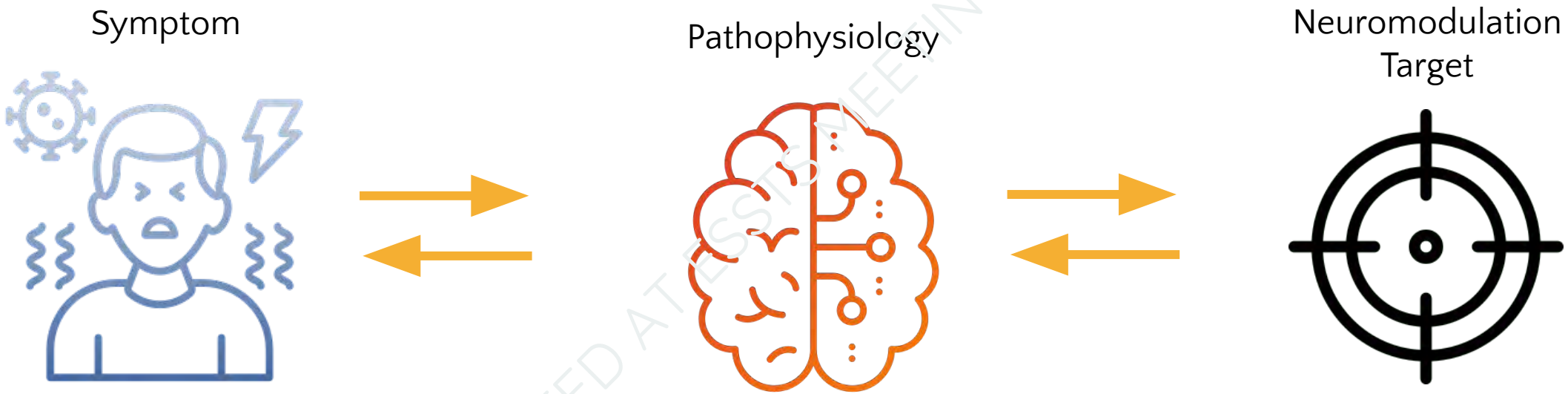
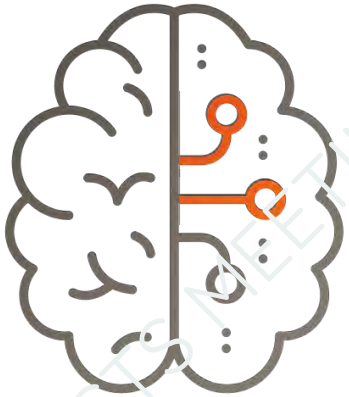


What Can Neuromodulation Tell Us About Pathophysiology?

Symptoms Improve

Brain Circuit 1



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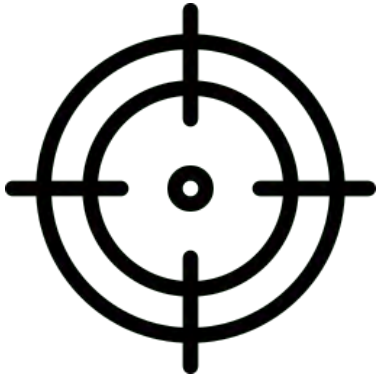

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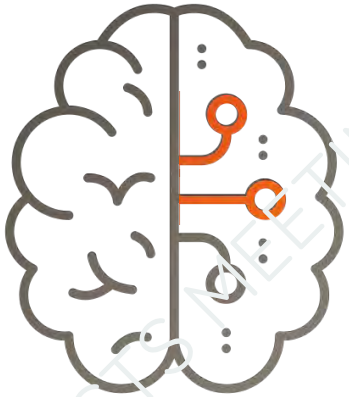

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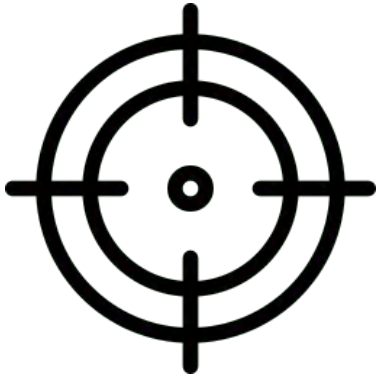
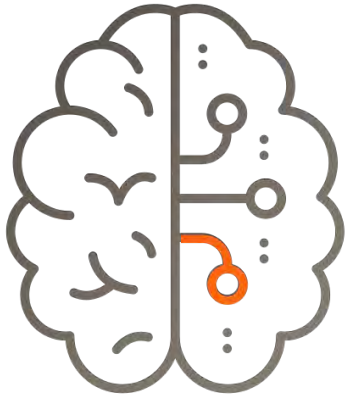


Symptoms Don't Improve

Brain Circuit 2



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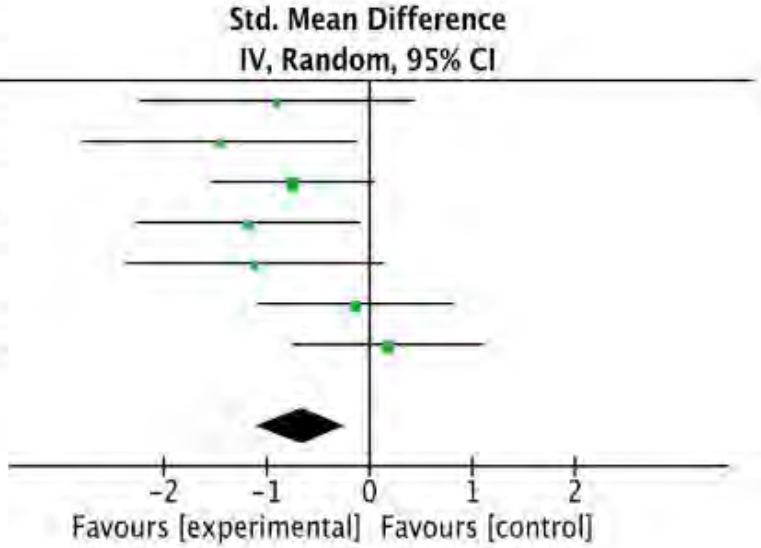

Wehmeyer et al. Front Neurol 2021

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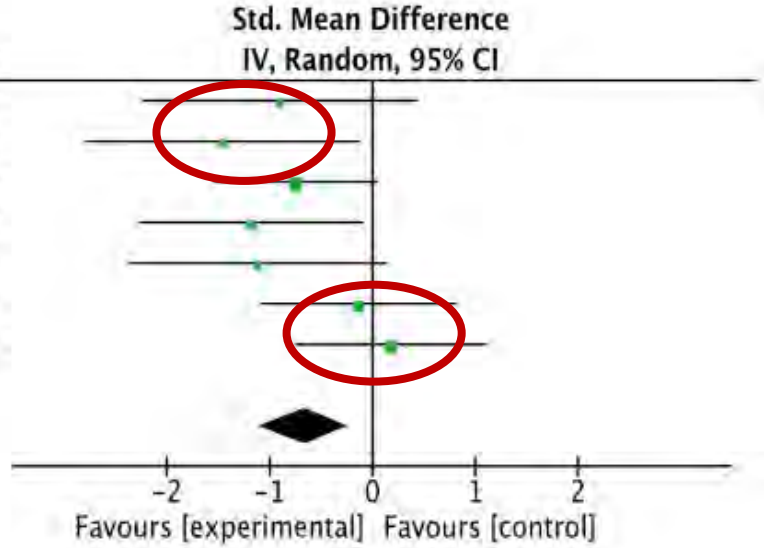

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Can Differences in Outcome be Explained By the Invidual Target Region or Network

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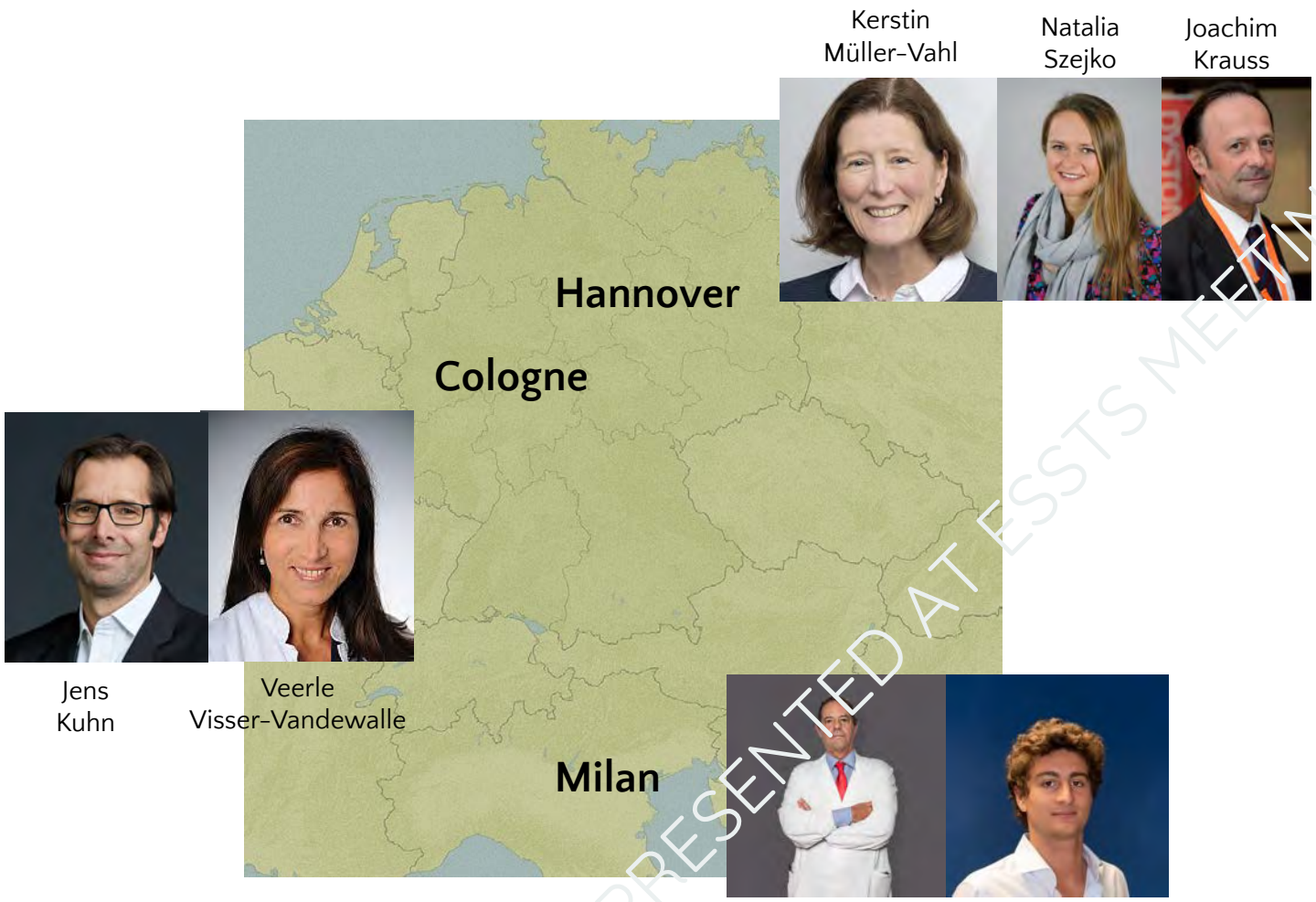

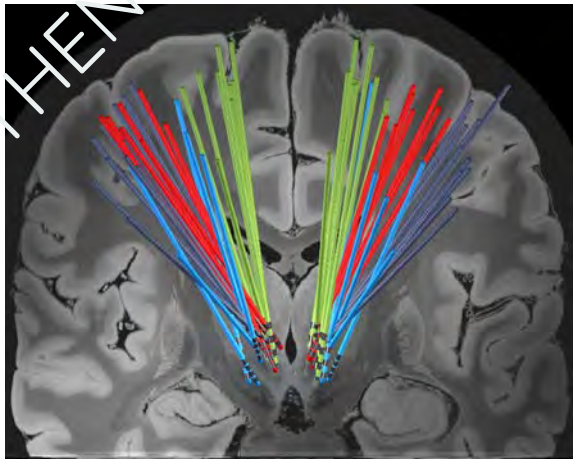

DBS outcome across three centers (N = 37)

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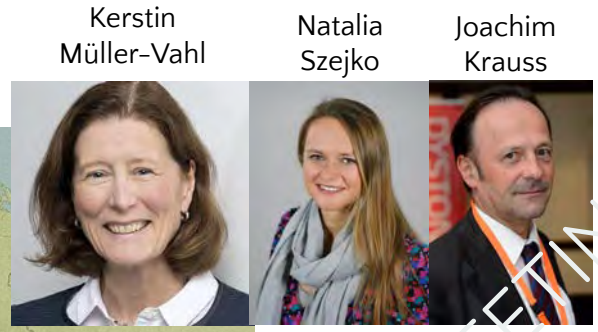


Kerstin Müller-Vahl

Natalia Szejko

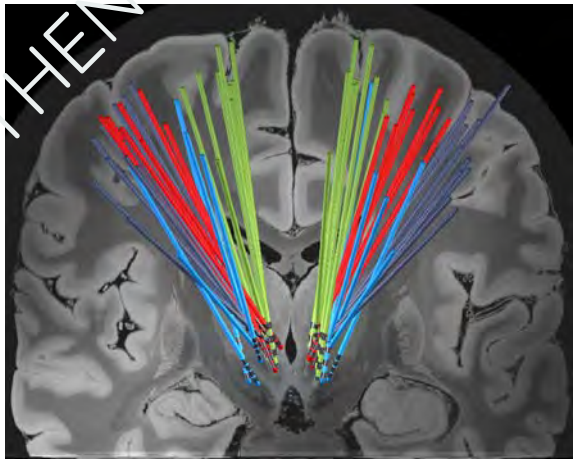
Joachim Krauss

Jens Kuhn

Veerle Visser-Vandewalle

Domenico Servello

Tommaso Galbiati



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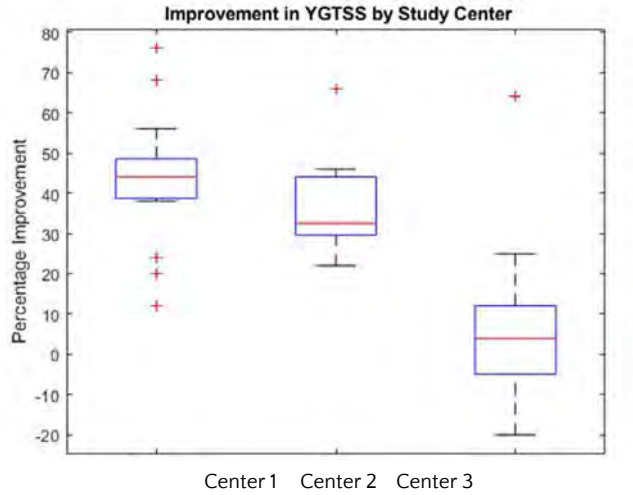
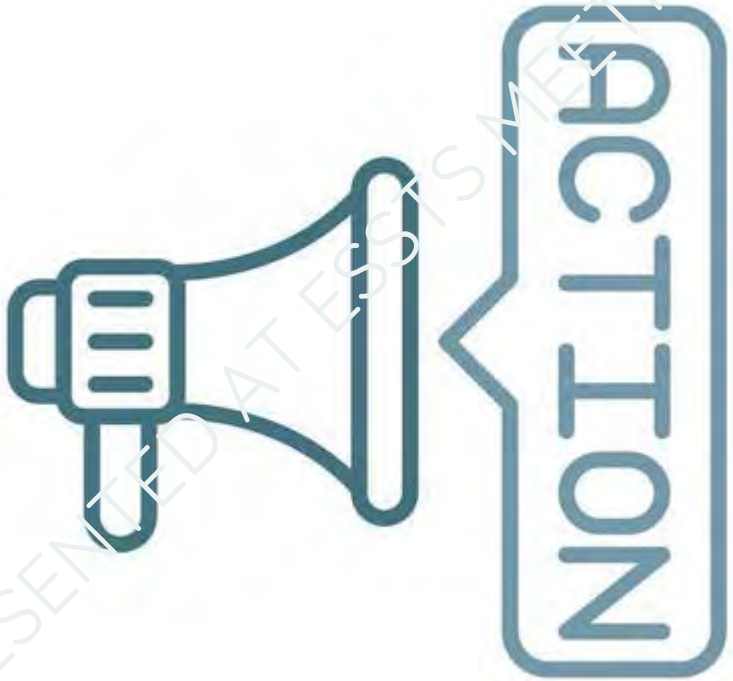
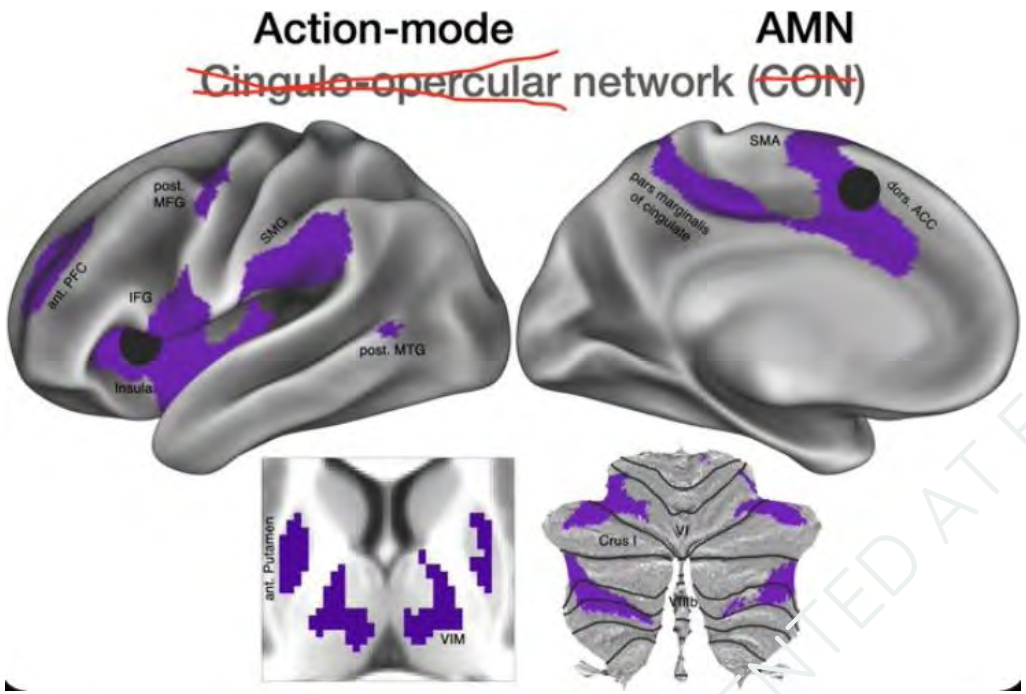


Action-Related Brain Networks

Excurse



The Cinculo-Opercular, or Action-Mode-Network



Dosenbach et al., Nat Rev Neurosc 20254

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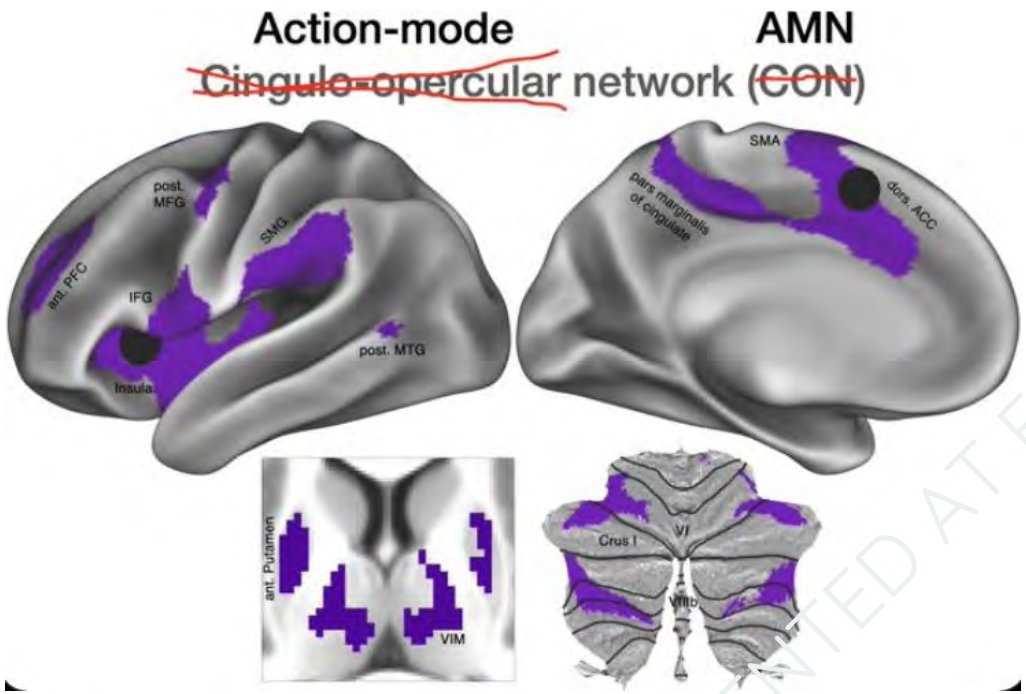

Dosenbach et al., Nat Rev Neurosc 20254

The Action-Mode Network is active during ....

- Pain
- Errors
- Hunger
- Action Plans
- Heightened Attention

A new Action Network:
The Somato-Cognitive Action Network (SCAN)

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Article | Open access | Published: 19 April 2023

A somato-cognitive action network alternates with effector regions in motor cortex

Evan M. Gordon ✉, Roselyne J. Chauvin, Andrew N. Van, Aishwarya Rajesh, Ashley Nielsen,

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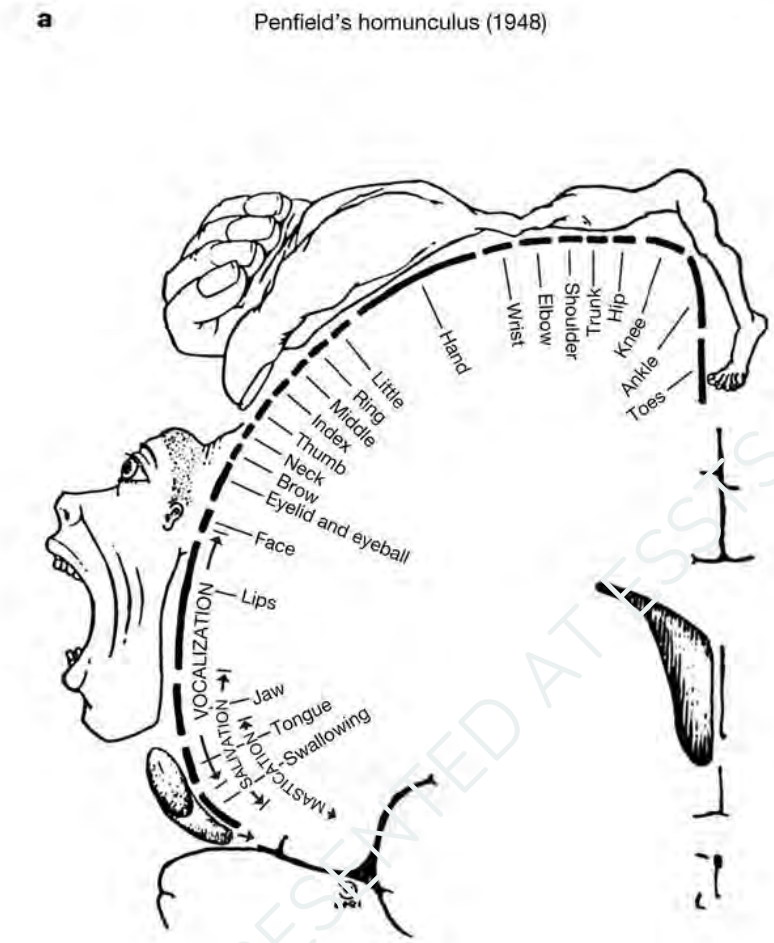

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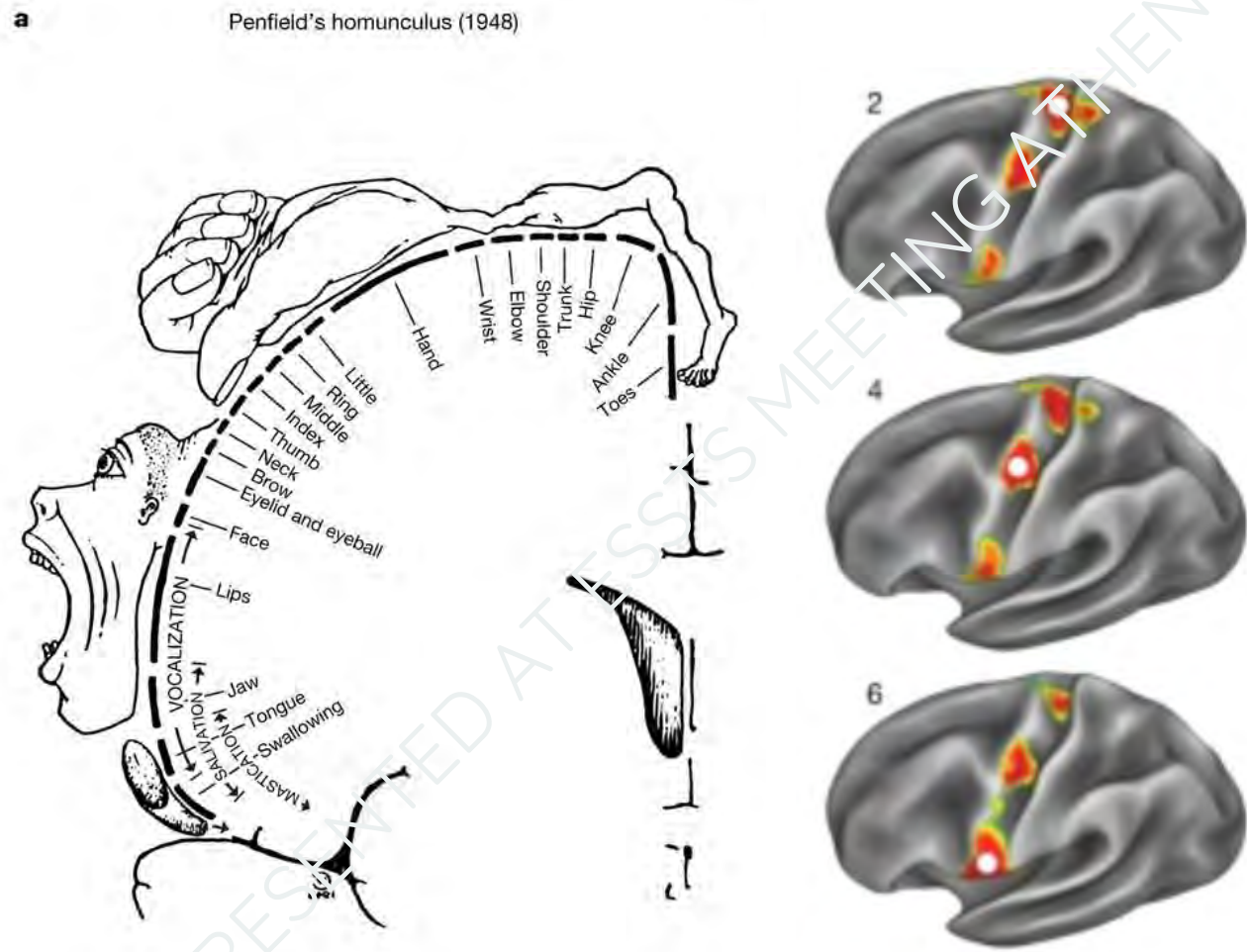

