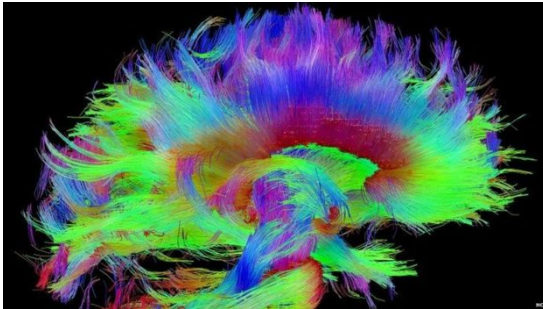


# CS 4884: Computing the Brain

## Computational Biology and Bioinformatics Capstone Course

T. M. Murali

January 21 and 23, 2020



**This course is NOT about  
neural networks or deep learning.**

# Course Information

- Meet on Tuesdays and Thursdays, 3:30pm–4:45pm, MCB 238.
- Office hours: by appointment, during class times in second half of semester.
- Course website: <http://bioinformatics.cs.vt.edu/~murali/teaching/2020-spring-cs4884/>. Consult this website regularly. Course schedule is subject to change.

## Textbook

Fundamentals of Brain Network Analysis  
(ISBN: 9780124077003)

ISBN 9780124077003

## Fundamentals of Brain Network Analysis

Alex Fornito, Andrew Zalesky, and Edward Bullmore

*Fundamentals of Brain Network Analysis* is a comprehensive and accessible introduction to methods for unraveling the extraordinary complexity of neuronal connectivity. From the perspective of graph theory and network science, this book introduces, motivates, and explains techniques for modeling brain networks as graphs of nodes connected by edges, and covers a diverse array of measures for quantifying their topological and spatial organization. It builds intuition for key concepts and methods by demonstrating how they can be practically applied across many different areas of neuroscience, ranging from the analysis of synaptic networks in the nematode worm to the characterization of large-scale human brain networks constructed with magnetic resonance imaging. This text is ideally suited to neuroscientists wanting to develop expertise in the rapidly developing field of neural connectomics, and to physical and computational scientists wanting to understand how these quantitative methods can be used to understand brain organization.

### From the Foreword

"This much needed primer on brain networks will become an indispensable addition to the bookshelves of all neuroscientists interested in the organization and function of nervous systems, from cellular to systems scales"

— Olaf Sporns, PhD, Distinguished Professor, Robert H Shaffer Chair, Indiana University

### Key Features:

- Extensively illustrated throughout by graphical representations of key mathematical concepts and their practical applications to analyses of nervous systems
- Comprehensively covers graph theoretical analyses of structural and functional brain networks, from microscopic to macroscopic scales, using examples based on a wide variety of experimental methods in neuroscience
- Designed to inform and empower scientists at all levels of experience, and from any specialist background, wanting to use modern methods of network science to understand the organization of the brain



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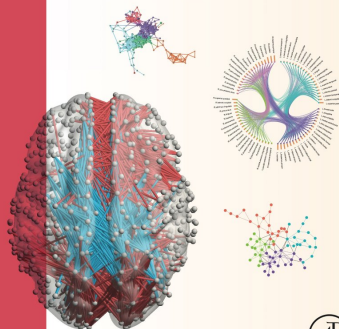
Fornito  
Zalesky  
Bullmore

## Fundamentals of Brain Network Analysis



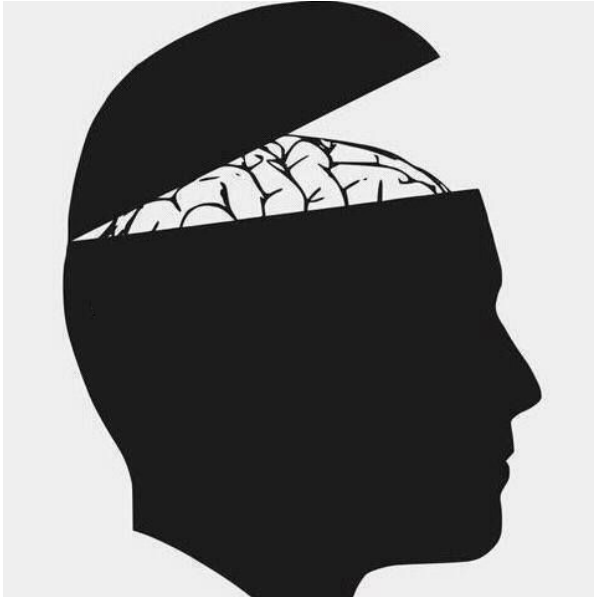
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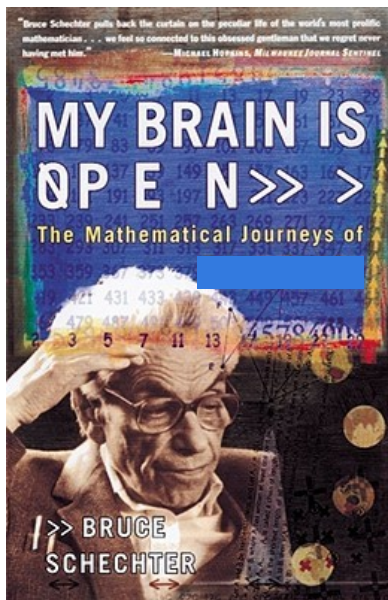
# Course Pre-requisite



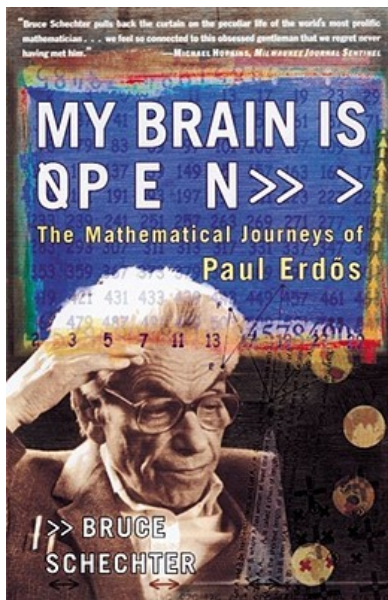
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# Course Structure

- Lectures based on the textbook

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- Assignments (2–3)

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- Lectures based on the textbook
- Assignments (2–3)
- Final project
- Participation in VTURCS Research Symposium, late April, 2020.



# Grading

- Assignments: 40%
- Final project: 60%

# Assignments

- Typically, I will ask you to write code to replicate analysis in one or two figures in the paper.
- These assignments may organically come about from class discussions.
- You will have about two weeks to complete assignments.
- What do you turn in?
  - ▶ Fully working code, e.g., on GitHub.
  - ▶ A short report on the results of your analysis, including the figures, discussion of difficulties you faced, how you solved them, and observations on your results.

# Ungraded Quiz

- Please fill out the ungraded quiz released on Canvas. **Deadline: 12pm, Jan 23, 2020.**
- I will tailor the materials in this courses to your responses as best as I can.

# Goals of the Course

Learn computational methods that use network/graph theory to understand the brain at three levels:

*Anatomical*

*Cellular*

*Molecular*

to gain insights into brain functions in health and disease.

# History of the Brain: Pre-History

- Trepanation (6500 BC, Incas, Peru): drilling holes in the skull to expose *dura mater* (outermost layer of the meninges) to treat health problems.



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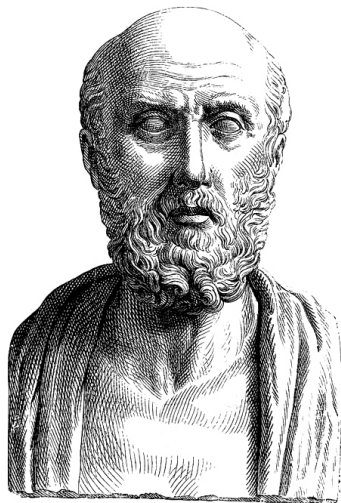


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- India (c. 400 BC): Charaka described symptoms and treatments of epilepsy.

# Ancient Greece

- Study of the brain was not based on dissection.
- Hippocrates (460–379 BC): Brain is the organ of sensation and intelligence.

