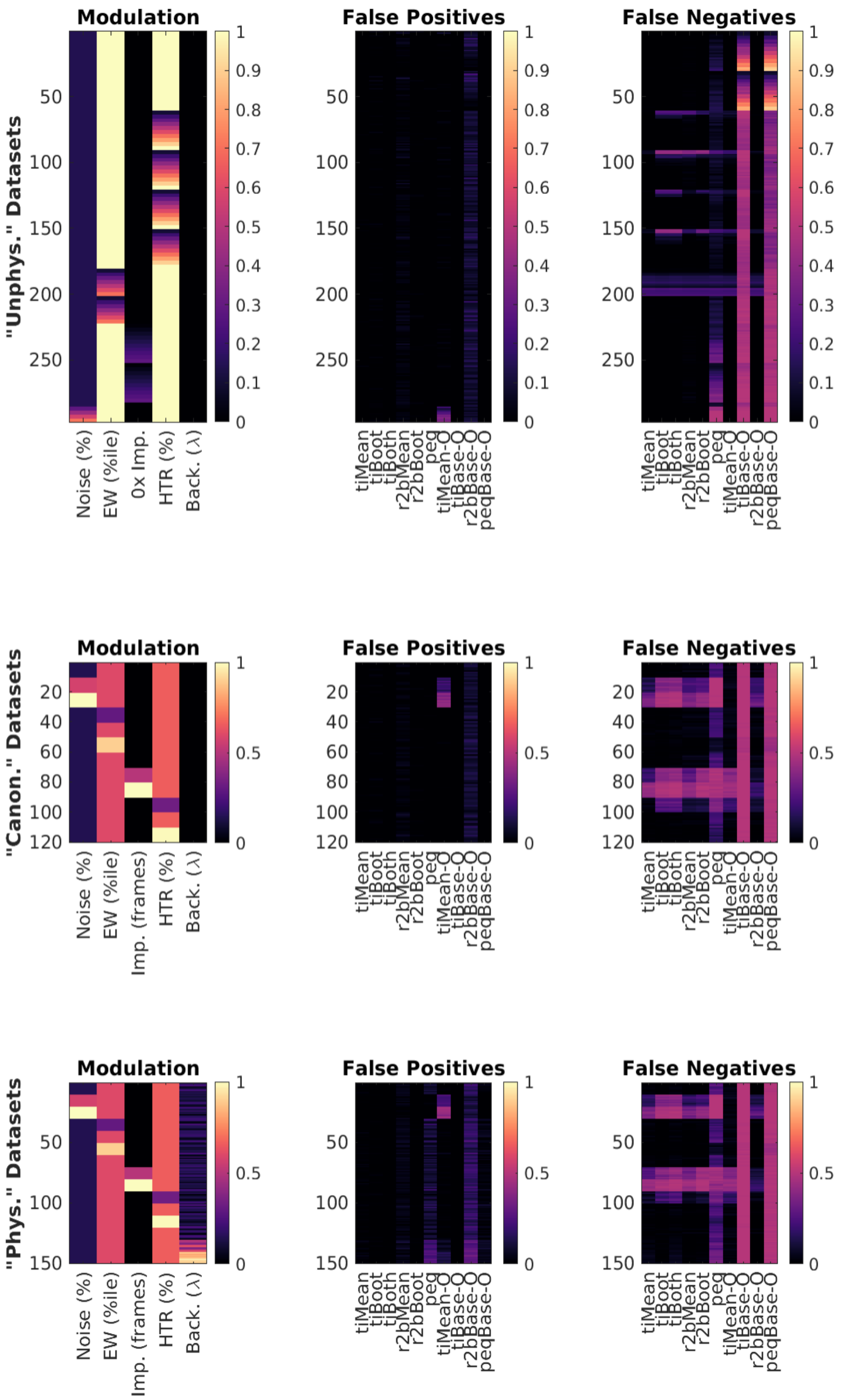
Extended Data Figures (Supplementary)

Extended Figure 1-1. Modulation profile along with the False Positive and False Negative rates per dataset, for important parameters configured in each of the 567 synthetic datasets generated. A-C: “Unphysiological Regime”, D-F: “Canonical Regime”, G-I: “Physiological Regime”.


