



RODENT FUNCTIONAL MRI

Valerio Zerbi
EPFL and CIBM

CIBM translational MR neuroimaging & spectroscopy, 05.05.2023



C I B M . C H

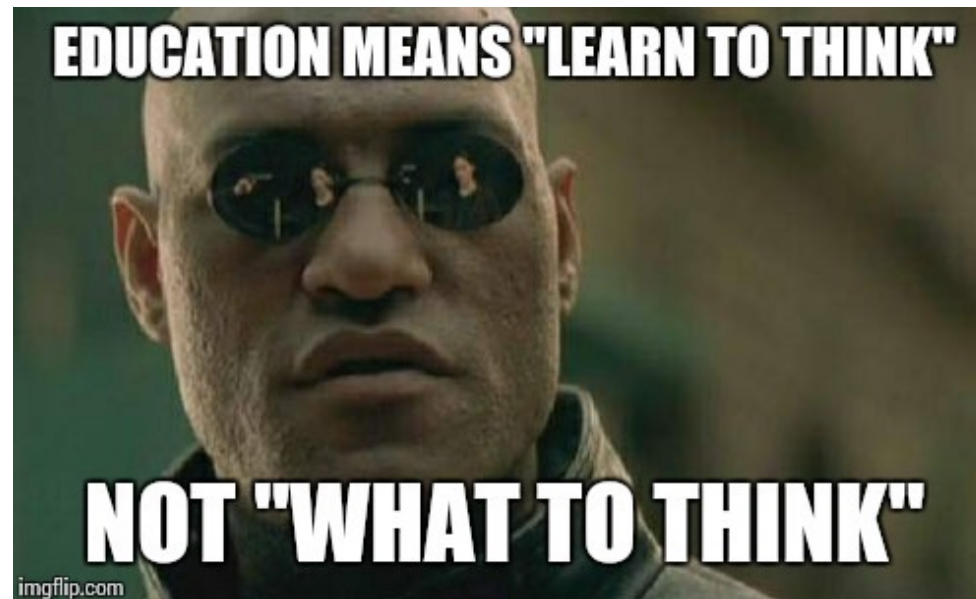
OVERVIEW OF THE MORNING

- **Preface: what are the limits of (human) fMRI?**
- **Part 1. fMRI in rodents. what do you need and what should you expect**
- **Part 2. The functional Connectome in rodents**
- **Part 3. fMRI in Transgenic rodent models for human disorders**
- **Part 4. Manipulating cell activity to observe network reaction**
- **Part 5. Translating fMRI results from rodent to humans**



BY THE END OF TODAY ..

- ✓ YOU HAVE DEVELOPED A **CRITICAL MINDSET** THAT CONSIDERS THE REASONS AND PRACTICAL IMPLICATIONS FOR PLANNING AN ANIMAL EXPERIMENT THAT INCORPORATES FUNCTIONAL MRI



FIRST, A RECAP FROM LAST WEEK ..

SUMMARY: WHAT IS FMRI

fMRI is a technique for measuring metabolic correlates of neuronal activity

Uses a standard MRI scanner and fast imaging sequences (EPI)

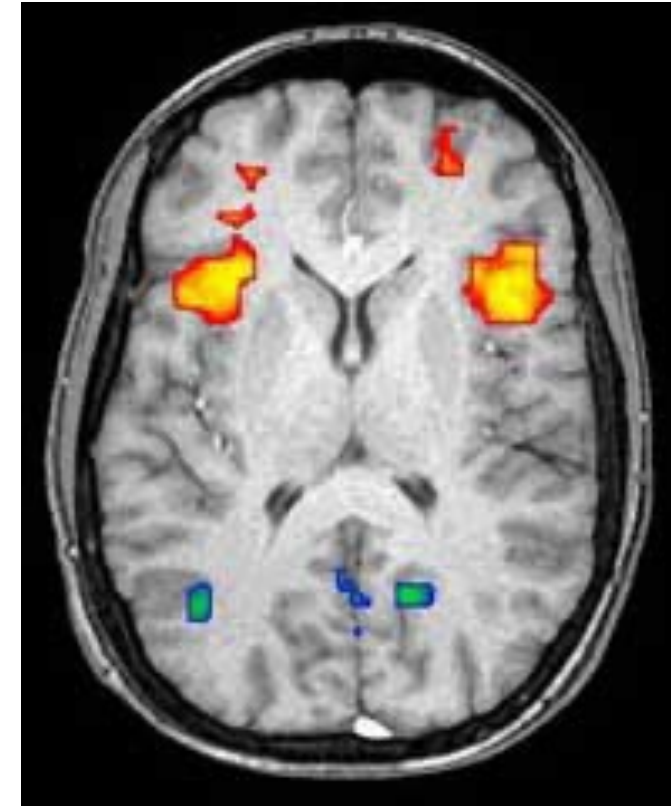
Acquires a series of images over time

Measures changes in blood oxygenation

Use non invasive, non ionizing radiation

Can be applied during a task or resting-state

Can be used for a wide range of applications

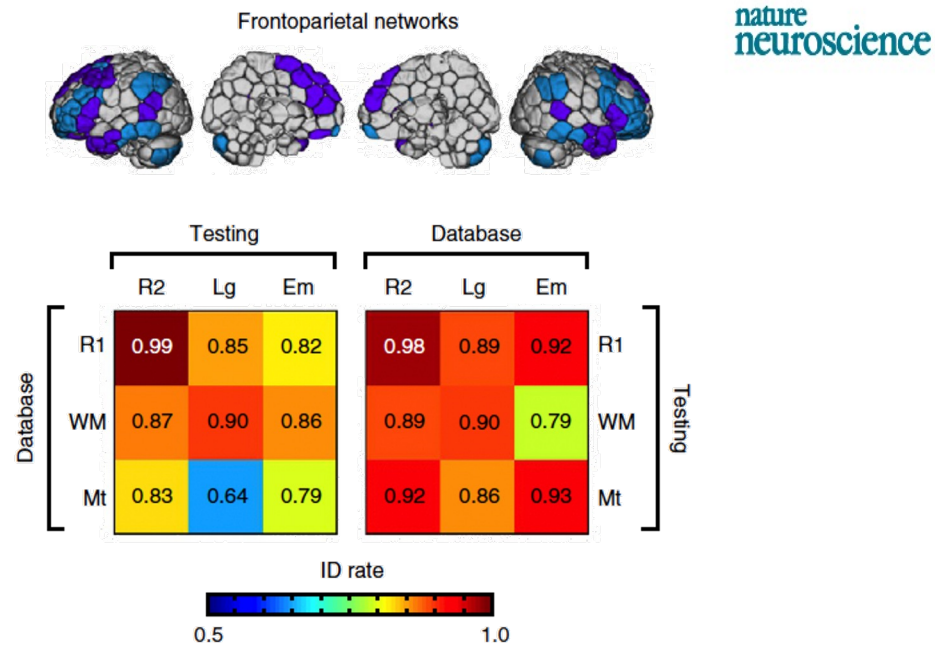


RECAP: NEUROSCIENCE APPLICATIONS OF FMRI

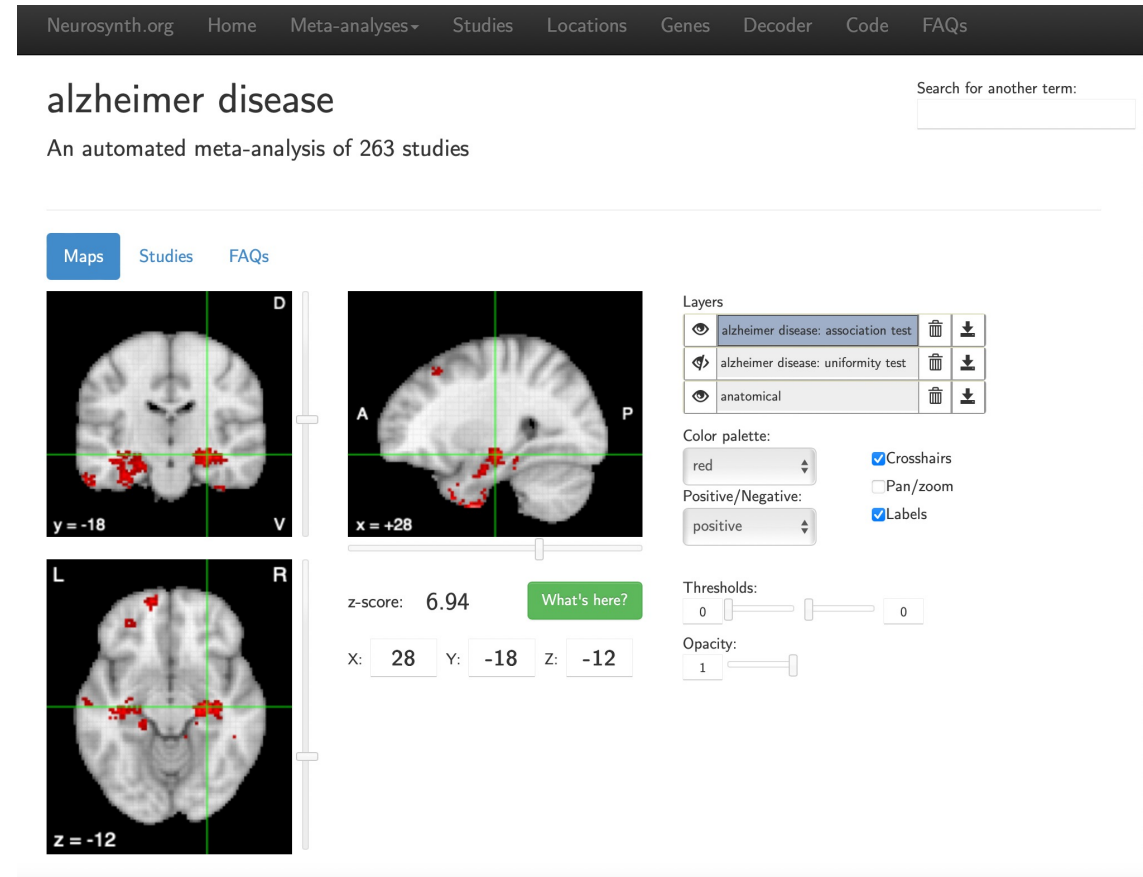
Resting-state fMRI

Functional connectome fingerprinting: identifying individuals using patterns of brain connectivity

Emily S Finn^{1,7}, Xilin Shen^{2,7}, Dustin Scheinost², Monica D Rosenberg³, Jessica Huang², Marvin M Chun^{1,3,4}, Xenophon Papademetris^{2,5} & R Todd Constable^{1,2,6}



Task-fMRI



RECAP: NEUROSCIENCE APPLICATIONS OF FMRI

ALWAYS A HOT TOPIC!!

nature

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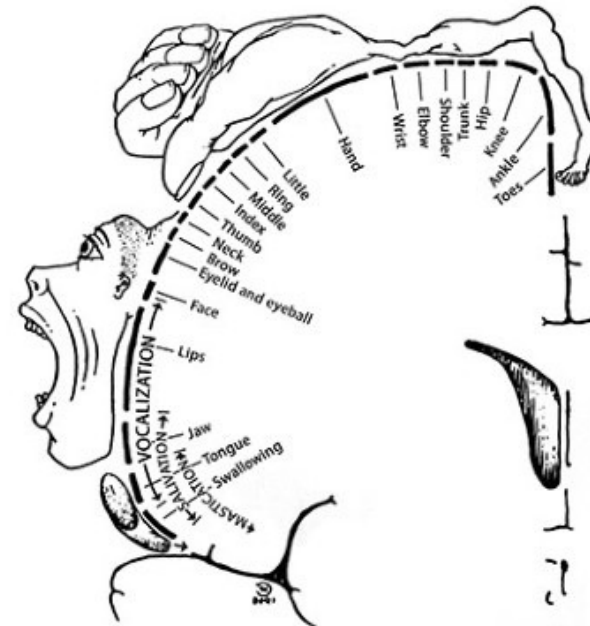
A somato-cognitive action network alternates with effector regions in motor cortex

[Evan M. Gordon](#) , [Roselyne J. Chauvin](#), [Andrew N. Van](#), [Aishwarya Rajesh](#), [Ashley Nielsen](#), [Dillan J. Newbold](#), [Charles J. Lynch](#), [Nicole A. Seider](#), [Samuel R. Krimmel](#), [Kristen M. Scheidter](#), [Julia Monk](#), [Ryland L. Miller](#), [Athanasia Metoki](#), [David F. Montez](#), [Annie Zheng](#), [Immanuel Elbau](#), [Thomas Madison](#), [Tomoyuki Nishino](#), [Michael J. Myers](#), [Sydney Kaplan](#), [Carolina Badke D'Andrea](#), [Damion V. Demeter](#), [Matthew Feigelis](#), [Julian S. B. Ramirez](#), ... [Nico U. F. Dosenbach](#)  [+ Show authors](#)

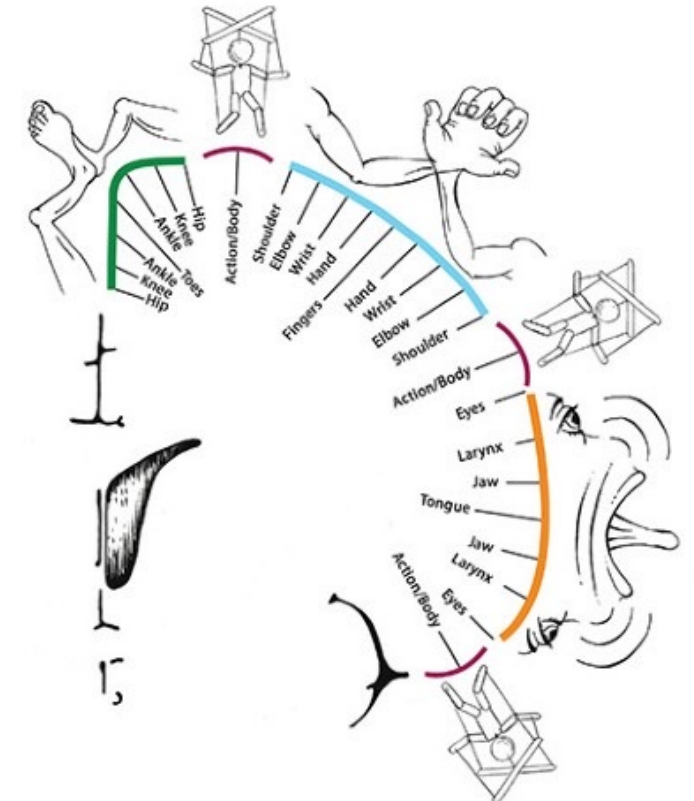
[Nature](#) (2023) | [Cite this article](#)

87k Accesses | 1 Citations | 1598 Altmetric | [Metrics](#)

a Penfield's Homunculus (1948)



b Integrate - Isolate model (2022)



RECAP: NEUROSCIENCE APPLICATIONS OF FMRI

ALWAYS A HOT TOPIC!!

nature neuroscience

Article

<https://doi.org/10.1038/s41593-023-01304-9>

Semantic reconstruction of continuous language from non-invasive brain recordings

Received: 1 April 2022

Jerry Tang¹, Amanda LeBel², Shailee Jain¹ & Alexander G. Huth^{1,2} ✉

Accepted: 15 March 2023

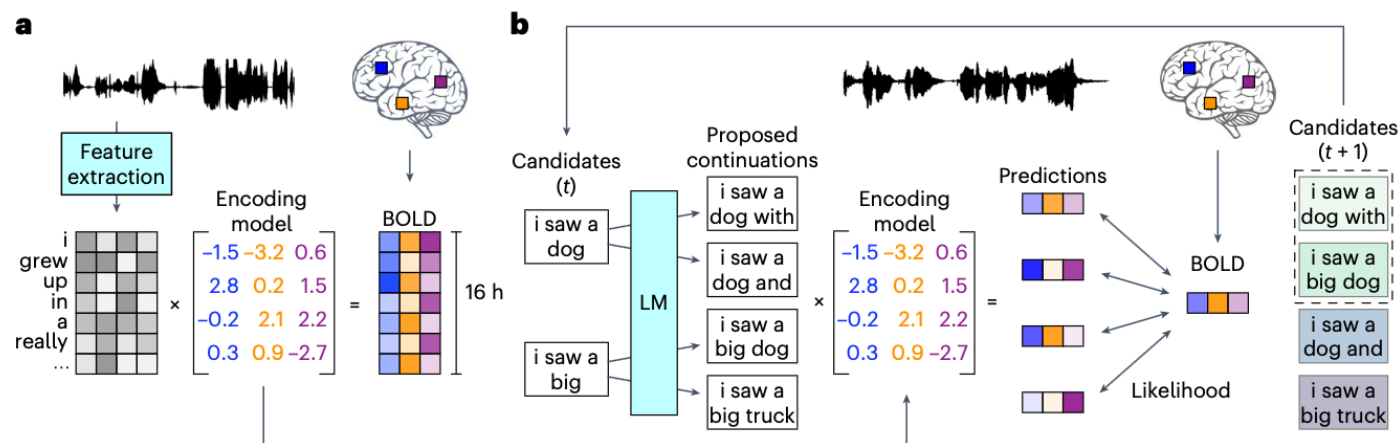
BIOTECHNOLOGY

Brain scans can translate a person's thoughts into words

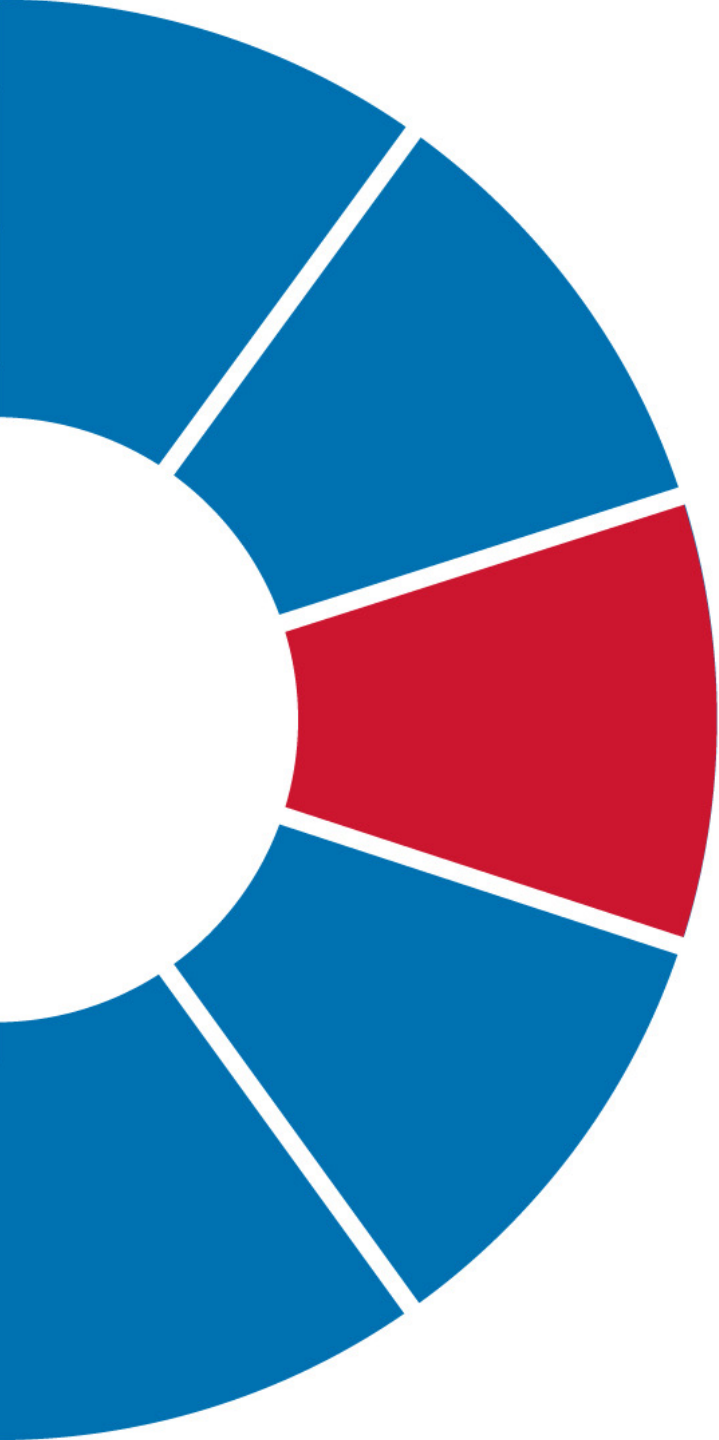
A new system was able to capture exact words and phrases from the brain activity of someone listening to podcasts.

By Rhiannon Williams

May 1, 2023



Actual stimulus	Decoded stimulus	
i got up from the air mattress and pressed my face against the glass of the bedroom window expecting to see eyes staring back at me but instead finding only darkness	i just continued to walk up to the window and open the glass i stood on my toes and peered out i didn't see anything and looked up again i saw nothing	Exact
i didn't know whether to scream cry or run away instead i said leave me alone i don't need your help adam disappeared and i cleaned up alone crying	started to scream and cry and then she just said i told you to leave me alone you can't hurt me anymore i'm sorry and then he stormed off i thought he had left i started to cry	Gist
that night i went upstairs to what had been our bedroom and not knowing what else to do i turned out the lights and lay down on the floor	we got back to my dorm room i had no idea where my bed was i just assumed i would sleep on it but instead i lay down on the floor	Error
i don't have my driver's license yet and i just jumped out right when i needed to and she says well why don't you come back to my house and i'll give you a ride i say ok	she is not ready she has not even started to learn to drive yet i had to push her out of the car i said we will take her home now and she agreed	

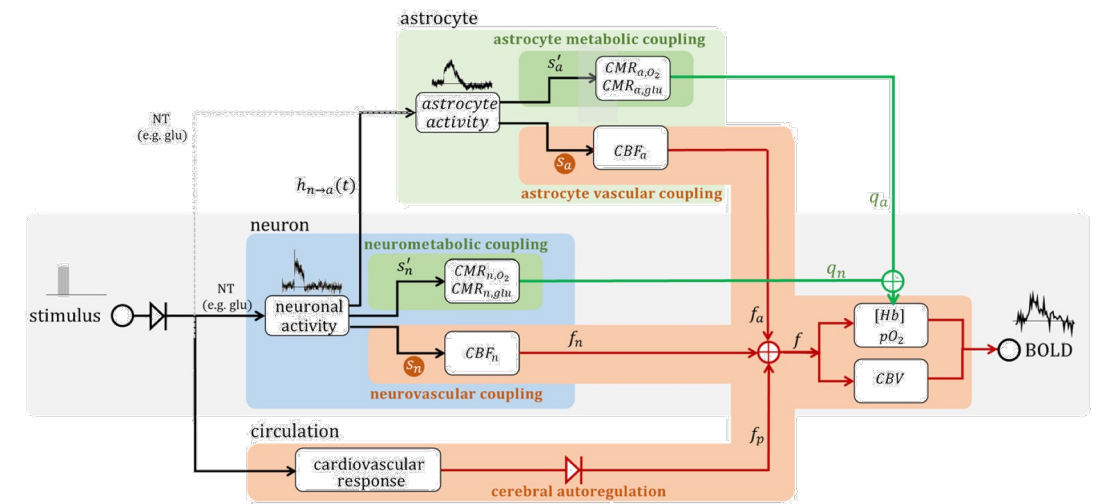


PREFACE: WHAT ARE THE LIMITS OF HUMAN FMRI?

“Keep your friends close but your enemies closer”
Sun Tzu

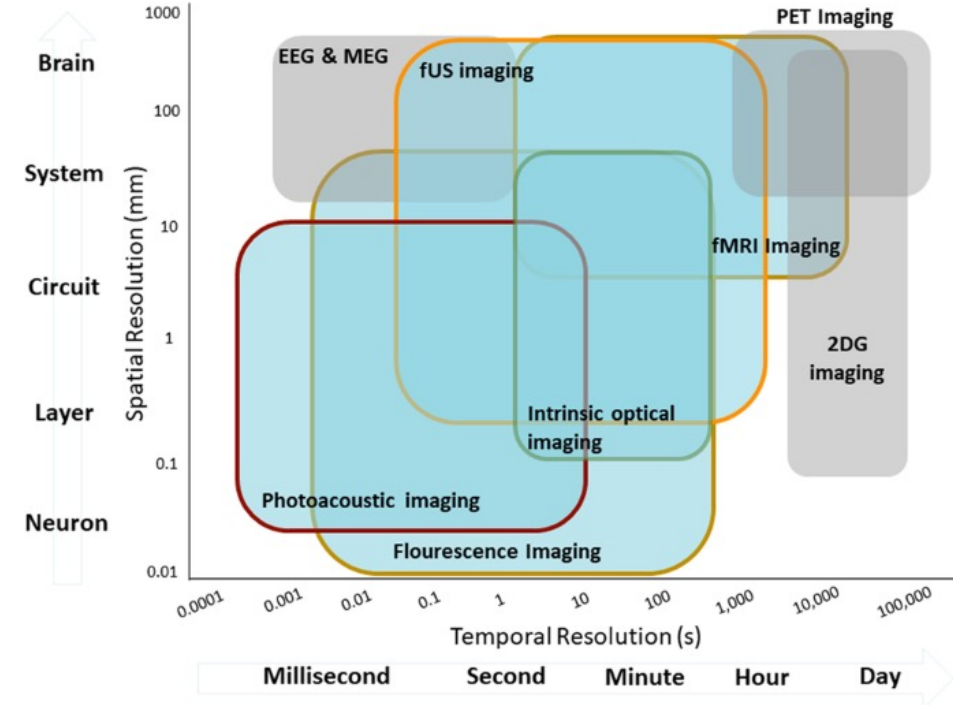
WHAT ARE THE LIMITS OF HUMAN FMRI?

- INDIRECT MEASURE OF BRAIN ACTIVITY



WHAT ARE THE LIMITS OF HUMAN FMRI?

- INDIRECT MEASURE OF BRAIN ACTIVITY
- LOW SPATIAL AND TEMPORAL RESOLUTION



WHAT ARE THE LIMITS OF HUMAN FMRI?

- INDIRECT MEASURE OF BRAIN ACTIVITY
- LOW SPATIAL AND TEMPORAL RESOLUTION
- INTRINSIC HETEROGENEITY OF fMRI RESPONSES AND FUNCTIONAL CONNECTIVITY

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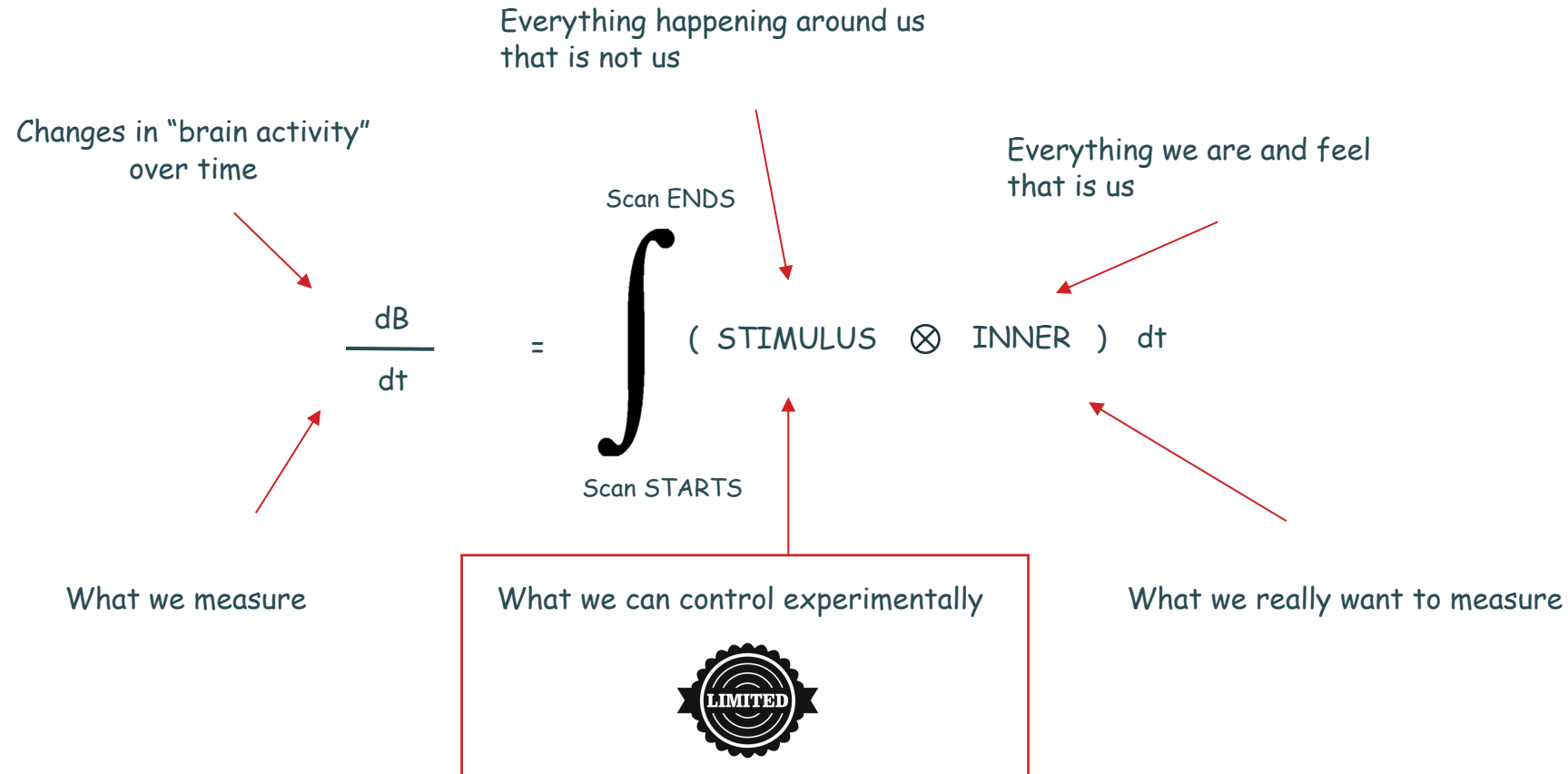
[nature](#) > [articles](#) > [article](#)

Article | [Open Access](#) | [Published: 16 March 2022](#)

Reproducible brain-wide association studies require thousands of individuals



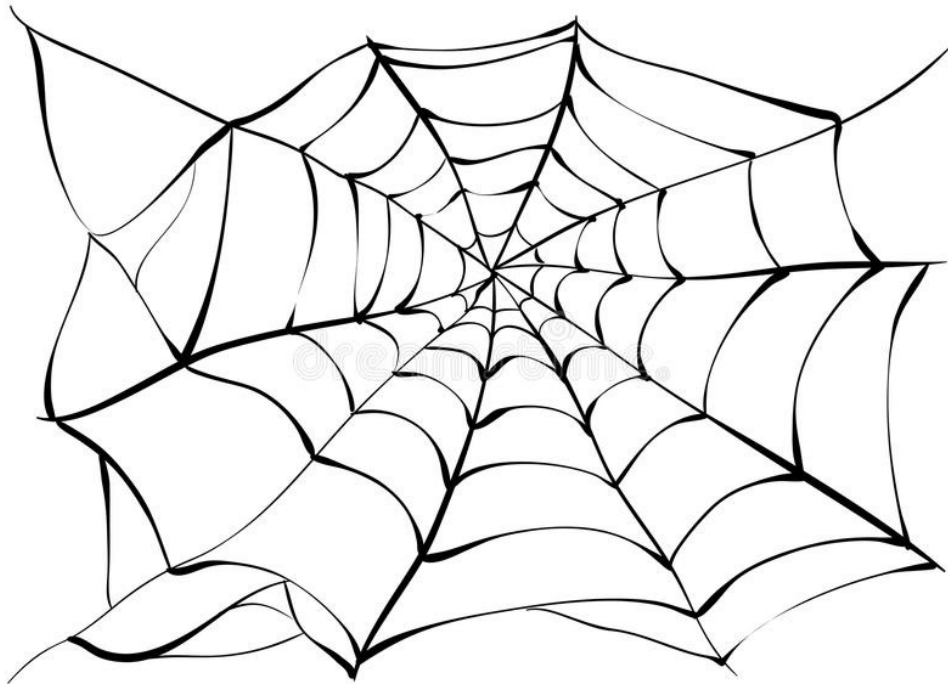
WHAT ARE THE LIMITS OF HUMAN FMRI?



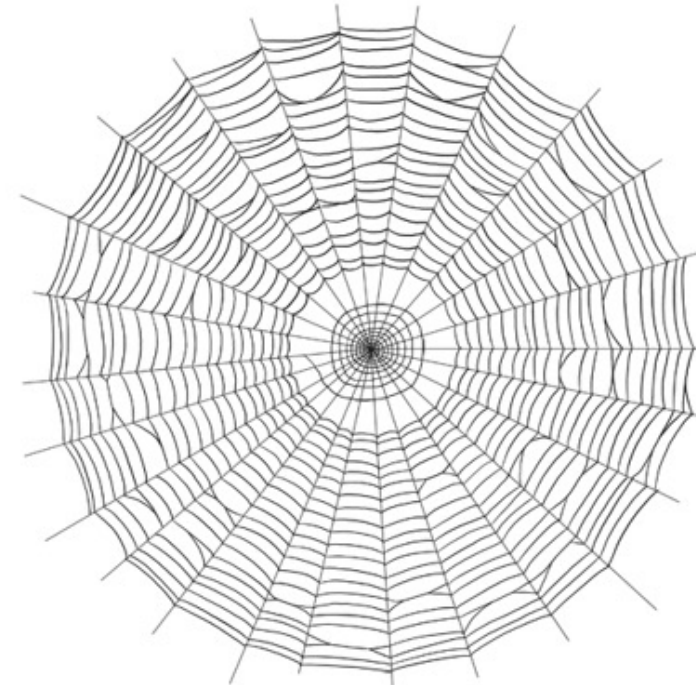
PROPRIETIES OF THE FUNCTIONAL CONNECTIVITY

ARE THEY DIFFERENT?

STUDY GROUP



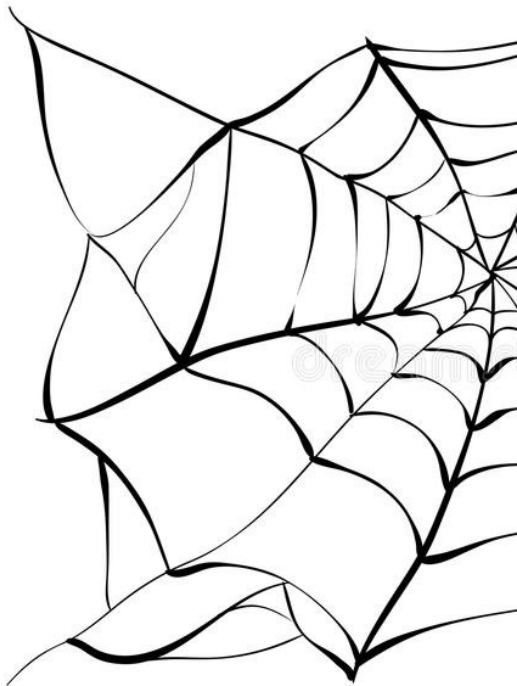
CONTROLS



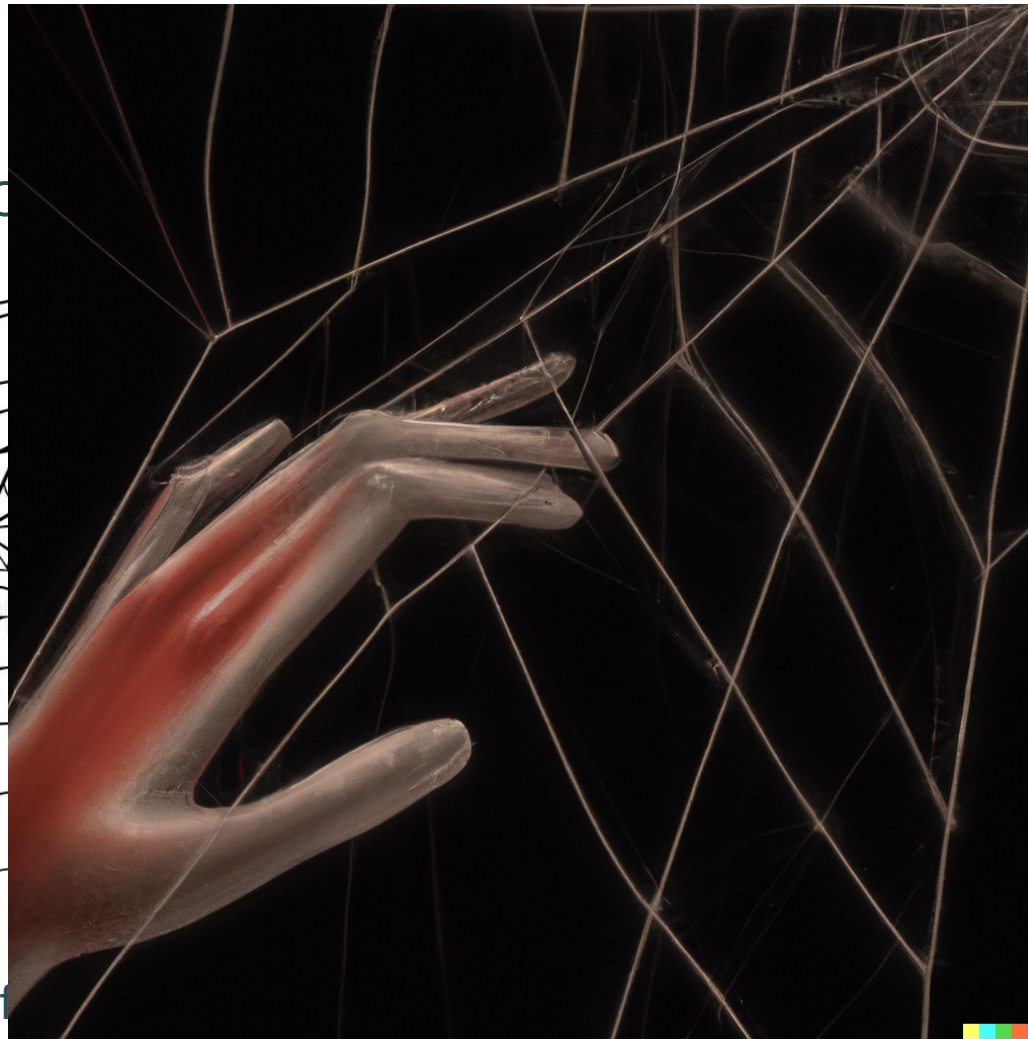
PROPRIETIES OF THE FUNCTIONAL CONNECTIVITY

ARE THEY DIFFERENT?

