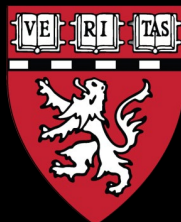


Brain Circuit Therapeutics

Michael D. Fox, MD, PhD

Professor of Neurology, Harvard Medical School
Director, Center for Brain Circuit Therapeutics
Raymond D. Adams Distinguished Chair in Neurology
Kaye Family Director of Psychiatric Brain Stimulation
Brigham and Women's Hospital

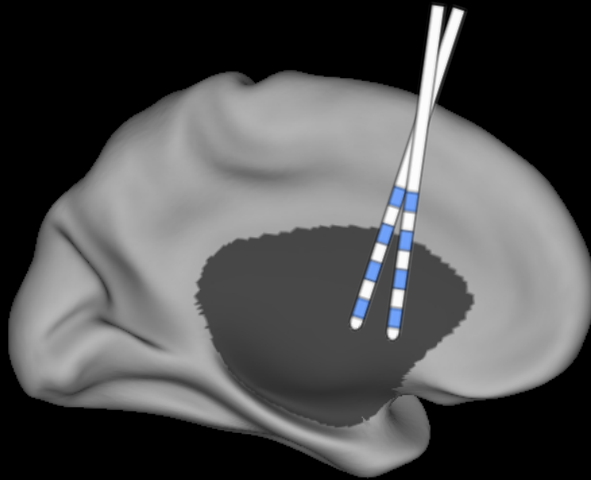


Disclosures

- Conflicts
 - Intellectual Property on using connectivity imaging to map lesions and guide neuromodulation
 - Consultant: Magnus Medical, Soterix, Abbott, Boston Scientific, Tal Medical, MDC Capital, 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
 - Industry: Neuronetics, Boston Scientific

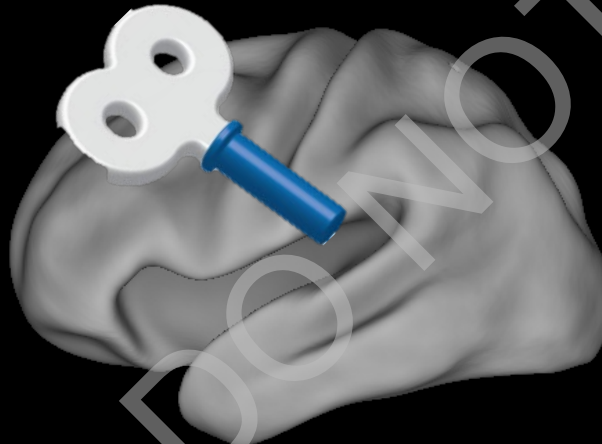
Therapeutic Neuromodulation

Deep Brain Stimulation (DBS)



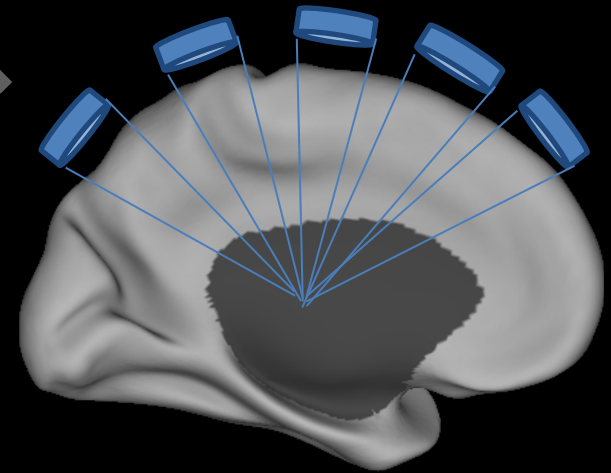
- FDA approved for **Parkinson's**, essential tremor, epilepsy, dystonia, OCD

Transcranial Magnetic Stimulation (TMS)



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

Focused Ultrasound (FUS)

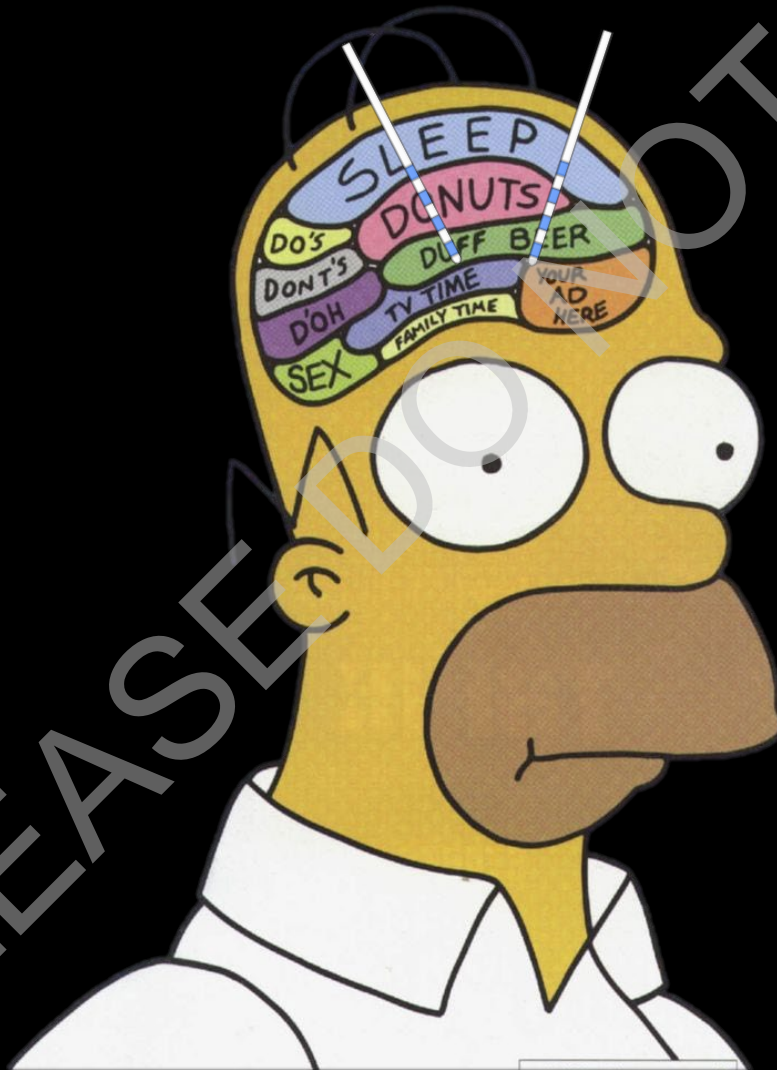


- FDA approved for **tremor**

How do we identify a therapeutic target?



How do we identify a therapeutic target?

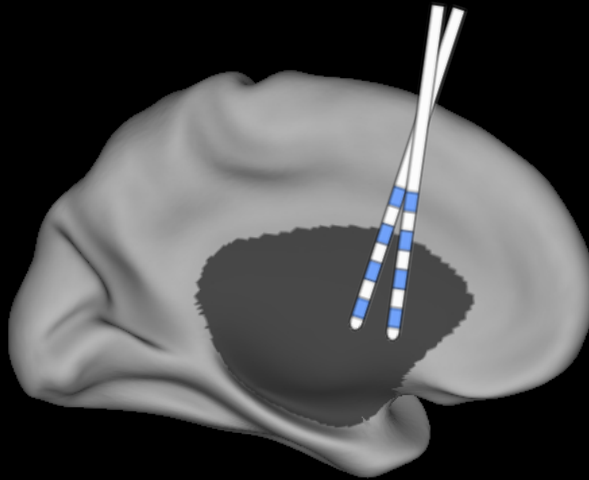


How do we identify a therapeutic target?



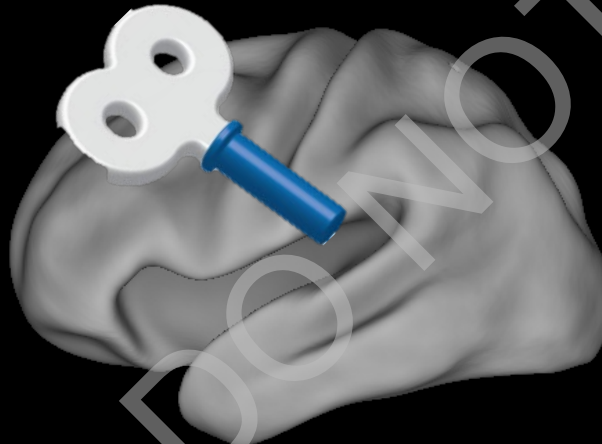
Therapeutic Neuromodulation

Deep Brain Stimulation (DBS)



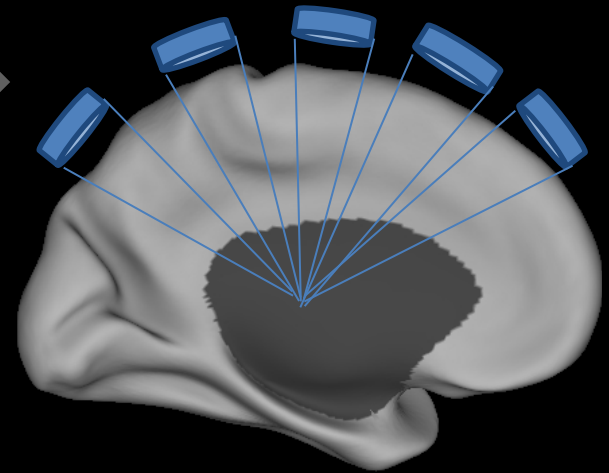
- FDA approved for **Parkinson's**, essential tremor, epilepsy, dystonia, OCD

Transcranial Magnetic Stimulation (TMS)



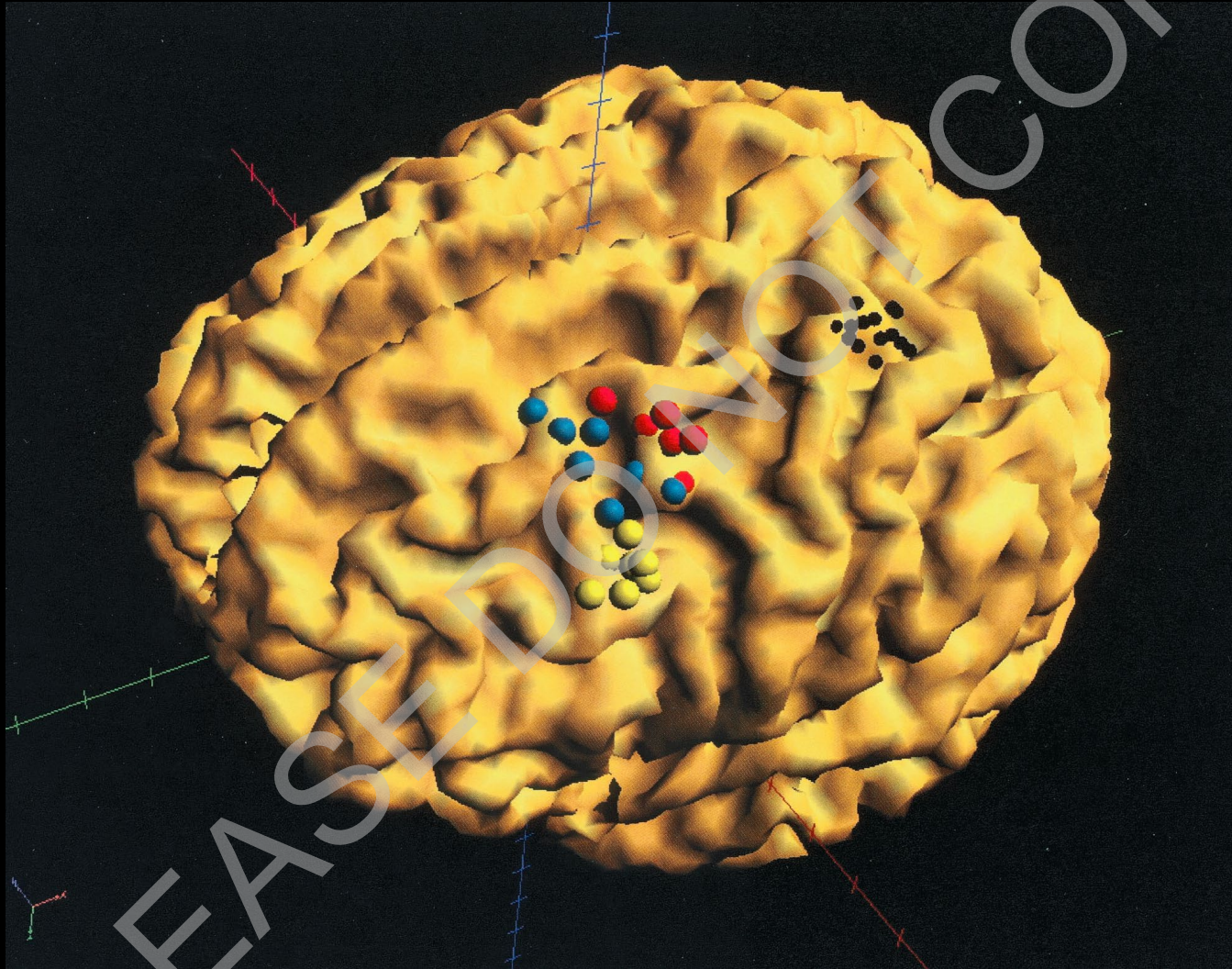
- FDA approved for **depression**, OCD, migraine, smoking addiction

Focused Ultrasound (FUS)

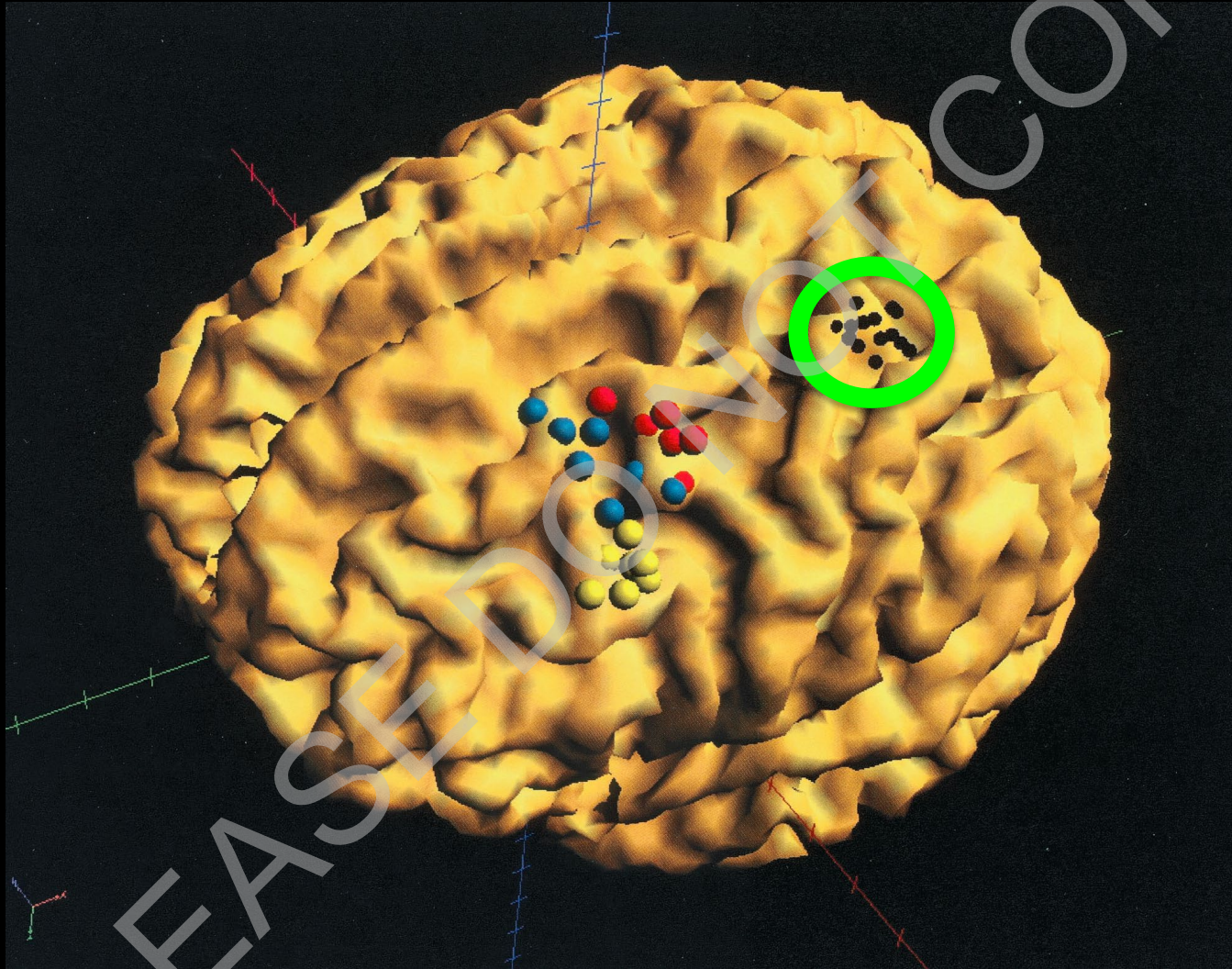


- FDA approved for **tremor**

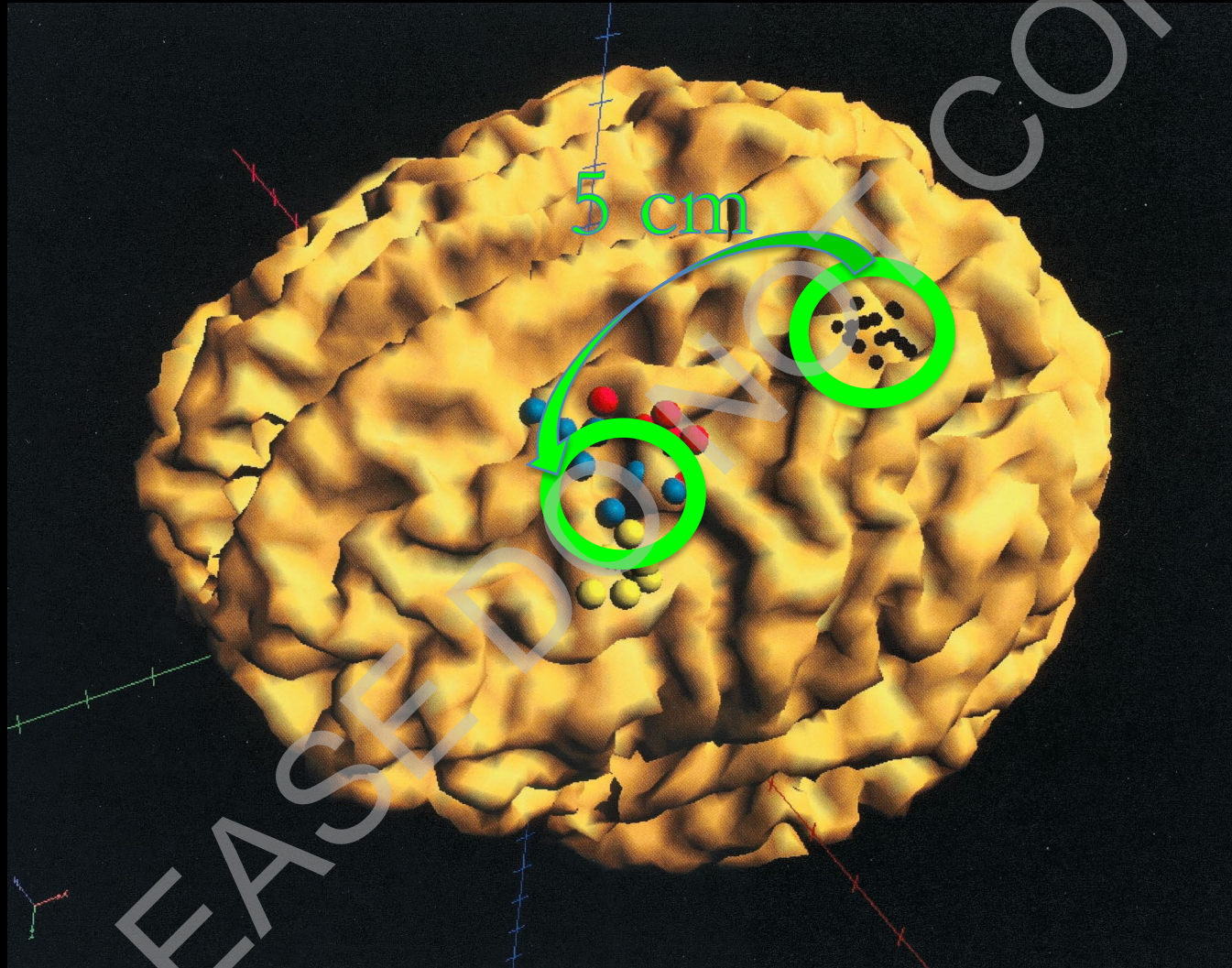
Targeting TMS in Depression: The 5 cm method



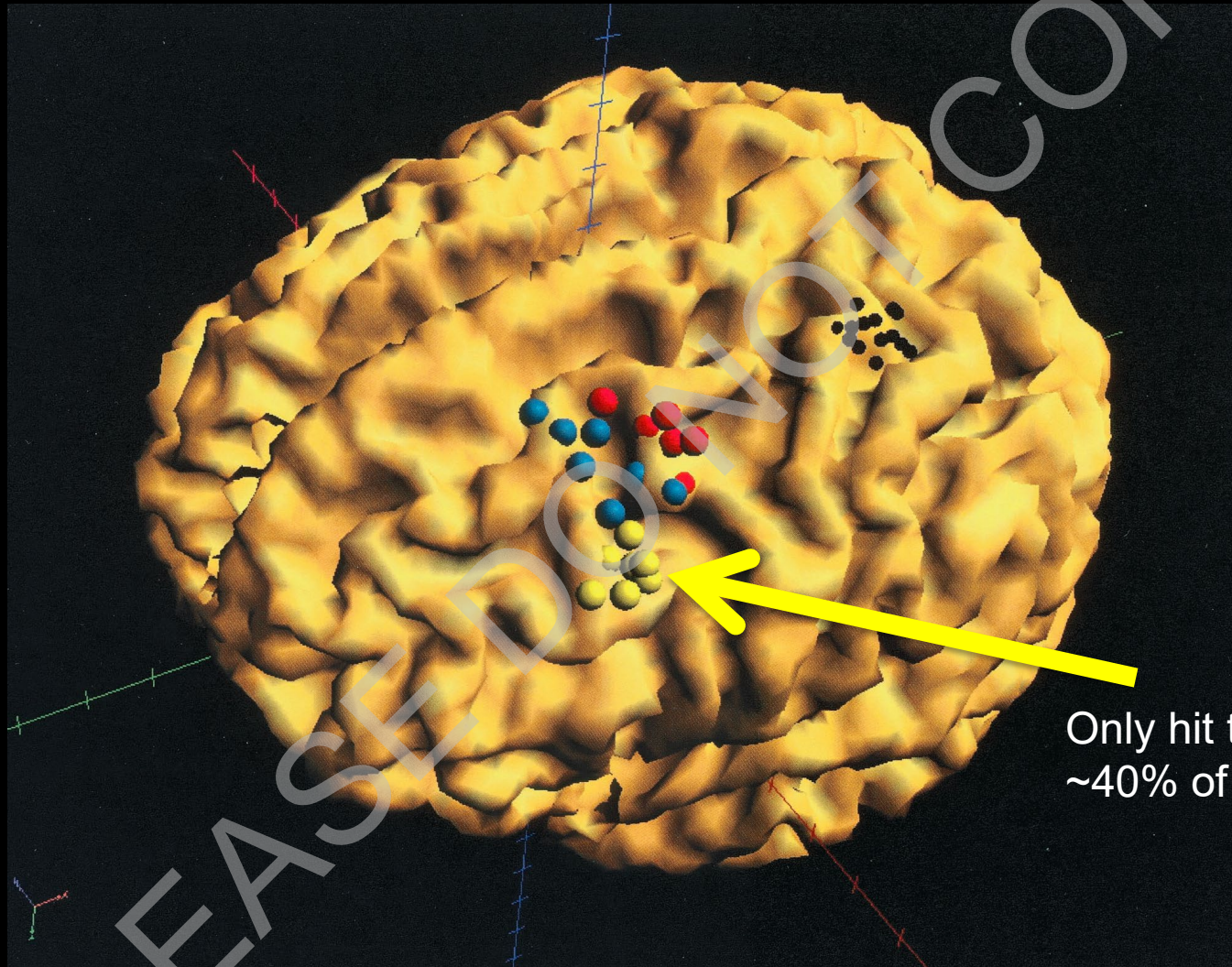
Targeting TMS in Depression: The 5 cm method



Targeting TMS in Depression: The 5 cm method

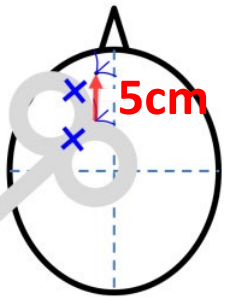


Targeting TMS in Depression: The 5 cm method



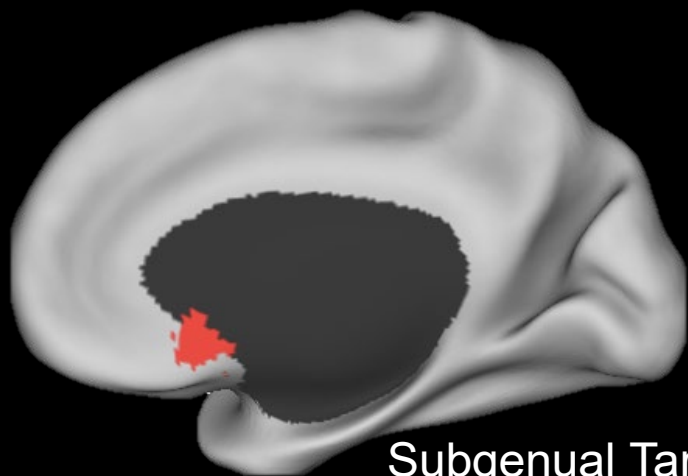
Only hit the "DLPFC"
~40% of the time

Targeting TMS in Depression

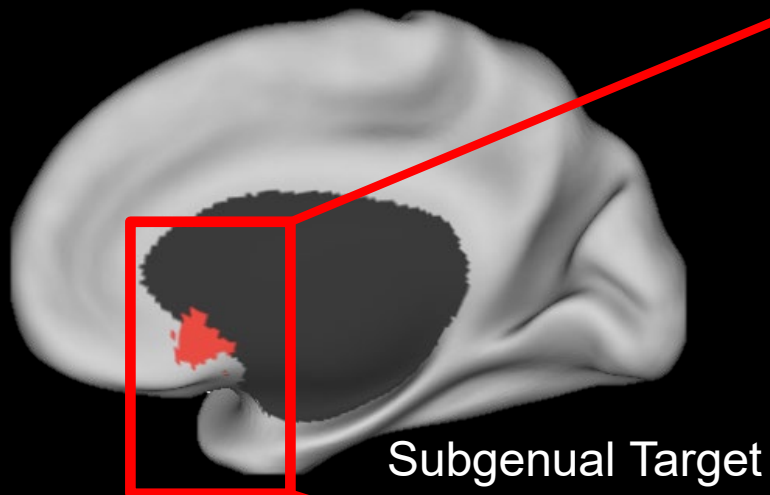


Targeting TMS in Depression

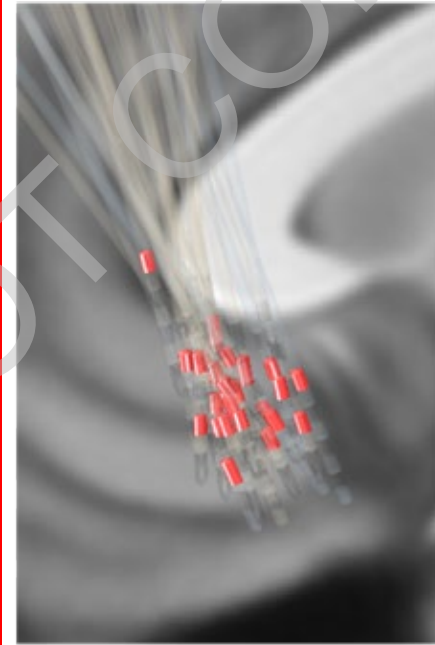


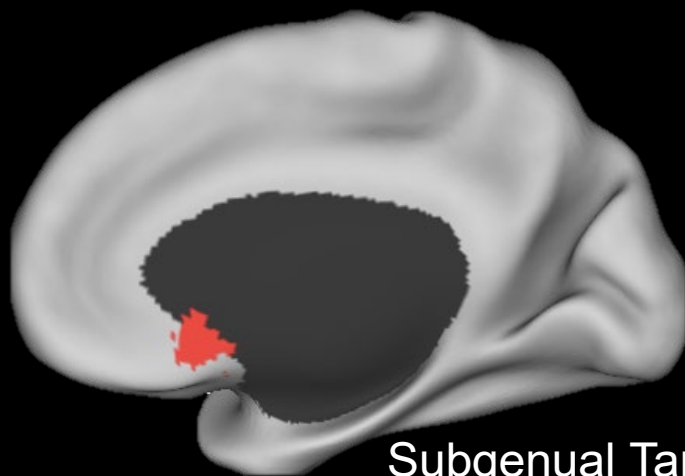


Subgenual Target

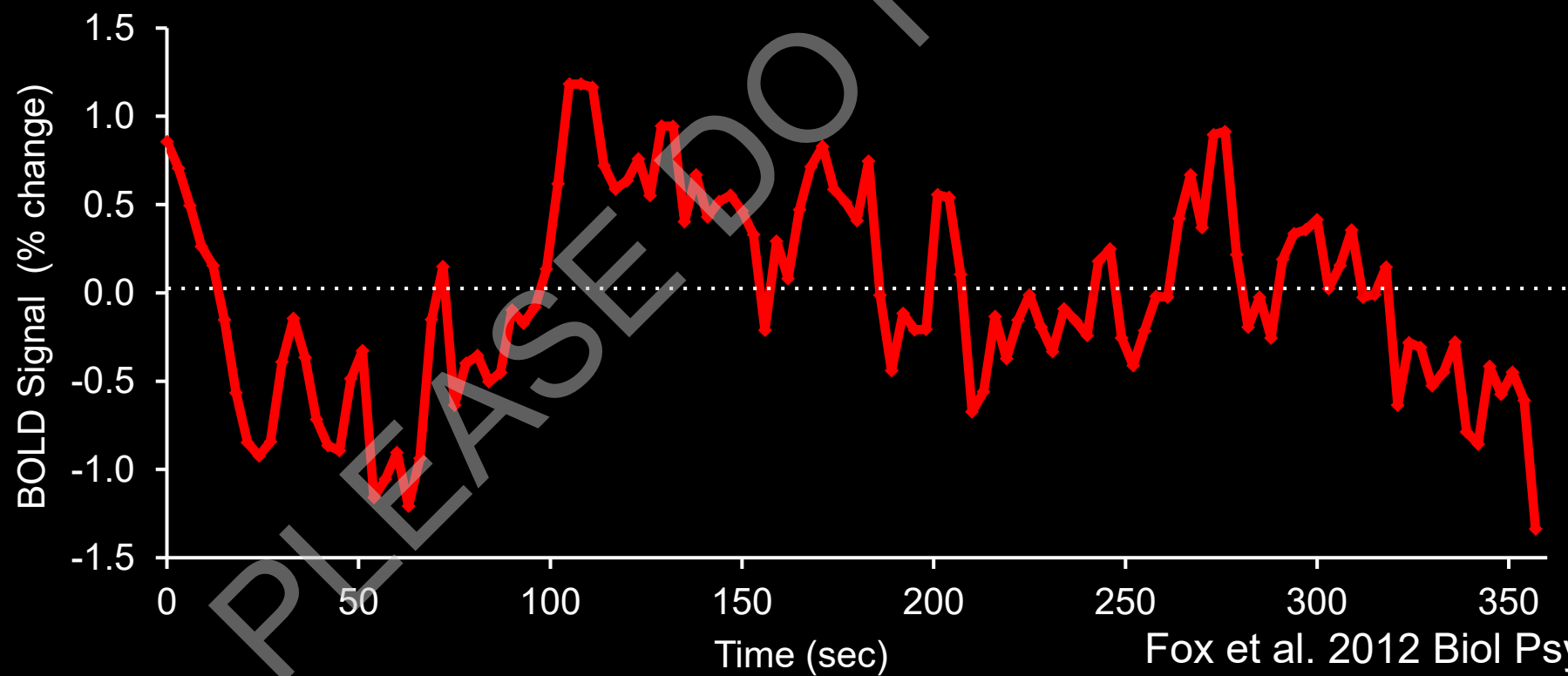


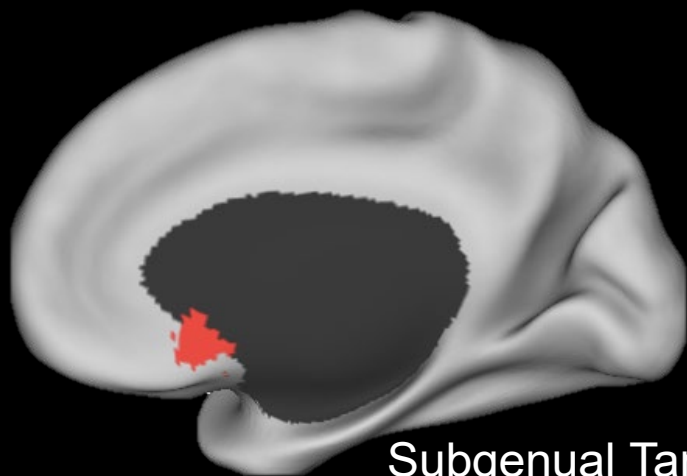
Atlanta (n=27)
sgACC (MDD)