"Unphys." Datasets
Modulation
Noise (%)
EW (%ile)
0x Imp.
HTR (%)
Back. (λ)
False Positives
False Negatives
tjMean
tjBoot
tjBoth
r2bMean
r2bBoot
peq
tjMean-O
tjBase-O
r2bBase-O
peqBase-O
"Canon." Datasets
Imp. (frames)
"Phys." Datasets

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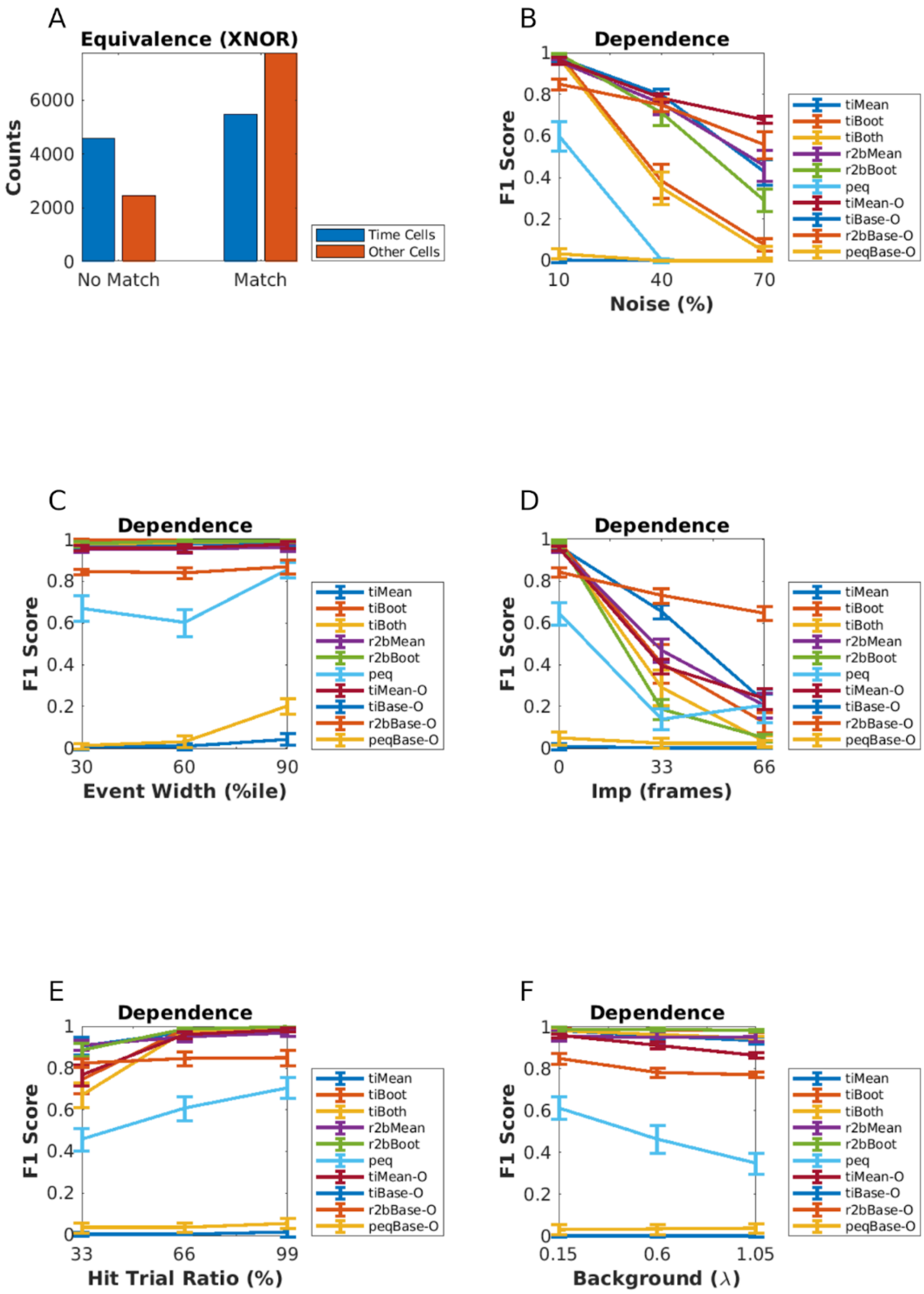
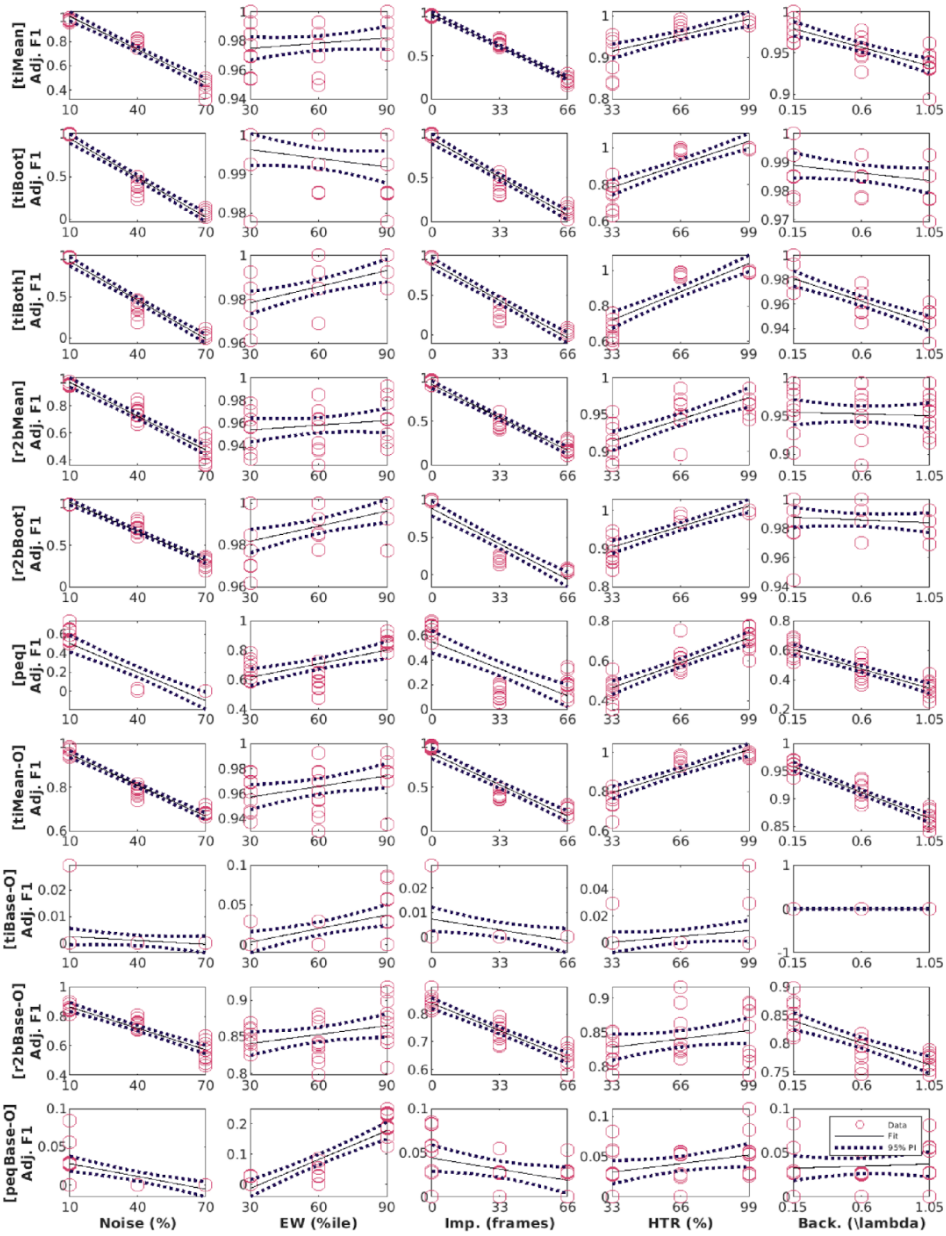
Extended Figure 6-1. A: Equivalence by XNOR matching the prediction lists from the top six detection algorithms (Blue: Time Cells; Red: Other Cells). B-F: Dependence of the predictive performance (F1 Score) on the various important synthetic dataset configuration parameters, B: Noise (%), C: Event Width (%ile), D: Imprecision (frames), E: Hit Trial Ratio (%), and F: Background Activity (λ).