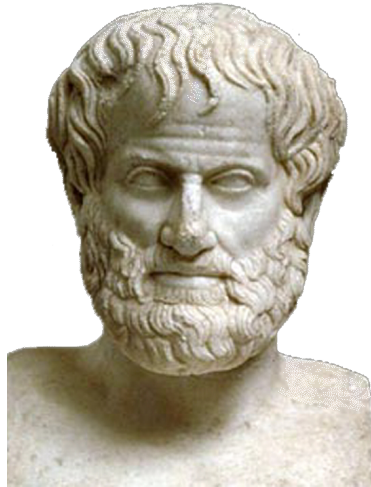


*The birth and evolution of neuroscience through cadaveric dissection, Moon K1, Filis AK, Cohen AR. Neurosurgery. 2010 Sep;67(3):799–809*



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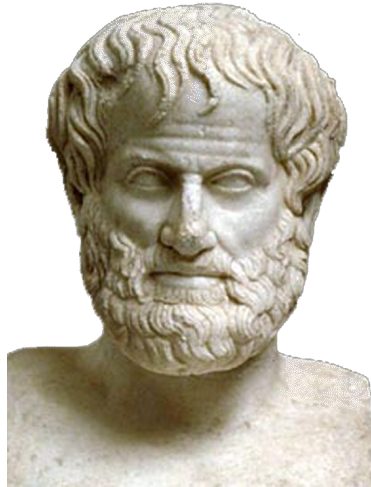
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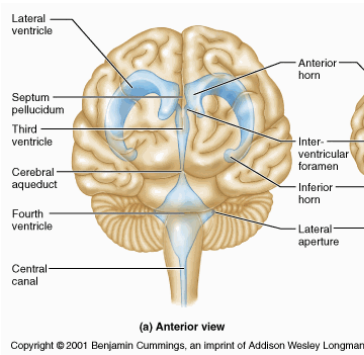
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- Herophilus (c. 325–255 BC):
  - ▶ Father of neuroanatomy, first dissector in the Western tradition.
  - ▶ Discovered ventricles, distinguished between cerebrum and cerebellum.

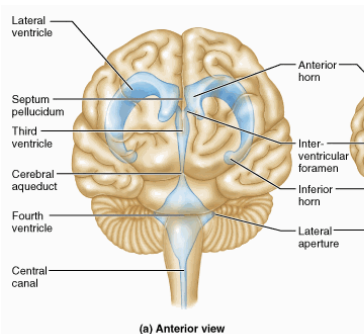


## Galen (130–200 AD)

- Theories dominated Western and Byzantine medicine till the 16th century.
- Used animal dissections.
- Structure-Function: cerebellum (hard) receives sensations and cerebrum (soft) stores memories.
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- Brain controls senses and motor functions by movement of fluids to and from ventricles through nerves (which are hollow, cf. arteries).



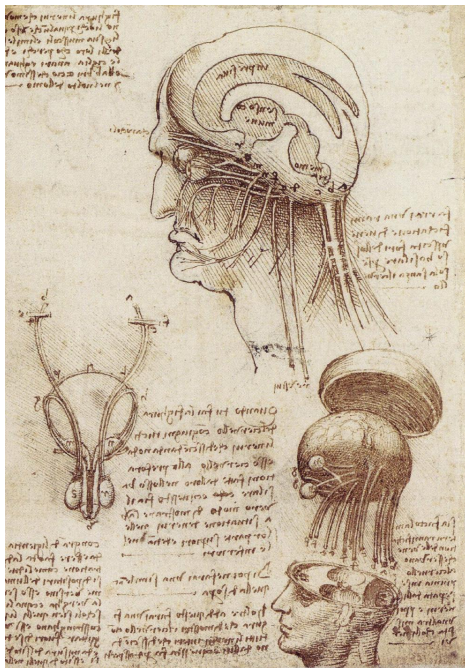
Copyright © 2001 Benjamin Cummings, an imprint of Addison Wesley Longman

# The Next 1300 Years

- Dark Ages in Europe.
- Arabs copied Galen's text among others.
- Islamic surgeon Abu al-Qasim al-Zahrawi (1000 AD) described several treatments for neurological disorders.

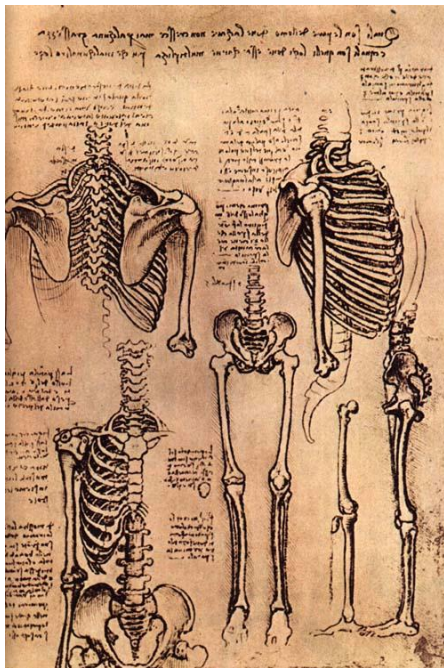
# Renaissance (14th–16th Centuries)

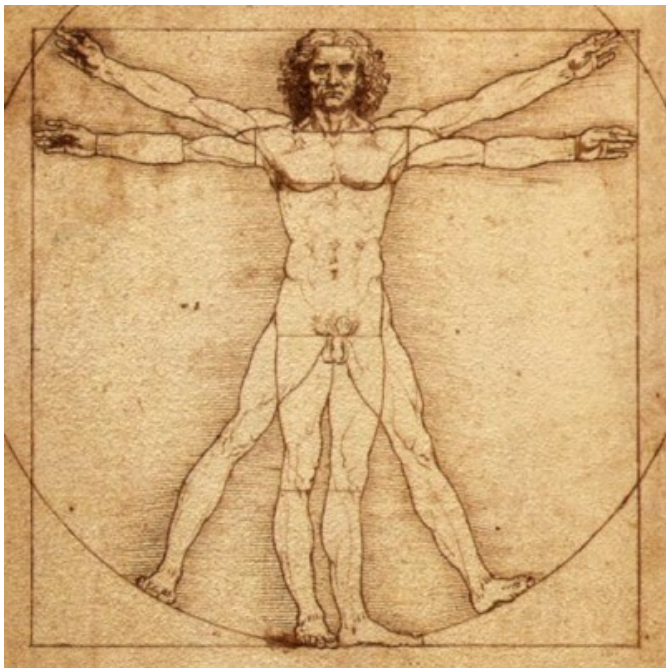
- Increased recognition of need for dissection to acquire new knowledge about the body's internal organs.
- Printing press (1439 AD) circulated Galen's works.
- Renaissance and Reformation of the Church promoted fresh thinking.
- Dissection resulted in detailed anatomical drawings.

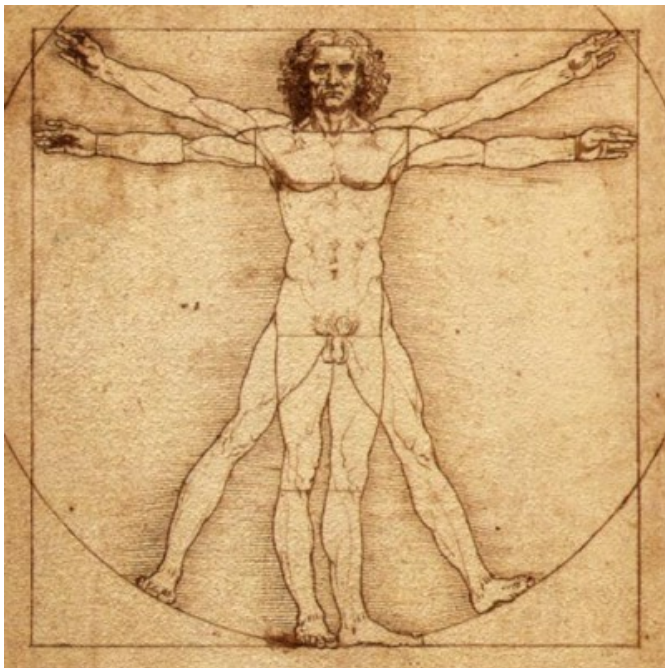










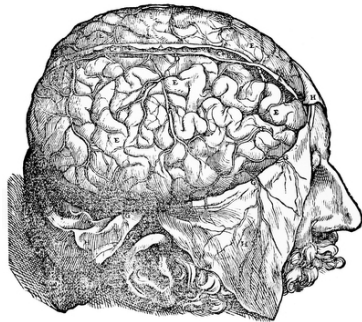


Leonardo da Vinci (1452–1519)



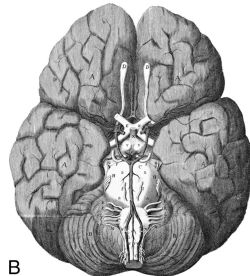
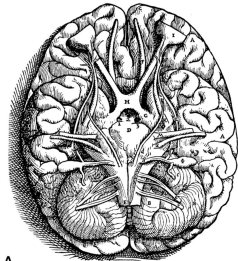
# Andreas Vesalius (1514–1564)

- Used skillful dissection of cadavers.
- *De humani corporis fabrica*: Documented and corrected 200 errors by Galen.




