camh
Centre for Addiction and Mental Health

Krembil Centre for Neuroinformatics

Using big data, artificial intelligence and brain modelling to fundamentally change our understanding of mental illness.

SUMMER SCHOOL 2021

Day 5

Whole-Brain Modelling and Neuroimaging Connectomics

Morning: Introduction to neuroimaging connectomics

CAMH Land Acknowledgement

CAMH is situated on lands that have been occupied by First Nations for millennia; lands rich in civilizations with knowledge of medicine, architecture, technology, and extensive trade routes throughout the Americas. In 1860, the site of CAMH appeared in the Colonial Records Office of British Crown as the council grounds of the Mississaugas of the New Credit, as they were known at the time.

Today, Toronto is covered by the Toronto Purchase, treaty No. 13 of 1805 with the Mississaugas of the Credit.

Toronto is now home to a vast diversity of First Nations, Inuit, and Métis who enrich this city.

CAMH is committed to reconciliation. We will honour the land through programs and places that reflect and respect its heritage. We will embrace the healing traditions of the Ancestors, and weave them into our caring practices. We will create new relationships and partnerships with First Nations, Inuit, and Métis and share the land and protect it for future generations.

Code of Conduct

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The KCNI Summer School is dedicated to providing a harassment-free learning experience for everyone, regardless of gender, gender identity and expression, sexual orientation, disability, physical appearance, body size, race, age or religion. We do not tolerate harassment of event participants in any form

Harassment includes, but is not limited to:

- Verbal comments that reinforce social structures of domination related to gender, gender identity and expression, sexual orientation, disability, physical appearance, body size, race, age or religion.
- Sexual images in public spaces
- Deliberate intimidation, stalking, or following
- Harassing photography or recording
- Sustained disruption of talks or other events
- Inappropriate physical contact
- Unwelcome sexual attention
- Advocating for, or encouraging, any of the above behaviour

Remember - many ways to engage

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? 👍

(during sessions) Use the chat or the ask question!

You can always return to the session and re-watch the vidos after the session ends

come chat with us in KCNI Summer School Slack :)

virtually meet with us in gather.town

Tell us how the session went (post session survey):
https://forms.gle/ji18qLMZEZ9L16Ln6

KCNISchool@camh.ca

Summer School Schedule

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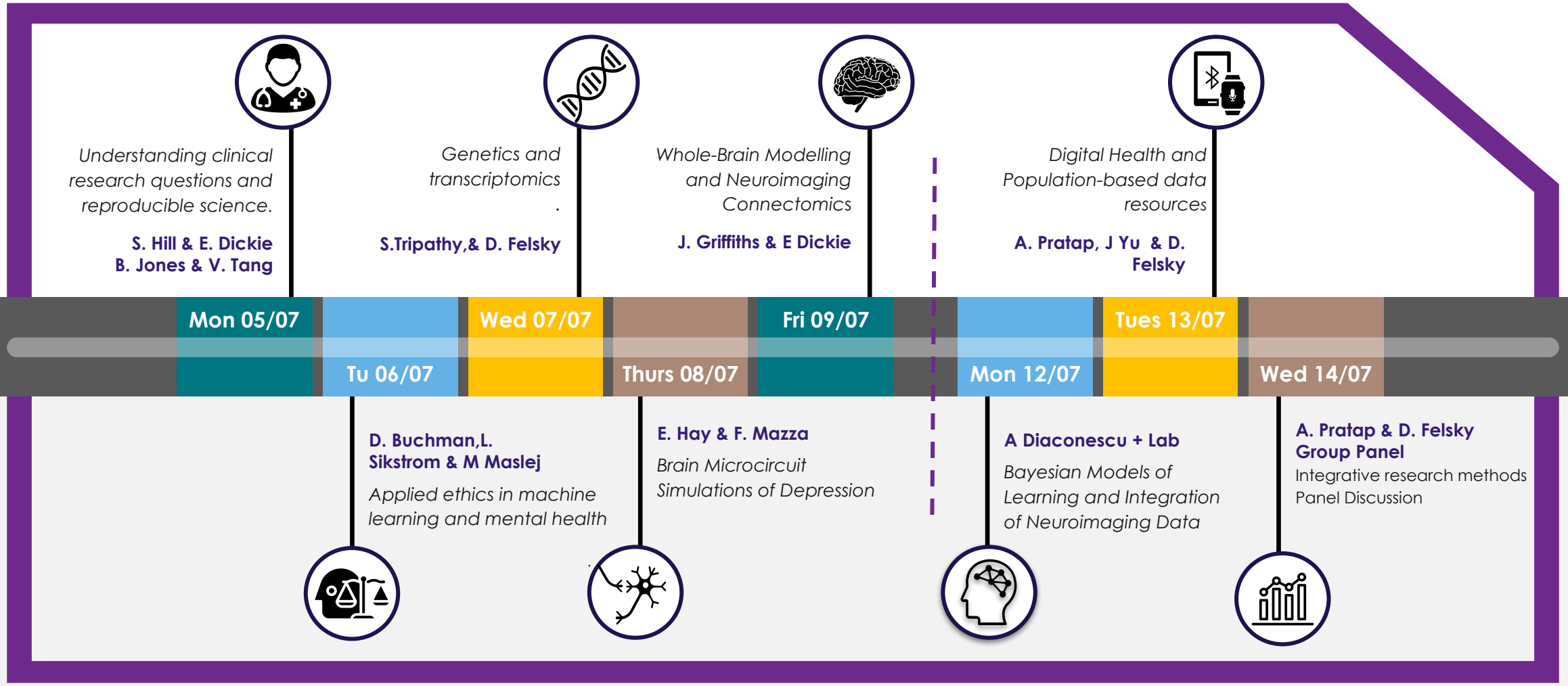

Today's Agenda

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Day 5:
Whole-Brain Modelling and Neuroimaging Connectomics

9:00 am - 10:30 am	*Lecture/Workshop: Neuroimaging connectomics - Brain Structure (sMRI and DMRI)* Erin Dickie & John Griffiths
10:45 am - 12:15 pm	*Lecture/Workshop: Neuroimaging connectomics - Brain Function (fMRI and EEG)* John Griffiths & Erin Dickie
1:00 pm - 2:30 pm	*Lecture: Intro to whole-brain modelling* John Griffiths
2:45 pm - 4:15 pm	*Workshop: simulating whole-brain activity, EEG, evoked responses, brain stimulation* John Griffiths

Instructors for this session

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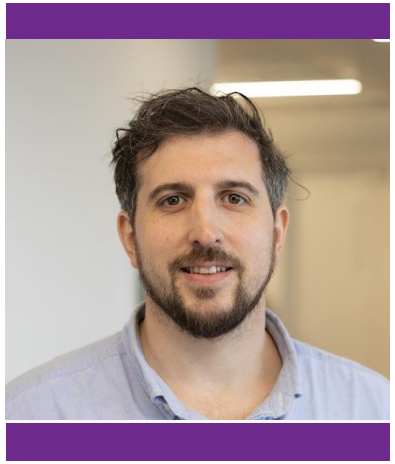

John Griffiths Ph.D

Lead - Whole Brain Modeling Group, Krembil Centre for Neuroinformatics - CAMH
Assistant Professor, University of Toronto Depts. Psychiatry & Medical Sciences

Twitter: @neurodidact
Github: @JohnGriffiths, @GriffithsLab
Website: grifflab.com

Erin Dickie Ph.D

Education and Knowledge Lead - KCNI
Scientist - Kimel Family Translational Imaging-Genetics Lab

Twitter: @ErinWDickie
Github: @edickie

Teaching Assistants for this section

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Kevin Kadak
MSc Student
Whole Brain Modelling Group - KCNI

Jerrold Jeyachandra
Research Methods Specialist
Kimel Family Translational Imaging-Genetics Lab

Shreyas Harita
PhD Student
Whole Brain Modelling Group - KCNI

Recapping...

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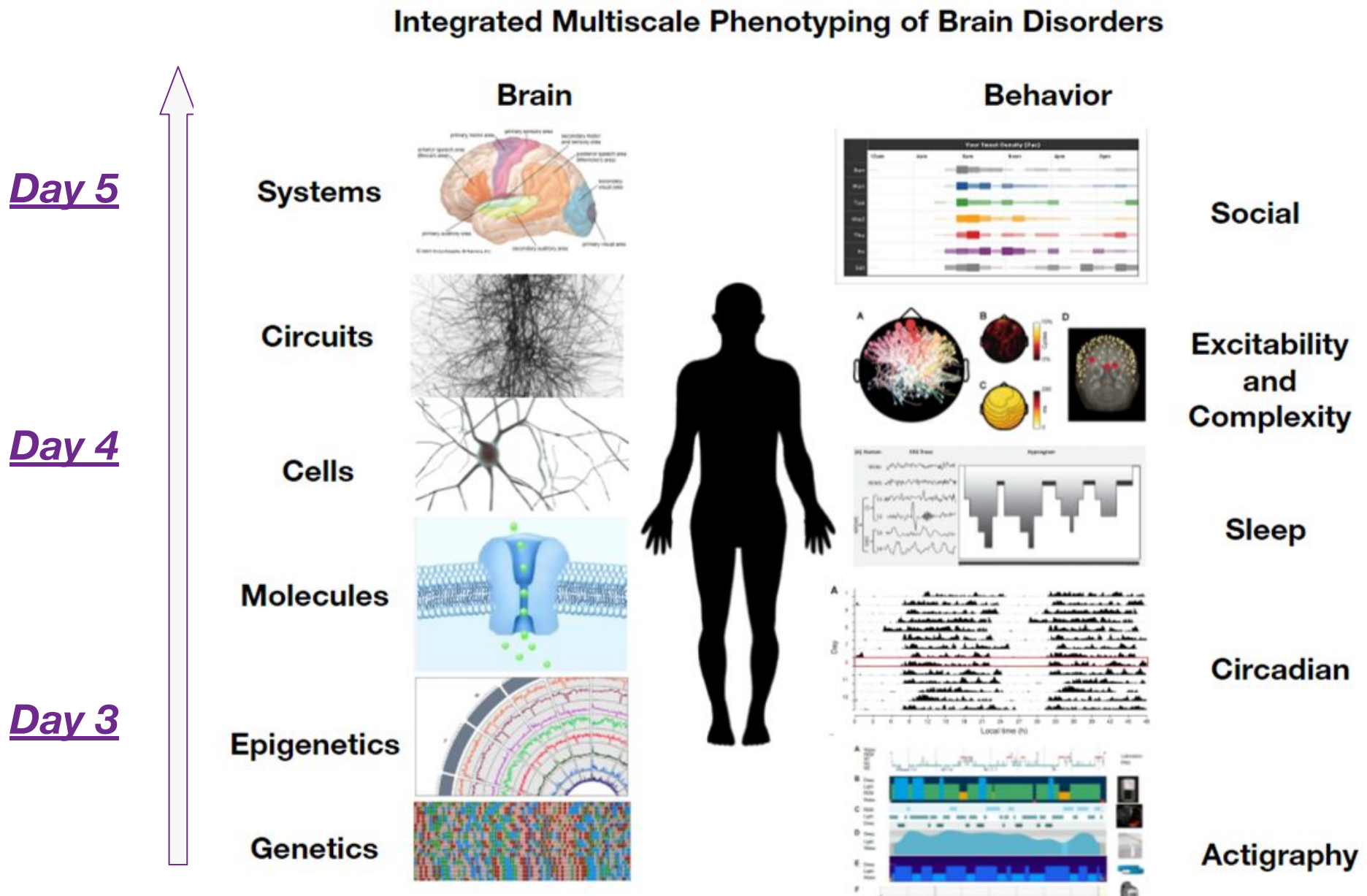

Recapping...

