THE HEBREW UNIVERSITY OF JERUSALEM

Nahsholim 2023: Abstracts

Click the title in order to reach the specific abstract page!

Table of Contents

Sessions and Talks

THE HEBREW
UNIVERSITY
OF JERUSALEM

Sessions and Talks

THE HEBREW UNIVERSITY OF JERUSALEM

Session I – From Sensation to Action

Neuronal Correlates of Task Difficulty in Mouse Auditory Cortex

Baruch Haimson

Learning is a fundamental ability of the brain. Perceptual learning is an implicit form of learning, in which perceptual performance is improved with training. For example, repetitive experience with stimuli that are closely related to each other improves the animal's ability to discriminate between them. The underlying physiological correlates of discrimination difficulty remain poorly understood. To address this issue, we trained mice on an auditory Go-NoGo perceptual learning discrimination task with a gradually increasing difficulty (sounds become closer in frequency). Then, after becoming experts on discriminating difficult sound pairs, mice were challenged with alternating easy and hard discrimination blocks while simultaneously imaging single neurons in the auditory cortex with two-photon calcium imaging. We imaged mice engaged in behavior and, separately, during passive listening. The task was designed such that one of the stimuli (NoGo) was fixed in both easy and hard tasks, and only the second stimulus was changed. This design allowed us to describe the influence of task difficulty on the response to the exact same stimulus and action under different perceptual contexts.

Advisor: Prof. Adi Mizrahi

THE HEBREW
UNIVERSITY
OF JERUSALEM

Seeing in the dark: face recognition, reading, and visual crowding under scotopic conditions

Deena Elul

In many cases, people can function visually in almost complete darkness. However, high-level vision has not been investigated thoroughly under scotopic conditions, where only rod photoreceptors are active. Under these conditions, acuity is low, and a foveal scotoma spreads for about 1 degree in the center of the visual field. We investigated how these limitations affect performance and eye movements in foveal tasks such as reading and face recognition. We recorded eye movements while testing the speed and accuracy of reading and upright/inverted face matching under photopic and scotopic conditions. We also tested scotopic crowding at different eccentricities since it could limit reading abilities. Compared to photopic conditions, under scotopic conditions participants could read accurately but slower, and they showed a similar pronounced face inversion effect (higher performance for upright than for inverted faces). Surprisingly, despite the foveal scotoma, fixations in both tasks were executed to the same locations as under photopic conditions. When viewing upright faces, participants first fixated on/near the eyes, and during reading, participants fixated on the expected preferred landing positions close to words' centers. However, the duration of fixations was longer under scotopic conditions compared to photopic conditions in both tasks. Scotopic crowding along the eccentric axis was similar to photopic results. We suggest that for reading, the lack of use of peripheral vision could be explained by the crowding experiment results, which showed that scotopic

crowding, similarly to photopic crowding, increases with eccentricity. For face recognition, it might be explained by the unharmed holistic nature of face recognition, which uses large receptive fields to achieve global perception. These results suggest that high-level visual tasks, even those that rely on foveal input, are solved in a similar manner under scotopic and photopic conditions.

Advisor: Prof. Netta Levin

THE HEBREW UNIVERSITY OF JERUSALEM

Accurate mechanistic modeling of zebrafish natural hunting behavior - a dynamical system approach

Yoav Rubinstein

Zebrafish movement repertoire is traditionally characterized by extracting dozens of body features of the body and clustering movements based on similarities in feature distributions. These clusters divide the continuous space of movements into a discrete set of 7 or 13 movement types depending on the clustering features and the behavioral context. Such descriptive approaches lack a mechanism underlying movement generation, provide limited insights on movement neural control, and struggle to identify the natural primitives of movement - all are gateways to understand the principles of sequences of movements. In this work we propose a complete dynamical model with sparse controls that accurately accounts zebrafish hunting movements. The model consists of two differential equations implementing a low-level internal oscillator with feedback on its amplitude, and a high-level control signal which represents the decision which reliably reconstruct the complete dynamics of 82% of movements. The model suggests that three types of movements cover the entire reportire. it predicts neural oscillation frequency, neural control strength, and control onset time. In addition, by reducing sequences of complex high dimensional movements into a sparse sequence of a low-dimensional control signal, it defines the primitives' space and forms a basis for understanding decision making and behavioral strategies.

Advisor: Dr. Lilach Avitan

THE HEBREW UNIVERSITY OF JERUSALEM

Organization of reward and motor signals in the oculomotor basal ganglia and cerebellum

Noga Larry

A key question in neuroscience is how the brain generates actions that maximize reward. Traditionally, the basal ganglia have been viewed as the reward center of the motor system, while the cerebellum was thought to fine-tune movement details However, we have found that cerebellar complex spikes signal the size of the future reward. These cerebellar reward signals are reminiscent of those in the basal ganglia and have reignited debate about the respective functions of the basal ganglia and cerebellum.

To shed light on this debate and provide a direct comparison of these signals, we recorded single-neuron activity from the basal ganglia and the cerebellum on the same task and in the same monkeys. We analyzed the variability of neuronal activity on a trial-by-trial basis, separating signals related to reward and eye movements, and compared coding within and across structures. Our results showed that reward expectation and movement signals were most prominent in the output structure of the basal ganglia, intermediate in the cerebellum, and weakest in the input structure of the basal ganglia. These findings suggest that information converges differently within these structures, which may have implications for our understanding of how they contribute to reward-based decision-making.

Advisor: Prof. Mati Joshua

THE HEBREW UNIVERSITY OF JERUSALEM

Session II - Computation in artificial neural networks

Discrete communication mediates effective regularization in chaotic recurrent networks

Jan Philipp Bauer

Disordered networks with discrete signaling are considered a poor substrate for computation, yet they are ubiquitous in the brain.

We show that such large chaotic networks can support reliable computation, with a surprisingly long working memory. To this end, we reformulate the recurrent network as a transparent input-output mapping that abstracts away its intractable internals. As a result, the system appears as Gaussian process, which is completely characterized by its transfer function from input to output correlations, termed the kernel.

By studying this object, we can assess the effect of chaos in networks on computation: We find that in a discrete signaling network, the sharp falloff in the transfer function acts as an effective regularizer. This allows for handling noisy observations in a robust fashion. Secondly, if the network is confronted with a regression task, a spectral decomposition of the kernel reveals that in the chaotic regime, the network exhibits a rich repertoire of modes that can explain complex observations.

In summary, our effective theory allows to assess the effect of the chaotic state in recurrent networks for computation in a tractable manner, providing a quantitative footing for its role for regularization and expressivity.

Advisor: Dr. Jonathan Kadmon

THE HEBREW UNIVERSITY OF JERUSALEM

Complete Description of Neural Network Dynamics in the Infinite Width Regime

Yehonatan Avidan

Artificial neural networks (ANNs) have revolutionized machine learning in recent years, but a complete theoretical framework for their learning process is still lacking. In the infinite width regime, there are two successful theories that capture different parts of the learning phase: the neural tangent kernel (NTK), which describes the initial phase of learning, and the neural network Gaussian process kernel (NNGP), which describes the equilibrium state of the network. However, these theories are not compatible with each other. In this work, we use the Langevin dynamics framework and tools from out-of-equilibrium statistical mechanics to describe the entire learning process of ANNs in the infinite width limit, from initialization to the equilibrium state. We introduce a new time-dependent Neural Dynamical Kernel (NDK) that plays an essential role in the dynamics. Our analysis shows that the new theory is compatible with both the NTK theory and the NNGP theory. Our findings provide a new theoretical understanding of the learning process in ANNs, and some practical insights into the role of different hyperparameters in the dynamics.

Advisor: Prof. Haim Sompolinsky

THE HEBREW UNIVERSITY OF JERUSALEM

Fishing for neurons in a foggy sea: Deep nets for wide-field imagery

Lior Golgher, PhD

Wide-field fluorescence microscopy is an affordable technique for monitoring neuronal population activity across a large field of view. However, its imagery offers no axial optical sectioning and suffers from poor lateral spatial resolution [1]. In this talk, we will discuss recent advances that enable the tracking of thousands of individual neurons [2-3], illuminating the entire brain [4], and optically accessing the entire mouse cortex [5-6]. We will also examine the potential applicability of [7] for demixing sparse neuronal firing. Taken together, these developments may allow you to tackle your biological questions using relatively simple imaging hardware.

[1] https://doi.org/10.7554/eLife.59841

[2] https://doi.org/10.1038/s41592-023-01838-7

[3] https://github.com/yuanlong-o/Deep_widefield_cal_inferece

[4] https://doi.org/10.1126/sciadv.abo6743

[5] https://doi.org/10.1016/j.isci.2020.101579

[6] https://doi.org/10.1016/j.xpro.2021.100542

[7] https://doi.org/10.1038/s41467-022-35733-0

Advisor: Prof. Mickey London

THE HEBREW UNIVERSITY OF JERUSALEM

Session IV – New Recruit lecture

Mapping the world around us: A topology-preserved schema of space that supports goal-directed navigation

Raunak Basu

Navigating from one location to another in search of food, shelter, or a mate is critical for the survival of both animals and humans. Successful goal-directed navigation requires estimating one's current position in the environment, representing the future goal location, and maintaining a map of the environment that preserves the topological relationship between positions. In addition, we often need to implement similar navigation strategies in a continuously changing environment, thereby necessitating a certain degree of invariance in the underlying spatial maps. Previous research has identified neurons in the hippocampus and parahippocampal cortices that fire specifically when an animal visits a particular location, implying the presence of a spatial map in the brain. However, this spatial map specifically encodes the current position but not the future goal location of an animal. Also, the hippocampal spatial map depends on the behavioral context whereby changing the room or shape of the arena results in the formation of a new map orthogonal to the previous one. These observations raise the question, how does the brain fulfill the cognitive requirements necessary for goal-directed navigation?

Our research has uncovered a novel spatial map in the orbitofrontal cortex (OFC) that represents an animal's future spatial goal and preserves topological relationships of positions in space while largely maintaining context invariance. We recorded the activity of OFC neural ensembles from rats trained to perform a goal-directed navigation task in an arena with multiple reward locations. We observed that OFC neurons exhibit distinct firing patterns depending on the

animal's goal location, and this goal-specific OFC activity originates even before the onset of the journey. Further, the difference in the ensemble firing patterns representing two target locations is proportional to the distance between these locations in physical space, implying the preservation of spatial topology in the OFC. Finally, carrying out the task in different rooms and across arenas with different geometrical shapes revealed that the spatial mapping of target locations in the OFC is largely preserved and that the maps formed in two different contexts occupy similar neural subspaces and could be aligned by a simple linear transformation. Taken together, the OFC forms a topology-preserved schema of spatial locations that is used to represent the future spatial goal. Our results point to the OFC as a potentially crucial brain region for planning context-invariant goal-directed navigational strategies.

THE HEBREW UNIVERSITY OF JERUSALEM

Session V – Spatial Cognition

On the computational principles of human exploration in complex environments

Lior Fox

Adapting to new environments is a hallmark of animal and human cognition. Such adaption necessitates exploration, and efficient exploration is a non-trivial task. Exploration is particularly challenging in complex environments, as identifying the actions which are exploratory beneficial requires learning about the environment, but such learning itself requires exploration. These challenges have been discussed in the theoretical Reinforcement Learning (RL) literature, but from an experimental perspective a characterization of the computational principles underlying human exploration in complex environments remains partial. A main reason for this limitation is that human exploration has been mostly studied in the context of *K*-armed bandit tasks, in which the uncertainty structure is ultimately simple. Particularly, in a bandit, local measures of uncertainty (e.g., visit-counters) are sufficient to inform directed exploration.

Using a novel experimental task, we study human exploration in complex environments. We find that human directed exploration is sensitive to long-term consequences, implying a strategy beyond a naïve "plug-in" of a counter-based, bandit like, exploration. This strategy includes a temporal-discounting component of future consequences, and, as reflected in the behavior dynamics, is consistent with uncertainty-driven exploration. We propose a computational model that encapsulates these key observations. According to the model, agents learn the exploratory "Value" of actions using Temporal-Differences (TD), in an analogous way to value learning in standard RL models. We explain how the model qualitatively reproduces the experimental results of uncertainty-driven, temporally-discounted, directed exploration in complex environments. Finally, we

discuss evidence for trajectory-based updates (rather than 1-step updates) in human learning.

Advisor: Prof. Yonatan Loewenstein

THE HEBREW UNIVERSITY OF JERUSALEM

A Unified Random Field Theory of Place Fields

Nischal Mainali

Animals generally navigate competently in space and the neuroscientific dogma tells us that they do so by using representations of space in the brain. This idea has motivated many studies to uncover the neural code of spatial information. A major breakthrough was the discovery of place cells in the mammalian hippocampus, which fire selectively at specific locations in space. These cells are often modeled as unimodal bumps of activity that form a sparse representation of space. However, due to technical difficulties most studies have focused on small environments that do not reflect the natural settings of animal navigation. Recent advances in recording techniques have allowed researchers to observe place cell activity in larger and more behaviorally relevant spaces, revealing unexpected features of the spatial code that challenge the classical view. We present a theoretical framework that accounts for these features and proposes a general principle of spatial coding for place cells across different scales and dimensions of space, such as 1D tracks or tunnels, 2D arenas, or 3D rooms. We demonstrate that our framework captures the observed properties of place cells in various experimental paradigms and makes novel predictions about the properties of place fields that are consistent with the data. Moreover, we show that our framework realizes an efficient coding scheme that ensures high readout accuracy of the spatial representation, as it reduces the error exponentially with respect to the number of neurons.