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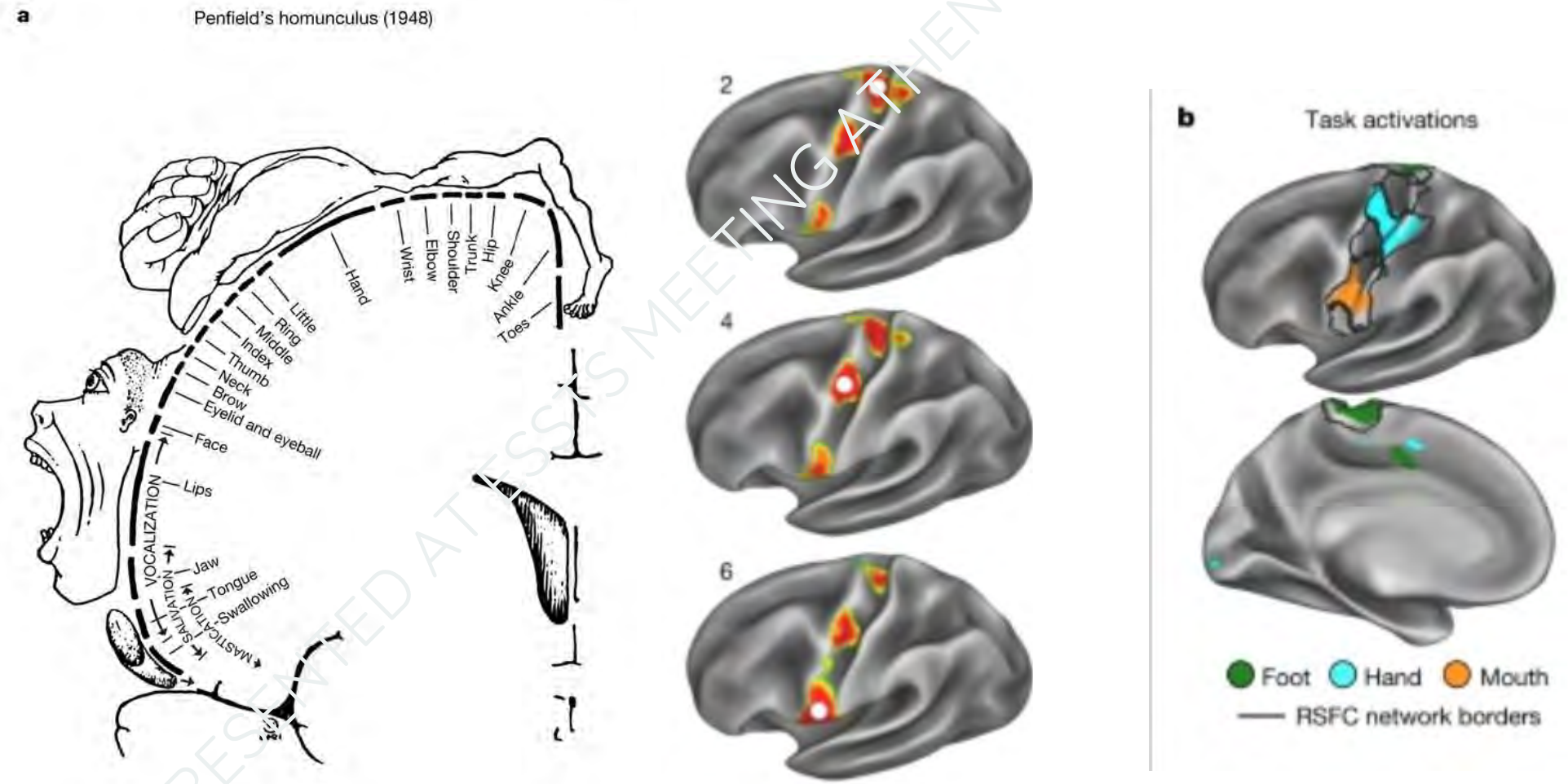
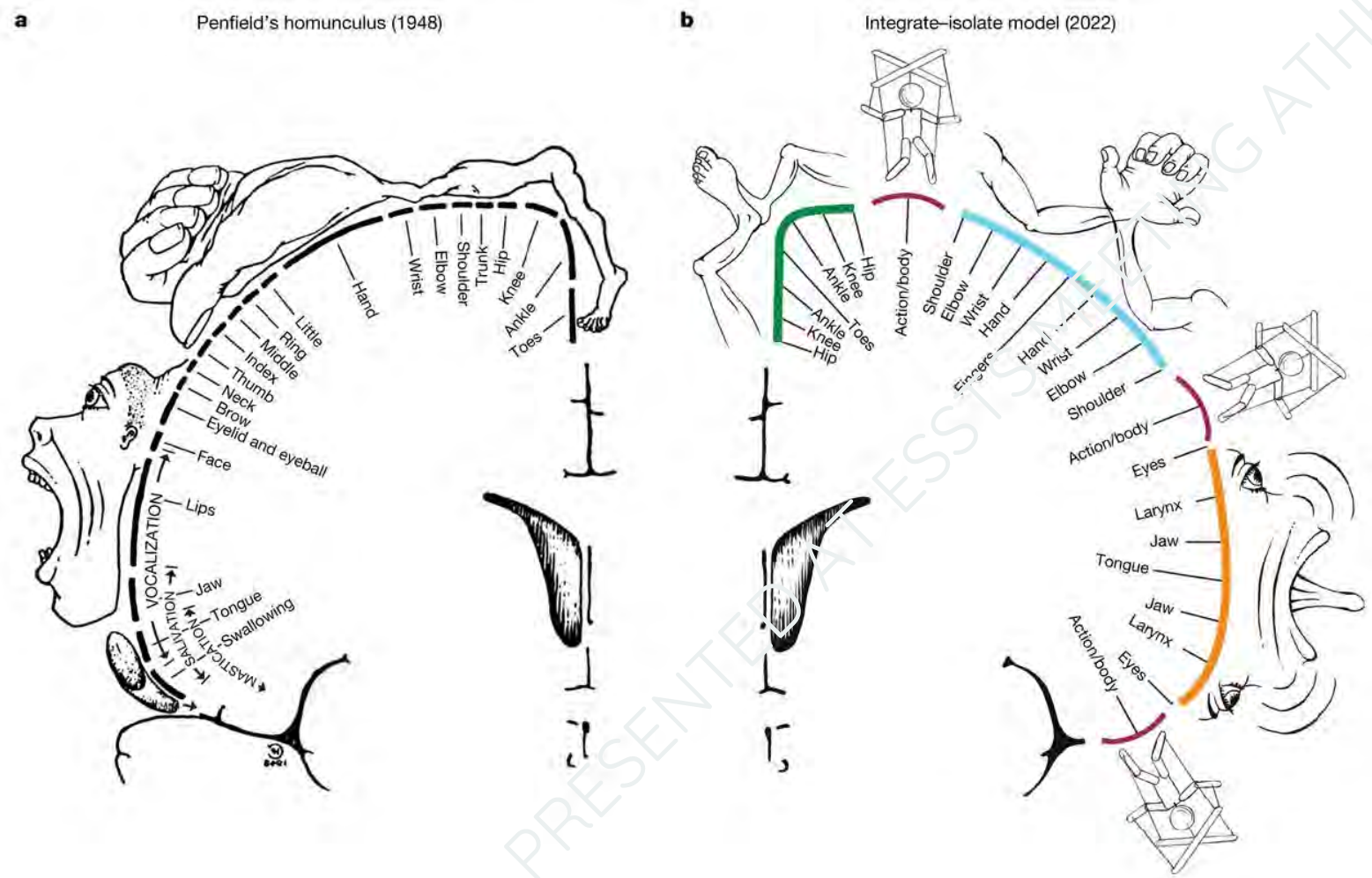


Gordon et al, Nature 2023

The Somato-Cognitive Action Network (SCAN) complements the Action-Mode Network



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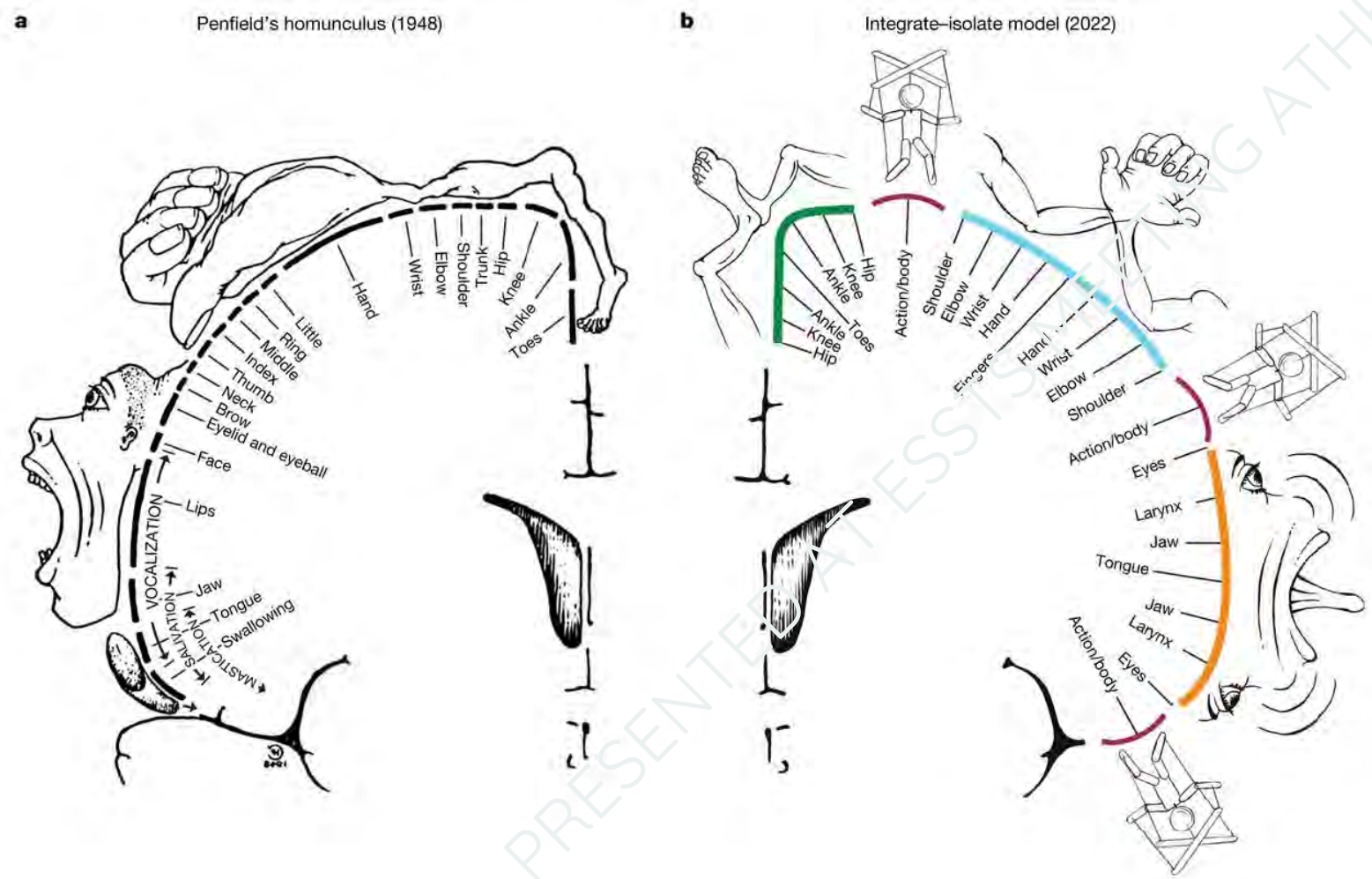

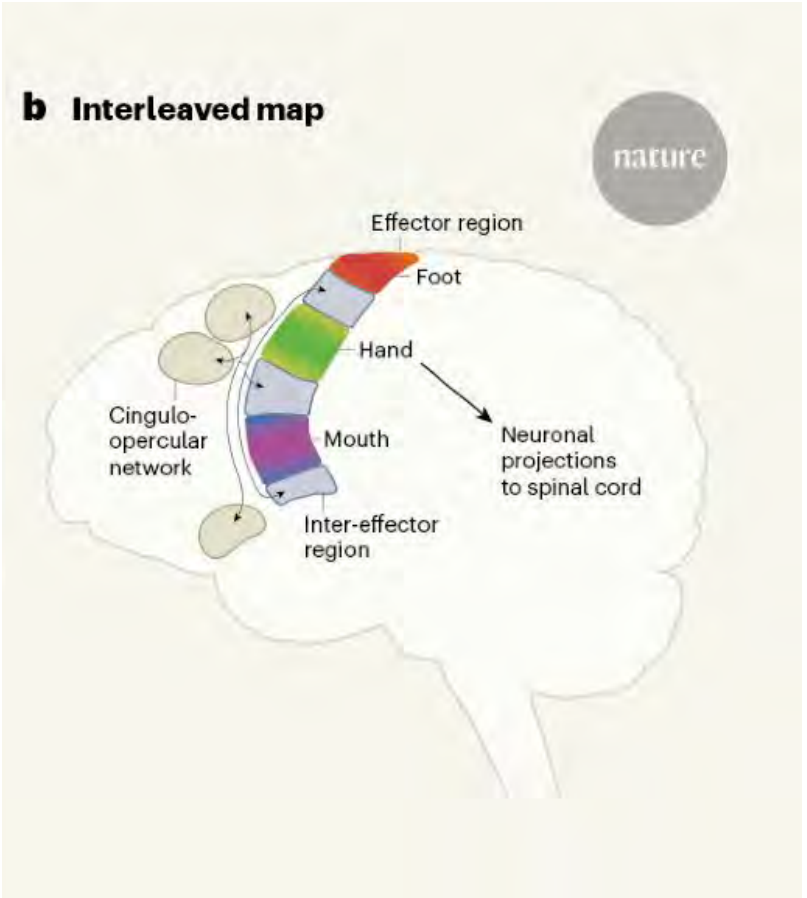

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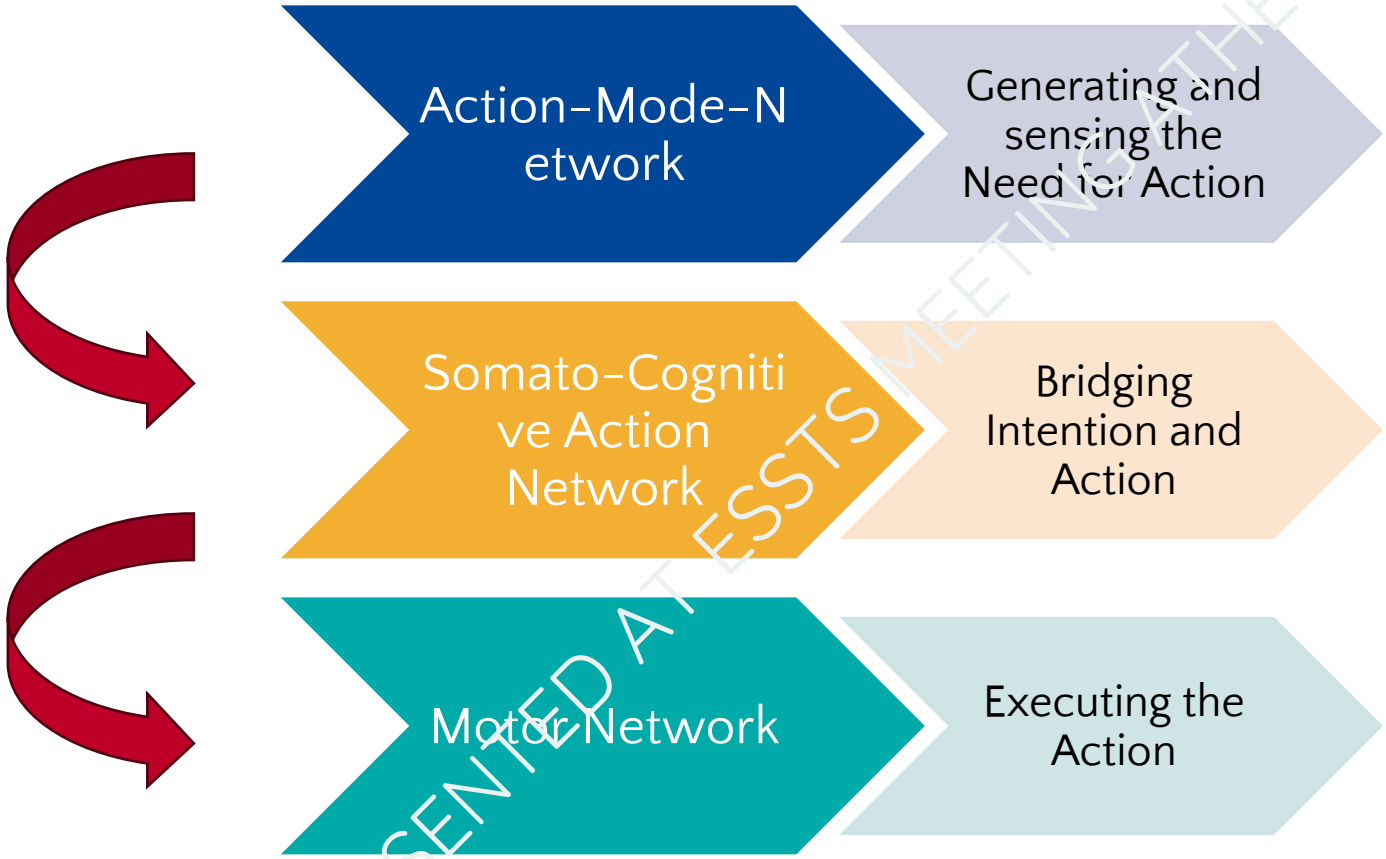
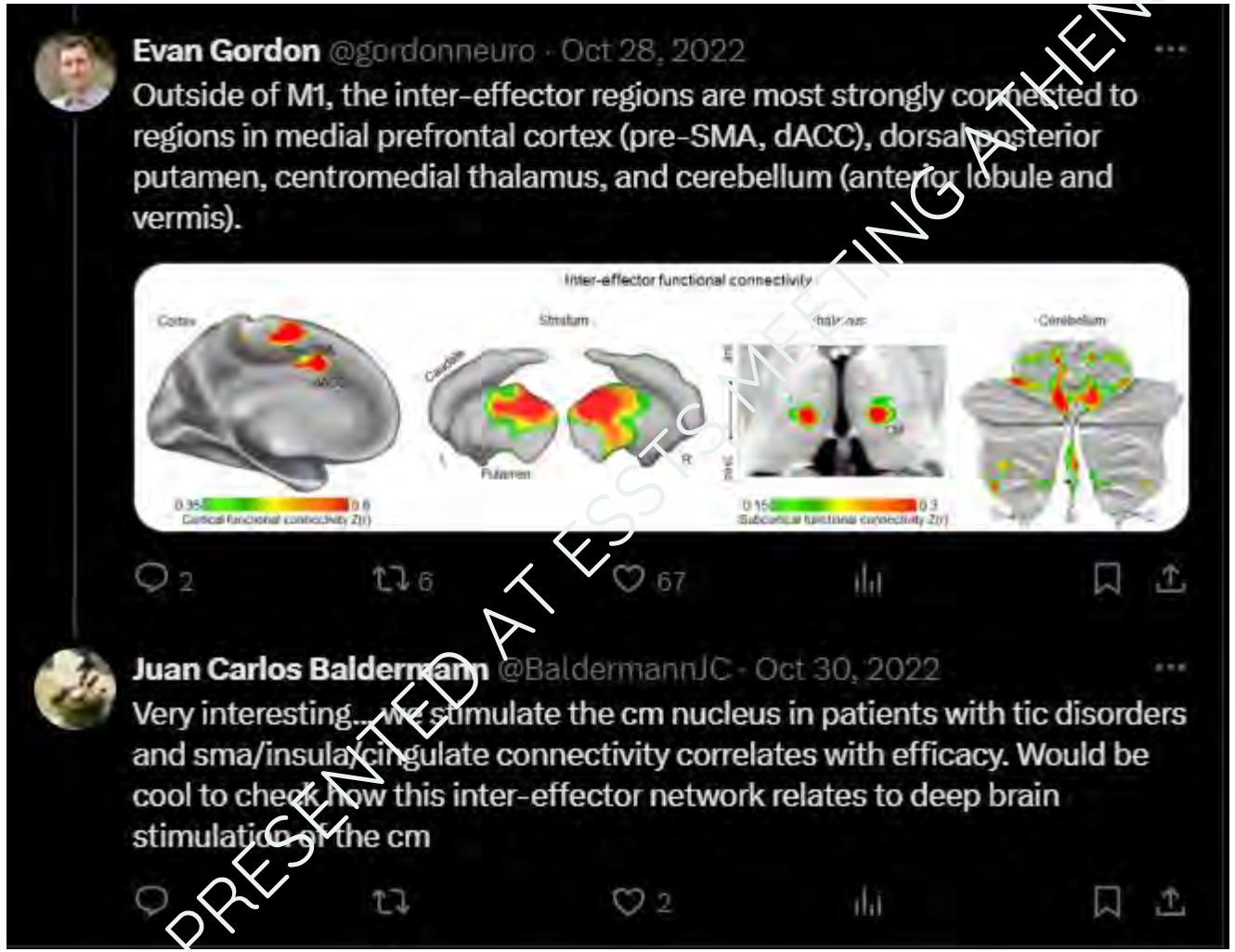
Summary: The Cascade of Action through Brain Networks



Adapted from D'Andrea et al., bioRxiv 2023

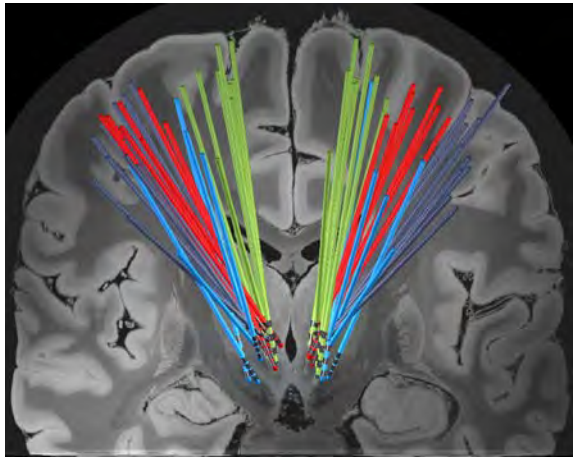
Are these Action-Networks Important for Tics?



Twitter Screenshot, 2022

Does Connectivity of Brain Stimulation with Functional Action Networks Explain Outcomes?