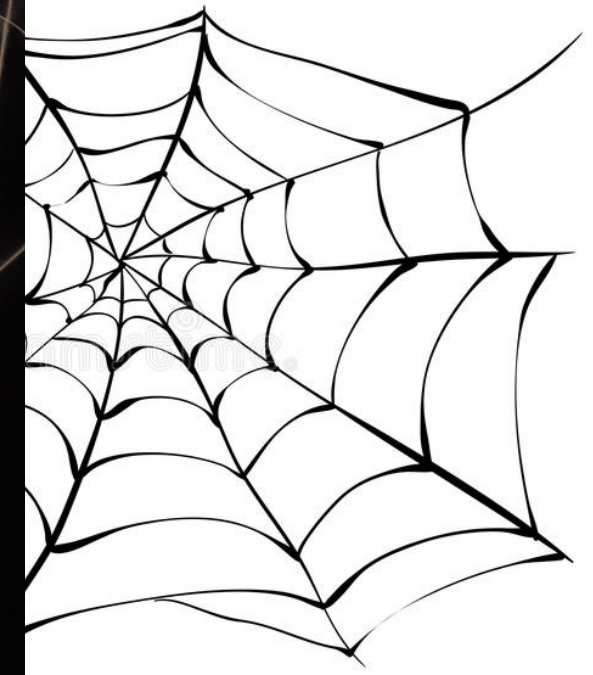
STUDY GROUP



made of

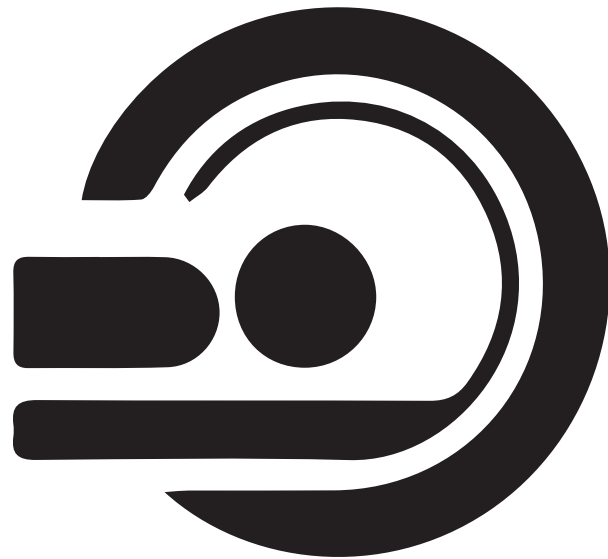


TROLS

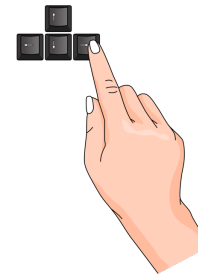


made of cotton

BIGGEST ADVANTAGE : MULTI-MODAL fMRI



Resting-state fMRI

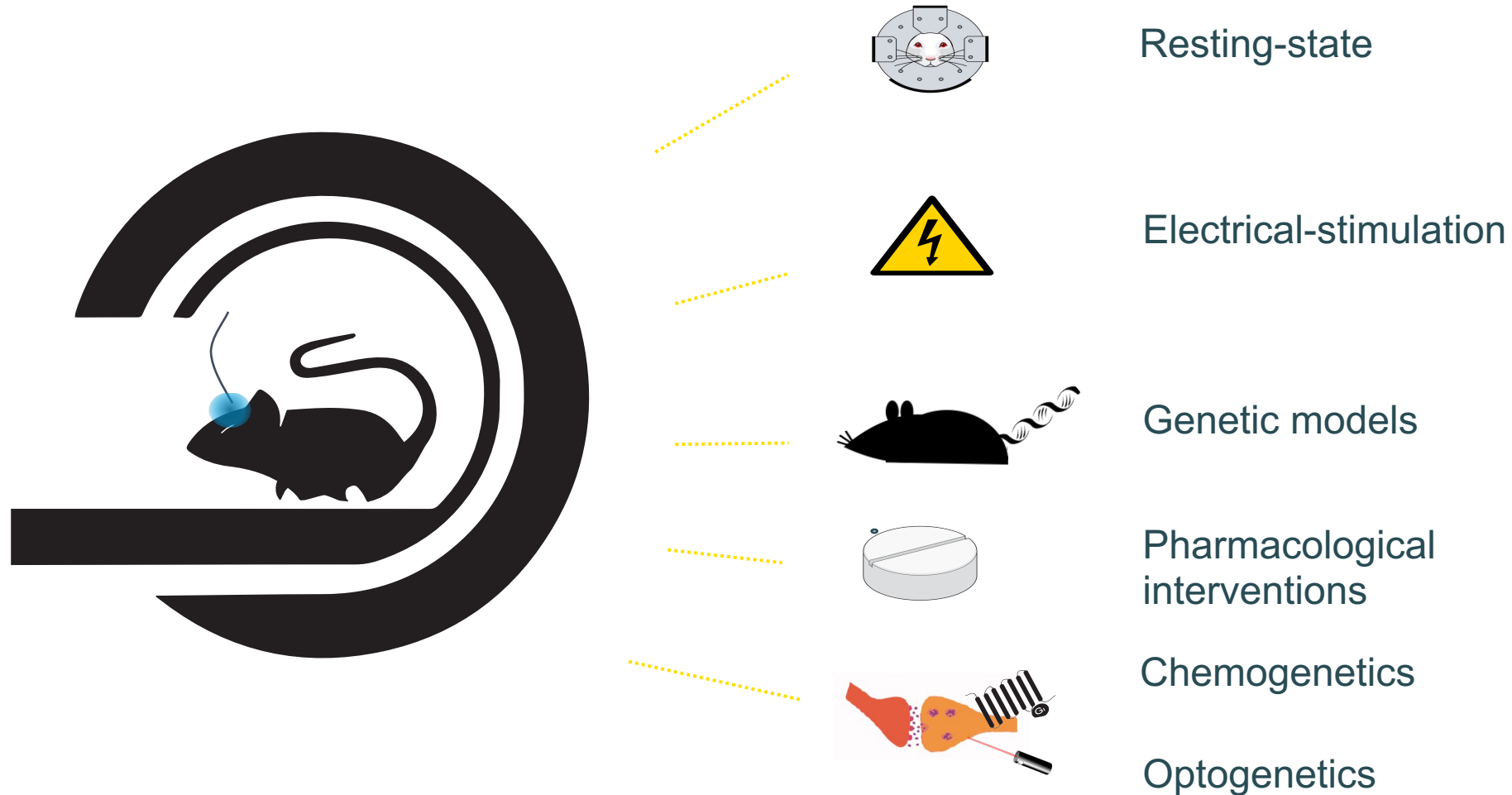


Task-based fMRI

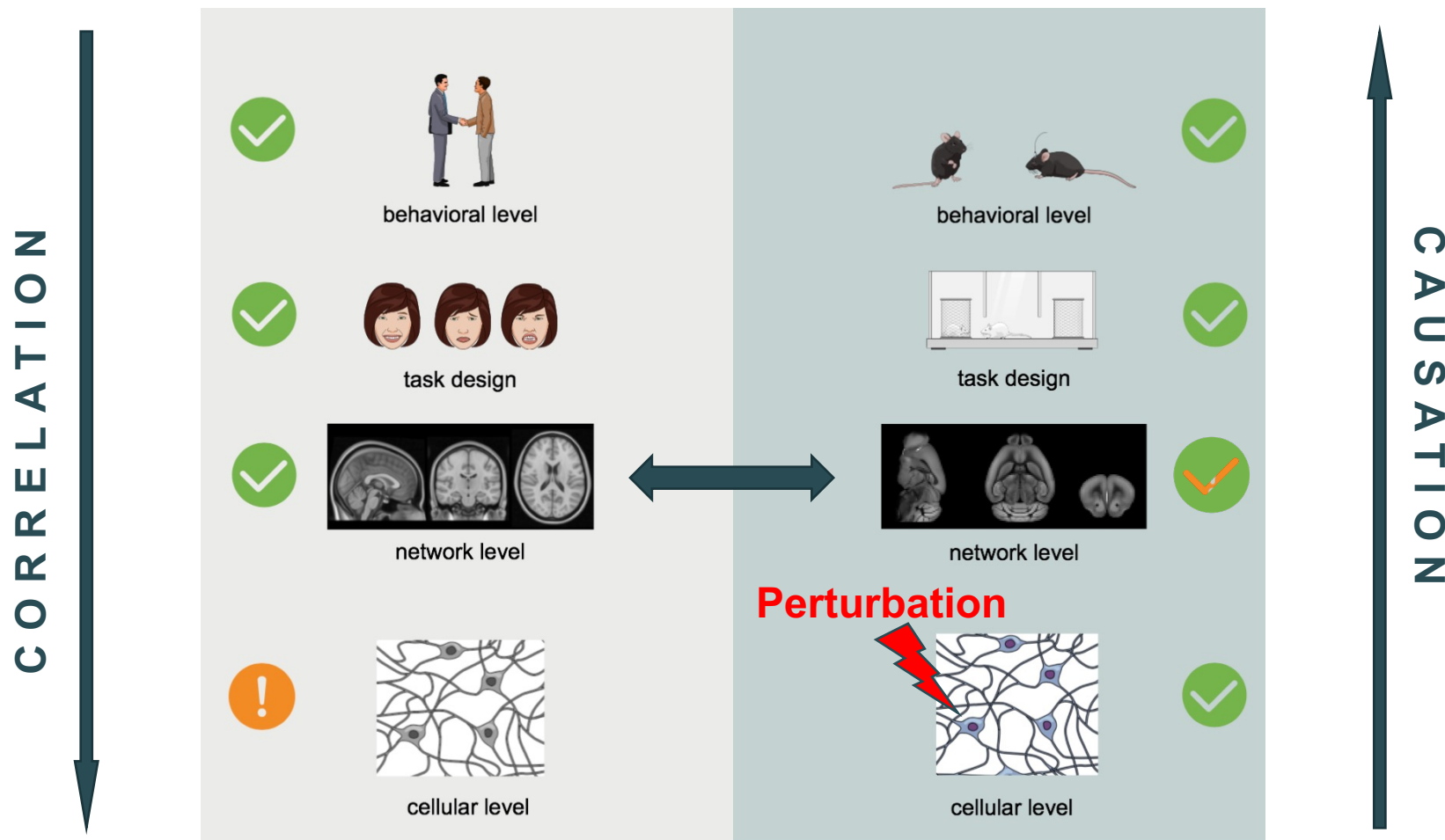


Pharmacological
interventions (rare &
expensive)

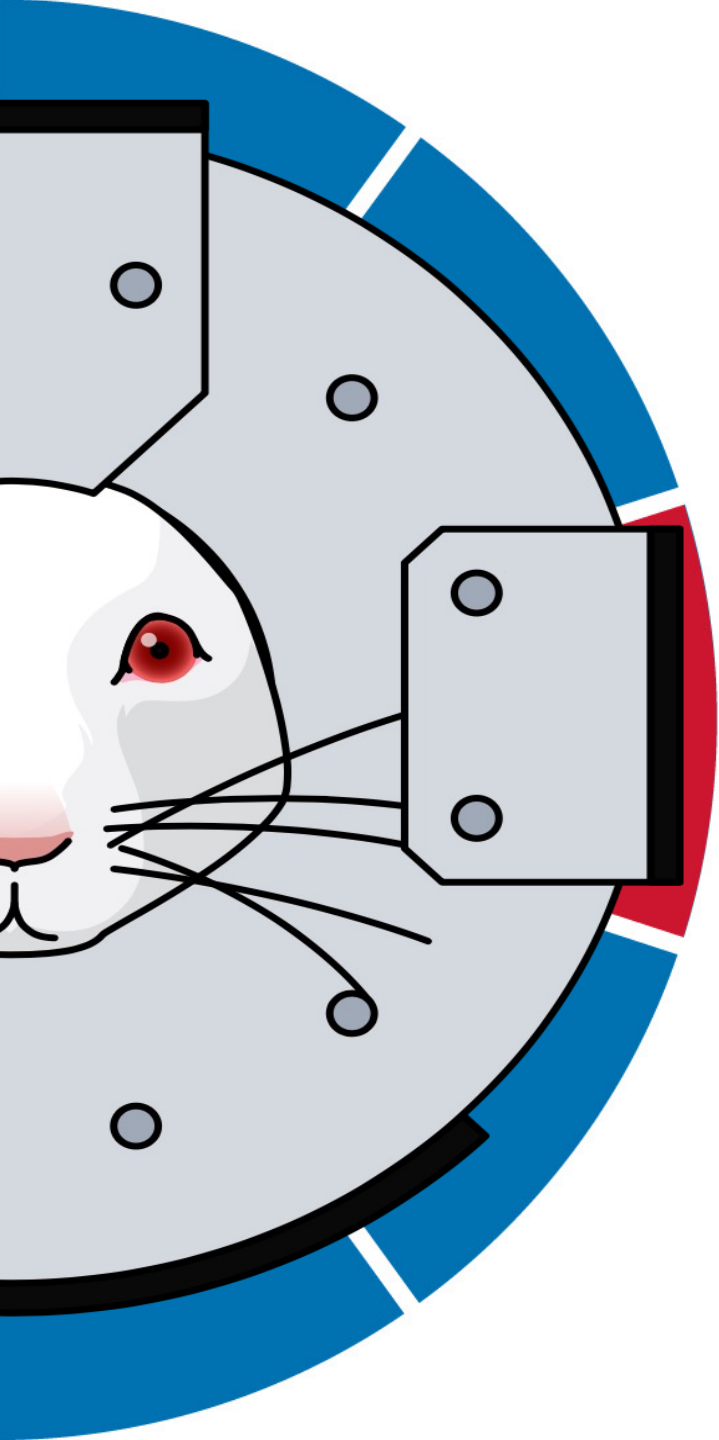
BIGGEST ADVANTAGE: MULTI-MODAL FMRI



BIGGEST ADVANTAGE: MULTI-MODAL FMRI

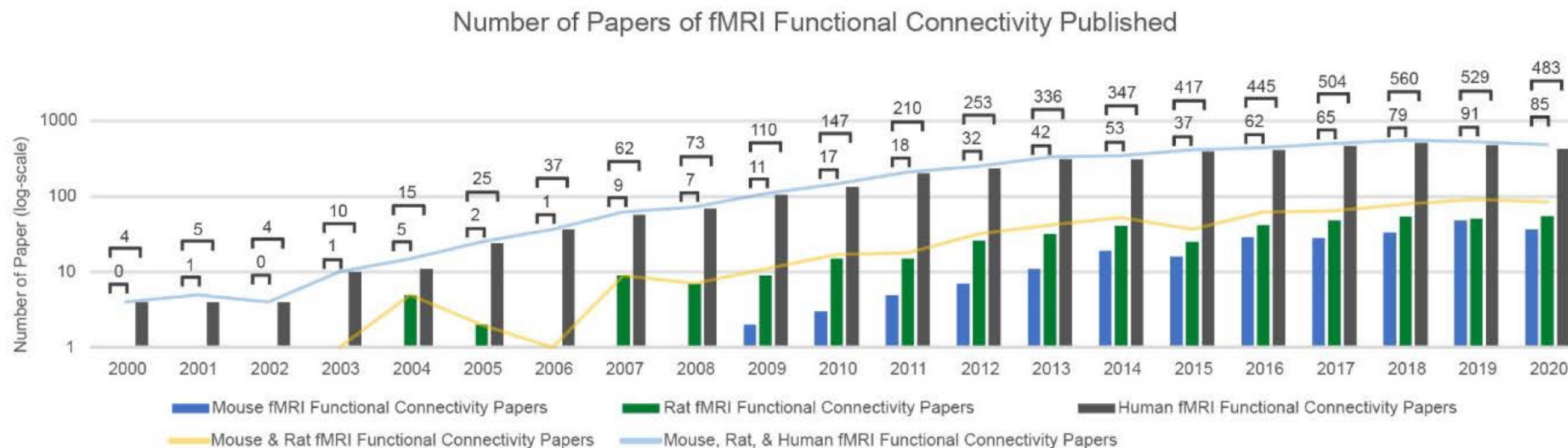


Grimm et al., The Neuroscientist, 2020



PART 1. FMRI IN RODENTS. WHAT DO YOU NEED AND WHAT SHOULD YOU EXPECT

RESTING-STATE FMRI IN RODENTS



RESTING-STATE FMRI IN RODENTS

Hardware & Software

- High-field MRI
- Tech for high SNR (e.g. cryogenic coil technology)
- Optimized light-anesthesia protocols
 - or protocols for accustom animals to head-fixation
- Dedicated (pre)processing pipeline



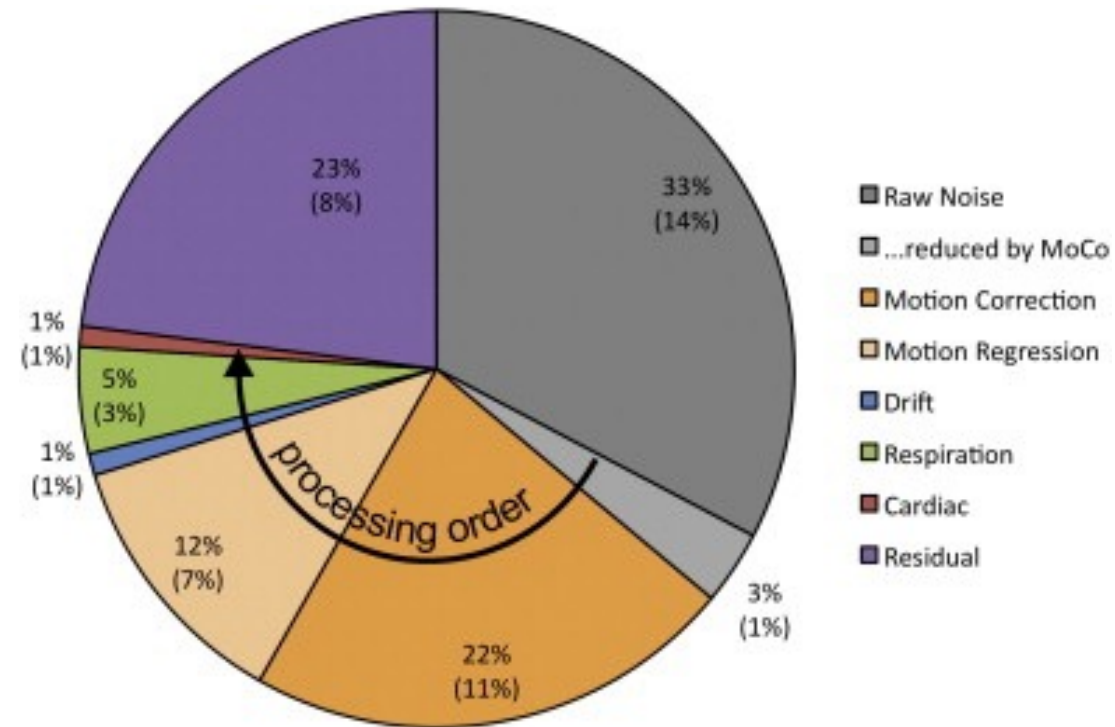
RESTING-STATE FMRI IN RODENTS

Why we need high-field scanners?

		Mouse	Rat	Human
Anatomy	Brain Volume	415 mm ³ (Kovacěvic et al., 2005)	1765 mm ³ (Welniak-Kaminska et al., 2019)	1200 cm ³ (Yu et al., 2013)
	Gyrification	Flat (Ventura-Antunes et al., 2013)	Flat (Ventura-Antunes et al., 2013)	Folded (Ventura-Antunes et al., 2013)
	Cortical Thickness	<1 mm (Lerch et al., 2008)	1 - 2 mm (Vetreno et al., 2017)	1 - 4.5 mm (Fischl & Dale, 2000)
MRI Parameters	Resolution	20 - 50 μ m (Turnbull & Mori, 2007)	90 - 150 μ m (Barrière et al., 2019)	0.1 - 3 mm (Edlow et al., 2019; Fischl & Dale, 2000)
	TR (seconds)	0.15-3 (Gilbert et al., 2019; Turnbull & Mori, 2007)	0.15-3 (Gilbert et al., 2019)	<0.25 – 5 (K. H. Chuang & Chen, 2001; Sahib et al., 2018; Van Dijk et al., 2010)
	Resting-State Scan Time (minutes)	~10-20 (Bauer et al. 2017; Belloy et al. 2018)	~10 (Christiaen et al., 2019)	~5-15 (Elliott et al., 2019)

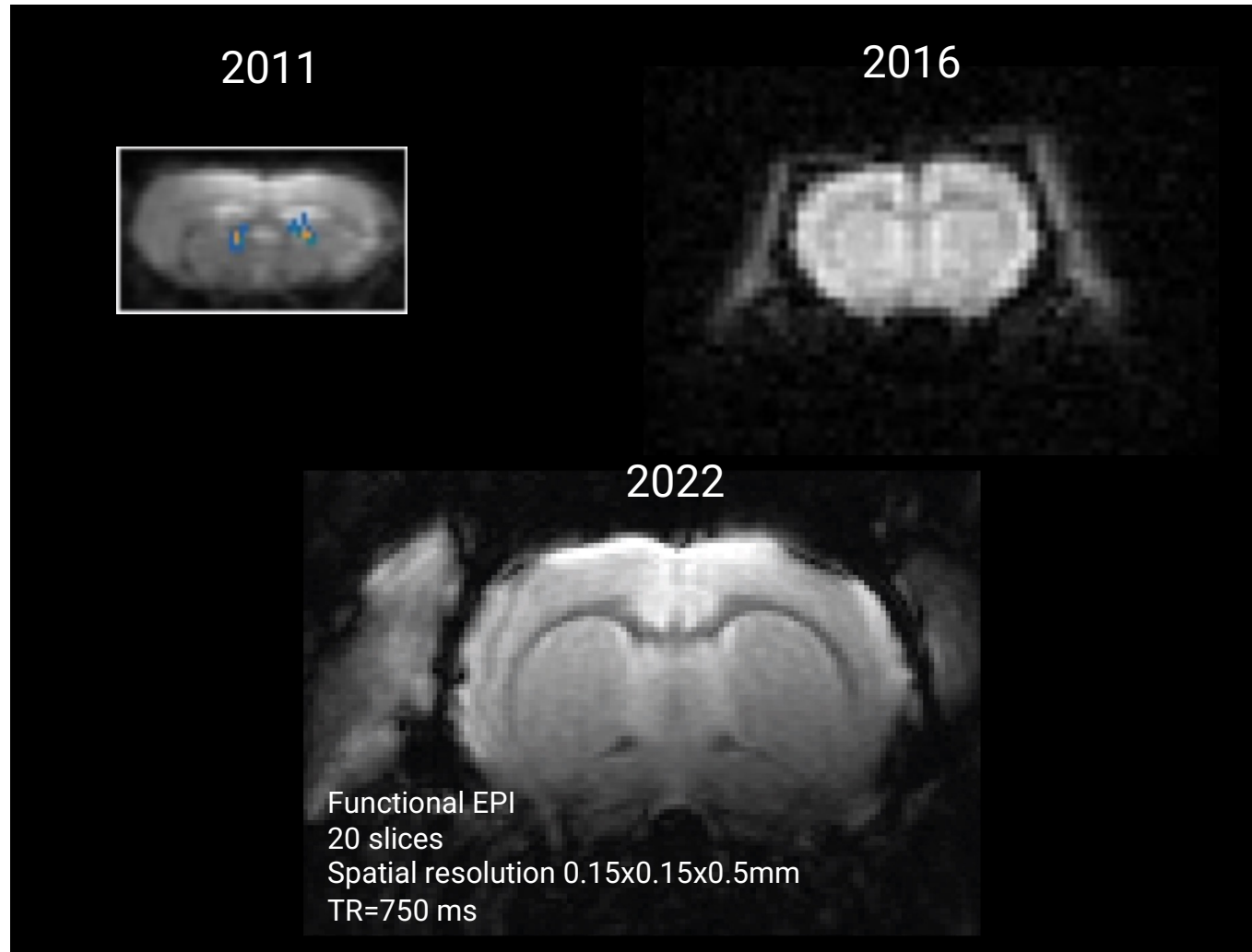
RESTING-STATE FMRI IN RODENTS

Why we need dedicated (pre)processing pipeline?



Functional connectivity in the rat at 11.7 T: Impact of physiological noise in resting state fMRI. NeuroImage 2010

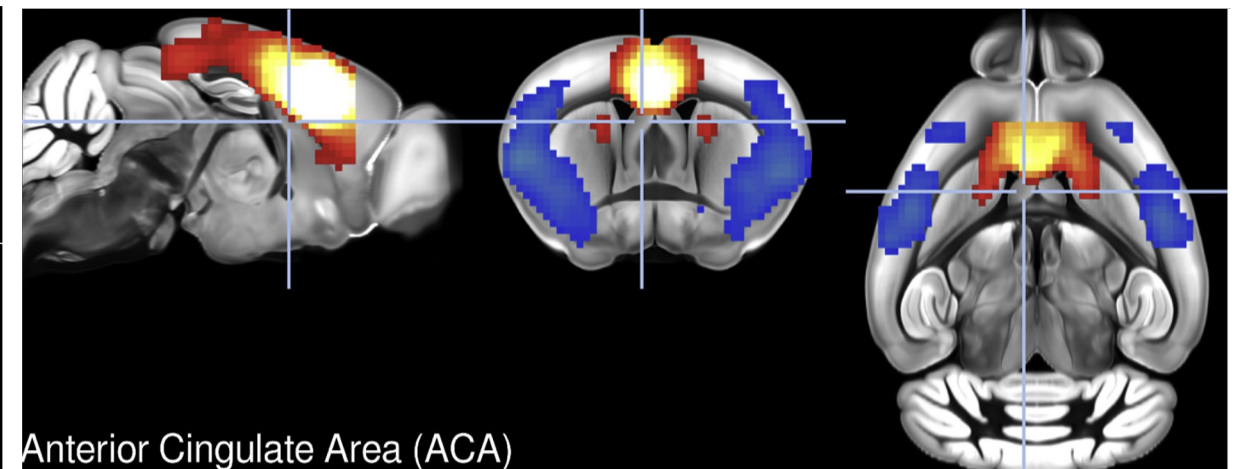
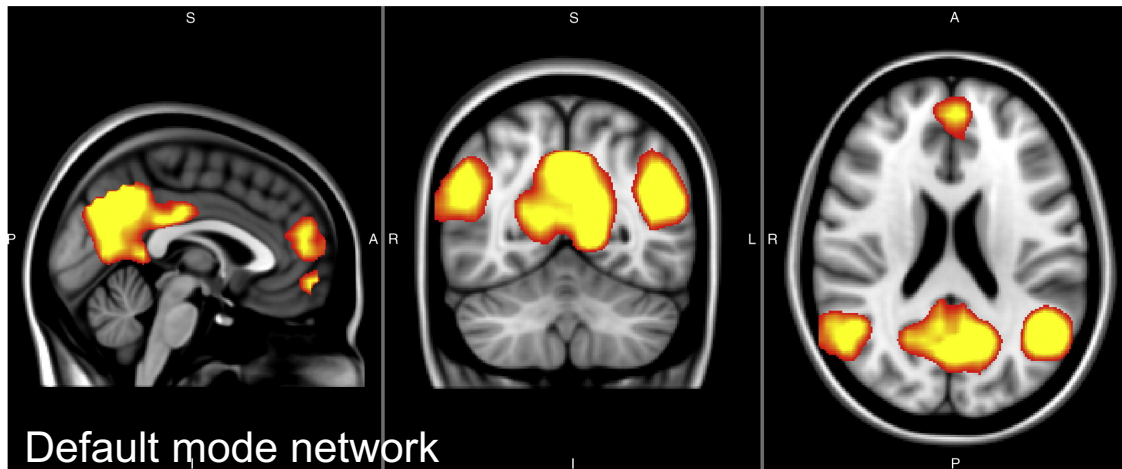
RESTING-STATE FMRI IN RODENTS



RESTING-STATE FMRI IN RODENTS

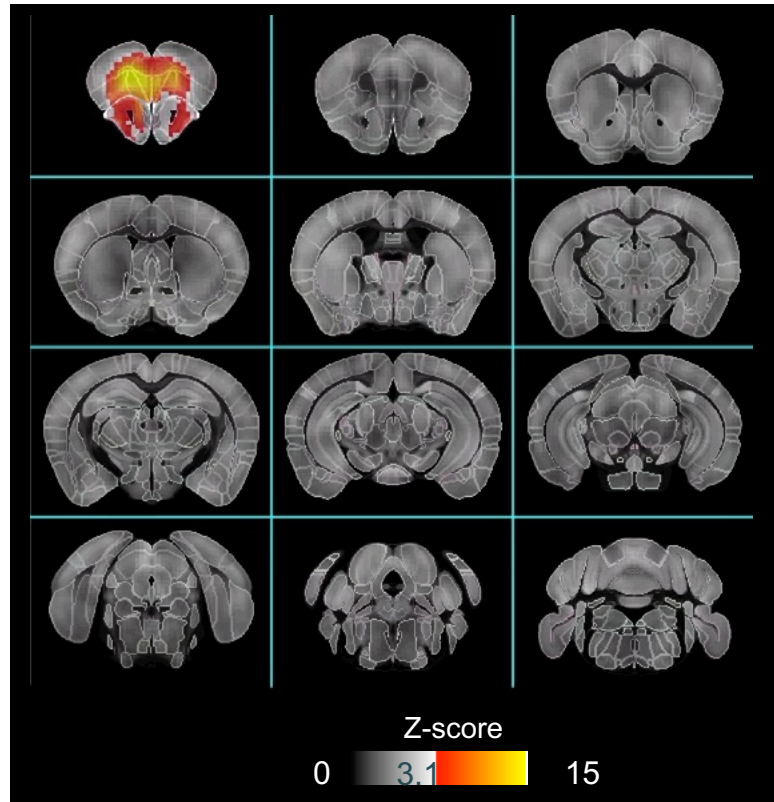
A matter of trust

- Functional MRI data are relatively easy to acquire, but their quality is extremely difficult to judge with simple visual inspections

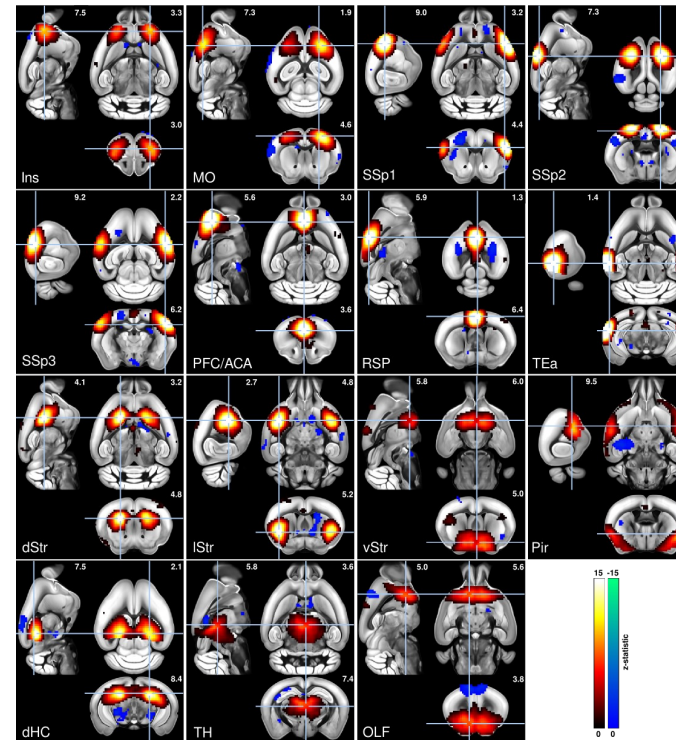


RESTING-STATE FMRI IN RODENTS

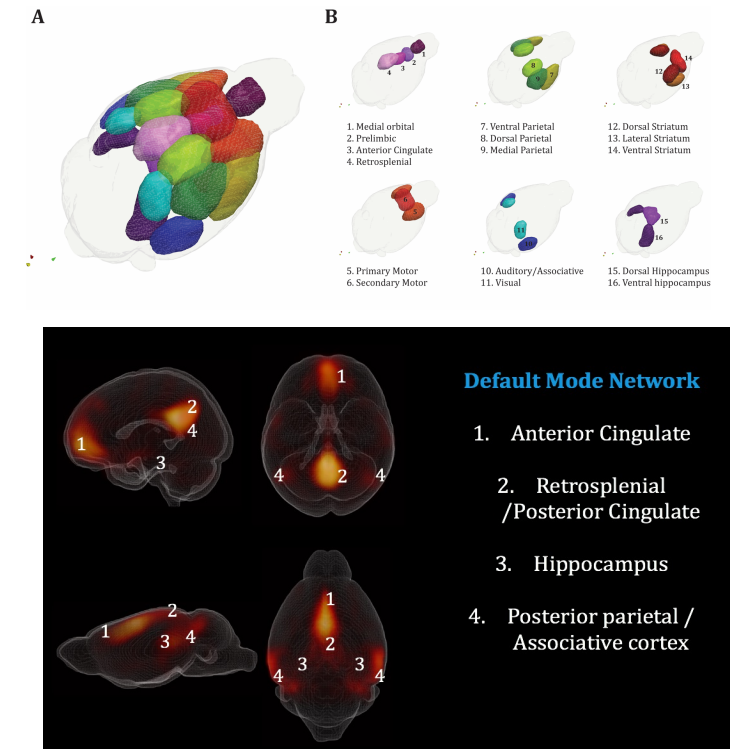
Mouse Brain Networks



Zerbi et al., NeuroImage, 2015



Grandjean et al., NeuroImage, 2020



Zerbi et al., Cerebral Cortex, 2018

RESTING-STATE FMRI IN RODENTS

- **Only 25% of datasets** collected from 17 groups worldwide showed specific spatial patterns of functional connectivity

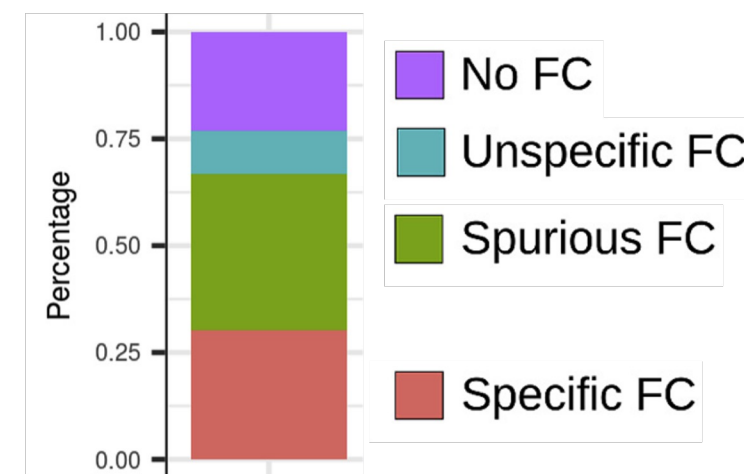
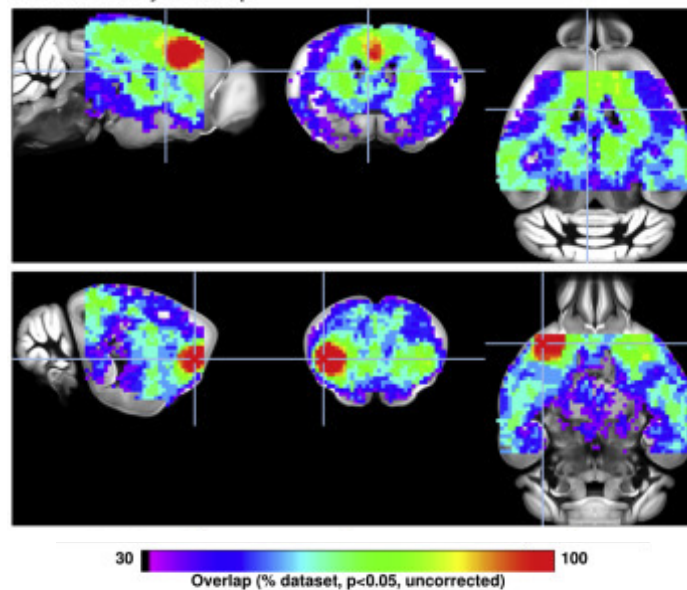
Multicenter Study > [Neuroimage](#). 2020 Jan 15;205:116278.

doi: 10.1016/j.neuroimage.2019.116278. Epub 2019 Oct 12.

Common functional networks in the mouse brain revealed by multi-centre resting-state fMRI analysis

Joanes Grandjean¹, Carola Canella², Cynthia Anckaerts³, Gülebru Ayranci⁴, Salma Bougacha⁵, Thomas Bienert⁶, David Buehlmann⁷, Ludovico Coletta², Daniel Gallino⁴, Natalia Gass⁸, Clément M Garin⁵, Nachiket Abhay Nadkarni⁵, Neele S Hübner⁶, Meltem Karatas⁹, Yuji Komaki¹⁰, Silke Kreitz¹¹, Francesca Mandino¹², Anna E Mechling⁶, Chika Sato¹³, Katja Sauer¹¹, Disha Shah¹⁴, Sandra Strobelt¹¹, Norio Takata¹⁵, Isabel Wank¹¹, Tong Wu¹⁶, Noriaki Yahata¹³, Ling Yun Yeow¹⁷, Yohan Yee¹⁸, Ichio Aoki¹³, M Mallar Chakravarty¹⁹, Wei-Tang Chang¹⁷, Marc Dhenain⁵, Dominik von Elverfeldt⁶, Laura-Adela Harsan²⁰, Andreas Hess¹¹, Tianzi Jiang²¹, Georgios A Keliris³, Jason P Lerch²², Andreas Meyer-Lindenberg²³, Hideyuki Okano²⁴, Markus Rudin²⁵, Alexander Sartorius⁸, Annemie Van der Linden³, Marleen Verhoye³, Wolfgang Weber-Fahr⁸, Nicole Wenderoth²⁶, Valerio Zerbi²⁶, Alessandro Gozzi²⁷

Seed-based analysis overlap



RESTING-STATE FMRI IN RODENTS

Are rats-fMRI scans better?

nature neuroscience

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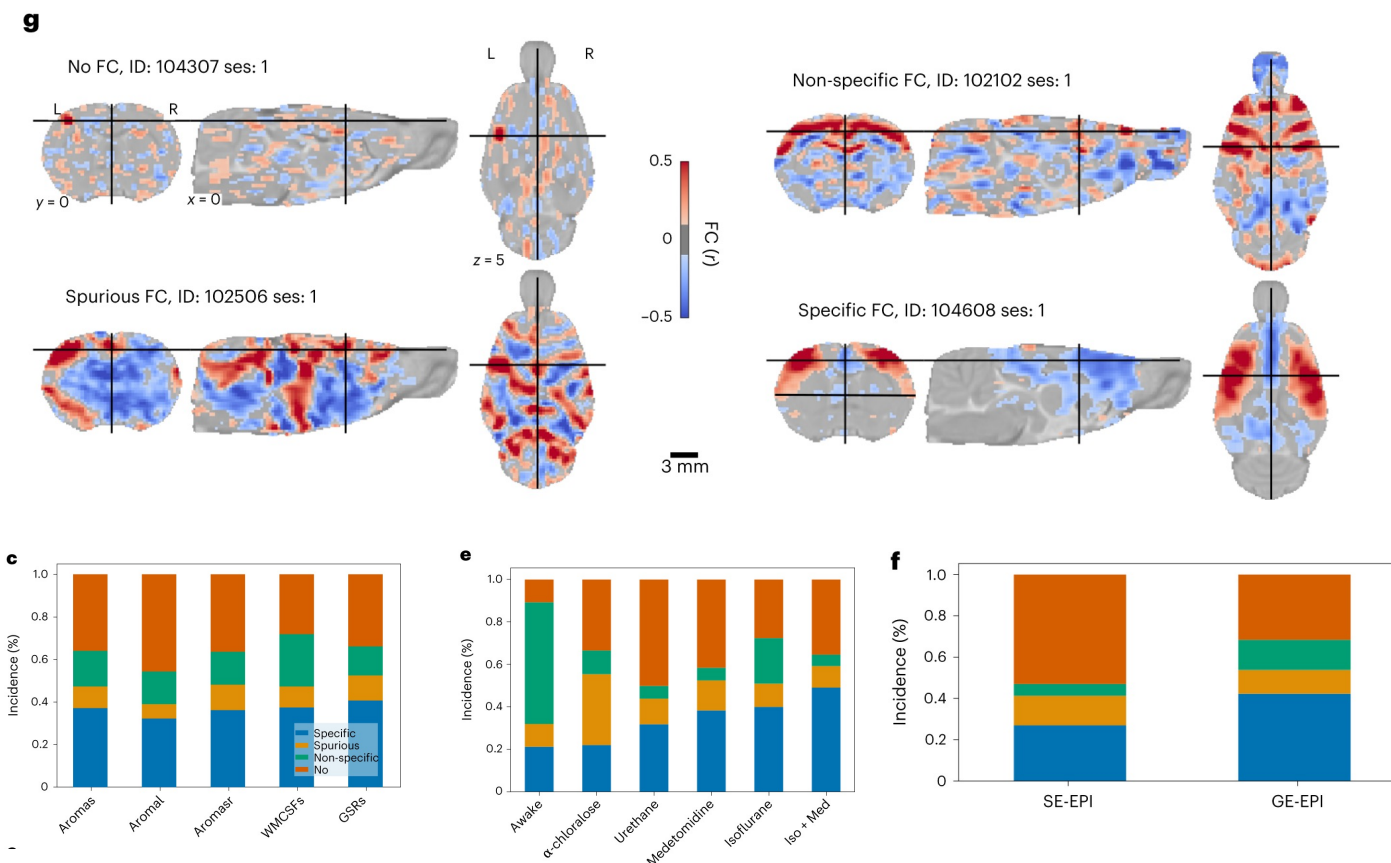
Resource | [Published: 27 March 2023](#)

A consensus protocol for functional connectivity analysis in the rat brain

[Joanes Grandjean](#) ✉, [Gabriel Desrosiers-Gregoire](#), [Cynthia Anckaerts](#), [Diego Angeles-Valdez](#), [Fadi Ayad](#), [David A. Barrière](#), [Ines Blockx](#), [Aleksandra Bortel](#), [Margaret Broadwater](#), [Beatriz M. Cardoso](#), [Marina Célestine](#), [Jorge E. Chavez-Negrete](#), [Sangcheon Choi](#), [Emma Christiaen](#), [Perrin Clavijo](#), [Luis Colon-Perez](#), [Samuel Cramer](#), [Tolomeo Daniele](#), [Elaine Dempsey](#), [Yujian Diao](#), [Arno Doelemeyer](#), [David Dopfel](#), [Lenka Dvořáková](#), [Claudia Falfán-Melgoza](#), ... [Andreas Hess](#) [+ Show authors](#)

[Nature Neuroscience](#) **26**, 673–681 (2023) | [Cite this article](#)

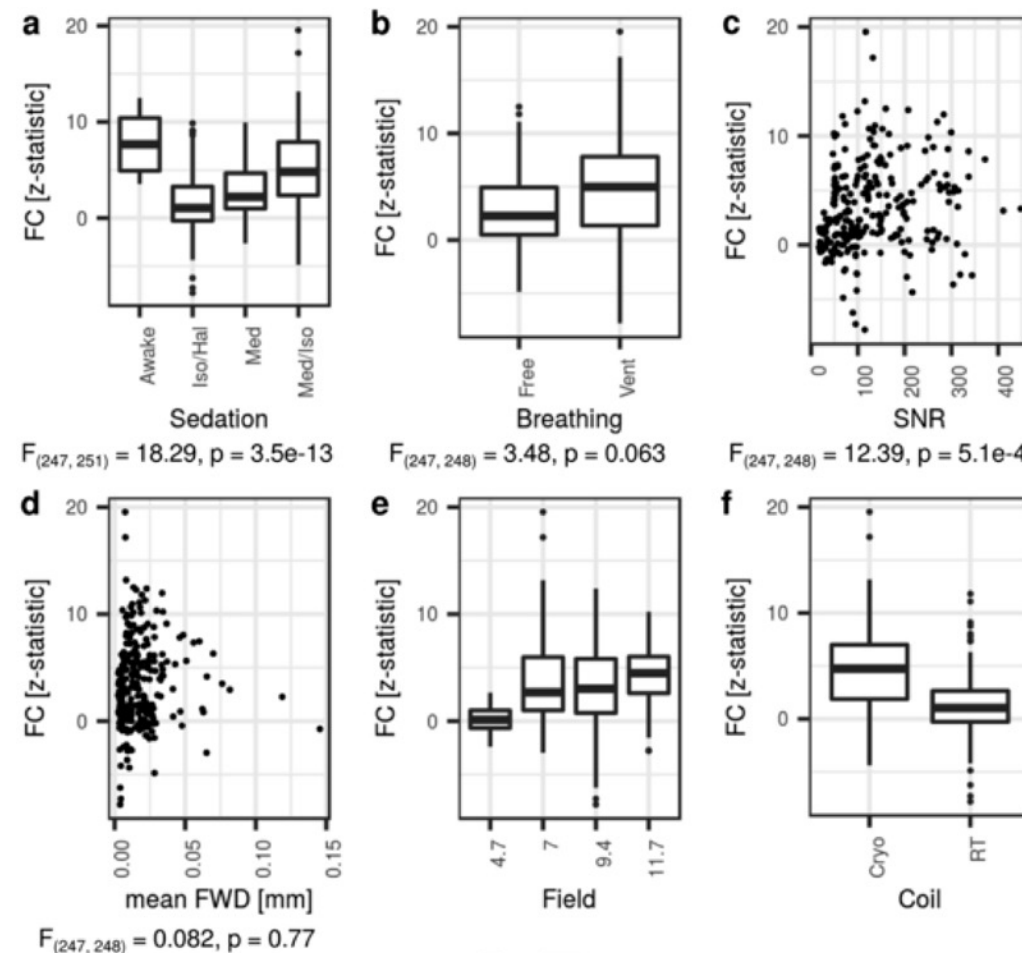
4218 Accesses | 1 Citations | 80 Altmetric | [Metrics](#)



HOW TO GET REPRODUCIBLE FMRI DATA?

