

Brain Stimulation Therapies in Neuropsychiatry

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Kaye Family Director of Psychiatric Brain Stimulation

Departments of Neurology, Psychiatry, Neurosurgery, and Radiology

Brigham and Women's Hospital / MGH / Harvard Medical School



Center for
BRAIN CIRCUIT
THERAPEUTICS

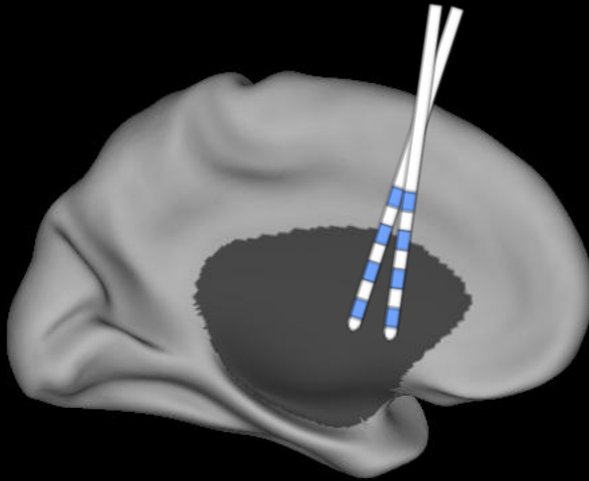


Disclosures

- Conflicts
 - Intellectual Property on using connectivity imaging to map lesions and guide neuromodulation
 - Consultant: Magnus Medical, Soterix, Abbott, Boston Scientific, Tal Medical, MDC Capital
 - SAB: Salma Health
 - May discuss non-FDA approved indications
- Funding
 - NIH: R01MH113929, R21MH126271, R21NS123813, R01NS127892, R01MH130666, UM1NS132358
 - Foundation: Kaye Family Research Endowment, the Ellison / Baszucki Family Foundation, Manley Family, Thomas May and Family, Once Upon a Time Foundation, Chuck and Kerri Bean Fund, BD2 Foundation
 - Industry: Neuronetics, Boston Scientific

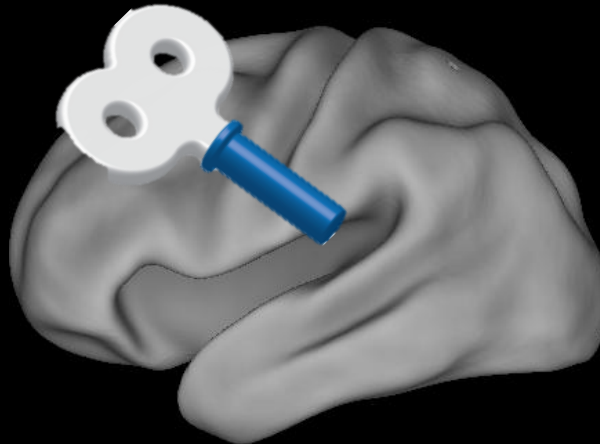
Therapeutic Neuromodulation

Deep Brain Stimulation (DBS)



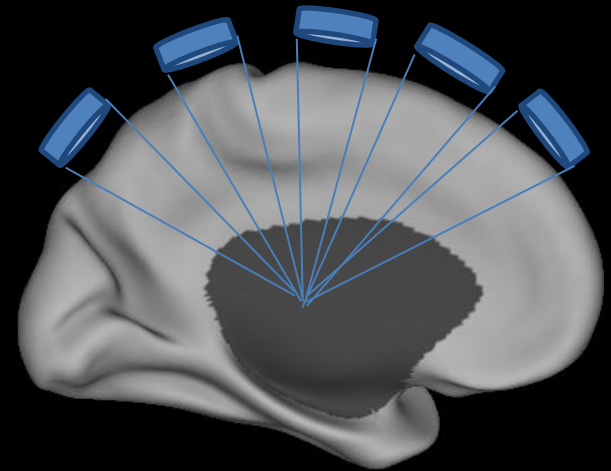
- FDA approved for **Parkinson's**, essential tremor, epilepsy, dystonia, OCD

Transcranial Magnetic Stimulation (TMS)



- FDA approved for **depression**, OCD, migraine, smoking addiction

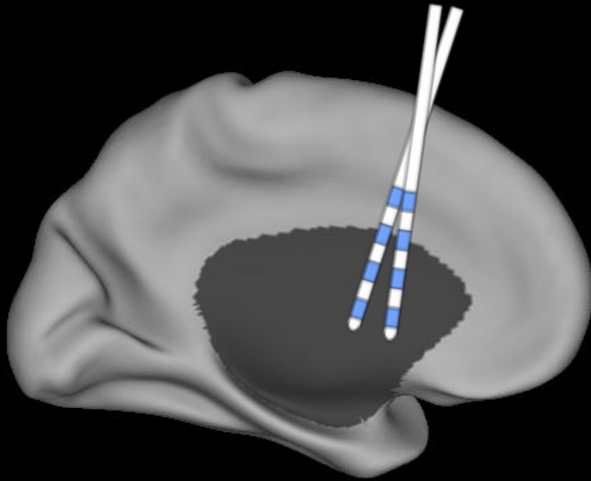
Focused Ultrasound (FUS)



- FDA approved for **tremor**

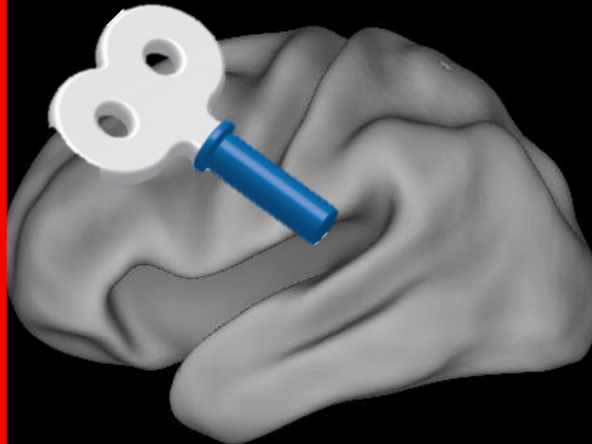
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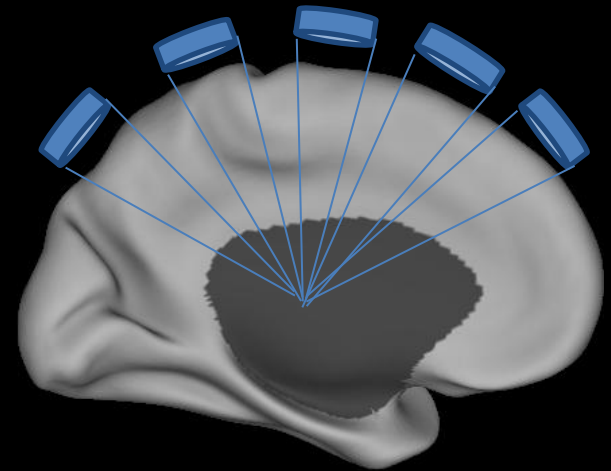
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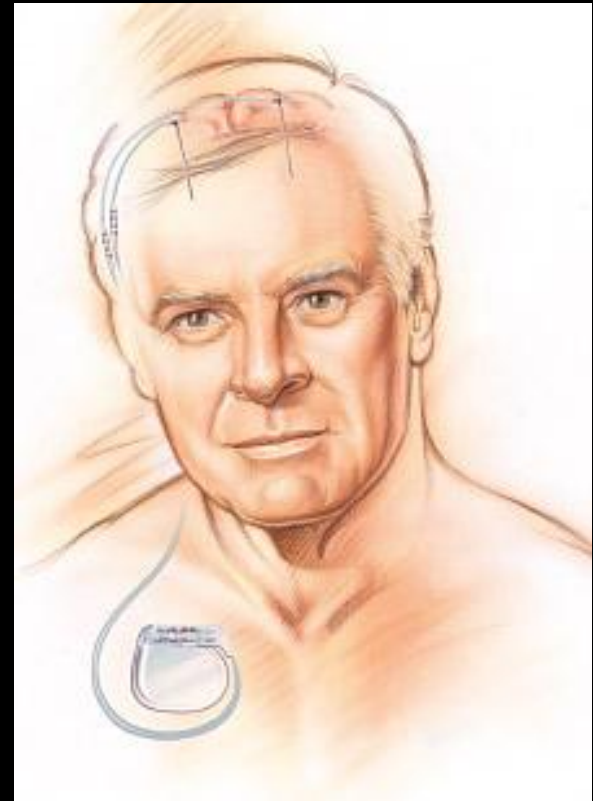
Focused Ultrasound (FUS)



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Deep Brain Stimulation (DBS)

- High frequency electrical stimulation of brain structures via electrodes implanted deep inside the brain
- Over 200,000 patients have been implanted worldwide; >2/3 are PD patients

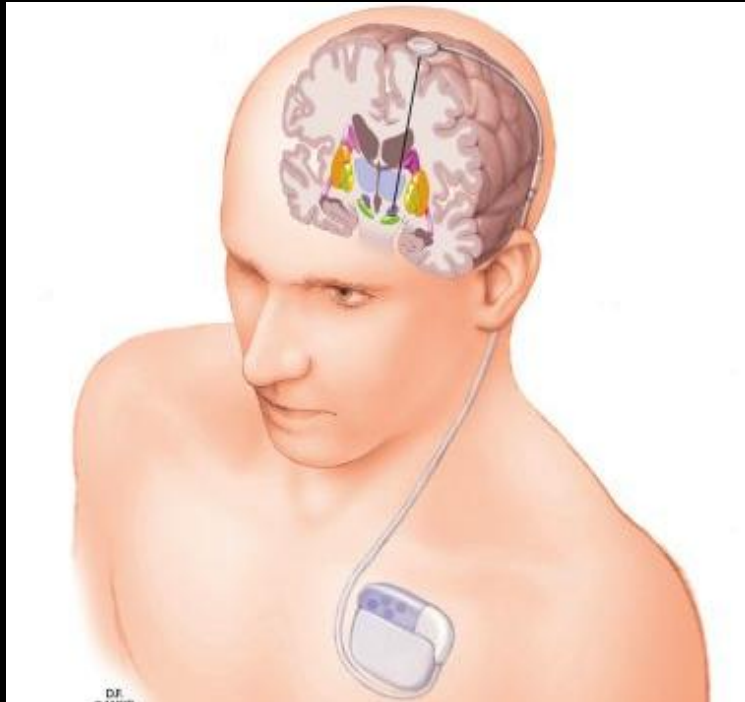


Deep Brain Stimulation

- 65-year-old professor with Parkinson's Disease and tremor for 10 years that has not responded to medication



Deep Brain Stimulation



Deep Brain Stimulation

- Component 1: Evaluation
 - Multiple appointments, MRI, testing
- Component 2: Surgery
 - Implant the DBS electrodes (1 day)
 - Implant the battery pack (1/2 day)
- Component 3: Programming
 - Initial programming (1-3 hours)
 - Follow up programming (multiple 30 minute session over 6-12 months)

What's good about DBS?

- We can dramatically help PD symptoms beyond what we can do with medications alone
 - Rigidity
 - Tremor
 - Dyskinesia
 - Motor fluctuations
 - Amount of medication

What's NOT good about DBS?

- Doesn't help and can actually worsen some symptoms
 - Swallowing
 - Bladder symptoms
 - Forgetfulness / thinking
 - Speech
 - Depression
 - Freezing, falls, imbalance

What's NOT good about DBS?

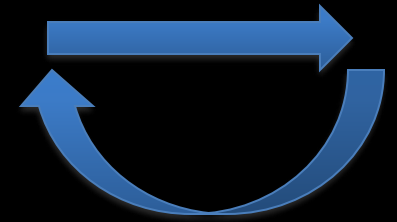
- Doesn't help and can actually worsen some symptoms
- Requires battery replacements every 3-5 years (or battery recharging each week)
- The surgery is uncomfortable and carries risk of bleeding and infection
- Takes lots of time to find the right settings
- Limitations on MRI

The Future of DBS

- Making the operation more pleasant
- Earlier intervention
- New types of stimulation
- Improving programming efficiency
- New targets / new indications

Future of DBS: Closed Loop

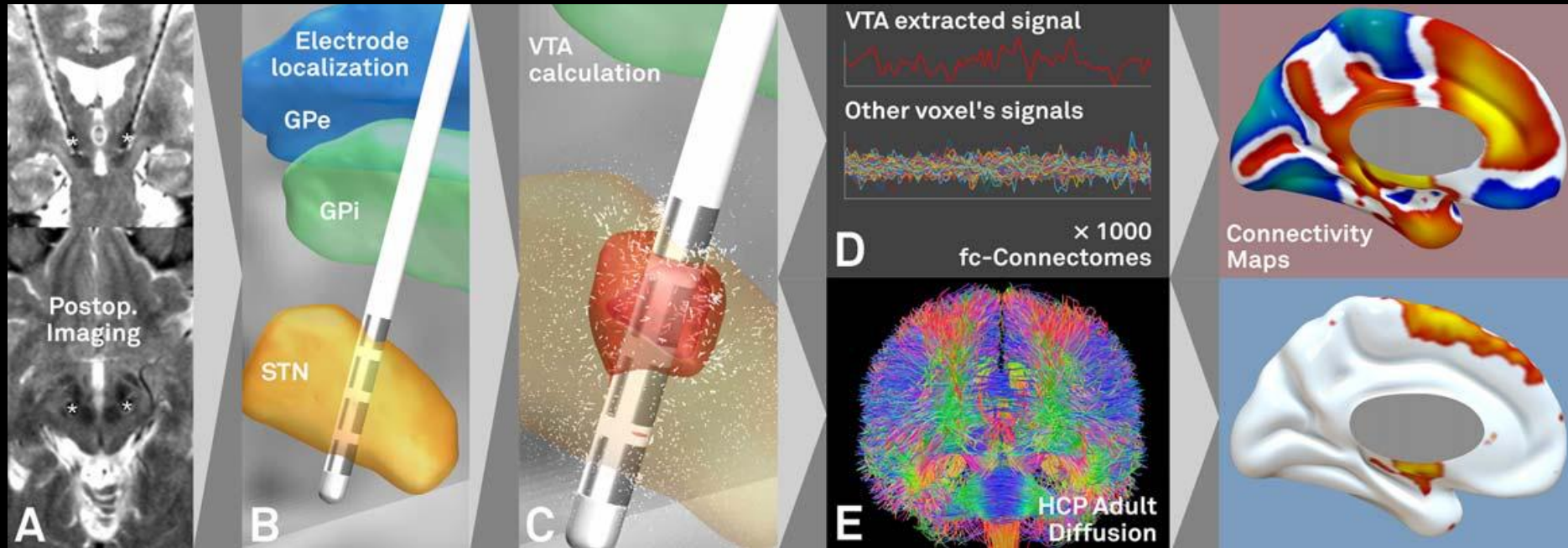
- Open loop DBS:
 - Constant stimulation 24 hours per day
- Closed loop DBS:
 - Records brain activity continuously and only gives a pulse of stimulation when it senses an abnormal Parkinson's rhythm



Future of DBS: Faster Programming

- Currently it can take months of trial and error to find the right settings
- New approaches use MRI and computer models to find the ideal settings

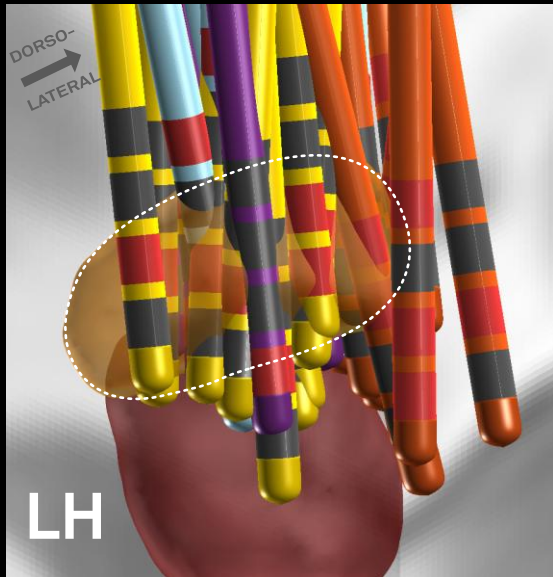
Future of DBS: Connectomics



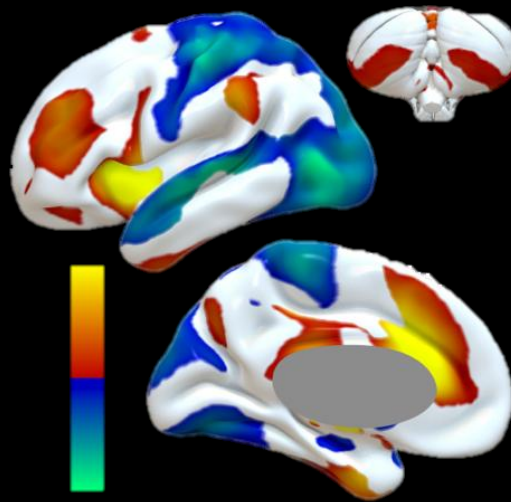
Horn et. al 2017 *Annals of Neurology*

DBS Network Mapping

Stim. Site Variability



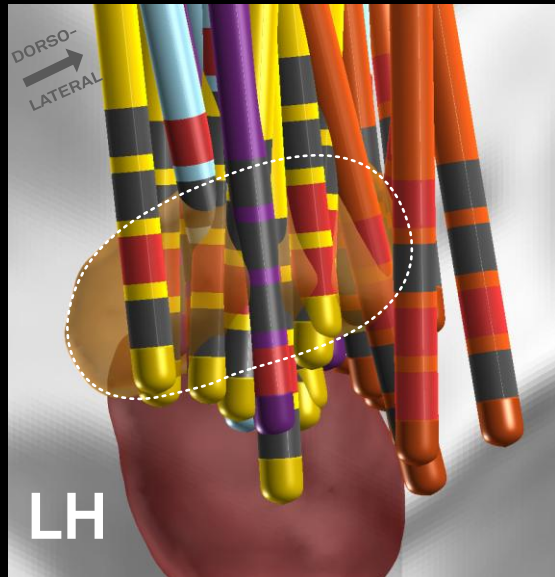
Important Connections



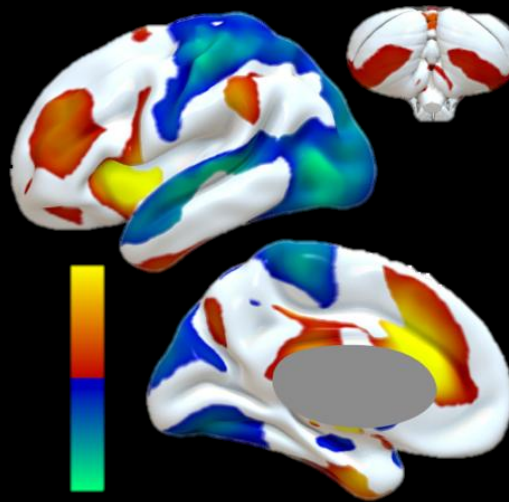
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DBS Network Mapping