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# Contemporaries and Descendants of Vesalius



## Mathematics Genealogy Project


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A service of the  
[NDSU Department of Mathematics](#), in  
 association with the  
[American Mathematical Society](#).

### Gemma (Jemme Reinerszoon) Frisius

[Biography](#)

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Magister Philosophiae, Medicinae Doctor [Université Catholique de Louvain](#) 1529, 1536 

Dissertation:

Advisor: [Petrus \(Pieter de Corte\) Curtius](#)

Students:  
 Click [here](#) to see the students listed in chronological order.

Name	School	Year	Descendants
<a href="#">John Dee</a>	University of Cambridge and Université Catholique de Louvain	1546	1
<a href="#">Gerardus Mercator</a>	Université Catholique de Louvain	1532	2
<a href="#">Johannes Stadius</a>	Université Catholique de Louvain		2
<a href="#">Andreas Vesalius</a>	Università degli Studi di Padova and Université Catholique de Louvain	1537	105089

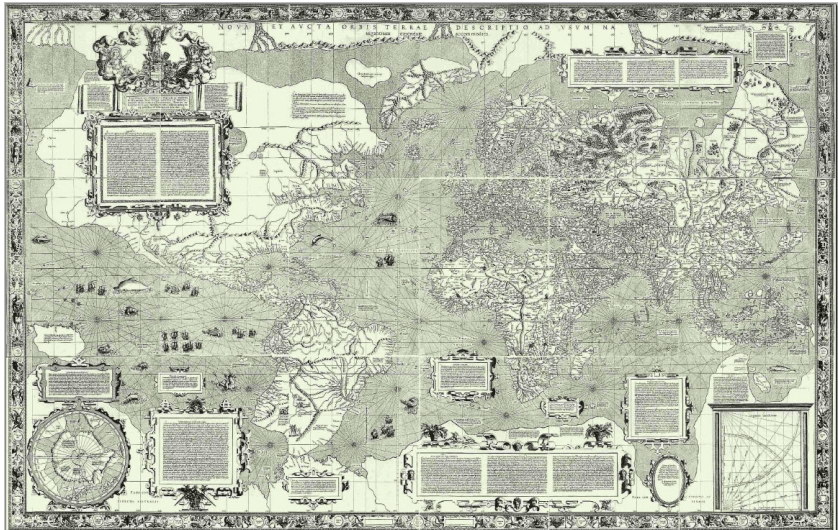
According to our current on-line database, Gemma Frisius has [4 students](#) and 105096 [descendants](#).  
 We welcome any additional information.



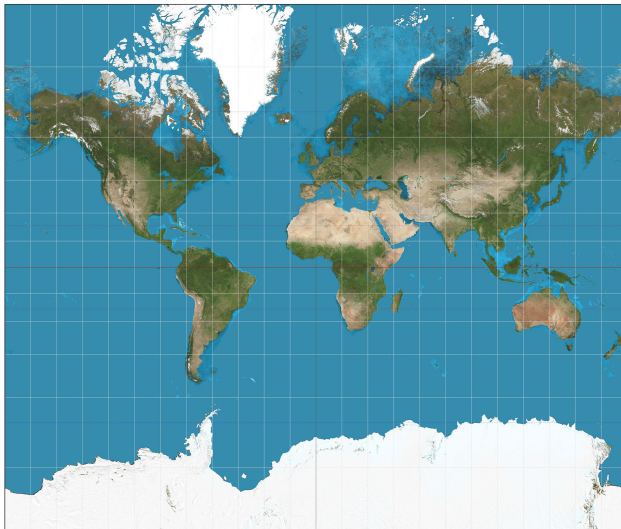
# Gerardus Mercator



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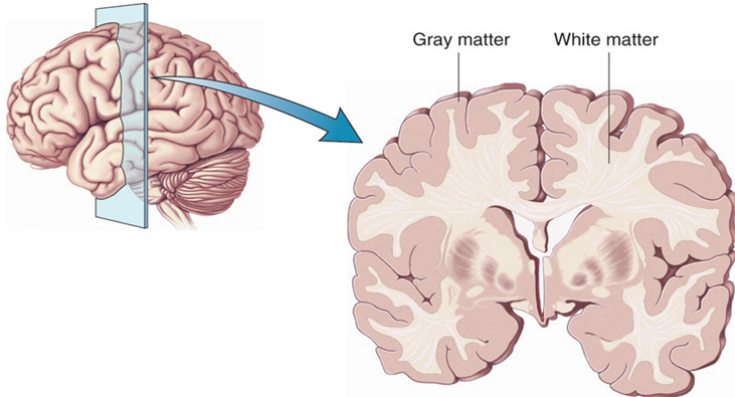
# Gerardus Mercator



# White Matter and Grey Matter (17th–18th centuries)

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He [Hercule Poirot] tapped his forehead. 'These little grey cells. It is 'up to them.'

(Agatha Christie)

izquotes.com

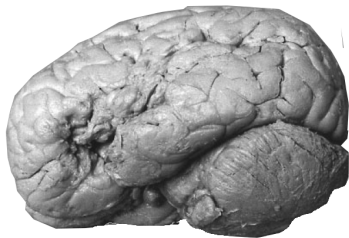
# Structure to Function

- Broca's area (1861): production of speech and language



# Structure to Function

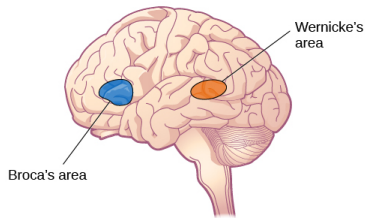
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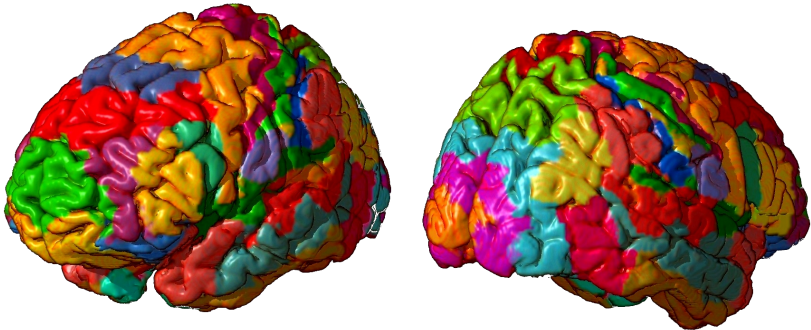
# Structure to Function

- Broca's area (1861): production of speech and language
- Wernicke's area (1874): comprehension of spoken and written word



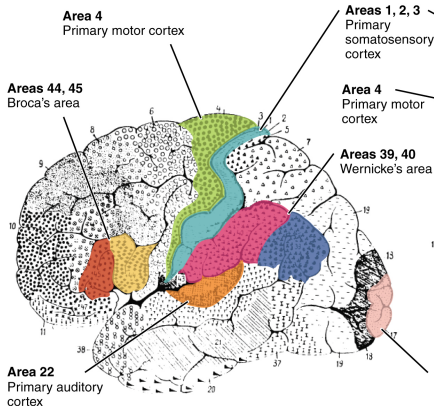
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Based on the cytoarchitectural organization of neurons Brodmann observed in the cerebral cortex using Nissl staining.

