How do animals wait?
Investigating patterns of neural activity during the waiting period

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Project by the Quiet Alligators Team
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Does neural activity in the waiting period correlate with correct task performance?

Neural correlates of attention and planning:

F(activity(waiting)) ⟷? activity(task)

Can we predict task activity levels and is it different for correct and incorrect trials?

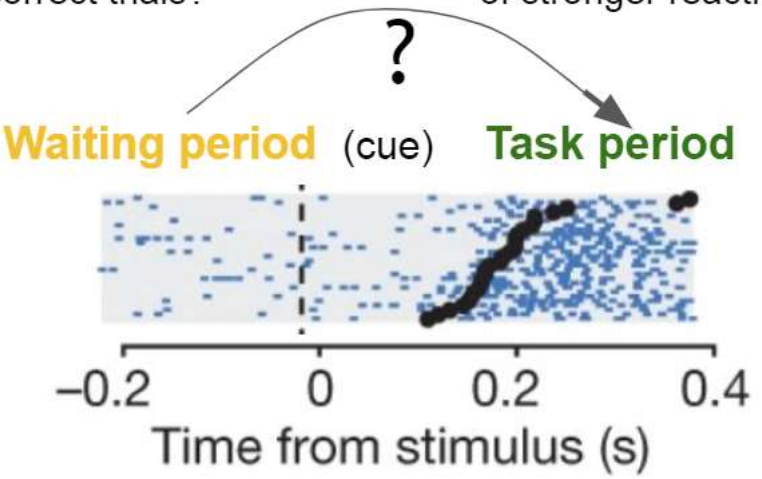
Linear Model Analysis

Reactivation of task related neural patterns facilitates correct task performance.

corr(activity(waiting)) ⟷? corr(task)

Are correct trials preceded by waiting periods of stronger reactivation? In what brain areas?

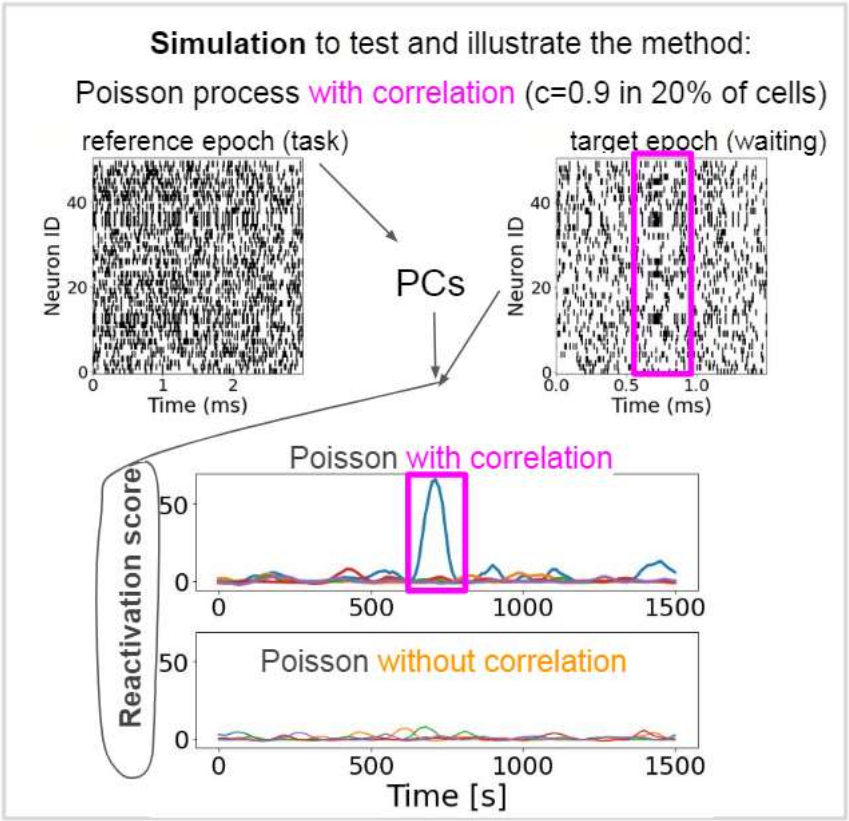
PCA Reactivation Analysis

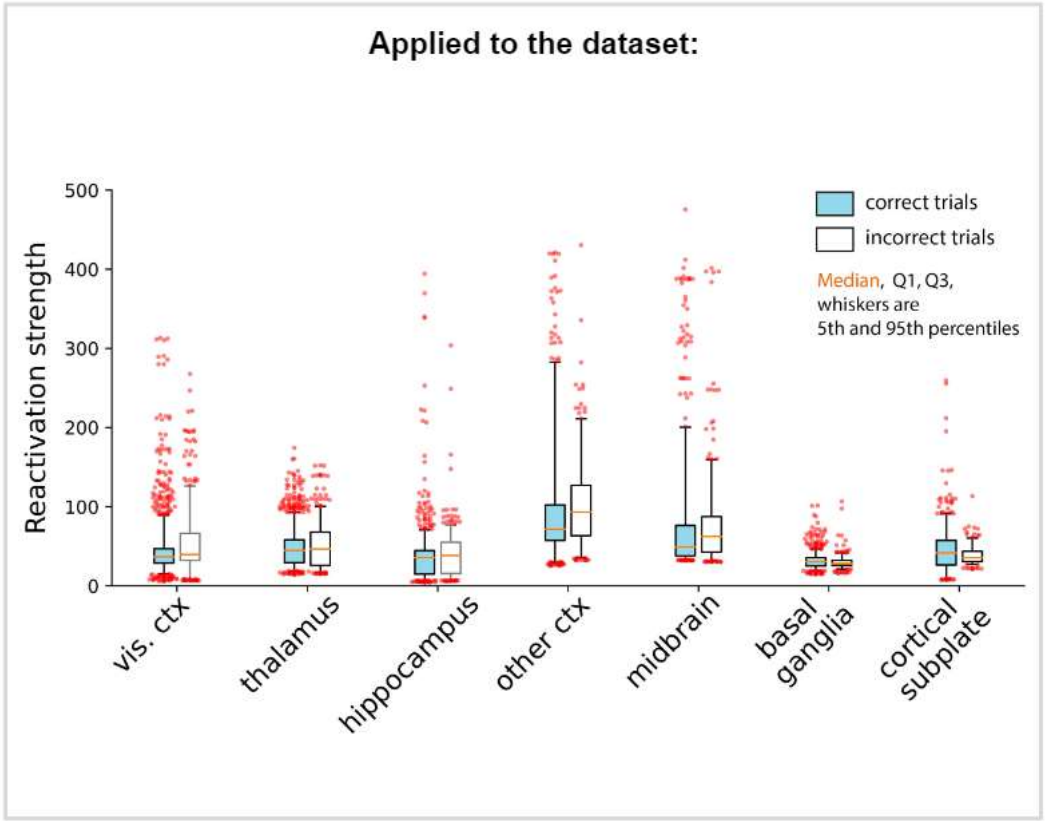


Choice of dataset: *Steinmetz et al., Nature, 2019*

Reactivation strength differs more between areas than between correct and incorrect trials

Based on *Peyrache, et al., Nat Neuroscience, 2009*

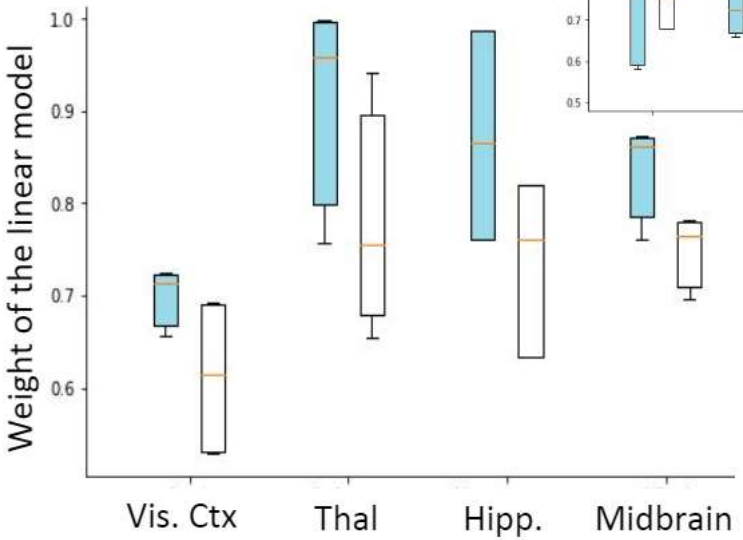


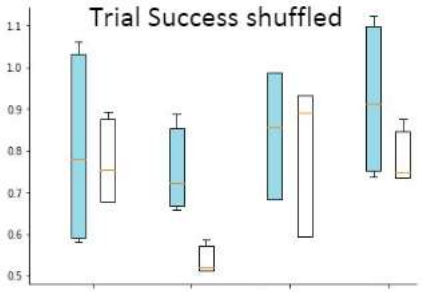


The mean activity of the neuron during the task period can be predicted by the mean activity during the wait period

$$\mu_{task} = w_1 \, \mu_{rest} + w_0$$

Mean firing rate, averaged over trials over time – 1 model per brain region





Prediction ✓

Correct != Incorrect

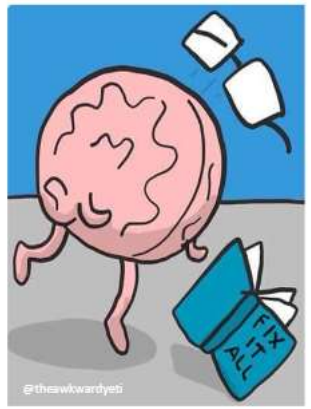
Logistic Regression ✗

Overfitting

Regularization ✗

60% choice accuracy

WE DID NOT SOLVE THE BRAIN



Task difficulty affects the dimensionality of neural population activity

By: Sydney Dimmock, Pui-Shee Lee, Daniel-Cosmin Marcu, Joram van Rheede, Heng Wei Zhu

