3- Uncovering single trial population dynamics

Data Science and AI for Neuroscience Summer School 2022, Chen Institute at Caltech

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EMORY UNIVERSITY

Georgia Tech

ML methods to uncover single-trial population dynamics

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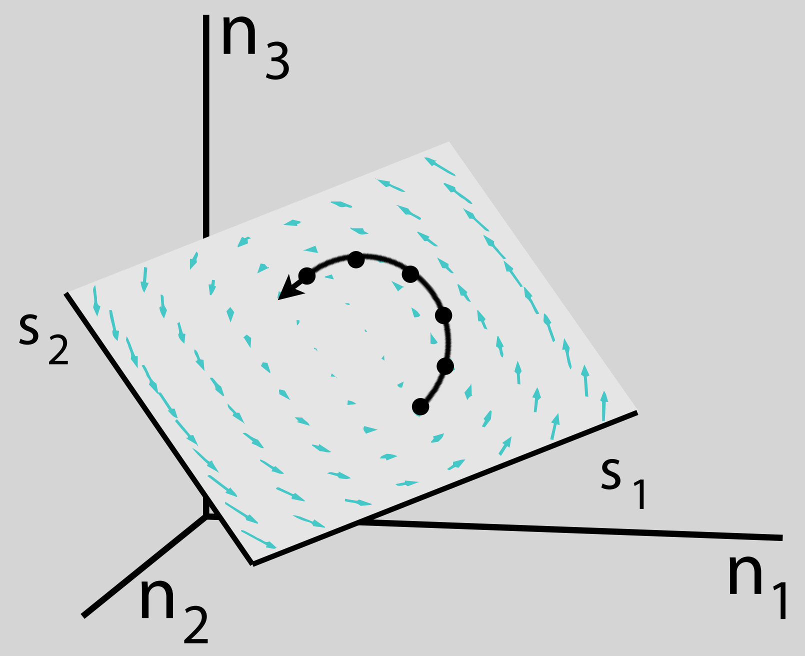
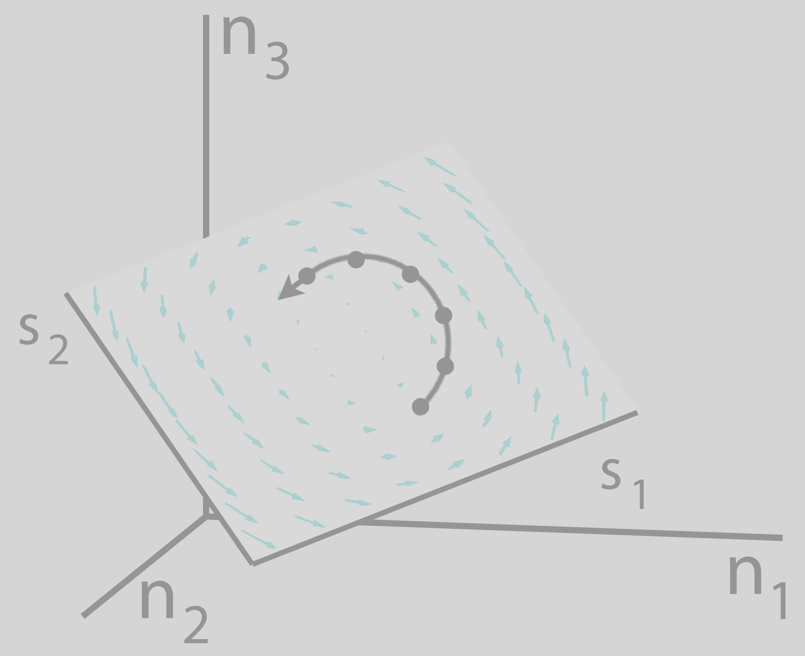


Predictable **neural activity: modeling autonomous dynamics using LFADS**

ML methods to uncover single-trial population dynamics



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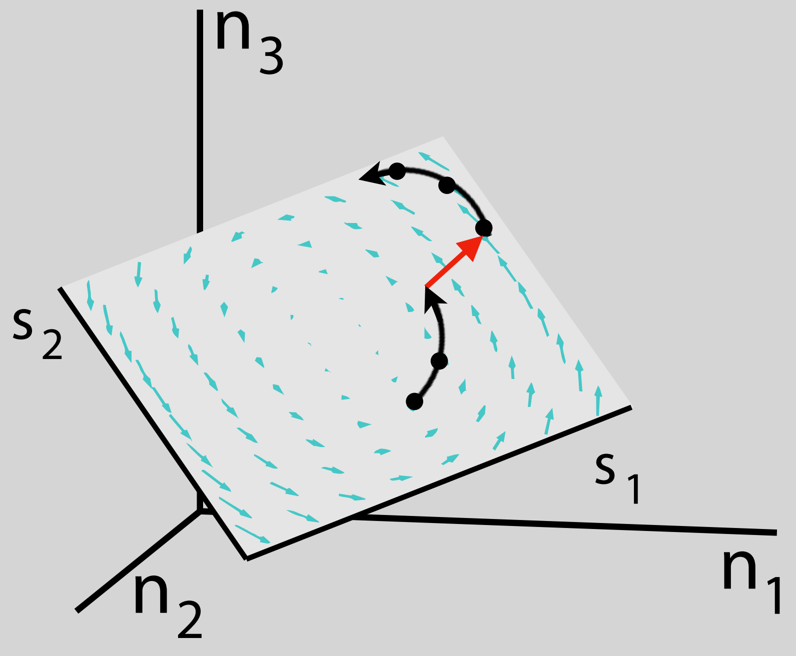
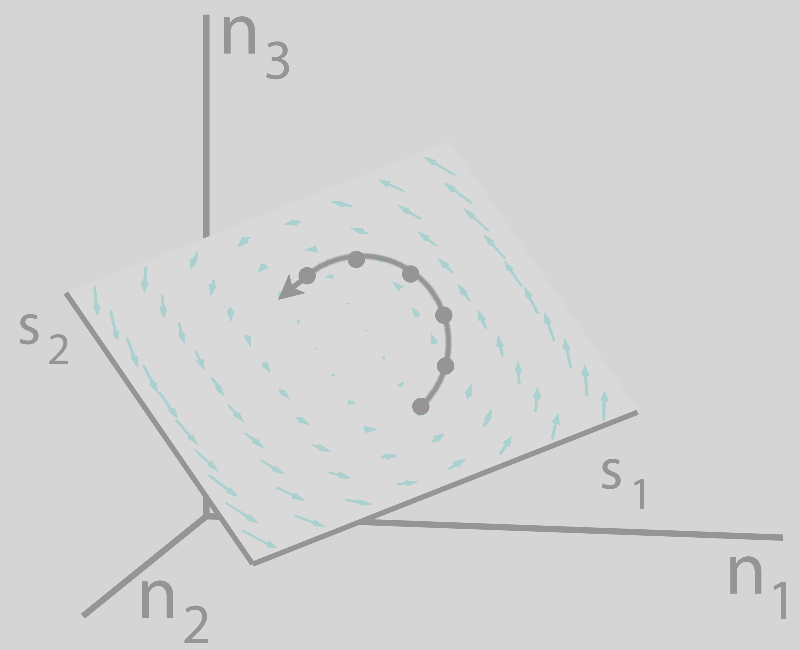
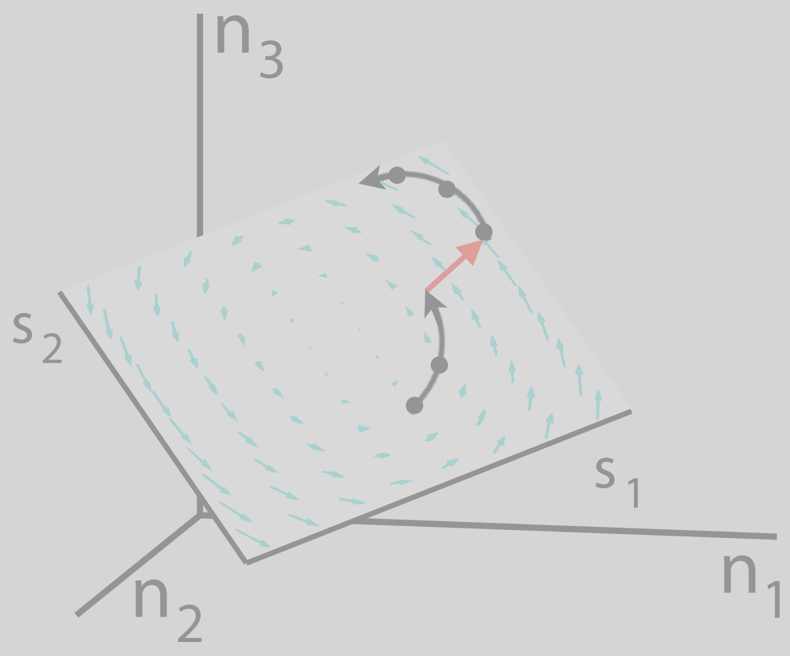
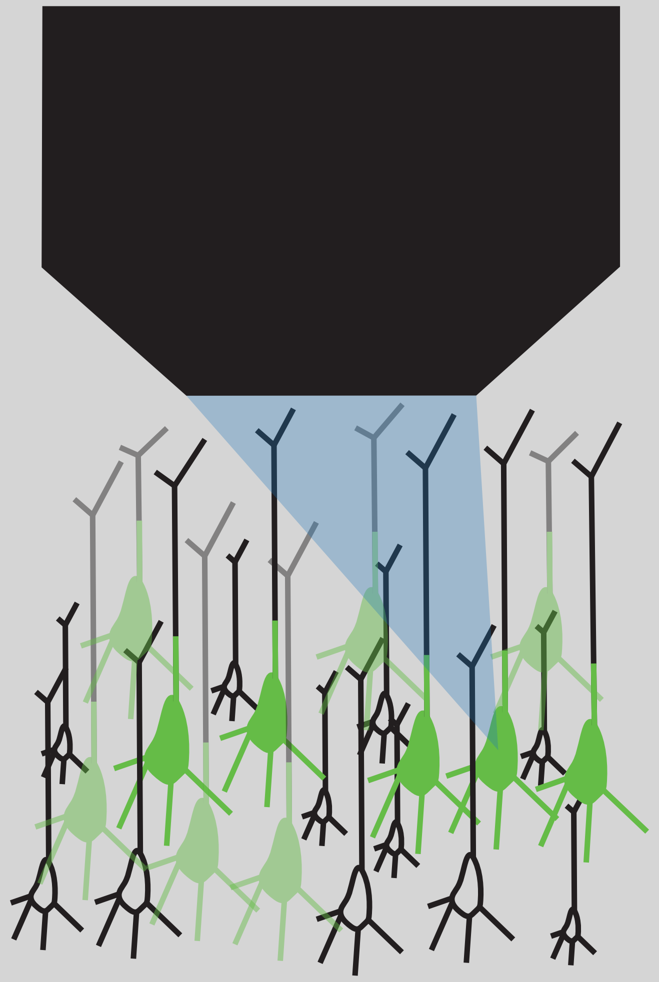


***Unpredictable* activity: non-autonomous dynamics and AutoLFADS**

ML methods to uncover single-trial population dynamics







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Applications to 2P Ca imaging: RADICaL

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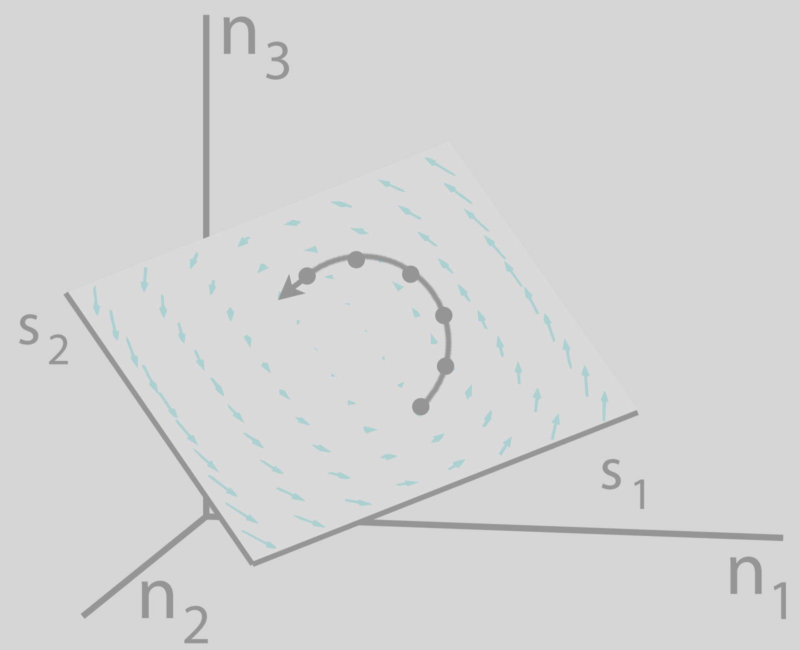

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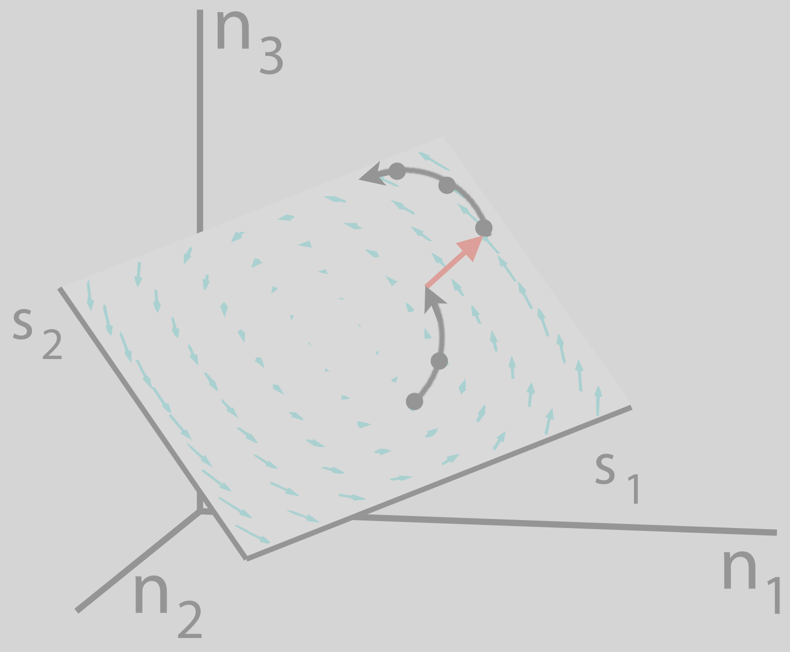

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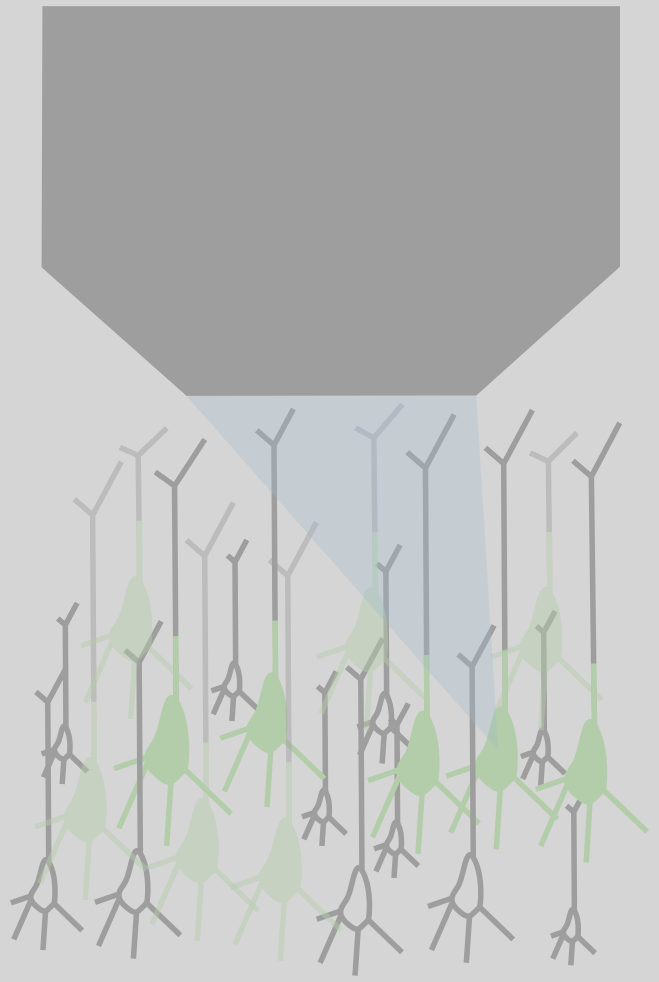
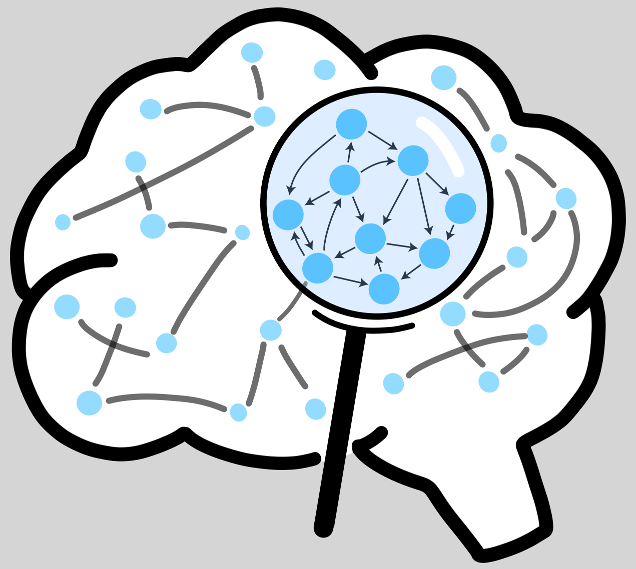


Applications to 2P Ca imaging: RADICaL



Applications to cognitive data

Changes in neurons’ firing rates are coordinated

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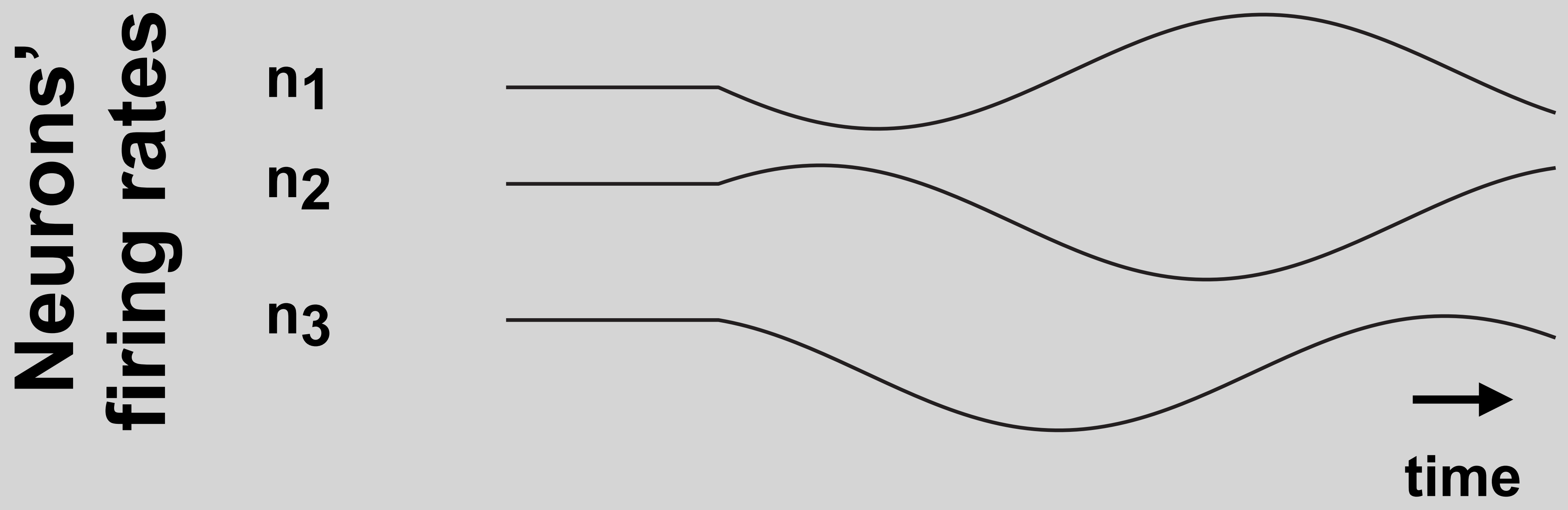

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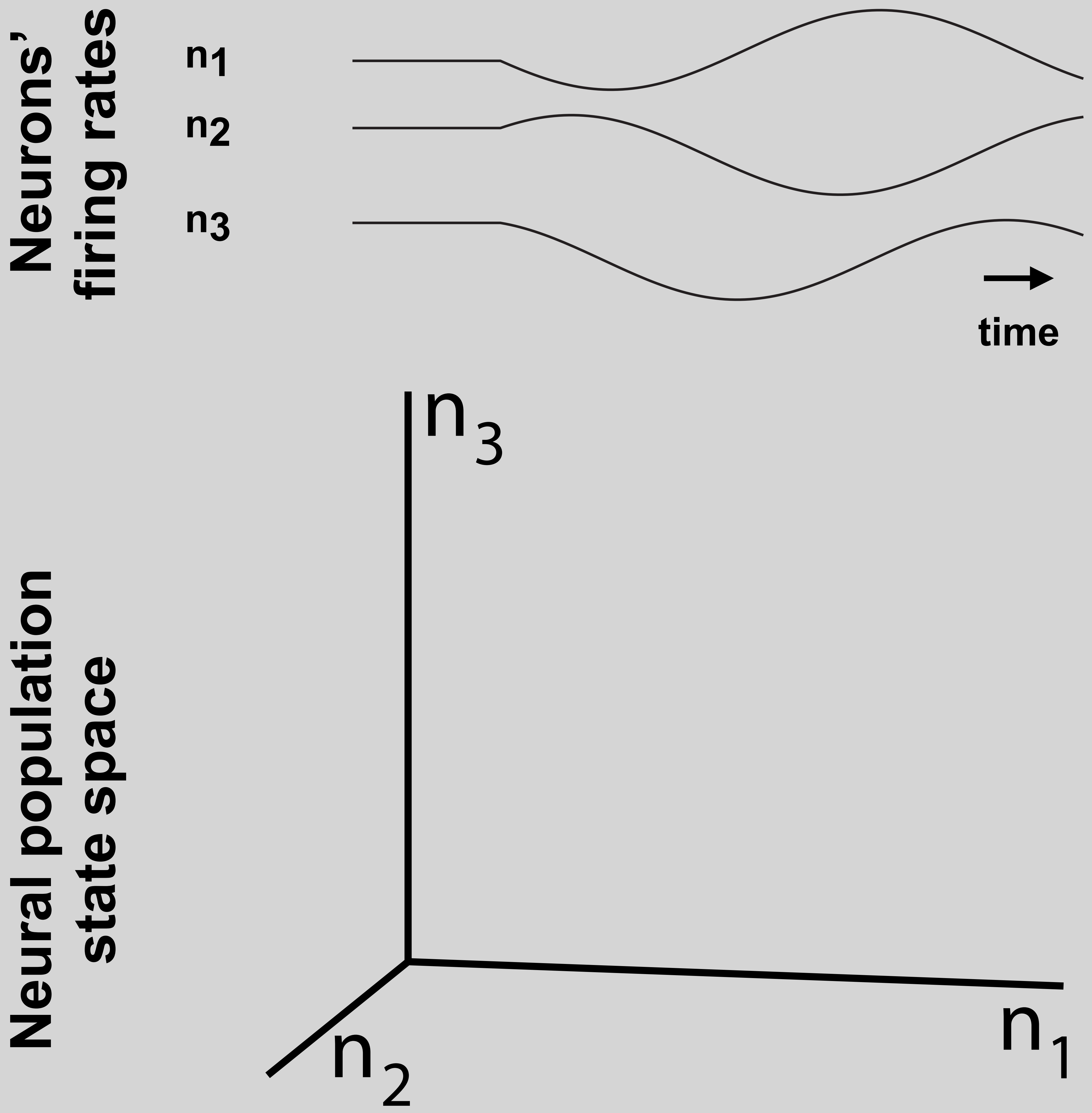

Adapted from Cunningham & Yu, *Nat Neuro* 2014

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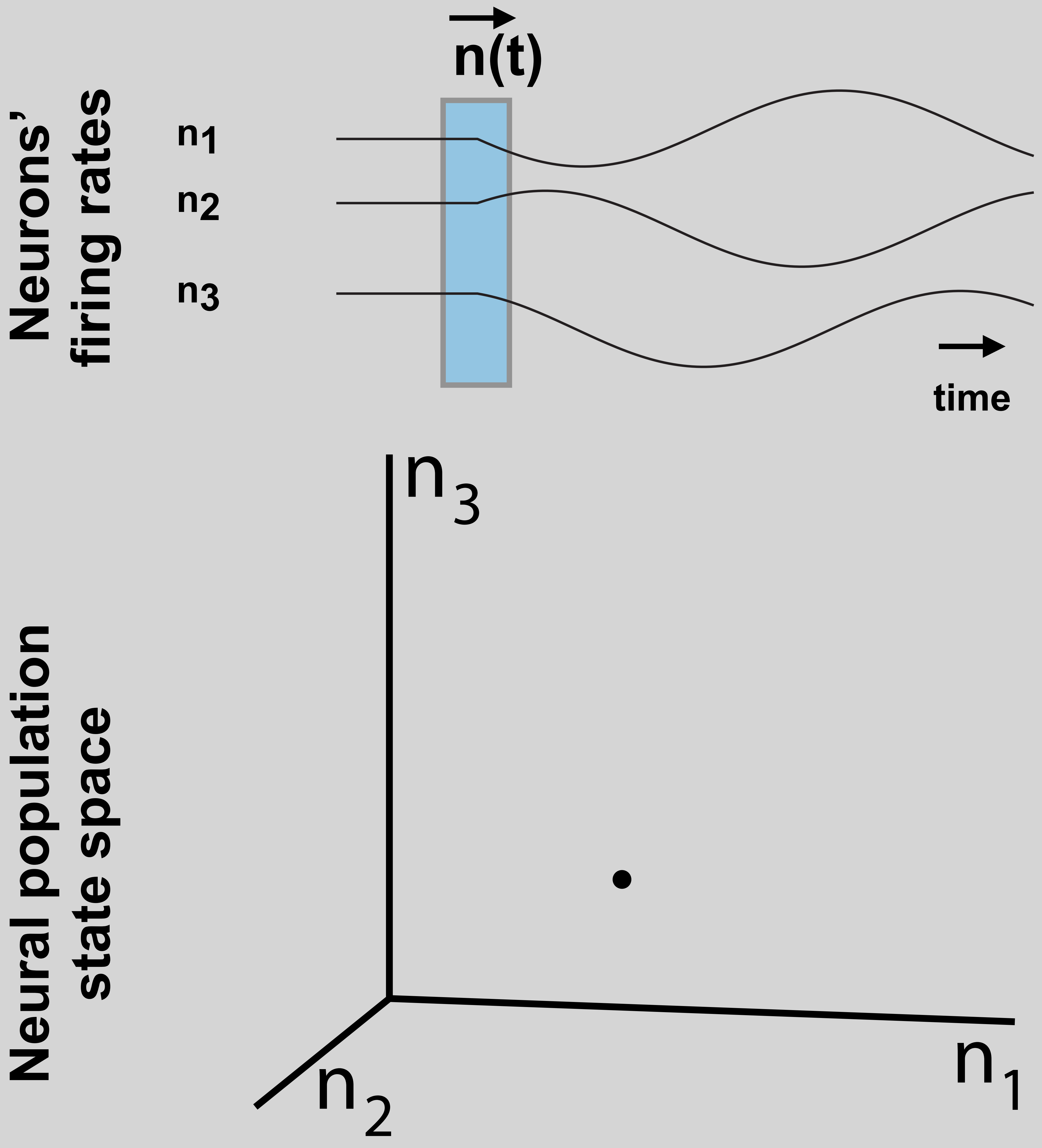

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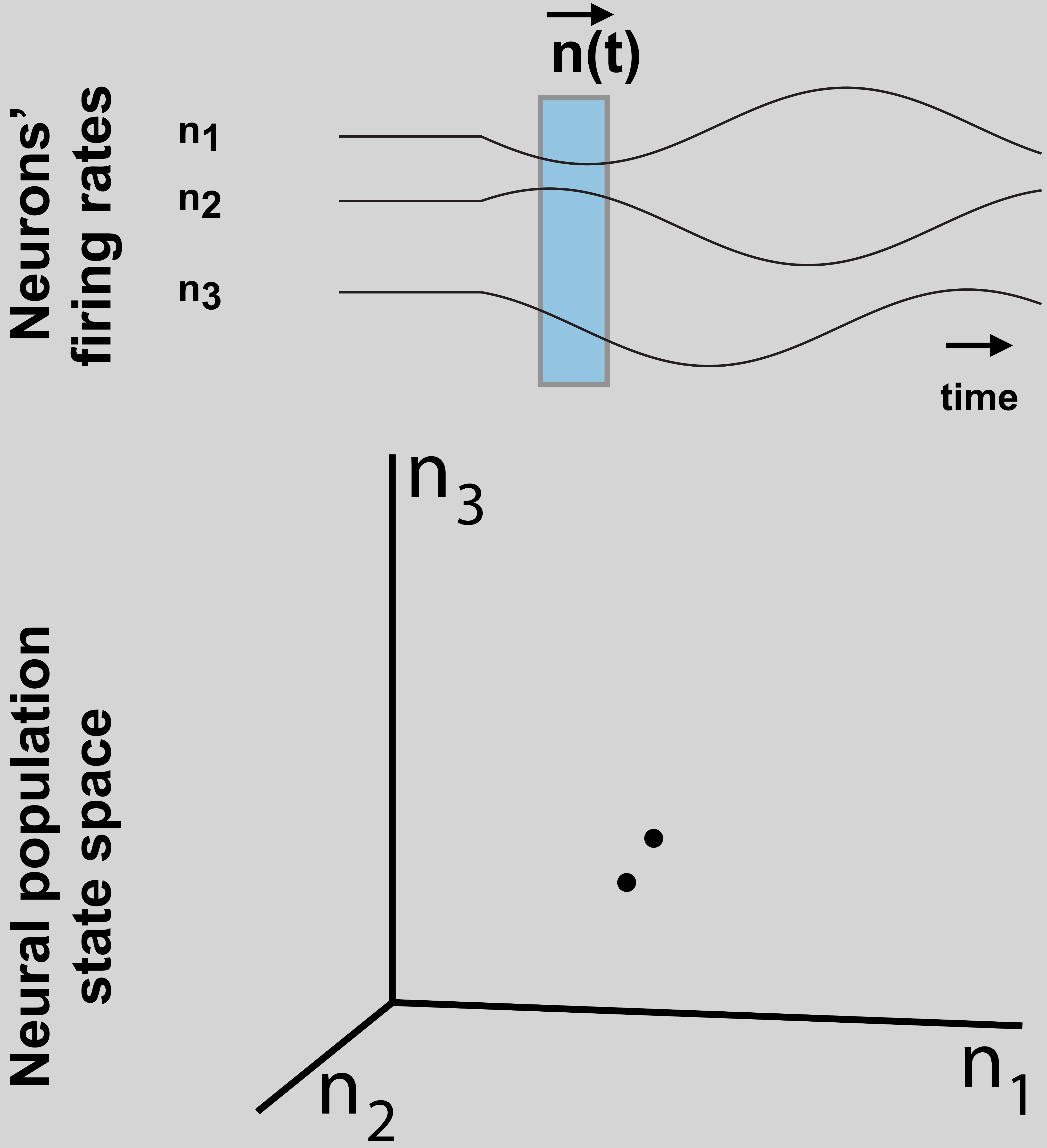

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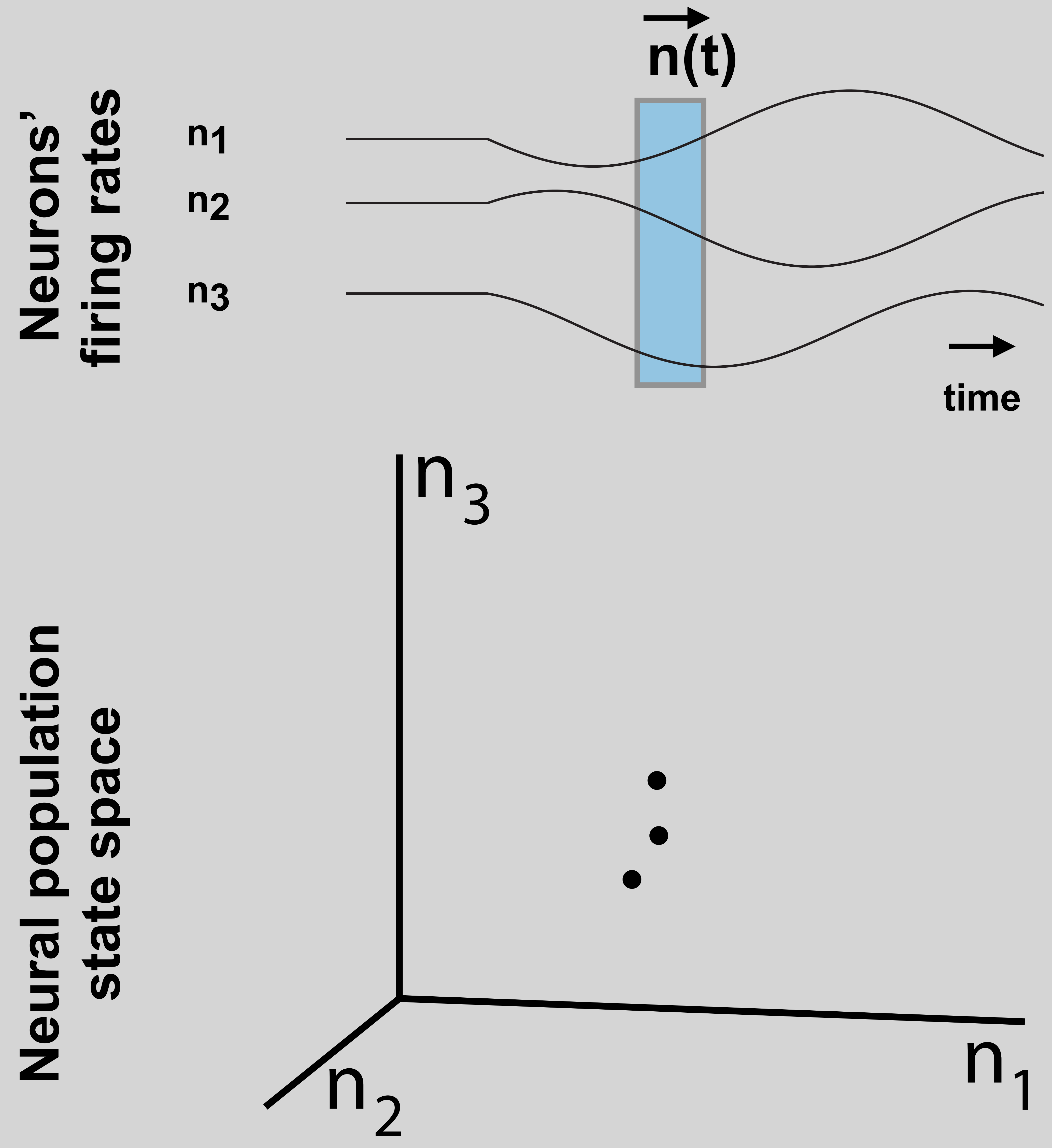

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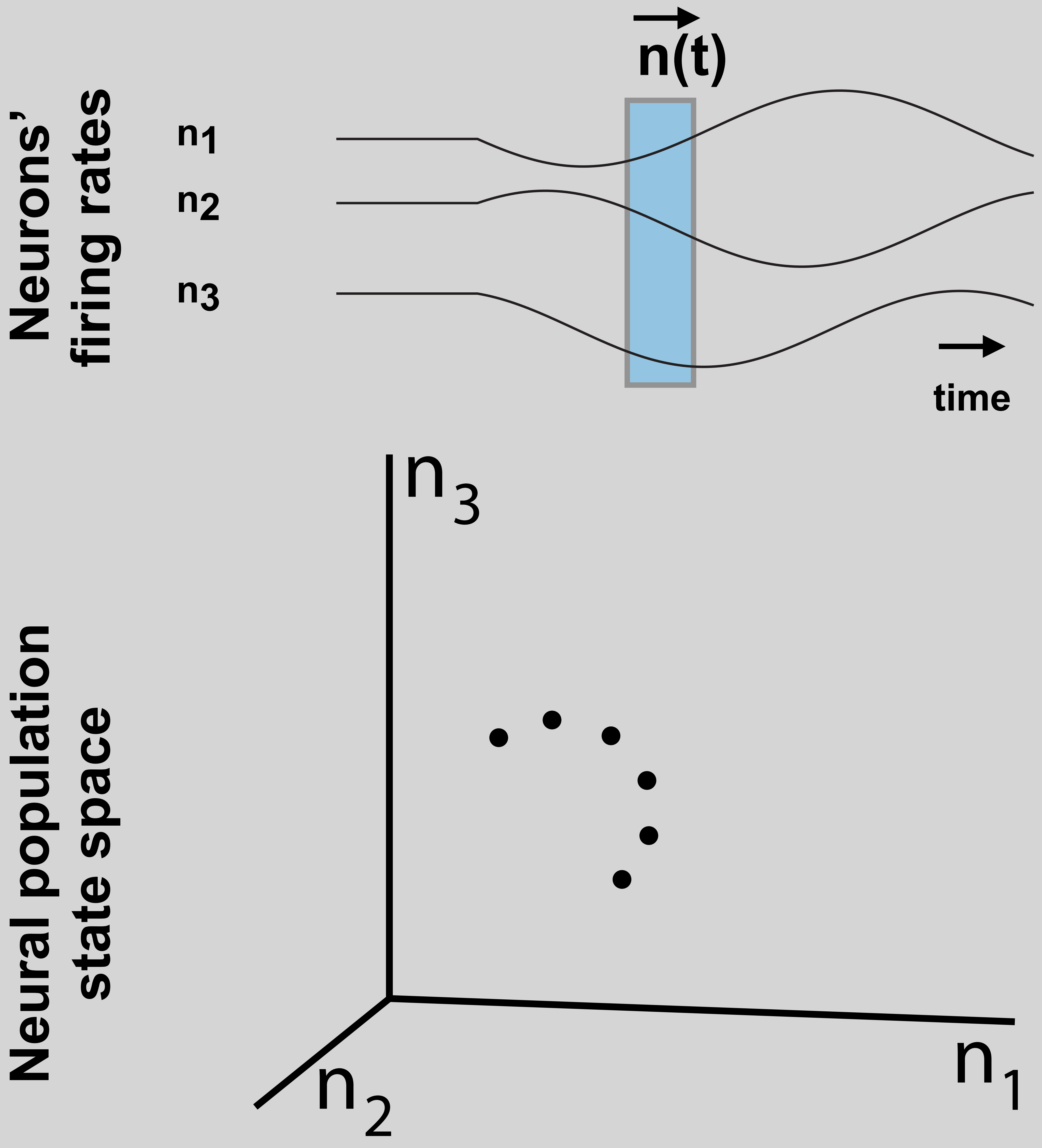

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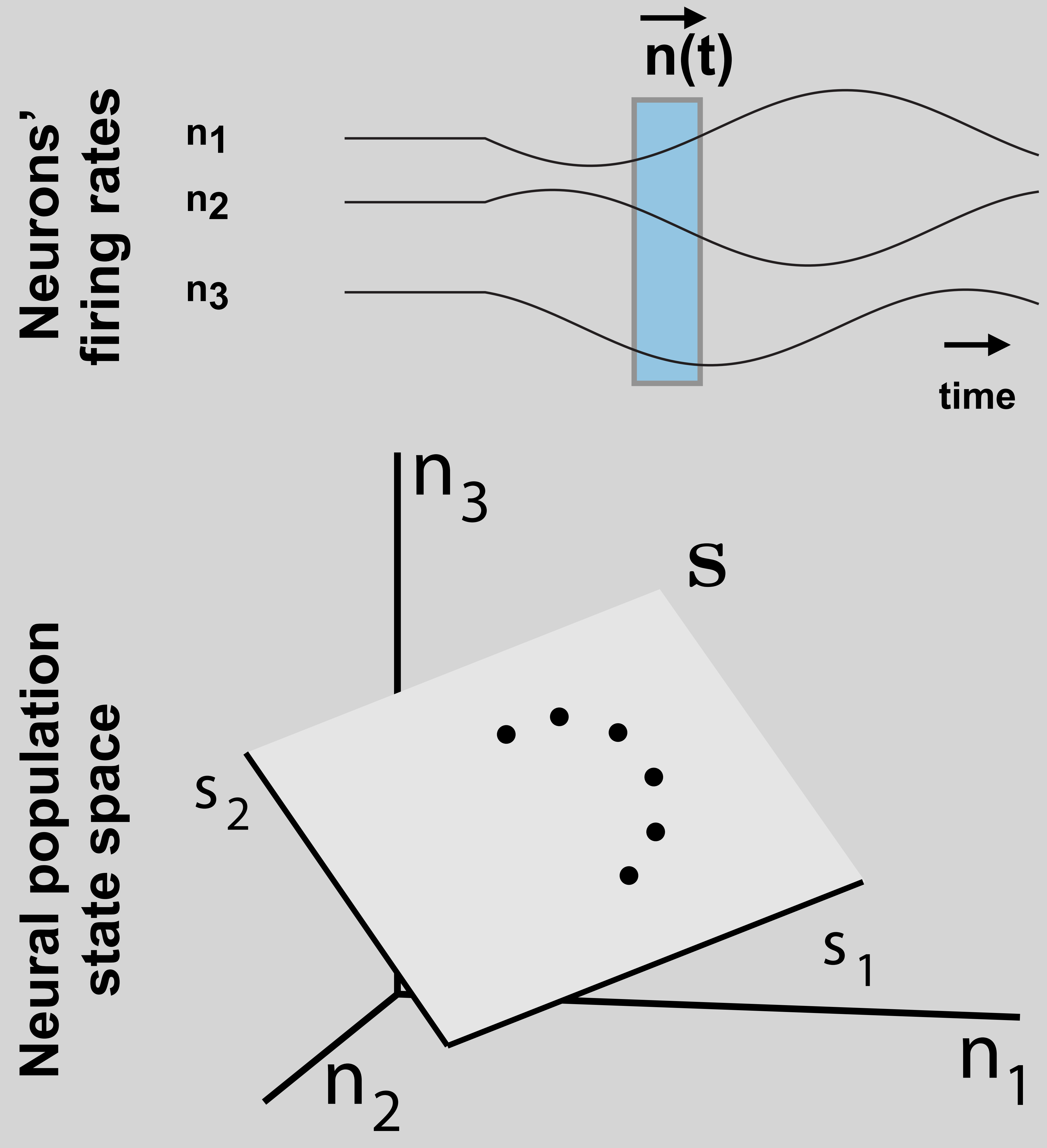

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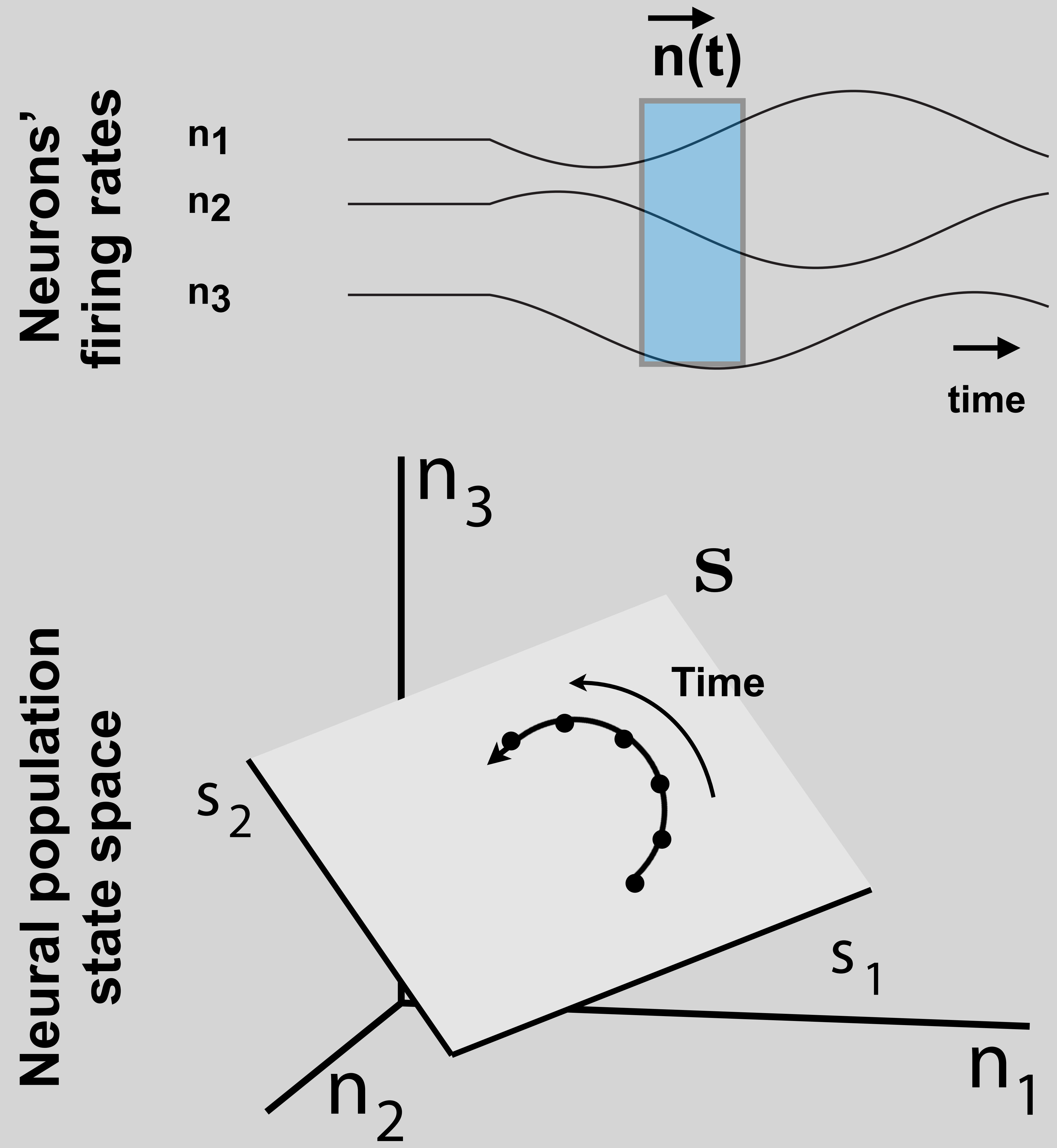
Uncovering neural population dynamics



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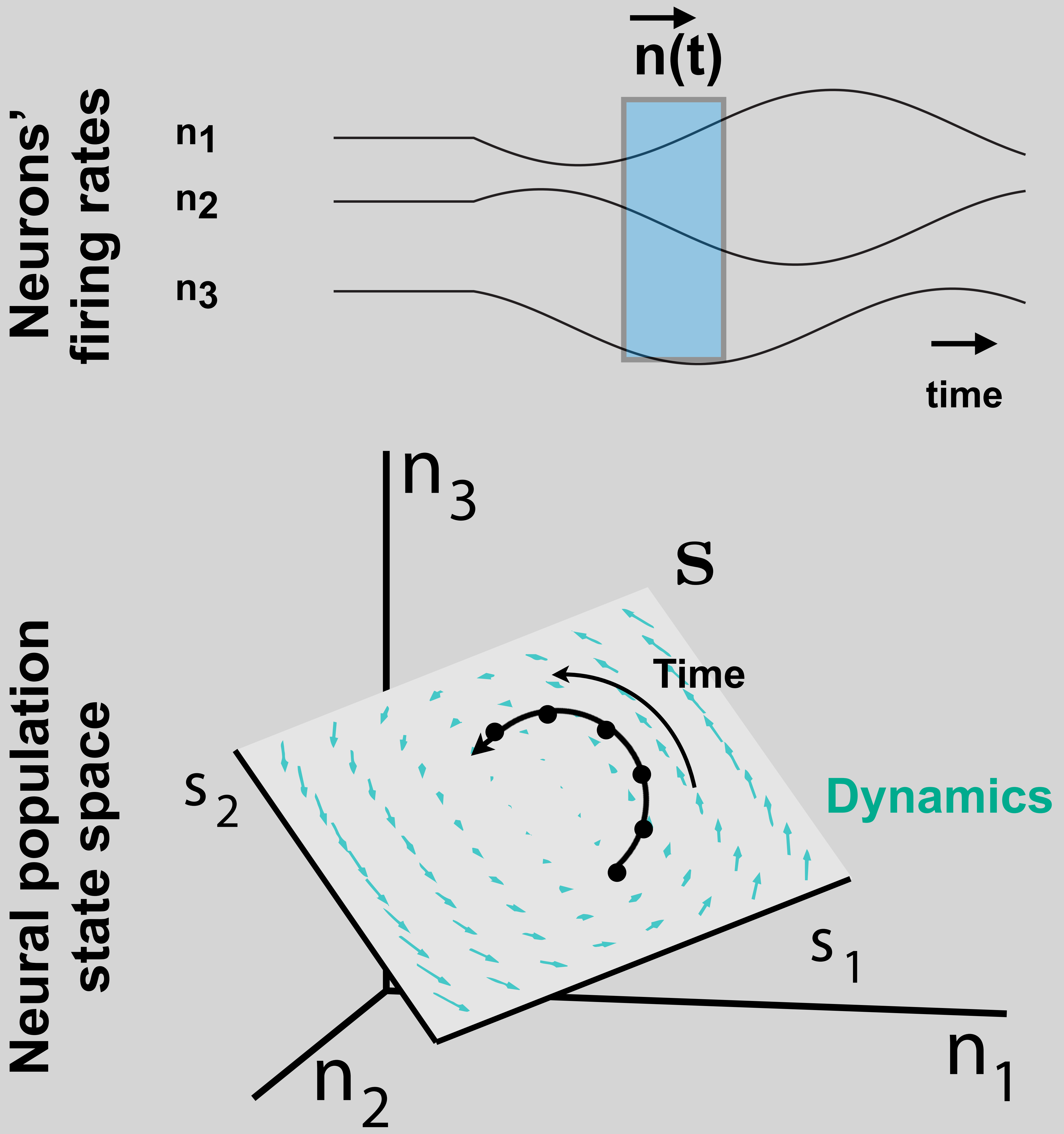

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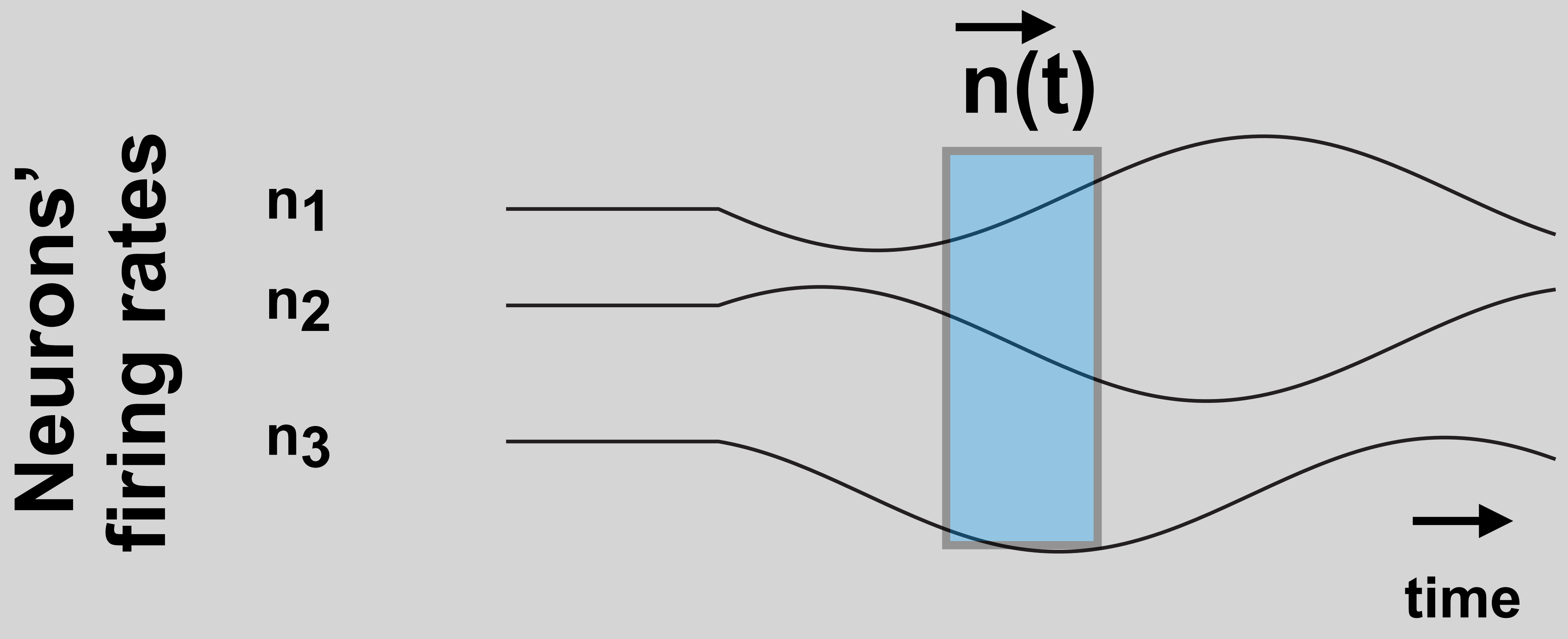
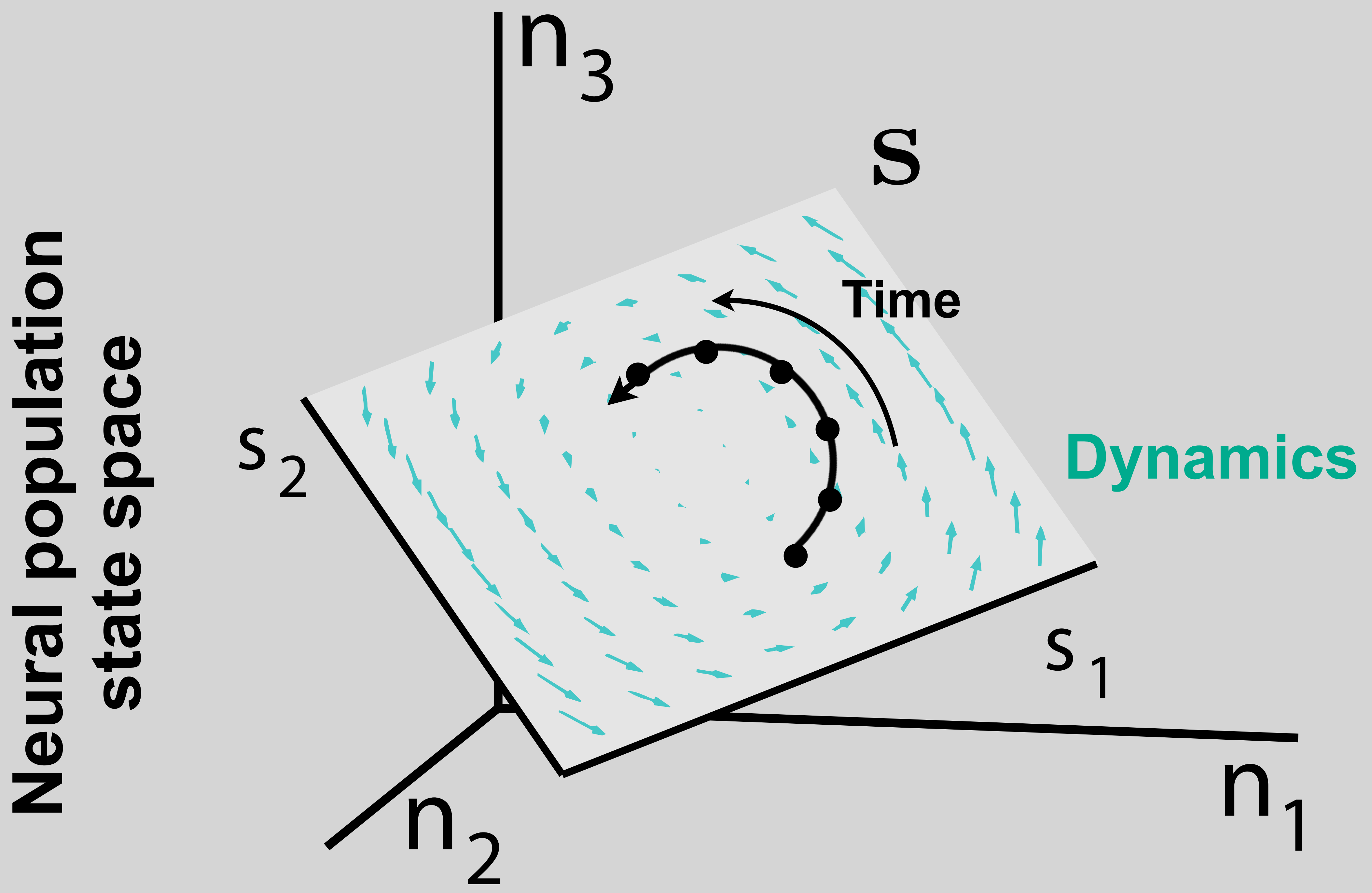


Predictable activity - modeled by *autonomous* dynamics

$$\frac{d\mathrm{s}}{dt} = f(\mathrm{s})$$

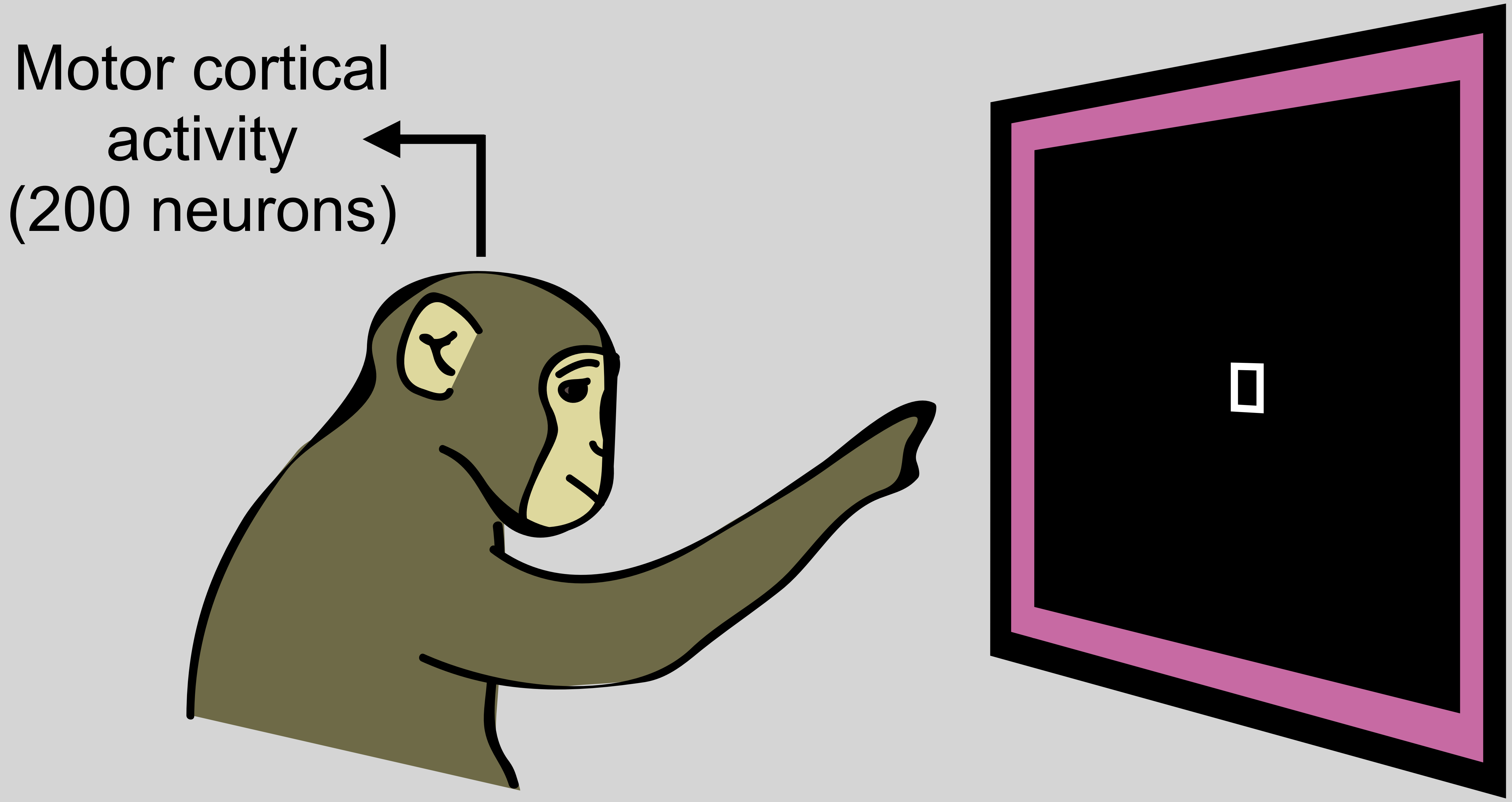


Predictable activity: delayed-reaching

"Maze" task

108 total conditions

- Motor cortex is set to an initial state during the preparatory phase
- Activity during movement execution is highly predictable based on initial state



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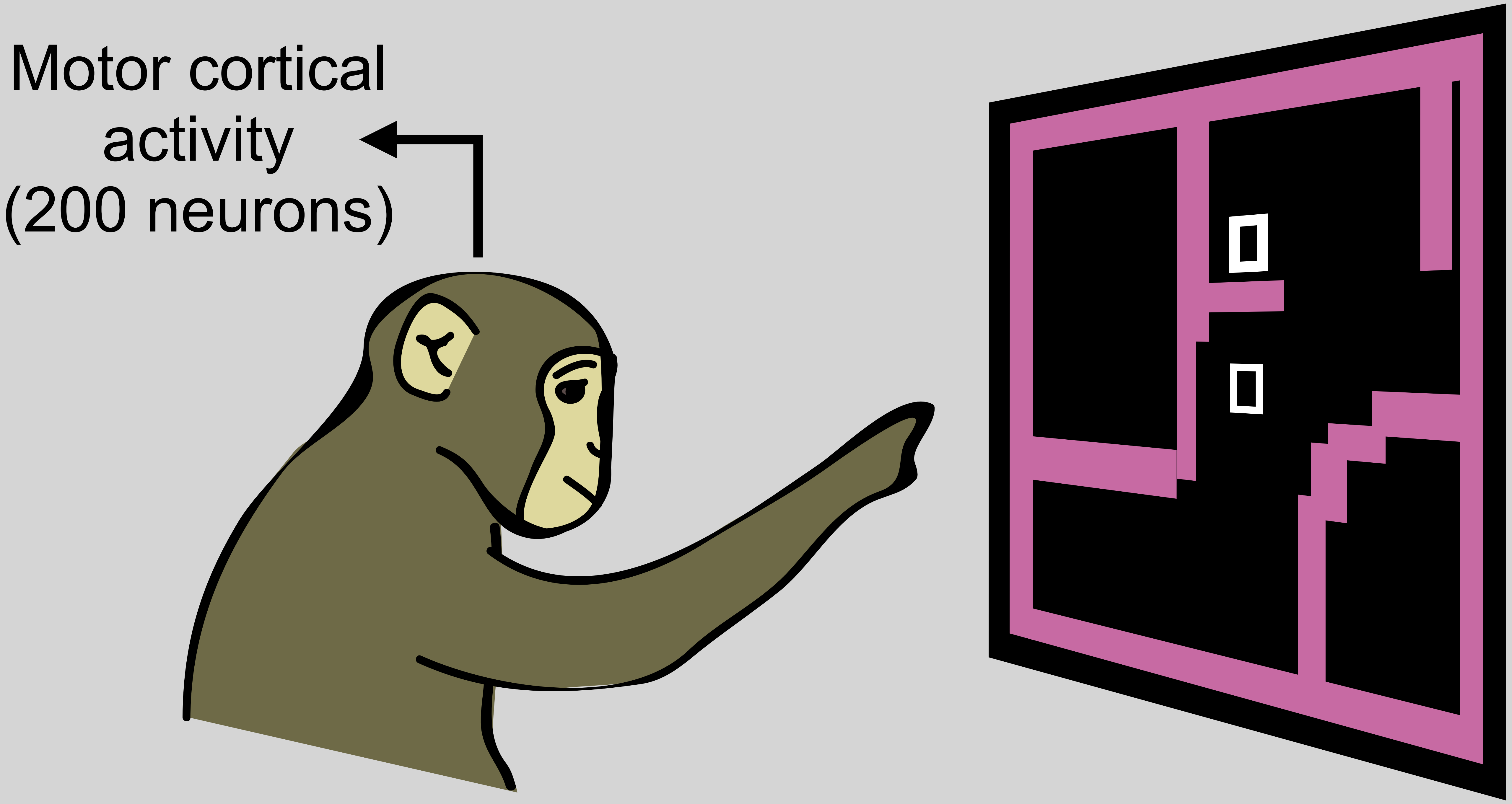

Condition 1

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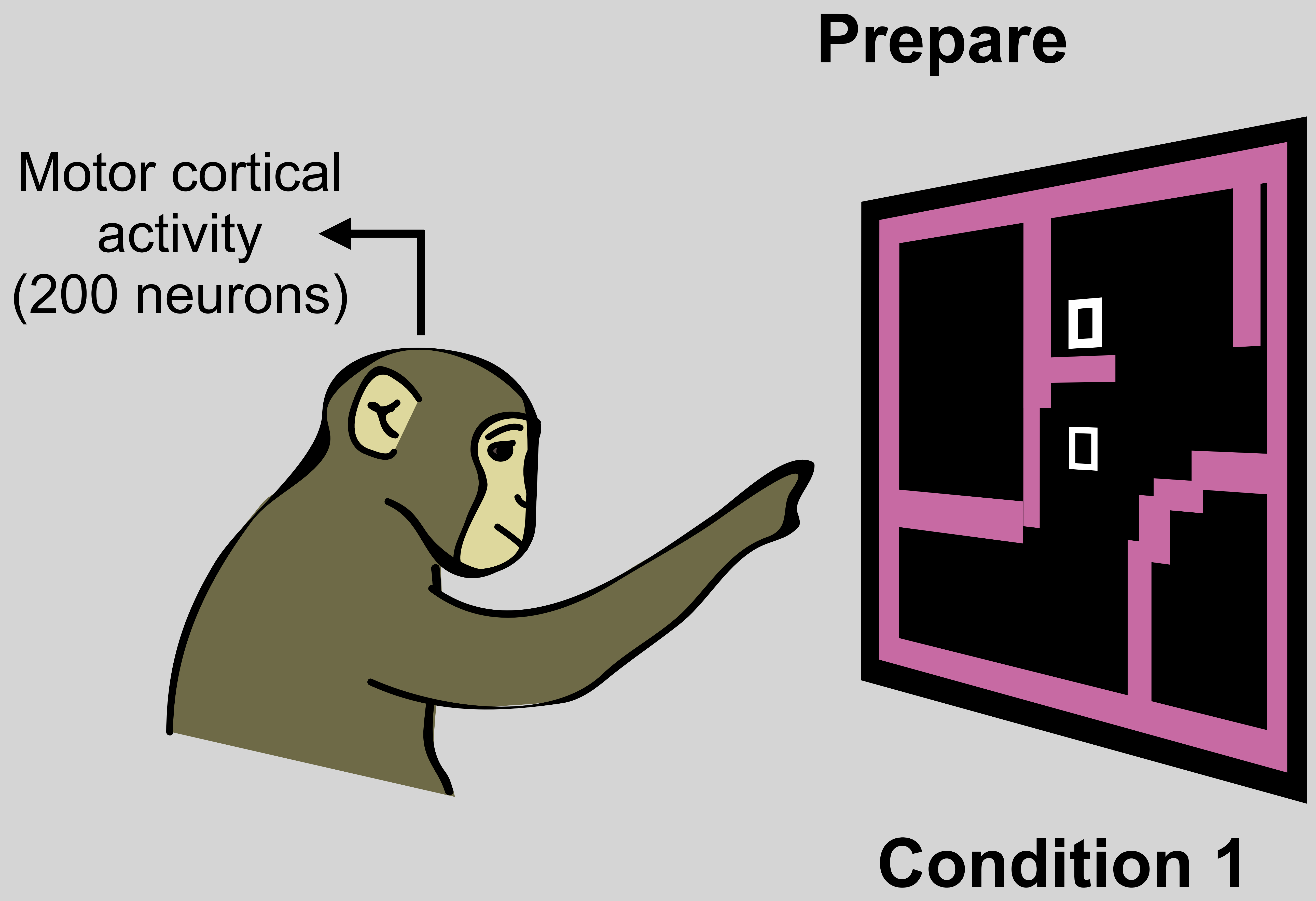

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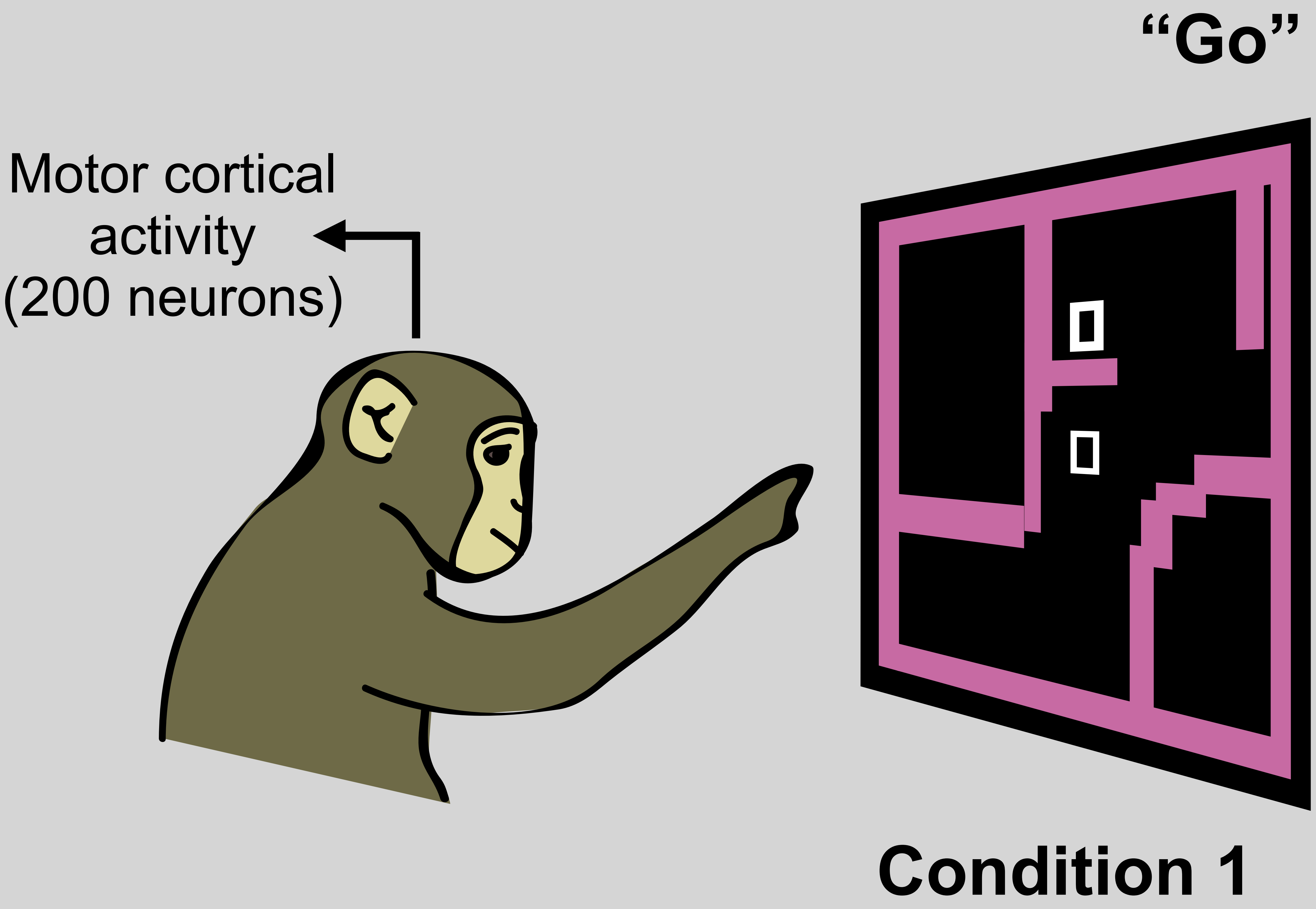

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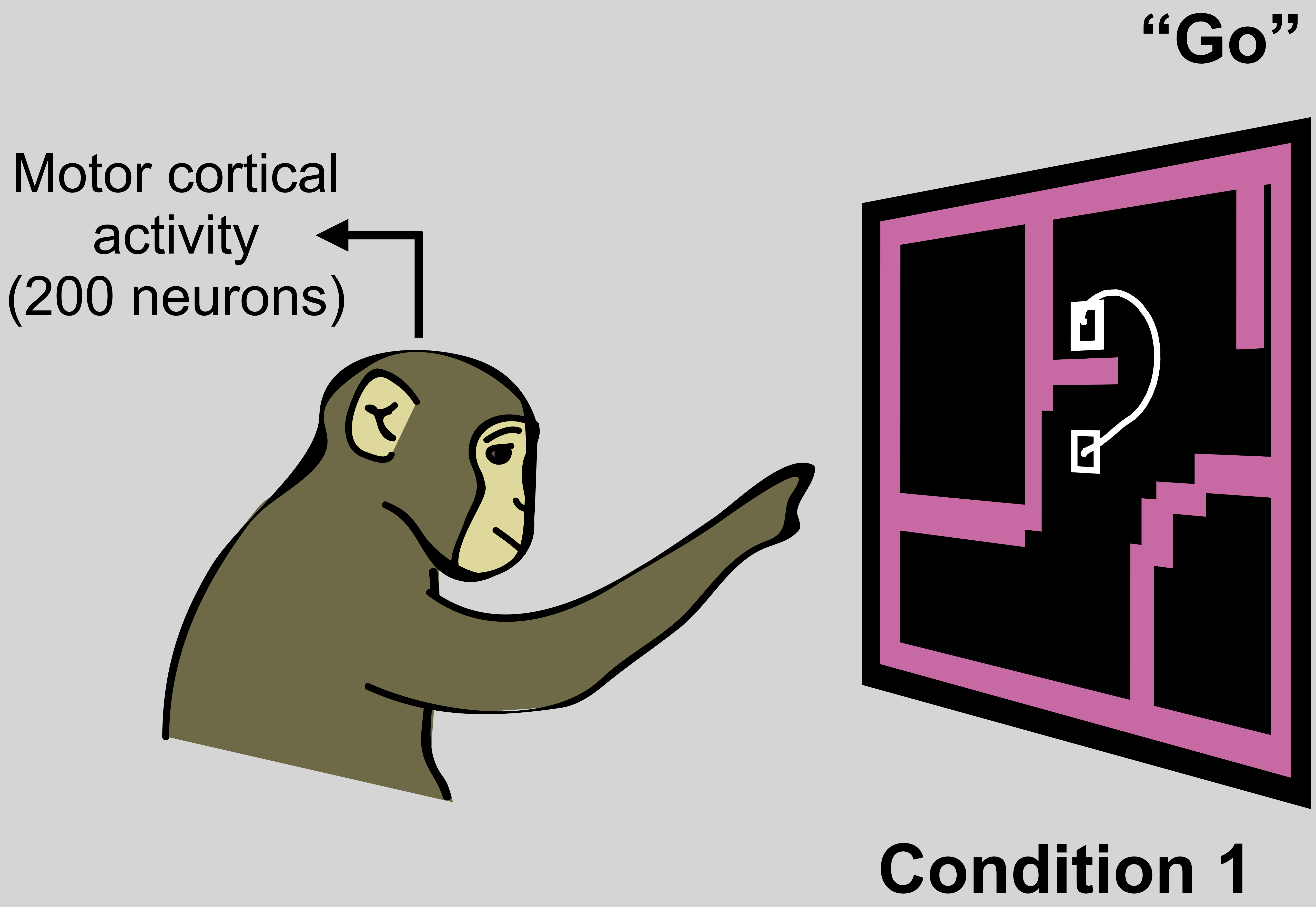

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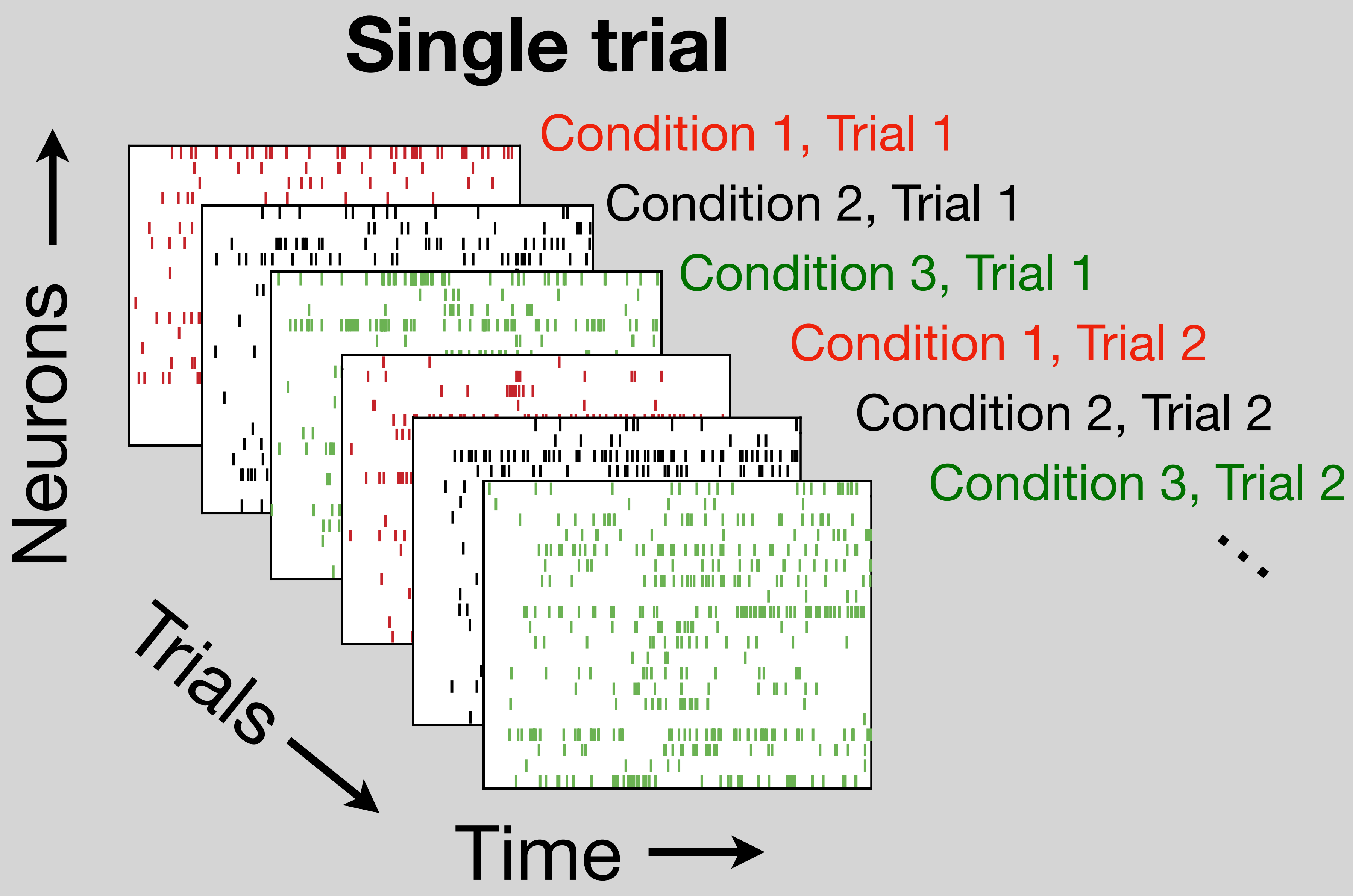

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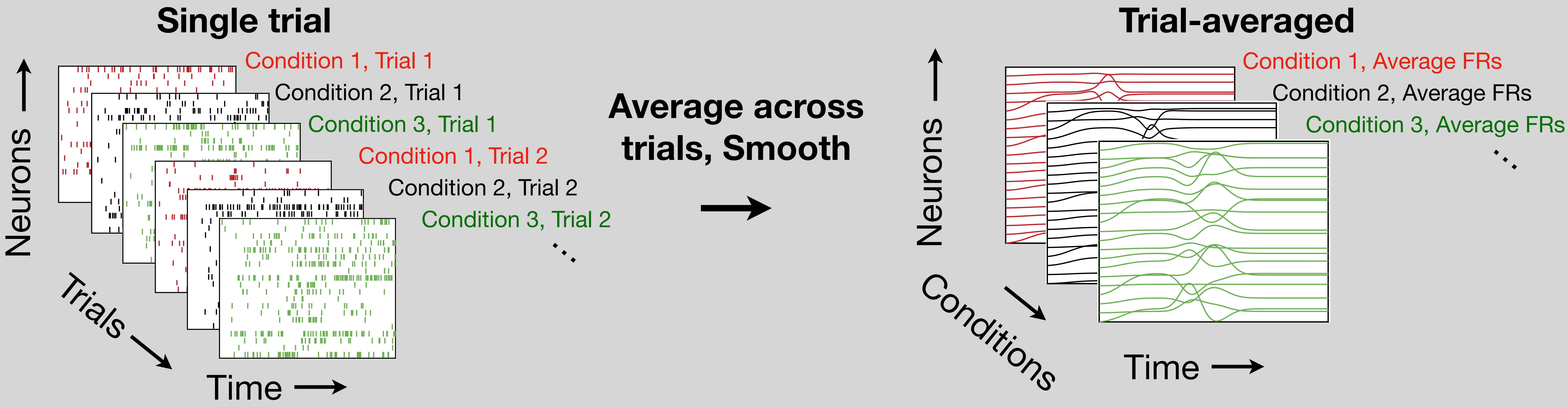