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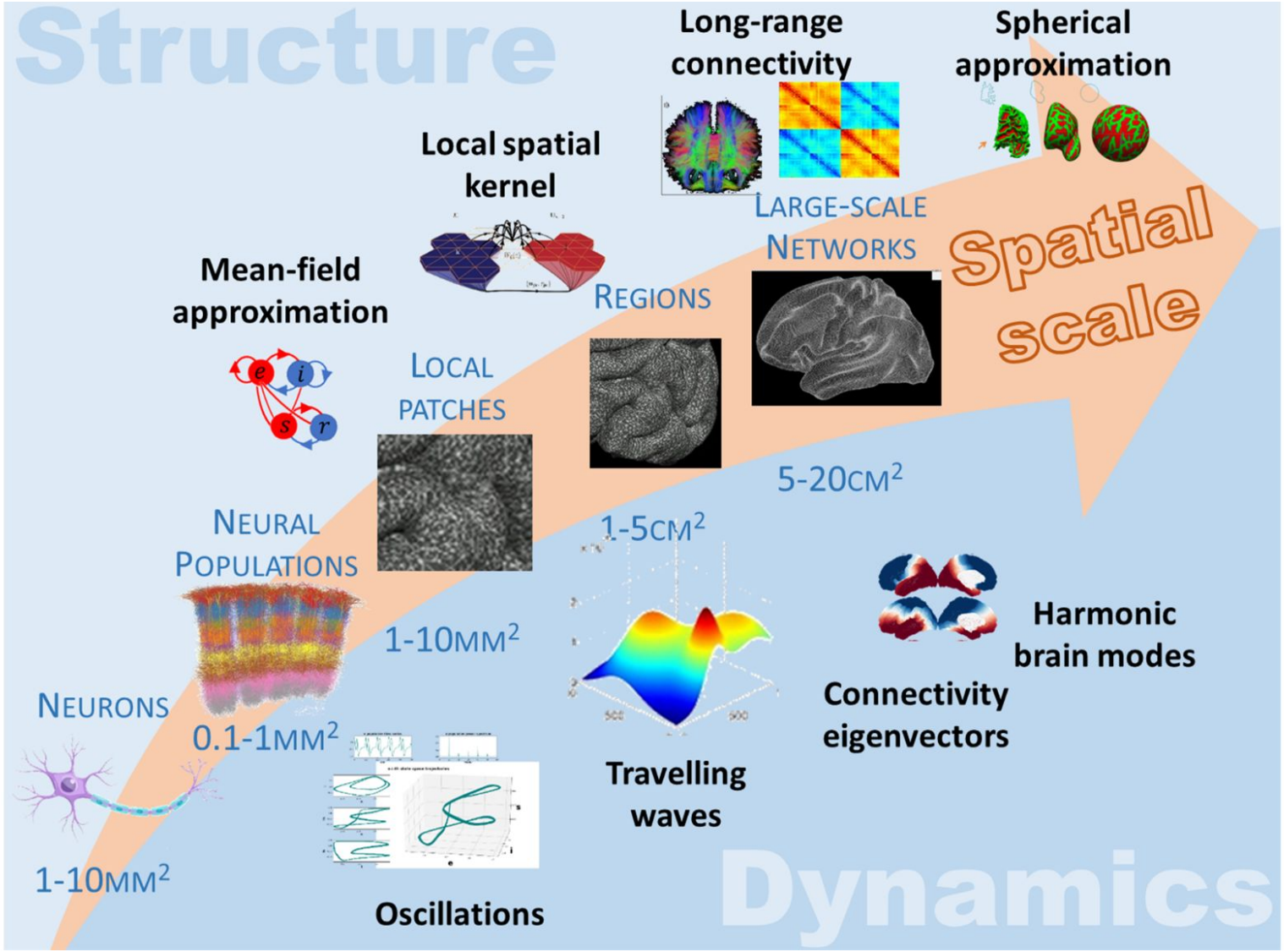
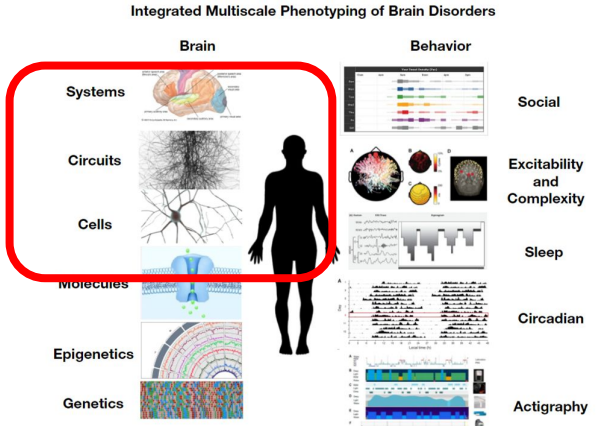
Day 5 (&6)

Day 4





Why does WBM go well together with NC?

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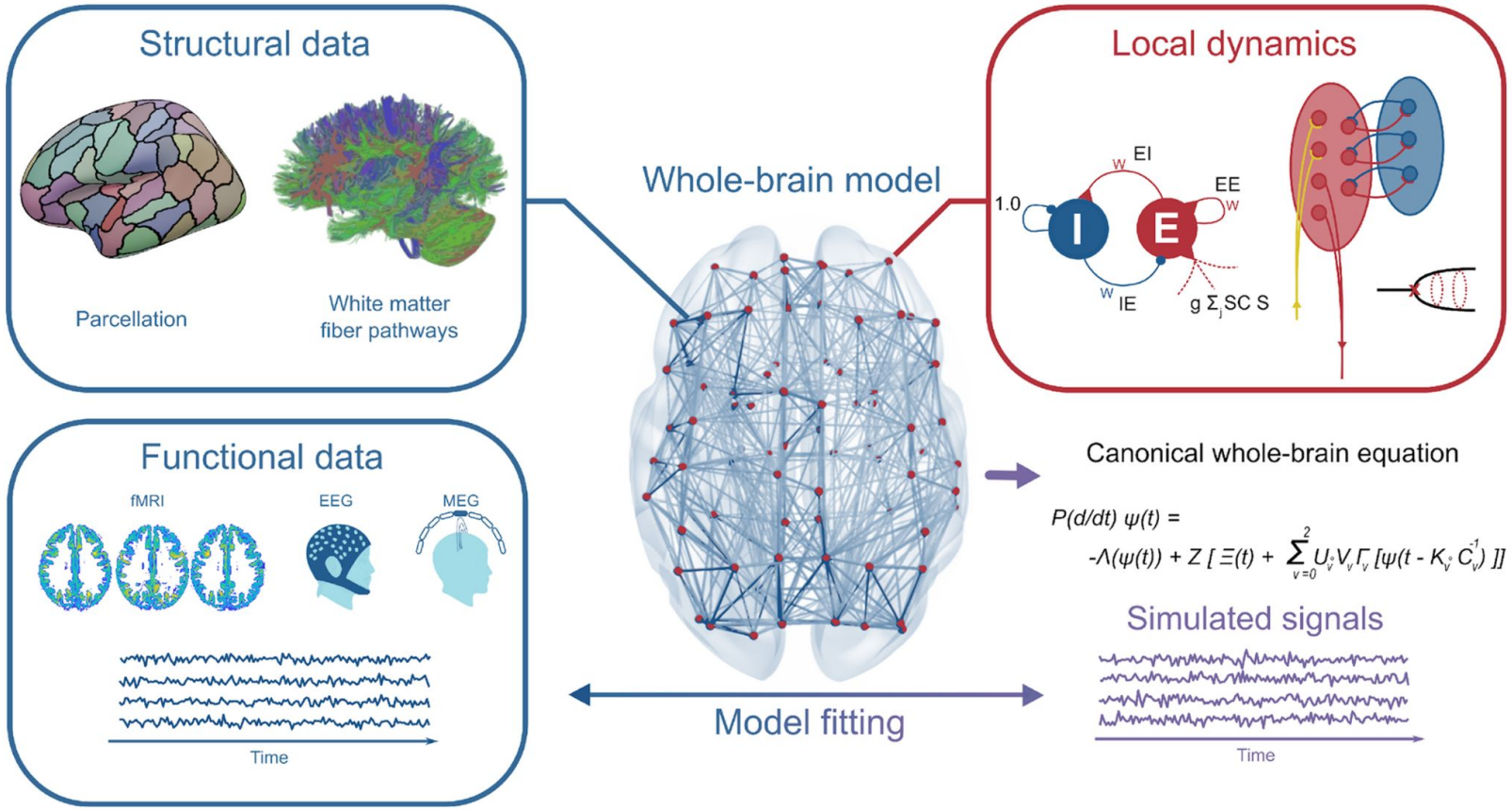

Griffiths et al. (2021)

Neuroimaging Connectomics

Whole-Brain Modelling

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Intro to Neuroimaging Connectomics

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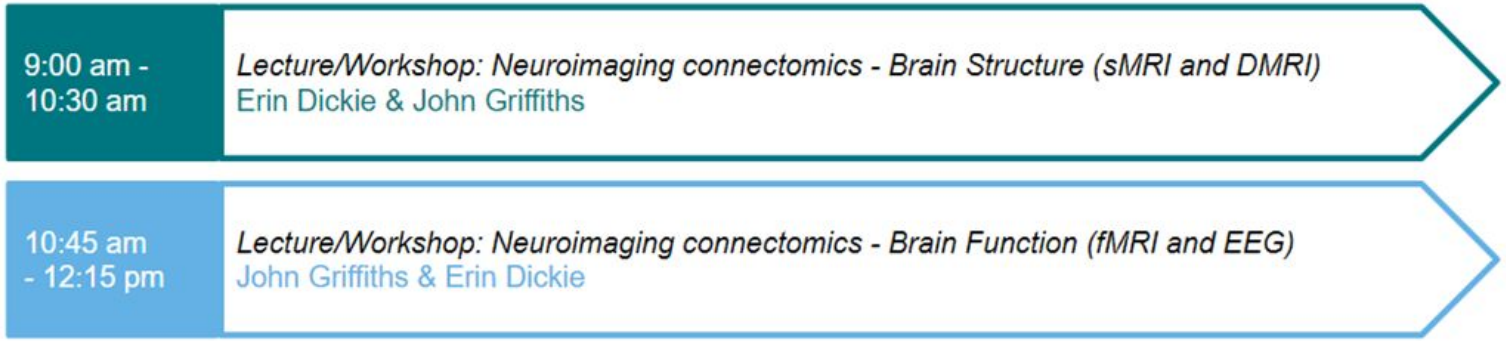

Plan for the morning session:

1. **Brain *structure***
   - Images
   - Surfaces
   - Atlases and Parcellations
   - DWI tractography
   - DWI connectomes

2. **Brain *activity***
   - fMRI timeseries -> connectomes
   - EEG timeseries -> connectomes

What is Magnetic Resonance Imaging?