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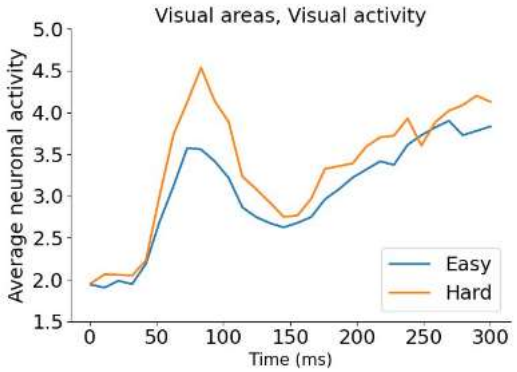
Project outline

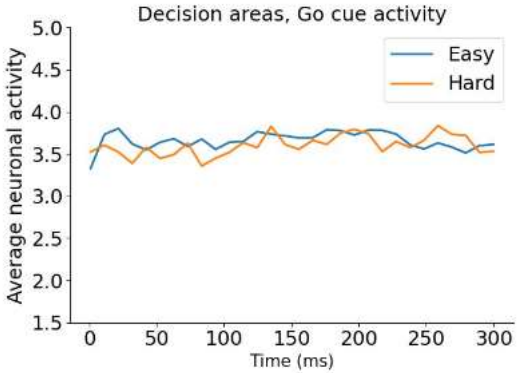
Brief scientific background: Decision uncertainty is the degree of confidence on whether a choice is correct. Challenging decisions are associated with higher uncertainty and more errors. However, how this is reflected in neural population activity in the brain remains unclear. It has been observed in rodents and primates that the dimensionality of frontal areas decreases when they perform incorrectly in tasks suggesting the importance of high dimensionality representations in executing the correct response. Are these changes in dimensionality directly reflected in the level of difficulty in the task?

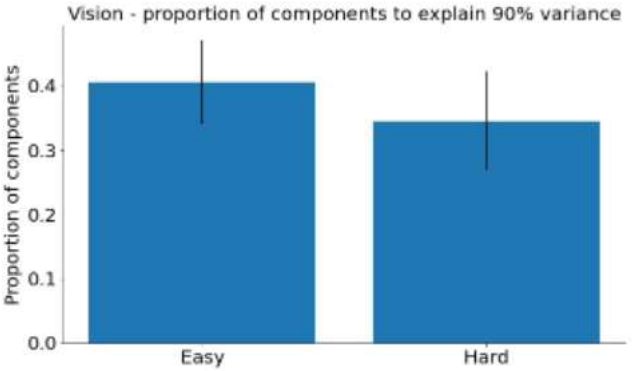
Scientific question: How does the dimensionality of neural population activity in the Steinmetz data set change when the animal is presented with easy and hard tasks? Does task difficulty predict how well neurons encode choice?

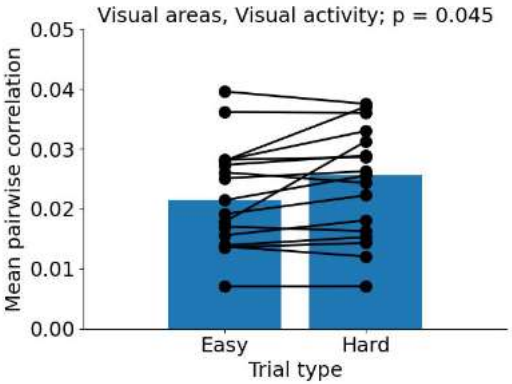
Approach: Compute pairwise correlations between neurons to establish redundancy; Run PCA to investigate dimensionality; Explore GPFA to investigate lower-dimensional dynamics; Ridge & reduced rank regression to establish dimensionality of inter-area communication; GLM & logistic regression to investigate how well neural population predicts behavioural response.

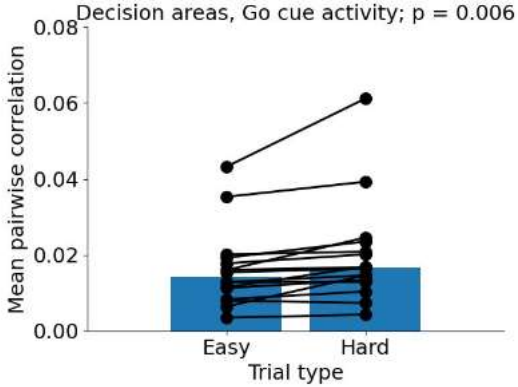
Pairwise correlations between neurons and PCA of neural population activity reveal more redundancy and lower dimensionality in hard trials

