Relating the structure of the brain to its function by tracking a net-wave of spikes up the visual hierarchy

Christof Koch

Chief Scientist

MindScope Program, Allen Institute

August 11th 2020

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Allen Brain Observatory - The Vision



- Record cellular level brain activity
- In a routine, reliable and high-throughput manner in behaving animals
- Several set of instruments
  - Multi-photon & multi-plane cellular fluorescent imaging
  - High-density electrical recordings

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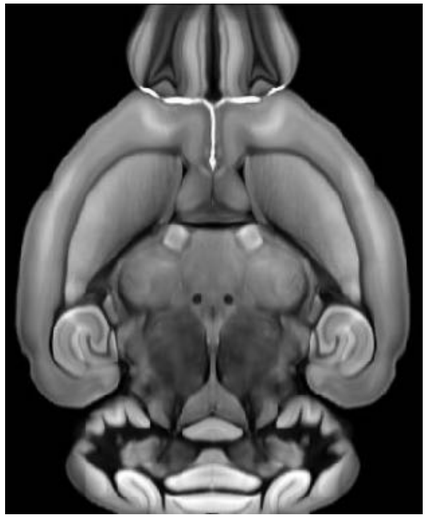
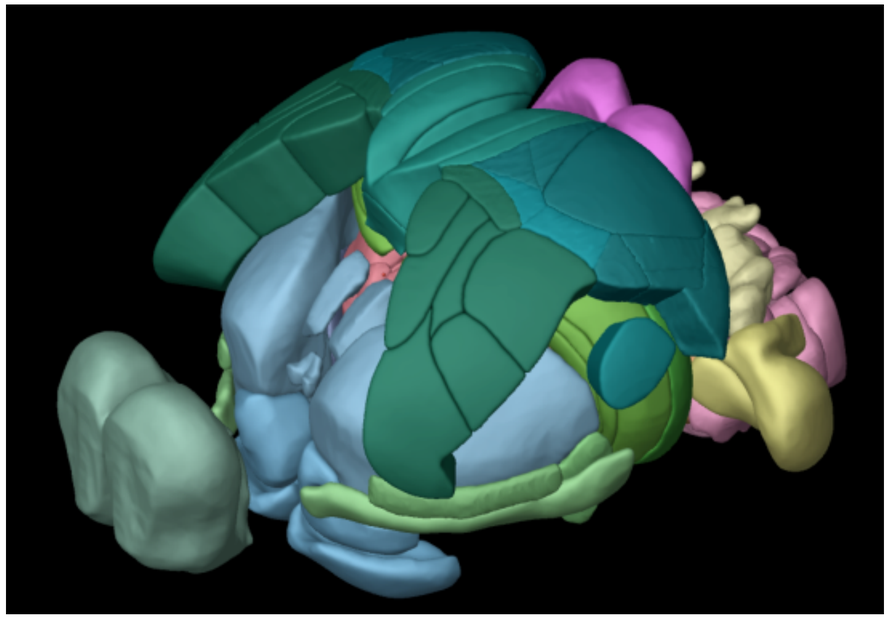
Koch & Reid *Nature* 2012

Common Coordinate Framework - CCFv3

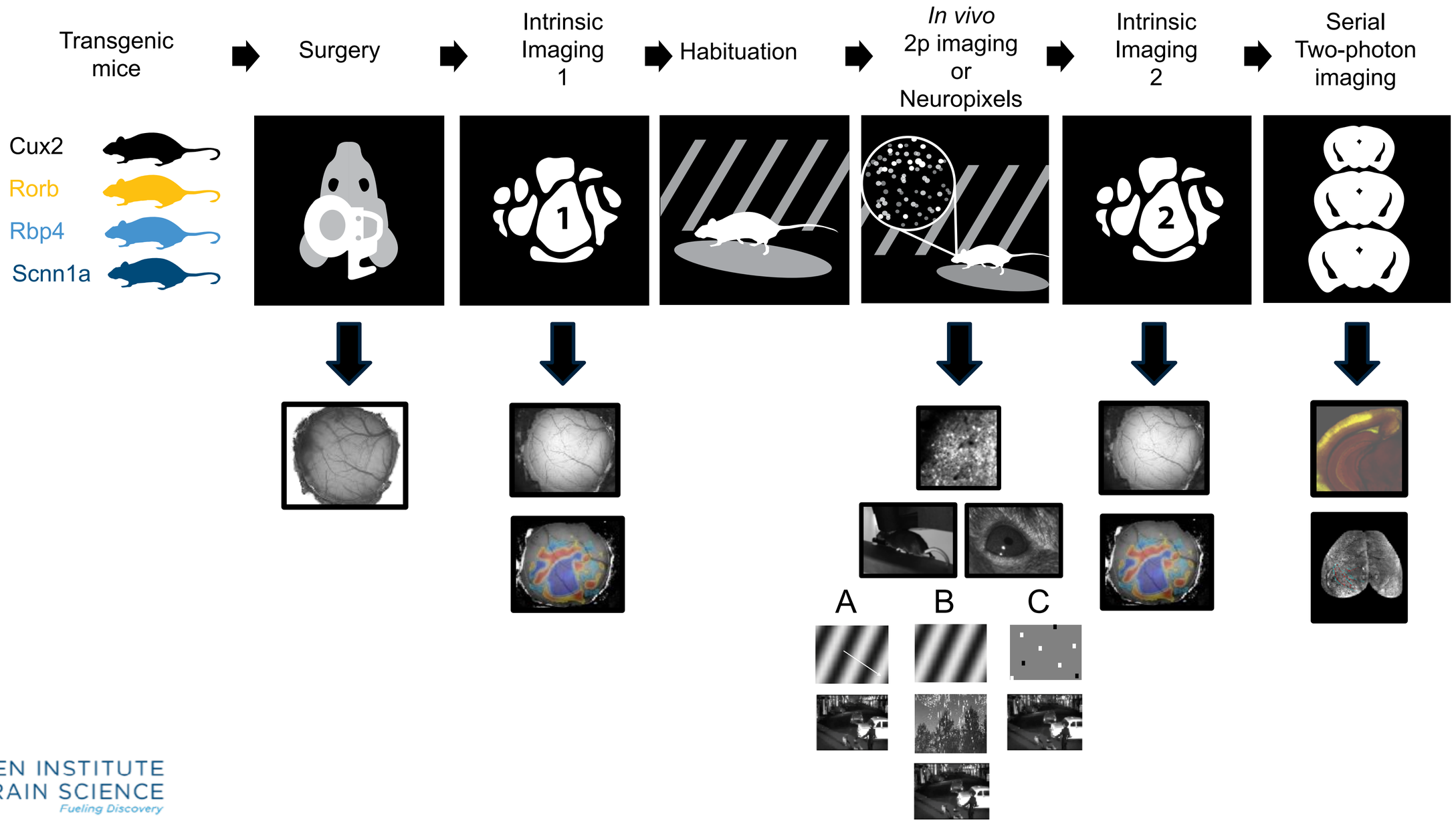


- True 3-D atlas with 500 million (10 μm)^3 pixels
- Based on brains of 1675 adult C57BL/6J mice
- 43 isocortical region, subdivided into layers
- 329 sub-cortical grey matter regions
- 81 fiber (white matter) structures
- Everything we do uses the CCFv3



Wang *et al. Cell* 2020

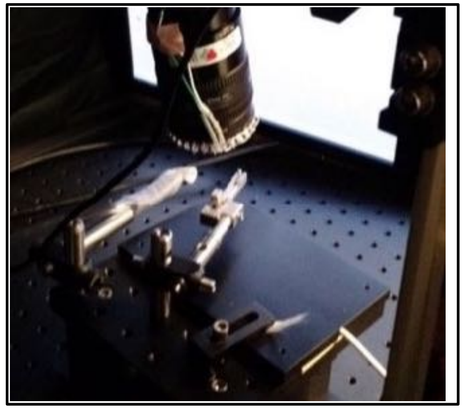
A High-Throughput Pipeline I



A High-Throughput Pipeline II



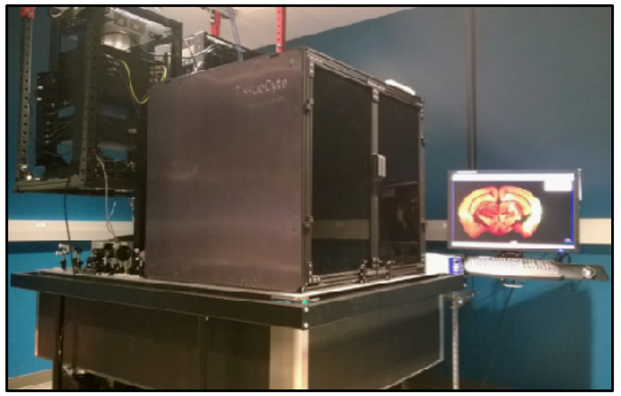
Surgery



Intrinsic imaging



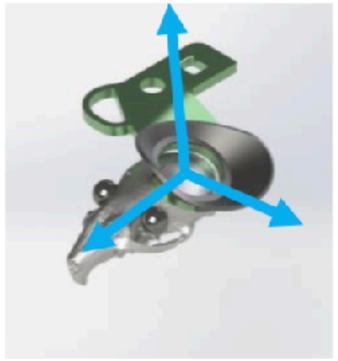
In vivo 2p Imaging or Neuropixels



Serial two-photon tomography

High-Resolution Cross-Platform Registration

Headframe



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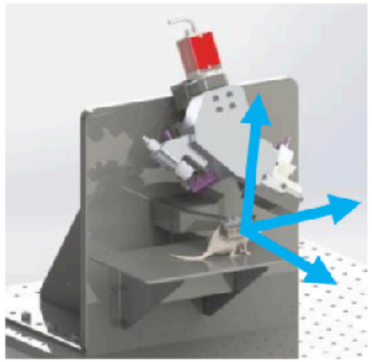
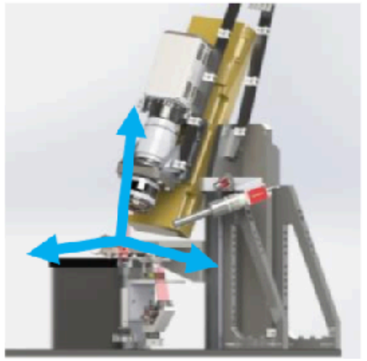
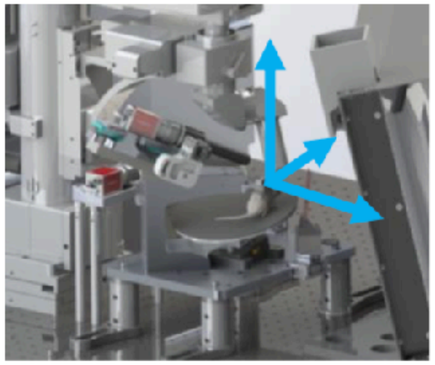


