Tzuba 2024: Abstracts

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Sessions and Talks

Session I

ACC-projecting claustrum cells modulate performance efficiency and sensory to motor coupling in the mPFC

Noa Perez-Rivlin

The claustrum is renowned for its extensive interconnections, especially with frontal cortex, and has been suggested to play a role in attention, engagement, rule switching, and sleep. Recent research conducted in our lab has highlighted the claustrum's capacity to regulate responsiveness to sensory stimuli. In this study, I investigated the impact of optogenetic modulation of claustrum neurons projecting to the ACC on performance in a cognitive task and on the representation of task parameters in the mPFC. The behavioral paradigm employed, the 'ENGAGE" task, requires a balance between response inhibition and cue detection. Mice were familiarized with the task rules in an automated behavioral cage, and were subsequently tested while head-fixed in the recording rig, in order to facilitate acute Neuropixels recordings. During the transition from freely moving to head-fixed conditions we observed that mice initially learned to generalize the pre-learned contingencies to the new environment, and then optimized their response strategies accordingly. Mice in which the activity of the claustrum was modulated during performance of the ENGAGE task were deficient in optimizing the behavior to the new settings. This was evidenced by decreased success rates, increased false alarm rates, and slower reaction times. In addition, compared to control mice, their cortical sensory responses during hit and miss trials were not well differentiated, and their pre-motor activity was delayed. Additionally, while in control mice the representation of a no-go cue was clearly differentiated between false alarm and correct trials, this representation was not evident in mice exposed to claustrum stimulation. Thus, a classifier trained to predict the behavioral outcome from neural activity performed worse in the ChR2 group. These finding suggest that adaptation in task performance involves an automation of sensory to motor signals in frontal cortex, which is disrupted upon perturbation of claustrum activity.

Advisor: Prof. Ami Citri

Immature cortical processing in adolescence constrains auditory discrimination

Benne Praegel

Adolescence is a profound period of physiological and cognitive maturation. Yet, the behavioral manifestations and the neural substrates during this developmental period remain a matter of controversy. Here, we aim to clarify how adolescents discriminate learned tone categories as compared to adults. To investigate the issue, we trained adolescent and adult mice to categorize pure tones in a Go/No-go task. Using automated-training in the home-cage of grouped mice, as well as head-fixed training of individual mice, we show that the behavioral performance of adolescent mice is lower compared to adult mice. We find evidence that the lower performance is attributed to a lack of response inhibition and high heterogeneity of the adolescents rather than their perceptual sensitivity. To assess how tones are encoded in the brain of adolescents and adults, we used Neuropixels probes to record from the auditory cortex while mice were engaged in the task and under passive listening conditions. Tone representations were assessed by several different parameters, all of which were different between adults and adolescents. Discriminability among the learned sounds was higher, faster, and more long lasting in adults. The immature auditory processing in adolescents was evident for task-, sound-, and choice-related activity; both at the single-neuron level, as well as at the level of the whole population. Recordings in passively listening mice revealed that neurons in the adolescent auditory cortex have wider tuning curves, denser responses, and higher signal and noise correlations as compared to adults. Our findings suggest that a significant maturation process still occurs during adolescence. Specifically, the temporal encoding of sensory and choice information remains immature. Taken together our results suggest that the functional attributes of auditory processing constrain both cognitive maturation and behavioral execution.

Advisor: Prof. Adi Mizrahi

Retinoic acid, an essential component of the RP organizer, promotes the spatio-temporal segregation of dorsal neural fates

Dina Rekler

Dorsal neural tube-derived retinoic acid promotes the end of neural crest production and transition into a definitive roof plate. Here we analyze how this impacts the segregation of central and peripheral lineages, a process essential for tissue patterning and function. Localized in-ovo inhibition of retinoic acid activity followed by single cell transcriptomics unraveled a comprehensive list of differentially expressed genes relevant to these processes. Importantly, progenitors co-expressed neural crest, roof plate and di1 interneuron markers indicating a failure in proper lineage segregation. Furthermore, we found that separation between roof plate and dI1 interneurons is mediated by Notch activity downstream of retinoic acid, highlighting their critical role in establishing the roof plate-dI1 boundary.

Within the peripheral branch, where absence of retinoic acid resulted in neural crest production and emigration extending into the roof plate stage, sensory progenitors failed to separate from melanocytes leading to formation of a common glia-melanocyte cell with aberrant migratory patterns. Together, we uncover and characterize a molecular mechanism responsible for segregation of dorsal neural fates during development.

Advisor: Prof. Chaya Kalcheim

Session II

Early music exposure shapes the behavioral and neural responses in adult mice

Kamini Sehrawat

During the critical development period, sensory experiences modify behavior through their effects on the structural and functional organization of the brain. We investigated the impact of early music exposure in mice. We exposed young C57BL/6 mice (both males and females) during the critical periods (P7-P40) to a sound environment that consisted of spaced presentations of excerpts from Beethoven's Symphony No. 9 with free access to food and water. We tested the sound preference behavior of the exposed mice in adulthood (>P60). We had two control groups: silence-exposed mice, that were exposed to a similar amount of silence-only environment, and naïve animals, who remained in the animal facility throughout the same. The mice could select between a silent zone or a music zone without any reinforcement. The music-exposed mice showed a significant preference for music over silence relative to control and naïve mice in a sex-dependent manner. We performed wide-field calcium imaging in the auditory cortex of these mice. The overall activity of the auditory cortex was suppressed in exposed compared to naïve mice. Remarkably, in male mice, evoked response size didn't correlate with sound preferences, but in female mice, a robust negative correlation was found between response size in auditory cortex and the time they spent in the music zone.

Advisor: Prof. Israel Nelken

Human-Machine Teaming in Strategic Games

David Shoresh

Machine learning systems have made substantial achievements, including superhuman performance in board and computer games. There are efforts to introduce such models in practical applications, such as finance, medicine and transportation, whether as autonomous systems or for decision-support. However, these systems also have well known weaknesses, such as biases, difficulties in generalizing to out-of-distribution events, getting stuck in local optima and more. Therefore, mission-critical applications will require leaving a human in the loop. Yet it is also the case that humans have their own strengths and weaknesses in decision-making. One interesting empirical result has shown that human-machine teams are capable of outperforming either human or machine alone. In 'freestyle' chess tournaments, participants can either play as a human, deploy a computer or play as a human-machine team – known as a 'centaur'. The centaur teams consistently topped the rankings in these competitions. However, not much is known about how the centaur teams operated or how they leveraged the relative advantages of the human and the machine in the team. This research draws inspiration from the freestyle chess competitions and tries to model the centaur teams. It makes use of two types of chess programs. One is based on a network trained to play chess from pure reinforcement learning, with zero human data or prior knowledge. The other is designed to be human-like, based on a network trained via supervised learning from human games only. The purpose is to demonstrate the existence and identifiability of relative advantages between pure machine learning and human-acquired knowledge, for sequential decision environments. It is demonstrated that such relative advantages can be leveraged for synergetic team play. It is hoped that insights from this exercise can contribute to the budding research field of human-machine teams.

Advisor: Prof. Yonatan Loewenstein

Vocal labeling of conspecifics by non-human primates

Authors: Guy Oren, Aner Shapira, Reuven Lifshitz, Ehud Vinepinsky, Roni Cohen, Tomer Fried, Guy P. Hadad, David Omer

Humans and dolphins are the only known species which vocally label their conspecifics. It remains unclear whether non-human primates share this language-based ability. We recorded spontaneous 'phee-call' dialogues between pairs of marmoset monkeys. We discovered that marmosets utilize these calls to vocally label their conspecifics. Moreover, they respond more consistently and correctly to calls that are specifically directed at them. Analysis of calls from multiple monkeys revealed that family members use similar calls and acoustic features to label others and perform vocal learning. These findings shed light on the complexities of social vocalizations among non-human primates and suggests that marmoset vocalizations may provide a model for understanding aspects of human language, thereby offering new insights into the evolution of social communication. Based on these findings, we hypothesize the existence of neural represetations of conspecifics in the primate hippocampus, awaiting the deciphering of their neural code.

Advisor: Dr. David Omer

bioIB: Identifying informative metagenes in single-cell RNA-seq with the Information Bottleneck algorithm

Serafima Dubnov

Rapid advancements in single-cell RNA-sequencing (scRNA-seq) technologies revealed the richness of myriad attributes encompassing cell identity, such as diversity of cell types, organ-of-origin, or developmental stage. However, due to the large scale of the data, obtaining an interpretable compressed representation of cellular states remains a computational challenge. For this task we introduce bioIB, a method based on the Information Bottleneck algorithm, designed to extract an optimal compressed representation of scRNA-seq data with respect to a desired biological signal. BioIB generates a hierarchy of weighted gene clusters, termed metagenes, that maximize the information regarding the signal of interest. Applying bioIB to a scRNA-seq atlas of differentiating macrophages and setting either the organ-of-origin or the developmental stage as the signal of interest provided two distinct signal-specific sets of metagenes that captured the attributes of the respective signal. BioIB's representation can also be used to expose specific cellular subpopulations, for example, when applied to a single-cell dataset of Alzheimer's Disease mouse model, it identified a subpopulation of disease-associated astrocytes. Lastly, the metagenes' hierarchy reveals interconnections between the corresponding biological processes and cellular populations. We demonstrate this over hematopoiesis data, where the metagene hierarchy reflects the developmental hierarchy of blood cell types.