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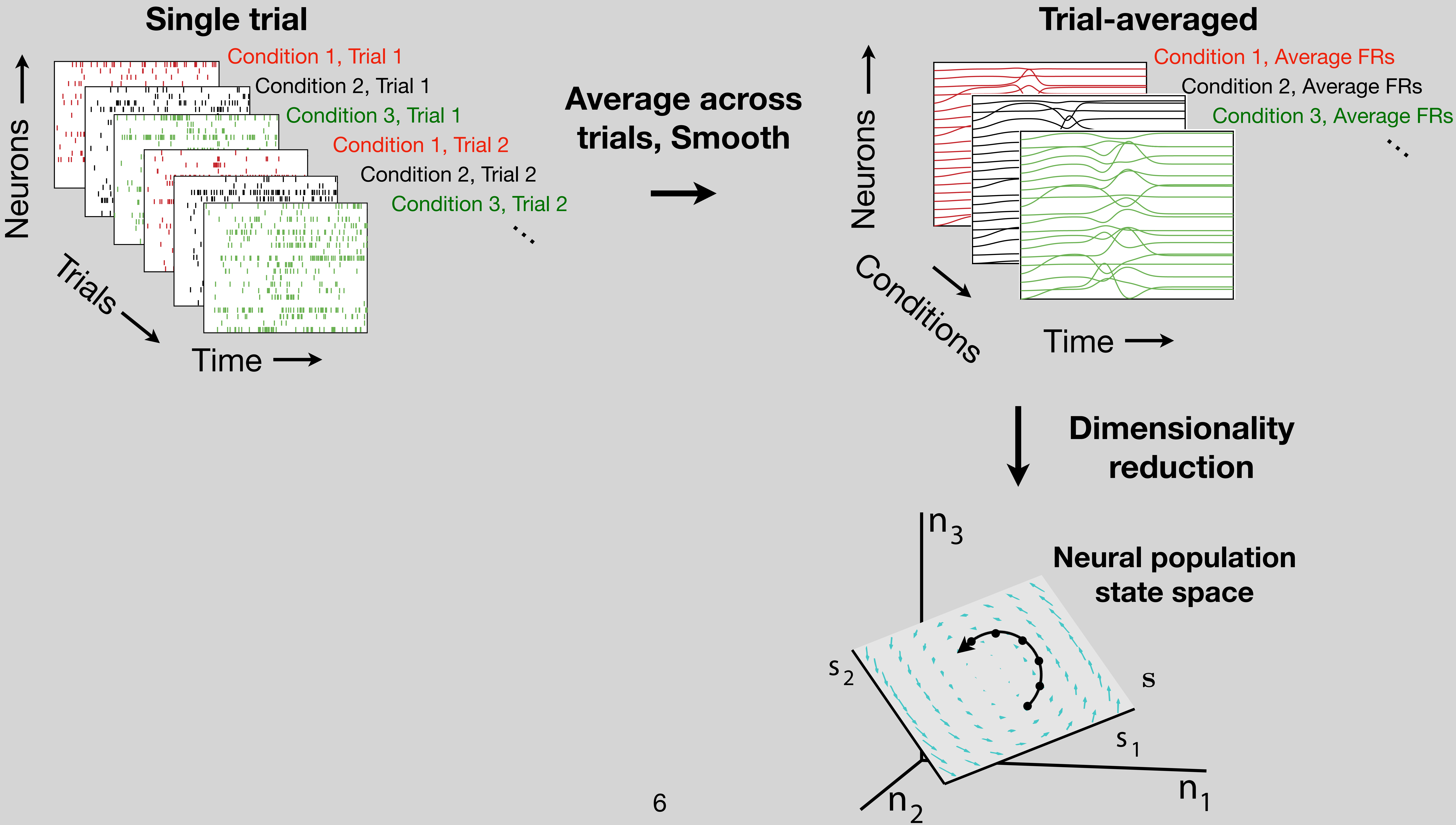
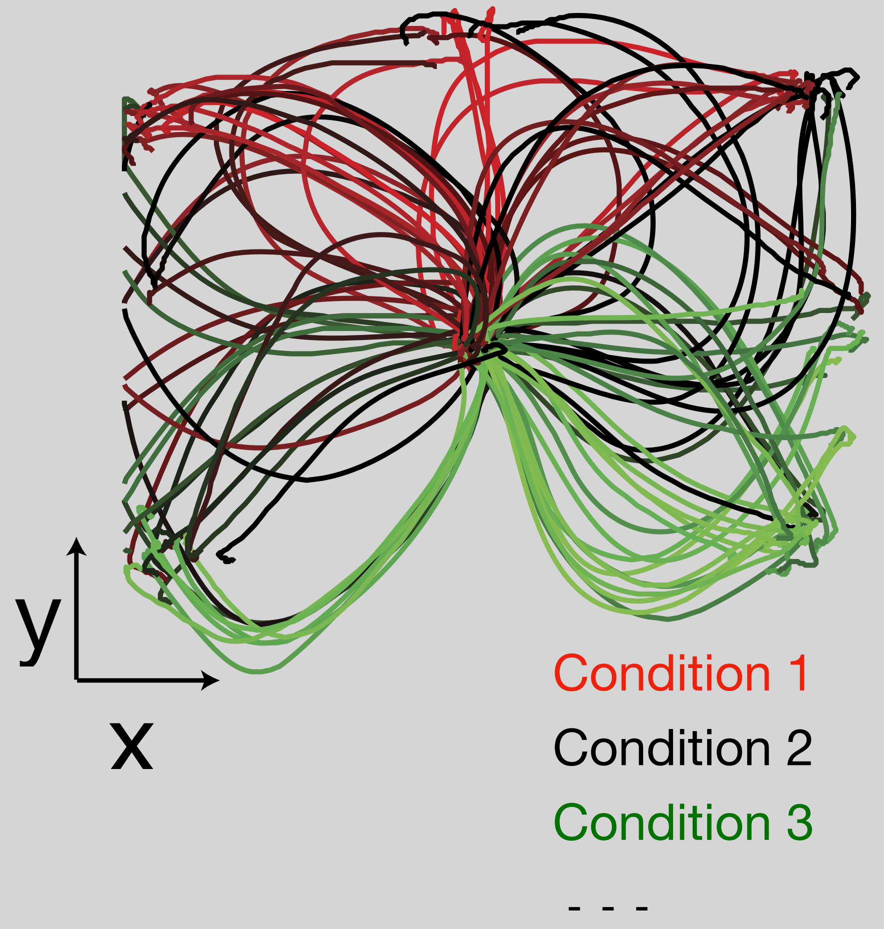


Predictable activity: delayed-reaching

Initial state **s**(0)

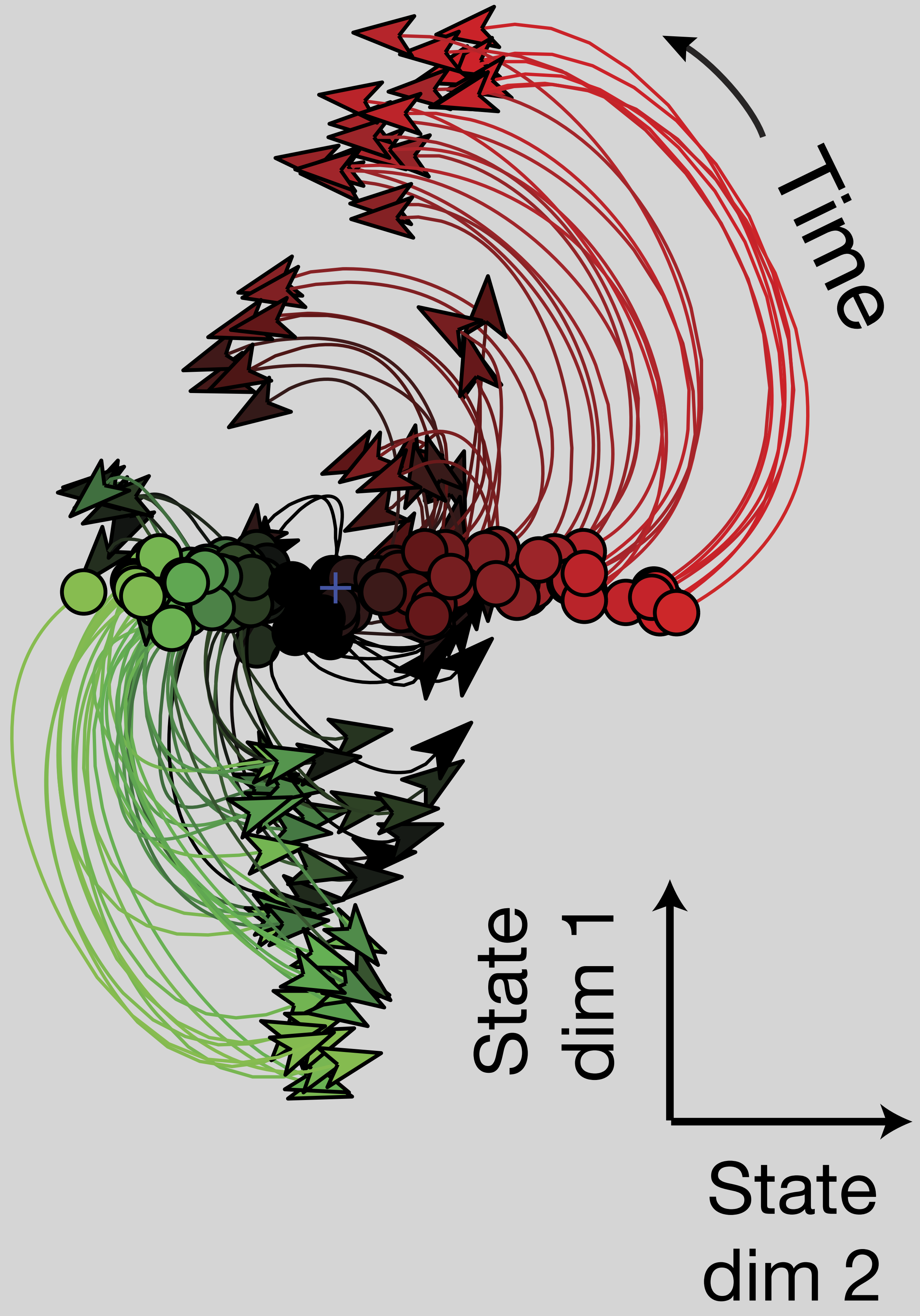
Trajectory **s**(t)

Hand kinematics



Neural population state space trajectories

(trial-averaged)



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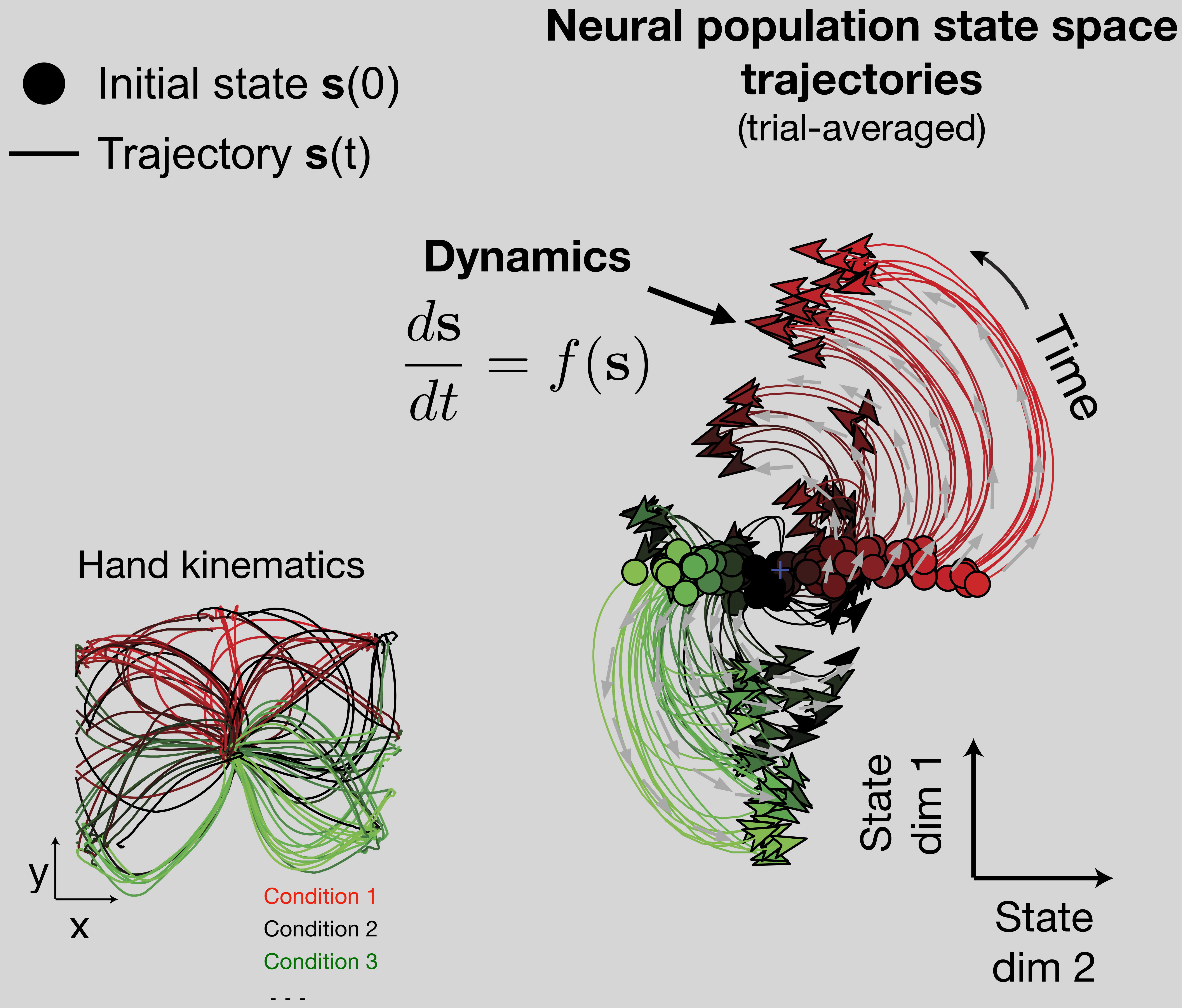

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Predictable activity: delayed-reaching

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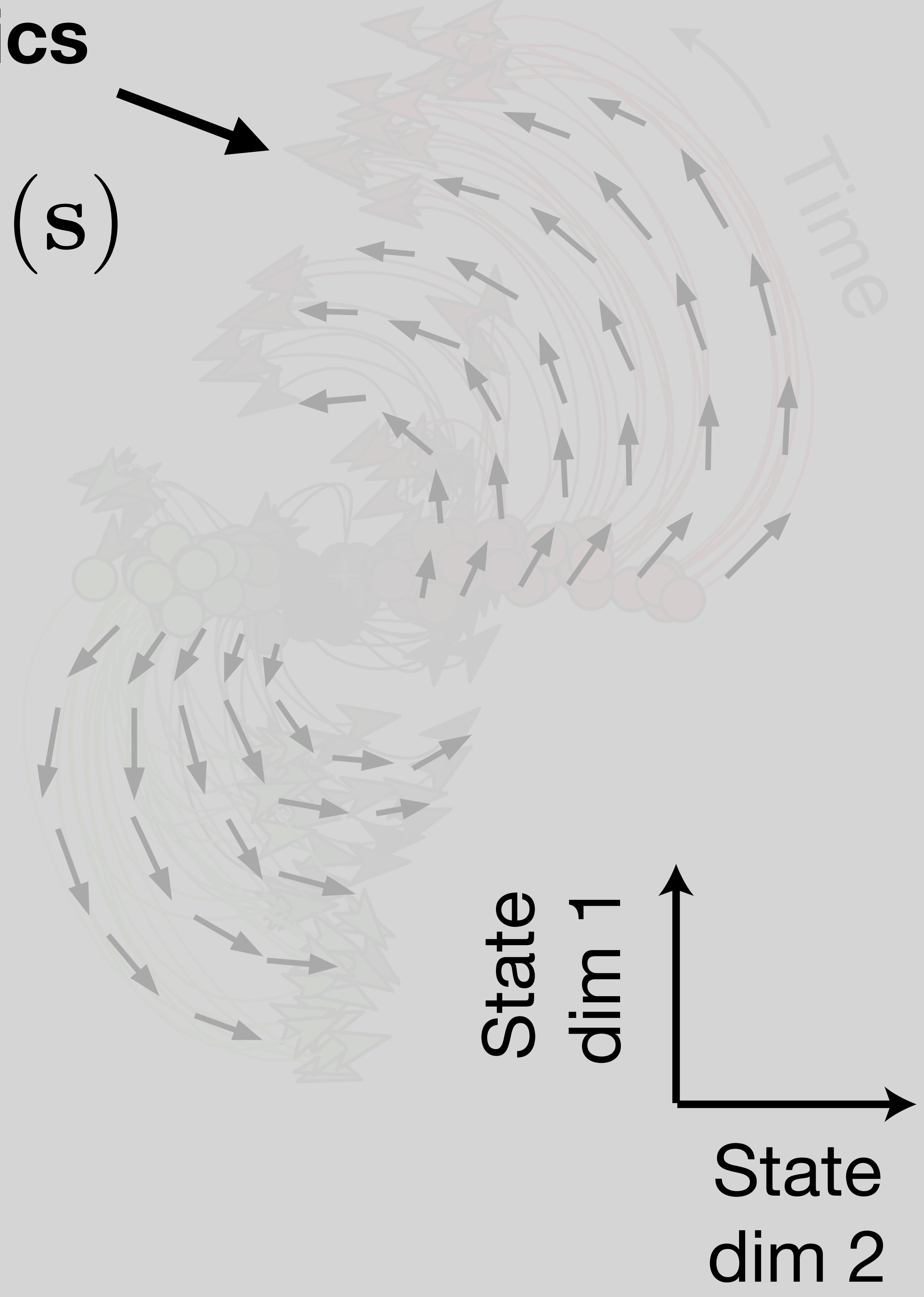
Neural population state space trajectories

(trial-averaged)

Dynamics

$$\frac{d\mathbf{s}}{dt} = f(\mathbf{s})$$



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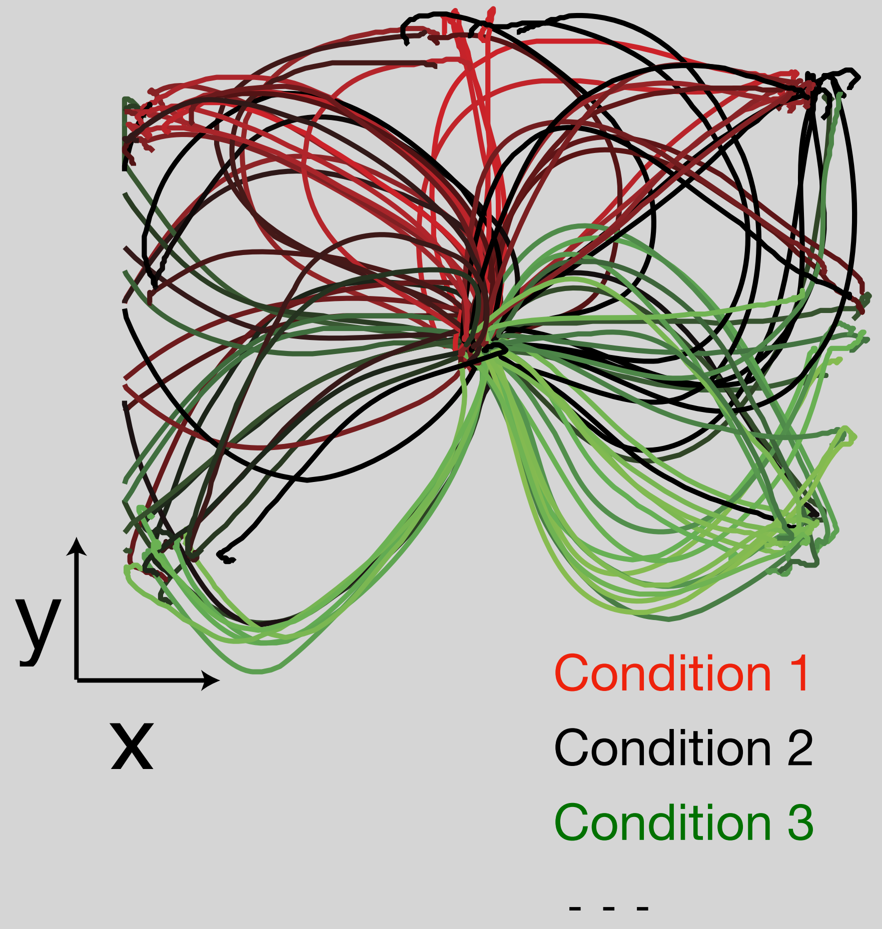

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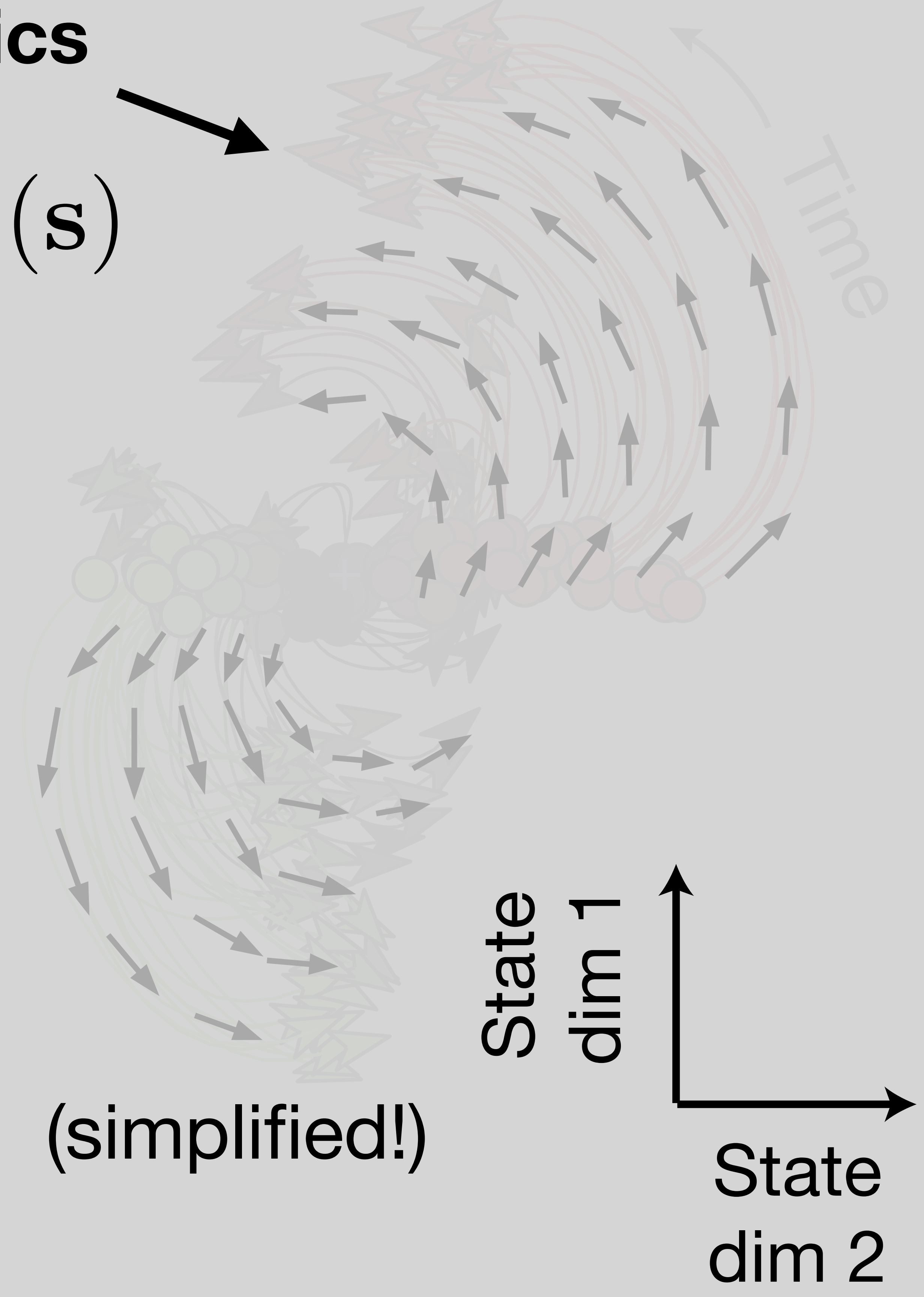
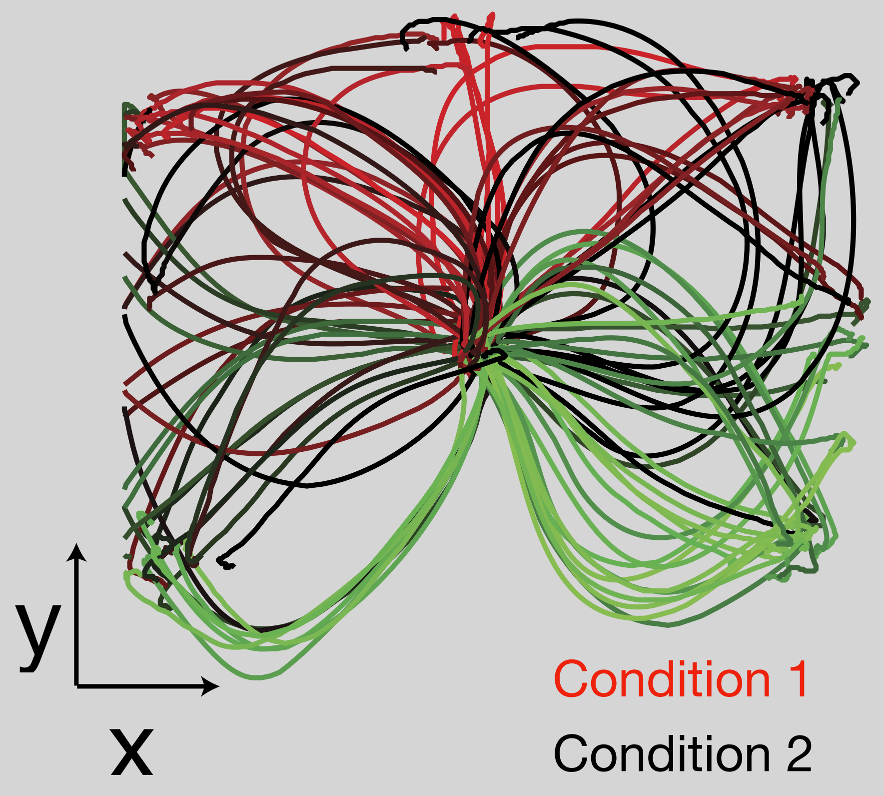


(simplified!)

Hand kinematics



Condition 1
Condition 2
Condition 3
- - -

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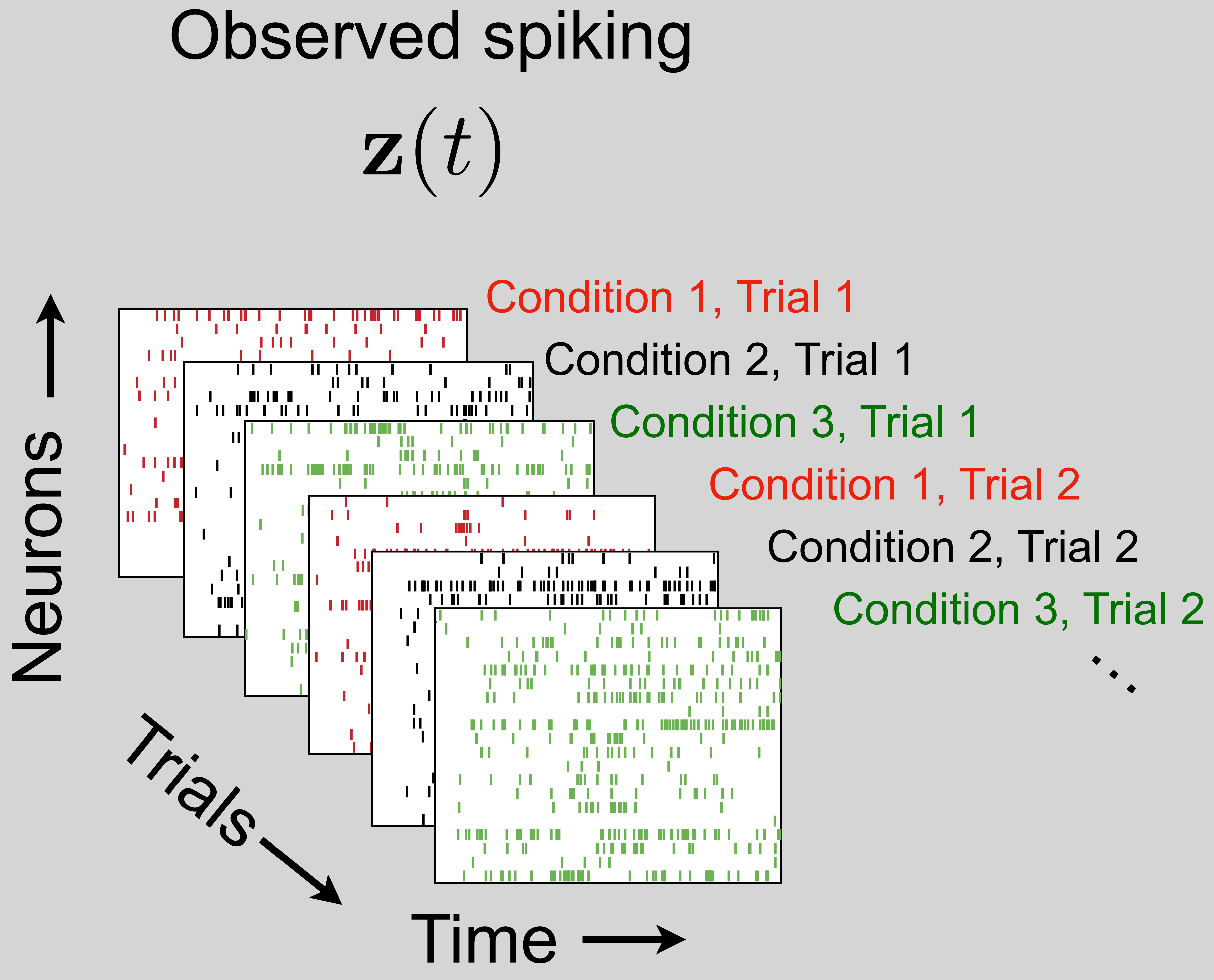
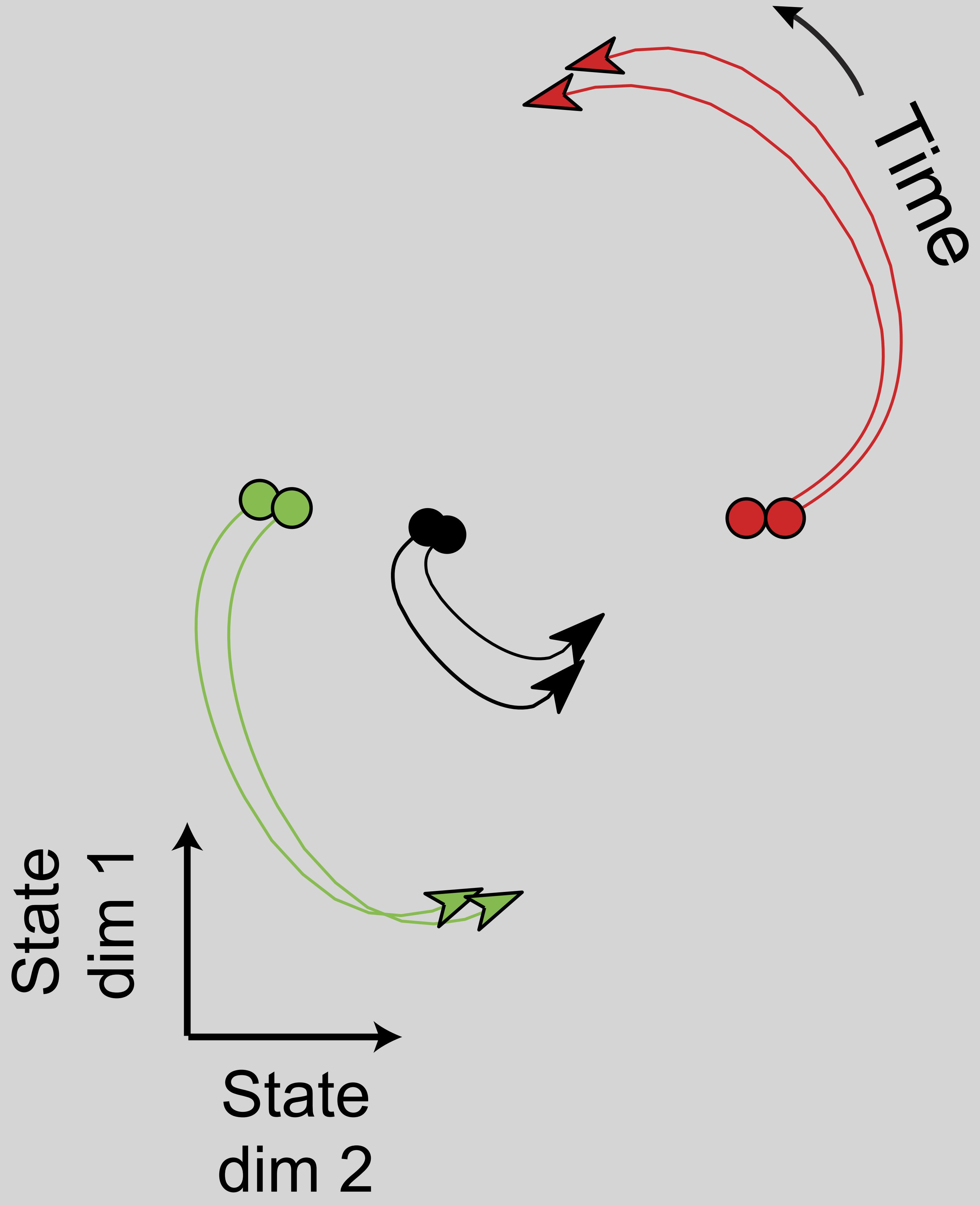
LFADS - inferring dynamics from single-trial activity





Sussillo…Pandarinath, *arxiv* 2016
Pandarinath…Sussillo, *Nature Methods* 2018

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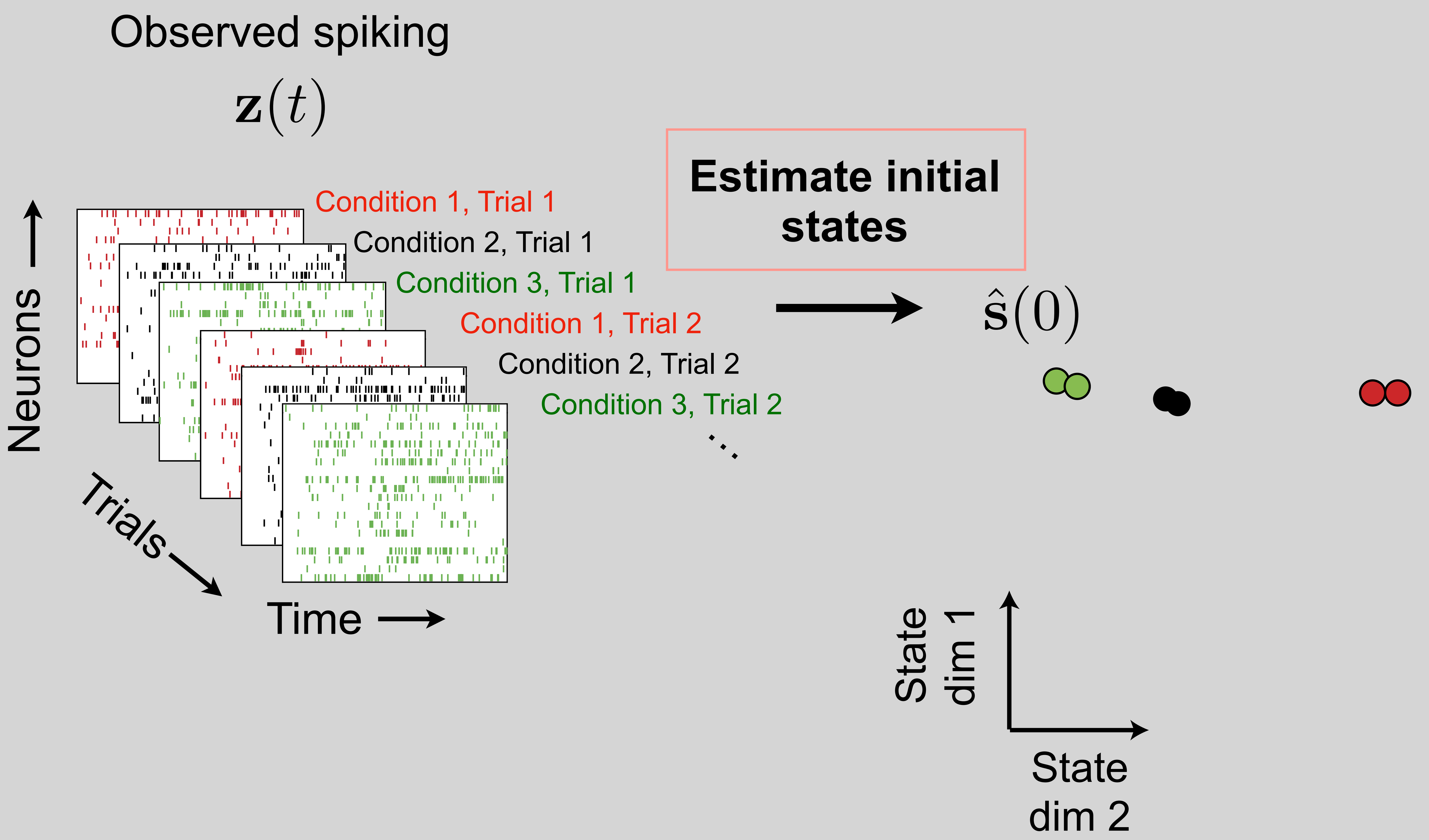

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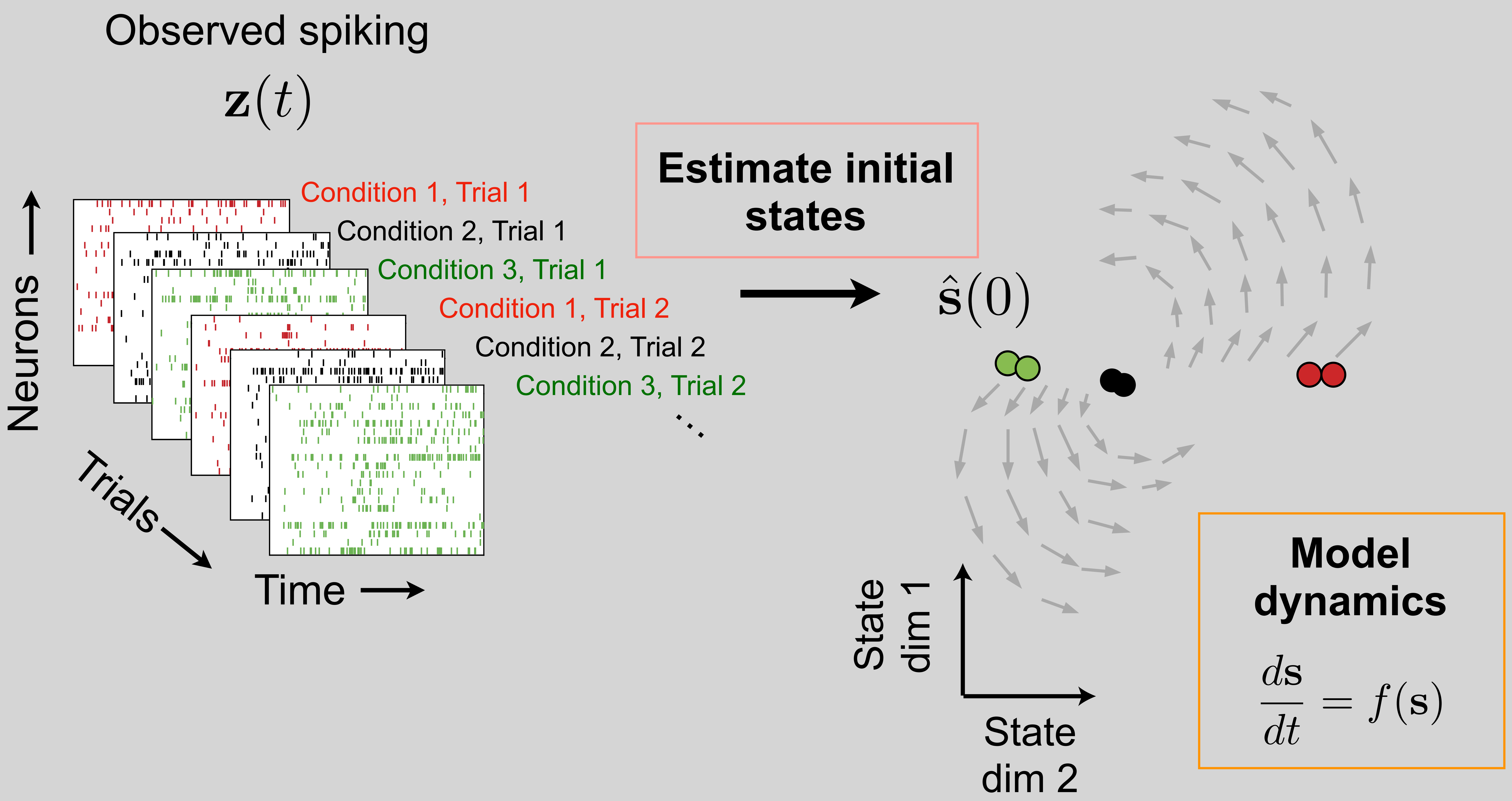

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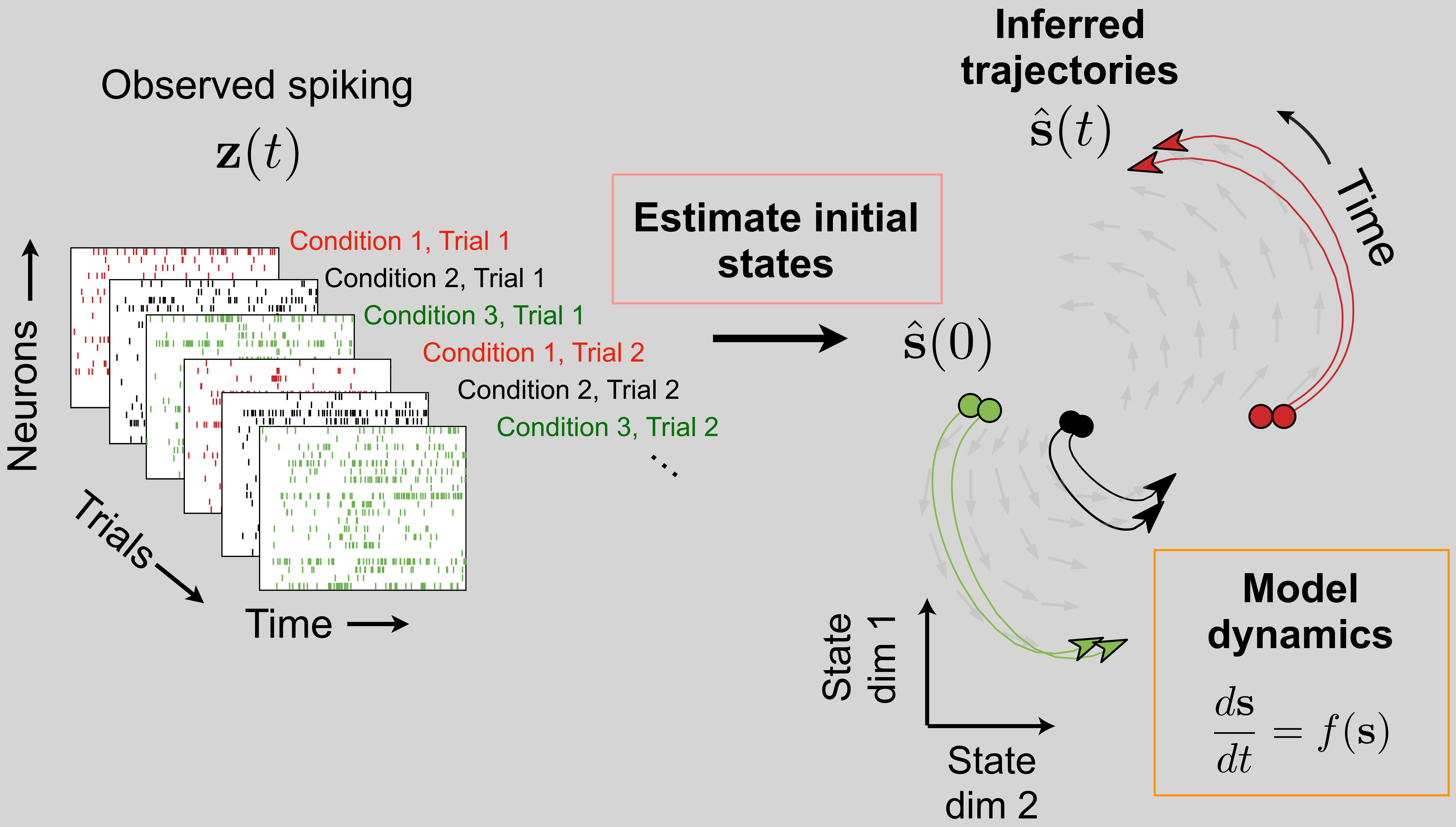

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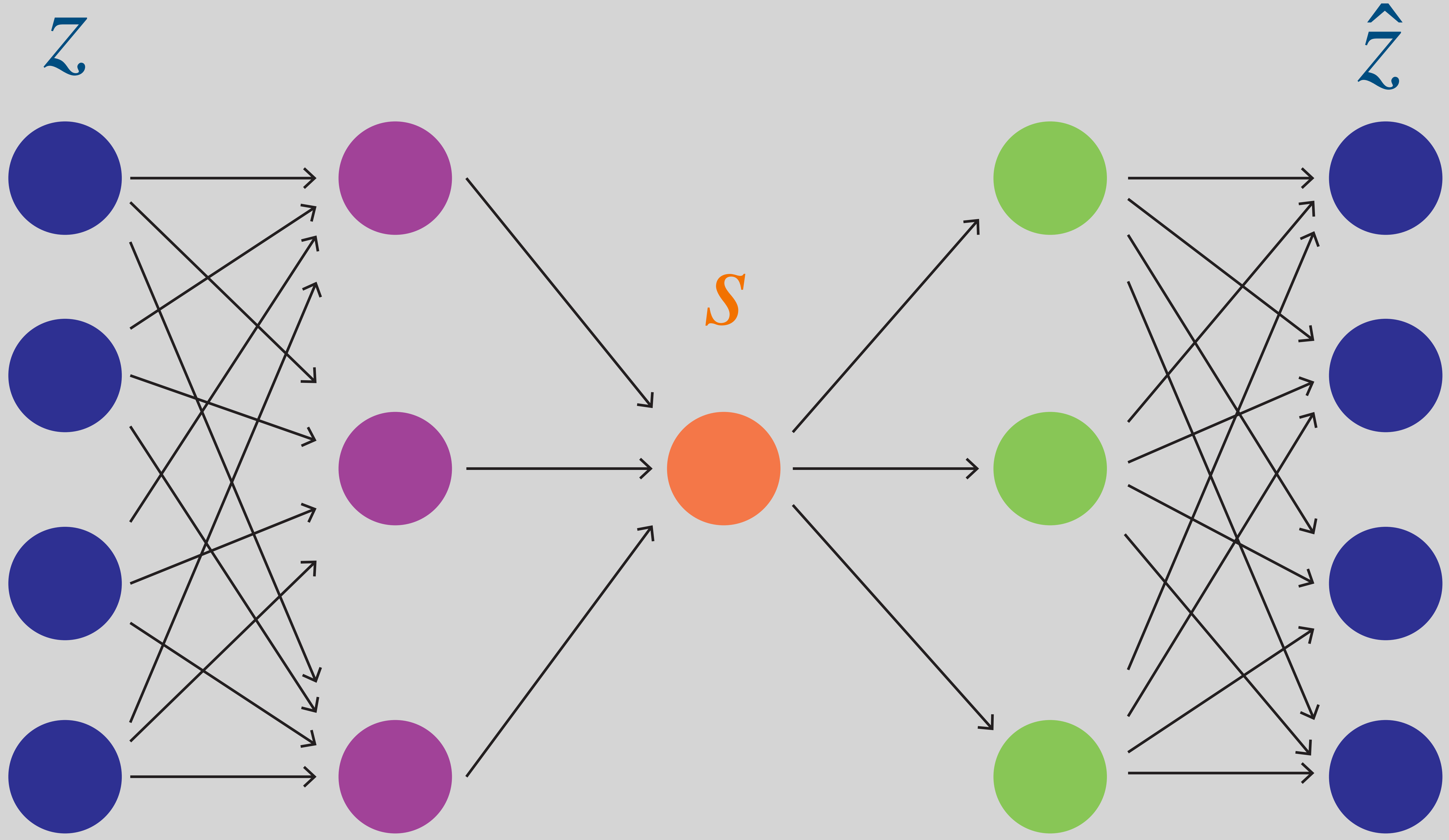
Finding compressed representations: autoencoders



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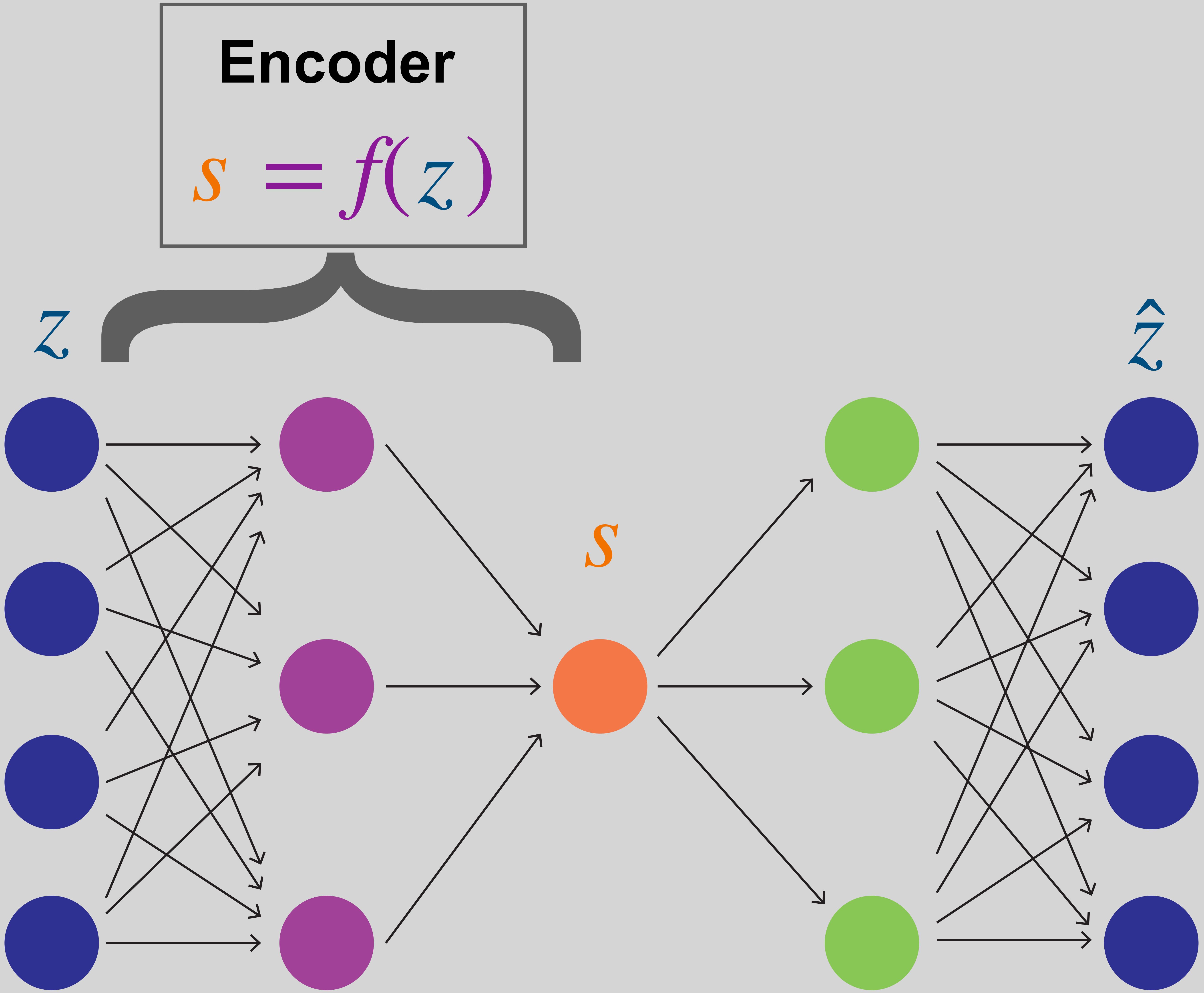

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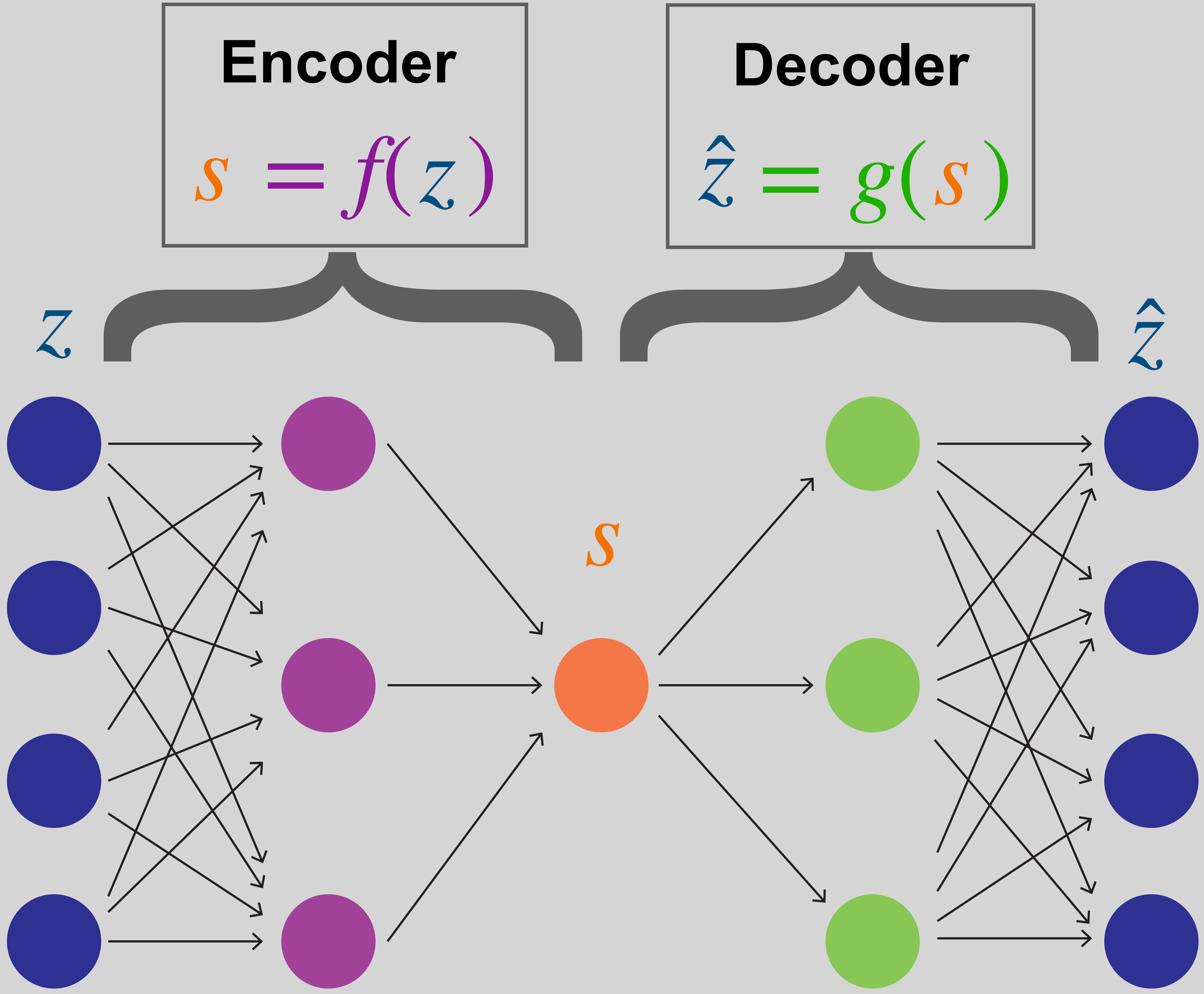
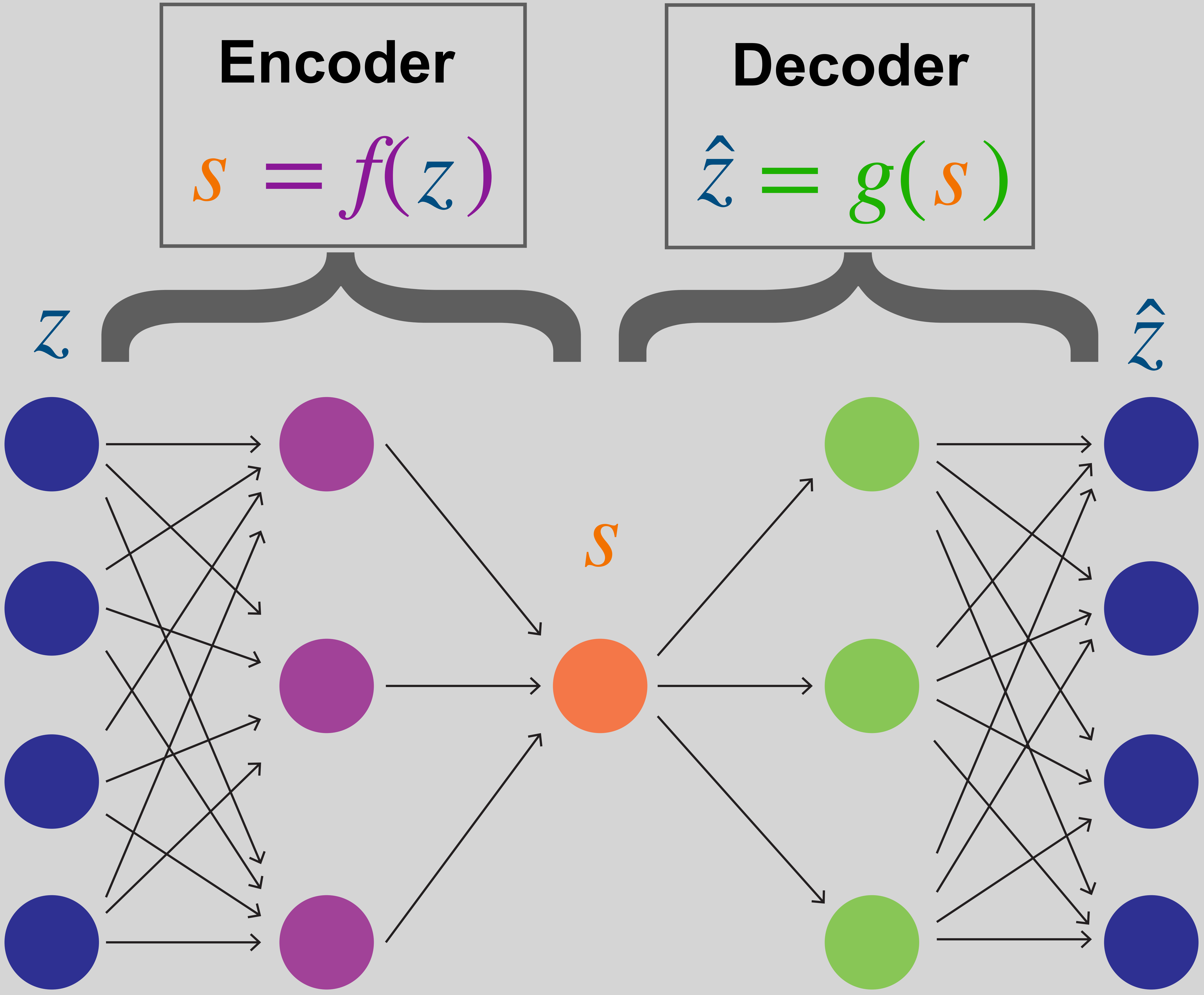


Finding compressed representations: autoencoders

- Finds a compressed representation of the data that best reconstructs it



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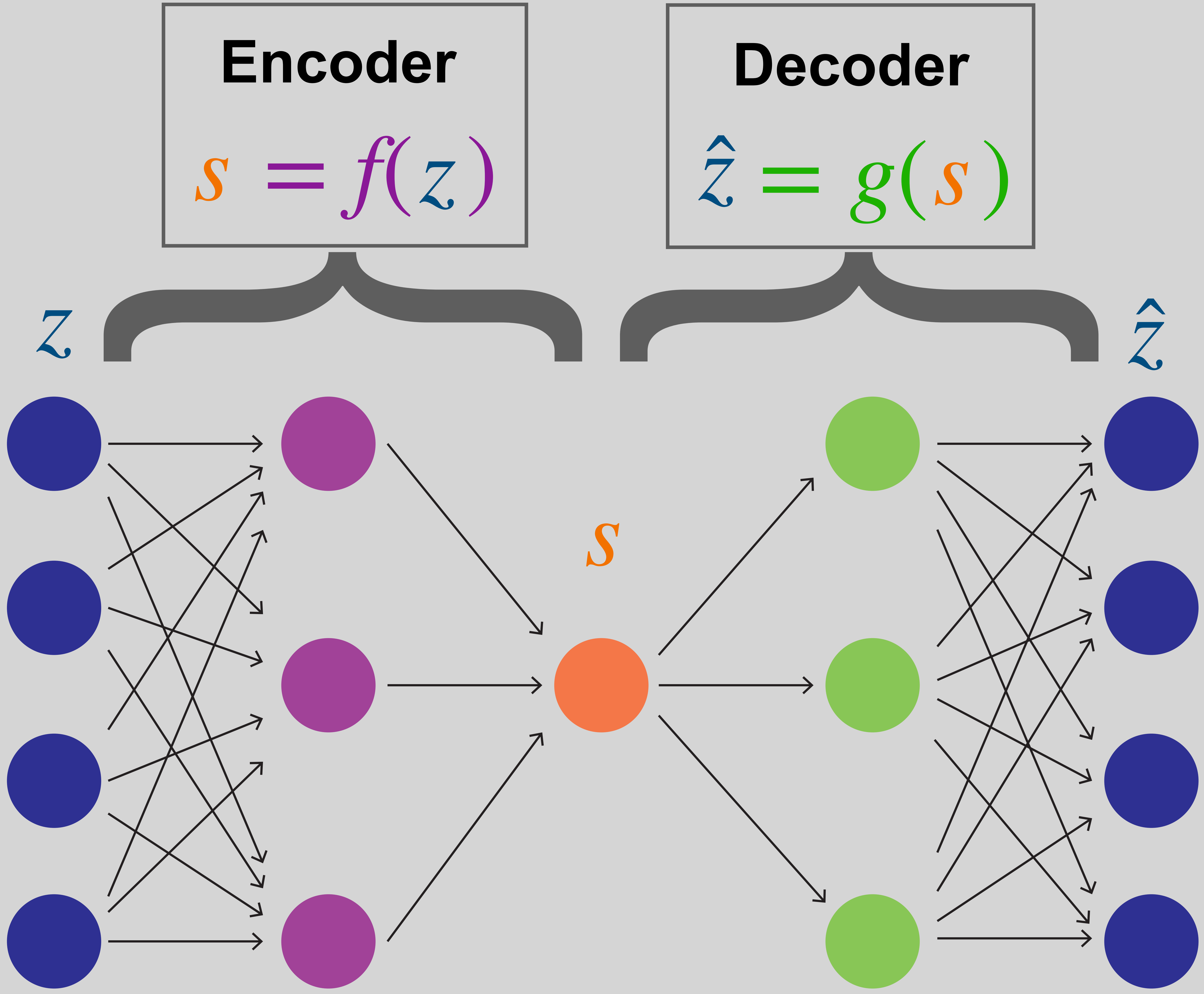
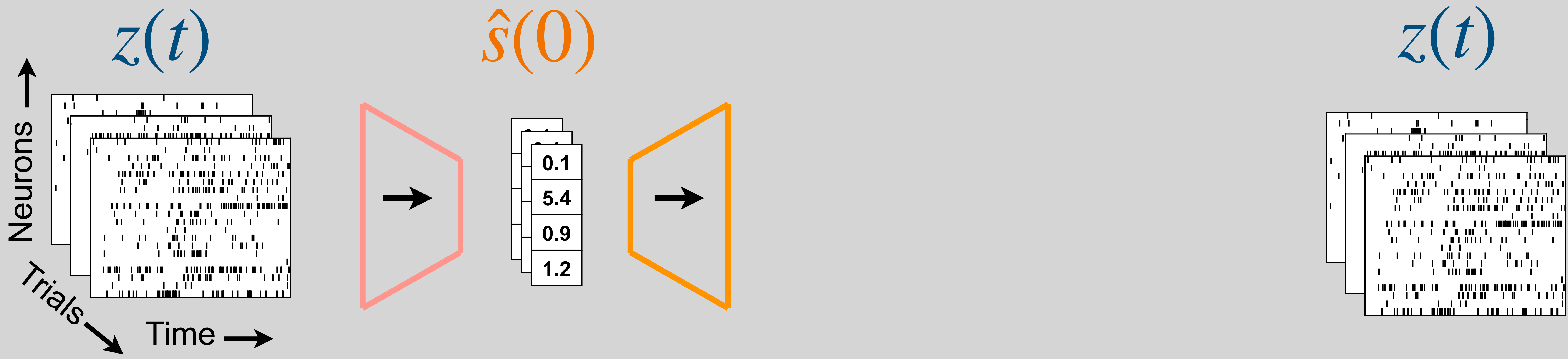


- Finds a compressed representation of the data that best reconstructs it

- Compression forces network to preserve important features, while discarding unimportant features (e.g., noise)

Latent Factor Analysis via Dynamical Systems (LFADS)

Sequential autoencoder (SAE)



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Sussillo…Pandarinath, *arxiv* 2016
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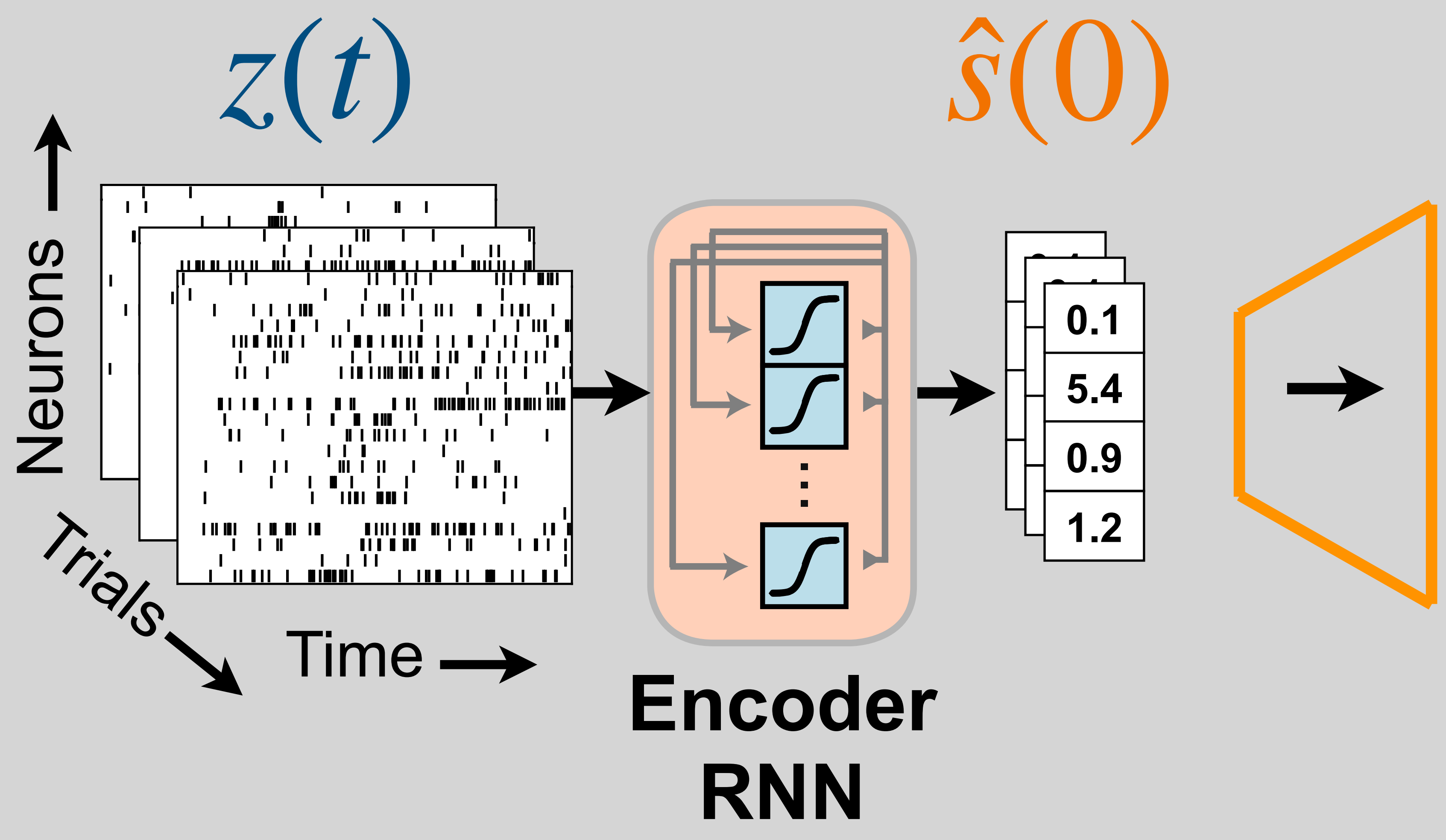

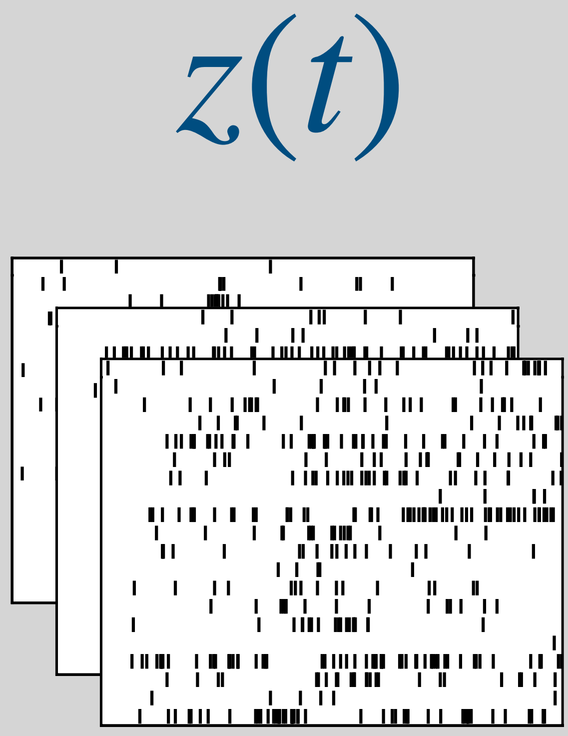

Learns mapping onto initial states

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Sussillo…Pandarinath, *arxiv* 2016
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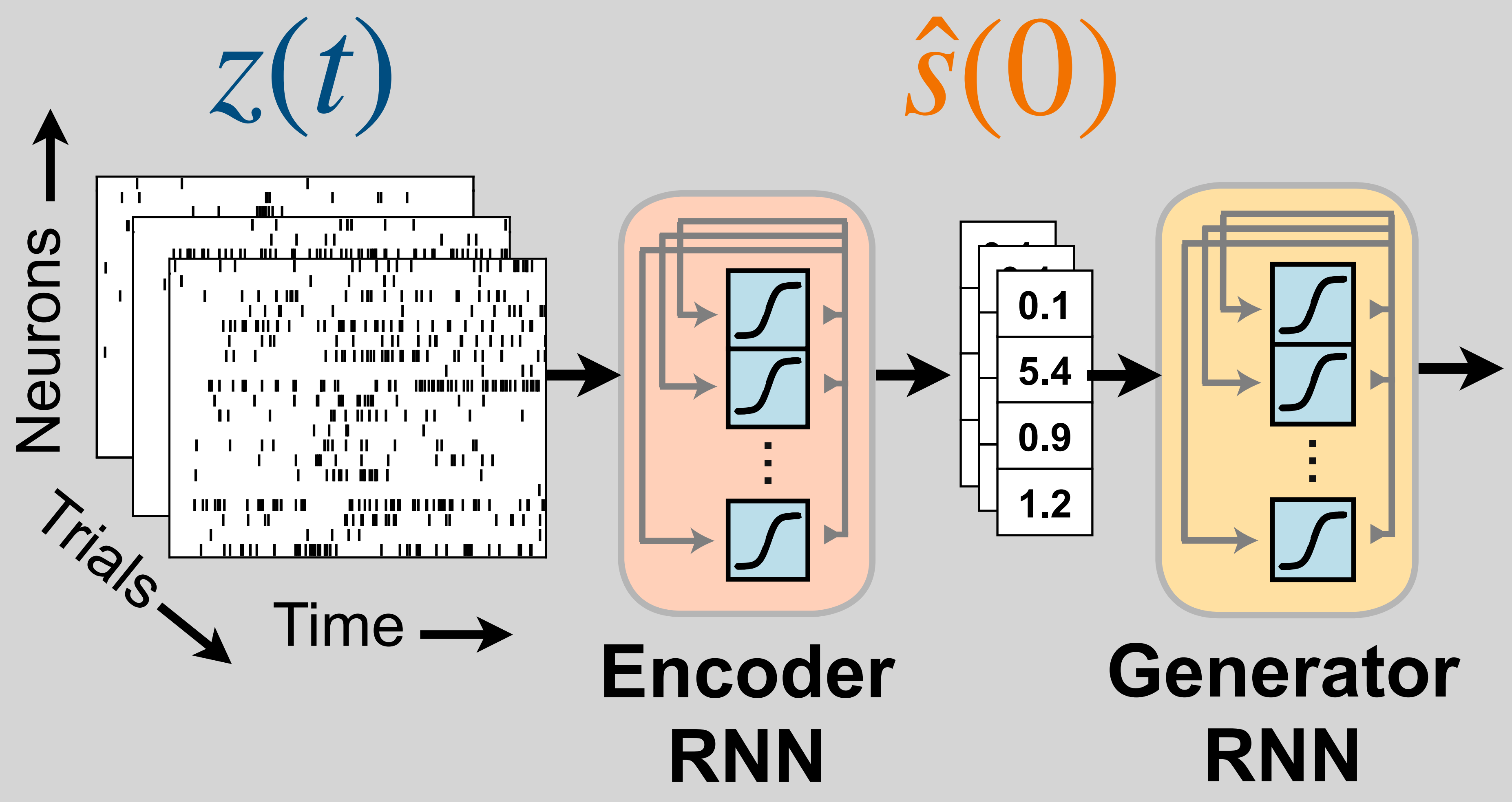

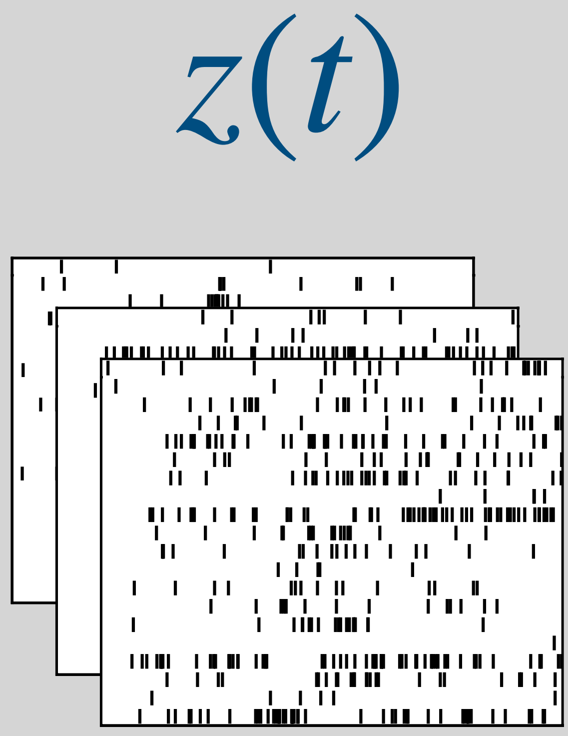

Learns mapping onto initial states

Approximates dynamics

$$\frac{d\mathbf{s}}{dt} = f(\mathbf{s})$$

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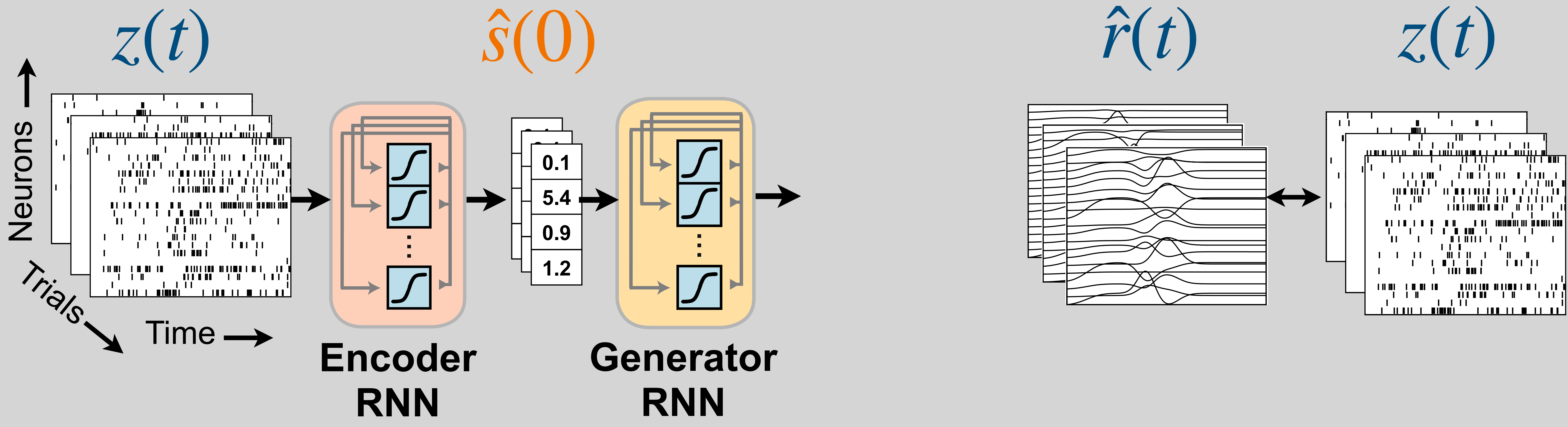

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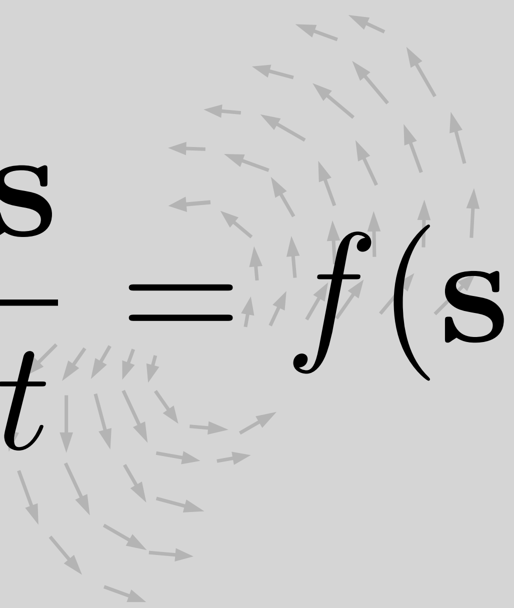

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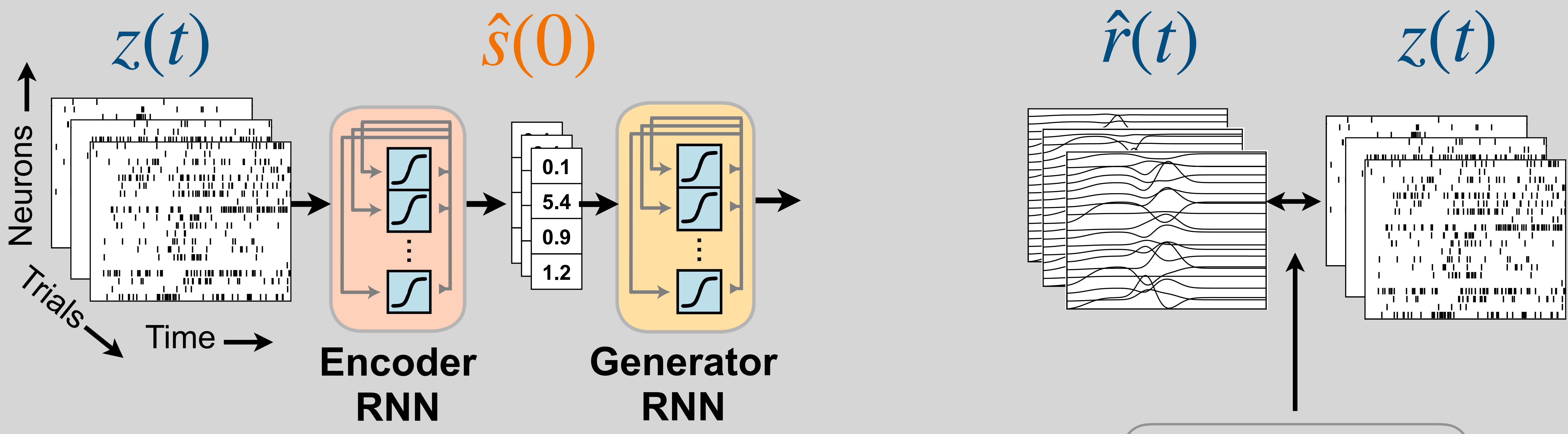

Learns mapping onto initial states

Approximates dynamics

$$\frac{ds}{dt} = f(\mathbf{s})$$

Cost function: Poisson likelihood

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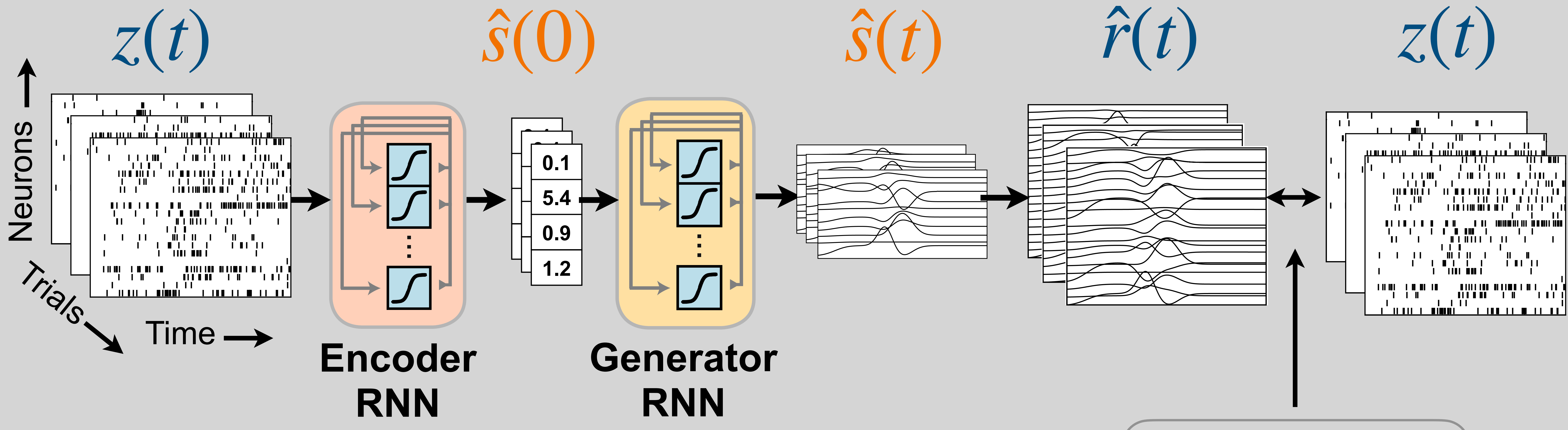

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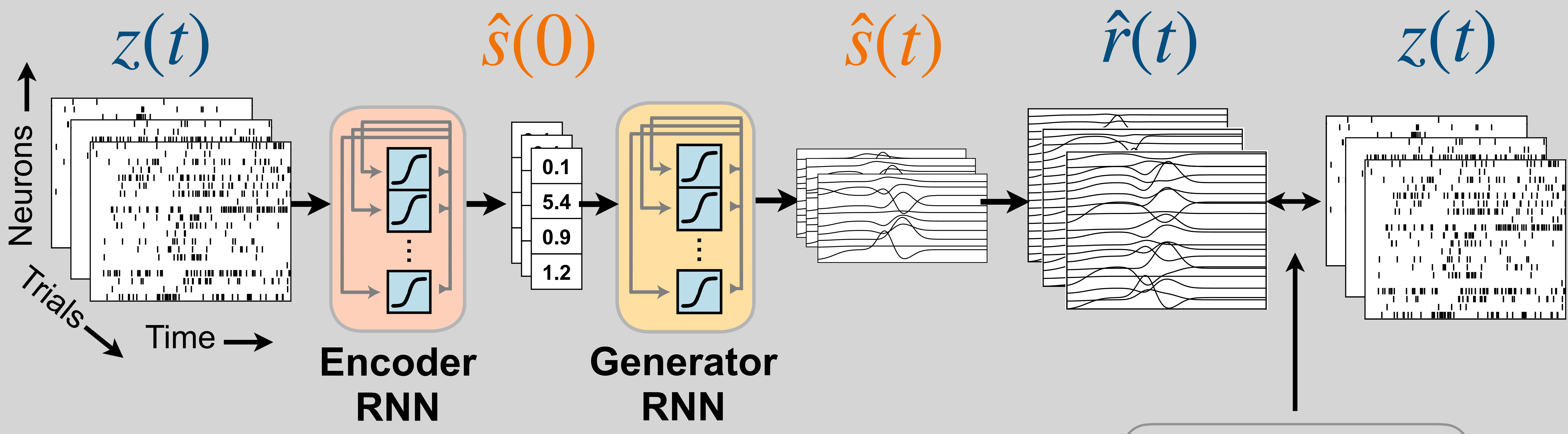
Latent Factor Analysis via Dynamical Systems (LFADS)

