ELSC
The Edmond & Lily Safra Center for Brain Sciences
מרכז אדמונד ולילי ספרא למדעי המוח

האוניברסיטה העברית בירושלים
The Hebrew University of Jerusalem

The ELSC Annual Retreat
KIBBUTZ EIN GEDI

January 26-28, 2014
Program & Abstracts

Lectures in English
ההרצאות תנתנה בשפה האנגלית

Organizing Committee:

Mickey London

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ELSC is grateful to all HUJI friends, who support brain sciences for many years, since The Interdisciplinary Center for Neural Computation (ICNC) was established. Their ongoing support led to the evolvement of ELSC – the Edmond and Lily Safra Center for Brain Science. We will always cherish their help.

ELSC RETREAT, EIN GEDI
PROGRAM
January 26-28, 2014

Sunday, January 26

9:00	Bus departing from Givat Ram Campus, main bus stop
11:00-11:35	**Roi Livni** **"***Computational algebraic geometric methods in semi supervised learning"* Advisor: Amir Globerson
11:35-12:10	**Matan Sorek** *"Associative learning in genetic regulatory networks"* Advisor: Eran Meshorer
12:10-12:45	**Michael Peer** *"Functional disintegration of the episodic memory network during transient global amnesia"* Advisor: Shahar Arzy
12:45-13:00	Lottery
13:00-14:00	Lunch & room allocation
14:00-14:45	Guest Lecturer **Sen Song** *"Increased boutons dynamics in aged animals"* IDG/McGovern Institute for Brain Research at Tsinghua University
14:45-15:20	**Itai Hershenhoren** *"Intracellular correlates of stimulus-specific adaptation"* Advisor: Israel Nelken
15:20-16:00	Panel 1 *"The Impact of behavioral training on cognitive and perceptual skills"* **Merav Ahissar, Amir Amedi, Udi Zohary**
16:00-17:00	Students/Faculty meetings
17:00-19:00	Poster session (refreshments)
19:00-20:45	Dinner
21:00	***Yosi Pollack & Zvi Fishzon: "The Brain of an Elephant"***
22:30	Wine, beer, cheese & posters

Monday, January 27

7:30-8:25	Breakfast
8:30-9:05	**Yael Shlomai-Fuchs** *"Parvalbumin interneurons underlie broad control of olfactory bulb output"* Advisor: Adi Mizrahi
9:05-9:50	Guest Lecturer **Daniel E. Shulz** *"Processing of complex tactile scenes in the somatosensory system of the rat: electrophysiological, imaging and computational approaches"* Director of Research CNRS - Sensory processing, Unit of Neuroscience, Information and Complexity
9:50- 10:05	Break
10:05-10:40	**Marc Deffains** *"Role of Basal Ganglia main axis in temporal* discounting" Lab: Hagai Bergman
10:40-11:15	**Lili Cai** ***"****Molecular-level functional magnetic resonance imaging of Dopaminergic signaling"* ELSC-RIS One Year Program
11:30-17:30	Desert Hike – Nahal Tze'elim
18:00-20:00	Dinner
20:00	Kumzitz - Social Activity

Tuesday, January 28

7:30-8:30	Breakfast & check out
8:30-9:05	Guest Lecturer **Ahmed El Hady** *"Non-invasive characterization of neurons with continuous dynamic photo-stimulation"* Max Planck Institute – Gottingen, Germany
9:05-9:50	Guest Lecturer **Zhiping Pang** *"Utilizing human neurons to study neuropsychiatric disorders"* Child Health Institute of New Jersey, Rutgers University Robert Wood Johnson Medical School
9:40-10:20	Panel 2 *"From bench to bedside"* **Adi Mizrahi, Hermona Soreq, Yosi Yarom, Shahar Arzy**
10:20-10:35	Break
10:35-11:20	Guest Lecturer **Mariano Sigman** *"The teaching instinct"* Integrative Neuroscience, Physics Dept., Buenos Aires University
11:20-11:45	**Ofri Raviv** *"Seemingly contradictory interval biases in discrimination tasks result from the influence of past stimuli on perception"* Advisors: Merav Ahissar & Yonatan Loewenstein
11:45-12:10	**Sagi Jaffe** *"The computational mechanisms underlying dyslexics' anchoring difficulties"* Advisor: Merav Ahissar
12:10-12:25	Break
12:25-13:00	**Uri Shalit** *"Modeling Influence and Innovation in Contemporary Music"* Advisor: Daphna Weinshall
13:00-13:30	Lottery results
13:30-13:40	Concluding remarks
13:40-15:00	Lunch
15:00	Return to Jerusalem

LECTURES

Computational Algebraic Geometric Methods in Semi Supervised Learning

Roi Livni

The study of supervised learning has seen great progress in recent years. However, it is commonly accepted that the supervised setting is very restrictive and does not capture the whole notion of ''learnability" as we see it. For example: In real life we do not have complete supervision (or labeled data) as in the classical supervised learning setting.

The theory of "Semi-Supervised Learning" (SSL) attempts to describe the phenomena where unlabeled data can help in classification tasks. While in practice it seems that unlabeled data may help, the theory often tends to be pessimistic and it seems that without very strong assumptions unlabeled data cannot help in classification tasks.

However, our recent results suggest that SSL does result in strong theoretical guarantees when learning rules that are related to algebraic manifolds. Furthermore, we have recently shown that learning the algebraic structure of data can be done efficiently. Taken together this means that the algebraic structure of the data is both learnable in an unsupervised manner and beneficial for supervised tasks.

We will outline these results, both theoretical and practical. We will then discuss the potential in constructing new- algebro-geometrically oriented algorithms that will benefit from unlabeled examples.

Advisor: Prof. Amir Globerson

Associative Learning in Genetic Regulatory Networks

Matan Sorek

It is generally believed that associative memory in the brain depends on multistable synaptic dynamics, which enable the synapses to maintain their value for extended periods of time. However, multistable dynamics are not restricted to synapses. In particular, the dynamics of some genetic regulatory networks are multistable, raising the possibility that even single cells, in the absence of a nervous system, are capable of learning associations.

