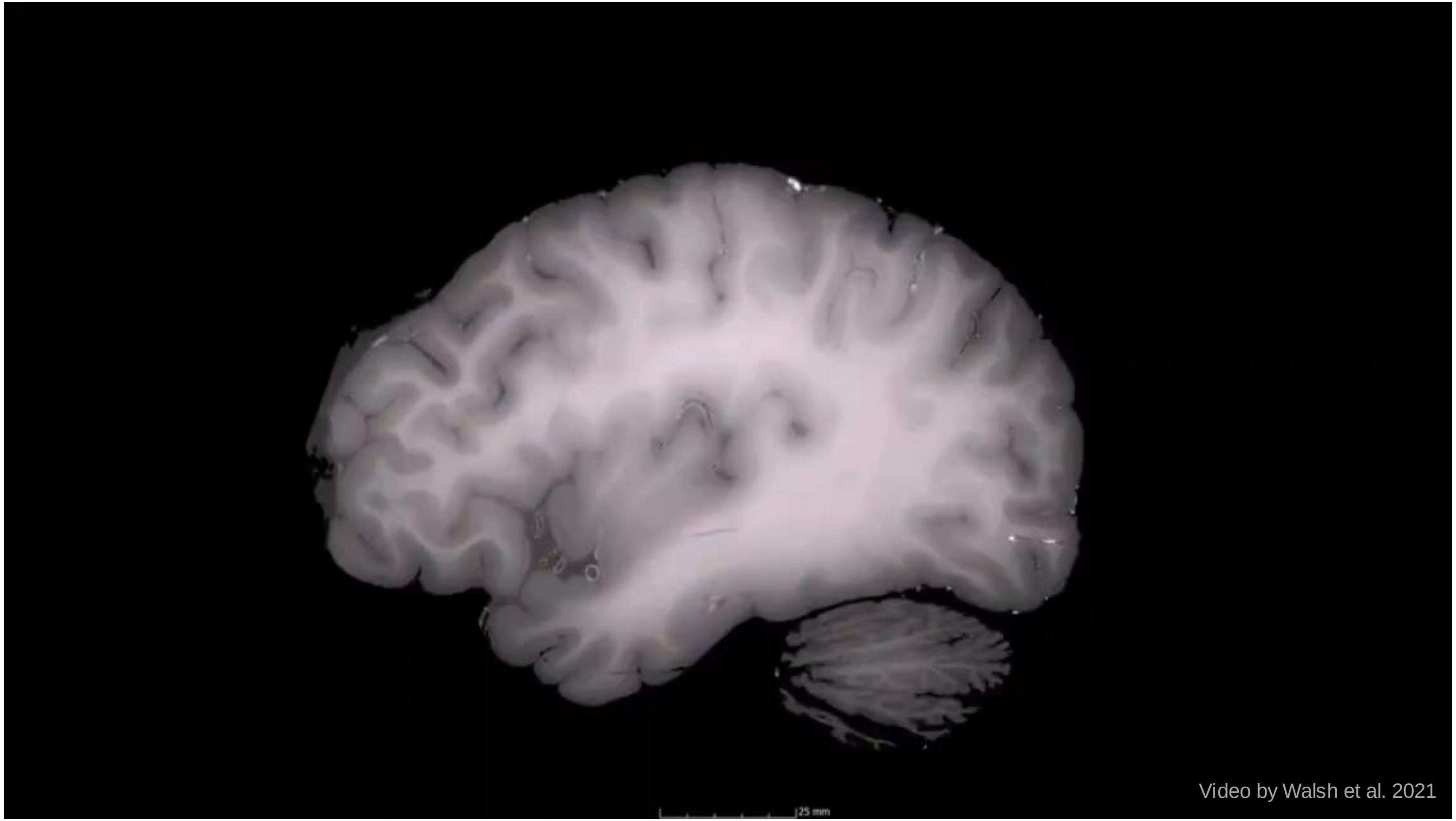
Structure-function coupling

Anatomy of the human brain



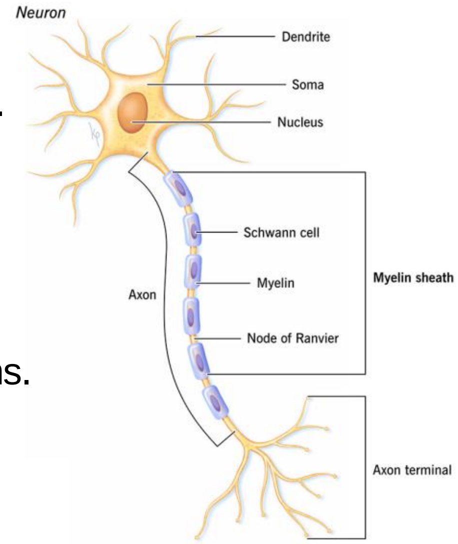
Video by Walsh et al. 2021

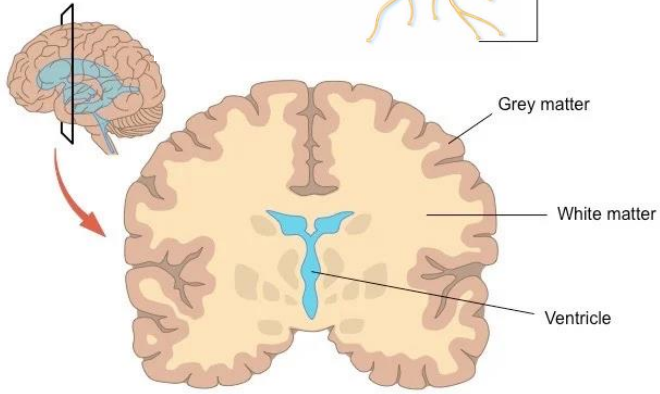
Anatomy of the human brain

Grey matter
- Contains neuronal cell bodies, dendrites, synapses, unmyelinated axons.
- Further contains many non-neural cells (e.g., glia cells).