Some rules of thumb

- Med/Iso anaesthesia protocols performs better
- Ventilation and head-motion: not too important
- Strive for High SNR
- High field (>7T)
- GE-EPI > SE-EPI
- Awake: higher FC but likely not specific

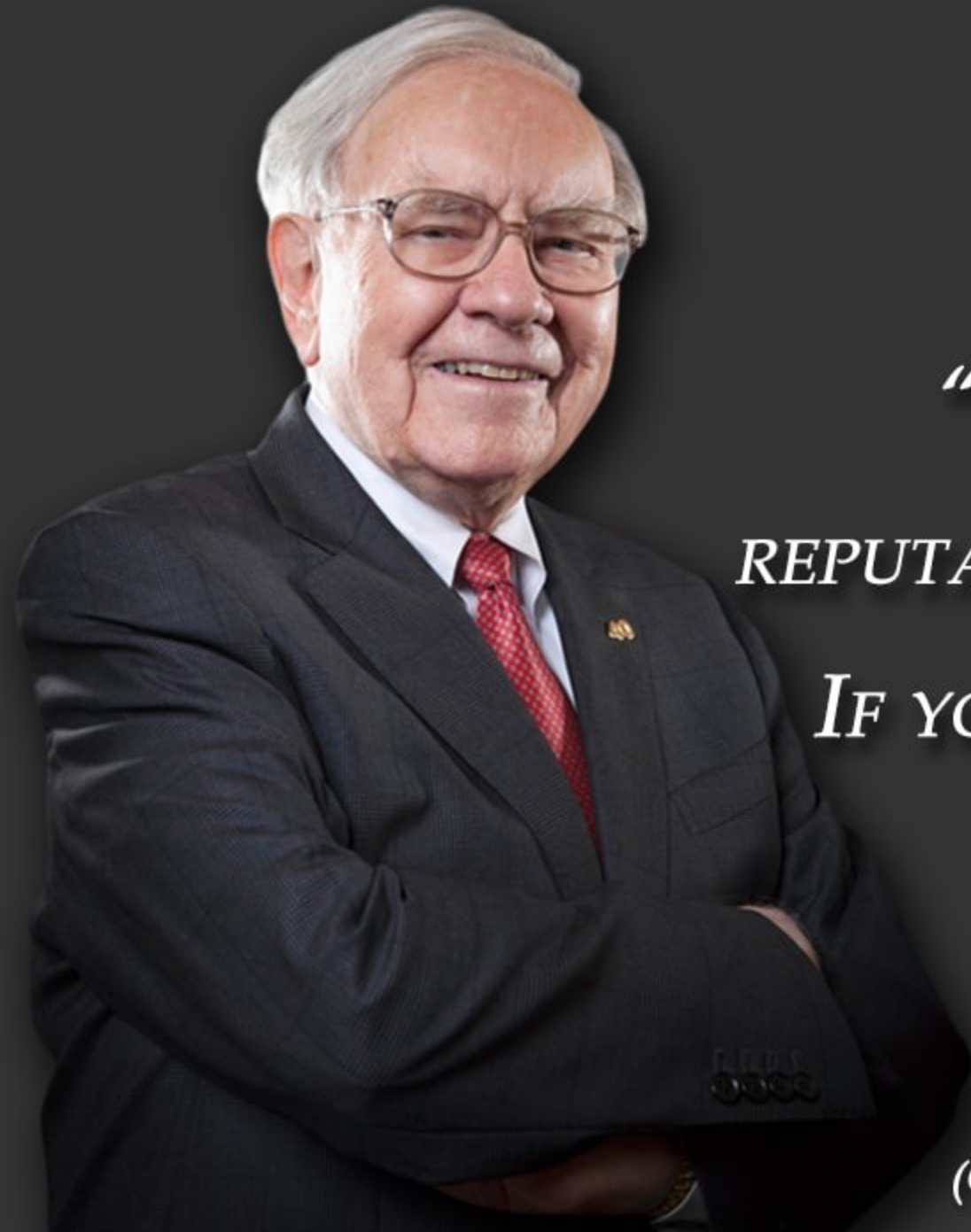


”

*“IT TAKES 20 YEARS TO BUILD A
REPUTATION AND FIVE MINUTES TO RUIN IT.
IF YOU THINK ABOUT THAT, YOU’LL DO
THINGS DIFFERENTLY.”*

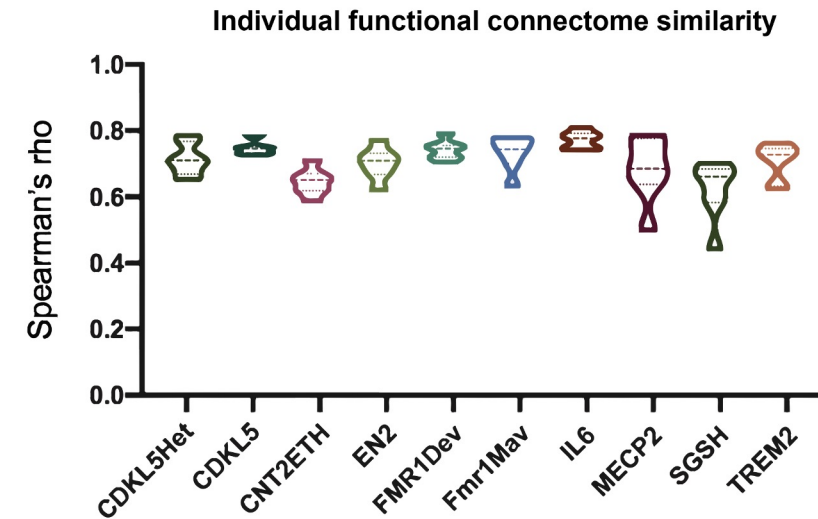
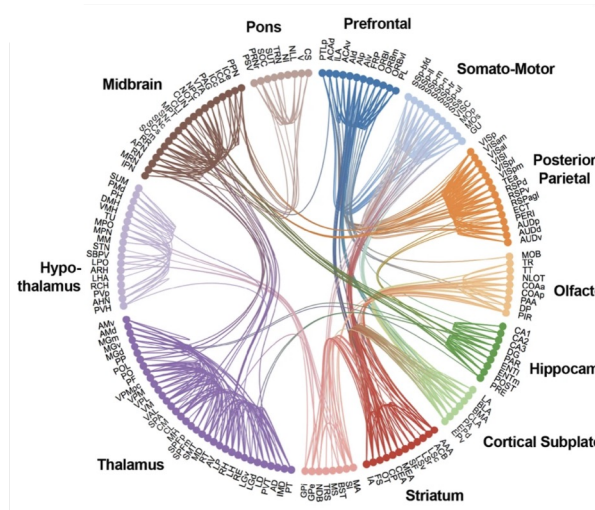
-WARREN BUFFET

(CEO, INVESTOR, BUSINESS TYCOON, & PHILANTHROPIST)



ALWAYS MANUALLY CHECK YOUR DATA!

“If you can’t replicate your findings, would you trust your data?”



High reproducibility ($r > 0.73$) of functional connectivity between **95 wildtype animals** across in **ten different cohorts**

Zerbi et al., J Neuroscience 2014; Zerbi et al., Neurolmage 2015; Haberl et al., Science Adv, 2015; Zerbi-Weismann M et al., Neur Plast. 2016; Arnoldussen et al., J Nutr Biochem, 2016; Sethi - Zerbi et al., Chaos, 2017; Wiesmann et al., Theranostic, 2017; Grandjean-Zerbi et al., J Neuroscience, 2017; Filipello et al., Immunity, 2018; Zerbi et al., C Cortex 2018; Schwab et al., Neurolmage 2018; Chelini-Zerbi et al., J Neuroscience 2019; Zerbi et al., Neurolmage 2019; Zerbi-Floriou-Servou et al., Neuron 2019; Fulcher et al., PNAS, 2019; Grandjean et al., Neurolmage 2020; Balsters-Zerbi et al., eLife 2020; Grimm ... Zerbi, The Neuroscientist, 2020; Markicevic.. Zerbi, C Cortex 2020; Zerbi et al., Mol Psy 2021

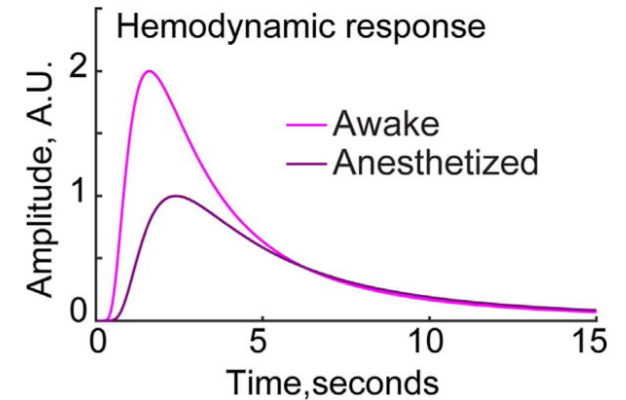
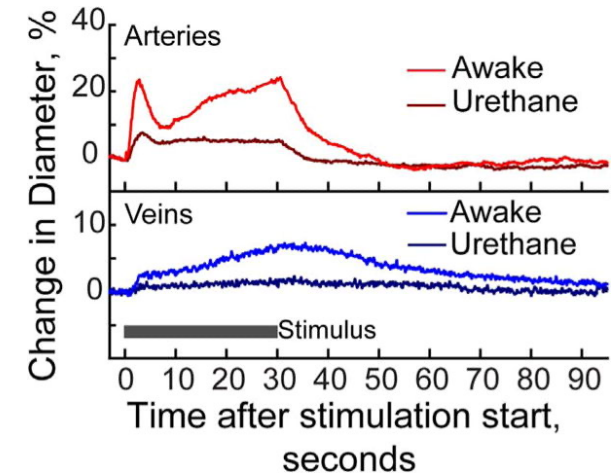
THE ISSUE OF ANESTHESIA

Good because

- Rodents are not usually compliant to human indications
- Massively reduce motion artifacts
- Easy handling and positioning
- Allow high throughput
- Remove “emotional” components from brain states

Bad because

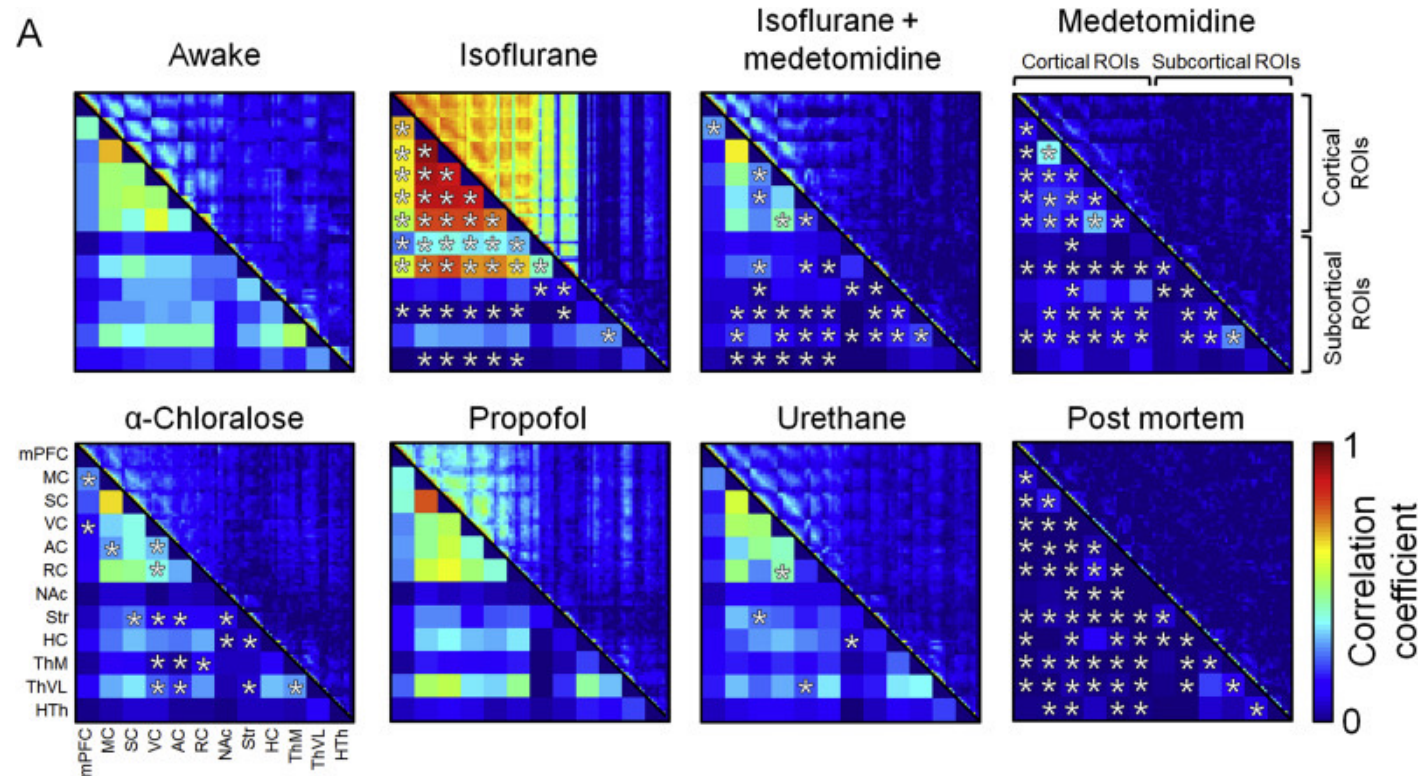
- Can change neurovascular coupling
- Many anaesthetics act on vasoconstriction/dilation



Gao et al., Neuroimage 2017

THE ISSUE OF ANESTHESIA

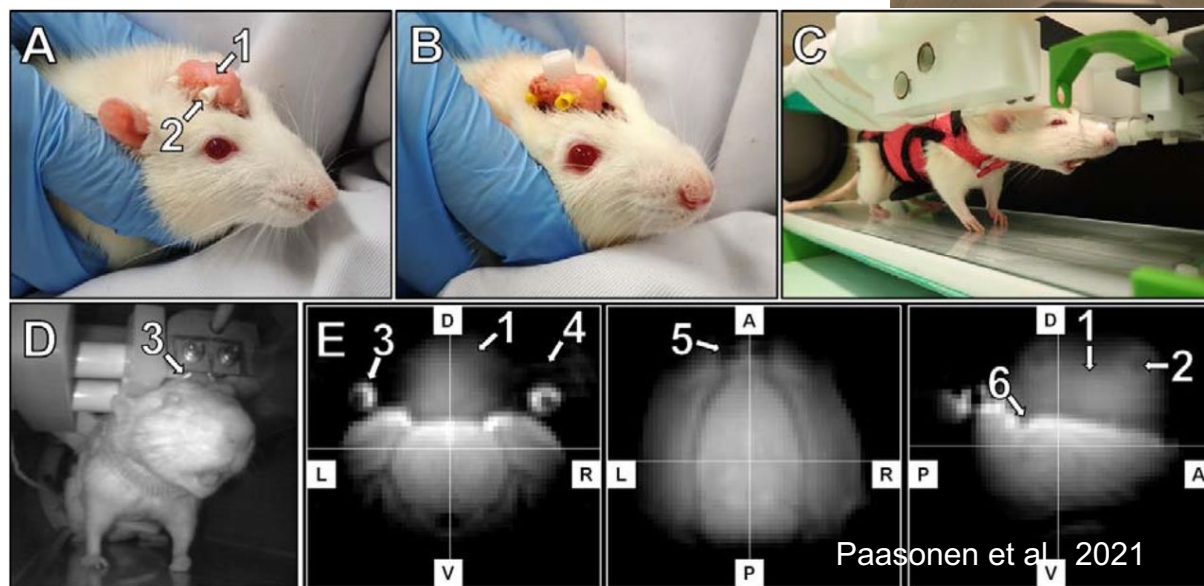
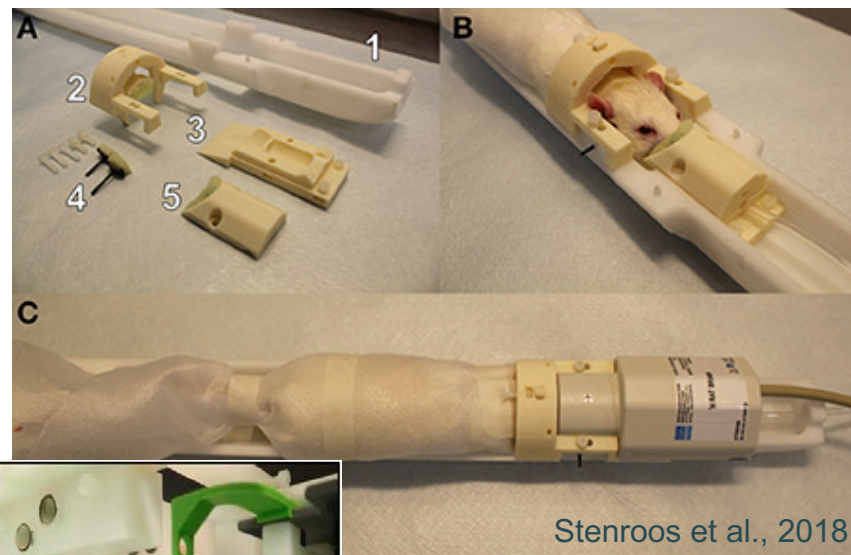
Be aware, all anaesthetics change the “state” of the brain

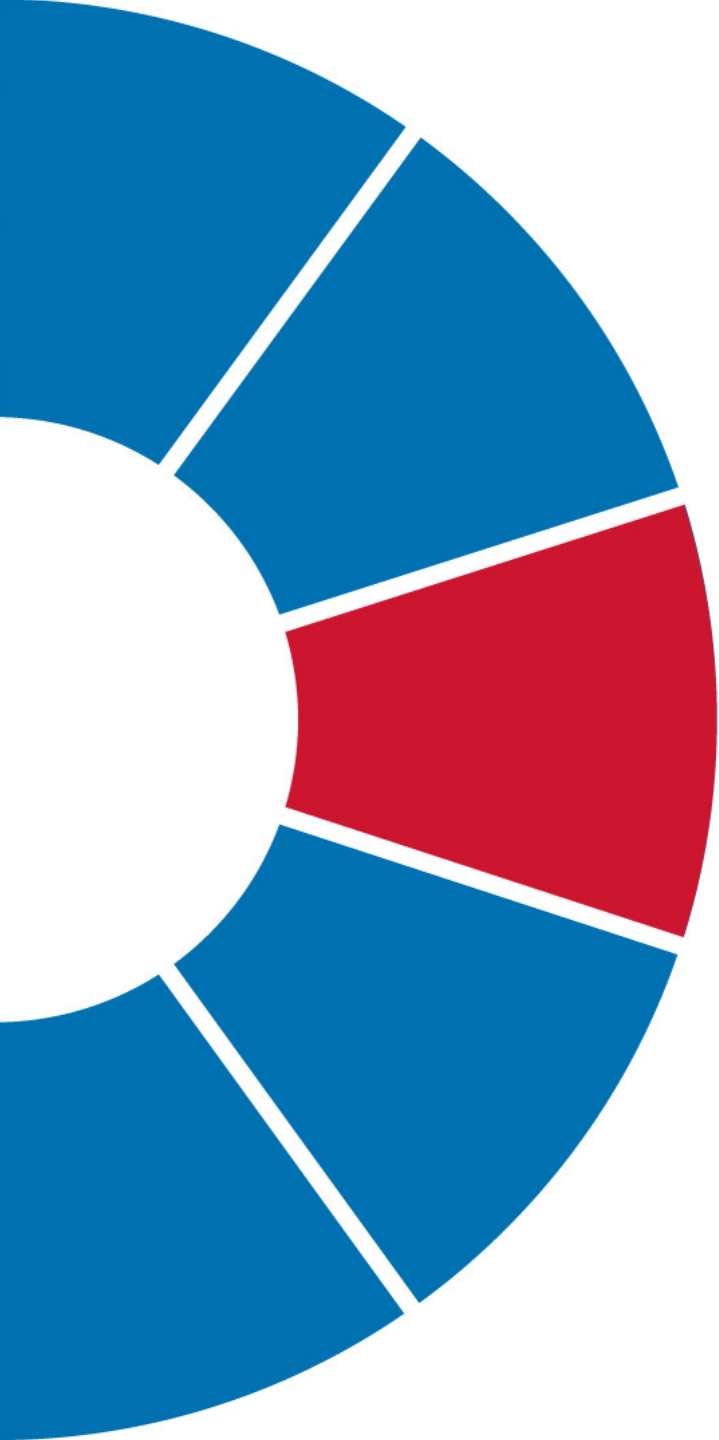


Paasonen et al., Neuroimage 2018

PATH TOWARDS AWAKE IMAGING

Awake functional imaging setup

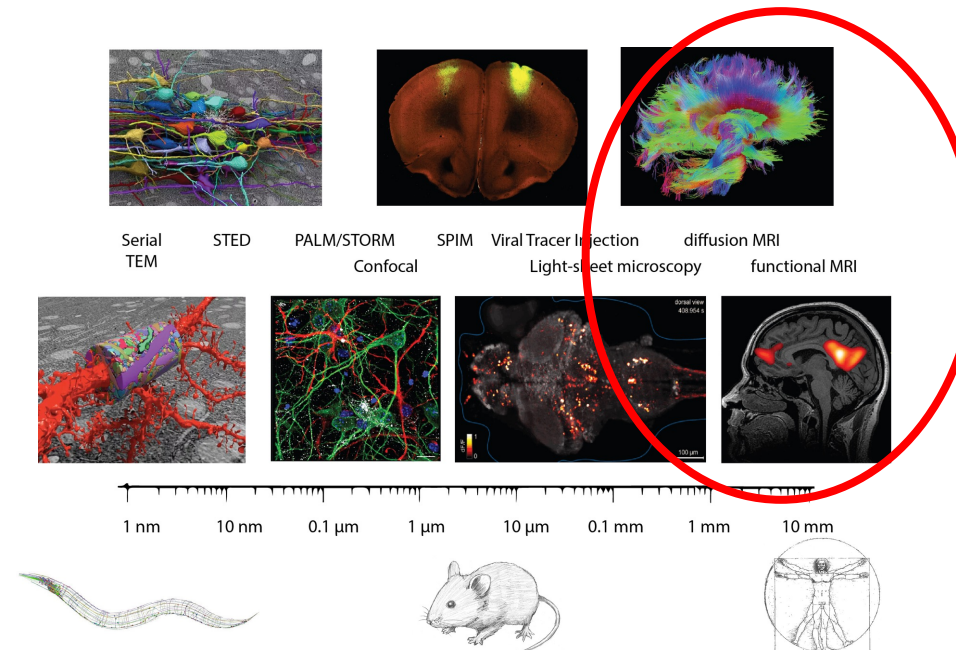




PART 2. THE FUNCTIONAL CONNECTOME IN RODENTS

ALWAYS THINK OF YOUR RESEARCH QUESTION

- **Q:** Is the MRI-based connectome ... meaningful?
- **A:** To answer this question we need to compare it with the current **GOLD STANDARD**



THE MOUSE STRUCTURAL CONNECTOME

A mesoscale connectome of the mouse brain

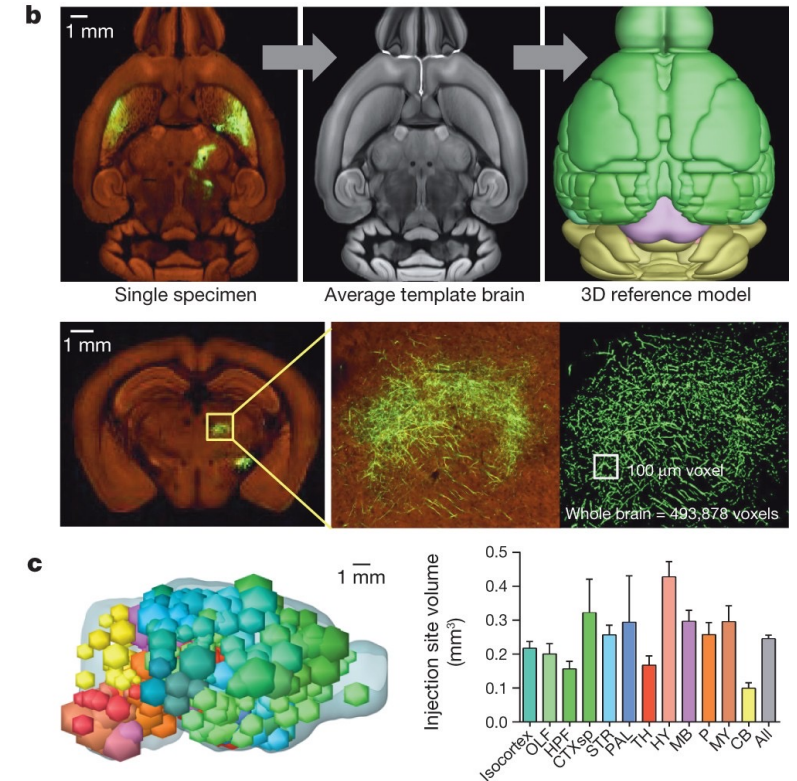
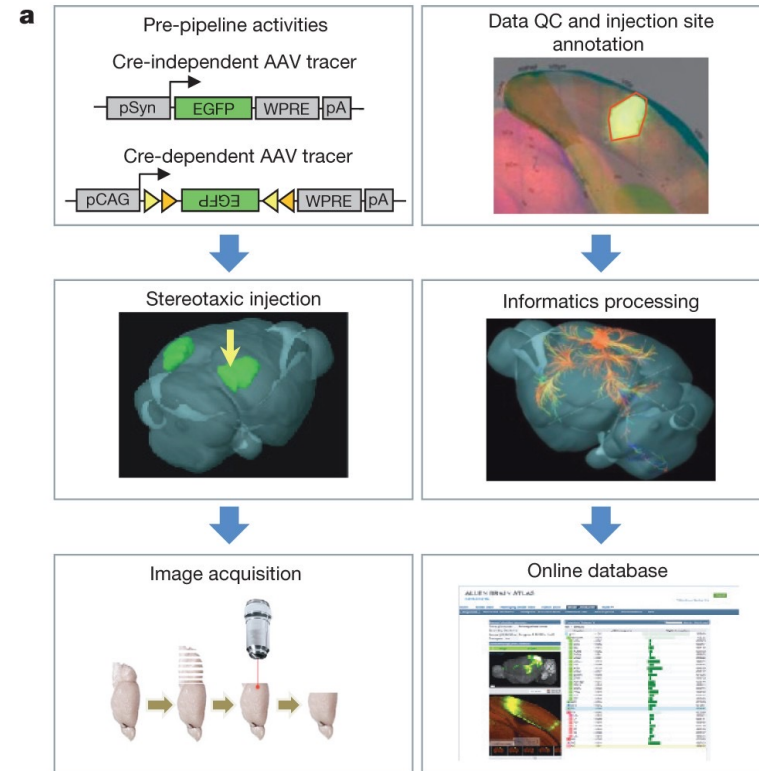
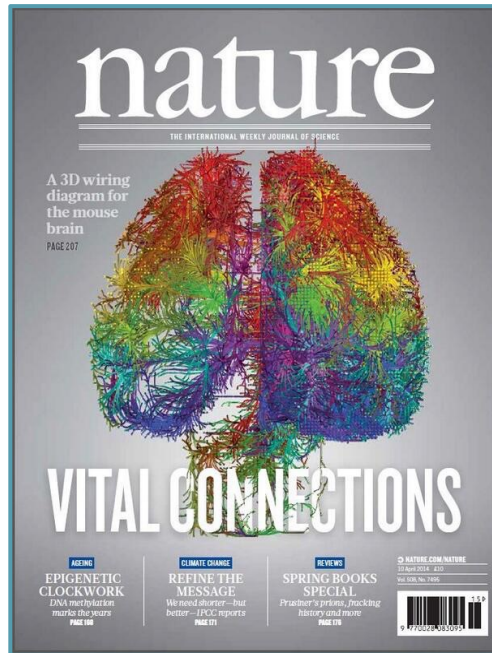
Seung Wook Oh^{1*}, Julie A. Harris^{1*}, Lydia Ng^{1*}, Brent Winslow¹, Nicholas Cain¹, Stefan Mihalas¹, Quanxin Wang¹, Chris Lau¹, Leonard Kuan¹, Alex M. Henry¹, Marty T. Mortrud¹, Benjamin Ouellette¹, Thuc Nghi Nguyen¹, Staci A. Sorensen¹, Clifford R. Slaughterbeck¹, Wayne Wakeman¹, Yang Li¹, David Feng¹, Anh Ho¹, Eric Nicholas¹, Karla E. Hirokawa¹, Phillip Bohn¹, Kevin M. Joines¹, Hanchuan Peng¹, Michael J. Hawrylycz¹, John W. Phillips¹, John G. Hohmann¹, Paul Wohnoutka¹, Charles R. Gerfen², Christof Koch¹, Amy Bernard¹, Chinh Dang¹, Allan R. Jones¹ & Hongkui Zeng¹

- Recombinant adeno-associated virus (AAV) expressing EGFP as anterograde tracer to map axonal projections
- EGFP-labelled axonal projections were systematically imaged using a two-photon tomography system



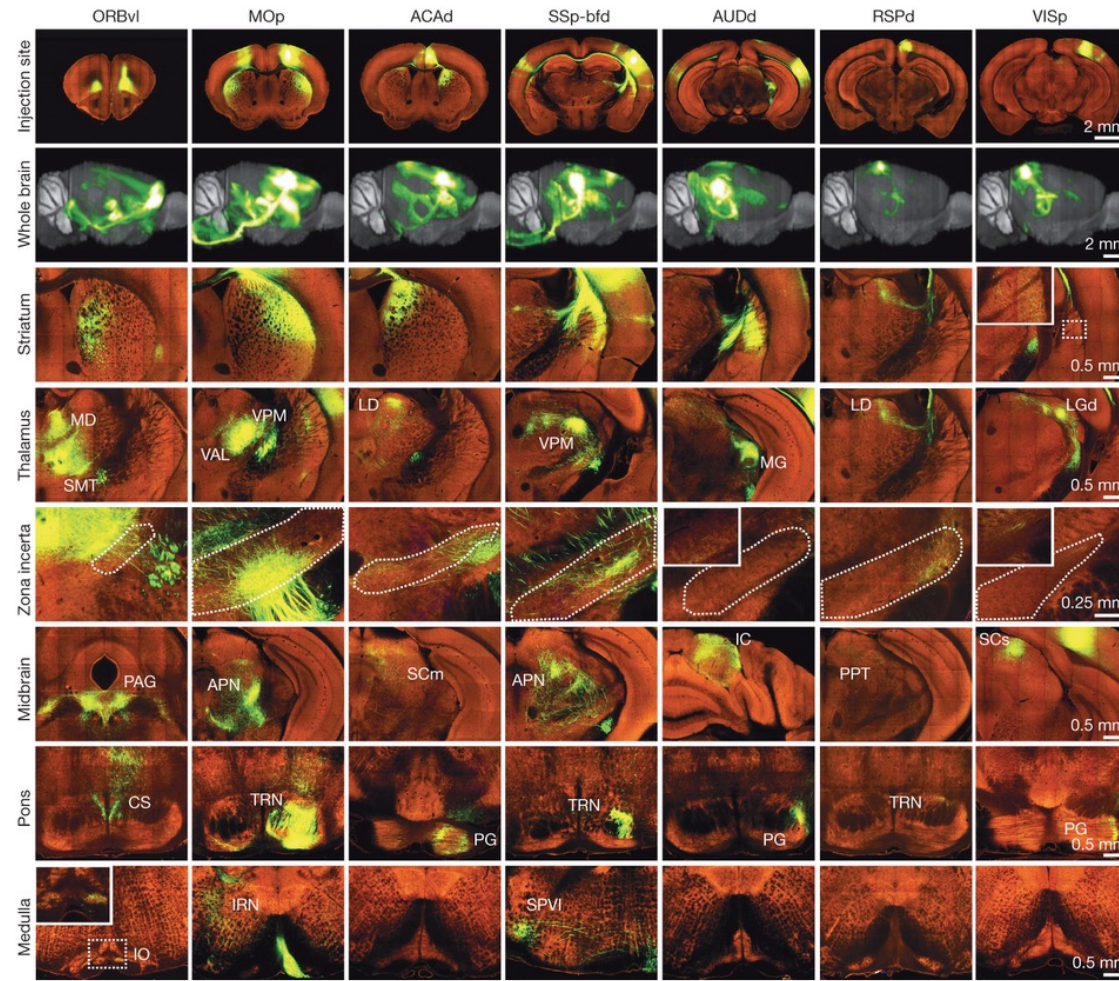
THE MOUSE STRUCTURAL CONNECTOME

Tracer Injection data (Structural Connectome)



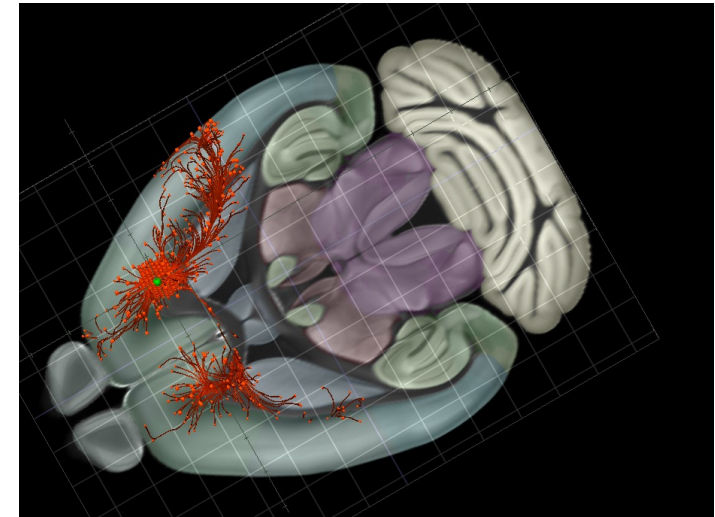
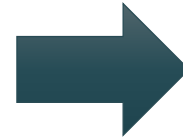
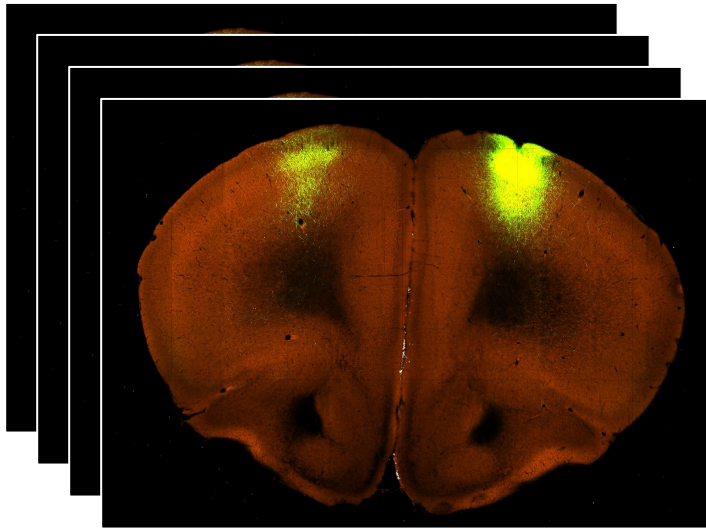
Oh et al., Nature 2014

THE MOUSE STRUCTURAL CONNECTOME



Oh et al., Nature 2014

THE MOUSE STRUCTURAL CONNECTOME

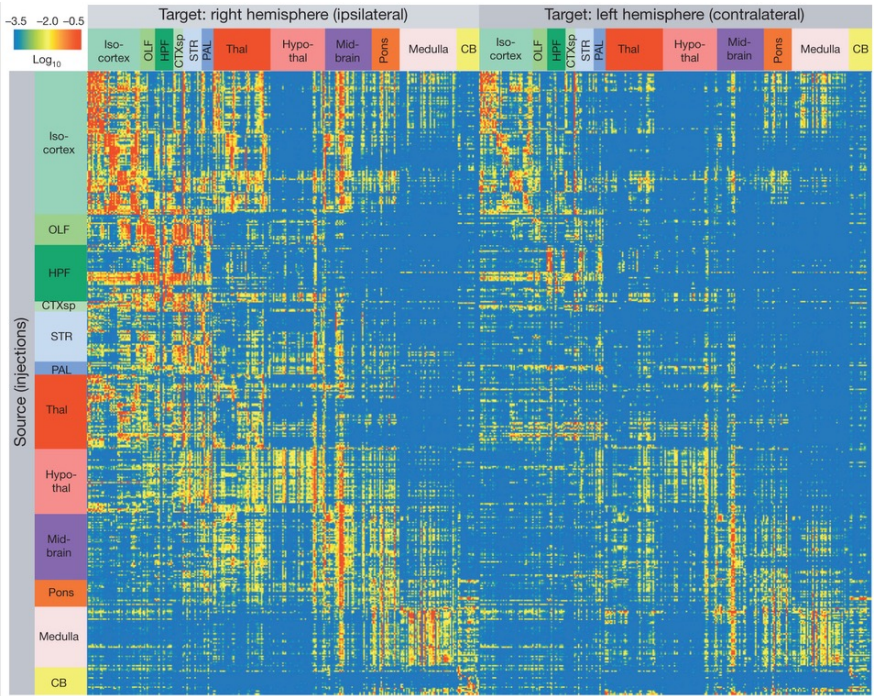
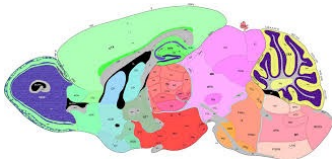
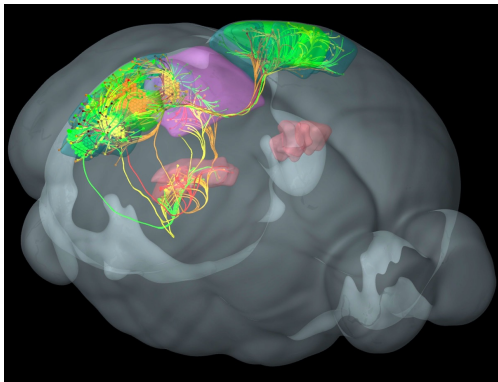
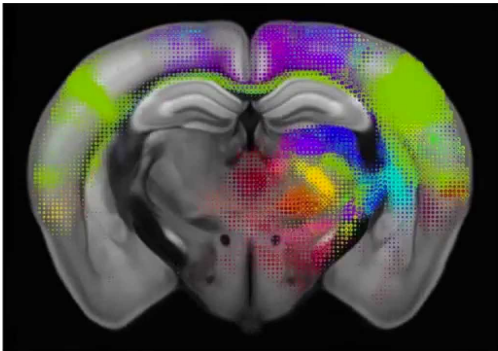
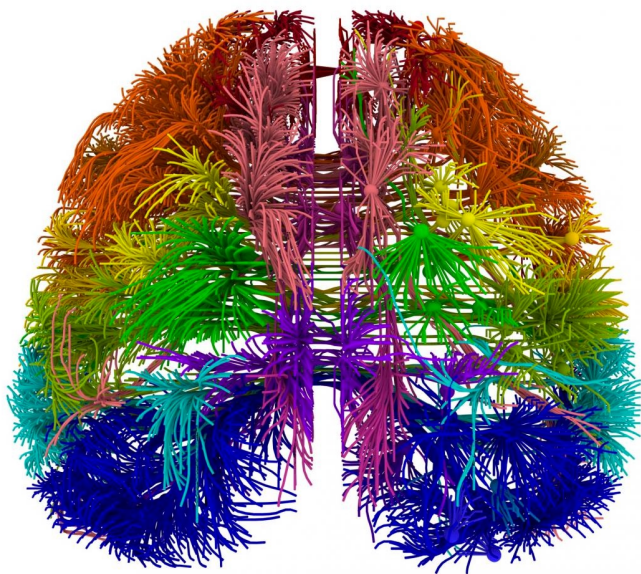


One mouse, one tracing experiment

Kuan L., et al., Neuroinformatics of the
Allen Mouse Brain Connectivity Atlas.
Methods. 2015 Feb;73:4-17.

