Ein Gedi 2020: Abstracts

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Sessions and Talks
Session I – Reinforcement Learning in Real Life

Exploring environments and learning their rules are essential for the development and survival of organisms. In this session we explore different kinds of complex behaviors and environments, and their analysis in terms of Markov Decision Processes and Reinforcement Learning. The talks cover a range of theoretical and experimental approaches:

Lior Fox - Planning and learning to explore in complex environments: a Maximum-Entropy approach

Johannes Niediek - Modeling rat behavior by reinforcement learning with information limits

Ana Polterovich - Spatial learning in a complex environment

Lilach Avitan - Hunting behavior in the developing larval zebrafish - behavioral incentives and informational constraints
Session II – Local and External Mechanisms of Cortical Modulation

The cortex is considered to play a crucial role in multiple cognitive and motor processes. However, it is constantly under heavy regulation by local circuit elements, as well as by subcortical afferents. In this session we aim to highlight several such mechanisms and their effect on the cortex and on behavior.

Amir Dudai (London lab) – Functional characterization of the VIP/ChAT interneurons in vivo

Yair Deitcher (London lab) – Nonlinear relationship between multimodal adrenergic responses and local dendritic activity in primary sensory cortices

Gal Atlan (Citri lab) – The mouse claustrum and its function in behavior under sensory load: from elusive anatomy to physiology
The Ventrolateral Striatum: A Brain Hub Connecting Stereotypies, Reinforcement and Drug Preference

Ben Jerry Gonzales, Diptendu Mukherjee, Reut Ashwal-Fluss, David Matthew Lipton, Hagit Turm, Itay Shalom, Ami Citri

The striatum is recognized as a structure driving motor output and implicated in the transition to compulsive behavior and drug addiction. In this study, we define neuronal ensembles within the ventrolateral striatum (VLS) supporting the encoding of cocaine experience and the development of drug preference, the activity of which drives reinforcement and behavioral stereotypies. Our work identifies dynamic recruitment of striatal ensembles at progressive states of cocaine experience and highlights a role for VLS Drd1-expressing spiny projection neurons in cocaine seeking and the gating of cocaine induced stereotypies. Future investigation of corticostriatal-limbic circuit inputs to the VLS and its SPN populations will be invaluable in dissecting the relative impact of incoming sensory and sensorimotor information on the behavioral output selected by these circuits.

Advisor: Dr. Ami Citri
Adult-Born Neurons Improve Odor Discrimination by Mitral Cells

Shani-Narkiss H, Vinograd A Tasaka G, Yayon N, Landau ID Terletsky S, Groysman M, Sompolinsky H, Mizrahi A

Adult-born neurons (abNs) are continuously generated in the sub ventricular zone, from which they migrate and integrate into the olfactory bulb circuitry. The role of abNs in odor processing has remained unknown, in part due to technical limitations in targeting these neurons with reasonable efficiency for causal manipulations. We show that a Nestin-CreER2 driver system with newly developed mice expressing histone-BFP as a reporter and tTA2 for additional genetic manipulation is highly efficient and specific in labeling and genetically accessing abNs. Using this genetic system, we induced expression of an inhibitory DREADD for temporarily silencing abNs. Using in vivo two-photon imaging in awake head-restrained mice, we compared the responses of mitral cells to a panel of 11 odors (6 monomolecular and 5 natural odors), before and after silencing of their presynaptic abNs. Surprisingly, we found a strong but paradoxical effect on mitral cell responses when silencing inhibitory abNs: while excitatory odor-responses were inhibited, inhibitory odor-responses were weakened. As our system allows us to track and manipulate the exact same neurons at different time points, we measured the effects of silencing abNs at different age points. Interestingly, the effects were limited to abNs that were ~1-2 month old, waning off as they matured. Computational analysis demonstrates that silencing abNs within the first month of age decreases the ability of mitral cells to discriminate odors. A network model of the OB reproduces these results and suggests a circuit phenomenon that underlies the role of abNs. Together, these data explain how a small population of abNs contribute to enhanced odor discrimination by mitral cells.

Advisor: Prof. Adi Mizrahi
Emotional States as Dynamic Organizations of Functional Brain Network

Rotem Dan

How emotion is encoded in the human brain remains a central unresolved question. Over the years, the study of the neural basis of emotion has shifted from examining brain regions to brain networks or circuits. Yet, the functional network structure of the human brain during emotional experiences remains mostly unexplored. Here, we aimed to define the modular organization of the brain during specific emotions: sadness and amusement, and quantify differences between these emotions in the functional segregation and integration of network communities. We hypothesized that the community structure of the brain is dynamic and shifts according to the subjective experience of emotion.

Fifty healthy participants (30 women, 20 men) underwent functional MRI scans during an emotion experience experiment using continuous exposure to sad and amusing film clips. A whole brain functional connectome was computed and a graph-theoretical framework was applied to identify the community structure for each emotion, using consensus clustering and Louvain modularity on the weighted positive graphs of functional brain networks. The similarity between participants in the modular decomposition of each emotional state was quantified using the normalized mutual information. For each module and emotion, the system segregation and participation coefficient (a measure of network integration) were computed, in addition to the strength of functional connectivity between pairs of modules.

Participants were more similar to each other in their brain’s functional organization and community structure during sadness relative to amusement. During amusement, increased system integration was found, specifically for prefrontal and basal-ganglia modules. Conversely, sadness was associated with increased segregation of limbic and opercular modules. Amusement was characterized by prefrontal-subcortical between-module connectivity in contrast to prefrontal- prefrontal and prefrontal-temporal between-module connectivity.
in sadness. These segregation and integration metrics were associated with the reported subjective experience of emotion. Our results indicate that emotions are represented by reconfiguration of large-scale functional brain networks, with overall greater integration in amusement and segregation in sadness, and may further shed light on the pathophysiology of emotional disorders.

Advisor: Prof. Gadi Goelman
Nonlinear Interactions and Where to Find Them - Discovery in Simulation and Experimental Data

Michael Doron

Neuroscientific data is often riddled with interesting unknown phenomena that remain hidden from researchers. The overwhelming amount of data in simulations and the noisy irregularly spaced nature of observational data in experiments often mean that these phenomena will not be discovered as early as they could have been, if at all, unless the scientists knew to look at the correct regions in the data.

