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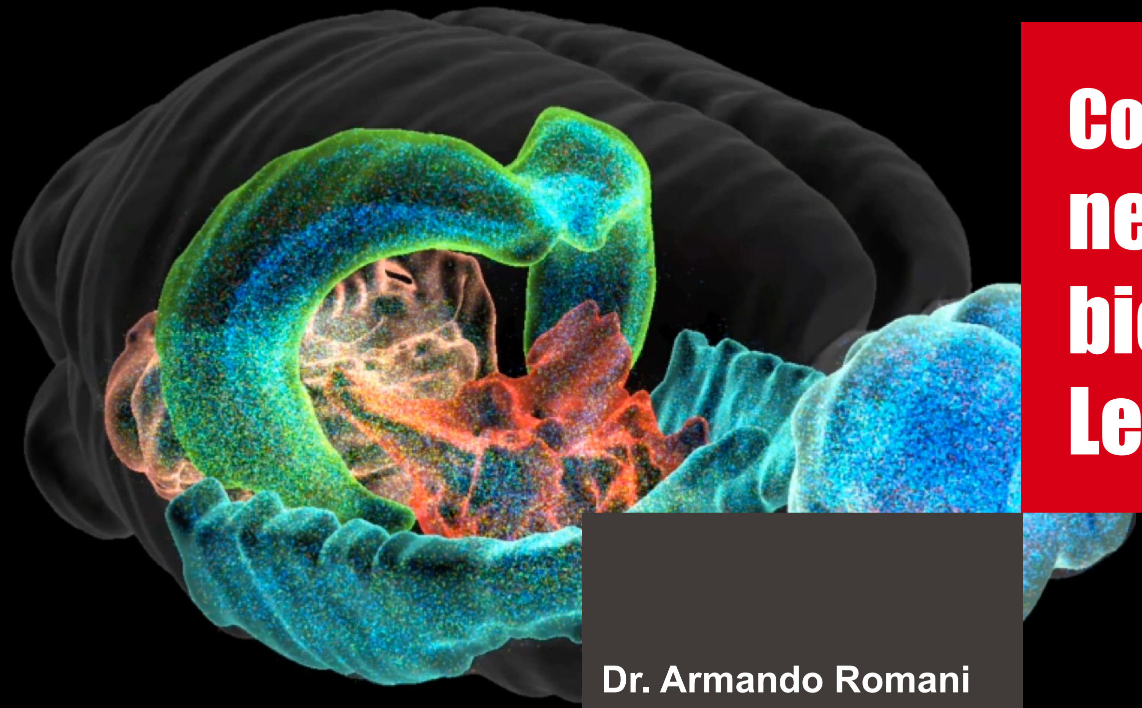


Computational neuroscience: biophysics – Lecture 14

Dr. Armando Romani

EPFL, 2023

Perspectives

Lecture Overview

- New techniques
- Neuroinformatics
- Large scale models
- Human

Lecture Overview

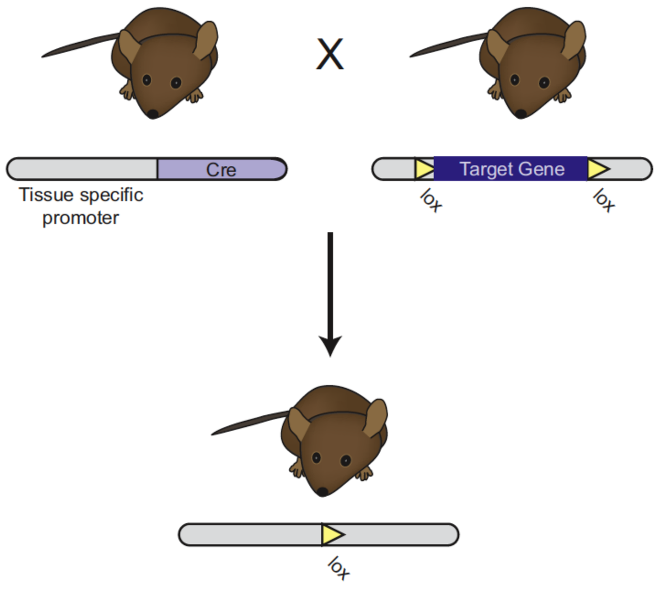
- **New techniques**
- Neuroinformatics
- Large scale models
- Human

New techniques

- More *in vivo* data
- High throughput data (bigger dataset, more dense)
- More standardized

Transegic mice: cre-lines

- Endogenous regulatory sequence + transgene of an “effector” protein (used to label, record, or manipulate target neuronal cell types).
- In binary expression systems, the regulatory sequence of an endogenous gene is used to express a “driver” transgene that encodes a transcription factor such as GAL4 or tTA, or a DNA recombinase such as **Cre** or FLP. The second, “responder” transgene, contains the coding sequence of an effector whose expression is regulated by either transcription factor binding sites such as UAS or TRE, or recombinase target sites such as **loxP** or FRT
- More control over timing and location of transgene expression
- Mix and match combination of transgenes



Guide to Research Techniques in Neuroscience

ALLEN BRAIN ATLAS
DATA PORTAL

HOME | MOUSE CONNECTIVITY | TOOLS

Search...

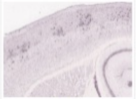
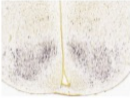
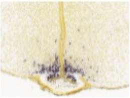
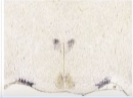
PROJECTION | BDA/AAV COMPARISON | TRANSGENIC CHARACTERIZATION | REFERENCE DATA | BRAIN EXPLORER | DOCUMENTATION | HELP

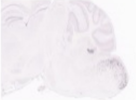
Tissue Location
- [x] Brain
- [x] Retina

Enter all or part of mouse line name, driver, or reporter:
*
Search
- [ ] Show exact matches only

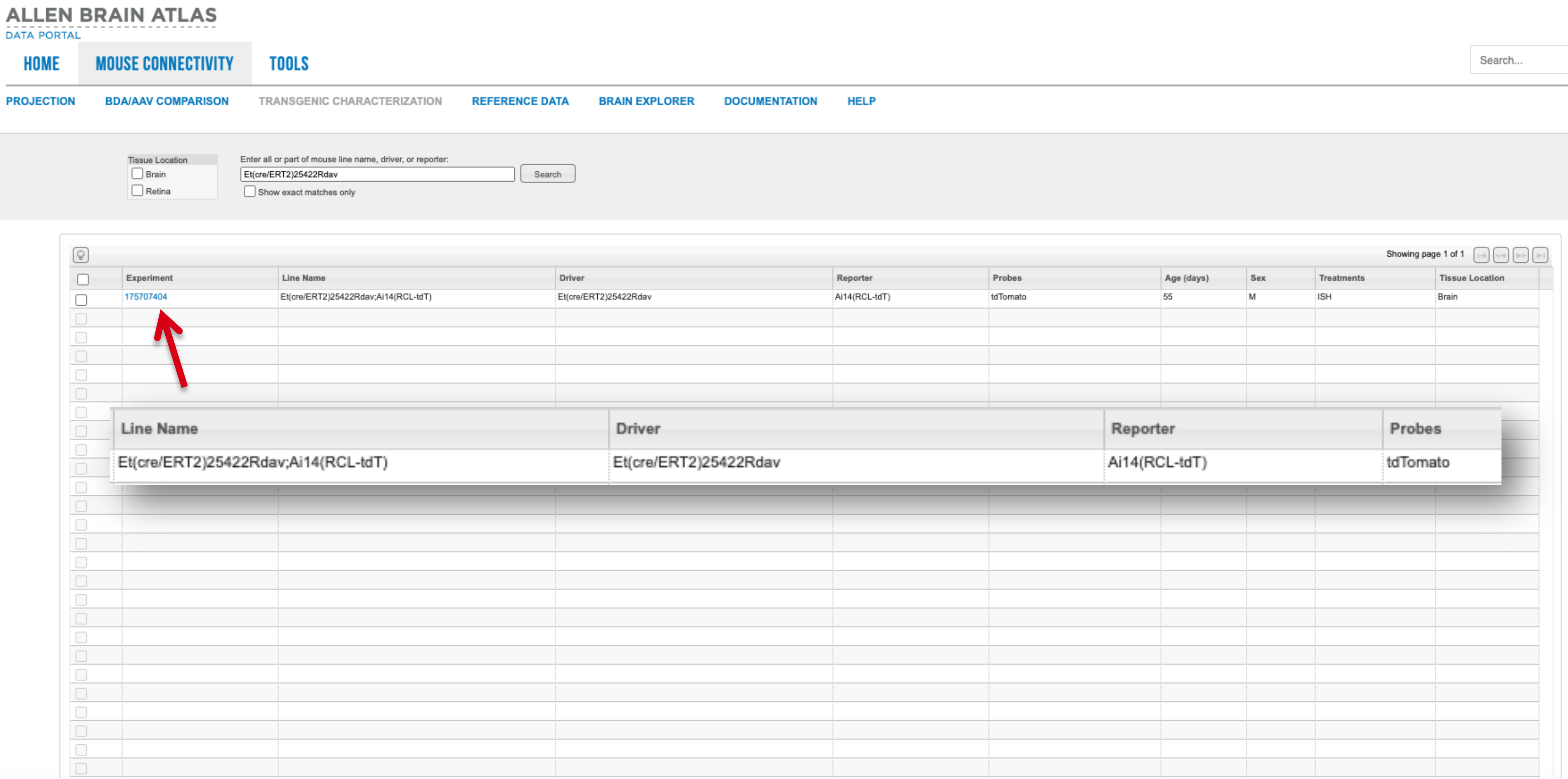
Drivers | Reporters

Data detailing transgene expression in Cre and other driver lines for adult and developing brain. Experiments include colorimetric in situ hybridization, fluorescent in situ hybridization and other histological methods.

Line Name	Example Image	Expression Pattern Summary
A930038C07Rik-Tg1-Cre Allen Institute for Brain Science		Widespread expression of reporter gene throughout the brain. Enriched in restricted populations within the olfactory areas, piriform cortex, hippocampus, and cerebellum. Adult Cre expression observed in restricted populations of striatum, layer 5 neocortex, hypothalamus, pons and medulla. This is different from the A930038C07Rik gene itself which is specifically expressed in layer 1.
A930038C07Rik-Tg4-Cre Allen Institute for Brain Science		Scattered populations within cortical layers 4 and 5, septum, thalamus, and midbrain. In the cortex, unlike A930038C07Rik which is specifically expressed in layer 1, Cre-directed reporter expression is found enriched in a scattered population of cells in layer 5.
Adcyap1-2A-Cre Allen Institute for Brain Science		Cre expression is enriched in restricted populations within the olfactory areas, hippocampus, striatum, thalamus, midbrain, pons, and medulla. Expression is scattered within the isocortex and hypothalamus. Reporter expression is widespread.
Agrp-IRES-Cre Bradford Lowell		Enriched in the arcuate nucleus of the hypothalamus.
Avp-IRES2-Cre Allen Institute for Brain Science		Expressed in restricted populations within the hypothalamus.

Et(cre/ERT2)2007Rdav Ronald L. Davis and Paul A. Overbeek		Widespread, scattered expression throughout the brain. Enriched in deep layers of neocortex and piriform cortex, and in restricted populations within hippocampus.
Et(cre/ERT2)2047Rdav Ronald L. Davis and Paul A. Overbeek		Expressed in strong scattered, widespread cells throughout the brain, particularly in midbrain and hindbrain.
Et(cre/ERT2)21Rdav Ronald L. Davis and Paul A. Overbeek		Expression in restricted populations within the medulla.
Et(cre/ERT2)25279Rdav Ronald L. Davis and Paul A. Overbeek		Strong scattered, sparse expression throughout the brain. Enriched expression in restricted populations in cortical subplate (amygdala), thalamus, midbrain, hindbrain, hypothalamus, and cerebellum granular cell layer.
Et(cre/ERT2)25378Rdav Ronald L. Davis and Paul A. Overbeek		Strong widespread expression in the cortex. Strong scattered cells in the striatum, hippocampus (particularly the dentate gyrus), pons, medulla, and enrichment in subregions of the cerebellar granular layer.
Et(cre/ERT2)25422Rdav Ronald L. Davis and Paul A. Overbeek		Strong expression in restricted populations in dentate gyrus. Strong widespread expression in cerebellum granular cell layer.
Et(cre/ERT2)25463Rdav Ronald L. Davis and Paul A. Overbeek		Strong scattered cells in restricted populations in dentate gyrus, thalamus, midbrain, hypothalamus, and cerebellum.
Ronald L. Davis and Paul A. Overbeek		Sparse expression throughout the brain, with a patchy pattern in cortex.

Et(cre/ERT2)25422Rdav Ronald L. Davis and Paul A. Overbeek		Strong expression in restricted populations in dentate gyrus. Strong widespread expression in cerebellum granular cell layer.



