Lectures Abstracts

Developing Next Generation Neuronavigation Technology

Jennifer A. McNab
Stanford School of Medicine

Precise location of specific brain regions is important for many clinical applications such as brain stimulation or neurosurgery. Our lab is developing magnetic resonance imaging technology for mapping fiber pathways and tissue microstructure in the in vivo human brain that can be used to identify the optimal target location for treatments such as deep brain stimulation, high intensity focused ultrasound or transcranial magnetic stimulation. We validate the MRI fiber mapping methods through comparisons with advanced 3D CLARITY histology. By applying both MRI and CLARITY serially in the same postmortem human brain specimens, we link the indirect, mesoscale MRI measurements with the microscopic tissue components directly visualized by CLARITY. We also evaluate neuronavigation approaches via retrospective clinical studies in which the projected optimal target based on MRI fiber mapping is compared with the lesion or DBS lead location and then correlated with patient outcomes. Lastly, we are developing augmented reality neuronavigation technology that allow the MRI fiber mapping data to be directly overlaid on the patient's head, providing an intuitive display for faster and more effective treatments.

Opening the black box of deep neural networks

Ravid Shwartz-Ziv

Recent advancements in Deep Neural Networks (DNNs) have driven phenomenal improvements in machine learning performance across various domains. Nonetheless, despite numerous breakthroughs, DNNs are often treated as "black boxes" owing to our poor understanding of their internal organization and optimization process. A recent effort attempted to address this limitation by suggesting that DNNS learn to optimize the mutual information that each layer preserves on the input and output variables, resulting from tradeoff in compression and prediction per each layer. Here, we extend this theory by showing that the dominant DNN optimization algorithm, Stochastic Gradient Decent (SGD) follows the information bottleneck trade-off principle by working in two phases, a fast empirical error minimization phase for data fitting followed by a slow representation compression phase. These phases are characterized by markedly different signal to noise ratios of the gradients for each layer. In the fitting phase the gradient norms are much larger than their stochastic fluctuations, while in the compression phase the SNR is much larger. We additionally show that the DNN layers converge proximal to the IB theoretical bound, resulting in a self-consistent relationship between the encoder and decoder distributions and thus presenting a theoretical argument for the computational benefit of the hidden layers. Finally, we show how SGD achieves this optimal bound, as the compression for each layer amounts to relaxation to a maximum conditional entropy state subject to the proper constraints on the error and information of the labels. Thus, our works suggests that DNNs are essentially a technique for solving the information bottleneck problem for large scale learning tasks.

Advisor: Prof. Naftali Tishby

Current Deep Learning Fail to Generalize in a Human-Like Fashion

Aharon Azulay

In recent years, approaches based on deep convolutional neural networks achieved state of the art performance on virtually any computer vision task. However, it is not clear whether the functions learned by these networks truly generalize in a way expected by humans.
Here we show that even the most successful network architectures fail to find functions that generalize in a way intuitive to humans, i.e. invariant to image translations, scalings, and other natural variations. We provide quantitative evidence for “photographer biases” that explain some aspects of the failures we observe. We complement these real-world results with a well-controlled toy task that sheds light on the source of the failures, and a discussion regarding possible remedies.

Advisor: Prof. Yair Weiss

Single Biological Neurons as Deep Artificial Neural Networks

David Beniaguev

The dendritic tree with its rich repertoire of nonlinear ion channels plays a key role in determining the function and plastic properties of biological neurons. Characterizing how the morpho-electrical complexity of a neuron's dendrites interacts with its synaptic input to shape the neuron's output usually requires simulations involving detailed biophysical models of a variety of neuron types. However, these simulations fail to provide a compact understanding of the input/output (I/O) function of neurons. In our study, we utilize machine learning approaches to fill this gap. Specifically, we use deep artificial neural networks (NN) to predict the spiking output of detailed biophysical neuron models in response to any synaptic input. The NN learns to predict the activity of the modelled neuron at a given time from the synaptic input in the preceding time window. We first test our methodology by training a single-unit neural network to map the I/O relationship of a simple integrate-and-fire (I&F) neuron model. Analysis of the learned weights of this NN recovers the temporal integration profile as well as the synaptic weights of the original I&F neuron in a clearly interpretable manner. Next, we emulated a single active basal dendritic branch of a L23 pyramidal cell model using our deep network approach. A single layer NN with three hidden units accurately captures the behavior of this dendritic branch, including its spatio-temporal discrimination properties (e.g. proximal-to-distal versus distal-to-proximal sequential synaptic activation). Analyzing the filters of the hidden units demonstrate the benefits of our approach, as it provides a clear and simple interpretation of the operation that the dendritic branch performs. Finally, we attempt to model a fully detailed biophysical neuron model of a layer 5 pyramidal cell (L5PC), with its full morphological and electrical complexity. We show that by using a deep convolutional neural network we can accurately capture the I/O relationship of the L5PC neuron, suggesting that single neurons are complex spatio-temporal pattern recognizers. We conclude by asserting that the process of "replacing" single neurons with their respective deep artificial neural networks may provide a compact and interpretable description of the functions of neurons and their computational complexity.

Advisors: Dr. Mickey London and Prof. Idan Segev

Research funding opportunities with the US Army Research Development and Engineering Command

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TBA

Deciphering the Cellular Landscape of the Alzheimer's Brain

Naomi Habib
Broad Institute

Neurodegenerative diseases and other age related pathologies are becoming more common in our society, exposing a large deficit in effective treatments. A growing body of evidence indicate that changes in the neuronal microenvironment, such as in resident glia cells, can play a primary pathogenic role in neurodegenerative diseases, however, the underlying mechanisms are yet unknown. We are using single nucleus RNA-sequencing technologies (sNuc-Seq) that enable high-throughput profiling of RNA in complex or frozen tissues at the single cell level, to study such pathological processes in high throughput. We have previously shown that we can use sNuc-Seq to characterize the cellular diversity of the adult mouse hippocampus region, to track RNA dynamics of adult neurogenesis in the brain, and to identify neurogenesis in the spinal cord. We currently apply sNuc-Seq to profile the cellular landscape of the Alzheimer's brain both in mouse models and in human post-mortem archived brain tissues of people ranging from mild cognitive decline to advanced Alzheimer's disease. Through these detailed investigations we are advancing our understanding of the complex cross talk between different cell types in the brain and its role in neurodegeneration.

Subjective surprise response as a probe for compressed hidden memory states

Hadar Levi Aharoni

Forgetting is a necessity for living beings as many experiments have shown. Recent studies have put forward different approaches to account for the limited capacity of working memory (WM), which leads to forgetting. Arguably, behavioral and neural responses to novel or rare stimuli are dependent on one's memory of past stimuli. In this paper, we present a quantitative method to estimate individual limits of WM capacity using a novelty-detection event-related potential commonly known as the P300. By calculating a trial-by-trial capacity-dependent theoretical surprise in an auditory oddball paradigm, we account for trial-by-trial variations in the P300 response and cross-subject variability in the response range. The surprise model provides a simple and powerful predictor for the P300 magnitude, while being highly parsimonious and originating from statistical theory principles. The experimental fit to the surprise predictors enabled us to extract two stimulus-compression parameters for each subject: memory length and representation accuracy, which together provide an estimate of the subject's WM capacity limit under the task conditions. Across subjects, the results show that a memory-efficient representation with high compression explains the P300 response better than low compression predictors. These results, taken together with recently published findings on single neurons, support the view that compression of past stimuli is an important construct in neural processing, and that it can characterize neural responses measured at different spatial scales and in different individuals under one framework.

Advisors: Prof. Naftali Tishby and Dr. Oren Shriki*

** Dept. of Cognitive and Brain Sciences, Ben-Gurion University*

Subthalamic oscillatory activity in obsessive-compulsive disorder correlates with clinical state

Pnina Rappel

Obsessive-Compulsive disorder (OCD) is a common and serious psychiatric disorder. Although subthalamic nucleus deep brain stimulation (DBS) has been studied as a treatment for OCD patients the underlying mechanism of this treatment is unknown.

To study the neural basis of subthalamic nucleus DBS in OCD patients, we used a novel, implantable DBS system with long-term local field potential sensing capability. We focus our analysis on two patients with OCD who experienced severe treatment-resistant symptoms and were implanted with subthalamic nucleus DBS systems. We studied them for a year at rest and during provocation of OCD symptoms (46 recording sessions), and compared them to four Parkinson's disease (PD) patients implanted with subthalamic nucleus DBS systems (69 recording sessions).

We show that the dorsal (motor) area of the subthalamic nucleus in OCD patients displays a beta (25-35Hz) oscillatory activity similar to PD patients whereas the ventral (limbic-cognitive) area of the subthalamic nucleus displays distinct theta (6.5-8Hz) oscillatory activity only in OCD patients. The subthalamic nucleus theta oscillatory activity decreases with provocation of OCD symptoms and is inversely correlated with symptoms severity over time.

Beta oscillations at the dorsal subthalamic nucleus in OCD patients challenge their pathophysiologic association with movement disorders. Theta oscillations at the ventral subthalamic nucleus in OCD patients suggest a new physiological target for OCD therapy as well as a promising input signal for future emotional-cognitive closed-loop DBS.