Advisor: Prof. Yoram Burak

THE HEBREW UNIVERSITY OF JERUSALEM

Voltage imaging of Hippocampal neurons during virtual reality navigation

Rotem Kipper, Yaniv Melamed, Qixin Yang, Liam Aisenberg, Omer Cooper, Shulamit Baror-Sebban, and Yoav Adam

Hippocampal place cells are thought to comprise the building blocks for a cognitive map of space. Conducting parallel intracellular recordings from the diversity of hippocampal cell types can help to elucidate the mechanism of place cell formation by providing access to the spiking output as well as the subthreshold inputs of identified inhibitory and excitatory cells in the hippocampal microcircuitry. However, conventional electrode-based techniques make such recordings challenging. To address this issue, we employed a recently developed voltage imaging technology that allows for optical intracellular recordings from genetically identified neurons. Specifically, we expressed Archon1, a genetically encoded voltage indicator, along with an optically orthogonal channelrhodopsin, to achieve all-optical control and readout of the activity of pyramidal cells (PCs) and dendrite-inhibiting Somatostatin (SST)-positive interneurons (INs) in the CA1 region of the hippocampus. We trained head-fixed mice to navigate a virtual environment and recorded the activity of cells belonging to these two populations in a familiar environment across weeks. To study place cell formation, we next imaged the change in the activity of the same cells while the animal was virtually "teleported" to a novel environment. These recordings yielded a rich and diverse dataset, and in this talk, I will describe some of our initial observations. As expected, a large fraction of PCs exhibited spatial tuning, with place fields tiling the entire virtual track, and a higher density of place cells around the reward zone. SST INs displayed diverse activity profiles with many spatially tuned cells but without a bias toward the reward zone. Other SST neurons were tuned to the running speed, and the rest showed high firing rates uniformly along the entire track. Transition to a novel space induced global

remapping of the spatially tuned cells from both populations. To our surprise, the SST population showed increased firing rates in the first few laps in the novel environment, suggesting that in contrast to the prevalent view, dendritic inhibition onto the PCs is increased during hippocampal remapping. These findings expand our knowledge of the activity and function of critical components of the CA1 microcircuit during spatial navigation and comprise a first step towards a detailed mechanistic understanding of hippocampal place cell formation.

THE HEBREW UNIVERSITY OF JERUSALEM

Session VI – Diagnosis and treatment of neuropathologies, and development

Selective Blockade of Visceral Pain in a Rodent Model of Inflammatory Bowel Disease

Nurit Engelmayer

Abdominal pain is the presenting symptom in up to 70% of patients with inflammatory bowel disease (IBD), and at least one-third of patients have persistent pain despite optimal anti-inflammatory treatment. This pain can have a devastating effect on the lives of IBD patients, with associated higher levels of anxiety, depression, social dysfunction and work disability. Furthermore, available analgetic treatment are non-specific, with considerable side effects including addiction and elevation in morbidity.

Animal and human models of IBD emphasize the role of enhanced activity of transient

receptor potential vanillin 1 (TRPV1) cation channels in developing and maintaining abdominal inflammation and pain. These large-pore non-selective-cation channels are expressed in nociceptive neurons and activated by various noxious and pro-inflammatory substances, thus promoting nociceptor activity. Unfortunately, attempts aimed at blocking TRPV1 channels in order to achieve a selective anti-nociceptive effect have failed due to life threatening side effects, caused by the crucial physiological roles TRPV1 channels are involved in, specifically thermal regulation.

Previously, we have demonstrated that the pore of these channels may be utilized as a natural drug delivery system to selectively shuttle a membrane-impermeable derivative of lidocaine, QX-314, into nociceptive neurons, by activating the

channels with the agonist capsaicin. This results in blocking their activity and thereby producing pain relief without associated motor or sensory deficits.

Here, we demonstrate that this method can be used to treat visceral pain in inflammatory bowel disease. Furthermore, we show that in states of inflammatory-mediated pain, TRPV1 channels are tonically activated and thus the charged QX-314 leads to analgesia without the requirement of a channel agonist. These results were confirmed to be due to specific blockade of nociceptors and not due to systemic absorption of the compound.

These findings undercover an important mechanism involved in inflammatory bowel disease pain as well as a potential treatment method.

Advisor: Prof. Alex Binshtok

THE HEBREW UNIVERSITY OF JERUSALEM

In-vivo water gap mapping as a new myelin packing marker

Rona Shaharabani

Magnetic resonance imaging (MRI) is a valuable diagnostic technique in multiple sclerosis (MS) and is commonly used to image brain lesions. Yet predicting the local microstructural changes and biomarkers in MS patients is difficult using current practice. The abnormalities occurring in MS are not readily accessible by current imaging methods. MS is characterized by loss of membrane adhesion, swelling across the water gaps, and eventual disintegration of the myelin structure[1]. Myelin water imaging methods are sensitive to MS demyelination processes[2]. This T2-based qMRI method is sensitive to myelin content and its integrity.

We hypothesize that combining the myelin water imaging with myelin content fraction from other quantitative MRI (qMRI) measurements will allow characterizing the size of the water gap between the myelin. This will reveal additional information on the myelination packing alteration and integrity and provide a biomarker for myelination integrity.

We develop a qMRI approach for the non-invasive mapping of the myelination biomarker, revealed by the myelin water gap. We established this approach with a biophysical model and validated it with specifically designed *in-vitro* biological systems[3,4], that mimic the biological assembly of myelin, and with comparison to known histological measurements. Our biological system is a well-designed multi-lamellar vesicle (like the myelin sheaths) with well-characterized water gap thickness.

Our *in-vitro* measurements validated our biophysical model and our *in-vivo* measurements on healthy adults were compared to *ex-vivo* histology. We were

THE HEBREW UNIVERSITY OF JERUSALEM

able to measure the myelin water gap and show changes in the myelin packing assembly.

1. Hafler, D. A. Multiple sclerosis. *J Clin Invest* **113**, 788–794 (2004).

2. Laule, C. & Moore, G. R. W. Myelin water imaging to detect demyelination and remyelination and its validation in pathology. *Brain Pathology* **28**, 750–764 (2018).

3. Shaharabani, R. *et al.* Structural Transition in Myelin Membrane as Initiator of Multiple Sclerosis. *J Am Chem Soc* **138**, 12159–12165 (2016).

4. Shtangel, O. & Mezer, A. A. A phantom system for assessing the effects of membrane lipids on water proton relaxation. *NMR Biomed* **33**, (2020).

Advisor: Prof. Aviv Mezer

THE HEBREW UNIVERSITY OF JERUSALEM

Updating motor plans in individuals with autism

Adi Glebotzki

Autistic spectrum disorder (ASD) is a neurodevelopmental disorder which is traditionally characterized by impaired social skills. However, a wide range of motor impairments is frequently observed in individuals with ASD, constituting one of the earliest observable symptoms. To date, motor deficits are not considered a diagnostic criterion due to apparently large heterogeneity in their expression and severity. Recent studies have shown that people with ASD are specifically impaired in their rate of updating perceptual predictions (Lieder et al., 2019) and online error-correction (Vishne et al., 2021). Based on these findings the current study aimed to test whether slow updating of motor plans underlies the motor difficulties exhibited by individuals with ASD.

To test this hypothesis, 80 adults (39 typically development (TD), 41 ASD) matched for age and intelligence preformed a target-reaching task using a touch screen. The task included two types of reaching movements triggered by a “go” signal: direct movements, in which participants were required to attain a pre-cued target using their forefinger; and update movements, where participants were required to rapidly update their motor plan in response to a change in target location, which occurred after the “go” signal (50-200 milliseconds). We hypothesized that individuals with ASD will be slower than control specifically in the update movement condition due to slow updating of motor plans.

Participants with ASD were slower than control in both types of movements, yet were particularly slow in reaching a target following an unpredictable change in its location. In the direct movements, the ASD group has shown longer and more varied reaction time (RT), which defined as the time from "go" to movement initiation (RT: p=.02, Cohen's d=.58; within subjects' RT variability: p=.016, Cohen's d=.57). In the update movements, the ASD group has shown substantially slower and unstable response to the target jump (update time - UT), which defined

as the time from the change in target location to the followed shift in the direction of movement trajectory towards the updated target (UT: $p < .001$, Cohen's $d = 1.24$; within subjects' UT variability: $p < .001$, Cohen's $d = .89$). In contrast, in both conditions the groups had shown similar movement time and kinematic profiles as manifested in similar amplitude and phase of the peak(s) velocity and acceleration.

These results reveal significant impairment in motor planning among individuals with ASD, with a particular difficulty in updating pre-planned motor programs based on newly available information. Nevertheless, superficially intact movement once initiated.

Advisor: Prof. Merav Ahissar and Prof. Yifat Prut

THE HEBREW UNIVERSITY OF JERUSALEM

A gene regulatory network responsible for the transition between peripheral and central lineages of the nervous system

Dina Rekler

The dorsal midline of the embryonic neural tube (dNT) is a highly dynamic region, populated first by the Neural Crest (NC), a migratory subset of cells that generate most of the peripheral nervous system, pigment cells and ectomesenchyme. After the completion of NC emigration, the dorsal midline is replaced by the definitive Roof Plate (RP), whose function is crucial for development and patterning of dorsal spinal interneurons. The mechanisms underlying the end of NC production and consecutive formation of the definitive RP, remained largely unknown.

We recently reported that dNT-derived retinoic acid is responsible for the completion of NC production and emigration, acting through suppresion of BMP signaling. Interestingly, inhibition of retinoic acid signaling prolonged the lifetime of the NC while partially affecting formation of the definitive RP. Using single-cell RNA transcriptomics, we now discover that retinoic acid is a key factor in segregating the RP lineage both from the NC progenitors as well as from the neighboring dorsal interneurons. Whereas several RP-specific genes are normally expressed in absence of retinoic acid activity, RP, NC and dorsal interneuron genes are co-expressed in single cells and this domain is also infiltrated by aberrant neuronal processes. Hence, the cellular and molecular architecture underlying fate segregation of the above lineages is dependent on a network comprising, at least, retinoic acid and BMP signaling.

Advisor: Prof. Chaya Kalcheim

THE HEBREW
UNIVERSITY
OF JERUSALEM

Posters

THE HEBREW UNIVERSITY OF JERUSALEM

A computational trade-off in tracking objects

Yotam Federman

Information processing in the brain is hierarchical. The biological nature of the connections between levels means information transfer could incur significant delays of about 100ms. If this delay is not accounted for, it will propagate and accumulate between levels. For example, for a moving object, the cognitive system will be unable to track its current position in real time. Real systems obviously excel in tracking and reacting to moving objects in real time, which raises the question of how.

One method to overcome this is to send information on the extrapolated position, based on the velocity of the object. However, extrapolation presents an inherent bias-variance tradeoff: while it removes the bias of the object's location, it relies on the noisy position derivative, thereby increasing the variance in the estimation of the position.

Our work investigates the bias-variance tradeoff between different extrapolation methods in response to variable noise levels. We modeled the system as a hierarchy of control mechanisms, each level designed to track a delayed, extrapolated signal from the level below it. This gives several predictions that can be tested in flash-lag effect experiments. In the flash-lag effect, a stationary object flashes next to a moving one; despite their alignment along the motion path, the flasher appears to lag behind the mover because of the extrapolation - the amount of extrapolation can be derived from the lag. The model predicts the variance of position estimation for each amount of extrapolation.

More broadly, computational systems predicting changing signals face a universal bias-variance tradeoff between delayed responses and noisy estimates. We hope that our study will open a theoretical path to evaluate characteristics of predictive processing in the brain.

THE HEBREW
UNIVERSITY
OF JERUSALEM

Advisor: Dr. Yuval Hart

THE HEBREW UNIVERSITY OF JERUSALEM

A dynamical mechanism of timing behavior

Evidence from Behavior and EEG

Shahar Haim

Timing is an important cognitive faculty, and the brain's capacity to follow temporal patterns and produce well-timed motor commands is crucial for a wide variety of behaviors. One elementary component of temporal cognition is interval timing. Sensorimotor interval timing requires subjects to self-initiate responses to a given stimulus only after a certain amount of time has elapsed. Although humans are capable of timing multiple overlapping unsynchronized intervals, current theories regarding the neural computations that give rise to interval timing fall short of explaining this capability.

To study this ability, we developed a novel multiple-interval timing task performed on two asynchronous auditory input streams. Optimally, solving the task requires subjects to maintain two separate and independent interval representations, each associated with a different action. We found that the subjects successfully timed behavior based on two simultaneous asynchronous input streams in a manner that was almost identical to their performance on simpler, single-action timing tasks. In addition, we recorded electroencephalography (EEG) while participants completed the behavioral task. Analysis of activity in fronto-central channels revealed a pattern that closely matched theoretically derived action-timing dynamics, which predicted temporal judgments. This activity switched rapidly between the two action-timing representations, multiplexing the timing of two intervals by a single decision variable. These results reveal a novel neural mechanism for flexible, multi-dimensional timing of behavior.

Advisors: Dr. Eran Lottem, Prof. Ayelet Landau

THE HEBREW UNIVERSITY OF JERUSALEM

A novel magnetic eye tracker in freely behaving primates

Guy Oren

In monkeys, hippocampal and entorhinal cells fire in patterns defined not by the animal's location in space but by where it moves its eyes on a visual scene. Furthermore, eye-gaze events such as social gaze and eye contact are a crucial part of social behavior in primates, particularly in humans. However, current methods to measure eye movements are not applicable for use in freely behaving animals, thus limiting our ability to study the role of eye movements in navigation and social behaviors. Here we present preliminary results on a novel magnetic eye tracker system for the recording of eye movements in freely behaving marmoset monkeys. The system is composed of three components: 1) A small surgically implanted magnet in the eye. 2) An array of highly sensitive magnetometers, placed on the animal's head, which are used to track the changes in magnetic field caused by eye movements in head coordinates, and 3) an array of cameras, positioned in the space which measure the head orientation. We developed a novel behavioral paradigm to calibrate the system, using a moving stimulus projected on a screen which is locked to the animal's head direction in real time. Preliminary results show the feasibility of the novel method to record eye-movements and saccades, and that eye-gaze can be successfully tracked via magnetic field orientation in freely behaving monkeys during natural social behaviors and navigation.