Here we study a standard genetic regulatory network model with bistable elements and stochastic dynamics. We demonstrate that such a genetic regulatory network model is capable of learning multiple, general, overlapping associations. I will show that the capacity of the network is proportional to the square root of the number of bistable elements in the genetic regulatory network. I will then discuss the capacity of a clonal population of cells, such as in a colony of bacteria or a tissue, to store associations. I will show that even if the cells do not interact, the capacity of the population to store associations substantially exceeds that of a single cell.

Advisor: Prof. Eran Meshorer

Reversible functional connectivity disturbances during transient global amnesia

Michael Peer

Transient global amnesia (TGA) is a rare neurological phenomenon characterized by an abrupt disruption of memory capabilities, resulting in severe anterograde episodic amnesia accompanied by repetitive questioning. Despite extensive research, there is no clear evidence for the underlying pathophysiological basis of TGA. Moreover, there is no neuroimaging method to evaluate TGA in real-time. Resting state functional MRI has emerged in the recent years as a reliable technique for characterization of brain networks and detection of functional changes in brain connectivity. We used resting state functional MRI recorded in ten patients during the acute phase of TGA together with connectivity and cluster analyses to detect changes in large-scale brain networks in TGA. Our results show a significant reduction in functional connectivity of the episodic memory network during TGA, which is more pronounced in the acute phase of the disorder than in the post-acute phase. This disturbance is bilateral, and reversible after recovery. Clustering analysis indicates that while the hippocampus and its connections are significantly impaired, other parts of the episodic memory network are impaired as well. Similar results were obtained for the analysis of the episodic memory network whether it was defined in a data-driven or literature-based manner. These results suggest that TGA is related to a functional disturbance in the brain's episodic memory network.

Advisor: Dr. Shahar Arzy

Increased Boutons Dynamics in Aged Animals

Sen Song
IDG/McGovern Institute for Brain Research at Tsinghua University

Synaptic plasticity is considered an essential process for the formation and maintenance of memory. It had been assumed for decades that cognitive deficits within the aging brain result from reduced synaptic density and plasticity. By imaging axonal arbors and boutons in the aged brain, we surprisingly find the opposite, i.e., dramatically increased rates of synapse formation, elimination, and destabilization in specific cortical circuits. Our observation suggests that learning and memory deficits in the aged brain may arise not through an inability to form new synapses but rather through decreased synaptic tenacity. I will also describe other ongoing work in the lab.

Intracellular correlates of stimulus-specific adaptation

Itai Hershenhoren

Stimulus-specific adaptation (SSA) is the reduction in response to a common stimulus which does not, or only partially, generalizes to rare stimuli. SSA is strong and widespread in primary auditory cortex (A1) of rats, but is weak or absent in the main input station to A1, the ventral division of the MGB. To study SSA in A1, we recorded neural activity in A1 intracellularly using sharp electrodes. We studied the responses to tone pips of the same frequency in different contexts: as standard and deviants in oddball sequences, in equiprobable sequences, in sequences consisting of rare tone presentations, and in sequences composed of many different frequencies each of which was rare. SSA was found both in subthreshold membrane potential fluctuations and in spiking responses of A1 neurons. SSA for changes in frequency was large at a frequency difference of 44% between standard and deviant, and clearly present with tones separated by as little as 4%, near the behavioral frequency difference limen in rats. When using equivalent measures, SSA in spiking responses was generally larger than SSA at the level of the membrane potential. This effect can be traced to the non-linearity of the transformation between membrane potential to spikes. Using the responses to the same tone in different contexts made it possible to demonstrate that cortical SSA could not be fully explained by adaptation in narrow frequency channels, even at the level of the membrane potential. We conclude that local processing significantly contributes to the generation of cortical SSA.

Advisor: Prof. Israel Nelken

Dissecting local circuits: Parvalbumin interneurons underlie broad control of olfactory bulb output

Yael Shlomai-Fuchs

In the olfactory bulb, odor information from sensory neurons is extensively processed by multiple local networks of interneurons. Local networks thus shape the activity of Mitral and Tufted (M/T) cells which convey odor information to higher brain areas. The precise function of these local networks remains elusive because of the vast heterogeneity of interneurons, their diverse physiological properties, and their complex synaptic connectivity. Here we identified the parvalbumin inhibitory interneurons (PVNs) as a prominent component of the M/T presynaptic landscape by using an improved rabies-based trans-synaptic tracing method for local circuits. *In vivo* two-photon targeted patch recording revealed that PVNs have exceptionally broad olfactory receptive fields, and exhibit strong and persistent odor responses. Additional Trans-synaptic tracing indicated that not only do PVNs heavily innervate M/T cells but they also receive direct input from widely distributed M/T cells, suggesting a mechanistic explanation for PVNs' wide receptive fields. Both the anatomical and functional extent of this broad M/T→PVN→M/T feedback circuit contrasts with the narrowly confined local circuits thus far examined in the OB. This demonstrates that olfactory information is processed by multiple local circuits operating at distinct spatial scales. We show that integrating *in vivo* physiology with cell type specific synaptic tracing allows to study local circuits individually, while retaining the context of their larger networks.

Advisor: Prof. Adi Mizrahi

Processing of complex tactile scenes in the somatosensory system of the rat: electrophysiological, imaging and computational approaches

Daniel E. Shulz
Director of Research CNRS - Unit of Neuroscience, Information and Complexity

The tactile sensations mediated by the whisker-to-barrel cortex system allow rodents to efficiently detect and discriminate objects and surfaces. The temporal structure of whisker deflections and the temporal correlation between deflections occurring on several whiskers simultaneously vary for different tactile substrates. We hypothesize that tactile discrimination capabilities rely strongly on the ability of the system to encode different levels of inter-whisker correlations.

To test this hypothesis, we generated complex spatio-temporal patterns of whisker deflections during electrophysiological recordings in the barrel cortex, the ventro-posterior medial (VPM) nucleus of the thalamus and the trigeminal ganglion. A piezoelectric-based stimulator featuring 24 independent and fully adjustable whisker actuators was built for this purpose (Jacob et al., 2010).