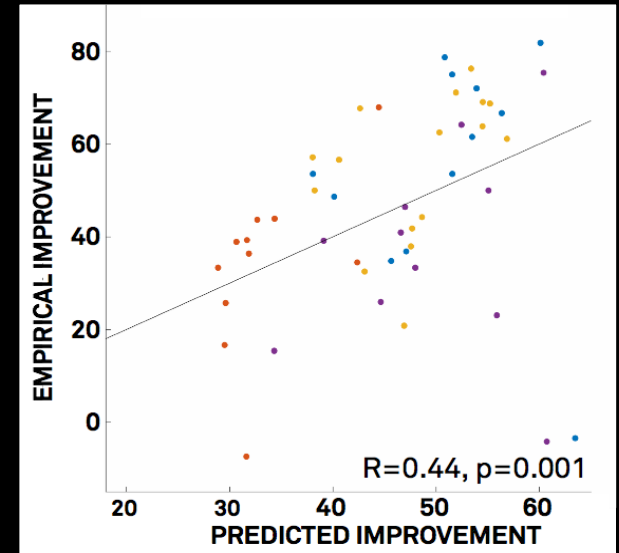
Stim. Site Variability



Important Connections



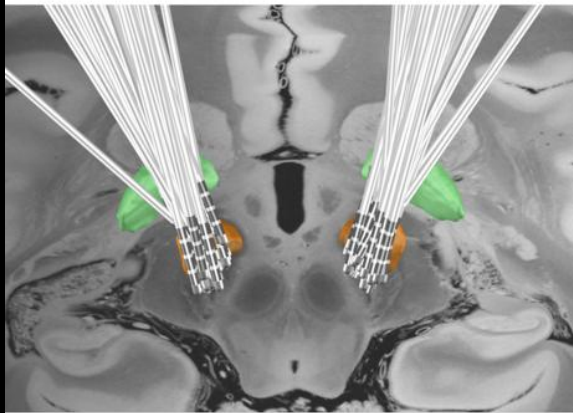
Response Prediction



Horn et. al 2017 Annals of Neurology

DBS Network Mapping

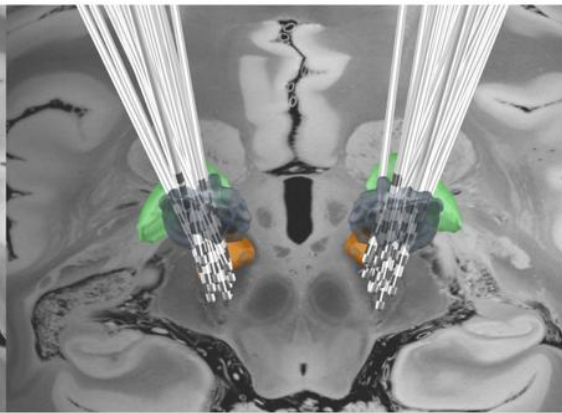
PARKINSON'S DISEASE



STN

GPi

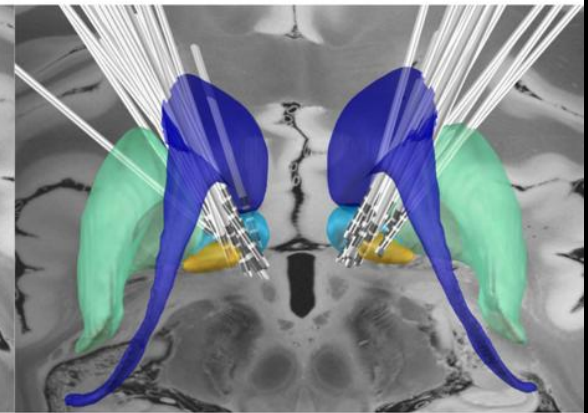
ESSENTIAL TREMOR



VIM

Ca

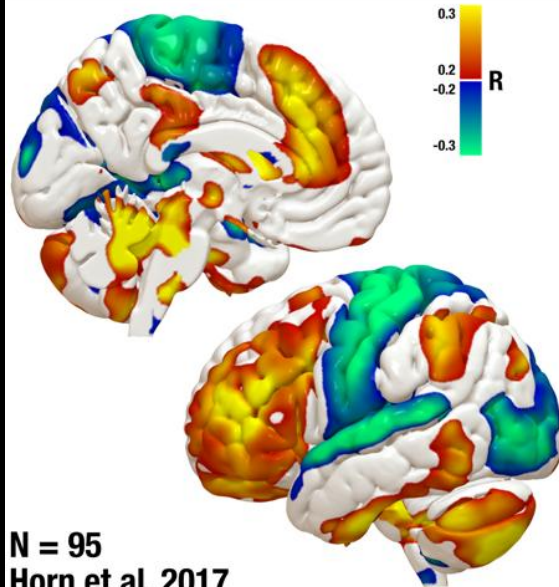
OBSESSIVE COMPULSIVE DISORDER



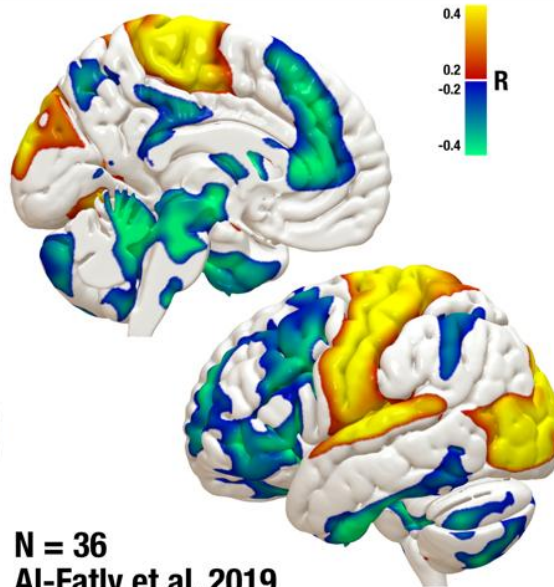
Pu

NAcc

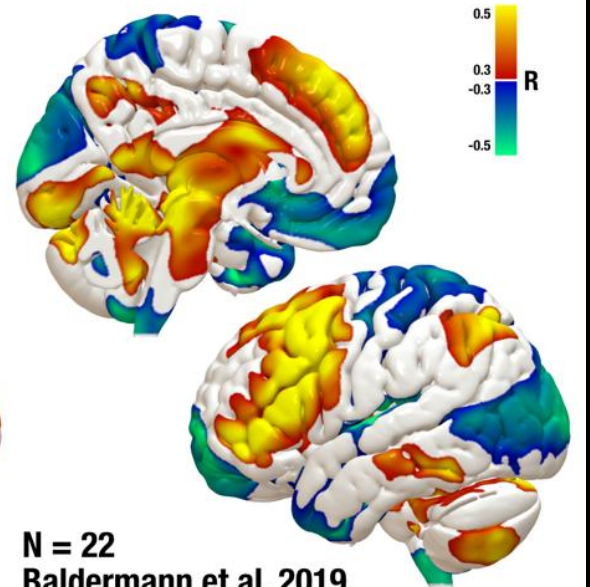
vPall



N = 95
Horn et al. 2017



N = 36
Al-Fatly et al. 2019

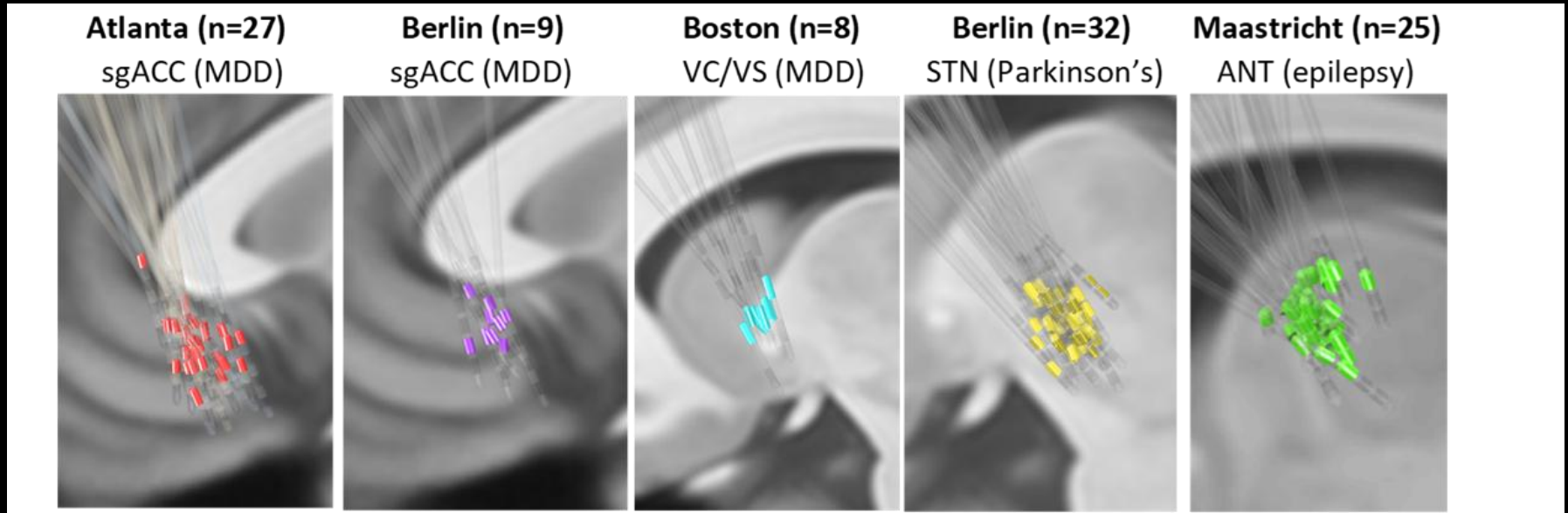


N = 22
Baldermann et al. 2019



Review: Horn and Fox 2020 Neuroimage

DBS Network Mapping: Depression

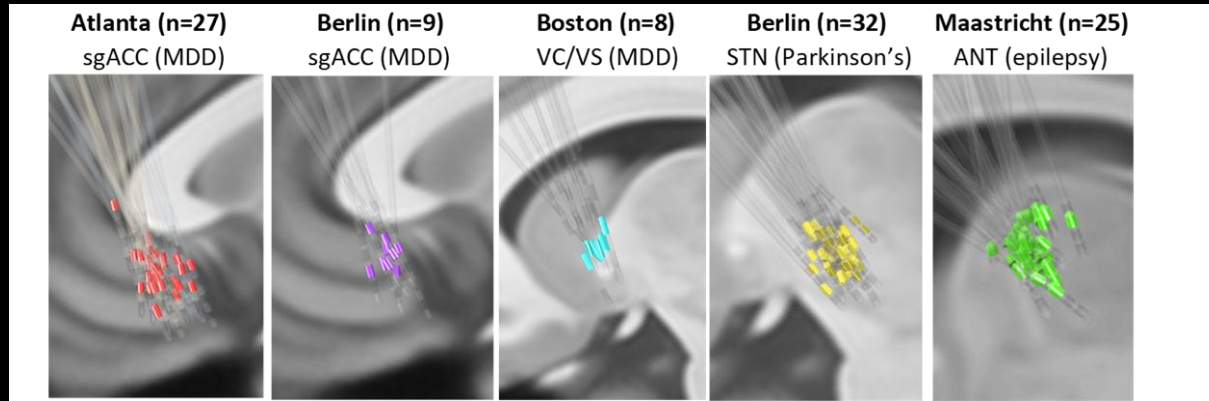


DBS for Depression: 5 cohorts, 101 electrodes

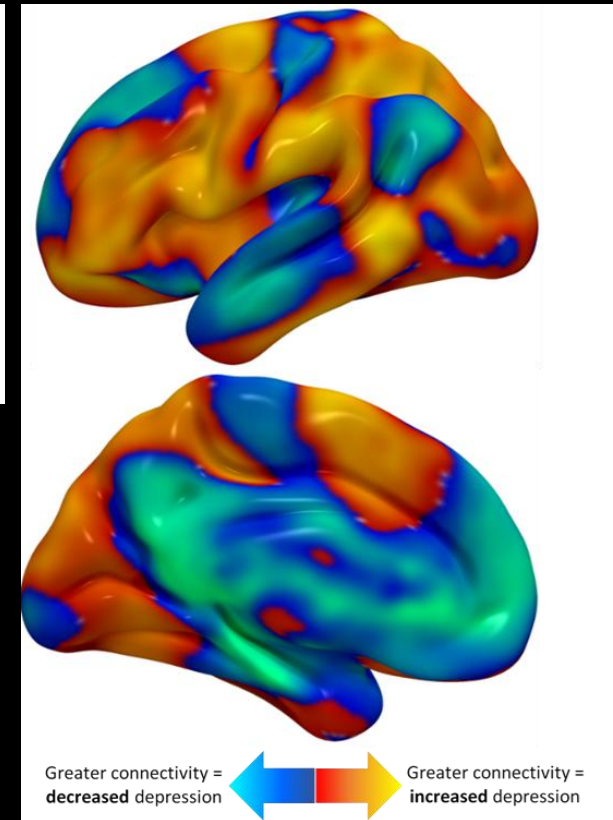


Siddiqi et al. 2021 Nature Hum Behav

DBS Network Mapping: Depression

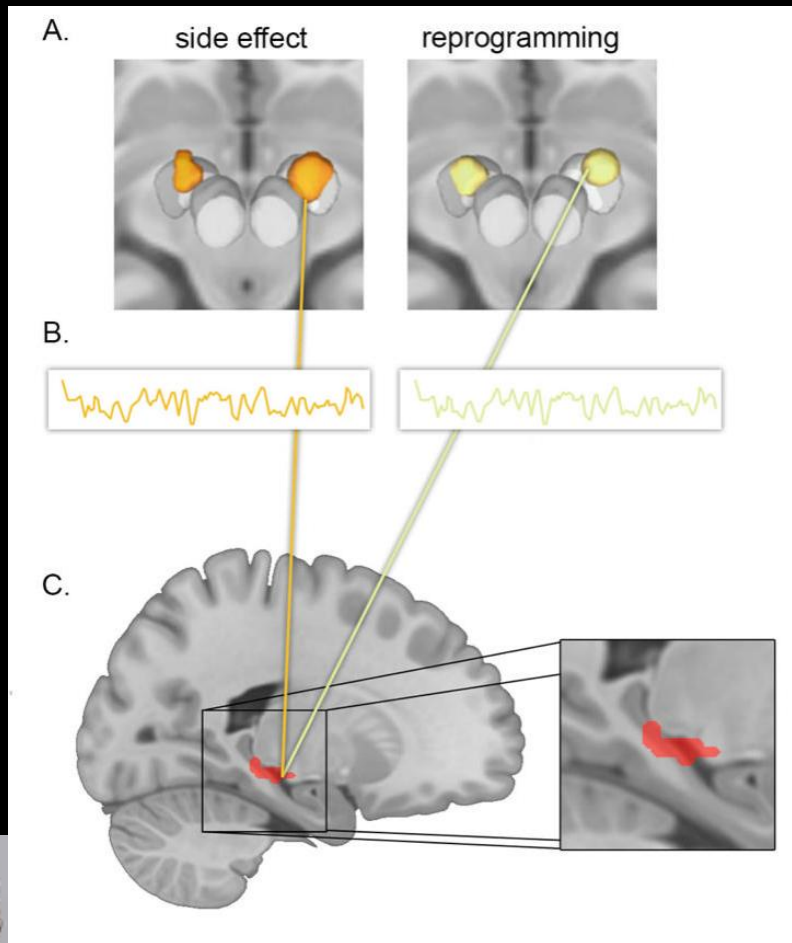


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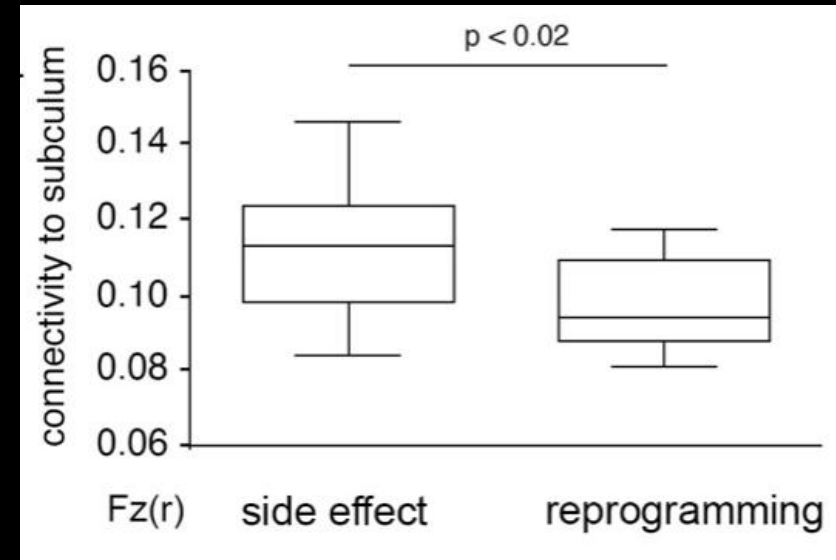
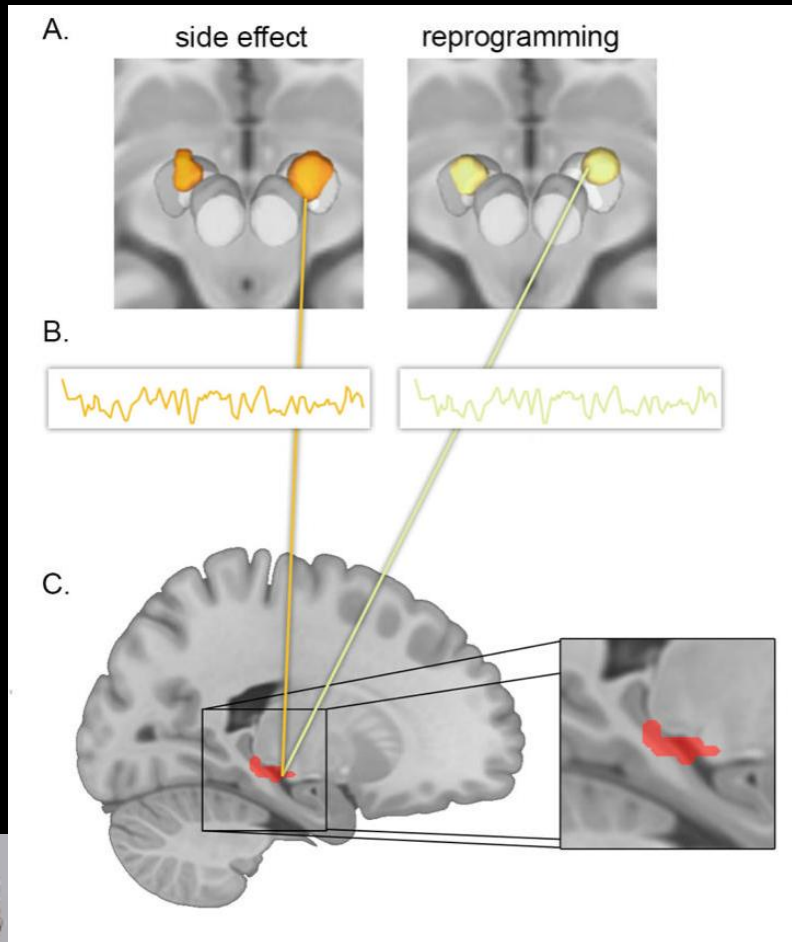
Siddiqi et al. 2021 Nature Hum Behav

DBS Network Mapping: Cognition



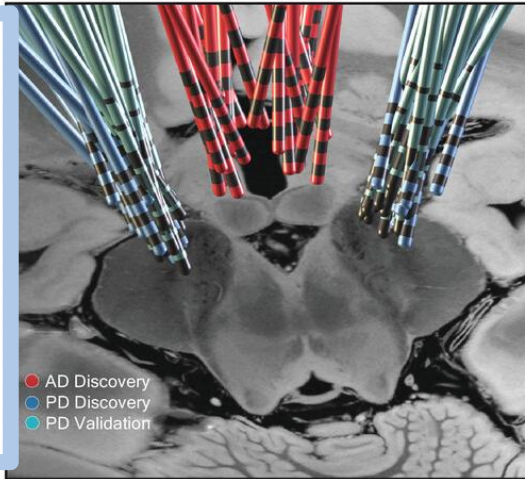
Reich et al. 2022 Brain

DBS Network Mapping: Cognition

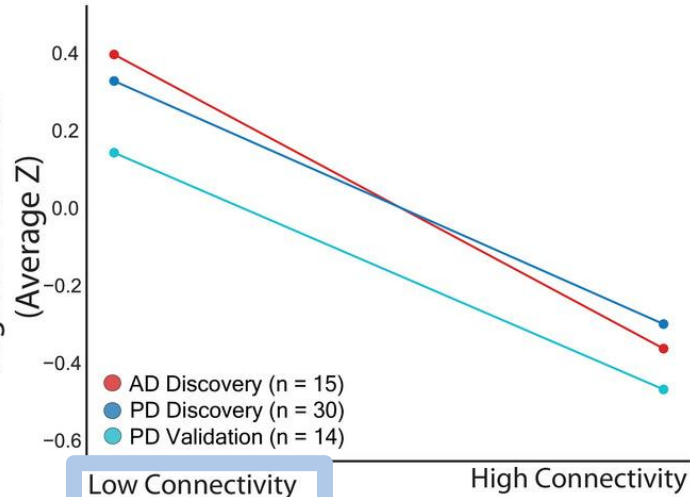


DBS Network Mapping: Cognition

Patients Under 65



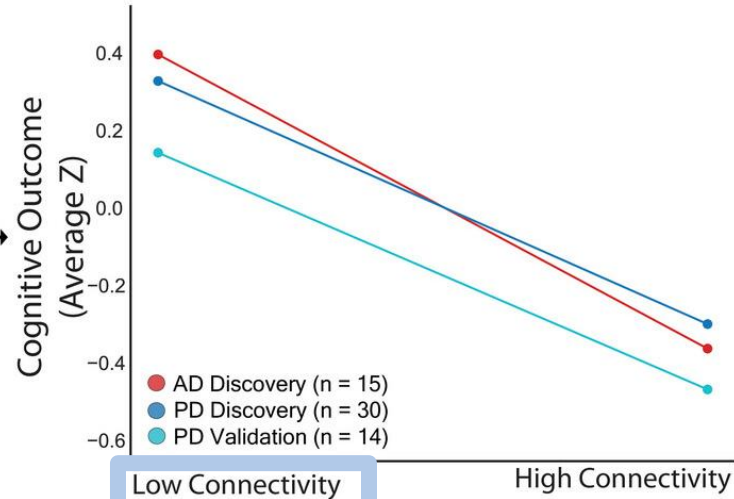
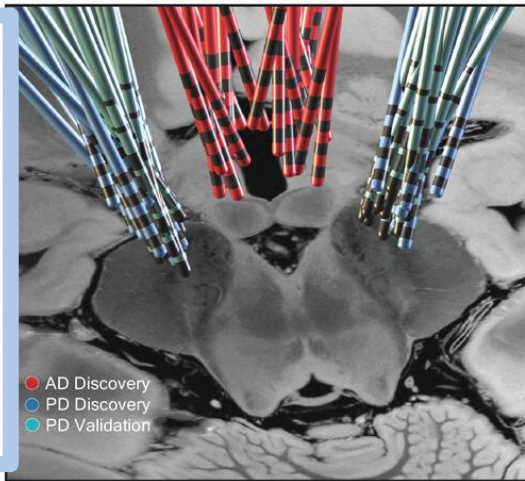
Cognitive Outcome
(Average Z)



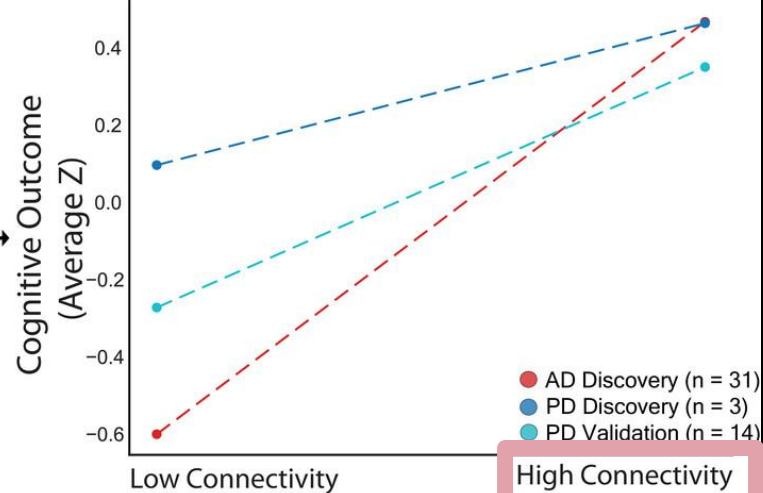
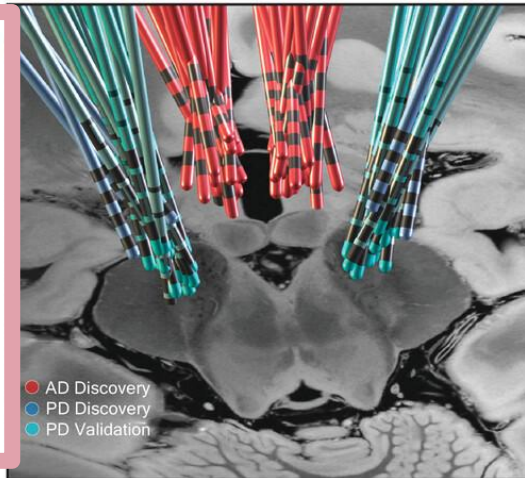
Howard et al. 2025 Alz and Dementia

DBS Network Mapping: Cognition

Patients Under 65



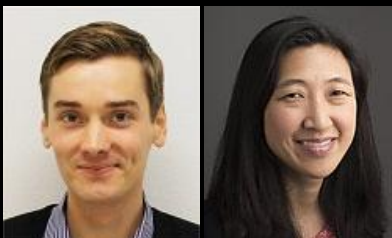
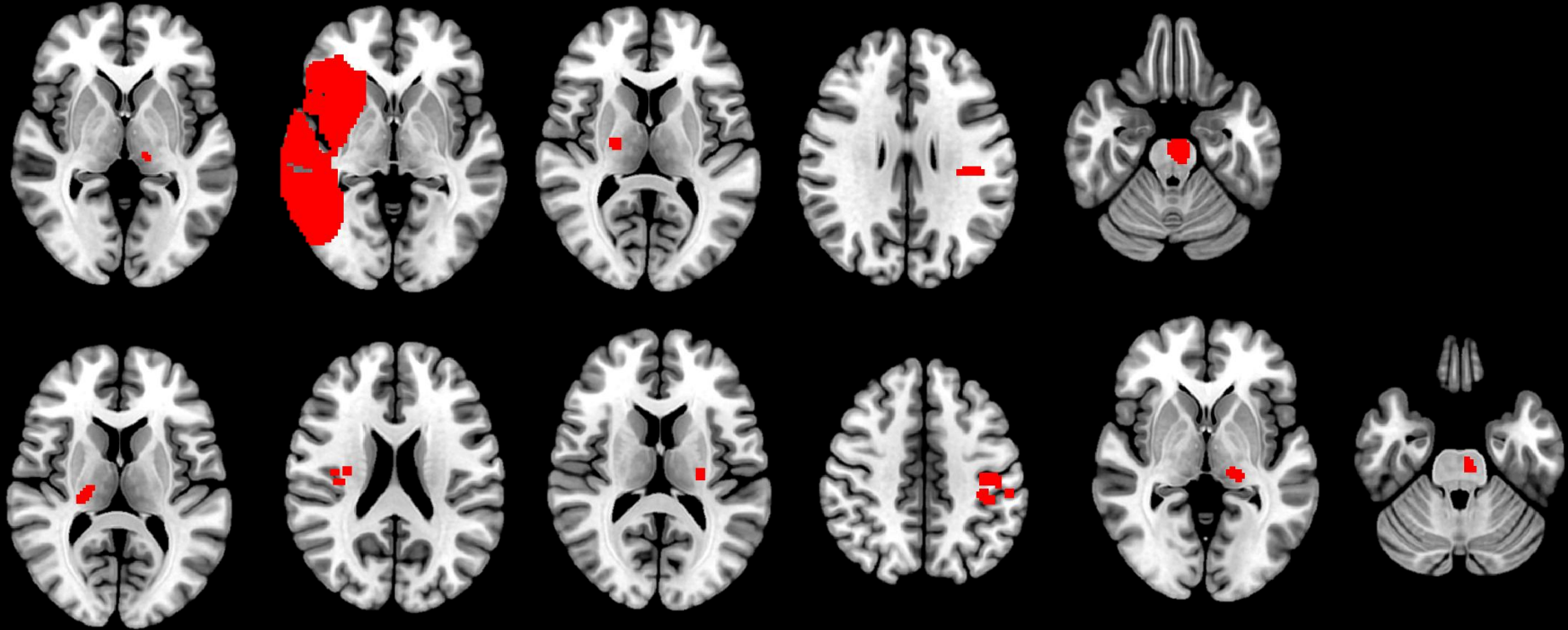
Patients Over 65



New surgical Targets

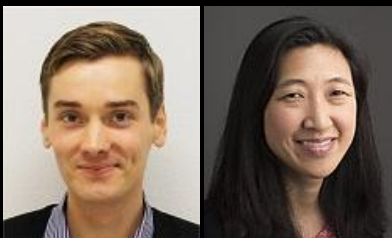
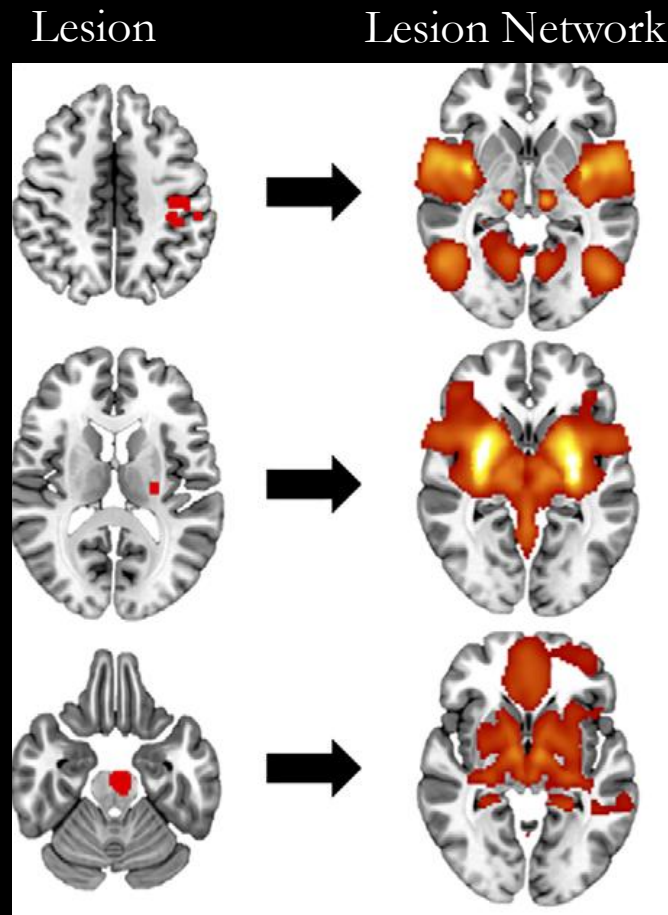
- Most existing DBS targets were identified through trial and error, often using lesions
- The search is on for new targets / indications

New Approach for Finding Targets



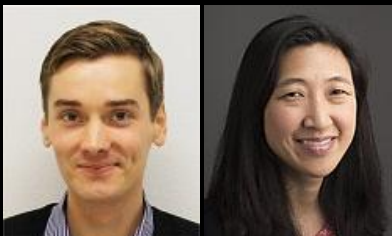
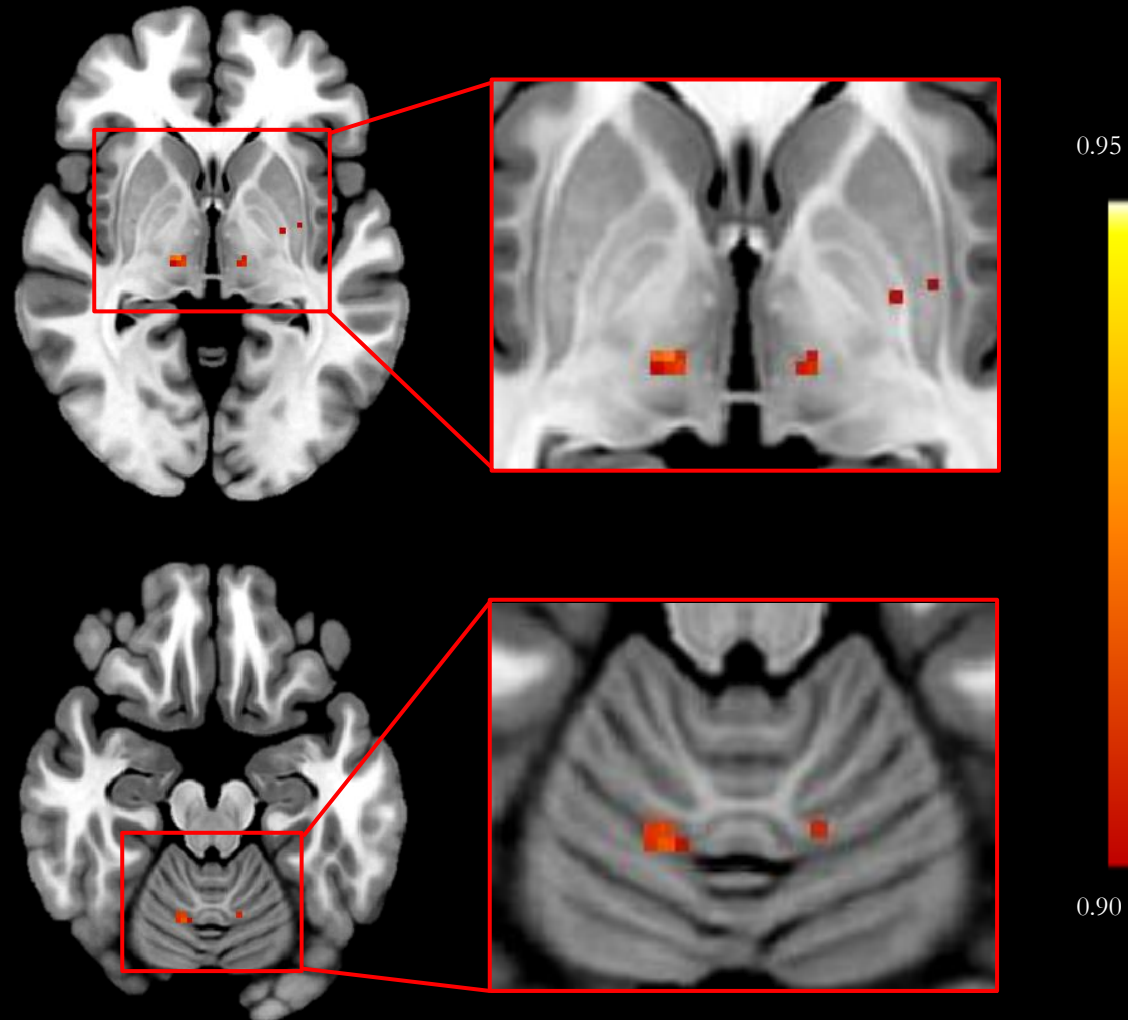
Joutsa, Shih et al. 2018 *Annals of Neurology*