Advisor: Prof. Hagai Bergman

Decoding percepts from EEG and MEG reveals influence of early sensory noise

Greta Vilidaite

Human contrast discrimination performance is limited by transduction nonlinearities and variability of the neural representation (noise). Whereas the nonlinearities have been well characterised, there is less agreement about the specifics of internal noise. Psychophysical models assume that it impacts late in sensory processing, whereas neuroimaging and intracranial electrophysiology studies suggest that the noise is much earlier. We investigated whether perceptually-relevant internal noise arises in early visual areas or later decision making areas. We performed EEG (N=22) and MEG (N=10) recordings during a two-interval-forced choice contrast discrimination task and used multivariate pattern analysis to decode target/non-target and selected/non-selected intervals from evoked responses. We found that perceptual decisions could be decoded from both EEG and MEG signals, even when the stimuli in both intervals were physically identical. Above-chance decision classification started <100ms after stimulus onset, suggesting that neural noise affects sensory signals early in the visual pathway. Classification accuracy increased over time, peaking at ~700ms. Applying multivariate analysis to separate anatomically-defined brain regions in MEG source space, we found that occipital regions were informative early on but then information spreads forwards across temporal and frontal regions. This is consistent with neural noise affecting sensory processing at multiple stages of perceptual decision making. The findings revealed a possible time and location of perceptually relevant neural noise as well as the timeline and spread of neural information during visual perception.

Advisor: Dr. Daniel Baker

Plasticity in Olfactory Circuits Following Parturition

Amit Vinograd

Motherhood is accompanied by new behaviors aimed at ensuring the survival and wellbeing of the offspring. Such behavioral changes are most likely associated with plastic changes in specific neuronal circuits across the brain, but these are not well characterized. We studied function and circuit connectivity in olfaction, which serves an essential sense in guiding maternal behaviors. First, we used in-vivo two-photon calcium imaging to study sensory representations of odors by Mitral\Tufted (M/T) cells - the projection neurons of the olfactory bulb. We found that responses of M/T cells in mothers show improved odor coding of natural odors, accompanied by an increased inhibitory tone. Second, we studied the underlying circuit motifs associated with maternal changes using cell specific monosynaptic rabies trans synaptic tracing. A rabies tracing screen revealed that long range inputs onto M/T cells was plastic. Specifically, we found a two fold increase in the number of feedback connections from the piriform cortex onto M/T cells. Moreover, Vasopressin neurons from the supraoptic nucleus made novel synapses onto M/T cells, exclusively in mothers. Taken together, our results describe the functional changes of olfactory circuits in motherhood and suggest that long range connectivity may serve as a unique mechanism underlying plasticity.

Advisor: Prof. Adi Mizrahi

Identification of an inhibitory hippocampal-thalamic pathway that is necessary for remote memory retrieval

Frances Xia

Systems consolidation requires time-dependent reorganization of brain regions that are necessary for memory retrieval. But how the memory retrieval circuits change over time is not fully understood. The anterodorsal thalamic nucleus (ADn) has been shown to be important for short-term spatial and working memory performance. However, how the role of ADn changes during systems consolidation, and its involvement in remote memory retrieval are unknown. We first show that the activity of ADn during contextual fear memory retrieval decreases over time (1 vs. 28 days post-training). While this could suggest that ADn is no longer necessary during remote memory retrieval, an intriguing alternative is that inhibition of ADn is required to allow successful retrieval at the remote time point. To explore the latter possibility, we first identified regions with monosynaptic projections to the ADn using retrograde tracers (retrobeads and fluorogold). Then we specifically labeled those projections that are inhibitory by infusing a cre-recombinase-dependent adeno-associated virus (AAV) carrying the fluorescence tag EYFP in various brain regions of VGAT-Cre mice. We identified strong long-range inhibitory projections from CA3 to the ADn that could mediate the inhibition of ADn. To test whether this CA3-ADn inhibitory pathway is necessary for remote memory retrieval, we bilaterally infused a cre-recombinase-dependent AAV carrying the inhibitory opsin iC++ in CA3 of VGAT-Cre mice to specifically inhibit GABAergic projections from CA3 to ADn. We trained mice in contextual fear conditioning, then inhibited the CA3-ADn projections during retrieval test. When we inhibited these projections 28 days, but not 1 day, post-training, mice showed memory deficits. These results suggest that the CA3 inhibition of ADn is required for remote memory retrieval. Our findings provide support for the time-dependent reorganization of memory retrieval circuits, and we show, for the first time, that a CA3-ADn inhibitory pathway is gradually recruited during consolidation and becomes functionally necessary for fear memory retrieval over time.

Advisor: Dr. Paul Frankland

Light activation of Channelrhodopsin2 (ChR2) diminishes electrical coupling between neurons

Vitaly Lerner

The use of optogenetic to activate neurons, became the main research approach in study the role of specific subpopulation of neurons. However, recent observations suggest that light activation of ChR2, in addition to activate the neuron, have side effects that questioning the specificity of light activation. Specific activation of cortical PV neurons became a popular approach to generate fast local inhibition of cortical area. We combine optic stimulation with dual whole cell recordings from ChR2 expressing PV neurons and found that optical activation significantly reduces electrical coupling between the ChR2-expressing neurons. This, unexpected results were confirmed in the electrical coupled network of the inferior olive nucleus.

Advisors: Prof. Yosef Yarom and Dr. Mickey London

Timed Synaptic Inhibition finely tunes NMDA Spikes

Michael Doron

The NMDA spike is a long-lasting nonlinear phenomenon initiated locally in the dendritic branches of cortical neurons. It plays a key role in synaptic plasticity and in single-neuron computation. We combined dynamic system theory and computational approaches in order to explore how the timing of synaptic inhibition affects the NMDA spike and its associated membrane current. When impinging on the NMDA spike's early phase, individual inhibitory synapses transiently dampen the spike, allowing it to recover. However, later inhibition of the same magnitude prematurely terminates the spike. A single inhibitory synapse can reduce the NMDA-mediated Ca2+ current, a key player in plasticity, by up to 45%. We further find that NMDA spikes in distal dendritic branches and spines are longer-lasting and more resilient to inhibition than NMDA spikes proximal to the soma, enhancing synaptic plasticity at these distal branches. We conclude that NMDA spikes are highly sensitive to dendritic inhibition, and even sparse weak inhibition can finely tune computation both locally at the dendritic branch level and globally at the level of the neuron's output. This work shows the importance of the temporal aspect of inhibition, shedding further light on non-linear computation in dendrites.

Advisor: Prof. Idan Segev

A New Spice to the inflammatory soup: Platelet-Derived Growth Factor activates peripheral pain neurons by inhibiting KV7/M-type potassium channels

Omer Barkai

When a tissue is injured, a “soup” of proinflammatory mediators is released into the site of injury, producing sensitization of peripheral pain-related neurons (nociceptors), hence leading to inflammatory pain. Among these factors is Platelet-Derived Growth Factor (PDGF), which is released after tissue injury and has been shown to be involved in inflammation and wound healing. Here we hypothesize that PDGF, in addition to its proinflammatory effects on cell migration, differentiation and proliferation in wound healing, also affects nociceptive excitability, thus leading to inflammatory pain. We examined this hypothesis using electrophysiological recordings from nociceptive neurons, behavior tests and computational modeling. We show that application of PDGF on acutely dissociated rat nociceptive neurons in culture leads to a substantial membrane depolarization, followed by a barrage of action potential firing. Furthermore, subcutaneous injection of PDGF leads to pain hypersensitivity in rats. We explored the underlying mechanism of PDGF-induced hyperexcitability and demonstrated that application of PDGF leads to blockade of potassium Kv7/M-current in nociceptors. We demonstrated that blockade of the Kv7/M-current is sufficient to induce nociceptive activation. Moreover, blockade of the PDGF receptor (PDGFR) with Imatinib, a clinically used PDGFR inhibitor, leads to a significant reduction of inflammatory pain, suggesting that the PDGF-Kv7/M-current pathway plays a pivotal role in development of inflammatory pain. Therefore, our results suggest that blockade of PDGFR with Imatinib may be clinically used to attenuate inflammatory pain.

Advisor: Prof. Alex Binshtok

Pain at its Source:
Signal Transduction and Propagation at the Nociceptive Peripheral Terminals

Robert H. Goldstein

Noxious signals are detected by terminals of nociceptive fibers situated among the keratinocytes and epithelial cells. These minute structures possess the functional elements for detecting, transmitting and modulating pain-related signals, thus being key structures for pain sensation, in normal and pathological conditions. However, little is known about the physiology of terminals mainly due to their miniature size and location. Hence, basic questions such as where is the location of action potential initiation and does this location undergo plastic changes to effect terminal excitability, are still unanswered. Here we have implemented fast optical recording from mice nociceptive terminals in vivo enabling us for the first time to directly study the activity terminals and distal axons in the most relevant conditions. We have examined changes in intra-terminal Ca2+ following electrical stimulation or focal application of capsaicin, using the genetically encoded Ca2+ indicator GCaMP6s. We found that blockade of Na(v)s did not affect the Ca2+ signals in the terminal tips, however, ~20 □m away from the tip, Ca2+ signals are partially dependent on Na(v)s. At ~30 □m from the tip the Ca2+ signal was fully and reversibly abolished by Na(v) blockade, suggesting that the spike initiation zone (SIZ) is located at this area of the nociceptive axon. Importantly, the SIZ moved closer to the terminal tip when we pharmacologically mimicked inflammatory conditions. These plastic changes in the location of SIZ could underlie inflammatory-induced increase in pain.