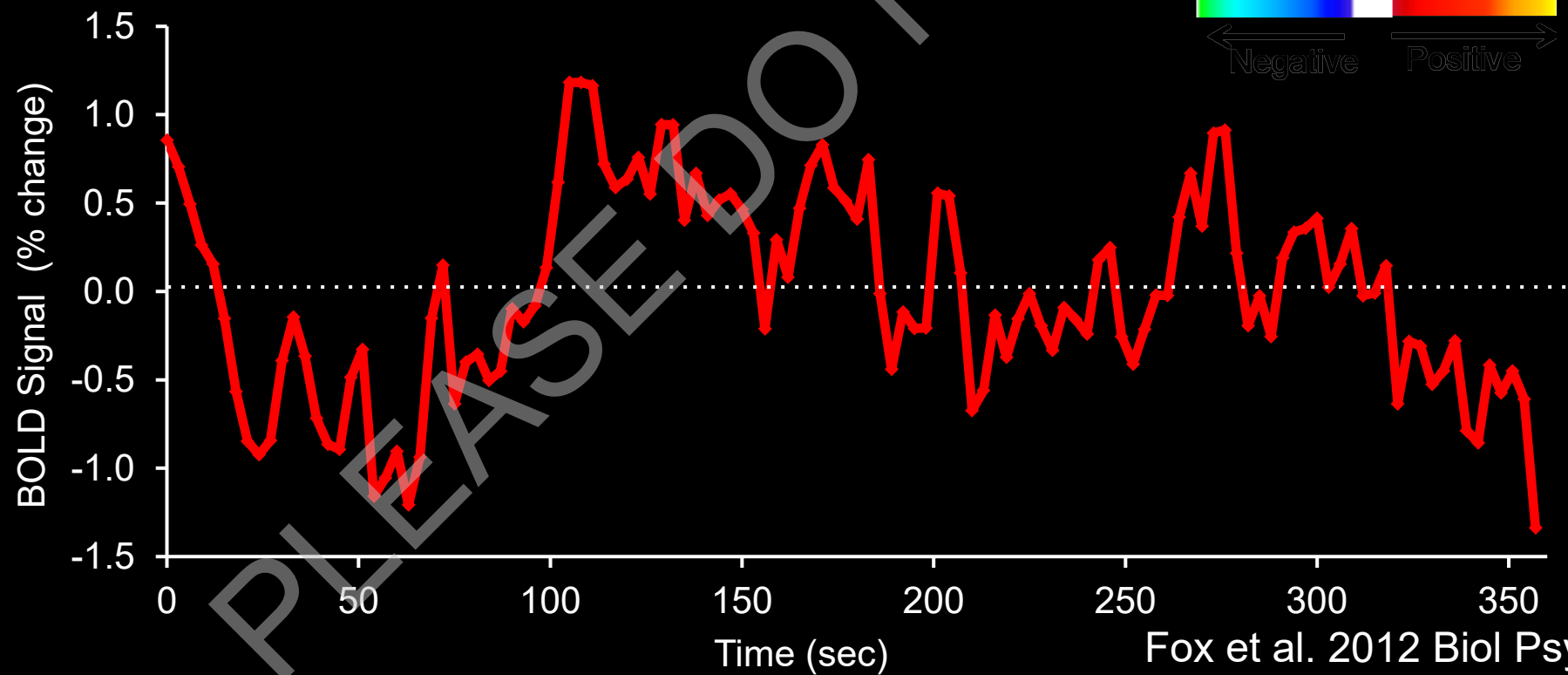
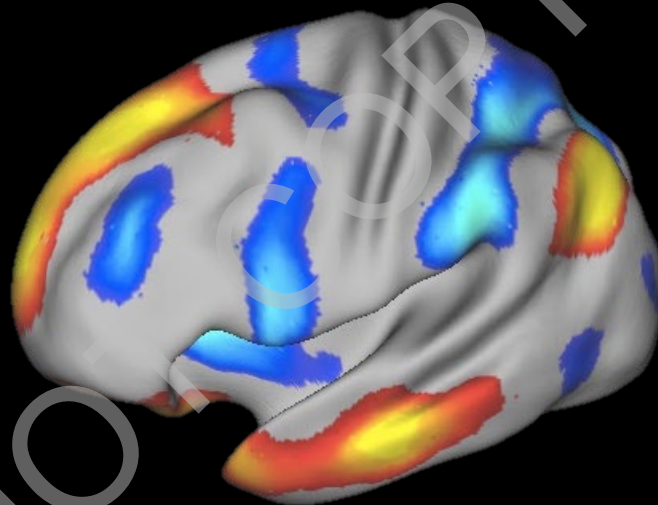


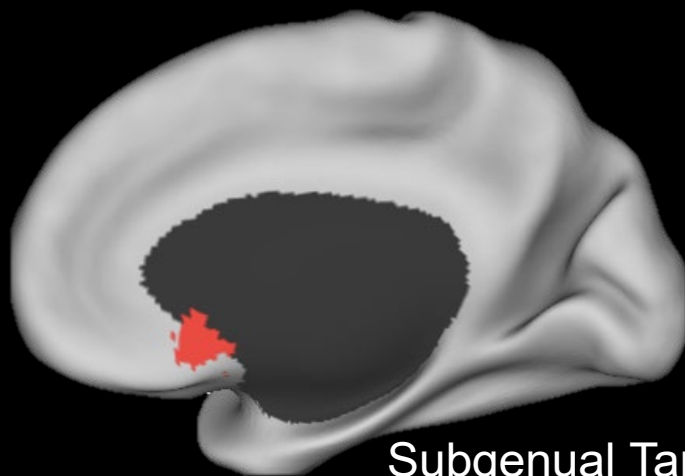
Subgenual Target



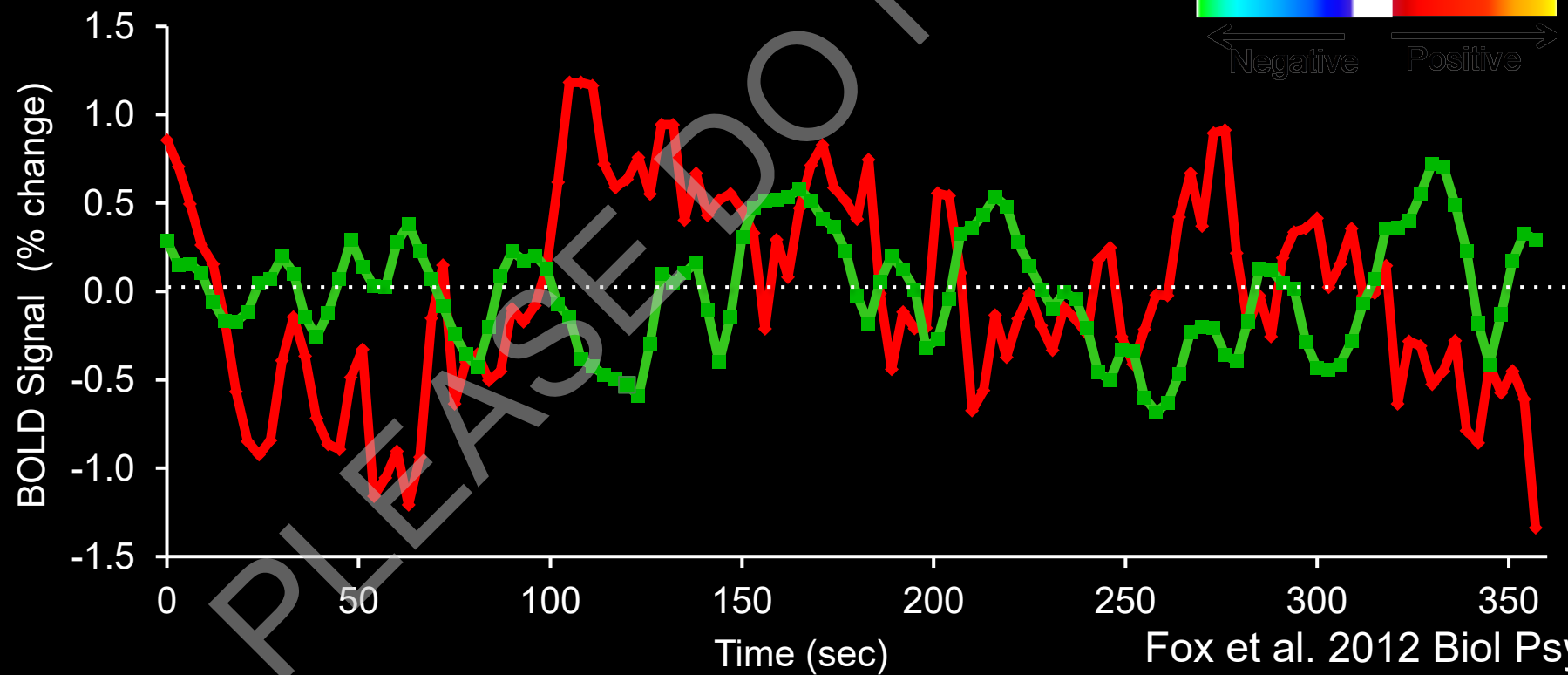
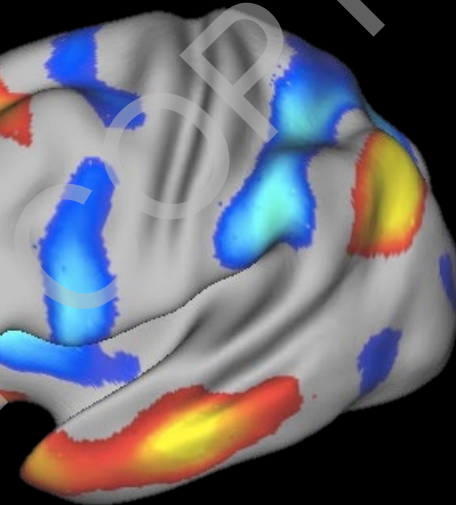
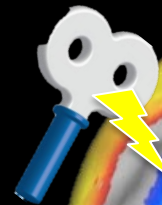


Subgenual Target

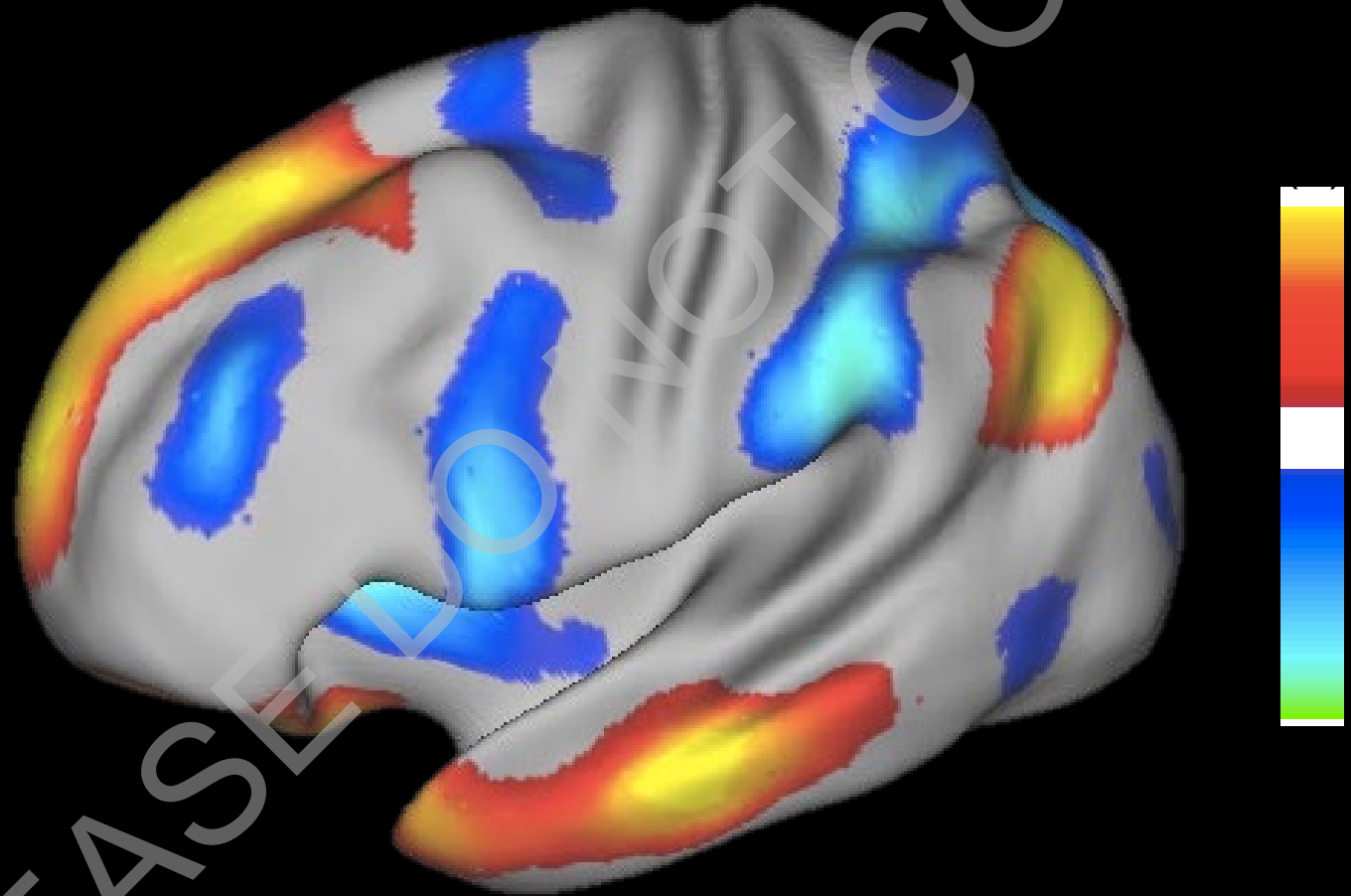




Subgenual Target

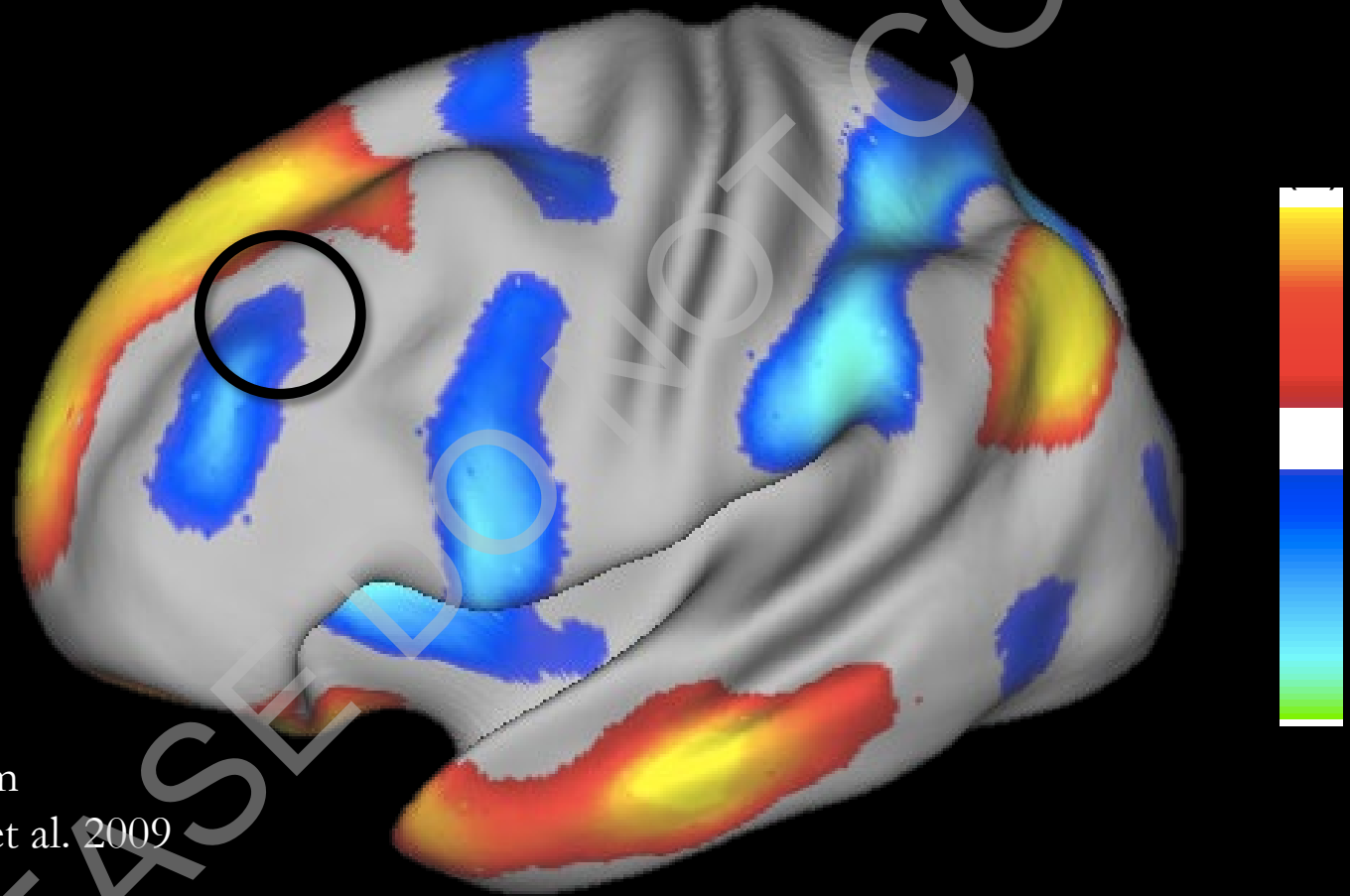


Can subgenual connectivity guide stimulation?



Fox et al. 2012 Biological Psychiatry

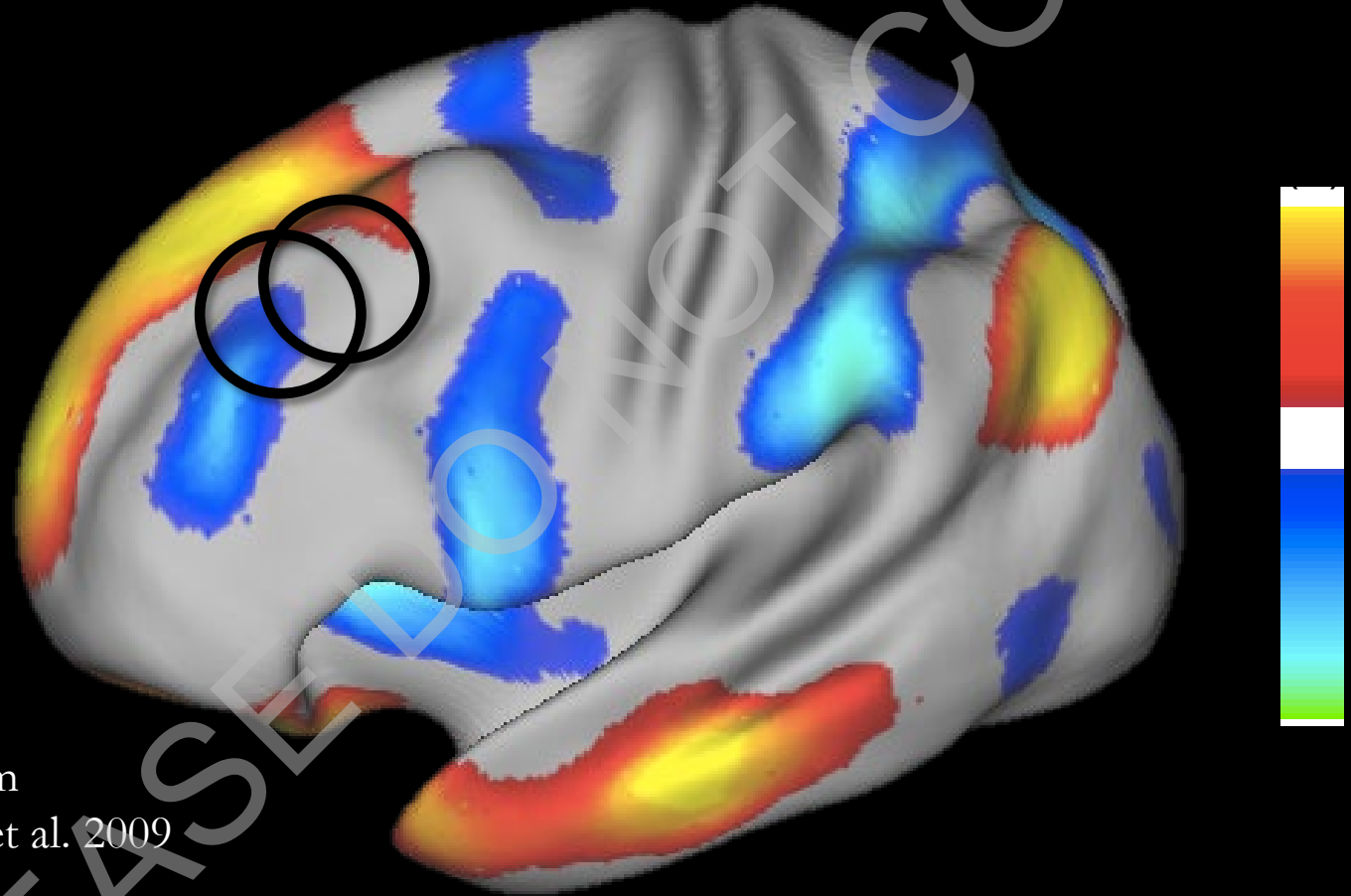
Can subgenual connectivity guide stimulation?



Targets from
Herbsman et al. 2009

Fox et al. 2012 Biological Psychiatry

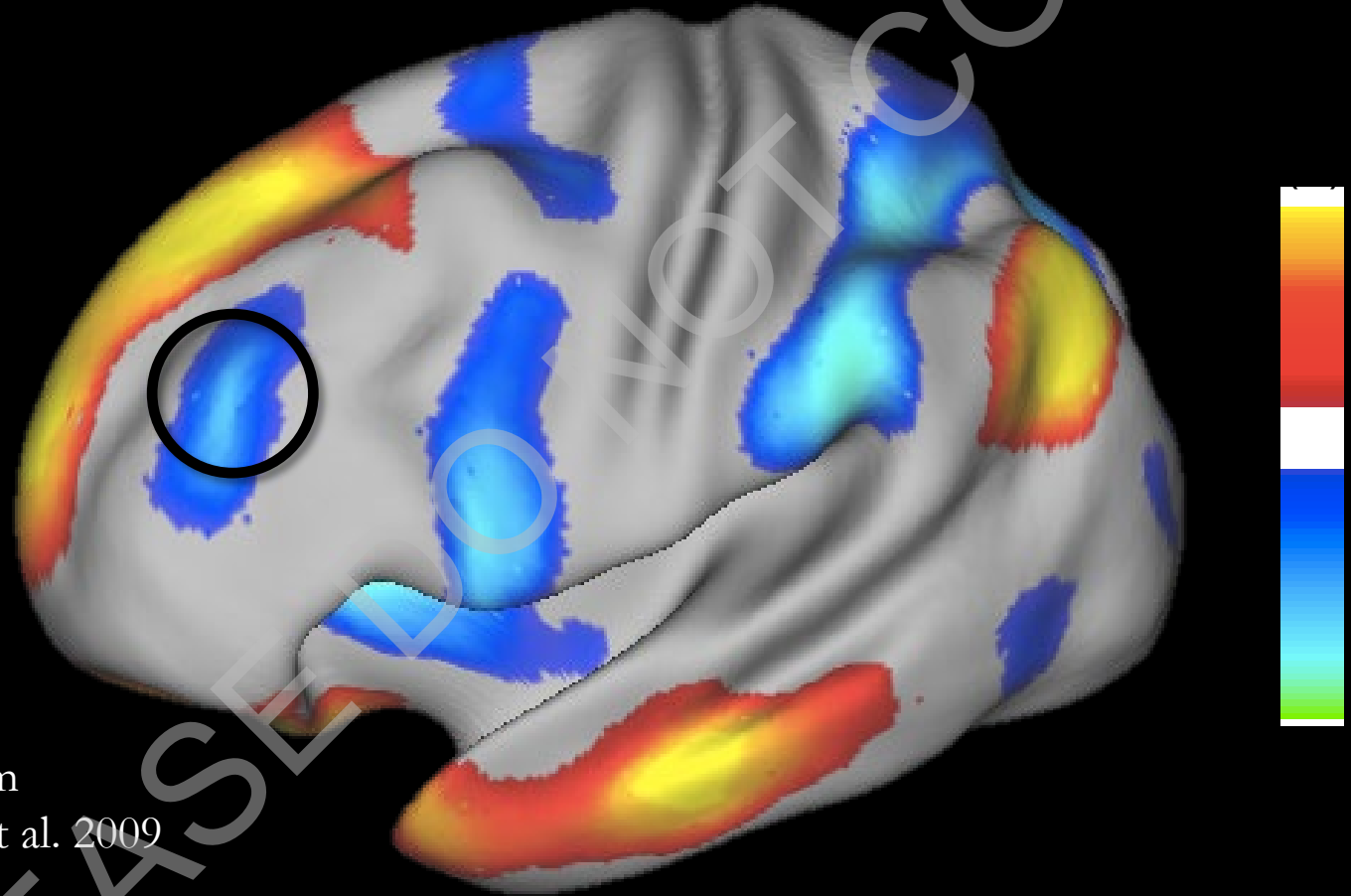
Can subgenual connectivity guide stimulation?



Targets from
Herbsman et al. 2009

Fox et al. 2012 Biological Psychiatry

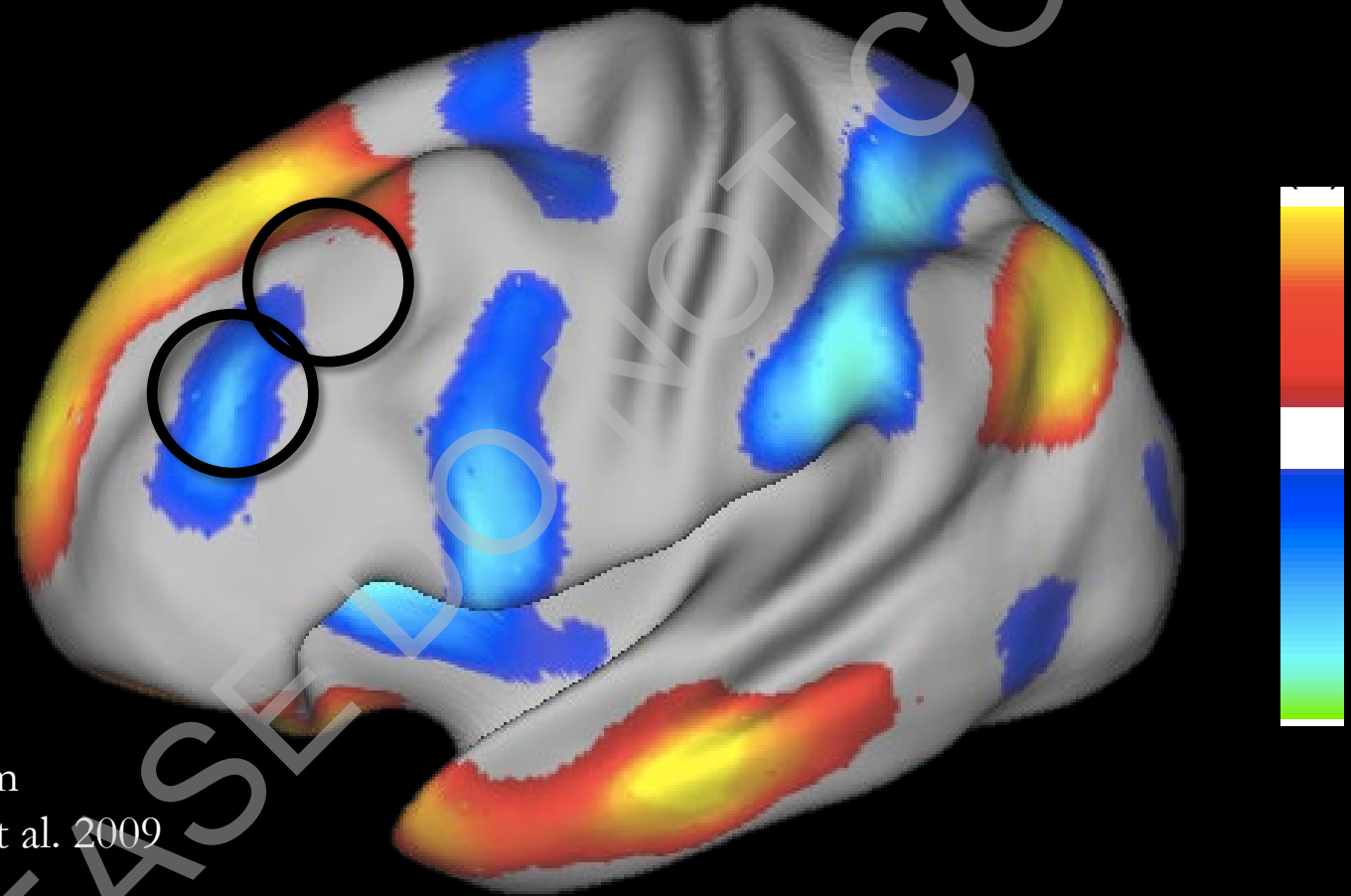
Can subgenual connectivity guide stimulation?