New Approach for Finding Targets



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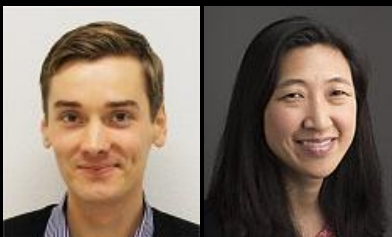
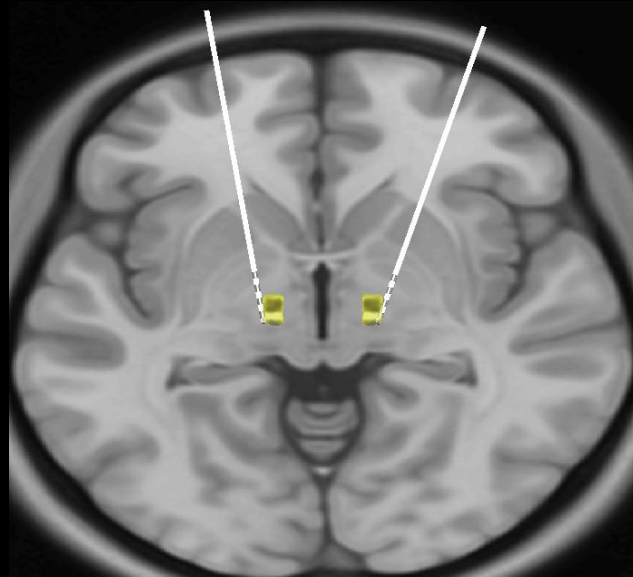
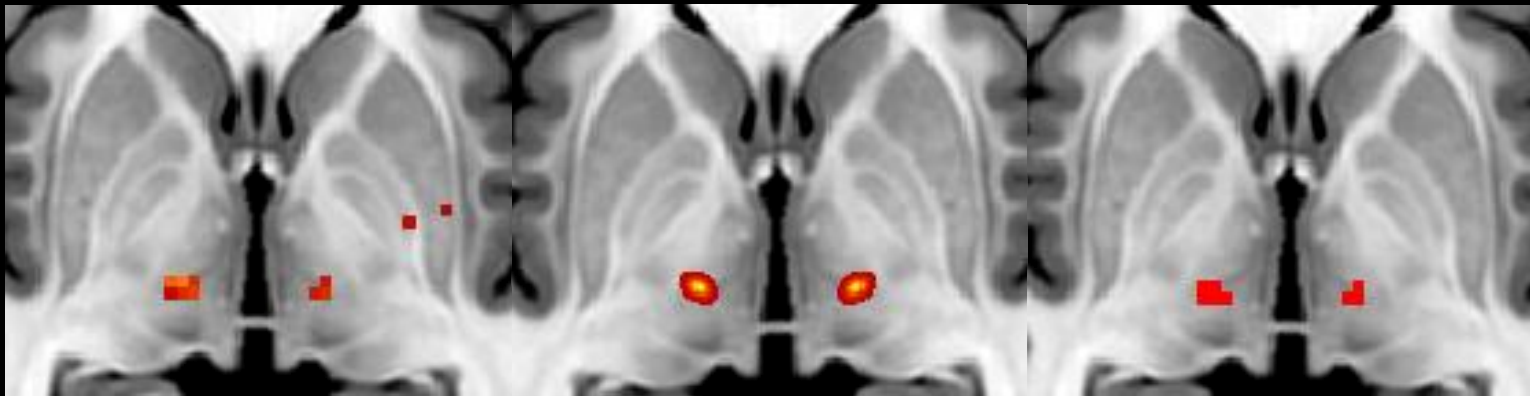
Joutsa, Shih et al. 2018 *Annals of Neurology*

New Approach for Finding Targets

Lesion connectivity

VIM target

Overlap



Joutsa, Shih et al. 2018 *Annals of Neurology*

Lesion Network Mapping

Addiction Remission

Joutsa et al. 2022 Nature Medicine

Aggression

Peng et al. 2025 Biol. Psych

Alice in Wonderland Syndrome

Friedrich et al. 2024 Annl. of Neuro

Amnesia

Ferguson, Lim et al. 2019 Nature Comm., Kletenik et al. 2023 J Neurol.

Anosognosia

Kletenik et al. 2023 Annl. of Neurology

Anxiety

Siddiqi et al. 2024 ResSq

Aphantasia

Kutsche et al. 2025 MedRxiv

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Cohen et al. 2023 Ann Neurol., Herman et al. Ann Child Neuro 2026

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Criminality

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Delusions

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Freezing of Gait

Fasano et al. 2017 Annl. of Neurology

Free Will

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Facial Recognition

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Luo et al 2026 medRxiv

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Psychiatric Comorbidity

Taylor et al. 2023 Nature Hum. Behav

Psychosis

Pines et al . 2025 JAMA Psych

Post Traumatic Stress Disorder

Siddiqi et al. 2024 Nature Neurosci.

Religion / Spirituality

Ferguson et al. 2022 Bio Psych, Ferguson et al. 2024 PNAS

Stroke Severity

Bonkhoff et al. 2024 ACTN

Spatial Orientation

Roseman et al. 2024 Cerebral Cortex

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Tremor Relief

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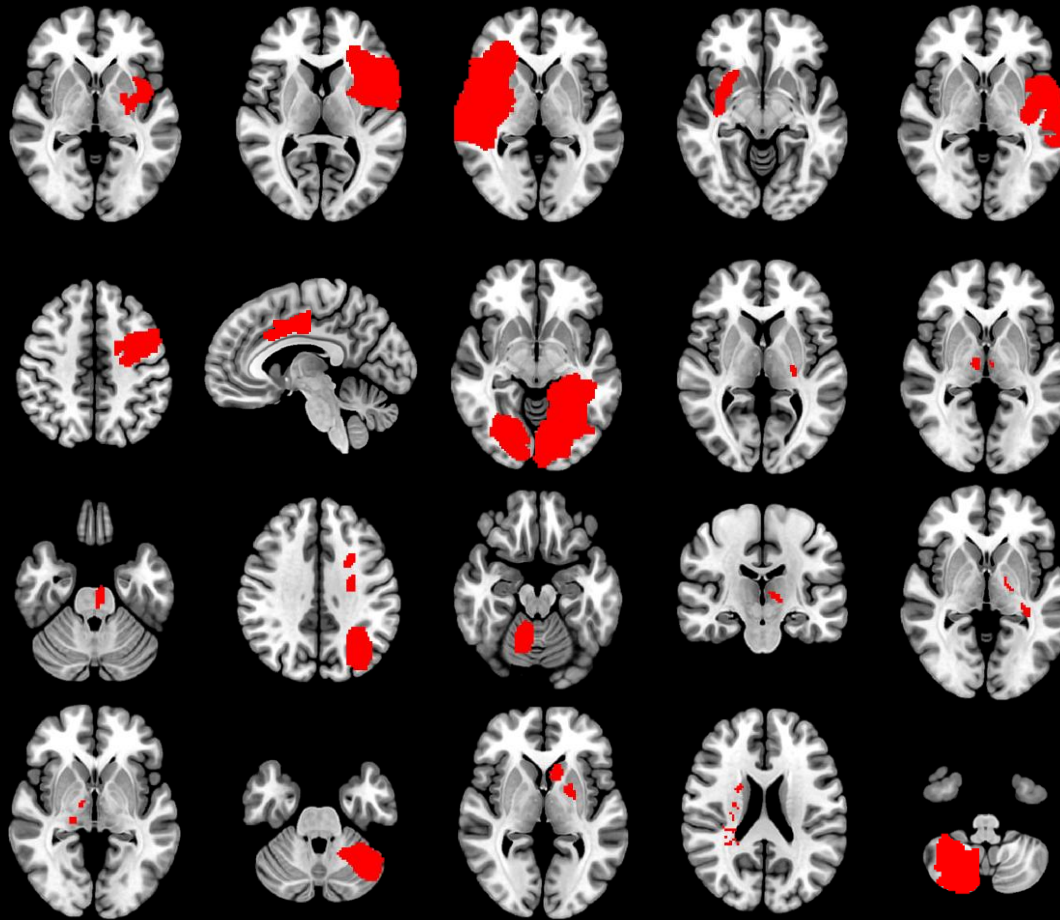
Friedrich et al. 2026 Brain

Vertigo

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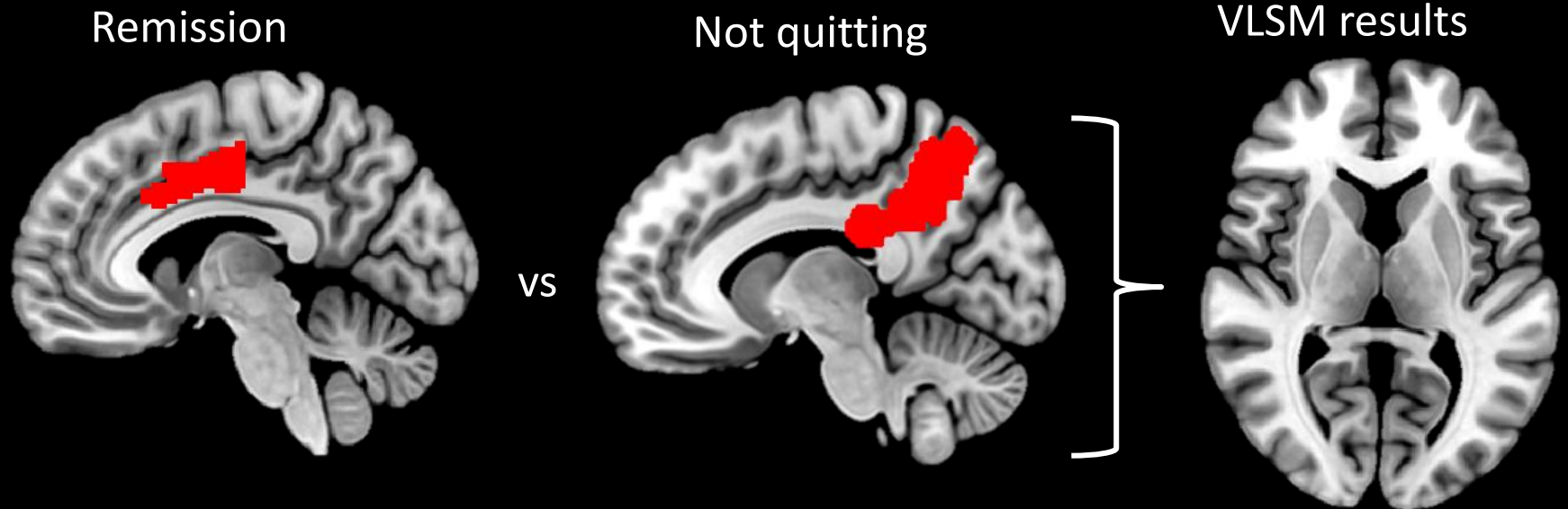
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Addiction Remission



Joutsa, Moussawi, Siddiqi et al. 2022 Nature Medicine

Addiction Remission



Joutsa, Moussawi, Siddiqi et al. 2022 Nature Medicine

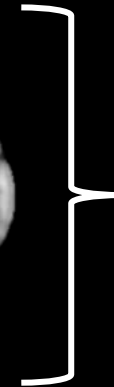
Addiction Remission

Remission

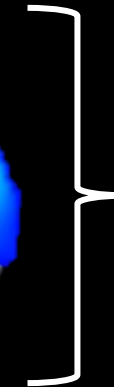
Not quitting

VLSM results

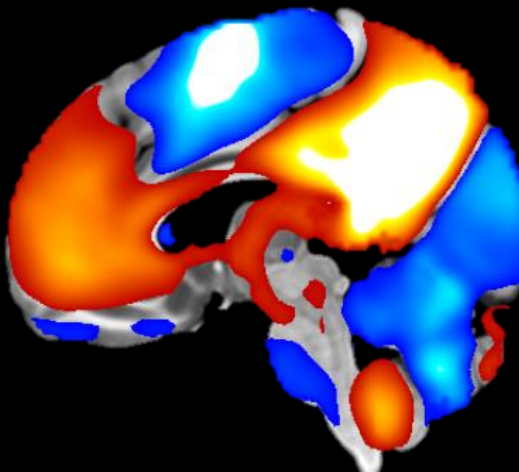
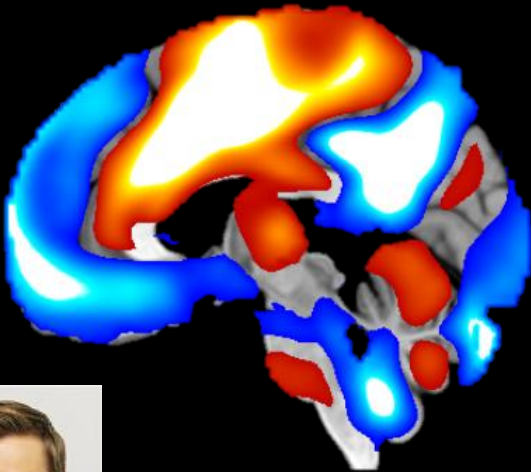
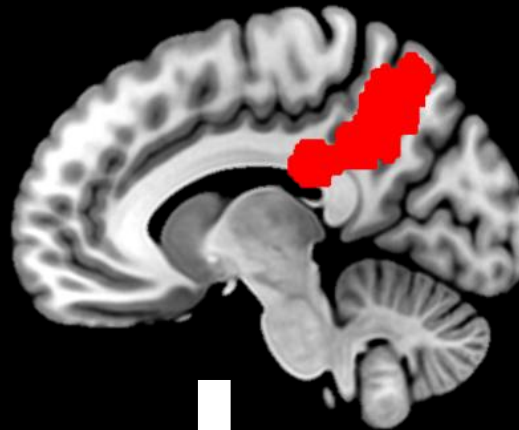
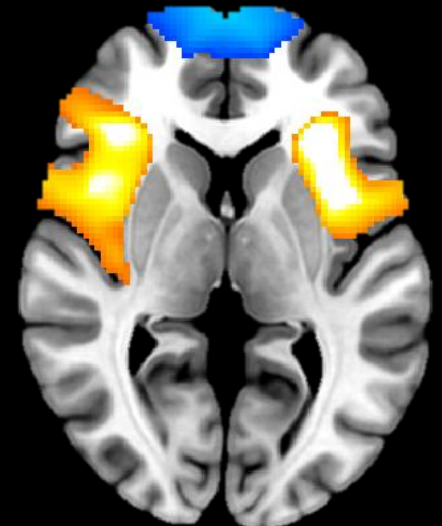
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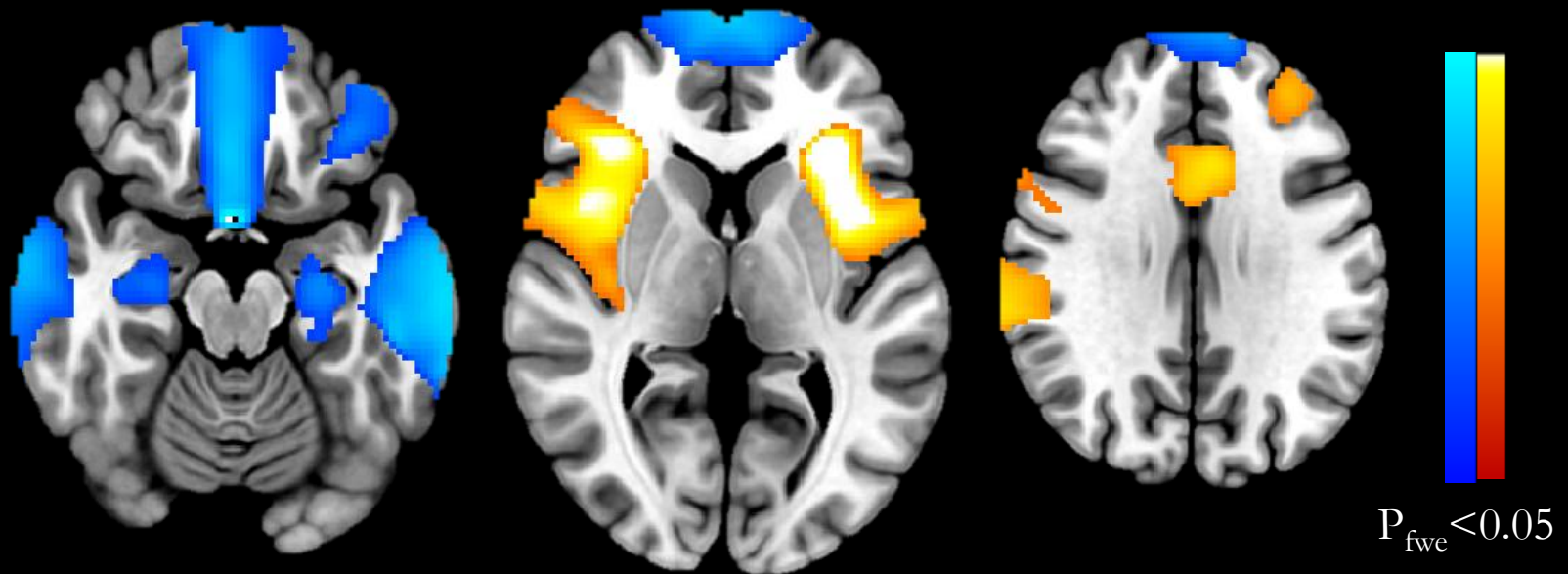


LNM results



Joutsa, Moussawi, Siddiqi et al. 2022 Nature Medicine

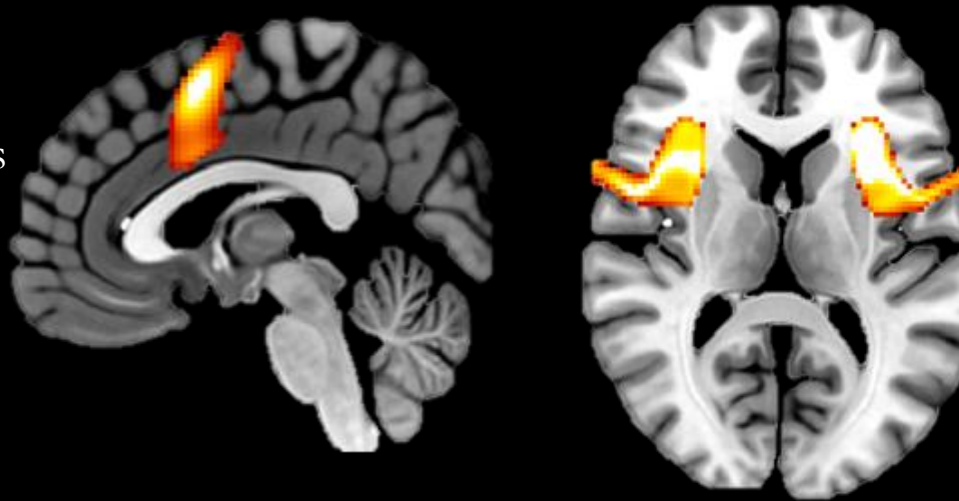
Addiction Remission



Joutsa, Moussawi, Siddiqi et al. 2022 Nature Medicine

Addiction Remission Targets

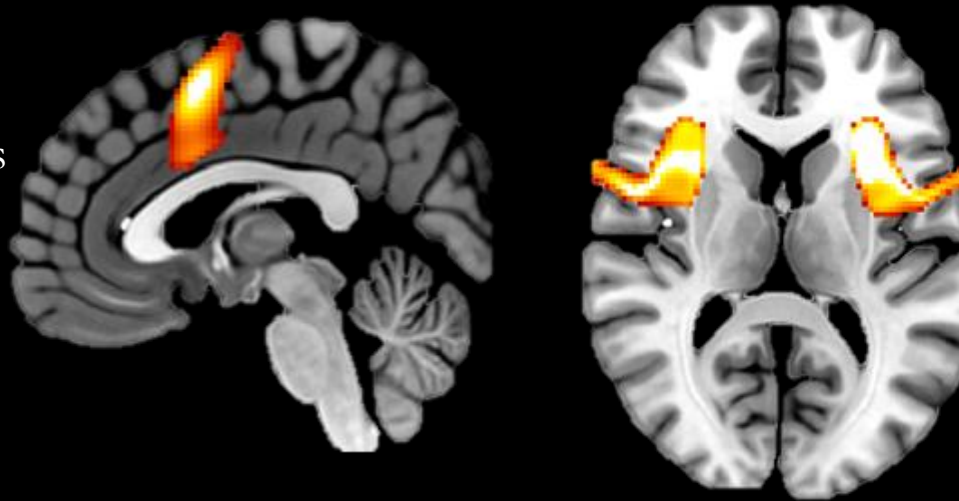
Lesion / DBS Targets



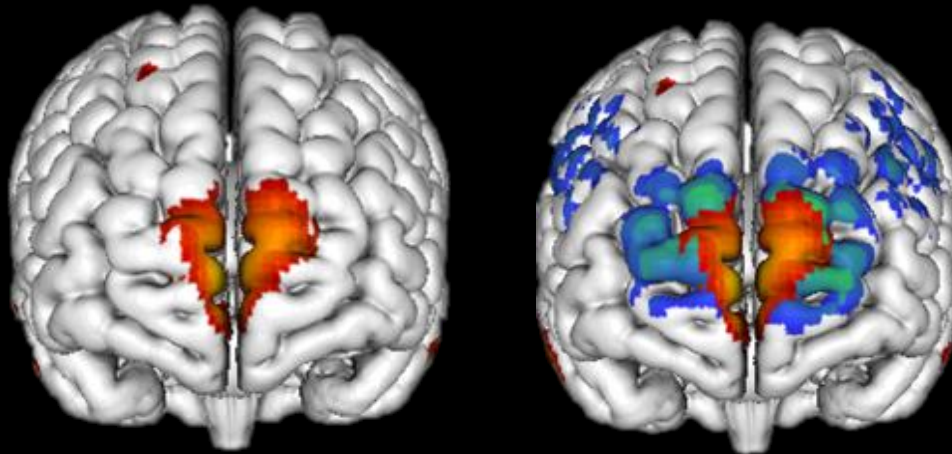
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Addiction Remission Targets

Lesion / DBS Targets

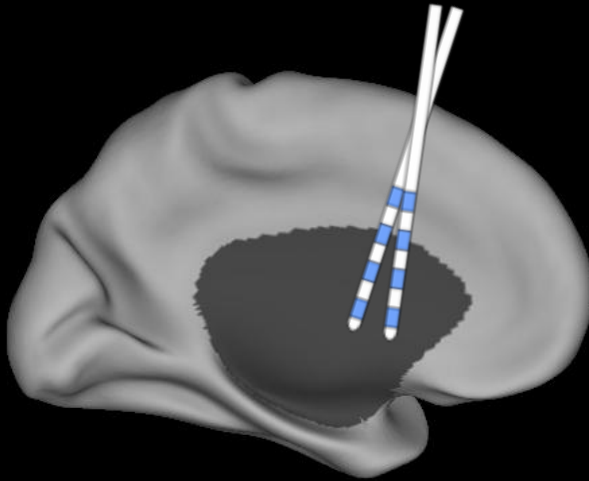


TMS Targets



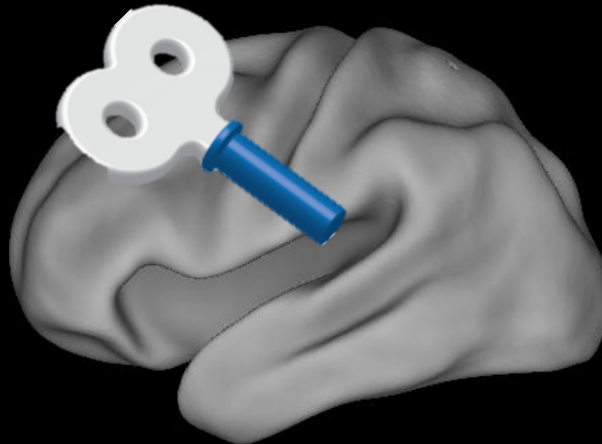
Therapeutic Neuromodulation

Deep Brain Stimulation (DBS)



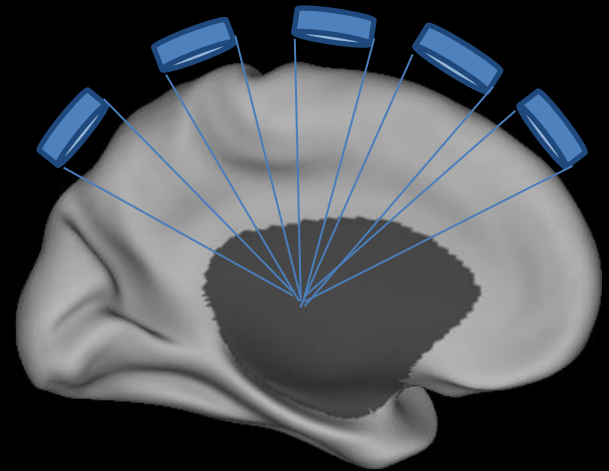
- FDA approved for **Parkinson's**, essential tremor, epilepsy, dystonia, OCD

Transcranial Magnetic Stimulation (TMS)



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Focused Ultrasound (FUS)



