Distributed networks underlying action, choice, and engagement across the mouse brain

Nick Steinmetz

With Peter Zatka-Haas, Matteo Carandini, and Kenneth Harris

University College London

Lab now open!

University of Washington, Seattle

www.steinmetzlab.net

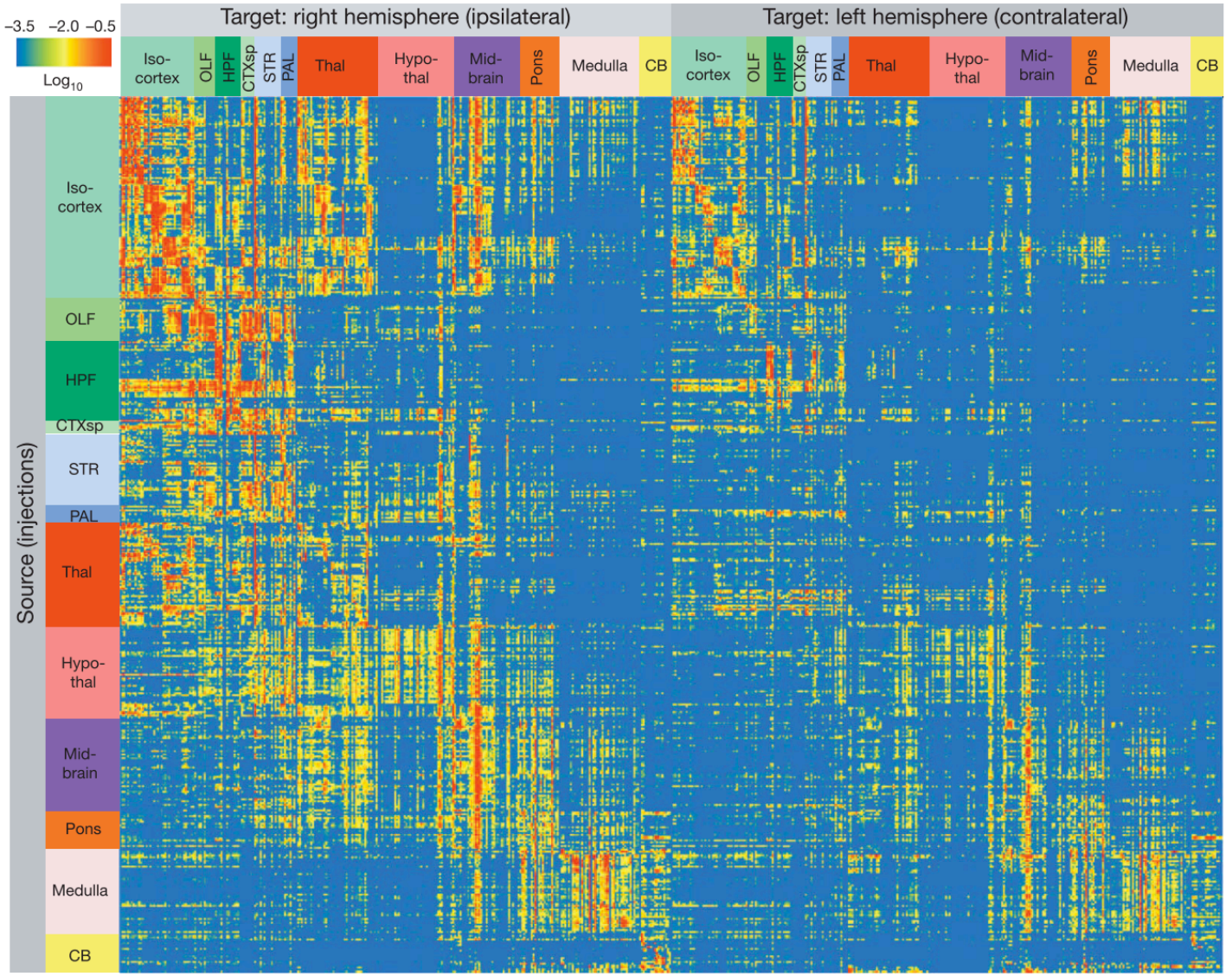
Detection

- Why are some stimuli perceived and others are not?

Discrimination

- How are multiple pieces of sensory evidence combined to make a choice?

How can activity be coordinated given dense connectivity?



Oh et al. *Nature* 2014

Is there a single brain region that 'chooses'?

- Probably not!
  - Multiple cortical areas (Hernandez et al. 2010)
  - Thalamus (Guo et al. 2017)
  - Basal ganglia (Wang et al. 2018)
  - Midbrain (Horwitz et al. 2004)
- But what is the *timing* and *nature* of the role of different areas in a single perceptual decision?

Goal: record from multiple cortical and subcortical areas in a single perceptual decision-making task

What are large-scale recordings good for?

- Increasing the pace and plausibility of experiments
- Find rare neurons or signals
- Improve statistical power
- Examine interactions between concurrently recorded areas
- Understanding population activity structure

A task for studying visually-guided behavior in mice

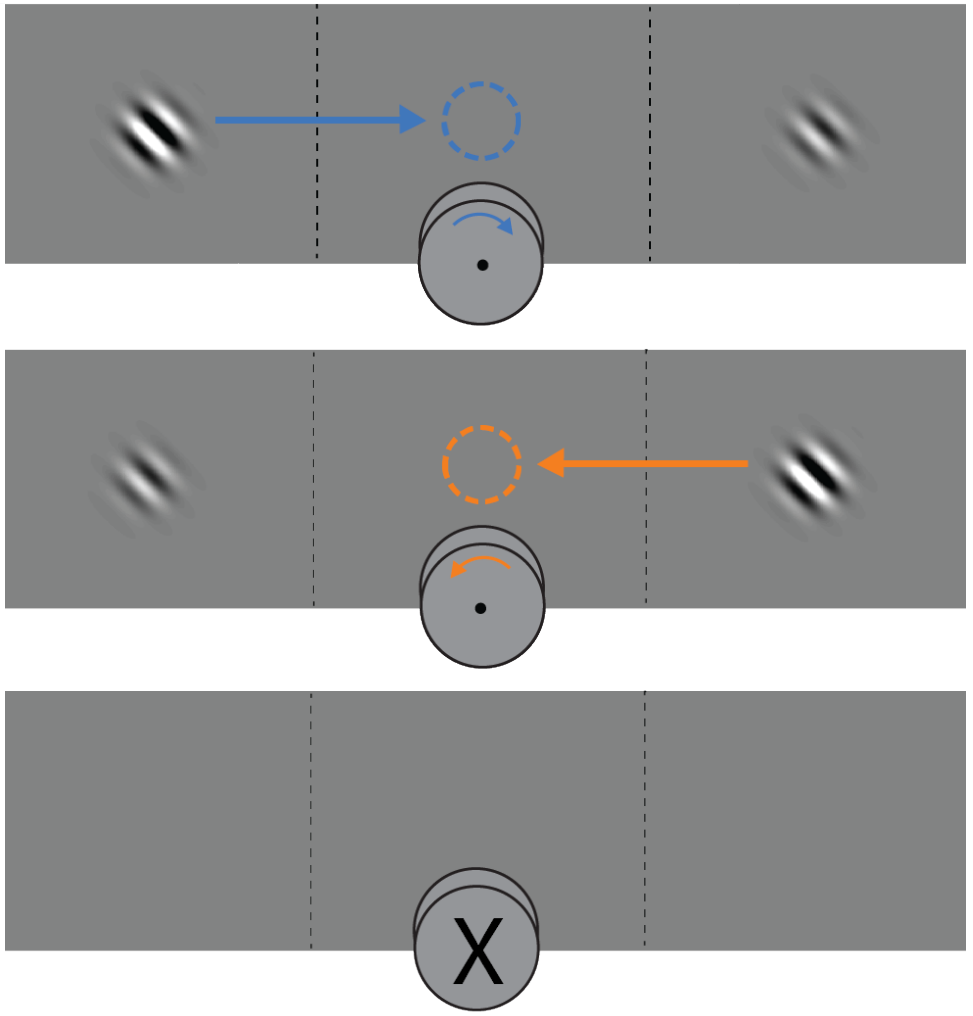
Burgess*, Lak*, Steinmetz*,
Zatka-Haas* et al,
Cell Reports 2017