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HELP
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Brain
Retina
Enter all or part of mouse line name, driver, or reporter:
Et(cre/ERT2)25422Rdav
Search
Show exact matches only
Showing page 1 of 1
Experiment
Line Name
Driver
Reporter
Probes
Age (days)
Sex
Treatments
Tissue Location
175707404
Et(cre/ERT2)25422Rdav;Ai14(RCL-tdT)
Et(cre/ERT2)25422Rdav
Ai14(RCL-tdT)
tdTomato
55
M
ISH
Brain
Line Name
Driver
Reporter
Probes
Et(cre/ERT2)25422Rdav;Ai14(RCL-tdT)
Et(cre/ERT2)25422Rdav
Ai14(RCL-tdT)
tdTomato

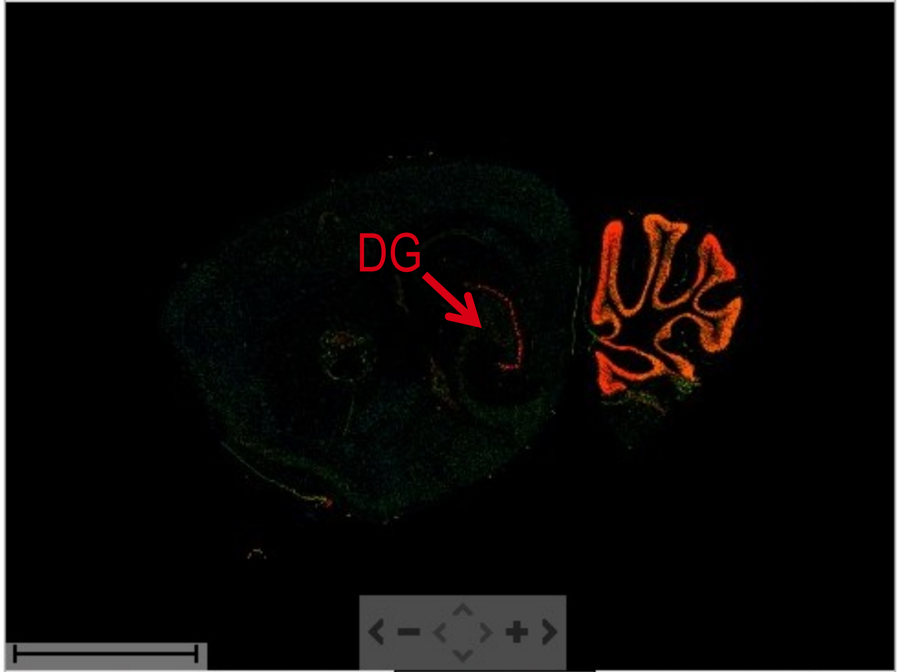
Et(cre/ERT2)25422Rdav;Ai14(RCL-tdT) - RP_120308_01_E02

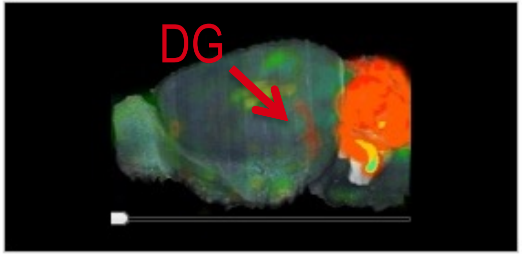
Experiment 175707404	
Transgenic Mouse	Et(cre/ERT2)25422Rdav;Ai14(RCL-tdT)
Driver	Et(cre/ERT2)25422Rdav
Reporter	Ai14(RCL-tdT)
Related Gene	
Probes	tdTomato (RP_120308_01_E02)
Plane of Section	sagittal
Treatments	ISH
Induction	Tamoxifen treated

Specimen Et(cre/ERT2)25422-173-Rdav;Ai14	
Organism	Mus musculus
Strain	B6.129
Age	55
Sex	M

Related Institute Data

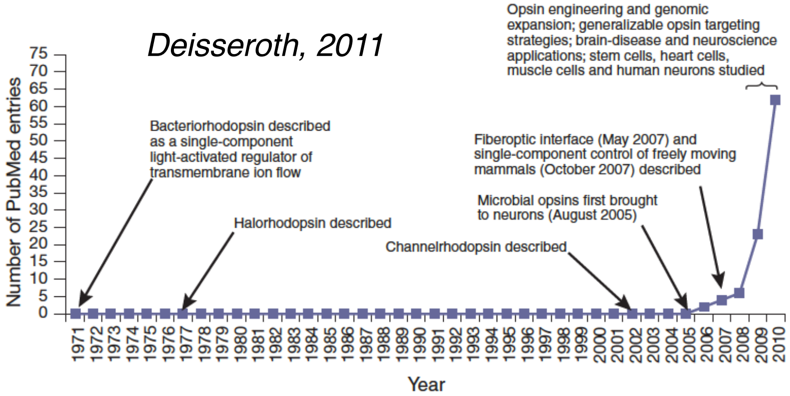
Expression



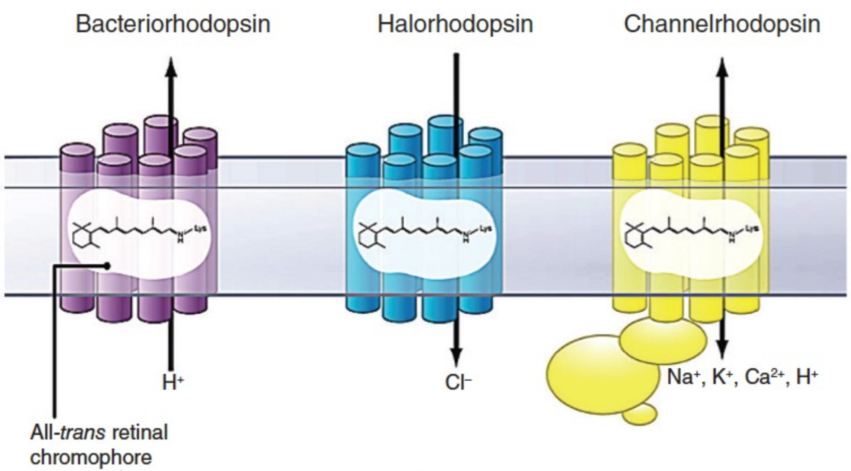


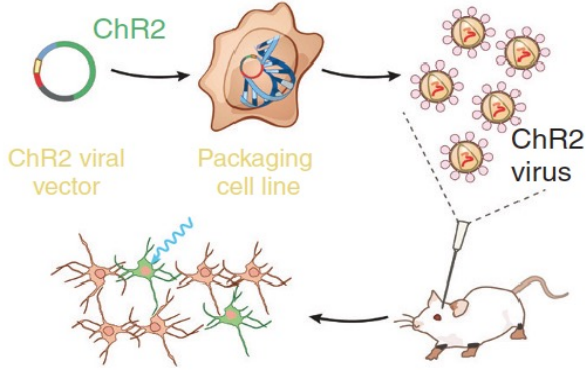
Optogenetics

- Microbial opsins
- Channelrhodopsin-2 (ChR2) causes depolarization
- Bacteriorhodopsin and Halorhodopsin cause hyperpolarization
- They can be inserted via virus infection or using transgenic animals



Deisseroth, 2011



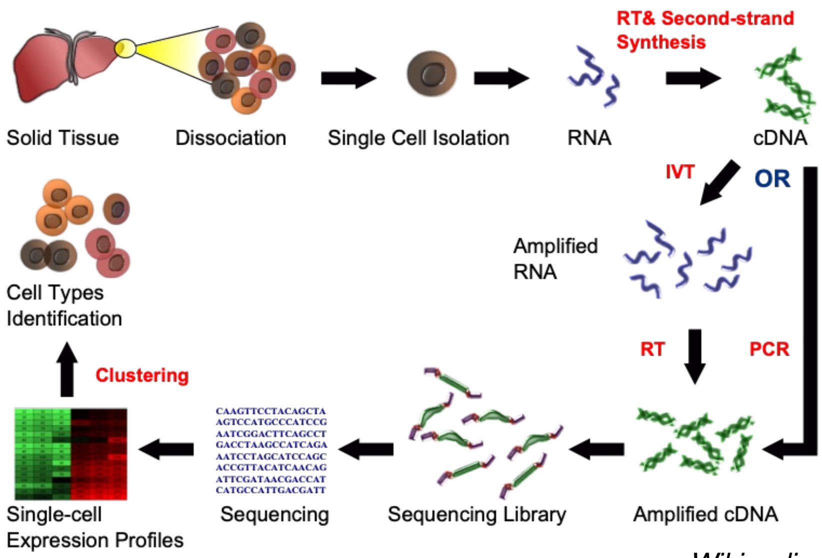


Deisseroth, 2015

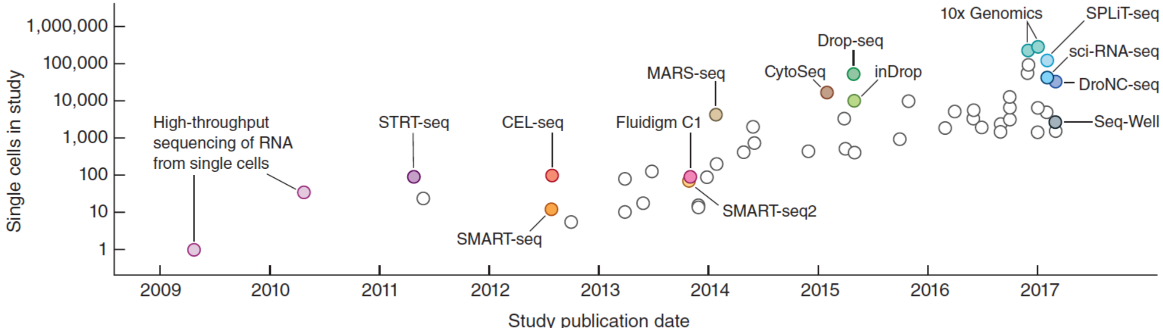
Transcriptomics

- Proteomics is limited to few preselected proteins
- Single-cell RNA-sequencing (scRNA-seq.)
- Sequencing of mRNA ~ proteins expressed by the cell ~ cell identity
- Large dataset requires statistics and machine learning to be analyzed

Single Cell RNA Sequencing Workflow



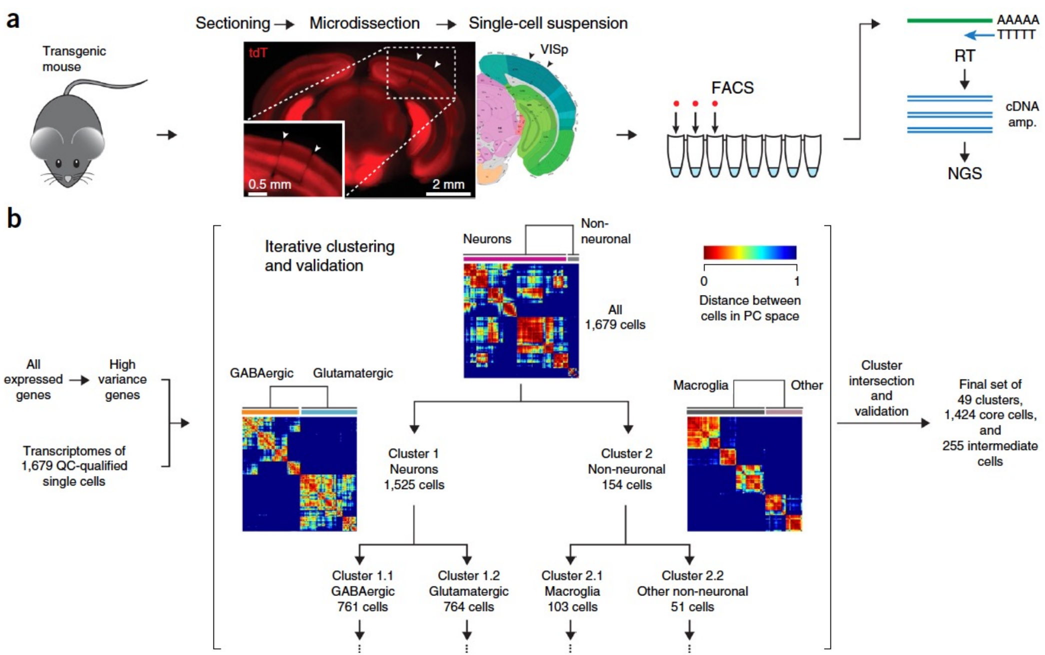
Wikipedia



Svensson et al., 2018

Tasic et al., 2016

- Primary visual cortex (VISp or V1)
- Methods for dimensionality reduction, clustering, machine learning, validation
- Gouwens et al., 2019 uses morpho-electrical features to classify the cells. The resulting classification is in a good agreement with Tasic et al., 2016



