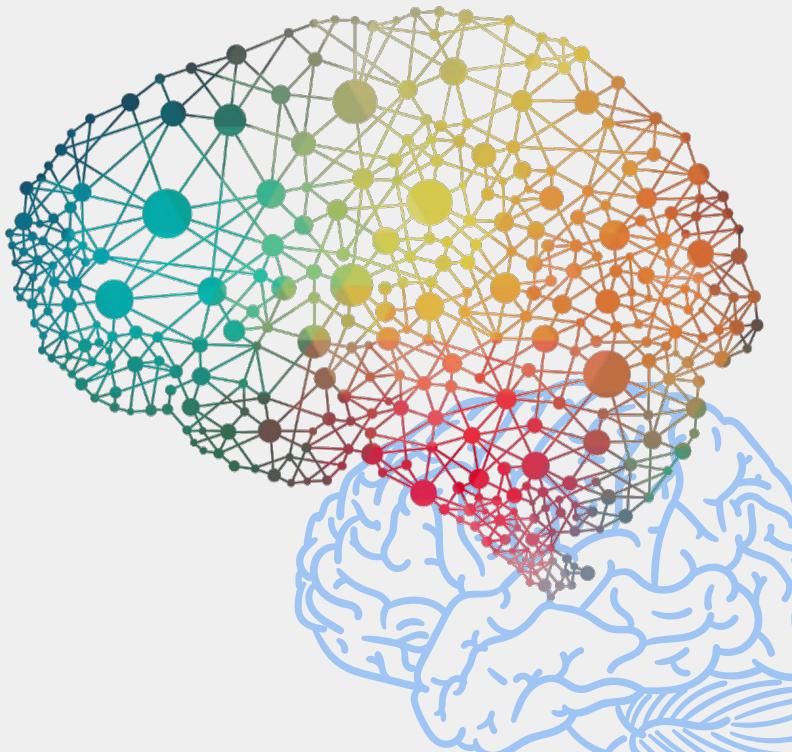
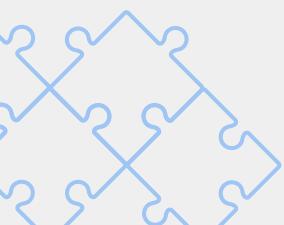


# Computational Network Neuroscience

Summer 2022  
College of Computing and Informatics  
Drexel University



# Overview of the Course



# Definition and Goals



## Description:

- a broad graduate-level introduction to computational neuroscience course,
- with a special focus on brain connectivity analysis and network neuroscience.

## Goals:

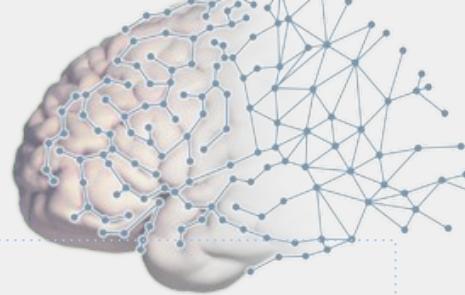
- to introduce this rapidly developing domain of medical research to students coming from a computing background
- to make you ready for a postgraduate level research experience in connectomics after this class
- to have draft of a conference paper on connectomics ready by the end of the term

# Course Components and Grading

1. Attendance	10%
2. Weekly readings	10%
3. Term project	60%
4. Peer review	20%

No exam!

- Self-grading (a.k.a. ungrading)
- Why?
  - To lower your stress
  - To increase your benefit from the class
- How?
  - the instructor will give qualitative feedback for each assignment, and the student will improve their reports for the next round
  - at the end of the term, you will suggest a letter grade for your effort along with a page of justification as to why you would give yourself such a letter grade
  - If I agree with your judgement, it will become the your final letter grade
  - If I disagree and think that the letter grade should be higher or lower, we will have a one-on-one meeting to re-evaluate the final letter grade



# Components of the course

1. Attendance
2. Weekly readings
3. Term project
4. Peer review

- Why?
  - I can teach better if the ideas bounce back from you
  - You can learn better if you share the same space-time with me, as you can ask/answer questions
  - To make sure you are on track with the course, we need to keep the interaction alive
- How?
  - Obvious for in person students
  - For online, watch the lecture live.
  - If you cannot attend/watch the lecture live, we need to catch up within the week either during my office hours or with an email detailing how the project/class is going



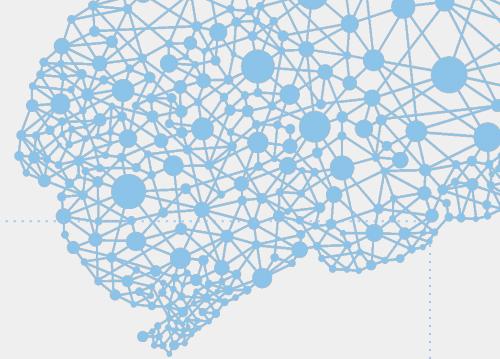
# Components of the course

1. Attendance
2. **Weekly readings**
3. Term project
4. Peer review

- Why?
  - To make you get familiar with
    - the network neuroscience literature
    - how to design a study
    - how to review papers to see the good and bad
  - Eventually to make you develop a literature summary repo, to be used when writing a paper's introduction
- How?
  - one journal article every week to be read and summarized in 1 page, and submitted before the class
  - summary should include the main highlights of the paper, and include your opinion about the study



# Components of the course



1. Attendance
2. Weekly readings
3. **Term project**
4. Peer review

- Why?
  - You will learn best by “doing”
- How?
  - Do connectomic analysis with real data
  - **either** design your own study **or** pick a research paper to replicate and expand
  - Four milestones
    - Week 3: Present project idea and background
      - find a problem and a data set, write a 2 page report stating the problem, as well as providing a background from the literature
      - Report should have 1 figure visually conveying the gist of the project
    - Week 5: Preliminary data analysis results report
      - do basic statistical analysis such as correlation, group difference over standard graph theory measures
      - Update previous report to 3 pages, includes methods, 1+ new figure(s)
    - Week 7: More advanced data analysis report
      - Do further analysis using more advanced methods such as linear regression, machine learning (classification, clustering), deep learning...
      - Update previous report to 4 pages, updated methods, includes 1+ new figure(s)
    - Week 10: Final report and presentation
      - Update previous report and analysis, add discussion and future work
      - should be a 6 page paper with references
      - There will be project presentations at week 10 in class.

Rep: Summary of replication results



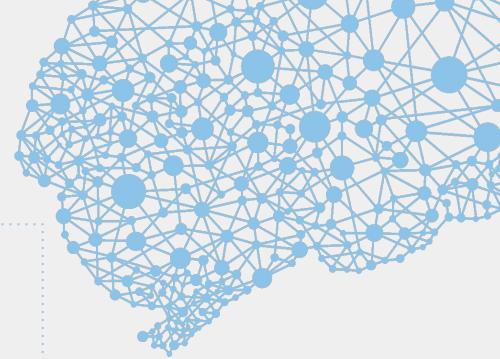
Rep: Expand data analysis



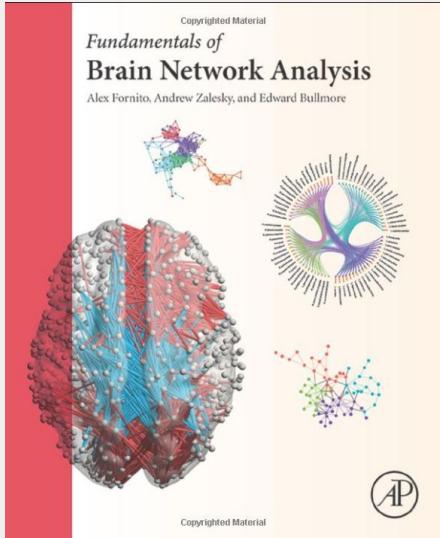
# Components of the course

1. Attendance
2. Weekly readings
3. Term project
4. Peer review

- Why?
  - You will learn how to review others' work
  - Help your peers in designing a better study
  - Get ideas from your peers
- How?
  - for each of the 4 reports, you will review the report of two of your peers
  - write a 1 page review to give feedback to each



# Textbook



## Fundamentals of brain network analysis

Fornito, A., Zalesky, A. and Bullmore, E., 2016

Academic Press

ISBN-13: 978-0124079083

ISBN-10: 0124079083

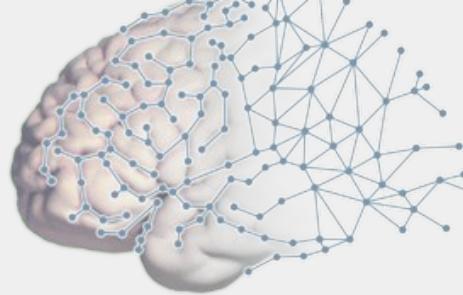
- You don't have to buy the textbook as the content of the lecture slides will cover a large portion of the material presented in the book.
- However, it is a very good reference text for the subject matter, and might be a good future investment if you are planning to work in the domain.
  - Can save you the time of reading multiple journal papers to get hold of a topic