A task for studying visually-guided behavior in mice

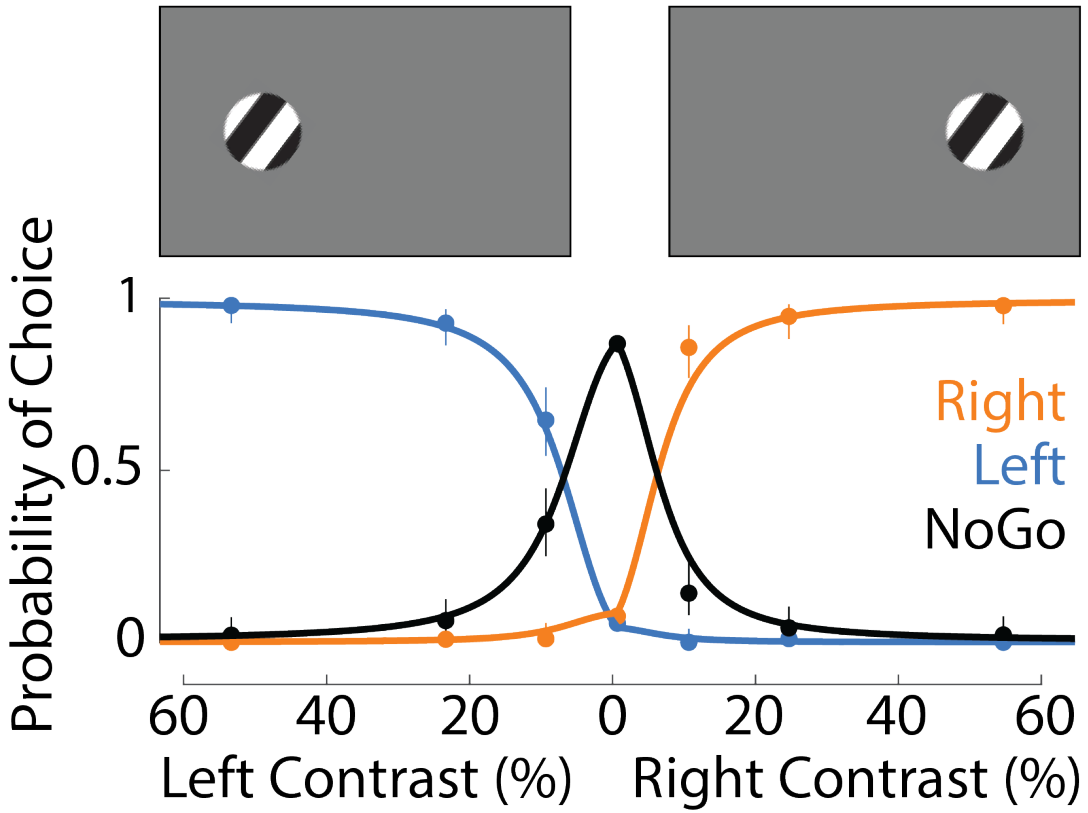
Choose left

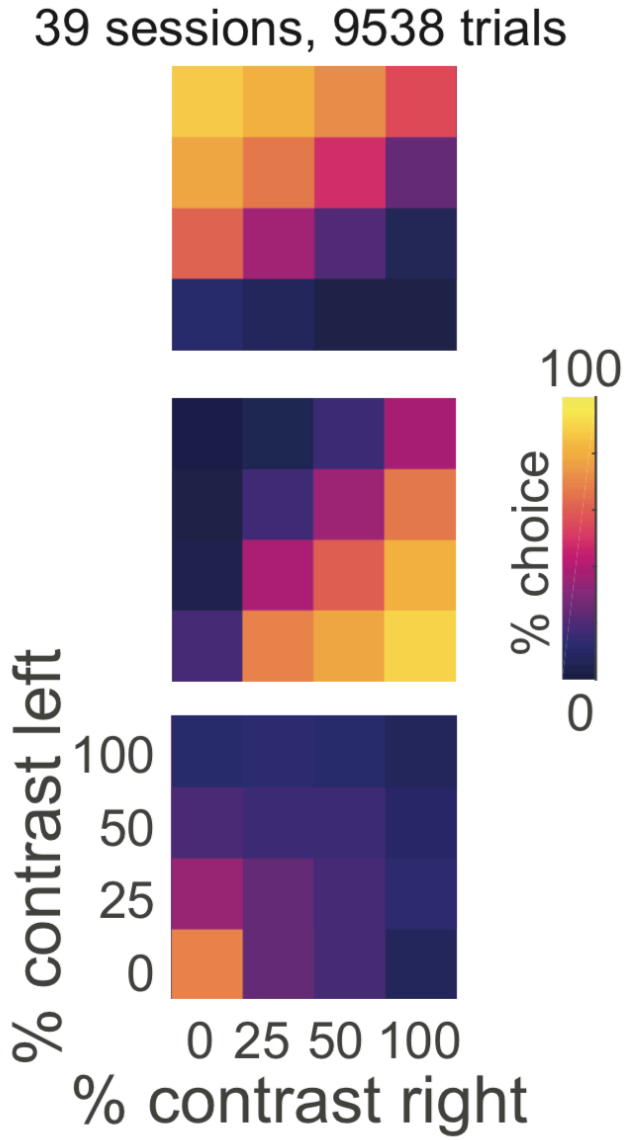
Choose right

Choose nogo

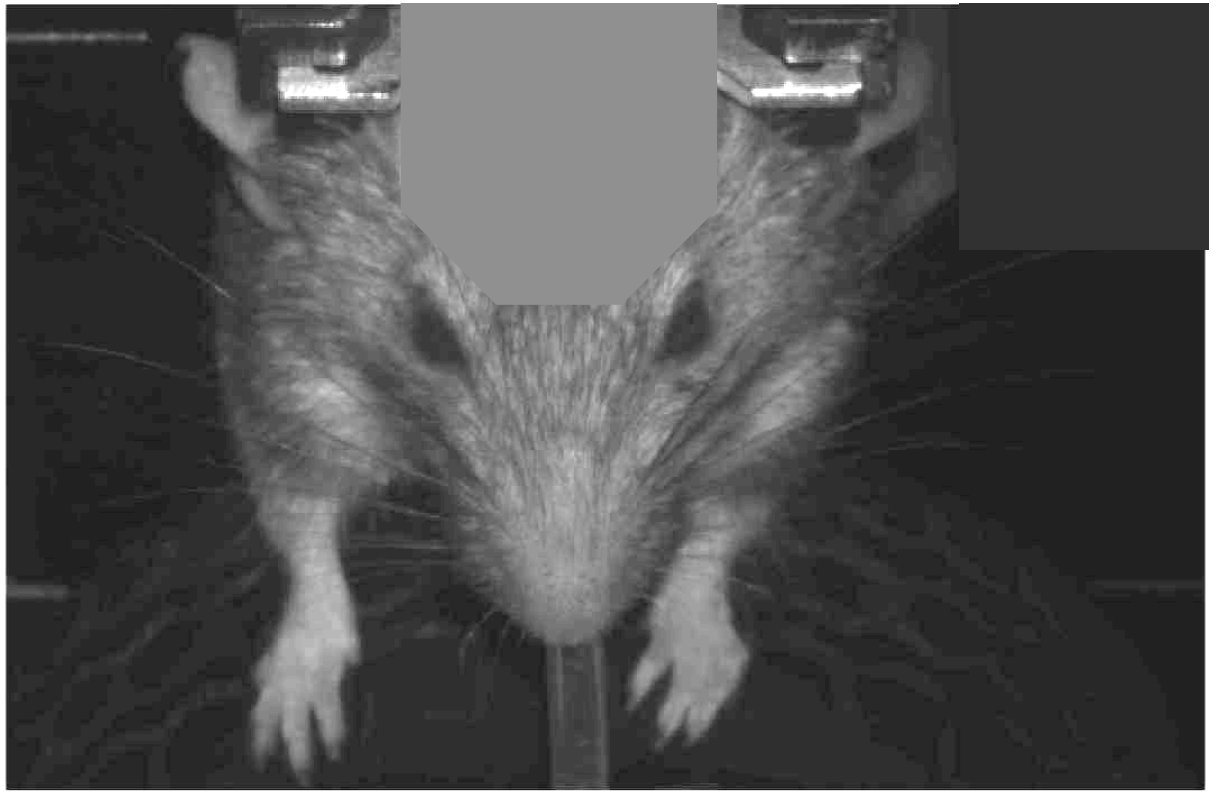


Choices depend strongly on contrast

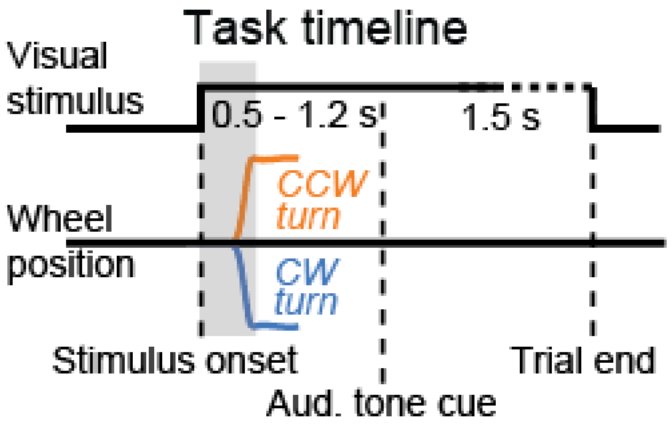


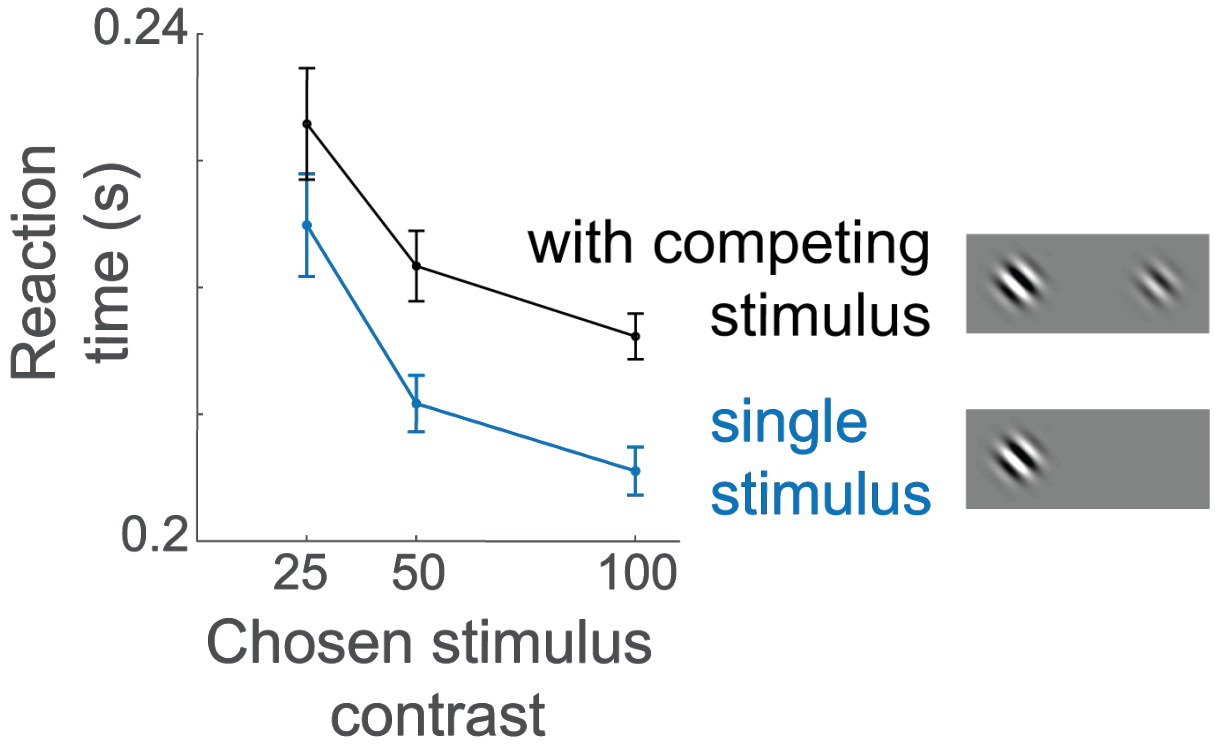


Contrast detection and discrimination task

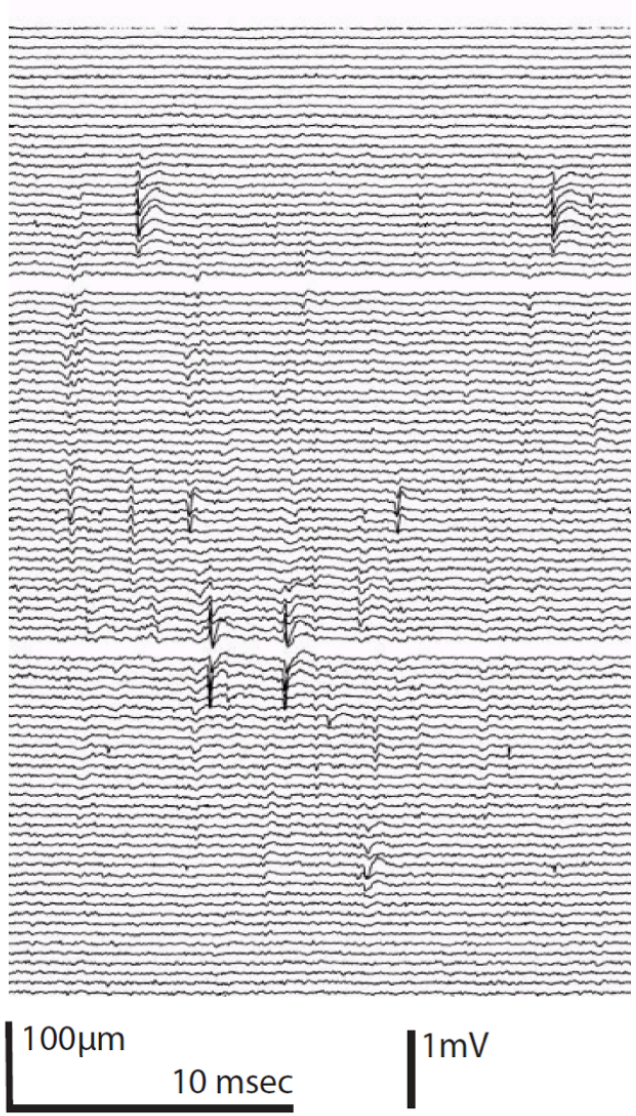


Reaction times reveal a competitive process

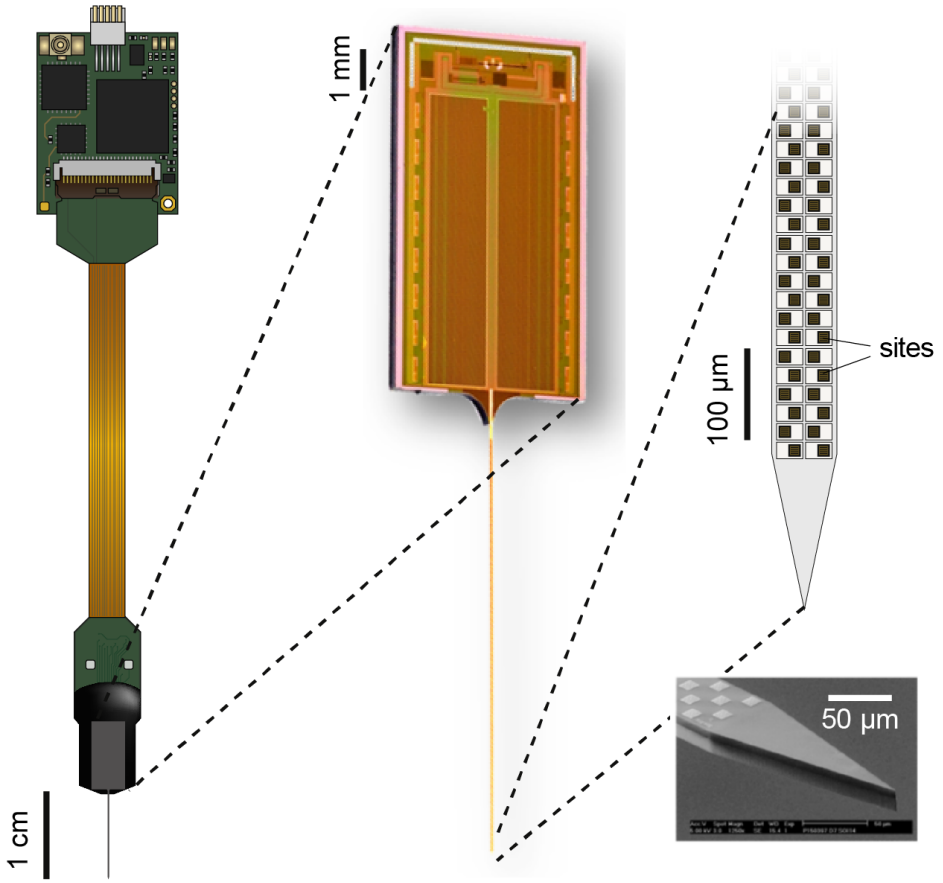




Neuropixels probes enable large-scale recording

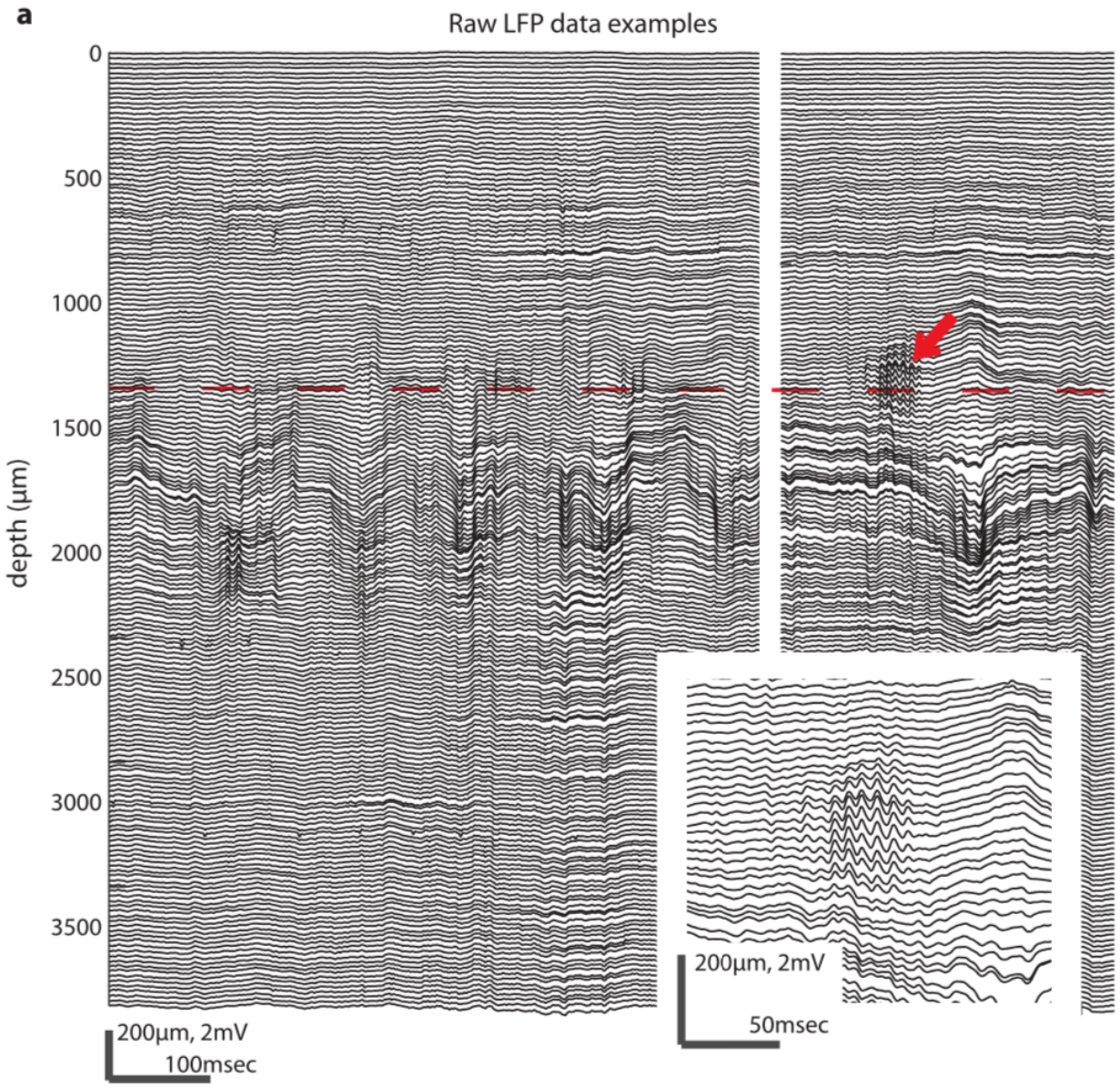


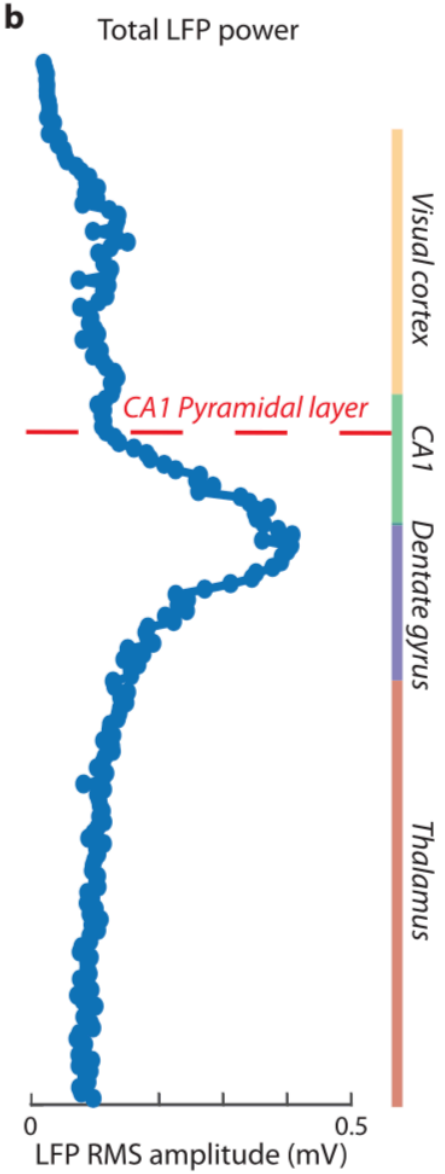
Led by Tim Harris, Janelia Research Campus

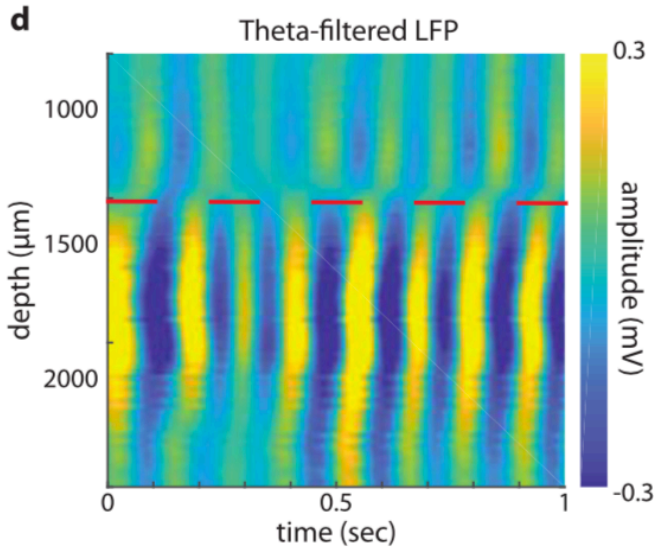


Jun*, Steinmetz*, Siegle*, Denman*, Bauza*, Barbarits*, Lee*, et al. *Nature* 2017

Example local field potential recordings

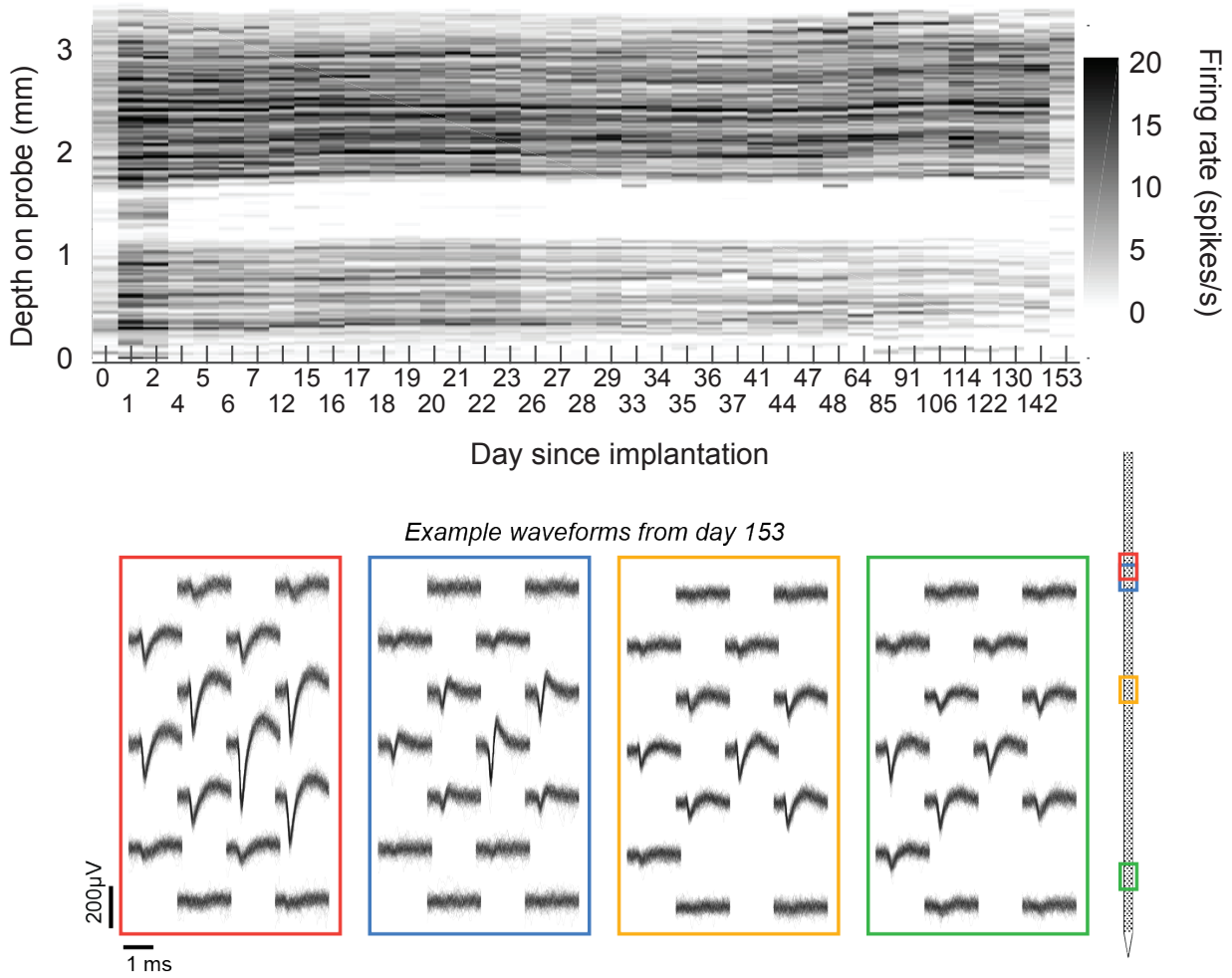




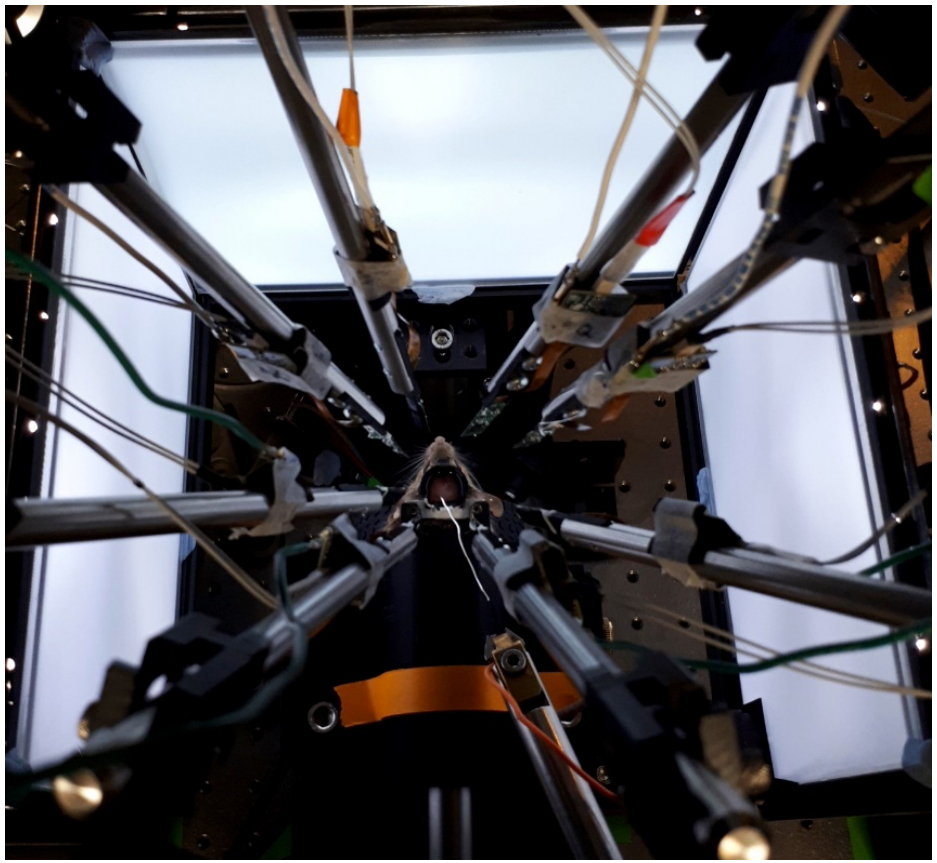


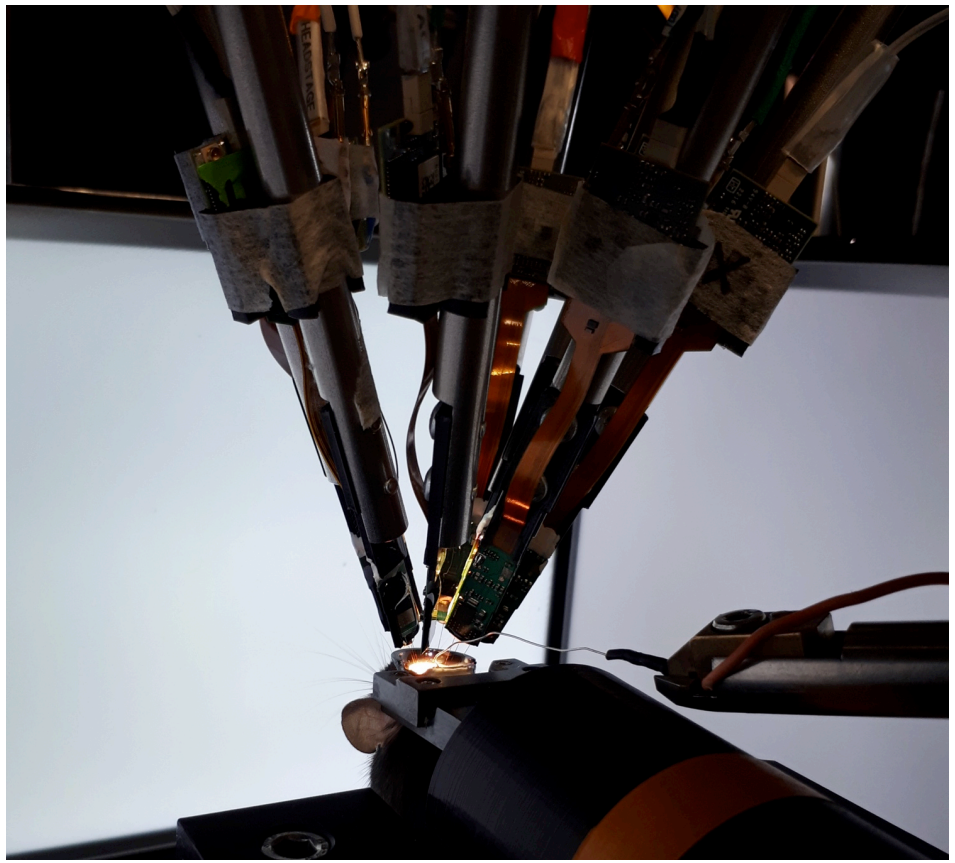
Chronic, freely-moving recordings of hundreds of neurons

With Michael Okun

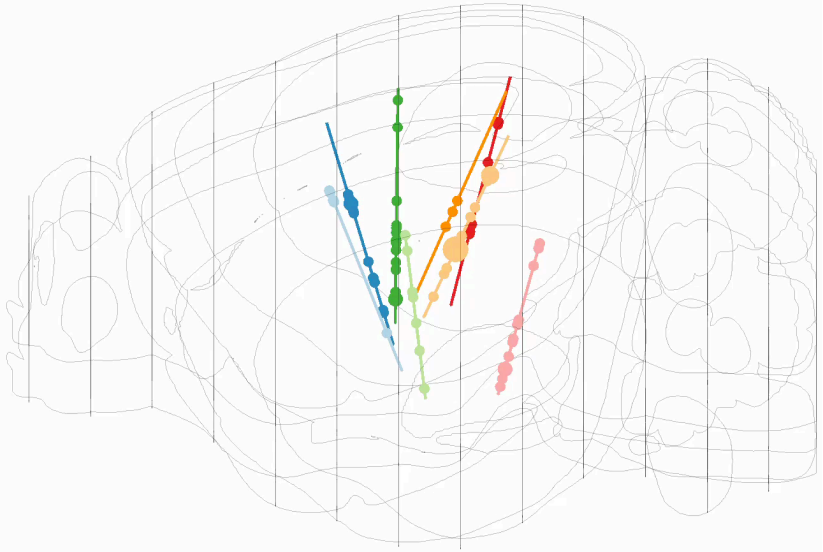


Recording with 8 Neuropixels simultaneously





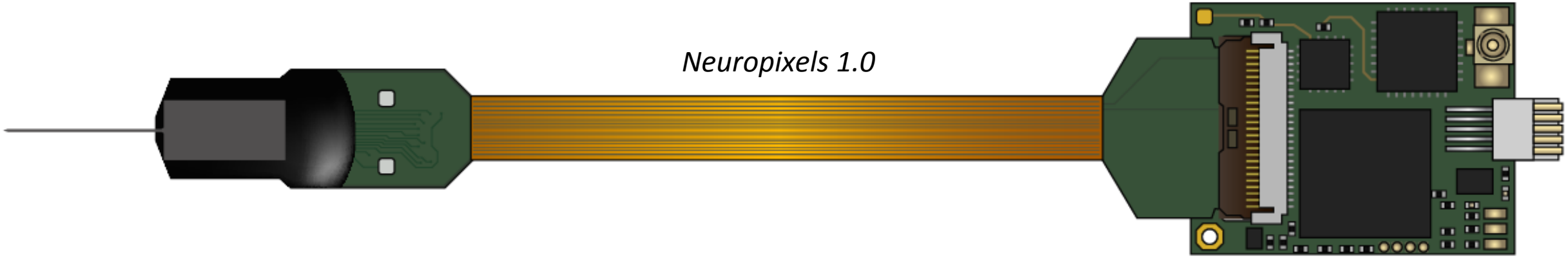
Recording with >3000 channels in an awake mouse



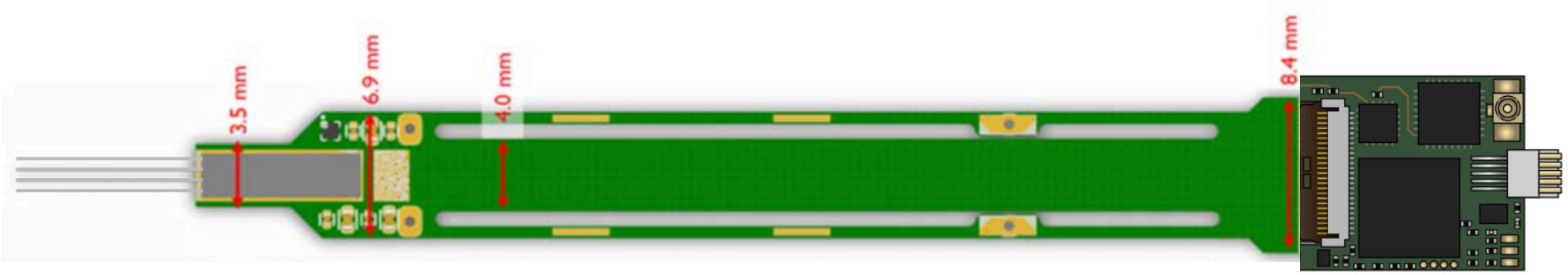
Stringer*, Pachitariu*, et al.
Science 2019