THE MOUSE STRUCTURAL CONNECTOME

A GREAT RESOURCE, BUT NOT SCALABLE!



THE MOUSE STRUCTURAL CONNECTOME

ALLEN BRAIN ATLAS
DATA PORTAL

HOME

MOUSE CONNECTIVITY

TOOLS

Search...

PROJECTIONBDA/AAV COMPARISONTRANSGENIC CHARACTERIZATIONREFERENCE DATABRAIN EXPLORERDOCUMENTATIONHELP

Source Search

Target Search

Spatial Search

Filter Source Structure(s)
grey x retina x

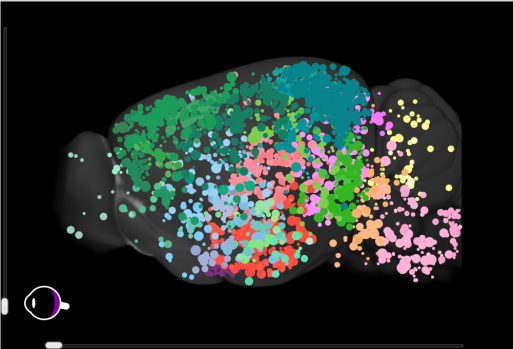
Filter Mouse Line
all (default)

Filter Tracer Type
all (default)

Primary Structure Only ☒ Intrinsic Signal Images ☐

Search Results

Injection Sites - Showing 2994 Experiments



Browse the Data

Narrow results with a source structure filter

Example: Isocortex, Hippocampal formation, Striatum, Pallidum, Thalamus, Hypothalamus, Pons, Medulla, Primary visual area, Primary somatosensory area, Primary motor area, Retina

Allen Mouse Brain Connectivity Atlas

Search the data

Use filters to narrow results to specific brain regions and mouse lines.

Click on an injection site marker on the map or result table row to view image data.

View the results table for the current search results by closing the browse panel.

About the Projection data

Image data detailing axonal projections labeled by rAAV tracers and visualized using serial two-photon tomography

- Specific anatomic regions throughout the brain
- Numerous defined neuronal populations
- Image stacks obtained by serial two-photon tomography

[more]

About the Allen Mouse Brain Connectivity Atlas

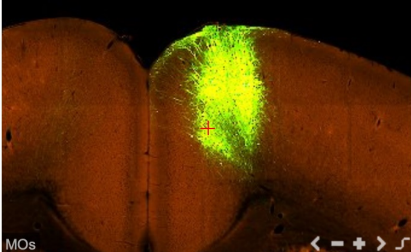
A high-resolution map of neural connections in the mouse brain, built on an array of transgenic mice genetically engineered to target specific cell types

Key features

- Projection Mapping image data detailing axonal projections labeled by viral tracers
- BDA vs. AAV Comparison dataset for comparing conventional and viral tracing methods
- Transgenic Characterization data detailing transgene

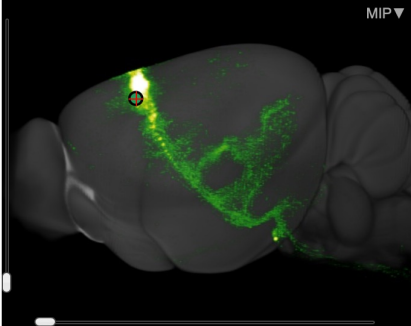
Experiment 277957202 - MOs

Section Images



MOs

Projection Density



MIP

Transgenic Line

Htr2a-Cre_KM207

Scattered expression throughout the brain. Enriched in layers 5 and 6b of cortex. Expression in restricted populations in septal complexes, hypothalamus and cerebellum. View [transgenic characterization](#).

AAV Injection Structures

MOs

ACAd

<https://connectivity.brain-map.org>
A GREAT RESOURCE, BUT NOT SCALABLE!

C I B M . C H

© CIBM | Center for Biomedical Imaging

42

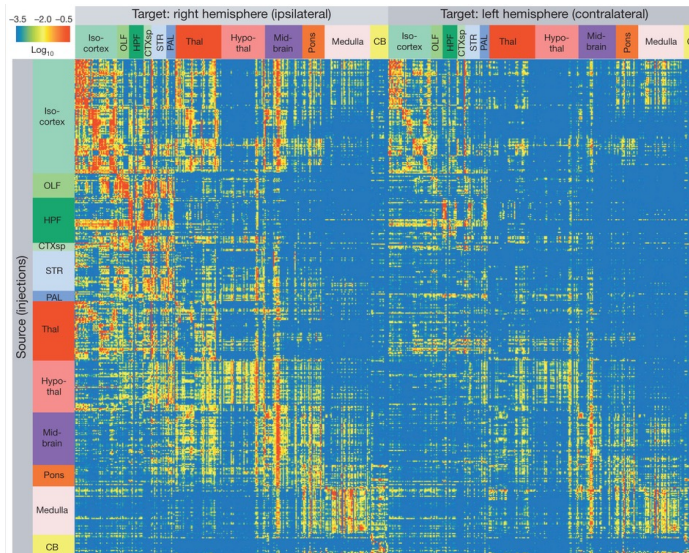
HOW GOOD IS DIFFUSION MRI CONNECTOMICS?

ORIGINAL ARTICLE

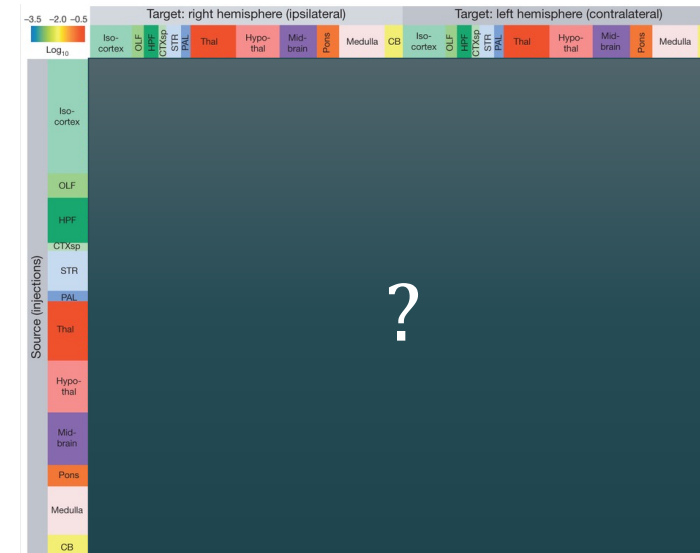
A Diffusion MRI Tractography Connectome of the Mouse Brain and Comparison with Neuronal Tracer Data

Evan Calabrese, Alexandra Badea, Gary Cofer, Yi Qi, and G. Allan Johnson

Center for In Vivo Microscopy, Duke University Medical Center, Department of Radiology,
Duke University Medical Center, Durham, NC 27710, USA



Allen brain mesoscale connectivity matrix

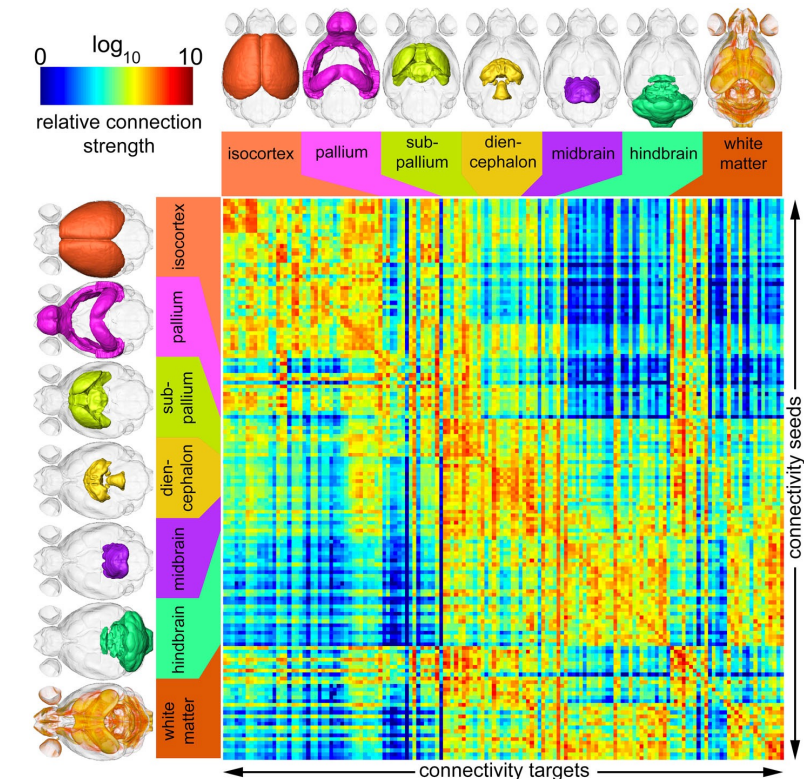
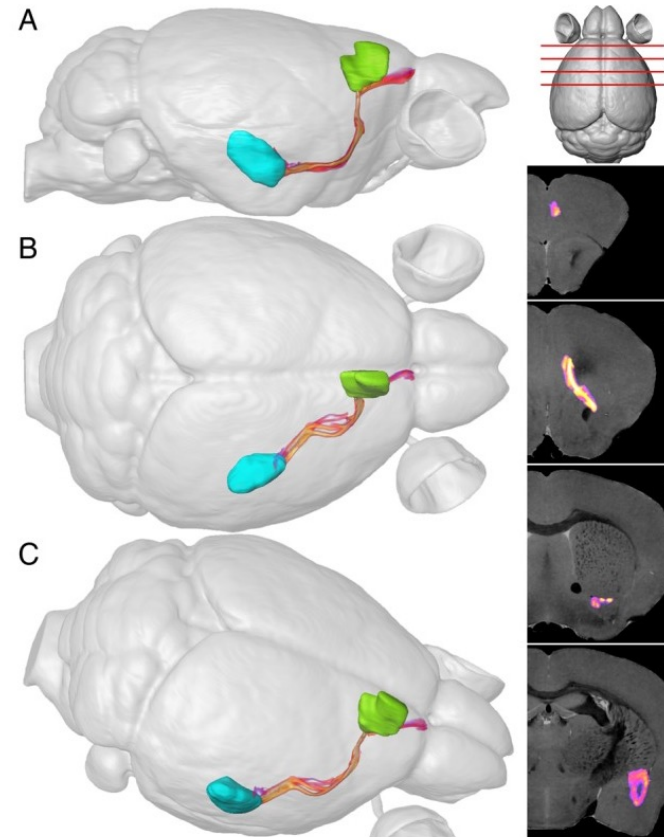


Diffusion-weighted macroscale connectivity matrix

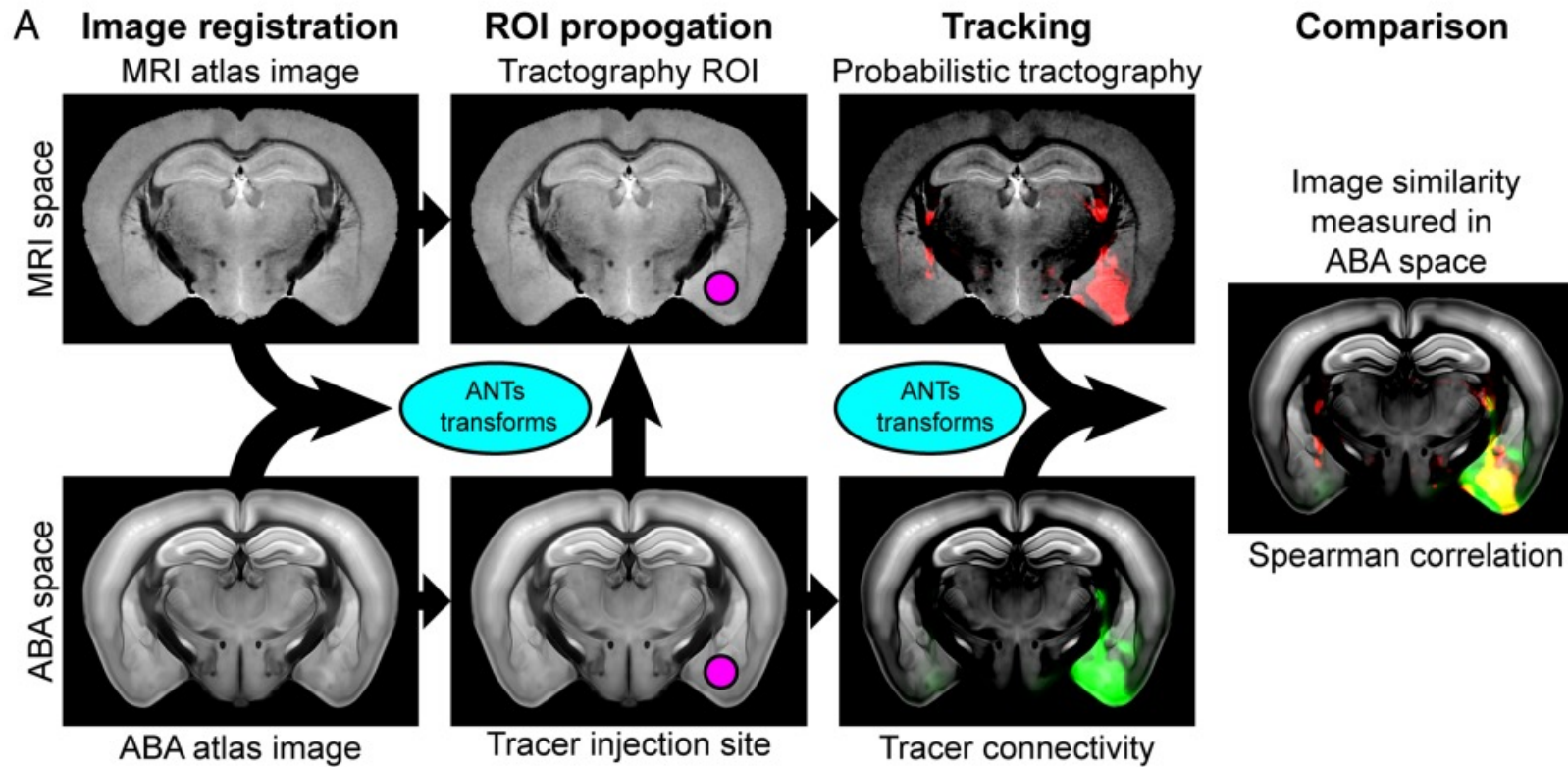
HOW GOOD IS DIFFUSION MRI CONNECTOMICS?



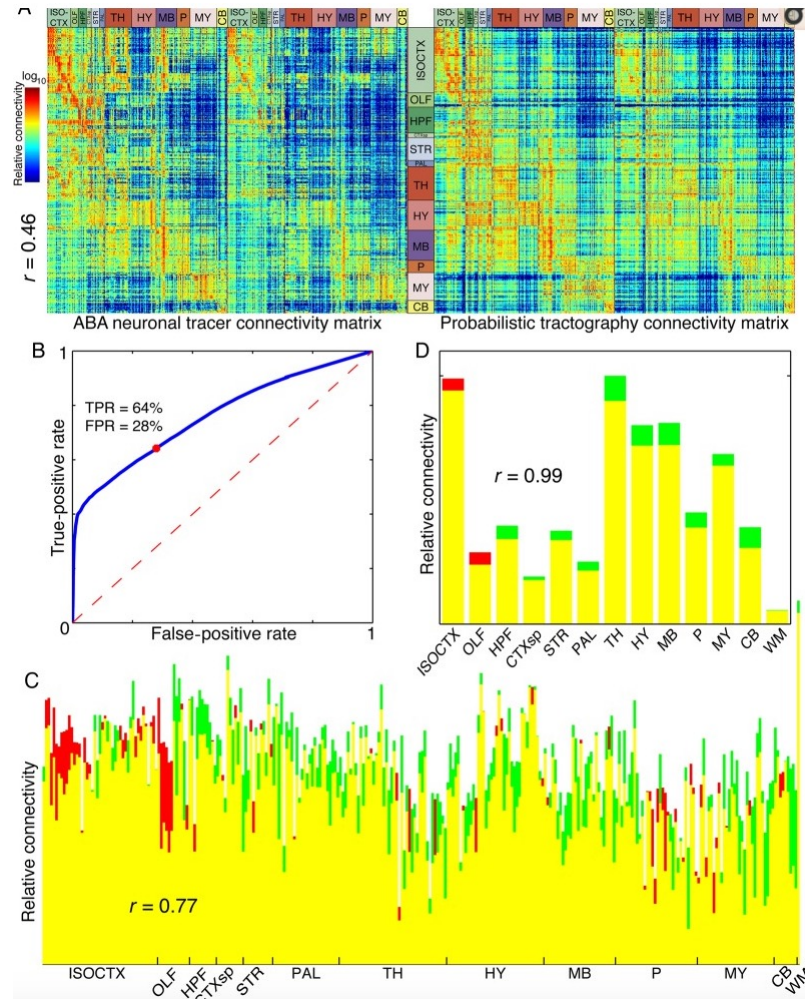
2 mice (Ex-vivo)
b-value = 4000 s/mm²
Resolution = 43um isotropic
120 directions + 11b0
Acquisition time = 235h
FSL PROBTRACKX



HOW GOOD IS DIFFUSION MRI CONNECTOMICS?



HOW GOOD IS DIFFUSION MRI CONNECTOMICS?



- Whole brain mouse DWI-tractography connectome
- Good overall similarity with Allen Institute tracer-connectome
- Requires ultra-high resolution (43um isotropic)
- 235 hours scans (ex-vivo) (!!)

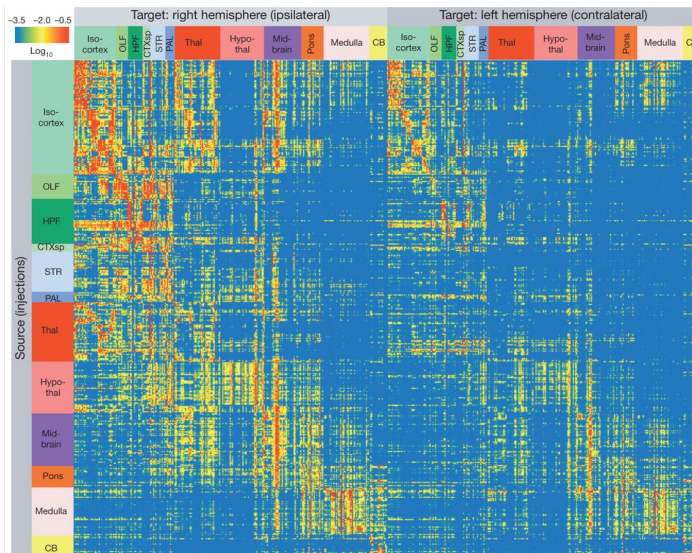
THE MOUSE FUNCTIONAL CONNECTOME

Research Articles, Systems/Circuits

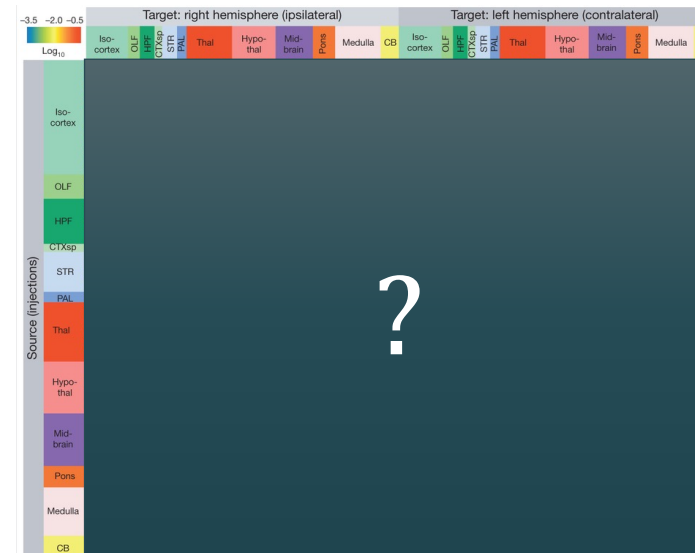
Structural Basis of Large-Scale Functional Connectivity in the Mouse

Joanes Grandjean, Valerio Zerbi, Joshua Henk Balsters, Nicole Wenderoth, and Markus Rudin

Journal of Neuroscience 23 August 2017, 37 (34) 8092-8101; DOI: <https://doi.org/10.1523/JNEUROSCI.0438-17.2017>

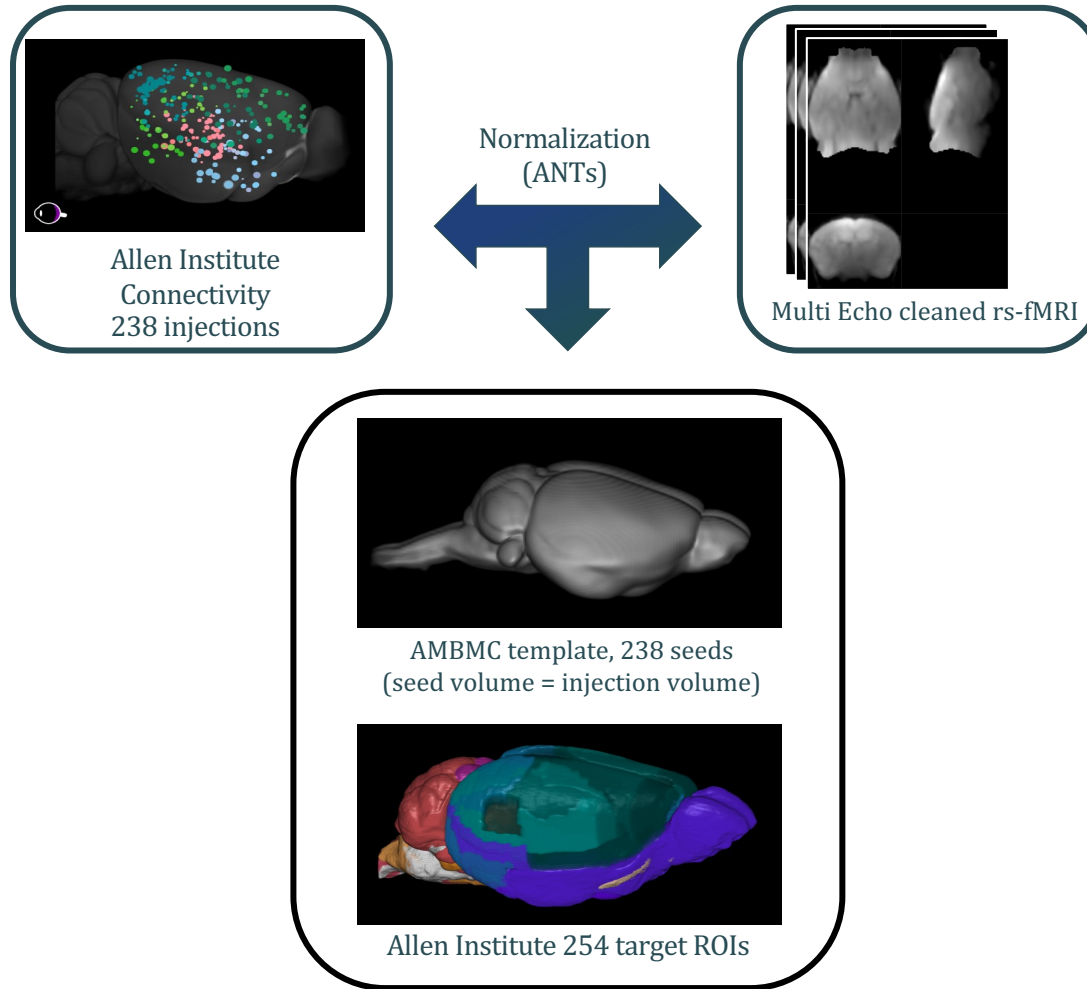


Allen brain mesoscale connectivity matrix



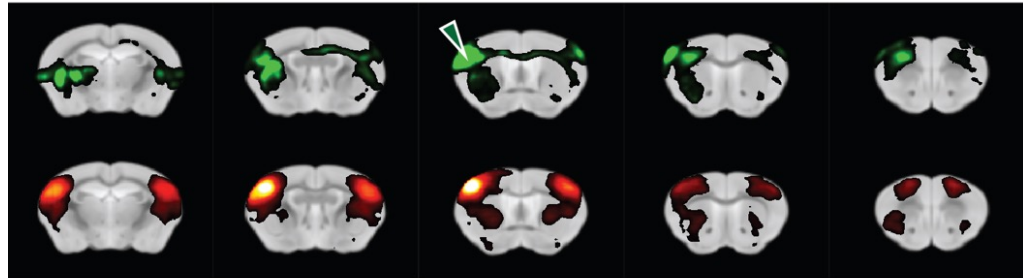
Resting-state fMRI connectivity matrix

THE MOUSE FUNCTIONAL CONNECTOME

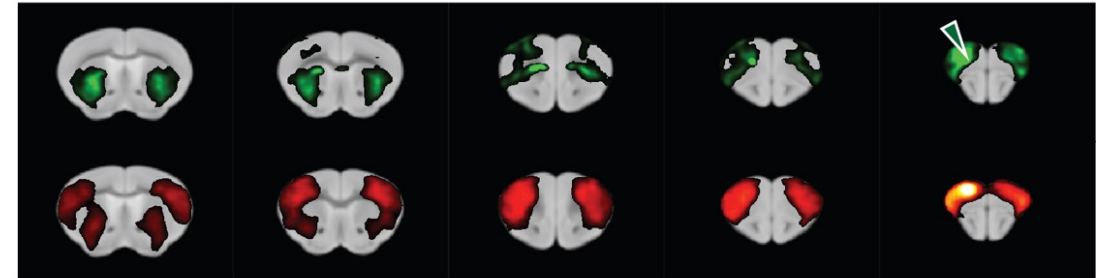


- 238 viral tracer experiments
- 238 seed-based rs-fMRI experiments
- 14 mice *in vivo*
- 10 minutes scans
- 9.4T with Cryocoil
- GE-EPI (MultiEcho)

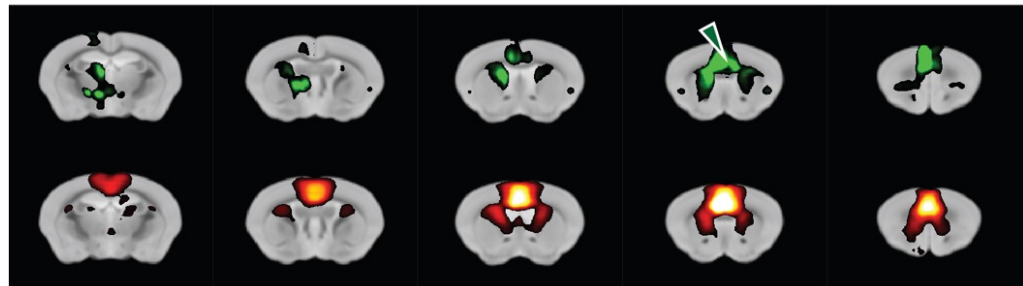
THE MOUSE FUNCTIONAL CONNECTOME



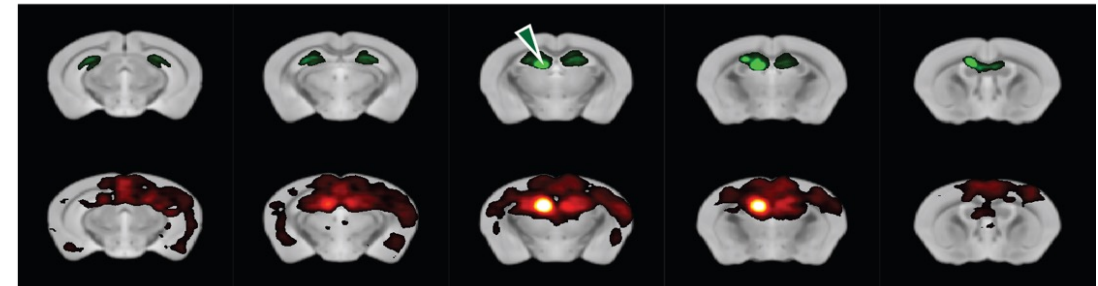
Injection ID: 112162251 Target: SSp-bfd



Injection ID: 100140756 Target: MOs



Injection ID: 112514202 Target: ACAv



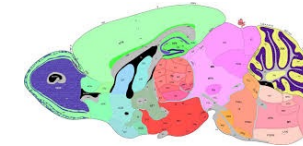
Injection ID: 100141214 Target: DG

1  100
Tracer's intensity projection [A.U.]

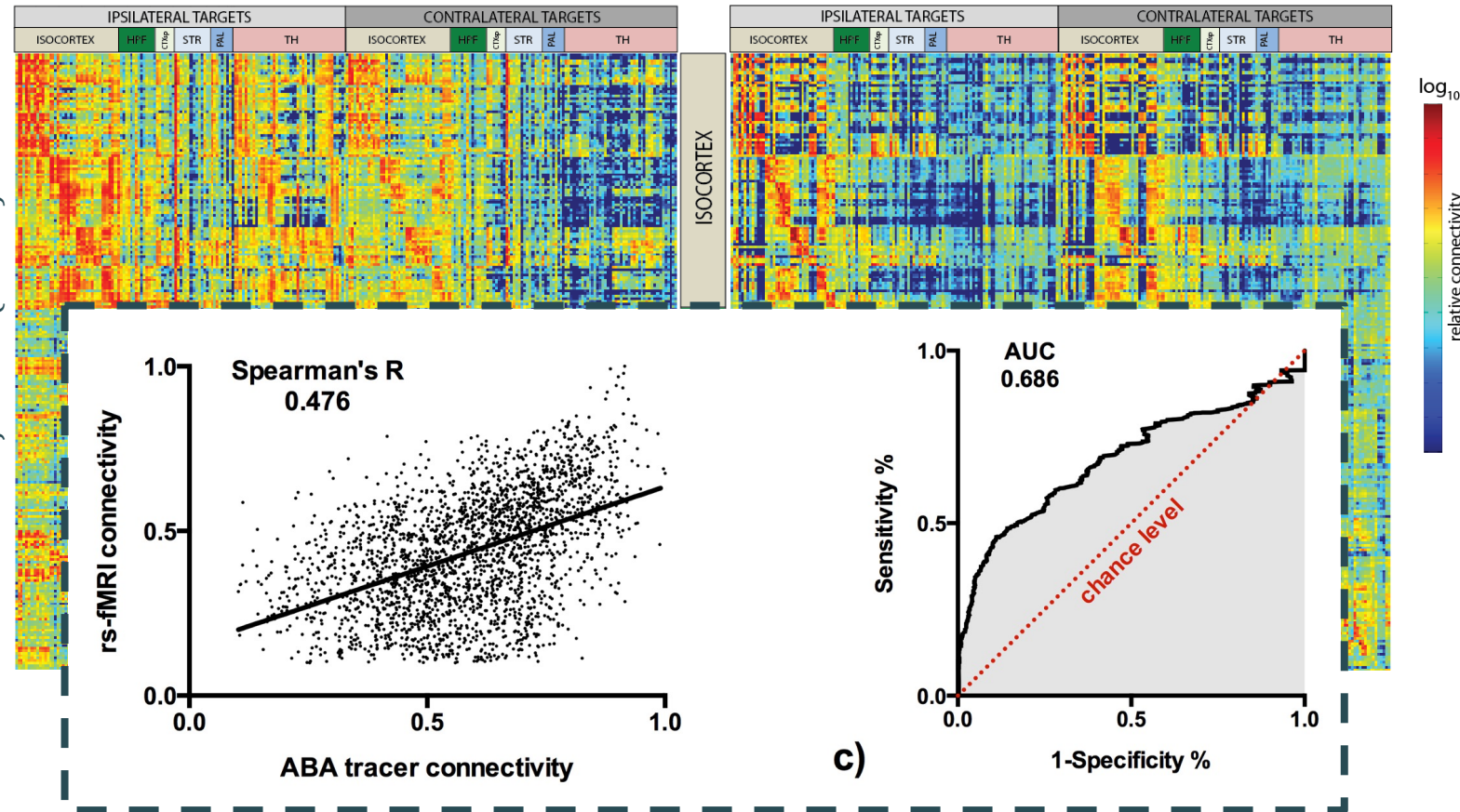
2.7  15
rsfMRI connectivity [Z-score]

THE MOUSE FUNCTIONAL CONNECTOME

Targets ROIs (n=254)

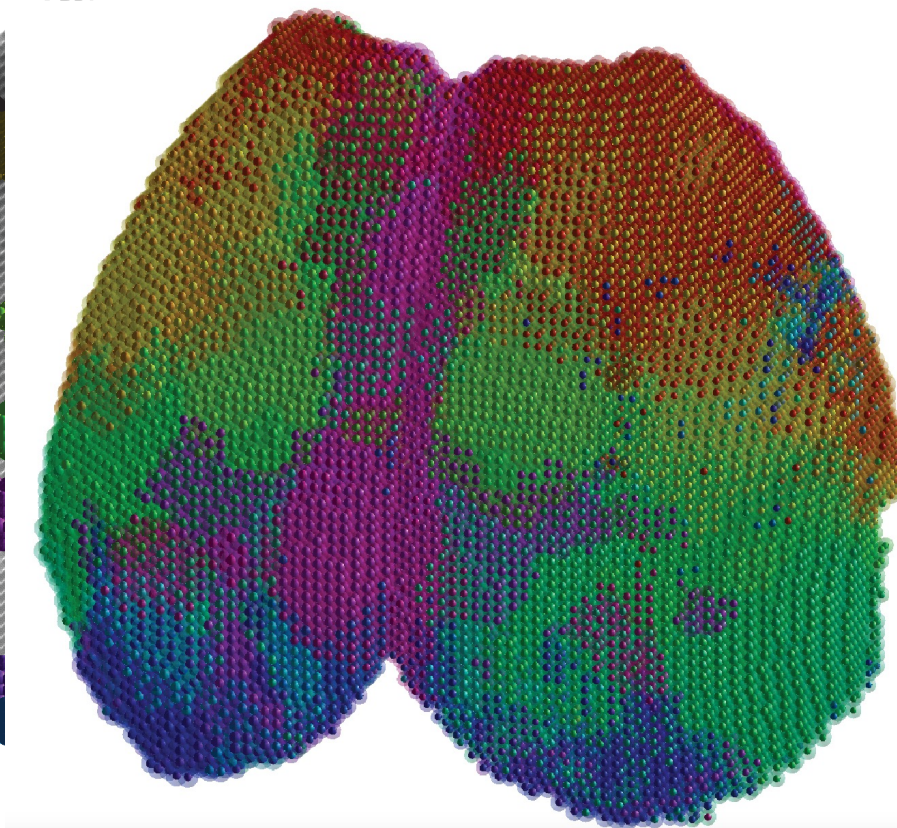
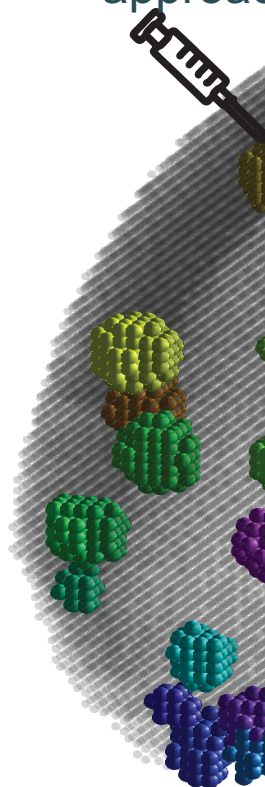


Injections (n=238)



THE MOUSE FUNCTIONAL CONNECTOME

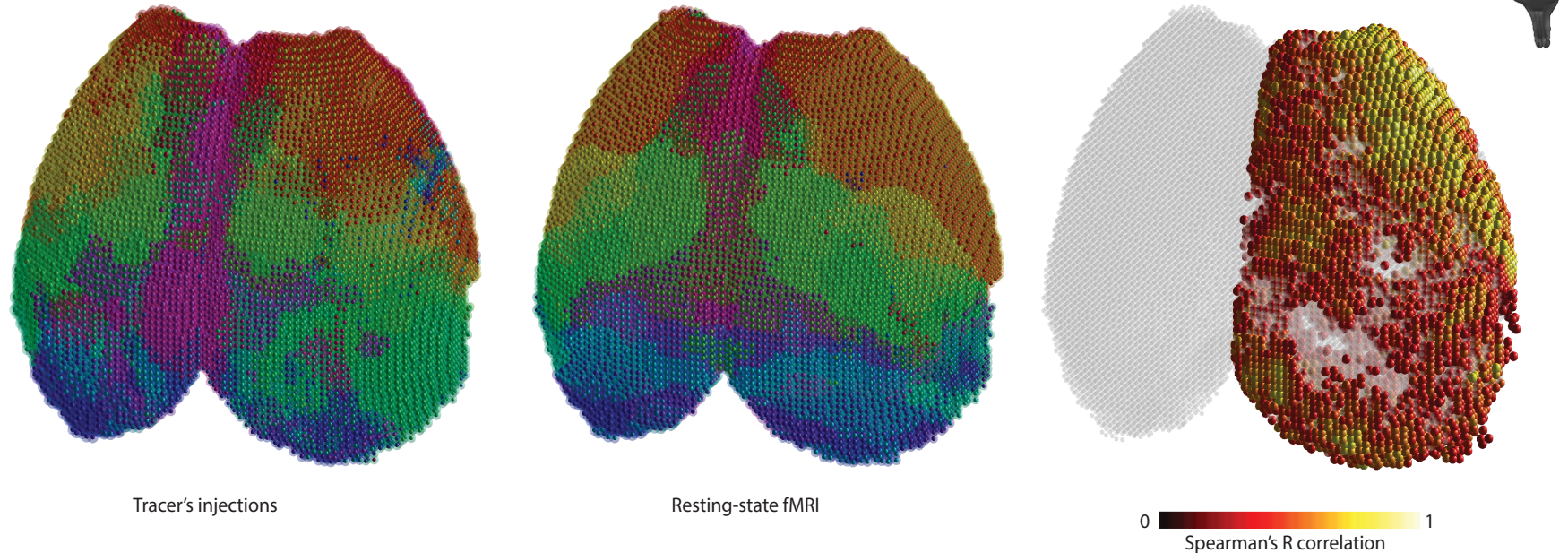
“Winner takes all”
approach



THE MOUSE FUNCTIONAL CONNECTOME

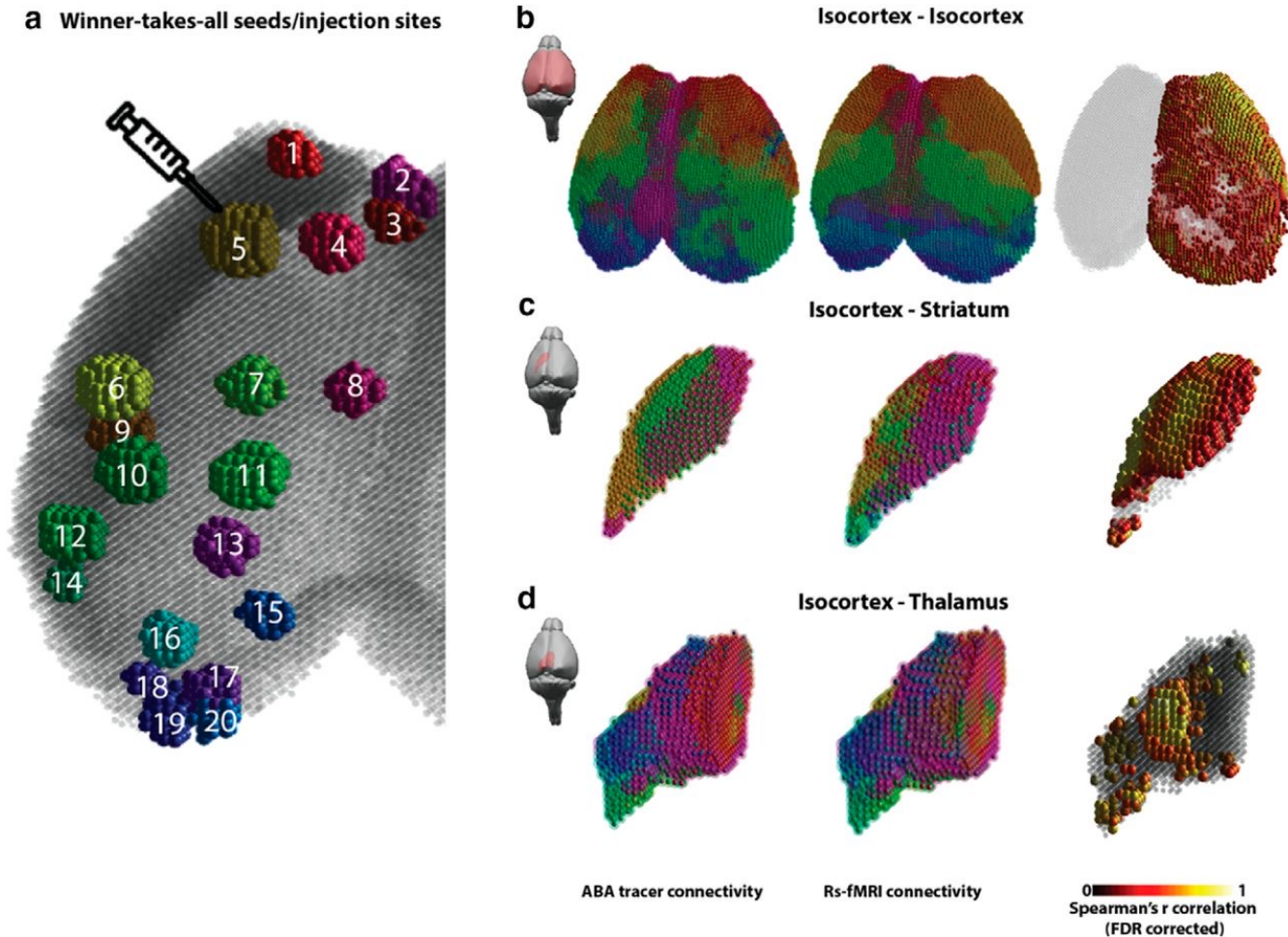
Isocortex topographical maps

Isocortex left --> Isocortex right



86.9% of contralateral isocortical voxel showed significant Spearman's correlation