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Tasic et al., 2016

pan-neuronal

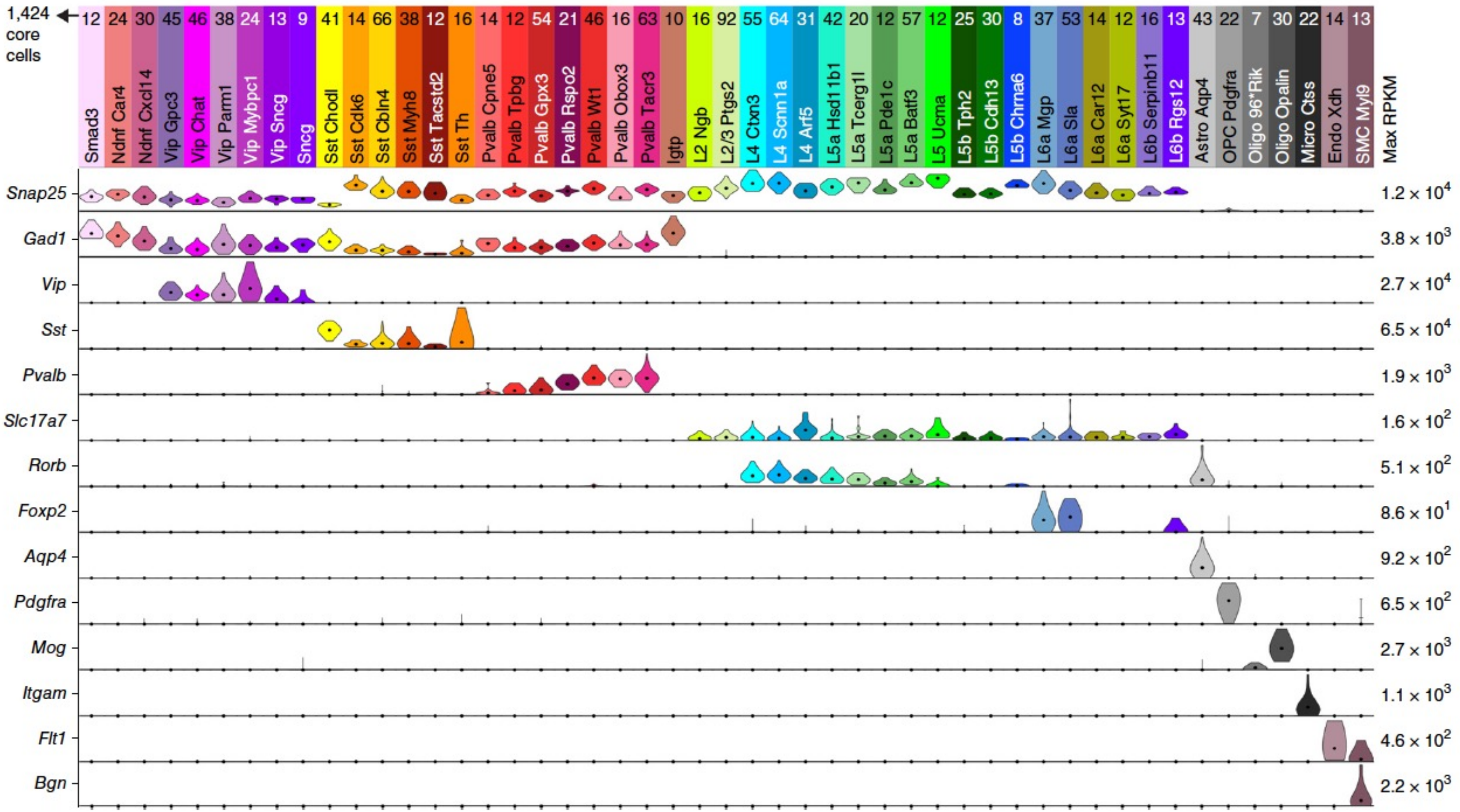
pan-GABAergic

pan-glutamatergic

mostly L4 and L5a

L6

non neuronal



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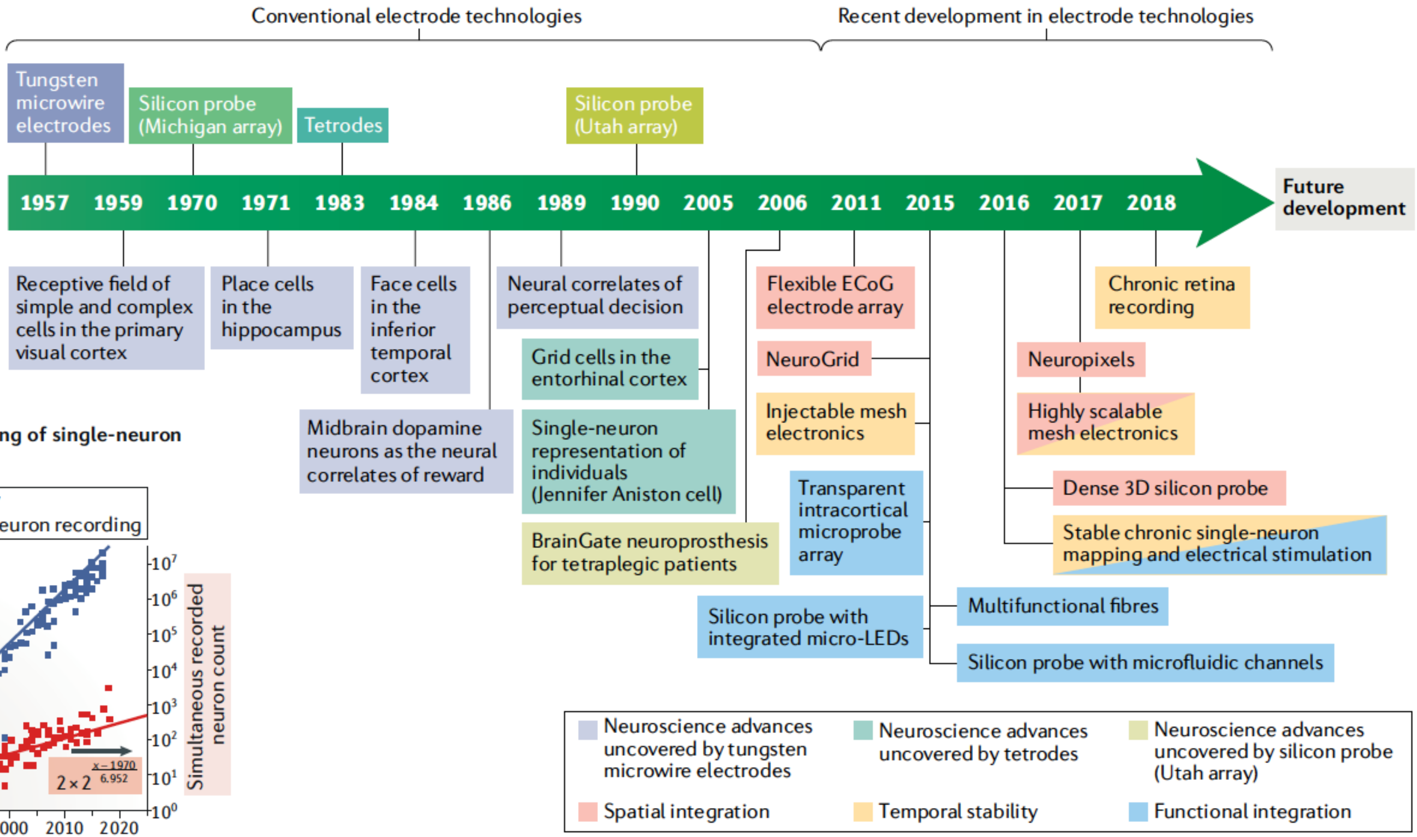
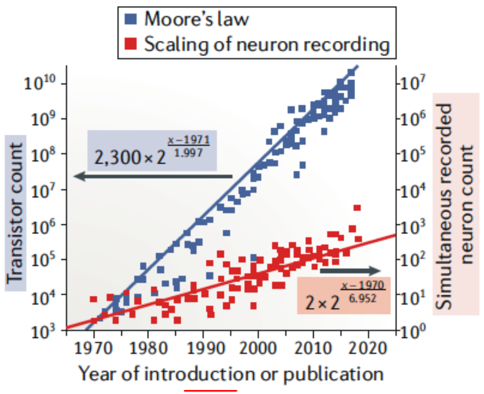
Electrode technologies

Hond and Lieber, 2019

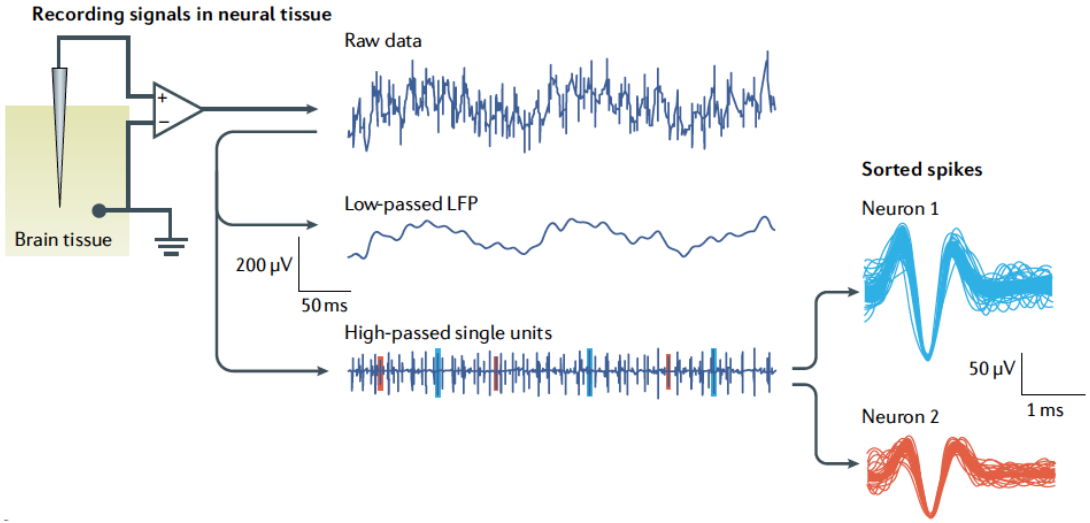


Moore's law vs scaling of single-neuron recording



Electrode technologies

- Extracellular electrode can record neurons within ~140 um
- Spikes recorded at the same electrode can be assigned to individual neurons
- Multi-unit activity (MUA) is the activity of several neurons that cannot be resolved



Hond and Lieber, 2019

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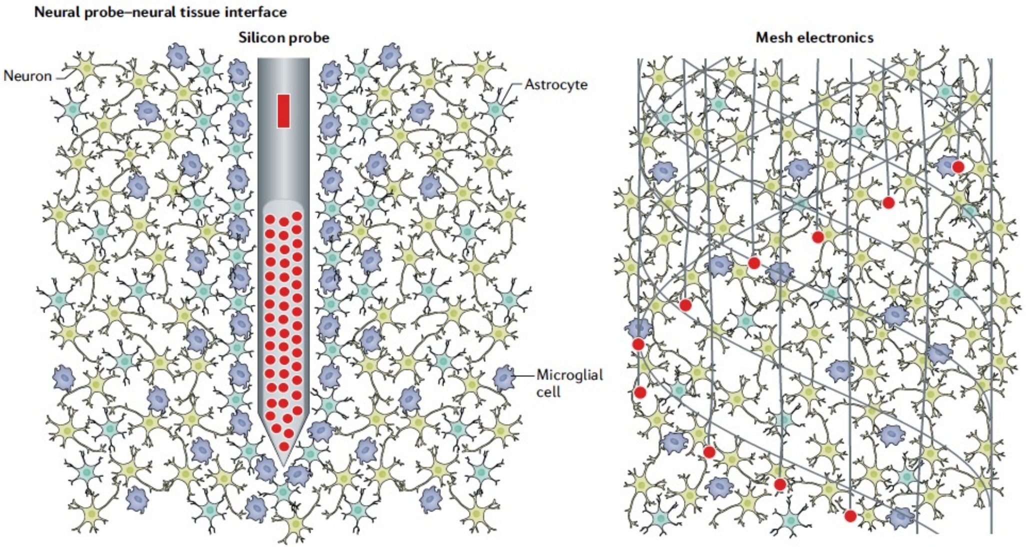
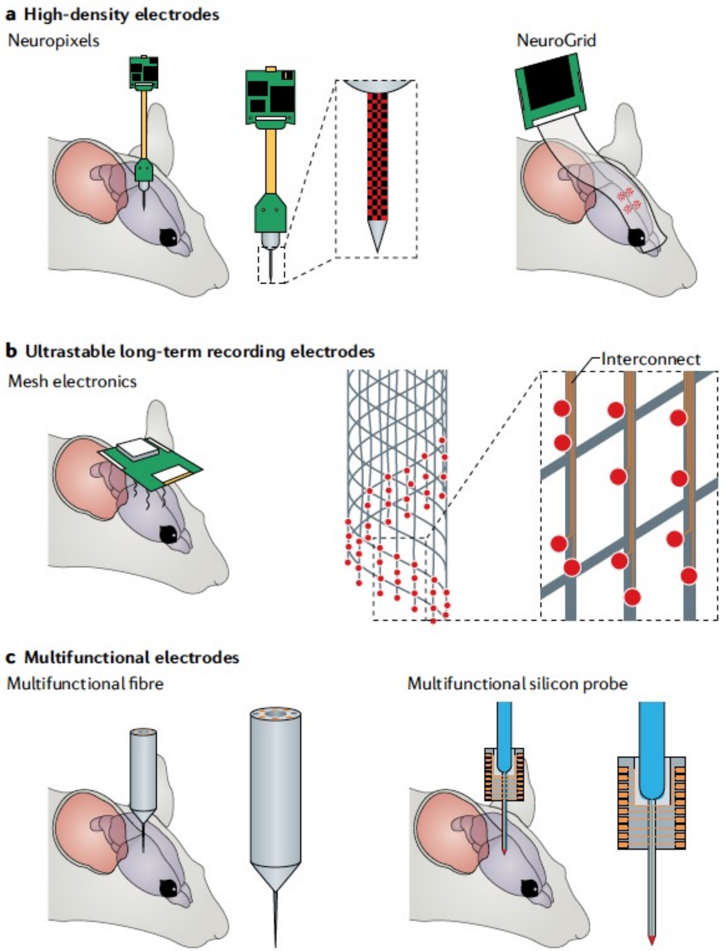
Electrode technologies