Advisors: Mor Nitzan and Hermona Soreq

Session III

It's about time: Robust temporal scaling of precise behavior and neural information processing using temperature

Shai Tishby

Biological and neural processes are heavily dependent on temperature for proper function. Survival for zebrafish necessitates independent hunting in the varying water temperatures of their natural habitat (ranging from 18°C to 33°C) which directly impact their body temperature. It remains unclear whether hunting behavior and its underlying visual processing are affected by temperature changes, whether zebrafish employ behavioral or neutral compensations for these non-optimal conditions, and how.

We recorded larval zebrafish hunting behavior in three ecologically relevant temperature conditions (cold, intermediate, and hot; 22°, 27°, and 32°C respectively) using a high-speed camera. Subsequently, we recorded neural activity and tail movements in response to prey-like stimuli using two-photon calcium imaging under the three temperature conditions in each fish. While hunting performance remained robust across the different thermal conditions, the temporal aspects of the hunt substantially changed. Specifically, hunting events were shorter in the hot condition and longer in the cold condition. Moreover, the duration of movements, as well as the duration of parsing of the visual field shortened and lengthened as a function of temperature. We identified neural correlates for this temporal scaling and further showed neural correspondence with the robust hunting performance across temperatures in the form of robust decoding performance of the visual stimuli. Our results suggest that this ecological range of 10°C modulates temporal aspects of information processing and behavior generation in larval zebrafish, without affecting performance or accuracy.

Advisor: Dr. Lilach Avitan

Value modulation of self-defeating impulsivithy

Zhe Liu, Robert Reiner, Yonatan Loewenstein, Eran Lottem

Impulse control is a critical aspect of cognitive functioning. Intuitively, whether an action is executed prematurely depends on its associated reward, yet the link between value and impulsivity remains poorly understood. Three frameworks for impulsivity offer contrasting views: impulsive behavior may be valuable because it is associated with hidden internal reward (e.g., reduction of mental effort). Alternatively, it can emerge from exploration, which is disadvantageous in the short term, but can yield long-term benefits. Finally, impulsivity may reflect Pavlovian bias, an inherent tendency that occurs even when its outcome is negative. To test these hypotheses, we trained mice to withhold licking while anticipating variable rewards. We found that higher reward magnitudes correlated with increased impulsivity. This behavior was well explained by a Pavlovian-bias model, a conclusion further bolstered by measurements and manipulations of dopamine release in the ventral striatum. Our observations of negative dopamine signals during premature licking and before feedback suggest that in this task, impulsivity is not merely an unsuccessful attempt at obtaining a reward. Rather, it is a failure to overcome the urge to act prematurely despite knowledge of the negative consequences of such impulsive action. Our findings thus underscore the integral role value plays in regulating impulsivity, and suggest that the dopaminergic system influences impulsivity through the mediation of value learning.

Advisor: Dr. Eran Lottem

Noise resilience of memory stored in low-dimensional manifolds through multiple synaptic timescales

Georg Chechelnizki

The reliable storage of information in short term memory is a crucial function of the brain. This function is challenged by the inherently noisy nature of neurons. Representations of continuous variables are particularly sensitive to noise, due to random drift that accumulates over time and can severely degrade memory accuracy. Here we identify a neural mechanism which effectively counteracts such deterioration by employing slow excitatory and fast inhibitory synapses. The mechanism is inspired by the derivative feedback mechanism (Lim and Goldman, 2013), which was previously shown to improve stability to certain forms of parameter mistuning in noise-free networks. We start by examining the simple case of a linear continuous attractor network (CAN), where we show that diffusivity can be made arbitrarily small if the timescale of excitation is larger than that of inhibition. We then show that similar principles generalize to a far more general class of nonlinear CANs. We successfully apply these principles to ring attractor networks, inspired by the insect head direction system. We find that our theory correctly predicts the improvement of memory stability as a function of synaptic timescale differences in such models, when endowed with the derivative feedback mechanism. This offers a plausible explanation for how the brain can stably store memories of continuous parameters, despite the ubiquity of noise. Furthermore, we identify how to engineer connectivity such that modes of activity other than motion along the attractor are not slowed down by the stabilization mechanism, allowing them to relax rapidly and tightly confining neural activity patterns to a one dimensional manifold. Insights from our theory allow us to conclude that neurons in head direction cell networks that are commonly thought to be utilized for velocity integration can also aid in stabilization against noise-driven motion.

Advisor: Prof. Yoram Burak

Session IV

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

Qixin Yang

Neural circuits in the hippocampus are essential for cognition, but the dynamics of excitation and inhibition (E/I) in these circuits are 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 probe E-I dynamics in identified cell types within the CA1 area during quiet and forced locomotion. We observed increased spontaneous firing rates in vasoactive intestinal polypeptide (VIP) interneurons (INs) and pyramidal neurons during rest, while somatostatin (SST) and parvalbumin (PV) INs were more active during locomotion. Optogenetic stimulation with varied light intensities revealed state-dependent neuronal excitability. We noted decreased excitability in SST, PV, and pyramidal neurons during locomotion, while pyramidal neurons exhibited a divisive reduction in firing rates compared to the additive increase in VIP INs, suggesting cell-type specific E-I modulation across behaviors. Theta oscillations, crucial for cognitive processing, were strongly detected in SST, PV, and VIP INs during locomotion but not in pyramidal neurons and were weaker in all cell types during quietude. We applied tonic optogenetic depolarization to discern whether these theta oscillations were driven by inhibitory or excitatory inputs and found that inhibitory inputs predominantly drove hippocampal theta activity in VIP and pyramidal neurons during locomotion. Overall, our study offers novel insights into the state-dependent regulation of hippocampal neuronal activity, E-I balance, and modulation of theta oscillations.

Advisor: Prof. Yoav Adam

Interrogation of inflammatory signaling in human brain cells using a 3D ex-vivo adult human brain model

Miriam Adam, Inbar Shapira, Daniel Kitzberg, Ido Palldor, Tal Shahar, Naomi Habib

One of the major challenges of studying the human brain in health and disease, is the lack of models of the adult human brain. Recently, a new human organotypic slice culture model was established, as an ex-vivo 3D model which is derived from brain tissue resected during surgery. The tissue is thinly sliced to allow proper oxygenation and nutrient diffusion and cultured under air-liquid interphase conditions, preserving neuronal survival and electrophysiological functions. However, a detailed investigation of this model and its ability to capture the cellular responses to stimuli is yet unknown, specifically in studying the functionality of glial cells. The long-term culturing of brain slices in this in-vitro model paves the way to pharmacological and genetic perturbations for the interrogation of cellular responses and interactions of human brain cells.

Here, we established the organotypic brain culture system and applied high-resolution profiling of cells by both bulk RNA sequencing and single nucleus RNA-sequencing (snRNA-seq). We have demonstrated that the cultured brain slices maintain the cellular diversity of the brain, including neuronal and glial cells, and that the broad cellular morphology and the overall tissue structure is intact. Moreover, cells can be infected by viruses and express various transgenes. Next, we showed that the brain cells in the cultured slices respond to external stimuli. Specifically, we investigated the response to TNFα, a pro-inflammatory cytokine, suggested as an early triggering event in aging and Alzheimer's Disease. We performed bulk RNA sequencing of the slices and detected a canonical inflammatory response, as well as stimuli specific reactions typical to certain cell types. Next, by applying snRNA-seq, we further dissected the cell-specific responses to the perturbation. We identified an induction of an expression program, including typical pro-inflammatory cytokines, that was shared across glial cell types, as well as cell type-specific expression programs. For example, we found upregulation of mitophagy related genes to be specific to astrocytes in response to TNF. By in-silico analysis of cellular interaction networks, we predicted an increase in unique cellular crosstalk following inflammatory stimuli compared to control. For instance, oligodendrocyte

precursor cell (OPC) expression of LIF, an anti-inflammatory cytokine, that is predicted to signal to astrocytes and might have a role in alleviating the inflammatory response. Moreover, we compared the TNF response to the response to a common bacterial toxin LPS, showing the inflammatory response of microglia cells is largely shared across both stimuli, yet astrocytes and OPCs display an additional TNF-specific response, that might point to the differences in clinical-associations between the two inflammatory signaling. Overall, we showed that human brain organotypic slice cultures provide an exciting model to functionally interrogate molecular mechanisms in brain cells on a multicellular level, advancing us toward a model to study the aging human brain and related diseases.

Advisor: Dr. Naomi Habib

Social face understanding after prolonged early-onset blindness

Ilana Naveh

Efficient extraction of face-information is key to social interaction. This core human skill develops throughout early childhood, but is prone to disruption during this period. Indeed, face recognition is hampered for life even after short post-natal visual deprivation (months). Whether recovery of social information from faces (e.g. gender, age, and emotion) has a similar developmental bottleneck, is currently unknown. To that end, we studied individuals with congenital bilateral cataracts, who were diagnosed and surgically treated only in late childhood. On average, the newly-sighted were poorer than typically-developing peers in all the above tasks. Interestingly, a substantial part of the variance in the patients' performance across all face tasks (35% to 53%) could be explained by their post-operative visual acuity. Thus, high resolution may be essential for learning these functions. Remarkably, patients with better visual acuity (> 8 cpd) could also perform the face tasks under severe image blur, similar to typically-developing age-matched peers. Such blur-resilience, apparent just months after surgery, typically develops slowly throughout childhood, well after attaining maximal resolution (30 cpd). Therefore, presumably, other age-dependent factors are necessary but not sufficient for blur-resilience buildup. Computational simulations using deep neural networks demonstrate that facial-information extraction (e.g. emotion) is possible following general visual training, but all models failed to show generalization when re-tested using blurred images. Apparently, the human visual system utilizes a mechanism for blur resilience, yet to be modeled by artificial networks. This study provides an elaborate account of the developmental trajectory of social information extraction from faces, in typical and atypical conditions, emphasizing the remarkable resilience of facial processing mechanisms.