Using this stimulator in anesthetized rats, we have previously shown that cortical neurons exhibit direction selectivity to the apparent motion of a multivibrissal stimulus (i.e. an emerging property of the global stimulus), uncorrelated to the local direction of individual whiskers (Jacob et al. 2008). Since a certain level of multiwhisker integration has been reported in the VPM, the nucleus relaying tactile information to the barrel cortex, we showed that emergent properties of multiwhisker stimulations are already coded by VPM neurons although to a lesser degree than in cortex (Ego-Stengel et al., 2012). We are currently exploring the global organization of this property in layers 2-3 (a global supra-barrel map) through voltage-sensitive dye imaging in the mouse.

Finally, we applied a reverse correlation approach to this problem by using Gaussian white noise stimulation on 24 whiskers and progressively varying the level of temporal correlation among them. Using a model-based analysis (spike-triggered covariance and L-NL models) for various levels of inter-whisker correlation, our recent findings (Estebanez et al., 2012) show that neuronal cortical networks implement coexisting coding schemes to cope with the varying statistics of the tactile sensory world. We propose a simple and comprehensive framework that not only accounts for most of the previous reported phenomenology of multiwhisker interactions but also provides a physiological role for this functional selectivity in terms of local contrast and global motion detection.

Role of Basal Ganglia main axis in temporal discounting

Marc Deffains

The Basal Ganglia (BG) are a set of sub-cortical structures that orchestrate the optimal tradeoff between behavioral cost and gain. To achieve this goal, BG are composed of modulators (e.g. dopamine, acetylcholine, serotonin) that adjust the neuronal activity along the main axis of the BG. The BG main axis contains the sub-cortical structures that connect cortical fields encoding current state of the subject with the motor centers of the brain. Electrophysiological recordings in behaving animal performing classical conditioning tasks revealed that BG modulators provide transient error prediction signal that encode the mismatch between prediction and reality to the BG main axis. In contrast to the extensive research on the role of BG modulators, only few studies have investigated the neuronal mechanisms underlying the motivational processes in the different structures of the BG main axis. In this study, we recorded the neuronal activity in the BG main axis in a monkey engaged in a classical conditioning task in which we manipulated the nature of the cue (appetitive and aversive) and the delivery time of the outcome (immediate or delayed). Our results showed that neurons of BG main axis exhibit modulations of activity in response to the cue which persist until the outcome delivery, even when the outcome is delayed (8 seconds). Therefore, we hypothesized that persistent/sustained modulations of the BG main axis might carry the information about the current (motivational) state of the subject from the cortical fields to the motor centers of the brain in order to selected the optimal action.

Lab: Prof. Hagai Bergman

Molecular-level functional magnetic resonance imaging of Dopaminergic signaling

Lili Cai

We demonstrate a new brain activity mapping approach that achieves both molecular specificity and spatial coverage using a neurotransmitter sensor detectable by magnetic resonance imaging (MRI). This “molecular fMRI” technique yields unprecedented time-resolved 3-dimentional measurements of dopamine release. We use this technique to spatially map dopamine release in the rat ventral striatum during a canonical reward-related stimulation paradigm. Peak dopamine concentrations were confirmed in established areas such as the nucleus accumbens core (NAcC), and substantial concentrations were observed in the less studied caudal areas. The amplitude of dopamine release correlates with rostrocaudal stimulation coordinates, suggesting local circuitry near stimulation site might modulate dopamine release. This is the first *in vivo* mapping of transient neurotransmitter signaling patterns in the brain and provides a foundation for developing quantitative molecular fMRI techniques towards understanding neural physiology.

Advisor: Prof. Alan Jasanoff

Non-invasive characterization of Neurons with continuous dynamic photo-stimulation

Ahmed El Hady
Max Planck Institute – Gottingen, Germany

Understanding information encoding by individual central neurons requires characterization of their input-output functions under near-natural input conditions, e.g. in the fluctuation driven regime, characteristic of cortical circuits. Controlling the input and registering on the order of 10.000 - 100.000 spikes as output, one can compute transfer metrics which are critical for collective network dynamics, such as dynamic gain, correlation gain or spike frequency vs current (FI-) curves. So far now such data are exclusively obtained in sharp electrode or patchclamp recordings, where the input to the cell body and therefore to the spike trigger zone in the axon initial segment is directly controlled. Due to the limited number of spikes obtained in invasive recordings, characterization of individual neurons is often not possible, dynamic gain curves, for instance, are averaged over tens of neurons.

We recently developed an alternative, non-invasive method for neuronal characterization. Spikes are recorded by an array of extracellular electrodes. Well-defined, fluctuating stimuli are delivered via light-activated channelrhodopsins to pharmacologically isolated neurons. Careful characterization of channelrhodopsin's transfer function warrants precise control over the waveform of the induced conductance. The setup delivers orders of magnitude more data than previously possible in the field of input-output characterization.

Neuronal responses were stable, measurement of intracellular pH showed only minor acidification under continuous stimulation. Comparison of our results with dynamic gain measurements and FI-curves obtain with traditional methods establishes the equivalence of the non-invasive, high-throughput method.

Utilizing human neurons to study neuropsychiatric disorders

Zhiping Pang
Child Health Institute of New Jersey
Rutgers University Robert Wood Johnson Medical School

The pathogenesis and etiology of many neuropsychiatric diseases, such as addiction, eating disorders, schizophrenia, autism spectrum disorders (ASDs) and Rett syndrome, remain an enigma because studies of the human brain in these patients are largely restricted to brain imaging or post-mortem analyses. Cellular analysis, such as characterization of synaptic transmission, is impossible due to the inaccessibility of human neurons from patients. Recent advancement in stem cell biology has made more in-depth analysis possible. However, modeling of human neuropsychiatric diseases is still in its infancy. Current technology of generating neurons from iPS cells is difficult, variable and time consuming. Development of better differentiation protocols and reproducibility of results across platforms are pressing questions to be addressed. I will describe three different methodologies in generating human neurons including: 1) direct conversion of human fibroblasts into functional neurons, i.e. induced neuronal (iN) cells; 2) generating dopaminergic neurons from iPS cells using small molecules and using iN technology; and 3) generating neurons from iPS cells via neural progenitor cells. Then I will describe characterization of human neurons derived from individuals carrying addiction risk genes (C*HRNA5)*, as well as from Rett syndrome patients. These “disease-in-a-dish” models using iPS cell-derived neurons, while limited in the explanation they provide for the holistic features of neuropsychiatric disorders, are useful in that they may capture cell-intrinsic properties and synaptic deficits of diseased neurons.