Targets from
Fitzgerald et al. 2009

Fox et al. 2012 Biological Psychiatry

Can subgenual connectivity guide stimulation?

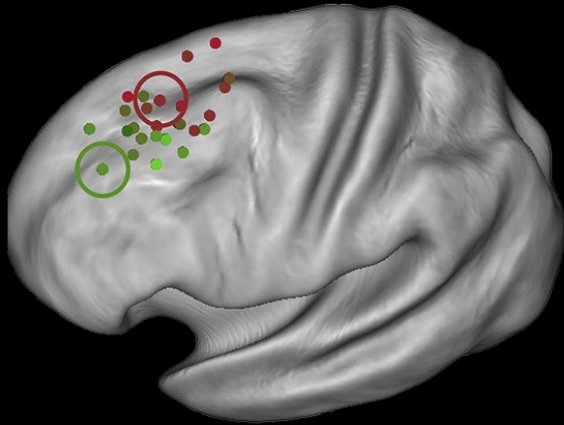


Targets from
Fitzgerald et al. 2009

Fox et al. 2012 Biological Psychiatry

TMS Network Mapping

Stim. Site Variability

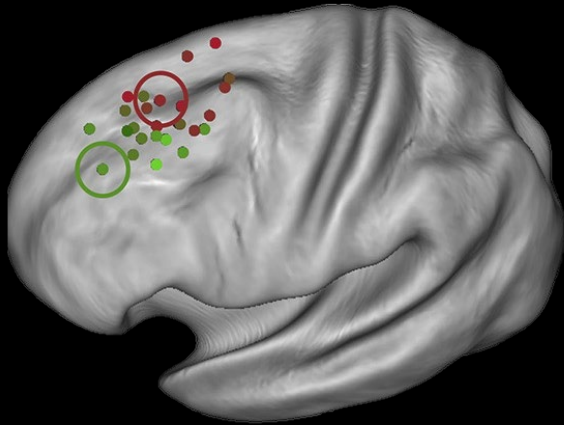


Weigand, Horn et al. 2018 Bio. Psych

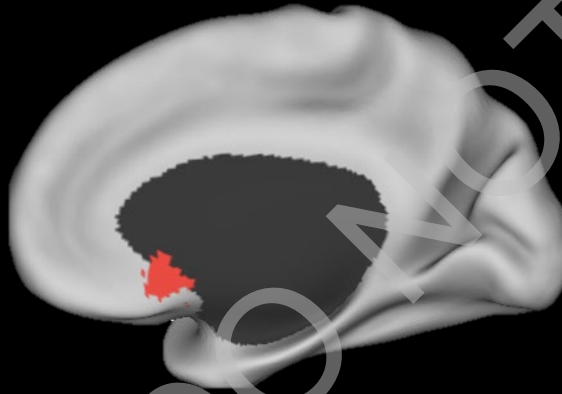


TMS Network Mapping

Stim. Site Variability



Important Connections

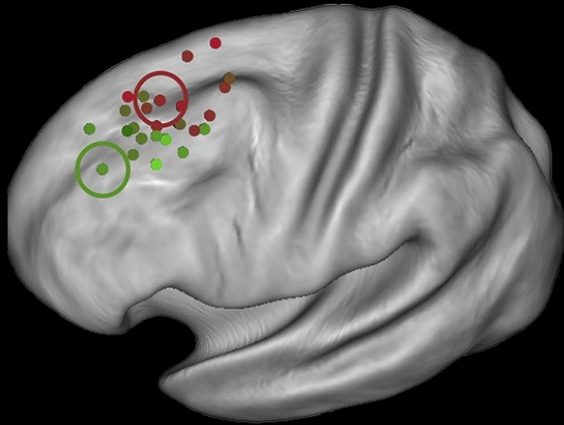


Weigand, Horn et al. 2018 Bio. Psych

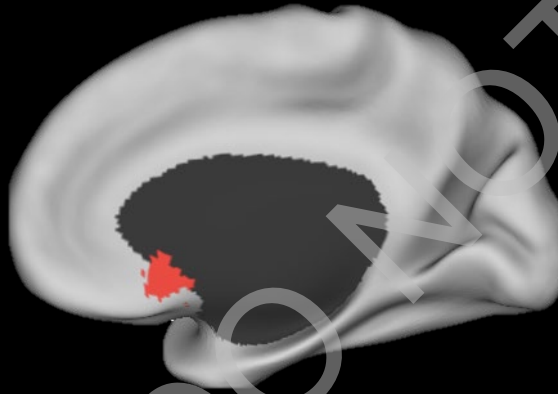


TMS Network Mapping

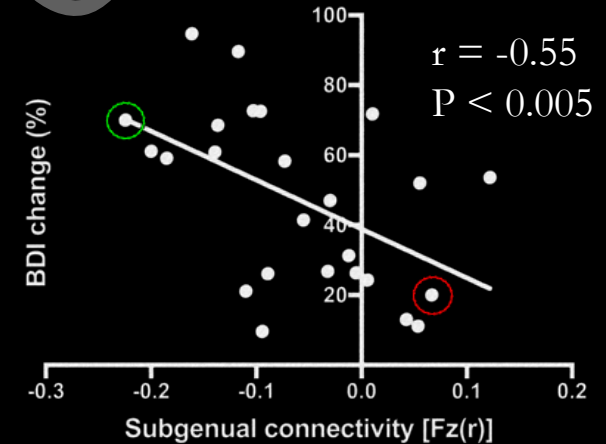
Stim. Site Variability



Important Connections



Response Prediction

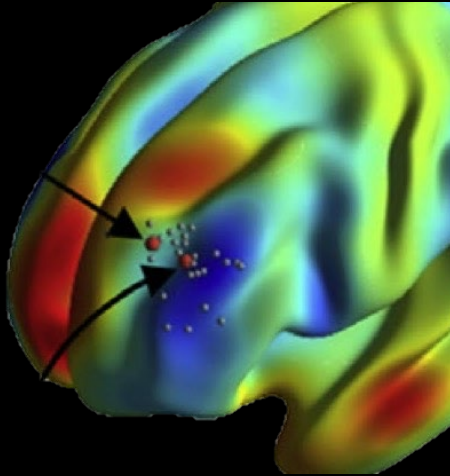


Weigand, Horn et al. 2018 Bio. Psych

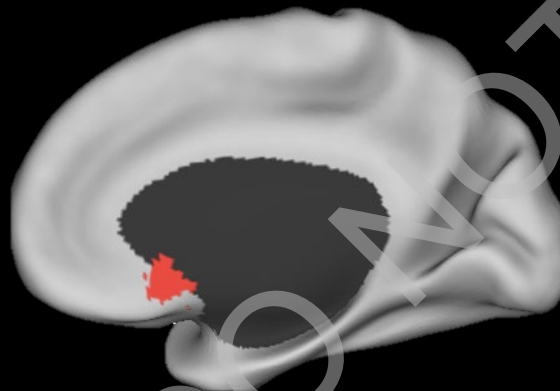


TMS Network Mapping

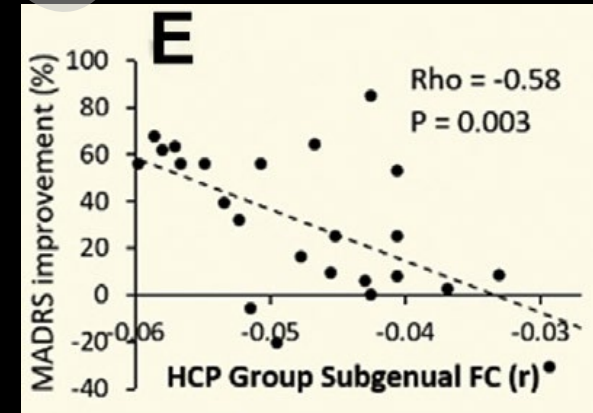
Stim. Site Variability



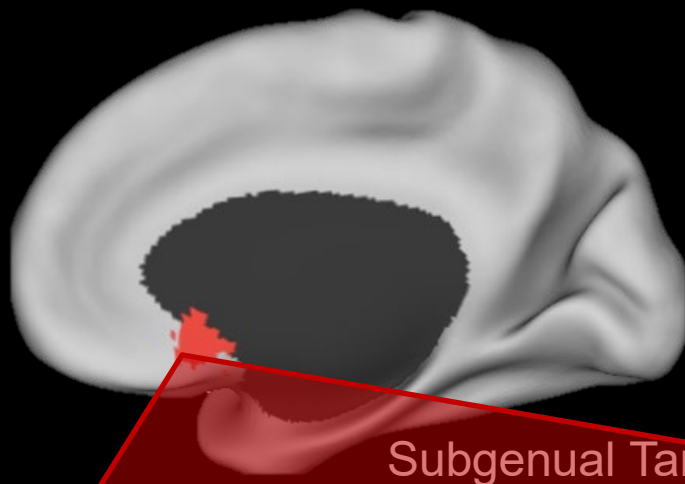
Important Connections



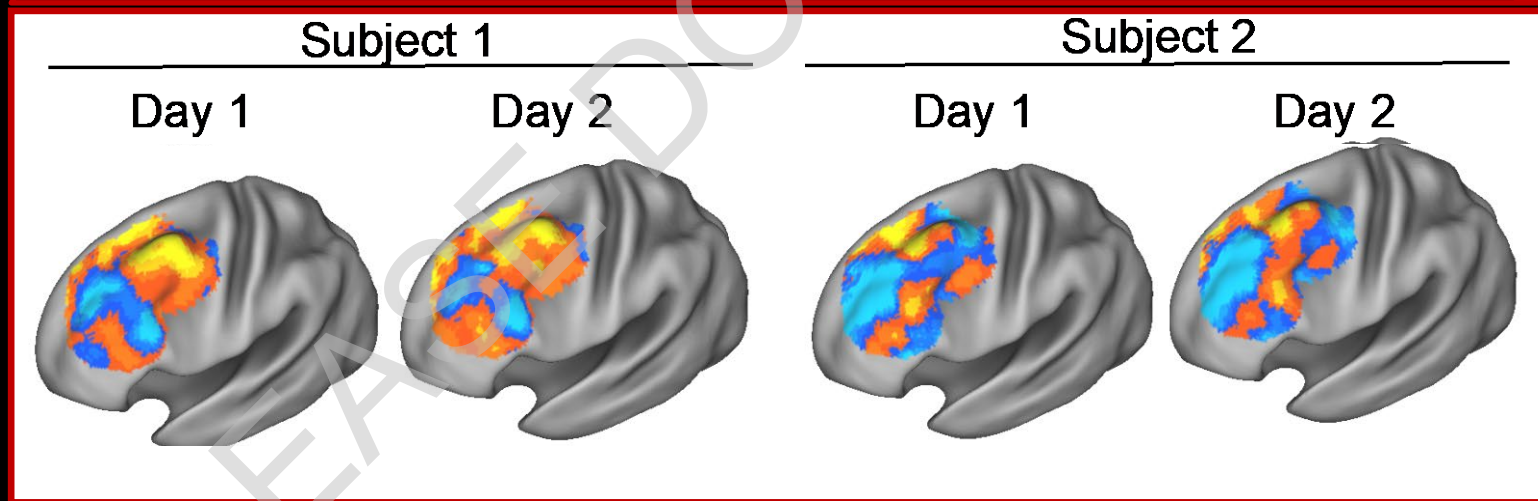
Response Prediction



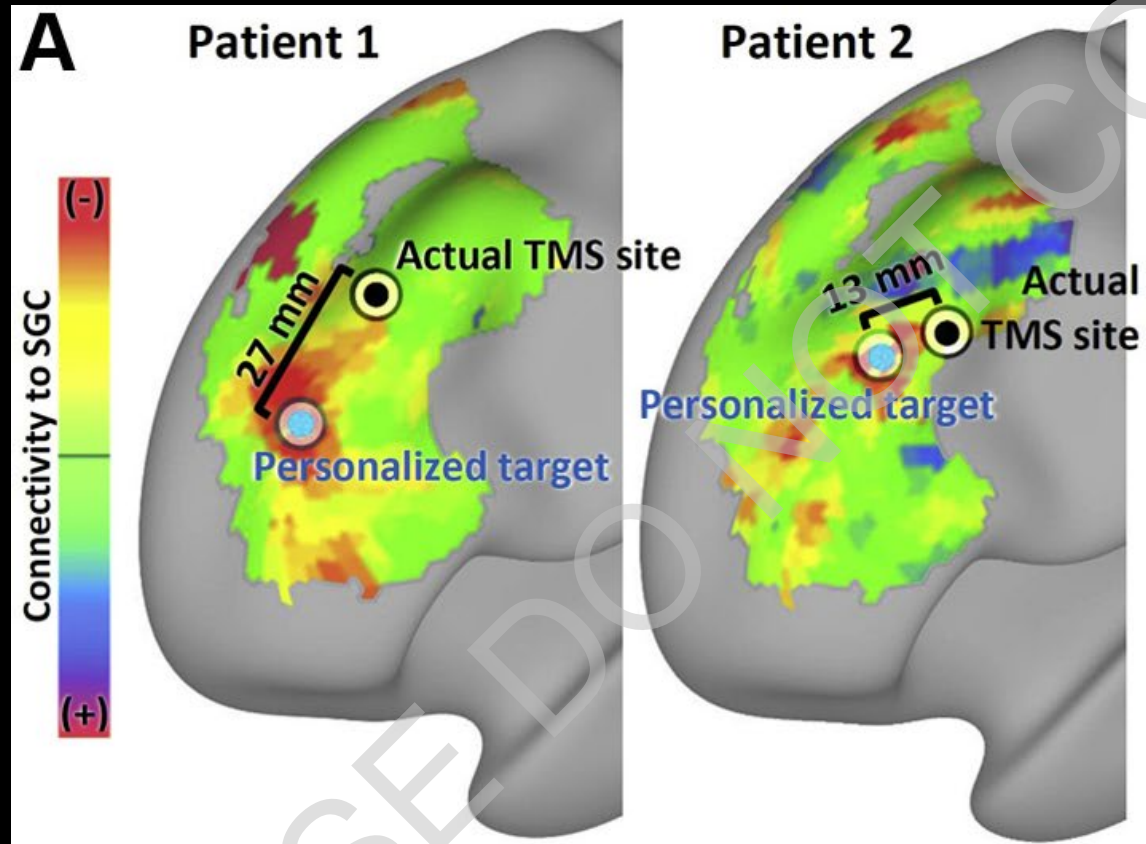
“Individualized” TMS Targets



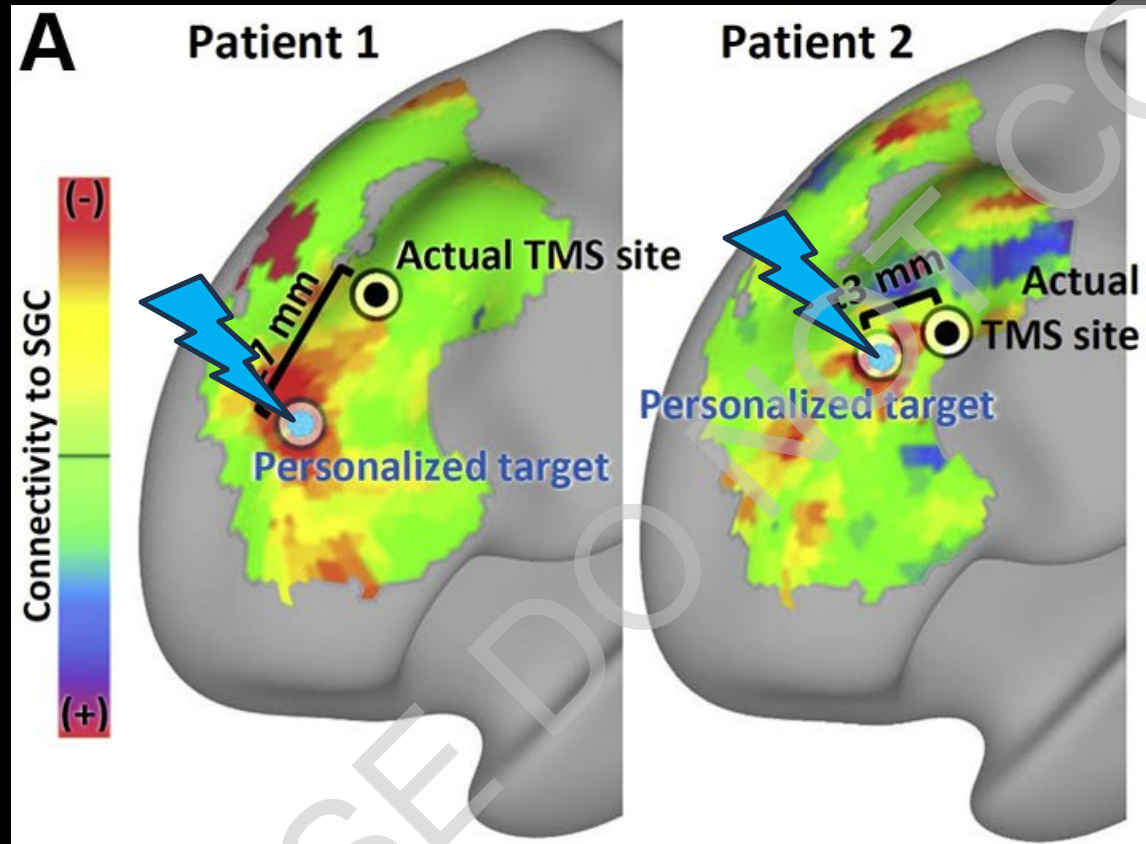
Subgenual Target



“Individualized” TMS Targets

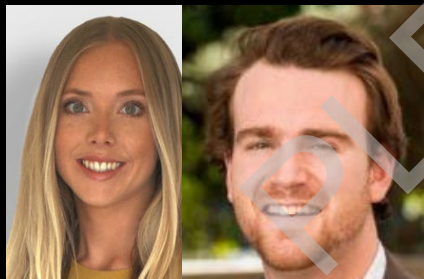


“Individualized” TMS Targets

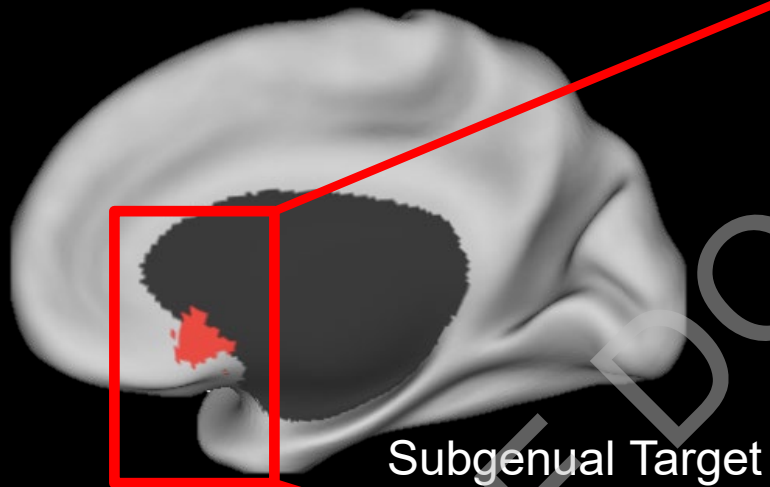


SAINT Neuromodulation System FDA approved 9/2022

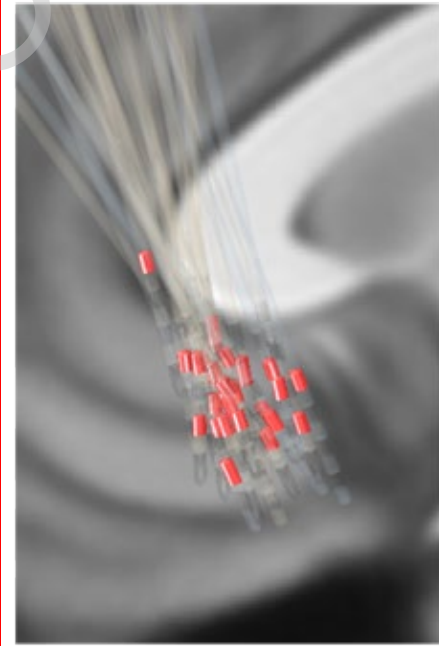
Cole et al. 2020 AJP, Cole et al. 2021 AJP : **>80% response rate**



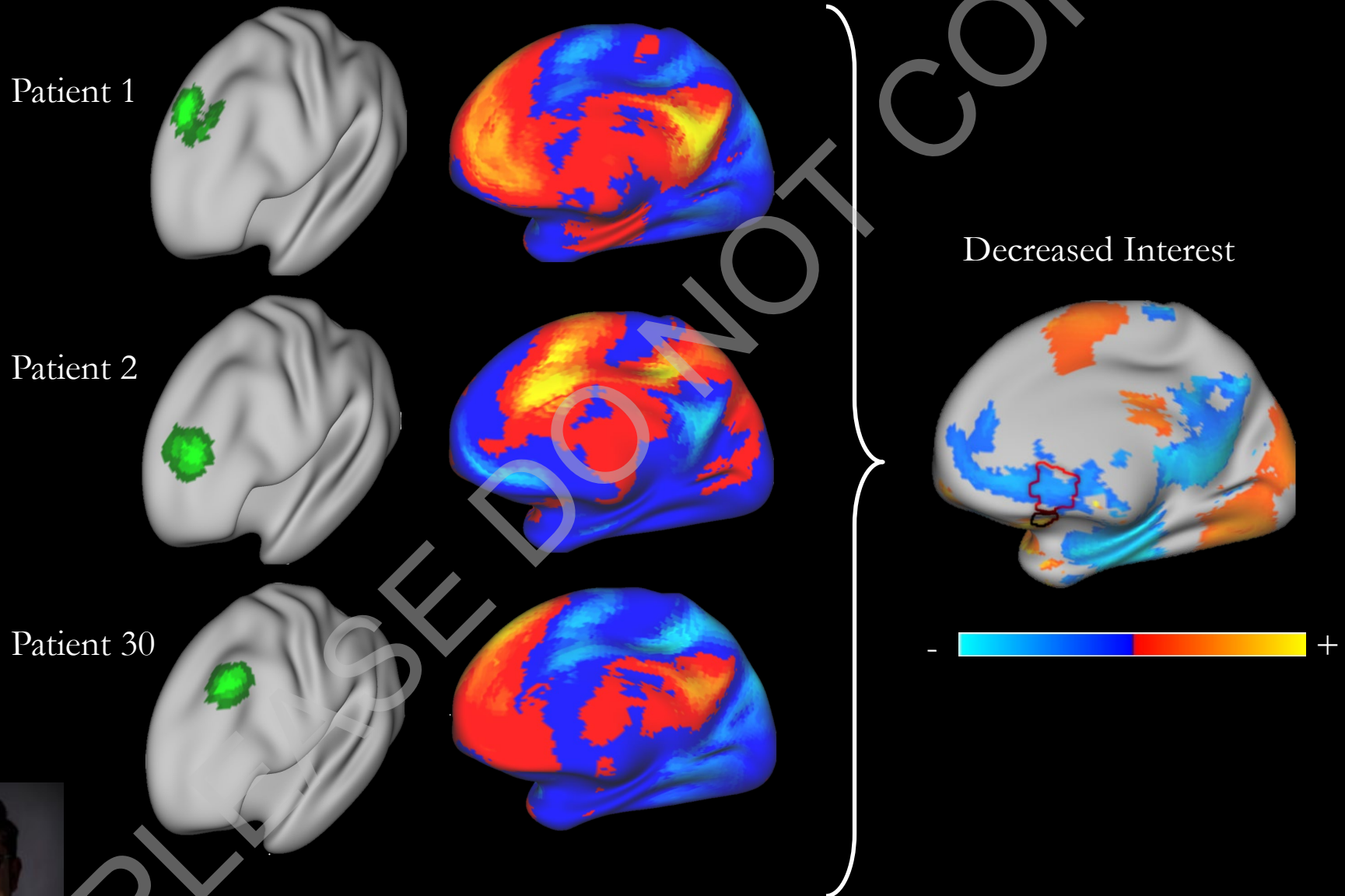
What if we're unsure of our target?



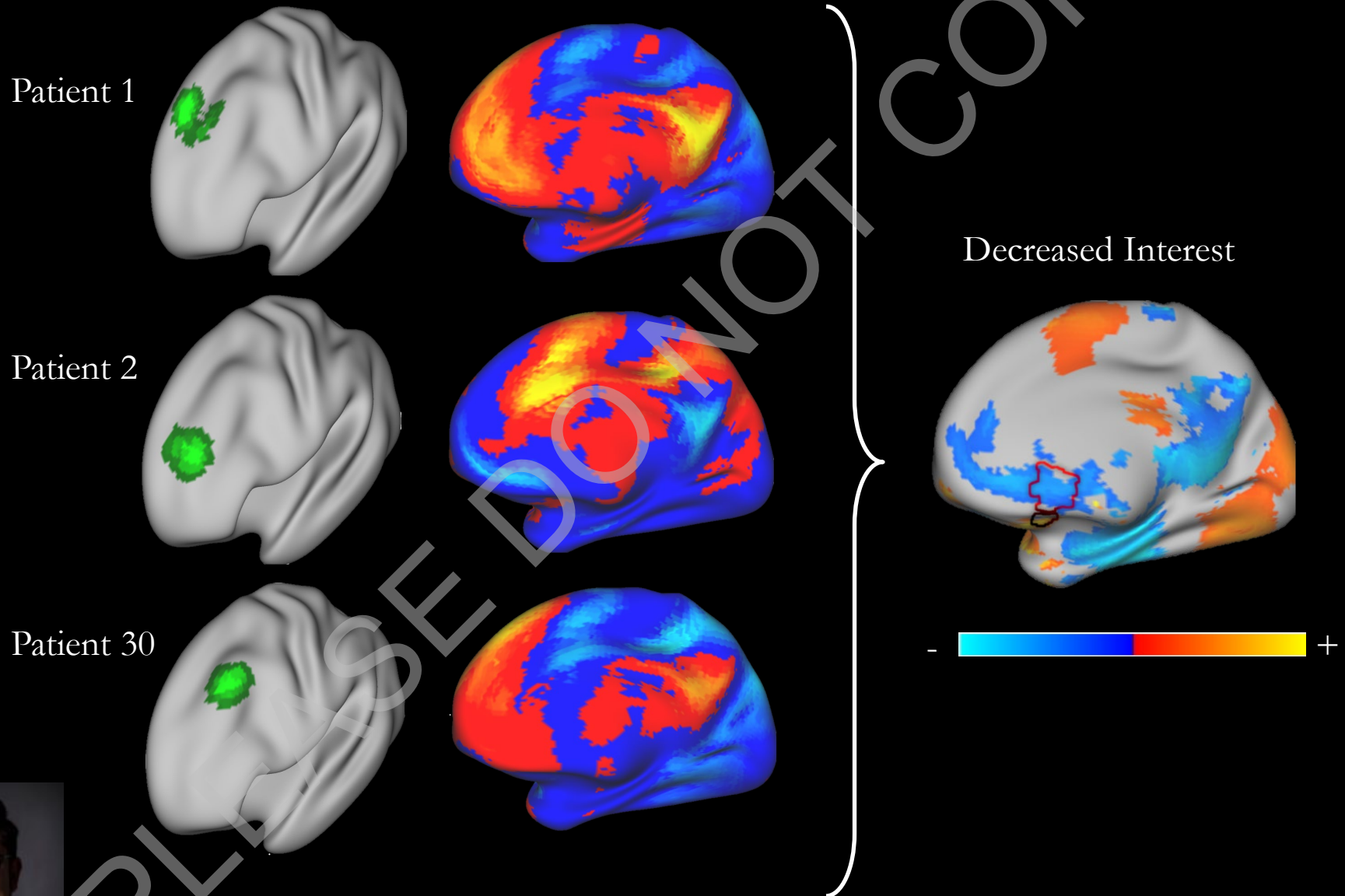
Atlanta (n=27)
sgACC (MDD)