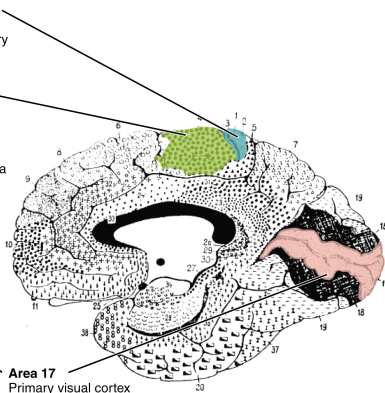


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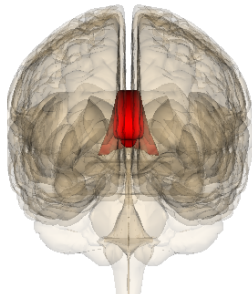
**Brodmann's cytoarchitectonic map (1909):**  
Lateral surface



**Brodmann's cytoarchitectonic map (1909):**  
Medial surface

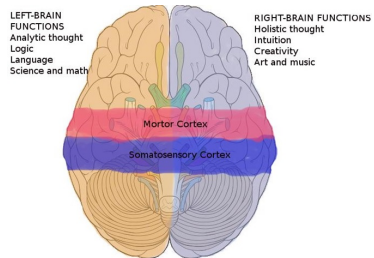
## Left and Right Brains (1960s)

- If the two hemispheres of the brain are separated by severing the corpus callosum,
  - ▶ information transfer between the hemispheres ceases,
  - ▶ an individual has two functionally different brains.



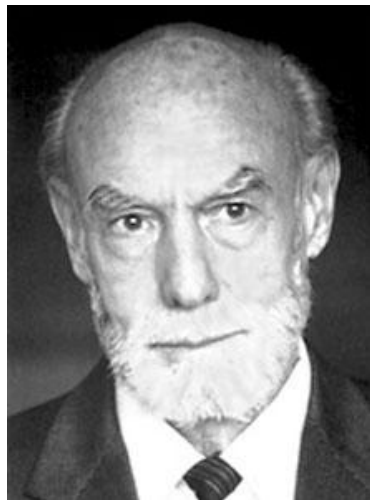
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- Right hemisphere: spatial comprehension, facial recognition, emotion.
- Roger Sperry received the Nobel Prize in 1981.



*"The great pleasure and feeling in my right brain is more than my left brain can find the words to tell you."*

# Left and Right Brains in Culture

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The New York Times Magazine / September 9, 1973

Two astonishingly different persons  
inhabit our heads

---

## We are left-brained or right-brained

---

**By Maya Pines**

Two very different persons inhabit our heads, residing in the left and right hemispheres of our brains, the twin shells that cover the central brain stem. One of them is verbal, analytic, dominant. The other is artistic but mute, and still almost totally mysterious.

This nonspeaking side of the human brain—the right hemisphere—is now the focus of intensive research by brain scientists. This sudden surge of interest is probably no accident at a time when Yoga, Arica, Tibetan exercises and other nonverbal disciplines are enjoying such a vogue. Some re-

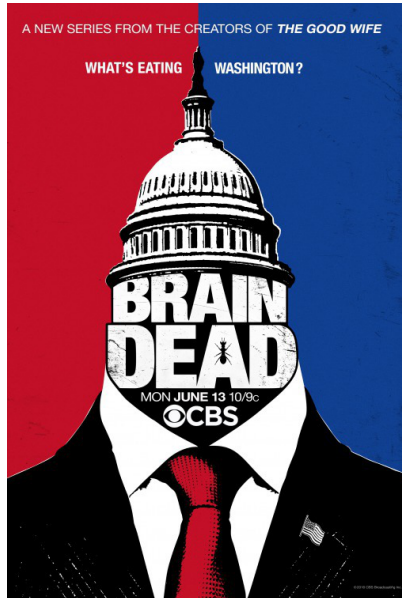
ample, those concerned with vision—to find their way through a tangle of other nerve fibers, even when obstacles are placed in their path, and somehow connect with the appropriate cells so as to reach specific terminals in the visual cortex. Next, he began to study visual perception and memory. He wanted to find out what happened when an animal learned certain discriminations that involved the visual cortex—when it learned, for instance, to push a panel marked with a circle rather than a square. Where in its brain was that knowledge stored?

He put the question to a young graduate student, suggesting that he investigate how cats that

between a circle and a square, knowing that the information they acquired would go to only one hemisphere. When he switched their eye patches to cover their trained eyes, however, the cats performed just as well as before. Their memory of this skill was intact. This meant either that the knowledge was stored in the central brain stem, well below the twin hemispheres, or that the knowledge acquired by one hemisphere had somehow been transmitted to the other.

"Obviously the *corpus callosum* was the next thing to test," recalls Dr. Myers. "But from the available evidence, cutting it would have no effect. If the surgery is properly done, the animals are

# Left and Right Brains in Culture





# Left and Right Brains in Culture



## Are You More Right-Brained Or Left-Brained?

Research says [it doesn't exist](#), but let's see where your personality falls.



Erin La Rosa  
BuzzFeed Staff



*justtransparentthings.tumblr.com*

Check off all that apply:

- ☐ 1. You're better with faces than names.

# Left and Right Brains in Culture

**LIVESCIENCE**

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## Left Brain vs. Right: It's a Myth, Research Finds

By Christopher Wanjek | September 3, 2013 12:21pm ET

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The idea that one side of the brain is dominant is a myth, researchers say.

Credit: [Human brain image](#) via Shutterstock

# Parts of the Brain (Now)

The Brain: Structure and Function (Video, 13:55)

# Automated Parcellation of the Human Brain

NATURE | ARTICLE



[日本語要約](#)

## A multi-modal parcellation of human cerebral cortex

Matthew F. Glasser, Timothy S. Coalson, Emma C. Robinson, Carl D. Hacker, John Harwell, Essa Yacoub, Kamil Ugurbil, Jesper Andersson, Christian F. Beckmann, Mark Jenkinson, Stephen M. Smith & David C. Van Essen

[Affiliations](#) | [Contributions](#) | [Corresponding authors](#)

Nature 536, 171–178 (11 August 2016) | doi:[10.1038/nature18933](https://doi.org/10.1038/nature18933)

Received 12 November 2015 | Accepted 15 June 2016 | Published online 20 July 2016

NATURE | NEWS



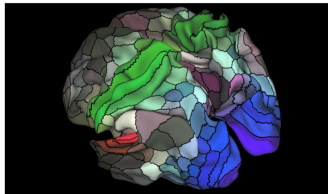
## Human brain mapped in unprecedented detail

Nearly 100 previously unidentified brain areas revealed by examination of the cerebral cortex.

[Linda Geddes](#)

20 July 2016

[Rights & Permissions](#)



Matthew F. Glasser, David C. Van Essen

Researchers have divided the brain into discrete areas based on structure and function.

(Video, 2")



# Brain Structure to Graphs

## [Neuroinformatics](#)

June 2004, Volume 2, [Issue 2](#), pp 145–162

# The small world of the cerebral cortex

Olaf Sporns , Jonathan D. Zwi

Review Article

DOI: [10.1385/Nl:2:2:145](#)

Cite this article as:

Sporns, O. & Zwi, J.D. Neuroinform (2004)  
2: 145. doi:[10.1385/Nl:2:2:145](#)

*Distributed Hierarchical in the Primate Cerebral Cortex*, Daniel J. Felleman and David C. Van Essen, *Cereb. Cortex*, 1: 1–47, 1991.

*The small world of the cerebral cortex*, Olaf Sporns, Jonathan D. Zwi, *Neuroinformatics*, 2: 145–162, 2004.

# Cells in the Brain (Late 19th and early 20th Century)

*Cell theory:* Cell is the fundamental unit of all living organisms (Video, 1:40")

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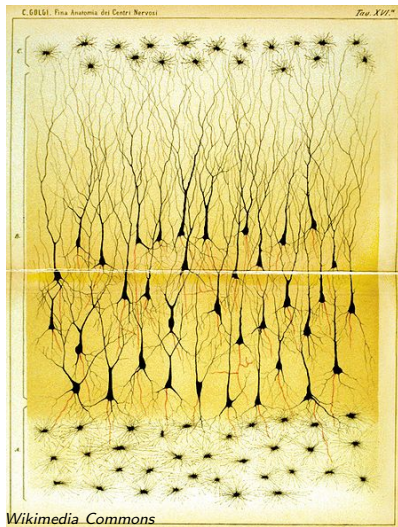
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- How many neurons in the brain? 100 billion and many more glial cells.
- Golgi and Nissl stains: allowed cells to be visualised and traced under the microscope.
- Cajal: catalogued many different types of nerve cells.