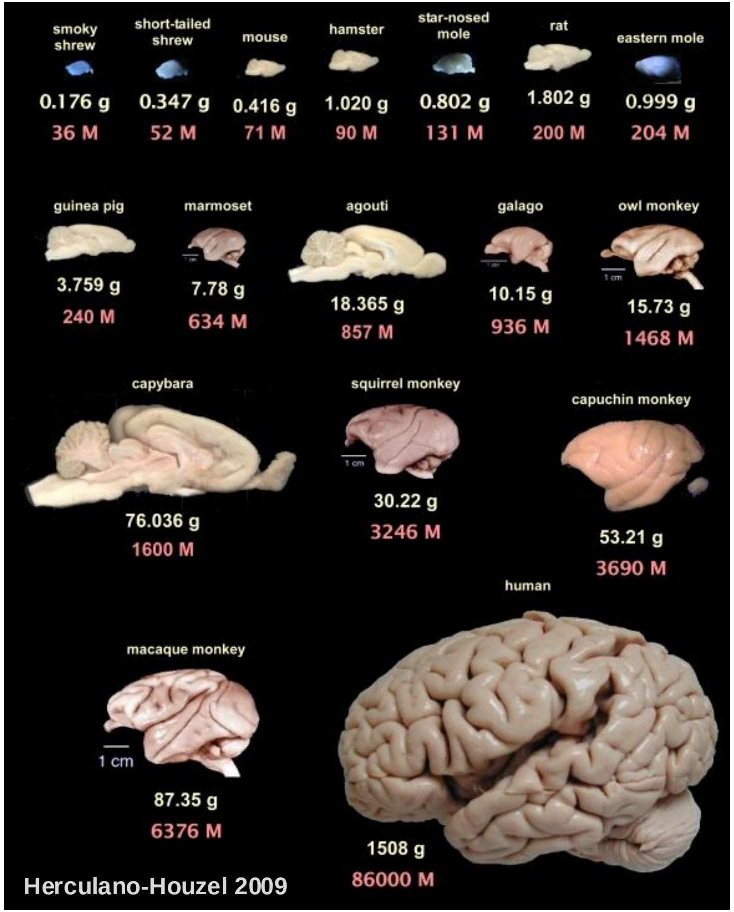
White matter
- Primarily contains myelinated axons that connect neurons.
- It is white because of the myelin, a fatty substance wrapped around axons.

Ventricles
- Cavities in the brain that contain cerebrospinal fluid (CSF).
- CSF provides nutrients to the brain and removes waste, but it also absorbs shocks and provides buoyancy (so that the brain does not get crushed underneath its own weight).





Anatomy of the human brain



Herculano-Houzel 2009

The brain in numbers

- Average volume: **1300 cm^3**
- Average mass: **1500 gram**
- Neurons: ~**86 billion**

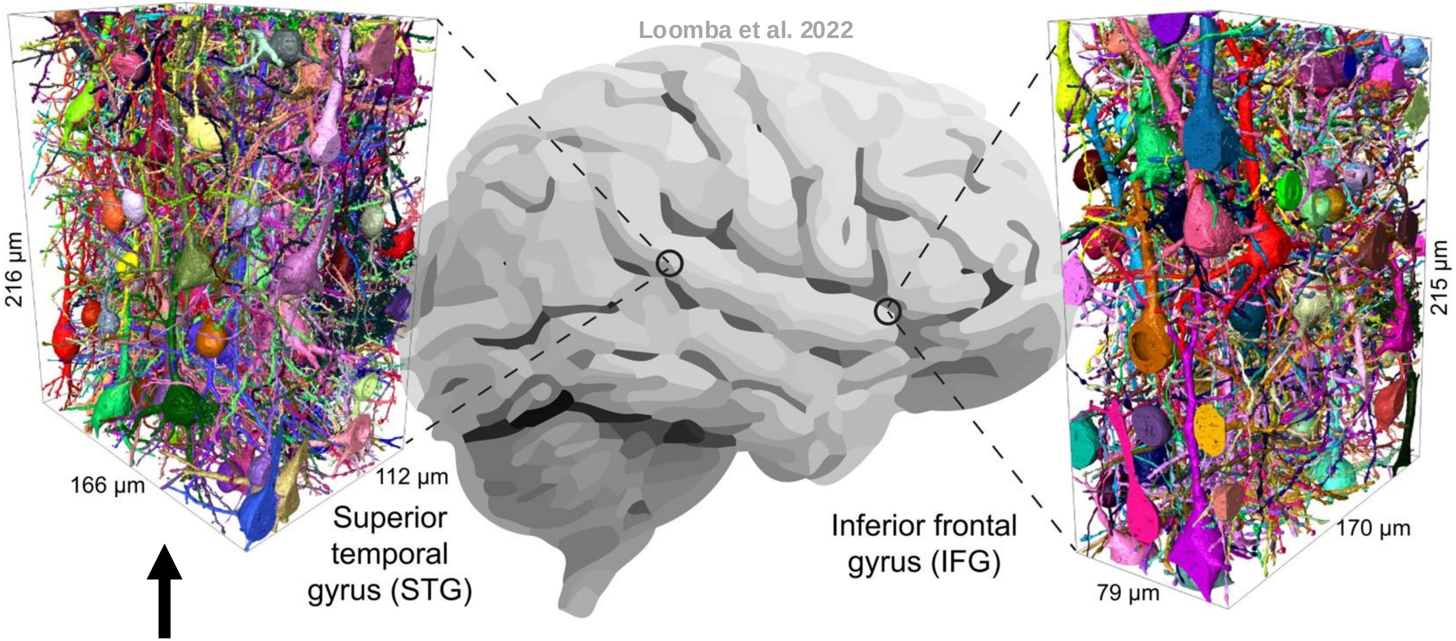
Only ~18% of neurons are in the cerebral cortex, even though it constitutes 80% of the brain’s mass (and is the main focus of research).

The cerebellum contains ~80% of neurons, while constituting 10% of the brain’s mass.

How is this possible?

- There are about ~85-110 billion **non-neural cells** in the brain, without which neurons would not function.
- Much of the cerebral cortex are **fiber tracts**
  → Wiring is important, not number of neurons.
- **Cell morphology** varies drastically across the brain.