# Computational Network Neuroscience

Birds eye view

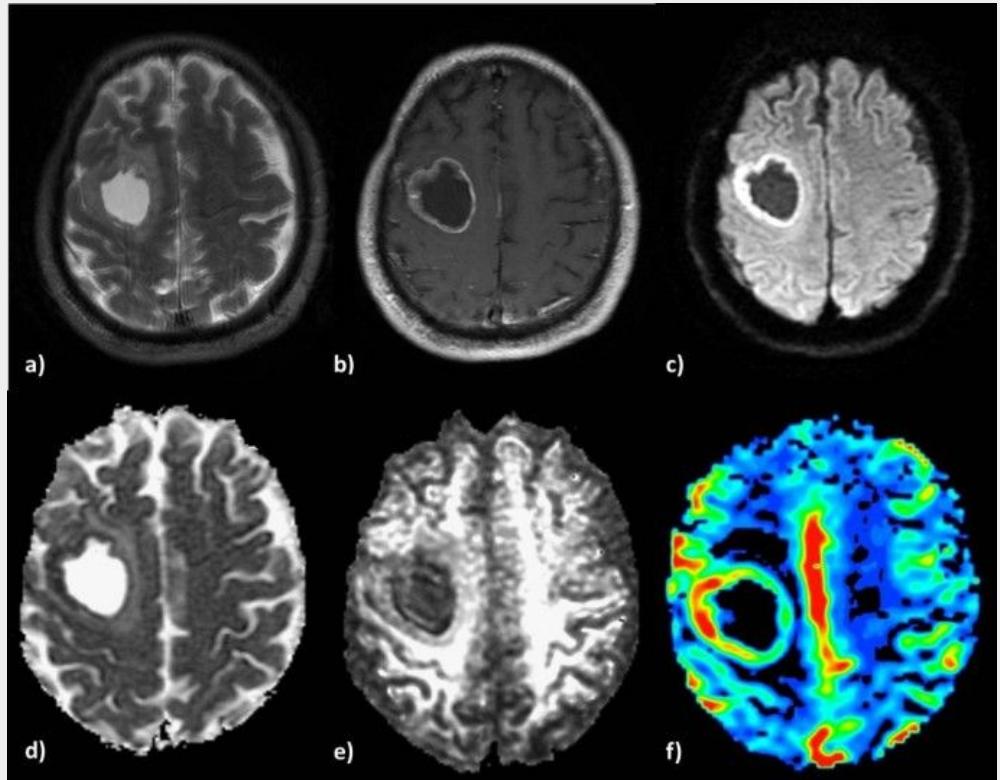


# Big Picture



- Understanding the brain
  - Brain is the most complex organ in human body, arguably the most complex structure in the universe
  - It is a network of  $\sim 100$  billion ( $10^{11}$ ) neurons connected by  $\sim 100$  trillion ( $10^{14}$ ) synapses.
  - This network is organized at multiple levels (systems), and is functionally active over time at multiple levels.
- Understanding diseases
  - What causes dementia or schizophrenia, for example?
  - Can we update our approach for the treatment of the diseases?
- Diagnosing diseases
  - Can we diagnose neurological diseases before they progress?
  - How early can we identify autism, for example?
- Prognosis of diseases
  - Can we estimate the trajectory of the disease progression?
  - How fast will Alzheimer's disease progress in a certain patient?
  - Does it progress faster/slower in certain populations?
- Helping doctors in decision making
  - How long the patient is estimated to live after a brain surgery?
  - Where should the brain surgeon open skull to minimize damage to healthy brain tissue?

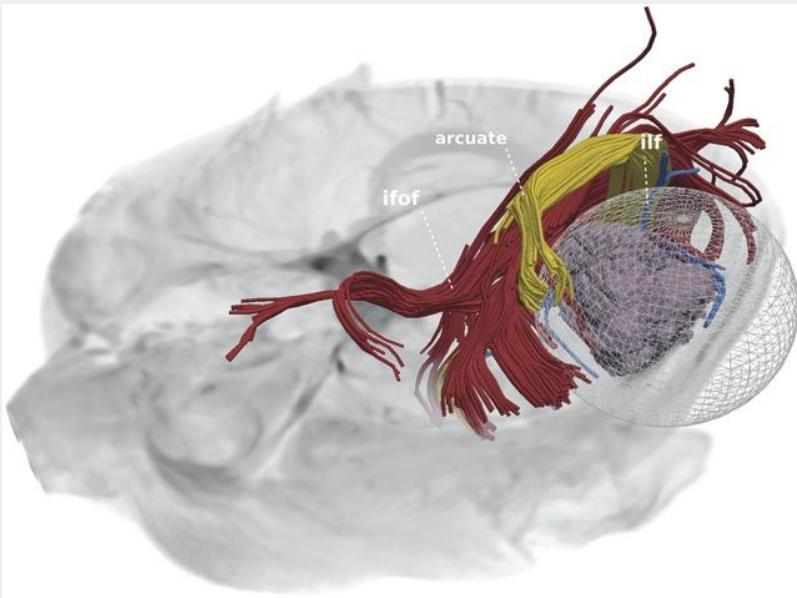
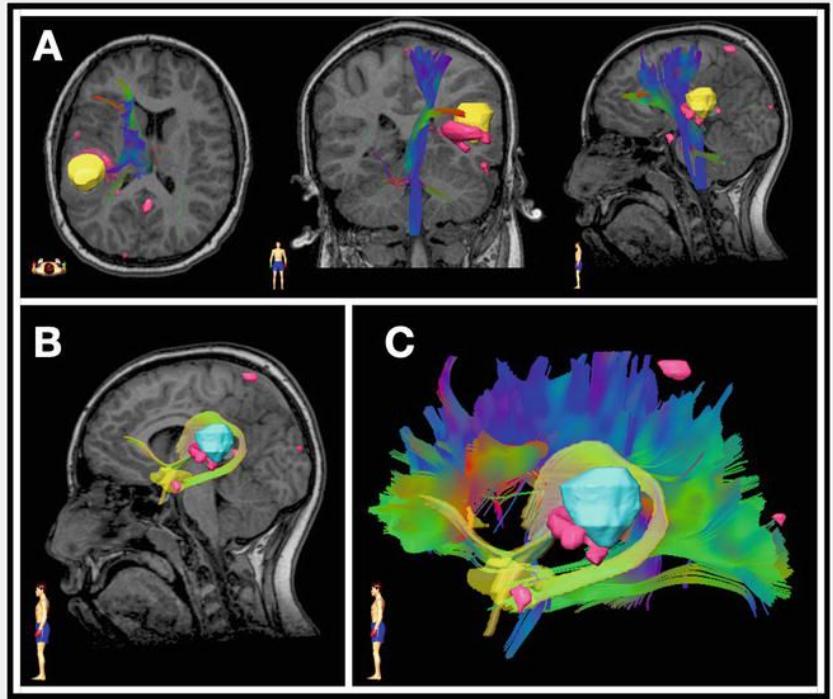
# Example: Brain Tumors



MR images of a brain tumor (a high-grade glioma) patient on varying contrast images

- a) T2-weighted image,
- b) ring-shaped enhancement on a T1-weighted post contrast edema,
- c) restricted diffusion in the periphery of the tumor.
- d) Increased intratumoral ADC
- e) decreased FA and
- f) elevated perfusion in the peripheral solid part of the lesion.

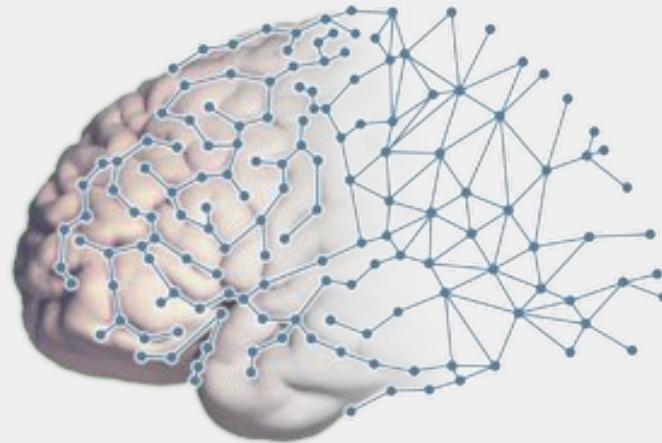
# Neurosurgical planning for brain tumor patients



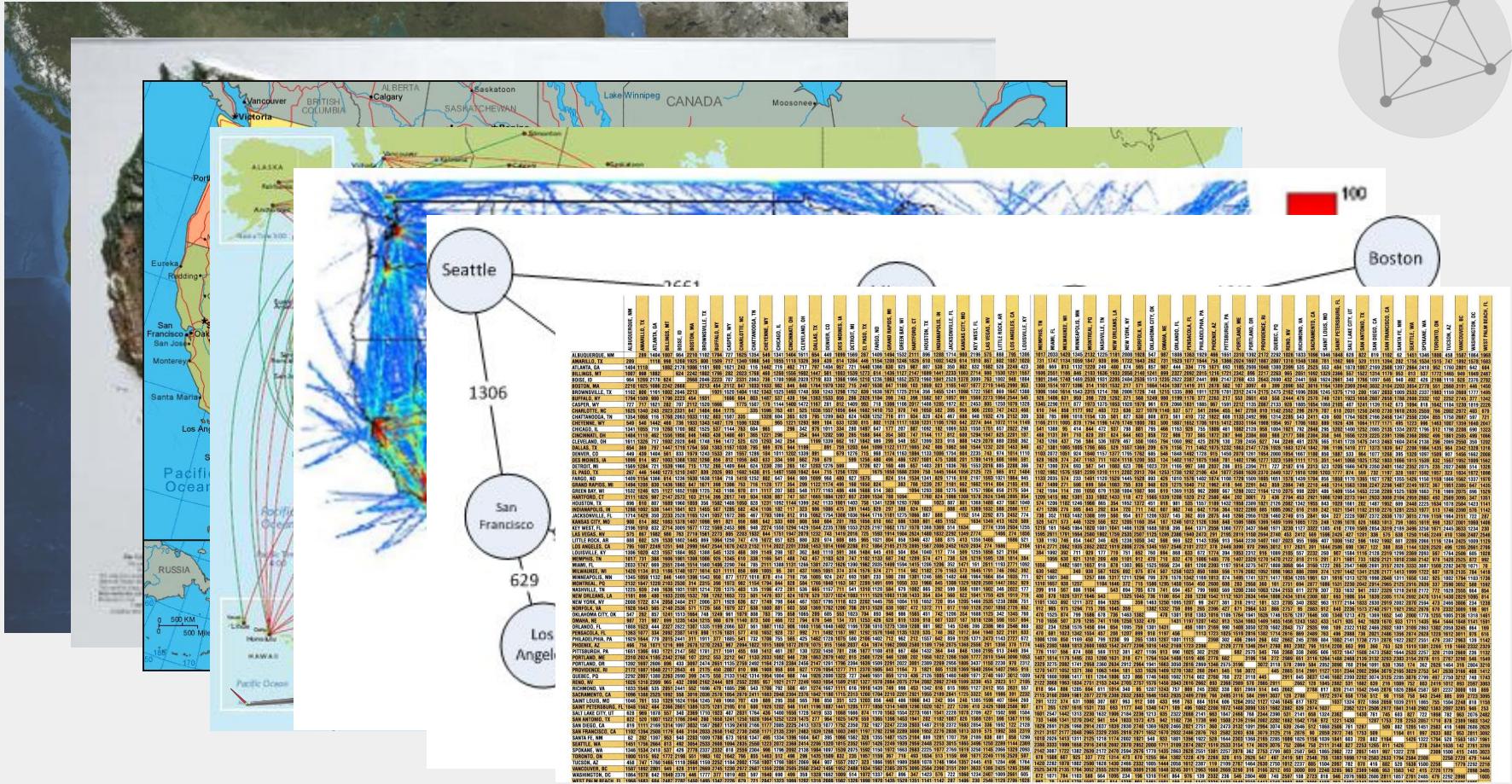
# Neurosurgical planning for brain tumor patients