Advisor: Prof. Alex Binshtok

The first human subject with a loss-of-function mutation in TRPV1: Implication on the in vivo function of TRPV1 in human

Rachel Zaguri

The Transient Receptor Potential Vanilloid 1 (TRPV1) channel is one of the most researched and targeted proteins due to its role in mediating inflammatory pain and itch. It is expressed in a subset of nociceptive neurons and is activated by variety of noxious stimuli. Typical activators include heat (>42oC), low pH, proinflammatory mediators and natural irritants such as capsaicin, the pungent ingredient of hot chili pepper. Here, we examined an 8-year-old patient, who consumes hot chili pepper without any taste aversion or tearing. Whole exome sequencing revealed a single nucleotide alteration, which causes a novel missense mutation in a conserved amino acid residue at the N'-terminal of TRPV1 channel. To examine the effects of the mutation on the TRPV1 function, we generated inducible stable cell lines expressing the native wild-type channel (hTRPV1WT) or the TRPV1 mutant channel (hTRPV1mut). Application of the known activators of TRPV1, capsaicin, low pH, heat and the tarantula DkTx toxin resulted in robust hTRPV1WT activation but had no effect on the expressed hTRPV1mut channel. Biochemical analysis revealed proper tetrameric assembly and plasma membrane localization of hTRPV1mut, suggesting that this is the first identified complete loss-of-function TRPV1 mutation found in a human patient. To reveal the effect of a non-functional TRPV1 channel in humans, we performed series of psychophysical sensory test examinations. General physical examination showed that the patient fits the normal growing curves with no apparent health problems. Taste examination revealed normal sensitivity to four taste modalities; sweet, sour, bitter and salty but total insensitivity to capsaicin. Quantitative sensory testing revealed highly reduced sensitivity to heat but normal mechanical hyperalgesia and sensitivity to noxious cold. Strikingly, skin application of mustard oil (AITC), which mimics neurogenic inflammation, induced a pronounced mechanical and thermal allodynia, contrary to results of similar experiments performed on TRPV1-KO mice. To conclude, this study is expected to promote our understanding on the participation of TRPV1 in human pain physiology and help develop new specific and effective TRPV1 antagonists for pain treatment.

Advisor: Professor Baruch Minke

Dissociable Actor-Critic Roles of Ventral Pallidal Neurons in the Basal Ganglia

Alexander Kaplan

The ventral pallidum (VP) in non-human primates is anatomically separated from the external segment of the globus pallidus (GPe) by the anterior commissure. The VP is commonly viewed as part of the limbic circuitry of the basal ganglia (BG) and is heavily studied in the contexts of reward and addiction.
Prominent reinforcement learning models regard the BG network as being composed of interacting actor and critic components. To explore whether the VP is part of the actor or the critic system, we recorded VP spiking activity and the activity of GPe cells (actor) and striatal cholinergic interneurons (TANs; critic) from monkeys engaged in a classical conditioning paradigm.
Here we report that VP neurons can be classified into two groups of persistent and transient cells. The persistent population displayed sustained activation in response to visual cue presentation. In addition, the spiking activity of these neurons was uncorrelated. In sharp contrast, the transient VP cells displayed phasic responses to cue presentation and exhibited correlated spiking activity. Moreover, the discharge rate of these neurons was correlated with the learning rate of the monkeys during the task, analogously to the discharge of TANs.
These findings shed new light on the computational physiology of the BG, and particularly the VP, which should not be regarded as merely the ventral, limbic extension of the GPe. Namely, the persistent VP neuronal population is functionally similar to the GPe and is part of the actor, whereas the transient VP population belongs to the BG critic system.

Advisor: Prof. Hagai Bergman

DORA The Explorer: Learning What and How to Explore

Lior Fox

Whether it is animals, humans, or artificial agents, the need for exploring one's environment is a fundamental part in learning a behavioral policy attempted to achieve some goal. Without it, a best policy or even just good policies may never be tried. However, what would be an effective way of finding these good policies?
We study these questions in the framework of Reinforcement Learning (RL). There are two important aspects required for effective exploration. First, it needs to prioritize the learning of more valuable states and actions; second, it has to be directed towards the state-actions less explored, for reducing the agent's missing knowledge.
The first requirement has been typically addressed by utilizing action-selection functions that stochastically prefer the seemingly more profitable actions. The second requirement has been partially addressed by combining visit counters, a measure of the exploration "return", with the estimated values in the action selection. However, major limitation of counters is their locality, i.e., they do not account for the exploratory long-term consequences of actions. This problem of propagating exploration resembles the challenge of estimating the value-function, which need represent not only the immediate reward, but also the temporally discounted sum of expected future rewards. While there are a few solutions to this difficulty in model-based RL, a model-free approach is still missing.
We propose E -values, a novel generalization of counters that accounts for the exploratory long-term consequences of actions. We show how E -values can be learned on-line, analogously to the learning of value functions: either directly (by a "look-up table") for small/discrete problems, or by function-approximation techniques (such as deep neural networks) for large or continuous problems. In addition, we analyze the relation between stochastic and deterministic action-selection, showing how stochastic rules can be "determinized" by using counters. Our Directed Outreaching Reinforcement Action-selection (DORA) scheme unifies all these ideas, and we show that it can outperform other commonly used RL techniques in hard exploration problems, including the Atari 2600 Freeway game.

Advisor: Prof. Yonatan Loewenstein

Neural implementation of an adaptable Bayesian prior for sensory-motor behavior

Timothy R. Darlington

Nearly all sensory-motor behaviors are guided by a complex interaction between expectation based on past experience and sensory information. This interaction has been well modeled by the Bayesian framework in which expectation is the “prior”, sensory information is the “likelihood”, and the interaction of the two derives the “posterior”, which guides behavior. While the Bayesian framework seems to explain behavior quite well, our goal is to understand how the operation of neural circuits give rise to adaptive Bayesian-like behavior. Previous work has shown that the smooth pursuit eye movement system utilizes an adaptable Bayesian prior for visual motion speed, that this Bayesian prior could be implemented by controlling the gain of visual-motor transmission, and that the smooth eye movement region of the frontal eye fields (FEFSEM) plays a major role in visual-motor gain control. Therefore, we recorded single units in the FEFSEM of rhesus macaques while they pursued moving visual targets. To manipulate the expectation of the pursuit system, we controlled the statistics of target speeds that the monkey experienced. During a fast context, 80% of the trials presented target speeds of 20 deg/s and 20% at 10 deg/s. During a slow context, 80% of the trials presented target speeds at 2 deg/s and 20% at 10 deg/s. To manipulate the strength of sensory evidence, we presented targets of high- (strong visual motion) and low-contrast (weak visual motion). The eye speed in response to the 10 deg/s target motion is faster in the fast context and slower in the slow context. Consistent with the principles of Bayesian inference, eye speed is modulated more by context for the low- compared to the high-contrast target. FEFSEM preparatory activity tracks the statistics of target speeds and therefore encodes the prior. Preparatory activity combines with visual-motion signals in a Bayesian-like manner to set the output of FEFSEM during pursuit initiation. Finally, the output of FEFSEM during pursuit initiation is sufficient to account for both the behavioral effects of speed context and target-contrast and the updating of the prior. We conclude that Bayesian-like behavior is accomplished in the smooth pursuit eye movement system by co-opting neural mechanisms in place for a different purpose, the control of visual-motor gain.

Advisor: Dr. Stephen G. Lisberger

Cerebellar circuit mechanisms for coordinated locomotion in mice

Megan Carey
Champalimaud Centre for the Unknown

Even relatively simple actions like walking require precise coordination of movement across the body. While the cerebellum is known to be critical for whole-body coordination, the circuit-level mechanisms responsible for coordinating movement remain poorly understood. In this talk I will describe our efforts to understand cerebellar circuit contributions to coordinated locomotion. We have developed an automated, markerless 3D tracking system (LocoMouse) to establish a quantitative framework for locomotion in freely walking mice (Machado et al., eLife 2015). Analyzing the locomotor behavior of visibly ataxic mice with cerebellar defects has revealed specific, cerebellum-dependent features of locomotor coordination that suggest that cerebellar ataxia results from an inability to predict the consequences of movements across the body. In current experiments we are testing this idea by investigating neural circuit mechanisms of locomotor learning, in which mice adapt their locomotor patterns to achieve a more symmetrical gait while walking on a split-belt treadmill. This approach is providing insight into how the highly stereotyped cellular architecture of the cerebellum supports a wide variety of behaviors, from relatively simple forms of learning to complex feats of coordination.