Advisor: Prof. Ehud Zohary & Dr. Daniel Harari (Weizmann)

Straight Forward Through Visual Feedback: How do Mammals do it?

Gal Atlan

University of California San Francisco

Motor functions in sighted animals rely on visual feedback. During locomotion, full-field shifts of the visual environment trigger corrective movements to maintain straight forward heading. This reflexive behavior is crucial for the ability to locomote, and as such it is conserved throughout evolution, from invertebrates to humans. However, this behavior has been difficult to study in mammals, and its underlying neural circuitry is poorly understood. We developed an assay to reliably evoke corrective turns in freely-locomoting mice via closed-loop manipulation of visual feedback, enabling the study of the mammalian neural circuitry for maintaining heading. We find that corrective turns are triggered by the eye experiencing a temporo-nasal shift of the visual environment. Furthermore, we find that mice rely on visual cortex during this behavior. This ongoing work sets the stage for addressing a wide range of fundamental questions regarding the anatomical circuitry and the physiological mechanism underlying an essential sensorimotor transformation for maintaining heading in mammals.

Posters

1A: Noceptive terminlas are spontaneously active

Efrat Sheinbach, Rachely Butterman, Alexander Binshtok and Yoav Adam

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 electrophysiology. In this study, we used genetically encoded voltage indicators (GEVIs) to directly monitor voltage dynamics in nociceptor terminals, enabling the characterization of their electrophysiological properties.

We expressed the GEVI Archon1 in pain-sensitive neurons innervating the cornea and used a custom patterned illumination microscope coupled with a high-speed camera to record electrical activity from single nociceptive terminals in anesthetized mice *in-vivo*. While recording the activity of nociceptive terminals we observed that the terminlas generate action potentials even without the application of noxious stimuli. This ongoing activity was observed in both cold-sensitive and hot-sensitive nociceptive terminals. Strikingly, we found that different terminals that are connected to the same axon often showed unsynchronized firing, and only activity from one terminal propgated to the downstream axon. This result suggests non-linear signal integration in the nociceptive terminals which involves complex filtering mechanisms.

We are establishing behavioral models of acute inflammatory pain to study the changes in the ongoing activity underlying spontaneous inflamamtory pain.

Moreover, to better understand how the excitability of the terminals changes in pathological conditions, we co-expressed the blue-shifted channelrhodopsin CheRiff together with the GEVI Archon1, to allow simultaneous voltage imaging and optogenetic activation (Optopatch) of the corneal nociceptors. The response profile to optogenetic stimulation resembled that of capsaicin or menthol application, characterized by burst spiking followed by a return to spontaneous firing rates. We will next examine how these patterns change in inflammatory condiitons.

Revealing the primary processes of pain encoding during health and disease will provide a novel understanding of the PNS spike initiation processes, and how it differs from the well-studied processes in CNS neurons.

Advisors: Prof. Alex Binshtok and Dr. Yoav Adam

2A: Voltage imaging of excitatory and inhibitory Hippocampal neurons during global remapping

Rotem Kipper, Yaniv Melamed, Gal Shturm, Qixin Yang, 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 challenge, we expressed the genetically encoded voltage indicator Archon1in CA1 pyramidal cells (PCs) and dendrite-inhibiting Somatostatin (SST)-positive interneurons (INs) and recorded the membrane potential from ensembles of cells during navigation in familiar and novel virtual spaces. As expected, a large fraction of PCs exhibited spatial tuning in their firing, 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 with broader place fields and 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 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.

Advisor: Dr. Yoav Adam

3A: 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 heterogeneous 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 designed a novel cre-mediated inverting construct that expresses the red calcium indicator jRGECO1a and a upon recombination switch to express the bright and stable GFP mGreenLantern. We injected this vector into CA1 together with the blue light-activated Cre recombinase (iCreV) and extensively optimized the conditions to achieve high levels of jRGECO while minimizing non-specific mGreenLantern 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 mGreenLantern expression in ~90% of the targeted cells. In a parallel effort, we trained these mice in a virtual reality (VR) spatial navigation task. We then transitioned the mice into a novel virtual space to induce global remapping of the hippocampal network and performed 2P calcium- imaging while switching back and forth between blocks of the two environments. This task will allow us to identify distinct types of place cells such as reward cells, early-generated, and late-generated place cells. We hypothesize that these unique functional types project their axons into distinct brain regions. To test this, we will next photo-tag functionally identified cells followed by tissue clearing and whole-brain light-sheet imaging. Here we pressentpreliminary results demonstrating the feasibility of axonal reconstruction of mLanternGreen expressing neurons from cleared brains.

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.

Advisor: Dr. Yoav Adam

4A: 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.

Advisors: Prof. Merav Ahissar and Prof. Yifat Prut

5A: Formation of two-dimensional location-value maps in Orbitofrontal Cortex

Abhishek Jangid

Choosing an appropriate goal location among various available options is critical for survival and likely requires arbitration of a location and its associated value. Moreover, the value associated with a location may change with time thereby requiring appropriate updating. However, how the brain flexibly integrates spatial information along with the value of a given location remains poorly understood. Separate lines of investigation have shown that the orbitofrontal cortex (OFC) plays a key role in representing goal locations during navigation and encoding the economic value of options during decision-making. However, whether OFC neurons simultaneously encode both the spatial location and the value of a reward site remains unknown. In this study, we employed a goal-based navigation task comprising multiple reward sites. In each trial, rats needed to navigate to a specific reward location. Importantly, the reward amount available at a given location varied throughout the session, necessitating flexible value updates. As animals performed this task, we recorded neural activity from the OFC and observed that neurons in this region represented both location and value information. In addition, a fraction of the OFC neurons exhibited conjunctive location and value encoding, indicating flexible integration of both place and reward signals. Our results suggest that the OFC may be a critical brain region involved in the formation of a conjunctive map of reward locations and their associated value, thereby being ideally poised to facilitate flexible decision-making in realistic scenarios where different locations offer different amounts of reward.

Advisor: Raunak Basu

6A: Subpopulations in the medial entorhinal cortex are sharply tuned to more than one grid module

Yishai Gronich

Since their discovery nearly two decades ago, grid cells have received considerable attention due to the remarkable symmetries in their spatial firing pattern, as well as their organization into subgroups (called grid modules), each characterized by a distinct spatial scale. Population analysis of individual grid modules has shown that each module internally represents a latent two-dimensional variable, manifested in the position of the joint activity on a manifold with toroidal topology. The toroidal structure is stable across behavioral states, suggesting that it arises from intrinsic network mechanisms within each module. Furthermore, the existence of separate toroidal manifolds suggests that modules constitute distinct sub-networks that are largely independent of each other. It is unknown, however, whether there are mechanisms that link the activity in different modules. In this study, we used simultaneous recordings from thousands of entorhinal cells to investigate the tuning of individual cells to the internally represented latent variables. We developed a method based on Hidden Markov Models to identify the toroidal tuning of each cell, and to subsequently decode the dynamics of the latent variables based on the neural recordings. Surprisingly, we next identified a previously unknown sub-population of neurons that are sharply tuned to two modules, a phenomenon we refer to as 'co-tuning'. This co-tuning property of the cells is manifested in their spatial firing patterns, which could otherwise be misinterpreted as distorted grid patterns. Intriguingly, co-tuned cells are predominantly observed in modules with consecutive grid spacings, and are anatomically distributed near the boundary between the two modules. We speculate that the co-tuned cells may be involved in an interaction between grid modules. The discovery of these cells highlights the importance of studying latent variables defined by mathematical invariants of network activity.

Advisor: Prof. Yoram Burak

7A: A Modeling Approach to Uncover Cellular Drivers of Alzheimer's Disease Progression

Yifat Haddad, Yuval Rom

Alzheimer's Disease (AD) is a progressive neurodegenerative disease and the most prevalent cause of dementia worldwide. While research has established that coordinated changes in cellular communication of sub-populations of different brain cell types play a key role in AD progression, much remains to be learned about the cascade of cellular and molecular events underlying the disease and its dynamics. Prior research in our lab profiled by snRNA sequencing of 1.7 million cells from 437 aging brains, which was used to develop a cellular atlas characterizing the cellular landscape within various stages of the disease, and two distinct aging trajectories were found, defined as the alternative brain aging (ABA) and progressive Alzheimer's disease (prAD). These trajectories highlighted notable shifts in cell population dynamics linked to AD compared to aging, yet the impact and contribution of such cellular changes as drivers of the various stages of the disease remain unclear.

Prompted by these discoveries, we sought to identify the cellular drivers of AD's progression. Hence, we trained a simple artificial neural network (ANN) over the shared individuals' brains to predict the aging trajectory of 1,067 aging individuals profiled by bulk-RNA sequencing. This approach lets us exploit a larger dataset with a higher statistical power. Exploring the learning dynamics by applying ML model explainability tools illuminated the critical cell states that we predict the directionality of the aging process.

By examining a broader dataset, we are now able to rigorously investigate various genetic risk factors present within the data, viewed as natural perturbations experiments, to discern downstream correlations and causal events altering the cellular landscape throughout the progression of the disease. We explored a set of known genetic risk factors, comparing the effect of the genetic carriers on the disease hallmark, and linking them to the abundance of specific cell sub-populations and their dynamics along the progression of the disease.

In summary, by performing these two independent methodologies, we suggested specific cellular states and genetic risk factors that potentially play a causal role in the

progression of Alzheimer's disease and distinguishing disease from the natural aging process.