- FDA approved for **tremor**

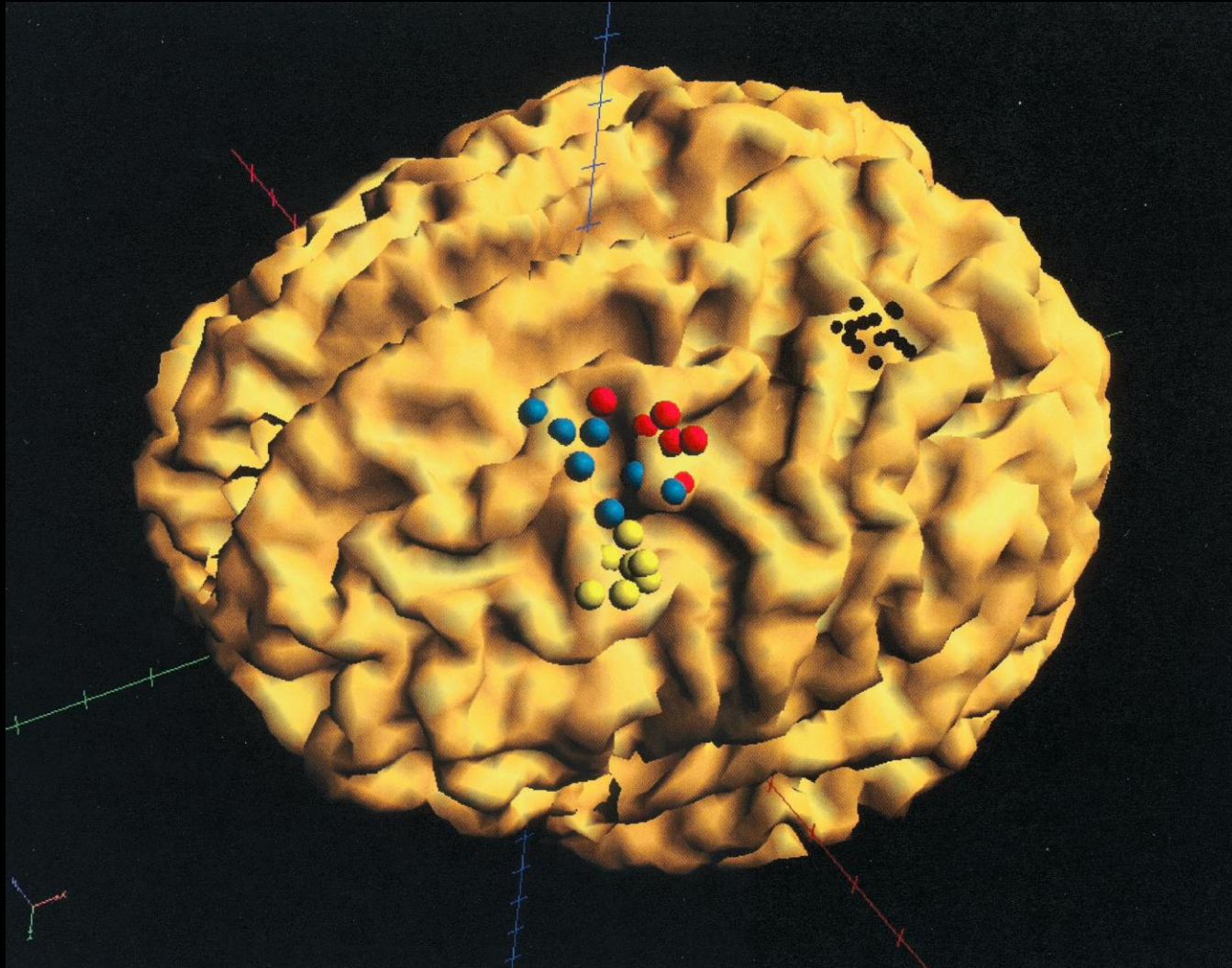
Transcranial Magnetic Stimulation (TMS)

- Electromagnet held outside the scalp
- Changing magnetic field induces an electric current in the underlying brain tissue
- Standard protocol is daily sessions for 4-6 weeks
- New “accelerated” protocols administer 10 sessions per day for 1 week

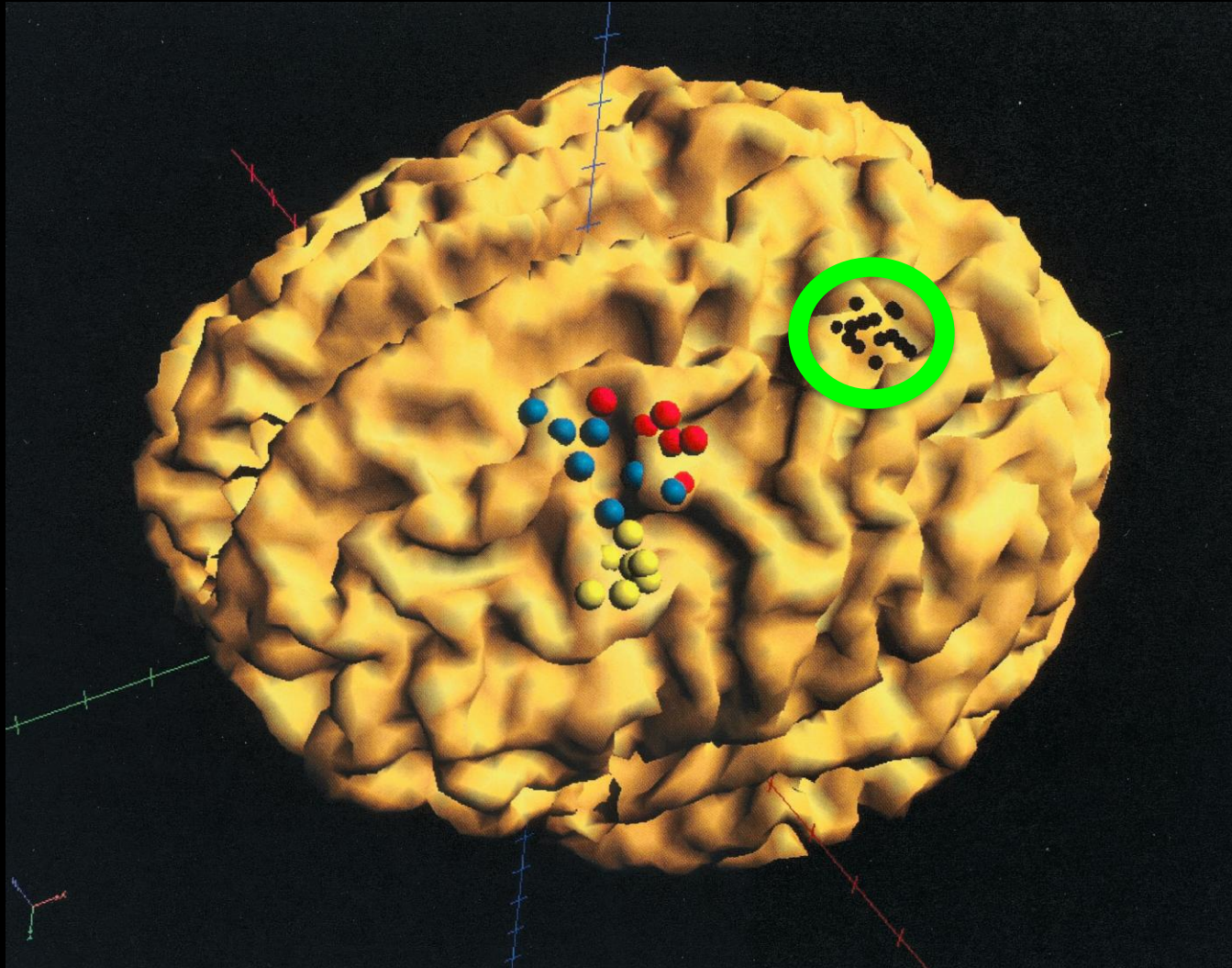
TMS for Depression

- High frequency “excitatory” stimulation to the left DLPFC
- ~60% of patients respond (defined as 50% reduction in depression symptoms)
- 20-30% remission (defined as no longer meeting criteria for depression)

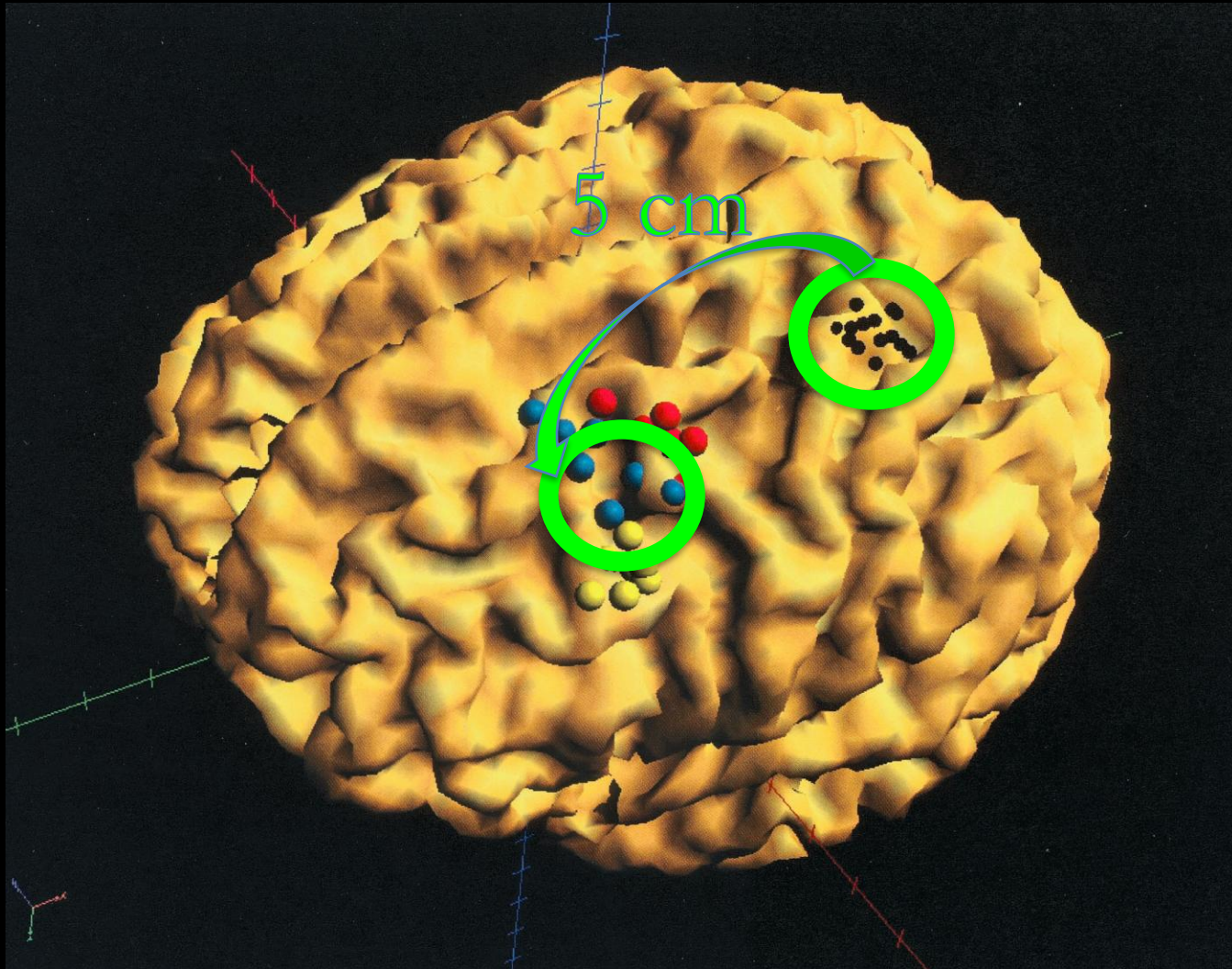
Targeting TMS in Depression: The 5 cm method



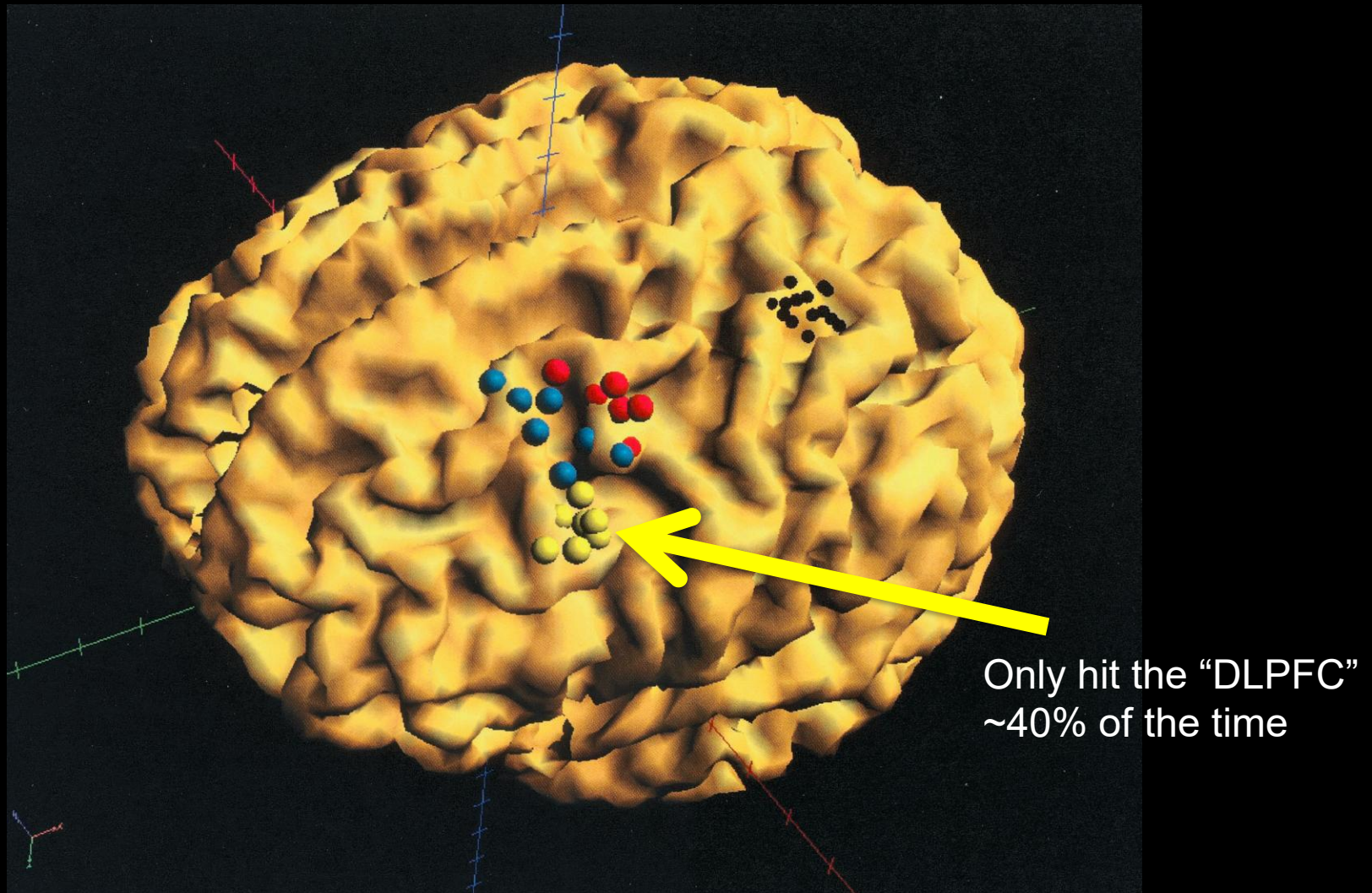
Targeting TMS in Depression: The 5 cm method



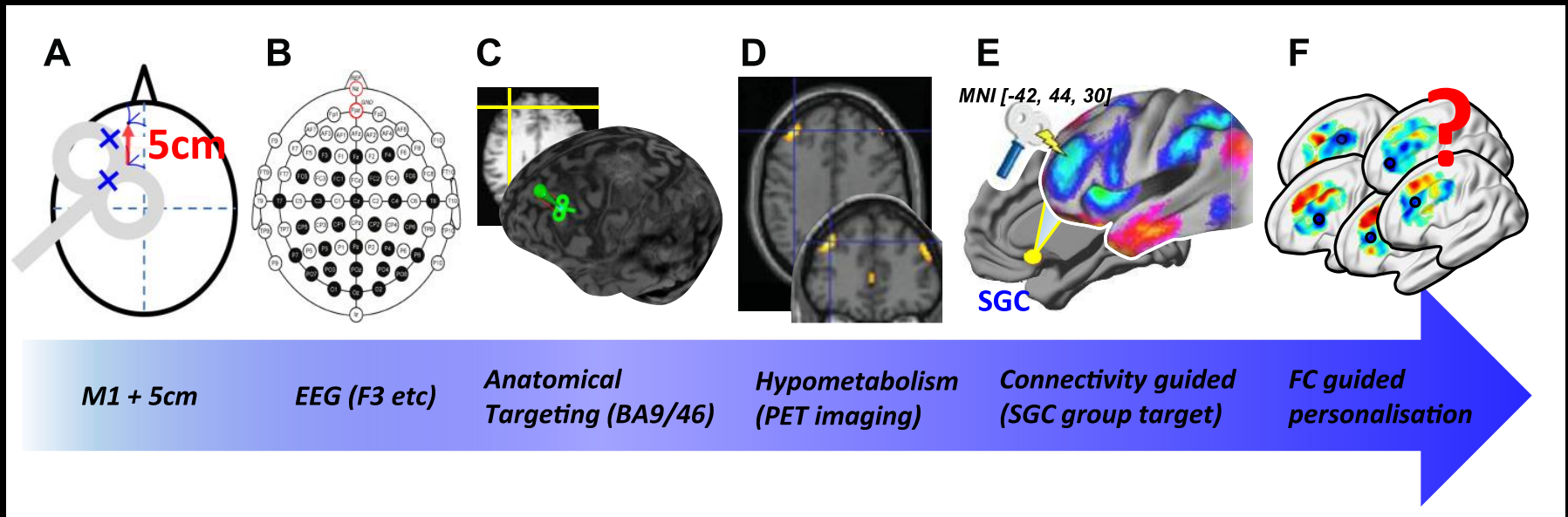
Targeting TMS in Depression: The 5 cm method



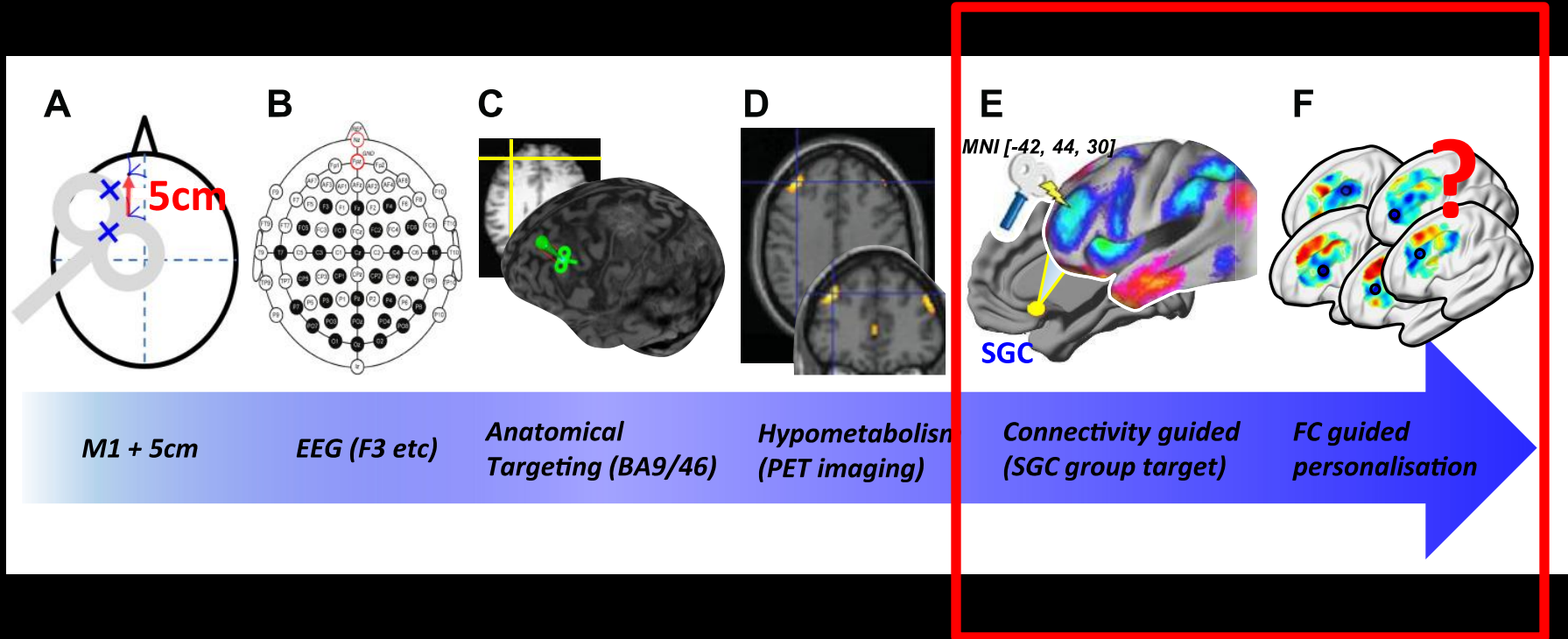
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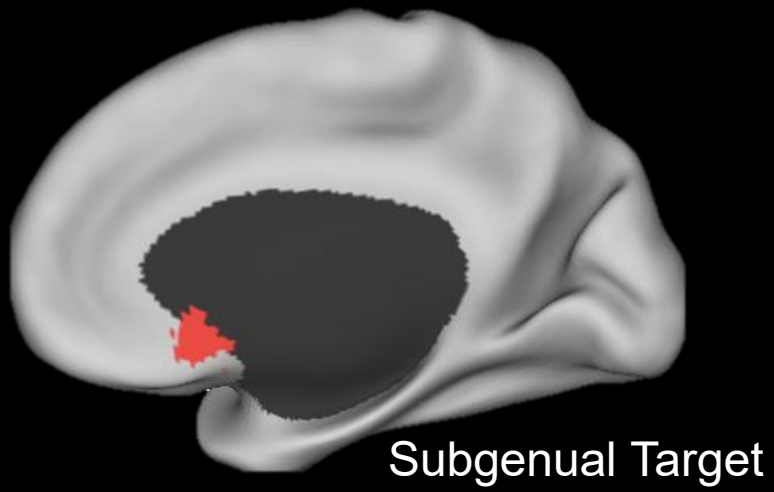


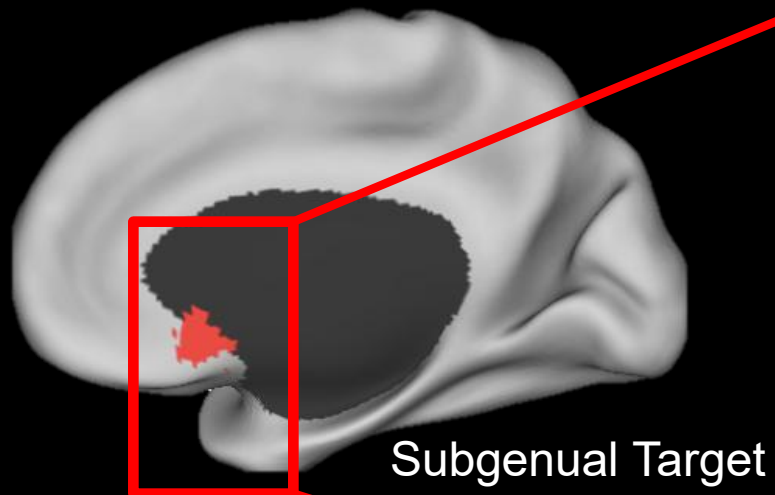
Targeting TMS in Depression



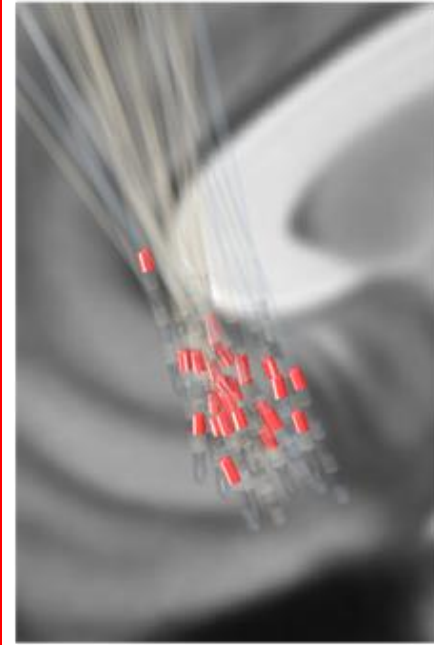
Targeting TMS in Depression

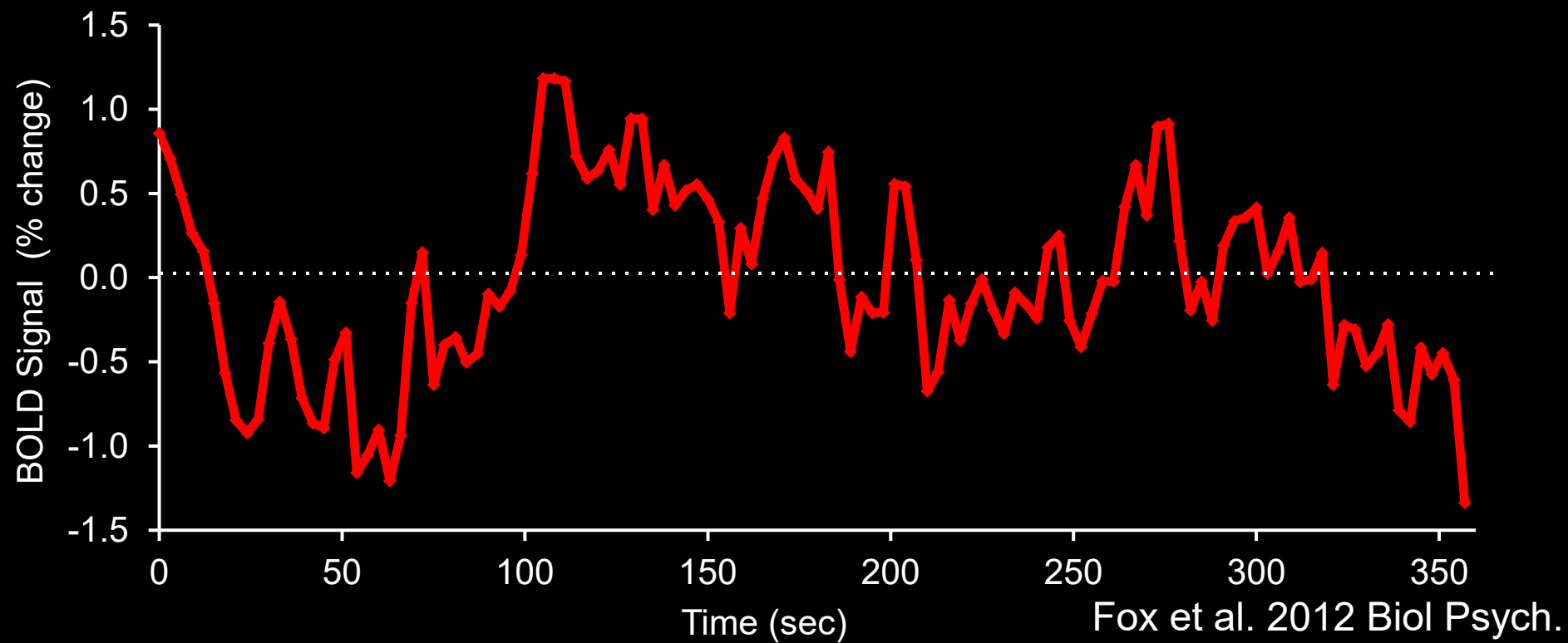
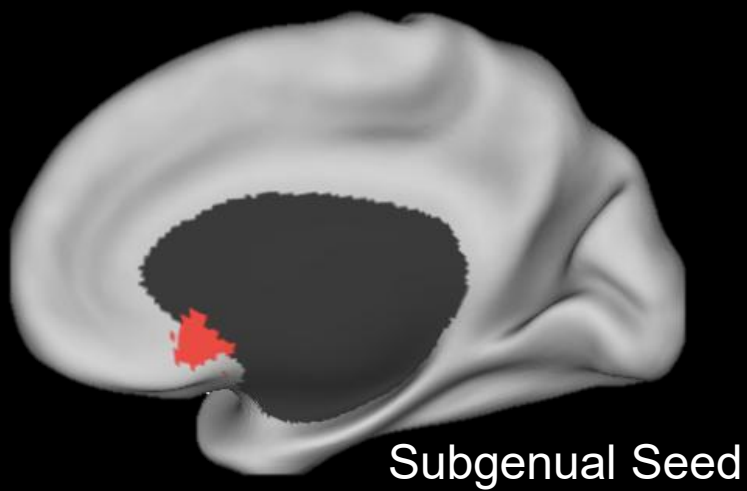