Advisor: Dr. David Omer

THE HEBREW UNIVERSITY OF JERUSALEM

All-optical electrophysiology reveals behavior-dependent dynamics of excitation and inhibition in the Hippocampus

Qixin Yang, Shulamit Baror-Sebban, Rotem Kipper, Yaniv Melamed, and Yoav Adam

The interplay of excitation and inhibition (E-I) is a fundamental property of neural circuits. In the hippocampus, the activity of principal cells is modulated by multiple types of local inhibitory interneurons (INs) as well as by long-range inhibitory and excitatory projections. However, the contribution of these diverse inputs to hippocampal activity is not fully understood. Voltage imaging using genetically encoded voltage indicators (GEVIs), allows optical intracellular recordings of both the spiking output and subthreshold inputs. Combining GEVIs with optically-orthogonal optogenetic actuators enables all-optical control and readout of neuronal activity. Here, we employ this all-optical electrophysiology approach to investigate the dynamics of excitation and inhibition of identified cell types in CA1 area during different behavioral states, specifically quiet versus forced locomotion.

We found that both vasoactive intestinal polypeptide (VIP) INs and pyramidal neurons exhibit higher spontaneous firing rates during quiet periods while somatostatin (SST) INs increase their firing rates during walking. By using optogenetic stimulation with increasing light intensities, we could measure neuronal excitability and revealed that SST and pyramidal neurons are significantly less excitable during walking, suggesting state-dependent gain control of the circuit. Theta oscillations, a hallmark of hippocampal network activity, are critical for cognitive processes such as learning, memory, and spatial navigation. We found that during walking, intracellular theta occurred in SST and VIP INs but was very weak in pyramidal neurons. At rest, theta oscillations were

absent in all cell types. To determine whether intracellular theta oscillations are driven by inhibitory or excitatory inputs, we used tonic optogenetic depolarization, which is expected to amplify inhibitory inputs and weaken the excitatory drive. We found that upon prolonged depolarization, all cell types exhibited strong theta oscillations during walking, suggesting that hippocampal theta activity is mostly driven by inhibitory inputs. Overall, our study offers novel insights into the state-dependent regulation of hippocampal neuronal activity, E-I balance, and how they modulate theta oscillations, all of which are essential for understanding hippocampus-dependent cognitive functions. Future research could leverage computational modeling to further explore the functional role of state-dependent E-I balance and theta oscillations by constructing networks of excitatory and inhibitory neurons using our detailed *in vivo* electrophysiological properties, thereby deepening our understanding of hippocampal function.

Advisor: Yoav Adam

THE HEBREW UNIVERSITY OF JERUSALEM

Auditory context sensitivity across tone position in multitone sequences

Maysan Bader

Sequences of images, sounds, or words are essential for memory, language acquisition, and mainly prediction. To further examine the sequence's roles in different brain functions, Electroencephalogram (EEG) data were recorded on 32 subjects while being exposed to task-irrelevant evenly-spaced permutations of 5 different tones. Event Related Potential (ERP) analysis showed that the P2 component is sensitive to tone position in the permutated sequence regardless of the tone pitch. These results represent a preliminary proof that the human auditory cortex can "count" to 5 (at least) without even being attentive. The extent and mechanism of this phenomenon are yet to be determined.

Advisor: Prof. Leon Deouell and Prof. Israel Nelken

THE HEBREW UNIVERSITY OF JERUSALEM

Auditory representations of place and identity for others in the primate hippocampus

Reuven Lifshitz

For almost half a century, the mammalian hippocampus was known to form representations of space, time and memory for self. This dogma is now changed by recent findings that revealed also hippocampal representations of others (social place-cells and social time-cells). While these social spatiotemporal representations rely mostly on vision, a key component of social behavior in mammals, and particularly in primates, rely on audition – vocal social communication. However, it is unknown if the hippocampus also encodes auditory spatial and social representations during vocal social communication. Here we investigated whether neurons in the marmoset hippocampus encode the location and identity of conspecifics during vocal social communication. Phee calls are social localization calls which are used by marmoset monkeys to exchange self-spatial information between two conspecifics in the absence of a visual sight. We recorded neurons across the dorsal-ventral axis of the hippocampus using a tetrodes array, while monkeys were engaged in phee calls communication with a closed-loop playback system. To this end, we used a database which includes 47,672 of labeled phee calls to manipulate the location and identity of the other's monkey calls. Our preliminary results reveal both classic place cells (tuned for self-position) and cells that are tuned to position × identity, thus revealing, for the first time in the mammalian hippocampus, auditory representations for place and identity.

Advisor: Dr. David Omer

THE HEBREW UNIVERSITY OF JERUSALEM

Bayesian Inference Between the Hemispaces- Exploring the Link Between Attention and Bayesian Inference Model in Hemispheric Differences

Karin Uritsky

In the field of Bayesian inference, there has been a significant amount of research conducted on how human observers integrate uncertain sensory information with learned prior knowledge. It has been established that people can integrate this information in an approximately Bayes-optimal manner, both under simple and complex task conditions. However, the proximity of participants to the Bayesian optimum is still a topic of debate. Moreover, the relationship between attention and Bayesian inference is still largely unexplored. To bridge this gap, this study aimed to explore the attentional asymmetry and its link to the Bayesian inference model. Specifically, the study aimed to investigate whether there are differences between the two hemispaces in the Bayesian inference model. To achieve this, 50 participants are given a complex spatial localization task. The task requires participants to estimate the position of a hidden cat, whose position is sampled from a location-contingent bimodal generative model with different variances around each mode.

It is hypothesized that participants would learn the a priori locations of the target (i.e., the bimodal generative model) and integrate this learned knowledge with the level of uncertainty of the sensory information on a trial-by-trial basis. Even so, it is also expected that participants would tend to over-rely on the likelihood information. For the attentional asymmetry, it is hoped that a difference would be found between the weight participants give to each kind of information, between the two hemispaces. Overall, this study aims to contribute to a better understanding of the complex relationship between attentional asymmetry and Bayesian inference under uncertainty.

THE HEBREW
UNIVERSITY
OF JERUSALEM

Advisor: Prof. Leon Deouell

THE HEBREW UNIVERSITY OF JERUSALEM

Behavioral and Neuronal Correlates of Pure Tone Discrimination in the Auditory Cortex of Adult and Adolescent Mice

Benne Praegel, Adria Dym & Adi Mizrahi

Alexander Silberman Institute of Life Science, Edmond & Lily Safra Center for Brain Sciences

Aims: Adolescence is known to be a period of uncertainty, exploration, and learning, yet there is little clarity about how even simple forms of auditory learning change with development and are supported by neuronal correlates in auditory cortex. Here, we focused on mice and asked whether auditory cortex is involved in the discrimination of pure tones and differs between adolescent and adult animals. **Methods:** To enable efficient learning of both adult and adolescent groups we trained freely behaving and head-fixed mice to perform a go no-go task of pure tone discrimination. After learning, we recorded single units in the auditory cortex of head-fixed adolescent and adult mice during discrimination performance. In addition, we inhibited single units in the auditory cortex using a GtACR2 opsin in adult mice. **Results:** We show that discrimination performance of adult mice is superior to adolescent mice. The difference in discrimination performance is significant both at single neuron and population representations of the auditory cortex. Moreover, we present evidence that inhibiting the auditory cortex leads to a deficit in the performance of the task. **Conclusions:** We identify clear differences between adolescent and adult auditory discrimination performance, which were accompanied by distinct neural correlates. We are currently evaluating the contribution of the auditory cortex on auditory discrimination and on cortical responses of adolescent compared to adult mice.

THE HEBREW UNIVERSITY OF JERUSALEM

Cerebellar output to the motor cortex aids in the formation and update of motor plan during free reaching movements.

Yaniv Pasternak, Nirvik Sinha, Yifat Prut

The role of the premotor cortex in movement planning is well established, and recent evidence indicates that the cerebello-thalamo-cortical (CTC) pathway might be instrumental in facilitating this process. This involvement is particularly pertinent to movements demanding error monitoring and subsequent behavioral adjustments to adapt to evolving task demands. Recent findings suggest that changing task demands necessitate a re-engagement of preparatory activity in the motor cortex to update the motor output. Considering this, our study aimed to evaluate the capacity to update motor plans when cerebellar signals are blocked. Our hypothesis posited that CTC blockage would disrupt the usual process of motor preparation during simple point-to-point reaching, as well as the updating process when the reaching target unexpectedly changed location. We employed a recently developed model of reversible CTC blockage in non-human primates (NHPs) through high frequency stimulation (HFS, 130 Hz) of the superior cerebellar peduncle, facilitated by a chronically implanted electrode. Two NHPs (*Macaque fascicularis*) were trained to execute center-out free-reaching movements towards targets placed in the vertical plane, using their right upper limb. In approximately 20% of trials, the target unexpectedly relocated during the task at variable times (0-200 ms) post the 'GO' signal. Hand movements of the NHPs were monitored via high-speed infra-red camera system and analyzed using a marker-less tracking software (DeepLabCut). We analyzed the effect of HFS on motor behavior. The reaction time of HFS trials (mean = 309 ms) was significantly higher than that of control trials (mean = 280 ms). For the trials where the reaching target changed to a new location, we calculated the time that elapsed from the target jump until the change in hand trajectory towards the newly

presented target. This 'update time' was significantly higher in HFS trials (197 ms) as compared to control trials (182 ms). Finally, we examined the relationship between the initial angle of reach of the hand and the time between target jump and movement onset. After fitting a sigmoid curve to this data, we calculated the time interval required to complete the update process (i.e., time difference between the 95th to 5th percentile of the sigmoid curve). This time interval was significantly longer under HFS (mean = 250 ms) vs. control (mean = 200 ms). These results suggest that the absence of cerebellar output to the motor cortex impedes the planning of simple point-to-point reaching, and additionally delays the process of updating the motor plan when the task requirement changes suddenly. The delayed update time in addition to the increase in reaction time may suggest a cerebellar involvement in high-level motor planning beyond its traditionally assigned role in online motor control. These novel behavioral findings pave the way for further investigations into how motor cortical activity is impacted during such tasks following CTC blockage.

THE HEBREW UNIVERSITY OF JERUSALEM

Choosing their battles: Improvement in zebrafish hunting behavior over development

Maayan Moshkovitz

Goal directed behavior consists of a sequence of actions performed by the organism in order to achieve a desired target. These sequences often become more efficient as the organism gains experience interacting with the world. It remains unknown what features of the interaction with the external world change with experience.

Zebrafish larvae exhibit goal-directed hunting behavior from very early age of 5 days post fertilization (dpf). They capture their prey by executing a series of movements in which they refine the localization of the prey, followed by intervals where they do not move and assess the visual field in order to select the next action. A hunting event terminates in three possible outcomes: hit- a strike toward the target with a successful prey capture, miss- a strike toward the target with an unsuccessful capture, or abort- no strike toward the target with the animal aborting the event. Over development and as the animal gains experience, hunting performance improves with an increase in hit rate and a decrease in miss and abort rates.

We recorded freely swimming fish (5-15 dpf) while hunting using a high-speed camera (500 fps). The duration of the last interval prior to the decision to strike or abort in young animals was shortest in hits, longer in misses, and longest in aborts. The length of this interval was correlated with the complexity of the visual field, where in hits the target was well positioned in front of the fish, and distractors were mostly not present or far from the target, while in misses and aborts, distractors were closer to the target in a prototypical position for each hunting outcome. Over development fish better choose their battles and more

efficiently handle complex visual scenes. These results form the basis to uncover the neural mechanism mediating improvement in hunting behavior.

Advisor: Dr. Lilach Avitan

THE HEBREW UNIVERSITY OF JERUSALEM

Cocaine-induced Plasticity of Input Connectivity to the Ventro-lateral Striatum

Tomer Sheinfeld

We have recently found (Gonzales, Shalom et al., in preparation) that the ventro-lateral aspect of the striatum (VLS) mediates behavioral plasticity following repeated exposure to high-dose cocaine, in the form of an increase in the prevalence of oral-facial stereotypic behaviors, at the expense of other behaviors.

This gradual narrowing of the behavioral repertoire is likely to be guided by brain wide changes in glutamatergic and GABAergic inputs to the VLS, arriving from the cortex, thalamus, amygdala and GPe.

These input regions projecting onto the different cell types in the striatum, including the two main output neurons, direct- and indirect- pathway spiny projection neurons (SPNs), which promote and inhibit motor actions, respectively. Thus, to understand the basis for the behavioral changes induced by cocaine, we aim to understand the change in information carried onto dSPNs and iSPNs in the VLS.

To this end, we implemented conditional pseudorabies virus (pRbV), identifying the neurons presynaptic to $Drd1^+$ vs $Drd2^+$ ($A2A^+$) neurons in the VLS. pRbV has been shown to be sensitive to synaptic changes. By injecting this virus to the VLS of Drd1-Cre or A2a-Cre transgenic mice, we were able to assess changes in the brain wide distribution of presynaptic cells projecting to dSPNs or iSPNs following repeated cocaine exposure, potentially reflecting behaviorally relevant changes. Our results indicate that dSPNs receive more motor and thalamic inputs while iSPNs receive more insula inputs in naïve mice. Following chronic cocaine exposure, we observed an increase in the relative number of insula inputs to both populations. Concurrently, we also observe a cocaine induced decrease in activity of insula inputs to the VLS, measured using fiber photometry on axons.