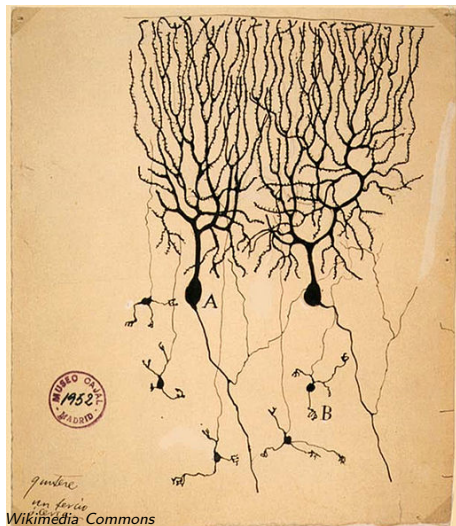


Wikimedia Commons

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# Reticular Theory vs. Neuron Doctrine

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- In 1896, Rudolph Albert von Kolliker coined the term “axon” to describe the long slender cables that transmit signals away from cell bodies.
- In 1889, William His used “dendrites” to name the thin branching fibers that ferry signals toward the cell body.

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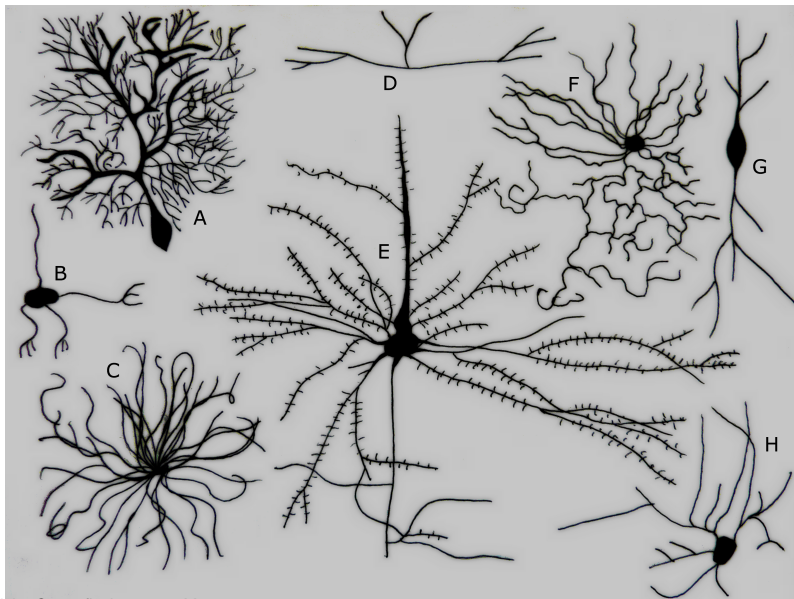
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**Neuron doctrine** Nerve cells are discrete entities that communicate by specialised contacts (Cajal and Sherrington)

- Both Golgi and Cajal received the Nobel prize in Physiology or Medicine in 1906.

# Cells in the Brain



Ferris Jabr, *Scientific American*, May 14, 2012



# Cells in the Brain

Types of Brain Cells (Video, 18:54" )

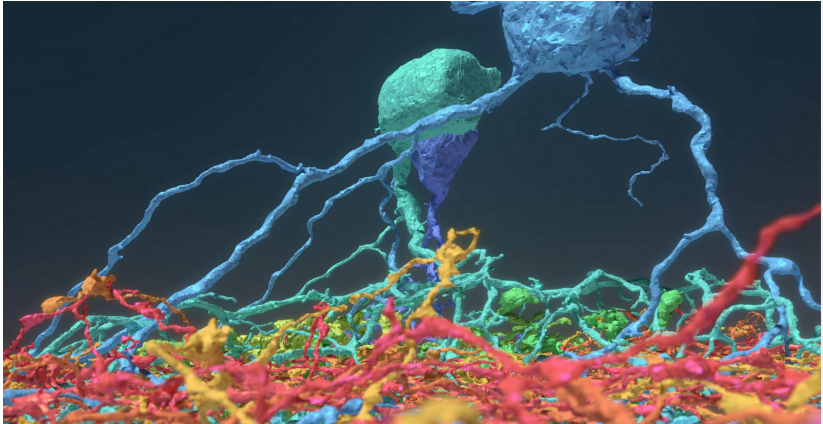
# Types of Neurons

- 100s of types of neurons, differentiated by structure, function, genetics ...
- [neuromorpho.org](http://neuromorpho.org): archive of digitally reconstructed neurons.

## Welcome to **NeuroLex**, the Neuroscience Lexicon.

A dynamic lexicon of **34,533** neuroscience terms , including 754 neurons and 1303 parts of the nervous system supported by The Neuroscience Information Framework and the International Neuroinformatics Coordinating Facility

# Types of Neurons



Princeton researchers crowdsource brain mapping with gamers, discover six new neuron types

Liz Fuller-Wright, Office of Communications

May 17, 2018 11 a.m.

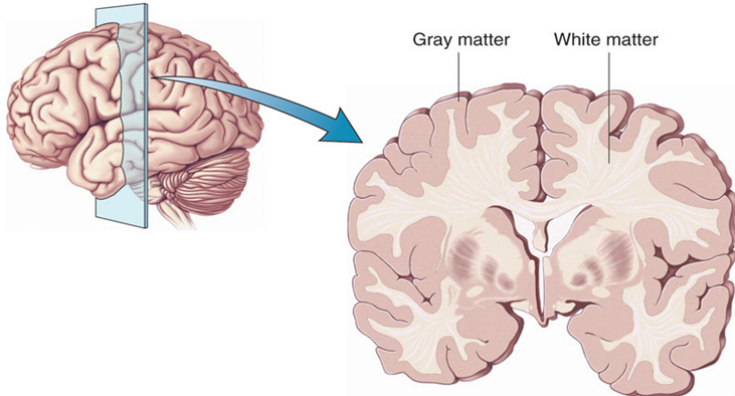
By turning a time-intensive research problem into an interactive game, Princeton neuroscientist Sebastian Seung has built an unprecedented data set of neurons, which he is now turning over to the public via the Eyewire Museum. These 17 retinal neurons, mapped by Eyewire gamers, include ganglion cell types in blue and green and amacrine cells in yellow and red.

Image by Alex Norton, Eyewire

# White Matter and Grey Matter (17th–18th centuries)

**White matter** Generic term for “stuff” that appears white in freshly dissected brain.

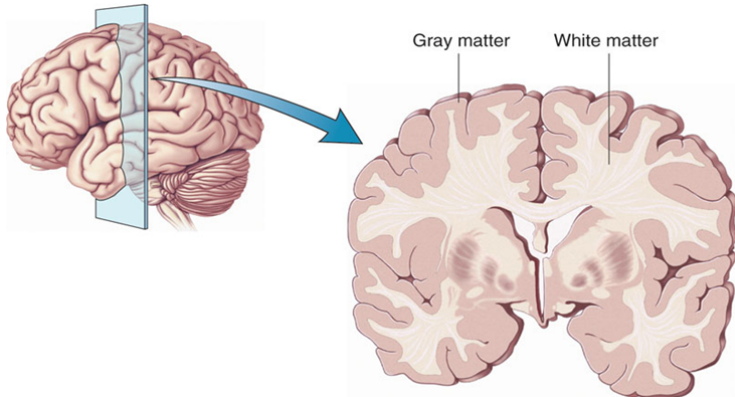
**Grey matter** Generic term for “stuff” that appears grey in a freshly dissected brain.



# White Matter and Grey Matter (17th–18th centuries)

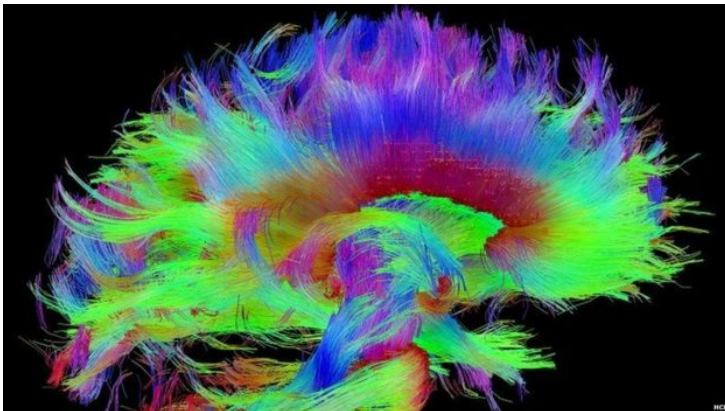
**White matter** Generic term for “stuff” a collection of axons, which appear white in freshly dissected brain.