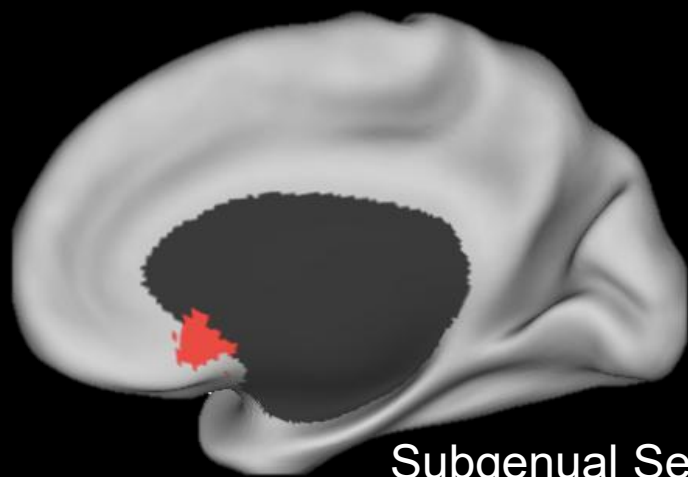




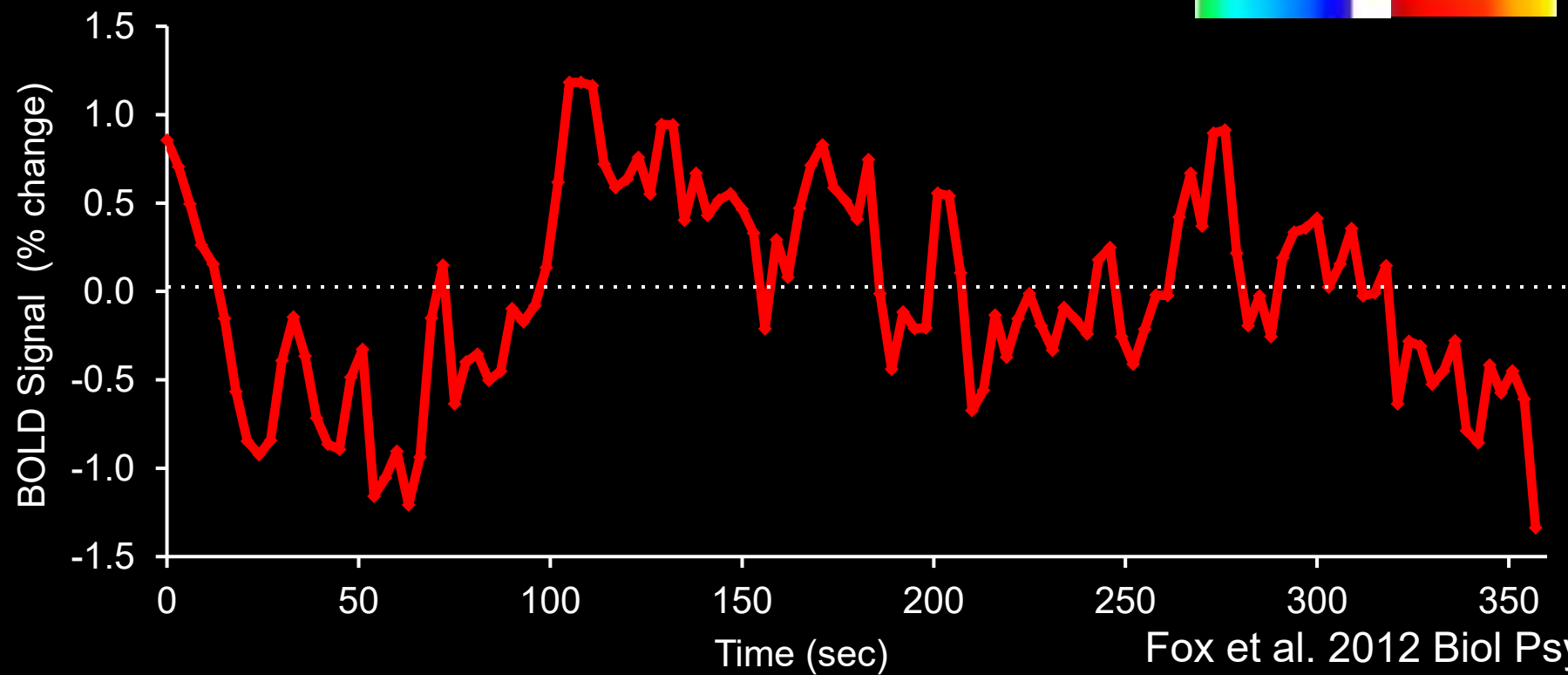
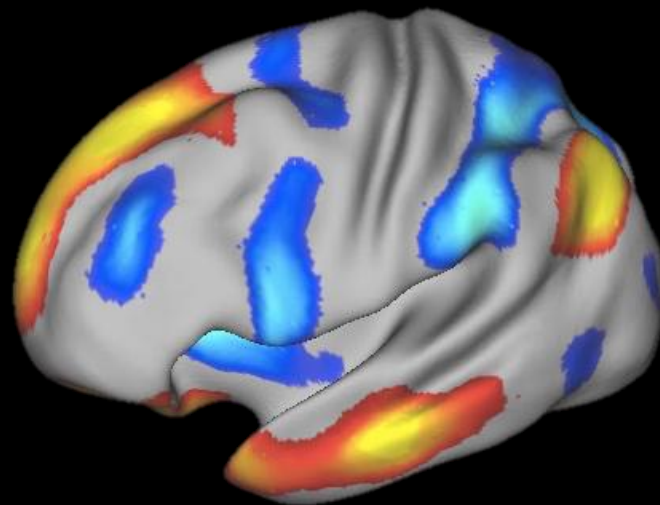
Atlanta (n=27)
sgACC (MDD)

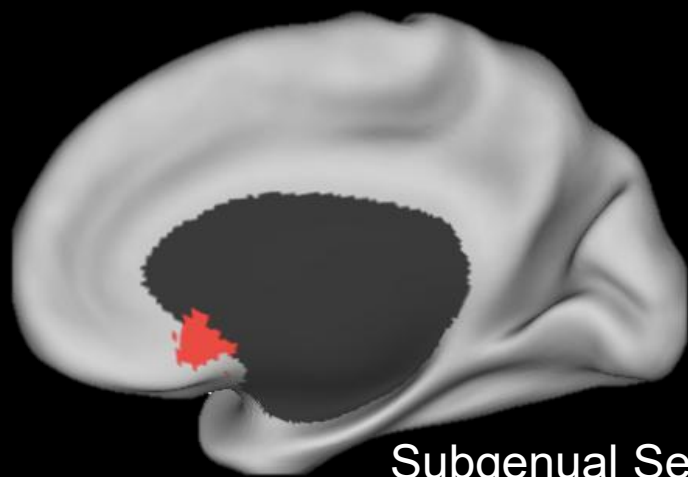




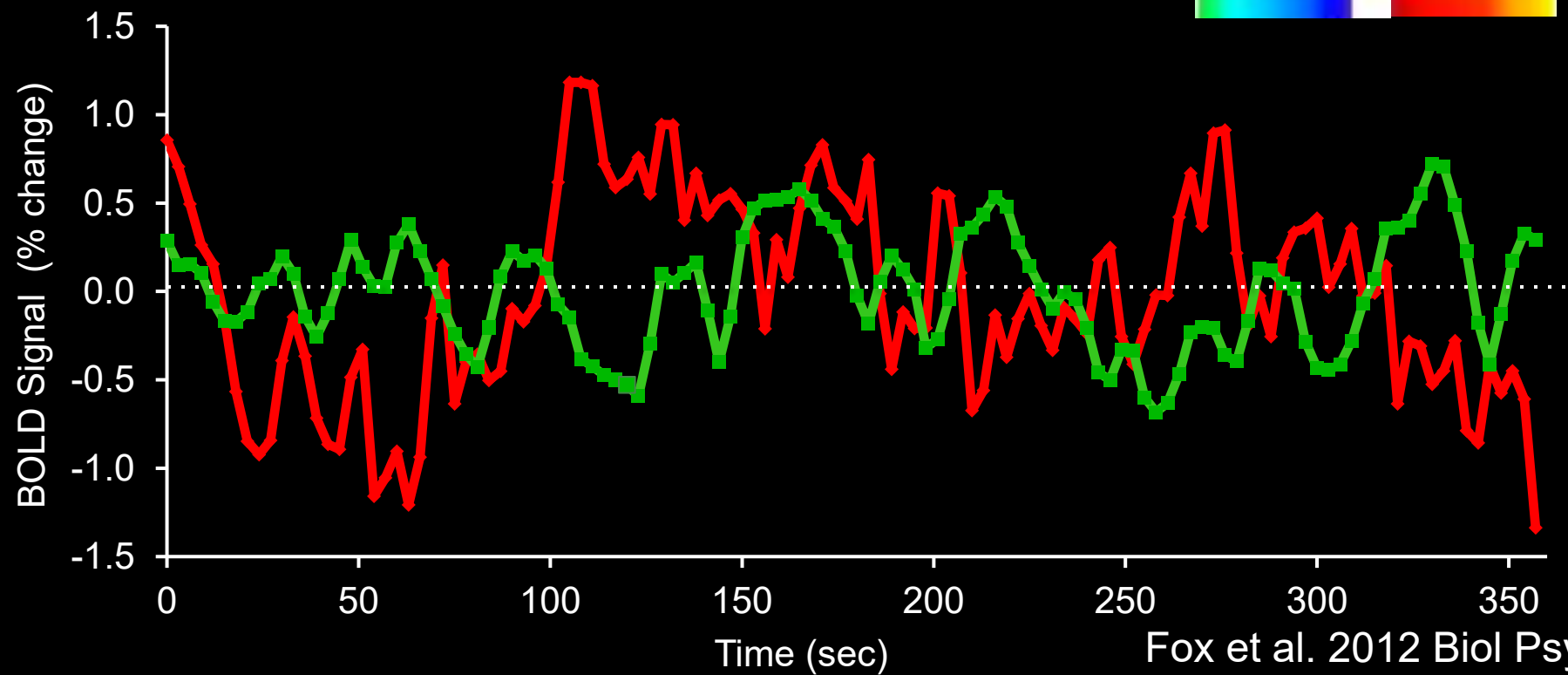
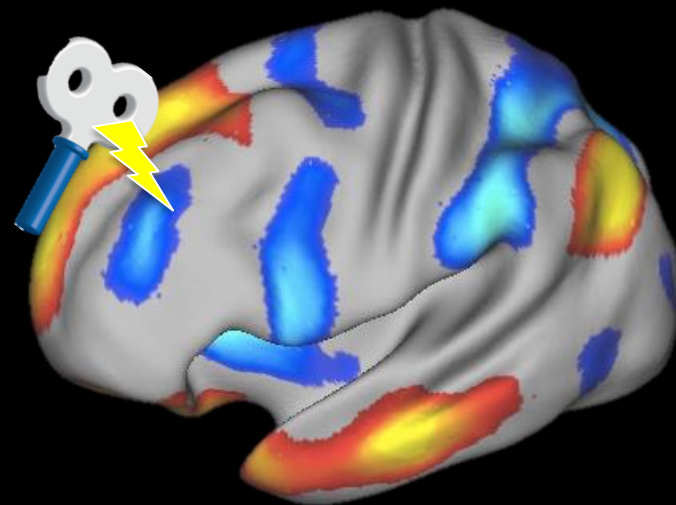


Subgenual Seed

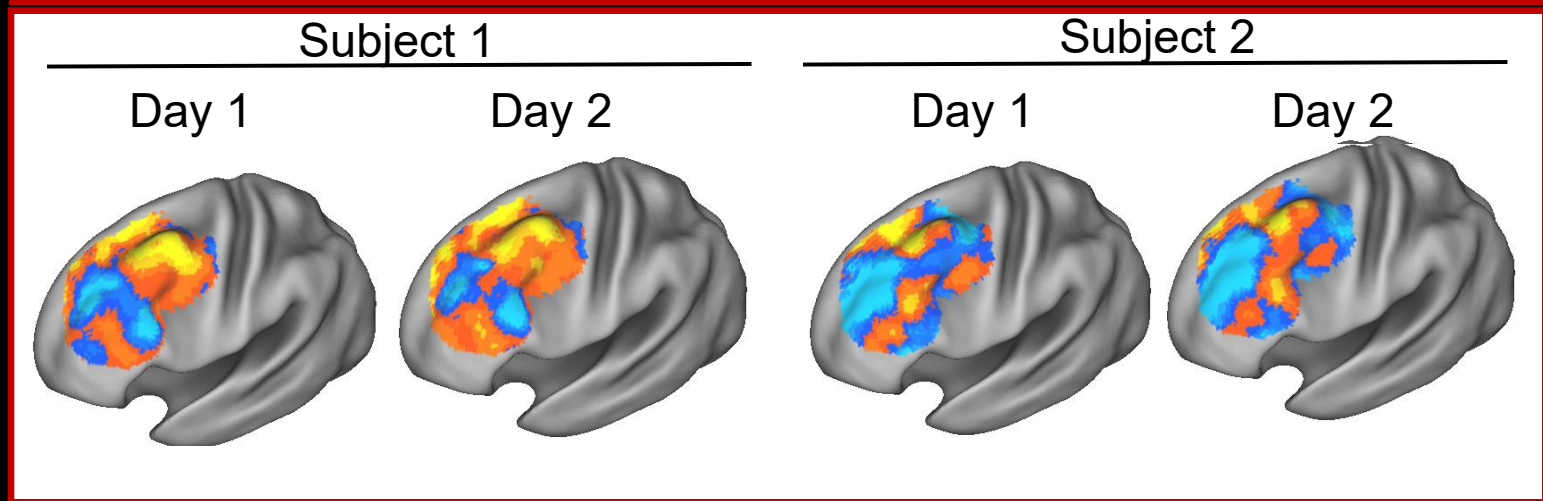
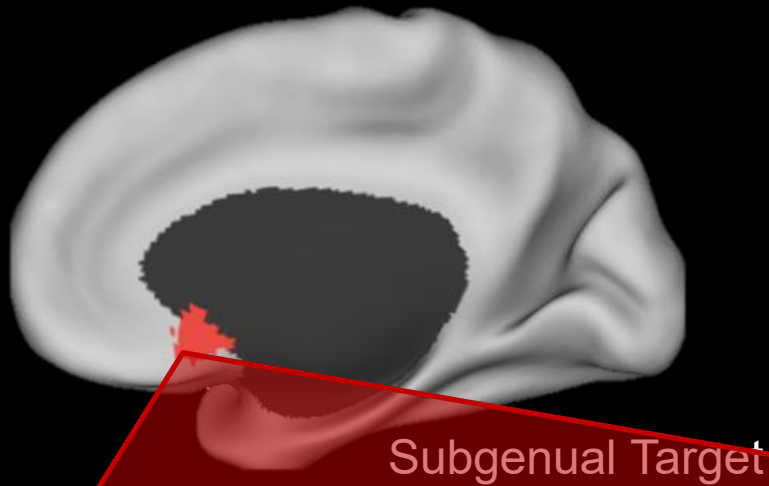




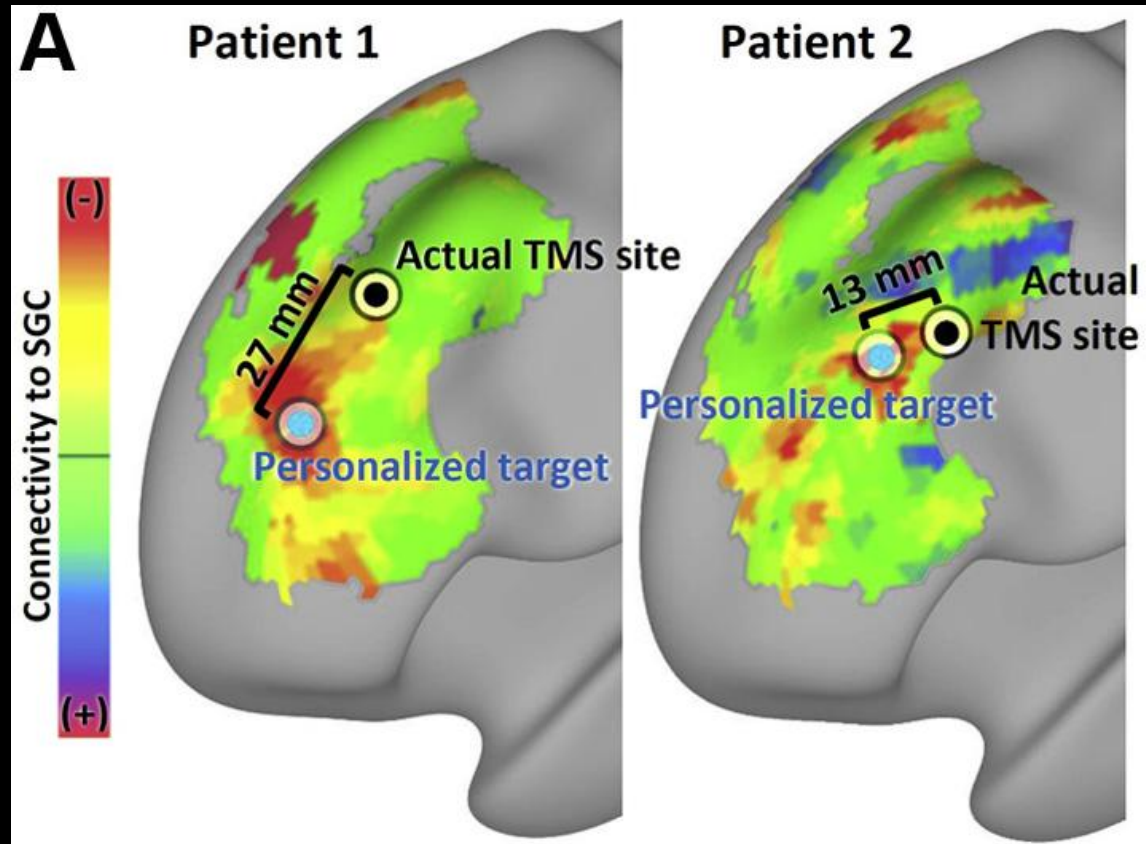
Subgenual Seed



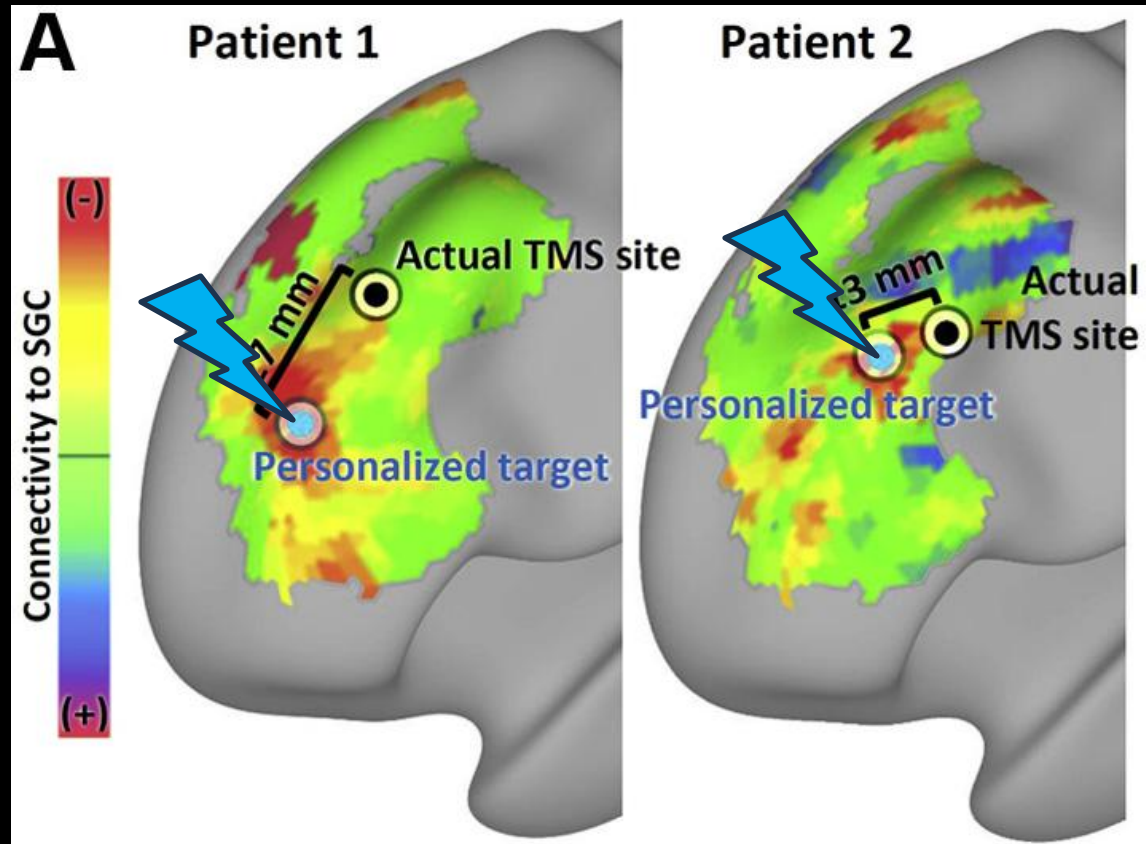
“Individualized” TMS Targets



“Individualized” TMS Targets

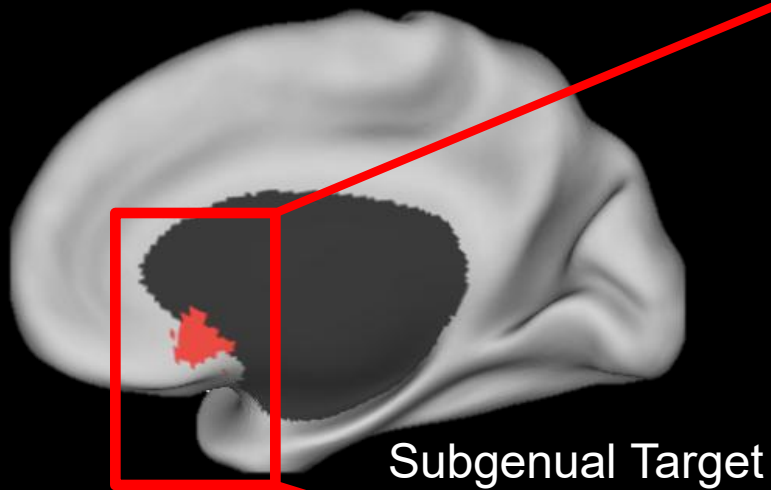


“Individualized” TMS Targets

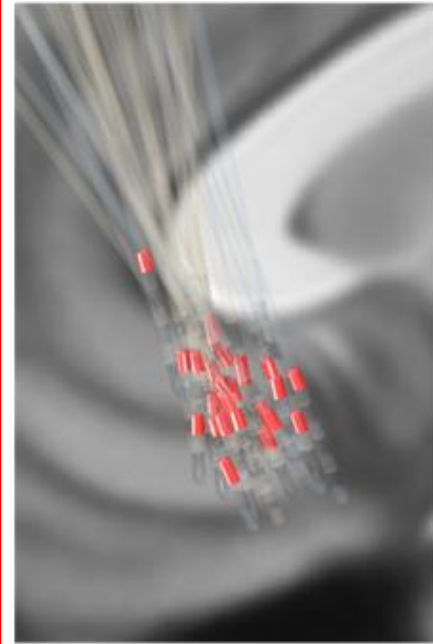


SAINT Neuromodulation System FDA approved 9/2022
Cole et al. 2020 AJP, Cole et al. 2021 AJP : **>80% response rate**

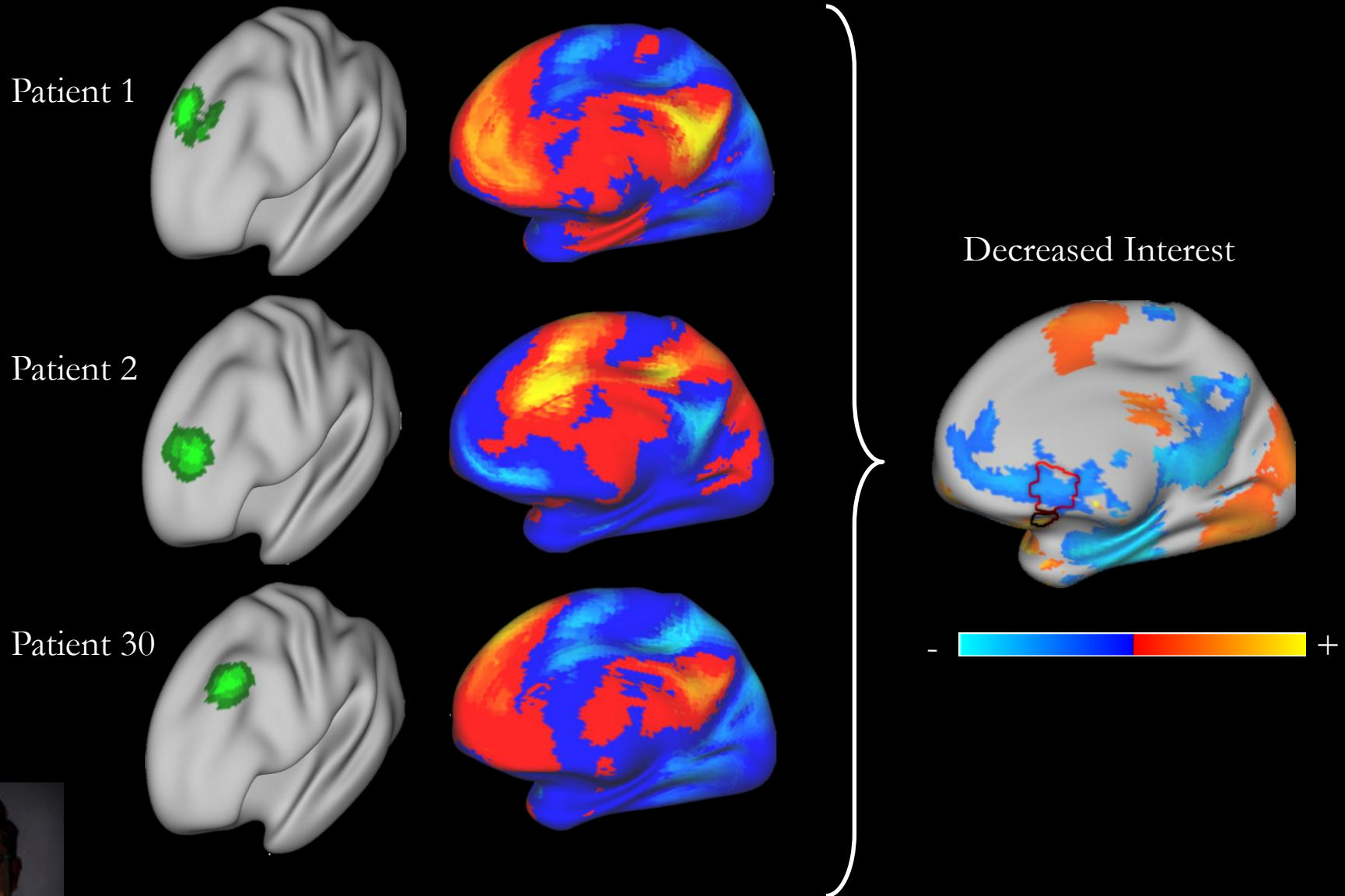
What if we're unsure of our target?