Anatomy of the human brain



Volume of the cube shown above: 216 x 166 x 112 µm = 0.004 mm^3

Typical fMRI voxel size at 3 Tesla: 2 x 2 x 2 mm = 8 mm^3

A typical fMRI voxel is 2000x larger than the cubes of cells you see above!

Anatomy of the human brain

How many neurons does an fMRI voxel contain?

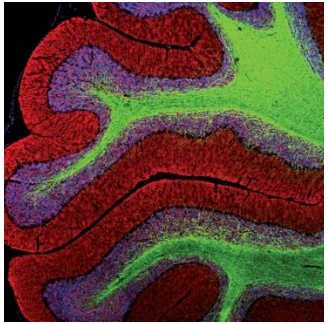
Good question but impossible to answer. Neuron density, size etc., vary strongly across the brain. However, here is a rough approximation.

- The human brain contains around **86 billion neurons**
- The average human brain has a **volume of 1.300.000 mm^3**
- A typical fMRI voxel has a **volume of 8 mm^3**

86.000.000.000 neurons / 1.300.000 mm^3 x 8 mm^3/voxel = >**500.000 neurons/voxel**

Take these numbers with a grain of salt, but the point is that we are talking about hundreds of thousands of neurons per voxel!

Moreover, each voxel contains large numbers of non-neural cells



Anatomy of the human brain

How many <u>types</u> of brain cells exist?

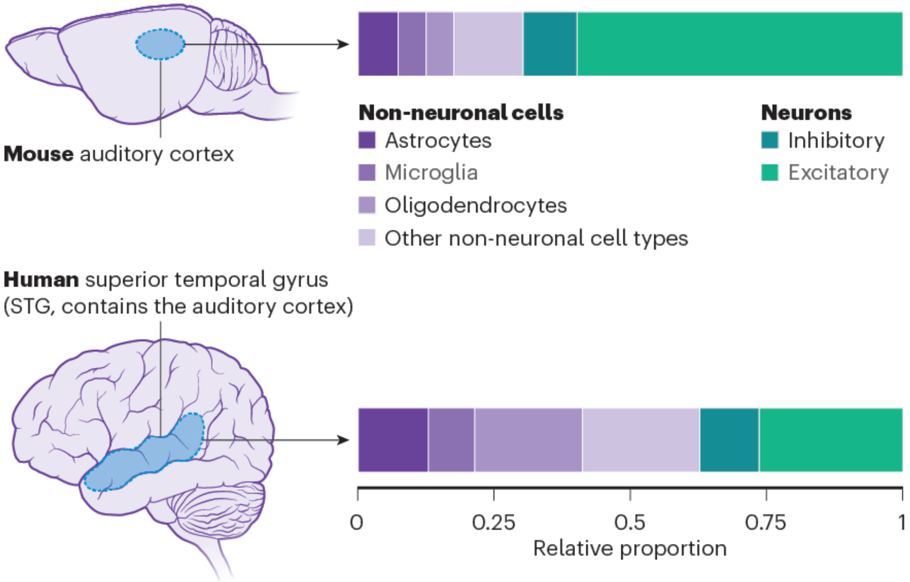
In humans, we do not know.

In the mouse brain, **>5.300 cell types** have been described (Yao et al. 2023)

Cells differ across brain regions.

Humans have 2.5x more **inhibitory interneurons** than mice, and those cells have 10x more connections.

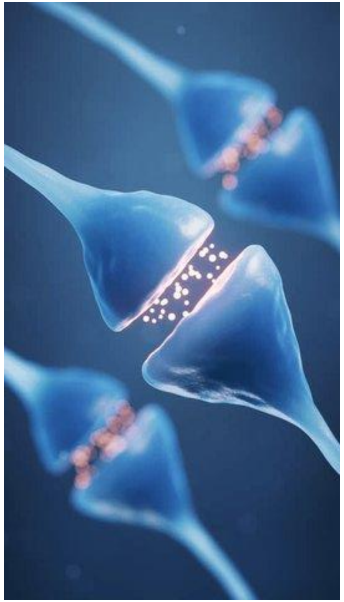
→ Not all brain cells are neurons, even neurons are extremely diverse, and the pattern of synaptic connections matters!

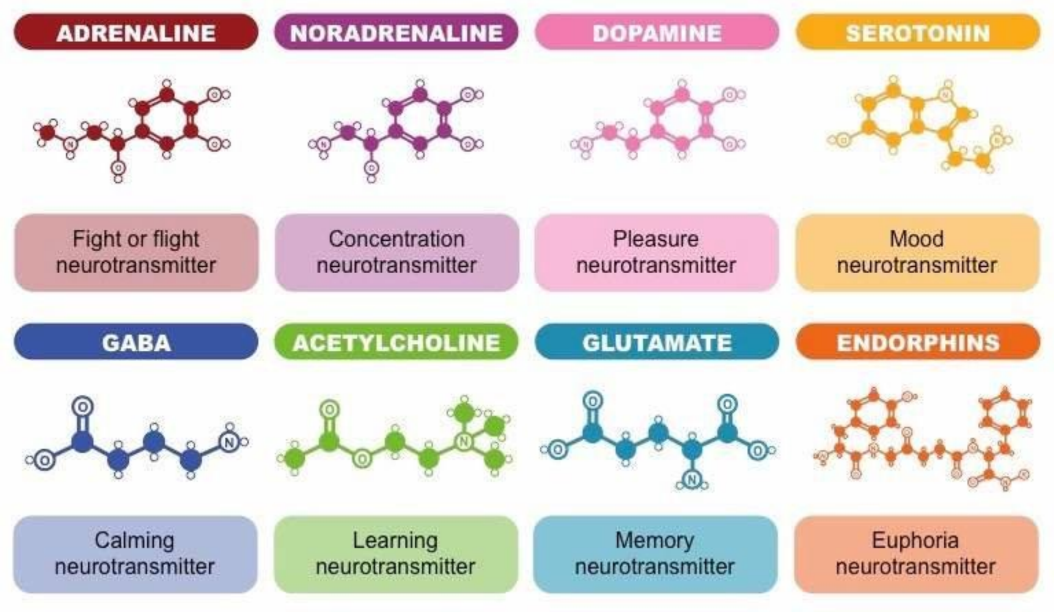


Fang et al. 2022

Anatomy of the human brain

There are many different neurotransmitters in the brain





The type of neurotransmitter affects the metabolic demands of the synapse, which likely affects blood supply and thus the BOLD signal.