Future work: Neuropixels 2.0

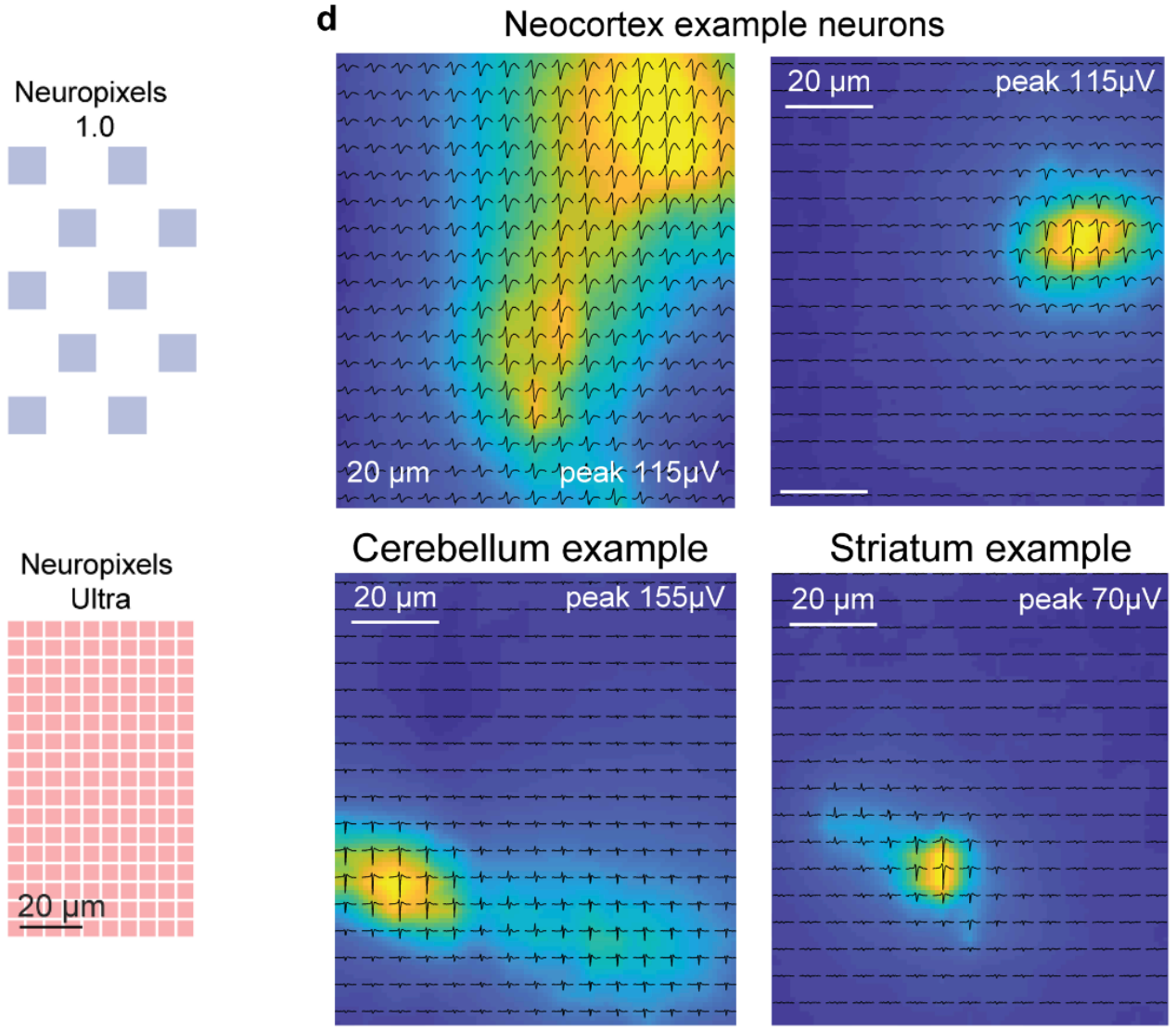
Neuropixels 1.0



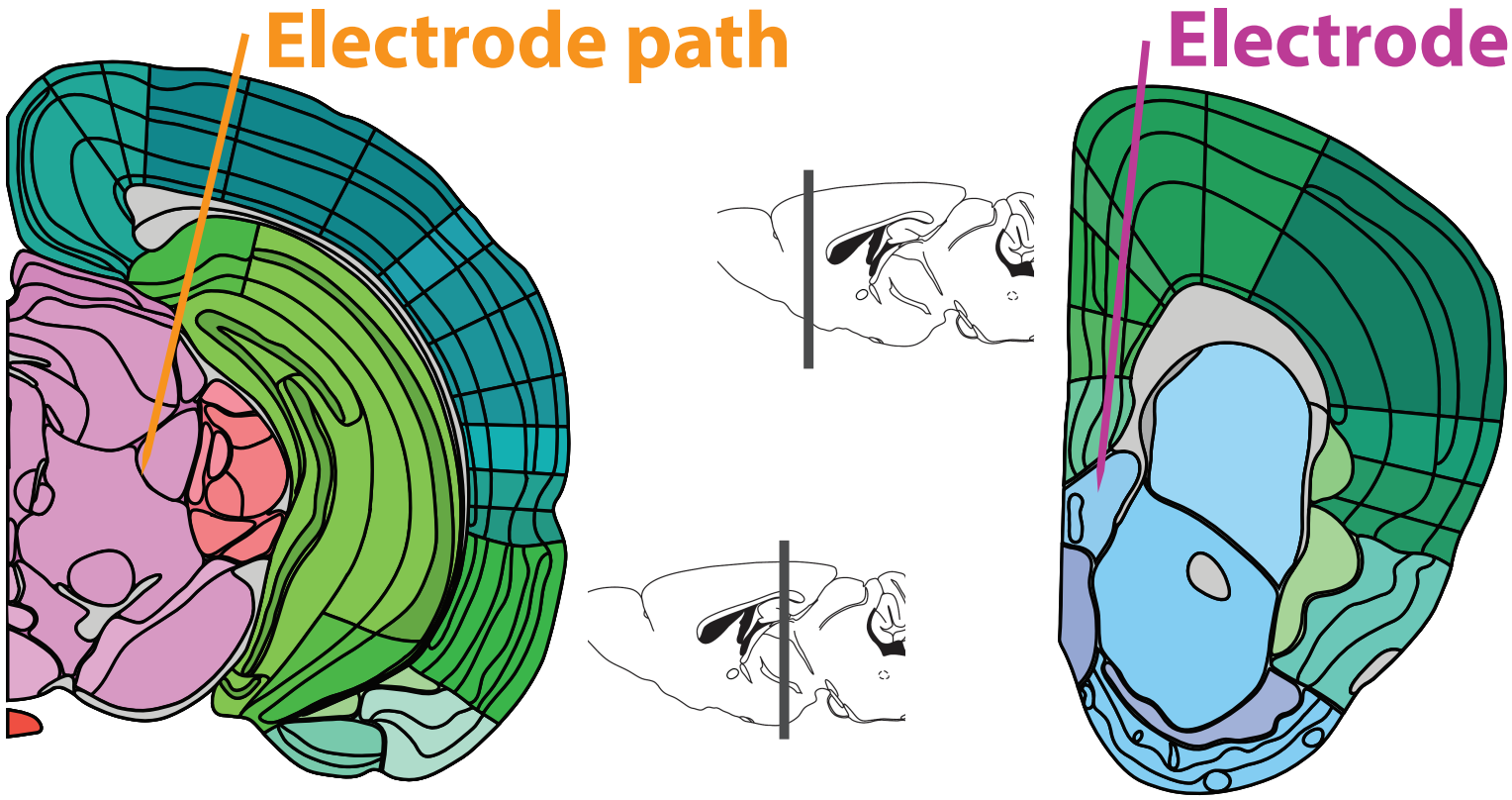
Neuropixels 2.0



Future work: Ultra-dense probes

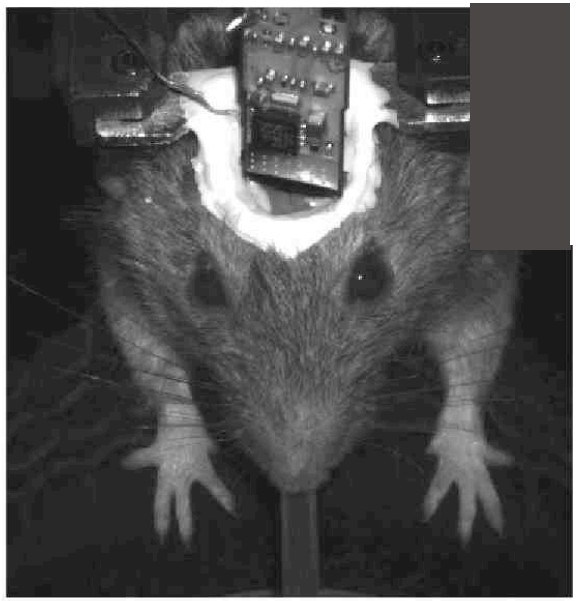


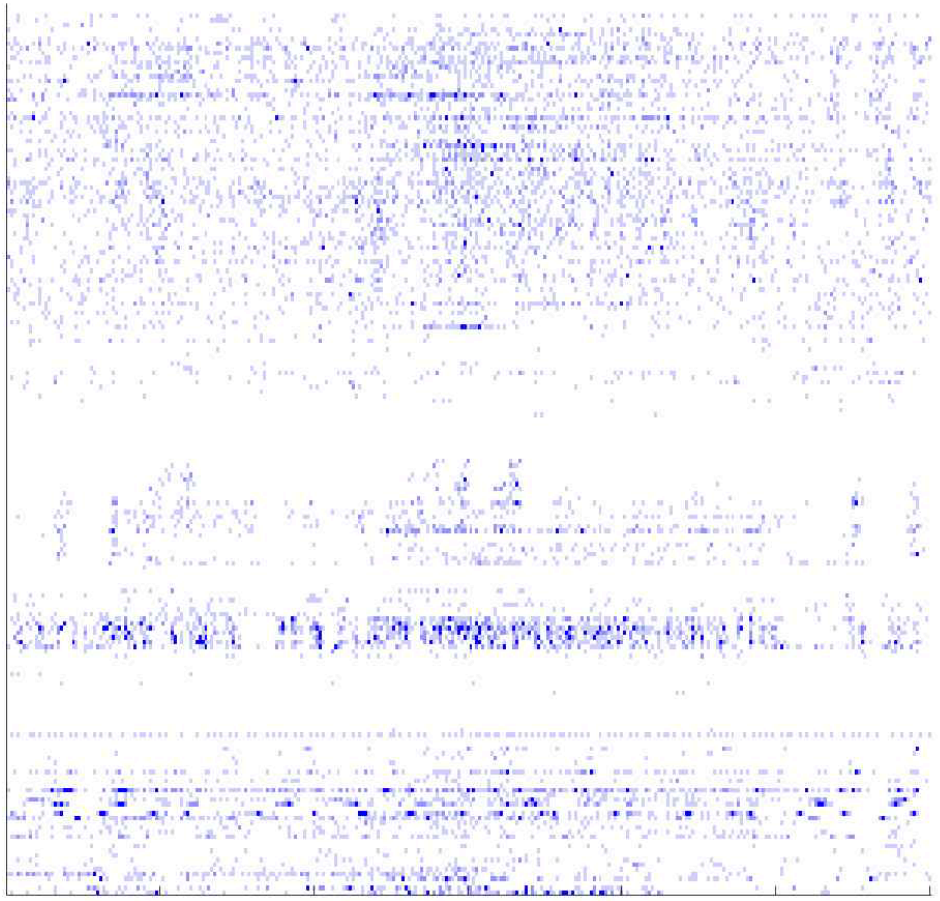
Example Neuropixels recording during behavior



Graphic: Allen Institute Reference Atlas

Example Neuropixels recordings during behavior





Secondary Motor cortex

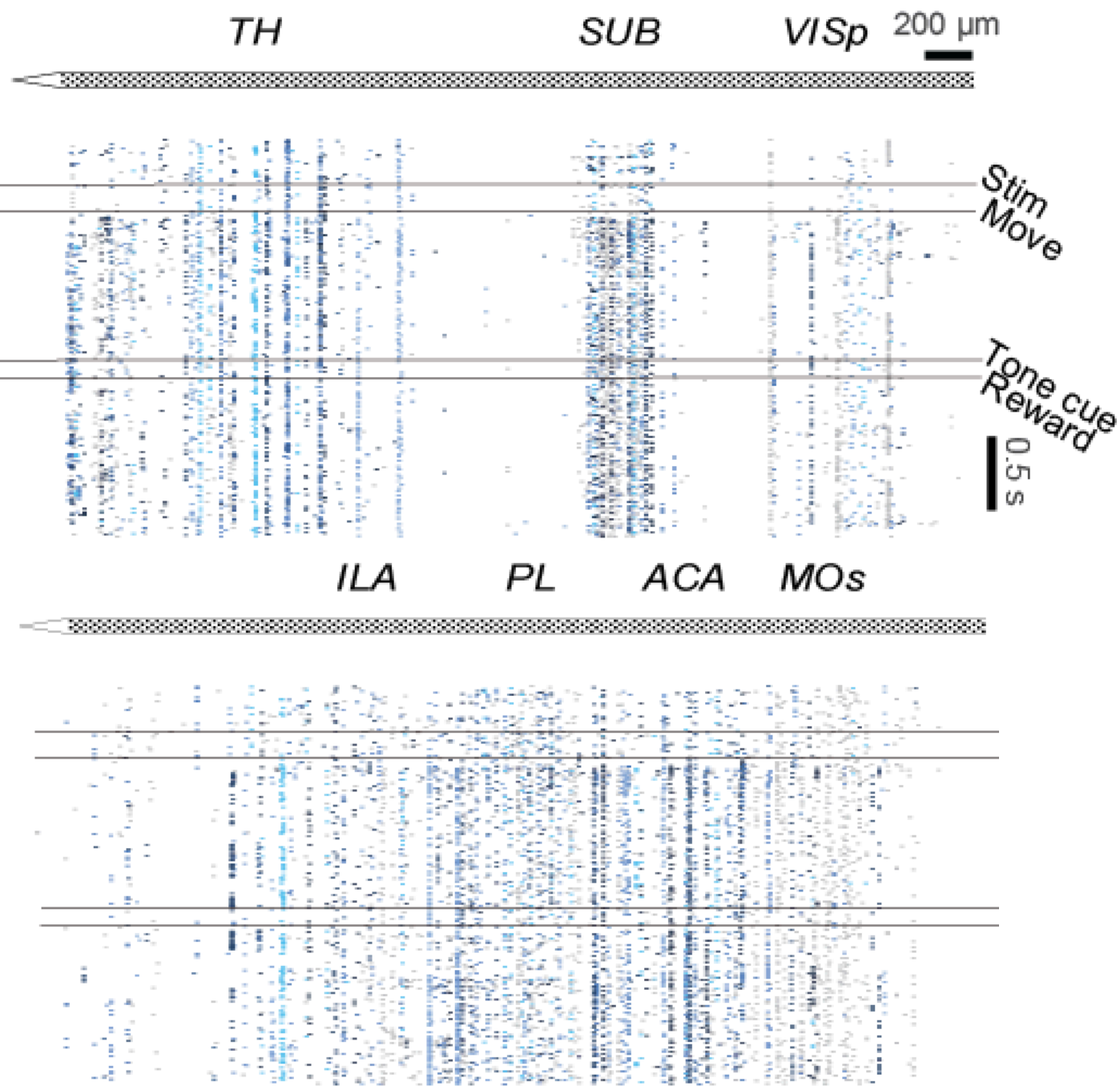
Anterior cingulate cortex

Prelimbic cortex

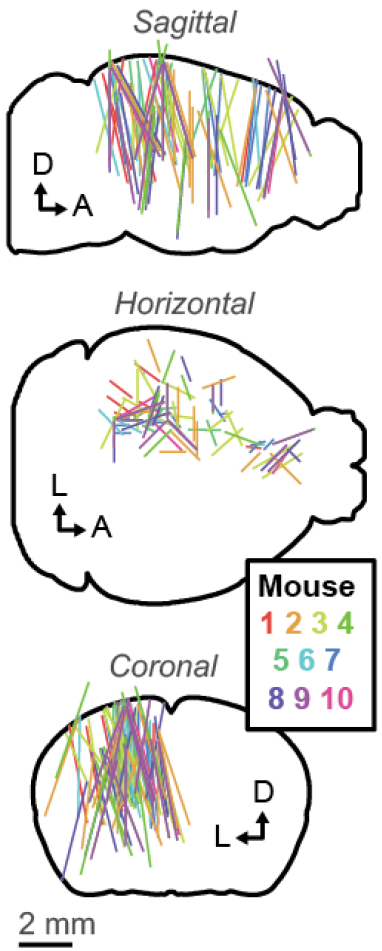
Primary visual cortex

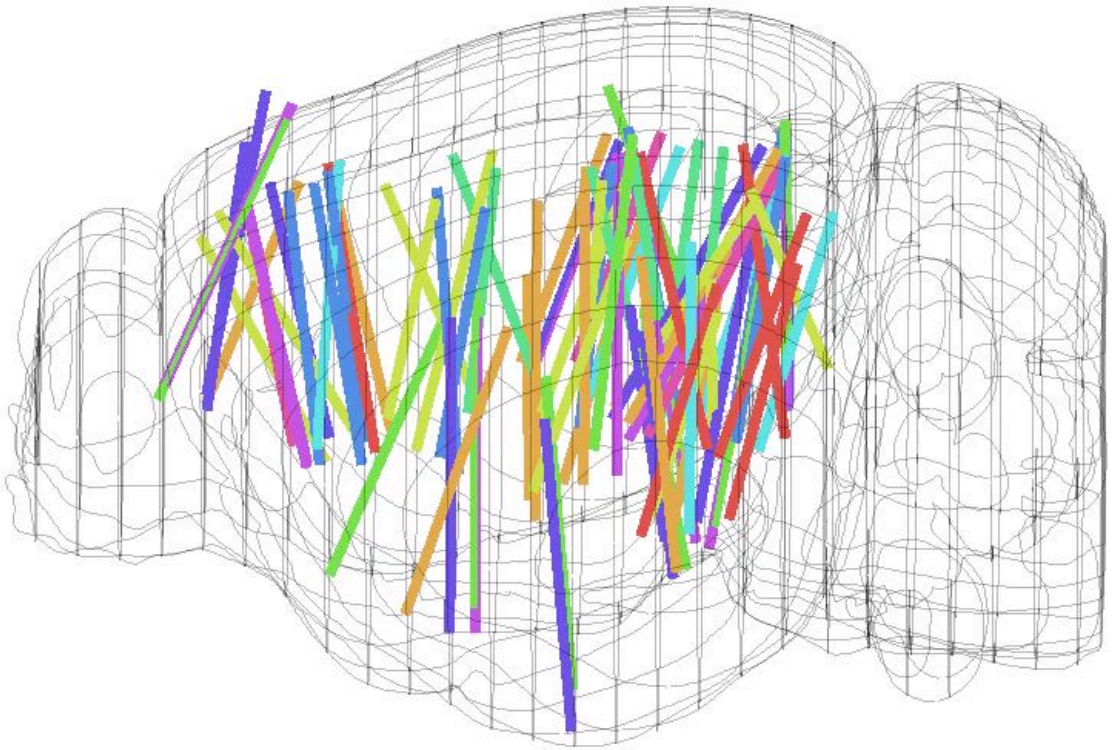
Dorsal subiculum

Thalamus

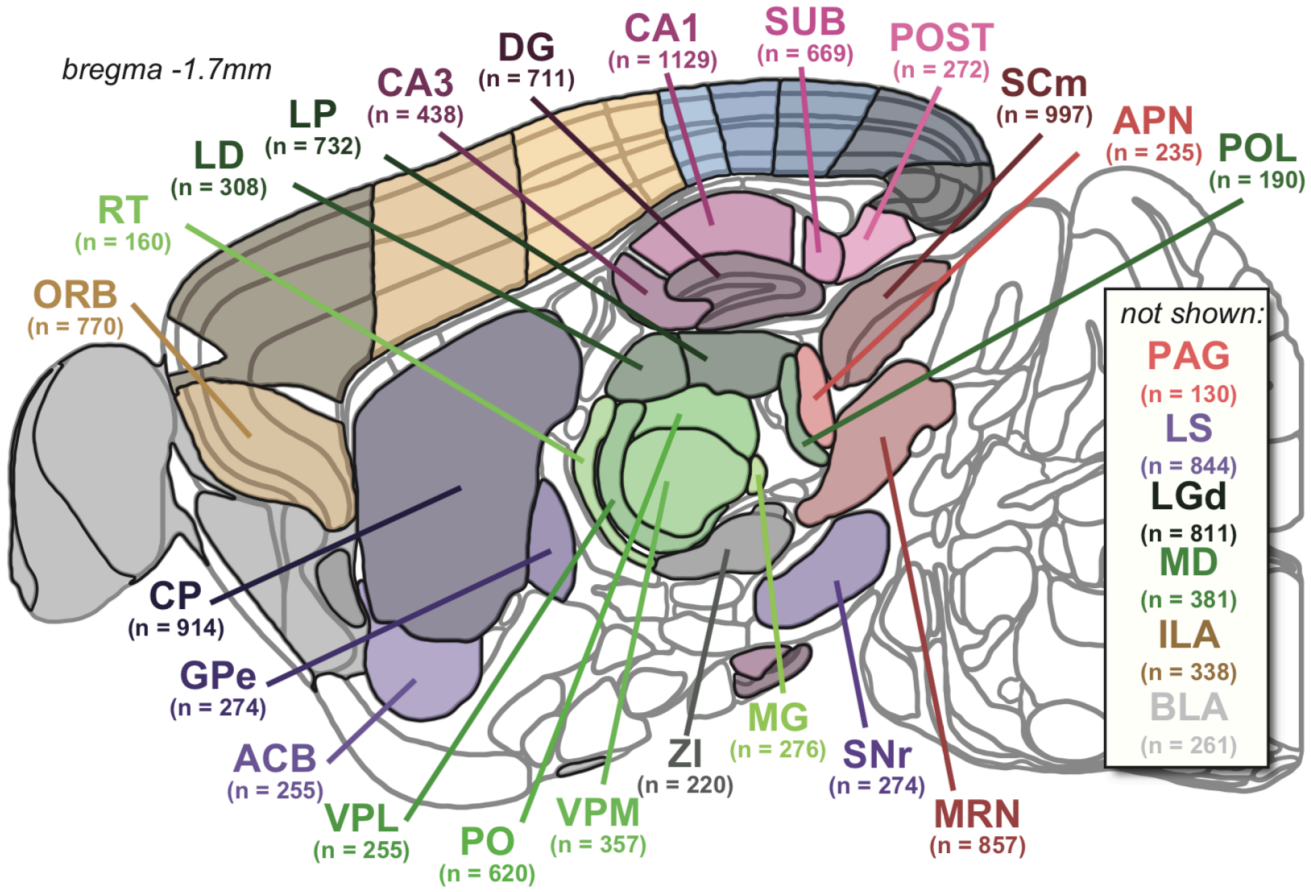

TH
SUB
VISp
200 µm
Stim
Move
Tone cue
Reward
0.5 s
ILA
PL
ACA
MOs

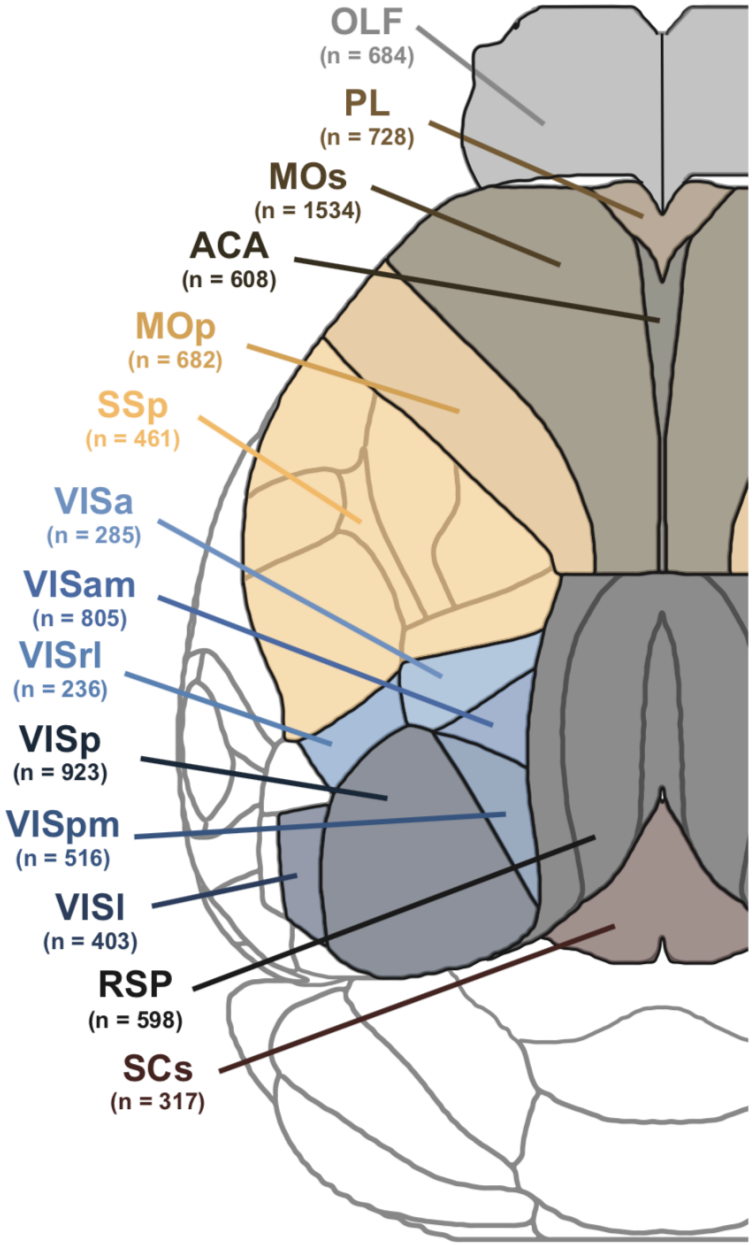
Recordings were made of 29134 neurons across 39 sessions in 10 mice