The teaching instinct

Mariano Sigman
Integrative Neuroscience, Physics Department, Buenos Aires University

While cognitive neuroscience has constructed a wealth corpus of knowledge about the mechanisms by which we learn, the science of how, what and why we teach remains largely unexplored. Paradoxically, teaching constitutes the landmark of knowledge spreading in humans. In my talk I will present our work towards the development of a cognitive science of teaching and of the teacher-student interaction.

Seemingly contradictory interval biases in discrimination tasks result from the influence of past stimuli on perception

Ofri Raviv

Biases such as the preference of a particular response for no obvious reason, are an integral part of psychophysics. In particular, such biases have been reported in the common two-alternative forced choice (2AFC) experiments in which participants are instructed to compare two consecutively presented stimuli. However, the principles underlying these biases are largely unknown, partly because different studies report different biases. Results of two 2AFC tone frequency discrimination experiments performed by human listeners utilizing two prevalent protocols are presented. Common to the two experiments is that one of the stimuli is a reference stimulus present in every trial. In one experiment, the reference stimulus is always lower than the non-reference stimulus whereas in the other experiment the reference is either lower or higher. In both experiments we report substantial interval biases. Namely, participants perform substantially better when the reference is in one of the intervals. However, the biases in the two experiments are opposite, which is inconsistent with previous accounts of interval biases. We hypothesize that the biases stem from an incorporation of sensory input with prior knowledge accumulated during the experiment. We show that such a computation can qualitatively and quantitatively account for both directions of the bias. These findings show that the observed interval biases are not due to an arbitrary preference of one of the responses. Rather, they stem from a computation that is inherent to the perceptual system, and can be used to improve performance when sensory information is noisy.

Advisors: Prof. Merav Ahissar & Dr. Yonatan Loewenstein

The computational mechanisms underlying dyslexics' anchoring difficulties

Sagi Jaffe-Dax

Dyslexics are diagnosed for their poor reading acquisition. Yet, a consistent difficulty is poor verbal memory, which often concurs with poor auditory discriminations. Several theories addressed this combined profile using broad cognitive terms. We now hypothesize that dyslexia can be understood computationally as a problem in combining prior information with noisy observations to improve performance. To test this hypothesis, we analyzed auditory perception in dyslexics using a two-parameter computational model. One parameter captures the internal noise in representing the current event and the other parameter captures the impact of recent history. We found that dyslexics' perceptual deficit can be accounted for by inadequate adjustment of these components, i.e. low, non-optimal weighting of their implicit memory in relation to their internal noise. Using ERP measurements we found that their automatic updating of recent history is impaired. These results suggest that Dyslexia can be characterized in terms of well-defined computational deficit.

Advisor: Prof. Merav Ahissar

Modeling influence and innovation in contemporary music

Uri Shalit

The role of musical influence has long been debated by scholars and critics in the humanities, but never in a data-driven way. In this work we approach the question of influence by applying topic-modeling tools (Blei & Lafferty, 2006; Gerrish & Blei, 2010)
to a dataset of 24,941 songs by 9,222 artists, from the years 1922 to 2010. We find the
models to be significantly correlated with a human-curated influence measure, and to
clearly outperform a baseline method.
Further using the learned model to study properties of influence, we find that musical influence and musical innovation are not monotonically correlated. However, we do find that the most influential songs were more innovative during two time periods: the early 1970's and the mid 1990's.

Advisors: Prof. Daphna Weinshall & Dr. Gal Chechik

POSTER SESSION

Single neurons responses in primary auditory cortex (A1) to pure tones in the halothane-anesthetized rat

Adi Amichai

Responses of neurons in primary auditory cortex (A1) to pure tones are characterized by a number of standard measures, including best frequency, activation bandwidth, and minimal threshold.

We recorded intracellular neural activity using sharp electrode in A1 of halothane-anesthetized rats in response to frequency sweeps at several attenuation levels. Here we analyze the frequency-response areas (FRAs) for membrane potential and spiking activity of single neurons and evaluate their tuning characteristics.

We found that while spike FRAs have similar characteristics to membrane potential FRAs, they are not identical. Both have V-shaped tuning curves. However, Spiking responses tend to have narrower activation bandwidths and are therefore better tuned compared with the underlying responses of the membrane potential. We suggest that a non-linear 'iceberg-effect' shape the transformation from membrane potential to spikes.

Advisor: Prof. Israel Nelken

Neural mechanisms of rule-based executive control

Flora Bouchacourt

How is the human brain able to be so flexible, i.e. to explore, adjust and exploit multiple behavioral strategies for a same task, depending on a changing context? A task set is an active representation of behavioral strategy, a context-dependent stimuli-response mapping rule. One of the lab's research group develop behavioral models explaining how we can learn multiple task rules, switch between them, create new ones, and link those with neural activity in the prefrontal cortex. However, models' parameter setting appears to be quite difficult, as neural hardware is not considered. Moreover, the implementation of task set is already assumed. This PhD project aims at understanding the neural implementation of task sets and the plasticity mechanisms leading to their development. It is constructing a biologically constrained rate-based network model of neural activity in the prefrontal cortex. This project is new in the lab, and involves also Dr. Koechlin's group, from which we are using human behavioral experiments.

The first model is composed of two interacting neural circuits with mixed selectivity of neurons:

The "associative" network, learns one to one associations between visual stimuli and outcome of action, but cannot learn the task sets.

The "context" network learns the representations of temporal contexts thanks to Hebbian and Temporal Sequence Learning mechanisms.

Finally, the second model we are exploring is an unstructured chaotic network that could also learn such a task.

This way, the PhD project is linking functional level and neuronal level in neurosciences with a bottom-up approach.