Summary I

Not all neurons are equal
Neurons differ drastically in their characteristics! (e.g., local morphology, projection patterns, neurotransmitters).

Your brain is not just neurons
There are many non-neural cells in the brain (e.g., glia), without which neuron's would not function.

fMRI voxels contain hundreds of thousands of neural & non-neural cells,
all of which work together as one glorious physiological mess that defines brain function.

→ Important points to remember when interpreting brain imaging results,
and when building models of the brain (#**NeuroAI**)!

Philos. Trans. R. Soc. B, cover, Jan 2021

The vasculature of the human brain

The vasculature of the brain

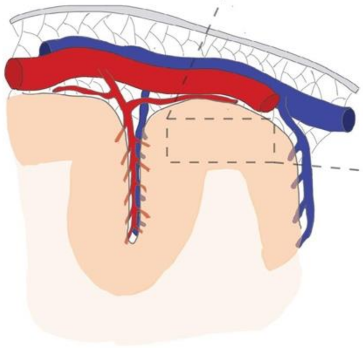
Arteries supply blood

Veins drain blood

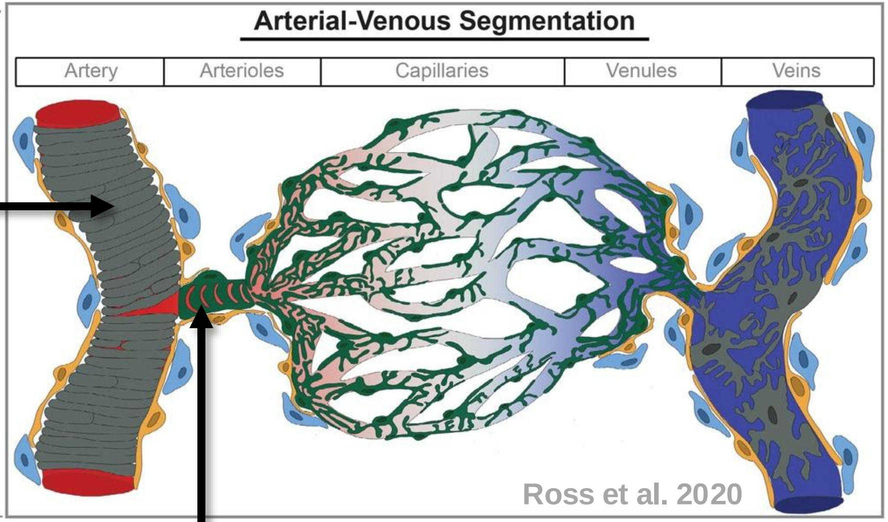
Blood vessels are made up of **endothelial cells.**

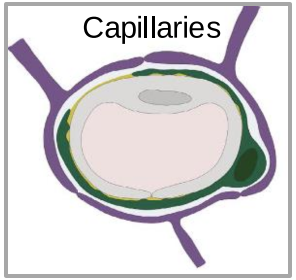
Smooth muscle cells help regulate blood flow by contracting/relaxing.

A



B



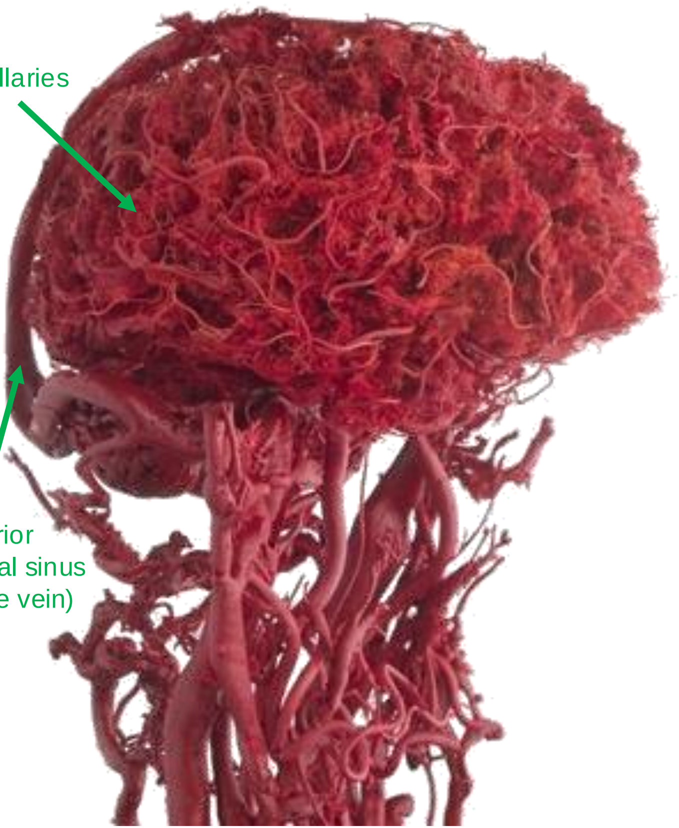


Astrocytes support neuron metabolism & modulate neurovascular coupling through vasoactive molecule release.

Pericytes modulate capillary diameter in response to neural and astrocytic cues.

Many more cell types involved, all working together.
Without these cells, neurons cannot function.
It's all connected (neurovascular coupling)!

The brain's vasculature is intricately linked to the BOLD signal



Changes in vasculature take time, <u>affecting the temporal dynamic</u> of BOLD signals

- Vessels dilate and affect blood flow rather slowly.
- Main reason why hemodynamic responses are slow.

The vasculature also <u>affects the spatial localization</u> of BOLD signals

- Deoxygenated hemoglobin is primarily found in veins.
- The signal is biased towards veins ("**venous bias**").
- Larger veins → stronger bias

Many analytical approaches exist that try to c**orrect for these biases** (e.g., to measure capillaries only).