- Recurrent neural networks (RNNs) are nonlinear dynamical systems

Sequential autoencoder (SAE)



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Sussillo…Pandarinath, *arxiv* 2016
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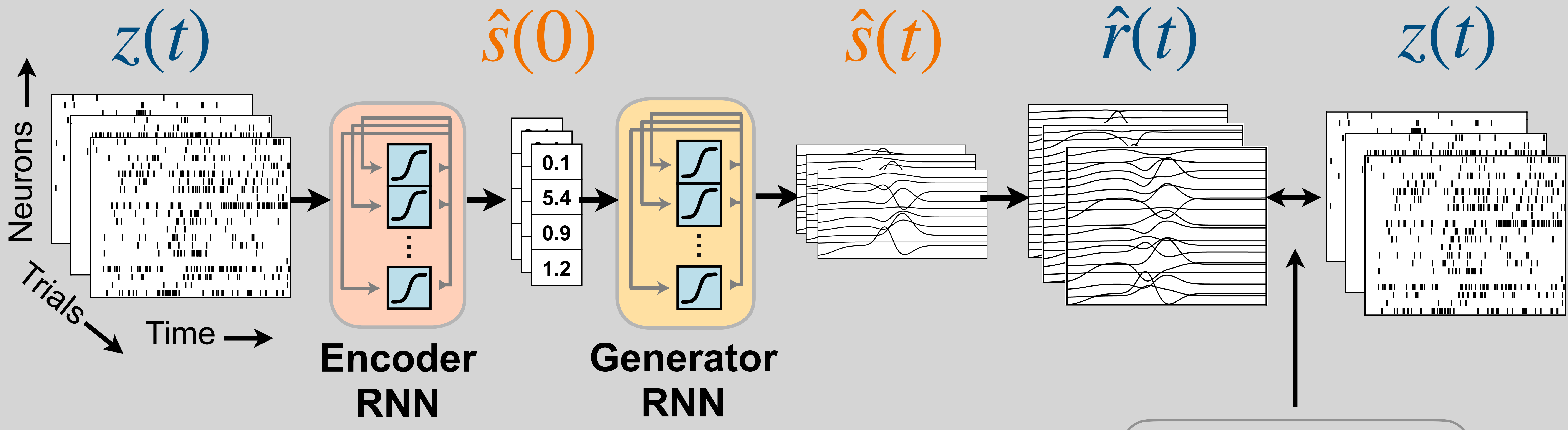
Latent Factor Analysis via Dynamical Systems (LFADS)

- Recurrent neural networks (RNNs) are nonlinear dynamical systems
- RNN's recurrent weights are adjusted during model training to approximate the system's dynamics

Sequential autoencoder (SAE)



Learns mapping onto initial states

Approximates dynamics

$$\frac{ds}{dt} = f(\mathbf{s})$$

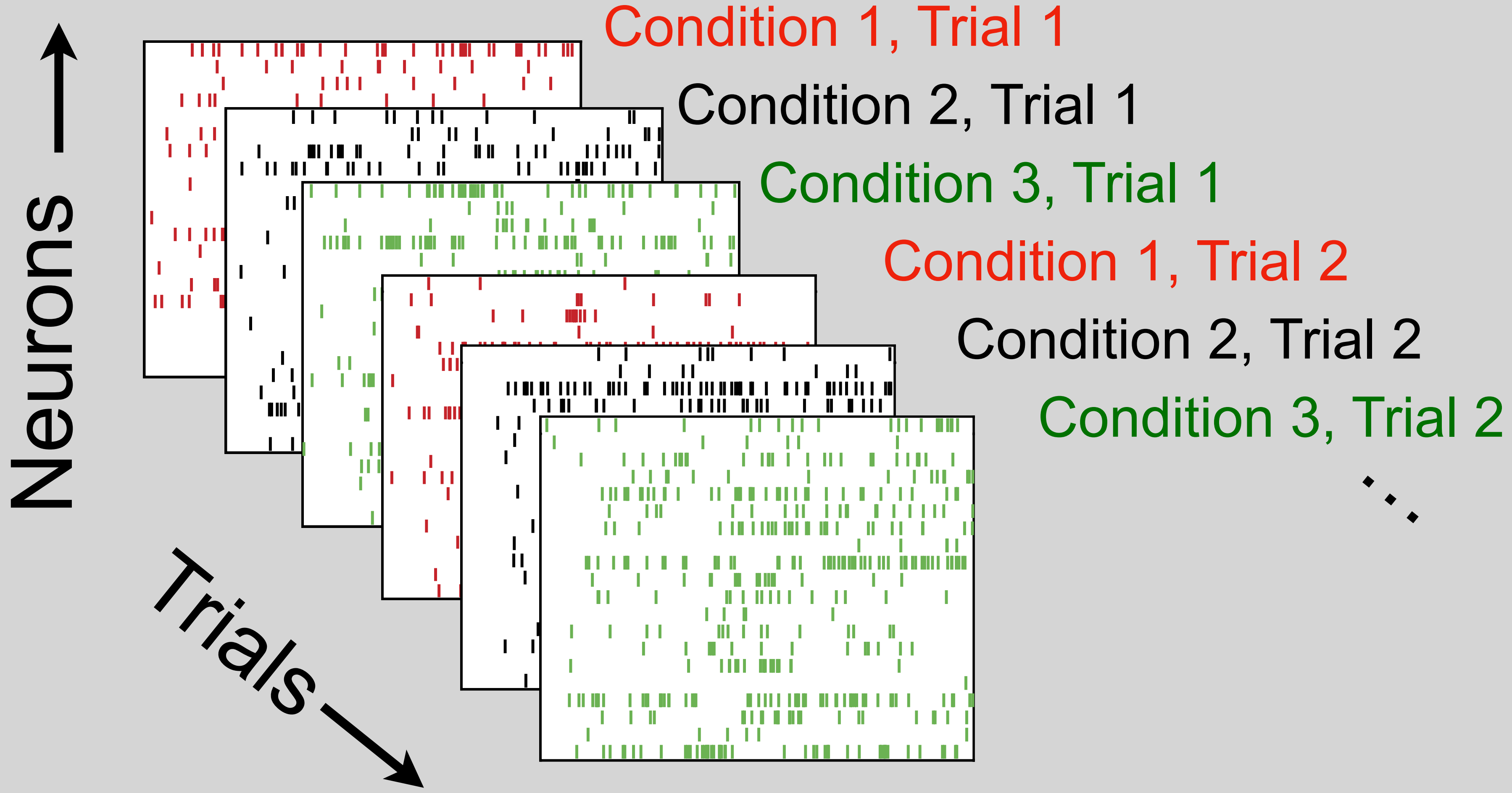
Cost function: Poisson likelihood

David Sussillo
Stanford

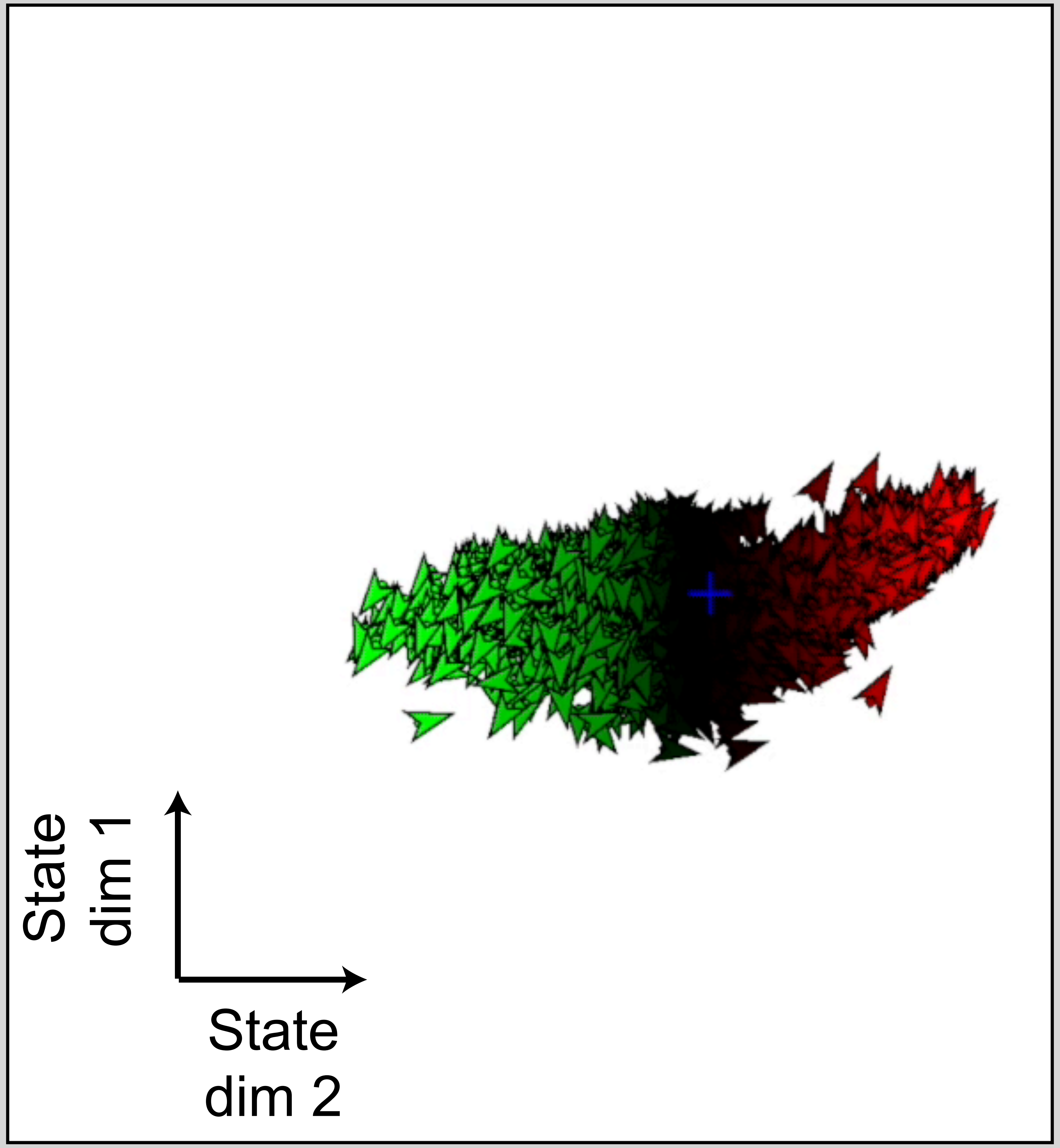
Sussillo…Pandarinath, *arxiv* 2016
Pandarinath…Sussillo, *Nature Methods* 2018

Observed spiking

$\mathbf{z}(t)$



State space trajectories inferred by LFADS

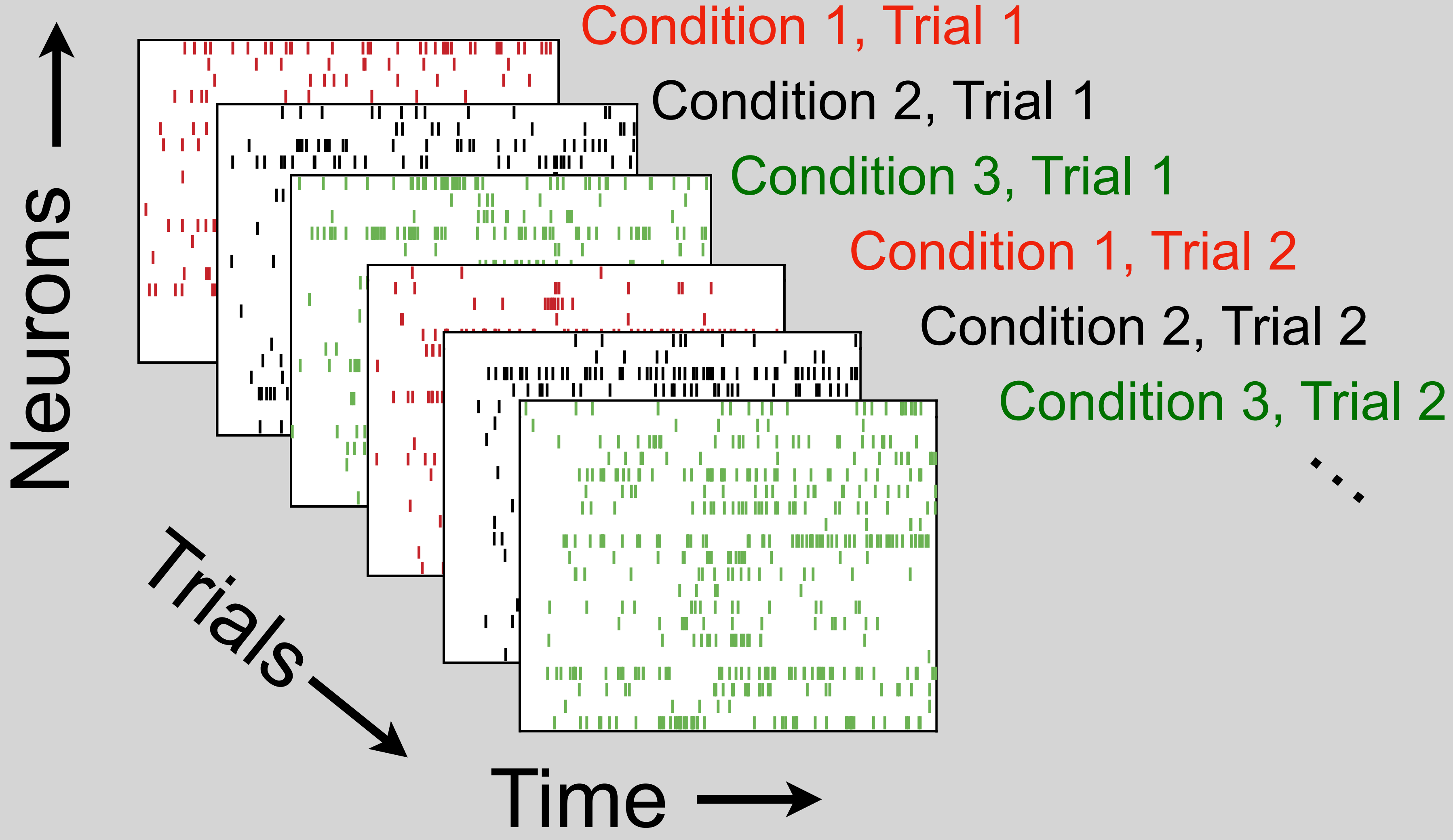


(simplified)

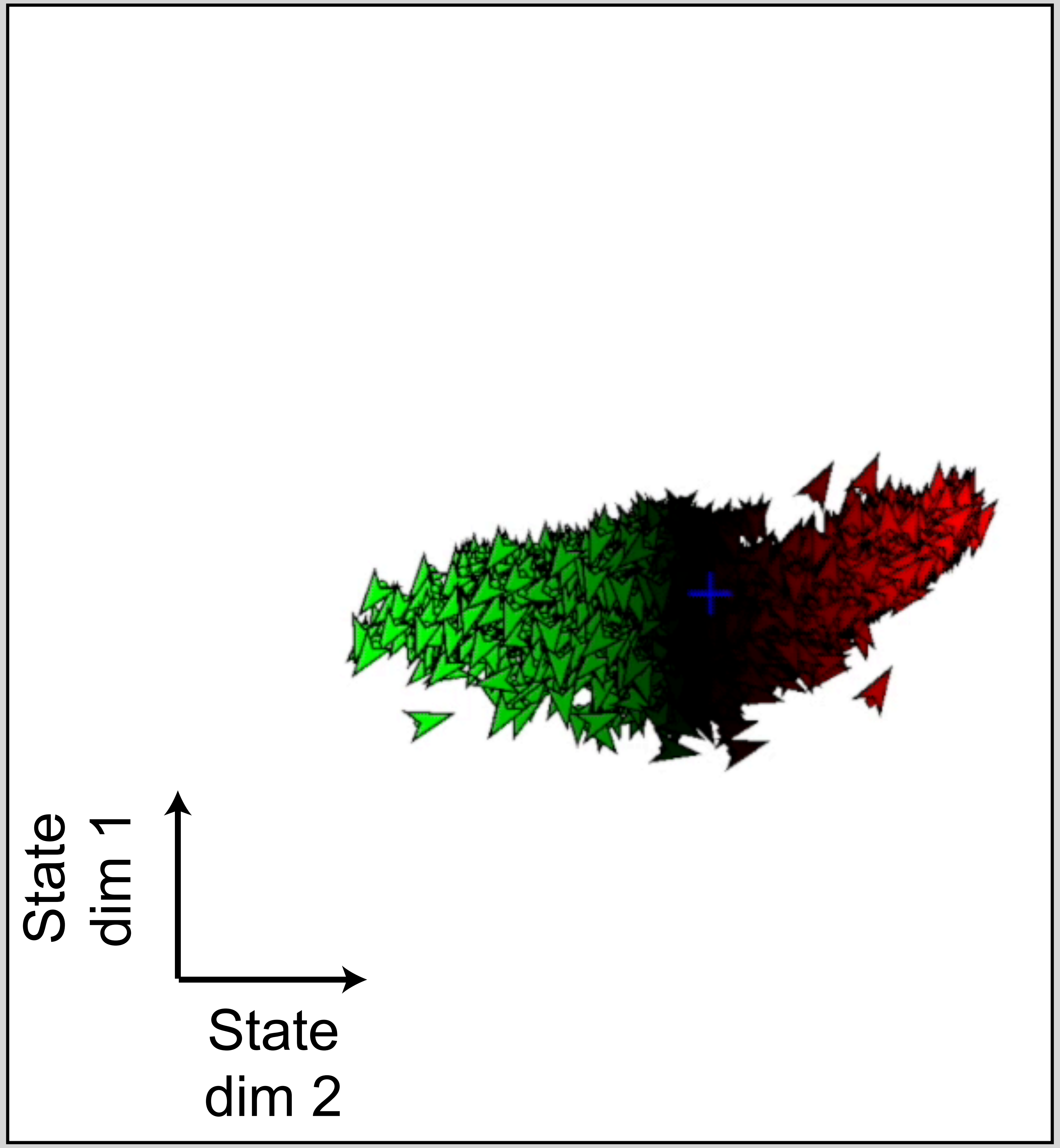
Pandarinath…Sussillo, *Nature Methods* 2018

Observed spiking

$\mathbf{z}(t)$



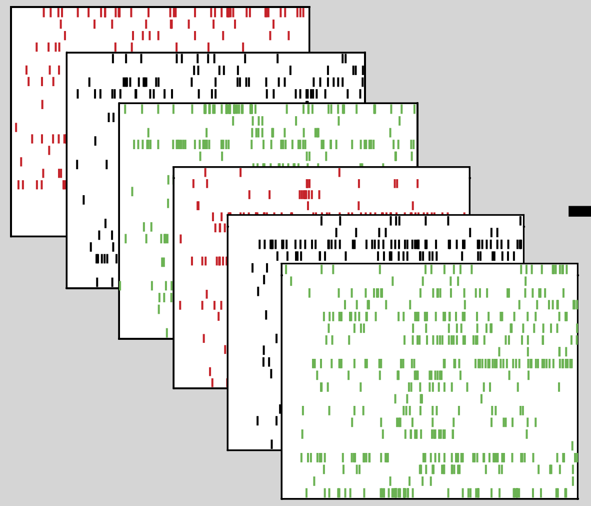
State space trajectories inferred by LFADS



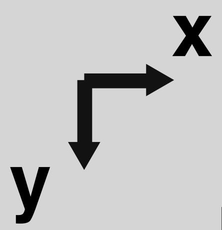
(simplified)

Pandarinath…Sussillo, *Nature Methods* 2018

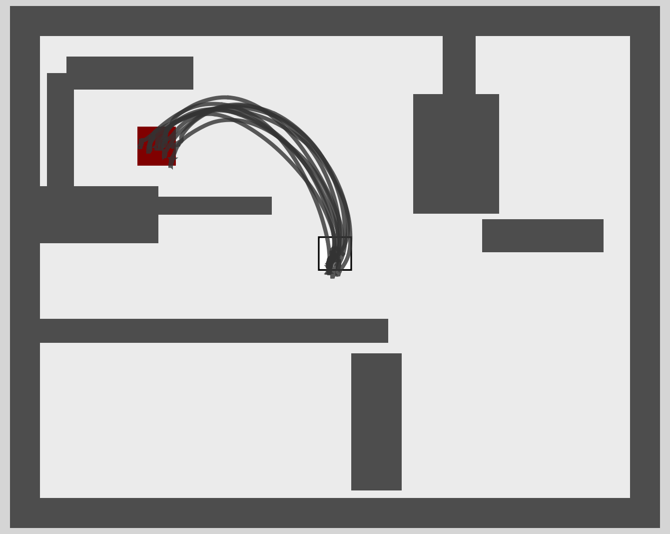
LFADS improves decoding of hand trajectories



→ Denoise (smoothing, GPFA, or LFADS) → Decode (optimal linear estimation)



Actual



Pandarinath…Sussillo, *Nature Methods* 2018

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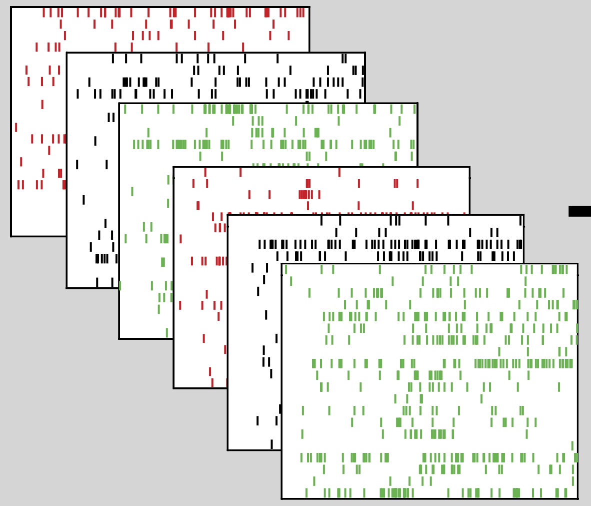

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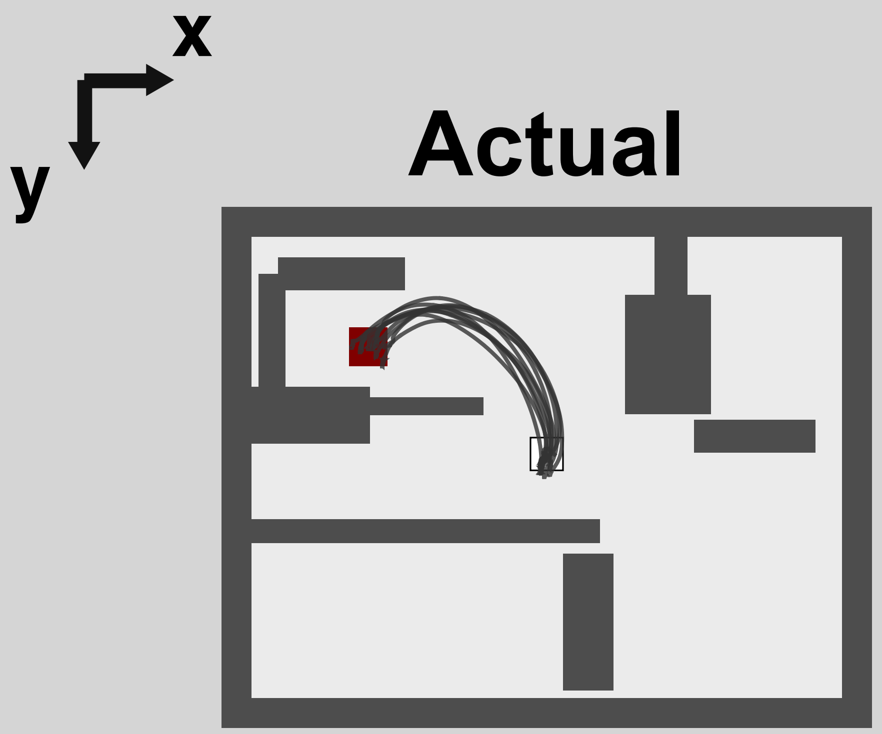
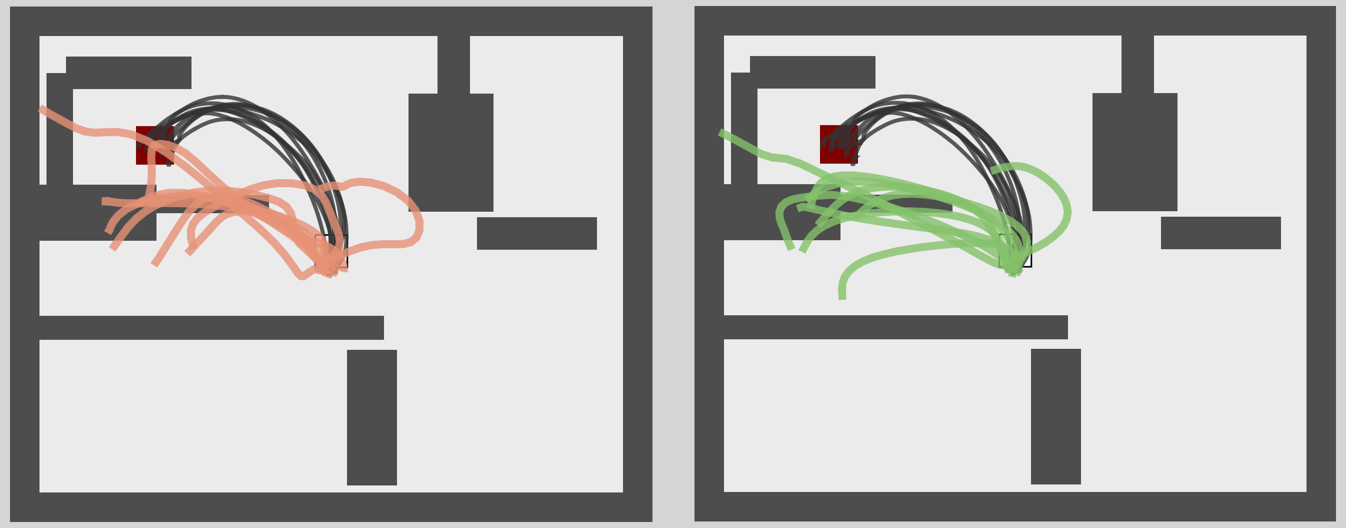


Smoothing GPFA



Pandarinath…Sussillo, *Nature Methods* 2018

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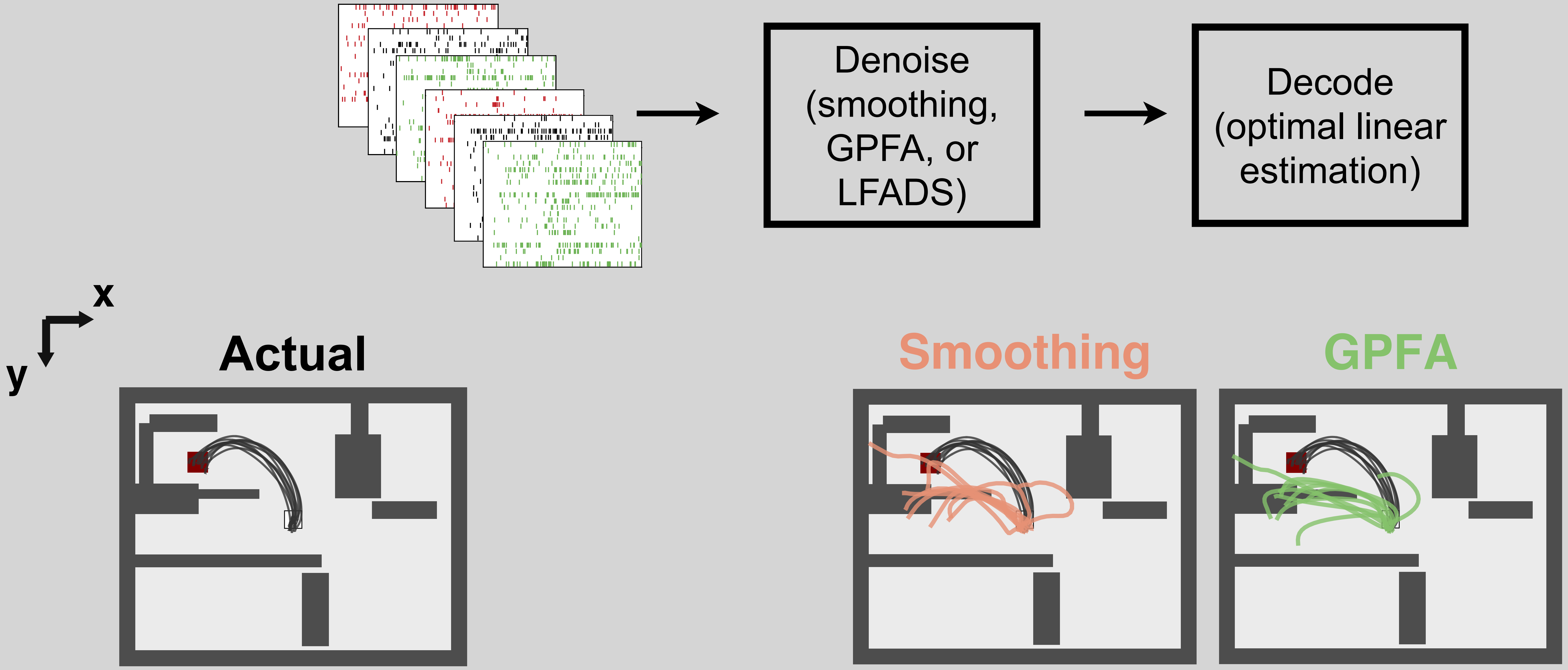
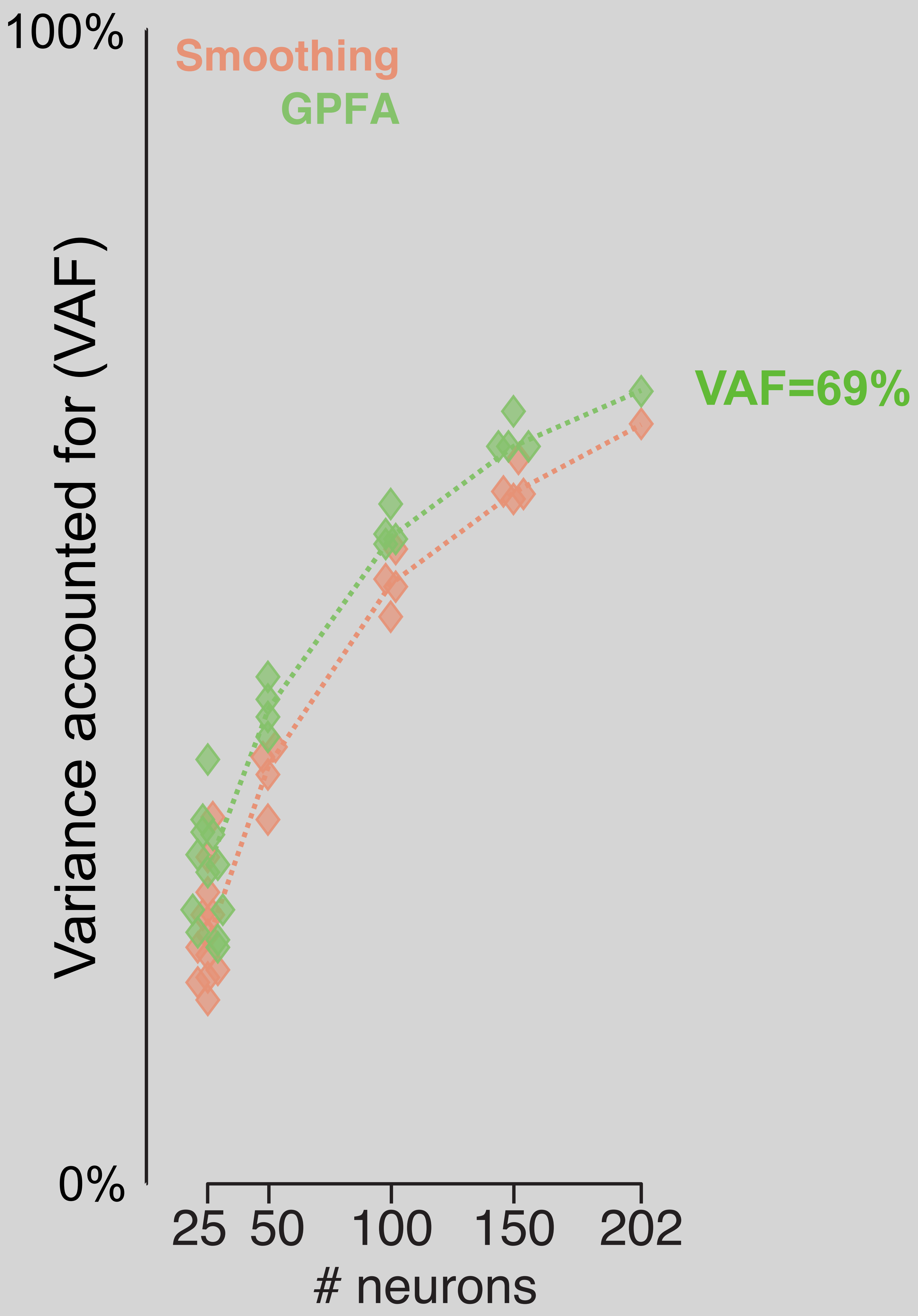
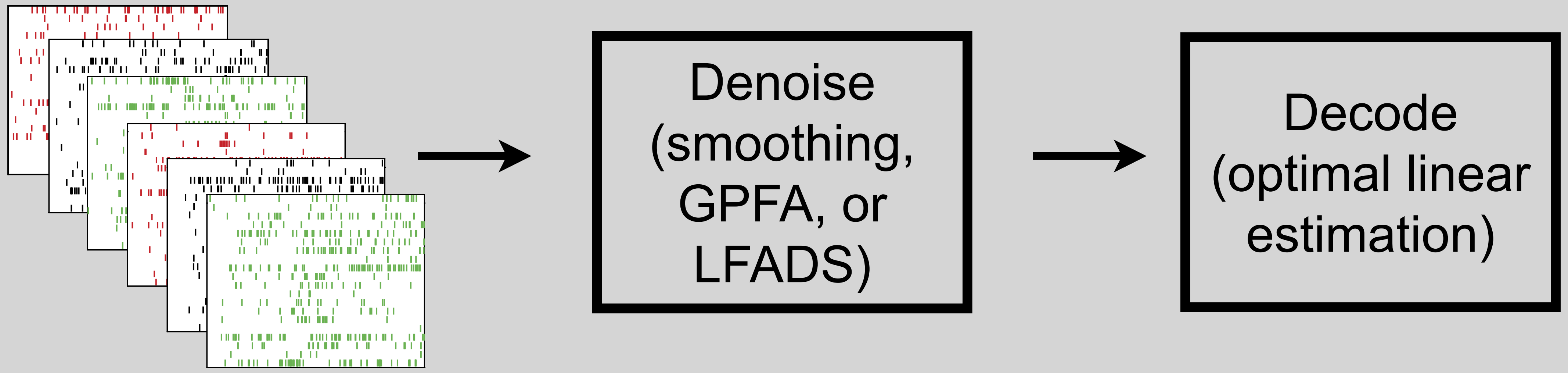
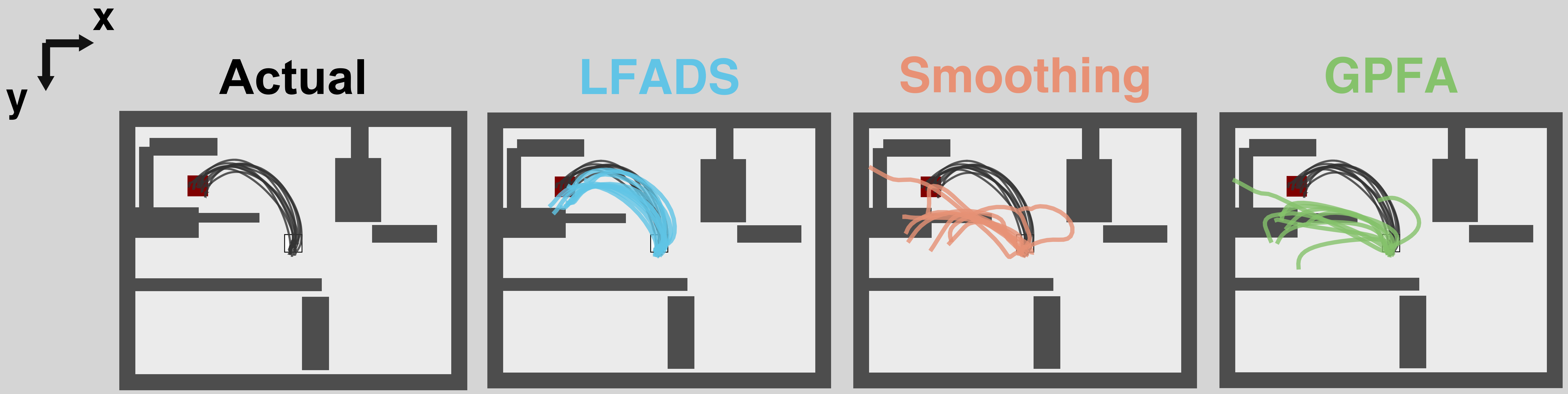


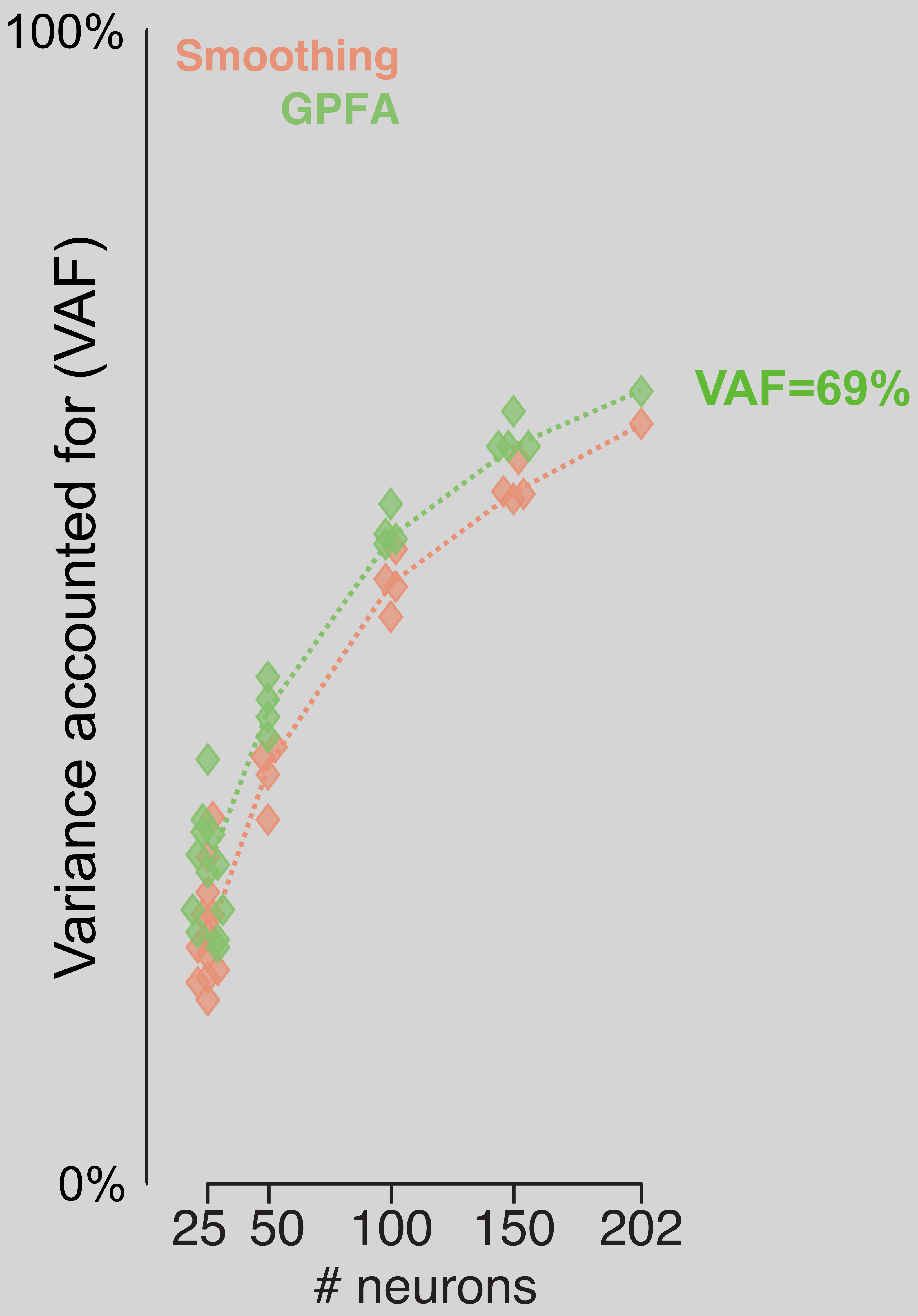


Pandarinath…Sussillo, *Nature Methods* 2018

LFADS improves decoding of hand trajectories







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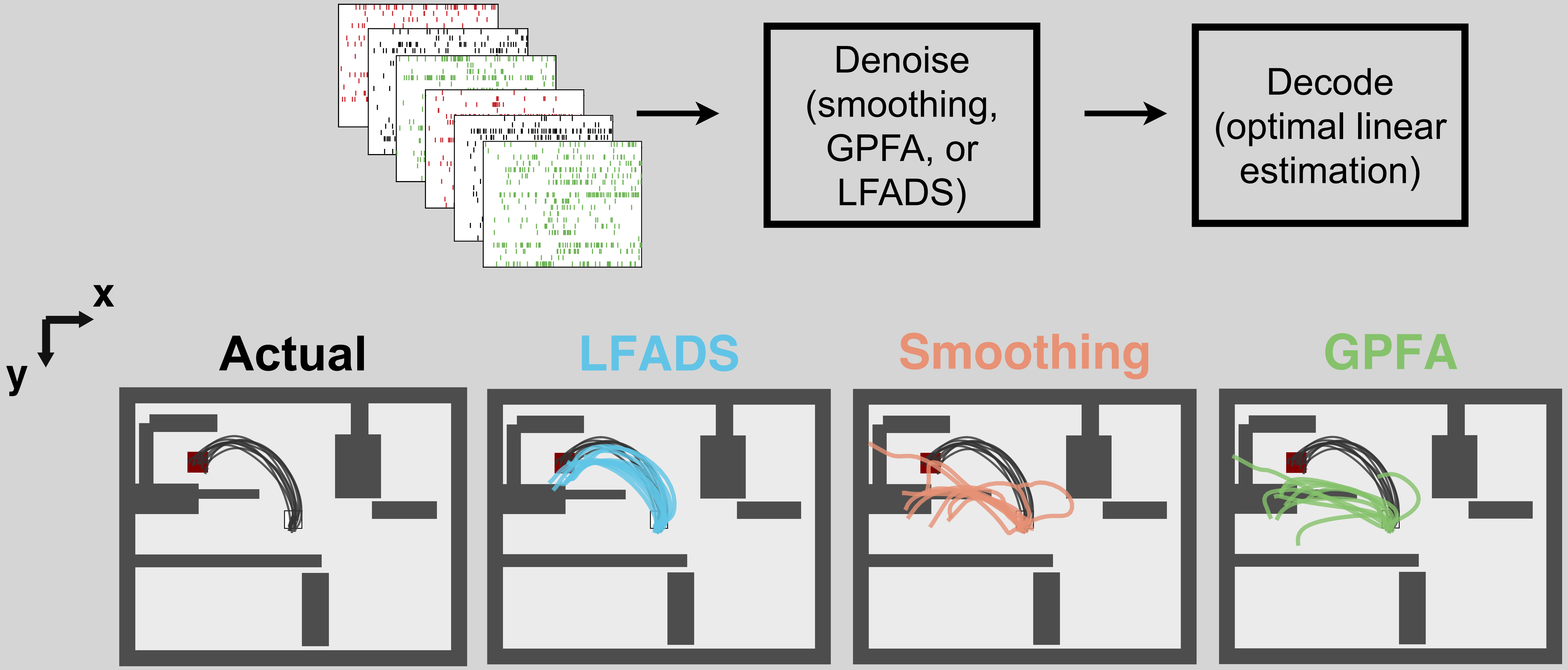

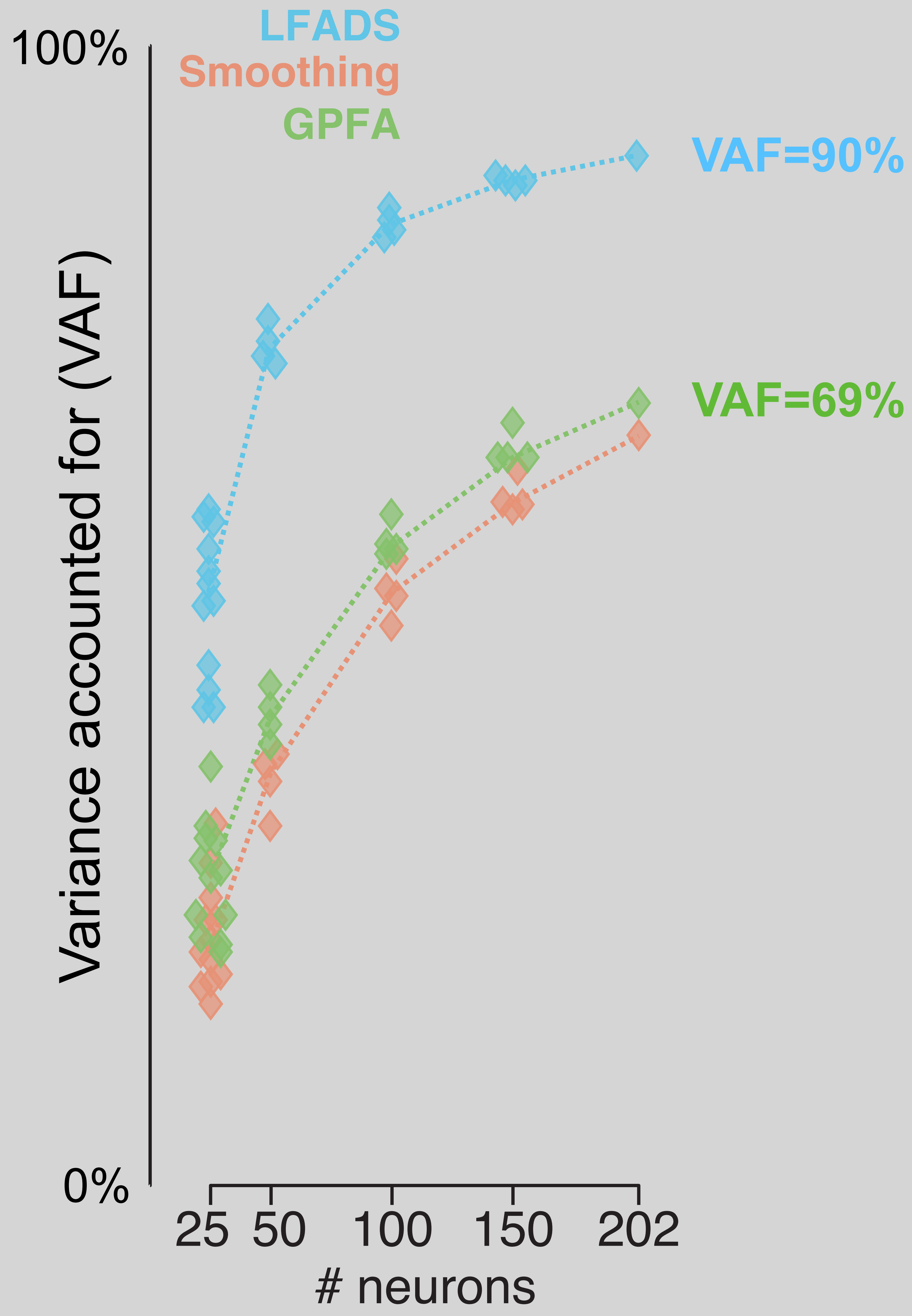

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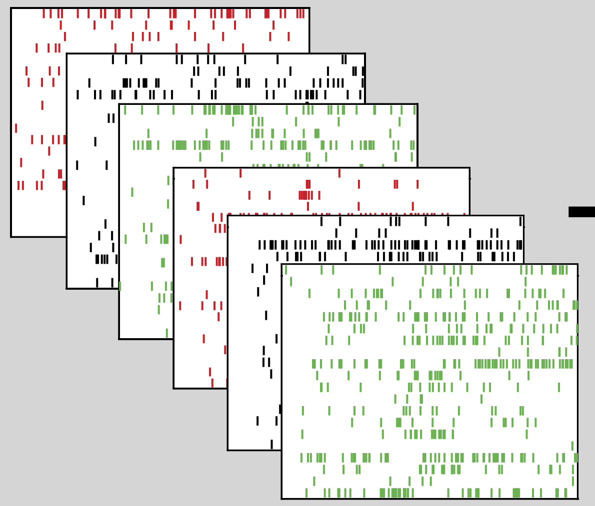
LFADS improves decoding of hand trajectories



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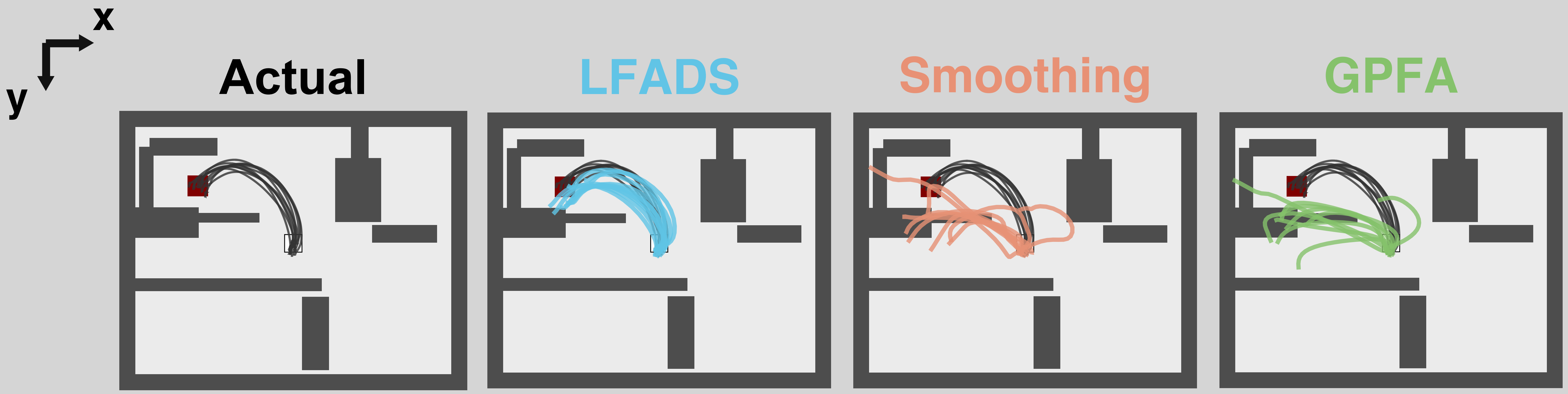
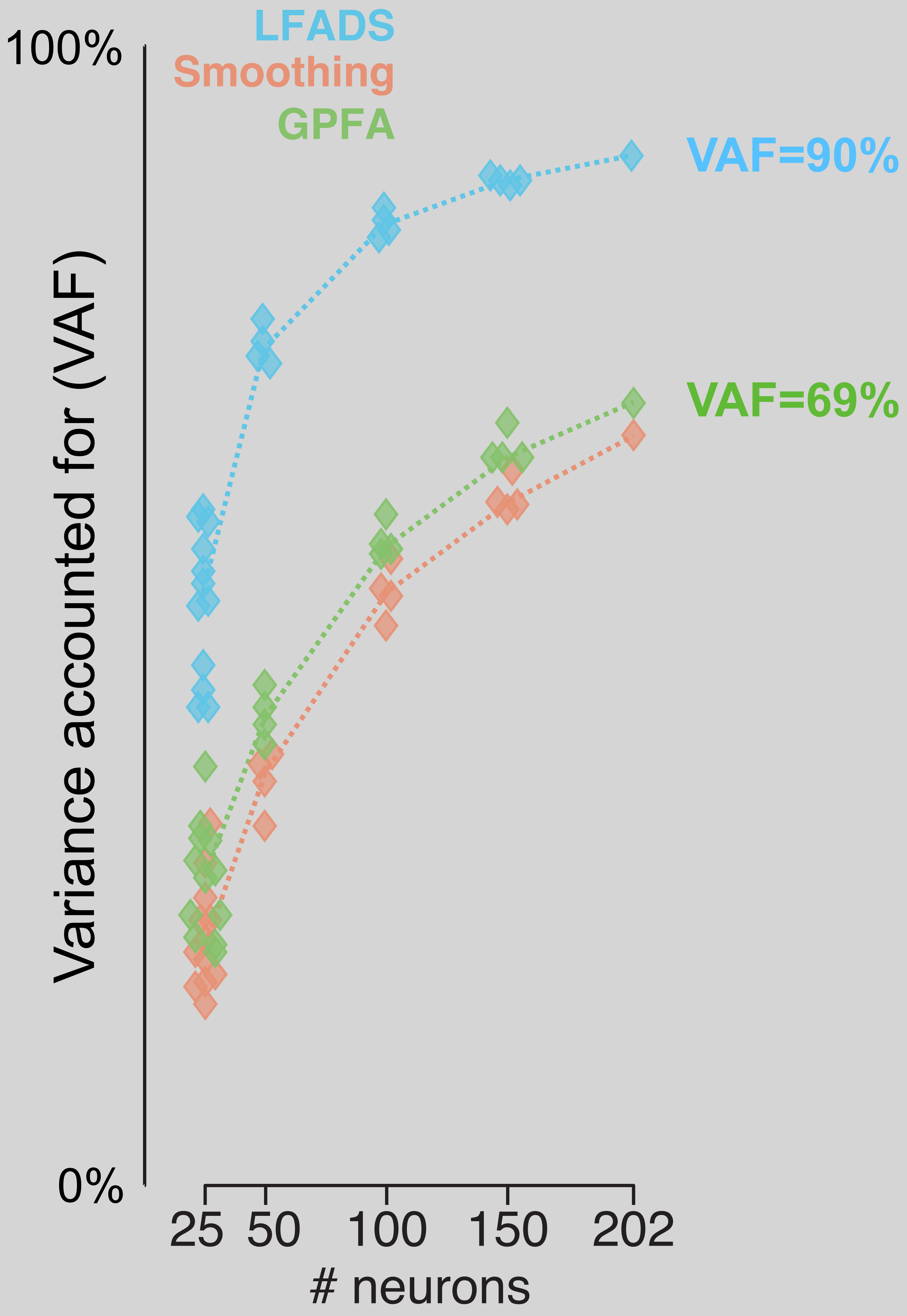


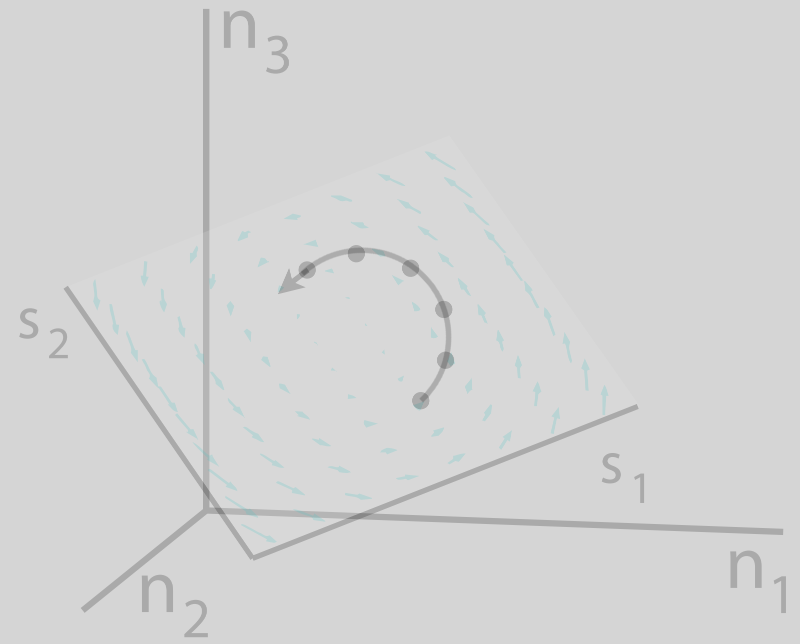
State-space / dynamics view goes *beyond visualization* - informative about behavior on single trials and millisecond timescales



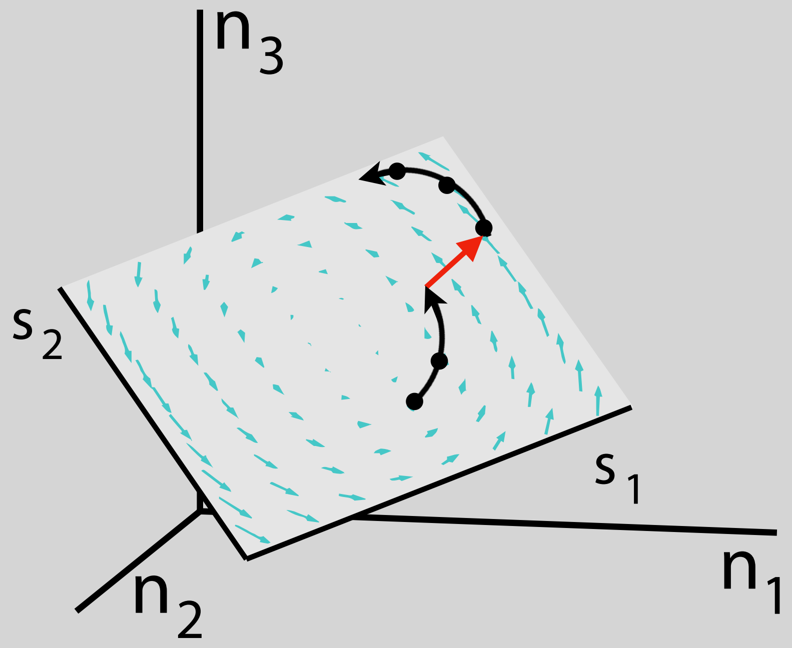
Pandarinath…Sussillo, *Nature Methods* 2018

12

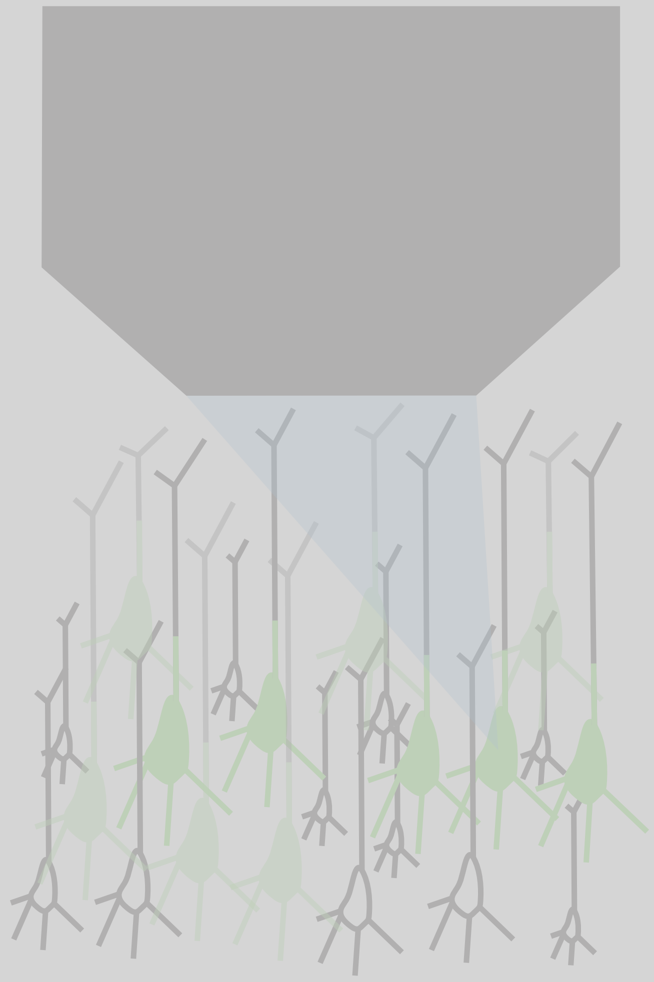
ML methods to uncover single-trial population dynamics



Predictable neural activity: modeling autonomous dynamics with LFADS



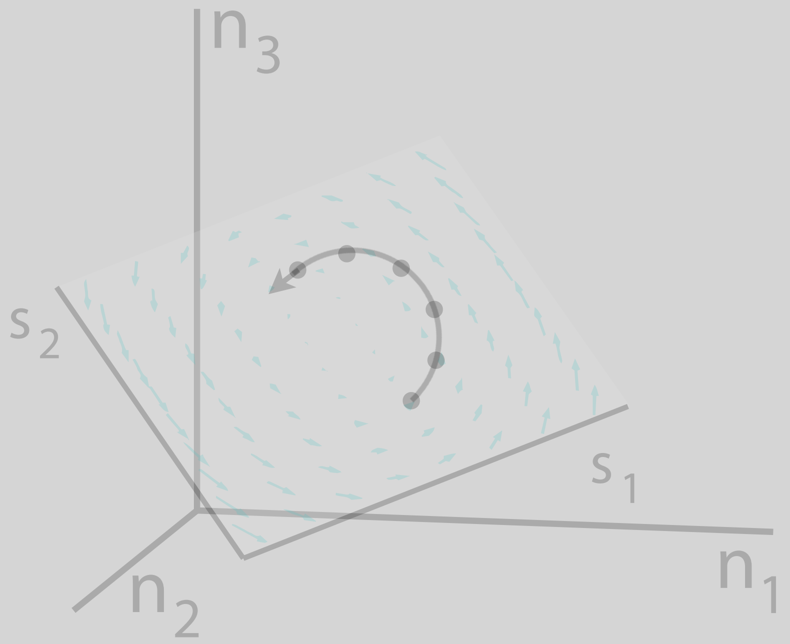
***Unpredictable* activity: non-autonomous dynamics and AutoLFADS**



Applications to 2P Ca imaging: RADICaL

Applications to cognitive data

ML methods to uncover single-trial population dynamics



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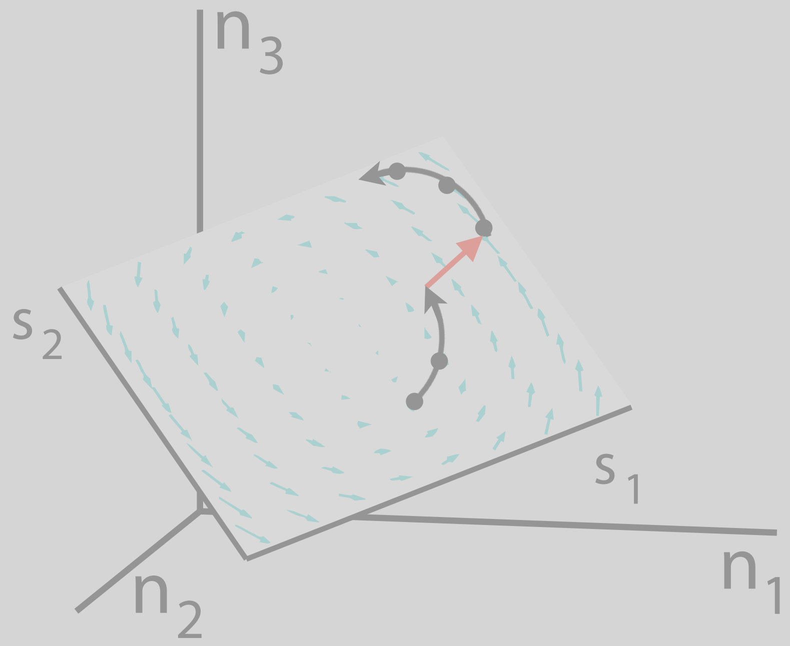
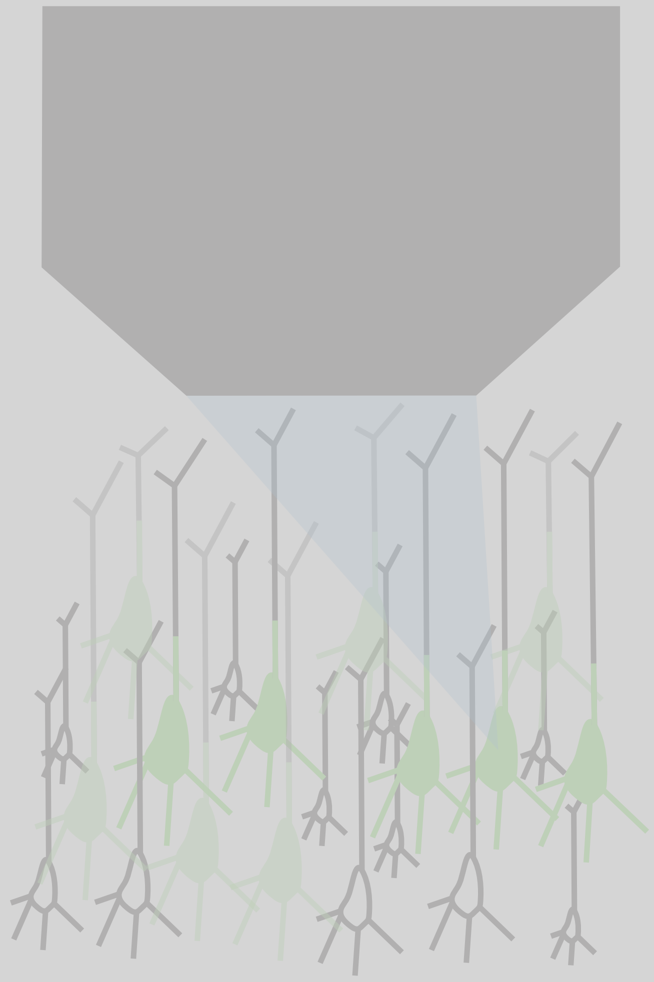


***Unpredictable* activity: non-autonomous dynamics and AutoLFADS**



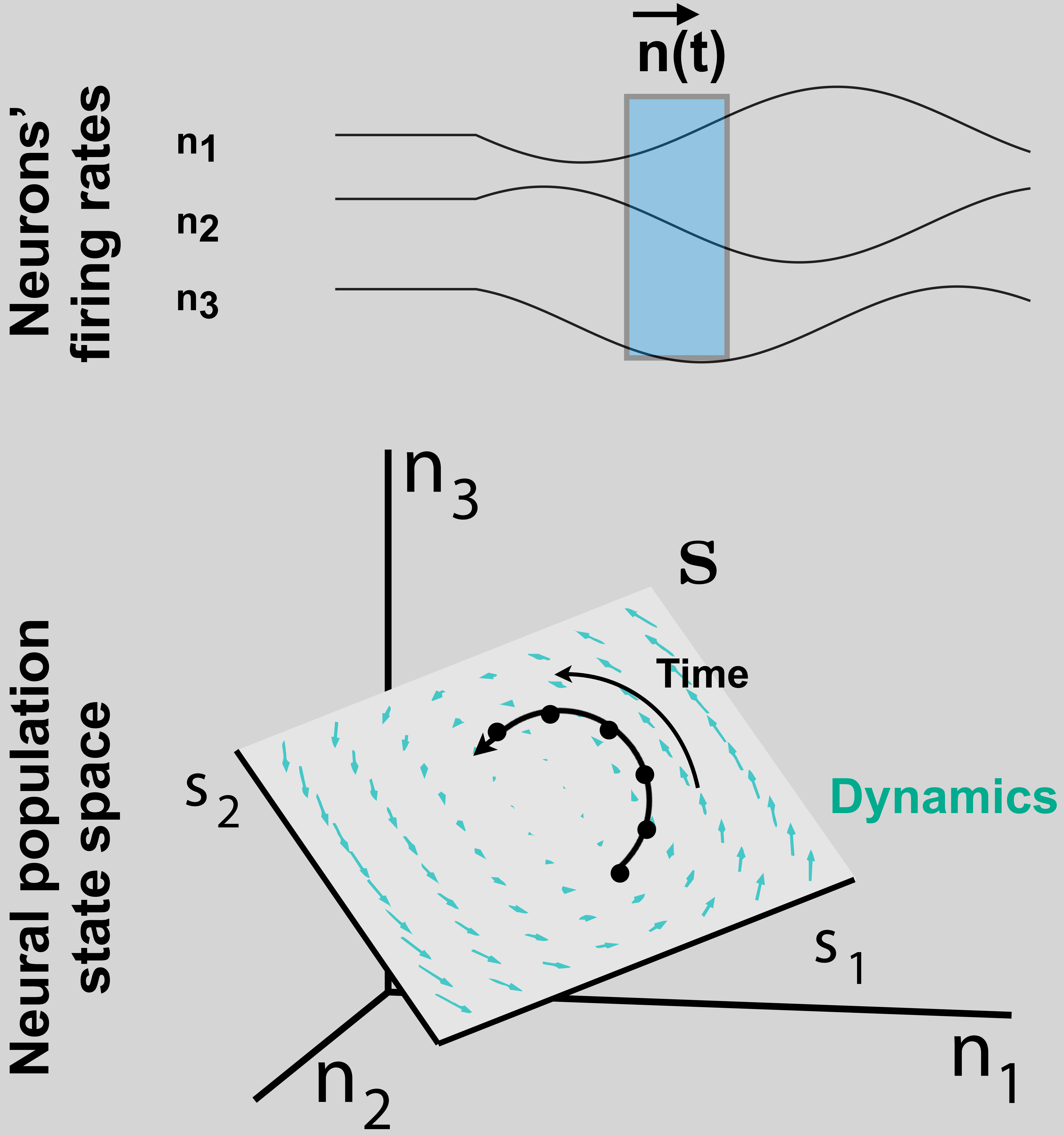
Applications to 2P Ca imaging: RADICaL

Applications to cognitive data

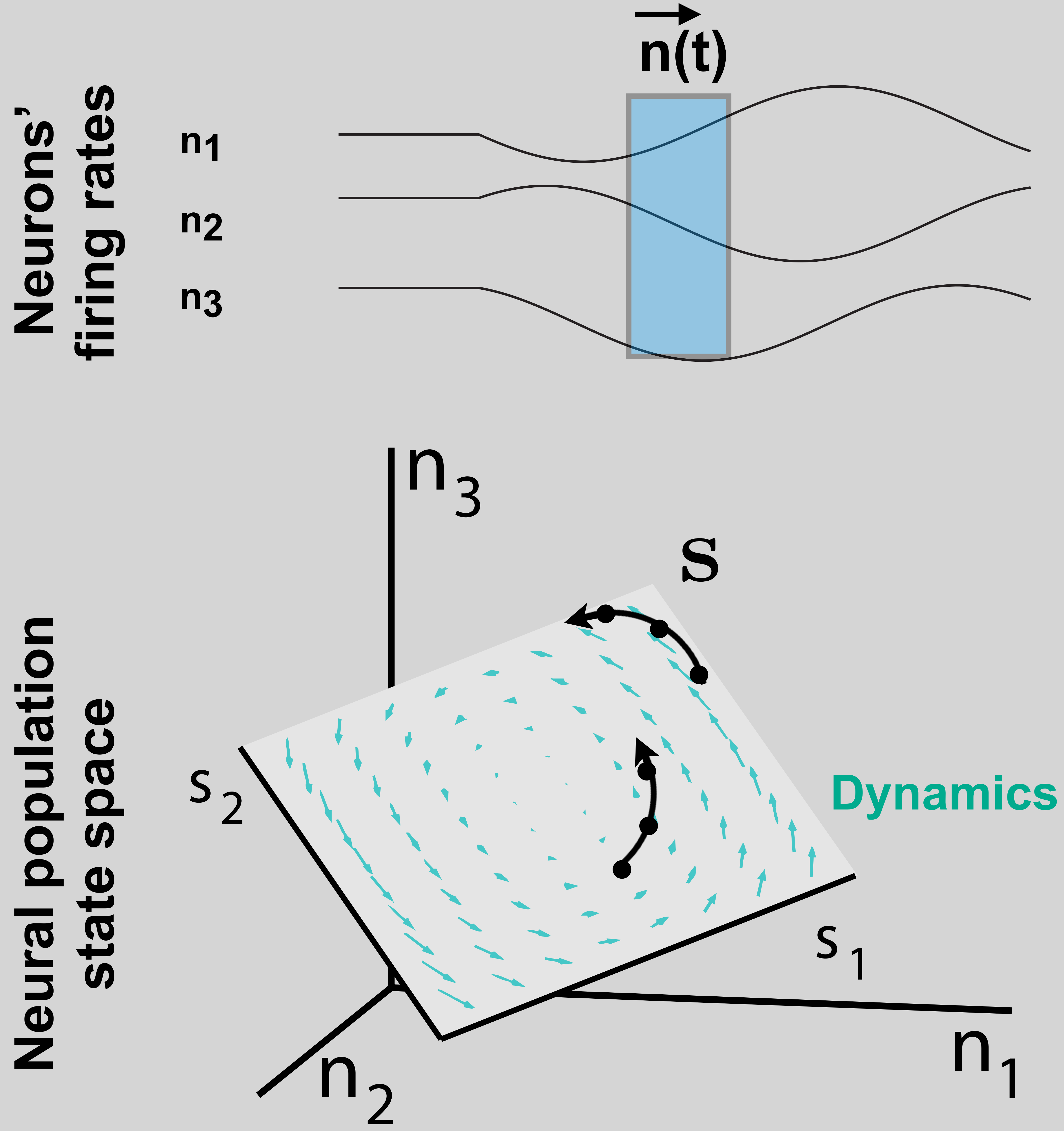
Uncovering neural population dynamics

Predictable activity - modeled by *autonomous* dynamics

$$\frac{ds}{dt} = f(s)$$



Uncovering neural population dynamics



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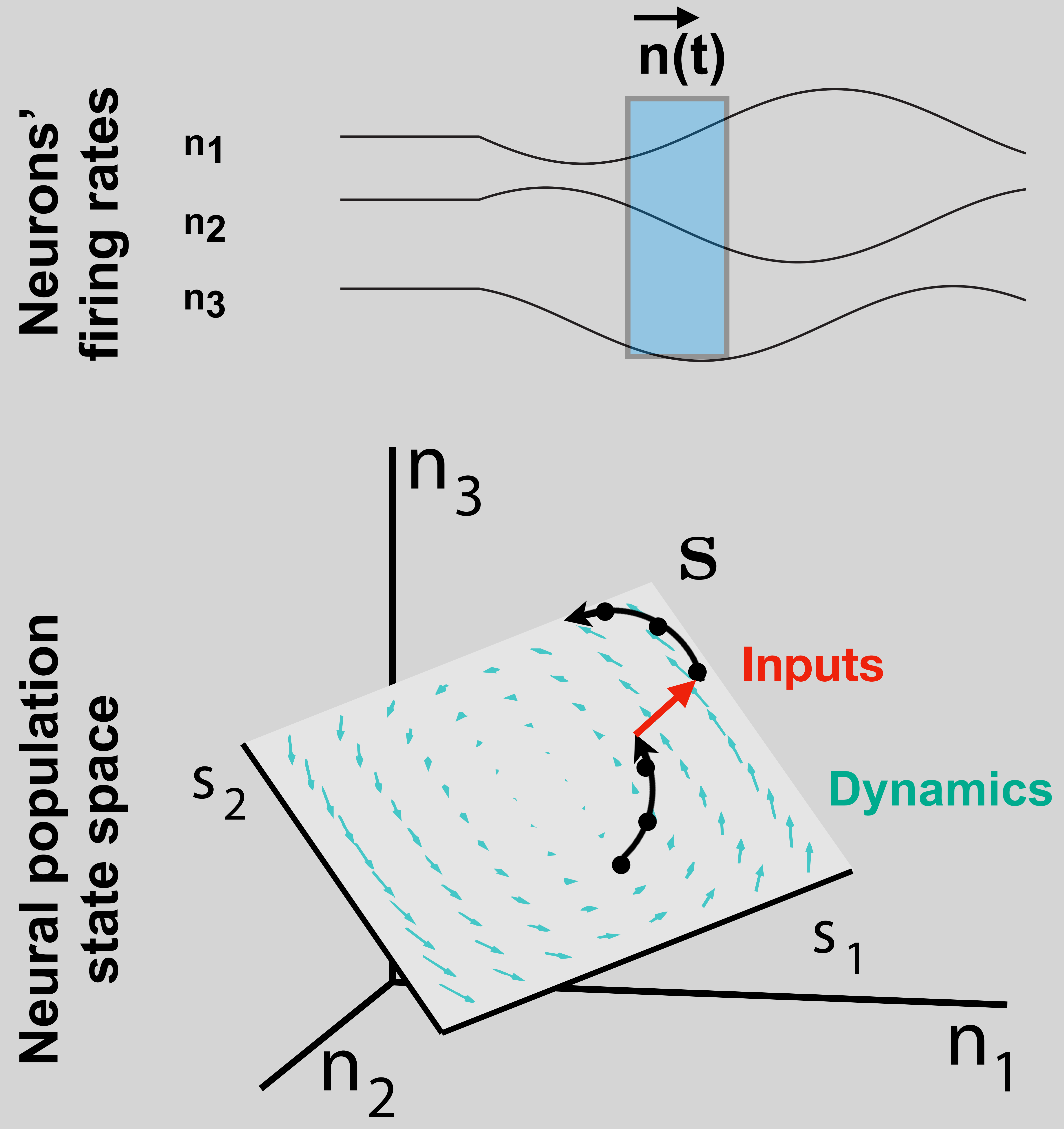

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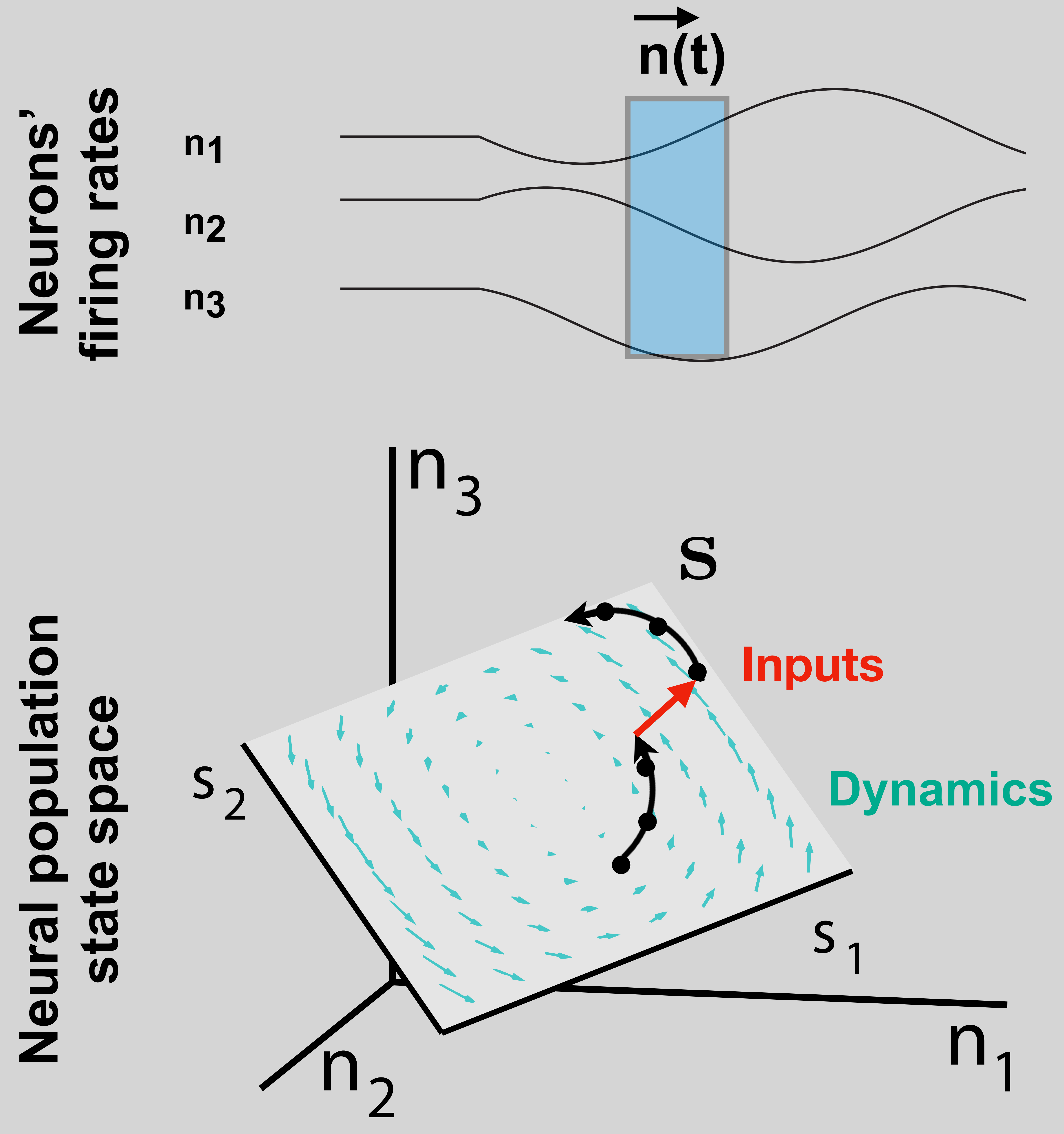
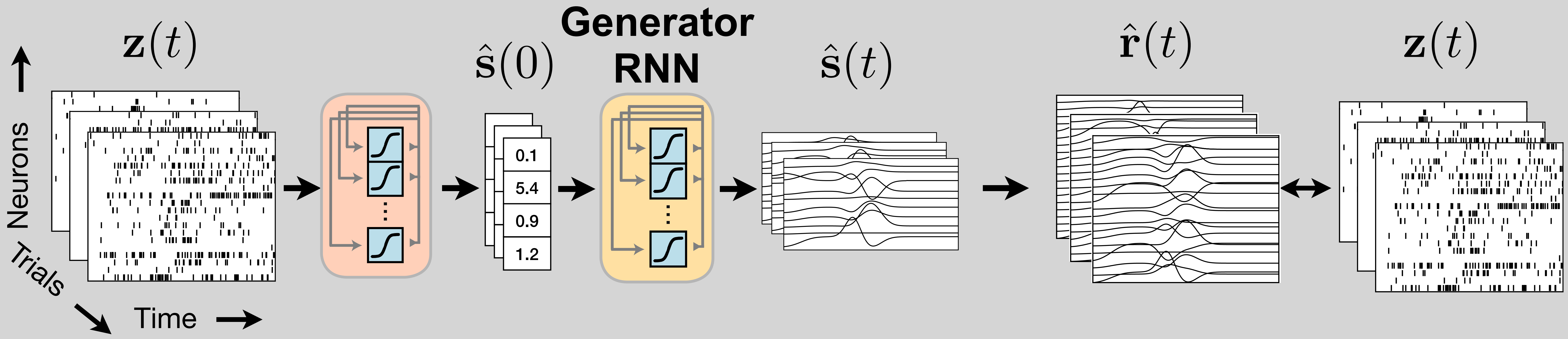


Unpredictable activity
- *non-autonomous*
dynamics

$$\frac{d\mathrm{s}}{dt} = f(\mathrm{s}, \mathrm{u})$$

Unpredictable activity: Non-autonomous dynamics model



Sequential autoencoder (SAE)