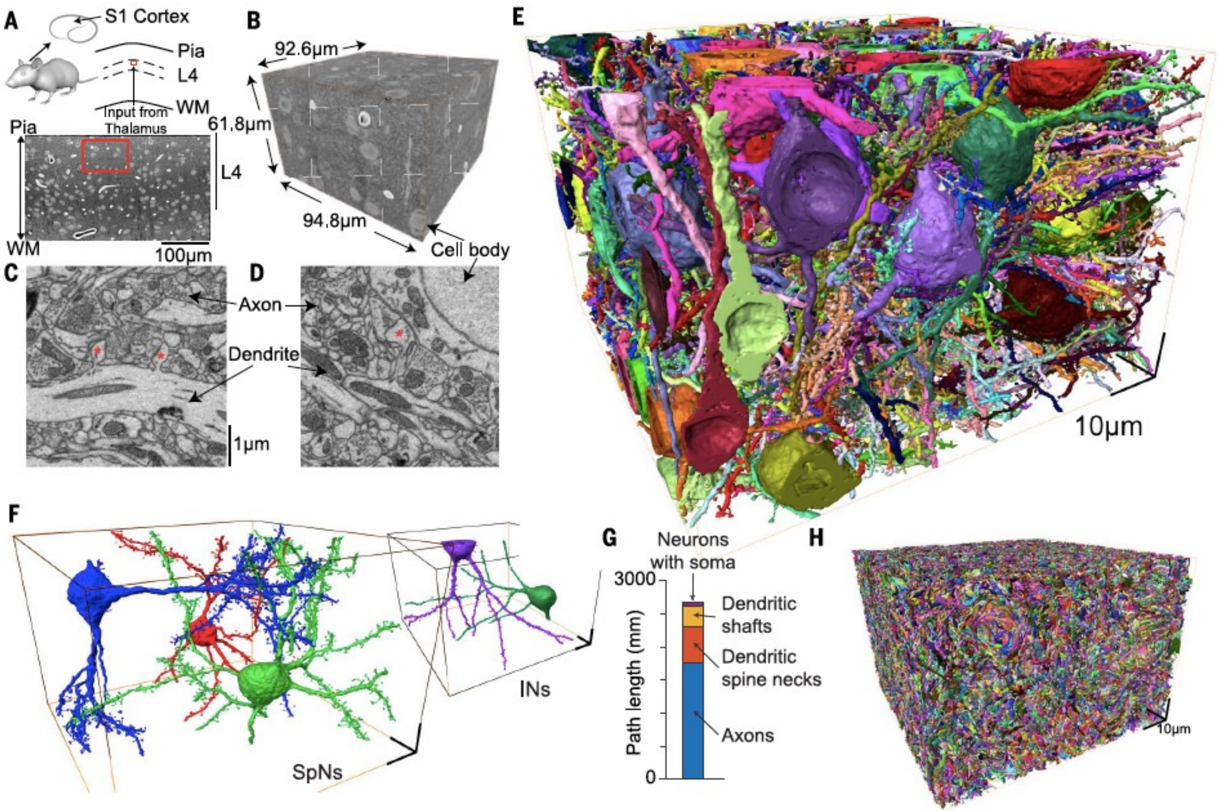




Hond and Lieber, 2019

Dense reconstruction of barrel cortex layer 4

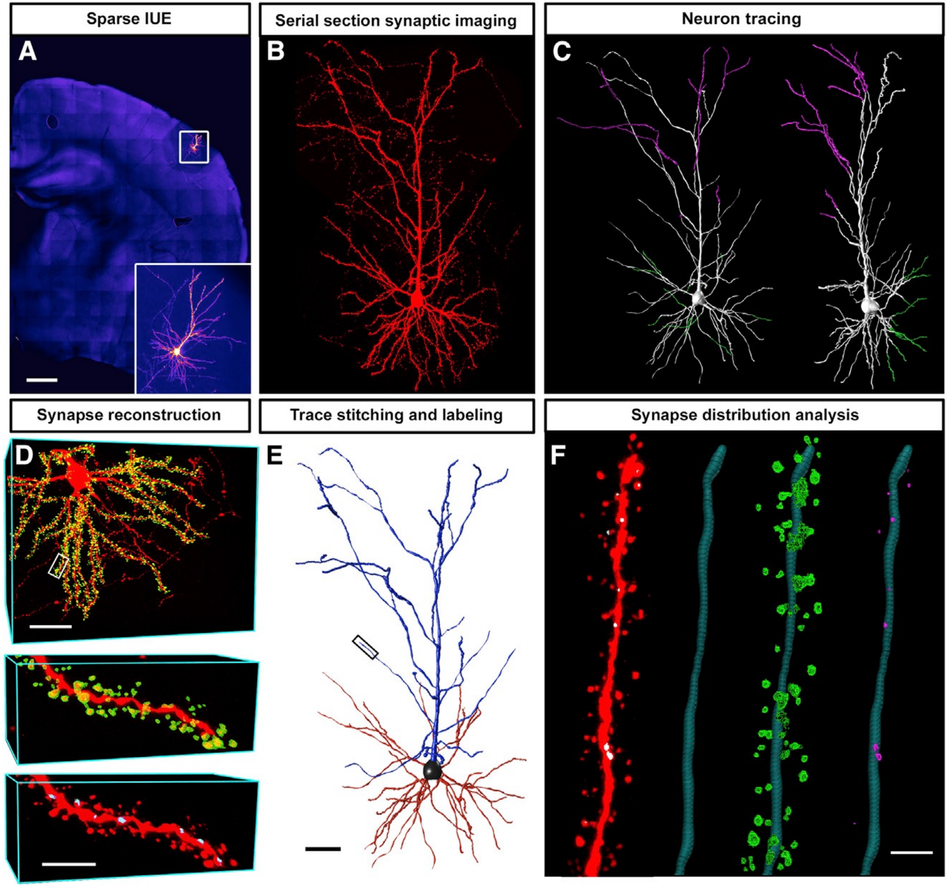
Dense reconstruction of ~500,000 μm^3 of cortical tissue yielding 2.7 m of neuronal cables (~3% shown, front) implementing a connectome of ~400,000 synapses between 34,221 axons and 11,400 postsynaptic processes.



Motta et al., 2019

Whole-Neuron Synaptic Mapping

- Sparsely labelled layer 2/3 pyramidal neuron
- Dendritic spines as a structural proxy for excitatory (E) synapses. They count for >90% of all E synapses
- Inhibitory (I) synapses labelled with the inhibitory postsynaptic scaffolding protein Gephyrin tagged with EGFP
- Synapse Detector toolkit within Vaa3D
- Mapped over 90,000 E and I synapses
- across twelve L2/3 PNs
- E/I ratio is balanced across the dendrites



Iascone et al., 2020

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Summary 1

- The list is not exhaustive, but it provides examples from the current most influential techniques
- New techniques produce datasets that are closer to an *in vivo* condition, larger, denser, and more standardized
- Despite new techniques produce larger datasets, it is still not possible to measure “everything”
- The new datasets are larger and more complex. We need new methods to handle them…

Lecture Overview

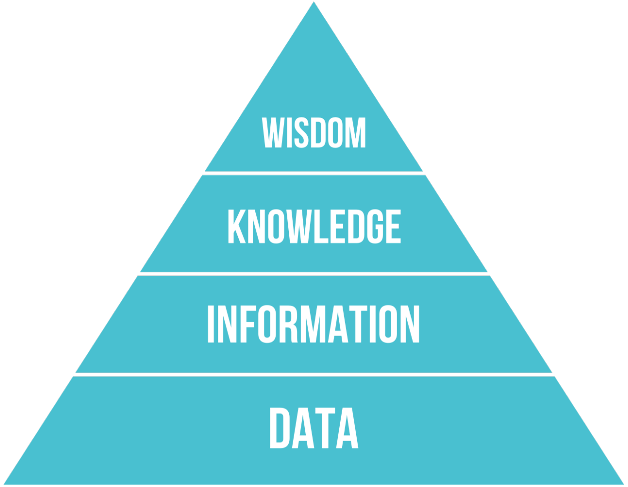
- New techniques
- **Neuroinformatics**
- Large scale models
- Human

Neuroinformatics (recap)

- Organize data
- Make data accessible
- Discover new patterns
- Highlight gaps in our knowledge
- Keep track of metadata, provenance, quality
- Keep track of data manipulation (curation, correction, conversion…)

Big data

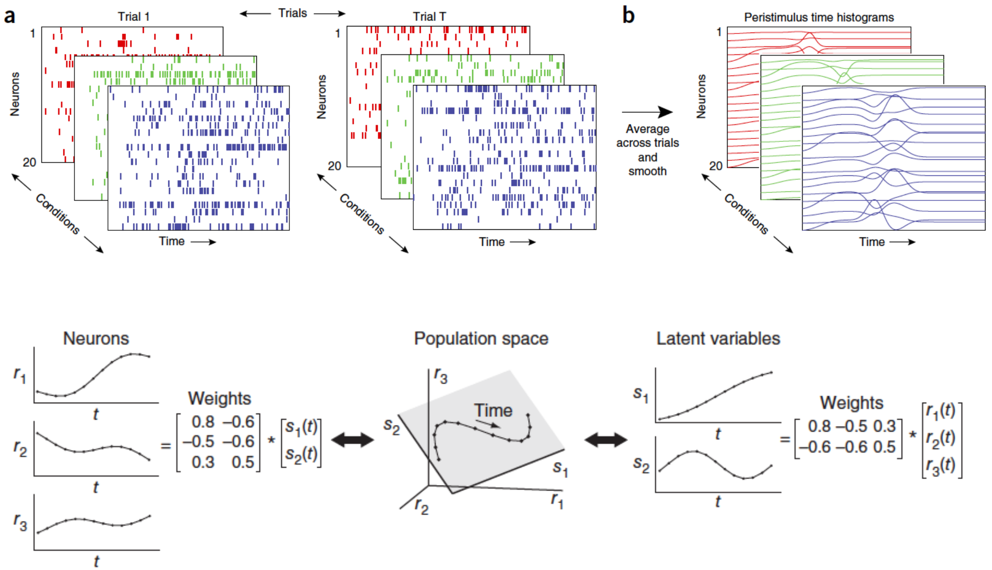
- Industrialization of neuroscience. Big data revolution. Brain initiatives
- How big? Gigabytes, terabytes, petabytes?
- Larger dataset may not be reducible to simpler descriptions. Statistics and machine learning may help
- The information content in raw data may be mostly irrelevant. Dimensionality reduction



DIKW pyramid

Statistics and machine learning

- Computer vision
- Automatic or semi-automatic neuron tracing
- Clustering
- Spike sorting
- Dimensionality reduction



Cunningham and Yu, 2014

Summary 2

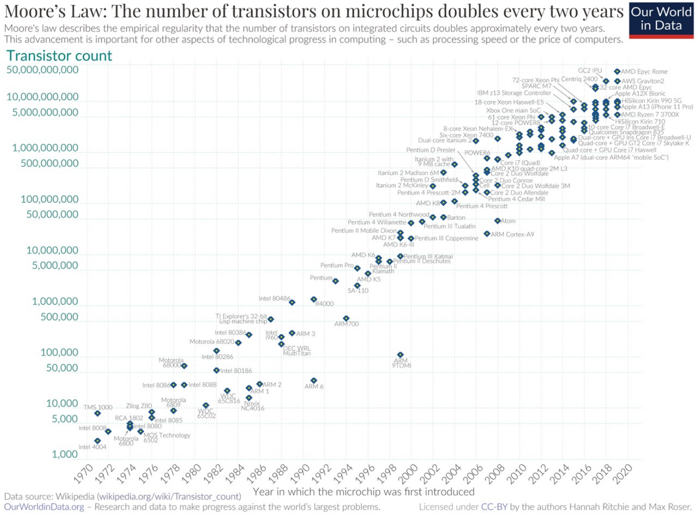
- Larger datasets require new strategies to be handled
- Large and raw datasets are often difficult to interpret. Salient information should be extracted from raw data
- Statistics and artificial intelligence are becoming indispensable tools for neuroscientists
- How all of that influence computer models?

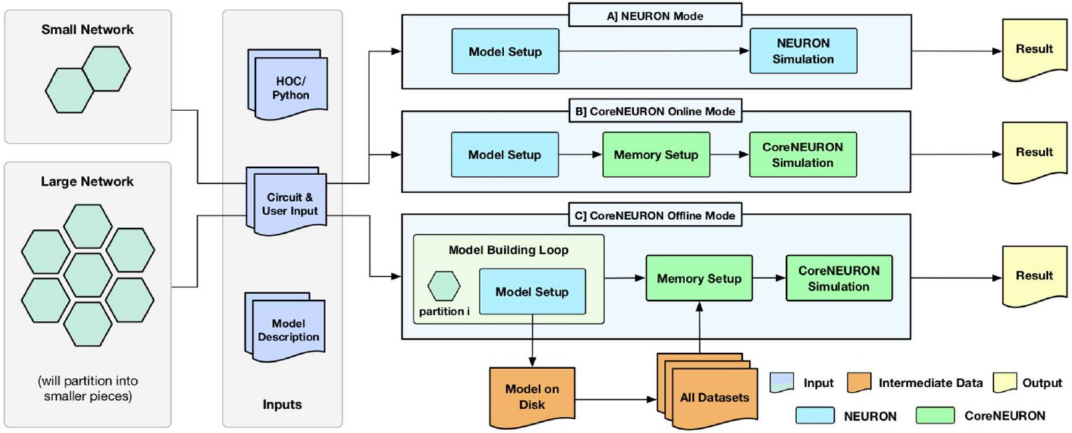
Lecture Overview

- New techniques
- Neuroinformatics
- **Large scale models**
- Human

Computing

- Moorse’s law
- More performing software
- Neuromorphic computing



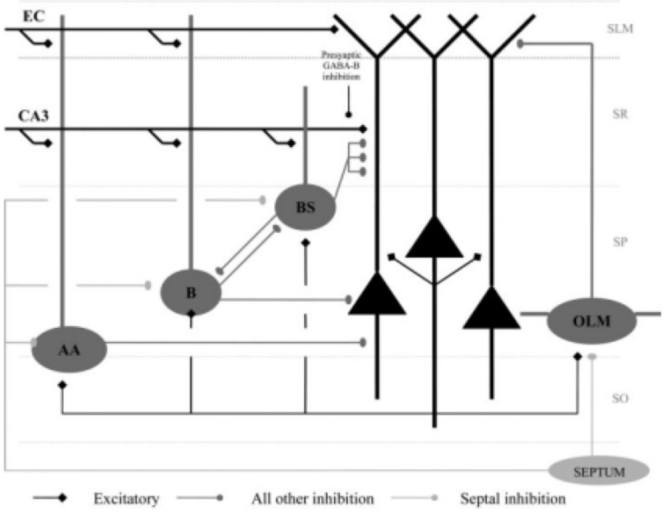


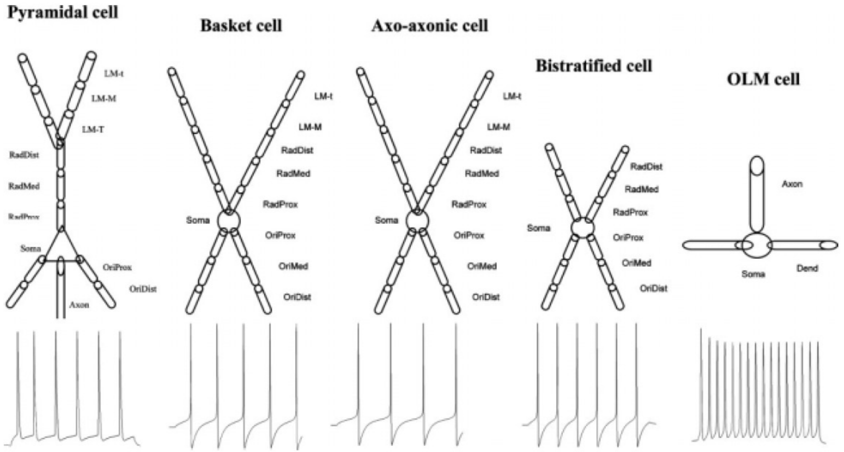
BrainScaleS

Kumbhar et al., 2019

Cutsuridis et al., 2010

- (Rat) CA1 microcircuit
- The model consists of 100 pyramidal (P) cells, 2 basket (B) cells, 1 bistratified (BS) cell, 1 axo-axonic (AA) cell, and 1 oriens lacunosum moleculare (OLM) cell
- Simplified morphologies including the soma, apical and basal dendrites and a portion of axon, were used for each cell type
- Arbitrary volume