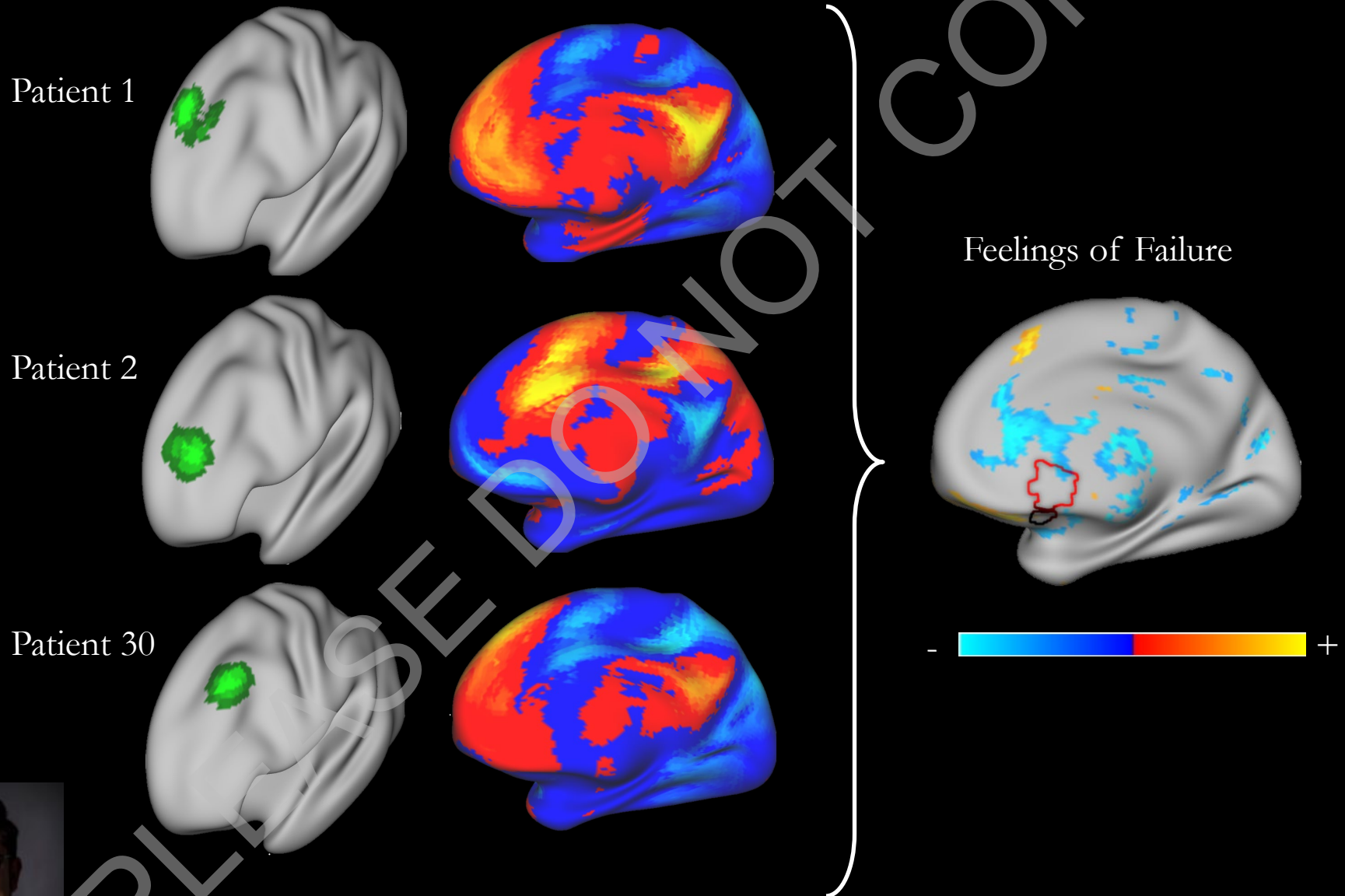
TMS Network Mapping



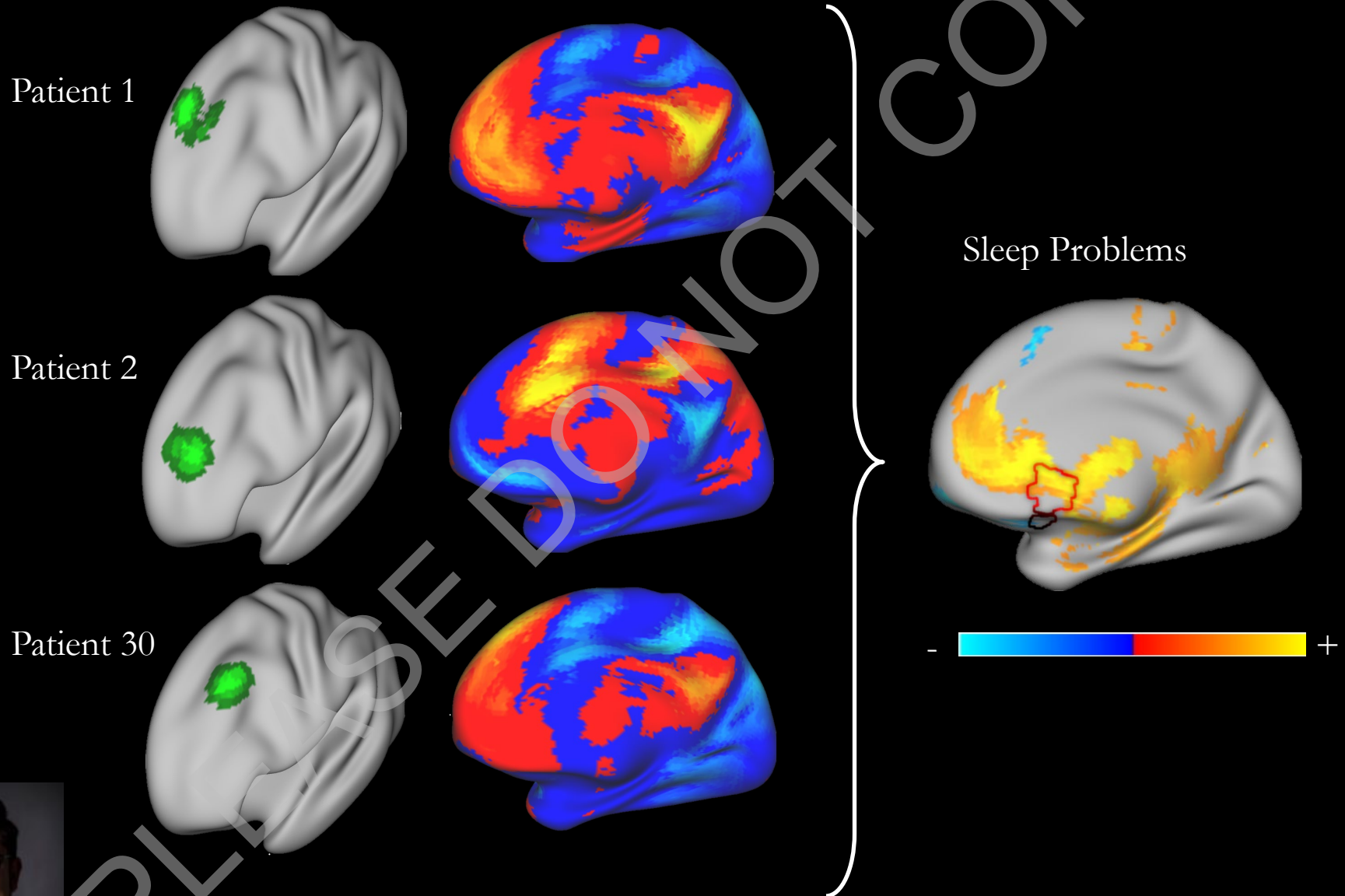
Symptom-Specific TMS Targets?



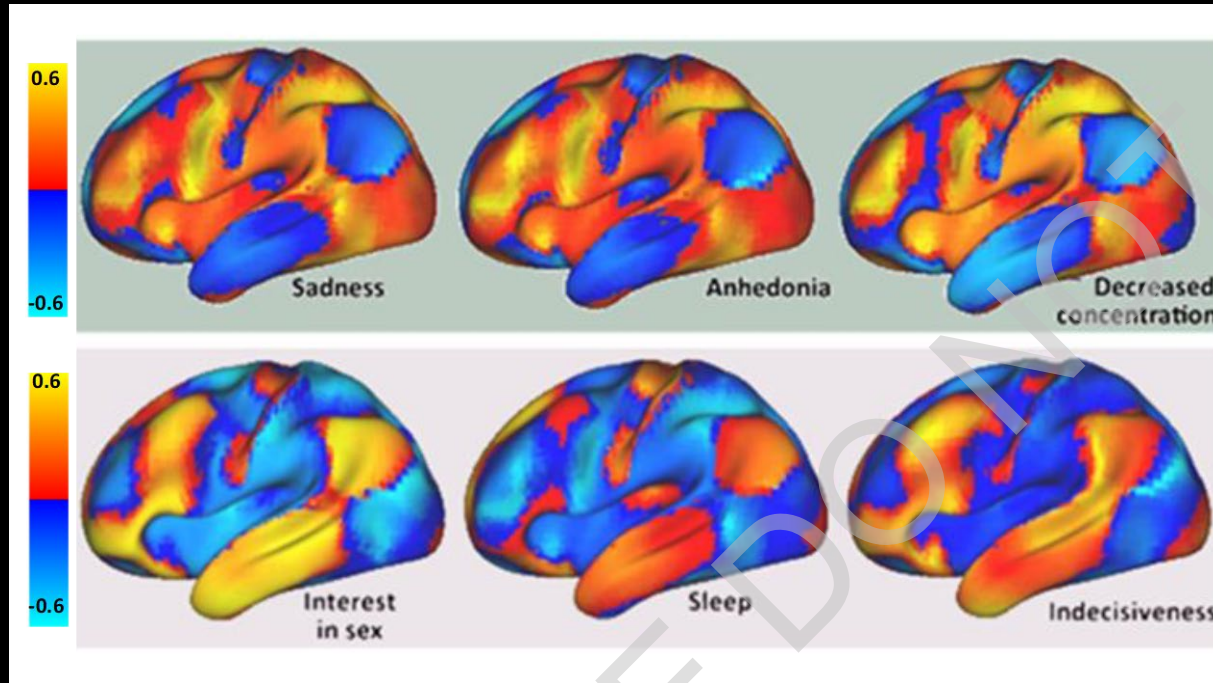
Symptom-Specific TMS Targets?



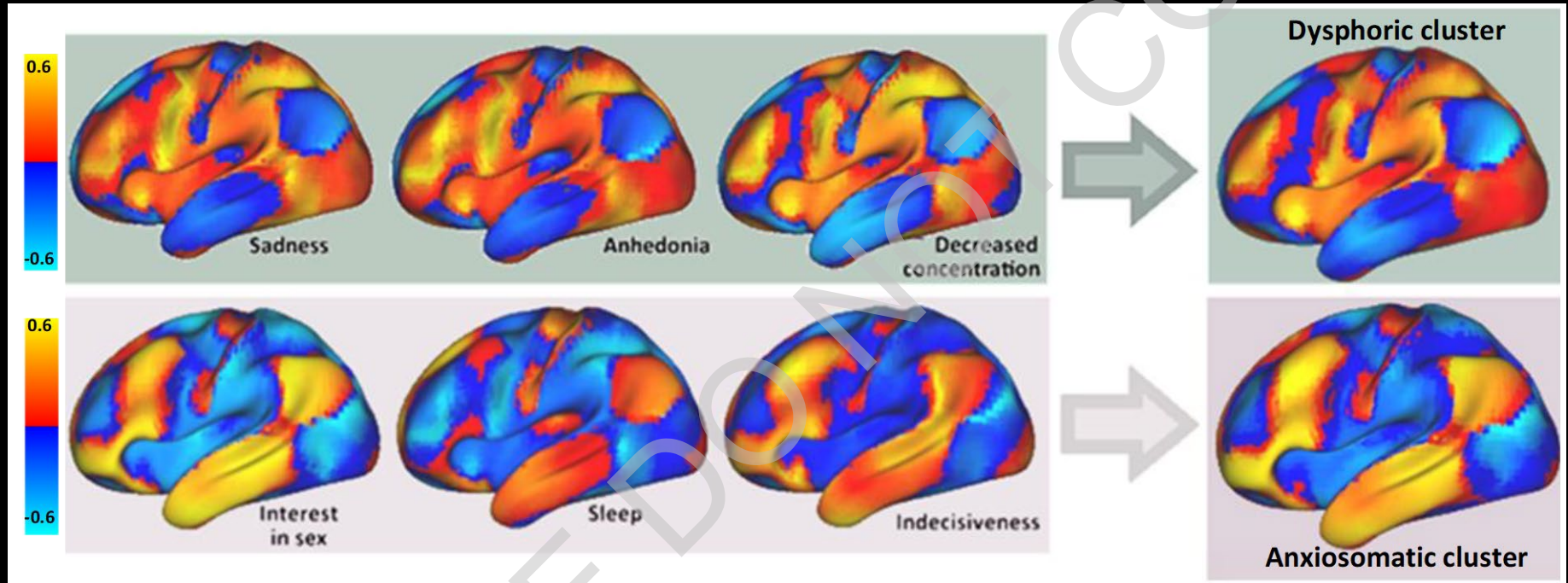
Symptom-Specific TMS Targets?



Symptom-Specific TMS Targets?



Symptom-Specific TMS Targets?

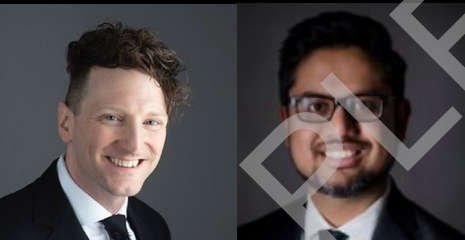
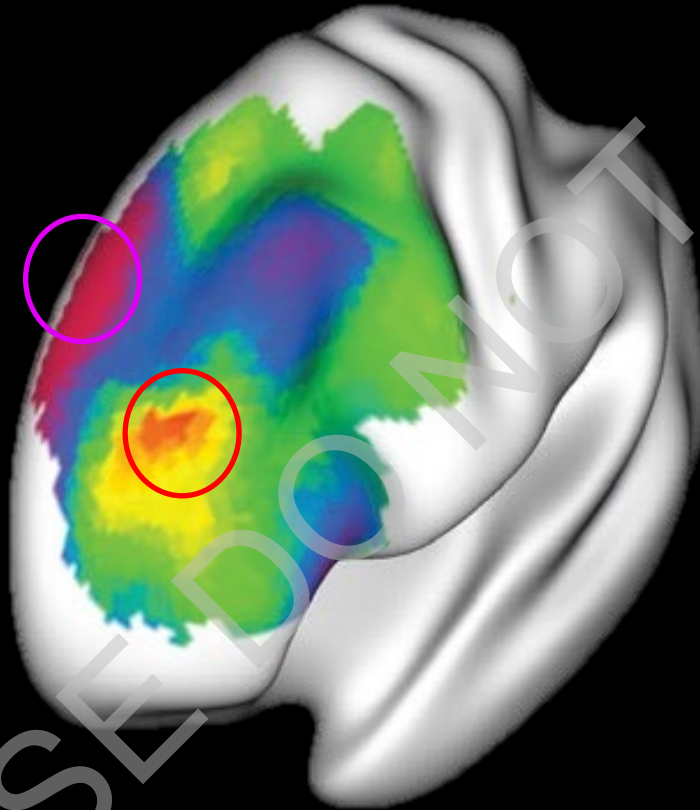


Symptom-Specific TMS Targets?

Dysphoric

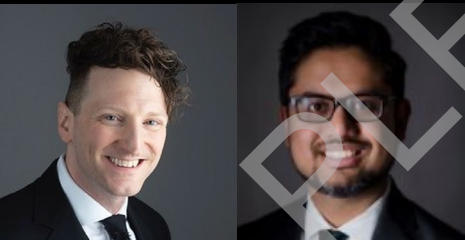
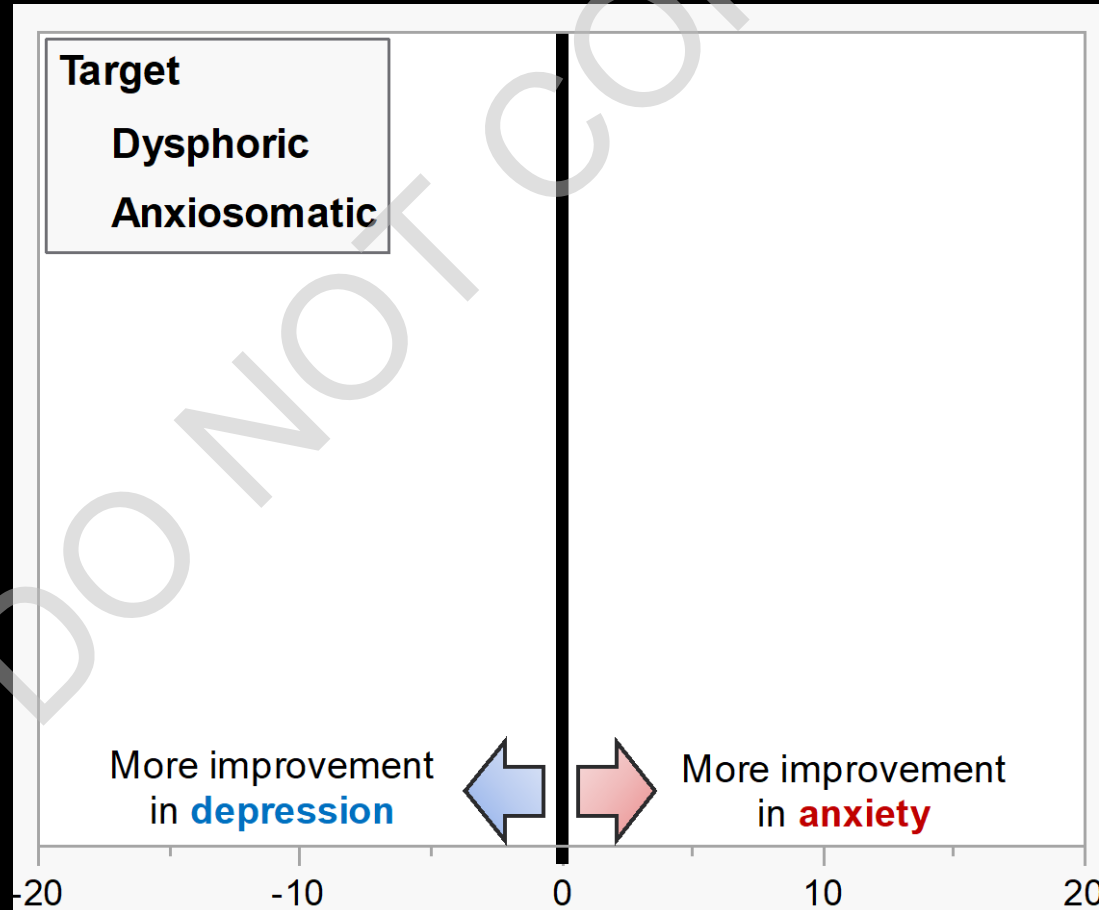
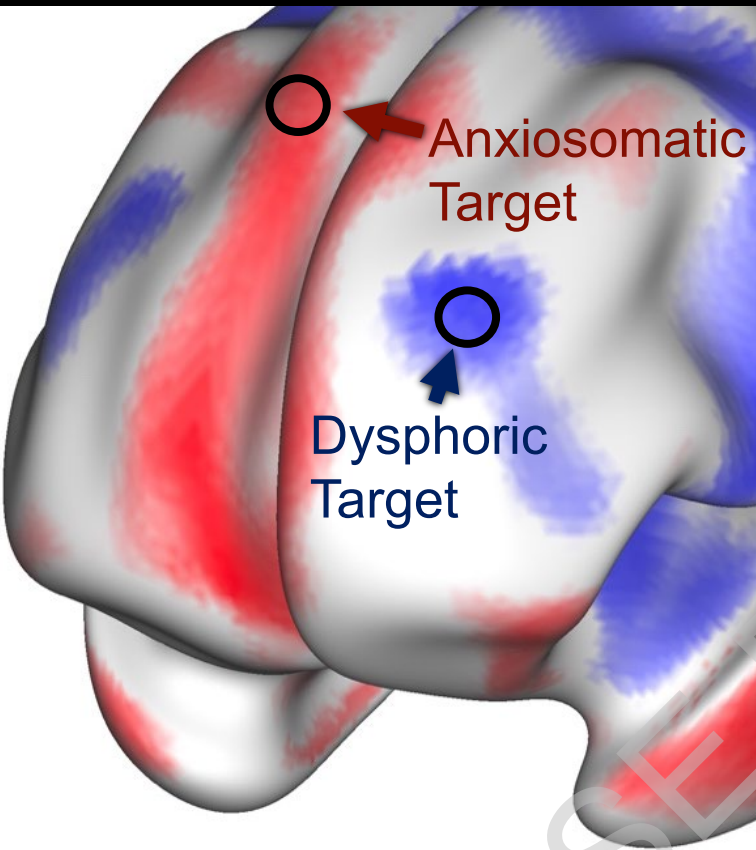


Anxiosomatic

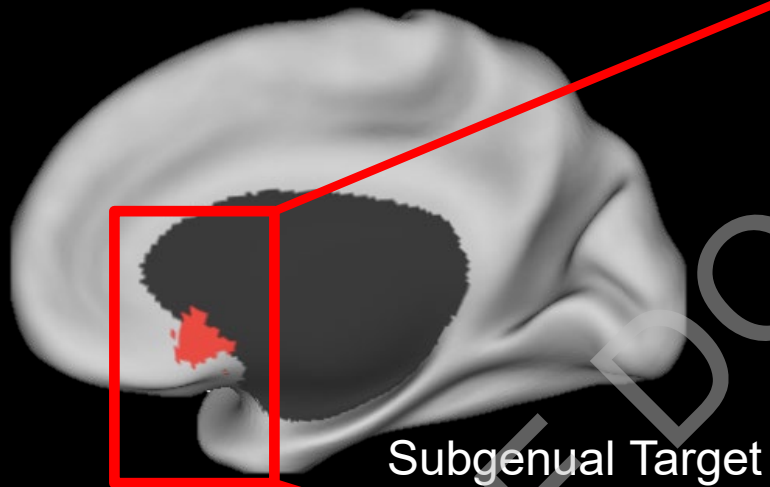


Taylor, Siddiqi et al., Submitted (pre-print on researchsquare)

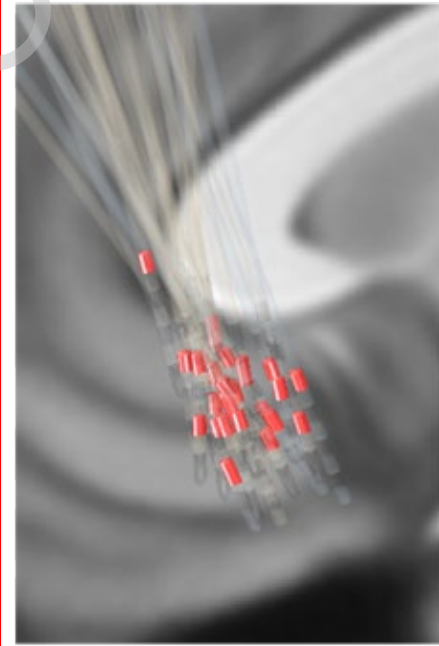
Symptom-Specific TMS Targets?



What if we're unsure of our target?

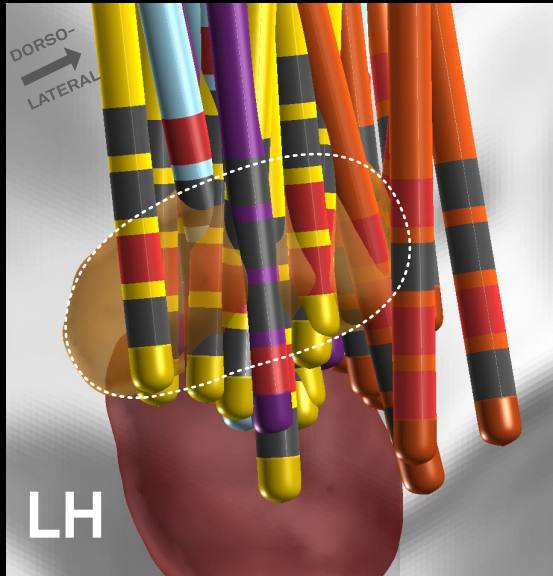


Atlanta (n=27)
sgACC (MDD)



DBS Network Mapping

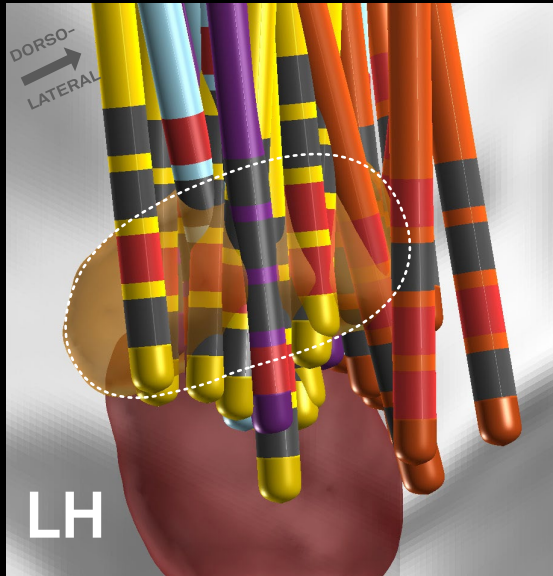
Stim. Site Variability



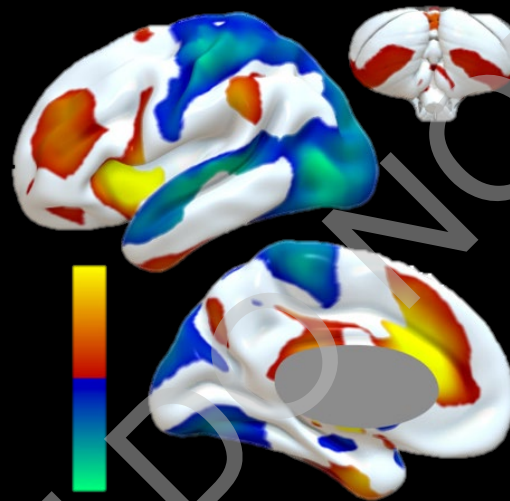
Horn et. al 2017 Annals of Neurology

DBS Network Mapping

Stim. Site Variability

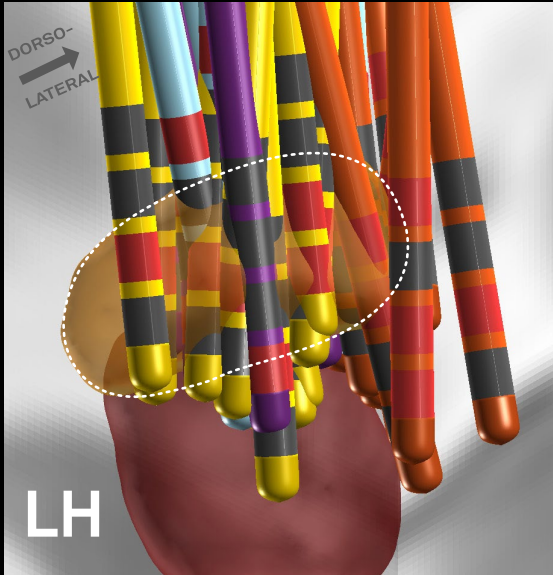


Important Connections

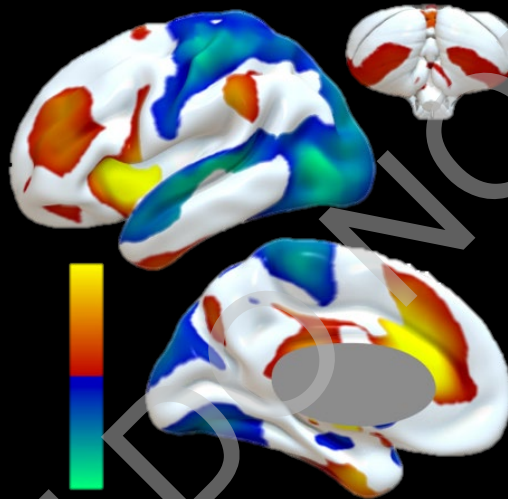


DBS Network Mapping

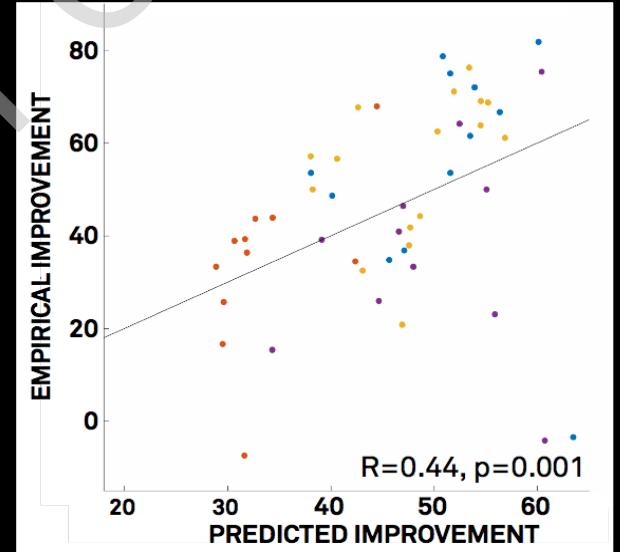
Stim. Site Variability



Important Connections

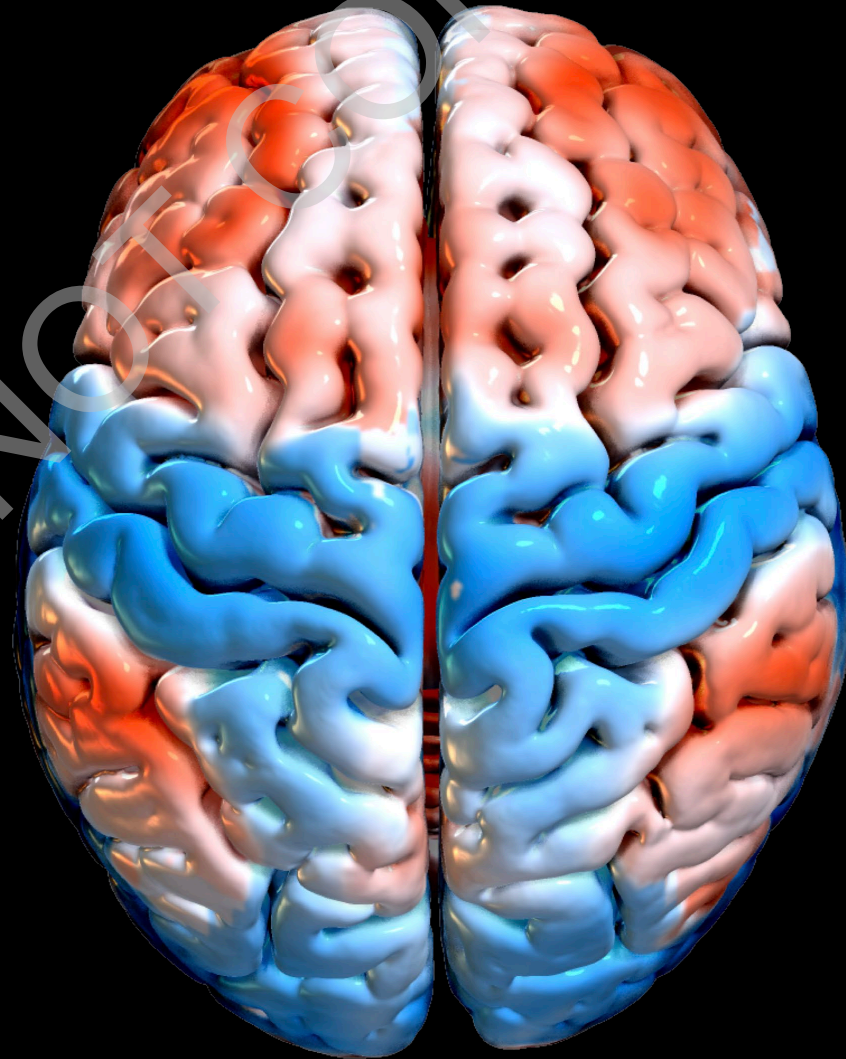
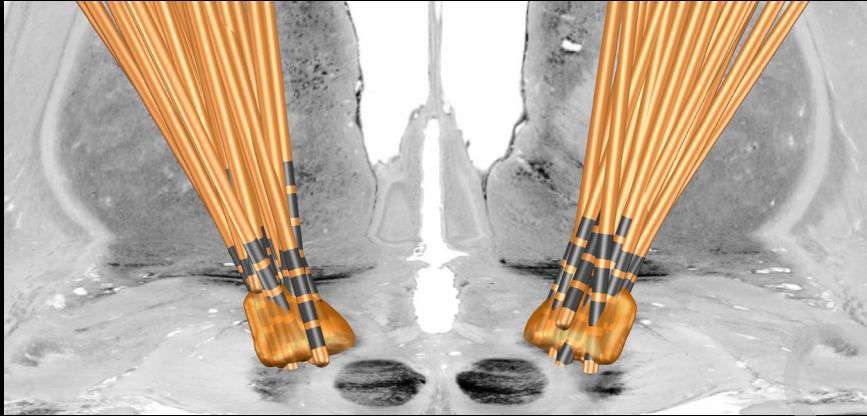