ISI



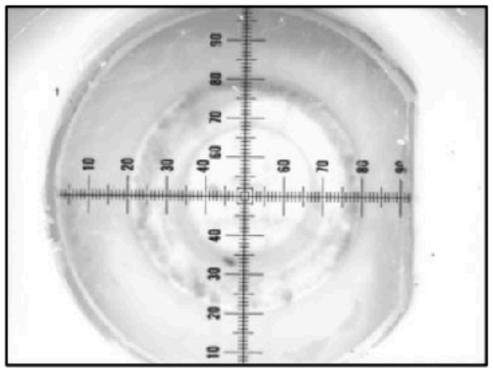
Physiology



Headframe Reticle



Surgery



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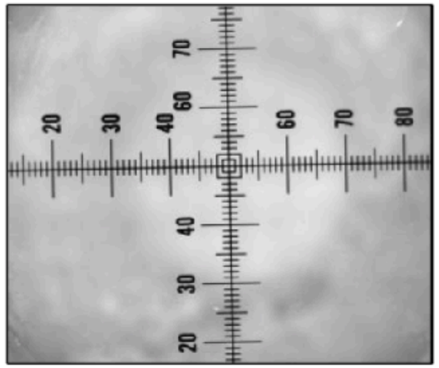
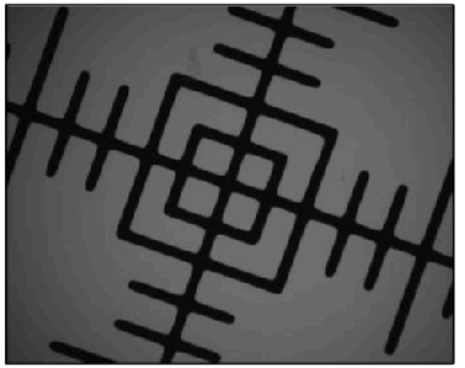
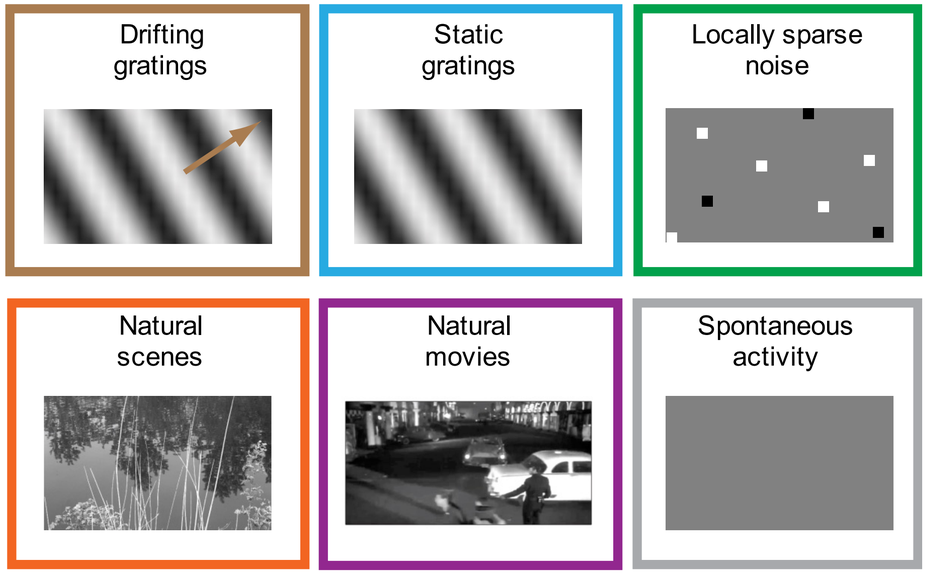
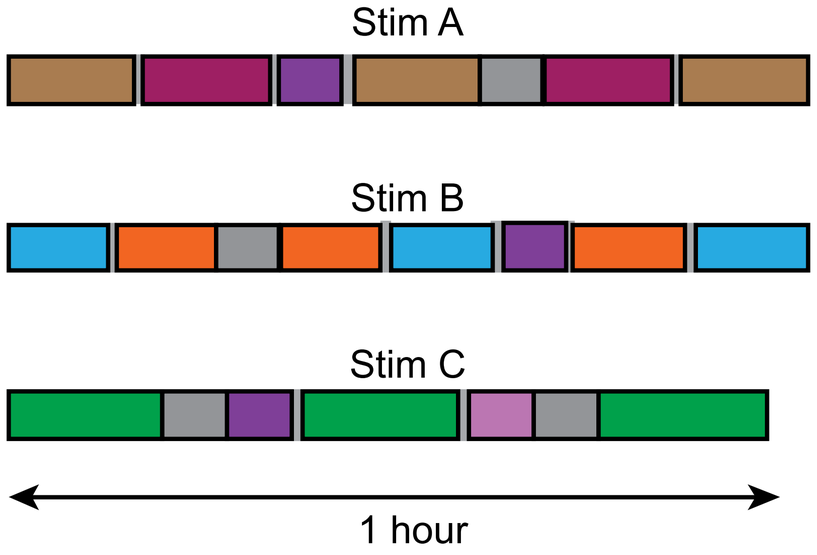


Physiology



Visual Coding - Multiple Hours of Visual Stimuli





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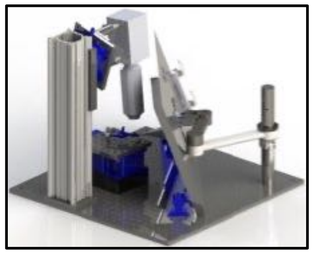
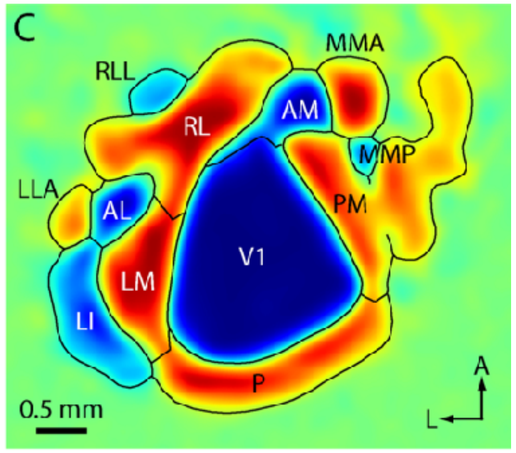
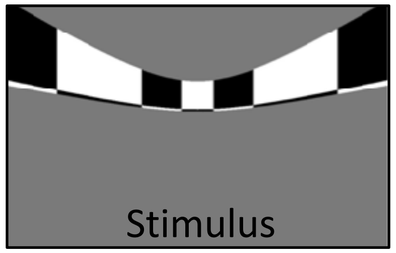
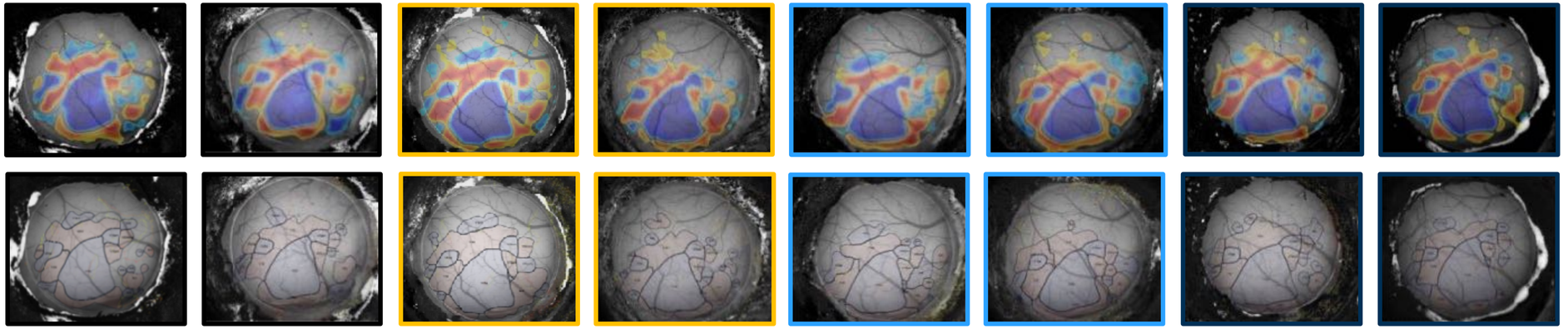
A High-Throughput Pipeline III







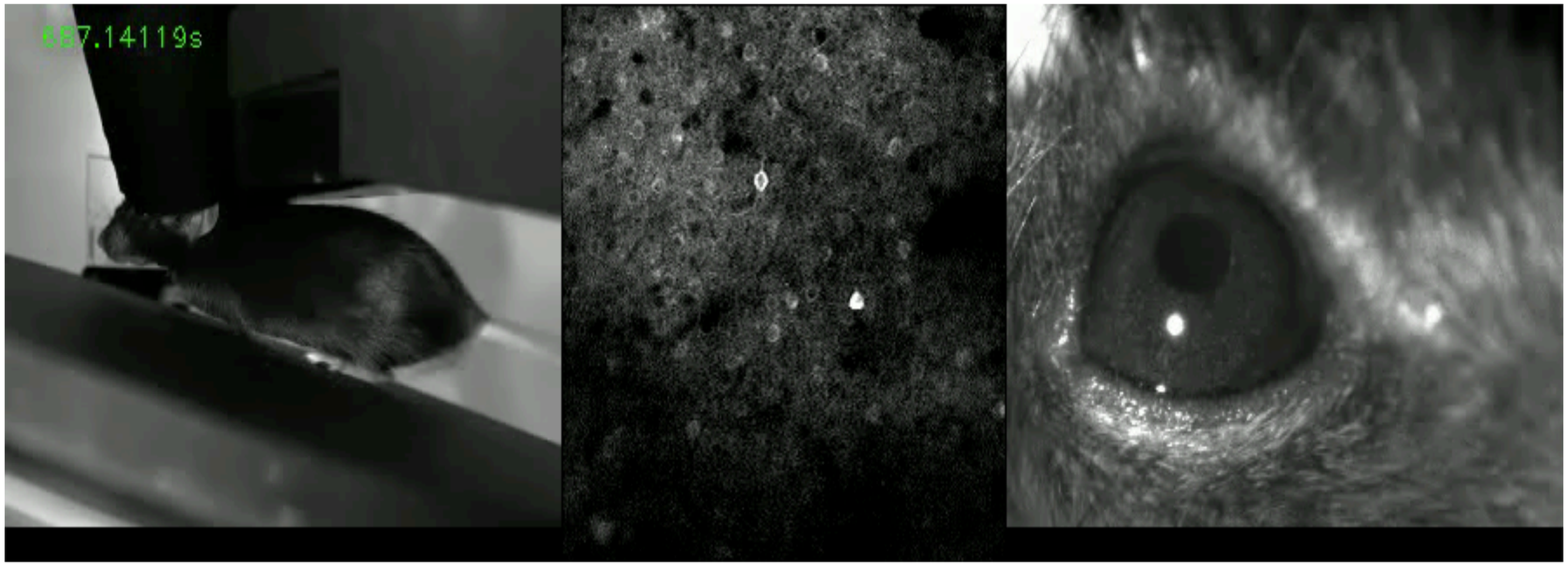


Cux2 Rorb Rbp4 Scnn1a

Intrinsic Signal Imaging for Every Experiment

Zhuang *et al*. *eLife* 2017

Watching the Brain of a Mouse
Watching A Touch of Evil



One experiment in a transgenic mouse (AL – Cux2 – Layer 2/3)

~60,000 cells at www.brain-map.org

Show filters | Clear filters | Current Filters: Experiment ID = 511510940 | Add/Remove Columns: Showing 16 of 19

Sort: P value - static gratings

Showing rows 1 through 4 of 285

Brain area	Cre driver	Imaging depth	Static gratings	Drifting gratings	Natural scenes	Locally sparse noise - off	Locally sparse noise - on	Natural
VISpm	Cux2-CreERT2	275	p: <= 0.001 osi: 0.86 po: 0 pp: 0.00 psf: 0.02 ttp: 0.30	p: 0.33 osi: NA pd: NA dsi: NA ptf NA	p: <= 0.001 pii 115 ttp 0.30			
VISpm	Cux2-CreERT2	275	p: <= 0.001 osi: 1.81 po: 150 pp: 0.50 psf: 0.16 ttp: 0.37	p: <= 0.001 osi: 0.96 pd: 270 dsi: 0.78 ptf 4	p: <= 0.001 pii 77 ttp 0.23			
VISpm	Cux2-CreERT2	275	p: <= 0.001 osi: 1.31 po: 90 pp: 0.50 psf: 0.08 ttp: 0.43	NA	p: <= 0.001 pii 106 ttp 0.23	NA	NA	
VISpm	Cux2-CreERT2	275	p: <= 0.001 osi: 0.87 po: 30 pp: 0.75 psf: 0.04 ttp: 0.20	p: <= 0.001 osi: 0.68 pd: 315 dsi: NA ptf 1	p: <= 0.001 pii 86 ttp 0.30			

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de Vries *et al. Nature Neurosci.* 2019

Neurodata Without Borders Standard

- Consortium project to develop a unified data format for neurophysiology data to breakdown barriers to data and tool sharing
- Standardized schema for data and metadata implemented in HDF5
- www.nwb.org
- Ecosystem of standards, tools, and methods for managing, storing, sharing, and analyzing complex neurophysiology data.