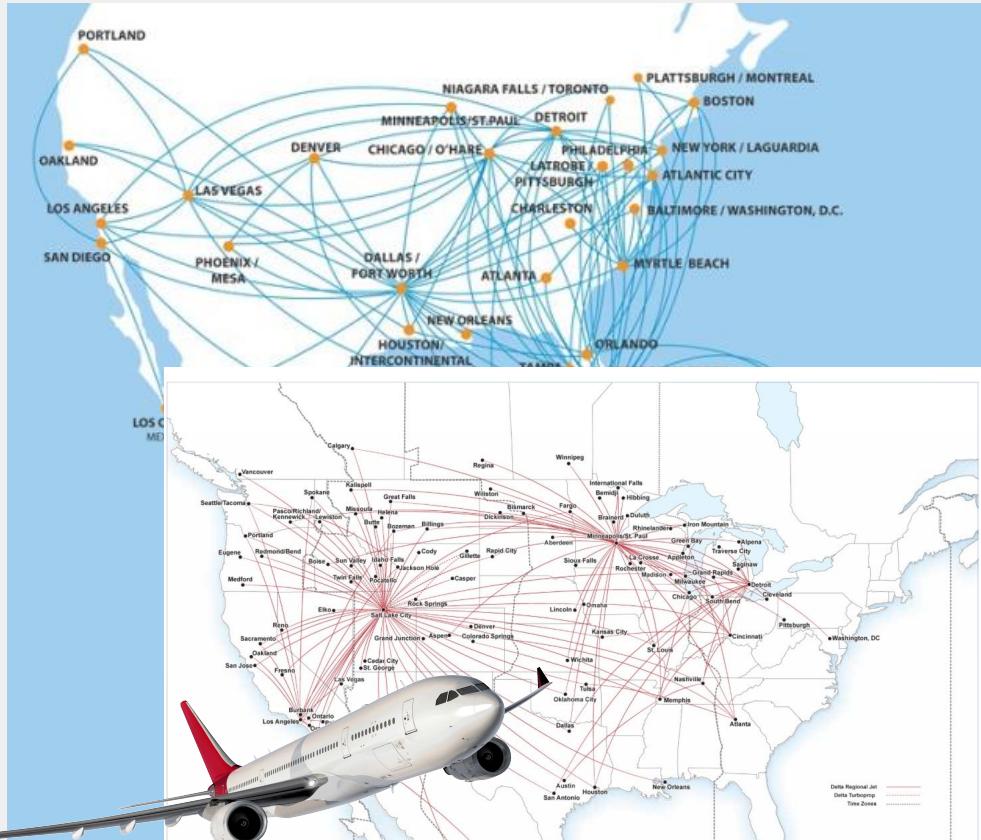
# Brain as a Network



# Maps and Networks

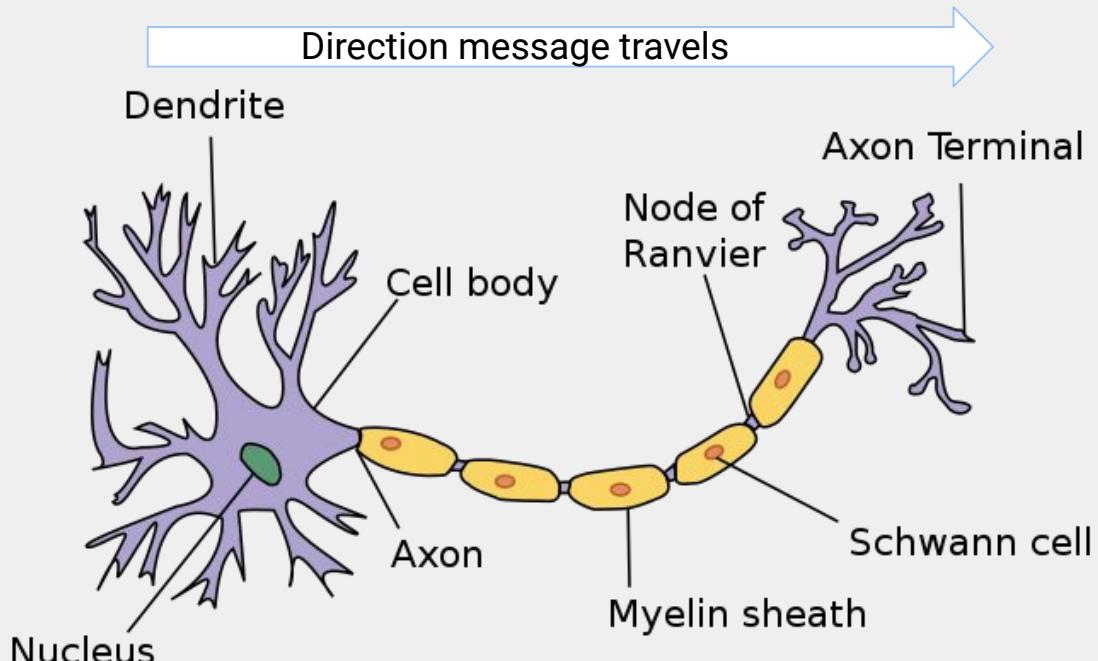
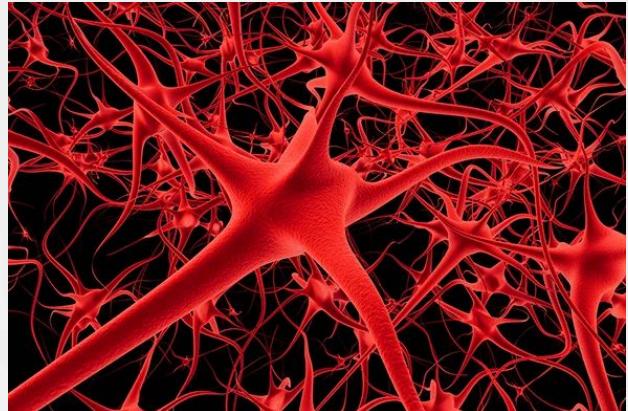
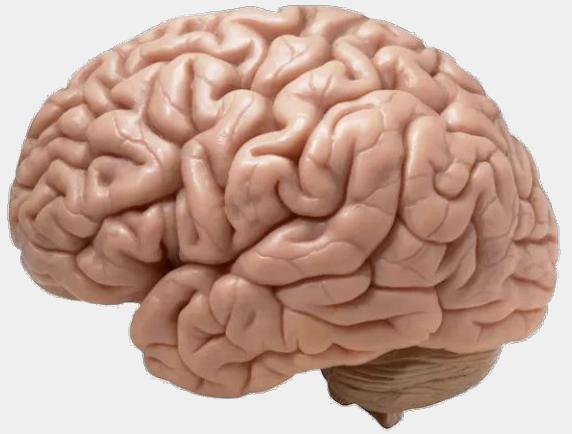


# Network: Airline travel

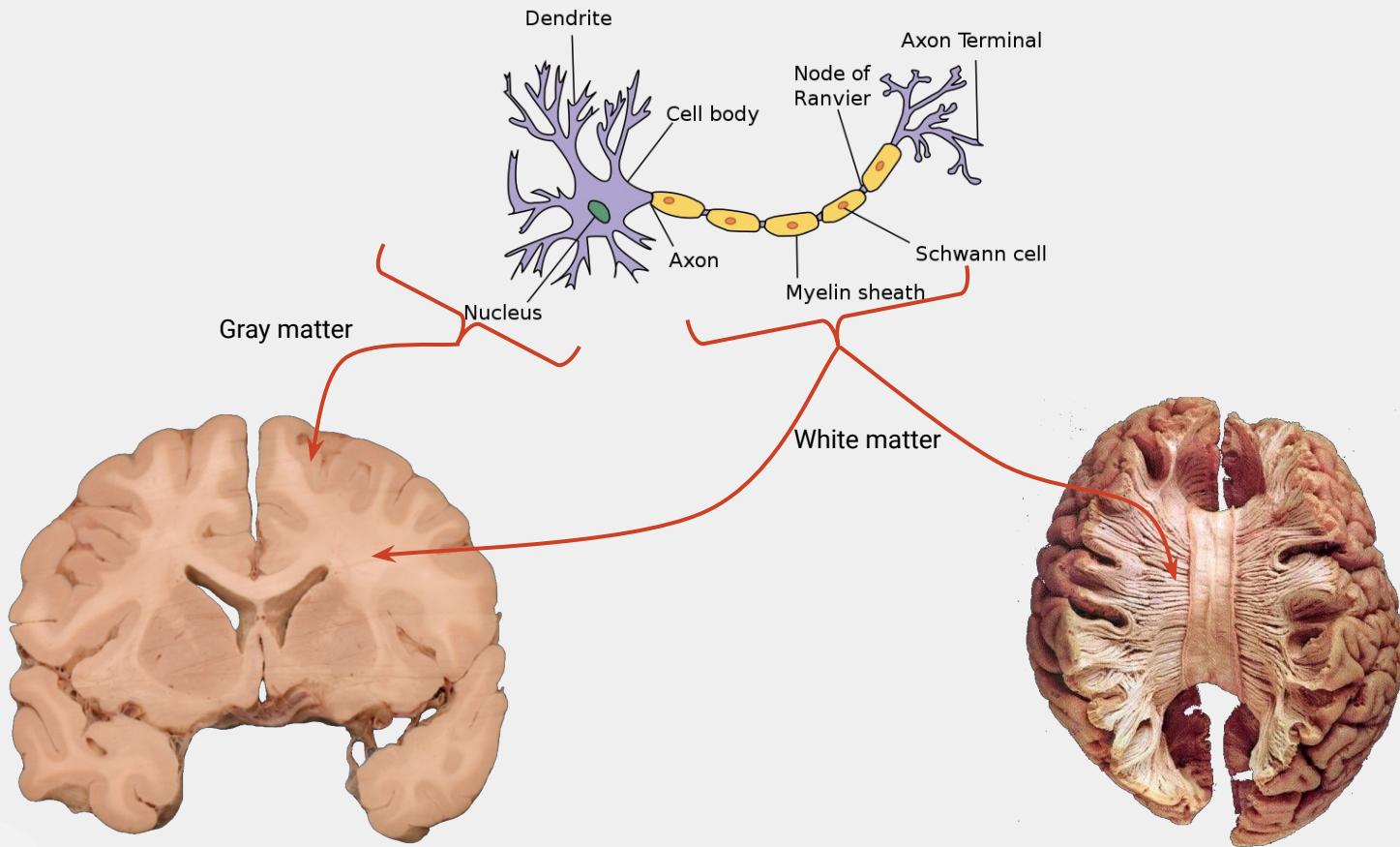


- In the absence of a direct flight, can I fly from Philadelphia to Las Vegas?
- If yes, what would be the
  - fastest
  - or cheapest
  - or shortest
- path for this travel?
- Which airport is the hub for this airline?
- What if I use multiple airlines?