These differences between inputs to dSPNs and iSPNs in naïve mice might provide insight into the role of input populations in mediating natural and learned behaviors. The changes that occur in insular cortex projections to the VLS following repeated cocaine exposure are suggestive of a role for this specific cortico-striatal input in the increased stereotypies observed following repeated exposure to cocaine.

Advisor: Prof. Ami Citri

THE HEBREW UNIVERSITY OF JERUSALEM

Cognitive Flexibility by Input Re-evaluation

John Schwarcz

The brain's ability to produce reliable behavior in a dynamic world is critical to survival. Animals can quickly adapt their behavior to environmental changes, suggesting reliance on neuronal activity rather than long term plasticity. However, it is unclear how a neural network can quickly change its response based on subtle changes in its inputs. We developed a change-detection task that requires fast responses to hidden-state changes under varying uncertainty levels. The agent must strike a balance between speed and accuracy: acting prematurely may result in an erroneous trial while waiting to remove uncertainty delays the reward—both reduce the overall reward rate. Importantly, the optimal waiting time depends on the uncertainty level, which we manipulate. We trained mice and artificial recurrent neural networks (RNNs); both quickly adjusted their waiting times to the noise level. We analyzed the trained RNNs' activity and discovered how context was extracted, represented and used to control a temporal integrator. Furthermore, updates to the uncertainty representation matches predictions of a Bayesian model with knowledge of the task structure. Our model dynamically re-evaluates the relevance of recent inputs to facilitate fast updates to the representation of the uncertainty level. Our results show that recurrent networks can learn flexible task structures and adapt their response online without needing to receive a contextual input. This study advances our understanding of how neural networks may represent complex and flexible cognitive tasks.

Advisors: Eran Lottem, Jonathan Kadmon

THE HEBREW UNIVERSITY OF JERUSALEM

Context-dependent selection of orofacial actions driven by activity in the ventrolateral striatum

David Lipton

The striatum integrates sensorimotor input with reward to support action selection. Different subregions of striatum receive biased input from distinct regions of cortex, defining a map of cortical space. Specific striatal sub-regions are thought to invigorate particular categories of actions. As such, the ventrolateral aspect of the striatum (VLS) has been associated with orofacial behaviors, receiving input from orofacial-associated cortical regions. We ask here how individual actions from the broad category of orofacial actions are represented in the VLS. Using fiber photometry to measure activity in VLS d/iSPNs we find that a range of orofacial actions, such as floor-licking, body-licking, and grooming, are associated with activity in multiple locations within orofacial striatum. At the same time, driving activity in VLS dSPNs with optogenetics produces a range of orofacial behaviors. Yet, the specific range of behaviors driven is predicted by topographical sub-locations, or 'channels', within striatum.

We then ask if the subset of orofacial actions invigorated by a given VLS striatal channel is invariant across different contexts. If so, this would suggest a more hard-wired action-encoding. However, we observe that contextual cues are a crucial determinant of the specific orofacial action driven by elevated VLS activity, such that the output of the same VLS SPNs could be converted from licking in one context to biting in another. This suggests that striatal SPNs work in concert with contextual information to invigorate a specific action from a subset of topographically defined relevant actions.

We are currently investigating the orofacial action-specific representation in neural circuits that directly interact with VLS, focusing on VLS inputs, such as

motor and sensory regions of cortex, and VLS outputs, namely SNr neurons that receive direct input from VLS.

Advisor: Prof. Ami Citri

THE HEBREW UNIVERSITY OF JERUSALEM

Continuous decision making in a closed-loop auditory navigation task

Shai Yellinek, Itai Wasserman, Robert Reiner

In recent years, neuroscientific research of rodent cognition and behavior has gained significant traction. However, most rodent decision-making paradigms have a unidirectional flow of information, where sensory stimuli guide the animal's behavior, but the behavior does not affect the stimuli. This approach differs from more ecological perspectives that consider control as a fundamental feature of behavior. According to these theories, behavior is embedded in perception-action loops, where animals respond to stimuli and change them in the process. Moreover, rather than being composed of discrete, isolated actions, natural behavior is more often continuous, involving uninterrupted cycling through perception-action loops.

To study the mechanisms of continuous behavioral control, we designed a closed-loop egocentric navigation task. This task involves mice searching for a randomly selected target location in an open arena to obtain water rewards. They rely on an auditory stimulus, a pure tone whose frequency continuously changes based on the mouse's orientation to the target. Hence, the stimuli that guide behavior also continuously change due to it. We observed that mice learn to perform this task, and ongoing analyses aim to identify the precise computations behind this behavior.

This task offers a unique approach to studying cognitive control and its neural basis. In the future, we plan to explore the roles of neuromodulators such as dopamine and serotonin during the learning of this task.

Advisor: Dr. Eran Lottem

THE HEBREW
UNIVERSITY
OF JERUSALEM

Custom analysis pipeline for Voltage Imaging Experiments in behaving animals

Yaniv Melamed, Rotem Kipper, Qixin Yang, and Yoav Adam

Our lab conducts voltage imaging experiments in mice navigating in virtual reality to study hippocampal place cells. Voltage imaging at cellular resolution is an emerging technology, that provides information on the spiking and subthreshold activity of multiple cells at unprecedented speed and sensitivity. This is a novel imaging modality using very high sampling rates generating large and noisy videos and thus imposes unique challenges in the processing and segmentation of the data. The recorded videos undergo a set of routine procedures, including motion correction, noise removal, cell segmentation, trace extraction, signal sharpening, and spike detection. A handful of algorithms that implement these steps were developed in recent years and helps to extract better signals from each experiment. Nevertheless, applying these algorithms routinely, fine tunning their hyper-parameters, and running the heavy computational processes on a computational cluster is time-consuming and delays the analysis of the neural signals.

To bridge this gap between experiment and analysis we developed a light weight Python software package that manages the processes. At the end of each experiment, with a few clicks, the experimentalist sends his experimental results to the ELSC cluster and has the ability to keep track of their progress. After the cluster job is completed, the different intermediate steps can be viewed, and one can examine them and decide if another round of processing is needed.

An additional software component is a database organizing module (DB). The experimentalists can manually choose the cells from each video and save them. Our DB helps to manage the whole experimental dataset and to display a basic

analysis of the neuronal supra- and subthreshold signals aligned to the mouse behavior.

We believe that the infrastructure we have created would be of interest to various labs at ELSC and help to improve the analysis of large-scale imaging datasets and accelerate progress inresearch.

Advisor: Dr. Yoav Adam

THE HEBREW UNIVERSITY OF JERUSALEM

Dynamics of Neuronal Reprogramming Along the Alzheimer's Disease Cascade Uncovered Vulnerability of Inhibitory Neurons

Roi Meir

Alzheimer's disease (AD) is a progressive neurodegenerative disorder affecting millions worldwide. It is characterized by the accumulation of amyloid-beta plaques and neurofibrillary tangles in the brain, which ultimately lead to neuronal damage and death causing cognitive decline.

Previous work on a large atlas of single-nucleus RNA-seq profiles from 424 human brains revealed two distinct aging trajectories, one of which leads to AD, and each is driven by a cascade of changes in cellular communities composed of different glial cell populations. Despite the known damage to neurons involved in AD progression, it is still unclear what processes and cell types cause the neuronal degeneration and at what point of disease the neurons are starting to be affected.

Here we used Topic Modeling to model the diversity of expression programs snRNA-seq profiles of the neuronal cells in a continuous manner. Each RNA profile is decomposed into multiple gene expression programs that together describe the cell activity. The gene expression programs are fitted using Non-negative matrix factorization (NMF) algorithms.

The gene expression programs capture both the different neuron sub-types and disease-associated aspects of the gene expression. We observe a coordinated change in the gene expression program of all inhibitory neuron subtypes along the AD trajectory. This change occurs early in the disease trajectory well before the cognitive decline. We also found similar gene programs in the excitatory neurons that share some of the genes and have similar dynamics. Additionally, other specific neuronal sub-type rise at late stages of the disease.

THE HEBREW
UNIVERSITY
OF JERUSALEM

Advisor: Dr. Naomi Habib

THE HEBREW UNIVERSITY OF JERUSALEM

EEG adaptation pattern reveals slow update of temporal predictions in autism

Yarden Weiss

Adaptation manifests our ability to detect regularities and filter out irrelevant cues. The dynamics of adaptation in autism, a neurodevelopmental condition partly characterized by sensory atypicality, is still an open question. We now asked whether it depends on the temporal predictability of the stimuli. Standard auditory adaptation protocols are either simple to predict (fixed temporal intervals) or unpredictable (random). We designed a protocol with a varying degree of temporal predictability, while recording EEG. Typically developing adults optimized the implicit regularity and showed adaptation when intervals were predictable. Autistic participants showed only bottom-up driven adaptation and did not benefit from the complex regularity.

Advisor: Prof. Merav Ahissar

THE HEBREW UNIVERSITY OF JERUSALEM

Encoding of Noxious stimulus in nociceptive terminals

Efrat Sheinbach

Nociceptive terminals detect and transmit information regarding noxious stimuli, thus initiating pain sensation. Due to the small size of the terminals, direct electrophysiological studies could not be applied, and therefore little is known about terminal physiology. We used genetically encoded voltage indicators (GEVIs) to directly monitor the voltage dynamics in the nociceptors terminals and thus characterize their electrical and functional properties. To this end, we expressed the GEVI Archon1 in nociceptive neurons innervating the cornea. Using a custom-patterned illumination microscope and a high-speed camera, we could monitor changes in the voltage of a single terminal *in vivo* in anesthetized mice. Surprisingly, We show that even without applying noxious stimuli, nociceptive terminals are not quiescent but generate spontaneous, sodium channel blocker-sensitive activity. This spontaneous activity was observed in the cold-sensitive and the noxious heat-sensitive nociceptive terminals. Furthermore, we show that the focal application of noxious stimuli evoked depolarization in the terminals and high-frequency spiking activity propagating along the adjacent fiber. We are currently examining the changes in spontaneous and evoked terminal activity in the inflammatory pain models. The approach that we developed allows us to finally access and characterize the input-output properties of nociceptive terminals and the changes in these properties in pathological conditions, leading to pathological pain.

Advisor: Prof. Alexa Binshtok and Dr. Yoav Adam

THE HEBREW UNIVERSITY OF JERUSALEM

Expectation and surprise in the sleeping brain: Auditory omission prediction error response in NREM and REM sleep using intermediate complexity irregularities

Sharon Yakim

Sleep is a reversible condition of reduced awareness and responsiveness to the external environment. Nevertheless, even during sleep, organisms must regularly sample the environment, create predictions, and detects their violation. Indeed, compelling evidence indicates that the sleeping brain can detect simple sensory deviation. However, only a few studies investigated more complex predictions, and it remains unclear how sleep modulates the formation of predictions and surprise responses. To answer this question, we recorded high-density EEG from 28 healthy participants in sleep and wakefulness while they passively heard an auditory oddball-omission paradigm. The paradigm included expected and unexpected omitted sounds with intermediate complexity rules, which enabled to disentangle between the neural response to the "pure" prediction error and the neural response to the stimulus's physical properties. ERP analysis showed a significantly increased negativity at 100-300ms following omission onset in the unexpected omission condition compared to the expected omission in wakefulness, N2 and, REM sleep, but not in N3. This result implies that the sleeping brain is able to create predictions more complex than a mere sensory deviation and that this ability is compromised in slow-wave sleep.

Advisor: Dr. Anat Arzi, Dr. Tristan Bekinschtein

THE HEBREW UNIVERSITY OF JERUSALEM

Hippocampal microglia dynamics and interactions with PV neurons during LPS-induced neuroinflammation

Lior Naggan

Ample evidence has been accumulating for alterations in the number, structure, and function of microglia following their activation by various immune, neural and behavioral challenges, but the spatial and functional dynamic alterations in the interactions between microglia and specific types of neurons in their vicinity have not been fully elucidated yet. Previous research implicated changes in hippocampal microglia activation status and parvalbumin (PV) GABAergic interneurons functioning in the cognitive and emotional disturbances associated with sickness, depression and neurodegenerative diseases, however, the interactions between these cell types have not been investigated. In the current study, we examine the dynamic and global changes in the interactions between hippocampal CA1 microglia and PV neurons in the CA1 layer of the hippocampus, following administration of the microglia stimulator lipopolysaccharide (LPS), using double-transgenic mice expressing GFP in microglia and tdTomato in PV interneurons. Repeated two photon (2P) microscopy imaging, at baseline, 24, 48 and 72 hr, following a saline or LPS (1 mg/kg) i.p. injection, showed increases in microglia area and volume at 24 hr, which were reversed at 48 hr and at 72 hr post-administration. Immunohistochemistry staining in brain slices of mice receiving either saline or LPS for the immediate early gene cFos, revealed an overall reduction (pyramidal and PV neurons to a similar degree) of activity in the CA1 of LPS treated mice. Using the CLARITY clearing technique we aim to investigate global changes in microglia states and spatial information. Utilizing these complementary imaging methodologies will enable us to characterize hippocampal microglia and their interactions with neurons during neuroinflammation.