Reconstruction of DBS Electrodes in Common Space



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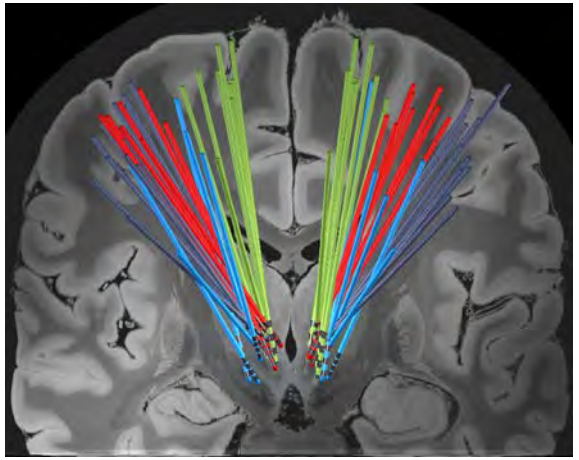
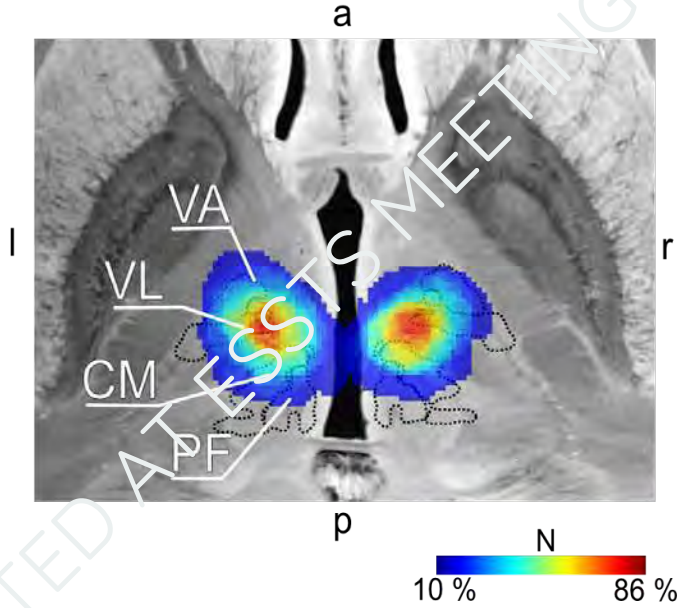


Modelling Stimulation Sites



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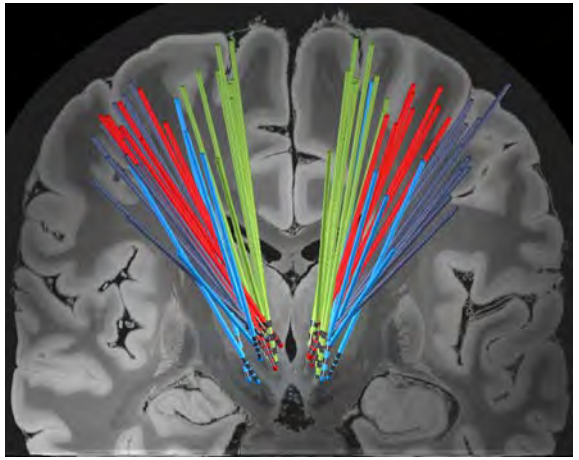

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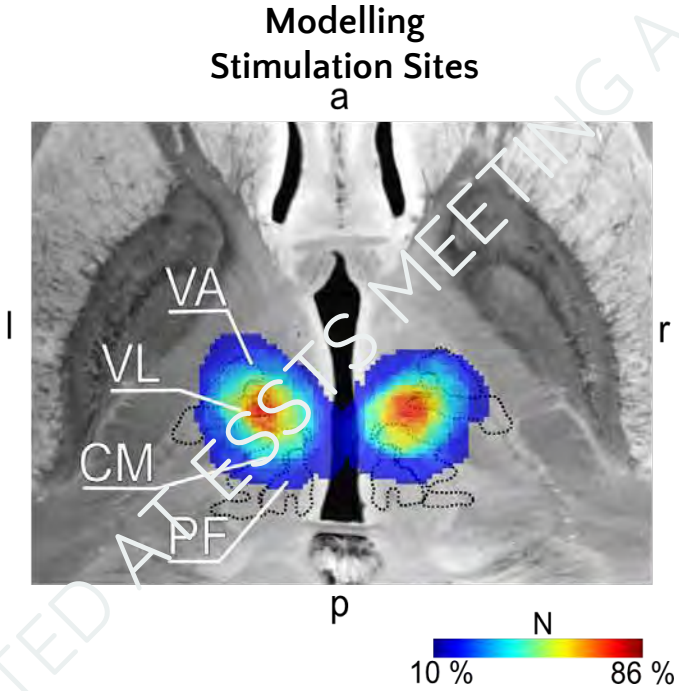
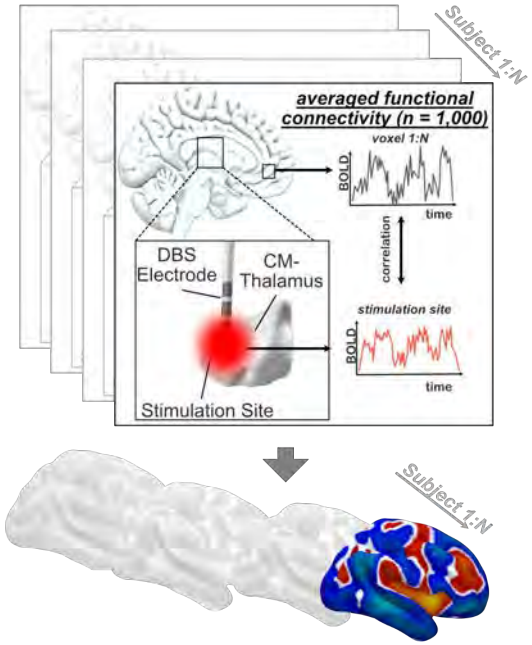
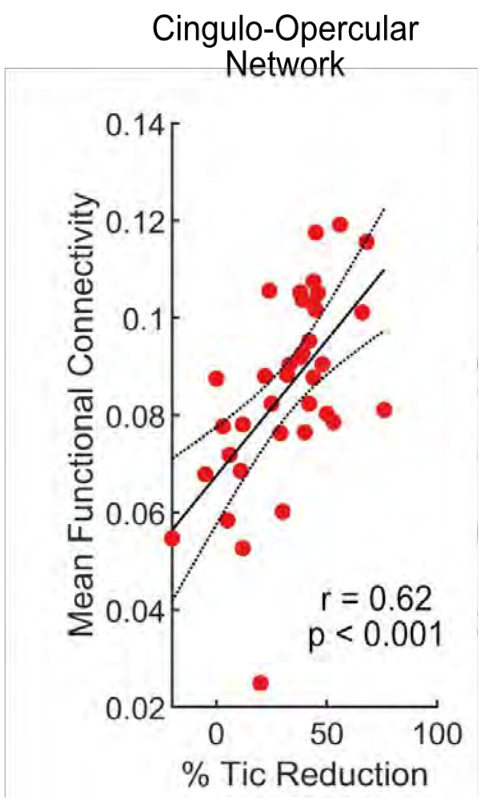
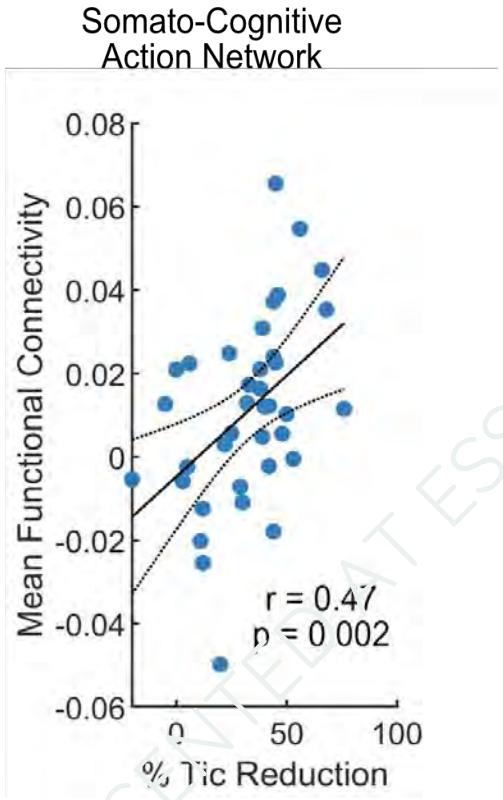


Modelling the Stimulated Functional Connectivity



Connectivity of DBS sites with CON & SCAN Explain Tic Reduction





Baldermann et al., Nat Comm 2024

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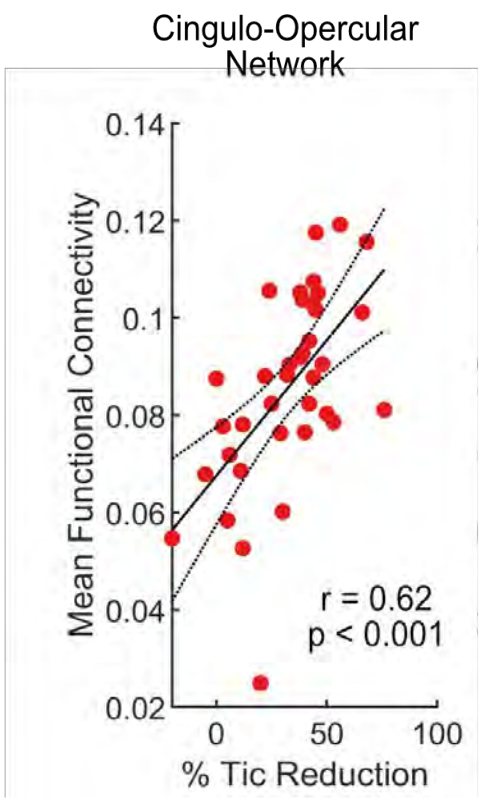
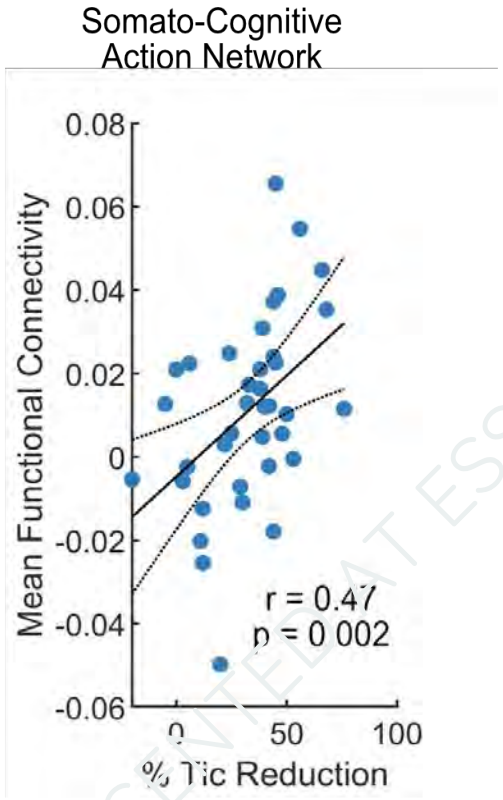
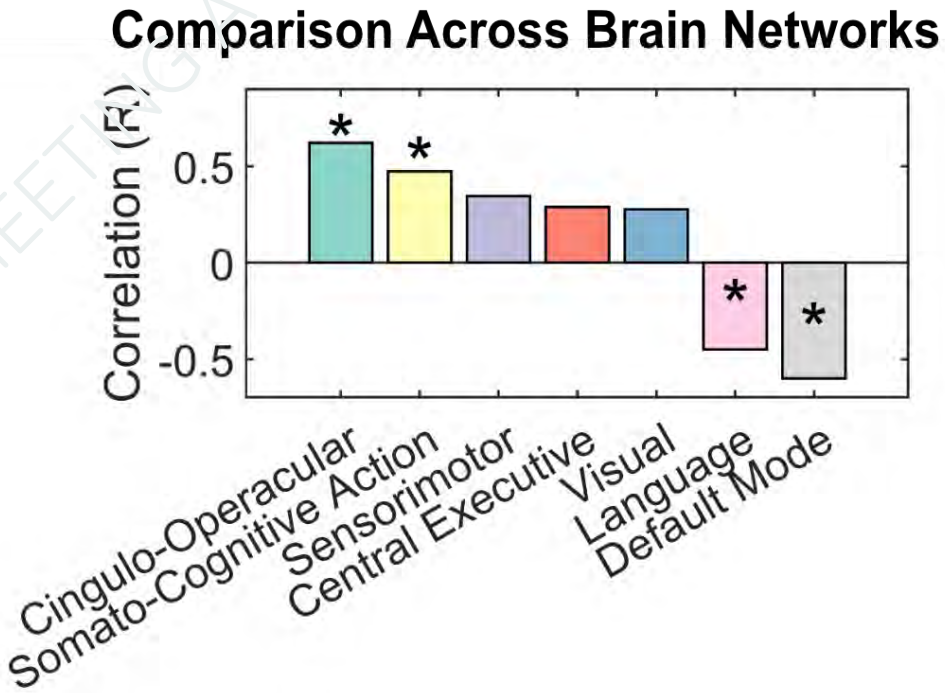
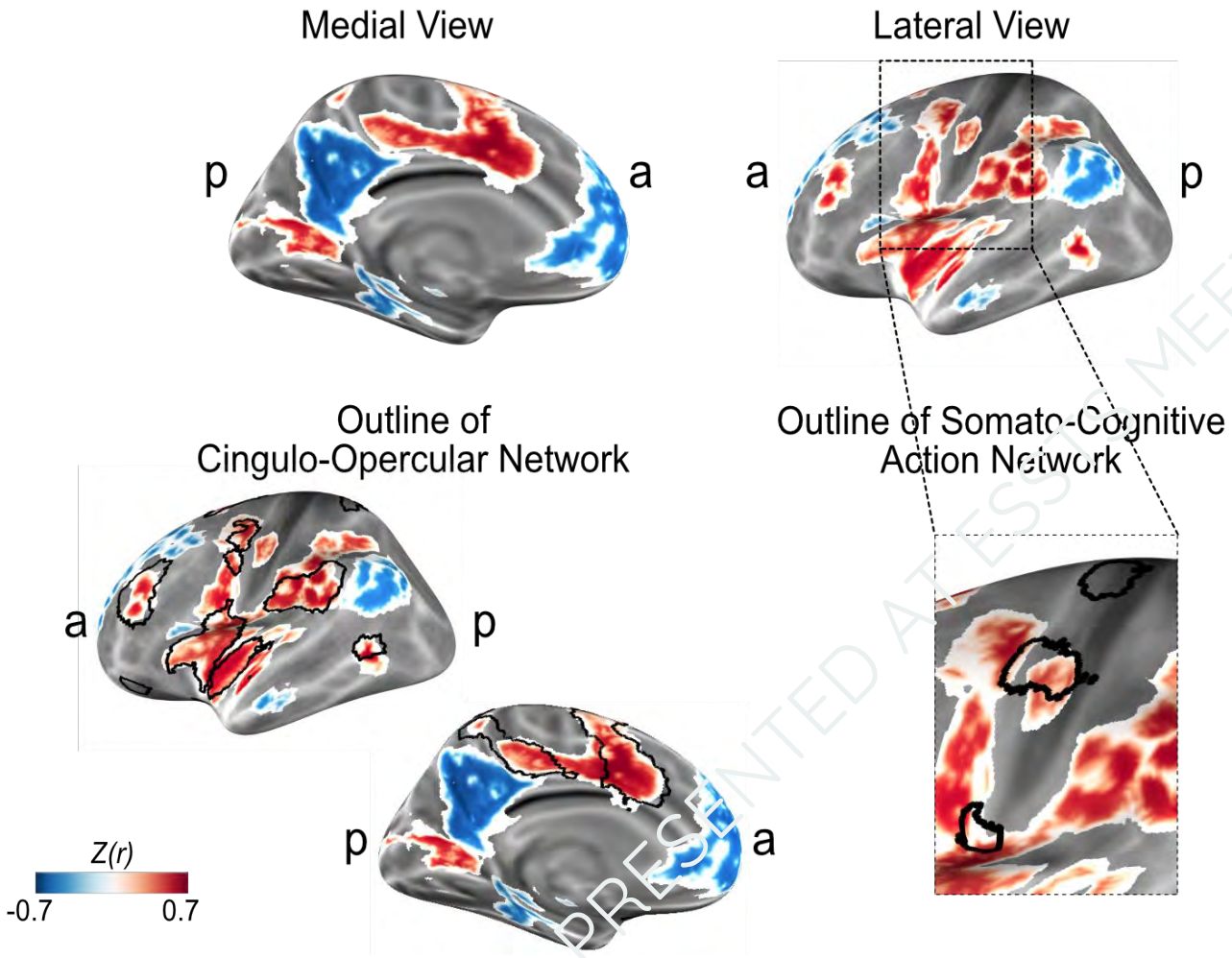






Baldermann et al., Nat Comm 2024

Whole Brain Analysis: Connectivity with CON and inferior/middle inter-effector region drive effects



Baldermann et al., Nat Comm 2024

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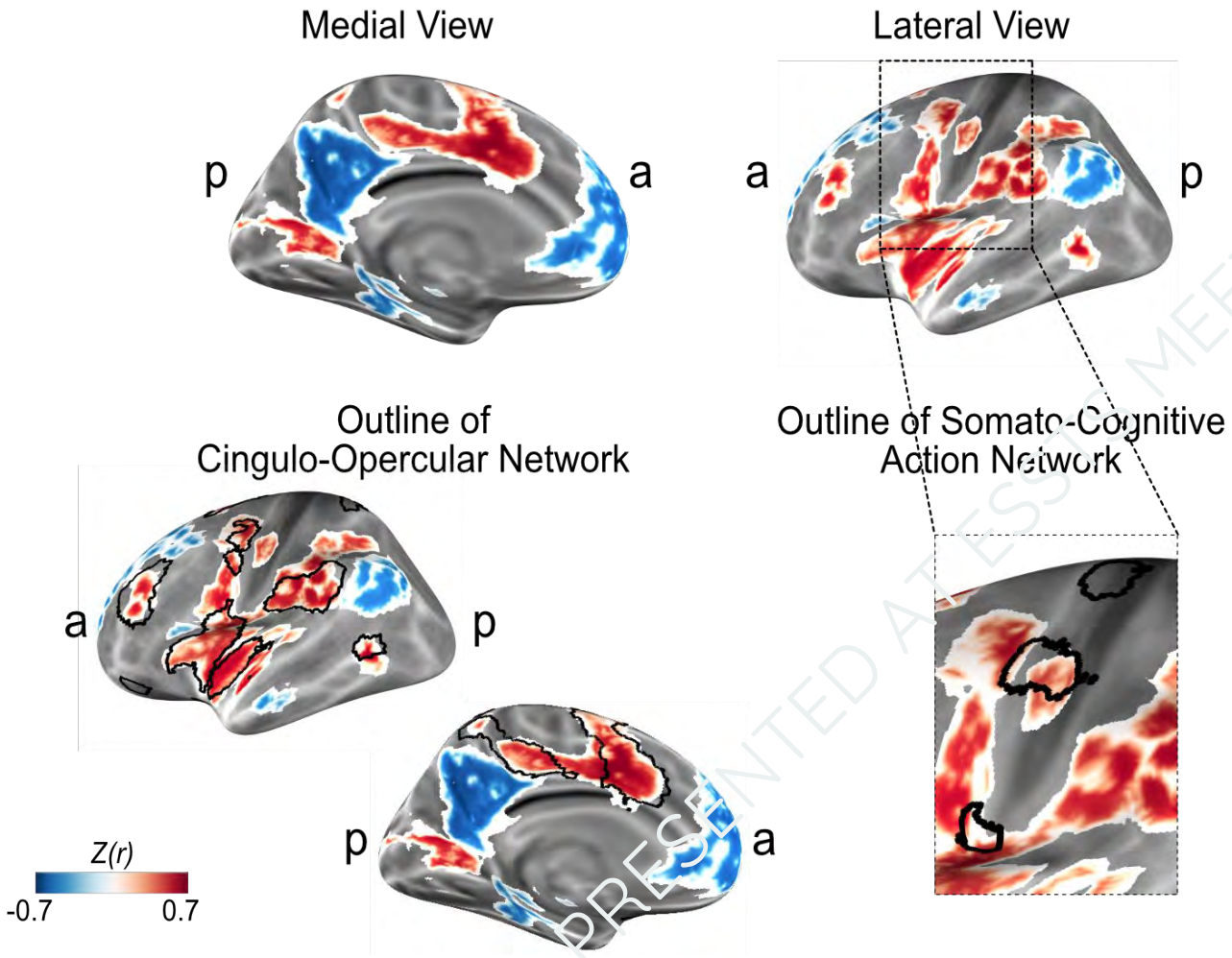

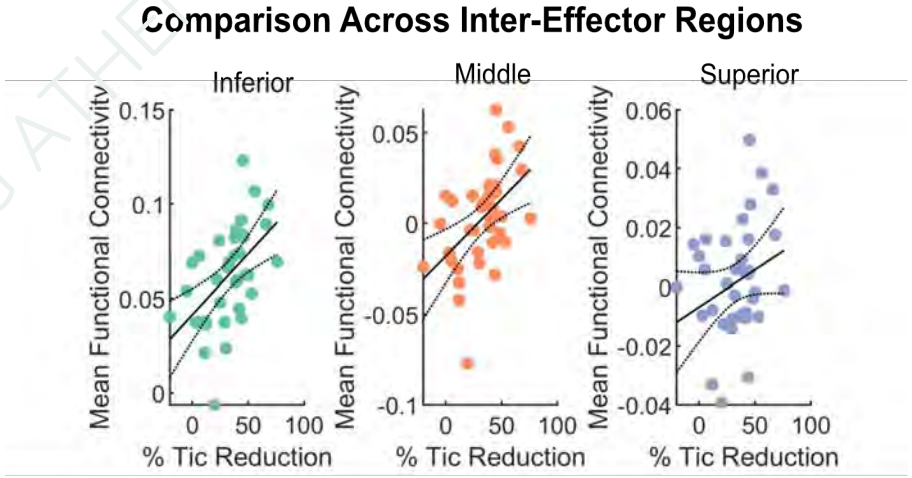

r = 0.596
p < 0.001

r = 0.513
p < 0.001

r = 0.276
p = 0.052

Baldermann et al., Nat Comm 2024

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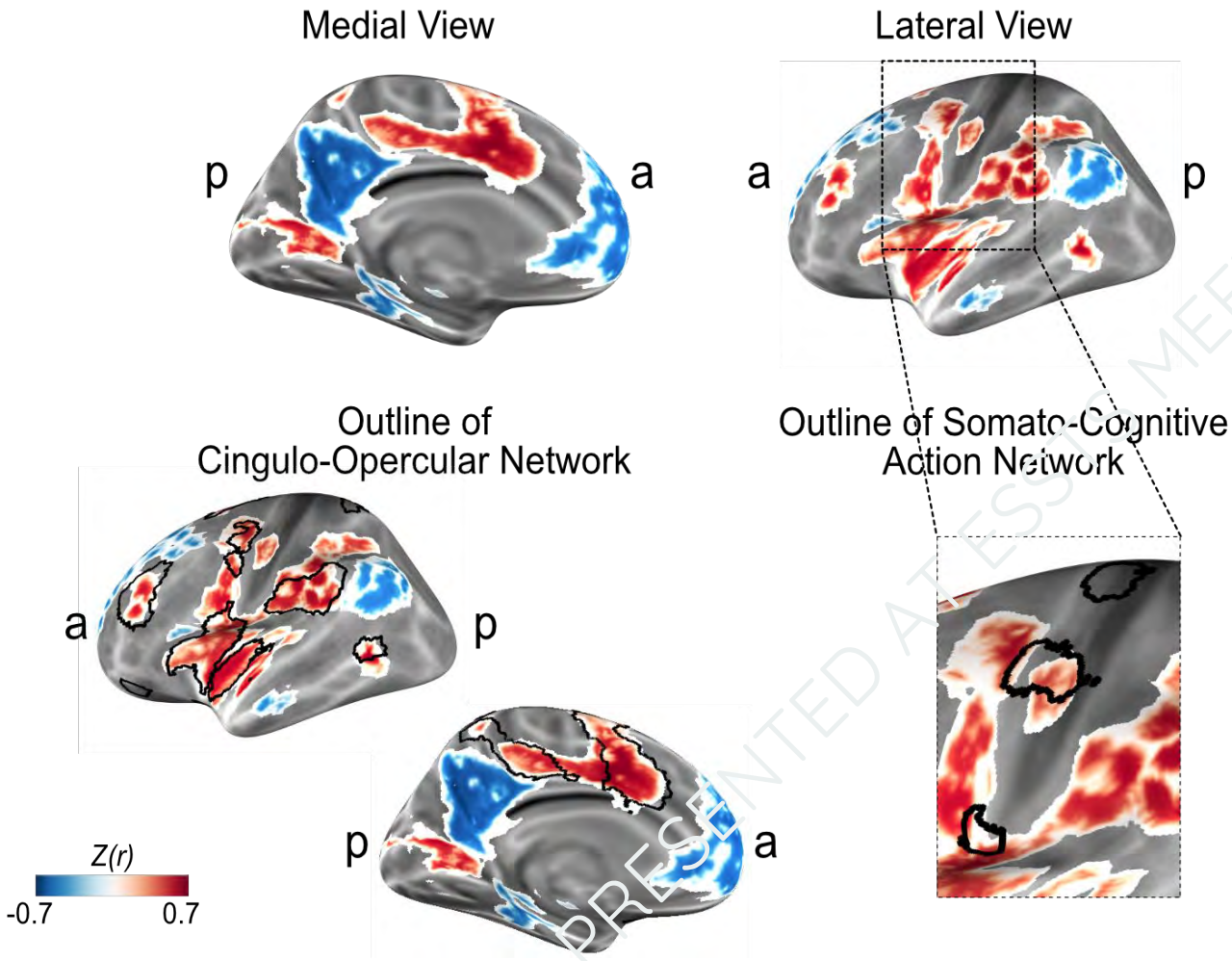
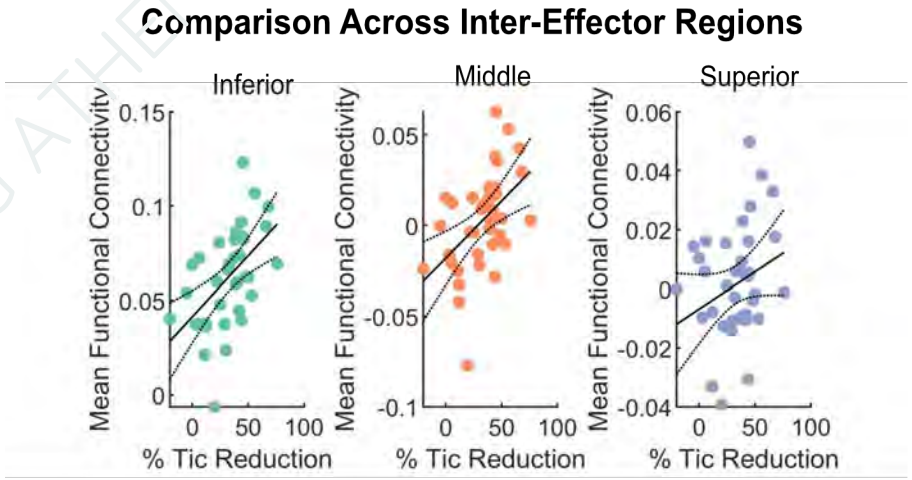
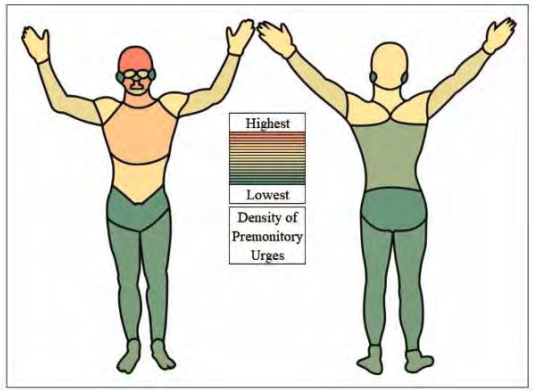