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hhmi janelia Research Campus

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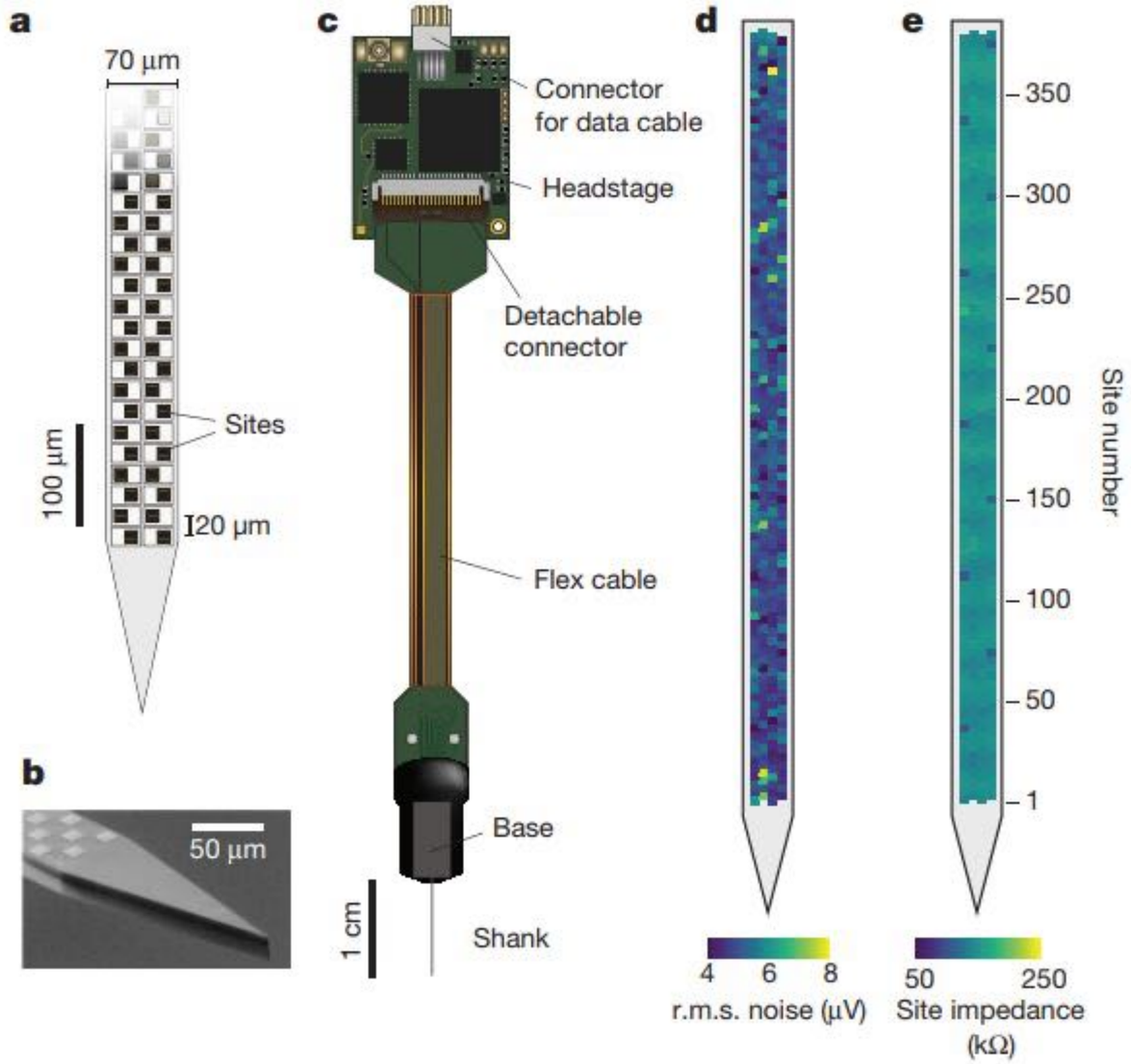
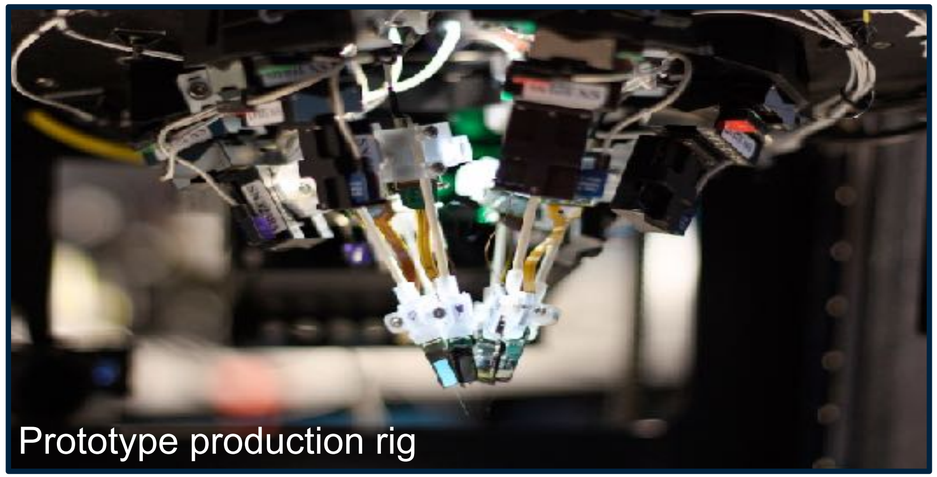
THE KAVLI FOUNDATION

Teeters *et al. Neuron* 2015

Neuropixels

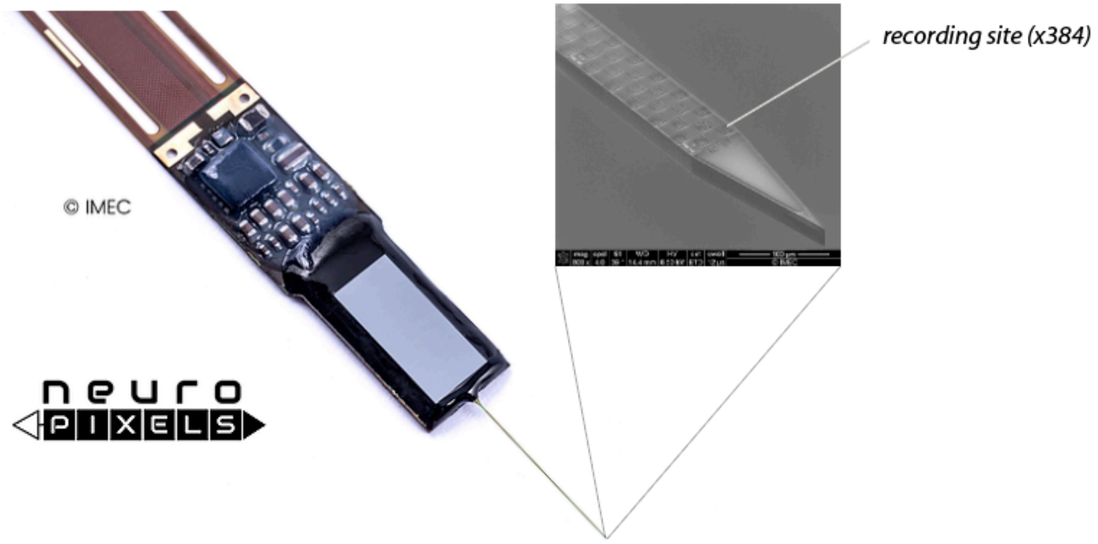



Prototype production rig

- 384 out of 966 selectable electrical pixels, ~7 µV
- 20 µm spacing
- Amplifiers, multiplexers and digitizers are in the base
- 1 gigabyte/min data rate weighting 0.25 gr

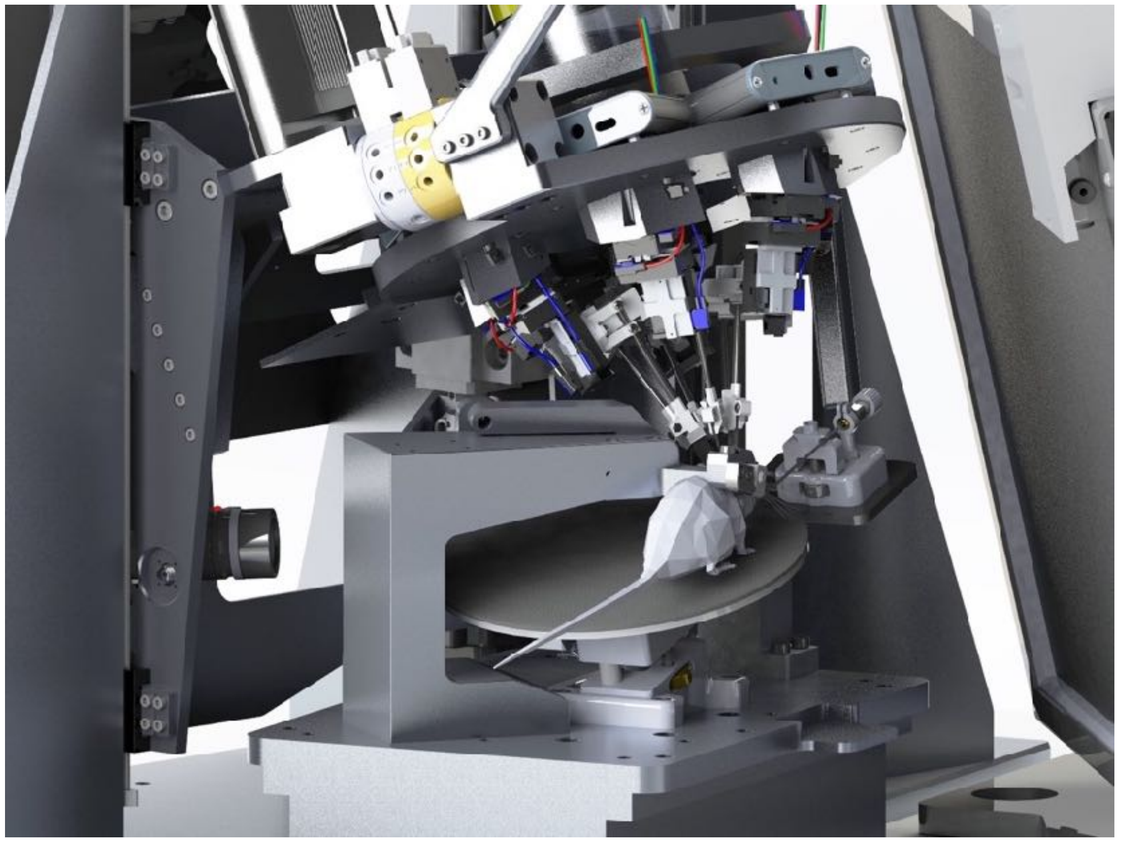
Jun *et al. Nature* 2017

Neuropixels Pipeline



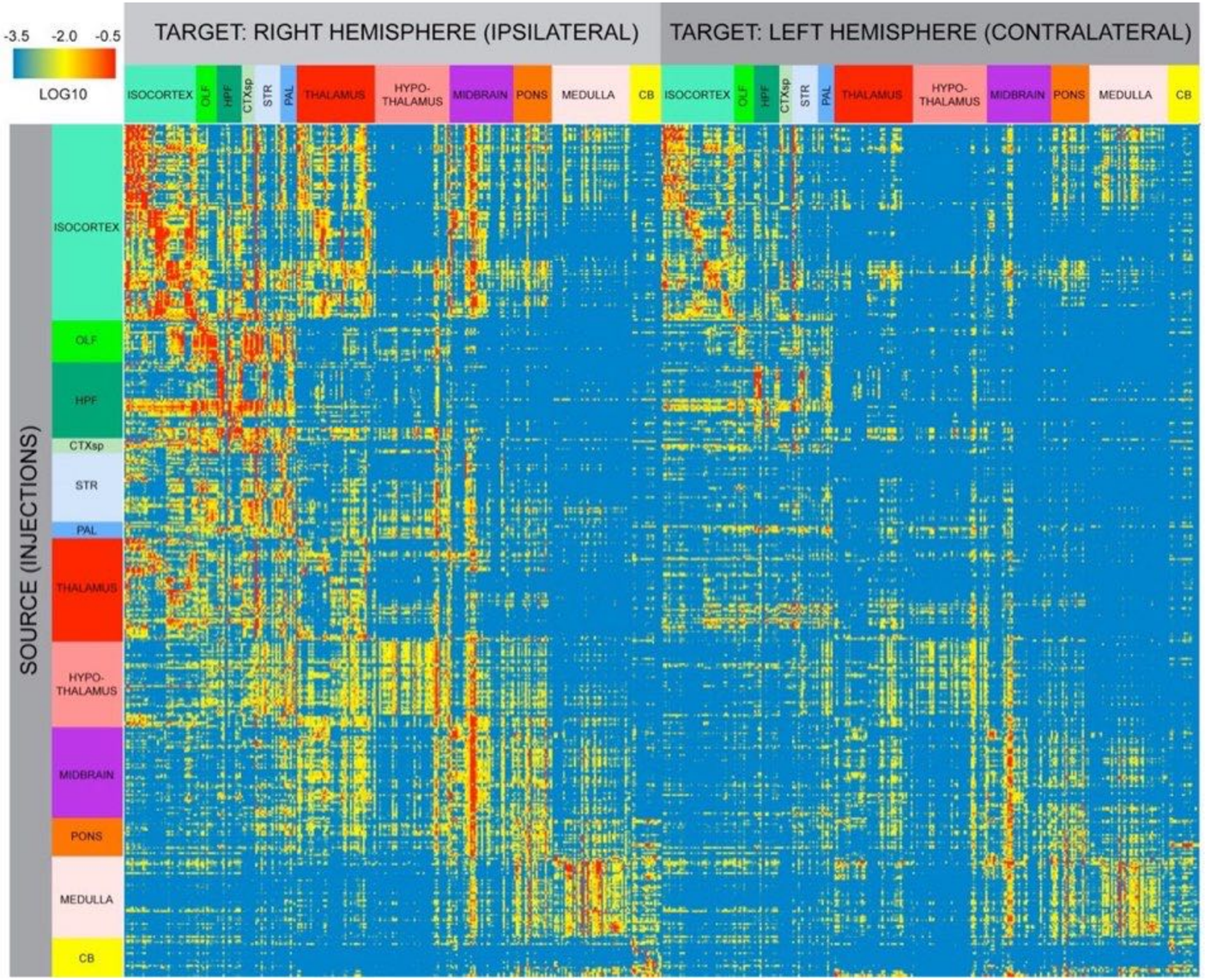


Transgenic mice | Surgery | Intrinsic imaging | Habituation | Ephys | Optical projection tomography

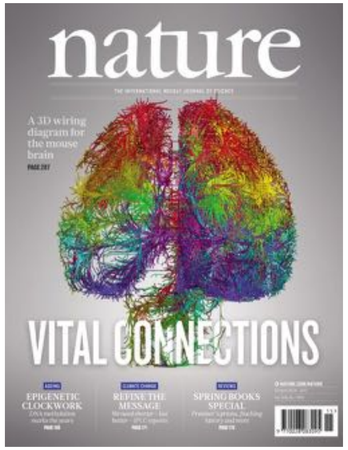


Ephys pipeline rig. Custom-built rig positions six Neuropixels probes over visual cortex. The running wheel and visual stimuli are the same as those used in the 2P Brain Observatory.