Here we will present two recent works from our labs, in which we use machine learning to automatically highlight potentially interesting phenomena in scientific simulations and experimental data. By assuming scientists are more aware of the effect each single parameter has in their experiments than they are aware of the local interaction between several parameters, we developed tools to accurately find and rank these local nonlinear interactions and to present them to the researchers.

Using these tools on simulation data, we were able to reproduce published experimental studies using single cell models that were created years and decades prior to the studies’ publication, as well as discover new interesting phenomena in more complex models. In addition, we show how these phenomena discovery tools can be used on large scale observational experimental data by exploring the Neuropixels data from the Allen brain institute.

Advisor: Prof. Idan Segev and Prof. Dafna Shahaf
Non-normal Amplification in the Barrel Cortex

Connectome

Gadi Mintz

With the availability of connectomics datasets, it remains unclear how to understand their implications on dynamics and functionality. We study a previously suggested dynamical feature of biological connectivity matrices: their ability to support transient amplification of incoming signals under linear rate dynamics. A necessary condition for the existence of such amplification is a non-normal connectivity matrix i.e. one that possesses non-orthogonal eigenvectors. Non-normality has been previously suggested as a desirable mechanism for amplification of sensory signals, where fast response times are required since it avoids dynamical slowing resulting from critical amplification (due to proximity of eigenvalues to instability). We quantify here for the first time the extent of non-normality found in a realistic biological network.

We analyze anatomically constrained connectivity data of the rat barrel cortex, containing the recurrent connectivity matrix within a cortical column as well as thalamic feedforward input, at the cell-type resolution. We quantify several dynamical amplification measures of the neuronal architecture implied by these connectivity data, corresponding to different input temporal and spatial structures. We explore the parameter space under two “budgets”: overall synaptic strength and maximum allowed dynamical slowing. Our findings are twofold: (1) For a wide parameter regime, under the two above constraints, all examined amplification measures were significantly larger in the anatomically constrained connectivity matrix relative to a comparable purely random E-I structure, implying that specific recurrent architecture found in the data contributes substantially to non-normal amplification on top of the division of neurons into E and I. (2) The thalamic input is particularly well-suited to exploit this capacity for amplification as it has a large overlap with the optimal input direction. Since the large scale architecture of cortical columns has similarities across species and cortical areas, it's likely that our findings hold for other cortical connectomes.

Advisor: Prof. Haim Sompolinsky
Functional and Emergent Consequences of Synaptic Coupling Between Grid Cells and Place Cells, Across Multiple Spatial Maps

Haggai Agmon

Grid cells and place cells play an important role in spatial encoding. Grid cells in the medial entorhinal cortex have multiple periodically spaced firing fields that form a hexagonal lattice and are largely similar between environments. Hence, they are considered as reasonable candidates to be associated with path integration. Hippocampal place cells, on the other hand, typically display at most a single environment specific receptive field, and are associated with contextual memory since they exhibit ‘global remapping’, drastically changing their firing field between environments.

In the past decade many experimental and theoretical studies examined the influence that grid cells and place cells might have on one another. Studies have demonstrated correlated phenomena between activities of grid cells and place cells under various manipulations, yet the exact mechanism and functional relationship between grid cells and place cells and its significance to encoding of spatial location is still unclear. Some studies have suggested that grid firing patterns are the main determinant of place cell firing while other studies have challenged this view arguing that grid fields are formed as a result of place cell input. Overall, studies so far were primarily concerned with uni-directional manipulations and their implications, namely, they dealt either only with the effects and emergence of grid cells from place cells inputs or vice versa.

Instead of treating grid cells and place cells as two separate populations in successive stages of a processing hierarchy, we develop in this work a detailed computational attractor model with mutual interacting connections between grid cells and place cells. In this framework grid cell and place cell activities serve as complementary and interacting representations that work in combination to support the reliable coding of large-scale space over multiple environments.
We demonstrate functional consequences the network is capable of performing as path-integration and coupling the distinct grid cell modules but more importantly, we demonstrate two properties that emerge naturally from this network architecture that have been observed experimentally and currently lack a theoretical explanation: (a) Variability in the firing rate of a single grid cell, across its different firing fields, and (b) Asymmetrical effects observed in place cells when depolarizing or hyperpolarizing grid cells, recently observed in Cliff Kentros, lab (NTNU). We provide possible mechanisms for these findings, which are currently lacking, and provide future predictions hence suggesting general principles in which encoding scheme is carried out simultaneously in grid cells and place cells across multiple environments.

Advisor: Prof. Yoram Burak
One of the unresolved questions in deep learning is the nature of the solutions that are being discovered. We investigate the collection of solutions reached by the same neural network (NN) architecture, with different random initialization of weights and random mini-batches. These solutions are shown to be rather similar -- more often than not, each train and test example is either classified correctly by all NN instances, or by none at all. Furthermore, all NNs seem to share the same learning dynamics, whereby initially the same train and test examples are correctly recognized by the learned model, followed by other examples that are learned in roughly the same order. When extending the investigation to heterogeneous collections of NN architectures, once again examples are seen to be learned in the same order irrespective of architecture, although the more powerful architecture may continue to learn and thus achieve higher accuracy. This pattern of results remains true even when the composition of classes in the test set is unrelated to the train set, for example, when using out of sample natural images or even artificial images. To show the robustness of these phenomena we provide an extensive summary of our empirical study, which includes hundreds of graphs describing tens of thousands of networks with varying NN architectures, hyper-parameters and domains. We also discuss cases where this pattern of similarity breaks down, which show that the reported similarity is not an artifact of optimization by gradient descent.

Advisor: Prof. Daphna Weinshall
Dopamine Modulation Shifts Beta Oscillation Frequency and Consequently the Properties of Beta Bursts in the Basal Ganglia

Pnina Rappel*, Liliya Iskhakova*, Zvi Israel, Renana Eitan, Hagai Bergman

Introduction: Beta oscillations (13-35 Hz) have been suggested as the core feature of basal ganglia abnormal activity following the loss of dopaminergic input in Parkinson’s disease. However, beta oscillations are also part of healthy basal ganglia activity and play a role in action suppression and maintenance of status quo. We aim to study whether pathological beta oscillations following dopamine modulation differ in their electrophysiological properties in comparison to physiological beta oscillations.