Advisor: Dr. Barak Raveh, Dr. Naomi Habib

8A: 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 for which there is no effective treatment. Several complex metabolic risk factors exist for AD, such as obesity, yet the molecular mechanism linking metabolic factors to AD is unknown. Moreover, sex-dependent differences in metabolism and in AD risk might be masking these effects, thus challenging the interrogation of the mechanism underlying the obesity-AD association. Recently we have shown that an AD-obesity comorbidity mouse model driven by a high-fat diet (HFD) accelerates memory impairment, through immune dysfunction driven by systemic levels of NANA sialic acid. We hypothesized that metabolic reprogramming of cells in the adipose tissue by HFD is directly involved in AD progression and could underlie the link between obesity and the increased risk for AD in a sex-dependent manner. We built a cellular atlas of the adipose tissue across conditions in the same AD-obesity comorbidity mouse model, by a single nucleus RNA-sequencing (snRNA-seq) of 243,598 cells from 38 mice including: males and females 5xFAD AD model and WT, fed with HFD or control diet (CD). We analyzed the diversity of expression programs within each cell type, including adipocytes, progenitors, immune, mesothelial, and endothelial cells, by applying an NMF topic-modeling approach. We identified expression programs linked to each of the different conditions: genotype-dependent programs (AD vs WT), diet-dependent (HFD vs. control), sex-dependent, or a combination of effects, mainly sex-specific diet or genotype programs. For example, we found a strong sex-specific diet-dependent reprogramming of mesothelial cells and an AD-dependent reprogramming in adipocyte stem progenitor cells (ASPC) as well as an HFD-AD co-morbidity dependent reprogramming in adipocyte cells specific to females. We also identified strong sex-specific differences across multiple cells such as the mesothelial cells. Integrative clustering uncovered a coordinated sex-dependent reprogramming across cell types in the adipose tissue that can be linked to AD and AD-HFD co-morbidity which might underlie the link between obesity and accelerated AD. Further, adipose-brain ligand-receptor analysis suggests potential secreted factors that might mediate between the

observed peripheral changes to the brain pathology. Overall, our results suggest that metabolic sex-specific reprogramming of cells in adipose tissue might be an early event affecting the progression and acceleration of AD in a sex-dependent manner.

Advisor: Dr. Naomi Habib

9A: Disease-associated committed OPCs emerge as secretory cells shaping the fate of astrocytes in early stages of Alzheimer's disease

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

Alzheimer's disease (AD) is a debilitating neurodegenerative disorder 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 brain cellular environment underlying AD. Therefore, unravelling the early cellular and molecular drivers leading to those changes might discover new treatments and prevent disease onset and progression.

As one of the first pathological hallmarks of AD is amyloid-β (Aβ), we have profiled the AD amyloidosis mouse model 5xFAD by single-nucleus RNA-seq and confirmed previously published coordinated transitions across all glial cell types to disease-associated states, including microglia, astrocytes (DAAs), oligodendrocyte precursor cells (OPCs), and oligodendrocytes. Within the oligodendrocyte lineage, we identified a new population of disease-associated committed OPCs (DA-COPs). By pseudotime and pathway analysis, DA-COPs appear to be arrested at a cellular state between healthy COPs and myelinating oligodendrocytes. Analysis of signalling networks between glial cell types highlighted DA-COPs as a signalling hub that is signalling to DAAs. Specifically, we found an enhanced expression of the growth factor BMP4, a regulator of developmental processes, including neurogenesis, and previously proposed to have a role in AD. Moreover, using spatial transcriptomics, we identified a spatial co-occurrence of COPs and DAAs in AD mice. We examined the effects of an increased secretion of BMP4 by exposing primary mouse astrocytes *in vitro* to BMP4 along a time-course. Those astrocytes showed a transient change in their cellular morphology and upregulated genes enriched for inflammatory and stress response pathways, lasting at least 72 hours post-stimuli. Moreover, astrocytes upregulated the expression of DAA signature genes within 24h, showing that a transition into a diseased state can be controlled by BMP4 signalling. Coordinately, in an aging human brains atlas of 1.7 million RNA profiles of single nuclei from 465 participants, we confirmed the presence of DA-COPs, and identified the expression of the BMP4-induced downstream signalling pathway in DAA-like, Aβ

pathology-associated astrocytes. Our work suggests that DA-COPs function as early signalling hubs which accelerate the transition of astrocytes into a diseased state along the AD progression via BMP4 signalling.

Advisor: Dr. Naomi Habib

10A: The brain-spleen axis affects microglia disease-associated state transition in an animal model of Alzheimer's Disease

Hodaya Polonsky

The relationship between the immune system and the CNS is essential in health and disease and was shown to take part in the progression of Alzheimer's disease (AD). One of the major pathways through which the CNS regulates the peripheral immune cell activity is the innervation of the spleen. The locus coeruleus (LC) brain area controls the splenic nerve that releases norepinephrine in the spleen which was shown to impact the activation, maturation, and migration of immune cells. Here, in the 5xFAD mouse amyloidosis model we unveiled an impaired LC-spleen connection using retrograde neuronal tracing. To better understand the impact of this connection on disease progression, we reproduced the impairment of the LC-spleen connection in the 5xFAD mice by denervation, before the spontaneous onset of symptoms. We found that splenic denervation caused earlier manifestations of cognitive loss, which was accompanied by reduced monocyte recruitment to the brain. To further explore the underlying mechanism, we profiled scRNA-seq immune cells in the spleen and in the brain comparing sham to denervated 5xFAD mice. In the spleen, we found downregulation of Ccr2 and Ly6c2, infiltrating monocytes markers, in monocytes of the denervated 5xFAD mice. In the brain, we uncovered a reduction in the disease-associated microglia (DAM) state in the denervated 5xFAD mice. Moreover, we found a strong shift in the signaling networks between microglia and other immune cells in the brain after the denervation. Specifically, the signaling pathways linking monocytes, and macrophages to DAM, and interactions including DAM genes, are no longer detected after the splenic denervation and might explain the observed lack of DAM. Overall, we suggest that the spleen-CNS axis affects the pathophysiology of AD.

Advisor: Dr. Naomi Habib

11A: Dynamics of Neuronal Reprogramming Along the Alzheimer's Disease Cascade Uncovered Early Neuronal Response

Roi Meir, Gali Schwartz, Anael Cain, Gilad Green, Naomi Habib

Alzheimer's disease (AD) is a progressive neurodegenerative disorder affecting millions worldwide. It is characterized by the accumulation of pathological proteins in the brain as well as neuronal and synaptic damage and death causing cognitive decline.

Previous work in our lab built a large atlas of single-nucleus RNA-seq profiles from 437 human prefrontal cortex samples revealed a trajectory leading to AD 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 which stage of the disease are the neurons first affected.

Here, instead of the commonly used discrete clustering analysis we used Topic Modeling to model the continuous diversity of expression programs in the aging prefrontal cortex using the snRNA-seq profiles of 1.7 million brain cells. Using Non-negative matrix factorization (NMF), theRNA profile of each cell is decomposed into multiple gene expression programs that together describe the activity of the cell.

In neuronal cells, our discovered gene expression programs captured both the known diversity of the different neuronal sub-types as well as other programs shared across neuronal sub-types, including disease-associated gene programs. Analyzing the dynamics of these disease-associated programs, we observed a coordinated change in the expression programs across neuronal subtypes along the AD trajectory. Along the AD cascade, we found down-regulation of expression of synaptic-associated genes and up-regulation of stress-associated genes as well as surprising up-regulation of cell-cycle genes. Interestingly, the neuronal expression changes occurred at an early disease stage, well before the cognitive decline, suggesting neuronal damage as an early driver event in the DA cascade.

Advisor: Dr. Naomi Habib

12A: SSA in awake non-behaving **rats**

Nimrod Agassi, Maciej Jankowski, and Israel Nelken

Stimulus-Specific Adaptation (SSA) refers to the decrease in response to frequently-presented stimuli that does not generalize, or only partially generalizes to rare (deviant) stimuli. SSA could occur either due to a depression in response to the frequent stimuli, or alternatively, due to the increase in response to the deviant stimuli by violation of expectations set by the frequent stimuli – which indicates true deviance detection. Here I analysed responses to sequences of pure tones recorded in the auditory cortex of awake rats using neuropixels electrodes. The sequences differed in their frequency composition and in the probability of each frequency. While SSA was clearly present, it was less prominent than in anesthetized animals.

Advisor: Prof. Israel Nelken

13A: Investigating learning-independent abstract reasoning with artificial neural networks

Tomer Barak

Imagine strolling through a museum, expecting awe-inspiring masterpieces. Suddenly, disrupting your expectations, you encounter, displayed in the vitrine,... a banana. Dissonance arises! There are two ways to resolve this dissonance: recalibrating your expectations from museum displays or finding a deeper appreciation for the artistic value of bananas. Our study investigates such cognitive dissonance scenarios that can be reconciled by two adaptation pathways. In these scenarios, *objects* violate their expected *relationships*. One solution is to readjust the expected relationships between the objects. The other is to reinterpret the objects, representing them differently to match the expected relationships. While the two adaptation pathways resolve the dissonance, they generalize differently to different tasks. Using artificial neural networks capable of relational learning, we demonstrate the existence of these two pathways and show that, in these networks, the chosen pathway depends on the magnitude of the dissonance. Large dissonance triggers representational changes, while small dissonance leads to relationship adjustments. This difference stems from how the input representations and relationships are coupled to the external reality.