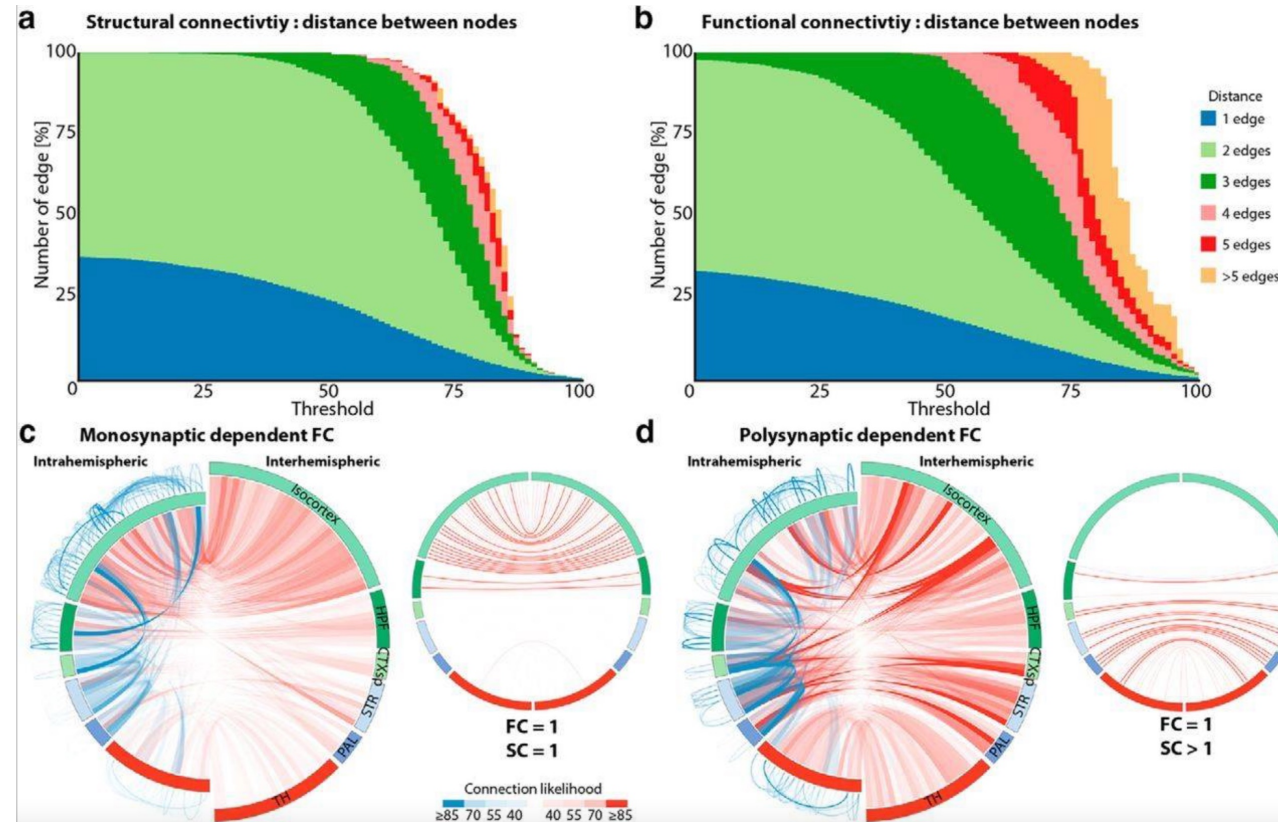
THE MOUSE FUNCTIONAL CONNECTOME



- Whole brain mouse resting-state fMRI connectome
- Good overall similarity with Allen Institute tracer-connectome
- Bad correlation between cortico-thalamic connections
 - Anaesthesia (?)
- 10 minute scans (in-vivo) → SCALABLE

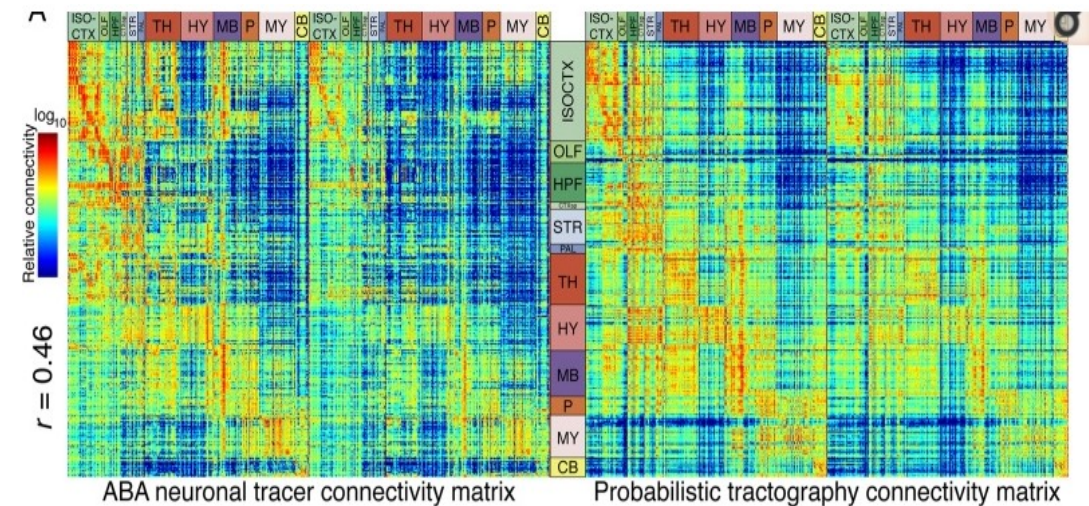
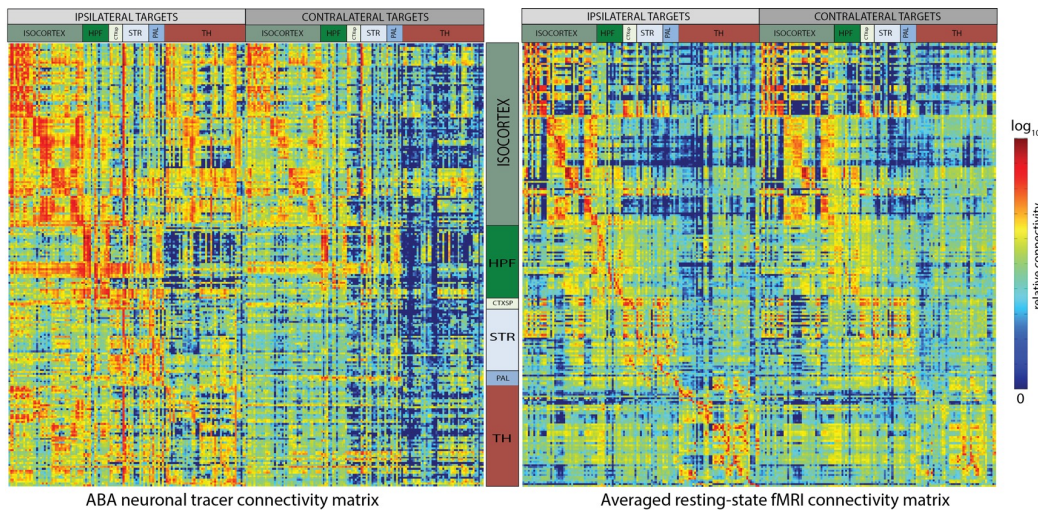
THE MOUSE FUNCTIONAL CONNECTOME

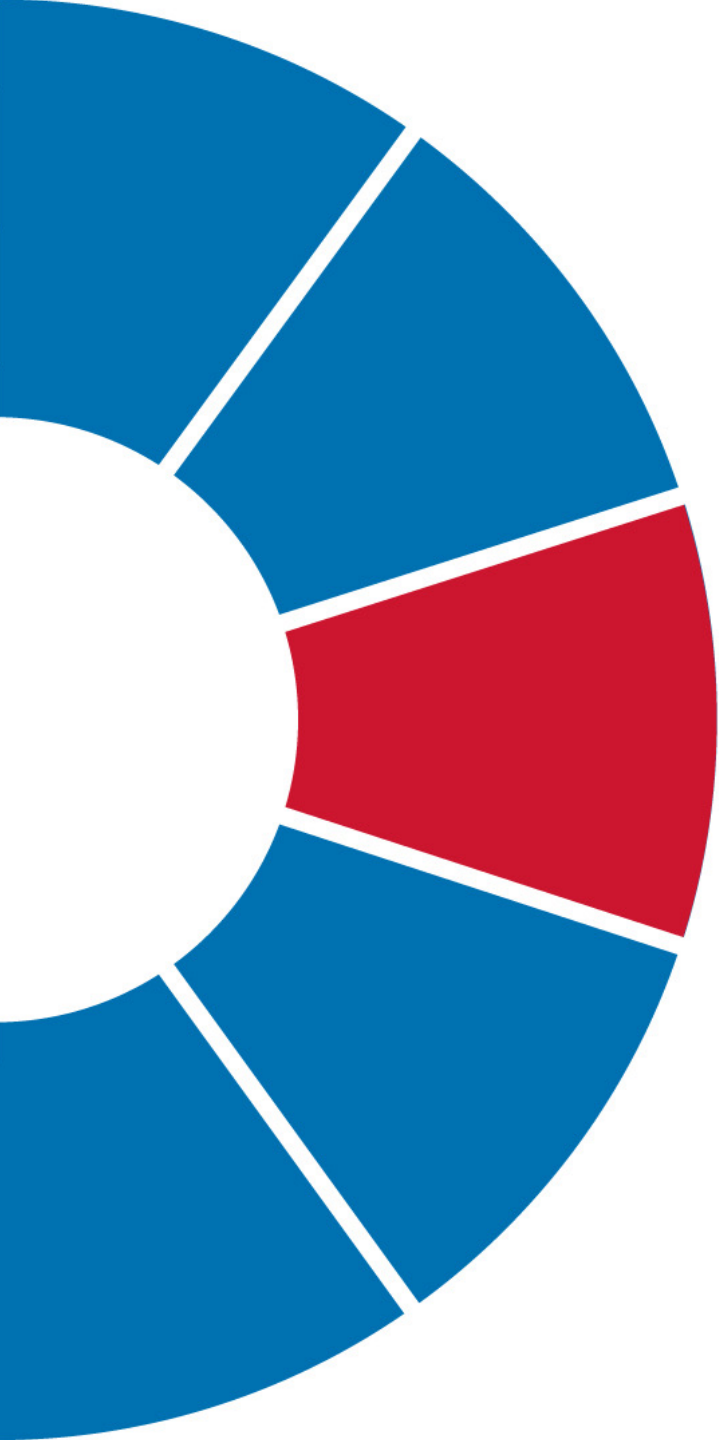
It may be useful to study also what is NOT similar..



TAKE HOME MESSAGE

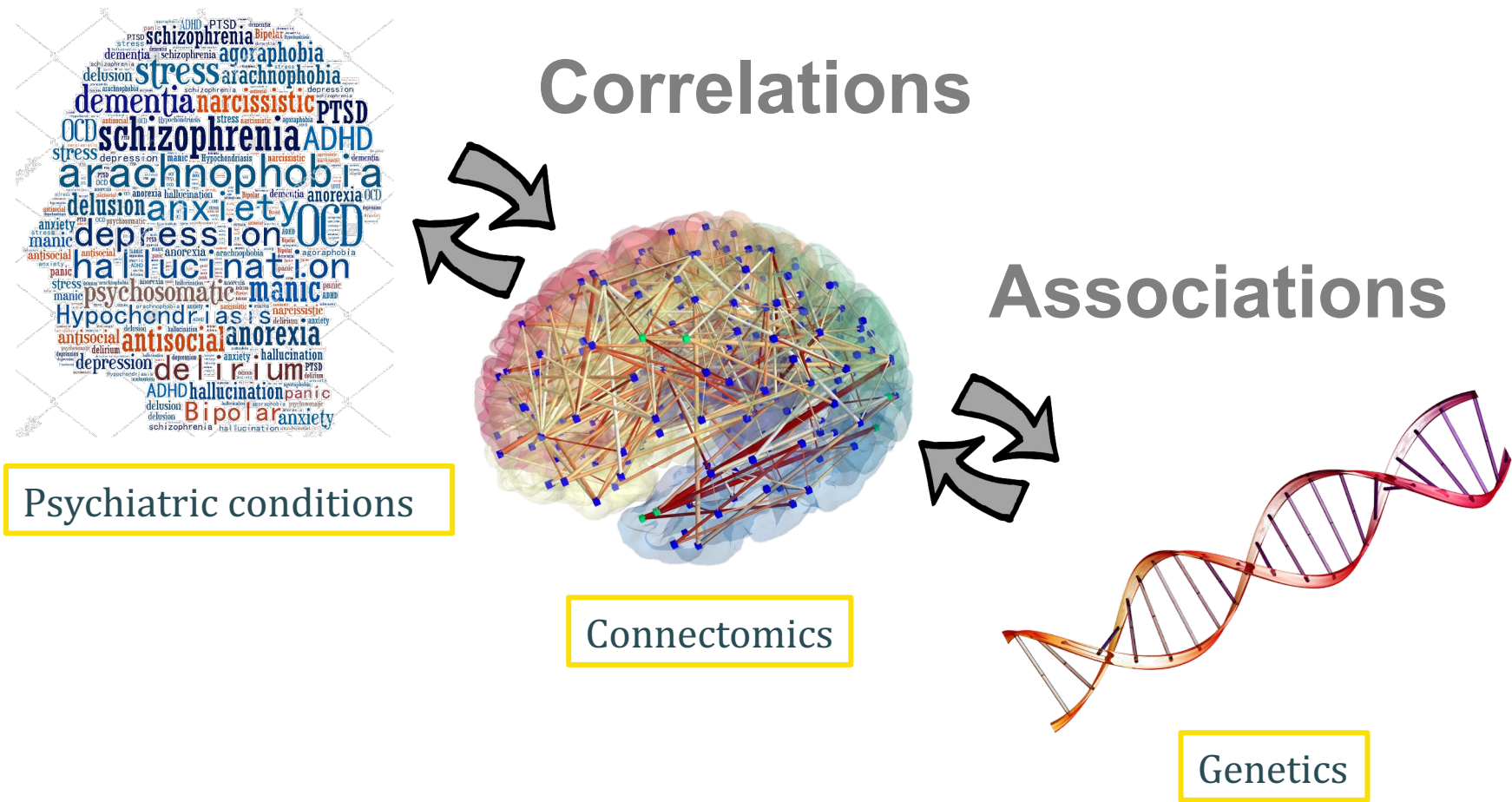
What we measure is **meaningful**. Both the structural and the functional connectome reflects the anatomical or axonal connectome. But they are not the same thing.





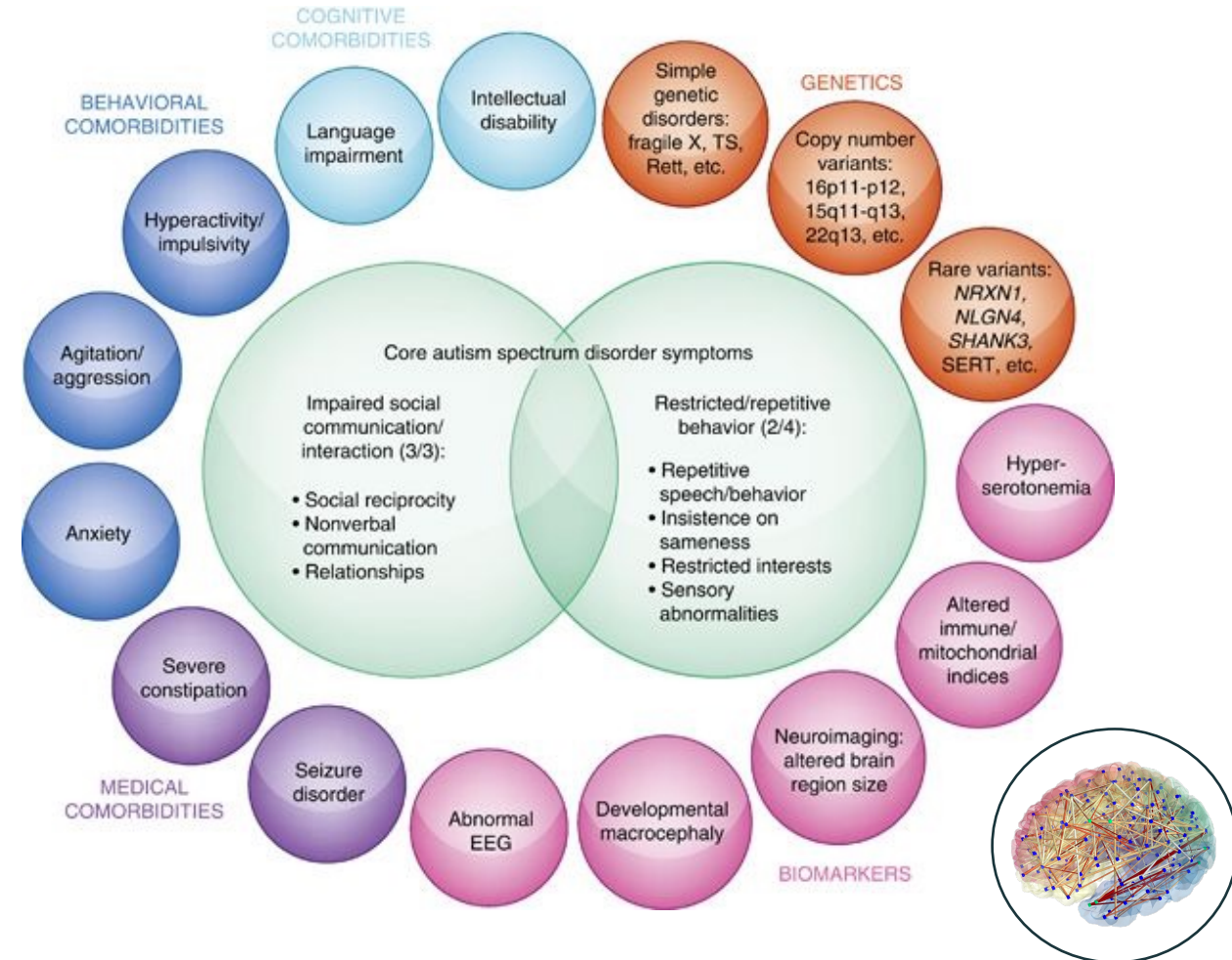
PART 3. FMRI IN TRANSGENIC RODENT MODELS FOR HUMAN DISORDERS

HOW ARE BRAIN DISORDERS, CONNECTOMICS AND GENETICS CONNECTED?



AUTISM SPECTRUM DISORDERS (ASD)

- Diagnosis based on behavioural symptoms
- High Prevalence: 1/54 children
- Highly heterogeneous (in both aetiology and symptoms)
- Genetic alterations are the largest contributors to ASD risk
- Many of these genes are linked to neuronal circuit wiring and neuronal communication.



BRAIN CONNECTIVITY AS ASD BIOMARKER: YES OR NO?



Published in final edited form as:
Mol Psychiatry. 2014 June ; 19(6): 659–667. doi:10.1038/mp.2013.78.

The Autism Brain Imaging Data Exchange: Towards Large-Scale Evaluation of the Intrinsic Brain Architecture in Autism

Adriana Di Martino, M.D.¹, Chao-Gan Yan, Ph.D.^{2,7}, Qingyang Li, M.S.^{3,*}, Erin Denio, B.A.¹, Francisco X. Castellanos, M.D.^{1,2}, Kaat Alaerts, Ph.D.^{1,4}, Jeffrey S. Anderson, M.D., Ph.D.^{5,6,7,8}, Michal Assaf, M.D.^{9,10}, Susan Y. Bookheimer, Ph.D.^{11,12,13,14}, Mirella Dapretto, Ph.D.^{11,12,13,15}, Ben Deen, B.S.^{10,16}, Sonja Delmonte, B.A.¹⁷, Ilan Dinstein, Ph.D.^{18,19}, Birgit Ertl-Wagner, M.D.²⁰, Damien A. Fair, Ph.D.²¹, Louise Gallagher, M.D., Ph.D.¹⁷, Daniel P. Kennedy, Ph.D.^{22,23}, Christopher L. Keown, B.S.²⁴, Christian Keysers, Ph.D.^{25,26}, Janet E. Lainhart, M.D.^{27,28}, Catherine Lord, Ph.D.²⁹, Beatriz Luna, Ph.D.³⁰, Vinod Menon, Ph.D.³¹, Nancy Minshew, M.D.³², Christopher S. Monk, Ph.D.³³, Sophia Mueller, M.D.²⁰, Ralph-Axel Müller, Ph.D.²⁴, Mary Beth Nebel, Ph.D.³⁴, Joel T. Nigg, Ph.D.²¹, Kirsten O'Hearn, Ph.D.³⁰, Kevin A. Pelphrey, Ph.D.¹⁰, Scott J. Peltier, Ph.D.³³, Jeffrey D. Rudie, Ph.D.^{12,13,14,15}, Stefan Sunaert, M.D., Ph.D.³⁵, Marc Thioux, Ph.D.²⁵, J. Michael Tyszka, Ph.D.³⁶, Lucina Q. Uddin, Ph.D.³¹, Judith S. Verhoeven, M.D., Ph.D.³⁵, Nicole Wenderoth, Ph.D.⁴, Jillian L. Wiggins, M.S.³³, Stewart H. Mostofsky, M.D.^{34,37}, and Michael P. Milham, M.D., Ph.D.^{2,3}

ABIDE I

1112 dataset from **539 individuals with ASD** and 573 controls (ages 7-64 years).

SCIENTIFIC DATA

OPEN Data Descriptor: Enhancing studies of the connectome in autism using the autism brain imaging data exchange II

Received: 21 September 2016
Accepted: 05 January 2017
Published: 14 March 2017

Adriana Di Martino^{1,*}, David O'Connor^{2,3}, Bosi Chen¹, Kaat Alaerts⁴, Jeffrey S. Anderson^{5,6,7,8}, Michal Assaf^{9,10}, Joshua H. Balsters¹¹, Leslie Baxter¹², Anita Beggiano^{13,14}, Sylvie Bernaerts⁴, Laura M.E. Blanken¹⁵, Susan Y. Bookheimer^{16,17,18,19}, B. Blair Braden^{12,20}, Lisa Byrge²¹, F. Xavier Castellanos^{1,2}, Mirella Dapretto^{17,18,19,22}, Richard Delorme^{13,14}, Damien A. Fair^{23,24,25}, Inna Fishman²⁶, Jacqueline Fitzgerald^{27,28}, Louise Gallagher^{27,28}, R. Joanne Jao Keehn²⁶, Daniel P. Kennedy²¹, Janet E. Lainhart^{6,7,29,30}, Beatriz Luna³¹, Stewart H. Mostofsky^{32,33,34}, Ralph-Axel Müller²⁶, Mary Beth Nebel^{32,33}, Joel T. Nigg^{23,24}, Kirsten O'Hearn³¹, Marjorie Solomon^{35,36}, Roberto Toro¹⁴, Chandan J. Vaidya^{37,38}, Nicole Wenderoth¹¹, Tonya White¹⁵, R. Cameron Craddock^{2,3}, Catherine Lord³⁹, Bennett Leventhal⁴⁰ & Michael P. Milham^{2,3}

ABIDE II

1114 datasets from **521 individuals with ASD** and 593 controls (age range: 5-64 years)

Resting-State Functional Connectivity in Autism Spectrum Disorders: A Review

Jocelyn V. Hull, Lisa B. Dokovna, Zachary J. Jacokes, Carinna M. Torgerson, Andrei Irimia and John Darrell Van Horn* for the GENDAAR Research Consortium



“Classifying autism using brain connectivity is complicated by the heterogeneous nature of the condition, allowing for the possibility of **widely variable connectivity patterns among individuals** with the disorder”



RESEARCH ARTICLE | Open Access |

Nonreplication of functional connectivity differences in autism spectrum disorder across multiple sites and denoising strategies

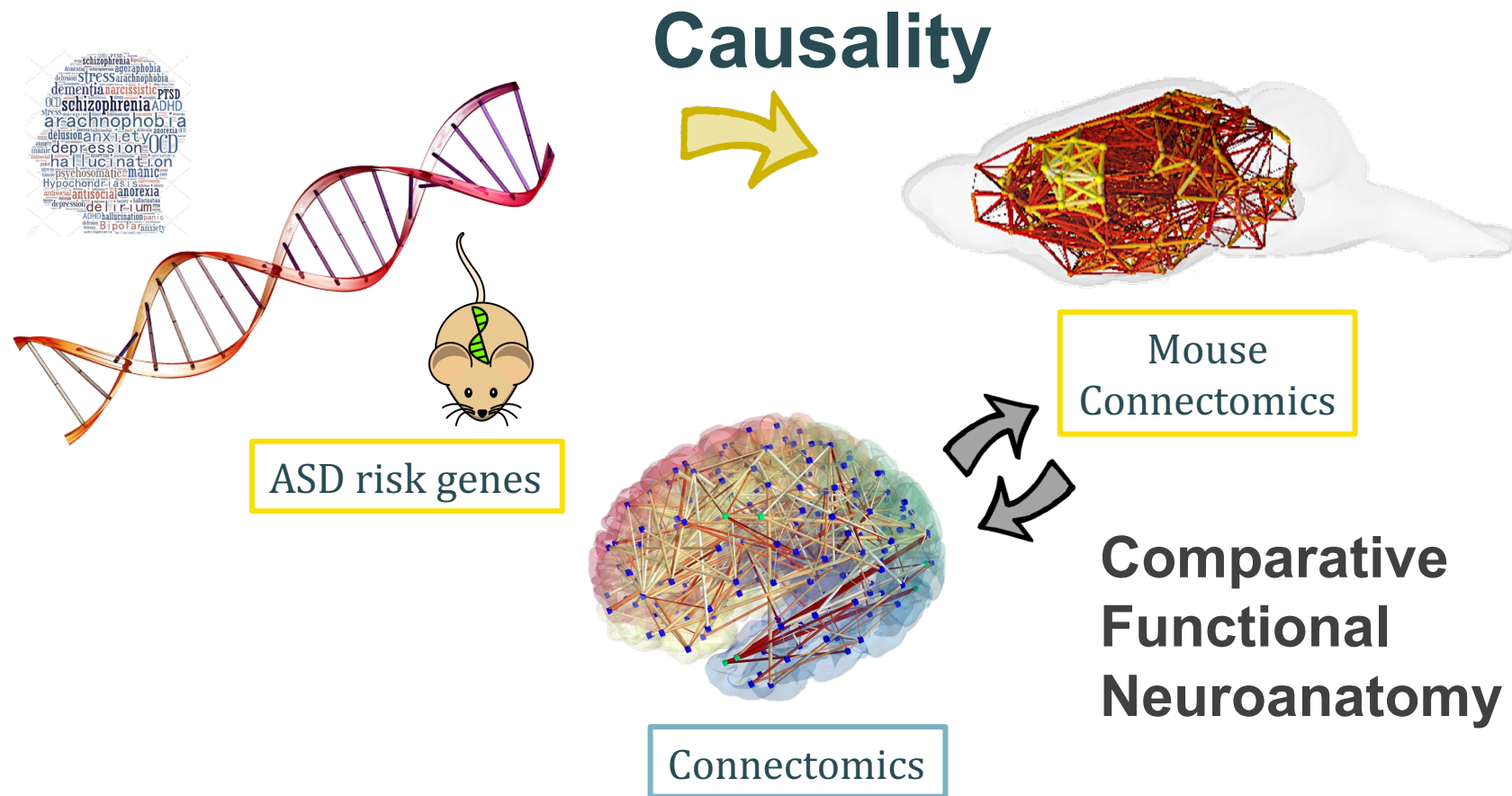
Ye He , Lisa Byrge, Daniel P. Kennedy

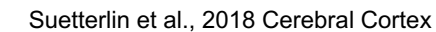
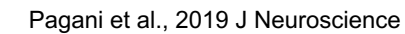
First published: 09 January 2020 | <https://doi.org/10.1002/hbm.24879>

"even the basic **directionality** of effects is still debated (i.e., systematic overconnectivity, underconnectivity, both, or neither)"

C I B M . C H

HOW ARE BRAIN DISORDERS, CONNECTOMICS AND GENETICS CONNECTED?





THE AUTISM MOUSE BRAIN CONNECTOME (AMBC)

Table 1. Available datasets

ASD mouse model	Control Strain	Sex	Age (weeks)	Behavioural traits *	Construct validity †	References	Scan Site
16p11.2 (df/+)	129/C57BL6J	males	18-20	3,5	c	¹¹	IIT



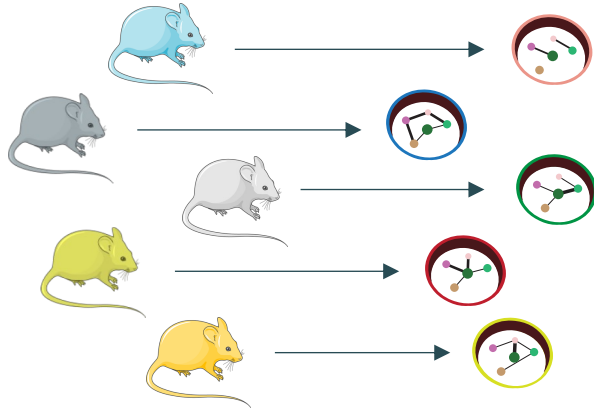
Overarching research question

Do genetic risk factors lead to (specific or unspecific) brain network dysfunction?

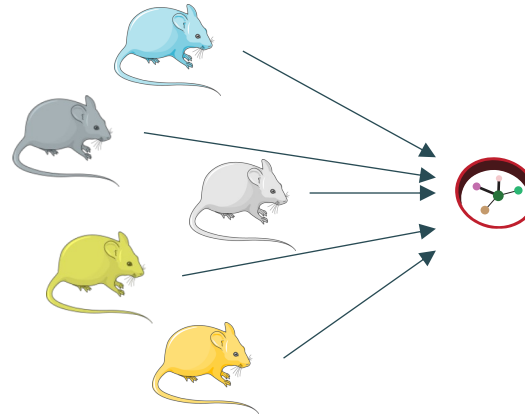
* Behavioural traits related to ASD reported by others in selected models: (1) social behavior deficits; (2) reduced vocalizations; (3) repetitive behavior; (4) cognitive behavior; (5) motor performance. † Construct validity includes: (a) Genetic association; (b) Related syndrome; (c) Autism copy number variants; (d) Autistic-like behavior; (e) Serotonin-related phenotype; (f) Synapse related

- Matched littermate controls

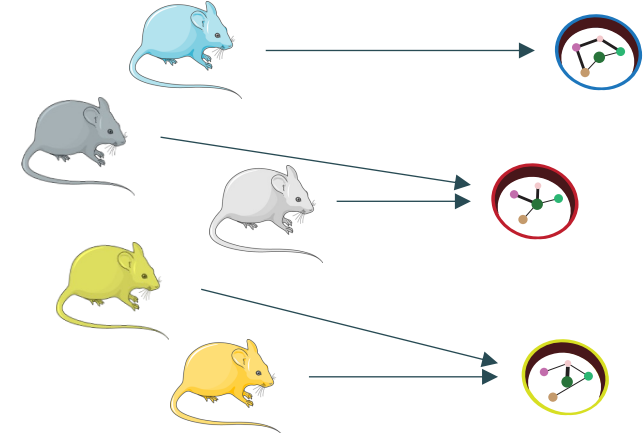
THREE POSSIBLE SCENARIOS



1. Each gene : One connectivity profile



2. All genes : One connectivity profile



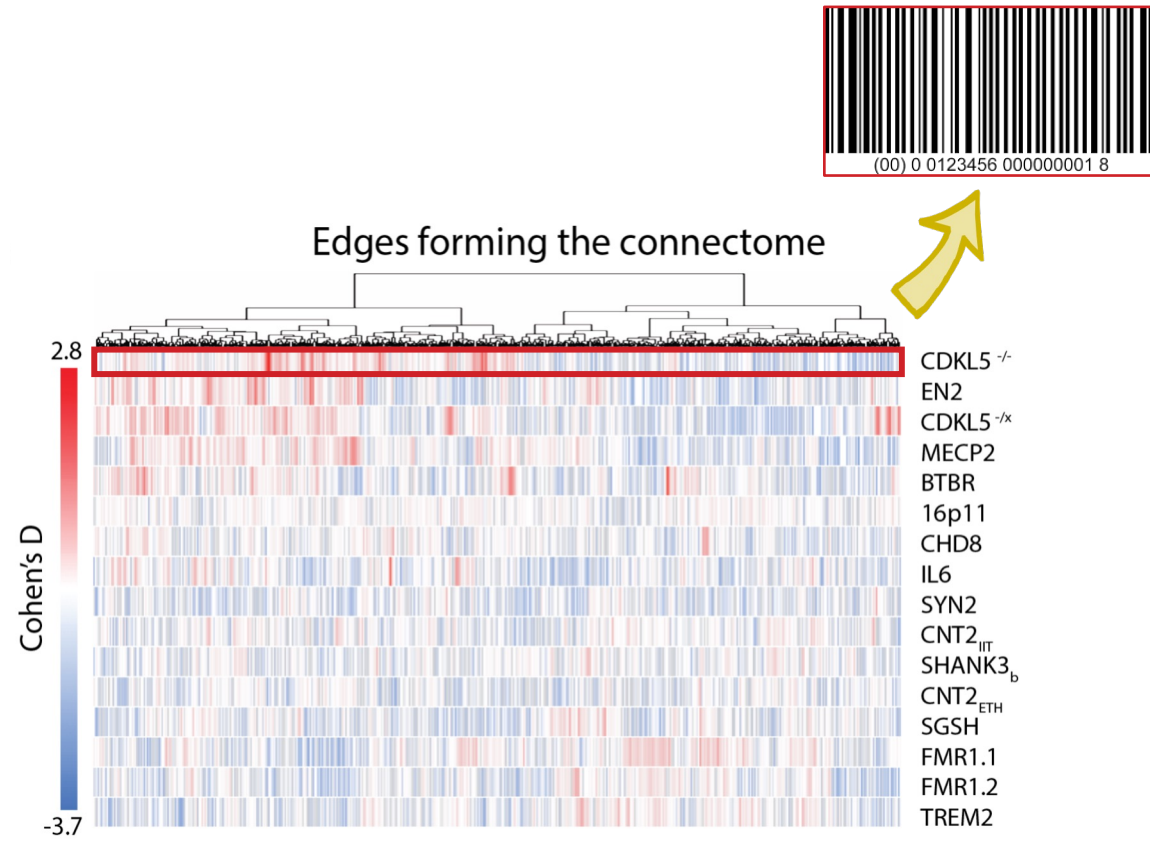
3. Gene-Clusters : One connectivity profile

THE AUTISM MOUSE BRAIN CONNECTOME (AMBC)

Table 1. Available datasets

ASD mouse model	Control Strain	Sex	Age (weeks)	Behavioural traits *	Construct validity †	References	Scan Site
16p11.2 (dF/+)	129/C57BL/6J	males	18-20	3,5	c	¹¹	IIT
BTBR T+tf/J	C57BL/6J	males	26	1,2,3,4,5	d	³⁴	IIT
CDKL5 KO	C57BL/6J	males	23-25	3,5	b,f	-	ETH
CDKL5 Het (+/-)	C57BL/6J	females	17-19	3,5	b,f	-	ETH
CHD8	C57BL/6J	mixed	15-18	3,4,5	a	²⁶	IIT
CNTNAP2_ETH (-/-)	C57BL/6J	mixed	14-16	1,4,5	a,f	¹⁶	ETH
CNTNAP2_IIT (-/-)	C57BL/6J	males	13-14	1,4,5	a,f	²³	IIT
En2 (-/-)	C57BL/6J	mixed	12-16	1,4,5	a,e,d	²⁴	ETH
FMR1.1 (-/y)	C57BL/6J	males	14-16	1,2,3,4	b,f	¹⁶	ETH
FMR1.2 (-/y)	C57BL/6J	males	13-15	1,2,3,4	b,f	³⁵	ETH
IL6	C57BL/6J	mixed	14	1,4	d	-	ETH
Mecp2 Het (+/-)	C57BL/6J	females	12-14	1,4,5	b,f	-	ETH
SGSH (-/-)	C57BL/6N	mixed	20-22	5	b	-	ETH
SHANK3b ex4-9	C57BL/6J	males	19-21	1,2,3,4,5	a,f	²⁵	IIT
Syn2	C57BL/6J	males	25-31		f	³⁶	IIT
TREM2 (-/-)	C57BL/6J	mixed	12-15	3,4	d	²⁹	ETH

* Behavioural traits related to ASD reported by others in selected models: (1) social behavior deficits; (2) reduced vocalizations; (3) repetitive behavior; (4) cognitive behavior; (5) motor performance. † Construct validity includes: (a) Genetic association; (b) Related syndrome; (c) Autism copy number variants; (d) Autistic-like behavior; (e) Serotonin-related phenotype; (f) Synapse related



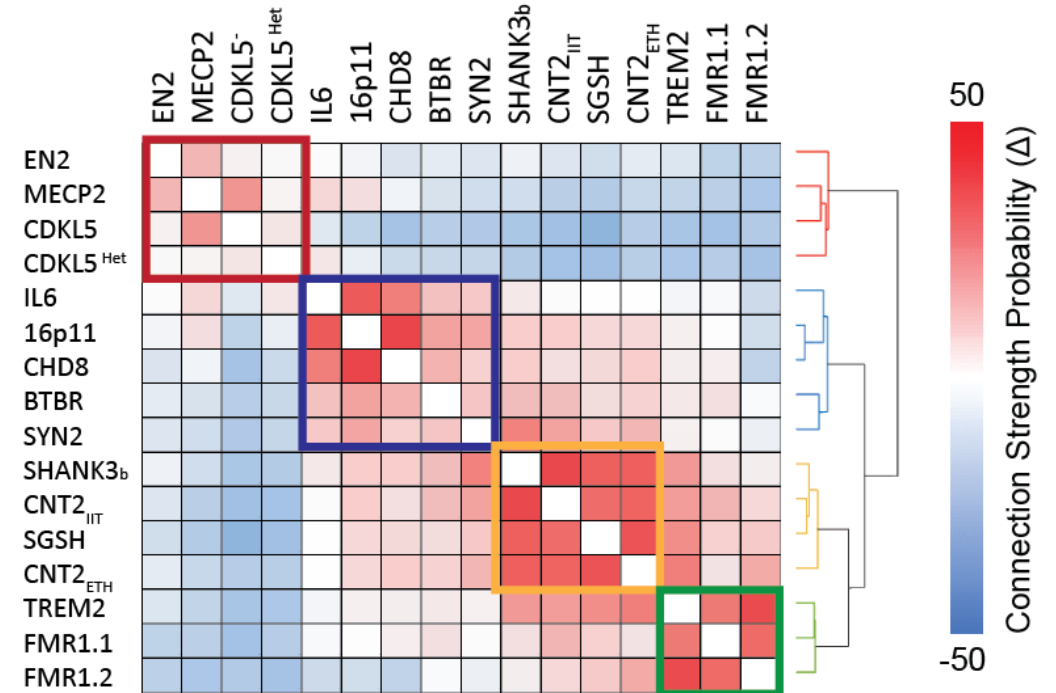
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Table 1. Available datasets