Neurons were recorded in each of 42 brain regions

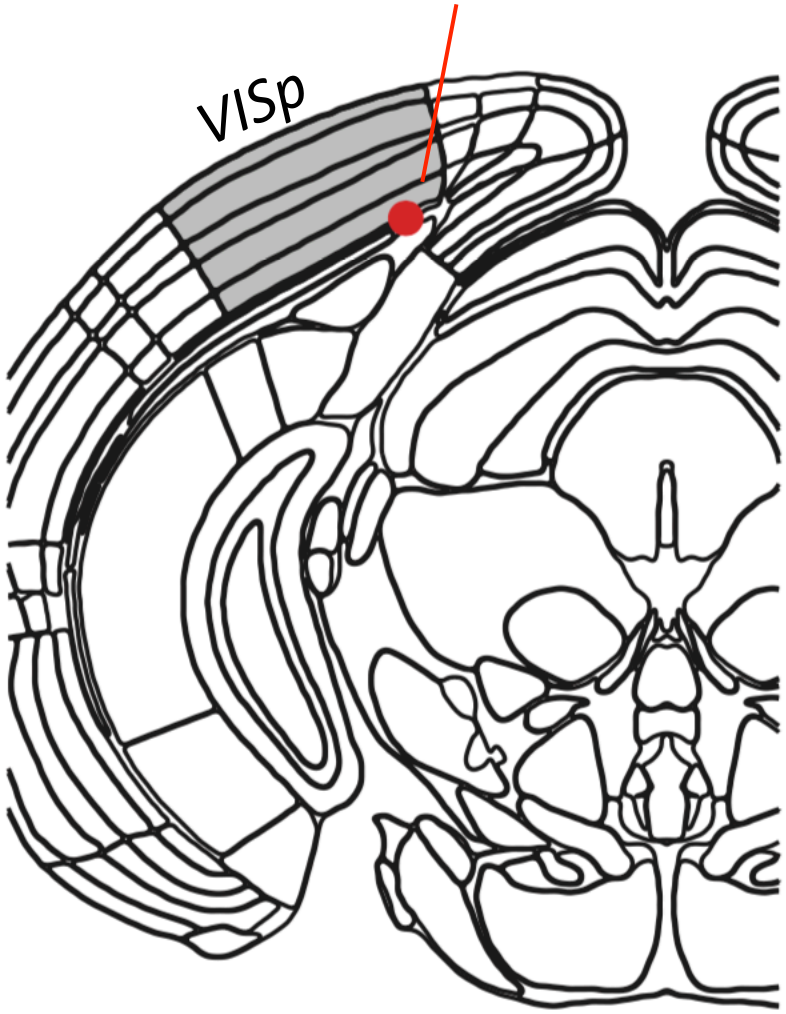




Steinmetz, Zatka-Haas, Carandini, Harris
bioRxiv 2018

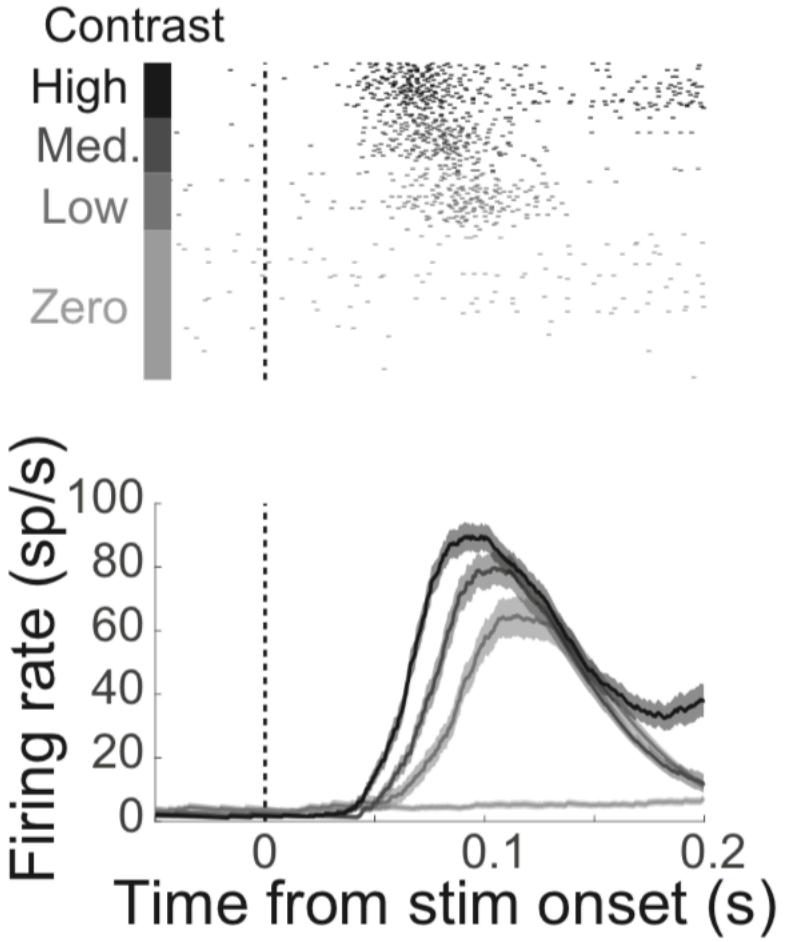
Example neuron: Primary Visual Cortex

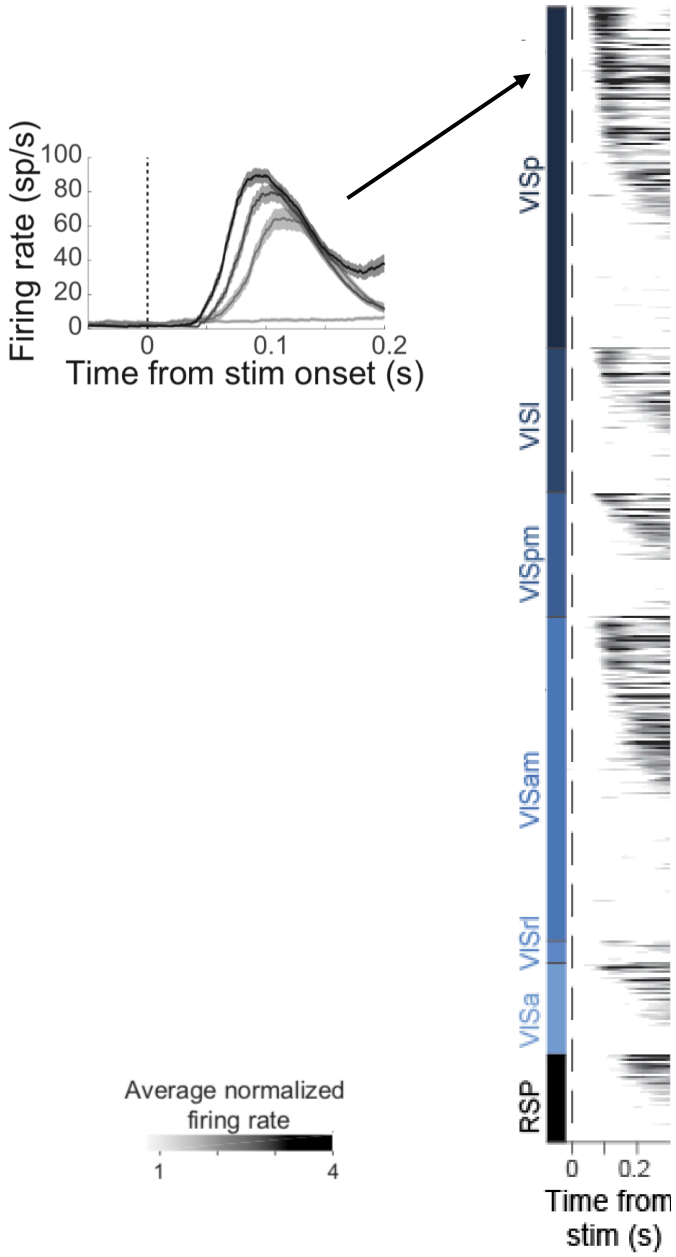
Neuron location



Waveform

Task activity




Firing rate (sp/s)
100
80
60
40
20
0
0
0.1
0.2
Time from stim onset (s)
VISp
VISl
VISpm
VISam
VISrl
VISa
RSP
Average normalized firing rate
1
4
0
0.2
Time from stim (s)

You must cross-validate sorted plots!!!

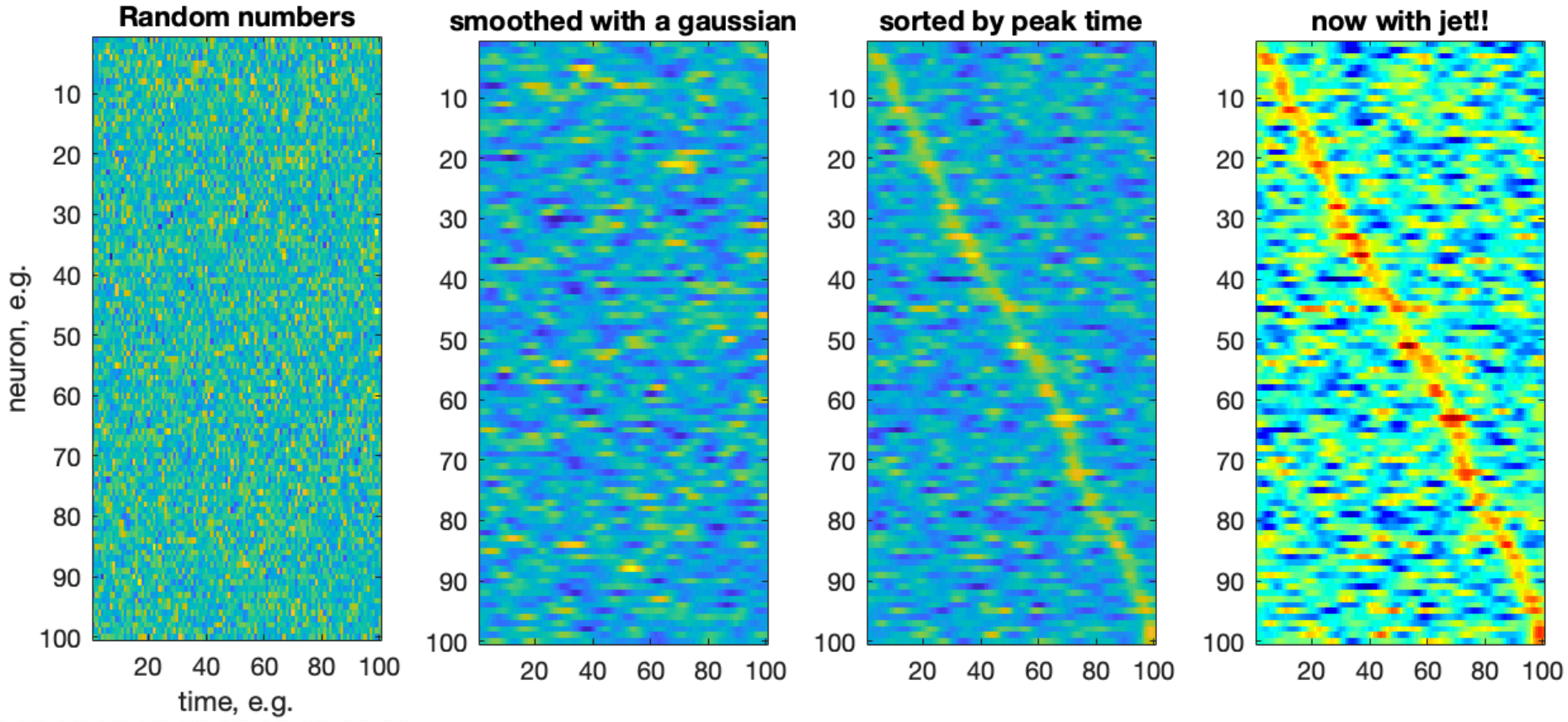
```
z = randn(100); % Generate gaussian-distributed random numbers
zs = conv2(1, gausswin(13), z, 'same'); % smooth rows with a gaussian
[~,mx] = max(zs, [], 2); % find the peak times of each row
[~,ii] = sort(mx); % sort the peak times to re-order the plot
```

imagesc(z)

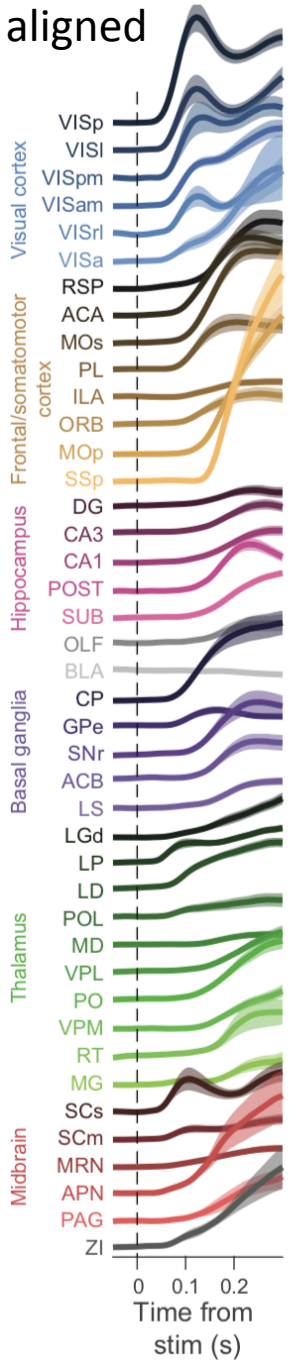
imagesc(zs)

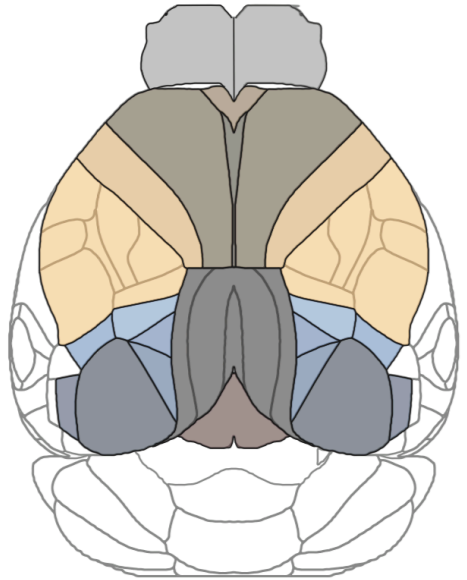
imagesc(zs(ii,:))