Posters
Abstracts

Astrocytes involvement in recent and remote memory

Adar Adamsky

Astrocytes were recently shown to monitor and directly modulate neuronal activity in their domain, and are therefore necessary for synaptic plasticity, the infrastructure for memory formation and stabilization. However, the majority of astrocyte research was conducted on a single cell level, and only few studies have directly investigated the role of astrocytes in cognitive functions in behaving animals. Here, we employ a novel chemogenetic tool to specifically manipulate astrocytic activity, in conjunction with behavior and histology, and examine their role in memory formation, consolidation and retrieval. The synthetic Gi-Coupled receptor hM4Di was selectively expressed in hippocampal CA1 astrocytes, allowing specific disruption of their activity by a designer drug. Gi-pathway recruitment in hippocampal astrocytes during memory acquisition resulted in intact recent recall one day after learning, but severely impaired remote recall one month later. Furthermore, this hippocampal astrocytic manipulation during acquisition resulted in decreased cFos levels in the anterior cingulate cortex, a region known to be involved in remote memory. These results suggest that astrocytes might affect long-distance communication between hippocampal and frontal memory ensembles, consequently affecting remote memory.

Advisor: Dr. Inbal Goshen

Predicting latency of visual evoked responses using structure of white-matter pathways

Shai Berman

Macro-level white-matter brain connections play a major role in brain function and human behavior. The white-matter fibers' main function is to conduct electrical signals between brain regions. The fibers connect cortical and non-cortical regions, forming networks which are necessary for cognitive functions and normal development. To this day, empirical studies of white matter in vivo have evaluated focused either on structural properties on of conduction properties, rarely both. Being able to explain temporal delays in the measured electrical signal using the structural properties of the long-range white-matter connections, could contribute to our understanding of the white-matter role in normal behavior and development, in disease, and its potential role in computation by neural networks.

In this work I test whether the variation in conduction properties along white-matter fibers can be explained by the variation in the fibers' microstructure. I use data collected by our colleagues Prof. Kaoru and Dr. Takamura from CiNet, Japan (N=20). I used the diffusion MRI and anatomical MRI to calculate microstructure properties of the optical pathway (i.e., Optic Tract and Optic Radiation). For the functional data I use the signal recorded with magneto-electroencephalography (MEG), as the subjects view checkerboard stimuli, which evokes a V1 response.
To relate the two sets of measurements (functional MEG and structural MRI) I use a biophysical model of signal conduction in the human white-matter. The model is based on the abundant literature describing signal conduction as a function of the fibers' structural parameters, and translated onto the in vivo measures.

Preliminary results suggest that the microstructure properties measured with MRI do partially explain the latency of the visual evoked responses. These results raise the question of whether the prediction could be improved with better resolution, more advanced modelling, or a different biophysical model. Addressing these questions may help to further explain dependencies of human behavior and function on white matter properties.

Advisor: Dr. Aviv Mezer

Auditory cortex drives discriminations of complex but not simple sounds

Sebastian Ceballo

An important goal of auditory neuroscience is to link sound representations in auditory cortex (AC) with auditory perception, which can be accessed in animals through different behavioral tasks. This however requires the behavioral tasks to be causally driven by AC neurons in a necessary and sufficient manner. Yet there exists no auditory task for which both necessity and sufficiency of AC are established. Using for the first time a full bilateral optogenetic AC silencing, calibrated in vivo, we show that AC is not necessary for Go/NoGo pure tone discrimination task down to 0.5 octave frequency differences, but that it is required for discriminating a pure tone from a chirp starting at the same frequency. To better understand this result, we then used patterned optogenetics to drive precise sub-ensembles of auditory cortex neurons. We first showed that mice can discriminate two patterns of light stimulation in AC, however their response latency was much larger than for the pure tone task, suggesting that AC can drive decisions but with a long delay and thus can be bypassed sub-cortically for simple tasks. In contrast, the chirp versus pure tone task is solved with larger latencies, compatible with the optogenetically-driven cortical task. In addition, catch-trials combining the pure tone (No-GO cue) with unilateral focal stimulations at tonotopically defined locations of AC biased the perceptual decision towards the chirp (Go cue) response. This effect was absent in pure tone tasks. The subset of tonotopic locations driving behavior was consistent with psychophysical measurements of the spectral cues used by the animal to solve the task. Thus AC information contributes to drive auditory-based decision only in complex tasks involving long responses delays. This result suggests that sound perception requires co-activation of cortical and subcortical pathways, and opens a new perspective for the central engineering of artificial percepts.

Advisor: Dr. Brice Bathellier

Model-free dopamine engages in a positive feedback loop with freezing to prevent model-based extinction of fear

Lili X. Cai

Dopamine is known to enable rewarding associations, but its role in aversive associations is unclear. To address this question, we used fiber photometry and optogenetics to record and inhibit dopamine neurons during auditory fear extinction in mice, which involves exposing mice to a tone that was previously paired with a foot shock and observing the gradual decrease in fearful freezing behavior. We find that all dopamine neurons in the ventral tegmental area (VTA) and some in the substantia nigra pars compacta (SNc) encode a positive prediction error during offset of the tone, which correlates with both trial-by-trial freezing and change in next-trial freezing. Inhibiting the positive prediction error in the medial VTA leads to increased freezing during the tone, while inhibiting the lateral VTA leads to decreased freezing during the tone and inhibiting the SNc leads to decreased freezing during the inter-trial interval. This suggests that the medial VTA plays a model-based role in updating the tone-shock association to enable fear extinction, while the lateral VTA plays a model-free role in directly reinforcing freezing to oppose fear extinction. Since animals with higher freezing also show higher reinforcement signals, this suggests freezing and dopamine engage in a positive feedback loop which further slows fear extinction. This work has impact for three reasons: first, we show that fear extinction is an instrumental process, and debunk its historical categorization as a Pavlovian process. Second, we show that aversive extinction uniquely provides a behavioral method for distinguishing between model-based and model-free representations, which was typically only distinguishable in computational models which focused on appetitive learning. Finally, we introduce evidence that dopamine is a major contributor to cue-triggered disorders such as post-traumatic stress disorder (PTSD): lateral VTA dopamine reinforces maladaptive behaviors and prevents extinction, while SNc dopamine reinforces non-cue specific perseveration of the maladaptive behavior.

Advisor: Dr. Ilana Witten

The Connection Between Repeats, Transcriptional Activity, and Neurodegenerative Disorders

Lea Cohen

Many genes in the human genome contain long tracts of trinucleotide repeats (TNR), resulting, when the repeat is inside the coding region, in proteins containing amino acid (AA) repeat tracts. Since TNRs are more common in the coding region of genes, it was suggested that they are functional, and that their function is related to transcription. While many different amino acids occupy repeat tracts inside human proteins, only Glutamine (Q) and Alanine (A) repeats are reported to cause neurodegenerative diseases. Our present research is addressing the possible function and the regulation of repeat-containing genes focusing on TNR expansion diseases.
Analyzing available datasets, we identified groups of proteins which contain polyAA tracts and tested whether proteins containing longer repeats share a common function. We found that proteins which contain repeat tracts are significantly enriched in Gene Ontology (GO) terms associated with transcriptional activity. For proteins which contain repeat tract of polyA/H/P/Q groups, the involvement in transcriptional activity was also conserved in mice. We then focused on transcription factors (TFs) and found that TFs are significantly enriched in repeat tracts in both humans and mice. By analyzing available ChIP-seq datasets in human embryonic stem cells (BindDB; http://bind-db.huji.ac.il), we found that repeat-containing genes are enriched with binding of TFs to their promoters. Several significantly enriched TFs may play a role in regulating the expression of the repeat-containing genes. We are currently testing their potential function, as well as exploring how transcription might be involved in expansion of TNRs resulting in polyQ and polyA disorders.

Advisor: Prof. Eran Meshorer

Striatal action-value neurons reconsidered

Lotem Elber-Dorozko

It is generally believed that during economic decisions, striatal neurons represent the values associated with different actions. This hypothesis is based on studies, in which the activity of striatal neurons was measured while the subject was learning to prefer the more rewarding action. Here we show that these publications are subject to at least one of two critical confounds. First, we show that even weak temporal correlations in the neuronal data may result in an erroneous identification of action-value representations. Second, we show that experiments and analyses designed to dissociate action-value representation from the representation of other decision variables cannot do so. We suggest solutions to identifying action-value representation that are not subject to these confounds. Applying one solution to previously identified action-value neurons in the basal ganglia we fail to detect action-value representations. We conclude that the claim that striatal neurons encode action-values must await new experiments and analyses.