Whole Brain Connectivity



An injected brain region in one of 495 mice



Oh *et al. Nature* 2012

One of 295 brain regions

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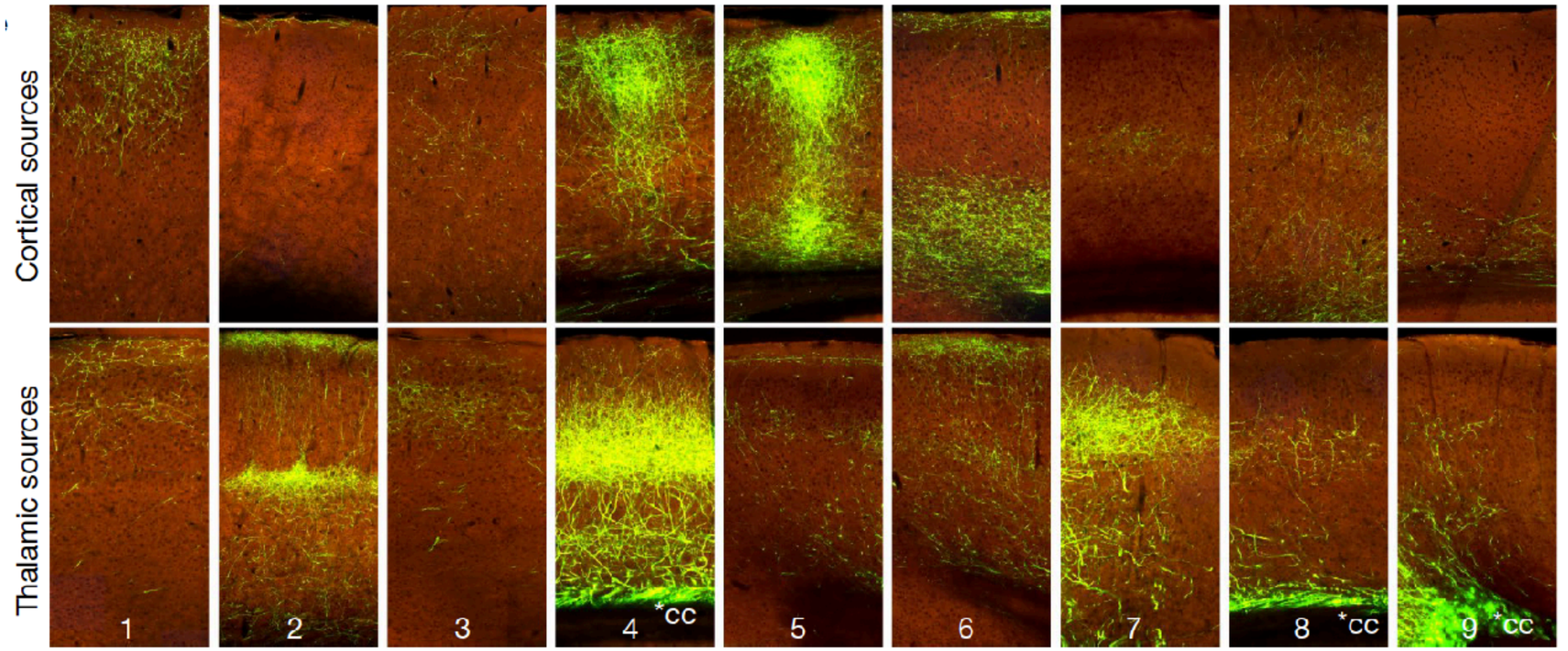
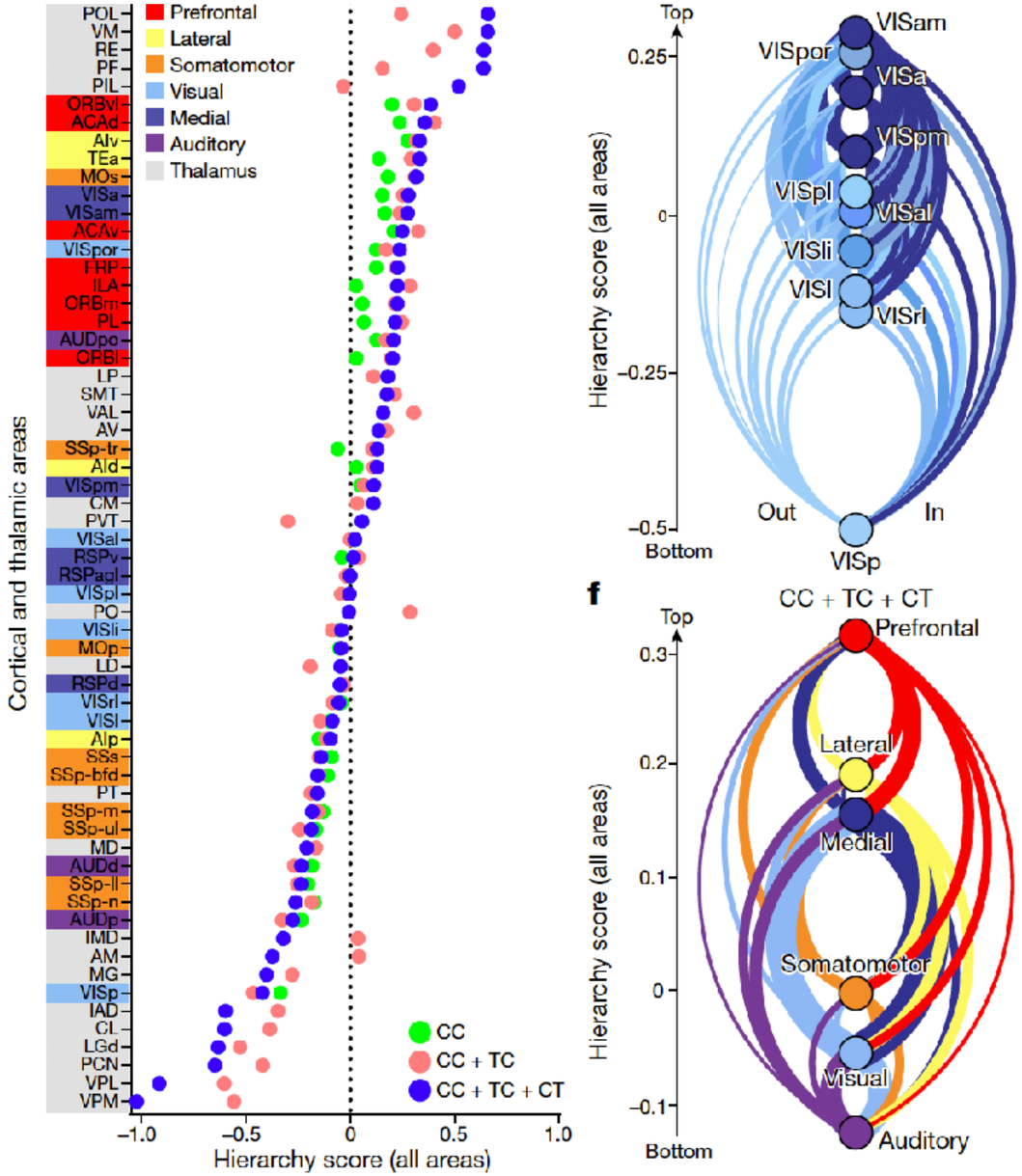
Hierarchical Organization of Cortico-Thalamic Connectivity



- Anterograde viral tracing with Cre-dependent AVV in 1,256 experiments in 50 distinct mouse lines
- We performed unsupervised hierarchical clusering of 849 cortical and 81 thalamic experiments to identify nine types of feed-forward and feed-back connections

Harris, Mihalas *et al. Nature* 2019

Hierarchical Organization of Cortico-Thalamic Connectivity



- Optimized hierarchy for 37 cortical areas & 24 thalamic nuclei
- Most thalamic nuclei are either at the bottom or the top
- V1 (VISp) is at the bottom and prefrontal area ORBvl at the top
- The hierarchy is a shallow one, with < two full levels

Harris, Mihalas *et al. Nature* 2019

A Survey of Spiking Activity in the Visual System

bioRxiv preprint first posted online Oct. 16, 2019; doi: http://dx.doi.org/10.1101/805010. The copyright holder for this preprint (which was not peer-reviewed) is the author/funder, who has granted bioRxiv a license to display the preprint in perpetuity. It is made available under a CC-BY-NC-ND 4.0 International license.

Neuropixels Survey of the Mouse Visual System

A survey of spiking activity reveals a functional hierarchy of mouse corticothalamic visual areas

Joshua H. Siegle[1,6]*, Xiaoxuan Jia[1,6]*, Séverine Durand[1], Sam Gale[1], Corbett Bennett[1], Nile Graddis[1], Greggory Heller[1], Tamina K. Ramirez[1], Hannah Choi[1,2], Jennifer A. Luviano[1], Peter A. Groblewski[1], Ruweida Ahmed[1], Anton Arkhipov[1], Amy Bernard[1], Yazan N. Billeh[1], Dillan Brown[1], Michael A. Buice[1], Nicolas Cain[1], Shiella Caldejon[1], Linzy Casal[1], Andrew Cho[1], Maggie Chvilicek[1], Timothy C. Cox[3], Kael Dai[1], Daniel J. Denman[1,4], Saskia E. J. de Vries[1], Roald Dietzman[1], Luke Esposito[1], Colin Farrell[1], David Feng[1], John Galbraith[1], Marina Garrett[1], Emily C. Gelfand[1], Nicole Hancock[1], Julie A. Harris[1], Robert Howard[1], Brian Hu[1], Ross Hytnen[1], Ramakrishnan Iyer[1], Erika Jessett[1], Katelyn Johnson[1], India Kato[1], Justin Kiggins[1], Sophie Lambert[1], Jerome Lecoq[1], Peter Ledochowitsch[1], Jung Hoon Lee[1], Arielle Leon[1], Yang Li[1], Elizabeth Liang[1], Fuhui Long[1], Kyla Mace[1], Jose Melchior[1], Daniel Millman[1], Tyler Mollenkopf[1], Chelsea Nayan[1], Lydia Ng[1], Kiet Ngo[1], Thuyahn Nguyen[1], Philip R. Nicovich[1], Kat North[1], Gabriel Koch Ocker[1], Doug Ollerenshaw[1], Michael Oliver[1], Marius Pachitariu[5], Jed Perkins[1], Melissa Reding[1], David Reid[1], Miranda Robertson[1], Kara Ronellenfitch[1], Sam Seid[1], Cliff Slaughterbeck[1], Michelle Stoecklin[1], David Sullivan[1], Ben Sutton[1], Jackie Swapp[1], Carol Thompson[1], Kristen Turner[1], Wayne Wakeman[1], Jennifer D. Whitesell[1], Derric Williams[1], Ali Williford[1], Rob Young[1], Hongkui Zeng[1], Sarah Naylor[1], John W. Phillips[1], R. Clay Reid[1], Stefan Mihalas[1], Shawn R. Olsen[1,7]*, Christof Koch[1,7]

All data - 100,000 units, registered to CCFv3, with > 2 billion spikes - at www.brain-map.org