Srdjan Ostojic Group for Neural Theory, Laboratoire de Neurosciences Cognitives,
Ecole Normale Supérieure

Neural correlates of perceptual continuity during eye blinks revealed in human ventral stream visual cortex

Tal Golan

The perceived continuity of the visual image despite frequent interruptions by eye blinks is a ubiquitous visual illusion. We investigated the neural correlates of this illusion using intra-cranial electrocorticography in epileptic patients. Patients were presented with blocks of still images. In some of the blocks the patients were instructed to blink at a constant pace and in others artificial darkenings of the screen ('gaps') mimicked the blinks' retinal impact. We found that in early visual cortex, the reappearance of the visual stimuli following the termination of either blinks or gaps produced a rebound of broadband gamma (50-150Hz) activation of a similar magnitude. In contrast, in higher level visual cortex, the rebound produced by gaps was significantly more pronounced than that produced by blinks. These results suggest that counterintuitively, perceptual continuity is associated with *the lack of* transient re-activation in ventral stream visual areas.

Supported by ICORE, HBP and Kimmel award to RM.

Advisors: Prof. Leon Y. Deouell & Prof. Rafael Malach

Homeostatic adaptations in synaptic responses of striatal cholinergic interneurons to diminished thalamic innervation in mouse models of Huntington's disease

Josh A. Goldberg
Department of Medical Neurobiology – Hebrew University

Huntington's disease (HD) is marked by a reduction in striatal cholinergic markers, despite the resiliency of cholinergic interneurons (ChIs) – that sustain basal striatal cholinergic tone – to the degeneration that decimates striatal projection neurons. A study of ChIs in the R6/2 mice and our own unpublished data from the BACHD and Q175 mice have failed to find a difference in autonomous ChI firing rates, suggesting that the basal cholinergic tone is unchanged in HD. An alternative explanation for the drop in cholinergic markers is that the excitatory drive of ChIs is impaired in HD. Indeed, a recent study has described a loss of thalamic synapses in the striatum. Because the thalamic intralaminar nuclei (ILN) gives rise to the dominant excitatory input to ChIs, we hypothesized that a loss of ILN in-nervation should be accompanied by a compensatory augmentation of the other excitatory input to ChIs that arises from cortex. To test this hypothesis, we combined optogenetics and slice electrophysiology in BACHD and Q175 mice that were crossed with mice expressing channelrhodopsin-2 (ChR2) under control of the Thy1 promoter. We found that activation of corticostriatal afferents drove spiking in HD ChIs more vigorously than in wild-type (WT) ChIs. This effect was not attributable to a difference in the strength of the synaptic connections but was rather a consequence of a postsynaptic amplification in HD ChIs. This conclusion was supported by the following findings: i) paired pulse ratios did not differ between HD and WT ChIs arguing against a change in release probability at corticostriatal synapses onto ChIs; ii) quantal excitatory postsynaptic currents (EPSCs) generated by minimal stimulation did not differ between HD and WT ChIs; but iii) strong stimulation evoked substantially larger EPSCs in HD ChIs. This latter difference was sensitive to block of voltage dependent Nav1 sodium (Na+) channels by inclusion of QX-314 in the recording pipette. Because the persistent Na+ current (NaP) is known to amplify the response to excitatory synaptic inputs, its amplitude in HD and WT ChIs was compared; indeed, it was larger in HD ChIs. Furthermore, blocking NaP with ranolazine normalized both the synaptic response and the transient spiking response in HD ChIs. Finally, we hypothesized that synaptic boosting of cortical inputs is consequence of the loss of group I metabotropic glutamate receptor (mGluR) activation that occurs because thalamostriatal innervation of ChIs is diminished in HD models. Indeed, we found that antagonizing group I mGluRs in WT mice generates the HD phenotype. We conclude that loss of thalamic input in HD, and with it the loss of group I mGluR activation, give rise to an up-regulation of NaP currents and synaptic boosting of cortical inputs in ChIs.

Signal correlation analysis indicates active de-correlation along the main axis of the basal ganglia network

Shiran Katabi

The basal ganglia (BG) network has been suggested to have an actor/critic architecture and to implement a reinforcement learning algorithm. Here, we examined the actor component that corresponds to the BG main axis. The BG main axis is characterized by a significant reduction in the number of neurons from the cortex to the striatum and to the globus pallidus. Therefore, there is high degree of common inputs to neighboring neurons, which are further connected by their axon collaterals. Thus, the functional connectivity of the BG main axis should naturally lead to highly correlated neuronal activity.

We recorded neurons in the primary motor cortex, the striatum, the globus pallidus external segment (GPe) and the substantia nigra pars reticulata (SNr) in five behaving monkeys. The monkeys were engaged in a classical conditioning task with cues predicting the probability or intensity of food, neutral or air-puff outcomes. We conducted a signal correlation analysis to measure the similarity of the responses to behavioral events of all pairs of (simultaneously and non-simultaneously) recorded neurons (n=266, 918, 577 and 148 in the cortex, striatum, GPe and SNr, respectively). The average discharge rate in the cortex, striatum, GPe and SNr was 6.6, 1.2, 70.95 and 49.51 spike/s, respectively. We found that the distributions of the signal correlation values for motor cortex and striatum projection neuron pairs had a long and heavy tail toward positive correlation values. However, the distribution of the GPe and SNr pairs were symmetrical around zero.

Our results distinguish between the behavioral functions of the different BG structures, and indicate active de-correlation along the transition between structures, with a low to high discharge rate in the main axis of the BG network.

Advisor: Prof. Hagai Bergman

Firing under Pressure

Avi Libster

Corticotropin-releasing factor (CRF) is a neuropeptide that plays a major role in stress response. CRF is also released from climbing fibers that originate in the inferior olive nucleus and innervate the cerebellar cortex. Previous studies have shown that CRF modulates Purkinje cell (PC) firing rate. Here we studied the CRF effect on PC firing activity, and investigated the underlying biophysical mechanisms. In vitro cell attached recordings were performed from PC somata in parasagittal slices of cerebellar vermis. The increase inPC's firing rate was quantified, and dose response curve was characterized. The underlying biophysical mechanism was investigated using whole-cell current and voltage clamp recordings. In the presence of CRF, an increase of the amplitude of the persistent sodium current was observed. Application of CRF, while TTX was present in the bath, resulted in a hyperpolarization of the membrane voltage that was accompanied by an increase in membrane conductance, indicating the involvement of potassium current. Most of the results can be reproduced by a single compartment model containing HH mechanism, assuming that CRF shifts the activation curves of the persistent sodium current and the delayed rectifying K current toward more negative values.