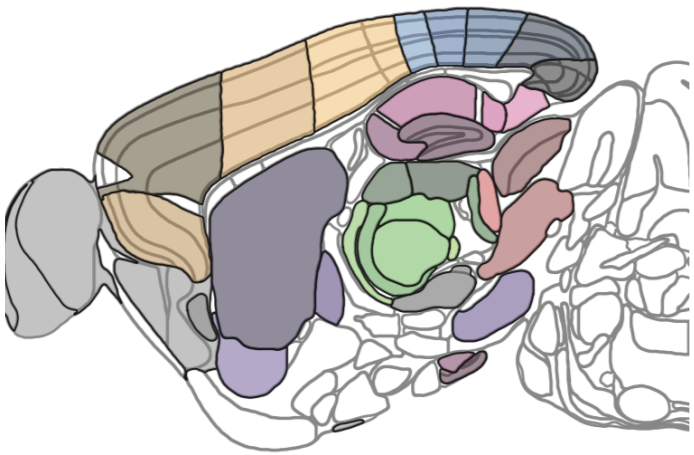
imagesc(zs(ii,:))
colormap jet

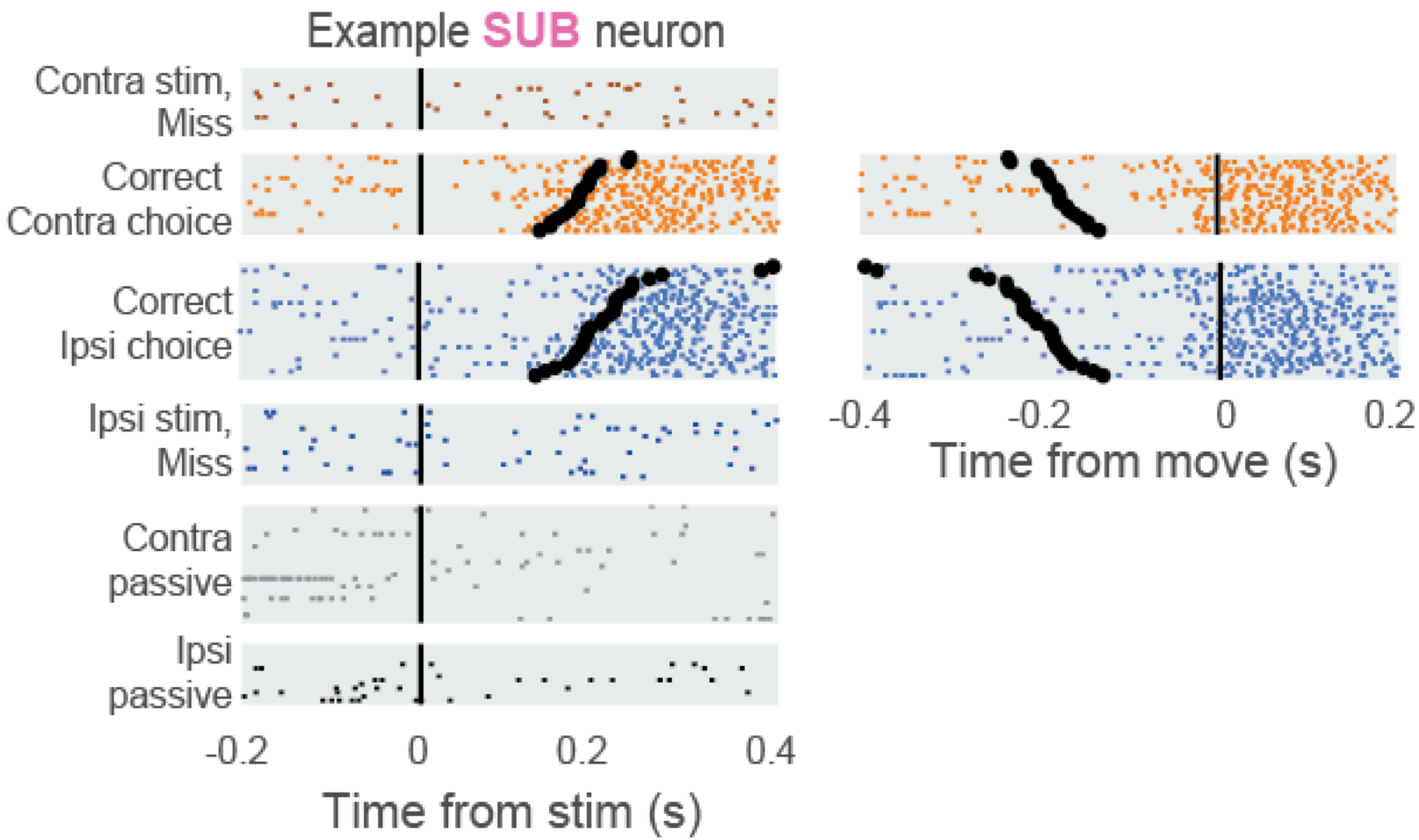


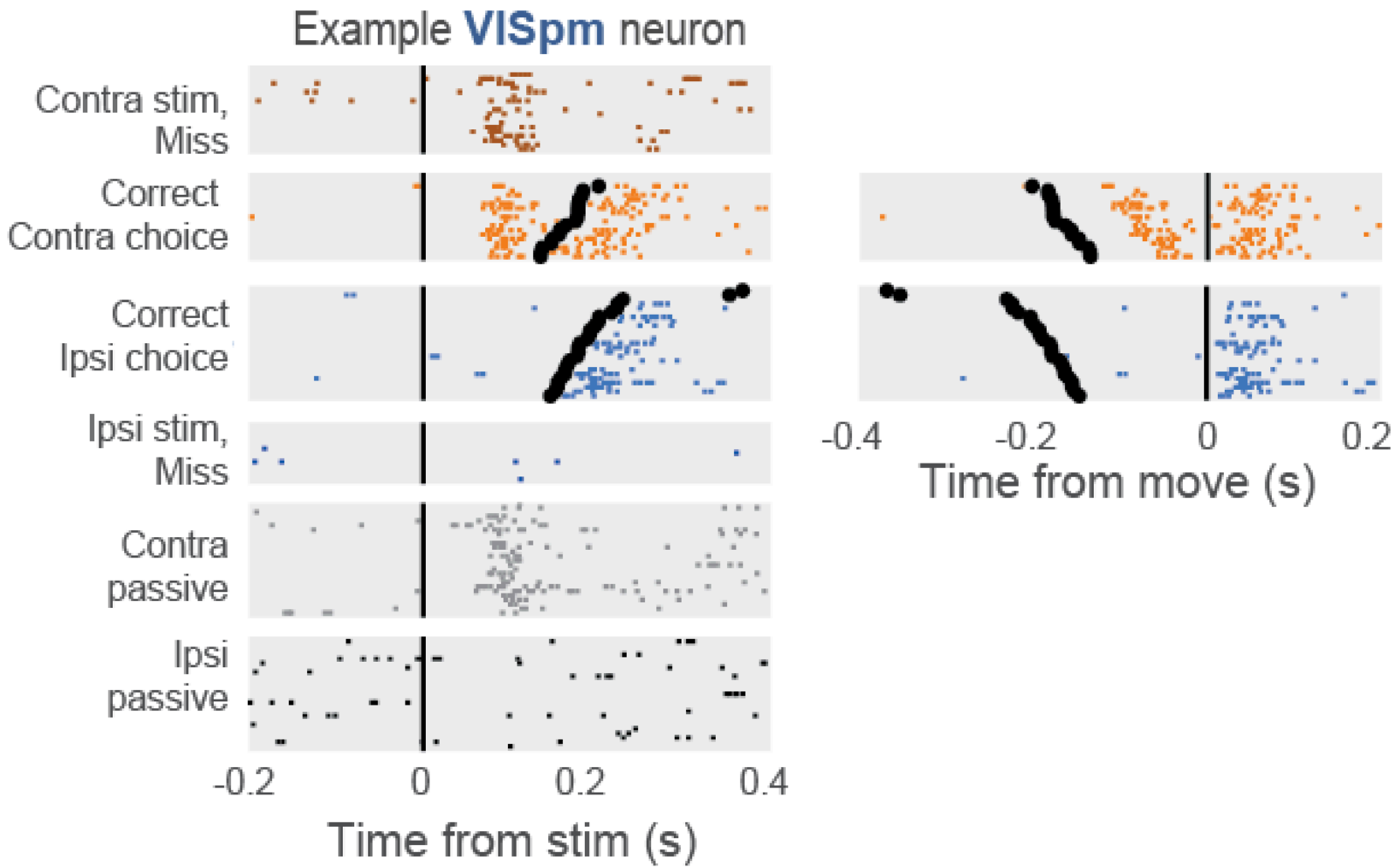
Visual stimulus aligned

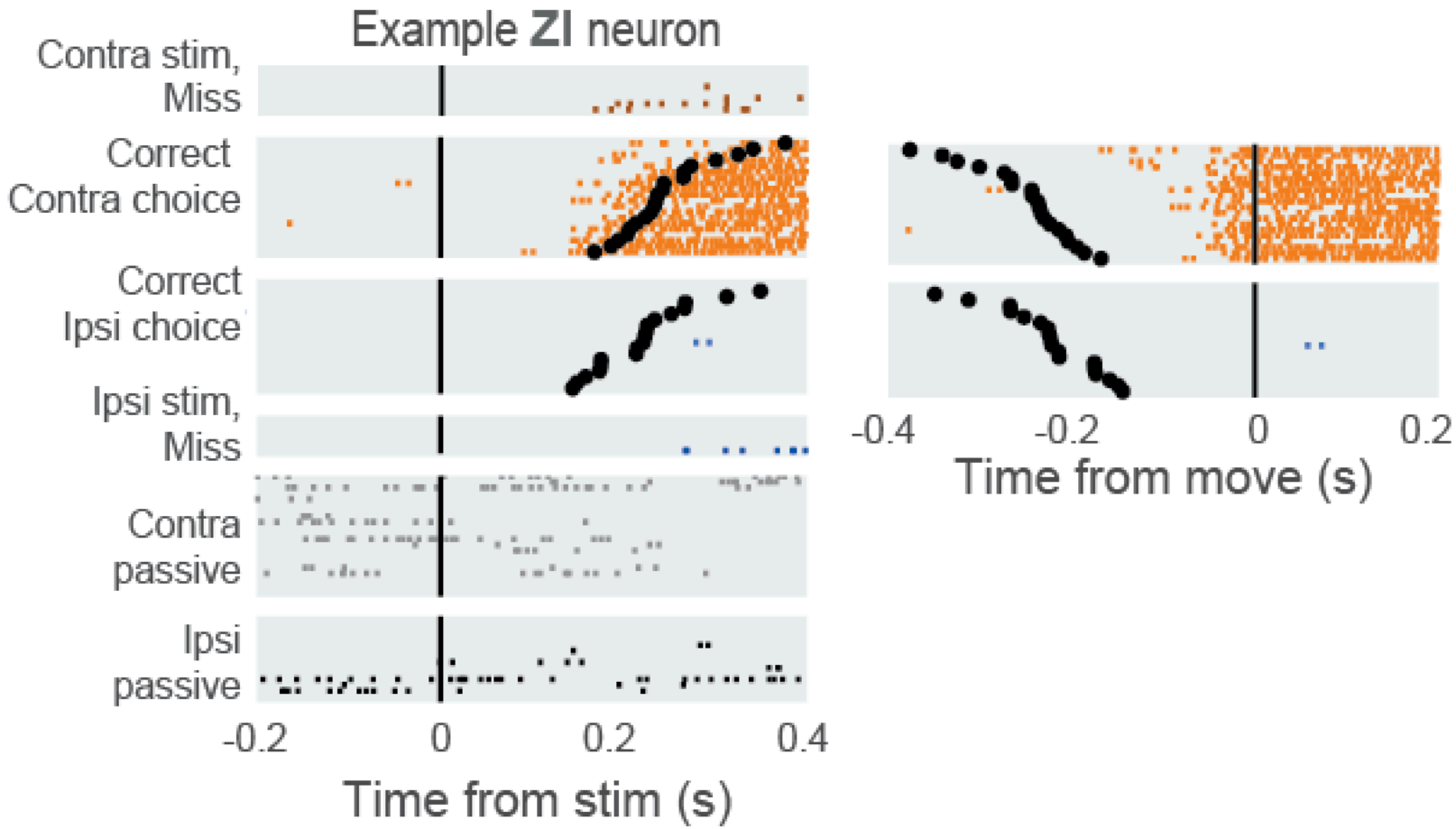




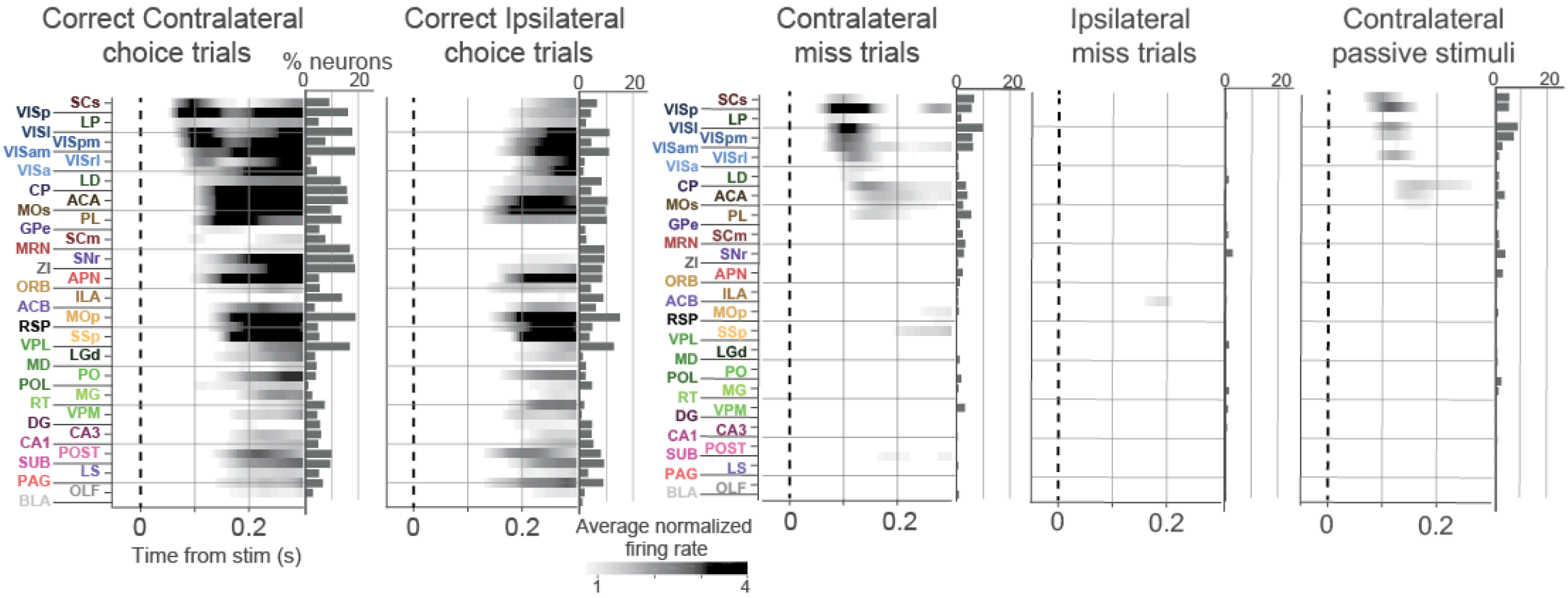



Example SUB neuron
Contra stim, Miss
Correct Contra choice
Correct Ipsi choice
Ipsi stim, Miss
Contra passive
Ipsi passive
-0.2
0
0.2
0.4
Time from stim (s)
-0.4
-0.2
0
0.2
Time from move (s)

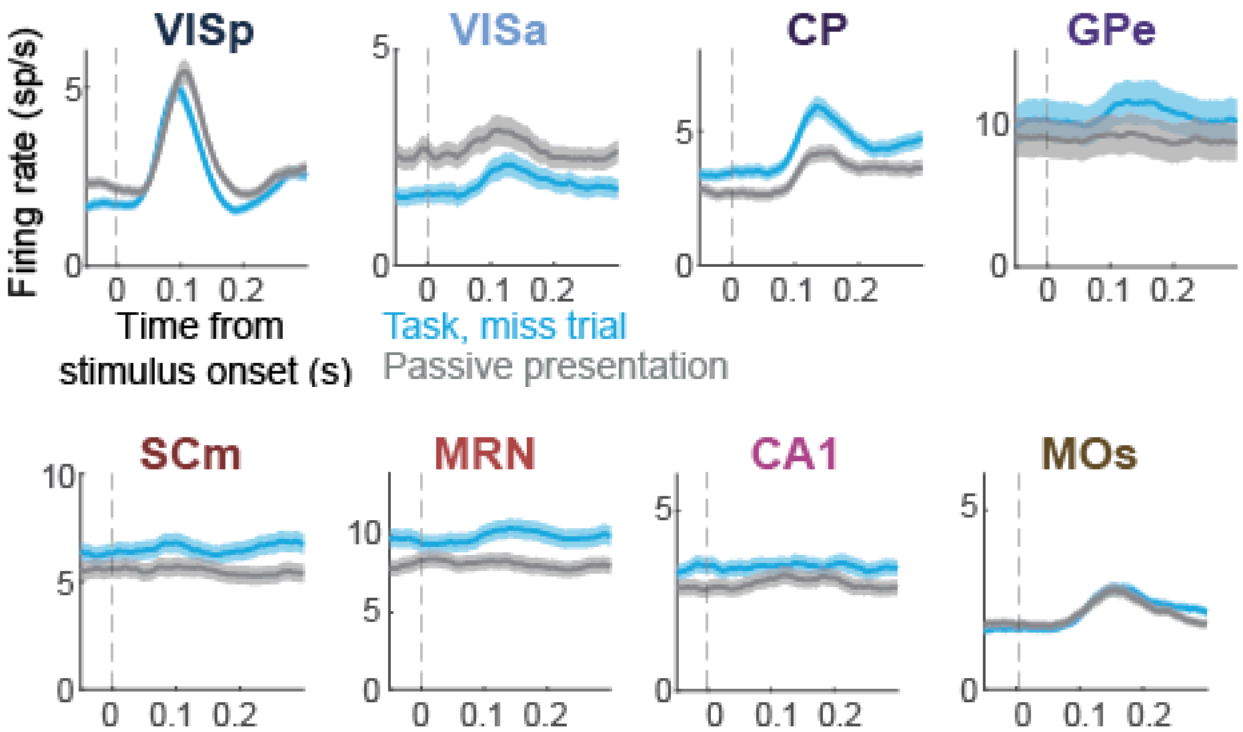

Example VISpm neuron
Contra stim, Miss
Correct Contra choice
Correct Ipsi choice
Ipsi stim, Miss
Contra passive
Ipsi passive
-0.2
0
0.2
0.4
Time from stim (s)
-0.4
-0.2
0
0.2
Time from move (s)

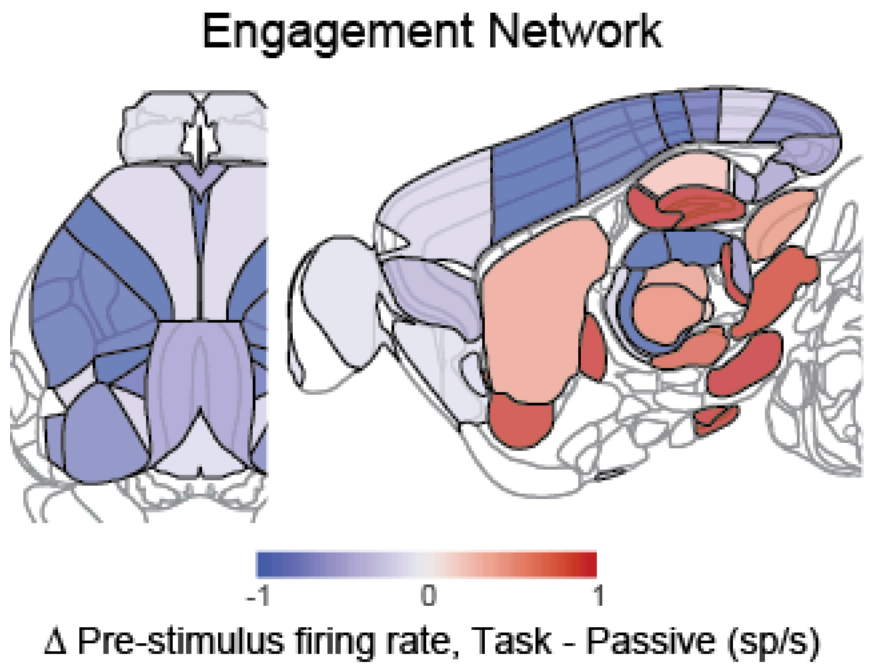

Example ZI neuron
Contra stim, Miss
Correct Contra choice
Correct Ipsi choice
Ipsi stim, Miss
Contra passive
Ipsi passive
-0.2
0
0.2
0.4
Time from stim (s)
-0.4
-0.2
0
0.2
Time from move (s)

Only a small fraction of the activity is purely visual

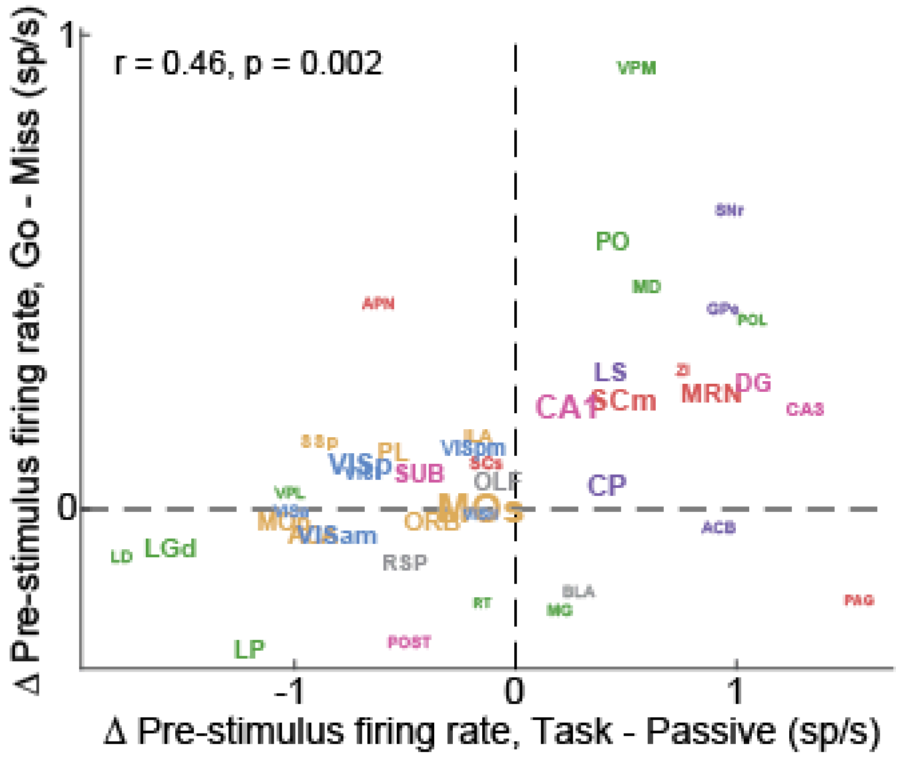


Pre-stimulus activity differs between task and passive conditions

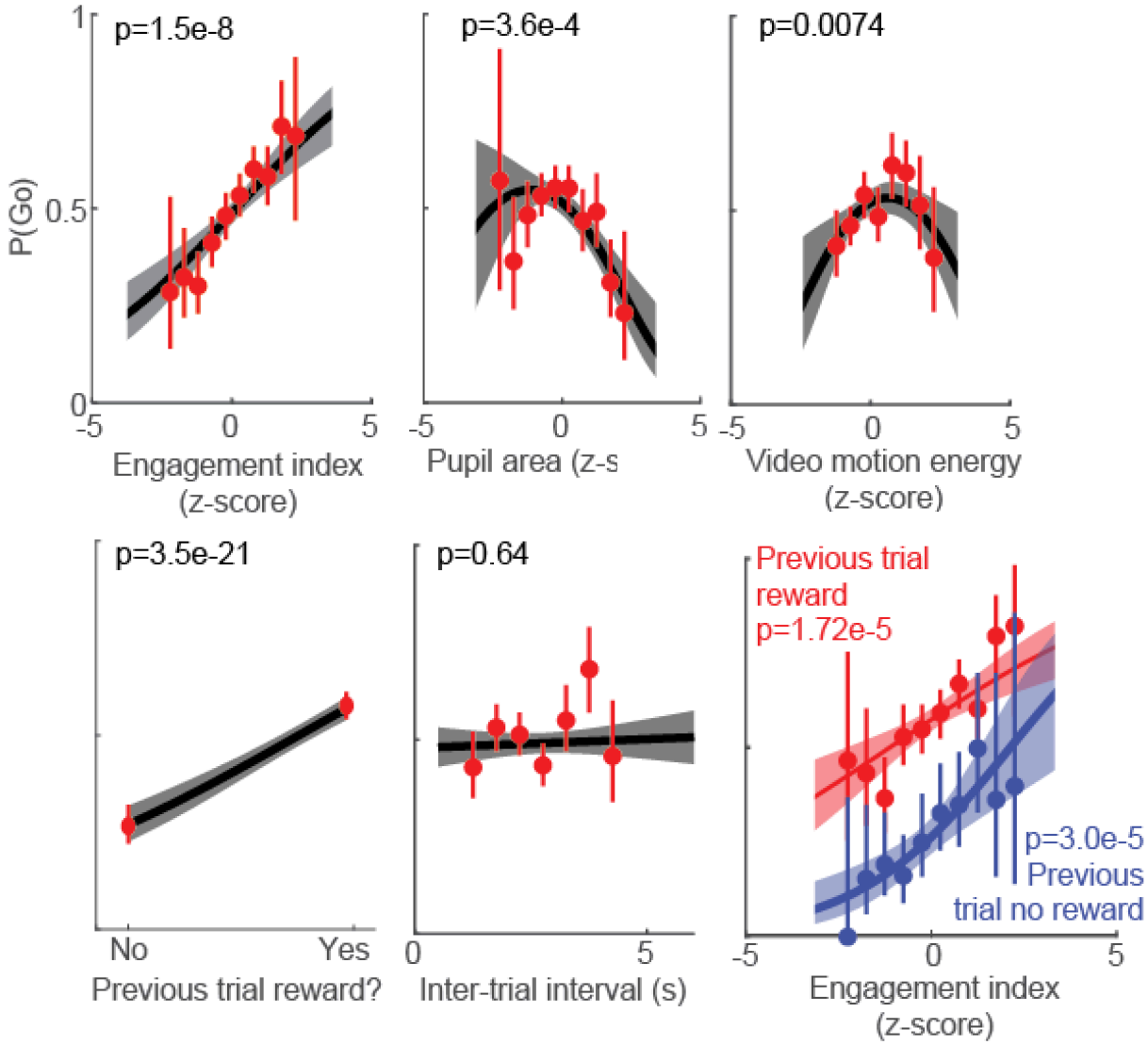




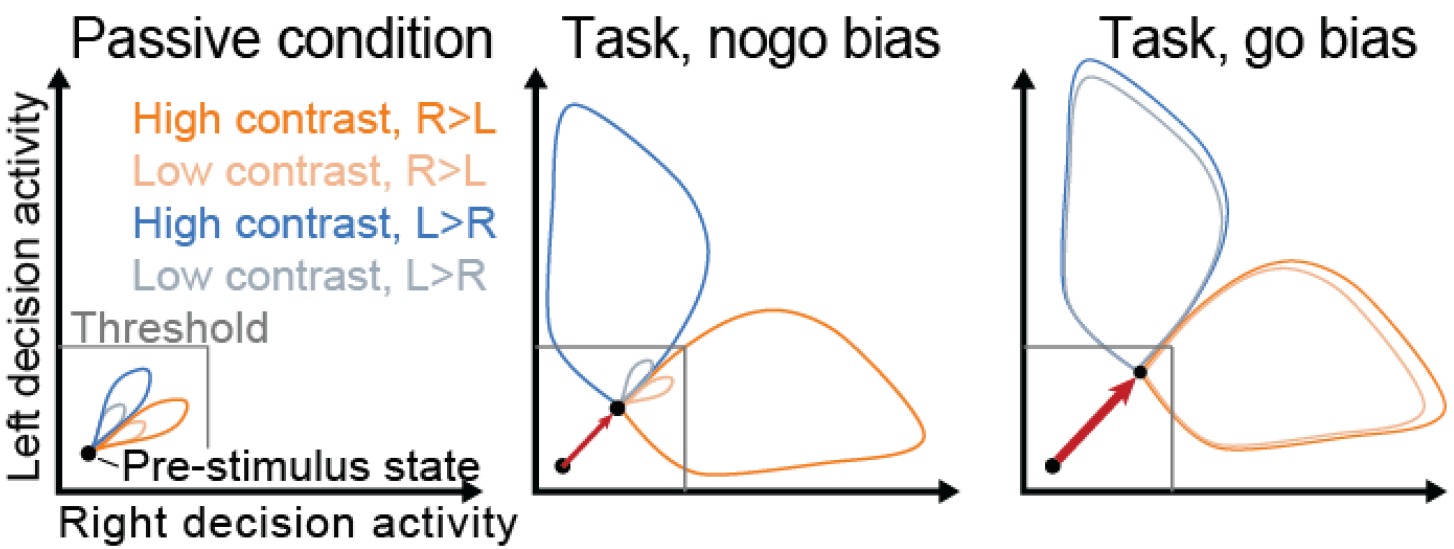
Distributed pre-stimulus activity is a signature of engagement distinct from arousal and reward