Approximates

$$\frac{d\mathrm{s}}{dt} = f(\mathrm{s})$$

Sussillo…Pandarinath, *arxiv* 2016
Pandarinath…Sussillo, *Nature Methods* 2018

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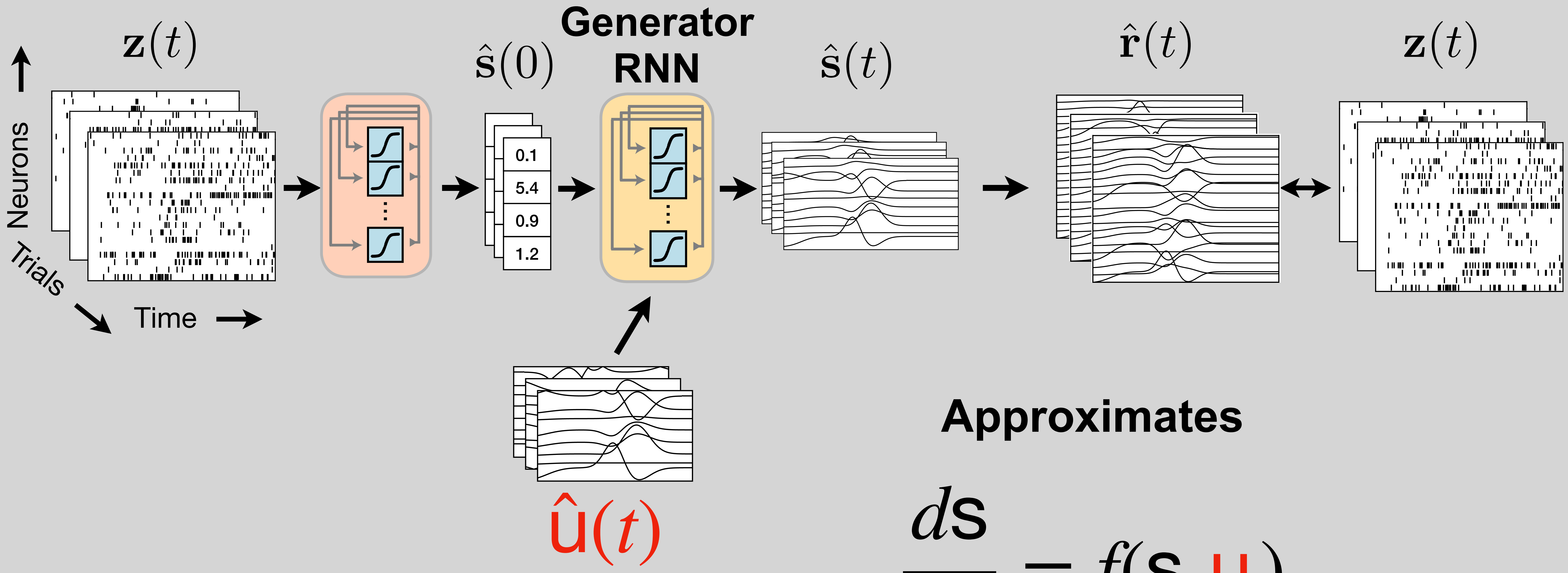

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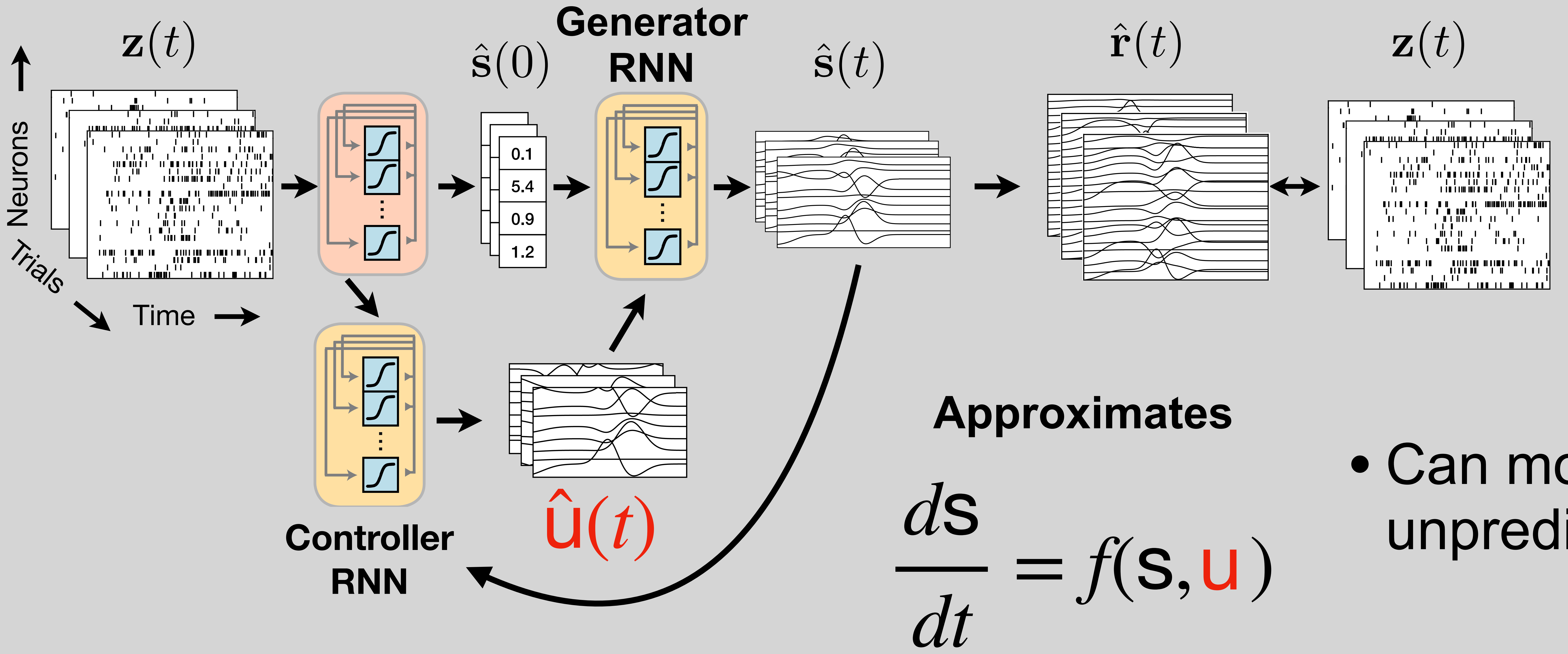

Modified sequential autoencoder (m-SAE)

Approximates

$$\frac{d\mathrm{s}}{dt} = f(\mathrm{s}, \mathrm{u})$$

- Can model activity with unpredictable events

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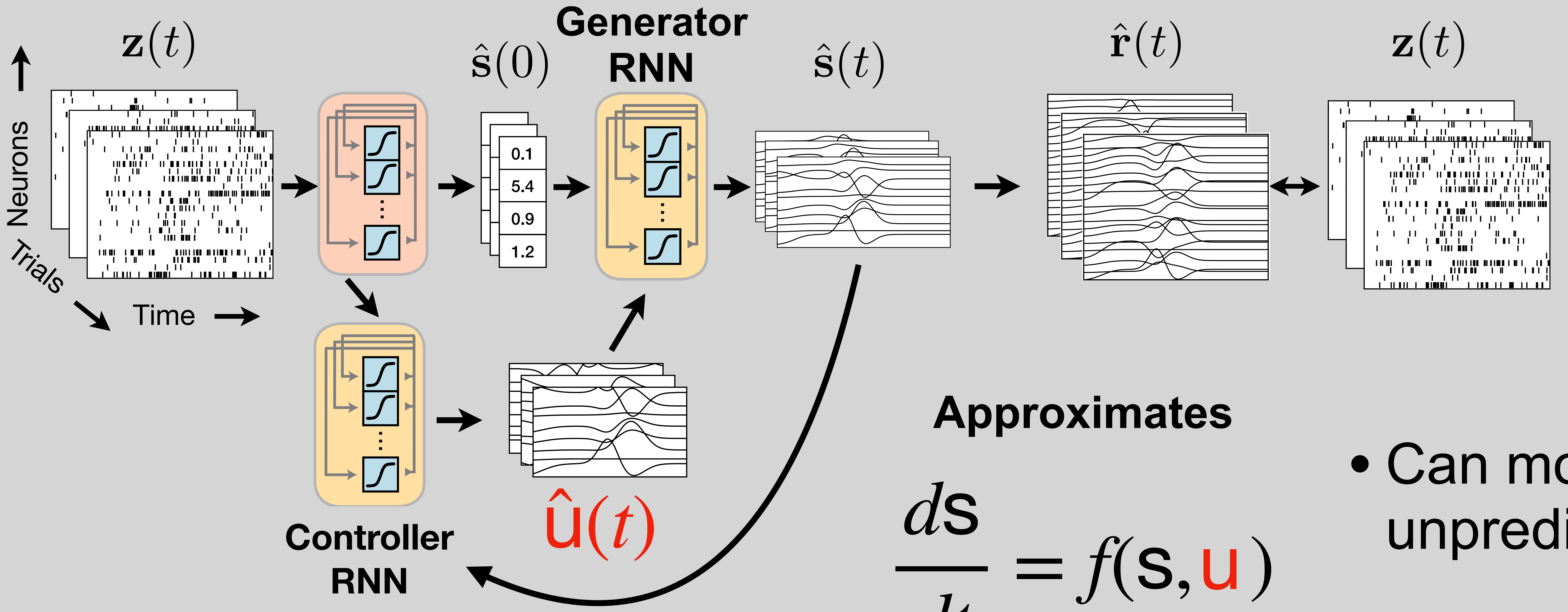
Pandarinath…Sussillo, *Nature Methods* 2018

Unpredictable activity: Non-autonomous dynamics model



Modified sequential autoencoder (m-SAE)

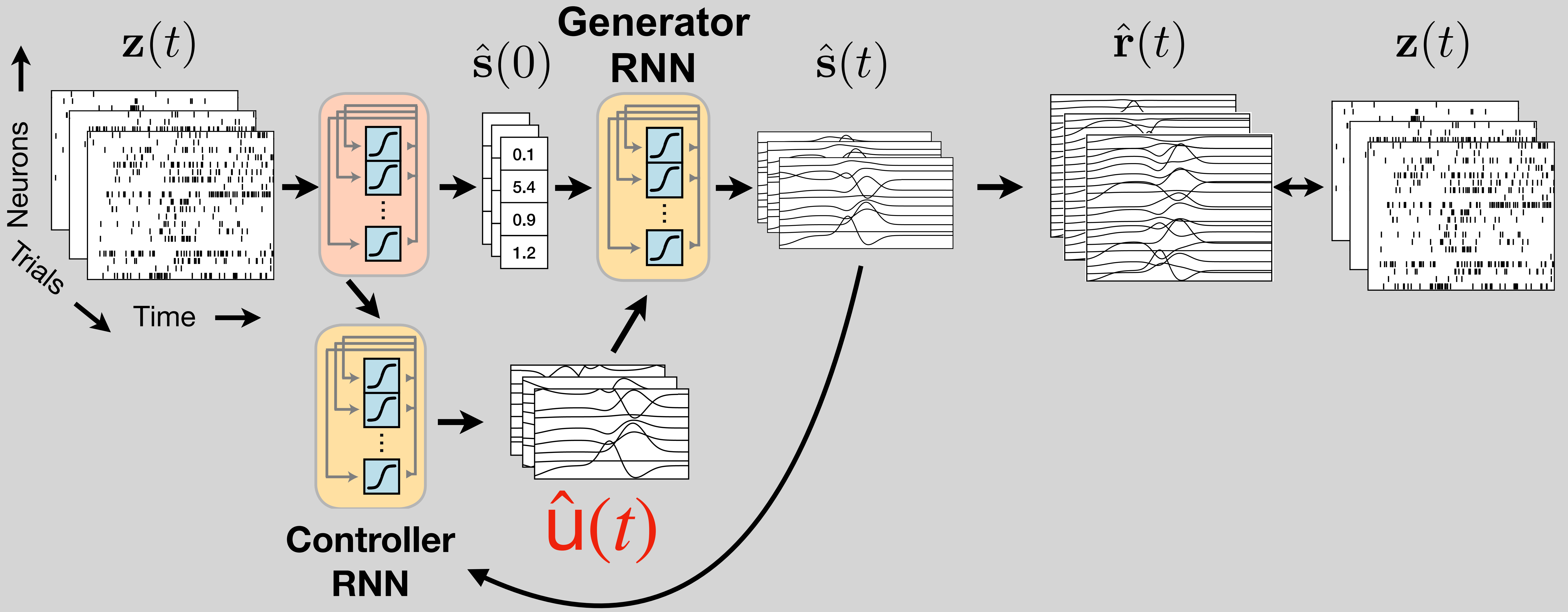
Approximates

$$\frac{d\mathbf{s}}{dt} = f(\mathbf{s}, \mathbf{u})$$

- Can model activity with unpredictable events
- Proof-of-principle: reaches under *unpredictable perturbations*, showed LFADS inferred the <u>presence</u>, <u>timing</u>, and <u>identity</u> of the perturbations

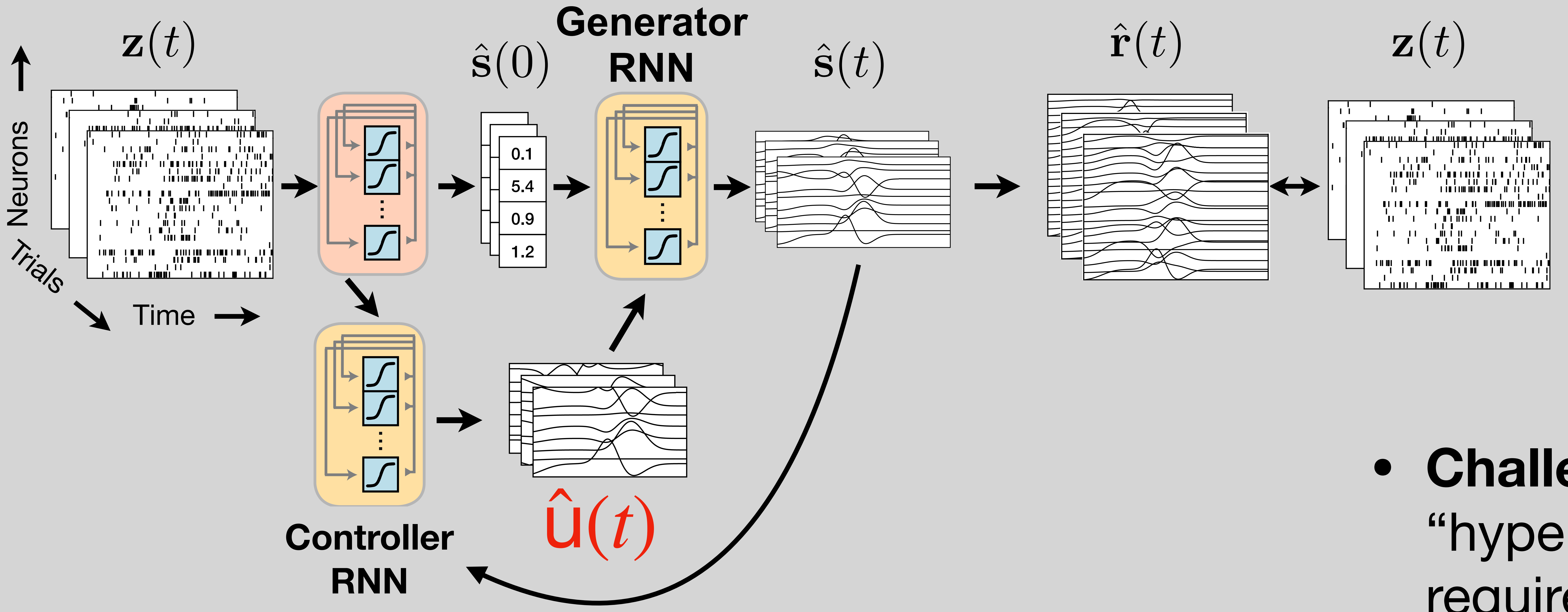
Sussillo…Pandarinath, *arxiv* 2016
Pandarinath…Sussillo, *Nature Methods* 2018

Unpredictable activity: Non-autonomous dynamics model



Modified sequential autoencoder (m-SAE)

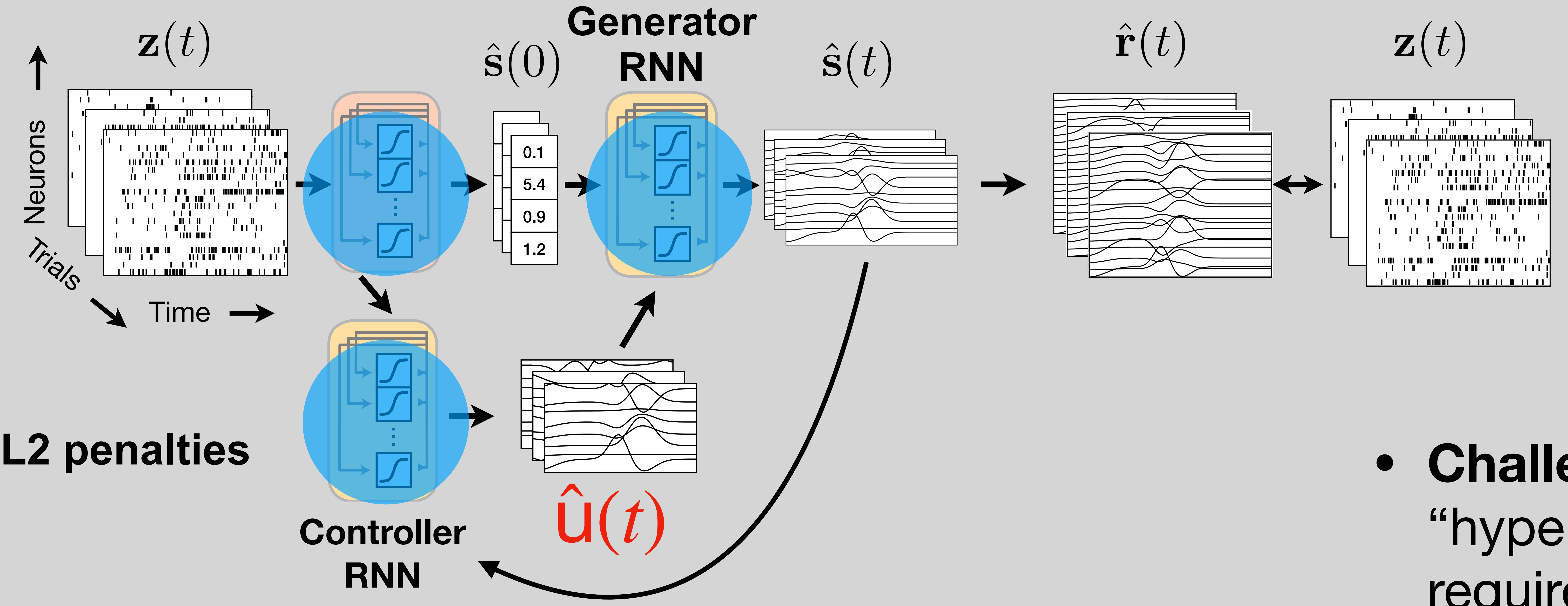
Unpredictable activity: Non-autonomous dynamics model



Modified sequential autoencoder (m-SAE)

- **Challenge**: complex. Many "hyperparameters" (HPs) that require careful tuning

Unpredictable activity: Non-autonomous dynamics model



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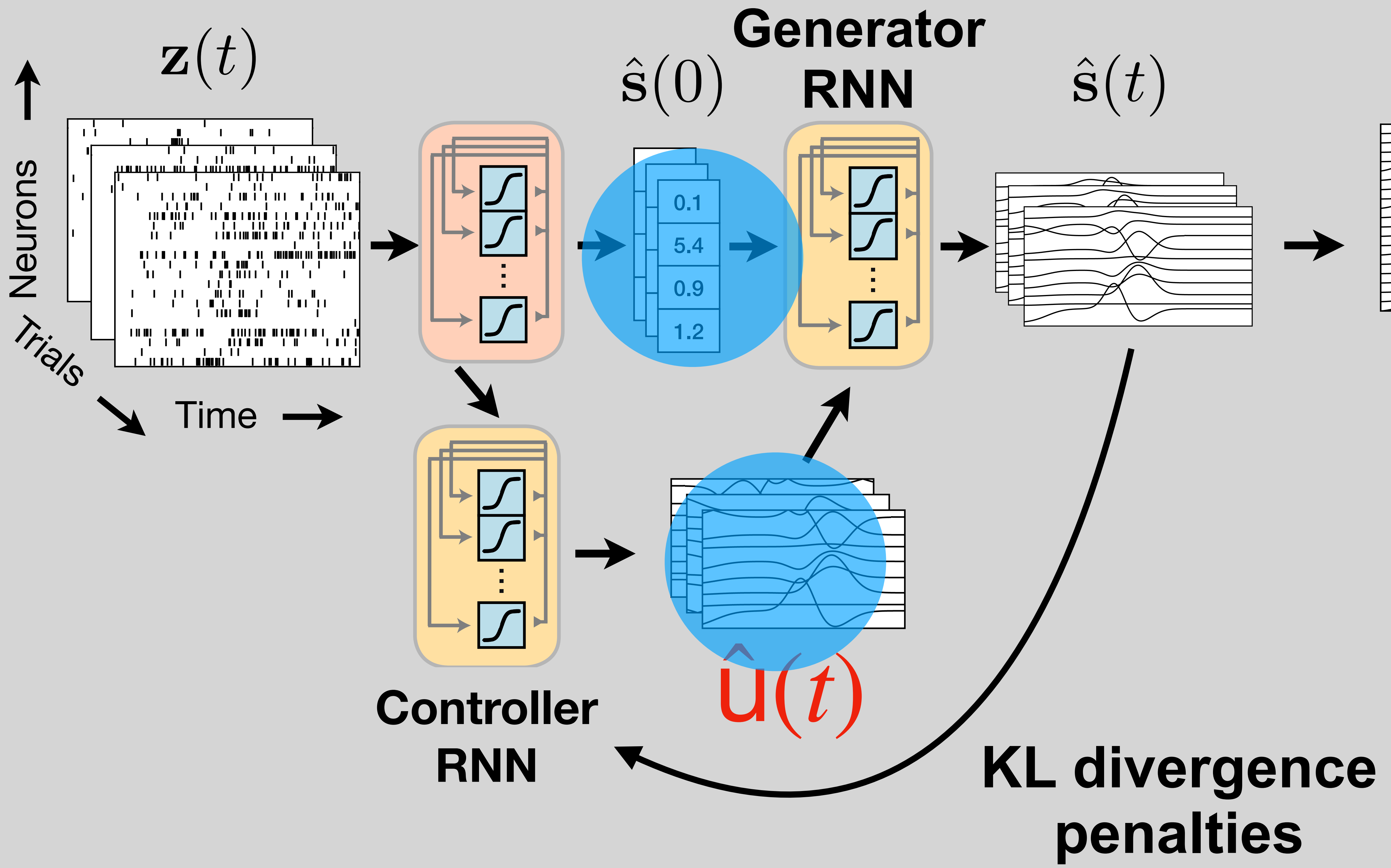

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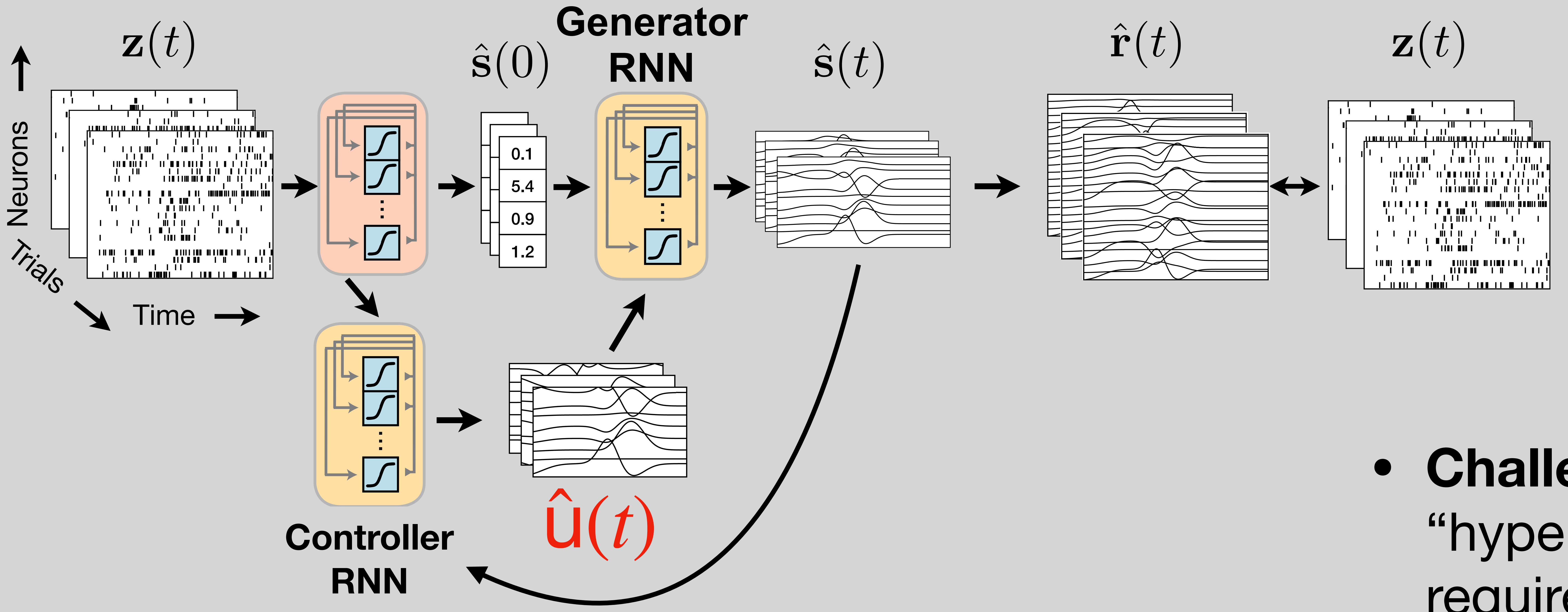
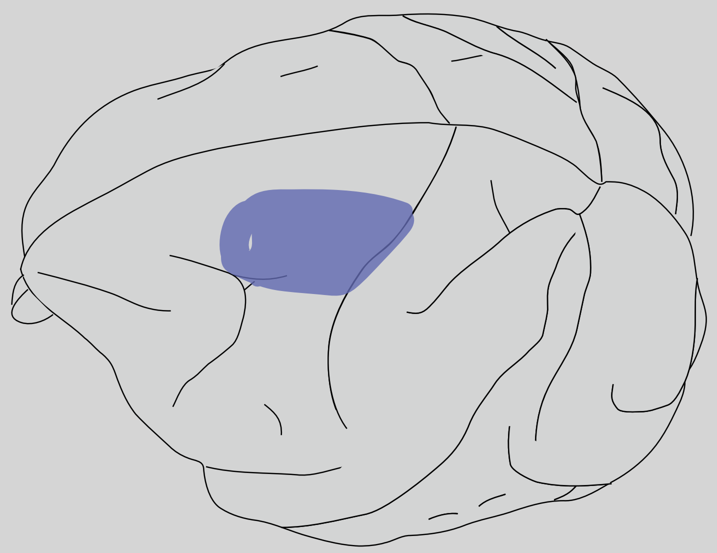


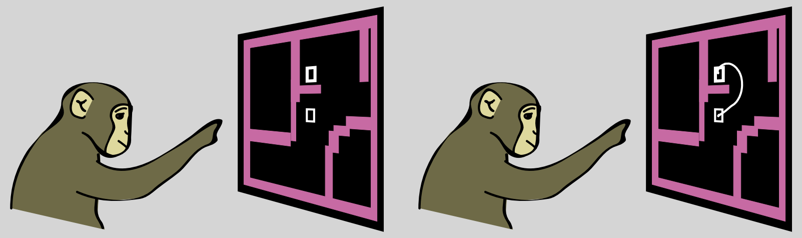
Modified sequential autoencoder (m-SAE)

- **Challenge**: complex. Many "hyperparameters" (HPs) that require careful tuning

- Proper HP settings might depend on dataset size, # of neurons, brain area, behavioral complexity, …

Motor cortex (MC)





Reza Keshtkaran

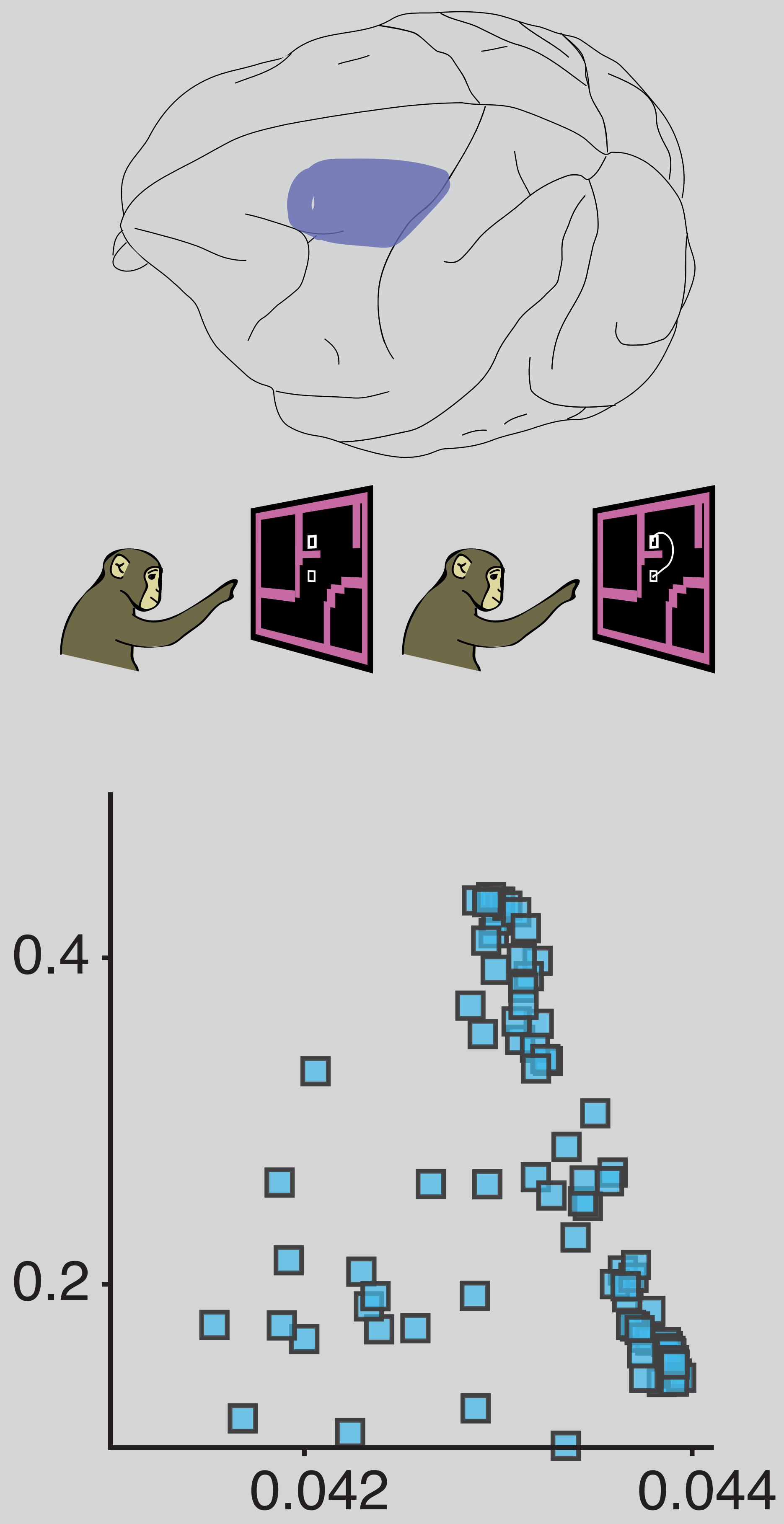
Andrew Sedler

AutoLFADS

Keshtkaran & Pandarinath, *NeurIPS* 2019

Keshtkaran*, Sedler*…Pandarinath, *in revision*; see BioRxiv

Motor cortex (MC)



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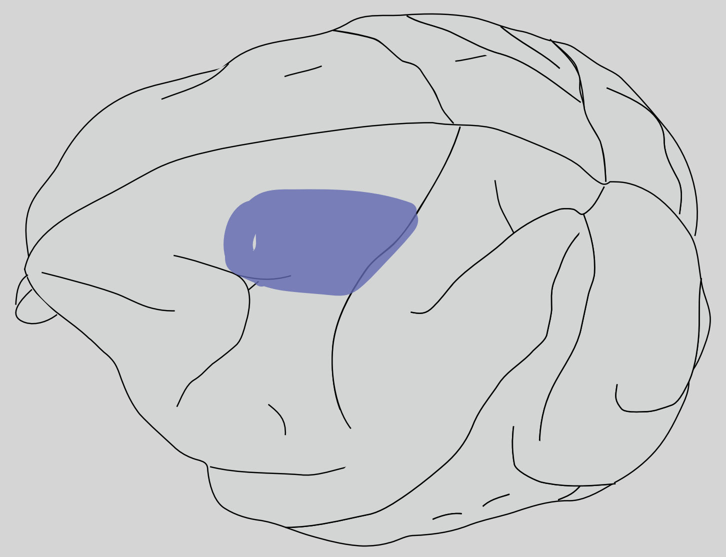

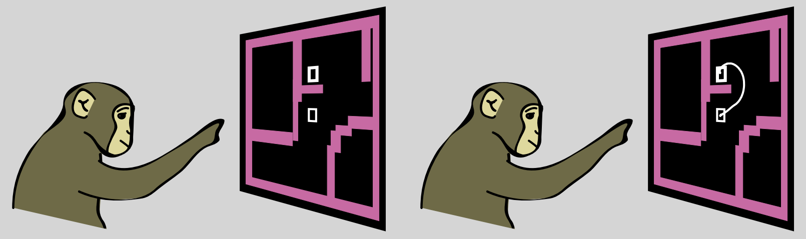

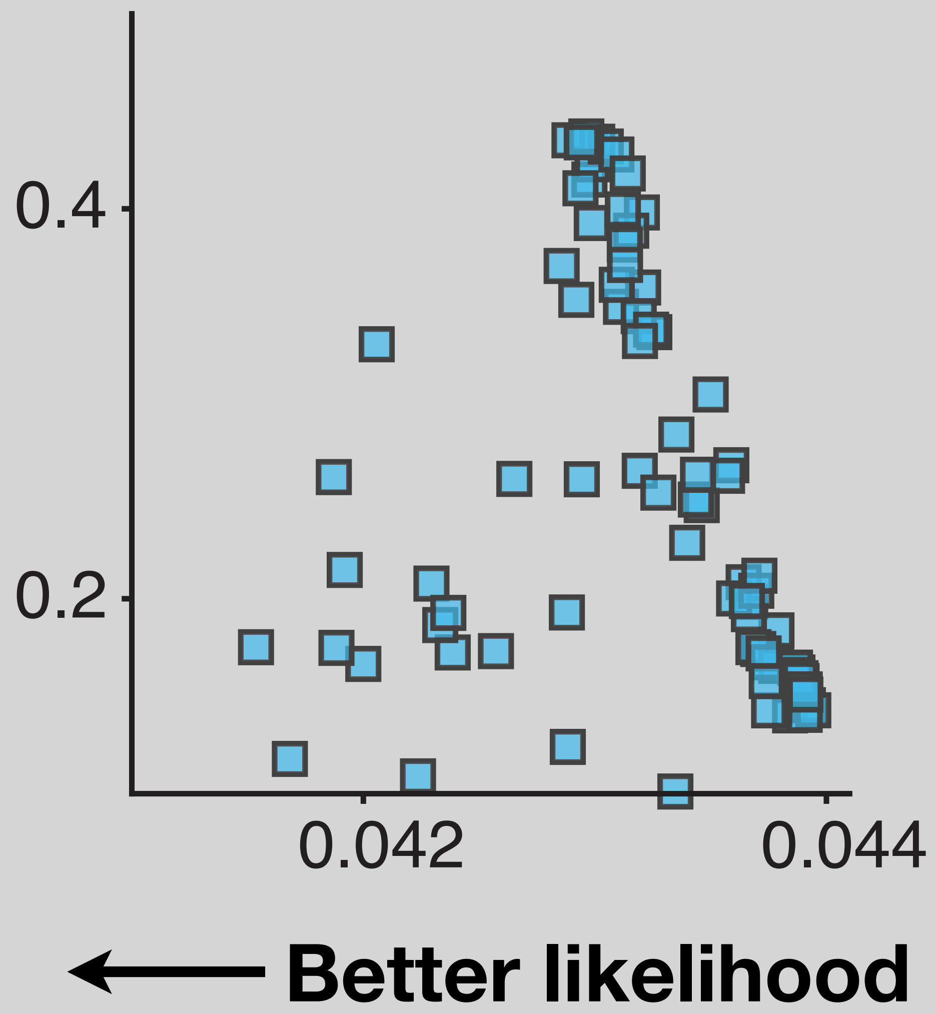

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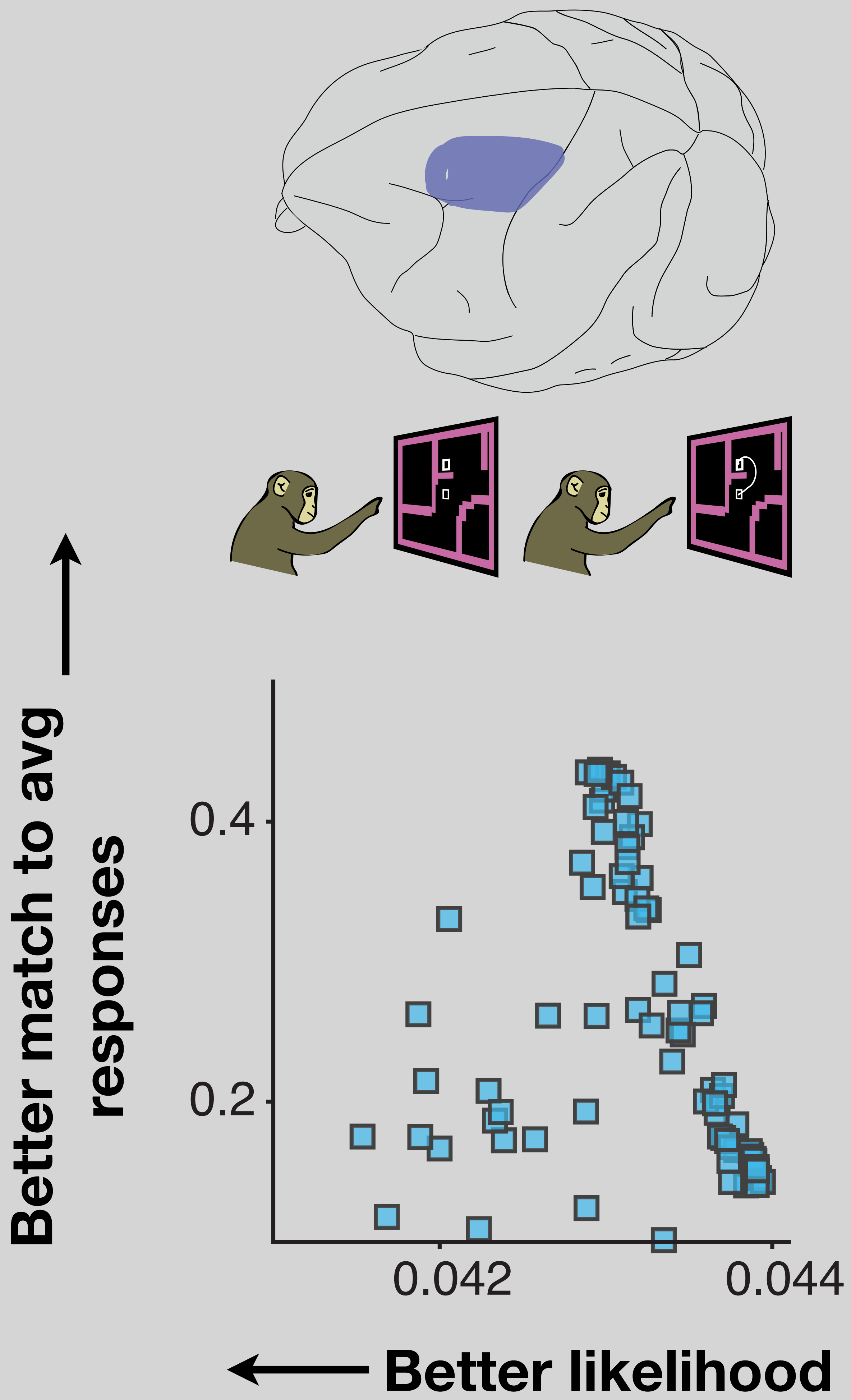

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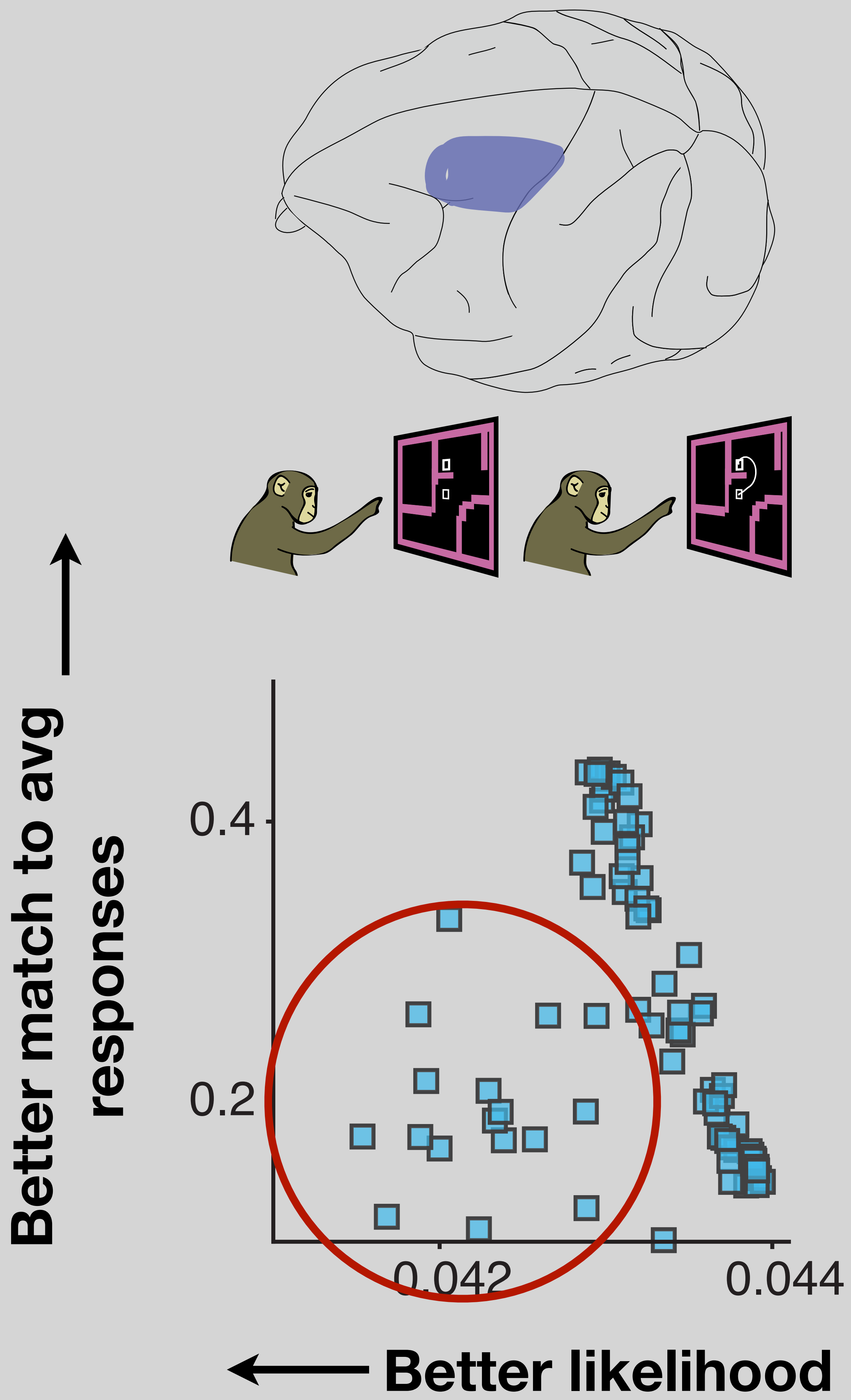
Motor cortex (MC)

1. Models we *thought* were doing better were not always doing better



“Pathological” Overfitting!

AutoLFADS

Keshtkaran & Pandarinath, *NeurIPS* 2019

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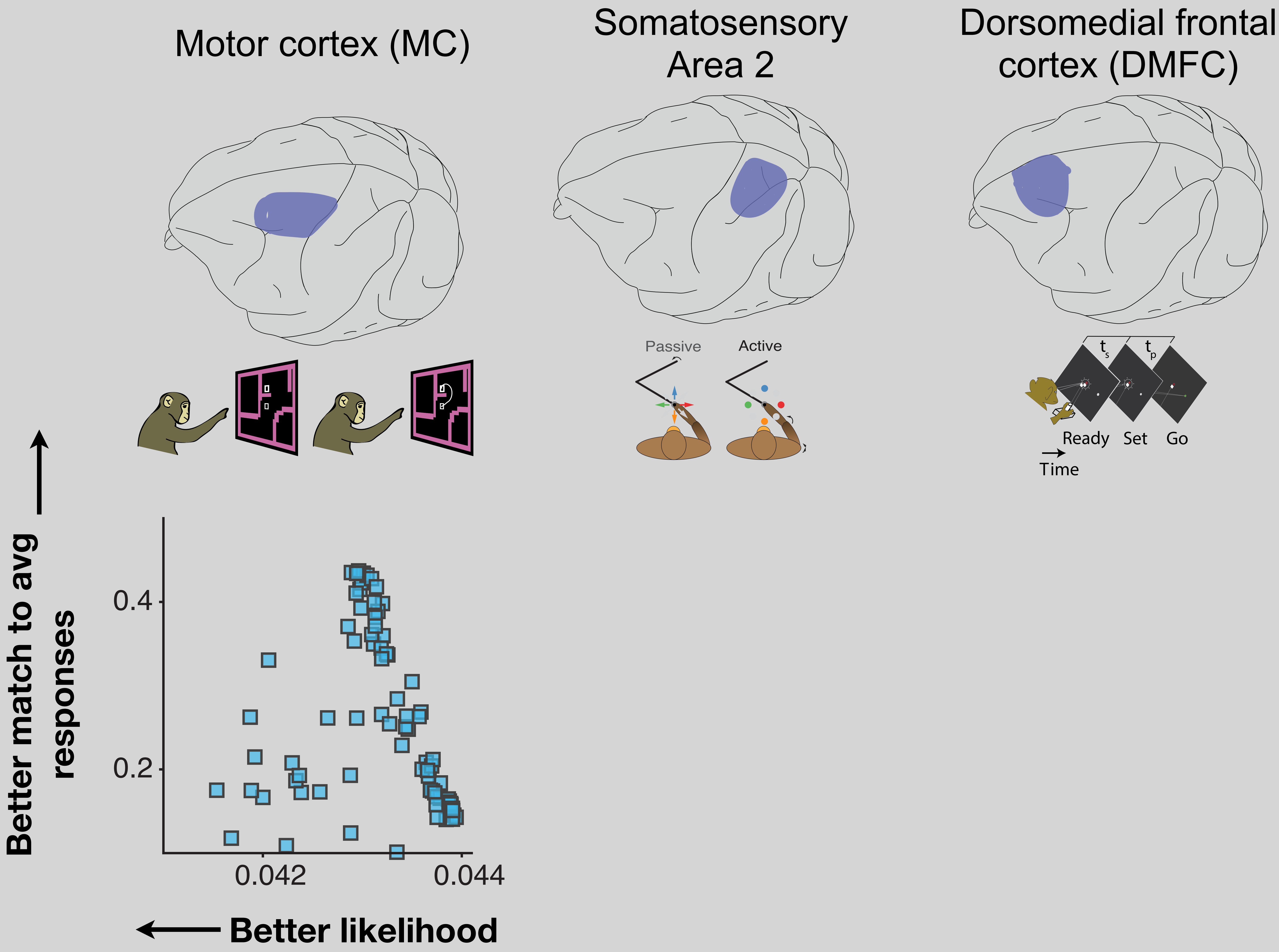

Area 2: Miller lab, Northwestern
DMFC: Jazayeri lab, MIT

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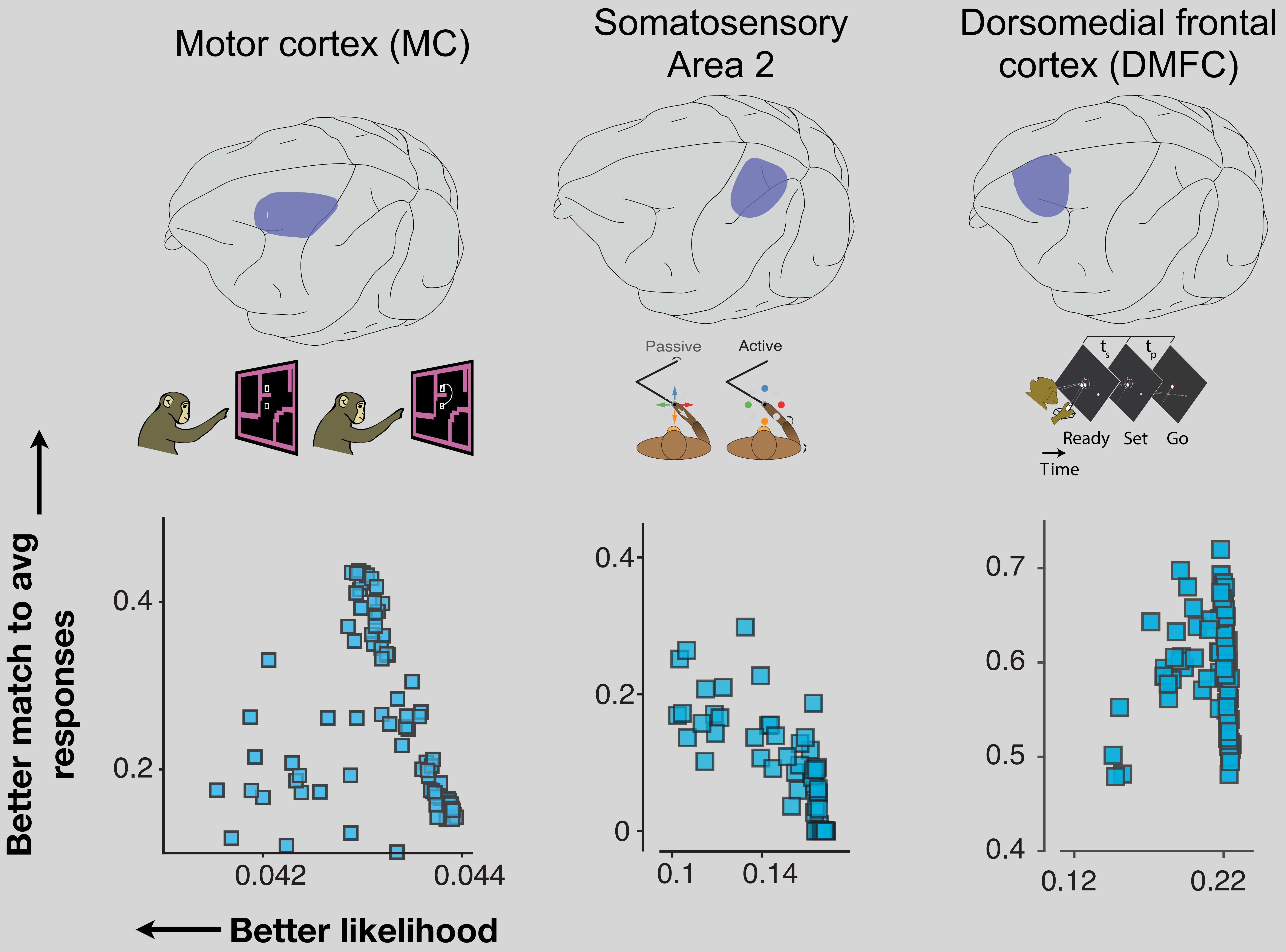

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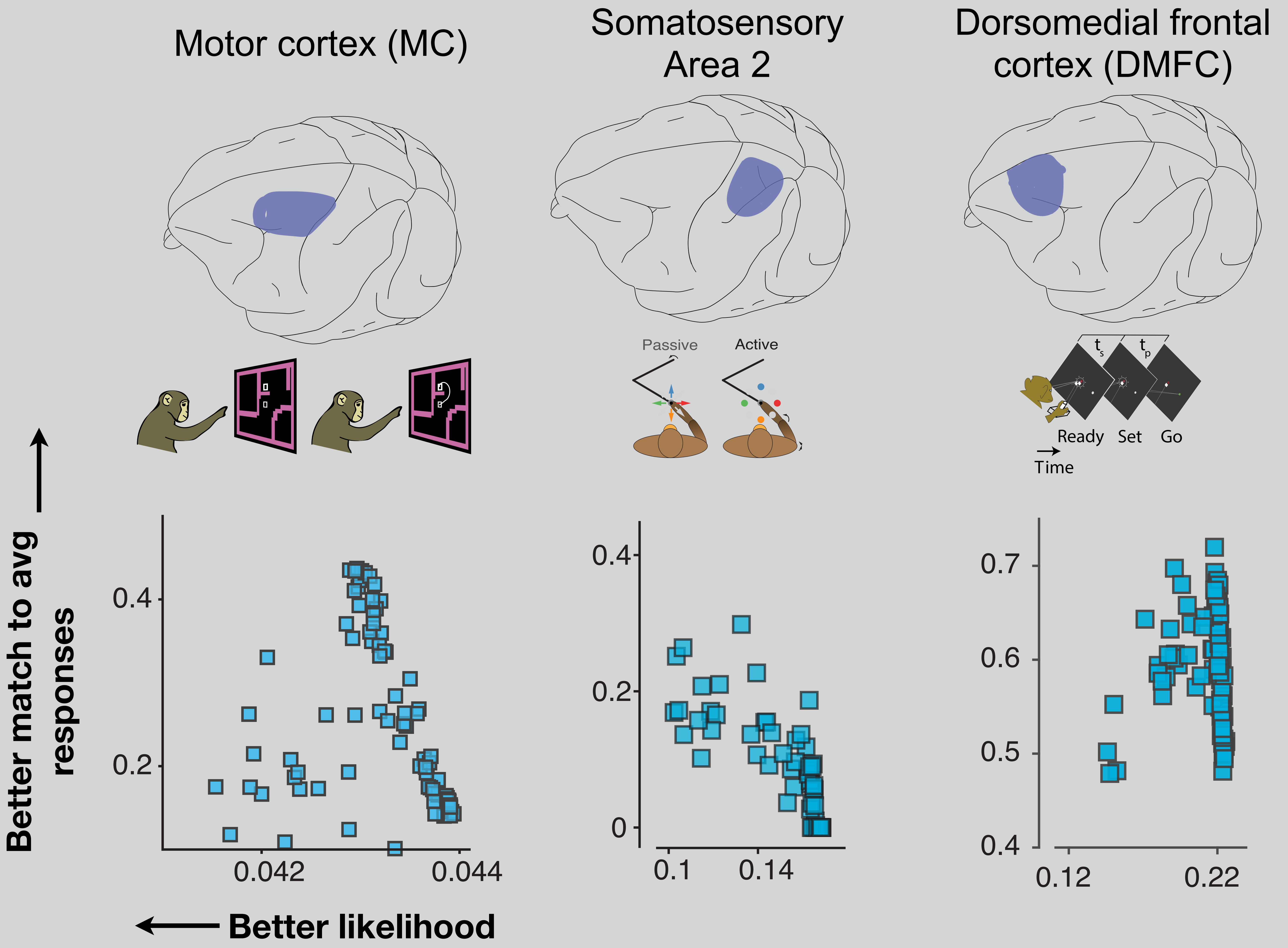
Keshtkaran & Pandarinath, *NeurIPS* 2019
Keshtkaran*, Sedler*…Pandarinath, *in revision*; see BioRxiv

1. Models we *thought* were doing better were not always doing better

2. Wide range of performance for different HP settings



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Keshtkaran*, Sedler*…Pandarinath, *in revision*; see BioRxiv

AutoLFADS - two key innovations

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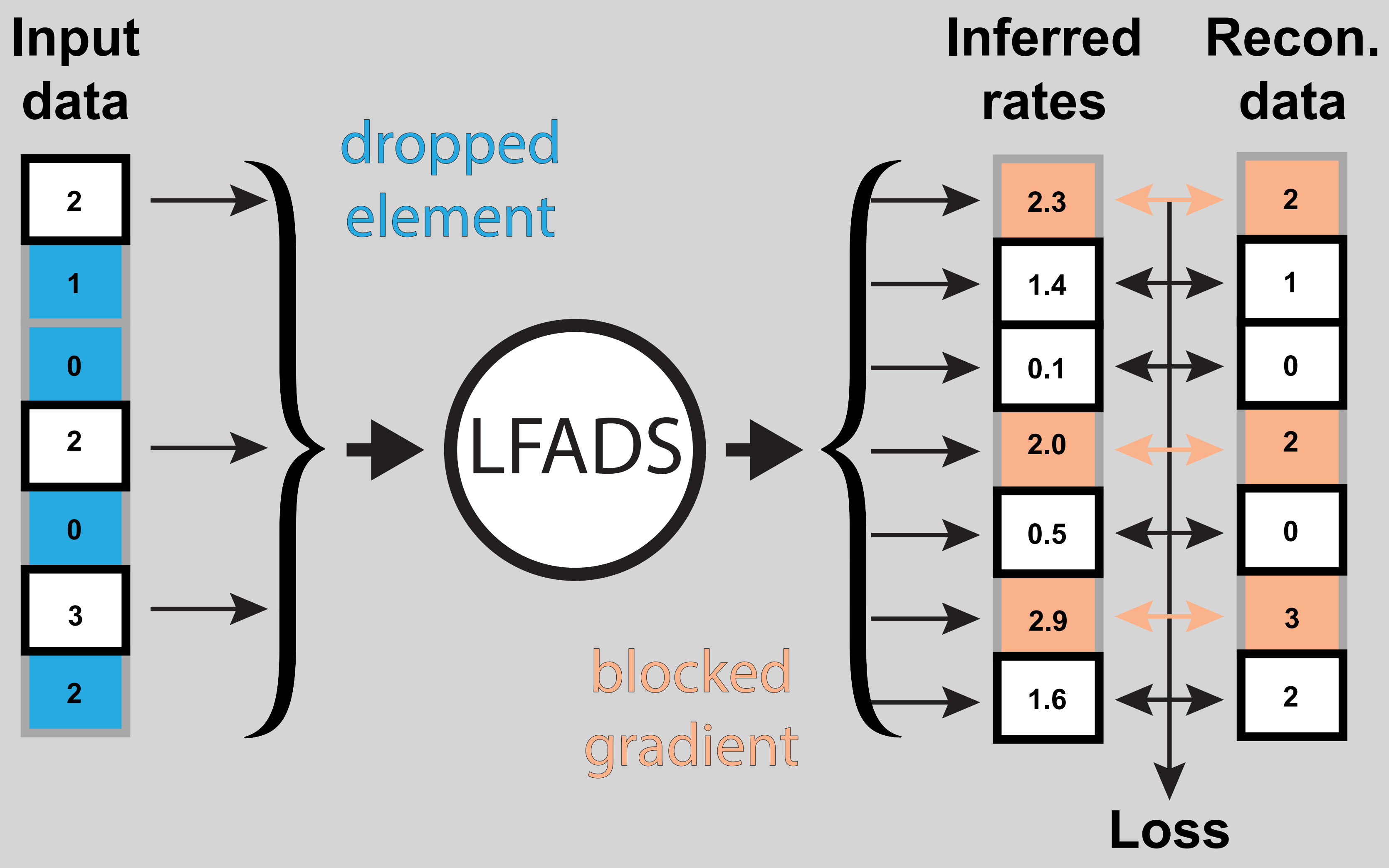
Keshtkaran & Pandarinath, *NeurIPS* 2019
Keshtkaran*, Sedler*…Pandarinath, *in revision*; see BioRxiv

AutoLFADS - two key innovations

Coordinated dropout to solve "pathological" overfitting: by forcing network to only model structure shared across neurons



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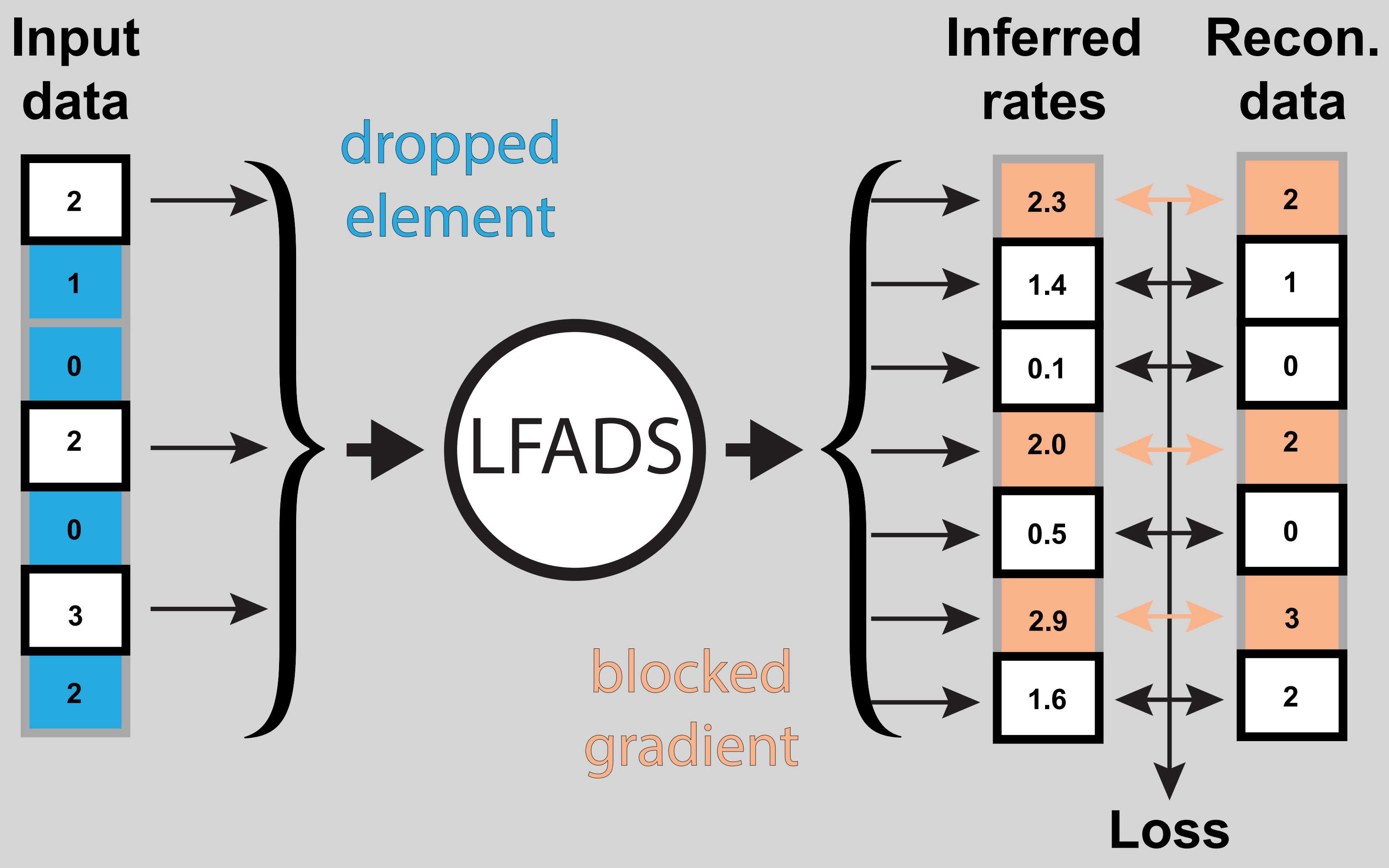
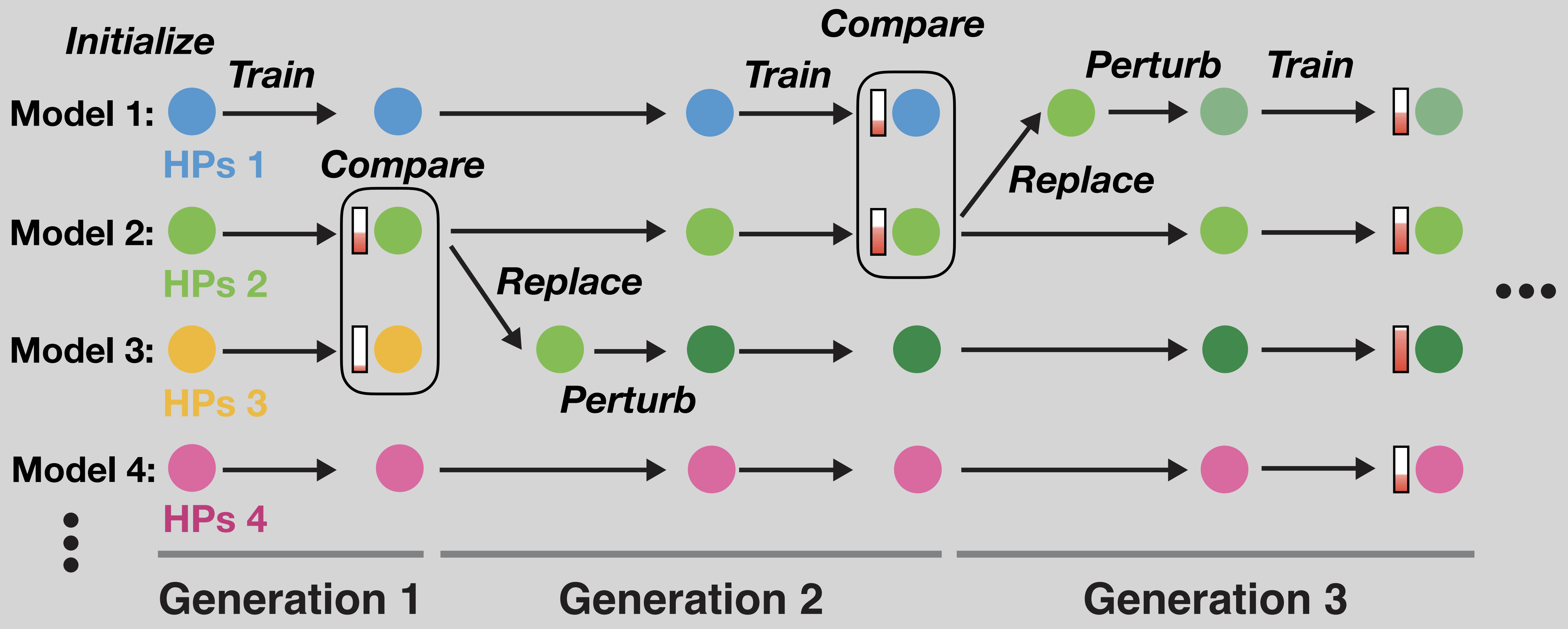


Population-based training (PBT) to find good HPs: train models with different HPs in parallel, use evolutionary algorithms to find good solutions



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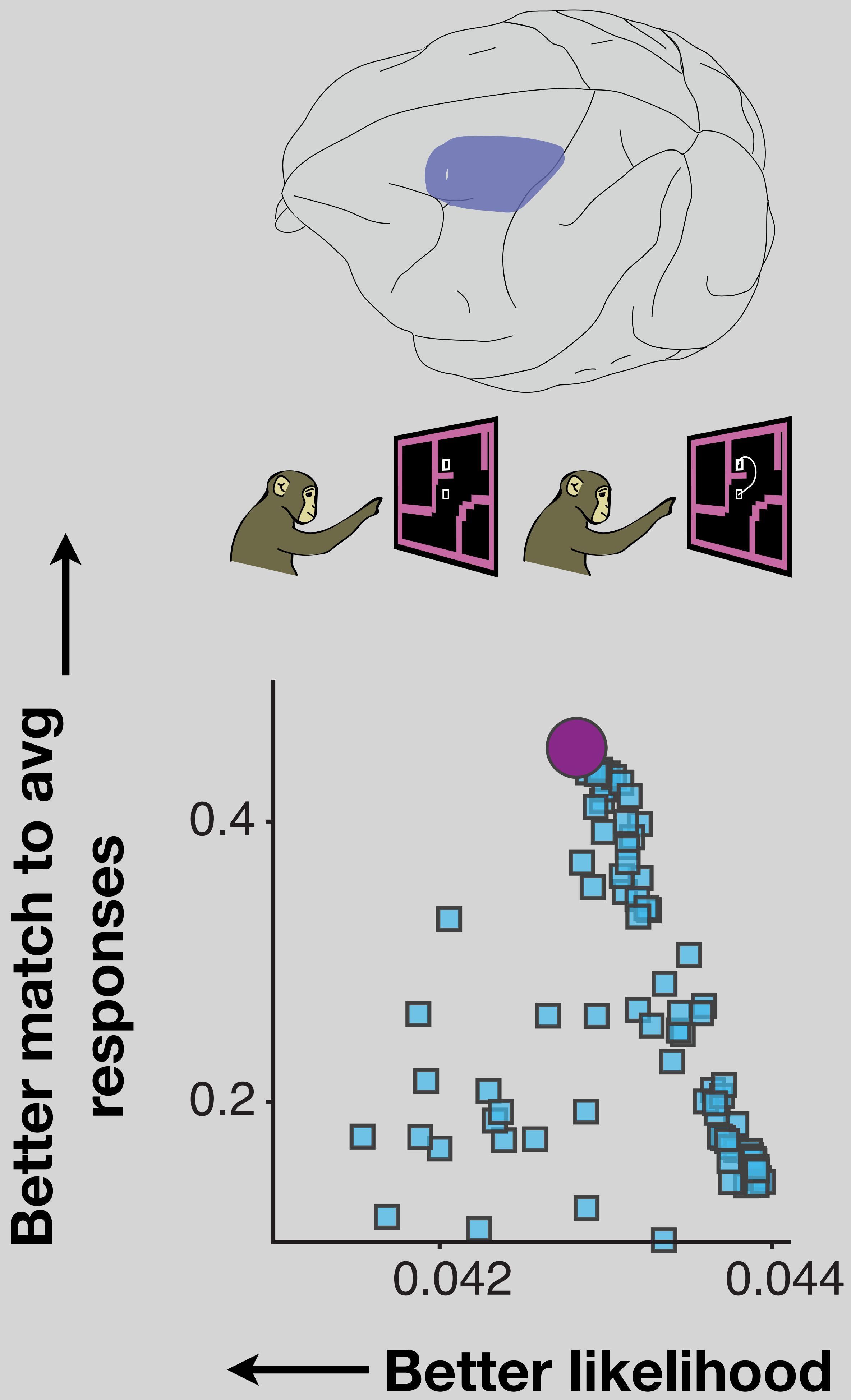
Motor cortex (MC)



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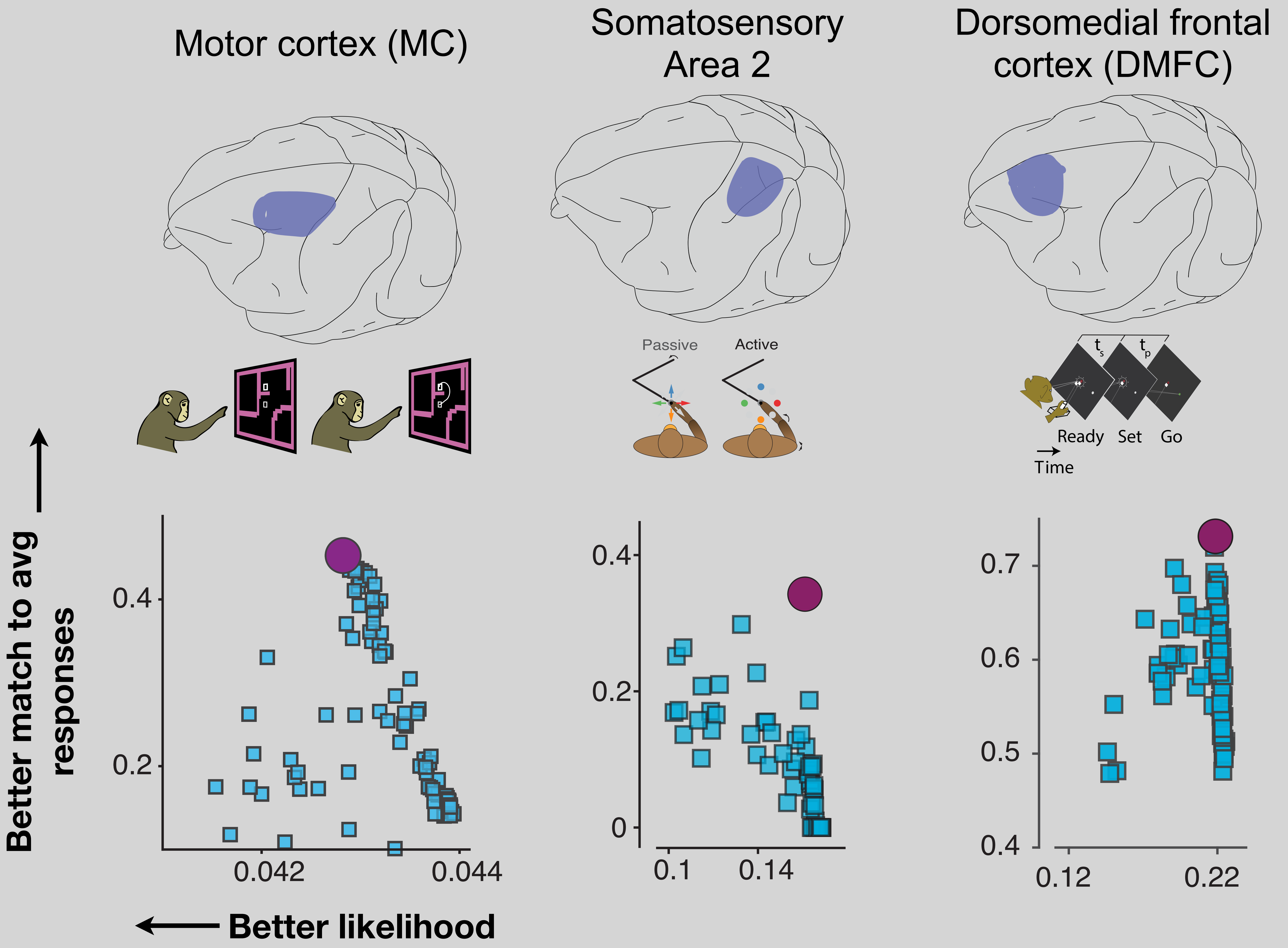

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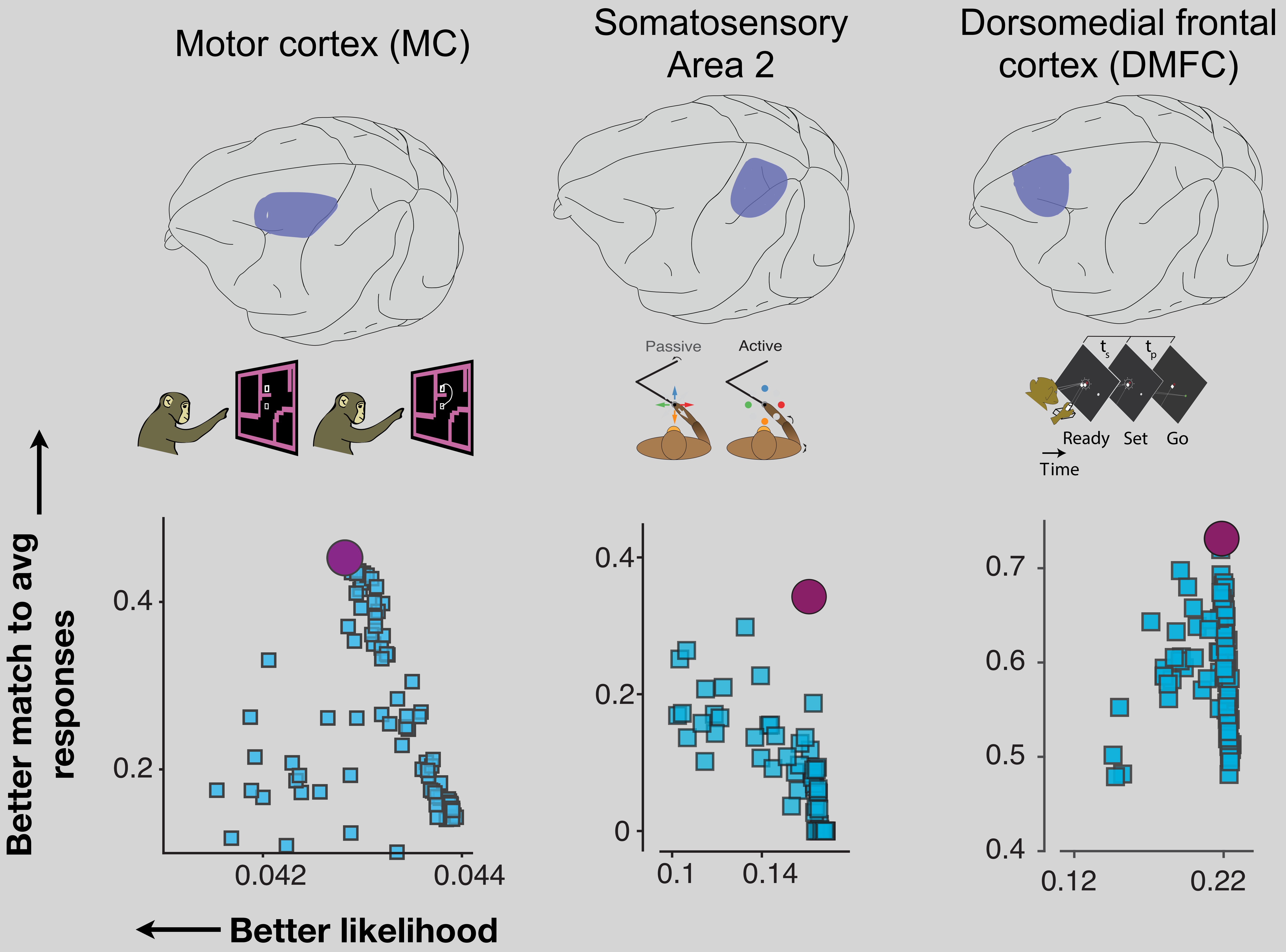
Keshtkaran*, Sedler*…Pandarinath, *in revision*; see BioRxiv

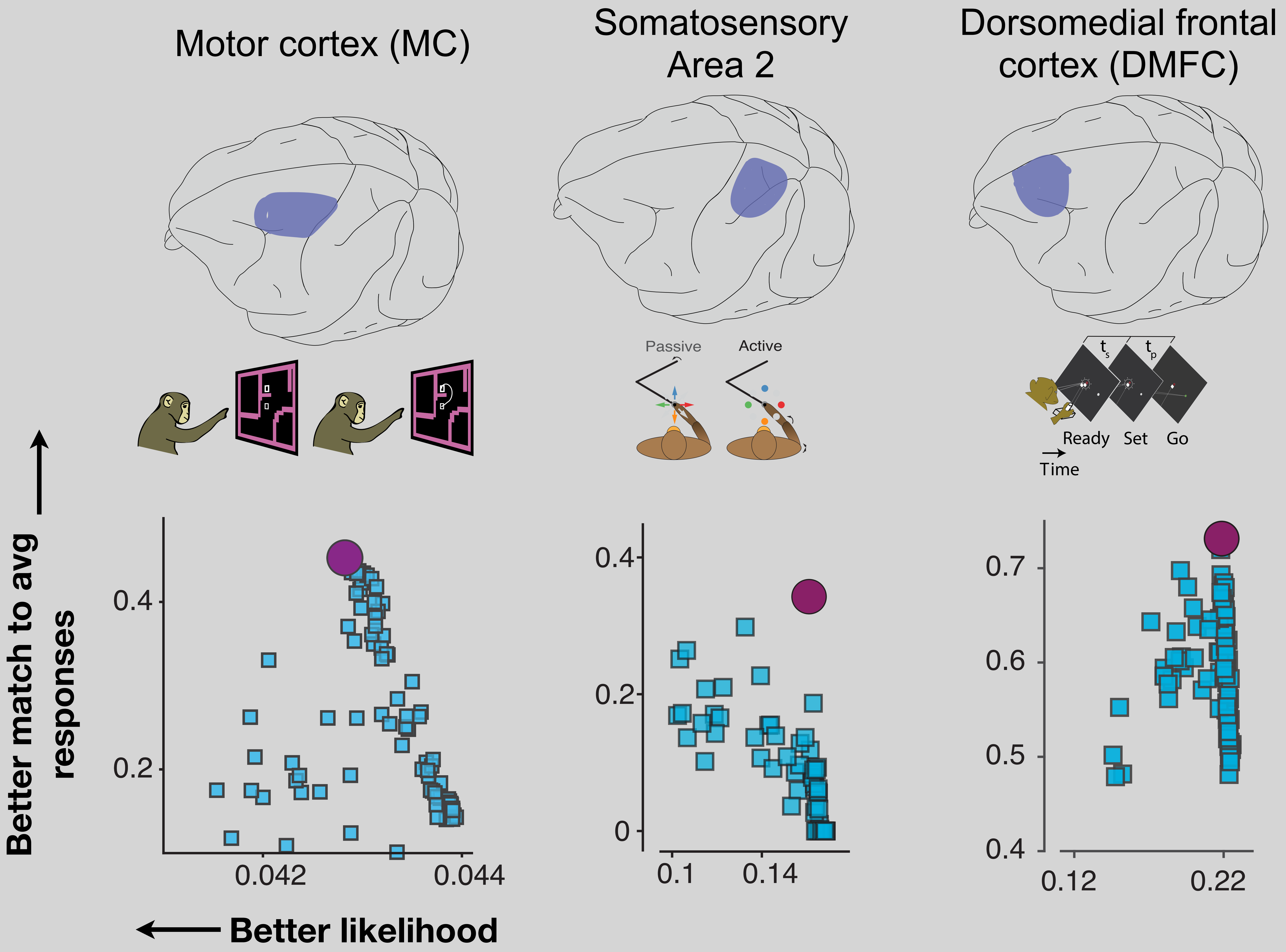
- Outperformed LFADS in all brains areas/behaviors tested



Area 2: Miller lab, Northwestern
DMFC: Jazayeri lab, MIT

AutoLFADS
Keshtkaran & Pandarinath, *NeurIPS* 2019
Keshtkaran*, Sedler*…Pandarinath, *in revision*; see BioRxiv

- Outperformed LFADS in all brains areas/behaviors tested
- Fully-automated, unsupervised discovery of high-performing models