Response Prediction



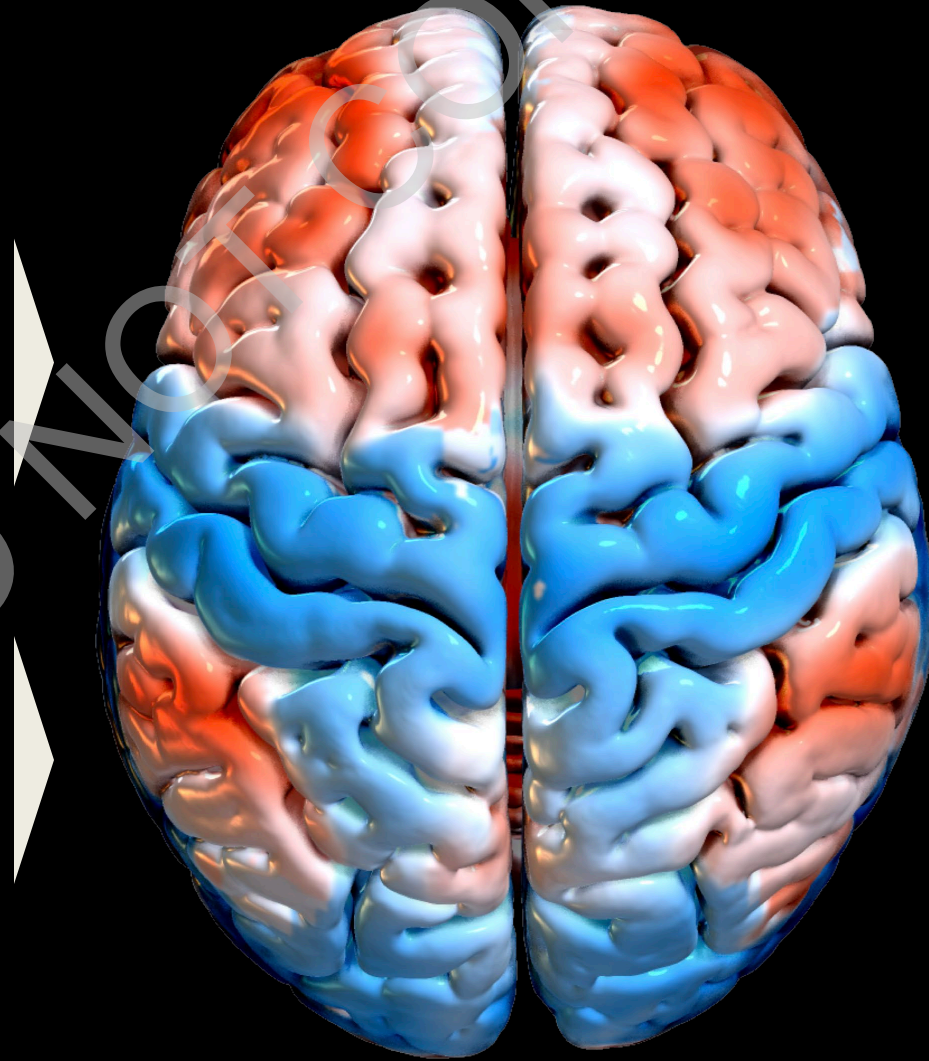
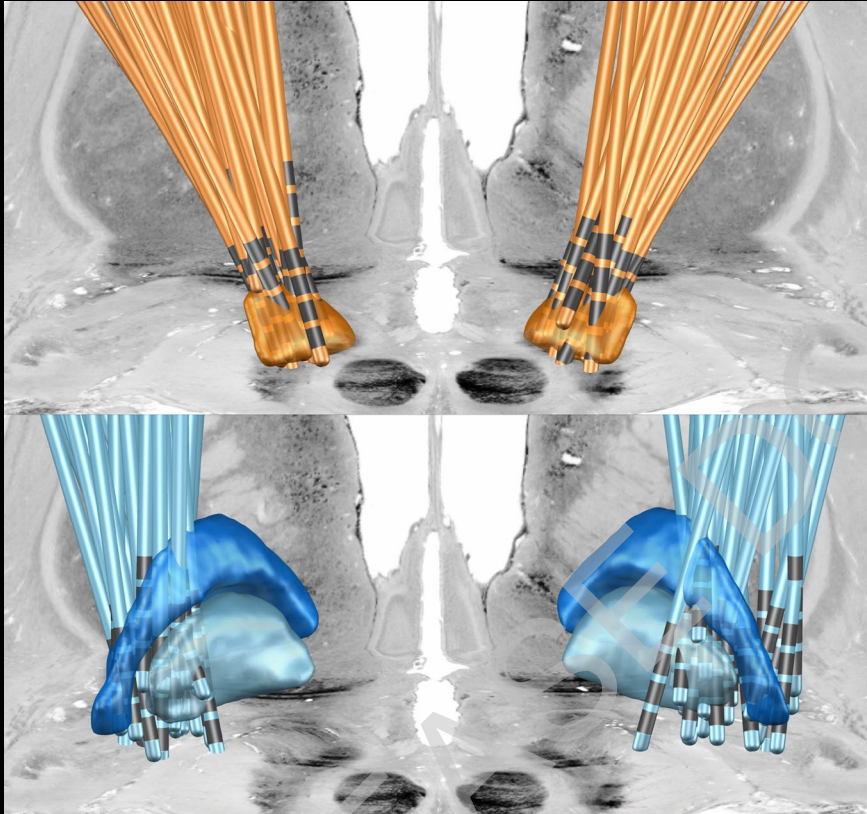
Horn et. al 2017 Annals of Neurology

DBS Network Mapping



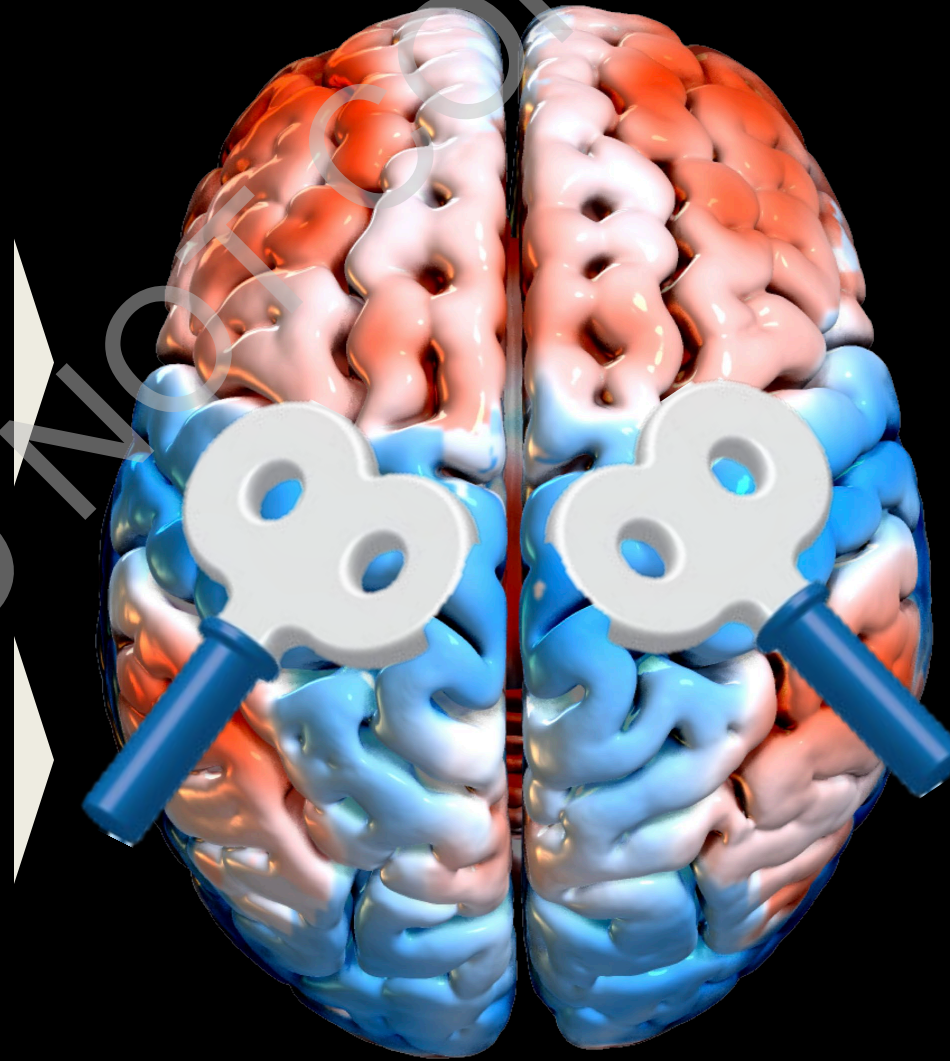
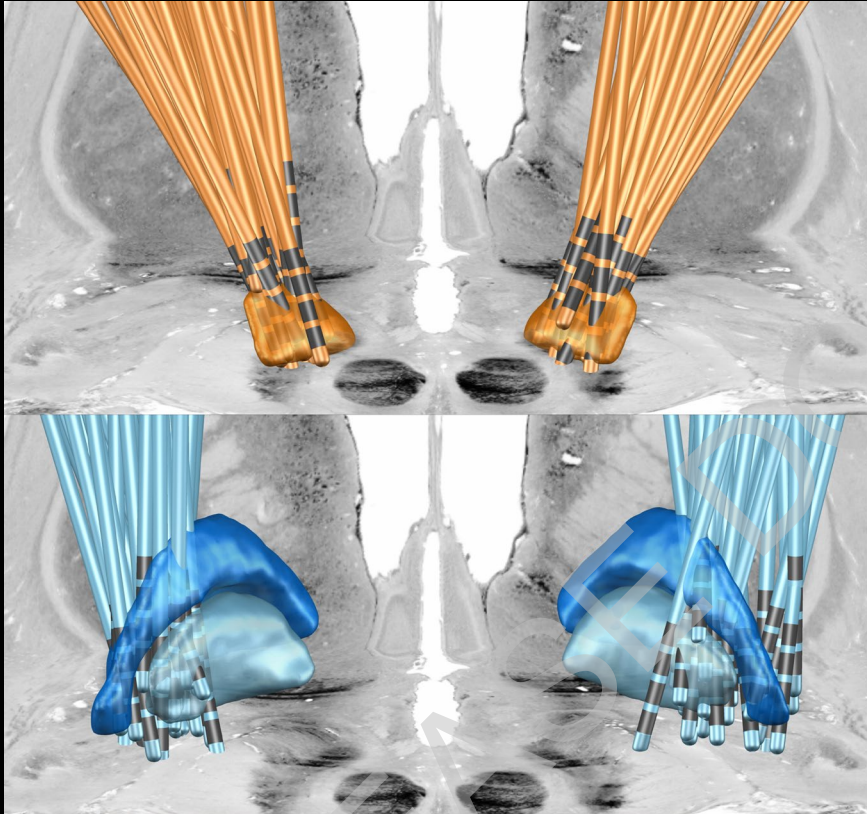
Horn et al., 2017. Annals of Neurology

DBS Network Mapping



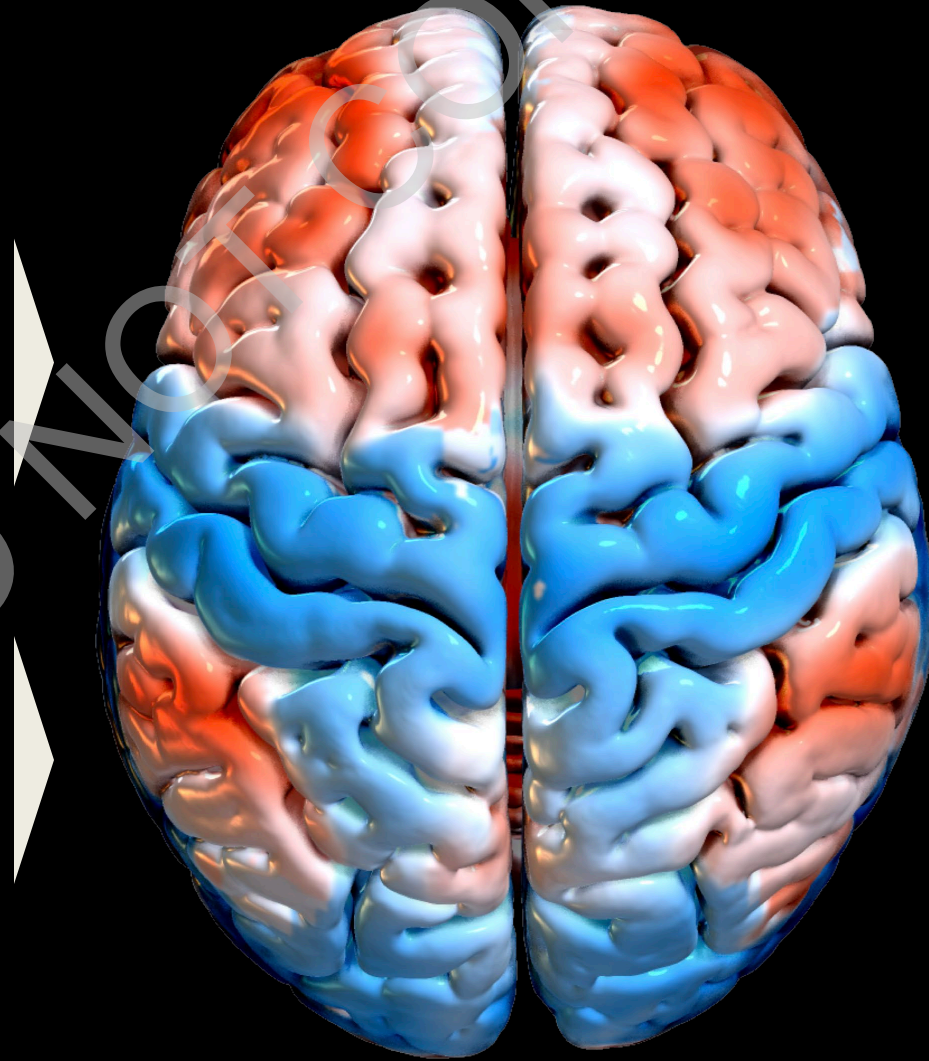
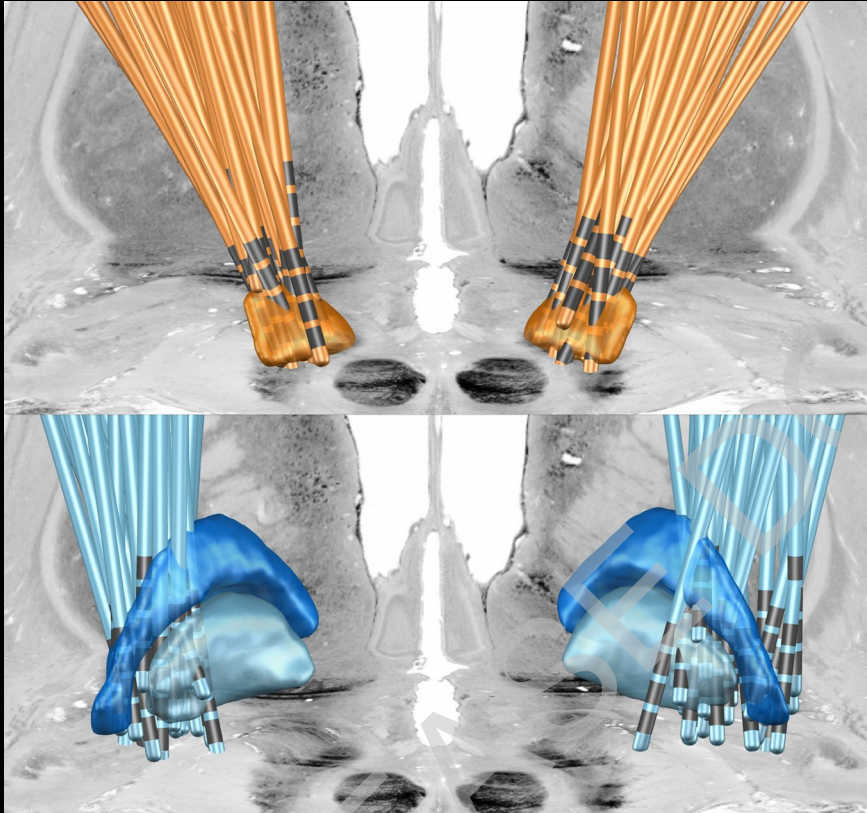
Horn et al., 2017. Annals of Neurology; Sobesky et al., 2022. Brain

DBS Network Mapping



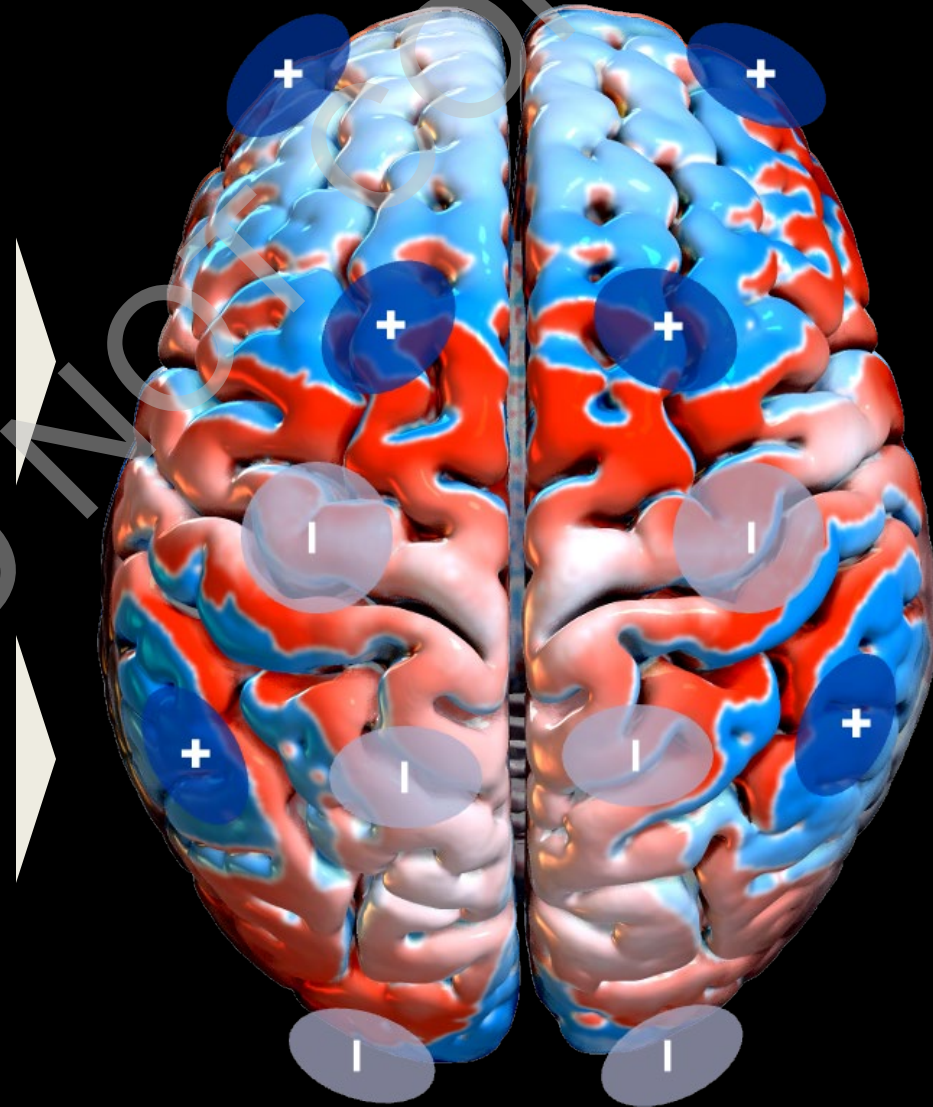
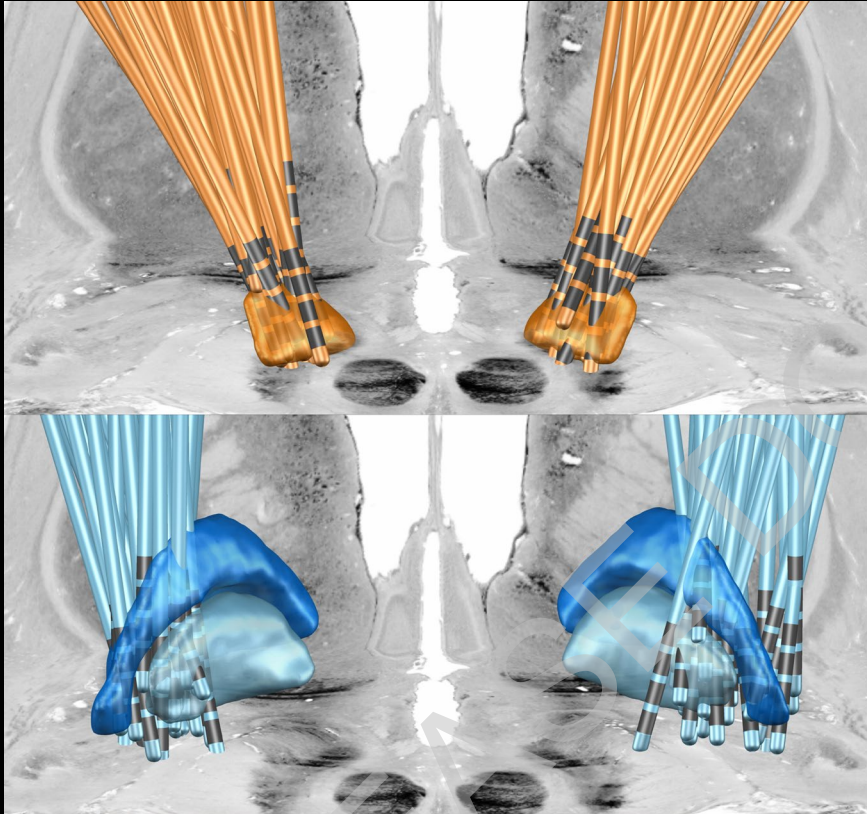
Brys, Fox, et al. 2017 Neurology