Advisor: Prof. Yonatan Loewenstein

Disentangling the contributions of brain tissue fraction and composition to quantitative MRI

Shir Filo

Introduction: In-vivo quantitative MRI (qMRI) aims at characterizing the structural and biological properties of brain tissue. However, as water content governs MR signal intensity, qMRI relaxation parameters are influenced by both the underlying variability in water content and the specific tissue composition. Water content can be estimated using qMRI. This measurement, along with its complementary the lipid and macromolecular tissue volume (MTV), are independent of tissue composition. Here we introduce a novel method that exploits the MTV quantification to overcome the confounding effect of water content on qMRI parameters and reveal tissue-specific properties. To this end, we propose to estimate the local linear dependency of qMRI parameters on MTV. This estimation provides a new transformation of qMRI measurements that enhances their sensitivity to the lipid and macromolecular content. First, we show that our approach can separate between phantoms containing different lipid compositions. Next, these novel qMRI contrasts were estimated in the human brain. We found unique tissue signature for different brain regions, along with age-related alterations.
Methods: Phantoms: We prepared liposomes with different phospholipid compositions and varying water concentrations. The phantoms were scanned using the same protocols used for the human subjects. Human subjects: 15 healthy volunteers (10 under 30, 5 over 55) were scanned on a 3T MRI scanner for multi-parametric mapping: MTV and R1, MT saturation (MTsat)7, R2*, R2 and diffusion imaging.
Results: We found linear dependency of qMRI parameters on MTV in phantoms with different phospholipids. This linear dependency changes as function of the phospholipid content. In addition, each qMRI parameter demonstrates a different sensitivity to the molecular composition. In agreement with the lipid phantoms, we also found a linear relationship between qMRI parameters and MTV in the human brain. Different brain regions exhibit distinct dependencies on MTV, that can be quantified by the slope of the linear fit. This slope is conserved across subjects. Moreover, each qMRI parameter presents a different slope compared to MTV. Thus, by combining the local dependencies of different qMRI parameters on MTV, a unique signature for different brain regions is revealed. In addition, the dependency of qMRI parameters on MTV change with age. We compared the tissue signatures of different brain regions between younger (under 30) to older (over 55) subjects. Our preliminary results demonstrate that these signatures reveal region-specific age-related changes.
Conclusion: We present a novel approach that strengthens the link between qMRI parameters and the underlying tissue characteristics. By expanding this framework to other qMRI parameters, we may be able to reveal a unique signature of various processes in the normal and diseased human brain.

Advisor: Dr. Aviv Mezer

Bursting Like it Counts: Emergence of burst activity in pyramidal cells, on bottom-up and top-down synaptic parameters, and implication for information processing

Eilam Goldenberg

Spike bursting of cortical pyramidal neurons is a sparse phenomenon compared to general spiking or silent neurons that is dependent on the dendritic Ca^{2+} spike. More specifically, high frequency bursts depend on the Na^{+} -dependent backpropagation AP that, when coincides with excitatory dendritic input it activates a nonlinear calcium mechanism (the BAC firing). This effect is thought to detect temporal coincidence between the bottom-up input that impinges on the basal tree (generating a single Na^{+} somatic spike) and the top-down input impinging on the distal apical tuft. The BAC firing is therefore assumed to contribute to: (i) Conserving two separate input streams to be transmitted by a single information channel; (ii) Maximizing information transfer by bursting selectively and maintaining selectivity from input to output; (iii) Tagging synapses to be kept in pruning. In this preliminary study we set to test what are the critical parameters for generating an axonal burst, and how they might serve information processing in cortical neurons. We used experimentally-constrained detailed nonlinear biophysical model of L5 pyramidal neuron, with random synaptic input with a set of confined parameters. We examined how the apical-basal synaptic ratio, the time delays between basal and apical synapses and synaptic clustering on dendrites impact the bursting behavior of the modeled cell. We found that the highest spikes per burst result from a 2:3 apical-basal ratio, and that fewer basal synapses decrease the burst probability. Furthermore, burst rate is maximal when basal synapses are active 20ms after apical. Lastly, small clusters of few synapses are optimal for burst firing. These findings support the notion that neurons emphasize selective responses to narrow input parameters with bursts.
These experiments show a combination of parameters that allows bursting, with highest spikes per burst in one parametric subspace. Our currently limited results show promise in connecting a cellular biophysical function with a fine-detail information manipulation, and perhaps later with the precise timing of the presynaptic network.

Advisor: Prof. Idan Segev

Multi-colored single-molecule fluorescence in-situ hybridization reveals complexity of neural ensemble representation of experience

Ben Jerry Gonzales

Long-term information coding in the nervous system requires temporally defined waves of induced transcription, the earliest of which is comprised of immediate early genes (IEGs). Individual IEGs are widely used to identify neuronal ensembles recruited by distinct salient experiences, with the assumption that different IEGs are co-expressed within ensembles encoding a common experience. However, this assumption has not been tested. We set out to address this notion and to investigate the complexity of neural ensembles recruited by distinct experiences.

We have previously observed that different experiences are encoded by unique and robust transcriptional responses, and identified subsets of IEGs sufficient to unambiguously decode the recent salient experience of an individual mouse. To identify the spatial expression within tissue, we performed RNA In-Situ Hybridization (RNA ISH) against robustly induced candidate IEGs following the rewarding experience of acute cocaine. We found that induced expression maps to sub-regions within defined brain nuclei of the reward circuitry. Within the striatum (Str), robust expression was localized to the dorsomedial (DM) and ventrolateral (VL) regions. To address whether induced IEGs co-localize in discrete populations with a common functional role, we utilized multi-colored single-molecule fluorescence ISH to compare induction within the two major neuronal populations of the striatum (D1R and D2R expressing neurons), known to have opposing roles in behavior, following acute and repeated cocaine. Strikingly, analysis of overlapping induced transcription of candidate IEGs including Egr2, cFos, Arc and Nr4a1, revealed specific enrichment in D1R- but not D2R- expressing neurons of the VL-Str. Conversely, in the DM-Str similar ratios of D1R and D2R expressing neurons were recruited according to induced IEG expression. Interestingly, following repeated cocaine the induction size in the vlStr shrunk compared to acute cocaine, whereas in the DM-Str the induction size remained constant but was induced from a lower baseline.

These results show that salient experiences induce unique spatially defined transcription signatures, recruiting specific neuronal ensembles. However, these data also imply that neuronal ensembles defined in this manner can be comprised of cells with opposing functionality, revealing unaddressed complexity of neuronal ensembles recruited in salient experiences. Precise manipulation of identified genes and defined engaged neuronal ensembles may determine novel and precise roles in memory formation underlying the development of adaptive behavior.

Supervisor: Dr. Ami Citri

Destructive circuit remodeling mediates neurogenesis-induced forgetting

Axel Guskjolen

Neurogenesis causes forgetting of previously acquired hippocampal-dependent information (Akers et al. 2014). To explain this phenomenon mechanistically, we have theorized that as newborn neurons form synaptic connections, they necessarily remodel the circuitry upon which hippocampal memories are dependent. This 'destructive remodeling' of the circuit would reduce the probability that a given environmental cue will reactivate the specific pattern of neural activity that mediates successful memory retrieval, culminating in forgetting (Frankland et al. 2013). Several predictions follow directly from this model. First, neurogenesis-mediated forgetting should correspond with less overlap between the neuronal ensemble that underlies memory encoding and that which underlies memory retrieval. Second, suppressing the capacity of immature neurons to remodel surrounding neural circuitry should alleviate the observed forgetting phenotype (i.e. hypo-remodeling should block forgetting). And third, the propensity of newborn neurons to cause forgetting should increase by enhancing the extent to which they remodel the surrounding circuit (i.e. hyper-remodeling should cause forgetting). Several transgenic mouse lines were used to test these predictions. First, arc-creERT2 x tdTomato mice were used to permanently 'tag' the engram and examine the probability of its reactivation following memory retrieval. To test whether suppressing circuit remodeling inhibits neurogenesis-mediated forgetting, nestin-creERT2 x Rac1 and nestin-creERT2 x Cadherin9 mice were used. And finally, to test whether upregulating circuit remodeling increases rates of forgetting, nestin-creERT2 x Sema5a and nestin-creERT2 x ChR2 mice were used. Results were consistent with the hypothesis that neurogenesis causes forgetting by remodeling the circuitry within which memories are embedded. Together, this work helps uncover the mechanism through which hippocampal neurogenesis causes forgetting, and perhaps how forgetting occurs more generally.

Advisor: Dr. Paul Frankland

Cerebellar Climbing Fibers can Signal Learned Sensory Prediction Errors

Jake Haffley

Classical models of cerebellar learning posit that climbing fibers operate according to a supervised learning rule to instruct changes in motor output by signaling the occurrence of movement errors. However, recent evidence has challenged this view by suggesting that climbing fiber-driven complex spiking can exhibit characteristics consistent with a reinforcement learning rule after the acquisition of learning in an aversive conditioning paradigm. To test whether sensory prediction error provides a generalizable model to explain the behavior of climbing fibers (CFs) in other behavioral paradigms and across other cerebellar regions, we have adapted a different classical conditioning paradigm that utilizes an appetitive stimulus to evoke CF inputs to Purkinje cells of superficial lobule simplex. Specifically, we have measured CF activity in a behavioral paradigm where head-fixed mice learn to associate a visual cue with an upcoming reward. In this regime, we have used a combination of mesoscale, single-photon imaging and resonant scanning two-photon imaging of virally expressed GCaMP6f in Purkinje cells, and measured CF activity both at the population level and within individual Purkinje cell dendrites across multiple learning sessions. This approach also allows us to measure CF input to the same neurons both before and after learning. Data from both single and multiphoton imaging sessions suggest that climbing fibers can signal learned prediction errors, suggesting a revised model of cerebellar learning for some behaviors where a reinforcement learning rule is appropriate.