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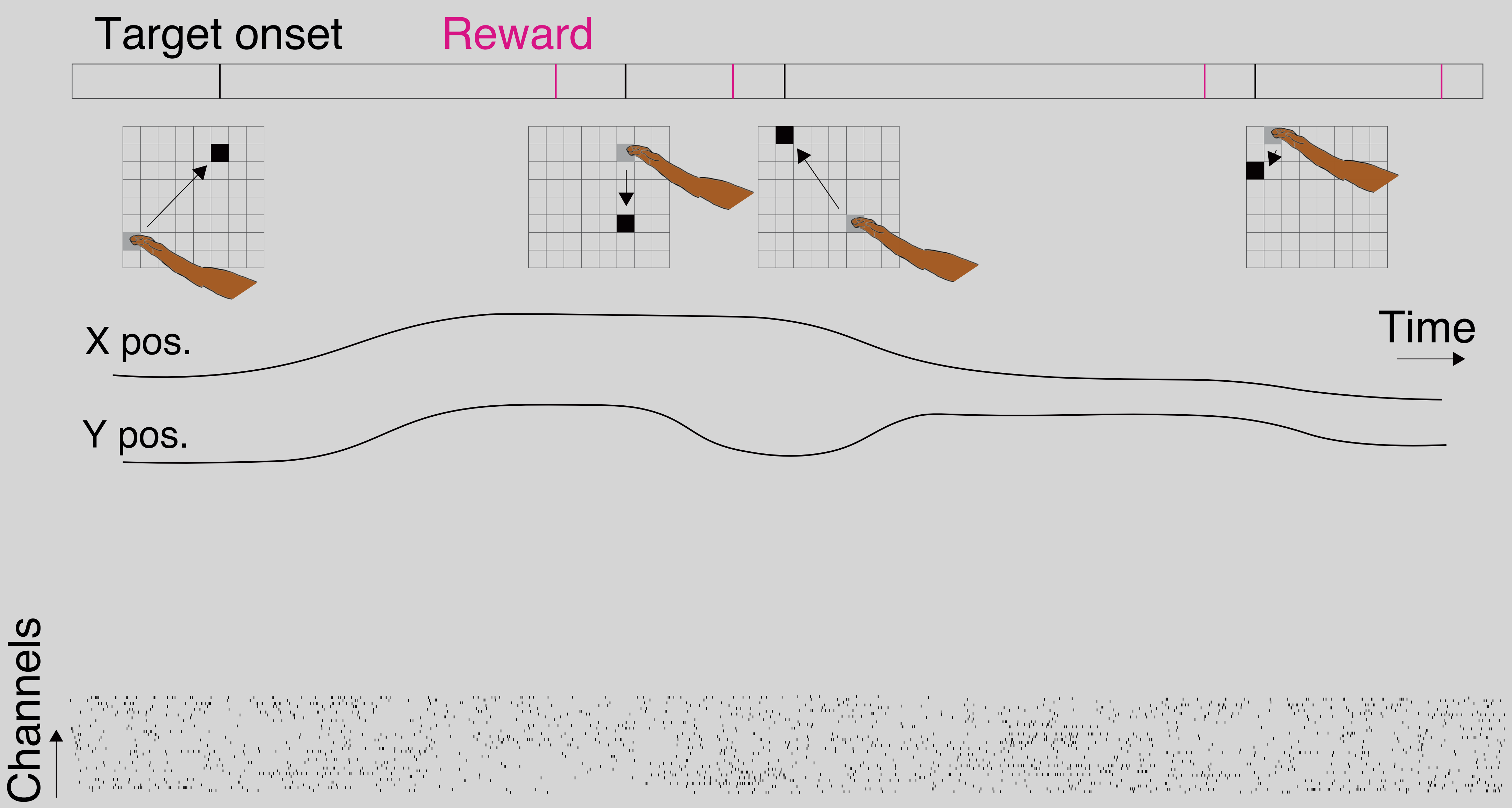
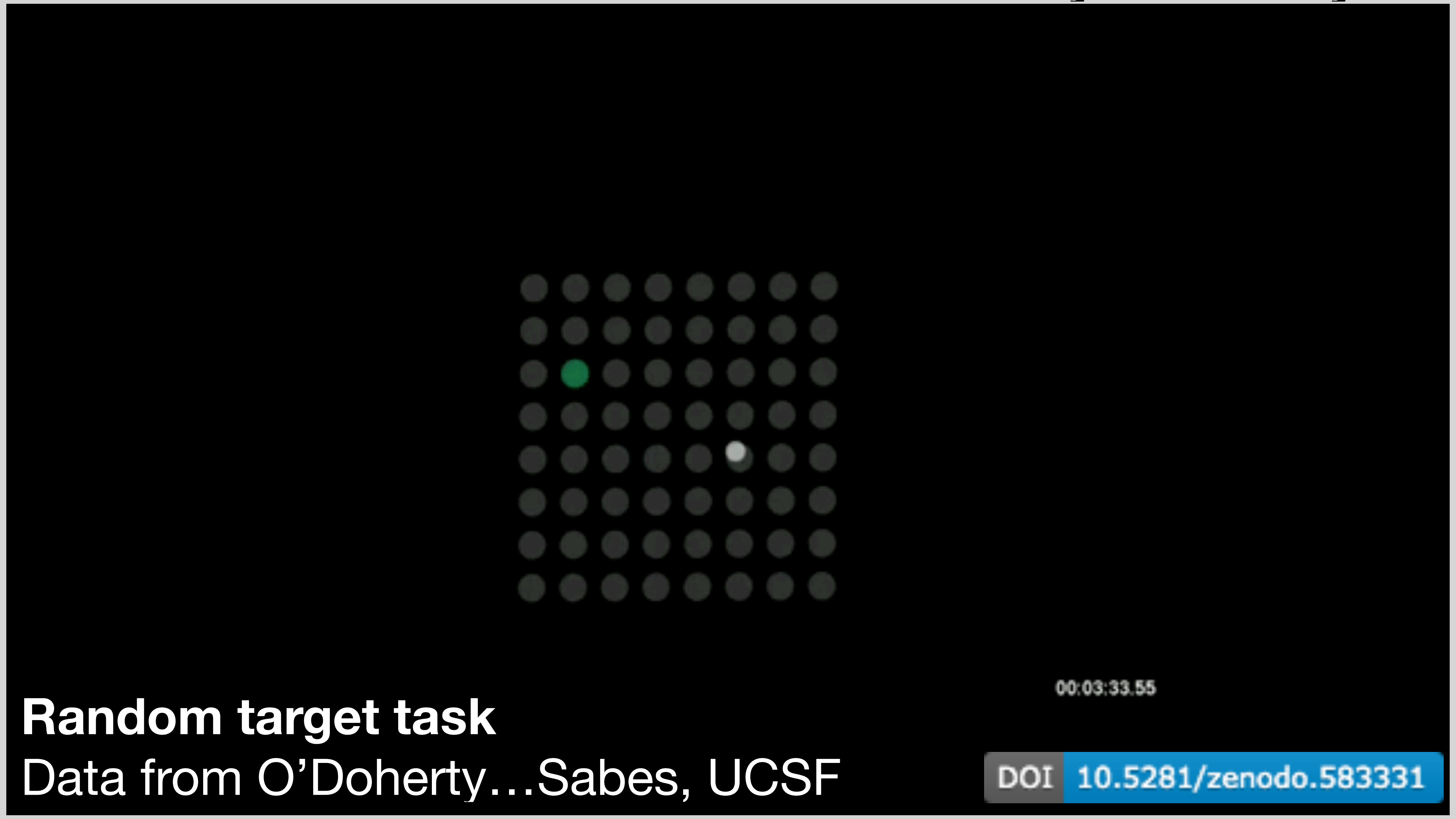
Keshtkaran & Pandarinath, *NeurIPS* 2019
Keshtkaran*, Sedler*…Pandarinath, *in revision*; see BioRxiv

Dynamics during non-stereotyped behaviors



100-electrode array in Monkey M1



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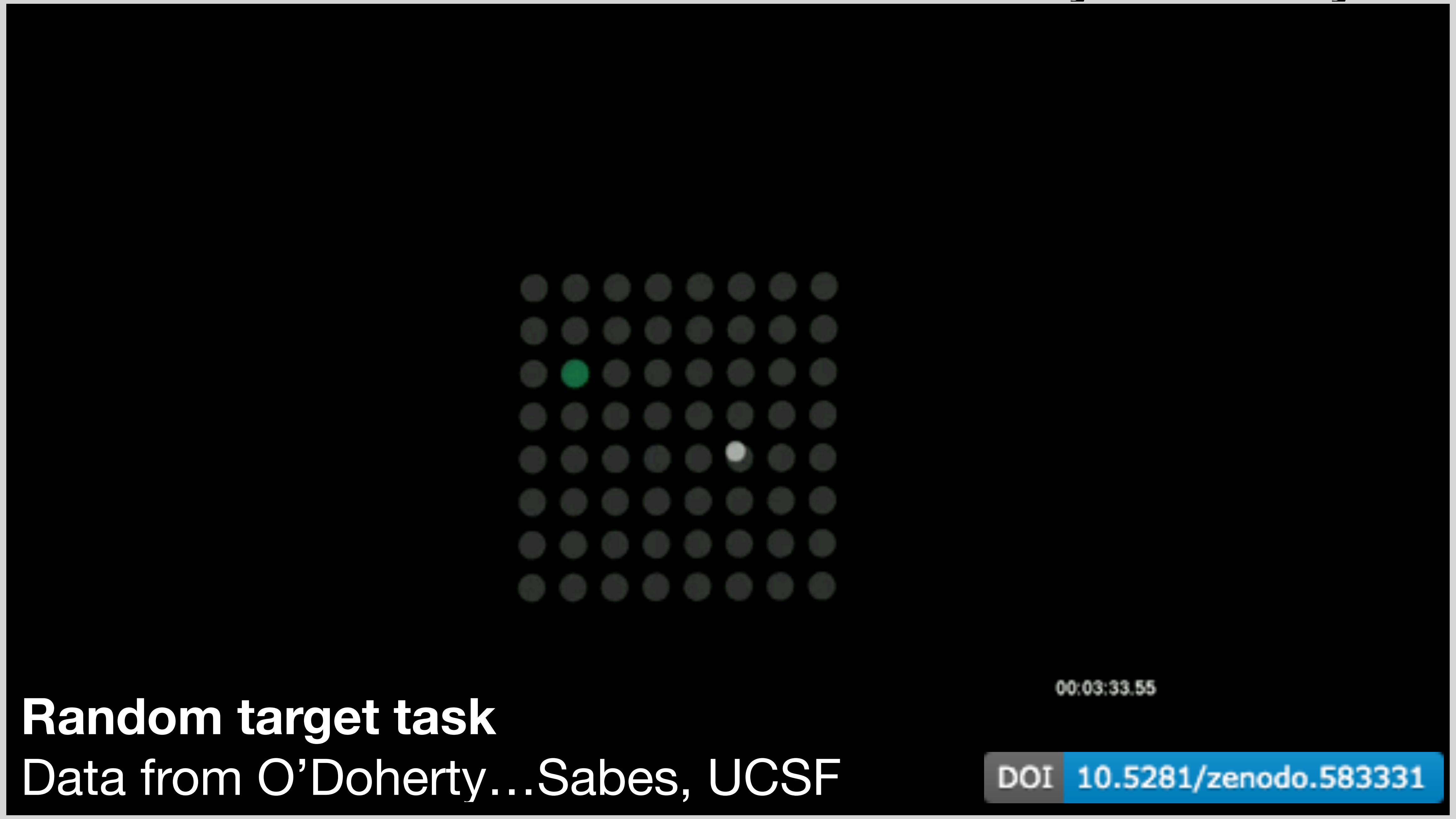

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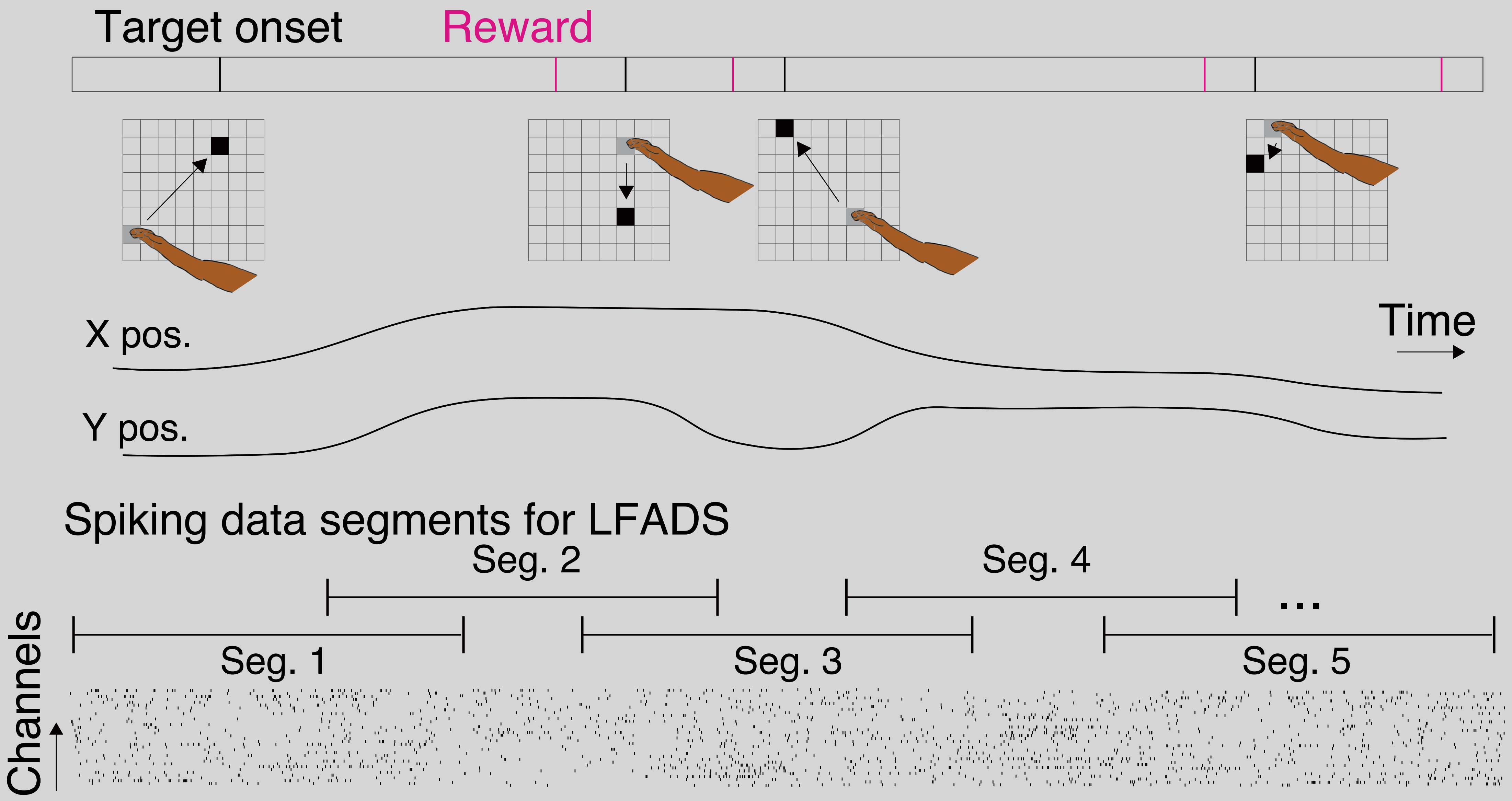

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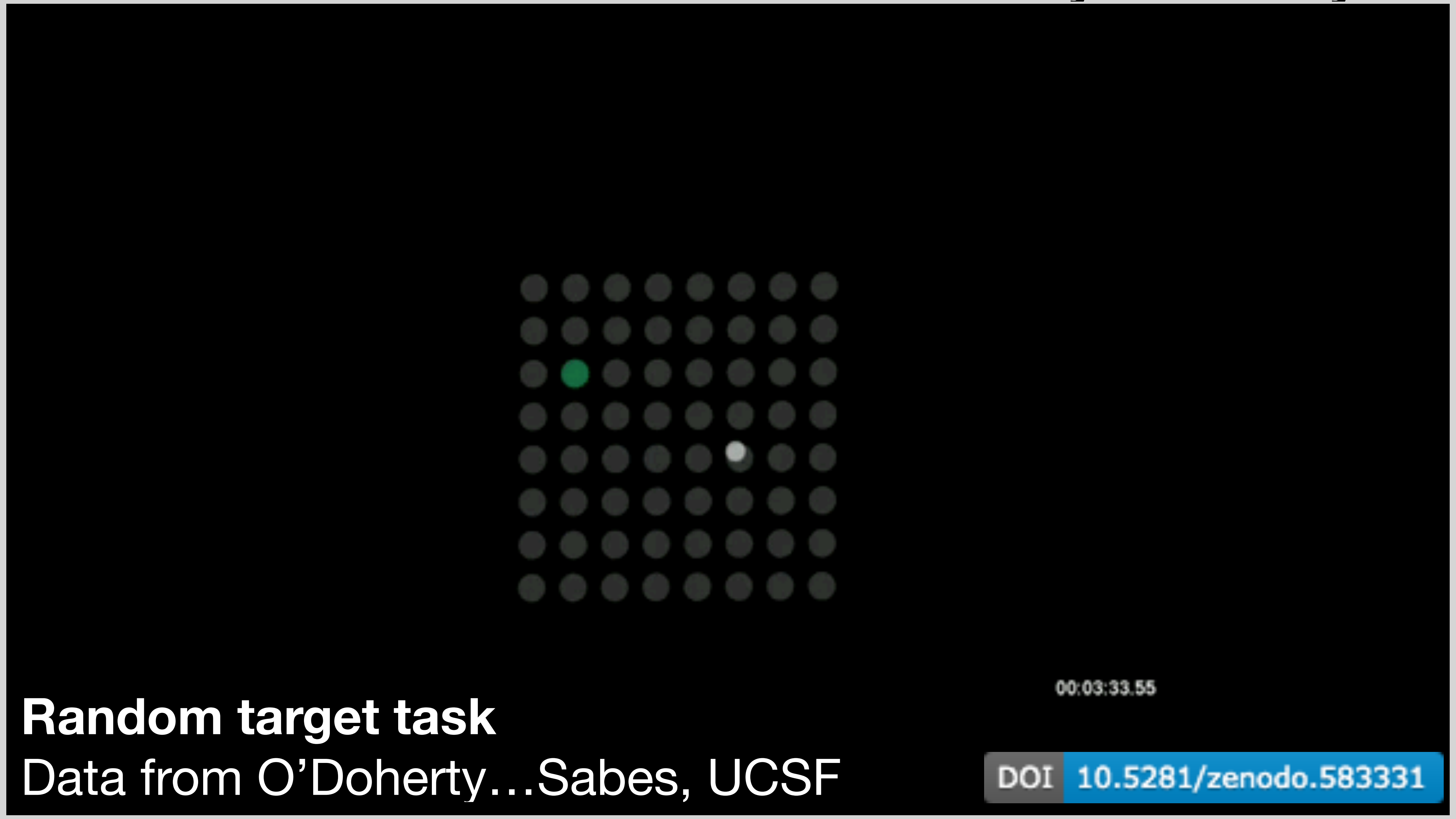

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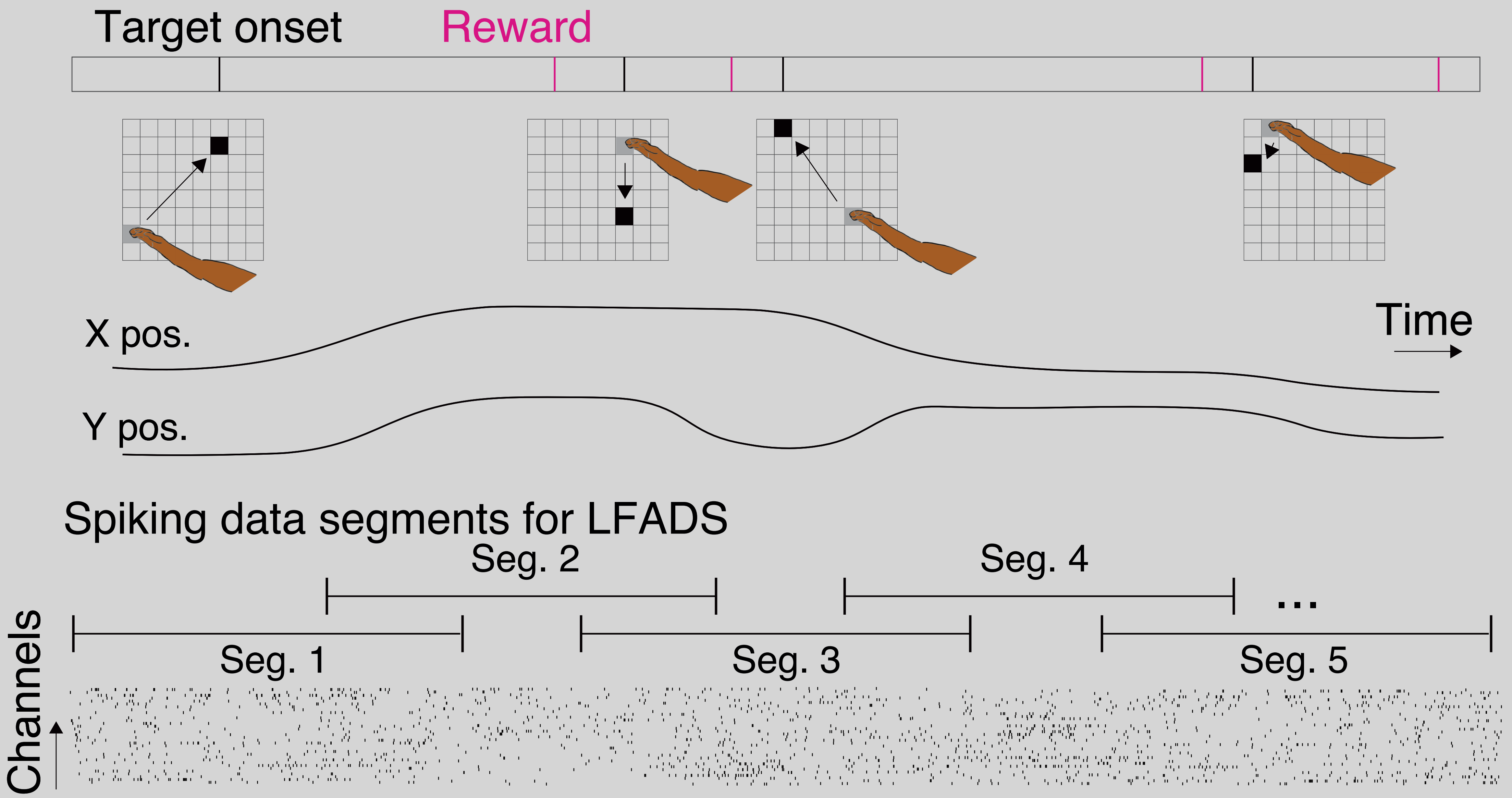

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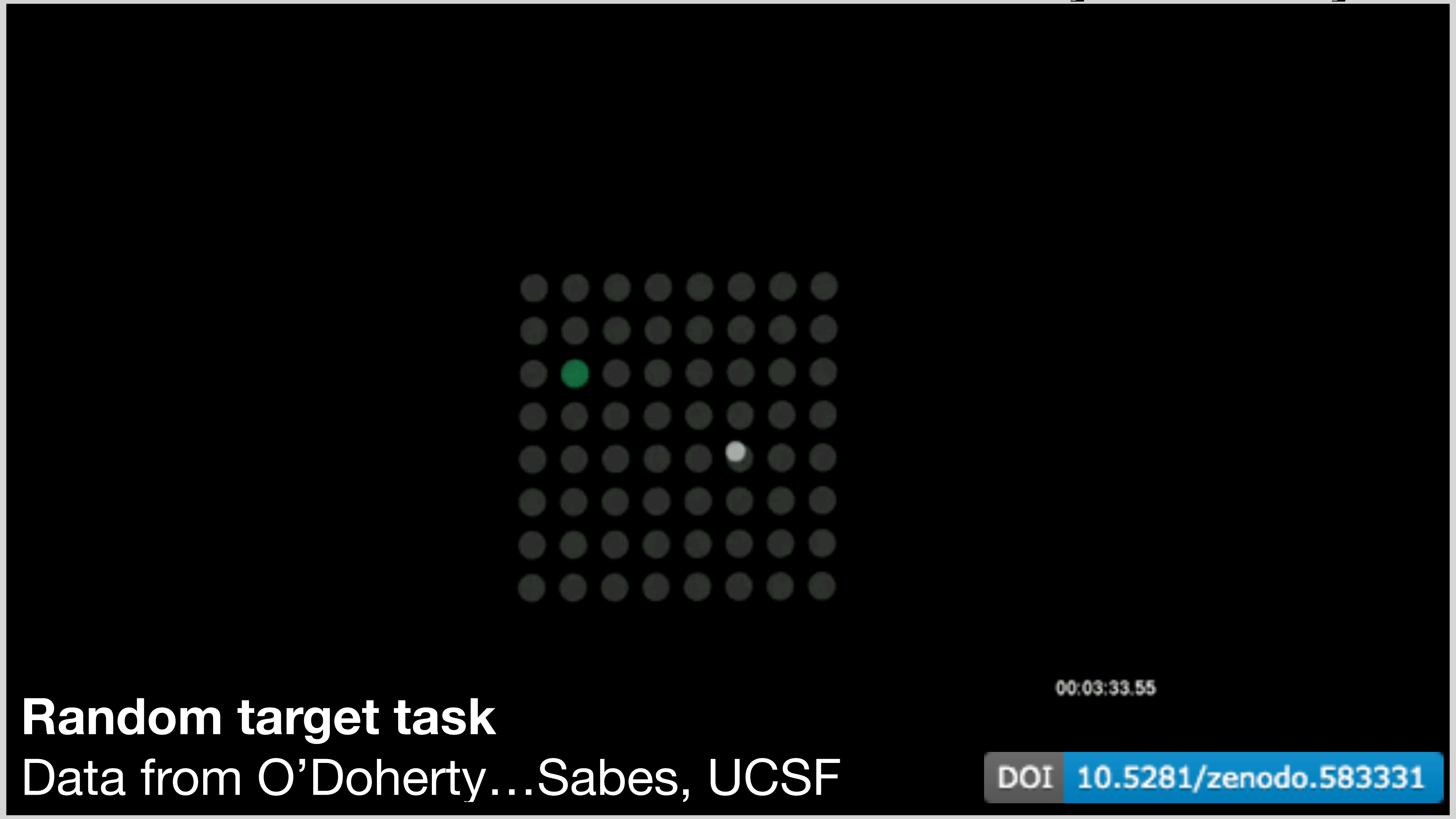

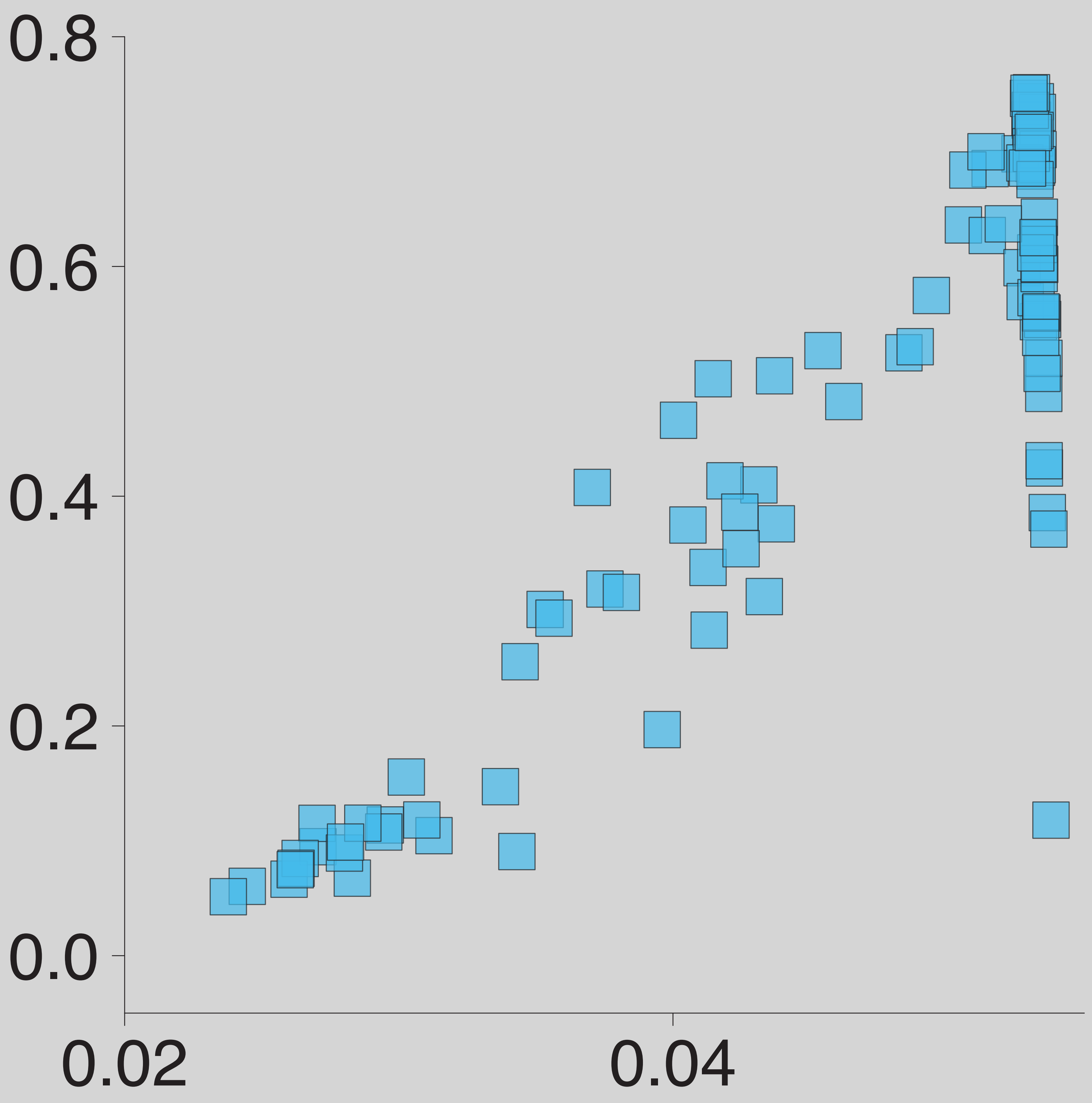

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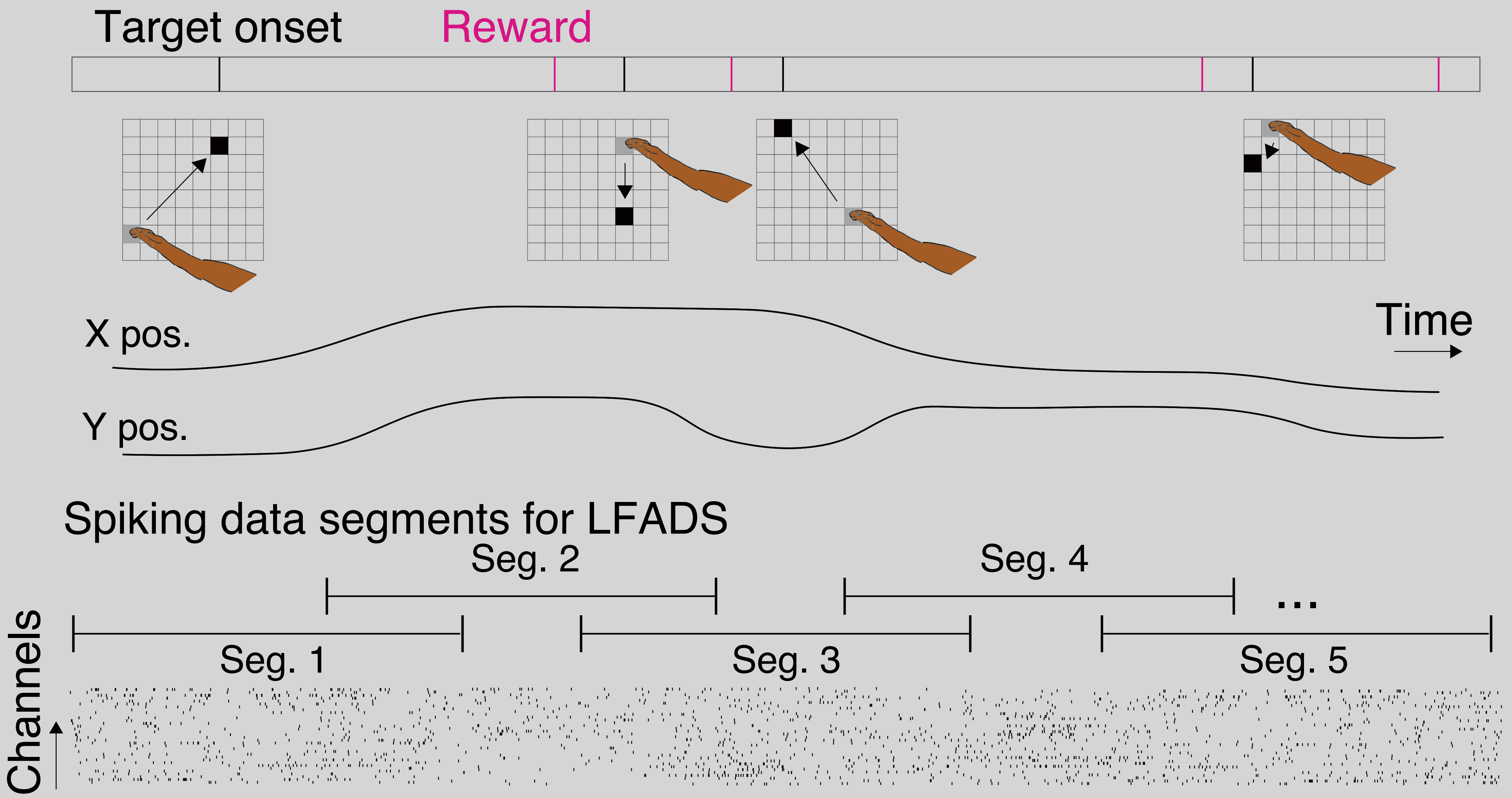

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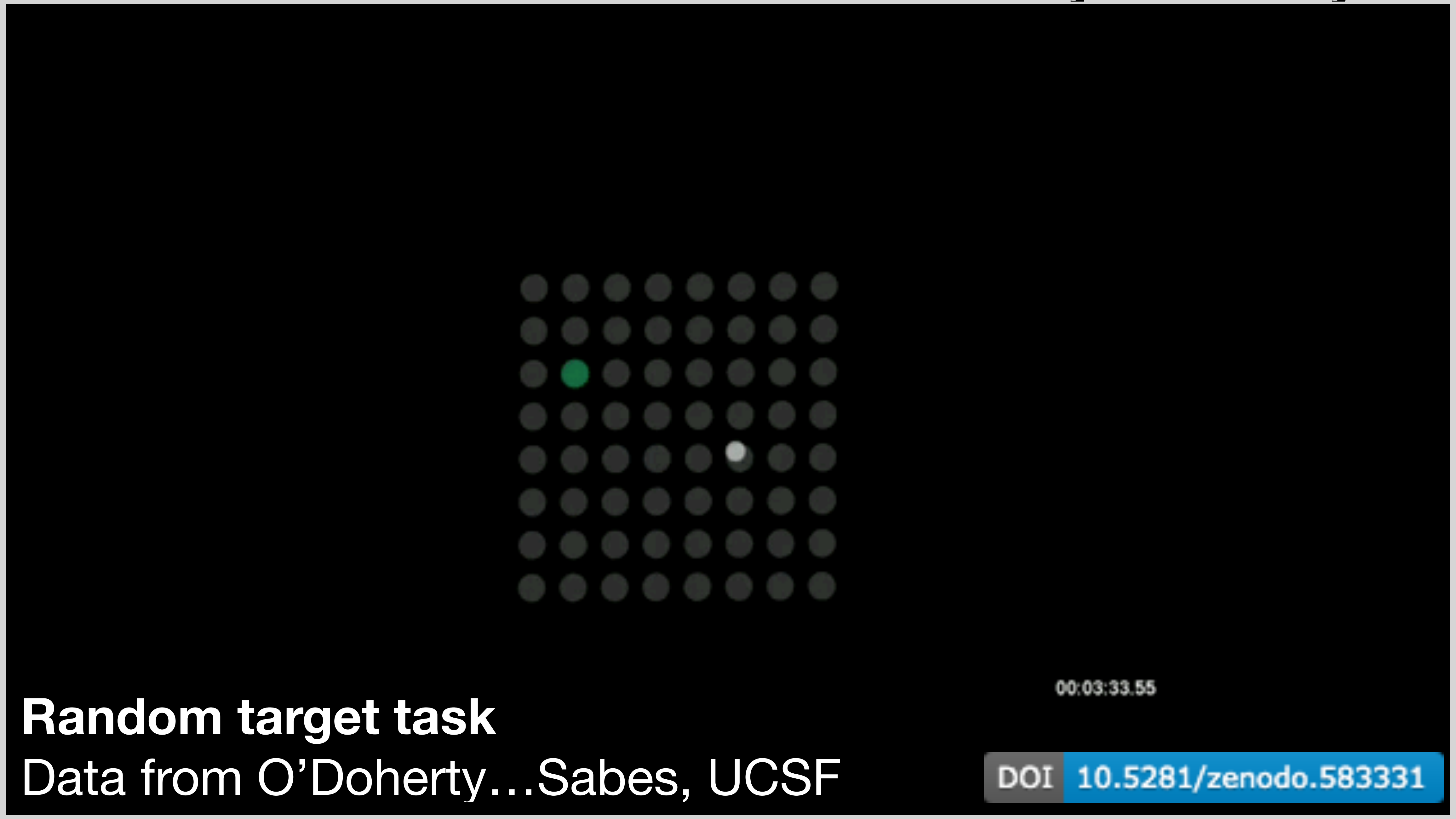

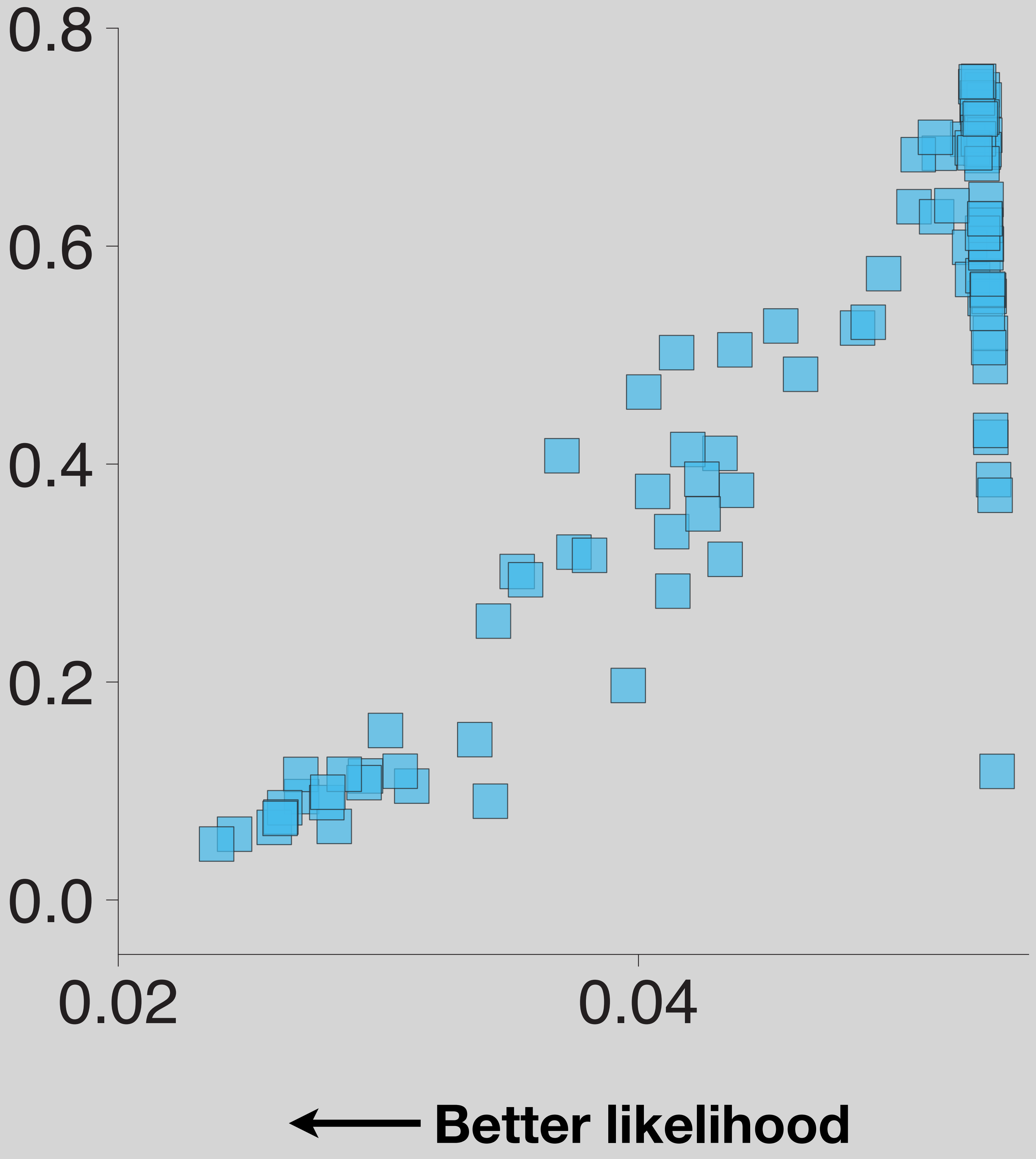

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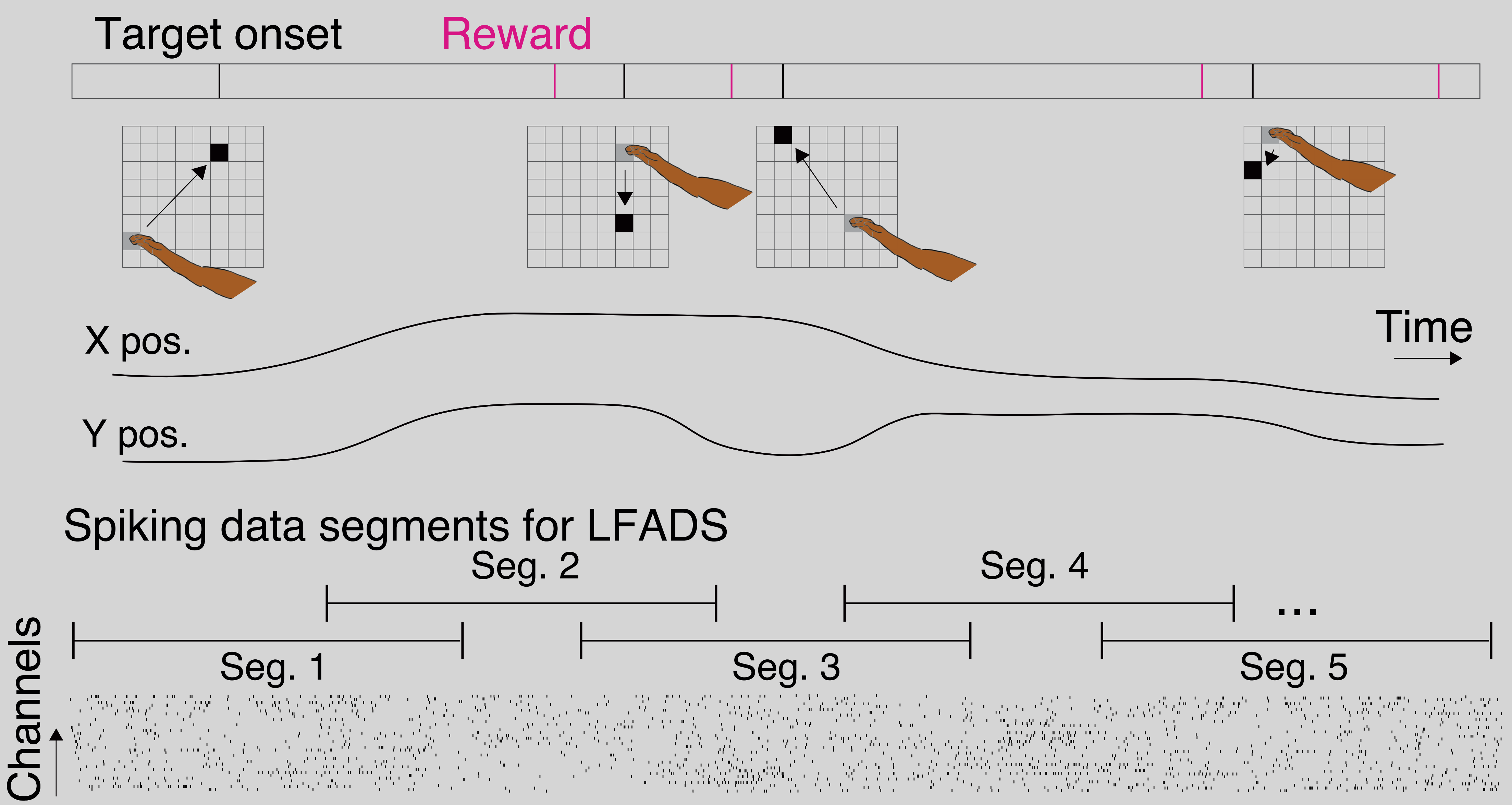

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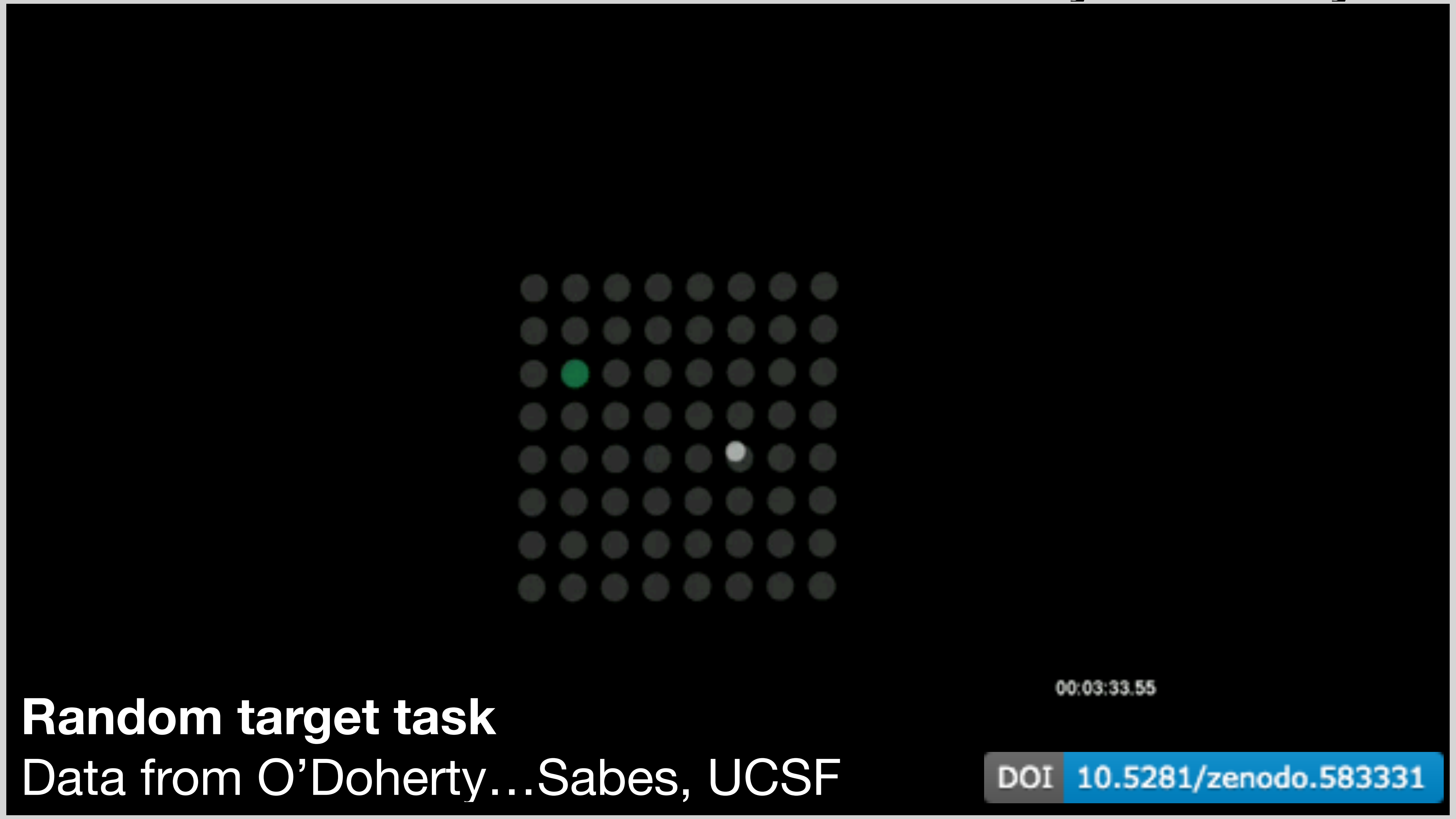
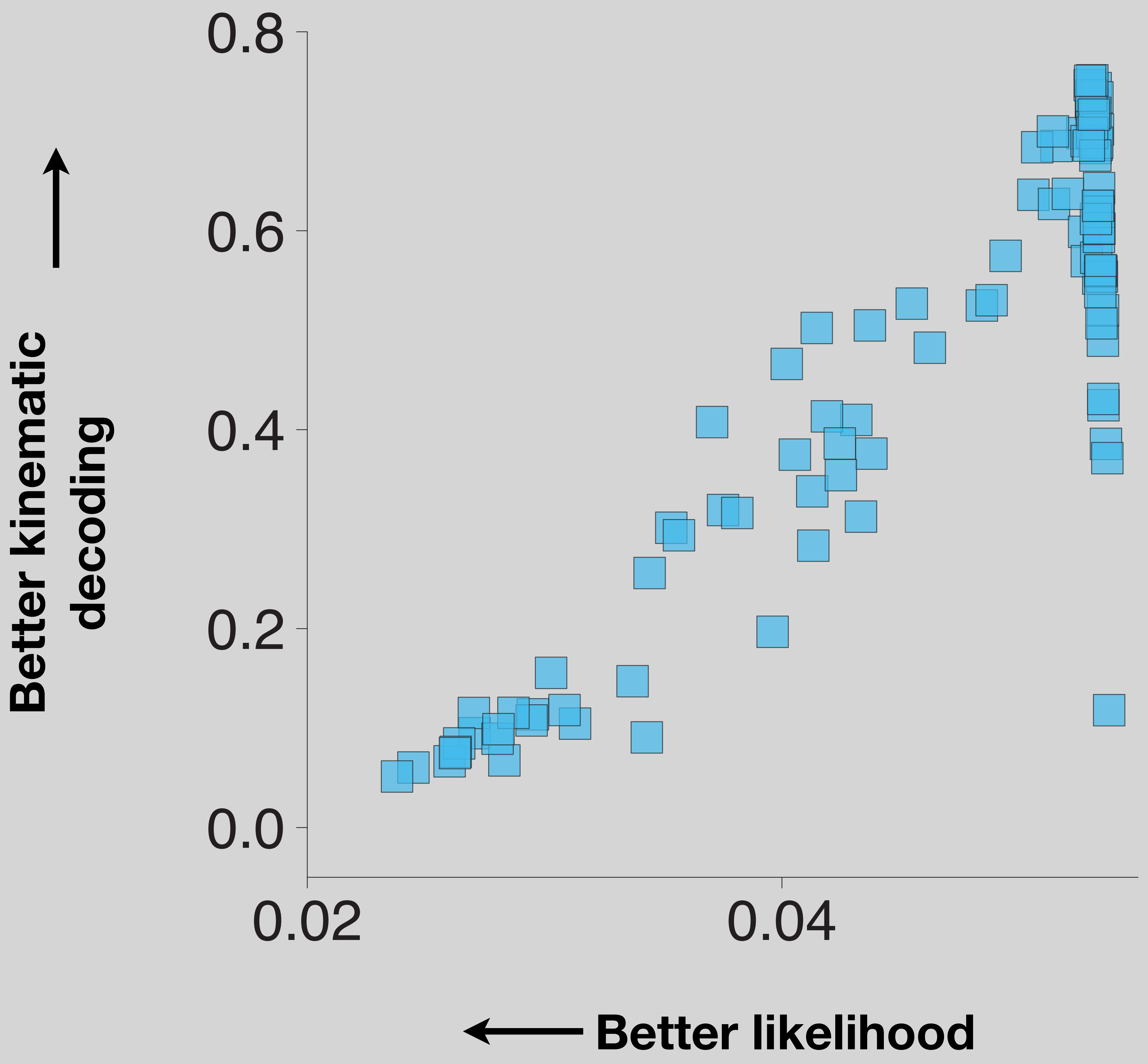


Random target task
Data from O'Doherty…Sabes, UCSF

DOI 10.5281/zenodo.583331



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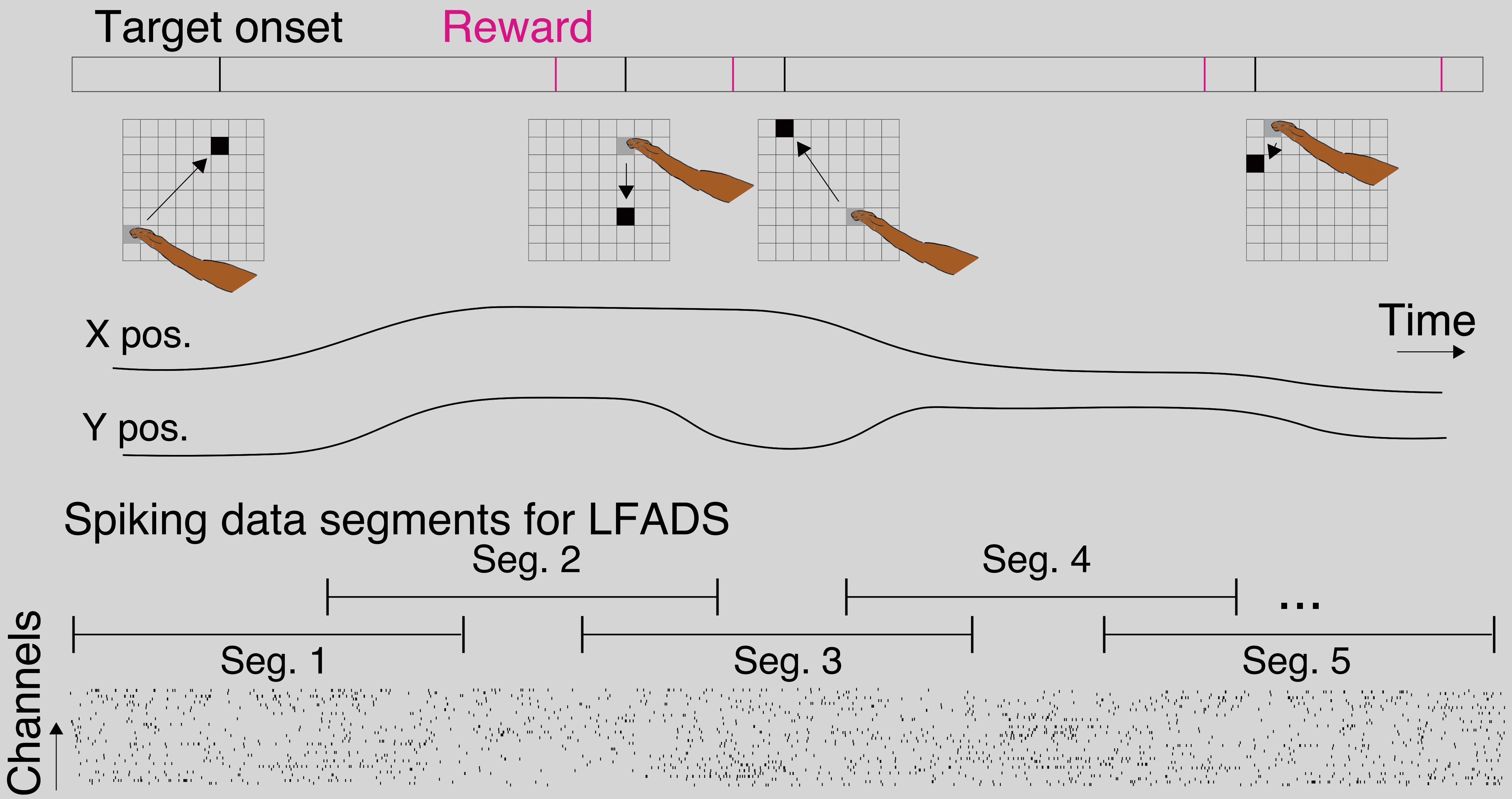

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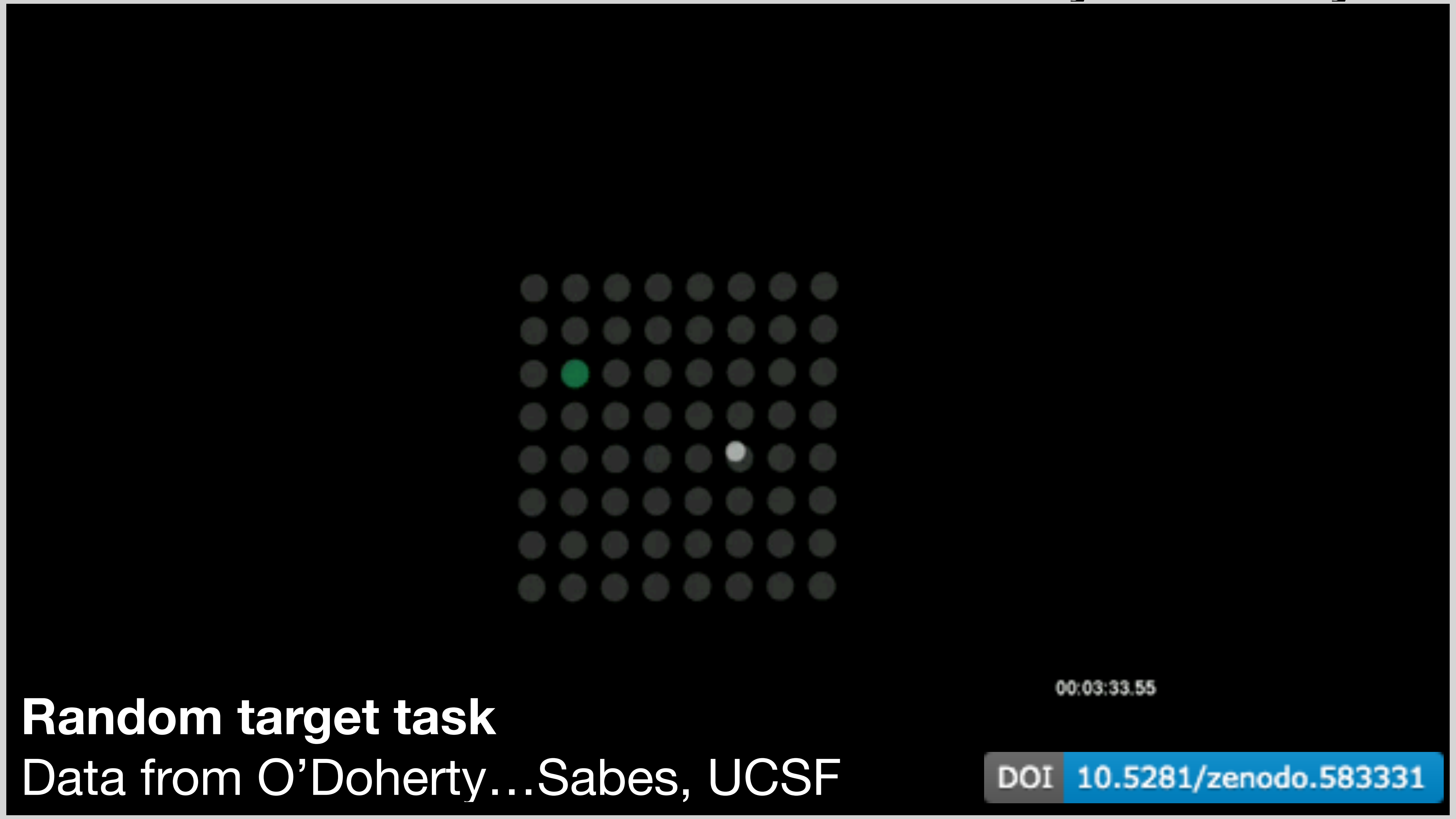

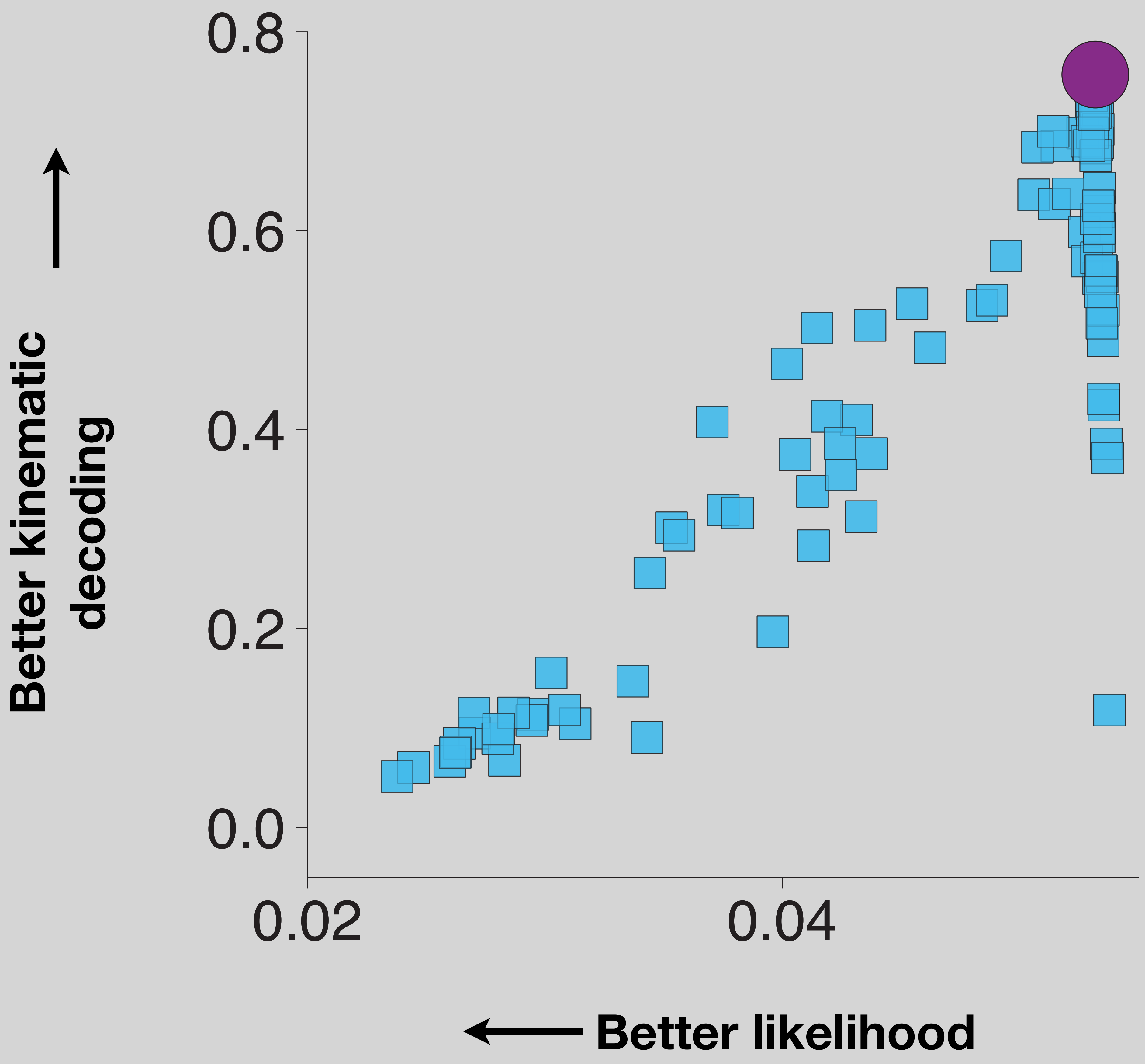

AutoLFADS

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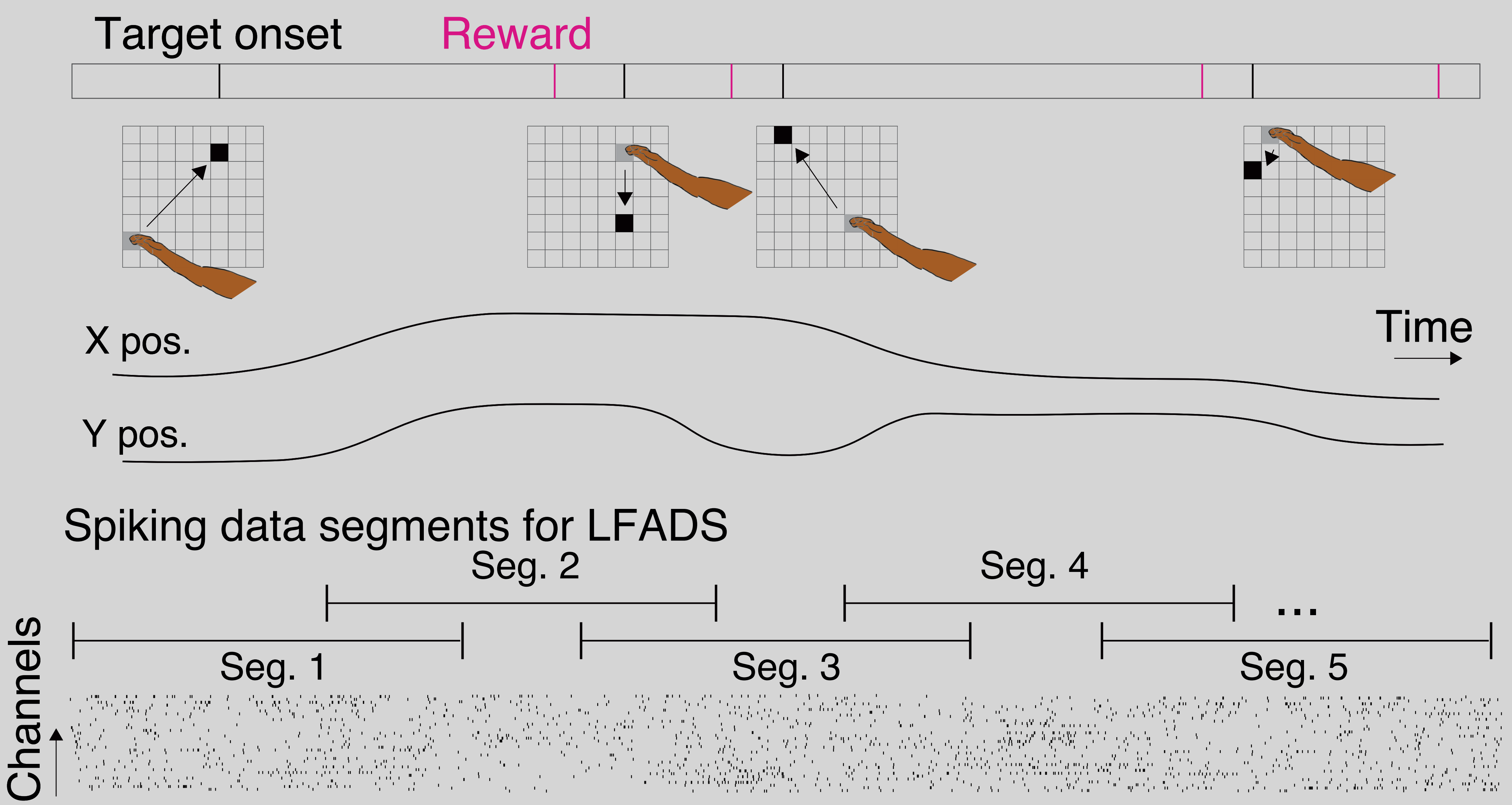

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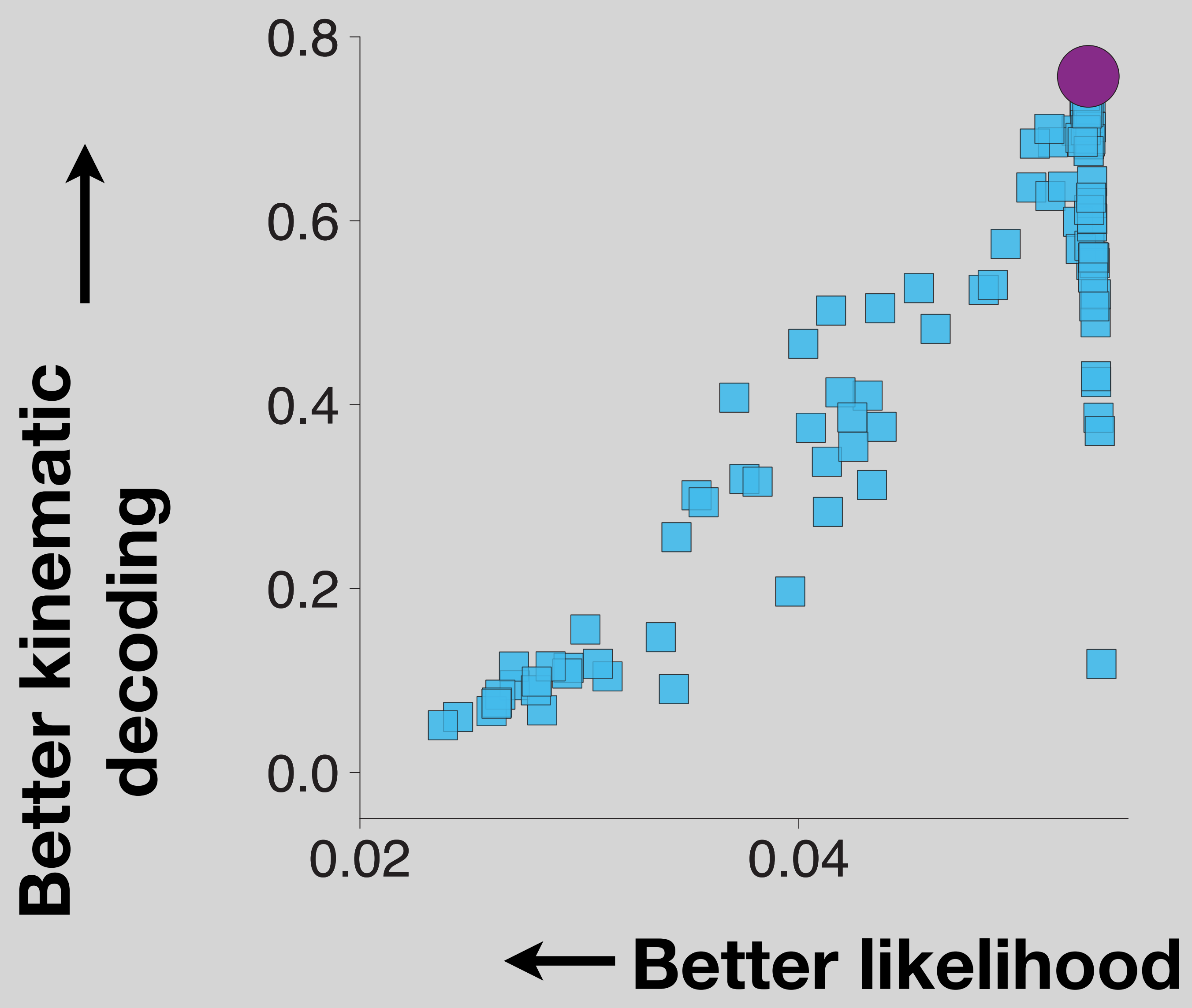

AutoLFADS

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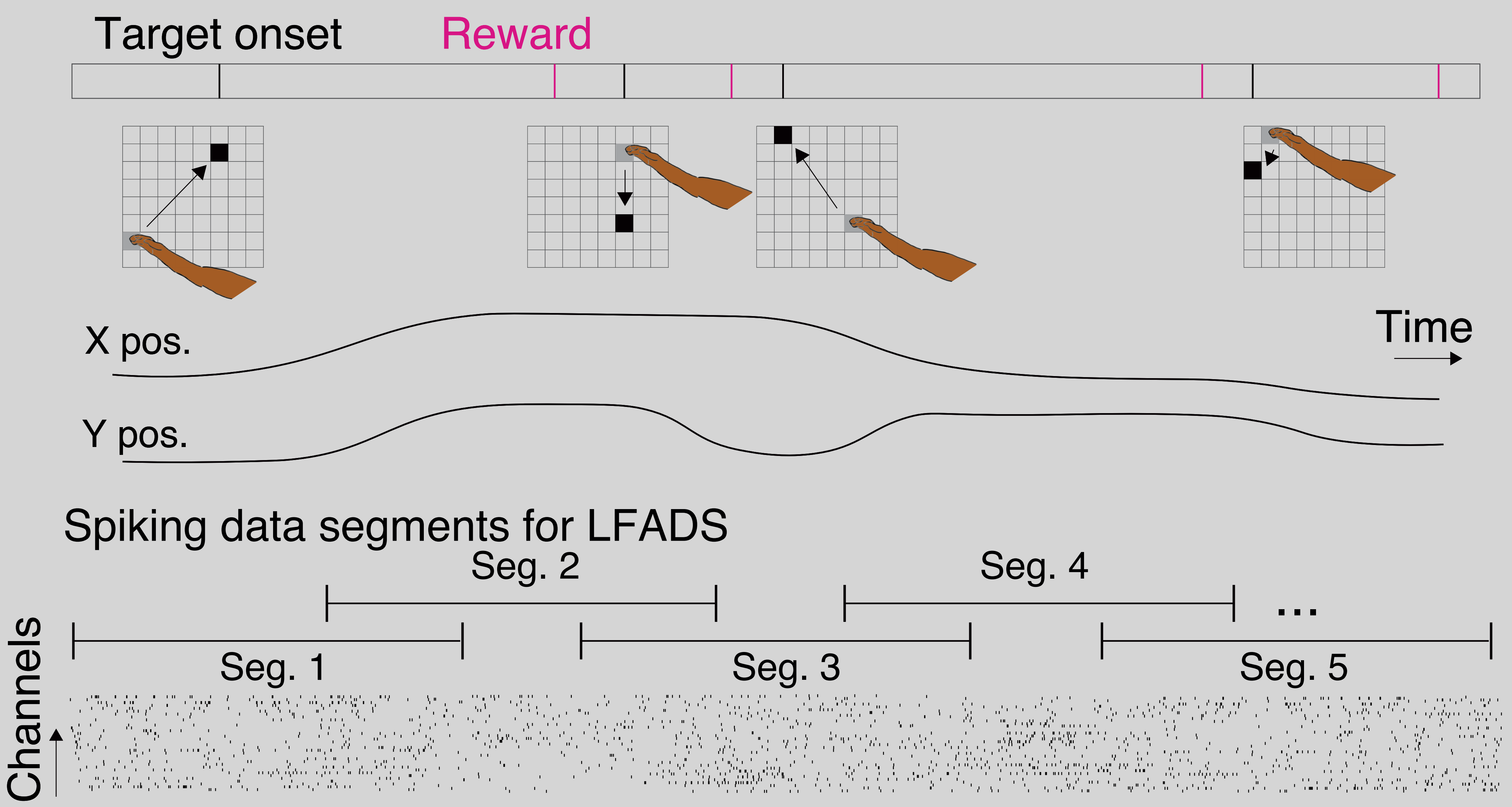

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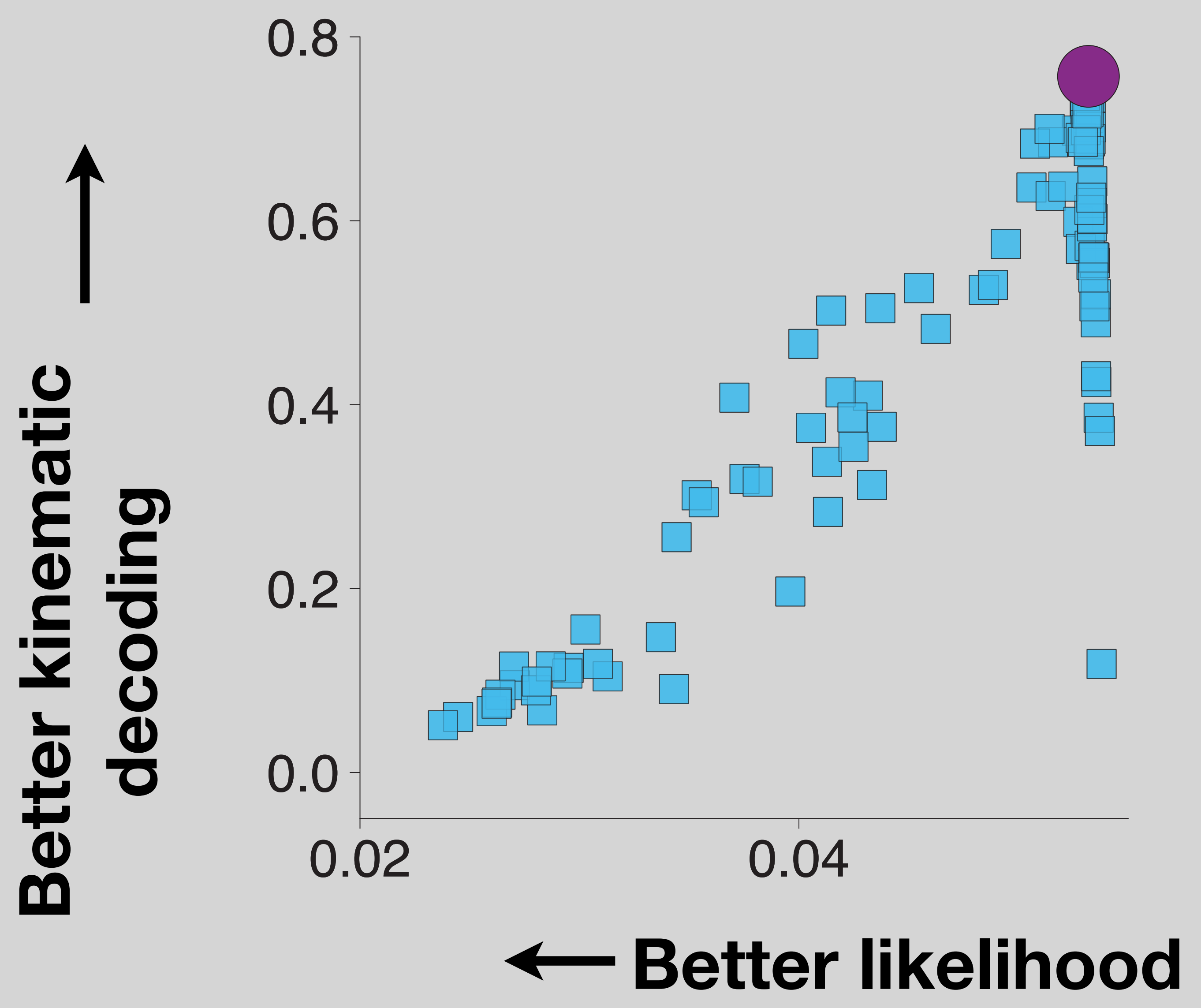

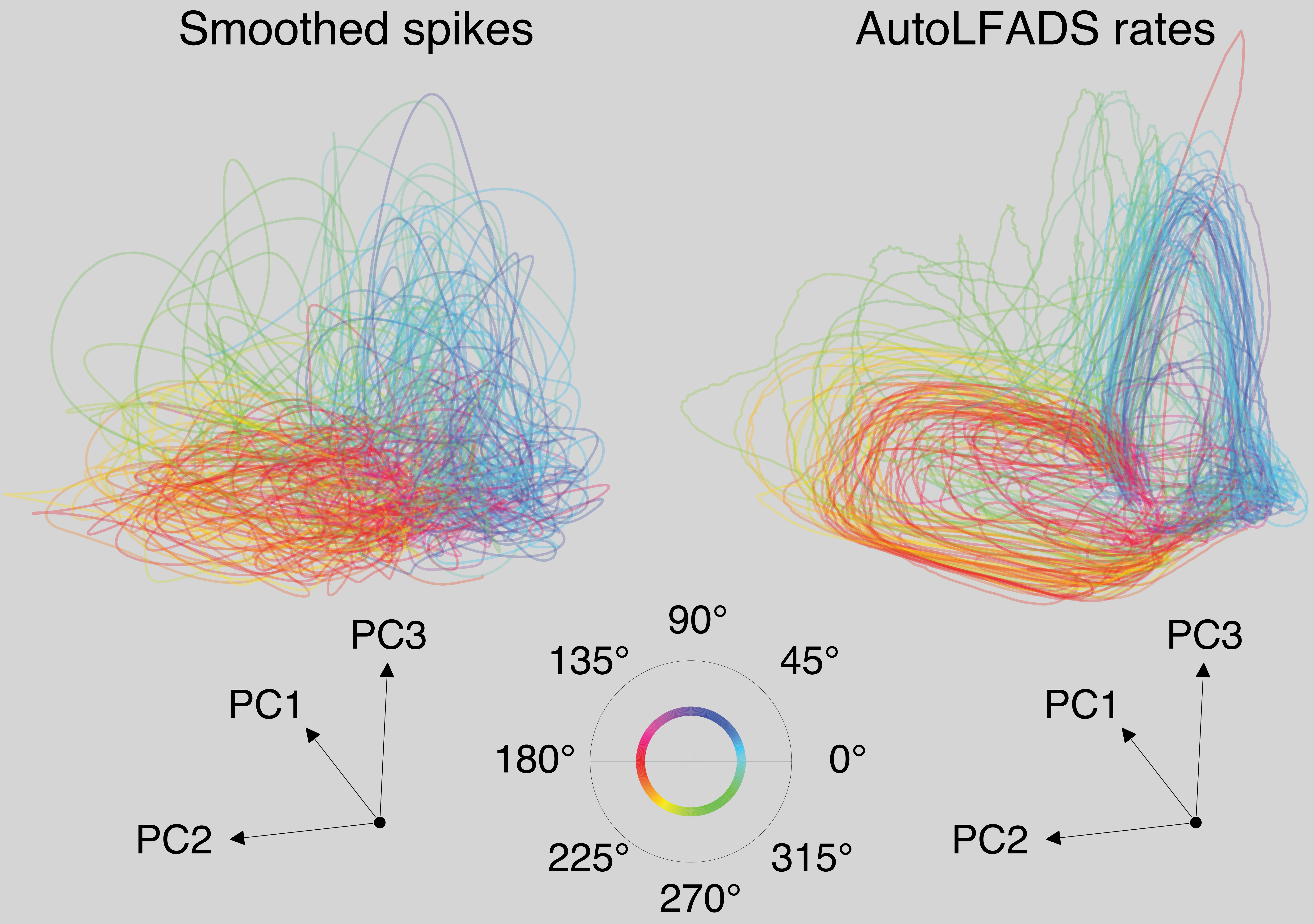

AutoLFADS
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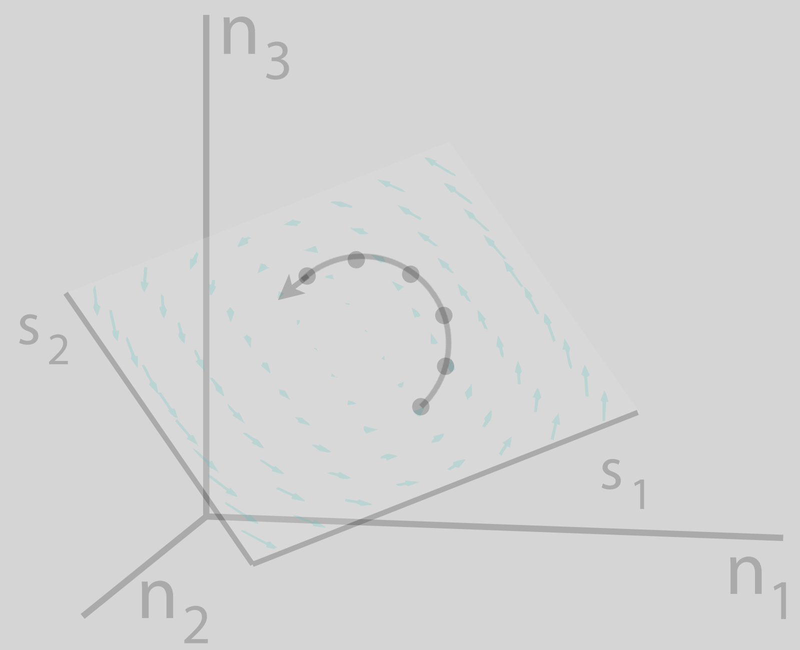
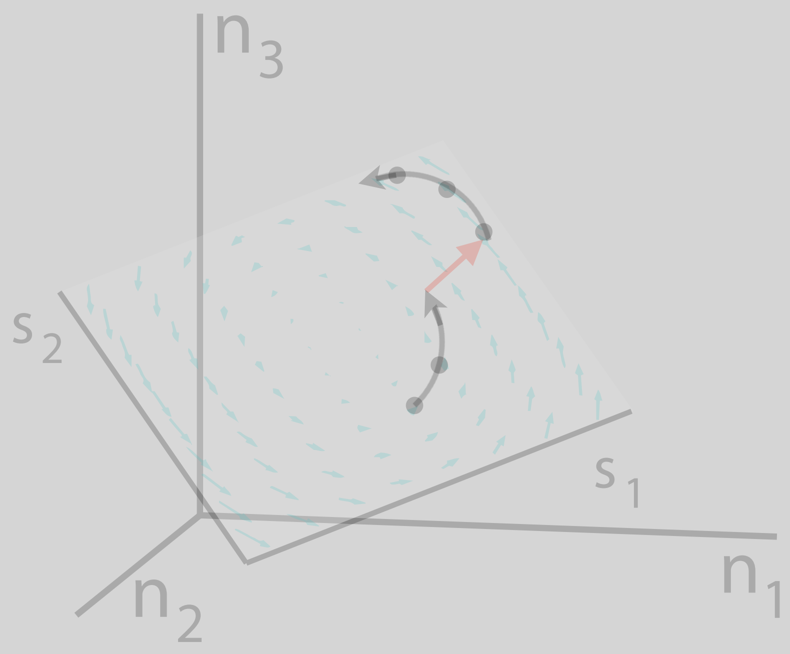
Keshtkaran*, Sedler*…Pandarinath, *in revision*; see BioRxiv