ASD mouse model	Control Strain	Sex	Age (weeks)	Behavioural traits *	Construct validity †	References	Scan Site
16p11.2 (dF/+)	129/C57BL/6J	males	18-20	3,5	c	¹¹	IIT
BTBR T+tf/J	C57BL/6J	males	26	1,2,3,4,5	d	³⁴	IIT
CDKL5 KO	C57BL/6J	males	23-25	3,5	b,f	-	ETH
CDKL5 Het (+/-)	C57BL/6J	females	17-19	3,5	b,f	-	ETH
CHD8	C57BL/6J	mixed	15-18	3,4,5	a	²⁶	IIT
CNTNAP2_ETH (-/-)	C57BL/6J	mixed	14-16	1,4,5	a,f	¹⁶	ETH
CNTNAP2_IIT (-/-)	C57BL/6J	males	13-14	1,4,5	a,f	²³	IIT
En2 (-/-)	C57BL/6J	mixed	12-16	1,4,5	a,e,d	²⁴	ETH
FMR1.1 (-/y)	C57BL/6J	males	14-16	1,2,3,4	b,f	¹⁶	ETH
FMR1.2 (-/y)	C57BL/6J	males	13-15	1,2,3,4	b,f	³⁵	ETH
IL6	C57BL/6J	mixed	14	1,4	d	-	ETH
Mecp2 Het (+/-)	C57BL/6J	females	12-14	1,4,5	b,f	-	ETH
SGSH (-/-)	C57BL/6N	mixed	20-22	5	b	-	ETH
SHANK3b ex4-9	C57BL/6J	males	19-21	1,2,3,4,5	a,f	²⁵	IIT
Syn2	C57BL/6J	males	25-31		f	³⁶	IIT
TREM2 (-/-)	C57BL/6J	mixed	12-15	3,4	d	²⁹	ETH

* Behavioural traits related to ASD reported by others in selected models: (1) social behavior deficits; (2) reduced vocalizations; (3) repetitive behavior; (4) cognitive behavior; (5) motor performance. † Construct validity includes: (a) Genetic association; (b) Related syndrome; (c) Autism copy number variants; (d) Autistic-like behavior; (e) Serotonin-related phenotype; (f) Synapse related

Clustering Probability Delta

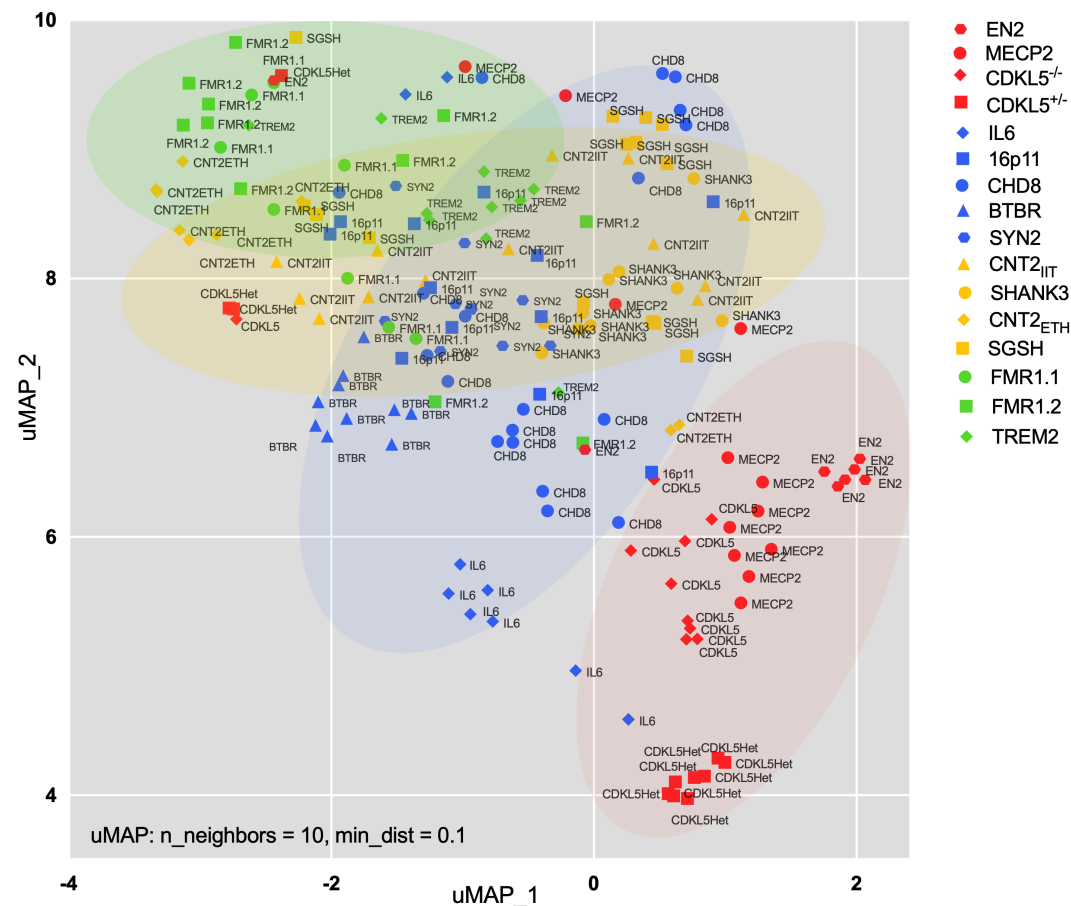


THE AUTISM MOUSE BRAIN CONNECTOME (AMBC)

Table 1. Available datasets

ASD mouse model	Control Strain	Sex	Age (weeks)	Behavioural traits *	Construct validity †	References	Scan Site
16p11.2 (d/f/+)	129/C57BL/6j	males	18-20	3,5	c	11	IIT
BTBR T+tf/J	C57BL/6j	males	26	1,2,3,4,5	d	34	IIT
CDKL5 KO	C57BL/6j	males	23-25	3,5	b,f	-	ETH
CDKL5 Het (+/-)	C57BL/6j	females	17-19	3,5	b,f	-	ETH
CHD8	C57BL/6j	mixed	15-18	3,4,5	a	26	IIT
CNTNAP2_ETH (-/-)	C57BL/6j	mixed	14-16	1,4,5	a,f	16	ETH
CNTNAP2_IIT (-/-)	C57BL/6j	males	13-14	1,4,5	a,f	23	IIT
En2 (-/-)	C57BL/6j	mixed	12-16	1,4,5	a,e,d	24	ETH
FMR1.1 (-/y)	C57BL/6j	males	14-16	1,2,3,4	b,f	16	ETH
FMR1.2 (-/y)	C57BL/6j	males	13-15	1,2,3,4	b,f	35	ETH
IL6	C57BL/6j	mixed	14	1,4	d	-	ETH
MeCP2 Het (+/-)	C57BL/6j	females	12-14	1,4,5	b,f	-	ETH
SGSH (-/-)	C57BL/6N	mixed	20-22	5	b	-	ETH
SHANK3b ex4-9	C57BL/6j	males	19-21	1,2,3,4,5	a,f	25	IIT
Syn2	C57BL/6j	males	25-31		f	36	IIT
TREM2 (-/-)	C57BL/6j	mixed	12-15	3,4	d	29	ETH

* Behavioural traits related to ASD reported by others in selected models: (1) social behavior deficits; (2) reduced vocalizations; (3) repetitive behavior; (4) cognitive behavior; (5) motor performance. † Construct validity includes: (a) Genetic association; (b) Related syndrome; (c) Autism copy number variants; (d) Autistic-like behavior; (e) Serotonin-related phenotype; (f) Synapse related

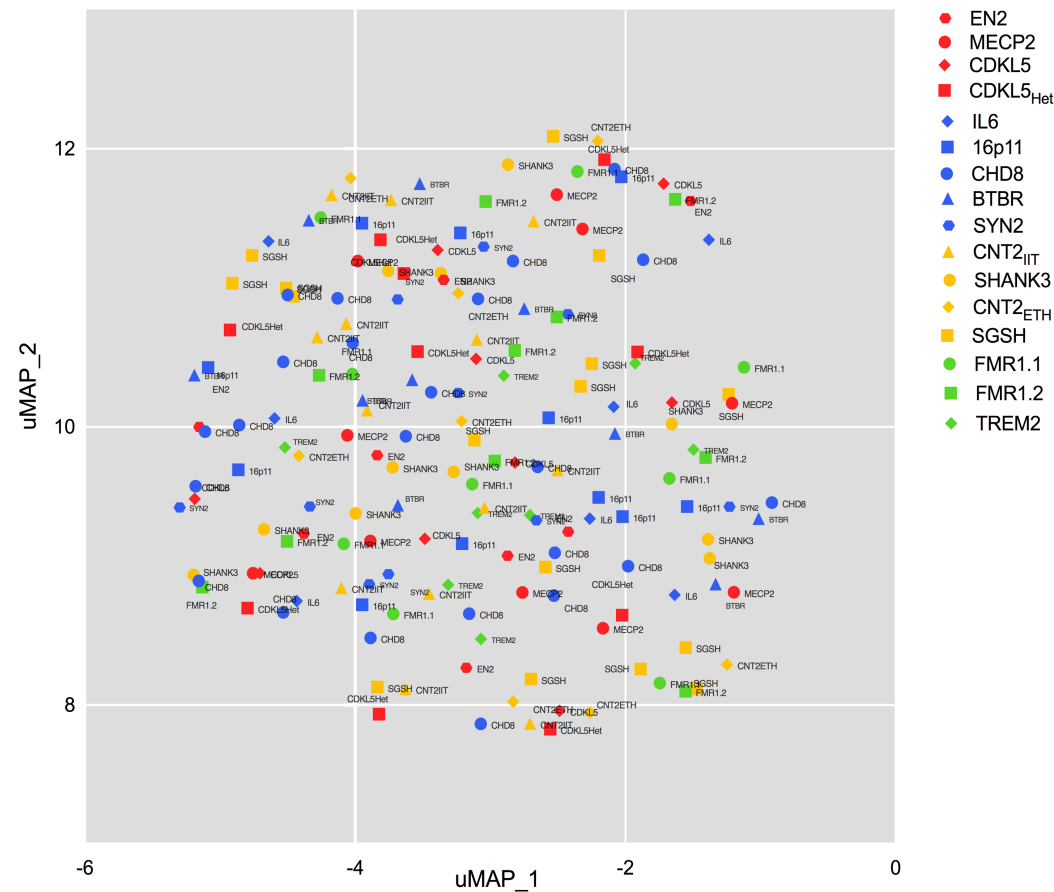


THE AUTISM MOUSE BRAIN CONNECTOME (AMBC)

Table 1. Available datasets

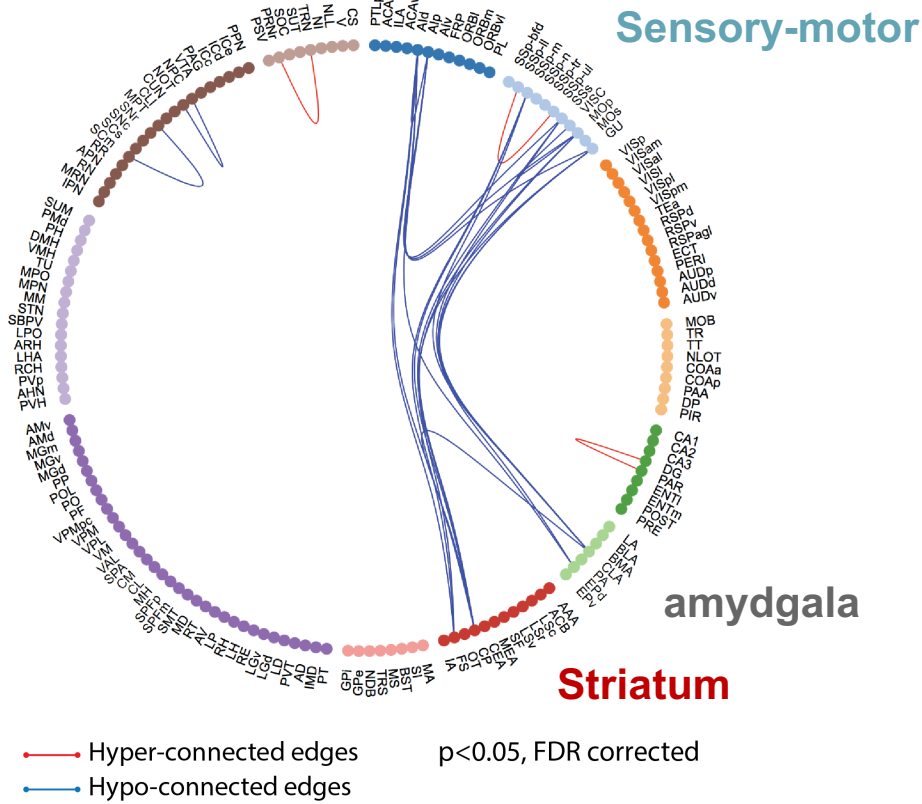
ASD mouse model	Control Strain	Sex	Age (weeks)	Behavioural traits *	Construct validity †	References	Scan Site
16p11.2 (dF/+)	129/C57BL6J	males	18-20	3,5	c	11	IIT
BTBR T+tf/J	C57BL/6J	males	26	1,2,3,4,5	d	34	IIT
CDKL5 KO	C57BL/6J	males	23-25	3,5	b,f	-	ETH
CDKL5 Het (+/-)	C57BL/6J	females	17-19	3,5	b,f	-	ETH
CHD8	C57BL/6J	mixed	15-18	3,4,5	a	26	IIT
CNTNAP2_ETH (-/-)	C57BL/6J	mixed	14-16	1,4,5	a,f	16	ETH
CNTNAP2_IIT (-/-)	C57BL/6J	males	13-14	1,4,5	a,f	23	IIT
En2 (-/-)	C57BL/6J	mixed	12-16	1,4,5	a,e,d	24	ETH
FMR1.1 (-/y)	C57BL/6J	males	14-16	1,2,3,4	b,f	16	ETH
FMR1.2 (-/y)	C57BL/6J	males	13-15	1,2,3,4	b,f	35	ETH
IL6	C57BL/6J	mixed	14	1,4	d	-	ETH
MeCP2 Het (+/-)	C57BL/6J	females	12-14	1,4,5	b,f	-	ETH
SGSH (-/-)	C57BL/6N	mixed	20-22	5	b	-	ETH
SHANK3b ex4-9	C57BL/6J	males	19-21	1,2,3,4,5	a,f	25	IIT
Syn2	C57BL/6J	males	25-31		f	36	IIT
TREM2 (-/-)	C57BL/6J	mixed	12-15	3,4	d	29	ETH

* Behavioural traits related to ASD reported by others in selected models: (1) social behavior deficits; (2) reduced vocalizations; (3) repetitive behavior; (4) cognitive behavior; (5) motor performance. † Construct validity includes: (a) Genetic association; (b) Related syndrome; (c) Autism copy number variants; (d) Autistic-like behavior; (e) Serotonin-related phenotype; (f) Synapse related

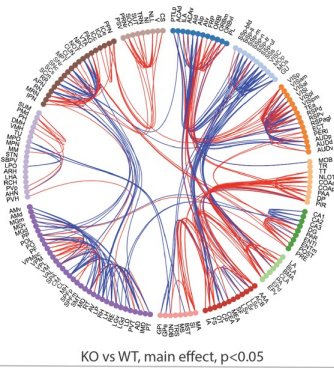


TWO IMPORTANT TAKES

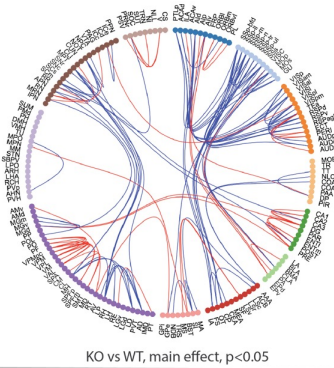
All models vs all wildtype



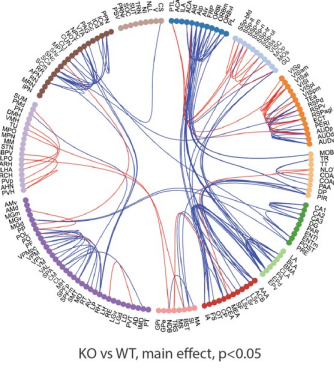
Cluster 1



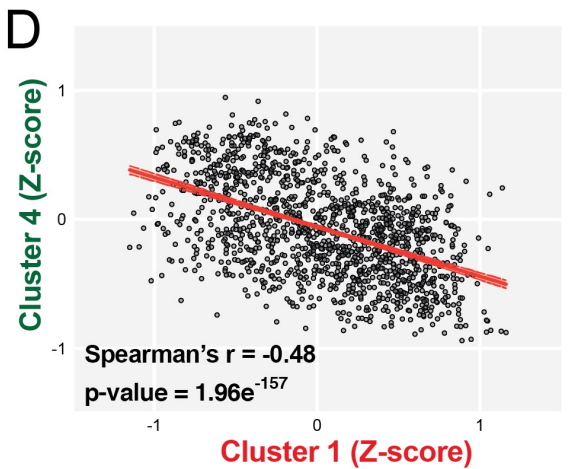
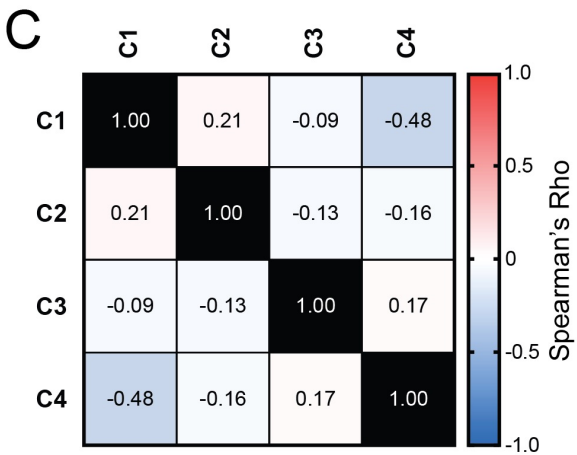
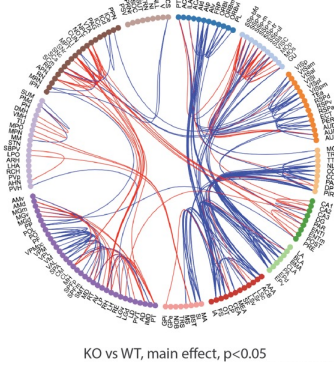
Cluster 2



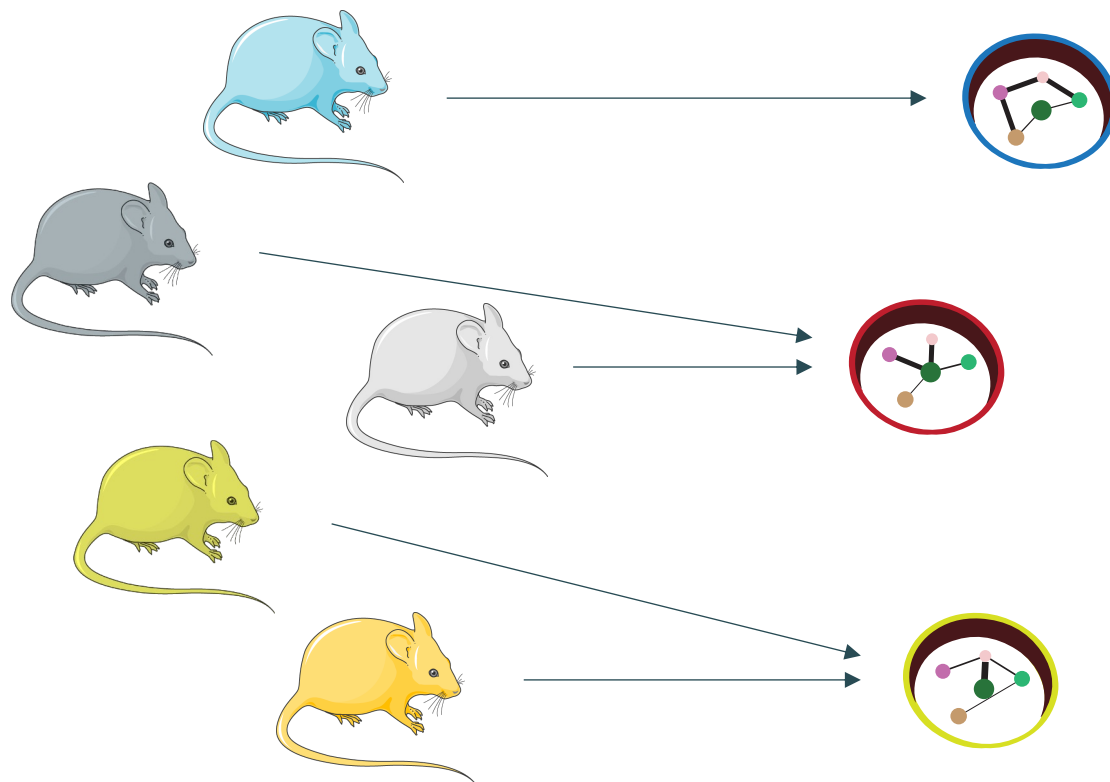
Cluster 3



Cluster 4



TAKE HOME MESSAGE



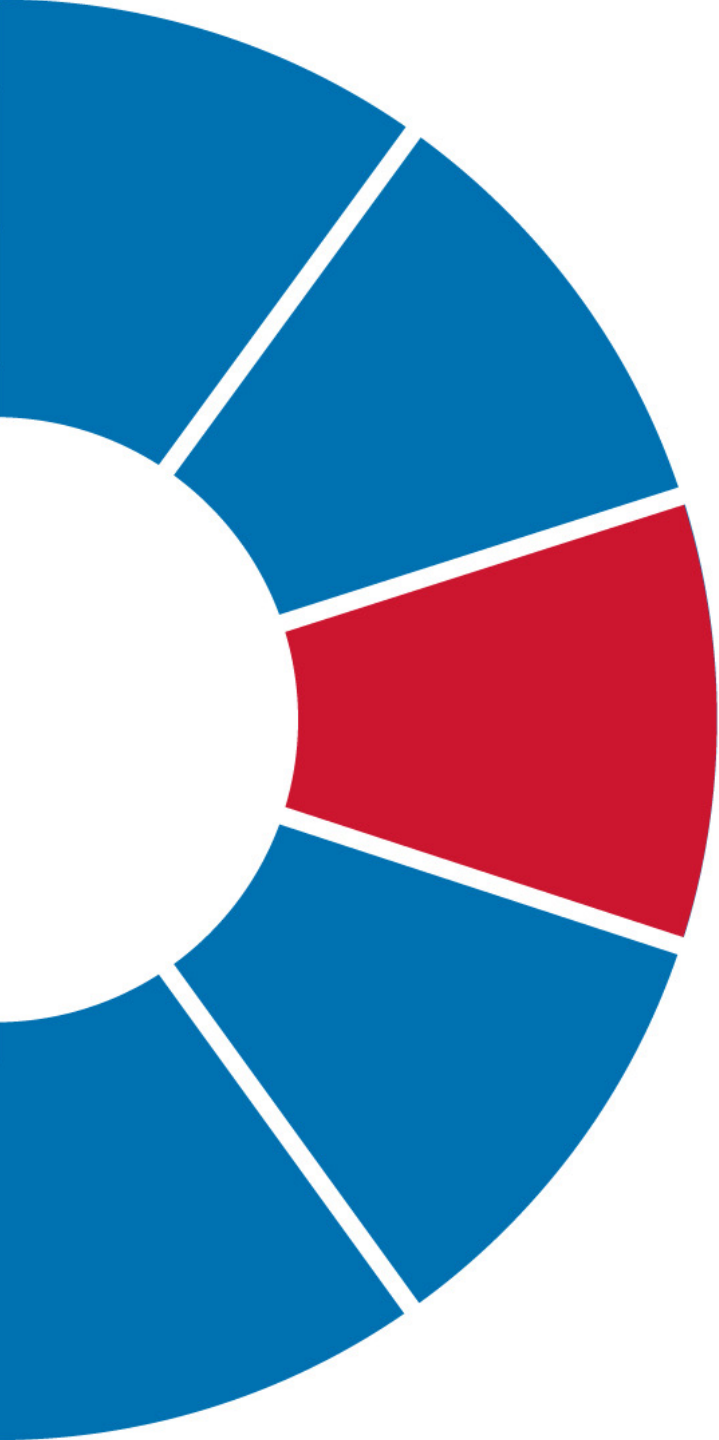
Good because

Helps understanding pools of genes that cause similar alterations at the network level (*mechanism*)

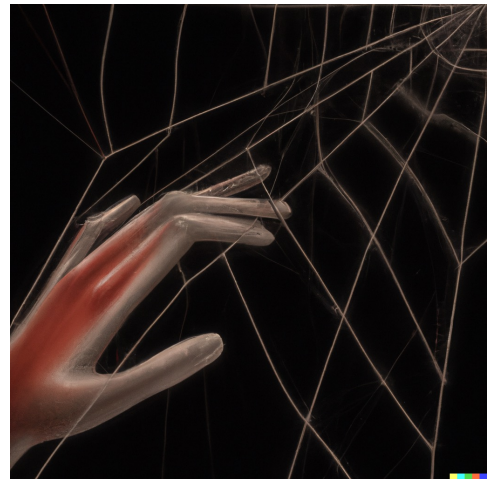
Proximity in the dys-connectivity landscape helps to define possible treatment options (*outcome*)

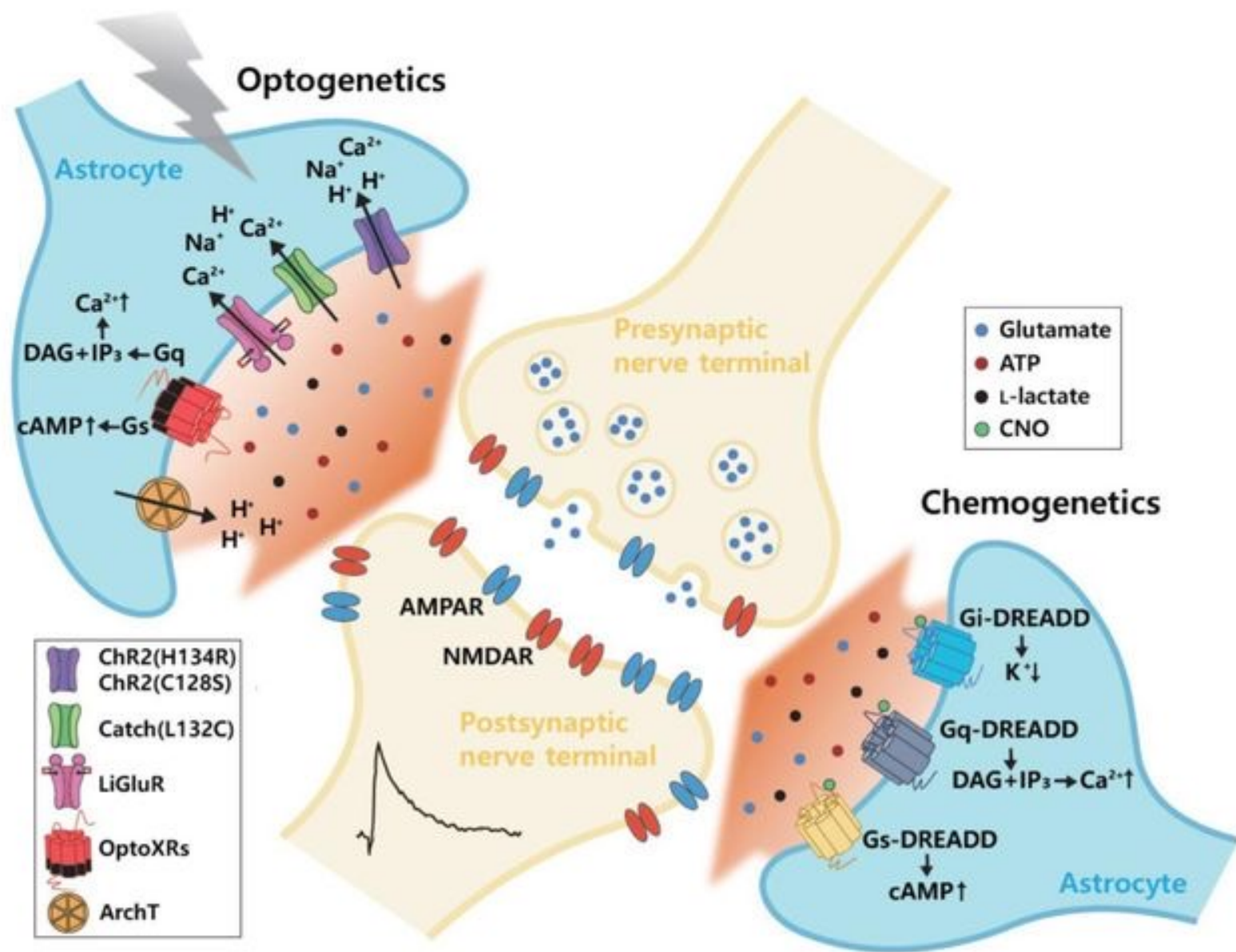
Careful at:

Group-level analyses, as done in humans, may reduce effect size



PART 4. MANIPULATING CELL ACTIVITY TO OBSERVE NETWORK REACTION





CHEMO-FMRI AND OPTO-FMRI

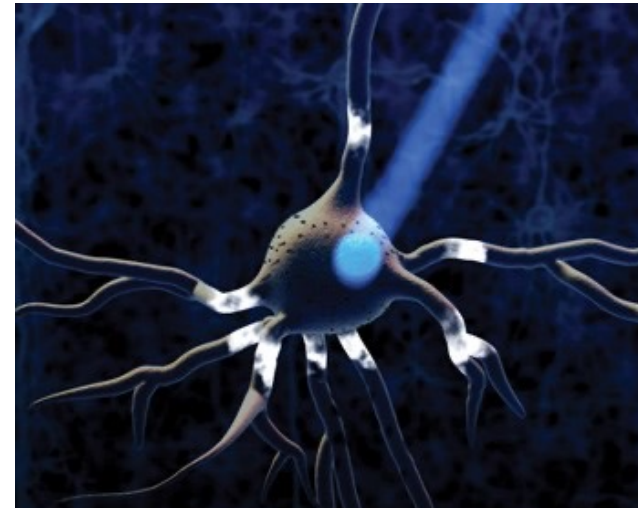
Chemogenetic

- AAV delivery
- Neuron-specific
- Activated systemically by drug
- Reversible
- Excite or inhibit
- No external implant
- Effect lasts 30min-2h (?)



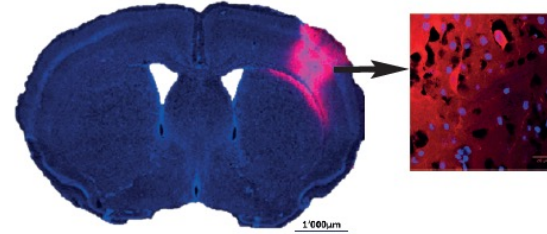
Optogenetics

- AAV delivery
- Neuron-specific
- Activated locally by light
- Reversible
- Excite or inhibit
- Requires external implant
- Millisecond control

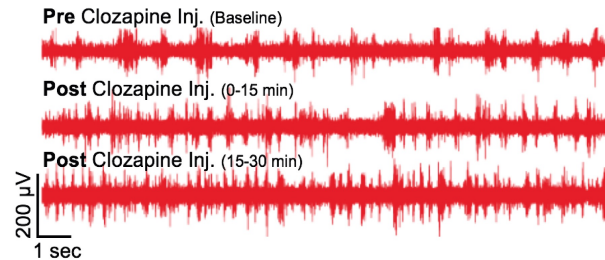


EXAMPLE 1. EXCITATION:INHIBITION IMBALANCE

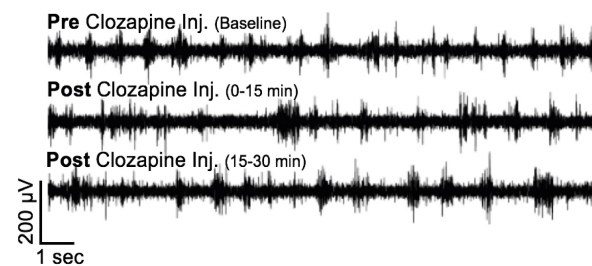
DREADDs EXCITATION OF PYRAMIDAL CELLS hM3Dq (CamKIIa)



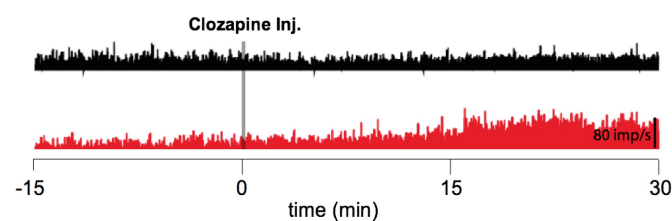
A Neuronal firing rate at the right SSctx (DREADD injection site)



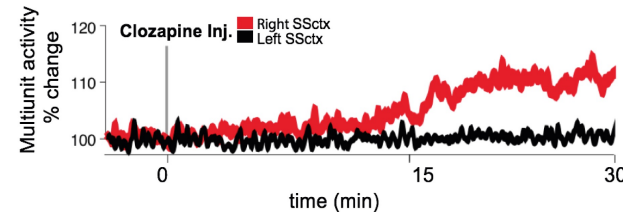
B Neuronal firing rate at the left SSctx (control region)



C Time-resolved firing rate for left and right SSctx



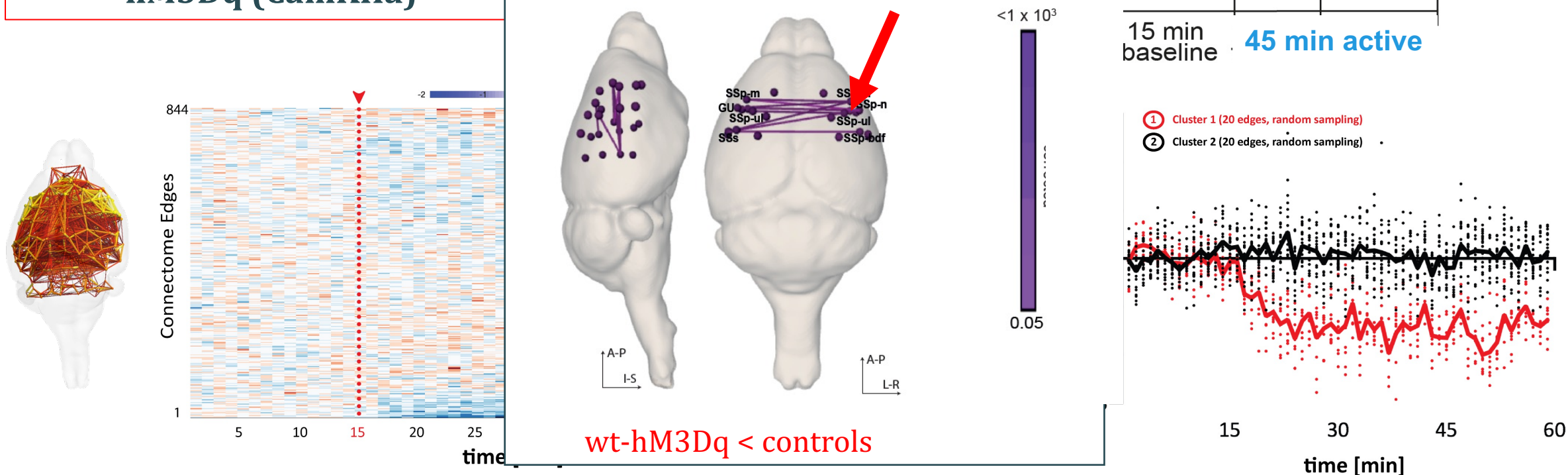
D Relative change of averaged multiunit activity



DREADDs manipulation
increased neuronal firing rate
in the targeted region

EXAMPLE 1. EXCITATION:INHIBITION IMBALANCE

DREADDs EXCITATION OF PYRAMIDAL CELLS hM3Dq (CamKIIa)



E:I imbalance at the **circuit level** propagates to the **network level** as **hypo-connectivity** and are **restricted to the targeted network**

EXAMPLE 1. EXCITATION:INHIBITION IMBALANCE

[nature](#) > [nature communications](#) > [articles](#) > [article](#)

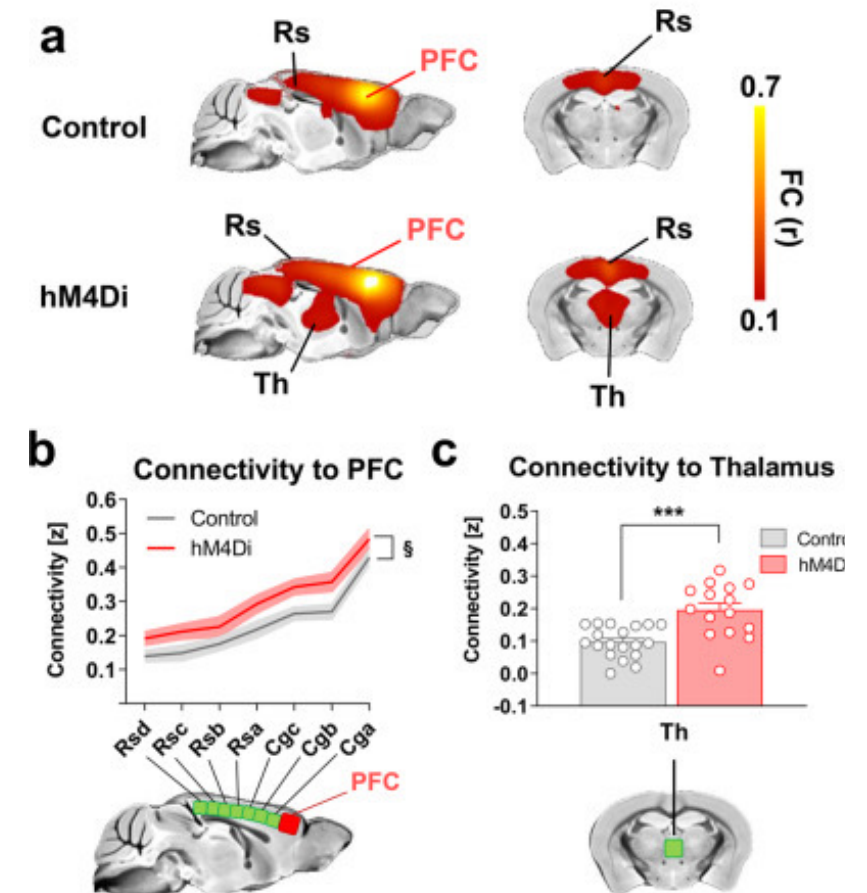
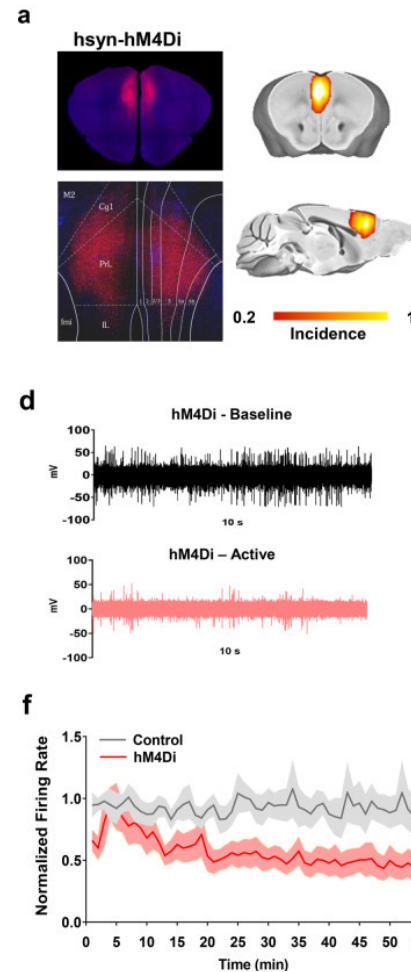
Article | [Open Access](#) | Published: 25 February 2022

Increased fMRI connectivity upon chemogenetic inhibition of the mouse prefrontal cortex

Federico Rocchi, Carola Canella, Shahryar Noei, Daniel Gutierrez-Barragan, Ludovico Coletta, Alberto Galbusera, Alexia Stuefer, Stefano Vassanelli, Massimo Pasqualetti, Giuliano Iurilli, Stefano Panzeri & Alessandro Gozzi

Nature Communications 13, Article number: 1056 (2022) | [Cite this article](#)

6338 Accesses | 8 Citations | 73 Altmetric | [Metrics](#)



EXAMPLE 1. EXCITATION:INHIBITION IMBALANCE

[nature](#) > [nature communications](#) > [articles](#) > [article](#)