Advisor: Prof. Yonatan Loewenstein

14A: Neural circuits for continuous control in an auditory navigation task

Shai Yellinek, Itai Wasserman, Robert Reiner, Eran Lottem

Adaptive decision-making behavior is essential for survival. However, most scientific studies on the neural underpinnings of decision-making rely on simple tasks where information flows in a one-way direction, from the environment to the subject. This approach significantly differs from natural behavior, where animals actively interact with and manipulate their surroundings rather than merely responding to them.

In this work, we present a novel paradigm and training protocol that engages mice in a continuous control task, allowing us to investigate the neural mechanisms behind this critical aspect of decision-making.

First, we demonstrate that mice can learn to solve this task and suggest a theoretical framework to model their behavior. To begin exploring the involved neural circuitry, we silence the Auditory Cortex during task execution to elucidate its role. Drawing on prior research, we sketch a conceptual cortico-striatal circuit model for continuous control in this context and plan future experiments to test it.

Advisor: Dr. Eran Lottem

15A: The orbitofrontal cortex contributes to latent state inference and context adaptation in mice

Haneen Rajabi, Gabrielle Marmur, John Schwarcz, Robert Reiner and Eran Lottem

Surviving uncertainty and inferring hidden features of the environment is a fundamental challenge for all organisms. To study the neural mechanisms that support the capacity for inference and uncertainty-related behavioral adjustments we developed a novel auditory change detection task in which head-fixed mice hear a random sequence of beeps in 2 hidden states, an 'Unsafe' and a 'safe' state. The transition between states is un-cued and licking is rewarded solely in the safe state in which only consecutive beeps are played. Importantly, since intermittent beeps are also played during the 'unsafe' state, mice should hear several consecutive beeps before reaching a decision. Uncertainty in this task is determined by the probability of the beeps during the 'unsafe' state – low probability corresponds to high certainty, as only a few beeps are sufficient to indicate that a reward is available. Behavioral data (n = 17) shows that mice indeed 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 used a combination of pharmacological manipulations and electrophysiological recordings from the orbitofrontal cortex (OFC), a brain regions thought to be important for latent state inference and flexible decision-making. We found that muscimol (GABA-A agonist) infusions to the OFC led to a marked deficit in the mice's ability to adapt to changing contexts (n = 9). Furthermore, a significant fraction of OFC neurons represented context. Taken together, these results demonstrate an important role for OFC in cognitive inference and flexibility.

Advisor: Dr. Eran Lottem

16A: Interacting Belief-States Enable Reward-Independent Adaptation Of Timing Behavior

John Schwarcz

Animals must develop adaptive strategies to rapidly optimize decision-making in dynamic environments, often without the benefit of immediate rewards. Existing literature posits that animals use internal ”belief” states as the foundation for their decision policy. However, the neural mechanism implementing reward-independent belief updates is poorly understood. This is a critical gap, especially in scenarios where trial-and-error approaches are inefficient and potentially perilous. To address this problem, we take a multidisciplinary approach integrating theoretical derivation, training artificial neural networks, and behavioral experiments in rodents to explore potential neural mechanisms.

A belief state is a joint probability distribution over all relevant latent variables of the environment. Updating the joint distributions is computationally demanding and nontrivial, particularly when the agent averts acting. To tackle these challenges, we develop a change-detection task to capture the complexity of partially observed dynamic environments while being accessible to experimental and analytical treatment. We formulate a Bayesian theory for sequentially updating joint probabilities and demonstrate that neural networks can accomplish the task near optimally, even without immediate rewards. In particular, we show that the network dynamics mirror the joint update of the Bayesian latent state estimators. Furthermore, the behavior of rodents trained on this task aligns with our theoretical model and neural network simulations, suggesting that mice utilize dynamic internal state representation and inference to solve this task. Overall, our findings elucidate the computational principles behind zero-shot adaptation to environmental changes without the need for trial and error.

Advisors: Dr. Eran Lottem & Dr. Jonathan Kadmon

17A: Neural signatures of flexible time arithmetic in multiple timing

Shahar Haim

The human ability to track overlapping and asynchronous time intervals is crucial for a myriad of tasks, from engaging in conversation to driving a car. The brain may implement this capability by employing multiple timers, each tracking a different interval. Alternatively, a single timer can implement multiple timing by tracking one interval at any given moment, and then, upon its completion, realigning with the next relevant interval through the addition or subtraction of a stored value, a process known as time arithmetic. However, discerning which of these mechanisms is employed based on behavioral data alone is challenging. Here we assessed participants' ability to track two simultaneously occurring asynchronous beep trains and indicate which one ended first. We found that that slowly evolving EEG signals coded a single interval – the one associated with the currently intended action. In agreement with the single-timer hypothesis, these signals were action non-specific, and displayed dynamic resetting upon changes in intended actions. In addition, immediately after a change in intended action, transient EEG signals were correlated with the extent of resetting, providing a mechanistic basis for time arithmetic operations. Finally, when participants were instructed to ignore one of the beep trains, we observed a qualitative difference in these transient signals, reflecting the altered computational demands under this condition. The findings highlight the flexibility and adaptability of timing mechanisms enabled by a single-timer framework, and emphasize the importance of neurophysiological data in distinguishing among competing cognitive models.

Advisor: Prof. Ayelet Landau, Dr. Eran Lottem

18A: Uncovering the neural circuitry underlying latent state inference in mice

Gabrielle Marmur, Haneen Rajabi, John Schwarcz, Robert Reiner, Eran Lottem

Essential features of the environment are often hidden and must be inferred based on indirect evidence. Here, we developed an auditory change detection task in which mice must infer the hidden state of the environment based on ambiguous auditory cues. Behavioral data collected from 15 mice indicate that mice successfully integrate auditory information to infer the latent state of the environment.

To uncover the neural circuit underlying the behavior in this task we used muscimol (a GABA-A agonist) to reversibly inactivate different regions of the brain in behaving mice. Reversible inactivation of the Inferior Colliculus (n=6) but not of the Auditory Cortex (n=6) rendered mice insensitive to the auditory cues in the task. Muscimol injections to the Anterior Cingulate Cortex (ACC, n=14) revealed that inactivation of an anatomically specific sub-region of the ACC led to a significant reduction in licking. Inactivating the Orbitofrontal Cortex of behaving mice (n=9) impaired their ability to integrate the auditory cues successfully, forcing them to change their strategy.

Together, these findings help elucidate the brain wide neural circuitry involved in inferring hidden environmental features.

Advisor: Dr. Eran Lottem

19A: Neural correlates of auditory category learning of FM sweeps in the mouse auditory cortex

Or Cotev Yudco

Category learning is a fundamental brain process that enables quick and accurate response for novel stimuli in complex sensory scenes. In the auditory modality, category learning underlies many processes of sound perception, such as understanding of language in humans. While the learning process has been shown to be accompanied by changes in neuronal representation, its underlying mechanisms are not yet clear. Using an automated learning platform, we trained female mice (n = 22) to discriminate between two categories: rising frequency modulated (FM) sweeps and falling FM sweeps. At the end of training, we presented mice with novel stimuli in order to decipher the learned categorization rule and found that they the used frequency content of the sweep as the categorical boundary cue, rather than the slope of the sweep. Using the multiarray silicon probe, Neuropixels, we performed electrophysiological recordings from the auditory cortex of awake mice (n = 9 experts, n = 4 naïve) while listening passively to FM sweeps and pure tones. We acquired data from primary auditory cortex (AUDp, n = 389 neurons) and the auditory temporal association cortex (TeA, n = 91 neurons) and found that more neurons of expert mice prefer the frequency of the category boundary comparing to naïve mice. Furthermore, neurons of expert mice as well their population activity have higher discriminability between sets of both FM sweeps and pure tones. Our results show that plastic changes in neuronal discriminability of sounds stands in correspondence with mice behavioural strategy.

Advisor: Prof. Adi Mizrahi

20A: Late development of innate olfactory circuitry

Taha E, Shapira S, Nahari R, Givon M, and Mizrahi A

In mammals, odor information is transmitted from olfactory sensory neurons to mitral cells (MC) in the olfactory bulb. In turn, MCs transmit information to brain areas downstream, which are then read and executed as distinct behavioral output. It has been proposed that innate and learned odor information are processed by distinct pathways. One common framework is that innate olfactory information is routed by MCs to the cortical amygdala (CoA), while learned information is routed through the piriform cortex (PC). Here, our aim was to reveal the organization and ontogeny of these circuits, and whether it dictates innate or learned behavior. Towards that end, we performed behavioral, anatomical, and physiological experiments.

Behaviorally, we used an attraction-avoidance assay and found that juvenile mice (postnatal day 21; P21) showed immature or complete lack of innate behavior as compared to adult mice (P54). However, juvenile mice showed intact learning in a conditioned odor preference assay. These behavioral data had a clear anatomical and physiological correlates. Anatomically, using both retrograde and anterograde staining we labelled MCs by their projection pattern. We found that juvenile mice have significantly less projections to the CoA as compared to adults, but similar levels of projections to the PC. Furthermore, the two populations show little overlap. Physiologically, innate odor induced c-Fos expression in the CoA was not significant in juveniles. Yet, c-Fos expression in the PC was similarly robust in both juveniles and adults. Currently, we are using two-photon calcium imaging from MCs to assess how these distinct circuits encode innate odor information in juvenile versus adult mice. Our data shows that innate behaviors and its underlying odor circuitry matures late. Counterintuitively, learning related odor circuits precedes the late innate maturation.