Advisor: Dr. Court Hull

Deep Multitask Learning for Transition-Based DAG Parsing

Daniel Hershcovich

We train a transition-based DAG parser on multiple semantic parsing tasks. In a multitask setting, we observe improvements on a low-resource task, Universal Conceptual Cognitive Annotation parsing, using other schemes as auxiliary tasks.

Despite various divergences between linguistic semantic representation schemes, there are many commonalities both structurally and in terms of semantic content. We convert these schemes into a unified format and investigate how the similarity between different tasks is related to the contribution of using one as an auxiliary task for another.

Given similar tasks, an LSTM-based neural network is able to generalize using a shared representation, and effectively gains more training data for the low-resource task, which yields an improvement in parsing accuracy.

Advisors: Prof. Ari Rappoport and Dr. Omri Abend

Modulation of Spontaneous Pallidal Beta Oscillations by Acute Up- and Down- Manipulation of Dopamine Tone in Behaving Monkey

Liliya A. Iskhakova

Increased synchronization of neuronal activity in the beta frequency band, especially within the basal ganglia (BG), has been found in patients with Parkinson's disease (PD). This beta activity can be suppressed by dopaminergic medication. Beta synchronization has also been detected in the chronically dopamine depleted MPTP-treated animal models of PD. This suggests that the dopamine tone could be responsible for the expression of beta oscillations.

To further elucidate this hypothesis, we aimed to examine whether acute changes in dopaminergic tone could affect expression of beta synchronization. Increases and decreases in dopaminergic transmission were induced by injecting dopamine agonists: amphetamine and apomorphine, and a dopamine antagonist: haloperidol into awake and behaving primates. Brain activity and behavior were recorded before and after administration.

In total 1,456 pallidal cells, recorded over 116 days were included in the analysis. Initial results show shifts in the average frequency of beta peaks and variability in the beta peak range after drug injection, with a significant haloperidol-induced reduction in peak frequency and variability. As expected, haloperidol induced dopamine suppression led to an increased expression of beta synchronization, however this phenomenon was accompanied by a decrease in the percent of cells exhibiting beta activity.

Cell cluster analysis is planned to dissect the differential effect of dopamine inhibition on pallidal cell populations. A thorough examination of beta synchronization responses to acute dopamine up- and down- modulation will provide vital clues about the BG neurotransmission and the nature of the relationship between beta synchronization and dopamine tone.

Advisor: Prof. Hagai Bergman

Population codes, trees and shapes

Alejandro Jimenez Rodriguez

Abstract: In recent years, the use of dimensionality reduction for analysing neural population data has become widespread among theoreticians and experimentalists altogether. PCA is a well studied method for multivariate analysis that is often used for that purpose. Being based in a fundamental transformation of hermitian matrices, it is part of a rich theory that is still under construction; as such, many aspects of the results are not well understood yet. Two of those aspects are, the structure of the components of the eigenvectors and the geometry of the trajectories obtained from the application of this method to estimated firing rates. The former is the source of one of the most common criticisms to the method, that is, the principal components being not independent. The later, is obscured by this non-independence. In this work, using some theoretical tools from combinatorics and related fields, I give an interpretation of the coefficients that aims to untangle some information about the ensemble structure in the population and, consequently, provide an informed reading of different aspects of the intrinsic geometry of the trajectories and the space itself in which they evolve in. I illustrate my results with real data measured in the basal ganglia of rats performing a go/no-go/stop task.

Advisor: Dr. Robert Schmidt

Exploring the effect of NE on dendritic Ca2+ spikes and plasticity through knockdown of Alpha2A adrenoceptor in L5PCs

Adi Kaduri Amichai

Previously we have shown that pharmacological application of guanfacine (an Alpha2a adrenoceptor agonist) increases the excitability of the apical tuft of layer 5 pyramidal neurons (L5PCs) in barrel cortex in vivo. Here we test the specificity of this mechanism by manipulation of the availability of the Alpha2a adrenoceptor specifically in these neurons. We have constructed a custom made AAV cre-dependent viral vector of shRNA to knockdown the alpha2A adrenoceptor. We express this shRNA and a scrambled version in RBP4-cre mice (expressing cre in a subpopulation of L5PCs). We use two photon imaging to measure the Ca2+ activity in the dendrites of the apical tuft while applying the agonist and compare the responses between neurons expressing the active shRNA and those expressing the scrambled version.
The effect of blocking Ca2+ activity in dendrites suggests that NE may have an important role in synaptic plasticity in the tuft of pyramidal neurons. Future experiments will use this tool to explore this direction.

Advisor: Dr. Mickey London

Notochord-derived Sonic hedgehog released into the sclerotome plays a major role in CNS development

Nitza Kahane

Sonic hedgehog (Shh) is necessary both for neural and mesodermal development. We report that Shh that is released from the notochord into the sclerotome constitutes a common pool of ligand for both tissues. Depletion of Shh in sclerotome by a membrane-tethered version of hedgehog-interacting protein significantly reduced motoneuron numbers, expanded Pax7 expression in the neural tube and affected myotome differentiation. These effects were a direct consequence of reducing Shh ligand. By gain and loss of Shh function, and by floor plate deletions, we show that the sclerotome constitutes a dynamic pool of notochord-derived Shh and that sclerotomal Shh is able to shuttle from mesoderm to neural tube. In addition, grafting notochord fragments in a basal, but not apical location vis-a-vis the neural tube, profoundly affected motoneuron development, suggesting that initial ligand presentation occurs at the basal side of epithelia corresponding to the sclerotome-neural tube interface. Together, our results show that Shh is able to act across tissues, and uncover the sclerotome as a previously unknown common pool of Shh that promotes development of both mesodermal and neural progenitors.

Advisor: Prof. Chaya Kalcheim

Acoustic Calibration in an Echoic Environment

Alex Kazakov

The sound fed to a loudspeaker may significantly differ from that reaching the ear of the listener. The transformation from one to the other is mainly affected by reflections and reverberations, resulting in spectral distortions. These distortions depend crucially on the relative location of the speaker, location of the listener and the geometry of the environment. With the increased importance of research in awake, freely-moving animals in large arenas, it becomes important to understand how animal location influences the corresponding spectral distortions.

We describe a full calibration pipeline that includes spatial sampling and estimation of the spectral distortions. We estimated the impulse responses of the environment using Golay complementary sequences. The Fourier transform of the impulse responses is the transfer function which quantifies the spectral distortion caused by the reverberations. In our arena, the impulse responses are dominated by a small number of strong reflections, making the interpretation of the transfer functions straightforward. Finally, we use this understanding to provide guidelines for designing the geometry of the environment as well as the presented sounds, in order to provide more uniform sound levels throughout the environment.

We also describe an acoustic 3D localization method for freely moving animals. Volumetric tracking of objects is an open challenge in many fields, especially in neuroscience where additional constraints are imposed on the tracking device, such as low body mass of the animal and electrical noise minimization. Our method achieves a 1 cm precision by the utilization of sound cues only, also based on Golay complementary sequences. We demonstrate its usefulness by comparing video and acoustic tracking of a freely moving rat.

Advisor: Prof. Israel Nelken

Reward modulation in the simple spikes of purkinje cells in the flocculus complex are explained by the encoding of eye kinematics

Adi Lixenberg

The cerebellum is essential for normal motor control. Recently evidence have accumulated to suggest that reward information also drive activity in cerebellum. However, missing is a functional understanding of how do neurons combine the encoding of reward and motor parameters. We used the well-established relation between eye kinematics and the activity of neurons to test if reward is encoded beyond the movement parameters.

We recorded the simple spikes activity from purkinje cells in the cerebellar flocculus complex while we manipulated the reward size. We applied tasks in which the monkey used smooth pursuit movements to track a single target, selected between two targets and learned to select between targets. We found that the reward information was encoded in the simple spikes of the cerebellar neuron. We then used the link between the neural activity and the eye kinematics to interpret these activity modulations. We found that the reward modulations were explained by the differences in the eye kinematics.

Our results indicate the reward acts on the smooth pursuit eye movement system upstream to the purkinje cerebellar flocculus. The reward signals propagate through flocculus to drive eye movements.