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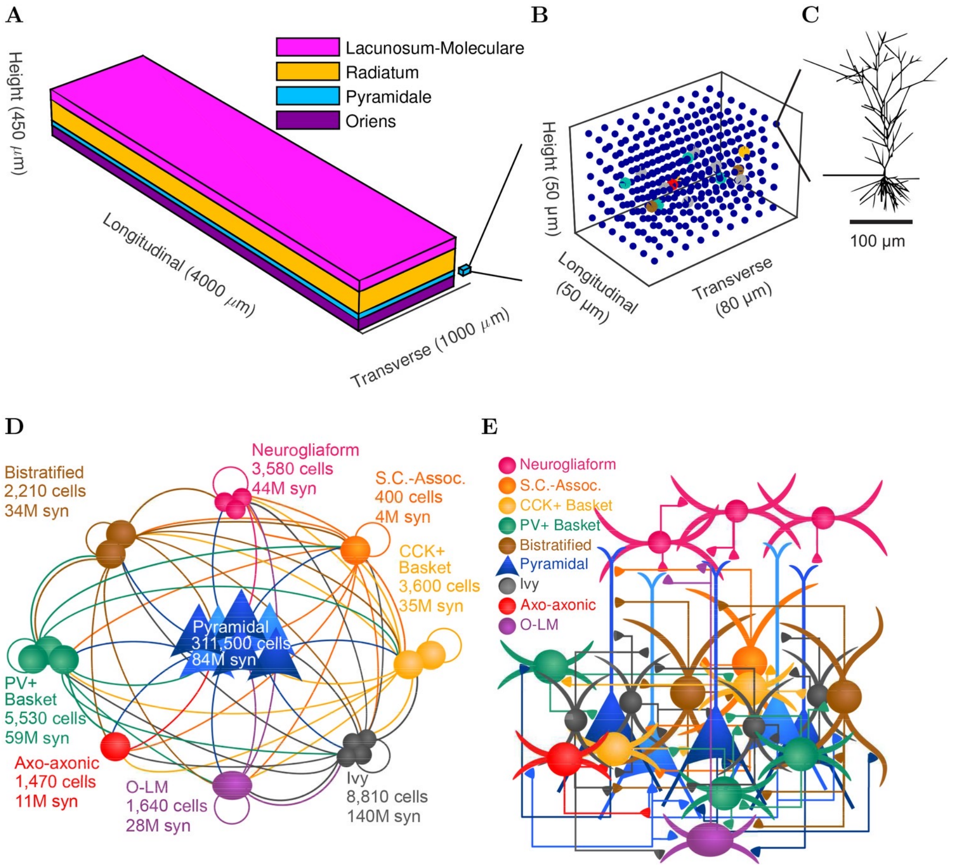
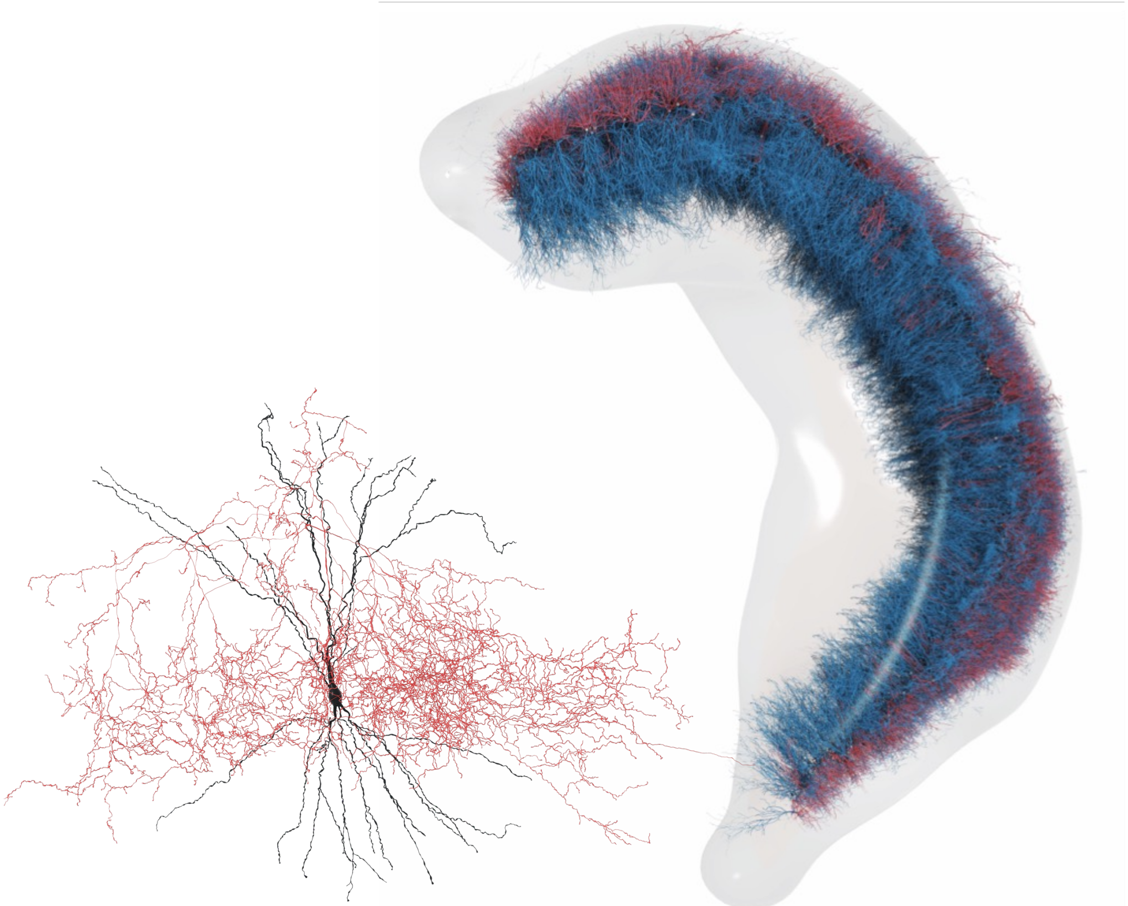
Bezaire et al., 2016

- Rat hippocampus CA1
- 350K neurons
- Detailed morphologies, no axons
- 9 morphological cell types
- Simplified volume
- Connectivity based on volume but not axon



Romani et al.

- Rat hippocampus CA1
- 400K neurons
- Detailed morphologies with axons
- 12 morphological cell types
- Atlas-based volume
- Connectivity based on volume and axons



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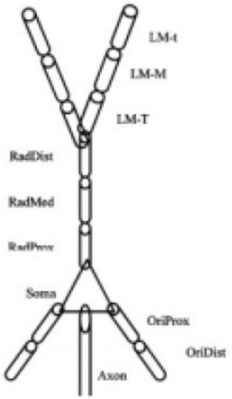
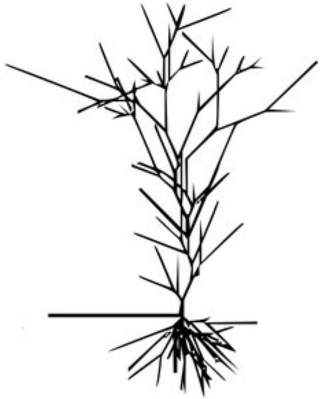
Bridging the scales

Previous examples already showed:

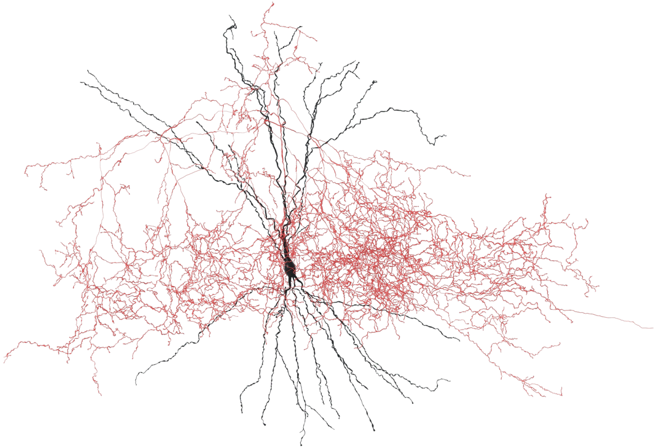
- a progress from microcircuitry to mesoscale circuit
- a trend towards more precise volume
- an increase in morphological details
- An increased granularity in defining cell types, connections…



Cutsuridis et al., 2010

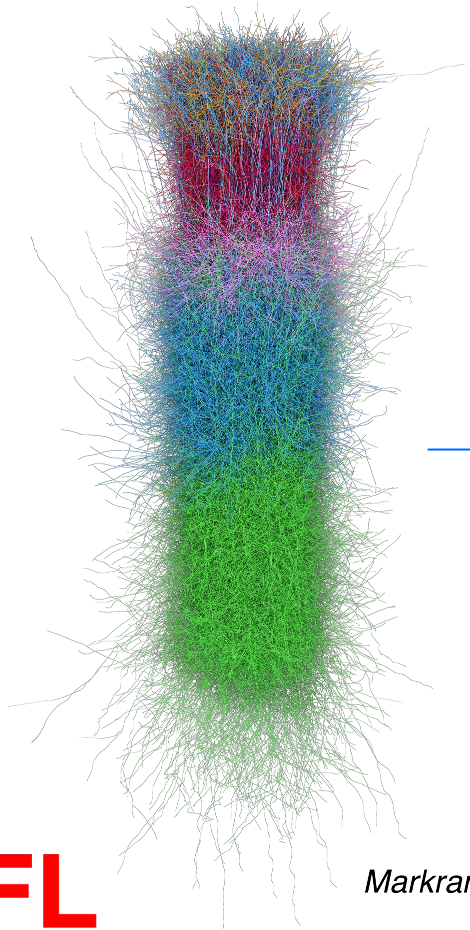


Bezaire et al., 2016



Romani et al.

Bridging the scales



Markram et al., 2015

VSDI, LFP, EEG…
(Newton et al., 2021; …)

Gap junction
(Amsalem et al., 2016)

LTP / LTD
(Chindemi et al., 2022)

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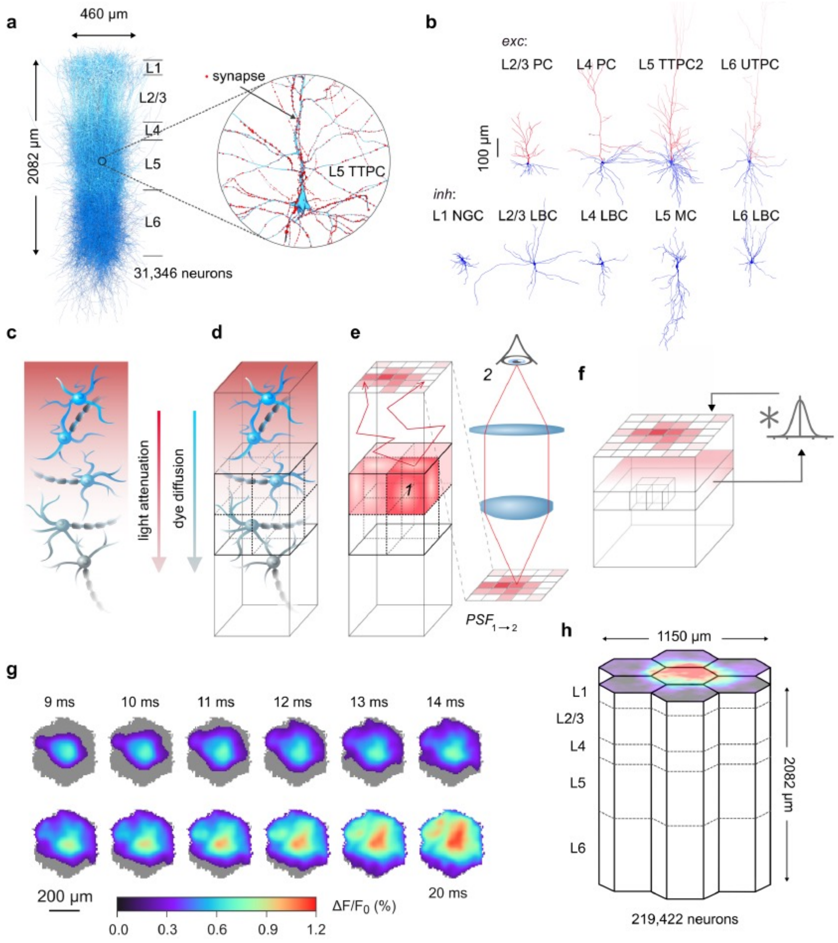
Voltage-sensitive dye imaging (VSDI)

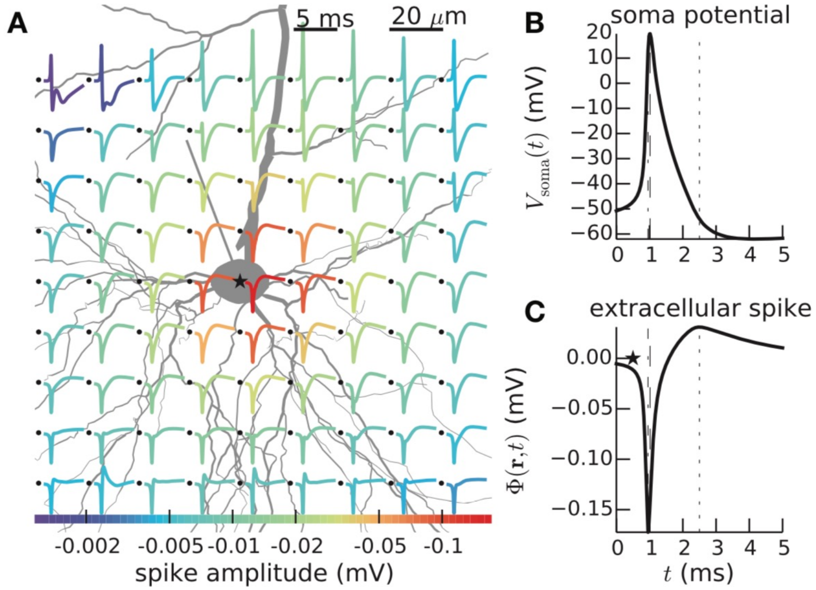
- Voltage-sensitive dyes are organic molecules or proteins which reside in a cell membrane and change their optical properties in response to a change in membrane potential. They have been used to follow population changes in membrane potential over large regions of the brain.
- Newton et al. (2019) developed a method to compute an in-silico VSD signal.