**Grey matter** Generic term for “stuff” a collection of neuronal cell bodies, which appear grey in a freshly dissected brain.



# Brain Structure to Graphs

- Diffusion tensor imaging.
- Tracking white matter (axon) bundles to connect voxels.
- Massive graphs: 15M nodes, 50M edges.

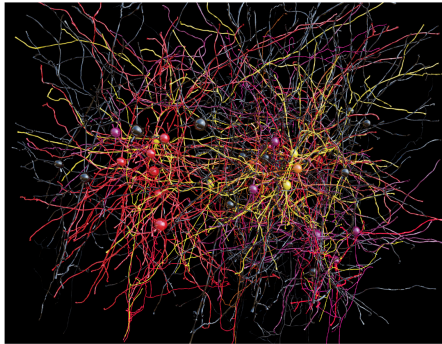


# Research on largest network of cortical neurons to date published in Nature

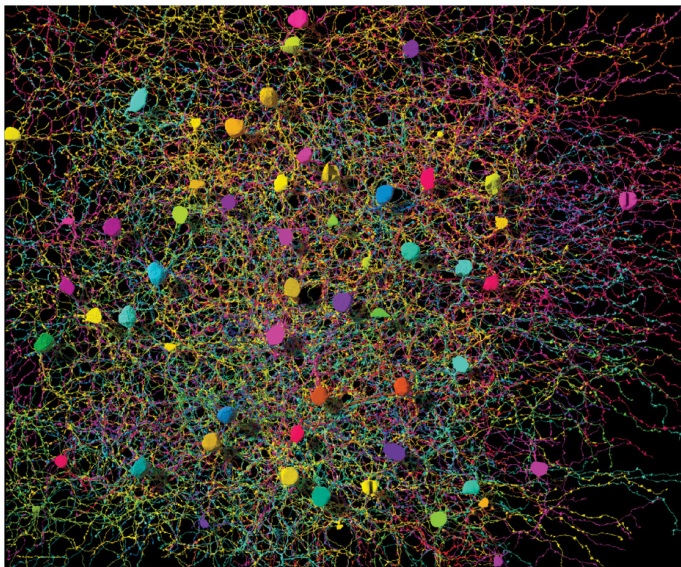
**Robust network of connections between neurons performing similar tasks shows fundamentals of how brain circuits are wired**

March 28, 2016 | [Download PDF](#)

Even the simplest networks of neurons in the brain are composed of millions of connections, and examining these vast networks is critical to understanding how the brain works. An international team of researchers, led by [R. Clay Reid](#), Wei Chung Allen Lee and Vincent Bonin from the Allen Institute for Brain Science, Harvard Medical School and Neuro-Electronics Research Flanders (NERF), respectively, has published the largest network to date of connections between neurons in the cortex, where high-level processing occurs, and have revealed several crucial elements of how networks in the brain are organized. The results are published this week in the journal *Nature*.



*Anatomy and function of an excitatory network in the visual cortex*, Lee et al., *Nature*, 532:370–374, 2016.



*Space-time wiring specificity supports direction selectivity in the retina*, Kim et al., *Nature*, 509:331–336, 2014.





## A GAME TO MAP THE BRAIN

[PLAY NOW](#)

*Space-time wiring specificity supports direction selectivity in the retina, Kim et al., Nature, 509:331–336, 2014.*

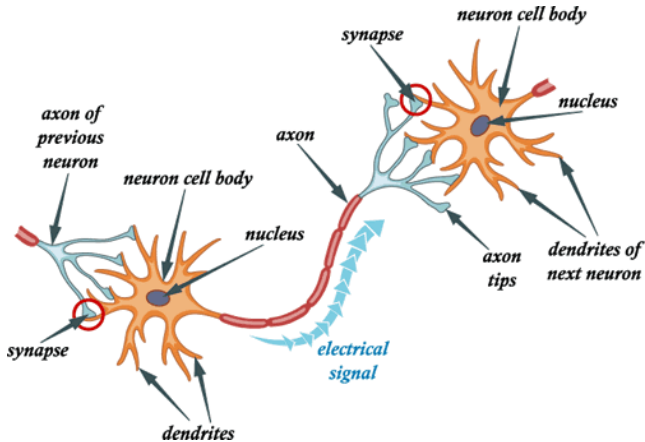
GREGORY BARBER

SCIENCE 01.22.2020 11:00 AM

# The Most Complete Brain Map Ever Is Here: A Fly's 'Connectome'

It took 12 years and at least \$40 million to chart a region about 250 micrometers across—about the thickness of two strands of hair.

# Cellular Communication: Neuron Firing

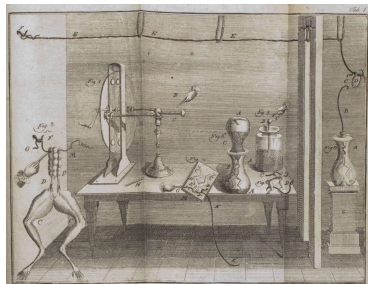


Neuron, YouTube, 11:20"

Neuron, YouTube, 5:14"

# Otto Loewi (1873–1961)

- Galvani showed that electric stimulation of sciatic nerve causes muscles in frog legs to twitch (1780).
- How do nerves communicate with muscles: electricity or chemicals?



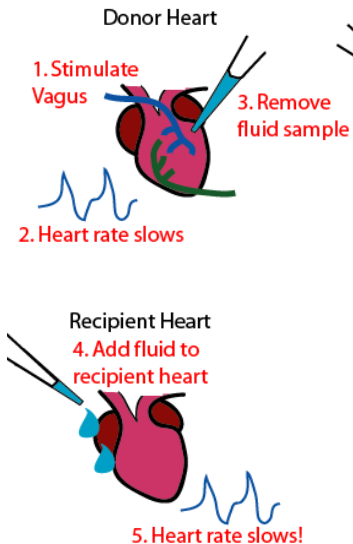
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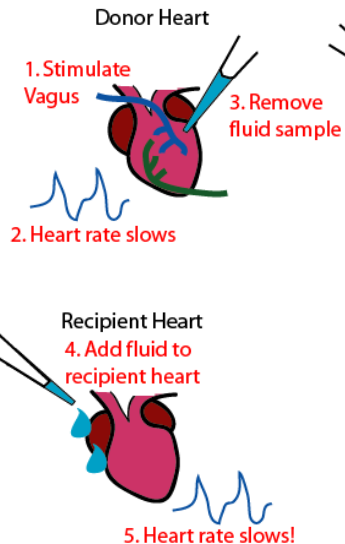
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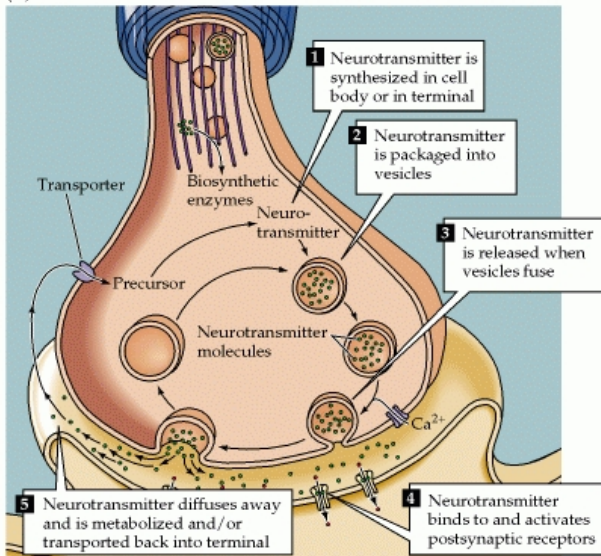
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- Later identified as acetylcholine, which had been discovered in 1914 by Sir Henry Dale. *The first neurotransmitter.*
- Loewi and Dale received the Nobel Prize in 1936.