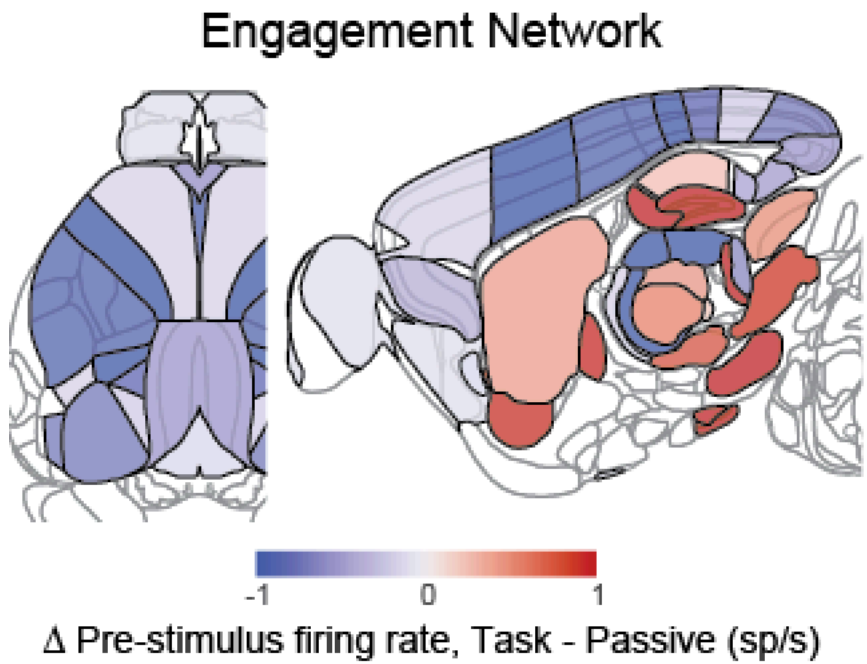


c.f. Allen et al 2019

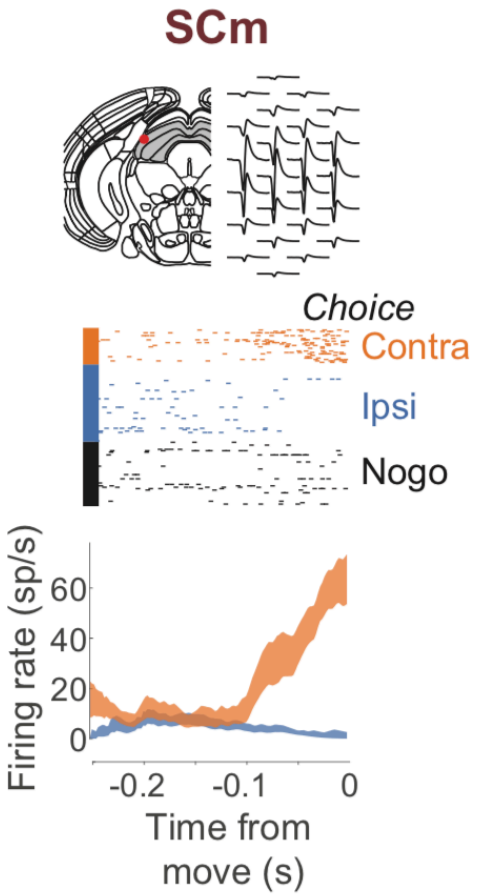


Engagement biases subcortical activity towards a detection threshold

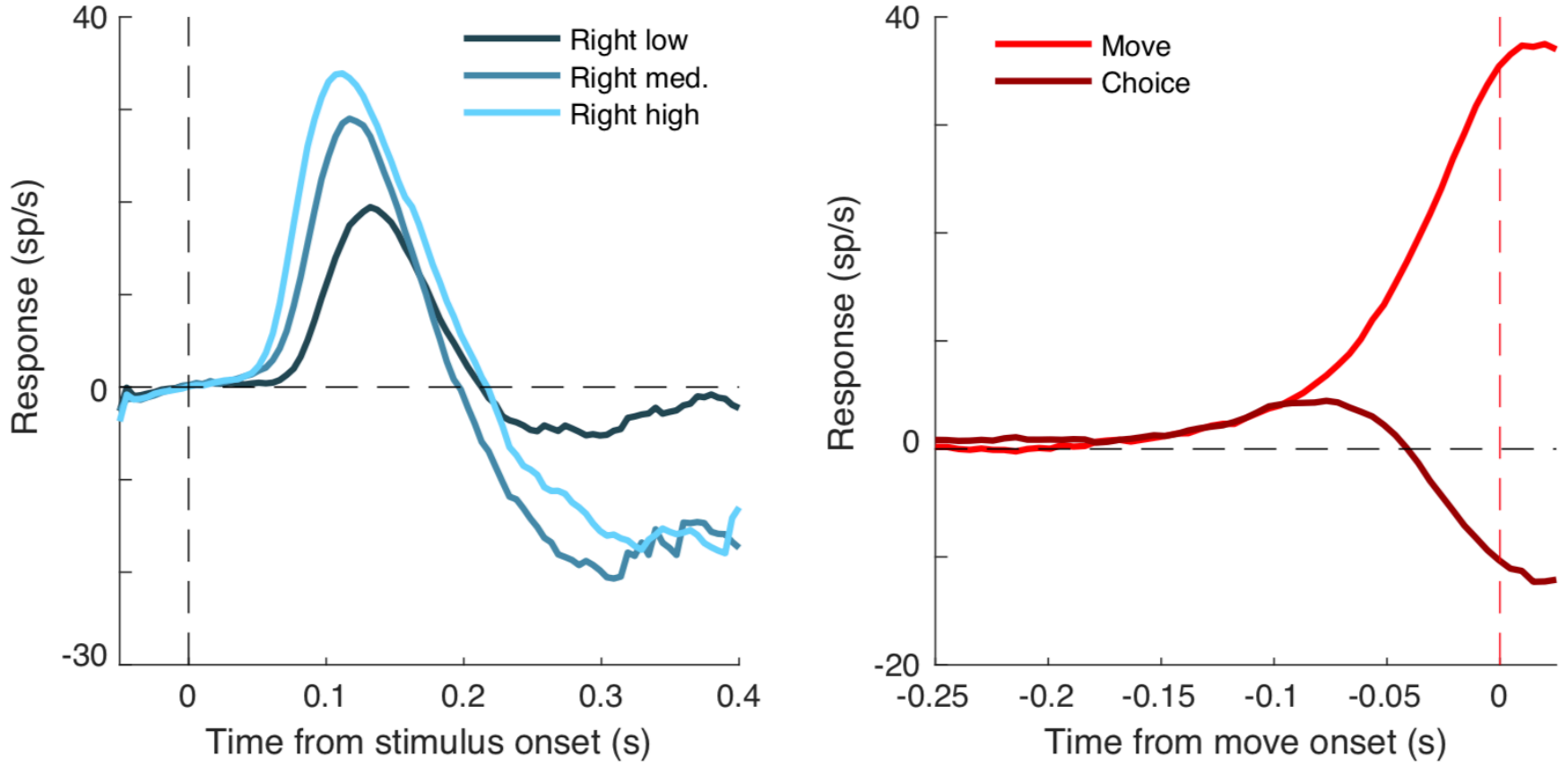




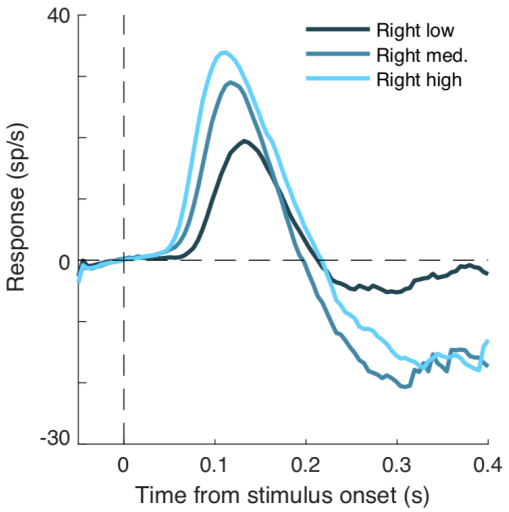
Rare cortical and subcortical neurons encode the upcoming decision

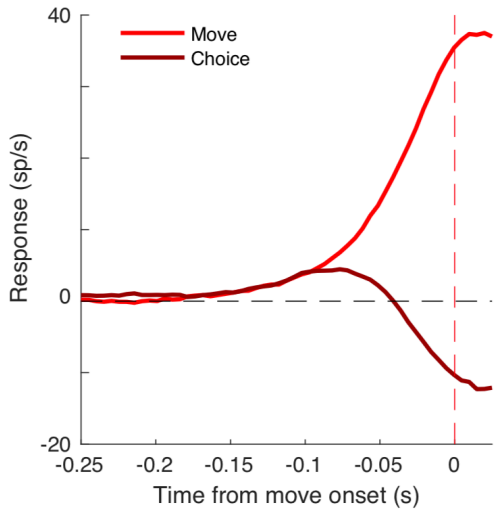


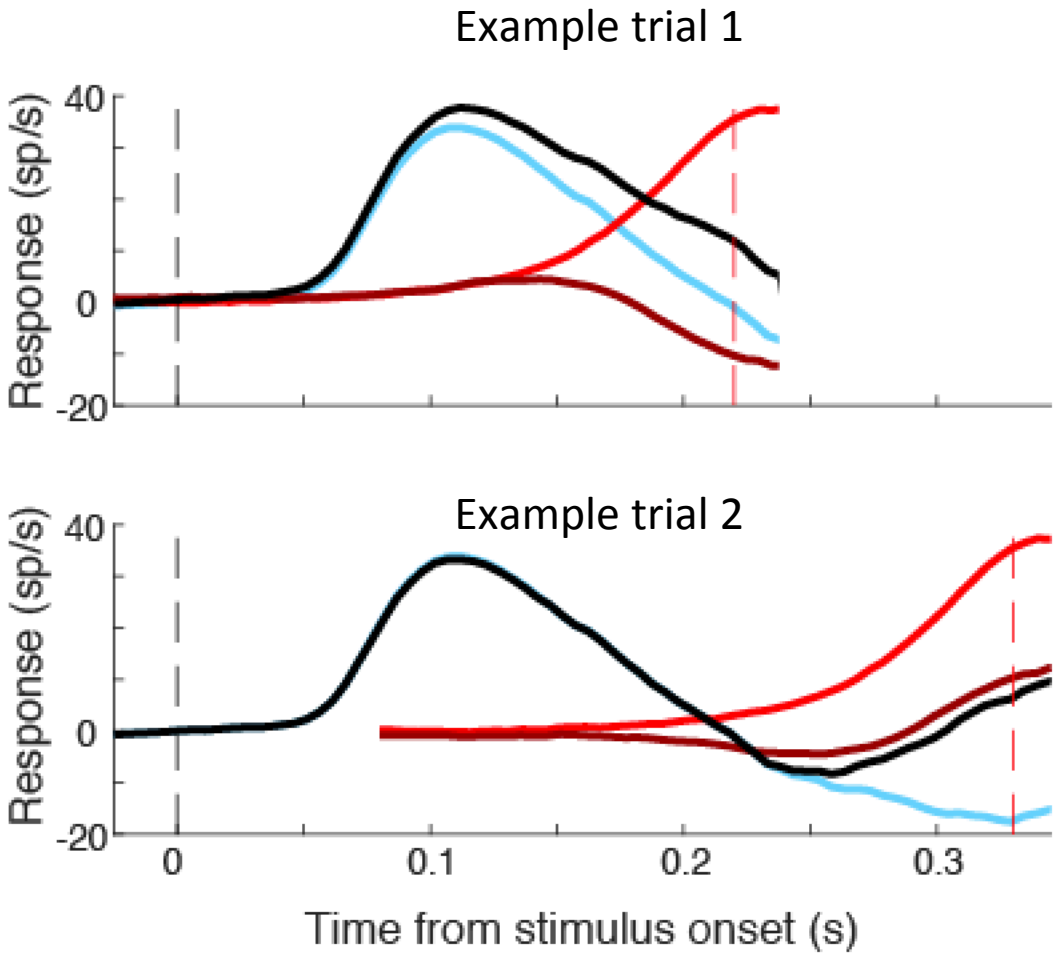
Kernel models



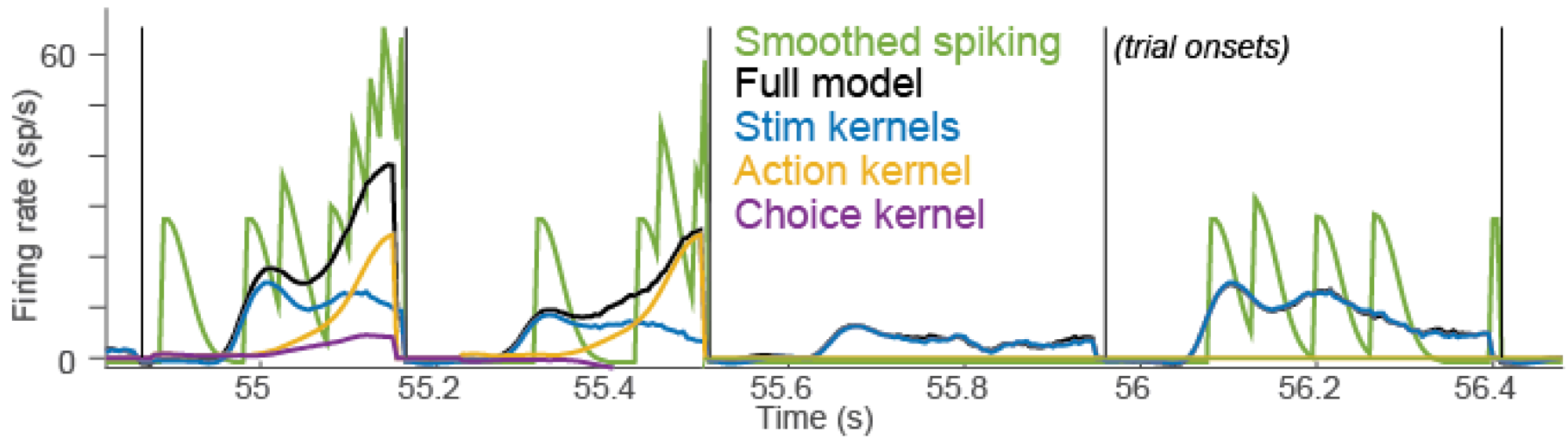
Kernel models



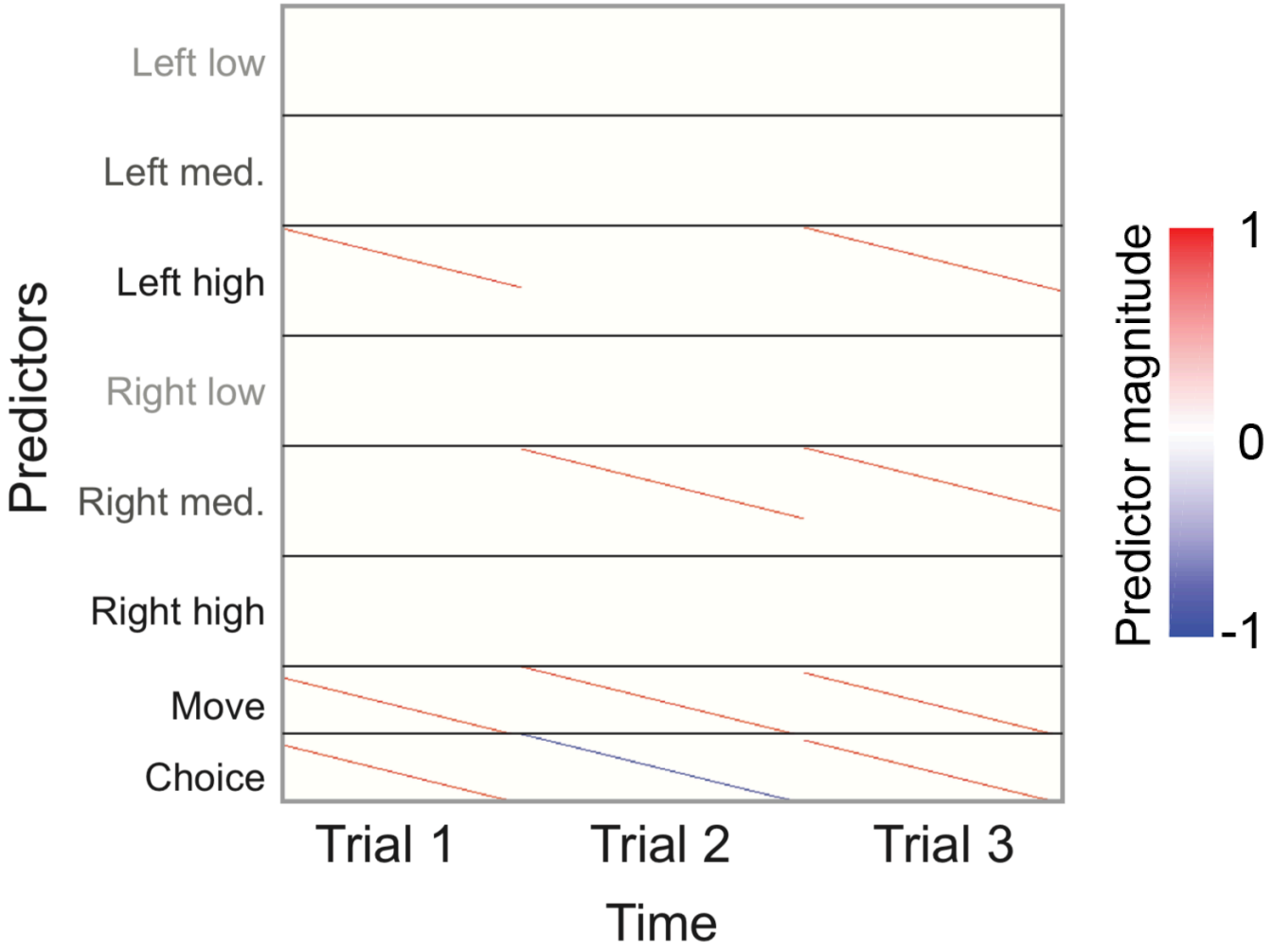


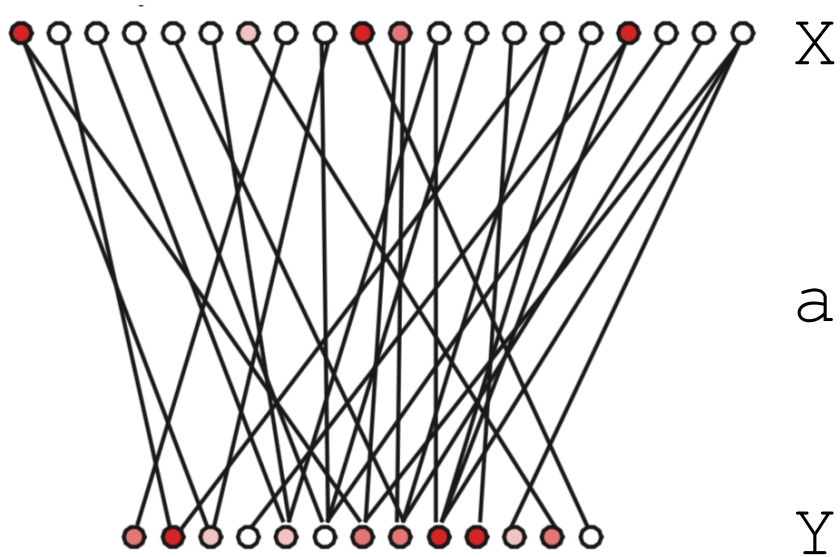


Example fit


Smoothed spiking
Full model
Stim kernels
Action kernel
Choice kernel
(trial onsets)
Firing rate (sp/s)
60
0
55
55.2
55.4
55.6
55.8
56
56.2
56.4
Time (s)

