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

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Chief Scientist
MindScope Program, Allen Institute

August 11th 2020
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
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

Transgenic mice → Surgery → Intrinsic Imaging 1 → Habituation → In vivo 2p imaging or Neuropixels → Intrinsic Imaging 2 → Serial Two-photon imaging

Cux2, Rorb, Rbp4, Scnn1a
A High-Throughput Pipeline II

- Surgery
- Intrinsic imaging
- *In vivo* 2p Imaging or Neuropixels
- Serial two-photon tomography
High-Resolution Cross-Platform Registration

Headframe

Surgery

ISI

Physiology

Headframe

Reticule

Surgery

ISI

Physiology
Visual Coding -
Multiple Hours of Visual Stimuli

Drifting gratings

Static gratings

Locally sparse noise

Natural scenes

Natural movies

Spontaneous activity

Visual Coding -
Multiple Hours of Visual Stimuli

Stim A

Stim B

Stim C

1 hour
A High-Throughput Pipeline III

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

devries et al. Nature Neurosci. 2019

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<th>Cre driver</th>
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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.

Teeters et al. Neuron 2015
Neuropixels

- 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**

**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

Oh et al. Nature 2012
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 clustering 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 reveals a functional hierarchy of mouse corticothalamic visual areas

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

All data - 100,000 units, registered to CCFv3, with > 2 billion spikes - at www.brain-map.org
Multiarea Neuropixels Recordings
Recording Throughout the Brain

Depth from brain surface (microns)

L1
L2/3
L4
L5
L6

AL
Recording >1000 Neurons Across 10 Visual Regions

Cortex

Hippocampus

Thalamus

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Siegle, Jia ... Olsen & Koch bioRxiv 2019
Recording from Many Structures Simultaneously
Cells are Visual Responsive

A

Gabor

Full-Field Flashes

Drifting Gratings

Dot Motion

Static Gratings

Natural Scenes

Natural Movies

B

temporal frequency

1 Hz

2 Hz

4 Hz

8 Hz

15 Hz

direction

2 s

15 trials

270°

180°

90°

0°

15 Hz

Star plot

C

Light flash

Dark flash

75 trials

Flash onset

50 ms

D

55°

35°

15°

-15°

-35°

20°

40°

60°

80°

100°

250 ms

45 trials

Spatial receptive field

E

Fraction with RFs

V1

LM

RL

AL

PM

AM

LGN

LP

HPC
Function Follows Structure

A. Anatomical hierarchy score

B. Example "sharp peak" CCG

C. Distribution of CCG time lags between V1 and LM (example mouse)

D. Anatomical hierarchy score difference

E. Median CCG time lag (ms)

F. Median CCG time lag (ms) vs. anatomical hierarchy score difference

\[ r_p = 0.87; P_p = 4 \times 10^{-7} \]
Classical Receptive Field Measures Follow Hierarchy
Classical Receptive Field Measures Follow Hierarchy
Mouse Performing Change Detection on BrainObservatory
Detecting a Changing Image

A. Time course of reward delivery and lick port activities.

B. Response probability and d' as a function of change and catch for 14 mice over 24 days.

C. Example units from LGN, V1, and AM showing the time from change.

D. Population means of spikes/s as a function of time from flash.
Visual Hierarchy Mimics the Functional Hierarchy
Visual Hierarchy Mimics the Functional Hierarchy

G

Labels learned by decoder:
pre-change  change
pre-change  change

Neurons (subsamples of 20)  Stimulus label

spikes/s  pre-ch.
spikes/s  change
spikes/s  pre-ch.
spikes/s  change

150 ms  trials

Decoding accuracy

Random Forest Classifier

Decoder output prediction

pre-ch.  change
40%  70%

Mouse response

change  No
60%

H

Correlation of decoder prediction and mouse behavior

$\rho = 0.88; \; P = 0.004$

$\rho_s = 0.83; \; P_s = 0.010$

Anatomical hierarchy score
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

Scientists across the world
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.
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.

alleninstitute.org
brain-map.org
High Reproducibility Across Very Different Datasets

Passive, whole-field flashes
different animals

Active, natural scenes
different animals

Siegle, Jia … Olsen & Koch bioRxiv 2019