Advisor: Prof. Yosi Yarom

Detection of neuronal sprouting during the development of neuropathic pain

Hodaya Leibovich

Neuropathic pain which results from a lesion or disease of the somatosensory system. In an attempt to understand the mechanism underlying neuropathic pain, several models have been developed and among the more useful is the Spared Nerve Injury (SNI) model. In this model the nerves innervating the middle paw area are dissected, while the nerves innervating the paw on both ends remain intact. This partial nerve lesion results in paw allodynia (pain due to a stimulus which does not normally induce pain) and hyperalgesia (increased sensitivity to painful stimuli) even in the denervated areas. Although SNI-mediated pain has been widely studied, the nerve rearrangement pattern which parallels with the developing pain has remained unexplored.

The objective of this study is to anatomically characterize the peripheral nerve rearrangement that follows nerve injury and correlate them with the developing pain. To this end, we used a new technique which allows us to anatomically characterize the cell population that innervates specific areas in the rat's paw under normal conditions, and to describe the nerve rearrangement process after the nerve lesion with the developing pain. A comprehensive description and analysis of this process will give profound understanding of the mechanisms involved in development of neuropathic pain in conjunction to neuronal rearrangements of nociceptive and other types of sensory neurons. This will ultimately lead to advances in development of treatments towards this as of now an untreatable debilitating condition.

Advisor: Prof. Alex Binshtok

Walking the footsteps of the blind: Computationally assessing navigation patterns of visual and non-visual navigation with different assistive devices

Shachar Maidenbaum

How does lack of vision affect the route one takes through an environment? How does this route change when different assistive tools are used? These questions have significant repercussions as Orientation and Mobility in unknown places pose one of the main challenges facing the blind.

Currently, dedicated programs exist for helping the blind learn to navigate using the traditional white-cane. Throughout the years these programs were refined and were shown to significantly improve mobility. From this research have also emerged navigation patterns of white-cane users. Over the past decades many new devices have been developed for the blind. These devices offer different, and often more, information than the traditional white-cane, and may require different patterns of navigation and training for optimal use. Additionally it is unclear how useful some of these parameters, such as increased distance, actually are for non-visual navigation.

We recently developed the EyeCane, an advanced mobility aid for the blind which transforms distance to auditory cues, augmenting the traditional white cane with a distance of 5 meters. We then created a virtual version, dubbed the virtual-EyeCane which is aimed at both helping the blind master the EyeCane's use, and learning novel environment in the safety of their own home.

Here, we use a series of virtual environments to explore the differences in navigation when using the virtual-EyeCane electronic travel aid (which offers increased distance information), when using a virtual version of the traditional white-cane, without using a device at all and when navigating visually.

We show that the characteristics of navigating with the virtual-EyeCane differ from those of white-cane users and from navigation without an assistive device, and that virtual-EyeCane users complete more levels successfully, taking a shorter path and with less collisions than users of the white-cane or no device. These differences are enough to enable classification between the groups based on their scores or on their paths. Finally, we demonstrate that virtual navigation with the virtual-EyeCane takes on patterns relatively similar to those of navigating visually.

In conclusion, these results suggest that navigation patterns learned from the white-cane are not necessarily optimal for other devices and that additional distance information is enough to change spatial perception and navigation patterns from those customarily used by the blind to patterns more similar to the sighted. Additionally, the classifiers obtained from these navigation patterns might potentially enable prediction of paths through novel environments.

Advisor: Prof. Amir Amedi

Cortical Plasticity following perceptual learning

Ido Maor

Perceptual learning is a cognitive phenomenon whereby perceptual capabilities improve with training. The neural substrate of perceptual learning is not well understood but probably involves multiple brain regions, one of which is the neocortex. Our work focuses on how learned information is encoded at the functional level by individual cortical neurons. Our model is the primary auditory cortex (A1) of the mouse. We study how different subpopulations of neurons in A1, e.g. inhibitory neurons and excitatory pyramidal cells, encode the learned information.

First, to study perceptual learning in mice, we developed an automated assay in a learning chamber that we named “the Educage”. The Educage is designed to train groups of mice (up to 6 mice simultaneously) on a two-tone ’go no-go’ discrimination task. Once the procedure is learned, task difficulty is gradually increased by decreasing the difference between the two tones. Using this procedure, mice became experts in this task and reached their perceptual limits within thousands of trials. Second, to study the physiological correlates of learning in A1, we used *in vivo* two photon targeted patch clamp to asses basic response properties of inhibitory and excitatory neurons of layer 2/3. As inhibitory neurons, we targeted Parvalbumin positive (PV^+) interneurons, the largest inhibitory subpopulation of the cortex. We used transgenic mice expressing TdTomato in PV neurons and used unlabeled neurons as controls (PV^-). We compared the frequency receptive fields and other response properties (e.g. response latency, spontaneous and evoked firing rate) of PV^+ and PV^- neurons in A1 of expert and naïve mice. To date, the data we collected already reveals that PV^+ and PV^- neurons changed in unique ways following learning. We suggest that specific modifications in inhibitory circuits within layer 2/3 of A1 contribute to auditory perceptual learning.

Advisor: Prof. Adi Mizrahi

Exploring the implications of miRNA-132 decline in Alzheimer's disease

Nibha Mishra

Alzheimer's disease (AD) is the leading neurodegenerative disorder and anti-AChEs are the leading therapy for AD patients. In my recent study, I found that anti-AChEs could ameliorate memory impairments, neuronal degeneration and amyloid deposition in an established mouse model, where amyloid plaque formation is induced by intracerebroventricular (i.c.v.) injection of the neurotoxic amyloid peptide $A\beta_{1-42}$, but the underlying molecular mechanism(s) are yet unknown. MicroRNAs (miRNAs) are short, 20-25 nucleotide long regulators of numerous biological mechanisms. Of those, miRNA-132 suppresses AChE, regulates neuro-inflammation, controls stress-inducible cognitive decline yet drastically decreases in AD. I currently explore the possibility that the AD-associated decline of miRNA-132 is causally involved with AD pathology, and that the suppression of Aβ neurotoxicity under anti-AChEs involves an induction of miR-132 increase. To find out if anti-AChEs confer changes in miR-132 and other amyloid-affecting miRNAs, I will combine anti-AChE treatment, deep sequencing to profile brain miRNAs, and potentiation of brain miR-132 levels by administering miR-132 via viral infection. By applying diverse neuropathology and behavioral tests, I hope to assess the outcome of these manipulations. Identifying such a mechanism of action may shed new light on the role of miRNA changes in AD and provide new means for discovery of targets for therapeutic interference.