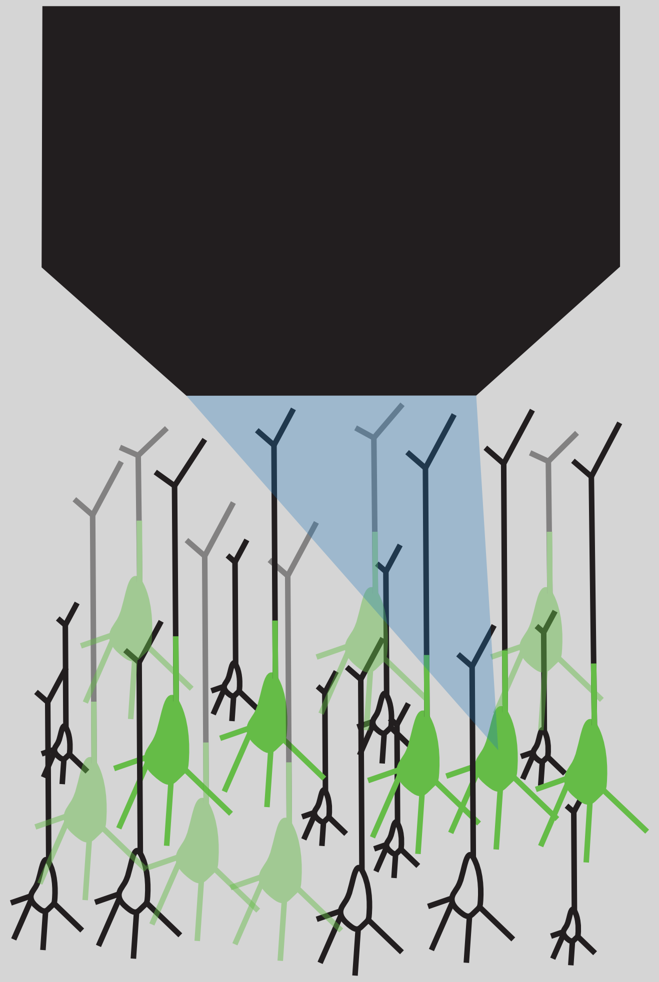
ML methods to uncover single-trial population dynamics



Predictable neural activity: modeling autonomous dynamics with LFADS



Unpredictable activity: non-autonomous dynamics and AutoLFADS

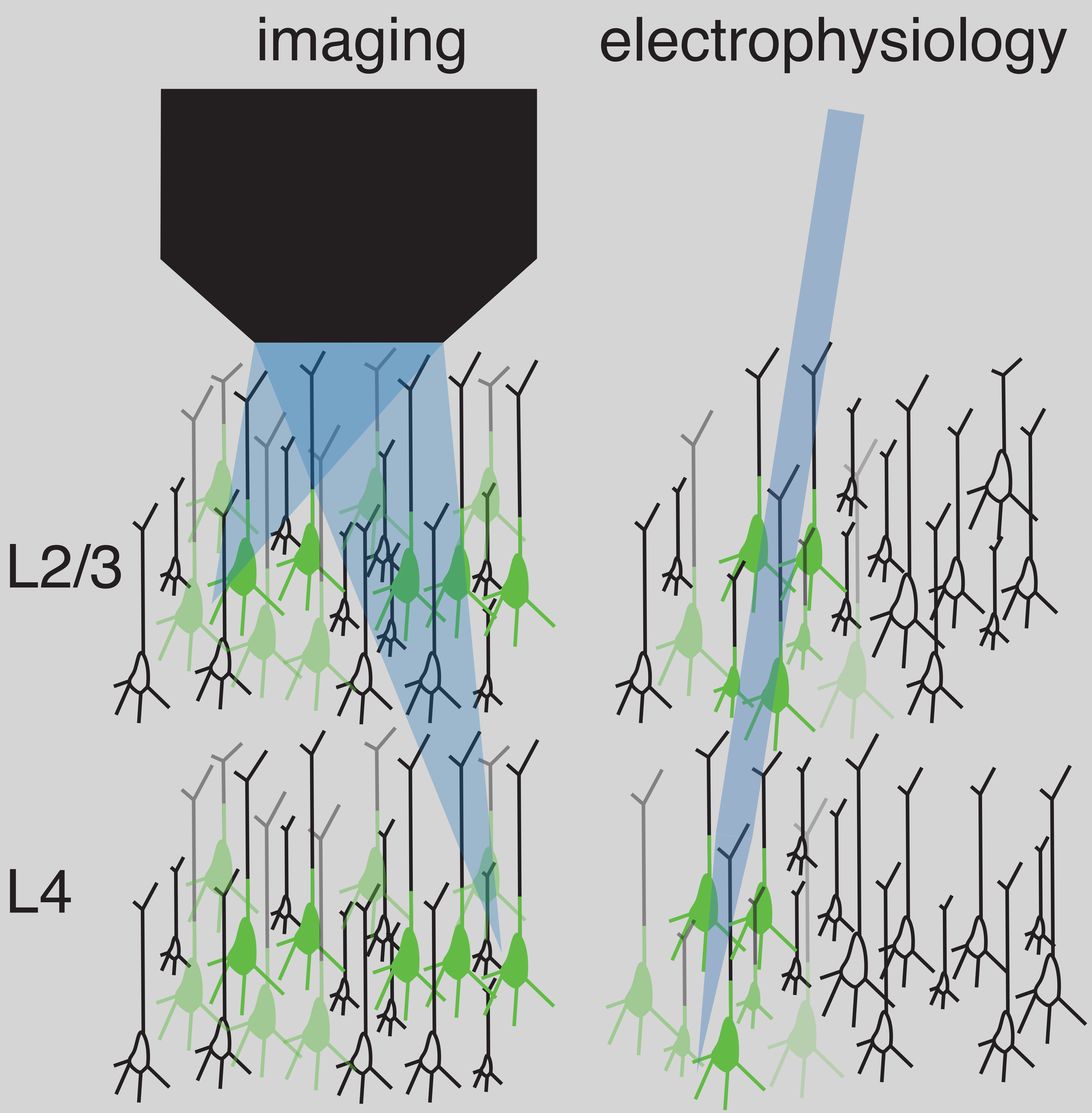


Applications to 2P Ca imaging: RADICaL

Feng Zhu

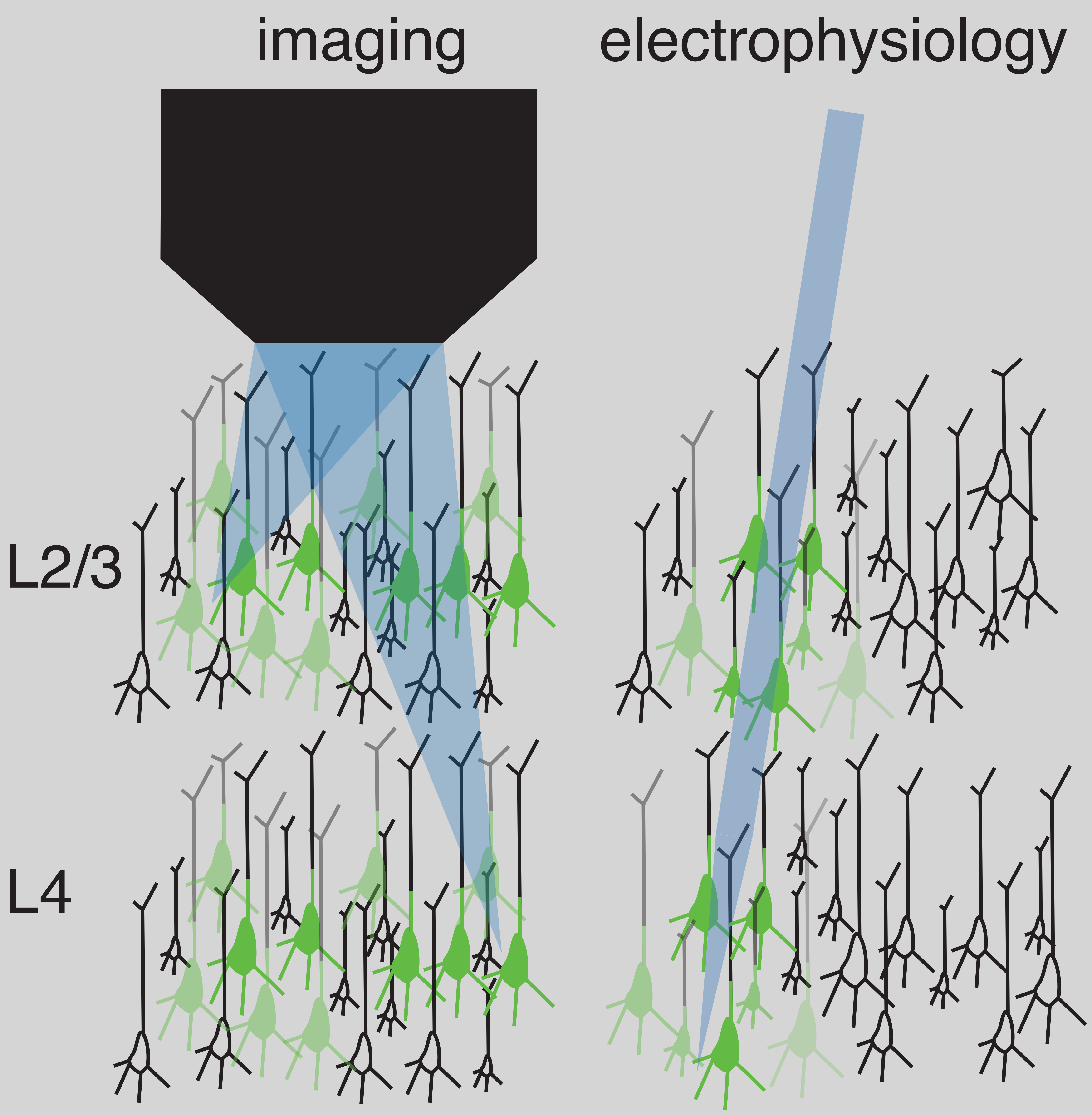
Recurrent Autoencoder for Discovering Imaged Calcium Latents (RADICaL)
Zhu*, Sedler*… Pandarinath, *NeurIPS* 2021
Zhu … Giovannucci, Kaufman**, Pandarinath**
in revision; see BioRxiv

Applicat



RADICaL
Zhu*, Sedler*… Pandarinath, *NeurIPS* 2021
Zhu … Giovannucci, Kaufman**, Pandarinath**
in revision; see BioRxiv

- 2P: Can monitor large populations w/ location and cell types identified



RADICaL

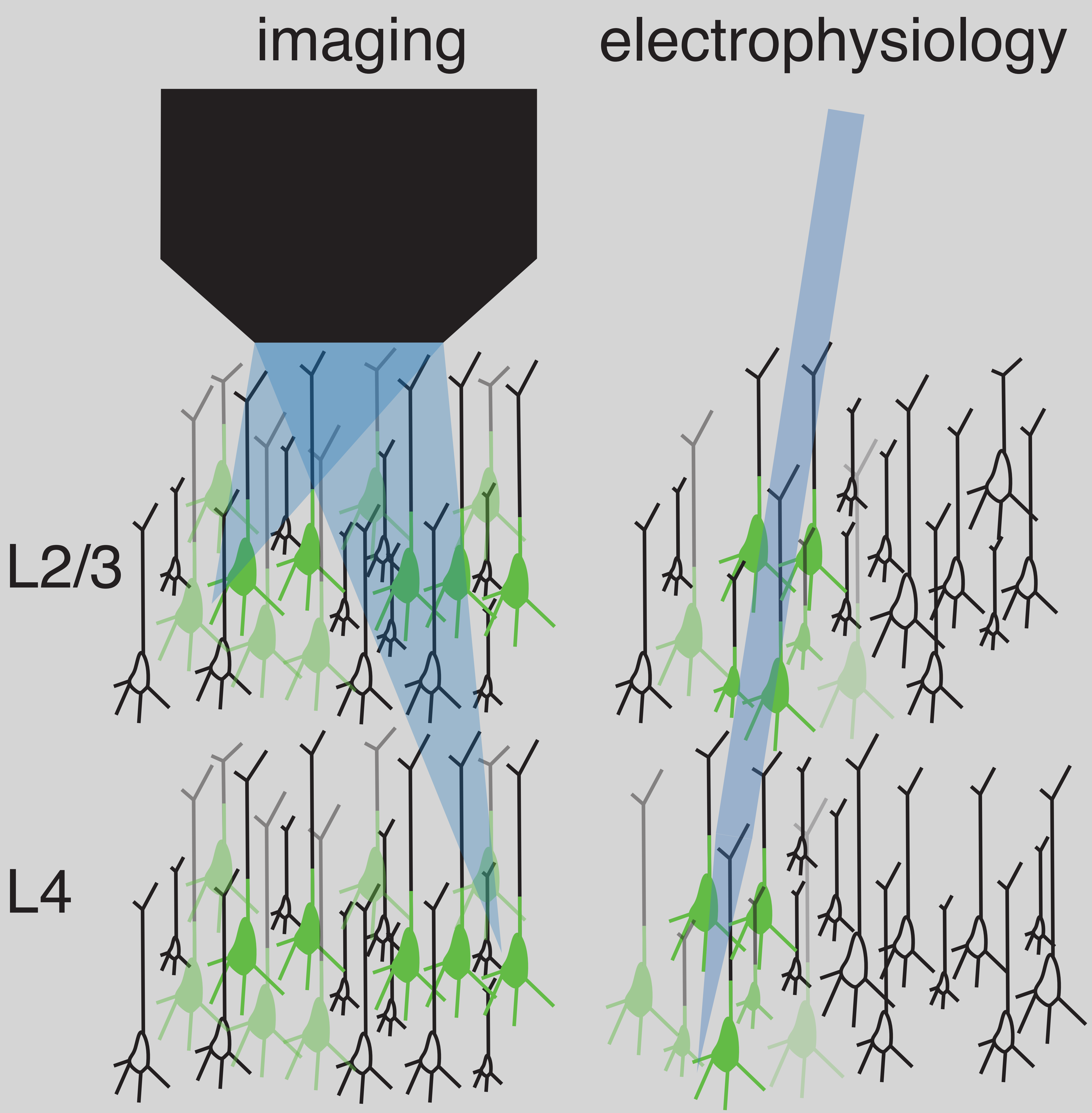
Zhu*, Sedler*… Pandarinath, *NeurIPS* 2021

Zhu … Giovannucci, Kaufman**, Pandarinath**

in revision; see BioRxiv

- 2P: Can monitor large populations w/ location and cell types identified

- Powerful tool to probe the actual neural circuitry that gives rise to population dynamics



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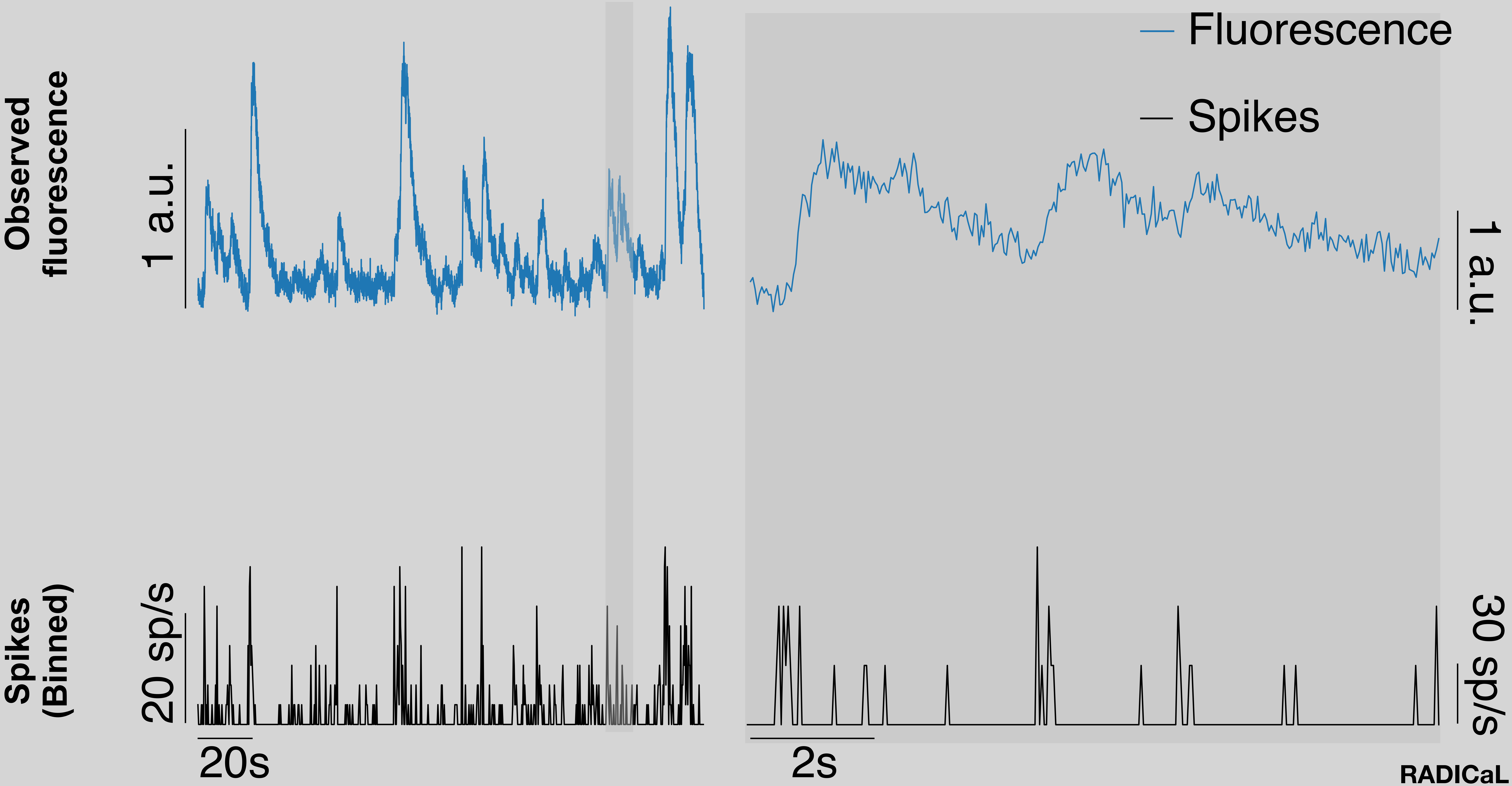

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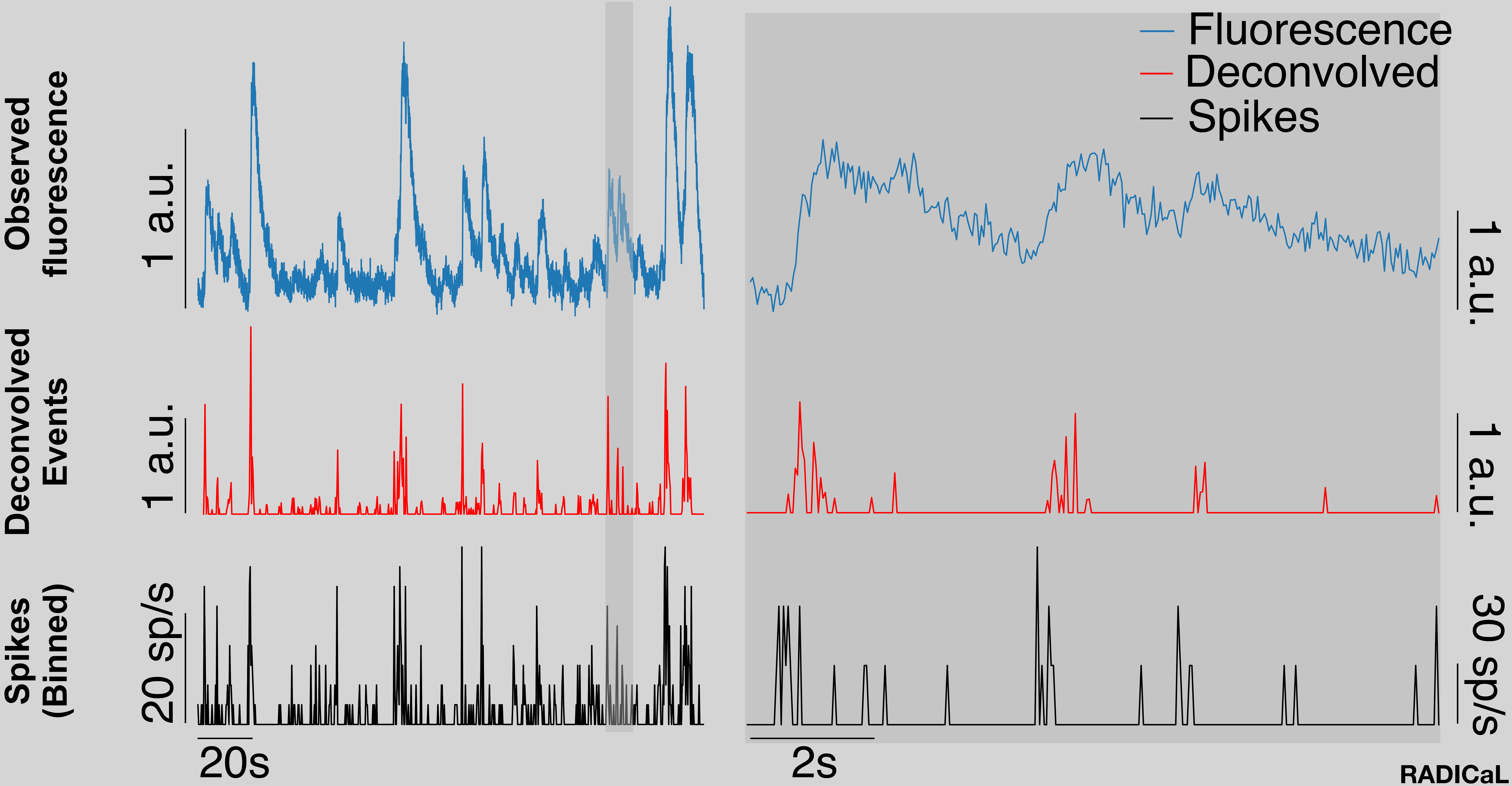

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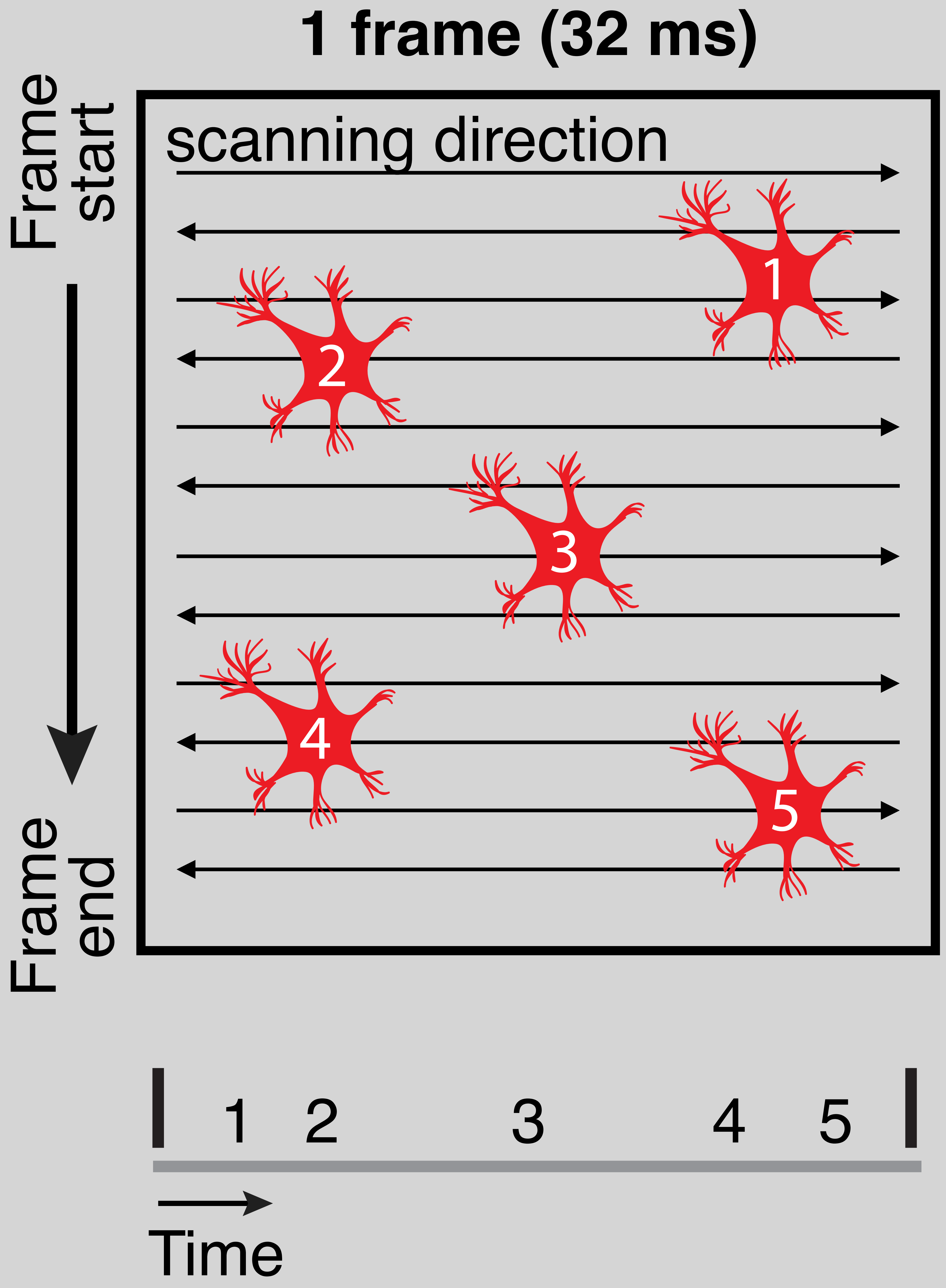
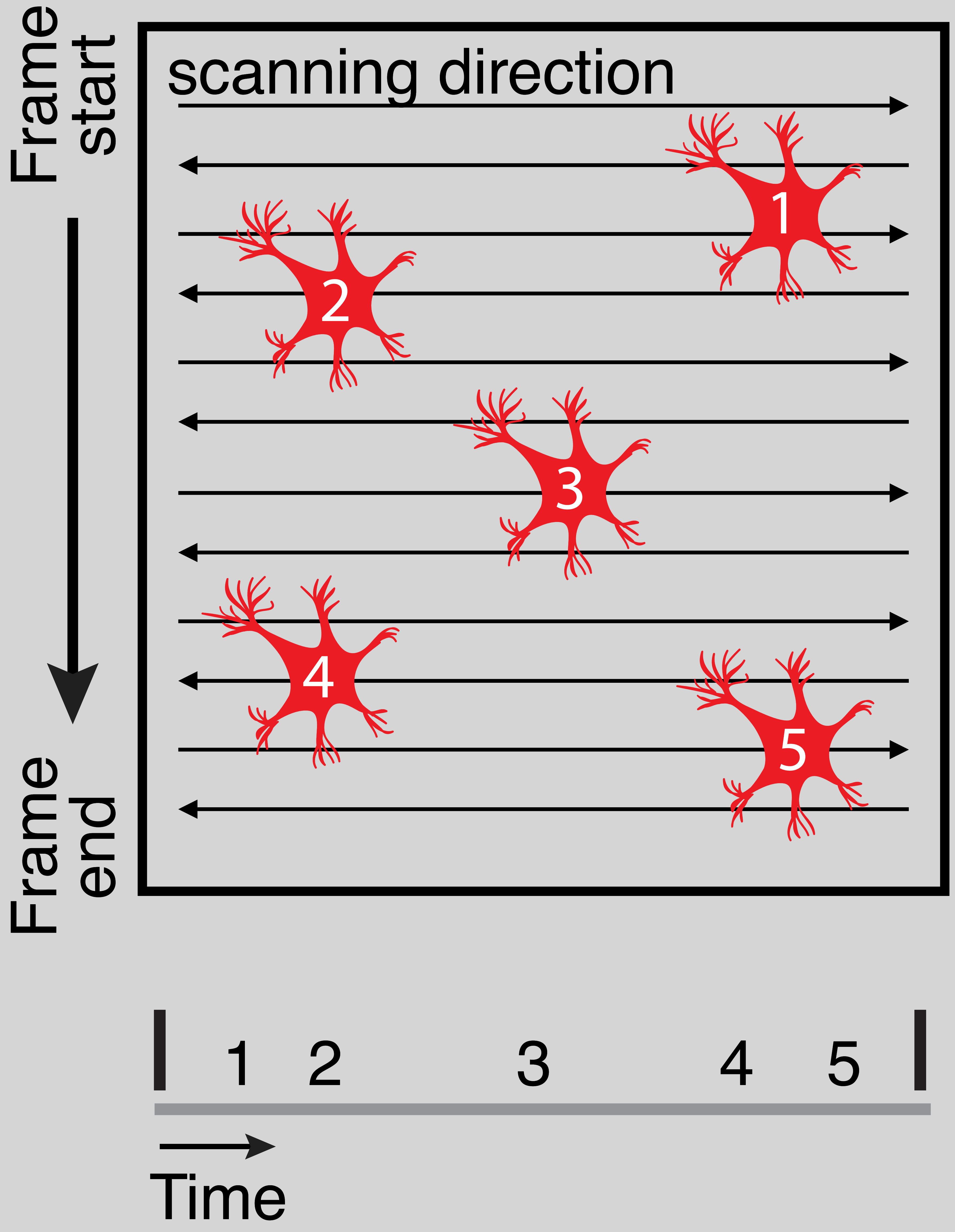


RADICaL
Zhu*, Sedler*… Pandarinath, *NeurIPS* 2021
Zhu … Giovannucci, Kaufman**, Pandarinath**
in revision; see BioRxiv

1 frame (32 ms)



wide bin - low temporal resolution

neurons	frame 1	frame 2	frame 3
1	1.28	0.23	0.59
2	0.26	2.02	0.19
3	0.65	0.42	0.97
4	1.54	1.22	0.66
5	0.14	0.89	1.20

Time

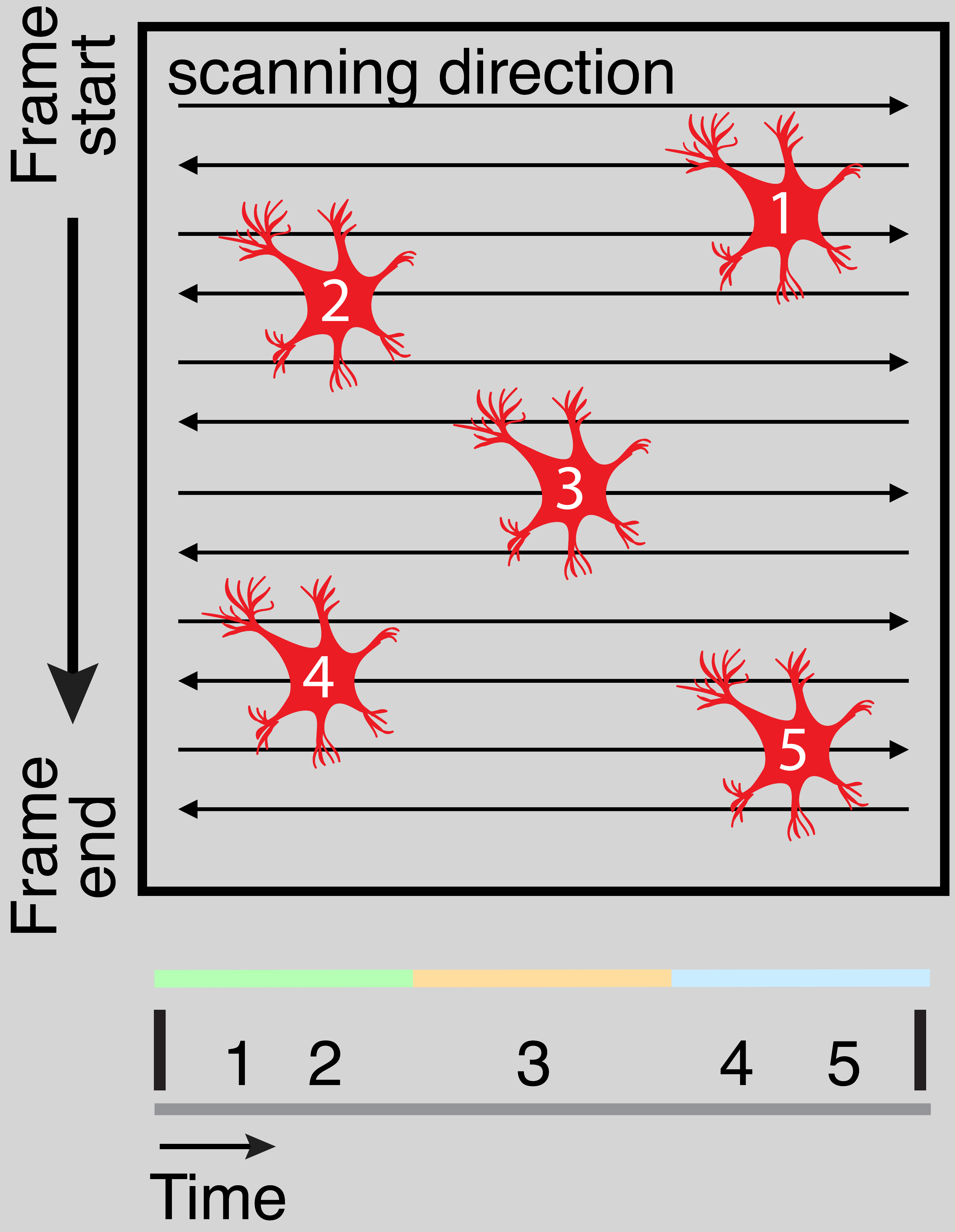
RADICaL

Zhu*, Sedler*… Pandarinath, *NeurIPS* 2021

Zhu … Giovannucci, Kaufman**, Pandarinath**

in revision; see BioRxiv

1 frame (32 ms)



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→ Time

narrow bin - high temporal resolution

neurons									
1	1.28			0.23			0.59		
2	0.26			2.02			0.19		
3		0.65			0.42			0.97	
4			1.54			1.22			0.66
5			0.14			0.89			1.20

RADICaL

Zhu*, Sedler*… Pandarinath, *NeurIPS* 2021

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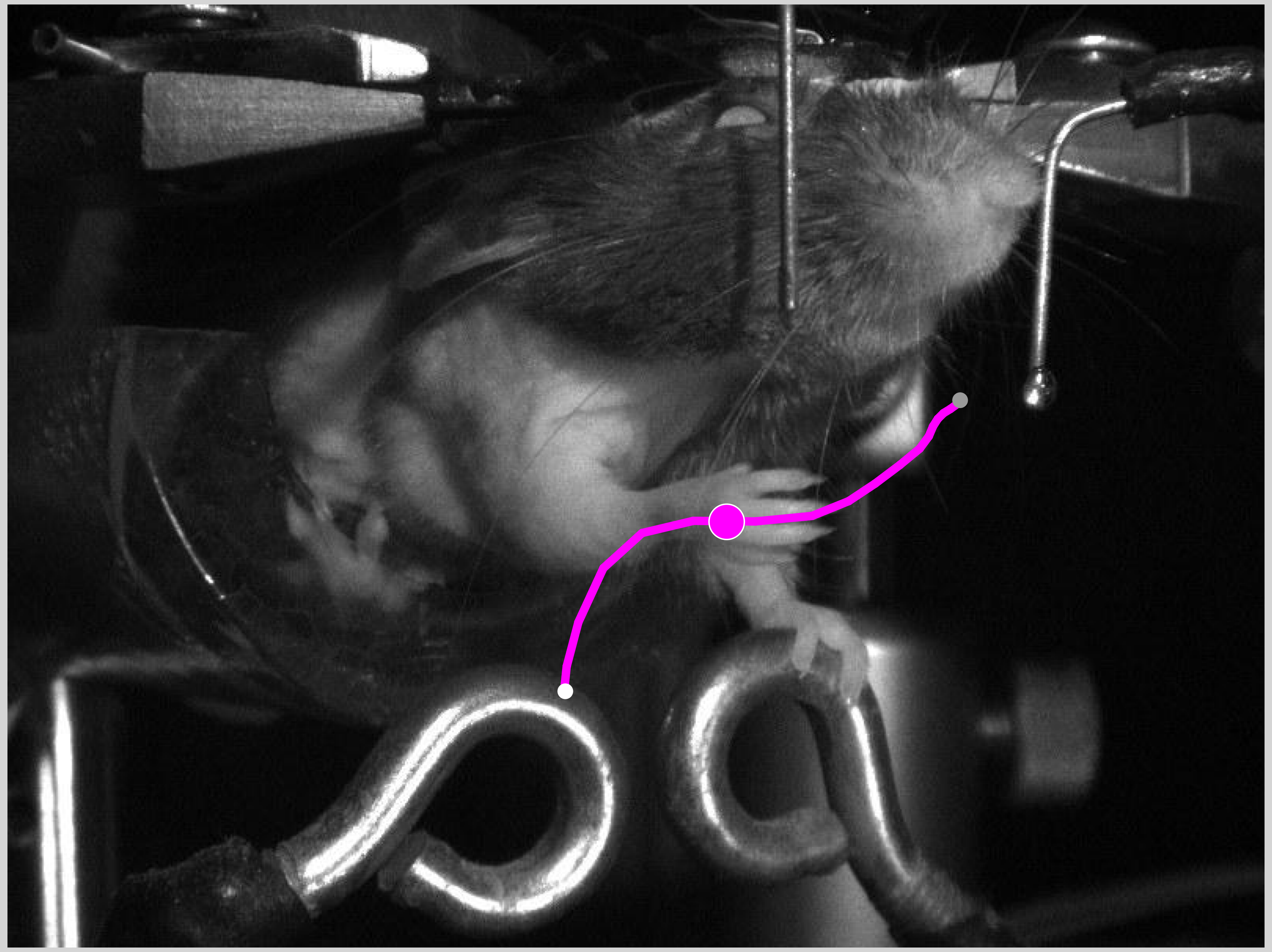
in revision; see BioRxiv

Two-spout water-grab task



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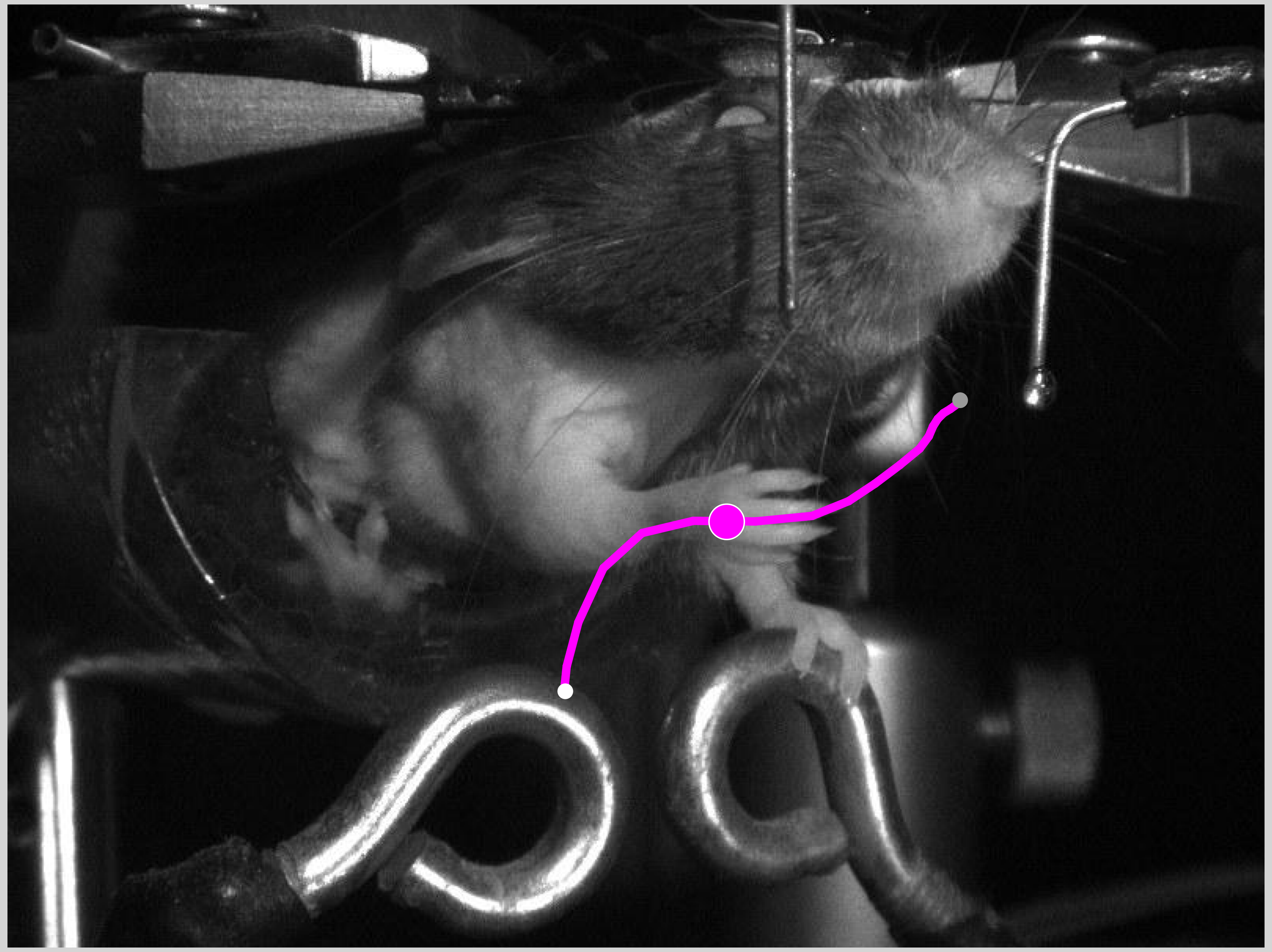
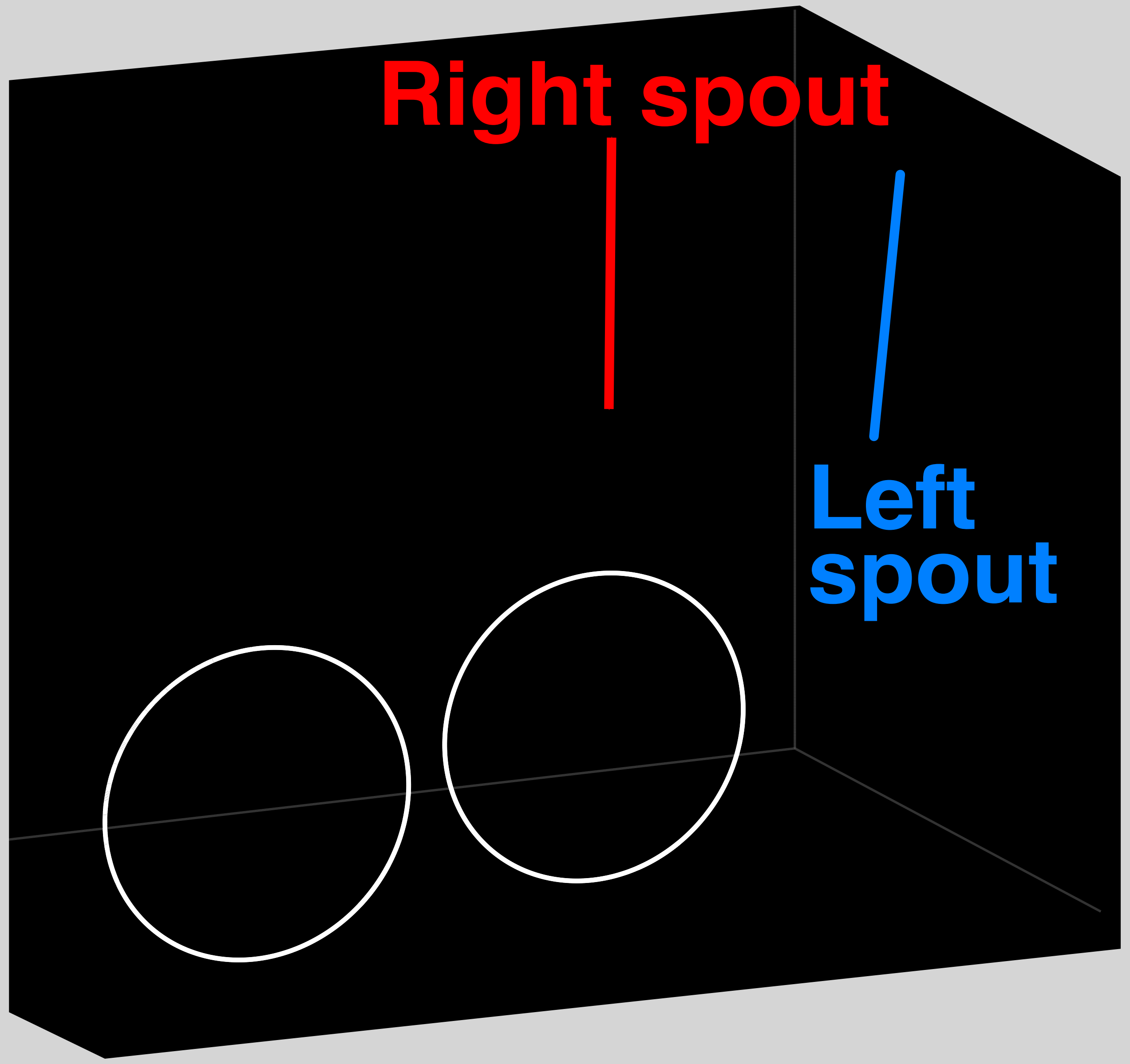


Subdivide trials into 4 conditions



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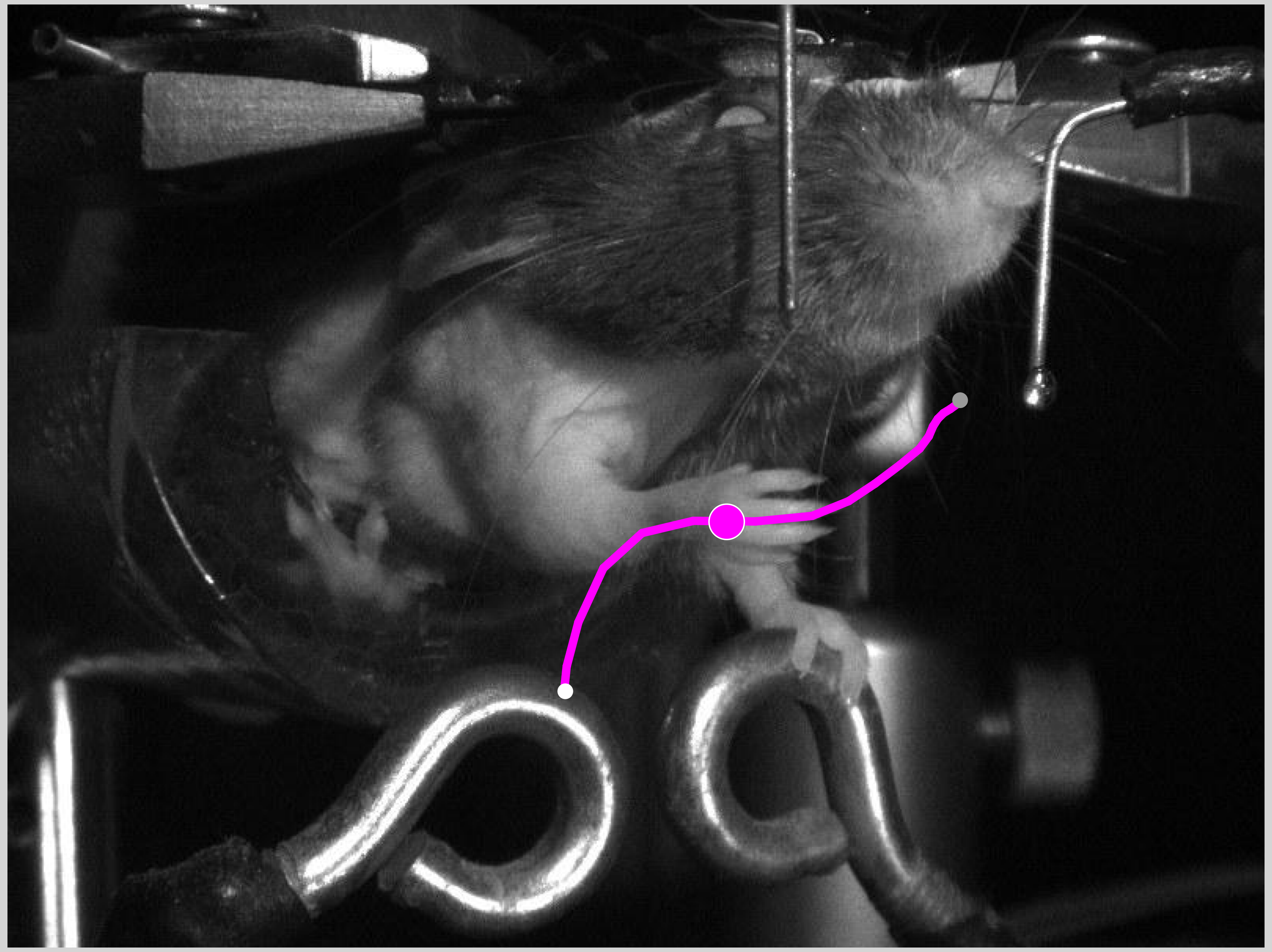

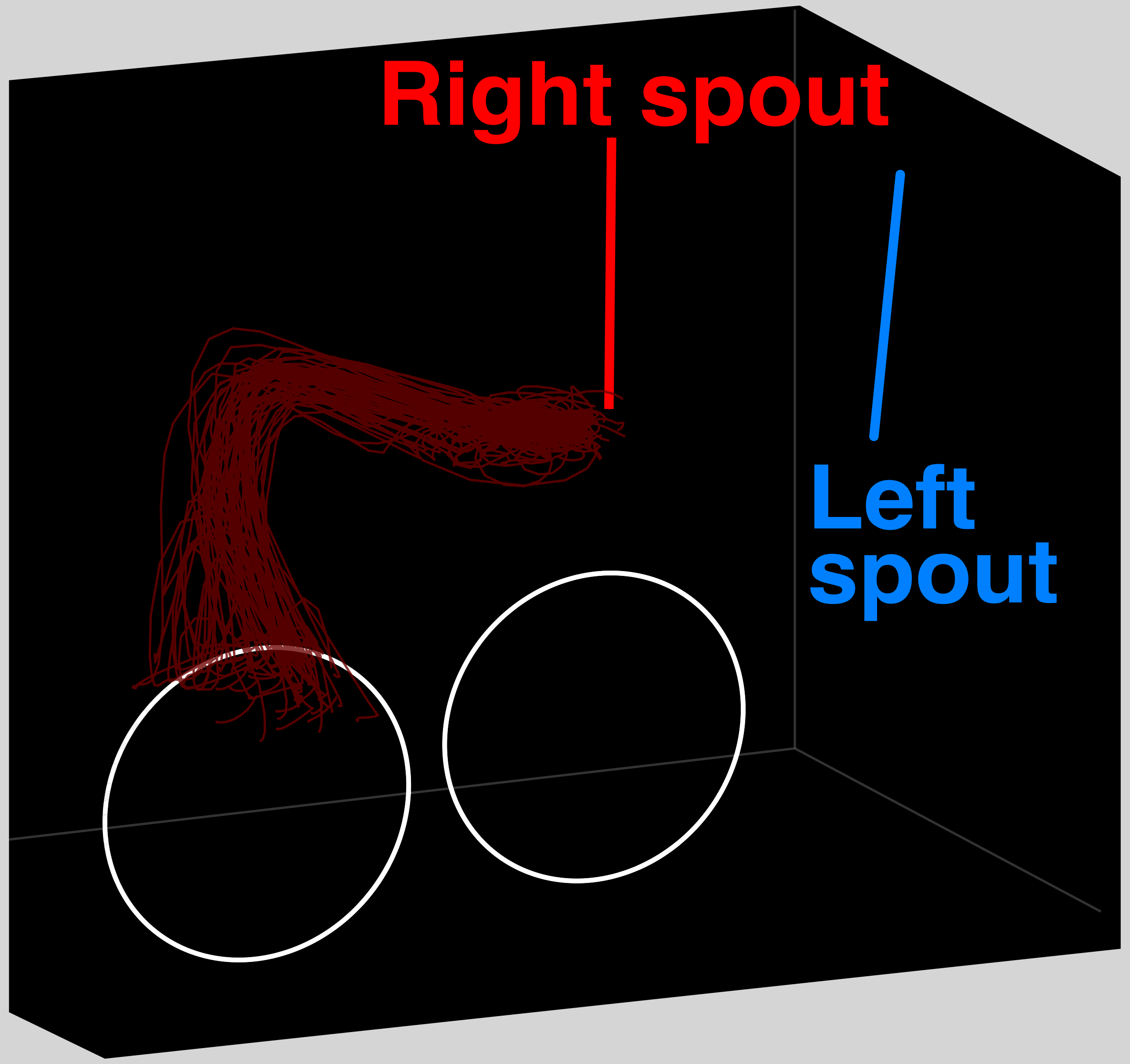

High right

RADICaL

Zhu*, Sedler*… Pandarinath, *NeurIPS* 2021

Zhu … Giovannucci, Kaufman**, Pandarinath**

in revision; see BioRxiv

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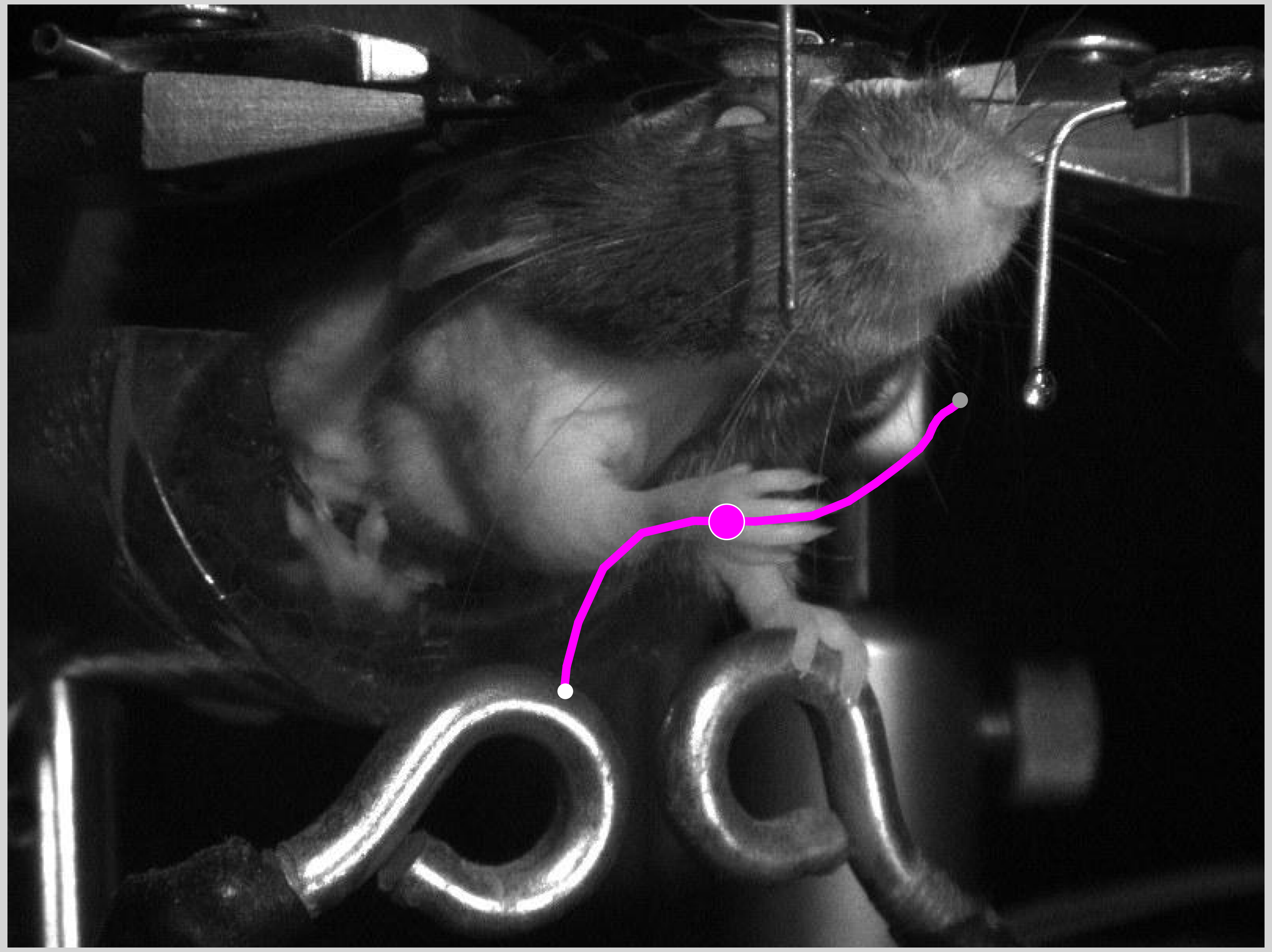

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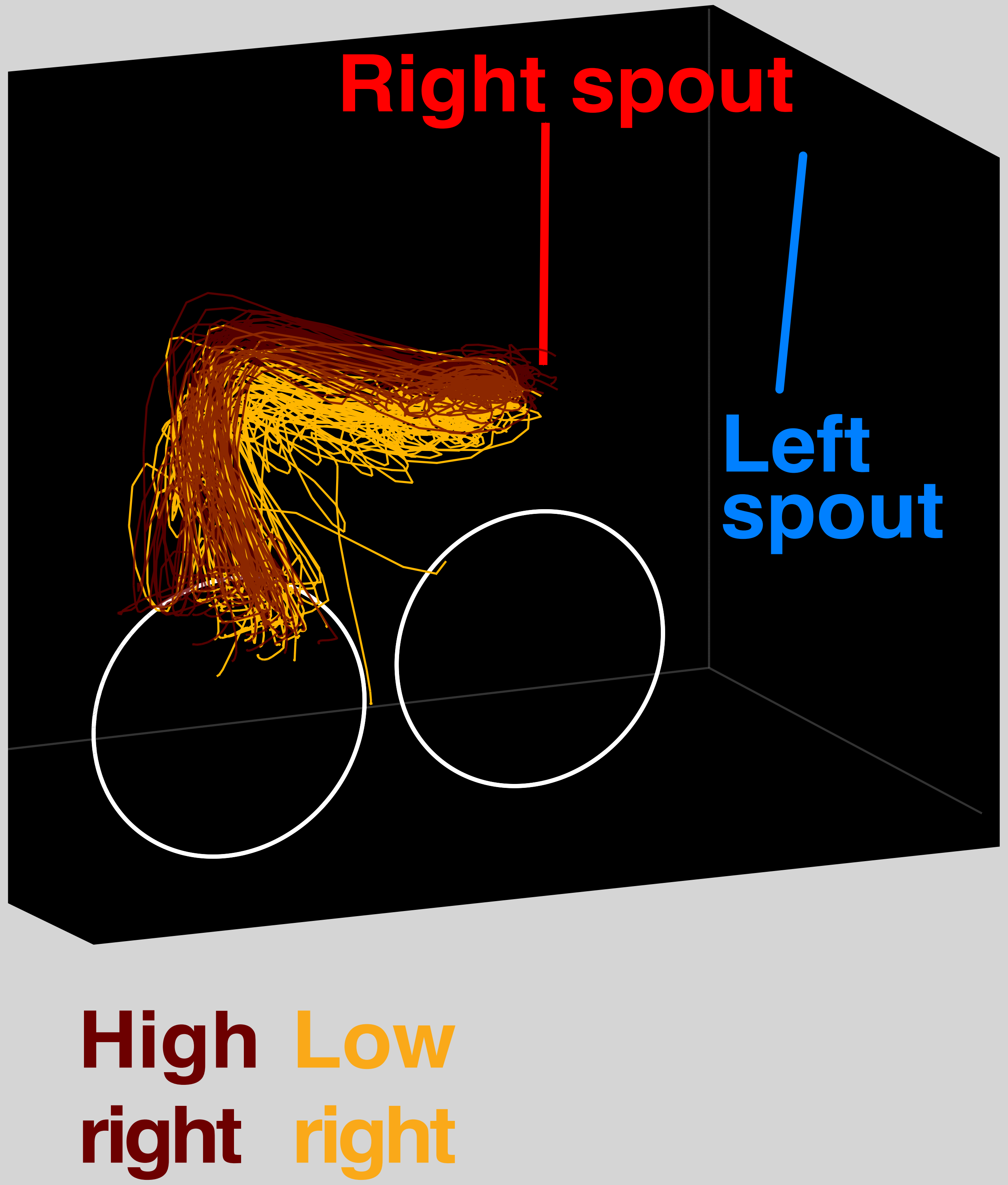

RADICaL
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Two-spout water-grab task

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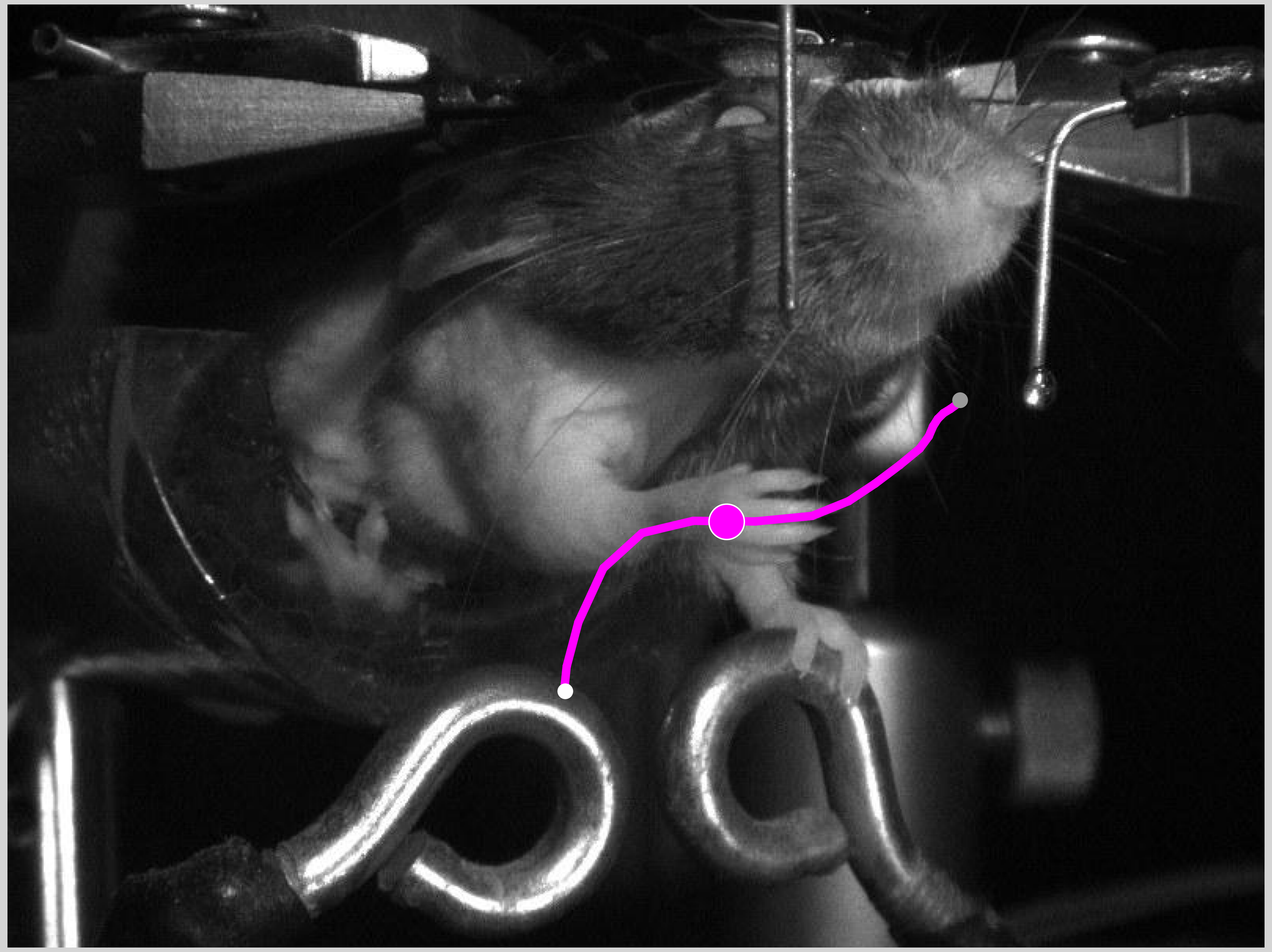

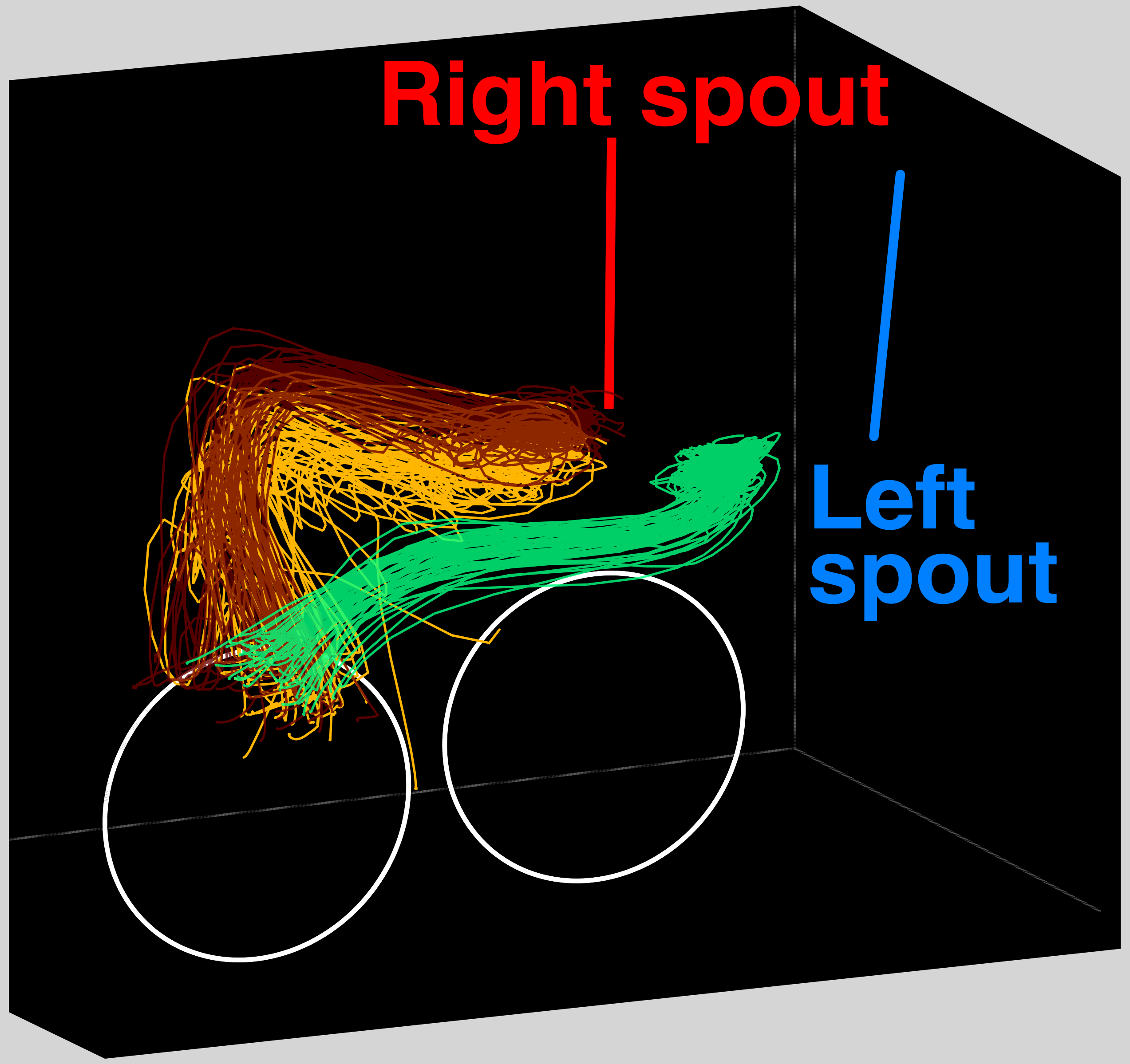

High right Low right High left

RADICaL

Zhu*, Sedler*… Pandarinath, *NeurIPS* 2021

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in revision; see BioRxiv

Two-spout water-grab task

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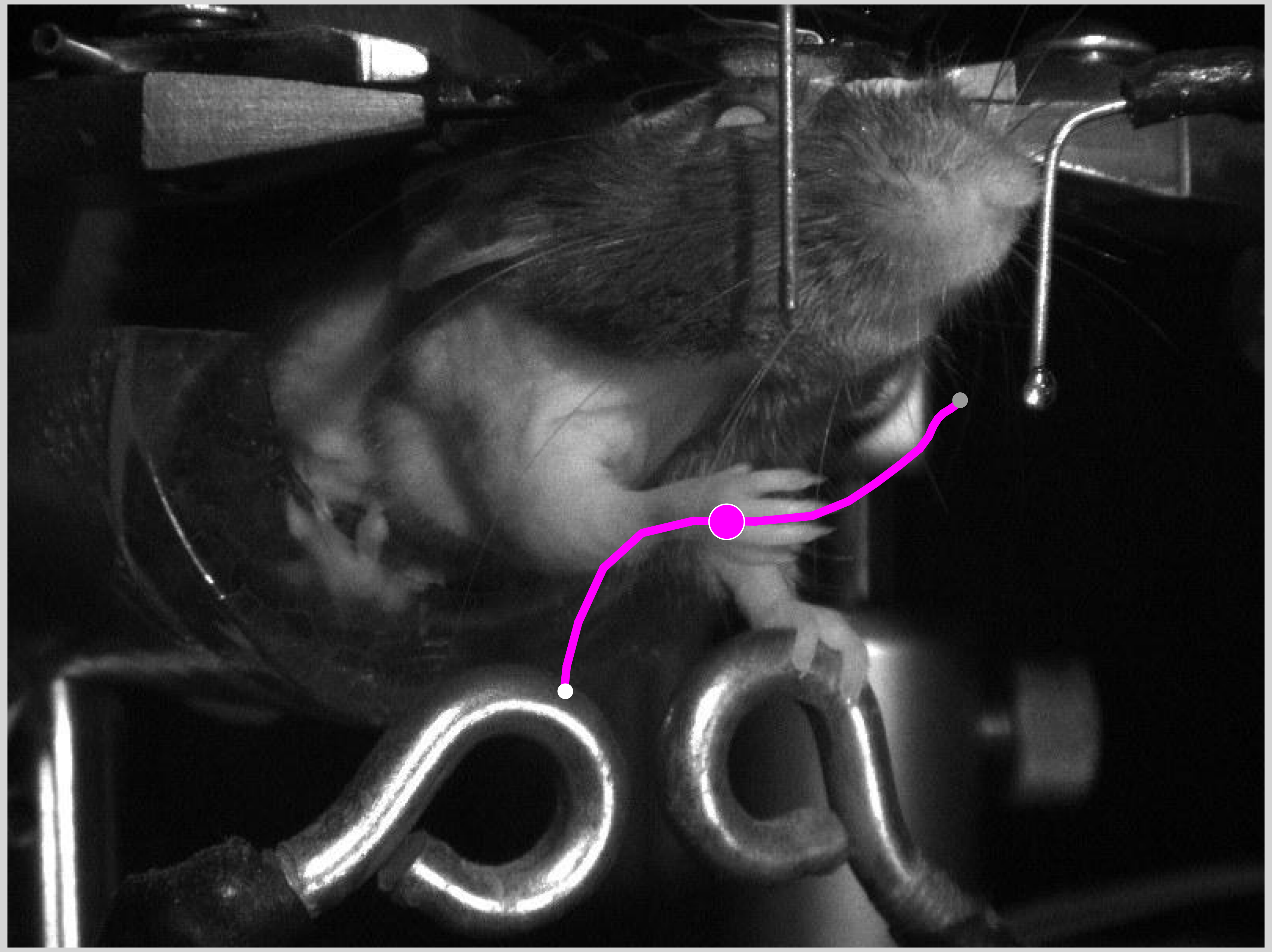

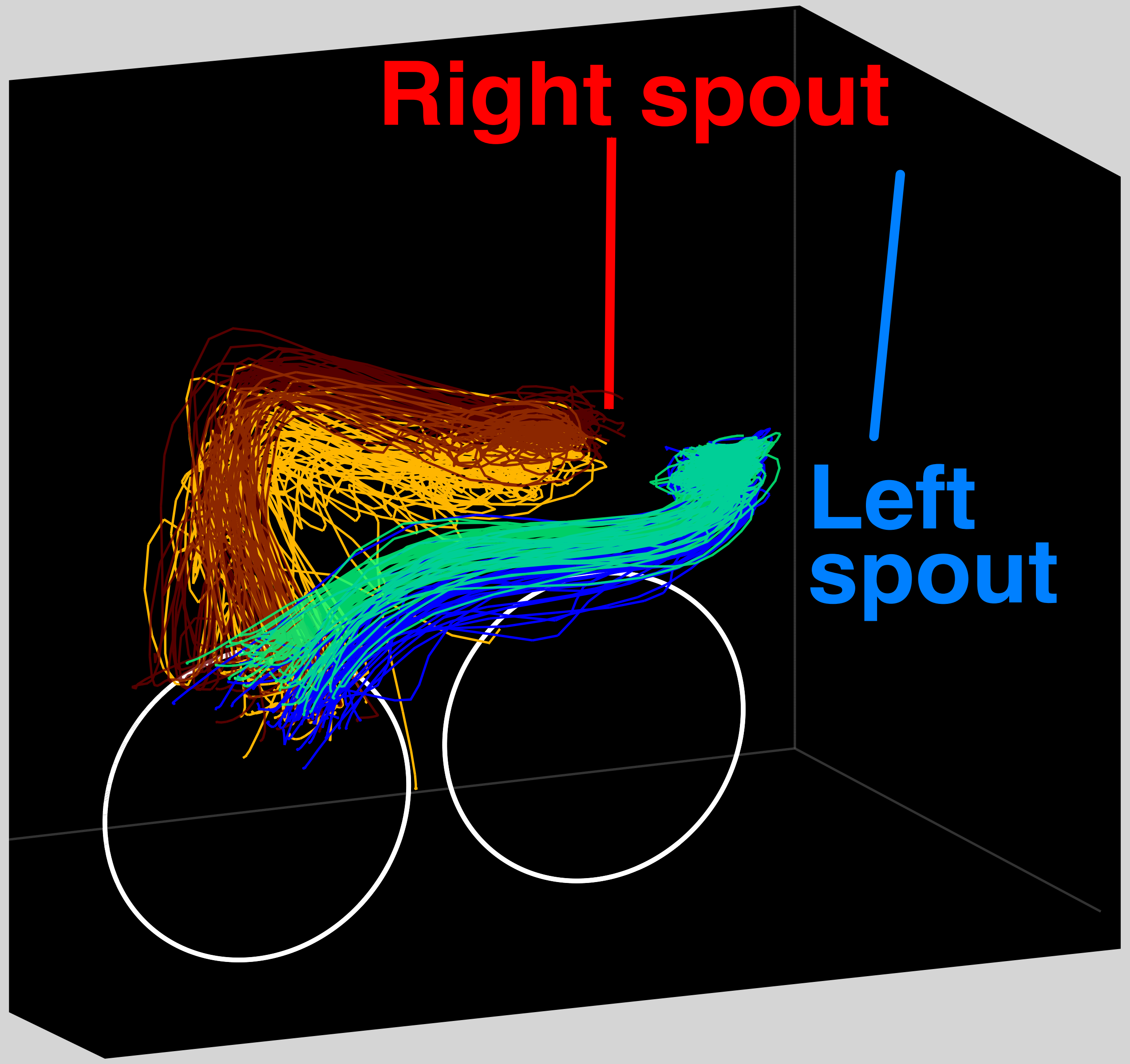

High right **Low right** **High left** **Low left**

RADICaL
Zhu*, Sedler*… Pandarinath, *NeurIPS* 2021
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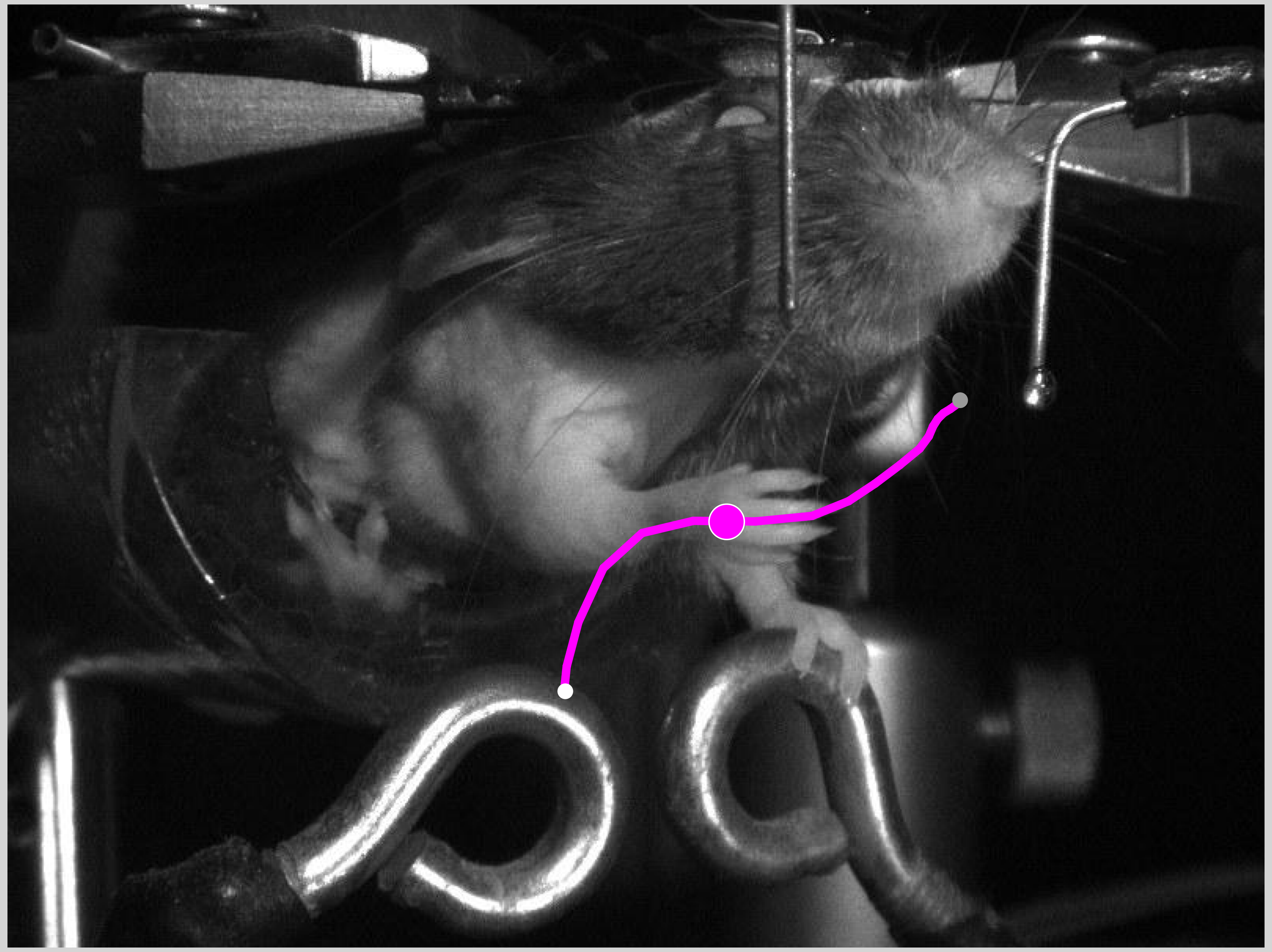

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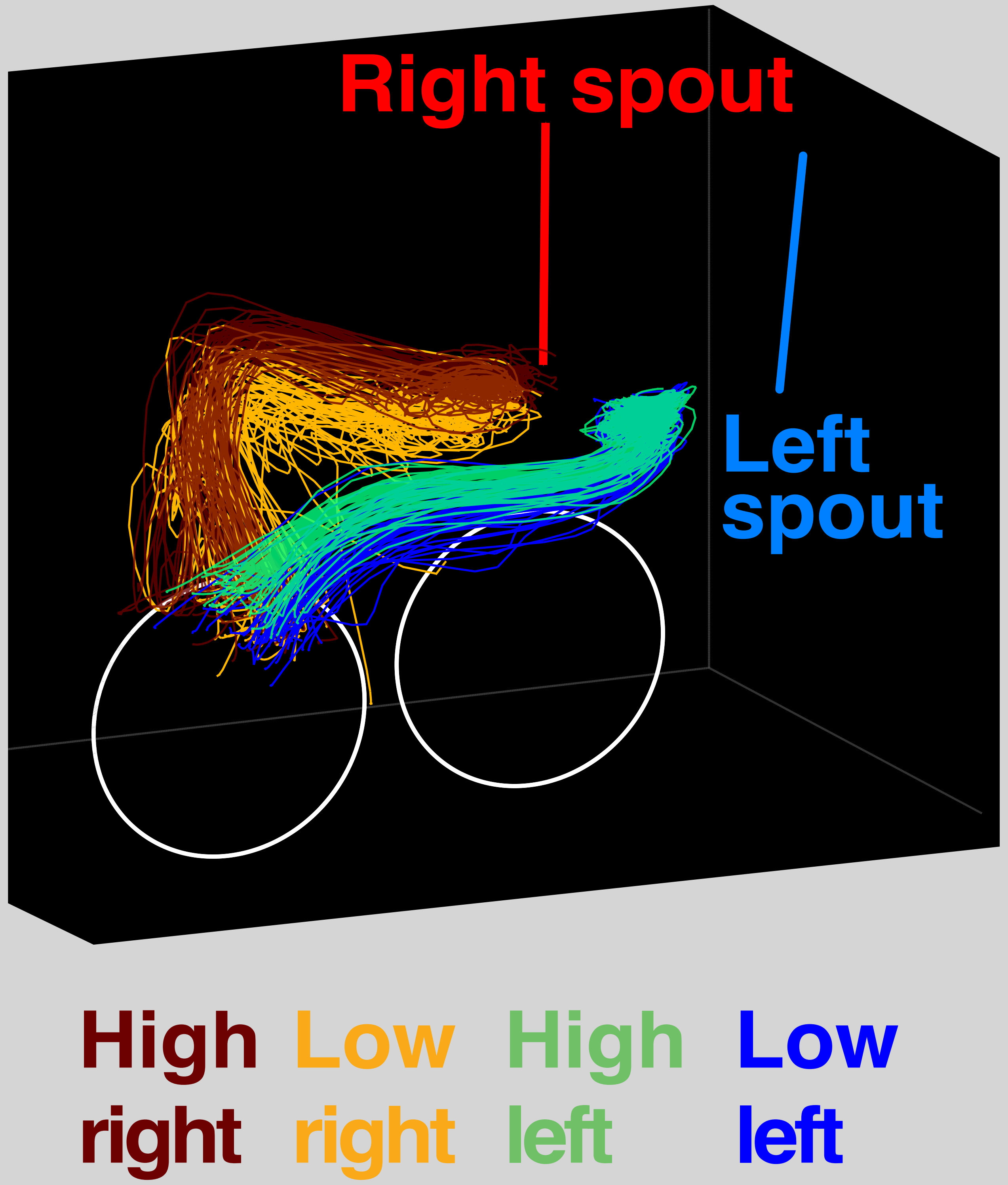
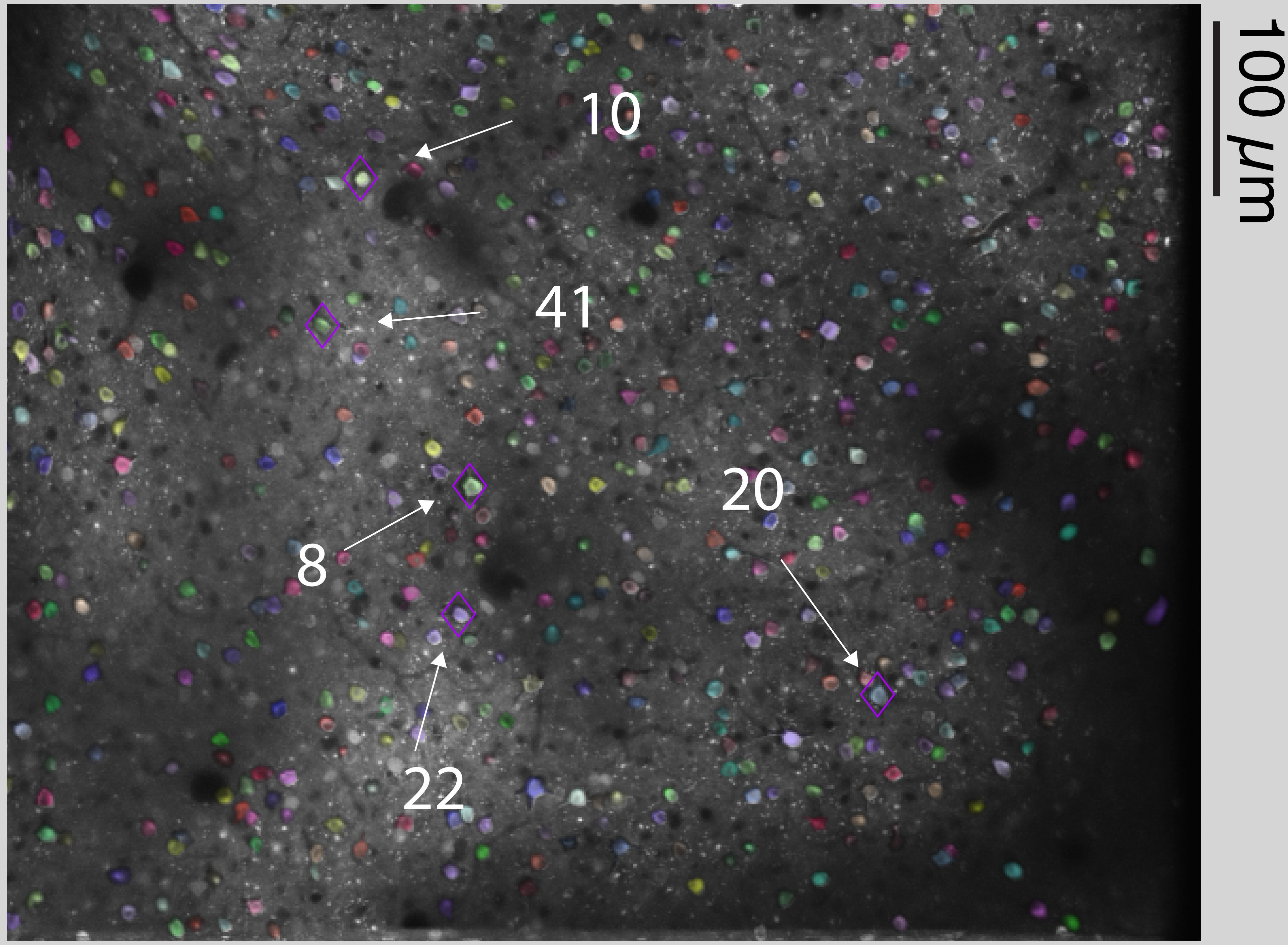