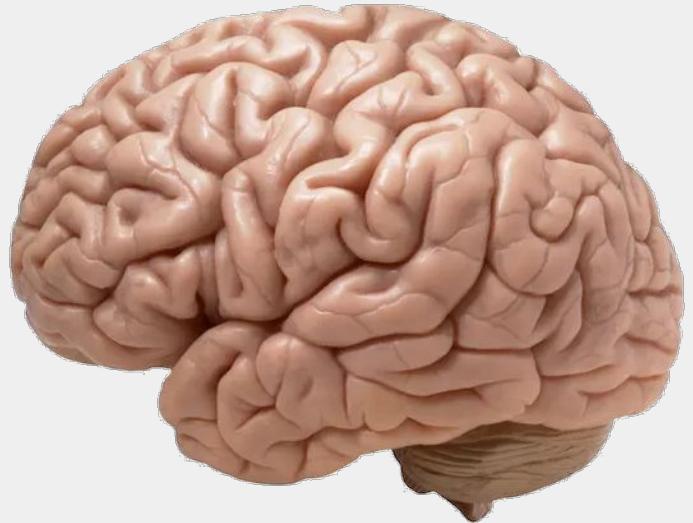
# Brain: a network of neurons



# Brain: a network of neurons



# Brain as a network: Connectome



# Graphs: abstract representation for network like structures

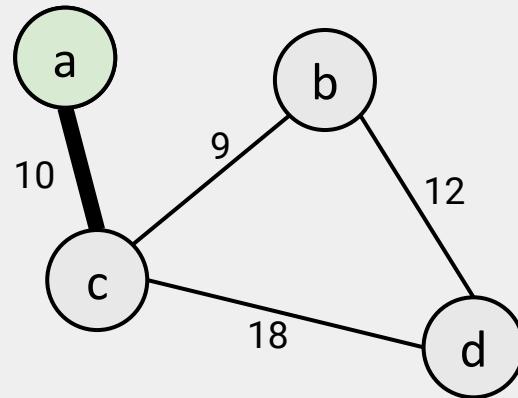
Graph is a data structure containing:

- a set of **vertices** V (also called nodes)
- a set of **edges** E, where an edge represents a connection between 2 vertices.

Edges can have **weights**, representing the strength of the relationship between corresponding objects (i.e., nodes)

Graphs are commonly represented using **matrices**

- called adjacency matrix, in the context of graphs

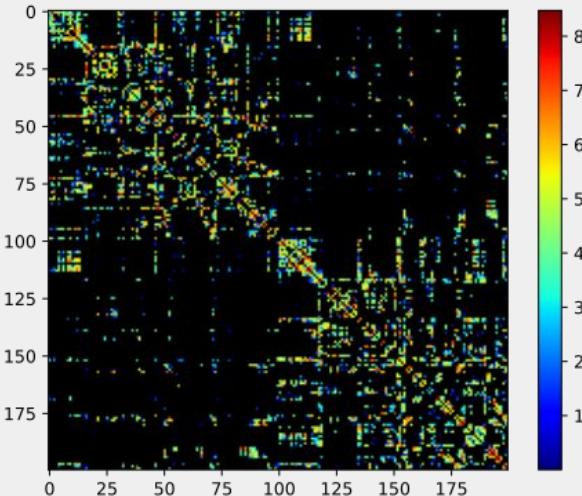
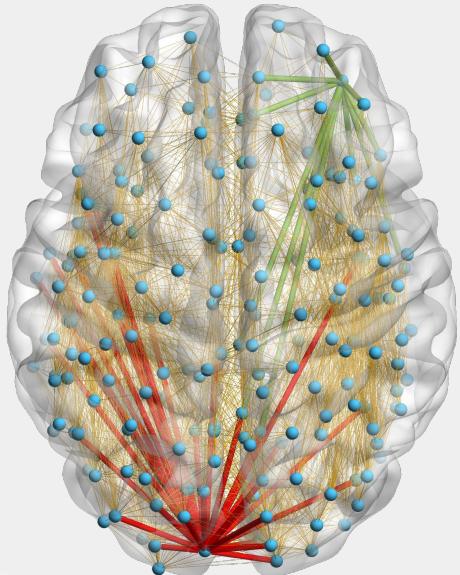


$$\begin{bmatrix} 0 & 0 & 10 & 0 \\ 0 & 0 & 9 & 12 \\ 10 & 9 & 0 & 18 \\ 0 & 12 & 18 & 0 \end{bmatrix}$$

# Brain as a network: Connectome

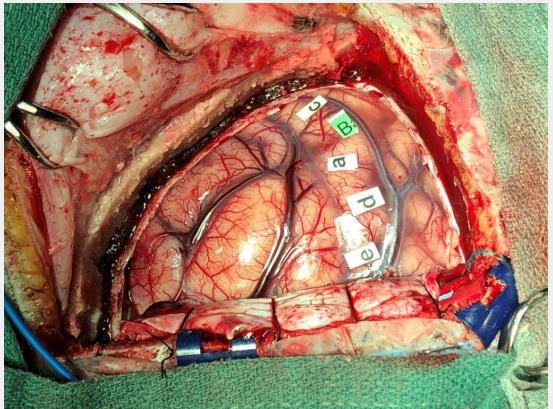


A brain network is called “connectome”: a **matrix** representing all possible **pairwise** anatomical **connections** between neural elements of the brain.



- How can we represent brain as a network?
- How can we identify nodes?
- How can we capture connectivity to designate edges?

# How to represent brain as a network?



Awake surgery can help in identifying regions and their connectivity...

- Definitely not feasible in most cases!

**Neuroimaging** offers several solutions!

- diffusion MRI (like Google maps of brain)
- functional MRI (traffic map of brain)
  - Also EEG/MEG to gather functional data



# From raw MR data to brain graphs: data processing



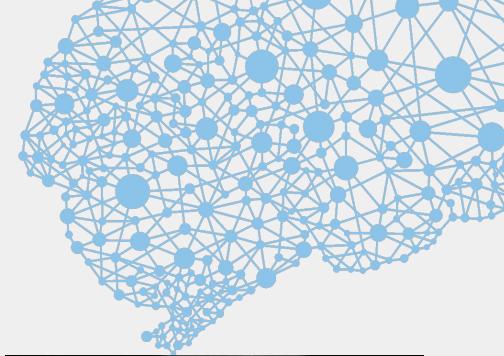
# Neuroimaging

The data:

- has a macroscopic spatial resolution of  $\sim 1\text{-}10 \text{ mm}^3$  (i.e., order of  $10^{-2}\text{m}$ )
  - compare this with the neuron size of neuron nucleus  $\sim 4\text{-}100 \text{ micrometers}$  (i.e.,  $10^{-6}\text{m}$ )
- in functional connectivity could have a low temporal resolution
  - $\sim 3\text{-}6 \text{ seconds}$  for fMRI
  - $\sim 1 \text{ millisecond}$  for EEG (but has source localization problem)
- is noisy and requires an intense preprocessing

We will focus on three types of data:

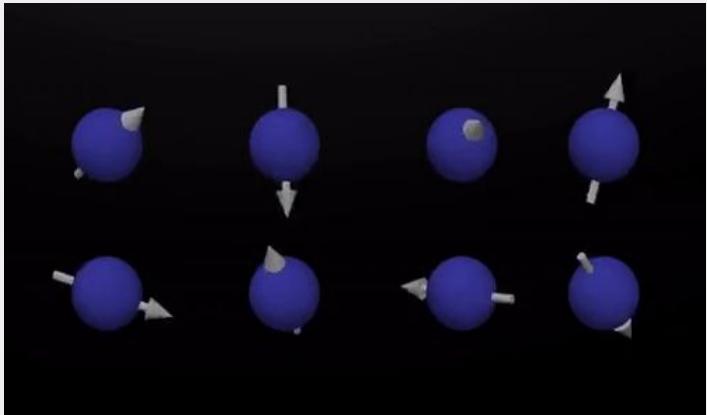
- Brain anatomy, which involves
  - T1/T2 weighted imaging
- Structural connectivity, which involves
  - Diffusion weighted imaging (i.e., DWI)
- Functional connectivity, for which we will use
  - Functional MRI (i.e., fMRI)



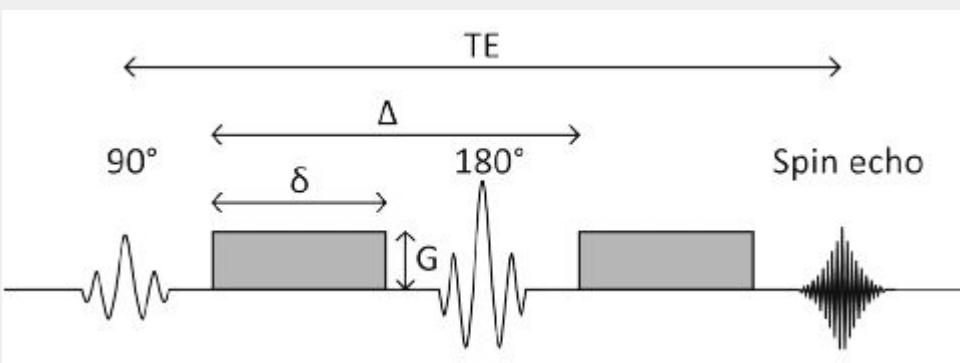
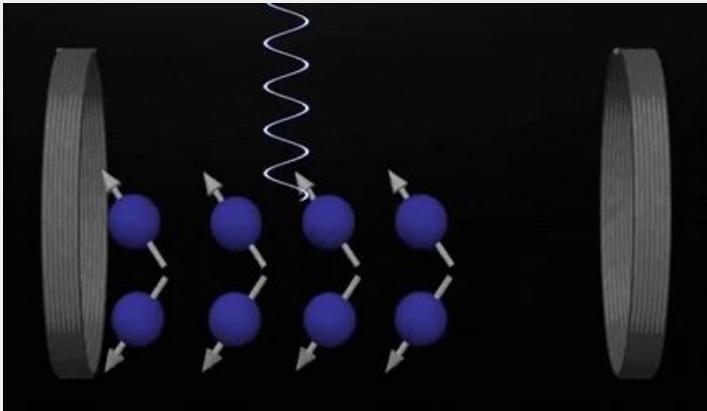
# MRI basics and T1-weighted imaging



# MRI: Magnetic Resonance Imaging



- Normally, water molecules have a random motion (called Brownian motion) in the cell
- When put under giant magnets, their motion is regularized, albeit temporarily
  - Then a reverse magnetization is done
  - And then the directionality of the water diffusion is measured