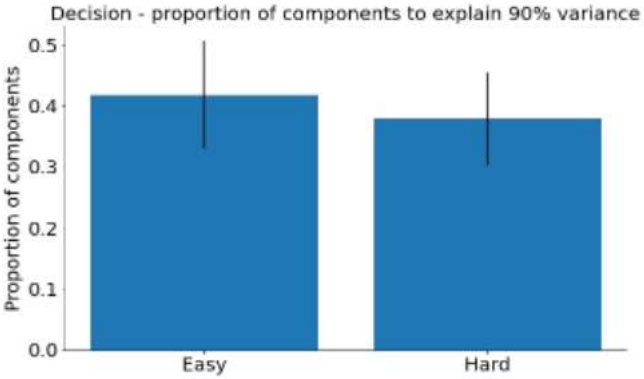


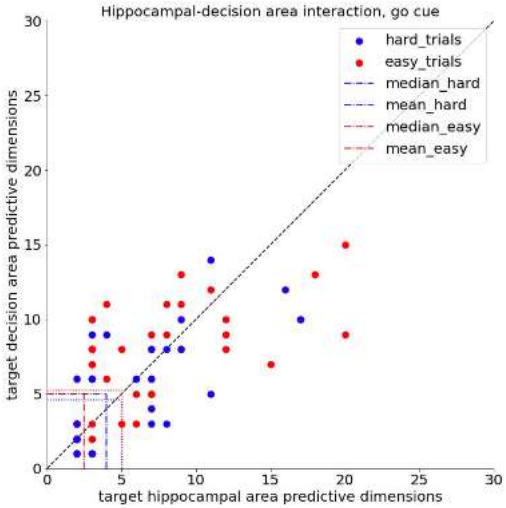


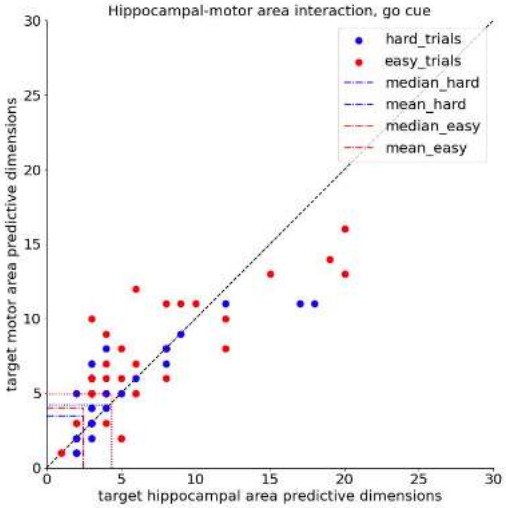






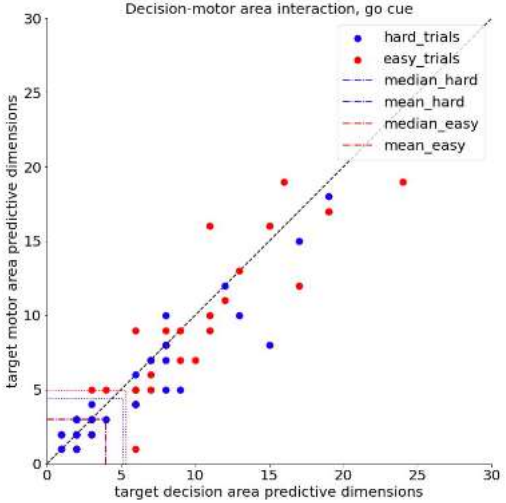


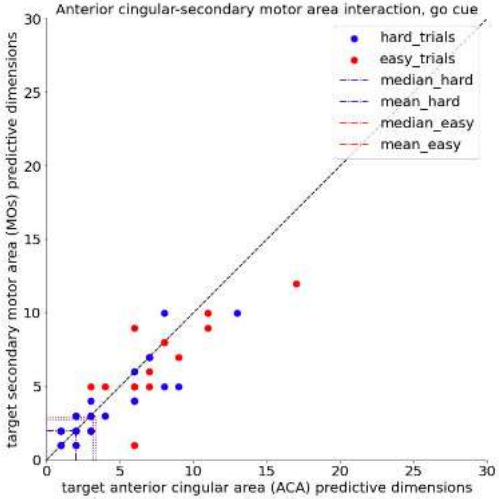


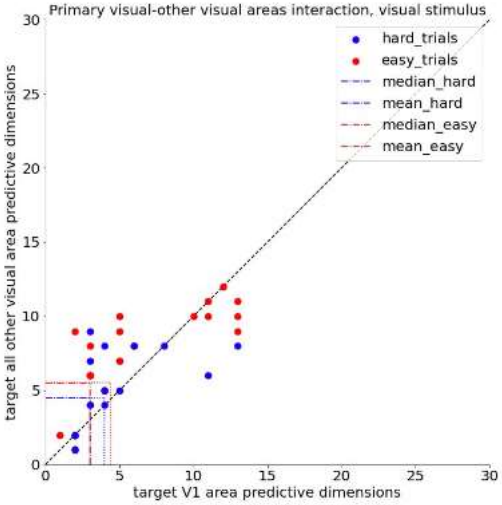


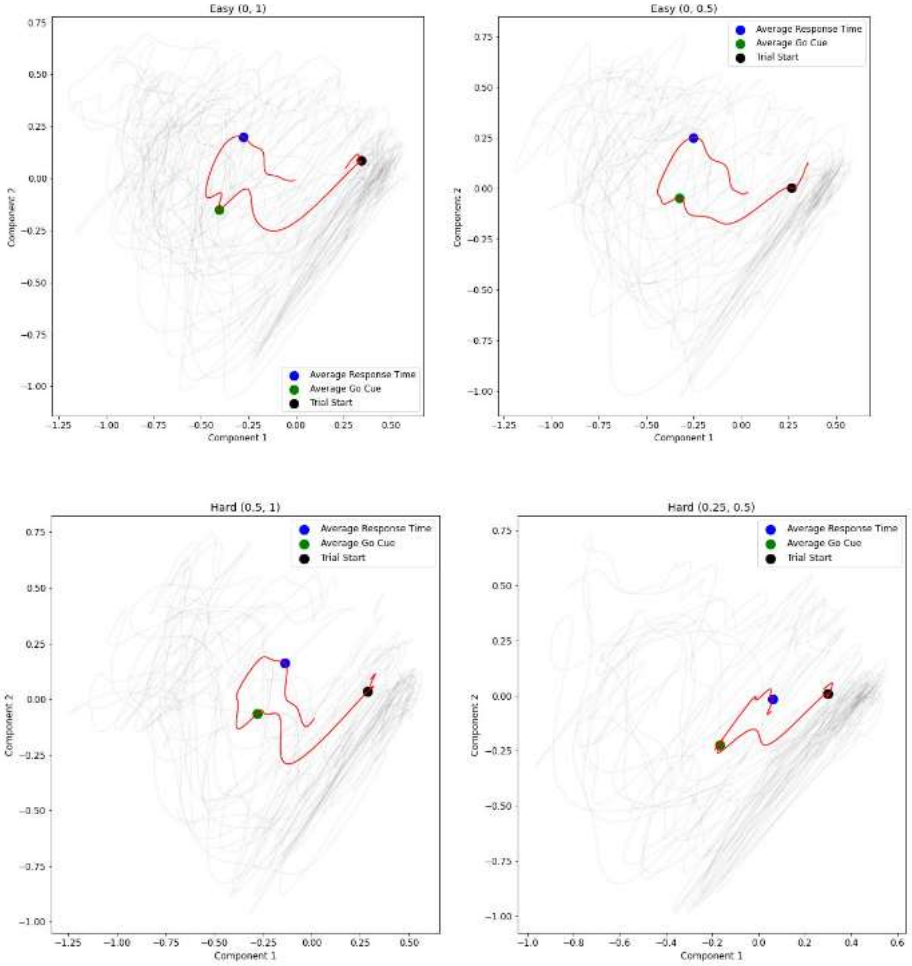
Communication subspace between within cortical area and inter-area are lower dimensional in hards trials compared to easy trials

Techniques: ridge regression, reduced rank regression



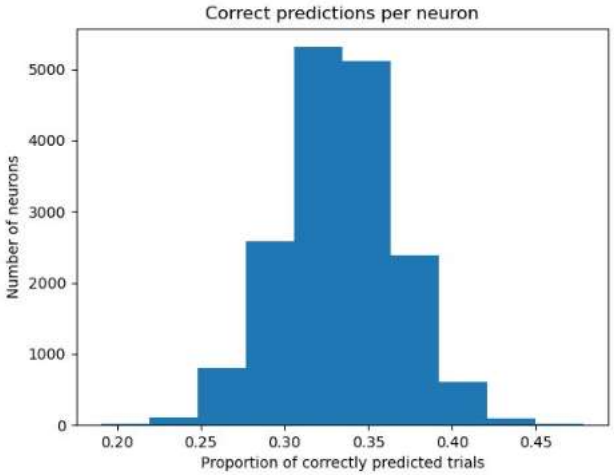


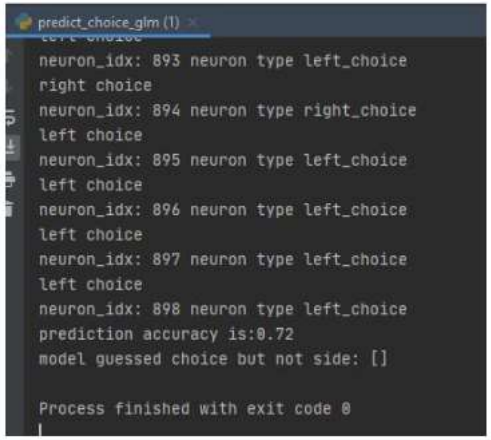




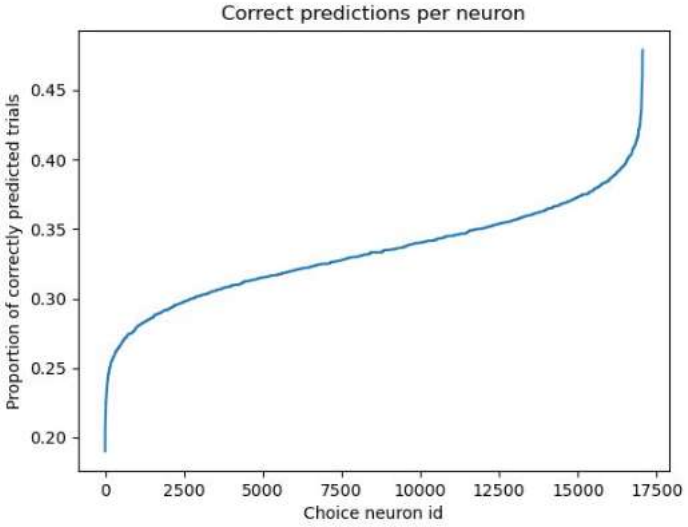
Gaussian Process Factor Analysis

- Gaussian process factor analysis was used to visualise the latent trajectories of easy and hard trials. Example trajectories from recording session four are given on the left.
- Whilst providing a visual insight into how neural activity evolved through the trial of interest, this was not a quantitative result.
- Significance tests were computed for extracted trajectory lengths over sessions, however a statistically significant conclusion was not reached.





Choice can be decoded from neuronal spiking patterns using GLMs



Conclusions & Lessons learnt

Conclusions - Increased task difficulty resulted in lower-dimensional neural population activity as captured in pairwise correlations and PCA of within-area activity as well as inter-area correlations. Lower-dimensional population dynamics did not appear quantitatively different for easy vs. hard trials. GLMs could be used to predict choice but we ran out of time for doing a trial difficulty comparison...

Lower dimensionality of the neural population response could reflect increased ambiguity about course of action (which we were hoping the GLM approach might address) or perhaps the effect of attention on neural synchrony.

Lessons learnt - Diving into a complex data set under time pressure with high-level dimensionality reduction methods is pretty ambitious; you realise there many basic elements of an experiment that may introduce confounds and need serious thought to be controlled for (e.g. unequal numbers of neurons between sessions; unequal numbers of easy / hard trials, more incorrect responses in the hard trial group).

A lot of groundwork needs to be done before doing all the fancy methods you want to do.