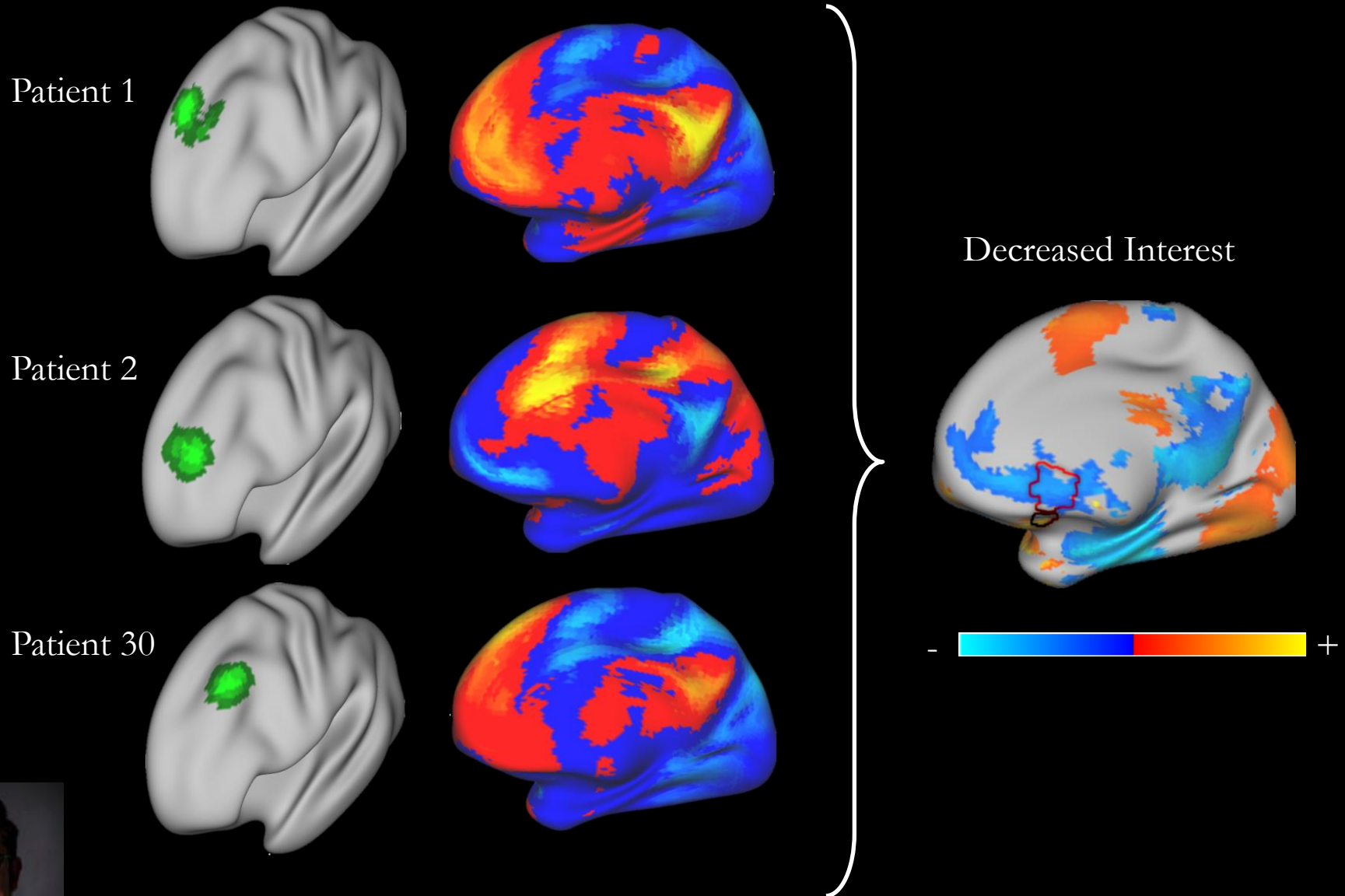
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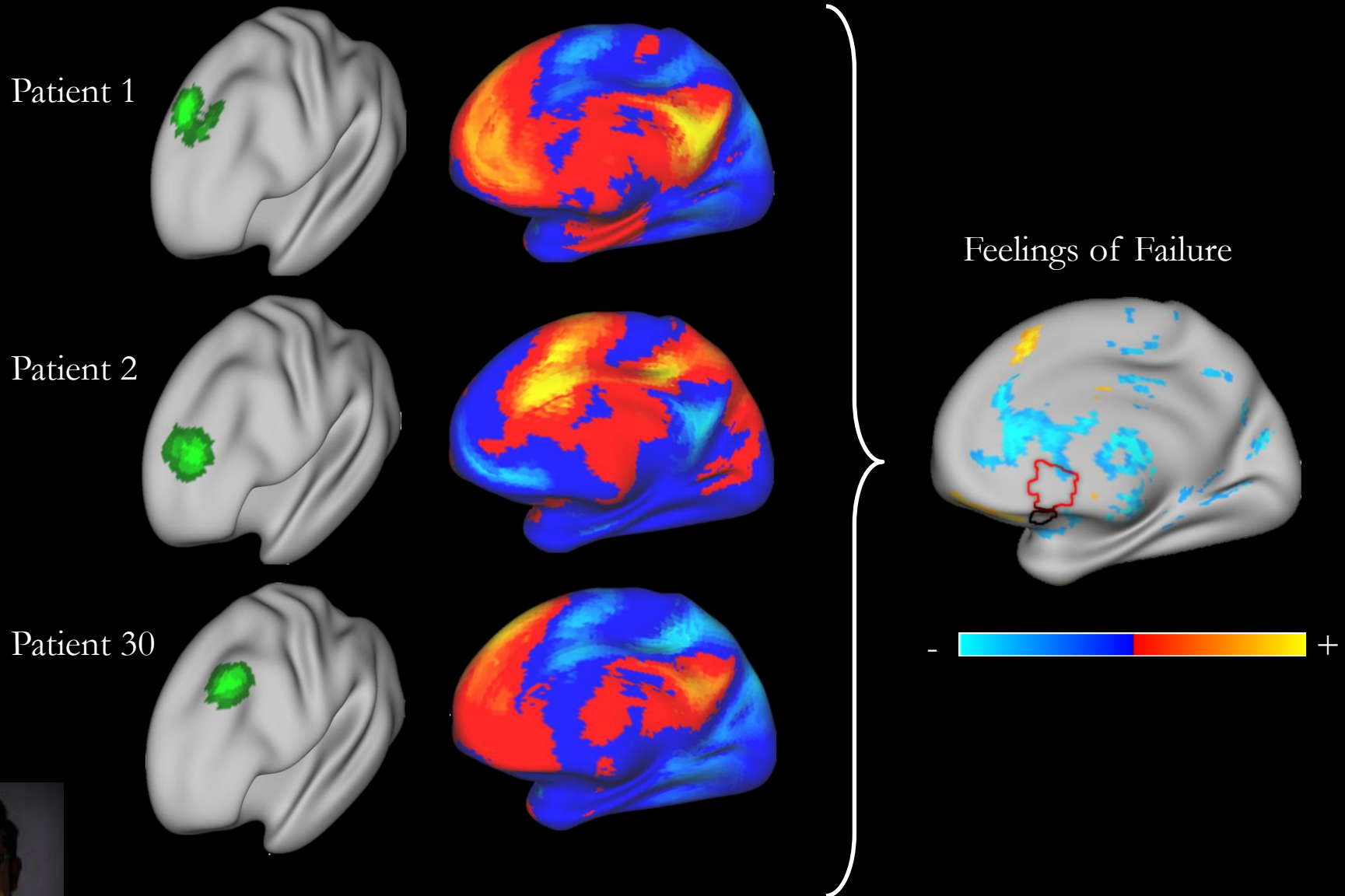
TMS Network Mapping



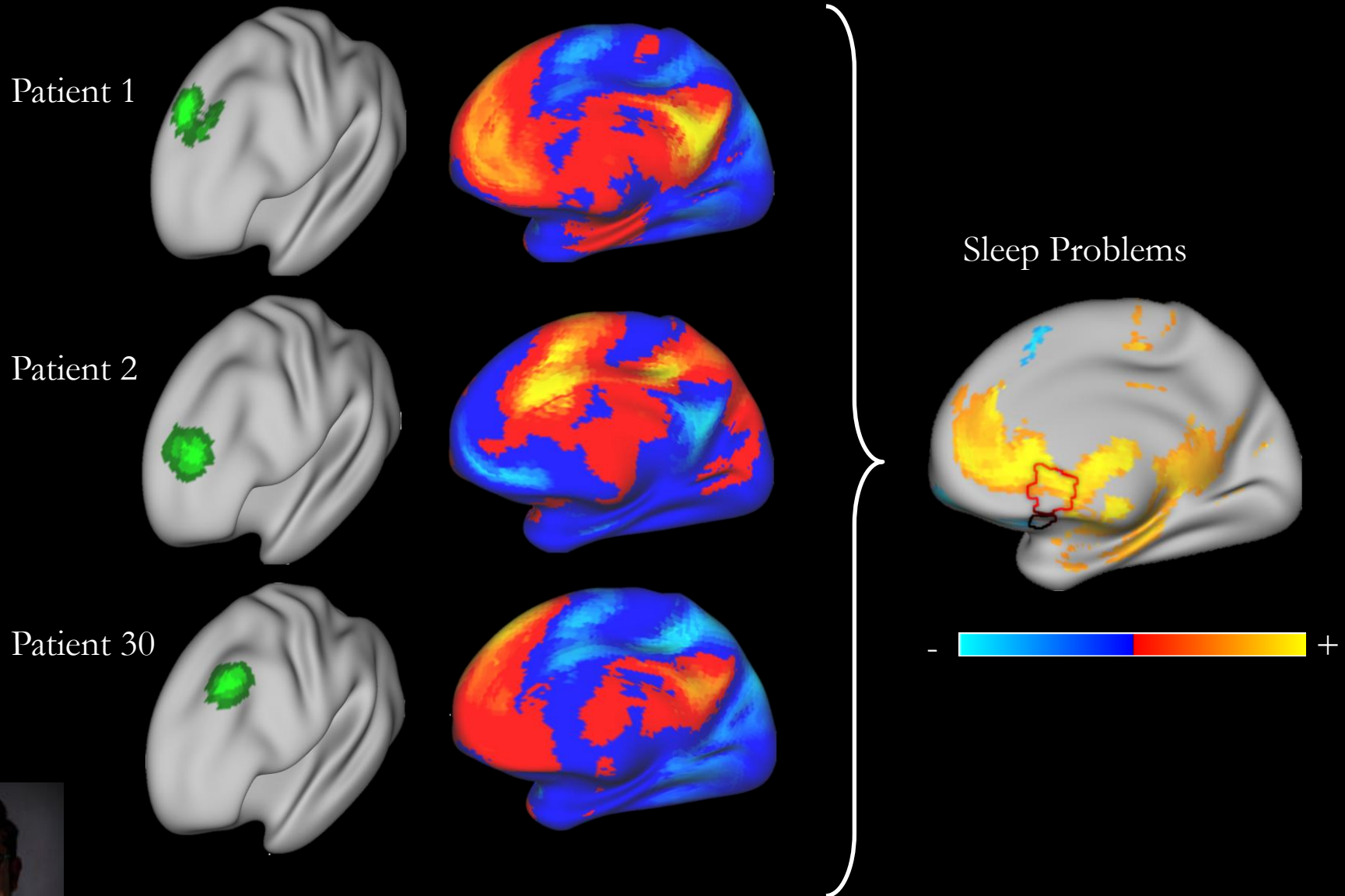
Symptom-Specific TMS Targets?



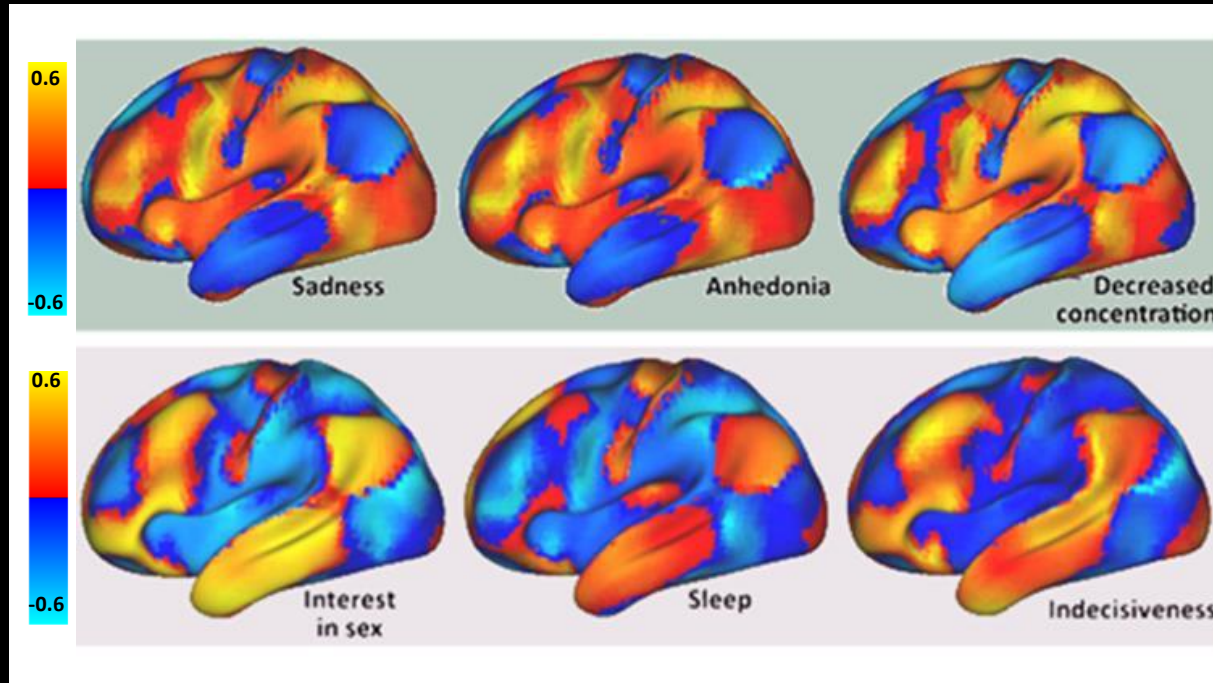
Symptom-Specific TMS Targets?



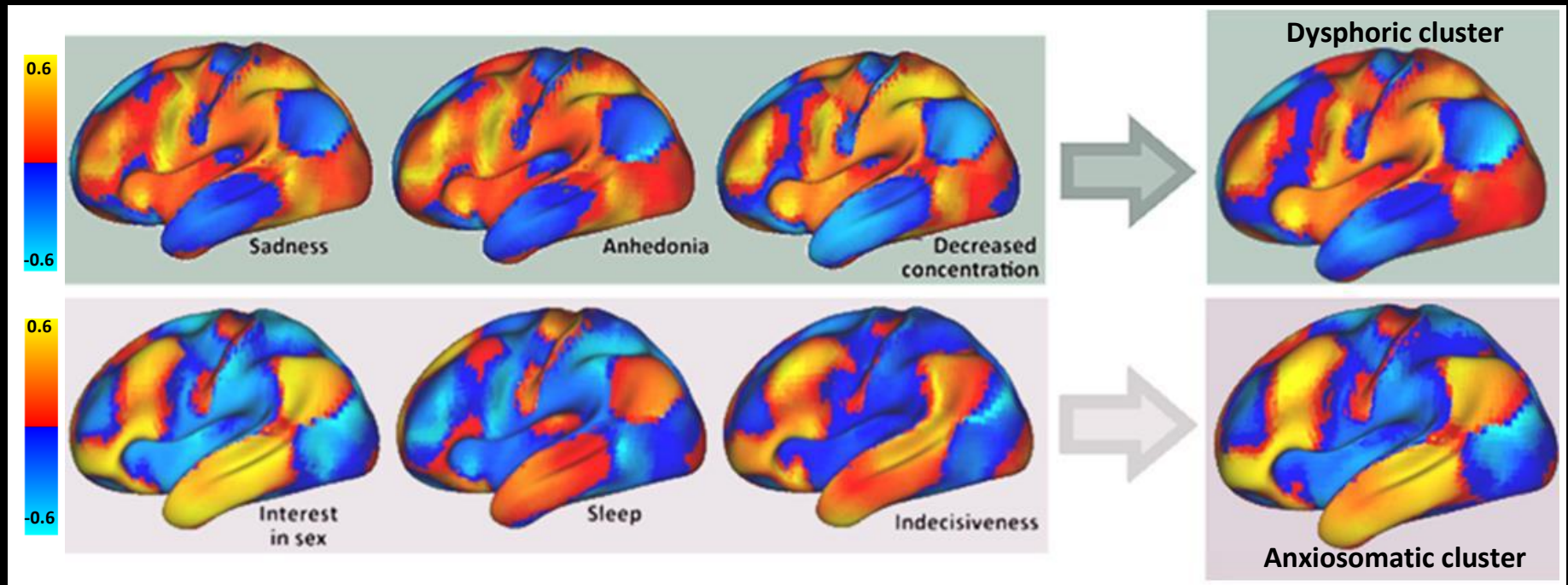
Symptom-Specific TMS Targets?



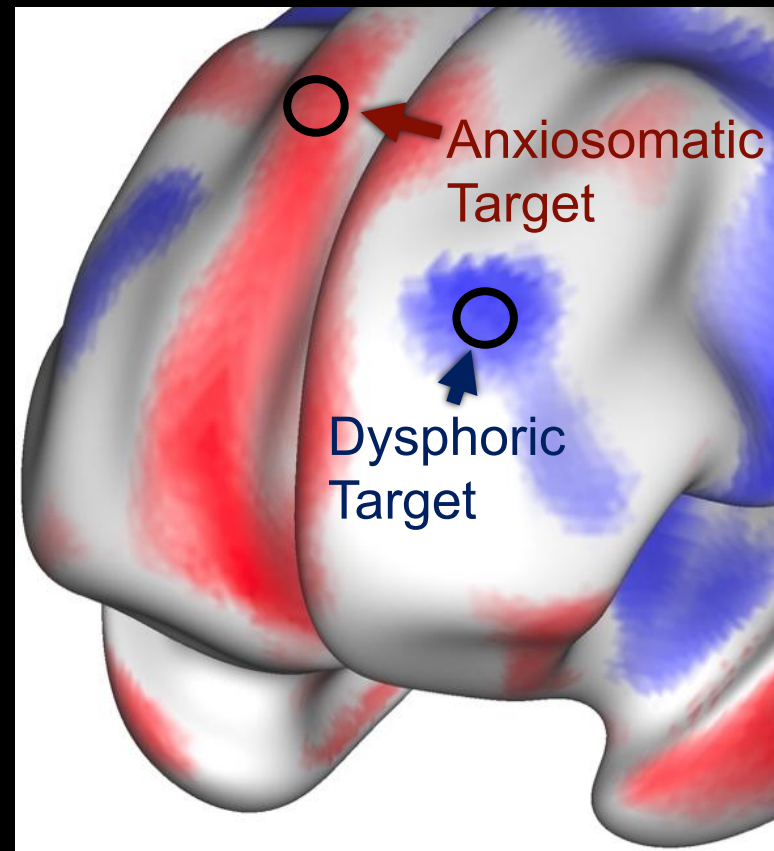
Symptom-Specific TMS Targets?



Symptom-Specific TMS Targets?

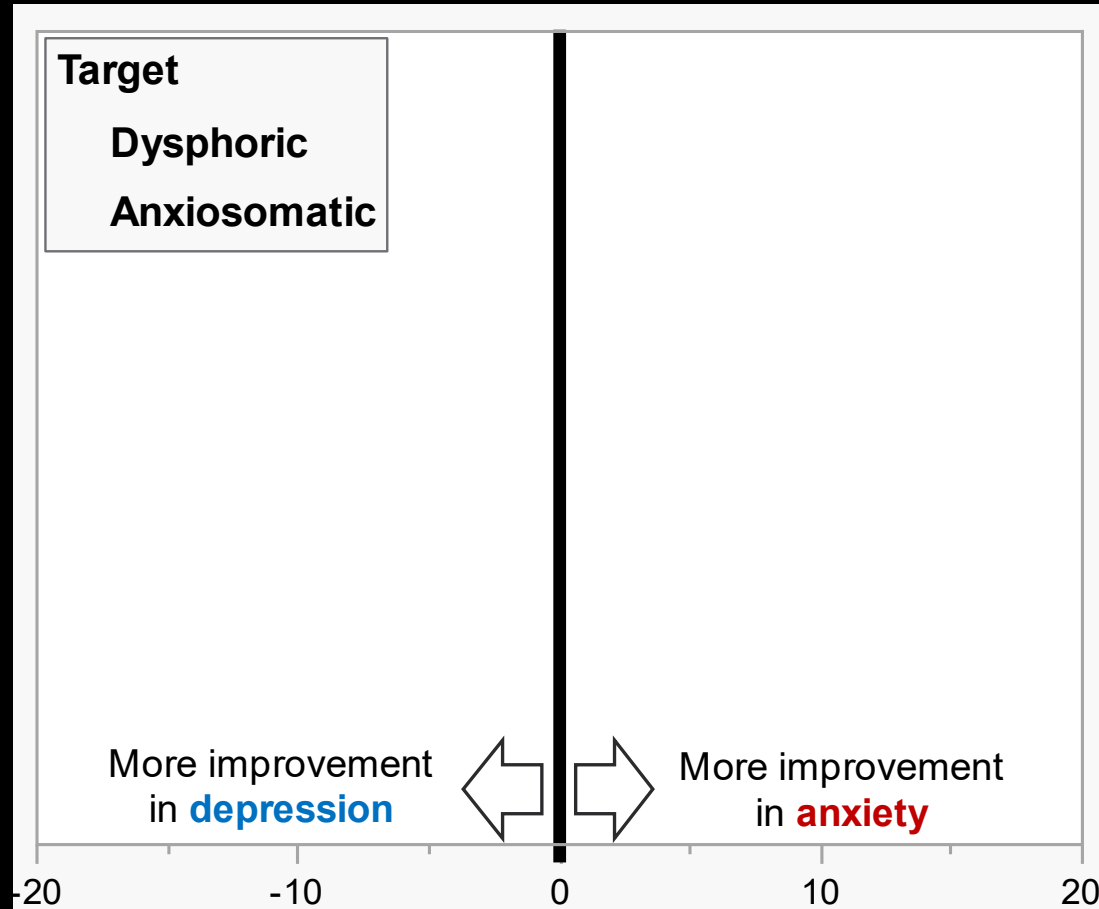
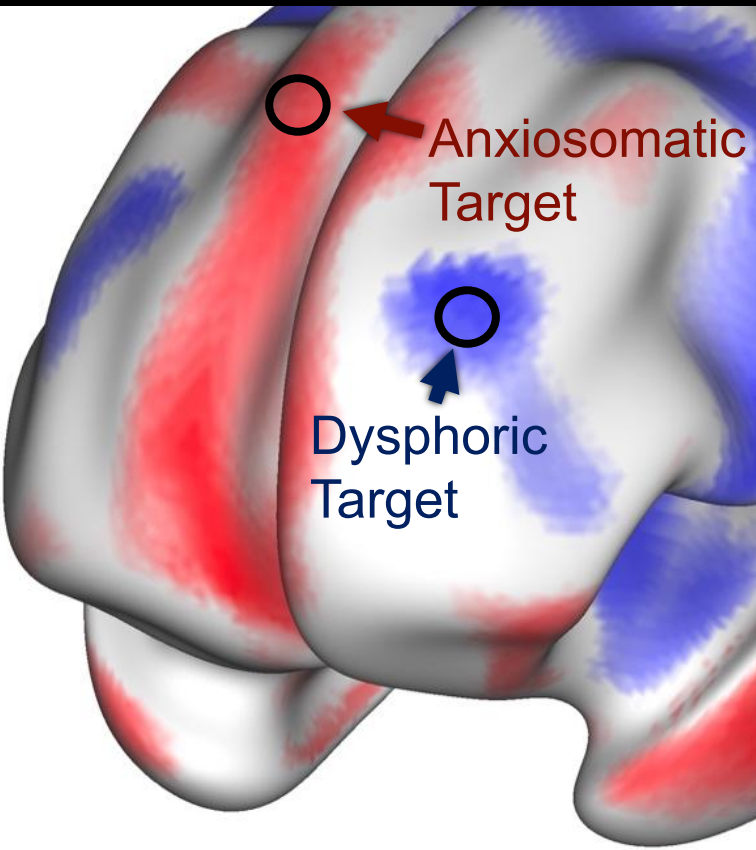


Symptom-Specific TMS Targets?



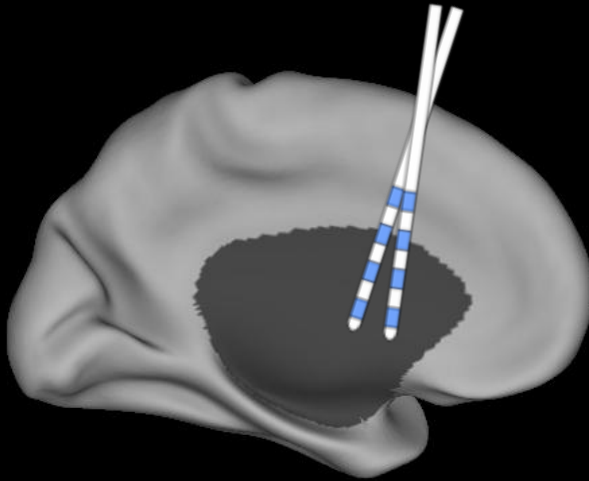
Taylor, Siddiqi et al., 2026 Mol Psych

Symptom-Specific TMS Targets?