A
Equivalence (XNOR)
Counts
No Match
Match
Time Cells
Other Cells
B
Dependence
F1 Score
Noise (%)
C
Dependence
F1 Score
Event Width (%ile)
D
Dependence
F1 Score
Imp (frames)
E
Dependence
F1 Score
Hit Trial Ratio (%)
F
Dependence
F1 Score
Background (λ)
tiMean
tiBoot
tiBoth
r2bMean
r2bBoot
peq
tiMean-O
tiBase-O
r2bBase-O
peqBase-O

Extended Figure 6-2: Linear Regression fits for all algorithm parameter dependence curves with data points (red circles), best fit line (black), and the 95% prediction interval (PI; dotted black lines). The columns represent the physiology regime modulation parameter (out of the 5 main parameters tested), and the rows represent the various implemented algorithms for time cell detection.


[tiMean]
[tiBoot]
[tiBoth]
[r2bMean]
[r2bBoot]
[peq]
[tiMean-O]
[tiBase-O]
[r2bBase-O]
[peqBase-O]
Adj. F1
Noise (%)
EW (%ile)
Imp. (frames)
HTR (%)
Back. (\lambda)
Data
Fit
95% PI

3634

Chapter 5 – Discussion

The study of hippocampal CA1 sequences

The standardized protocols described in the thesis are expected to aid in future experiments studying hippocampal CA1 sequences. Our simultaneous 2-photon calcium imaging recordings and behavioural training provided us the platform to study neural activity from ~100-150 cells/animal at behaviourally relevant timescales (~70 ms per frame).

We standardized a multi-day Trace Eye-Blink Conditioning or TEC ("Chapter 2 - Behaviour") training system for mice based on previous literature (Siegel et al., 2015) and could demonstrate several types of behavioural adaptations that experimental animals could learn under a variety of experiment conditions and modulations. Notably,

1. The animals typically learnt the tasks quickly, within 1-2 weeks of training.
2. Modulating the inter-stimulus interval (ISI) between the CS and US results affected the expression of the conditioned response (CR).
3. A wide palette of stimuli may now be incorporated into existing protocols as either of the presented stimuli (data not shown). TEC experiments with multiple CS, viz., blue LED and Tone, have been tried in the lab. They form the primary behavioural modulation being investigated by a lab colleague. These experiments are now directly possible due to the standardization efforts.
4. In our experiments where we extended the Trace Duration, animals show retention of previously learnt CR times (Figures 19-21), showcase complex blinks (Figure 19) without change to CR onset (Figure 20).

5. We could also train animals on very long Trace durations (550 ms, and 750 ms), which have previously not been reported for head-fixed mice.
6. Across all the single interval training experiments, the animals only produce one conditioned response, with time of peak adjusted relative to the timing of the US.
7. Complex blinks were only observed in animals trained to more than one trace interval.

Simultaneous large-scale recordings have been fundamental to the discovery of long spatiotemporal activity patterns with several participant CA1 neurons (Davidson et al., 2009; Foster, 2017). Electrical recordings provide many orders of magnitude better temporal resolution, not to mention being a direct readout of action potentials. However at the time of the design of the thesis, imaging based approaches could yield more recorded neurons per experiment animal. We standardized 2-photon fluorescence based chronic imaging of hippocampal CA1 neurons to allow calcium imaging based recording of the spatiotemporal sequences across multiple days (”Chapter 3 - Imaging”). This gave us the ability to

1. Record neurophysiology over a large population of neurons (~100), in conjunction with temporally relevant behavioural contexts and modulations, albeit at ~100 ms temporal resolution.
2. Chronically track cells across various behaviour sessions without ambiguity.
3. Allow for scalability in the per animal yield of recording neurons with the use of faster and modern 2-photon microscope hardware utilizing Resonant Scanning instead of galvo-scanning, as well as multi-channel imaging.

We could identify time cells with the ability to retain, de-tune, or even re-tune, over the course of multiple sessions. Given no change in the behaviour protocol variables, it is unlikely we would have found such adaptations without scaling up the yield of cells or improving our temporal resolution while recording each individual session. Since the behaviour task is typically learnt to ~70-80% performance levels over the course of multiple sessions, our methodology gives us the ability to look into learning mechanisms utilized by the CA1 in the interim. Production quality datasets were quickly obtained by colleagues in the lab, following the protocols standardized and described here.