Advisor: Prof. Adi Mizrahi

21A: 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 yet 3-5% of mammalian species exhibit paternal care. Males undergo a significant transition when they become fathers, including a behavioral shift from infanticide of pups towards paternal care. To study the mechanisms underlying this behavioral transition, we probed functional plasticity in the auditory cortex of male mice as they become fathers. Using longitudinal two-photon calcium imaging before, during and after fatherhood we measured single neuron responses to pup calls versus their responses to the corresponding narrow band noise (NBN). We found a significant improvement in neuronal discriminability between pup calls and NBN in fathers. Next, we studied the hormonal mechanism underlying these neuronal changes by conducting a set of molecular, transcriptomic and metabolomic analyses in the auditory cortex. We found that several receptors of hormones show different expression levels during fatherhood as compared to before 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 its activation during fatherhood, specifically in the auditory cortex. We are currently testing whether there is a causal link between prolactin and the physiological and/or behavioral phenotypes in fathers.

Advisor: Prof. Adi Mizrahi

22A: Organizational effects of pubertal hormones in the processing of social cues in females

Hadar Sagi

Adolescence is a crucial period of development characterized by physical, hormonal, and behavioral changes. Puberty marks the start of the adolescent period, which is accompanied by a surge of gonadal hormones. In females, puberty is characterized by an increase in estrogen levels - a steroid hormone which has been shown to modulate various neuronal processes. During adolescence individuals become sensitive to specific social cues in their environment like, e.g., the sensory detection of the other sex. We set out to test whether the pubertal rise in estrogen contributes to the development of how females detect male cues. Specifically, we tested whether the pubertal surge of estrogen has organizational effects.

First, we show that the prominent behavioral attraction of adult females to male urine is absent in juveniles. Second, we found this behavior is diminished in adults following a prepubertal ovariectomy but not following post-pubertal ovariectomy - suggesting a role for estrogen in the organization of social odor-preference behavior. We are currently using replacement therapy in an effort to causally tie this finding to estrogen. Next, we will use electrophysiology to reveal the organizational effects of estrogen-mediated plasticity in olfactory circuits.

Advisor: Prof. Adi Mizrahi

23A: Neural correlates of rapid learning in the Orbitofrontal cortex

Mousa Karayanni

Rapid learning, also referred to as few-shot learning, enables us to swiftly grasp new knowledge and skills with little guidance or reinforcement. The capability for learning from few examples garnered considerable attention, as evidenced by extensive efforts within the field of machine learning to emulate this ability for solving various computational challenges. Nevertheless, in widely used experimental paradigms in neuroscience, learning requires a large number of trials and reinforcements to reach adequate performance rates. I investigate the neural correlates of fast, few-shot learning. To do this, I implemented a behavioral arena with characteristics that have been recently found to promote fast learning. I developed a behavioral task that tests learning and exploration strategies in freely-moving rats. To study neural correlates of fast learning, I recorded electrophysiological activity from the Orbitofrontal cortex (OFC) using high-count silicon electrodes (Neuropixels). Rats demonstrated rapid learning using hierarchical problem-solving strategies, leveraging their knowledge of the task structure. Heterogeneous yet robust responses around task-related events were found in the OFC, constructing task-related representations in the OFC. Moreover, these representations were found to be modulated by the task state and the animals' learning progress.

Advisor: Prof. Eli Nelken & Prof. Yonatan Loewenstein

24A: Early music exposure affects neural activity in the ventral tegmental area (VTA)

Samira Souffi[1], Israel Nelken[1]

Dopaminergic neurons of the ventral tegmental area (VTA) have been widely studied for their roles in reward prediction error encoding, behavioral reinforcement, motivational salience and learning processes. While dopamine release has been implicated in determining sound preferences, this role is less well characterized. We exposed male and female mice in their homecage to human music (1st movement of Beethoven's 9th symphony) or silence from P7 to P40, covering both early and late auditory critical periods. At early adulthood, we performed a free-choice behavioral test in which mice could choose to dwell in a music zone or in a silence zone of the test box. Following the test, we performed fiber photometry in the VTA of these mice, while they moved freely and heard simple (broadband noise and pure tones) and complex (exposed and unexposed music excerpts) sounds. On average, we found that exposed mice (music- or silence-exposed) spent a longer time in the music zone than in the silence zone compared to naive mice, with noticeable differences between males and females. All sounds were associated with both excitatory and inhibitory transients. The music-exposed mice showed a large decrease in VTA activity to all sounds compared to naive mice; silence-exposed mice showed a decrease in activity (males) or no significant change (females). Finally, in naive males, we revealed a positive relationship between VTA activity and the time spent in the music area. Further experiments are currently conducted on naive TH-cre mice using GCaMP virus allowing chronic recordings of the dopaminergic neurons only.

Overall, these data indicate that early sound experience music or silence exposure had a strong effect both behaviorally on music preference behavior as well as on VTA activity. Whether and how the changes in activity in VTA affect music preferences in the exposed mice needs further work.

Advisor: Prof. Israel Nelken

25A: Auditory cortex maximizes task-relevant information in freely-moving, behaving rats

Ana Polterovich, Maciej M. Jankowski, Johannes Niediek, Alex Kazakov

In auditory-guided tasks, sound presentations occupy a small fraction of the time. What happens in the auditory cortex in between sound presentations? How does this activity shape sound responses? In this study, we examined the neuronal activity of the auditory cortex in awake, freely moving rats performing a combined localization-discrimination task in the Rat Interactive Foraging Facility (RIFF). We show distinct differences in neuronal responses between active behavior and passive listening conditions: responses to target stimuli during the active sessions were weaker but more informative compared to passive listening sessions. Furthermore, we identified slow firing rate transients in the activity of neurons in auditory cortex. These transients were locked to specific time points in the task, spanning its whole duration, similar to the responses of time-sensitive neurons in the hippocampal formation and other brain areas. These transients often were not driven by sounds, although they could be larger than the sound evoked responses. Using a model, we show that these transients explain the differences between the sensory responses in the active and passive listening conditions, by shifting the sound-driven responses in auditory cortex from population spikes (which are invariant to sound properties) that are typical to the passive condition and into weaker, but more sound-sensitive, responses.

Advisor: Prof. Israel Nelken

1B: Synchrony as a basis for social behavior in zebrafish

Imri Lifshitz

To survive and reproduce, animals significantly rely on social interactions with their conspecifics. Variability in social behavior is observed in the general adult as well as the developing populations. Nevertheless, little is known about the precise behavioral algorithm, the underlying neural mechanism that coverts sensory information into social actions, and the neural basis for inter-individual variability. To address these questions, we established a novel experimental setup to record whole-brain neural activity from a head-fixed and tail-free (focal) larval zebrafish observing a freely swimming conspecific, simultaneously with high-speed behavioral recording of both fish. We identified a fraction of focal fish which elicited movements after a typical delay from a conspecific movement (synchronized movements). Overall, these fish were more likely to approach the conspecific. Moreover, the intended angle of their synchronized movements was correlated with the position of the conspecific. Searching for the neural basis for this social cognition, we identified neurons correlated with the conspecific's angular position and directionality. In addition, we observed a ramping activity before each movement. These findings suggest that the movements of others drive a characteristic synchrony of social actions. These results lay the foundations to study the underlying neural mechanisms of social actions and inter-individual variability.

Advisor: Dr. Lilach Avitan

2B: Choosing their battles: Improvement in larval zebrafish hunting behavior over development

Maayan Moshkovitz

Goal directed behavior consists of a sequence of actions performed by the organism 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. To address this question we recorded freely swimming fish (5-15 dpf) while hunting using a high-speed camera. We found that even when the fish place their targets in a region they can strike upon and succeed in capturing the prey, some of the events were unsuccessfully completed. We show that the complexity of the visual field plays a major role in determining the fate of the event. We show that over development, the behavioral performance improves, with fish selecting sparser scenes to initiate their hunting events, and more efficiently handling complex visual scenes. These results form the basis for uncovering the neural mechanism mediating the improvement in hunting behavior and point to specific features of the visual system that develop to allow the animal to better interact with its environment.

Advisor: Dr. Lilach Avitan

3B: Imitation of Life: A Search Engine for Biologically Inspired Design

Hen Emuna

Biologically Inspired Design (BID), or Biomimcry, is a problem-solving methodology, applying analogies from nature to solve engineering challenges. For example, Speedo engineers designed swimsuits based on shark skin. Finding relevant biological solutions for real-world problems poses significant challenges, both due to the limited biological knowledge engineers and designers typically possess, and to limited BID resources. Existing BID datasets are hand-curated and small, and scaling them up require costly human annotations.

In this paper, we introduce BARcode (Biological Analogy Retriever), a search engine for automatically mining bio-inspirations from the web at scale. Using advances in natural language understanding and data programming, BARcode identifies potential inspirations for engineering challenges. Our experiments demonstrate that BARcode is able to retrieve inspirations which are valuable to engineers and designers tackling real-world problems, as well as recover famous historical BID examples. We release data and code; we view BARcode as a step towards addressing the challenges that have historically hindered the practical application of BID to engineering innovation.

Advisor: Prof. Dafna Shahaf

4B: Dimensionality bottleneck uncovers simple action selection rules in hunting larval zebrafish

Yoav Rubinstein

Animal movements are complex, high-dimensional, and lead to many different outcomes. Thus, efficiently quantifying the behavior and uncovering the underlying representation used by the animal pose a great challenge. Tracking freely behaving zebrafish larvae using a high-speed camera and analyzing their movements, we reveal that zebrafish movements can be described using exactly two parameters. Mapping all possible two-dimensional movement representations, we identified the representation used by the fish. We show that fish do not trivially represent distance and angles as separate parameters, but rather mix them nonlinearly. Moreover, when hunting, this specific nonlinear relation depends on the prey angle and further dictates a particular set of potential movements. These results uncover, for the first time, the underlying action selection principles of hunting behavior, suggesting that behind this complex behavior there is a simple and low-dimensional process.