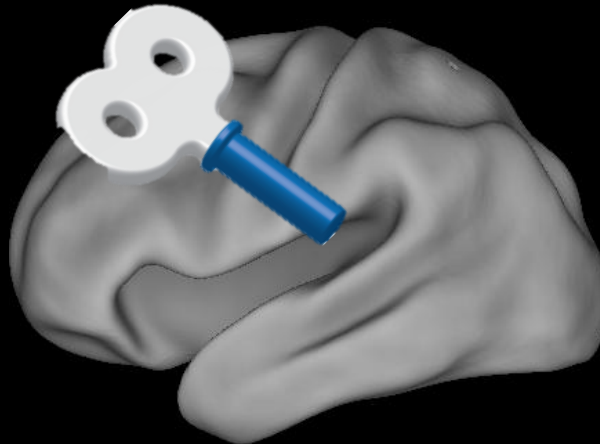
Therapeutic Neuromodulation

Deep Brain Stimulation (DBS)



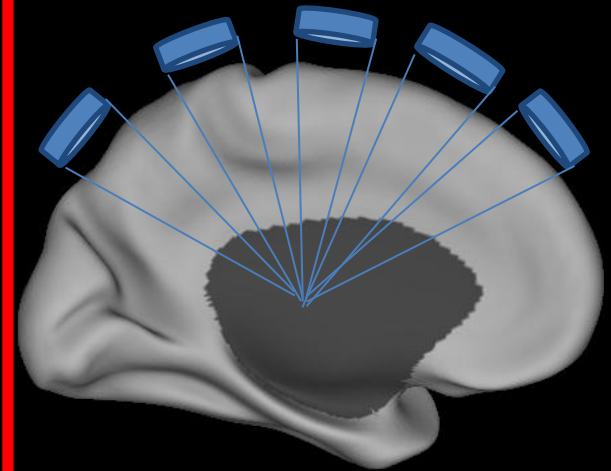
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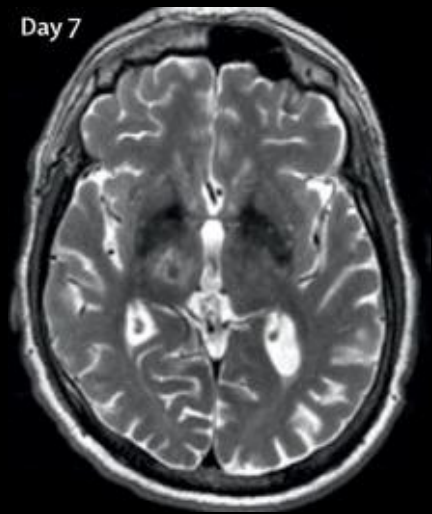
Focused Ultrasound (FUS)



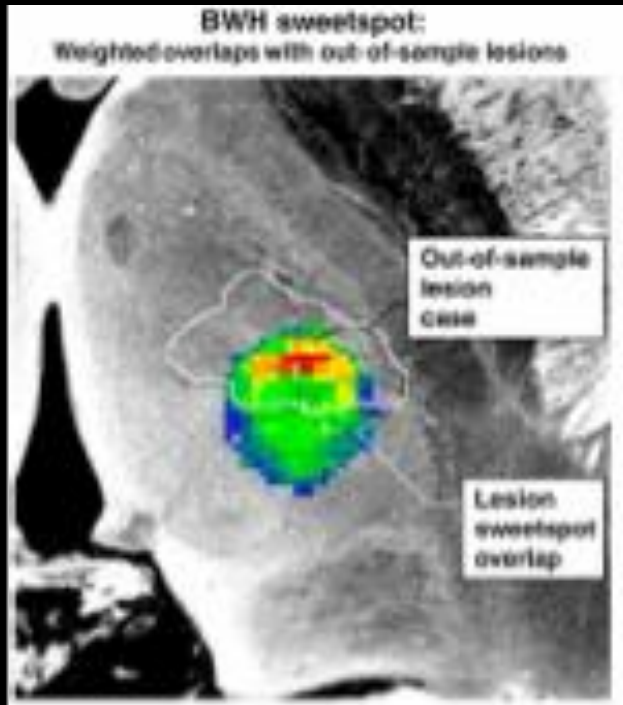
- FDA approved for **tremor**

High Intensity Focused Ultrasound (HIFU)

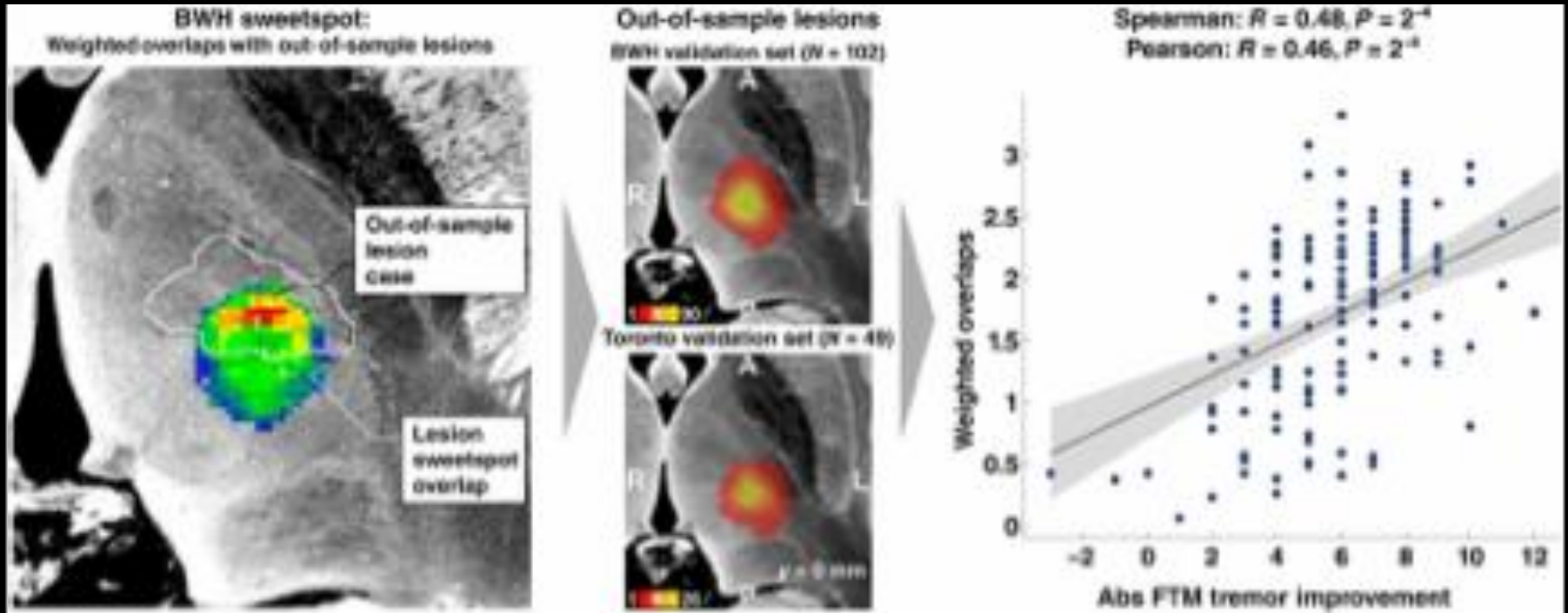
- Uses multiple ultrasound emitters on the scalp and MRI guidance to create a lesion in the brain
- The lesion (and any clinical effects) may be irreversible
- FDA approved for tremor (essential tremor and Parkinson's tremor)



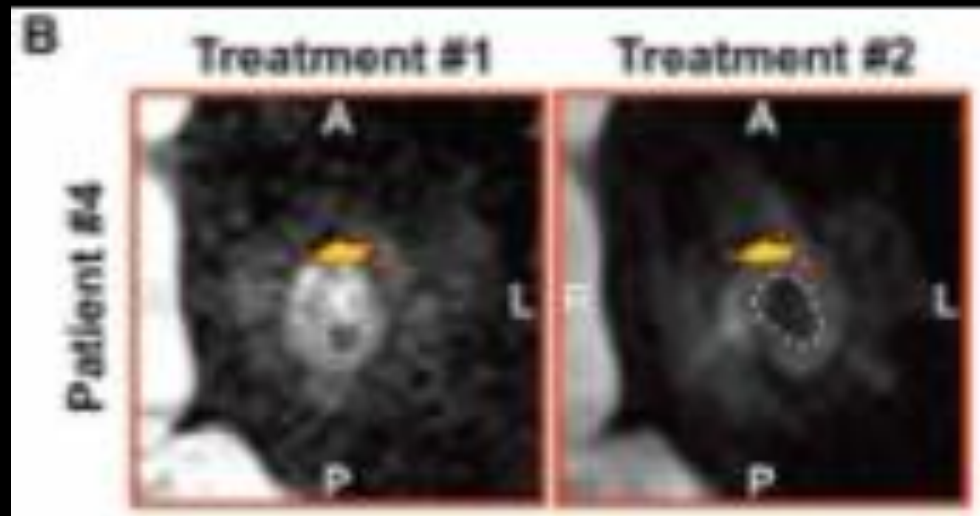
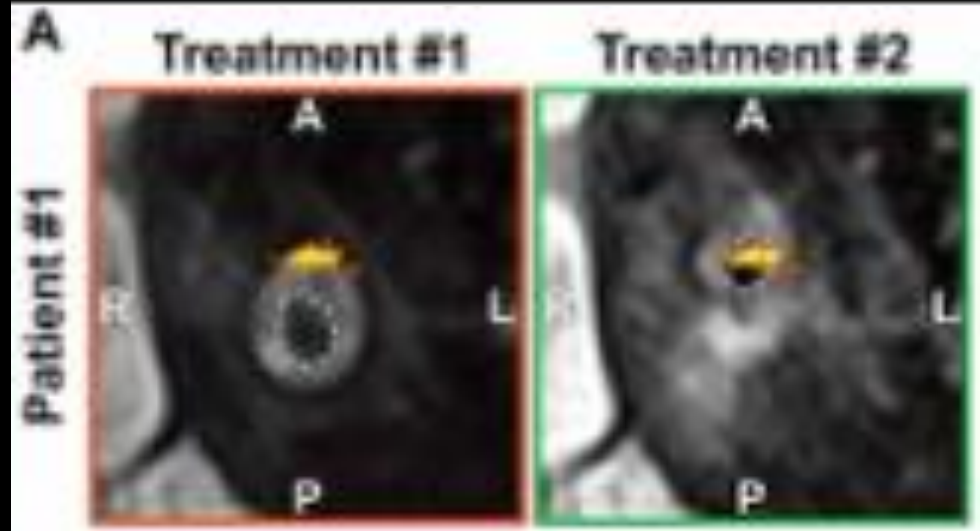
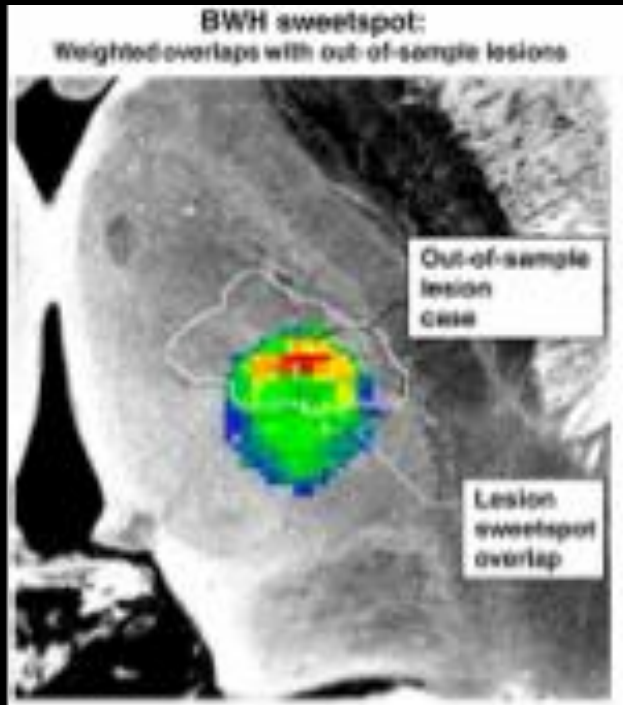
HIFU – increasing precision



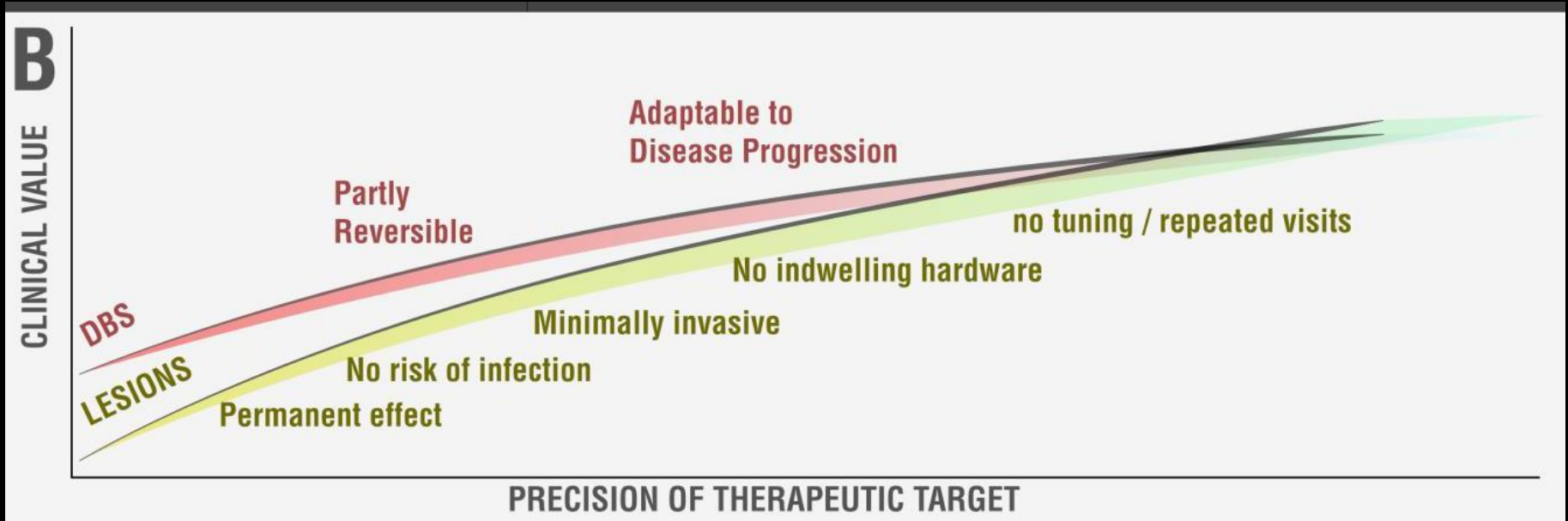
HIFU – increasing precision



HIFU – increasing precision



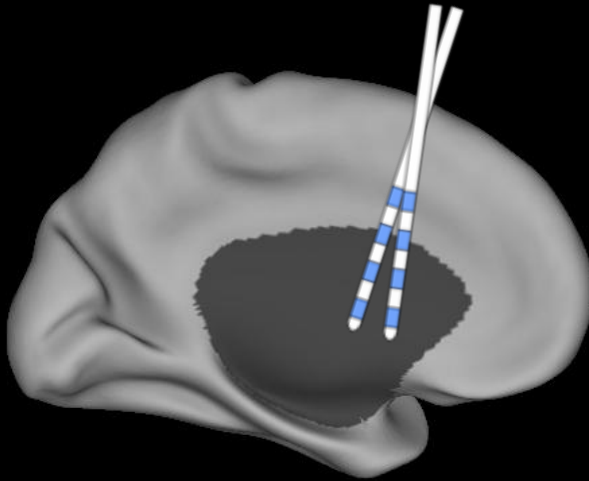
HIFU versus DBS



Joutsa et al. Brain 2023

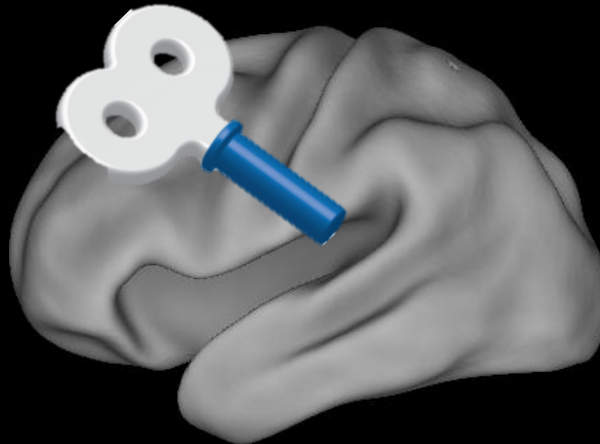
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Deep Brain Stimulation (DBS)



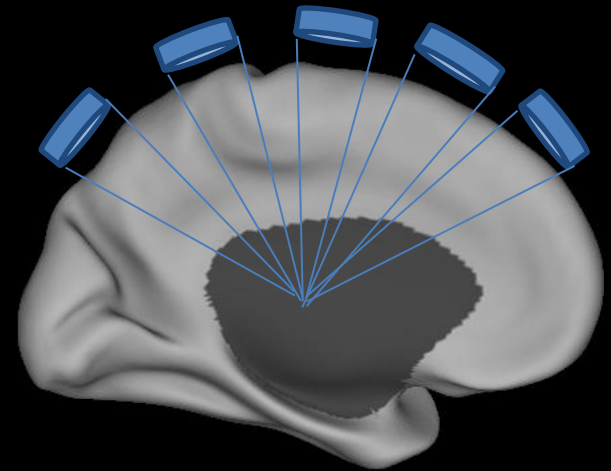
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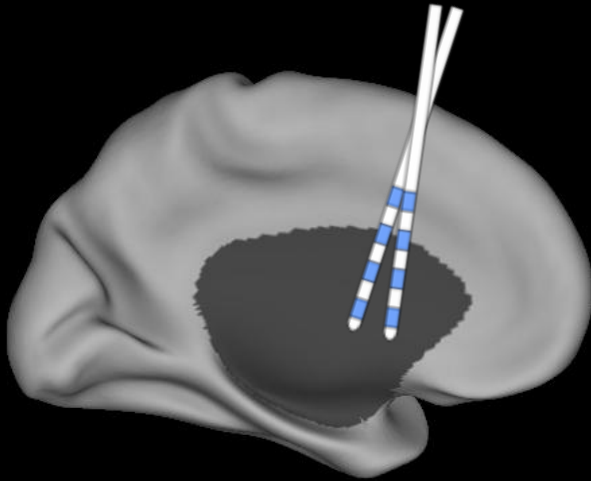
Focused Ultrasound (FUS)



- FDA approved for **tremor**

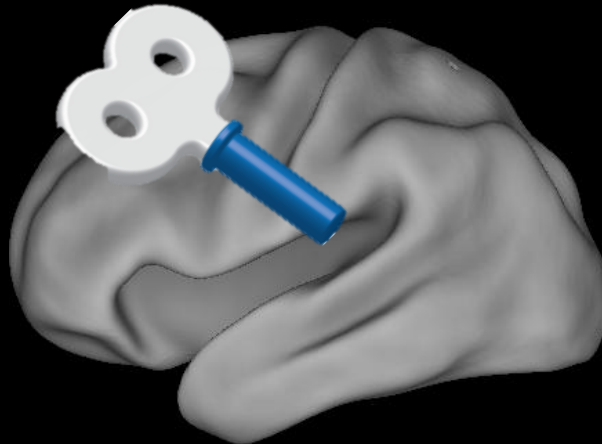
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Deep Brain Stimulation (DBS)



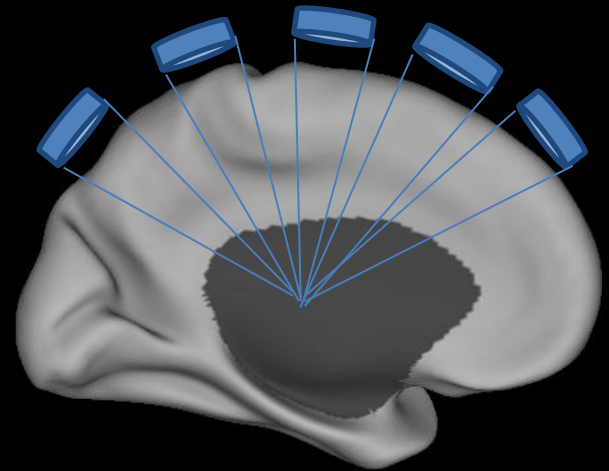
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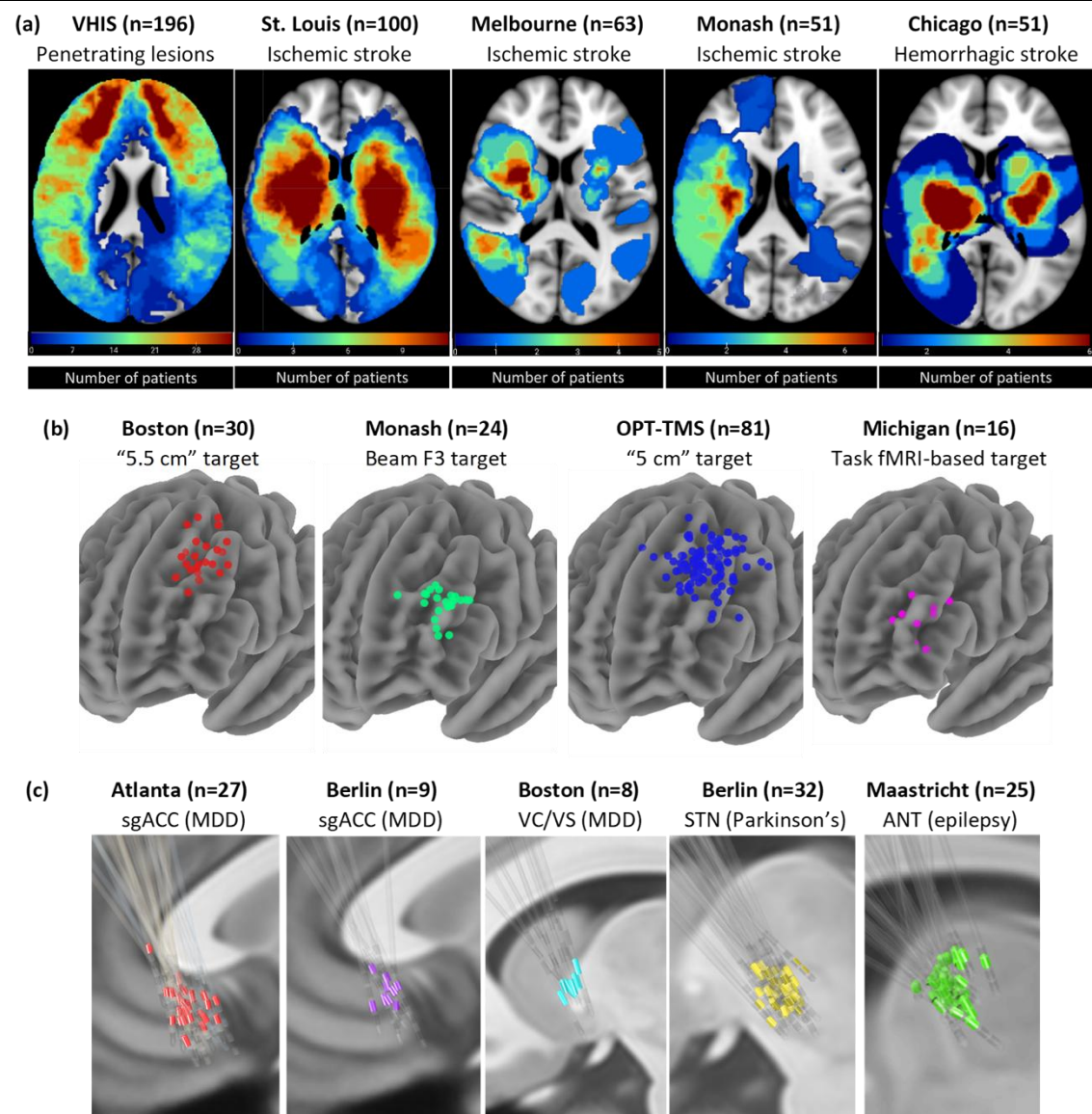
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Convergent Depression Circuit