From our preliminary data, the largest proportion of re-tuned cells had tuning peaks shift to earlier time points (Chapter 3 – “Imaging”, Figure 37), with subsequent sessions. Early in training, the timing of tuning peaks would typically occur near the time of the Unconditioned Stimulus (US; air-puff to eye). Our experiments presenting stimuli to naive animals (in accordance with Dhawale, 2013) suggested that somatosensory stimuli may be able to modulate CA1 responses, while many neutral stimuli may not (Chapter 3 – “Imaging”, Figure 29), without training. These results do allow for speculation on how initially neutral Conditioned Stimuli (CS; Light LED pulse) could develop behavioural valence for the animal, viz., the selective suppression of Response Inhibition to the previously neutral CS. An as yet unknown fraction of time cells may initially be triggered by the Unconditioned Stimulus (US; air-puff), but over the course of multiple training sessions, shift tuning fields to respond to the CS at the level of the CA1 network. However, many more datasets would be required to firmly establish any mechanistic insight into the phenomenon.

Standardizing combined behaviour and recording experiments

Hippocampal CA1 time cells had been previously described to fire in reliable sequences, as observed in animals that learnt a single-session version of the TEC paradigm (Modi et al., 2014). We wished to further develop the paradigm and more fully study time cells, especially during the early or acquisition phase of training (sessions 1-7). It was not considered trivial to bundle behaviour and recording in a non-interfering way. For instance, we needed to study time cells longitudinally or chronically, and this is likely achieved by ensuring that the experimental animals were not overtly stressed, but rather, were reasonably compliant to the experiment in terms of motivation.

Towards this,

1) We focused on performing only one surgery, viz., head-bar implant and hippocampus to minimize surgery-induced trauma, rather than multiple surgery strategies.

2) We incorporated a treadmill for the animals to run on during the experiments, at the potential cost of observing z-axis drift in the imaging.

3) Imaging requires that the sample (experimental animals) be illuminated only by the excitation laser and that the sensor systems for the emitted photons receive only the photons from the excited sample. We considered and designed the filter sets before our photomultiplier tube (PMT) in the emission path, to reject all IR and partially red frequencies, not just to protect the sensor from the excitation 2-photon

laser, but also the red/short IR illumination on the animal's eye for the behaviour camera.

Through our experiments, we were able to provide some evidence that somatosensory stimuli, but not other neutral stimuli, could trigger CA1 responses but the effect of behavioural training results in the development of CA1 responses to the CS, now triggering a whole spatiotemporal sequence of activation. Altogether, we were able to observe preliminary results regarding the tuning, de-tuning, and re-tuning of time cells to temporal fields during learning, as described in Chapter 3 – "Imaging".

Mapping sequences to abstract variables

Visual cues are typically considered important to place cell activity and tuning. The specific requirement of vision, however, was tested in a study published in 2015. Experimenters switched off the lights as their animals navigated a maze. The animals were provided only olfactory cues at specific locations in the maze, yet place cell activity and tuning could be recorded. This suggested that the hippocampus could use non-visuospatial resources to generate spatial representations, when vision was compromised (Zhang & Manahan-Vaughan, 2015).

In a sound manipulation task (SMT) rats changed the frequency of auditory tones in their environment, by self-initiated joystick control, ramping logarithmic sweeps of frequency space. The rate of change in frequency could be manipulated either by the animal or pseudorandomly by the experimenter. This study describes neural activity recorded from the medial entorhinal cortex (MEC) as well as the hippocampal CA1 with sub-populations that were found tuned to specific frequency “landmarks” during the auditory sequence (Aronov et al., 2017). The CA1 were, thus, argued to be capable of tuning to abstract variables and were designed to map out sequences of events/stimuli in their own spatiotemporal patterns of activity.

The ubiquity of neural sequences in a wide variety of systems has been discussed previously (Bhalla, 2019; Conen & Desrochers, 2022; S. Zhou et al., 2020) and over a century of research has discovered remarkable physiological features that may be used to identify neurons that participate in these sequences. However, research is still required to carefully dissect out the contribution that each participant neuron has to behaviour, an important goal in neuroscience (Ranck, 1973, 1975).