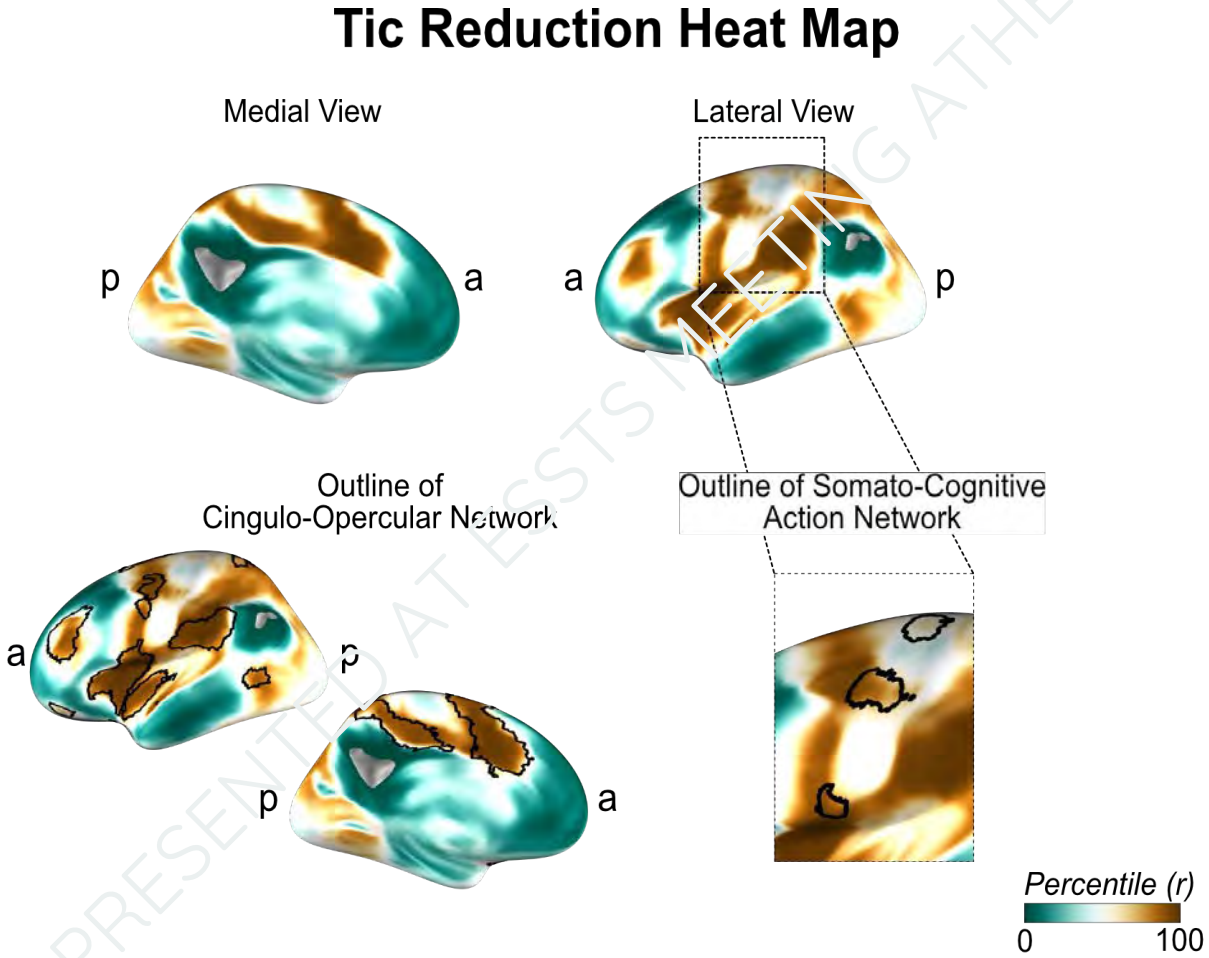




Essing et al., J Mov Dis 2022

Baldermann et al., Nat Comm 2024

Tic Reduction Heat Map: Potential Cortical Neuromodulation Targets Derived from DBS



Baldermann et al., Nat Comm 2024

Replication in GTS-DBS Registry Data

Baldermann et al., Nat Comm 2024

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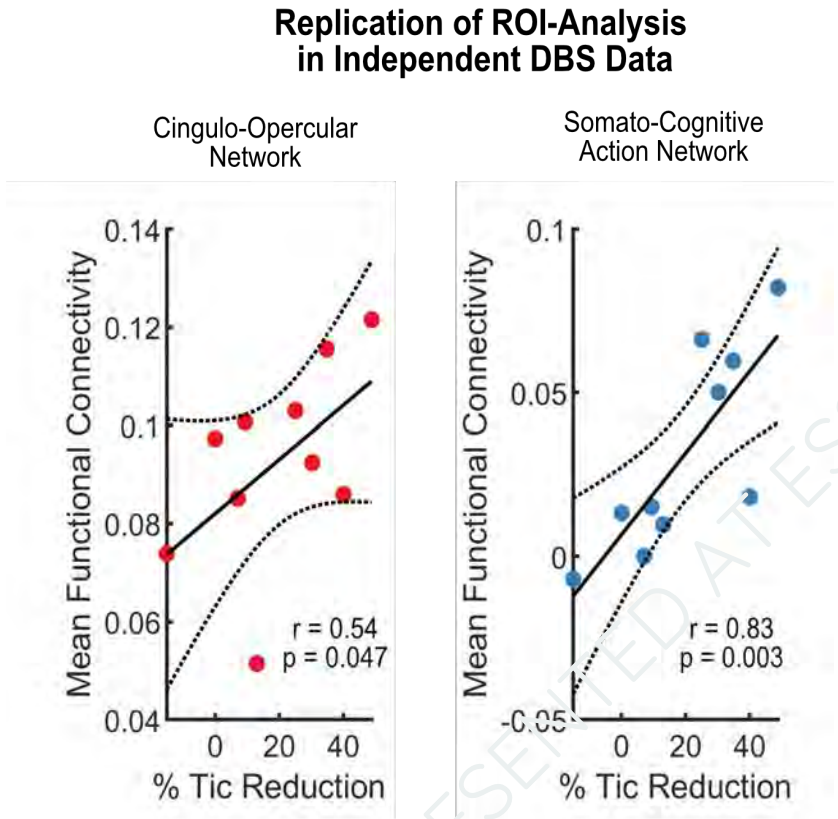

Baldermann et al., Nat Comm 2024

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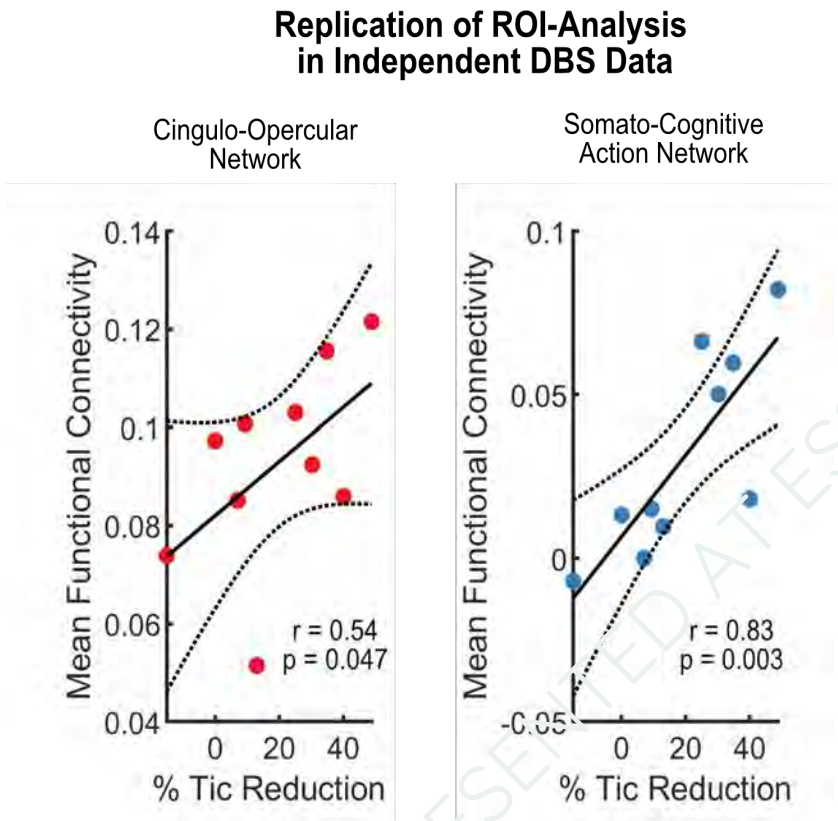
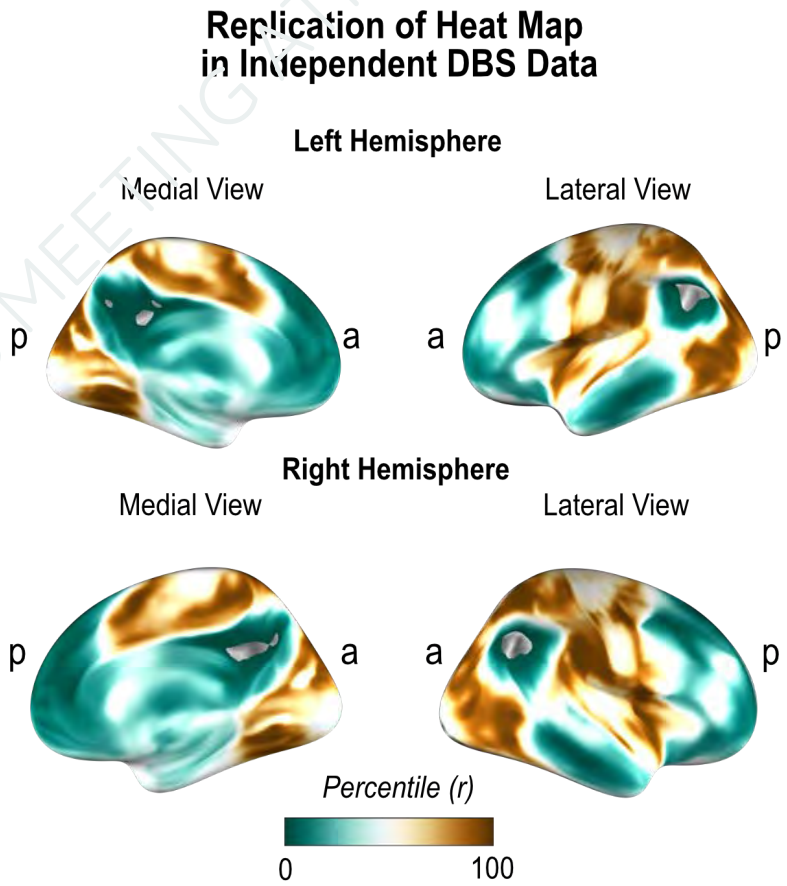




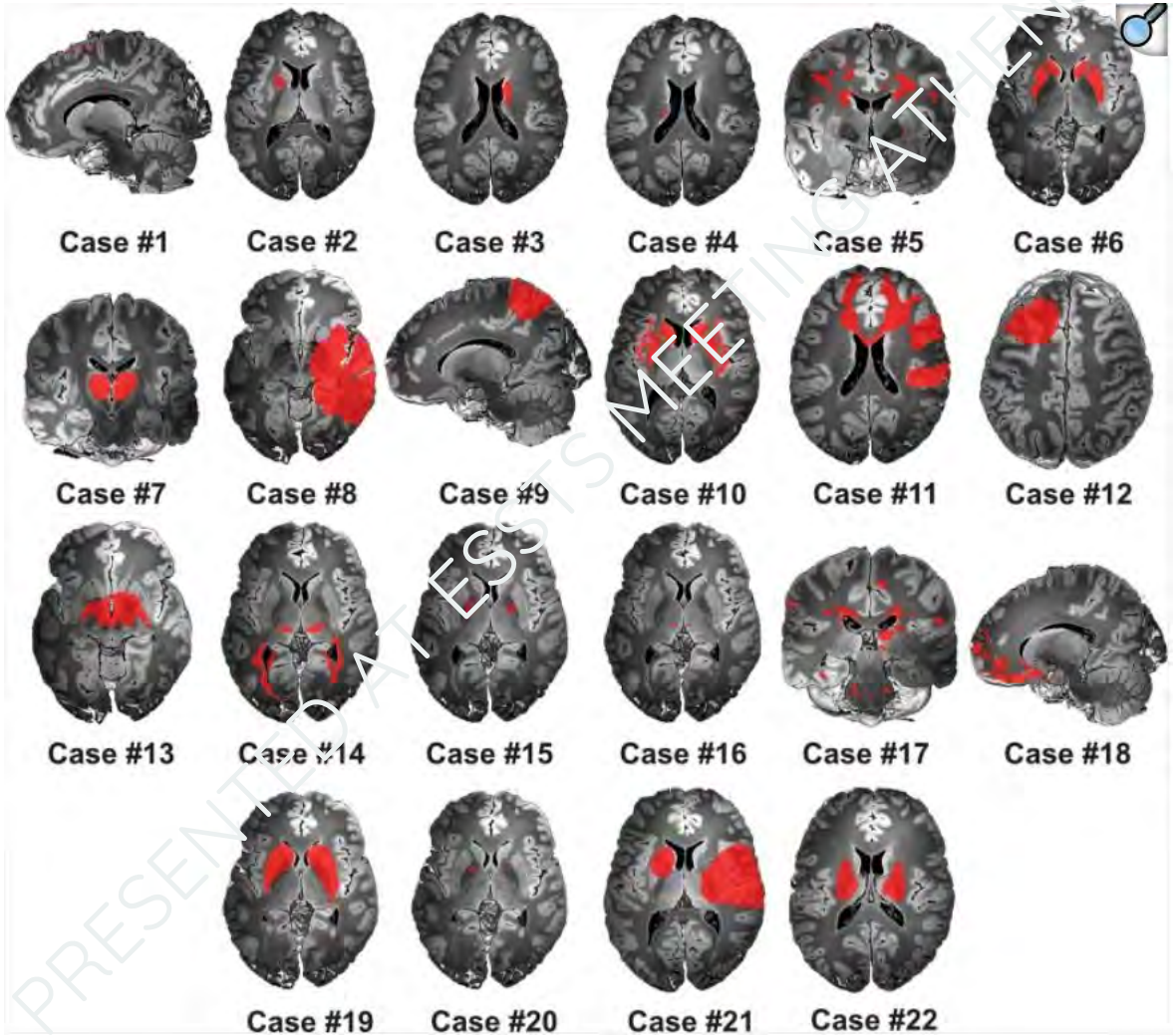
Baldermann et al., Nat Comm 2024

Replication In Lesion Network Map of Tic-inducing brain lesions (N = 22)


Christos Ganos


Andreas Horn


Bassam Al-Fatly

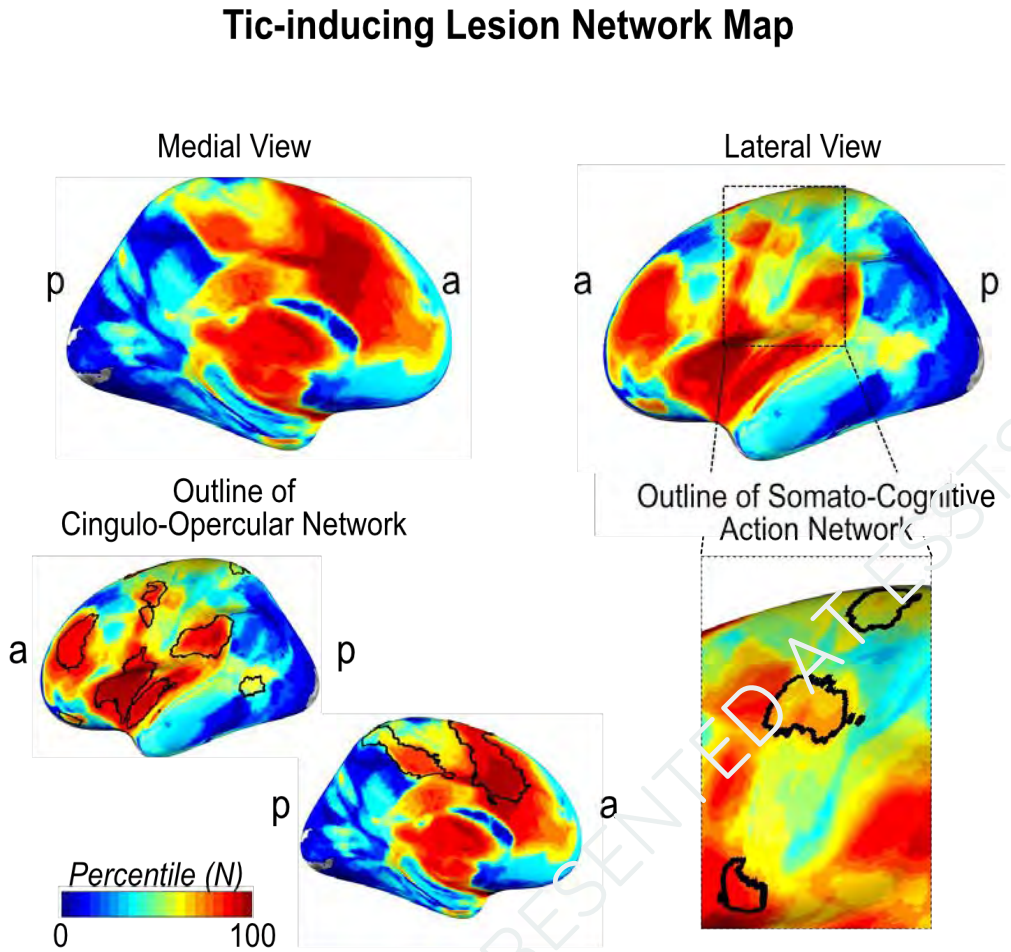


Ganos et al., Brain 20222

Replication In Lesion Network Map of Tic-inducing brain lesions (N = 22)



Christos Ganos Andreas Horn Bassam Al-Fatly



Baldermann et al., Nat Comm 2024

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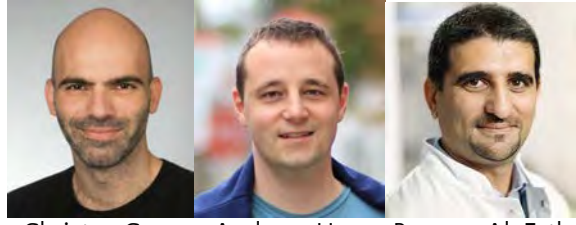

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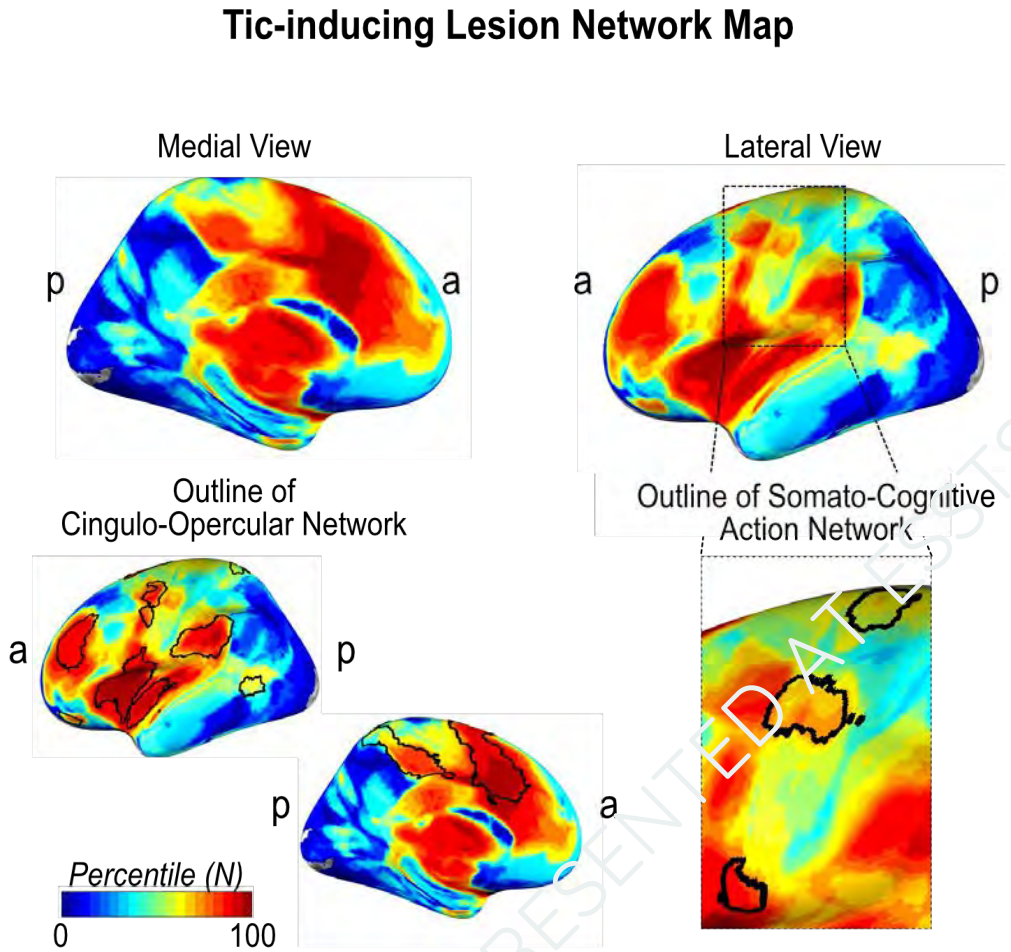

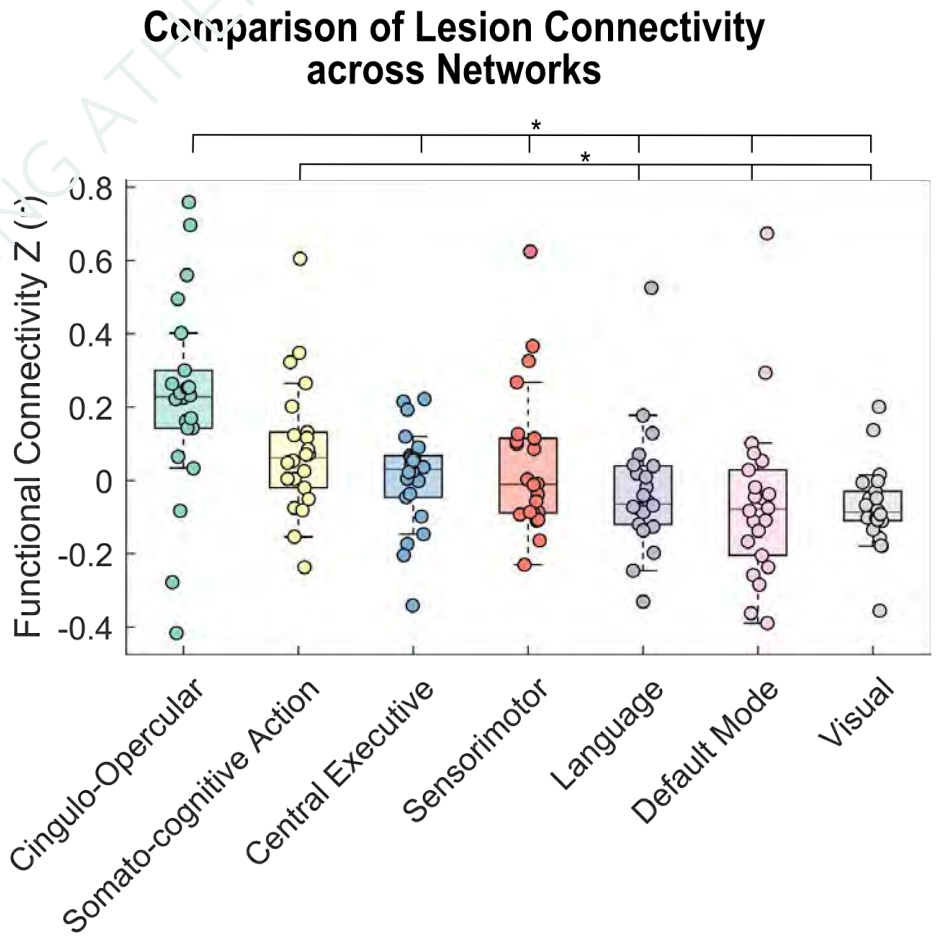

Baldermann et al., Nat Comm 2024

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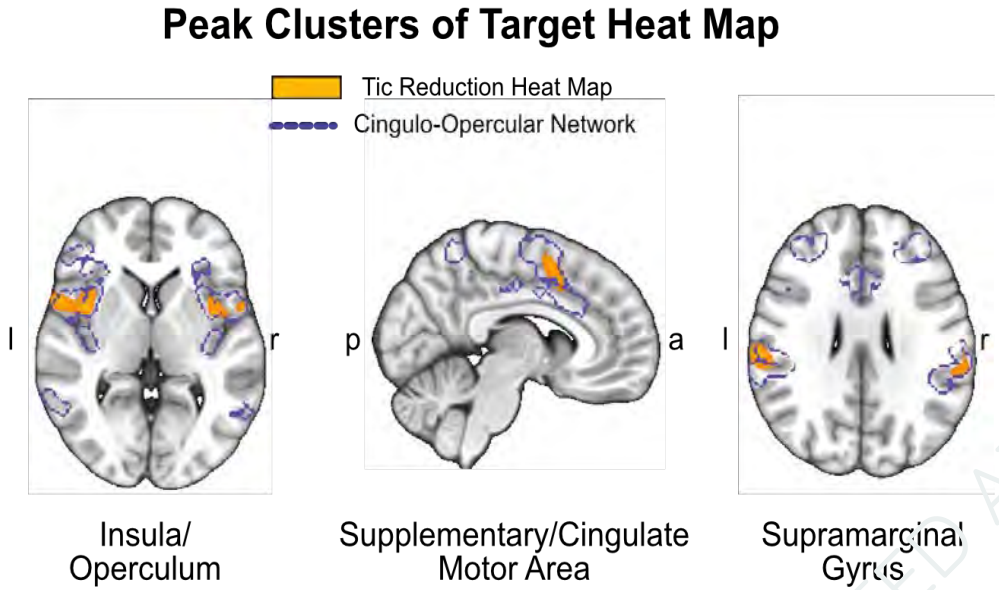
Tic Reduction Heat Map Matches General Urge Activity



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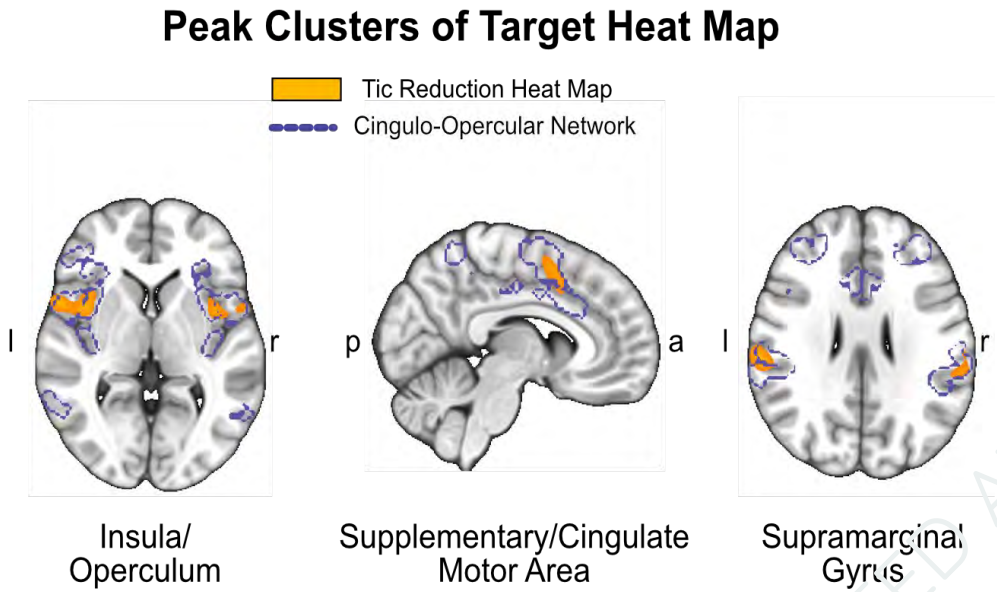
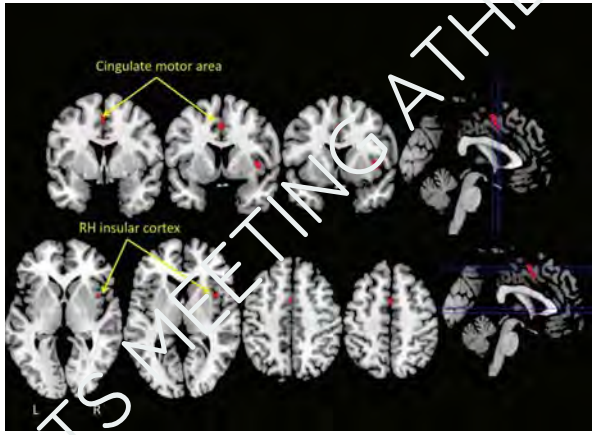
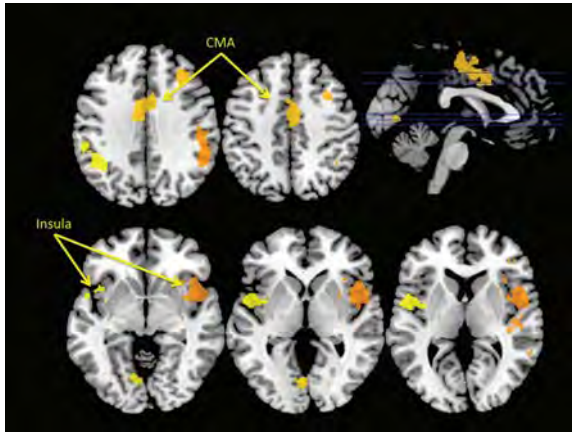