Methods: We recorded local field potential (LFP) and single-unit activity from two monkeys under pharmacological dopamine up- and down-modulation by IM injections of Haloperidol, Apomorphine, and Amphetamine (Dopamine antagonist, agonist, and reuptake inhibitor, respectively). We also recorded LFP from four Parkinson’s patients on and off dopaminergic medications. We analyzed activity in the beta range to isolate the dopaminergic effect on beta properties.

Results: We found that the level of dopamine activity modulates beta frequency. Low levels of dopamine activity lead to oscillations in lower beta frequencies and vice versa for high dopamine activity levels. Beta burst analysis revealed that the probability of low-frequency (10-20 Hz) beta bursts increases following dopamine down-modulation. However, the amplitude and duration of the beta bursts are frequency-dependent. Thus, the drug effect on burst amplitude and duration is mediated by the drug-induced shift of burst frequency. In particular, low-frequency beta bursts are long and of high amplitude irrespective of drug manipulation.
Conclusions: Beta frequency can serve as a marker for abnormal beta activity in the basal ganglia. Therefore, it can be used as an optimal trigger for future closed-loop deep brain stimulation.

Advisor: Hagai Bergman
Identifying Biological Mechanisms Associated with Poly-Glutamine Aggregate Formation in Huntington’s Disease

Walaa Oweis

Huntington’s disease (HD) is an incurable, neurodegenerative disorder and a member of the group of polyQ-related diseases. HD is characterized by cell loss, mostly GABAergic medium spiny neurons, in the striatum and cortex. The genetic defect of the disease is an abnormal number of tri-nucleotide CAG repeats in the Huntingtin (HTT) gene, which encodes a polyglutamine (polyQ) expansion. These polyQ tracts lead to HTT protein misfolding and aggregation. While the genetic mutation causing HD has been identified over 25 years ago, the pathological mechanisms underlying HD are still not clear. In order to elucidate the pathological pathways involved in HD, we established different cell lines to track polyQ aggregate formation. Comparing RNA-seq in polyQ-containing versus polyQ-less iPSC-derived neuronal progenitor cells, we identified several candidates, including several key transcription factors, involved in the activation of cellular stress response. In addition, we developed an imaging-based polyQ siRNA screen for potential candidates involved in HD in our polyQ-containing cell lines, and demonstrated that highly variable genes are relevant to the pathology of the disease. Our platform enables an unbiased discovery of polyQ disease relevant pathways, identifying both factors involved in aggregate formation/clearance.

Advisor: Prof. Eran Meshorer
A major challenge in systems neuroscience is linking animal behavior to the underlying neuronal activity. In recent years, there have been a significant progress in the development of both optical and electrophysiological tools that allow recording of neuronal dynamics from increased number of neurons in multiple brain regions at improved spatiotemporal resolution. In this session we will discuss three approaches to study neuronal activity at different spatial and temporal scales.

**Mesoscale recording of cortical and sub-cortical neuronal dynamics**  
*Ariel Gilad, Dept. of Medical Neurobiology, Faculty of Medicine, HUJI.*

In this talk I will discuss novel optical approaches for mesoscale recording of aggregated neuronal activity from multiple brain regions. I will first present my work on widefield imaging of neuronal activity in the cortex. Then I’ll discuss a novel technique called ‘High-density multi-fiber photometry’ which allows the study of large-scale circuit dynamics from multiple sub-cortical brain regions.

**Recording neuronal representations using Neuropixels**  
*Ido Maor, Adi Mizrahi’s lab, ELSC*

I will present ‘Neuropixels’, a new type of high-density silicon probes which allows extracellular recordings of single units and LFP from hundreds of sites within multiple brain regions. I will discuss the capabilities of this tool and present its application in studying the neuronal representation along the auditory pathway.

**All-Optical dissection of hippocampal circuits using voltage imaging.**  
*Yoav Adam, ELSC*

In this talk I will present the new voltage imaging technology I developed which allows to image the spiking and subthreshold activity of multiple cells in behaving animals, and to perturb membrane potential with orthogonal optogenetic probes. I will describe the technology and discuss its application for the study of hippocampal dynamics at the microcircuit level.
Posters
Context-Dependent Action Selection in Striatal Circuits

David Lipton

The Striatum is a brain hub integrating sensorimotor drive with selective reinforcement to select appropriate action repertoires. Habits, compulsions, and addictions rely on plasticity within striatal circuits. A central question concerning the striatum regards the representation of specific action repertoires within ensembles of striatal spiny projection neurons (SPNs). A simple hypothesis is that action repertoires (e.g. grooming, feeding, biting, nesting) are represented by discrete, spatially confined, SPN cell populations organized in the striatum according to body region, so that each time an ensemble is activated a very specific action repertoire is selected. An alternate hypothesis would be that populations of SPNs gate the motivation and vigor of engaging in multiple related action repertoires, with broad mapping of body regions to striatal circuits and with the identity of the action selected depending upon the context. Using optogenetic activation of D1-receptor containing “Go-pathway” Spiny Projection Neurons (SPN's) in the ventrolateral striatum in several different contexts, we observe increased stereotypic action, the content of which relies on the context in which the activity is generated. Thus, our results support a function for striatal SPNs in supporting motivation and vigor to participate in a spectrum of actions in a context-dependent manner.

Professor: Ami Citri
Functional Mapping of the Auditory Cortex Subfields Using Flavoprotein Autofluorescence Imaging

Dr. Dina Moshitch

The precise identification of the location of the auditory cortex subfields in mice according to stereotactic coordinates, skull geometry, or the shape of blood vessels was found to be very challenging with low success rates. The reasons for this difficulty are the small size of the targeted areas in the mouse and the large individual differences between mice, even of the same strain, in the exact location of the targeted area.

To overcome this problem, we adopted a new imaging technique based on transcranial functional brain imaging of endogenous fluorescence of mitochondrial flavoproteins. These are intrinsic signals that are coupled to aerobic metabolism and have relatively high spatial resolution. Imaging can be done through the intact skull, which is thin and sufficiently transparent in mice.

The center points of the autofluorescence changes evoked by 5, 10 and 20-kHz pure tone stimulation were used to define the tonotopic axis of subfields of the auditory cortex. The tonotopic axis is used to pinpoint the location of a specific isofrequency band. This can be used for example as a target for bolus loading with calcium-sensitive dye for two-photon microscopy in acute experiments, or as a well-defined target for viral injection of excitatory or inhibitory opsins.