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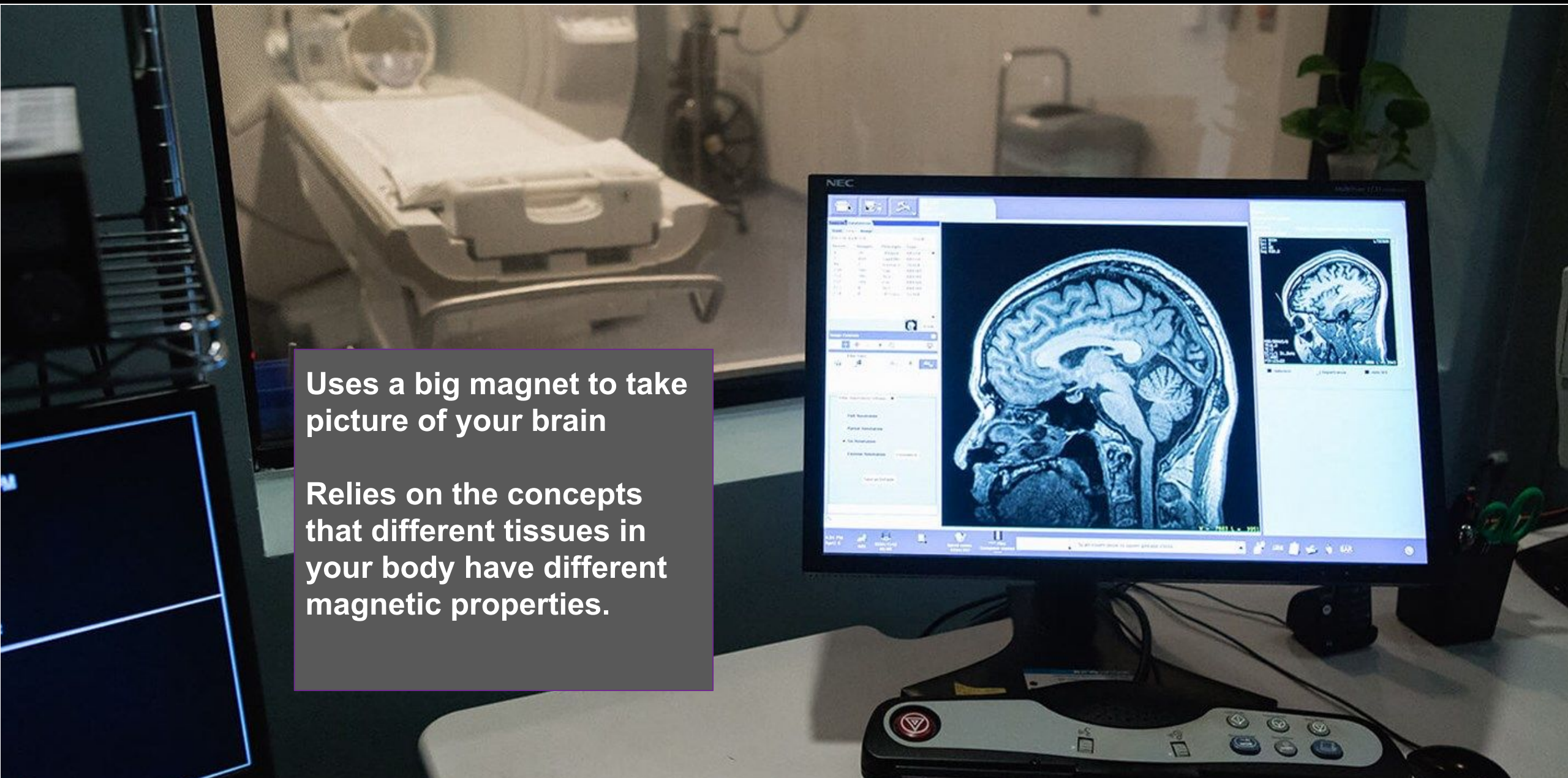

Uses a big magnet to take picture of your brain

Relies on the concepts that different tissues in your body have different magnetic properties.

What has MRI told psychiatry?

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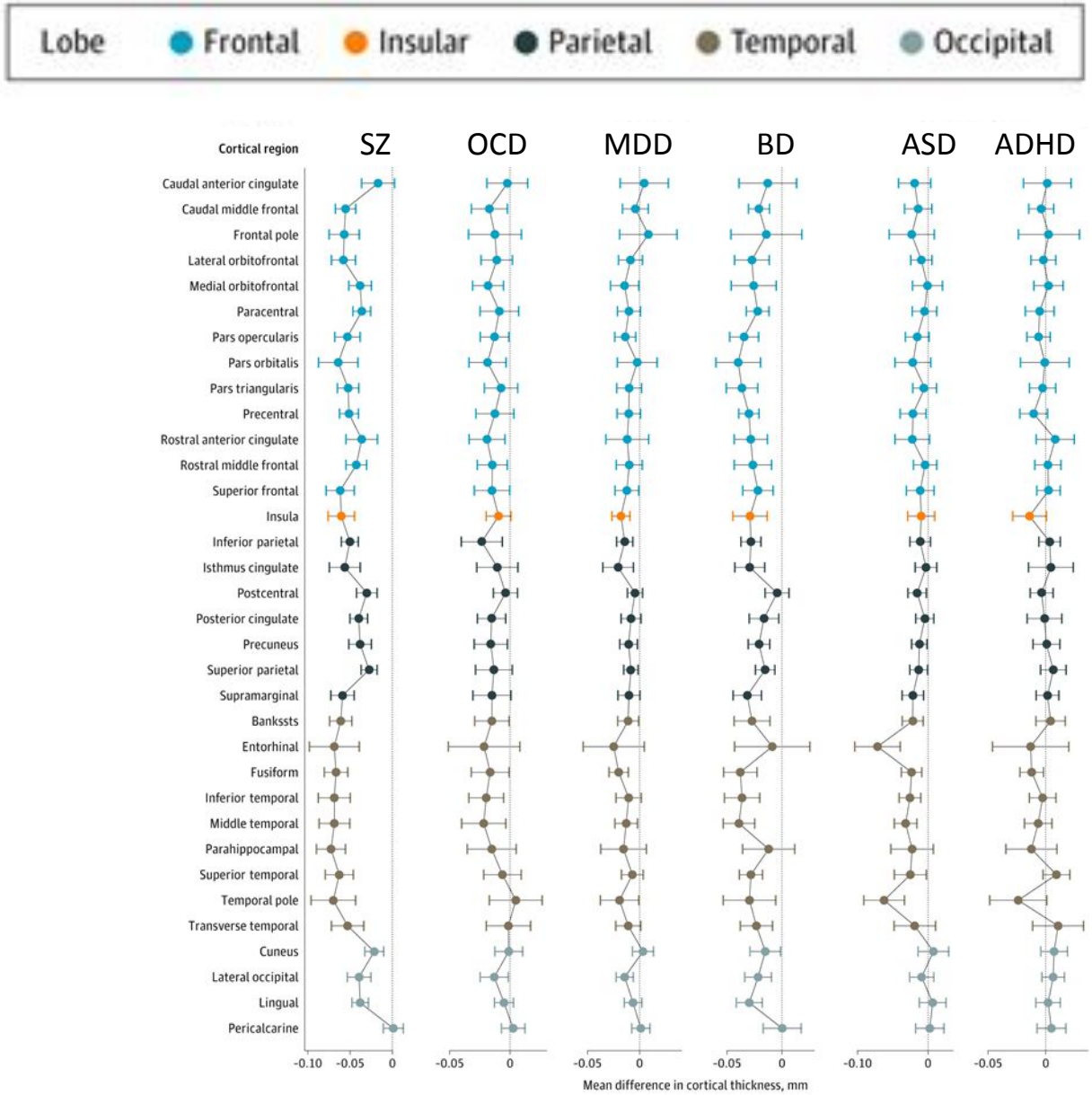
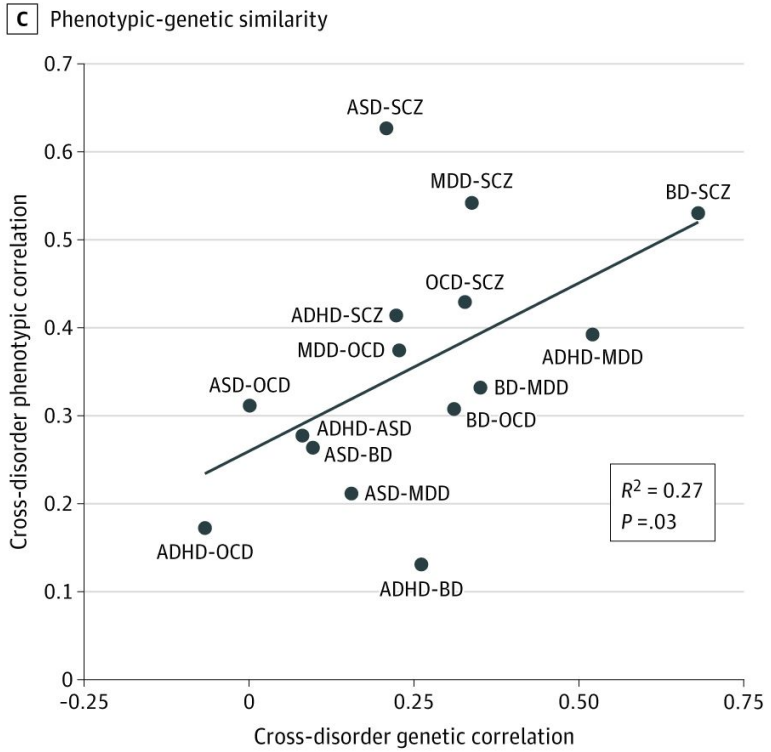