DBS Network Mapping



Brys, Fox, et al. 2017 Neurology

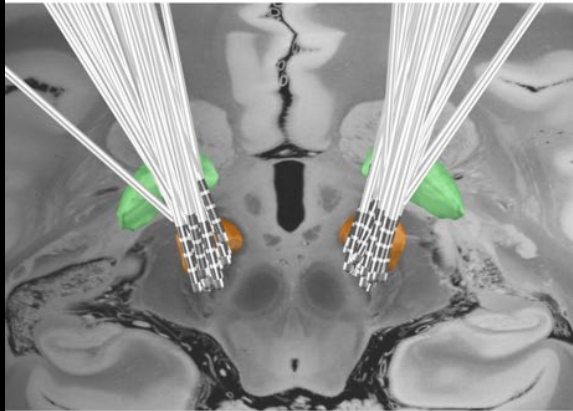
DBS Network Mapping



Goede, Horn et al., 2024
Movement Disorders

DBS Network Mapping

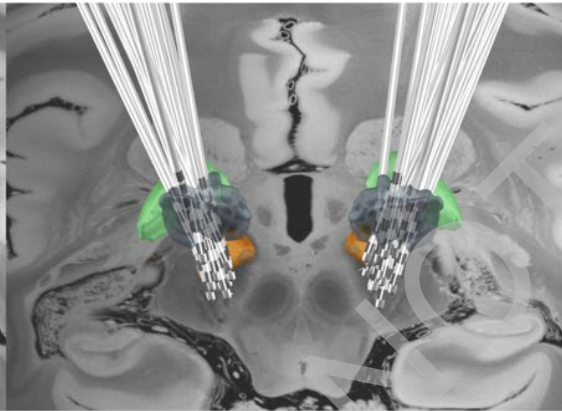
PARKINSON'S DISEASE



STN

GPi

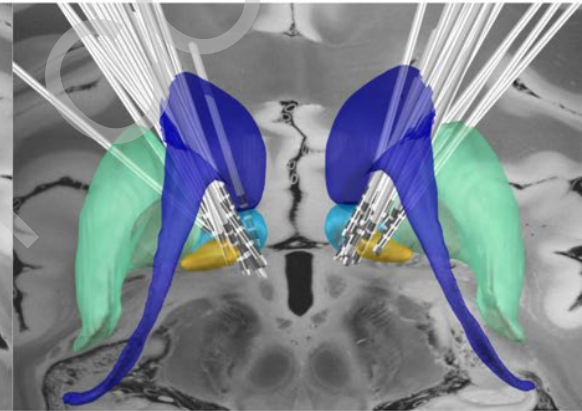
ESSENTIAL TREMOR



VIM

Ca

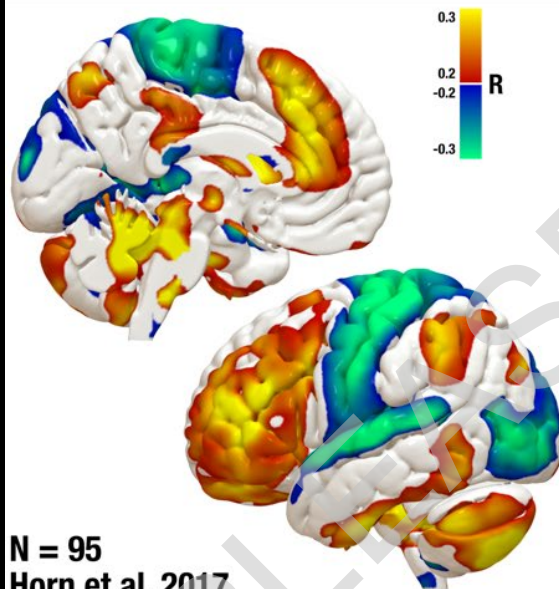
OBSESSIVE COMPULSIVE DISORDER



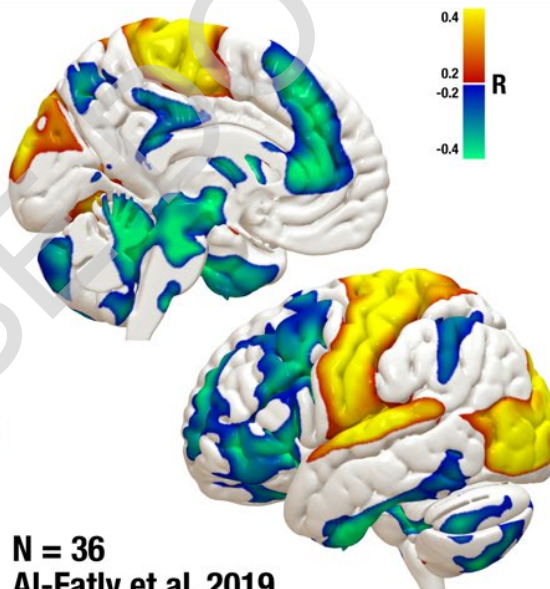
Pu

NAcc

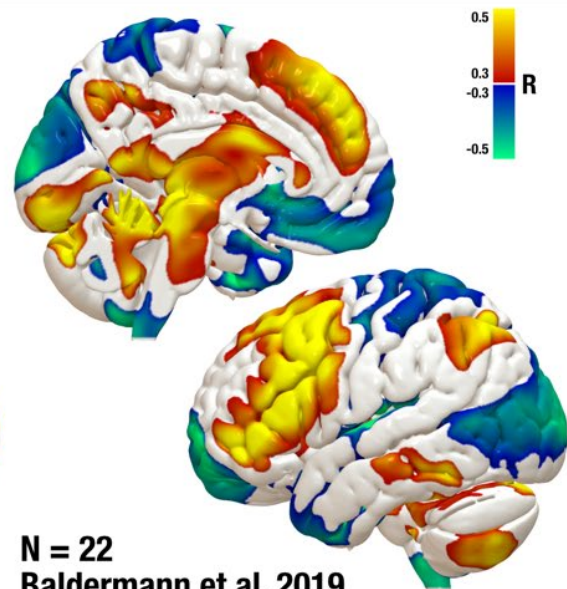
vPall



N = 95
Horn et al. 2017



N = 36
Al-Fatly et al. 2019



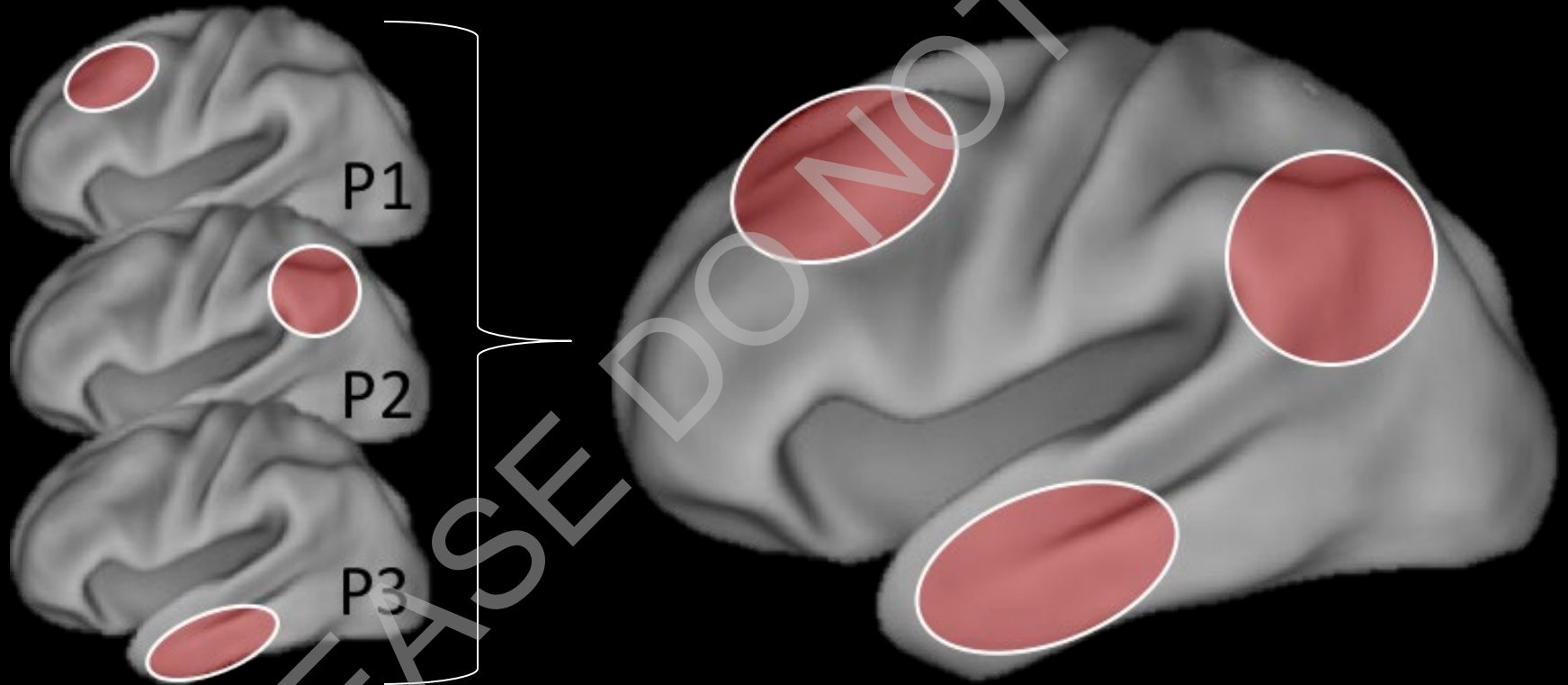
N = 22
Baldermann et al. 2019

Review: Horn and Fox 2020 Neuroimage

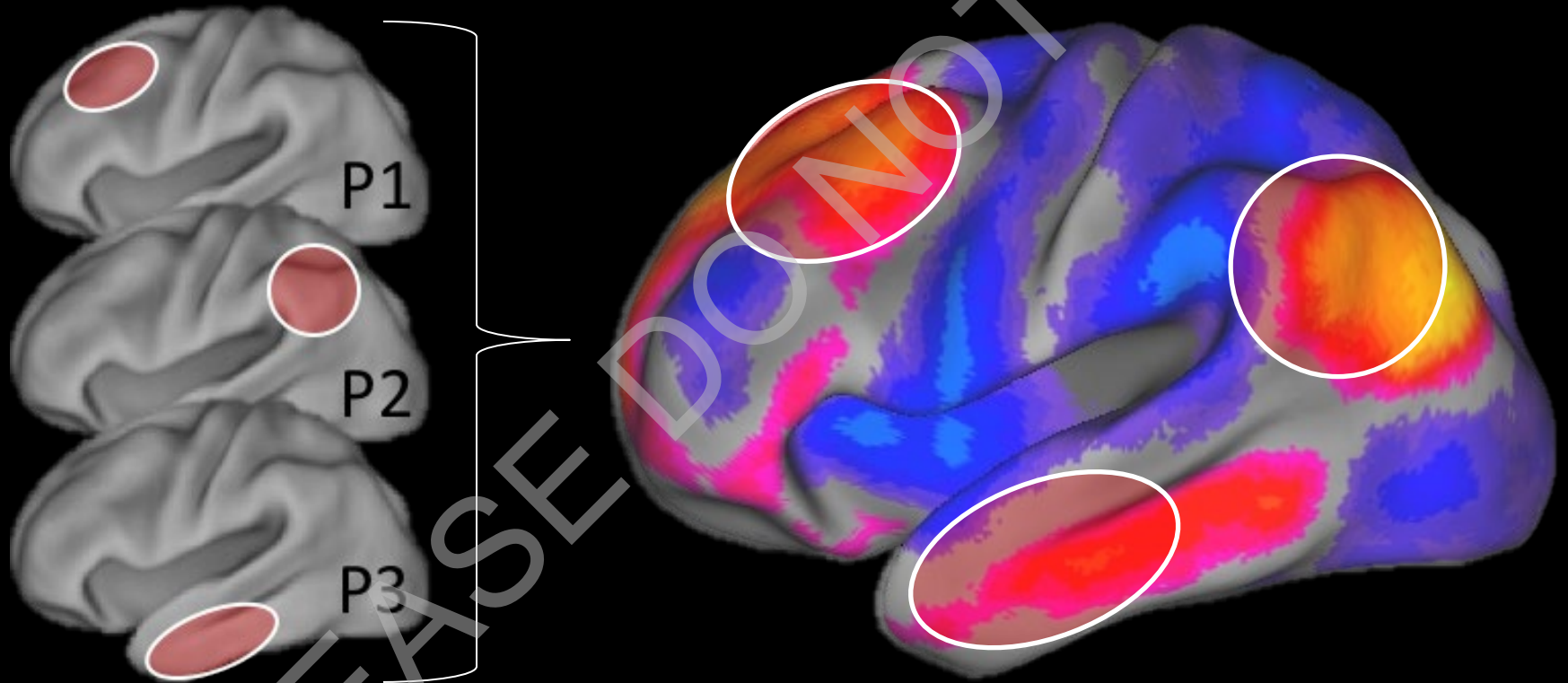
What if we're (VERY) unsure of our
target?

PLEASE DO NOT COPY

Lesion Localization



Lesion “Network” Localization



Lesion Network Mapping

Motor and speech disorders		Nonmotor symptoms		Behavioral changes	
Akinetic mutism	<i>Darby, 2018</i>	Amnesia	<i>Ferguson, 2019</i>	Criminality	<i>Darby, 2018</i>
Alien limb	<i>Darby, 2018</i>	Anosognosia for hemiplegia	<i>Klingbeil, 2020</i>	Mind wandering	<i>Philippi, 2021</i>
Aphasia	<i>Wawrzyniak, 2022</i>	Autoscopic phenomena	<i>Blondiaux, 2021</i>	Pedophilia	<i>Scarpazza, 2021</i>
	<i>Boes, 2015</i>	Blindsight	<i>Kletenik, 2022</i>	Spirituality and religiosity	<i>Ferguson, 2021</i>
Central hypoventilation syndrome	<i>Prabhakar, 2020</i>	Bodily awareness disorders	<i>Herbet, 2019</i>		
Cervical dystonia	<i>Corp, 2019</i>	Bodily self-consciousness failure	<i>Wawrzyniak, 2018</i>		
Falling risk	<i>Crockett, 2022</i>	Cerebellar cognitive affective syndrome	<i>Albazron, 2019</i>		
Foreign accent syndrome	<i>Higashiyama, 2021</i>	Cognitive impairment	<i>Reber, 2021</i>		
Freezing of gait	<i>Fasano, 2017</i>		<i>Crockett, 2021</i>		
Infantile spasms	<i>Cohen, 2021</i>	Coma	<i>Fischer, 2016</i>		
Hemichorea	<i>Laganieri, 2016</i>	Decision-making impairment	<i>Sutterer, 2016</i>		
Holmes' tremor	<i>Joutsa, 2019</i>	Delusional misidentification	<i>Darby, 2017</i>	Improvement of symptoms	
Parkinsonism	<i>Joutsa, 2018</i>	Depression	<i>Padmanabhan, 2019</i>	Addiction remission	<i>Joutsa, 2022</i>
Poststroke motor outcomes	<i>Lee, 2020</i>	Epilepsy	<i>Bdaiwi, 2021</i>	Essential tremor improvement	<i>Joutsa, 2018</i>
Poststroke sensorimotor outcomes	<i>Jimenez-Marin, 2021</i>		<i>Mansouri, 2020</i>		
Step length asymmetry	<i>Kyeong, 2021</i>	Executive function impairment	<i>Hwang, 2020</i>		
Poststroke functional outcomes ^a	<i>Bowren, 2022</i>	Hallucinations	<i>Boes, 2015</i>		
	<i>Cohen, 2021</i>		<i>Kim, 2021</i>		
	<i>Pini, 2021</i>	Loss of consciousness	<i>Snider, 2020</i>		
	<i>Salvalaggio, 2020</i>	Mania	<i>Cotovio, 2020</i>		
Tics	<i>Ganos, 2022</i>		<i>Lee, 2019</i>		
		Pain	<i>Boes, 2015</i>		
			<i>Elias, 2020</i>		
		Pathological laughter and crying	<i>Klingbeil, 2021</i>		
		Prosopagnosia	<i>Cohen, 2019</i>		
		Spatial delusions	<i>Alves, 2021</i>		

Review: Joutsa 2022 Cur. Opin. Neuro

Lesion Network Mapping

Motor and speech disorders		Nonmotor symptoms		Behavioral changes	
Akinetic mutism	Darby, 2018	Amnesia	Ferguson, 2019	Criminality	Darby, 2018
Alien limb	Darby, 2018	Anosognosia for hemiplegia	Klingbeil, 2020	Mind wandering	Philippi, 2021
Aphasia	Wawrzyniak, 2022	Autoscopic phenomena	Blondiaux, 2021	Pedophilia	Scarpazza, 2021
	Boes, 2015	Blindsight	Kletenik, 2022	Spirituality and religiosity	Ferguson, 2021
Central hypoventilation syndrome	Prabhakar, 2020	Bodily awareness disorders	Herbet, 2019		
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Foreign accent syndrome	Higashiyama, 2021	Cognitive impairment	Reber, 2021		
Freezing of gait	Fasano, 2017		Crockett, 2021		
Infantile spasms	Cohen, 2021	Coma	Fischer, 2016		
Hemichorea	Laganieri, 2016	Decision-making impairment	Sutterer, 2016		
Holmes' tremor	Joutsa, 2019	Delusional misidentification	Darby, 2017	Improvement of symptoms	
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Poststroke motor outcomes	Lee, 2020	Epilepsy	Bdaiwi, 2021	Essential tremor improvement	Joutsa, 2018
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	Cohen, 2021		Kim, 2021		
	Pini, 2021	Loss of consciousness	Snider, 2020		
	Salvalaggio, 2020	Mania	Cotovio, 2020		
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		Pain	Boes, 2015		
			Elias, 2020		
		Pathological laughter and crying	Klingbeil, 2021		
		Prosopagnosia	Cohen, 2019		
		Spatial delusions	Alves, 2021		

> 40 symptoms
> 50 papers
> 8 groups

Review: Joutsa 2022 Cur. Opin. Neuro

Lesion Network Mapping

Addiction Remission

Joutsa et al. 2022 Nature Medicine

Aggression

Peng et al. 2025 Biol. Psych

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Friedrich et al. 2024 Annl. of Neuro

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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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Kutsche et al. 2025 JAMA Net Open

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Luo et al 2026 medRxiv

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Taylor et al. 2023 Nature Hum. Behav

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Pines et al . 2025 JAMA Psych

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Friedrich et al. 2026 Brain

Vertigo

Li et al. 2023 Brain Comm.

Reviews: Fox 2018 NEJM, Joutsa et al. 2022 Cur. Opin. Neuro, Joutsa et al. 2023 Brain

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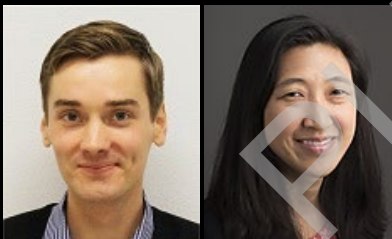
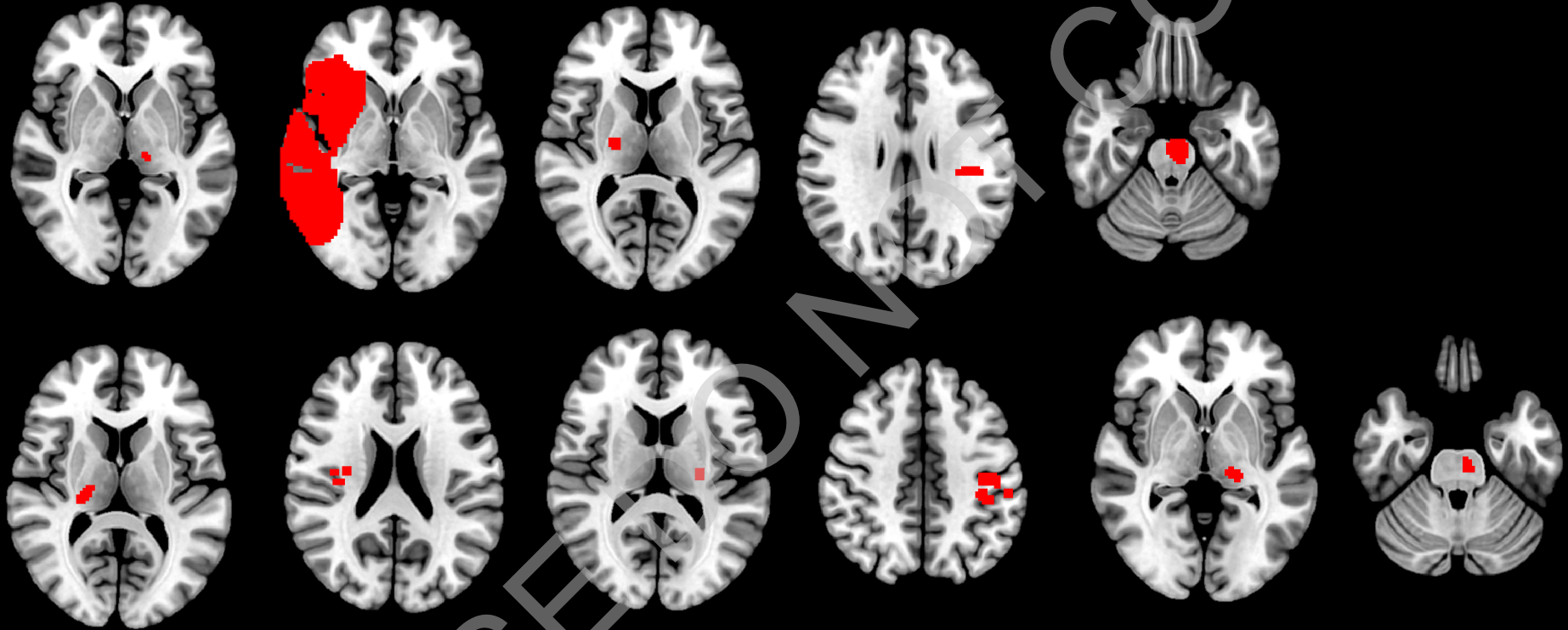
Friedrich et al. 2026 Brain

Vertigo

Li et al. 2023 Brain Comm.

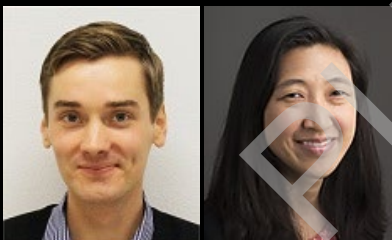
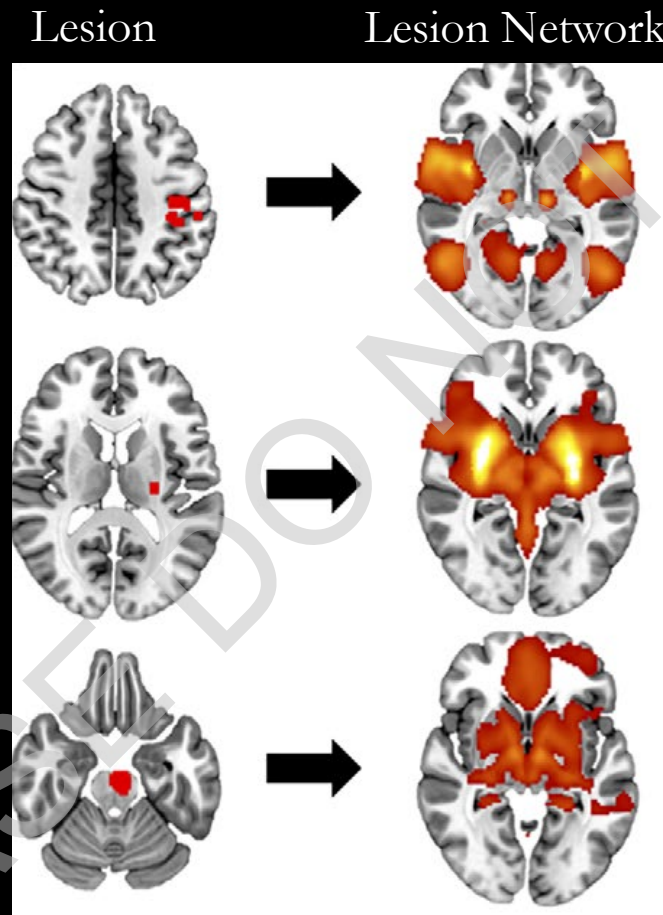
Reviews: Fox 2018 NEJM, Joutsa et al. 2022 Cur. Opin. Neuro, Joutsa et al. 2023 Brain

New Approach for Finding Targets



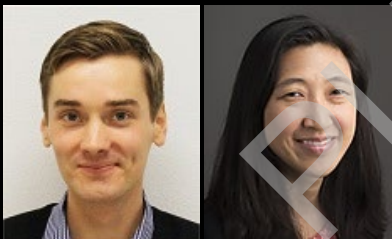
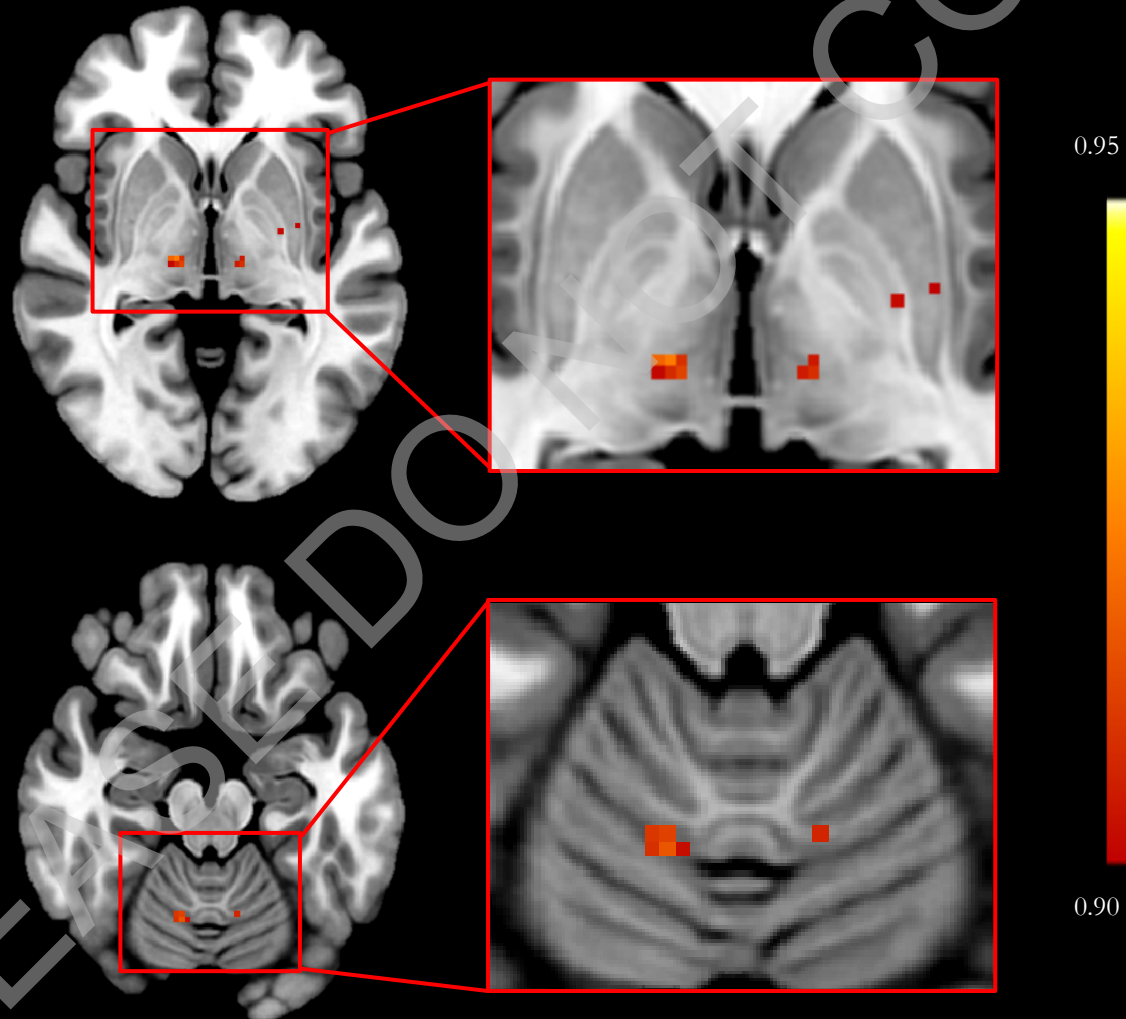
Joutsa, Shih et al. 2018 Annals of Neurology

New Approach for Finding Targets



Joutsa, Shih et al. 2018 Annals of Neurology

New Approach for Finding Targets



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

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Addiction Remission

Joutsa et al. 2022 Nature Medicine

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Ganos et al. 2022 Brain

Tremor Relief

Joutsa et al. 2018 Annl. of Neurology, Goede et al. 2025 Nature Comms.

Vergence

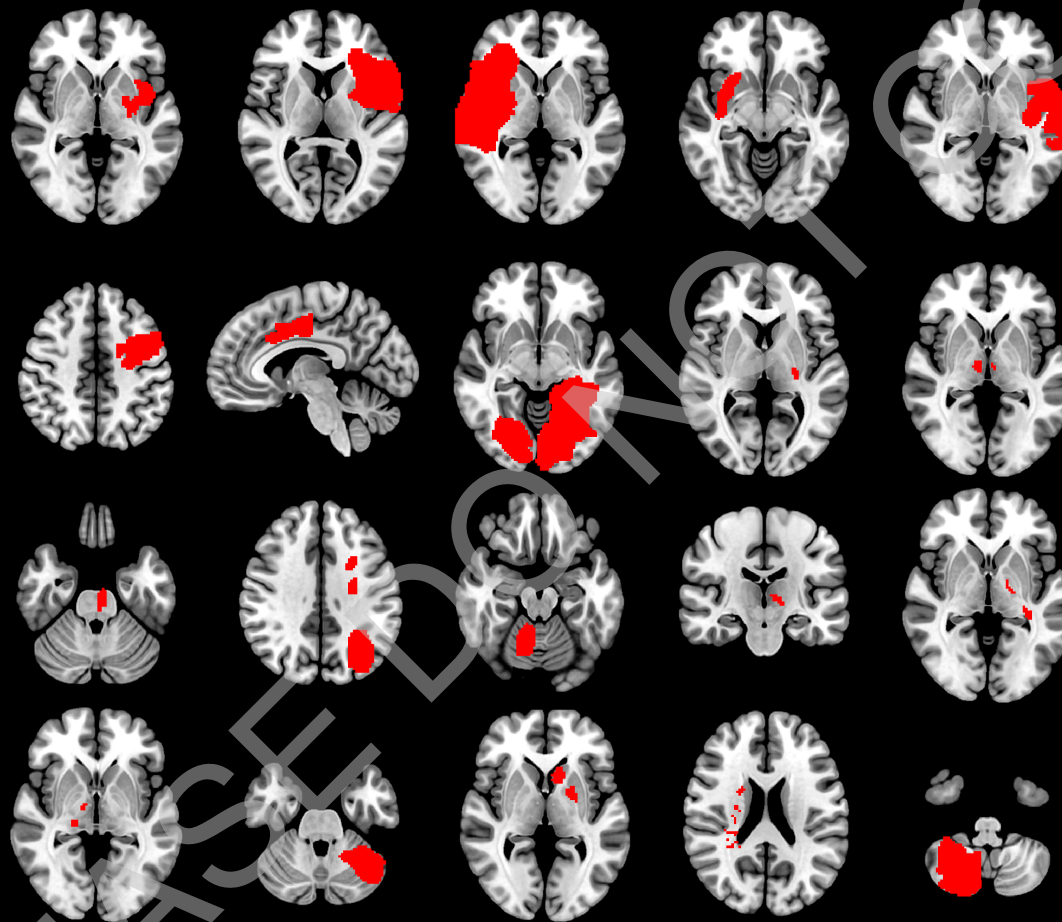
Friedrich et al. 2026 Brain

Vertigo

Li et al. 2023 Brain Comm.

Reviews: Fox 2018 NEJM, Joutsa et al. 2022 Cur. Opin. Neuro, Joutsa et al. 2023 Brain

Addiction Remission



Joutsa, Moussawi, Siddiqi et al. 2022 Nature Medicine

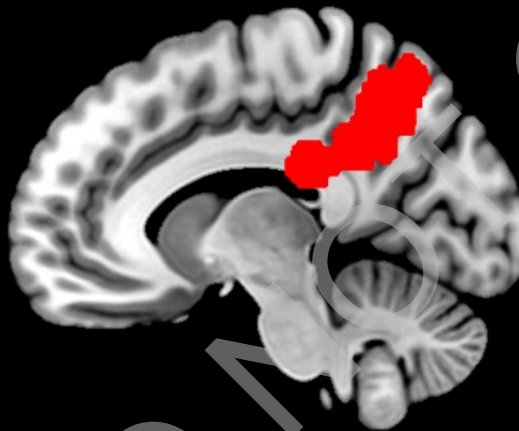
Addiction Remission

Remission



vs

Not quitting



VLSM results



Addiction Remission

Remission

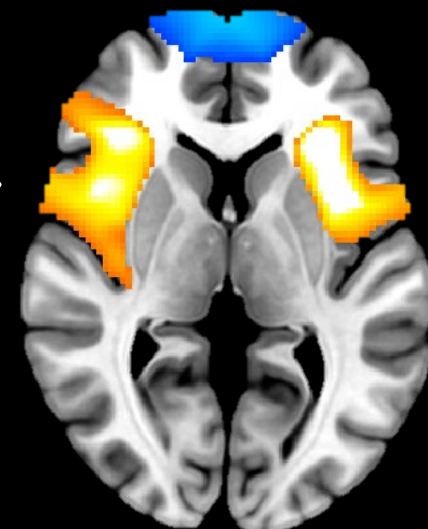
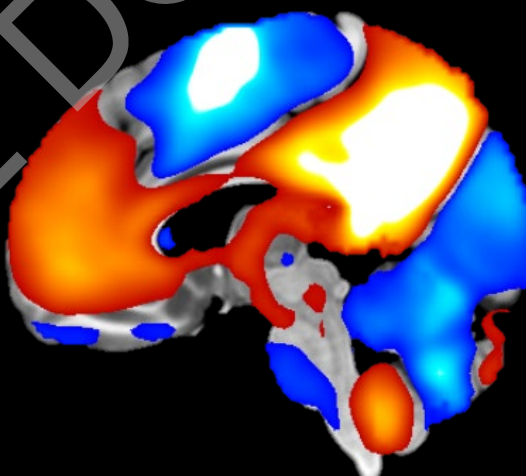
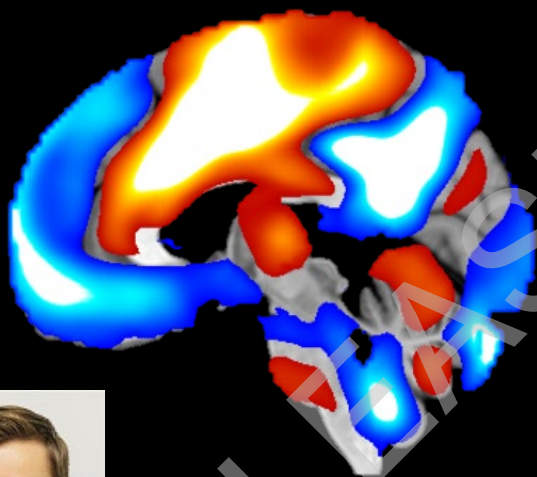
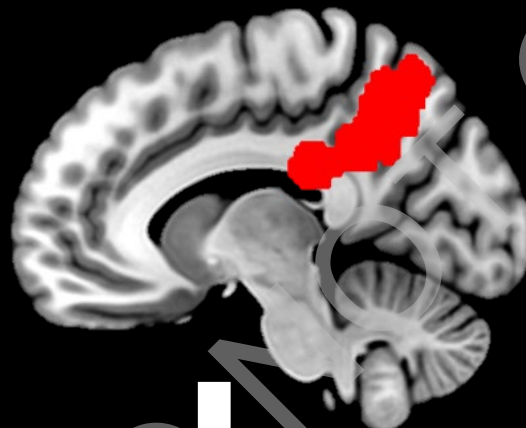
Not quitting