Advisor: Prof. Israel Nelken
The auditory cortex is sensitive to statistical regularities and temporal patterns in stimulus sequences. This context sensitivity is reflected in the differences between sound-evoked responses to the same sounds in different contexts. Previous studies in non-human mammals showed that predicted sounds tend to evoke smaller responses than the same sounds when less predictable. Remarkably, studies by Chait and her colleagues in humans showed that the MEG response to sound sequences containing regular acoustic patterns were greater than the responses to the same sounds presented in random sequences. The sensitivity to regularity appeared as a large, steady shift in the magnetic field size. In an attempt to resolve this contradiction, we recorded from the primary auditory cortex of awake rats. The data were collected as part of control sound recordings of a different experiment. We used sound sequences generated in the same way as those used in the MEG study. In the regular condition, N pure tone frequencies (N=5 or 15) were selected from a fixed table and permuted randomly. That permutation was repeatedly presented cycle after cycle, resulting in a periodic sequence of sounds. In the random condition, N pure tone frequencies were selected and presented in cycles, but their order was permuted randomly in each cycle. We found that the responses to the tones in the regular condition were significantly weaker than the responses to the tones in the random condition. Surprisingly, a significant effect of the order within the cycle was found. Specifically, in the regular sequences of length N=5, the responses increased from the first to the fourth sound in the sequence and then decreased back, independent of the frequency composition of the sequence. In random sequences, a significant order effect was found as well, although it was smaller and had a different structure. Consistent with previous animal studies, we conclude that responses to less-predictable sounds in such sequences are larger in A1. The contradiction with human data may be due to measurements from different auditory areas.
Importantly, we also conclude that there is an explicit representation of the cycle length in A1 of rats.

Advisor: Prof. Israel Nelken
RNA Isolation of Fluorescently Labeled Neuronal and Glial Populations from Lightly Fixed Mouse Brains

Or Yakov

Cholinergic neurotransmission is linked to a variety of brain functions such as learning, attention and memory, and through its malfunction to mental and neurodegenerative disorders, but the molecular regulators of this system are insufficiently understood. Cortical cholinergic neurons in the mammalian brain are largely understudied. Due to their sparsity, investigating this population is difficult. Hence, isolating RNA and comparing between the different cholinergic populations in the brain, is especially challenging. Using the standard Papain dissociation protocol, we could not isolate sufficient amounts of cells for RNA extraction and attempts to follow protocols of nuclear isolation resulted in loss of cytoplasmic fluorescent signals. We hence developed a new method for isolating these cells which enables separating fluorescently tagged neurons from lightly fixed tissue using flow cytometry. Isolation from the fixed tissue maintains the cells’ fluorescent tags and keeps significant amounts of mature cytoplasmic mRNAs and microRNAs. Using this method, we were able to specifically sort cholinergic neurons from the mouse cortex and striatum with high yield of cells and extract good quality RNA from these populations (RIN 6.5-8.5). In particular, the RNA extracted from these cells was amenable for qPCR and RNA sequencing procedures. Moreover, we found this method to be useful for searching other cell populations from the brain, indicating its wider utility. Finally, we believe that this robust method could apply also to older mice which is especially important when studying neurodegenerative disorders.

Advisor: Prof. Hermona Soreq
Insights into Automized Training of Mice for an Attentional Task, Identification of Trends and Strategies in Learning Mice

Idit Yvgi, Noa Rivlin, Gal Atlan, Efrat Sheinbach

While we are constantly exposed to extensive sensory input, only the relevant information is selected, enabling us to pursue our everyday tasks. The neural circuitries underlying this intriguing cognitive function are not fully understood. We have recently found that the claustrum, a broadly connected structure that lays between the striatum and insular cortex, functions in supporting resilience to distraction. As we further address this hypothesis regarding the function of the claustrum, we train mice for a task in which they are required to pay attention to a cue while ignoring distraction, allowing us the opportunity to examine and manipulate neural activity of interest. The training of mice for a task relevant for such a distinctive cognitive function is challenging, leading to the need of a complex system that can efficiently teach the mice the task through flexible adjustment to the differences between individual mice. We have developed an automated system that is capable of training mice in their home cages and serves as a platform in which the mice perform the task they have been trained for as they undergo optogenetic stimulation, fiber photometry or neuropixel recordings, all while collecting large amounts of informative data regarding behavior of individual mice. The data collected through the periods of training provides us with an opportunity to closely study the process of learning in mice. Looking into these data, we have identified trends in learning, different strategies used by the mice and principles regarding motivation and reward. These findings may benefit efficient training of mice for a task relevant for aspects of attention and resilience to distraction, as well as provide more general insights into training of mice for complex tasks, and into efficient tracking of behavior.

Advisor: Prof. Ami Citri
Oculomotor Adaptation in the Absence of Feedback on Behavioral Errors

Matan Cain and

Background

Motor adaptation is an error-driven learning process that can account for predictable changes in the environment. To move precisely, motor commands need to adjust to counteract these changes. The general consensus is that these adjustments are driven by feedback on behavioral errors.

Paradigm

We used a smooth pursuit eye movement learning paradigm to test whether movement errors are needed to adjust behavior to a predictable change. Monkeys were trained to track a single moving target that changed direction 250 ms after the onset of motion. After repeated presentations, the monkeys adapted to the change in direction by moving their eyes in the upcoming direction of motion.

Results

To test whether eye movements were needed for this adaptation, we added learning blocks in which the target moved in the same trajectory while the monkeys were not tracking this target but rather had to fixate on an additional target in the center of the screen. We found that in infrequent (10%) probe trials in which the fixation target did not appear, the monkeys exhibited learning by moving their eyes prior to the change in direction. We verified that learning was not due to movement in the infrequent probe trials since the probed learned response was substantially smaller in sessions during which the monkeys maintained fixation while the moving target did not change direction. Furthermore, learning was not eliminated in sessions where the moving target changed direction on the fixation trials but not on the probe trials.

Conclusion
Tracking a moving target is not necessary for the adjustment of behavior implying that learning occurred even in the absence of feedback on behavioral errors. The standard model assumes that the interaction between movement and error signals in the cerebellum underlies adaptive learning. Our results indicate that additional mechanisms exist and need to be explored.