ALE: Urge to Swallow and Micturate



Urge to Yawn



Jackson et al., Cog Neurosc 2011

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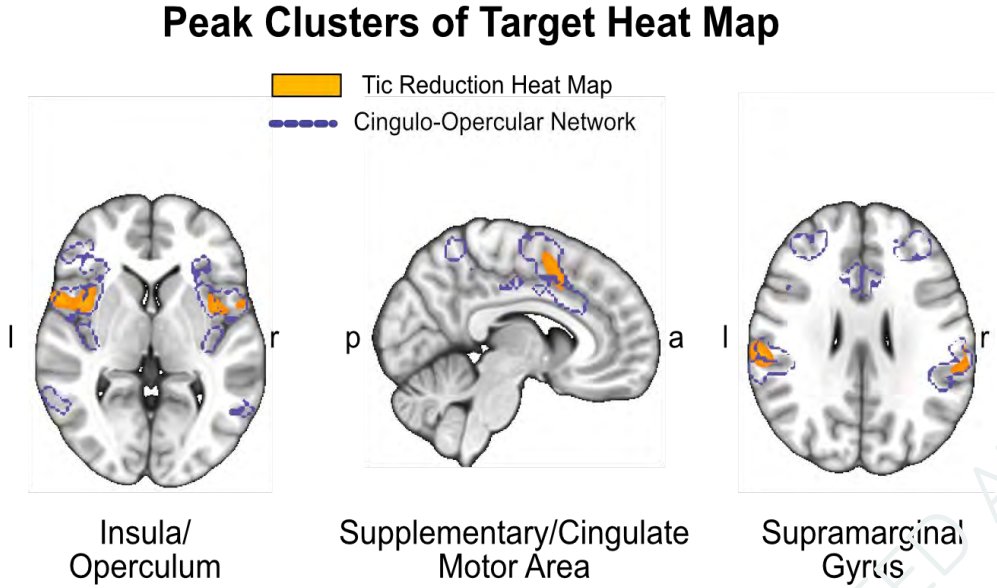

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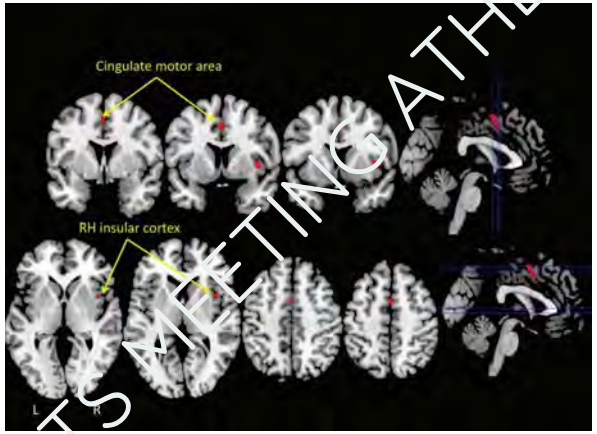
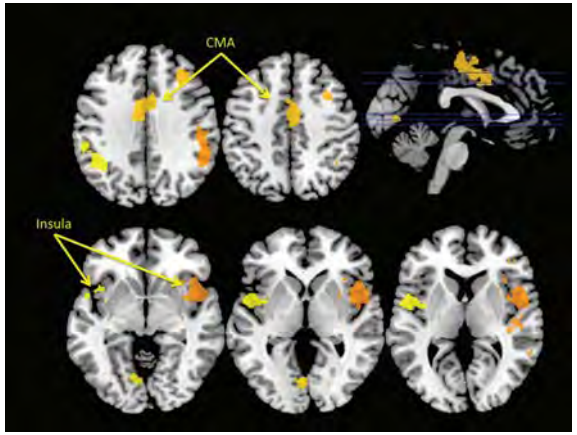
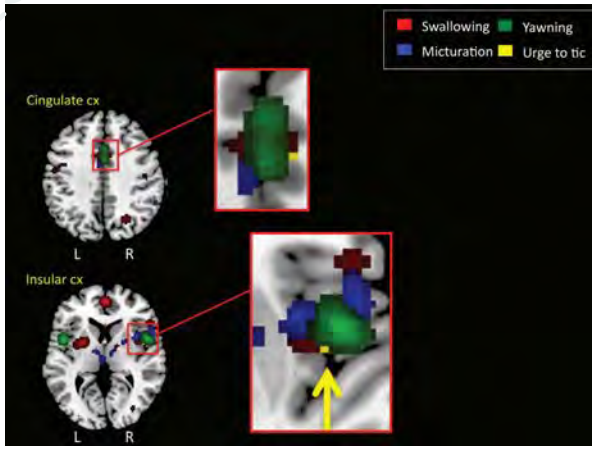


Urge to Yawn



Overlap with Urge to Tic Activity



Jackson et al., Cog Neurosc 2011

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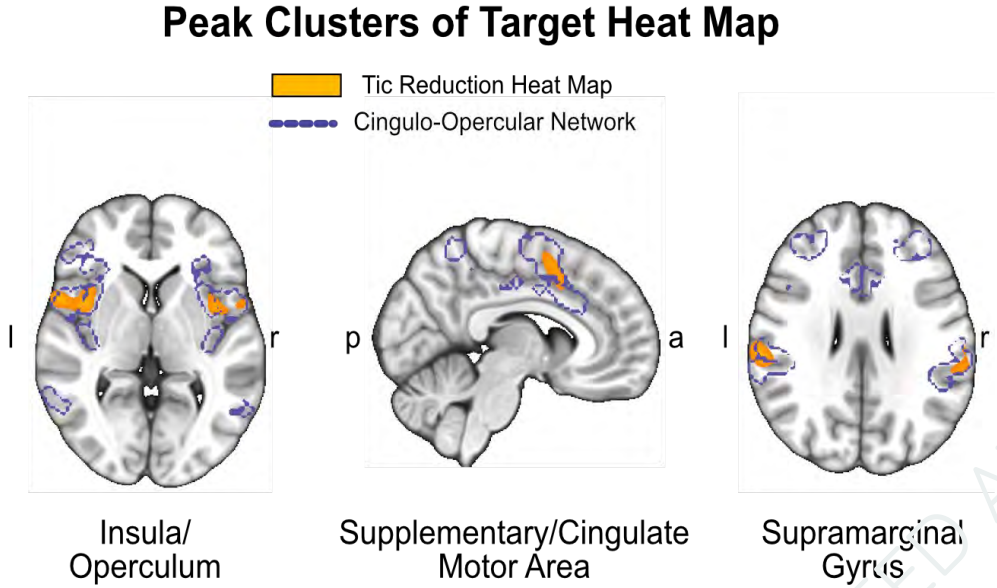

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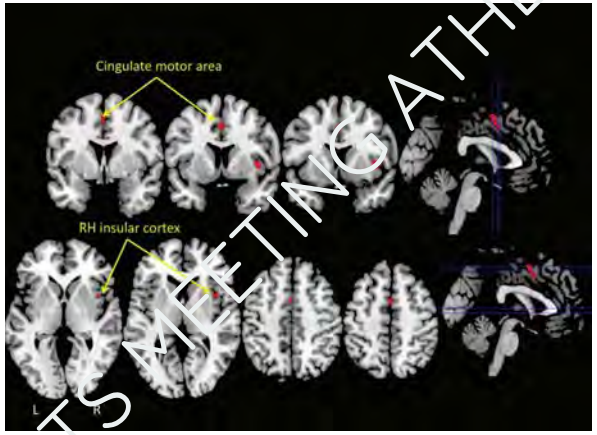
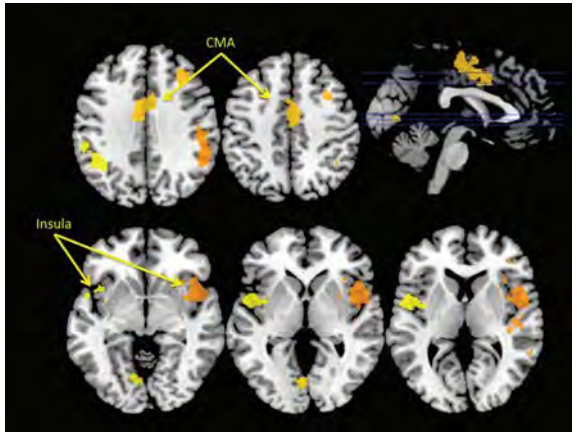


Urge to Yawn



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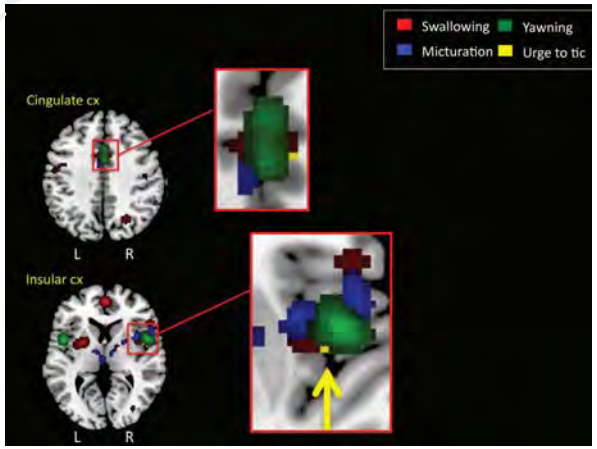
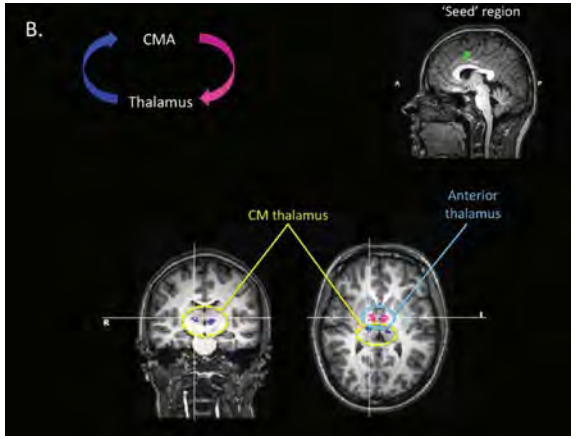


Involvement of Thalamic Nuclei



Jackson et al., Cog Neurosc 2011

DBS for Tics

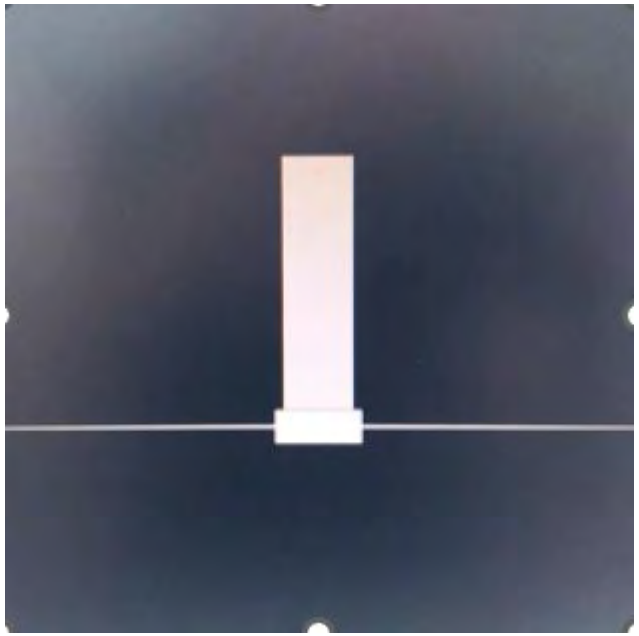
~~DBS for Tics~~

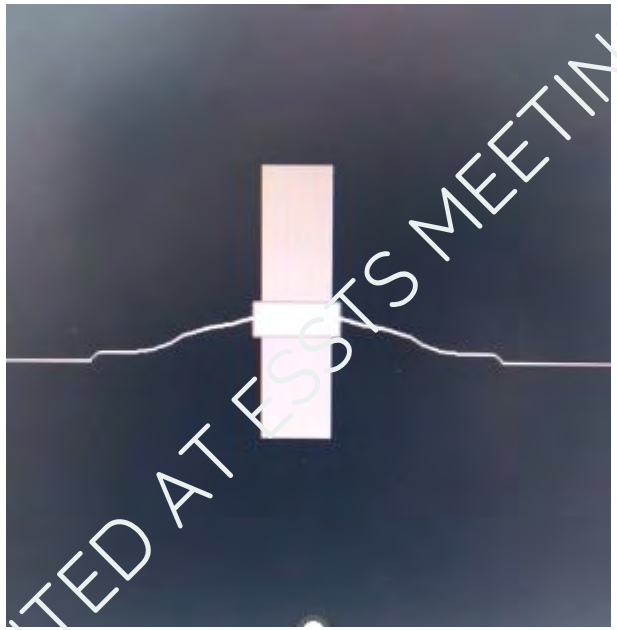
DBS for Urges?

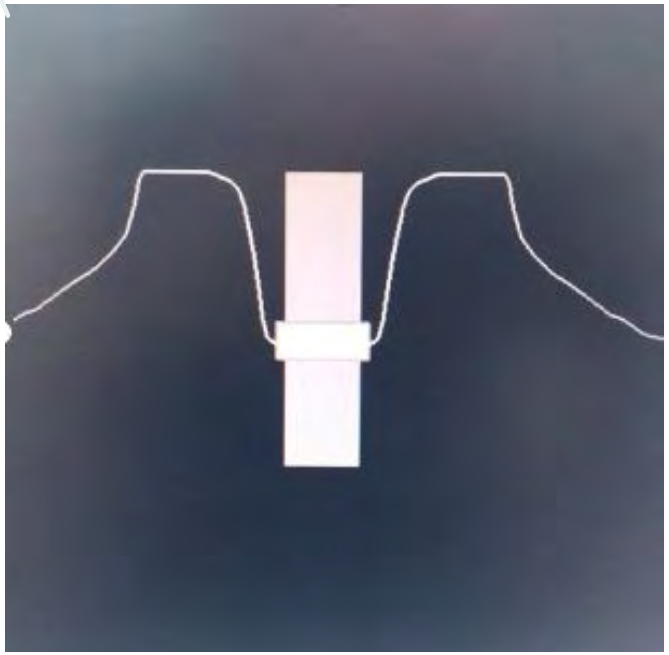
Premonitory Urge to Tic during CM-VOI DBS

Thomas Schüller

Valerie Brandt

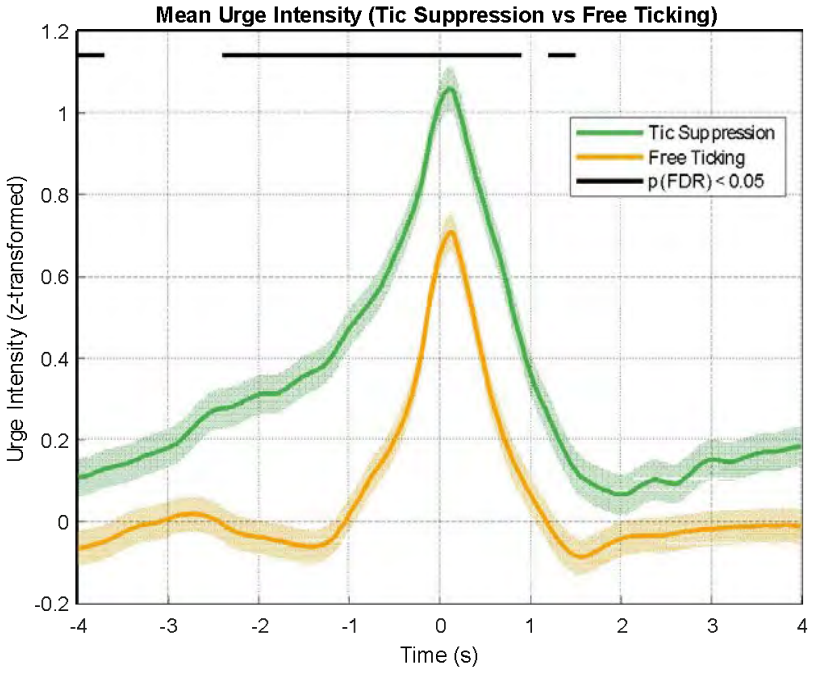






Acute Switching ON/OFF CM–VOI DBS Mitigates Premonitory Urge Dynamics

Thomas Schüller PhD



Schüller et al., in preparation

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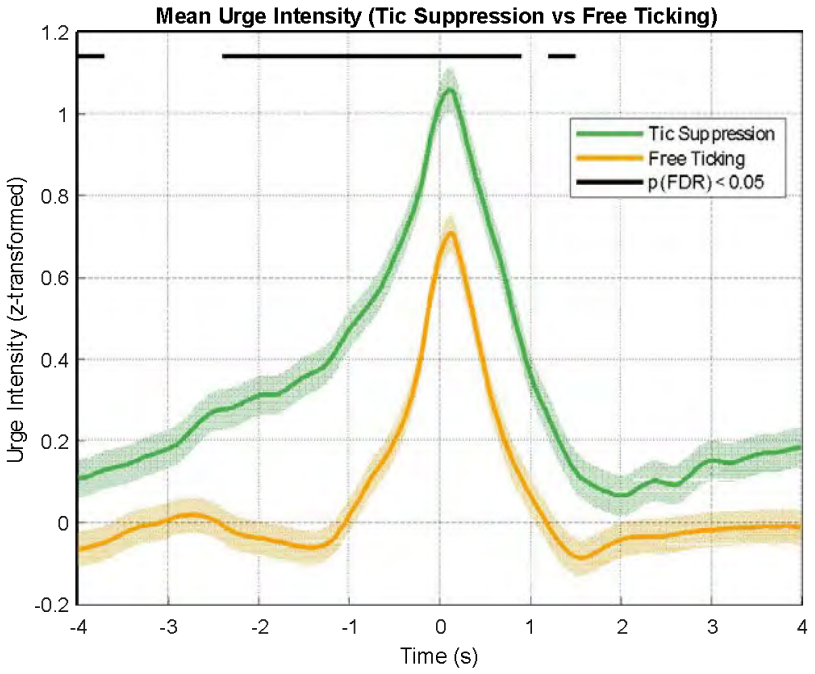
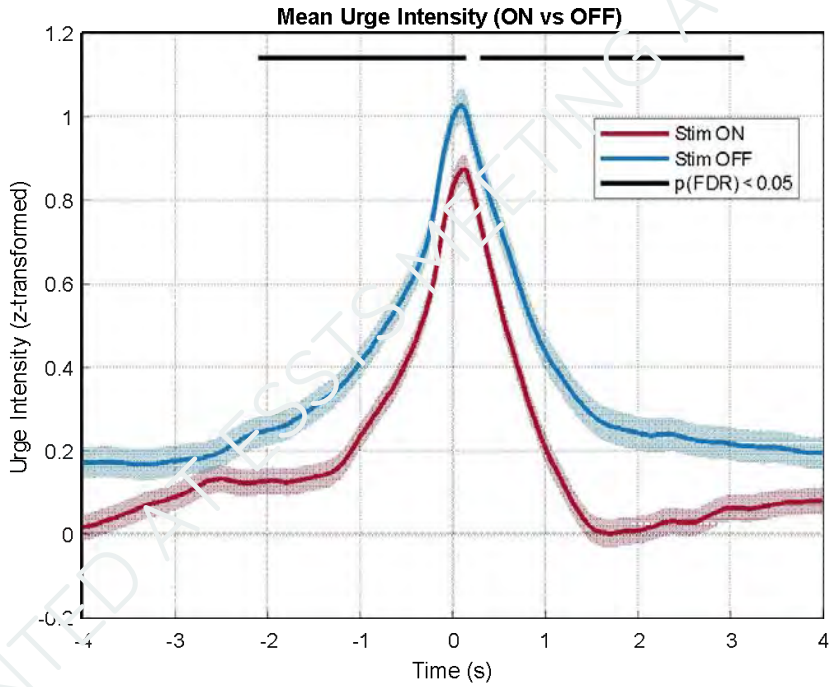
Acute Switching ON/OFF CM–VOI DBS Mitigates Premonitory Urge Dynamics

Thomas Schüller PhD





Schüller et al., in preparation

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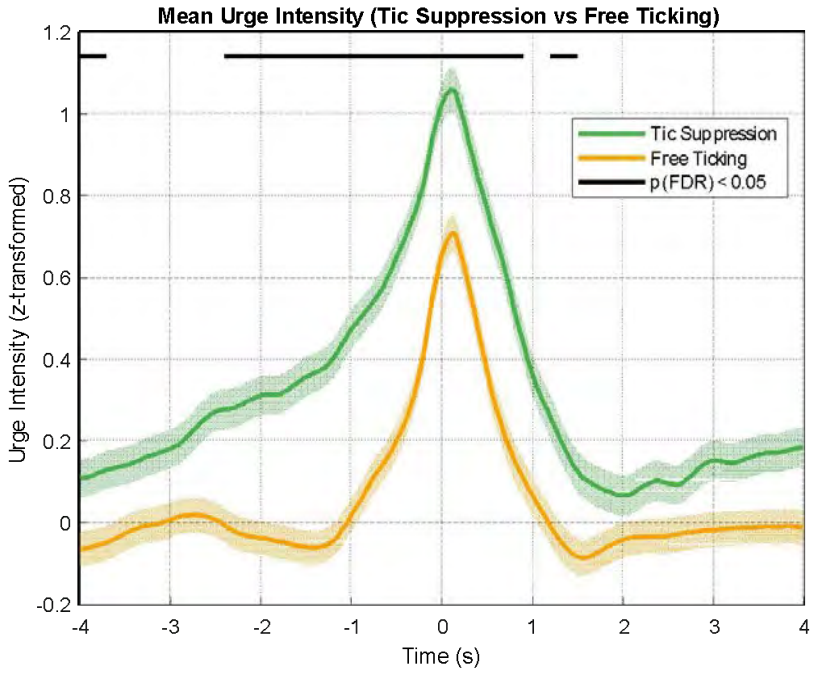
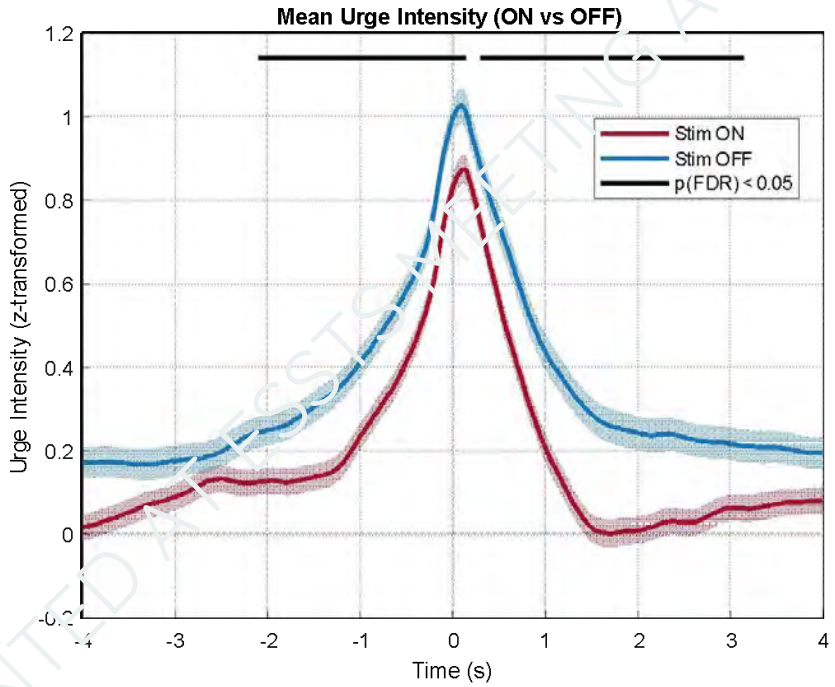
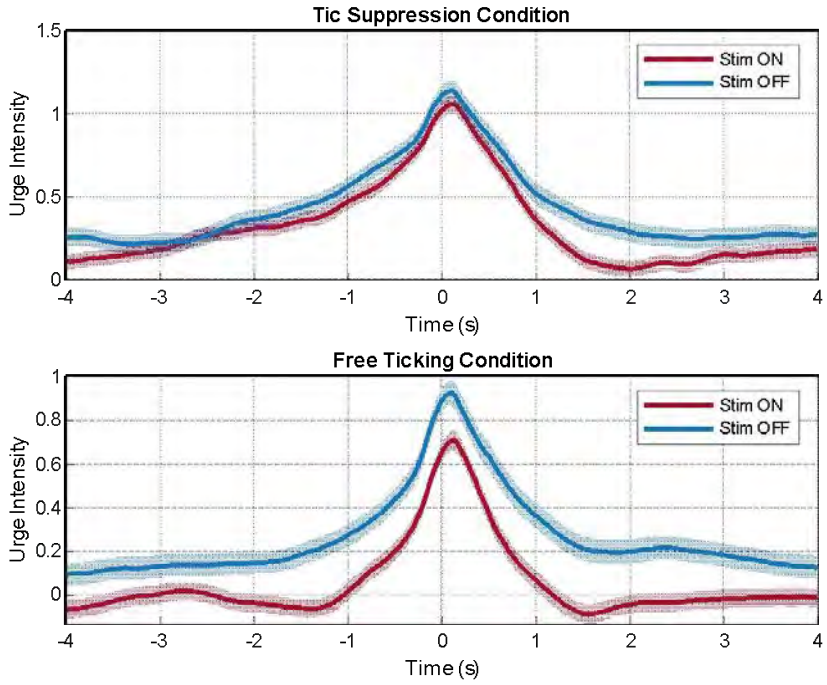