# Neurotransmitters

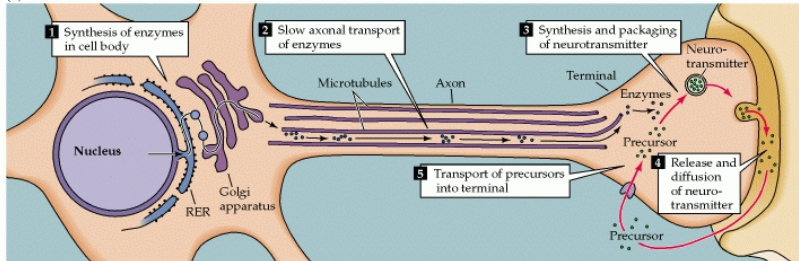
(A) LIFE CYCLE OF NEUROTRANSMITTER



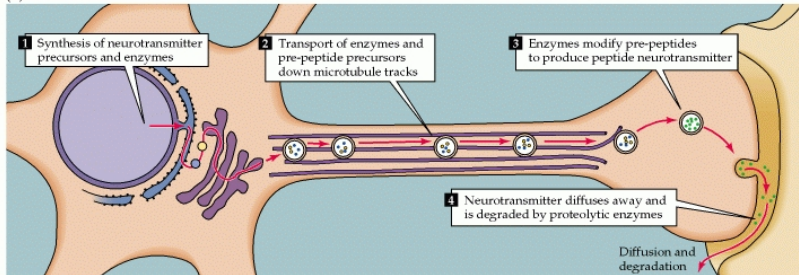


# Neurotransmitters

(B) SMALL-MOLECULE TRANSMITTERS



(C) PEPTIDE TRANSMITTERS



# Neurotransmitters

**TABLE 47-1****Neurotransmitters and Their Relationship to Mental Disorders**

NEUROTRANSMITTER	PHYSIOLOGIC EFFECTS	RELATIONSHIP TO MENTAL DISORDERS
Acetylcholine	Sleep/wake cycle. Signals muscles to become active.	Decreased in Alzheimer's and Parkinson's diseases.
Dopamine	Controls complex movements, cognition, motivation, and pleasure. Regulates emotional responses.	Increased in schizophrenia and mania. Decreased in depression and Parkinson's.
Norepinephrine	Affects attention, learning, memory, and regulation of mood, sleep, and wakefulness.	Decreased in depression. Increased in schizophrenia, mania, and anxiety.
Serotonin	Affects sleep and wakefulness, especially falling asleep. Affects mood and thought processes.	Probably plays a role in thought disorders of schizophrenia. Decreased in depression. Possibly decreased in anxiety and obsessive-compulsive disorder.
Gamma-aminobutyric acid (GABA)	Amino acid that modulates other neurotransmitters.	Decreased in anxiety and schizophrenia.

## Rita Levi-Montalcini (1909–2012)

- M.D. at University of Turin (1936).
- Lost her job due to laws barring Jews (1938).
- Secret lab in bedroom to study nerve growth in chicken embryos (WWII).



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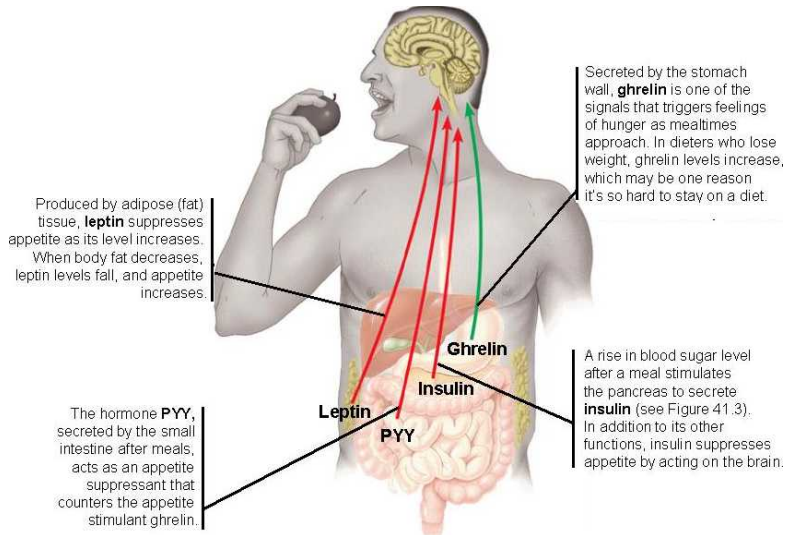


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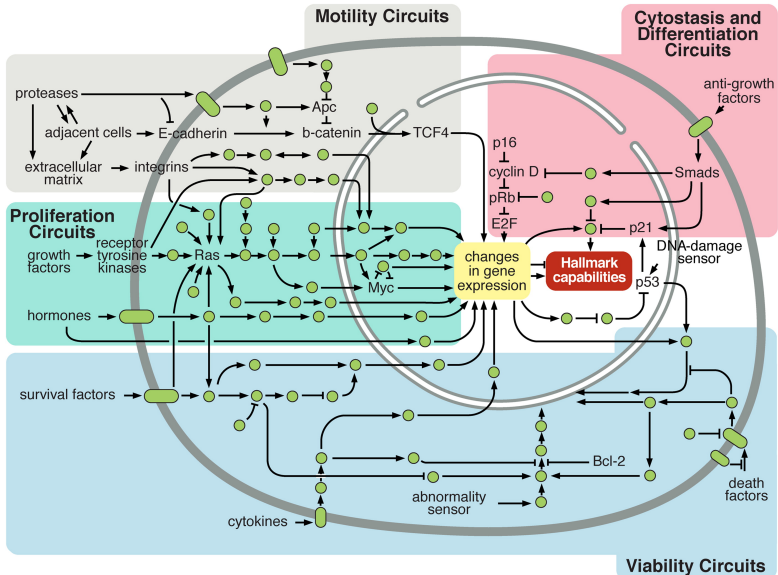
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- Received Nobel prize (with Stanley Cohen, 1986).



# Cellular Communication: Hunger Response

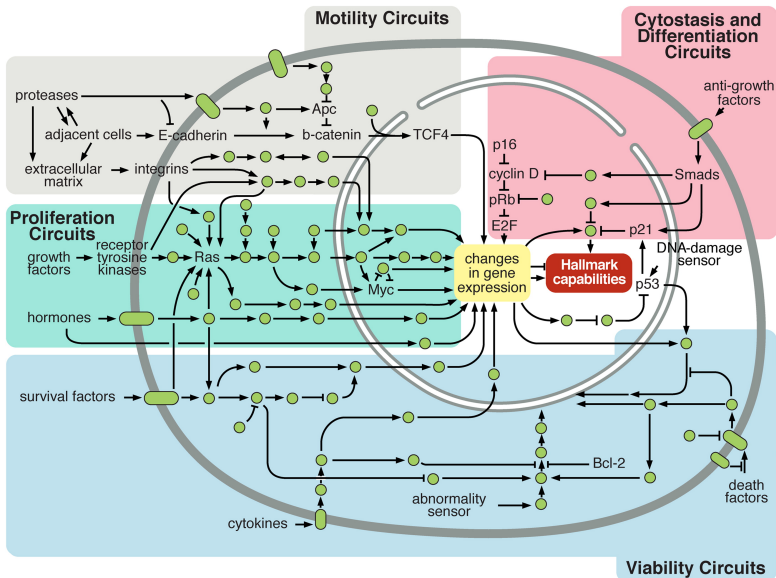


# Cellular Response to External Signals



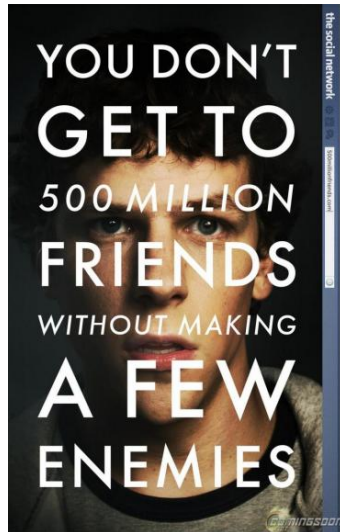
Hanahan and Weinberg. *Hallmarks of cancer: the next generation*. Cell, 2011.