# MRI: varying contrasts

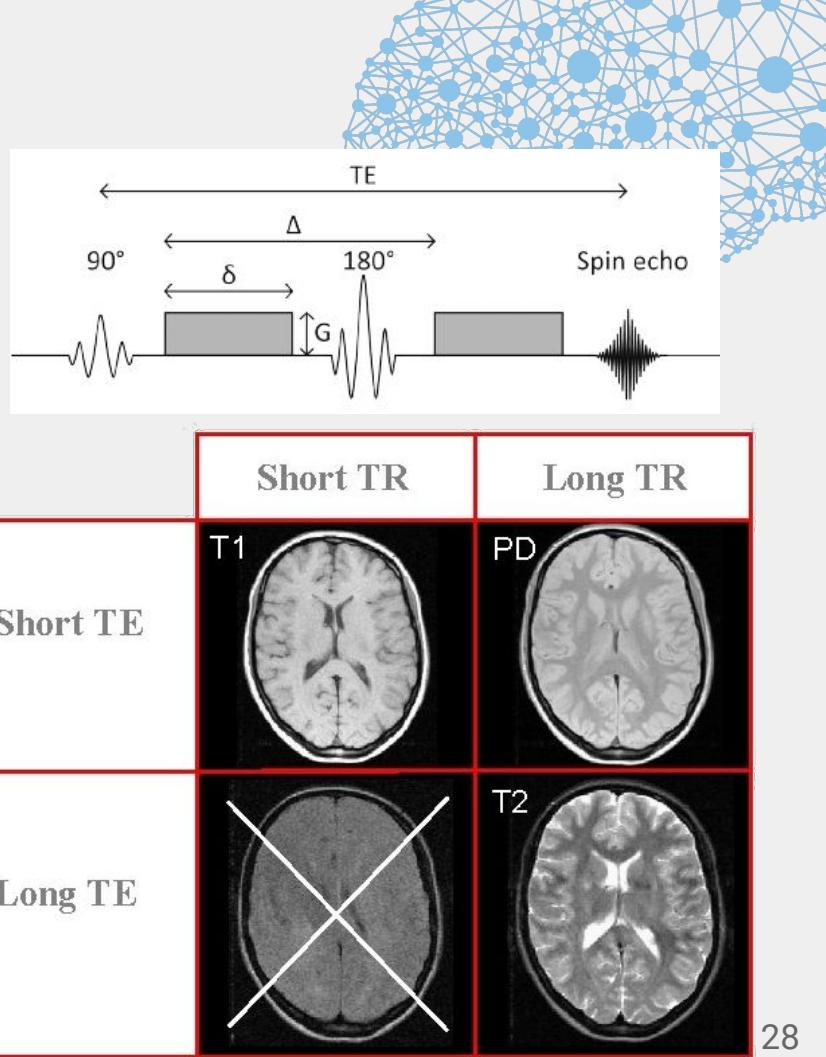
Contrast in images change depending on the timing of signals:

- **Repetition Time (TR)** is the amount of time between successive pulse sequences applied to the same slice.
- **Time to Echo (TE)** is the time between the delivery of the RF pulse and the receipt of the echo signal

T1/T2 are 3 dimensional images, and provides a good anatomical detail of the brain tissue as well as skull.

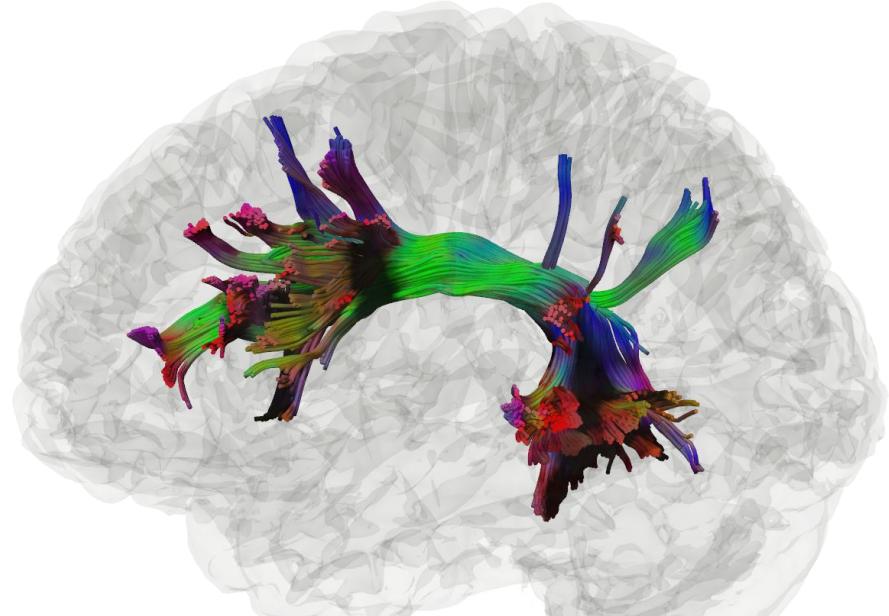
Sample data acquisition text from a paper:

High-resolution T1-weighted anatomic images were also obtained using a 3D MPRAGE imaging sequence with TR = 1620 ms, TI = 950 ms, TE = 3 ms, flip angle = 15°, 160 contiguous slices of 1 mm thickness, FOV = 192 × 256 mm<sup>2</sup>, 1NEX, resolution = 1 × 1 × 1 mm.



# Structural connectivity in brain

Diffusion MRI



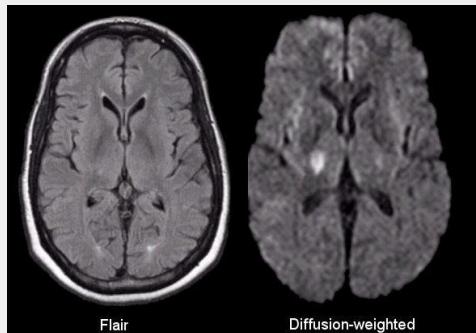
# Diffusion MRI

Diffusion MRI is a 4 dimensional data, with a relatively lower spatial resolution (2x2x2 mm) compared to T1/T2 images (1x1x1 mm).

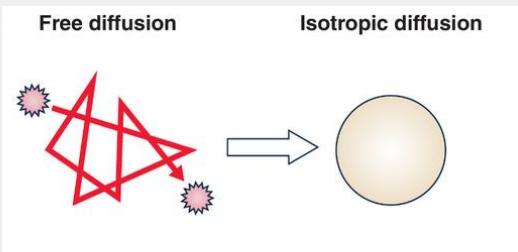
- Image of the brain is taken from 30-60+ angles, each image after magnetizing the brain from a different perspective, hence the 4th dimension.
- Utilizes the restricted motion of water in the brain tissue to derive axonal structure of the brain!

Sample data acquisition text from a paper:

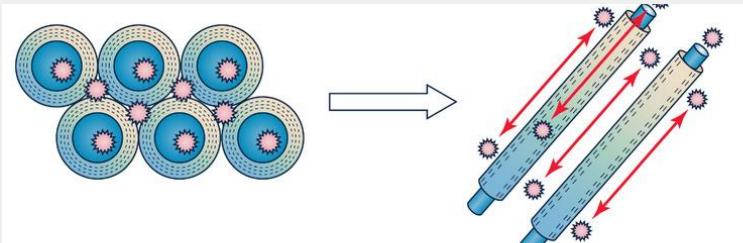
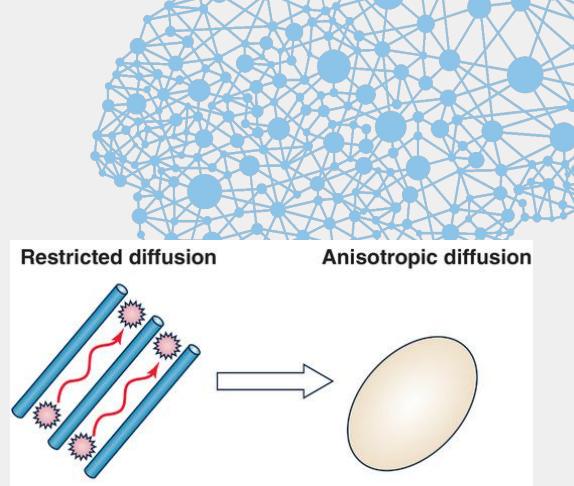
DWI scans were acquired using a twice-refocused spin-echo single-shot echo-planar imaging sequence (TR/TE = 8100/82 ms, flip angle = 90/180/180, FOV = 240 × 240mm, resolution = 1.9 × 1.9 × 2mm, gap = 0, volumes = 71, 64 diffusion directions with b = 1000 s/mm<sup>2</sup> and 7 b = 0 images).



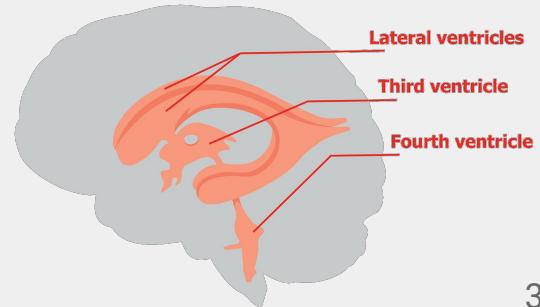
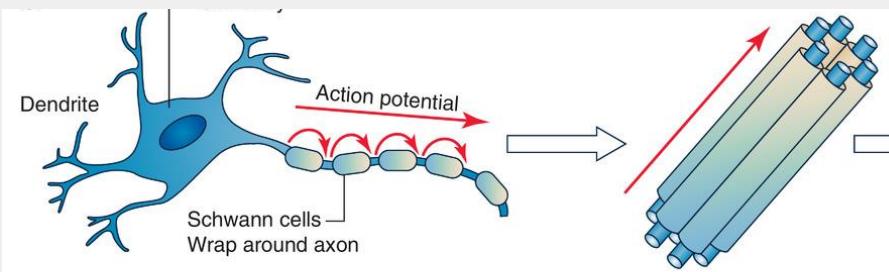
# Diffusion of water in tissue



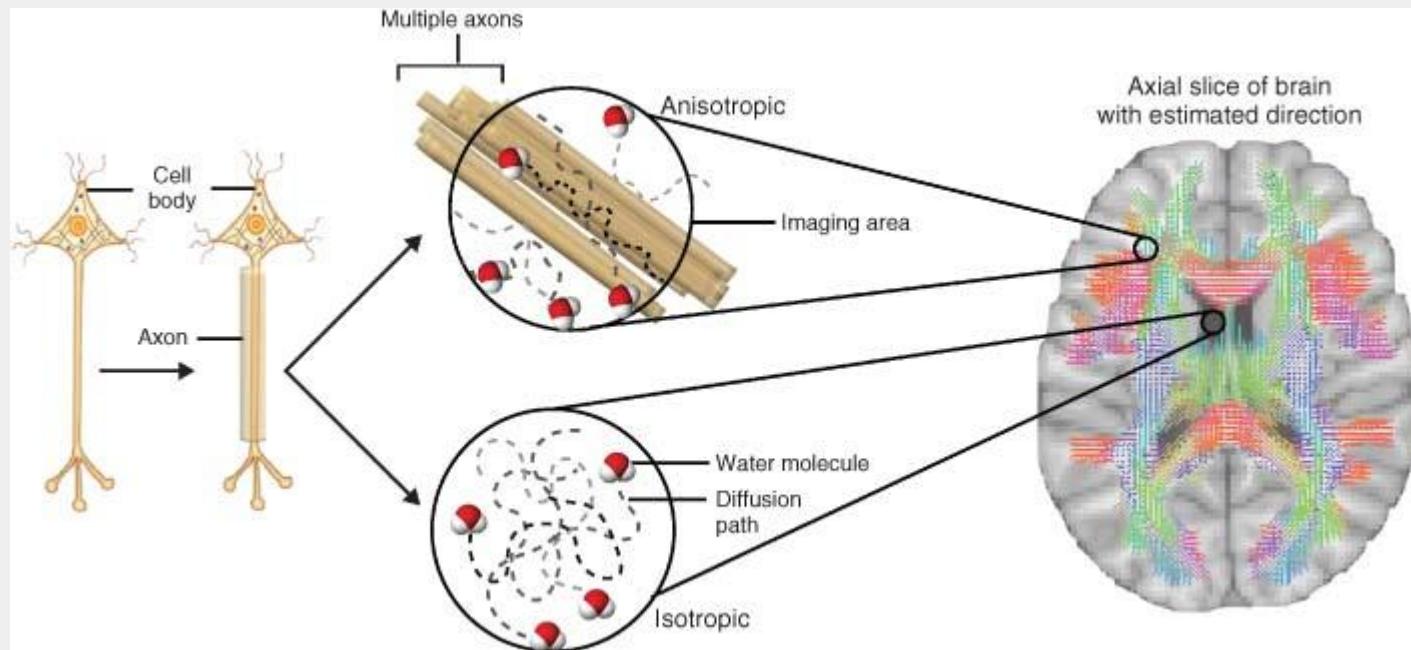
- Water without any boundaries around will diffuse freely
- Water trapped in and between boundaries will diffuse directionally.