Advisor: Prof. Hermona Soreq

Using Tweedie distributions for fitting spike count data

Dina Moshitch

Background:
The nature of spike count distributions is of great practical concern for the analysis of neural data. These distributions often have a tendency for 'failures' and a long tail of large counts, and may show a strong dependence of variance on the mean. Furthermore, spike count distributions often show multiplicative rather than additive effects of covariates. We analyzed the responses of neurons in primary auditory cortex to transposed stimuli as a function of interaural time differences (ITD). In more than half of the cases, the variance of neuronal responses showed a supralinear dependence on the mean spike count.
New Method:
We explored the use of the Tweedie family of distributions, which has a supralinear dependence of means on variances. To quantify the effects of ITD on neuronal responses, we used Generalized Linear Models (GLMs), and developed methods for significance testing under the Tweedie assumption.
Results:
We found the Tweedie distribution to be generally a better fit to the data than the Poisson distribution for over-dispersed responses.
Comparison with Existing Methods:
Standard analysis of variance wrongly assumes Gaussian distributions with fixed variance and additive effects, but even generalized models under Poisson assumptions may be hampered by the over-dispersion of spike counts. The use of GLMs assuming Tweedie distributions increased the reliability of tests of sensitivity to ITD in our data.
Conclusions:
When spike count variance depends strongly on the mean, the use of Tweedie distributions for analyzing the data is advised.

Lab: Prof. Israel Nelken

Phase-based analysis reveals propagating waves during single-trial voltage sensitive dye imaging of visual cortex in awake behaving monkey

Lyle Muller

New multichannel recording methods at the mesoscopic scale have recently generated much interest in the spatiotemporal interactions within and among brain areas. Large, low-frequency propagating waves of activity have been observed during anesthetized brain states in many species, while voltage-sensitive dye imaging (VSDI) in awake behaving monkeys has typically observed a unimodal spread of activity in response to stimuli. Because of the technical and noise limitations of VSD imaging, however, averaging over many trials was necessary in previous studies, and potentially precluded the detection of trial-variable propagating events. With the aid of denoising methods developed specifically for analyzing VSDI data at the single-trial level, here we report the existence of spontaneous and stimulus-evoked propagating waves of activity in the primary visual cortex of the awake, behaving monkey. We quantify these stimulus-evoked propagating waves using a phase-based approach, and observe that the response latency and the distribution of propagation speeds differ across trials, limiting the extent to which averaged signals can capture these variable dynamics. We go on to examine potential functional roles of these trial-based propagating events in the context of the interaction between multiple stimuli and brain areas on the planar surface of the cortex, and relate these new findings to previous studies of the population activity in primary visual cortex.

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Ecole des Neurosciences de Paris Ile de France: Graduate Program

Laura Peeters

The ENP was created by the French Ministry of Research and Higher Education as a Thematic Network for Advanced Research and became a private foundation in 2007. It was founded by the French research agencies CEA, CNRS and Inserm, and two universities (Université Pierre et Marie Curie and Université Paris Sud). In 2008, additional partners joined the ENP, including Université Paris Descartes, the Brain and Spinal Cord Institute (ICM), Fondation Voir et Entendre, Okayama University and the Labex Biopsy. The ENP is a research training network that brings together 112 teams in 22 research centers in the Paris region. Research areas include: molecular and cellular neurobiology, systems neuroscience, cognitive neuroscience, computational and theoretical neuroscience, and neurological and psychiatric disorders.

Since 2007, the ENP has launched several programs. The ENP Graduate Program has recruited and funded 49 international students, 16 of whom have received their doctoral degrees. The ENP has also awarded 5 young group leaders, helping them to obtain positions at French national research agencies, to set up their teams quickly and to access the latest technology. The ENP has funded requests from its members to host 13 internationally renowned scientists such as Jack Feldman (UCLA), Peter Brophy (University of Edinburgh), and Marla Feller (University of California Berkeley). The ENP also helps the neuroscience community to create multidisciplinary exchanges in the broad field of neuroscience. In this way, several scientific events such as summer schools (Optical Imaging and Electrophysiological Methods in Neuroscience) and conferences (CNS 2013 Computational Neuroscience Meeting) have been sponsored by the ENP.

In conclusion, all of these programs have the same aim: to promote neuroscience research at its highest level, by supporting innovative research and multidisciplinary approaches, and by developing an international training network.

General Secretary and ENP Administrative team

Towards the development of naturalistic setups for studying auditory cortex responses in freely moving rats

Ana Polterovich and Amit Yaron

The auditory environment of animals is complex: it contains many types of sounds from different sources that have different meanings and can elicit rewards or punishments. 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. Our goal is to investigate the abilities of rats to extract behaviorally-relevant information using a natural-like sensory environment.

To understand how rats perform complex auditory discriminations, we are now developing a setup for recording from awake, freely moving animals. We are recording the electrophysiological responses in primary auditory cortex with a 16-electrode array, implanted on the same day. The rats move around a computer-controlled behavioral environment under video control, while listening to different auditory stimuli. We were able to record responses to different sounds, and found stimulus-specific adaptation (SSA) to both pure tones and complex sounds.

Using this setup we are planning to develop an operant conditioning paradigm by assigning behavioral meaning to different auditory stimuli, and letting the rats learn these meanings. We will record the electrophysiological responses in primary auditory cortex to these stimuli during the conditioning and observe how they change while the rats are learning.