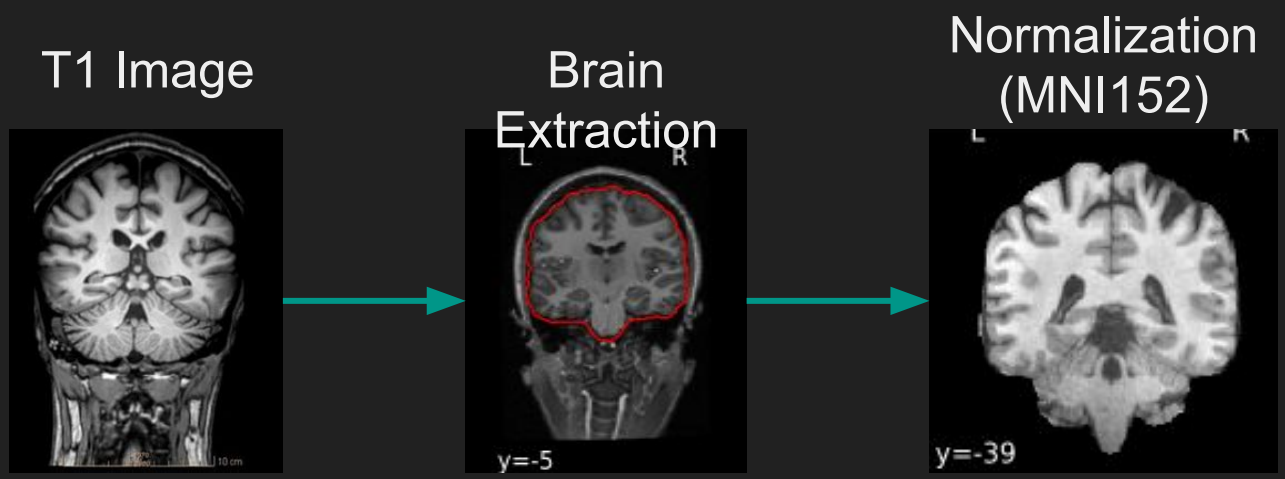
Profiles of Group Differences in Cortical Thickness (Left Hemisphere Only) Between Cases and Controls

Writing Committee for the Attention-Deficit/Hyperactivity Disorder, Autism Spectrum Disorder, Bipolar Disorder, Major Depressive Disorder, Obsessive-Compulsive Disorder, and Schizophrenia ENIGMA Working Groups, Yash Patel, et al. 2021. "Virtual Histology of Cortical Thickness and Shared Neurobiology in 6 Psychiatric Disorders." *JAMA Psychiatry* 78 (1): 47–63.

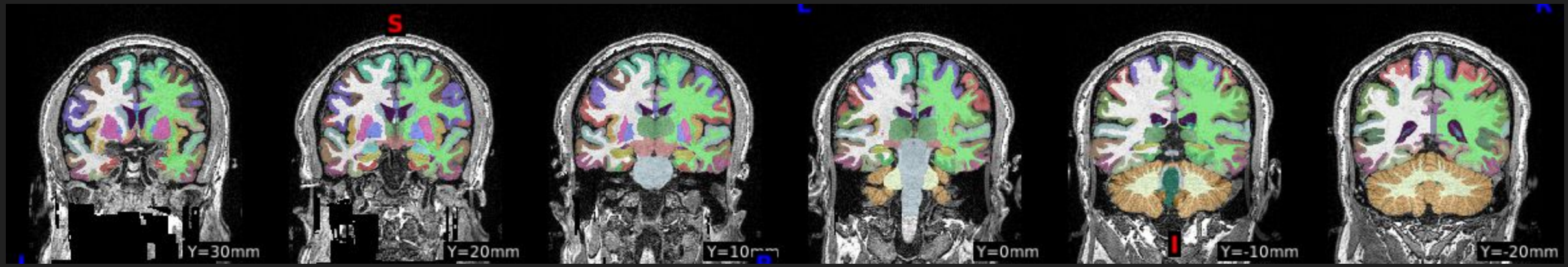


Visual Guide to Pre-processing (T1/fMRI)

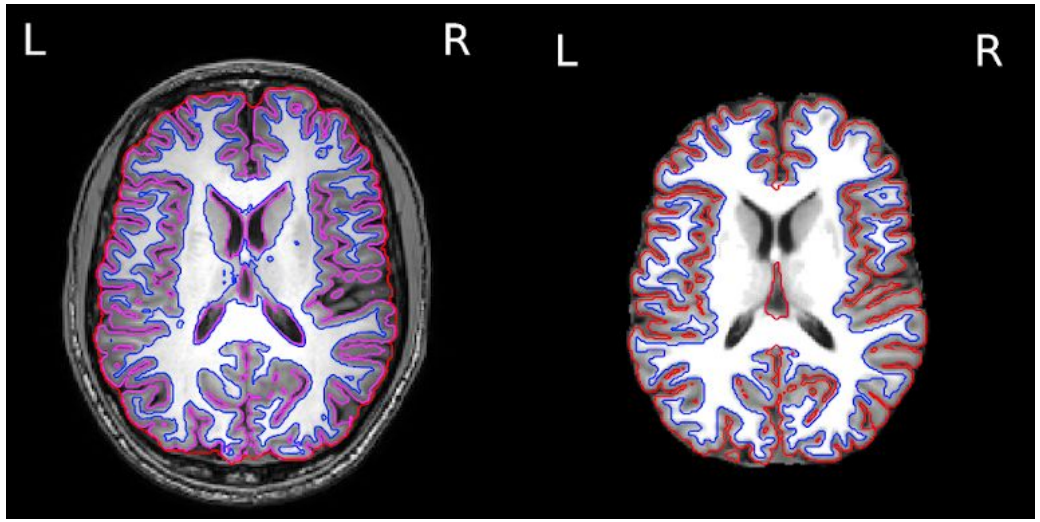
T1
Pre-processing



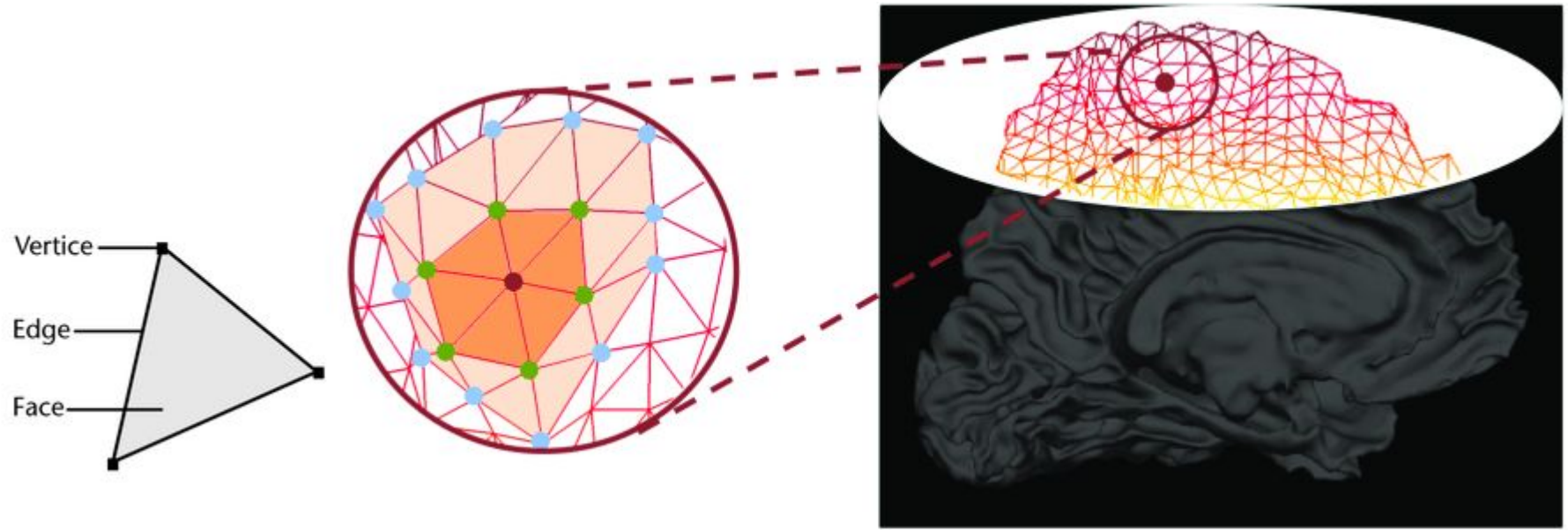
The some other fanciness cna occur



Finding the cortical surface



Anatomical pipelines (i.e. freesurfer) will segment images into gray, matter, white, matter and cerebral spinal fluid (CSF) than use that information to fit a tetrahedral mesh to **individual participant surfaces**

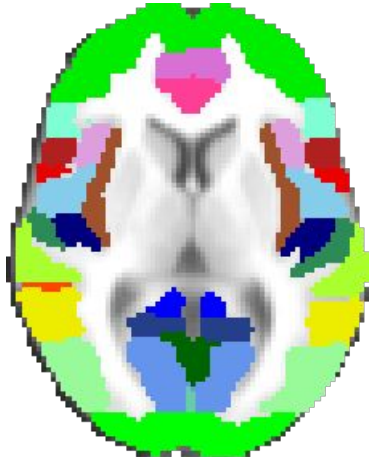


Atlases and Parcellations

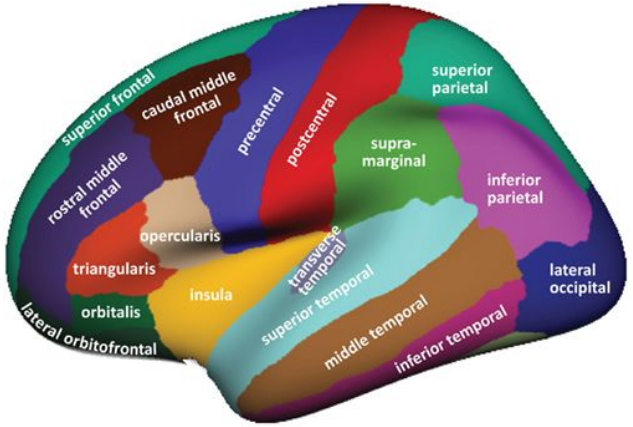
When we do “connectomics” we tend to talk about *how one brain regions communicates with another brain region.*

Atlases or **parcellations** are ways of breaking up brain images into different bits.

What is a brain region? - There are a lot of different answers..