Making (causal) interpretations about lower-dimensional neural population activity that generate predictions for further experiments is not straightforward - we are still debating what is going on...

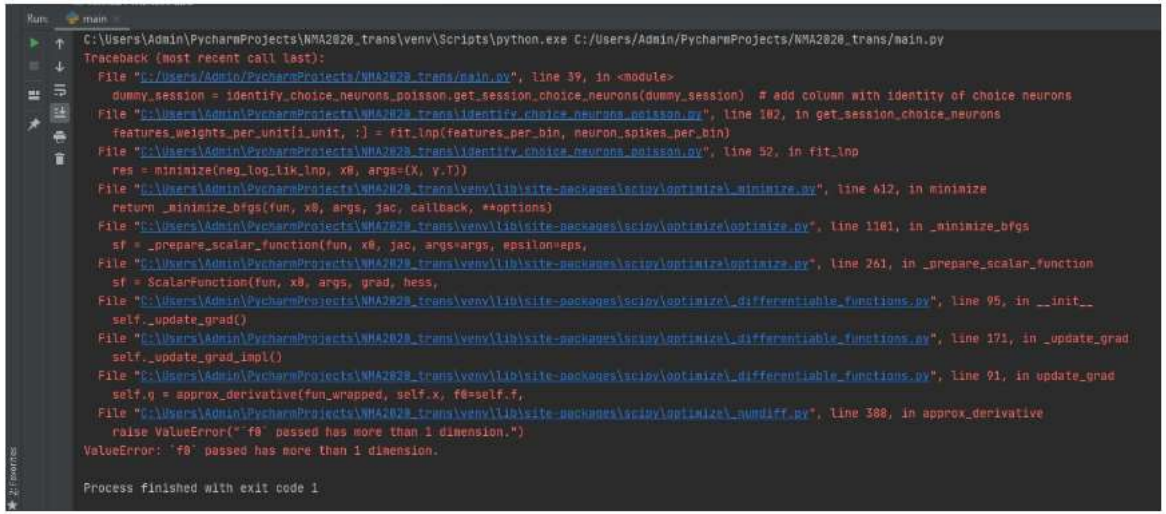
Task distribution in a remote project is an art; and so is merging individual contributions into a single project narrative!

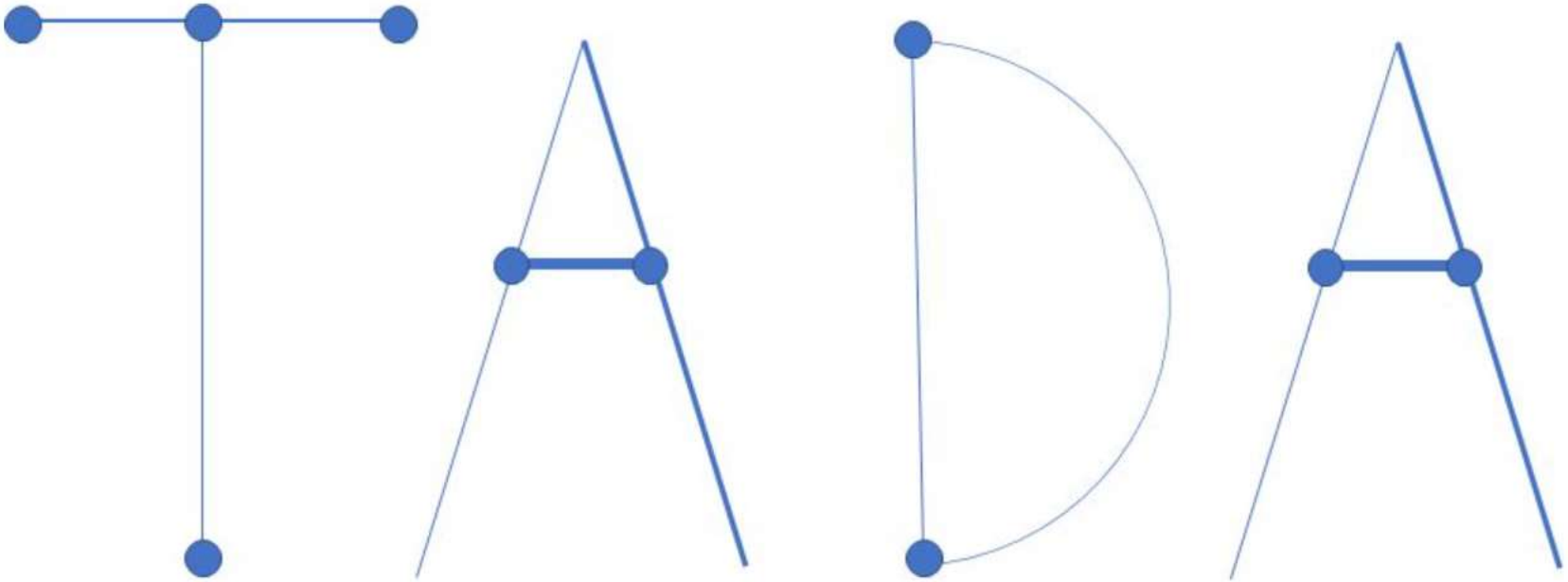
Appendix A: Python error hall of fame

```
     63   # for i in range(4):
---> 64     all_spikes.append(contrast_data['correct_spikes'][brain_area_idx,i,gocue[i]:response_time[i]].reshape(NN, -1)) # go cue to response
     65     # all_spikes.append(contrast_data['correct_spikes'][brain_area_idx,i,50:gocue[i]].reshape(NN, -1)) # stim onset to go cue
     66     # print(contrast_data['correct_spikes'][brain_area_idx,i,gocue[i]:response_time[i]].shape)

ValueError: cannot reshape array of size 0 into shape (0,newaxis)
```

SEARCH STACK OVERFLOW

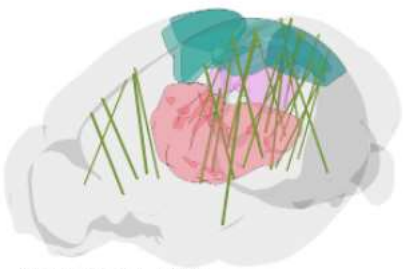
```
<ipython-input-16-30c4c4a7f90d> in comparison_bar(vals_1, vals_2, area_name, event_type)
     33   # for j in range(n_vals):
     34   #   print(j)
---> 35   is_not_nan[j]    = ~np.isnan(vals_1) & ~np.isnan(vals_2);
     36
     37   print(is_not_nan)

TypeError: ufunc 'isnan' not supported for the input types, and the inputs could not be safely
coerced to any supported types according to the casting rule ''safe''
```



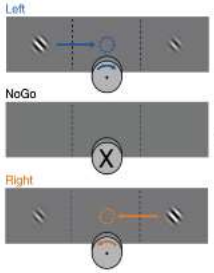


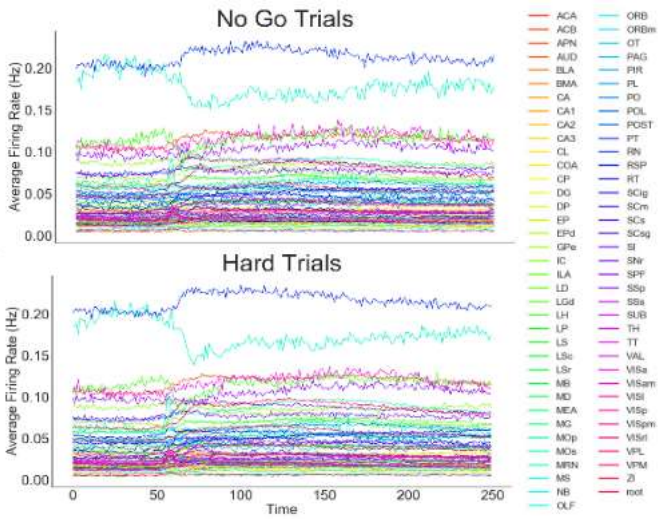
Top-down Influences and functional connectivity in a contrast discrimination task

What is the influence of task difficulty on functional connectivity, within and between regions outside of primary visual areas?