Advisor: Prof. Mati Joshua
Higher Order Auditory Responses in the Insular Cortex of the Anesthetized Rat

Mousa Karayanni

**Background:** The insular cortex (InsC) is a multi-modal cortical area composed of functionally distinct subregions characterized by different patterns of connectivity with other brain areas. Rat InsC possess an auditory responsive subregion which is anatomically distant from other auditory cortical fields. In order to characterize the location and auditory responses of the insular auditory field, we used arrays of 9 single tungsten electrodes as well as neuropixel probes to record neuron activity in InsC of halothane anesthetized rats. Response properties of neurons in InsC to simple sounds are remarkably similar to those of neurons in A1. Here I studied higher-order processing of simple and complex sounds in the InsC by analyzing the response properties of neurons to tone sequences with various statistical properties. I focus on stimulus specific adaptation (SSA), in which response magnitude to a common stimulus decreases with partial or no generalization to another, rare stimulus. To further analyze the responses, an SSA model based on the adaptation of feedforward synapses relaying the auditory signals was used. **Results:** Histological reconstruction of the electrode tracks localized the auditory responsive region mainly in granular InsC. InsC neurons showed pronounced adaptation to repeated pure tones, moderate SSA to pure tones, minor SSA to complex spectrally balanced tones and minor deviance sensitivity. The model showed that neurons in InsC and in A1 had diverging profiles of sensitivity to the structure of tone sequences. **Conclusions:** Under anesthesia, in spite of the similarity in responses to simple sounds, the computations performed by neurons in the rat insular auditory field differ significantly from those performed by neurons in A1.

Advisor: Prof. Israel Nelken
Predicted Archaic 3D Genome Organization Reveals Genes Related to Head and Spinal Cord Separating Modern from Archaic Humans

Daniel Batyrev

High coverage sequences of archaic humans enabled the reconstruction of their DNA methylation patterns. This allowed comparing gene regulation between human groups, and linking such regulatory changes to phenotypic differences. In a previous work, a detailed comparison of DNA methylation in modern humans, archaic humans and chimpanzees revealed 873 modern human-derived differentially methylated regions (DMRs). To understand the regulatory implications of these DMRs, we defined differentially methylated genes (DMGs) as genes that harbor DMRs in their promoter or gene body. While most of the modern human-derived DMRs could be linked to DMGs, many others remained unassigned. Here, we used information on 3D genome organization to link ~70 out of the remaining 288 unassigned DMRs to genes. Combined with the previously identified DMGs, we reinforce the enrichment of these genes with vocal and facial anatomy, and additionally find significant enrichment with the spinal column, chin, hair, and scalp. These results reveal the importance of 3D genomic organization in understanding gene regulation by DNA methylation.

Advisor: Prof. Eran Meshorer
Developmental dyslexia is an impairment in the acquisition of expert reading skills. It has been associated with a difficulty in efficient use of long-term statistics of both speech and simple sounds (Lieder et al., 2019), and was related to faster decay of implicit memory (Jaffe-Dax et al., 2017). We now asked whether individuals with dyslexia would show a similar bias for complex visual stimuli. To do so we used the serial dependence effect for faces, a bias in the perception of faces towards recently seen faces (Liberman et al., 2014). We created morphs of two faces (face A and face B) and asked participants to categorize each morph as one of the two faces. We manipulated the Inter-Trial-Interval (ITI) to test for a difference in the temporal dynamics of the effect between the two groups. Both groups managed to perform the task, and their categorization curve was sigmoidal-shaped. We divided the trials to two conditions based on whether the previously seen stimulus was more similar to face A or to face B. We fitted a logistic function to each condition in each participant, and calculated serial dependence as the difference in the point of subjective equality (PSE) between the two conditions. Preliminary analyses suggest that while controls demonstrate a stable serial dependence effect, for individuals with dyslexia the effect exists in a shorter ITI (3.5 sec) but is reduced in a longer ITI (5 sec). This implies that the faster decay of implicit memory in dyslexia is domain-general.

Advisor: Prof. Merav Ahissar
Minocycline: A Novel Sex-Dependent Antidepressant That Alters Microglia and the Gut Microbiome

Anna Schmidtner

Major depressive disorder is the main cause of disability worldwide with treatment options that are not effective in 30% of patients. Therefore, novel therapeutic approaches are evaluated, from augmentation strategies to novel treatments that target the immune system or the microbiome-gut-brain axis. The pleiotropic effects of the antibiotic minocycline on both systems indicate a promising new treatment approach. Thus, we examined the potential beneficial effects of chronic minocycline treatment, alone or as augmentation of the conventional antidepressant escitalopram, on behaviour, microglial density in the prefrontal cortex (PFC), and the gut microbiome composition in male and female rats, selectively bred for high anxiety-like behaviour (HAB).

Concomitant with their high innate anxiety- and depressive-like behaviour, HAB rats display a decreased microglial density in the PFC and an altered microbiota composition compared with controls. Minocycline was able to alleviate the depressive-like phenotype, further reduced microglial density, exclusively in male HAB rats, and reduced the plasma concentration of pro-inflammatory cytokines. Escitalopram alone was not effective and prevented the beneficial effects of minocycline when administered in combination. In addition, minocycline robustly shifted the cecal microbial composition in both HAB rats and controls and markedly increased the relative abundance of two bacterial families, known for their butyrate production, with a corresponding increase and positive correlation in plasma 3-OH-butyrate levels in a trait-dependent manner.

These results indicate that the antidepressant effect of minocycline is trait- and sex-dependent and associated with a reduced PFC microglial density as well as changes in cecal microbiota and their metabolites. Further, they point towards a complex network of interaction between numerous systems in the body to be involved in the pathophysiology of major depressive disorder and support the microbiome-gut-brain axis as a promising novel treatment target.

Advisor: Prof. Inga D. Neumann, Prof. Naomi Habib
Chromatin Structure and Dynamics in Diffuse Intrinsic Pontine Glioma (DIPG)

Lea Cohen

Change in chromatin structure and function underlie many different pathologies, which affect the brain. One disorder, which is caused by a direct point mutation in one of the genes encoding for histones is Diffuse Intrinsic Pontine Glioma (DIPG). DIPG is a specific type of cancer occurring in glial cells in the brain stem in children. Specific point mutations (K27M) in the histone variant H3.3 induce this type of glioma in a dominant negative fashion, potentially due to antagonizing Polycomb function. Other mutations in this histone variant are involved in other types of cancers. We developed a cellular model, based on mouse embryonic stem cells, where Doxycyclin (Dox) addition induces the expression of the mutant gene, H3.3K27M. Using RNA-seq and epigenomic profiling of different histone modifications, we report the initial molecular changes that occur once H3.3 is mutated. Moreover, using Time-seq (ChIP-seq for WT/Mut H3.3 at different time points), we were able to follow the dynamic turnover of WT and mutant H3.3, and identify the subset of differentially expressed genes which show altered histone turnover. Our systems provide a first glimpse into the epigenetic changes that occur after the acquisition of the H3.3 mutation, allowing us to study the very first and dynamic effects of the mutated protein in healthy cells before the development and progression of cancer.

