Advances in Understanding the Wiring of the Brain: Neuroimaging and Big Data in Connectomics

Syllabus MBB 980V Fall 2024

Instructor: Lisa Nickerson, Ph.D.
Email: lisa_nickerson@hms.harvard.edu
Time: Tuesdays 3 PM – 5 PM
Office Hours: Tuesdays 2 PM – 3 PM
Location: William James Hall 950
Office Hours Location: WJH Basement Lounge

Catalyst Profile: https://connects.catalyst.harvard.edu/Profiles/display/Person/65562

General Information

Constructing a map of the connections between the 86 billion neurons in the human brain has been a goal of neuroscience since the field originated. Connectomics research, which aims to understand how the brain is wired together into this map, has shown the human brain to be a complex network with the same properties that other complex networks exhibit. Much like our social networks, the world wide web, and our travel systems, the brain demonstrates organization of the gray matter into a "functional connectome" comprised of modules called brain networks that orchestrate their functions to support our everyday activities. More recently, advances in another MRI technique called diffusion MRI have made it possible to study the organization of the brain's white matter "highways", or structural connectome, that transmit information from brain region-to-brain region, brain network-to-brain network. MRI-based connectomics is a rapidly growing field, with new methods and applications evolving at an incredibly fast pace and there are now numerous large-scale neuroimaging initiatives across the world that are aimed at mapping the human brain connectome. These studies aim to map the human brain connectome across the lifespan, from *in utero* to the oldest old, and in brain disorders such as mental illnesses, developmental disorders, neurological disorders and other health conditions. The goal of this class is to understand how MRI can be used to study the living human brain connectome and the latest advances these approaches have revealed in our understanding of the wiring of the brain. We will also dive into some of the large-scale neuroimaging datasets to see how we can leverage these open access resources for connectomics research. This course is designed for students in the MBB programs who are interested in learning about how we study brain connectivity and how the brain is organized, including those who are interested in neuroscience applications and brain disorders and those interested in bioinformatics/computer science/statistics/physics applications in neuroimaging.

To unravel the "black box" nature of the sophisticated MRI methods used for connectomics research, we will learn the basics of the workhorse MRI connectomics methods, functional and diffusion MRI, from a conceptual perspective. We will learn how each of these techniques is used for connectomics and some key methodological and interpretational issues for each. Then we will focus on the brain's connectome. We will discuss brain organization, including how to construct a brain graph as the mathematical embodiment of the brain's connectome and how to evaluate the brain's network properties using graph theory and other approaches, the brain networks that have been reported in the literature, and the links between structural and functional connectomes. We will do a survey of widely used open access tools for connectivity and connectome analyses, and open access connectome datasets with sample sizes up to the hundred thousands, including the Human Connectome Lifespan and Disease Connectome studies, the ABCD study, and the UK Biobank, which will also be the hypothetical data sources for your final research projects. Last, we will discuss ethical, computational, and statistical issues when working with these large open access datasets.

There will be no mid-term or final exams on the course material. Instead, throughout the course you will be working on a mock research proposal for a connectomics-based research study involving secondary analyses of the large-scale open access datasets that we will discuss in class. Various elements of the research proposal will be due throughout the term and we will spend time in class developing, critiqueing and presenting components of your proposal as exercises to better learn the concepts covered in the course readings and lecture components. The research project will be modeled after an HMS postdoctoral fellowship application to provide experience in designing your own research study and in writing research proposals, with hypotheses, aims, and approach. Students may also use this opportunity to develop their proposal for a senior thesis or other real-life project (for example, NIH pre-doctoral fellowships) focused on connectomics/machine learning if appropriate.

Grading is based on the following:

Class Participation	25%
Abstract	10%
Aims & Hypotheses	15%
First Draft	10%
Presentation on Final Project	15%
Final Project (Written)	25%

Class Participation: The success of this course depends upon your participation. You will be expected to read all assigned articles ***prior*** to each class and be prepared to discuss your thoughts, ideas, and questions on each topic. There will be a combination of activities and assignments in and out of class that will be required to facilitate student participation. Class attendance is required as we will spend so much time developing your final project throughout the course.

Assigned readings may be changed a bit if I find something that seems like a better compliment to the topic.

Final Project: Each student will prepare a four-page research paper modeled after the Research Plan for an HMS fellowship application. I will provide additional details of the structure of the application.

Presentations on Final Project Elements: Each student will do two short presentations on the elements of the Final Project. The first will be on the Specific Aims & Significance to get feedback from the class on your project topic, the second will be on the final project (all sections). You will be expected to prepare powerpoint slides (or similar) for these presentations. The length of the presentations will depend on final class enrollment. Guidelines on the elements of the Final Project, including all presentations, will be given to you.