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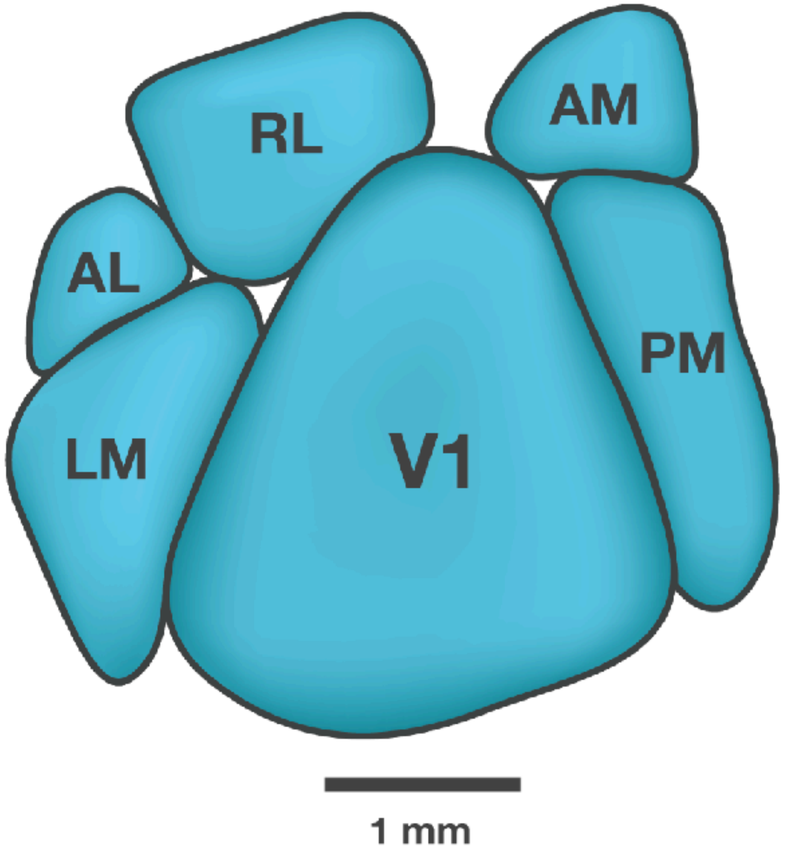
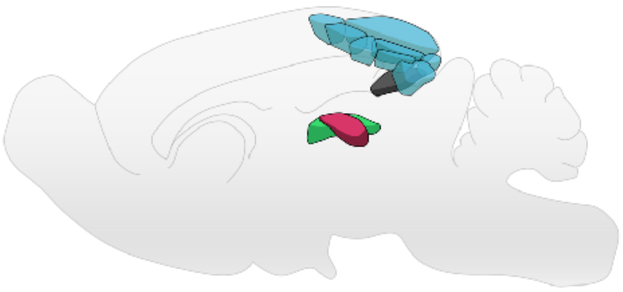
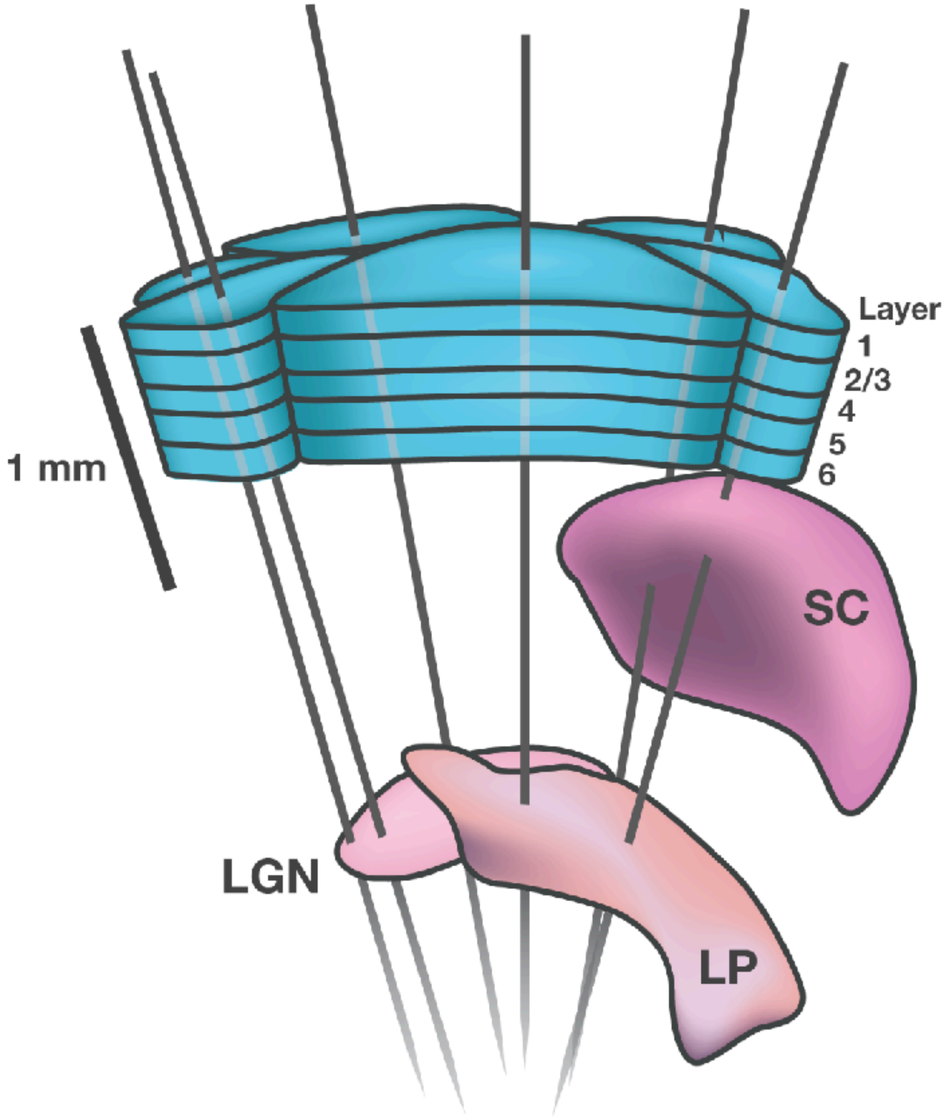
Multiarea Neuropixels Recordings







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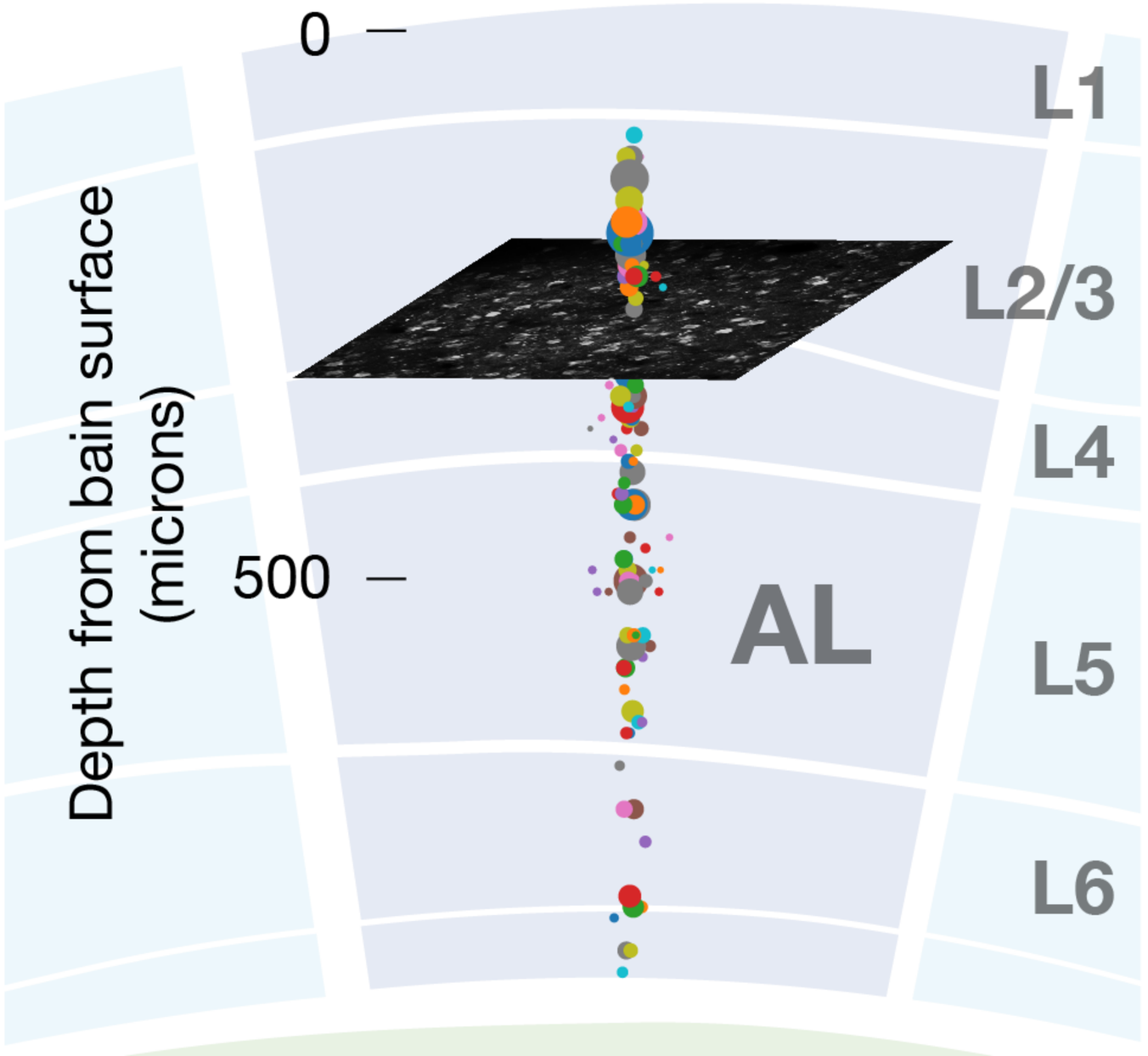
Recording Throughout the Brain



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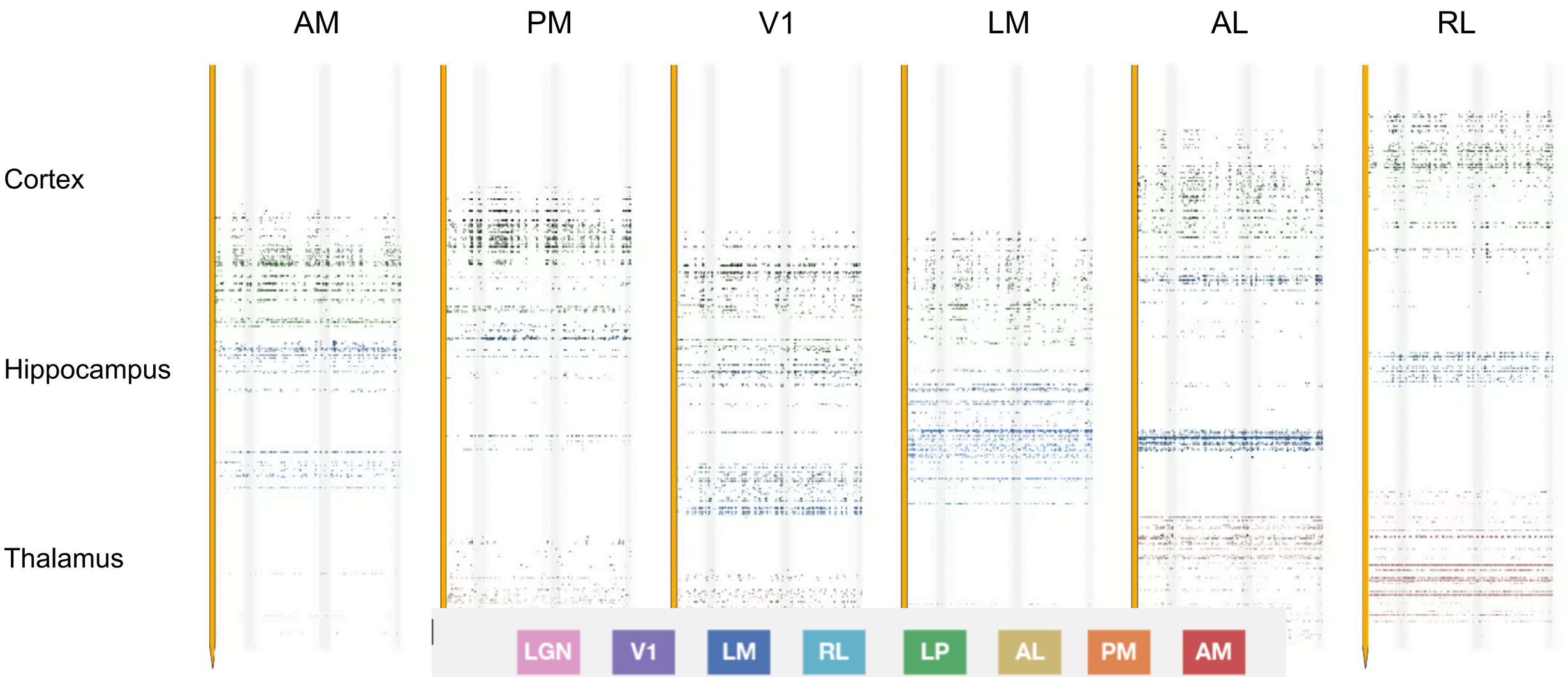
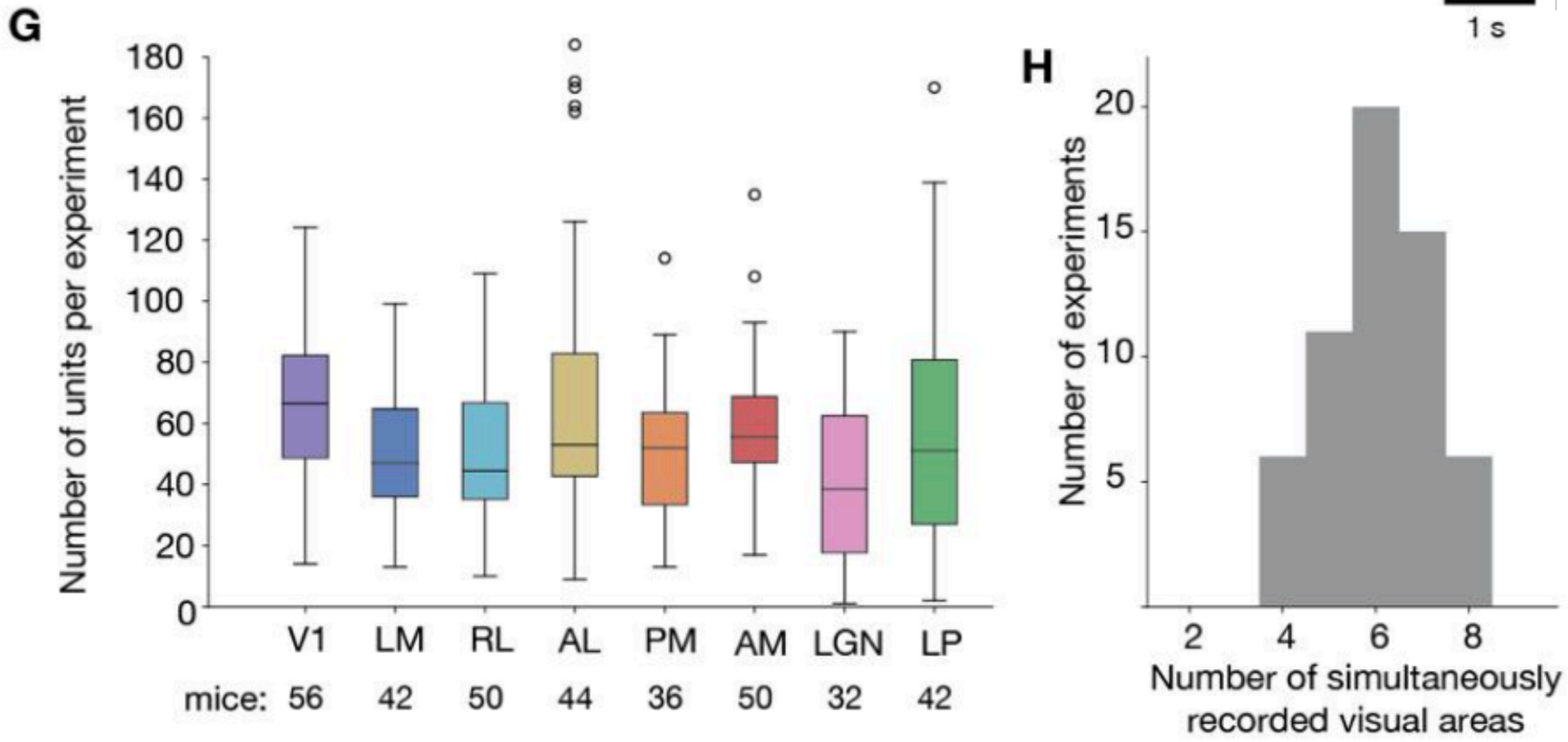
Recording >1000 Neurons Across 10 Visual Regions