Advisor: Dr. Mati Joshua

Heightened sensitivity to social exclusion in chronic MDMA users

Matthias S. Luethi

3,4-Methylenedioxymethamphetamine (MDMA, 'ecstasy') is one of the most widely used illegal drugs worldwide. Acute effects of MDMA include increases in empathogenic and prosocial feelings, and sociability. However, long-term effects of MDMA usage on social cognitive functioning have received little attention in research so far. The current study examined processing of social exclusion in abstinent, chronic MDMA users. Twenty-one MDMA users and 21 matched, MDMA-naïve control participants participated in a virtual ball-tossing game (“Cyberball”), while their brain activity was recorded with fMRI. In the course of the game, participants were excluded by their two co-players. In both groups, social exclusion activated areas related to social cognition, emotion, and emotion regulation, such as the anterior cingulate cortex (ACC), the inferior frontal gyrus (IFG), the medial orbitofrontal cortex, and the insula. MDMA users activated the ACC and the IFG more strongly than control participants. On behavioral measures, MDMA users did not report to feel more excluded than control participants. An objective measure of drug usage, as obtained by hair analyses, did not correlate with brain activity or behavioral measures in MDMA users. In sum, chronic MDMA users exhibited a heightened sensitivity to social exclusion. The absence of a dose-dependent effect suggests that abnormal social cognitive functioning might be a predisposing factor for, rather than a consequence of, MDMA abuse.
Keywords: MDMA, ecstasy, drug abuse, social cognitive functioning, social exclusion, cyberball, fMRI

Advisor at HUJI/ELSC: Prof. Leon Deouell
Advisor for this project: Prof. Boris Quednow

Title: Circuit-Specific Role of Ventral Hippocampal ΔFosB in Resilience to Social Defeat Stress

Claire E. Manning

The dorsal hippocampus (dHPC) is essential for spatial learning and memory, while ventral hippocampus (vHPC) appears to regulate emotional and motivated behaviors. vHPC efferents modulate reward circuitry and emotional behavior through projections to nucleus accumbens (NAc) and amygdala (BLA), and the vHPC-NAc circuit is critical for resilience to chronic social defeat stress (CSDS; Bagot et al., 2015). However, it is unknown how CSDS alters vHPC gene expression and function, and whether such alterations may underlie resilience. We find that multiple FosB gene products, including ΔFosB, are induced in dentate gyrus (DG), CA1, and CA3 of vHPC by CSDS or fluoxetine treatment. We show that general inhibition of ΔFosB function throughout the vHPC (but not dHPC) promotes susceptibility to subchronic (microdefeat) stress. We demonstrate a novel CRISPR-based method for circuit-specific genome editing, and use it to silence the FosB gene in specific vHPC projection cells. Importantly, we find that specific silencing of FosB gene expression in vHPC cells projecting to NAc promotes susceptibility to CSDS and reduces cocaine preference, while inhibition in vHPC-BLA cells reduces anxiety. Finally, we show that overexpression of ΔFosB in HPC cells reduces excitability. We therefore suggest that vHPC-NAc ΔFosB may drive the expression of genes critical for cell excitability and subsequent resilience to stress and/or antidepressant function.

Advisor: Dr. A.J. Robison

Involvement of rabbit claustral neurons in associative learning tasks

Maria del Mar Reus-García

The claustrum (CL) has been the subject of different theoretical studies about its role in integrative neural functions, including consciousness. Anatomical studies have revealed that the CL is a sheet-like neural structure located between the putamen and the insular cortex. CL neurons are originated from the insula. The CL sends projections and receive afferents from all cortical regions. Although it is assumed that CL neurons could be involved in cognitive processes and in the integration of different sensory-motor modalities, CL functions studied in alert behaving animals remain unknown. We have recorded in behaving rabbits the firing activities of CL neurons during the acquisition of a classical eyeblink conditioning task. Recorded cells were identified by their synaptic and/or antidromic activation from the medial prefrontal (mPFC) or motor (M1C) cortices of both sides. For conditioning, we used a delay paradigm: a tone as conditioned stimulus (CS) followed by an air puff as unconditioned stimulus (US) that co-terminated with it. Conditioned (CRs) and unconditioned (URs) responses were determined from the rectified electromyographic (rEMG) activity of the orbicularis oculi muscle. Neurons were recorded with glass and multiple metal electrodes across habituation and conditioning sessions. CL neurons were rarely activated by single stimuli of different sensory modalities (air puffs, tones, light flashes). In contrast, CL neurons were activated during sessions of paired CS-US presentations, and their firing was more active immediately after the acquisition of the CR. Neurons activated from the M1C were located more dorsally in the nucleus and presented different firing profiles than those projecting to the mPFC. Local field potentials recorded in the CL presented a characteristic ≈ 40-50 Hz oscillation during CS-US presentations. Electrical stimulation of the CL did not evoke any noticeable eyelid motor response even in trained animals. We developed recombinant adeno-associated viruses (rAAVs) equipped with chemically-controlled genetic switches for inducible and reversible silencing of synaptic transmission by expressing a novel destabilized tetanus toxin light chain in the two CLs of rabbits. Silencing of synaptic transmission of CL projecting neurons was effective to delay the acquisition of eyeblink CRs but did not evoke any significant effect on the rate of CRs in well trained animals. Interestingly, the total area of rEMG responses (both CRs and URs) was diminished when the claustrum was silenced during the first days of training. In conclusion, the CL seems to play an important role in the acquisition of associative learning tasks, mostly in relation to the novelty of CS-US association, but also in the expression of conditioned eyelid responses.

Advisor: Dr. José María Delgado-García

The Biophysical Perceptron

Toviah Moldwin

Since the seminal work of McCulloch and Pitts, it has been theorized that neurons perform a thresholded sum of their weighted synaptic inputs. This formulation of the input-output function of a neuron led to the discovery of the perceptron learning algorithm, which describes a simple procedure, similar to Hebbian learning, by which a neuron can update its weights in order to solve a classification task. While the perceptron learning algorithm and its multiple-layer analogue — the backpropagation algorithm — are the foundations of contemporary machine learning, there have been few attempts to explore whether perceptron-like learning can be implemented in a real neuron. Because real neurons have many properties not shared by simple MCP neurons, including a complex morphology, multifarious ion channels and receptors, and various nonlinear phenomenon due to passive neuronal cable properties, it is not trivial that a real neuron would behave similarly to a perceptron. In this work, we directly implement the perceptron learning algorithm in a detailed biophysical model of a layer 5 rat pyramidal cell and compare the computational capacity of the biophysical perceptron to that of a McCulloch and Pitts (MCP) perceptron. We demonstrate that while the biophysical perceptron can indeed learn to separate large numbers of patterns using the perceptron learning algorithm, the empirically observed capacity of the biophysical perceptron is smaller than that of the MCP perceptron, meaning that the biophysical cell needs more synapses in order to classify the same number of patterns as the MCP neurons. We argue that the primary reason for this discrepancy is the substantial attenuation of distal synapses, which are unable to affect the soma in a manner proportional to proximal synapses even as the learning algorithm attempts to increase the synaptic conductance to very high values. Our results indicate that while the perceptron learning algorithm is not a wholly inaccurate theory about how real neurons might learn, it is insufficient for understanding the role of tuft synapses.

Advisor: Prof. Idan Segev

The molecular basis underlying the transition between peripheral and central nervous system during development

Shai Ofek and Dina Rekler

Upon closure of the neural folds, the resulting dorsal midline region of the neural tube is generally termed the roof plate (RP). This domain is highly dynamic and complex being first transiently inhabited by prospective neural crest (NC) cells that sequentially emigrate from the neuroepithelium. Only later, it becomes the definitive RP, the dorsal midline cells of the spinal cord. We previously showed that at the trunk level of the axis, prospective RP progenitors originate ventral to the premigratory NC and progressively reach the dorsal midline following NC emigration. However, the molecular mechanisms underlying the end of NC production and formation of the definitive RP remain virtually unknown.

In a previous study we showed that the transition between NC and RP is associated with the end of responsiveness to BMP and the advent of Hairy1/Hes signaling, the latter inhibiting BMP activity and BMP receptor expression.

To better define the molecular differences between NC and RP progenitors, and as a basis for further functional testing, we performed a transcriptome analysis of cells at each stage using the CelSeq method adapted for low amounts of RNA. This analysis revealed the presence of about 1000 genes that were either down- or upregulated in RP when compared to NC. Several genes were further validated by in situ hybridization and functional analysis is already underway.

Among the salient family of differentially expressed genes, we found a decrease in cell cycle genes that is associated with the RP becoming a post-mitotic structure. Additionally, NC-specific genes such as FoxD3, Snail2, Dact2 were negative in RP. Reciprocally, Rspo1, BAMBI, Gdf7, Crabp1, etc were specifically upregulated in RP, thus generating a battery of differential molecules for further study.

Most notably, retinoic acid (RA) synthesis and regulation (Raldh2 and Cyp26a1) were unraveled in RP exclusively. Initial data reveal that, by abrogating RA signaling, BMP activity is maintained. This suggests that RA acts to end responsiveness to BMP, a key process required for NC to RP transition. Consistently, our data suggest that RA induces expression of Hairy1/Hes and of BAMBI, a BMP antagonist.

Together, these results begin to uncover a network of genes and gene interactions that mediate the transition between the peripheral and central branches of the nervous system.

Advisor: Prof. Chaya Kalcheim

Studying rat behavior in a complex auditory environment

Ana Polterovich

In order to survive, animals must be able to extract relevant information from the environment to predict what is going to occur next and plan their reactions appropriately. The natural environment follows certain patterns: certain configurations of sensory stimuli have significant behavioral consequences while others are not associated with any, and the temporal sequence of events may have behavioral importance. Animals must extract relevant information from the statistics of the environment to be able to maximize their reward accumulation.