Imaging the brain's vasculature

Koroshetz et al. 2018

Visualizing veins and arteries

1) Time-of-flight imaging
- Repeated excitation of tissue results in reduced signal.
- Fresh blood → strong signal
- Great for visualizing arteries but also works for veins.

2) Contrast-enhanced angio- & venography
- Uses tracers (e.g., Gadolinum) to visualize blood flow.

3) Susceptibility-Weighted Imaging (SWI)
- Veins contain much deoxygenated blood.
- Deoxygenated blood → strong effect on MRI signal.
- Unlike BOLD imaging, SWI measures static susceptibility effects.

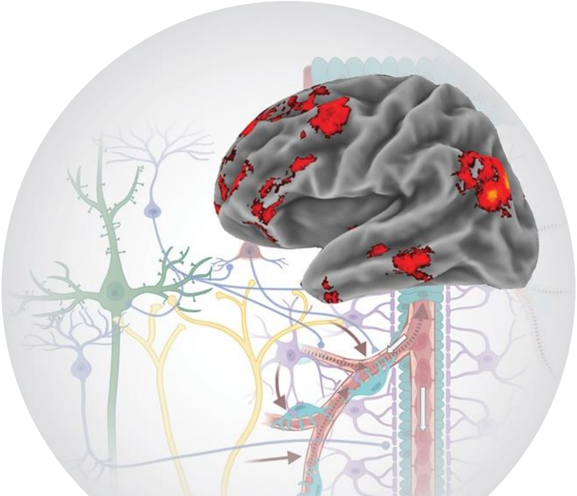
All of these techniques are routinely used in clinical practical (e.g., to detect strokes).

Summary II

The BOLD signal is sensitive to changes in vasculature,
which affect the temporal & spatial characteristics of fMRI.

Many non-neural cells link neural activity to the vasculature.
(e.g., pericytes, astrocytes, smooth muscle cells)

fMRI does not measure neural activity, and that's ok!
It is an extremely useful technique for understanding the brain
as long as we remain aware of what we are measuring.



Philos. Trans. R. Soc. B, cover, Jan 2021

We are likely measuring a complex physiological compound signal,
which is driven by blood flow and reflects covarying processes of neural & non-neural cells.

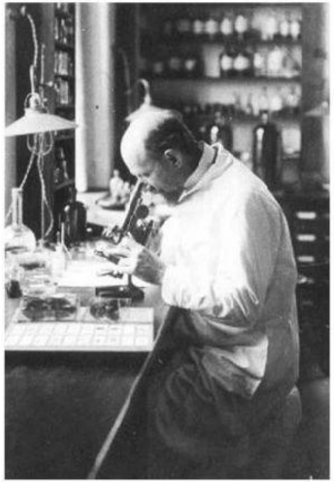
Given everything that we discussed so far, how modular do we think the brain is
(i.e. separable into parts)?

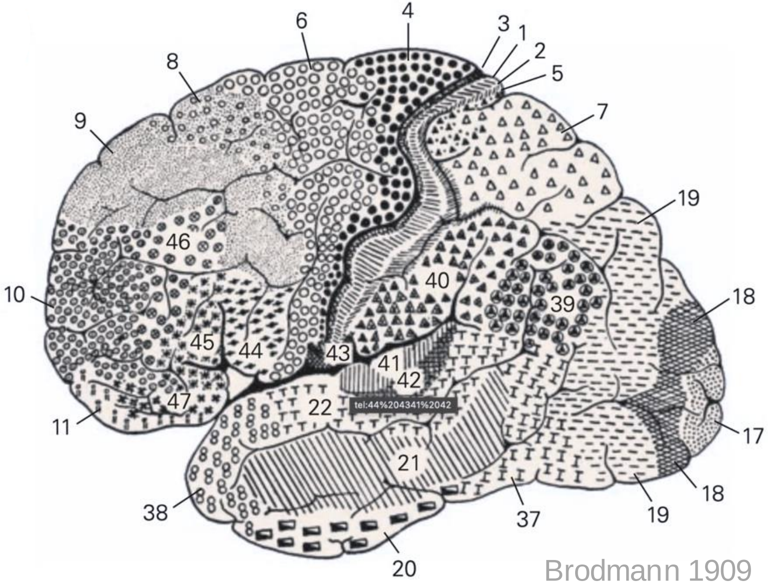
Brain modularity & Functional localization

Brain modularity & Functional localization

Parcellating the brain into brain areas

Korbinian **Brodmann** was the first to parcellate the cerebral cortex into distinct brain **areas** based on **cytoarchitectonics**



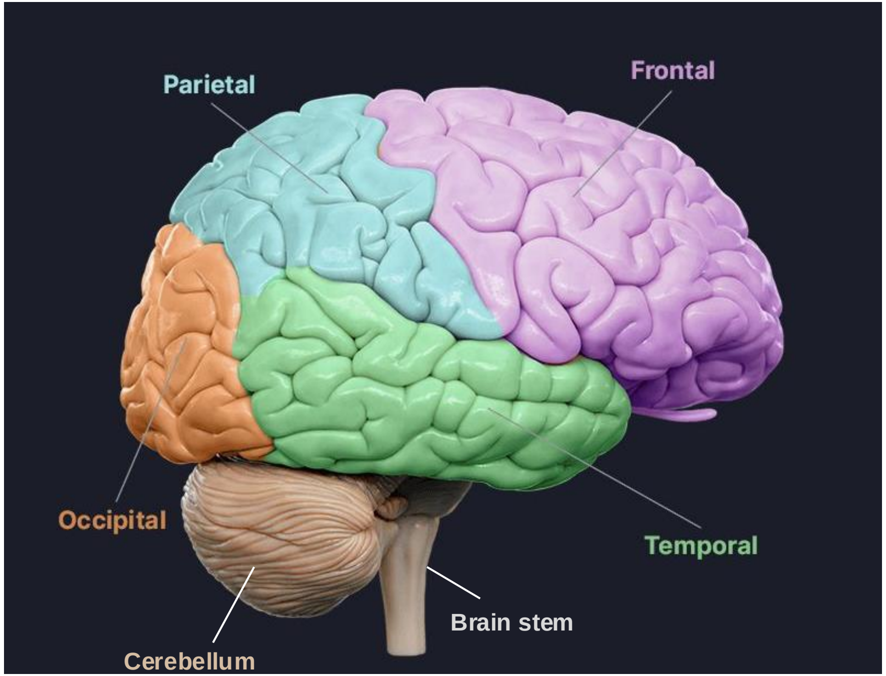


Brodmann 1909

A large number of other parcellations followed, each of which used different metrics (e.g., Connectivity, local morphology, RNA sequencing, fMRI…)