Advisors: Prof. Raz Yirmiya and Prof. Inbal Goshen

THE HEBREW UNIVERSITY OF JERUSALEM

Increased Stability of Memory Retention through Multiple Synaptic Timescales

Georg Chechelnizki

Short term memory in the brain is theorized to often be implemented by continuous attractor networks, which represent stored variables in persistent neural activity. Since neurons are noisy, the variability in their activity degrades the memory, which can manifest as random diffusion. It was shown in (Lim and Goldman, 2013) that slow excitatory and fast inhibitory synaptic timescales can help decrease memory drift by providing negative derivative feedback to the system. Negative derivative feedback is known from control theory to increase robustness against various common perturbations. Building on this, it was shown that such a timescale difference also greatly reduces memory diffusion in a linear attractor network, as was shown in (Shaham and Burak, 2018). In this work we show for a far more general class of models that the degradation of memories by random diffusion can be mitigated by fast inhibition in conjunction with slow excitation. We derive a general expression for the diffusion coefficient of a stored variable in an attractor network of Poisson neurons with arbitrary connectivity and synaptic timescales as a generalization of a previous result for networks with a single synaptic timescale (Burak and Fiete, 2012). We then show that when we apply our theory to the negative derivative feedback scenario, it correctly predicts the increase of memory stability as a function of synaptic timescale difference in an exemplary ring model.

Advisor: Prof. Yoram Burak

THE HEBREW UNIVERSITY OF JERUSALEM

Information Bottleneck for scRNA-seq: Revealing a hierarchy of metagenes that explain the difference between the experimental groups

Serafima Dubnov, Zoe Piran

Development of single cell RNA-sequencing approach (scRNA-seq) took the transcriptomic field onto the next level, allowing to quantify the RNA at the level of single cells. Such a vigorous method provides an opportunity to disentangle specific molecular processes and cellular interactions responsible for development of various phenotypes, such as disease. The output of scRNA-seq is a count matrix quantifying gene levels in each individual cell. This high-dimensional matrix is extremely complex, combining multiple signals from different factors. Since the experimental setting often implies elucidating a specific signal of interest, there is a need in efficient computational analysis tools for disentanglement. We are proposing a novel method for scRNA-seq data analysis, which allows to extract the relevant gene clusters, or metagenes, explaining the major source of variance underlying the signal of interest. This approach is based on the Information Bottleneck algorithm (IB), which was designed to achieve the optimal trade-off between accuracy and complexity in compressing big data. Applying IB to scRNA-seq data elucidates groups of genes featuring similar expression patterns between the

experiment groups and corresponding to molecular pathways explaining the relevant biological variance. Moreover, IB produces a metagene hierarchy which exposes the relationship between distinct gene programs and biological pathways, easing the data interpretation. We applied IB to single-nucleus RNA-seq data of astrocytes from AD mouse model and from aged wild-type mice. Our results show that IB metagenes identify specific disease associated cellular subpopulations, given the genotype only, thus avoiding additional pre-clustering of the cells. In summary, we propose IB as a novel approach to analyze scRNA-seq data, which

allows to explain the relevant cellular heterogeneity with a sparse hierarchical representation of data.

Advisors: Prof. Hermona Soreq, Mor Nitzan

THE HEBREW UNIVERSITY OF JERUSALEM

Intentional Rehearsal Bypasses the Hippocampus During Episodic Memory Encoding

Ofer Perl [1], Noga Cohen [2] , Ido Toren [3], Rik Henson [4], Aya Ben-Yakov [1]

[1] The Edmond and Lily Safra Center for Brain Sciences ,The Hebrew University of Jerusalem, Israel;
[2] University of Haifa, Israel;
[3] Weizmann Institute of Science, Rehovot, Israel;
[4] MRC Cognition and Brain Sciences Unit, University of Cambridge, UK

Perhaps the most traditional method of engraving information in our minds is by rehearsing it. Using naturalistic film clips as memoranda, we find that intentional rehearsal of an episode immediately upon its conclusion indeed increases subsequent memory. But how does this transpire? We focus particularly on the potential role the hippocampus may play given recent findings linking hippocampal activity at event boundaries with subsequent memory. These findings give rise to two contradicting hypotheses. As hippocampal activity at the offset of events is linked to successful encoding, the effect of rehearsal on memory may be mediated by an increase in hippocampal offset activity. In contrast, active tasks have been shown to inhibit the hippocampal boundary response, relative to rest. This suggests rehearsal may inhibit the hippocampal response, and exert its effect via other regions. In two independent fMRI experiments we find that memorization does not increase hippocampal activity. Moreover, it eliminates the subsequent memory effect observed at event offset during passive viewing. This indicates that rehearsal promotes memory via an alternate route, with initial evidence suggesting this may be linked to an increase in cortical activation. A new theoretical framework suggests that memory retrieval may act as a rapid consolidation event. Thus rehearsal, a form of retrieval, may bypass the hippocampus and rapidly form a semanticised, cortical representation of the event.

THE HEBREW
UNIVERSITY
OF JERUSALEM

Advisor: Aya Ben-Yakov

THE HEBREW UNIVERSITY OF JERUSALEM

Quantify Parkinson's striatal changes with clinical MRI data

Shachar Moskovich

Parkinson's Disease (PD) is the second most common neurodegenerative disease, characterized by motor and non-motor symptoms. Although MRI is the most common method of imaging the human brain, PD is currently diagnosed (and treated) based solely on its clinical symptoms. According to post-mortem studies, striatal spatial gradients vary among PD patients. According to a recent study, these gradients have also been observed in MRI clinical data of PD subjects, using two weighted MRI images (T1w/T2w). In this study, we investigate whether additional clinical images can be analysed to obtain more information about patients with Parkinson's disease.

Both the biophysical properties of the brain tissue and the scanning parameters affect the clinical weighted MRI image contrast. Thus, different scanning parameters make weighted MRI images non-quantitative. T1w/T2w ratios have been proposed to be semi-quantitative indicators of tissue integrity and can be used to measure symptoms of PD. With this approach, we extend the semi-quantitative approach and obtain five new semi-quantifiers – T1w/PDw, T2w/PDw, dT1w/dT2w, dT1w/dPDw, dT2w/dPDw from three common weighted images (T1w, T2w, PDw) .

Using a phantom system, we compared semi-quantitative and quantitative data (R1, R2 and Proton density) and observed a strong agreement. Measurements in the human brain showed that striatal gradients differed between healthy controls and Parkinson's patients. Further, these gradients were also correlated with motor symptoms in patients with Parkinson's disease.

THE HEBREW
UNIVERSITY
OF JERUSALEM

Our findings suggest that weighted MRI images commonly available in clinical settings can be used to produce semi-quantitative images that can be compared between subjects and regions of the brain. The new contrasts can be used to differentiate between PD patients and healthy controls in clinical settings.

Advisor: Prof. Aviv Mezer

THE HEBREW UNIVERSITY OF JERUSALEM

Involvement of Amygdala neurons in male predominance in Autism Spectrum Disorder

Noa Montefiore

Male predominance is one of the least understood characteristics of the Autism Spectrum Disorder (ASD). While more than a hundred genes are involved in ASD, recently it has had been suggested that only a few of them show sex differences in behavior. One of these genes is POGZ. Hence, in order to identify the molecular and physiological basis of male predominance we use Pogz+/- transgenic mice, a model for sex-specific effect in ASD (Suliman et al., 2019). Preliminary results from high resolution mapping and cFOS indicate the localization of the cells activated in social behavior differently in males and females in basolateral amygdala (BLA), a brain area which has been previously shown to be involved in sex difference social behavior tasks. In order to characterize the morphophysiological properties of the BLA neurons, which related to social behavior and are sexually dimorphic, we perform in vitro whole cell recordings targeted to arc-dVenus-labeled cells of Pogz+/- mice. We aim to identify the populations of BLA neurons active in social behavior in Pogz+/- males and females and thus to suggest possible molecular and morphophysiological mechanisms of male predominance in ASD. The results of this study will shed a light on sex difference in ASD and thus advance the understanding of ASD.

Advisor: Prof. Yosef Yarom

THE HEBREW UNIVERSITY OF JERUSALEM

Learning and perception under uncertainty

Chaviva Moshavi

Our environment constantly changes, either due to random local fluctuations, or to long-lasting factors that have future impact. Inference of these two sources of change determines what we expect to encounter next and how certain we are about this expectation. Individual biases in these inferences may thus result in distorted expectations. Such biases are often considered in terms of a tradeoff between these two kinds of inferences, such that if one explanation of change is overused, the other must be underused. However, in the presence of sensory noise, both sources of change may in fact be simultaneously overestimated or underestimated, since the change itself can be exaggerated or, alternatively, ignored. We developed a paradigm that exploits this idea and incorporates a behavioral experiment and computational modeling to more fully evaluate how people track sources of uncertain change over time, how this contributes to the expectations that they form, and how their expectations in turn affect their perception of subsequent sensory input.

Advisor: Dr. Eran Eldar

THE HEBREW UNIVERSITY OF JERUSALEM

Linking cognitive decline to coordinated reprograming of cortical, spinal cord and muscle cells

Anael Cain

The body is composed of several systems that influence one the other. With age there is an increased risk to develop motor decline as well as cognitive decline, and there is a strong link between the two impairments. However, how the degeneration of the central nervous system and the motor system affect one another is yet unknown. Understanding the interactions between the muscle, spinal cord and brain tissues and the coordination between them on the molecular level could help prevent their impairments with advanced age. To investigate the relationship of the two systems, we used bulk RNA sequencing of three motor-associated regions: the supplementary motor cortex (SMA), spinal cord and muscle. We profiled over 300 individuals that span from healthy states to different levels of motor and cognitive impairments. We first described the cellular landscapes and RNA profiles of each of the three regions using gene co-expression network analysis, finding a diversity of expression programs capturing distinct molecular pathways and cell types. We next searched for expression programs associated with disease traits, and we surprisingly found both in the muscle and in the spinal cord multiple expression programs associated with cognitive decline and AD pathologies in the brain. In the SMA we found a weak association to tangles pathology, yet we found a high similarity between the cellular landscape of the SMA and the cognitive associated cortical region, the DLPFC, suggesting a upstream effector driving cellular states across cortical regions. Comparing the three tissues, we found several co-expression programs in the muscle, spinal-cord and the brain, coordinated across individuals. Within the coordinated programs across tissues we found shared molecular functions, such as common upregulation of inflammation genes, suggesting a common systemic driver of these programs.

THE HEBREW
UNIVERSITY
OF JERUSALEM

Advisor: Dr. Naomi Habib

THE HEBREW UNIVERSITY OF JERUSALEM

Multiparametric qMRI and dMRI gradients in the striatum are associated with Parkinson's disease motor dysfunction

Elior Drori

The striatum is involved in motor control and goal-directed behavior, which are affected in neurodegenerative diseases such as Parkinson's disease (PD). Using semi-quantitative ratio of clinical T1 and T2 weighted images (T1w/T2w), it was recently shown that microstructural gradients in the putamen change in early-stage PD patients. To shed light on the biological sources of this observation quantitatively, we scanned a dataset of PD and control subjects (N=85) for multiparametric quantitative MRI (qMRI) and diffusion MRI (dMRI) mappings. We apply the same gradient method to measure the spatial variation of quantitative biophysical measurements such as the relaxometry rates R1, R2 and R2*, magnetization transfer saturation (MTsat), the macromolecular tissue volume (MTV), the mean diffusivity (MD) and the fractional anisotropy (FA). We uncover distinct spatial profiles of these different measurements in the striatum, as well as different PD-related changes in these profiles. Moreover, we corroborate the previous findings by showing relationships between profile asymmetry and the asymmetry in motor dysfunction, assessed clinically using MDS-UPDRS-III. Importantly, this relationship is dependent both on the biophysical measurement and the degree of symptom asymmetry. Hence, our multiparametric qMRI data provides an important framework for understanding specific tissue sources underlying PD phenotype in the single subject, which may prove useful for diagnostic applications.

Results: We found distinct spatial profiles of qMRI parameters (R1, R2, R2*, MTV, MTsat), and dMRI parameters (MD, FA) in the putamen and caudate of our subjects. Moreover, all these qMRI gradients were correlated with the mean T1w/T2w gradient reported recently in an independent PD dataset2, suggesting

that T1w/T2w spatial variability in the striatum indeed reflects variability in biophysical properties. Importantly, we found that R1, R2 and MTV gradients were less steep in PD compared to healthy controls, and the largest difference between groups was in the posterior putamen. In these three qMRI parameters, we found that the interhemispheric asymmetry in the posterior putamen was contralaterally correlated with motor symptoms asymmetry (assessed with MDS-UPDRS-III), in PD patients with mild motor asymmetry. All these qMRI results replicate previous findings in T1w/T2w.

Including patients with extreme motor asymmetry tampered the relationship, though it remained significant in MTV. Importantly, the relationship between MTV and motor dysfunction suggests that the measured structural change associated with motor dysfunction mainly reflects decreased tissue density, i.e., increased water fraction. While R1, R2 and MTV showed associations with motor asymmetry – R2*, MTsat and diffusion parameters (MD, FA) did not show such relationships. However, MD was increased in the posterior putamen of PD patients, providing further evidence for an increased water fraction.

Conclusions: Our study provides quantitative multiparametric mapping of the biophysical spatial variability in the striatum of PD patients. Our approach provides another crucial contribution to non-invasive characterization of PD biological mechanisms in individual patients, and may promote early diagnosis and personalized medicine.

Advisor: Prof. Aviv Mezer

THE HEBREW UNIVERSITY OF JERUSALEM

Notch signaling is a critical initiator of roof plate formation

Sarah Kagan, Shai Ofek, Sophie Wiszniak, Markus Tondl, Quenten Schwarz, Chaya Kalcheim

The dorsal part of the neural tube is a dynamic region inhabited sequentially by Neural Crest (NC) progenitors, then Roof Plate (RP) cells, and interneurons located ventral to RP. The NC stage is characterized by cell proliferation and delamination, while definitive RP cells become post-mitotic and regain epitheliality. The mechanisms responsible for the transition between NC and RP are yet to be unraveled.