Academic Honesty

I expect that all students will uphold the standards of academic integrity according to the Harvard honor code. You are strongly encouraged to interact with your classmates on your Final Project to refine, focus, and develop your research study, and you will have ample opportunities in class to obtain feedback from me and your classmates on your proposed study. However, your written project must be the result of your own research and writing. You will be expected to produce your own academic work of integrity – that is, work that adheres to the scholarly and intellectual standards of *accurate attribution of sources and transparent acknowledgement of the contribution of others to their ideas, discoveries, interpretations, and conclusions*. Please see the Harvard Guide to Using Sources for further information (https://usingsources.fas.harvard.edu/).

Week 1 (09/03): History of the Human Brain Connectome and Intro to Neuroimaging

Assigned Readings:

Catani M et al. 2013. Connectomic approaches before the connectome. Neuroimage 80:2-13.

Please watch *before class*:

The hidden networks of everything (Barbasi)
https://www.youtube.com/watch?v=RfgjHoVCZwU&pp=ygUPbmV0d29yayBzY2llbmNl (7:27)

The pattern in natures networks
https://www.youtube.com/watch?v=Lq5hlsJAOfc (3:24)

In class, we will watch and discuss several concepts related to neuroimaging and studying the brain with MRI

1. How does MRI work?
    a. https://www.youtube.com/watch?v=nFkBhUYynUw (3:10)
2. How does functional MRI work?
    a. https://www.youtube.com/watch?v=Rb_mdzgw-Jc&t=2s (6:41)
3. How does diffusion MRI work?
    a. https://www.youtube.com/watch?v=Be51OqnBbdc (4:44)
4. How does connectomics with MRI work? (3:28)
    a. https://youtu.be/diPiSHxfGyE

Week 2 (09/10): Introduction to Human Brain Connectomics

Assigned Readings:
Sporns O. 2011. The human connectome: A complex network. Annals NY Acad Sci 1224: 109-125.

Week 3 (09/17): Nodes, Edges and Parcellations

Assigned Readings: TBD

Week 4 (10/01): Properties of the Brain Connectome.

Assigned Readings:
Ardesch 2019. The human connectome from an evolutionary perspective. Progress in Brain Research 250:129-141.

Sporns O. 2013. The human connectome: Origins and challenges. Neuroimage 80:53-61. **Only the section on "Challenges" (pp. 56-58).**

Week 5 (10/15): The HCP Lifespan and Disease Connectome Projects and Other Open Access Datasets

<u>Assigned Readings:</u>
Madan 2021. Scan once, analyse many: Using large open-access neuroimaging datasets to understand the brain. Neuroinformatics https://doi.org/10.1007/s12021-021-09519-6

<u>Extra Resources:</u>

Philosophy behind the HCP study design that may give you ideas for your mock proposal study:

Barch D. 2017. Resting state functional connectivity in the Human Connectome Project: Current status and relevance to understanding psychopathology. Harvard Rev Psychiatry 25:209-217.
https://www.nytimes.com/2014/01/07/science/the-brain-in-exquisite-detail.html

In case you're interested in the neuroinformatics aspect of open-access medical imaging/data sharing:

Diaz et al., 2021. Data preparation for artificial intelligence in medical imaging: A comprehensive guide to open-access platforms and tools. Phys Medica 83:25-37.

Week 6 (10/29): Flash Talks on Scientific American connectomics articles

Assigned Readings: Sign up on google doc. Prepare a flash talk on your article for presentation in class.

Dataset Descriptions + Pre-proposals due.

Week 7 (11/05): Functional Connectivity

Fox M. and Raichle M. 2007. Spontaneous fluctuations in brain activity observed with functional magnetic resonance imaging. Nature Neuroscience Reviews 8:700-711.

Optional Readings:
Van den Heuvel M and Pol HEH. 2010. Exploring the brain network: A review on resting-state fMRI functional connectivity. European Neuropsychopharm 20:519-534.

Week 8 (11/12): Intrinsic Connectivity Networks and Challenges of FMRI Connectivity

Assigned Readings:
Uddin et al. 2019. Towards a universal taxonomy of macro-scale functional human brain networks. Brain Topography 32:926-942.
Bijsterbosch et al. 2020. Challenges and future directions for representations of functional brain organization. Nature Neuroscience 23:1484-1495.

Proposal Abstracts due.

Week 9 (11/19): Structural Connectivity and Visualization the Human Brain Connectome

Margulies et al., Visualizing the human connectome. Neuroimage 80:445-461, 2013.

Aims and Hypotheses are due.

Week 10 (11/26): Computational, Statistical, Diversity and Ethical Considerations for Large-Scale Open Access Neuroimaging Datasets

Assigned Readings:
White et al., 2022. Data sharing and privacy issues in neuroimaging research: Opportunities, obstacles, challenges, and monsters under the bed. Human Brain Mapp 43:278-291.

Student Reviews of Abstracts, Aims and Hypotheses are due + In Class Discussion.

Wed Nov 27 – Sun Dec 1 is Thanksgiving Recess

Week 11 (12/03): Connectivity Analysis Processing Streams and Demos or Breakthroughs in Brain Connectivity Research

In class Proposal Presentations.

Rough draft of written proposal is due.

Final Exam Period: **Final Project written proposals due, exact date TBD.**