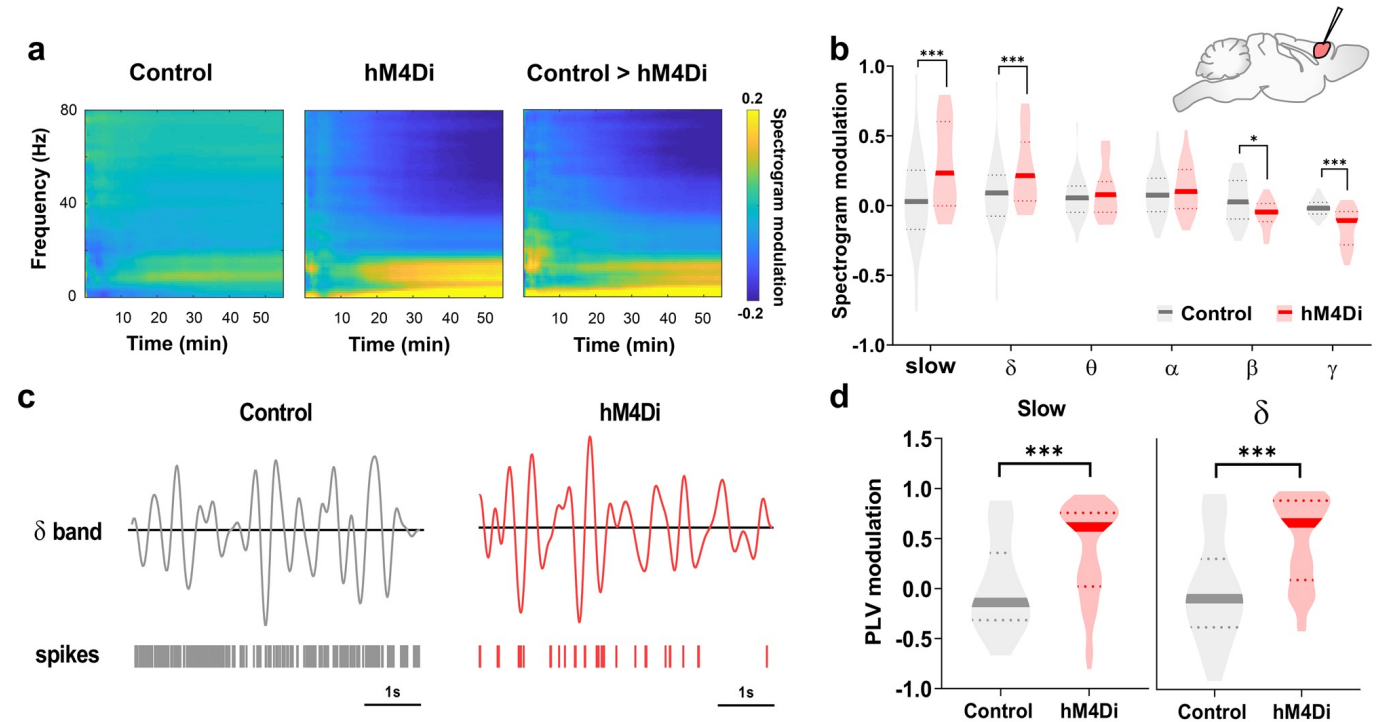
Article | [Open Access](#) | [Published: 25 February 2022](#)

Increased fMRI connectivity upon chemogenetic inhibition of the mouse prefrontal cortex

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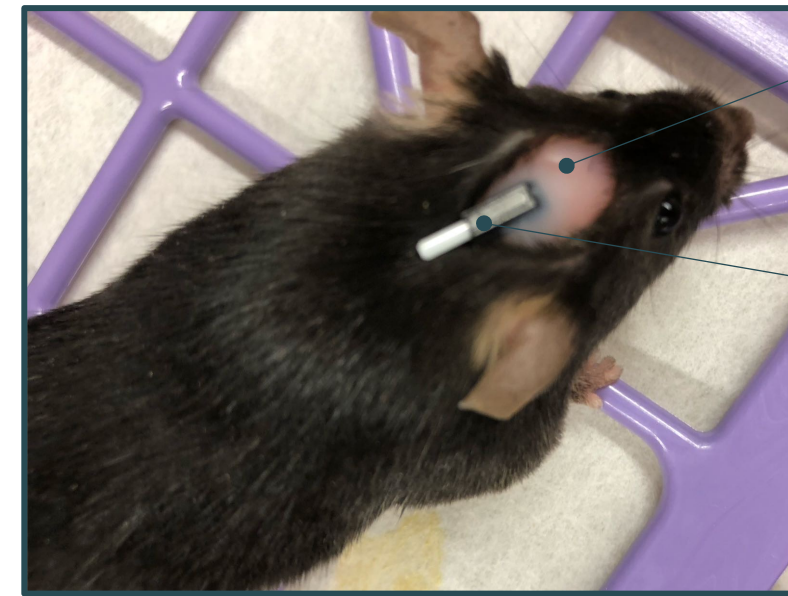
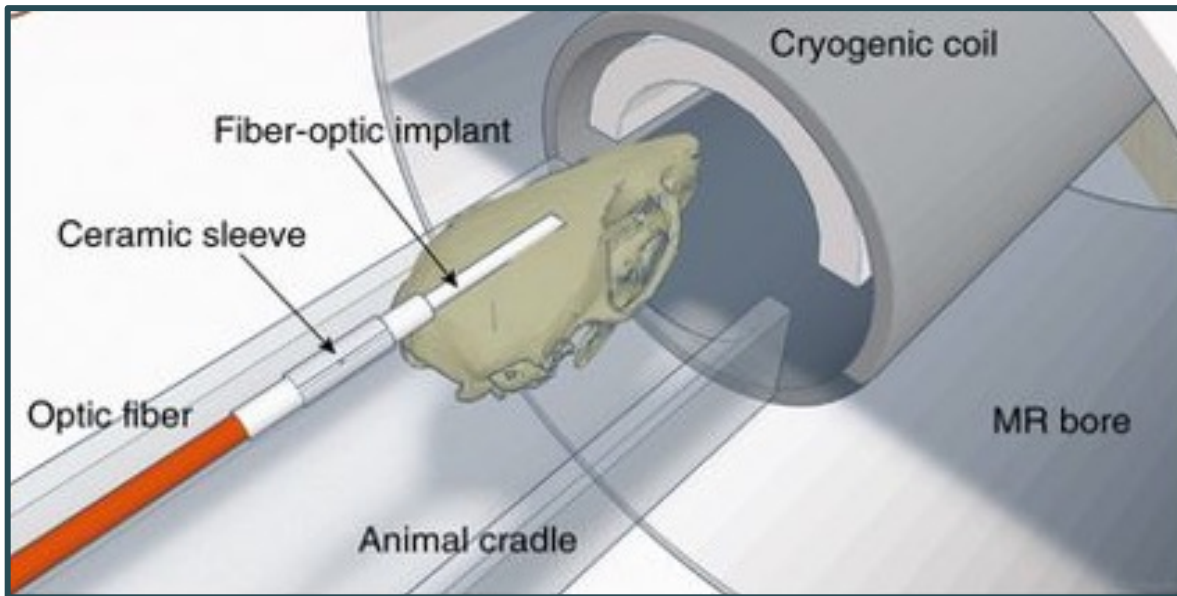
[Nature Communications](#) **13**, Article number: 1056 (2022) | [Cite this article](#)

6338 Accesses | 8 Citations | 73 Altmetric | [Metrics](#)



OPTOGENETICS-FMRI: IMPLANT

Hardware constraints



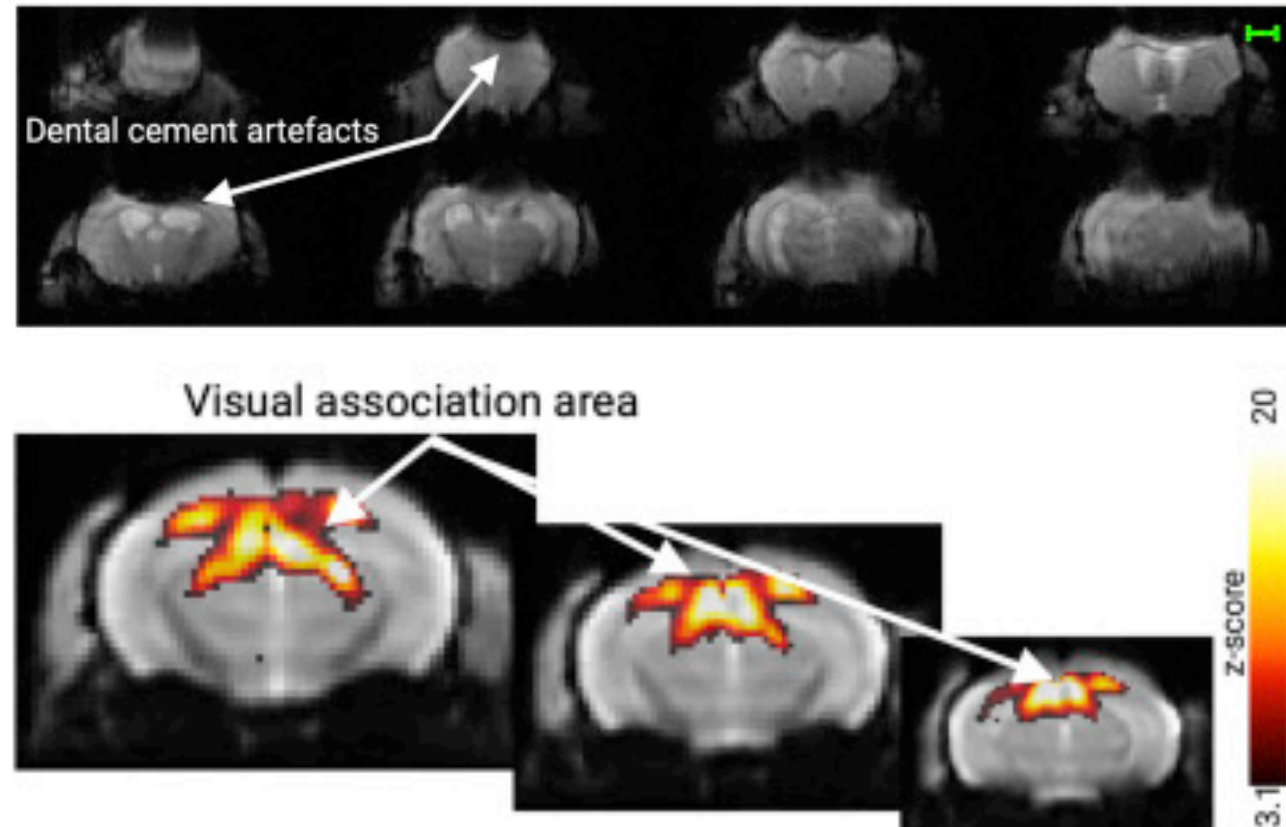
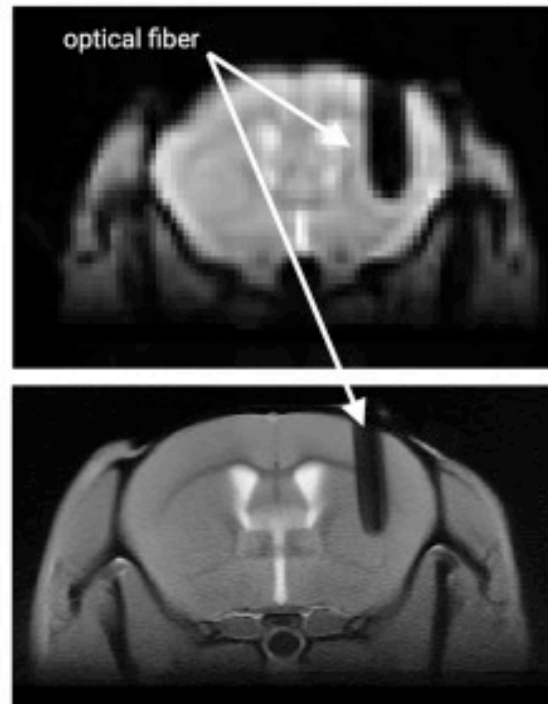
Non-magnetic

Flat optical implant

Schlegel et al., Nature Protocols 2019

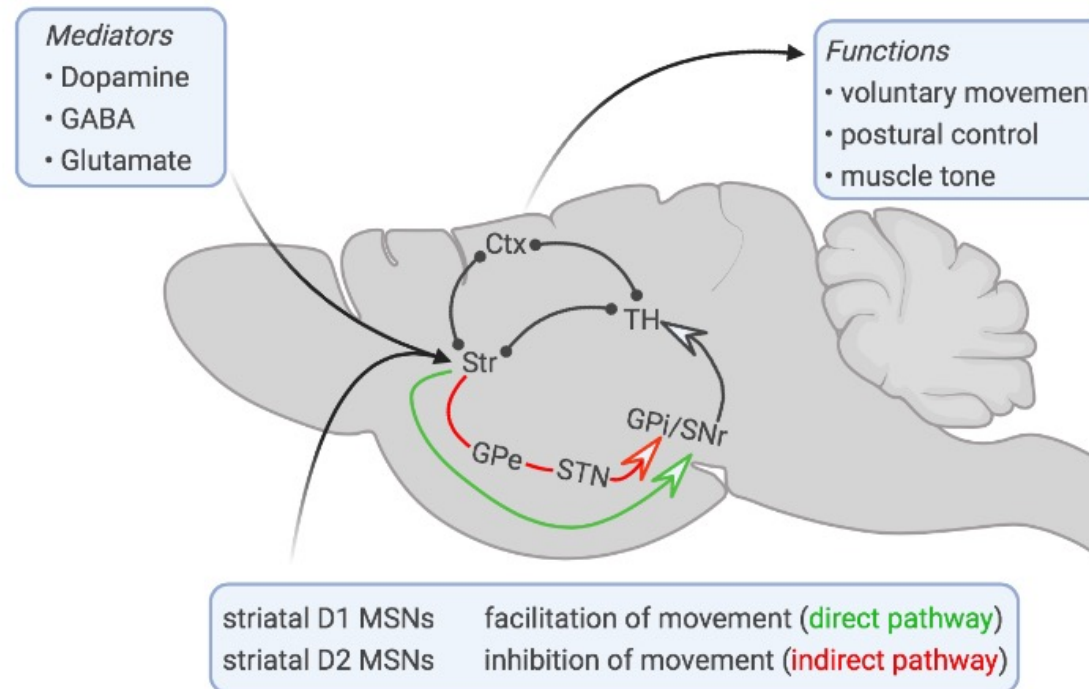
OPTOGENETICS-FMRI: CHALLENGES

Watch out for:



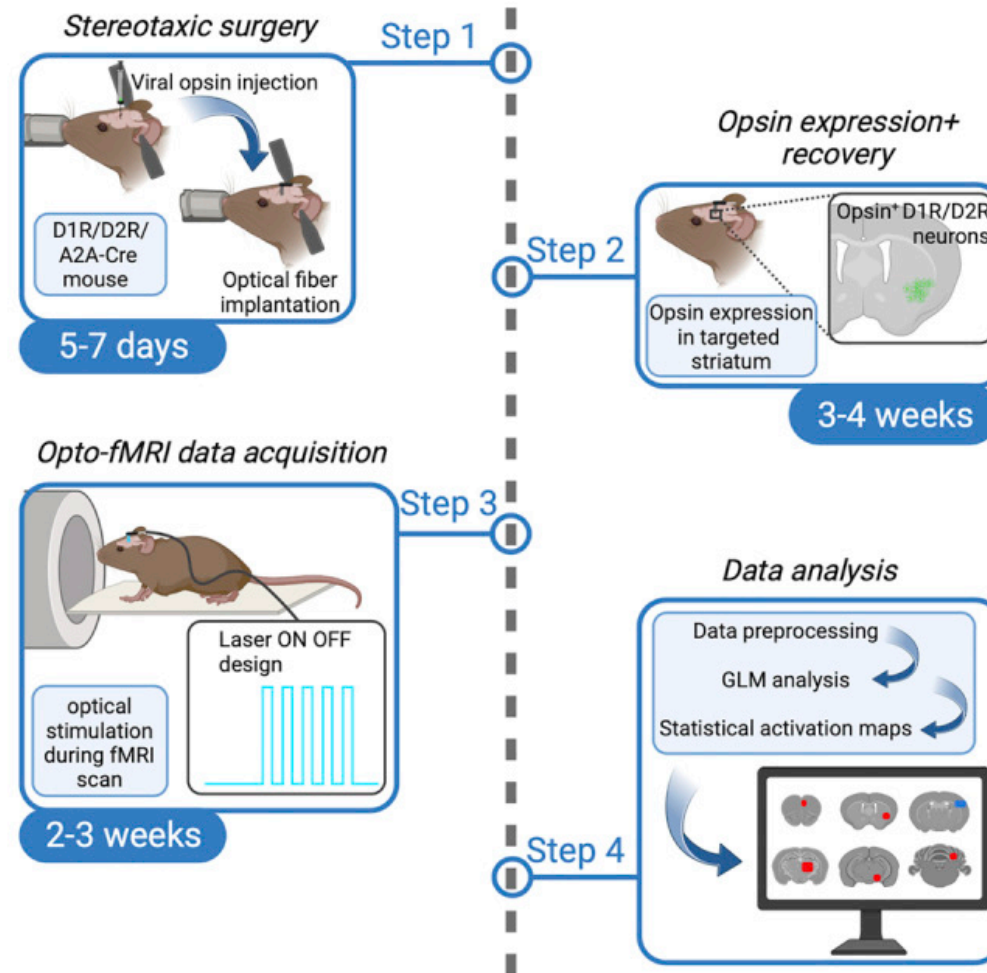
OPTOGENETICS-FMRI: EXAMPLE 1

RQ: Can we use opto-fMRI to study different cell types within a circuit?



Grimm et al., 2022

OPTOGENETICS-FMRI: EXAMPLE 1

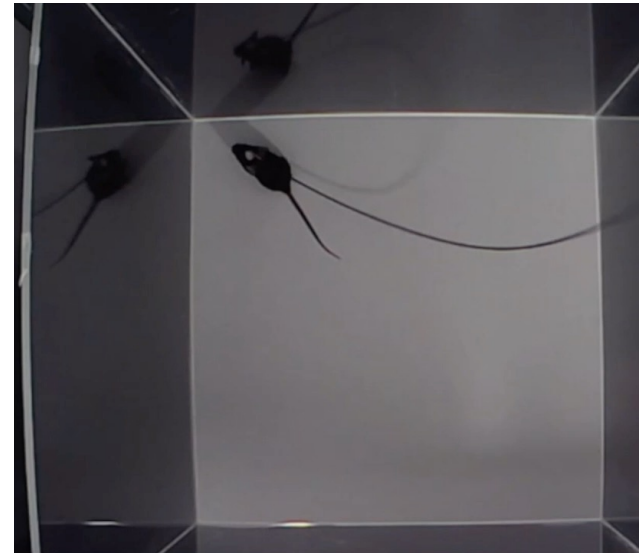
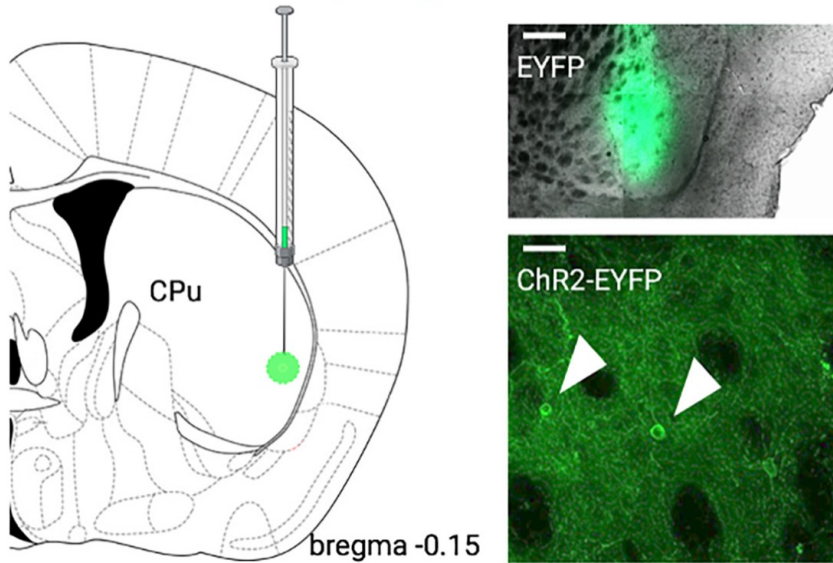


Grimm et al., 2022

OPTOGENETICS-FMRI: EXAMPLE 1

Results: immunohistochemistry and behaviour

AAV5-hEF1a-DIO- hChR2(H134R)-EYFP



D1r

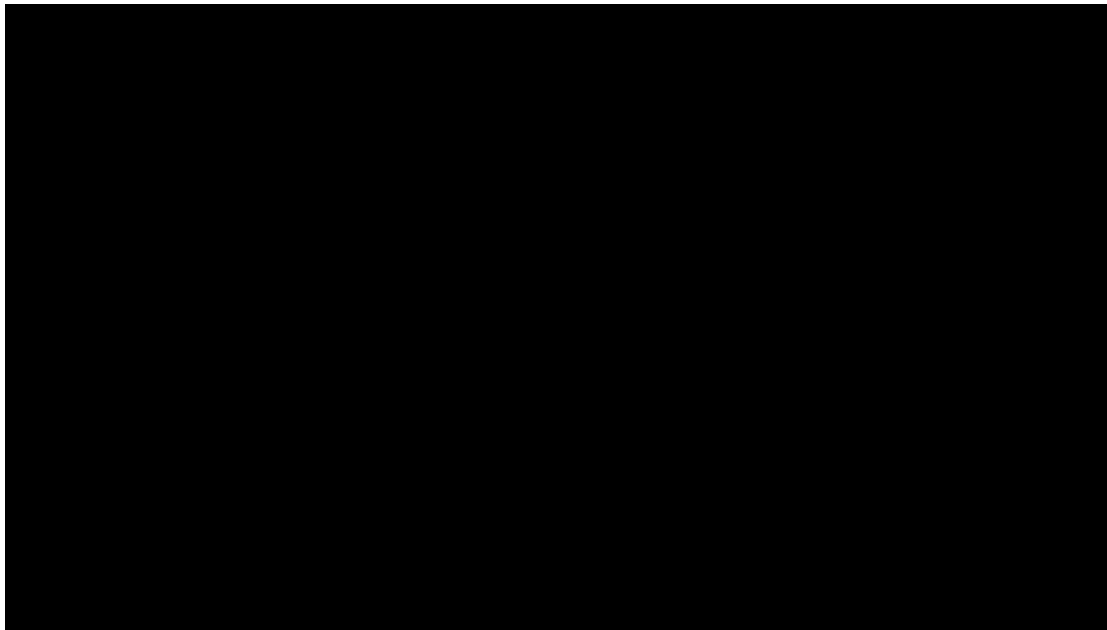


D2r

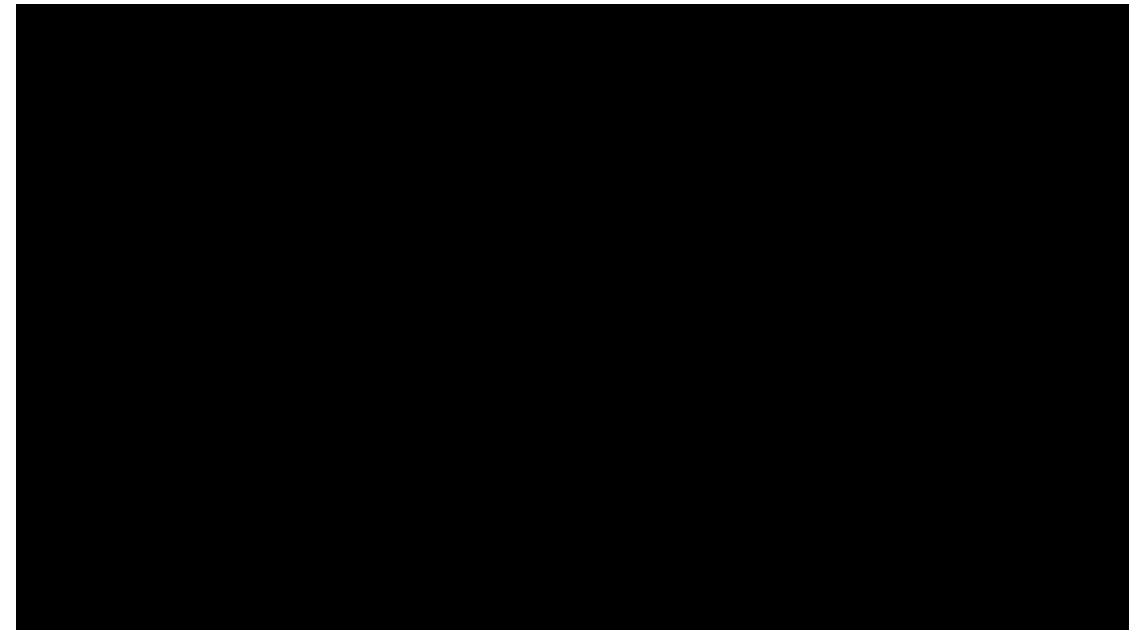
OPTOGENETICS-FMRI: EXAMPLE 1



Results: fMRI



D1r

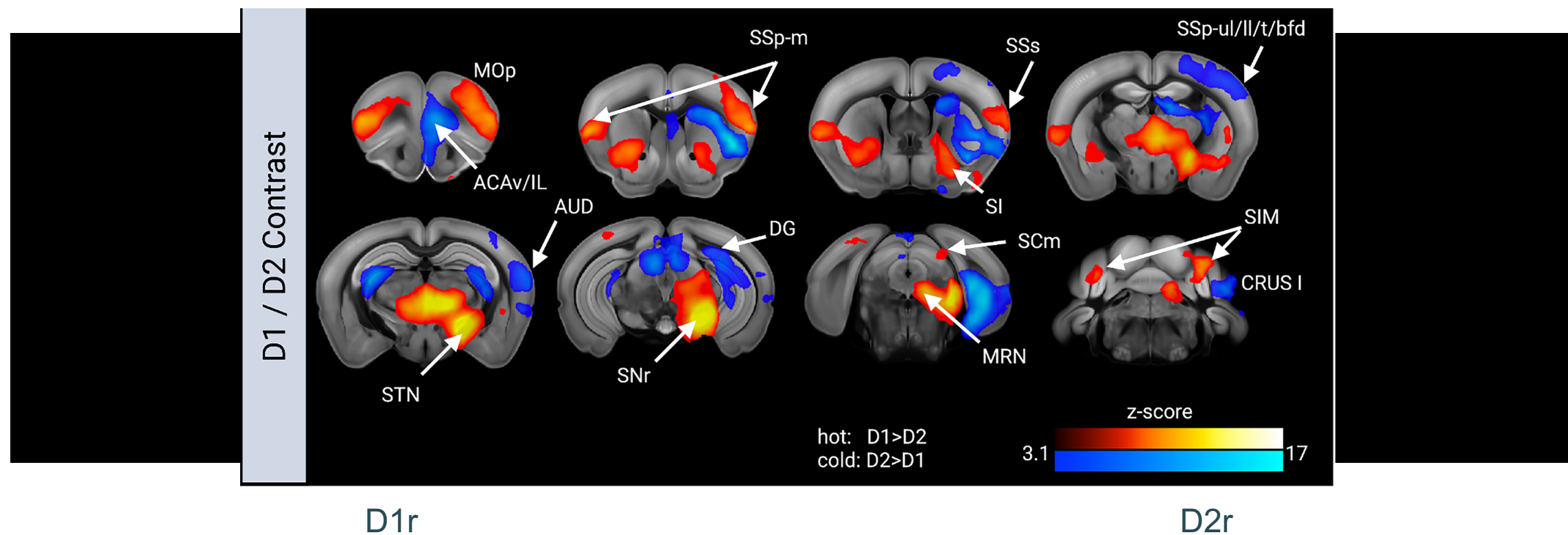


D2r

OPTOGENETICS-FMRI: EXAMPLE 1

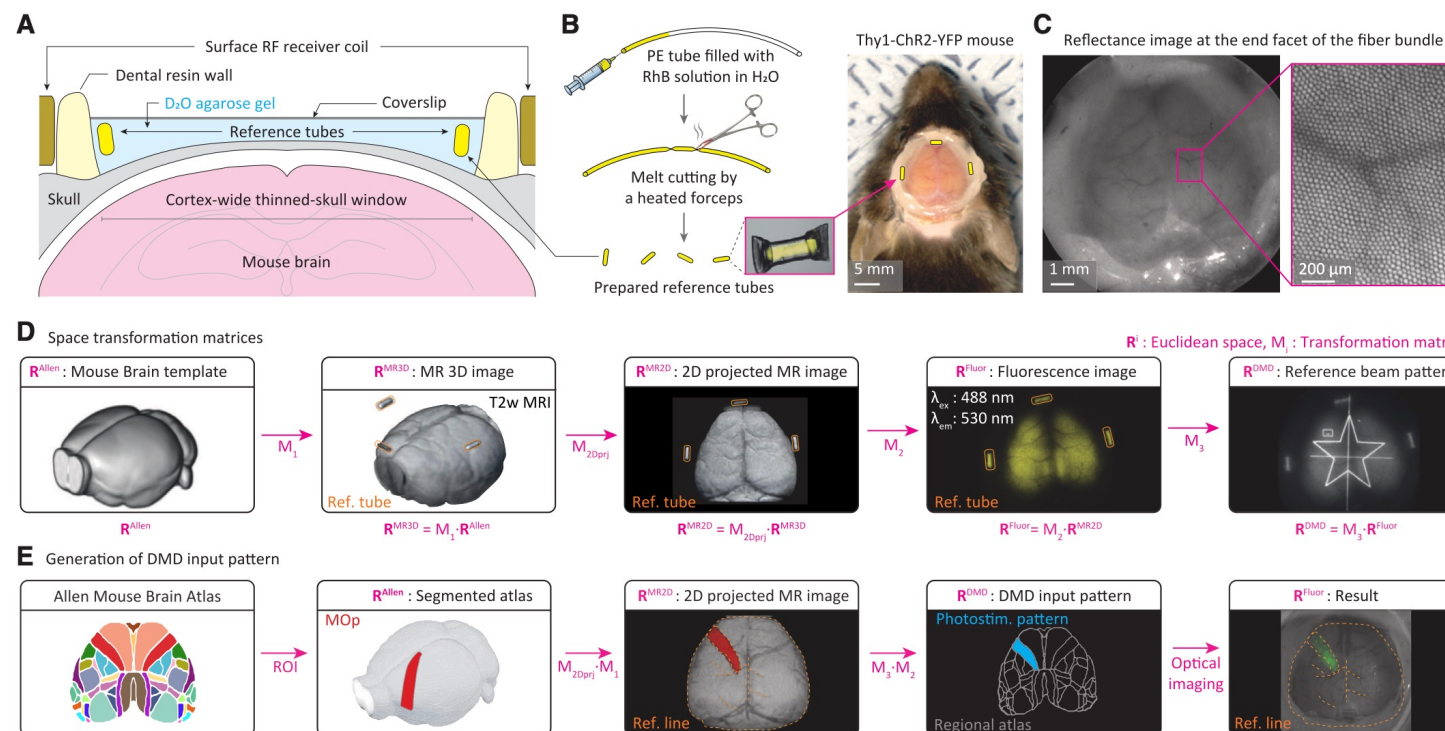
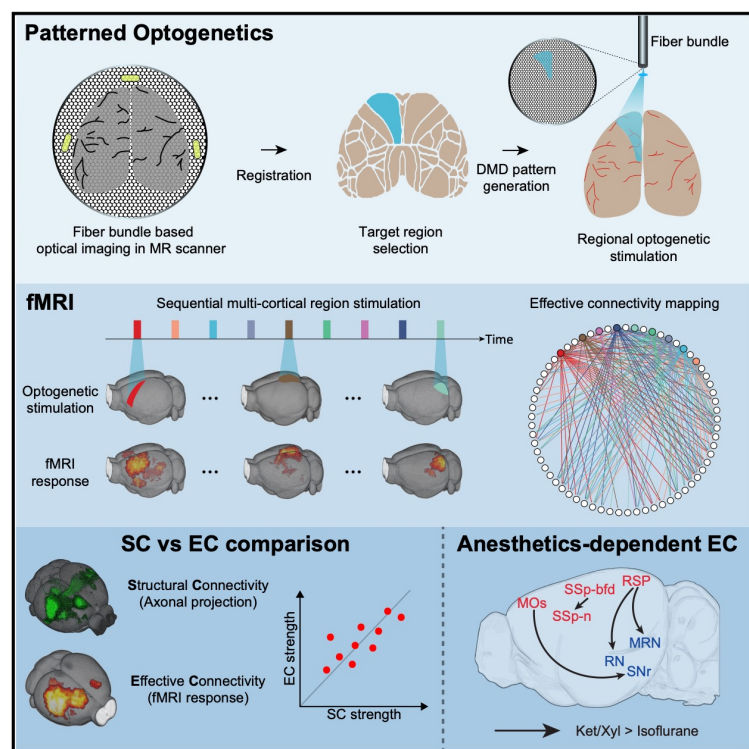


Results: fMRI



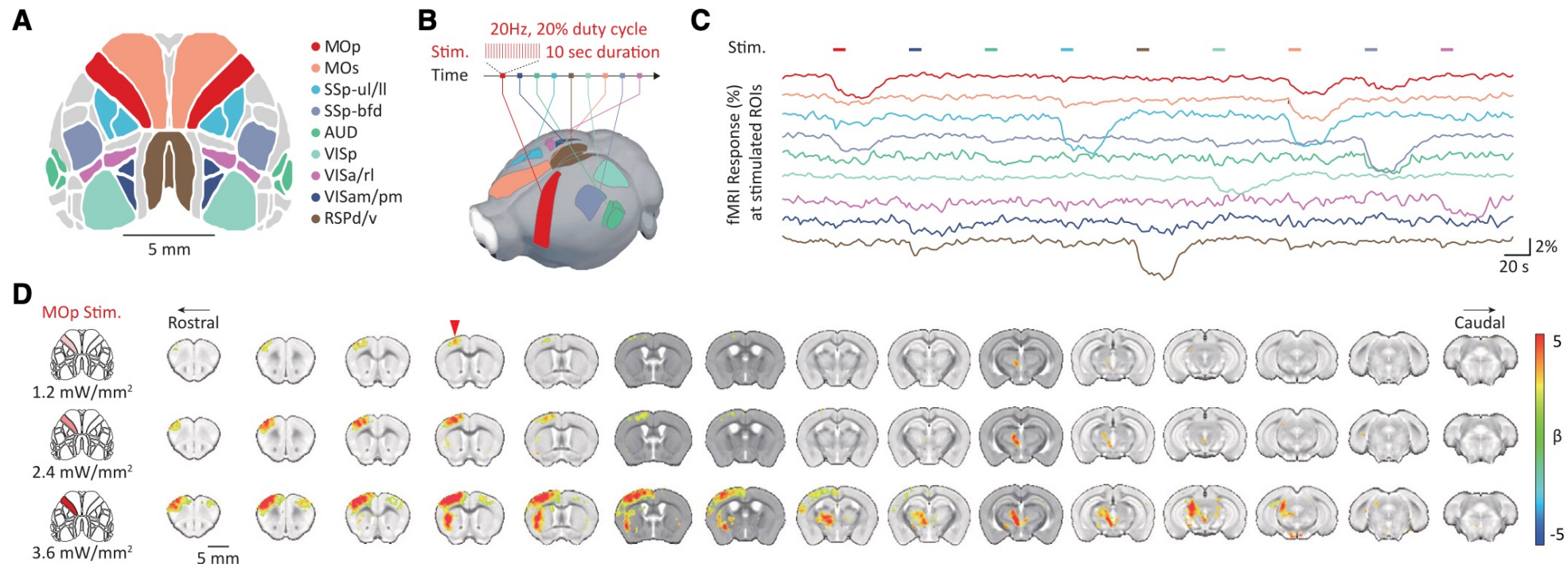
OPTOGENETICS-FMRI : EXAMPLE 2

RQ: Can we use opto-fMRI to perform whole-brain mapping of effective connectivity?



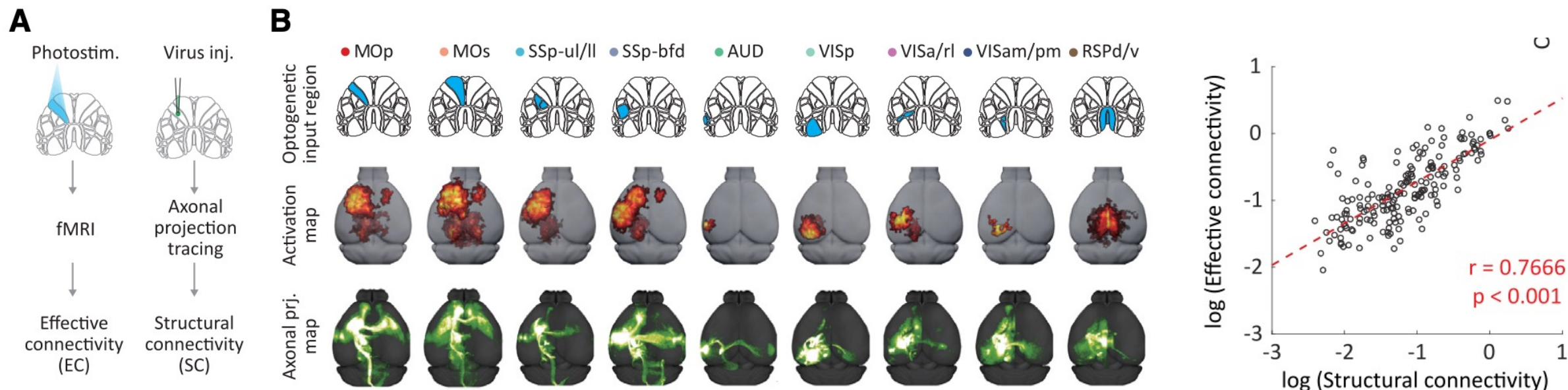
OPTOGENETICS-FMRI : EXAMPLE 2

RQ: Can we use opto-fMRI to perform whole-brain mapping of effective connectivity?