To this end, we performed a comparative transcriptome analysis of RP and premigratory NC cells, respectively. We unraveled more than 1000 differentially expressed genes up- or down-regulated at either stage and discovered novel RP-specific markers.

Among the upregulated genes in RP were components of the Delta-Notch pathway, expressed and active at the ventral border of the RP.

Gain of Notch function within the RP resulted in downregulation of specific RP genes (e.g; Rspo1, Bambi, Raldh2, and draxin), whereas Notch activation in cells adjacent to RP caused ectopic RP properties at the expense of interneuronal traits. Reciprocally, loss of Notch function in the mouse dorsal neural tube, resulted in downregulation of RP markers, absence of a RP and lack of DI1 interneurons. Hence, Notch signaling is crucial for determining the ventral limit of the RP adjoining the DI1 domain. Furthermore, it is also sufficient and necessary for RP formation.

Advisor: Prof. Chaya Kalcheim

THE HEBREW UNIVERSITY OF JERUSALEM

ODE-based Mechanistic Modeling for Alzheimer's Disease Progression

Yifat Haddad

Alzheimer's Disease (AD) has emerged as an increasingly pressing public health concern in recent years. While research has established that cellular communication between different brain cell types plays a major role in AD progression, much remains to be learned about the cascade of cellular and molecular events underlying the disease and their dynamics. Specifically, we have recently discovered specific cell populations associated with the disease, yet their contribution to the different stages of the disease is yet unknown.

To address these knowledge gaps, we have built a causal ordinary differential equation (ODE) model that mechanistically describes the dynamics of the classic disease pathologies along the disease progression, and the contribution of specific cell populations as well as risk factors to this dynamic. Our approach involves a Bayesian approach to identify the optimized model parameters based on a prior dataset of single cell RNA profiles in 424 aged human brains. Through investigating the model's properties, we aim to gain a more comprehensive understanding of the causal role of each cell population or risk factor on the progression and dynamics of the disease.

Our work places particular emphasis on the specific impact of different risk factors on the progression of AD, including ApoE4 genetic risk, age and sex. Ultimately, we hope that our research will shed light on the cellular pathways that drive AD progression, and inform the identification of potential therapeutic targets.

Advisors: Dr. Naomi Habib & Dr. Barak Raveh

THE HEBREW UNIVERSITY OF JERUSALEM

Pause then hold your horses: Striatum encodes for both attentional capture and inhibition of movement

Indrajeet

Inhibition of impending movement in response to a sudden stop-signal is crucial for flexible goal-directed behavior. For example, when someone is in a hurry to cross the road; but suddenly the pedestrian light turns red, warranting the person to inhibit the movements to cross. Stop-signal task (SST) is used to study inhibition of preplanned movements. In SST, a movement is elicited by a go-signal in the majority of trials; but needs to be canceled in response to a stop-signal, occurring randomly at variable intervals from the go-signal. Recent studies have shown that the performance in SST is conflated with two intricate but dissociable sources of information: (1) involuntary pause triggered by the sudden onset of any infrequent signal attributed to attentional capture, and subsequently (2) voluntary cancelation/inhibition of the movements. This has stimulated a recent theoretical debate whether the inhibition process is unitary (classical race model) or two-stage process (pause-then-cancel model). To address this problem, we trained a monkey to perform a saccadic eye movement version of SST with an additional infrequent continue signal instructing to ignore it and continue (generate) the movement. It acted as a control for attentional capture by infrequent signals. We recorded the activity of neurons in Caudate (*N=1308*) and Putamen (*N=1795*) while the monkey was performing the task.

We found that neurons in both Caudate (*N=248*) and Putamen (*N=132*) with selectivity to contralateral go saccades, were movement-related in contralateral direction, i.e., increased their activity for go saccades but decreased their activity if the saccade was inhibited. Interestingly, these neurons were stop-related in ipsilateral direction. These neurons were modulated in continue saccades similar to stop condition; albeit for brief duration and with less magnitude. In contrast, non-direction selective neurons in Caudate (*N=144*) were stop-related in both

contra and ipsilateral direction but did not differentiate between go and continue saccades. Unlike Caudate, the non-direction selective neurons in Putamen (*N=194*) were not related to stop in both contra and ipsilateral direction, rather differentiated between go and continue saccades but only in the contralateral direction. Thus, direction selective neurons were similarly related to attentional capture and inhibition in both Caudate and Putamen. But non-direction selective neurons were modulated differentially for attentional capture and inhibition in Caudate and Putamen. These findings imply for both common and distinct underlying neural mechanism for pause and cancel sub-processes of inhibition.

Advisor: Dr. Mati Joshua

THE HEBREW UNIVERSITY OF JERUSALEM

Phee calls conveys callee identity information in marmoset monkeys

Aner Shapira

The common marmoset is a small, non-human primate, that displays complex social vocal communication. Marmosets use specific localization calls to communicate self-location to conspecifics when loosing visual sight, in a turn taking manner. We hypothesized that phee calls convey also identity information of the callee, independent the caller's voice features. To test this hypothesis, we recorded pairs of monkeys while they were engaged in spontaneous phee call conversations. We constructed a large data set which includes 47,672 calls, labeled by the caller and callee identity. Callee identity labels were classified from spectrograms of calls made by different monkeys, using a random forest classifier. The classifier significantly classified the callee identity with average success rate of ~80%, suggesting that each monkey uses a unique call to address each of the other monkeys, and that phee calls convey identity information of the callee. Classification of callee identity using calls from all monkeys also yielded identity classification significantly above chance level, but to a lesser extent, which may suggest that similar identity calls are used only within members of the same social group. These preliminary results may provide the first evidence for *vocal labeling*—the ability to use novel auditory signals to label objects, and *vocal learning* in non-human primates, and suggests that marmosets, together with dolphins and humans, are the only known mammalian species that transmitting auditory identity information.

Advisor: Dr. David Omer

THE HEBREW UNIVERSITY OF JERUSALEM

Plasticity in Auditory Cortex During Fatherhood

Tamar Preminger and Baruch Haimson

Parental care is a fundamental and highly prevalent behavior found throughout the animal kingdom, from lower vertebrates to humans. Parental behavior is often sexually dimorphic and varies across species and strains. In mammals, the female is the main caregiver and only 3-5% of mammalian species exhibit paternal care. Becoming a parent is accompanied by significant physiological, hormonal, and behavioral changes that enable optimal care of the offspring. For example, one of the most stereotypical parental behaviors in mice is pup retrieval of distant pups back into the nest as a response of their distress calls. Although less studied compared to females, males also undergo significant changes during pregnancy and parturition, including a shift from infanticide or ignorance of pups to paternal care. The mechanisms behind this remarkable behavioral transition are still unknown. Parental behaviors, mothers, and fathers alike, are accompanied and supported by numerous neural changes in the brain at disparate levels of organization. Differences as diverse as adult neurogenesis, synaptic plasticity, activity patterns, transcriptomic and epigenetic signatures, were demonstrated in different brain regions. The main body of work that studied the neural substrate of parenthood pointed to the hypothalamus and other subcortical regions, which have been shown to be crucial for the proper development of parental behaviors. In this current work, we aim to probe the plastic events occurring in the auditory cortex in male mice following fatherhood. Using longitudinal two-photon calcium imaging before, during and after fatherhood to inspect auditory cortex response to pup calls and corresponding narrow band noise (NBN), we found that there is a significant improvement of neuronal discriminability between pup calls and NBN in fathers. We further sought to unravel the hormonal mechanism underlying these neuronal changes by conducting a set of molecular, transcriptomic and metabolomic analysis of the expression level of different hormonal receptors and

their corresponding ligands in the auditory cortex. We found that several hormones show significantly different expression levels during fatherhood. As recent work has implicated the hormone prolactin in regulating male parental behavior, we focused on this hormone and found a significant rise in prolactin-related activity in the auditory cortex of fathers. Further work is required to causally link between the rise in prolactin concentrations and the induction of auditory-related paternal behavior and the corresponding neuronal plasticity.

Advisor: Prof. Adi Mizrahi

THE HEBREW UNIVERSITY OF JERUSALEM

Prefrontal cortex contributes to latent state inference and context adaptation in mice

Gabrielle Marmur, Haneen Rajabi, John Schwarcz, Robert Reiner

Essential features of the environment are often hidden and must be inferred based on indirect evidence. Here, we developed a novel auditory change detection task to investigate the mechanisms involved in the process of inference. In this task, on each trial, head-fixed mice hear a sound train that is composed of a random sequence of intermittent beeps in 2 hidden states, a 'No lick' and a 'Lick' state. The duration of the 'No lick' state is drawn from an exponential distribution. At the end of this state (the change point), a 7 second response window starts, in which only consecutive beeps are played. The transition to the safe state is un-cued and licking is only rewarded in this state.

During the task, the true state of the environment ("lick" or "no lick") is hidden and must be inferred. Since beeps occur in both states and since the length of the "no lick" state is random, mice are required to reach their decisions based on the length of the beeps that they hear: the longer the beep, the more likely it is that licking will be rewarded. Uncertainty in this task is determined by the probability of the misleading beeps during the 'No lick' state. Low probability corresponds to high certainty, as only a few beeps are sufficient to indicate that reward is available.

Optimally, the mice should integrate consecutive beeps to threshold to infer an increasing probability of being in the 'safe' state given a specific 'misleading beep' probability. Alternatively, the mouse can simply lick in response to the beeps with some probability in a non-integrating policy. Behavioral data collected from 17 mice indicates that mouse behavior indeed relies on integration of consecutive go-cues to threshold. The mice succeed in detecting the change points between the 'safe' and 'unsafe' to lick states. Furthermore, they adapt their response times to

different levels of uncertainty, waiting longer for higher 'misleading beep' probabilities.

To study the brain mechanisms of integration in this task, we tested the involvement of prefrontal cortical areas by reversibly inactivating them using muscimol (a GABA-A agonist). We show results of inactivation of the Orbitofrontal Cortex (OFC) and the Anterior Cingulate Cortex (ACC) in behaving mice. By uncovering the behavioral strategies and neural circuitry involved in inferring hidden environmental features, this research advances our understanding of the cognitive processes underlying adaptive behavior and decision-making.

Advisor: Dr. Eran Lottem

THE HEBREW UNIVERSITY OF JERUSALEM

Reconstructing glial dynamics and interactions underlying early pathological events in Alzheimer's mouse models

Schmidtner, A; Ravid, A; Schwartz, G; Eliash, N; Kitsberg, D; Adam, M; Habib, N

Alzheimer's disease (AD) is a debilitating neurodegenerative disorder that affects about 46 million people worldwide, with no effective treatments. Recent studies revealed diverse AD-associated states in brain cell types that occur before the onset of cognitive symptoms, suggesting a systemic change of the cellular environment underlying AD. Therefore, unravelling the early cellular and molecular drivers leading to those changes might discover new treatments.

As one of the first pathological hallmarks of AD is amyloid-β (Aβ), to better understand the role of glial cells in AD, we have profiled the AD amyloidosis mouse model 5xFAD by single-nucleus RNA-seq. We identified coordinated transitions across all glial cell types to disease-associated states, including microglia, astrocytes, oligodendrocytes and OPCs, and built a dynamic mathematical model to infer the cellular cascade in response to Aβ that leads to the observed disease-associated glial states. As the time scales of this cellular cascade and interactions cannot be captured in the mouse model, to experimentally identify and characterize the temporal dynamics and interactions of glial responses to Aβ, we refined a primary mouse brain culture to generate an improved model system, including a serum-free growth medium to maintain the state of glia cells that recapitulates their characteristics in the healthy brain *in vivo*. Subsequently, by single-cell RNA-seq we profiled the changes in expression programs in response to Aβ across the different glial cells, exposing a fast turnover of microglia followed by astrocytes. For astrocytes, we identified five distinct expression programs that capture the dynamics of state transitions, starting with homeostatic astrocytes

that turn on an inflammation program, upregulating interferon response pathways, transitioning to upregulation of metabolic and stress pathways, and gradually converging within 48h to a cellular state resembling the disease-associated astrocytes found in adult 5xFAD mice with an upregulation of Aβ-formation pathways. Whereas, in microglia we detected a rapid transition to an inflammatory state, which we infer drives the initial responses of astrocytes to Aβ through the release of a specific combination of cytokines. Of note, our discovered Aβ-response, although resembling previously defined inflammatory signatures, was significantly different from the response to an inflammatory agent like LPS.

Overall, our findings plot a specific cascade of events and interactions underlying the transition of homeostatic to disease-associated states in glial cells in an early response to Aβ that we suggest drive the dramatic changes observed in the entire cellular environment in AD brains and provides new therapeutic targets for early interventions.

Advisor: Dr. Naomi Habib

THE HEBREW UNIVERSITY OF JERUSALEM

Representation and attention of an unconscious change

Rotem Krispil

When making sense of their surroundings, a rational agent should consider both the information they receive from their senses, and their uncertainty about this information. Past experiments have shown that agents' behavior resembles that of an optimal observer that weights information according to the uncertainty regarding possible outcomes and the estimated variance of different sensory signals, as reflected in choice, motor reaching, gaze location and duration, and other forms of behavior. Gaze behavior specifically was shown to reflect both uncertainty about future location of a target, future location of a planned saccade, and uncertainty about possible rewards. However, it is unclear how does sensory uncertainty affect gaze behavior, as it was difficult to separate the effects of the detection of movement, known to attract overt attention, and sensory variance. Similarly, it is still unclear whether prediction updating can happen unconsciously, or whether it always elicits an experience of change, as experimental paradigms eliciting prediction errors usually utilize uncertainty in reward or location, which is hard to claim aren't conscious. Here, we made use of slowly changing stimuli eliciting change blindness to test whether gaze is attracted to locations exhibiting change when this change is unconscious. Additionally, we test whether updating following the detection of prediction error can happen when one is unconscious to the change, and if so whether a conscious experience

of change is necessarily elicited when one updates their currently held model of the world.