Steinmetz *et al*., 2020,
Brain rendering by Federico Claudi, Branco Lab



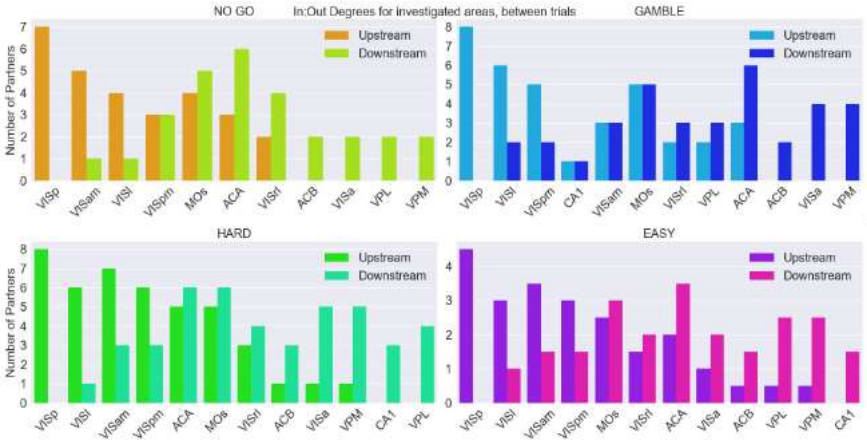


Granger Causality

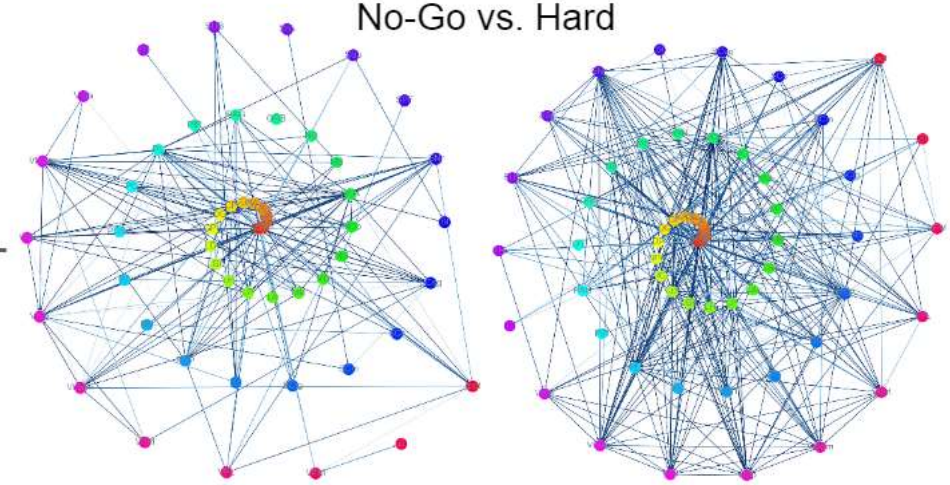
$$H_0 : y_t = a_0 + a_1 y_{t-1} + \epsilon_t$$

$$H_a : y_t = a_0 + a_1 y_{t-1} + b_1 x_{t-1} + \epsilon_t$$

Comparing Upstream & Downstream Partner number:
Hard task has greater functional connectivity across brain areas

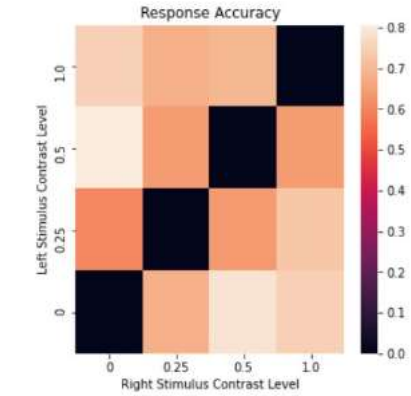


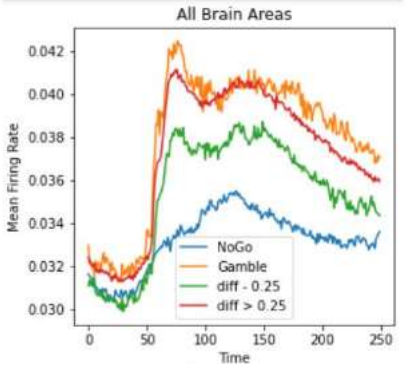
Functional Connectivity:
No-Go vs. Hard



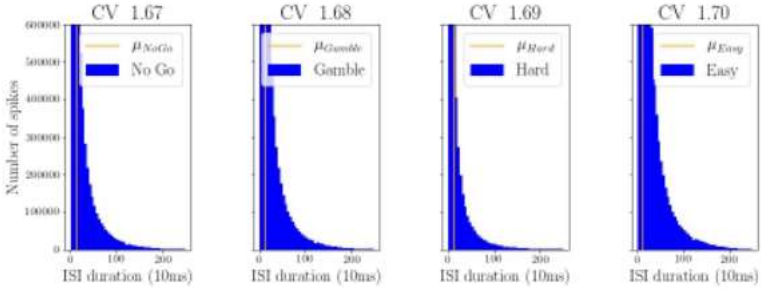
Helpful insights and learning experience

- Different statistics of the raw data might tell a different story/ show the effect differently (ISIs, mean firing rates, dimensionality reduction)
- Getting from spikes to continuous time series can be tedious

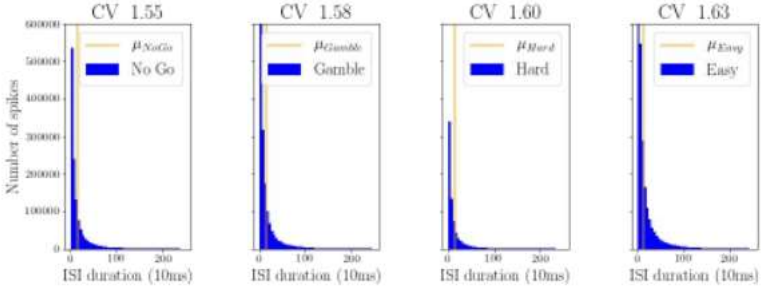




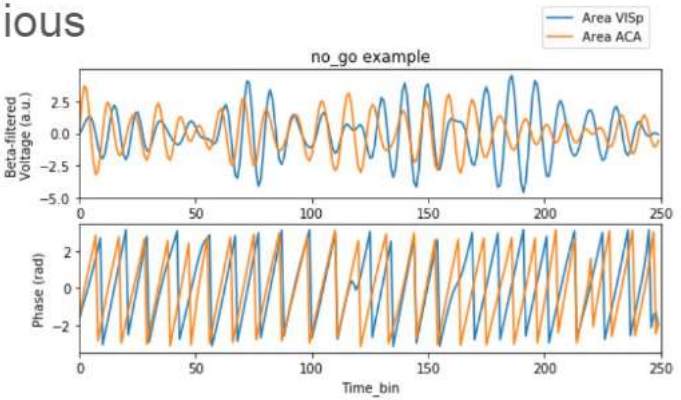
All areas

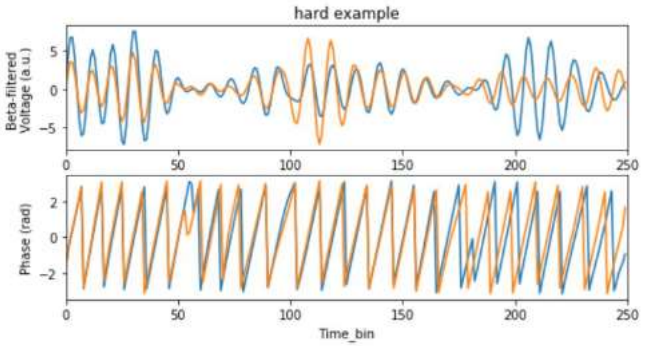


Total areas selection*



* VISp, MOp, ACA, ACB, CA1





- Granger causality seems straightforward to apply at first but there are different pitfalls, one has to be aware about (multiple comparisons correction [bonferoni correction], stationary, autocorrelation of the data)
- Limit the selection of areas to look at when you have ALL the data is HARD!
- Set time limits for theoretical discussion and project outlines

⇨ We can still do cool science during and despite the pandemic!

Who did the work: Aspiring Toad pod members

Junji Hua | Ada Duan | Markus W. Pleijzier | Daniel Giffney | Patricia Rubisch

Special thanks to the “Gambling Mice” : Cori, Lederberg, Theiler, Tatum, Richards, Radnitz, Müller, Moniz, Hench, Forssmann

Behavioral and neural correlates of choice confidence

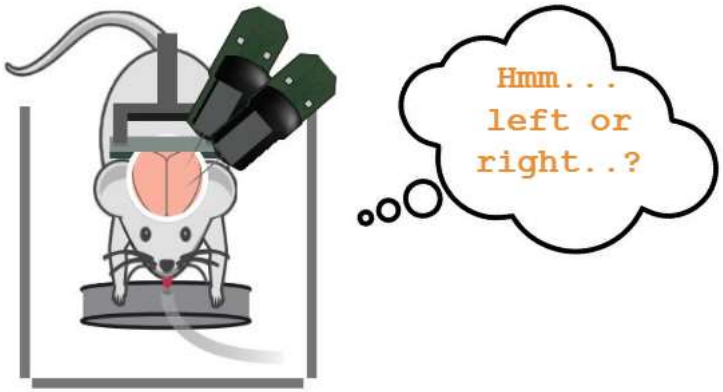
By: Alex Chagovetz, Butovens Médé, Shuqi Liu, Claire Warriner

150-Accomplished Wrasse / Team Earth, Syn & Fire

neuromatch academy

What are the behavioral and neural correlates of choice confidence or uncertainty?

Background



Animals need to make choices every day, but how are these choices made? Choice uncertainty and confidence are important aspects of this phenomenon.