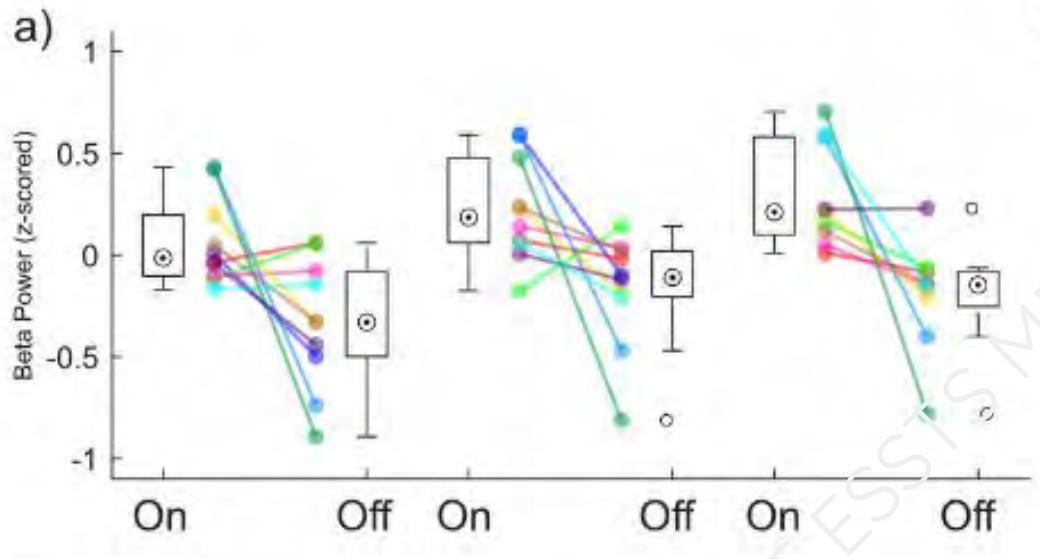




Schüller et al., in preparation

Thalamic DBS Increases Premotor Beta Activity During Resting-State

Thomas Schüller PhD

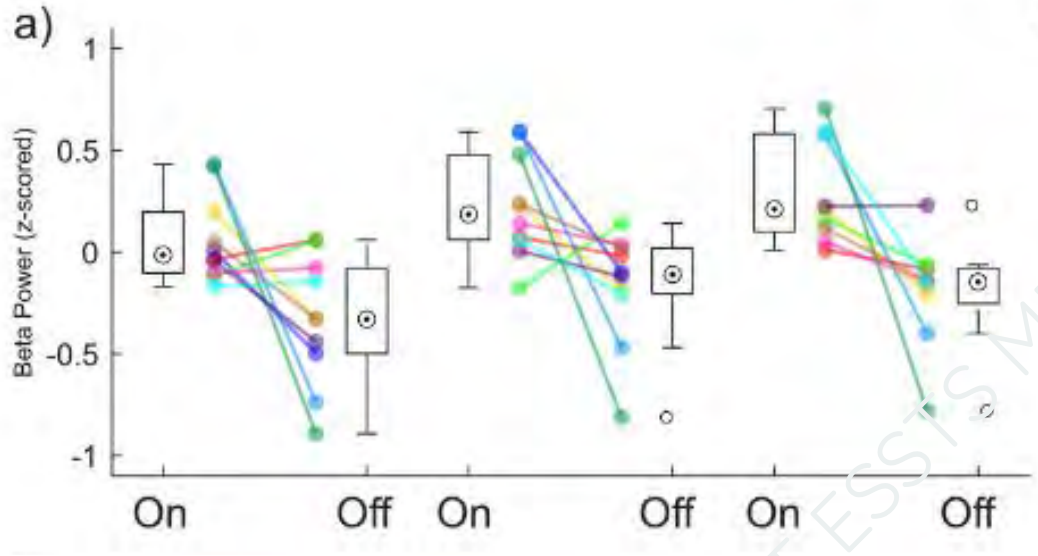


(t_{55} = 6.45, p < .001)

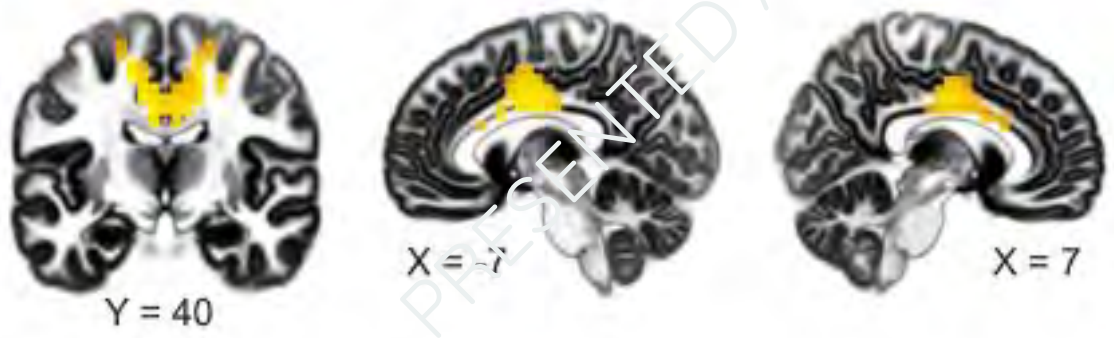
Schüller et al., Brain Stim 2024

Thalamic DBS Increases Premotor Beta Activity During Resting-State

Thomas Schüller PhD



(t_{55} = 6.45, p < .001)



Schüller et al., Brain Stim 2024

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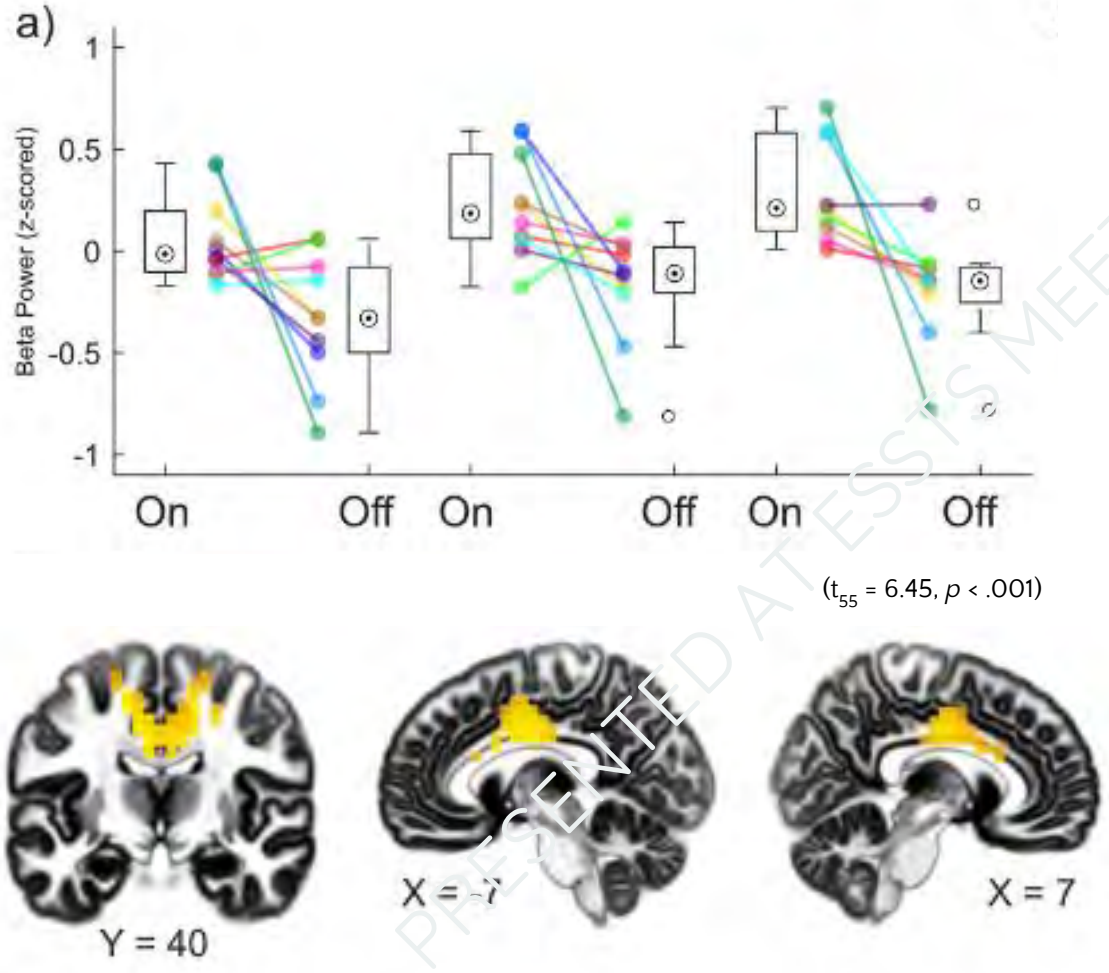
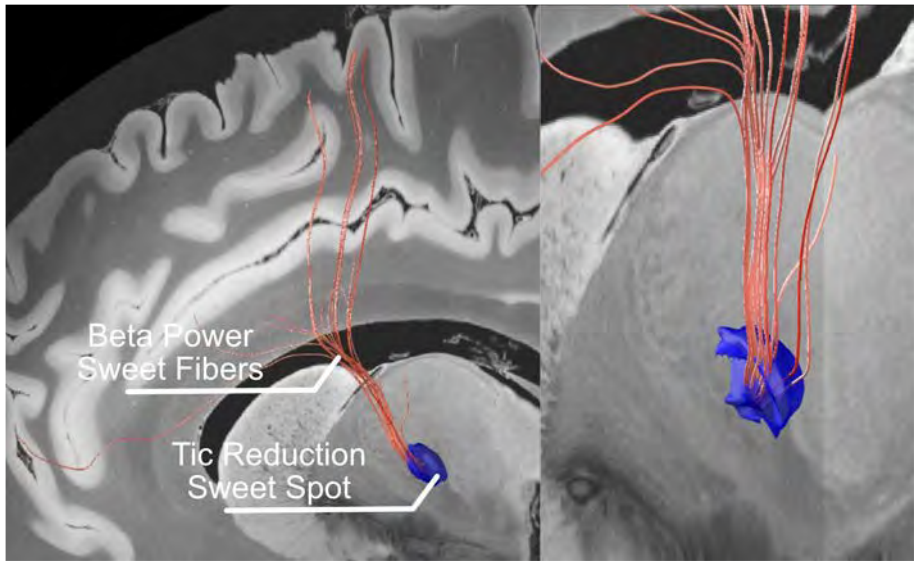


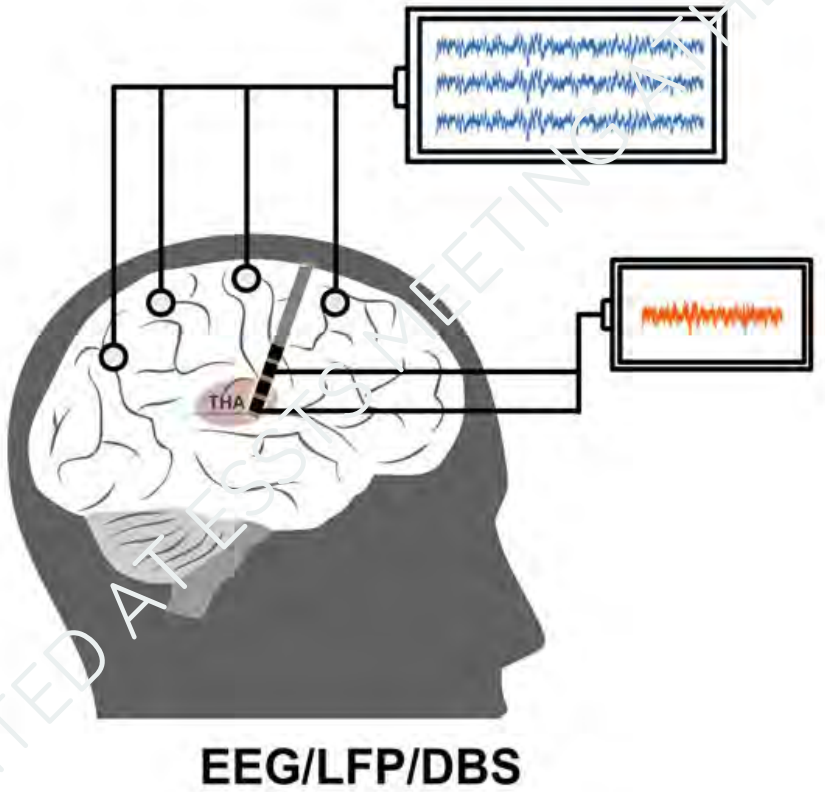


unpublished

Schüller et al., Brain Stim 2024

How Does the Thalamus Influence the Cortex During Tics

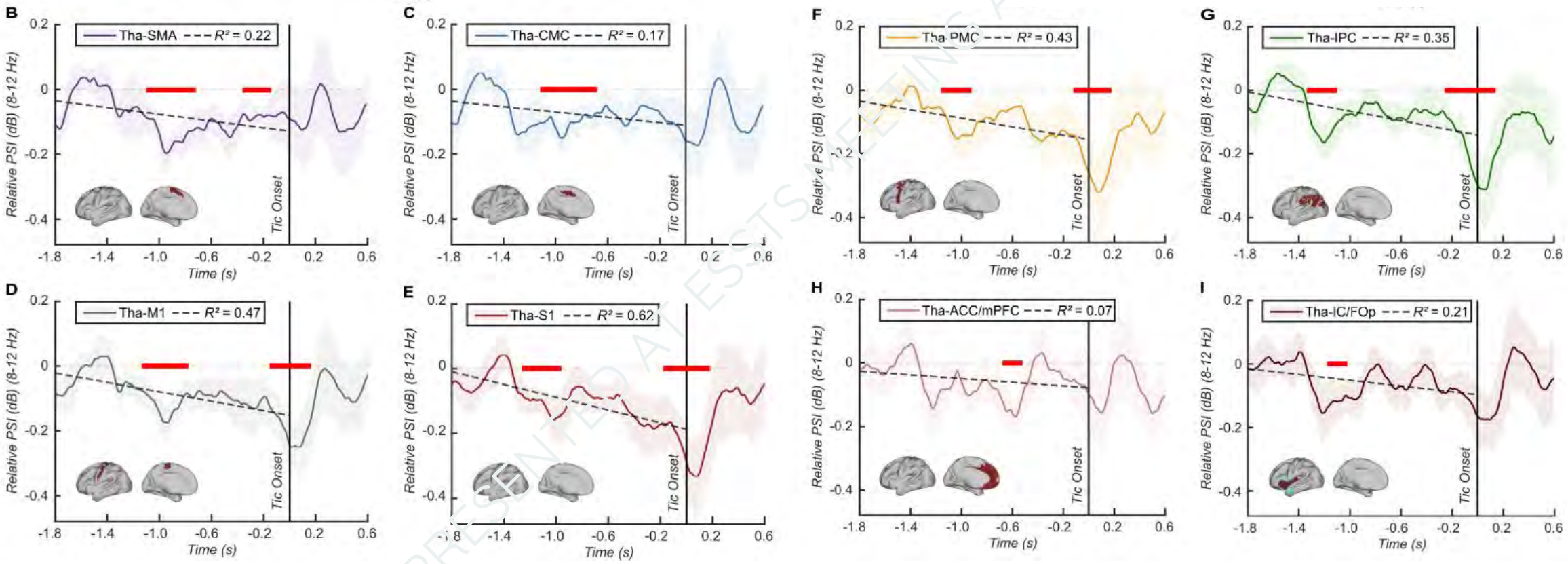
Laura Wehmeyer PhD



Wehmeyer et al., under review

Reduction in Thalamo-Cortical Alpha Power in Action-Mode Regions Precedes Tic Onset

Laura Wehmeyer PhD



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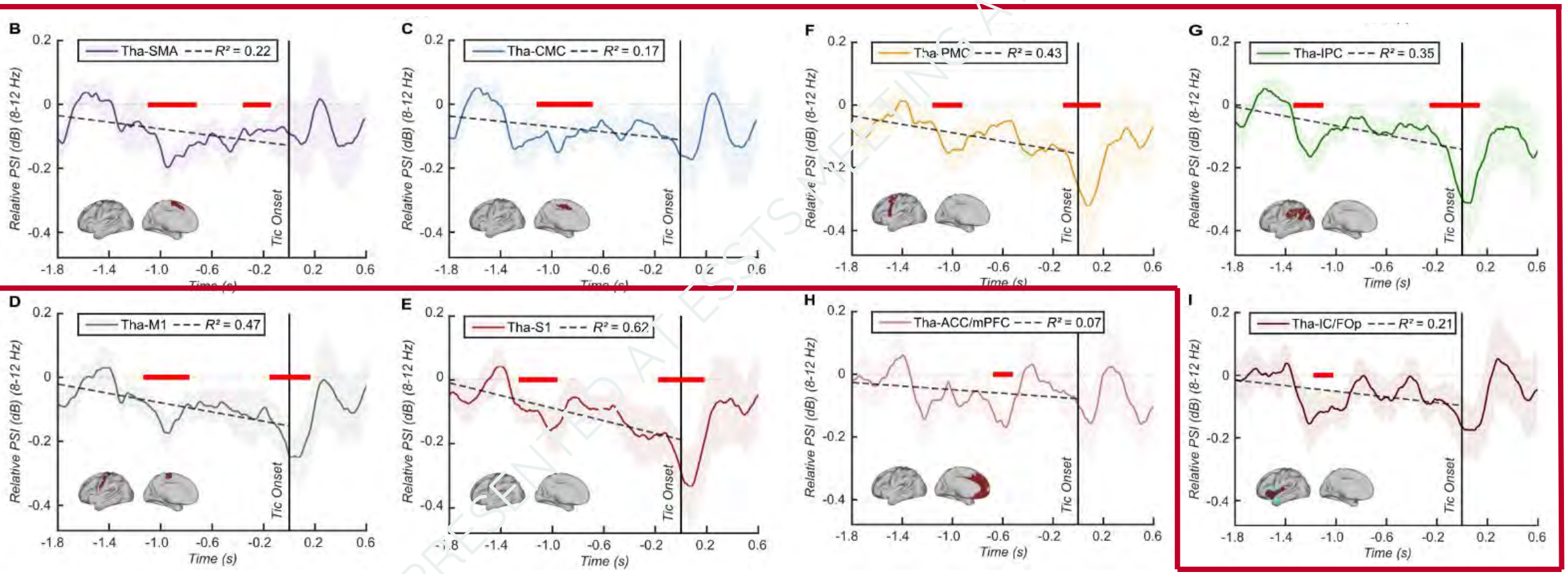

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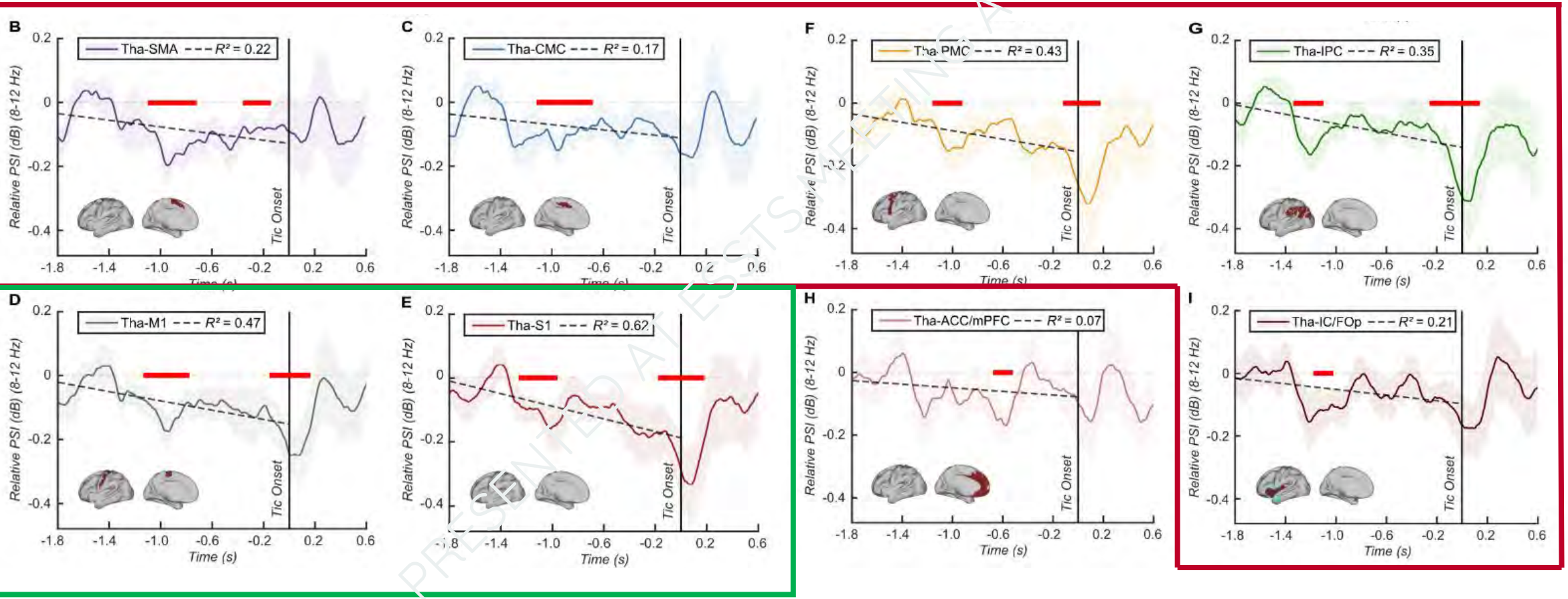

- SCAN & Sensorimotor Network

Wehmeyer et al., BioRxiv 2024, under review

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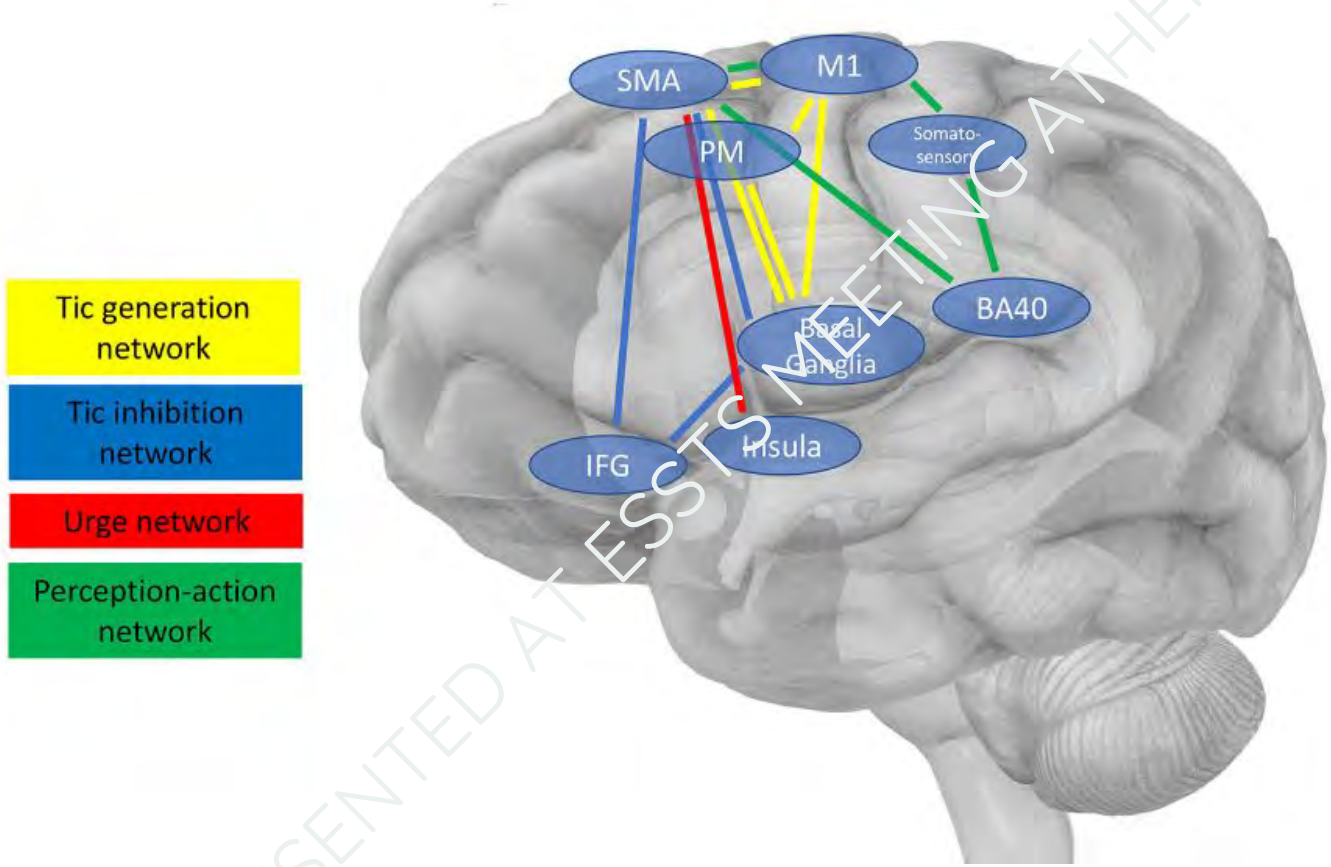
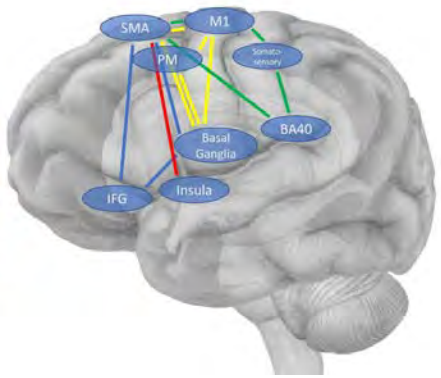
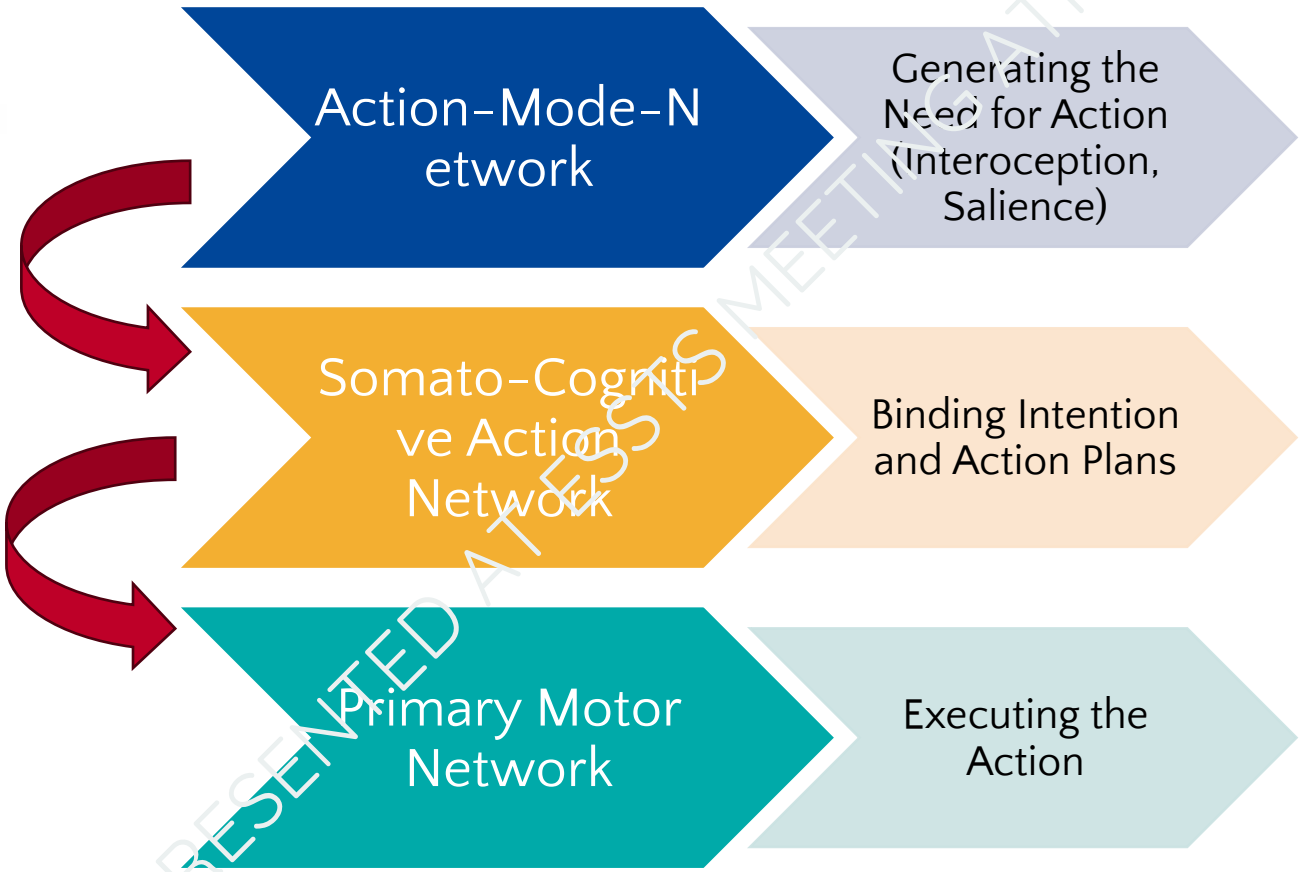
Tic Disorders as Multi-Network-Disorders