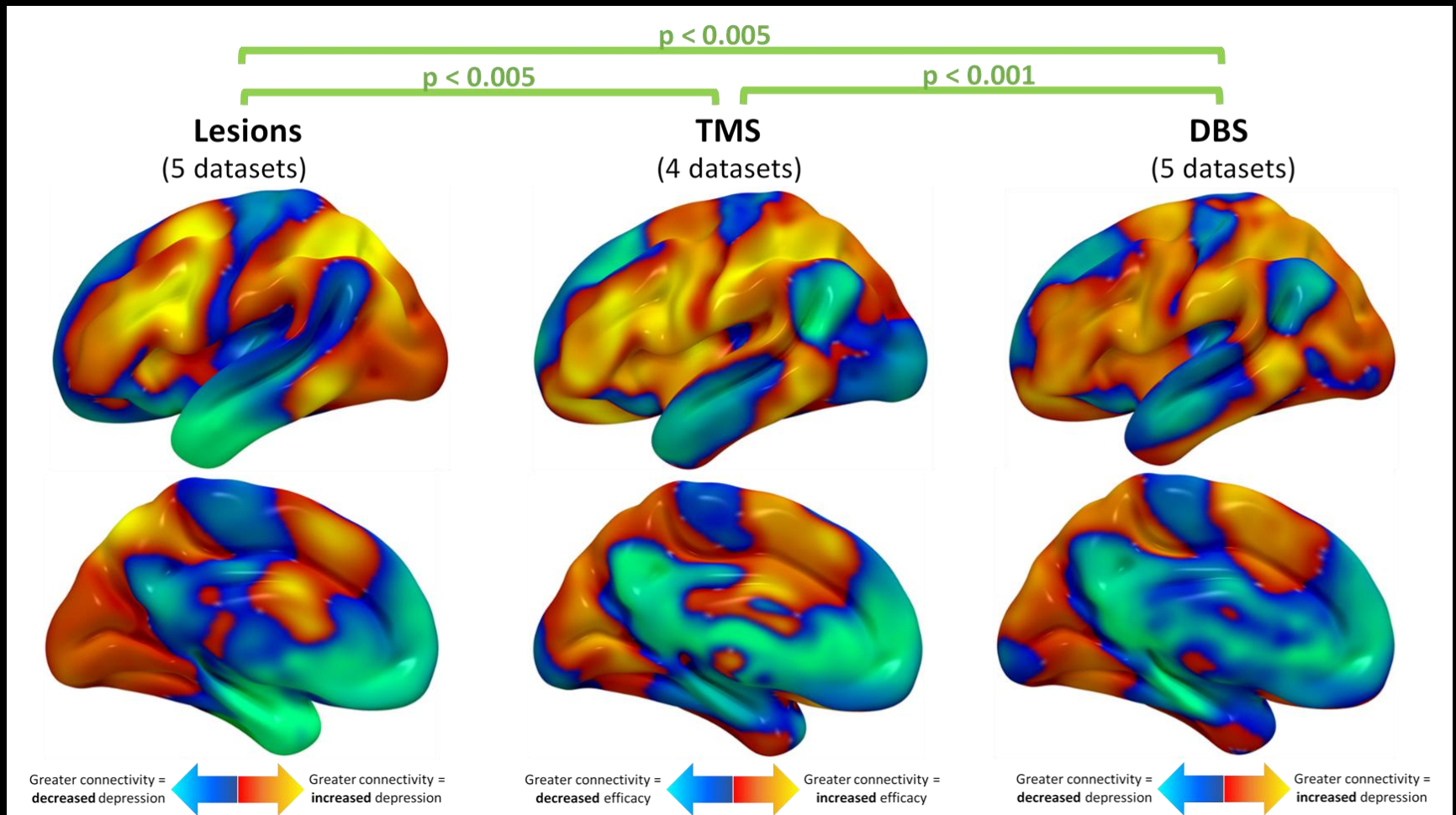
Lesions
5 cohorts
465 lesions

TMS Sites
4 cohorts
151 sites

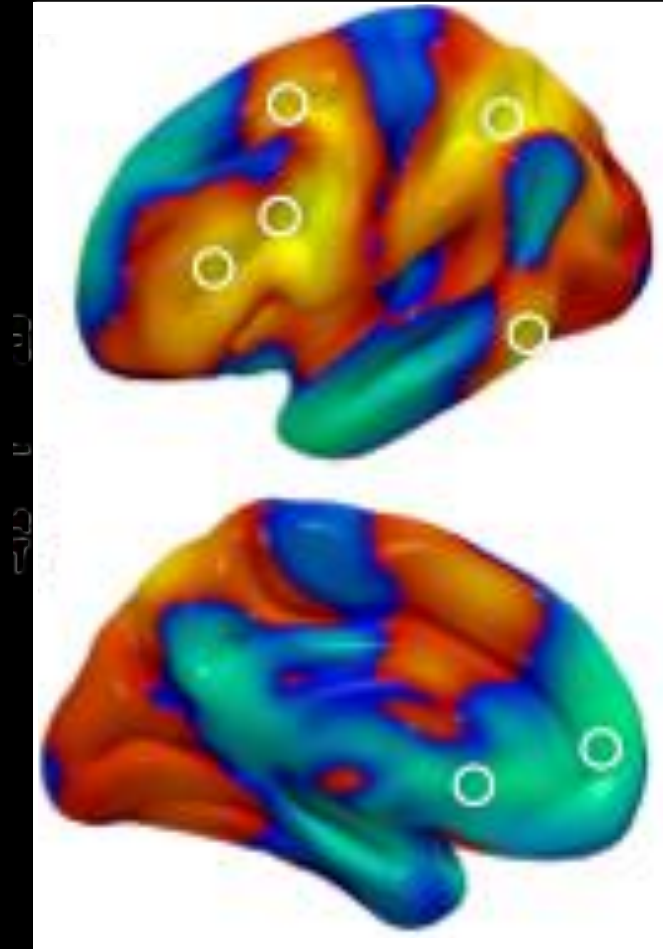
DBS Sites
5 cohorts
101 sites



Convergent Depression Circuit

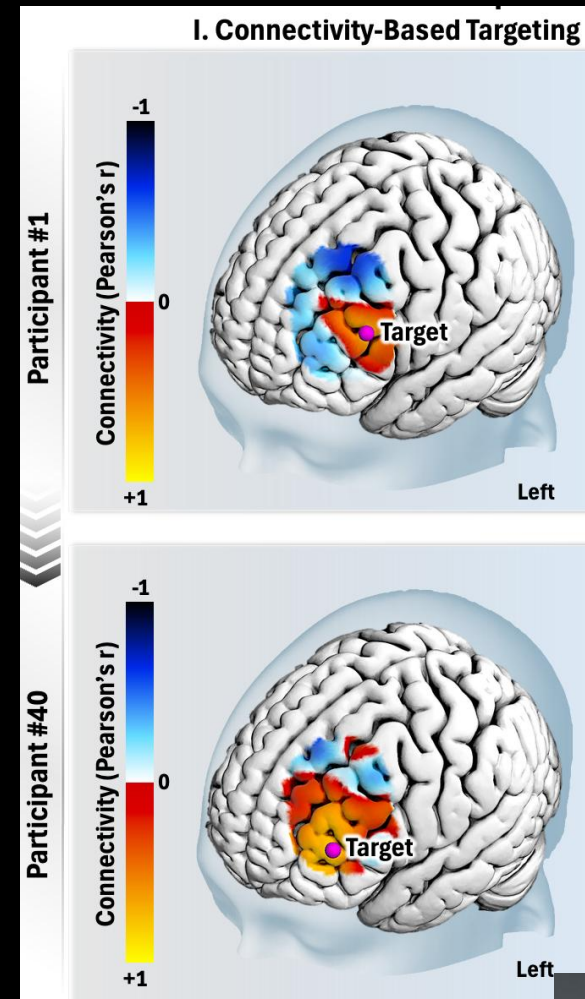
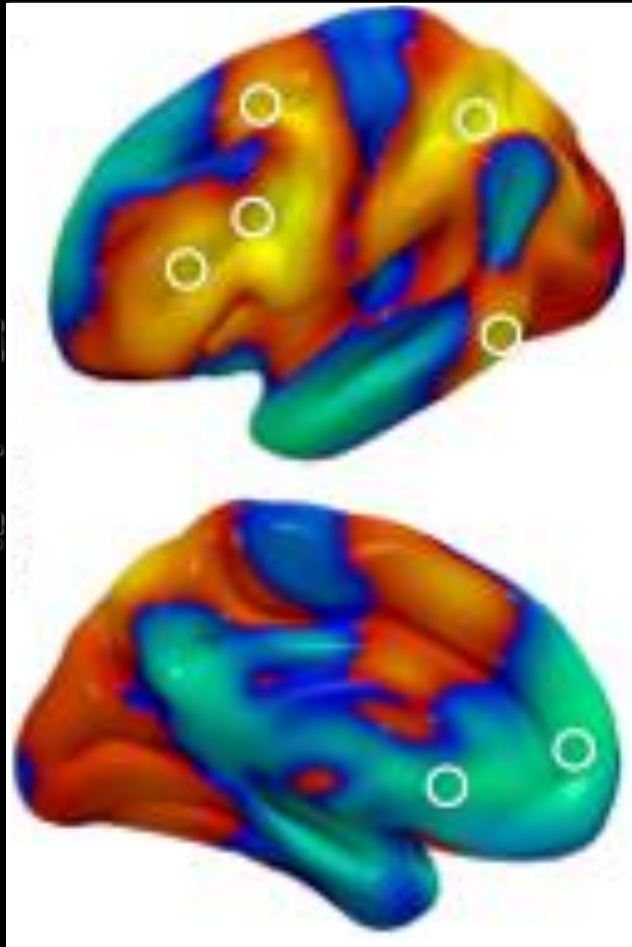


Convergent Depression Circuit



Siddiqi et al. 2021
Nature Hum Behav

Convergent Depression Circuit

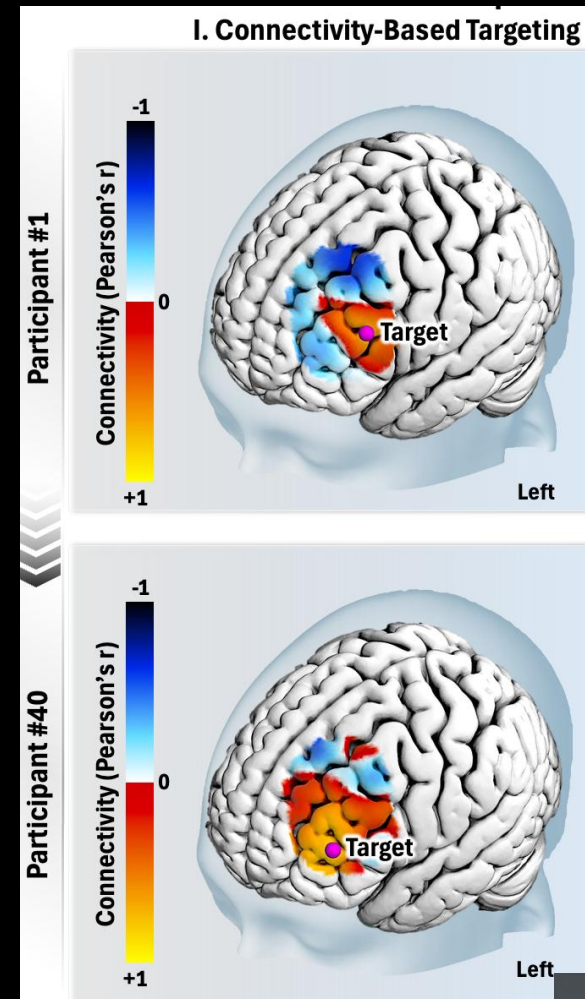
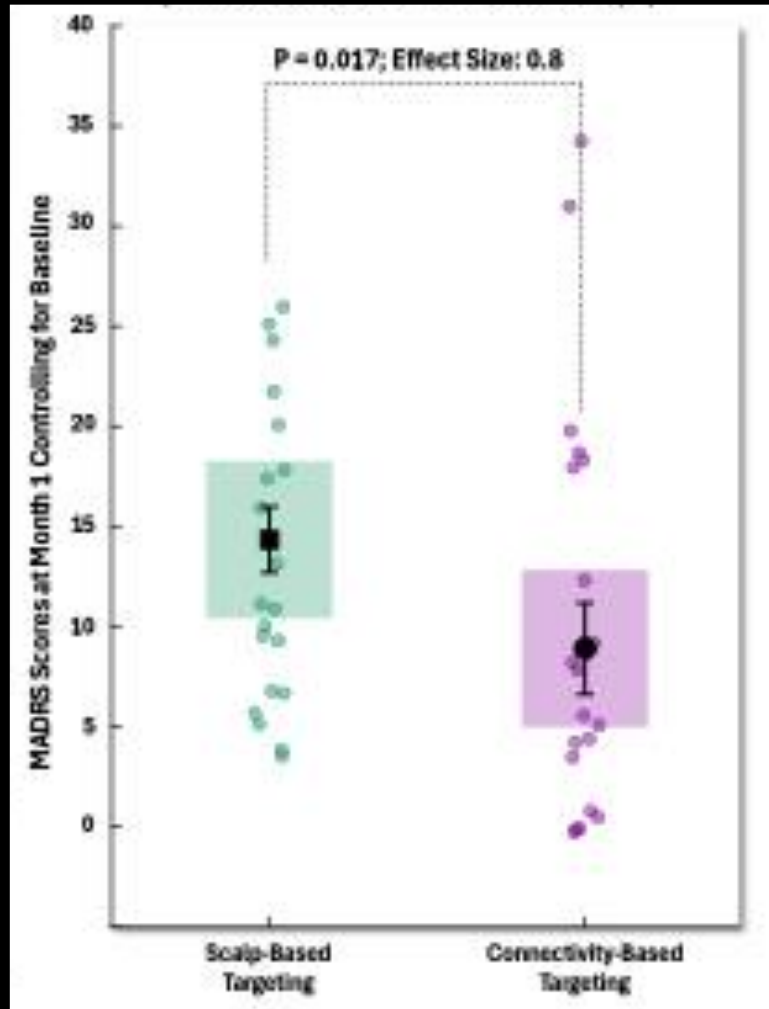


Siddiqi et al. 2021
Nature Hum Behav

Taylor et al. 2026
JAMA Psych

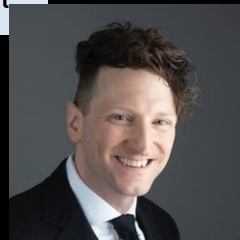


Convergent Depression Circuit



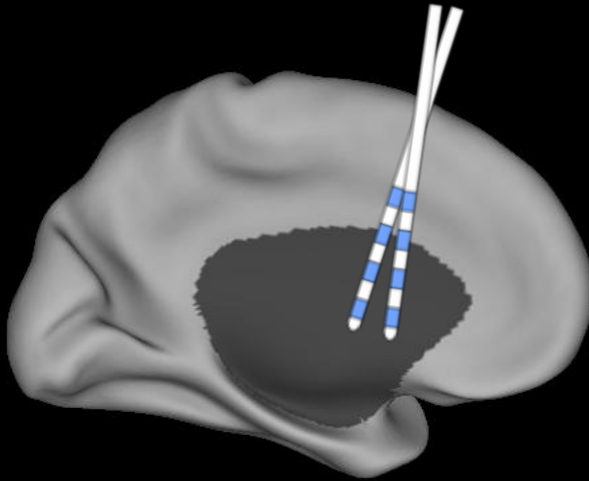
Number Needed to Scan = 5

Taylor et al. 2026
JAMA Psych



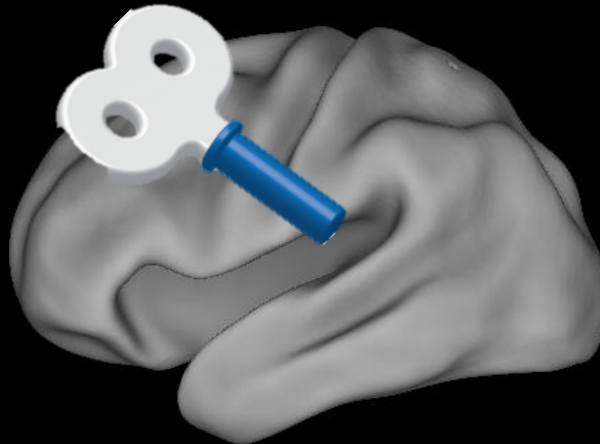
Therapeutic Neuromodulation

Deep Brain Stimulation (DBS)



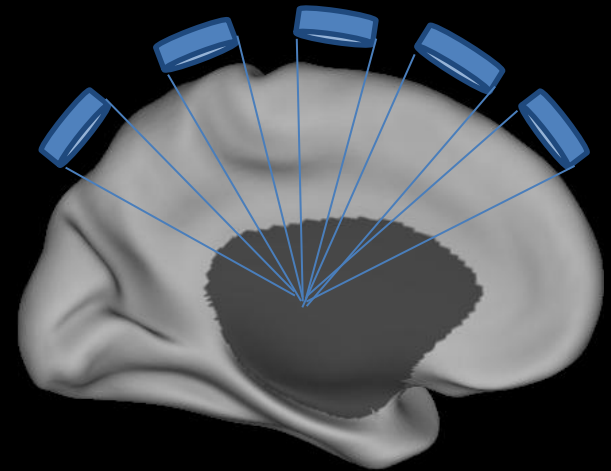
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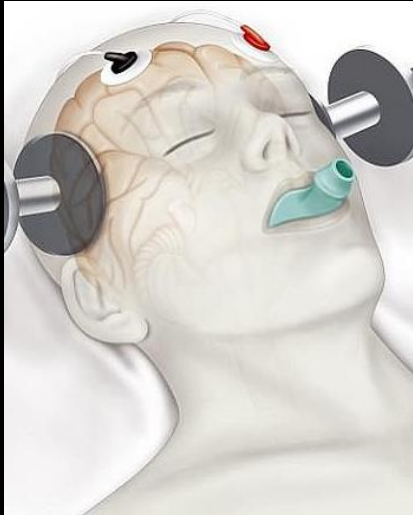
Focused Ultrasound (FUS)



- FDA approved for **tremor**

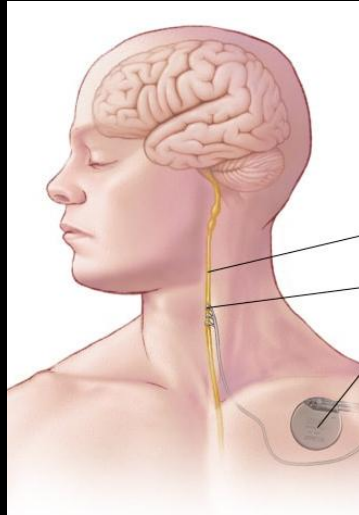
Therapeutic Neuromodulation

Electroconvulsive
Therapy (ECT)



FDA approved
for **depression**,
catatonia, bipolar
disorder

Vagus Nerve
Stimulation (VNS)



FDA approved
for depression,
epilepsy, stroke
recovery

Cranial Nerve
Stimulation (CNS)



FDA approval
for **depression**

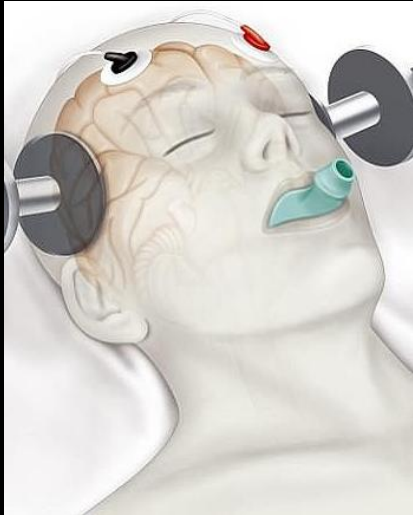
Transcranial Current
Stimulation (tCS)



FDA approval
for **depression**

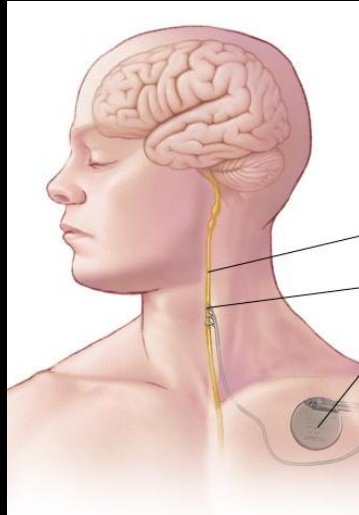
Therapeutic Neuromodulation

Electroconvulsive Therapy (ECT)



FDA approved for **depression**, catatonia, bipolar disorder

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FDA approved for depression, **epilepsy**, stroke recovery

Cranial Nerve Stimulation (CNS)



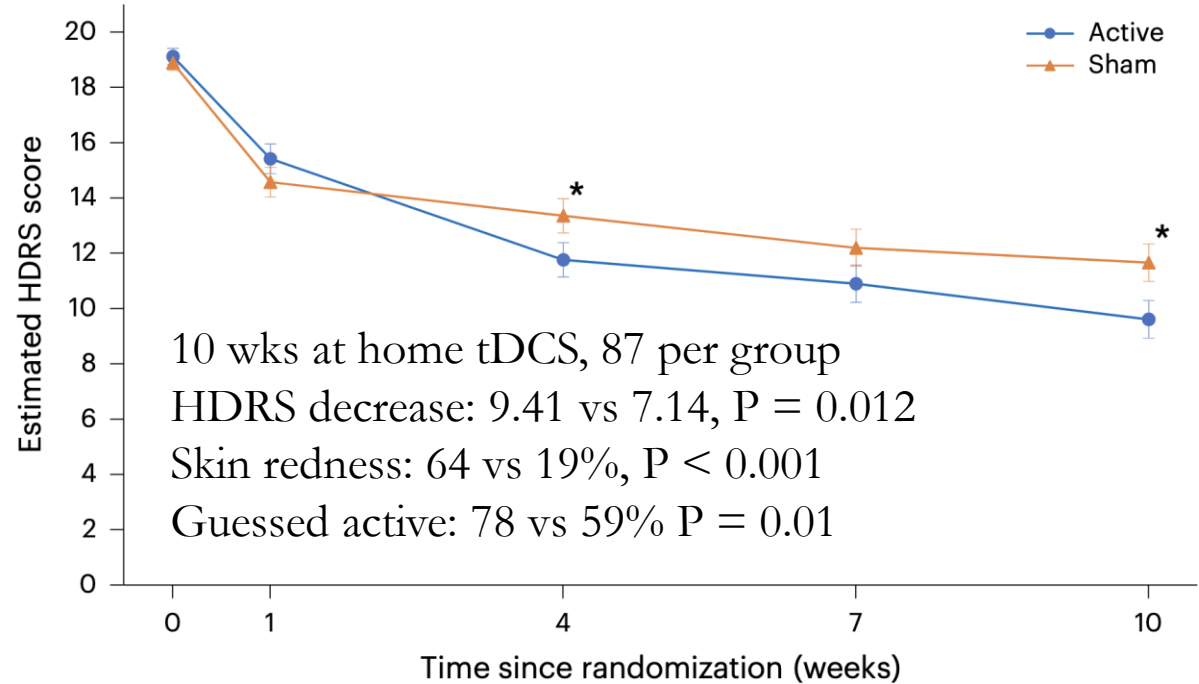
FDA approval for **depression**

Transcranial Current Stimulation (tCS)



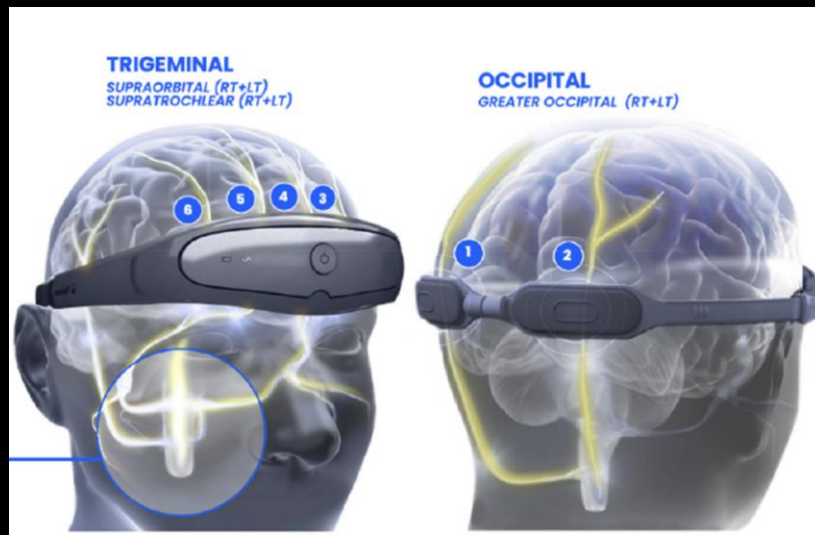
FDA approval for **depression**

Home-based transcranial direct current stimulation treatment for major depressive disorder: a fully remote phase 2 randomized sham-controlled trial

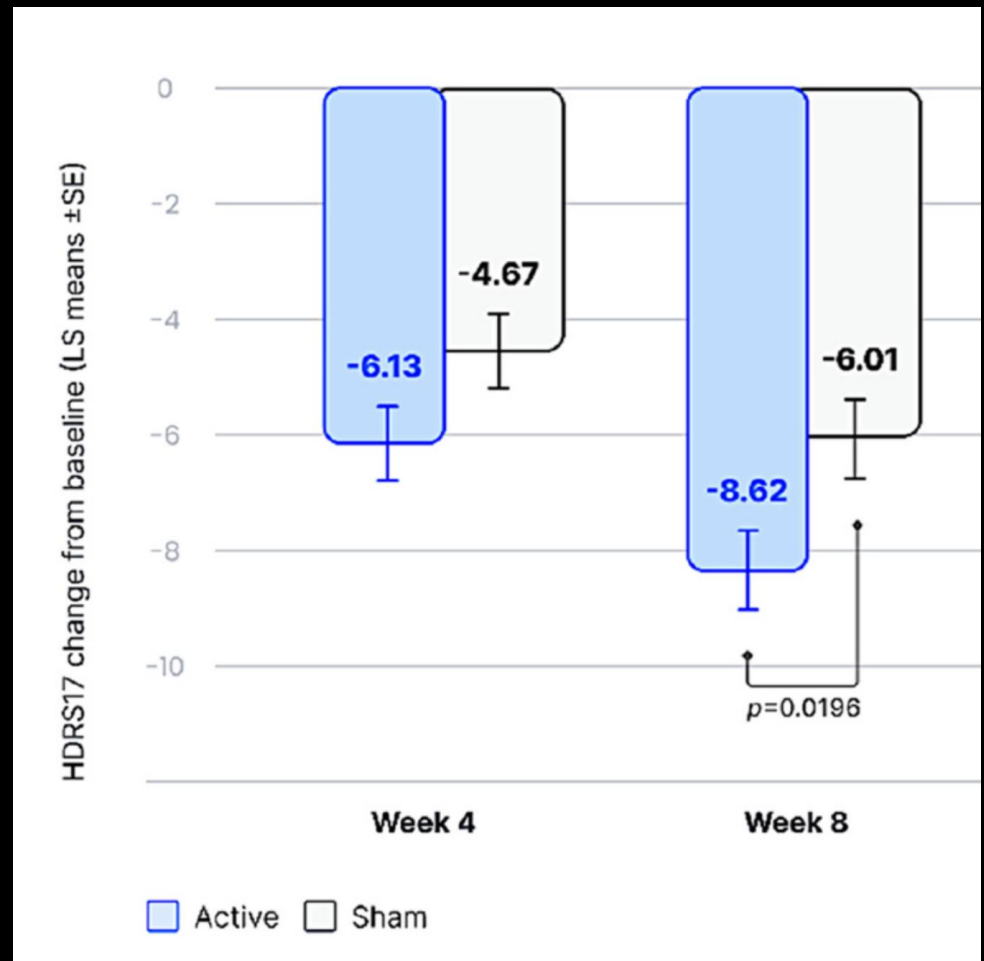


A novel home-based, combined occipital and trigeminal afferent stimulation therapy for major depressive disorder: Efficacy and safety results from a double-blind multicenter randomized sham-controlled study

Linda L. Carpenter^{a,*} , Mark S. George^{b,c}, Nancy Navarro^d, Lisa Deutsch^e ,
Andrew F. Leuchter^f 



8 wks at home stim, 62 per group
HDRS decrease: 8.62 vs 6.01, $P = 0.02$
Adverse effects: 16 vs 8%, $P = \text{NR}$
Guessed correctly: 15 vs 6%, $P = \text{NR}$



Take Home Points

- 1) Different neuromodulation techniques can be used to treat neuropsychiatric symptoms
- 2) All neuromodulation techniques have effects beyond the target region and impact connected brain circuits
- 3) The human brain connectome can be helpful in localizing and refining therapeutic targets for neuromodulation



Center for
BRAIN CIRCUIT
THERAPEUTICS



Brigham and Women's Hospital
Founding Member, Mass General Brigham



Acknowledgements

Lab / Center

Current

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Sheena Baratano
Stephan Palm
Sanaz Khosravani
David Lawson
Joseph Turner
Menguyan Ding
Grace Burt
Lauren Sanderson
Mae Morton-Dunn
Ross Mcfadyen
Arun Garimella

Former

Aaron Boes
Matt Burke
Ruth Caballero
Danielle Cooke
Daniel Corp
Ryan Darby
David Fischer
Andreas Horn
Joey Hsu
Juho Joutsa
Tyler Ketchebaw
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Jaya Padmanabhan
Martin Reich
Lois Soussand
Daniel Talmasov
Anne Weigand
Rimona Weil
Molly Schineller
Sandrine Jabbour
Ali Jannati
Jing Jiang
Christopher Lin
William Drew
Max Friedrich

Collaborators

Local

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Ron Alterman
Ludy Shih
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Adam Stern
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Randy Buckner
Verne Caviness
Sashank Prasad
Darin Dougherty
Ellen Bubrick
Lipeng Ning
Tracy Barbour
Joan Camprodan
AND MORE

Non-local

Andrea Kuhn (Charite)
Helen Mayberg (Mt. Sinai)
Ki Sueng Choi (Mt. Sinai)
Jens Volkmann (Wurzburg)
Alfonso Fasano (Toronto Western)
Andreas Lozano (Toronto Western)
Maurizio Corbetta (Wash U)
Jordan Grafman (Northwestern)
Mark George (MUSC)
Linda Carpenter (Butler)
Paul Fitzgerald (Monash)
Stephan Taylor (Michigan)
Goncalo Cotovio (Champalimaud)
Albino J. Oliveira Maia (Champalimaud)
Joel Voss (Northwestern)
Andrew Naidech (Northwestern)
Robin Cash (Monash)
Kevin Johnson (Neuronetics)
Natalia Egorova (Melborne)
Sophia Gozzi (Monash)
Fredrike Irmén (Charite)
Rob Rouhl (Maastricht)

AND SOOO MANY OTHERS

Questions?

Contact: foxmdphd@gmail.com

Twitter: foxmdphd

<https://www.brighamandwomens.org/neurosciences-center/center-for-brain-circuit-therapeutics>