We examined the Steinmetz et al., 2019 dataset to address this question.

Methods

Easy trials: contrast >= 75%
Hard trials: contrast <= 25%

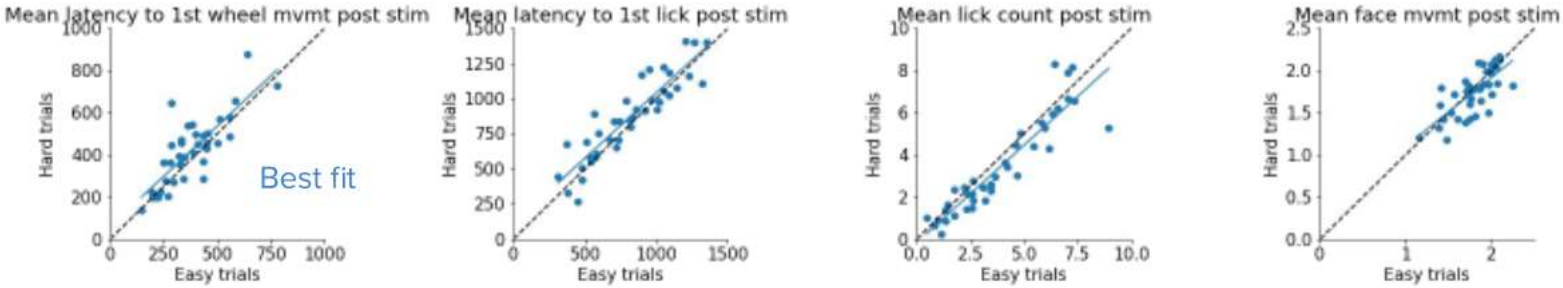
We examined behavioral correlates pre- and post-reward and assessed significance using paired and non-paired non-parametric tests (Wilcoxon signed rank and rank sum).

We examined neural data by reducing dimensionality via PCA, predicting trial difficulty with linear regression, and visualized clusters using tSNE.

Behavioral correlates of trial difficulty

Pre-reward presentation
(stimulus onset)

Paired session means

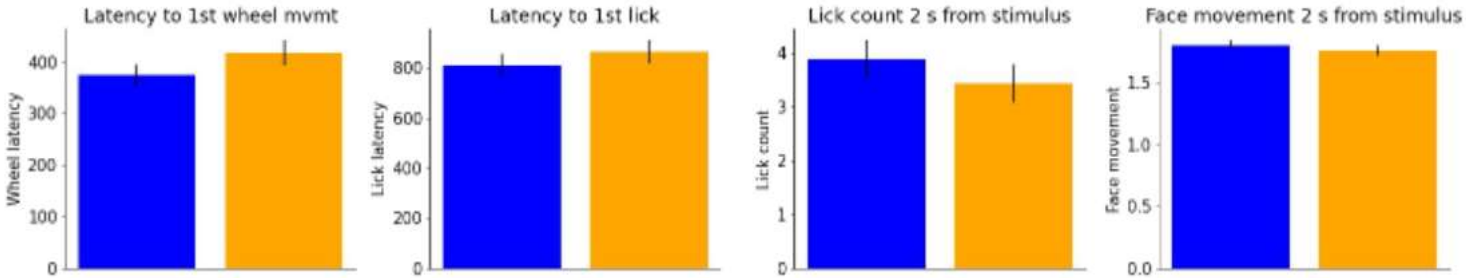


Wilcoxon signed rank test:

p = 0.012 | p = 0.024 | p = 0.001 | p = 0.209

Unpaired trial means

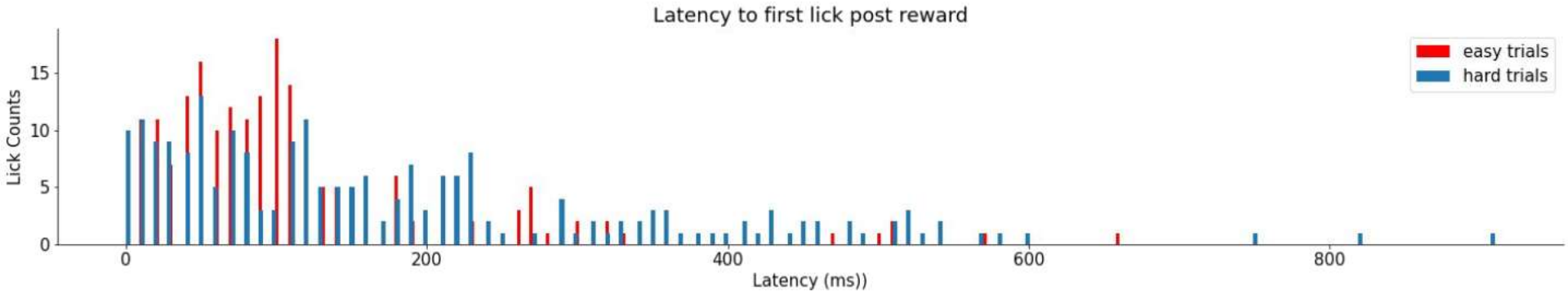
Easy trials
Hard trials



Wilcoxon ranked sum test:

p = 8.2e-07 | p = 0.062 | p = 0.003 | p = 0.0001

Behavioral correlates of trial difficulty

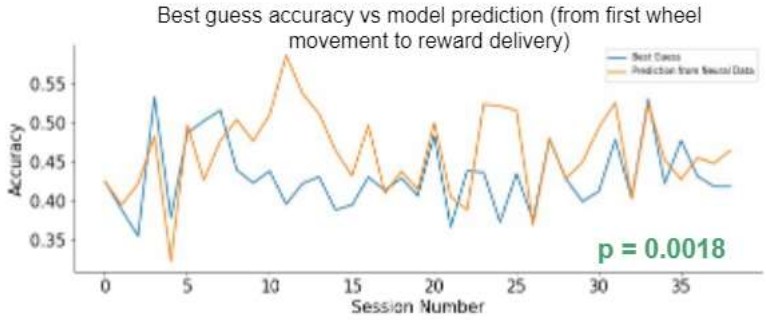


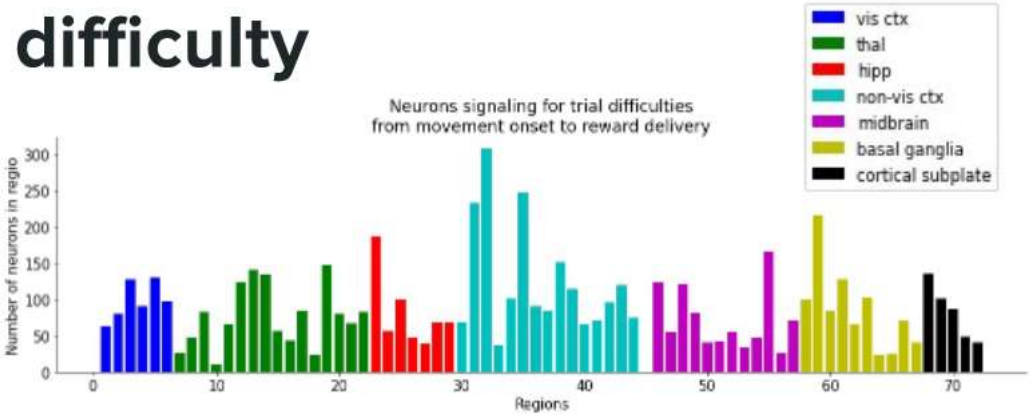
Easy Trials : Mean latency to first lick = 115.73 ±7.51
Hard Trials : Mean latency to first lick = 179.95 ±11.32

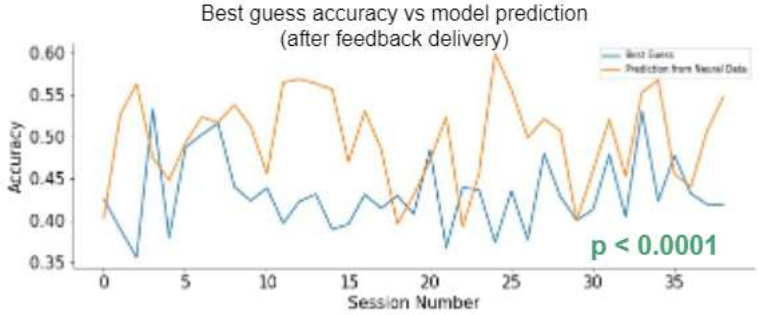
T-test (parametric)
p - value = 3.72e-06