The use of user-configurable, categorically labeled synthetic calcium activity profiles allowed us to probe and compare a range of different time cell detection algorithms, identifying strategies to best classify time cells. We were able to identify Temporal Information as a strong contender for the choice of algorithm for such classification (Ananthamurthy & Bhalla, 2023). The algorithms developed along the way were tested within the time scales of ~100 ms, that correspond to Replay Sequences or other behaviour timescale sequences. We expect the analysis routines to be useful in a variety of different experiments that could potentially help describe the neural code in more detail.

Better temporal resolution requires new techniques

There are many other techniques that experimenters in the field have employed to record activity. Many of these techniques do, in fact, achieve much better temporal resolution. Here are some examples:

1) Resonant Scanning based 2p calcium imaging can achieve even up to 30 Hz for 4x larger fields of view, or more frame rates for smaller fields of view (Bonin et al., 2011; Leybaert et al., 2005; Nguyen et al., 2001; Rochefort et al., 2009). At the time when we started the experiments for the thesis, Resonant scanning microscopes required a lot of additional, expensive components to be purchased. Towards this, we co-wrote a sanctioned DBT grant application (BT/PR12255/MED/122/8/2016) and began setting up the new microscope. However, we did not have this technology available for experiments before 2020.

2) High-density tetrodes can be used to perform electrical recordings at >=20 kHz, as compared to ~14.5 Hz for our galvo-scanning 2p calcium imaging experiments. This technique typically achieves yields of ~40 cells for hippocampal recordings, and we argued that we could achieve a higher yield (>100 cells) with galvo-scanning 2p calcium imaging. The relative sparsity of the hippocampal neural code in terms of cells participating in any engram, mandates high-yield recordings to identify the full temporal sequence of CA1 activations (Foster, 2017).

3) Neuropixels (Jun et al., 2017) can be used to perform electrical recordings at >=20 kHz. At the time when we started the experiments for the thesis, these sorts of electrical probes had yet to be successfully deployed in published literature.

We discuss all these techniques while comparing electrical- vs. imaging-based recording strategies in Chapter 1 – “Introduction”. Fundamentally, given the technological constraints at the time, we had devised combined behaviour with galvo-scanning 2p calcium imaging as the principle for the experiments described in this thesis.

Does the brain create or predict?

An important direction to neuroscience research is to understand the brain and nervous system, in how these structures allow animals to interact meaningfully with their environment. More conservatively, however, the goal of this thesis was to help provide a multi-disciplinary toolkit to study time cells in the hippocampus. Predictive coding has been considered as a way for the brain to ultimately use external sensory information to minimize prediction errors during tasks (Doya et al., 2007; Rao & Ballard, 1999). One of the core ideas of Bayesian approaches to neurophysiology and behaviour is that the brain could be modeled as a prediction machine that is constantly modeling the change of variables. These variables may be external or internal yet salient concepts to any experimental animal, arguably expressed in neurophysiology as the dynamics of engrams. The ability of the mammalian hippocampus to bind both information streams to create new, more elaborate engrams, is likely crucial to the learning of new concepts behaviourally (N. J. Cohen & Eichenbaum, 1993; Eichenbaum, 2017).

Attentional states have been shown to have a bidirectional relationship with the expression of memory and learning (Chun & Johnson, 2011;

Hutchinson & Turk-Browne, 2012; Uncapher et al., 2011). Specifically, Trace Eye-Blink Conditioning (TEC) performance has been suggested to be positively correlated with attention (Manns et al., 2000). The question of the effect of attentional states on the dynamics of the associated engram motivated an important milestone for the Thesis, *viz.*, to combine stable, adaptable behaviour studies with large-scale neurophysiology.

We were able to train head-fixed mice to TEC and confirm adaptable conditioned responses to task variables. We were also able to simultaneous record from ~100 hippocampal CA1 cell bodies as the animals acquired top behavioural performance. We observed in our preliminary results that many identified time cells showcased the ability to tune to different time points across sessions or days, as has been previously reported (Mau et al., 2018). This standardization of simultaneous behaviour and imaging ensured that colleagues from our lab were able to generate production quality data, quickly.

Several more high quality recordings and behaviour modulations would be required to conclusively describe time cells physiology and engram dynamics, at least at the level of a sub-population of hippocampal CA1. However, progress has been made to suggest the best time cell detection algorithm(s) based on their sensitivity to different recording parameters (Ananthamurthy & Bhalla, 2023). We hope that the Thesis is of aid to future research on the neural mechanisms of Learning and Memory by the nervous system.

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