2P imaging in M1 or S1, 430-510 neurons per mouse



RADICaL

Zhu*, Sedler*… Pandarinath, *NeurIPS* 2021

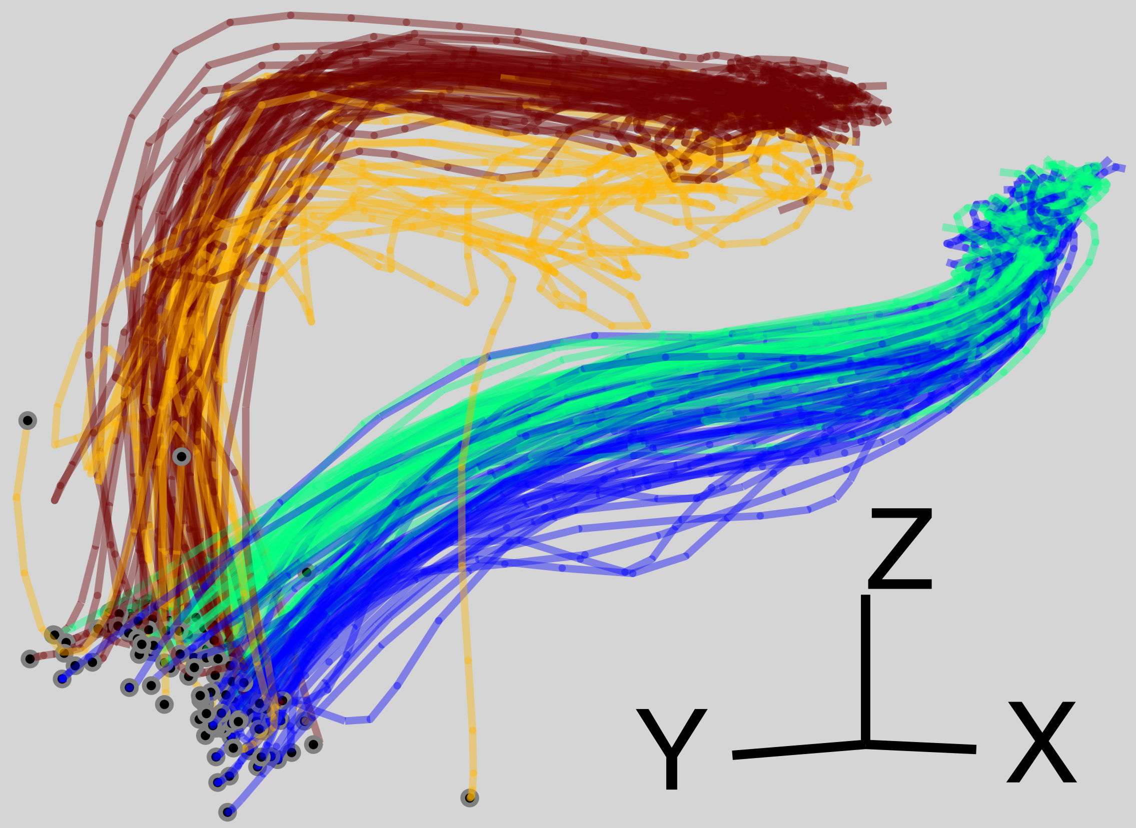
Zhu … Giovannucci, Kaufman**, Pandarinath**
in revision; see BioRxiv

Decoding single-trial hand trajectories

High right Low right High left Low left

Mouse1/M1

True



RADICaL

Zhu*, Sedler*… Pandarinath, *NeurIPS* 2021

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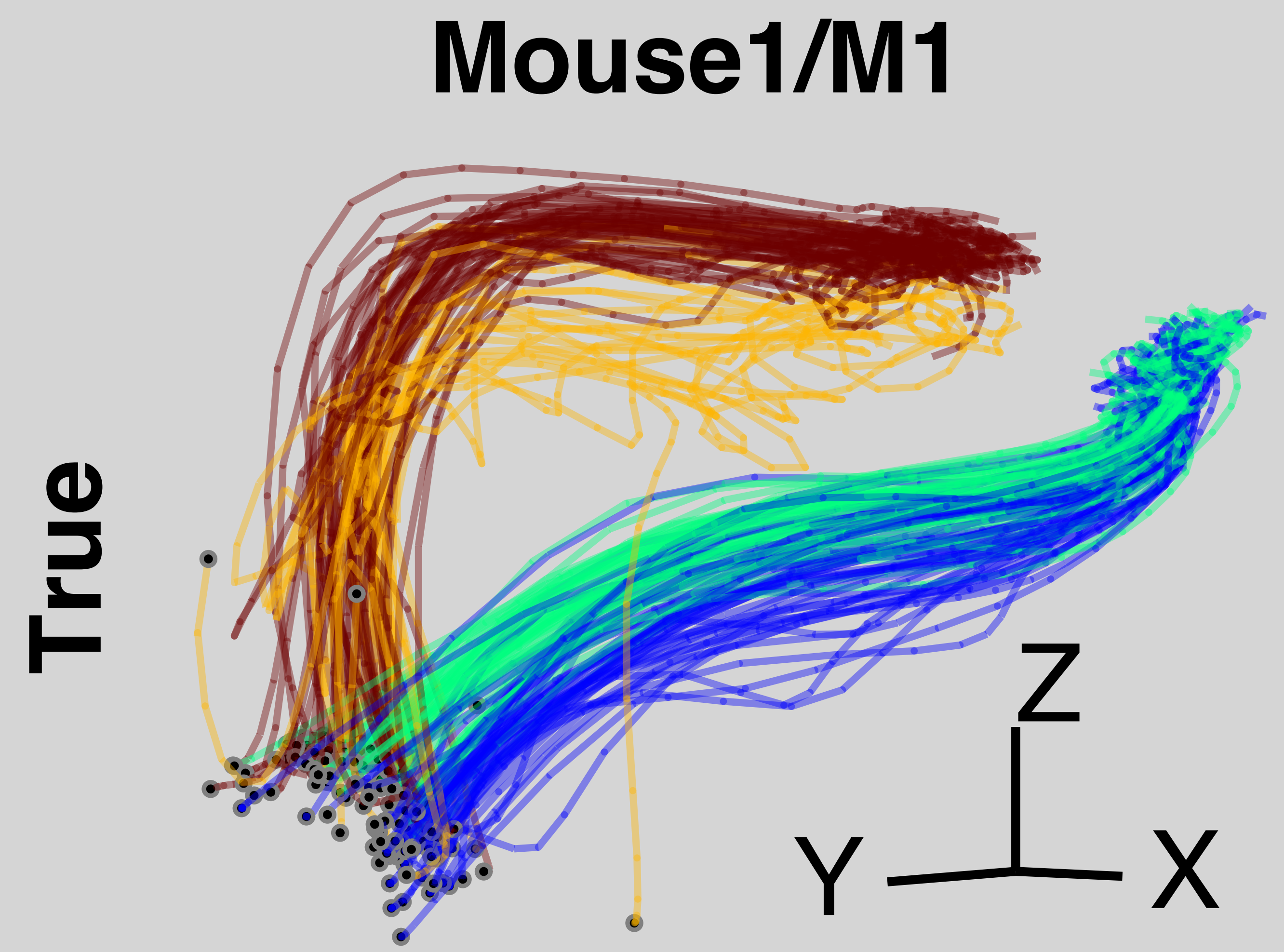
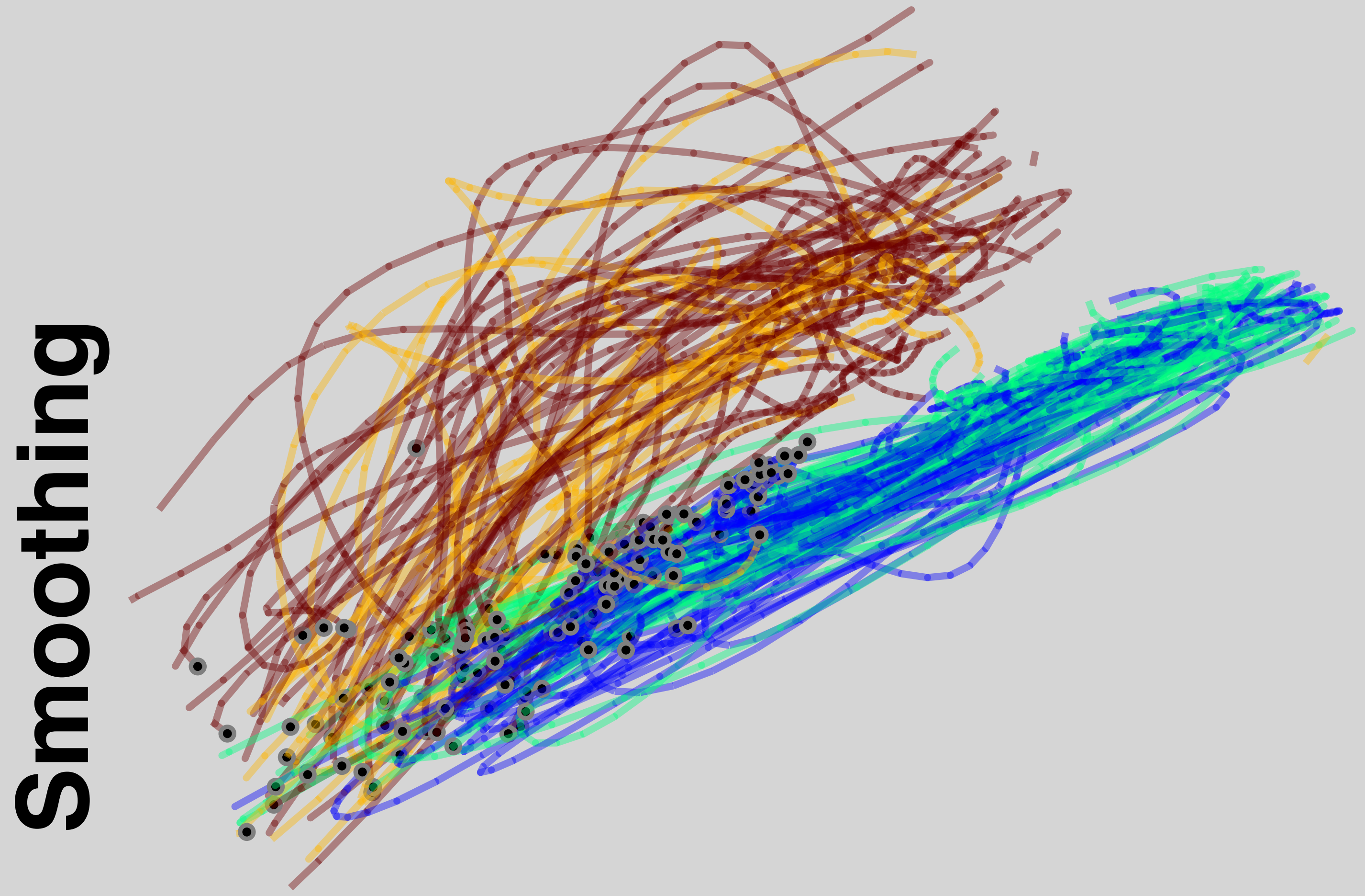
in revision; see BioRxiv

Decoding single-trial hand trajectories

High right · Low right · High left · Low left





RADICaL

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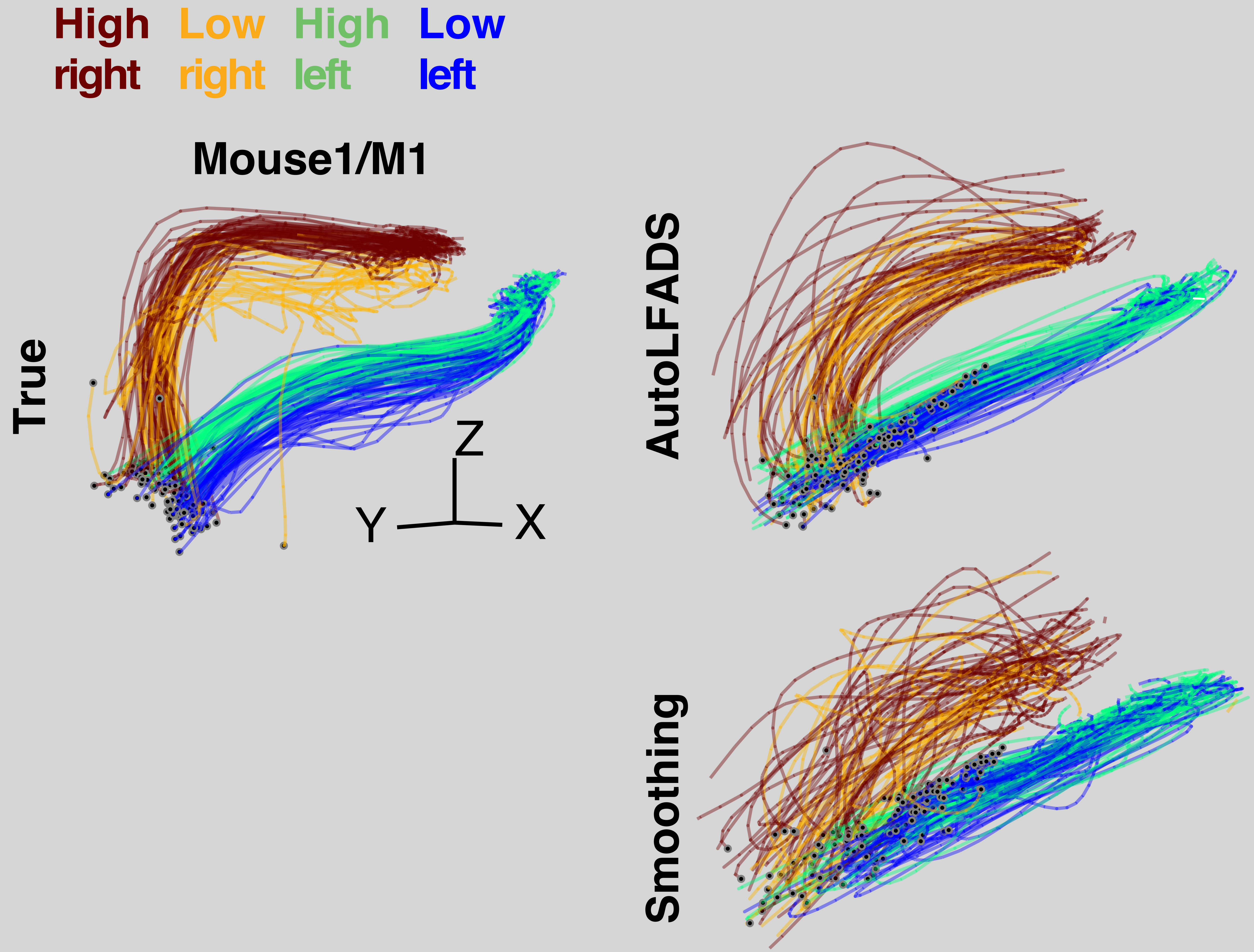

RADICaL

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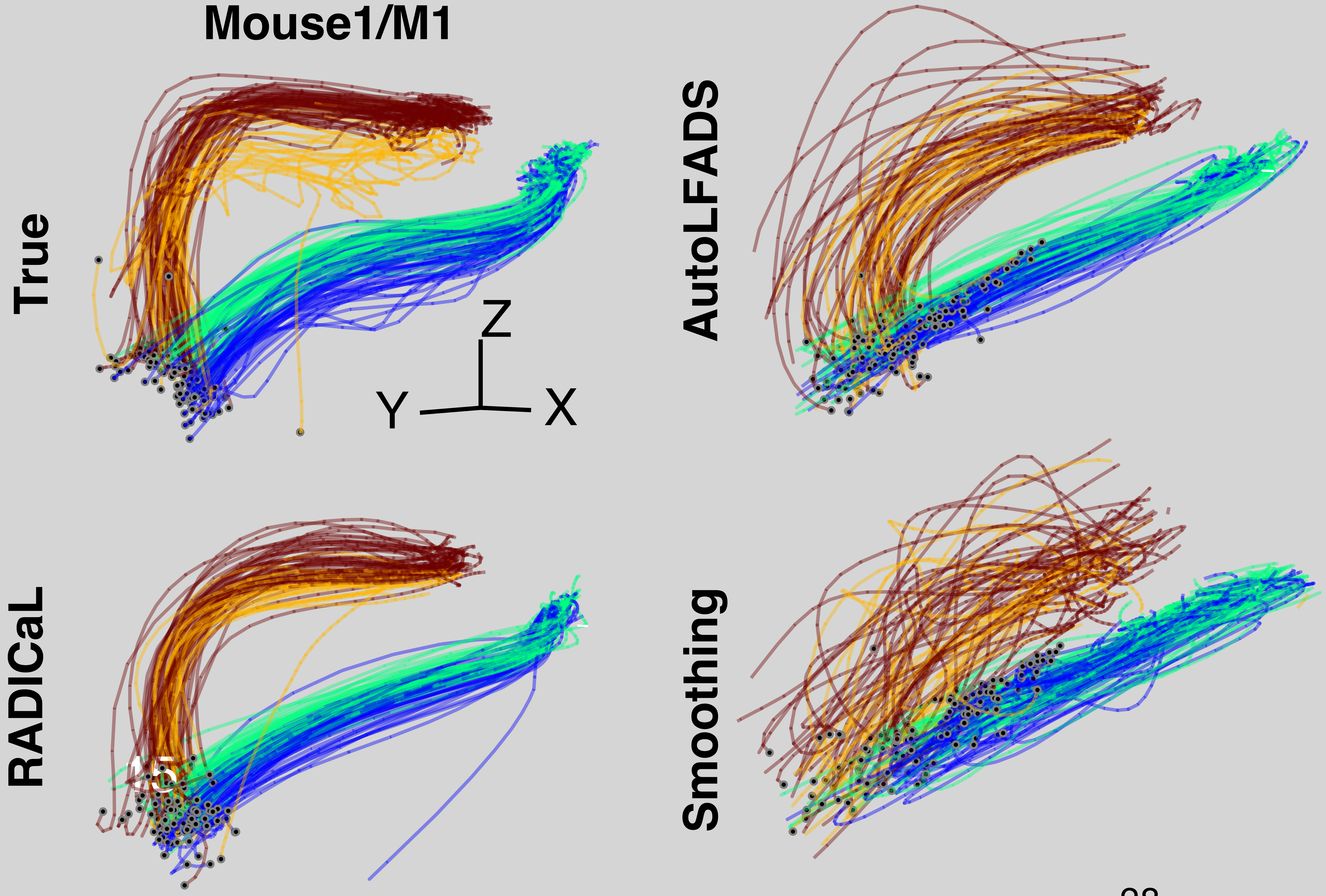
in revision; see BioRxiv

Decoding single-trial hand trajectories

High right   Low right   High left   Low left



RADICaL
Zhu*, Sedler*… Pandarinath, *NeurIPS* 2021
Zhu … Giovannucci, Kaufman**, Pandarinath**
in revision; see BioRxiv

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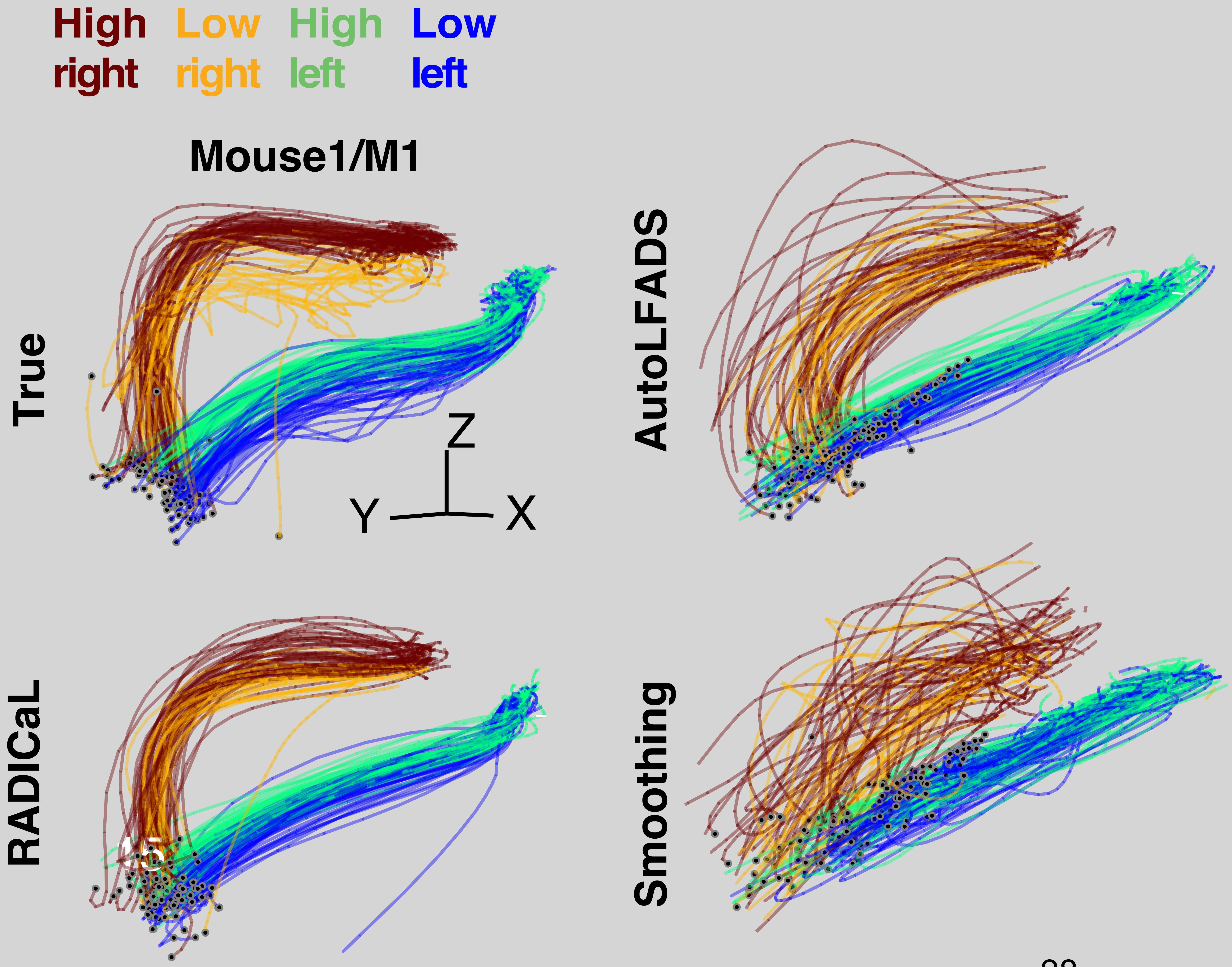

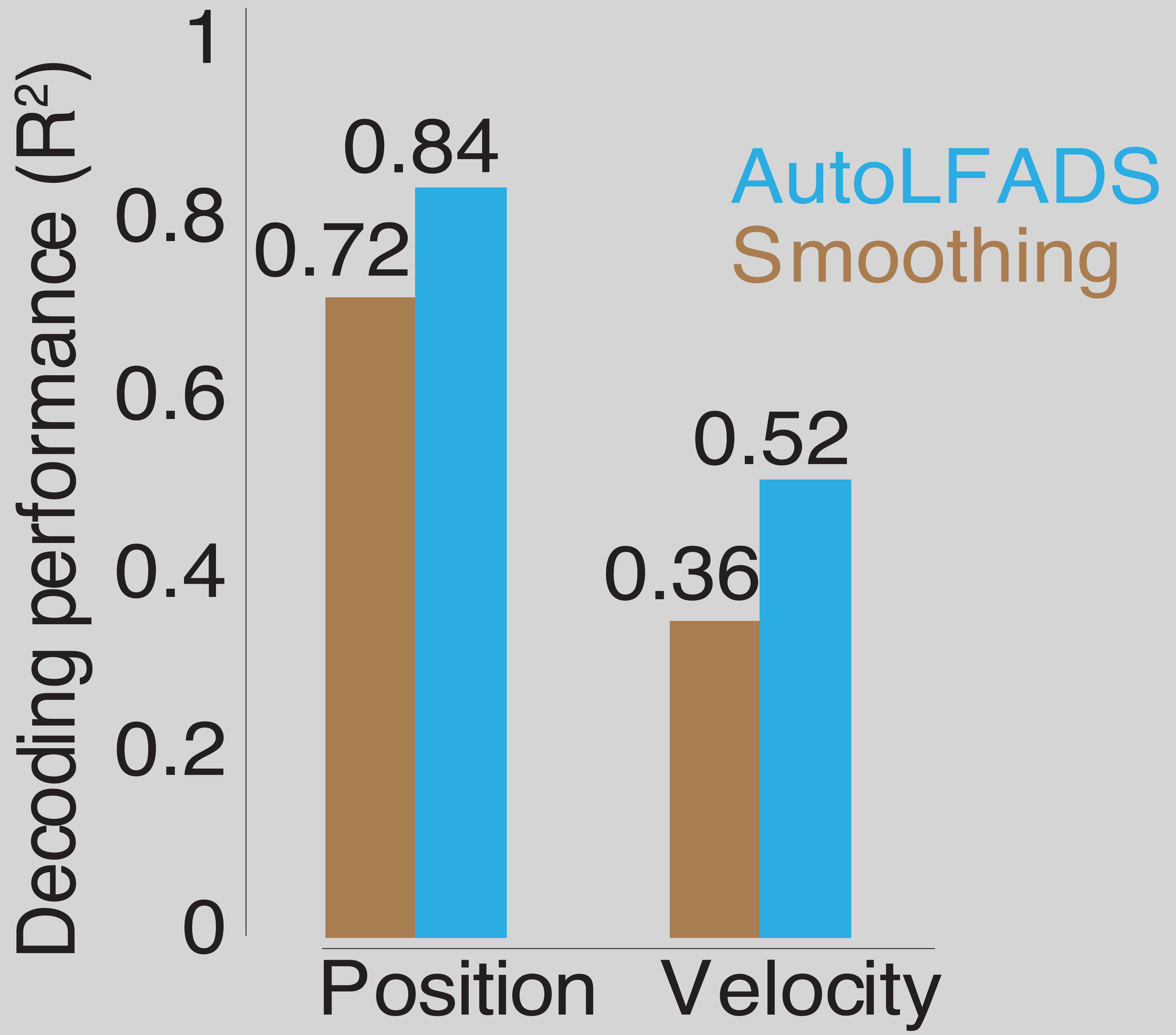

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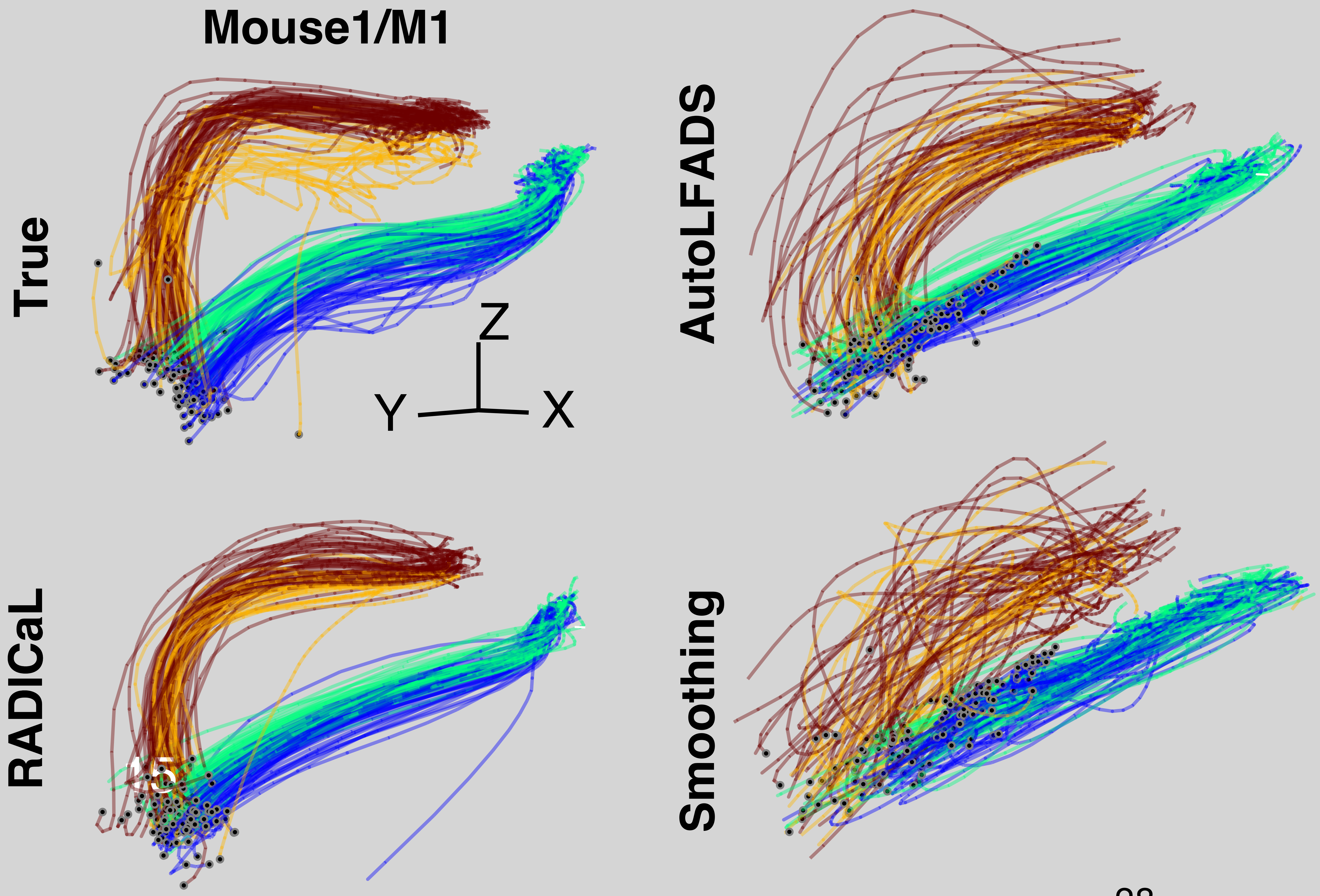

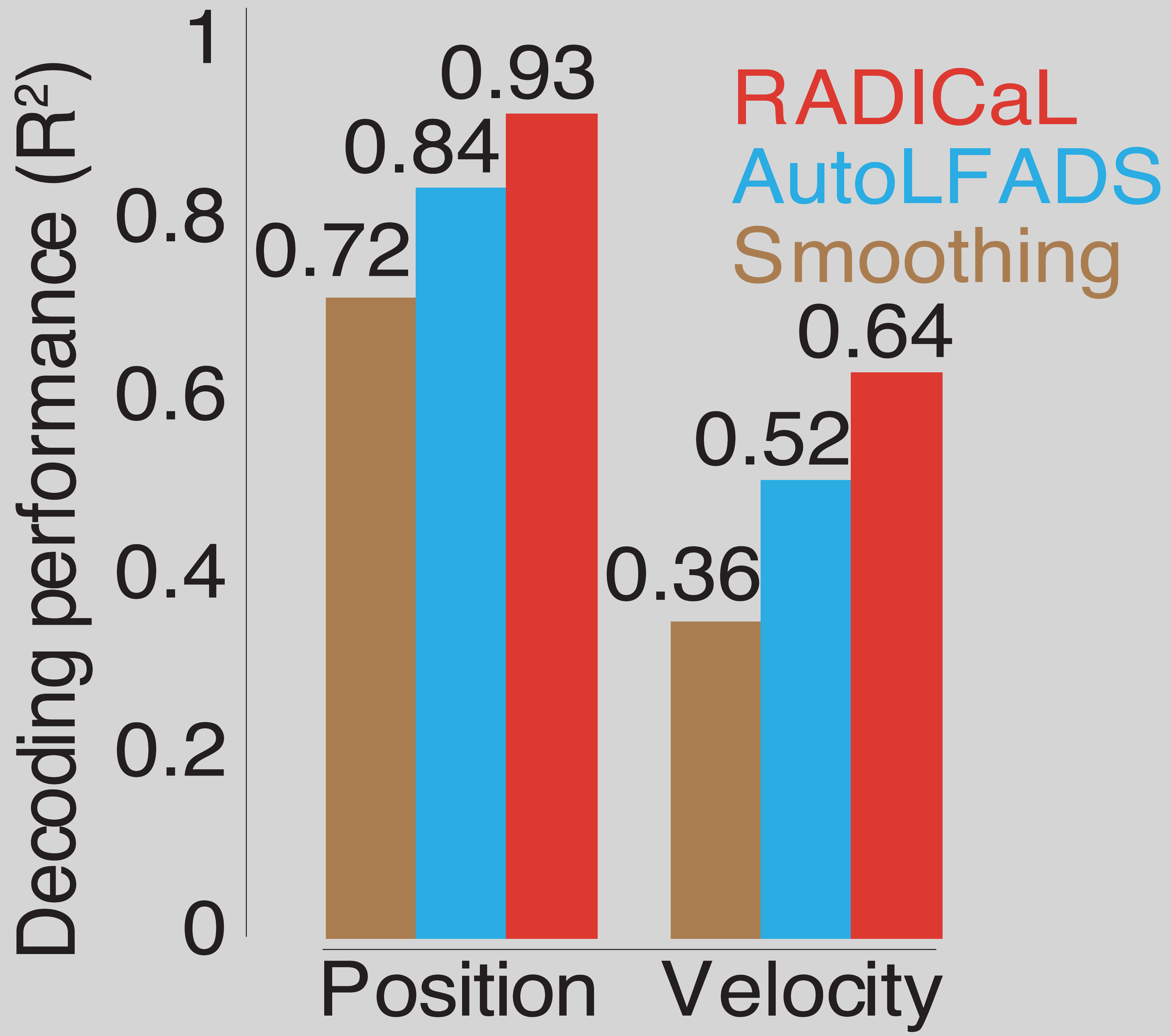

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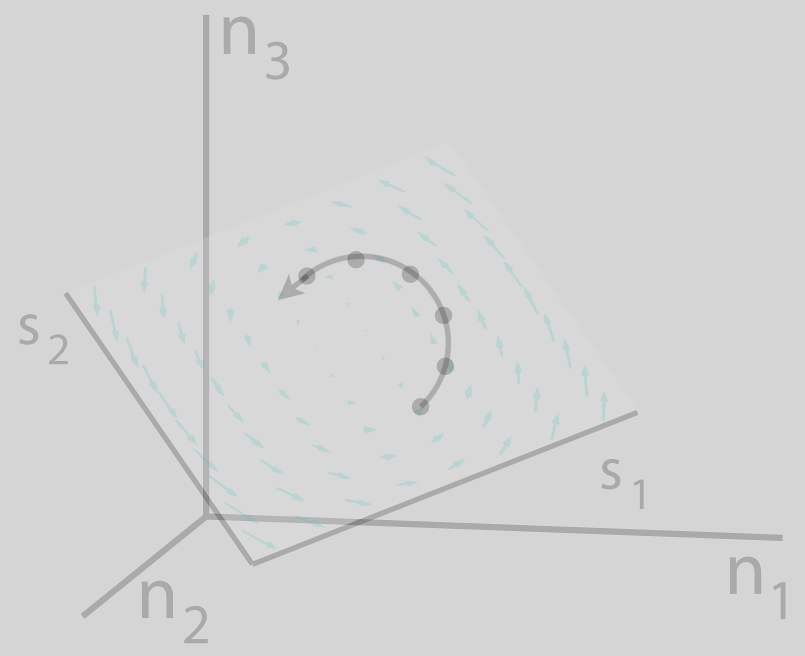
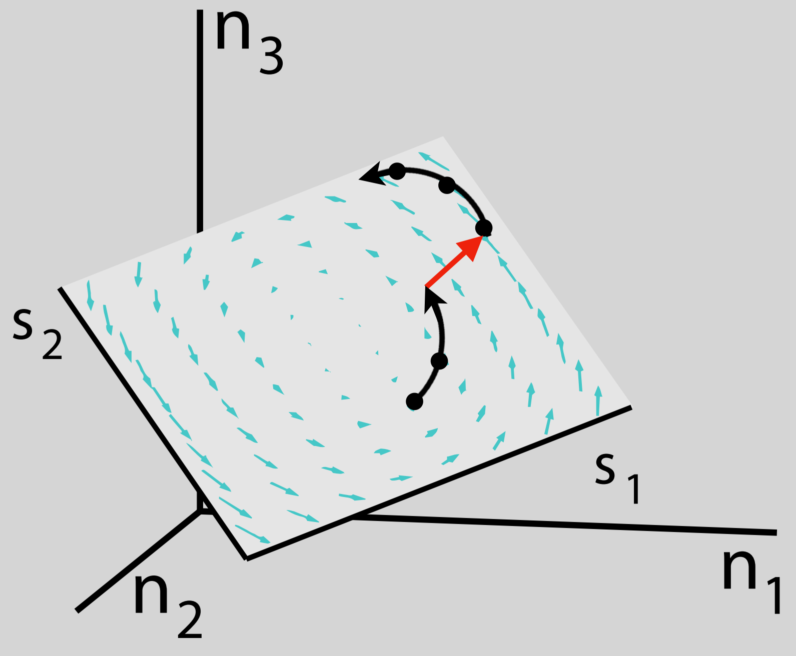
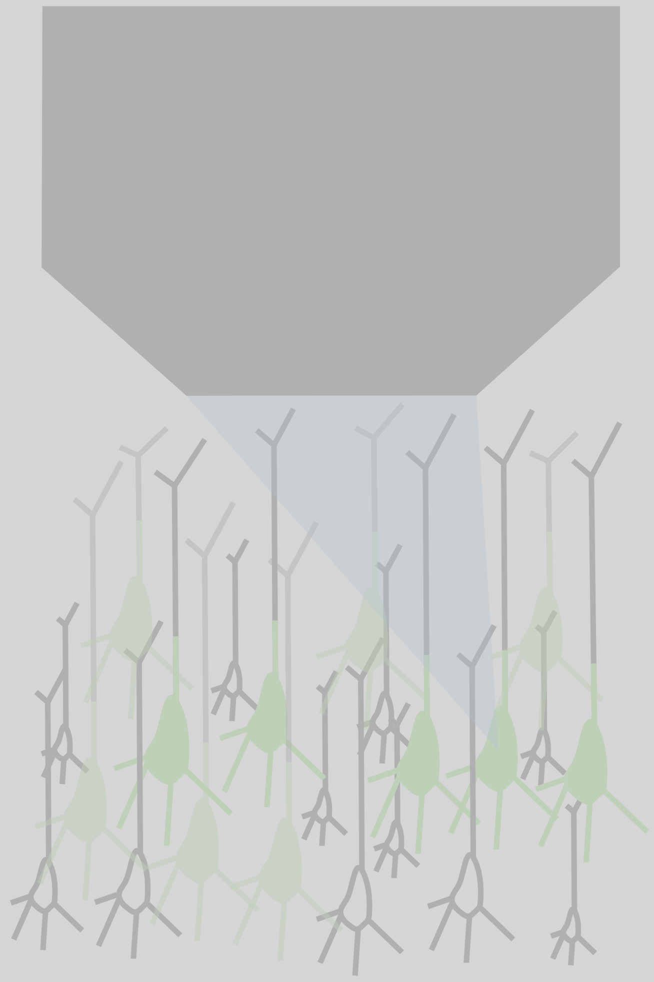
ML methods to uncover single-trial population dynamics



Predictable neural activity: modeling autonomous dynamics with LFADS



Unpredictable activity: non-autonomous dynamics and AutoLFADS



Applications to 2P Ca imaging: RADICaL

Applications to cognitive data

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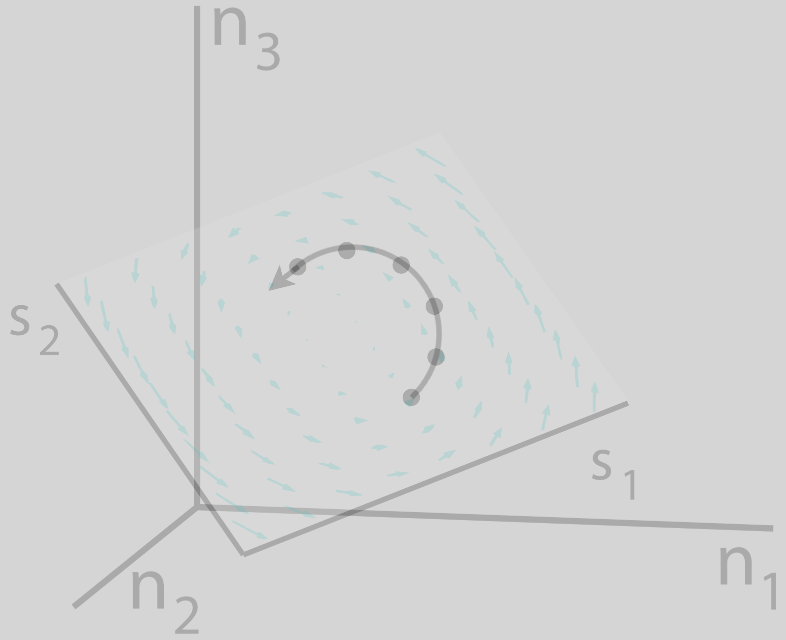

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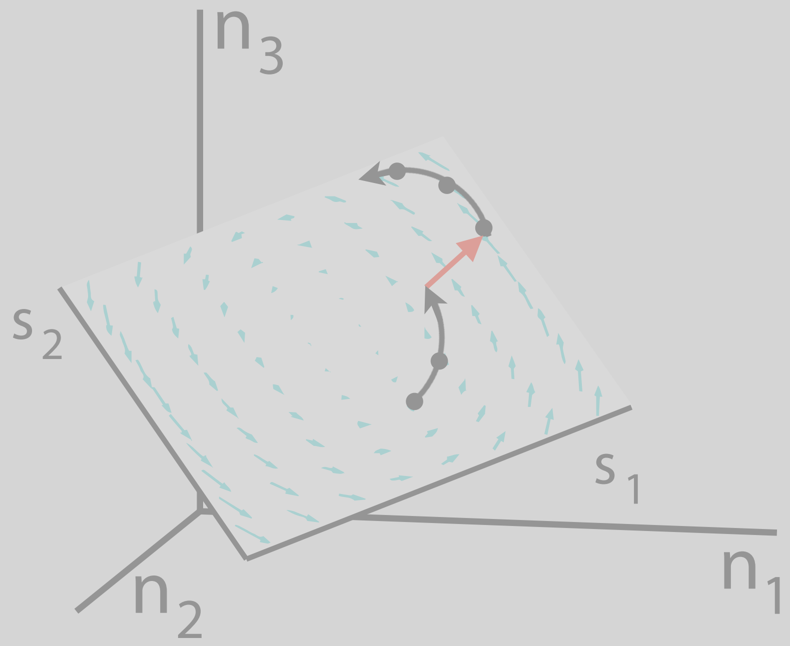

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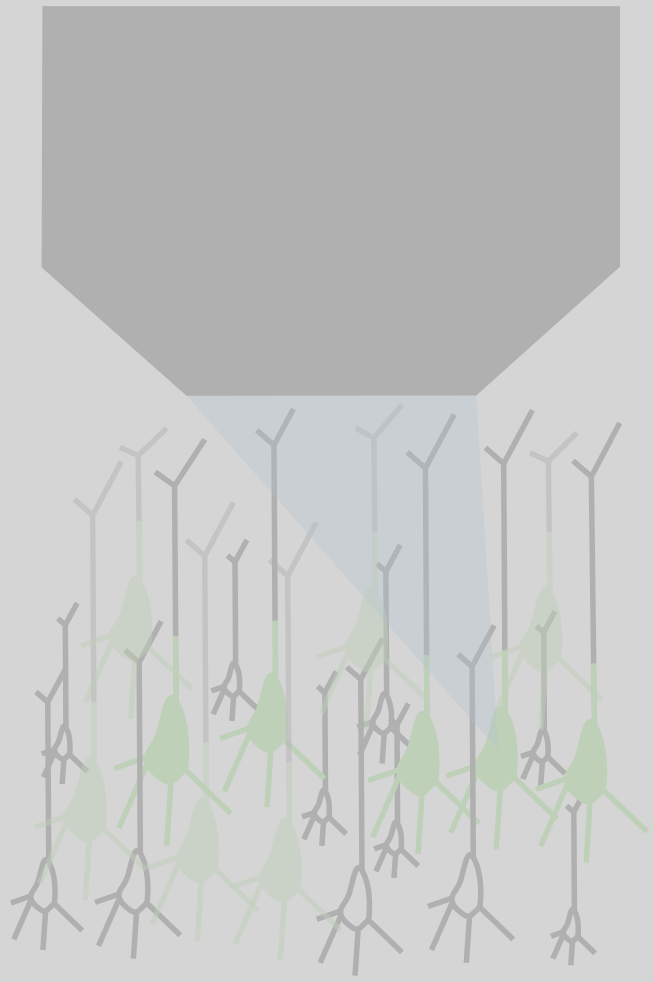
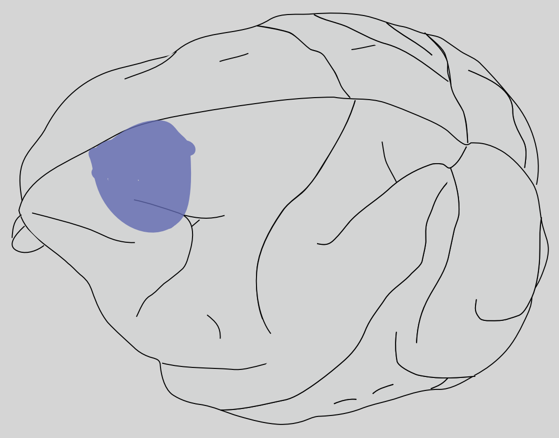
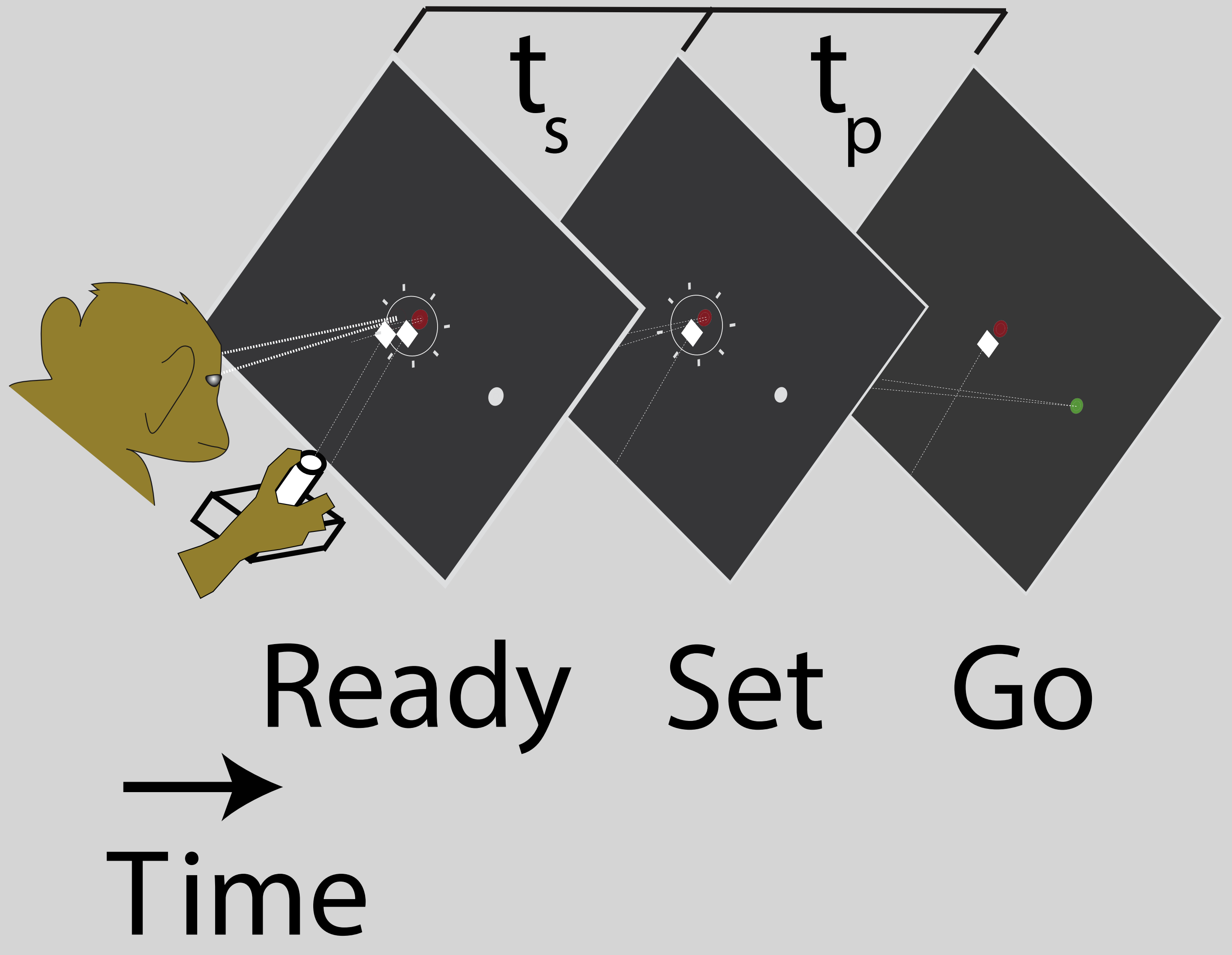


Applications to 2P Ca imaging: RADICaL

Applications to cognitive data

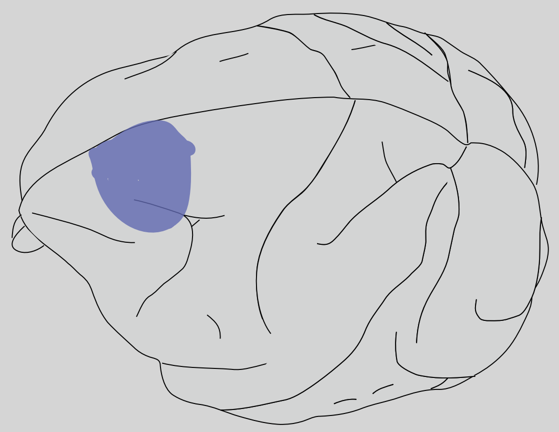
Ready-set-go task (Jazayeri lab, MIT)

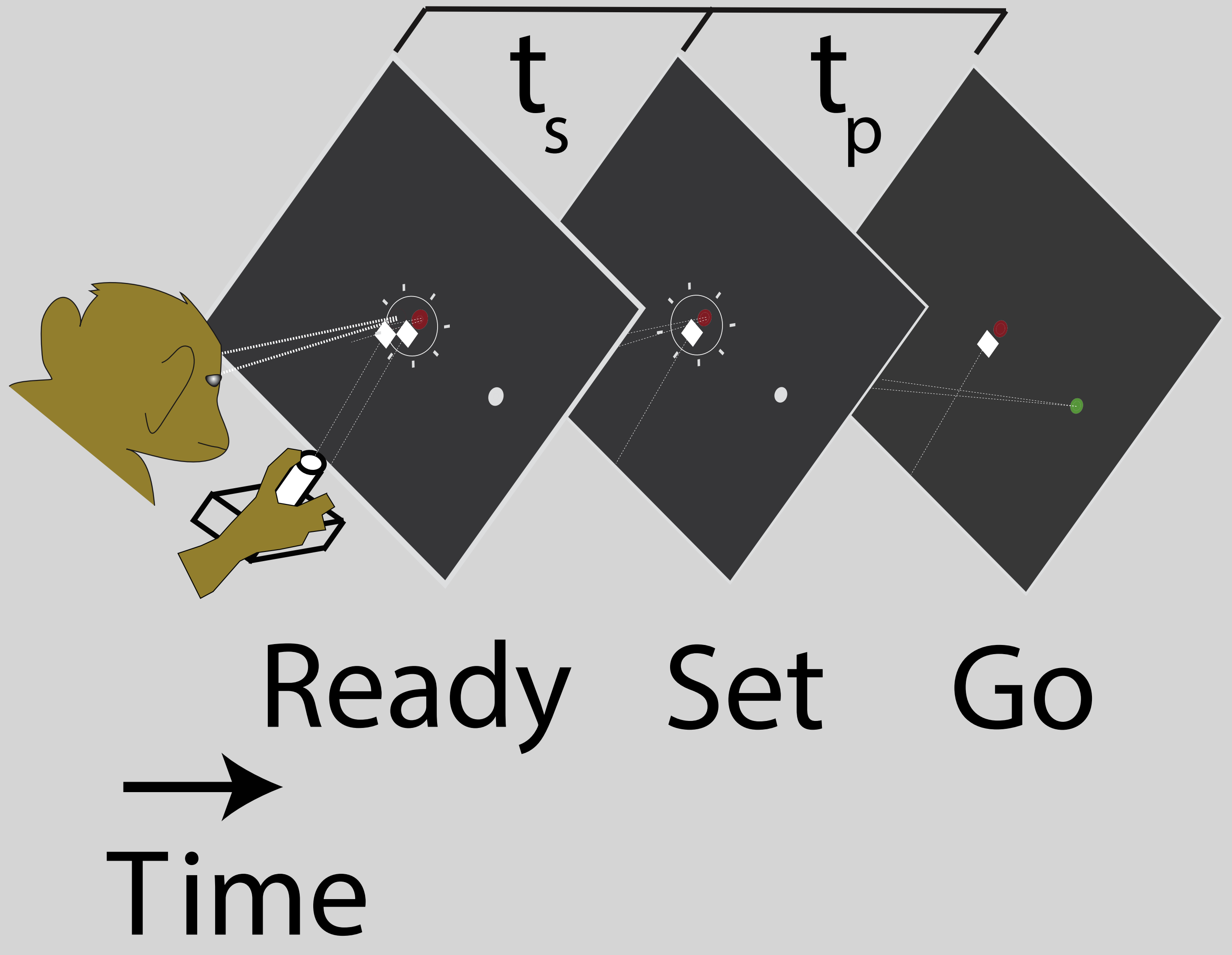


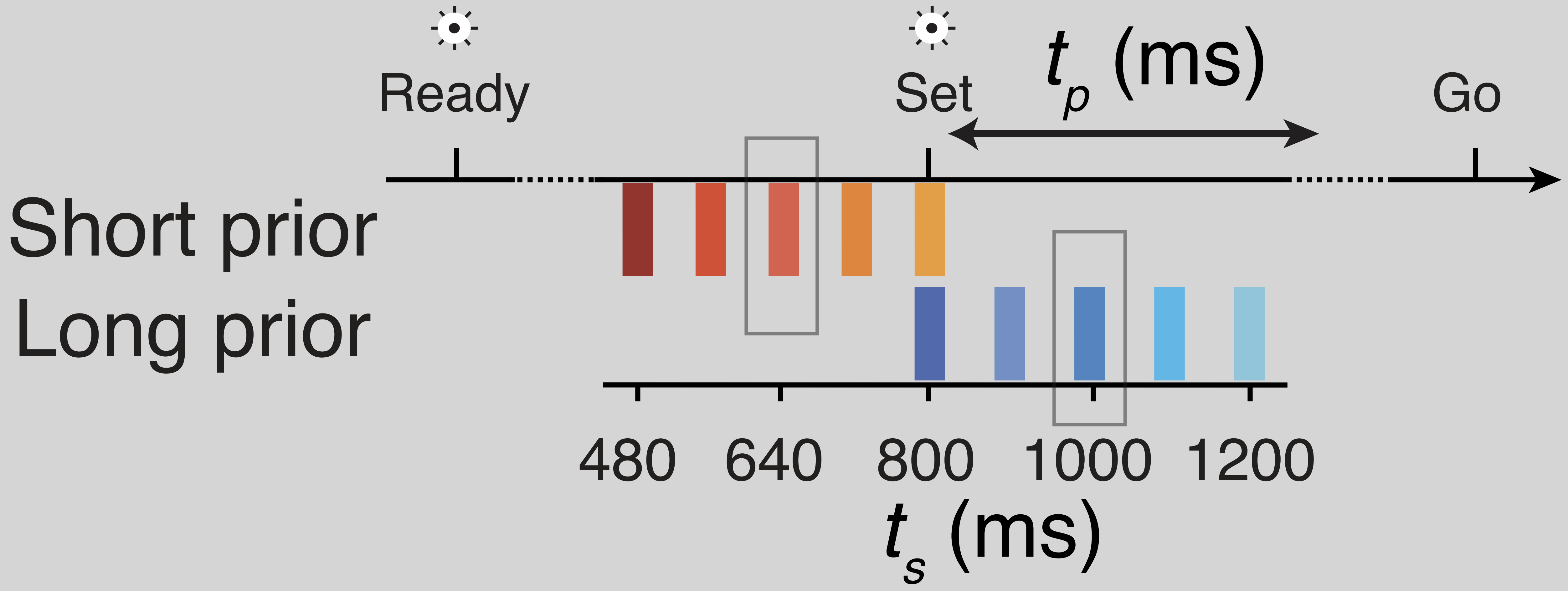


Ready-set-go task (Jazayeri lab, MIT)

Dorsomedial frontal cortex (DMFC)







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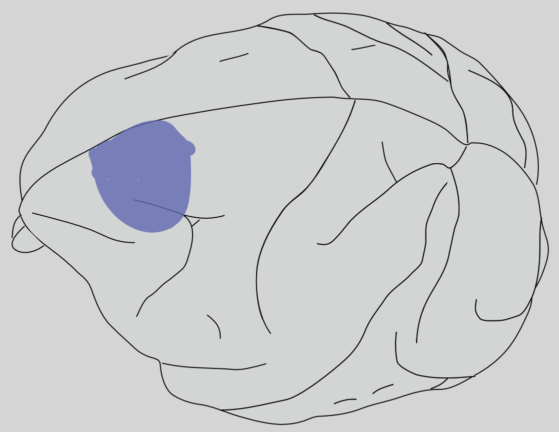

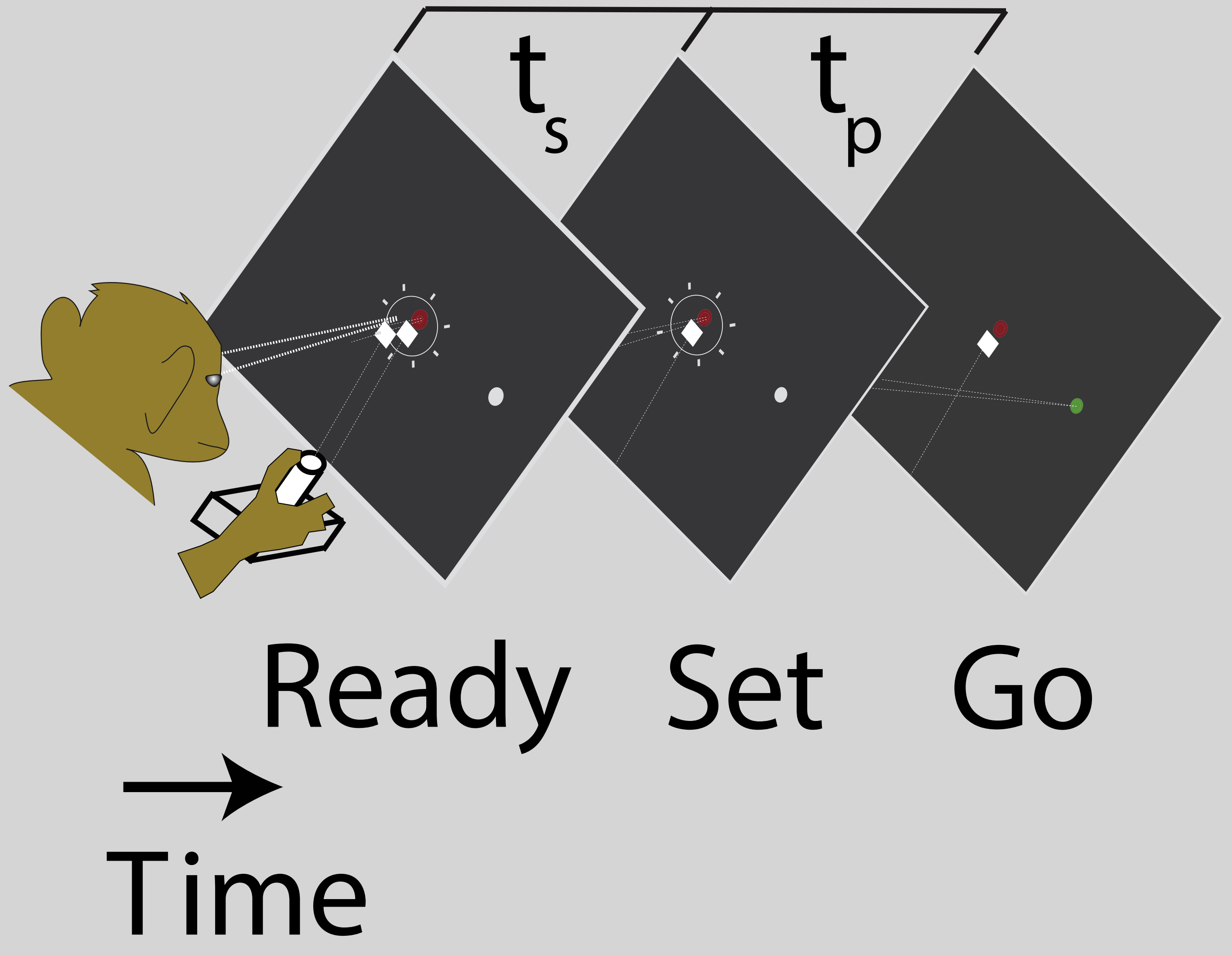

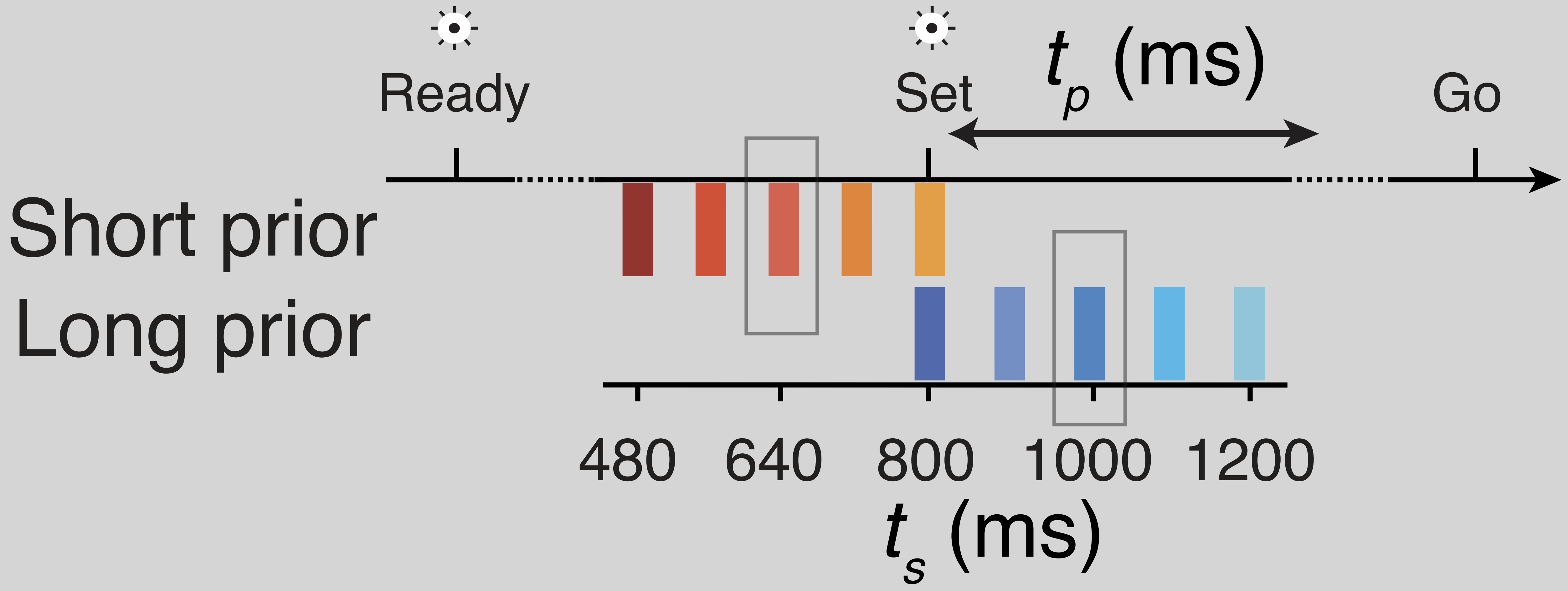

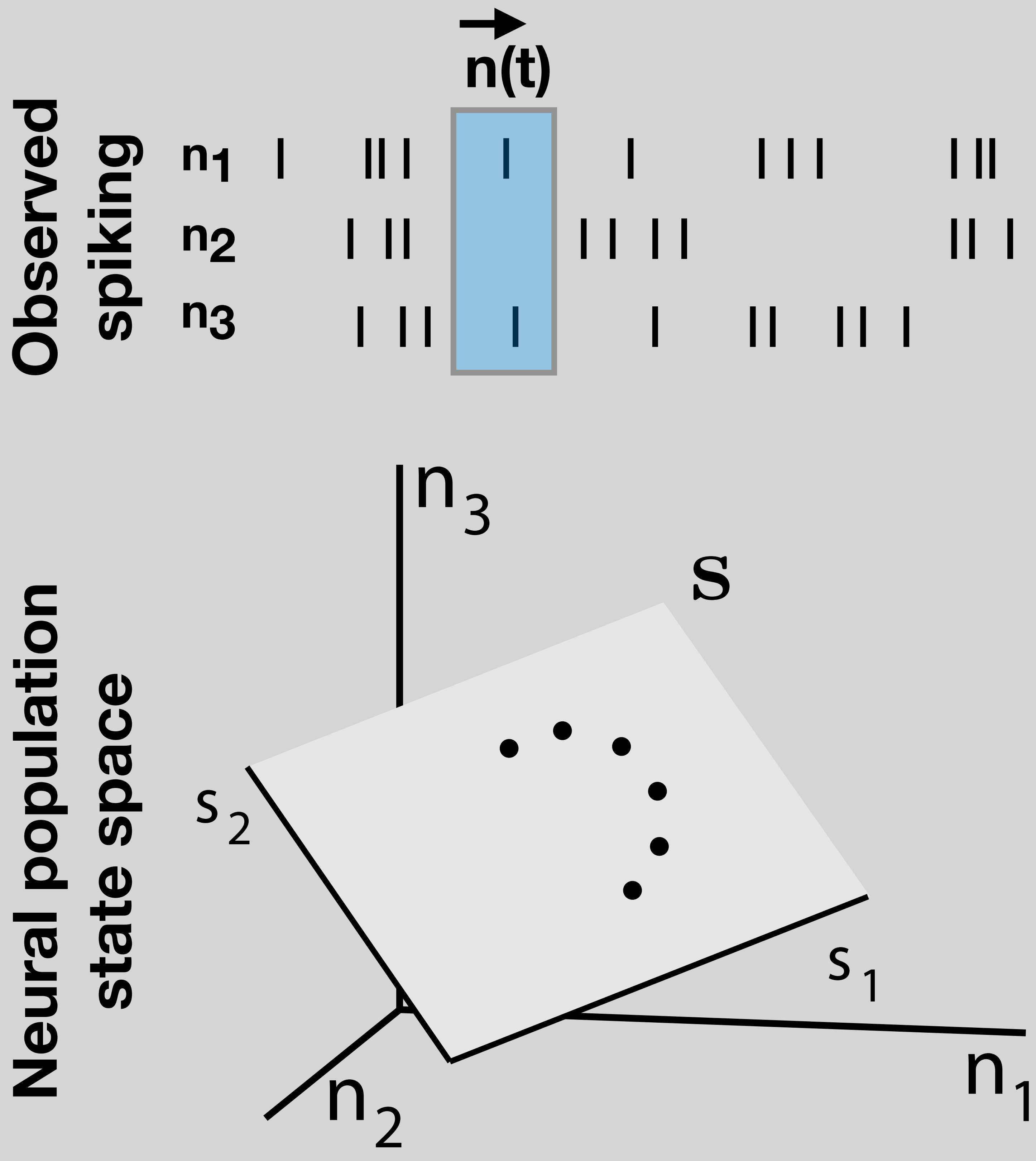

Adapted from Cunningham & Yu, *Nat Neuro* 2014
Dimensionality reduction for large-scale neural recordings

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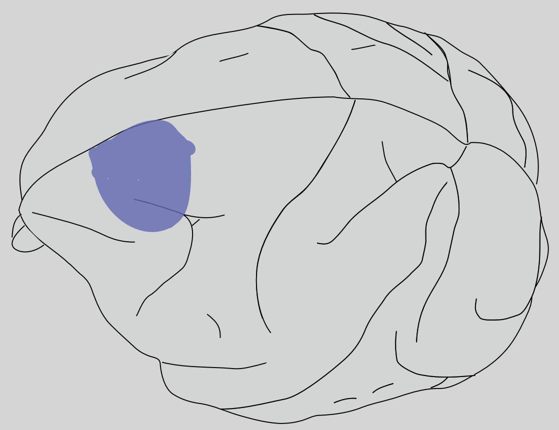
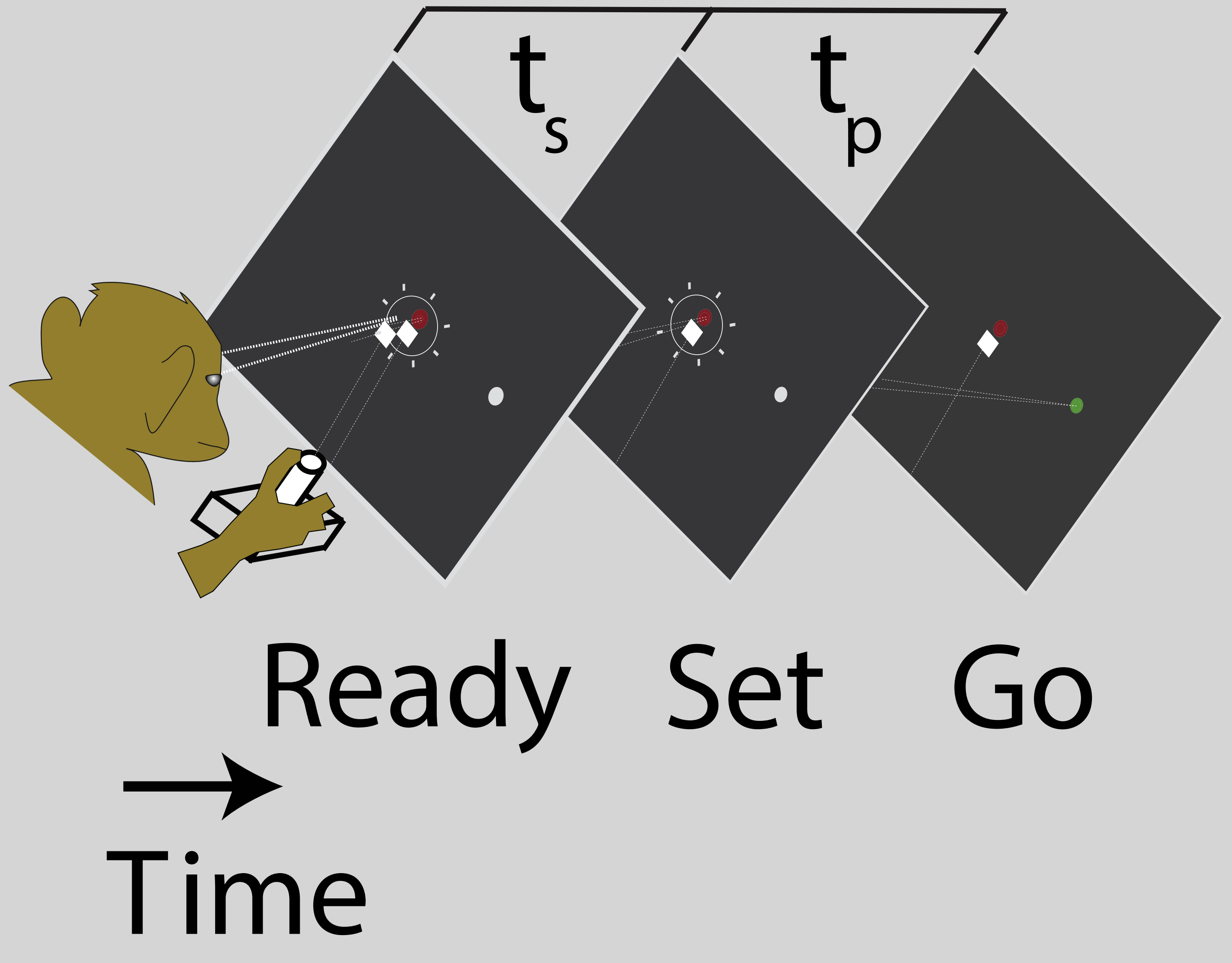
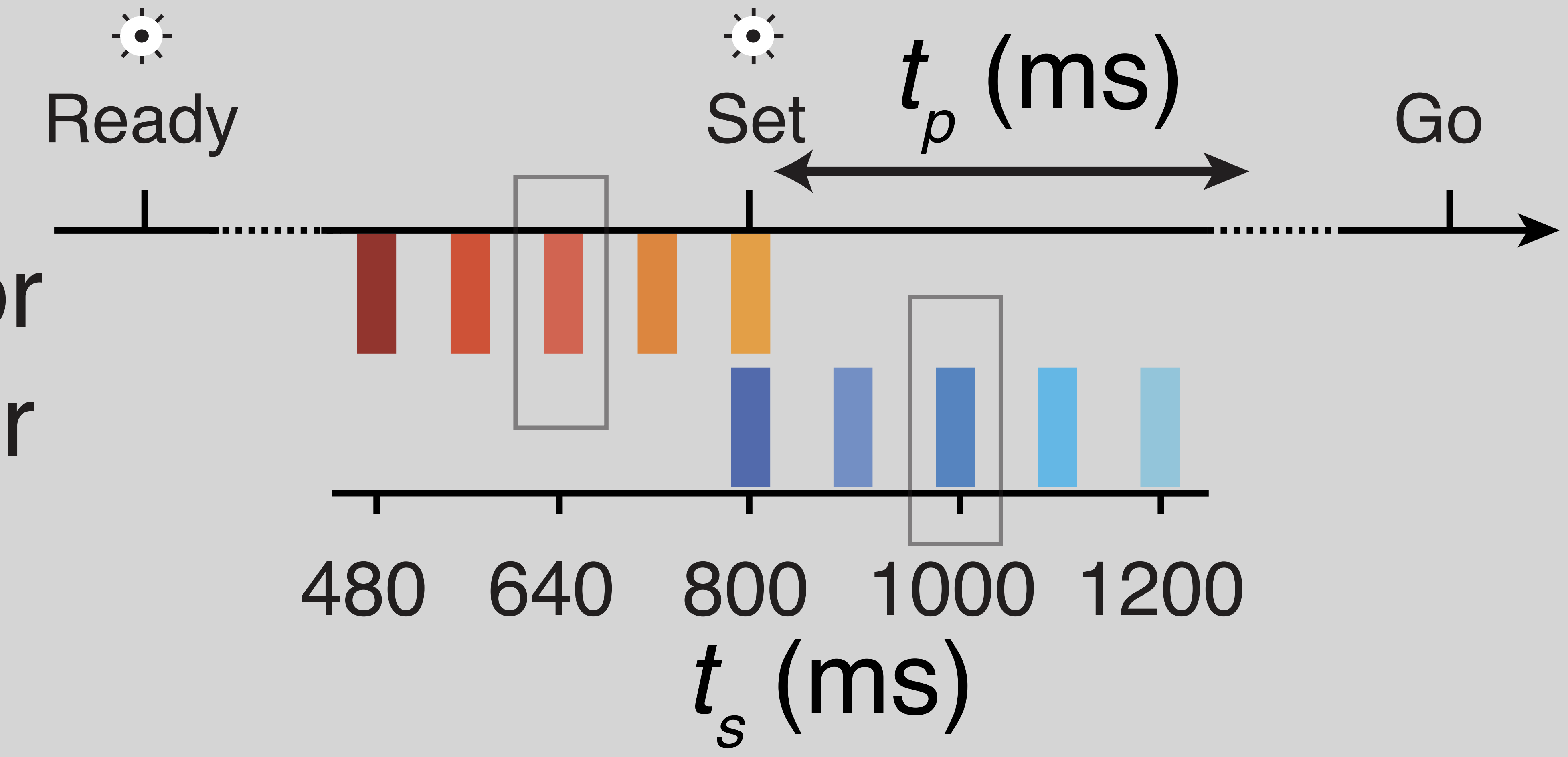


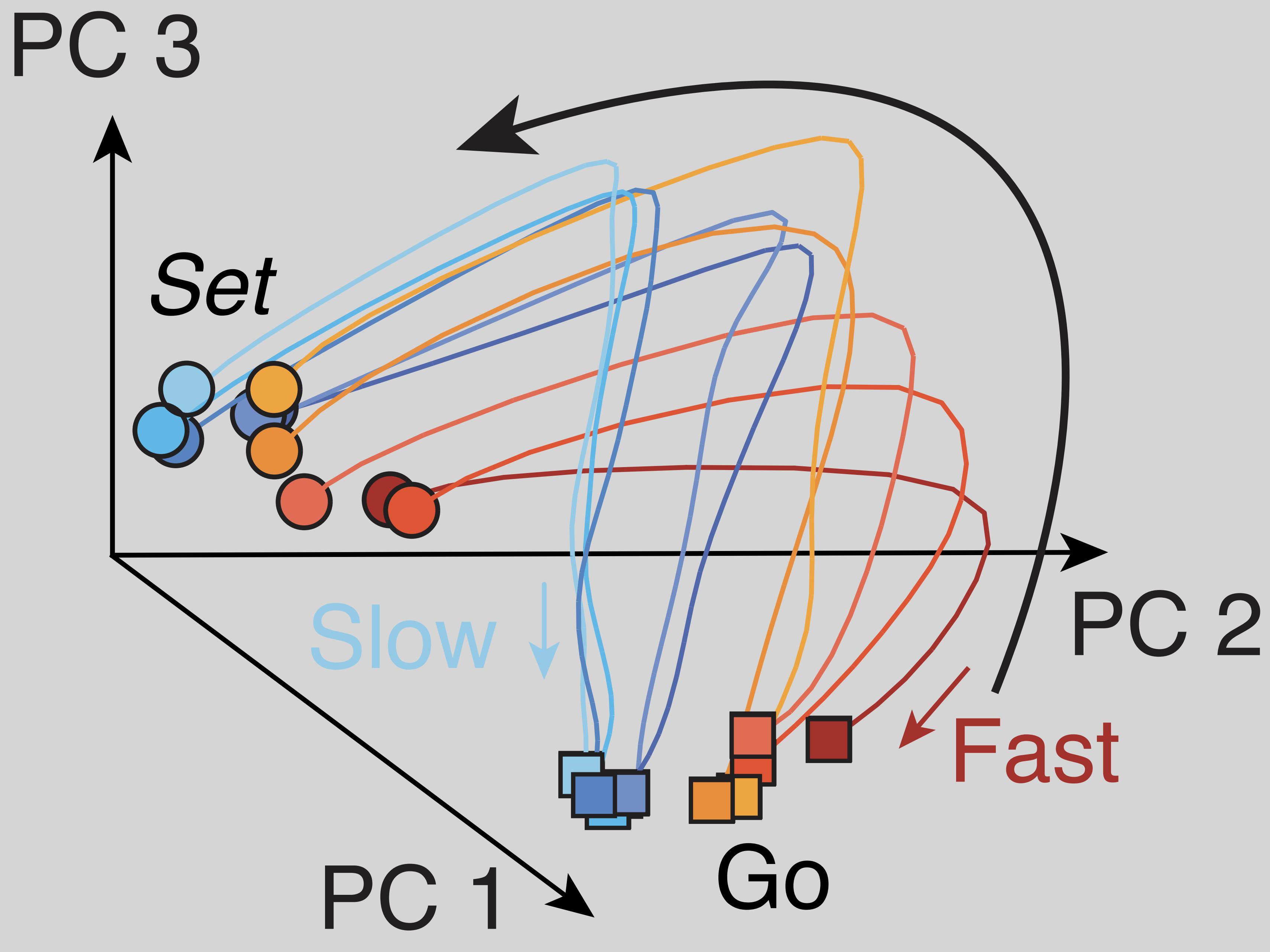




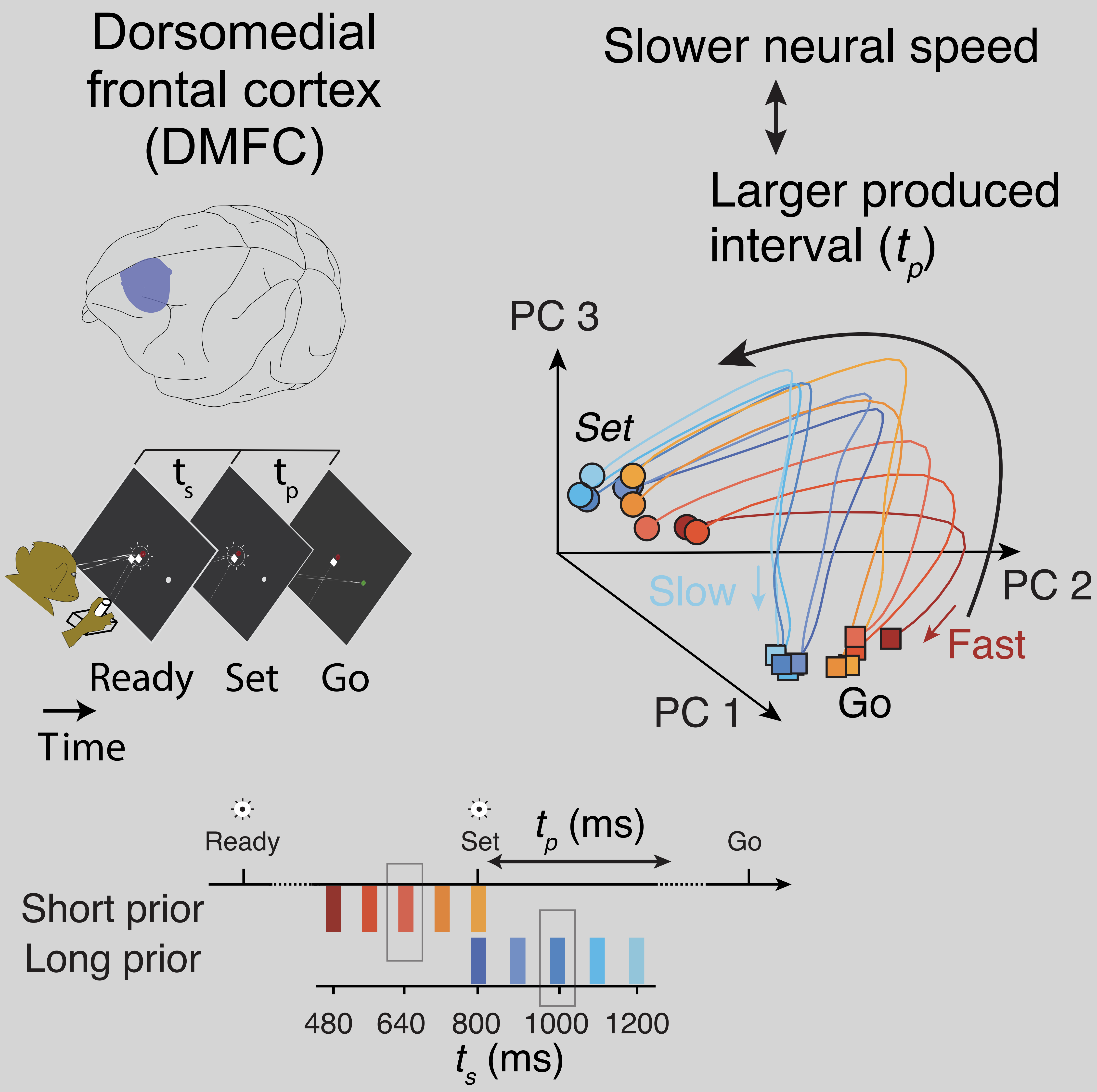
Slower neural speed

↕

Larger produced interval (t_p)