Harvard-Oxford Atlas



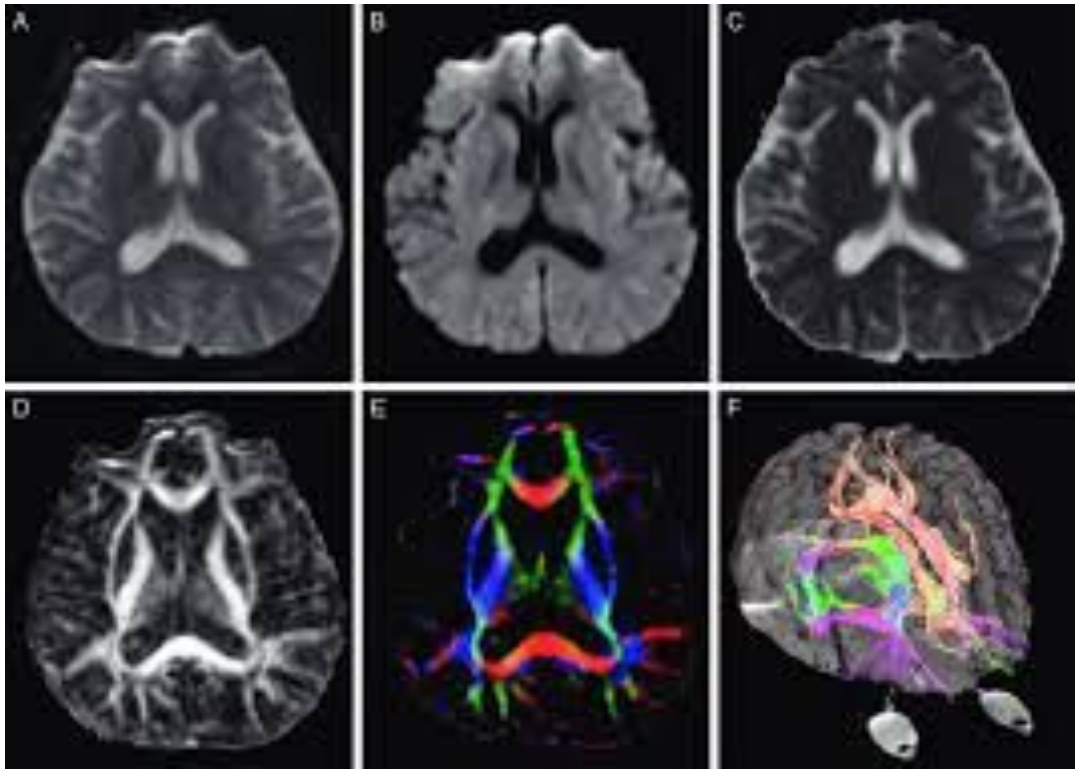
'Desikan-Killiany' cortical atlas (aparc)

Schaefer 2018 (local-global functional brain parcellations (400 parcel)

Time for some code

https://github.com/krembilneuroinformatics/kcni-school-lessons/tree/master/day5

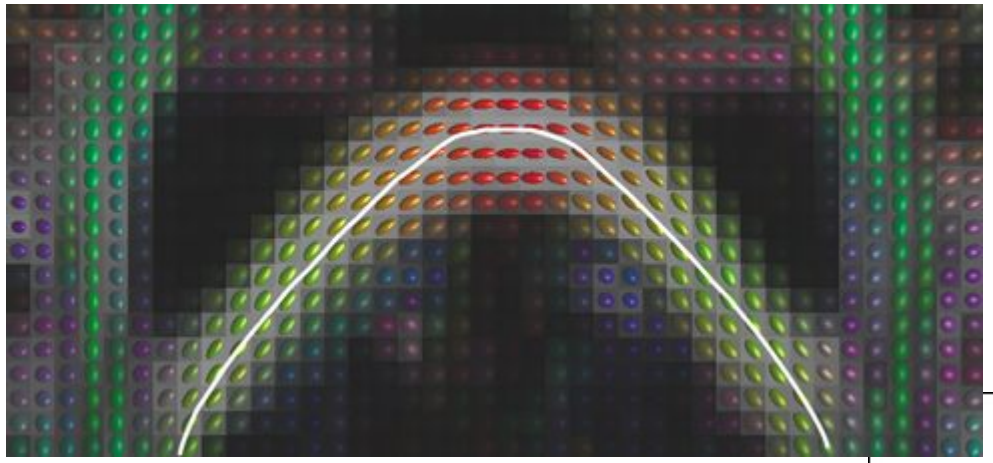
What is diffusion?



DWI = *Diffusion Weighted Imaging*

- Measures diffusion of water in order to model tissue microstructure
- 4-dimensional image
- X,Y,Z + direction of diffusion
- Strength and direction of diffusion *gradient*

What is diffusion?



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What is diffusion?

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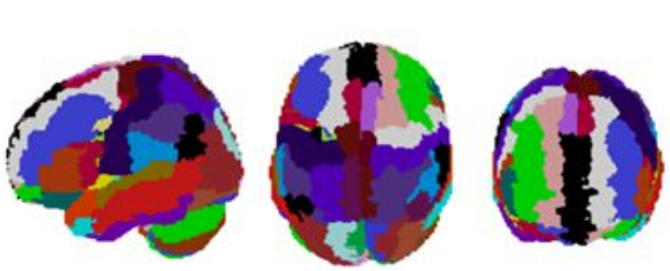

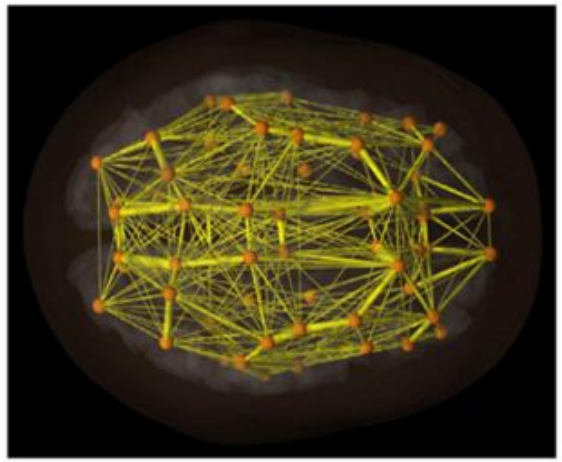

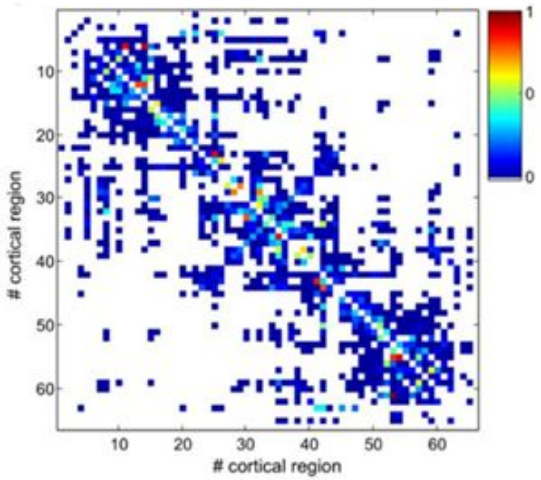

Tractography + Parcellation ->

Anatomical Connectivity matrix

DWI tutorial section

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Time for a Break!

Intro to Neuroimaging Connectomics

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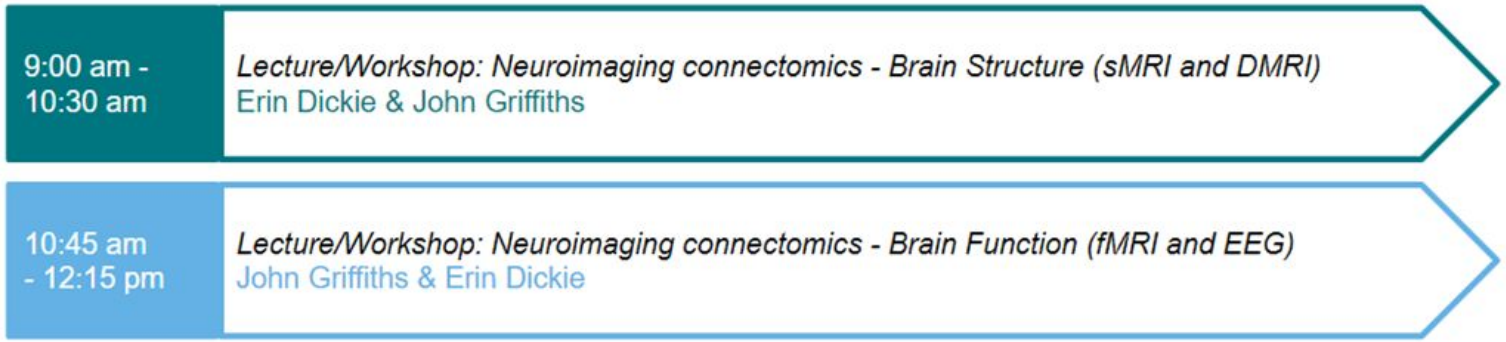

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   - DWI connectomes

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   - fMRI timeseries -> connectomes
   - EEG timeseries -> connectomes

What is fMRI?

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functional MRI (“func” data in BIDS)

- Track the Blood Oxygen Level Dependant (BOLD) signal
- It’s 4-dimensional
  - X,Y,Z + time!
- Sometimes we ask people to do something and look at how the blood oxygen level changed
  - they usually need an _event.tsv file
- but sometime people just lay there
  - "it's task-rest" or resting-state

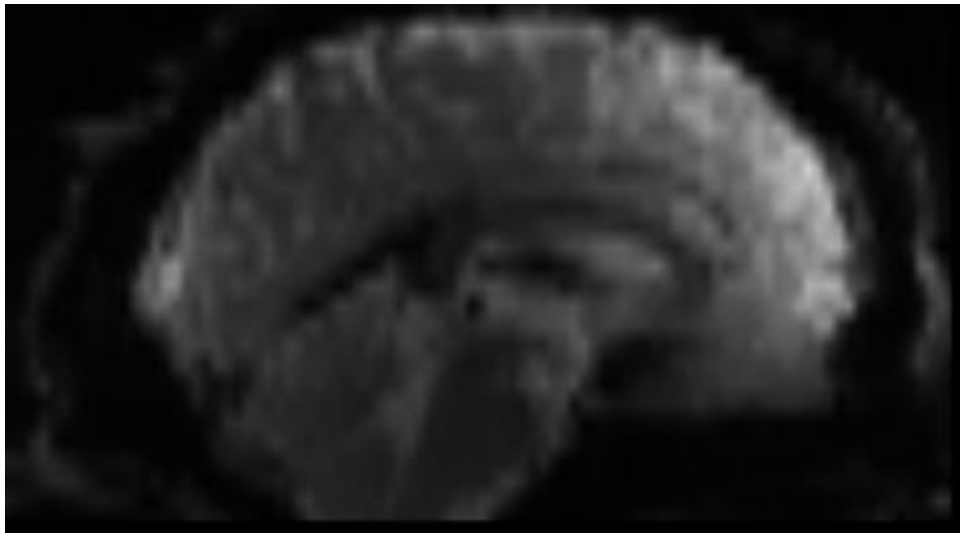
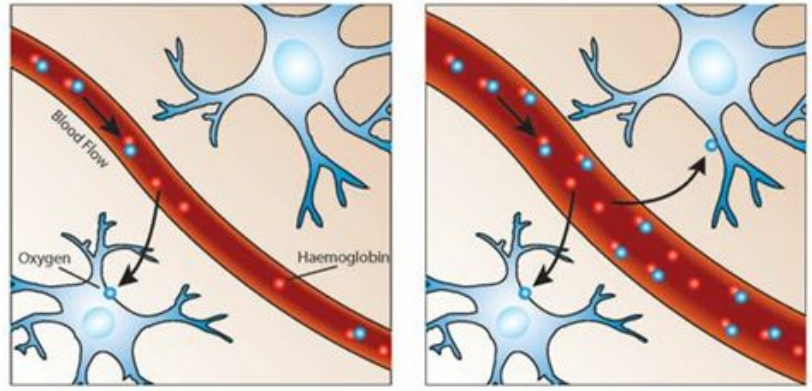


Image from :https://www.win.ox.ac.uk//fmrib-about/what-is-fmri



How do we get a connectome from fMRI?