Advisor: Dr. Lilach Avitan

5B: Exploring Neural Prediction Mechanisms: Investigating Specific and Nonspecific Prediction Modes

Noa Guttman

The brain's ability to use previous knowledge to anticipate expected inputs and enhance information processing has been extensively studied. However, much of the evidence is based on scenarios where there's a single expected input rather than a range of possibilities. It's still unclear how the brain predicts inputs when there are multiple possible options.

To investigate the distinctions between specific and nonspecific prediction, we designed experiments involving pairs of visual cues and auditory stimuli. In one condition, the cue didn't predict the sound, while in another, the cue predicted a single sound, and in a third condition, the cue predicted several possible sounds. By applying cluster permutation analysis to EEG data, we identified clusters (spanning time and electrodes) with significant differences between predictable and unpredictable conditions, as well as clusters with significant differences between conditions involving single and multiple predictions.

We will utilize these Regions of Interest (ROIs) to compare the response to each tone within the multiple prediction condition.

Advisor: Prof. Leon Deouell

6B: Neural Markers of Conscious and Non-conscious Speech Processing

Gal Chen

The processing of stimuli of which subjects are unaware is highly debated, with studies focusing mostly on visual perception. As auditory inputs are profoundly different from visual, and rely on different processing streams, processes, and brain areas, examining audition is likely to bring with it novel insights and inform theories of consciousness.

Using a new paradigm, we conducted two EEG experiments (total N=67; the second preregistered) in which participants performed a difficult visual task (1-back) while an ongoing stream of pseudowords was played. Single meaningful words, with lexical properties matched to the pseudowords, were embedded in this stream, and we tested awareness of word presence. In the second experiment we added a manipulation for the relevance of word detection: before the introducing the word detection task, participants performed only the visual task without informing or asking them about the presence of words.

Our analyses revealed a late (>600 ms) frontal positivity evoked for words vs pseudowords that were processed without awareness, reflecting lexicality processing. This response was significant for subjectively unaware trials in which participants were objectively incorrect regarding word category, weakening the possibility of unreported weak conscious processing. When word detection was irrelevant, the lexicality response disappeared.

This result show that words can be processed even though subjects are subjectively as well as objectively unaware of their presence. It also highlights that auditory unconscious processes are not mandatory, but goal dependent: if we need to hear something relevant, we may process it even when it evades consciousness.

Advisor: Prof. Leon Deouell, Prof. Ran Hassin

7B: Inferring and Utilizing Probabilistic Properties of Ambiguous Observations

Chaviva Markind

Perception of ambiguous observations is informed by what we expect to observe. Forming expectations, however, is complicated by the fact that our environment constantly changes – either due to stochasticity, random local fluctuations, or to volatility, long-lasting changes 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. Moreover, if the sensory inputs themselves are ambiguous, inferring the underlying volatility and stochasticity is more difficult because the change itself can be exaggerated or, alternatively, disregarded. It is currently not known whether people learn these probabilistic properties in the presence of sensory noise. We ran a sound-localization task and found that people can track the expected directions of the sounds, demonstrating their ability to differentiate between the volatility and the stochasticity of the ambiguous sensory inputs. Furthermore, people use these expectations to inform their percepts of new sensory inputs in a manner that accounts for all three sources of noise: volatility, stochasticity, and sensory ambiguity.

Advisor: Dr. Eran Eldar

8B: Astrocytes induce cognitive enhancement in Alzheimer mouse model

Yaara Aram

Long-lasting memories define who we are and how we experience the world. Inability to form and access these memories, as in neurodegenerative conditions such as Alzheimer's disease (AD), degrade the quality of life and impose a major burden on healthcare systems and society. Unfortunately, medical treatments that can prevent, slowdown, or reverse memory deficits are almost non-existent. To develop new strategies for targeting diseases associated with memory impairments, a better understanding of how the brain acquires and encodes memories is urgently needed, and novel mechanisms must be effectively harnessed for therapeutic value.

Interestingly, several studies reported abnormalities in both the number and function of astrocytes in human AD patients and in animal models of this disease. Recently, work from our lab and others has revealed unique abilities of astrocytes to communicate with, and affect, neurons in the brain. Specifically, we have found that in normal mice direct astrocytic activation using chemogenetic or optogenetic tools is sufficient to induce hippocampal long-term synaptic potentiation and activation of astrocytes during learning improves memory allocation, resulting in enhanced recall.

To test whether astrocytes can increase cognitive function not just in normal mice but also in impaired memory in Alzheimer's model mice, we expressed the Gq-coupled designer receptor hM3Dq which allowed their time-restricted manipulation by the application of the designer drug clozapine-N-oxide (CNO), in the CA1 of 5XFAD mice.

Chronic C

NO administration for 2 weeks in the drinking water caused an improvement in memory in the radial arm water maze task (RAWM) and a decrease in Aβ plaques, that was accompanied by a decrease in microglia number and an increase in neuronal activation. The 5XFAD mice not just showed enhanced memory, but reached the same level as the controls, that have improved themselves.

Chronic astrocytic activation for a year resulted in a long improvement in memory in 5xfad mice in the RAWM, to the same level of control mice receiving CNO, and a decrease in Aβ plaques.

In summary, astrocytic activation can rescue memory performance after it already deteriorated, and partially clear existing Aβ plaques.

Advisor: Prof. Inbal Goshen

9B: Optimal Coding of Event Structure in Episodic Memory

Isaac Ashkenazi

Implicit in the behavioral and neural accounts of episodic memory is the segmentation of continuous experience into discrete episodes, corresponding to encoded neural patterns. Event boundaries – moments in experience where a transition between remembered episodes occurs – are perceived with high intersubjective agreement and have profound effects on the encoding and recall of memories. While event boundaries have been linked to prediction error and to temporal and causal structures, there is to date no principled theory to mechanistically explain segmentation and its related effects. Based on the theory that memory systems are geared toward learning and prediction, I hypothesize that event segmentation is driven by optimal compression of experience, aimed at learning the relevant generalizable structure, i.e. the generative process. Event segmentation is thus formalized in terms of the Minimum Description Length (MDL) principle, which captures the trade-off between accuracy and parsimony of representation. Preliminary results indicate that this formalism can quantitatively determine the timing of boundaries with specificity and serve as a framework for studying related memory effects.

Advisor: Dr. Yuval Hart

10B: Reward and eye movement signals in the corticostriatal projection neurons

Adi Lixenberg

The drive for rewards controls almost every aspect of our behavior, from stereotypic reflexive behaviors to complex voluntary action. It is therefore not surprising that the symptoms of neurological disorders that interrupt reward processing, such as those stemming from drug-abuse and depression, include deficits in the capacity to make even simple movements. Accordingly, how do rewards drive and shape movements? One of the major subcortical networks to drive behavior is the basal ganglia. This area is essential for the control of movement as damage to the structure leads to severe motor disabilities. Research on the basal ganglia has highlighted their importance in the control of reward-driven behavior-but how the reward information interacts with sensorimotor signals to drive the motor periphery is unknown. My goal is to study the cortical pathways to the basal ganglia in order to understand how the computations underlying the influence of reward on action are implemented in the brain. I hypothesize that rewards drive and shape the motor commands in the basal ganglia in a way that information about reward is used to mediate selection between multiple actions. I used the monkey saccade eye movement systems as a powerful model motor system to study the neural mechanisms by which reward influences motor processing. I combined the use of novel behavioral paradigms together with novel application of neural recording and optogenetic stimulation in primates to probe activity of neurons in the cerebral cortex and basal ganglia.

Advisor: Prof. Mati Joshua

11B: Implementing arbitrary nonlinear low-dimensional dynamical systems in large neural networks

Zhenyi Wang

An increasing amount of findings highlight the significance of low-dimensional neural dynamics in the motor system, sensory pathways, and cognitive task representations. Recent studies have linked structure to low-dimensional activities by considering low-rank corrections to random synaptic efficacy matrices. However, these studies focused on Gaussian statistics, restricting the networks' dynamic repertoire. To understand how neural circuits implement diverse computations, we need a theory that deals with complex structures and accounts for arbitrary nonlinear low-dimensional dynamics.

In this work, we go beyond the current paradigm and consider low-rank matrices with higher-order statistics. For tractability, we use synaptic weights sampled from discrete statistics. We derive a dynamic mean-field theory for the low-dimensional activity generated by the low-rank weights. First, we show that i.i.d. weights with second-order statistics can produce only linear effective dynamics. Next, we show that appropriately choosing higher-order correlations can yield non-trivial collective dynamics. As an example, we generate a low-dimensional chaotic attractor. The low-dimensional chaos is different from chaos generated by large random networks and is characterized by higher correlations. Finally, we prove a universality theorem stating that a large low-rank nonlinear network can implement any smooth dynamical system. Importantly, we calculate the error bound for approximating arbitrary dynamical nonlinear dynamical systems and show it falls exponentially as the rank increases. Our work provides an essential missing link between structure and neural dynamics; it provides a prescription for constructing neural networks that implement non-linear dynamical systems using low-rank structures and a framework for analyzing trained networks.

Advisor: Prof. Jonathan Kadmon

12B: Spatio-temporal dynamics of Roof plate to Radial glial transformation during avian neural development

Susanna Ventriglia

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 cells (RG) which eventually generate dorsal ependyma, a stem cell niche of the central nervous system.