Advisor: Prof. Israel Nelken

Early visual response in human posterior parietal cortex revealed by visual onset latency estimation using electrocorticographic (ECoG) recordings

Tamar Regev

Much of what is known about the timing of visual information processing in the human
brain is inferred from studies in monkeys, and substantially less is known about the precise spatio-temporal evolution of visual responses in humans. We performed an analysis of visual onset latencies, derived from electrocorticographic (ECoG) recording in a patient who was implanted with 112 subdural electrodes, distributed across the occipital, parietal and temporal cortices of the right hemisphere, for pre-surgical evaluation of intractable epilepsy. The patient was presented with images of objects from several categories. Event Related Potentials (ERPs) were calculated across all non-target categories, and statistically reliable onset latencies were determined using a bootstrapping procedure over the single trials baseline activity in individual electrodes. The distribution of onset latencies reflected the known hierarchy of visual areas. However, we found also robust, statistically reliable and spatially localized, very early responses on the bank of the posterior intra-parietal sulcus (IPS). The response in the IPS started nearly simultaneously with responses detected in V1, around 50 ms post-stimulus onset.
It has been suggested that fast processing through the dorsal system serves to prepare the ventral system towards processing of information at a given location, but evidence for such a fast track in humans is circumstantial. It has also been suggested that parietal regions get direct input from sub-cortical areas. Such mechanisms may explain preserved visual abilities after loss of primary visual cortex, a neuropathological condition known as 'blindsight'. Our results support the notion of early visual processing in the posterior parietal lobe, not respecting traditional hierarchies, and give direct evidence for the upper limit of onset times of visual responses across the human cortex.

Advisor: Prof. Leon Deouell

Sensitivity to location, hand-, and object-identity in the patterns of activation in ventral and dorsal visual pathways

Zvi Roth

Visual information processing in the cortex is typically divided between two major pathways. The common notion is that the ventral stream is mainly involved with deciphering the *identity* of visual objects, while the dorsal stream encodes the *location* of objects for visually guided action. Here we test this proposed division of labor by measuring the amount of information available about the identity and location of objects in classical regions of the ventral and dorsal visual streams. To that end, subjects viewed video clips of a (left or right) hand grasping a tool, in 49 different retinal (and screen) locations while maintaining fixation. The subjects covertly named the identity of each tool and the hand used to grasp it. We characterized the information available in the patterns of multivoxel activity of early visual cortex (EVC), a high-level dorsal visual area (intraparietal sulcus; IPS) and a high-level ventral visual area (lateral occipital complex; LOC). As expected, the EVC pattern elucidates stimulus-location quite accurately but carries no stimulus-identity information. Surprisingly, however, IPS activity patterns contain a high level of stimulus-identity information (higher than LOC) and a low level of stimulus-location information (lower than LOC).

Advisor: Prof. Ehud Zohary

Coding of natural sounds in the mouse auditory cortex

Amos Shalev

The auditory system is used to code sounds from the environment. Early in the auditory hierarchy, circuits are organized and highly specialized for detecting basic sound features. The primary auditory cortex (A1) has been proposed to code complex features of the soundscape but its underlying coding principles and their mechanisms are not well understood. Coding in A1 has been investigated mostly using highly simplified sound stimuli like pure tones. But pure tones are quite different than the sounds animals encounter in their natural environments. Our work focuses on understanding coding principles of cortical neurons to natural sounds with special emphasis on vocalizations.

Vocalizations contain several complex auditory features. For example, vocalizations are several seconds long and contain numerous syllables with varying inter-stimulus intervals. In addition, syllables have complex features like harmonics, amplitude modulations (AM), and frequency modulations (FM). To study how A1 neurons code vocalizations, we first recorded a library of pup vocalization. Then, recorded vocalizations (as well pure tones) were used as stimuli while we recorded the spiking activity of single neurons in A1. We found that neurons in A1 responded with highly heterogeneous patterns of activation to pup vocalizations. Interestingly, neurons in A1 showed preference for specific and sometimes unique syllables in the sentence. Neuronal response parameters like basic frequency and amplitude tuning could not explain the syllable preference leading us to hypothesize that other mechanisms are responsible for neuronal response profiles. We are currently testing other response properties such as time and context to explain the complex responses of cortical neurons to natural sounds.

Advisors: Prof. Adi Mizrahi & Prof. Israel Nelken

Figure-Background processing in a seemingly low-level olfactory station

Amit Vinograd

One of the most basic computations of the olfactory system is odor discrimination. Discrimination is fundamental for a wide range of behaviors like locating food, and identifying predators vs. prey. Under natural conditions, odor detection and discrimination can be challenging because odors appear against other odorous backgrounds. Thus, odors must be separated from their background – a process called Figure Background Separation (FBS). Little is known about where and how FBS is computed in the olfactory system. However, according to the current dogma, this computation is performed at the level of the olfactory cortex. We reevaluated this dogma by testing whether computations associated with FBS occur already at the level of the olfactory bulb (OB), which is the first station of olfactory processing in the brain. To do so, we imaged calcium activity of mitral cells (MCs) in response to a FBS protocol (combinations of 'figure', 'background' and 'figure over background'). Imaging was carried out using *in vivo* two photon microscopy which allowed us to screen hundreds of MCs. We imaged ~600 neurons from 6 mice and our initial analyses reveal that ~60% of responsive MCs show adaptation, and at least 15% show responses akin to FBS computation (e.g. different response to figure over background as compared to a binary mixture). Thus, we argue that FBS is computed already at the level of the OB. Furthermore, these results suggest that the OB can perform a higher-level computation and not only low-level computations as previously suggested.

Advisor: Prof. Adi Mizrahi

Firing patterns and synaptic events in the Deep Cerebellar Nuclei

Yasmin Yarden

The Deep Cerebellar Nuclei (DCN) form the main output of the cerebellum. DCN neurons are densely innervated by Purkinje cells' inhibitory inputs while receiving excitatory inputs from climbing and mossy fiber collaterals. The firing of these cells is the end result of the computations occurring in the cerebellar cortex, which is then delivered to the rest of the brain.

In-vitro studies showed that these neurons can respond to hyperpolarizing input with a robust burst of spikes also known as a 'rebound response'. This property enables the neurons to represent Purkinje cell's activity. On the other hand if these neurons respond only to depolarizing input, they represent climbing or mossy fibers activity. Using intracellular recordings in anesthetized mice we studied what makes the DCN neurons fire in in-vivo conditions. Our results indicate that action potentials seem to be triggered by excitatory synaptic events and are not a result of a rebound response.

Advisor: Prof. Yosi Yarom