Kim et al., 2023

OPTOGENETICS-FMRI : EXAMPLE 2

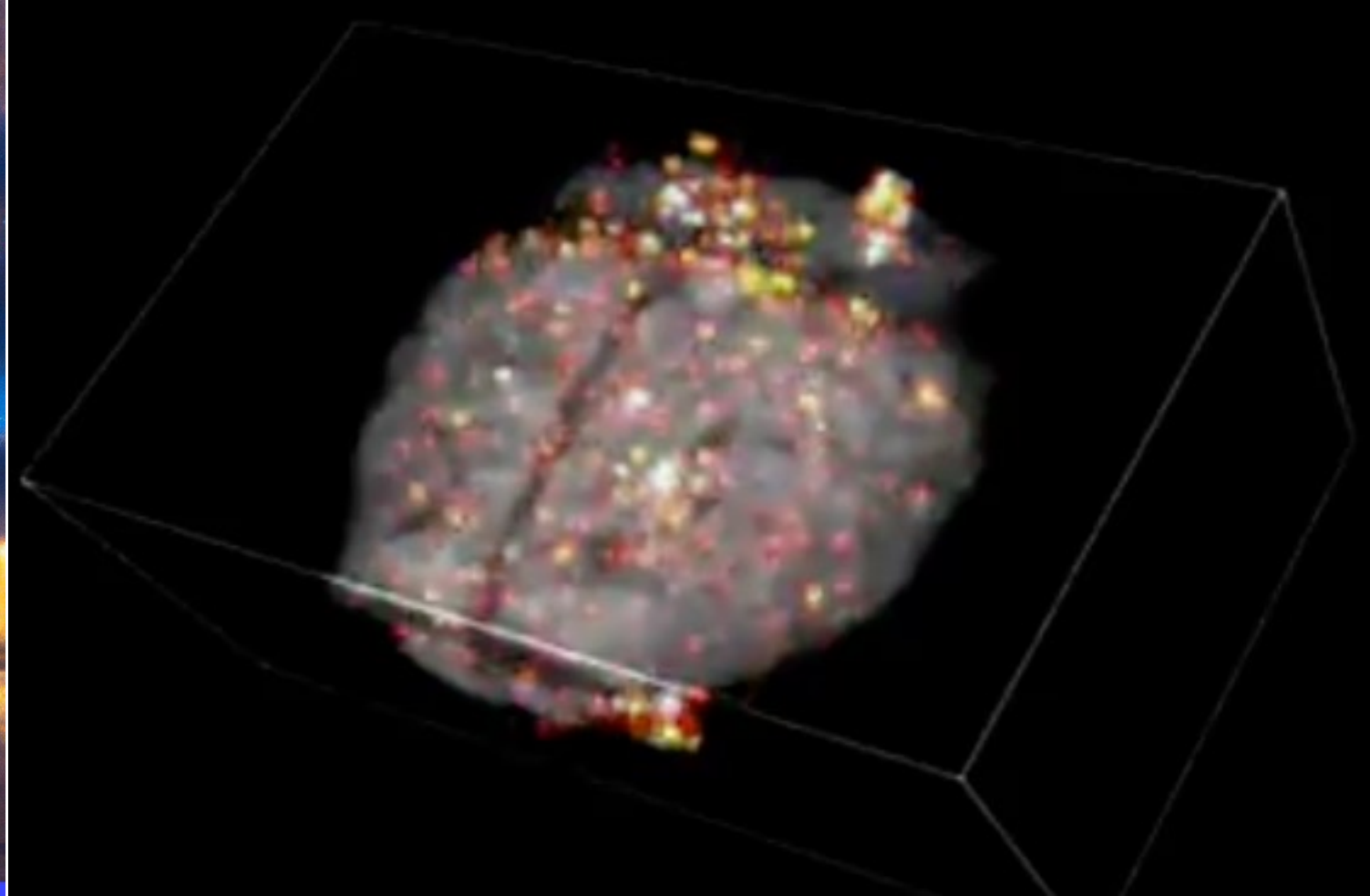


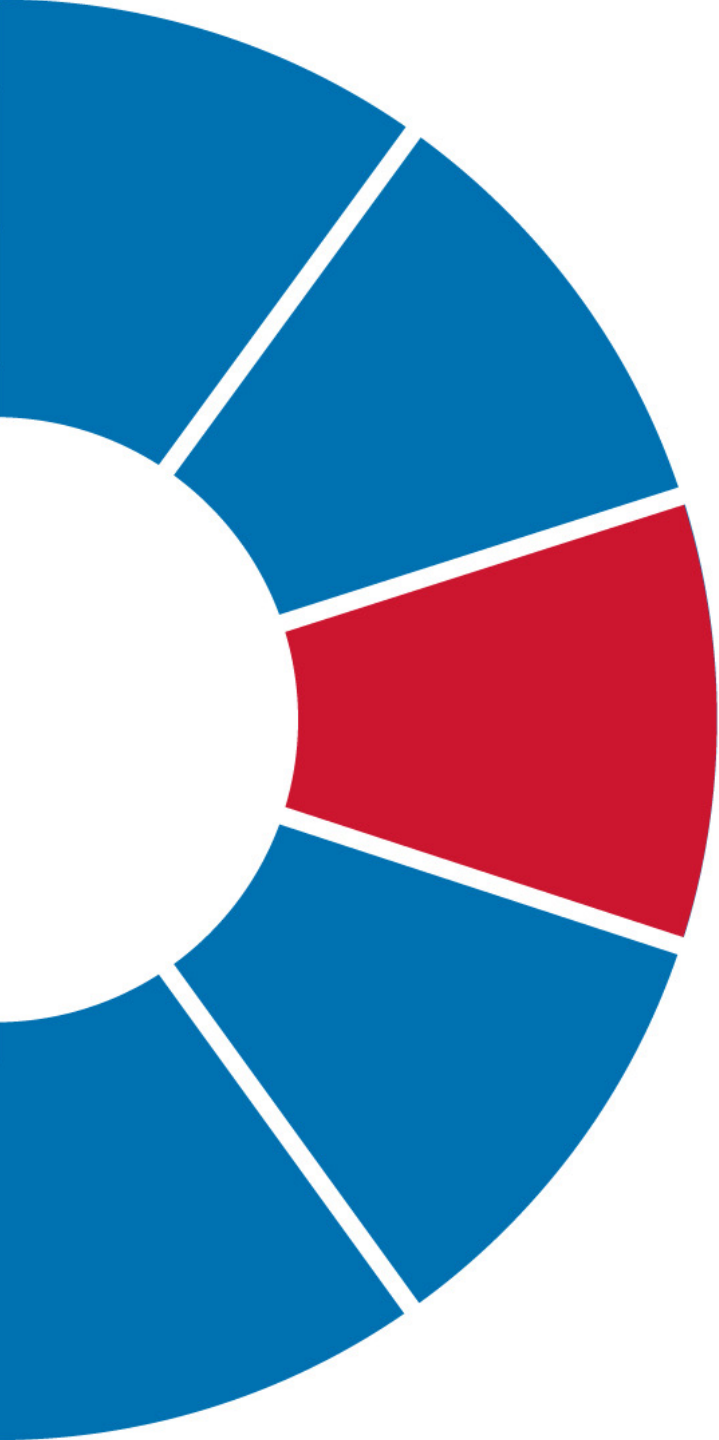
Excellent agreement between effective FC and structural axonal connectivity
(but only from the cortex)

Kim et al., 2023

C I B M . C H

OPTOGENETICS-FMRI : FIREWORKS IN THE BRAIN





PART 5. TRANSLATING FMRI RESULTS FROM RODENT TO HUMANS

“Many argue about that we can’t compare mouse fMRI data with human fMRI data because of the anaesthesia,. Those people forget the elephant in the room. Of course we can’t compare it. **We are measuring fMRI in a bloody mouse!**”

*Prof. Nicole Wenderoth
ETH Zürich*

FROM RODENTS TO HUMANS.. AND BACK

If our goal is to translate fMRI findings between animals and humans, which part of the brain (or brain networks) should we study?

What is special about the human brain?

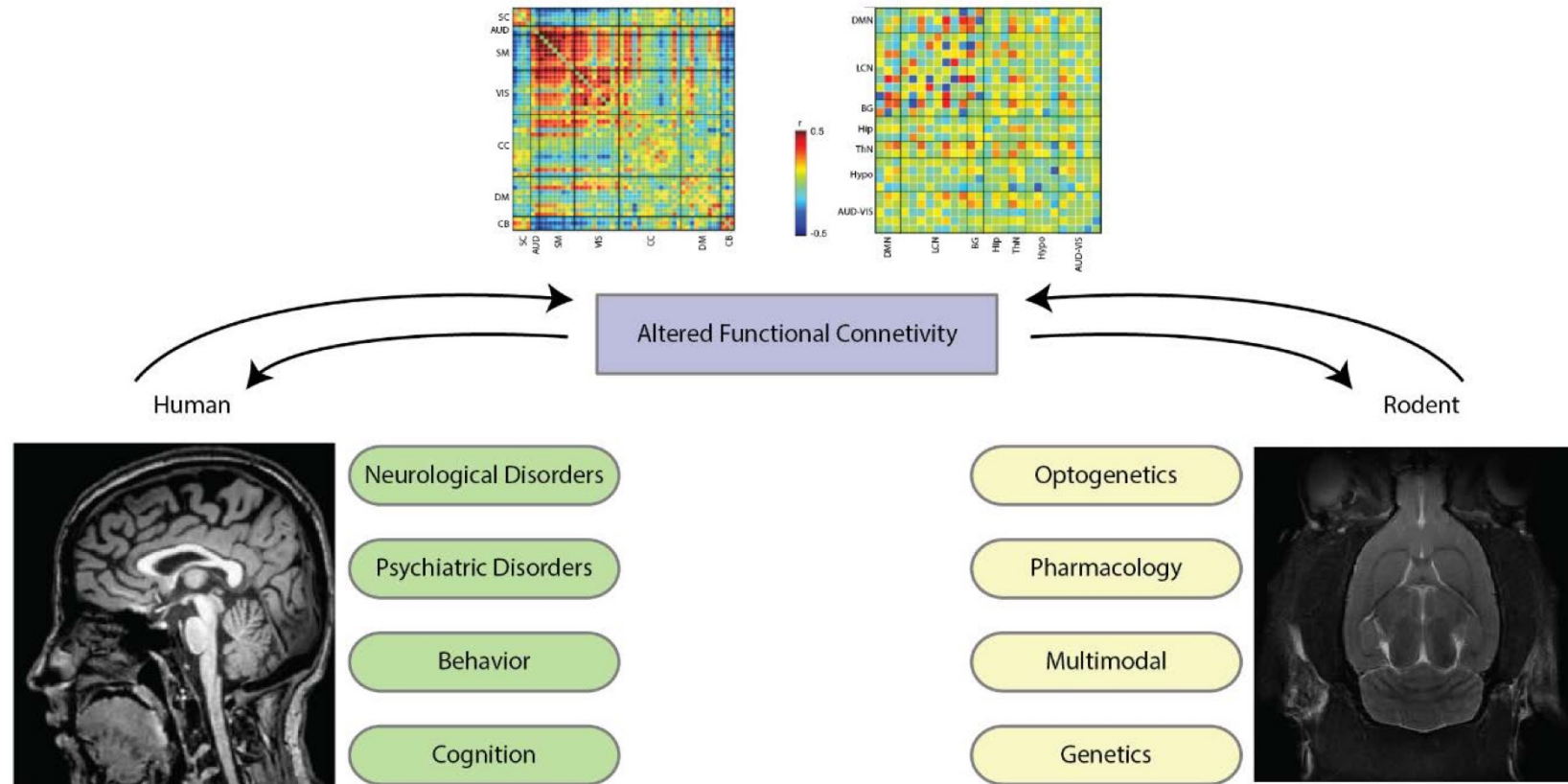


What makes brains different?

www.neuroecologylab.org

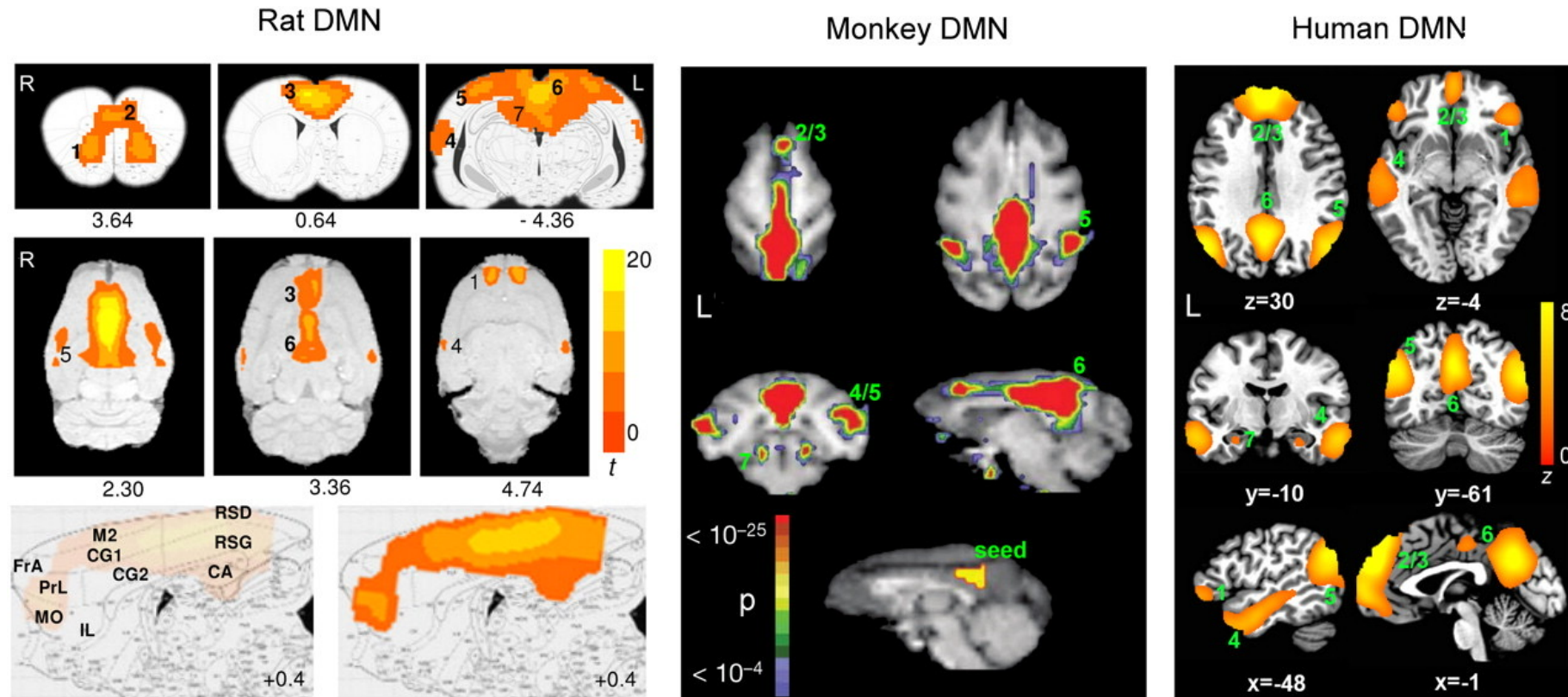
FROM RODENTS TO HUMANS.. AND BACK

Positive Feedback Cycle of Cross Species Comparison



MATCHING FUNCTIONAL NETWORKS

Comparing network anatomy



Hanbing et al., PNAS 2012

MATCHING FUNCTIONAL NETWORKS

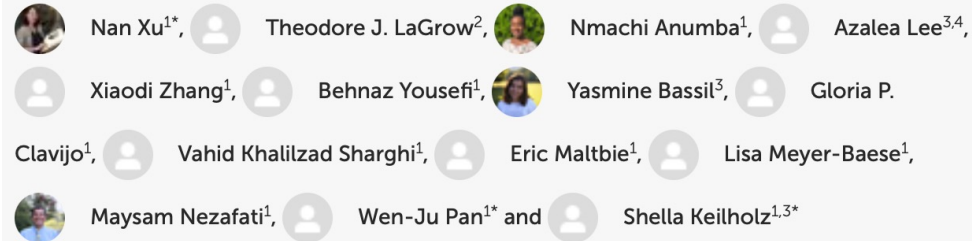
REVIEW article

Front. Neurosci., 08 March 2022

Sec. Brain Imaging Methods

Volume 16 - 2022 | <https://doi.org/10.3389/fnins.2022.816331>

Functional Connectivity of the Brain Across Rodents and Humans

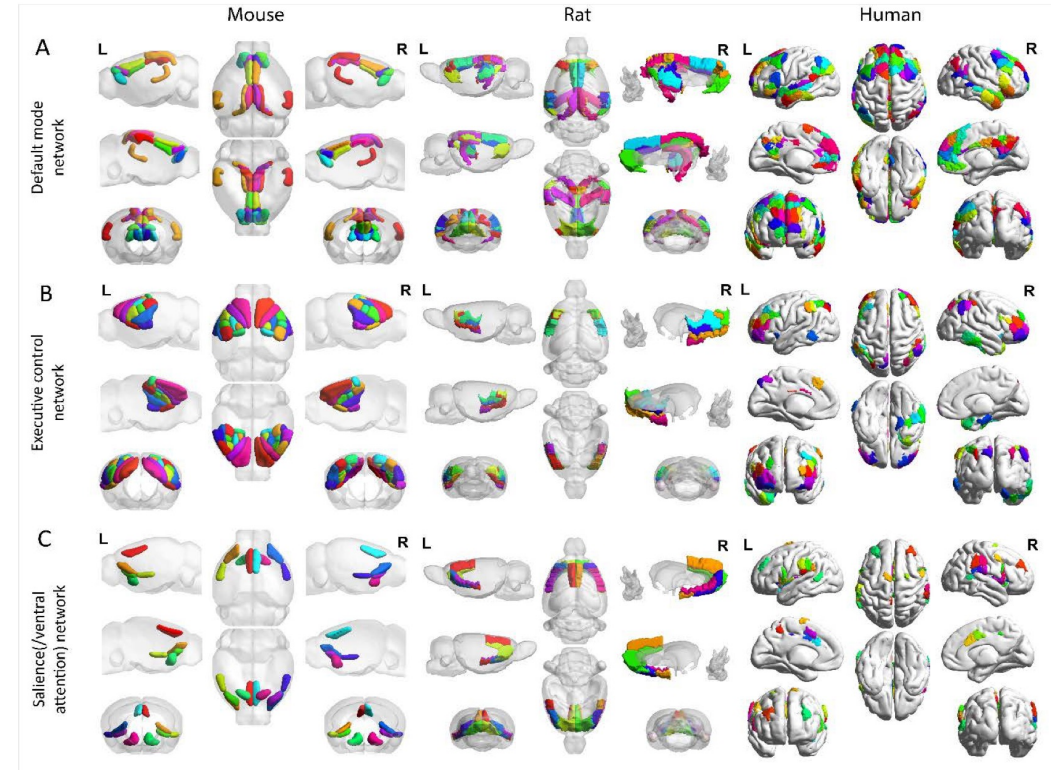


¹ Biomedical Engineering, Emory University and Georgia Tech, Atlanta, GA, United States

² Electrical and Computer Engineering, Georgia Tech, Atlanta, GA, United States

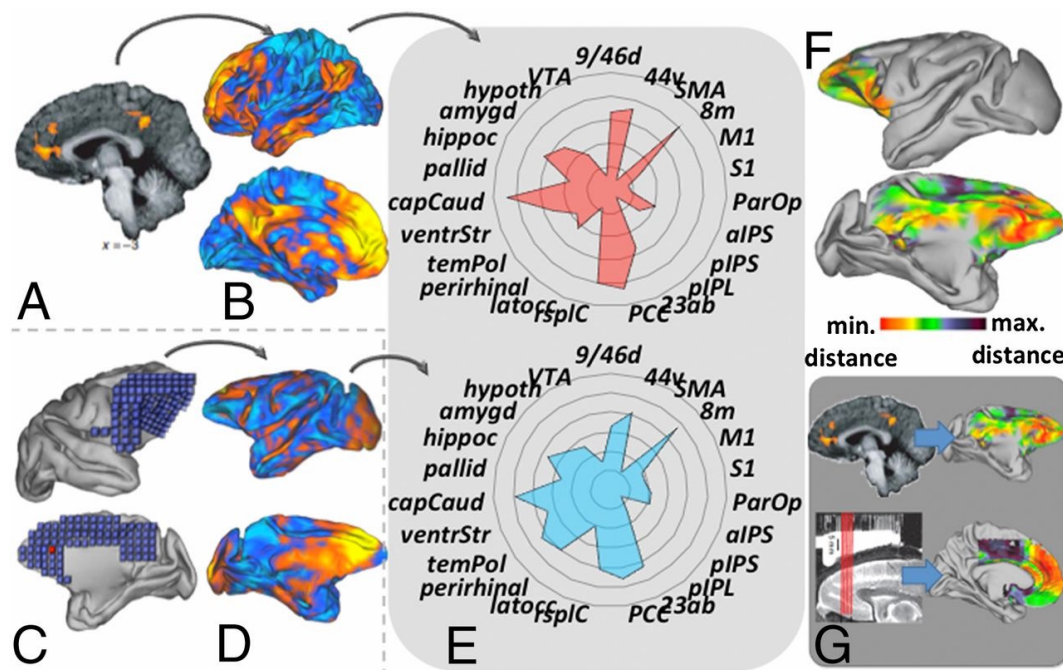
³ Neuroscience Graduate Program, Emory University, Atlanta, GA, United States

⁴ Emory University School of Medicine, Atlanta, GA, United States

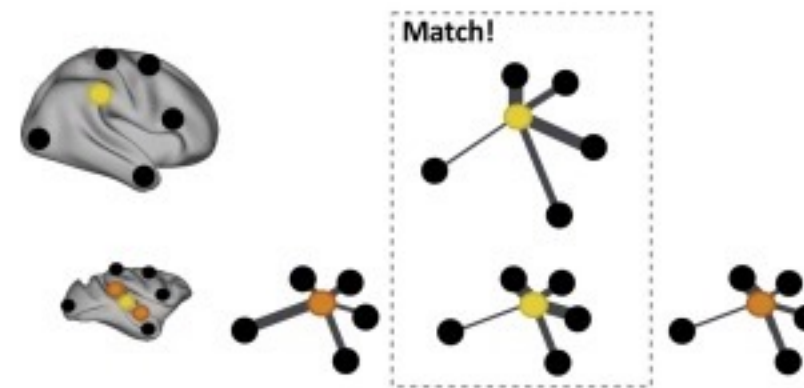


MATCHING CONNECTIVITY FINGERPRINTS

KEY HYPOTHESIS: If we can define a set of homologous anatomical/functional regions, we should be able to define homologous connectivity fingerprints in every voxel



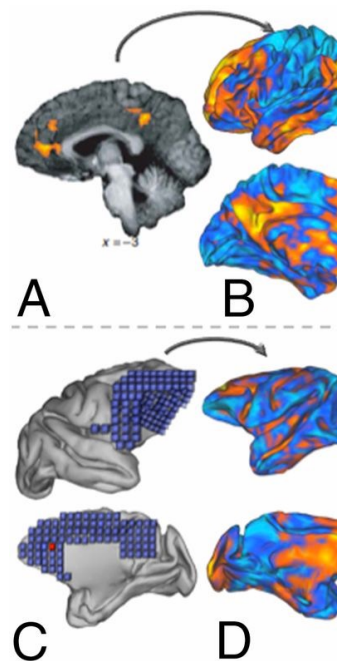
Connectivity fingerprints



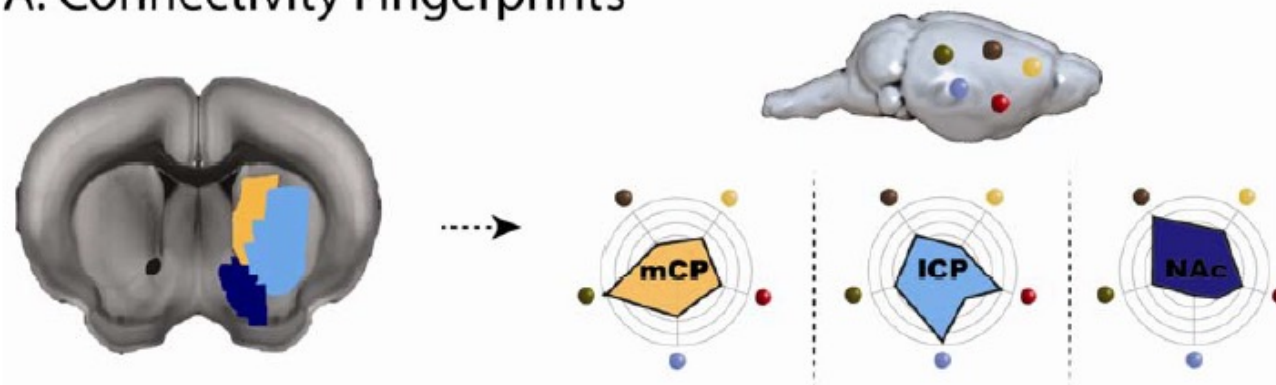
Mars et al., Trends in Cognitive Sciences, 2018

MATCHING CONNECTIVITY FINGERPRINTS

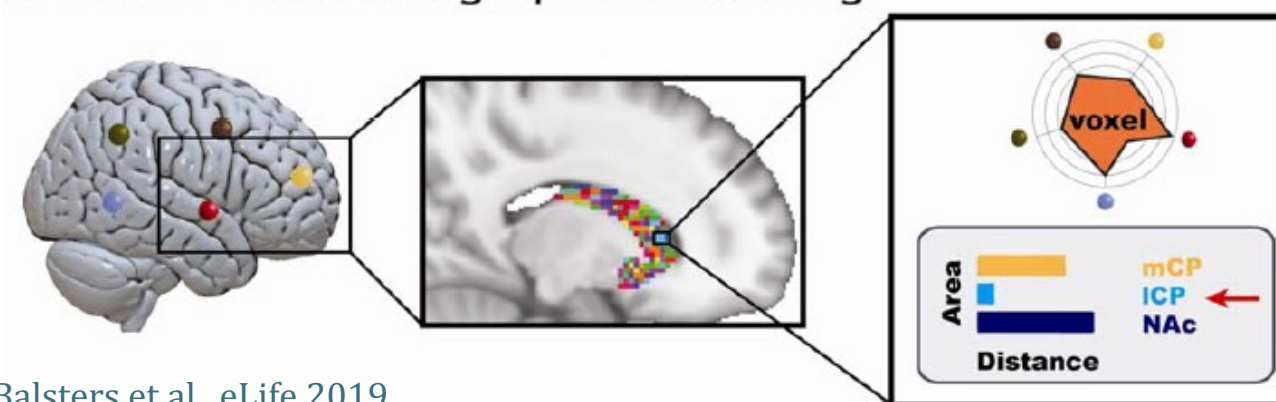
KEY HYPOTHESIS
regions, we should
every voxel



A. Connectivity Fingerprints



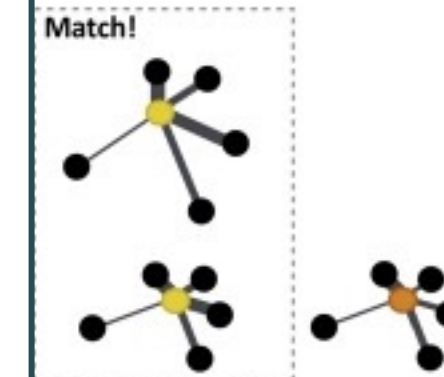
B. Mouse-Human fingerprint matching



Balsters et al., eLife 2019

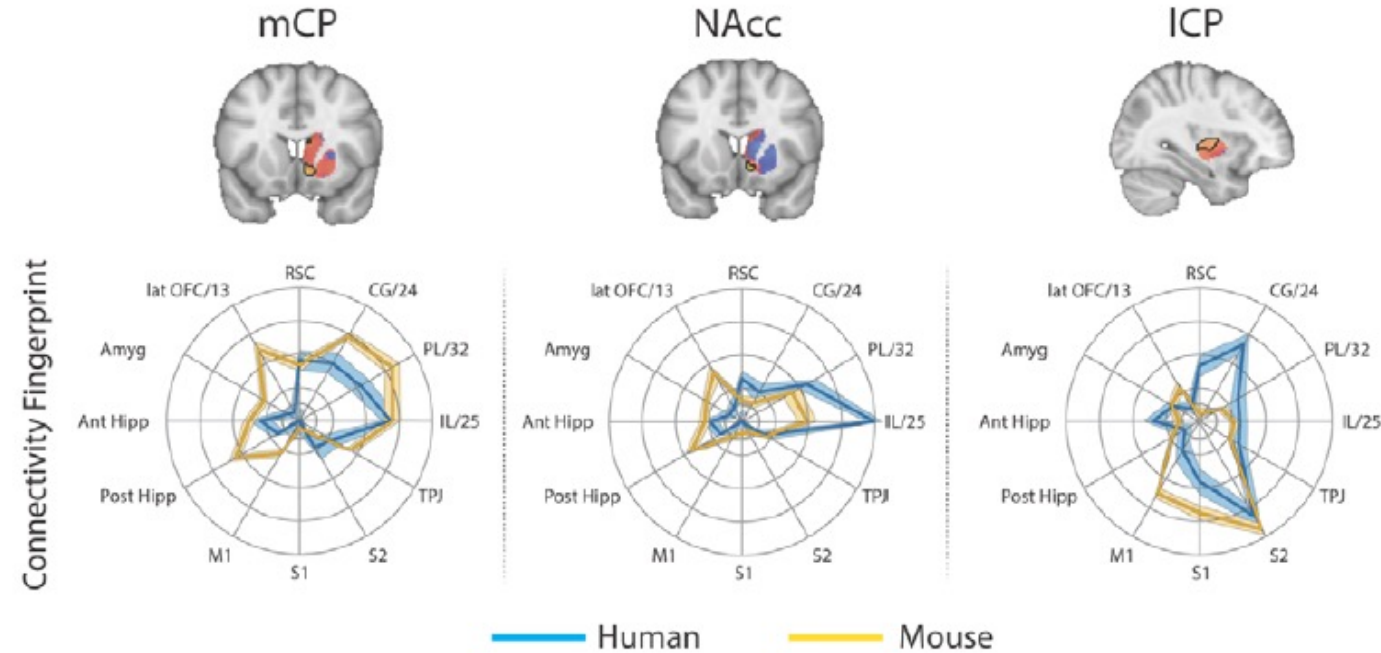
omical/functional
fingerprints in

vity
nts



, Trends in Cognitive Sciences, 2018

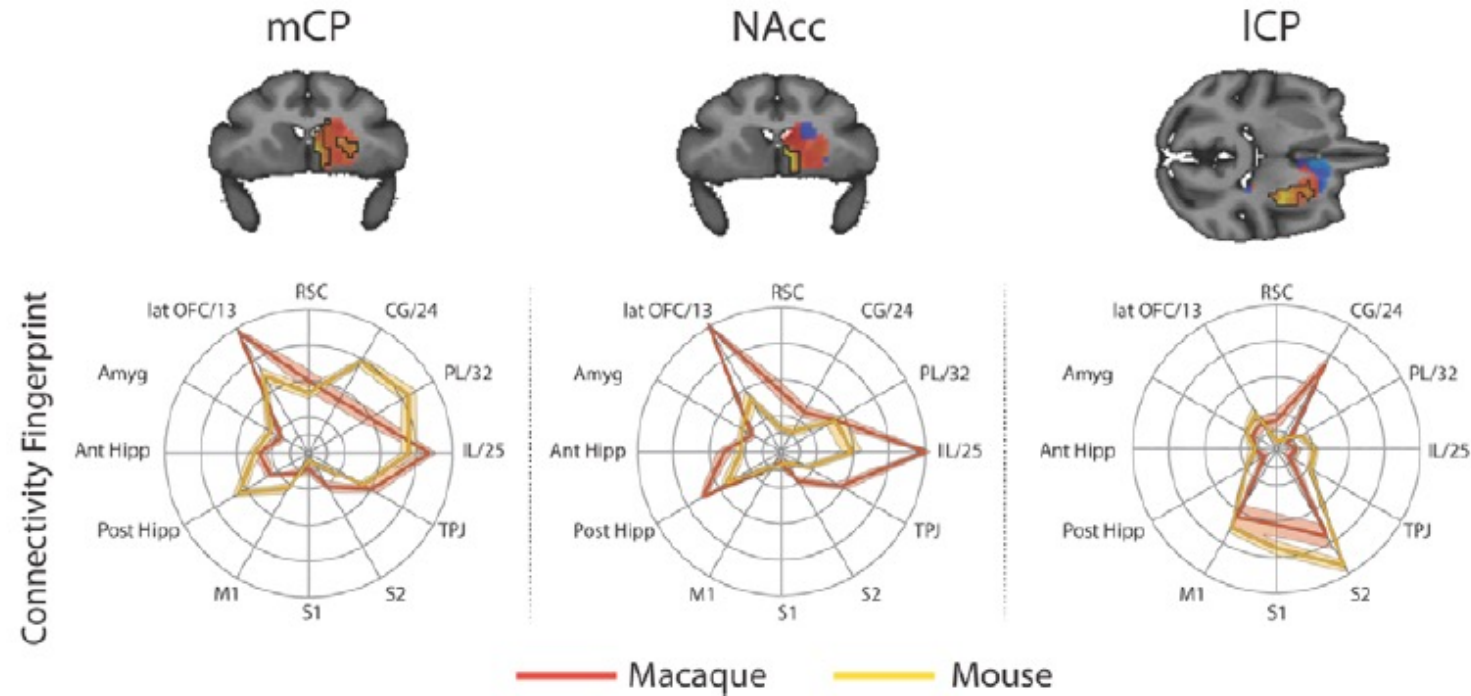
FROM RODENTS TO HUMANS



- Unassigned voxels accounted for 85% of the caudate nucleus volume, 77% of the putamen volume, and 5% of the NAcc volume

Balsters et al., eLife 2019

FROM RODENTS TO MACAQUES



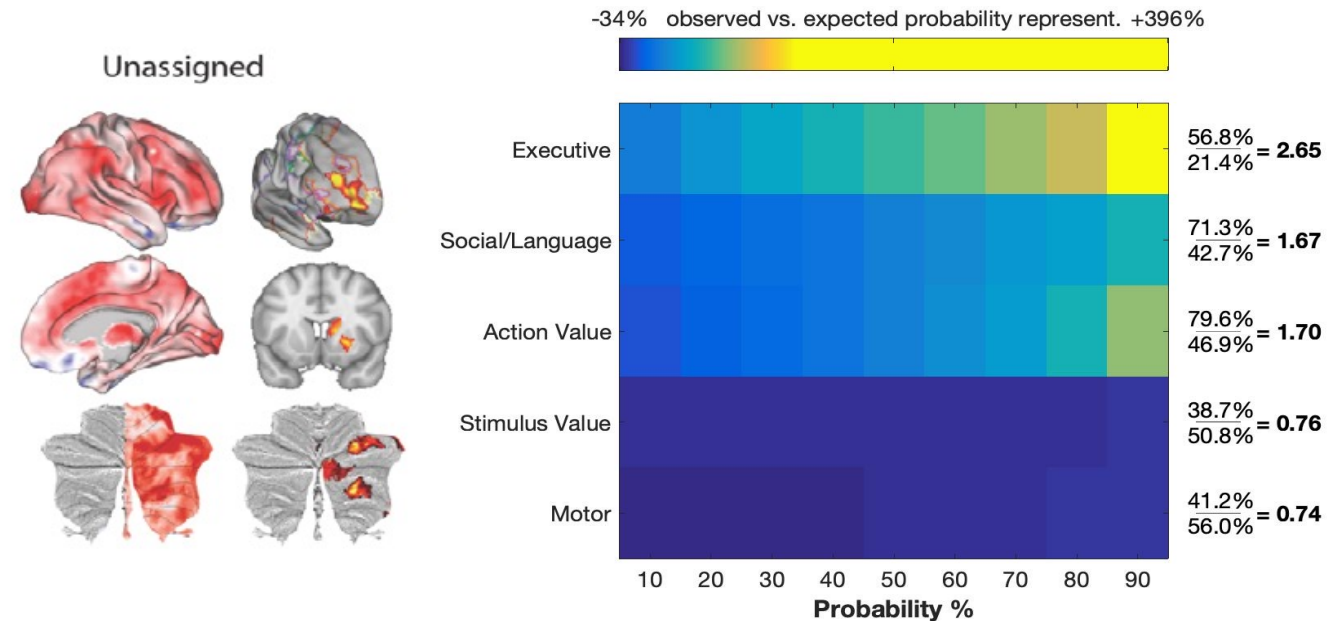
- Unassigned voxels accounted for 79% of the caudate nucleus volume, 62% of the putamen volume, and 9% of the NAcc volume.

Balsters et al., eLife 2019

WHAT IS UNIQUE OF HUMANS?

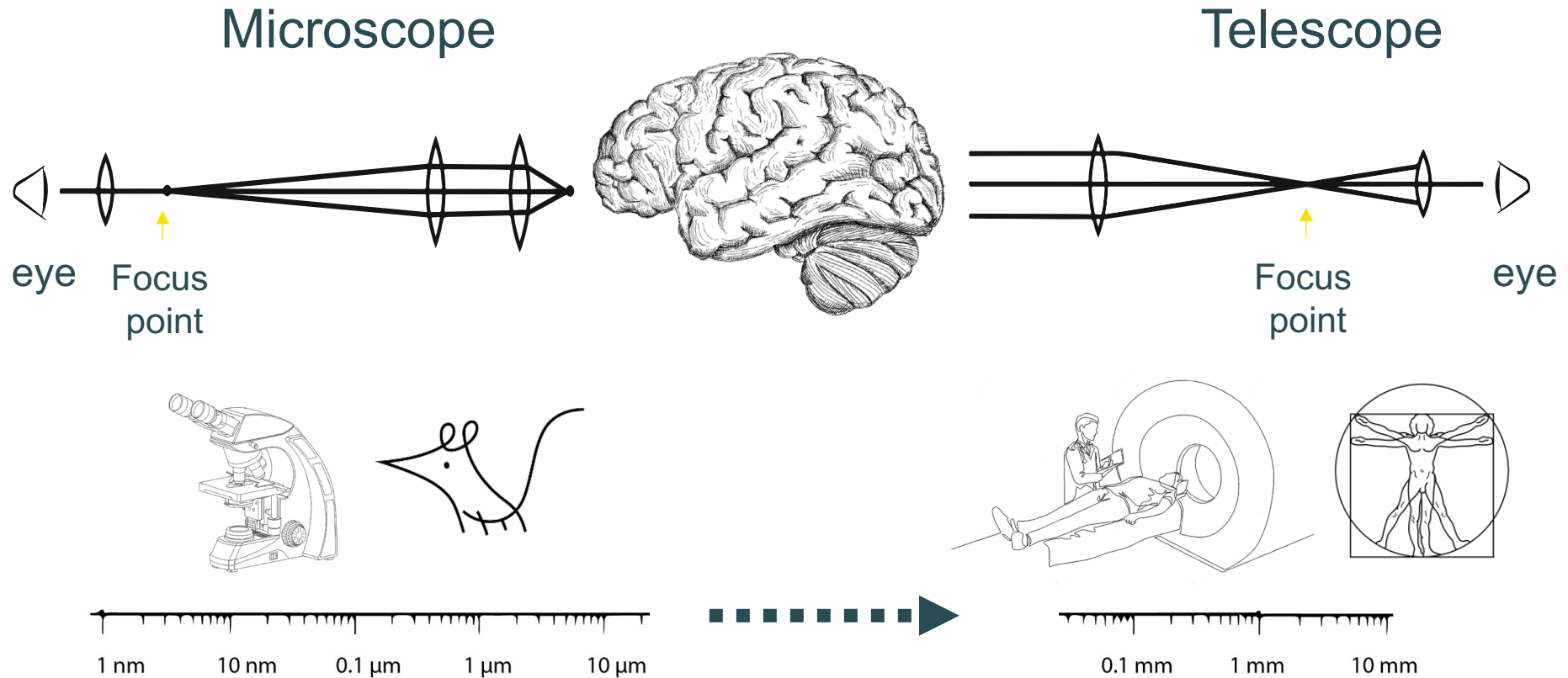
Neurosynth.org

- The unassigned voxels were located to striatal regions associated with **executive function**, social/language, and action value (Pauli et al., 2016).
- These unassigned voxels map the expansion of the prefrontal cortex in primates.



Balsters et al., eLife 2019

TAKE HOME MESSAGE

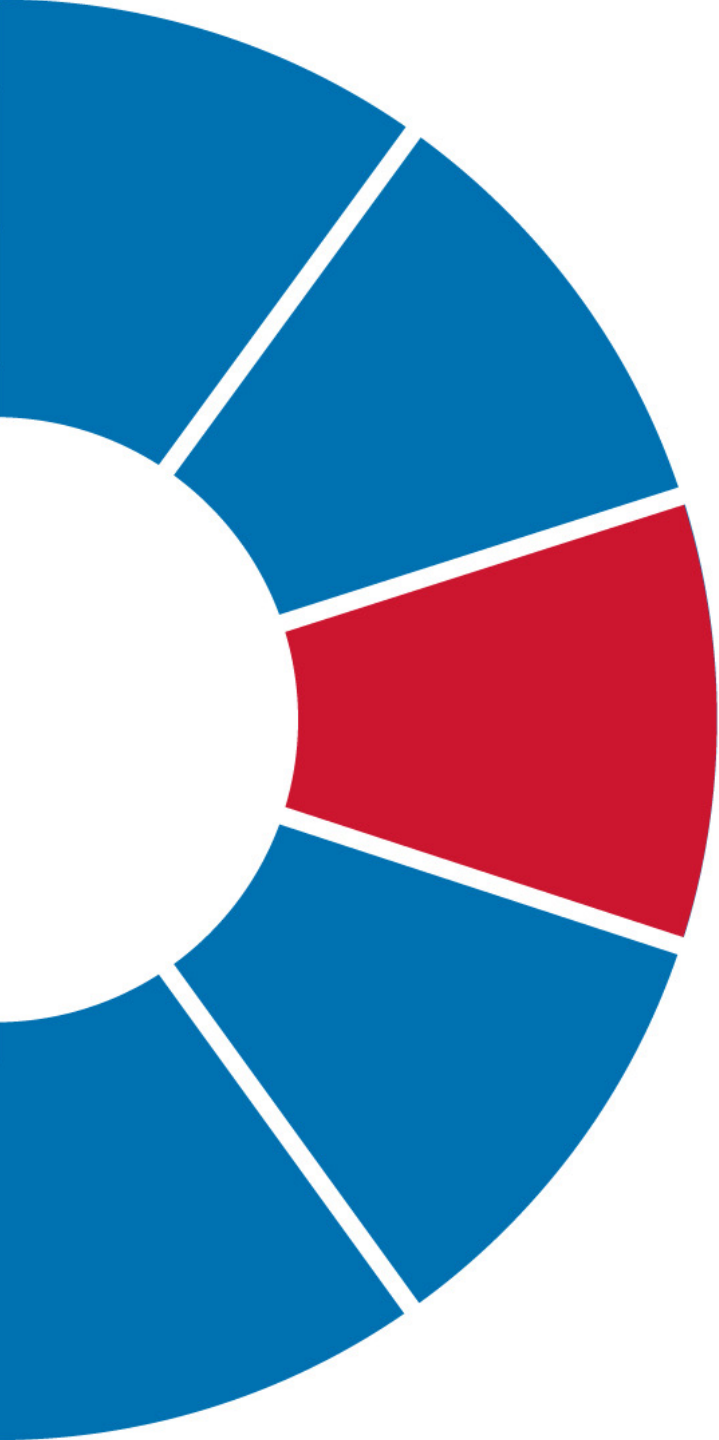




THANK YOU FOR YOUR ATTENTION



C I B M . C H



FOR ANY QUESTIONS YOU MAY HAVE,
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