We developed a rich behavioral environment, called the Rat Interactive Fantasy Facility (RIFF), where rats are challenged to extract rules about the environment using auditory clues, and receive rewards or punishments in accordance with their reactions to the sounds. Rat behavior is followed online using a combination of video tracking and reports for nose-pokes. Neural responses from the rat brain can be recorded using telemetry.

The RIFF implements a general Partially-Observable Markov Decision Process (POMDP). A state of this process is characterized by the reactions of the RIFF to any rat action (motion or noise poke) as well as by the transitions to the next state. Observability of the states is achieved by using the sounds, and partial observability can be manipulated for example by presenting ambiguous auditory cues. Importantly, we can construct POMDPs which have optimal policies, so that we can explicitly quantify behavioral optimality.

As an initial test of the concept, we show here data on a multiple arbitrary association task using human words as the auditory cues. When a rat approached an interaction area, it heard either a reward cue (in which case nose pokes were rewarded by food and water) or a neutral cue (in which case nose pokes were unrewarded, but not punished). These cues were different in each area. We followed the behavior of the rat while exploring the RIFF and learning these associations.

Advisor: Prof. Israel Nelken

In vivo tract identification using diffusion MRI tractography and quantitative MRI

Roey Schurr

Diffusion MRI (dMRI) tractography algorithms reconstruct streamlines that represent the underlying white matter (WM) fascicles, allowing to study the human connectome in vivo. Yet Grouping multiple streamlines together to identify a specific WM tract, and separating it from nearby tracts, is still challenging. Many fiber clustering methods are based on anatomical landmarks or fiber termination points, but these fiber properties are not well-captured by current tractography algoriths. A major source contributing to this difficulty is the inherent ambiguity in the dMRI signal. Different fascicle configurations can give rise to the same dMRI signal at the voxel level, and any local error in fiber tracking can propagate and lead to global effects in tractography results. More information is therefore required to disambiguate the dMRI signal and obtain a more accurate mapping of the long range WM projections.

The goal of this work is to test the hypothesis that tractography results can be optimized by introducing complementary information derived from other quantitative MRI (qMRI) measurements. Specifically, we used quantitative T1 mapping.

Here we show that T1 mapping can be used for accurate identification of specific WM tracts. For this aim we developed a method for qMRI-based tract identification. We showed that the vertical occipital fasciculus (VOF) and the nearby posterior arcuate fasciculus (pAF) can be separated based on their T1 profiles. Specifically, we identified the border between them as the point of sharpest increase in median T1 values along the posterior-anterior axis. We further tested the correspondence between the estimated cortical projections of the two tracts and three different cortical parcellations – functional, cytoarchitectonical and gyrification-based atlases.

Our results provide substantial evidence for benefits of using streamlines' T1 profiles both for delineating specific WM pathways.

Advisor: Dr. Aviv Mezer

Monitoring striatal cholinergic cell assemblies in awake behaving mice

Lior Tiroshi

The basal ganglia (BG) are a collection of forebrain nuclei involved in various aspects of motor control and habit formation. Cholinergic interneurons (ChIs) make up a tiny fraction of cells in the striatum, a main BG input unit, but they are key modulators of the canonical corticostriatal and thalamostriatal circuits. Importantly, ChIs are implicated in Parkinson's disease (PD), and anticholinergic therapy was an effective treatment for PD until it was supplanted by dopamine replacement therapy.

The striatum is widely viewed as essential for the selection of the appropriate motor plan during ongoing behavior. It is, however, largely accepted that the tonic activity of ChIs, as well as the stereotypical pause response that they exhibit, code for the value of the selected action rather than the movement itself. However, experiments supporting this claim were performed on animals that were both head-fixed and and over-trained in executing task related movements. It is possible that under these conditions ChIs have no role to play. If, however, animals were free to self-initiate their own movements, or if the movements were not so highly rehearsed, ChI activity might indeed be found to be movement-related.

We challenge this dogma by studying the collective activity of ChIs in the naturalistic setting of a freely-moving mouse. We perform endoscopic calcium imaging of dorsal striatum ChIs using genetically encoded calcium indicators. This novel experimental approach allows us to study the collective dynamics of ChI spontaneous activity as the mouse performs self-initiated movements. Our preliminary results show strong movement associated neural activation, consisting of somata lighting up on top of a neuropil activation background. Cell body fluorescence change, induced by bursting activity, is accompanied by activation of the background. Movement onset is followed by a progressive recruitment of cell bodies, with their activity showing a positive correlation. Background signals are highly correlated creating a "global mode", which is strongly associated with movement. These results suggest a close relationship between the bursting activity of ChIs and self-initiated movement.

Advisor: Dr. Josh Goldberg

State-Specific Neural Activity in the Medial Prefrontal Cortex and Hippocampus that Encodes Fear Learning and Extinction Behavior

Cong Wang

The medial prefrontal cortex (mPFC) and the hippocampus (HPC) have been shown to play an important role in modulating fear learning and extinction, processes that underlie many mental disorders, including post-traumatic stress disorder. Even though fundamental principles are known, the neural activity and connectivity of the subregions of the mPFC and the HPC during fear learning and extinction and how they encoding the corresponding behavior are not widely studied.

Tetrodes were implanted in the prelimbic (PL), infralimbic (IL) of mPFC and the dorsal CA1 of HPC in each male SD rat. Single-unit activity and local field potentials (LFP) were recorded simultaneously in freely-moving rats during fear learning and extinction to study dynamic activity patterns.

As expected, the conditioned rats showed a significantly increased freezing behavior in the early extinction phase when retrieving fear memory. In this high fear state, a rise in theta (4-7Hz) activity power in both the PL and IL was observed during the presentation of conditioned stimuli (CS). Also, these two prefrontal regions showed an elevated firing rate of single units at the onset of the CS presentation, suggesting that both regions are highly involved in CS-evoked fear expression. In low fear state, animals which were successfully extinguished showed a descending freezing rate in late extinction stage. Theta power increased in the HPC but decreased in the PL. Single unit analysis revealed lower firing rates in the IL and a higher level of synchronized theta oscillation between the IL and HPC, whereas the firing rates and synchronized theta oscillations between PL and HPC weren't changed substantially.

Here, we identified different discrete neural activity- and functional connectivity-patterns in and between the PL, IL and HPC during different behavioral states. It suggests that these investigated brain-regions all have separate roles but together form a dynamic local network to encrypt distinct behavioral modes.

Advisor: Prof. Pankaj Sah

An automatic solver for the Alternative Uses Test

Stav Yardeni

The Alternative Uses Test is a test used by Psychologists to assess creativity. In this test, participants state as many alternative uses as they can for given objects in a specified time frame. These uses can be also referred to as affordances. Our goal is to solve the Alternative Uses Test automatically using large amounts of data. Our approach involves a concept called “object replacement”: when given an object to find uses for, our algorithm looks for similar objects and their uses. Then, it suggests the uses of those similar objects as possible uses for the original object. For example, when the given object is a cup, our algorithm looks for similar objects, such as a vase or a bowl. It then suggests their uses as possible uses for a cup (put flowers in it, eat from it, etc.). This strategy was shown as one of the strategies human participants use when performing this task.
To find similar objects, we use both visual and textual representations of the objects: the visual representations are achieved using an object recognition neural network (VGG19 with ImageNet weights) and represent shape information. They are used in order to find similarly shaped objects, so that they offer relevant affordances. We use textual representations (Word2vec) to exclude objects which appear in a very similar context in the language, to ensure our suggestions are novel.
This work will enable us to compare a computer's performance to the per formance of humans and learn more about human creativity.

Advisor: Dr. Dafna Shahaf

Climbing fibers encode the size of the expected reward in monkeys

Merav Yarkoni

Theoretical and experimental studies of cerebellum have indicated that climbing fibers inputs to the cerebellar cortex encode a sensory prediction error signal that drives motor learning. Recently, evidence have accumulated to suggest that information about the reward also drives activity in the cerebellum. To test whether and how information about reward is encoded in the cerebellum we recorded the manifestation of the climbing fiber activity as complex spikes in the purkinje cells of the cerebellum. Monkeys were engaged in smooth pursuit eye movement task in which the color of the target indicated that size of the upcoming reward. We found that after the target changed color to cue the size of the reward, complex spikes firing rate was larger in trials that the monkey expected a large versus a small reward. By contrast, the complex spike rate was not modulated by the reward size at the end of the eye movement when the reward was delivered. The pattern of complex spike modulation was different from the pattern of licking that did not distinguish between reward sizes at the cue epoch but did strongly discriminate between the sizes of the reward at outcome delivery.

We conclude that the climbing fiber signal is modulated by reward. This signal is akin to the reward prediction error signal that was identified in the dopaminergic neuron in the basal ganglia. We suggest that this signal could instruct learning that was so far hypothesized to be accomplished outside of the cerebellum.

Advisor: Dr. Mati Joshua