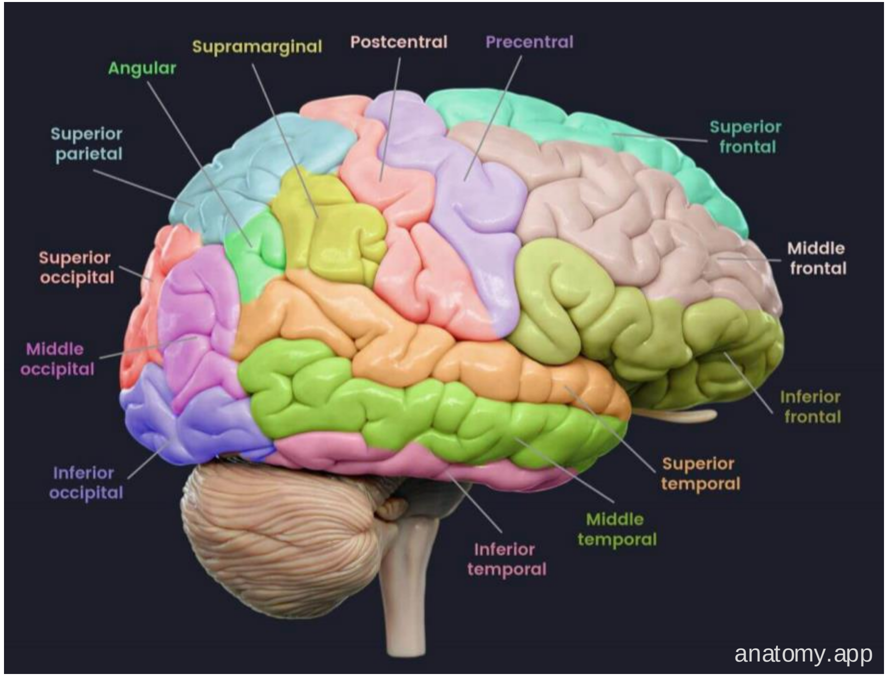
Brain modularity & Functional localization

Largest scale parcellation



Not shown: Limbic system, Thalamus, Basal ganglia, major fiber tracts such as the Corpus Callosum…

Major cerebral gyri



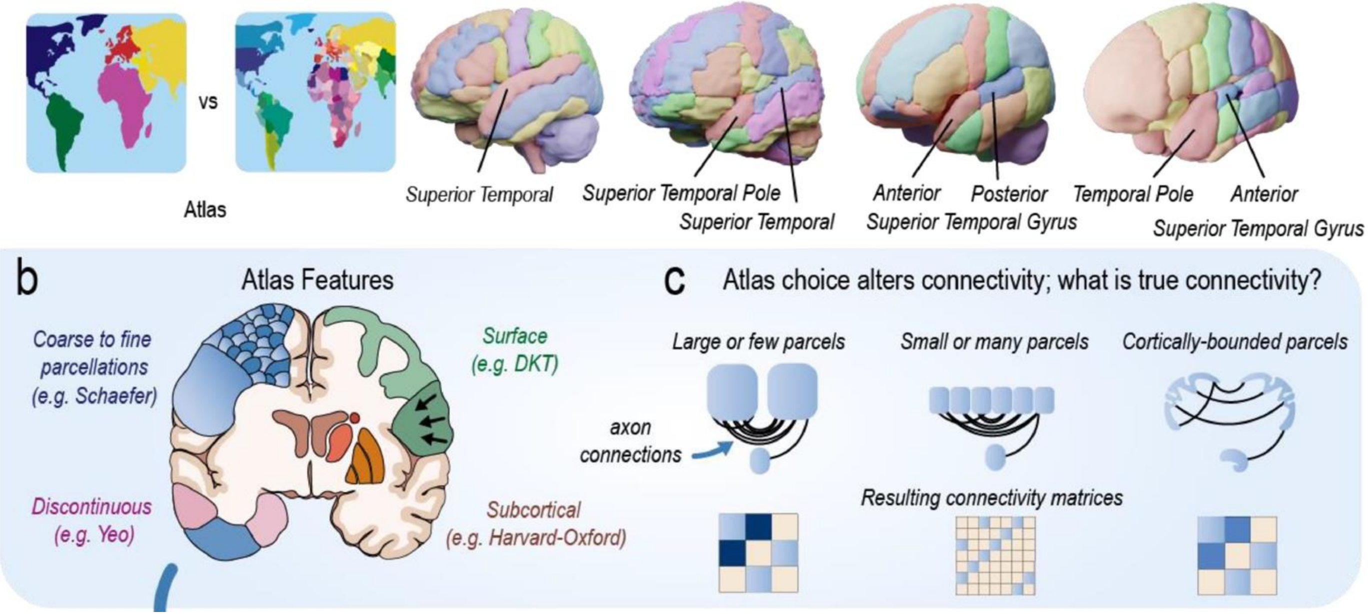
A lot not shown, but the point is that there is not one but many ways of parcellating this interconnected network.

For interactive 3D brain model, check out: https://www.brainfacts.org/3d-brain

Brain modularity & Functional localization

The Atlas Concordance Problem

Revell et al. 2022



Parcellations are “descriptions”. There is no “ground-truth” parcellation, not even based on anatomy.

Discussion: Why do we want to parcellate the human brain into brain areas?