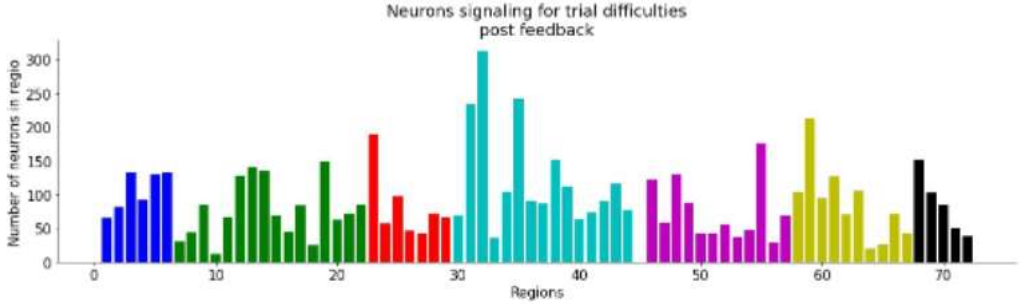
Wilcoxon signed rank test (non-parametric)
p - value = 4.63e-06

Neural correlates of trial difficulty









Closing observations

Behavioral

- Latency to first wheel movement and lick count (2 s from stimulus onset) were significantly difference for easy and hard trials when examined on session means and trial level, and lick latency post-reward was significant for a representative session.
- These parameters are good candidates for behavioral correlates of choice certainty
- To better study this question, the behavioral task could be modified to include a direct read-out of the animal's confidence using a betting paradigm as in Miyamoto et al., 2017, though this was done in primate

Neural

- We can predict trial difficulty from neural data, and this signal is observed broadly across regions but is strong in non-visual cortical areas (AUD,COA,MOp).
- To better address our question, further recordings could be made in areas associated with decision making and confidence: wide-field imaging during behavior could indentify these candidate regions for high volume multiarray recordings
- Optical techniques could then be used to perturb activity in these regions to test predictions on their contributions to choice confidence

State sequences in population dynamics across cortical areas

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Main project questions:

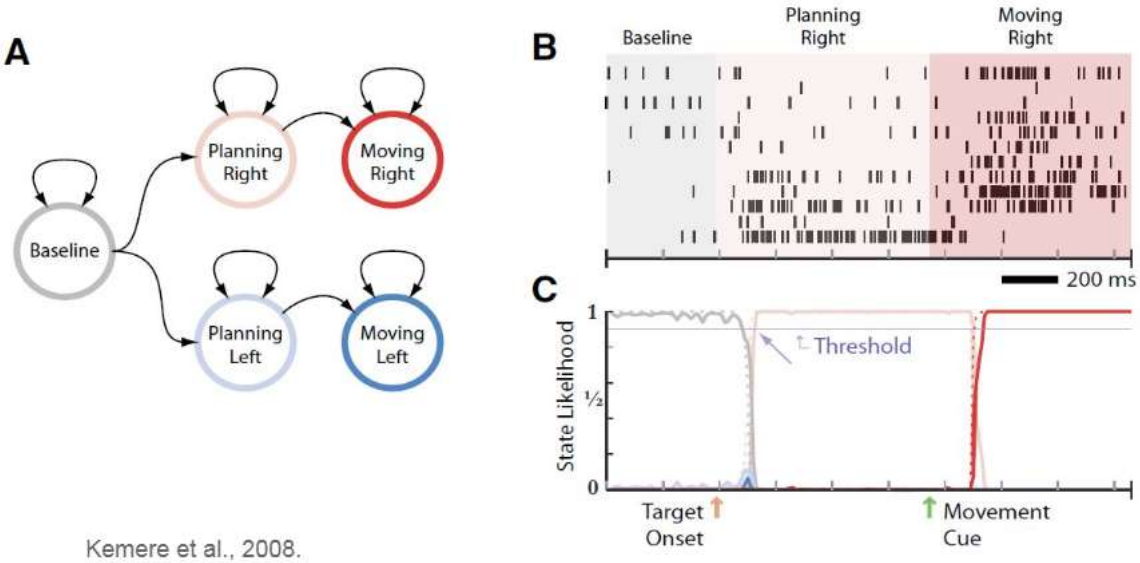
Can we predict an animal's behavior or stimulus, which was presented to an animal, from the brain state?
What are the time lags between behavior/stimulus and transition from one brain state to another in different brain areas?

Brain state is a set of firing rates of a small group of neurons in a particular period of time.

We used a **Hidden Markov Model (HMM)** to reveal these brain states and find transition probabilities between them.

Main tools:

- Steinmetz dataset
- SSM package in Python

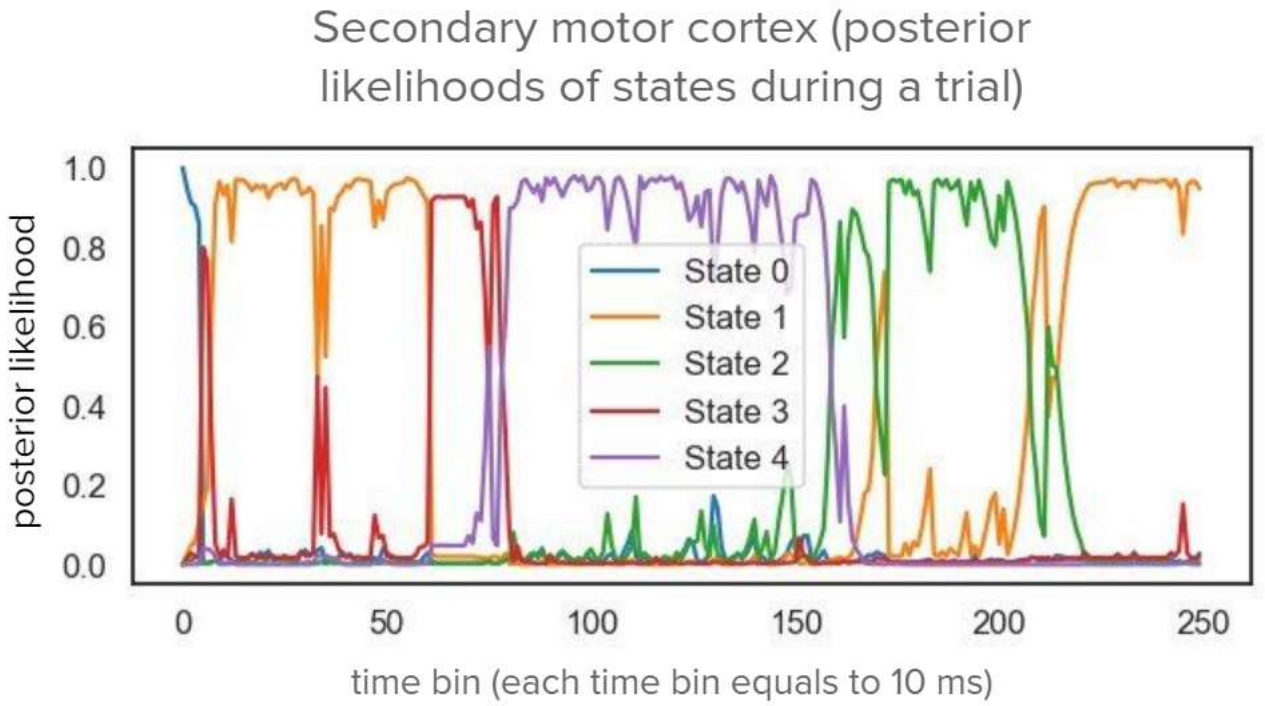


Kemere et al., 2008.
Detecting Neural-State Transitions Using Hidden Markov Models for Motor Cortical Prostheses.

An example of successful analysis

We can see that in secondary motor cortex states are strongly associated with animal's behavior:

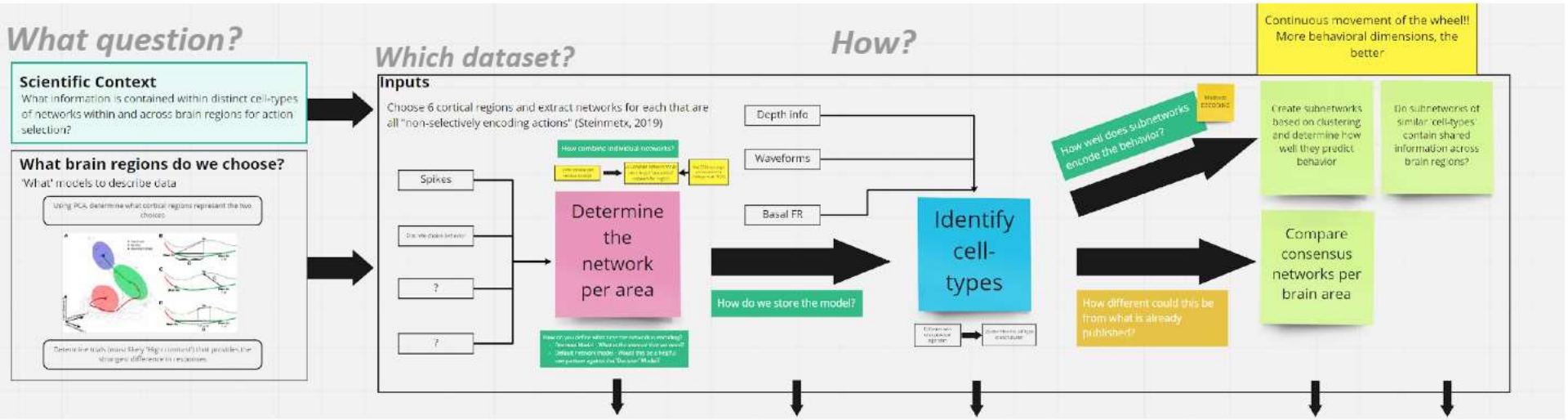
1. Baseline (state 1) - before stimuli presentation (500 ms)
2. Planning (state 3) - decision-making process (550-800 ms)
3. Motion (state 4) (800-1500 ms)
4. Reward (state 2) (1500-2000 ms)
5. Baseline (state 1) to the end of the trial



Challenges we faced

1. **Difficulties with implementations in Python** of cross-validation to find the right number of brain states (= number of hidden states in the HMM) and the Baum-Welch algorithm to identify the transition matrix between them
2. **Selection of neurons** for model creation and fitting
   We have several hundreds of neurons from each brain area but for the model we should have chosen 10-20 neurons. We have just chosen 15-20 the most active neurons for model building but it did not improve our model
3. **Huge difference between trials**
   Because of that we cannot have estimated time lag between behavior/stimulus and transition from one brain state to another - too significant variation because of not well enough created HMM

Action encoding across brain regions, but how?