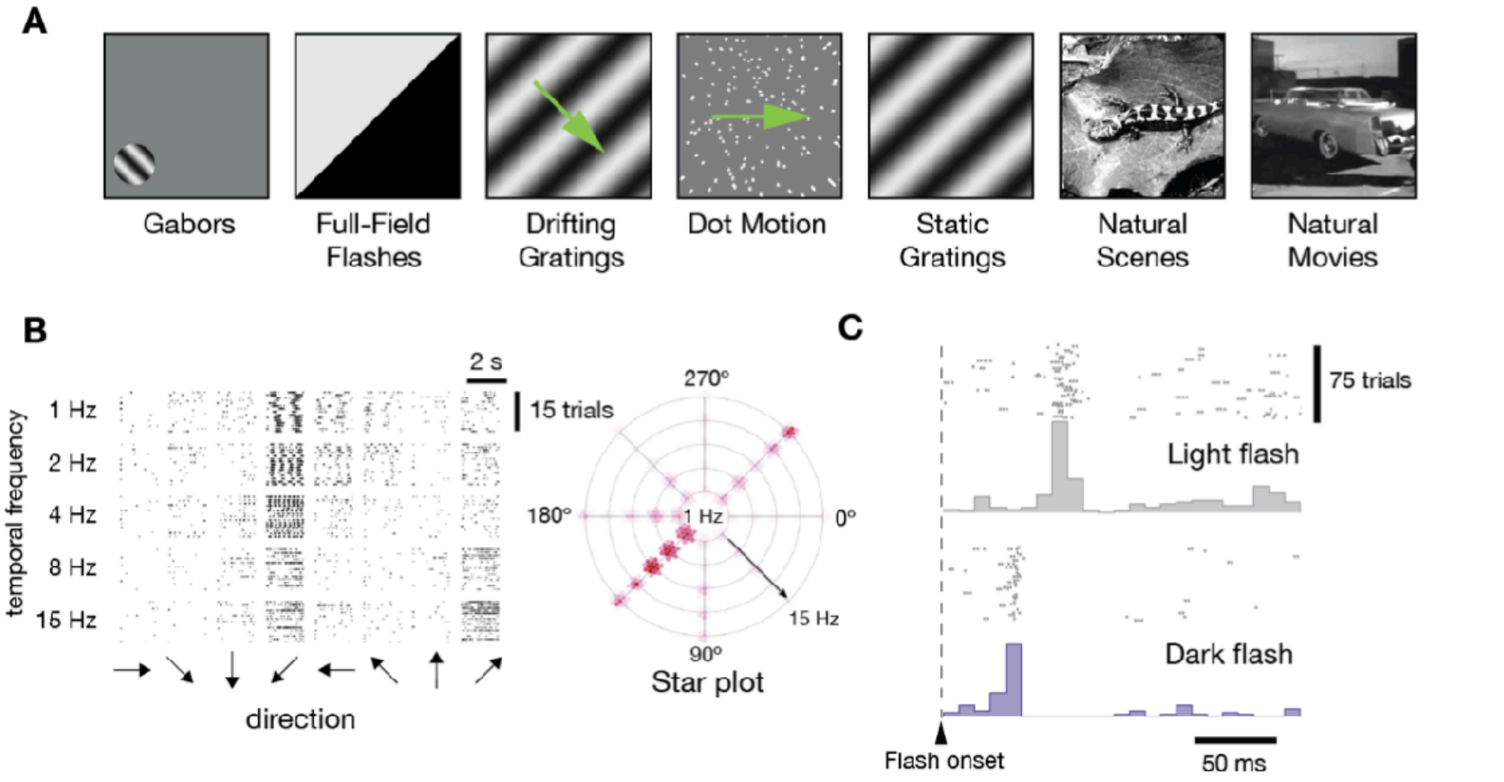
	LGN	V1	LM	RL	LP	AL	PM	AM
units:	1209	5529	2892	3065	2046	3714	2188	3491
mice:	32	54	42	49	40	44	35	50

Siegle, Jia … Olsen & Koch *bioRxiv* 2019

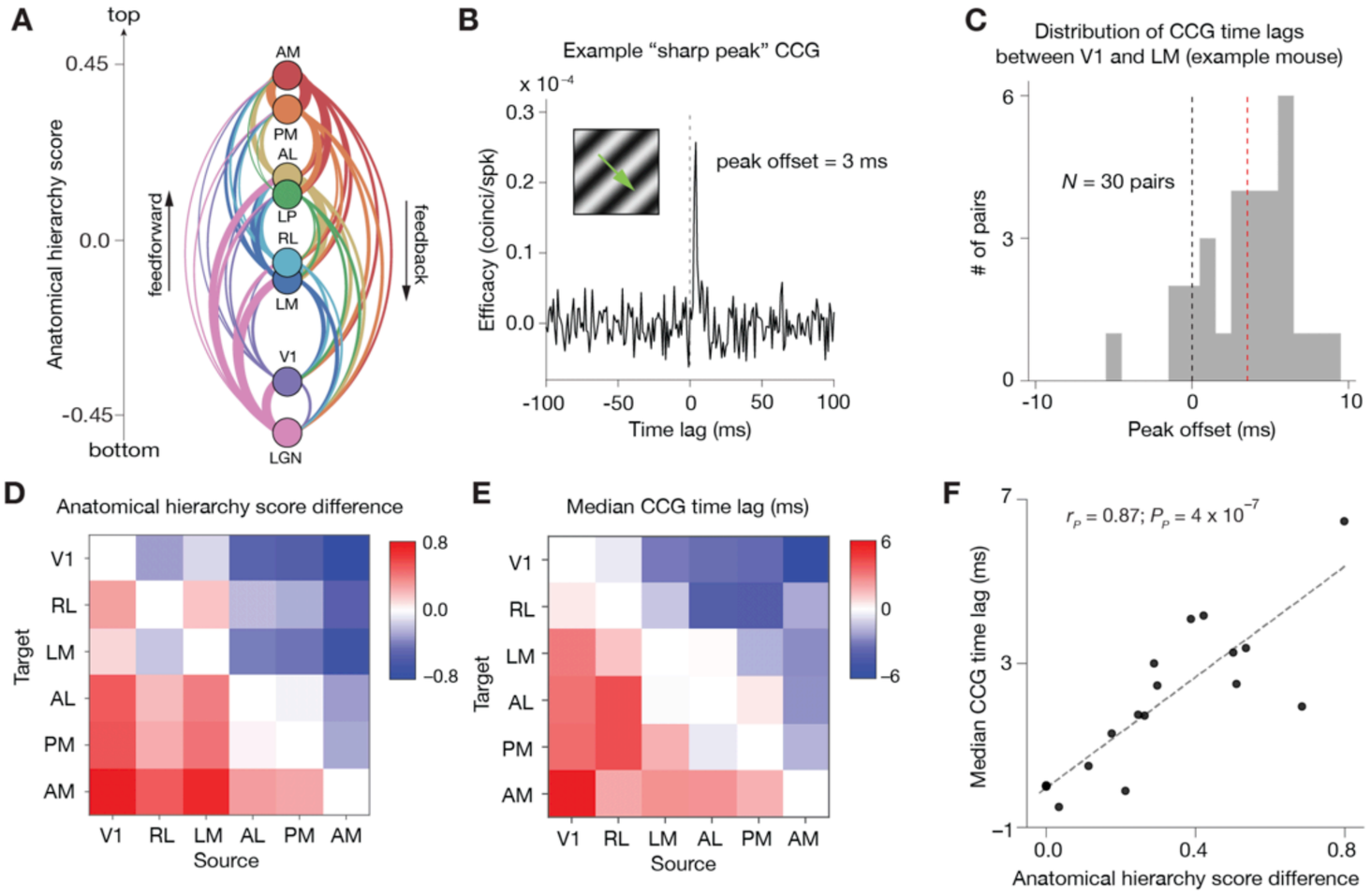
Recording from Many Structures Simultaneously