Advisor: Prof. Leon Deouell

THE HEBREW UNIVERSITY OF JERUSALEM

Sex Differences of Cerebellar Activity and Related Behaviors in WT and ASD Mice

Inbar Kotzer

The growing interest in sex differences in the brain reflects the undisputable demonstrations of sex differences in a range of neurological and psychological disorders. One of the most documented sex differences has been in autism spectrum disorder (ASD), where the prevalence of ASD in boys is four times higher than in girls. It is also well-documented that cerebellar abnormalities are the most reproducible observation in ASD patients. However, sex differences in cerebellar activity are not well documented.

Here we use a mouse model for ASD with a mutation in the chromatin regulator *Pogz* gene and WT littermates to study sex differences in cerebellar activity. Purkinje Cell (PC) activity was measured from different cerebellum areas in anesthetized mice. Mice were also tested in a three-chamber task (testing social behavior) and an eyeblink conditioning task (testing cerebellar-related learning).

We found that in the vermis of WT mice, males had a higher complex spike (CS) frequency. Simple spike (SS) mean frequency was similar, but females had a more irregular firing pattern. In ASD mice, the trend in CS activity was similar but not as significant. In SS activity, male mice had a significantly higher mean frequency, but there was no difference in the irregularity of the firing pattern. These differences were not seen in the cerebellar hemisphere. Females displayed better learning in both the WT and ASD groups. ASD male mice were found to be more social, while there was no difference in sociability in the WT group.

The mechanism underlying the differences is still unknown, and we are in the process of checking the cellular properties of PCs as well as inferior olive cells. We are also looking into the involvement of certain proteins (predominantly Zebrin).

THE HEBREW
UNIVERSITY
OF JERUSALEM

Advisor: Prof. Yosef Yarom, Prof. Sagiv Shifman

THE HEBREW UNIVERSITY OF JERUSALEM

Sex Specific Metabolic Reprogramming of Adipose Tissue Linked to Alzheimer's Disease

Adi Avni

Alzheimer's disease (AD) is a progressive neurodegenerative disease of advanced age and the most common form of dementia to which there is no effective treatment. Several complex metabolic risk factors exist for AD, including obesity and diabetes, yet the molecular mechanism linking the metabolic morbidities with AD is yet unknown. Moreover, other risk factors for AD might be masking the effects of the metabolic risk, such as the increased prevalence of AD among women. Recently we have shown that an AD-obesity comorbidity mouse model driven by high fat diet (HFD) accelerates memory impairment, through immune dysfunction driven by NANA sialic-acid. We hypothesized that metabolic reprogramming of cells in the adipose tissue are directly involved in AD progression and could underlie the link between obesity and the increased risk for AD in a sex-depedant manner. Using a single nucleus RNA-sequencing (snRNA-seq) dataset of 243,598 cells from 38 mice including: males and females 5xFAD AD model and WT, fed with HFD or control diet (CD). Analysing the diversity of cells among the different cell types in the adipose tissue (immune, mesothelial, endothelial, adipocyte, progenitors etc.), we identified expression programs linked to each of the different conditions: genotype-dependent programs (AD vs WT), diet-dependent (HFC vs. control), sex-depedant, or a combination of effects. For examples, we found a strong diet-dependent reprogramming of macrophages in both males and females, and we found AD-dependent reprogramming in dendritic cells as well as HFD-AD co-morbidity dependent reprogramming in mesothelial cells exclusively among females. We also identified strong sex-specific differences across multiple cells such as the mesothelial cells. Overall, we found reprogramming of multiple cell types in the adipose tissue that can be linked to

THE HEBREW
UNIVERSITY
OF JERUSALEM

AD and AD-HFD co-morbidity which might underlie the link between obesity and AD in sex-depedant manner.

Advisor: Dr. Naomi Habib

THE HEBREW UNIVERSITY OF JERUSALEM

Single neurons can solve the XOR problem

Ido Aizenbud

Various characteristics of single cortical neurons, such as the morphology of the dendritic tree, nonlinear membrane ion channels, and nonlinear synapses play a key role in determining the computational properties of neurons. Detailed biophysical models, implementing these characteristics and constrained by experimental results, provide an accurate description of the input/output (I/O) function of single neurons. However, a systematic exploration of the computational and learning capabilities of single cortical neurons as described by their respective detailed biophysical models is largely missing. Here, we developed a learning rule for both the synaptic weights and the axon-synapse wirings of detailed biophysical models of cortical pyramidal cells, using analogous deep neural network (DNN) models as surrogates. Specifically, we attempted to explore the space of learnable parameters of the neuron, as spanned by both functional plasticity and structural plasticity, by implementing surrogate gradient descent on nondifferentiable detailed biophysical models using surrogate differentiable DNNs. Using the learning rule, we show that a single cortical neuron can solve the XOR problem, which is famously known to be unsolvable by the perceptron model. We compare the performance of single neurons with different morphological, biophysical, and synaptic characteristics on the XOR problem, to assess the computational roles of such characteristics. We suggest a natural generalization for this problem, the n-parity problem, and suggest showing that a single cortical pyramidal neuron can solve this problem for some $n > 2$. Overall, this novel learning rule and the interplay between the biophysical and respective DNN model of the neuron enabled us to systematically explore the computational capabilities of single neurons on a variety of computational tasks.

Advisors: Professor Idan Segev and Professor Mickey London

THE HEBREW UNIVERSITY OF JERUSALEM

Spatio-temporal dynamics of Roof plate to Radial glial transformation during avian neural development

Susanna Ventriglia and Chaya Kalcheim

Dept. of Medical Neurobiology

IMRIC and ELSC

Hebrew University of Jerusalem

Hadassah Medical School

The development of the dorsal spinal cord is a highly dynamic process. It begins from a neural tube harboring neural crest progenitors that generate the peripheral nervous system. Next, this domain is replaced by the roof plate (RP), a patterning center for dorsal interneurons. Through a process of dorsal collapse, the RP gives rise to radial glial (RG) cells (RG) which eventually generate dorsal ependyma, a stem cell niche of the central nervous system.

We aim at understanding how does the RP transform into RG at both morphological and molecular levels. First, we implemented knowledge stemming from RNA-seq data to investigate the spatio-temporal molecular repertoire that characterizes the above transition. To this end, we performed a series of *in-situ* hybridizations in quail embryos between embryonic days 4 to 13. Expression of BMP inhibitors present in RP, such as *Bambi*, *Raldh2*, *Hes4*, and *Grem1,* persist in the stretched RG. Likewise, components of the Wnt pathway such as *Axin2*, *Wnt3a*, *Wnt1,* and its regulator *Rspo1* are present at both stages. In contrast, *Crabp1*, *Rdh10, Gbe1*, *Fabp7,* absent in RG, discriminates between RP and RG stages. By implementing the above genes, we are currently examining the functions of various morphogen signals, the dynamics of cell proliferation and the morphological changes in selected aspects of RP-to-RG transition.

THE HEBREW UNIVERSITY OF JERUSALEM

Spinal Cord Network Activity Involved in Inflammatory Hyperalgesia-Related Pain

Rachely Butterman

In pathological conditions, the nociceptive information transmitted to the brain through a complex neural network in the spinal dorsal horn (SDH) is altered. In this study, we aim to investigate the nociceptive response of the spinal cord to noxious stimuli during inflammatory pain. We simultaneously recorded the activity of hundreds of SDH neurons in vivo in response to noxious stimuli to mouse paws using in vivo two-photon microscopy from the L5 segment of the spinal cord. We demonstrated that although the overall activity of the neuronal network increases during the noxious stimulus, only about half of the cells increase their activity. Other cells did not respond to stimuli or reduced their activity following noxious stimuli. We hypothesized that the overall activity of the network would increase due to an increase in the activity of activated cells when the same stimuli were applied to lightly burned skin. However, we observed that although the activity of the general network does increase in inflammatory conditions, there is no change in the overall activity of the activated cells. Instead, we observed that the number of cells that decreased their activity during noxious stimuli was significantly reduced, and cells that were quiescent under naive conditions became activated following inflammation, suggesting an overall change in the network's activation pattern. Finally, we injected a GCamp Retro-Virus into the PBN in the brain to examine how the alteration in the activity of the spinal cord network impacts the output of projection neurons to higher brain centers during inflammatory conditions.

THE HEBREW UNIVERSITY OF JERUSALEM

Statistical Learning with Limited Attentional Capacity

Dan Hilman Amir

The extraction of statistical regularities out of a sensory stream is believed to be at the core of our ability to understand and interact with the world around us. A great body of research demonstrated the central role of statistical learning in human language acquisition and its generality across modalities. In contrast, much less attention has been given to the dynamics of the learning process and how our limited cognitive capacity shapes them. In this work we suggest a model for attention driven mechanism, where limited processing resources are dynamically distributed across the sensory space, to maximize the amount of information gained about the statistical regularities of the stimuli. We show through simulations and theoretical analysis that such a model predicts an hierarchical learning process where attention resources are first drawn to frequent items which convey a maximal amount of information about the underlying distribution and are gradually distributed between a larger pool of information sources. We then demonstrate that for a learner with finite accuracy, our model predicts higher learnability of rare items in skewed distributions compared to uniform ones, in line with recent empirical results in the field. Finally, to test our model predictions, we developed a new experimental paradigm for assessing the continual process of statistical learning of human participants and present preliminary behavioral results to support our computation model.

Advisor: Dr. Yuval Hart

THE HEBREW UNIVERSITY OF JERUSALEM

STEREO, A supervised platform for the annotation of freely-behaving mice yields insights on the role of ventrolateral striatal SPNs in mediating orofacial behaviors

Itay Shalom, Ben Jerry Gonzales, David Matthew Lipton, Ami Citri

'Neuroscience only makes sense in light of behavior', yet behavior is hard to measure and quantify. Neuroethology emphasizes the need to measure animals' behavior in natural environment and focus on naturalistic behaviors. Quantifying behavior of freely moving animals is a technologically challenging task. Here we propose *STEREO*, a supervised, efficient, high-throughput system that provides a high-resolution description of freely-moving mouse behavior. *STEREO* is built of Convolution Neural Network (CNN) and Long-Short-Term Memory (LSTM) layers and operates on sequences of frames. Spatio-temporal features are implicitly learned during the training of the network, and account for time-dependencies present in the behavioral data, since behavior is time-evolving. Applying *STEREO* to video recordings of mice following repeated exposure to cocaine enabled the quantification of nuanced orofacial behaviors and revealed a gradual narrowing of the subjects' behavioral repertoire. To further investigate the underlying circuitry governing motor execution, we used *STEREO* to align the dynamics of $Drd1^+$- vs $A2A^+$- ventrolateral striatal (VLS) spiny projection neurons (SPNs) Ca^{2+} activity to behavior. Doing so, we observed a differential activity pattern of the two striatal projection populations with respect to the performed behavior. Finally, we used *STEREO* to quantify the changes induced in the landscape of behavior following optogenetic and chemogenetic modulation of VLS dSPN and iSPN activity, illustrating the causal relationship between the activity of these cells and the motor execution of orofacial/upper-limb actions.

THE HEBREW
UNIVERSITY
OF JERUSALEM

Advisor: Prof. Ami Citri

THE HEBREW UNIVERSITY OF JERUSALEM

Stimulus-specific adaptation (SSA) in auditory cortex in awake mice under 2-photon microscopy

Moran Aharoni, Dina Moshitch, Israel Nelken

Stimulus-specific adaptation (SSA) is the response reduction to a common stimulus that does not, or only partially generalize, to other rare stimuli. SSA has been proposed to be a correlate of 'deviance detection', an important computational task of sensory systems. Human Electrophysiological correlates of deviance detection have been studied extensively using various brain potentials. The best known is mismatch negativity (MMN), which peaks ~150–200 ms after the deviant stimulus. SSA is similar, but not identical, to MMN. One difference between SSA in single cells and MMN is their time course. SSA 'rides' on the early cortical responses to sounds, whereas MMN occurs about 100 ms later.

Using fiber photometry of calcium signals in the mouse primary auditory cortex, we uncovered large and robust late response components which show deviance sensitivity at ~100-150 ms after stimulus onset. These signals are believed to reflect the average spiking activity of a local network.

To search for the single-neuron basis of those late population responses, we used two-photon microscopy to resolve the responses of multiple adjacent neurons. In the anesthetized mouse, we observed population activity that was robust and resembled the late responses components found using fiber photometry. However, single neurons hardly showed auditory responses independent of their surrounding neuropile. We therefore recorded in awake, head-fixed mice. In the awake mouse, we found more single neurons that responded to auditory stimuli independently of the surrounding neuropile. The late responses were however highly variable. We suggest that the reproducible late response components observed in the population activity reflect neuronal ensembles' activity whose membership varies between trials.

THE HEBREW
UNIVERSITY
OF JERUSALEM

Advisor: Prof. Israel Nelken

THE HEBREW UNIVERSITY OF JERUSALEM

Structural mapping of hippocampal neurons based on their functional profile

Mor Margolin, Shulamit Baror-Sebban, Qixin Yang, Maya Groysman, and Yoav Adam

The hippocampus is critical for the formation of episodic memories and its role in spatial memory has been extensively studied. While the traditional view suggests that each hippocampal subregion consists of a homogenous population of principal neurons, cumulative evidence indicates that each subregion is composed of a diverse and heterogenous population of pyramidal cells. However, since the different subtypes are partially intermingled, the relationship between function and anatomy is vaguely understood. Relating structure to function has been a long-standing challenge in neuroscience, and here we aim to bridge this gap by developing a toolkit for functional two-photon (2P) calcium imaging followed by non-invasive, labeling of selected single-neurons based on their activity profile, for subsequent detailed anatomical mapping.