Fitting kernel models with linear regression



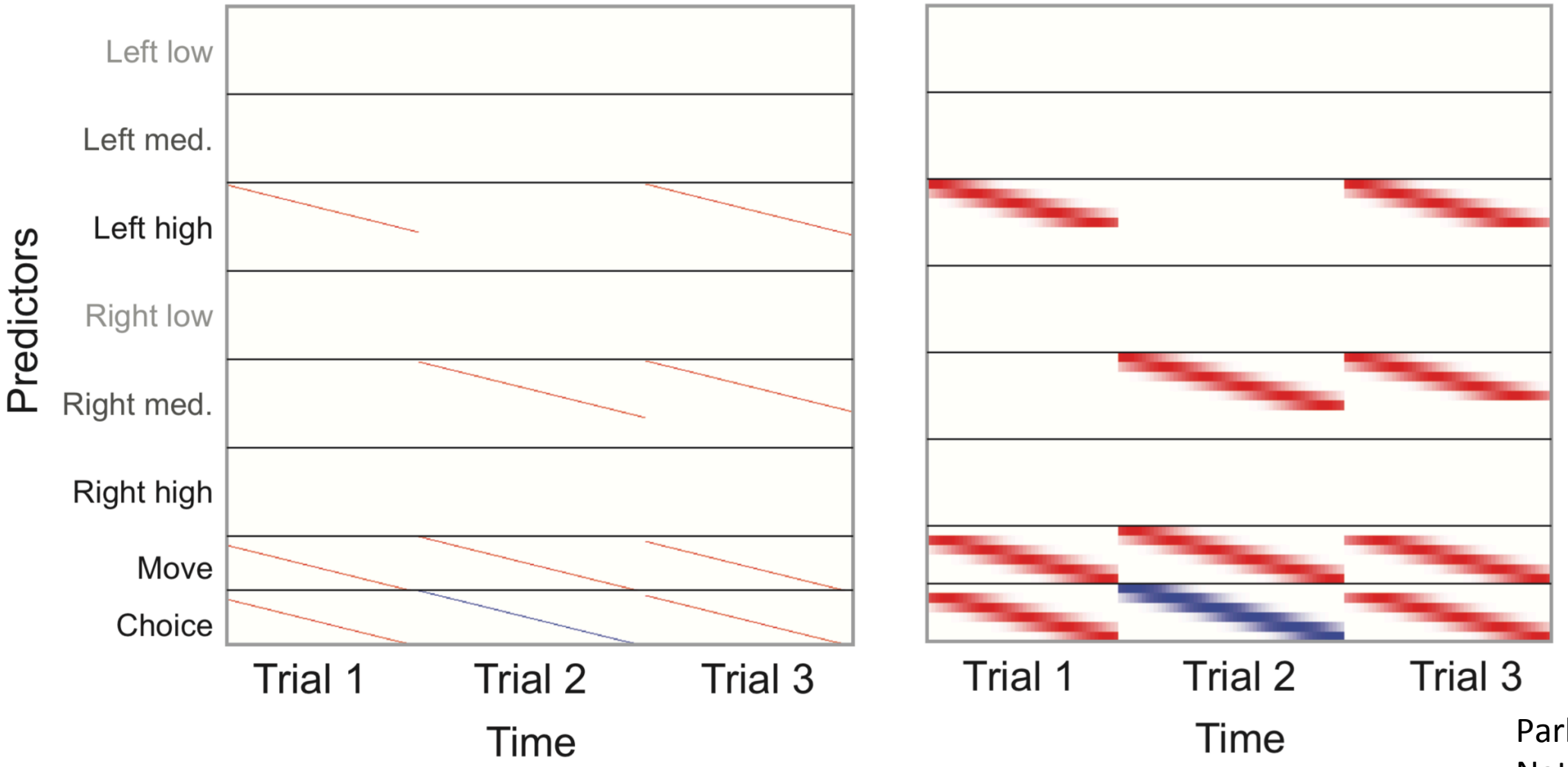


$$Y = X * a$$

Spike counts

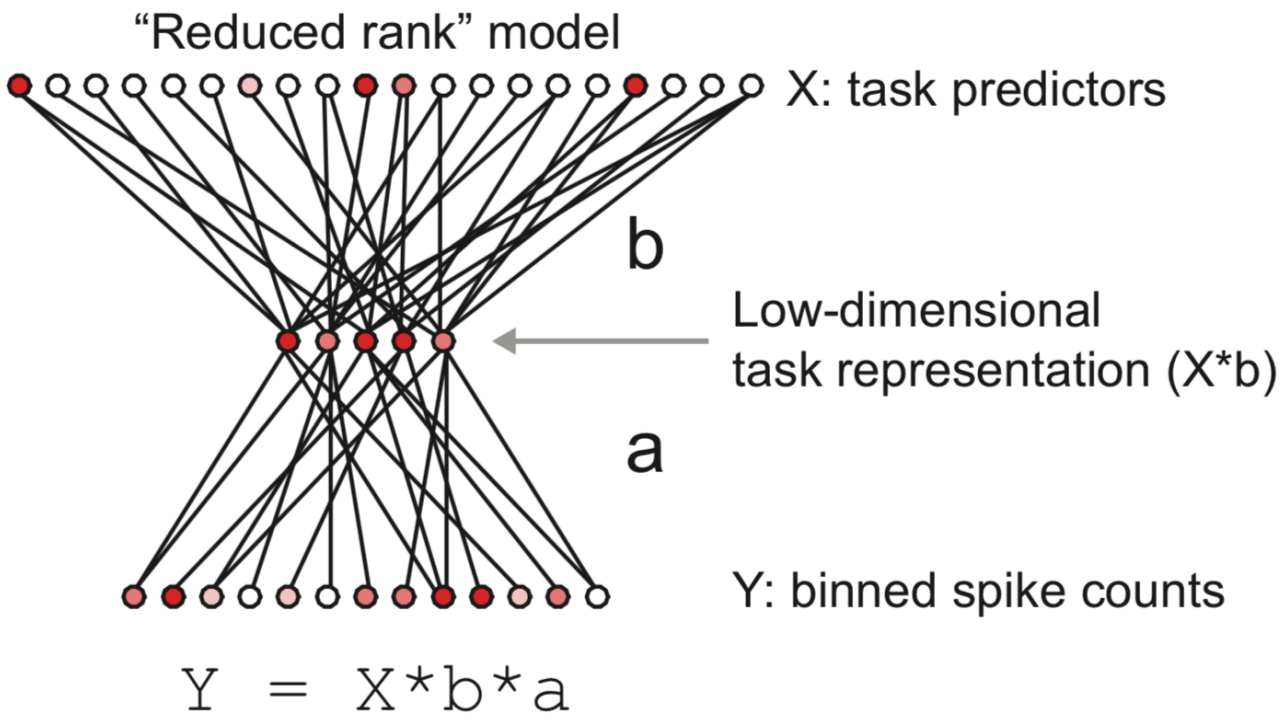
Task predictors

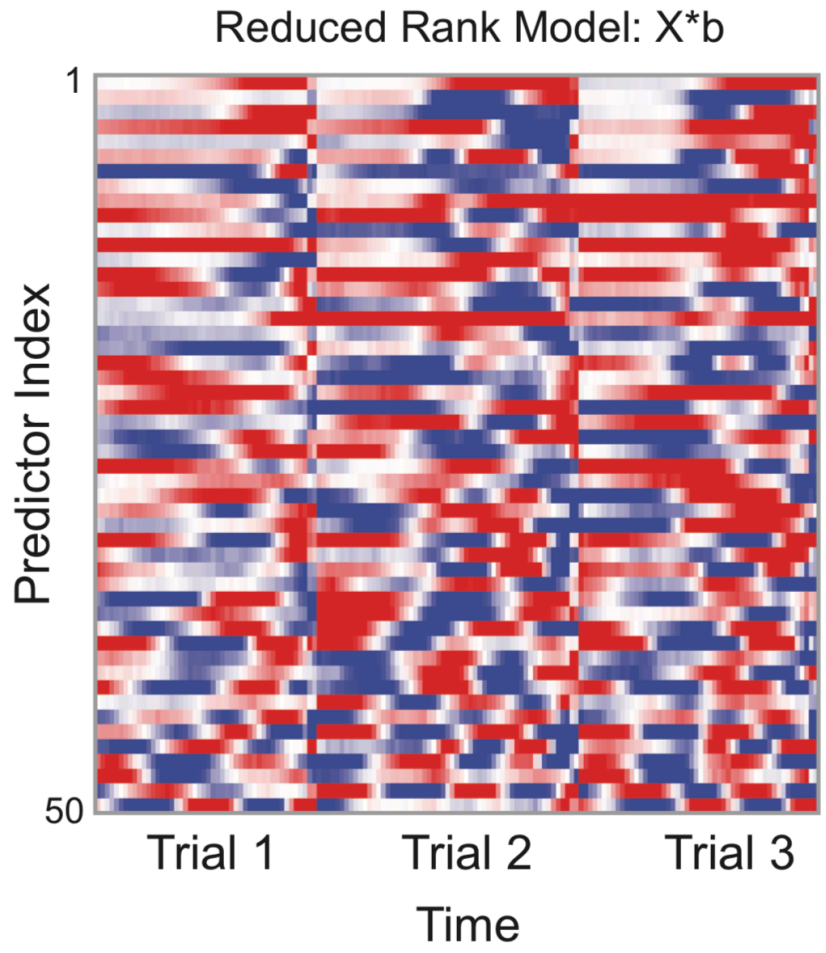
Basis functions can help overfitting



Park & Pillow
Nat. Neuro. 2014

“Reduced rank regression” fitting





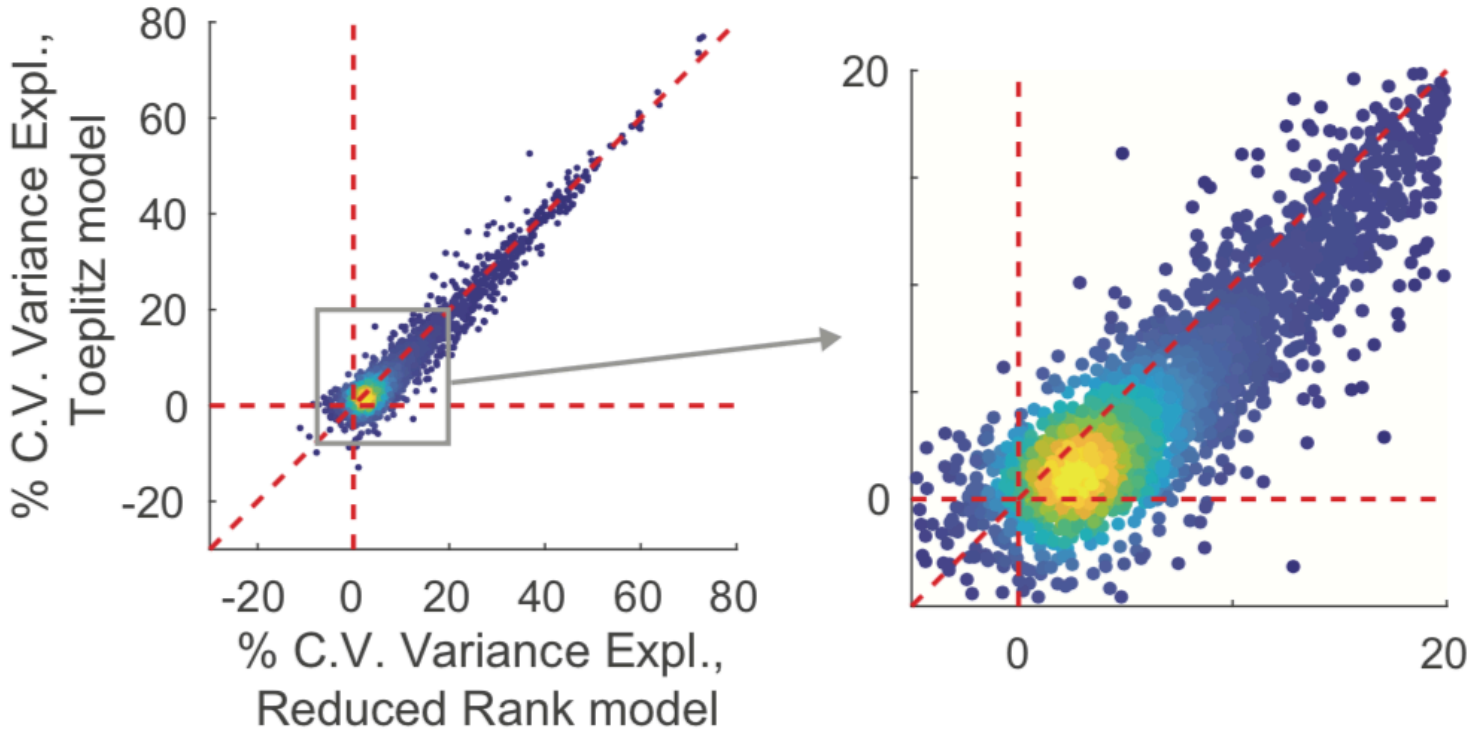
Trick: combining all recordings to improve fits to individual neurons

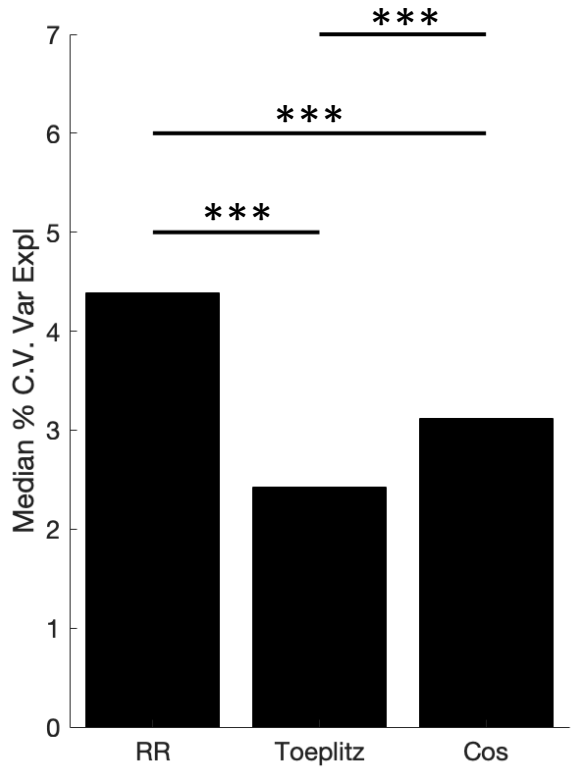
$$U\Sigma V = \underbrace{Cov_{YX}}\underbrace{Cov_{XX}^{-1/2}}$$

Covariance of spike counts with predictors
[nPredictors x nNeurons]
Concatenate Cov_{YX} from each recording

Covariance of predictors
[nPredictors x nPredictors]
Concatenate each recording into X_{all}, then take covariance

Reduced rank regression improves fits

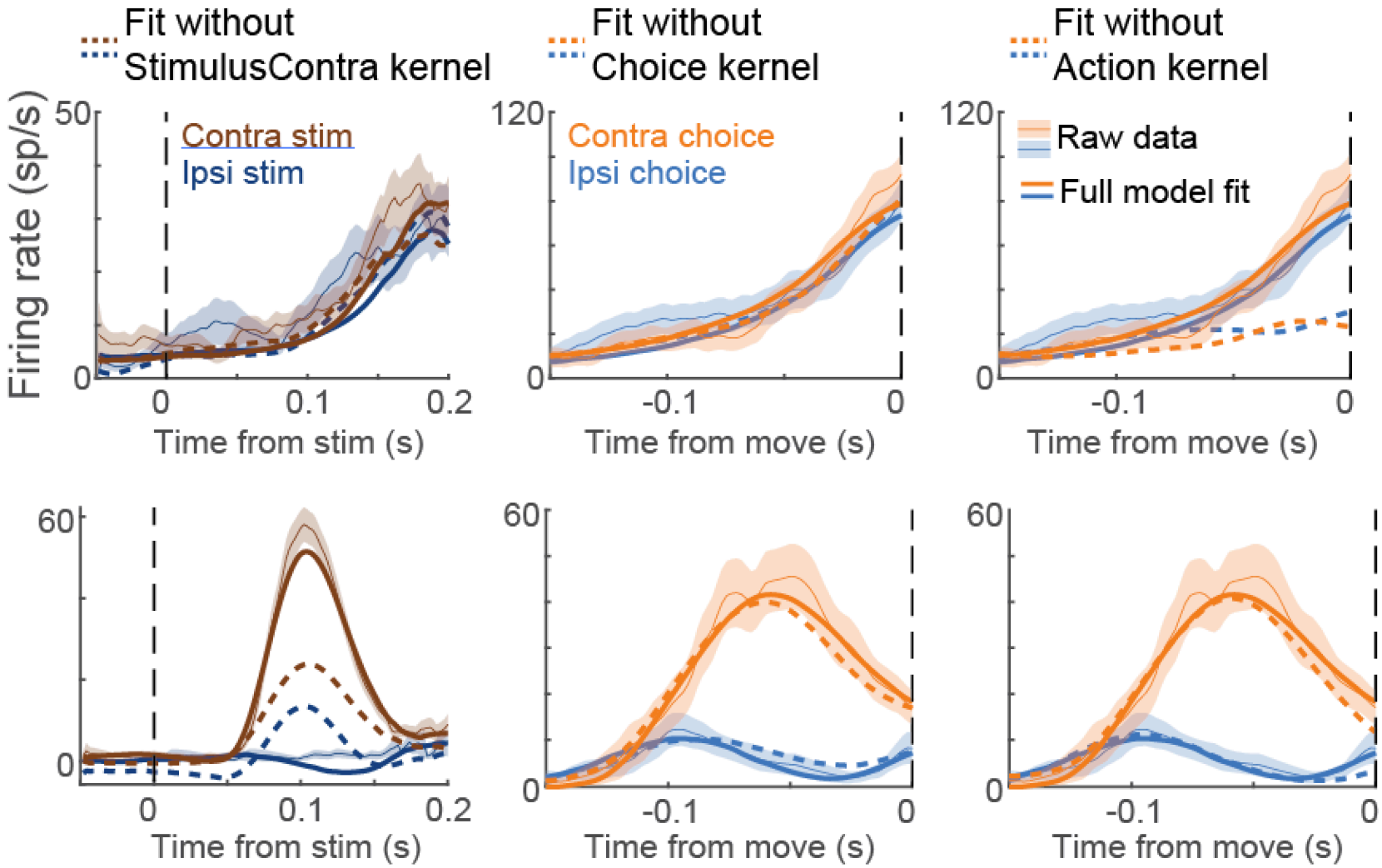




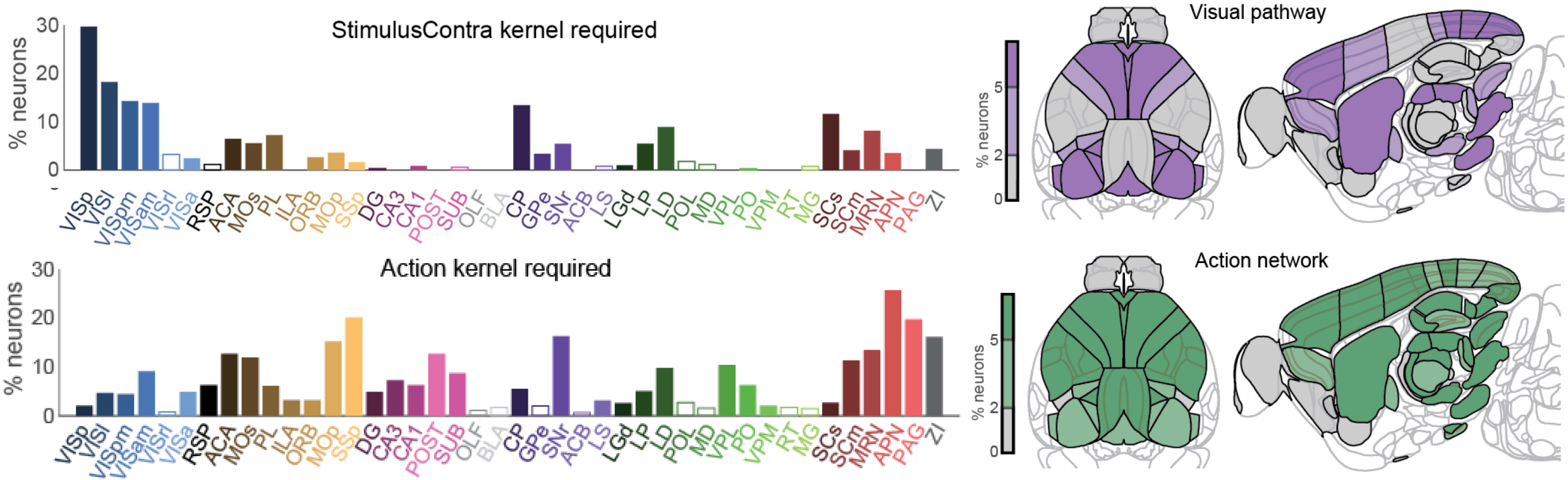
Kernel models isolate choice-related information

Example **SUB** neuron

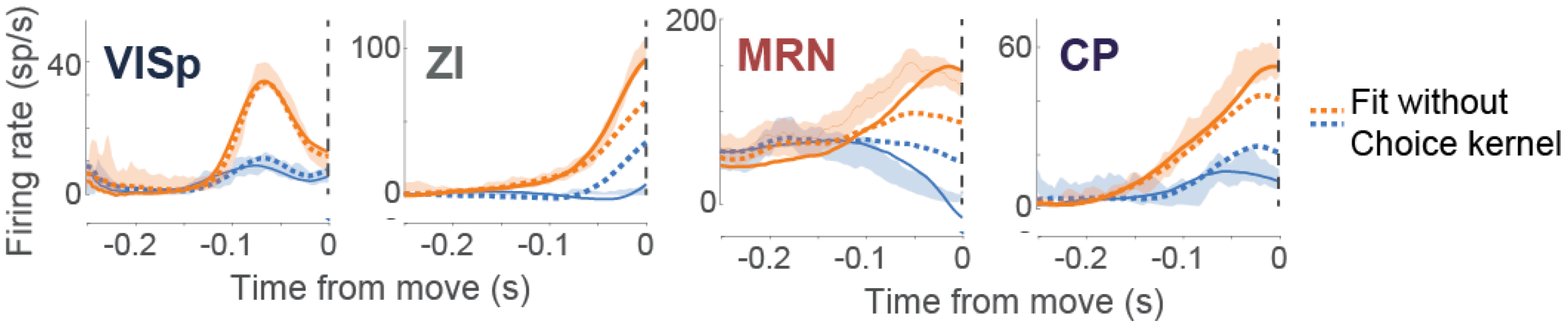
Example **VISpm** neuron

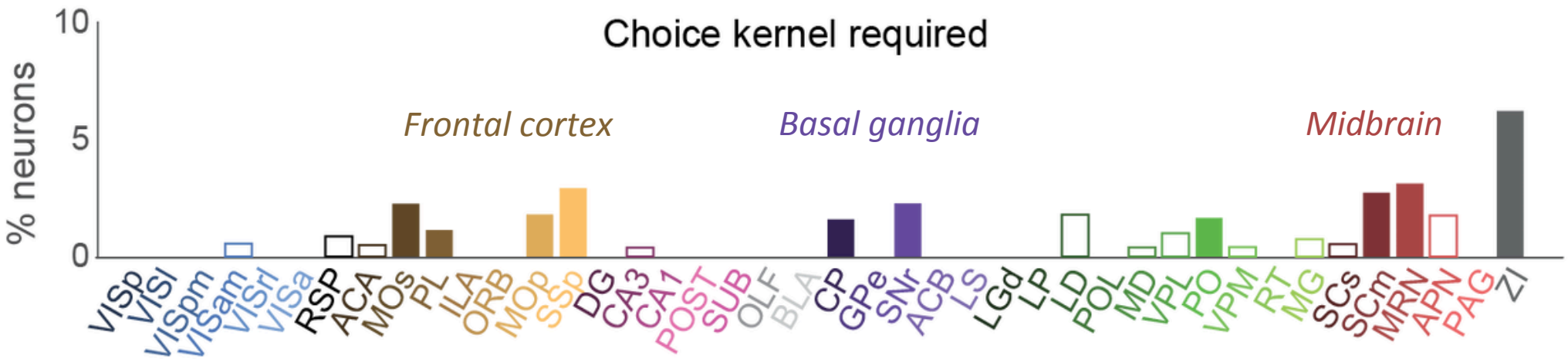


Kernel analysis defines Visual and Action networks



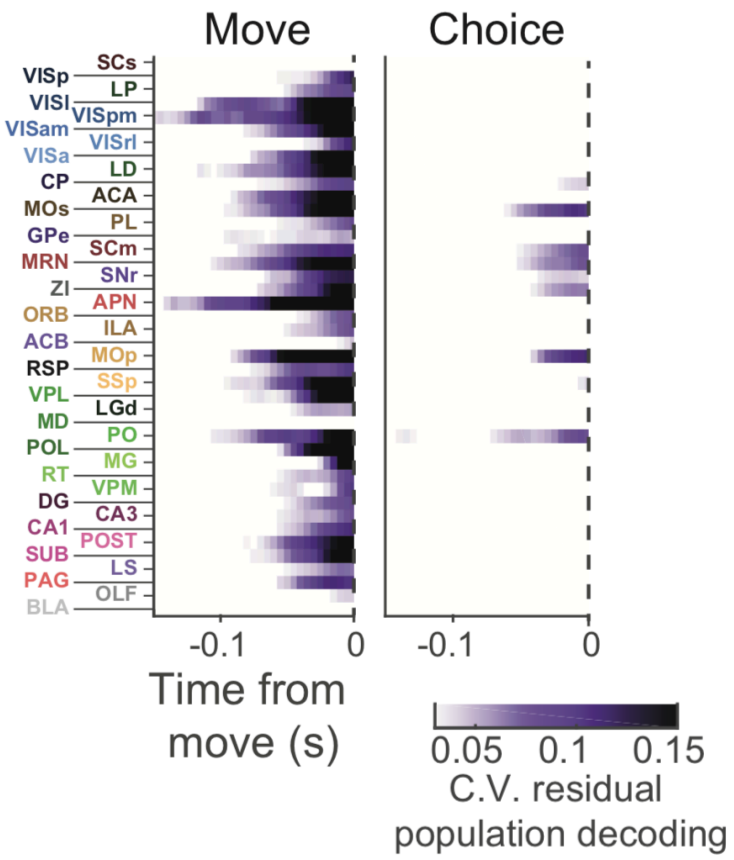
Rare cortical and subcortical neurons encode the upcoming decision