Newton et al., 2021

Local-field potential (LFP)

- The local field potential (LFP) refers to the electric potential in the extracellular space around neurons. The LFP is a widely available signal in many recording configurations, ranging from single-electrode recordings to multi-electrode arrays.
- Several methods are available to estimate LFP from network parameters (Reimann et al. 2013; Linden et al., 2014).



Linden et al., 2014

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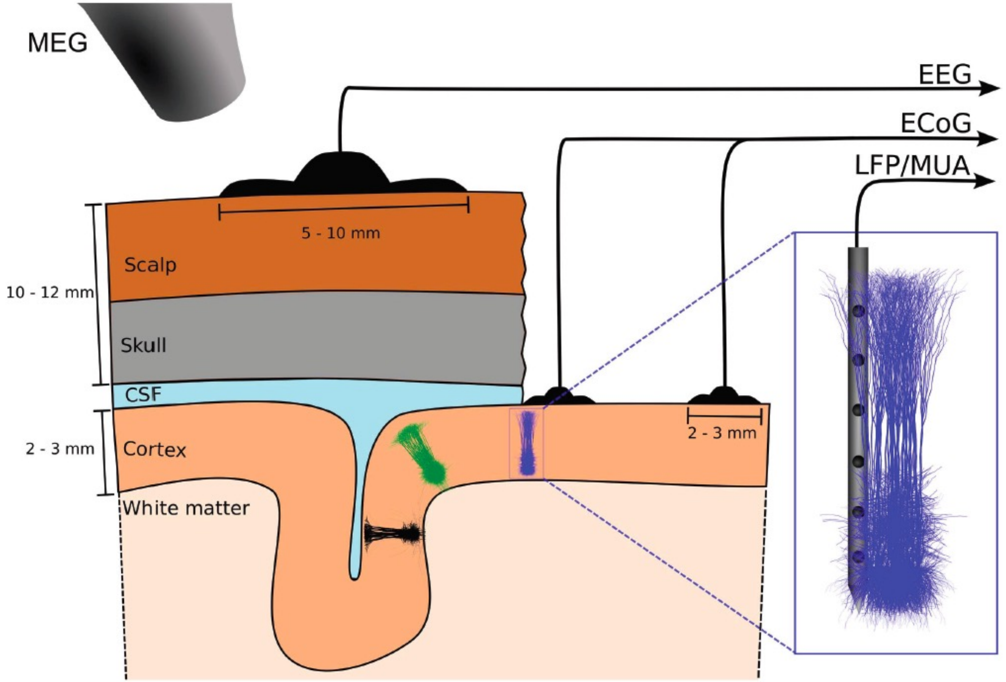
MEG, EEG, ECoG

- Improvement of LFPy (Linden et al., 2014)
- Magnetoencephalography (MEG), electroencephalography (EEG), electrocorticography (ECoG)



Hangen et al., 2018

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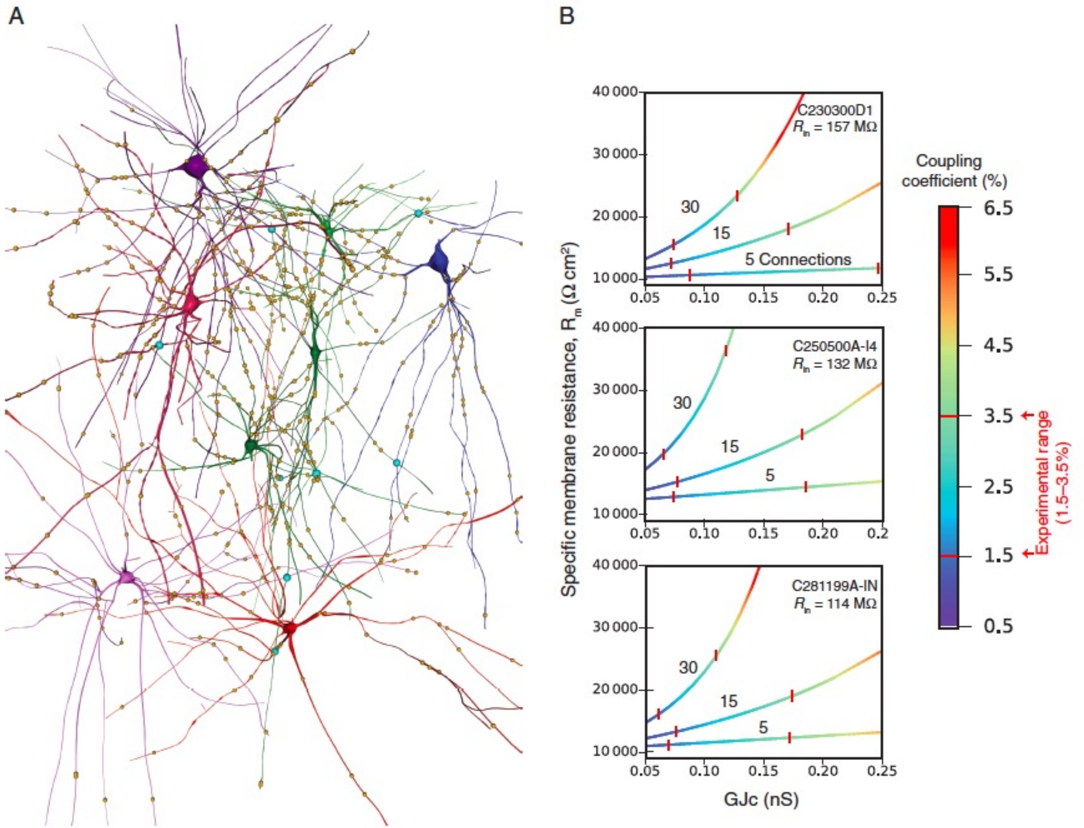
Gap junction

- Important in phenomena like high-frequency oscillations
- Model of GJs between L2/3 large basket cells
- Passive properties measured in vitro incorporate the effect of GJs
- Introduction of GJs requires to readjust the passive properties



Amsalem et al., 2016

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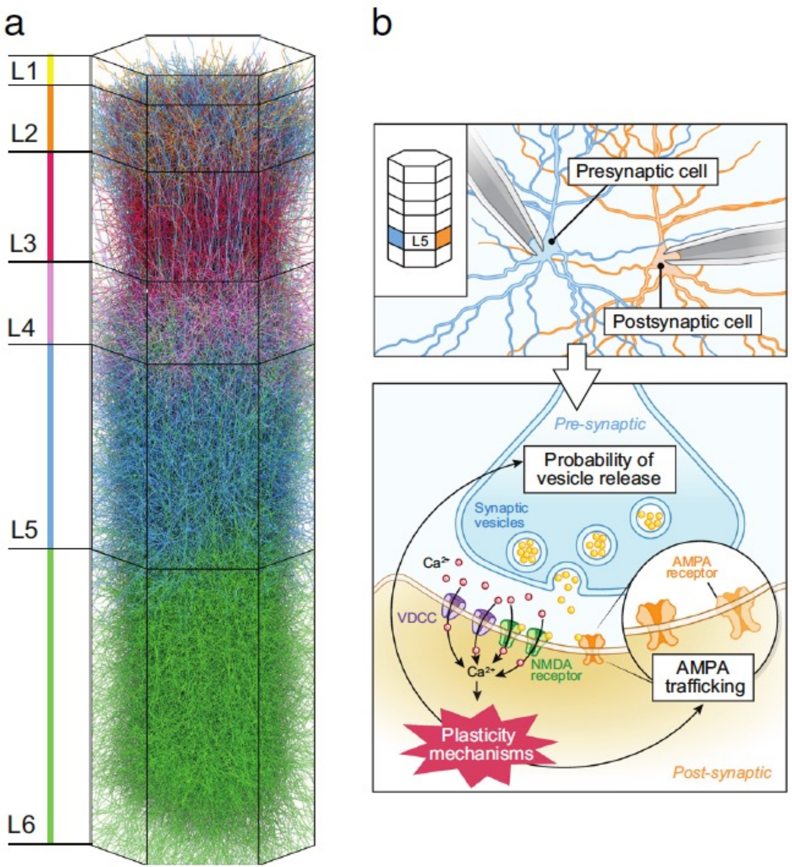
Plasticity

- Experimental data suggesting connection-type-specific mechanisms
- A calcium-based plasticity rule regulating L5-TTPC synapses holds also for several other pyramidal to pyramidal connections
- Synaptic physiology, cell morphology and innervation patterns jointly determine LTP/LTD dynamics without requiring a different model or parameter set for each connection type.

Chindemi et al., 2022



Summary 3

- With the growth of computer capabilities and data availability, the models become larger and more complex
- New details can be added to existing models
- We start merging different scales in space and time
- New experimental techniques, new neuroinformatics methods, new models, all tends to one goal: better understand the human brain

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Lecture Overview

- New techniques
- Neuroinformatics
- Large scale models
- **Human**

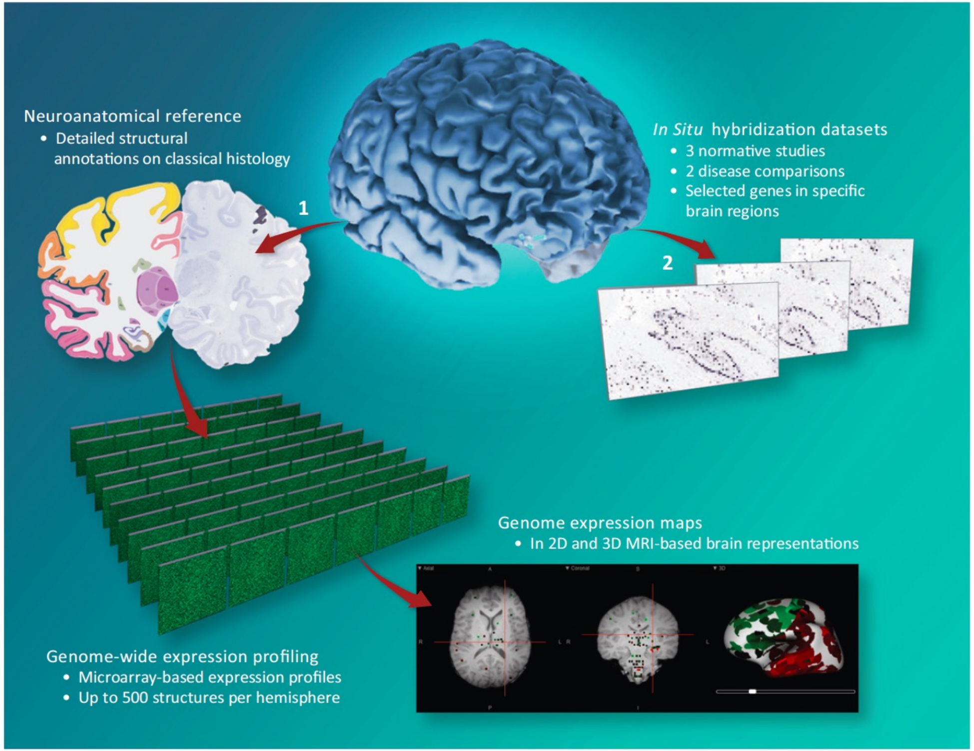
National/international initiatives

- Blue Brain Project (Switzerland)
- Human Brain Project (EU)
- BRAIN initiative (US)
- Brain Canada (Canada)
- Australian Brain Alliance (Australia)
- China Brain Project (China)
- Korea Brain Initiative (Korea)
- Allen Institute for Brain Science (US)
- Brain/MINDS (Japan)
- Israel Brain Technologies (Israel)

EPFL

Allen Human Brain Atlas

- Two principal gene expression resources: (i) a global 'all genes, all structures' survey of gene expression (microarray); and (ii) structure- and gene-specific cellular resolution in situ hybridization (ISH) datasets
- Magnetic resonance (MR) image-based 3D anatomic framework
- Microarray. 400–500 tissue samples are collected per hemisphere