AutoLFADS uncovers cognitive dynamics



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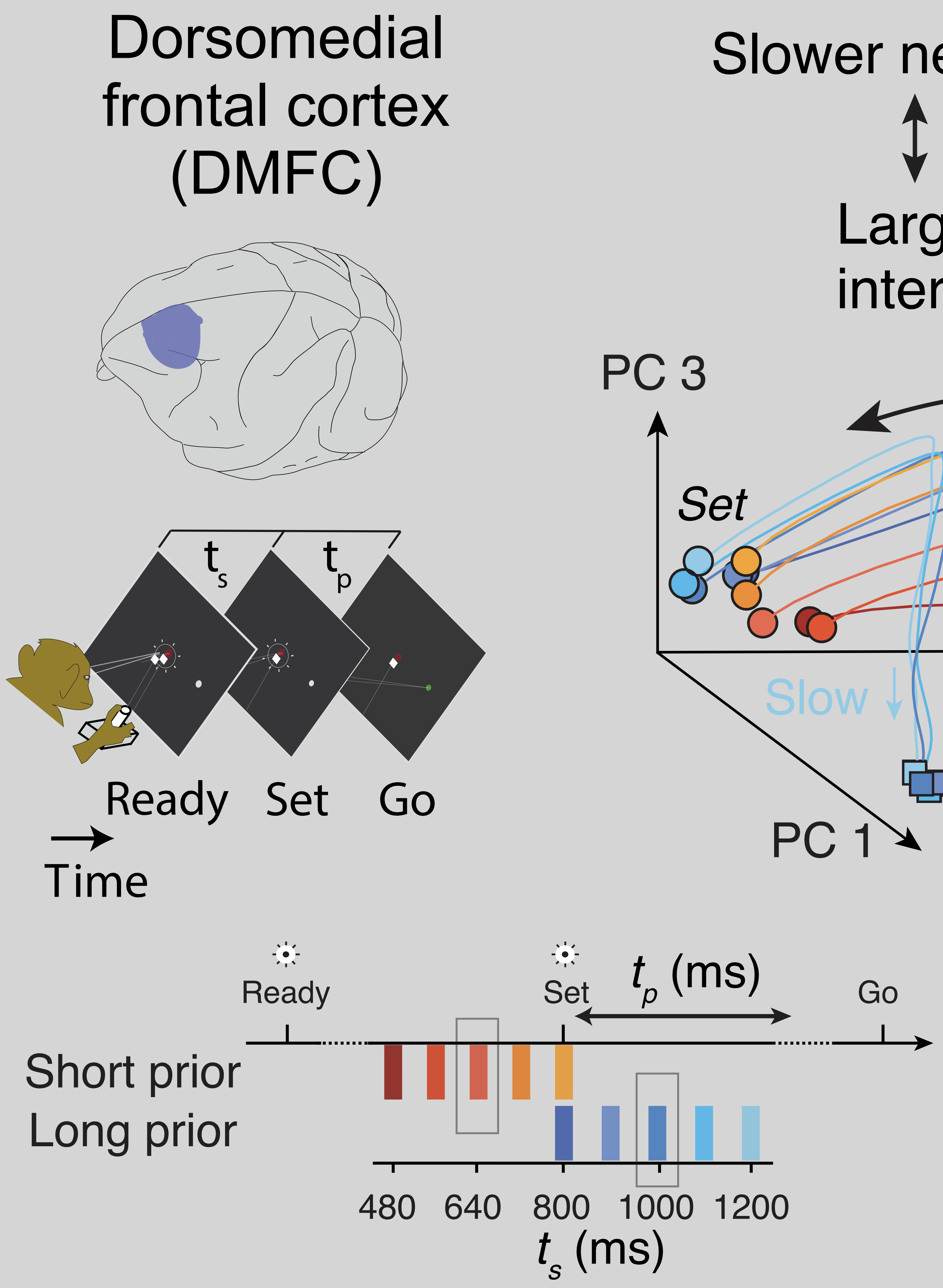

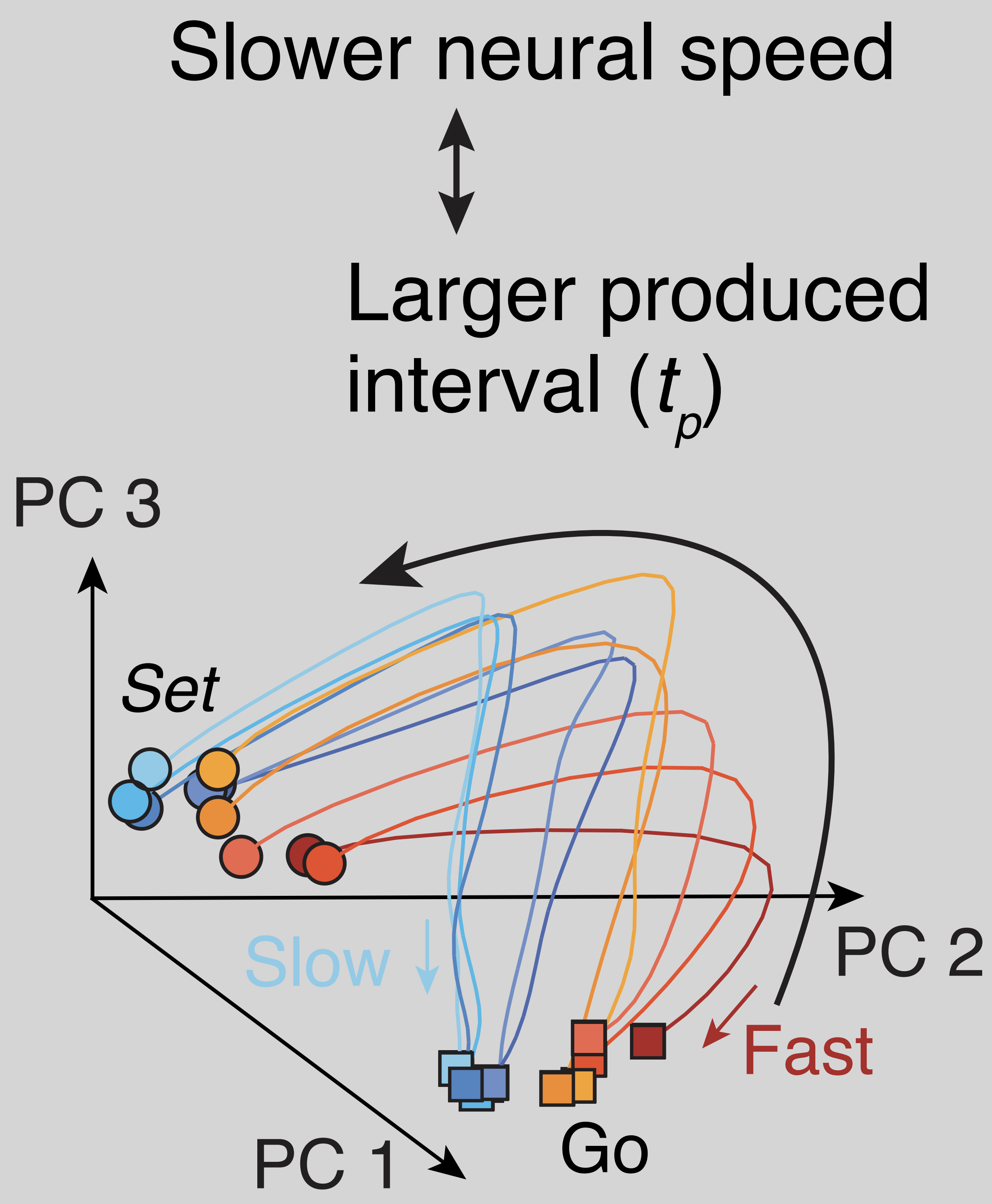

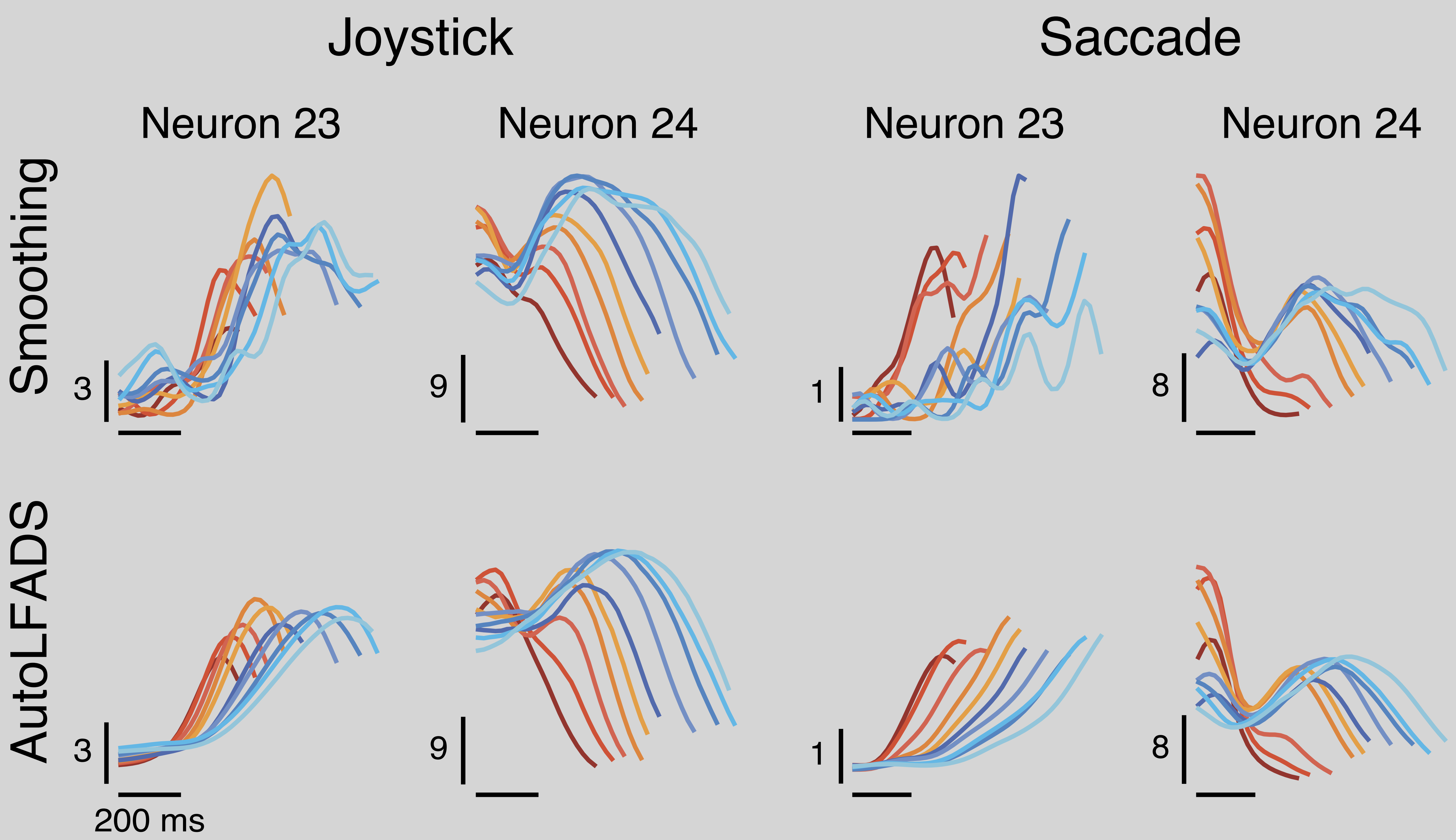

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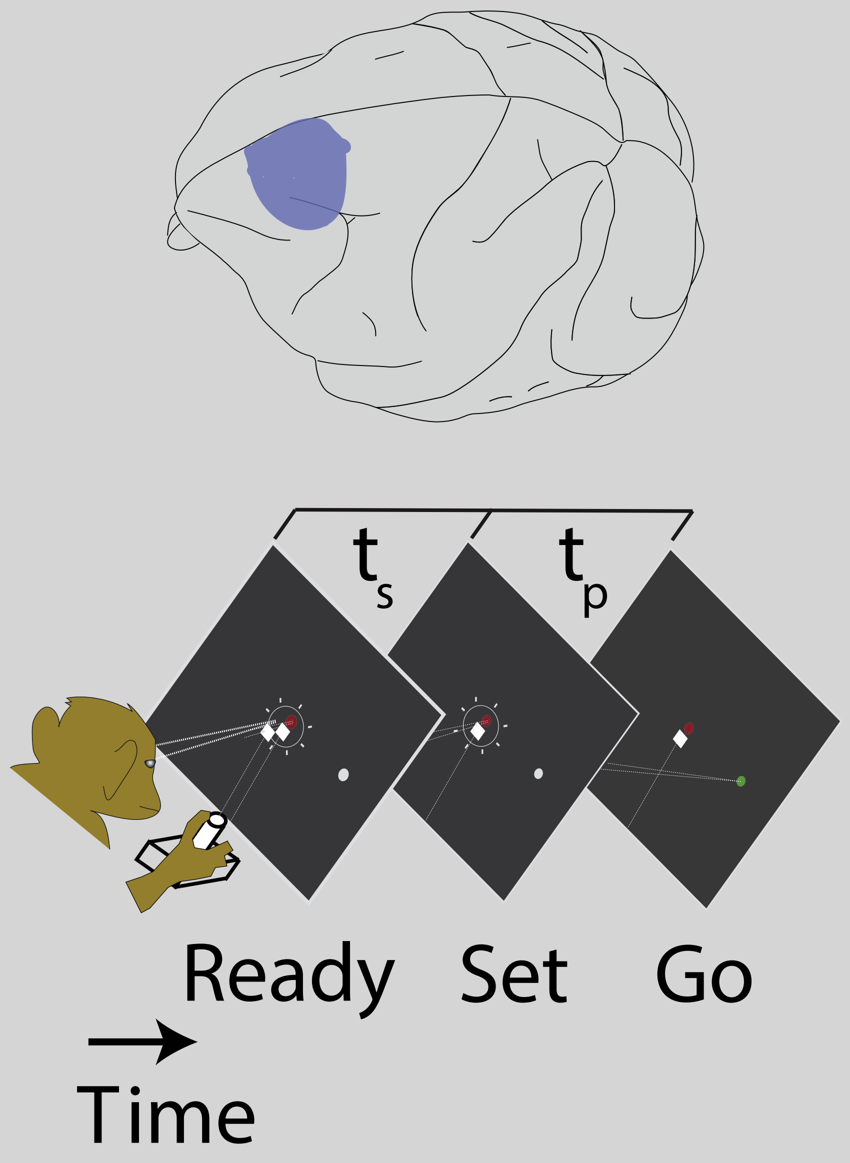

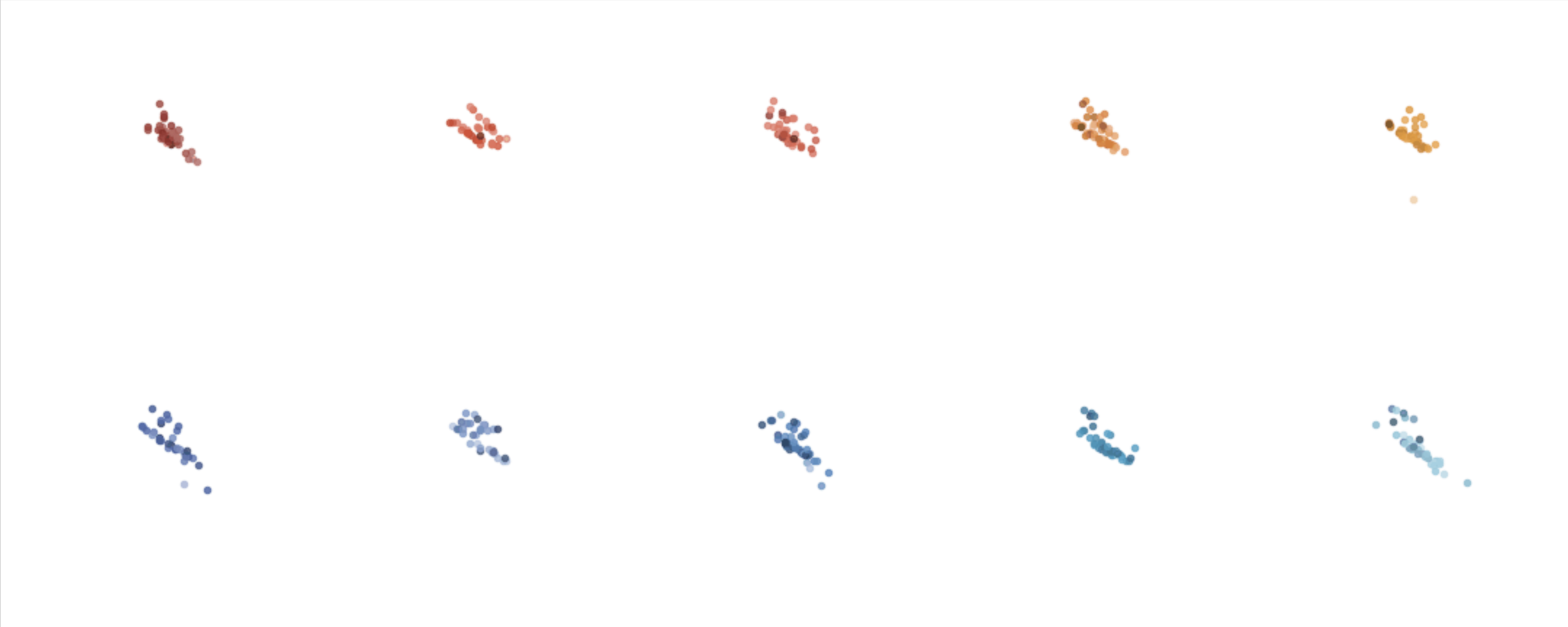

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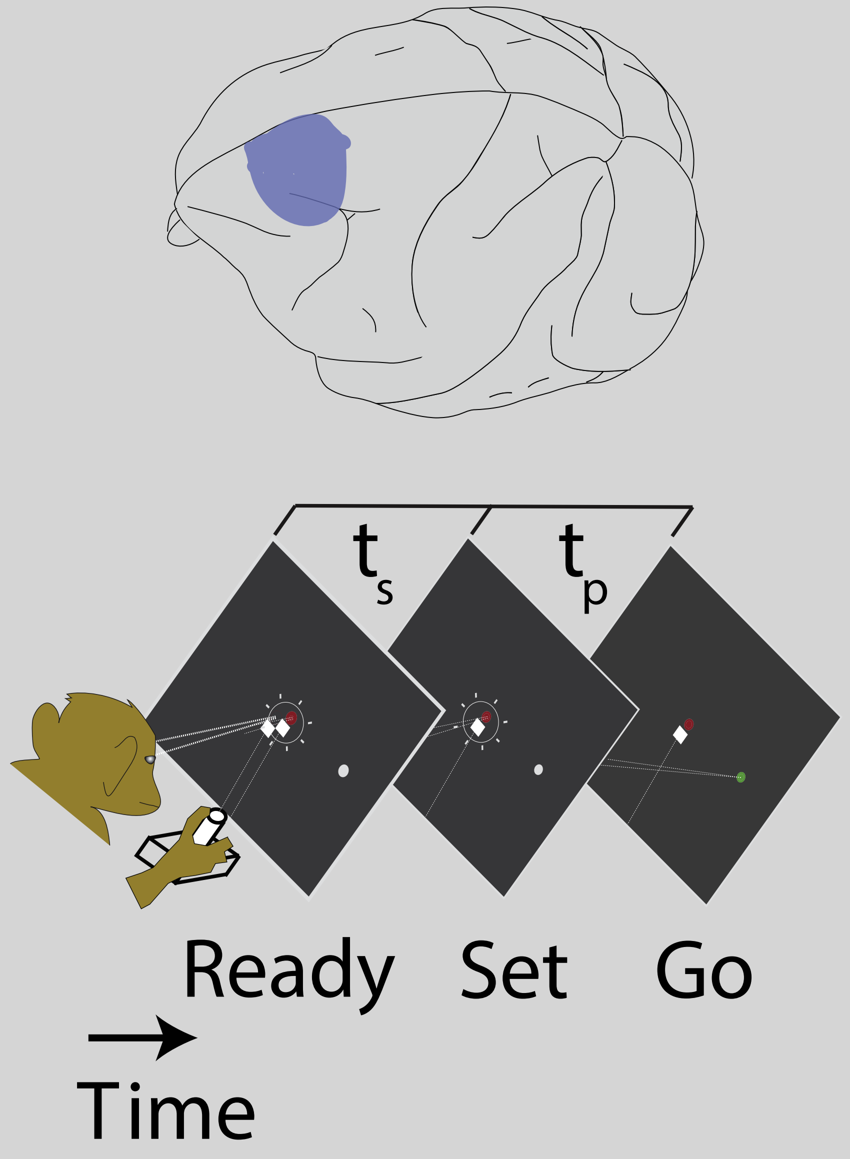

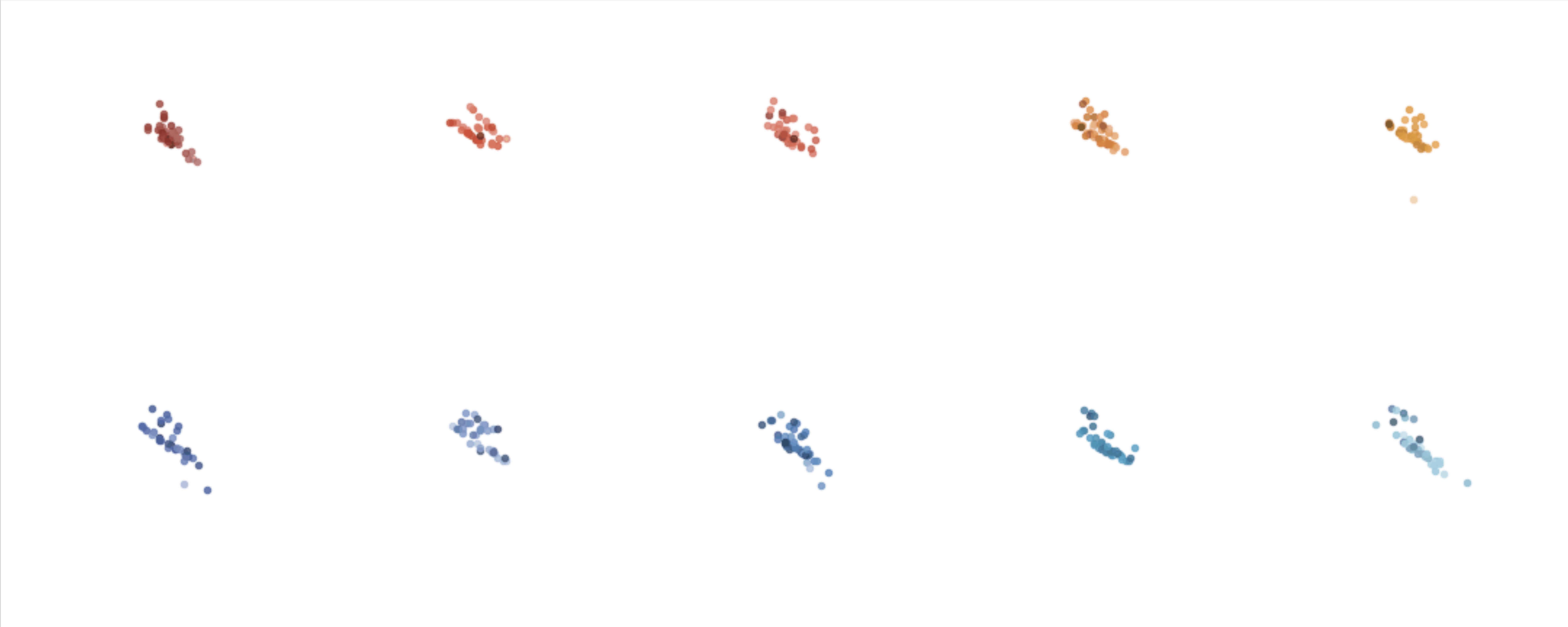

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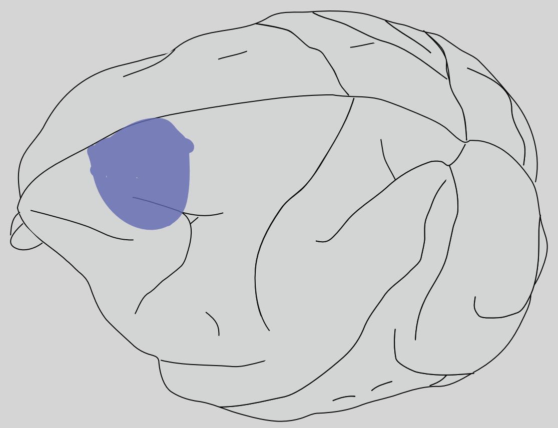

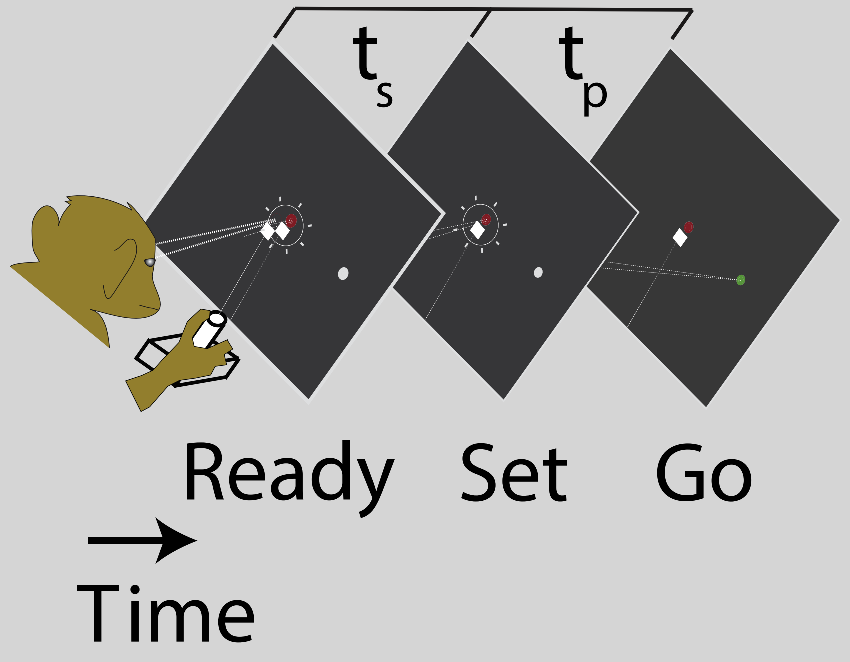

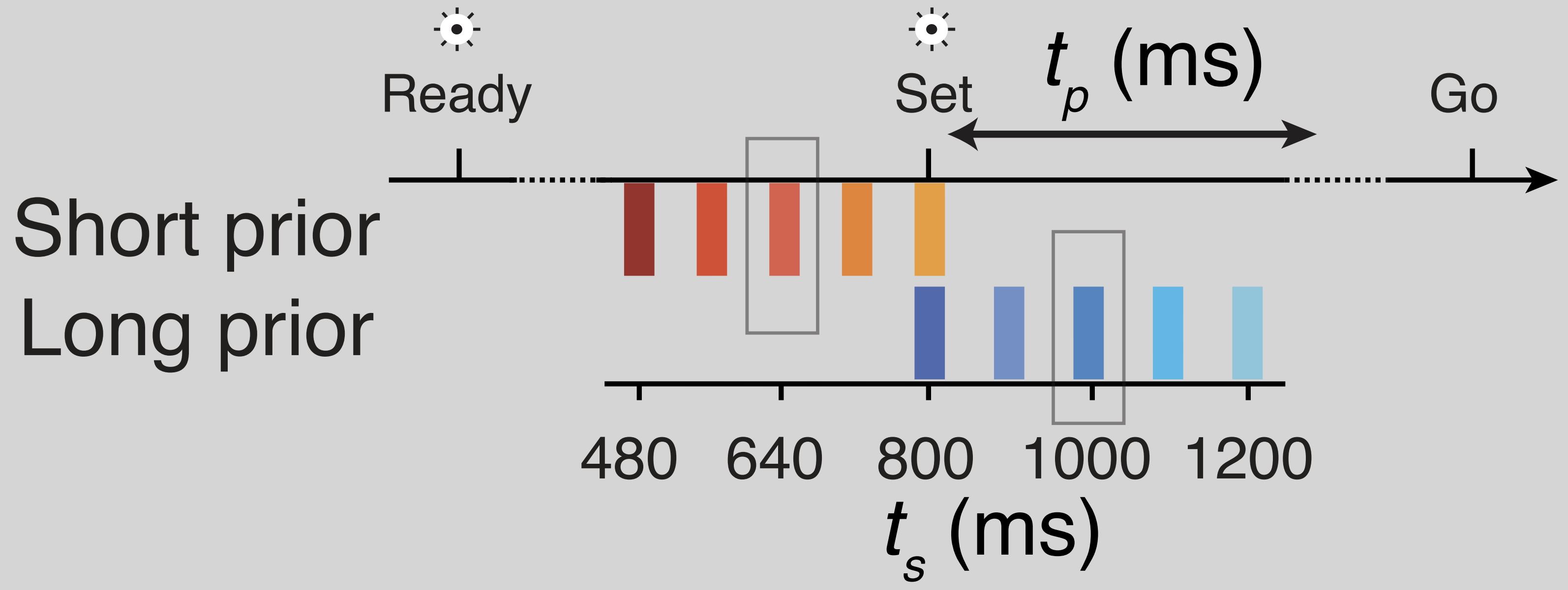

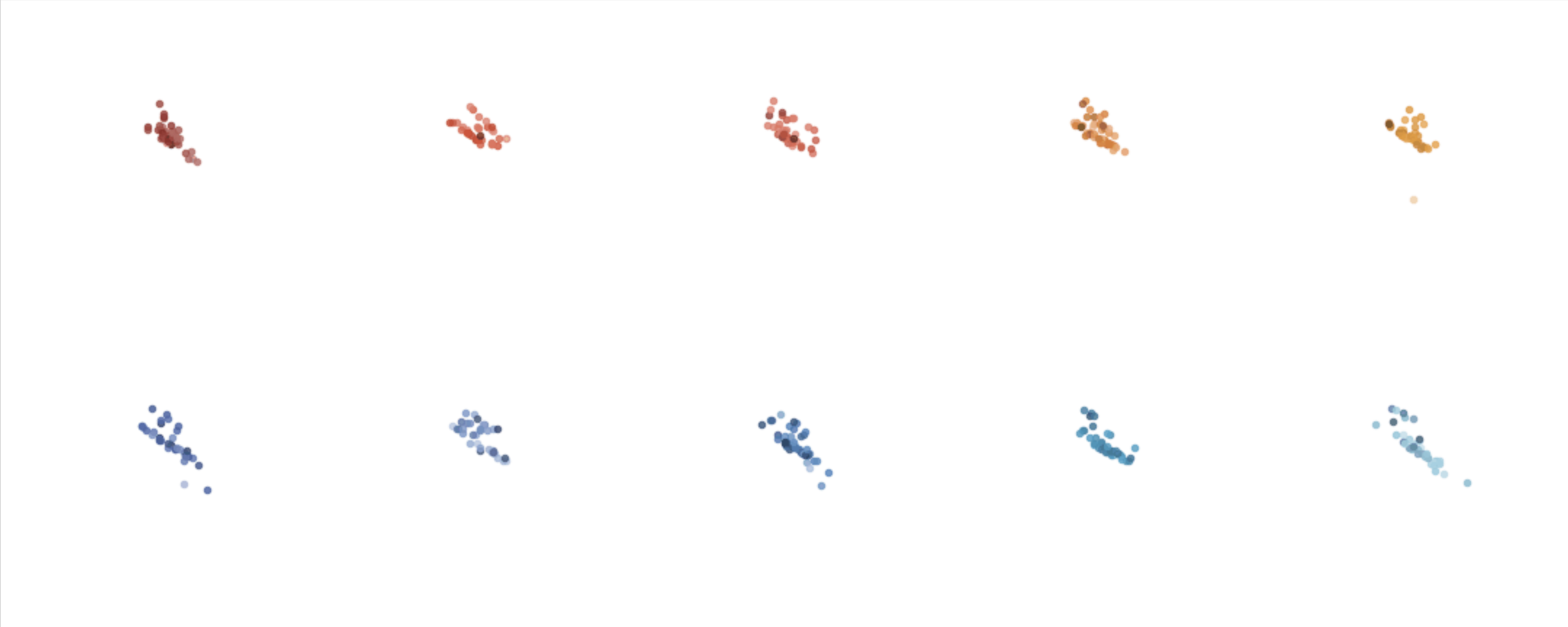

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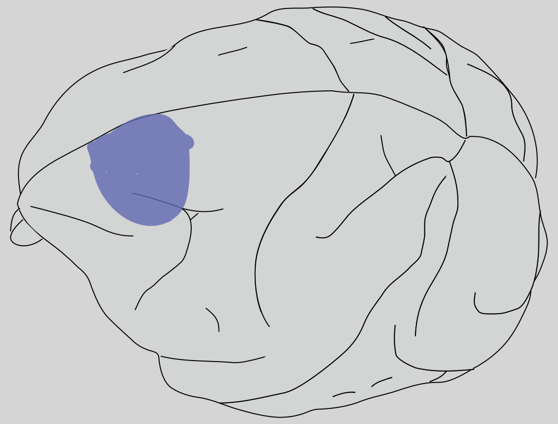

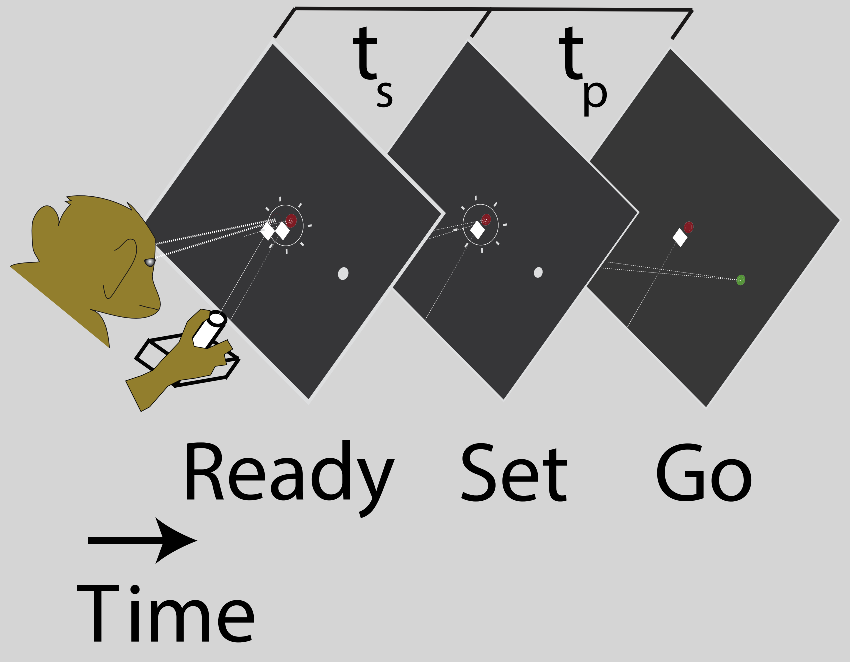

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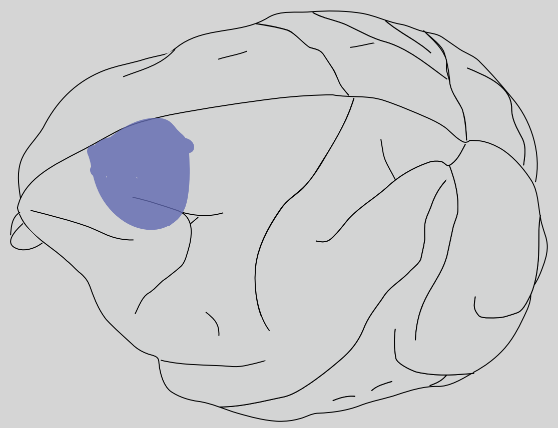

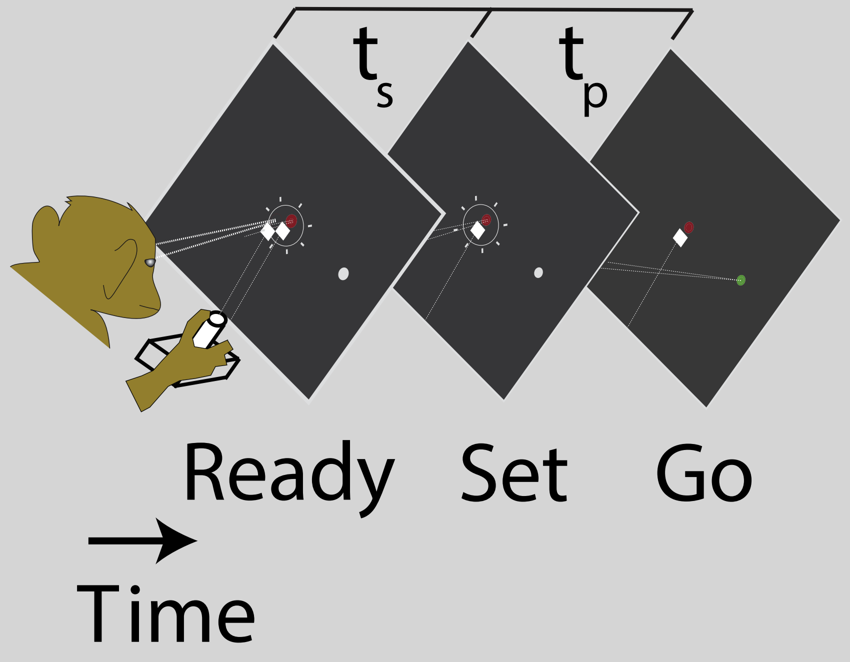

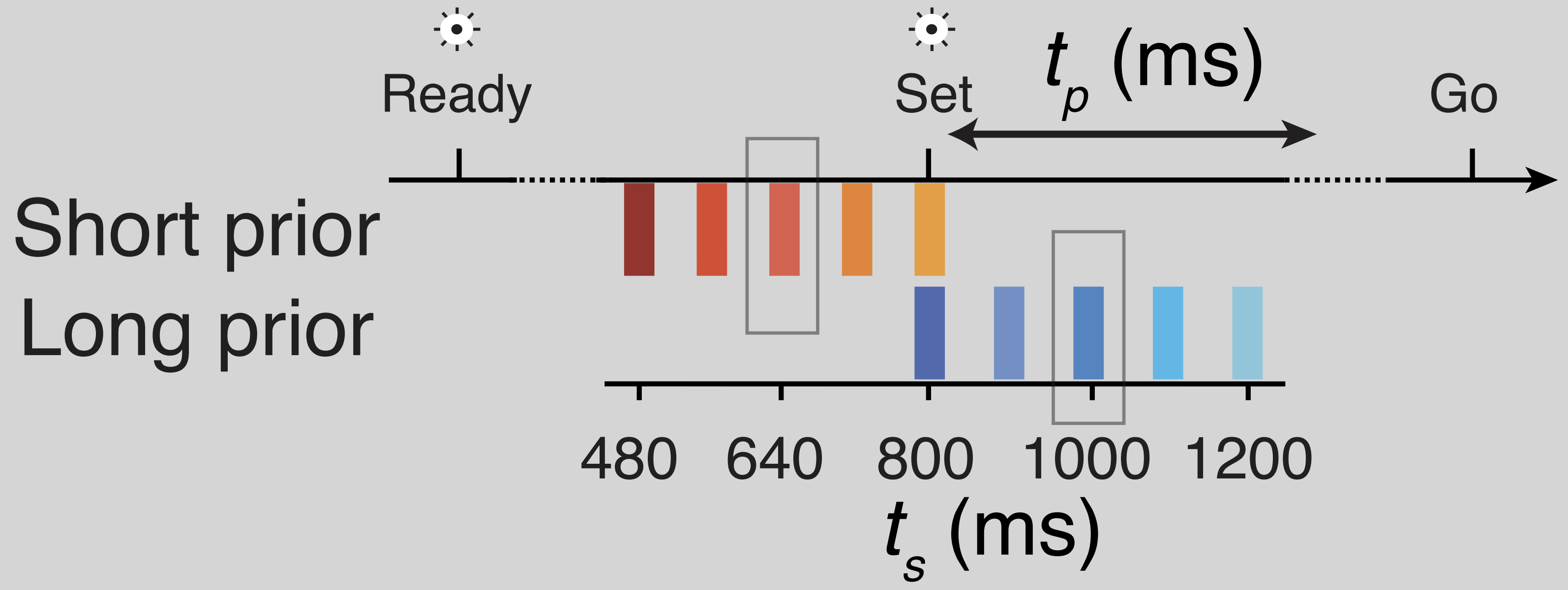

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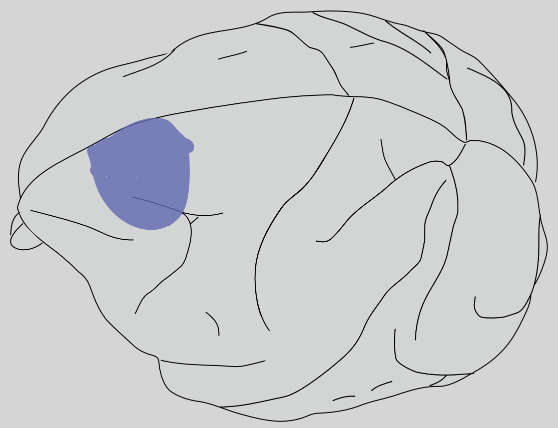

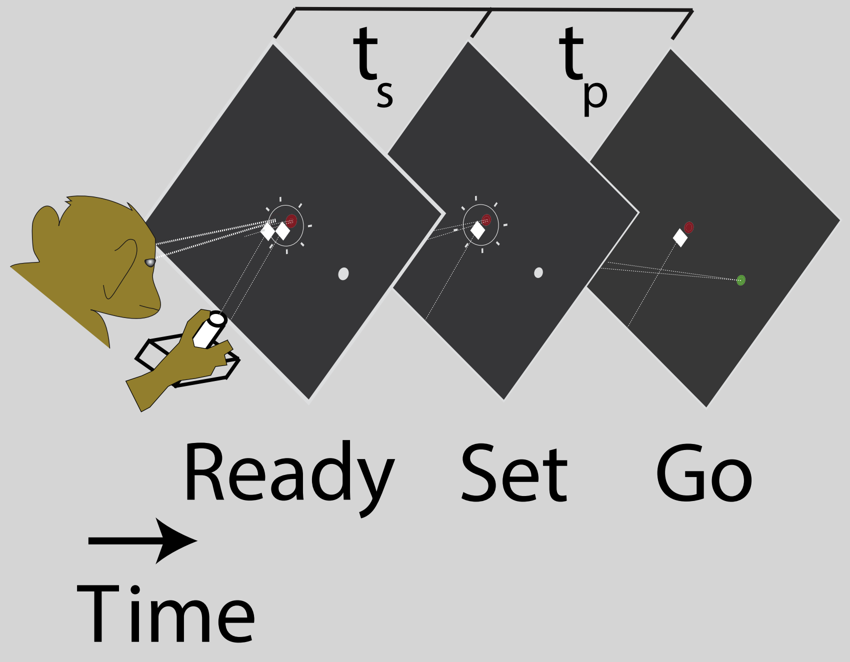

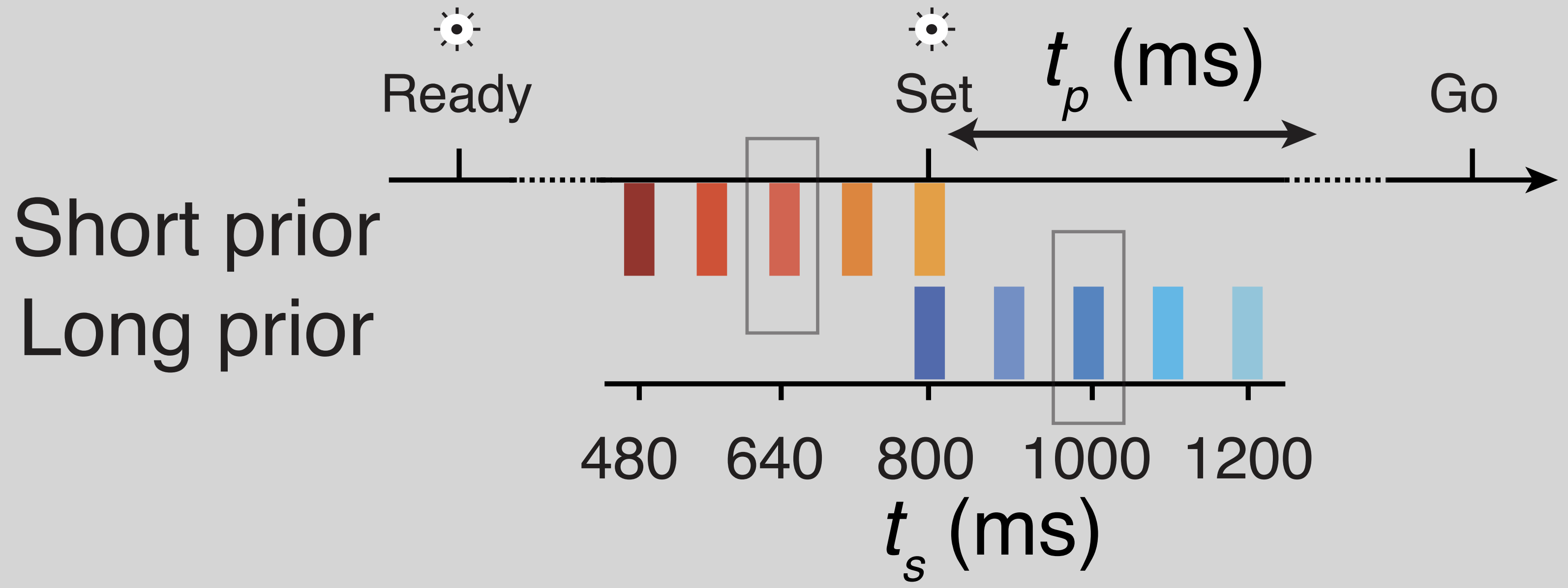

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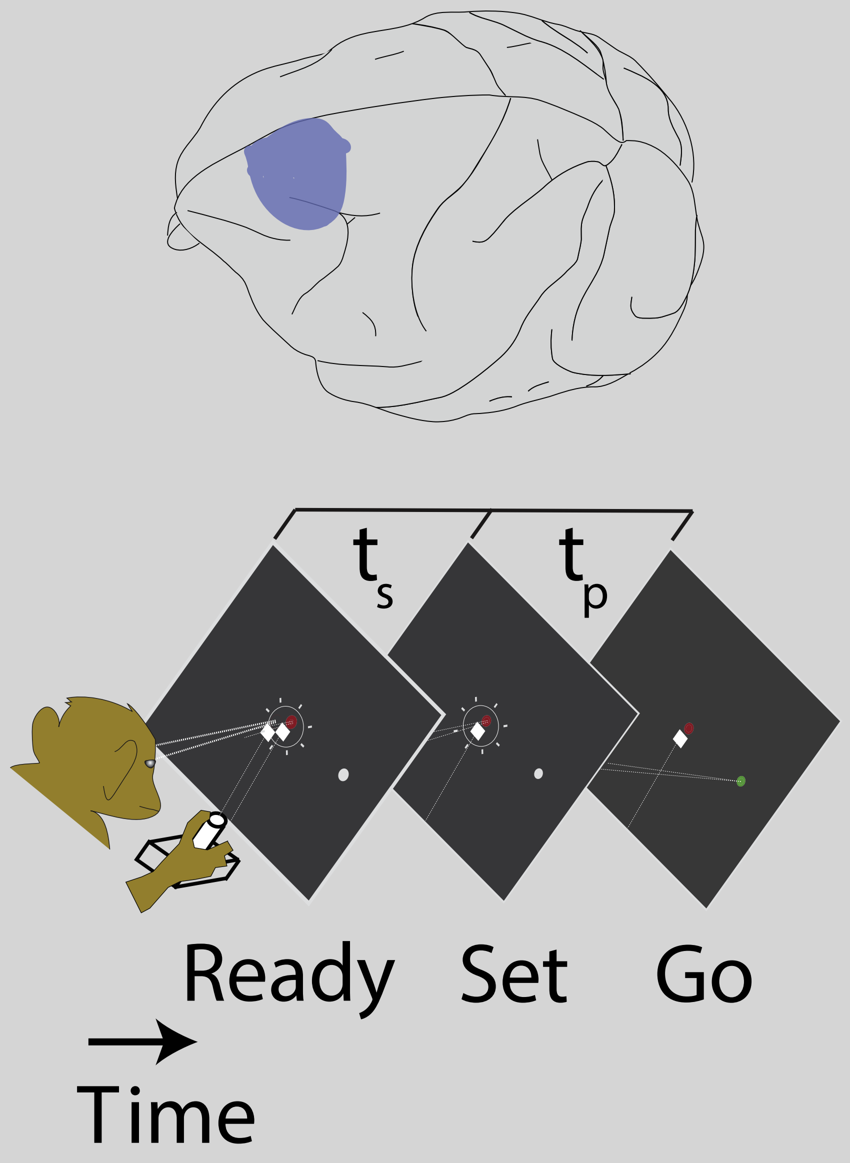

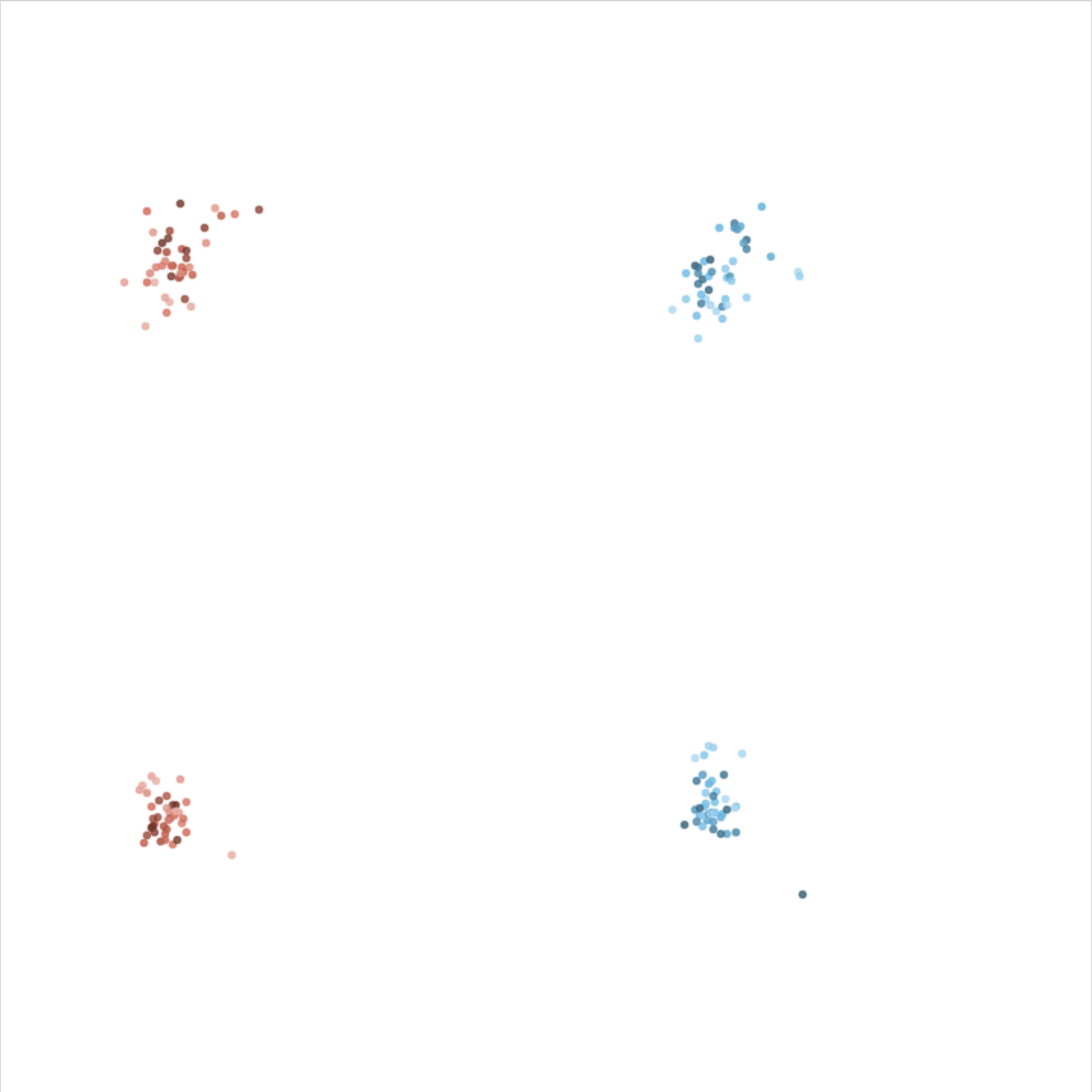

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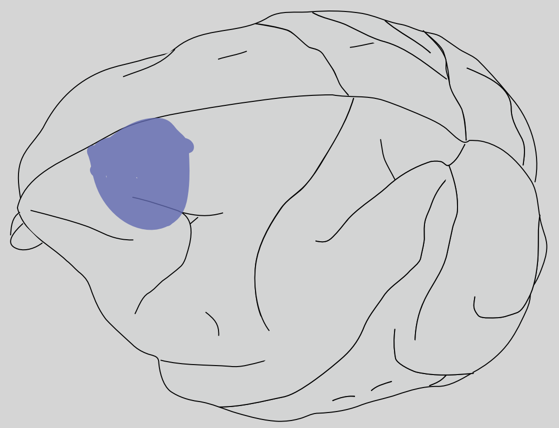

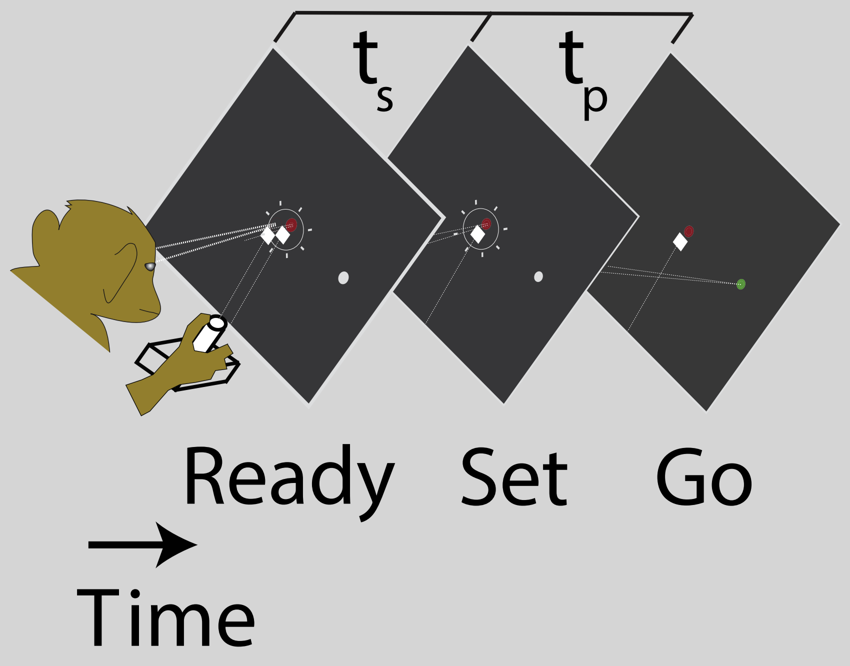

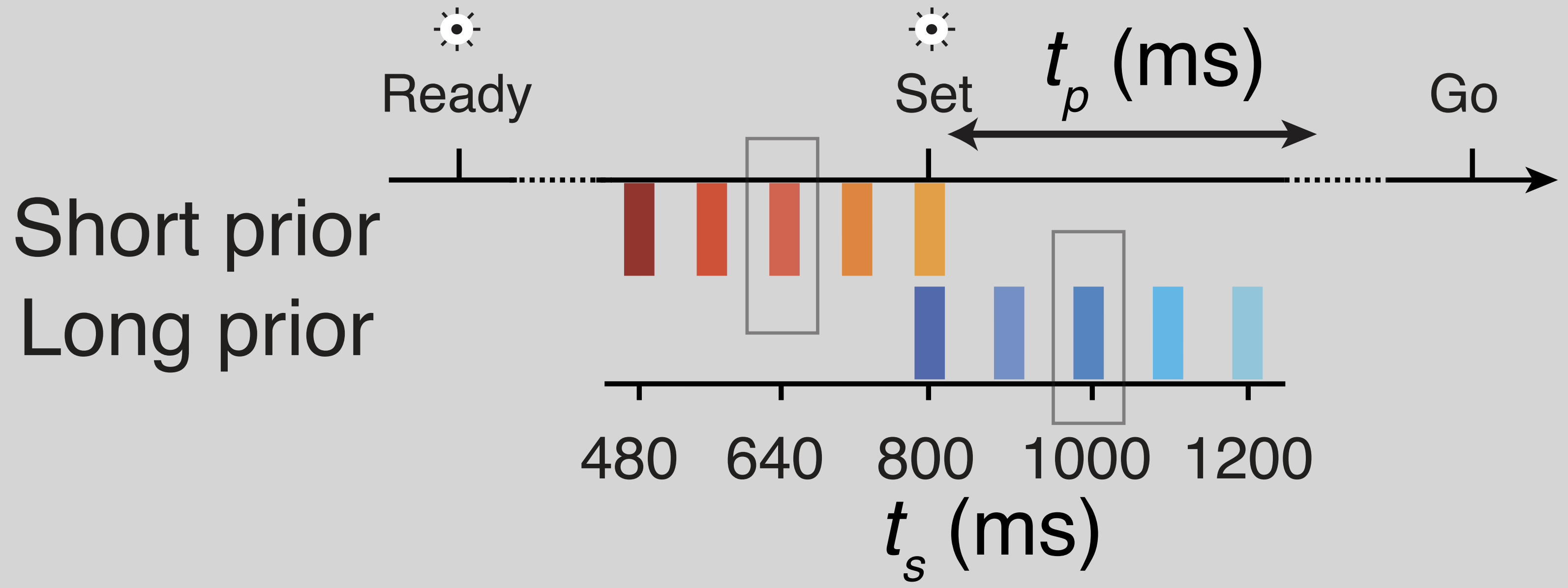

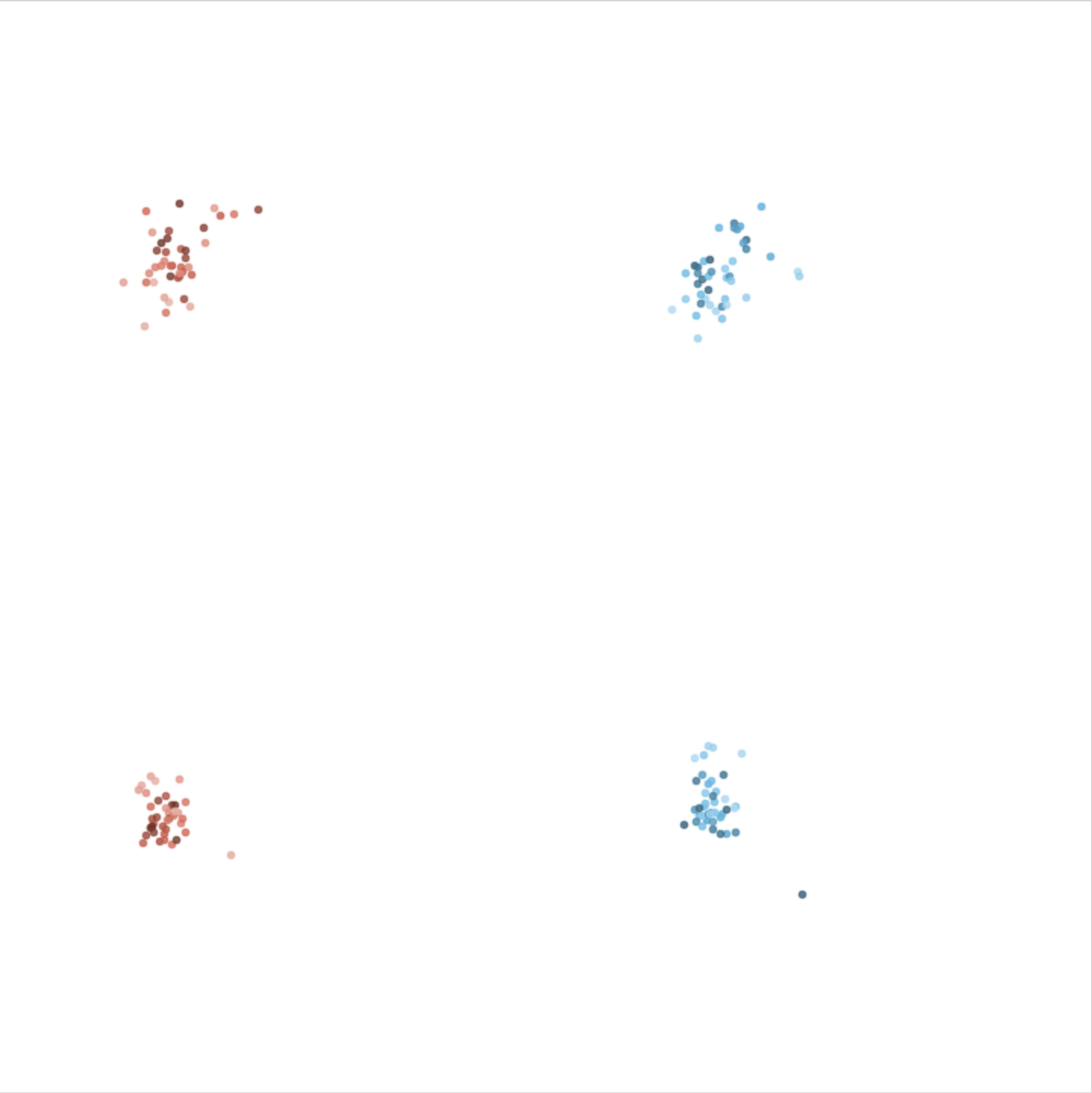

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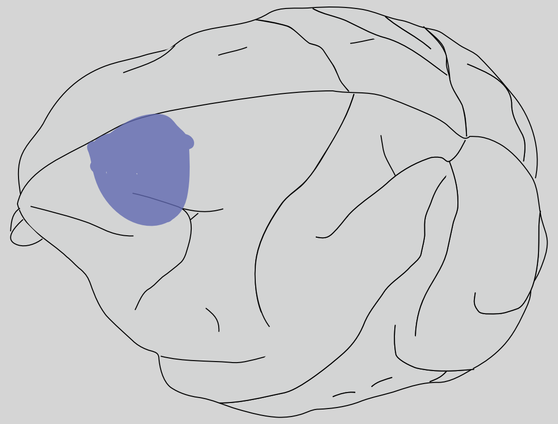

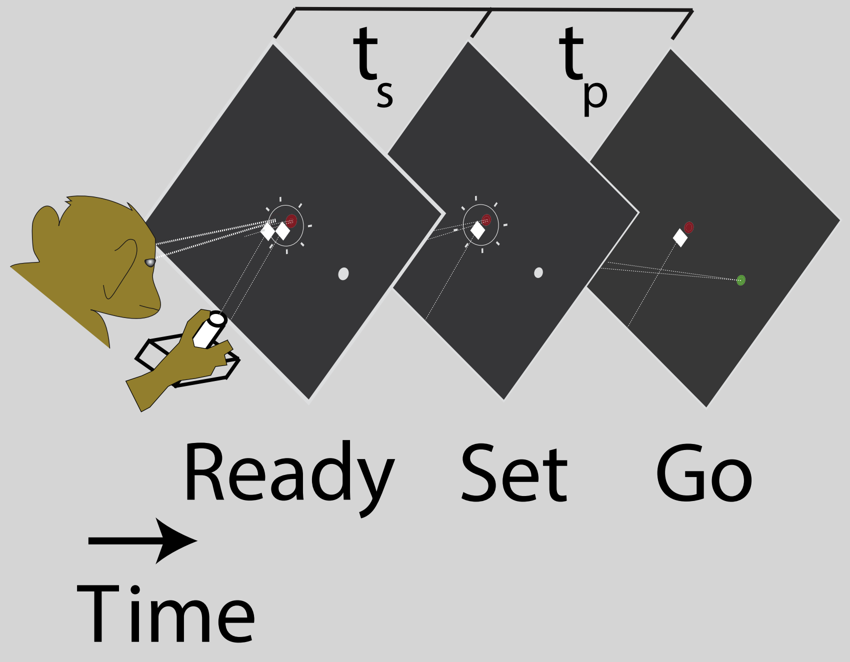

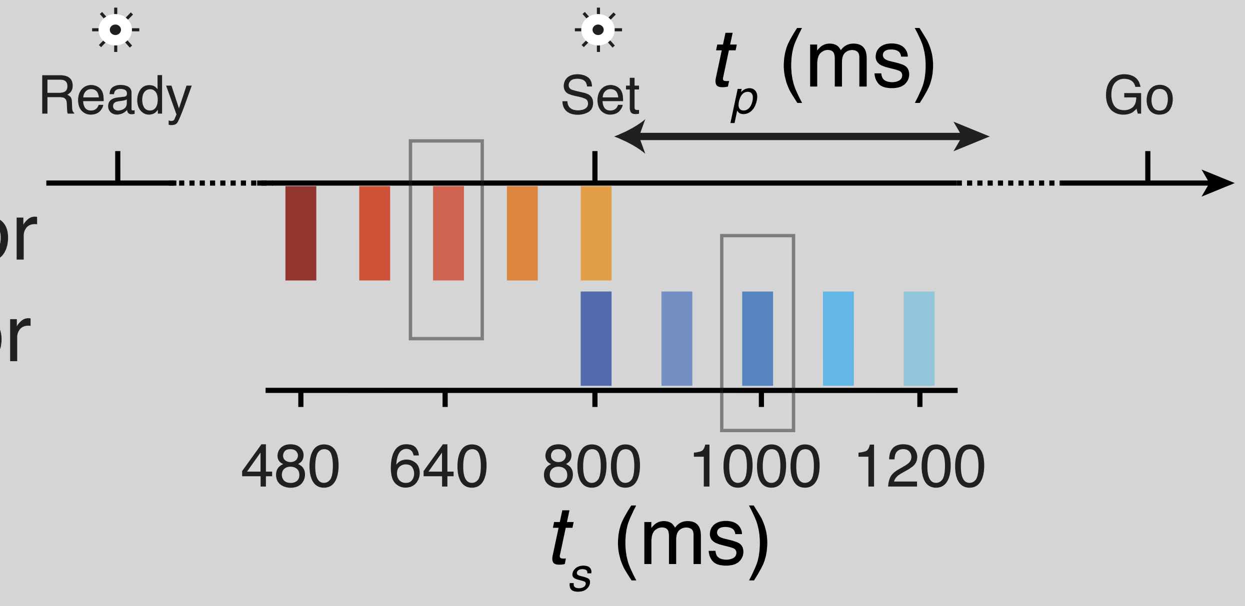

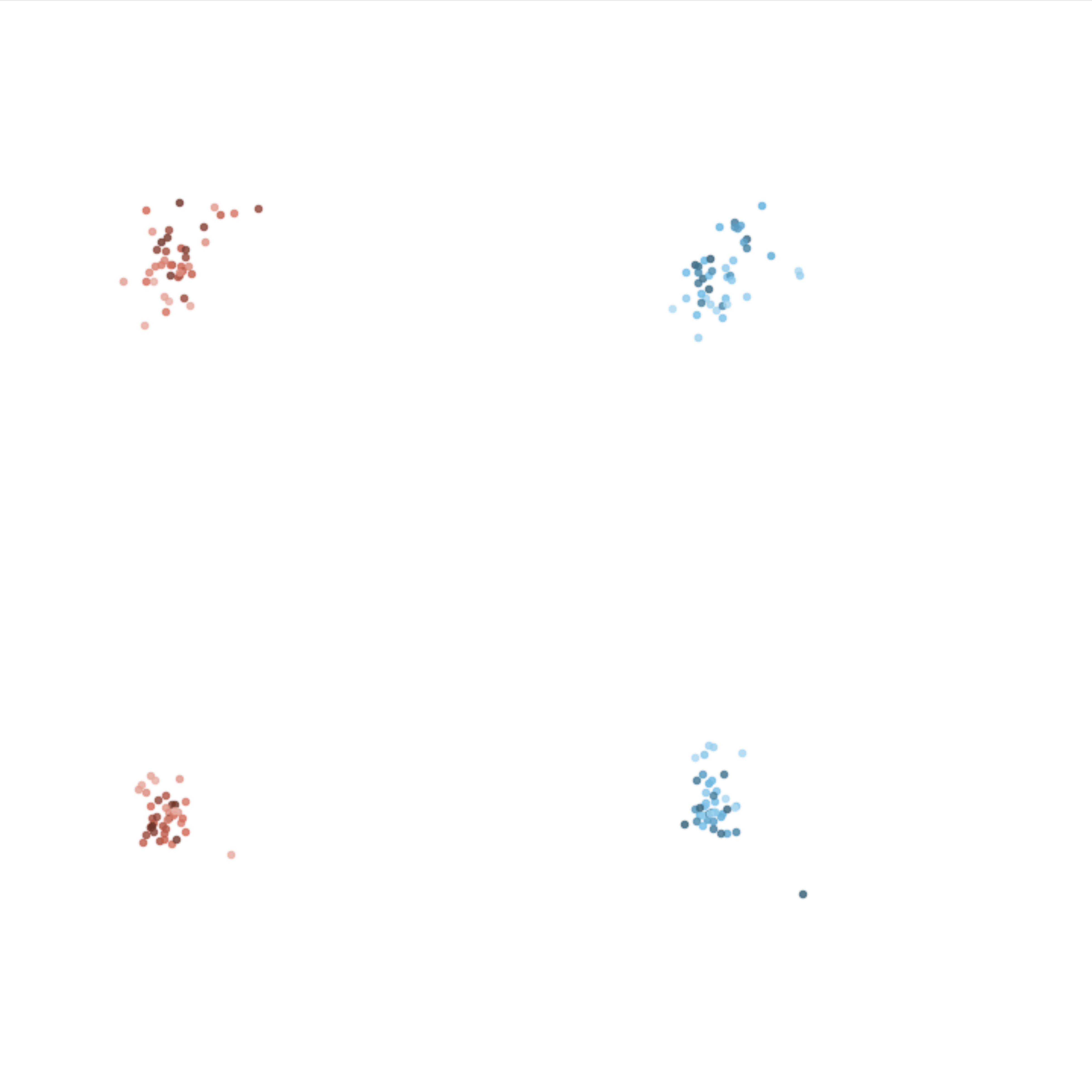

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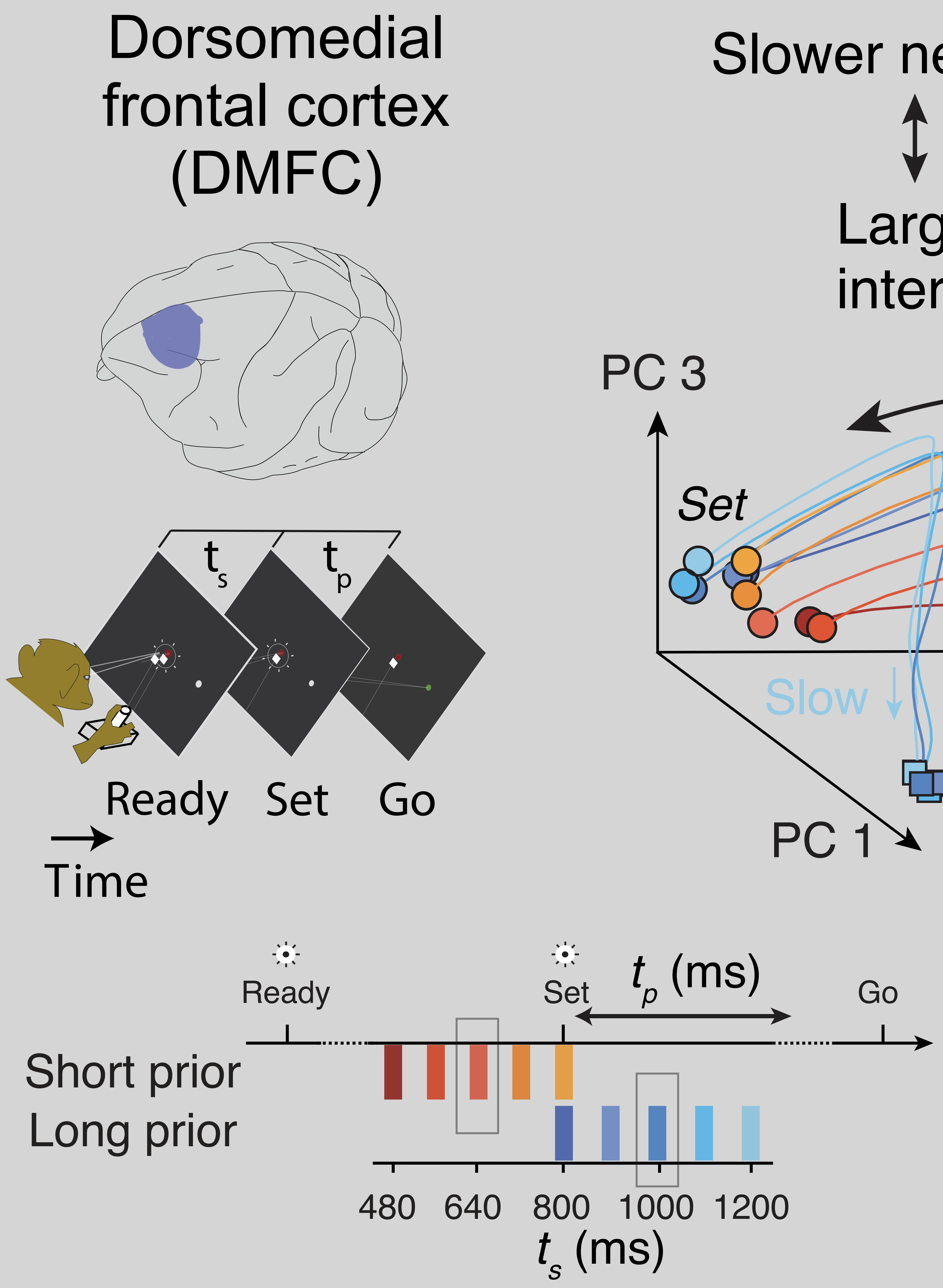

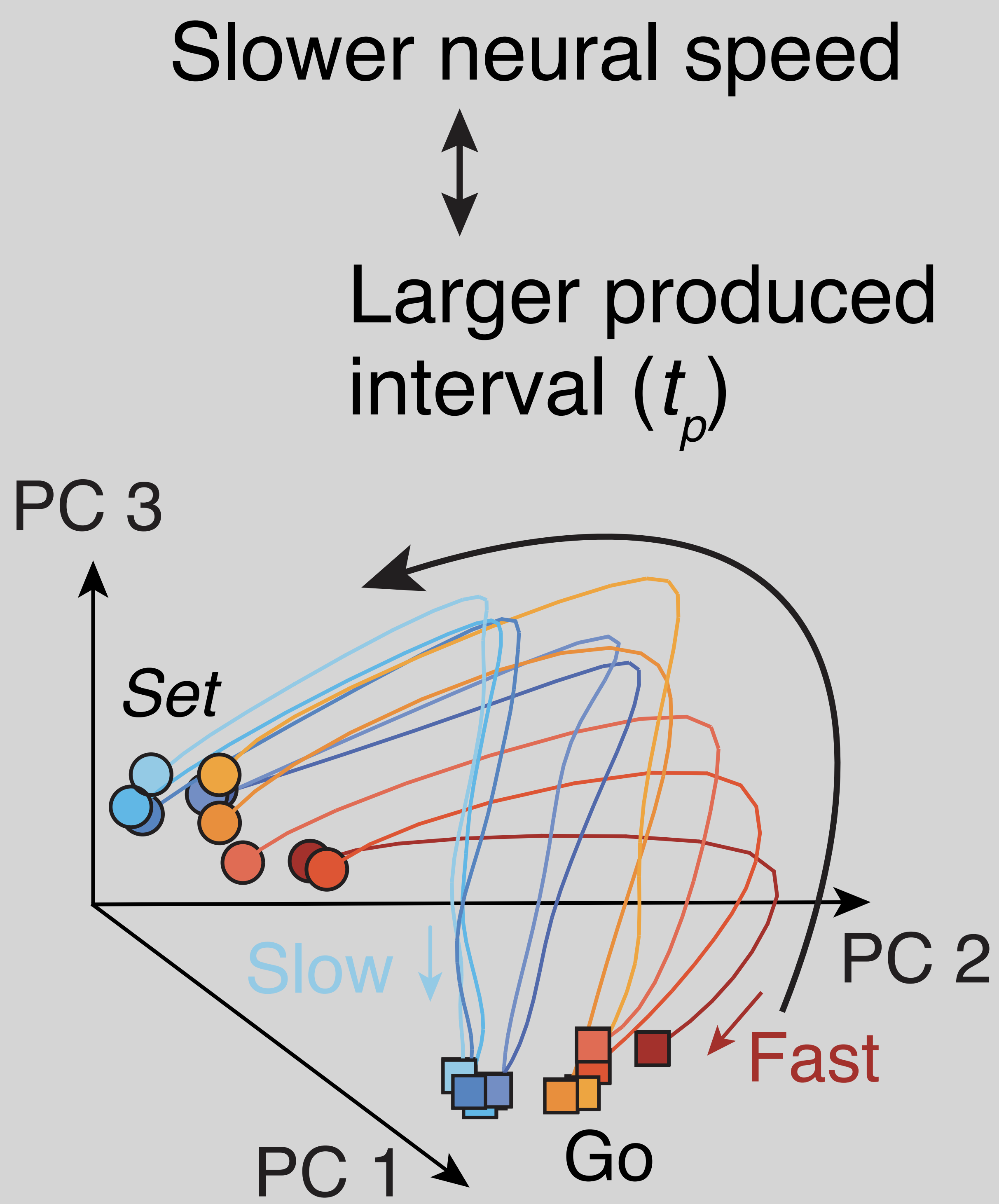

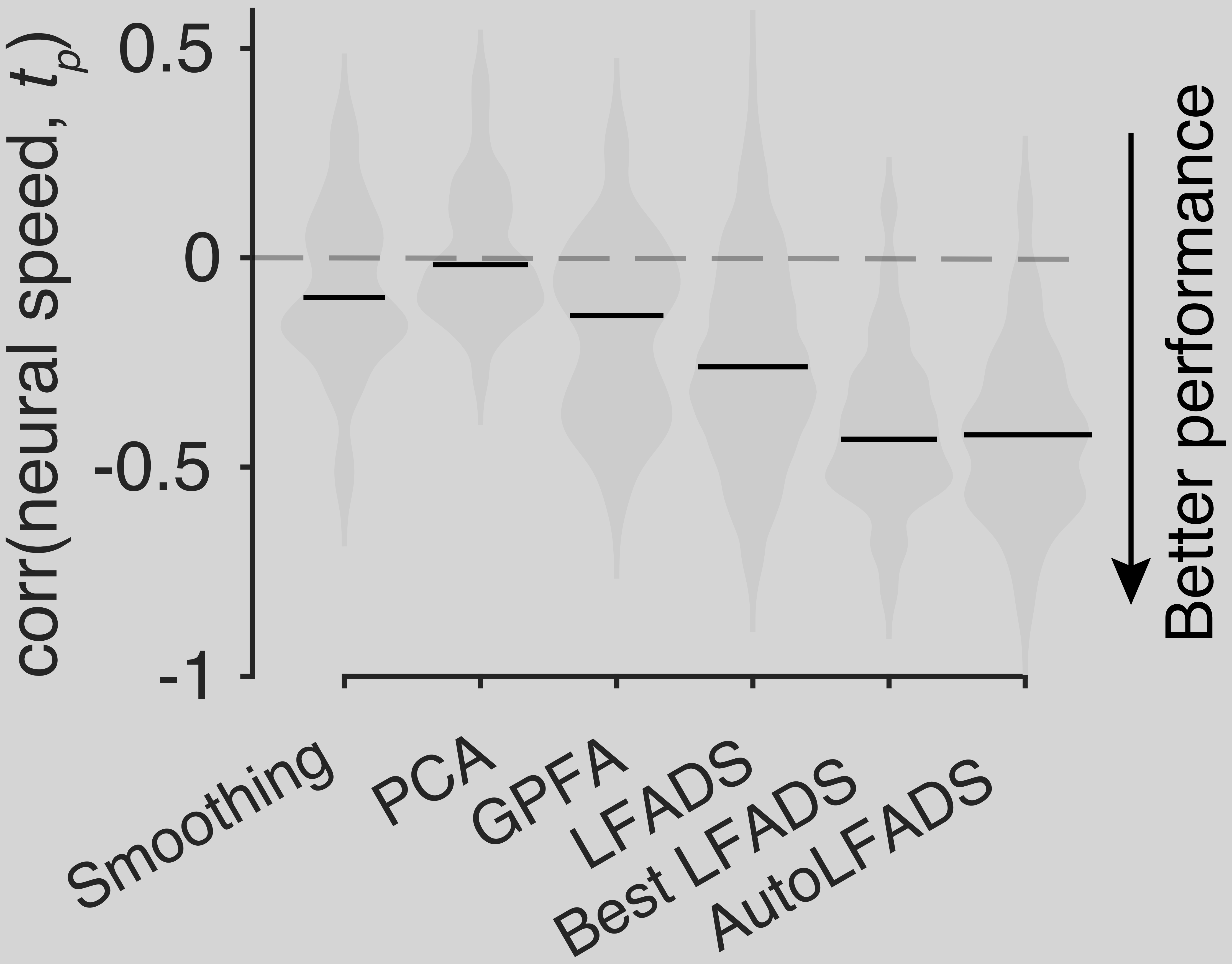

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