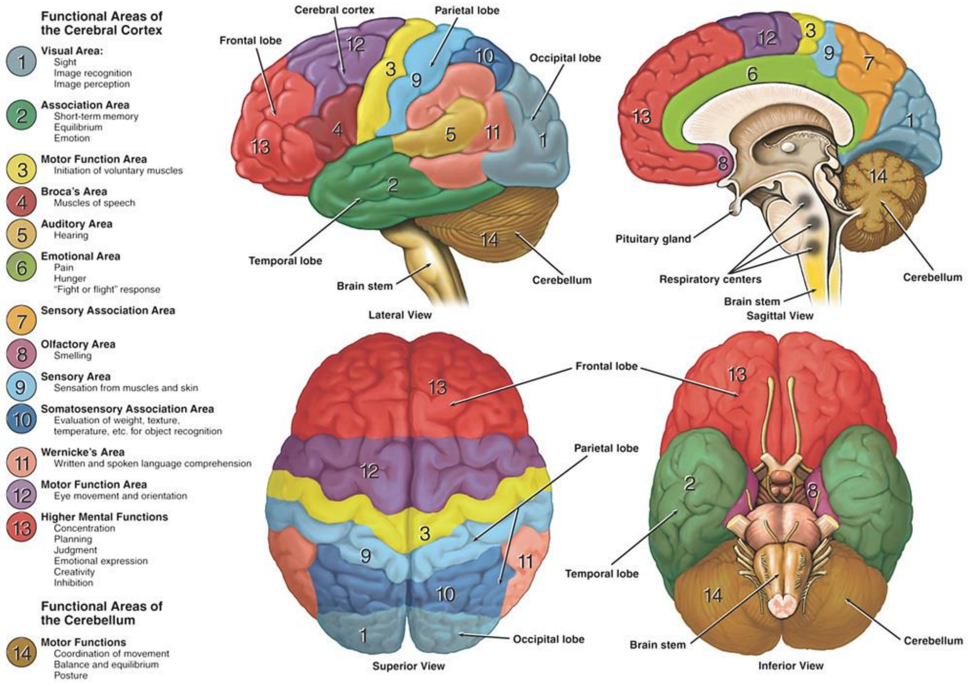
Brain modularity & Functional localization

Traditional “modular” view of the brain

- Different areas have different functions.
- Areas communicate with each other.
- The brain is a hierarchical system
  (i.e., there are lower- & higher-level areas).
- ”We will understand cognition by piecing together all brain areas and their function”

The strongest evidence for this view comes from **lesion studies**, showing that **local brain damage** causes **selective deficits** in cognition.

Another major source of evidence was and still is **brain imaging**, identifying regions activated during specific tasks (”Blobology”).



https://dana.org/resources/neuroanatomy-the-basics

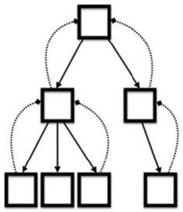
Discussion: When losing your right eye, you lose stereopsis (binocular depth vision). Does that mean that the function of your right eye was stereopsis?

Brain modularity & Functional localization

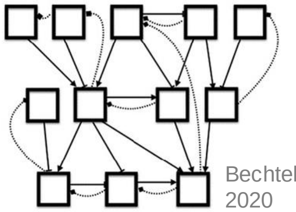
Shifting from functional localization to network dynamics (a more modern view?)

- The brain may operate as an interconnected network with strong recurrencies.
- Each “sub-circuit” exhibits local specificity & global constraints (i.e. no true independence of parts).
- The brain may be better described as a “heterarchy” than a “hierarchy”.
- Emergent network properties can give rise to “functions” that go beyond the sum of all modules.
- Functions are inherently task-dependent (thought experiment: what is the general function of your thumb?)

Hierarchy



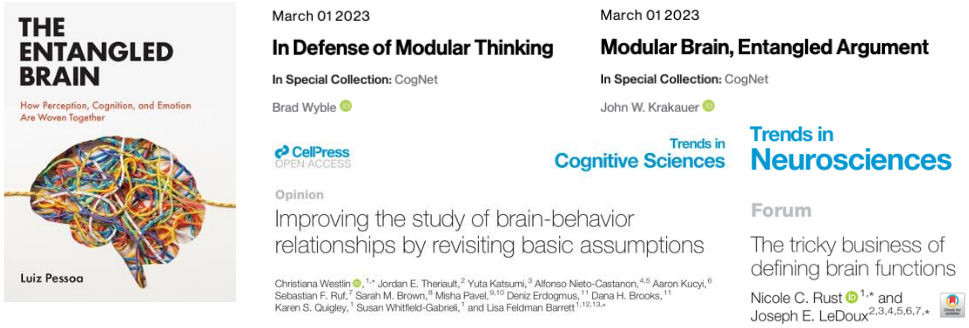
Heterarchy



Bechtel 2020

Each node in the network may be at the top or at the bottom of the hierarchy depending on what the network is doing.

Modularity & functional localization remain very debated!



+ Many more in the past few years alone!

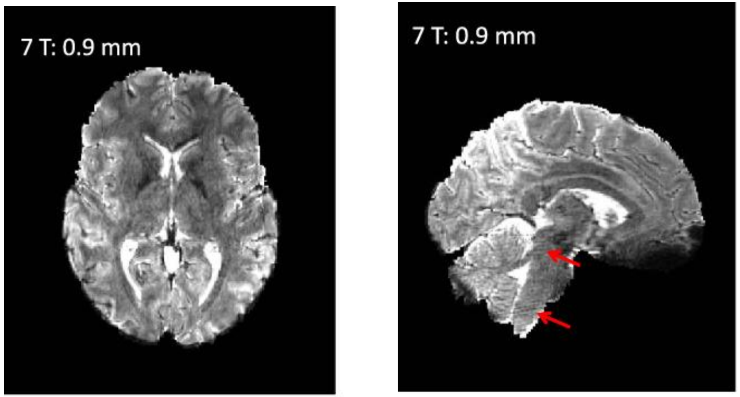
Brain modularity & Functional localization

Good news:

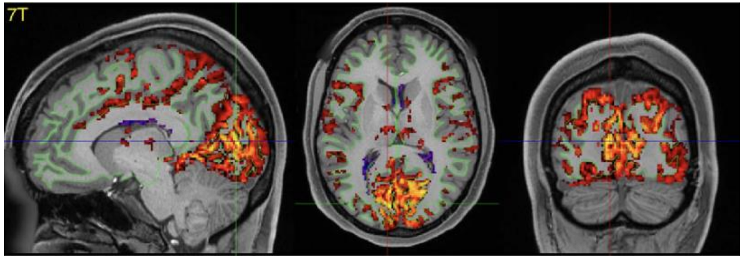
fMRI is a great tool to study both functional localization and network-level interactions!