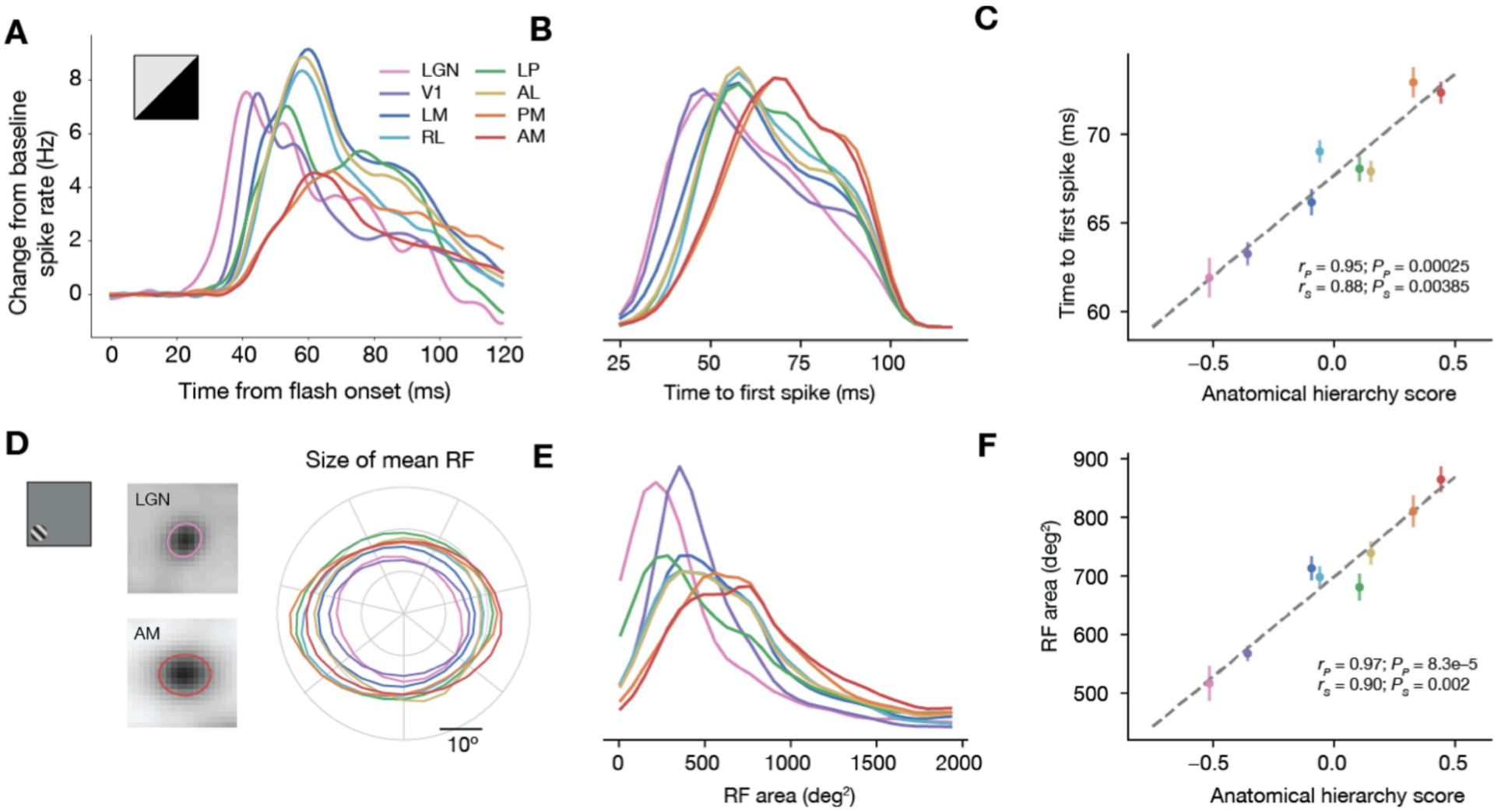
Cells are Visual Responsive



Function Follows Structure



Classical Receptive Field Measures Follow Hierarchy



	LGN	V1	LM	RL	LP	AL	PM	AM
units:	1209	5529	2892	3065	2046	3714	2188	3491
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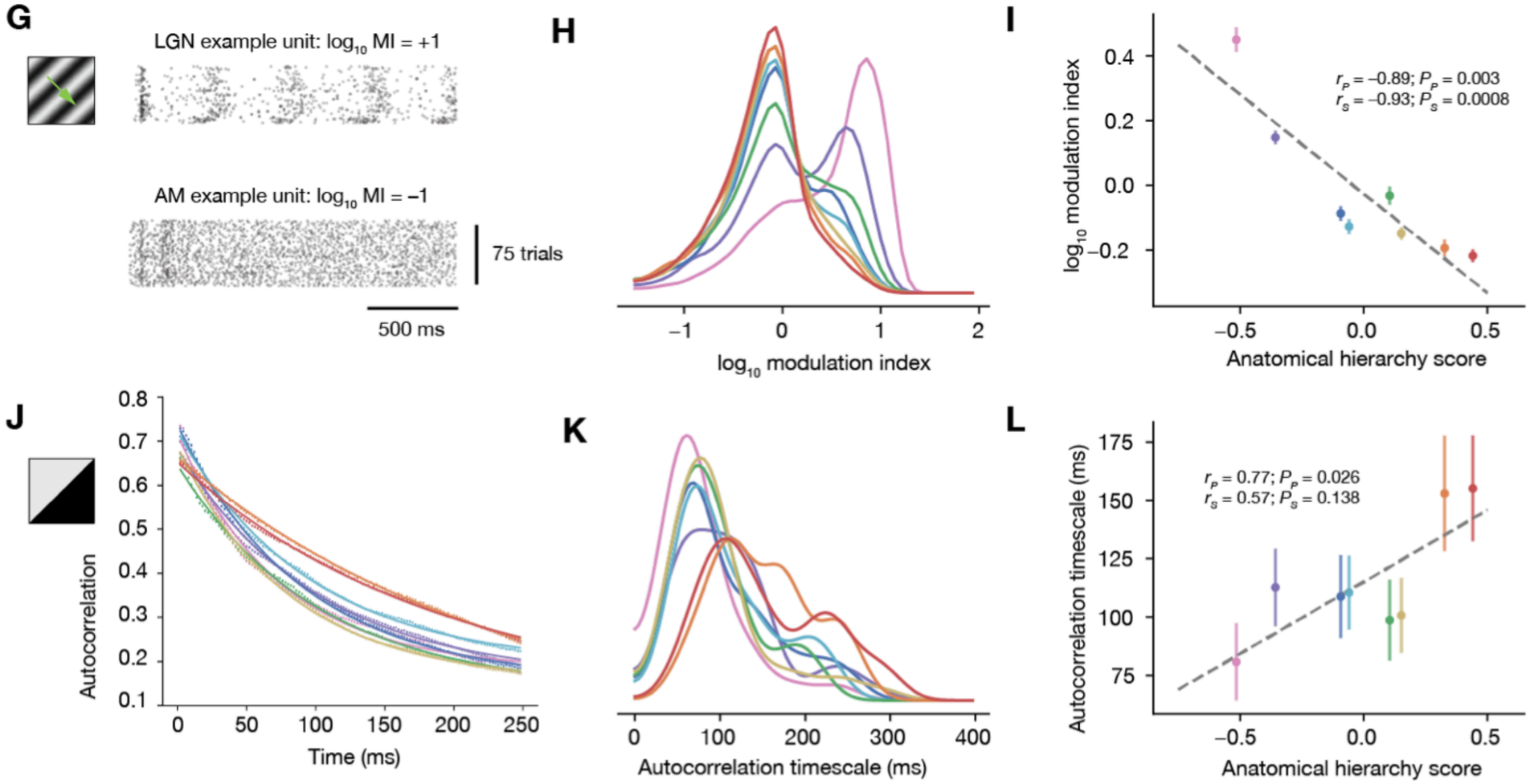
Classical Receptive Field Measures Follow Hierarchy



	LGN	V1	LM	RL	LP	AL	PM	AM
units:	1209	5529	2892	3065	2046	3714	2188	3491
mice:	32	54	42	49	40	44	35	50

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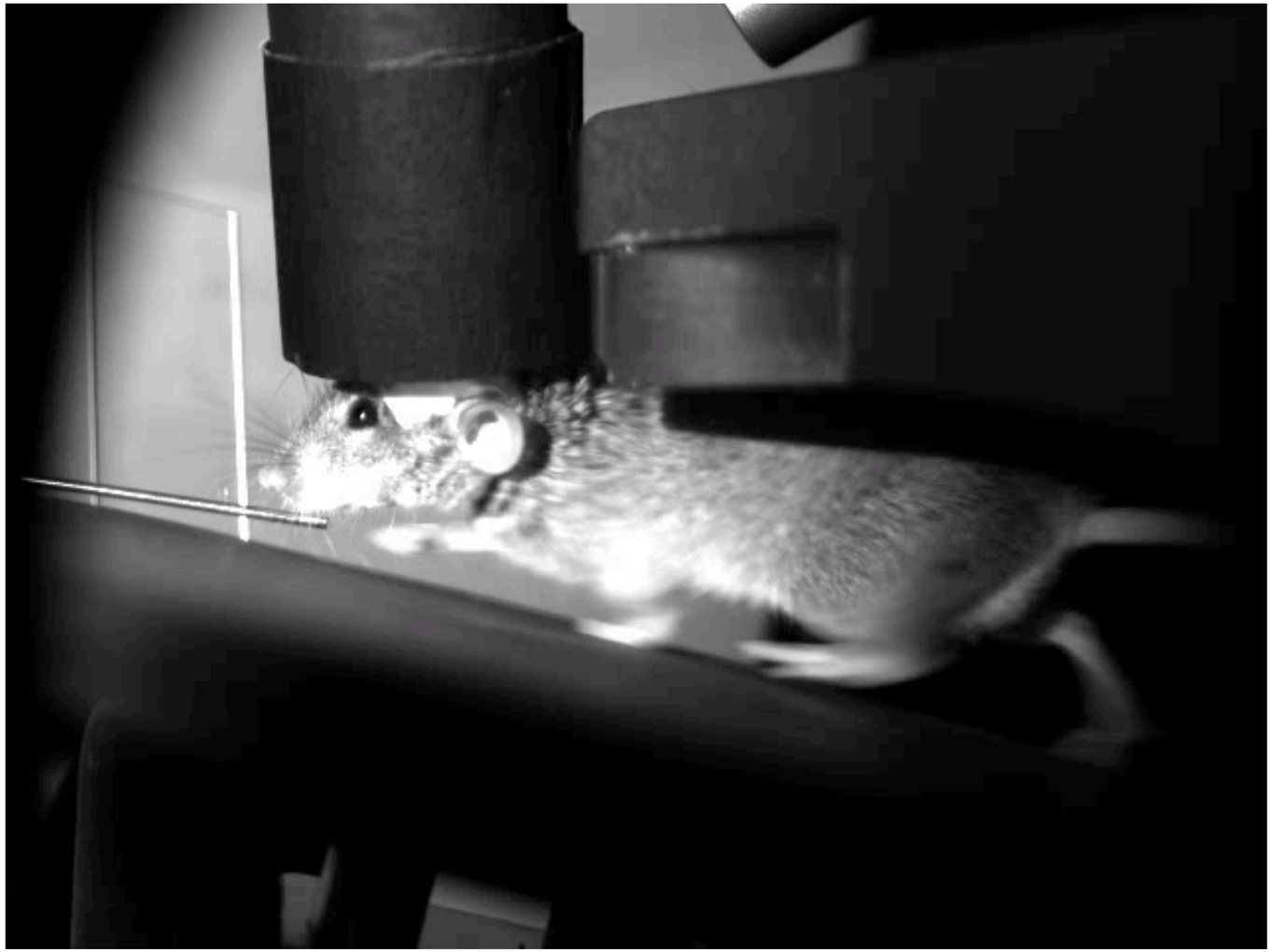
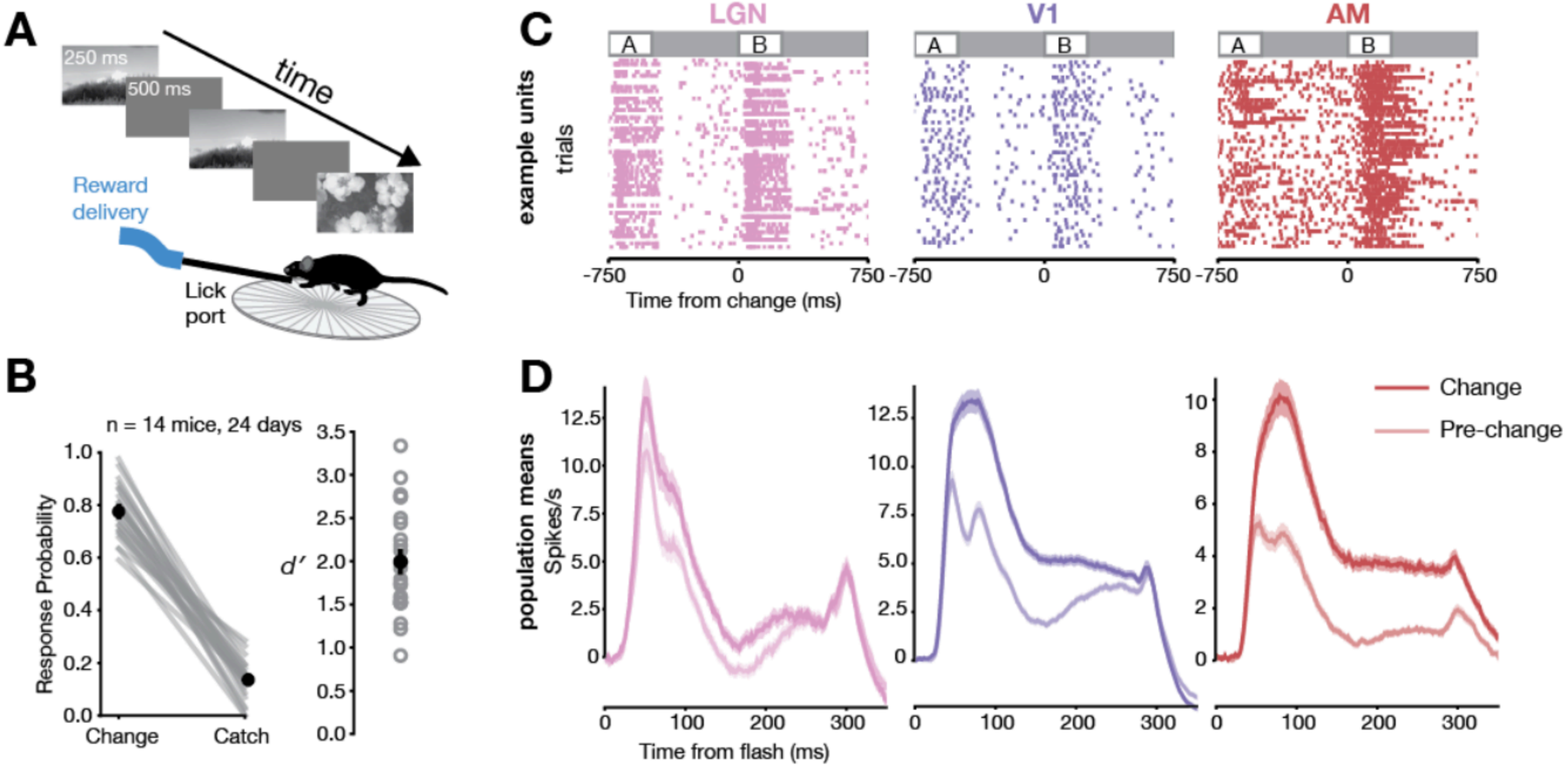
Mouse Performing Change Detection on BrainObservatory