Advisor: Prof. Eran Meshorer
Healthy Aging Prediction Using qMRI

Asier Erramuzpe

Aging is a dynamic process that encompasses a systemic time-dependent decline. Individuals with the same chronological age might exhibit different trajectories of the biological age [1].

Quantitative MRI (qMRI) can provide accurate information with biophysical meaning regarding aging [2]. qMRI is sensitive to brain changes in Multiple Sclerosis (MS) [3], a disease which is considered to predominantly affect white matter.

Here, we test:

○ Can qMRI be used for age prediction in healthy subjects?

○ Can the age prediction model be used to identify cases where the biological age has been altered due to a disease?


Advisor: Dr. Aviv Mezer
Distributed Representation of Temporally Persistent Visual Categories

Gal Vishne

Research on visual perception has thoroughly characterized the neural activity in response to the appearance of visual stimuli. These responses often reflect the category of the stimuli, but they are transient. Our visual experience is composed of many moments without change, where we still maintain information about our surroundings. We set out to fill this gap and characterize neural tracking of category information beyond the initial moment of change. This was done using intracranial recordings from 10 subjects undergoing surgery for intractable epilepsy (1067 electrodes). Patients viewed images of variable durations (300-1500ms) from several categories, coupled with an identification task to maintain attention. Previously (Gerber et al., 2017), we identified the single electrode correlates of persistent categorical information and found only two electrodes that were sensitive to category membership until the end of the stimulus duration. Here, we move to characterize the dynamics of ongoing category selectivity using multi-variate pattern analyses. We trained a classifier (LDA) to distinguish between viewing of objects and faces on a moment by moment basis (based on broadband high frequency activity (70-150Hz) which was shown to correlate with local neural firing). We found sustained categorical selectivity in several subjects, even when no local sensitivity was found, showing that category information might be maintained by more extended regions. In many cases category representation was dynamic: the distinguishing pattern of activity changed across time. We identified a posterior group of electrodes where face selectivity re-emerged with a distinctive pattern after the initial feed-forward sweep. We conclude that category representation shifts in space and time.

Advisor: Prof. Leon Deouell
Rats and VRats: Using Virtual Rats to Study the Behavior and Neural Activity of Freely Moving Rats in a Complex Environment

Alex Kazakov

Reinforcement learning together with deep learning (RL-DL) is a powerful paradigm for solving real-world control problems. We developed two parallel setups to investigate biological and computational reinforcement learning – The first one is a large interactive environment (RIFF, rat interactive fantasy facility; diameter, 1.6 m) where rats train to maximize rewards (food/water) over time. The RIFF operates according to a Markov Decision Process, based on the rat location and activity. The rats interact with the arena via 12 ports, comprised of a food or water dispenser, an air-puff valve and a nose poke detector ("interaction areas", IAs). The rat is tracked in real-time by a ceiling-fixed camera (30 Hz). We taught adult rats (Sabra, female, N=5) to behave as instructed by different sounds that are presented in the RIFF, in order to maximize rewards (food/flavored water) and to avoid air-puffs. The rats performed hundreds of short trials (10-30 seconds, each ending with a reward or a punishment) in a single session (1 hour long, over many weeks). Neural responses were recorded from insular or auditory cortices by 16 tungsten electrodes (flexDrive) with a Neurologger system (Deutron). The other setup is an in-silico replica of the RIFF, a computer model that performs similar tasks under similar environmental laws and constraints. The full observability of the virtual setup allows us to develop hypotheses that we test on the biological one. The RIFF was replicated in-silico as a 2D arena with similarly located IAs, driven by the same MDP. The virtual rat (VRat) is modeled as a point inside this arena, with constraints on acceleration and turns to resemble the biological rat. The VRat brain is comprised of an artificial neural network (Deep Q-Network, 300 neurons in total) that emits an action based on the observed state. The VRat was trained through reinforcement learning, and converged to near-optimal policies that were surprisingly similar to the policies of the biological rat as compared by reward return, trajectory features and action distribution. We currently investigate what causes the rats and VRats to converge to similar policies, and to what extent the internal representations (as judged by neural
responses in the rats and by the full state of the neural network in the VRat) are related to each other.

Advisor: Prof. Israel Nelken
Development of a Flexible Automated Behavioral Setup Supporting Investigation of the Claustrum-Frontal Cortex System in Attention

Noa Peretz-Rivlin, Gal Atlan, Idit Yvgi, Efrat Sheinbach & Ami Citri

The claustrum exhibits massive connectivity to cortical and subcortical structures, the function of which is a topic of active investigation. We recently uncovered a role for the claustrum in attention and resilience to distraction, and reported on the capacity of the claustrum to effect cortical sensory processing (Atlan et al. 2018).

The most massive input and output target of the claustrum is the frontal cortex, including the mPFC, OFC and ACC. The claustral projection to the PFC has been shown to dramatically impact the activity of frontal neurons (Jackson et al. 2018, Liu et al. 2019), and has been implicated in regulating impulsivity (Liu et al. 2019). The finding regarding the involvement of the claustrum in attention processes as well as its effect on cortical activity may be in line with the suggested part for the claustrum in global neural networks such as the default mode network (including CLA–mPFC connections), the salience network (including CLA-ACC connections) and the executive control network (Smith et al. 2019), as well as the suggested involvement of the claustrum in the transition between those. The different projections from the claustrum to the ACC and OFC can comprise aspects of different networks.