VLSM results

vs

vs

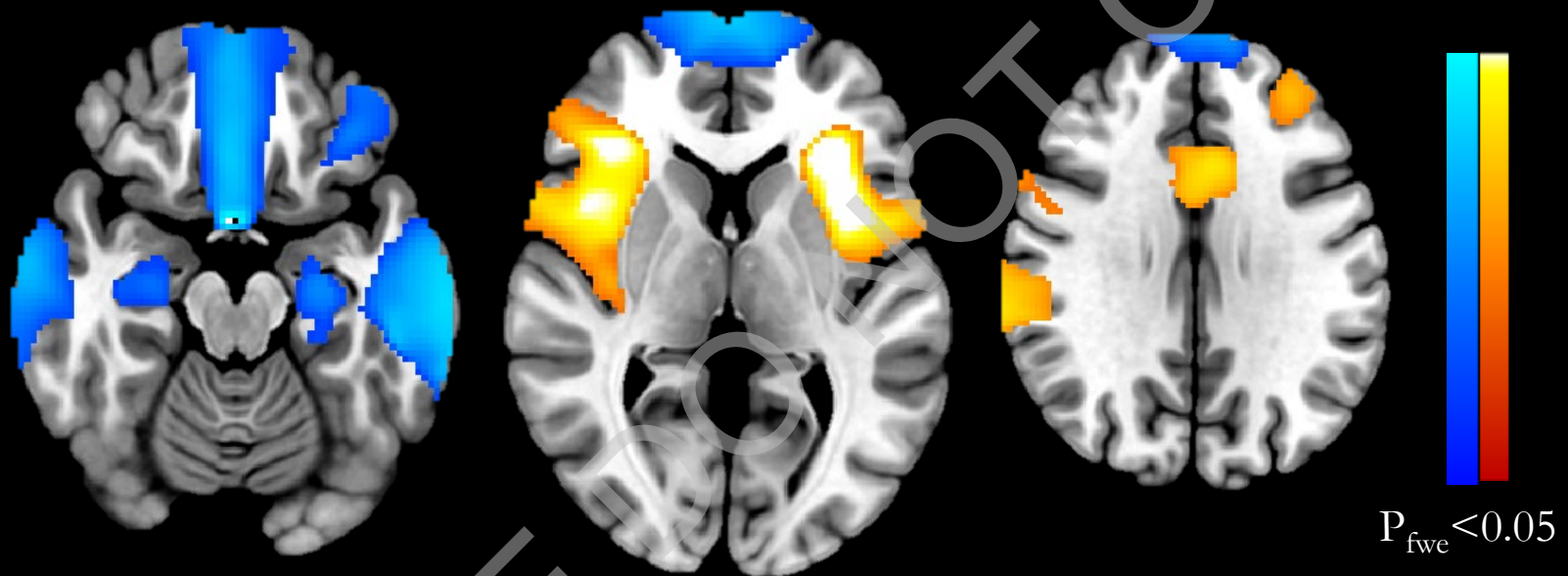
LNM results



Joutsa, Moussawi, Siddiqi et al. 2022 Nature Medicine



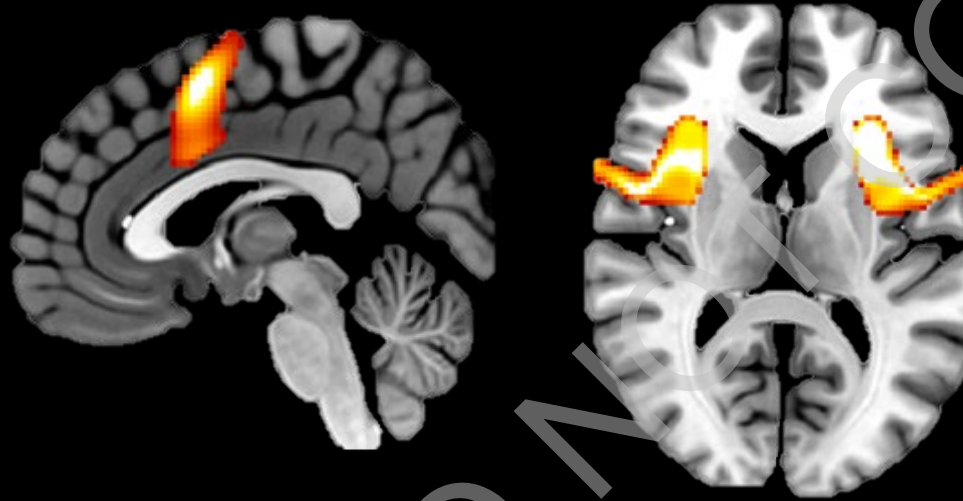
Addiction Remission



Joutsa, Moussawi, Siddiqi et al. 2022 Nature Medicine

Addiction Remission Targets

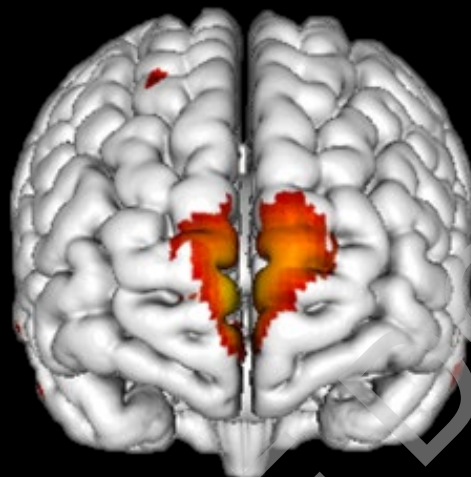
Lesion / DBS
Targets



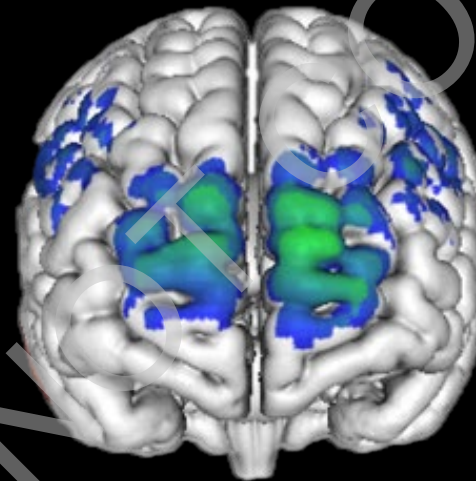
Joutsa, Moussawi, Siddiqi et al. 2022 Nature Medicine



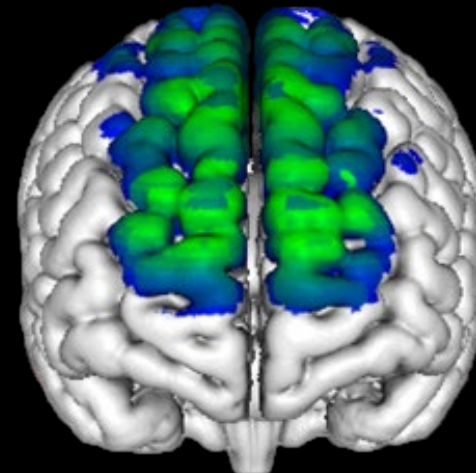
Addiction Remission Targets



TMS Target

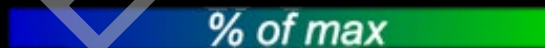


Smoking (H4 Coil)

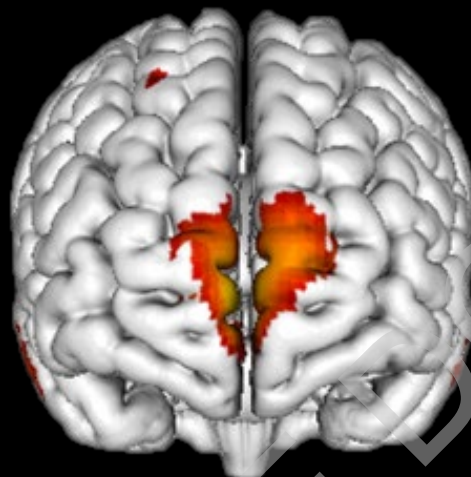


Alcoholism (H7 Coil)

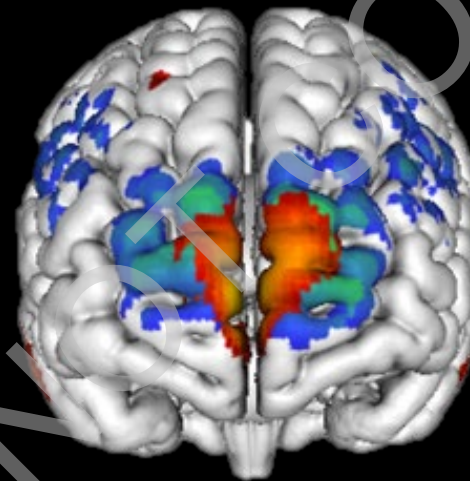
Electric Field Intensity



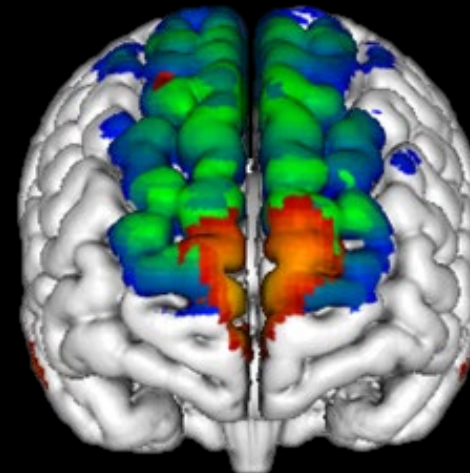
Addiction Remission Targets



TMS Target

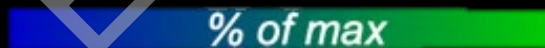


Smoking (H4 Coil)



Alcoholism (H7 Coil)

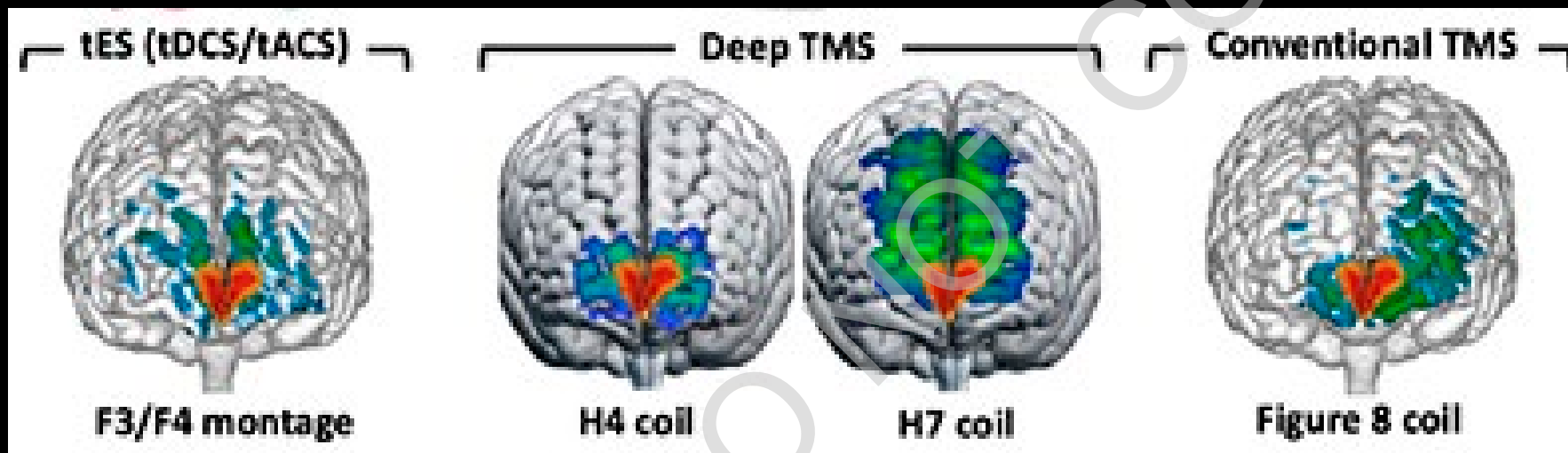
Electric Field Intensity



% of max



Addiction Remission Targets



Soleimani.. Ekhtiari et al. 2024
American Journal of Psychiatry



Lesion Network Mapping

Addiction Remission

Joutsa et al. 2022 Nature Medicine

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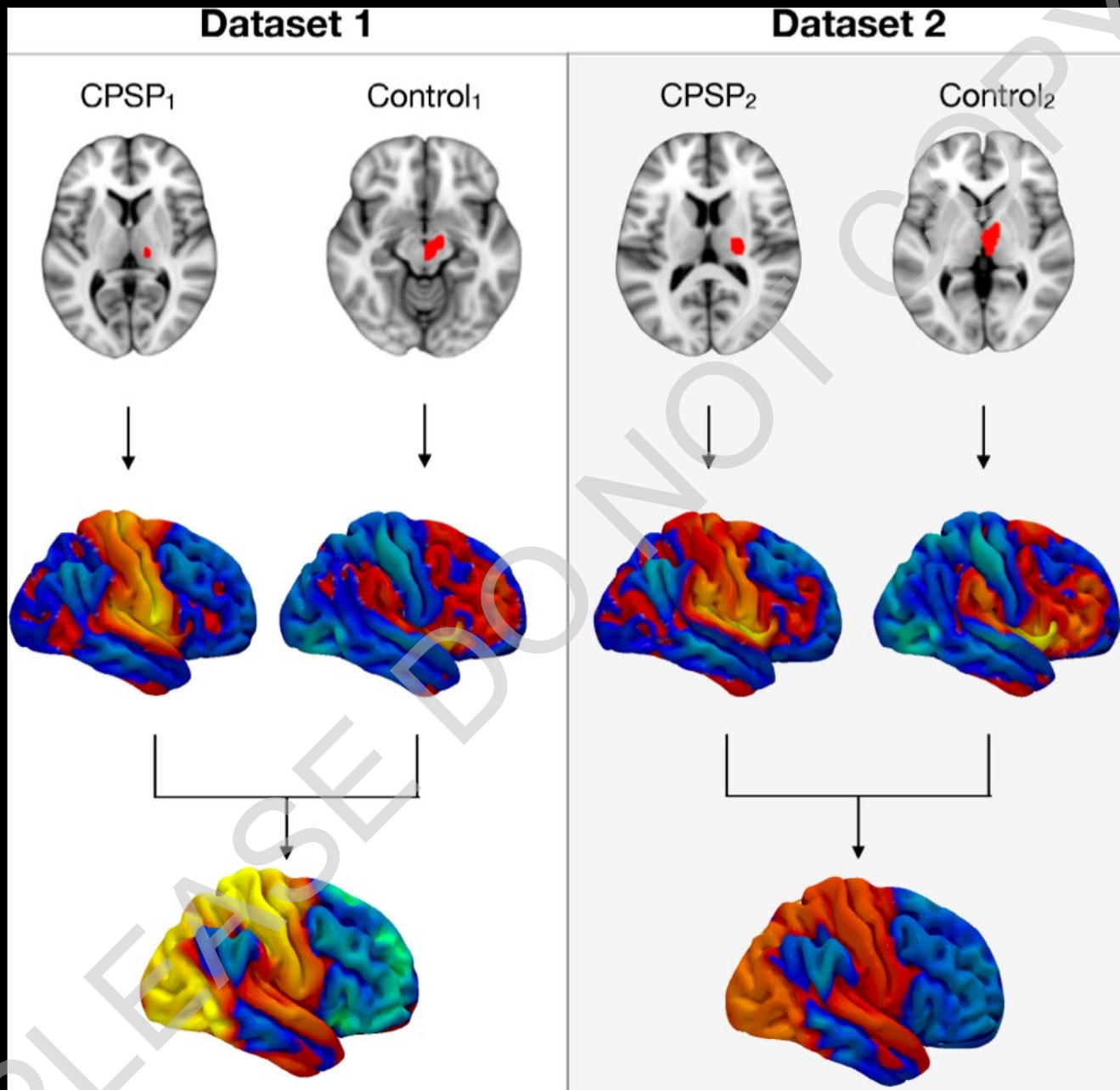
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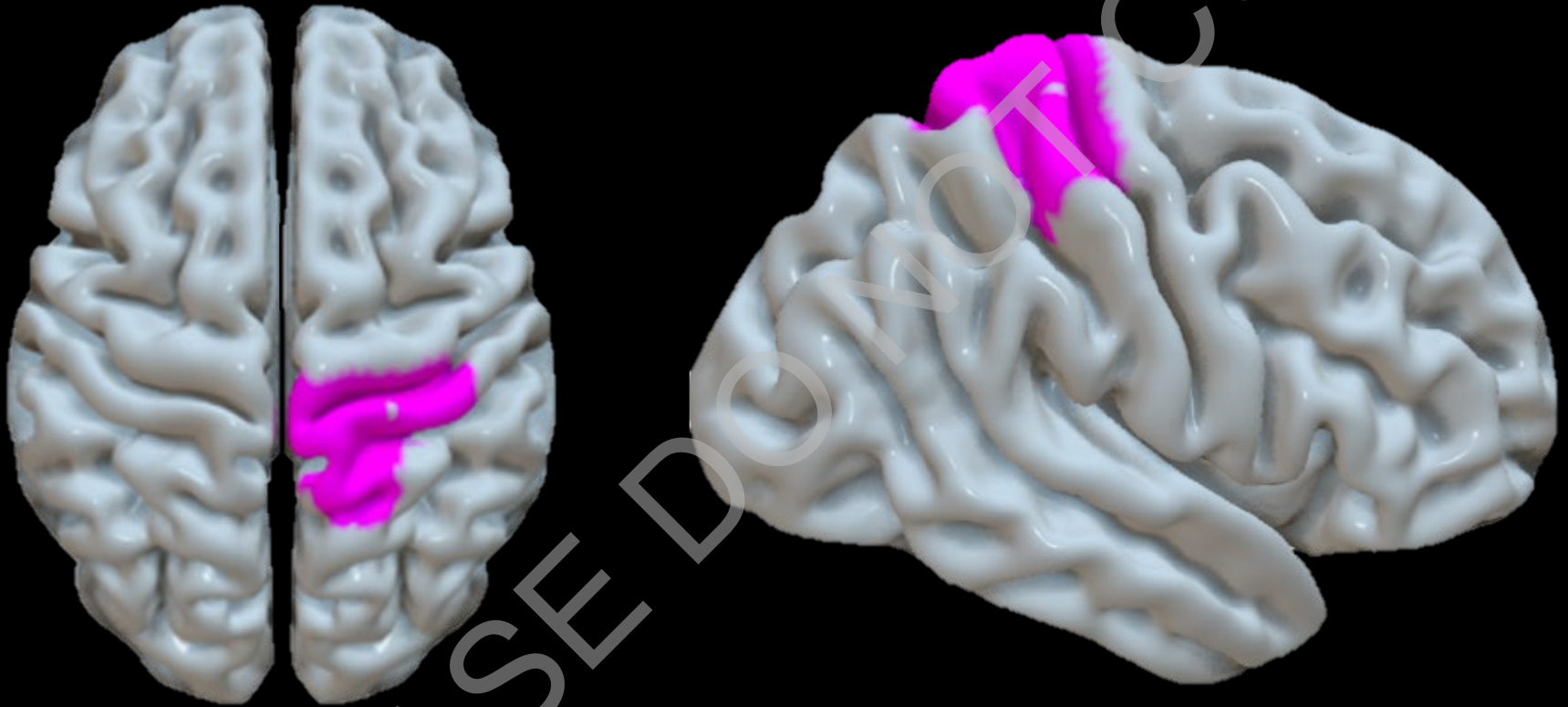
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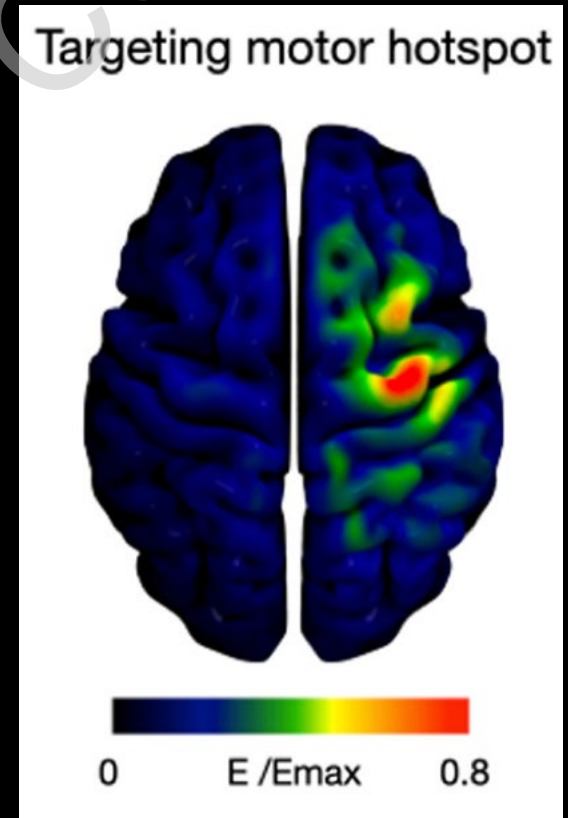
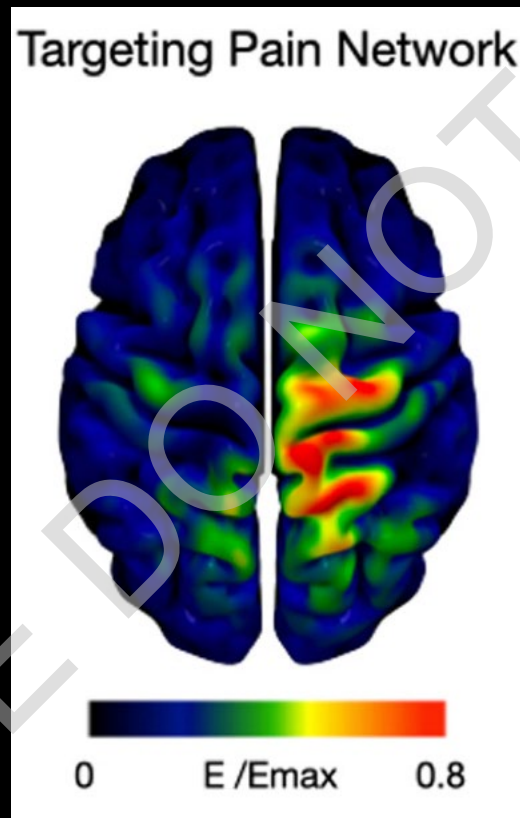


Neuropathic Pain

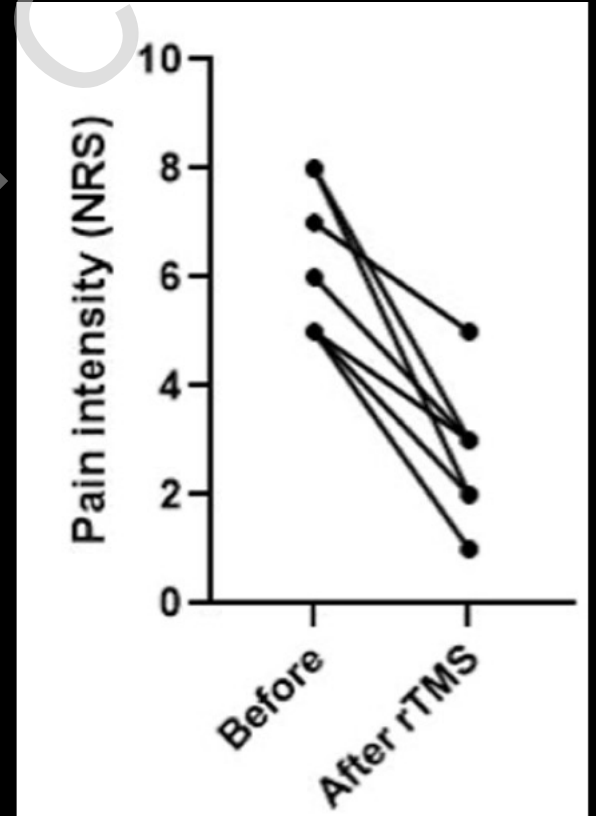
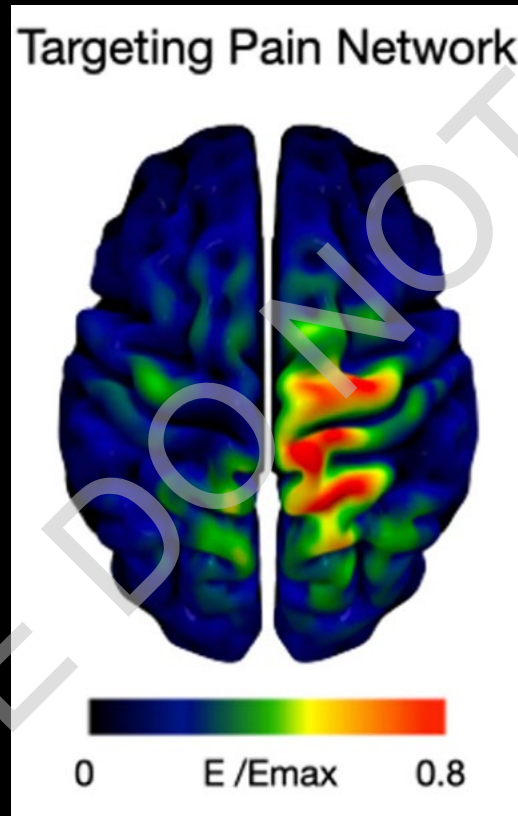


Kim et al. 2022 Annals of Neurology

Neuropathic Pain



Neuropathic Pain



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

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Aphantasia

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Siddiqi et al. 2024 Nature Neurosci.

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

Stroke Severity

Bonkhoff et al. 2024 ACTN

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Roseman et al. 2024 Cerebral Cortex

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Theys et al. 2024 Brain

Tics

Ganos et al. 2022 Brain

Tremor Relief

Joutsa et al. 2018 Annl. of Neurology, Goede et al. 2025 Nature Comms.

Vergence

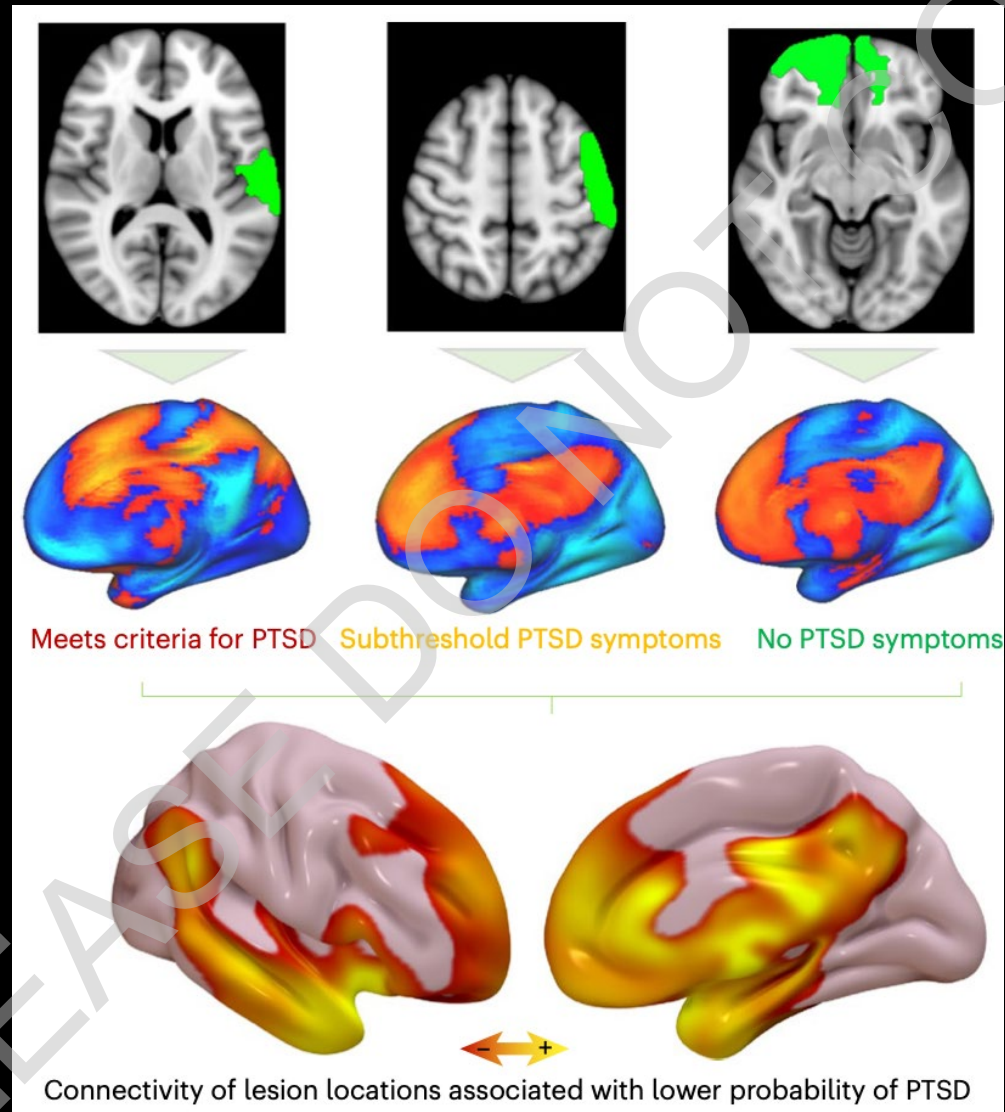
Friedrich et al. 2026 Brain

Vertigo

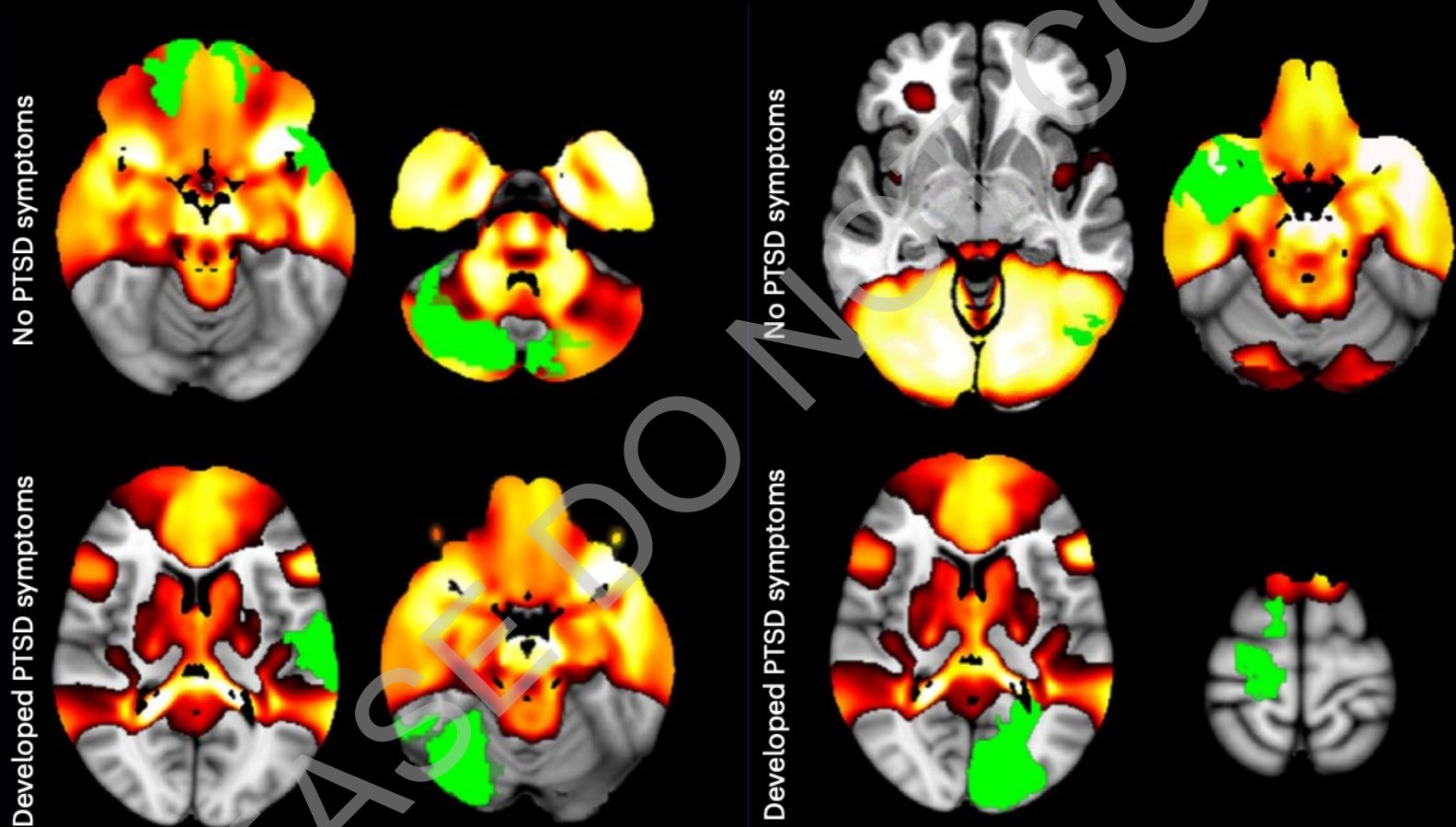
Li et al. 2023 Brain Comm.