Kleimaker et al., Front Neurol 2020

Hypothesis:
An Extended Brain Network Model for Tics





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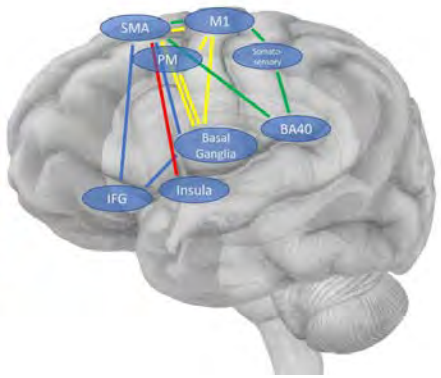

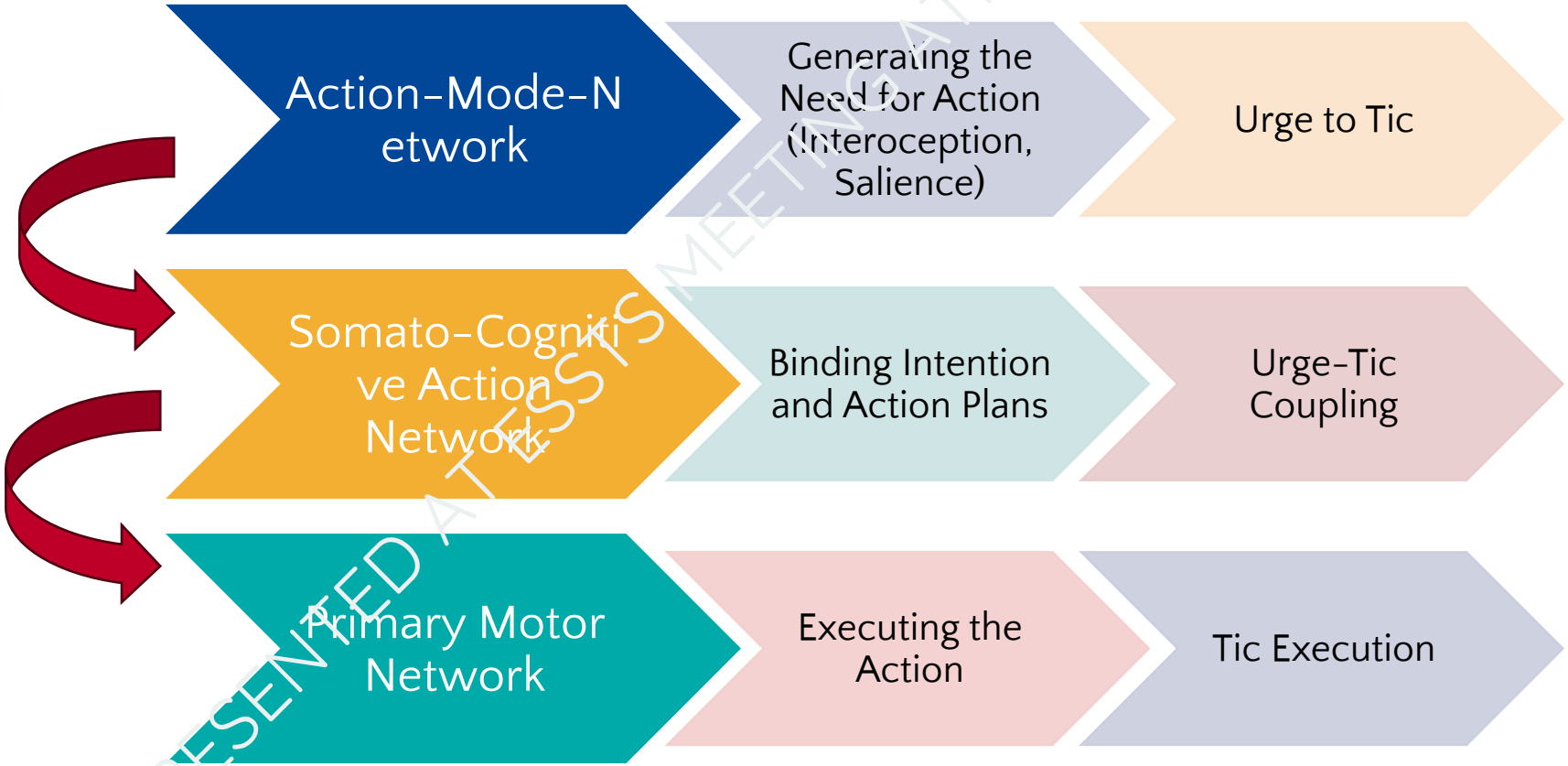

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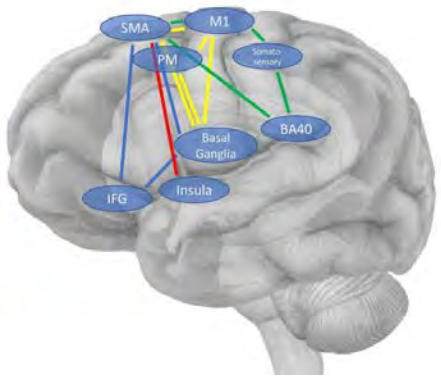

Oscillatory State Transition

Action-Mode-Network	Generating the Need for Action (Interoception, Salience)	Urge to Tic
Somato-Cognitive Action Network	Binding Intention and Action Plans	Urge-Tic Coupling
Primary Motor Network	Executing the Action	Tic Execution

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Summary

- Targeting action-related functional networks is critical for DBS for tics – and may inform non-invasive neuromodulation as well

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- Targeting action-related functional networks is critical for DBS for tics – and may inform non-invasive neuromodulation as well

- Lesion-induced tics and urge-activity map to the same networks, suggesting a potential role tic-pathophysiology

- Oscillatory state changes within these networks may be further critical for urge-tic dynamics and their treatment

Thank you for your attention

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MOTOR SFB 1451

Else Kröner Fresenius Stiftung

Faculty of Medicine
BERTA-OTTENSTEIN-PROGRAMME
FOR CLINICIAN SCIENTISTS

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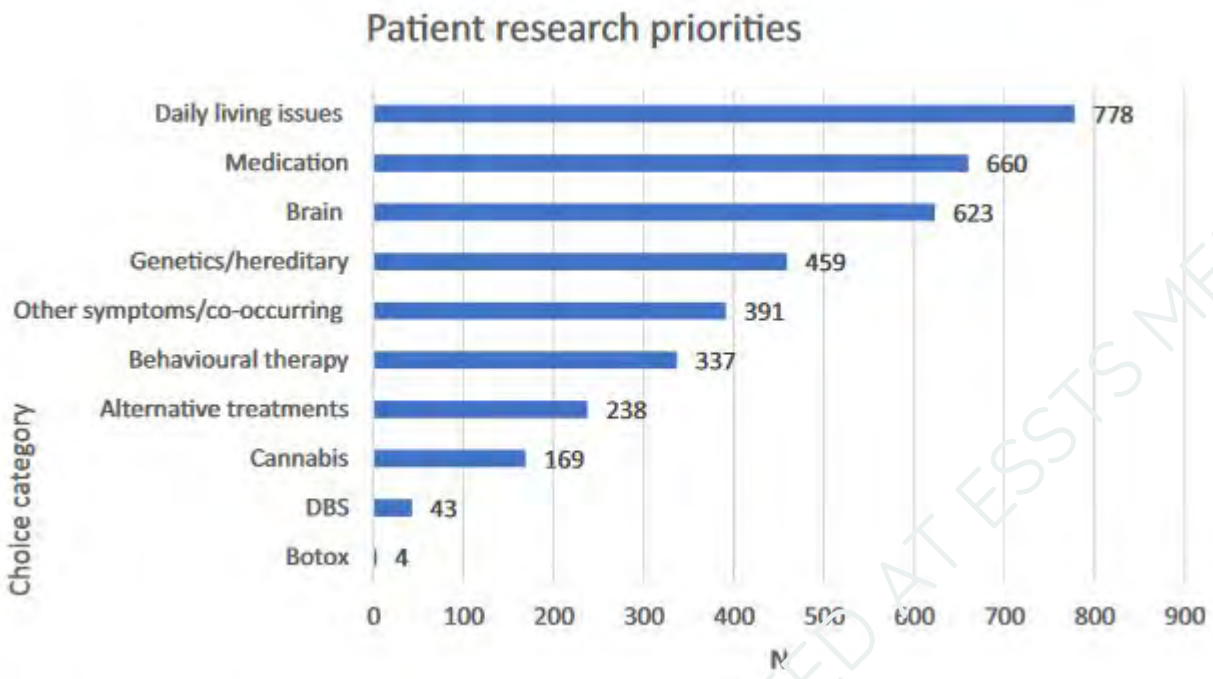
The Patient‘s Perspective



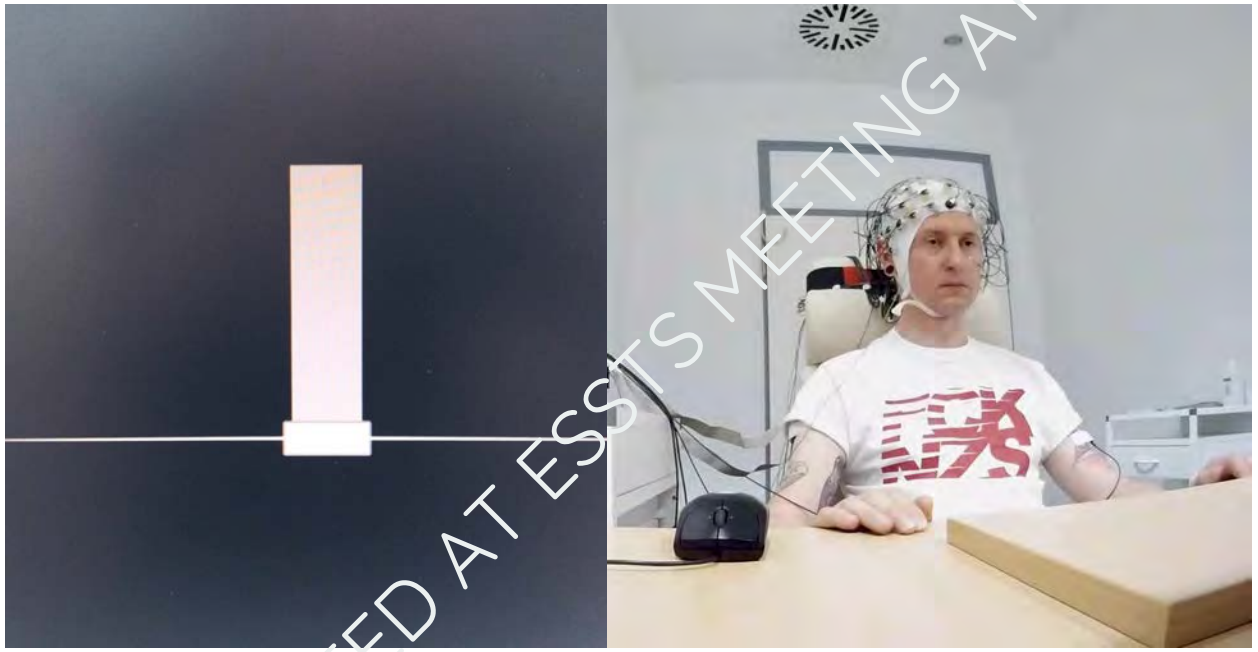
Anderson et al. Europ Child & Adolsec Psychiatry 2022

Pitfalls of Closed-Loop DBS for Tic Disorders

- Subcortical recordings may not be enough to capture urges and tics
- The location of a potential cortical recording site remains vague
- Variability of symptoms (i.e. urge and tic location, quality of urges) may require individual phenotyping
- We must distinguish tic activity from other actions
- A biomarker of pathology and a biomarker of treatment efficacy may not be the same

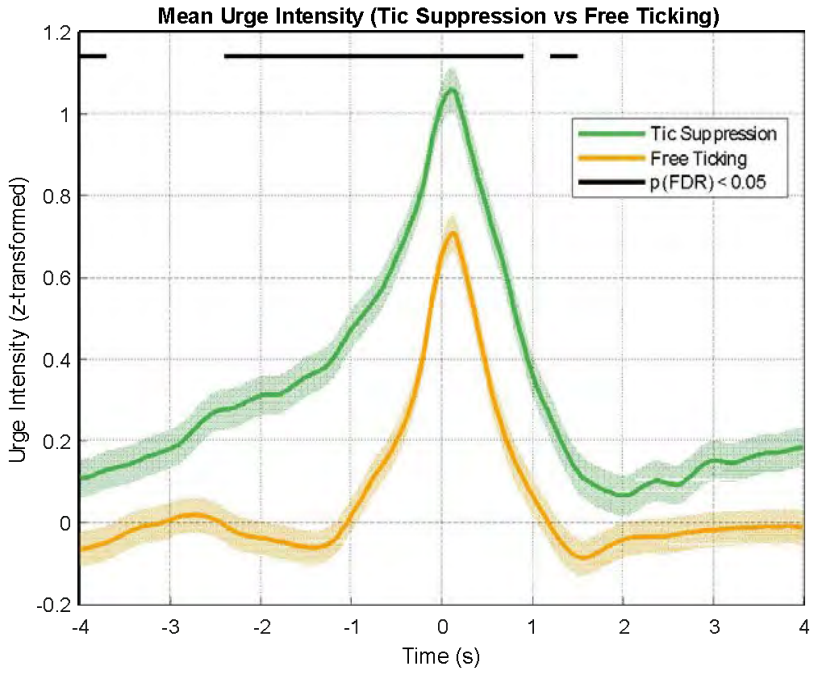
Premonitory Urge to Tic during CM-VOI DBS

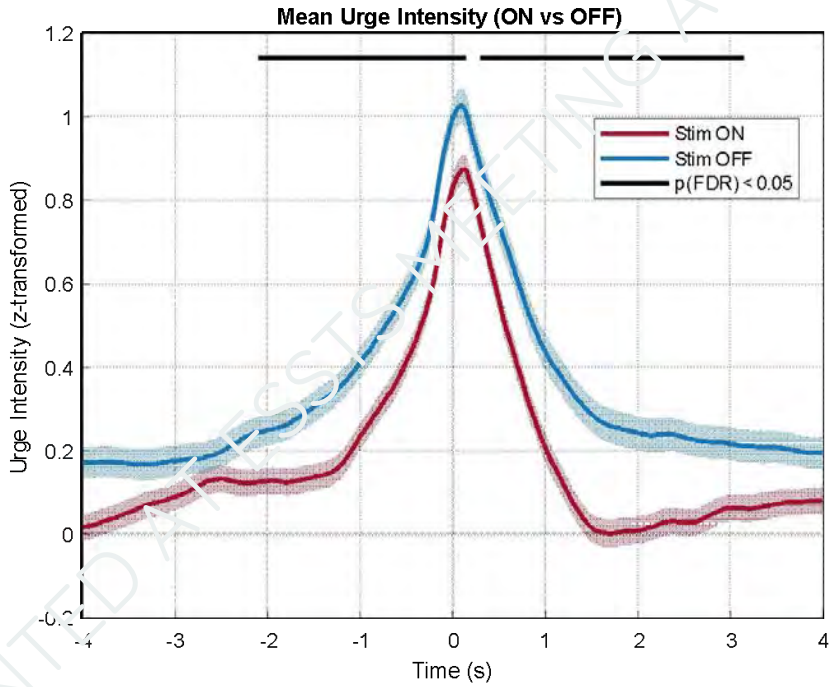
Thomas Schüller PhD

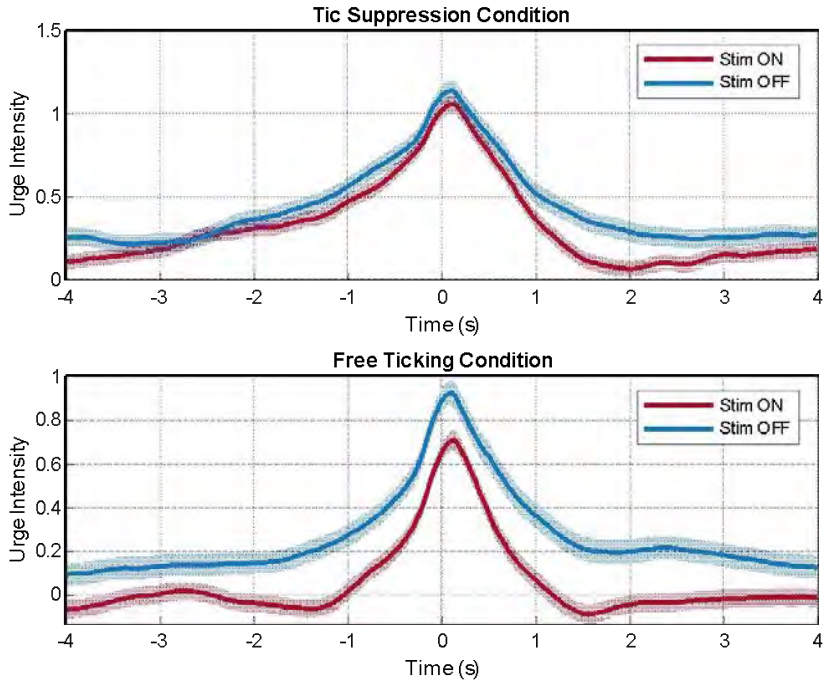


Acute Switching ON/OFF CM–VOI DBS Mitigates Premonitory Urge Dynamics

Thomas Schüller PhD







Schüller et al., in preparation

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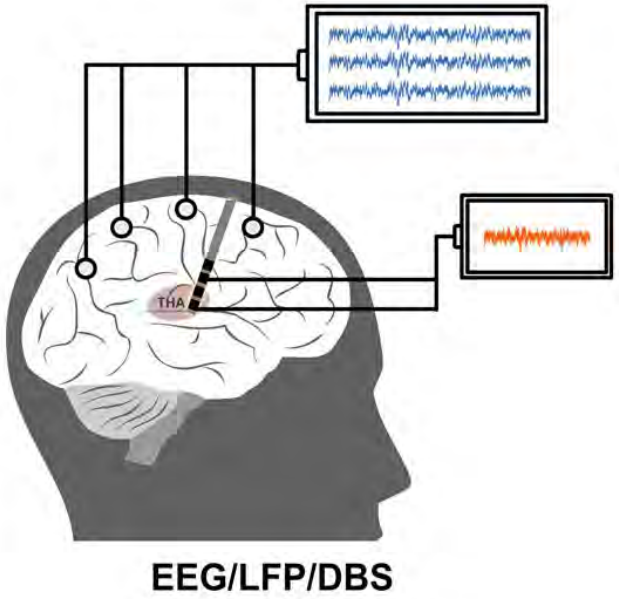
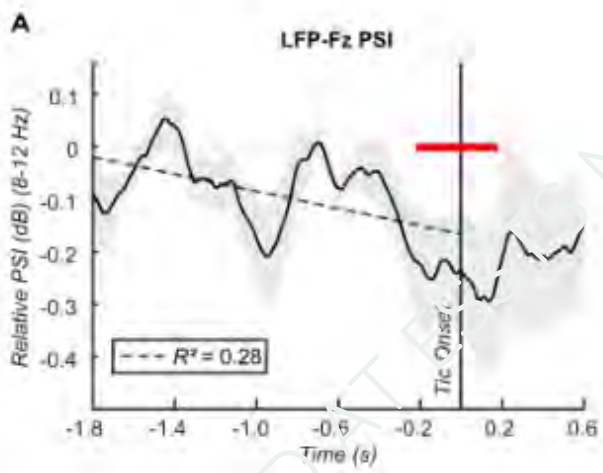
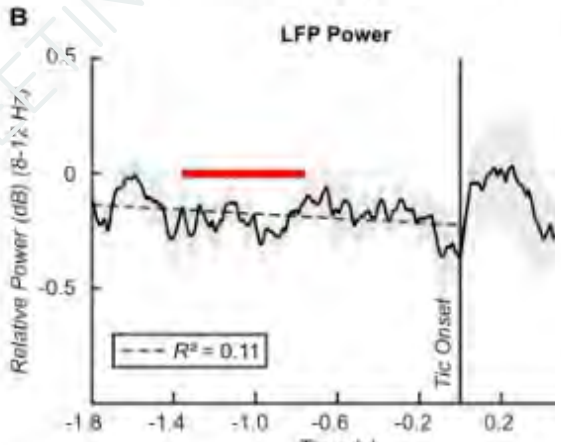
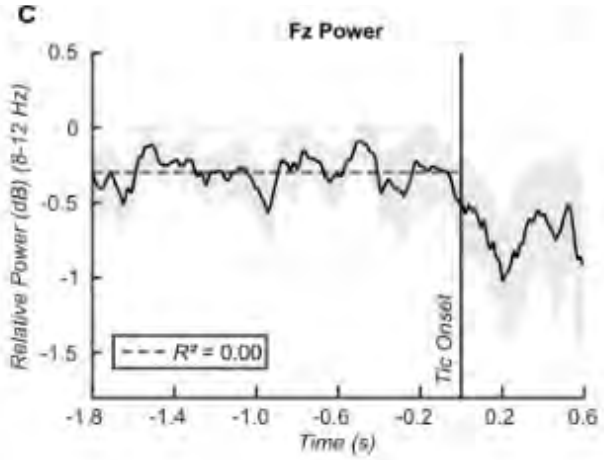
Thalamo-Frontal Alpha Connectivity Decreases Before Tic Onset

Laura Wehmeyer PhD









Wehmeyer et al., under review

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Reduction in Thalamo-Cortical Alpha Power in Action-Mode Regions Precedes Tic Onset

Laura Wehmeyer PhD

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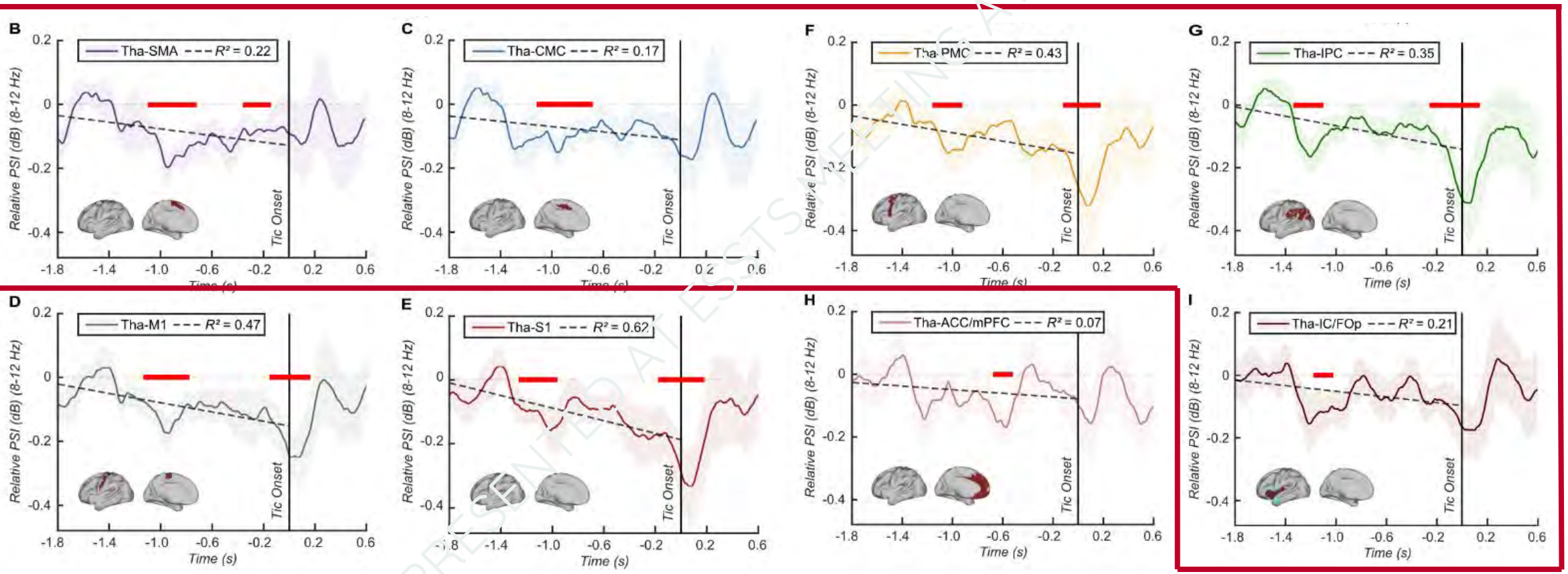