We first developed a set of AAV viruses enabling co-expression of the red calcium indicator jRGECO1a, a blue light-activated Cre recombinase (iCreV), and a Cre-dependent GFP. We injected these vectors into CA1, and extensively optimized the conditions to achieve high levels of jRGECO while minimizing non-specific GFP expression. We then performed 2P calcium imaging using a 1050 nm laser. By locally scanning selected cells with a 920 nm laser we could induce GFP expression in ~70% of the targeted cells. In a parallel effort, we trained these mice in a virtual reality (VR) spatial navigation task, performed 2P calcium imaging, and identified hippocampal place cells. In the next experiments, we will transition the mice into a novel virtual space during imaging in order to induce global remapping of the hippocampal network. This will allow us to identify distinct types of place cells such as reward cells, early-generated place cells, and late-generated place cells.

We hypothesize that these unique types of place cells project their axons into distinct brain regions. To test this, we will photo-tag such cells and reconstruct their axonal projection pattern following whole-brain tissue clearing. This set of tools will help to reveal how the hippocampal map is conveyed to other brain regions, and might pave the path for similar structure-function studies in other systems.

THE HEBREW UNIVERSITY OF JERUSALEM

Temperature effects on visual information processing and hunting behavior in the larval zebrafish

Shai Tishby, Maayan Moshkovitz, Netta Livneh, Yoav Rubinstein, Lilach Avitan

Biological and in particular neural processes are heavily dependent on temperature to properly function. Zebrafish are ectothermic animals; thus, their body temperature is similar to the water temperature. To survive, zebrafish must independently hunt their food in natural environments where the water temperature varies greatly (18°-33°C). This behavior is visually guided and requires accurate visual processing and motor outputs. While zebrafish were shown to change their general swim statistics when exploring their surrounding in different thermal conditions, it is unclear whether hunting behavior and its underlying visual processing are affected by temperature changes.

We recorded hunting behavior in three ecologically relevant temperature conditions (cold, intermediate, and hot; 22°, 27°, and 31°C respectively) using a high-speed camera (500 fps). Furthermore, we recorded neural activity in response to prey-like stimuli using two-photon volumetric calcium imaging under similar temperature conditions. While movement statistics in all three conditions substantially differed, hunting performance was not affected. We further observed a decrease in the number of tuned neurons in the optic tectum and inferior decoding performance under the hot condition, which hints at a mechanistic change in the neural processing of visual information, leading to the changes observed in behavior.

Our preliminary results show that while thermal deviations modulate visual processing and alter behavior, the animal can still capture targets. This suggests a compensation mechanism allowing visual information processing and behavior execution under varying conditions.

THE HEBREW
UNIVERSITY
OF JERUSALEM

Advisor: Dr. Lilach Avitan

THE HEBREW UNIVERSITY OF JERUSALEM

Temporal specificity in the impact of reward on motor learning

Yirat Henshke*, Yehudit Botschko* and Mati Joshua

* These authors contributed equally

Motor learning is an adaptive trial-and-error process in which the accuracy of movement improves with the repetition of behavior. Research has highlighted the importance of sensorimotor errors in driving motor learning. However, these errors are only one of many signals that could participate in motor learning. Importantly, reward expectation and outcome impact motor learning as well. The timing of the sensorimotor error signals and the information regarding reward might be different, raising the question of how the temporal proximity between these signals impacts motor learning. We sought to examine whether the efficacy of learning is affected by the timepoint at which the subject is informed of the reward size for completing the task.

We used a smooth pursuit eye movement task in which monkeys learned to predict the change in target direction, reflected by an adaptive early change in eye movement direction. A color cue signaled the size of the reward the monkey would receive at the end of each trial. This cue was provided at different time points over the course of the trial. We found that learning is optimized when the reward cue is given at the time of motion onset of the target before the target changes direction. The monkeys were better able to predict the upcoming change in direction, as displayed by the initiation of eye movement before the target's direction changed. The learned eye movement was negligible to insignificant when the cue appeared a second before the target moved, during the change in target direction, or did not appear at all.

Thus, we have found that there is specificity regarding the timing in which reward information affects motor learning in a smooth pursuit task. These results suggest

principles that might be used to optimize motor learning in other systems and tasks.

Advisor: Prof. Mati Joshua

THE HEBREW UNIVERSITY OF JERUSALEM

The role of context in segmentation and continuity

Shira Baror

What governs the interplay between continuity and discontinuity in human experience? Studies in perception show that the sense of continuity is achieved partly by 'serial dependence', which refers to the bias of current perceptual decisions (e.g., line orientation judgements) towards preceding ones. According to a Bayesian interpretation of this phenomenon, predictions regarding the similarity between consecutive events are incorporated into our perceptual processes. In parallel to continuity-maintaining processing, research shows that people naturally segment continuous experience into discrete events ("event segmentation"). Event boundaries (perceived transitions from one event to the next) are hypothesized to arise due to prediction failure, and have been shown to shape long-term memory (e.g., better item-context associative memory is found for inputs that occur at event boundaries, and memory for the order of elements is enhanced for elements within the same event).

From a Bayesian standpoint, serial dependence is associated with predictions, and segmentation with prediction failure, which could suggest that the two are driven by a shared mechanism. To our knowledge this has not been tested yet because the two are studied as part of different fields of research. Here we bridged these lines of work and examined whether serial dependence and event segmentation are directly linked. Specifically, we hypothesized that context stability promotes continuity and dependence between events, while context change triggers segmentation between events, ultimately shaping long-term memory.

To examine our hypothesis, we optimized a unique paradigm that tests serial dependence and event-boundary effects on memory in a single setup. Participants viewed tilted everyday objects, each surrounded by a coloured circle frame which served as context for the objects, and performed an object-orientation task, which classically exhibits serial dependence. This was followed by two memory tasks-

associative memory for the colour of the frame that surrounded each object, and temporal-order memory for pairs of objects.

The results show that both serial dependence and boundary effects on memory coexist in the task. First, serial dependence was observed, such that object orientation judgements were biased both towards the previous response as well as towards the previous object's orientation. In both cases, the maximum bias towards previous events was observed at ~20-degree tilt. Second, memory was influenced by context change in the task, such that associative memory between the object and the colour of its surrounding frame was enhanced at event boundaries. Event boundaries did not significantly influence temporal order memory, though a trend towards enhanced temporal order memory for objects within the same event was observed. Critically, serial dependence, measured both by the mean bias towards the previous orientation as well as by the mean bias towards the previous response, decreased at event boundaries, hinting towards a shared contextual mechanism.

These results begin to elucidate how perceptual continuity and memory-related discontinuity converge on contextual predictions, and shed new light on how our cognitive systems interact with the outer environment. Future studies that target several forms of contextual change are planned, to support a thorough investigation of the context-based account of continuity and segmentation.

Advisor: Dr. Aya Ben-Yakov

THE HEBREW UNIVERSITY OF JERUSALEM

The role of intentional expectations in predictive sensory perception

Chen Frenkel

Predictive Processing (PP) theory suggests that the brain is an active agent constantly building predictions, based on prior knowledge of the environment, with the goal of minimizing surprise and selecting the most adaptive course of action. This is typically viewed as an intrinsic, hardwired mechanism applied in both sensory and motor systems. However, in order to apply PP theory to high level psychological processes a deeper understanding of how intentional expectations fit into the framework of PP theory in humans is required. The current study manipulates participant's intentions to form expectations using task demands while recording EEG data to measure predictive activity and prediction errors in the brain. This manipulation is achieved by exposing participants to a multi-feature stream of information that contains regularities in the task relevant feature. The main test condition requires participants to actively predict the next stimuli. This condition is compared to two control conditions: a neutral condition in which participants attend to the currently presented stimulus and a condition in which intentional expectations are likely inhibited, using a one back task. Since there is no well-established neural correlate of predictive activity using EEG, a multivariate decoding model is applied to inspect differences in neural activity prior to the onset of a stimulus. Additionally, an exploratory analysis of the stimulus evoked activity is applied in order to detect differences in prediction error between the conditions. I will present the study design and rational, as well as initial results.

Advisor: Prof. Leon Deouell

THE HEBREW UNIVERSITY OF JERUSALEM

Transfer RNA fragment regulators of cholinergic cortical neuromodulation in mental disorders

Tamara Zorbaz

Proper integration of sensory stimuli is crucial for the development and maintenance of adequate cognitive functions, which tend to decline with age and are the hallmark of both neurodegenerative (Alzheimer's disease, AD) and neuropsychiatric disorders (e. g. schizophrenia, bipolar disorder, (SCZ, BD)). Cholinergic neuromodulation is crucial for the maintenance of these cortical cognitive functions. Correspondingly, cognitive decline precedes psychotic episodes in mental disorder patients and is perturbed in individuals chronically treated by antipsychotics with anticholinergic properties. Together, this may reflect interrelated transcriptomic-morphological alterations of the cholinergic network, supported by our findings that early sensory whisker deprivation leads to dendrite branching impairments of murine cortical cholinergic interneurons via the ELMO1 and SEMA5B transcripts, among others (Yayon et al 2023).

We identified altered age-related dynamics of cholinergic-regulated cognitive function in the BD/SCZ spectrum of phenotypes. In-depth analysis of transcriptomics data from the dorsolateral prefrontal cortex (dlPFC) of individuals with SCZ and BD highlighted distinct distribution of cholinergic-regulated clusters compared to those of healthy controls. Emphasizing disease-specific patterns, SCZ profiles segregated together with those of aged controls into the cluster characterized by low cholinergic input, whereas BD individuals segregated into the cluster of high cholinergic input. Reflecting impaired synaptic connectivity and plasticity, the low cholinergic input subgroup lost the correlation between M1 muscarinic receptor levels and those of the dendritic branching regulator SEMA5B and the potassium channel KCNQ2 transcript. To challenge the working hypothesis that small non-coding RNA regulators, mainly tRNA-derived

fragments (tRFs) may play a prominent role in cholinergic cortical neuromodulation, we subjected brain samples of aged individuals with BD and AD to small RNA-seq and identified tRF candidates that are predictably involved in synaptic plasticity. To experimentally challenge these concepts, we currently treat human-originated neuronal cellular models with synthetic tRFs and/or tRF brain-isolated fractions to test their capacity for regulating muscarinic receptor-induced Ca++ signaling, which is crucial for modulating cortical synaptic plasticity. Our goal is to elucidate tRF-regulated mechanisms underlying age-related cognitive impairments in neurodegenerative and mental disorders.

Advisor: Prof. Hermona Soreq

THE HEBREW UNIVERSITY OF JERUSALEM

Unraveling the visuomotor transformations underlying social behavior in zebrafish

Imri Lifshitz

To survive and reproduce, animals significantly rely on the ability to maintain social interactions with their conspecifics. These interactions are observed across various species, and the underlying neural circuits are largely conserved across all vertebrates. Nevertheless, little is known about the precise behavioral algorithm and the underlying neural mechanism that integrate sensory information and transform it into social actions. To address this question, we recorded whole-brain neural activity from a head-fixed and tail-free larval zebrafish observing a freely swimming conspecific, along with high-speed behavioral recording of both fish.

Previous studies showed that fish movements are well captured by the principal components of their tail flicks. We found that these components are highly reproducible across different behaviors, as well as in head-fixed fish, allowing the accurate prediction of changes in distance and angle. Using this method, we predicted the intended movement of a head-fixed fish engaged in social behavior. This behavior was characterized by a typical time lag, where the movement of the fixed fish was likely to occur around 100 milliseconds after a corresponding movement of a conspecific. Interestingly, the predicted angle of movements obeying this time lag was associated with the relative location of the conspecific. We defined these movements as social movements, thus providing a mechanism to distinguish them from spontaneous swim bouts.

These findings suggest that movements of others drive social actions and are integrated to allow the characteristic temporal synchrony of social behavior. Lastly, these results lay the foundations to study the underlying neural mechanisms of social vs. non-social actions.

THE HEBREW
UNIVERSITY
OF JERUSALEM

Advisor: Dr. Lilach Avitan

THE HEBREW UNIVERSITY OF JERUSALEM

Value Modulation of Impulsivity

Zhe Liu

Impulse control is an important cognitive faculty, and failure to exert such control is a core symptom of a wide range of psychological disorders. Intuitively, whether an action is executed prematurely or not depends on the reward's value and delay. However, the links between value, timing and impulsivity, particularly at the neuronal level, remain poorly understood.

To investigate this link, we developed novel value-based waiting tasks for head-fixed mice, and focused our investigation on the ventral striatum (VS), a major component of the ventral striatum that is known to be involved in both value processing and impulse control.

We found that both reward size and time affect impulsive behavior. These effects were captured by a dynamic Pavlovian-bias reinforcement-learning model. Using fiber photometry to measure VS dopamine, we found that dopamine levels coded reward prediction errors following impulsive choices, and that these signals correlated with changes in mouse impulsivity levels on a trial-by-trial level. These findings suggested that VS dopamine may act as a teaching signal, updating expected value functions following each trial's outcome to modify subsequent behavior.

To test this hypothesis, we optogenetically stimulated VS dopamine axons following reward omissions, and found that indeed, this manipulation disrupted negative value learning that was observed under control conditions.

These findings suggest that the VS plays a critical role in regulating value based impulsive behaviors.

Advisor: Dr. Eran Lottem