Reviews: Fox 2018 NEJM, Joutsa et al. 2022 Cur. Opin. Neuro, Joutsa et al. 2023 Brain

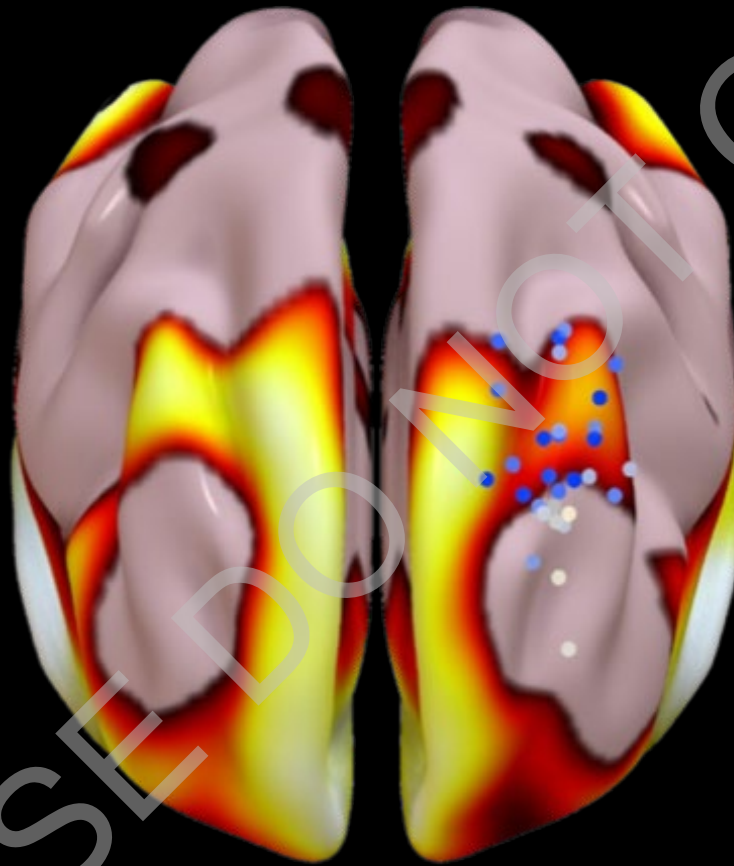
PTSD: Lesion Network Mapping



PTSD: Lesion Network Mapping



PTSD: TMS Targets



Anxiosomatic Symptom Benefit



Dysphoric Symptom Benefit



Siddiqi et al. 2024 Nature Neuros.

PTSD: TMS Targets

Cohen 2004: HF > LF or sham

Boggio 2009: HF > sham

Leong 2020: LF > sham

Kozel 2018: LF > sham

Kozel 2019: LF = HF

Proposed

HF/iTBS
Target

'5 cm' or EEG F3 target

Yesavage 2018: HF
< sham (one-tail)

Proposed

LF/cTBS
Target

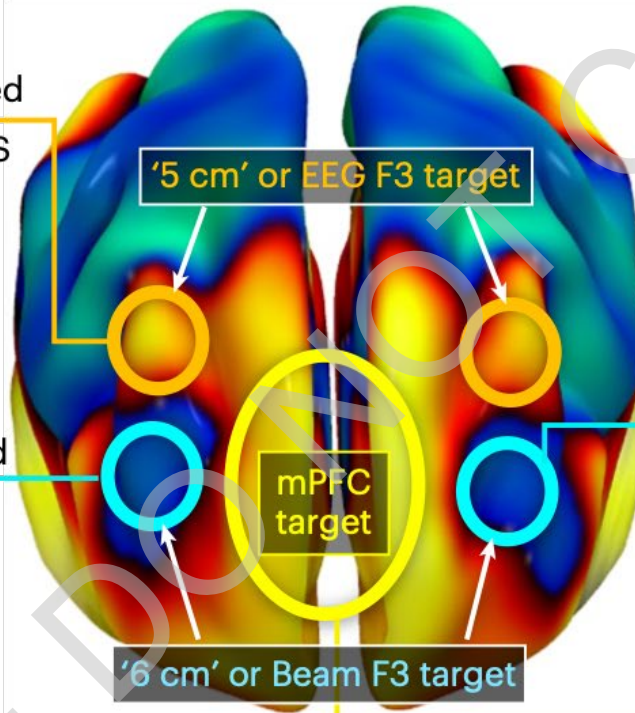
Proposed

LF/cTBS
Target

mPFC
target

'6 cm' or Beam F3 target

Proposed ideal
target



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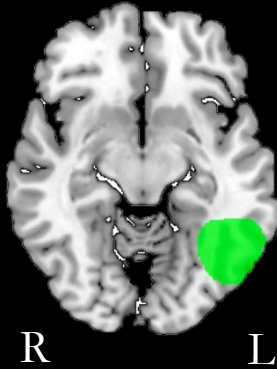
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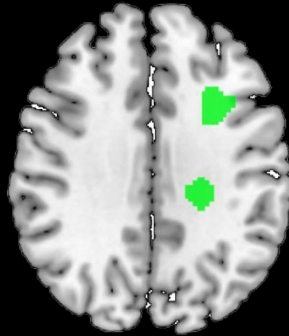
Lesion mapping of depression (n = 461)

Depression lesions (n = 58)

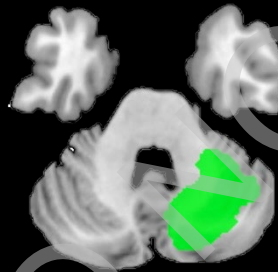
Dataset 1



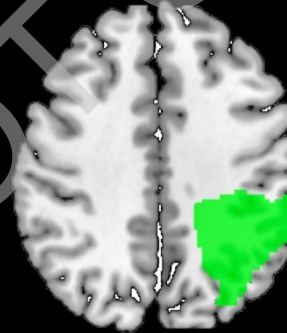
Dataset 2



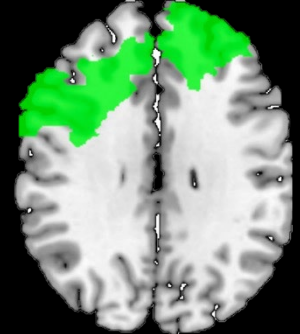
Dataset 3



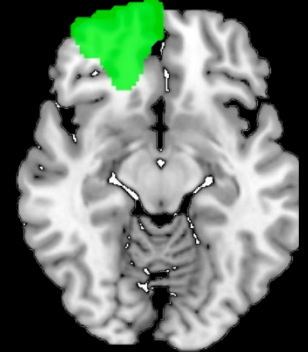
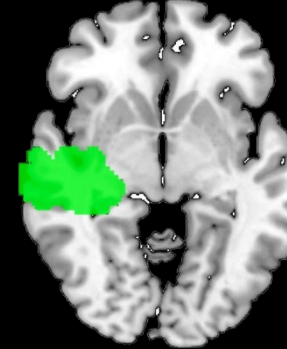
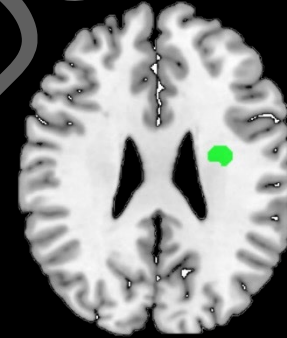
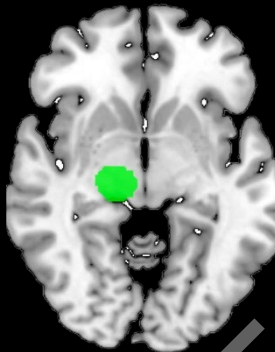
Dataset 4

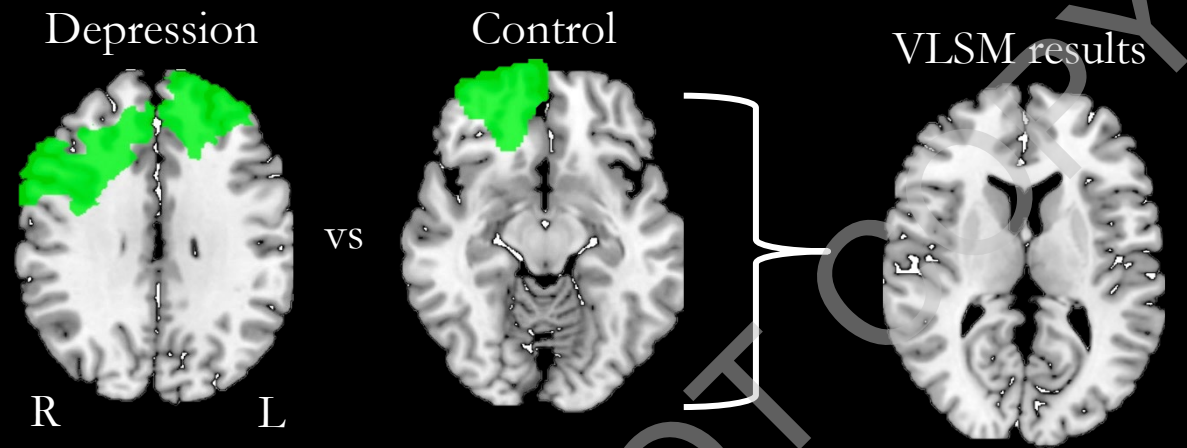


Dataset 5

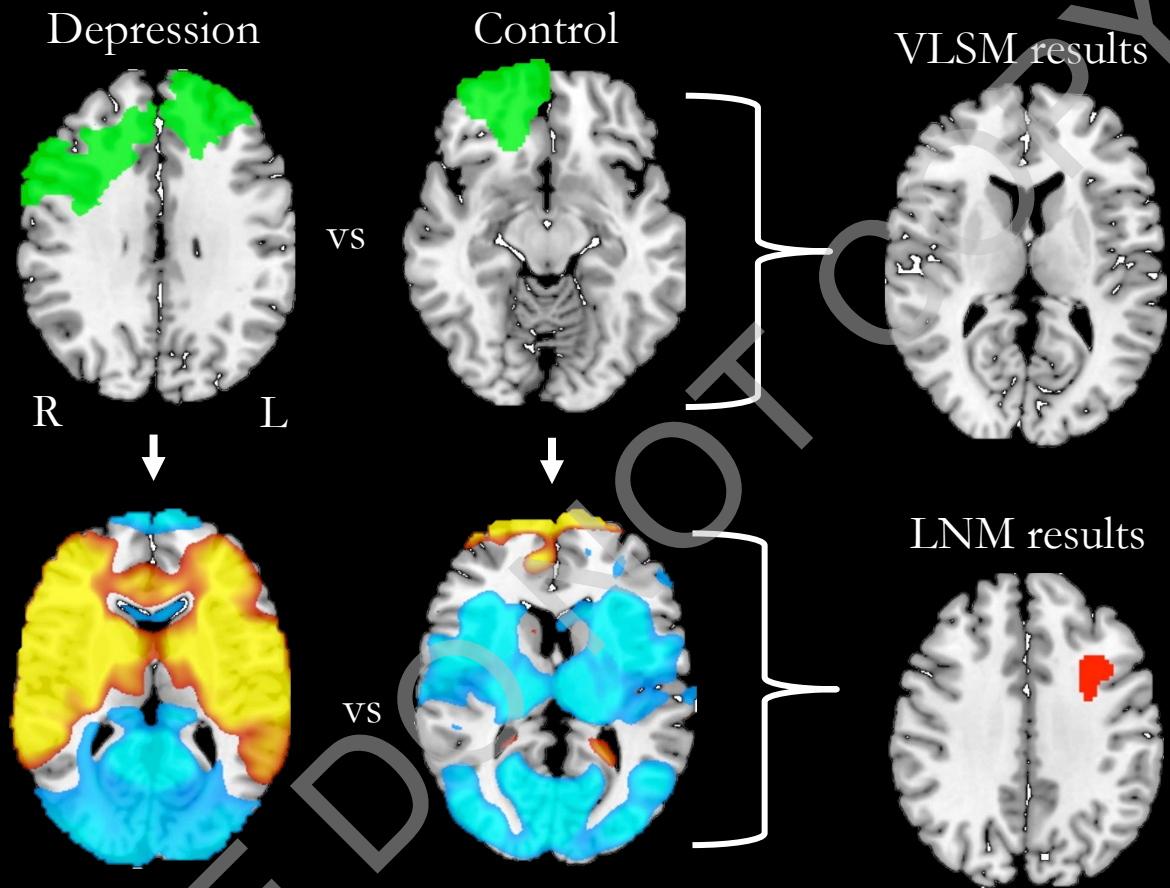


Control lesions (n = 300)



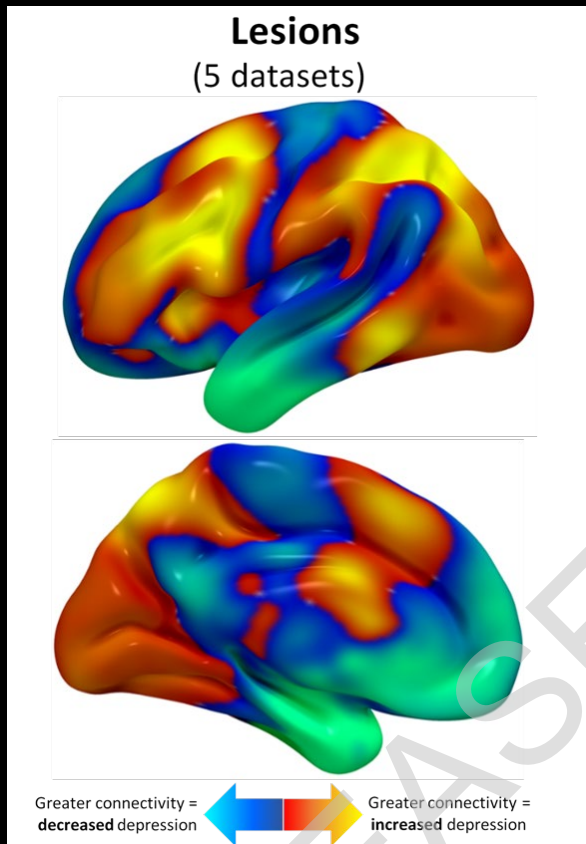


Padmanabhan et al. 2019
Bio. Psych.



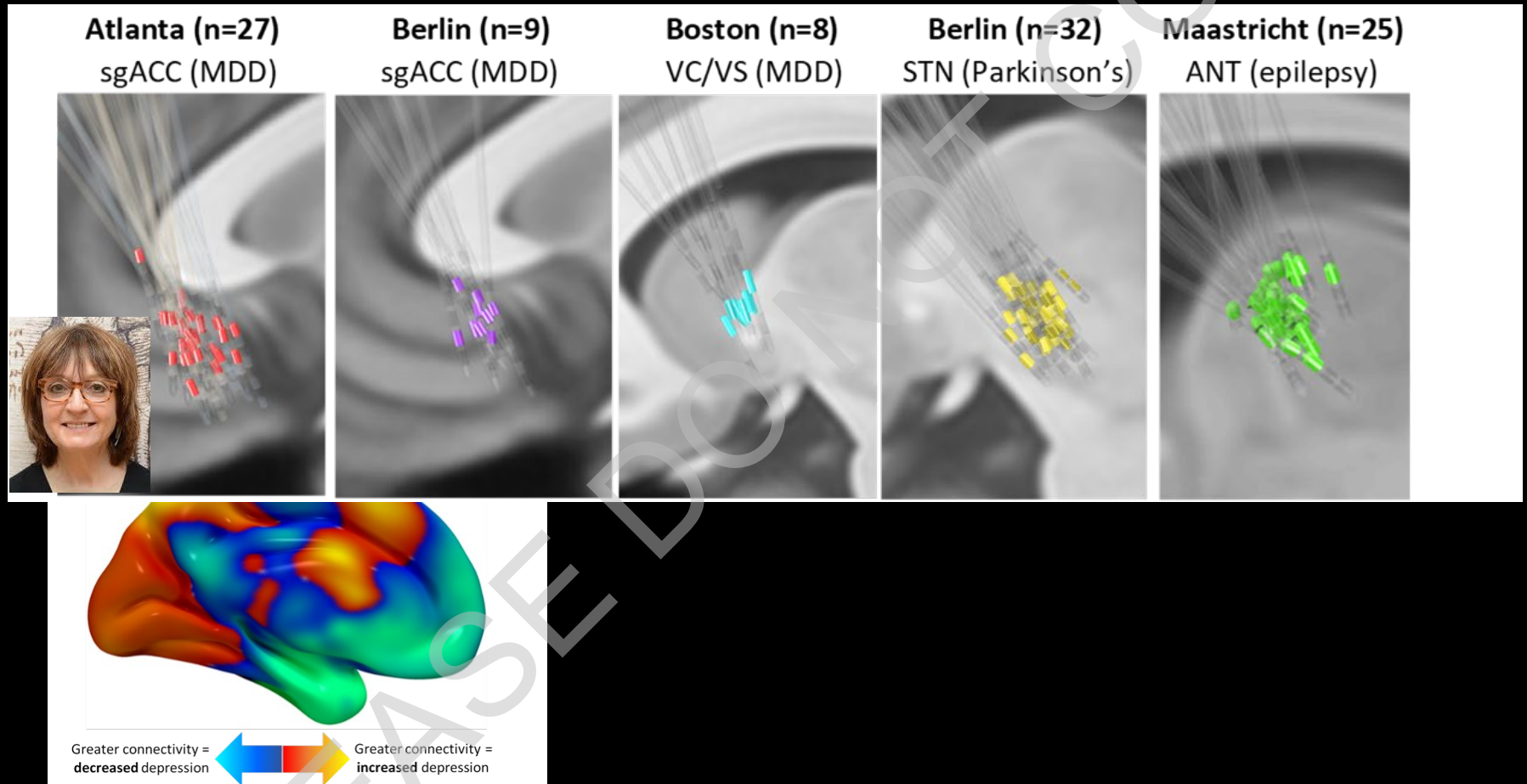
Padmanabhan et al. 2019
Bio. Psych.

Convergent Depression Circuit

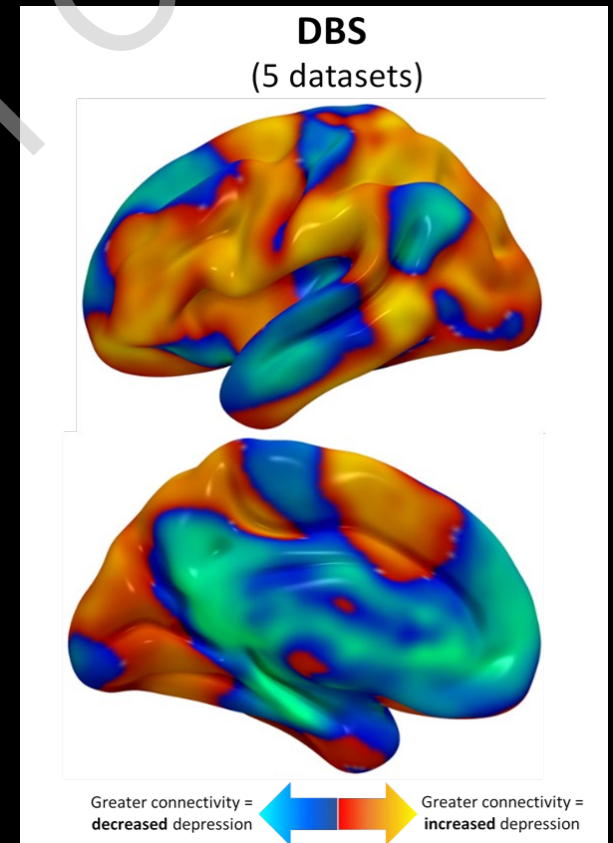
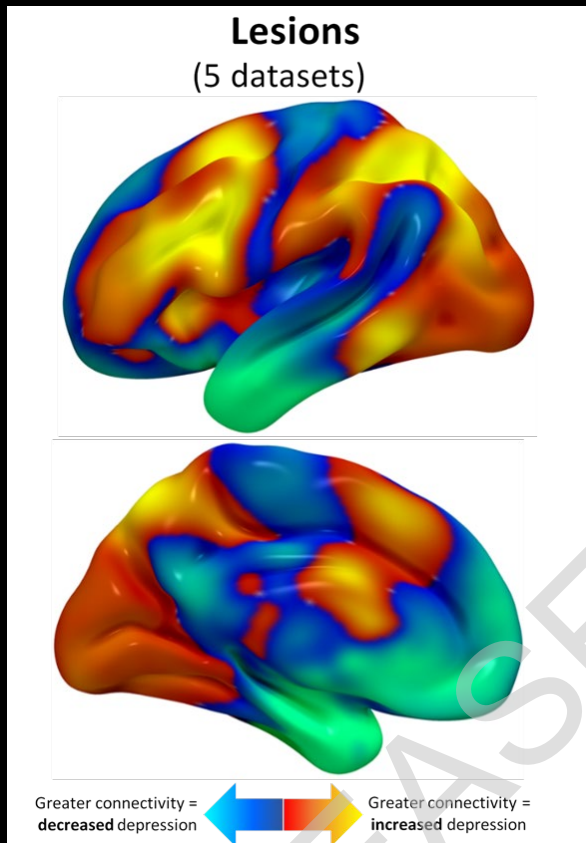


Siddiqi et al. 2021 Nature Hum Behav; Siddiqi et al. 2022 Nature Rev Neuros.

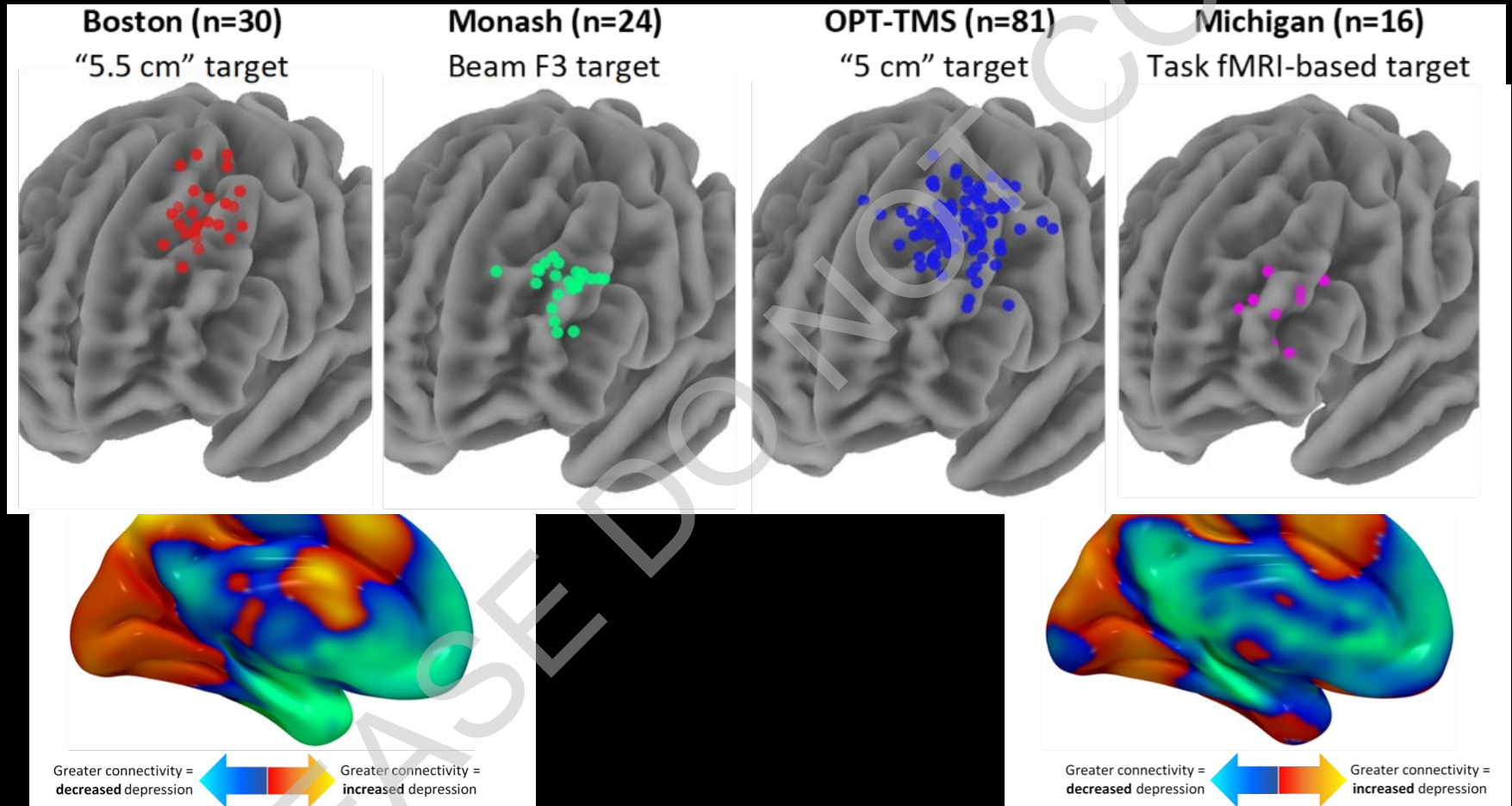
Convergent Depression Circuit



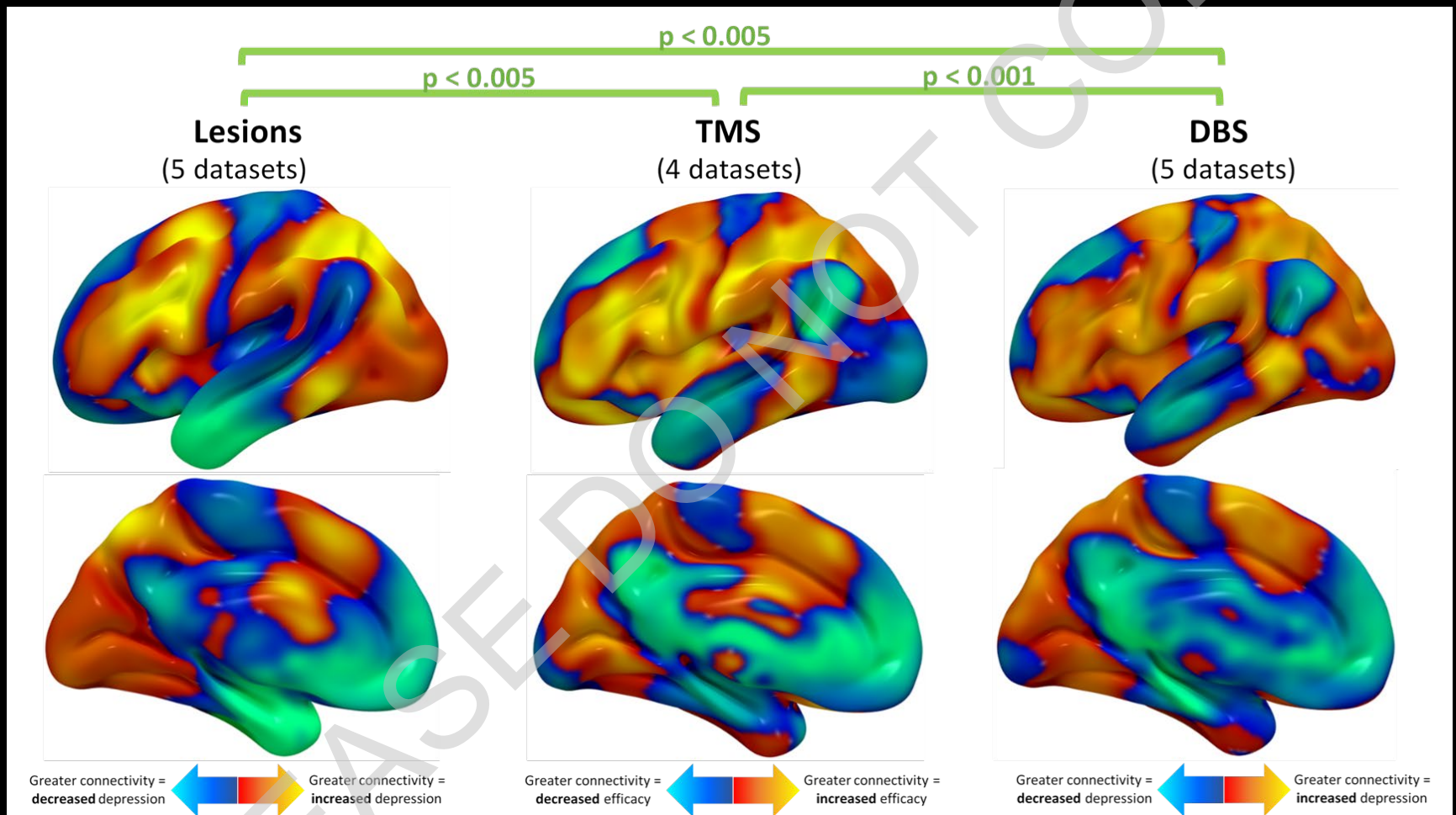
Convergent Depression Circuit



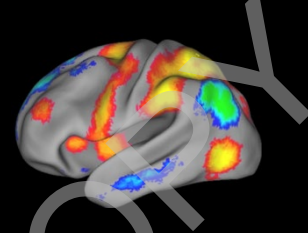
Convergent Depression Circuit



Convergent Depression Circuit



Conclusions



- TMS propagates beyond the stimulation site to modulate brain circuits
- The human connectome can be used to map lesion and stimulation effects to brain circuits
- These brain circuits can be used as therapeutic targets for different forms of neuromodulation



Center for
BRAIN CIRCUIT
THERAPEUTICS



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



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Lab / Center

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Lipeng Ning
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Joan Camprodan
AND MORE

Non-local

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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>