- Water in nucleus or in ventricles diffuse freely
- Water trapped in and between axons diffuse along the axons



# Diffusion MRI: diffusion to connectivity



Directionality of the water diffusion in the brain reveals axonal connectivity!

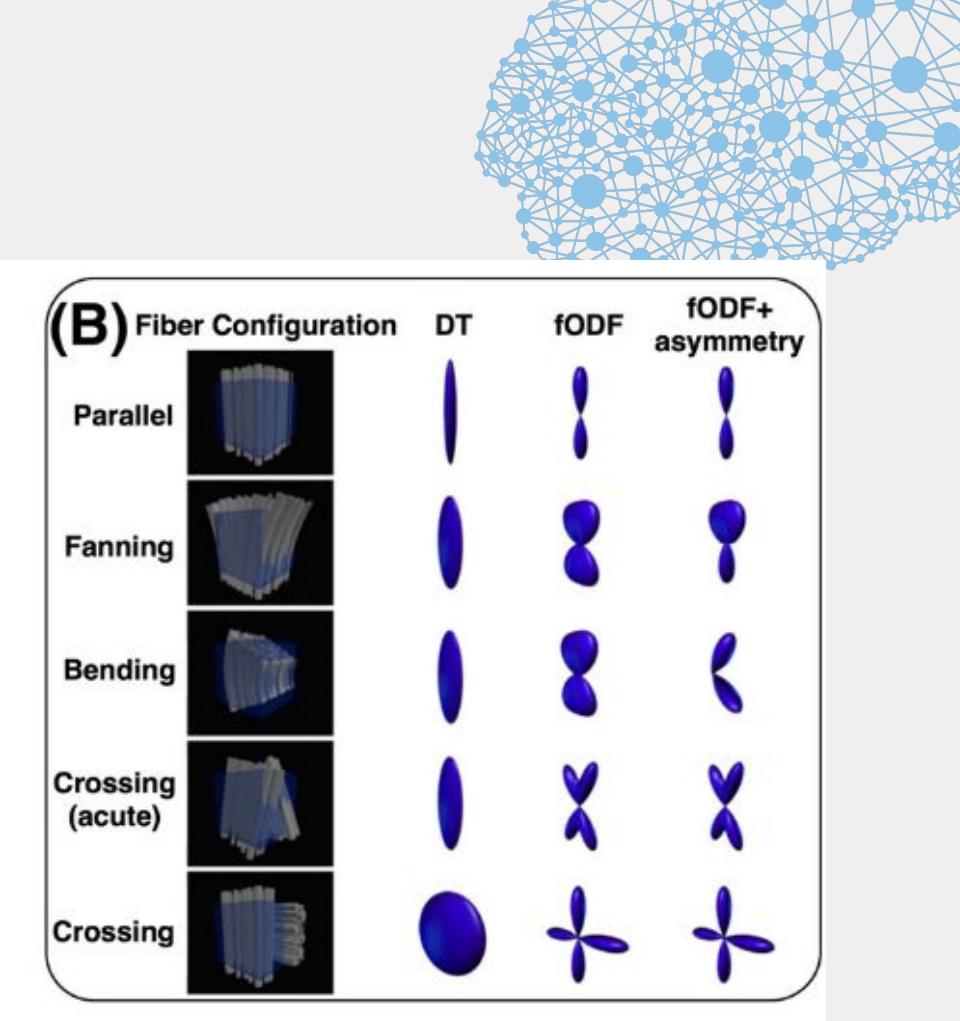
- How?

# Tractography

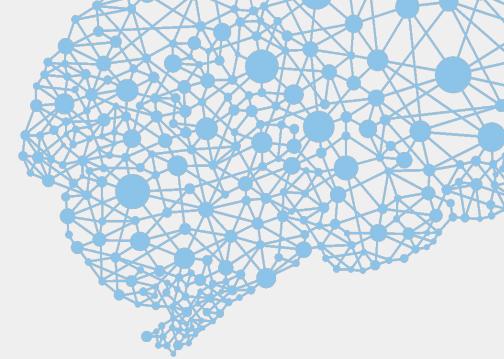
Raw information of directionality of the water can be used to model the underlying anatomical tissue.

Multiple methods exist:

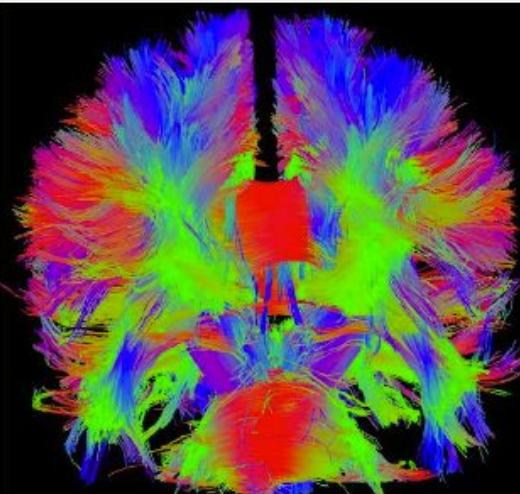
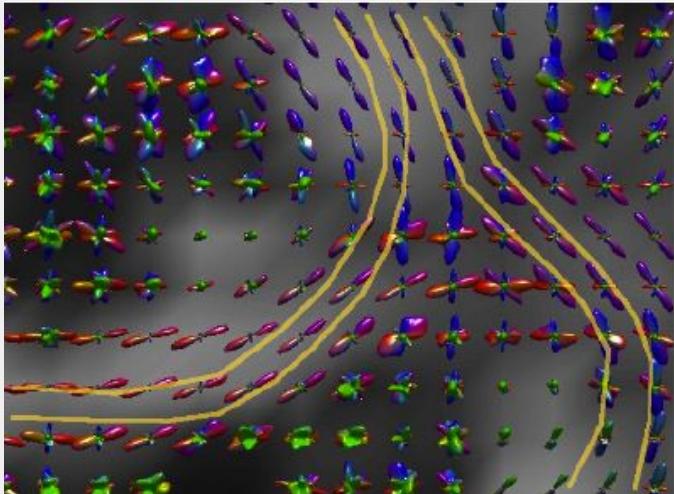
- Diffusion Tensor Imaging (DTI)
  - Uses a disc as the model
  - Needs at least 6 directional image, the more is the better
- Constrained Spherical Deconvolution (CSD)
  - Uses sphere as the model
  - Involves calculation of Orientation Distribution Function (ODF) for each voxel



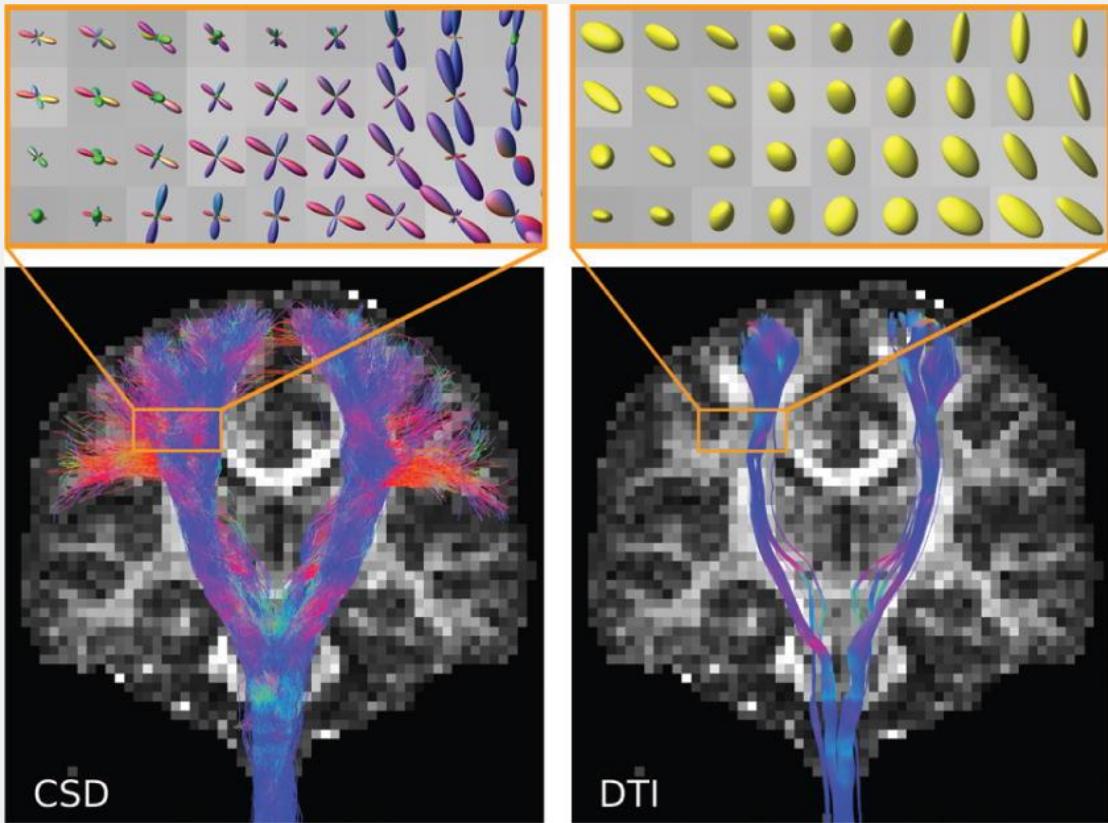
# Tractography: diffusion to connectivity



- Calculate ODFs for each voxel
- Starting from a “seed” voxel, follow the orientation to get to the next voxel
  - Number of seeds are practically between 1-10 million
  - Very time consuming computation taking several hours for a single brain
- Tracking can be done in two ways:
  - Deterministic: follow where the direction of the tensor points to
  - Probabilistic tractography: with a probability distribution, follow where ODF points to



# Tractography: CSD vs DTI



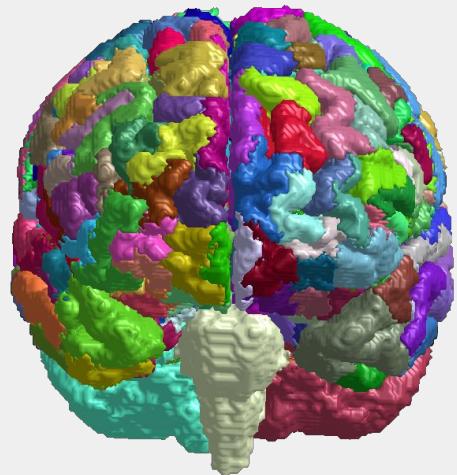
CSD is more robust to artifacts such as crossing and kissing fibers, relative to DTI, due to:

- The model allowing better directionality information
- ODF providing a probability field of directionality, allowing for probabilistic tracking.