- Whole-brain coverage (including cerebellum etc.)
- Good spatial and sufficient temporal resolution
- Wide range of interesting cognitive tasks feasible
- Many established analyses to map task-related activity changes across the brain
- Many established analyses to study covariations of different brain structures
- Fantastic and diverse community
- \+ Many more reasons

Whole-brain coverage at 0.9mm voxel size

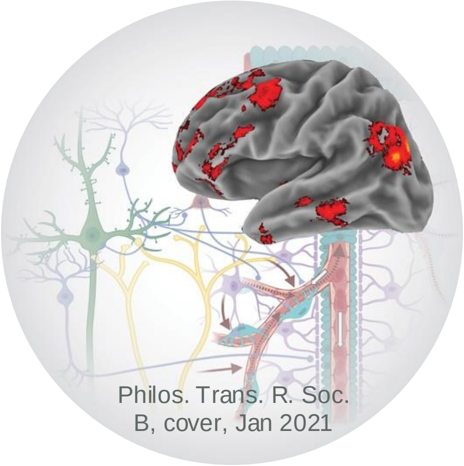


Seed-based covariation analysis (V1 voxel)



Jamison et al. 2017

Summary III



Philos. Trans. R. Soc. B, cover, Jan 2021

The brain has been parcellated into sub-parts in many different ways,
mainly because of the assumption that different parts have different functions.

There is no ground-truth parcellation of the brain,
leading to the Atlas concordance problem among many other confusions.

Modularity & functional localization remain strongly debated in the field,
but network-dynamics and distributed-processing frameworks gain in popularity.

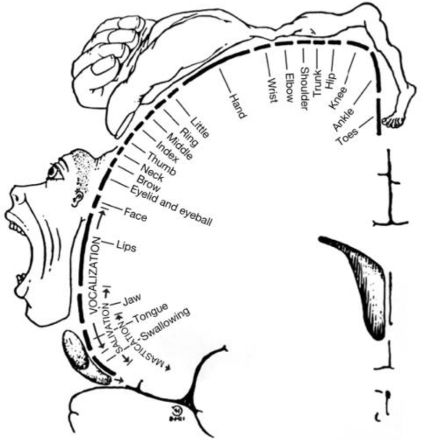
The definition of a brain area's function is trickier than it often seems,
even if local lesions cause selective deficits, and fMRI blobs suggest localized activity.

fMRI is a fantastic technique to study both the localization of task-related activity and network-level interactions, as long as we remain cognizant of what it does and does not measure.

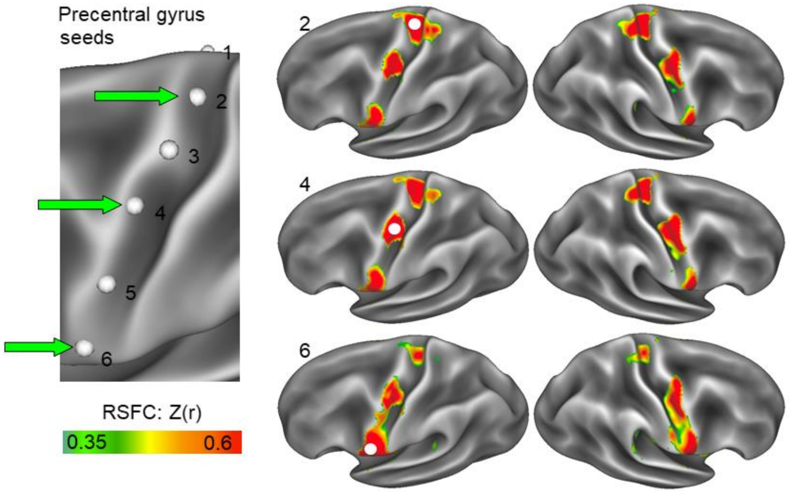
Example of how fMRI continues to change our understanding of the brain's functional organization

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

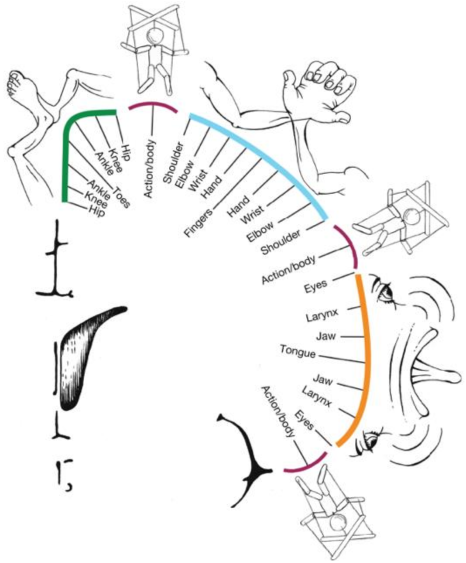
Penfield's Homunculus
Every textbook since 1937



fMRI covariation analysis reveals patterns strikingly inconsistent with Penfield (in 2023!)



Revised textbooks
(for now! ;)



Gordon et al. 2023

Key terms to remember

- Grey matter
- White matter
- Cerebrospinal fluid
- Ventricles
- Myelin
- Glia cells
- Neurotransmitters
- Vasculature
- Arteries & Veins
- Venous bias
- Time-of-flight imaging
- Angiography & Venography
- Parcellation
- Brain areas
- Brodman areas
- Brain atlases
- Atlas condordance problem
- Modular vs. non-modular brain theories
- Hierarchy vs. Heterarchy
- Functional localization

Image: amberusa.com

Thanks! See you next week!