To investigate the spatio-temporal molecular repertoire and morphological changes that characterize the above transitions, a series of in-situ hybridizations were performed 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, Wnt1, Wnt3a and its regulator Rspo1 are present at both stages. In contrast, Ism1, Sox9, CXCR4, Fabp7 are absent in RG, discriminating 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. Along this line, we began exploring the role/s the Wnt pathway by implementing a loss of function approach, using time-dependent misexpression of a dominant negative Lef1 (dNLef1) construct subsequent to the neural crest stage. In dNLef1-treated embryos, the development of RP traits was impaired, subsequently leading to abnormal radial glia formation. Experiments in progress will clarify the role of Wnt signaling at selected time windows spanning the period between RP and RG.

Advisor: Prof. Chaya Kalcheim

13B: Ultrastructural analysis and functional implications of dendritic spines of an entire pyramidal neuron

Netanel Ofer

Pyramidal neurons are decorated with thousands of dendritic spines over their dendritic tree. These spines, which receive excitatory synapses over their head membrane, exhibit a wide range of shapes and sizes. However, how excitatory synaptic inputs are integrated over these spines and how distal synapses impact the neuron's output remains a fundamental open question in neuroscience.

Early observations have shown that long thin spines are more frequent at distal dendritic locations, whereas 'stubby' spines are more common near the cell body (Jones and Powell, 1969). W. Rall (1974) noted that this seems paradoxical because it implies extreme voltage attenuation to the soma from synapses located on distal dendrites, due to both, the large neck resistance of spines with thin neck and the filtering effect of the dendritic cable. This led Rall to suggest a novel design principle by demonstrating that, if the spine-neck resistance (Rneck) is matched with the input resistance at the spine base (Rbase), then albeit sacrificing maximum synaptic efficacy, one obtains an optimal gain control over the impact of the spinous excitatory synapse.

In this study, we reconstruct human and mouse pyramidal neurons in 3D from serial electron microscopy (EM) data in the nano-scale resolution. This enables us to objectively separate and measure, in unprecedented accuracy, the spine head membrane area and spine neck dimensions (Ofer et al., 2021) as a function of the position of the spine along the dendritic tree. This EM data enables us to systematically explore the morphological properties of dendritic spines over the whole dendritic surface of cortical pyramidal neurons and combine it with numerical simulations to provide new insights into the fundamental mechanisms underpinning synaptic integration in these neurons.

Advisor: Prof. Idan Segev

14B: Predictability of Dendritic Voltages from Local Input

Submitted by Shir Levy

This study delves into the predictability of dendritic voltages in neurons, emphasizing the differential contributions of local segment environments—specifically, parent and child segments—to prediction accuracy. Utilizing a detailed biophysical compartmental model of a Layer 5 pyramidal cell, we conducted simulations to predict dendritic voltage traces (DVTs) using various machine learning models, with a focus on Ridge and Bayesian Ridge Regression, and compared these to neural network predictions. Our findings reveal region-specific variations in predictive accuracy, with basal dendrites showing uniform predictability, while oblique and tuft dendrites display distinct preferences for parent and child segments, respectively. These insights into dendritic processing not only advance our understanding of neuronal computation but also hold implications for the design of artificial neural networks and neuromorphic computing.

Advisor: Dr. David Beniaguev and Prof. Idan Segev

15B: Cortical pyramidal neurons can solve complex classification tasks in high dimensions

Ido Aizenbud

Neurons are the computational building blocks of the brain. It was suggested that properties such as extended dendritic tree morphology, nonlinear membrane ion channels, and nonlinear synapses could expand the computational capabilities of neurons. Still, it remains unclear as to what is the space of computational functions that neurons can implement. Detailed biophysical models of neurons allow us to explore the input/output (I/O) function of single neurons. However, there is no systematic approach to exploring single neurons' computational and learning capabilities, as represented by detailed biophysical models, because we lack efficient learning algorithms that will exploit the computational implications of the fine-scale morpho-electrotonic properties of neurons. Here, we developed a novel learning algorithm (DendMapping) for biophysically realistic neuron models, utilizing synaptic weight adjustments (functional plasticity) and synaptic rewiring (structural plasticity). Because biophysical models are not directly differentiable, DendMapping uses deep neural networks (DNNs) as its efficient differentiable surrogates. Using DendMapping we challenged biophysical neuron models with n-dimensional generalizations of the exclusive OR (XOR) problem (the n-parity problems). These problems are famously unsolvable by a single-layer perceptron. We show that counter to previous suppositions, a single cortical pyramidal neuron can effectively solve n-parity problems and, therefore, may implement arbitrary complex classification in high dimensions. Our findings offer new methods for systematically exploring single-neuron computational capabilities across diverse tasks. It provides new insights into the computational implications of the morphological and biophysical properties of neurons, and into the contribution of structural versus functional synaptic plasticity to learning in neural systems.

Advisors: Prof. Idan Segev and Prof. Mickey London

16B: Pre-symptomatic Parkinson's disease qPCR-based Blood test detecting a conserved sequence motif in transfer RNA fragments

Nimrod Madrer

Rapid, simple and reliable Parkinson's disease (PD) blood tests may enable pre-symptomatic diagnosis and facilitate disease-changing treatments. In our work, we found elevated levels in PD patients' *substantia nigra*, cerebrospinal fluid and blood of PD-specific nuclear genome-originated tRNA fragments (PD-tRFs) carrying a conserved sequence motif. A dual whole blood RNA-based test using qPCR primers for elevated PD-tRFs and reduced mitochondrial-originated tRFs (MT-tRFs) successfully distinguished pre-symptomatic PD patients from controls, outperforming traditional clinical scoring (ROC-AUC of 0.86 vs. 0.73). Strengthening relevance to disease characteristics, symptomatic PD patients carrying PD-related mutations presented higher blood PD-tRFs/MT-tRFs ratios than mutations-carrying non-symptomatic individuals. Furthermore, PD-tRFs complementarity to ribosomal RNA and the translation-supporting LeuCAG3 tRF might escalate disease symptoms via 'dual-lock' translational inhibition. Correspondingly, PD-tRFs levels declined in patients' blood following deep brain stimulation and their ribosomal association was disrupted in depolarized neuroblastoma cells. Our findings facilitate a sensitive, simple and safe blood test for pre-symptomatic PD.

Advisor: Prof. Hermona Soreq

17B: LncRNA MEG3 regulation by phalanx tRNA^{Ala} fragments in Parkinson's and mental diseases

Tamara Zorbaz

The relevance of epigenetic regulation of behavior by long non-coding RNAs (lncRNAs) is evident yet unclear. Here, we report the sex-specific link of amyloid/necroptosis-related short isoform of lncRNA MEG3 ('short MEG3') to psychiatric symptoms in Parkinson's disease (PD), bipolar disorder (BD) and schizophrenia (SCZ) and regulation of brain-specific MEG3 long isoform ('long MEG3') crucial for social fear extinction by fragments of neuron-enriched tRNA^{Ala} (3'tRFs-Ala). In human PD substantia nigra (SN), RNA-Seq profiles revealed female-specific increase of short MEG3, while the long MEG3 was suppressed by oxidative stress and sex-independently increased in PD suggesting a mechanism of related social behavior impairment. Intriguingly, 3'tRFs-Ala form "phalanx" RNA-duplexes within the long MEG3 and their levels in SN associated both with PD disease severity and MEG3 isoform balance. Diversion of 3'tRFs-Ala in cultured human neurons enabled long MEG3-originated miR-770-5p expression and its downregulation of short MEG3. Moreover, preventing 3'tRFs-Ala functions altered many protein-coding transcripts, including β-actin, suggesting more profound involvement in cell plasticity. Furthermore, short MEG3 and 3'tRFs-Ala blood profiles in PD, SCZ and BD were generally lower in female sex, in genetic PD, and in males with SCZ and BD, while elevated in patients with PD. However, MEG3 negatively associated with cognitive and motor symptoms severity in PD suggesting the MEG3-increase connection to acute disease stages. Conversely, MEG3 levels were positively linked with BD-related depression but negatively associated with PANSS SCZ symptoms. These findings present a role for 3'tRFs-Ala as phalanx-based dynamic regulators of MEG3-mediated re-shaping of brain networks reflected in sex-specific blood-to-brain behavioral regulation.

Advisor: Prof. Hermona Soreq

18B: Involvement of amygdala neurons in male predominance of autism spectrum disorder

Noa Montefiore

Male predominance is one of the least understood characteristics of Autism Spectrum Disorder (ASD). While more than a hundred genes are involved in ASD, only a few of them show sex differences in behavior. In previous work, we found that male mice harboring a mutation in the Pogz gene (Pogz+/-) show sexually dimorphic overly friendly behavior in several sociability assays. Mapping the engaged neurons during social recognition revealed that in Pogz+/- males, there are more activated neurons in the basolateral amygdala (BLA) than in control and Pogz+/- female mice. To characterize the morphophysiological properties of these BLA neurons, we conducted in-vitro whole-cell recordings from both Pogz+/- and control mice. We employed targeted recombination in active populations (Trap2) in response to a social smell test to label the neurons. Preliminary results from single cell recording from the BLA present different types of principal neurons, characterized by unique AHP and spike trains of action potentials with varying degrees of spike frequency adaptation in response to a long current injection. Initial results also indicate that the neurons active during the social smell test exhibit some characteristics similar to the principal neurons we identified in the BLA. Further results are needed, and experiments are currently underway to collect more data. Our overall aim is to identify the possible differences in population makeup or the activity of BLA neurons, leading to the differences in social behavior between Pogz+/- and control mice.

Advisor: Prof. Yosef Yarom