The resulting structure, which consist of fiber tracts, is called **tractogram**.

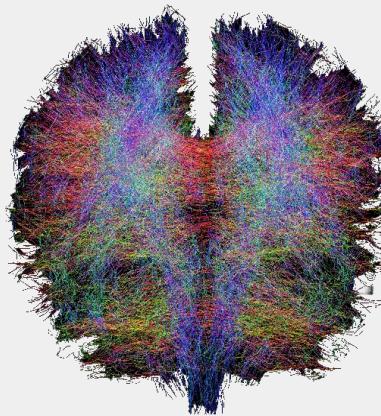
# Identifying nodes: Parcellating brain into regions

- Anatomically and/or functionally similar parts of the brain are considered to form a region of the brain.
- Generating a map of the brain as such is called “parcellation”.
- Can be mainly done in two ways:
  - Anatomically: experts identify regions on a 3D brain model
  - Functionally: functional activation of brain is measured, and voxels that coactivate and that are within the neighborhood of each other are group together to form regions.
- Parcellations are also known as “brain atlases”

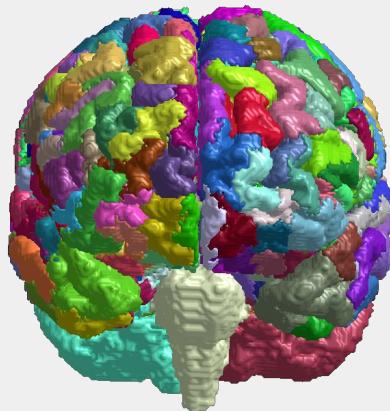


# Putting it together: Structural Connectome

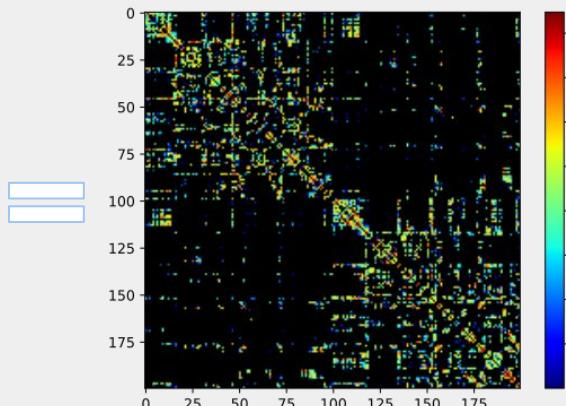
- Transposing the parcellation atlas over the tractogram, we obtain pairwise connectivity between regions of brain
  - That is, fiber tracts become our weighted edges!
- When represented on a matrix, we then have a structural connectome!



Tractogram



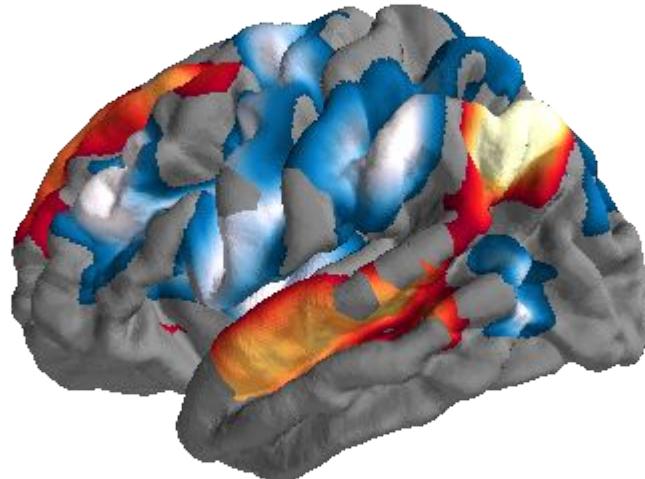
Parcellation atlas



Structural Connectome

# Functional connectivity in brain

Functional MRI

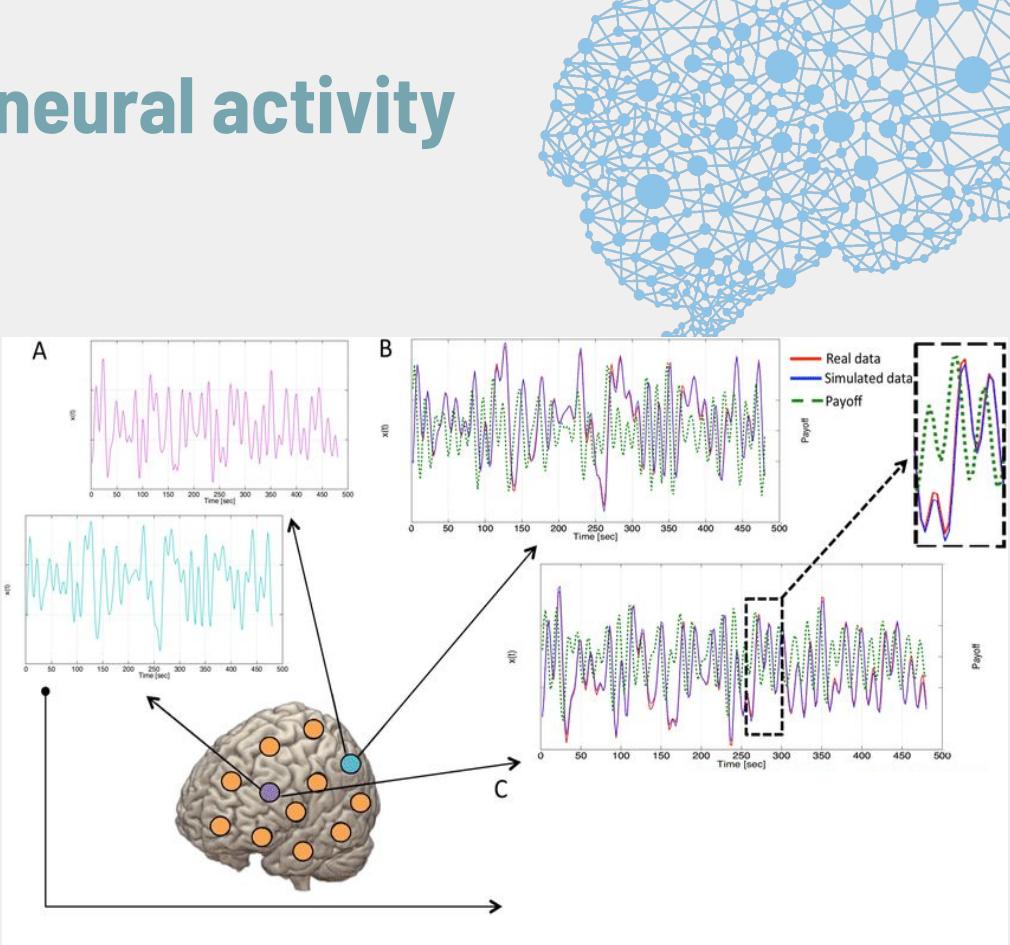


# Indirect measurement of neural activity

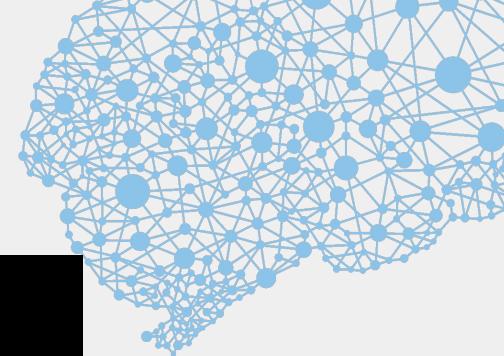
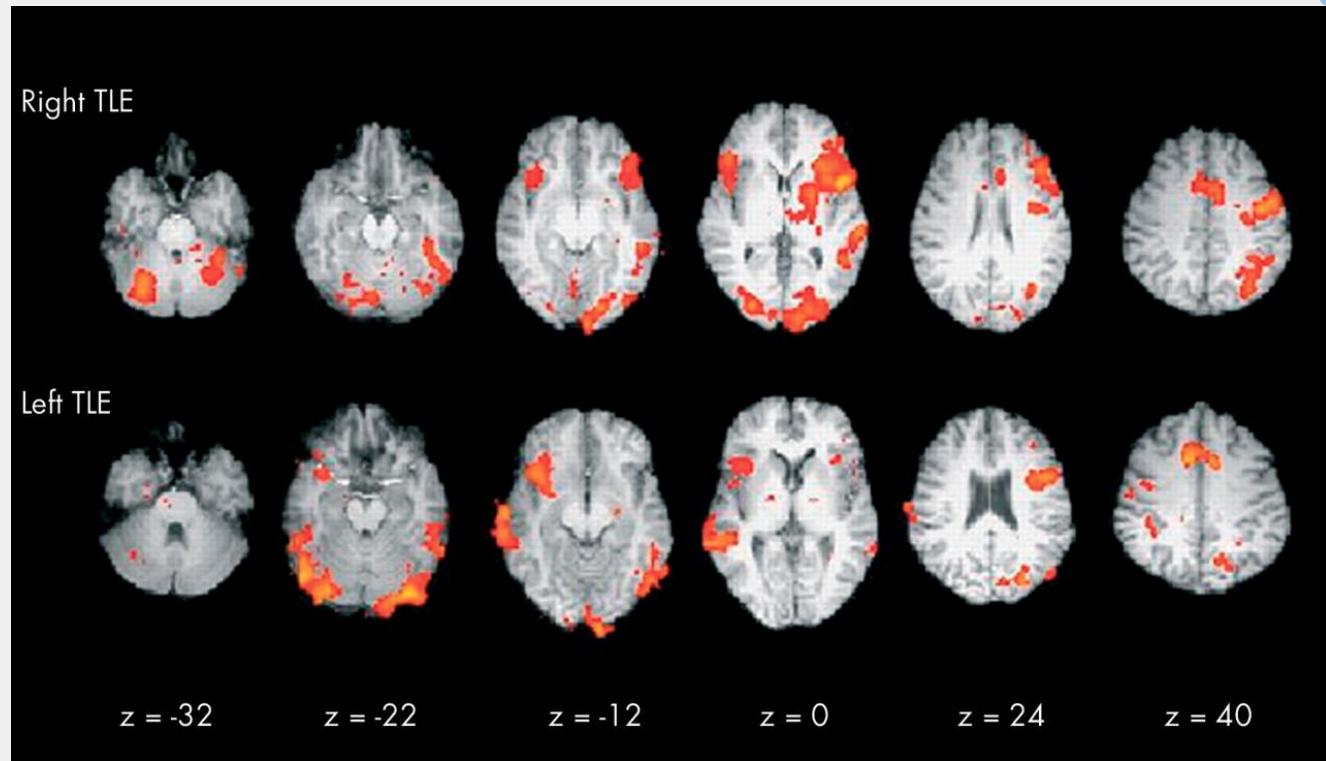
- fMRI measures brain activity by detecting changes associated with blood flow.
- It relies on the fact that cerebral blood flow and neuronal activation are coupled.
  - When an area of the brain is in use, the body responds by adjusting its blood flow to deliver nutrients such as oxygen and glucose to stressed tissues and allow them to function.
  - Active neurons = increased blood flow to that region
  - The primary form of fMRI uses the blood-oxygen-level dependent (BOLD) contrast.