Detecting a Changing Image



	LGN	V1	LM	RL	LP	AL	PM	AM
units:	271	1096	799	553	288	477	398	665
mice:	3	13	11	10	8	9	7	11

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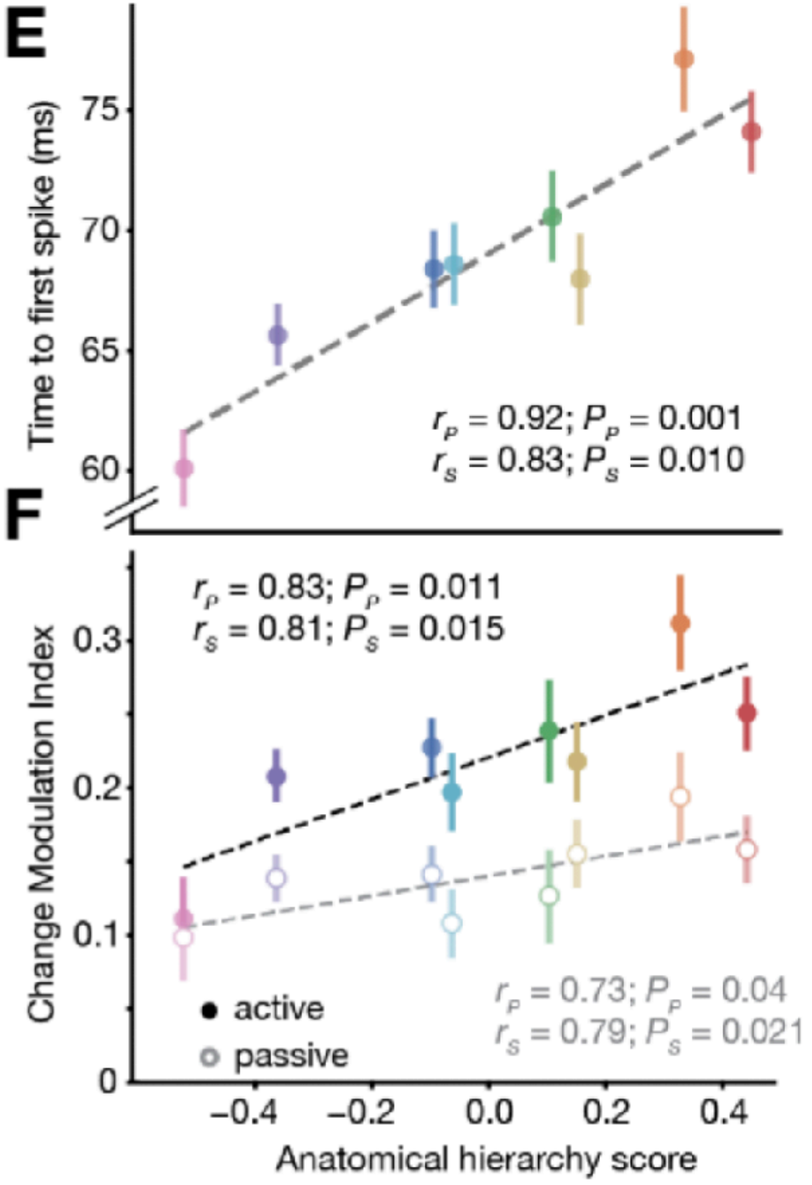
Visual Hierarchy Mimics the Functional Hierarchy



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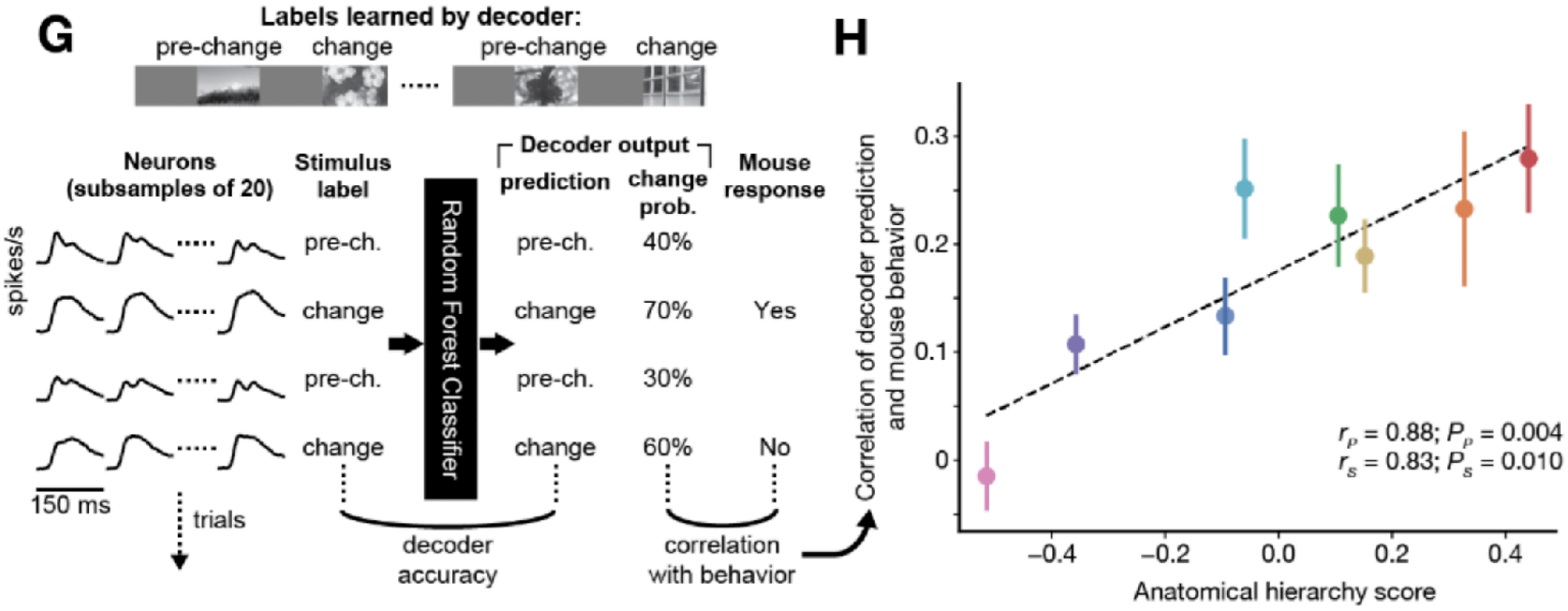
Visual Hierarchy Mimics the Functional Hierarchy



OpenScope

Scientists across the world



1. Perform small scale experiments

2. Form hypothesis

3. Submit experimental protocols to the OpenScope RFP

4. Proposals are reviewed scientifically

5. We perform best and most impactful experimental designs

6. Data is analyzed by proposal team

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Summary

- The *Allen Brain Observatory* records large number of neurons under highly standardized visual conditions in a high-res 3-D coordinate-system.
- All data (in NWB 2.0) and meta-data is freely available via a SDK
- We are now moving to an *OpenScope environment* in which new experiments from the external community compete to be run on our Brain Observatory
- A first analysis of the Neuropixels survey reveals highly significant evidence for a functional and behavioral relevant hierarchy that replicates the structural hierarchy discovered in our large scale neuroanatomical database.
- The vast majority of this data has not been analyzed


570
SEATTLE



THANK YOU
We wish to thank the Allen Institute founder, Paul G. Allen, for his vision, encouragement and support.

We honor his legacy today, and every day into the long future of the Allen Institute, by carrying out our mission of tackling the hard problems in bioscience and making a significant difference in our respective fields.

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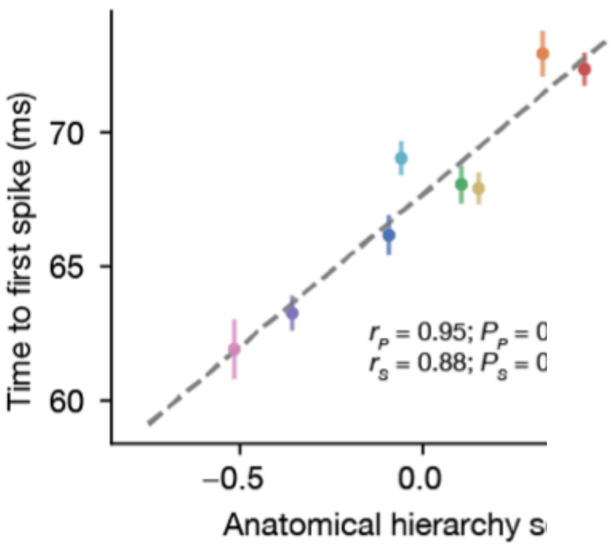
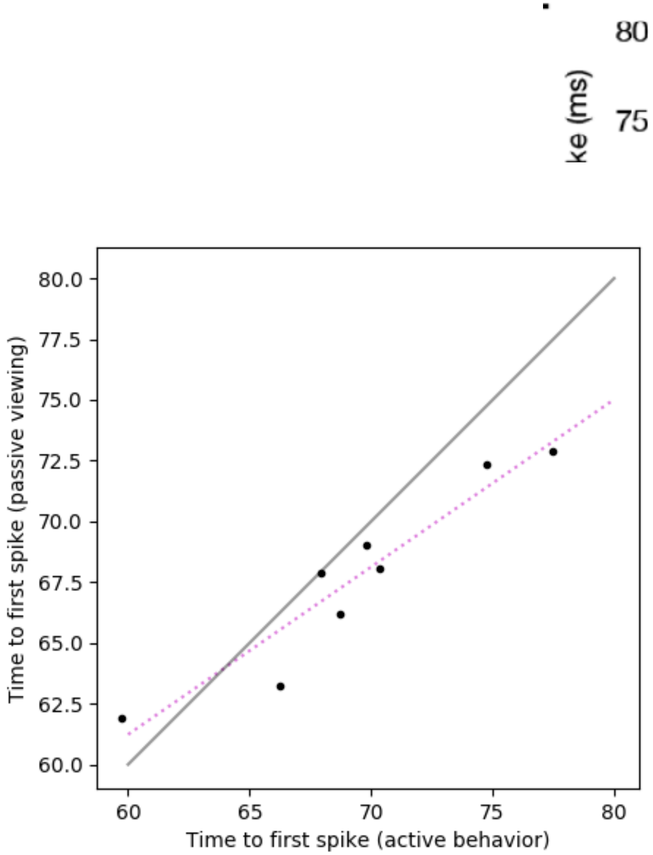
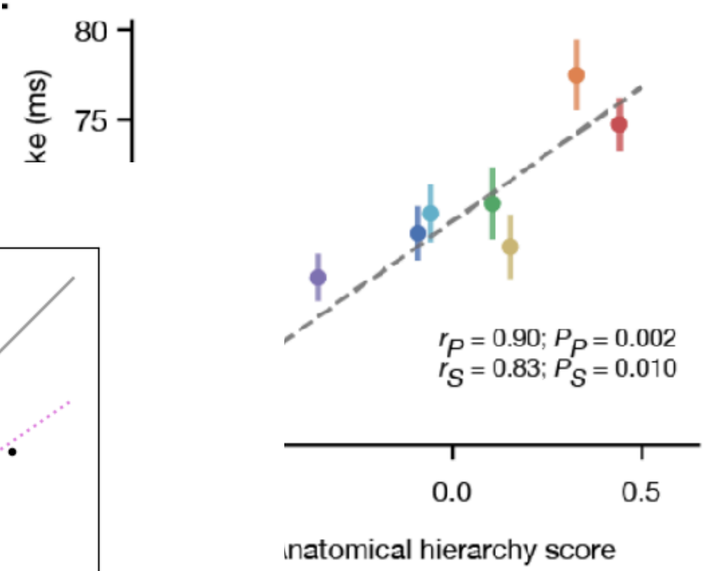
High Reproducibility Across Very Different Datasets

Passive, whole-field flashes
different animals

Active, natural scenes
different animals







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Siegle, Jia … Olsen & Koch *bioRxiv* 2019