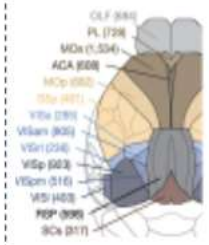


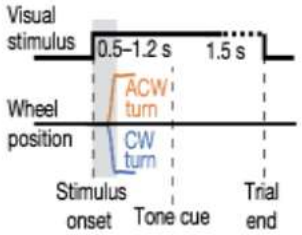
We hypothesize that functional subnetworks encode actions with similar trajectories through neural space and contain similar cell-type specific contributions.

Who? Aishling Cooke, Jane Huang, Kevin Mastro, Sara Mahallati, and Asim Waqas
Mentor: Pouya Bashivan

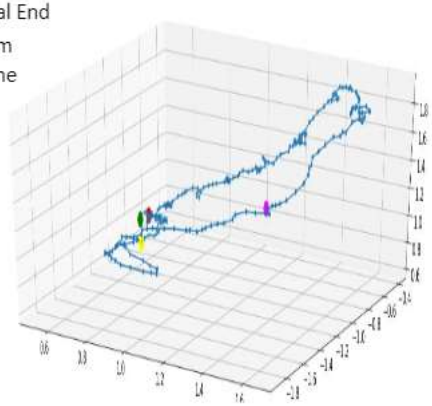
Computational Workflow

Visualize Action encoding across cortex



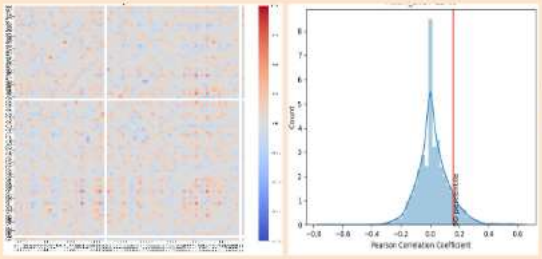


- Trial Start
- Trial End
- Stim
- Tone



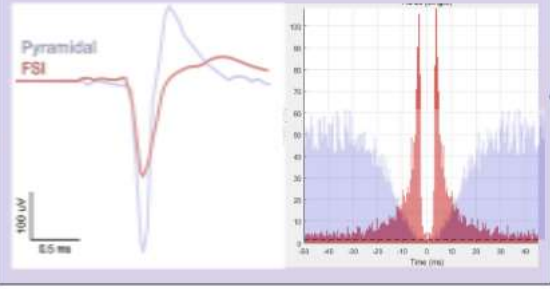
Extract Function Subnetwork

Identify relationships via covariance matrix



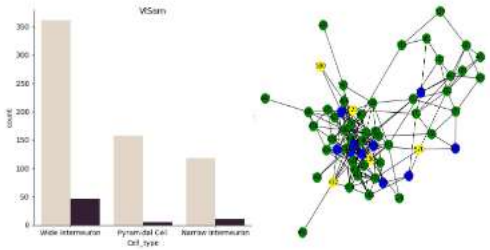
Identify Cell-types

Putatively identified via waveform and passive properties



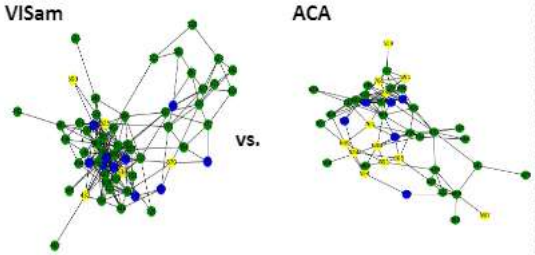
Model Comparisons

What makes up these subnetworks?

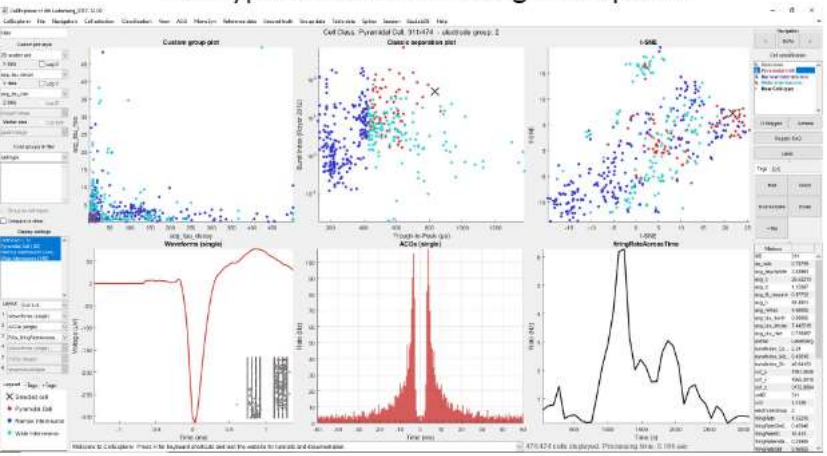


Do subnetworks of similar cell-types predict behavior?

VISam vs. **ACA**

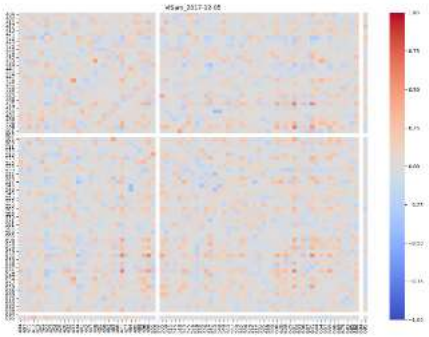


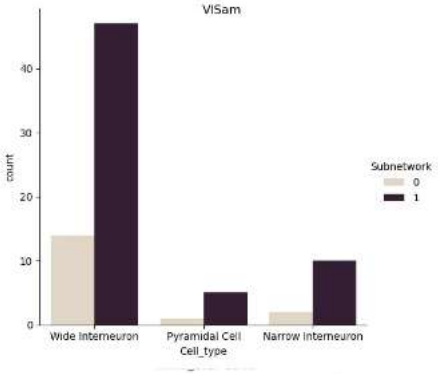
Cell type classification using CellExplorer*

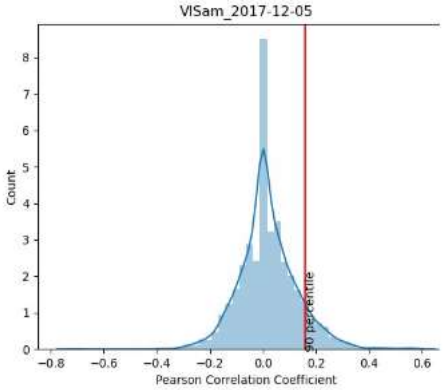


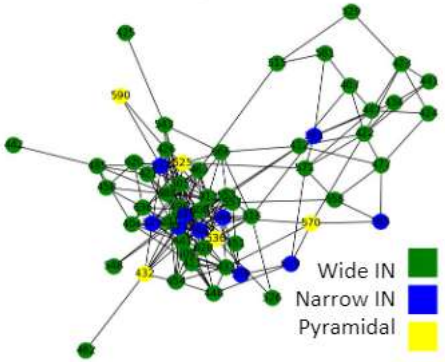
* https://cellexplorer.org/
Data from Peter Peterson on databases of Buzsaki lab

Determine the network per area









Relationship between subnetworks and behaviour: Can spiking and pupil area predict behavior?

$$y = \sigma(\theta^T X)$$

Left vs. Right	Spike counts	Pupil area
0	15	0.0337
1	7	0.0014
0	3	0.0173
1	8	0.0346
1	1	0.0157
0	0	0.0029

```
train_accuracy = compute_accuracy(X, y_response.values, log_reg)...

Accuracy on the training data: 50.18%
```