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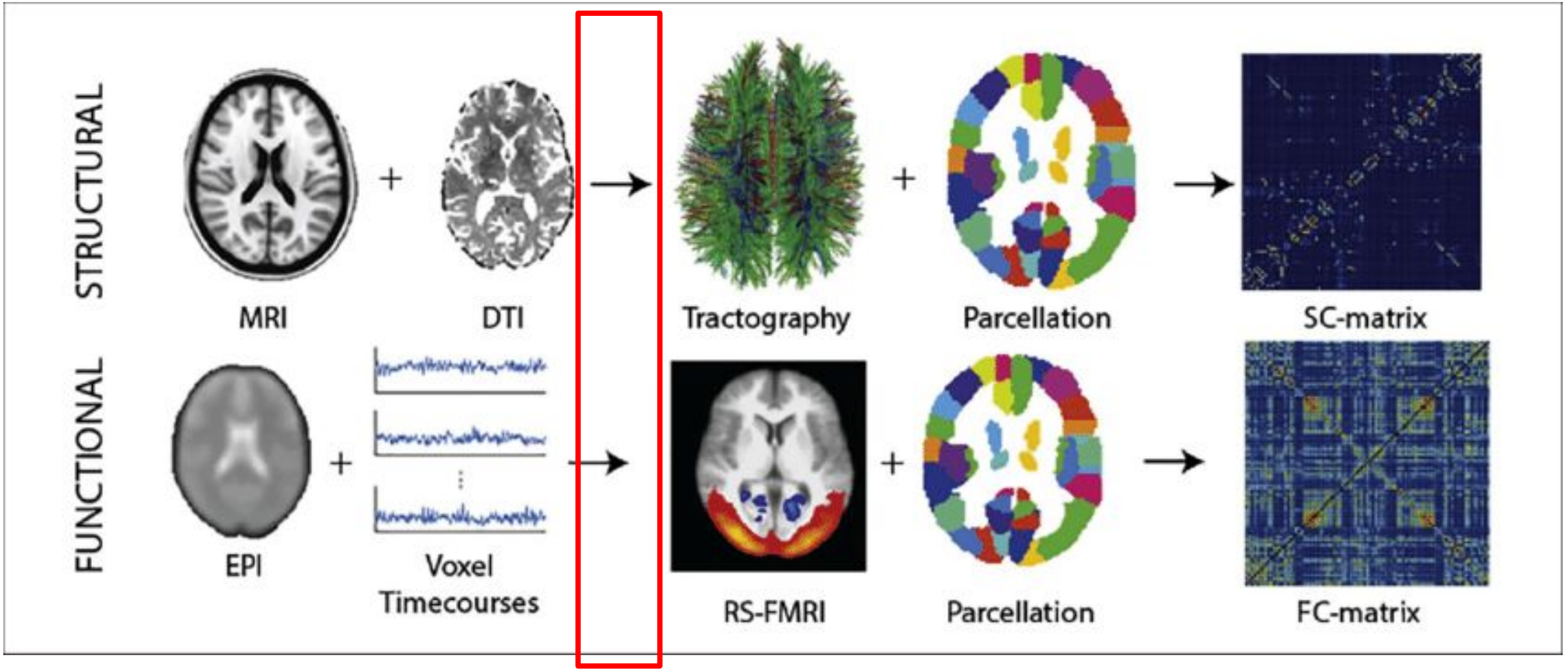

Many hours of preprocessing (hopefully using a BIDS app container)

Can fMRI be used to predict treatment response?

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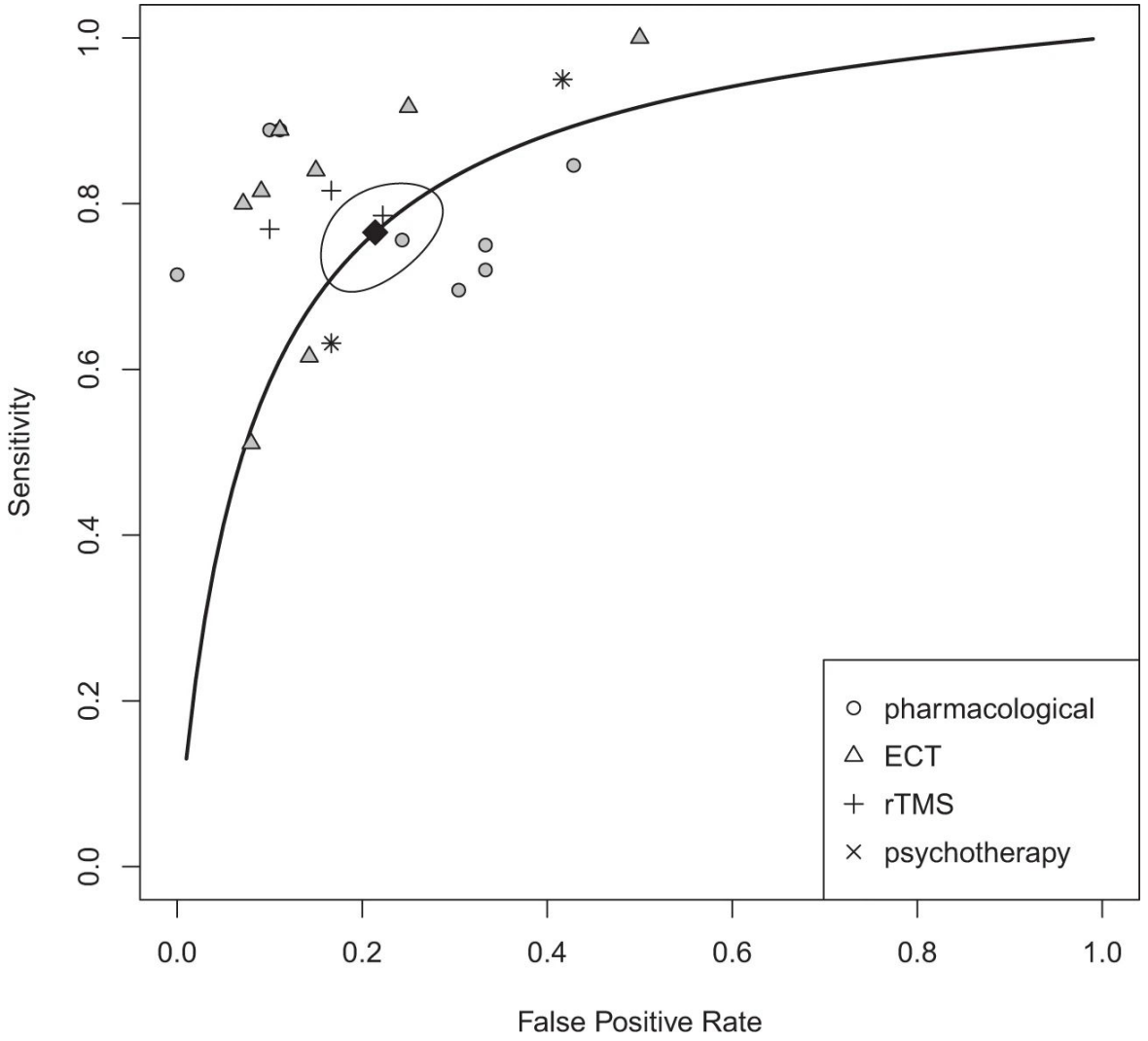
Maybe? - meta analysis of MDD treatment response with MR modalities
https://www.nature.com/articles/s41398-021-01286-x

-

note: sample sizes for these individual studies ranges n=16-124 and most use Leave-one-out cross-validation



What has fMRI told us about MDD?

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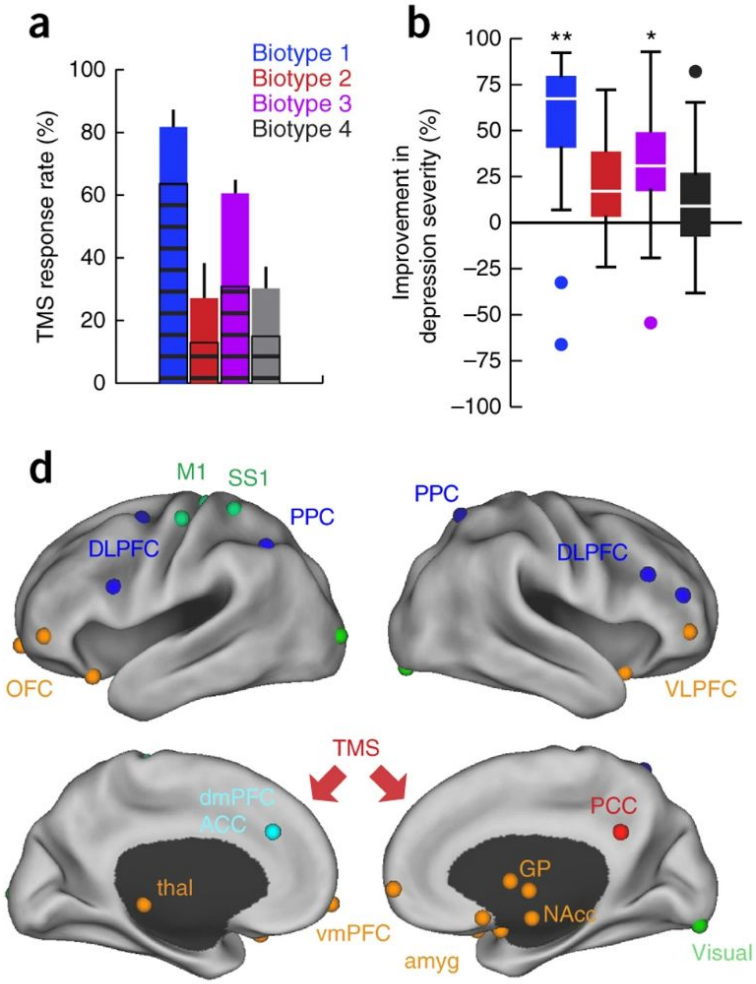
Drysdale, et al. 2017. "**Resting-State Connectivity Biomarkers Define Neurophysiological Subtypes of Depression.**" *Nature Medicine* 23 (1): 28–38.

BUT - Dinga, R. et al. **Evaluating the evidence for biotypes of depression: methodological replication and extension** of Drysdale et al. *Neuroimage Clin.* 2019, 101796 (2017).

Then:

Sun,, et al. 2020. "Preliminary Prediction of Individual Response to Electroconvulsive Therapy Using Whole-Brain Functional Magnetic Resonance Imaging Data." *NeuroImage. Clinical* 26: 102080.