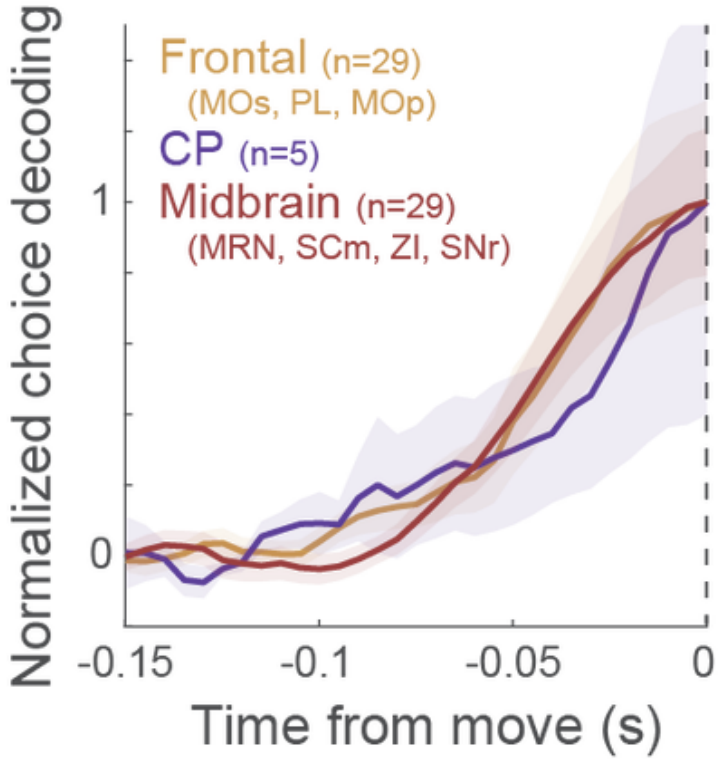




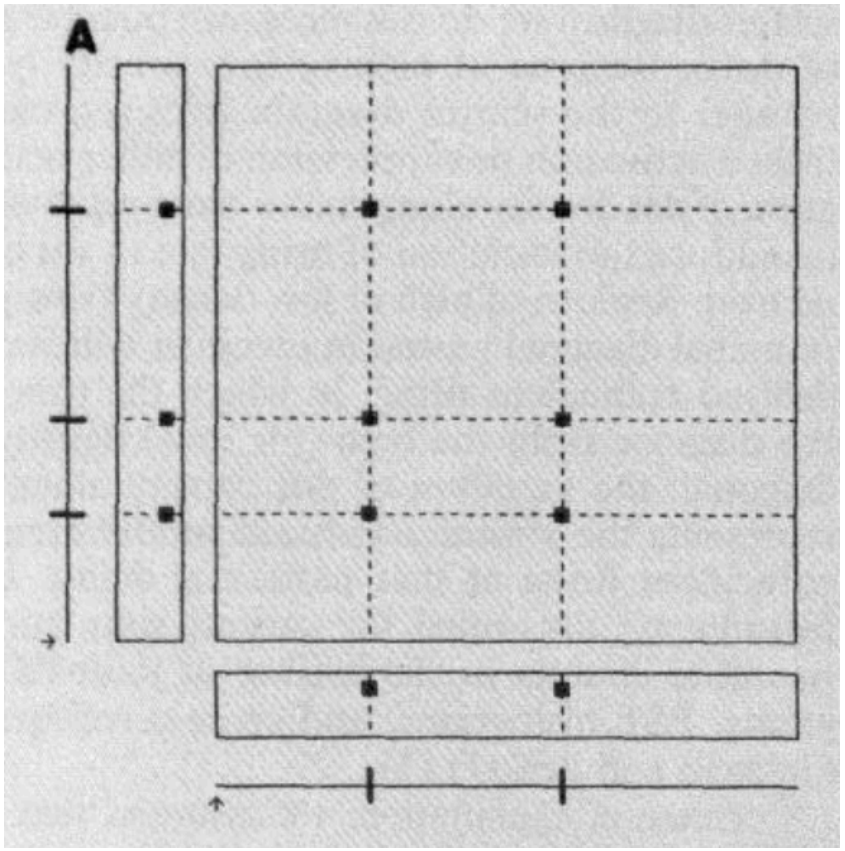
Choice encoding arises with similar timing in frontal cortex and midbrain

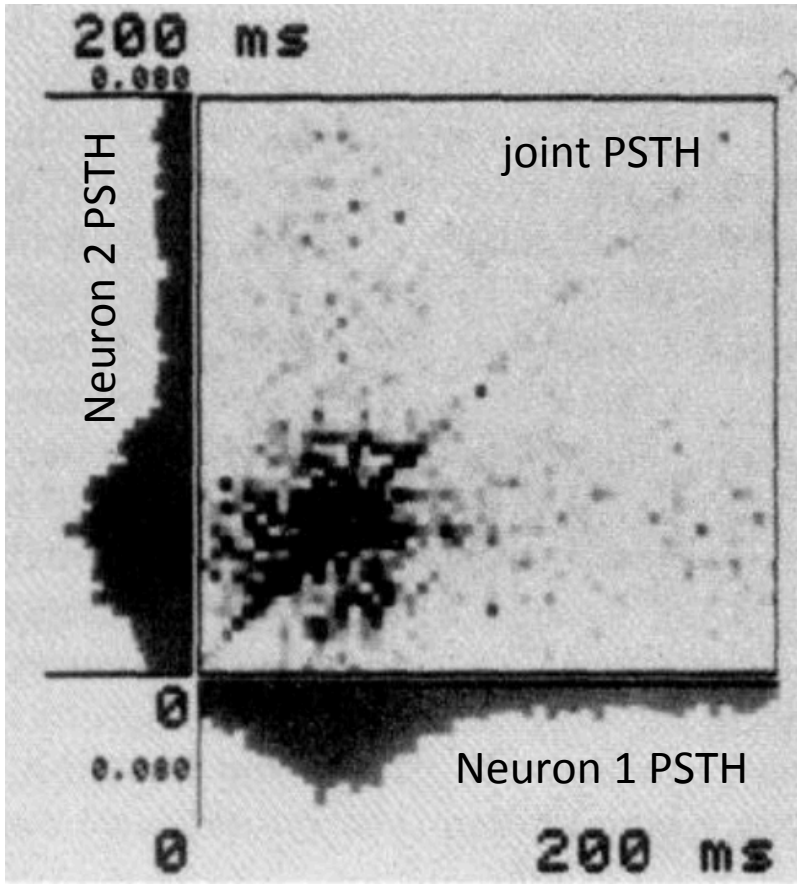
Population decoding analysis



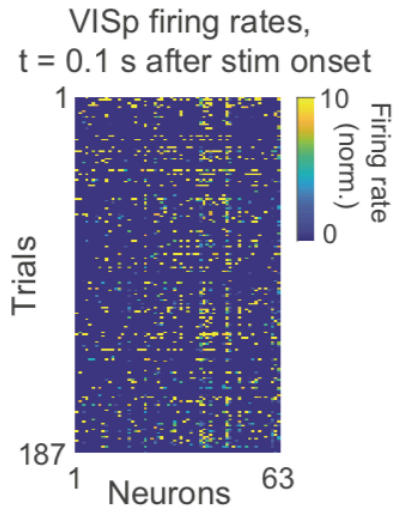


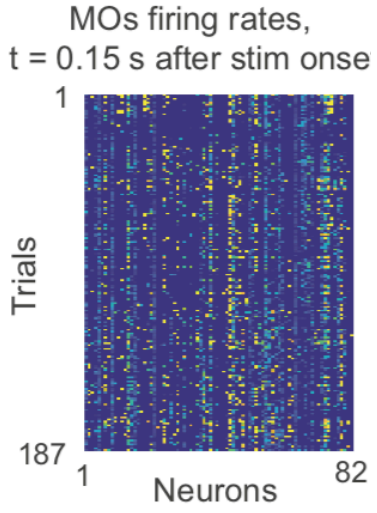
joint Peri-stimulus Time Histogram (jPSTH)



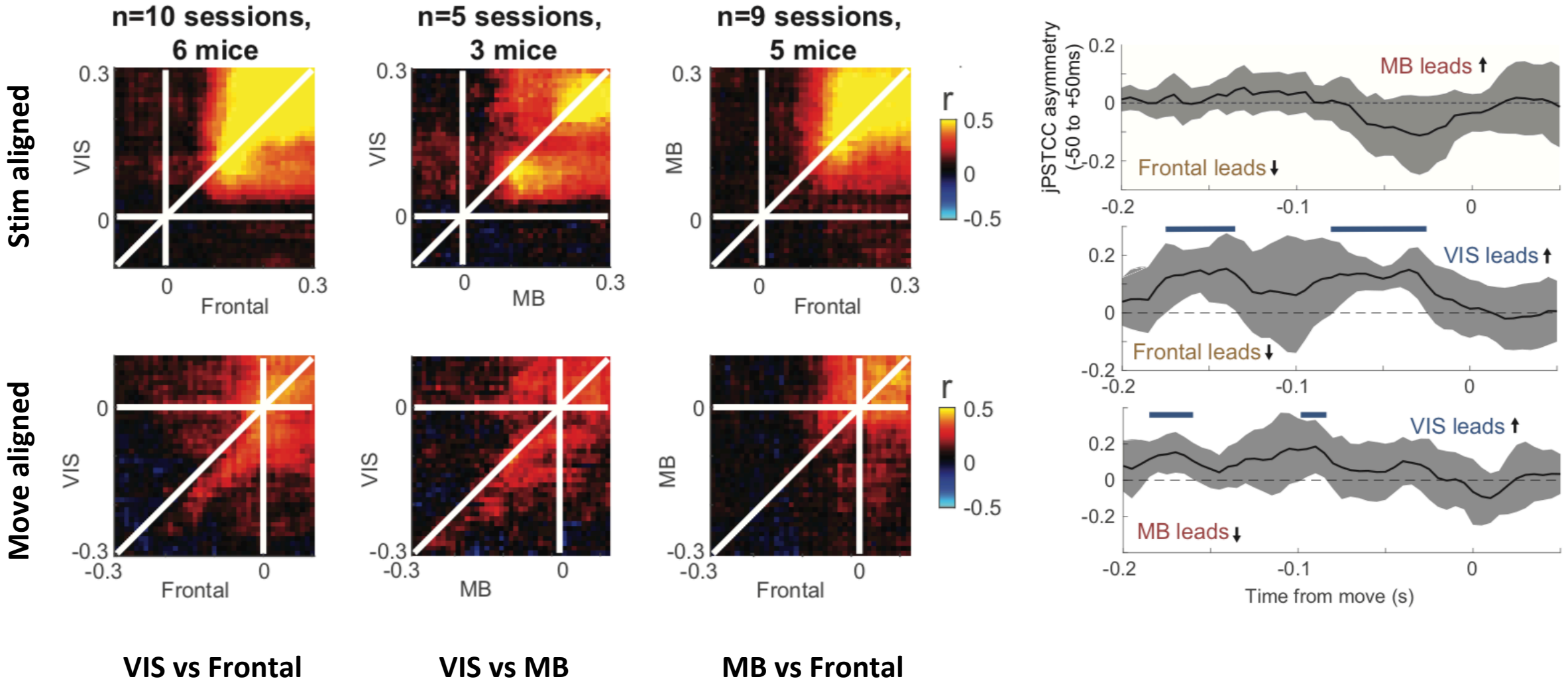


joint Peri-Event Canonical Correlation (jPECC)

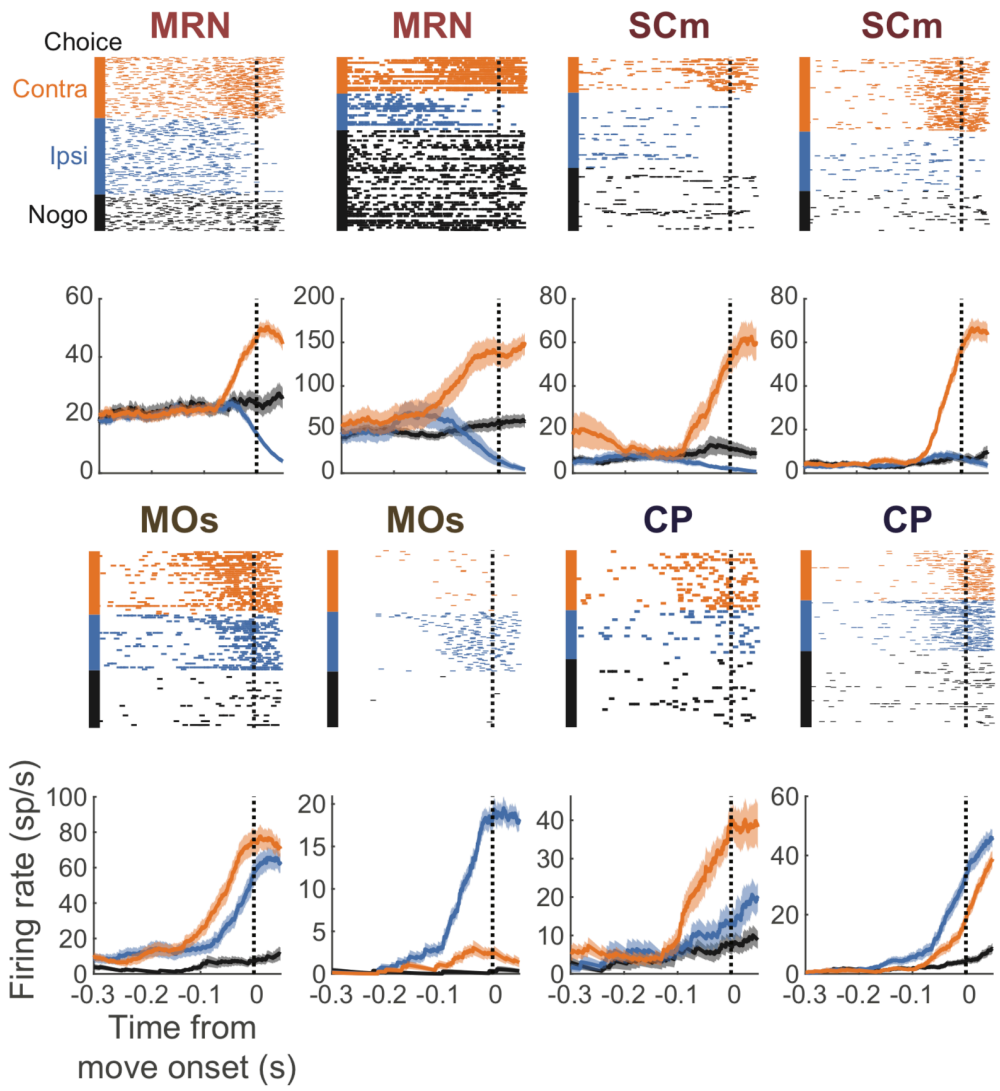


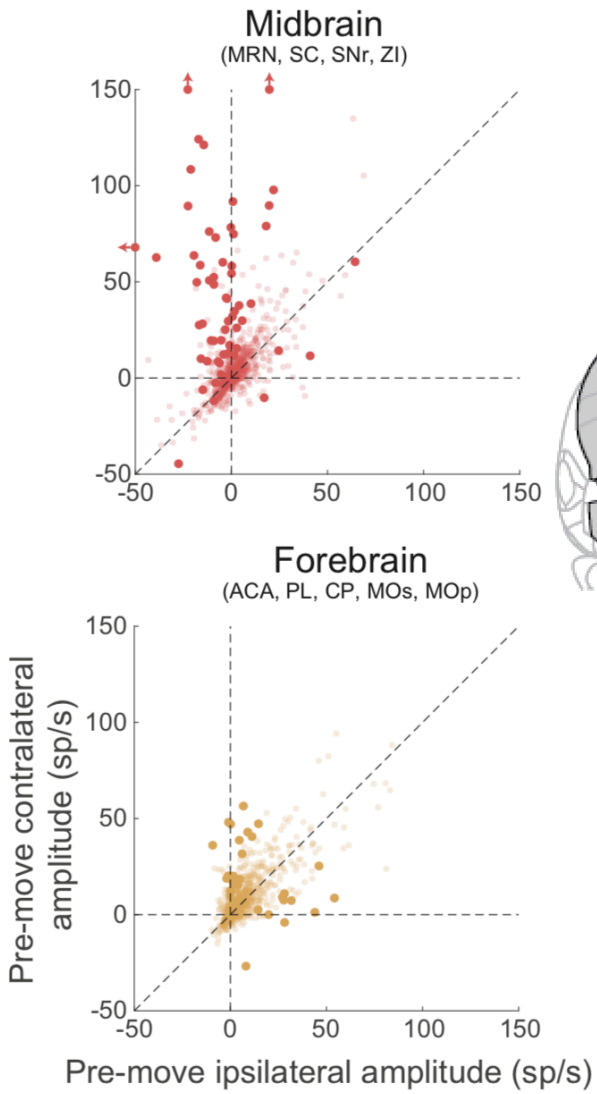


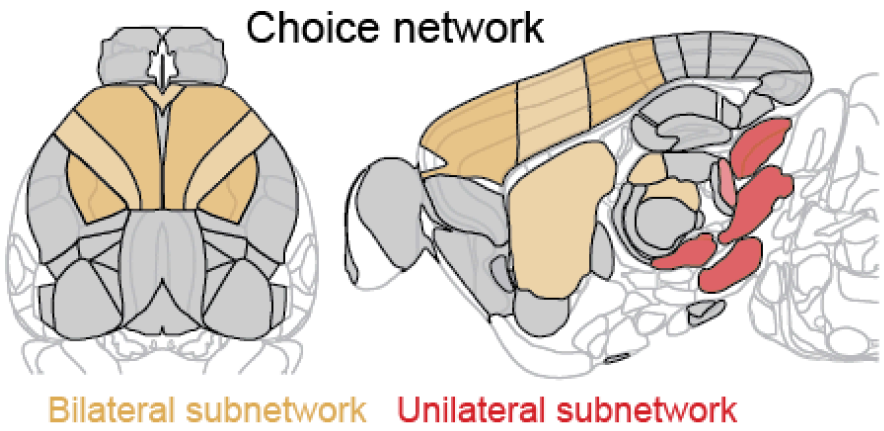
joint Peri-Event Canonical Correlation (jPECC)

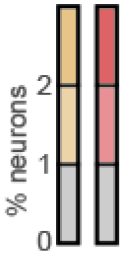


Midbrain neurons encode the choice unilaterally, while forebrain neurons encode bilaterally





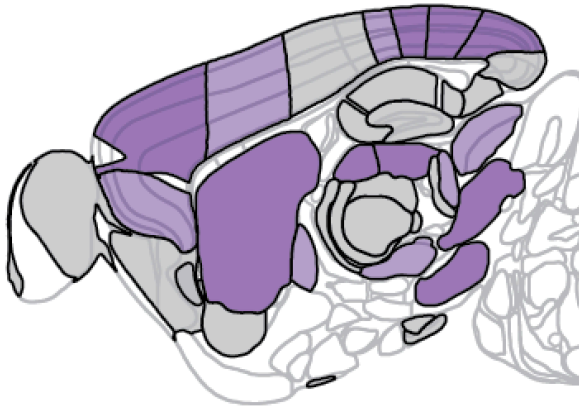




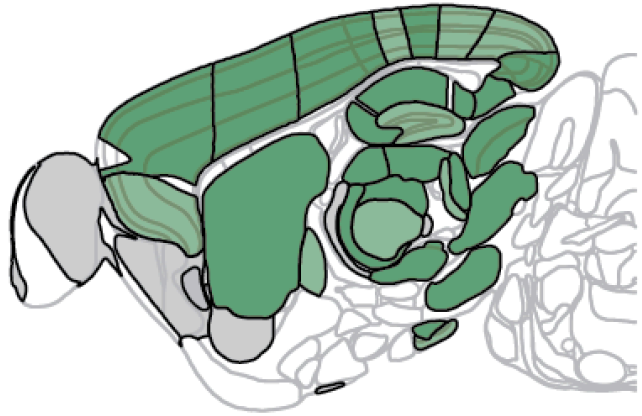
Conclusions

- Purely visual signals propagate through a restricted pathway
- When the mouse detects the stimulus and responds, nearly all brain regions become active
- Enhanced subcortical activity and suppressed cortical activity predict successful detection
- Choice-related activity arises in a multifocal network of neurons within a set of interconnected structures: frontal cortex, basal ganglia, and midbrain areas
- Choice encoding is bilateral in frontal cortex but unilateral in midbrain

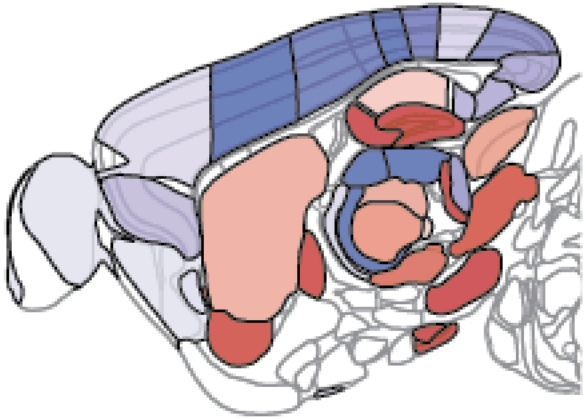
Visual pathway



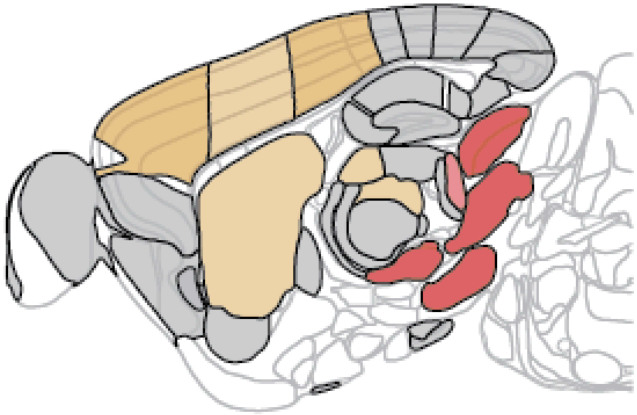
Action network



Engagement network



Choice network



Thanks to funding from:
Wellcome Trust | EU Horizon 2020 | Human Frontier Sciences Program | European Research Council | Gatsby Charitable Foundation | Simons Foundation | Howard Hughes Medical Institute | Allen Institute for Brain Science