Unpublished work from our lab has identified spatial segregation, as well as differential recruitment in attention-demanding tasks of claustral neurons projecting to different frontal cortical structures (ACC vs OFC). In this work I am taking advantage of the Neuropixels multielectrode probe in order to record neural activity in the ACC and OFC simultaneously, while aiming to activate different neural populations in the claustrum defined by their projections properties. This system supports direct comparison of the effect of claustral neurons on those two structures, and tests their effect on performance in attention.
demanding task. An efficient experimental pipeline involving recording from behaving animals and requires the utilization of a flexible and robust automated training platform. To this end, we modified an open source behavioral platform “BPOD” to support multiple animals in the same cage, while applying individual task parameters based on the mice’s performance. We trained mice on a detection task including a response inhibition delay, and established a pipeline for developing generalization from the automated training cage to the head fixed configuration in the recording setup.

Future experiments will combine the recording system with the behavioral paradigm, in order to assess the role of the claustrum in attention or in transition to “attentive state”. Recording of neural activity in the OFC and ACC simultaneously will be performed, while optogenetic activation of the claustrum will be delivered in different phases of a task as well as during rest periods between trials. Analysis of the anticipated dataset is expected to provide resolution to multiple questions. Do the differentially projecting populations within the claustrum impact cortical targets differentially? Does claustrum activation affect the cortex in a different manner depend on the context (during task vs. during rest). Does claustrum activation contribute to the correlation of activity within and between cortical structures? Does modulation of CLA-cortex pathways impact behavioral performance? Can we predict behavioral performance based on recorded data?

Advisor: Dr. Ami Citri
A Distributed Network of Noise-Resistant Neurons in the Central Auditory System

Souffi S, Huetz C, Lorenzi C, Edeline J-M.

In daily life, background noise strongly penalizes auditory perception of target stimuli such as speech in humans or vocalizations in animals. Despite this, auditory neurons successfully detect and discriminate behaviorally salient sounds even when the signal to noise ratio (SNR) is quite low. Several recent studies showed that cortical neurons are robust to noise addition and develop strategies to adapt to the noise statistics. For example, in a recent study (Ni et al., 2017), it was reported that auditory cortex neurons can be assigned to categories depending upon their robustness to noise. More precisely, by testing the responses to conspecific vocalizations in different SNRs, this study has described four types of responses classes (robust, balanced, insensitive and brittle) in the marmoset primary auditory cortex, and has pointed out that depending upon the background noise the same neuron can exhibit different response classes (Ni et al., 2017). However, no study has systematically evaluated the robustness to noise at each level of the auditory system. Here, we recorded neurons from the cochlear nucleus up to the secondary auditory cortex in response to a set of four vocalizations presented either in a stationary noise or in a chorus noise at three SNRs.

We used exactly the same methodology as in Ni and colleagues (2017) to assign the neurons to a response class. The Extraction Index (EI, defined by Schneider and Woolley, 2013) was computed at the three SNR levels and a clustering approach (based on k-means algorithm) was implemented to reveal groups of EI profile. This approach led to classify auditory neurons in categories revealing five distinct neuronal behaviors in the auditory system. We provide evidence that neurons robust to noise can be found at all levels of the auditory system with a considerable fraction of them in the inferior colliculus and thalamus. In addition, from one background noise to the other, the neurons behavior can change at all stages of the auditory system, revealing that the context-dependence of auditory processing is a general property of the whole auditory system. We propose here
that the noise-robustness observed in many studies at the cortical level stems, at least partially, from subcortical mechanisms, thus allowing the cortical networks to focus on higher-level processing such as classifying the target stimuli into phonetic or linguistic features.
Variance in VEP Delays in Progressive MS Patients Can Be Explained by the Structural Properties of the Visual Pathways

Shai Berman

Multiple sclerosis (MS) is a chronic demyelinating disease of the central nervous system, in which myelin is attacked, changing white matter structure and leaving lesions. A wide variety of measures is used for tracking and prognosis of MS, many of which use visual measures, partly due to the high occurrence rate of posterior visual system damage i.e. optic radiation (OR) lesions. We wanted to ask whether different structural properties of the visual system, both of the retina and of the white matter, could explain the variance of the VEP latency, which is delayed in patients with MS.

We used data collected as part of a longitudinal stem-cell therapy clinical trials, performed on primary by Hadassah medical center. The trial includes 48 progressive MS patients, out of which 27 had no history of optic neuritis, and were therefore used in this study. The participants underwent conventional MRI scanning over six consecutive points in time, prior to and following two treatment sessions. The MRI protocols are designed to evaluate changes in the brain’s lesions volume and degree of atrophy. The patients are also monitored through monthly evaluations, EDSS records and psychophysical testing. In addition to the trials’ MRI scans, dMRI and qMRI sequences are being added, to enable the cutting-edge analyses proposed by my lab. We find that the relationship between the retinal damage and the VEP latency persists after the subjects have undergone treatment.

Second, we show that in the progressive MS patients, the OR lesion load is also correlated with VEP latency. We found that qMRI values, which are sampled along the OR, are also correlated with VEP latency. Finally, we show that combining these parameters with PCA we can explain more than 40% of the inter-subject variance in VEP latency. Establishing the understanding of the relationship between the structural measurements and conduction in the visual system in health and disease is valuable to the general scientific effort of other brain systems.

Advisor: Dr. Aviv Mezer
Spatial Segregation of Claustral Neurons Projecting to Different Cortical Targets

Efrat Sheinbach

The claustrum is a thin & elongated structure, located between the striatum and insular cortex. The claustrum is famous for being the most highly connected structure in the brain (per regional volume), and extensive efforts have gone into mapping the connectivity of the claustrum. Yet, it is still unclear whether claustral neurons associate into discrete networks with divergent connectivity, or form repeated units with overlapping connections.

Moreover, while it is clear that the claustrum largely forms reciprocal connections across the brain, it is unclear whether claustral sub-networks form specifically reciprocal connections. To approach those questions, we used retrograde AAVs expressing Cre, enabling us to ask questions regarding the overlap of populations in the claustrum and their spatial organization. Our results demonstrate a spatial segregation within the claustrum of neurons projecting to the orbitofrontal cortex (OFC) vs. the anterior cingulate cortex (ACC).

The overlap between the different populations was found to be small. These results imply that claustral projection neurons associate into distinct parallel networks, forming the basis for intriguing hypotheses regarding the function of the claustrum.

Advisor: Prof. Ami Citri
Measuring Biological Gradients along the Human Dorsal Striatum in Vivo using Quantitative MRI

Elior Drori

Introduction: The dorsal striatum is the main input structure of the basal ganglia and is critically involved in motor control and goal-directed behaviors. It is composed of the putamen and the caudate nucleus, which are heterogeneously organized, with structural and functional gradients along the anterior-posterior and medial-lateral axes. Irregularity in the organization of the striatum is linked to diseases of the basal ganglia and to age-related declines. Therefore, we have developed a quantitative MRI (qMRI) method to quantify structural variations along the main axes of the human dorsal striatum in vivo, and to study their relation to aging.