Using fMRI in stimulation targeting

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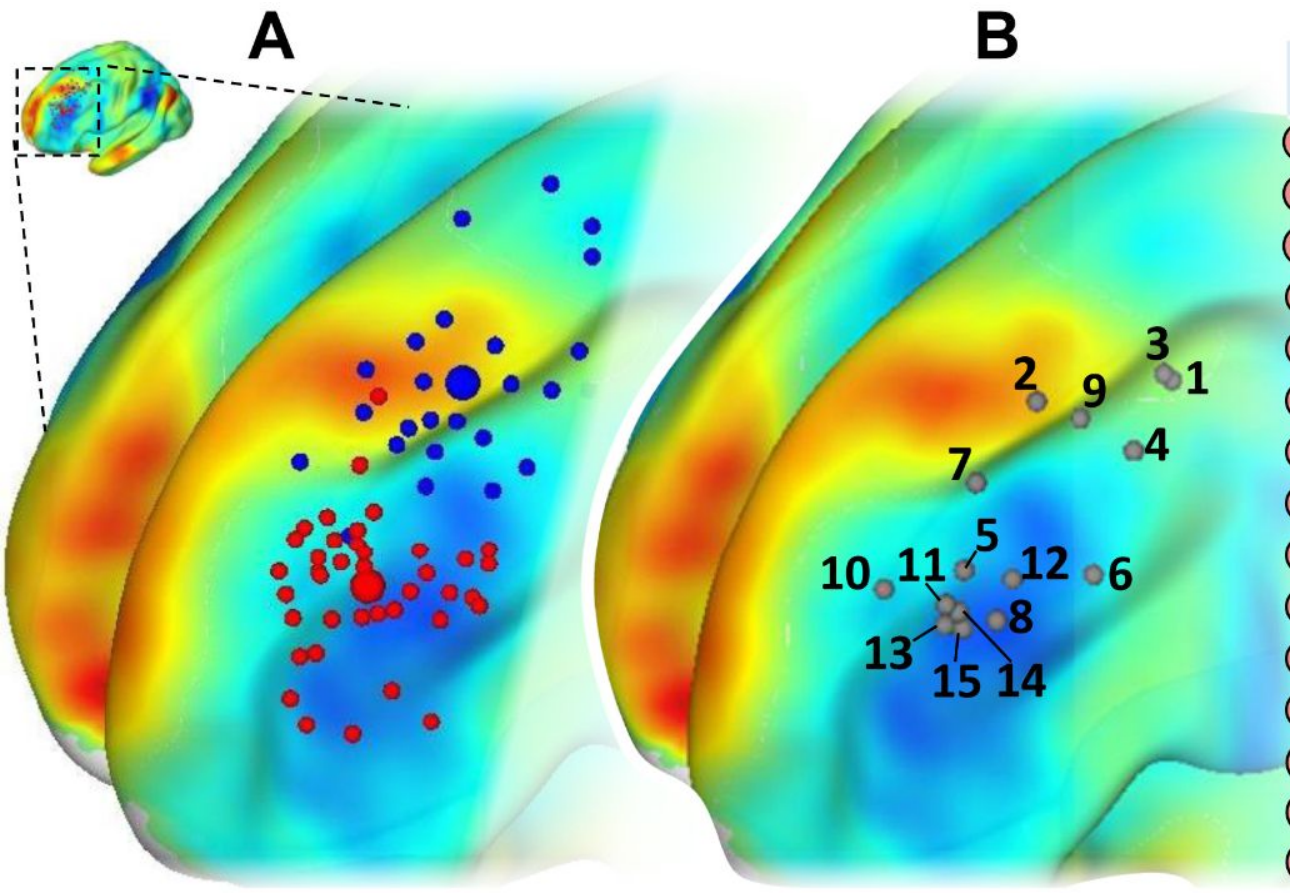

	Target	x	y	z
1	5cm average (Fox et al., 2012) (6)	-41	16	54
2	5.5cm average (Weigand et al., 2018) (7)	-33	30	50
3	Non-responders (Herbsman et al., 2009) (13)	-41	17	55
4	Responders (Herbsman et al., 2009) (13)	-46	23	49
5	TMS Target (Fitzgerald et al., 2009) (22)	-46	45	38
6	TMS Target (Rusjan et al., 2010) (47)	-50	30	36
7	BA9 Definition (Rajkowska et al., 1995) (45)	-36	39	43
8	BA46 Definition (Rajkowska et al., 1995) (45)	-44	40	29
9	EEG F3 site (Herwig et al., 2003) (14)	-37	26	49
10	EEG F3 site (Okamotu et al., 2004) (158)	-43	58	40
11	Beam F3 (Cash et al., 2019) (5)	-43	46	32
12	Optimal FC Group Target #1 (Fox et al., 2012, N=98) (6)	-44	38	34
13	Optimal FC Group Target #2 (Fox et al., 2012, N=98) (6)	-38	44	26
14	Optimal FC Group Target (Weigand et al., 2018, N=1000) (7)	-42	44	30
15	Optimal FC Group Target (Cash et al., 2019, N=2000) (104)	-41	43	27

Heterogeneity in transcranial magnetic stimulation (TMS) sites for depression.
From: Cash, Robin F. H., Anne Weigand, Andrew Zalesky, Shan H. Siddiqi, Jonathan Downar, Paul B. Fitzgerald, and Michael D. Fox. 2020. “Using Brain Imaging to Improve Spatial Targeting of Transcranial Magnetic Stimulation for Depression.” *Biological Psychiatry*, June. https://doi.org/10.1016/j.biopsych.2020.05.033.

rTMS target in depression

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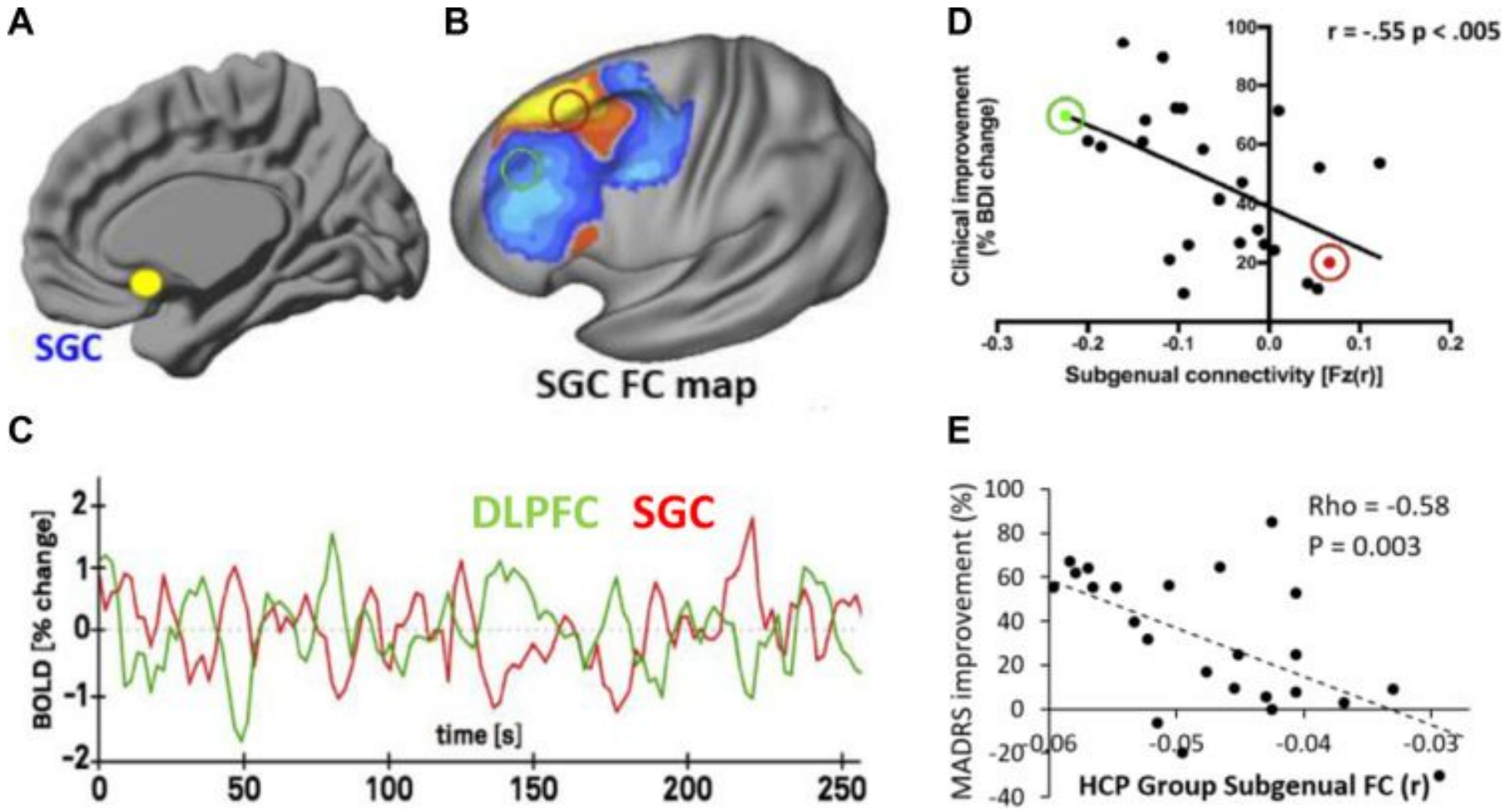
Figure 3. Antidepressant response to repetitive transcranial magnetic stimulation is associated with functional connectivity (FC) between the stimulation site and the subgenual cingulate cortex (SGC)



From: Cash, Robin F. H., Anne Weigand, Andrew Zalesky, Shan H. Siddiqi, Jonathan Downar, Paul B. Fitzgerald, and Michael D. Fox. 2020. "Using Brain Imaging to Improve Spatial Targeting of Transcranial Magnetic Stimulation for Depression." *Biological Psychiatry*, June. https://doi.org/10.1016/j.biopsych.2020.05.033.

One more step: Pre-processing

Data needs to be harmonized before analysis

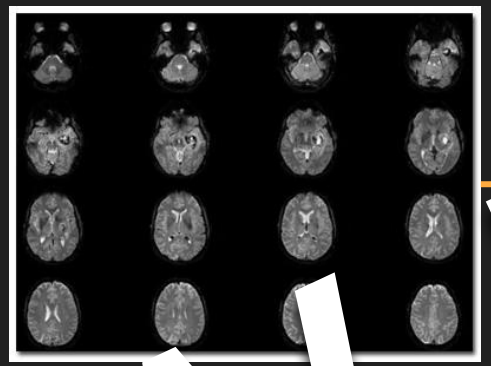
Issues we need to account for:

1. We have whole head images, **we just want the brain**
2. fMRI image and T1 image are **not aligned**
3. **fMRI is distorted** due to changing magnetic field in some areas of brain
4. Participants move in scanners, **fMRI image isn't aligned to itself**
5. **Movement actually influences the fMRI signal**, we want "brain signals" not motion signals!
6. All subject images **aren't aligned to each-other**, need to warp images to a template (we need some sort of normalization)

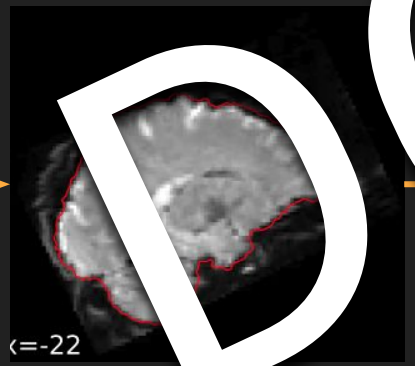
fMRI Preprocessing

HOW I DO?