Shen et al., 2012

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Planar View
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In:
For:
[All Donors]
For this probe:
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Donor H0351.2001
trigeminal nuclei (5)
Gene Symbol
Probe Name
CACHD1 A_24_P943922
CACHD1 CUST_5345_PI416261804
CACNA1A A_24_P130559
CACNA1A CUST_16843_PI416261804
CACNA1A CUST_16845_PI416261804
CACNA1B A_23_P159622
CACNA1B A_23_P84849
CACNA1B A_32_P153773
CACNA1C A_23_P373028
CACNA1C A_23_P373031
CACNA1C CUST_123_PI416408490
CACNA1D A_23_P365767
CACNA1D CUST_124_PI416408490
CACNA1D CUST_13825_PI416261804
CACNA1D CUST_13828_PI416261804
CACNA1E A_23_P34554
CACNA1E CUST_125_PI416408490
CACNA1E CUST_6489_PI416261804
CACNA1F A_23_P148327
CACNA1F CUST_9275_PI416261804
CACNA1G A_23_P107247
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CACNA1G CUST_12173_PI416261804
CACNA1G CUST_126_PI416408490
CACNA1H A_23_P26294
CACNA1H A_23_P3483
CACNA1I A_24_P399871
CACNA1I A_24_P945096
CACNA1I CUST_127_PI416408490
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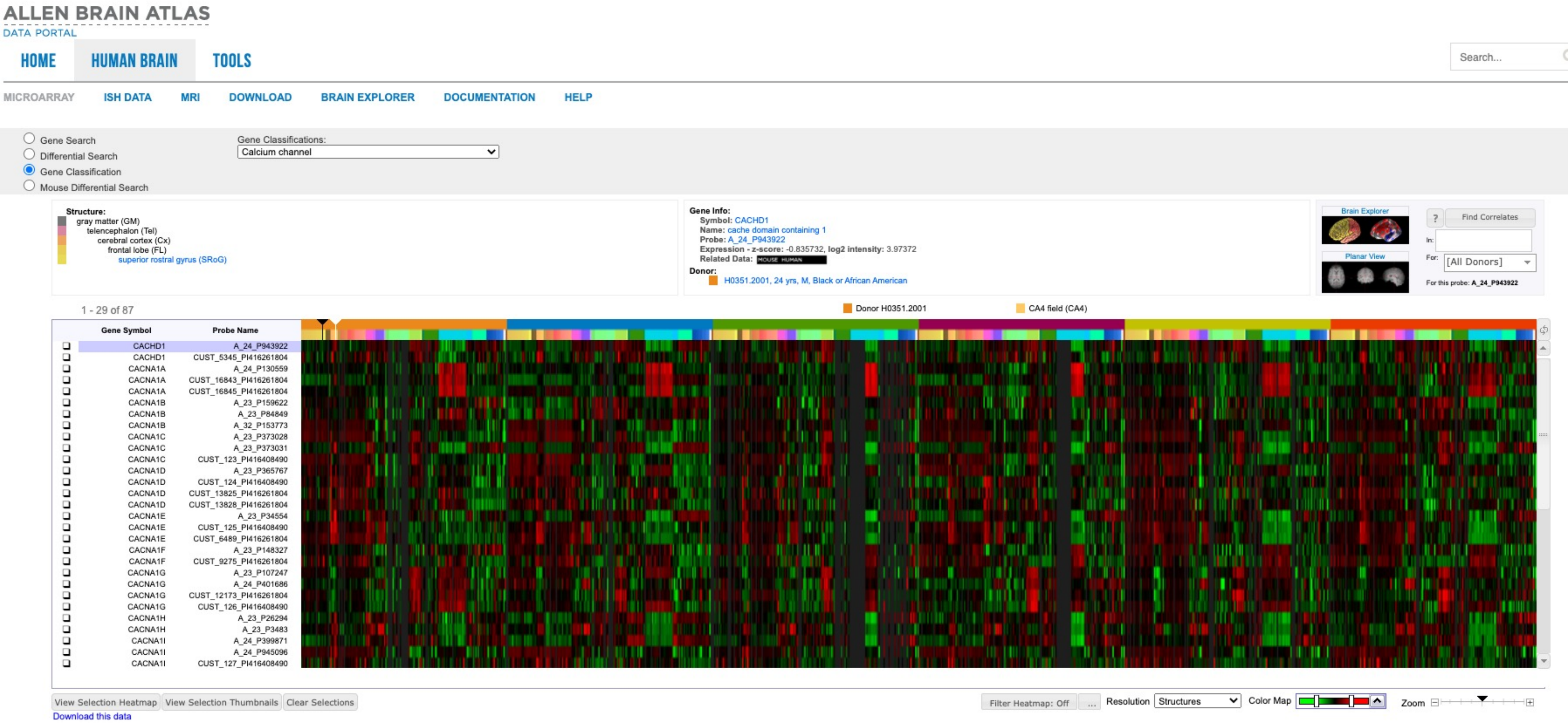

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Gene Classifications:
Calcium channel
Structure:
gray matter (GM)
telencephalon (Tel)
cerebral cortex (Cx)
frontal lobe (FL)
superior rostral gyrus (SRoG)
Gene Info:
Symbol: CACHD1
Name: cache domain containing 1
Probe: A_24_P943922
Expression - z-score: -0.835732, log2 intensity: 3.97372
Related Data: MOUSE HUMAN
Donor:
H0351.2001, 24 yrs, M, Black or African American
Brain Explorer
Planar View
Find Correlates
In:
For: [All Donors]
For this probe: A_24_P943922
1 - 29 of 87
Donor H0351.2001
CA4 field (CA4)
Gene Symbol
Probe Name
CACHD1 A_24_P943922
CACHD1 CUST_5345_PI416261804
CACNA1A A_24_P130559
CACNA1A CUST_16843_PI416261804
CACNA1A CUST_16845_PI416261804
CACNA1B A_23_P159622
CACNA1B A_23_P84849
CACNA1B A_32_P153773
CACNA1C A_23_P373028
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CACNA1I CUST_127_PI416408490
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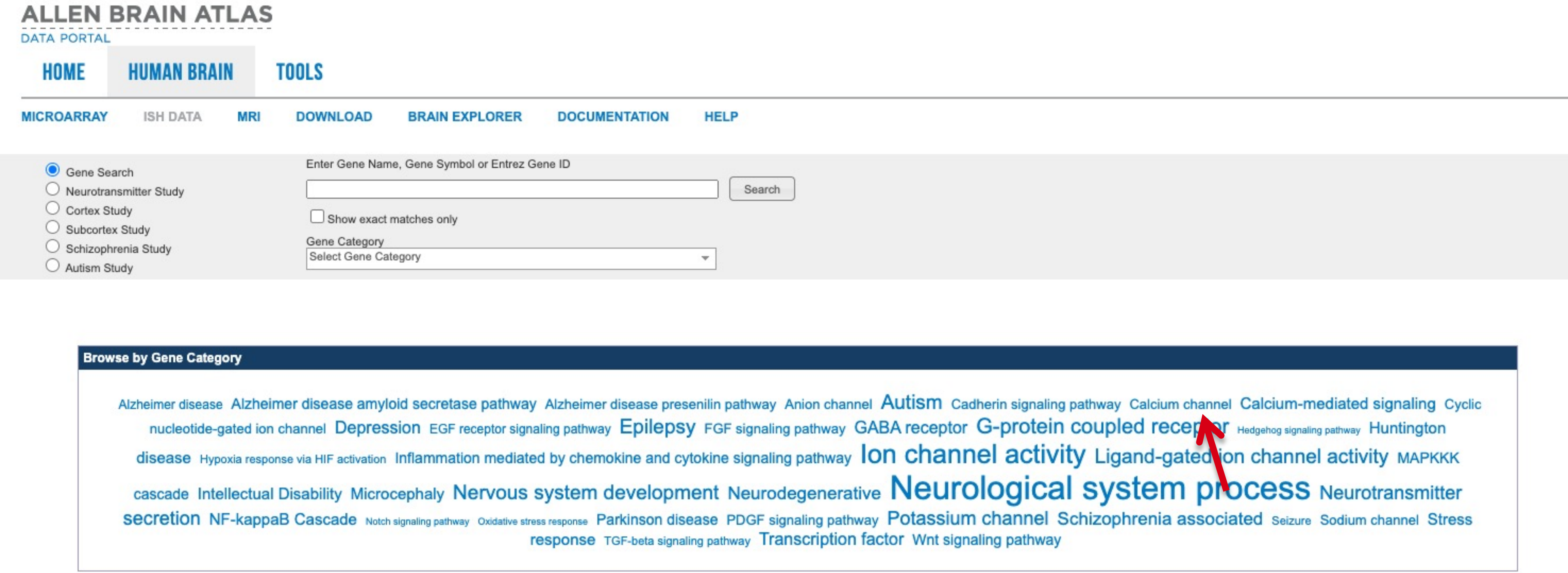
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- ( ) Neurotransmitter Study
- ( ) Cortex Study
- ( ) Subcortex Study
- ( ) Schizophrenia Study
- ( ) Autism Study

Enter Gene Name, Gene Symbol or Entrez Gene ID

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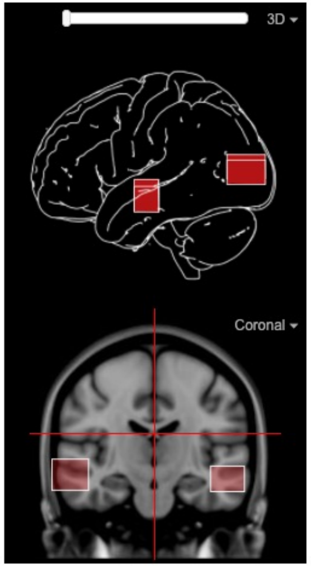
[ ] Show exact matches only

Gene Category
Calcium channel



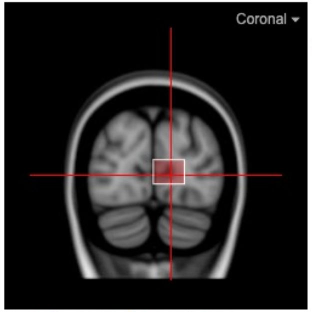
Blocks selected: 0 Clear Selections

Results table lists specimens with the data matching your search criteria

Click on a virtual block in the images above to further filter results

Specimen	Study	Donor	Tissue Location
78721338	Ctx	H07-0036, 46 yrs, Male, control	Visual cortex
7872139[illegible]	Ctx	H07-0036, 46 yrs, Male, control	Temporal cortex
78865009	Ctx	H07-0038, 31 yrs, Male, control	Visual cortex
78865025	Ctx	H07-0038, 31 yrs, Male, control	Temporal cortex
79205589	Ctx	H07-0050, 24 yrs, Male, control	Visual cortex
79205634	Ctx	H07-0050, 24 yrs, Male, control	Temporal cortex
79205713	Ctx	H07-0051, 44 yrs, Female, control	Temporal cortex
79368714	Ctx	H07-0065, 31 yrs, Male, control	Visual cortex
79489705	Ctx	H07-0068, 41 yrs, Male, control	Visual cortex
79489791	Ctx	H07-0069, 22 yrs, Male, control	Visual cortex
79489795	Ctx	H07-0069, 22 yrs, Male, control	Visual cortex
79489803	Ctx	H07-0069, 22 yrs, Male, control	Temporal cortex
79489807	Ctx	H07-0069, 22 yrs, Male, control	Temporal cortex
79851151	Ctx	H08-0006, 38 yrs, Female, control	Visual cortex
79851185	Ctx	H08-0006, 38 yrs, Female, control	Temporal cortex
79913142	Ctx	H08-0007, 42 yrs, Female, control	Visual cortex
79913161	Ctx	H08-0007, 42 yrs, Female, control	Temporal cortex
79946168	Ctx	H08-0010, 42 yrs, Male, control	Visual cortex
80168563	Ctx	H08-0010, 42 yrs, Male, control	Temporal cortex
80324388	Ctx	H08-0026, 35 yrs, Male, control	Temporal cortex
80324440	Ctx	H08-0027, 24 yrs, Male, control	Visual cortex
80324460	Ctx	H08-0027, 24 yrs, Male, control	Temporal cortex
80431286	Ctx	H08-0031, 21 yrs, Male, control	Visual cortex
80431306	Ctx	H08-0031, 21 yrs, Male, control	Temporal cortex
80431336	Ctx	H08-0032, 24 yrs, Male, control	Visual cortex
80431359	Ctx	H08-0032, 24 yrs, Male, control	Temporal cortex
80431493	Ctx	H08-0034, 41 yrs, Female, control	Visual cortex

Specimen H07-0036.01.02			
Age	46 yrs	Sex	M
Tissue Location	Visual cortex	Hemisphere	left
RNA Integrity	6.6	pH	6.6
Race	White or Caucasian	Handedness	unknown
Conditions	disease categories - control, smoker - yes		



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Section Information	
Gene	CACNG2
Experiment	78876416
Section Number	5
Treatments	ISH
Study	Human Brain ISH Cortex Study

Genes evaluated in this specimen

Select genes below to limit the images shown.

	Gene
☑	CACNG2
☑	CACNG3
☑	CACNG4
☑	CACNG5
☑	CACNG8
☐	CACNG1
☐	CARTPT
☐	CHRNA3
☐	CHRNA6
☐	CHRNA9
☐	CHRNB3

ISH Image

Symbol: **CACNG2**
Name: **calcium channel, voltage-dependent, ga...**

☑ Sync

1 of 14

section position within the specimen

Nearest Reference Image

Acronym:
Name:

☐ Add the 'CACNG2' experiment for this specimen to your selections

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This data is also available as XML

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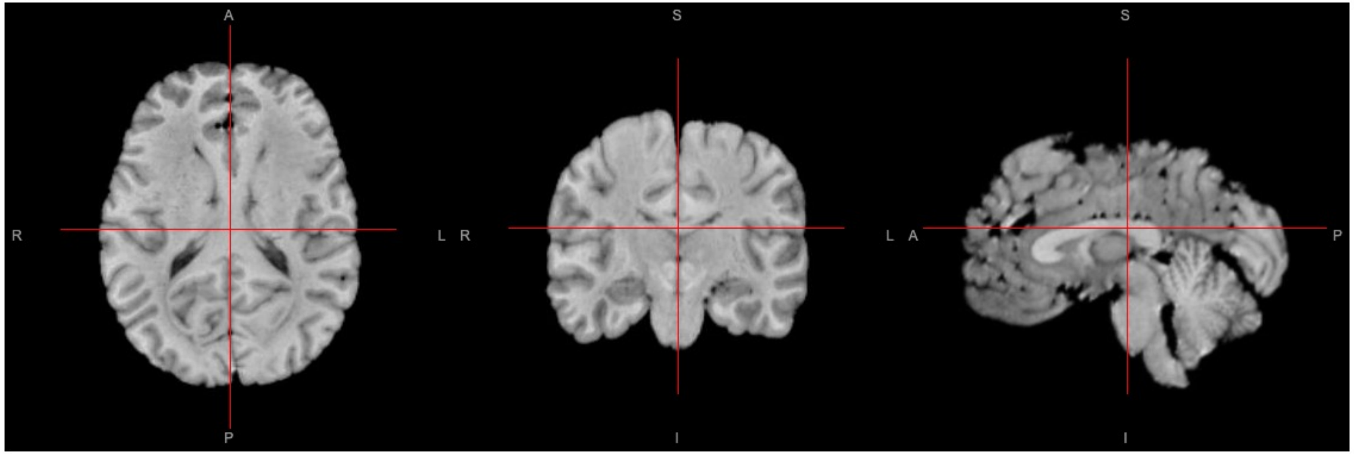
H0351.1009