# A Cell is Like

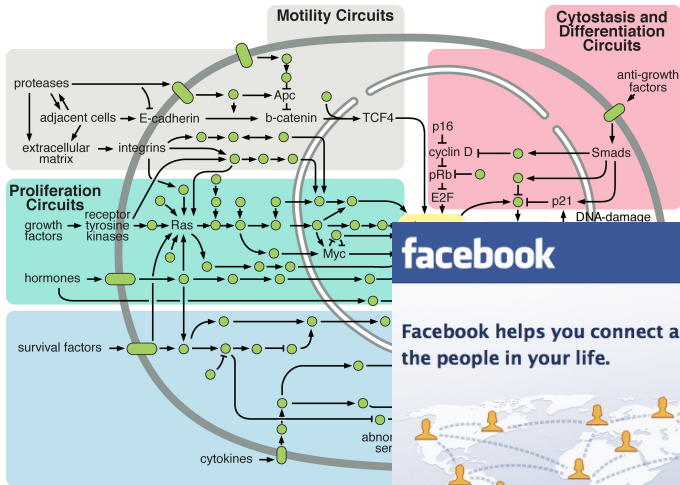




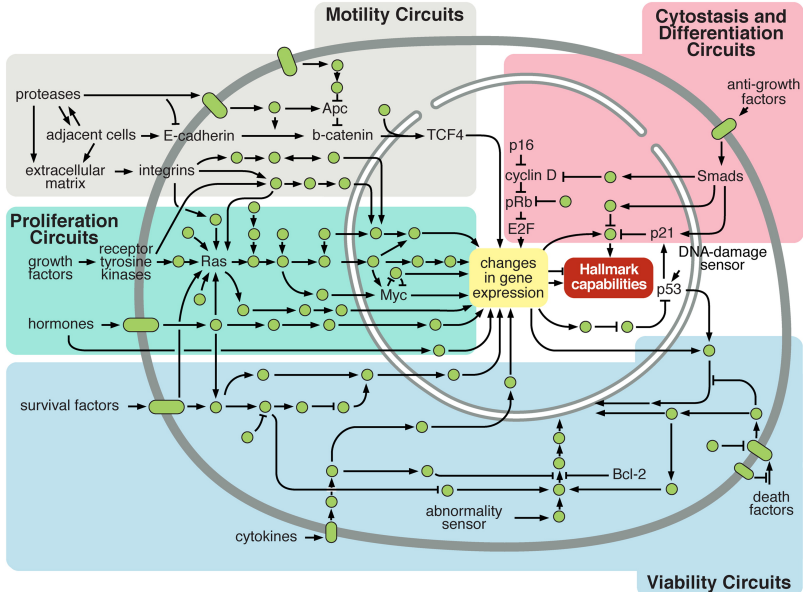
## A Cell is Like



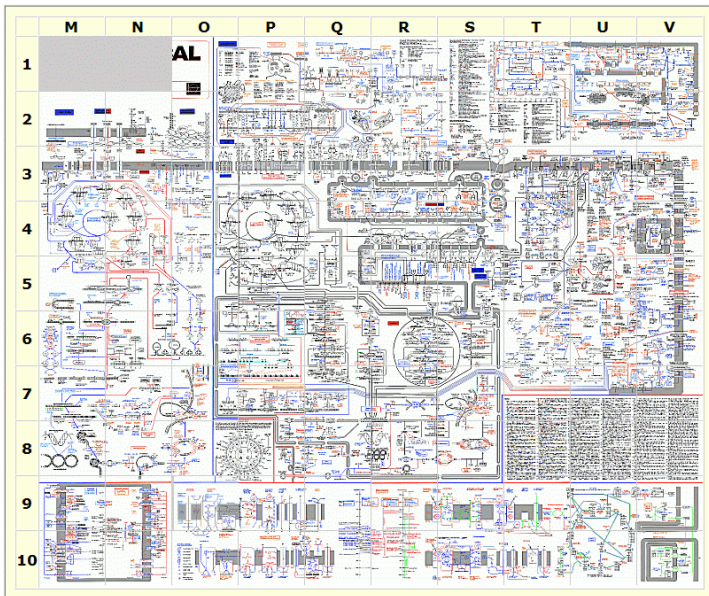
# A Cell is Like facebook



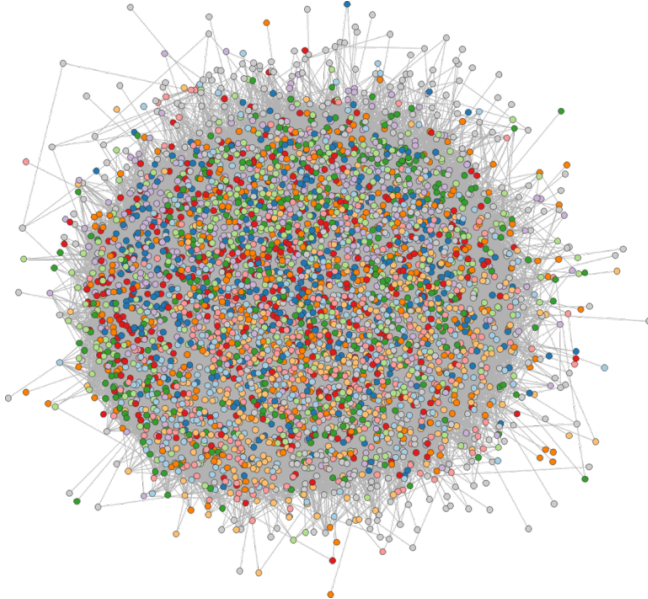
# Network is Complex



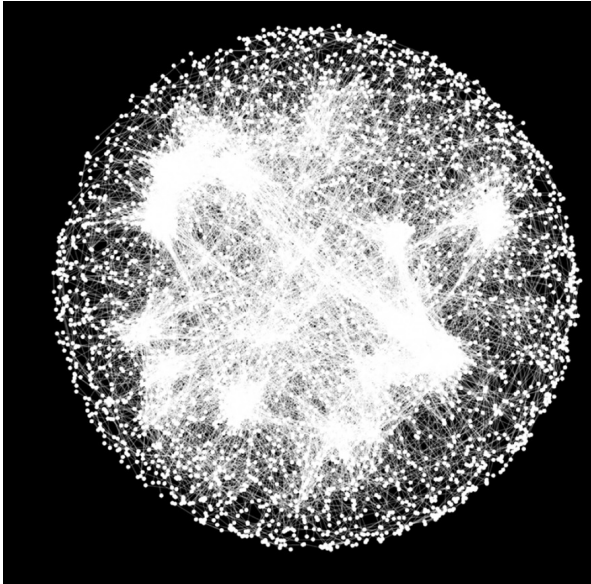
# Network is Complex



# Network is Complex but Very Poorly Understood








# Network is Complex but Very Poorly Understood



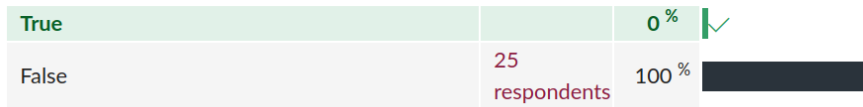
# Survey Results

What are the most important things you expect from this course? You can select multiple options. If your choice does not appear, please add it in your answer to the final question.

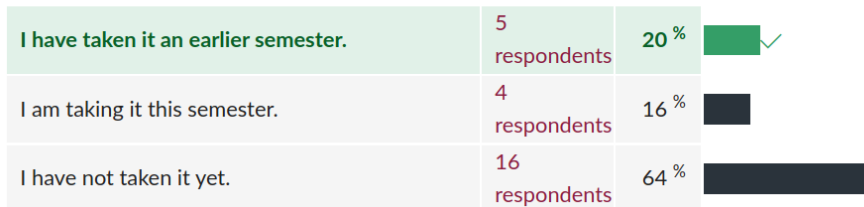
Learn about the structure of the brain	16 respondents	64 %	 ✓
Learn graph algorithms	16 respondents	64 %	
Work on a software project	19 respondents	76 %	
Learn how to work collaboratively in a team	11 respondents	44 %	
Study and present research papers	9 respondents	36 %	

# Survey Results

Have you taken a capstone class before?



Have you taken "Data and Algorithm Analysis" (CS 4104)?





## Survey Comments

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- Videos are a good visual way. 2x speed is good. Please keep them at most 5 minutes long.
- Break up the long class times with in-class activities.
- *I am open to whatever this class throws at me, ready to hopefully take it all in and learn a lot of really cool things.*

# Course Structure

- Designed with the following goals in mind:
  - ▶ You will almost always work collaboratively.
  - ▶ You will often be called upon to learn independently from multiple sources (life-long learning).

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- After spring break, use classroom times and additional times as office hours.
- I will give detailed feedback on software projects.
- I will help you prepare the poster for the VTURCS Symposium.