Method: MRI scans were performed on 20 young adults (27±2) and 18 older adults (67±6), and quantitative T1 maps were acquired. Using singular value decomposition (SVD) of voxels’ 3D position, we computed the three main spatial axes of each structure. Then we measured the mean T1 in segments along these axes, which largely correspond to the anterior-to-posterior (a-p), ventral-to-dorsal (v-d) and medial-to-lateral (m-l) axes of each structure.

Results: We find significant spatial gradients of T1 along the main axes of the dorsal striatum structures, that show high reliability across subjects, and are evident in both young and older adults. In addition, we find group differences between young and older adults. T1 values are generally higher in older adults, and we see interaction effects between age and position along the axes of the putamen. Finally, in the putamen we find high inter-hemispheric similarity of the gradients, while in the caudate we witness asymmetry between hemispheres.

Conclusions: We provide a first in vivo evidence for the gradual change in microstructure along the main axes of the human dorsal striatum, using qMRI measures. We found effects of aging as well as laterality effects. The identification of reliable basal ganglia gradients in vivo might prove useful for clinical populations such as Parkinson’s disease and ADHD, where structural irregularity and asymmetries are linked to behavioral symptoms.

Advisor: Dr. Aviv Mezer
Blood Gene Transcripts May Identify Parkinson's Disease Patients with and Without Dementia

Shani Vaknine

Parkinson's disease (PD) is the most prevalent movement disability disorder, with non-motoric symptoms including sleep impairments, cognitive decline and autonomic dysfunction. These may reflect cholinergic impairments that have been linked to dementia in the elderly. However, at present no blood test exists to identify PD patients, with or without dementia. We sought molecular biomarkers for these characteristics by RNA-sequencing of postmortem whole blood samples from 25 male PD Patients with and without dementia (14 PDD, 11 NDPD) and 13 non-demented control males (NDC) from the Netherlands Brain Bank. Differential expression (DE) analysis identified 41 and 343 significantly differentially expressed (DE) mRNA transcripts between NDPD and NDC donors and between PDD and NDC donors, respectively (P≤0.05, Wald test). However, no DE genes reached significance between the two PD groups. Moreover, weighted gene correlation network analysis (WGCNA) identified two modules of closely segregated transcripts which positively correlated with the patients' diagnosis or Braak Lewy bodies' scores; and gene ontology (GO) Enrichment analysis demonstrated involvement of this modules' genes in protein folding and heat shock regulation. Another module showed a negative correlation with both characteristics and GO-Enrichment analysis, indicating involvement of its genes in cell cycle and DNA replication pathways. Furthermore, several significant transcripts in each comparison showed positive correlation with transcript levels of cholinesterase (AChE, BChE) enzymes in individual NDC and NDPD patients, suggesting a protective role of the cholinergic system. Taken together, these findings point at a promising signature of blood biomarkers which segregate between PD patients with and without dementia.

Advisor: Prof. Hermona Soreq
Activation of the eEF2 Pathway in the Dentate Gyrus Excitatory Neurons Enhances Cognitive Function and Neurogenesis in Young and Old Mice

Elham Taha

Regulation of the translation mRNAs into protein plays a pivotal role in learning and memory formation. Protein synthesis is a dynamic process, which is regulated at three main phases: initiation, elongation, and termination. While the initiation phase of translation is considered to be the rate-limiting step, regulation of the elongation phase via eukaryotic elongation factor 2 kinase (eEF2K) has also been suggested to be important for memory and synaptic plasticity consolidation (Taha E et al., 2013, 2017, 2018). During the elongation phase, eukaryotic elongation factor 2 (eEF2) promotes ribosomal translocation that leads to ribosomal movement along the mRNA. Phosphorylation of eEF2 on Thr56 by its specific kinase, eEF2K, inactivates eEF2 and leads to protein synthesis inhibition. Here, we aim at examining the function of the eEF2 pathway in the dentate gyrus (DG) of the hippocampus in mice.

Proteomic analysis of hippocampus from mice with genetic deletion of eEF2K (knock-out, KO), which leads to complete loss of eEF2 phosphorylation, revealed enriched fraction of proteins that are crucial for neurogenesis. Indeed, both neurogenesis and dentate gyrus-dependent context discrimination learning were enhanced in the eEF2K-KO mice compare to wild-type. Using injection of viruses harboring Cre recombinase under the excitatory neuron-specific CaMKII promoters into the DG of eEF2K floxed mice, we observed enhanced neurogenesis. In addition, electrophysiological analysis of perforant path evoked transmission in the dentate gyrus in vivo identified altered LTP maintenance in CaMKII Cre injected mice relative to control. Importantly, enhanced neurogenesis and context discrimination can also be observed in aged CaMKII Cre injected mice.

Together, our findings reveal that the eEF2K pathway in granular DG excitatory neurons plays a specific and critical role in neurogenesis and DG-dependent behavior. In addition, rejuvenation of the DG by modulating eEF2 phosphorylation
in adulthood and aging enhanced memory precision. Our study suggest that eEF2K inhibition has potential therapeutic significance in the cognitive decline associated with aging.

Advisor: Prof. Kobi Rosenblum, Haifa University
Synaptic clustering on neuronal dendrites has been theorized to play an important role in pattern recognition in the brain. Neighboring synapses on a dendrite can interact in a synergistic, cooperative manner via the nonlinear voltage-dependence of NMDA receptors. Bartlett W. Mel's 1992 paper entitled 'The Clusteron: Toward a Simple Abstraction for a Complex Neuron' proposed an algorithm to take advantage of this nonlinearity which randomly shuffled the locations of "under-performing" synapses on the dendrite to enable the neuron to solve a classification task. We propose an alternative algorithm based on an analytically-derived gradient descent rule where synapses are "attracted to" or "repelled from" each other in an input- and location- dependent manner. We demonstrate the classification ability of this algorithm by testing it on the MNIST handwritten digit dataset and comparing our algorithm's performance to that of the original Clusteron algorithm as well as to a one-layer artificial neural network (logistic regression).

Advisor: Prof. Idan Segev