1cm MNI Coordinate: 0, -18, 18 Structure: n/a

Donor	Age	Sex	Ethnicity	PMI (hours)	Image Files
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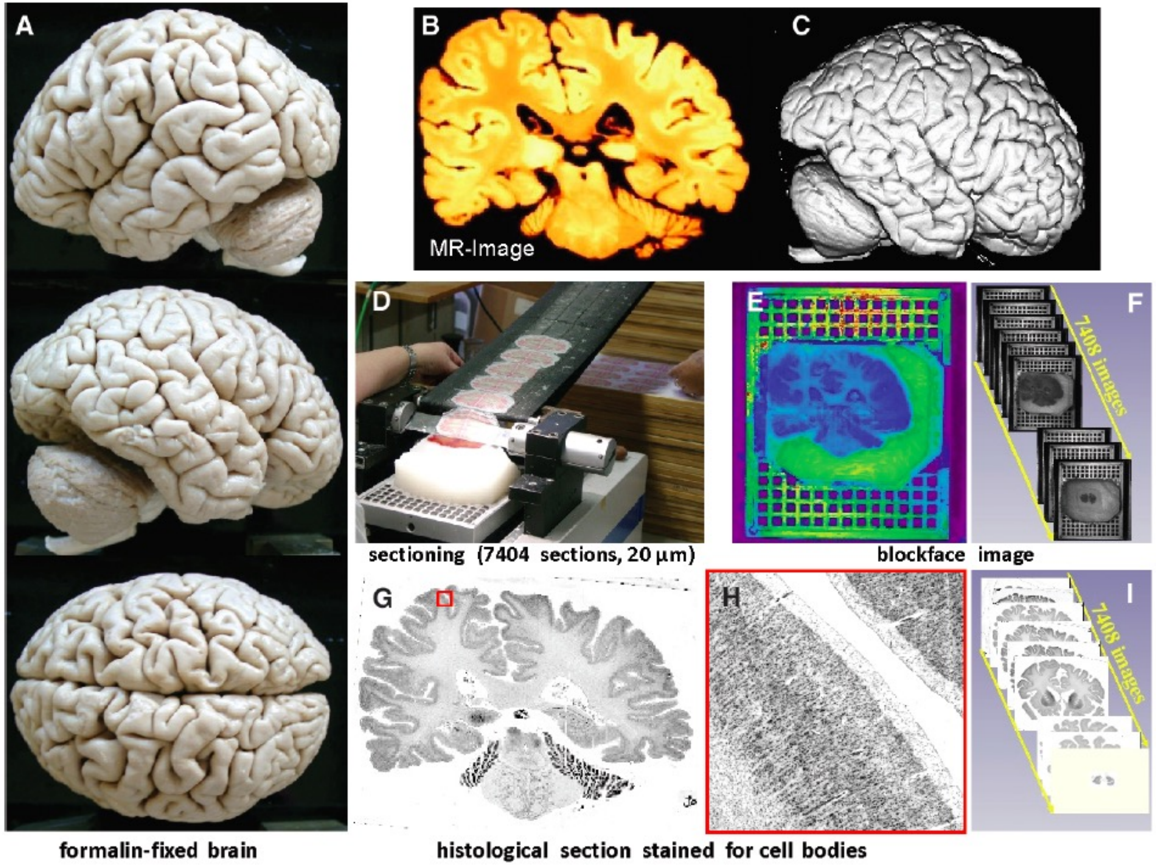
H0351.2002	39 yrs	M	Black or African American	10	DTI T1 T2
H372.0006	44 yrs	M	White or Caucasian	24	DTI T1 T2
H0351.2003	48 yrs	F	White or Caucasian	24	DTI T1 T2
H0351.1009	57 yrs	M	White or Caucasian	26	T1 T2
H0351.1012	31 yrs	M	White or Caucasian	17	T1 T2
H0351.1015	49 yrs	F	Hispanic	30	T1 T2
H0351.1016	55 yrs	M	White or Caucasian	18	T1 T2

Big Brain

Ultrahigh-resolution three-dimensional (3D) model of a human brain at nearly cellular resolution of 20 micrometers



Amunts et al., 2013

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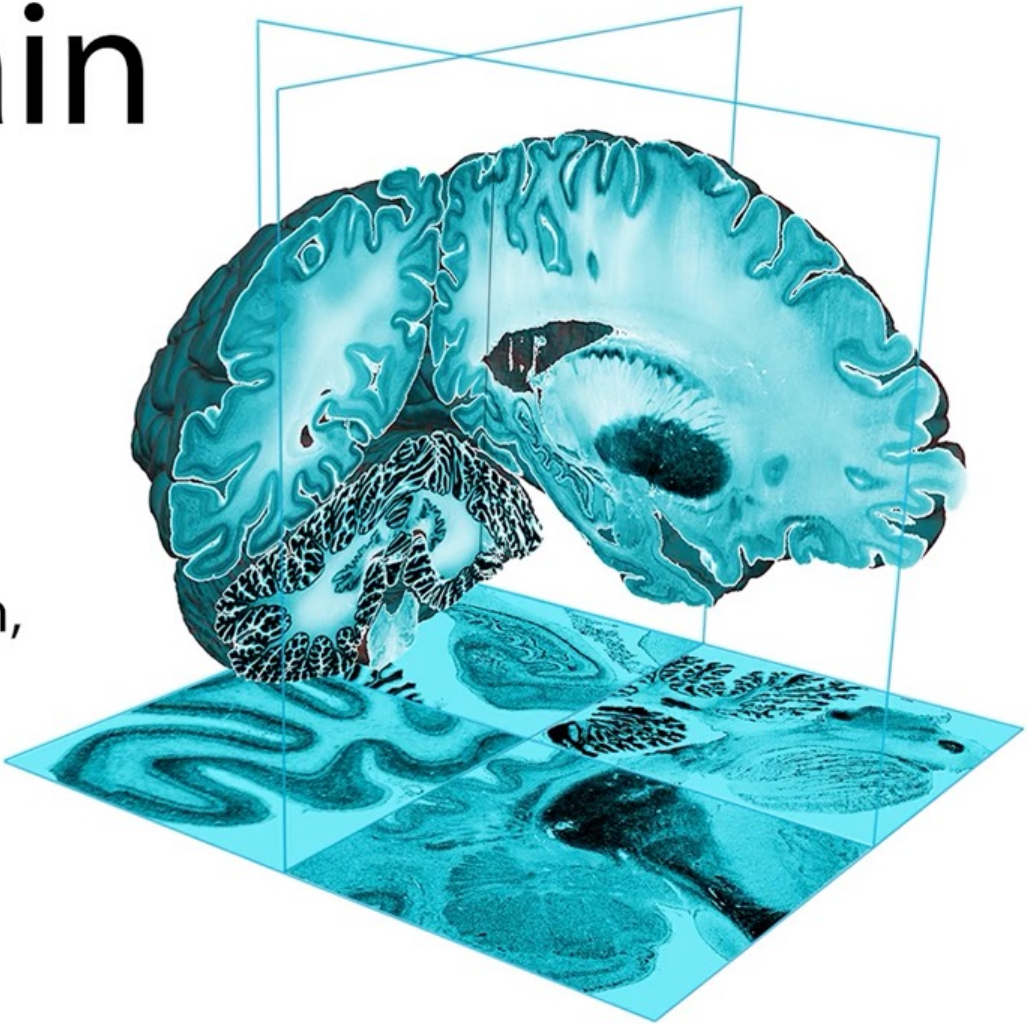
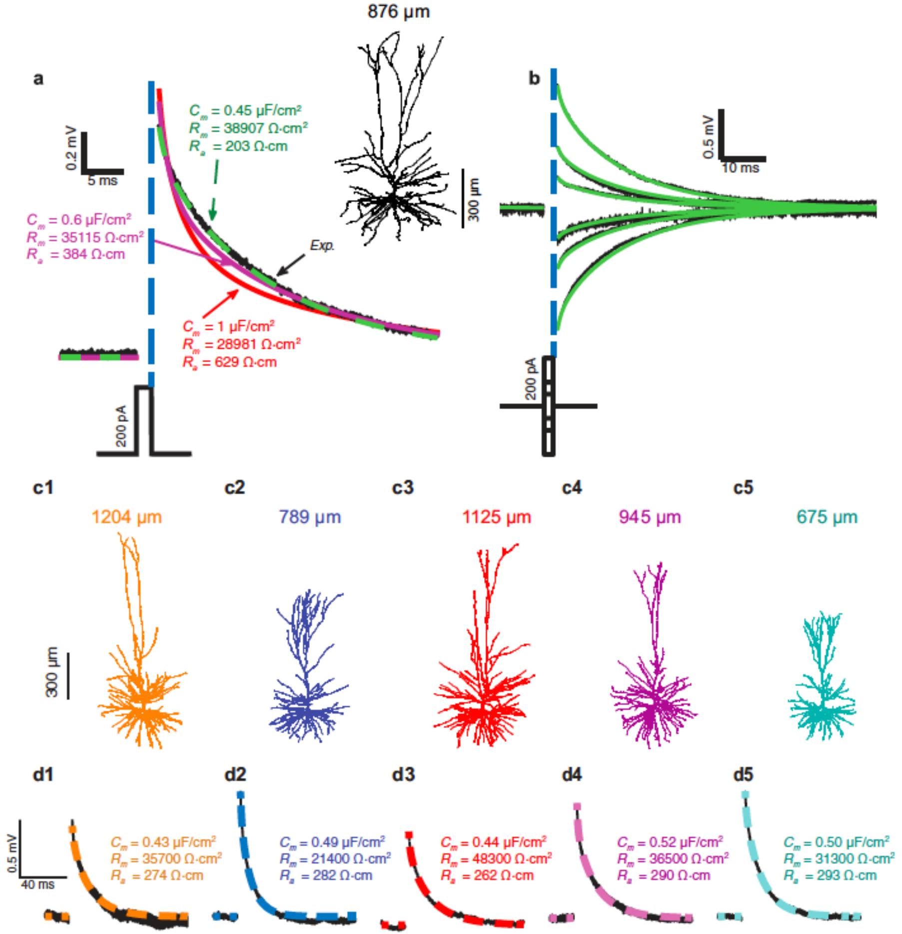
The BigBrain

- 65-year-old male
- 7,404 20-μm-thick coronal sections
- 10x10 μm^2 in-plane resolution, downsampled to 20 μm^3 isotropic resolution
- ~1 Tbyte storage



Human cell model

- L2/3 PCs from human temporal cortex
- Cm, Ra, Rm optimized with 'Multiple Run Fitter' tool of NEURON
- Cm of ~0.5 mF/cm^2, instead of 'universal' value of ~1 mF/cm^2
- such low Cm value significantly enhances both synaptic charge-transfer from dendrites to soma and spike propagation along the axon.



Eyal et al., 2016

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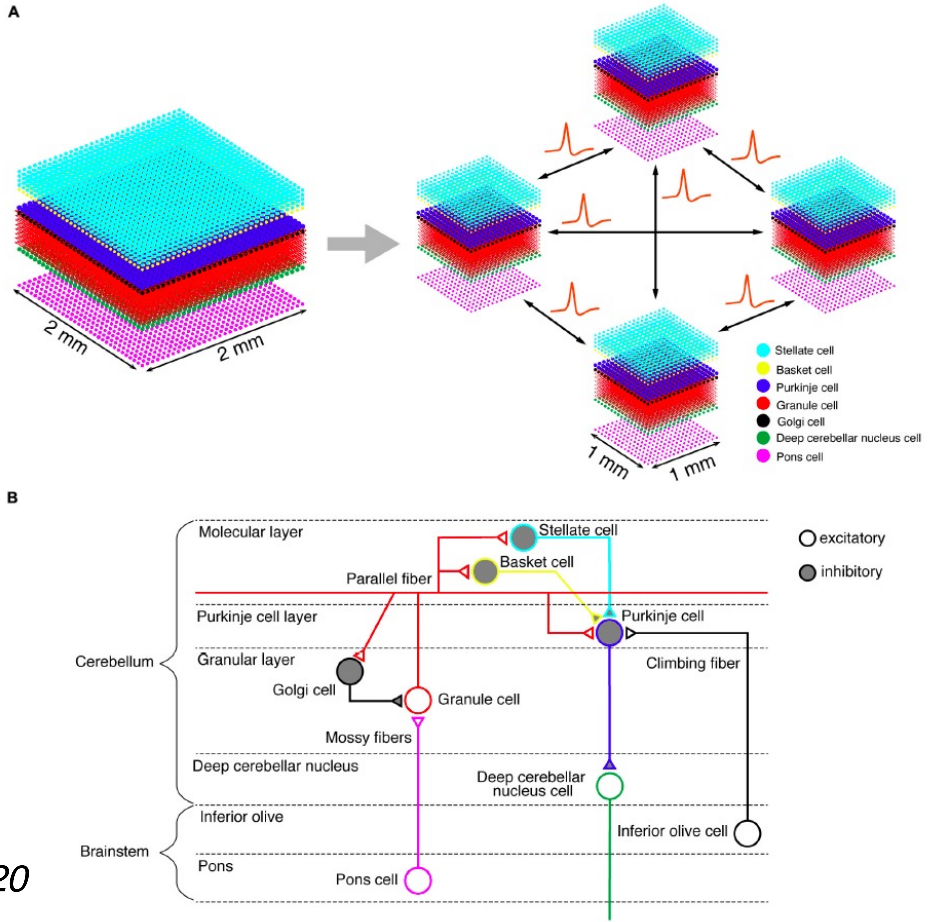
Human-Scale Cerebellar Network Model

- 68 billions of neurons (80% of the human brain)
- A tile of 1 mm^2 repeated
- Neurons were modeled as conductance-based leaky integrate-and-fire units
- Simplified volume
- Connections were set as a two dimensional Gaussian



Yamaura et al., 2020

The Virtual Brain

- Open-source cloud ecosystem on EBRAINS
- constructing, simulating and analyzing brain network models
- magnetic resonance imaging (MRI) processing pipelines
- multiscale co-simulation of spiking and large-scale networks
- Bayesian inference of epilepsy spread

www.thevirtualbrain.org

Summary 4

- We started to describe the human brain at cellular and subcellular level
- While the research proceeds slowly due to obvious ethical reasons, we can take advantage from decades of research on animal models
- The trends we observed in animal research also appear in the human research. Allen provided an extensive characterization of the gene expression, and Big Brain an high-resolution reconstruction of the human brain.
- Several models also appear, from detailed single neuron model (Eyal et al., 2016) to large scale models with leaky integrate-and-fire neurons (Yamaura et al., 2020) to neural-fields model of the whole brain (The Virtual Brain).

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Lecture Summary

- The last decades show the emergence of new groundbreaking techniques that provide unprecedent high-quality large data
- Mathematic tools and artificial intelligence allow us to extract salient information from the big data
- This, together with more efficient computers, allows us to build more realistic models of the brain
- Modeling the human brain remains challenging, yet it is already happening