Wehmeyer et al., under review

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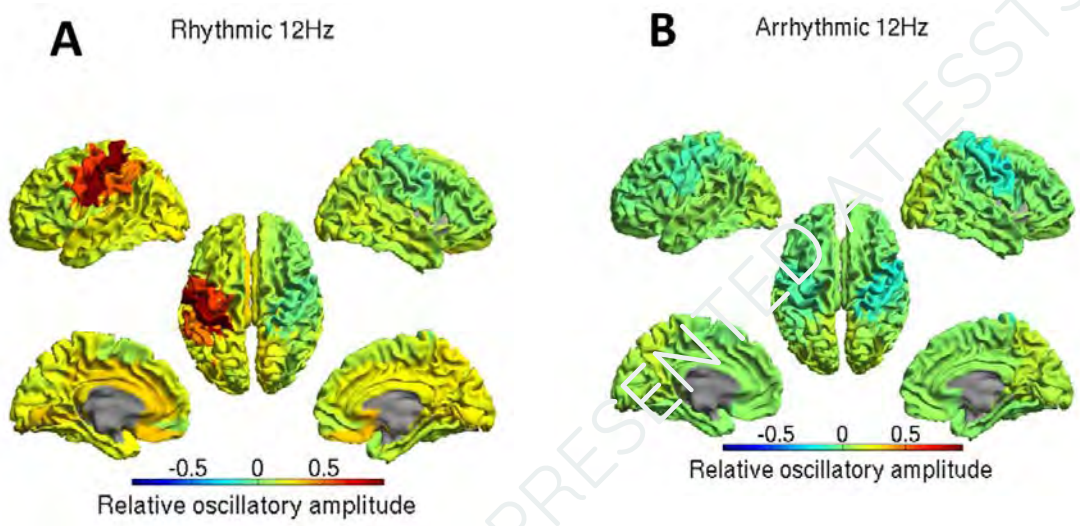
Median-Nerve-Stimulation (MNS)

- Transkutane elektrische Stimulation des N. medianus
- Rhythmische Applikation über ca. 15 Minuten täglich
- Wirkprinzip: Entrainment spezifischer Oszillationen im (prä-) motorischen System

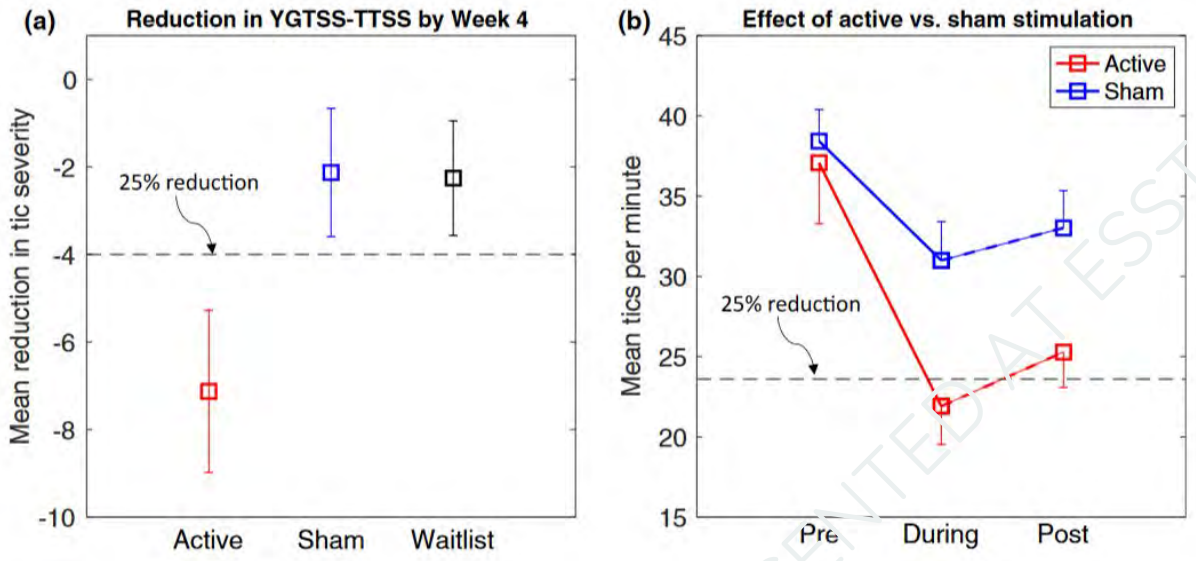


Houlgreave et al., Neuroimage 2022

Median-Nerve-Stimulation (MNS)

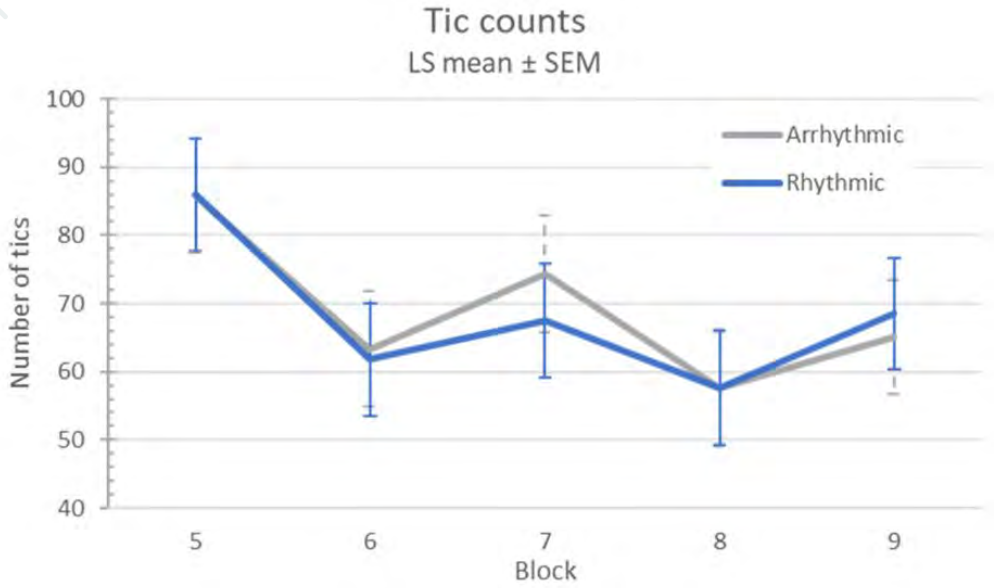
Ergebnisse aus zwei RCTs

- Zweiarmiger RCT
- Active: N = 41; Sham N = 39



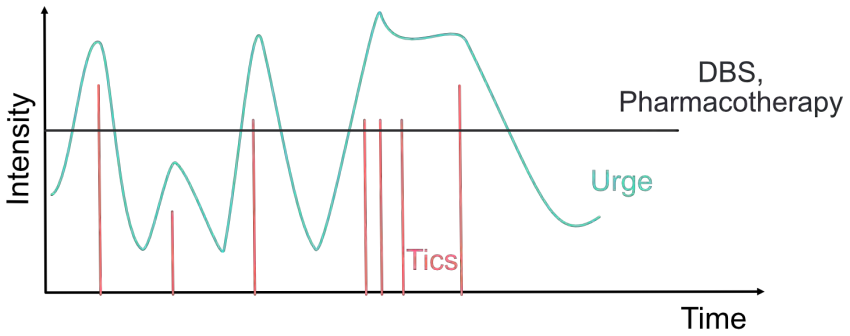
Morera Maiquez et al., J Neuropsychol 2023

- Einarmiger cross-over RCT mit aktiver Kontroll-bedingung
- N = 32, arrythmische vs. rhythmische Stimulation



Iverson et al., J Clin Med 2023

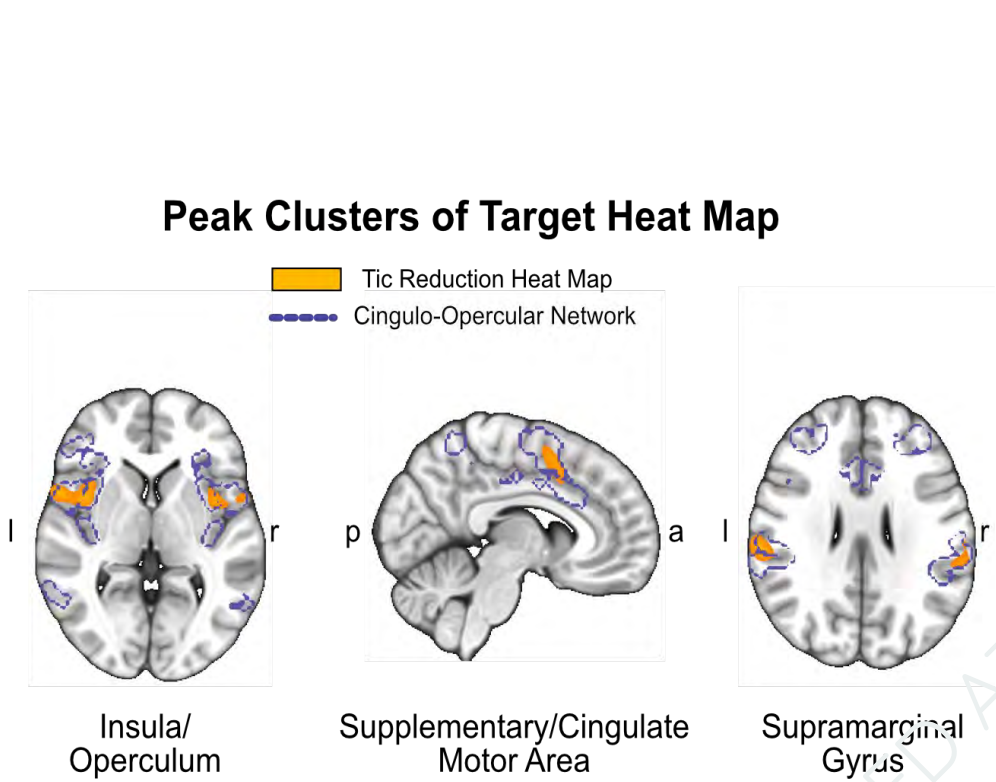
Closed loop DBS for Tic Disorders



Potential Biomarkers

- Thalamo-Cortical Alpha Connectivity (marks upcoming tic)
- Premotor Cortical Beta Power may indicate efficacy

Tic Reduction Heat Map Matches General Urge Activity

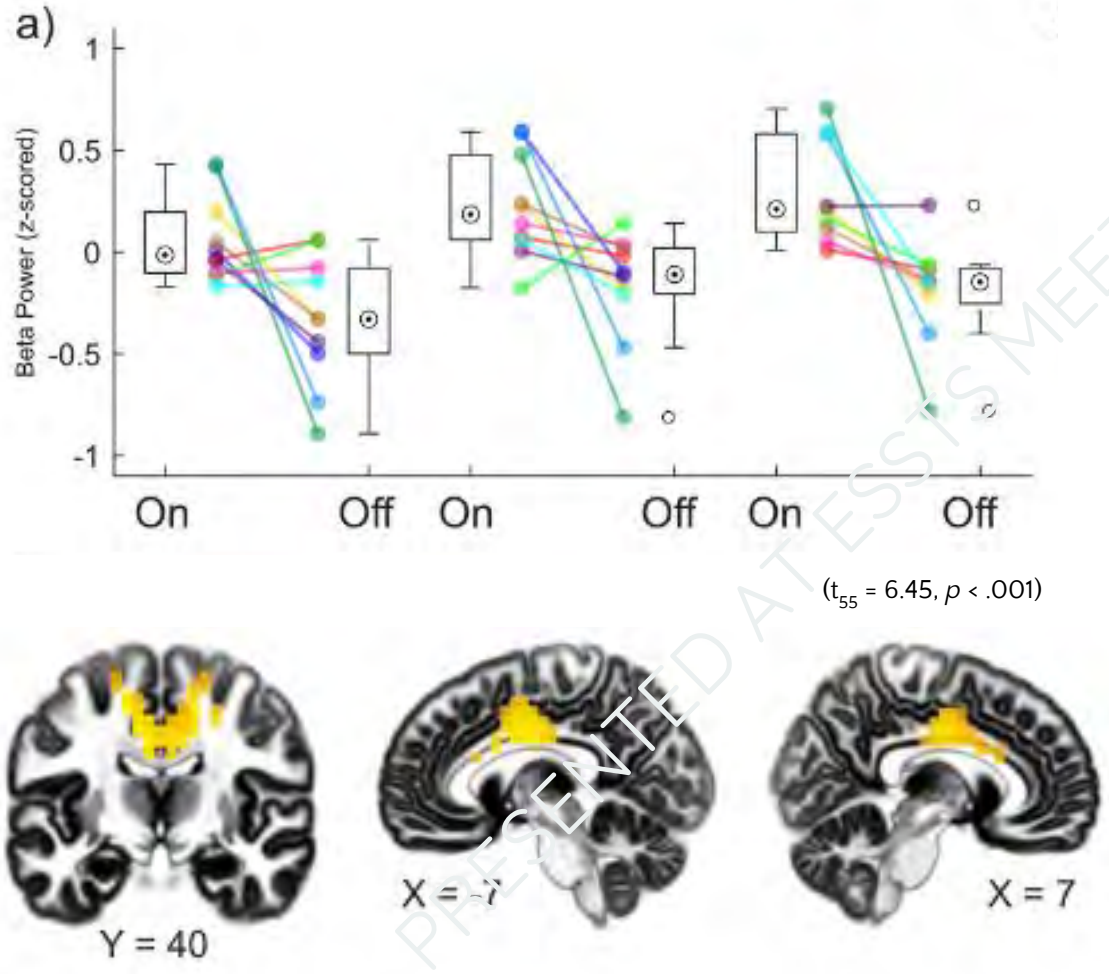


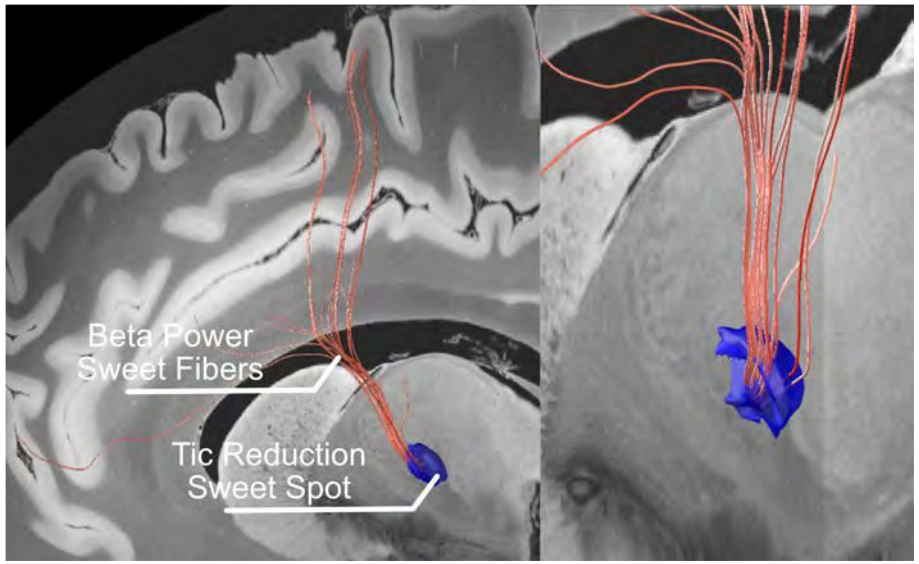
	Insula/ Operculum	Supplementary/Cingulate Motor Area	Supramarginal Gyrus
Relevance in Tic Disorders	Active during urge/ before tic onset [19-21] Increased funct. Insula-SMA Connectivity [16] Urge- and tic-related structural alterations [17]	Active during urge/ before tic onset [19-21,48] Increased Insula-SMA connectivity [16] Tic-related structural alterations [47] Abberant activity during motor tasks [49, 50]	Active during urge/ before tic onset [19-21] Impaired perception-action integration in tic disorders [51-53]
Evidence as Neuro-Modulation Target		rTMS: sign. tic reduction in OLT [57-60], but not RCTs [61,62] tDCS: sign. tic reduction in single blinded trial [63] fMRI-Biofeedback: sign. tic reduction in RCT [64]	rTMS: sign. tic reduction in RCT [65]

Jackson et al., Cog Neurosc 2011

Thalamic DBS Increases Premotor Beta Activity During Resting-State

Thomas Schüller PhD





Schüller, ..., **Baldermann** & Smith, Brain Stim 2024

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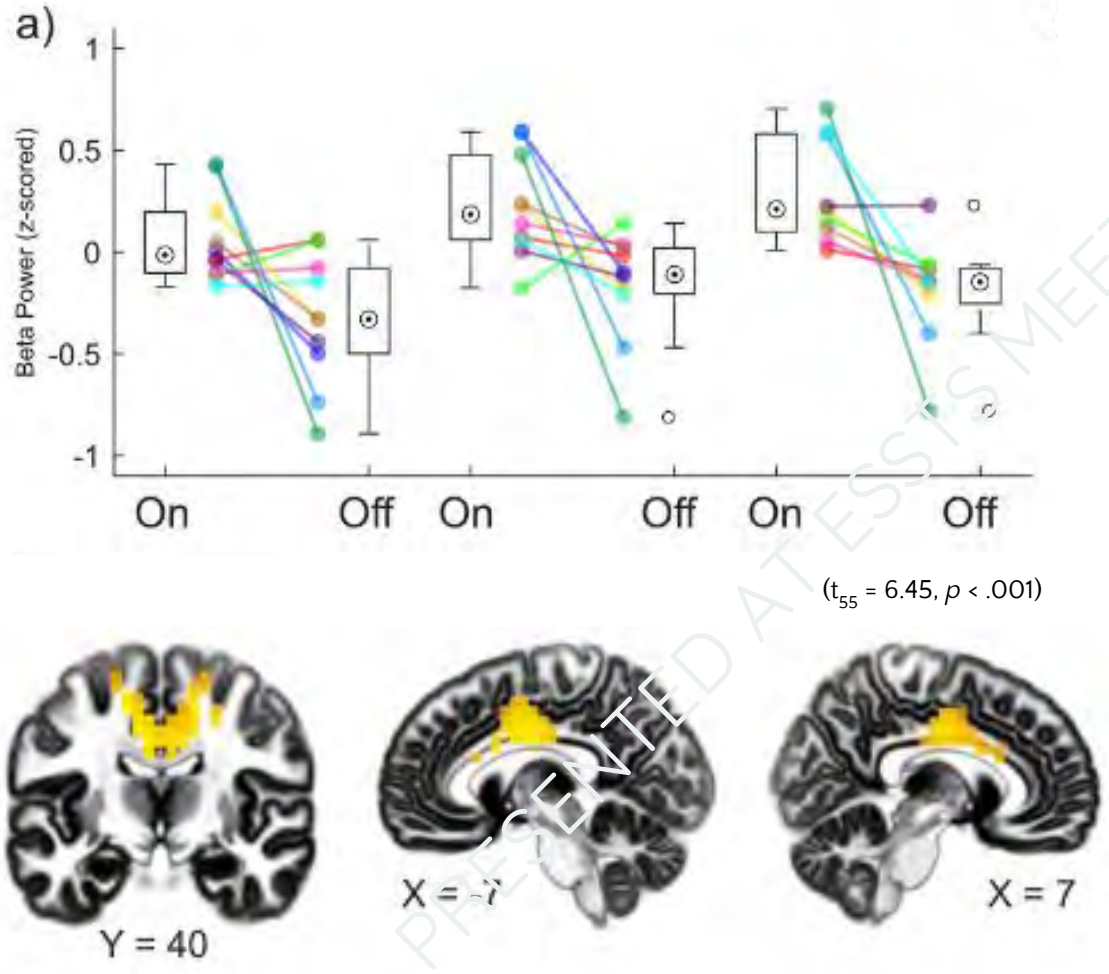

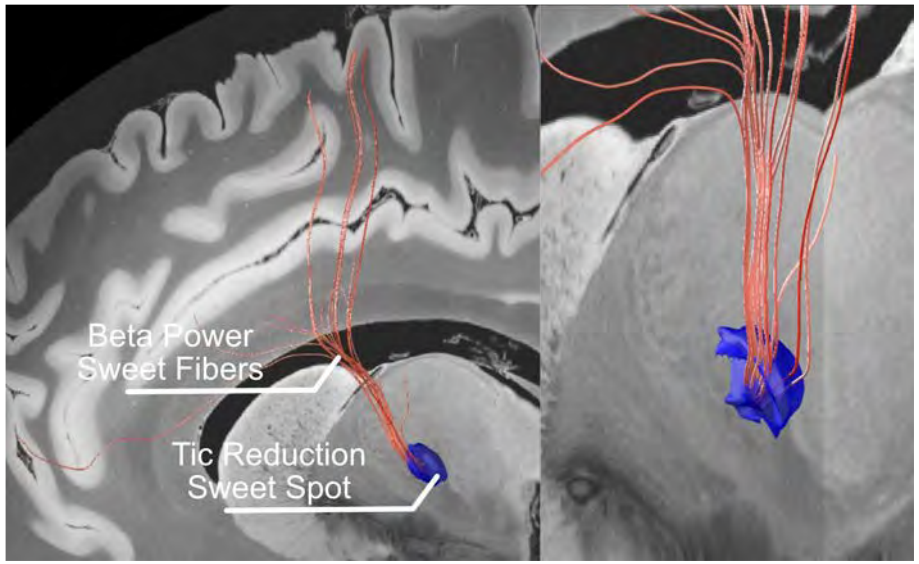

unpublished

Schüller et al., Brain Stim 2024

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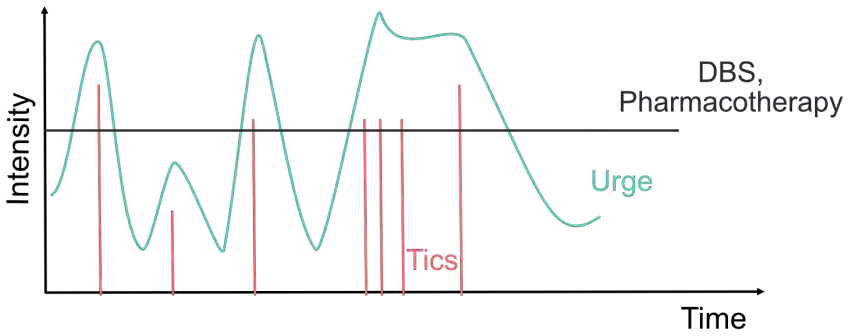
Closed loop DBS for Tic Disorders



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Long-Term Data and RCTs support efficacy of DBS for Tourette Syndrome

Patient Characteristics	
Number of Patients (N)	16
male (n)	11
female (n)	5
Age at DBS surgery in years (mean ± SD)	30.4 ± 10.0
Follow-up time in years (mean ± SD)	5.9 ± 2.7
Minimum Follow-up time (years)	1.9
Maximum Follow-up time (years)	10.3
Stimulation at latest Follow-up	
ON (n)	15
OFF (n)	1

unpublished

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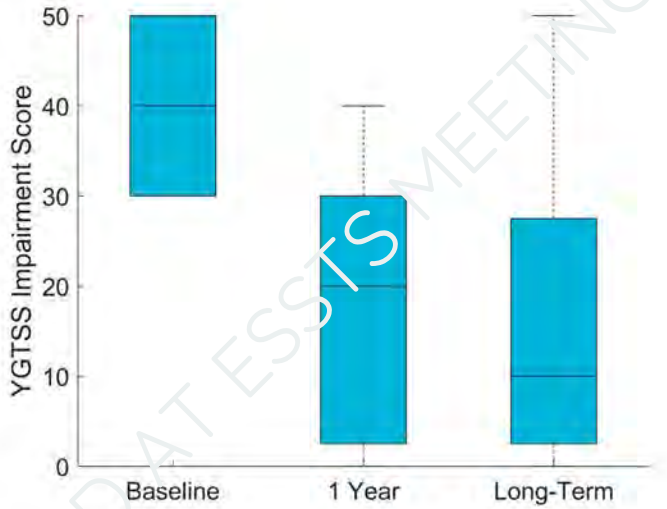

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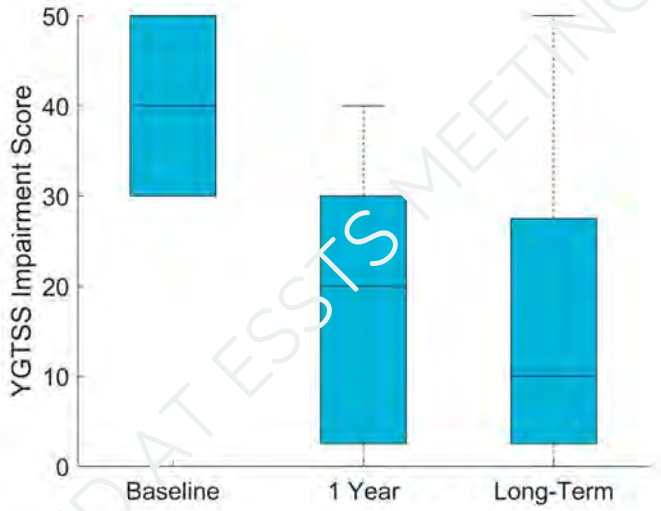
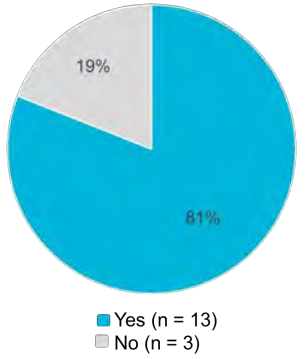
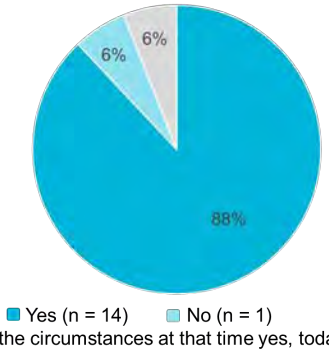


Were your expectations fulfilled?



Would you choose DBS again?



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