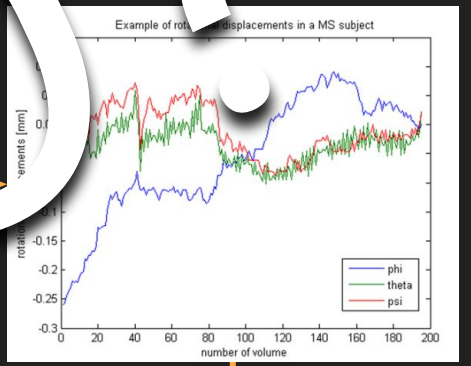
Raw fMRI



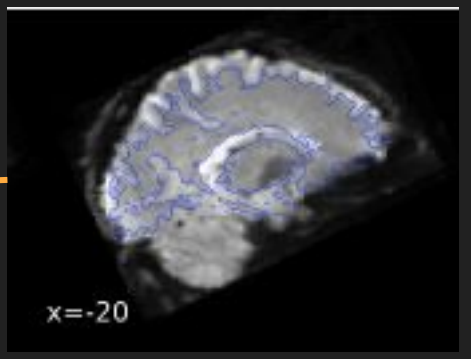
Brain Extraction



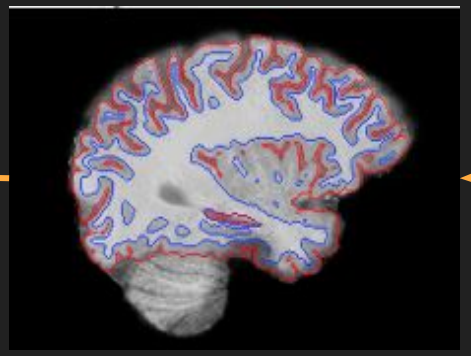
Motion Correction



Susceptibility Distortion Correction



Alignment to T1 image

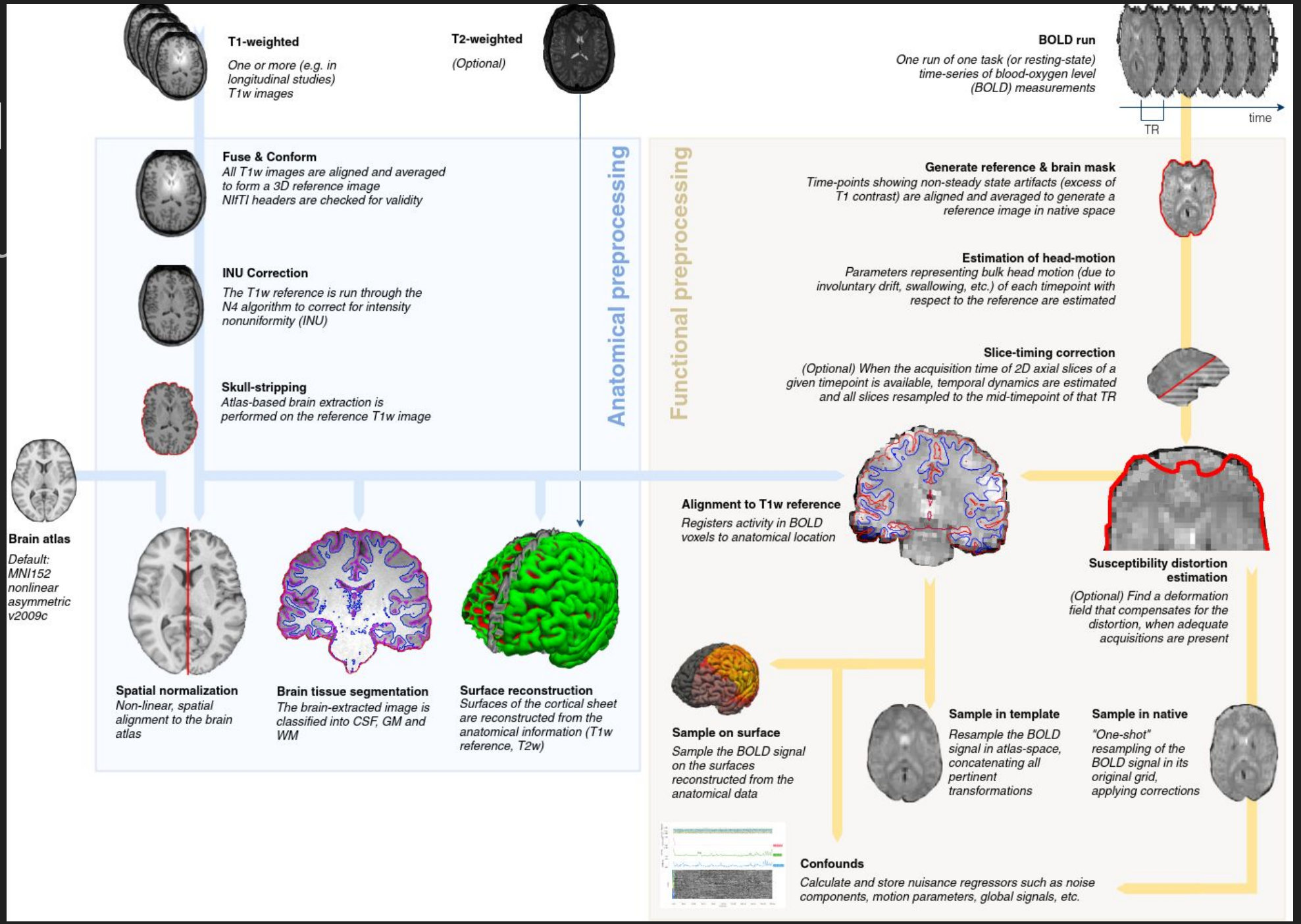


MNI152 Transformation

Confound Regression

FM

If you


T1-weighted
One or more (e.g. in longitudinal studies) T1w images
T2-weighted
(Optional)
BOLD run
One run of one task (or resting-state) time-series of blood-oxygen level (BOLD) measurements
TR
time
Anatomical preprocessing
Functional preprocessing
Fuse & Conform
All T1w images are aligned and averaged to form a 3D reference image
NIfTI headers are checked for validity
INU Correction
The T1w reference is run through the N4 algorithm to correct for intensity nonuniformity (INU)
Skull-stripping
Atlas-based brain extraction is performed on the reference T1w image
Generate reference & brain mask
Time-points showing non-steady state artifacts (excess of T1 contrast) are aligned and averaged to generate a reference image in native space
Estimation of head-motion
Parameters representing bulk head motion (due to involuntary drift, swallowing, etc.) of each timepoint with respect to the reference are estimated
Slice-timing correction
(Optional) When the acquisition time of 2D axial slices of a given timepoint is available, temporal dynamics are estimated and all slices resampled to the mid-timepoint of that TR
Brain atlas
Default: MNI152 nonlinear asymmetric v2009c
Alignment to T1w reference
Registers activity in BOLD voxels to anatomical location
Susceptibility distortion estimation
(Optional) Find a deformation field that compensates for the distortion, when adequate acquisitions are present
Spatial normalization
Non-linear, spatial alignment to the brain atlas
Brain tissue segmentation
The brain-extracted image is classified into CSF, GM and WM
Surface reconstruction
Surfaces of the cortical sheet are reconstructed from the anatomical information (T1w reference, T2w)
Sample on surface
Sample the BOLD signal on the surfaces reconstructed from the anatomical data
Sample in template
Resample the BOLD signal in atlas-space, concatenating all pertinent transformations
Sample in native
"One-shot" resampling of the BOLD signal in its original grid, applying corrections
Confounds
Calculate and store nuisance regressors such as noise components, motion parameters, global signals, etc.

The data in the tutorial today

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Midnight Scan Club
@club_scan Follows you

- N = 10
- Data collection costs = $12,000
- MSC team articles = 16; citations = 1,969
  - Neuron: 5
  - PNAS: 3
  - NIMG: 3
  - Cerebral Cortex: 2
  - Lancet Neurology
  - Cell Reports
  - BioRxiv
- OpenNeuro: 16/526 by #downloads

https://openneuro.org/

Tutorial NB 3: fMRI Activity + Connectivity

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Intro to Neuroimaging Connectomics

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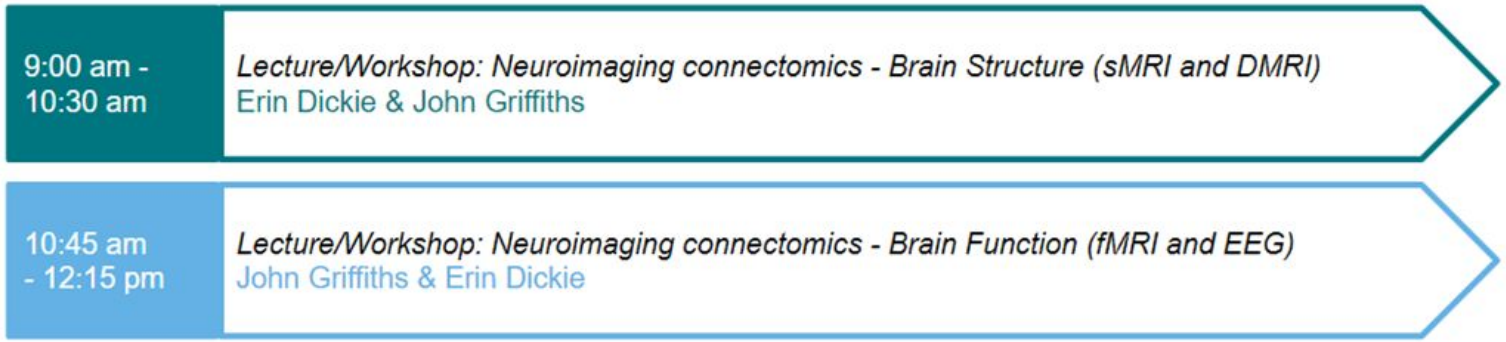

Plan for the morning session:

1. **Brain *structure***
   - Images
   - Surfaces
   - Atlases and Parcellations
   - DWI tractography
   - DWI connectomes

2. **Brain *activity***
   - fMRI timeseries -> connectomes
   - EEG timeseries -> connectomes

Tutorial NB 4: M/EEG Activity + Connectivity

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That’s a wrap!

Today's Agenda

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Day 5:
Whole-Brain Modelling and Neuroimaging Connectomics

9:00 am - 10:30 am	*Lecture/Workshop: Neuroimaging connectomics - Brain Structure (sMRI and DMRI)* Erin Dickie & John Griffiths
10:45 am - 12:15 pm	*Lecture/Workshop: Neuroimaging connectomics - Brain Function (fMRI and EEG)* John Griffiths & Erin Dickie
1:00 pm - 2:30 pm	*Lecture: Intro to whole-brain modelling* John Griffiths
2:45 pm - 4:15 pm	*Workshop: simulating whole-brain activity, EEG, evoked responses, brain stimulation* John Griffiths

Remember - many ways to engage

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? 👍

(during sessions) Use the chat or the ask question!

You can always return to the session and re-watch the vidos after the session ends

come chat with us in KCNI Summer School Slack :)

virtually meet with us in gather.town

Tell us how the session went (post session survey):
https://forms.gle/ji18qLMZEZ9L16Ln6

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