Sample data acquisition text from a paper:

Resting-state BOLD fMRI was acquired using a whole-brain, single-shot, multislice, gradient-echo planar sequence (TR/TE = 3000/2 ms, flip angle = 90°, FOV = 192 × 192 mm, matrix = 64 × 64, gap = 0, resolution = 3 × 3 × 3 mm, volumes = 124).

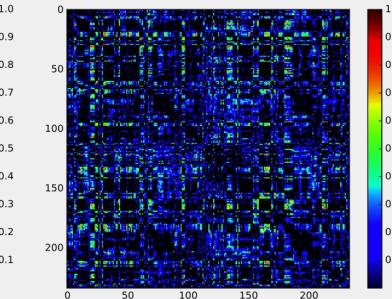
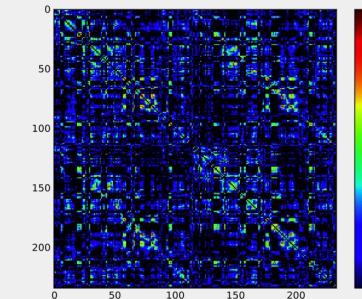
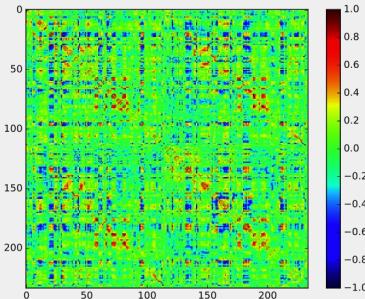
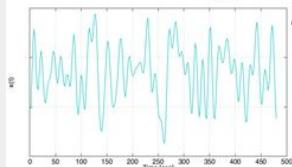
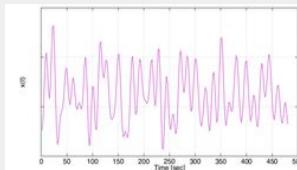


# Functional activation



# Functional connectivity

- Functional connectivity between brain regions is obtained by calculating Pearson's correlation between the functional timeseries of region pairs.
- This leads to a value between -1 to 1:
  - +1: the two regions are perfectly in synchrony with each other
    - They talk and keep silent at the same time
  - -1: the two regions are inversely synchronous with each other
    - One talks while the other listens
  - 0: the two regions are asynchronous
    - They talk and listen arbitrarily, relative to each other
- We obtain a functional connectivity matrix with edge weights in range [-1,1]
  - Generally, positive weighted edges are used since the meaning of negative edges are not well understood

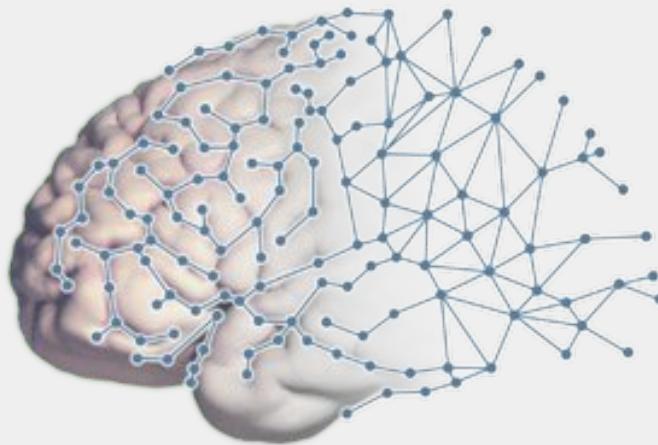


# Types of functional connectivity



- Full correlation yields pairwise connectivity between every two node
  - However, not all nodes are anatomically directly connected with each other
  - This indicates an indirect functional connectivity
- To obtain only direct functional connectivity, partial correlation can be calculated.
  - Partial functional correlation can be thought of as the counterpart of the direct structural connectome
- The formula to calculate partial correlation involves taking the inverse of the covariance matrix.
- Another method is by first solving two linear regression problems for each pair of nodes, then calculate residuals, and then calculating the correlation between the residuals.
- The system is generally underdetermined, since the number of regions are generally around 200+, while number of timeseries is generally lesser than that.
  - Each time series can handle the direct connectivity between two regions.
  - Having  $C(n,2)$  pairs for large n despite having a smaller number of timeseries makes the system underdetermined.
  - Regularization methods are used to estimate partial correlation.

# Data to Analyze for Projects



# Data resources for connectomes

- Diffusion MRI tractography filtering techniques change the topology of structural connectomes
  - [Link to data](#)
  - [Link to paper](#): Frigo, M., Deslauriers-Gauthier, S., Parker, D., Ismail, A.A.O., Kim, J.J., Verma, R. and Deriche, R., 2020. Diffusion MRI tractography filtering techniques change the topology of structural connectomes. *Journal of Neural Engineering*.
  - Raw connectomes, obtained from 100 HCP subjects on Desikan atlas.
- Human Connectome Project (HCP) structural connectomes from diffusion MRI
  - [Link to data](#)
  - [Link to paper](#) : Civier, O., Smith, R.E., Yeh, C.H., Connelly, A. and Calamante, F., 2019. Is removal of weak connections necessary for graph-theoretical analysis of dense weighted structural connectomes from diffusion MRI?. *Neuroimage*, 194, pp.68-81.
  - Same 100 HCP subjects, on 84 node connectome, with a subset of 10 being available on 234 node Atlas.
- Human Connectome Project (HCP) directed and undirected structural connectomes
  - [Link to data](#)
  - [Link to paper](#): Varga, B. and Grolmusz, V., 2021. The braingraph.org database with more than 1000 robust human connectomes in five resolutions. *Cognitive Neurodynamics*, pp.1-5.
  - 1064 HCP subjects, structural connectomes obtained by probabilistic tractography using 1M streamlines 10 times. They generated 5 different scales of Lausanne atlas from ~80 to 1000+ ROIs. They also provided directed connectomes but it was not clear to me how they generated direction for DWI. They provide data in graph format, by also providing mean fiber length and mean FA for each edge.
- HCP twin data connectomes along with genetical data for brain regions on average healthy controls
  - [Link to data](#)
  - [Link to paper](#): Arnatkeviciute, A., Fulcher, B.D., Oldham, S., Tiego, J., Paquola, C., Gerring, Z.F., Aquino, K.M., Hawi, Z., Johnson, B., Ball, G.M. and Klein, M., 2021. Genetic influences on hub connectivity of the human connectome. *Nature Communications*.
  - "For each of 234 monozygotic (MZ) twins and their 69 non-twin siblings as well as 120 dizygotic (DZ) twins and 48 of their non-twin siblings, we reconstruct macroscale cortical connectomes using DWI."



# More data resources for connectomes

- Brain Connectivity Toolbox (Neuroscience Networks)
  - <https://sites.google.com/site/bctnet/> - Under “Connectivity Network Data Sets”
- Dynamic Connectome Lab (Neuroscience Networks)
  - <http://www.biological-networks.org/> - Under “Resources”
- Mark Newman’s Website (Non-Neuroscience Networks)
  - <http://www-personal.umich.edu/~mejn/netdata/>
  - Also the section entitled “Other sources of network data: at the bottom of the page
- Stanford Large Network Dataset Collection (Non-Neuroscience Networks)
  - <https://snap.stanford.edu/data/>
- Human Connectome Project (Neuroscience Networks)
  - <http://umcd.humanconnectomeproject.org>
- Complex Systems Group
  - <https://complexsystemsupenn.com/codedata/>
- My Connectome Project
  - <http://myconnectome.org/wp/>
- Colorado Index of Complex Networks
  - <https://icon.colorado.edu/#/>



# Even more data resources for connectomes

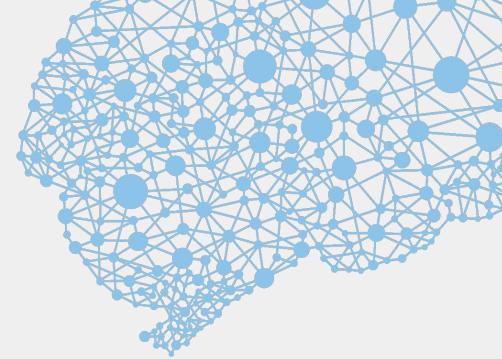
- I will have a meeting this Friday with my previous research lab to get:
  - Autism dataset (200+ kids of age lower than 8)
  - Healthy developmental dataset (750+ healthy people of age [8-22])
  - Possibly more to come...
- You can look at recent papers in reputable journals for papers that publish their connectomes:
  - Check for papers in: Neuroimage, Human Brain Mapping, PNAS, Nature Neuroscience, Network Neuroscience





# Project Ideas

# Potential ideas to explore



- Diseases and disorders
  - Network changes
  - Biomarkers for the diseases
    - Alzheimer's Disease
    - Autism Spectrum Disorder
    - ADHD
    - Traumatic Brain Injury
    - Multiple Sclerosis
- Developmental changes in brain network
  - Typical/atypical developmental groups
- Structure-function coupling
  - How does brain communicate (check for papers in the journal Network Neuroscience)
- Sex differences
- Limitations of tractography
- Data harmonization
- Test/retest data stability